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**DEVELOPMENT OF NEW CHIRAL PHOSPHORUS
AND CARBENE LIGANDS
FOR ASYMMETRIC CYCLOPROPANATION**

by

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A Doctoral Thesis

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Abbreviations used in the text

Ac	acetyl
aq.	aqueous
Ar	aromatic
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenyl
BOC	<i>tert</i> -butoxycarbonyl
BOP	benzotriazolyloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
<i>t</i> -Bu	<i>tert</i> -butyl
°C	degrees Celsius
cat.	catalytic
cm ⁻¹	wave number
cod	cyclooctadiene
DAST	diethylaminosulfur trifluoride
DBA	dibenzylidene acetone
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
δ	chemical shift
Deoxo-Fluor	bis-(2-methoxyethyl)aminosulfur trifluoride
DFI	2,2-difluoro-1,3-dimethylimidazolidine
DIEA	diisopropylethylenediamine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
eq.	equivalents
EI	electron impact
Et	ethyl
FAB	fast atom bombardment
Fmoc	9-fluorenylmethyloxycarbonyl
g	grams
h	hours
IR	infrared

M	molar
Me	methyl
Mes	mesityl
min.	minute(s)
mg	milligram(s)
mL	millilitre(s)
mp	melting point
NMM	<i>N</i> -methylmorpholine
NMR	nuclear magnetic resonance
O/N	overnight
Pd-C	palladium on carbon
Pd(OH) ₂ -C	palladium hydroxide on carbon
Ph	phenyl
PtO ₂ -C	platinum oxide on carbon
ppm	parts per million
<i>i</i> -Pr	<i>iso</i> -propyl
py	pyridine
PyBOP	benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluoro-phosphate
quant.	quantitative
rt	room temperature
s.m.	starting material
TCT	2,4,6-trichloro-(1,3,5)-triazine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tosyl	<i>p</i> -toluenesulfonyl

Abstract

This thesis has been divided into four main sections. The first section is the introduction, which contains a review of both cyclopropane/enes and carbene chemistry. Results and discussion are compiled in chapters three through six, and experimental details are provided in chapter seven. Finally the appendix, chapter eight, contains X-Ray crystallographic data, as well as IR, ^1H NMR and ^{13}C NMR spectroscopic data of a number of the compounds.

Chapter three contains preliminary investigations into the synthesis of resin bound nitrocyclopropanes/enes *via* the derivatisation of Wang and 2-chlorotrityl resins. A novel methodology for the synthesis of these compounds was proposed.

Chapter four describes work carried out on the synthesis of several chiral phosphorus ligands from a range of chiral diols, amino-alcohols, amino-thiols and diamines. These phosphorus ligands could be used to form rhodium catalysts to be employed in the synthesis of cyclopropanes/enes.

Chapter five contains investigations into the synthesis of several chiral imidazolinium tetrafluoroborate salts, and their use in the attempted synthesis of carbene metal complexes. Several unexpected products were isolated and identified by X-Ray crystallography.

Chapter six contains preliminary investigations into the synthesis of several chiral analogues of 2,2-difluoro-1,3-dimethylimidazolidine (DFI).

Chapter seven contains full experimental details for the synthetic studies carried out in the preceding chapters.

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INTRODUCTION

CHAPTER 1: Cyclopropanes and Cylopropanation Reactions

1.1 Introduction

Cyclopropanes are three-carbon containing ring compounds that belong to the same family as aziridines and epoxides, as shown in **Figure 1**.

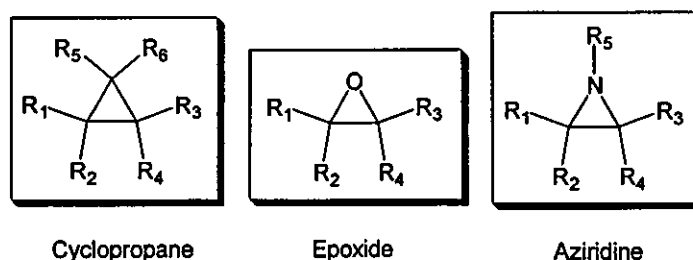


Figure 1

Cyclopropanes can be found in a wide variety of natural products, such as fatty acid metabolites, unusual aminoacids, pheromones and terpenes, as well as in synthetic compounds possessing important biological properties. Several reviews have been published on the synthesis of cyclopropane containing natural products.¹

1.2 Structure of cyclopropanes

Cyclopropanation ring formation requires that three -CH₂- groups have to be accommodated into a cyclic arrangement with all C-C-C bond angles equal to 60°, as shown in **Figure 2**, while the ideal C-C bond angle is 109.5°, for sp³ hybridized orbitals. Therefore cyclopropanes depart by this ideal value by a very large amount, 49.5°. This compression of the internal bond angle results in angle strain, since the sp³ orbitals of the carbon atoms cannot overlap as effectively as they do in alkanes, as shown in **Figure 2**.

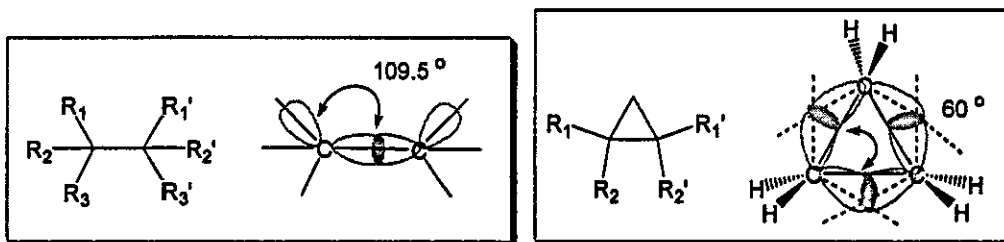


Figure 2

The carbon-carbon bonds of cyclopropane are often described as being bent. The orbitals used for these bonds are not purely sp^3 , they contain more p character. These carbon-carbon bonds are weaker, and as a result the molecule has greater potential energy.

Moreover, cyclopropanes also suffer from torsional strain because the coplanar arrangement of the carbon atoms makes the C-H bonds eclipsed, as shown in **Figure 3**.

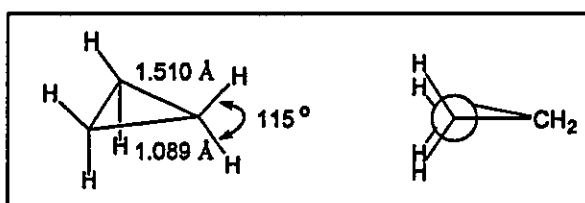
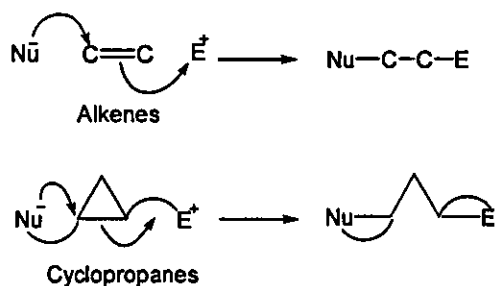


Figure 3

1.3 Reactivity of cyclopropanes

Cyclopropane derivatives are very versatile tools in organic chemistry, since they undergo a variety of ring-opening reactions that are favoured by the thermodynamic driving force that the ring strain provides. The chemistry of cyclopropane rings resembles that of a C-C double bond, due to the greater p character in the C-C σ -bonds, as shown in **Scheme 1**.



Scheme 1

1.4 Anticancer-properties

A common feature of cyclopropane compounds is that they form an initial physical complex with DNA, before covalently bonding to it. Their vital purpose is to kill bacteria by disrupting the synthesis of DNA and RNA. Many of them have also shown anti-tumour activity. Two examples are the compounds FR-900848 **1**² and U-106305 **2**³, which have shown strong bioactivity. Their structures are shown in Figure 4.

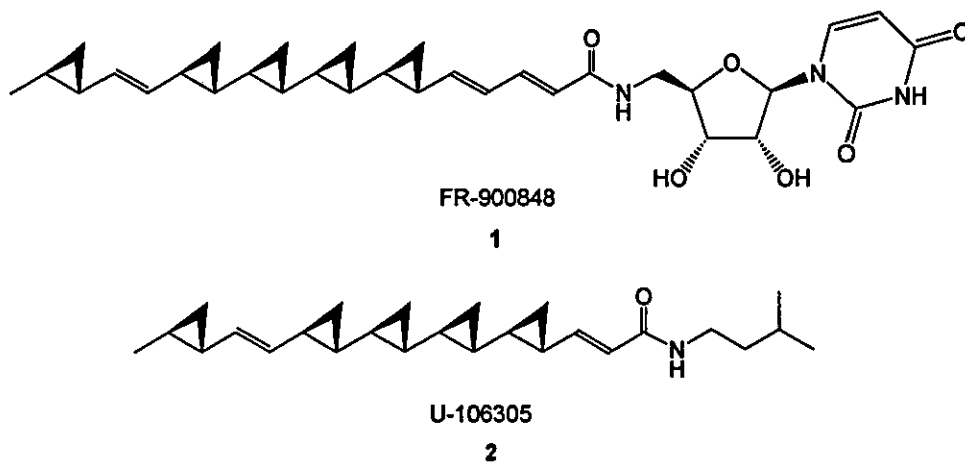


Figure 4

The presence of electron withdrawing groups in the cyclopropanes makes DNA alkylation easier, as shown in Figure 5.

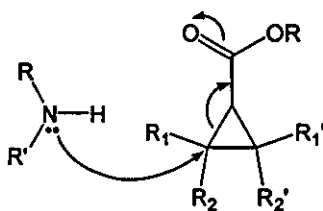


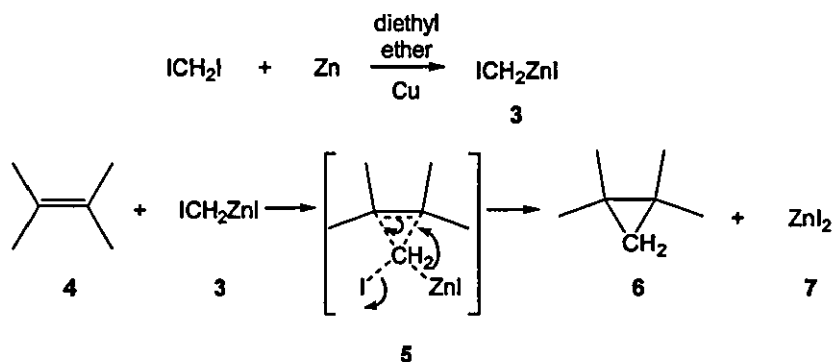
Figure 5. Stabilization of negative charge

1.5 Methods of cyclopropanation

Olefin cyclopropanation has been proven to be a useful tool for synthetic organic chemists, since cyclopropane structures often serve as intermediates in the synthesis of more functionalised cycloalkanes⁴ and acyclic compounds.⁵ This has led to the development of several methods for cyclopropanation reactions.⁶ The main methods have been previously reviewed⁷ and very recently a review of stereoselective cyclopropanation reactions has been published.⁸

1.5.1 Simmons-Smith cyclopropanation

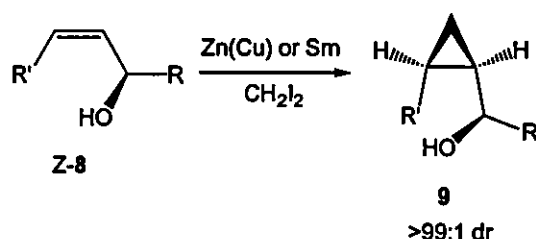
This method of cyclopropanation consists of a reaction of a zinc-copper couple (zinc that has had its surface activated with copper) with diiodomethane in ether, to give a solution containing iodomethylzinc iodide **3**, which after reaction with an alkene **4** affords a cyclopropane **6**, as shown in **Scheme 2**. The reaction seems to proceed by a direct transfer of a methylene unit from the organometallic compound **3** to the alkene **4**.



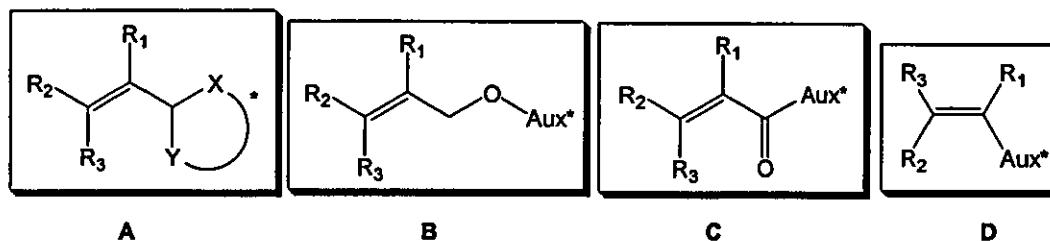
Scheme 2

The Simmons-Smith reaction has also been used asymmetrically to prepare optically active cyclopropane containing compounds. These can be prepared in high enantiomeric excess by enantioselective Simmons-Smith reactions of chiral alkenes with the reagents prepared from Zn(Ag), Zn(Cu),⁹ diethylzinc¹⁰ or ethylzinc iodide/ I_2 ¹¹ and diiodomethane. Iodomethylzinc, $I\text{ZnCH}_2\text{I}$, is the reactive intermediate in these reactions, and behaves as a weak nucleophile. The reaction is stereospecific with respect to the geometry of the alkene, and despite free carbenes being involved, side reactions do not generally occur.

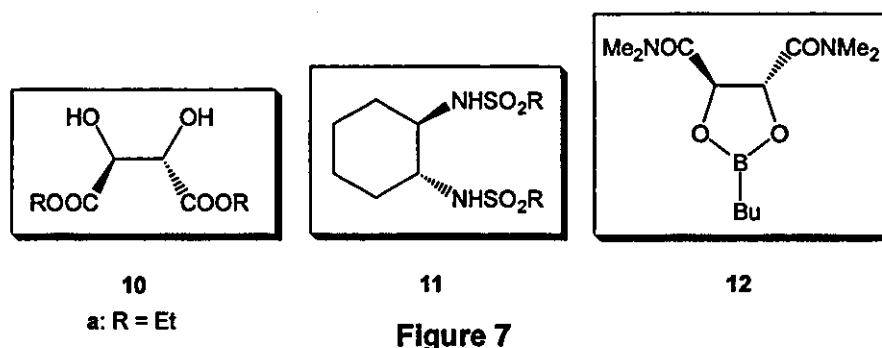
Allylic hydroxyl substituents have been shown to direct the diastereoselectivity in either cyclic or acyclic compounds, and give a large rate enhancement. Cyclopropanation of (Z)-allylic secondary alcohols **Z-8** with activated zinc or samarium and diiodomethane proceeds with high diastereoselectivity to give the compound **9**, as shown in **Equation 1**.¹²



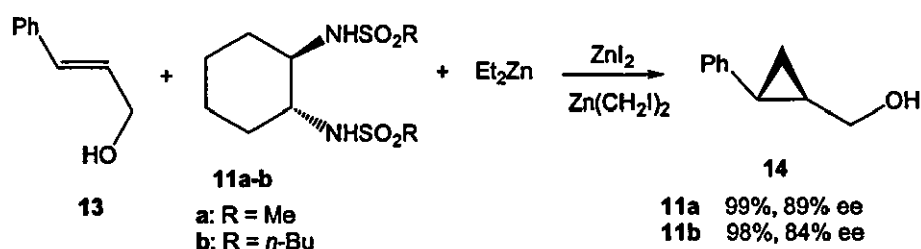
Several chiral auxiliaries have been developed in order to produce enantiomerically pure cyclopropyl derivatives. They can be compiled in four general classes: acetals (**A**), allylic ethers (**B**), α - β -unsaturated carbonyl derivatives (**C**) and enamines and enol ethers (**D**), as shown in **Figure 6**.



For example, chiral ligands, such as diethyl tartrate **10a**,¹³ bis-(sulfonamide) **11**¹⁴ and the dioxaborolane compound **12**,^{6f,15} shown in **Figure 7**, can be precomplexed to allylic alcohols (forming a class **B** chiral auxiliary), to afford, after Simmons-Smith cyclopropanation, cyclopropylcarbinols in high yields and with excellent enantiomeric excess.^{7b,16-18}



Equation 2 shows an example of the conversion of an allylic alcohol **13** to a cyclopropylmethanol **14** using bis-(sulfonamide) **11a-b** as chiral controller.^{14b}



In the transition state, it is believed that the free hydroxyl group is possibly complexed as a zinc alkoxide, as is shown in **Figure 8**, producing an effective chiral environment.^{14a}

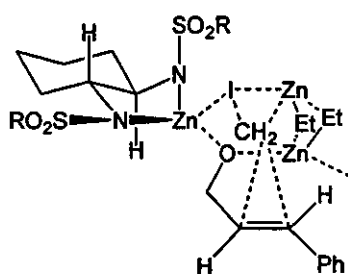
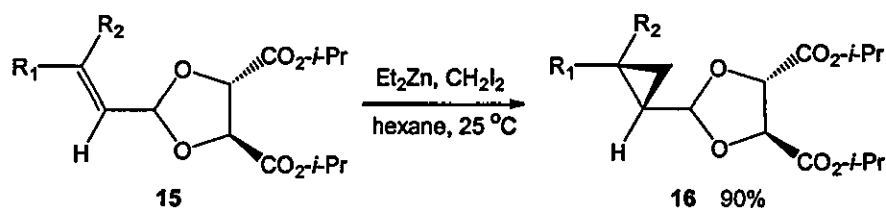


Figure 8

Cyclopropanation of α,β -unsaturated esters derived from tartrate esters,^{19,20} such as diisopropyl tartrate **15**, is directed by coordination of $\text{Zn}(\text{CH}_2\text{I})_2$ to both the adjacent ester carbonyl and the acetal oxygen, as shown in **Figure 9**, yielding cyclopropanes **16** with >88% diastereomeric excess and 81-90% yield, as shown in **Equation 3**.



Equation 3

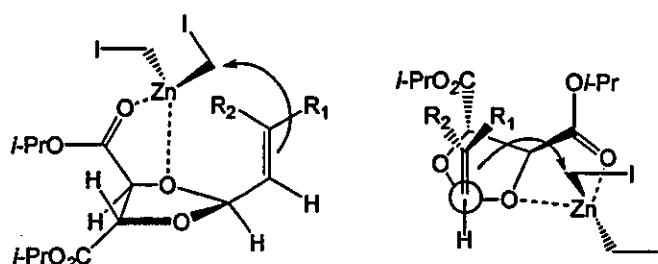


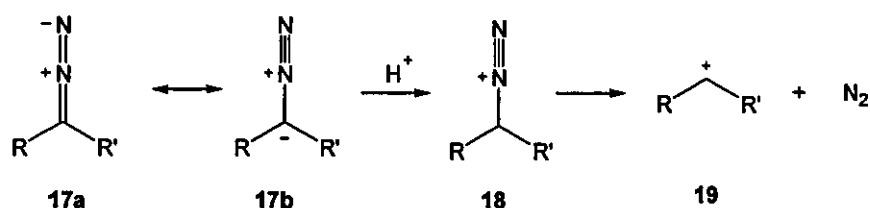
Figure 9

Other examples reported in the literature include cyclopropanes prepared from acetals of α -enones with 1,4-di-O-benzyl-L-threitol,²¹ (S,S)-hydrobenzoin,^{21c,22} anguidine degradation products,²³ or adducts of prochiral enone with (*N*-methylphenylsulfonimidoyl)methane.^{23a}

1.5.2. Photochemical and thermal synthesis

It has been shown that photolysis and thermolysis of diazoalkanes can provide carbenes, which can add to double bonds to form cyclopropanes.

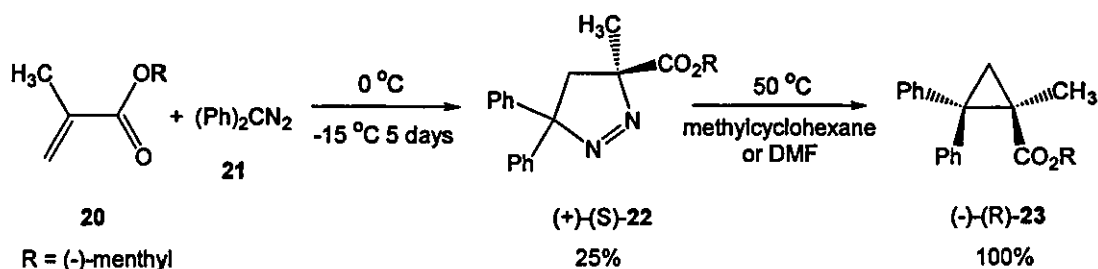
The formation of carbenes *via* the photolysis of diazoalkanes **17a-b** occurs quite generally in aprotic solvents. When a protic solvent is used it is likely that the decomposition of the diazoalkanes involves a prior protonation, so that a carbocation **19**, rather than a carbene, is formed after elimination of nitrogen, as shown in **Scheme 3**.



Scheme 3

Photolysis of diazoalkanes is often not a good way to form cyclopropanes, since the carbenes formed are highly energetic species and their reactions may be indiscriminate: insertion into primary, secondary and tertiary C-H bonds can occur as well as addition to double bonds.

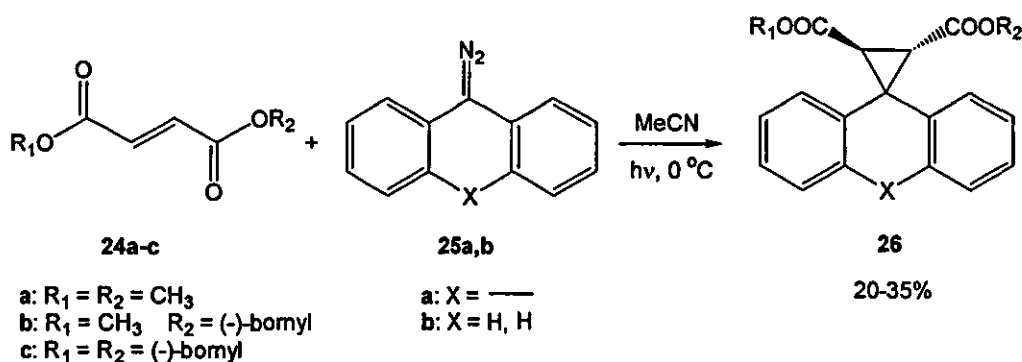
Thermal decomposition may produce a less energetic carbene, but it has the disadvantage that other modes of reaction of the diazoalkane, not involving carbenes, become important. An example is the formation of pyrazolines (+)-(S)-**22**, as shown in **Scheme 4**.²⁴



Scheme 4

Also, some diazoalkanes, such as diazoesters, are rather thermally stable, and therefore the reaction temperature may be high.

Several examples of photochemical and thermal cyclopropanation have been published in the literature, such as irradiation of diazofluorene **25a** or diazophenylmethane **25b** in the presence of fumarates **24a-c**, as shown in **Equation 4**,²⁵ photoinduced diastereoselective isomerization of cyclopropanes,²⁶ cyclopropane irradiation in the presence of optically active photosensitizers²⁷ and photolysis of cyclopropene derivatives.²⁸

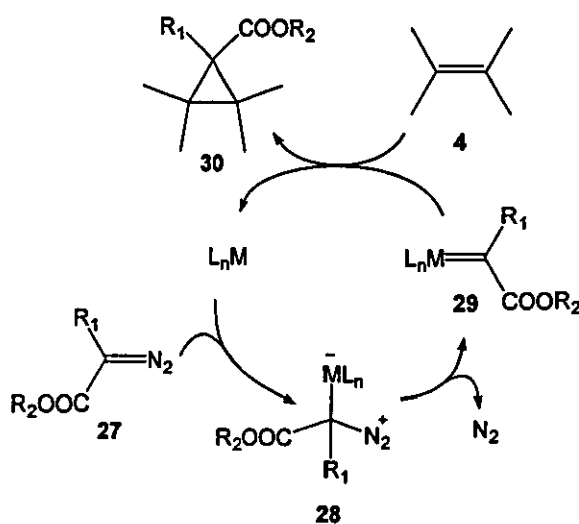


Equation 4

1.5.3 Transition metal-catalysed decomposition of diazocarbonyl compounds

Nowadays, catalytic methods for the synthesis of cyclopropanes have supplanted the thermal and photochemical methods.

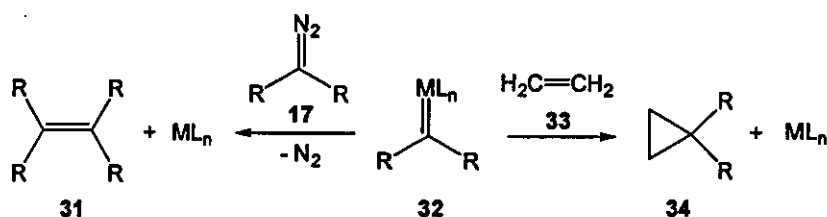
The coordination unsaturation at the metal centre of transition-metal compounds affects their catalytic activity, making possible electrophilic attack towards diazocarbonyl compounds (α -diazocarbonyl compounds **27** are the most widely used for these transformations). This results in loss of dinitrogen from the diazocarbonyl, affording a metal-stabilized carbene **29** ($L_nM=CR_1COOR_2$), which is transferred to an alkene **4** to complete the catalytic cycle. The catalytic cycle employed is shown in Scheme 5.



Scheme 5

1.5.3.1 Rate of addition of diazocompounds

When there is competition between olefin **33** and diazo compound **17** for the metal carbene **32**, minimizing the available concentration of diazo compound should afford optimal yields of cyclopropanes even when equivalent amounts of olefin and diazo compound are employed, as shown in **Scheme 6**. This observation was proven when $\text{Rh}_2(\text{OAc})_4$, $\text{Rh}_6(\text{CO})_{16}$ and $\text{CuCl}\cdot\text{P}(\text{O}-i\text{-Pr})_3$ were employed. However, control of the rate of addition of the diazo compound using $\text{PdCl}_2\cdot 2\text{PhCN}$ or $\text{Cu}(\text{OTf})_2$, had a very small influence in the cyclopropane yield.



Scheme 6

1.5.3.2. Asymmetric induction

In order to investigate asymmetric induction in cyclopropane reactions, the olefins, catalysts and diazocompounds employed, were individually studied to determine their effect on the reaction.

1.5.3.2.1 Diazocompounds

The diazo precursors **17**, used for transition metal-catalysed cyclopropanation reactions, can be divided into several groups (I-IV) according to their electronic properties, as shown in **Figure 10**.

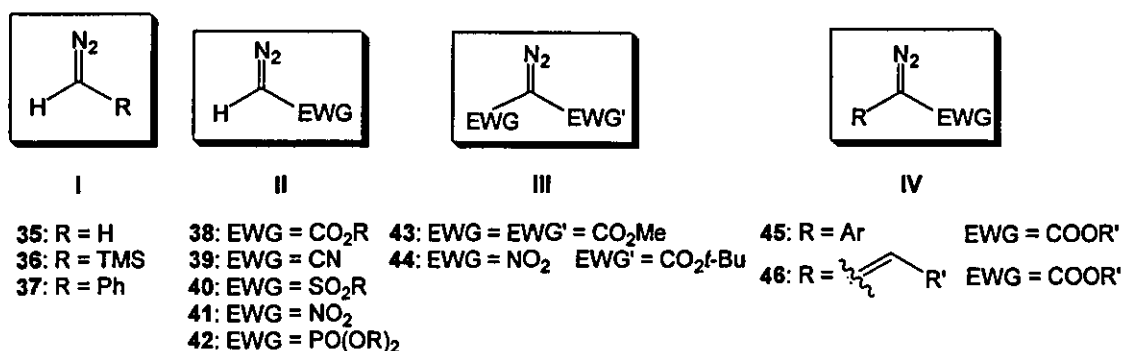


Figure 10

The selection of the catalyst is intimately related to the chosen diazo compound. For example, for diazo compounds **35-37**, the most efficient catalysts are palladium catalysts²⁹ (such as palladium (II) acetate and palladium (II) acetylacetonate).

In our study of cyclopropanation reactions, we were especially interested in those reactions carried out using diazoacetates as the diazo reagents.

α -Diazoesters are the diazo reagents that have been most exhaustively studied for intermolecular cyclopropanation reactions.^{30a-f} It has been shown that catalytic methods are most effective when diazo carbonyl compounds are employed, and their use in cyclopropanation reactions have been known almost 100 years. A wide range of metal catalysts have been reported to catalyse diazo carbonyl decomposition.^{30g} These include catalysts containing rhodium, copper, cobalt, osmium, palladium, platinum, iron, ruthenium and chromium.

By changing the steric bulk of the ester group the diastereo- and enantioselectivity of the reaction can be modified. This can also be achieved by modifying the metal-ligand system of the catalyst.^{6a,6e,31-33}

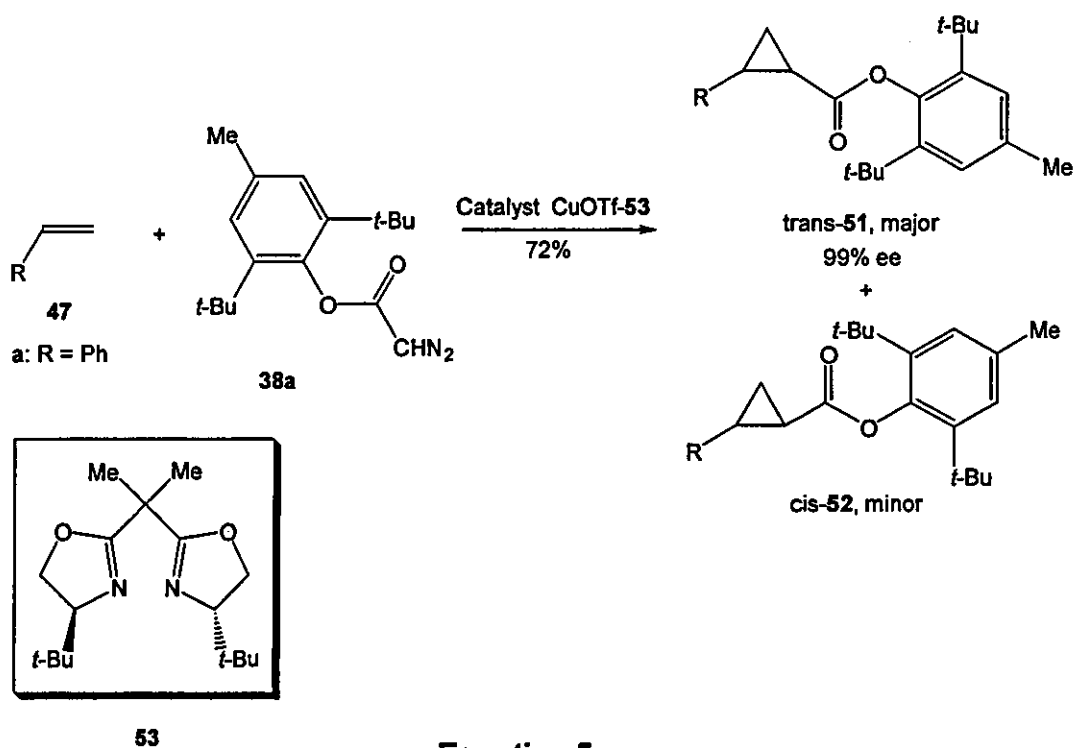
Generally, increasing the bulk of the ester group favours the transition state **Tt** leading to the *trans* cyclopropane isomer **49**, as is shown in **Scheme 7**.



An example of this is the use of bulky diazoacetates, such as 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **38a**³⁴ or dicyclohexylmethyl diazoacetate **38b**,³⁵ whose structures are shown in Figure 11. High diastereoselectivity for the *trans*-isomer can be achieved.



12



Equation 5

1.5.3.2.1 Optically active diazocompounds

Work has been carried out in determining the effectiveness of using chiral diazocompounds,³⁷ but the introduction of a chiral auxiliary on the diazo reagent was not very successful. **Figure 12** shows some examples of chiral diazo compounds (**38c-d**, **54** and **55**) employed for the intermolecular cyclopropanation of styrene **47a**, using rhodium (II) acetate as the catalyst, along with the observed diastereoselectivities.³⁸

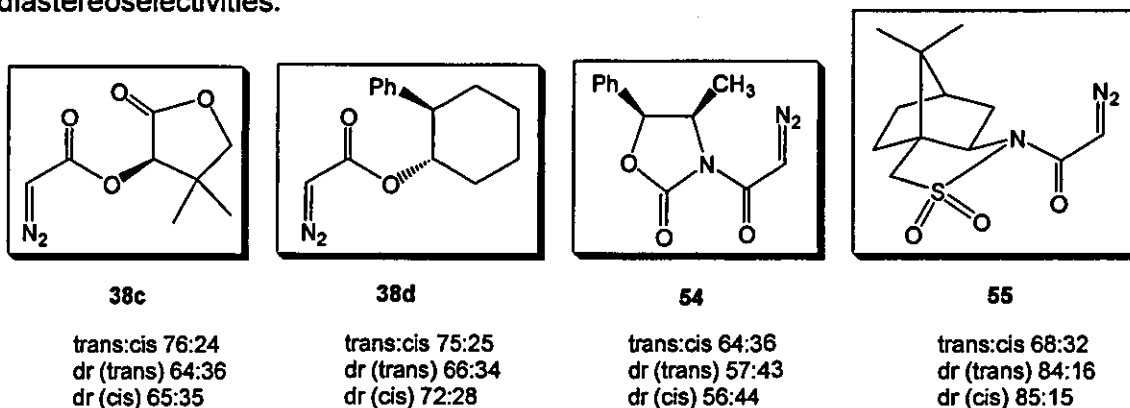
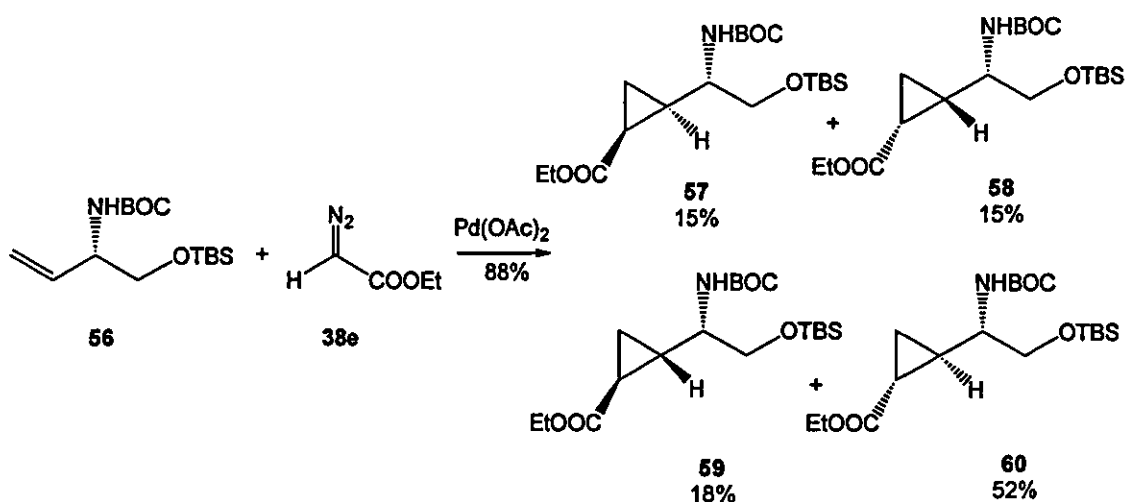


Figure 12

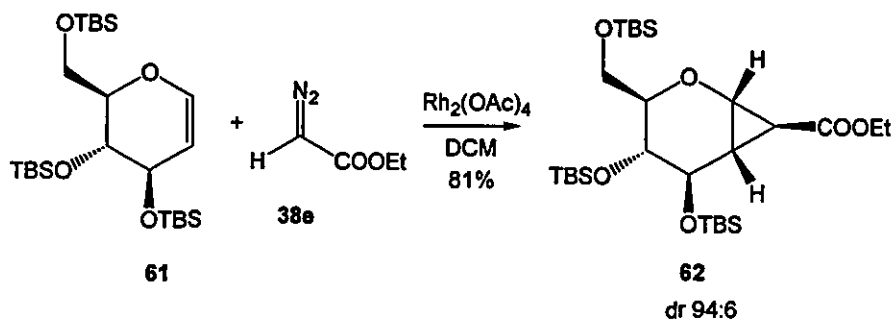
1.5.3.2.2 Chiral Olefins

Chiral olefins have been employed in catalytic cyclopropanation. Usually (except in very few cases), cyclopropanation of an acyclic chiral alkenes leads to mixtures of stereoisomers. For example, reaction of alkene **56** with ethyl diazoacetate in the presence of palladium acetate, gave a mixture of all four possible diastereoisomers, as shown in Equation 6.³⁹



Equation 6

On the other hand, cyclopropanation reactions of chiral cyclic alkenes, such as protected glycols,⁴⁰ can proceed with almost complete stereocontrol. An example is shown in Equation 7, where reaction of TBS-protected D-glucal **61** with ethyl diazoacetate **38e** and rhodium (II) acetate proceeds with very good stereocontrol.⁴¹



Equation 7

1.5.3.2.3 Catalysts

Until 1960, insoluble copper bronze and cupric sulfate (heterogeneous catalysts) were used for decomposition of diazo compounds. Then, Nozaki and Mosser introduced soluble copper chelates, such as bis-(acetyl-acetonato)copper (II)⁴² and (trialkyl and triaryl phosphite) copper (I)⁴³ respectively.

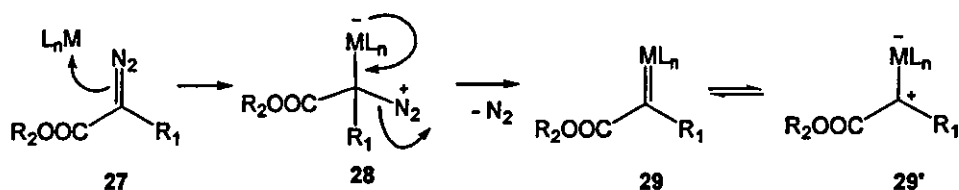
In 1972, Salomon and Kochi introduced copper (II) triflate as a very active catalyst for the cyclopropanation of olefins with diazo compounds, and they found out, in agreement with Wittig and Schwarzenbach,⁴⁴ that diazo compounds caused the reduction of copper (II) to copper (I). Although copper (I) was the active catalyst in carbenoid transformation, due to the difficulties of handling copper (I) triflate,⁴⁵ copper (II) triflate was preferentially used and reduced *in situ* by the diazo compounds. Further evidence for this has also been provided by the observation that copper (II) salts complexed with chiral ligands need to be preactivated for the reaction to proceed. Wulfsberg and co-workers suggested that copper (II) is the active catalyst in carbenoid transformations where $\text{Cu}(\text{acac})_2$ and $\text{CuCl}\cdot\text{P}(\text{OR})_3$ are used,⁴⁶ and under certain conditions undergo nucleophilic addition to a copper-olefin complex.⁴⁷ On the other hand, when iodorrhodium (III) mesotetraporphyrin was employed in cyclopropane reactions of ethyldiazoacetate with olefins, the oxidation state of the active catalyst could not be determined.⁴⁸

In the 70's, Tessier and co-workers introduced palladium (II) acetate²⁹ and rhodium (II) acetate,^{49,50} as alternatives to copper catalysts. Palladium (II) acetate was the catalyst of choice for cyclopropanation of terminal olefins and α,β -unsaturated carbonyl compounds, whereas with rhodium (II) acetate high yields of cyclopropane products could be obtained throughout the spectrum of olefin reactivities.

Interestingly, Pietruszka noticed that in palladium (II) acetate/diazomethane cyclopropanations, the diastereoselectivity obtained was the opposite to that found in Simmons-Smith cyclopropanation of similar compounds.⁵¹ This was due to the fact that the palladium-carbene species generated, approached the olefin *via* the

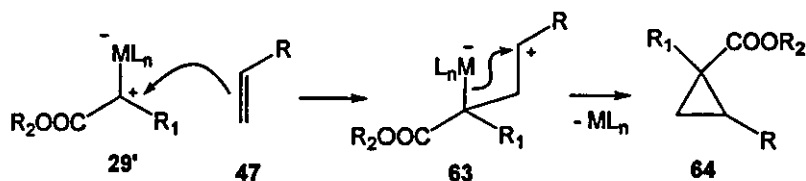
less hindered face, with no complex formation, as it occurred in Simmons-Smith cyclopropanation.

Transition metal Lewis acids of copper (I), palladium (II) and rhodium (II) catalyze decomposition of diazo compounds as follows. Firstly, elimination of nitrogen leads to the formation of the unstabilized electrophilic metal carbene **29**, which can be regarded as an ylide of inverted polarity or inverse ylide, as shown in **29'**. This inverse ylide is stabilized by electron donation from the metal, but it is also destabilized by the adjacent electron-withdrawing carbonyl group, as shown in **Scheme 8**.



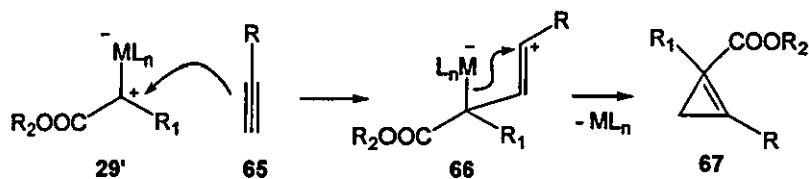
Scheme 8

Cyclopropanation starts by electrophilic attack to the alkene, to give the compound **63**, which ring closes to form the cyclopropane **64**, with regeneration of the metal catalyst, as is shown in **Scheme 9**.



Scheme 9

Following a similar mechanism, cyclopropenes could be obtained if alkynes were employed instead of alkenes, as is shown in **Scheme 10**.



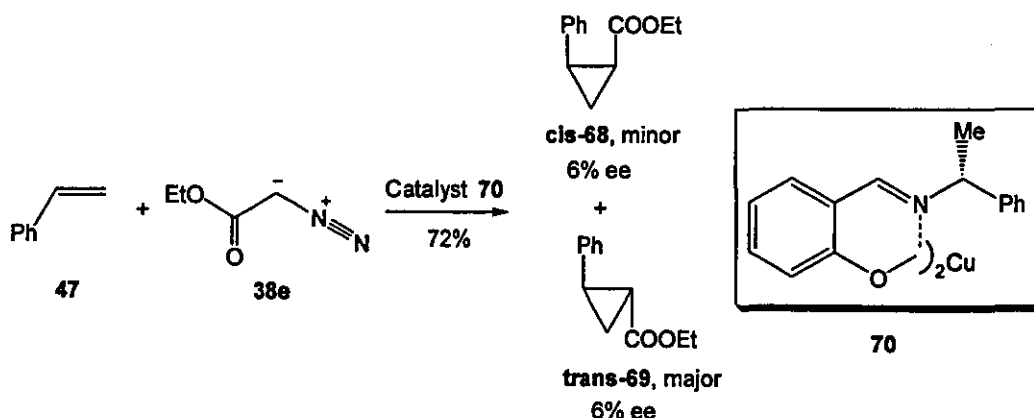
Scheme 10

1.5.3.2.3.1 Chiral transition metal complexes.

A) Copper Catalysts

It has been shown that copper-based catalysts are the most effective in cyclopropanation for the preparation of the *trans* isomer.^{30g}

In 1966 Nozaki and co-workers prepared the first example of enantioselective copper-based intermolecular cyclopropanation⁵² using an *N*-benzylethylamine-based chiral salicylaldimino complex **70**, as shown in **Equation 8**. Since then, more chiral copper complexes have been widely studied and used in cyclopropanation reactions.^{52b,53-55}



Equation 8

Some further examples are shown in **Figure 13**. The catalyst **71**, bearing a salicylaldimine ligand, was developed by Aratani in 1985 and is now applied in the enantioselective synthesis of ethyl-2,3-dimethoxycyclopropane-carboxylate^{31a} (key intermediate in the synthesis of cilastatin). The chiral semicorrin ligand **72**,^{31b,55b,56} introduced by Pfaltz *et al.* in 1986 has been found to improve enantiocontrol in the cyclopropanation of monosubstituted olefins.

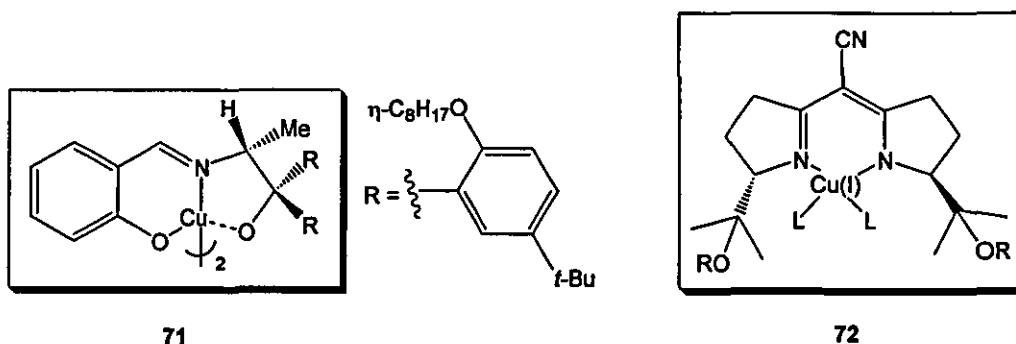


Figure 13

Reiser *et al.*⁵⁷ Massamune *et al.*,^{35,36a} and Evans *et al.*^{31c,58} have reported the chiral bis-(oxazoline) ligands **73**, **74** and **53** (the most widely used ligand), respectively. Figure 14 shows the structure of these complexes along with the diastereoselectivities and enantiomeric excesses observed for the cyclopropanation of styrene.

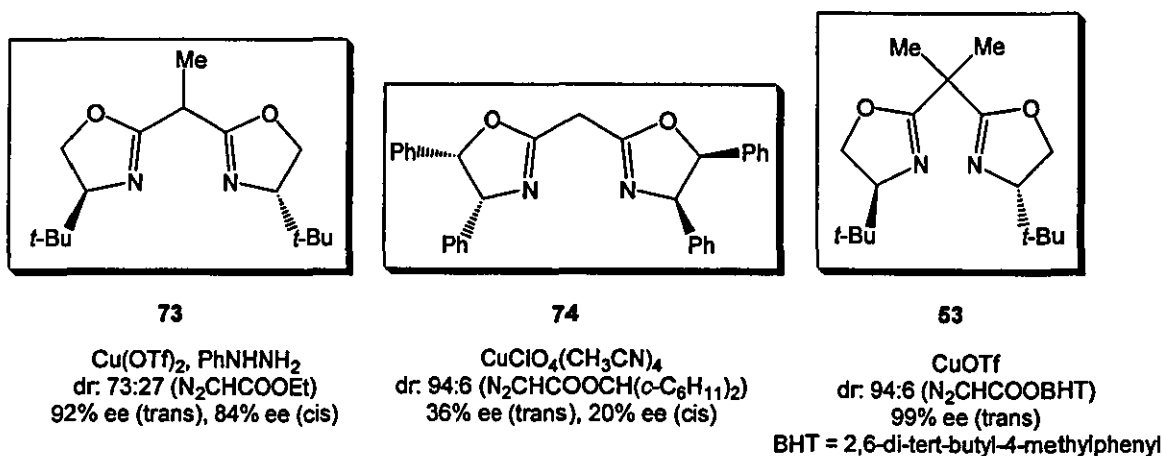


Figure 14

Katsuki *et al.*⁵⁹ reported asymmetric cyclopropanation reactions using the chiral ligands **75-78**, shown in Figure 15.

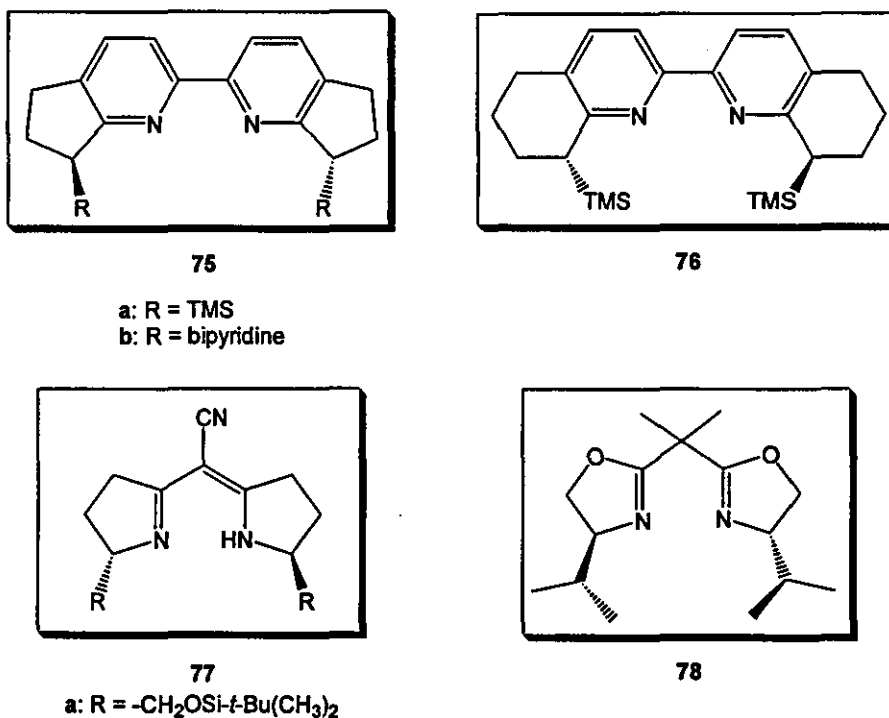
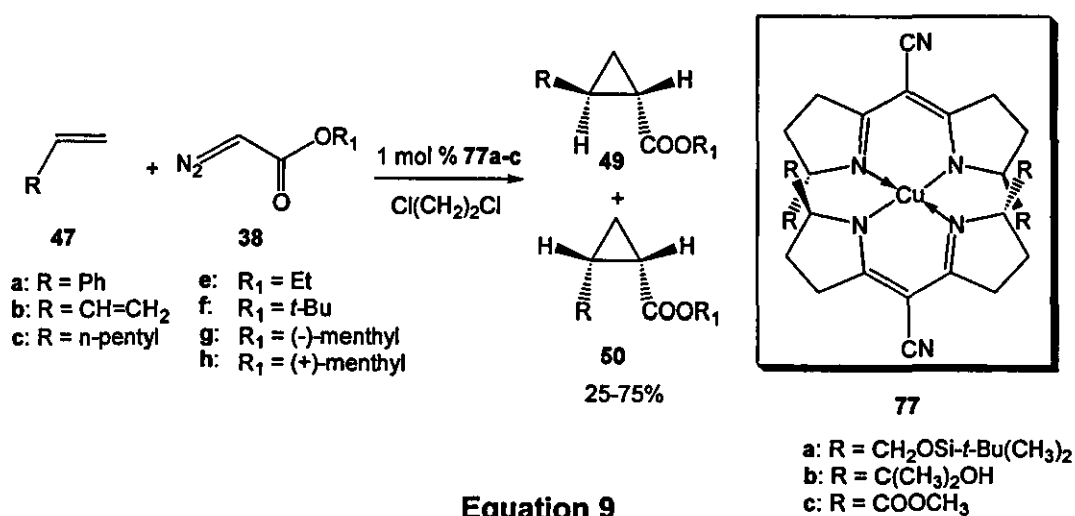


Figure 15

Copper (II) chelate complex **77** has been employed for synthesis of optically active cyclopropanes. Enantiomeric excess can be substantially changed depending on the substitution of the R groups of the complex **77**; the efficiency increases in the order **77c**<**77b**<**77a**, as shown in Equation 9.



The following bis-(oxazolanyl)pyridine compounds **79-81**, shown in **Figure 16**, have also been used for asymmetric cyclopropanation, but only moderate enantioselectivity have been achieved.⁶⁰

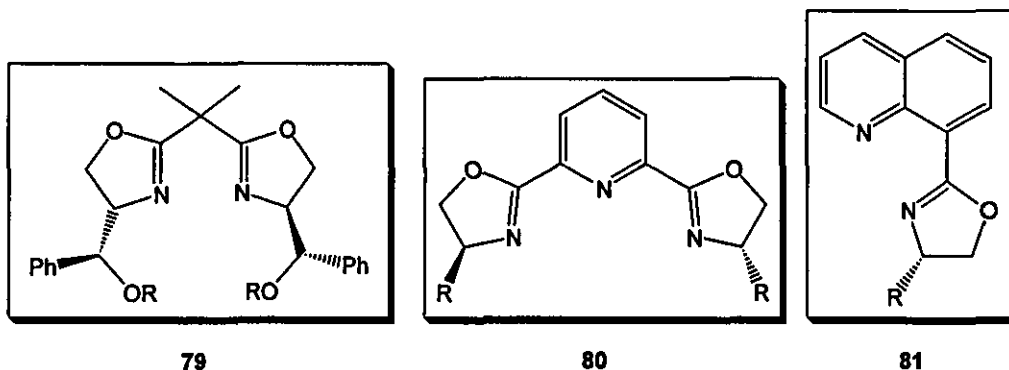
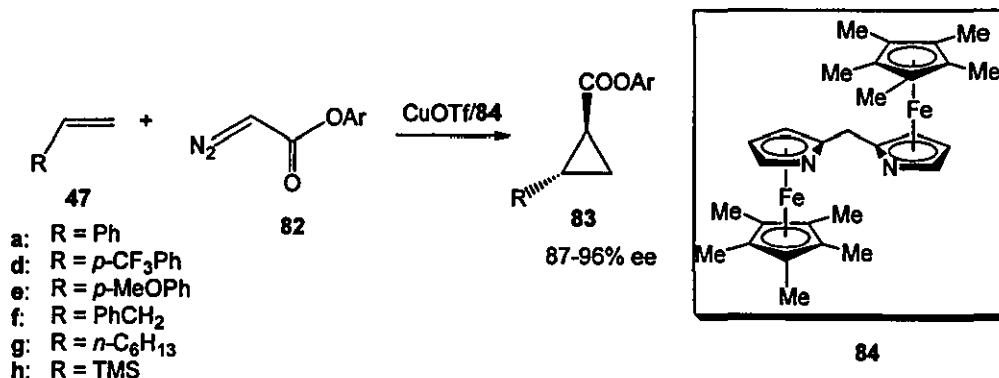


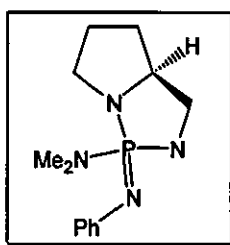
Figure 16

A planar-chiral catalyst **84** was reported by Fu *et al.*⁶¹ for enantioselective cyclopropanation. An example is shown in **Equation 10**.



Equation 10

Most of the previously described chiral catalysts require a bulky ester to maximize the trans:cis ratio. Buono *et al.*⁶² reported an exception to this; cyclopropanation of 1-aryl-substituted alkenes with ethyl diazoacetate using as catalyst the iminodiazaphospholidine ligand **85** with a stoichiometric amount of copper triflate gave excellent enantio- and diastereoselectivities. **Figure 17** shows the structure of ligand **85**, along with diastereoselectivities and enantiomeric excesses observed for the cyclopropanation of styrene.



85

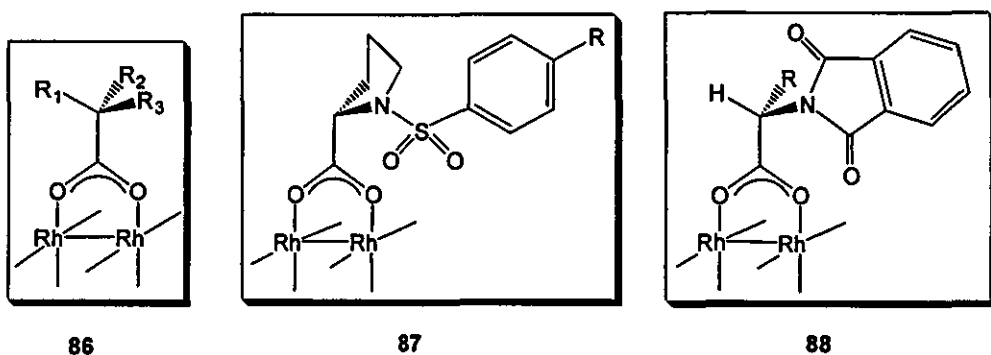
CuOTf
dr 99:1 (N₂CHCOOEt)
94% ee (trans)

Figure 17

B) Rhodium Catalysts

Rhodium-based catalysts are very effective in cyclopropanation reactions, but generally they produce lower enantio- and diastereomeric ratios than copper-based catalysts. In some cases enantioselectivity can be excellent, but diastereocontrol is not very good.^{33b,33d,63}

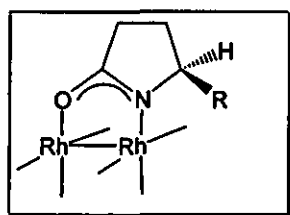
There are two general classes of rhodium-based chiral catalysts: tetrasubstituted dirhodium (II) carboxylates, such as **86**,^{64a} **87**,^{64b-e} **88**,⁶⁵ and carboxamides, such as **89**,⁶⁶ **90**,⁶⁷ **91**⁶⁸ and **92**,^{33d} as shown in **Figure 18**. These complexes have nowadays become the catalysts of choice for cyclopropanation, although intermolecular cyclopropanation reactions carried out with simple alkenes using dirhodium (II) carboxylates proceed with low enantioselectivity. Although the carboxamidate-ligated dirhodium (II) compounds **89-92** are less reactive towards diazo compounds than rhodium (II) acetate, they provide higher selectivities.



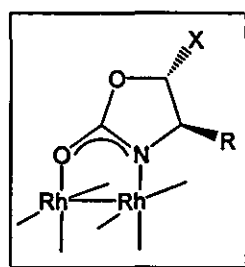
a: R = H d: R = OH
 b: R = Me e: R = NHAc
 c: R = Ph f: R = CF₃

a: R = H Rh₂(2S-BSP)₄
 b: R = *t*-Bu Rh₂(2S-TBSP)₄
 c: R = C₁₂H₂₅ Rh₂(2S-DOSP)₄

a: R = PhCH₂
 b: R = *t*-Bu



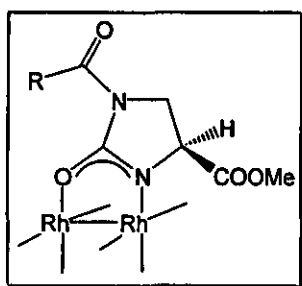
89



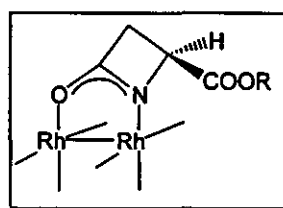
90

a: R = COOMe Rh₂(5S-MEPY)₄
 b: R = COOCH₂CHMe Rh₂(5S-NEPY)₄
 c: R = COO(CH₂)₁₇CH₃ Rh₂(5S-ODPY)₄
 d: R = CONMe₂ Rh₂(5S-DMAP)₄

a: R = COOMe X = H Rh₂(4S-MEOX)₄
 b: R = COOMe X = CH₃ Rh₂(4S-THREOX)₄
 c: R = Bn X = H Rh₂(4R-BNOX)₄
 d: R = *i*-Pr X = H Rh₂(4R-IPOX)₄
 e: R = Ph X = H Rh₂(4R-PHOX)₄



91



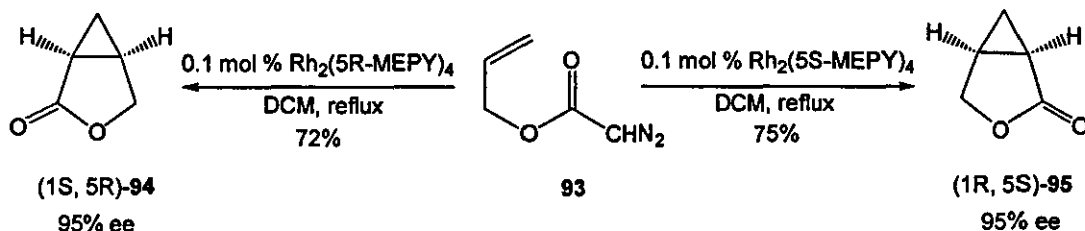
92

a: R = Me Rh₂(4S-MACIM)₄
 b: R = PhCH₂CH₂ Rh₂(4S-MPPIM)₄
 c: R = *p*-C₆H₄C(Me)₃ Rh₂(4S-TBOIM)₄
 d: R = Ph Rh₂(4S-MBOIM)₄
 e: R = Bn Rh₂(4S-MPAIM)₄
 f: R = *o*-C₆H₁₁CH₂ Rh₂(4S-MCHIM)₄

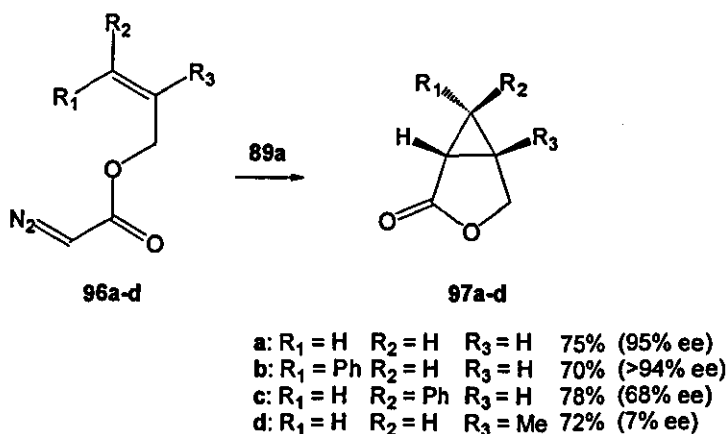
a: R = Me Rh₂(4S-MEAZ)₄
 b: R = *i*-Bu Rh₂(4S-IBAZ)₄
 c: R = Bn Rh₂(4S-BNAZ)₄
 d: R = *i*-menthyl Rh₂(4S-R-MenthAZ)₄
 e: R = *o*-C₆H₁₁ Rh₂(4S-CHAZ)₄

Figure 18

Dirhodium (II) carboxamidates are the most effective catalysts for intramolecular cyclopropanation reactions of diazoacetate and diazoacetamide,⁶⁹ as shown in **Scheme 11** and **Equation 11**, and they also can be used to induce asymmetric cyclopropanation reactions.⁷⁰

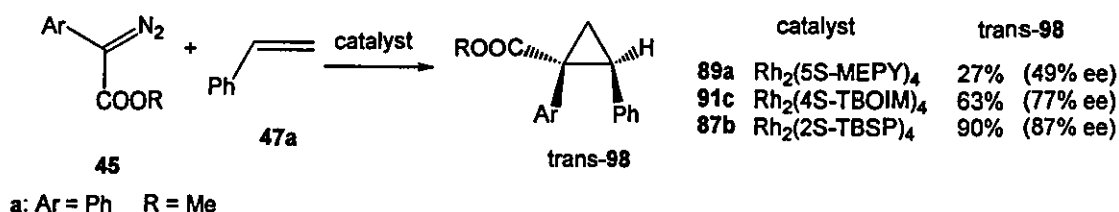


Scheme 11



Equation 11

The catalyst **87b** afforded intermolecular cyclopropanation of diazoester **45a**, with very good enantiomeric excess for unsubstituted and Z-substituted alkenes, as shown in **Equation 12**.



Equation 12

Figure 19 shows some common dirhodium catalysts for inter- and intramolecular cyclopropanations.

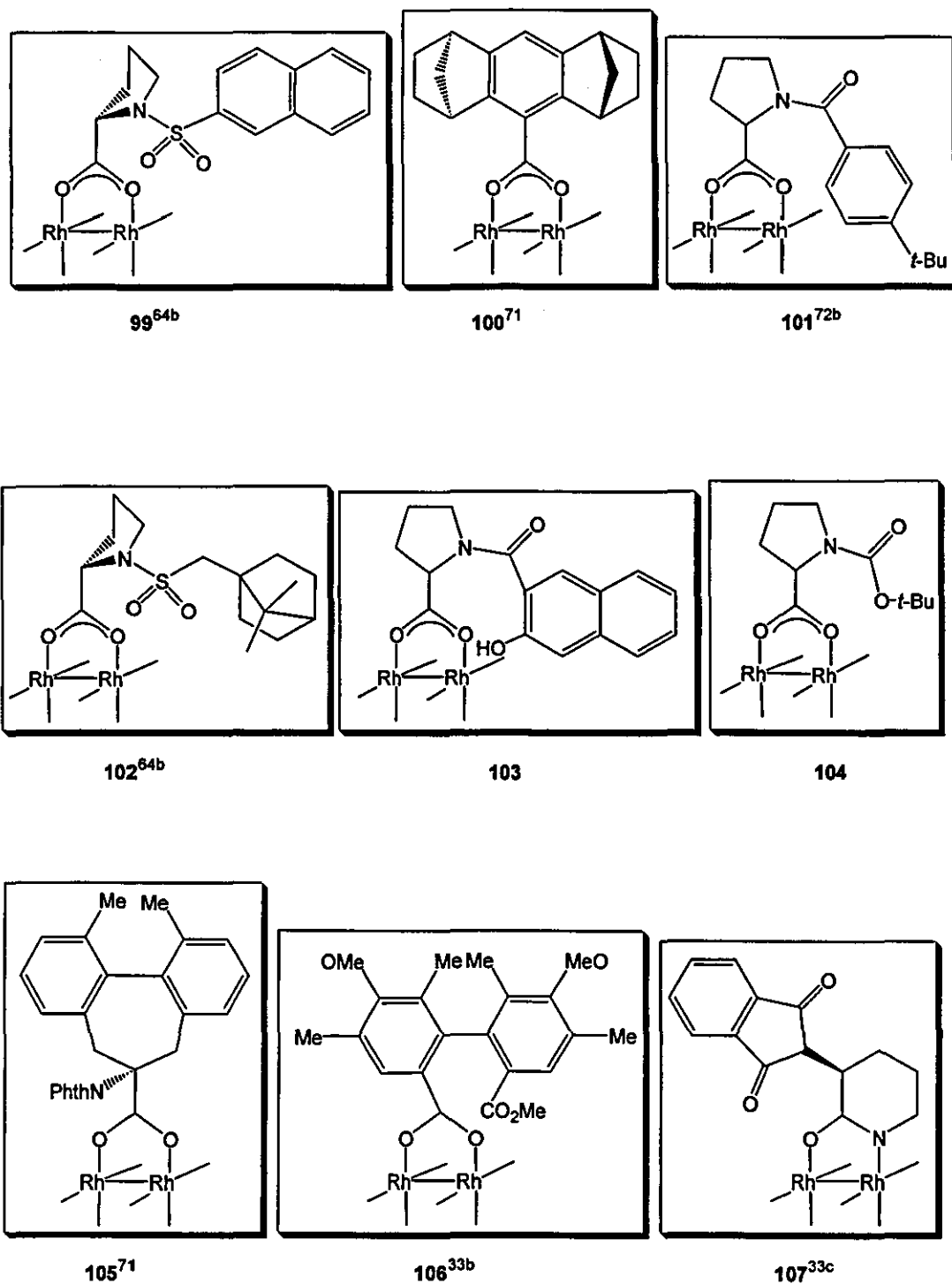


Figure 19

C) Ruthenium Catalysts

Generally, ruthenium-based chiral catalysts are less reactive than those derived from copper or rhodium. Most of them afford low yields in cyclopropanation reactions of alkyl-substituted alkenes, but yields improve when aryl-substituted alkenes are employed.

The first very effective reported ruthenium-based chiral catalyst was the pybox-Ru catalytic complex **108** reported in 1994 by Nishiyama *et al.*,^{30d,32a,73} as shown in **Figure 20**. This led to the development of new ruthenium-based chiral catalysts containing the pybox-Ru catalytic system, which are the most studied ruthenium catalysts for cyclopropanation.^{60b,74} An example is the complex **109**, shown in **Figure 20**. Diastereoselectivities and enantiomeric excesses observed for the cyclopropanation of styrene are shown in **Figure 20**.

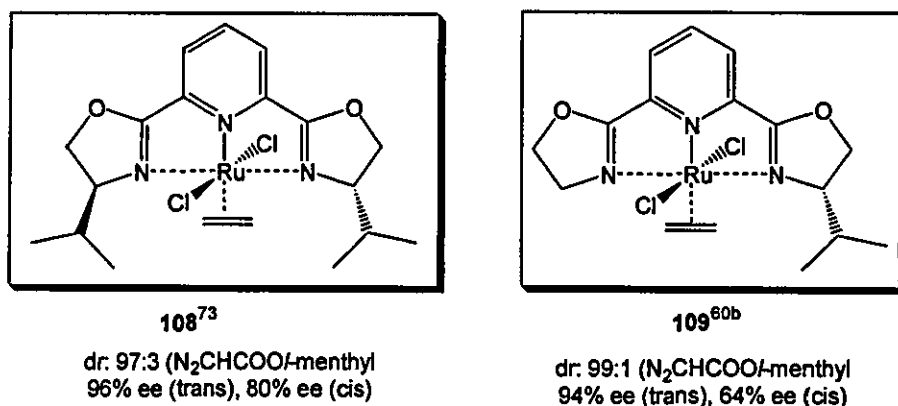
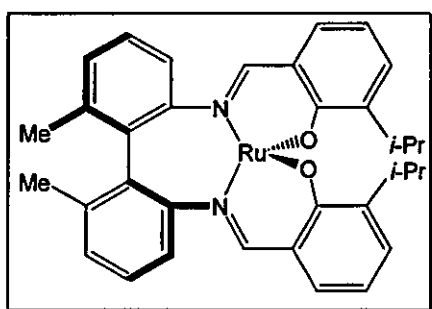


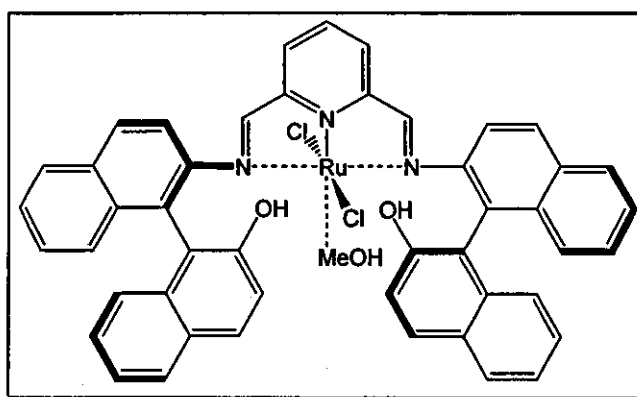
Figure 20

The most effective ruthenium-based chiral catalysts have been recently reviewed.⁸ The complexes **110**⁷⁵ and **111**⁷⁶ produce excellent level of enantio- and diastereocontrol. Diastereoselectivities and enantiomeric excesses observed for the cyclopropanation of styrene are shown in **Figure 21**.



110⁷⁵

dr: 98:2 ($\text{N}_2\text{CHCOOEt}$)
95% ee (trans)



111⁷⁶

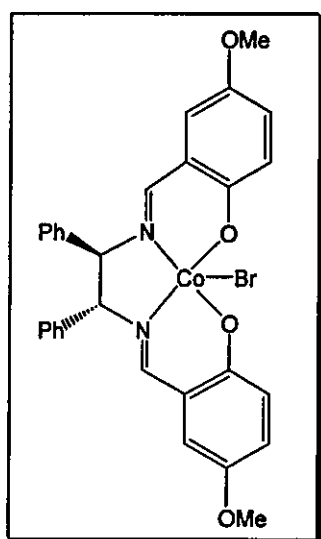
dr: 99:10 ($\text{N}_2\text{CHCOOEt}$)
96% ee (trans), 83% (cis)

dr: 97:3 ($\text{N}_2\text{CHCOOt-Bu}$)
86% ee (trans), 54% (cis)

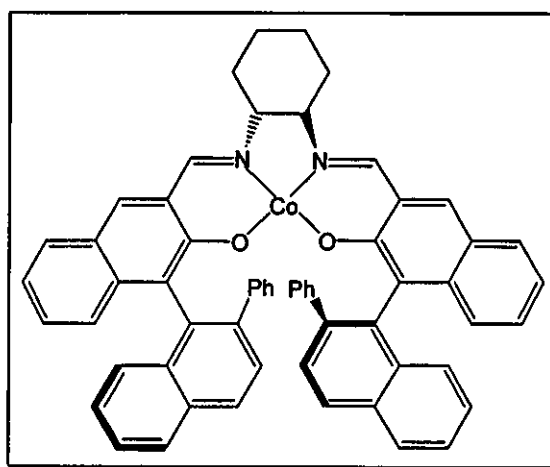
Figure 21

D) Cobalt Catalysts

Early reports of cyclopropanation reactions with cobalt complexes showed low levels of enantio- and diastereocontrol. This fact has limited their use in synthesis.⁷⁷ Katsuki has recently developed new cobalt complexes, such as **112**^{33a,78} and **113**⁷⁹, as shown in Figure 22, which, used in the presence of *N*-methylimidazole (NMI), afford either the trans- or cis-cyclopropane, respectively, with good reactions rates as well as good levels of enantioselectivity.



112^{33a,78}



113⁷⁹

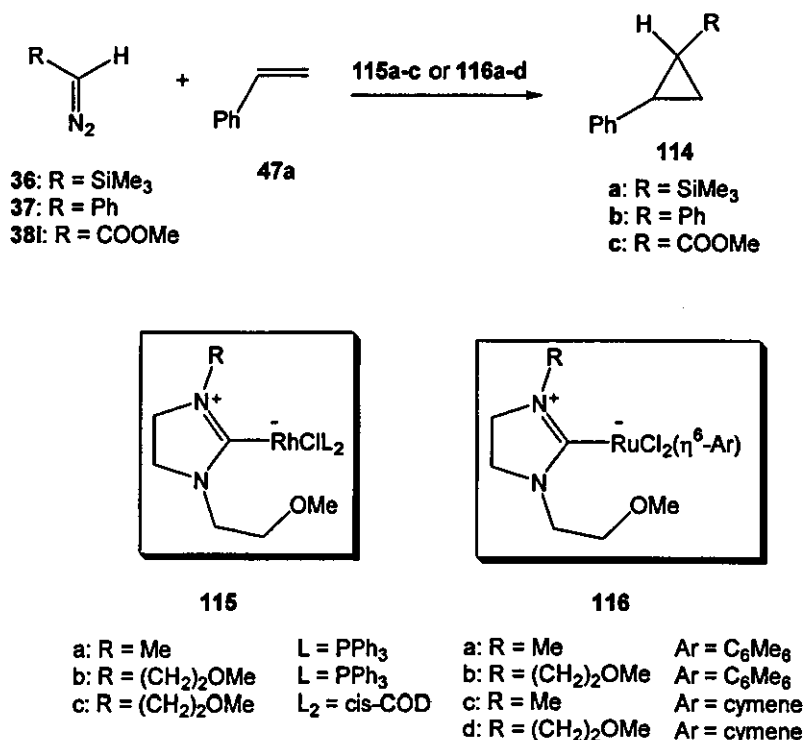
Figure 22

1.5.4 Transition metal-carbene complexes

Carbene complexes of transition metals, such as chromium, tungsten and molybdenum, were introduced in cyclopropanation reactions by Fischer and Dötz in the early 70's.⁸⁰

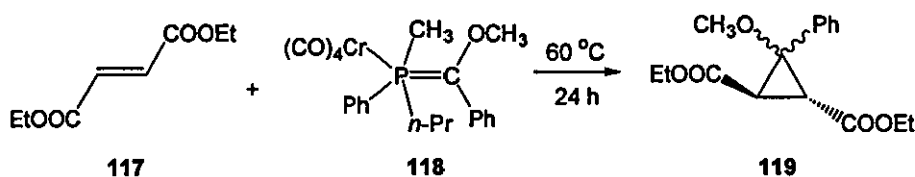
This is a useful and general method for the enantioselective synthesis of cyclopropanes. It consists of transferring carbene ligands from optically active transition metal-carbene complexes to alkenes *via* formation of carbenoids.

These carbenoid reactions can be induced by several complexes of transition metals, such as chromium,⁸¹ iron,⁸² nickel, cobalt,^{77a-c,83} copper, ruthenium, rhodium and palladium. An example is shown in Equation 13, where cyclopropanation of styrene **47a**, in the presence of diazoalkanes **36**, **37** and **38i**, is catalysed by rhodium (I) **115a-c** and ruthenium (II) **116a-d** complexes.⁸⁴



Equation 13

Several cyclopropanation reactions using transition metal-carbene complexes, such as **118**, have been carried out in the absence of diazo compounds,^{81,82a,83,85} as shown in Equation 14.⁸¹



Equation 14

1.5.5 Other methods of cyclopropanation

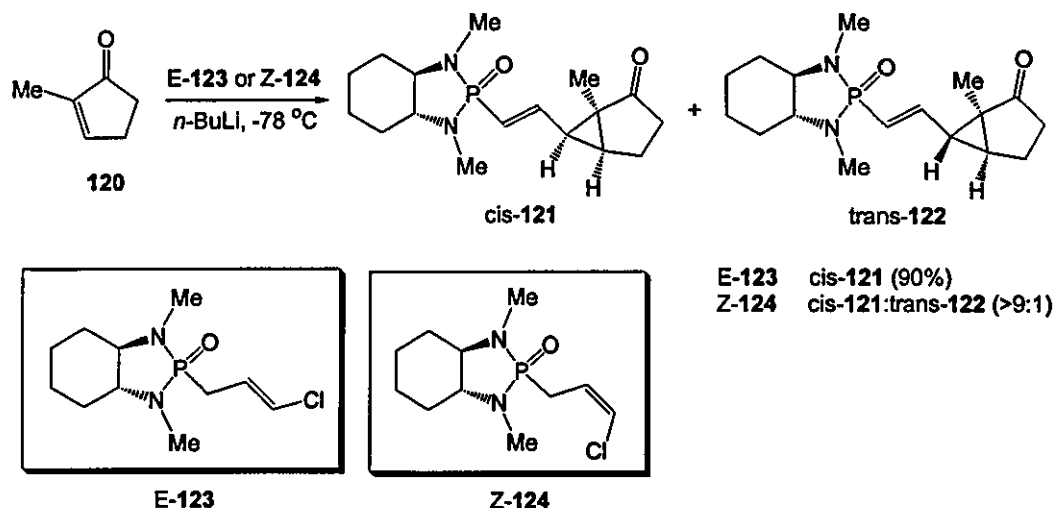
1.5.5.1 Using asymmetric-inducing agents

- With asymmetric-inducing groups, such as oxazolidinones, oxazolidines,⁸⁶ sulfoxides and phenylmenthyl carboxylates, optically active cyclopropanes can be prepared.
- Lithiated bases with chiral complexing agents are a useful reagent to afford optically active cyclopropanes.⁸⁷
- The enantiotopic differentiation of functional groups by means of chiral auxiliaries has also been used for the synthesis of optically active cyclopropanes.

1.5.5.2 Cyclopropanation using Michael acceptors

α,β -Unsaturated ketones can afford the corresponding cyclopropyl ketones⁸⁸ when treated with methylsulfoxonium methylide; the reaction occurs *via* Michael addition, followed by intramolecular displacement of dimethylsulfoxide. Addition of other carbanions bearing a good leaving group in the α -position would also lead to cyclopropane formation.⁸⁹

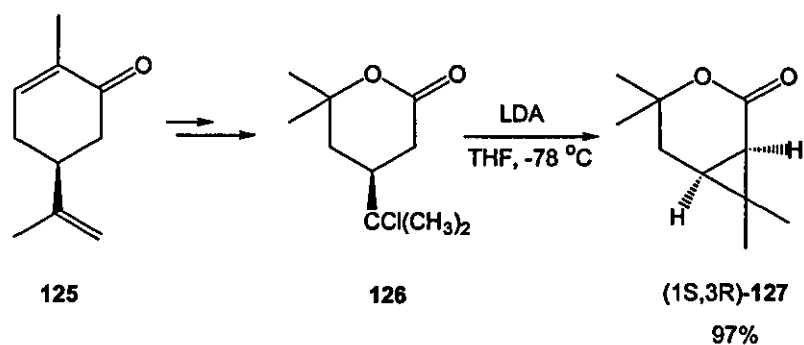
Hanessian *et al.*⁹⁰ reported cyclopropanation of α,β -unsaturated ketones with chloroallyl phosphonamides E-123 and Z-124. Relative stereochemistry and enantioselectivity can be controlled by modifying the chloroallyl group and the chirality of the phosphonamide, respectively, as shown in Equation 15.



Equation 15

1.5.5.3 Cyclopropanes from Natural Products

Some natural occurring products can be sources of chiral cyclopropanes, for example, preparation of optically active chrysanthemolactone (1S,3R)-127 can be prepared in many steps from the natural product (+)-carvone 125, as shown in Scheme 12.⁹¹



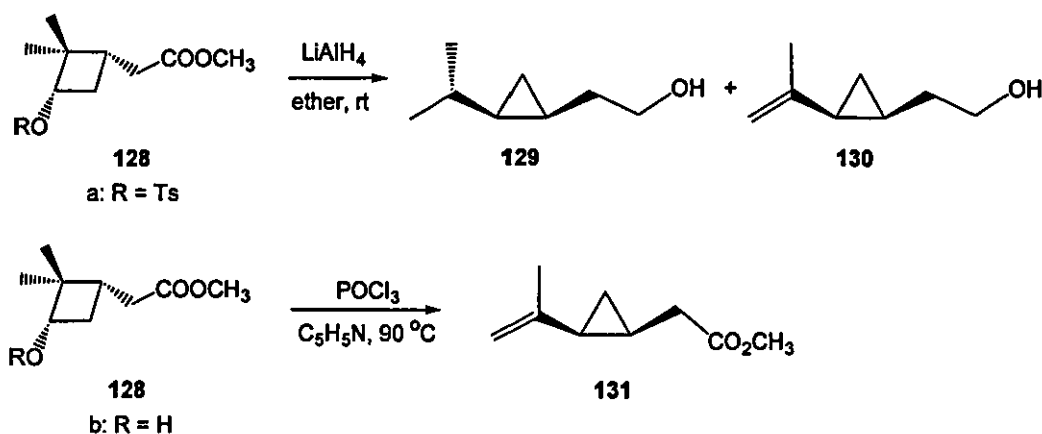
Scheme 12

More examples of synthesis of optically active cyclopropanes from natural compounds have been reported; reaction of sulfuranylidene^{88,92,93} or phosphoranylidene⁹³ with carbohydrates or their derivatives, degradation of natural three membered-ring compounds ((+)-3-carene⁹⁴ and (-)-car-3-en-5-one⁹⁵), reaction of copper-zinc couple and diiodomethane with olefins derived from (-)- β - and (+)- α -pinenes,⁹⁶ and degradation of citronellal.⁹⁷

1.5.5.4 Ring Contraction $C_4 \rightarrow C_3$

Another method for synthesising cyclopropanes in high enantiomeric excess consists of the contraction of a four-membered ring (such as cyclobutanols, 1,2-cyclobutanediones and α -chlorocyclobutanones)⁹⁸ to afford the corresponding three-membered ring.

Cyclobutanol **128**, obtained from oxidations of α -pinene, underwent stereospecific $C_4 \rightarrow C_3$ contraction when it was treated with several hydride reagents ($LiAlH_4$, $NaBH_4$, $LiEt_3BH$) in order to afford cyclopropanes **129** and **130**, along with some other by-products, as shown in **Scheme 13**. Dehydration of **128** with phosphorus oxychloride in pyridine yielded cyclopropylacetate **131**, as shown in **Scheme 13**.⁹⁹

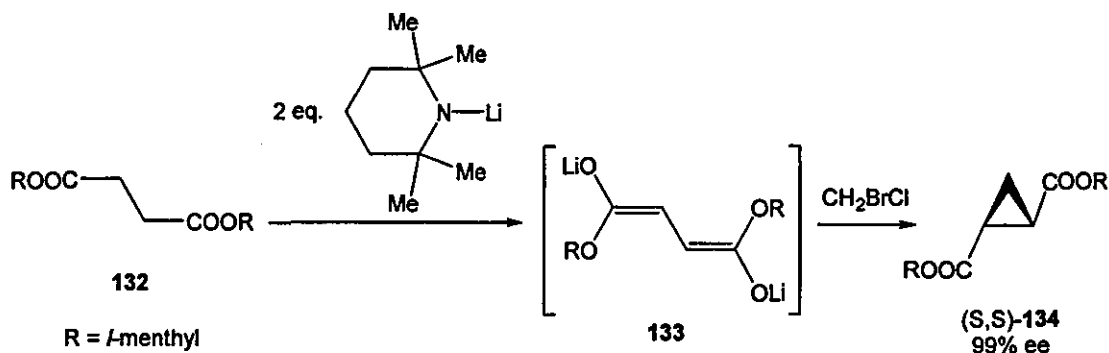


Scheme 13

1.5.5.5 Intramolecular displacement reactions

This method consists of intramolecular alkylation of active methylene compounds via a 3-exo-tet ring closure. Yamamoto *et al.*¹⁰⁰ reported alkylation of dimethyl

succinate **132** with bromochloromethane, *via* transition state **133** (generated after a double deprotonation) to yield cyclopropane (S,S)-**134** with 99% ee, as shown in Scheme 14.

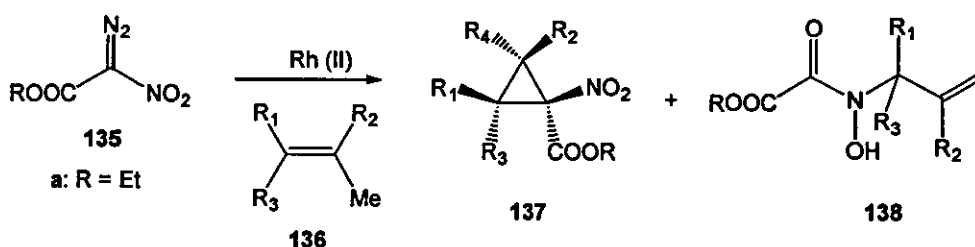


Scheme 14

1.6 Nitrocyclopropanes

Nitrocyclopropanes are very interesting high energy materials, as well as very explosive compounds. Their formation can generally be achieved *via* addition of a nitrodiazoacetate to an alkene, in the presence of a catalyst. In a similar fashion, nitrocyclopropenes can be obtained if alkynes instead of alkenes are employed.

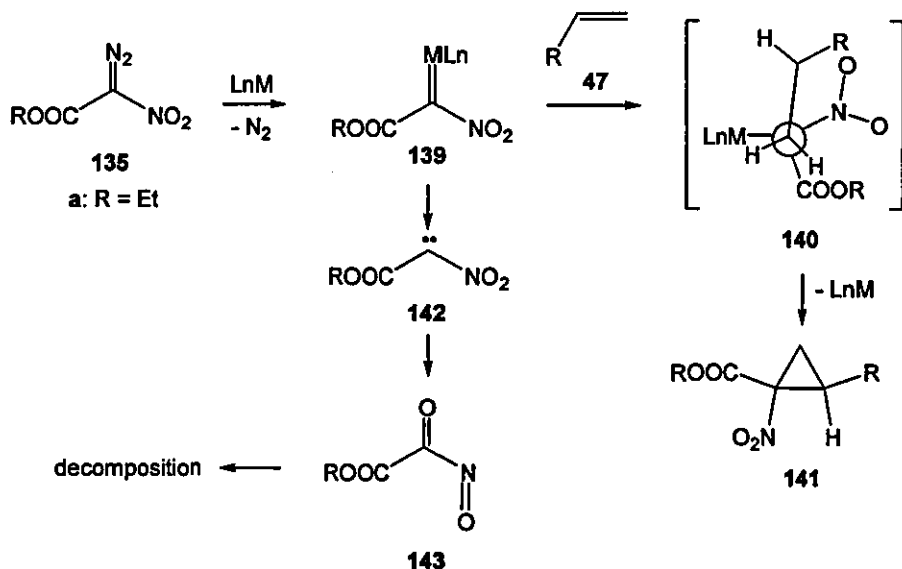
Dailey *et al.*^{101a} reported cyclopropanation reactions with nitrodiazoacetate **135a** and several alkenes, in the presence of a catalytic amount of $\text{Rh}_2(\text{OAc})_4$, as shown in Equation 16.



Equation 16

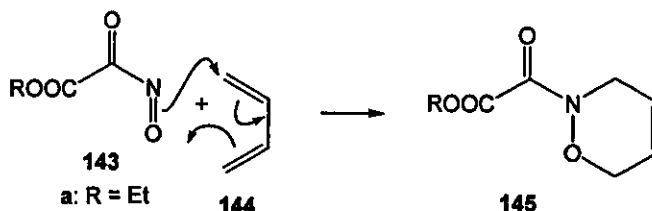
It was observed that the course of the reaction was highly dependent on the substitution of the alkene; electron-rich and sterically undemanding alkenes gave the best yields of cyclopropane products **137**, and less reactive crowded alkenes

gave poor yields of cyclopropanes and enhanced yields of ene products **138**. They based the explanation of the results obtained on the ideas of Doyle model for catalytic cyclopropanation, shown in **Scheme 15**.^{101b} In his model, the ethyl diazoacetate **135a** undergoes nitrogen extrusion to form a nitrocarbene, and the carbene moiety is transferred from an intermediate metal carbene **139** to the alkene *via* a π -complex **140**.

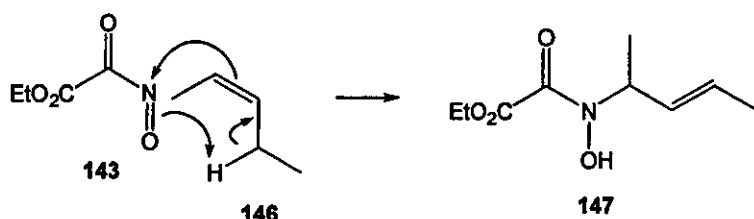


Scheme 15

So, if the alkene is not sufficiently reactive, the nitrocarboethoxy carbene **139** dissociates from the metal and undergoes an irreversible rearrangement to form an acyl nitroso compound **143**, which either decomposes to yield diethyl oxalate or reacts as an enophile or dienophile; in the presence of dienes **144** will afford the Diels-Alder product **145**, as shown in **Scheme 16**, and reaction with the allylic hydrogens of the alkenes **146** will yield ene products **147**, as shown in **Scheme 17**.



Scheme 16



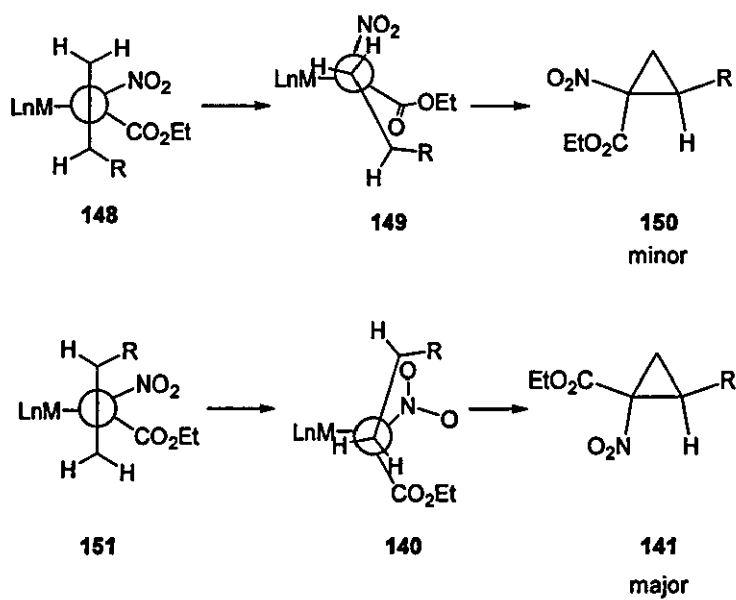
Scheme 17

1.6.1 Use of ethyl nitrodiazoacetate versus ethyl diazoacetate

When ethyl nitrodiazoacetate is employed instead of ethyl diazoacetate, the introduction of the nitro group onto the carbenic carbon increases the electrophilicity and the size of the intermediate carbenoid, making the nitrocarboethoxy carbenoid more sensitive to the electronic and steric nature of the alkene than the unsubstituted carboethoxy carbenoid. So, electron-rich and sterically undemanding alkenes are more reactive toward the nitrocarboethoxy derivative than toward the parent carboethoxy carbenoid and give the best yields of cyclopropanes. Less reactive and crowded alkenes give poor yields of cyclopropanes and enhanced yields of ene products.^{101a}

1.6.1.1 Stereochemistry

Ethyl nitrodiazoacetate gives greater diastereoselection than ethyl diazoacetate, and the *cis* isomer **141** is obtained preferentially to the *trans* isomer **150**. This is due to the fact that the oxygen atoms of the nitro group stabilize the electrophilic β -carbon of the original alkene better than a carbonyl oxygen, thus resulting in the observed stereochemistry, as shown in **Scheme 18**.^{101a}



Scheme 18

The isomers obtained are not easily separable, but generally the minor and less hindered isomer could be separated from the major isomer through selective saponification.

CHAPTER 2: Carbenes

2.1 Introduction

Since 1964, when Fischer and co-workers¹⁰² introduced carbenes in inorganic and organometallic chemistry, they have become quite significant due to the important role they play in macromolecular chemistry, catalysis and especially in organic chemistry.

Carbenes are uncharged compounds with a divalent carbon atom with only six electrons in its valence shell. This carbon atom has two covalent bonds to other groups and two non-bonding orbitals containing two electrons between them. If the two electrons are spin-paired, the carbene is a singlet, since the spin multiplicity is given by $2S+1$, where the total spin $S=\frac{1}{2}-\frac{1}{2}=0$ for two spin-paired electrons, and therefore $2S+1=1$. If the spins of the electrons are parallel the carbene is a triplet, since $S=\frac{1}{2}+\frac{1}{2}=1$ and $2S+1=3$.

Depending on the degree of hybridisation, the carbon atom can be either of linear geometry, with an sp -hybridised carbene centre with two nonbonding degenerate orbitals p_x and p_y , or of bent geometry, the most common one for carbenes, featuring sp^2 -type hybridisation where the p_y orbital, called p_π , remains almost unchanged, and the orbital p_x , called σ , is stabilised, acquiring some s character, as shown in **Figure 23**.

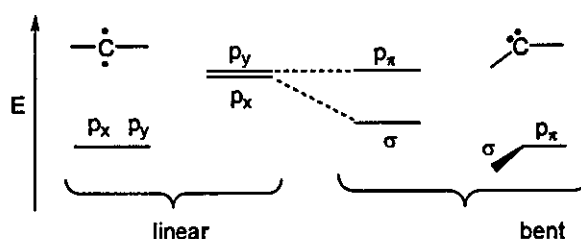


Figure 23

2.2 Electronic configuration of carbenes

There are four possible electronic configuration of carbenes, depending on how the two nonbonding electrons are distributed between two orbitals of different energy, as shown in **Figure 24**.

- $\sigma^1 p_\pi^1$ configuration (3B_1 state); where the two electrons are in two different orbitals with parallel spins (triplet state).
- σ^2 and p_π^2 configurations (1A_1 state); in which the two electrons are paired in the same σ or p_π orbital (singlet state).
- $\sigma^1 p_\pi^1$ configuration (1B_1 state); two electrons are placed in two different orbitals with anti-parallel spins (excited singlet state).

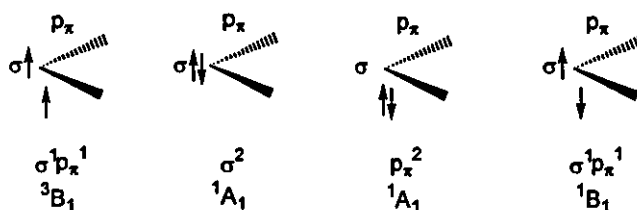


Figure 24

Depending on the relative energies between the σ and p_π orbitals either the singlet or the triplet state could be favoured: according to Hoffmann a value of 2 eV for the σ - p_π separation would lead to a singlet state, while a value below 1.5 eV would favour a triplet state.^{103a} The ground-state multiplicity of the carbenes rules their reactivity^{103b}; singlet carbenes are expected to show both nucleophilic as well as electrophilic character, since they have a filled and an vacant orbital, while triplet carbenes, behave as diradicals, since they have two singly occupied orbitals.

2.3 Carbene substituents; steric and electronic effects

Steric and electronic effects of the carbene substituents can help us to analyse the carbene ground-state multiplicity;

2.3.1 Steric effects

Generally, all types of carbenes are kinetically stabilised by bulky substituents. Since the carbene triplet state is favoured by a linear geometry, this state could also be favoured increasing the bulk of the carbene substituents, since the carbene bond angle would be broadened.

2.3.2 Electronic effects

A) Inductive effects

The carbene multiplicity is influenced by the electronegativity of the substituents.^{104,105} For example, σ -electron-withdrawing substituents, stabilize the σ nonbonding orbital increasing its s character, so the σ - p_{π} separation increases as well, and therefore favours the singlet state. On the contrary, σ -electron-donating substituents induce a small σ - p_{π} gap, favouring the triplet state.

B) Mesomeric effects

Carbenes can be classified into three types according to the nature of their substituents,¹⁰⁶ as shown in **Figure 25**: i) highly bent (X,X)-carbenes, ii) linear (Z,Z)-carbenes and iii) quasi-linear (X,Z)-carbenes, where X is π -electron-donating groups, such as -F, -Cl, -Br, -I, -NR₂, -OR, -PR, -SR₃ and -SR, and Z is π -electron-withdrawing groups, such as -CN, -COR, -BR₂, -CF₃, -PR₃⁺ and -SiR₃.

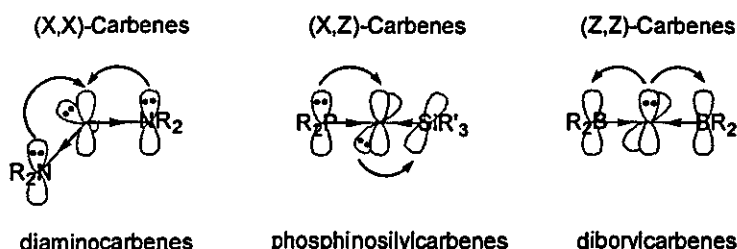
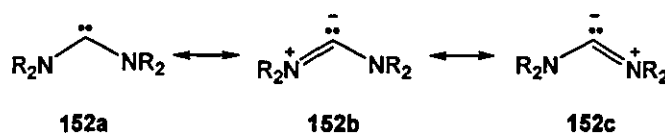


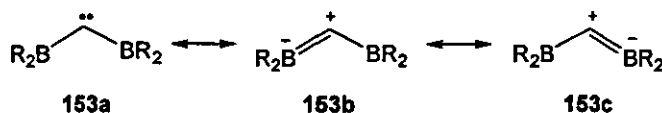
Figure 25

i) **(X,X)-Carbenes**;¹⁰⁵ both substituents of the carbene are π -electron-donating, so the p_π orbital increases in energy and the σ orbital remains almost unchanged. Therefore the σ - p_π separation increases, favouring the singlet state. The C-X bonds acquire some multiple bond character, and these highly bent singlet carbenes can be described as two superimposed zwitterionic structures with a negative charge at the carbene atom, as shown in **Scheme 19**.



Scheme 19

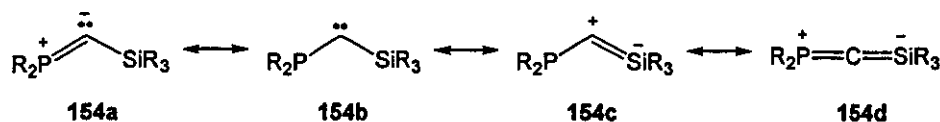
ii) **(Z,Z)-Carbenes**;¹⁰⁵ these type of carbenes are bonded to two π -electron-withdrawing groups, whose vacant orbitals interact with the carbene p_y orbital, leaving the p_x orbital unchanged. Although they are linear, since degeneracy is broken, the singlet state is favoured. The C-Z bonds have also some multiple bond character, and these (Z,Z) carbenes can be described as two superimposed zwitterionic structures with a positive charge at the carbene centre, as shown in **Scheme 20**.



Scheme 20

iii) **(X,Z)-Carbenes**; they have a π -electron-donating substituent, whose lone pair interacts with the carbene p_y orbital (destabilizing it in energy), and a π -electron-

withdrawing group, whose vacant orbital interacts with the carbene p_x orbital (stabilizing it in energy). Both interactions are stabilizing and favour the singlet state. The carbene structure can be described as a polarized allene-type system with X-C and C-Z multiple bonds, as shown in **Scheme 21**.



Scheme 21

2.4 Catalytic properties

Diaminocarbene compounds are able to form stable complexes with transition metals. Since the early 80's, these complexes have received a lot of interest due to their catalytic properties, compared with those of the phosphine and phosphite complexes. Several chiral diaminocarbene complexes, as shown in **Figure 26**, have been prepared and tested in asymmetric catalysis.¹⁰⁷⁻¹¹²

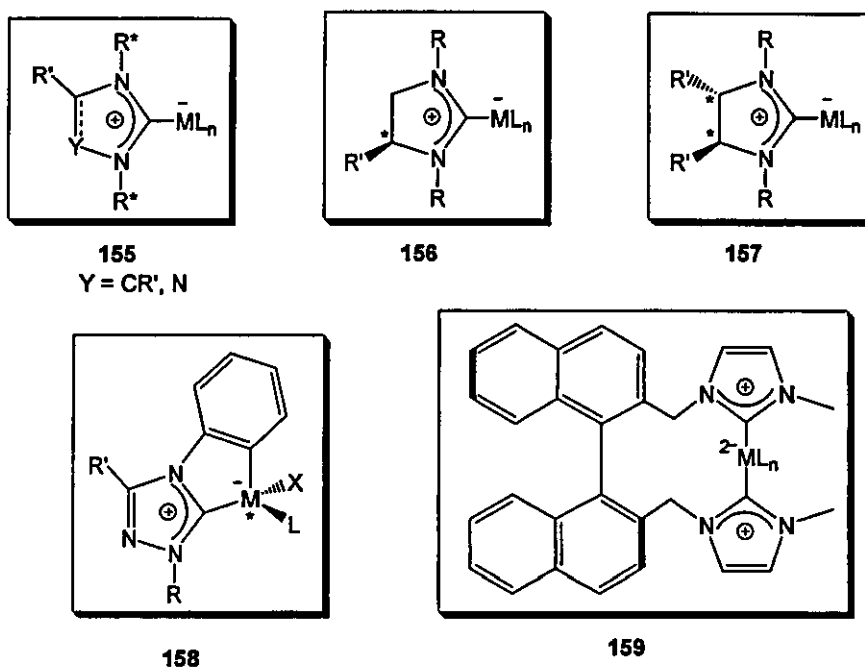


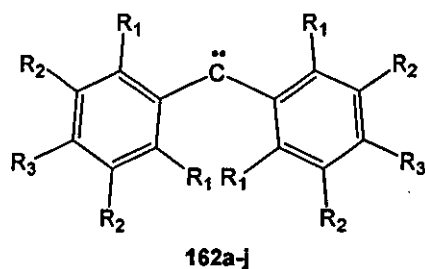
Figure 26

We were especially interested in the use of these catalysts in cyclopropanation reactions, since the aim of our project was to develop new chiral *N*-heterocyclic complexes and test them in this type of reaction.

2.5.1 Synthesis and reactivity.

Chemical reaction scheme showing the photolysis of compound **160** to form compound **161**. Compound **160** is a 2,4,6-trimethyl-1-phenyl-1-diazo-1,2,3,4-tetrahydronaphthalene derivative. Upon irradiation with UV light ($h\nu$), it loses N_2 to form compound **161**, which is a 2,4,6-trimethyl-1-phenyl-1,2,3,4-tetrahydronaphthalene derivative with a carbene intermediate.

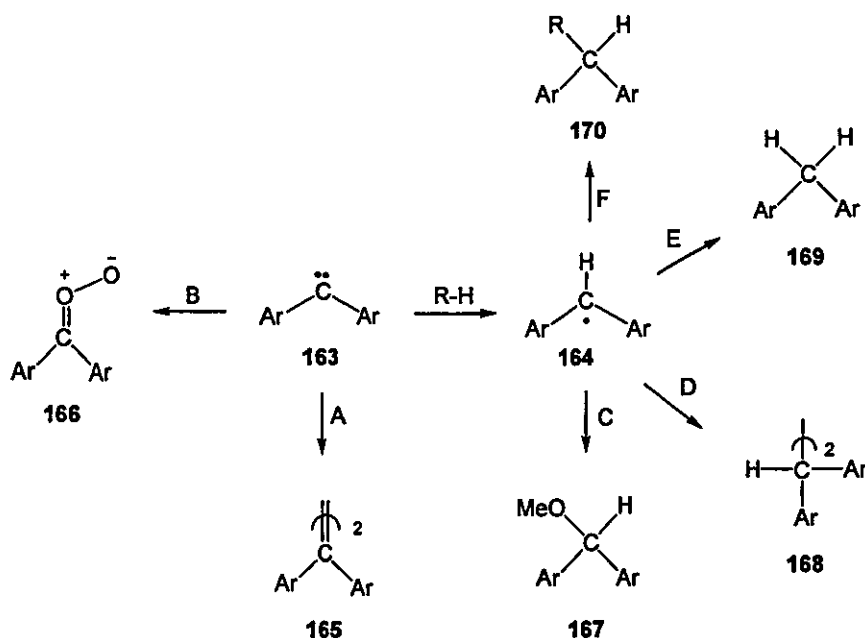
Measuring the half-life time of these carbenes in benzene by laser flash photolysis quantified the stability of triplet carbenes at room temperature, with **162j**¹³⁹ being the most stable one, as shown in **Table 1**.



162a-j	a	b	c	d	e	f	g	h	i	j
R ₁	H	F	Cl	Cl	Me	Me	Me	Br	Br	Br
R ₂	H	F	H	Cl	H	Me	Me	H	H	H
R ₃	H	F	Cl	Cl	Me	H	Me	Br	Me	t-Bu
t _{1/2} (ms)	0.002	0.0015	18	28	160	410	180	1000	220	16000

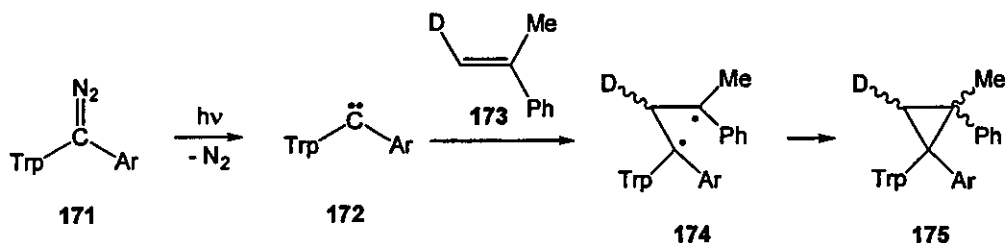
Table 1

Depending on the different reaction conditions of photolysis of the diazo precursors, different compounds could be isolated. In degassed benzene, carbene dimerization¹⁴², shown in reaction A of **Scheme 22**, was observed for the polychlorinated diphenylcarbene **162c** since the carbene centre is not as hindered as in polybrominated compounds **162h-j**,¹³⁹. In the presence of oxygen, diaryl ketone oxides **166** were formed, as shown in reaction B of **Scheme 22**.^{135,137-140,143} When photolysis was carried out in methanol, O-H insertion lead to the formation of the corresponding methyl esters **167**, as shown in reaction C of **Scheme 22**.^{135-138,140} In 1,4-cyclohexadiene, several reactions were favoured, such as dimerization of radicals **164** to afford the compounds **168**,¹³⁶ as shown in reaction D of **Scheme 22**, hydrogen-abstraction reactions to furnish the compounds **169**, as shown in reaction E of **Scheme 22**, and R-H insertion reactions to yield the compounds **170**, as shown in reaction F of **Scheme 22**.



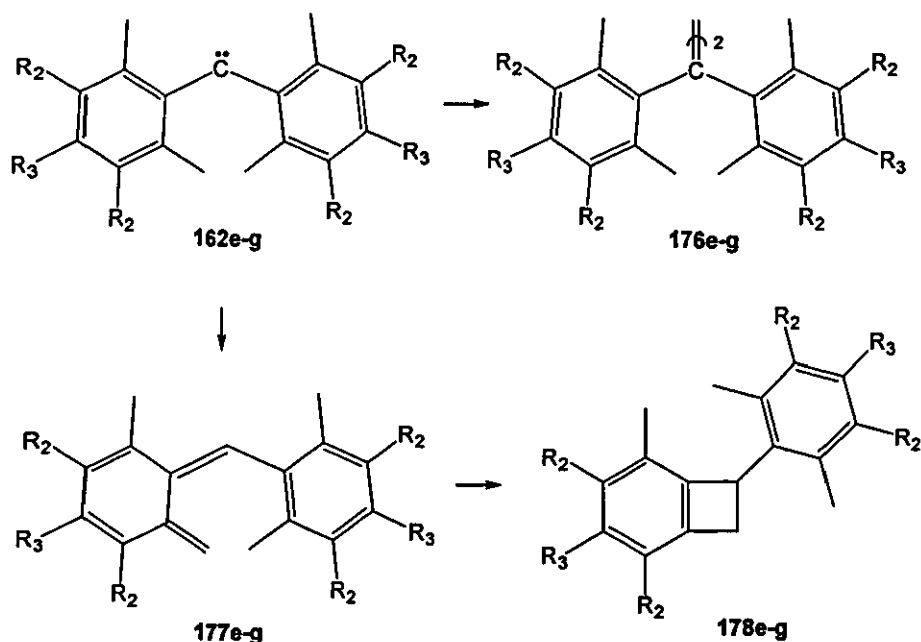
Scheme 22

Reaction of the carbene **172** with an olefin, such as (E)- β -deuterio- α -methylstyrene **173**, afforded cyclopropane **175**,¹⁴⁰ with loss of stereochemistry as a consequence of the free rotation around the σ C-C bond of the transient biradical, as shown in **Scheme 23**.



Scheme 23

For polymethylated diphenylcarbenes **162e-g**, dimerization to give the compounds **176e-g**, as well as intramolecular hydrogen-abstraction followed by electrocyclisation to give benzocyclobutenes **178e-g** was observed, as shown in **Scheme 24**.^{38, 44}



Scheme 24

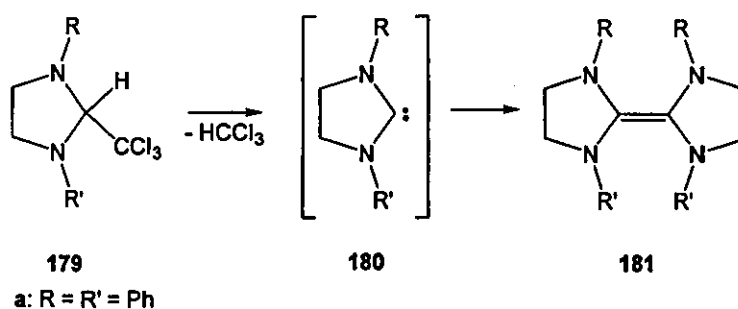
2.6 Singlet carbenes

2.6.1 Synthesis of stable singlet carbenes

As mentioned before, carbenes can be classified according to the electronic interaction with their substituents, in (X,X), (X,Z) and (Z,Z)-carbenes.

2.6.1.1 (X,X)-Carbenes

First attempts to synthesise carbenes started in the 1960's when Wanzlick *et al.*^{122,145} tried to isolate 1,3-diphenylimidazolidin-2-ylidene **180** by thermal elimination of chloroform, but instead, the dimer **181** was isolated, as shown in **Scheme 25**. Several cross-coupling experiments of differently substituted dimers, showed that they were not in equilibrium with the two carbene units.



Scheme 25

In 1968, shortly after the first metal-carbene complex **182** was synthesised, shown in **Figure 27**, Öfele¹⁴⁶ and Wanzlick *et al.*,¹⁴⁷ reported the synthesis of the chromium and mercury *N*-heterocyclic carbene complexes, **184** and **186** respectively, from the corresponding imidazolium salts **183** and **185**, as shown in **Equation 18** and **Equation 19**.

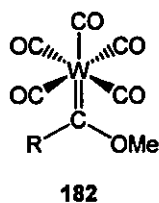
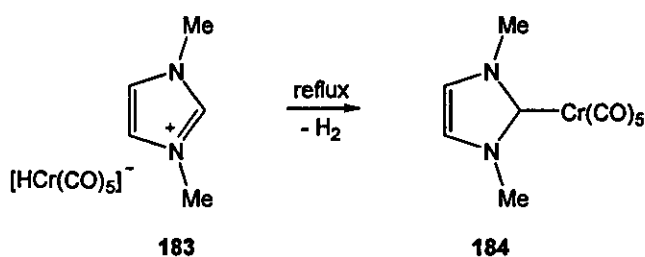
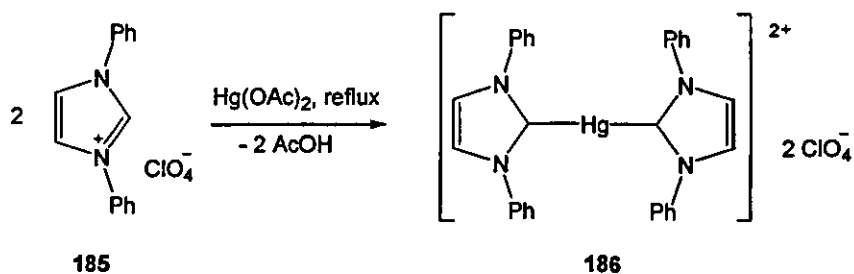


Figure 27

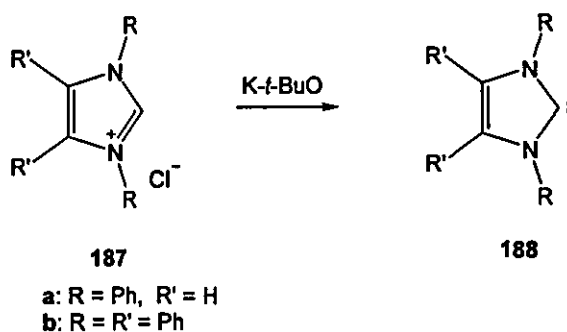


Equation 18



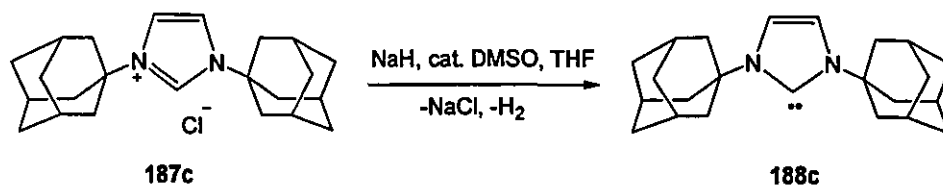
Equation 19

Shortly after, in 1970, Wanzlick *et al.* showed that formation of the imidazol-2-ylidenes **188a-b** was possible by deprotonation of the corresponding imidazolium chloride salts **187a-b** using potassium *tert*-butoxide, as shown in Equation 20. Finally, they only managed to trap them using isothiocyanates or metal-containing precursors, but they could not isolate them.^{148,149}



Equation 20

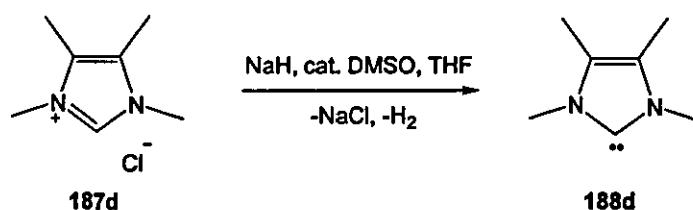
Following similar studies, in 1991 Arduengo *et al.*¹⁵⁰ yielded the first stable crystalline carbene **188c** (R'=H, R=Ad), by deprotonation of 1,3-di-1-adamantylimidazolium chloride **187c** (R'=H, R=Ad), using sodium or potassium hydride, in the presence of a catalytic amount of either potassium *tert*-butoxide or dimethylsulfoxide anion, as shown in Equation 21. Surprisingly, the carbene was formed as colourless crystals, which possessed sufficient kinetic and thermodynamic stability to be easily isolated and characterised, without decomposition. It was shown that the carbene was stable in the absence of oxygen and moisture and could be easily manipulated using conventional laboratory techniques, even to the extent of its melting point being determined.



Equation 21

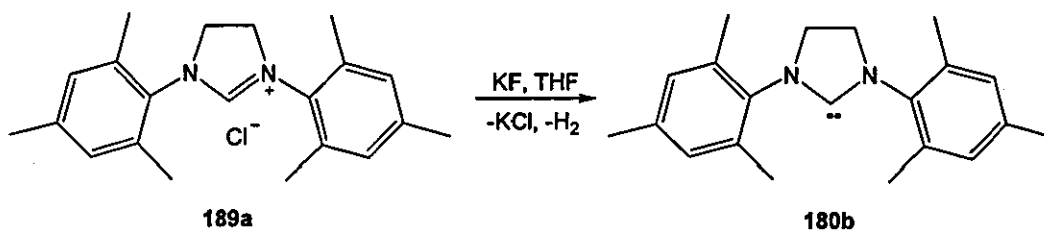
The stability of the carbene was attributed to a number of factors. Namely, it enjoys both steric and electronic stabilisation. The electronic stabilisation includes a π -donation into the carbene out-of-plane p orbital by the electron rich π -system

and also an electronegativity effect. These π -interactions lead to a number of resonance forms whereby the positive charge is delocalised around the imidazole ring. Also, a steric stabilisation effect was suggested. It was argued that the two adamantyl groups contributed to the carbenes kinetic stability by protecting the reactive centre from attack by electrophilic species. Subsequent results from the same group cast doubt on the importance of this steric effect.¹⁵¹ In particular, it was found that 1,3,4,5-tetramethylimidazol-2-ylidene **188d** ($R'=R=Me$),¹⁵² was obtained in excellent yield by the treatment of 1,3,4,5-tetramethylimidazolium chloride **187d** ($R'=R=Me$) with one equivalent of sodium hydride and a catalytic amount of either potassium *tert*-butoxide or dimethylsulfoxide anion in tetrahydrofuran, as shown in **Equation 22**. As before, the formed carbene was a stable colourless crystalline solid that could be recrystallised from toluene.



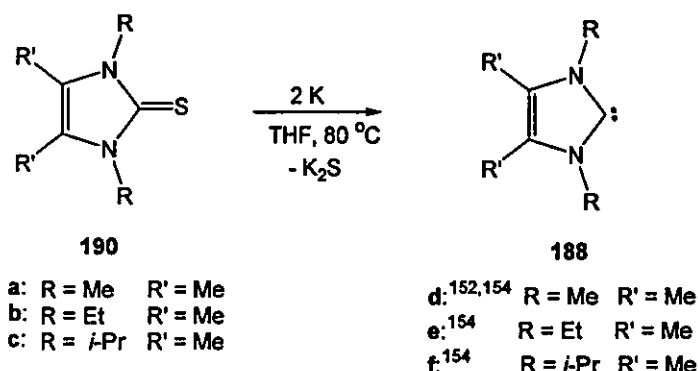
Equation 22

Arduengo and co-workers also succeeded in synthesising imidazolin-2-ylidene **180b** ($R=Me$),¹⁵³ which was isolated as a stable crystalline solid, as shown in **Equation 23**. These fully saturated compounds showed that the different degree of aromaticity had no effect on deprotonation of the imidazolium salt and the stability of the resulting carbene species.



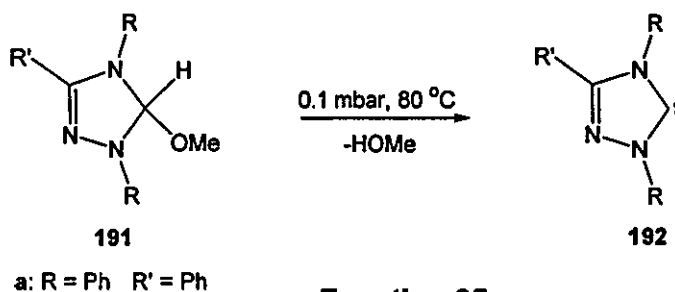
Equation 23

A different approach to synthesise *N*-heterocyclic carbenes **188d-f** was published by Kuhn *et al.*¹⁵⁴ in 1993. It consisted of reduction of 2-(3*H*)-thiones **190a-c** with potassium in boiling tetrahydrofuran, as shown in Equation 24.



Equation 24

In 1995 Enders *et al.*¹⁵⁵ prepared the first commercially available carbene, compound **192a**, from triazole **191a**, by thermal elimination of methanol *in vacuo*, as shown in Equation 25.



Equation 25

Herrmann and co-workers¹⁵⁶ carried out the synthesis of new carbenes **188g-h** and **193a-d**, shown in Figure 28, using liquid ammonia as solvent, in which deprotonation occurred much faster.

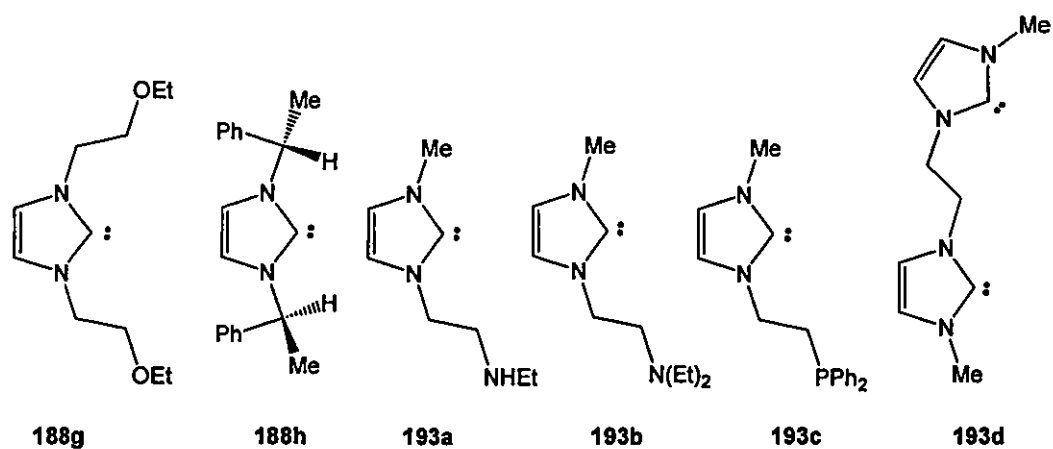
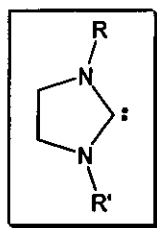


Figure 28

Continuing these studies, several carbenes bearing two σ -donor substituents, of which at least one was an amino group, have been synthesised. Some examples are the compounds **180c-f**, **188g-n** and **194-198**, shown in **Figure 29**.



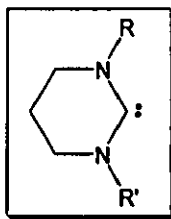
180

c:¹⁵⁷ R = R' = *i*-Pr

d:¹⁵⁷ R = R' = Et

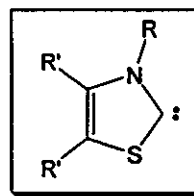
e:¹⁵⁷ R = R' = Me

f:¹⁵⁷ R = R' = *t*-Bu



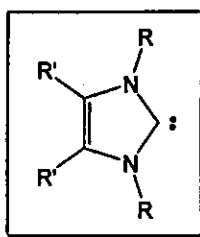
194

a:¹⁵⁸ R = R' = *i*-Pr



195

a:¹⁶² R = 2,6-(*i*-Pr)₂-C₆H₃ R' = Me



188

g:¹⁵⁹ R = Ph

R' = Ph

k:¹⁵¹ R = Me

R' = H

h:¹⁵¹ R = Mes

R' = H

l:¹⁵² R = *t*-Bu

R' = H

i:¹⁵¹ R = Tol

R' = H

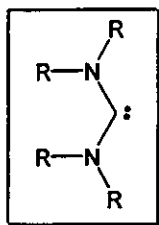
m:¹⁶⁰ R = Mes

R' = Cl

j:¹⁵¹ R = *p*-ClPh

R' = H

n:¹⁶¹ R = -CH₂-C(CH₃)₃ R' = (CH)₄

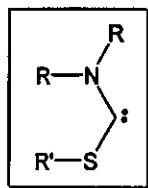


196

a:¹⁶³ R = *i*-Pr

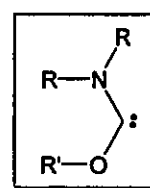
b:¹⁶⁴ R = piperidino

c:¹⁶⁴ R = Me



197

a:¹⁶⁵ R = Me R' = 2,6-(*t*-Bu)₂-C₆H₃



198

a:¹⁶⁵ R = *i*-Pr

R' = 2,6-(*t*-Bu)₂-C₆H₃

b:¹⁶⁵ R = Me

R' = 2,6-(*t*-Bu)₂-C₆H₃

c:¹⁶⁵ R = *i*-Pr

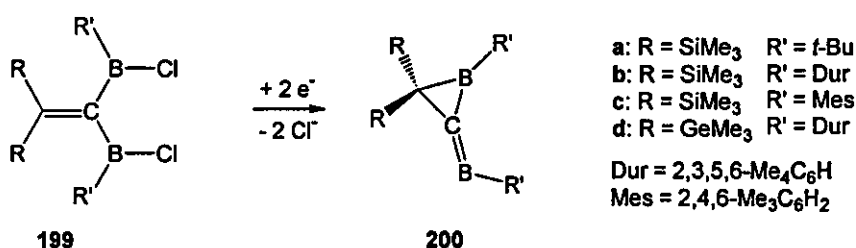
R' = 2,6-Me₂C₆H₃

d:¹⁶⁵ R = piperidino R' = Me

Figure 29

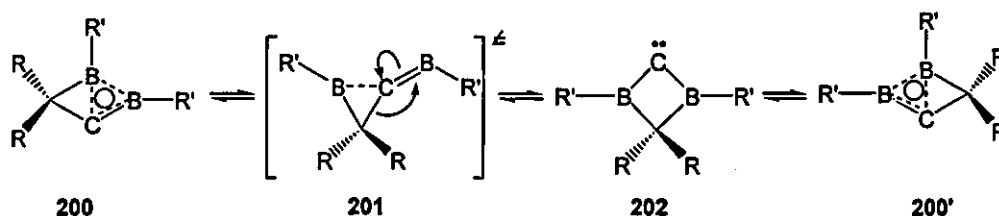
2.6.1.2 (Z,Z)-Carbenes

Isolation of diborylcarbenes has not been possible yet. Instead borylmethyleneboranes **200a-d** and **203a-c**, also called “masked” diborylcarbenes, have been prepared by Berndt *et al.*¹⁶⁶ and they can be used as their synthetic equivalents. The first ones were reported in the 80's, and they were obtained from reduction of the corresponding 1,1-bis-(chloroboryl)ethylenes **199a-d**, as shown in Equation 26.



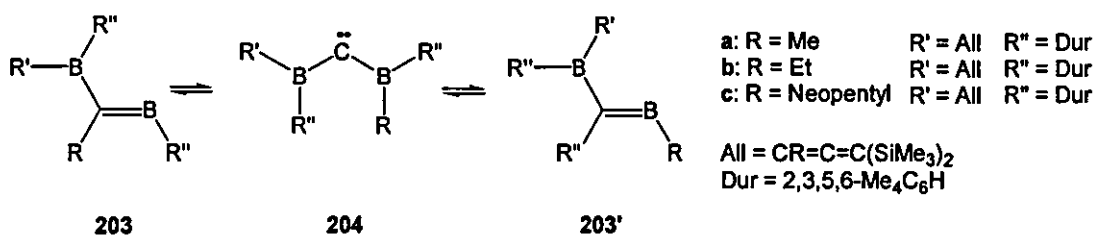
Equation 26

Compounds **200** feature both σ - and π -three centre-two electron bonds, and in solution, at room temperature, they exhibit a topomeric equilibrium which proceeds via the transition state **201**. According to Schleyer the equilibrium proceeds as shown in Scheme 26.¹⁶⁷



Scheme 26

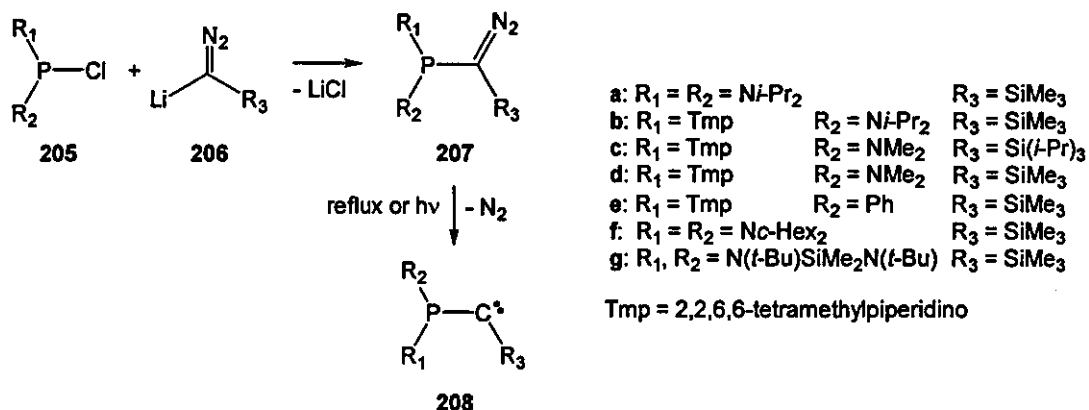
In 1995, Berndt proposed another topomeric equilibrium for acyclic compounds **203a-c**, as shown in Scheme 27.¹⁶⁸



Scheme 27

2.6.1.3 (X, Z)-Carbenes

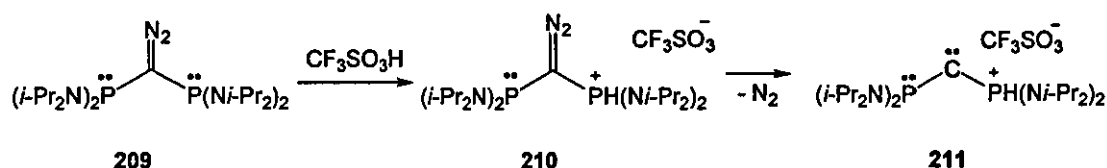
Phosphinosilyl- and phosphinophosphoniocarbenes can be prepared from decomposition of the corresponding α -diazophosphine. The first α -diazophosphine **207a** was synthesised by Baceiredo *et al.*¹⁶⁹ in 1985, by treatment of the lithium salt of trimethylsilyldiazomethane **206a** with one equivalent of bis-(diisopropylamino)chlorophosphine **205a**. Following this procedure, several α -diazophosphines (**207b-g**) have been obtained, and they can be converted into the respective phosphonio carbenes **208** by photolysis or thermolysis, as shown in Scheme 28.



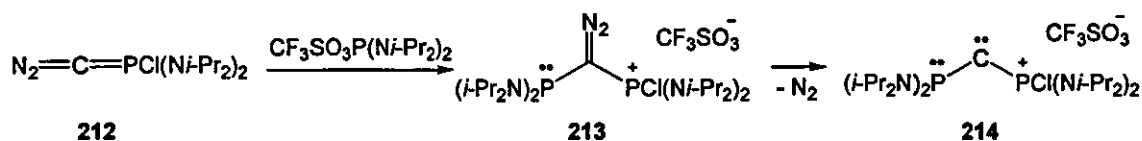
Scheme 28

Phosphino carbenes are kinetically stabilised by bulky substituents and their stability is inversely proportional to that of the diazo precursors.

If the lithium salt of phosphoniodiazomethane is used as starting material to prepare the α -diazophosphine, the following phosphinophosphonio-carbenes **211**¹⁷⁰ and **214**¹⁷¹ can be obtained, as shown in Scheme 29 and Scheme 30.

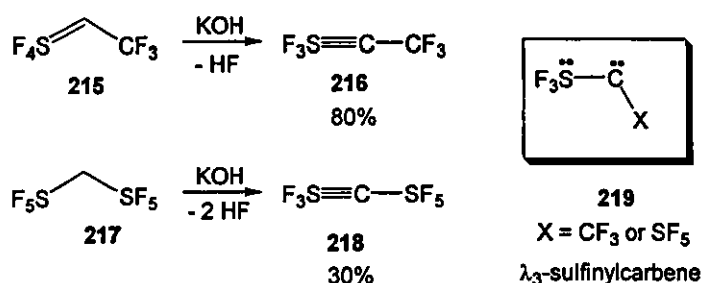


Scheme 29



Scheme 30

Compounds **216**¹⁷² and **218**¹⁷³ were synthesised in the 80's by Seppelt *et al.* by gas-phase dehydrofluorination of the corresponding compounds **215** and **217**, using potassium hydroxide at 70-80 °C, as shown in **Scheme 31**.¹⁷⁴



Scheme 31

According to their reactivity these types of carbon-sulfur triple-bonded compounds **216** and **218** can be considered as "masked" sulfinylcarbenes **219**.

2.6.2 Reactivity of stable singlet carbenes

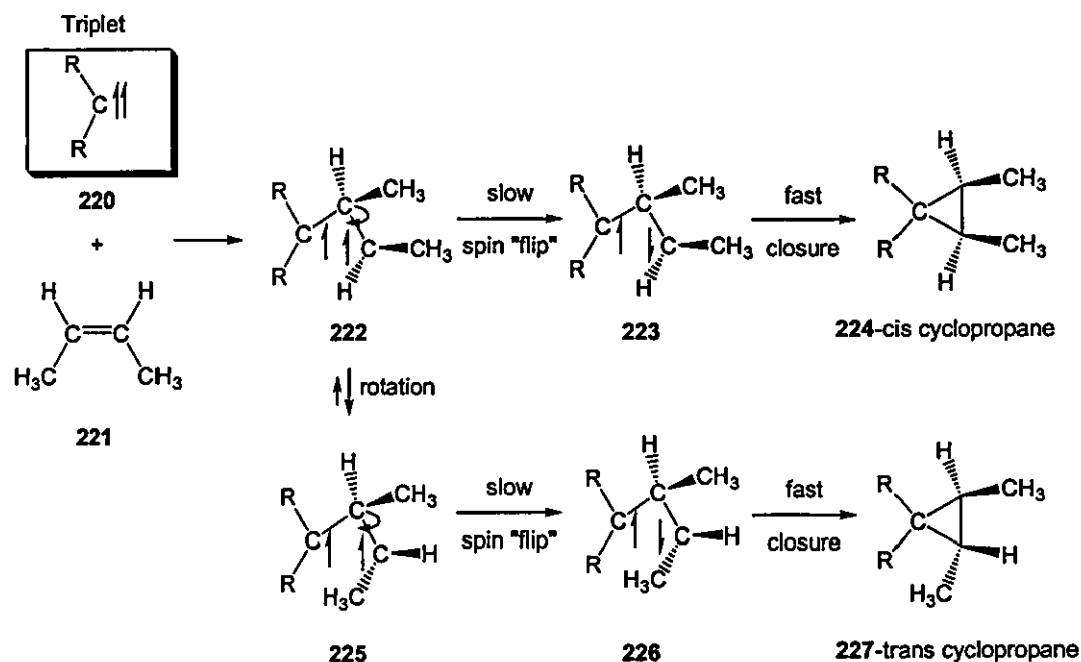
Singlet carbenes are ambiphilic by nature; they can behave as electrophiles as well as nucleophiles, depending if it is either their vacant orbital or their lone pair of electrons that takes place in the reaction.

The most common reactions that they are involved in are: 1,2 migration reactions, carbene dimerization and carbene-carbenoid coupling reactions, addition to multiple bonds (such as addition to carbon-carbon double bonds, addition to carbonyl derivatives, addition to carbon-heteroatom triple bonds, addition to cumulenes and addition to 1,3 dipoles), insertion reactions (into polarized X-H bonds and unpolarized C-H bonds) formation of carbene-Lewis acids adducts, carbene-Lewis base adducts and carbene-metal adducts.

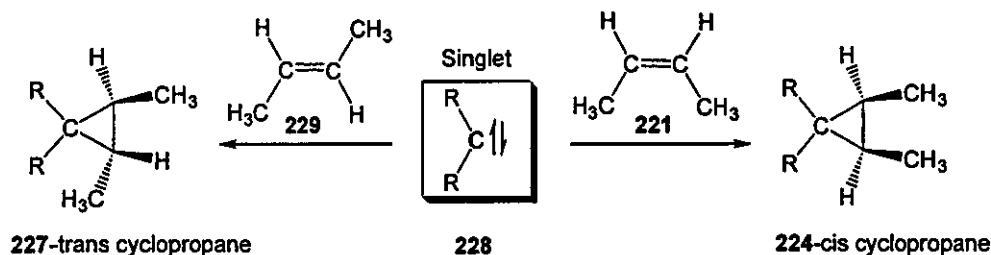
We will only discuss the addition to carbon-carbon double bonds and the synthesis of carbene-metal adducts, since we are especially interested in the formation of cyclopropanes, as well as in the synthesis of carbene-metal catalysts for cyclopropanation reactions.

2.6.2.1 Addition to carbon-carbon double bonds

Reaction of both triplet **220** and singlet **228** carbenes with alkenes afford cyclopropanes *via* different mechanisms, as shown in **Scheme 32** and **Scheme 33**.



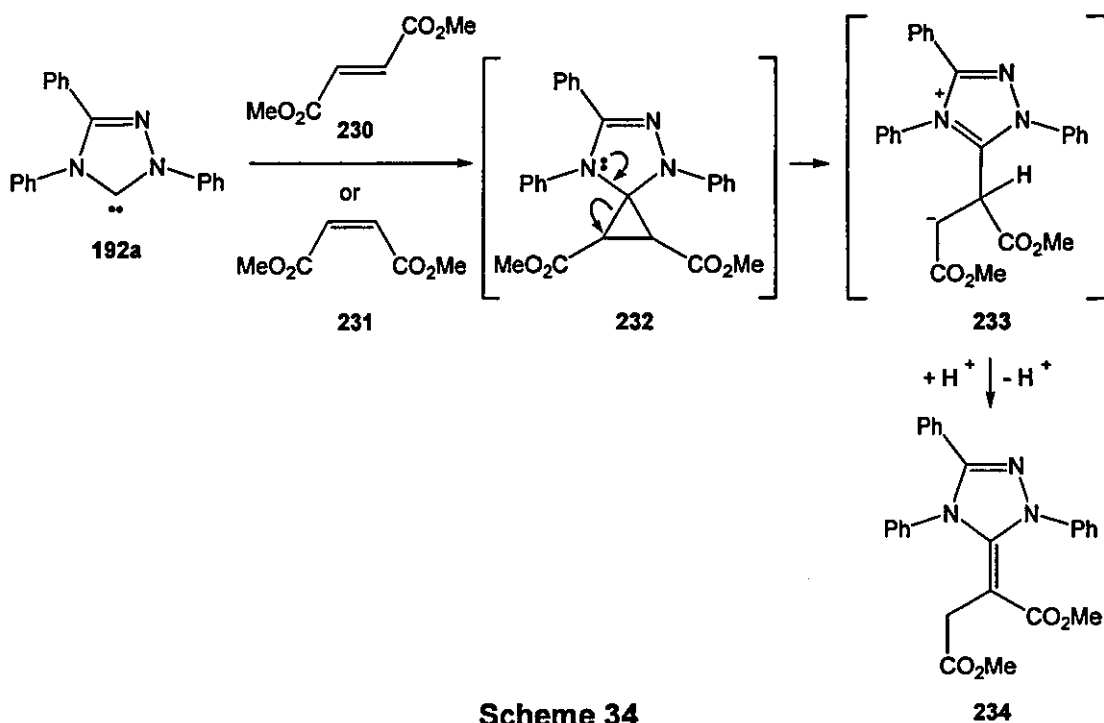
Scheme 32



Scheme 33

Nucleophilic carbenes, whose singlet state is stabilised by the interaction of the lone pair of a heteroatom substituent with its vacant p_π orbital, reacts with electrophilic alkenes rather than with electron-rich ones.

Sometimes, during the course of the reaction between carbenes and alkenes, rearrangements of the formed cyclopropanes lead to different products, as occurs when 1,2,4-triazol-5-ylidene **192a** reacts with either dimethyl fumarate **230** or dimethyl maleate **231**, as shown in Scheme 34, so that cyclopropanes are not isolable.¹⁵⁵



Scheme 34

Some phosphinosilyl carbenes react with dimethyl fumarate, but not with dimethyl maleate, to afford cyclopropanes with retention of configuration about the double bond.¹⁷⁵ They also react stereoselectively with monosubstituted electron-poor alkenes *via* "syn-attack" to give the corresponding cyclopropanes in high yields.

RESULTS AND DISCUSSION

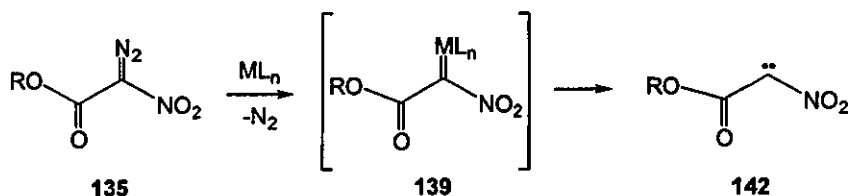
CHAPTER 3: Attempted Synthesis of Nitrocyclopropanes/enes

3.1 Introduction

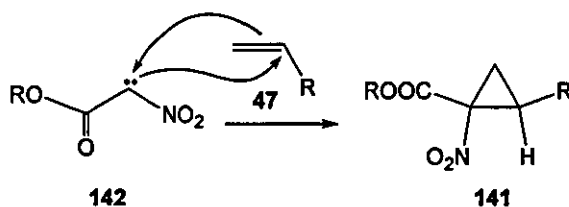
Strained rings that include nitro substituents are very interesting as high-energy materials.¹⁷⁶ We were interested in the synthesis of nitro substituted cyclopropanes and nitro substituted cyclopropenes, which are the simplest members of this class of compounds. We envisaged that nitro substituted cyclopropanes/enes should make useful synthons for a variety of theoretically and biologically interesting molecules.

There are only a handful of methods published in the literature describing the synthesis of nitro cyclopropanes/enes. The most common method to prepare them is by reaction of a nitrodiazoacetate **135**, with an alkene or alkyne,¹⁰¹ in the presence of a transition metal catalyst, such as rhodium (II) acetate.

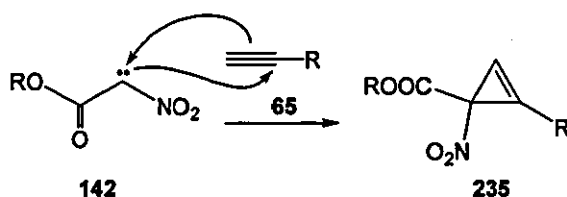
The proposed mechanisms of formation of nitro cyclopropanes/enes are similar to those described for the synthesis of cyclopropanes/enes, as shown in **Schemes 8-10**. In the presence of a transition metal catalyst (ML_n), extrusion of nitrogen from the nitrodiazoacetate **135** takes place in a first step to furnish the carbenoid **139**, as shown in **Scheme 35**. Elimination of the catalyst from the carbenoid **139**, affords the carbene **142**, that can undergo insertion either into a double carbon-carbon bond of an alkene, as shown in **Scheme 36**, or into a triple carbon-carbon bond of an alkyne, as shown in **Scheme 37**, to afford the nitro cyclopropane **141** or the nitro cyclopropene **235** respectively.



Scheme 35



Scheme 36



Scheme 37

It is known that nitro derivatives are very explosive,¹⁷⁷ so in order to synthesise nitro substituted cyclopropanes and nitro substituted cyclopropenes, we envisaged the isolation of the nitro precursors onto a solid phase support would furnish stable materials.

The use of polymeric supports in organic synthesis offers several advantages over conventional solution phase methodology;¹⁷⁸

- (i) The elimination of purification steps en route. For each step in a multiple-step synthesis, the only purification needed is a resin-washing step. Following the completion of a reaction, the desired target and the insoluble polymer supported reagent can be separated by simply filtration. Only the final product of cleavage needs to be purified.
- (ii) Reactions can be accomplished in only three steps: addition of reagents, filtering and washing the resin. This allows many simple automated procedures to be developed, such as high-throughput screens. For polymer-supported catalysts, the possibility exists to develop both insoluble and soluble derivatives. Insoluble derivatives have the advantage that they can be removed by filtration, allowing for rapid recycling and re-use. With soluble polymers, the catalysis takes place in an homogeneous medium, which may

be beneficial to a particular reaction, with the catalysts subsequently being rendered insoluble for re-isolation by precipitation.

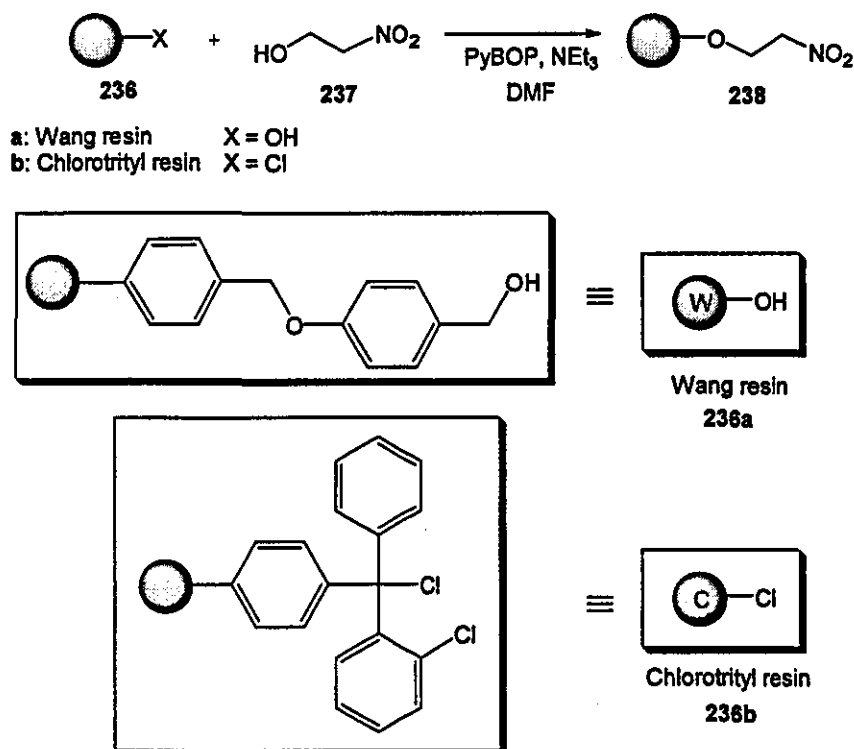
- (iii) In a solid phase synthesis, high concentrations of reagents can be used to drive reactions to completion.
- (iv) Cleaner synthetic methods. Cross-linked polymers are insoluble, non-volatile and most importantly environmentally friendly. In addition, toxic chemicals can be rendered inert and harmless through attachment to a polymer support.
- (v) Ready recovery of supported catalytic systems for reuse. In the case of polymer-supported catalysts, this enables quantitative re-isolation for re-use, therefore increasing efficiency.
- (vi) In the current research, we envisaged that attaching potentially explosive compounds to solid supports should render them safe to work with. The isolation, and steric protection, of individual nitrodiazo molecules on the solid support should prevent spontaneous decomposition at one site spreading to adjacent molecules thus greatly reducing the chance of a run away propagation leading to an explosion.

Choosing the solid support and the mode of attachment and cleavage of materials from the resin matrix is crucial in solid-phase synthesis.

3.2 Synthetic plan

3.2.1 Coupling the nitro compounds into the resins

We planned to isolate the nitro derivatives onto either Wang **236a** or 2-chlorotrityl chloride **236b** resins. This was to be carried out *via* coupling reactions of α -unsubstituted nitro compounds (such as dipotassium salt of nitroacetic acid or 2-nitroethanol) to both Wang and 2-chlorotrityl chloride resins. Equation 27 shows the synthesis of nitroethyloxy resin derivatives **238a** and **238b**.

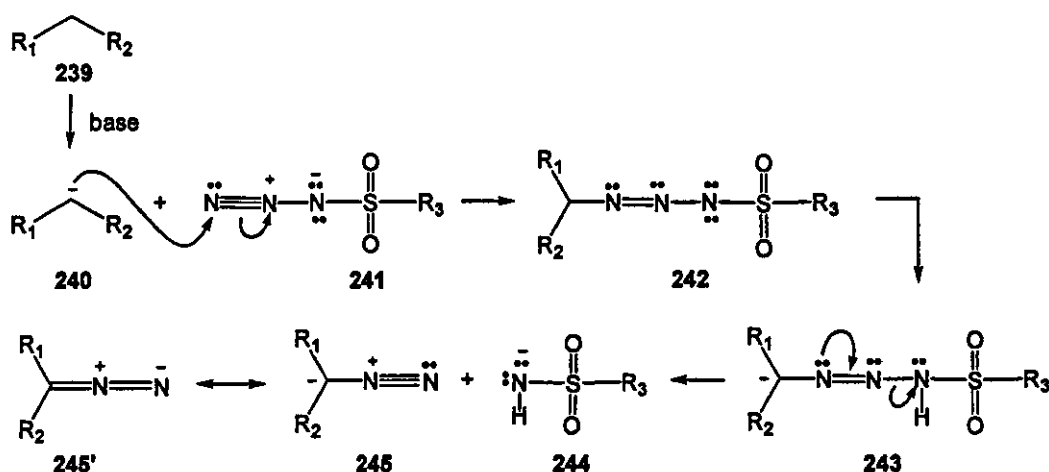


Equation 27

3.2.2 Insertion of the diazo function into the nitro resin derivatives

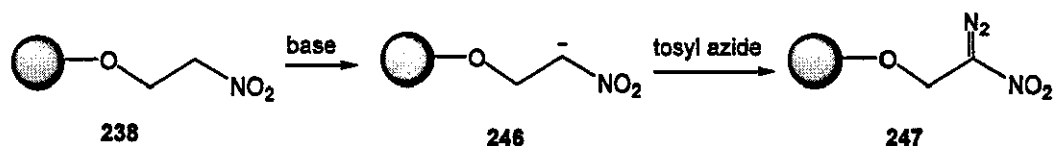
The next step would be the insertion of a diazo functionality onto the nitro resin derivative. The most common method used for introducing a diazo functionality into a molecule is based on a diazo transfer reaction.¹⁷⁹ This involves an anionic attack onto a reagent that possesses a diazo group attached to a leaving group;

generally the reagent employed is a sulfonyl azide. A general mechanism for this reaction is described in **Scheme 38**, and was first proposed by Doering *et al.*¹⁸⁰ Either one or both functional groups R_1 or R_2 of compound **239**, must be electron-withdrawing groups, so that an active methylene compound **240** can be formed after reaction with a base. Attack of the active methylene compound to the diazo group of the sulfonyl azide **241** generates the compound **242**, that undergoes an internal hydrogen transfer reaction to furnish the compound **243**, which rearranges to form the desired diazo compound **245** and the sulfonamide **244**.



Scheme 38

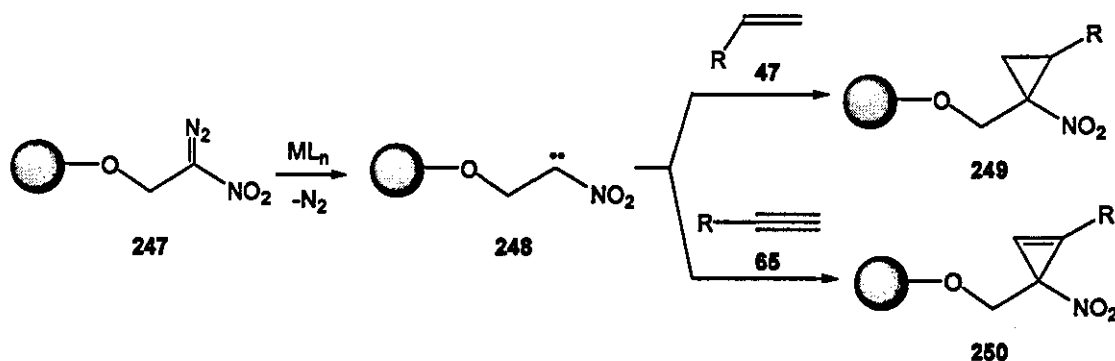
Since *para*-toluenesulfonyl azide **241a** ($R_3=p\text{-Tol}$) has been shown in the literature to accomplish diazo transfer reactions of a wide range of substrates in good yield,^{179,181} we decided to use it in order to achieve the insertion of the diazo group in α to the nitro group, in the derivatised resins **238**. Our planned synthesis of diazo nitroethyloxy resin derivatives **247** is shown in **Scheme 39**.



Scheme 39

3.2.3 Formation of nitro cyclopropanes/enes resin derivatives

The final step would be the formation of the resin bound cyclopropane/ene. Treatment of the nitro diazo derivatives **247** with a transition metal catalyst would furnish, after extrusion of nitrogen, the corresponding carbenes **248**, which would undergo insertion into either an alkene or an alkyne to give the desired nitro substituted cyclopropanes/enes **249** and **250** respectively, bound to the resin support, as shown in Scheme 40.



Scheme 40

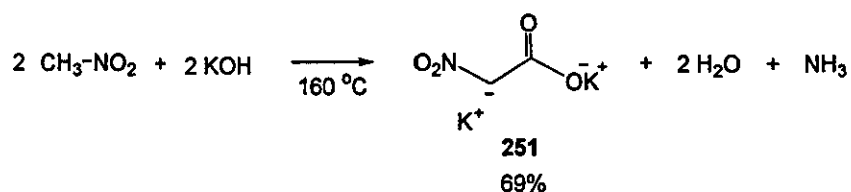
Similar reactions could also be envisaged when the dipotassium salt of nitroacetic acid was employed instead of 2-nitroethanol.

The cleavage of the desired nitro cyclopropanes/enes from the solid support could be achieved with an acid, or further reactions could be carried out on the nitro cyclopropanes/enes.

3.3 Synthetic results

3.3.1 Preparation of dipotassium salt of nitroacetic acid

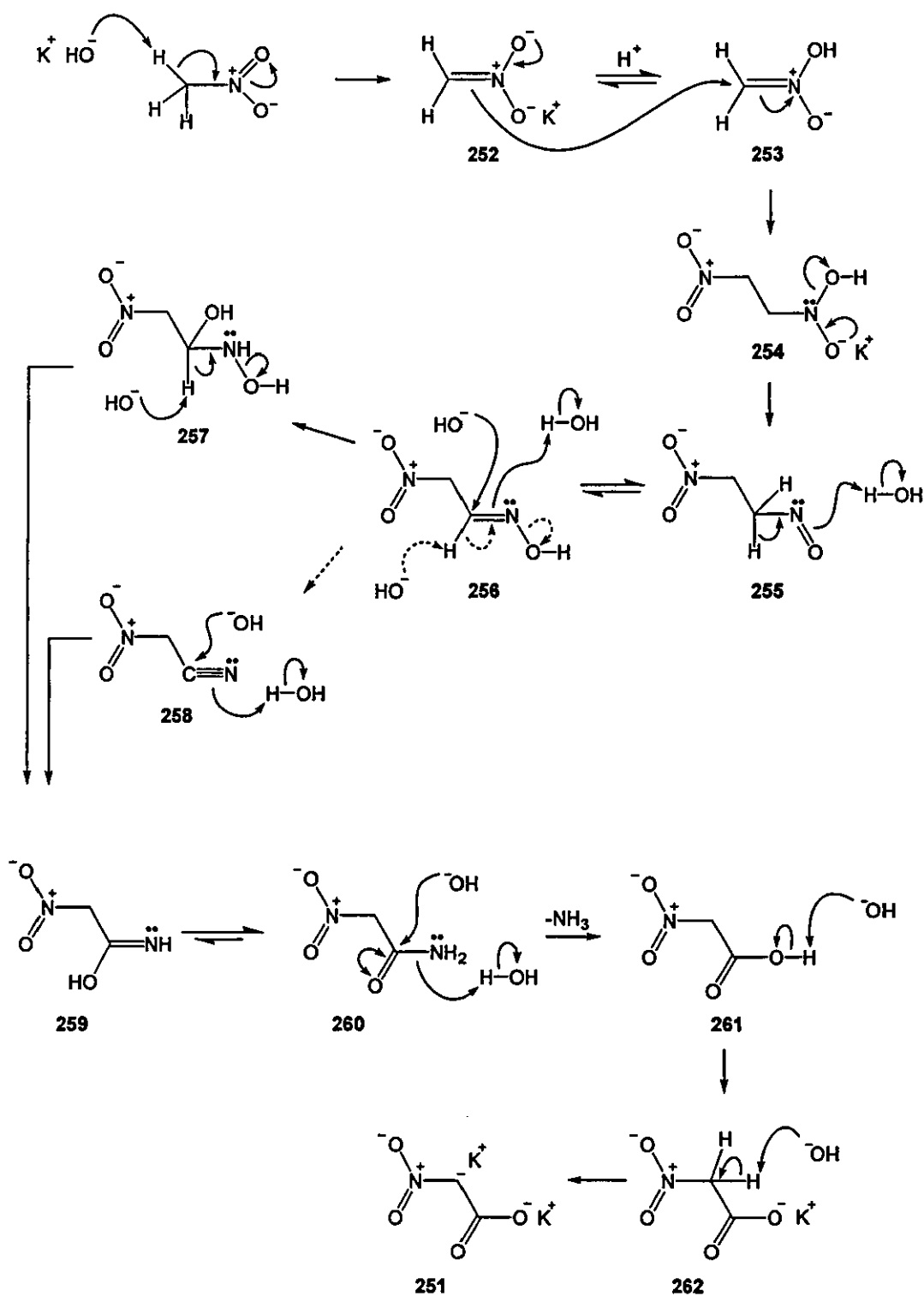
Initially, the dipotassium salt of nitroacetic acid **251** was chosen as the α -unsubstituted nitro compound. Treatment of nitromethane with an aqueous solution of potassium hydroxide under the conditions reported by Koto *et al.*¹⁸² gave the desired product **251** as an orange solid in moderate yield, as shown in Equation 28.



Equation 28

The IR spectrum showed a band at 1595 cm^{-1} and a peak at 1329 cm^{-1} , corresponding to nitro group stretches, and a peak at 820 cm^{-1} , due to the C-N stretching. The carbonyl peak could not be observed by IR spectroscopy, probably because it was obscured by the broad band at 1595 cm^{-1} .

The following mechanism for the synthesis of the dipotassium salt of nitroacetic acid **251** was proposed, as shown in **Scheme 41**.

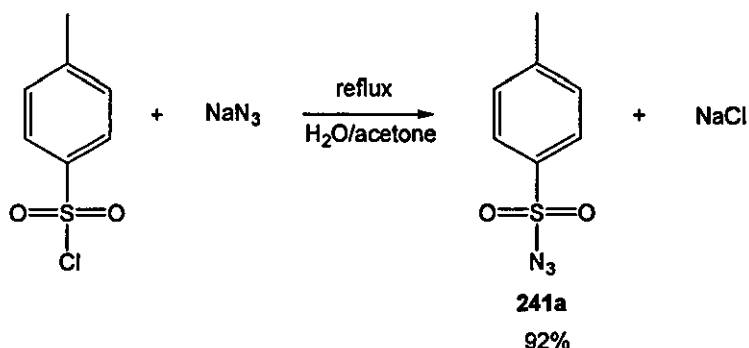


Scheme 41

The compounds **258**, **259** and **260** will be largely deprotonated during the reaction.

3.3.2 Preparation of *para*-toluenesulfonyl azide

The synthesis of *para*-toluenesulfonyl azide **241a** was straightforward,¹⁸³ and involved the reaction of sodium azide with *para*-toluenesulfonyl chloride in a mixture of acetone:water. The desired product **241a** was formed in excellent yield along with sodium chloride as a by-product, as shown in Equation 29.



Equation 29

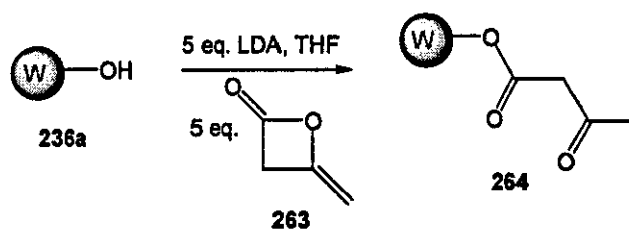
Analysis by IR spectroscopy showed a peak at 2128 cm^{-1} due to the azide group stretching, and two peaks at 1371 and 1167 cm^{-1} , corresponding to $-\text{N}-\text{SO}_2$ stretchings.

3.3.3 Model study

A model study was undertaken in order to determine whether the resin bound diazo moiety could be detected by IR spectroscopy. A diketone system was chosen to be coupled onto the resin, since this system could be easily deprotonated, and the resulting anion could react with a wide range of electrophiles, such as *para*-toluenesulfonyl azide.

3.3.3.1 Synthesis of Wang-3-oxo-butyric acid resin derivative

The preparation of the polymer bound diketone **264** was carried out by treatment of Wang resin **236a** with diketene **263** in the presence of LDA, as shown in Equation 30.



Equation 30

The IR spectrum, shown in the appendix, was difficult to interpret; two new peaks observed at 1654 and 1618 cm^{-1} , were possibly due to the carbonyl stretching. Although we were not completely sure if the reaction had worked, the resin derivative **264** was used for the next experiment, in order to synthesise the diazo derivative **265**. If the IR spectrum confirmed, as it did, the presence of the characteristic band of the diazo group, it would also confirm that this reaction had worked, at least to some extent.

3.3.3.2 Synthesis of Wang-2-diazo-3-oxo-butyric acid resin derivative

Following the procedure reported for solution phase,¹⁸⁴ the diketone resin derivative **264** was treated with triethylamine in dichloromethane, followed by reaction with *para*-toluenesulfonyl azide, as shown in Equation 31, in order to afford the desired product **265**.



Equation 31

Analysis by IR spectroscopy showed a sharp peak at 2138 cm^{-1} , corresponding to the diazo group stretching. The peaks at 1654 and 1618 cm^{-1} , likely to be due to the carbonyl stretching, were also observed. The IR spectrum is shown in the appendix.

This sequence of reactions showed that it was possible to detect the resin bound diazo group by IR spectroscopy.

3.3.4 Synthesis of Wang resin derivatives

3.3.4.1 The use of PyBOP

In 1990 Coste *et al.*¹⁸⁵ prepared benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate, PyBOP **267**, as a replacement for benzotriazolyloxy-tris(dimethylamino)-phosphonium hexafluorophosphate, BOP **266**, an excellent reagent for peptide coupling in solution and in solid phase. The structures of both PyBOP and BOP are shown in Figure 30. The use of BOP involved the formation of HMPA, which is highly toxic, carcinogenic and moreover relatively volatile.

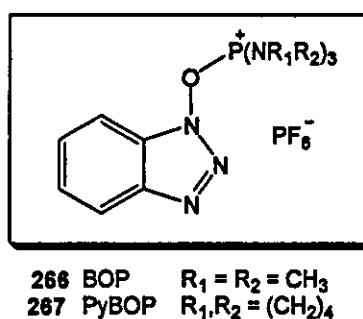
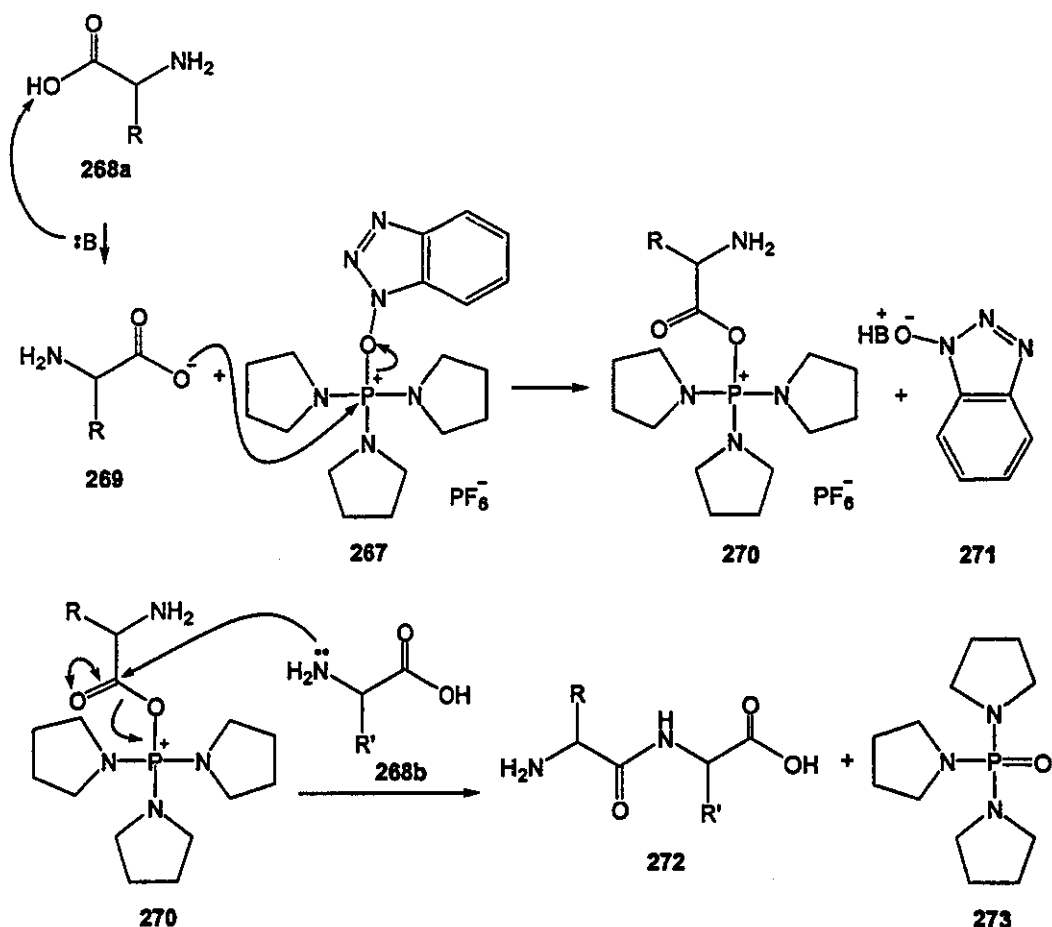


Figure 30

Using PyBOP as a coupling reagent did not generate toxic by-products and the coupling rates obtained were as good, and sometimes even better, than in those reactions where BOP was employed.

The following mechanism has been proposed for the synthesis of peptides and is shown in Scheme 42. In the first step an amino acid **268a** is deprotonated after treatment with a base, to form the anion **269**. Attack of the carboxylate anion of the compound **269** to the phosphonium centre affords the compound **270**, with elimination of benzotriazol-1-olate **271**. Attack of another amino amino acid **268b** is facilitated by formation of the double bond phosphorus-oxygen in the phosphine oxide **273**.



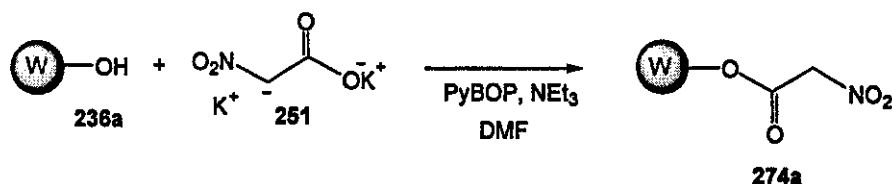
Scheme 42

3.3.4.2 Wang-nitro resin derivatives

3.3.4.2.1 Wang-nitro-acetic acid resin derivative

We thought that using PyBOP would facilitate the coupling of both the dipotassium salt of nitroacetic acid **251** and 2-nitroethanol **237** onto Wang resin **236a**. The reaction would proceed along a similar reaction pathway, with formation of tripyrrolidine phosphine oxide **273** in the last step. Washing the resin thoroughly would remove the by-products formed during the course of the reaction, as well as unreacted reagents. In order to synthesise the Wang resin derivative **274a**, coupling the dipotassium salt **251** onto the resin, in the presence of PyBOP **267**, was carried out as shown in **Equation 32**. The reagents were combined in

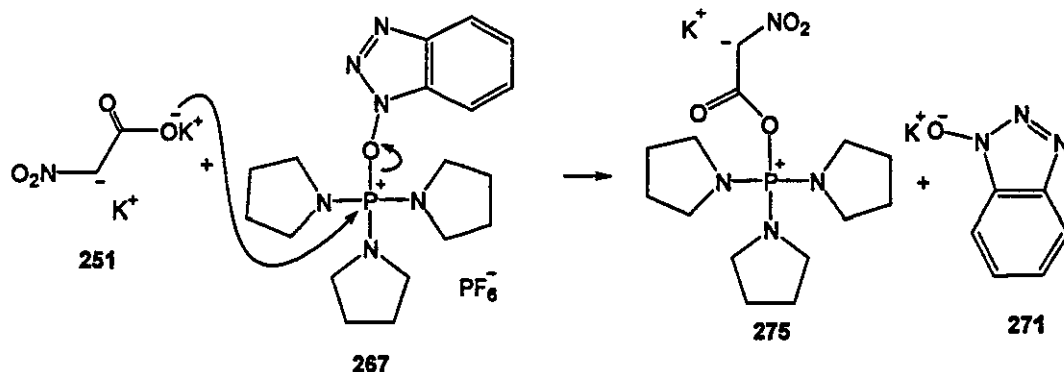
dimethylformamide, and the suspension was shaken for 5 minutes before being left to stand for 2 hours. The unreacted reagents were washed away using dimethylformamide, dichloromethane and methanol.



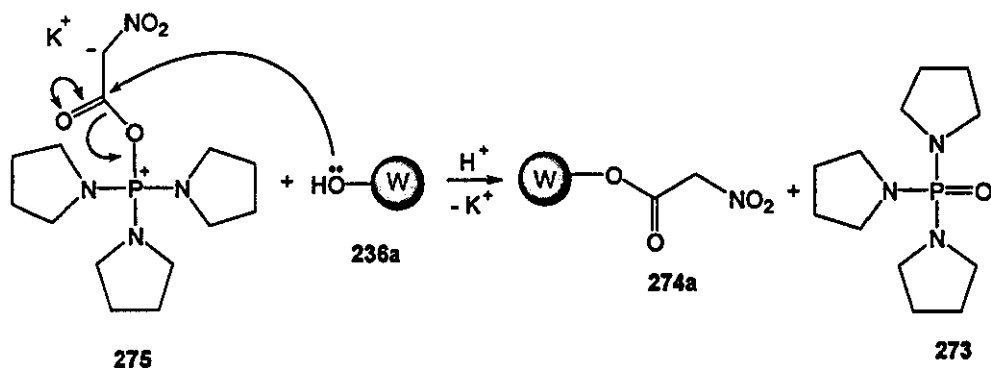
Equation 32

It was quite complicated to interpret the IR spectrum; the two peaks most likely to be due to the stretching of the nitro group, were observed at 1600 and 1330 cm^{-1} . Therefore, we thought that the reaction might have worked to some extent because, although the starting Wang resin showed a peak at 1597 cm^{-1} , no peak around 1330 cm^{-1} was present. The IR spectrum is shown in the appendix.

The mechanism of the reaction is proposed in **Scheme 43** and **Scheme 44**. Initially the compound **275** is formed by attack of the carboxylate anion, of the dipotassium salt **251**, to the phosphonium centre of the PyBOP, with subsequent elimination of potassium benzotriazol-1-olate **271**, as shown in **Scheme 43**. This is followed by attack of the Wang resin **236a** to the activated carbonyl group of compound **275**, with subsequent loss of tripyrrolidine phosphine oxide **273**, to generate the compound **274a**, as shown in **Scheme 44**. The formation of the phosphorus oxygen double bond is the driving force of the reaction.



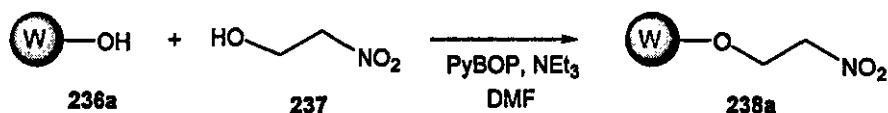
Scheme 43



Scheme 44

3.3.4.2.2 Wang-nitro-ethanol resin derivative

Similar reactions were undertaken using 2-nitroethanol **237** as the nitro group source, in order to synthesise the Wang resin derivative **238a**. Wang resin **236a** and PyBOP were combined in dimethylformamide and after shaking the suspension for 15 minutes, the reaction mixture was treated with 2-nitroethanol and triethylamine, as shown in Equation 33 (Table 2, entry 1). The unreacted reagents were washed away using dimethylformamide, dichloromethane and methanol.



Equation 33

The IR spectrum was difficult to interpret; two peaks at 1602 and 1385 cm⁻¹, could be due to the symmetrical and asymmetrical stretching of the nitro group. The IR spectrum is shown in the appendix.

In order to check if the reaction could be driven to completion, the reaction was repeated shaking the reaction mixture for 1 hour (Table 2, entry 2). No changes were observed in the IR spectrum.

Entry	Conditions	time	Product
1	PyBOP (10 eq.), NEt ₃ (10eq.), 2-nitroethanol (10 eq.), DMF, rt	5 min. ^b , 1 h ^a	238a
2	PyBOP (5 eq.), NEt ₃ (10eq.), 2-nitroethanol (10 eq.), DMF, rt	1 h ^b	238a

^a Standing, ^b Shaking

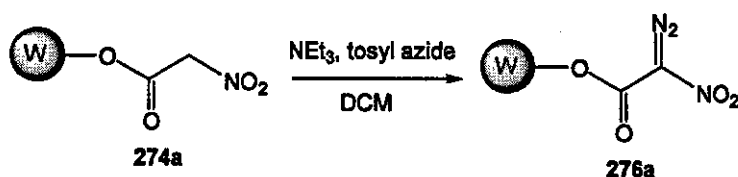
Table 2

In both experiments, the desired product **238a** had been possibly formed to some extent.

3.3.4.3 Synthesis of Wang-nitro-diazo resin derivatives

3.3.4.3.1 Wang-diazo-nitro-acetic acid resin derivative

The next step was the insertion of the diazo group α to the nitro group of the Wang resin derivative **274a**. This reaction was attempted as shown in **Equation 34**. The Wang-nitro-acetic acid resin derivative **274a** was treated with a base in dichloromethane, followed by reaction with *para*-toluenesulfonyl azide (**Table 3**, entry 1). The unreacted reagents were washed away with dichloromethane, methanol and diethyl ether.



Equation 34

The reaction was repeated using different bases (triethylamine or DBU), amounts of reagents and reaction times, as compiled in **Table 3**, entries 2-3.

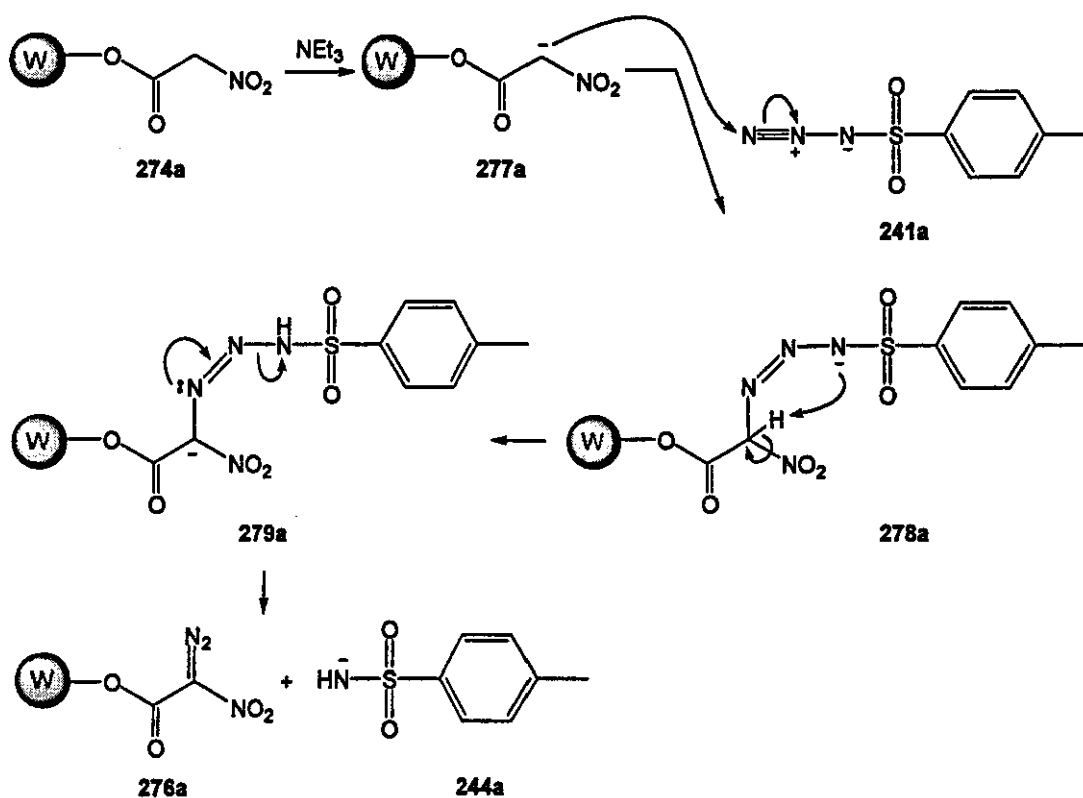
Unfortunately, in all the attempts analysis of the resin by IR spectroscopy did not show the diazo band. Instead, the starting resin **274a** was reisolated.

Entry	Conditions	time	Product
1	NEt ₃ (3 eq.), tosyl azide (3 eq.), DCM, rt	~5 min. ^b , 1 h ^a	s.m. 274a
2	DBU (3 eq.), tosyl azide (3 eq.), DCM, rt	~5 min. ^b , 2 h ^a	s.m. 274a
3	NEt ₃ (10 eq.), tosyl azide (10 eq.), DCM, rt	~5 min. ^b , 2 h ^a	s.m. 274a

^a Standing, ^b Shaking

Table 3

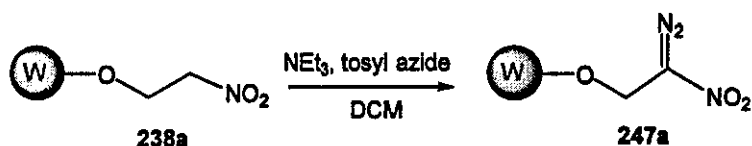
The mechanism of the proposed reaction is shown in **Scheme 45**. Deprotonation of the position α to the nitro group with triethylamine to give the nitro compound **277a**, followed by reaction with *para*-toluenesulfonyl azide **141a**, afforded the nitro diazo compound **276a** and the sulfonamide **244a**.



Scheme 45

3.3.4.3.2 Wang-2-diazo-2-nitro-ethanol resin derivative

The synthesis of diazo nitro compound **247a** was attempted as follows. The Wang-2-nitro-ethanol resin derivative **238a** was treated with triethylamine in dichloromethane, followed by reaction with *para*-toluenesulfonyl azide **241a**, as shown in Equation 35. The unreacted reagents were washed away with dichloromethane, methanol and diethyl ether.



Equation 35

Again, no signs of the characteristic band correspondent to the stretching of the diazo group ($\sim 2100\text{ cm}^{-1}$) were observed in the IR spectrum. Instead, the starting resin **238a** was reisolated.

A similar mechanism to that proposed in the Scheme 45 could be proposed for this reaction.

3.3.4.4 Visual test for detection of hydroxyl groups on resin

Taddei *et al.*¹⁸⁶ have reported a method to determine the presence of an OH group on a resin. They used this test in order to detect primary, secondary and tertiary hydroxyl groups present in several compounds linked either to Wang or trityl resins. The molecules that were tested are shown in Figure 31.

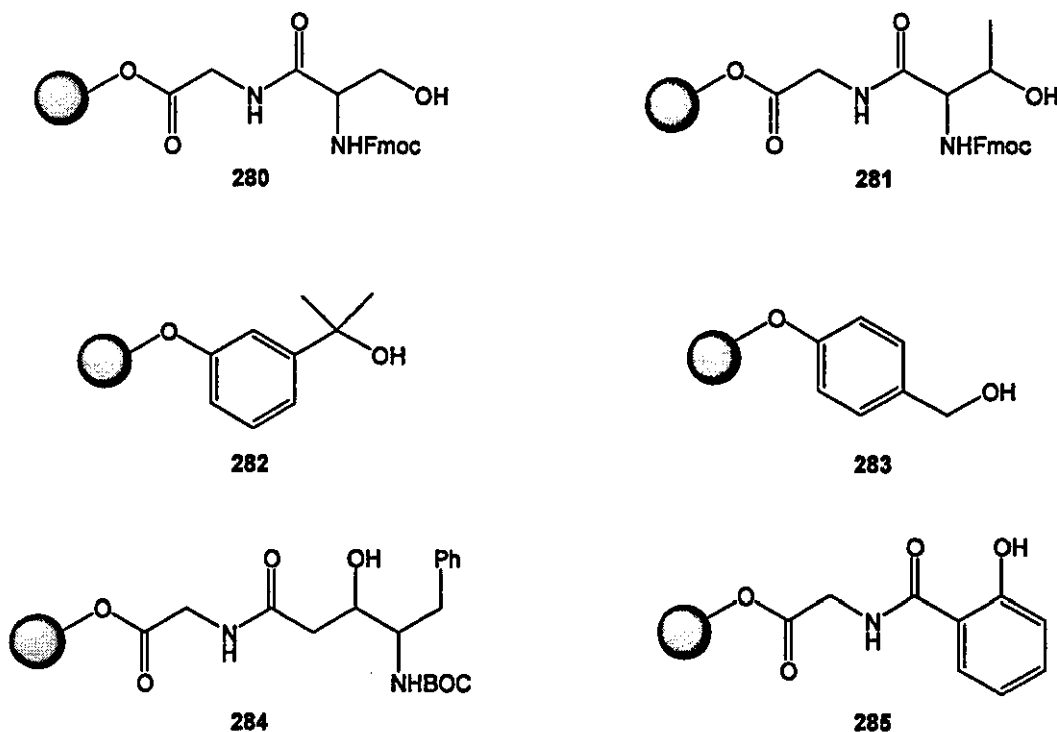
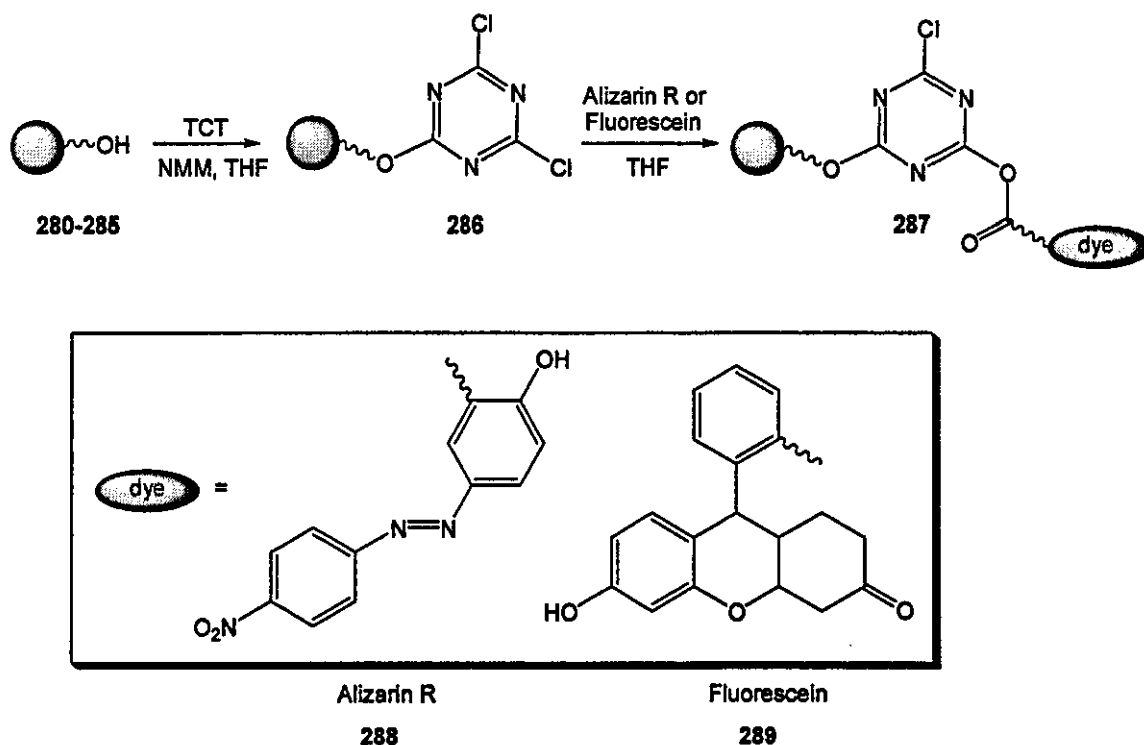


Figure 31

As it is shown in Scheme 46, the test consists of the addition of a chlorotriazine (such as 2,4,6-trichloro-(1,3,5)-triazine (TCT)) that, as it is known, in the presence of a base (such as *N*-methylmorpholine (NMM)) reacts selectively with free hydroxyl groups present on the resin beads 280-285, in order to give 2-alkoxy-4,6-dichloro-(1,3,5)-triazine 286.¹⁸⁷ If this compound was formed, it would react with a carboxylic acid dye, such as Alizarin R 288 or Fluorescein 289 (as the sodium salt) in order to afford the compound 287, changing the colour of the beads into red or yellow-green respectively.¹⁸⁸



Scheme 46

We thought we could also use this test, but instead of for detection of OH groups in the beads of the products, we would look for their disappearance in the products derivatised from Wang resin (such as **238a** and **274a**); therefore, if this colorimetric test of detection of hydroxyl groups gave a positive result when carried out with the beads of our Wang derivatised resins, it would mean that no reaction took place in those beads, since the presence of OH groups shows the starting Wang resin.

To carry out this test, a few beads of the derivatised Wang resins **238a** and **274a** were placed in a test tube and reacted with 2,4,6-trichloro-(1,3,5)-triazine and *N*-methyl morpholine in tetrahydrofuran. After 10 minutes the beads were washed several times with dimethylformamide and tetrahydrofuran. The beads were then suspended in tetrahydrofuran and reacted with Alizarin R **288** or fluorescein **289**, in the presence of *N*-methyl morpholine. A few minutes later, the beads were rinsed several times with dimethylformamide until the solution was no longer coloured. The result of the test suggested that the hydroxyl groups were not present, due to the fact that the beads did not change colour.

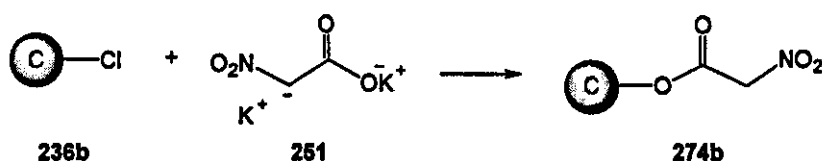
The same test was also carried out using the starting Wang resin, in order to be able to compare the beads obtained from the previous test with these positive beads.

3.3.5 Synthesis of 2-chlorotrityl resin derivatives

3.3.5.1 Synthesis of 2-chlorotrityl-nitro resin derivatives

3.3.5.1.1 2-Chlorotrityl-nitro-acetic acid resin derivative

We now turned our attention to the use of 2-chlorotrityl chloride resin **236b**. Coupling the dipotassium salt **251** onto the 2-chlorotrityl chloride resin, was carried out as shown in Equation 36. 2-Chlorotrityl chloride resin was reacted with the dipotassium salt in dimethylformamide (Table 4, entry 1).



Equation 36

The IR spectrum, which is shown in the appendix, showed a band at 1591 cm⁻¹ and a peak at 1330 cm⁻¹, likely to be due to the symmetric and asymmetric stretching of the nitro group. The carbonyl peak was not observed by IR spectroscopy of the product, possibly because it was obscured by the 1591 cm⁻¹ band. In the IR spectrum of the starting 2-chlorotrityl-chloride resin, two peaks very close to the ones thought to be due to the nitro stretching were also present, at 1597 and 1322 cm⁻¹, but the latter one was much more intensified in the IR spectrum of the product. Therefore, the reaction had probably worked to some extent.

In order to check if the reaction could be taken to completion, the reaction was repeated using larger amount of the dipotassium salt, dimethylformamide and dimethylsulfoxide as solvents, and longer reaction times, as compiled in Table 4.

In both reactions, the IR spectrum showed two peaks at 1600 and 1334 cm^{-1} , likely to correspond to the stretching of the nitro group, although they were not as intense as the ones observed before. Therefore, the reaction had probably worked to a lesser extent.

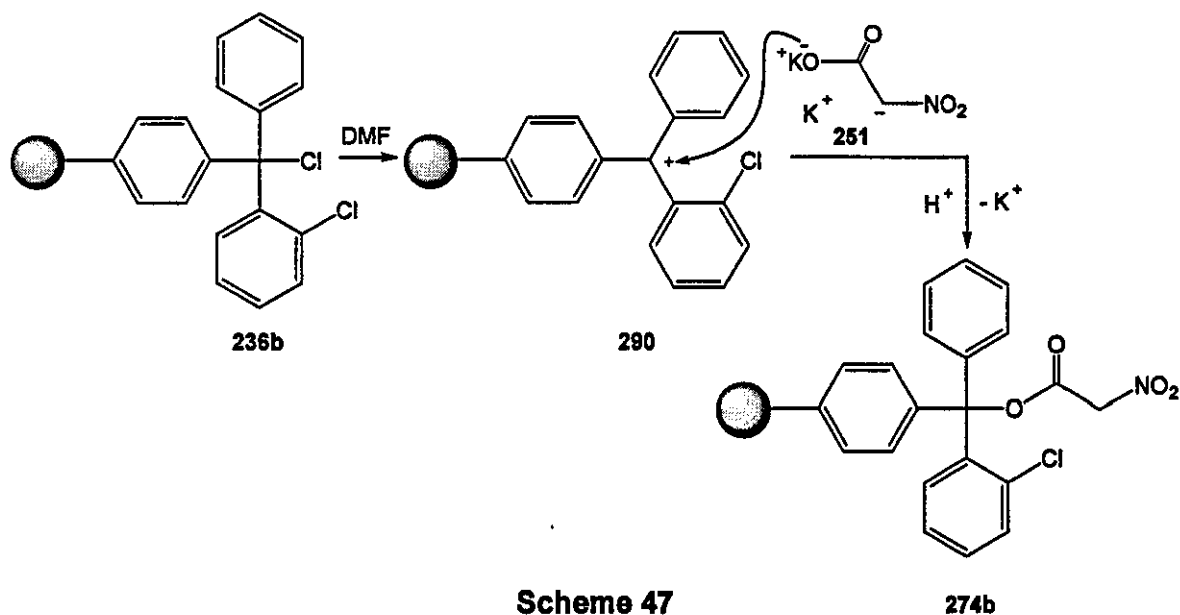
The reaction was also carried out using a smaller amount of the dipotassium salt, dimethylformamide as solvent, and increasing the reaction time up to two days (Table 4, entries 2-4), but no improvements were observed by the IR spectrum.

Entry	Conditions	time	Product
1	dipotassium salt (10 eq.), DMF, rt	~5 min. ^b , 2 h ^a	274b
2	dipotassium salt (20 eq.), DMF, rt	O/N ^b	274b
3	dipotassium salt (20 eq.), DMSO, rt	O/N ^b	274b
4	dipotassium salt (5 eq.), DMF, rt	2 days ^b	274b

^a Standing, ^b Shaking

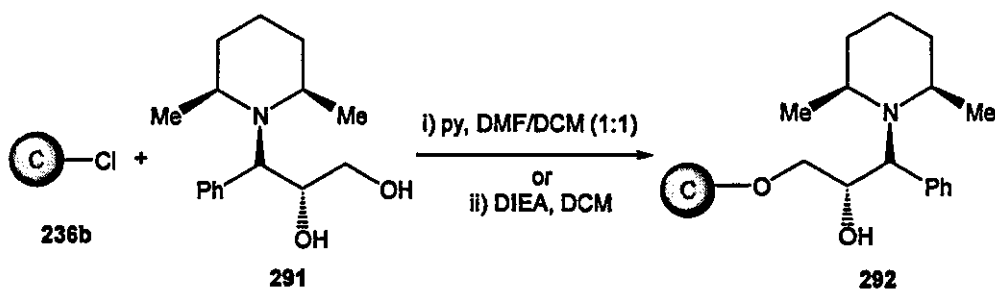
Table 4

The mechanism of the reaction is proposed in **Scheme 47**. Initially, when the resin is swollen in dimethylformamide the carbocation **290** is formed by a SN_1 reaction, facilitating the subsequent attack of the dipotassium salt to afford the nitroethanoate derivative **274b**.



3.3.5.1.2 2-Chlorotrityl-nitro-ethanol resin derivative

In 1998, Pericàs *et al.*¹⁸⁹ reported a method for anchoring the amino alcohol 291 to 2-chlorotrityl chloride resin 236b using two different reaction conditions, as shown in Equation 37.



Equation 37

We thought that this methodology could be followed in order to synthesise our desired resin derivative 238b. Therefore, following the procedure given by Pericàs *et al.*, 2-chlorotrityl chloride resin 236b was reacted with 2-nitroethanol 237 and pyridine in a mixture of anhydrous dimethylformamide: dichloromethane, as shown in Equation 38 (Table 5, entry 1). The unreacted reagents were washed away using dimethylformamide, dichloromethane, methanol and diethyl ether.



Equation 38

The IR spectrum, shown in the appendix, was difficult to interpret. It showed two peaks at 1600 and 1331 cm^{-1} , which could be due to the stretching of the nitro group, but these peaks were also present in the starting 2-chlorotrityl-chloride resin. We were unsure whether this reaction had worked or not. This resin was used for the next reactions, so that if formation of the product **247b** was observed it would confirm that the reaction to obtain the compound **238b** had worked to some extent.

The same reaction was carried out using different bases (such as triethylamine and sodium hydride), solvents (dimethylformamide and dimethylsulfoxide) and different amounts of reagents, as compiled in **Table 5**, entries 2-5, but we were not sure if the reactions had taken place since all the IR spectra obtained were very similar to the starting resin **236b**.

Entry	Conditions	time	Product
1	py (5.9 eq.), 2-nitroethanol (2.7 eq.), DCM:DMF (1:1), rt	3 days ^b	238b
2	NEt ₃ (10 eq.), 2-nitroethanol (10 eq.), DMF, rt	~5 min. ^b , 1 h ^a	?
3	NEt ₃ (10 eq.), 2-nitroethanol (10 eq.), DMF, rt	1 h ^b	?
4	NaH (25 eq.), 2-nitroethanol (21 eq.), DMF, rt	O/N ^b	?
5	NaH (25 eq.), 2-nitroethanol (21 eq.), DMSO, rt	O/N ^b	?

^a Standing, ^b Shaking

Table 5

A similar mechanism to that proposed in the **Scheme 47** could be proposed for this reaction.

3.3.5.2 Synthesis of 2-chlorotrityl-diazo-nitro resin derivatives

3.3.5.2.1 2-Chlorotrityl-diazo-nitro-acetic acid resin derivative

2-Chlorotrityl-nitro-acetic acid resin derivative **274b** was treated with DBU in dichloromethane, and then reacted with *para*-toluenesulfonyl azide, as shown in **Equation 39** (**Table 6**, entry 1). The unreacted reagents were washed away with dichloromethane, methanol and diethyl ether.



Equation 39

A small band at 2103 cm^{-1} was observed in the IR spectrum, therefore we thought the reaction might have worked to a small extent. The IR spectrum is shown in the appendix.

The reaction was carried out using different amounts of reagents and different bases (triethylamine and DBU), as compiled in **Table 6**, entries 2-4, but no signs of the product **276b** being formed were observed.

Entry	Conditions	time	Product
1	DBU (5 eq.), tosyl azide (5 eq.), DCM, rt	1 day ^b	276b
2	NEt ₃ (3 eq.), tosyl azide (3 eq.), DCM, rt	~5 min. ^b , 1 h ^a	s.m. 274b
3	DBU (3 eq.), tosyl azide (3 eq.), DCM, rt	~5 min. ^b , 2 h ^a	s.m. 274b
4	NEt ₃ (5 eq.), tosyl azide (5 eq.), DCM, rt	~5 min. ^b , 2 h ^a	s.m. 274b

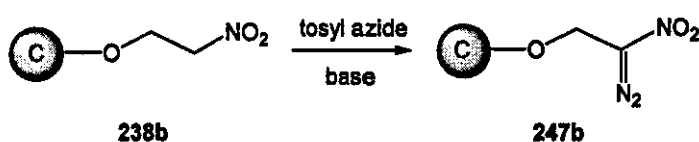
^a Standing, ^b Shaking

Table 6

A similar mechanism to that proposed in the **Scheme 45** could be proposed for this reaction.

3.3.5.2.2 2-Chlorotrityl-2-nitro-ethanol resin derivative

2-Chlorotrityl-2-nitro-ethanol resin derivative **238b** was treated with DBU in dichloromethane, followed by reaction with *para*-toluenesulfonyl azide, as shown in **Equation 40**. The unreacted reagents were washed away with dichloromethane, methanol and diethyl ether.



Equation 40

The IR spectrum, which is shown in the appendix, showed a small band at 2104 cm^{-1} . We thought that the reaction had probably worked to a small extent.

The same reaction was carried out using triethylamine and bigger excesses of the reagents (**Table 7**, entry 2), but no sign of the characteristic band of the diazo group could be observed in the IR spectrum.

Entry	Conditions	time	Product
1	DBU (5 eq.), tosyl azide (5 eq.), DCM, rt	1 day ^b	247b
2	NEt ₃ (10 eq.), tosyl azide (10 eq.), DCM, rt	1h ^b	s.m. 238b

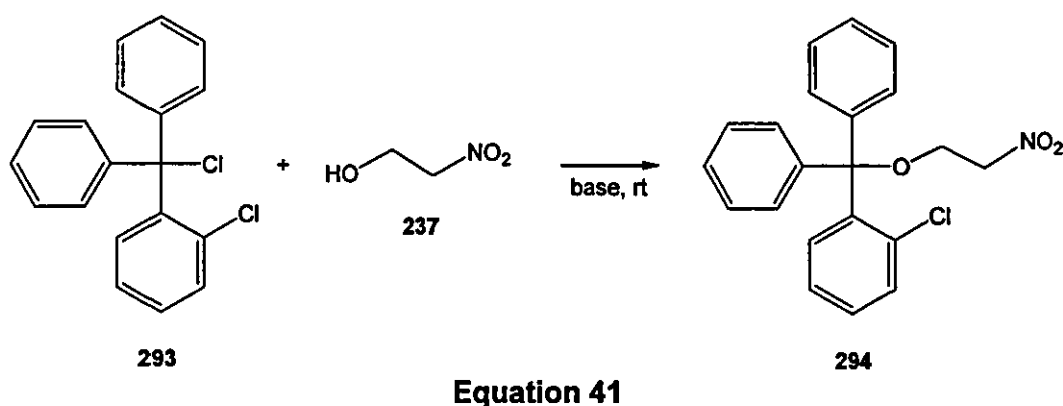
^a Standing, ^b Shaking

Table 7

A similar mechanism to that proposed in the **Scheme 45** could be proposed for this reaction.

3.3.6 Experiments in solution phase

We decided to attempt the coupling reaction of 2-nitroethanol **237** onto 2-chlorotrityl chloride **293** in solution phase using the conditions reported by Pericàs *et al.*¹⁸⁹ for solid phase. 2-Chlorotrityl chloride and 2-nitroethanol were reacted in dry dichloromethane and treated with Hünig's base at room temperature, as shown in **Equation 41**. Silica gel flash chromatography did not furnish the desired product **294**. Instead, the ¹H NMR spectrum showed that 2-chlorotrityl chloride had been reisolated, and the mass spectrum showed a peak at 277 m/z, probably due to the chlorotrityl chloride cation.



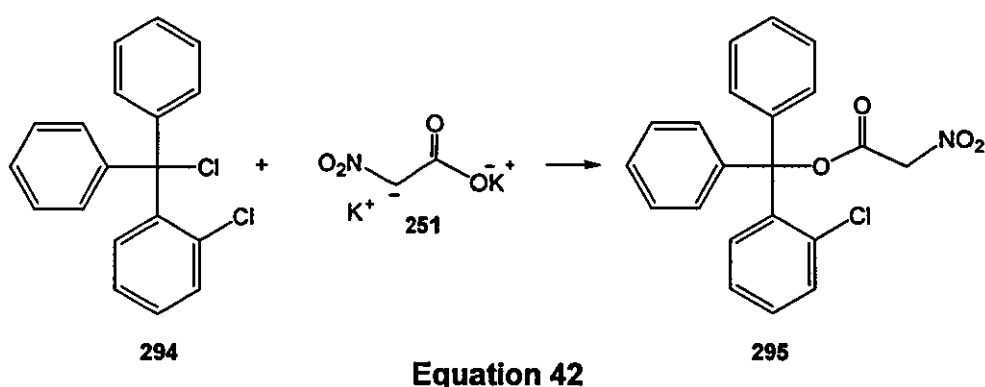
The same reaction was attempted using pyridine as the base and a mixture of dichloromethane:dimethylformamide as the solvent (**Table 8**, entry 2), but unfortunately the product could not be isolated.

Entry	Conditions	time	Yield (%)
1	DIEA (2.1 eq.), 2-nitroethanol (1.4 eq.), DCM, rt	O/N	s.m. 293
2	py (5.9 eq.), 2-nitroethanol (2.7 eq.), DCM:DMF (1:1), rt	O/N	s. m. 293

Table 8

We also attempted coupling the dipotassium salt of nitroacetic acid **251** onto 2-chlorotrityl chloride **294**. 2-Chlorotrityl chloride was reacted with dipotassium salt

of nitroacetic acid in dimethylformamide, as shown in **Equation 42** (**Table 9**, entry 1). A complex mixture was recovered, and isolation of the desired compound **295** was not possible.



The same reaction was attempted using a larger excess of the dipotassium salt, (**Table 9**, entry 2), but unfortunately the product could not be isolated.

Entry	Conditions	time	Yield (%)
1	dipotassium salt (1 eq.), DMF, rt	O/N	complex mixture
2	dipotassium salt (5 eq.), DMF, rt	O/N	complex mixture

Table 9

3.4 Conclusion

Work has been carried out in the attempt to synthesise resin bound nitro substituted cyclopropanes/enes **249** and **250**. We thought that these could be synthesised *via* the derivatisation of Wang **236a** or 2-chlorotrityl chloride **236b** resins with a nitromethylene group followed by insertion of diazo functionality. Treatment with a suitable catalyst in the presence of an alkene or alkyne would give the resin bound nitrocyclopropane/ene.

Initially we carried out a model study to investigate whether infrared spectroscopy would be an effective technique for analysis of the resin derivatives. Reaction of Wang resin with diketene **263** in the presence of LDA afforded the resin derivative **264**. Insertion of a diazo group using *para*-toluenesulfonyl azide **241a** and

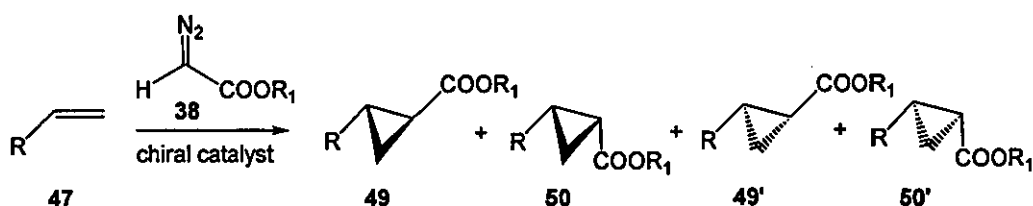
triethylamine gave the α -diazo dicarbonyl compound **265**, which was detectable by IR spectroscopy. We subsequently reacted Wang and 2-chlorotrityl resins with the dipotassium salt of nitroacetic acid **251** and 2-nitroethanol **237**. IR spectroscopy was difficult to interpret, although it suggested that the reactions had worked to some degree due to the observation of the corresponding nitro groups.

The insertion of the diazo group was less successful, with a reaction possibly occurring only in the cases where the 2-chlorotrityl resin derivatives **247b** and **276b** were obtained from reaction of the corresponding 2-chlorotrityl resin derivatives **238b** or **274b**, respectively, with *para*-toluenesulfonyl azide in the presence of DBU.

CHAPTER 4: Synthesis of Phosphorus Ligands

4.1 Introduction

As discussed in the introduction, several chiral tetrasubstituted rhodium (II) catalysts have been developed in order to synthesise enantiomerically pure cyclopropanes, as shown in Equation 43.



Equation 43

Our aim was to develop new chiral catalysts for the synthesis of enantiomerically pure cyclopropanes, and for that purpose, we proposed the synthesis of the catalyst 296, shown in Figure 32. This catalyst is composed of four phosphorus containing chiral ligands 297 complexed to two rhodium atoms.

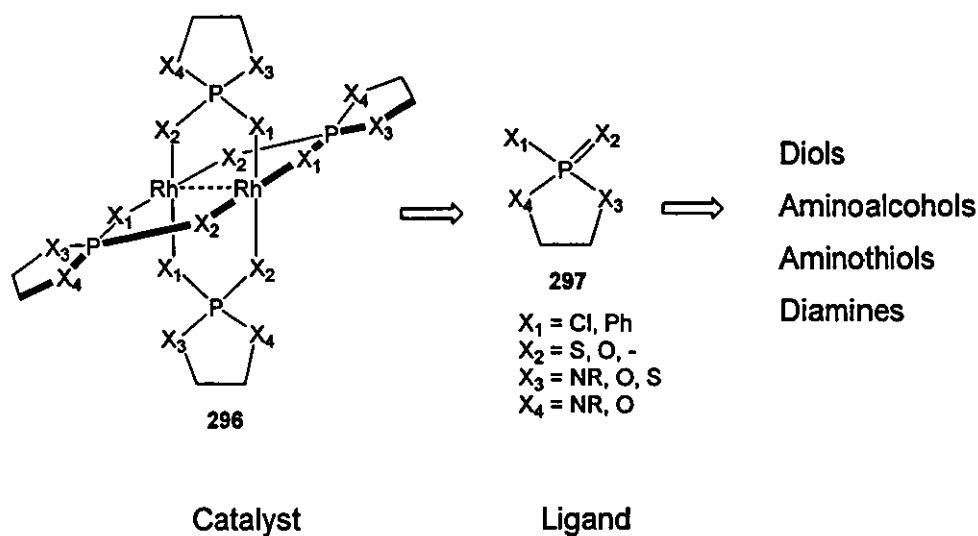
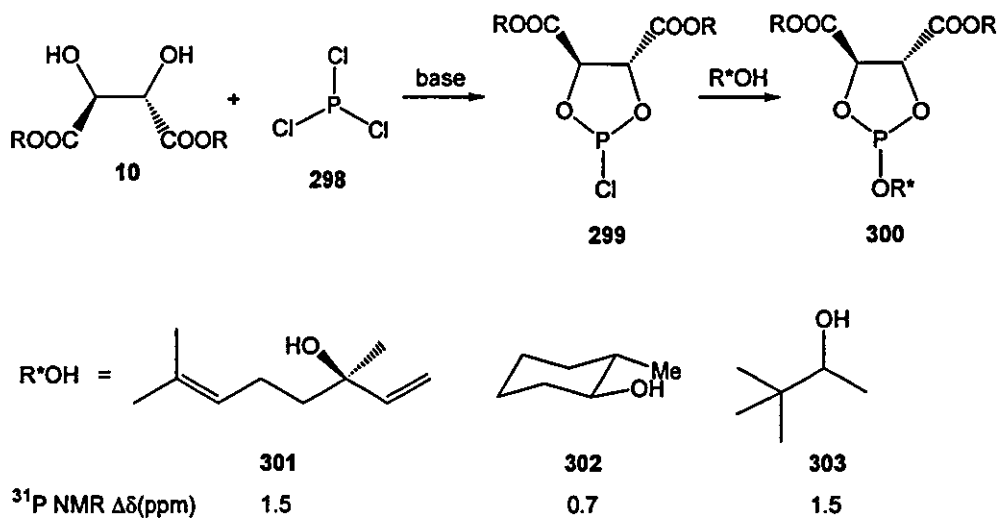


Figure 32

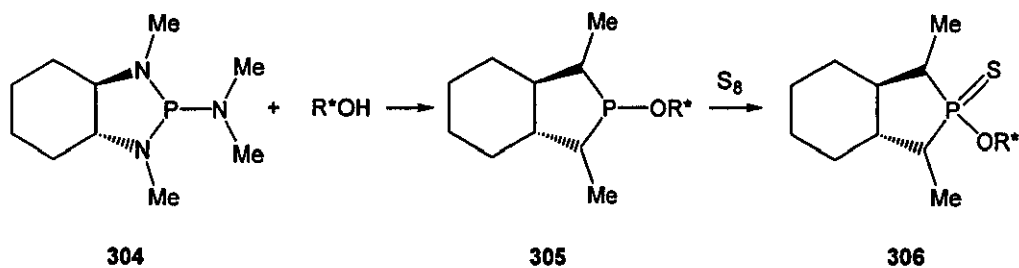
The synthesis of several phosphorus containing ligands was required in order to form several chiral catalysts. Several chiral phosphorus containing compounds

with a similar structure to the ligands **297** that we were interested in, have been developed in order to determine enantiomeric compositions. **Scheme 48** shows an example of how enantiomeric purity of alcohols can be determined using ^{31}P NMR spectroscopy.¹⁹⁰ Some racemic alcohols, such as **301**, **302** and **303**, were reacted with the compound **299**, and the diastereomeric pairs of the derivative obtained **300**, exhibited clear differences in their ^{31}P NMR spectra, and their enantiomeric composition was easily measured.



Scheme 48

More examples of efficient reagents that can be used as chiral derivatizing agents for determining the enantiomeric composition of chiral alcohols using the ^{31}P NMR method are shown in **Scheme 49** and **Figure 33**.¹⁹¹



Scheme 49

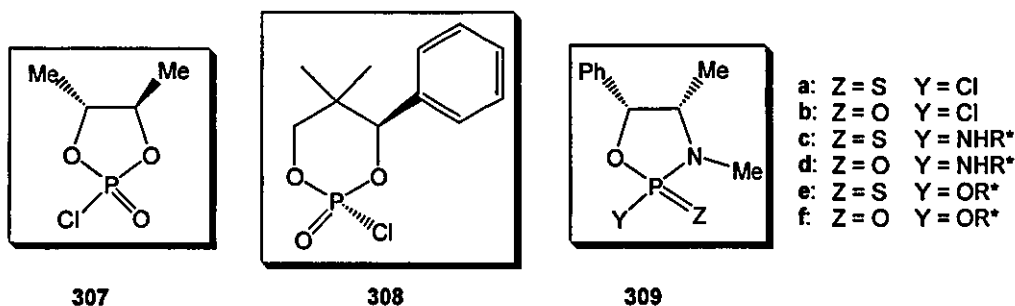
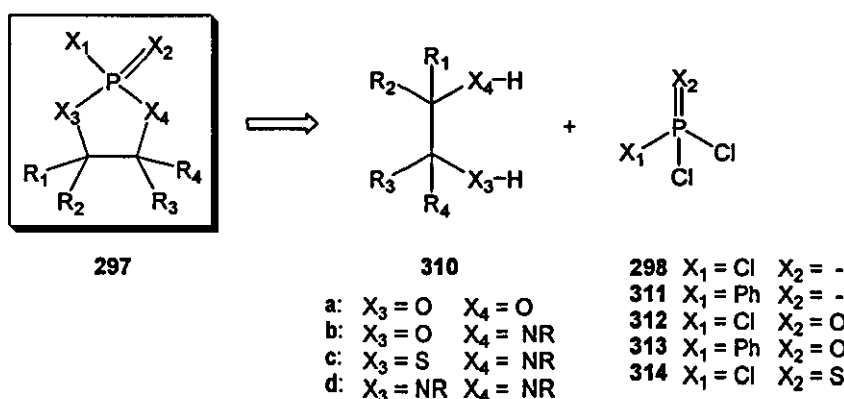


Figure 33

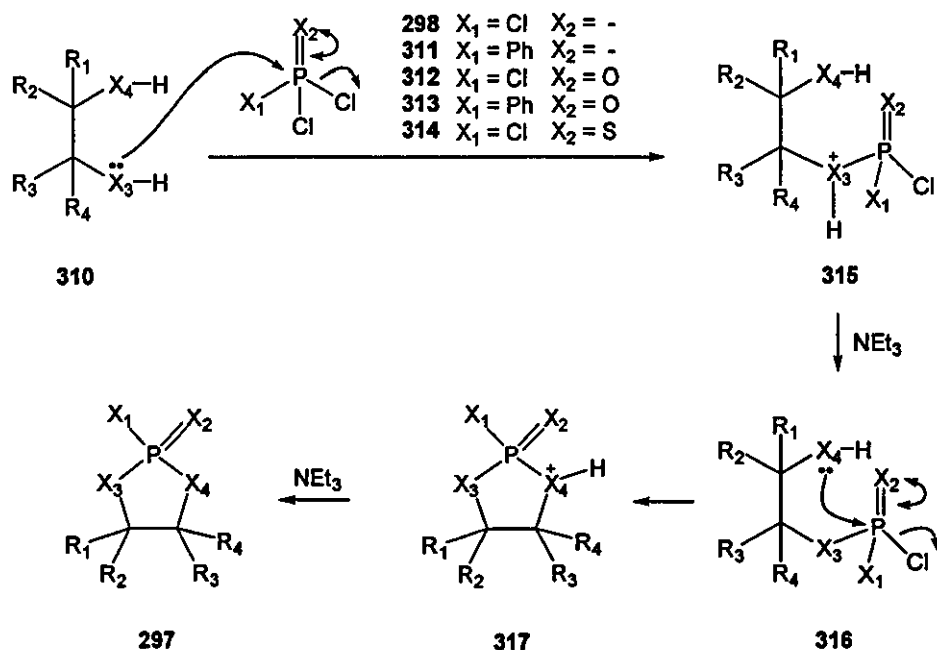
In the ligand **297**, the phosphorus can be in oxidation state (III) or (V), as shown in **Scheme 50**. We anticipated that the synthesis of our ligands could be achieved by reaction of diols **310a** (such as L-(+)-diethyl tartrate **10a** and (R)-1,1'-bi(2-naphthol) **318**), aminoalcohols **310b** (such as S-(+)-prolinol **336** and L-(+)-serine benzyl ester hydrochloride **340**), aminothiols **310c** (such as L-(+)-cysteine **343**) or diamines **310d** (such as our synthesized chiral diamines, **346**, **348** and **350**, as shown in chapter 5) with several phosphorus containing compounds, such as phosphorus trichloride **298**, dichlorophenyl phosphine **311**, phosphorus oxychloride **312**, phenylphosphonic dichloride **313** and thiophosphoryl chloride **314**, as shown in **Scheme 50**.



Scheme 50

A general mechanism for these reactions is shown in **Scheme 51**. Initially, an alcohol/amine/thiol group of the starting material **310** (X₃) attacks at the

phosphorus centre in order to generate the cation **315**, which is deprotonated in the presence of an equivalent of base, such as triethylamine, in order to generate the intermediate compound **316**. Then, another alcohol/amine group of the compound **316** (X_4) can attack the phosphorus centre generating the cation **317**, which again, can be deprotonated in order to generate the desired compound **297**.

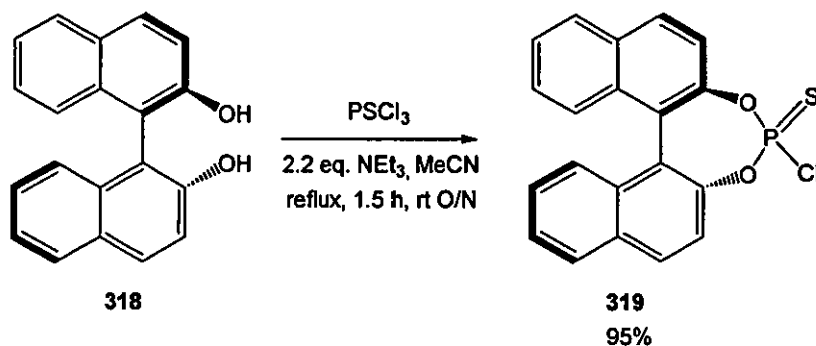


Scheme 51

4.2 Synthesis of phosphorus ligands derived from diols

4.2.1 Synthesis of (R)-4-chloro-3,5-dioxa-4-phospha-cyclohepta[2,1- α ;3,4- α']dinaphthalene-4-sulfide

(R)-(+)-1,1'-bi(2-naphthol) **318** was reacted with thiophosphoryl chloride **314**, in the presence of triethylamine, in anhydrous acetonitrile, as shown in the **Equation 44**. The desired product was obtained in excellent yield, and a portion was purified by recrystallisation from dichloromethane and hexane.

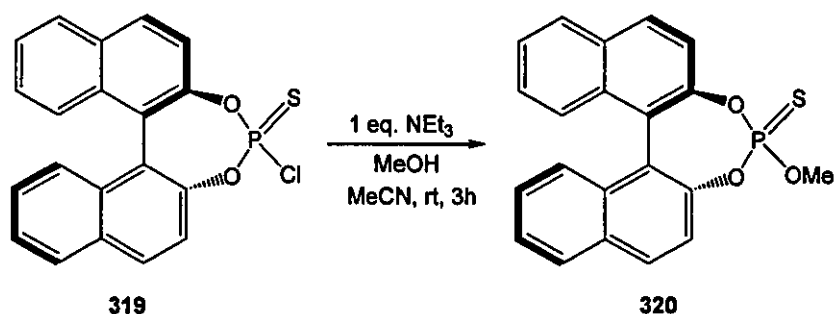


Equation 44

Analysis by IR spectroscopy showed a peak at 734 cm^{-1} , probably due to the $\text{P}=\text{S}$ stretching, two peaks at 1217 and 1188 cm^{-1} , probably due to the stretching of both P-OAr , and a peak at 957 cm^{-1} , possibly due to the P-Cl stretching. The ^{31}P NMR spectrum showed a peak at 74 ppm , and two small ones at 67 and 53 ppm .

4.2.2 Attempted synthesis of (R)-4-methoxy-3,5-dioxa-4-phosphacyclohepta[2,1- α ;3,4- α']dinaphthalene-4-sulfide

The synthesis of compound **320** was attempted by reacting the compound **319** with methanol and triethylamine in acetonitrile, as shown in the Equation 45.

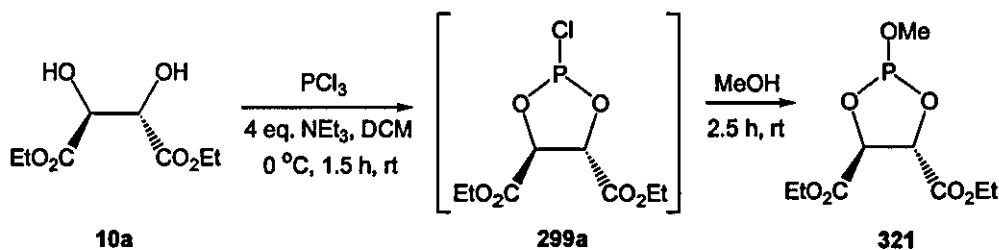


Equation 45

Unfortunately, mass and IR spectroscopy showed that the desired compound was not formed and starting material, compound **319**, was recovered.

4.2.3 Attempted synthesis of (4S,5S)-2-methoxy-[1,3,2]-dioxaphospholane-4,5-dicarboxylic acid diethyl ester

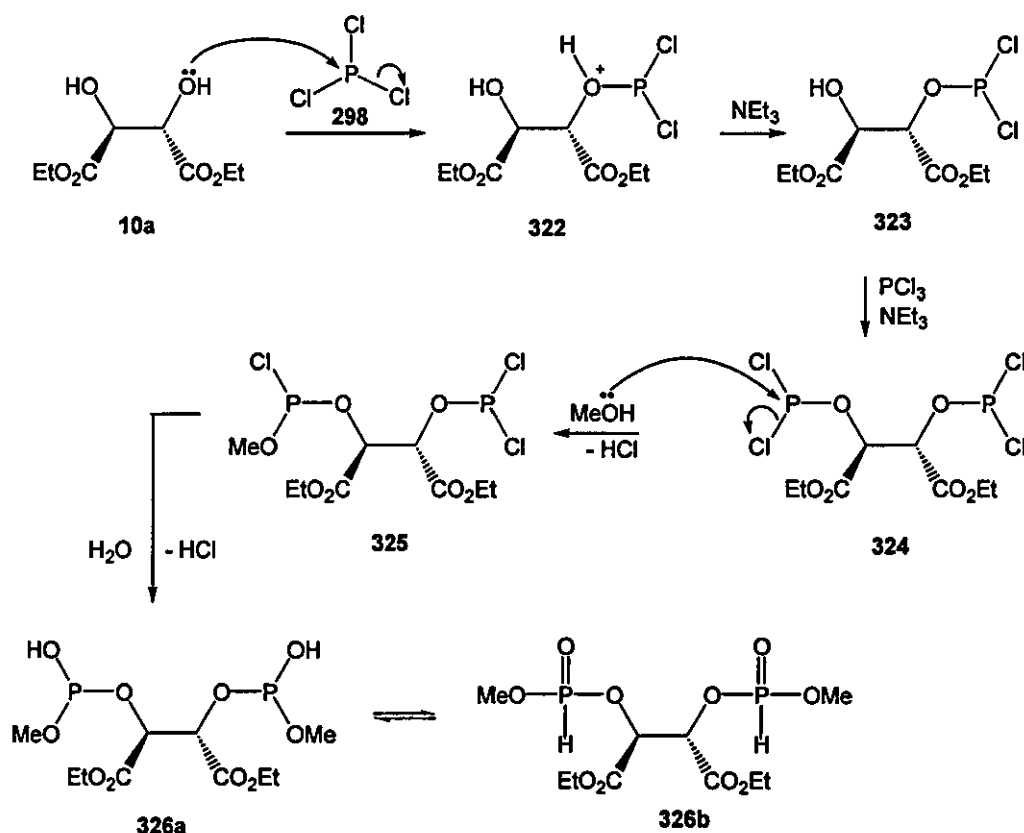
L-(+)-diethyl tartrate **10a** was reacted with phosphorus trichloride **298**, in the presence of triethylamine, in dichloromethane, in order to synthesise the compound **299a**. The reaction mixture was then treated with methanol, as shown in the **Scheme 52**. The desired compound **321** was not isolated.



Scheme 52

According to the spectroscopic data obtained, we thought that instead of the desired product **321**, the ring opened compound **326** (in two tautomeric forms **326a** and **326b**), (2S,3S)-bis-hydroxy-methoxy-phosphanyloxy)-succinic acid diethyl ester, shown in **Scheme 53**, might have been formed in quantitative yield. Analysis by IR spectroscopy showed a band at 3418 cm^{-1} , probably due to the presence of the alcohol groups in the tautomeric form **326a**, a peak at 1745 cm^{-1} possibly due to the stretching of the carbonyl of the ester groups, a peak at 1045 cm^{-1} , probably due to the POCH_2 stretching, a band at 1238 cm^{-1} , possibly due to the O=P-OMe stretching, a peak at 1136 cm^{-1} , probably due to the P=O stretching and a peak at 983 cm^{-1} , probably due to the stretching of the P-O (of the P-OH groups). The ^{31}P NMR spectrum showed a major peak at 11.2 ppm, and a small one at 3.0 ppm. The ^{13}C NMR spectrum was difficult to interpret. The carbonyl carbon was present at 171.5 ppm. The ^1H NMR spectrum showed the P-OMe groups at 3.80 ppm, the P-OH groups at 3.64 ppm and the P-H groups at 8.18 ppm.

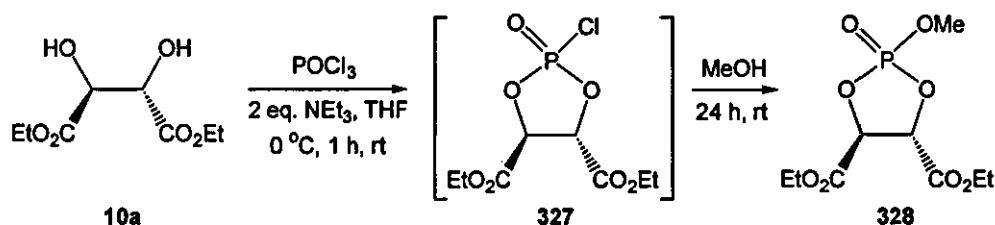
The mechanism shown in **Scheme 53** was proposed.



Scheme 53

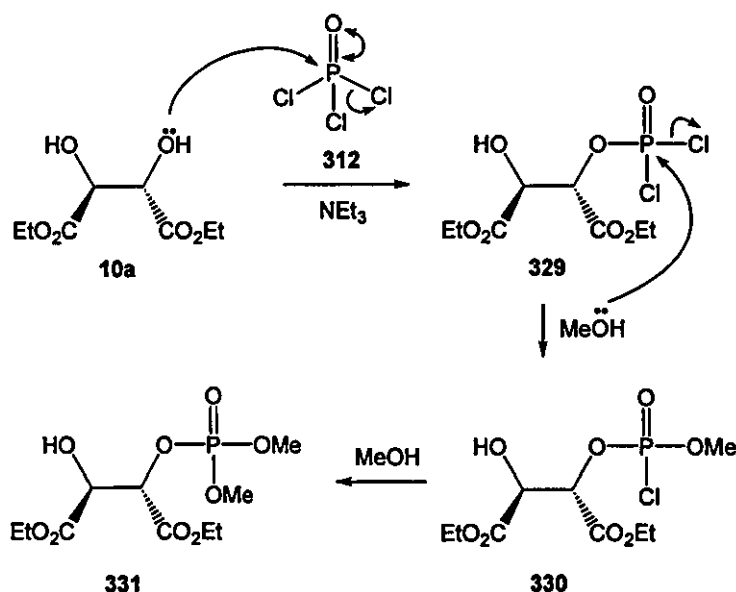
4.2.4 Attempted synthesis of (4S,5S)-2-methoxy-2-oxo-2 λ^5 -[1,3,2]dioxaphos-pholane-4,5-dicarboxylic acid diethyl ester

The synthesis of the compound **328** was attempted by reaction of L-(+)-diethyl tartrate **10a** with phosphorus oxychloride **312**, in the presence of triethylamine, in anhydrous tetrahydrofuran, followed by treatment of the reaction mixture with methanol, as shown in the **Scheme 54**. Silica gel flash chromatography did not furnish the desired compound **328**. Instead analysis by IR and ^1H NMR spectroscopy suggested the ring opened compound **331**, (2S,3S)-2-(dimethoxyphosphoryloxy)-3-hydroxy-succinic acid diethylester, shown in **Scheme 55**, had been formed.



Scheme 54

A mechanism for formation of the compound **331** is proposed in **Scheme 55**.

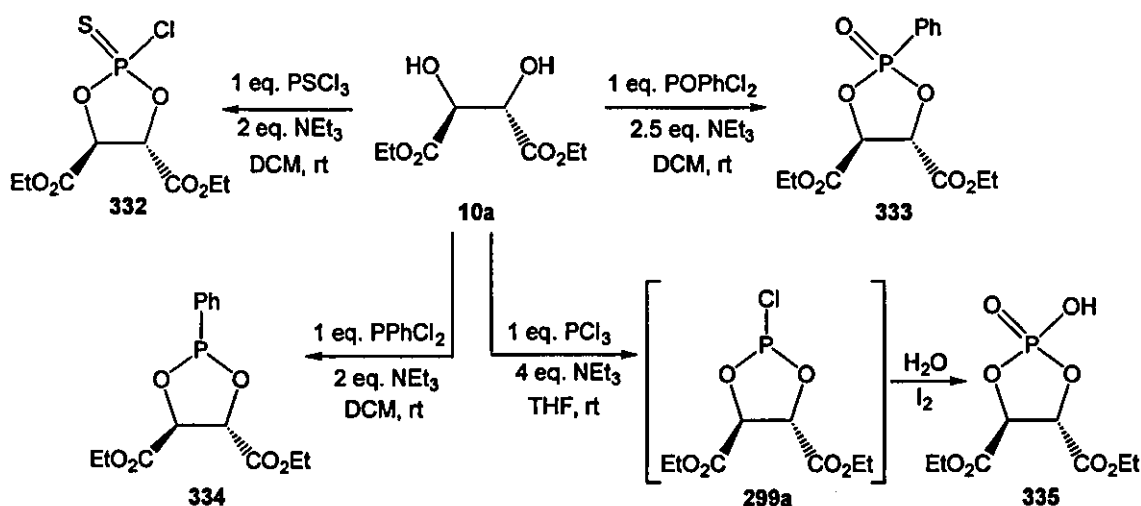


Scheme 55

Analysis by IR spectroscopy showed a band at 3348 cm^{-1} , probably due to the presence of the alcohol group, a peak at 1757 cm^{-1} possibly due to the stretching of the carbonyl of the ester groups, a band at 1048 cm^{-1} , probably due to the POCH_2 and POCH_3 stretchings, a peak at 1139 cm^{-1} , probably due to the $\text{P}=\text{O}$ stretching and a band at 1270 cm^{-1} , possibly due to the $\text{O}=\text{P}-\text{OMe}$ stretching. The ^{31}P NMR spectrum showed a peak at 0.5 ppm. By ^1H NMR spectroscopy, the methoxy groups were observed as doublets at 3.73 and 3.88 ppm, which in the ^{13}C NMR spectrum appeared at 62.3 and 62.6 ppm. The carbonyl carbons of the ester groups were present at 160.7 and 170.5 ppm in the ^{13}C NMR spectrum, and the peaks of the methoxy and the CH groups were shown duplicated, probably due to a coupling of these carbons with the phosphorus.

4.2.5 Attempted synthesis of other diethyl tartrate derivatives

The syntheses of compounds **332-335** were attempted as shown in **Scheme 56**, but in all the cases complex mixtures were obtained, and the desired compounds were not isolated.

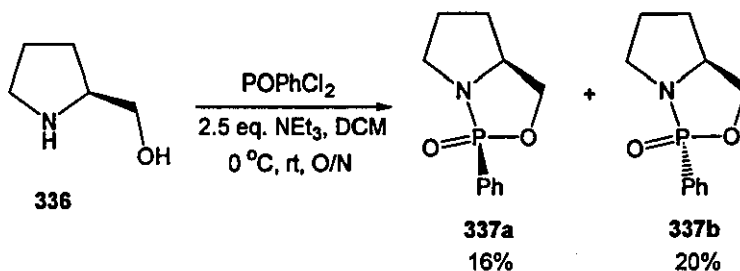


Scheme 56

4.3 Synthesis of phosphorus ligands derived from amino-alcohols

4.3.1 Synthesis of (6a*S*)-1-phenyl-tetrahydro-pyrrolo[1,2-*c*][1,3,2]oxazaphosphole-1-oxide

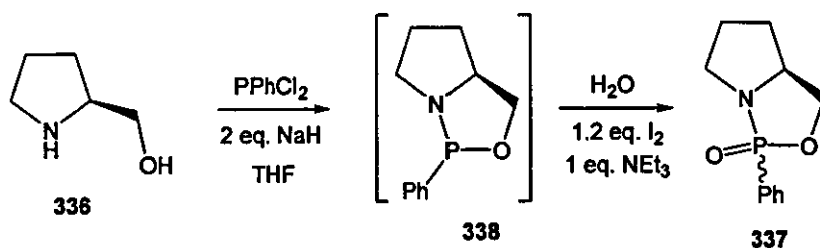
Following the procedure reported by Wills *et al.*,¹⁹² (*S*)-(+)-prolinol **336** was reacted with phenylphosphonic dichloride **313**, in the presence of triethylamine, in dichloromethane, as shown in the **Equation 46**. Both diastereomers, **337a** and **337b**,^{192,193} were separated by silica gel flash chromatography in low yields.



Equation 46

Analysis by IR spectroscopy showed a peak at 1234 cm^{-1} for the compound **337a**, and at 1242 cm^{-1} for the compound **337b**, probably due to the P=O stretching, a peak shown at 1437 cm^{-1} for the compound **337a**, and at 1438 cm^{-1} for the compound **337b**, were probably due to the P-Ph stretching, and a peak at 1007 cm^{-1} for the compound **337a**, and at 1013 cm^{-1} for the compound **337b**, were possibly due to the POCH₂ stretching. The ³¹P NMR spectrum showed a peak at 39 ppm for the compound **337a**, and at 34 ppm for the compound **337b**.

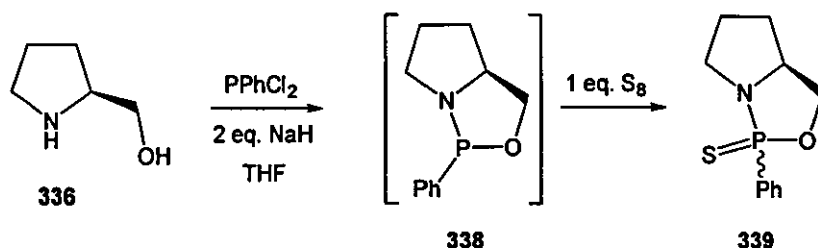
The synthesis of compound **337** was also attempted by reacting (S)-(+)-prolinol **336** with dichlorophenyl phosphine **311**, in the presence of sodium hydride, in order to generate the compound **338** *in situ*, which could be oxidized with iodine in water, in the presence of triethylamine, to afford the desired compound **337**, as shown in **Scheme 57**. A complex mixture was recovered, and isolation of the desired compound **337** was not possible.



Scheme 57

4.3.2 Attempted synthesis of (6aS)-1-phenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxaphosphole-1-sulfide

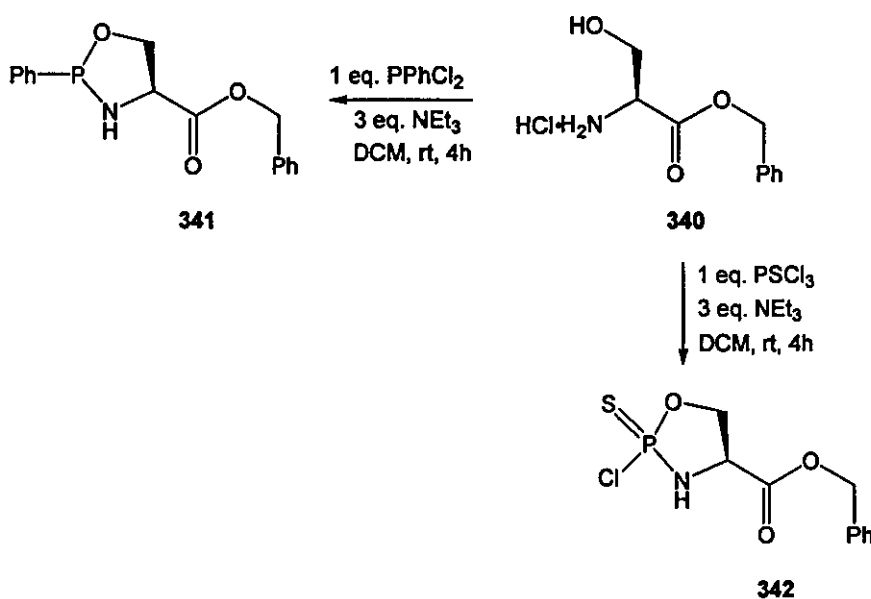
An attempt to synthesise the compound **339** was carried out by reacting (S)-(+)-prolinol **336** with dichlorophenyl phosphine **311**, in the presence of sodium hydride, in order to generate the compound **338** *in situ*, followed by reaction with sulfur, as shown in **Scheme 58**. Unfortunately, the desired compound **339** was not isolated, and a complex mixture was obtained.



Scheme 58

4.3.3 Attempted synthesis of (4S)-2-phenyl-[1,3,2]oxazaphospholidine-4-carboxylic acid benzyl ester **341** and (4S)-2-chloro-thioxo-2 λ^6 -[1,3,2]oxazaphospholidine-4-carboxylic acid benzyl ester **342**

Attempts to synthesise the phosphorus ligands **341** and **342** were carried out by reacting L-(+)-serine benzyl ester hydrochloride **340** with triethylamine and either dichlorophenyl phosphine **311** or thiophosphoryl chloride **314**, in dichloromethane, as shown in **Scheme 59**. An extra equivalent of base was required in order to convert the hydrochloride salt of L-(+)-serine benzyl ester to the free base. Unfortunately, all the attempts gave a complex mixture and the desired products could not be isolated.

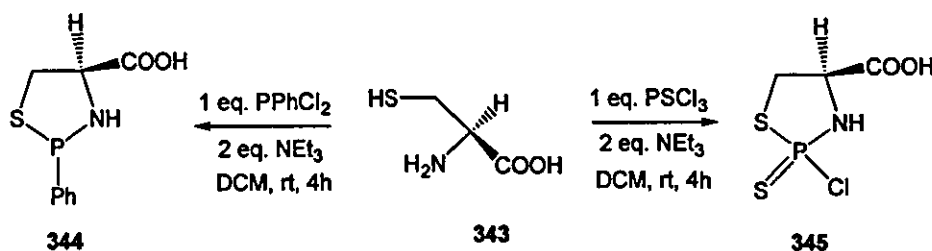


Scheme 59

4.4 Synthesis of phosphorus ligands derived from amino-thiols

4.4.1 Attempted synthesis of (4S)-2-phenyl-[1,3,2]thiazaphospholidine-4-carboxylic acid **344** and (4S)-2-chloro-2-thioxo-2 λ^5 -[1,3,2]thiazaphospholidine-4-carboxylic acid **345**

In order to synthesise the phosphorus ligands **344** and **345**, L-(+)-cysteine **343** was reacted with triethylamine and either dichlorophenyl phosphine **311** or thiophosphoryl chloride **314**, in dichloromethane, as shown in **Scheme 60**. In both attempts a complex mixture was obtained and the desired products could not be isolated.

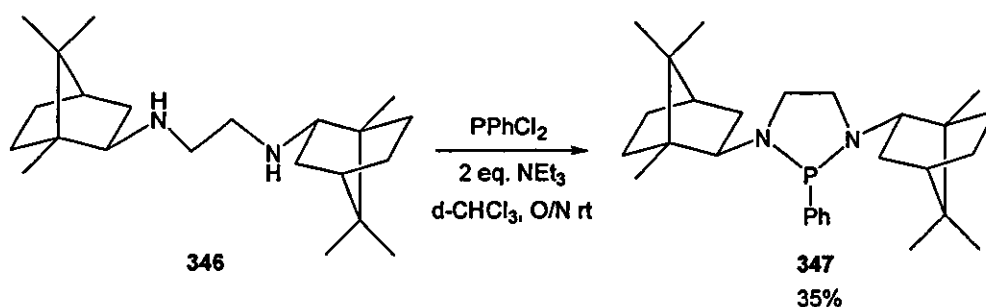


Scheme 60

4.5 Synthesis of phosphorus ligands derived from diamines

4.5.1 Synthesis of 2-phenyl-1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl] [1,3,2]diazaphospholidine

Following the procedure reported by Zuckerman *et al.*,¹⁹⁴ the diamine **346** (for a discussion of the synthesis of **346** see chapter 5) was reacted with freshly distilled dichlorophenyl phosphine **311**, in the presence of triethylamine, in deuterated chloroform, as shown in the **Equation 47**. The reaction was followed by ³¹P NMR spectroscopy in order to check the progress of the reaction. Separation by silica gel flash chromatography afforded the diazaphospholane product **347**, in moderate yield.

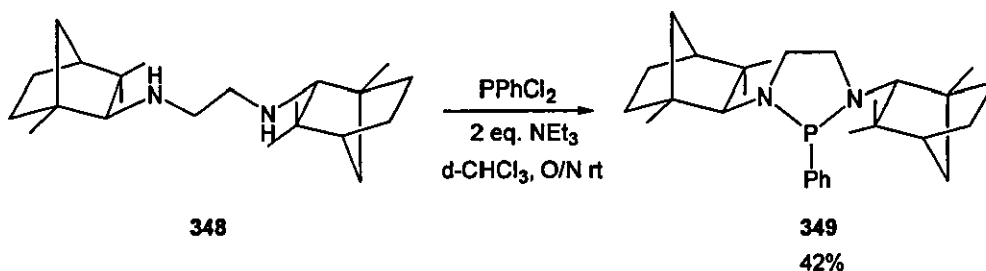


Equation 47

Analysis by IR spectroscopy showed a band at 1453 cm^{-1} , probably due to the P-Ph stretching. The ^{31}P NMR spectrum showed a major peak at 86.6 ppm and two small ones at 94.0 and 97.4 ppm. By ^1H NMR spectroscopy, the methylene groups of the diazaphospholidine ring were possibly the multiplets shown at 3.11-3.19 ppm and 3.31-3.39 ppm, which in the ^{13}C NMR spectrum appeared at 51.1 and 51.2 ppm and at 56.47 and 56.53 ppm. In the ^{13}C NMR spectrum the peaks were shown duplicated, possibly due to the coupling of the phosphorus atom with the carbons.

4.5.2 Synthesis of 2-phenyl-1,3-bis-[(1R,2R,4S)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl] [1,3,2]diazaphospholidine

Following the procedure reported by Zuckerman *et al.*,¹⁹⁴ the diamine **348** (for a discussion of the synthesis of **348** see chapter 5) was reacted with freshly distilled dichlorophenyl phosphine **311**, in the presence of triethylamine, in deuterated chloroform, as shown in the Equation 48. We followed this reaction by ^{31}P NMR spectroscopy to check the progress of the reaction. Separation by silica gel flash chromatography afforded the diazaphospholidine **349** in moderate yield.

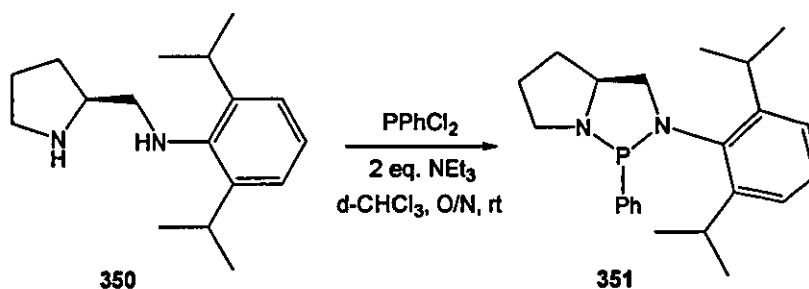


Equation 48

Analysis by IR spectroscopy showed a band at 1459 cm^{-1} , probably due to the P-Ph stretching. The ^{31}P NMR spectrum showed a major peak at 101.3 ppm and two small ones at 94.6 and 95.4 ppm. By ^1H NMR spectroscopy, the methylene groups of the diazaphospholidine ring were possibly the multiplets shown at 3.10-3.17 ppm and 3.20-3.26 ppm, which in the ^{13}C NMR spectrum were present at 50.9 and 51.0 ppm and at 52.46 and 52.52 ppm. In the ^{13}C NMR spectrum the peaks were shown duplicated, possibly due to the coupling of the phosphorus atom with the carbons.

4.5.3 Attempted synthesis of 2-(2,6-diisopropyl-phenyl)-(6aS)-1-phenyl-hexahydro-pyrrolo[1,2,c][1,3,2]diazaphosphole

Following the procedure reported by Zuckerman *et al.*,¹⁹⁴ the diamine **350** (for a discussion of the synthesis of **350** see chapter 5) was reacted with freshly distilled dichlorophenyl phosphine **311**, in the presence of triethylamine, in deuterated chloroform, as shown in the Equation 49. No signs of the desired diazaphospholidine **351** being formed were shown by ^1H NMR and ^{31}P NMR spectroscopy.



Equation 49

The ^{31}P NMR spectrum showed unreacted dichlorophenyl phosphine, along with some unidentified minor products.

4.6 Conclusion

A number of chiral phosphorus ligands have been synthesised from a range of chiral diols, amino-alcohols, amino-thiols and diamines. Unfortunately, the majority of these compounds have been shown to be unstable and therefore isolation and

purification have proved difficult. In some cases undesired products have been isolated and structures proposed based on spectral data.

Three chiral phosphorus ligands were formed and isolated successfully and to our knowledge compounds **347** and **349** derived from *N,N'*-bis-[(1*R*,2*R*,4*S*)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-ethane-1,2-diamine **346** and *N,N'*-bis-[(1*R*,2*R*,4*S*)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-ethane-1,2-diamine **348** have not been synthesised before. At this time no attempts have been made to form rhodium catalysts using these new ligands, and further work should be carried out in this area.

CHAPTER 5: Synthesis of Transition Metal Complexes of Chiral *N*-Heterocyclic Carbenes

5.1 Introduction

Since the first isolation of stable imidazol-2-ylidenes by Arduengo in 1991,¹⁵⁰ the interest in the use of *N*-heterocyclic carbene ligands in organometallic catalysis has increased considerably, especially in palladium catalyzed coupling reactions and ruthenium catalyzed olefin ring closing metathesis.

Transition metal-*N*-heterocyclic carbene complexes have especially received considerable attention as possible alternatives for the widely used phosphine ligands in homogeneous catalysis,¹⁹⁵ therefore they are often described as “phosphine mimics”. The key advantage of these carbene complexes is that their metal-carbon bonds are much stronger than the metal-phosphorus bond of typical phosphine complexes, therefore they do not dissociate from the metal centre, particularly in the case of electron-rich catalytically active metals like palladium or rhodium. Moreover, an excess of ligand is not required in order to avoid aggregation of the catalyst to yield the bulk metal.^{195c} Also these “phosphine mimics” are less toxic and can be synthesised more readily than many conventional phosphine ligands.

However, only a few examples of asymmetric catalysis using diaminocarbene-based metal complexes have been reported.^{109,196}

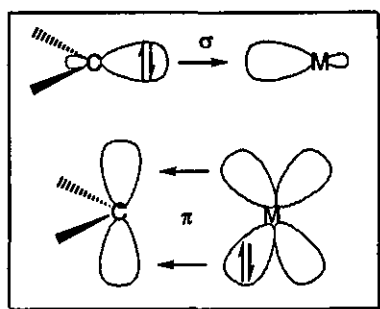
We were interested in the synthesis of new optically active transition metal-*N*-heterocyclic carbene complexes as new catalysts for asymmetric cyclopropanation.

5.1.1 Carbene-metal adducts

Depending on the nature of the carbon-metal double bond, carbene metal-complexes can be divided into two groups:

- Fischer-type carbene complexes, featuring a donor-acceptor bond, that results from a σ -donation of the carbene to the metal, and a π -backdonation from the metal to the carbene, as shown in **Figure 34**. They are normally formed with low-valent metals and carbenes with at least a π -donor substituent.
- Schrock-type carbene complexes, featuring a covalent bond that results from the interaction of a triplet carbene with a triplet metal fragment, as shown in **Figure 34**. Generally, they are formed with metals in high oxidation state and carbenes with alkyl substituents.

Fischer-type carbene complexes



Schrock-type carbene complexes

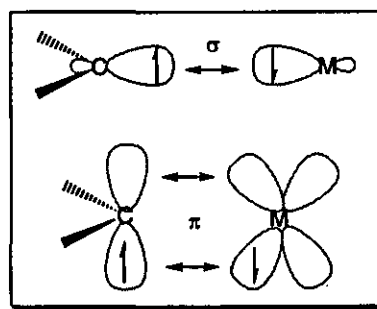


Figure 34

5.1.2 Carbene-transition metal adducts

-With *N*-heterocyclic carbenes

Transition metal-*N*-heterocyclic carbene complexes can be classified as Fischer-type compounds. In these complexes, especially for imidazol- and imidazolidin-2-ylidenes, bonding to the metal occurs predominantly through σ donation from the carbene lone pair, the π -back-bonding being insignificant.

Imidazolyliidines **188** and imidazolinylidines **180**, shown in Figure 35, are able to stabilize low oxidation states to give robust complexes,^{128,197} which have been used for several catalytic applications.

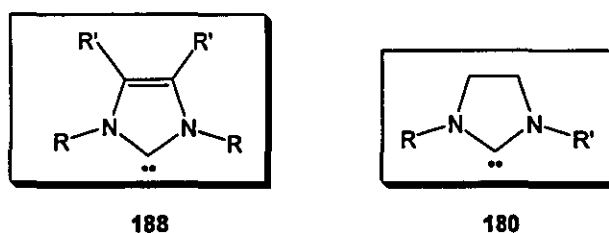
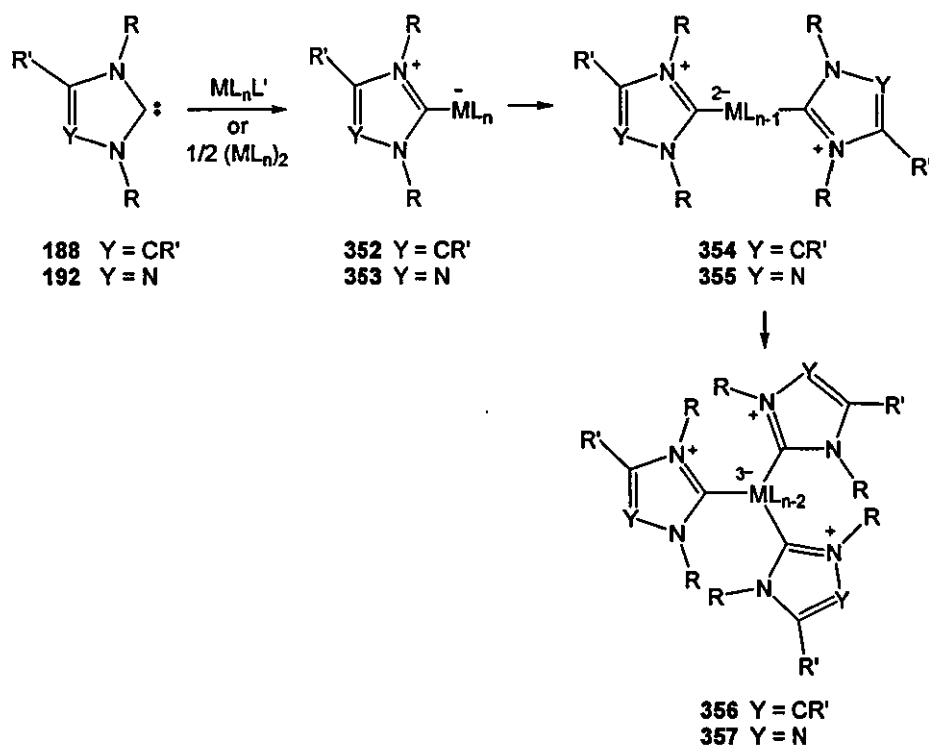


Figure 35

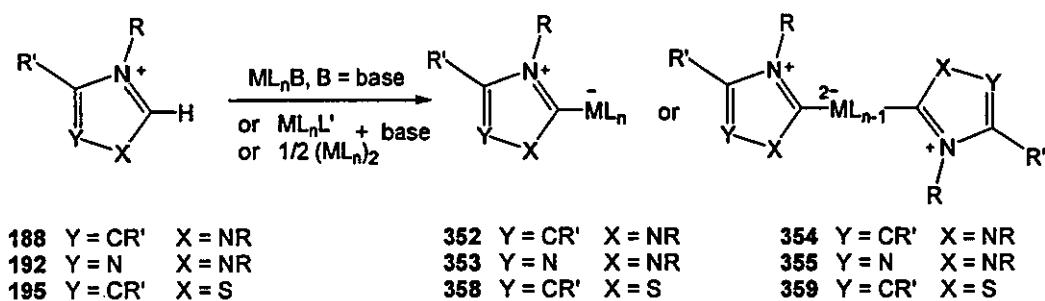
There are six different known ways to synthesise transition metal complexes of *N*-heterocyclic carbenes.

1-. Reaction of imidazol-2-ylidenes **188** and triazol-2-ylidenes **192** with organometallic precursors ML_nL' afforded the mononuclear complexes **352** and **353**, after replacement of a two-electron donor ligand^{125,198,199} (carbon monoxide, tetrahydrofuran, phosphines, nitriles, pyridine, etc), or either the bis- **354** and **355** or triscarbenes **356** and **357** complexes if further ligand substitution occurred, as shown in Scheme 61. Reaction of these ylidenes with dinuclear precursors featuring aceto or halo bridges $(ML_n)_2$ gave the corresponding mononuclear complexes **352** and **353**.^{156a}



Scheme 61

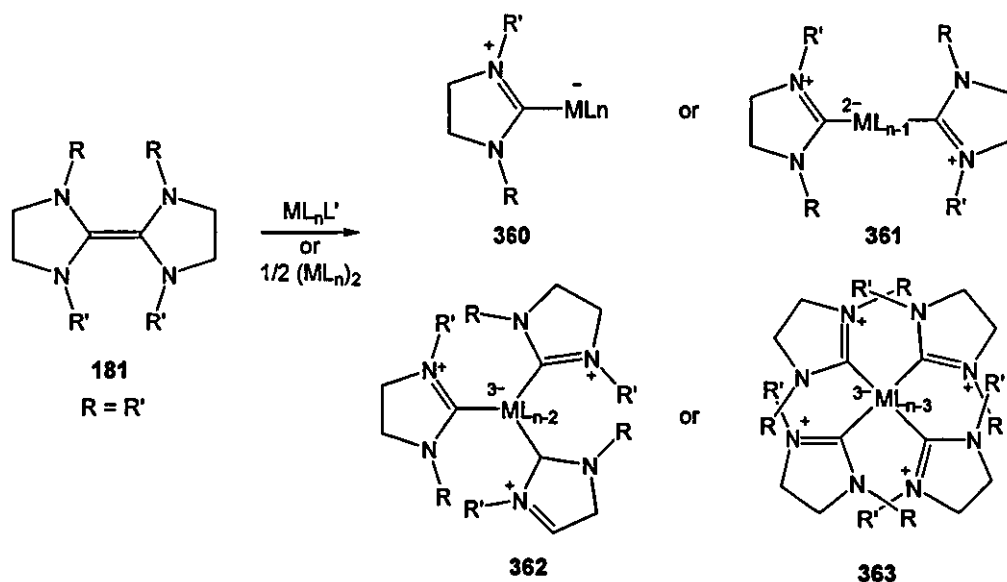
2-. The azolium salts **188**, **192** and **195** can be deprotonated in the presence of organometallic precursors ML_nB (where B is a basic ligand such as a hydride,^{146a,200} alkoxide,²⁰¹ or acetate¹¹⁴), or with a organic base¹⁰⁷ in the presence of either ML_nL' or $(ML_n)_2$, to afford mono- (**352**, **353** and **358**) and bis-carbene complexes(**354**, **355** and **359**).²⁰² See Equation 50.



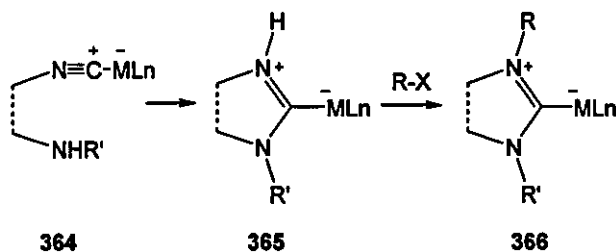
Equation 50

3-. Mono- (**360**), bis- (**361**), tris- (**362**) and tetrakis- (**363**) imidazolidin-2-ylidene complexes of several metals can be synthesised by reaction of the corresponding

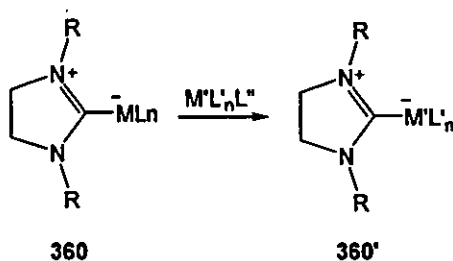
electron-rich olefin dimers **181** with organometallic precursors ML_nL' and $(ML_n)_2$, as shown in Equation 51.¹⁰⁸



4-. This method consists of transforming a C-bound ligand bonded to an amino group (such as coordinated isocyanides) *via* inter- or intramolecular *N*-nucleophilic attack, to furnish cyclic and acyclic transition metal-diaminocarbene complexes **366**, as shown in Scheme 62.²⁰³

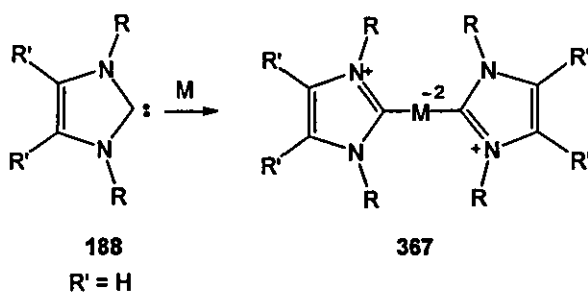


5-. Group 9 and 10 metal-imidazolidin-2-ylidene complexes can be prepared from the corresponding group 6 metal-carbene complexes *via* carbene transfer reactions, as shown in Equation 52.²⁰⁴



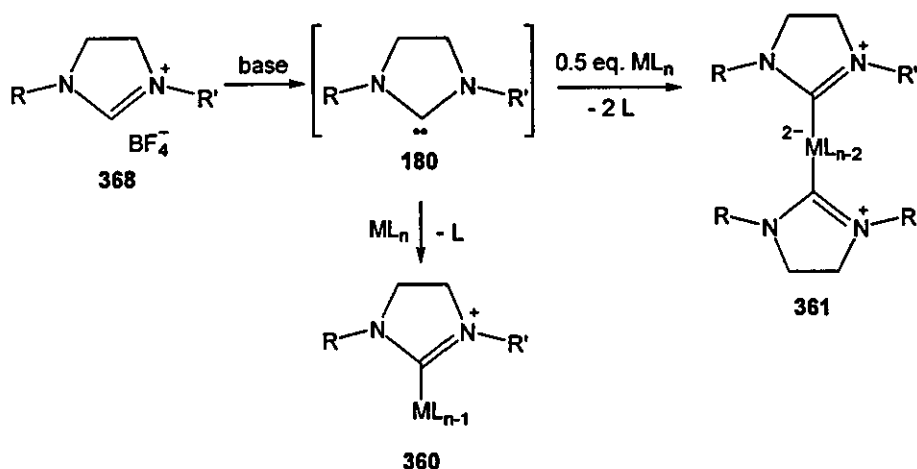
Equation 52

6-. Condensation of group 10 metal vapour with imidazol-2-ylidenes **188**, can be use to prepare homoleptic metal-carbene complexes **367**.²⁰⁵ See Equation 53.



Equation 53

One of the most common methods to synthesise mono- and bis-carbene transition metal complexes is the method 2, which consists of generating the carbene **180** *in situ*, by treating the corresponding imidazolinium salt **368** with a base, followed by the reaction of the carbene with either one or half an equivalent of metal complex in order to afford the mono-carbene complex **360** or the bis-carbene complex **361** respectively, as shown in Scheme 63.



Scheme 63

Following this procedure we hoped to obtain optically active transition metal mono- and bis-carbene complexes, in order to be able to test them for asymmetric synthesis of cyclopropanes.

Therefore, the first step for the synthesis of the transition metal mono- and bis-carbene complexes was the formation of several chiral imidazolinium tetrafluoroborate salts, with either similar ($R=R'$) or different R groups.

5.2 Synthesis of imidazolinium tetrafluoroborate salts

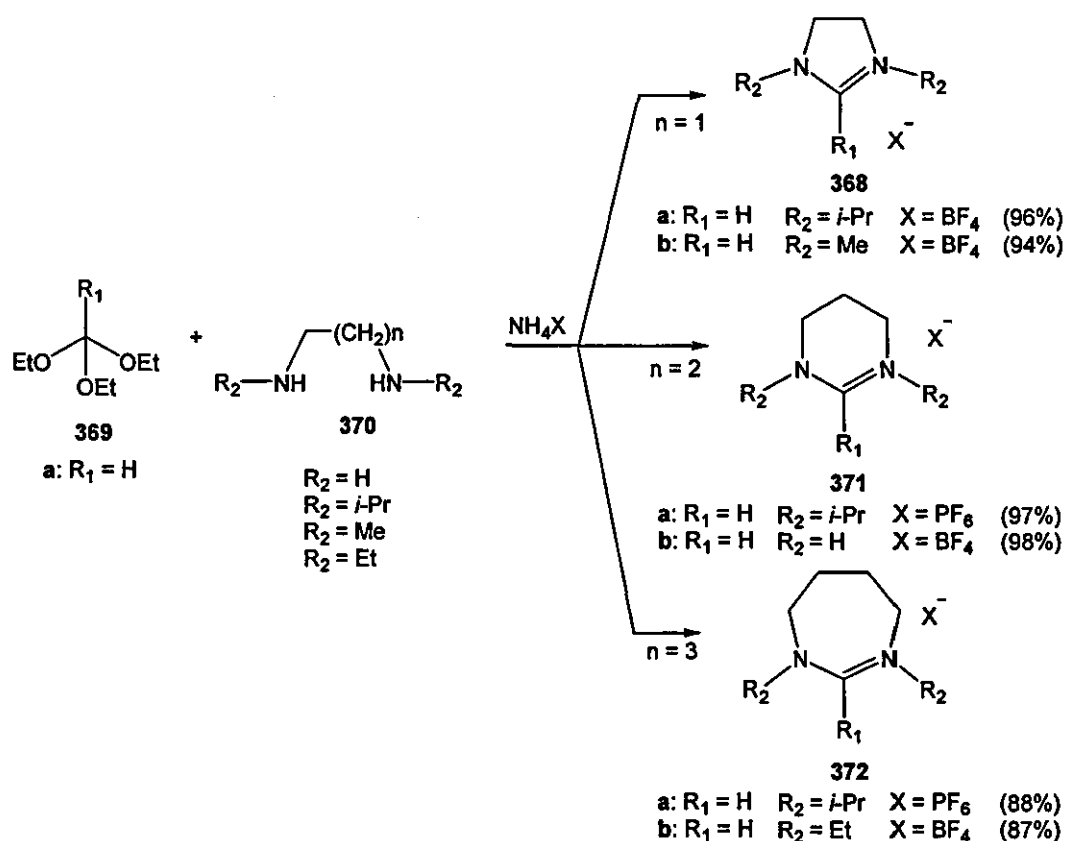
5.2.1 Introduction

Saturated and unsaturated imidazolium salts have been reported to have biological activity, including antifungal and antibacterial (1-alkyl-3-(alkyl-thio) imidazolium chlorides),^{206a} antiarrhythmic (1,3-disubstituted imidazolium halides),^{206b} thromboxane synthesis inhibition (1,3-disubstituted imidazolium halides),^{206c} hypoglycemic (phenacylimidazolium halides) and antiinflammatory (enol betaines of phenacyl halides)^{206d} activity.

However, recently they have attracted considerable interest since it was discovered that they are precursors to *N*-heterocyclic carbene ligands, which are an important class of compounds for coordination chemistry and catalysis.¹⁰⁶

Saba *et al.*²⁰⁷ have reported an efficient method for the synthesis of imidazolinium **368**, pyrimidinium **371** and diazepinium **372** salts by reaction of a triethyl orthoester **369** with either 1,4-, 1,5- or 1,6-diamines **370**, respectively, and an ammonium salt (NH₄X), such as ammonium tetrafluoroborate (X=BF₄⁻) or ammonium hexafluorophosphate (X=PF₆⁻), as shown in **Scheme 64**.

After Saba *et al.* reported this method, the preparation of more saturated and unsaturated imidazolium salts with different counter ions, such as tetrafluoroborate,²⁰⁸ triflate (such as *N*-alkyl-*N'*-arylimidazolium salts)²⁰⁹ and halide²¹⁰ (such as *N*-carbamoyl,²¹¹ *N*-pyridine²¹² and *N*-benzyl²¹³ imidazolium salts, and 2,6-pyridyl and 2,6-lutidinyl bis-imidazolium²¹⁴ salts), have been developed for different purposes.

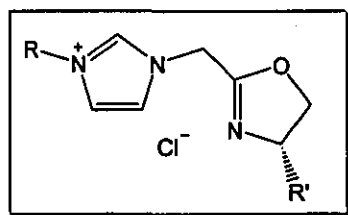


Scheme 64

5.2.1.1 Chiral imidazolium and imidazolinium salts

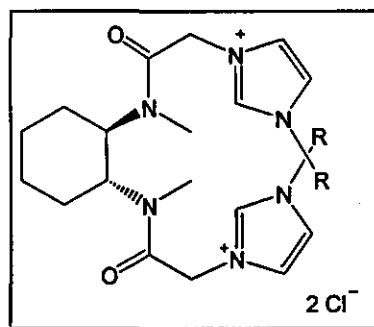
More interestingly, a number of chiral unsaturated imidazolium salts, such as oxazoline-imidazolium chloride salts **373**,¹¹¹ bis-imidazolium salts **374**,²¹⁵ and ferrocenyl imidazolium salts **375** and **376**,²¹⁶ shown in Figure 36, as well as saturated^{196,217} imidazolium salts have recently been developed and used in a range of asymmetric processes.

The synthesis of chiral unsaturated oxazoline-imidazolium chloride salts **373**, shown in Figure 36, have been reported by Herrmann *et al.*¹¹¹ as an alternative to oxazoline-phosphines and pyridine-oxazolines, in order to form rhodium and palladium carbene complexes and employ them in several asymmetric catalytic reactions.



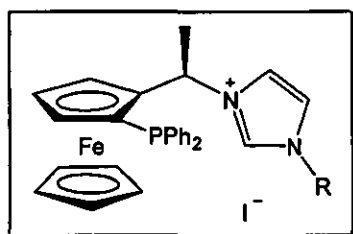
373

- a: R = methyl R' = benzyl
 b: R = methyl R' = isopropyl
 c: R = *t*-butyl R' = benzyl
 d: R = *t*-butyl R' = isopropyl



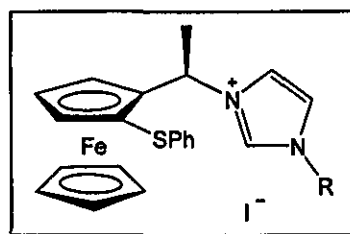
374

- a: R = *t*-butyl d: R = cyclohexyl
 b: R = isopropyl e: R = 2,6-diisopropyl phenyl
 c: R = methyl f: R = benzhydryl



375

- a: R = methyl
 b: R = phenyl

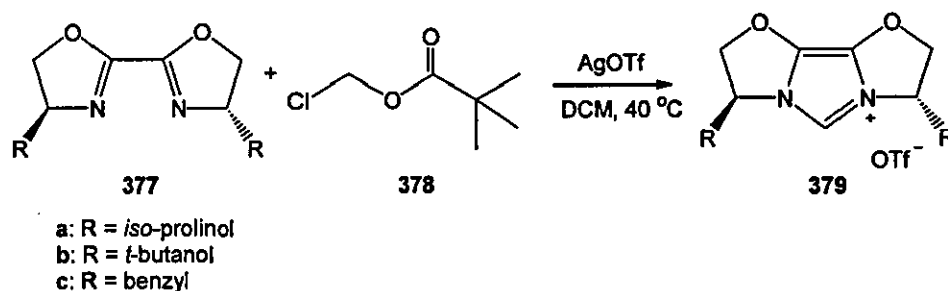


376

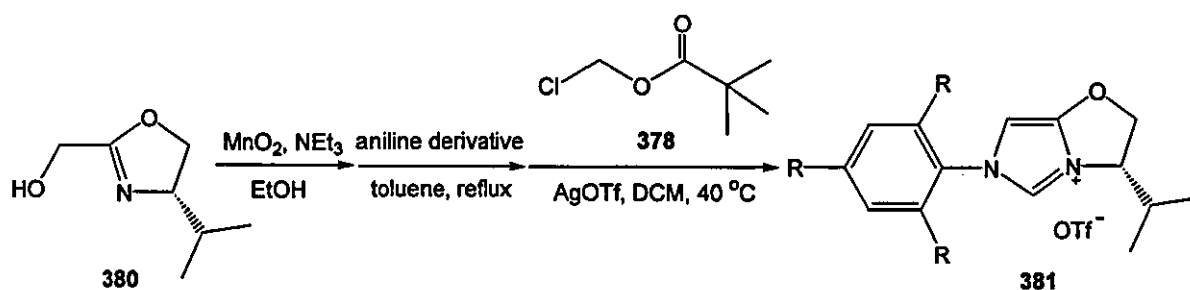
- a: R = methyl
 b: R = 4-*t*-butyl-phenyl

Figure 36

A very recent example of chiral imidazolium salts has been published by Glorius *et al.*²¹⁸ In this example they synthesised C_2 symmetric imidazolium salts **379a-c** from readily available *S*-valinol derived bioxazolines **377a-c**, as shown in **Equation 54**. They also reported the synthesis of the chiral imidazolium salt **381**, from the readily available alcohol **380**, as shown in **Scheme 65**.



Equation 54



Scheme 65

It was shown that the imidazolium triflates **379** and **381** could be converted to the corresponding carbene species and subsequently form palladium complexes in order to be used in the enantioselective α -arylation of amides. These reactions proceeded with moderate ee's, of up to 43%.

In 1999, Grubbs *et al.*^{208a} reported the synthesis of the chiral imidazolium tetrafluoroborate salts **382** and **383**, shown in Figure 37, in order to form ruthenium-based catalysts, which exhibited high olefin metathesis activity in ring-closing metathesis reactions.

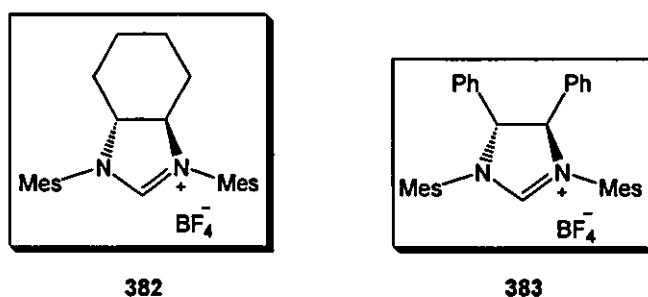
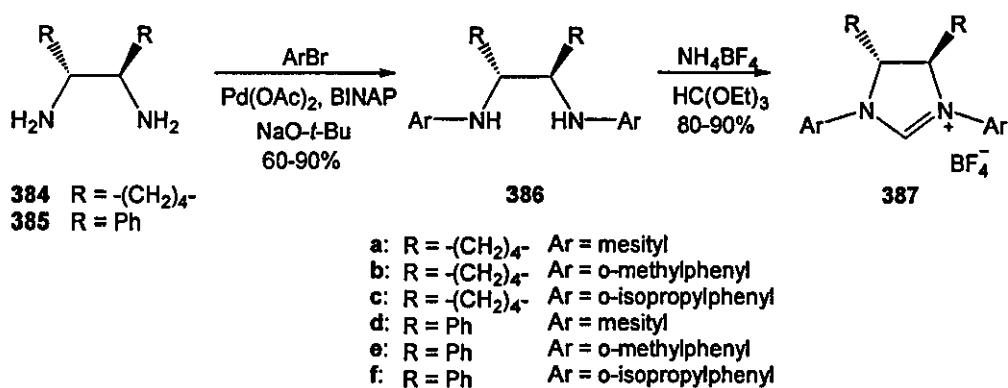


Figure 37

Two years later, Grubbs *et al.*^{196c} reported the synthesis of the chiral imidazolium tetrafluoroborate salts **387a-f**, as shown in Scheme 66. The diamines **386a-f** were obtained by palladium-catalysed amination of the appropriate aryl bromides and the corresponding readily available chiral diamines **384** and **385**. Condensation of the diamines **386a-f** with triethyl orthoformate and ammonium tetrafluoroborate gave the corresponding imidazolium tetrafluoroborate salts **387a-f**, which were employed to form imidazol-2-ylidene-ruthenium catalysts for the ring-closing metathesis of achiral trienes, giving high enantioselectivities (up to 90% ee).



Scheme 66

At the same time, Alexakis *et al.*^{196b} reported the synthesis of the following chiral imidazolium tetrafluoroborate salts **388-391**, as shown in **Figure 38**, in order to prepare imidazol-2-ylidene-copper catalysts for the 1,4-conjugate addition of diethylzinc to enones, giving moderate enantioselectivities (up to 51% ee).

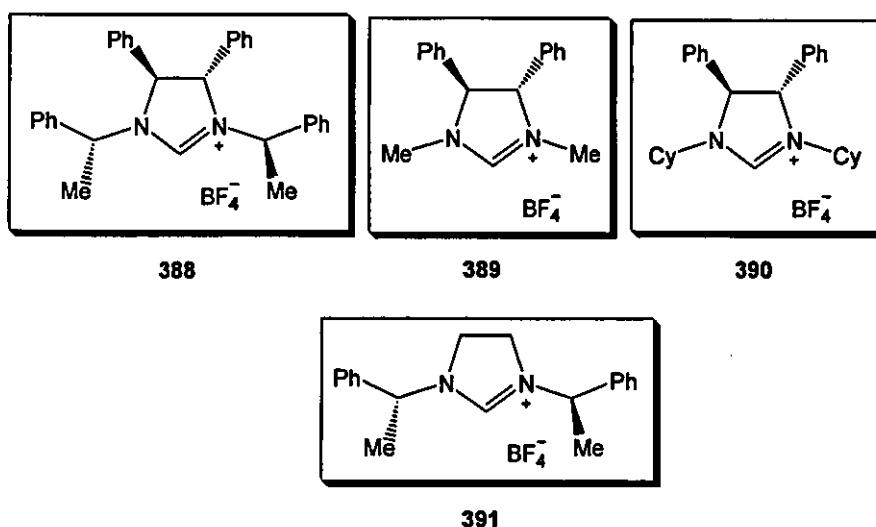


Figure 38

Hartwig *et al.*^{196a} reported the synthesis of the chiral imidazolium tetrafluoroborate salts **392-394**, shown in **Figure 39**, during the course of this work, in order to form imidazol-2-ylidene-palladium catalysts for enantioselective formation of oxindoles, providing good enantioselectivities (up to 71% ee).

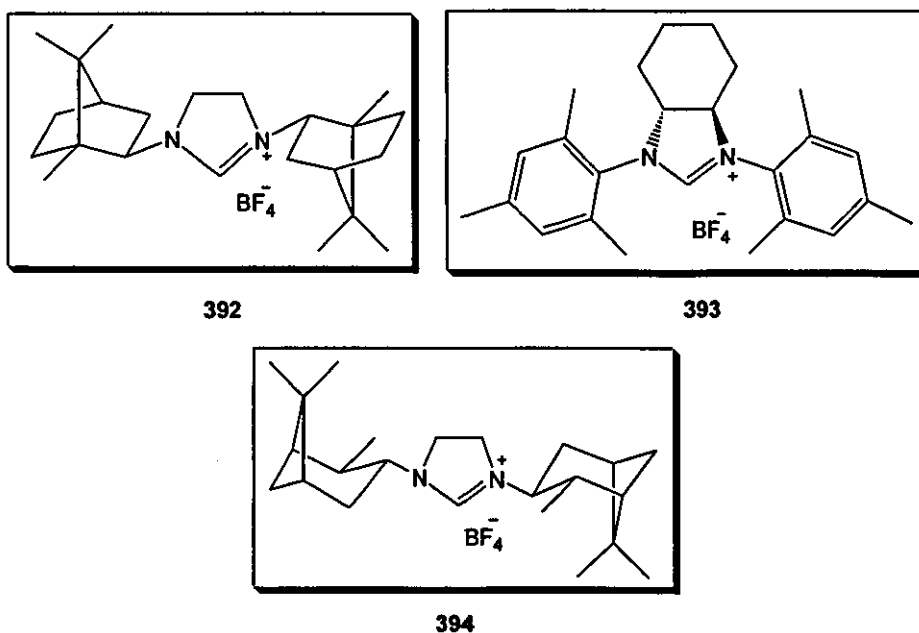


Figure 39

Roland *et al.*²¹⁹ reported the synthesis of the chiral imidazolium salts **395a-b** and **396a-c**, shown in **Figure 40**, in order to form imidazol-2-ylidene-silver complexes, which can act as an effective carbene transfer agent for the synthesis of palladium and gold carbene complexes.

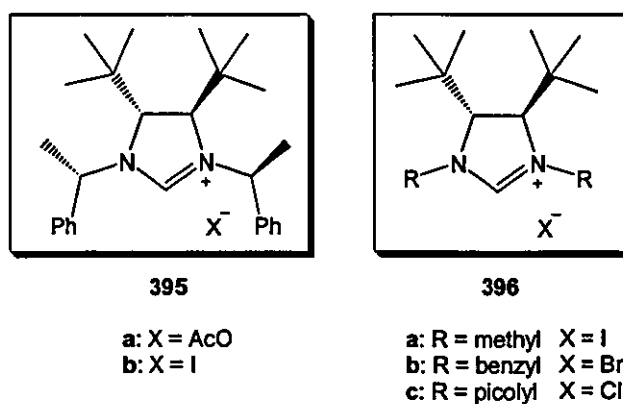


Figure 40

Diver *et al.*²²⁰ reported the synthesis of the chiral benzimidazolium tetrafluoroborate salts **397a-g**, **398** and **399a-f**, as shown in **Figure 41**, in order to form benzimidazole carbenes.

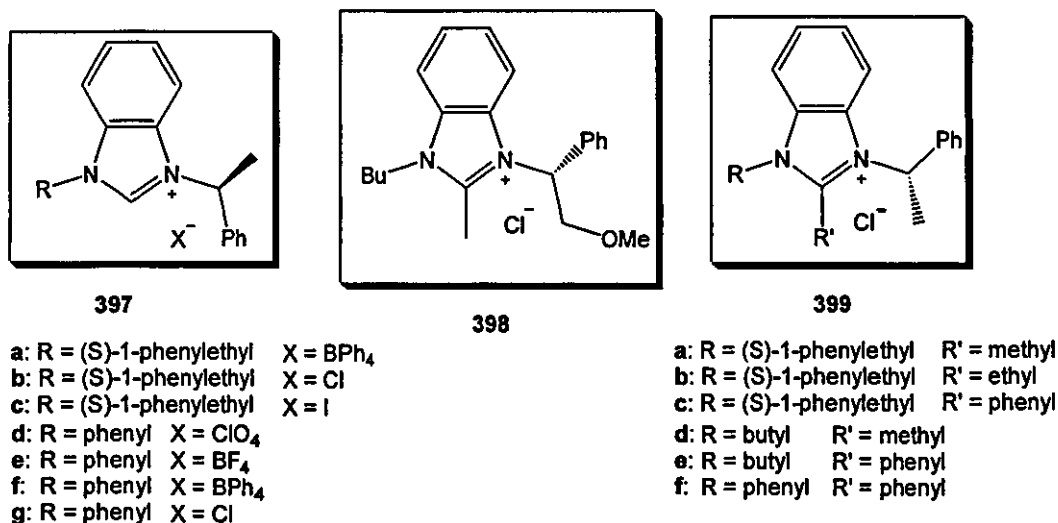


Figure 41

Hoveyda *et al.*²²¹ reported the synthesis of the chiral imidazolinium chloride salt **400**, whose structure is shown in **Figure 42**, in order to use it as a bidentate ligand for the formation of a imidazol-2-ylidene-ruthenium catalyst for asymmetric ring-closing/cross metathesis, giving excellent enantioselectivities (up to 96% ee).

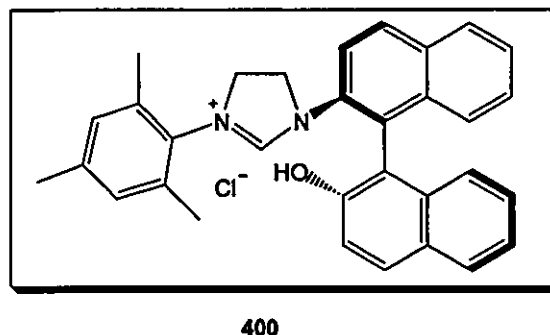
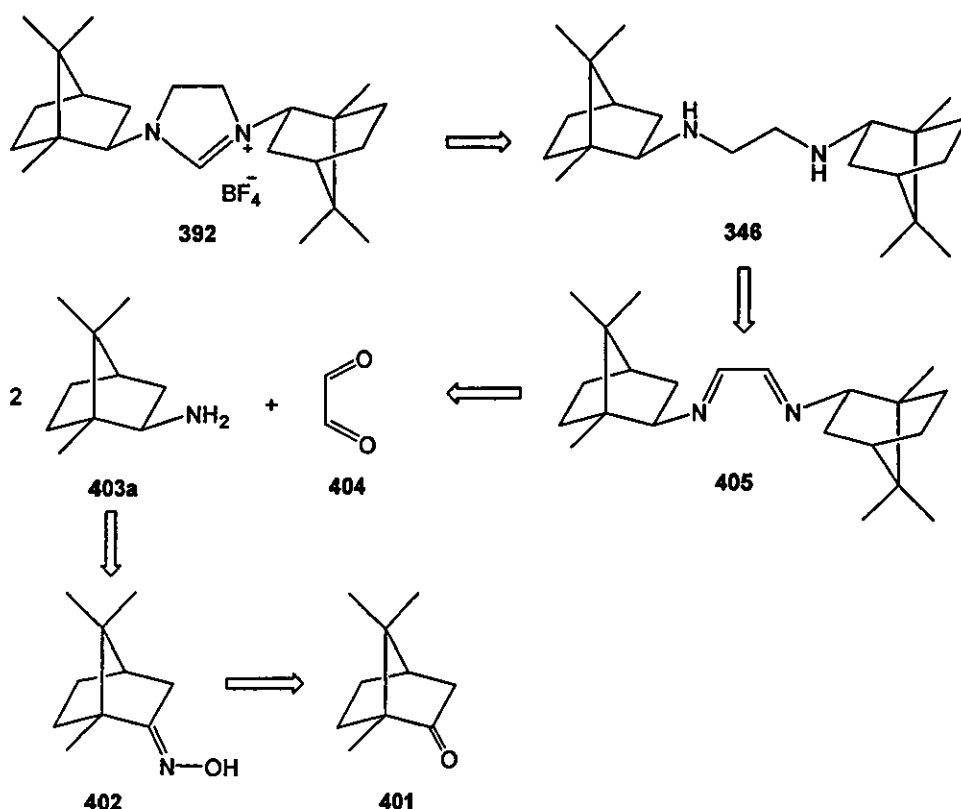


Figure 42

5.2.2 Synthesis of imidazolinium tetrafluoroborate salt derived from (1R)-(+)-camphor

5.2.2.1 Introduction; retrosynthetic analysis

At the start of this work, we were interested in devising a simple and versatile route to a range of chiral imidazolinium salts. Searching the literature, it was found that only few examples of chiral groups on nitrogen had been reported, as shown in the section 5.2.1.1. It was noticed that imidazolinium salts derived from camphor, fenchone and isopinocampheylamine had not been reported. We thought that the steric bulk of these groups would contribute to the carbene's kinetic stability by protecting the reactive centre from attack by electrophilic species, as postulated by Arduengo in his synthesis of the adamantyl carbene derivatives.^{150,151} In addition, the increased bulk of the chiral groups may increase the enantiocontrol in asymmetric reactions. To this end, the following retrosynthesis, shown in **Scheme 67**, was proposed.

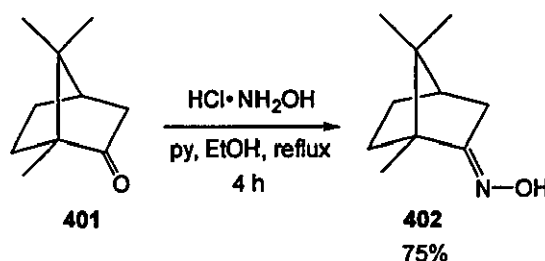


Scheme 67

Reaction of commercially available camphor **401** with hydroxylamine hydrochloride, in the presence of pyridine, would give the camphor oxime **402**, which could be then be reduced to the corresponding bornylamine **403a**. The next step would be the conversion of the bornylamine **403a** to the diimine **405** by reaction with aqueous glyoxal **404**, followed by reduction to the diamine **346**. Cyclisation following the procedure of Saba *et al.* would give the desired imidazolinium salt **392**.

5.2.2.1.1 Synthesis of (1R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one oxime or (1R)-(+)-camphor oxime

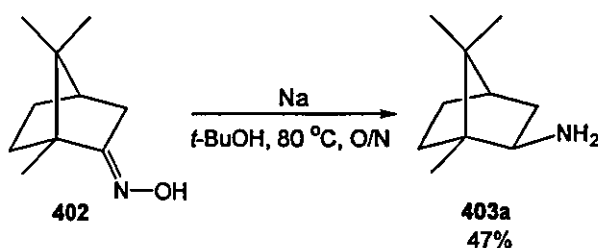
(1R)-(+)-camphor **401** was reacted with hydroxylamine hydrochloride and pyridine in ethanol, following the procedure reported by Leon,²²² as shown in Equation 55. The crude product was recrystallised from absolute ethanol to afford pure (1R)-(+)-camphor oxime **402**²²³ in good yield.



Equation 55

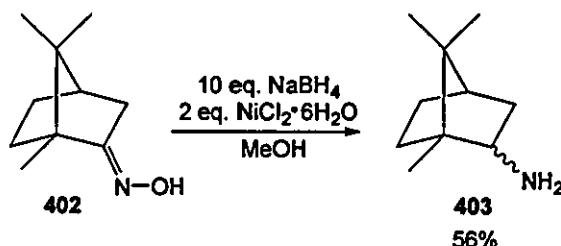
5.2.2.1.3 Synthesis of (1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamine or exo-bornylamine

In order to convert the (1R)-(+)-camphor oxime **402** to the bornylamine **403a**, a reduction was carried out using sodium, in *tert*-butanol, following a similar procedure reported by Paquette *et al.*,²²³ as shown in Equation 56. The desired diastereoisomer **403a** was isolated after column chromatography.



Equation 56

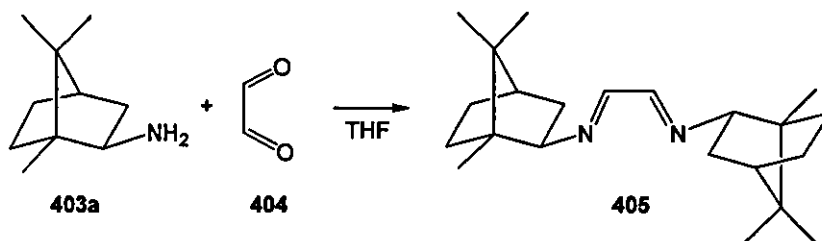
Reduction of the camphor oxime **402** was also carried out using sodium borohydride and nickel chloride hexahydrate, in methanol, following the procedure reported by Ipaktschi,²²⁴ as shown in Equation 57. The desired amine **403** was obtained as a mixture of diastereoisomers in moderate yield.



Equation 57

5.2.2.1.4 Synthesis of (1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl-[(1R,2R,4S)-2-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylimino-ethylidene]-amine

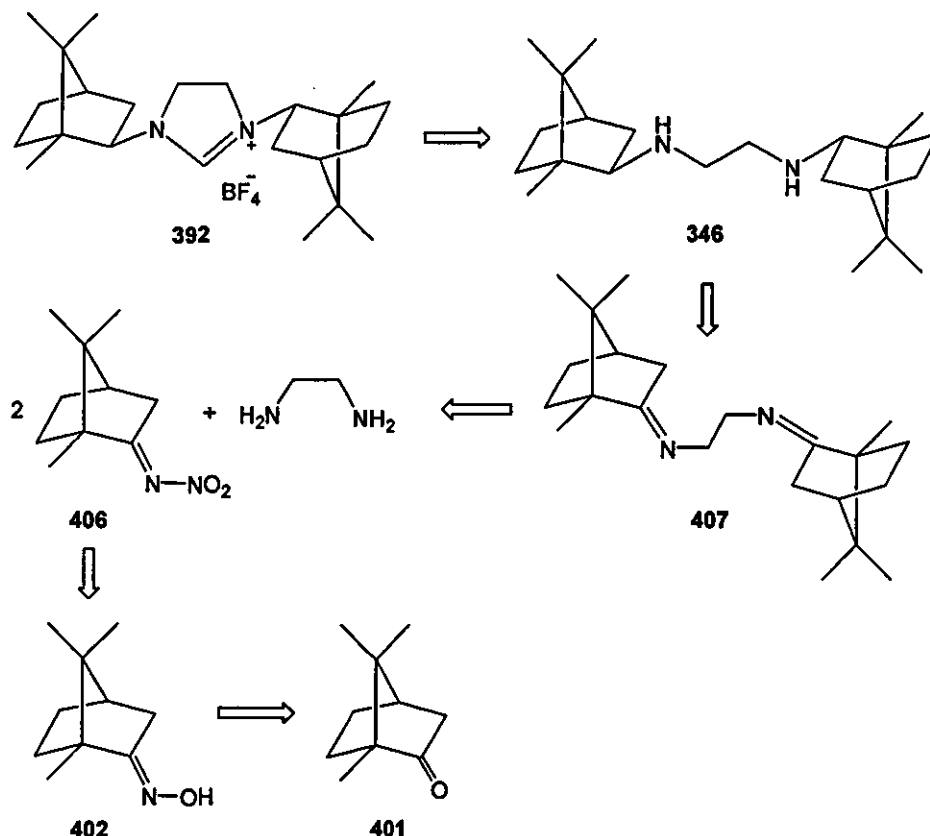
The synthesis of diimines from amines has been widely reported.^{210c,225} It consists of treating the corresponding amine with aqueous glyoxal, and the desired diimine is obtained in good yield. Therefore, bornylamine **403a** was reacted with an aqueous solution of glyoxal **404**, as shown in Equation 58. Examination of the crude reaction mixture by ¹H NMR spectroscopy showed the desired product **405** to have formed, but purification proved difficult.



Equation 58

5.2.2.2 New approach for the synthesis of (1R,2R,4S)-N,N'-dibornylimidazolinium tetrafluoroborate salt **392**

Due to the problems encountered in the purification of the diimine **405**, we decided to modify our approach. We thought that diimine **407** could be obtained by reaction of one equivalent of ethylenediamine with two equivalents of nitroimine **406**. Our revised retrosynthesis is shown in **Scheme 68**.

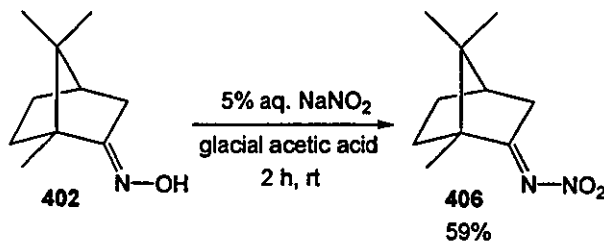


Scheme 68

In this new scheme, the camphor oxime **402** would be synthesized as before, and then after treatment with aqueous sodium nitrite, in the presence of acid, it would be converted to the camphor nitroimine **406**. Reaction with ethylenediamine would lead to the diimine **407**, which upon reduction would give the desired diamine **346**. Cyclisation using the methodology of Saba *et al.*²⁰⁷ would give the desired imidazolinium salt **392**.

5.2.2.1.2 Synthesis of (1R,4S)-1-oxo-2-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yliden)hydrazinium-1-olate or (1R)-(+)-camphor nitroimine

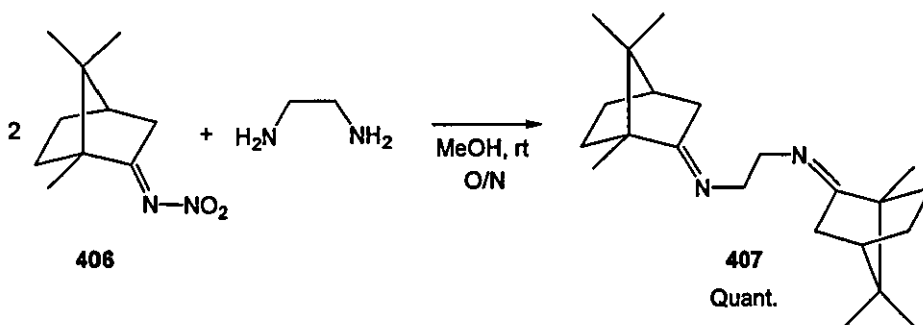
A solution of (1R)-(+)-camphor oxime **402** in glacial acetic acid was treated with aqueous sodium nitrite, under the same conditions as Leon²²² and Morris *et al.*,²²⁶ as shown in Equation 59. (1R)-(+)-camphor nitroimine **406** was isolated in good yield.



Equation 59

5.2.2.2.1 Synthesis of *N,N'*-bis-[(1R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylidene]-ethane-1,2-diamine

(1R)-(+)-Camphor nitroimine **406** was reacted with ethylenediamine in methanol, as shown in Equation 60. The desired diimine **407**²²⁷ was isolated in quantitative yield.

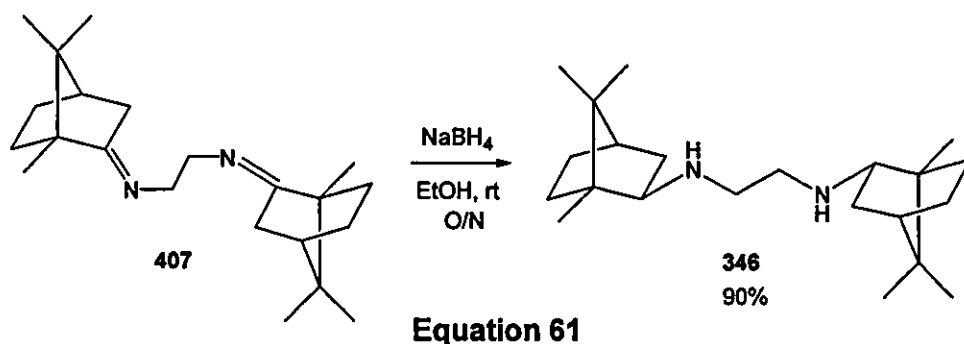


Equation 60

Analysis by IR spectroscopy showed a peak at 1685 cm⁻¹, due to the stretching of the imino groups. The ¹H NMR spectrum showed the methylene groups of the bridge at 3.42-3.55 ppm, which by ¹³C NMR spectroscopy were observed at 53.3 ppm. The ¹³C NMR spectrum showed the imino carbons at 182.7 ppm.

5.2.2.2.2 Synthesis of *N,N'*-bis-[(1*R*,2*R*,4*S*)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-ethane-1,2-diamine

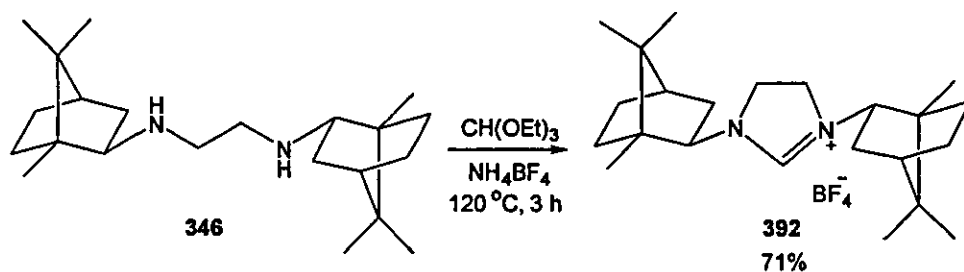
Reduction of the diimine **407** was carried out using sodium borohydride, in dry ethanol, as shown in Equation 61. The desired diamine **346**,^{196a} was obtained in excellent yield. The ¹H NMR and ¹³C NMR spectra showed a trace of unreacted starting material present.



Analysis by ¹H NMR spectroscopy showed the methylene groups of the bridge at 2.63-2.69 ppm, which by ¹³C NMR spectroscopy were observed at 48.2 ppm. The two new CH's resulting from the reduction were observed at 66.5 ppm in the ¹³C NMR spectrum.

5.2.2.2.3 Synthesis of 1,3-bis-[(1*R*,2*R*,4*S*)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-4,5-dihydro-3*H*-imidazol-1-ium tetrafluoroborate

By reaction of the diamine **346** with triethyl orthoformate and ammonium tetrafluoroborate, under the conditions reported by Saba *et al.*,²⁰⁷ as shown in Equation 62, the desired imidazolium tetrafluoroborate salt **392**^{196a} was isolated in good yield.



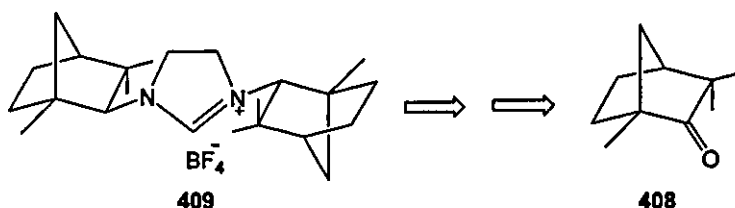
Equation 62

Analysis by IR spectroscopy showed a peak at 1635 cm^{-1} , probably due to the iminium group. The ^1H NMR spectrum showed the iminium proton at 8.06 ppm, and by ^{13}C NMR spectroscopy the iminium carbon was present at 158.9 ppm. The methylene groups of the bridge were observed at 4.09-4.16 ppm in the ^1H NMR spectrum, which by ^{13}C NMR spectroscopy were observed at 49.9 ppm.

5.2.3 Synthesis of imidazolinium tetrafluoroborate salt derived from (1R)-(-)-fenchone

5.2.3.1 Introduction

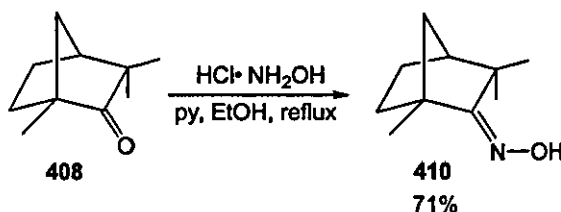
With the success of the synthesis of the camphor derived imidazolinium salt **392** achieved, the same route was employed starting from commercially available fenchone in order to synthesise the corresponding imidazolinium salt **409**, as shown in **Scheme 69**.



Scheme 69

5.2.3.1.1 Synthesis of (1R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]heptan-2-one oxime or (1R)-(-)-fenchone oxime

The first step in the synthesis was the conversion of commercially available (1R)-(-)-fenchone **408** to fenchone oxime **410**. This was carried out by the reaction of (1R)-(-)-fenchone with hydroxylamine hydrochloride and pyridine in ethanol, following the procedure reported by Leon,²²² as shown in **Equation 63**. The crude product was recrystallised from absolute ethanol to afford pure (1R)-(-)-fenchone oxime **410**²²⁸ in good yield.



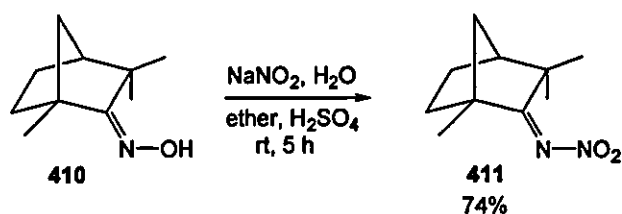
Equation 63

Analysis by IR spectroscopy showed a band at 3142 cm⁻¹, due to the stretching of the alcohol group, and a strong peak at 927 cm⁻¹, due to the -N-O stretching. The

^1H NMR spectrum showed the alcohol group of the oxime at 8.99 ppm. The carbon of the oxime group was shown at 172.3 ppm by ^{13}C NMR spectroscopy.

5.2.3.1.2 Synthesis of (1R,4S)-1-oxo-2-(1,3,3-trimethylbicyclo[2.2.1]hept-2-yliden)hydrazinium-1-olate or (1R)-(-)-fenchone nitroimine

In order to synthesise (1R)-(-)-fenchone nitroimine **411**, a solution of (1R)-(-)-fenchone oxime **410** in diethyl ether was treated with an aqueous solution of sodium nitrite and an aqueous solution of sulfuric acid, following the procedure reported by Leon,²²² as shown in Equation 64. The desired nitroimine **411**²²⁹ was obtained as a mixture of the *syn* and *anti* diastereoisomers, in a 2:1 ratio approximately, although it is not known which is the *syn* or the *anti* isomer.

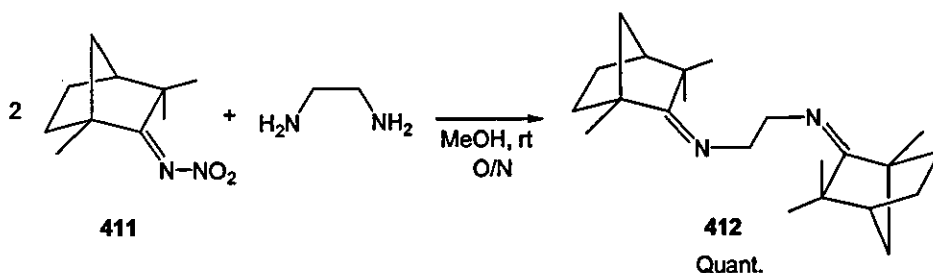


Equation 64

Analysis by IR spectroscopy showed a peak at 1638 cm^{-1} , due to the stretching of the imino group, and two peaks at 1550 and 1370 cm^{-1} , due to the stretching of the nitro group. Due to the formation of diastereoisomers, all the signals were doubled in both the ^1H NMR and ^{13}C NMR spectrum. The imino carbon was shown at 189.9 and 190.0 ppm by ^{13}C NMR spectroscopy.

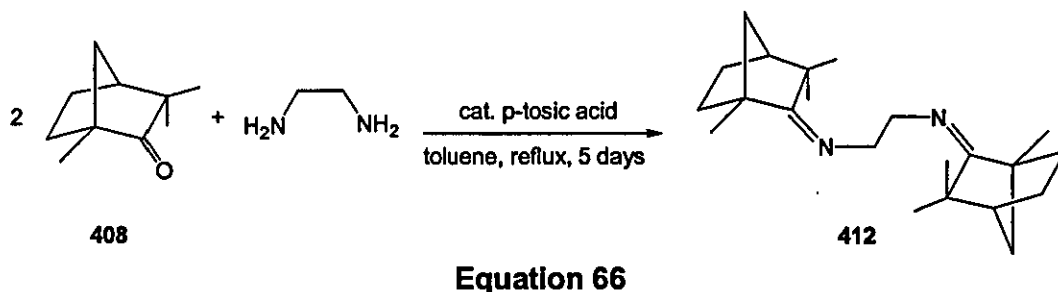
5.2.3.1.3 Synthesis of *N,N'*-bis-[(1R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-ylidene]-ethane-1,2-diamine

In order to convert the fenchone nitroimine **411** to the diimine **412**, the mixture of the *syn* and *anti* diastereoisomers of the fenchone nitroimine was reacted with ethylenediamine in methanol, as shown in Equation 65. The desired diimine **412**²²⁷ was probably isolated as a mixture of the *syn* and *anti* diastereoisomers, in quantitative yield, although it was difficult to tell conclusively by ^1H and ^{13}C NMR spectroscopy.



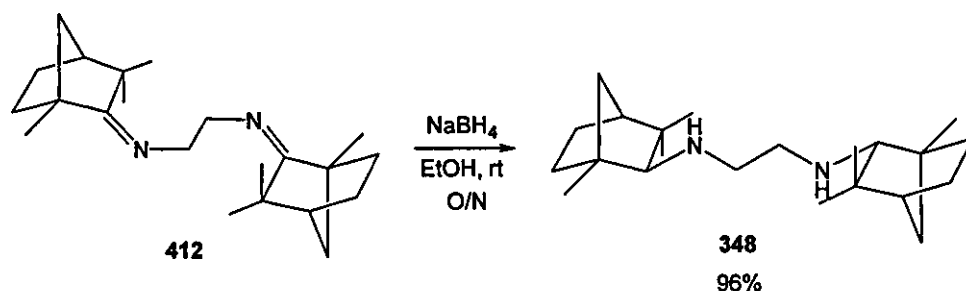
Analysis by IR spectroscopy showed a peak at 1682 cm^{-1} , due to the stretching of both imino groups. The ^1H NMR spectrum showed the methylene groups of the bridge at 3.65-3.85 ppm, which by ^{13}C NMR spectroscopy were observed at 52.9 ppm. The ^{13}C NMR spectrum showed the imino carbons at 184.5 ppm.

This reaction was also attempted starting from (1R)-(-)-fenchone **408**, by reaction with ethylenediamine, in the presence of a catalytic amount of *para*-toluenesulphonic acid, under Dean-Stark conditions, as shown in Equation 66. The desired diimine **412** was not formed, probably due to steric reasons, and the starting materials were reisolated.



5.2.3.1.4 Synthesis of *N,N'*-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-ethane-1,2-diamine

Reduction of the diimine **412** was carried out using sodium borohydride, in dry ethanol, as shown in Equation 67. The desired diamine **348**, was obtained in excellent yield.

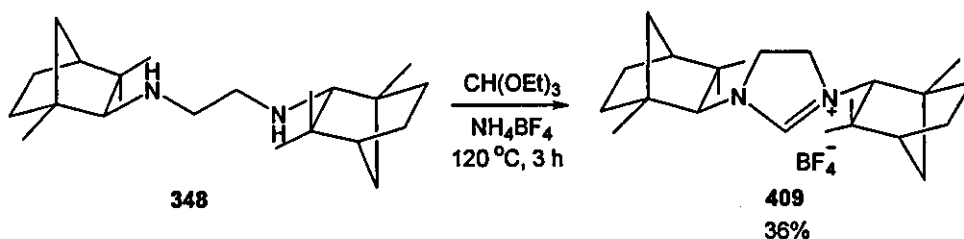


Equation 67

Analysis by ^1H NMR spectroscopy showed the methylene groups of the bridge were shown as two multiplets at 2.58-2.63 and 2.75-2.78 ppm, which by ^{13}C NMR spectroscopy were observed at 50.4 ppm. The two new CH groups resulting from the reduction were observed at 73.7 ppm in the ^{13}C NMR spectrum.

5.2.3.1.5 Synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-4,5-dihydro-3H-imidazol-1-ium tetrafluoroborate

In order to synthesise the imidazolinium tetrafluoroborate salt **409**, the diamine **348** was reacted with triethyl orthoformate and ammonium tetrafluoroborate under the conditions reported by Saba *et al.*²⁰⁷ as shown in **Equation 68**. The crude product was recrystallised from absolute ethanol to furnish the desired imidazolinium salt **409** in moderate yield.

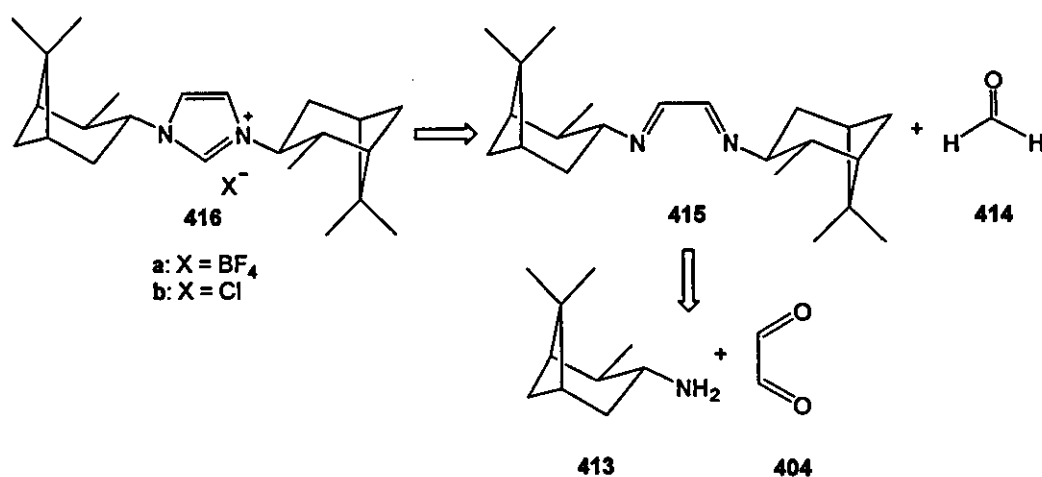


Equation 68

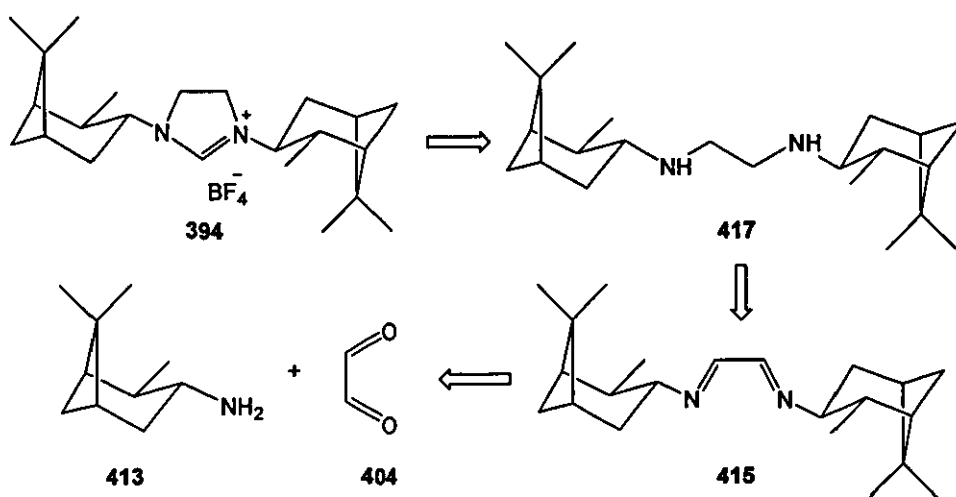
A peak at 1633 cm^{-1} , probably due to the iminium group, was shown by IR spectroscopy. The ^1H NMR spectrum showed the iminium proton at 8.11 ppm, and by ^{13}C NMR spectroscopy the iminium carbon was present at 157.7 ppm. The methylene groups of the bridge were observed at 4.13 ppm in the ^1H NMR spectrum, which by ^{13}C NMR spectroscopy were observed at 51.2 ppm.

5.2.4 Synthesis of tetrafluoroborate salt derived from (1S,2S,3S,5R)-(+)-isopinocampheylamine

The following retrosynthesis were devised for the synthesis of the imidazolium salts **416a-b** and the imidazolinium salt **394**. In both retrosynthetic analysis, the first step is the reaction of commercially available (1S,2S,3S,5R)-(+)-isopinocampheylamine **413** with glyoxal **404** to form the diimine **415**, which can undergo either direct cyclisation after reaction with paraformaldehyde **414** to form the unsaturated imidazolium salts **416a-b**, or reduction to form the diamine **417**, which would then undergo cyclisation to form the imidazolinium salt **394**, as shown in Scheme 70 and Scheme 71.



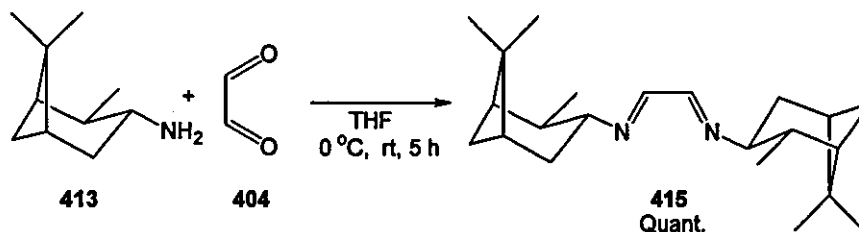
Scheme 70



Scheme 71

5.2.4.1 Synthesis of *N,N'*-bis-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylidene]-ethane-1,2-diamine

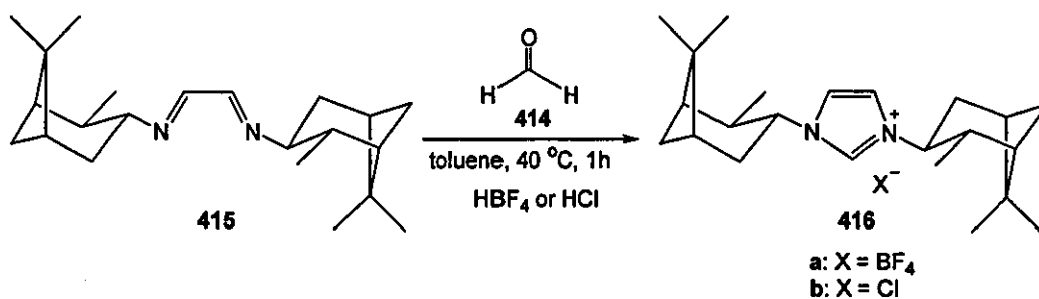
(1*S*,2*S*,3*S*,5*R*)-(+)-Isopinocampheylamine **413** was reacted with an aqueous solution of glyoxal, in dichloromethane, as shown in Equation 69. The desired diimine **415** was obtained quantitatively.



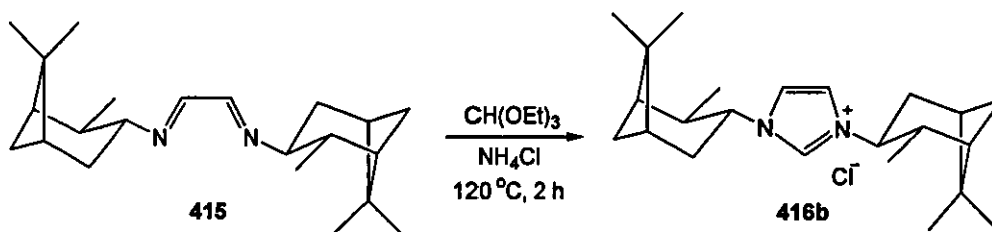
Analysis by IR spectroscopy showed a peak at 1622 cm^{-1} due to the stretching of the imino groups. The ^1H NMR spectrum showed the peak of the imino protons at 7.79 ppm, and by ^{13}C NMR spectroscopy both imino carbons were shown at 159.8 ppm.

5.2.4.2 Attempted synthesis of 1,3-bis-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-3*H*-imidazol-1-ium chloride/tetrafluoroborate salts

The synthesis of the imidazolium salts **416a-b** was attempted using a range of different conditions. The diimine compound **415** was treated with paraformaldehyde **414** and with either an aqueous solution of hydrochloric acid or a solution of tetrafluoroboric acid in diethyl ether, in anhydrous toluene, as shown in Equation 70. The desired products **416a-b** were not isolated. The reaction to obtain the imidazolium salt **416a** was also attempted by treating the diimine **415** with paraformaldehyde at a higher temperature and for a longer time (at $135\text{ }^{\circ}\text{C}$ for 3 hours) before the addition of the solution of the tetrafluoroboric acid. Also, we attempted the synthesis of the chloride salt **416b** by reacting the diimine compound **415** with triethyl orthoformate and ammonium chloride as shown in Equation 71. In each case, the desired product was not isolated, and therefore the synthetic route was abandoned.



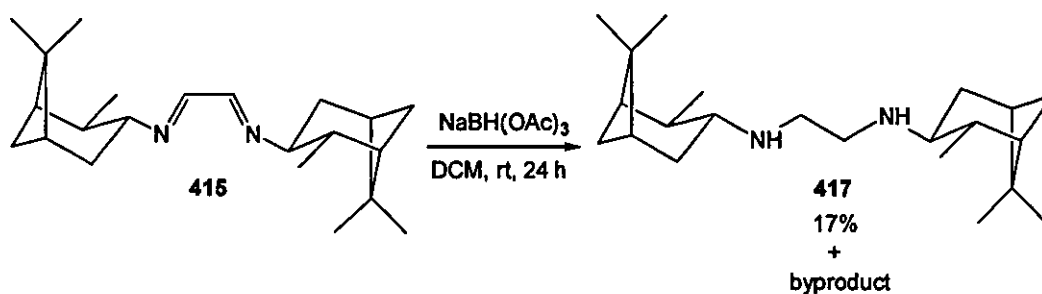
Equation 70



Equation 71

5.2.4.3 Synthesis of *N,N'*-bis-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-ethane-1,2-diamine

At this time we turned our attention to the synthesis of the diamine **417** via reduction of the diimine **415**. As we were starting this work, Hartwig *et al.*^{196a} reported the synthesis of the imidazolium salt **394**, following the same retrosynthetic analysis as we proposed in Scheme 71. We therefore decided to follow their conditions for the reduction. The diimine **415** was treated with sodium triacetoxyborohydride, in dichloromethane, as shown in Equation 72. Purification by silica gel flash chromatography of the crude mixture, furnished the desired diamine **417** in low yield. An unidentified byproduct was also isolated.

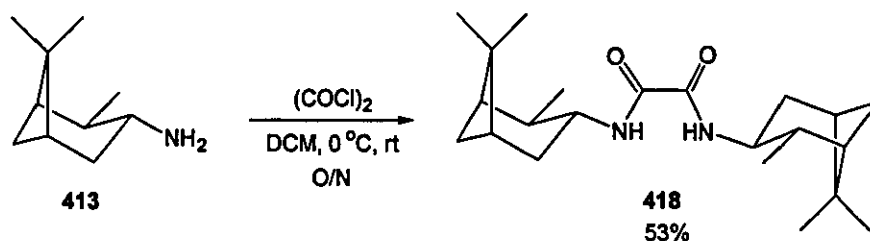


Equation 72

Analysis by ^1H NMR spectroscopy of the diamine **417**, showed a new peak for the methylene groups, resulting from the reduction of the imino groups, at 2.63 ppm. The ^{13}C NMR spectrum showed the carbons of these methylene groups at 48.4 ppm. The unidentified by-product was analysed by a variety of spectroscopic methods. IR spectroscopy showed a peak at 3280 cm^{-1} , that we thought could be due to the stretching of the amine groups, and a peak at 1648 cm^{-1} , which could be due to the presence of a carbonyl group. This was confirmed by analysis of the ^{13}C NMR spectrum, which showed a peak at 169.5 ppm, which is diagnostic of a carbonyl group of a carboxylate derivative. We therefore decided to synthesise the diamide **418**, in order to compare the spectroscopic data to determine whether the diamide **418** was the unidentified byproduct.

5.2.4.3.1 Synthesis of *N,N'*-bis-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-oxalamide

(1*S*,2*S*,3*S*,5*R*)-(+)-Isopinocampheylamine **413** was treated with triethylamine and oxalyl chloride in dichloromethane, as shown in Equation 73. The diamide **418** was obtained in moderate yield.



Equation 73

Analysis by IR spectroscopy, showed a peak at 3280 cm^{-1} , due to the stretching of the amino groups. The ^{13}C NMR spectrum showed the carboxylic carbons at 158.5 ppm. We therefore concluded that the by-product was not the diamide **418**. The structure of the by-product was finally shown to be the compound **419**, *N*-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-acetamide or *N*-pinan-3-yl-acetamide by X-Ray crystallography, as shown in Figure 43. A possible mechanism of formation is outlined in Scheme 72. The acetyl group being most likely derived from the triacetoxyborohydride used.

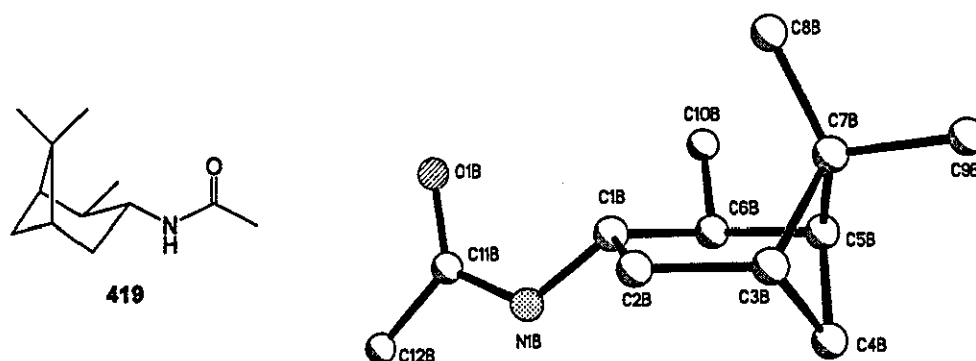
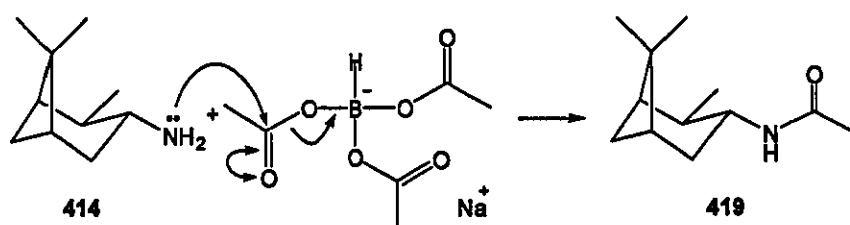


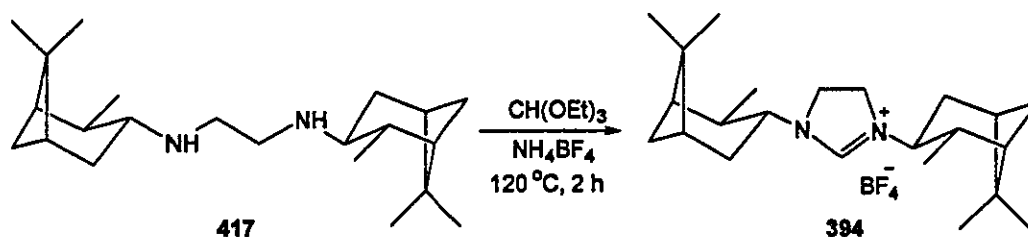
Figure 43



Scheme 72

5.2.4.4 Attempted synthesis of 1,3-bis-[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-4,5-dihydro-3H-imidazol-1-ium tetrafluoroborate

Stoichiometric amounts of the diamine **417**, ammonium tetrafluoroborate and triethyl orthoformate were reacted under the conditions reported by Saba *et al.*,²⁰⁷ as shown in Equation 74. Recrystallisation of the crude product from ethanol furnished a solid, which was not soluble in deuterated chloroform or methanol. The ¹H NMR spectrum obtained in deuterated dimethylsulfoxide was too broad to identify the product.

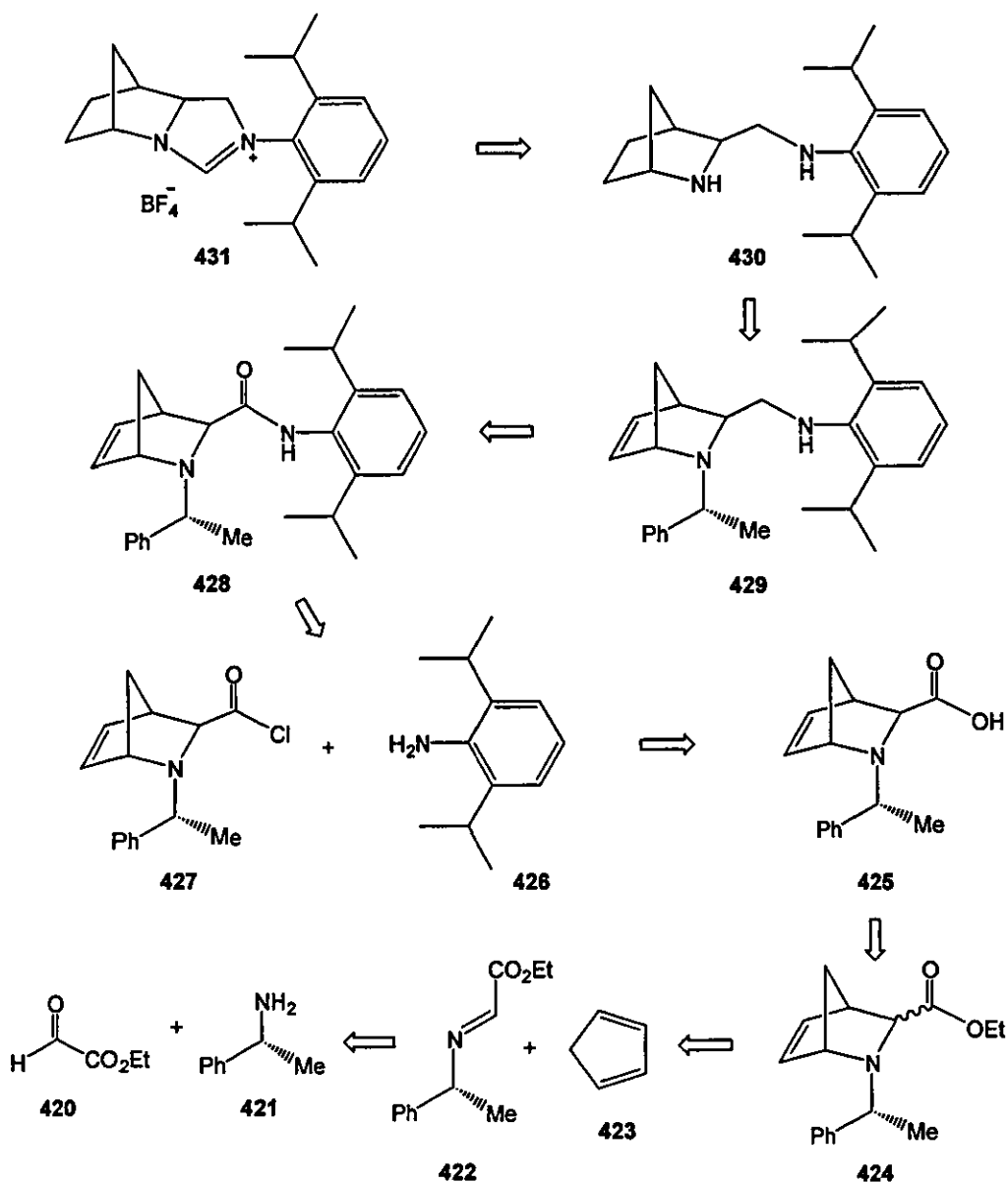


Equation 74

5.2.5 Synthesis of imidazolinium tetrafluoroborate salt derived from (1R,3S,4S)-2-[(1R)-phenyl-ethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid ethyl ester

5.2.5.1 Introduction; retrosynthetic analysis

We anticipated that a further example of a chiral imidazolinium salt **431** could be derived from the azabicyclo[2.2.1]hept-5-ene-3-carboxylate **424** and we proposed the following retrosynthetic analysis for its synthesis, as shown in **Scheme 73**.

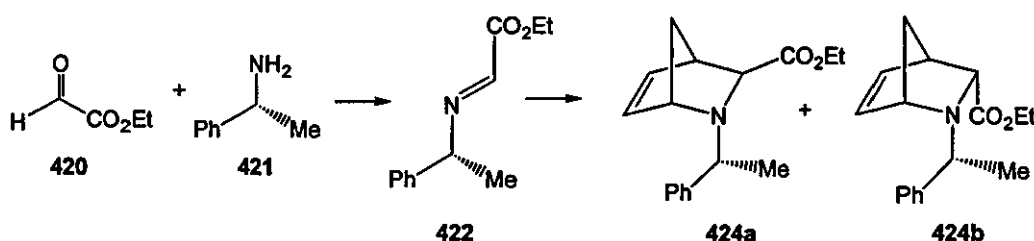


Scheme 73

The synthesis would involve the condensation of ethyl glyoxalate **420** and α -phenylethylamine **421** to form the imine **422**. This would then undergo an aza Diels-Alder reaction with cyclopentadiene to form the bicyclic compound **424**. Hydrolysis of the ester **424**, conversion to the acid chloride **427**, followed by reaction with 2,6-diisopropylaniline would give the amide **428**. Removal of the carbonyl group by reduction, removal of the α -phenylethyl group and the double bond by hydrogenation and subsequent cyclisation using the conditions reported by Saba *et al.*²⁰⁷ would give the desired imidazolinium salt **431**.

5.2.5.2 Synthesis of (1R,3S,4S) and (1R,3R,4S)-2-[(1R)-phenyl-ethyl]-2-aza-bicyclo[2.2.1] hept-5-ene-3-carboxylic acid ethyl ester

The synthesis of the cycloadducts **424a** and **424b** has been described by Bailey *et al.*²³⁰ It involves the formation of the imine **422** from the condensation of ethyl glyoxalate **420** and (R)-(+)- α -phenylethylamine, followed by a hetero Diels-Alder reaction with cyclopentadiene to furnish the desired cycloadduct as a mixture of diastereoisomers, **424a** and **424b**, as shown in **Scheme 74**. It has been shown that it is possible to separate these diastereoisomers by silica gel flash column chromatography.

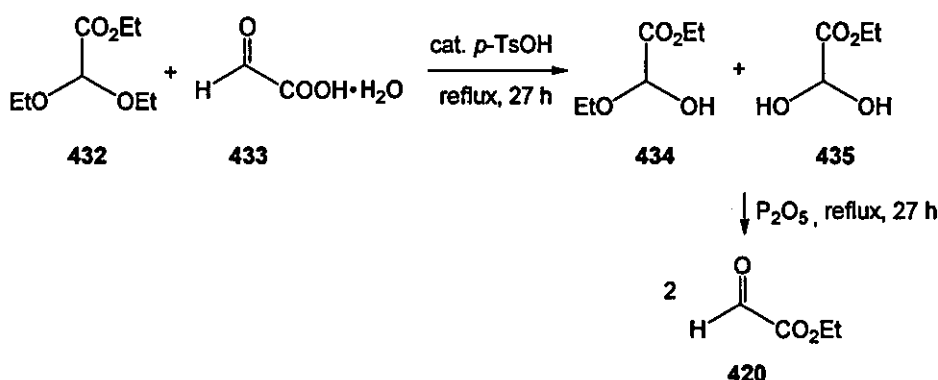


Scheme 74

5.2.5.2.1 Synthesis of ethyl glyoxalate

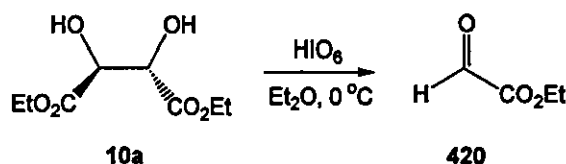
The synthesis required a large amount of pure ethyl glyoxalate. This can be obtained *via* a number of procedures. Initially, we synthesised it following the method reported by Hook,²³¹ as shown in **Scheme 75**. Ethyl diethoxyacetate **432** was reacted with glyoxylic acid monohydrate **433** and phosphorus pentoxide in the

presence of a catalytic amount of *para*-toluene sulphonic acid monohydrate. The desired product was isolated in reasonable yield, but it was difficult to remove from some polymeric impurities.



Scheme 75

An alternative method has been described by Kelly *et al.*²³² This involved the oxidative cleavage of L-diethyl tartrate **10a** using *para*-periodic acid, as shown in Equation 75. Following these conditions, ethyl glyoxalate **420** was isolated, but again it was difficult to purify fully.



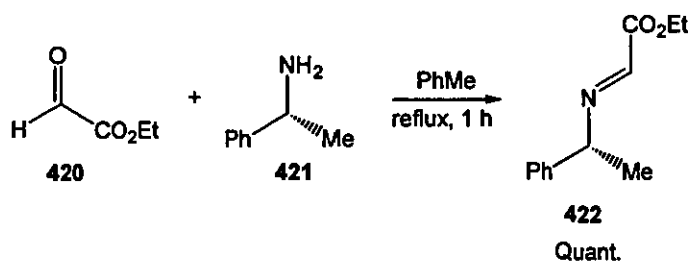
Equation 75

The best results were obtained following the procedure reported by Evans *et al.*²³³ A toluene solution of commercially available ethyl glyoxalate was heated to 110°C , in order to crack the polymer. The mixture was then heated to 140°C and most of the toluene was removed by distillation. Finally the mixture was heated up to $160\text{--}170^\circ\text{C}$, and the pure ethyl glyoxalate **420** was collected by distillation. During our first attempts only a small amount of ethyl glyoxalate was isolated. However, we found the yield could be improved by heating the solution to $160\text{--}170^\circ\text{C}$ directly after the initial period at 110°C . Following this procedure we were able to isolate large amounts of pure ethyl glyoxalate quickly and easily.

Analysis by ^1H NMR spectroscopy showed the aldehyde proton at 9.41 ppm, and the ester group at 1.43 ppm ($-\text{OCH}_2\text{CH}_3$) and 4.42 ppm ($-\text{OCH}_2\text{CH}_3$).

5.2.5.2.2 Synthesis of [(1R)-phenyl-ethylimino]-acetic acid ethyl ester

The next step in the synthesis was the formation of the chiral imine **422**, via the condensation of a solution of ethyl glyoxalate **420** in toluene with (R)-(+)-phenylethylamine **421**, following the procedure reported by Evans *et al.*²³³ This is described in Equation 76. We isolated the desired imine **422**²³¹ in quantitative yield.

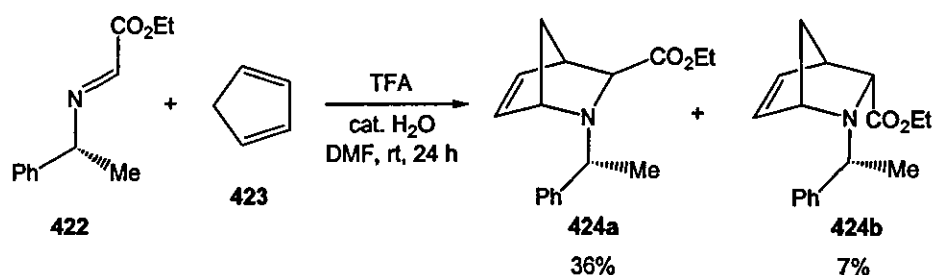


Equation 76

The structure of this compound was confirmed by spectroscopic analysis. IR spectroscopy showed the peaks for the carbonyl of the ester group and for the imino group at 1747 and 1720 cm^{-1} . The ^1H NMR spectrum showed the peak for the imino proton at 7.73 ppm, and the peaks for the ethyl group of the ester at 1.34 ppm ($-\text{OCH}_2\text{CH}_3$) and at 4.34 ppm ($-\text{OCH}_2\text{CH}_3$). Analysis by ^{13}C NMR spectroscopy showed the imino carbon at 152.3 ppm, and the carbonyl of the ester at 163.3 ppm.

5.2.5.2.3 Synthesis of (1R,3S,4S)-2-[(R)-(1-phenyl-ethyl)]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid ethyl ester

The final step in the synthesis of the cycloadduct **424** was a hetero Diels-Alder reaction between the imine **422** and freshly cracked cyclopentadiene **423**. The hetero Diels-Alder reaction was carried out in the presence of trifluoroacetic acid and water, as shown in Equation 77.²³⁰ The diastereoisomers **424a** and **424b**^{230,234} were isolated by silica gel flash chromatography, in moderate and low yield respectively.



Equation 77

Analysis by IR spectroscopy showed the carbonyl peak of the ester group at 1742 cm^{-1} , for the compound **424a**, and at 1745 cm^{-1} , for the compound **424b**. The ^1H NMR spectrum showed the peaks for the ethyl group of the ester at 0.95 ppm ($-\text{OCH}_2\text{CH}_3$) and 3.81 ppm ($-\text{OCH}_2\text{CH}_3$) for **424a**, and at 1.29 ppm ($-\text{OCH}_2\text{CH}_3$) and 4.22 ppm ($-\text{OCH}_2\text{CH}_3$) for **424b**. The protons of the double bond were observed at 6.27 and 6.40-6.44 ppm for **424a**, and at 6.01 and 6.37-6.41 ppm for **424b**, by ^1H NMR spectroscopy. The methylene group of the bridge was shown at 2.14 and 2.20 ppm for **424a**, and at 1.92 and 2.46 for **424b**, in the ^1H NMR spectrum and they appeared at 45.4 and 46.2 ppm, for **424a** and **424b** respectively, in the ^{13}C NMR spectrum.

The explanation of the need of a catalytic amount of water for the cycloaddition reaction to be accomplished, under acidic conditions, was given by Bailey *et al.*²³⁵ They hypothesised that the intermolecular hydrogen-bonding between the water and the imine afforded a seven membered ring complex, as shown in **Figure 44**. Due to steric preferences, the diene approached this π -stabilised iminium intermediate from the *Si* face.

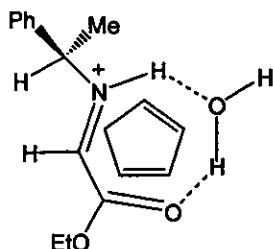


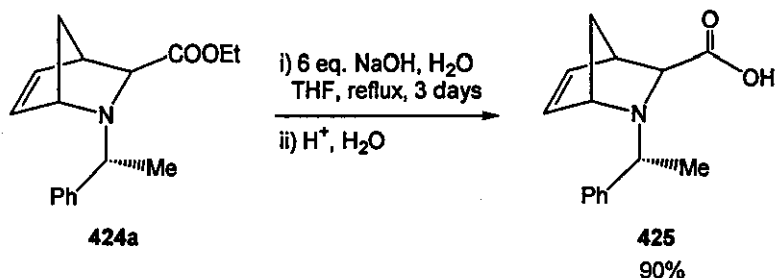
Figure 44

Therefore it was concluded that:

- The role of a catalytic amount of water was possibly to minimise the rotation of the iminium dienophile *via* seven-membered ring hydrogen-bonding.
- The *Si* face of the imine derived from ethyl glyoxalate and (R)-(+)-phenylethylamine was the preferred direction of approach of cyclopentadiene, suggesting that the selection of an (R)- or (S)- auxiliary might, in general, lead to a predominance of *Si* or *Re* attack respectively.

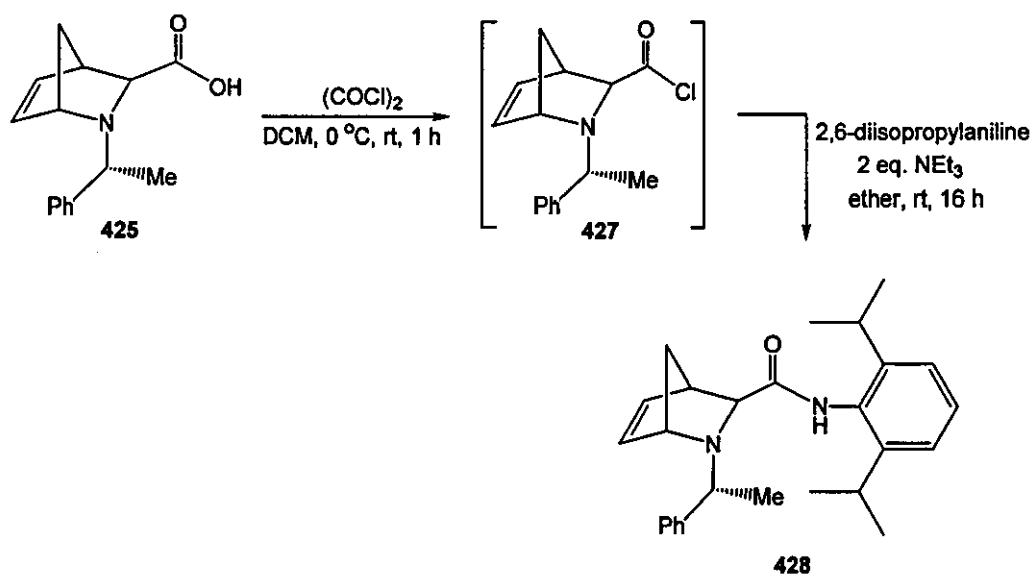
5.2.5.3 Synthesis of (1R,3S,4S)-2-[(R)-(1-phenyl-ethyl)]-2-aza-bicyclo[2.2.1]hept-5-ene-3 carboxylic acid

The manipulation of the cycloadduct **424a** initially involved the hydrolysis of the ester to the corresponding acid using an aqueous solution of sodium hydroxide in tetrahydrofuran, as shown in **Equation 78**. The desired acid **425** was obtained in excellent yield.



5.2.5.4 Attempted synthesis of (1R,3S,4S)-2-[(R)-(1-phenyl-ethyl)]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid(2,6-diisopropyl-phenyl)amide

Conversion of the acid **425** to the corresponding acid chloride **427** with oxalyl chloride, followed by reaction of the acid chloride with 2,6-diisopropylaniline **426**, in the presence of triethylamine, to obtain the amide **428**, was attempted as shown in **Scheme 76**. Unfortunately, the desired product **428** was not isolated and only starting materials were recovered.

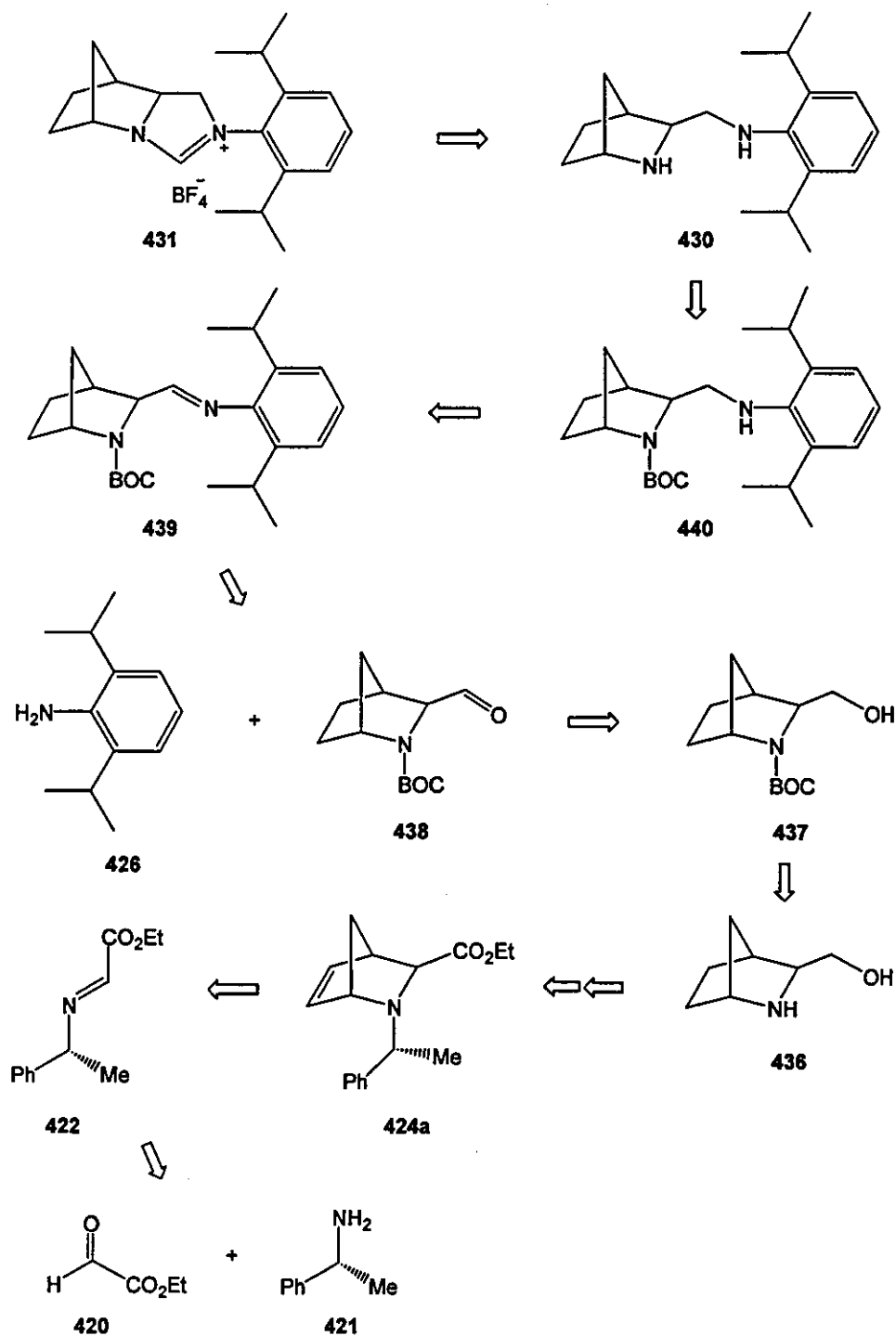


Scheme 76

Because of the failure of the formation of the amide **428** this retrosynthetic route was abandoned.

5.2.5.5 New approach for the synthesis of (1R,3S,4S)-4-(2,6-diisopropyl-phenyl)-2-aza-4-azonia-tricyclo [5.2.1.0^{2,6}] dec-3-ene tetrafluoroborate

Our modified retrosynthesis is shown in Scheme 77.

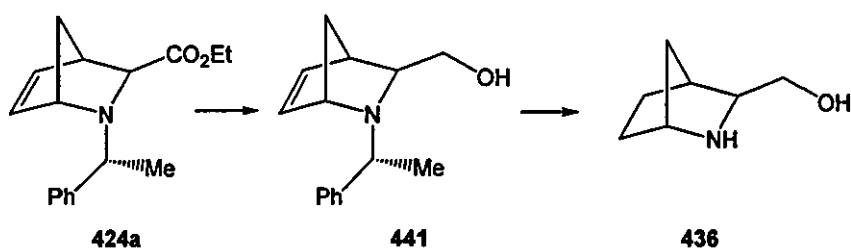


Scheme 77

In common with the previous retrosynthetic analysis (**Scheme 73**), this new approach also went *via* the exo cycloadduct **424a**. In our new scheme we wanted to obtain the aldehyde **438** *via* reduction of the ester group of the cycloadduct **424a**, removal of the α -phenylethyl group and the double bond by hydrogenation, BOC protection of the free nitrogen followed by oxidation of the *N*-BOC protected alcohol **437**. Condensation of the aldehyde **438** with 2,6-diisopropylaniline **426** would afford the imine **439**, which upon reduction would give the BOC protected intermediate **440**. Removal of the BOC group followed by cyclisation would give the desired imidazolinium salt **431**.

5.2.5.5.1 Attempted synthesis of (1R,3S,4S)-(2-aza-bicyclo[2.2.1]hept-3-yl)-methanol

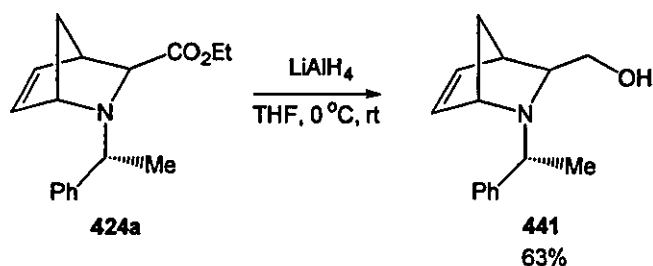
We wanted to convert the cycloadduct **424a** to the corresponding amino alcohol **436**. In our initial attempt, we decided to carry out reduction of the ester group of the cycloadduct **424a** to obtain the alcohol intermediate **441**, followed by hydrogenolysis to furnish the desired amino alcohol **436**, as shown in **Scheme 78**.



Scheme 78

5.2.5.5.1.1 Synthesis of (1R,3S,4S)-2-[[*(R)*-(1-phenyl-ethyl)]-2-aza-bicyclo[2.2.1]hept-5-en-3-yl]-methanol

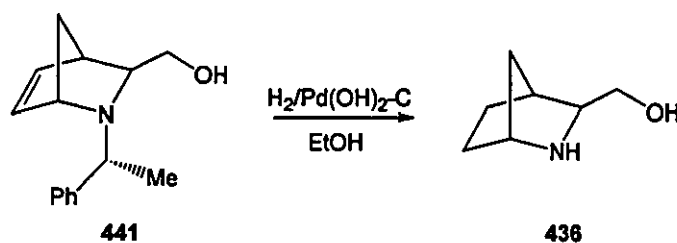
Treatment of the cycloadduct **424a** with lithium aluminium hydride, in anhydrous tetrahydrofuran, gave the desired alcohol **441** in good yield, as shown in **Equation 79**.



Equation 79

5.2.5.5.1.2 Attempted synthesis of (1R,3S,4S)-(2-aza-bicyclo[2.2.1]hept -3-yl)-methanol

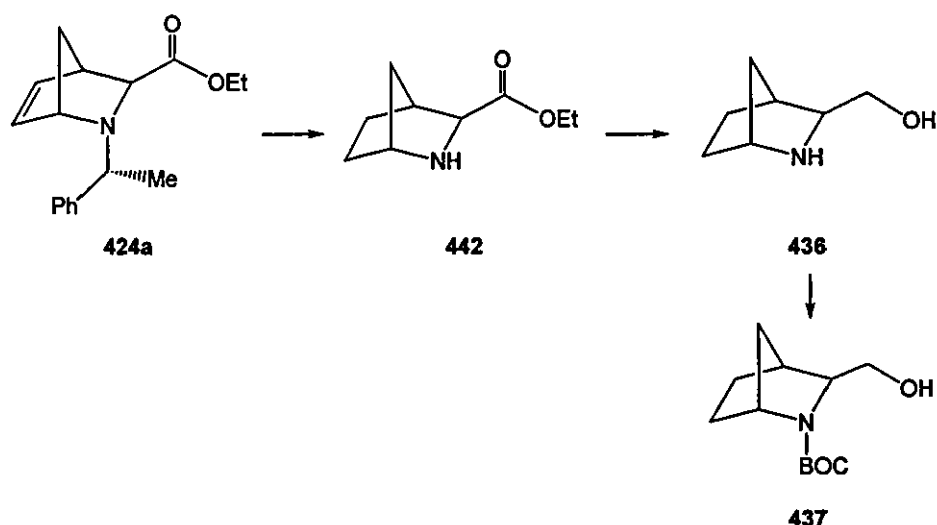
We next subjected the alcohol **441** to a range of hydrogenation conditions to attempt to remove the α -phenylethyl group and the double bond. The alcohol **441** was reacted with palladium hydroxide on carbon in ethanol, under a balloon of hydrogen, as shown in **Equation 80**. Unfortunately, only a complex mixture was observed by ^1H NMR spectroscopy and no signs of the desired product **436** were detected.



Equation 80

5.2.5.5.2 Synthesis of (1R,3S,4S)-3-hydroxymethyl-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

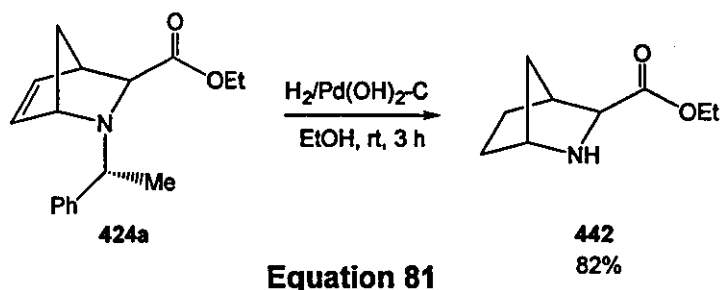
Because of the failure of the hydrogenation of the compound **441**, we decided to synthesise the amino alcohol **436** *via* the amino ester **442**, as proposed in **Scheme 79**. In this new pathway, hydrogenolysis was carried out first, and then the amino ester **442** was reduced to the desired amino alcohol **436**, which after reaction with di-*tert*-butyl dicarbonate could afford the amino protected alcohol **437**.



Scheme 79

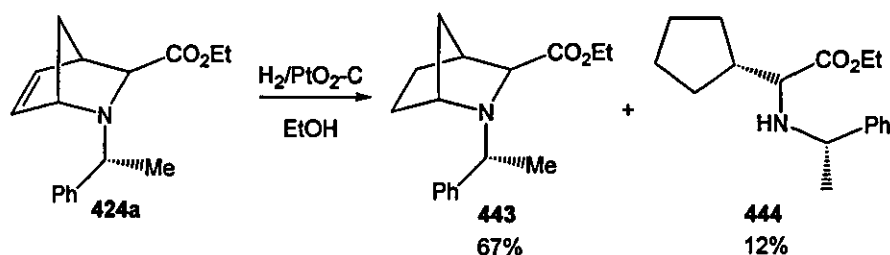
5.2.5.5.2.1 Synthesis of (1R,3S,4S)-2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid ethyl ester

We anticipated that the synthesis of the amino ester **442** could be carried out by hydrogenation of the cycloadduct **424a**. Therefore, a degassed solution of the cycloadduct **424a** in ethanol was added to palladium hydroxide on carbon and the reaction mixture was stirred under a balloon of hydrogen, as shown in **Equation 81**. We were pleased to isolate the desired amino ester **442**^{236,237} in good yield.



Analysis by IR spectroscopy showed a new peak at 3385 cm^{-1} , due to the stretching of the amino group. The ^1H NMR spectrum showed that neither the peaks at 6.27 and 6.40-6.44 ppm due to the double bond, nor the peaks corresponding to the phenylethylamine at 1.41 (ArCHCH_3), 3.04 (ArCHCH_3), and 7.13-7.40 (ArH) ppm, were no longer present, and a new singlet observed at 2.08 ppm was probably due to the NH. In the ^{13}C NMR spectrum the two new methylene groups were observed at 28.5 and 31.1 ppm.

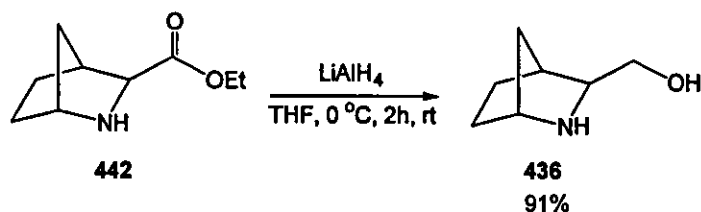
The reaction was also attempted using platinum oxide on carbon as the catalyst, but instead of isolating the desired product **442**, the compounds **443**,²³⁸ (1R,3S,4S)-2-[(1R)-phenyl-ethyl]-2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid ethyl ester, and **444**,²³⁹ (R)-cyclopentyl-N-[(1R)-phenyl-ethylamino]-acetic acid ethyl ester, were isolated, as shown in Equation 82.



Equation 82

5.2.5.5.2.2 Synthesis of (1R,3S,4S)-(2-aza-bicyclo[2.2.1]hept-3-yl)-methanol

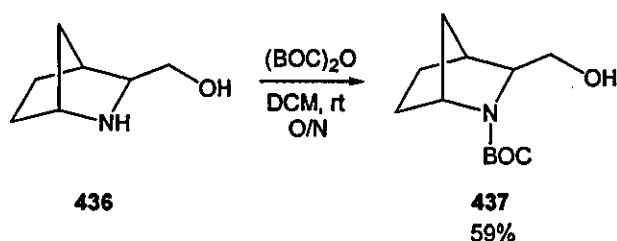
Reduction of the compound **442** was carried out using lithium aluminium hydride, as the reducing agent, in anhydrous tetrahydrofuran as shown in Equation 83. The amino alcohol **436**²³⁸ was obtained in excellent yield.



Equation 83

5.2.5.5.2.3 Synthesis of (1R,3S,4S)-3-hydroxymethyl-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

BOC protection of the amino alcohol **436** was carried out as shown in Equation 84. The amino alcohol **436** was reacted with a solution of di-*tert*-butyl dicarbonate in dichloromethane. Purification by silica gel flash chromatography furnished the desired amino protected alcohol **437**²⁴⁰ in moderate yield.

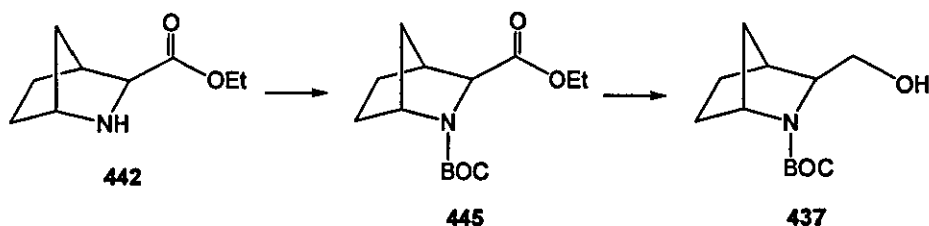


Equation 84

Analysis by IR spectroscopy showed the peak due to the carbonyl of the ester group present in BOC at $1694+1669\text{ cm}^{-1}$, and the band for the alcohol at 3419 cm^{-1} . The ^1H NMR spectrum showed a new peak for the three methyl groups at 1.47 ppm. The ^{13}C NMR spectrum showed three new peaks at 28.8 ppm, for the three methyl groups, 80.6 ppm, for the quaternary carbon and at 157.7 ppm, for the carbonyl carbon.

5.2.5.5.3 Alternative synthesis of (1R,3S,4S)-3-hydroxymethyl-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

This alternative synthesis of *N*-BOC protected alcohol **437**, shown in **Scheme 80**, was devised in case our previous synthesis, shown in **Scheme 79**, failed. This route involved the BOC protection of the amine **442** prior to reduction of the ester group.

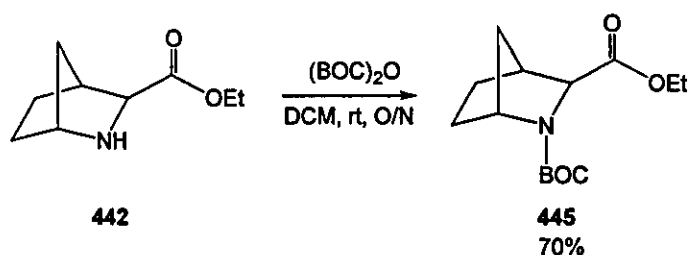


Scheme 80

5.2.5.5.3.1 Synthesis of (1R,3S,4S)-2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid-2-*tert*-butyl ester-3-ethyl ester

In order to carry out the BOC protection reaction, the amino ester **442** was reacted with a solution of di-*tert*-butyl dicarbonate in dichloromethane, as shown in

Equation 85, following a similar procedure reported by Madalengoitia *et al.*²⁴¹ The desired *N*-BOC amino ester **445**, was isolated in good yield, after purification by silica gel flash chromatography.



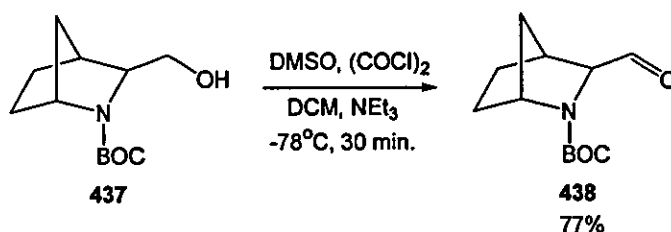
Equation 85

Analysis by IR spectroscopy showed the peak due to the free amine at 3385 cm^{-1} was not present, and both ester groups were shown at 1701 and 1751 cm^{-1} . The ^1H NMR spectrum showed the product existed as a mixture of rotamers, therefore a double peak for the new three methyl groups at 1.40 and 1.47 ppm , which by ^{13}C NMR spectroscopy were observed at 28.7 and 28.9 ppm . The ^{13}C NMR spectrum showed two peaks for each carbonyl carbon of the ester groups at 153.5 and 154.6 ppm and at 171.4 and 171.6 ppm , and also two peaks were shown for the quaternary carbon to which the three methyl groups are attached, at 80.0 ppm .

In the event, this alternative route was not taken any further, due to the fact that isolation of the BOC-protected amino alcohol **437** was achieved earlier from the amino alcohol **436**, when the retrosynthetic pathway shown in **Scheme 79** was followed.

5.2.5.5.4 Synthesis of (1R,3S,4S)-3-formyl-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

The next step in the sequence was to convert the *N*-BOC amino alcohol **437** to the corresponding *N*-BOC amino aldehyde **438**. This was achieved using the Swern conditions,²⁴¹ as shown in **Equation 86**. Reacting the *N*-BOC amino alcohol **437** with a mixture of dimethylsulfoxide and oxalyl chloride at $-78\text{ }^\circ\text{C}$, gave the desired *N*-BOC amino aldehyde **438**^{240,242} in good yield.

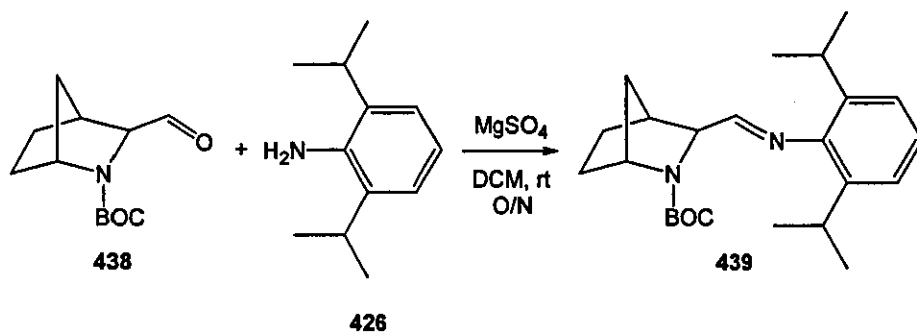


Equation 86

Analysis by IR spectroscopy showed a new peak due to the carbonyl of the aldehyde at 1694 cm^{-1} . Due to the formation of either rotamers or diastereoisomers (epimerisation at C-2), the ^1H NMR spectrum showed two new peaks for the aldehyde at 9.53 and 9.58 ppm, instead of one only peak. For the same reasons, the ^{13}C NMR spectrum showed a double peak for the carbonyl carbon of the aldehyde at 201.7 and 201.8 ppm.

5.2.5.5.5 Synthesis of (1R,3S,4S)-3-[(2,6-diisopropyl-phenylimino)-methyl]-2-aza-bicyclo[2.2.1] heptane-2- carboxylic acid *tert*-butyl ester

In order to obtain the imine **439**, the amino protected aldehyde **438** was reacted with 2,6-diisopropylaniline **426** in the presence of magnesium sulfate, in dichloromethane, as shown in Equation 87. The *N*-BOC protected imino compound **439** was isolated along with some traces of 2,6 diisopropylaniline.



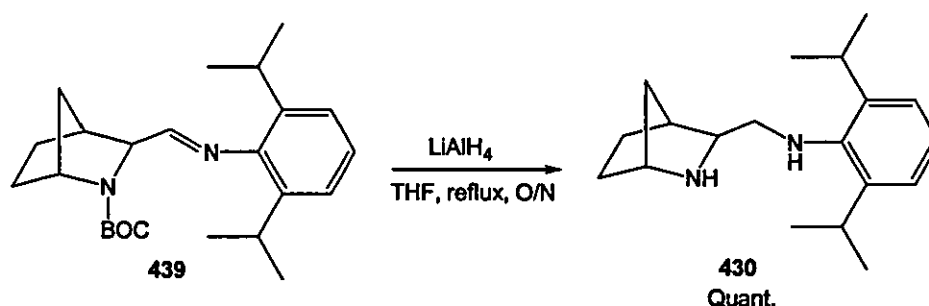
Equation 87

The interpretation of the ^1H NMR and ^{13}C NMR spectra was quite difficult due to the existence of rotamers. The ^1H NMR spectrum of the crude product showed the proton of the imine as two doublets at 7.54 and 7.56 ppm. By ^{13}C NMR spectroscopy, two peaks for the imine carbon were observed at 167.8 and

168.4 ppm. Before HETCOR and COSY spectra could be obtained decomposition of the product was observed.

5.2.5.5.6 Synthesis of (1R,3S,4S)-(2-aza-bicyclo[2.2.1]hept-3-ylmethyl)-(2,6-diisopropyl-phenyl)-amine

Reduction of the imine compound **439** was accomplished by reaction with a suspension of lithium aluminium hydride in anhydrous tetrahydrofuran, as shown in Equation 88. According to ^1H NMR and ^{13}C NMR spectra, deprotection occurred in the same step, to give the diamine **430** in quantitative yield.

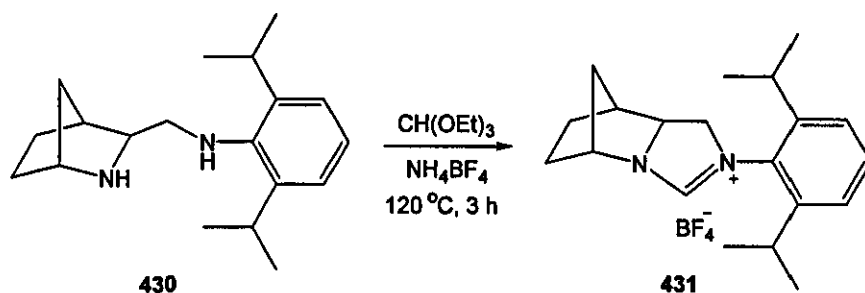


Equation 88

The ^1H NMR and ^{13}C NMR spectra were very complicated to interpret. Both are shown in the appendix. By ^1H NMR and ^{13}C NMR spectroscopy it was observed that the peaks corresponding to the BOC group had disappeared, indicating that deprotection took place, and the new methylene group resulting from the reduction was present at 56.2 ppm by ^{13}C NMR spectroscopy.

5.2.5.5.7 Synthesis of (1R,3S,4S)-4-(2,6-diisopropyl-phenyl)-2-aza-4-azonia-tricyclo [5.2.1.0^{2,6}] dec-3-ene tetrafluoroborate

Stoichiometric amounts of the diamine **430**, ammonium tetrafluoroborate and triethyl orthoformate were reacted under the conditions reported by Saba *et al.*,²⁰⁷ as shown in Equation 89. Recrystallisation of the crude product from ethanol was unsuccessful. According to both ^1H NMR and ^{13}C NMR spectra, the desired product **431** was formed, but some impurities and unreacted diamine **430** were also present.



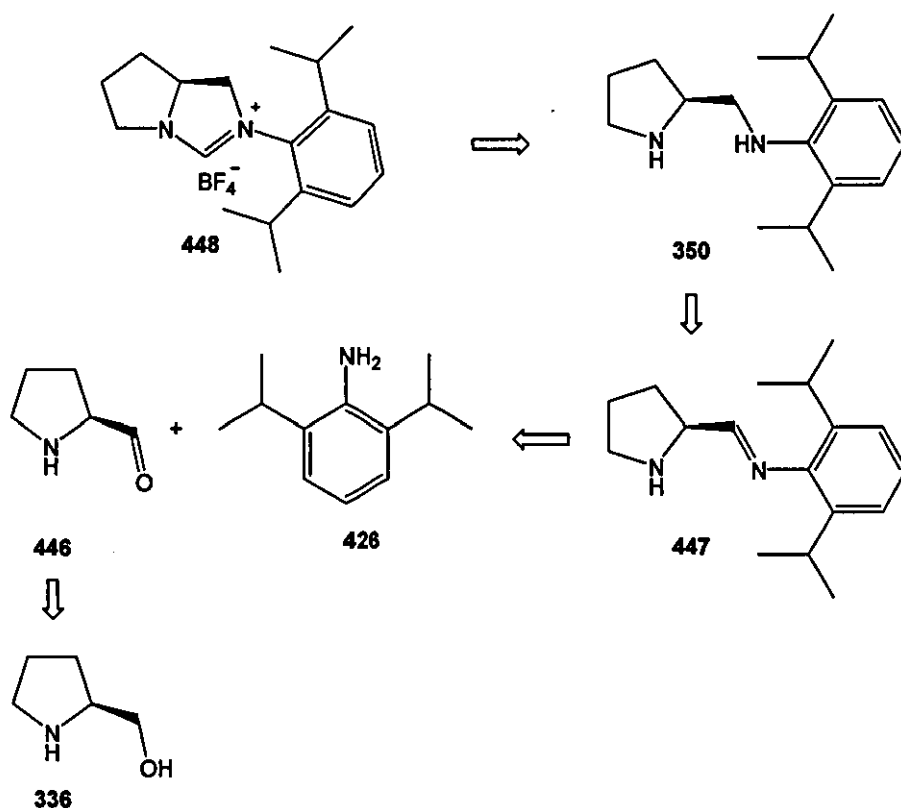
Equation 89

The interpretation of the ^1H NMR and ^{13}C NMR spectra was quite difficult. Evidence for the formation of the product **431** was provided by the fact that a peak corresponding to the imidazolinium proton appeared at 8.01-8.06 ppm in the ^1H NMR spectrum. In addition a peak at 163.3 ppm corresponding to the newly formed imidazolinium carbon centre was observed in the ^{13}C NMR spectrum.

5.2.6 Synthesis of imidazolinium tetrafluoroborate salt derived from (S)-prolinol

5.2.6.1 Introduction; retrosynthetic analysis

Prolinol is a cheap and readily available chiral material that can be purchased in either enantiomeric form. We thought that it could be used in the synthesis of novel chiral imidazolinium salts, according to the retrosynthesis shown in **Scheme 81**.

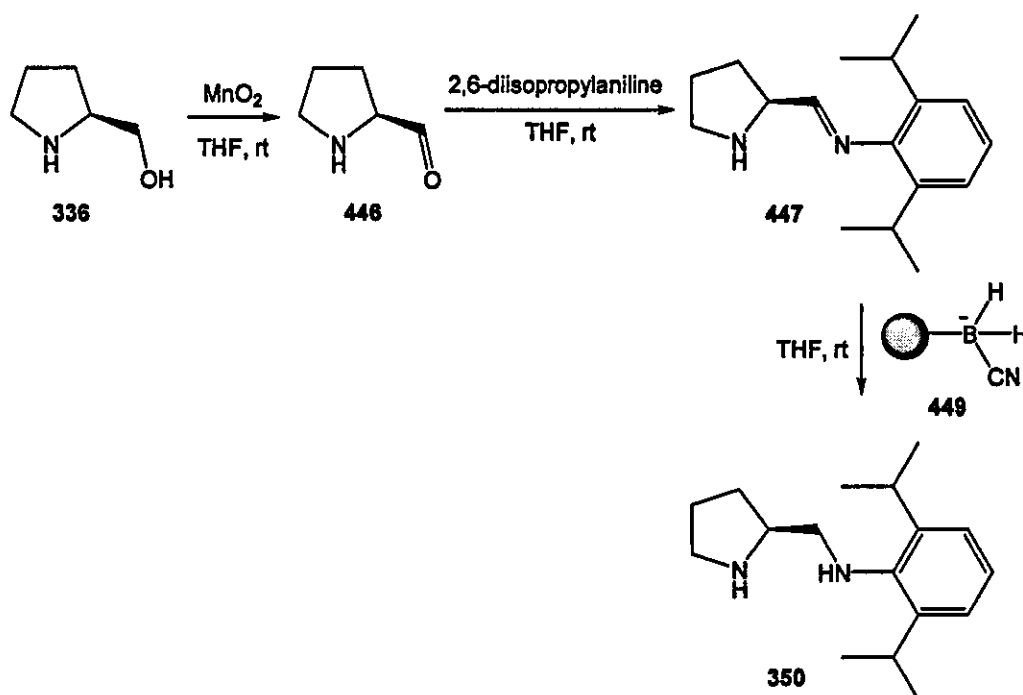


Scheme 81

Oxidation of (S)-prolinol **336**, followed by reaction with 2,6-diisopropylaniline **426** would give the imine **447**, which upon reduction would give the enantiomerically pure diamine **350**. Cyclisation using the conditions reported by Saba *et al.*²⁰⁷ would give the desired imidazolinium salt **448**.

5.2.6.2 Attempted one-pot synthesis of (2,6-diisopropyl-phenyl)-(2S)-pyrrolidin-2-ylmethyl-amine

We anticipated that the formation of diamine **350** could be carried out using a one-pot procedure, as shown in **Scheme 82**. Unfortunately, stirring a mixture of manganese oxide, (S)-prolinol **336**, 2,6-diisopropylaniline and (polystyrylmethyl)-trimethylammoniumcyanoborohydride **449** in anhydrous tetrahydrofuran at room temperature, only resulted in the isolation of starting materials. The reaction was repeated using dichloromethane as solvent, but again the desired product was not isolated.

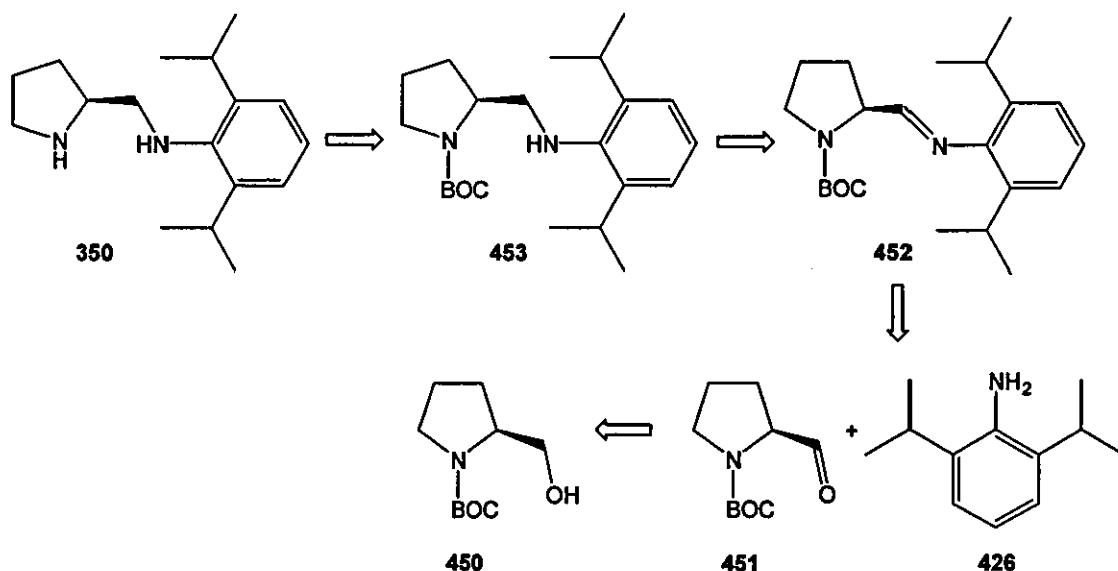


Scheme 82

5.2.6.3 New stepwise approach for the synthesis of (2,6-diisopropyl-phenyl)-(2S)-pyrrolidin-2-ylmethyl-amine

Due to the failure of this one-pot approach it was decided to attempt a stepwise pathway. In addition, it was thought to be prudent to start with *N*-BOC-(S)-prolinol **450** to prevent any possible side reactions occurring. *N*-BOC protected (S)-prolinol was chosen due to the fact that it was commercially available and also the BOC

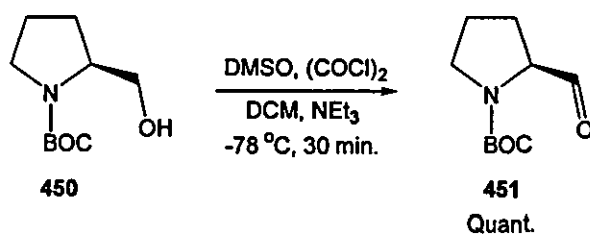
group could be easily removed upon treatment with acid. Our modified retrosynthesis is shown in **Scheme 83**.



Scheme 83

5.2.6.3.1 Synthesis of (2S)-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester or *N*-(*tert*-butoxycarbonyl)-(S)-prolinal

The oxidation of *N*-BOC-(S)-prolinol **450** has been shown to occur in excellent yield using the Swern conditions.²⁴¹ Therefore, reacting *N*-BOC-(S)-prolinol with a mixture of dimethylsulfoxide and oxalyl chloride at -78 °C, gave quantitatively the desired *N*-BOC-(S)-prolinal product **451**, as shown in **Equation 90**.



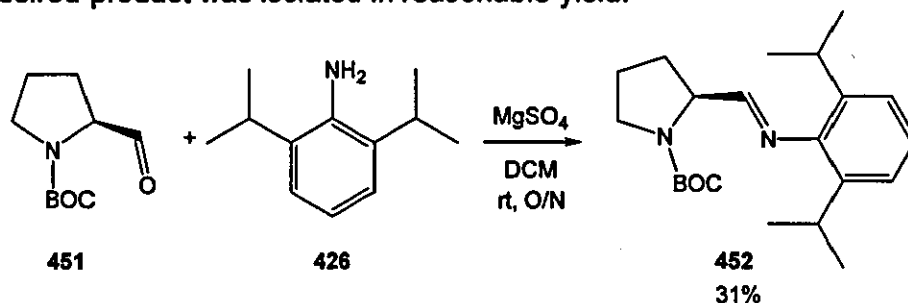
Equation 90

Analysis by IR spectroscopy showed two peaks at 1694 and 1736 cm^{-1} , due to the stretching of the carbonyl group present in BOC, and to the aldehyde. The ^1H NMR spectrum showed the product existed as a mixture of rotamers, probably

due to restricted rotation around the C-N carbamate bond. Therefore, two peaks for the aldehyde proton were observed at 9.46 and 9.56 ppm. Thus also, by ^{13}C NMR spectroscopy two sets of peaks were observed at 154.0 and 154.9 ppm, corresponding to the carbonyl carbon of the ester group, and at 200.4 and 200.6 ppm due to the carbonyl carbon of the aldehyde.

5.2.6.3.2 Synthesis of (2,6-diisopropyl-phenylimino)-methyl-(2S)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

Preparation of the compound **452** was accomplished by carrying out the reaction described in **Equation 91**. Stoichiometric amounts of *N*-BOC-(S)-prolinal **451** and 2,6-diisopropylaniline **426** were reacted at room temperature in dichloromethane, in the presence of magnesium sulfate. After silica gel flash chromatography and the desired product was isolated in reasonable yield.

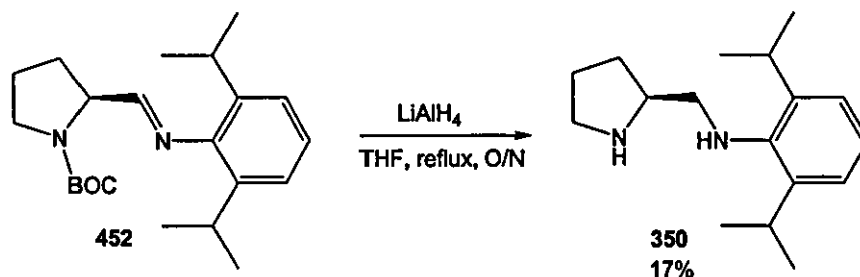


Equation 91

The imine peak was shown at 1698 cm^{-1} by IR spectroscopy, and at 7.58-7.63 ppm by ^1H NMR spectroscopy. The desired compound was shown to be unstable, decomposing by the time the ^{13}C NMR was obtained, and therefore this product was reacted in the next reaction as soon as possible. Although the ^{13}C NMR spectrum was very difficult to interpret, probably due to decomposition of the product, the signal corresponding to $\text{CH}=\text{N}$ was observed at 167.1 ppm.

5.2.6.3.3 Synthesis of (2,6-diisopropyl-phenyl)-(2S)-pyrrolidin-2-ylmethylamine

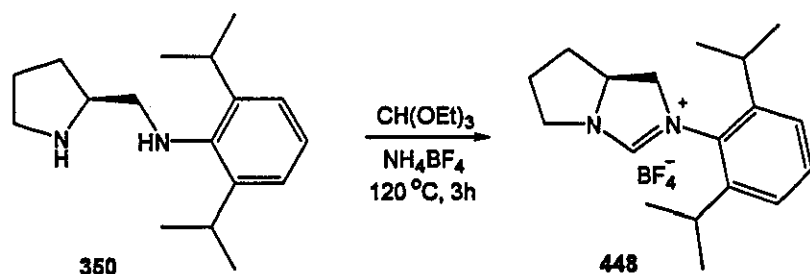
Reduction of the imine **452** was accomplished with lithium aluminium hydride in anhydrous tetrahydrofuran, as shown in Equation 92. Deprotection of the amino group occurred in the same step.



The imine peak was not present in the IR spectrum, and a new peak at 3354 cm^{-1} could be the one due to the stretching of the amino groups. The ^{13}C NMR spectrum showed the peaks for both $\text{CH}_2\text{-NH}$ groups at 53.7 and 58.1 ppm.

5.2.6.3.4 Synthesis of 2-(2,6-diisopropyl-phenyl)-(7aS)-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-2-ium tetrafluoroborate

Saba *et al.*²⁰⁷ have shown the formation of imidazolinium salts from 1,4-diamines occurs readily by reaction with triethyl orthoformate and ammonium tetrafluoroborate. Therefore, stoichiometric amounts of diamine **350**, ammonium tetrafluoroborate and triethyl orthoformate were reacted together, as shown in Equation 93. Recrystallisation of the crude product from ethanol was unsuccessful. Silica gel flash chromatography afforded the amide **454**, *N*-(2,6-diisopropyl-phenyl)-*N*-[(2S)-1-methyl-pyrrolidin-2-ylmethyl]-formamide, which was identified, after recrystallisation by diffusion from dichloromethane and diethyl ether, by X-Ray crystallography, as shown in Figure 45. This showed the compound formed was not the imidazolinium salt, but the formyl derivative **454**. Surprisingly the nitrogen of the proline ring has become methylated. It is not clear how this has occurred, or what the source of the methyl group is.



Equation 93

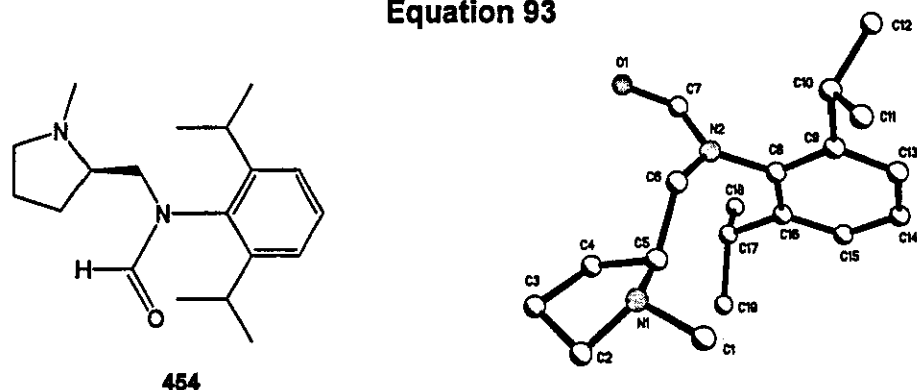


Figure 45

Analysis by IR spectroscopy showed a peak at 1673 cm^{-1} , due to the stretching of the carbonyl group, which was shown at 164.5 ppm in the ^{13}C NMR spectrum. By ^{13}C NMR spectroscopy it was observed that all the peaks, except the one at 41.5 ppm corresponding to $-\text{NCH}_3$, were duplicated in a ratio 6:1. This was probably due to the fact that either a small amount of the desired imidazolinium salt or an unidentified compound had been formed. Another explanation for this was that the molecule could exist as a mixture of the cis and trans compounds **454a** and **454b**, as shown in Figure 46. However, ^1H NMR spectroscopy carried out at $60\text{ }^{\circ}\text{C}$ did not show any changes. Both ^1H NMR and ^{13}C NMR spectra are shown in the appendix.

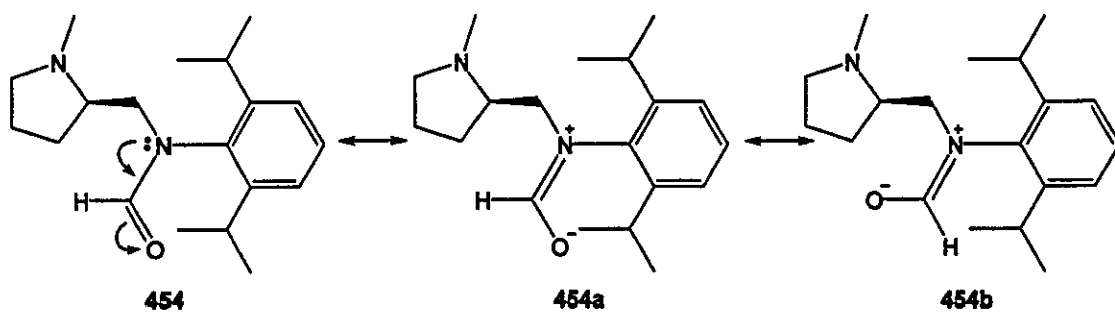
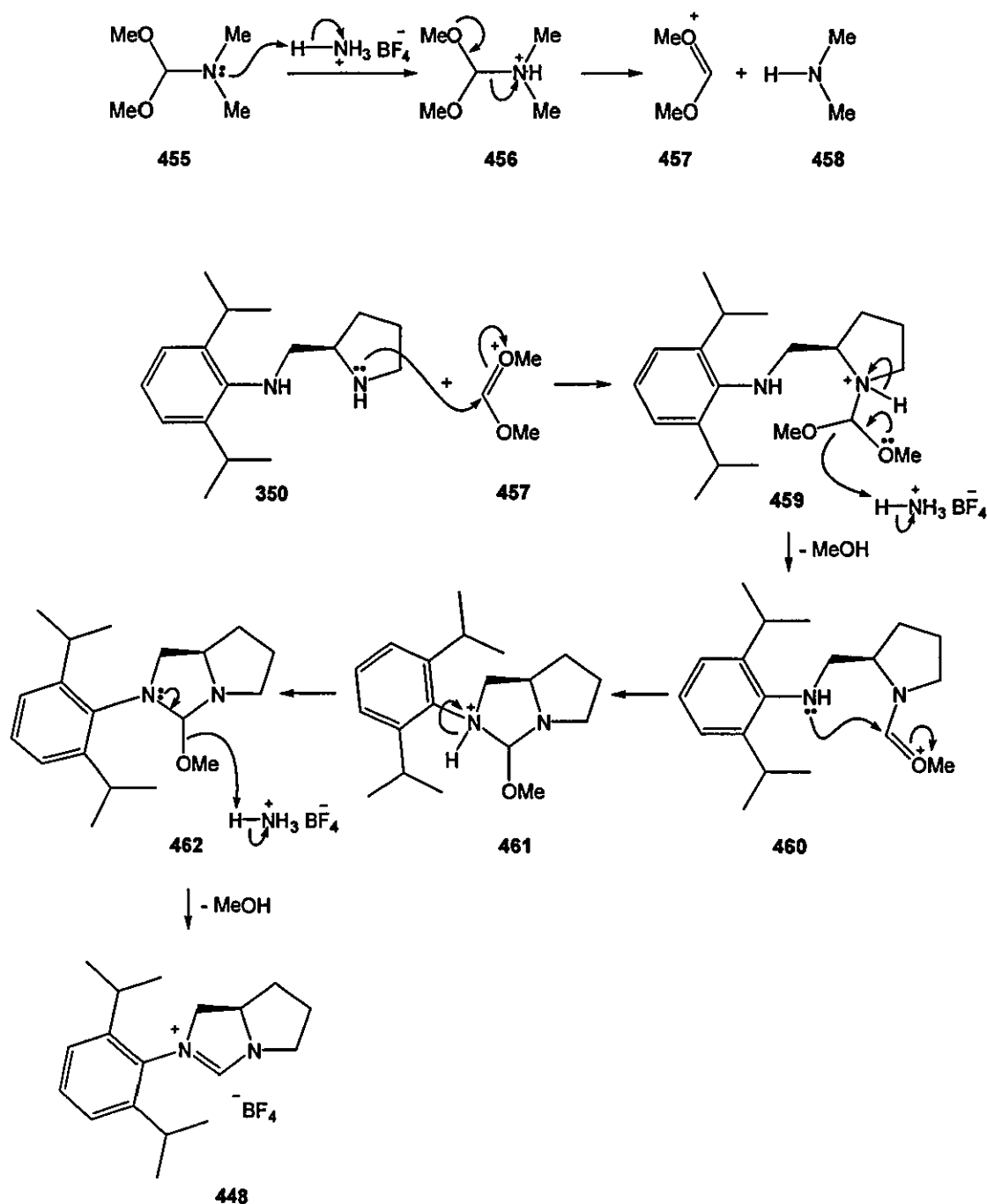


Figure 46

The reaction was also attempted using *N,N*-dimethylformamide dimethylacetal **455** instead of triethyl orthoformate as starting material, but no peak corresponding to the imidazolinium proton was observed in the ^1H NMR spectrum. The following mechanism was proposed for this reaction, as shown in **Scheme 84**.



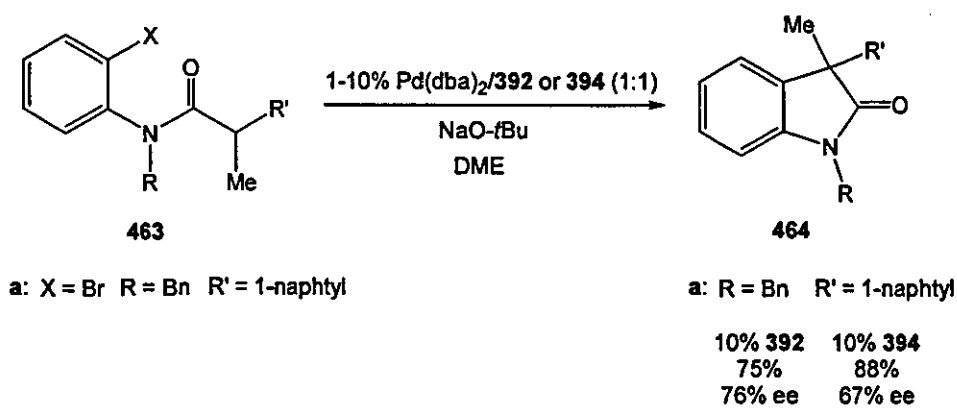
Scheme 84

5.2.7 Conclusion

We have successfully synthesised a number of new enantiomerically pure imidazolinium salts; **392**, with two pendant bornyl residues, **409** bearing two fenchyl groups and **431**, derived from (1R,3S,4S)-2-[(1R)-phenyl-ethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid ethyl ester **424a**. In addition, the synthesis of the imidazolinium salt **394**, bearing two isopinocampheyl groups, and the synthesis of the imidazolinium salt **448**, derived from (S)-prolinol, have both reached an advanced stage.

In the case of the imidazolinium salts bearing the bornyl, fenchyl and isopinocampheyl groups the chirality was derived from commercially available starting materials. In the case of the imidazolinium salt **431**, the chirality was a result of an aza Diels-Alder reaction in which both diastereomers were formed and separated. Therefore the other diastereomer could in theory be used in the same sequence of reactions to give the corresponding imidazolinium salt of opposite configuration. The same could also apply to the imidazolinium salt **448**, derived from (S)-prolinol **336**.

During this work, Hartwig *et al.*^{196a} published the synthesis and characterisation of *N,N'*-dibornyl imidazolinium salt **392** and *N,N'*-diisopinocampheyl imidazolinium salt **394**. The synthesis they followed was similar to our initial retrosynthesis, in that they reacted the required amine with aqueous glyoxal to give the corresponding diimines **404** and **415**, which were subsequently reduced using sodium triacetoxyborohydride to give the diamines **346** and **417**. Cyclisation using the conditions reported by Saba *et al.*²⁰⁷ gave the corresponding imidazolinium salts **392** and **394**. They used these ligands for the asymmetric synthesis of α -methyl, α -aryl oxindoles, starting from the corresponding 2-haloanilides, an example is shown in **Equation 94**.

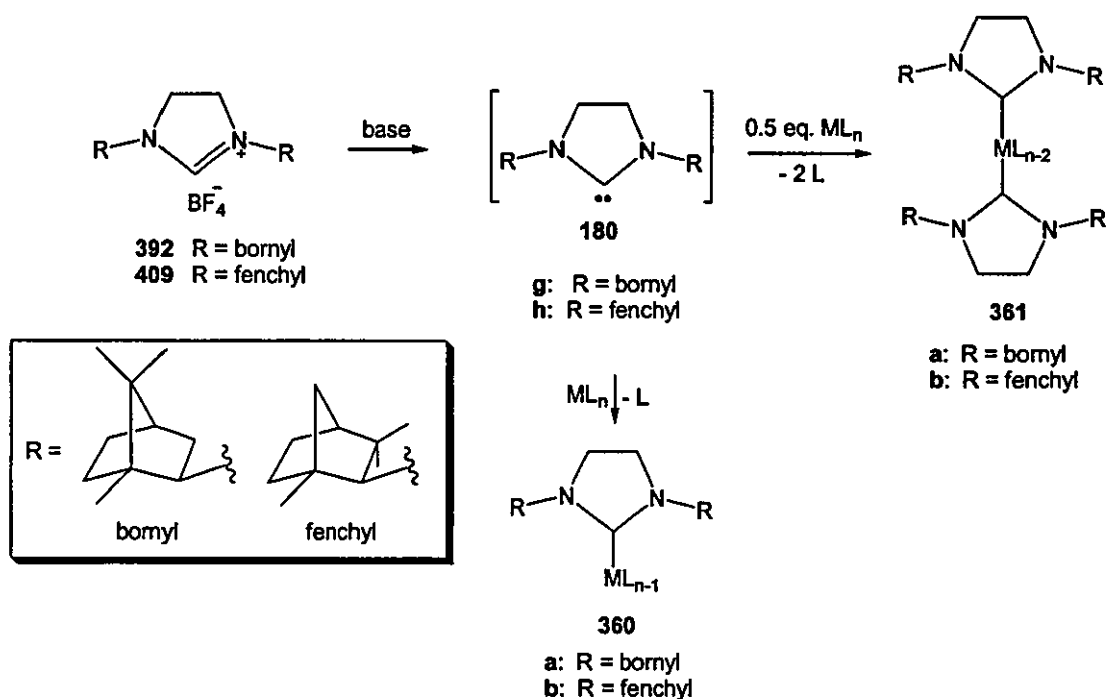


Equation 94

They obtained the corresponding α,α -disubstituted oxindoles **464** with good enantioselectivities, of up to 76 and 69% ee, using the ligands **392** and **394** respectively, much higher than those obtained when the same reactions were previously carried out with mono- or biphosphines, which gave enantioselectivities of 0-61% ee.

5.3 Attempted synthesis of fenchyl and bornyl transition metal-carbene complexes

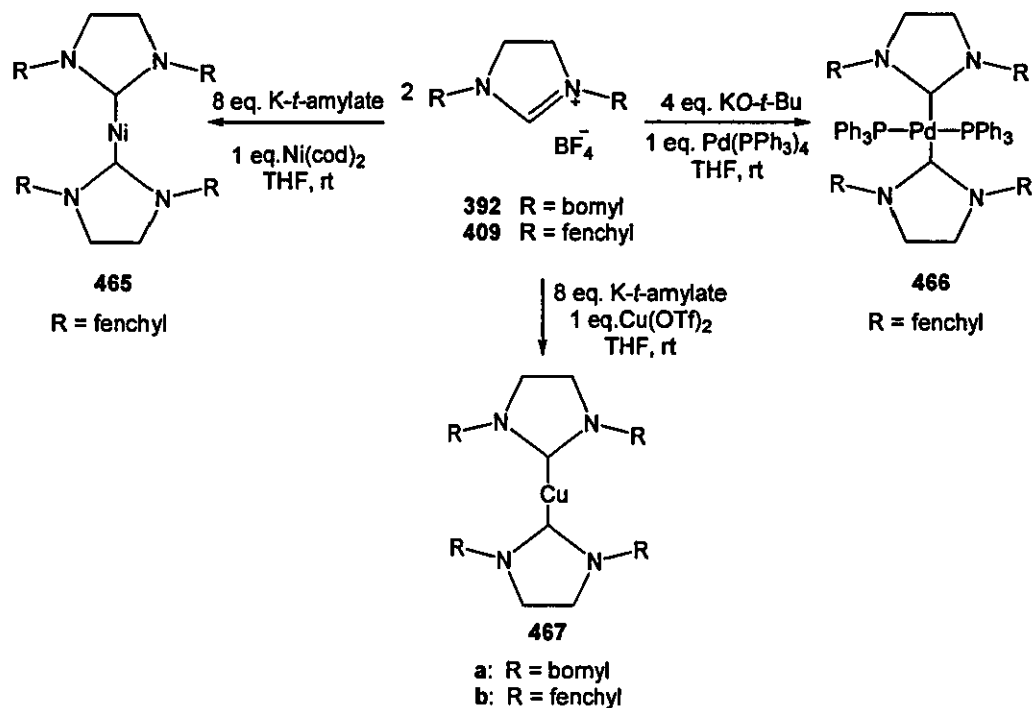
We were interested in the synthesis of mono- **360** and bis- **361** carbene transition metal complexes, using our newly formed fenchyl and bornyl chiral imidazolinium salts and a range of transition metals. It has been reported in the literature that 1,3-disubstituted-imidazol-2-ylidenes **180** can easily replace weaker donor ligands, such as triflates, phosphines, nitriles, carbon monoxide, pyridine or tetrahydrofuran.^{125,198,199} This clean, quantitative substitution of two-electron donor ligands is unprecedented, and clearly reflects the extraordinary strong σ -donor properties of the nucleophilic imidazol-2-ylidenes. We proposed to form the following carbene metal complexes **360** and **361** via deprotonation of the corresponding imidazolinium salt **392** or **409**, using a suitable base, in order to form the active carbene species **180g-h**, followed by the addition of the required transition metal complex, ML_n . Displacement of either one or two ligands from the metal would give either the mono- **360** or bis- **361** carbene transition metal complex. This is outlined in **Scheme 85**.



Scheme 85

5.3.1 Attempted synthesis of bis-(carbene) metal complexes

Some examples of formation of bis-(carbene) transition metal adducts derived from either chiral imidazolinyliidines (nickel,¹¹⁰ palladium¹⁰⁷ and rhodium²⁴³) or imidazolyliidines (ruthenium and rhodium)^{208a,243} have been reported. In general, the carbene is generated *via* the treatment of the required imidazolium salt with a base, such as potassium *tert*-amylate, potassium *tert*-butoxide or lithium *tert*-butoxide, in tetrahydrofuran. In our initial experiments we decided to follow this methodology. Several reactions were attempted in order to furnish the nickel bis-imidazolinyliidene complex **465**, bis-imidazolinyliidene bis-(triphenylphosphine) palladium complex **466** and bis-imidazolinyliidene copper complexes, **467a** and **467b**, as shown in Scheme 86. Starting from the imidazolium tetrafluoroborate salts **392** and **409**, the corresponding carbenes were generated *in situ*, after reaction with either potassium *tert*-amylate or potassium *tert*-butoxide. The metal complexes were then added to the carbene solution in order to afford the desired bis-carbene complexes. Unfortunately, we did not manage to get these reactions to work, and no sign of the products were observed by ¹H NMR spectroscopy.



Scheme 86

The only product isolated from the reaction of the difenchyl imidazolium tetrafluoroborate salt **409**, potassium *tert*-amylate and nickel cyclooctadiene was the urea derivative **468**, 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolidin-2-one, which was identified by X-Ray crystallography, as shown in **Figure 47**, and was obtained in moderate yield. Possibly it was formed due to a rapid oxidation of the nickel cyclooctadiene complex.

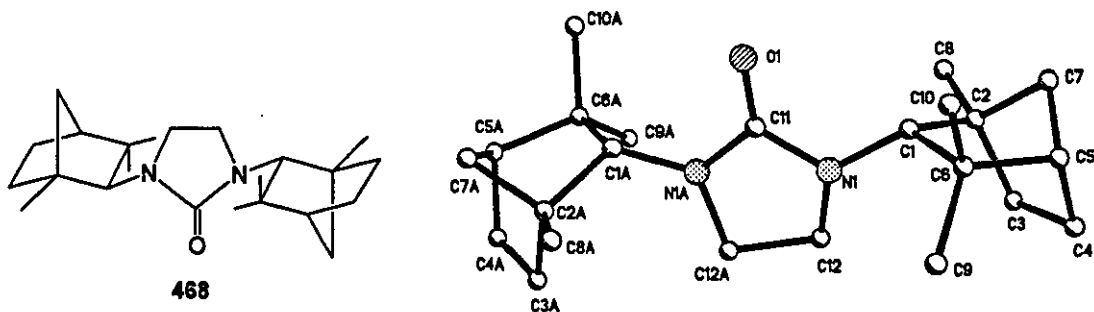


Figure 47

The carbonyl group was observed at 1672 cm^{-1} by IR spectroscopy, and at 163.7 ppm by ^{13}C NMR spectroscopy.

A similar urea derivative **469**, 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolidin-2-one, was also isolated in the complex forming reaction when the dibornyl imidazolium tetrafluoroborate salt **392**, potassium *tert*-amylate and copper triflate were reacted. This compound **469** was also identified by X-Ray crystallography, as shown in **Figure 48**, and it was obtained in low yield.

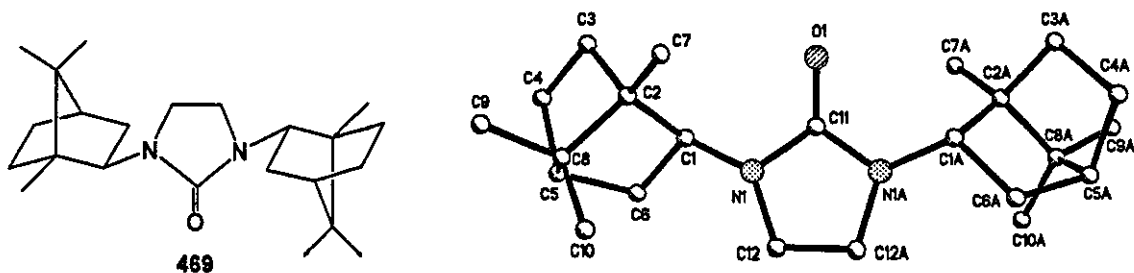


Figure 48

Analysis by IR spectroscopy the carbonyl group was shown at 1685 cm^{-1} , and in the ^{13}C NMR spectrum it was observed at 164.1 ppm .

Curiously, when the same reaction was carried out using difenchyl imidazolinium tetrafluoroborate salt **409**, potassium *tert*-amylate and copper triflate in order to obtain the compound **467b**, the urea derivative **468** and the compound **470**, 1,4-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-piperazin-2-one, were instead obtained. The piperazin-2-one **470** was also identified by X-Ray crystallography, as shown in **Figure 49**.

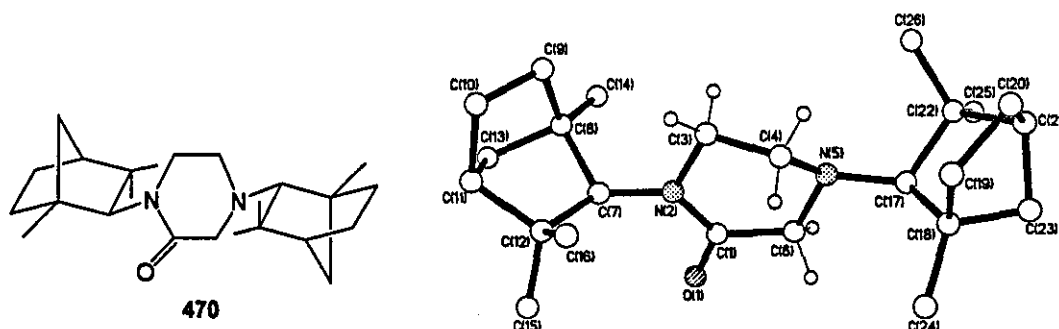
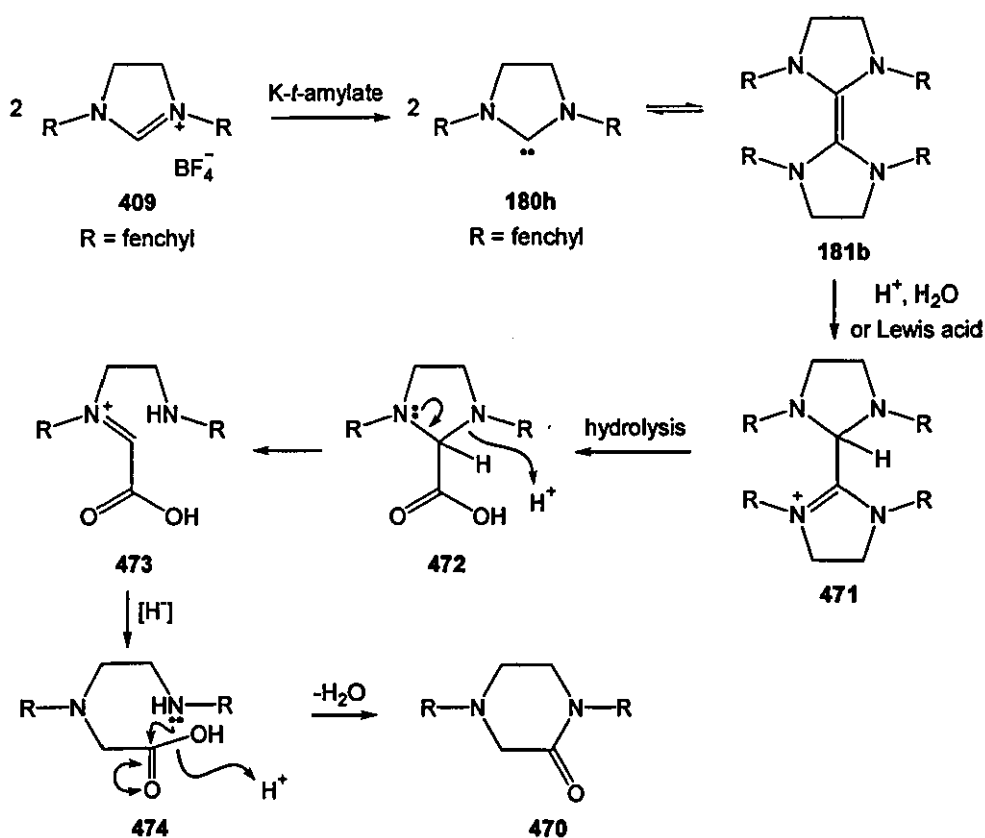


Figure 49

The ^1H NMR and ^{13}C NMR spectra were very complicated to interpret due to the fact that they showed more signals than expected. This was probably due to rotation of the C-N bonds. Analysis by IR spectroscopy showed the carbonyl peak at 1649 cm^{-1} , and the ^{13}C NMR spectrum showed the carbonyl carbon at 169.6 ppm .

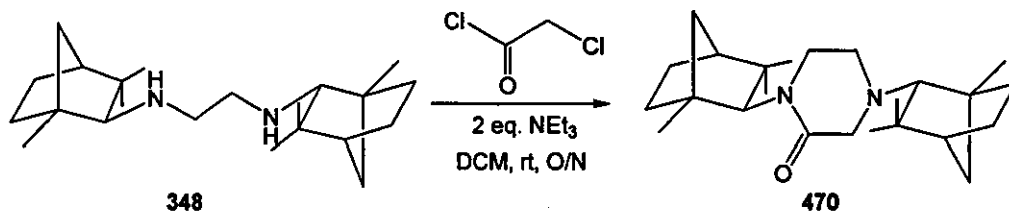
A possible mechanism for the formation of the piperazin-2-one **470** is suggested in **Scheme 87**. In the presence of potassium *tert*-amylate the imidazolinium salt **409** could be deprotonated to afford the carbene **180h**. In the next step, probably two molecules of carbene **180h** could have dimerised, to give the compound **181b**, although it seems unlikely to be due to the bulky substituents. Protonation of the double bond of the dimer **181b**, could have occurred next, to furnish the imidazolinium salt **471**. Hydrolysis of this salt could afford the imidazolidine-2-carboxylic acid **472**, which could ring-open to afford the iminium salt **473**. Reduction of the compound **473** could have occurred in the following step, although it is not clear what the reducing agent is, possibly a molecule of **471** or **472** could have acted as a hydride transfer agent, or maybe a low valent copper species acted as the reducing agent. Cyclisation of compound **474** takes probably

place in the last step, with subsequent elimination of water, in order to give the piperazin-2-one **470**.



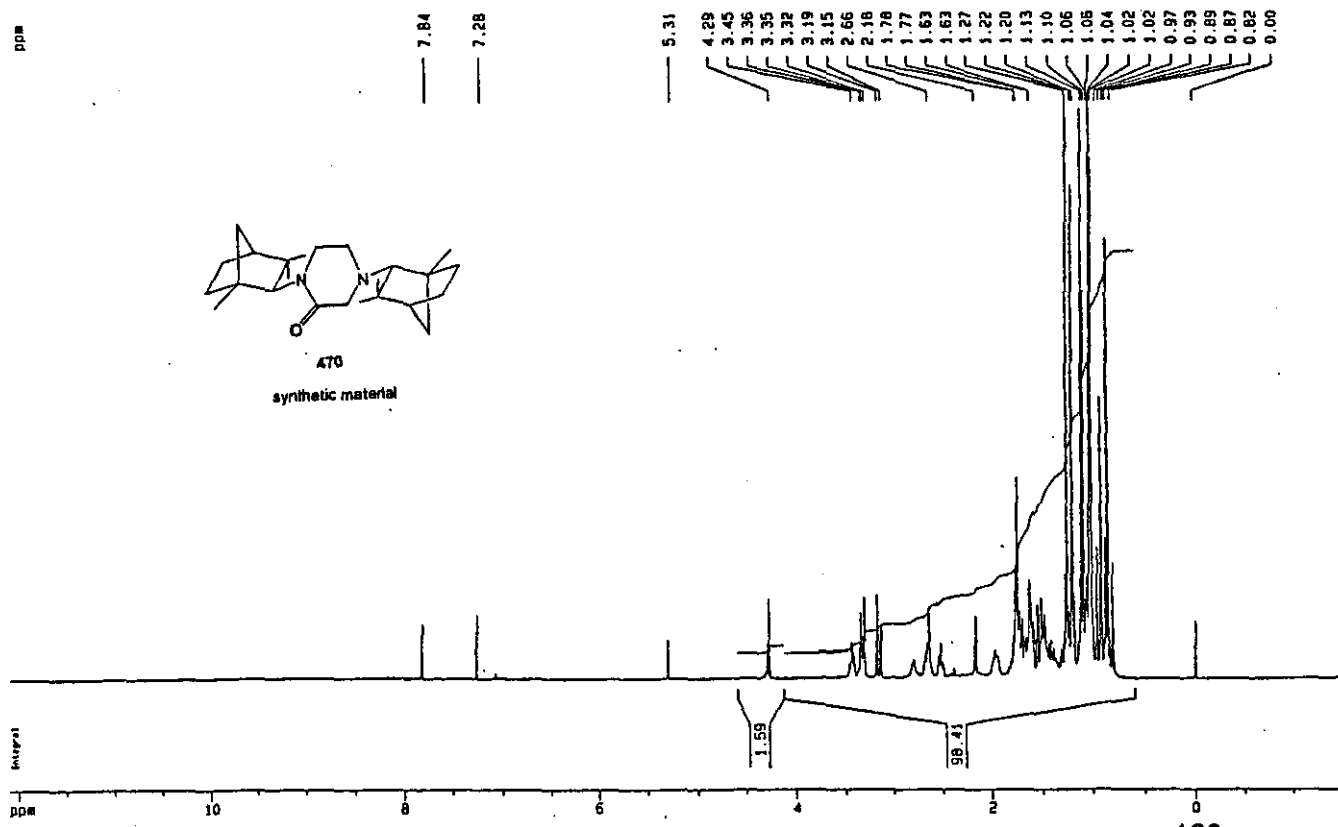
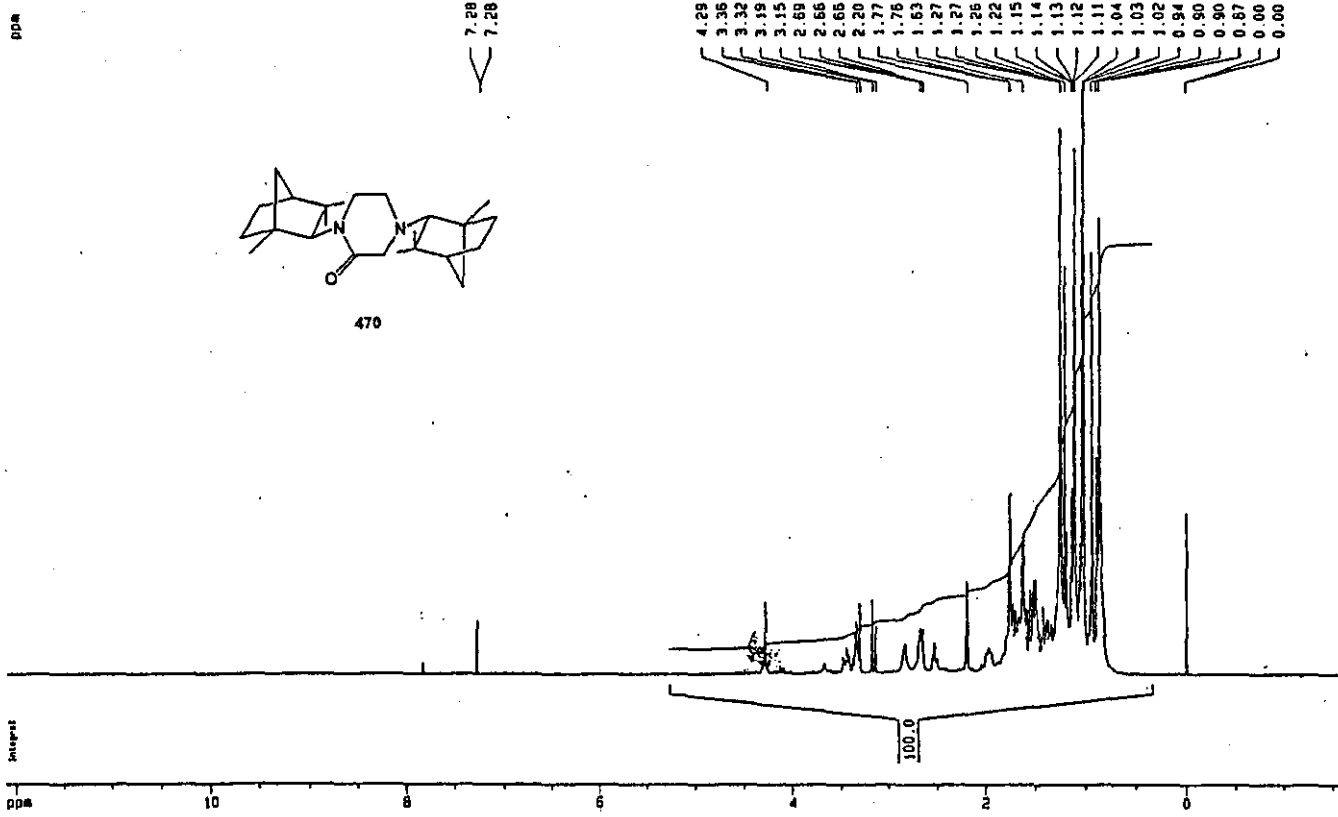
Scheme 87

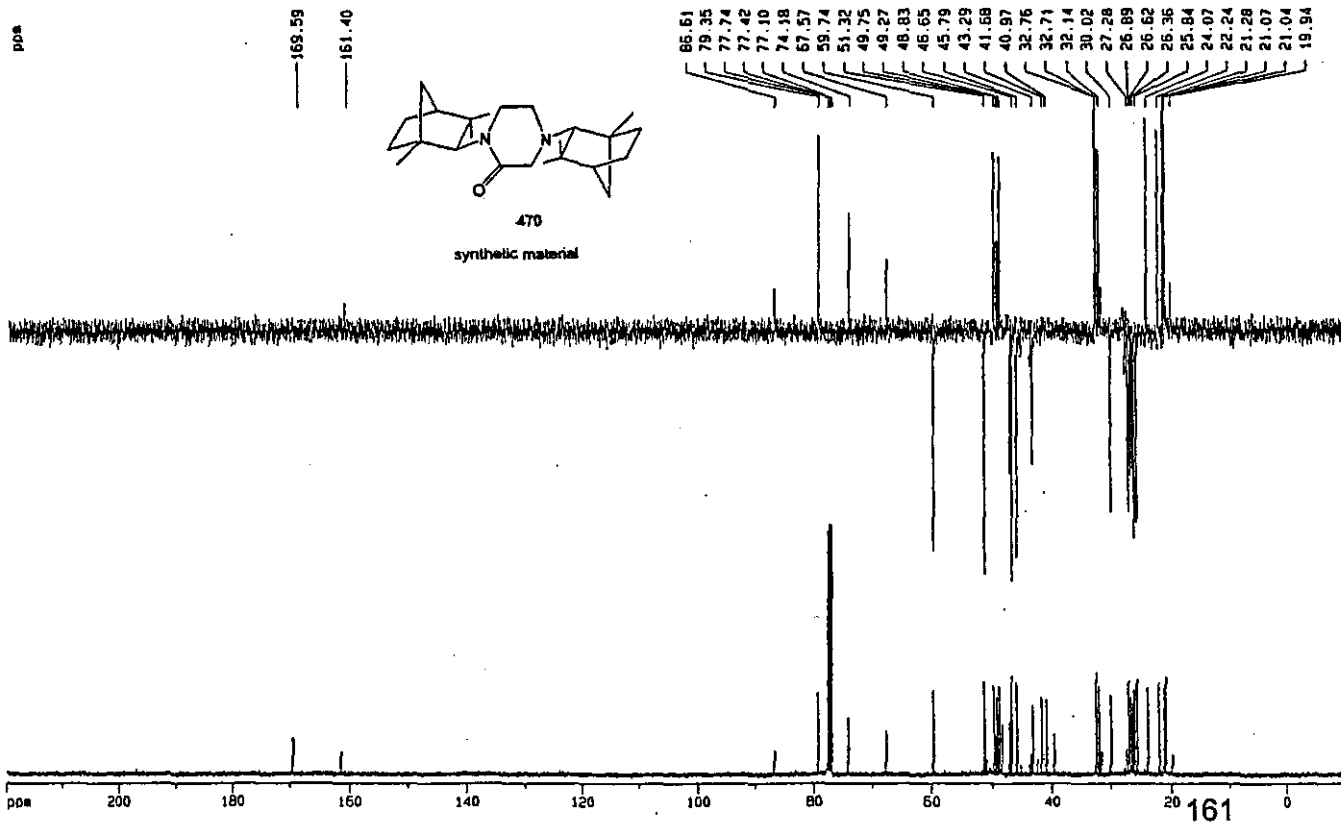
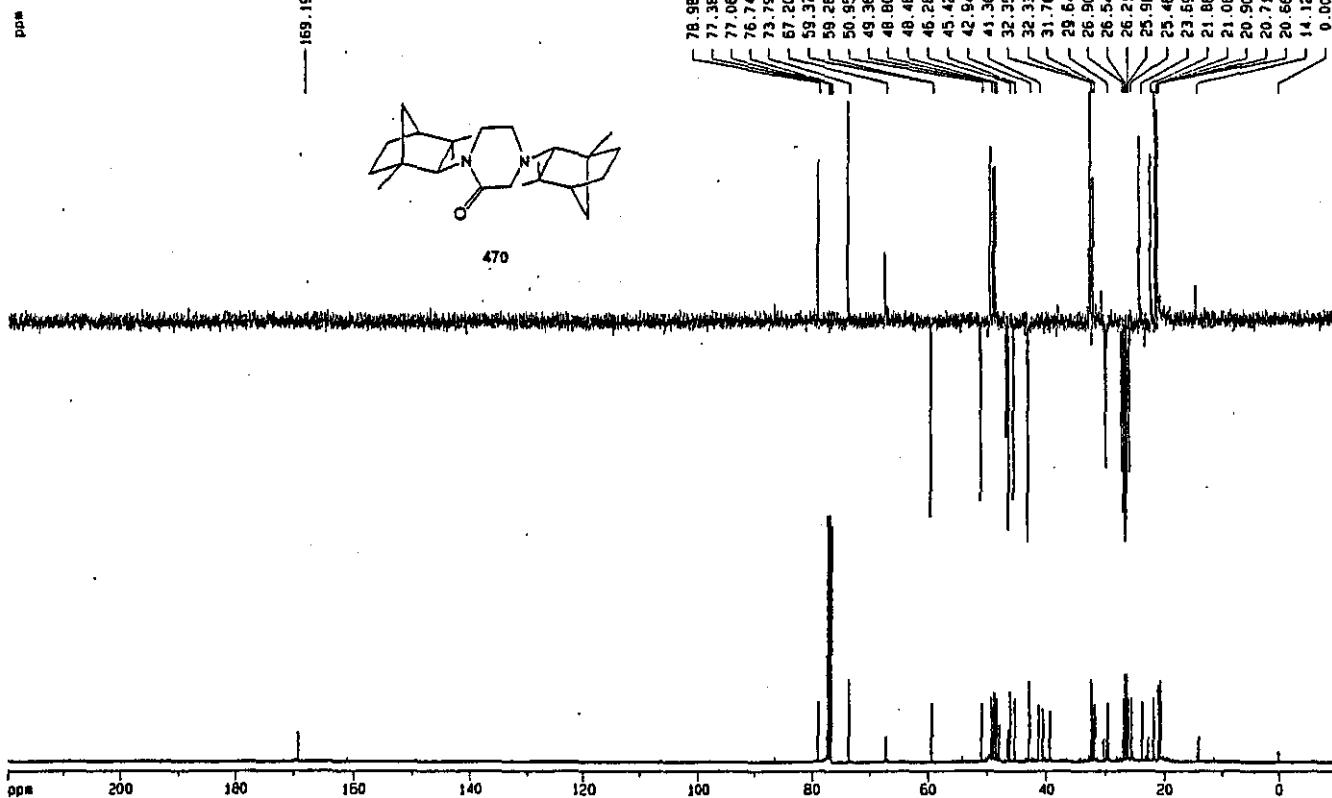
To further confirm the structure of the piperazin-2-one **470** we decided to synthesise it *via* another method. The diamine **348** was reacted with chloroacetyl chloride, in the presence of triethylamine, in dichloromethane, as shown in **Equation 95**. The piperazin-2-one **470** was obtained in low yield.



Equation 95

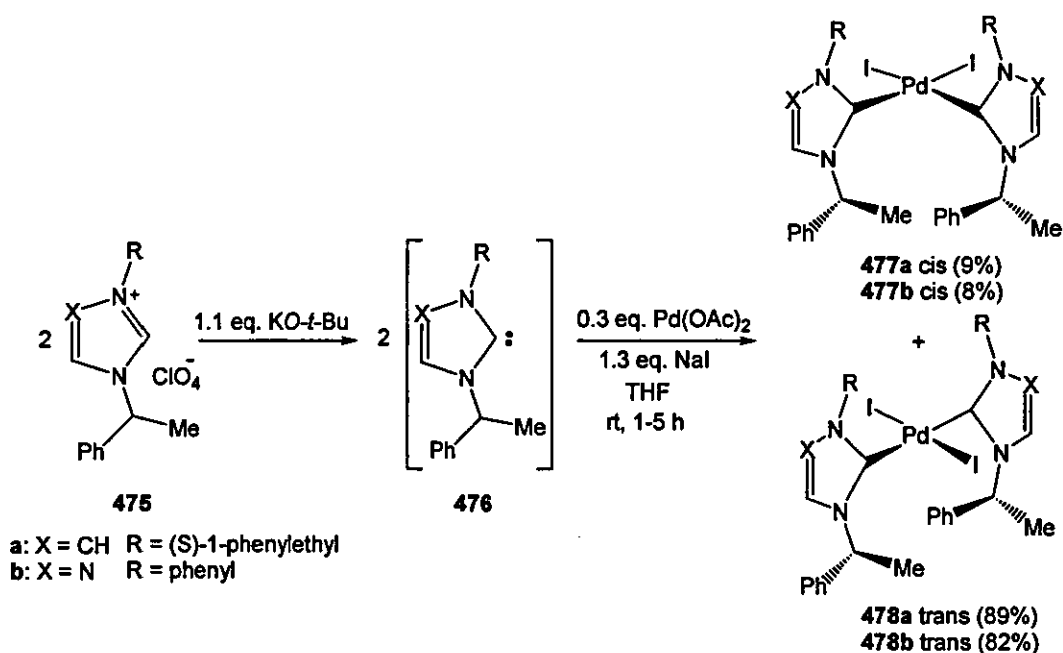
The spectral data of the two materials were identical, and comparison of both ¹H and ¹³C NMR is shown in pages 160 and 161.





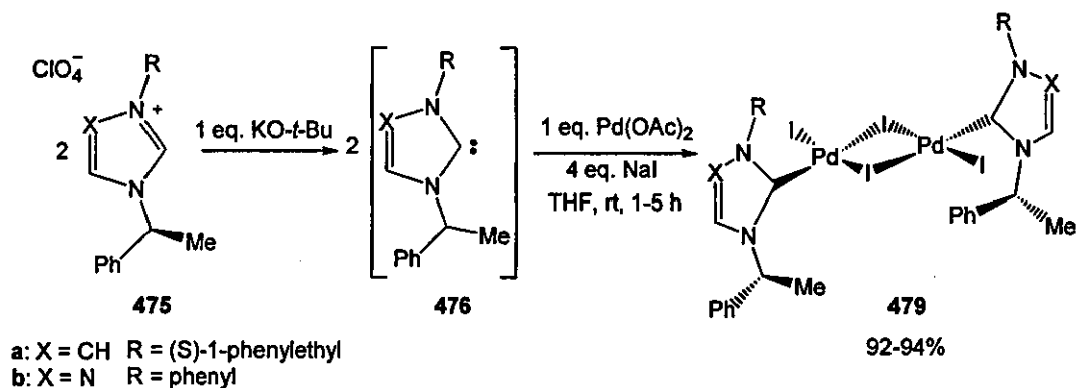
5.3.1.1 Palladium-iodide carbene adducts

In 1996, Enders *et al.*¹¹² reported the synthesis of the unsaturated chiral dicarbene-diiodopalladium (II) complexes **477a-b** and **478a-b** by the reaction of a chiral imidazolium **475a** or triazolium **475b** perchlorate with palladium acetate, sodium iodide and a base, as shown in **Scheme 88**. For the non-symmetric cis and trans complexes with the triazolinylidene ligand, **477b** and **478b**, different rotamers can be formed; syn, if the two 1-phenylethyl groups are pointing in same direction or anti, if they point in different directions.



Scheme 88

When the same reaction was carried out using 1 equivalent of palladium acetate, instead of 0.3 equivalents, the binuclear complex **479**, with bridging iodine atoms, was obtained as shown in **Scheme 89**.



Scheme 89

We attempted the synthesis of the saturated bis-(carbene) complexes **480** and **481**, shown in **Figure 50**, using as the starting salt the difenchyl imidazolinium tetrafluoroborate **409**, following the conditions reported by Enders *et al.*¹¹² but unfortunately, we did not manage to isolate any of these complexes.

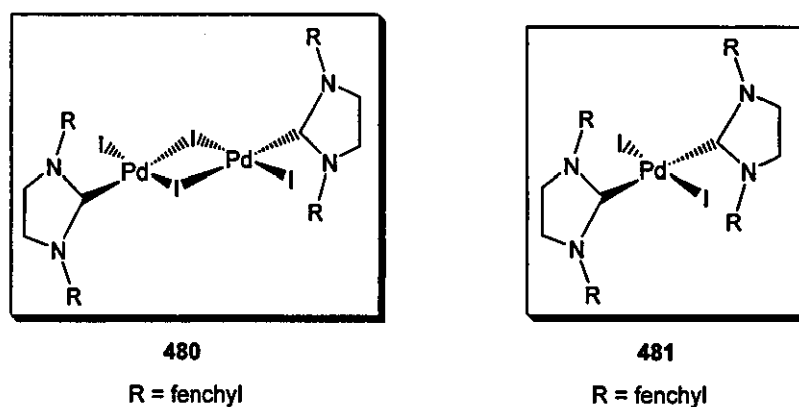


Figure 50

Surprisingly, in the attempt to synthesise the palladium bis-(carbene) complex **480**, the salt **482**, bis-[1,3-bis-(1R,2R,4S)-(1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-4,5-dihydro-3H-imidazol-1-ium] diiodo- $\mu\mu'$ -diiododipalladium, was isolated in very low yield. The structure of the compound was identified by X-Ray crystallography, as shown in **Figure 51**.

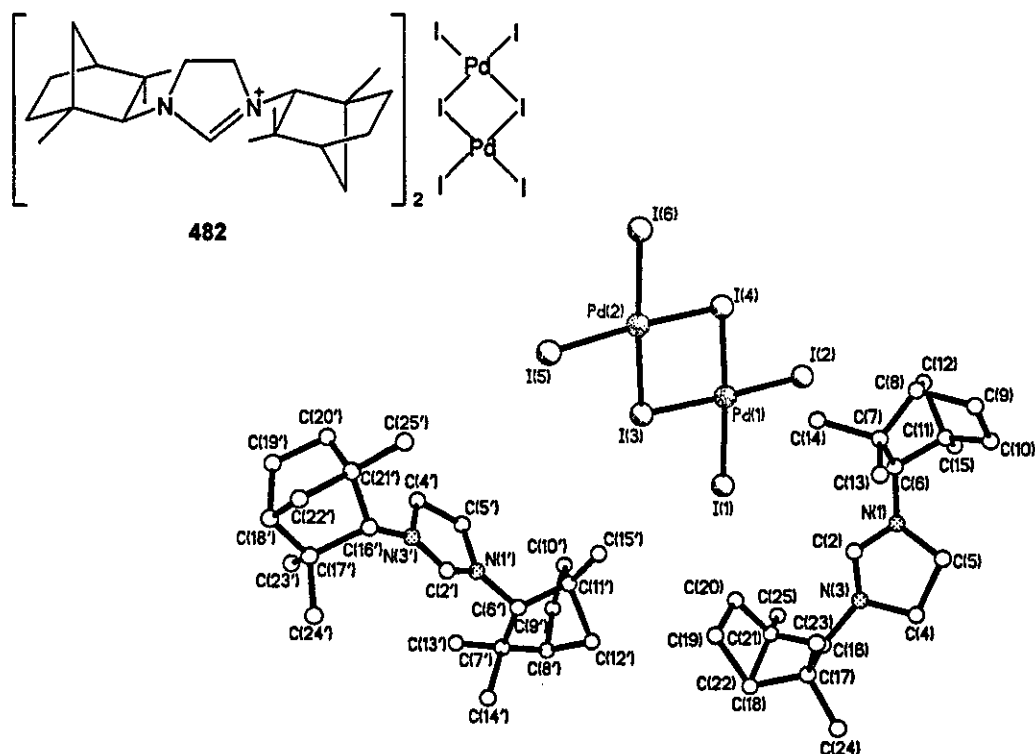


Figure 51

In the attempt to synthesise the palladium bis-(carbene) complex **481**, the salt **482**, was also isolated in very low yield. The same reaction was attempted on a larger scale, using an excess of base, but again isolation of the desired palladium complex **481** was not achieved. Instead a small amount of the ring-opened amide **483**, *N*-[(1*R*,2*R*,4*S*)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-*N*-{2-[(1*R*,2*R*,4*S*)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-ylamino]ethyl}-formamide, was isolated in moderate yield. The structure of this product was identified by X-Ray crystallography, as shown in **Figure 52**.

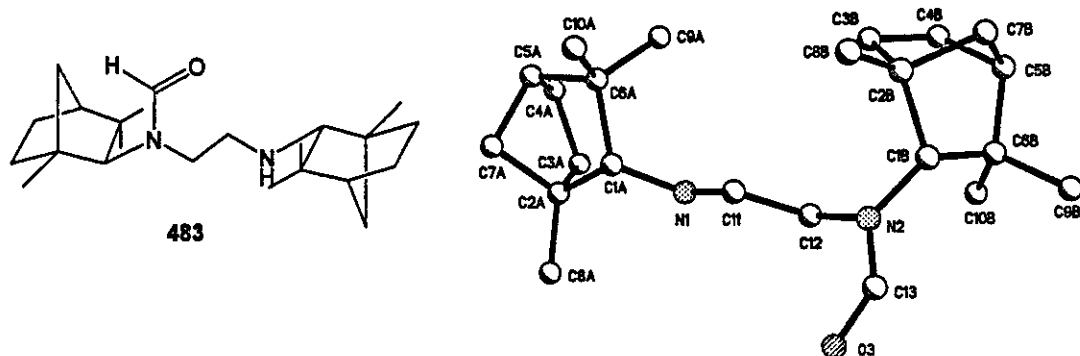


Figure 52

The ^1H NMR and ^{13}C NMR spectra of compound **483** were very difficult to interpret, probably due to the fact that the molecule existed as a mixture of the cis and trans compounds **483a** and **483b**, shown in **Figure 53**, since two peaks were observed, in a ratio 2.5:1, for the proton of the aldehyde at 8.27 and 8.29 ppm by ^1H NMR spectroscopy. Although the ^{13}C NMR spectrum was too complicated to be fully interpreted, the carbonylic carbon was shown at 164.0 ppm. The ^1H NMR spectrum is shown in the appendix.

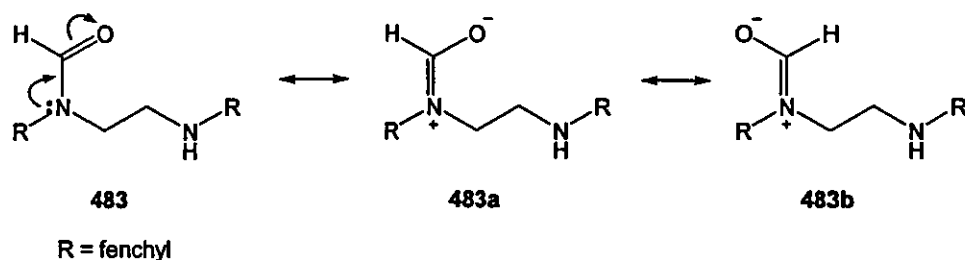
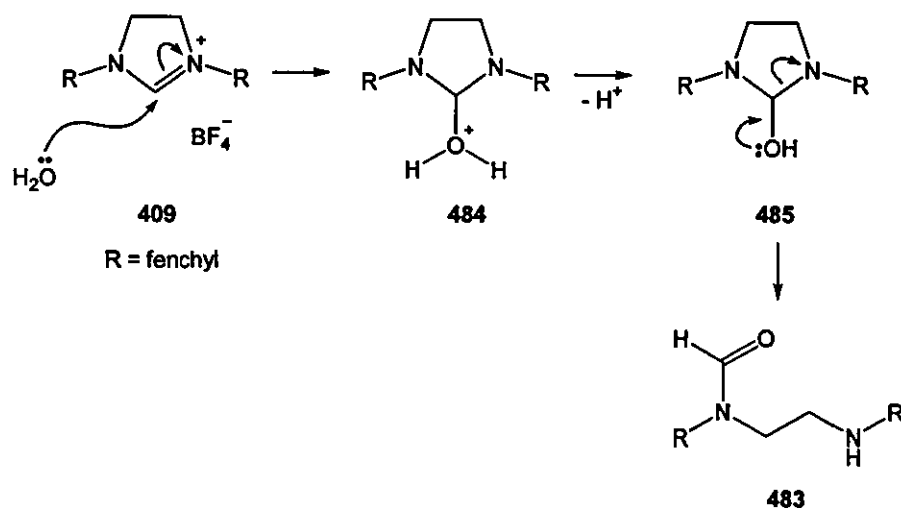


Figure 53

Scheme 90 shows a possible mechanism of formation of the amide **483**. Attack of a molecule of water to the imidazolinium salt **409** could afford the compound **484**, which after losing a proton could lead to the compound **485**. This compound could then ring-open to afford the compound **483**.



Scheme 90

The reaction was also attempted using sodium hydride instead of potassium-*tert*-butoxide, and heating the reaction mixture under reflux conditions for 2 hours

before the addition of sodium iodide and palladium acetate. Again, the desired product **481** was not isolated.

5.3.2 Attempted synthesis of monocarbene adducts

5.3.2.1 Ruthenium carbene adducts

In an effort to improve thermal stability of ruthenium catalysts, such as **486**, shown in **Figure 54**, the groups of Grubbs,^{127,208a} Nolan²⁴⁴ and Hermann^{125d} simultaneously reported a new class of alkylidene complexes bearing *N*-heterocyclic carbene ligands. These carbenes were prepared from the corresponding imidazolium salts by the addition of a base, and many could be isolated as stable species.

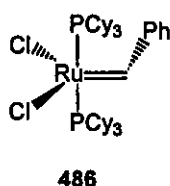
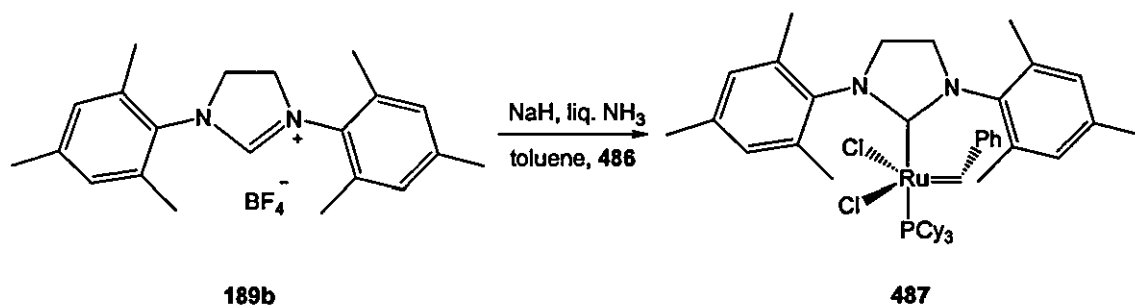
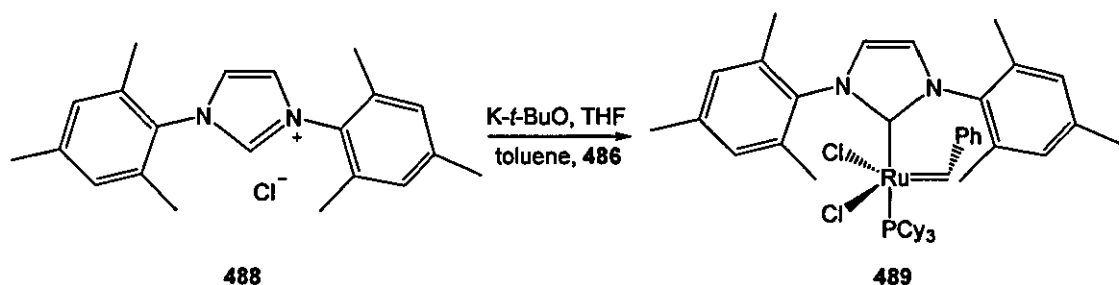


Figure 54

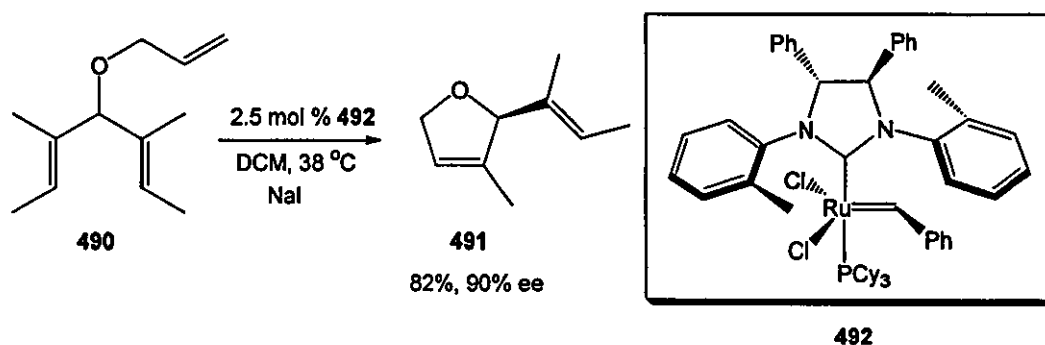
Substitution of one of the phosphine ligands by an Arduengo type imidazolylidene ligand furnished a new series of highly active catalysts **487** and **489**, as shown in **Equation 96** and **Equation 97**, as brown-pink microcrystalline solids. These novel catalysts maintained the desired air/moisture stabilities of the first generation ruthenium-complexes.^{127,208a}



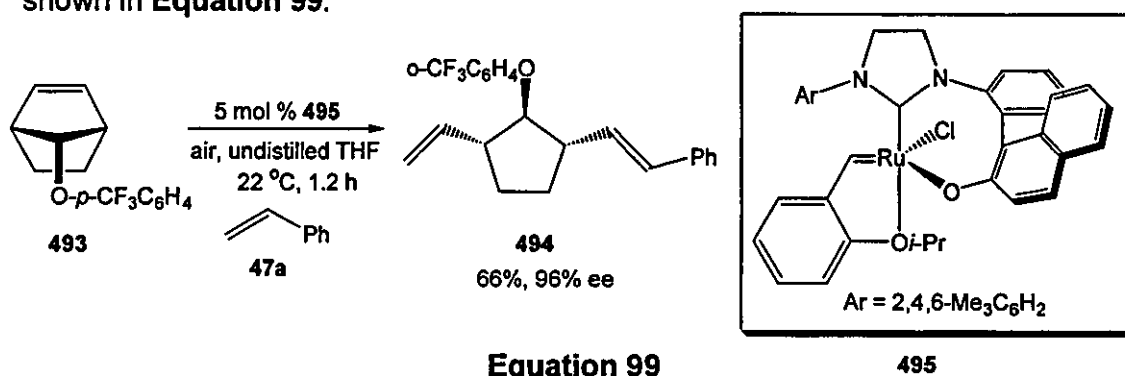
Equation 96



The first report where an asymmetric ruthenium *N*-heterocyclic complex **492** was employed as a catalyst for olefin metathesis was made in 2001 by Grubbs *et al.*^{196c} The ring closing metathesis reaction outlined in **Equation 98** proceeded with 90% ee, showing the potential of these catalysts for achieving useful levels of enantiomeric purity. The stereogenicity in the imidazolylidene was relayed through the *N*-aryl substituents and thus closer to the metal centre.

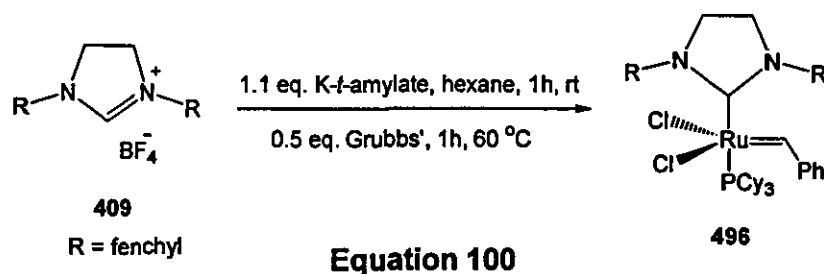


Hoveyda *et al.*²¹⁷ have developed the air stable phosphine-free ruthenium catalyst **495**, which is stereogenic at the metal centre and has been found to furnish very high levels of enantioselectivity in ring opening cross metathesis. Moreover, these reactions could be run in air without loss of reactivity or enantioselectivity, as shown in **Equation 99**.



This increase in activity observed when *N*-heterocyclic ligands are employed, coupled with the air/moisture stability inherent to the ruthenium systems suggest that they will continue to grow in popularity.

The synthesis of the carbene adduct **496** was attempted by reaction of the imidazolinium salt **409** with potassium *tert*-amylate, followed by the reaction with Grubbs' catalyst, in hexane, as shown in the Equation 100, but the reaction did not work, and the desired product was not isolated.

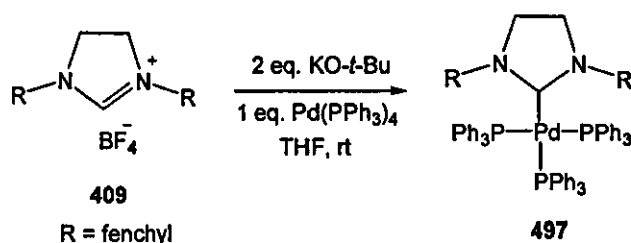


Analysis by ^1H NMR spectroscopy showed a peak at 8.29 ppm, probably due to the formation of an imidazolinium salt, different to the starting imidazolinium salt **409**, but the spectrum was too complicated to identify which product had been formed.

The same reaction was also attempted without heating the reaction mixture, but the desired product **496** was not isolated. Other attempts were carried out using different bases, such as potassium-*tert*-butoxide and lithium-*tert*-butoxide in tetrahydrofuran, stirring the reaction mixture overnight at room temperature, but we did not manage to isolate the desired compound.

5.3.2.2 Palladium carbene adducts

The synthesis of the palladium carbene complex **497**, was attempted by reacting the imidazolinium salt **409** with potassium *tert*-butoxide, followed by the reaction with tetrakis triphenylphosphine palladium (0), in anhydrous tetrahydrofuran, as shown in the Equation 101.

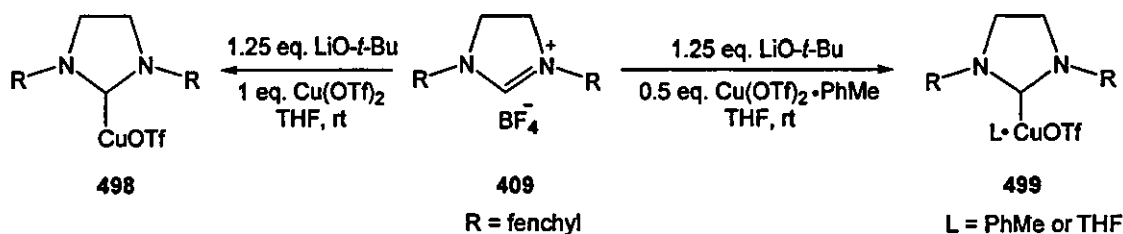


Equation 101

The desired palladium complex **497** was not isolated, instead a complex mixture was obtained.

5.3.2.3 Copper carbene adducts

The synthesis of the copper carbene adducts **498** and **499** was attempted by reaction of the imidazolium salt **409** with lithium *tert*-butoxide, followed by the reaction with the copper triflate:toluene 2:1 complex or with copper triflate, respectively, in anhydrous tetrahydrofuran, as shown in the **Scheme 91**. None of the desired products were isolated.



Scheme 91

In the attempt to synthesise the copper mono-carbene complex **498**, the starting imidazolium tetrafluoroborate salt **409** was reisolated after silica gel flash chromatography.

In the attempt to synthesise the copper mono-carbene complex **499**, the bis-(ammonium) triflate salt **500**, 1,3-bis-(1*R*,2*R*,4*S*)-(1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-ethyl bis-ammoniumtriflate, was obtained in very low yield. This compound was identified by X-Ray crystallography, as shown in **Figure 55**.

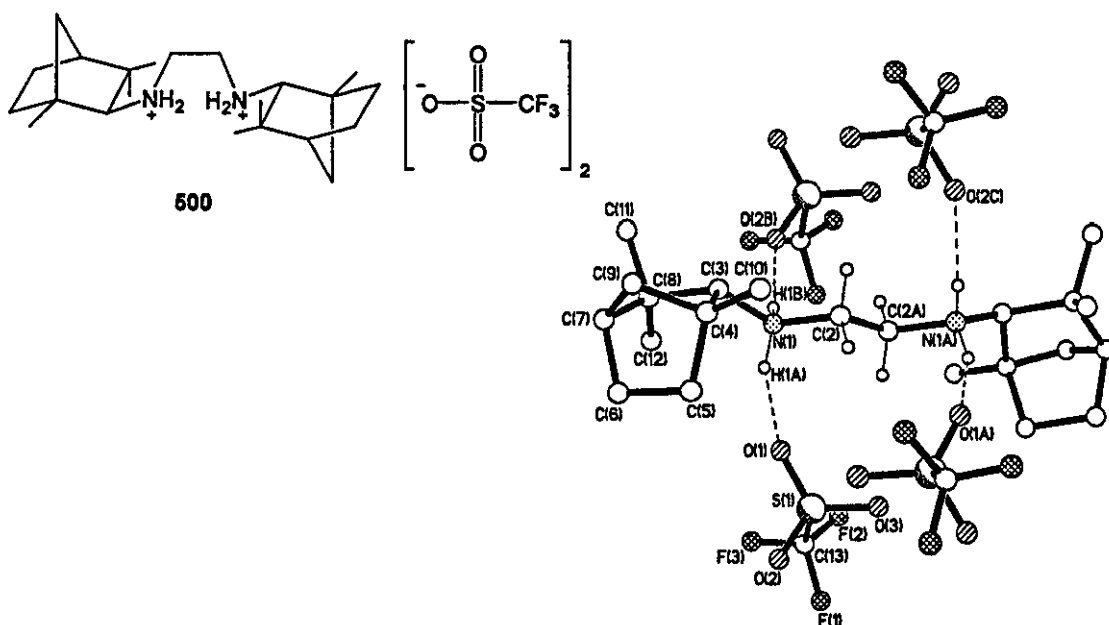
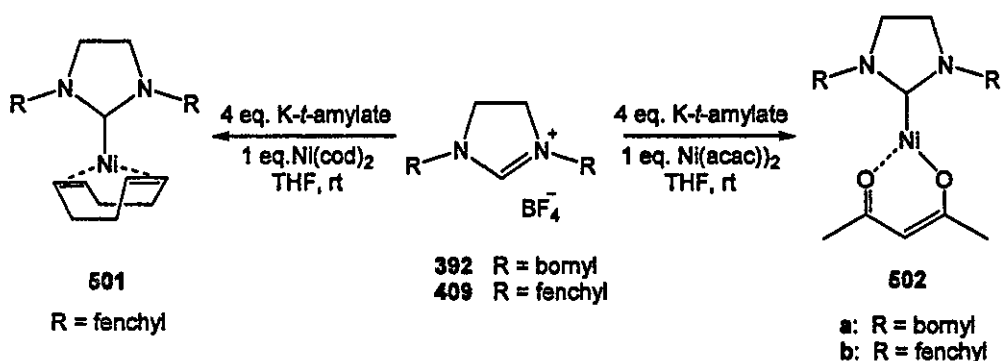


Figure 55

The amount of material obtained was too little to allow ^1H or ^{13}C NMR spectra to be obtained.

5.3.2.4 Nickel carbene adducts

The synthesis of the nickel carbene adducts **501** and **502a-b** was attempted by reaction of the corresponding imidazolium salt **392** or **409** with potassium *tert*-amylate, followed by the reaction with either nickel (II) acetylacetonate or nickel (0) cyclooctadiene, in anhydrous tetrahydrofuran, as shown in the **Scheme 92**.



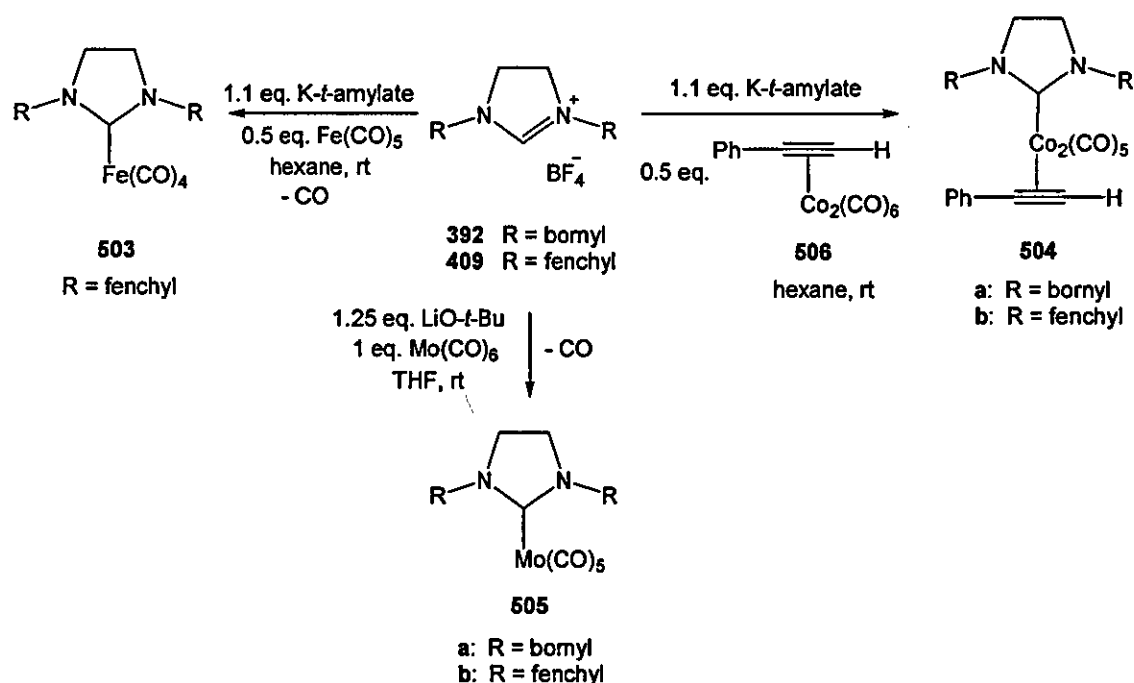
Scheme 92

In the attempt to synthesise the nickel carbene complex **501**, the urea compound **468** was obtained (as it happened when the synthesis of the nickel bis-(carbene) complex **464** was attempted). Again, we thought that this was possibly due to a rapid oxidation of the nickel cyclooctadiene complex.

In the attempt to synthesise the nickel carbene complex **502b**, as shown in the **Scheme 92**, the amide **483** was isolated after silica gel flash chromatography, instead of the desired product. The same reaction was also attempted using 1.25 equivalents of lithium-*tert*-butoxide (1 M solution in tetrahydrofuran) instead of potassium *tert*-amylate. After silica gel flash chromatography, the starting imidazolinium tetrafluoroborate salt **409** was reisolated, as well as $\text{Ni}(\text{acac})_2(\text{H}_2\text{O})_2 \cdot \text{H}_2\text{O}$, which was identified by X-Ray crystallography.

5.3.3 Carbonyl-metal carbene adducts

The synthesis of the tetracarbonyliron carbene adduct **503**, pentacarbonyldicobalt complexes **504a-b** and the pentacarbonyl-molybdenum carbene adducts **505a-b** were attempted as shown in the **Scheme 93**. Starting from the corresponding imidazolinium salts **392** or **409**, several bases were used in order to generate the carbenes *in situ*, which were treated either with pentacarbonyliron, hexacarbonyldicobalt or hexacarbonylmolybdenum complex **506**, respectively.



Scheme 93

In the attempts to synthesise the tetracarbonyliron carbene adduct **503** and the pentacarbonylmolybdenum carbene adducts **505a-b**, complex mixtures were obtained.

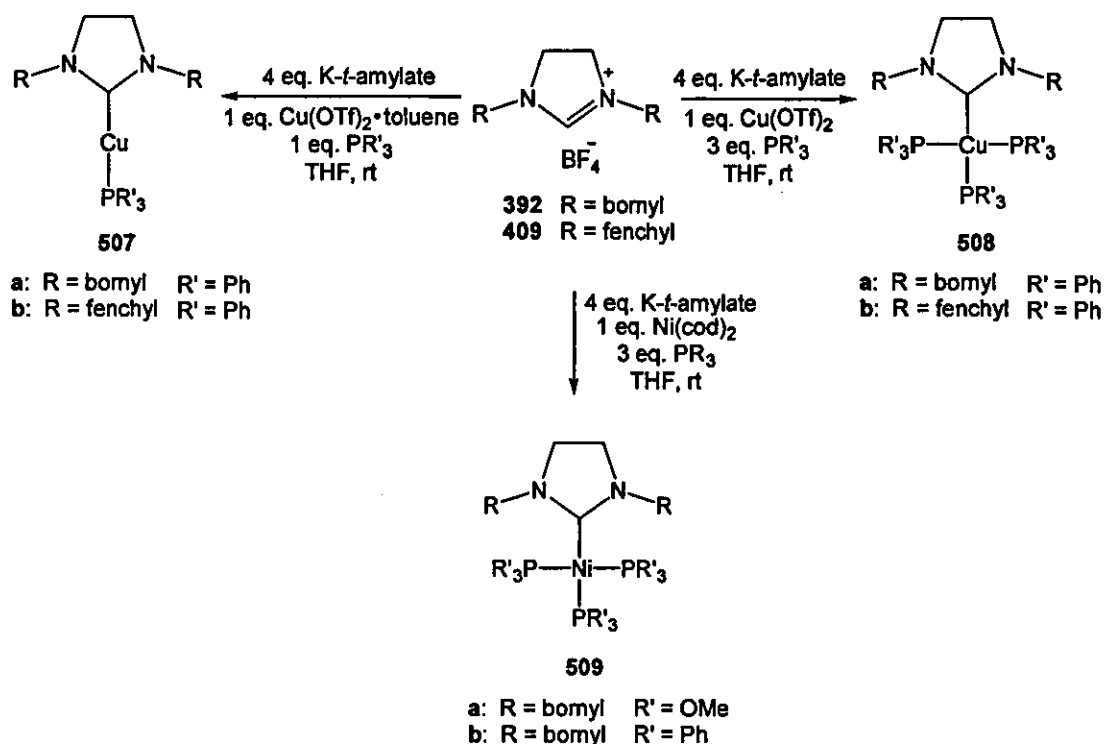
The reaction to synthesise the tetracarbonyliron carbene adduct **503** was also attempted using potassium-*tert*-amylate, in anhydrous tetrahydrofuran, stirring the reaction mixture for 1 hour at 73 °C, and overnight at room temperature, but the desired product was not isolated and a complex mixture was obtained.

When the reaction to synthesise the pentacarbonyldicobalt complex **504b** was carried out, a band at 1882 cm^{-1} was observed by IR spectroscopy. This was maybe due to the stretching of the Co-CO (different to the one observed in the starting cobalt complex, which was shown at 2020 cm^{-1}), indicating that possibly the product had been formed, but the ^1H NMR spectrum obtained was too broad to identify if the desired product had been formed or not. The mass spectrum (FAB) showed a peak at 602 m/z , which could possibly be due to the formation of the desired complex with loss of the alkyne moiety, although it was difficult to decide whether the loss of the alkyne took place in the spectrometer or during the course

of the reaction. Also, peaks at 574 and 547 m/z were observed, possibly due to the loss of one and two carbonyl groups respectively. We were not able to decide whether the desired adduct had been formed or not. Analogously, the crude product obtained in the reaction to synthesise the pentacarbonyldicobalt complex **504a** showed a band at 1883 cm^{-1} by IR spectroscopy and the ^1H NMR spectra obtained was too broad to identify if the desired product had been formed or not.

5.3.4 Nickel and copper-carbene adducts with phosphine ligands

The synthesis of the following copper **507a-b** and **508a-b** and nickel **509a-b** carbene adducts was attempted as shown in the Scheme 94. Starting from the corresponding imidazolium salts **392** and **409**, potassium *tert*-amylate was used in order to generate the carbenes *in situ*, which then were treated with copper (II) triflate or nickel cyclooctadiene, followed by the addition of the phosphorus reagent (triphenylphosphine or trimethyl phosphite) to obtain the final complexes.



Scheme 94

In the attempts to synthesise all these nickel and copper carbene complexes a complex mixture was obtained, all of them showing a peak at 29.7 ppm in the ^{31}P NMR spectrum, along with unreacted triphenylphosphine.

5.3.5 Conclusion

Attempts have been made to form a range of different transition metal complexes containing the imidazol-2-ylidene ligands **180g** or **180h**. Our strategy firstly involved the generation of the active carbenes from the corresponding imidazolium salt **392** or **409** by treatment with a suitable base, generally potassium-*tert*-butoxide, potassium-*tert*-amylate or lithium-*tert*-butoxide. The required transition metal complex was then added to the generated carbene solution in the hope that the imidazol-2-ylidene would substitute one or two ligands in order to form the corresponding novel mono- or bis-substituted transition metal complexes.

Unfortunately, in general, all our attempts at forming new complexes were unsuccessful, with none of the desired complexes being formed. We were unsure whether this was due to the carbene not being formed, or whether the formed carbene was not undergoing substitution with the starting transition metal complexes. A number of unexpected products have been isolated and identified by X-Ray crystallography, and mechanisms have been proposed for their formation.

Some indirect evidence for the formation of a carbene was provided in the reaction of *N,N'*-difenchylimidazolium salt **409** with potassium-*tert*-butoxide and copper triflate, as shown in **Scheme 86**. Instead of the desired product we isolated the piperazin-2-one **470**. We have proposed a possible mechanism for its formation that goes *via* a carbene intermediate **180h**, as shown in **Scheme 87**. The most promising reaction was that carried out with *N,N'*-difenchylimidazolium salt **409** with potassium-*tert*-amylate and the cobalt complex **506** in order to afford the compound **504b**. IR spectroscopy of the product showed a new band probably corresponding to the Co-CO stretching. In addition, mass spectrometry showed a peak corresponding to the desired complex minus the alkyne ligand, and peaks for some of the subsequent removal of the carbon monoxide ligands.

CHAPTER 6: Attempted Synthesis of New Chiral Fluorinating Agents

6.1 Introduction

Several compounds that act as fluorinating agents, such as 2-chloro-1,1,2-trifluoroethyldiethylamine **510** (Yarovenko agent),²⁴⁵ hexafluoropropyldiethylamine **511** (Ishikawa agent),²⁴⁶ diethylaminosulfur trifluoride **512** (DAST)²⁴⁷ and bis-(2-methoxyethyl)aminosulfur trifluoride **513** (Deoxo-Fluor),²⁴⁸ shown in Figure 56, have been reported. However, they all have several disadvantages, such as not being stable on storage or not reacting with aldehydes and ketones.

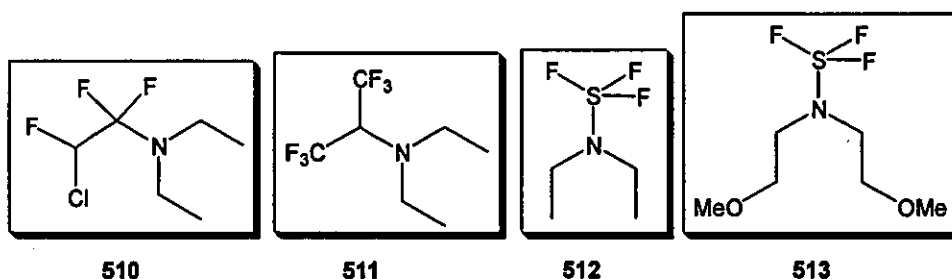
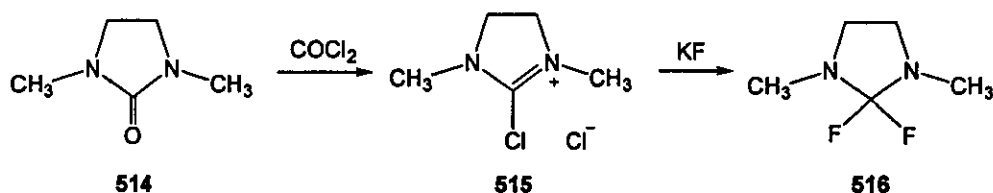


Figure 56

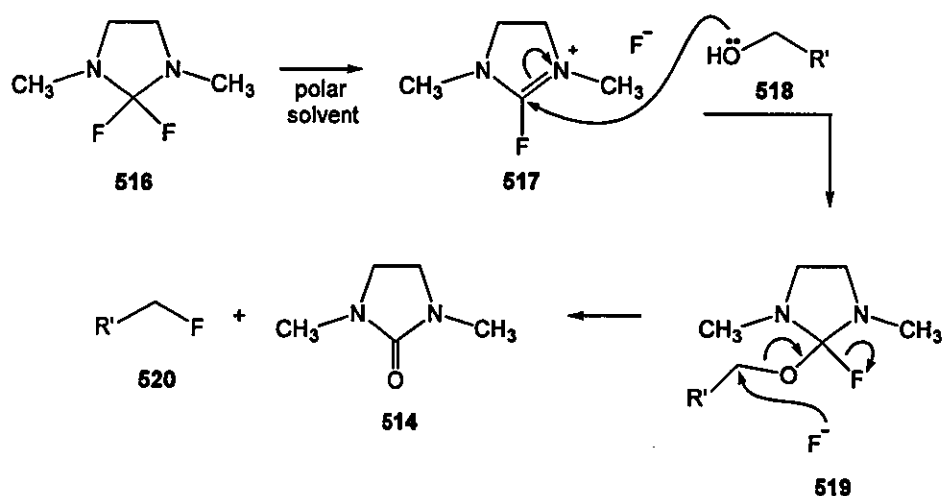
Hayashi *et al.*²⁴⁹ have reported the synthesis of 2,2-difluoro-1,3-dimethylimidazolidine **516** (DFI) as a new deoxo-fluorinating agent. It has been shown to be much more thermally stable than other typical deoxofluorinating agents (such as DAST and Deoxo-Fluor). Therefore it is safer to handle and use. Its synthesis is shown in Scheme 95. In the first step, formation of the 2-chloro imidazolinium chloride salt **515** takes place by reaction of the urea **514** with phosgene. Then, the desired fluorinating agent **516** is formed by reaction of the 2-chloro imidazolinium chloride salt **515** with potassium fluoride.



Scheme 95

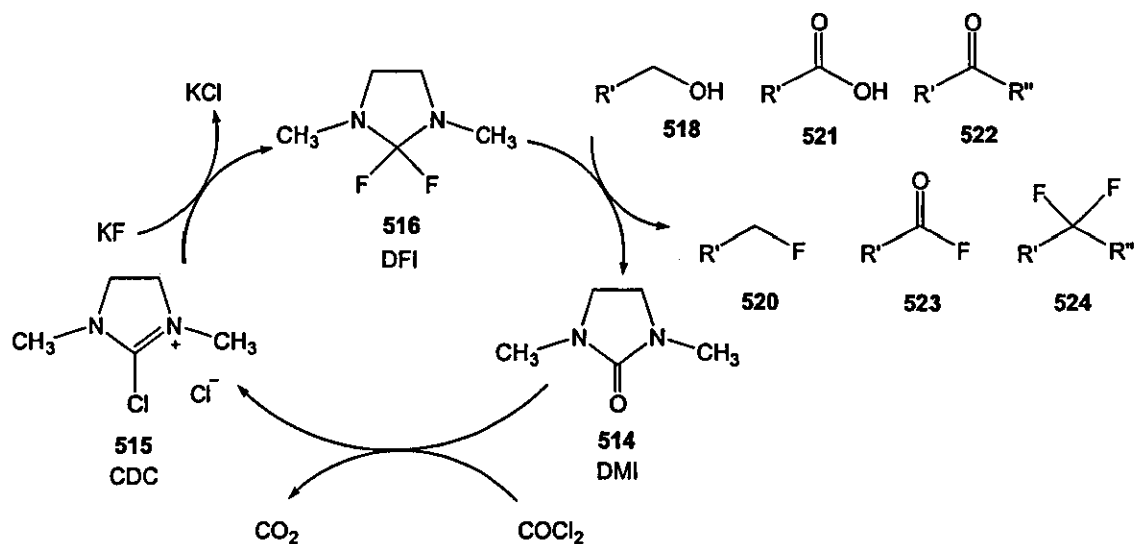
Synthesis of alkyl fluorides from primary, secondary and tertiary alcohols using DFI was achieved in good yields under mild conditions, as well as the synthesis of *gem*-difluorides from aldehydes and ketones. Formation of by-products, such as alkyl vinyl fluorides and alkyl acetylene was observed in reactions using carbonyl compounds containing an α -hydrogen. The mechanism of formation of these compounds has not yet been determined.

We thought that the mechanism for the fluorinating reaction might proceed as shown in **Scheme 96**. Formation of the 2-fluoro imidazolinium fluoride salt **517**, starting from the 2,2-difluor imidazolidine **516**, is followed by attack of an alcohol **518** to the imine carbon to give the corresponding 2-alkoxy-2-fluoro imidazolidine **519**, which can then be attacked by fluoride anions to generate the fluorinated compound **520** and the urea **514**.



Scheme 96

Since the starting material, the urea **514**, is recovered after the reaction, it can be reused in order to recycle the fluorinating agent **516**, as shown in **Scheme 97**. Fluorine containing compounds can be prepared from alcohols **518**, carboxylic acids **521**, aldehydes and ketones **522** by deoxo-fluorination; therefore alcohols would furnish monofluorides **520**, carboxylic acids would afford carbonyl fluorides **523** and aldehydes and ketones would give *gem*-difluorides **524**.



Scheme 97

We thought we could utilize our existing diamines **346** and **348**, previously synthesised in chapter 5, in order to synthesise several chiral analogues of DFI **516**, as shown in **Figure 57**.

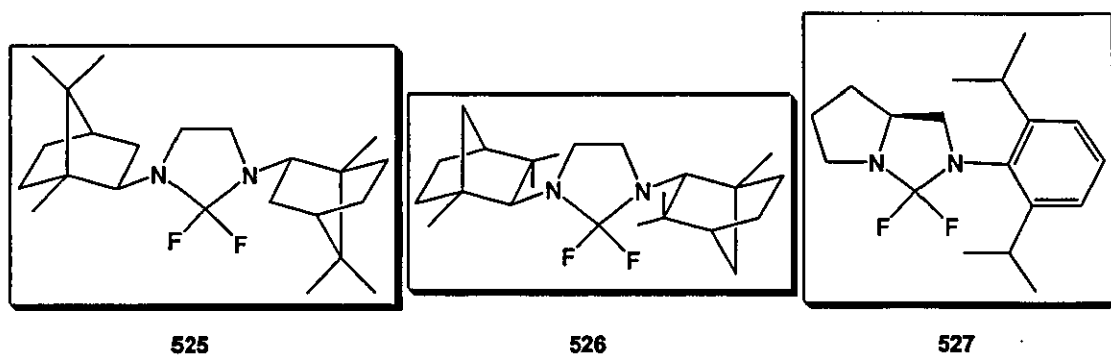
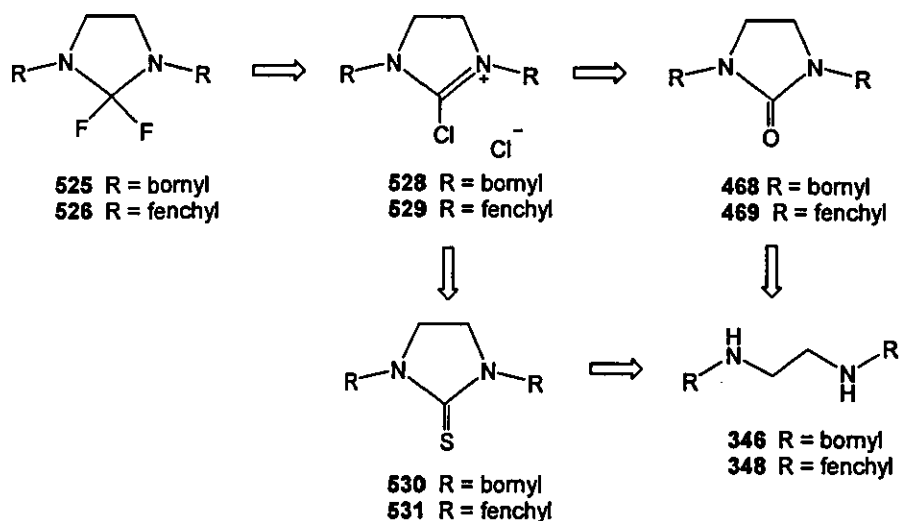


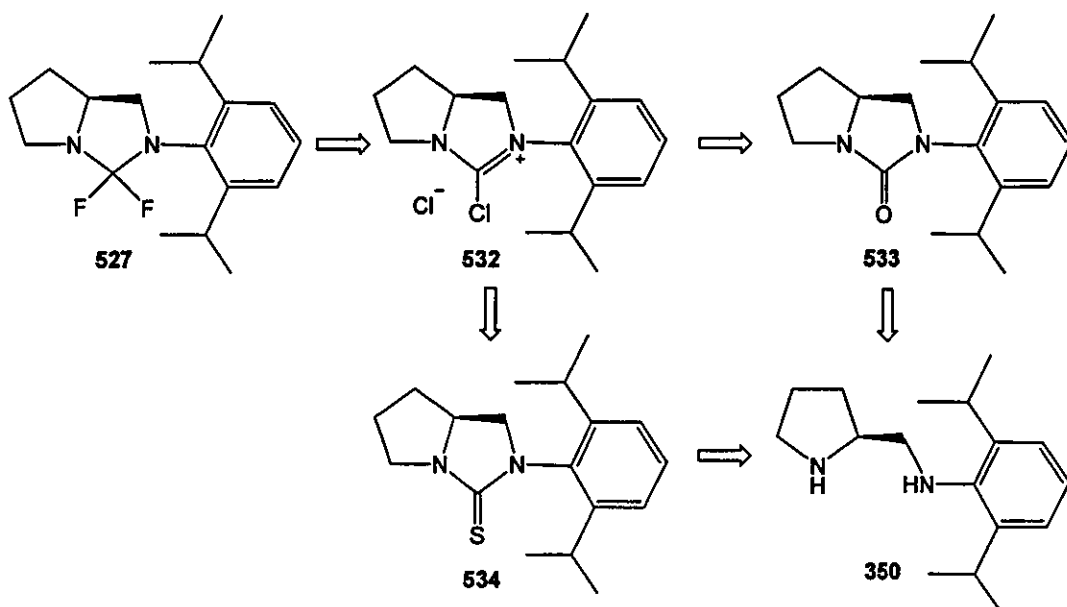
Figure 57

We envisaged that the compounds **525**, **526** and **527** could be synthesized following a similar synthetic method to that reported by Hayashi *et al.*²⁴⁹ **Scheme 98** shows the proposed synthesis of the compounds **525** and **526**; Synthesis of the chloride salts **528** and **529** from the corresponding urea compound **468** or **469**, respectively, followed by reaction of the chloride salt with potassium fluoride would furnish the 2,2-difluoro imidazolidines **525** and **526**. The analogous compound **527** could be synthesized following a similar scheme, as shown in **Scheme 99**.

We could also synthesize the chloride salts **528**, **529** and **532** starting from the thiourea compound **530**, **531** or **534**, respectively, instead of forming the urea compounds, as shown in **Scheme 98** and **Scheme 99**, and the synthesis of the difluoroimidazolidine **525**, **526** and **527** would continue as indicated before.



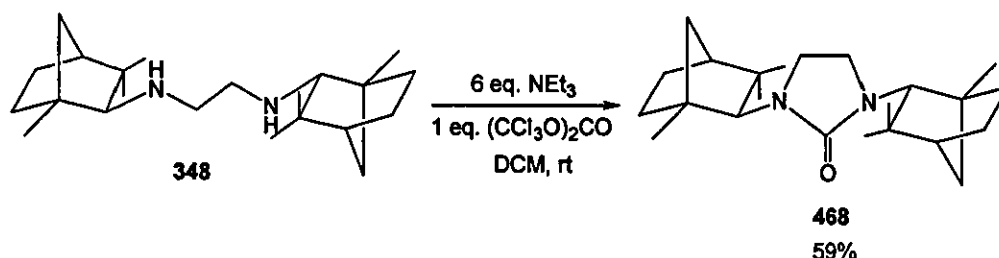
Scheme 98



Scheme 99

6.2 Synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolidin-2-one

The first step of the synthesis of the difluoroimidazolidine **526** was to prepare the urea compound **468**, starting from the diamine **348**. The reaction of diamine **348** with triphosgene, in the presence of triethylamine, was carried out as shown in **Equation 102**. Phosgene was produced during the course of the reaction, and because of its high toxicity the excess was removed by washing the reaction mixture thoroughly with an aqueous solution of sodium hydroxide. The crude product was purified by silica gel flash chromatography to give the desired product **468** in moderate yield.

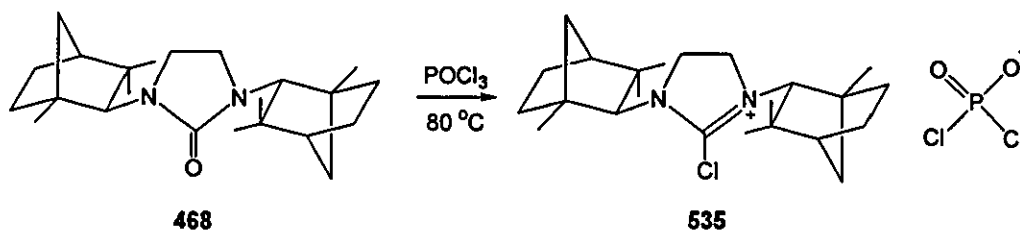


Equation 102

Analysis by IR spectroscopy showed the carbonyl peak at 1672 cm^{-1} , and the ^{13}C NMR spectrum showed the carbonyl peak at 163.7 ppm .

6.3 Synthesis of 2-chloro-1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-4,5-dihydro-3H-imidazol-1-ium dichloro-(oxo)-phosphanolate

In order to synthesise the chloride salt **529**, chlorination of the cyclic urea **468** was carried out by reaction with an excess of phosphorus oxychloride, as shown in **Equation 103**. Initially we expected that the chloride salt **529** would be formed, but instead the dichloro phosphanolate salt **535** was isolated.



Equation 103

By ^{13}C NMR spectroscopy the new peak for the quaternary carbon C-Cl appeared at 159.3 ppm. The ^{31}P NMR spectrum showed a peak at -1.5 ppm, different to that for phosphorus oxychloride at 5.0 ppm.

The same reaction was attempted using as starting materials oxalyl chloride, thionyl chloride or phosphorus oxychloride, under different reaction conditions, as compiled in Table 10, entries 1-7. In some cases, procedures found for the synthesis of chloroamidinium²⁵⁰ or chlorouronium²⁵¹ were followed. In all these attempts the starting urea **468** was reisolated.

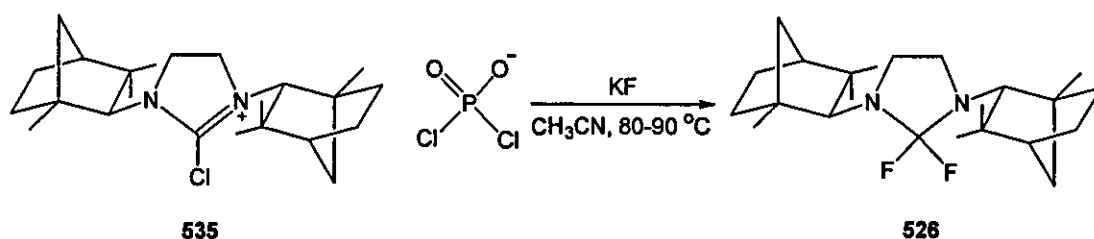
Entry	Conditions	time	Product
1	oxalyl chloride (1.1 eq.), CHCl_3 , 70 °C ²⁵⁰	5 h	s.m. 468
2	oxalyl chloride (1.1 eq.), CHCl_3 , 70 °C	3 days ^a	s.m. 468
3	oxalyl chloride (1.2 eq.), cat. DMF, DCM, reflux conditions ²⁵¹	24 h	s.m. 468
4	oxalyl chloride, rt	O/N	s.m. 468
5	thionyl chloride, reflux conditions	O/N	s.m. 468
6	phosphorus oxychloride (1 eq.), DCM, rt	3 days	s.m. 468
7	phosphorus oxychloride (1 eq.), CDCl_3 , rt	3 days	s.m. 468
8	phosphorus oxychloride, 80 °C	O/N	535

^aAfter 24 h stirring at 70 °C, another 1.1 eq. of phosphorus oxychloride was added.

Table 10

6.4 Attempted synthesis of 2,2-difluoro-1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolidine

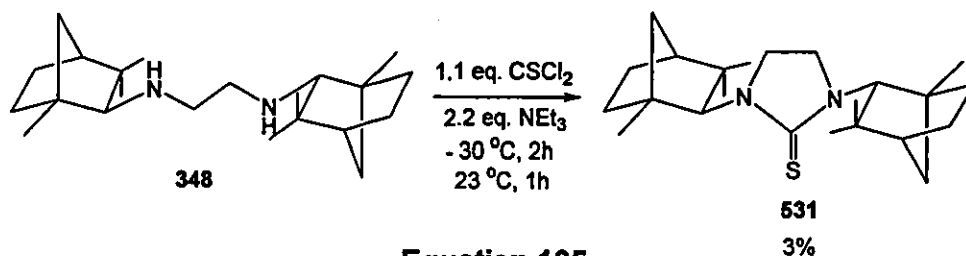
The dichloro phosphanolate salt **535** was treated with potassium fluoride in anhydrous acetonitrile, as shown in Equation 104. A new unidentified compound, which according to ^{19}F NMR spectroscopy did not contain any fluorine residues had been formed.



Equation 104

6.5 Synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolidine-2-thione

Diamine **348** was reacted with thiophosgene, in the presence of triethylamine, in dichloromethane at $-30\text{ }^\circ\text{C}$, as shown in **Equation 105**. The excess of thiophosgene was removed by washing the reaction mixture thoroughly with a sodium hydroxide aqueous solution. The crude product was purified by silica gel flash chromatography to give the pure thiourea **531**, in very low yield.



Equation 105

Analysis by IR spectroscopy showed a peak at 1254 cm^{-1} , due to the stretching of the thione group. The ^{13}C NMR spectrum showed a new peak at 188.5 ppm for the quaternary carbon $\text{C}=\text{S}$. This compound was also identified by X-Ray crystallography, as shown in **Figure 58**.

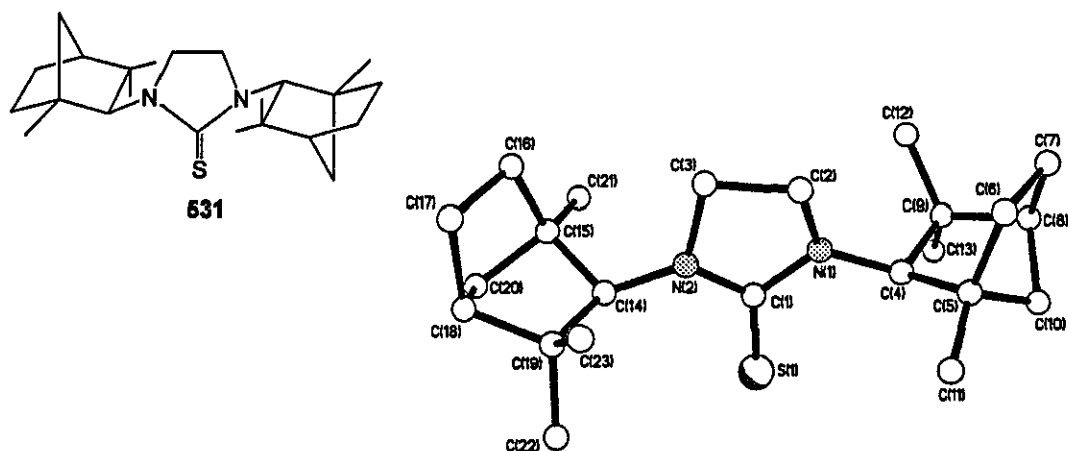


Figure 58

6.6 Conclusion

Work has been carried out into the synthesis of several chiral analogues of DFI **516** utilising our previously synthesised chiral diamine **348**. Several potential retrosyntheses were identified and a number of intermediates were isolated. Unfortunately due to time constraints this work was not taken any further, but certainly warrants further investigation in the future.

EXPERIMENTAL

CHAPTER 7: Experimental Procedures

7.1 General experimental procedures

7.1.1 Purification of reagents, compounds and solvents

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

Flash chromatography was carried out using silica gel 60 Fluka and hand bellows to apply pressure to the column. Analytical thin layer chromatography was carried out using aluminium backed plates coated with silica gel 60 Fluka. Plates were visualized under UV light (at 254 nm), staining with potassium permanganate solution followed by heating or by exposure to an ethanolic solution of phosphomolybdic acid, acidified with concentrated sulfuric acid, followed by charring where appropriate.

Light petroleum refers to the fraction of petroleum ether that boils between 40 °C and 60 °C and was distilled from anhydrous CaCl_2 before use. Ethyl acetate and dichloromethane were distilled from anhydrous CaCl_2 and phosphorus pentoxide, respectively. Tetrahydrofuran was distilled from the sodium/benzophenone ketyl radical before use. Methanol and ethanol were distilled from the corresponding magnesium alkoxide prior to use. Triethylamine and diisopropylethylamine were stored over sodium hydroxide pellets.

7.1.2 Preparation of glassware

Highly air and moisture sensitive reactions were carried out using glassware that had been dried overnight in an oven at 150 °C. This was allowed to cool in a desiccator over self-indicating silica pellets, under a nitrogen atmosphere. All organometallic and air sensitive reactions were carried out under slight static

positive pressure of nitrogen, and reagents and solvents were introduced using syringe or cannula technique, through a septum cap.

7.1.3 Melting points

Melting points were measured on an Electrothermal-IA 9100 apparatus and are uncorrected.

7.1.4 Infrared and mass spectra (IR, MS)

Fourier Transform infrared absorption spectra were recorded on a Perkin Elmer Paragon 2001 instrument in the range 600–4000 cm^{-1} . Solid samples were run on sodium chloride discs or as thin films. Liquid samples were run diluted in dichloromethane on sodium chloride discs. Solid phase resins were run as potassium bromide discs.

High and low-resolution mass spectra were recorded on Jeol (JMX)SX102 instrument using electron impact (EI) or fast atom bombardment (FAB) ionization techniques.

7.1.5 Nuclear magnetic resonance (NMR)

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded using Bruker AC-250 and Bruker DPX-400 instruments operating at 250.13 and 400.13 MHz, respectively. The experiments were conducted in deuterated solvents in tetramethylsilane as the internal standard. The following symbols have been adopted in the description of NMR spectra: J = Coupling constant, multiplicities were recorded as broad signals (br), singlets (s), doublets (d), triplets (t), quartets (q), quintuplets (quin), septets, doublet of doublets (dd), doublet of triplets (dt) and multiplets (m).

Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a Bruker AC-250 and Bruker DPX-400 instruments operating at 62.86 and 100.62 MHz, respectively. Normally the ^{13}C NMR spectrum for each compound

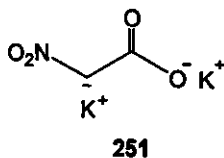
was recorded in the same deuterated solvent as that used for the ^1H NMR spectrum, unless otherwise stated. Tetramethylsilane was used as the internal standard. DEPT, NOE and COSY analyses were recorded on the same instruments.

7.1.6 X-Ray crystallography

Data sets were collected on a Bruker SMART 1000 diffractometer. Details of the data collections and structure solution are given in **Table 1** for each compound, in the appendix, section 8.1. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using SHELXTL (G.M. Sheldrick, SHELXTL version 5.1, Bruker-AXS, Madison WI, 1998). All non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model, except for those on the amine nitrogen atoms, which were located from difference maps and not further refined.

7.2 Experimental for chapter 3; Attempted synthesis of nitrocyclopropane /ene precursors

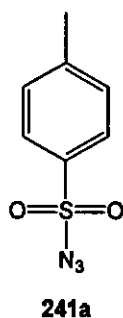
7.2.1 Dipotassium salt of nitroacetic acid



Potassium hydroxide (22.40 g, 0.40 mol) and water (16 mL) were stirred for 1 hour at room temperature. The reaction was quite exothermic, therefore a condenser with a calcium chloride drying tube was placed on top of the flask. The solution was heated at 60-80 °C and nitromethane (6.10 g, 0.10 mol) was added dropwise. The temperature was then increased to 160 °C and the stirring was stopped to avoid decomposition of the product. After 1 hour the reaction mixture was allowed to cool to room temperature and the orange-pale brown solid which precipitated was recovered by filtration and washed several times with methanol to afford the dipotassium salt **251**, 6.24 g, 69%.

Lit. mp¹⁸² 262°C (decomp.); mp decomp. > 250 °C; ν_{\max} (KBr disc) 1595, 1488, 1432, 1329, 1172, 1051, 948, 820, 774 cm⁻¹.

7.2.2 *para*-Toluenesulfonyl azide



A solution of *para*-toluenesulfonyl chloride (7.00 g, 36.7 mmol) and sodium azide (5.00 g, 76.9 mmol) in acetone (61 mL) and distilled water (43 mL) was heated under reflux for 2 hours and then cooled to room temperature and stirred for 2 hours. After this time, a large quantity of water was added and the liberated oil

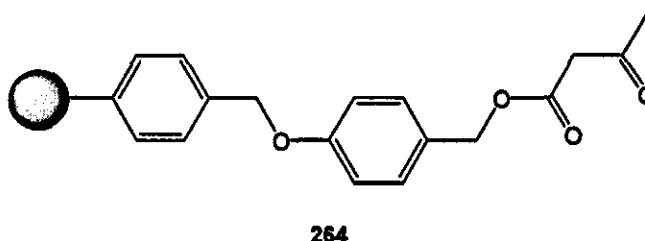
was extracted into dichloromethane (80 mL). The organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo* to furnish the desired product **241a** as a colourless liquid, which crystallised upon cooling, 6.69 g, 92%.¹⁸³

ν_{max} (CH_2Cl_2) 2128, 1595, 1371, 1167, 1086, 814, 748, 662 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) 2.48 (s, 3H, ArCH_3), 7.40 (d, 2H, ArH , $J = 7.5$ Hz), 7.84 (d, 2H, ArH , $J = 7.5$ Hz).

7.2.3 Synthesis of Wang resin derivatives

7.2.3.1 Wang resin derivatives for model study

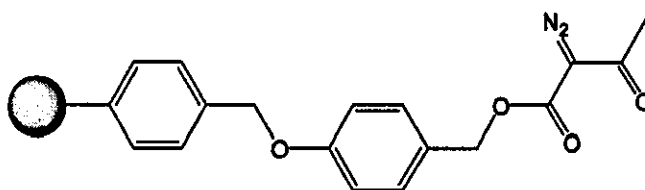
7.2.3.1.1 Wang-3-oxo-butyric acid resin derivative



Wang resin (0.50 g, 0.37 mmol) was washed twice with anhydrous tetrahydrofuran. It was then swollen in anhydrous tetrahydrofuran and treated with LDA (0.20 g, 1.9 mmol). The suspension was then shaken for 2 min. at room temperature and the resin was filtered and washed twice with tetrahydrofuran. The resin was then swollen in anhydrous tetrahydrofuran and treated with diketene (0.16 g, 1.9 mmol). The mixture was shaken for 40 min. at room temperature, filtered and washed sequentially with dichloromethane and methanol, and finally with diethyl ether to furnish a dark orange resin. The IR spectrum suggested that the reaction had possibly worked to some extent.

ν_{max} (KBr disc) 3448, 3028, 2923, 1654, 1618, 1508, 1451, 1379, 1121, 758, 698 cm^{-1} .

7.2.3.1.2 Wang-2-diazo-3-oxo-butyric acid resin derivative



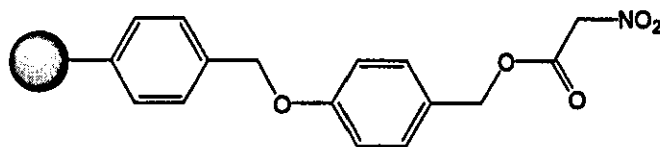
265

Wang-3-oxo-butyric acid resin derivative **264** (0.50 g, 0.37 mmol) was suspended in dichloromethane and treated with triethylamine (0.52 mL, 3.7 mmol) at room temperature. The suspension was then shaken for 5 min., treated with *para*-toluenesulfonyl azide (0.75 g, 3.8 mmol), and shaken for 1.7 hours at room temperature. The resin was then filtered and thoroughly washed sequentially with dichloromethane and methanol, and finally with diethyl ether to furnish a brown resin. By IR spectroscopy the typical band of the diazo group stretching mode was observed.

ν_{\max} (KBr disc) 3448, 3025, 2926, 2138, 1654, 1618, 1508, 1491, 1451, 1381, 1116, 756, 697 cm^{-1} .

7.2.3.2 Wang-nitro resin derivatives

7.2.3.2.1 Wang-nitro-acetic acid resin derivative



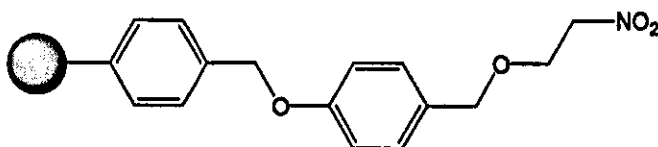
274a

Wang resin (0.50 g, 0.37 mmol) was suspended in dimethylformamide and treated with PyBOP (1.93 g, 3.70 mmol) and dipotassium salt of nitroacetic acid (0.67 g, 3.7 mmol). The suspension was shaken and left standing for 2 hours. After this time, the resin was filtered and thoroughly washed sequentially with

dimethylformamide, dichloromethane and methanol. The IR spectrum suggested that some of the desired product might have been formed.

ν_{max} (KBr disc) 3438, 2924, 1746, 1667, 1600, 1514, 1492, 1434, 1330, 1173, 1101, 1052, 949, 823, 766, 700 cm^{-1} .

7.2.3.2.2 Wang-nitro-ethanol resin derivative



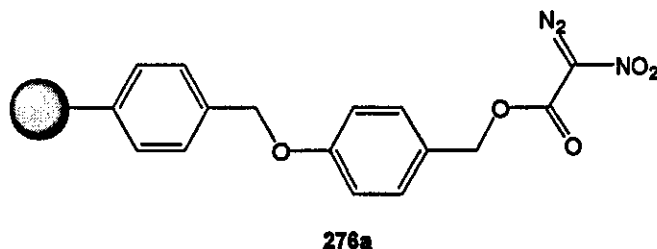
238a

Wang resin (0.50 g, 0.37 mmol) was suspended in anhydrous dimethylformamide (5mL) and treated with PyBOP (1.93 g, 3.70 mmol). The suspension was shaken for 15 min. and treated with 2-nitroethanol (0.27 mL, 3.7 mmol) and triethylamine (0.52 mL, 3.7 mmol). The reaction mixture was shaken and then left standing for 1 hour at room temperature. After this time, the resin was filtered and thoroughly washed sequentially with dimethylformamide, dichloromethane and methanol, and finally with diethyl ether. According to the IR spectrum, it could be suggested that the reaction had work to some extent.

ν_{max} (KBr disc) 3422, 1654, 1602, 1508, 1492, 1451, 1385, 1240, 1027, 822, 757, 698 cm^{-1} .

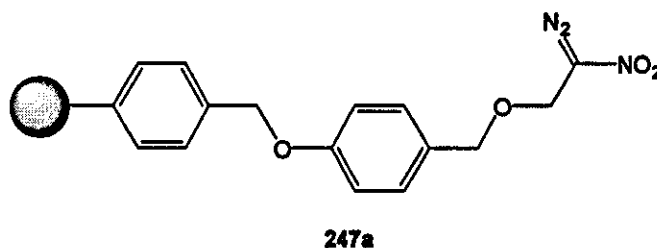
7.2.3.3 Synthesis of Wang-nitro-diazo resin derivatives

7.2.3.3.1 Attempted synthesis of Wang-diazo-nitro-acetic acid resin derivative



Wang-nitro-acetic acid resin derivative **274a** (0.50 g, 0.37 mmol) was treated with a solution of *para*-toluenesulfonyl azide (0.22 g, 1.1 mmol) and triethylamine (0.16 mL, 1.1 mmol) in dichloromethane. The reaction mixture was shaken and left standing for 1 hour. After this time, the resin was filtered and thoroughly washed sequentially with methanol and dichloromethane. Analysis of the product by infrared spectroscopy did not show the band corresponding to the diazo group. The IR spectrum showed similar peaks as those present in the starting resin **279a**, so it was concluded that the starting material was reisolated.

7.2.3.3.2 Attempted synthesis of Wang-2-diazo-2-nitro-ethanol resin derivative

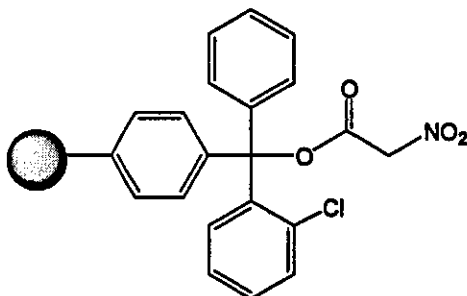


Wang-2-nitro-ethanol resin derivative **238a** (0.50 g, 0.37 mmol) was suspended in dichloromethane and treated with triethylamine (0.52 mL, 3.7 mmol). After shaking the reaction mixture for 5 min., *para*-toluenesulfonyl azide (0.73 g, 3.7 mmol) was added and the mixture was shaken for 1 hour at room temperature. The resin was filtered and thoroughly washed sequentially with dichloromethane and methanol, and finally with diethyl ether. The IR spectrum showed similar peaks to those present in the starting resin **238a**, and no signs of the diazo group were observed.

7.2.4 Synthesis of 2-chlorotrityl resin derivatives

7.2.4.1 Synthesis of 2-chlorotrityl-nitro resin derivatives

7.2.4.1.1 2-Chlorotrityl-nitro-acetic acid resin derivative

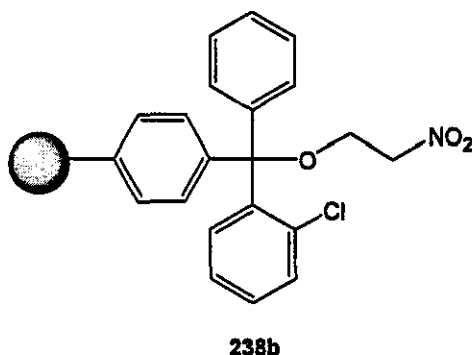


274b

2-Chlorotrityl chloride resin (0.20 g, 0.20 mmol) was suspended in dimethylformamide and treated with dipotassium salt of nitroacetic acid (0.36 g, 2.0 mmol). The suspension was shaken for 5 min. and left standing for 2 hours. After this time, the resin was filtered and thoroughly washed sequentially with dimethylformamide, dichloromethane and methanol. The IR spectrum showed a band at 1591 cm^{-1} and a peak at 1330 cm^{-1} (more intense than a similar peak observed at 1322 cm^{-1} in the starting chlorotrityl resin), probably due to the symmetric and asymmetric stretching of the nitro group. Therefore, the reaction had probably worked to some extent.

ν_{max} (KBr disc) 3439, 3123, 3104, 1591, 1516, 1488, 1432, 1329, 1171, 1051, 949, 821, 774 cm^{-1} .

7.2.4.1.2 2-Chlorotrityl-nitro-ethanol resin derivative

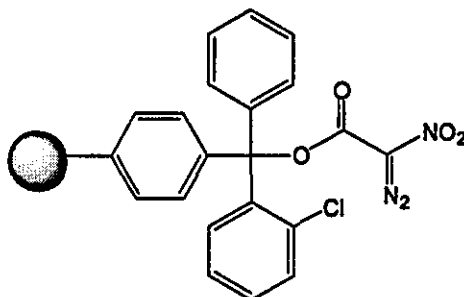


2-Chlorotrityl chloride resin (0.25 g, 0.20 mmol) was swollen in a mixture of anhydrous dimethylformamide:dichloromethane (1:1) (4mL) and treated with 2-nitroethanol (0.06 mL, 0.81 mmol) and pyridine (0.14 mL, 1.8 mmol). The reaction mixture was shaken for 3 days at room temperature. After this time, the resin was filtered and thoroughly washed sequentially with dimethylformamide, dichloromethane and methanol, and finally with diethyl ether. The IR spectrum was very similar to the starting chlorotrityl resin. The peaks due to the stretching of the nitro group could be the ones observed at 1600 and 1331 cm^{-1} , but because these peaks were also present in the starting resin it could not be decided if the reaction had worked or not. The resin was used for the next reaction without further analysis.

ν_{max} (KBr disc) 3434, 2924, 1664, 1600, 1491, 1446, 1383, 1265, 1155, 1039, 827, 754, 698, 631 cm^{-1} .

7.2.4.2 Synthesis of 2-chlorotrityl-diazo-nitro resin derivatives

7.2.4.2.1 2-Chlorotrityl-diazo-nitro-acetic acid resin derivative

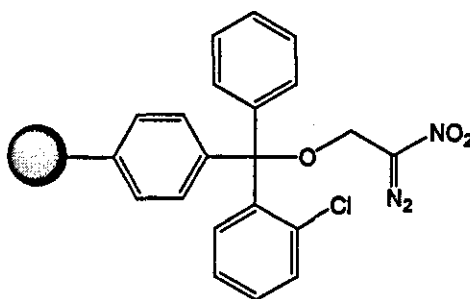


276b

2-Chlorotrityl-nitro-acetic acid resin derivative **274b** (0.25 g, 0.3 mmol) was treated with a solution of *para*-toluenesulfonyl azide (0.30 g, 1.5 mmol) and DBU (0.23 mL, 1.5 mmol) in dichloromethane (10 mL). The reaction mixture was shaken for 24 hours at room temperature. After this time, the resin was filtered and thoroughly washed sequentially with methanol and dichloromethane. The IR spectrum showed a small band at 2103 cm^{-1} , probably due to the stretching of the diazo group.

ν_{max} (KBr disc) 3565, 3442, 3024, 2923, 2847, 2103, 1948, 1808, 1734, 1668, 1600, 1566, 1502, 1490, 1446, 1414, 1329, 1263, 1155, 1119, 1034, 1010, 893, 825, 755, 727, 696 cm^{-1} .

7.2.4.2.2 2-Chlorotrityl-2-diazo-2-nitro-ethanol resin derivative



247b

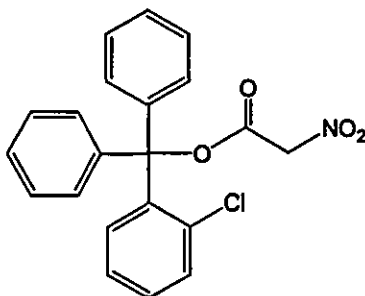
2-Chlorotrityl-2-nitro-ethanol resin derivative **238b** (0.25 g, 0.3 mmol) was suspended in dichloromethane (10 mL) and treated with DBU (0.23 mL,

1.5 mmol). After shaking the reaction mixture for 5 min., *para*-toluenesulfonyl azide (0.30 g, 1.5 mmol) was added and the mixture was shaken for 24 hours at room temperature. After this time, the resin was filtered and thoroughly washed sequentially with dichloromethane and methanol, and finally with diethyl ether. The IR spectrum showed a small band at 2104 cm^{-1} , indicating that possibly the product had been formed to a small extent.

ν_{max} (KBr disc) 3568, 3430, 3058, 3025, 2923, 2844, 2104, 1948, 1809, 1738, 1664, 1600, 1564, 1491, 1466, 1446, 1414, 1329, 1264, 1155, 1122, 1055, 1035, 1012, 893, 826, 754, 729, 697 cm^{-1} .

7.2.4.3 Experiments in solution phase

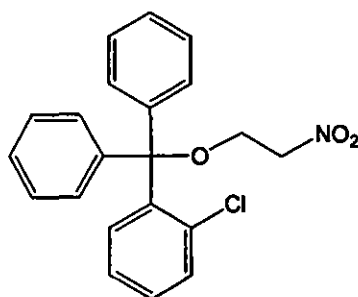
7.2.4.3.1 Attempted synthesis of 2-chlorotrityl-nitro-acetic acid derivative



295

2-Chlorotrityl chloride (0.15 g, 0.48 mmol) and dipotassium salt of nitroacetic acid (87 mg, 0.48 mmol), were dissolved in dimethylformamide (7 mL). The reaction mixture was stirred at room temperature overnight. After this time, it was diluted in diethyl ether and washed several times with brine. The organic phase was separated, dried over magnesium sulfate and concentrated under vacuum, to furnish an orange-red solid. By ^1H NMR spectroscopy a complex mixture was recovered, and isolation of the desired compound 295 was not possible.

7.2.4.3.2 Attempted synthesis of 2-chlorotrityl-nitro-ethanol derivative



294

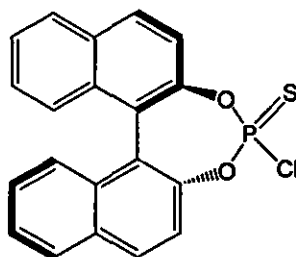
A solution of chlorotrityl chloride (0.30 g, 0.96 mmol) and 2-nitroethanol (0.10 mL, 1.3 mmol) in dry dichloromethane, were treated with diisopropylethylenediamine (0.26 mL, 2.0 mmol) at room temperature. The reaction mixture was stirred overnight at room temperature. A bright pink colour developed after the addition, turning into a red- brown colour, which dispersed overnight. Then, the reaction mixture was diluted with dichloromethane and washed three times with water. The organic phase was separated, dried over magnesium sulfate and concentrated *in vacuo*, to give the crude mixture as a yellow oil. Flash chromatography (silica gel, ethyl acetate:hexane) of the crude mixture did not furnish the desired product **294**. The 2-chlorotrityl cation and 2-chlorotrityl chloride were identified by mass spectrum and ^1H NMR spectra respectively.

The same reaction was repeated following another procedure,¹⁸⁹ using pyridine (0.46 mL, 5.7 mmol) as base and a mixture of dichloromethane:dimethylformamide (1:1) as the solvent. The reaction mixture was stirred overnight at room temperature. After that time, it was partitioned between ether and brine, in order to eliminate the remaining dimethylformamide. The organic phase was separated, dried over magnesium sulfate and concentrated *in vacuo*, but unfortunately the spectroscopic data did not shown evidence of the desired product being formed.

7.3 Experimental for chapter 4; synthesis of phosphorus ligands

7.3.1 Synthesis of phosphorus ligands derived from diols

7.3.1.1 (R)-4-Chloro-3,5-dioxa-4-phospha-cyclohepta[2,1- α ;3,4- α']dinaphthalene-4-sulfide

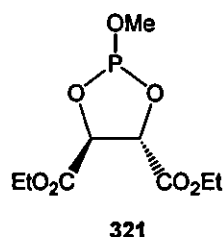


319

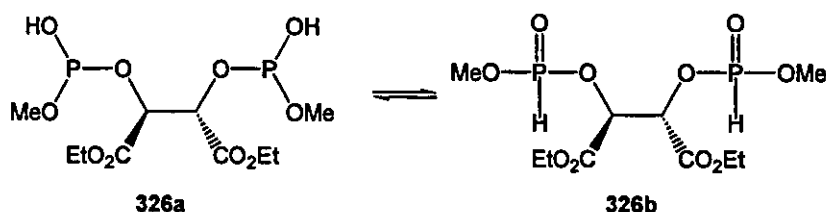
A solution of thiophosphoryl chloride (0.56 mL, 2.57 mmol) in anhydrous acetonitrile (3 mL) was added dropwise, *via* syringe pump, to a solution of (R)-(+)-1,1'-bi(2-naphthol) (0.74 g, 2.6 mmol) and triethylamine (0.79 mL, 5.7 mmol) in anhydrous acetonitrile (10 mL). The reaction mixture was heated under reflux for 1.5 hour, and then cooled to room temperature and stirred overnight. After this time, the solvent was evaporated under reduced pressure, and the residue obtained was dissolved in dichloromethane and washed three times with water. The organic phase was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure, to give the crude product as a white-pale yellow solid, 0.93 g, 95%. A portion of the product was recrystallised from dichloromethane and hexane to afford the desired product **319** as a white solid.²⁵²

$[\alpha]_D^{25}$ -351.02 ($c = 0.98$, CH_2Cl_2); mp decomp >160 °C; HRMS (EI): (m/z) calcd. for $\text{C}_{20}\text{H}_{12}\text{ClO}_2\text{PS}$ (M^+) 381.9984; Found: 381.9978; ν_{max} (CH_2Cl_2) 3057, 1588, 1461, 1321, 1217, 1188, 1156, 1067, 957, 878, 813, 734, 687 cm^{-1} ; ^{31}P NMR (250 MHz, CDCl_3) δ 74 (major), 67, 53; ^1H NMR (250 MHz, CDCl_3) δ 7.23-7.63 (m, 4H), 7.86-8.10 (m, 8H).

7.3.1.2 Attempted synthesis of (4S,5S)-2-methoxy-[1,3,2]dioxaphospholane-4,5-dicarboxylic acid diethyl ester

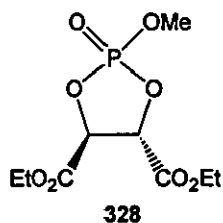


Phosphorus trichloride (0.2 mL, 2 mmol) in dichloromethane (5 mL) was added dropwise to a solution of L-(+)-diethyl tartrate (0.35 mL, 2.0 mmol) and triethylamine (1.2 mL, 4.0 mmol) in dichloromethane (15 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 hours. After this time, methanol (10 mL) was added, and stirring continued for 2.5 hours at room temperature. The reaction mixture was then partitioned between dichloromethane and water. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated *in vacuo*, to afford the ring opened compound **326**, that existed in two tautomeric forms **326a** and **326b**, (2S,3S)-bis-hydroxy-methoxy-phosphanyloxy)-succinic acid diethyl ester, in quantitative yield. The desired compound **321** was not isolated.

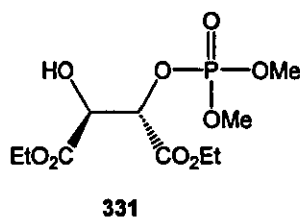


ν_{\max} (CH₂Cl₂) 3418, 2985, 1745, 1644, 1449, 1371, 1238, 1136, 1091, 1045, 983, 830 cm⁻¹; ³¹P NMR (250 MHz, CDCl₃) δ 11.2 (major), 3.0; ¹H NMR (250 MHz, CDCl₃) δ 1.33 (t, 6H, 2x-OCH₂CH₃, *J* = 7.2 Hz), 3.64 (bs, 1H, -OH tautomeric), 3.80 (d, 6H, 2x-POCH₃, *J* = 11.9 Hz), 4.31 (q, 4H, 2x-OCH₂CH₃, *J* = 7.2 Hz), 4.56 (s, 2H, 2x-CH-), 8.18 (s, 2H, 2x-PH); ¹³C NMR (400 MHz, CDCl₃) δ 8.5, 14.1, 45.2, 52.05 and 52.14, 61.2, 72.3 (2xCH), 171.5 (2xC).

7.3.1.3 Attempted synthesis of (4S,5S)-2-methoxy-2-oxo-2λ⁵-[1,3,2]dioxaphospholane-4,5-dicarboxylic acid diethyl ester



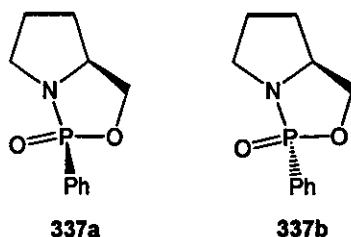
Phosphorus oxychloride (0.2 mL, 2 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise to a solution of L-(+)-diethyl tartrate (0.36 mL, 2.0 mmol) and triethylamine (1.2 mL, 8.0 mmol) in anhydrous tetrahydrofuran (15 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. After this time, methanol (10 mL) was added, and stirring continued for 24 hours at room temperature. The solvent was then evaporated under reduced pressure, and the resulting residue was partitioned between water and dichloromethane. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated *in vacuo*, to yield the crude product as a brown oil. Separation of the crude mixture by flash chromatography (silica gel, dichloromethane:ethyl acetate (7:3)) afforded the ring opened compound **331**, (2S,3S)-2-(dimethoxy-phosphoryloxy)-3-hydroxy-succinic acid diethylester, in low yield. The desired compound **328** was not isolated.



ν_{\max} (CH₂Cl₂) 3348, 2964, 1757, 1450, 1372, 1270, 1139, 1048, 964, 886, 856, 810, 735 cm⁻¹; ³¹P NMR (250 MHz, CDCl₃) δ 0.5; ¹H NMR (250 MHz, CDCl₃) δ 1.34 (dt, 6H, 2x-OCH₂CH₃-, *J* = 4.8, 7.2 Hz), 3.73 (d, 3H, -POCH₃, *J* = 11.2 Hz), 3.88 (d, 3H, -POCH₃, *J* = 11.4 Hz), 4.22-4.38 (m, 4H, 2x-OCH₂CH₃-), 4.73 (t, 1H, -CH-), 5.09 (bs, 1H, -OH), 5.23 (dd, 1H, -CH-, *J* = 2.1, 9.5 Hz); ¹³C NMR (400 MHz, CDCl₃) δ 13.9 (CH₃), 14.0 (CH₃), 54.7 and 54.8 (CH₂), 55.0 and 55.1 (CH₂), 62.3 (CH₃), 62.6 (CH₃), 71.5 and 71.6 (CH), 76.36 and 76.44 (CH), 160.7 (C), 170.5 (C).

7.3.2 Synthesis of phosphorus ligands derived from amino-alcohols

7.3.2.1 (6a*S*)-1-Phenyl-tetrahydro-pyrrolo[1,2-*c*][1,3,2]oxazaphosphole-1-oxide



A solution of (*S*)-(+)-prolinol (0.59 g, 5.8 mmol) in dichloromethane (20 mL) was treated with triethylamine (2.0 mL, 14.5 mmol) and the resulting mixture was cooled in an ice bath. Phenyl phosphonic dichloride (0.91 mL, 6.4 mmol) in dichloromethane (5 mL) was then added dropwise *via* syringe pump. The reaction mixture was allowed to warm to room temperature, and then stirred overnight. After this time, the reaction was quenched by the addition of a saturated aqueous ammonium chloride solution (20 mL) and the product was extracted into dichloromethane. The organic phase was washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo* to furnish the desired products as a mixture of diastereomers, **337a** and **337b**, as a yellow oil. The two diastereomers were separated by flash chromatography (silica gel, ethyl acetate) to furnish **337a** as a white solid, 0.21 g, 16%, and **337b** as a yellow solid, 0.26 g, 20%.^{192,193} By the time the ¹³C NMR spectrum of the compound **337b** was obtained, the product had decomposed.

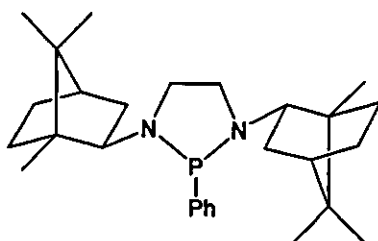
337a; [α]_D²⁵ +34.90 (*c* = 1.02, CH₂Cl₂); Lit. mp¹⁹² 115-117 °C ; mp 116-121 °C; HRMS (EI): (*m/z*) calcd. for C₁₁H₁₄NO₂P (M⁺) 223.0762; Found: 223.0765; ν_{\max} (CH₂Cl₂) 3443, 2971, 2875, 1437, 1263, 1234, 1203, 1132, 1116, 1068, 1046, 1007, 965, 829, 806, 770, 750, 694 cm⁻¹; ³¹P NMR (250 MHz, CDCl₃) δ 39; ¹H NMR (400 MHz, CDCl₃) δ 1.70-1.78 (m, 1H, -CH₂CH₂-), 1.90-2.03 (m, 3H, -CH₂CH₂-), 2.82-2.93 (m, 1H, -CH₂N-), 3.67-3.76 (m, 1H, -CH₂N-), 3.80-3.86 (dt, 1H, -CH₂O-, *J* = 2.4, 8.4 Hz), 4.03-4.11 (m, 1H, -CH₂O-), 4.23-4.32 (m, 1H, -CHCH₂O-), 7.38-7.44 (m, 2H, ArH), 7.45-7.51 (m, 1H, ArH), 7.77-7.84 (m, 2H, ArH); ¹³C NMR (400 MHz, CDCl₃) δ 27.73 and 27.74 (CH₂), 30.15 and

30.18 (CH₂), 45.6 (CH₂), 63.3 and 63.4 (CH), 69.9 and 69.9 (CH₂), 128.5 and 128.7 (CH), 130.4 (C), 131.8 and 131.9 (CH), 132.2 and 132.3 (CH).

337b; HRMS (EI): (*m/z*) calcd. for C₁₁H₁₄NO₂P (M⁺) 223.0762; Found: 223.0766; ν_{\max} (CH₂Cl₂) 3449, 2968, 2877, 1438, 1242, 1123, 1072, 1013, 982, 813, 749, 698 cm⁻¹; ³¹P NMR (250 MHz, CDCl₃) δ 34; ¹H NMR (250 MHz, CDCl₃) δ 1.51-1.67 (m, 1H, -CH₂CH₂-), 1.72-2.12 (m, 3H, -CH₂CH₂-), 2.79-2.93 (m, 1H, -CH₂N-), 2.96-3.11 (m, 1H, -CH₂N-), 3.99-4.10 (m, 1H, -CH₂O-), 4.18-4.32 (m, 1H, -CH₂O-), 4.66-4.80 (m, 1H, -CHCH₂O-), 7.44-7.62 (m, 3H, ArH), 7.70-7.81 (m, 2H, ArH).

7.3.3 Synthesis of phosphorus ligands derived from diamines

7.3.3.1 2-Phenyl-1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl][1,3,2]diazaphospholidine



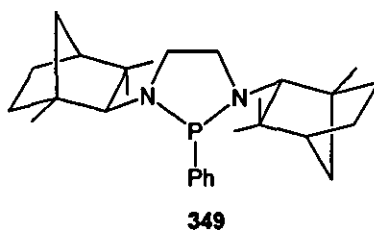
347

A solution of freshly distilled dichlorophenyl phosphine (0.81 g, 4.5 mmol) in deuterated chloroform (6 mL) was slowly added to a mixture of diamine **346** (1.50 g, 4.51 mmol) and triethylamine (1.26 mL, 9.02 mmol) in deuterated chloroform (6 mL) at room temperature. The reaction mixture was stirred overnight at room temperature and then concentrated *in vacuo*. The resulting crude mixture was purified by flash chromatography (silica gel, 15:1 hexane/ethyl acetate) to give the diazaphospholidine **347** as a white solid, 0.69 g, 35%.

mp 111-122 °C; [α]_D²⁵ -102.33 (*c* = 1.20, CH₂Cl₂); HRMS (EI): *m/z* calcd. for C₂₈H₄₃N₂P 438.3164; Found: 438.3157; ν_{\max} (CH₂Cl₂) 2947, 2872, 1474, 1453, 1386, 1367, 1193, 1080, 744, 698 cm⁻¹; ³¹P NMR (250 MHz, CDCl₃) δ 86.6; ¹H NMR (400 MHz, CDCl₃) δ 0.71 (s, 3H, -CH₃), 0.74 (s, 3H, -CH₃), 0.84 (s, 3H, -CH₃), 0.89 (s, 3H, -CH₃), 0.95 (s, 3H, -CH₃), 1.06 (s, 3H, -CH₃), 0.95-1.03 (m, 4H, 4x-CH₂-), 1.32-1.50 (m, 2H, 2x-CH₂-), 1.52-1.64 (m, 5H, 3x-CH₂-, 2x-CH-), 1.65-

1.73 (m, 1H, 1x-CH₂-), 2.35-2.45 (m, 2H, 2x-CH₂-), 2.50-2.59 (m, 1H, 1x-CH₂-), 2.64-2.78 (m, 3H, 1x-CH₂-, 2x-CH-), 3.11-3.19 (m, 1H, 1x-CH₂-), 3.31-3.39 (m, 1H, 1x-CH₂-), 7.11-7.22 (m, 3H, ArH), 7.35-7.43 (m, 2H, ArH); ¹³C NMR (400 MHz, CDCl₃) δ 14.35 and 14.38 (2xCH₃), 20.6 and 20.7 (CH₃), 20.9 and 21.0 (CH₃), 21.28 and 21.34 (2xCH₃), 27.6 and 27.8 (2xCH₂), 36.8 and 37.2 (2xCH₂), 38.7 and 39.0 (CH₂), 40.2 and 40.5 (CH₂), 45.8 and 45.8 (2xCH), 47.2 and 47.5 (2xC), 50.90 and 50.94 (C), 50.97 and 51.00 (C), 51.1 and 51.2 (CH₂), 56.47 and 56.53 (CH₂), 66.9 and 67.0 (CH), 73.1 and 73.3 (CH), 127.76 and 127.81 (2xCH), 128.0 (CH), 131.0 and 131.2 (2xCH), 144.5 and 144.8 (C).

7.3.3.2 2-Phenyl-1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl) [1,3,2]diazaphospholidine

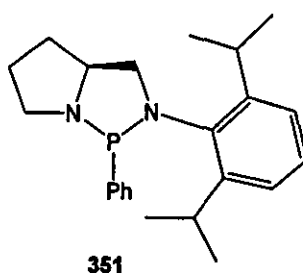


A solution of freshly distilled dichlorophenyl phosphine (0.63 g, 3.5 mmol) in deuterated chloroform (6 mL) was slowly added to a mixture of diamine **348** (1.18 g, 3.54 mmol) and triethylamine (1.0 mL, 7.2 mmol) in deuterated chloroform (6 mL). The reaction mixture was stirred overnight at room temperature, and then the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 15:1 hexane/ethyl acetate) to give the desired diazaphospholidine **349** as a yellow oil, 0.66 g, 42%.

[α]_D²⁵ +29.60 (c = 1.00, CH₂Cl₂); ν_{max} (CH₂Cl₂) 2948, 2867, 1459, 1381, 1173, 1139, 1083, 743, 700 cm⁻¹; ³¹P NMR (250 MHz, CDCl₃) δ 95.4; ¹H NMR (400 MHz, CDCl₃) δ 0.94 (s, 3H, -CH₃), 0.99 (s, 3H, -CH₃), 1.02 (s, 3H, -CH₃), 1.05 (s, 3H, -CH₃), 1.08 (s, 3H, -CH₃), 1.12 (s, 3H, -CH₃), 0.99-1.10 (m, 4H, 4x-CH₂-), 1.35-1.46 (m, 2H, 2x-CH₂-), 1.50-1.57 (m, 2H, 2x-CH₂-), 1.58-1.66 (m, 2H, 2x-CH₂-), 1.67-1.82 (m, 2H, 2x-CH₂-), 1.93-2.03 (m, 1H, 1x-CH₂-), 2.07-2.18 (m, 1H, 1x-CH₂-), 2.55 (dd, 1H, -CH-, J = 1.6, 8.8 Hz), 2.90-2.96 (m, 1H, 1x-CH₂-), 3.00 (dd, 1H, -CH-, J = 1.6, 12.0 Hz), 3.10-3.17 (m, 1H, 1x-CH₂-), 3.20-3.26 (m, 2H, -CH₂-), 7.22-7.32 (m, 3H, ArH), 7.52-7.57 (m, 2H, ArH); ¹³C NMR (400 MHz,

CDCl₃) δ 22.59 and 22.60 (CH₃), 22.90 and 22.94 (CH₃), 22.96 and 22.99 (CH₃), 23.07 and 23.09 (CH₃), 26.85 and 26.89 (CH₂), 27.09 and 27.12 (CH₂), 27.8 and 27.9 (CH₂), 28.5 and 28.6 (CH₂), 32.59 and 32.60 (CH₃), 33.04 and 33.05 (CH₃), 41.63 and 41.64 (C), 42.48 and 42.51 (C), 45.0 and 45.9 (2xCH₂), 48.9 and 49.2 (2xCH), 50.15 and 50.20 (C), 50.3 and 50.4 (C), 50.9 and 51.0 (CH₂), 52.46 and 52.52 (CH₂), 76.2 and 76.3 (CH), 76.8 and 76.9 (CH), 127.45 and 127.52 (2xCH), 128.4 (CH), 131.6 and 131.7 (2xCH), 146.2 and 146.6 (C).

7.3.3.3 Attempted synthesis of 2-(2,6-diisopropyl-phenyl)-(6aS)-1-phenyl-hexahydro-pyrrolo[1,2,c][1,3,2]diazaphosphole

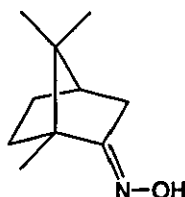


Distilled dichlorophenyl phosphine (30 μ L, 0.20 mmol) was added to a solution of diamine **350** (53 mg, 0.20 mmol) and triethylamine (56 μ L, 0.40 mmol) in deuterated chloroform (3 mL) at room temperature. The reaction mixture was stirred overnight at room temperature, and then the solvent was evaporated under reduced pressure. The desired diazaphospholidine **351**, was not isolated. The ³¹P NMR spectrum showed starting material, unreacted dichlorophenyl phosphine, along with some unidentified minor products.

7.4 Experimental for chapter 5; Synthesis of transition metal complexes of chiral *N*-heterocyclic carbenes

7.4.1 Imidazolinium tetrafluoroborate salt derived from (1*R*)-(+)-camphor

7.4.1.1 (1*R*,4*S*)-1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-one oxime or (1*R*)-(+)-camphor oxime

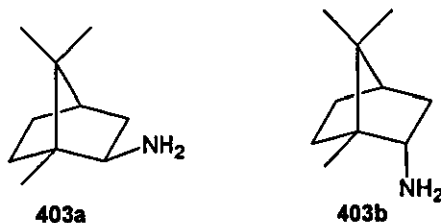


402

(1*R*)-(+)-Camphor (50.00 g, 328 mmol), hydroxylamine hydrochloride (50.20 g, 722 mmol) and pyridine (39.8 mL, 492 mmol) were combined and heated under reflux in ethanol (500 mL) for 4 hours. The mixture was then cooled to room temperature and most of the ethanol was removed *in vacuo*. Water was added to the crude mixture, and the oxime precipitated out of the solution as white crystals, which were isolated by filtration and washed several times with distilled water. The product was dried under vacuum and recrystallised from absolute ethanol to afford pure (1*R*)-(+)-camphor oxime **402** as white crystals, 41.10 g, 75%. This compound spectral data were consistent with that already reported in the literature.^{222,228}

$[\alpha]_D^{25}$ -47.92 ($c = 1.06$, CH_2Cl_2); Lit. mp^{228} 119-120 °C; mp 117-119 °C; ν_{max} (CH_2Cl_2) 3298, 2959, 1686, 1440, 1388, 1371, 924, 723 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.80 (s, 3H, $-\text{CH}_3$), 0.92 (s, 3H, $-\text{CH}_3$), 1.01 (s, 3H, $-\text{CH}_3$), 1.17-1.29 (m, 1H), 1.41-1.51 (m, 1H), 1.64-1.95 (m, 3H), 2.06 (d, 1H, $-\text{CH}_2\text{C}=\text{NOH}$, $J = 17.8$ Hz), 2.55 (dt, 1H, $-\text{CH}_2\text{C}=\text{NOH}$, $J = 3.9, 17.8$ Hz), 8.84 (s, 1H, $-\text{OH}$).

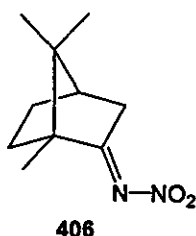
7.4.1.2 (1R,2R,4S) and (1R,2S,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylamine or exo/endo bornylamine



A solution of (1R)-(+)-camphor oxime **402** (1.67 g, 10.0 mmol) in *tert*-butanol (80 mL) was treated with sodium (2.3 g, 0.10 mol). The reaction mixture was heated at 80 °C overnight. After cooling the reaction mixture to room temperature, the reaction was quenched by the addition of ethanol, and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in dichloromethane and washed with water, and the organic layer was separated, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was dissolved in dichloromethane and washed with a solution of hydrochloric acid (2 M, aqueous solution) in order to eliminate the camphor oxime that was still remaining. The aqueous solution was basified with a solution of sodium hydroxide (2 M, aqueous solution), and the white precipitate was dissolved in dichloromethane. The organic layer was dried over magnesium sulfate, filtered and evaporated *in vacuo*, to furnish the desired product **403** as a mixture of both diastereoisomers **403a** and **403b** as a yellow oil, 0.72 g, 47 %. A portion of the product was further purified by flash chromatography (silica gel, 1:1 hexane/dichloromethane, 2% triethylamine) to give the analytically pure amine **403a** as a yellow solid.

403a: Lit. mp²²⁴ 182-183 °C; mp 180-184 °C; Mass spectrum (FAB+) *m/z* calcd. for C₁₀H₁₉N 153.1518; Found: 153.1513; ν_{\max} (CH₂Cl₂) 2947, 1455, 1386, 101, 942 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.81 (s, 3H, -CH₃), 0.87 (s, 3H, -CH₃), 0.97 (s, 3H, -CH₃), 0.93-1.12 (m, 1H), 1.25-1.32 (m, 1H), 1.45-1.58 (m, 2H), 1.63-1.79 (m, 3H), 2.70 (dd, 1H, -CHNH₂, *J* = 5.1, 8.6 Hz); ¹³C NMR (400 MHz, CDCl₃) δ 11.8 (CH₃), 20.3 (CH₃), 20.9 (CH₃), 27.2 (CH₂), 36.4 (CH₂), 40.6 (CH₂), 45.0 (CH), 46.6 (C), 48.1 (C), 60.4 (CH).

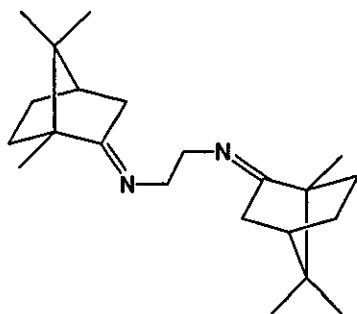
7.4.1.3 (1R,4S)-1-Oxo-2-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yliden)hydrazinium-1-olate or (1R)-(+)-camphor nitroimine



A solution of (1R)-(+)-camphor oxime **402** (30.00 g, 0.18 mol) in glacial acetic acid (900 mL) was treated with 5% aqueous sodium nitrite (450 mL). The reaction mixture was stirred for 2 hours at room temperature. A bright yellow colour developed and dispersed during the first 30 min. Most of the solvent was removed *in vacuo* and water was added to precipitate the crude product, which was recovered by filtration and washed several times with distilled water to afford (1R)-(+)-camphor nitroimine **406** as a white solid, 21.05 g, 59%.^{222,226}

$[\alpha]_D^{25}$ -28.24 ($c = 1.02$, CH_2Cl_2); Lit. mp²²² 41-42 °C; mp 40-42°C; ν_{max} (CH_2Cl_2) 2965, 1644, 1562, 1314, 1293, 1278, 897, 839, 759 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.89 (s, 3H, $-\text{CH}_3$), 0.99 (s, 3H, $-\text{CH}_3$), 1.05 (s, 3H, $-\text{CH}_3$), 1.23-1.37 (m, 1H), 1.50-1.65 (m, 1H), 1.75-2.06 (m, 3H), 2.13 (d, 1H, $-\text{CH}_2\text{C}=\text{N}-$, $J = 18.5$ Hz), 2.61-2.75 (m, 1H, $-\text{CH}_2\text{C}=\text{N}-$); ^{13}C NMR (400 MHz, CDCl_3) δ 10.4 (CH_3), 19.4 (CH_3), 20.1 (CH_3), 26.7 (CH_2), 31.6 (CH_2), 35.4 (CH_2), 43.4 (CH), 50.2 (C), 54.2 (C), 189.5 (C).

7.4.1.4 *N,N'*-Bis-[(1*R*,4*S*)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-ylidene]-ethane-1,2-diamine

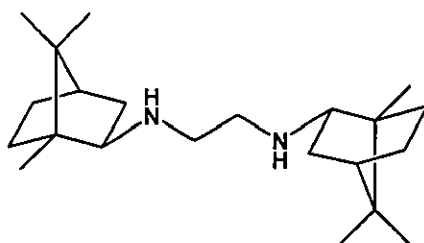


407

Ethylenediamine (4.1 mL, 61 mmol) was added dropwise to a solution of (1*R*)-(+)-camphor nitroimine **406** (23.95 g, 122.0 mmol) in methanol (200 mL). The reaction mixture was stirred overnight at room temperature. After this time, removal of the solvent under reduced pressure furnished the desired diimine **407** as a white solid, in quantitative yield.²²⁷ The ¹H NMR spectrum showed some minor impurities were present. This product was used in the next experiment without further purification.

$[\alpha]_D^{25}$ -28.60 ($c = 1.79$, CH₂Cl₂); Lit. mp²²⁷ 40 °C; mp 63-65°C; Mass spectrum (FAB+) m/z calcd. for C₂₂H₃₆N₂ (M+H) 329.2957; Found: 329.2960; ν_{\max} (CH₂Cl₂) 2955, 1685, 1447, 1388, 1370, 1062 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.74 (s, 6H, 2x-CH₃), 0.91 (s, 6H, 2x-CH₃), 0.93 (s, 6H, 2x-CH₃), 1.17-1.23 (m, 2H, 2x-CH₂-), 1.30-1.37 (m, 2H, 2x-CH₂-), 1.64 (dt, 2H, 2x-CH₂-, $J = 4, 12.8$ Hz), 1.80-1.93 (m, 6H, 2x-CH₂-, 2x-CH₂-, 2x-CH-), 2.41 (dt, 2H, 2x-CH₂-, $J = 4, 16.8$ Hz), 3.42-3.55 (m, 4H, 2x-NCH₂-); ¹³C NMR (400 MHz, CDCl₃) δ 11.4 (2xCH₃), 19.0 (2xCH₃), 19.8 (2xCH₃), 27.1 (2xCH₂), 32.3 (2xCH₂), 35.5 (2xCH₂), 43.9 (2xCH), 46.9 (2xC), 53.3 (2xCH₂), 53.5 (2xC), 182.7 (2xC).

7.4.1.5 *N,N'*-Bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-ethane-1,2-diamine

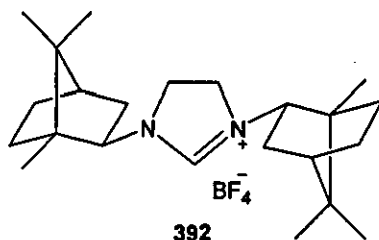


346

Diimine **407** (20.70 g, 63.0 mmol) was dissolved in dry ethanol (250 mL) and stirred at room temperature. Sodium borohydride (5.24 g, 139 mmol) was added in several portions to the previous solution, and the reaction mixture was left stirring overnight at room temperature. The reaction was quenched by the addition of water and the mixture was then stirred at room temperature for 30 min. After this time, the solvent was removed under reduced pressure and the residue obtained was dissolved in dichloromethane and washed three times with brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the diamine **346** as a white solid 18.82 g, 90%. The product had a trace of unreacted starting material present.^{196a}

$[\alpha]_D^{25}$ -73.43 ($c = 1.34$, CH_2Cl_2); mp 85-87 °C; ν_{max} (CH_2Cl_2) 2949, 1685, 1472, 1450, 1387, 1368, 1124 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.80 (s, 6H, 2x- CH_3), 0.86 (s, 6H, 2x- CH_3), 1.00 (s, 6H, 2x- CH_3), 1.01-1.10 (m, 6H), 1.46-1.69 (m, 10H), 2.49-2.55 (m, 2H, - CH_2NH -), 2.63-2.69 (m, 2H, - CH_2NH -). ^{13}C NMR (400 MHz, CDCl_3) δ 12.2 (CH_3), 20.6 (2x CH_3), 27.4 (CH_2), 37.0 (CH_2), 39.1 (CH_2), 45.3 (CH), 46.6 (C), 48.2 (CH_2), 48.4 (C), 66.5 (CH).

7.4.1.6 1,3-Bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-4,5-dihydro-3H-imidazol-1-ium tetrafluoroborate

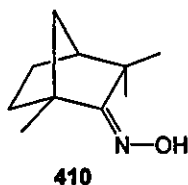


Diamine **346** (18.78 g, 56.48 mmol), ammonium tetrafluoroborate (5.92 g, 56.5 mmol) and triethyl orthoformate (9.4 mL, 56 mmol) were combined and heated at 120 °C for 3 hours. After this time, the reaction mixture was concentrated under reduced pressure to give the crude product, which was recrystallised from absolute ethanol to yield the imidazolinium salt **392**, as white crystals, 17.15 g, 71%.

$[\alpha]_D^{25}$ -98.56 ($c = 1.12$, CH_2Cl_2); Lit. mp^{196a} 280-282 °C; mp 280-285 °C; Mass spectrum (FAB+) m/z calcd. for $\text{C}_{23}\text{H}_{39}\text{N}_2^+$ 343.3113; Found: 343.3117; ν_{max} (CH_2Cl_2) 2951, 1635, 1265, 1063, 1030, 737 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.87 (s, 12H, 2x-(CH_3)-), 0.95 (s, 6H, 2x-(CH_3)-), 1.19-1.23 (m, 2H, 2x- CH_2 -), 1.27-1.34 (m, 2H, 2x- CH_2 -), 1.57-1.63 (dt, 2H, 2x- CH_2 -, $J = 4.8, 12.4$ Hz), 1.70-1.78 (m, 2H, 2x- CH_2 -), 1.84-1.89 (m, 4H, 2x- CH_2 -, 2x- CH -), 2.04-2.09 (m, 2H, 2x- CH_2 -), 3.65-3.70 (m, 2H, 2x- CHN -), 3.85-3.96 (m, 2H, 2x- CH_2N -), 4.09-4.16 (m, 2H, 2x- CH_2N -), 8.06 (s, 1H, - $\text{NCH}=\text{N}$ -); ^{13}C NMR (400 MHz, CDCl_3) δ 13.2 (2x CH_3), 20.5 (2x CH_3), 21.1 (2x CH_3), 26.8 (2x CH_2), 34.4 (2x CH_2), 37.2 (2x CH_2), 45.0 (2x CH), 47.4 (2x C), 49.9 (2x CH_2), 50.8 (2x C), 67.6 (2x CH), 158.9 (CH).

7.4.2 Imidazolinium tetrafluoroborate salt derived from (1R)-(-)-fenchone

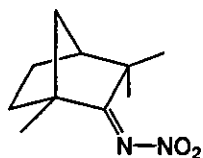
7.4.2.1 (1R,4S)-1,3,3-Trimethyl-bicyclo[2.2.1]heptan-2-one oxime or (1R)-(-)-fenchone oxime



(1R)-(-)-Fenchone (50.00 g, 328 mmol), hydroxylamine hydrochloride (50.20 g, 722 mmol) and pyridine (39.8 mL, 492 mmol) were combined and heated under reflux in ethanol (500 mL) for 4 hours. The mixture was then cooled to room temperature and most of the ethanol was removed *in vacuo*. Water was added to the reaction mixture, and the resulting precipitated oxime, was isolated by filtration and washed several times with distilled water. The crude product was dried under vacuum and recrystallised from absolute ethanol to afford pure (1R)-(-)-fenchone oxime **410** as white crystals, 38.7 g, 71%. This compound spectral data were consistent with that already reported in the literature.^{222,228}

$[\alpha]_D^{25}$ -48.24 ($c = 1.02$, CH_2Cl_2); Lit. mp²²⁸ 169-170 °C; mp 166-168 °C; Mass spectrum (FAB+) m/z (MH^+) calcd. for $\text{C}_{10}\text{H}_{17}\text{NO}$ 168.1390; Found: 168.1390; ν_{max} (CH_2Cl_2) 3142, 2917, 1429, 927 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.22 (s, 3H, $-\text{CH}_3$), 1.30 (s, 3H, $-\text{CH}_3$), 1.33 (s, 3H, $-\text{CH}_3$), 1.32-1.35 (m, 1H), 1.40-1.64 (m, 3H), 1.68-1.84 (m, 3H), 8.99 (s, 1H, $-\text{NOH}-$); ^{13}C NMR (400 MHz, CDCl_3) δ 17.1 (CH_3), 22.1 (CH_3), 22.9 (CH_3), 25.3 (CH_2), 34.2 (CH_2), 43.3 (CH_2), 44.2 (C), 48.6 (CH), 50.1 (C), 172.3 (C).

7.4.2.2 (1R,4S)-1-oxo-2-(1,3,3-trimethylbicyclo[2.2.1]hept-2-yliden)hydrazinium-1-olate or (1R)-(-)-fenchone nitroimine

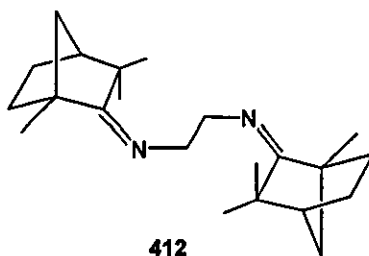


411

A solution of sodium nitrite (16.92 g, 245.0 mmol) in water (120 mL) was added to a solution of (1R)-(-)-fenchone oxime **410** (25.0 g, 150 mmol) in diethyl ether (300 mL), in a separatory funnel. The mixture was then treated with a solution of sulfuric acid (0.5 M, aqueous solution) (250 mL), with occasional vigorous swirling over 2 hours. A dark red-fuchsia colour developed during the course of the reaction which dispersed after leaving the reaction mixture to stand for 3 hours. The ether layer was separated, washed twice with saturated sodium hydrogen carbonate aqueous solution, dried over sodium sulfate, filtered and evaporated under reduced pressure to give the crude product, (1R)-(-)-fenchone nitroimine **411** as a pale yellow solid, which was used without further purification 21.91 g, 74%. The product was shown to be a mixture of *syn* and *anti* diastereoisomers of the nitroimine **411**, in a 2:1 ratio approximately. The major and minor diastereoisomer are represented by A and B, although it is not known which is the *syn* or the *anti* isomer.^{222,229}

$[\alpha]_D^{25}$ -27.00 ($c = 1.20$, CH_2Cl_2); Lit. mp²²² 63-65 °C; mp 59-61 °C; ν_{max} (CH_2Cl_2) 2968, 1638, 1550, 1464, 1450, 1370, 1303 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 1.18 (s, 3H_B, -CH₃), 1.21 (s, 3H_A, -CH₃), 1.23 (s, 3H_B, -CH₃), 1.26 (s, 3H_A, -CH₃), 1.30 (s, 3H_{A+B}, -CH₃), 1.35-1.52 (m, 1H_{A+B}, -CH-), 1.54-2.06 (m, 6H); ^{13}C NMR (400 MHz, CDCl_3) δ 15.1 and 16.2 (CH₃), 22.6 and 23.7 (CH₃), 24.5 and 24.7 (CH₂), 25.3 and 26.0 (CH₃), 33.7 and 34.1 (CH₂), 42.2 and 45.1 (CH₂), 46.8 and 47.4 (C), 45.6 and 49.8 (CH), 52.4 and 53.7 (C), 189.9 and 190.0 (C).

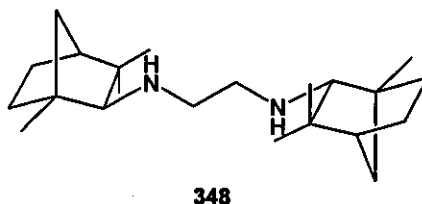
7.4.2.3 *N,N'*-Bis-[(1*R*,4*S*)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-ylidene]-ethane-1,2-diamine



Ethylenediamine (3.73 mL, 56.0 mmol), was added dropwise to a solution of (1*R*)-(-)-fenchone nitroimine **411** (mixture of *syn* and *anti* isomers) (21.91 g, 112.0 mmol) in methanol (200 mL). The reaction mixture was stirred overnight at room temperature. After this time, removal of the solvent under reduced pressure furnished the desired diimine **412** as a yellow solid, in quantitative yield. This product was used in the next experiment without further purification.

$[\alpha]_D^{25}$ -49.41 ($c = 1.19$, CH_2Cl_2); Lit. mp^{227} 52-55 °C; mp 50-53 °C; Mass spectrum (FAB+) m/z calcd. for $\text{C}_{22}\text{H}_{36}\text{N}_2$ ($\text{M}+\text{H}$) 329.2957; Found: 329.2960; ν_{max} (CH_2Cl_2) 2963, 1682, 1540, 1464, 1037 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 1.12 (s, 6H, 2x- CH_3), 1.23 (s, 6H, 2x- CH_3), 1.27 (s, 6H, 2x- CH_3), 1.30-1.39 (m, 4H, 4x- CH_2 -), 1.49-1.60 (m, 4H, 4x- CH_2 -), 1.61-1.69 (m, 2H, 2x- CH_2 -), 1.71-1.80 (m, 2H, 2x- CH_2 -), 1.79-1.84 (m, 2H, 2x- CH_2 -), 3.65-3.85 (m, 4H, 2x- NCH_2 -); ^{13}C NMR (400 MHz, CDCl_3) δ 18.2 (2x CH_3), 24.6 (2x CH_3), 25.3 (2x CH_3), 25.7 (2x CH_2), 34.2 (2x CH_2), 42.8 (2x CH_2), 44.5 (2xC), 50.2 (2xCH), 52.9 (2x CH_2), 184.5 (2xC).

7.4.2.14 *N,N'*-Bis-[(1*R*,2*R*,4*S*)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-ethane-1,2-diamine

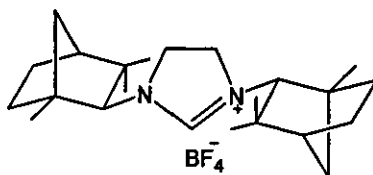


Diimine **412** (18.64 g, 56.74 mmol) was dissolved in dry ethanol (250 mL) and stirred at room temperature. Sodium borohydride (4.72 g, 125 mmol) was added in several portions and the reaction mixture was stirred overnight at room

temperature. The reaction was quenched by the addition of water and the mixture was then stirred at room temperature for 30 min. After this time, the solvent was removed under reduced pressure and the residue obtained was dissolved in dichloromethane and washed three times with brine. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the crude product **348** as a colourless oil, 18.18 g, 96%. The product was used in next experiments without further purification.

$[\alpha]_D^{25} +33.61$ ($c = 1.19$, CH_2Cl_2); HRMS (EI): m/z calcd. for $\text{C}_{22}\text{H}_{40}\text{N}_2$ (M^+) 332.3192; Found: 332.3190; ν_{max} (CH_2Cl_2) 2947, 1459, 1363, 1142, 1102 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.91 (s, 3H, $-\text{CH}_3$), 0.94-0.97 (m, 1H, $-\text{CH}_2-$), 1.02 (s, 3H, $-\text{CH}_3$), 1.06-1.08 (m, 1H, $-\text{CH}_2-$), 1.09 (s, 3H, $-\text{CH}_3$), 1.33-1.41 (m, 1H, $-\text{CH}_2-$), 1.43-1.52 (m, 2H, $-\text{CH}_2-$, $-\text{CH}_2-$), 1.61-1.67 (m, 2H, $-\text{CH}_2-$, $-\text{CH}-\text{C}(\text{CH}_3)_2$), 2.16 (d, 1H, $-\text{CHNH}-$, $J = 1.6$ Hz), 2.58-2.63 (m, 1H, $-\text{NHCH}_2-$), 2.75-2.78 (m, 1H, $-\text{NHCH}_2$); ^{13}C NMR (400 MHz, CDCl_3) δ 20.7 (2x CH_3), 21.0 (2x CH_3), 26.3 (2x CH_2), 26.5 (2x CH_2), 32.4 (2x CH_3), 39.3 (2x C), 42.9 (2x CH_2), 48.9 (2x CH), 48.9 (2x C), 50.4 (2x CH_2), 73.7 (2x CH).

7.4.2.5 1,3-Bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-4,5-dihydro-3H-imidazol-1-ium tetrafluoroborate



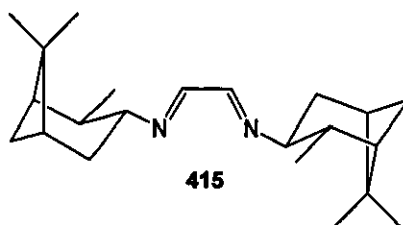
409

Diamine **348** (18.18 g, 54.65 mmol), ammonium tetrafluoroborate (5.73 g, 54.7 mmol) and triethyl orthoformate (9.1 mL, 55 mmol) were combined and heated at 120 °C for 3 hours. After this time, the reaction mixture was concentrated under reduced pressure and the residue obtained was recrystallised from absolute ethanol to yield the imidazolium salt **409**, as white crystals, 8.45 g, 36%.

$[\alpha]_D^{25}$ -8.80 ($c = 1.00$, CH_2Cl_2); mp 180-190 °C; Mass spectrum (FAB+) m/z calcd. for $\text{C}_{22}\text{H}_{39}\text{N}_2^+$ 343.3113; Found: 343.3117; ν_{max} (CH_2Cl_2) 2953, 2876, 1633, 1462, 1267, 1097, 1057 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.97 (s, 6H, 2x- CH_3), 1.15 (s, 6H, 2x- CH_3), 1.21 (s, 6H, 2x- CH_3), 1.28-1.32 (m, 2H, 2x- CH_2 -), 1.36-1.44 (m, 2H, 2x- CH_2 -), 1.53-1.64 (m, 4H, 2x- CH_2 -, 2x- CH_2 -), 1.66-1.72 (m, 2H, 2x- CH_2 -), 1.76-1.81 (m, 2H, 2x- CH_2 -), 1.85-1.87 (m, 2H, 2x- $\text{CHC}(\text{CH}_3)_2\text{CHN}$ -), 3.37 (s, 2H, 2x- $\text{C}(\text{CH}_3)_2\text{CHN}$ -), 4.13 (s, 4H, 2x- CH_2N -), 8.11 (s, 1H, $-\text{CH}=\text{N}^+$ -); ^{13}C NMR (400 MHz, CDCl_3) δ 20.0 (2x CH_3), 21.8 (2x CH_3), 26.5 (2x CH_2), 28.0 (2x CH_2), 31.5 (2x CH_3), 40.4 (2xC), 44.3 (2x CH_2), 48.0 (2xCH), 49.1 (2xC), 51.2 (2x CH_2), 74.7 (2xCH), 157.7 (CH).

7.4.3 Synthesis of tetrafluoroborate salts derived from (1S,2S,3S,5R)-(+)-isopinocampheylamine

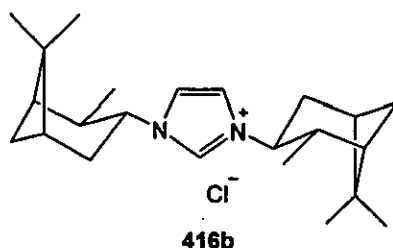
7.4.3.1 *N,N'*-Bis-[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-ylidene]-ethane-1,2-diamine



Glyoxal 40% solution in water (0.38 mL, 3.3 mmol) was added dropwise to a solution of (1S,2S,3S,5R)-(+)-isopinocampheylamine (1.00 g, 6.5 mmol) in dichloromethane (8 mL), at 0 °C. The reaction mixture was allowed to warm to room temperature and it was stirred for 5 hours. After this time, the mixture was partitioned between diethyl ether and water. The organic phase was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish quantitatively the diimine **415** as a white-pale yellow solid, 1.05 g, 99%.^{196a}

Mass spectrum (FAB+) m/z calcd. for $C_{22}H_{36}N_2$ ($M+H$) 329.2957; Found: 329.2953 (MH^+); ν_{max} (CH_2Cl_2) 2903, 1622, 1471, 1451, 1384, 1366, 1331, 1158 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 6H, 2x- $CHCH_3$ -, $J = 7.2$ Hz), 0.97 (s, 6H, 2x- CH_3), 1.12 (d, 2H, 2x- CH_2 -, $J = 9.6$ Hz), 1.18 (s, 6H, 2x- CH_3), 1.78-1.83 (m, 4H), 1.89-1.94 (m, 2H), 1.97-2.05 (m, 2H), 2.16-2.25 (m, 2H), 2.32-2.36 (m, 2H), 3.36-3.41 (m, 2H, 2x- CHN -), 7.79 (s, 2H, 2x- $CH=N$ -); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.2 (2x CH_3), 23.9 (2x CH_3), 28.3 (2x CH_3), 34.3 (2x CH_2), 36.1 (2x CH_2), 39.2 (2xC), 41.9 (2xCH), 43.7 (2xCH), 47.9 (2xCH), 70.4 (2xCH), 159.8 (2xCH).

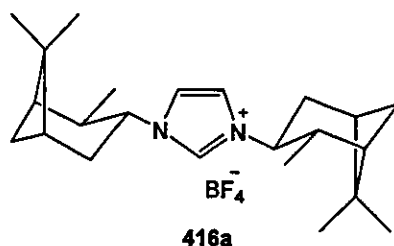
7.4.3.2 Attempted synthesis of 1,3-bis-[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-3H-imidazol-1-ium chloride



A mixture of the diimine compound **415** (0.29 g, 0.89 mmol) and paraformaldehyde (28 mg, 0.92 mmol) in anhydrous toluene (10 mL) was heated at 100 °C, until most of the paraformaldehyde was dissolved. After this time, the temperature was reduced to 40 °C, and a solution of hydrochloric acid (4 M in 1,4-dioxane) (0.22 mL, 0.88 mmol) was added. The reaction mixture was stirred at 40 °C for 1 hour, and then at room temperature overnight. The solvent was evaporated under vacuum, to give a complex mixture as a dark brown solid, and the desired product **416b** was not isolated. .

The reaction was also carried out under different conditions: the diimine compound **415** (19 mg, 0.06 mmol), triethyl orthoformate (5 µL, 0.3 mmol) and ammonium chloride (6 mg, 0.1 mmol) were combined and heated at 120 °C for 1.5 hours. After this time, ethanol (1 mL) was added, and the reaction mixture was stirred at 120 °C for 2 hours. Unfortunately, the desired product **416b** could not be isolated.

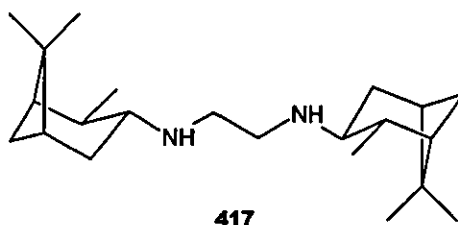
7.4.3.3 Attempted synthesis of 1,3-bis-[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-3H-imidazol-1-ium tetrafluoroborate



The diimine compound **415** (0.29 g, 0.89 mmol), paraformaldehyde (28 mg, 0.92 mmol) and tetrafluoroboric acid (54% in diethyl ether) (0.12 mL, 0.85 mmol) were reacted together according to the procedure of the previous experiment.

The reaction was also carried out in a small scale in a carousel tube: a mixture of the diimine compound **415** (54 mg, 0.16 mmol) and paraformaldehyde (5 mg, 0.2 mmol) in anhydrous toluene (5 mL) was heated at 135 °C for 3 hours. After this time, the temperature was reduced to 40 °C, and a solution of tetrafluoroboric acid (54% in diethyl ether) (12 μ L, 0.16 mmol) was added. The mixture was stirred for 1 hour at 40 °C, and solvent was evaporated *in vacuo*. Unfortunately, the desired product **416a** could not be isolated.

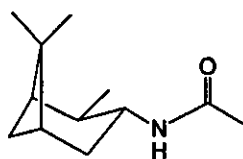
7.4.3.4 *N,N'*-Bis-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-ethane-1,2-diamine



Sodium triacetoxyborohydride (1.78 g, 8.40 mmol) was added portionwise to a solution of diimine **415** in dichloromethane (15 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 hours. After this time, the reaction was quenched by the addition of a saturated aqueous ammonium chloride solution and the product was extracted into diethyl ether. The organic phase was washed with brine, separated, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the crude product. The crude mixture was separated by flash chromatography (silica, hexane:ethyl acetate (1:1) to furnish the desired diamine **417**,^{196a} as a brown solid, 0.18 g, 17%, and the amide **419**, *N*-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-acetamide or *N*-pinan-3-yl-acetamide,²⁵³ which was identified by X-Ray crystallography, as shown in **Figure 43**, and obtained as colourless crystals, 66 mg, 11%.

417; $[\alpha]_D^{25} +50.40$ ($c = 0.50$, CH_2Cl_2); mp decomp > 93 °C; ^1H NMR (400 MHz, CDCl_3) 0.91 (d, 2H, 2x- CH_2 -, $J = 10$ Hz), 0.98 (s, 6H, 2x- CH_3), 1.09 (d, 6H, 2x- CH_3 , $J = 7.2$ Hz), 1.91 (s, 6H, 2x- CH_3), 1.77 (dt, 2H, 2x- CH -, $J = 2.0, 6.0$ Hz), 1.82-1.88 (m, 4H, 2x- CH_2 -), 1.89-1.94 (m, 2H, 2x- CH -), 2.07-2.13 (m, 2H, 2x- CH -), 2.19-2.25 (m, 2H, 2x- CH_2 -), 2.63 (bs, 4H, 2x- CH_2 -), 2.81-2.88 (m, 2H, 2x- CH -); ^{13}C NMR (400 MHz, CDCl_3) δ 22.7 (2x CH_3), 23.6 (2x CH_3), 27.7 (2x CH_3), 30.4

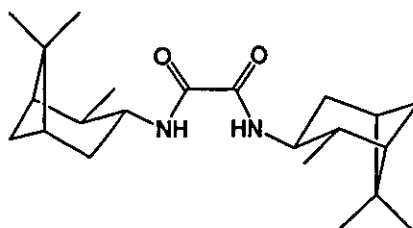
(2xCH₂), 32.4 (2xCH₂), 37.6 (2xCH), 38.8 (2xC), 41.6 (2xCH), 47.5 (2xCH), 48.4 (2xCH₂), 36.5 (2xCH).



419

419; $[\alpha]_D^{25} +25.42$ ($c = 0.96$, CH₂Cl₂); Lit. mp²⁵³ 108-110 °C; mp 108-112 °C; Mass spectrum (FAB+) m/z calcd. for C₁₂H₂₁NO (M+H) 196.1701; Found: 196.1701 (MH⁺); ν_{\max} (CH₂Cl₂) 3280, 3076, 2904, 1648, 1533, 1453, 1375, 1297, 1162, 733 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 0.88 (d, 1H, $J = 15.5$ Hz), 1.03 (s, 3H, -C(CH₃)₂), 1.10 (d, 3H, -CHCH₃, $J = 11.1$ Hz), 1.22 (s, 3H, -C(CH₃)₂), 1.48-1.57 (m, 1H), 1.73-1.83 (m, 2H), 1.89-2.10 (m, 1H), 1.98 (s, 3H, -COCH₃), 2.33-2.45 (m, 1H), 2.51-2.69 (m, 1H), 4.19-4.32 (m, 1H), 6.02 (bd, 1H, -NH, $J = 12.2$ Hz); ¹³C NMR (400 MHz, CDCl₃) δ 20.7 (CH₃), 23.5 (CH₃), 23.6 (CH₃), 28.0 (CH), 35.1 (CH₂), 37.6 (CH₂), 38.4 (C), 41.6 (CH), 46.1 (CH), 47.8 (CH), 169.5 (C). CH₃ obscured by other signal.

7.4.3.5 *N,N'*-Bis-[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-oxalamide

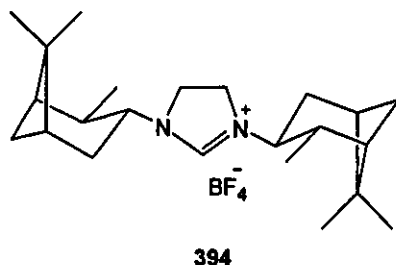


418

A solution of (1S,2S,3S,5R)-(+)-isopinocampheylamine (55 μ L, 0.33 mmol) in dichloromethane (3 mL) was cooled in an ice bath and treated with a solution of triethylamine (45 μ L, 0.33 mmol) in dichloromethane (1 mL), and with a solution of oxalyl chloride (14 μ L, 0.16 mmol) in dichloromethane (1 mL). The reaction mixture was left stirring overnight at room temperature. After this time, evaporation of the solvent *in vacuo* furnished the desired product **418** as a white solid, 32 mg, 53%.

$[\alpha]_D^{25} +18.11$ ($c = 0.95$, CH_2Cl_2); mp 184-188 °C; Mass spectrum (FAB+) m/z calcd. for $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) 361.2855; Found: 361.2849 (MH^+); ν_{max} (CH_2Cl_2) 3280, 2903, 1643, 1509, 1452, 1374, 1289, 1156, 732 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.91 (d, 2H, 2x- CH_2 -, $J = 9.6$ Hz), 1.06 (s, 6H, 2x- CH_3), 1.17 (d, 6H, 2x- CH_3 , $J = 8$ Hz), 1.24 (s, 6H, 2x- CH_3), 1.58-1.64 (m, 2H, 2x- CH_2 -), 1.85 (dd, 2H, 2x-CH-, $J = 1.6, 6.0$ Hz), 1.91 (dd, 2H, 2x-CH-, $J = 2.0, 7.0$ Hz), 1.93-2.00 (m, 2H, 2x-CH-), 2.41-2.46 (m, 2H, 2x- CH_2 -), 2.54-2.60 (m, 2H, 2x- CH_2 -), 4.18-4.27 (m, 2H, 2x- CH_2 -). ^{13}C NMR (400 MHz, CDCl_3) δ 19.8 (CH_3), 22.4 (CH_3), 27.0 (CH_3), 34.0 (CH_2), 35.4 (CH_2), 37.4 (C), 40.4 (CH), 44.6 (CH), 46.7 (CH), 47.4 (CH), 158.5 (C).

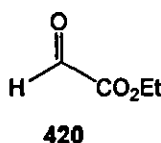
7.4.3.6 Attempted synthesis of 1,3-bis-[(1S,2S,3S,5R)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-4,5-dihydro-3H-imidazol-1-ium tetrafluoroborate



Diamine **417** (0.17 g, 0.50 mmol), ammonium tetrafluoroborate (52 mg, 0.50 mmol) and triethyl orthoformate (0.09 mL, 0.50 mmol) were combined in dichloromethane (3 mL). The reaction mixture was heated at 120 °C for 2 hours. After this time, the solvent and the evolved ethanol were removed under reduced pressure, and the crude product obtained was recrystallised from absolute ethanol to furnish a purple solid. The solid was not soluble in deuterated chloroform or methanol. The ^1H NMR spectrum obtained in deuterated dimethoxysulfoxide was too broad to identify the product.

7.4.4 Synthesis of imidazolinium tetrafluoroborate salt derived from (1R,3S,4S)-2-[(1R)-phenyl-ethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid ethyl ester

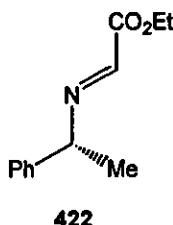
7.4.4.1 Ethyl glyoxalate



A solution of commercially available ethyl glyoxalate in 50% toluene was heated at 110 °C for 1 hour, in order for it to undergo depolymerisation. After this time, the temperature was increased to 160-170 °C to furnish by distillation a 40% solution of ethyl glyoxalate in toluene as a yellow liquid, 35.80 g.²³¹

¹H NMR (250 MHz, CDCl₃) δ 1.43 (t, 3H, -OCH₂CH₃, *J* = 7.2 Hz), 4.42 (q, 2H, -OCH₂CH₃, *J* = 7.2 Hz), 9.41 (s, 1H, -CHCO).

7.4.4.2 [(1R)-Phenyl-ethylimino]-acetic acid ethyl ester



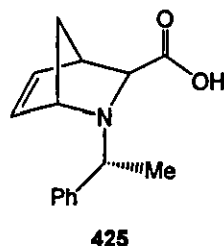
Ethyl glyoxalate **420** (40% solution in toluene) (35.8 g, 142 mmol) and (R)-(+)-phenylethylamine (17 mL, 133 mmol) were combined in toluene (80 mL) and the resulting solution was heated under Dean-Stark conditions for 1 hour. The solvent was evaporated under reduced pressure to give quantitatively the chiral (R)-(+)-imine **422** as an orange oil.²⁵⁴

HRMS (EI): (*m/z*) calcd. for C₁₂H₁₅NO₂ (*M*⁺) 205.1103; Found: 205.1105; ν_{max} (CH₂Cl₂) 2978, 1747, 1720, 1301, 1201, 1033, 700 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.34 (t, 3H, -OCH₂CH₃, *J* = 7.2 Hz), 1.62 (d, 3H, ArCHCH₃, *J* = 6.7 Hz), 4.34 (q, 2H, -OCH₂CH₃, *J* = 7.2 Hz), 4.61 (q, 1H, ArCH, *J* = 6.7 Hz), 7.2-7.4 (m,

22.6 (CH₃), 45.4 (CH₂), 49.1 (CH), 60.3 (CH₂), 62.6 (CH), 63.9 (CH), 65.0 (CH), 127.0 (CH), 128.1 (CH), 128.4 (CH), 133.0 (CH), 136.4 (CH), 145.1 (C), 174.3 (C).

424b: HRMS (EI): (m/z) calcd. for C₁₇H₂₁NO₂ (M⁺) 271.1572; Found: 271.1574; ν_{max} (CH₂Cl₂) 3061, 2978, 2904, 1745, 1453, 1372, 1323, 1269, 1246, 1172, 766, 702, 567 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.22 (d, 3H, ArCHCH₃, *J* = 6.2 Hz), 1.29 (t, 3H, -OCH₂CH₃, *J* = 7.2 Hz), 1.92 (bd, 1H, -CH₂-, *J* = 8.3 Hz), 2.46 (s, 1H, -CH₂-), 3.03 (q, 1H, ArCH, *J* = 6.2 Hz), 3.08 (bs, 1H, -CHCH=CH-), 3.53 (bs, 1H, -NCHCH=CH-), 4.22 (q, 2H, -OCH₂CH₃, *J* = 7.2 Hz), 6.01 (dd, 1H, -CH=CH-, *J* = 1.6, 5.6 Hz), 6.37-6.41 (m, 1H, -CH=CH-), 7.19-7.47 (m, 5H, ArH); ¹³C NMR (400 MHz, CDCl₃) δ 14.7 (CH₃), 24.1 (CH₃), 46.2 (CH₂), 49.9 (CH), 61.1 (CH₂), 64.0 (CH), 64.8 (CH), 127.5 (CH), 128.0 (CH), 128.7 (CH), 129.0 (CH), 133.7 (CH), 136.5 (CH), 145.2 (C), 174.9 (C).

7.4.4.4 (1R,3S,4S)-2-[(1R)-Phenyl-ethyl]-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid

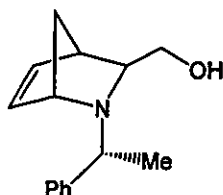


A solution of the cycloadduct **424a** (0.20 g, 0.74 mmol) in tetrahydrofuran (5 mL) was treated with a solution of sodium hydroxide (0.10 g, 2.5 mmol) in water (3 mL). The reaction mixture was heated under reflux for 7 hours, and then at room temperature overnight. After this time, TLC showed starting material to be still present, so more sodium hydroxide (0.10 g, 2.5 mmol) was added to the reaction mixture, and it was again heated under reflux for 3 days. After this time, the solvent was evaporated *in vacuo* and the black solid obtained was washed with ethanol and water, 0.16 g, 90%. Evaporation of the filtrates gave a pale brown solid. The ¹H NMR spectrum of both filtrate and solid, showed the desired product **425** had been formed, although a number of signals were slightly different, possibly due to a pH effect.

mp > 200 °C; ^1H NMR (250 MHz, MeOD) δ 1.30 (d, 1H, $-\text{CH}_2-$, $J = 8.1$ Hz), 1.37 (d, 3H, ArCHCH_3 , $J = 6.5$ Hz), 2.04 (d, 1H, $J = 8.1$ Hz), 2.17 (s, 1H, $-\text{CH}=\text{CHCHCH}-$), 2.90 (bs, 1H, $\text{CH}=\text{CHCHN}-$), 3.08 (q, 1H, ArCHCH_3 , $J = 6.5$ Hz), 4.23 (s, 1H, $-\text{CHCOOH}$), 6.24 (dd, 1H, $-\text{CH}=\text{CH}-$, $J = 1.4, 5.6$ Hz), 6.43-6.52 (m, 1H, $-\text{CH}=\text{CH}-$), 7.04-7.22 (m, 3H, ArH), 7.27-7.38 (m, 2H, ArH).

mp > 200 °C; ^1H NMR (250 MHz, MeOD) δ 1.27 (d, 1H, $-\text{CH}_2-$, $J = 8.1$ Hz), 1.34 (d, 3H, ArCHCH_3 , $J = 6.5$ Hz), 2.10 (d, 1H, $J = 7.9$ Hz), 2.14 (s, 1H, $-\text{CH}=\text{CHCHCH}-$), 2.89 (bs, 1H, $\text{CH}=\text{CHCHN}-$), 3.08 (q, 1H, ArCHCH_3 , $J = 6.5$ Hz), 4.18 (s, 1H, $-\text{CHCOOH}$), 6.18-6.26 (bdd, 1H, $-\text{CH}=\text{CH}-$), 6.41-6.49 (m, 1H, $-\text{CH}=\text{CH}-$), 7.00-7.22 (m, 3H, ArH), 7.27-7.42 (m, 2H, ArH).

7.4.4.5 (1R,3S,4S)-2-[[[(1R)-Phenyl-ethyl]-2-aza-bicyclo[2.2.1]hept-5-en-3-yl]-methanol



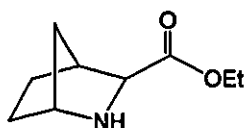
441

A solution of the cycloadduct **424a** (0.50 g, 1.8 mmol) in anhydrous tetrahydrofuran (8 mL) was added dropwise to a suspension of lithium aluminium hydride (0.14 g, 3.7 mmol) in anhydrous tetrahydrofuran (7 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 hours. After this time, the reaction mixture was quenched by the addition of water and the mixture was then stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and the residue obtained was dissolved in dichloromethane and washed three times with brine. The organic layer was separated, dried over magnesium sulfate, filtered and evaporated to dryness to yield the desired product **441** as a white-pale yellow oil, 0.27 g, 63%.

HRMS (EI): (m/z) calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}$ (M^+) 229.1467; Found: 229.1471; ν_{max} (CH_2Cl_2) 3384, 2971, 1492, 1453, 1373, 1325, 1081, 1030, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ ; 1.36 (d, 1H, $-\text{NCHCH}=\text{CHCH}-$, $J = 9.2$ Hz), 1.41 (d, 3H, ArCHCH_3 , $J = 6.4$ Hz), 1.81 (m, 2H, $-\text{CH}_2-$), 2.74 (m, 2H, $-\text{CH}_2\text{OH}$), 3.04-3.10 (m,

2H, ArCH₂CH₃, NCH=CH), 4.19 (s, 1H, -CHCH₂OH), 6.27 (m, 1H, -CH=CH-), 6.47 (bs, 1H, -CH=CH-), 7.20-7.33 (m, 5H, ArH); ¹³C NMR (400 MHz, CDCl₃) δ 22.0 (CH₃), 44.0 (CH), 45.0 (CH₂), 47.2 (CH), 63.0 (CH), 63.6 (CH), 64.0 (CH), 64.9 (CH₂), 127.5 (CH), 127.7 (CH), 128.5 (CH), 131.7 (CH), 137.8 (C).

7.4.4.6 (1R,3S,4S)-2-Aza-bicyclo[2.2.1]heptane-3-carboxylic acid ethyl ester

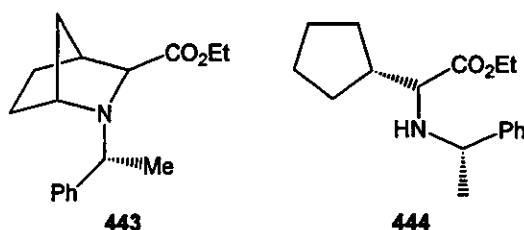


442

Cycloadduct **424a** (1.01 g, 3.72 mmol) was dissolved in absolute ethanol (100 mL) and the resulting solution was degassed three times under an atmosphere of nitrogen. This solution was added to palladium hydroxide on carbon (25 mg, 5 mol %), in a round-bottomed flask. The reaction mixture was stirred at room temperature, under a balloon of hydrogen, for 3 hours or until the reaction was complete by TLC. The palladium hydroxide on carbon was removed by filtration through Celite and the solvent was removed under reduced pressure to give the pure NH amino ester **442** as a dark green oil, which was used for next reaction without further purification, 0.52 g, 82%.^{236,237}

Mass spectrum (FAB+) m/z calcd. for C₉H₁₅N₂O 170.1182; Found: 170.1190; ν_{max} (CH₂Cl₂) 3385, 2960, 1729, 1438, 1205 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.23 (d, 1H, J = 10 Hz), 1.28 (t, 3H, -OCH₂CH₃, J = 7.2 Hz), 1.35-1.68 (m, 5H), 2.08 (bs, 1H, NH), 2.62 (s, 1H), 3.30 (s, 1H), 3.53 (s, 1H), 4.18 (q, 2H, -OCH₂CH₃, J = 7.2 Hz); ¹³C NMR (400 MHz, CDCl₃) δ 14.3 (CH₃), 28.5 (CH₂), 31.1 (CH₂), 35.8 (CH₂), 41.8 (CH), 56.3 (CH), 60.6 (CH₂), 63.7 (CH), 174.6 (C).

7.4.4.7 (1R,3S,4S)-2-[(1R)-Phenyl-ethyl]-2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid ethyl ester 443 and (R)-cyclopentyl-N-[(1R)-phenyl-ethylamino]-acetic acid ethyl ester 444



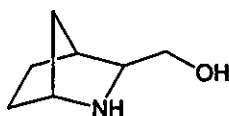
Cycloadduct **424a** (0.50 g, 1.8 mmol) was dissolved in absolute ethanol (30 mL) and the resulting solution was degassed three times under an atmosphere of nitrogen. This solution was added to platinum oxide on carbon (25 mg, 5 mol %), in a round-bottomed flask. The reaction mixture was stirred overnight at room temperature, under a balloon of hydrogen. After this time, the platinum oxide on carbon was removed by filtration through Celite, and the filtrates were concentrated under reduced pressure. Purification by flash chromatography (silica gel, 10:1 hexane/ethyl acetate) furnished the products **443**,²³⁸ as a colourless oil, 0.29 g, 67%, and **444**,²³⁹ as a colourless oil, 58 mg, 12%.

443: Mass spectrum (FAB+) m/z calcd. for $C_{17}H_{23}NO_2$ (M+H) 274.1807; Found: 274.1804; ν_{\max} (CH_2Cl_2) 2970, 1744, 1452, 1194, 1162, 1060, 1036, 700 cm^{-1} ; 1H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, 3H, $-OCH_2CH_3$, $J = 7.2$ Hz), 1.29 (d, 1H, CH_2 , $J = 9.7$ Hz), 1.34 (d, 3H, $ArCHCH_3$, $J = 6.5$ Hz), 1.38-1.42 (m, 1H, $-CH_2-$), 1.42-1.49 (m, 1H, $-CH_2-$), 1.59-1.72 (m, 1H, $-CH_2-$), 1.88-2.06 (m, 1H, $-CH_2-$), 2.08-2.18 (m, 1H, $-CH_2-$), 2.28 (bd, 1H, $-CH-$, $J = 3.5$ Hz), 2.55 (s, 1H, $-NCH-$), 3.51 (q, 1H, $ArCHCH_3$, $J = 6.5$ Hz), 3.71 (bq, 2H, $-OCH_2CH_3$, $J = 7.2$ Hz), 3.75 (bs, 1H, $-NCH-$), 7.12-7.35 (m, 5H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.3 (CH_2), 22.8 (CH_3), 29.5 (CH_2), 36.0 (CH_2), 43.2 (CH), 58.0 (CH), 59.9 (CH_2), 61.3 (CH), 70.3 (CH), 127.1 (CH), 128.0 (CH), 128.2 (CH), 144.9 (C), 173.8 (C).

444: ν_{\max} (CH_2Cl_2) 2957, 1730, 1452, 1185, 1159, 1027, 700 cm^{-1} ; 1H NMR (250 MHz, $CDCl_3$) δ 1.18 (t, 3H, $-OCH_2CH_3$, $J = 7.2$ Hz), 1.31 (d, 3H, $ArCHCH_3$, $J = 6.7$ Hz), 1.36-1.43 (m, 1H, $-CH_2-$), 1.35-1.70 (m, 6H, $3x-CH_2-$), 1.71-1.86 (m, 1H, $1x-CH_2-$), 1.94-2.12 (m, 1H, $-CHCHNH-$), 3.12 (d, 1H, $-CHCHNH-$, $J = 7.9$ Hz),

3.70 (q, 1H, ArCHCH₃, J = 6.7 Hz), 3.93–4.09 (dq, 2H, -OCH₂CH₃, J = 2.8, 7.2 Hz), 7.17–7.25 (m, 5H, ArH); ¹³C NMR (400 MHz, CDCl₃) δ 14.4 (CH₃), 22.3 (CH₃), 25.2 (CH₂), 25.2 (CH₂), 29.0 (CH₂), 31.4 (CH₂), 43.5 (CH), 57.1 (CH), 60.2 (CH₂), 63.7 (CH), 126.9 (CH), 127.0 (CH), 128.3 (CH), 145.9 (C), 175.5 (C). NH signal obscured by other signals.

7.4.4.8 (1R,3S,4S)-(2-Aza-bicyclo[2.2.1]hept-3-yl)-methanol

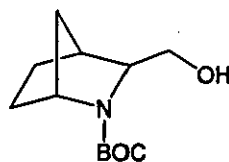


436

A solution of the NH amino ester **442** (0.52 g, 3.0 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a suspension of lithium aluminium hydride (0.25 g, 6.6 mmol) in anhydrous tetrahydrofuran (5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours or until reaction was complete by TLC. After this time, the reaction was quenched by the addition of water and the mixture was then stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure and the residue obtained was partitioned between dichloromethane and water. The organic layer was separated, dried over magnesium sulfate, filtered and evaporated to dryness to afford the title product, amino alcohol **436**, as a white solid, 0.35 g, 91%.²³⁶

Lit. mp²³⁶ 43–45 °C ; mp 42–46 °C; ν_{\max} (CH₂Cl₂) 3287, 1538, 1410, 1372, 1049, 1018 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.16–1.26 (m, 1H), 1.35–1.43 (m, 2H), 1.53–1.73 (m, 3H), 2.19–2.21 (m, 1H), 2.62 (bs, 1H), 2.86 (dd, 3H, J = 5.6, 8.1 Hz), 3.21 (dd, 1H, J = 8.1, 10.9 Hz), 3.41 (d, 1H, J = 5.3 Hz), 3.44–3.47 (m, 1H).

7.4.4.9 (1R,3S,4S)-3-Hydroxymethyl-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

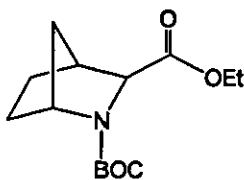


437

A solution of di-*tert*-butyl dicarbonate (0.72 g, 3.3 mmol) in dichloromethane (5 mL) was slowly added to a solution of amino alcohol **436** (0.35 g, 2.7 mmol) in dichloromethane (5 mL). The reaction mixture was stirred overnight. After this time, the solvent was evaporated under reduced pressure. Purification by flash chromatography (silica gel, 5% methanol/dichloromethane) furnished the amino protected alcohol **437**²⁴⁰ as a pale yellow oil, 0.37 g, 59%.

Mass spectrum (FAB+) m/z calcd. for $C_{12}H_{21}NO_3$ 228.1600; Found: 228.1601; ν_{\max} (CH_2Cl_2) 3419, 2972, 1694, 1669, 1393, 1366, 1164, 1117, 1101, 1045 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.23-1.28 (m, 1H, $-CH_2-$), 1.42-1.50 (m, 1H, $-CH_2-$), 1.47 (s, 9H, 3x- CH_3), 1.53 (s, 1H, $-CH_2-$), 1.58-1.64 (m, 2H, $-CH_2-$), 1.67-1.75 (m, 1H, $-CH_2-$), 2.31 (d, 1H, $CHCHCH_2OH-$, $J = 3.2$ Hz), 3.44-3.50 (m, 1H, $CHCH_2OH$), 3.57 (d, 2H, $-CH_2OH$, $J = 7.2$ Hz), 4.10 (s, 1H, $-CHN-$), 4.51 (s, 1H, $-OH$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 28.3 (CH_2), 28.8 (3x CH_3), 30.0 (CH_2), 36.1 (CH_2), 40.0 (CH), 58.3 (CH), 67.0 (CH), 67.5 (CH_2), 80.6 (C), 157.7 (C).

7.4.4.10 (1R,3S,4S)-2-Aza-bicyclo[2.2.1]heptane-2,3-dicarboxylic acid-2-*tert*-butyl ester-3-ethyl ester



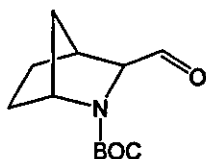
445

A solution of di-*tert*-butyl dicarbonate (0.87 g, 4.0 mmol) in dichloromethane (10 mL) was slowly added to a solution of the amino ester **442** (0.56 g, 3.3 mmol) in dichloromethane (4 mL). The reaction mixture was stirred overnight. After this time, the solvent was removed under reduced pressure to furnish the crude

product as a yellow oil. Purification by flash chromatography (silica gel, 5% methanol/ dichloromethane) furnished the amino protected ester **445** as rotamers, as a pale yellow oil, 0.62 g, 70%.

$[\alpha]_D^{25}$ -66.27 ($c = 1.02$, CH_2Cl_2); Mass spectrum (FAB+) m/z calcd. for $\text{C}_{14}\text{H}_{23}\text{NO}_4$ 270.1705; Found: 270.1702; ν_{max} (CH_2Cl_2) 2978, 1751, 1701, 1400, 1189, 1119, 1070, 845 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.24-1.30 (m, 4H, $-\text{OCH}_2\text{CH}_3$, 1x- CH_2 -), 1.40 and 1.47 (s, 9H, 3x- CH_3), 1.44-1.60 (m, 1H, 1x- CH_2 -), 1.61-1.65 (m, 1H, 1x- CH_2 -), 1.65-1.77 (m, 2H, 2x- CH_2 -), 1.91-1.95 (m, 1H, 1x- CH_2 -), 2.65-2.68 (m, 1H, $-\text{CHCHCO}-$), 3.72 and 3.82 (s, 1H, $-\text{NCH}-$), 4.13-4.21 (m, 2H, $-\text{OCH}_2\text{CH}_3$), 4.22 and 4.35 (bs, 1H, $-\text{NCH}-$); ^{13}C NMR (400 MHz, CDCl_3) δ 14.5 and 14.7 (CH_3), 28.1 and 28.4 (CH_2), 28.7 and 28.9 (3x CH_3), 30.6 and 30.9 (CH_2), 35.0 and 35.7 (CH_2), 42.3 and 43.0 (CH), 56.5 and 57.8 (CH), 61.2 and 61.3 (CH_2), 64.5 and 64.8 (CH), 79.99 and 80.02 (C), 153.5 and 154.6 (C), 171.4 and 171.6 (C).

7.4.4.11 (1R,3S,4S)-3-Formyl-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

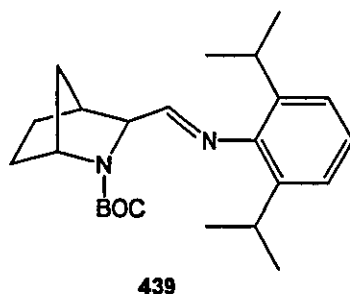


438

Dimethylsulfoxide (0.29 mL, 4.2 mmol) was added dropwise to a solution of oxalyl chloride (0.24 mL, 2.8 mmol) in dichloromethane (20 mL), previously cooled to $-78\text{ }^\circ\text{C}$. After 15 min. stirring at that temperature, a solution of the amino protected alcohol **437** (0.31 g, 1.4 mmol) in dichloromethane (8 mL) was added dropwise over 15 min., and the resulting mixture was maintained at $-78\text{ }^\circ\text{C}$ for 30 min. Triethylamine (0.77 mL, 5.5 mmol) was added dropwise to the mixture and the solution was cooled to room temperature. The reaction mixture was dissolved in dichloromethane and washed three times with distilled water and once with 1% aqueous solution of hydrochloric acid. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the amino protected aldehyde **438**^{240,242} as a pale yellow oil, 0.24 g, 77%.

Mass spectrum (FAB+) m/z calcd. for $C_{12}H_{19}NO_3$ 226.1443; Found: 226.1447; ν_{\max} (CH_2Cl_2) 2975, 1694, 1392, 1163, 1103 cm^{-1} ; 1H NMR (rt, 400 MHz, $CDCl_3$) δ 1.30-1.34 (m, 1H, 1x- CH_2 -), 1.42 and 1.49 (s, 9H, 3x- CH_3), 1.44-1.53 (m, 2H, - CH_2 -), 1.62-1.81 (m, 3H, 2x- CH_2 -), 2.76 and 2.79 (s, 1H, - CH -), 3.59 and 3.72 (s, 1H, - CH -), 4.24 and 4.39 (s, 1H, - CH -), 9.53 and 9.58 (s, 1H, -CHO); 1H NMR (90 °C, 400 MHz, $CDCl_3$) δ 1.30-1.33 (m, 1H, 1x- CH_2 -), 1.41-1.53 (m, 2H, - CH_2 -), 1.42 (s, 9H, 3x- CH_3), 1.59-1.76 (m, 3H, 2x- CH_2 -), 2.51 and 2.72 (s, 1H, - CH -), 3.66 (s, 1H, - CH -), 4.20 (s, 1H, - CH -), 9.50 (s, 1H, -CHO); ^{13}C NMR (400 MHz, $CDCl_3$) δ 27.8 and 28.2 (CH_2), 28.7 and 28.8 (3x CH_3), 30.5 and 30.8 (CH_2), 35.9 and 36.5 (CH_2), 40.5 and 41.8 (CH), 56.8 and 57.9 (CH), 70.7 and 70.6 (CH), 80.5 and 80.7 (C), 153.8 and 155.3 (C), 201.7 and 201.8 (CH).

7.4.4.12 (1R,3S,4S)-3-[(2,6-Diisopropyl-phenylimino)-methyl]-2-aza-bicyclo [2.2.1]heptane-2-carboxylic acid *tert*-butyl ester

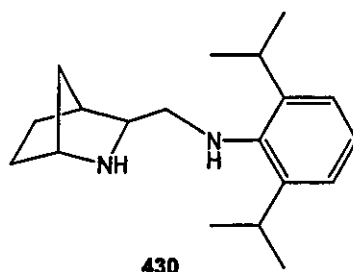


2,6-Diisopropylaniline (0.15 mL, 0.80 mmol) and a spatula of magnesium sulfate were added to a solution of the amino protected aldehyde **438** (0.18 g, 0.80 mmol) in dichloromethane (9 mL). The reaction mixture was stirred overnight at room temperature. After this time, filtration and evaporation under reduced pressure of the solvent, afforded the crude product **439** as rotamers, as an orange oil. The 1H NMR and IR spectra showed traces of starting material 2,6-diisopropylaniline. The product was used for the next reaction without further purification.

Mass spectrum (FAB+) m/z calcd. for $C_{24}H_{36}N_2O_2$ 385.2855; Found: 385.2856; ν_{\max} (CH_2Cl_2) 2961, 1696, 1458, 1438, 1390, 1364, 1162, 744 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 1.12-1.18 (m, 5H), 1.27 (d, 12H, 2x- $CH(CH_3)_2$, J = 6.8 Hz), 1.46 (s, 9H, - $O(CH_3)_3$), 1.41-1.82 (m, 2H), 2.94 (septet, 2H, 2x- $CH(CH_3)_2$, J = 6.8 Hz), 4.07 (m, 1H), 4.29 (m, 1H), 6.78-7.14 (m, 3H, ArH), 7.54 and 7.56 (d,

^1H , $-\text{CH}=\text{N}-$, $J = 3.6$ Hz). ^{13}C NMR (400 MHz, CDCl_3) δ 22.9 ($4\times\text{CH}_3$), 27.8 and 28.0 (CH_2), 28.3 ($2\times\text{CH}$), 28.9 ($3\times\text{CH}_3$), 30.4 and 31.1 (CH_2), 35.7 and 36.2 (CH_2), 42.1 and 43.5 (CH), 57.7 and 58.0 (CH), 66.5 and 67.3 (CH), 79.8 and 80.5 (C), 118.9 (C), 123.2 (CH), 123.4 (CH), 132.8 (C), 137.7 (C), 138.0 (C), 140.7 (C), 168.5 and 167.8 (CH).

7.4.4.13 (1R,3S,4S)-(2-Aza-bicyclo[2.2.1]hept-3-ylmethyl)-(2,6-diisopropyl-phenyl)-amine

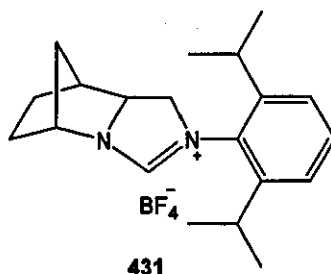


Lithium aluminium hydride (57 mg, 1.5 mmol) was suspended in anhydrous tetrahydrofuran (5 mL), and the resulting suspension was cooled to 0 °C. Then a solution of the imine **439** (0.29 g, 0.75 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise to the previous suspension, and the resulting reaction mixture was heated under reflux overnight. The mixture was cooled to room temperature and it was quenched by the addition of water. After 30 min. stirring at room temperature the mixture was concentrated under reduced pressure. The residue obtained was dissolved in dichloromethane and washed twice with water. The organic layer was separated, dried over magnesium sulfate, filtered and evaporated to dryness to afford quantitatively the crude product **430** as an orange oil.

Mass spectrum (FAB+) m/z calcd. for $\text{C}_{19}\text{H}_{30}\text{N}_2$ 287.2487; Found: 287.2492; ν_{max} (CH_2Cl_2) 3390, 2960, 2968, 1686, 1619, 1459, 1439, 1383, 1364, 1264, 1290, 1164, 1115, 1066, 1044, 744 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 1.18-1.30 (m), 1.27 (d, 12H, $4\times\text{CH}_3$, $J = 6.7$ Hz), 1.43-1.48 (m), 1.58-1.99 (m), 2.02-2.11 (m), 2.23-2.28 (m), 2.38-2.51 (m), 2.39 (s), 2.73-2.79 (m), 2.84-3.01 (septet, 2H, $2\times\text{CH}(\text{CH}_3)_2$, $J = 6.7$ Hz), 3.21-3.35 (m), 3.72 (bs, 1H, $-\text{NH}$), 6.74-6.83 (m, 1H, ArH), 7.01-7.11 (m, 2H, ArH); ^{13}C NMR (400 MHz, CDCl_3) δ 21.85 (CH_2), 22.86 ($2\times\text{CH}_3$), 24.70 ($2\times\text{CH}_3$), 28.06 (CH), 28.32 (CH), 28.81 (CH_2), 36.79 (CH_2),

37.97 (CH), 41.43 (CH), 56.19 (CH₂), 62.73 (CH), 118.92 (CH), 123.17 (CH), 123.88 (CH), 132.82 (C), 140.64 (C), 142.66 (C), 144.05 (C). There is an extra quaternary carbon, therefore one of the last four peaks might be a spike, but it could not be decided which one.

7.4.4.14 (1R,3S,4S)-4-(2,6-Diisopropyl-phenyl)-2-aza-4-azonia-tricyclo[5.2.1.0^{2,6}]dec-3-ene tetrafluoroborate

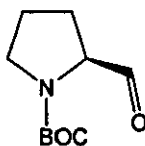


Diamine **430** (177 mg, 0.62 mmol), ammonium tetrafluoroborate (67 mg, 0.62 mmol) and triethyl orthoformate (0.20 mL, 1.2 mmol) were combined and heated at 120 °C for 3 hours. The reaction mixture was concentrated under reduced pressure. By ¹H NMR spectroscopy, it was observed that the desired product **431** had been formed. The product contained a trace of an unidentified compound and unreacted diamine **430**. Recrystallisation from absolute ethanol was attempted, but isolation of the pure product was unsuccessful.

ν_{max} (CH₂Cl₂) 3414, 2967, 2871, 1664, 1590, 1560, 1460, 1386, 1365, 1288, 1057, 810, 764 cm⁻¹; ¹³C NMR (400 MHz, CDCl₃) δ 12.7 (CH), 23.8 (2xCH₃), 23.9 (2xCH₃), 25.7 (CH₃), 28.6 (2xCH), 42.6 (CH₂), 49.8 (CH₂), 58.6 (CH₂), 66.8 (CH), 72.9 (CH), 124.7 (2xCH), 129.7 (CH), 135.3 (C), 148.1 (2xC), 163.3 (CH).

7.4.5 Synthesis of imidazolinium tetrafluoroborate salt derived from (S)-prolinol

7.4.5.1 (2S)-Formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester or *N*-(*tert*-butoxycarbonyl)-(S)-prolinal

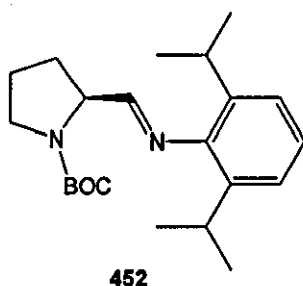


451

A solution of oxalyl chloride (1.73 mL, 19.9 mmol) in dichloromethane (10 mL) was added dropwise to a solution of dimethylsulfoxide (2.12 mL, 29.8 mmol) in dichloromethane (25 mL), at -78 °C. After stirring for 10 min., a solution of *N*-BOC-(S)-prolinol (2.00 g, 9.9 mmol) in dichloromethane (15 mL) was added dropwise over 15 min., and the resulting mixture was maintained at -78 °C for 30 min. After this time, triethylamine (5.54 mL, 39.8 mmol) was added dropwise to the mixture and the solution was allowed to warm to room temperature. The reaction mixture was diluted in dichloromethane and washed three times with distilled water and once with 1% aqueous solution of hydrochloric acid. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated to dryness to afford quantitatively *N*-BOC prolinal **451** as a yellow oil, which was used for the next experiment without further purification. The ^1H NMR spectrum was in agreement with the literature and indicated that two isomers were present.²⁵⁵

Lit. $[\alpha]_{\text{D}}^{25}$ -99.5 ($c = 0.61$, CHCl_3); $[\alpha]_{\text{D}}^{25}$ -79.08 ($c = 1.74$, CH_2Cl_2); HRMS (EI): m/z calcd. for $\text{C}_{10}\text{H}_{17}\text{NO}_3$ ($\text{M}+\text{H}$) 200.1287; Found: 200.1289; ν_{max} (CH_2Cl_2) 3367, 2975, 1736, 1694, 1397, 1366, 1164, 1124 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 1.43 and 1.48 (s, 9H, 2x- $\text{C}(\text{CH}_3)_3$), 1.79-2.24 (m, 4H, 2x- CH_2 -), 3.33-3.64 (m, 2H, - NCH_2 -), 4.00-4.11 and 4.13-4.26 (m, 1H, - NCHCOH -), 9.46 (s) and 9.56 (d) (1H, - CHO); ^{13}C NMR (400 MHz, CDCl_3) δ 24.0 and 24.6 (CH_2), 26.7 and 28.0 (CH_2), 28.3 and 28.4 (3x CH_3), 46.7 and 46.9 (CH_2), 65.0 and 65.9 (CH), 80.2 and 80.6 (C), 154.0 and 154.9 (C), 200.4 and 200.6 (CH).

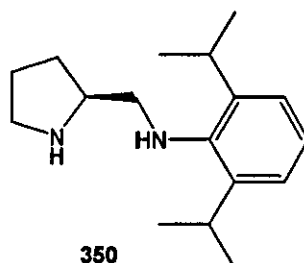
7.4.5.2 (2,6-Diisopropyl-phenylimino)-methyl-(2S)-pyrrolidine-1-carboxylic acid *tert*-butyl ester



2,6-Diisopropylaniline (1.16 mL, 6.15 mmol) and a spatula of magnesium sulfate were added to a solution of *N*-BOC prolinal **451** (1.23 g, 6.15 mmol) in dichloromethane (20 mL). The reaction mixture was stirred overnight at room temperature. After this time, the reaction mixture was filtered, and the solvent was evaporated under reduced pressure to furnish the crude product as an orange oil. Purification by flash chromatography (silica gel, 15:1 hexane/ethyl acetate) gave the title compound **452** as an unstable orange oil, containing a trace of 2,6-diisopropylaniline, 0.69 g, 31%.

$[\alpha]_D^{25}$ -6.32 ($c = 1.52$, CH_2Cl_2); Mass spectrum (FAB+) m/z calcd. for $\text{C}_{22}\text{H}_{34}\text{N}_2\text{O}_2$ ($M+H$) 359.2699; Found: 359.2693; ν_{max} (CH_2Cl_2) 2961, 1698, 1457, 1392, 1364, 1171, 1114, 757 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 1.13-1.17 (m, 6H, 4x CH_3), 1.47 (s, 9H, 3x CH_3), 1.92-2.03 (m, 2H), 2.10-2.41 (m, 2H), 2.82-3.10 (m, 2H), 3.38-3.55 (m, 2H), 4.53-4.63 (m, 1H, $-\text{CHCH}=\text{N}-$), 7.01-7.14 (m, 3H, ArH), 7.58-7.63 (m, 1H, $-\text{CH}=\text{N}-$).

7.4.5.3 (2,6-Diisopropyl-phenyl)-(2S)-pyrrolidin-2-ylmethyl-amine

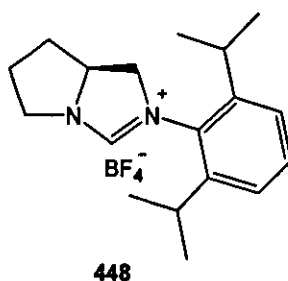


A solution of the imine **452** (1.54 g, 4.30 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise to a suspension of lithium aluminium hydride (0.33 g, 8.6 mmol) in anhydrous tetrahydrofuran (5 mL) at 0 °C. The reaction mixture was

heated under reflux overnight. After this time, the reaction was allowed to cool to room temperature and quenched by the addition of water. The reaction mixture was concentrated under reduced pressure and the resulting residue was diluted in dichloromethane and washed three times with brine. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated to dryness to yield the crude product as a brown oil. Separation of the crude mixture by flash chromatography (silica gel, 15:1 hexane/ethyl acetate) furnished the reduced product **350** as a pale yellow solid, 193 mg, 17%.

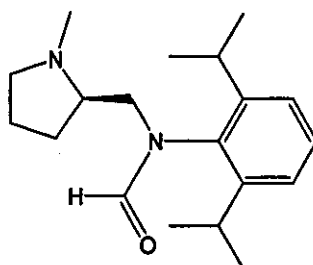
mp 50-52 °C ; Mass spectrum (FAB+) m/z calcd. for $C_{17}H_{28}N_2$ (M-2H+H) 259.2174; Found: 259.2171; ν_{\max} (CH_2Cl_2) 3354, 2960, 1457, 1448, 1361, 1208, 753 cm^{-1} ; 1H NMR (250 MHz, $CDCl_3$) δ 1.24 (d, 12H, 2x-CH(CH_3)₂, J = 6.9 Hz), 1.73-1.83 (m, 2H, -CH₂-), 1.93-2.00 (m, 2H, -CH₂-), 2.20-2.28 (m, 1H, -CH₂-), 2.36-2.41 (m, 3H, -CH₂-, 2x-NH), 2.86-2.91 (m, 1H, -CH₂-), 2.95-2.99 (m, 1H, -CH₂-), 3.12 (bdt, 1H, -CH-, J = 1.6, 7.2 Hz), 3.30 (septet, 2H, 2x-CH(CH_3)₂, J = 6.9 Hz), 6.97-7.11 (m, 3H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.0 (CH_2), 24.5 (2x CH_3), 24.9 (2x CH_3), 28.2 (CH), 29.1 (CH_2), 41.5 (CH), 53.7 (CH_2), 58.1 (CH_2), 66.7 (CH), 124.1 (CH), 124.3 (2XCH), 138.9 (C), 142.8 (C), 144.3 (C).

7.4.4 2-(2,6-Diisopropyl-phenyl)-(7aS)-5,6,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazol-2-ium tetrafluoroborate



Diamine **350** (0.13 g, 0.50 mmol), ammonium tetrafluoroborate (53 mg, 0.50 mmol) and triethyl orthoformate (0.80 mL, 5.0 mmol) were combined and heated at 120 °C for 3.5 hours. After this time, the reaction mixture was allowed to warm to room temperature and concentrated *in vacuo* to give the crude product as a brown solid. Recrystallisation from absolute ethanol of the resulting residue was attempted. Flash chromatography (silica gel, 5% methanol/dichloromethane)

afforded the amide **454**, *N*-(2,6-diisopropyl-phenyl)-*N*-[(2*S*)-1-methyl-pyrrolidin-2-ylmethyl]-formamide, as a yellow solid, along with some traces of either an unidentified compound or the desired imidazolinium salt **448**.



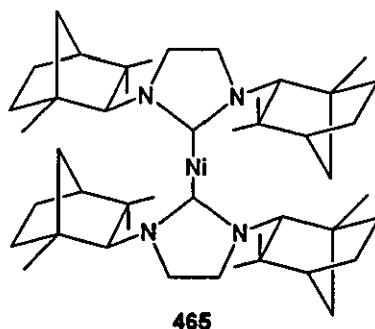
454

$[\alpha]_D^{25}$ -4.34 ($c = 0.83$, CH_2Cl_2); mp 82-87 °C ; HRMS (EI): m/z calcd. for $\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}$: 302.2358; Found: 302.2363; ν_{max} (CH_2Cl_2) 2967, 1673, 1463, 1386, 1366, 1328, 1284, 1256, 1056, 914, 810, 764, 729 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 1.14 (dd, 6H, $-\text{CH}(\text{CH}_3)_2$, $J = 2.4, 6.8$ Hz), 1.29 (dd, 6H, $-\text{CH}(\text{CH}_3)_2$, $J = 3.2, 6.8$ Hz), 1.73-1.90 (m, 3H), 1.92-2.00 (m, 1H), 2.36-2.43 (m, 1H), 2.63-2.70 (m, 1H), 2.49 (s, 3H, $-\text{NCH}_3$), 2.96 (septet, 2H, $-\text{CH}(\text{CH}_3)_2$, $J = 6.8$ Hz), 3.20 (m, 1H), 3.63 (dd, 1H, $J = 9.2, 13.6$ Hz), 3.80 (dd, 1H, $J = 2.8, 13.6$ Hz), 7.20-7.40 (m, 3H, ArH), 8.08 (s, 1H, $-\text{CHO}$). ^{13}C NMR (400 MHz, CDCl_3) δ 23.5 (CH_2), 23.8 (CH_3), 23.9 (CH_3), 25.9 (CH_3), 26.2 (CH_3), 28.6 (CH), 28.7 (CH), 30.8 (CH_2), 41.5 (CH_3), 51.8 (CH_2), 57.1 (CH_2), 64.8 (CH), 124.98 (CH), 124.99 (CH), 129.9 (CH), 136.0 (C), 147.6 (C), 147.8 (C), 164.5 (CH).

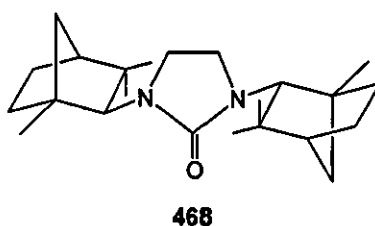
7.4.6 Attempted synthesis of carbene-metal complexes

7.4.6.1 Attempted synthesis of bis-(carbene) metal complexes

7.4.6.1.1 Attempted synthesis of bis-{1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene} nickel



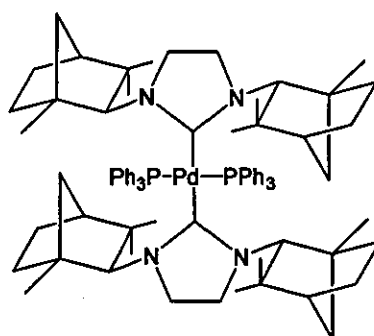
A solution of the tetrafluoroborate salt **409** (1.57 g, 3.64 mmol) and potassium-*tert*-amylate 25% in toluene (8.45 mL, 14.6 mmol) in anhydrous tetrahydrofuran (10 mL) was stirred 30 min. at room temperature. Bis-(1,5)-cyclooctadiene nickel (0) (0.50 g, 1.8 mmol) was added to the reaction mixture, and it was stirred for 4 hours at room temperature. Solvent was concentrated under reduced pressure, and the residue obtained was purified by flash chromatography (silica gel, 15:1 hexane/ethyl acetate). Analysis by ^1H NMR spectroscopy showed that the desired product **465** was not formed. Instead, the product **468**, 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolidin-2-one, was identified by X-Ray crystallography, as shown in **Figure 47**, 0.11 g, 8%.



$[\alpha]_{\text{D}}^{25} +15.20$ ($c = 1.00$, CH_2Cl_2); mp 193-203 °C; HRMS (EI): m/z calcd. for $\text{C}_{23}\text{H}_{38}\text{N}_2\text{O}$: 358.2984; Found: 358.2976; ν_{max} (CH_2Cl_2) 2984, 1672, 1427, 1254 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.84 (s, 6H, 2x- CH_3), 1.11 (s, 6H, 2x- CH_3), 1.13 (s, 6H, 2x- CH_3), 1.13-1.18 (m, 2H, 2x- CH_2 -), 1.19-1.27 (m, 2H,

2x-CH₂-), 1.40-1.55 (m, 2H, 2x-CH₂-), 1.65-1.77 (m, 2H, 2x-CH₂-), 1.73-1.86 (m, 2H, 2x-CH₂-), 2x-CH₂-), 2x-CH₂-), 2XCHC(CH₃)₂), 3.50-3.61 (m, 4H, 2x-CH₂N-), 3.70 (d, 2H, 2x-CHN-, *J* = 1.6 Hz); ¹³C NMR (400 MHz, CDCl₃) δ 20.8 (2xCH₃), 21.5 (2xCH₃), 26.4 (2xCH₂), 29.2 (2xCH₂), 31.6 (2xCH₃), 40.7 (2xC), 43.9 (2xCH₂), 44.8 (2xCH₂), 48.1 (2xC), 48.3 (2xCH), 67.6 (2xCH), 163.7 (C).

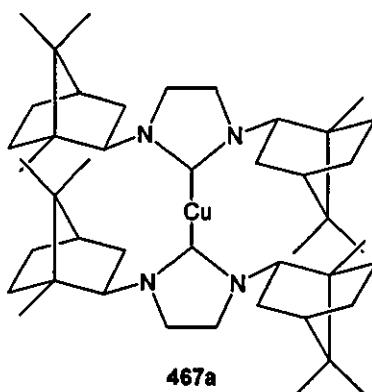
7.4.6.1.2 Attempted synthesis of bis-{1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene} bis-(triphenylphosphine)-palladium



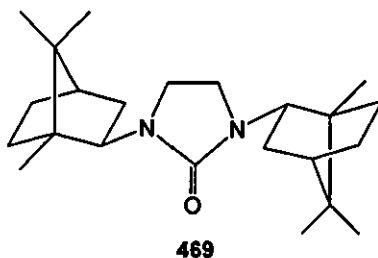
466

A suspension of the tetrafluoroborate salt **409** (0.22 g, 0.52 mmol) and potassium-*tert*-butoxide (0.12 g, 1.3 mmol) in anhydrous tetrahydrofuran (15 mL), was stirred for 30 min. at room temperature. Tetrakis palladium triphenylphosphine (0.30 mg, 0.3 mmol) was added to the reaction mixture, and it was stirred overnight at room temperature. The solvent was removed under reduced pressure to give a complex mixture as a brown oil. The desired product **466** was not isolated.

7.4.6.1.3 Attempted synthesis of bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene} copper



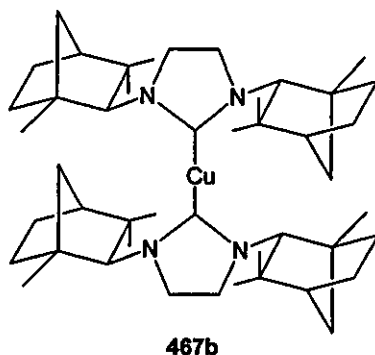
A solution of the tetrafluoroborate salt **392** (0.60 g, 1.4 mmol) and potassium-*tert*-amylate 25% in toluene (3.2 mL, 5.5 mmol) in anhydrous tetrahydrofuran (5 mL) was stirred 30 min. at room temperature. Copper triflate (0.25 g, 0.69 mmol) was added to the reaction mixture, and it was stirred for 2 days at room temperature. Solvent was concentrated under reduced pressure, and the residue obtained was purified by flash chromatography (silica gel, 15:1 hexane/ethyl acetate) to give a small quantity of the urea **469**, 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolidin-2-one. Recrystallisation by diffusion from dichloromethane and petroleum ether furnished the urea **469** as colourless crystals, which was identified by X-Ray crystallography, as shown in Figure 48.



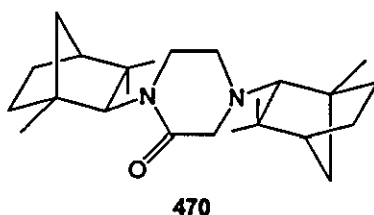
$[\alpha]_D^{25}$ -45.71 ($c = 0.28$, CH_2Cl_2); Mass spectrum (FAB+) m/z calcd. for $\text{C}_{23}\text{H}_{38}\text{N}_2\text{O}$ 359.3064; Found: 359.3069; ν_{max} (CH_2Cl_2) 2953, 2923, 2869, 1685, 1385, 1250, 1088, 791 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.83 (s, 6H, 2x- CH_3), 0.84 (s, 6H, 2x- CH_3), 0.87 (s, 6H, 2x- CH_3), 1.15-1.21 (m, 2H, 2x- CH_2 -), 1.31-1.37 (m, 2H, 2x- CH_2 -), 1.51-1.57 (m, 4H, 2x- CH_2 -, 2x- CH_2 -), 1.67-1.72 (m, 4H, 2x- CH_2 -, 2x- CH -), 1.81-1.88 (m, 2H, 2x- CH_2 -), 3.25-3.37 (m, 4H, 2x- CH_2N -), 3.90 (t, 2H,

2x-CHN-, $J = 8.4$ Hz); ^{13}C NMR (400 MHz, CDCl_3) δ 12.0 (2xCH₃), 21.1 (2xCH₃), 21.4 (2xCH₃), 27.2 (2xCH₂), 32.9 (2xCH₂), 37.6 (2xCH₂), 42.2 (2xCH₂), 45.2 (2xCH), 46.4 (2xC), 50.5 (2xC), 61.4 (2xCH), 164.1 (C).

7.4.6.1.4 Attempted synthesis of bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene} copper



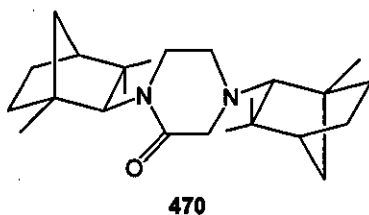
The same procedure was followed as in the previous experiment to synthesise **467a**, except the difenchyl tetrafluoroborate salt **409** was used. Flash chromatography (silica gel, 15:1 hexane/ethyl acetate) afforded two different compounds; the urea derivative **468**, as a pale yellow solid, 75 mg, 15%, and the compound **470**, 1,4-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-piperazin-2-one, as a white solid, 0.10 g, 20%, that had been formed instead of the desired product **467b**. The data of compound **468** was in agreement with that reported in the experiment where the compound **465a** was attempted to be synthesised. A portion of the compound **470** was further purified by recrystallisation by diffusion from dichloromethane and diethyl ether to afford colourless crystals, and it was identified by X-Ray crystallography, as shown in Figure 49.



$[\alpha]_D^{25} +45.15$ ($c = 1.01$, CH_2Cl_2); mp decomp. > 140 °C; Mass spectrum (FAB+) m/z calcd. for $\text{C}_{24}\text{H}_{40}\text{N}_2\text{O}$ (M+H) 373.3219; Found: 373.3218; ν_{max} (CH_2Cl_2) 2949, 1649, 1460, 1382, 1363, 1338, 1318, 1143, 1086 cm^{-1} ; ^1H NMR (400 MHz,

CDCl₃) δ 0.87 (s, 3H, -CH₃), 1.02-1.04 (m, 6H, 2x-CH₃), 0.93-1.25 (m, 4H), 1.10-1.13 (m, 3H, -CH₃), 1.22 (s, 3H, -CH₃), 1.27 (s, 3H, -CH₃), 1.28-1.80 (m, 12H), 1.95-1.99 (m, 1H, 1x-CH₂-), 2.18 (bs, 1H, -CH-), 2.51-2.56 (m, 1H, 1x-CH₂-), 2.65-2.70 (m, 1H, 1x-CH₂-), 3.15-3.19 (m, 1H, 1x-CH₂-), 3.32-3.36 (m, 2H, 2x-CH₂-), 3.42-3.47 (m, 1H, 1x-CH₂-), 4.29 (s, 1H, -CH-), 7.84 (s); ¹³C NMR (400 MHz, CDCl₃) δ 21.0, 21.1, 21.3, 22.2, 24.1, 25.8 (CH₂), 26.4 (CH₂), 26.6 (CH₂), 26.9 (CH₂), 27.3 (CH₂), 30.0 (CH₂), 32.1, 32.7, 32.8, 39.7 (C), 41.0 (C), 41.7 (C), 43.3 (CH₂), 45.8 (CH₂), 46.7 (CH₂), 47.0 (CH₂), 48.3 (C), 48.8 (CH), 49.2 (CH), 49.3 (C), 49.5 (C), 49.8 (CH), 51.3 (CH₂), 59.7 (CH₂), 67.6 (CH), 74.2 (CH), 79.4 (CH), 169.6 (C). Both ¹H NMR and ¹³C NMR spectra showed more signals than expected, probably due to rotation.

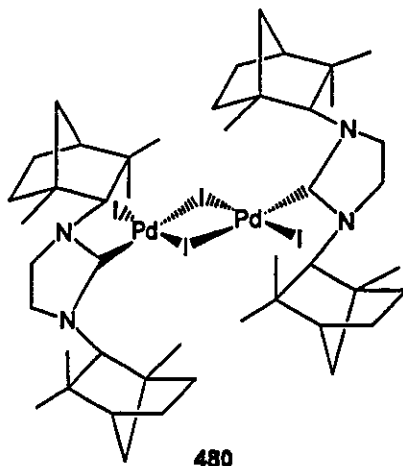
7.4.6.2 1,4-Bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-piperazin-2-one



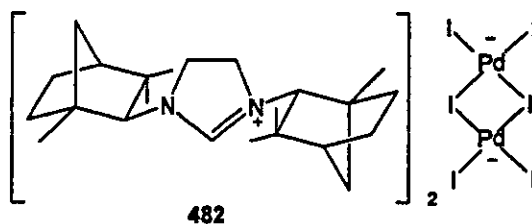
A solution of chloroacetyl chloride (53 μ L, 0.66 mmol) in dichloromethane (5 mL) was slowly added to a mixture of the diamine **348** (0.22 g, 0.66 mmol) and triethylamine (0.18 mL, 1.3 mmol) in dichloromethane (5 mL). The reaction mixture was stirred overnight at room temperature. After this time, the reaction mixture was diluted in dichloromethane and washed with distilled water. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated to dryness. The residue obtained was subjected to flash chromatography (silica gel, 15:1 hexane/ethyl acetate) to give the piperazin-2-one **470** as a yellow solid, contaminated with some impurities, 83 mg, 34%. The data of this major compound was in agreement with that reported in the previous experiment.

7.4.6.3 Palladium-iodide carbene adducts

7.4.6.3.1 Attempted synthesis of bis-{1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene} (diiodo- $\mu\mu'$ -diiododipalladium)

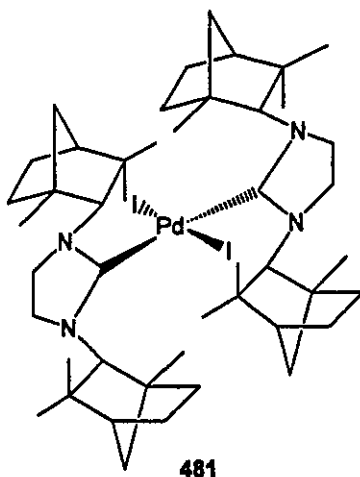


The tetrafluoroborate salt **409** (0.11 g, 0.25 mmol), sodium iodide (0.15 g, 1.0 mmol), potassium-*tert*-butoxide (33 mg, 0.30 mmol) and palladium acetate (56 mg, 0.30 mmol) were combined in anhydrous tetrahydrofuran (20 mL) and the resulting mixture was stirred overnight at room temperature. After this time, the reaction mixture was concentrated *in vacuo*, furnishing a brown oil. Purification by flash chromatography (silica gel, 1:1 hexane/ethyl acetate) gave a small quantity of dark red crystals, which turned out to be the compound **482**, bis-{1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-4,5-dihydro-3*H*-imidazol-1-ium} diiodo- $\mu\mu'$ -diiodo-dipalladium, after identification by X-Ray crystallography, as shown in **Figure 51**. The ^1H NMR spectrum showed that the desired product **480** had not been formed.



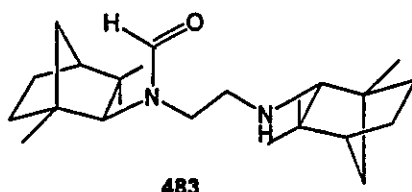
Mass spectrum (FAB+) m/z calcd. for $\text{C}_{23}\text{H}_{39}\text{N}_2^+$ (M^+) 343.3113; Found: 343.3117. The amount of material obtained was too little to allow ^1H NMR or ^{13}C NMR spectra to be obtained.

7.4.6.3.2 Attempted synthesis of bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene} diiodopalladium



Tetrafluoroborate salt **409** (0.32 g, 0.75 mmol), sodium iodide (0.15 g, 1.0 mmol), potassium-*tert*-butoxide (90 mg, 0.80 mmol) and palladium acetate (56 mg, 0.30 mmol) were combined in anhydrous tetrahydrofuran (20 mL) and the resulting mixture was stirred for 2 days at room temperature. After this time, the reaction mixture was concentrated *in vacuo*, furnishing a brown-dark orange oil. Purification by flash chromatography (silica gel, 1:1 hexane/ethyl acetate) gave a small quantity of dark red crystals, which X-Ray crystallography showed to be the salt **482**. The desired product **481** could not be isolated.

The reaction was also attempted using larger amounts of reagents (tetrafluoroborate salt **409** (1.00 g, 2.3 mmol), sodium iodide (0.46 g, 3.1 mmol)), and a larger excess of base (0.521 g, 4.64 mmol). A yellow solid was obtained after silica gel flash chromatography, and it was recrystallised by diffusion from dichloromethane and diethyl ether to give the compound **483**, *N*-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-*N*-(2-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-ylamino]ethyl)-formamide, 0.36 g, 44%. The structure of this product was identified by X-Ray crystallography, as shown in Figure 52.

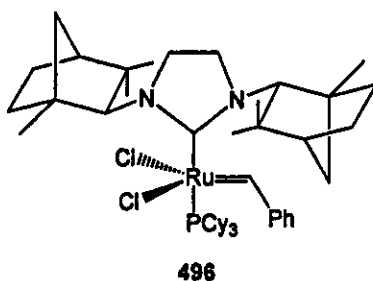


Mass spectrum (FAB+) m/z calcd. for $C_{23}H_{40}N_2O$ (M+H) 361.3219; Found: 361.3221; ν_{\max} (CH_2Cl_2) 2917, 2865, 1653, 1445, 1425, 1381, 1363, 1284, 1255, 1146, 742 cm^{-1} ; 1H NMR (250 MHz, $CDCl_3$) δ 0.88 (s, 3H, $-CH_3$), 0.92 (s, 3H, $-CH_3$), 1.02 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$), 1.12 (s, 3H, $-CH_3$), 1.14 (s, 3H, $-CH_3$), 1.23-1.44 (m), 1.44-1.68 (m), 1.68-1.85 (m), 2.04-2.16 (m, 1H), 2.60-2.93 (m, 2H, $-CH_2-$), 3.04 (s, 1H, $-NH$), 3.26-3.38 (m, 1H, $-CH_2-$), 3.45-3.58 (m, 1H, $-CH_2-$), 8.27 and 8.29 (s, 1H, $-COH$); The ^{13}C NMR spectrum was too complicated to be interpreted.

7.4.6.4 Attempted synthesis of monocarbene adducts

7.4.6.4.1 Ruthenium carbene adducts

7.4.6.4.1.1 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene ruthenium

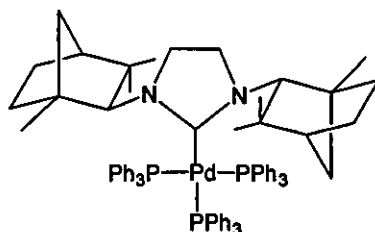


A solution of the tetrafluoroborate salt **409** (0.10 g, 0.2 mmol) and potassium-*tert*-amylate 25% in toluene (0.13 mL, 0.23 mmol) in hexane (5 mL) was stirred for 1.5 hours at room temperature. Grubbs' catalyst (0.13 g, 0.15 mmol) was added to the previous solution in several portions, and the reaction mixture was heated at 60 °C for 2 hours. The reaction mixture was cooled to room temperature and a brown solid precipitated was removed from the mixture by filtration. Analysis by

^1H NMR spectroscopy showed a complex mixture and no signs of the desired product **496** being formed were observed.

7.4.6.4.2 Palladium carbene adducts

7.4.6.4.2.1 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene tris-(triphenylphosphine)-palladium

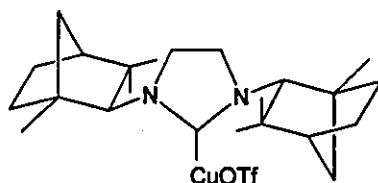


497

A suspension of the tetrafluoroborate salt **409** (0.11 g, 0.25 mmol) and potassium-*tert*-butoxide (56 mg, 0.50 mmol) in anhydrous tetrahydrofuran (15 mL) was stirred for 30 min. at room temperature. Tetrakis palladium triphenylphosphine (0.29 g, 0.25 mg) was added to the reaction mixture and it was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure to give a brown oil that was shown to be a complex mixture. The desired product **497** was not isolated.

7.4.6.4.3 Copper carbene adducts

7.4.6.4.3.1 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene copper triflate

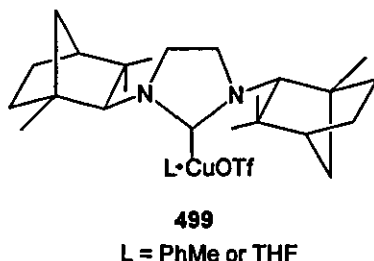


498

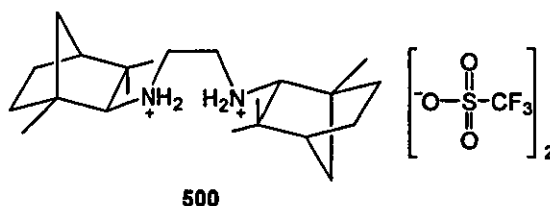
A suspension of the imidazolinium tetrafluoroborate salt **409** (0.30 g, 0.7 mmol) in anhydrous tetrahydrofuran (5 mL) was added to a suspension of copper triflate

(0.26 g, 0.70 mmol) and lithium-*tert*-butoxide (1 M solution in tetrahydrofuran) (0.87 mL, 0.87 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred overnight at room temperature. Flash chromatography (silica gel, 5% methanol /dichloromethane) afforded the starting imidazolinium tetrafluoroborate salt **409**, 53 mg, 18%, and no signs of the desired product **498** being formed was observed.

7.4.6.4.3.2 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene copper triflate



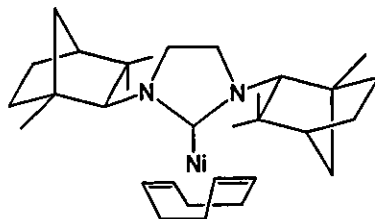
The same procedure as carried out in the previous experiment was followed, using copper triflate-toluene 2:1 complex. Flash chromatography was not attempted, instead the product obtained was recrystallised from dichloromethane and diethyl ether. Colourless crystals were obtained in low yield, and X-Ray crystallography showed the salt **500**, 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-ethyl bis-ammoniumtriflate, had been formed, as shown in **Figure 55**.



mp decomp. > 130 °C; Mass spectrum (FAB+) m/z calcd. for $C_{22}H_{42}N_2$ 333.3270 (M-2H+H); Found: 333.3279. The quantity of material obtained was too little to allow 1H or ^{13}C NMR spectra to be obtained.

7.4.6.4.4 Nickel carbene adducts

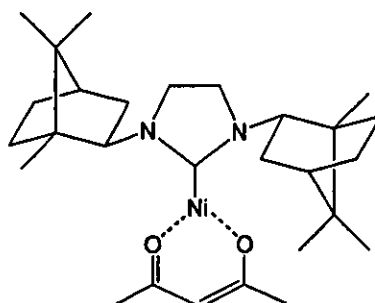
7.4.6.4.4.1 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene nickel cyclooctadiene



501

A solution of the tetrafluoroborate salt **409** (0.78 g, 1.8 mmol) and potassium-*tert*-amylate 25% in toluene (4.22 mL, 7.28 mmol) in anhydrous tetrahydrofuran (6 mL) was stirred 30 min. at room temperature. Bis-(1,5)-cyclooctadiene nickel (0) (0.50 g, 1.8 mmol) was added to the reaction mixture, and it was stirred for 4 hours at room temperature. After this time, the solvent was evaporated under reduced pressure, and the residue obtained was subjected to flash chromatography (silica gel, 10:1 hexane/ethyl acetate), furnishing a white solid. A small portion of it was recrystallised by diffusion from dichloromethane and diethyl ether, and X-Ray showed the urea derivative **468**, 0.24 g, 36%. The desired product **501** was not isolated.

7.4.6.4.4.2 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene nickel acetylacetonate

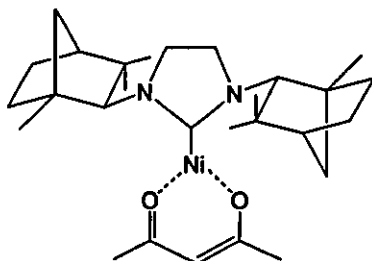


502a

A solution of the tetrafluoroborate salt **392** (0.30 g, 0.7 mmol) and potassium-*tert*-amylate 25% in toluene (1.62 mL, 2.79 mmol) in anhydrous tetrahydrofuran (5 mL)

was stirred 30 min. at room temperature. Nickel acetylacetonate (0.20 g, 0.7 mmol) was added to the reaction mixture. The reaction mixture was stirred for 2 days at room temperature. Solvent was concentrated *in vacuo*, and purification of the crude product obtained by flash chromatography (silica gel, 15:1 hexane/ethyl acetate) did not afford the desired product **502a**.

7.4.6.4.4.3 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene nickel acetylacetonate

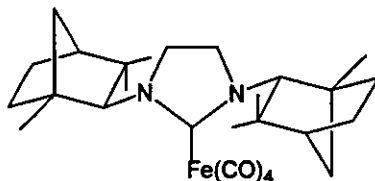


502b

A solution of the tetrafluoroborate salt **409** (0.30 g, 0.7 mmol) and potassium-*tert*-amylate 25% in toluene (1.62 mL, 2.79 mmol) in anhydrous tetrahydrofuran (5 mL) was stirred 30 min. at room temperature. Nickel acetylacetonate (0.20 g, 0.7 mmol) was added to the reaction mixture. The reaction mixture was stirred for 2 days at room temperature. Solvent was concentrated *in vacuo*, and the residue obtained was subjected to flash chromatography (silica gel, 15:1 hexane/ethyl acetate). The ^1H NMR spectra did not show the desired product **502b** to be present. Instead the amide **483** was obtained.

7.4.6.4.5 Carbonyl-metal carbene adducts

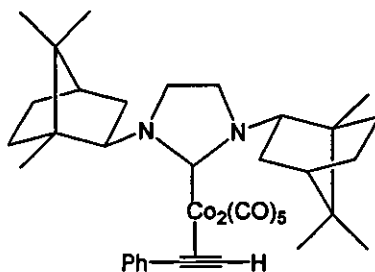
7.4.6.4.5.1 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene tetracarbonyliron



503

A suspension of the tetrafluoroborate salt **409** (0.52 g, 1.2 mmol) and sodium hydride (0.24 g, 6.0 mmol) in anhydrous tetrahydrofuran (5 mL) was heated at 73 °C for 30 min. After this time, the reaction mixture was cooled to room temperature and treated with pentacarbonyliron (0.16 mL, 1.2 mmol). The mixture was stirred overnight at room temperature. The ¹H NMR spectra showed a complex mixture, and the desired product **503** could not be obtained.

7.4.6.4.5.2 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene phenylacetylenepentacarbonyldicobalt

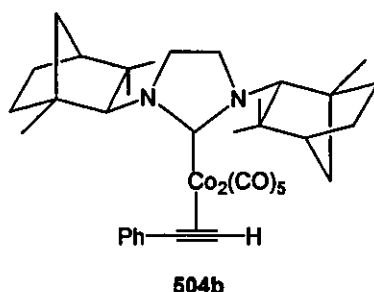


504a

A suspension of the tetrafluoroborate salt **392** (0.33 g, 0.77 mmol) in dry hexane (15 mL) was treated with potassium-*tert*-amylate 25% solution in toluene (0.50 mL, 0.85 mmol). The reaction mixture was stirred for 1 hour at room temperature. After this time, a solution of the cobalt pentacarbonyl complex **506** (0.15 g, 0.39 mmol) in hexane (10 mL) was added to the reaction mixture, and it was heated at 72 °C for 1 hour. A brown solid precipitated from the reaction mixture, and it was recovered by filtration. The ¹H NMR spectrum was too broad to

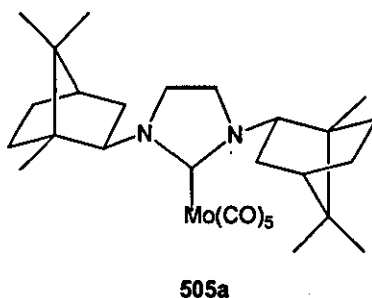
identify if the product had been formed. By IR spectroscopy a band was observed at 1883 cm^{-1} , which could possibly be due to the stretching of the Co-CO of a newly formed complex. The product was subjected to flash chromatography (silica gel, 4:1 petrol/ether and petrol:4% methanol) in an attempt to purify it, but this was unsuccessful.

7.4.6.4.5.3 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene phenylacetylenepentacarbonyldicobalt



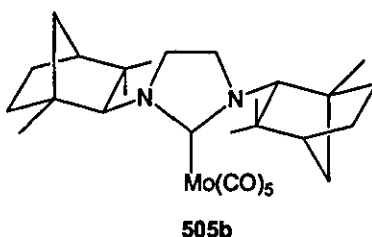
A suspension of the tetrafluoroborate salt **409** (0.33 g, 0.77 mmol), in dry hexane (15 mL), was treated with potassium-*tert*-amylate 25% solution in toluene (0.50 mL, 0.85 mmol). The reaction mixture was stirred for 1 hour at room temperature. After this time, a solution of pentacarbonyl cobalt complex **506** (0.15 g, 0.39 mmol) in hexane (10 mL) was added to the reaction mixture, and it was heated at $72\text{ }^{\circ}\text{C}$ for 1 hour. Some of the solvent was evaporated *in vacuo*, and the reaction mixture was kept under nitrogen in the freezer overnight. A brown solid precipitated, and it was recovered by filtration. The ^1H NMR spectrum was too broad to identify if the product had been formed. By IR spectroscopy a band at 1882 cm^{-1} was observed, possibly due to the stretching of the Co-CO, different to that observed for the starting cobalt complex **506**. The mass spectrum (FAB) showed a peak at 602 m/z , which could possibly be due to the formation of the desired complex **504b** with loss of the alkyne moiety.

7.4.6.4.5.4 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene pentacarbonylmolybdenum



A suspension of the tetrafluoroborate salt **392** (0.30 g, 0.7 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with a solution of lithium-*tert*-butoxide (1 M solution in tetrahydrofuran) (0.87 mL, 0.87 mmol) and hexacarbonyl molybdenum (0.18 g, 0.70 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was stirred overnight at room temperature. Solvent was concentrated under reduced pressure and the residue obtained was dissolved in dichloromethane and washed three times with water. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure to furnish a white solid. The product did not dissolve in any of the common solvents for ^1H NMR spectroscopy.

7.4.6.4.5.5 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene pentacarbonylmolybdenum

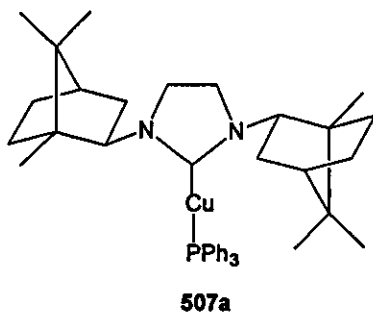


A suspension of the tetrafluoroborate salt **409** (0.30 g, 0.7 mmol) in anhydrous tetrahydrofuran (5 mL) was added to a solution of lithium-*tert*-butoxide (1 M solution in tetrahydrofuran) (0.87 mL, 0.87 mmol) and hexacarbonyl molybdenum (0.18 g, 0.70 mmol) in anhydrous tetrahydrofuran (5 mL). The reaction mixture was stirred overnight at room temperature. Solvent was evaporated *in vacuo*. The

^1H NMR spectrum of the crude product did not show that the desired product **505b** had been formed.

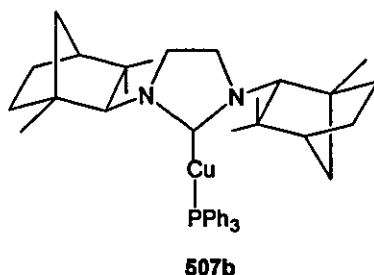
7.4.6.4.6 Copper and nickel carbene adducts with phosphine ligands

7.4.6.4.6.1 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolin-2-ylidene triphenylphosphine copper



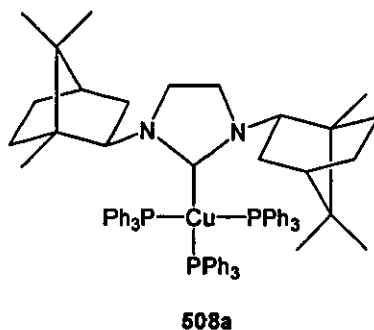
A solution of the tetrafluoroborate salt **392** (0.30 g, 0.7 mmol) and potassium-*tert*-amylate 25% in toluene (1.62 mL, 2.79 mmol) in anhydrous tetrahydrofuran (5 mL) was stirred 30 min. at room temperature. Copper triflate-toluene 2:1 complex (0.36 g, 0.70 mmol) was added to the reaction mixture. After stirring for 30 min. at room temperature, a solution of triphenyl phosphine (0.18 g, 0.70 mmol) in anhydrous tetrahydrofuran (5 mL) was added, and the reaction mixture was stirred for 2 days at room temperature. Flash chromatography was not attempted. Analysis by ^1H NMR spectroscopy showed no signs of the desired product being formed. Instead, a complex mixture was obtained along with unreacted triphenylphosphine.

7.4.6.4.6.2 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene triphenylphosphine copper



The same procedure was followed as in the previous experiment to synthesise **507a**, but using the tetrafluoroborate salt **409**. The reaction mixture was stirred overnight at room temperature. Solvent was concentrated *in vacuo*, and the residue obtained was subjected to flash chromatography (silica gel, 15:1 hexane/ethyl acetate). Analysis by ^1H NMR spectroscopy showed no signs of the desired product **507b** being formed. A complex mixture was obtained along with unreacted triphenylphosphine.

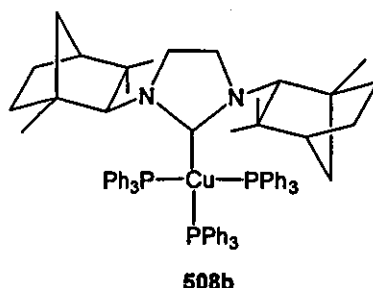
7.4.6.4.6.3 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene tris-(triphenylphosphine) copper



A solution of the tetrafluoroborate salt **392** (0.30 g, 0.7 mmol) and potassium-*tert*-amylate 25% in toluene (1.62 mL, 2.79 mmol) in anhydrous tetrahydrofuran (5 mL) was stirred 30 min. at room temperature. Copper triflate (0.25 g, 0.70 mmol) was added to the reaction mixture. After stirring for 30 min. at room temperature, a solution of triphenyl phosphine (0.55 g, 2.1 mmol) in anhydrous tetrahydrofuran (5 mL) was added, and the reaction mixture was stirred overnight at room temperature. Solvent was concentrated *in vacuo*, and the residue obtained was

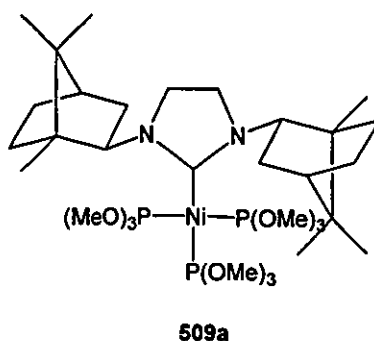
subjected to flash chromatography (silica gel, 15:1 hexane/ethyl acetate). Analysis by ^1H NMR spectroscopy showed a complex mixture with unreacted triphenylphosphine. No signs of the desired product **508a** being formed were observed.

7.4.6.4.6.4 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene tris-(triphenylphosphine) copper



The same procedure was followed as in the previous experiment to synthesise **508a**, but using the tetrafluoroborate salt **409**. Flash chromatography (silica gel, 15:1 hexane/ethyl acetate) did not furnish the desired product **508b**. Instead a complex mixture was obtained, as well as unreacted triphenylphosphine.

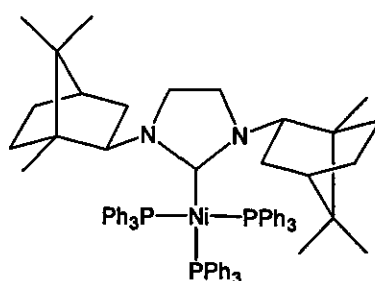
7.4.6.4.6.5 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolin-2-ylidene tris-(trimethylphosphite) nickel



A solution of the tetrafluoroborate salt **392** (0.78 g, 1.8 mmol) and potassium-*tert*-amylate 25% in toluene (4.2 mL, 7.3 mmol) in anhydrous tetrahydrofuran (5 mL) was stirred 30 min. at room temperature. Bis-(1,5)-cyclooctadiene nickel (0) (0.50 g, 1.8 mmol) was added to the reaction mixture. After stirring for 30 min. at room temperature, a solution of trimethyl phosphite (1.43 g, 5.46 mmol) in

anhydrous tetrahydrofuran (4 mL) was added. After 3 hours stirring at room temperature, solvent was concentrated *in vacuo* to furnish a brown solid. The product obtained was subjected to flash chromatography (silica gel, 20:1 hexane/ethyl acetate) to give a complex mixture. The desired product **509a** was not isolated.

7.4.6.4.6.6 Attempted synthesis of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-4,5-dihydro-1H-imidazol-3-ium tris-(triphenylphosphine) nickel

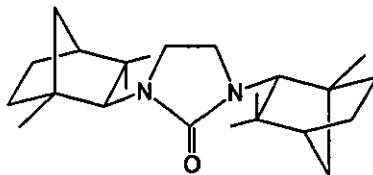


509b

The same procedure was followed as in the previous experiment to synthesise **509a**, but triphenylphosphine (1.43 g, 5.46 mmol) was used instead of trimethyl phosphite. After stirring the reaction mixture for 1 hour at room temperature, solvent was concentrated *in vacuo* to furnish a brown-yellow solid. The residue obtained was subjected to flash chromatography (silica gel, 20:1 hexane/ethyl acetate) to afford the urea derivative **468** in low yield. The desired product **509b** was not isolated and a complex mixture was obtained along with some unreacted triphenylphosphine.

7.5 Experimental for chapter 6; Attempted synthesis of new chiral fluorinating agents

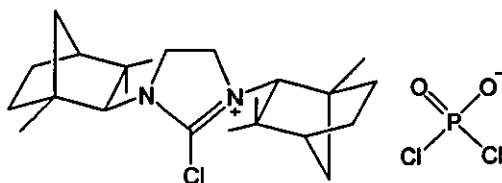
7.5.1 1,3-Bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolidin-2-one



468

A solution of triphosgene (2.68 g, 9.02 mmol) in dichloromethane (5 mL) was slowly added to a solution of diamine **348** (3.00 g, 9.0 mmol) and triethylamine (7.5 mL, 54 mmol) in dichloromethane (10 mL) at room temperature. The reaction mixture was stirred overnight at room temperature, before being diluted with dichloromethane and washed three times with a sodium hydroxide solution (0.1 M, aqueous solution). The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was purified by flash chromatography (silica gel, 15:1 hexane/ethyl acetate) to give the desired product **468** as a white solid, 1.90 g, 59%. Spectroscopic data is shown in page 235.

7.5.2 2-Chloro-1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-4,5-dihydro-3H-imidazol-1-ium dichloro-(oxo)-phosphanolate

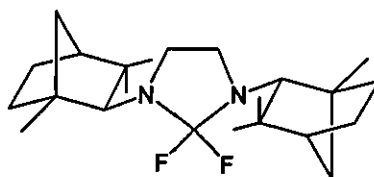


535

The urea derivative **468** (0.20 g, 0.56 mmol) was treated with phosphorus oxychloride (1.0 mL, 11 mmol) and heated at 80 °C overnight. After this time, the excess of phosphorus oxychloride was removed under reduced pressure to furnish the crude product as a brown solid. The ^1H and ^{13}C NMR spectra showed some minor impurities present.

$[\alpha]_D^{25}$ -11.60 ($c = 1.19$, CH_2Cl_2); Mass spectrum (FAB+) m/z calcd. for $\text{C}_{23}\text{H}_{38}\text{ClN}_2^+$ 377.2724; Found: 377.2717; ν_{max} (CH_2Cl_2) 3390, 2159, 1568, 1495, 1460, 1263, 1074 cm^{-1} ; ^{31}P NMR (250 MHz, CDCl_3) δ -1.5; ^1H NMR (400 MHz, CDCl_3) δ 0.90 (s, 3H, $-\text{CH}_3$), 1.02 (s, 3H, $-\text{CH}_3$), 1.13 (s, 3H, $-\text{CH}_3$), 1.14 (s, 3H, $-\text{CH}_3$), 1.20 (s, 6H, 2x- CH_3), 1.22-1.49 (m, 4H), 1.54-1.92 (m, 10H), 3.73-3.77 (m, 1H, 1x- CH_2 -), 3.77-3.78 (m, 2H, 2x- CH_2 -), 3.83-3.86 (m, 1H, 1x- CH_2 -), 4.30 (bs, 1H, 1x- CH_2 -), 4.50 (bs, 1H, 1x- CH_2 -), 14.02 (bs) (unknown signal, possibly due to water); ^{13}C NMR (400 MHz, CDCl_3) δ 20.3 (2x CH_3), 21.4 (2x CH_3), 25.6 (CH_2), 25.9 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 31.6 (CH_3), 31.8 (CH_3), 40.7 (C), 41.6 (C), 44.5 (CH_2), 44.7 (CH_2), 45.3 (CH_2), 47.4 (CH), 48.3 (CH), 48.5 (C), 49.7 (C), 49.8 (CH_2), 68.7 (CH), 74.7 (CH), 159.3 (C).

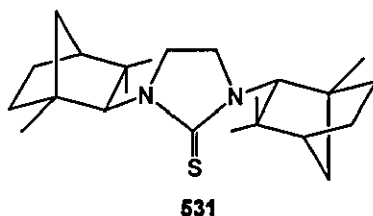
7.5.3 Attempted synthesis of 2,2-difluoro-1,3-bis-[(1R,2R,4S)-1,3,3-trimethylbicyclo [2.2.1]hept-2-yl]-imidazolidine



526

The phosphanolate salt **535** (0.21 g, 0.41 mmol) was treated with potassium fluoride (0.24 g, 4.1 mmol) in anhydrous acetonitrile (10 mL) and the reaction mixture was heated at 80-90 °C overnight. After this time, the reaction mixture was filtered and the product was taken up in hexane. Evaporation under reduced pressure gave a new unidentified compound, along with some traces of impurities.

7.5.4 1,3-Bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-imidazolidine-2-thione



Diamine **348** (2.00 g, 6.0 mmol) was dissolved in dichloromethane (15 mL) and treated with triethylamine (1.84 mL, 13.2 mmol) at room temperature. The mixture was cooled to -30 °C and a solution of thiophosgene (0.52 mL, 6.6 mmol) in dichloromethane (5 mL) was slowly added. The reaction mixture was stirred at -30 °C for 2 hours before being allowed to warm to room temperature overnight. After this time, the mixture was diluted with dichloromethane and washed three times with a sodium hydroxide solution (0.1 M, aqueous solution). The organic solution was separated, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained was purified by flash chromatography (silica gel, 15:1 hexane/ethyl acetate) to give the pure thiourea **531**, which was identified by X-Ray crystallography, as shown in **Figure 58**, and obtained as a pale yellow solid, in very low yield, 76 mg, 3%.

$[\alpha]_D^{25}$ -18.80 ($c = 1.00$, CH_2Cl_2); mp 257-261 °C; HRMS (EI): m/z calcd. for $\text{C}_{23}\text{H}_{38}\text{N}_2\text{S}$ 374.2756; Found: 374.2751; ν_{max} (CH_2Cl_2) 2946, 1427, 1321, 1254, 1151 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.89 (s, 6H, 2x- CH_3), 1.09 (s, 6H, 2x- CH_3), 1.11-1.26 (m, 4H, 2x- CH_2 -, 2x- CH_2 -), 1.24 (s, 6H, 2x- CH_3), 1.48-1.54 (m, 2H, 2x- CH_2 -), 1.75-1.82 (m, 8H, 6x- CH_2 -, 2x- CH -), 3.55-3.58 (m, 2H, 2x- CH_2 -), 3.81-3.84 (m, 2H, 2x- CH_2 -), 4.93 (d, 2H, - CHN -, $J = 1.6$ Hz); ^{13}C NMR (400 MHz, CDCl_3) δ 20.6 (2x CH_3), 21.4 (2x CH_3), 26.0 (2x CH_2), 29.7 (2x CH_2), 32.0 (2x CH_3), 40.9 (2xC), 44.9 (2x CH_2), 47.6 (2x CH_2), 48.5 (2xCH), 48.9 (2xC), 70.3 (2xCH), 188.5 (C).

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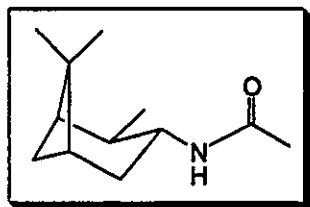
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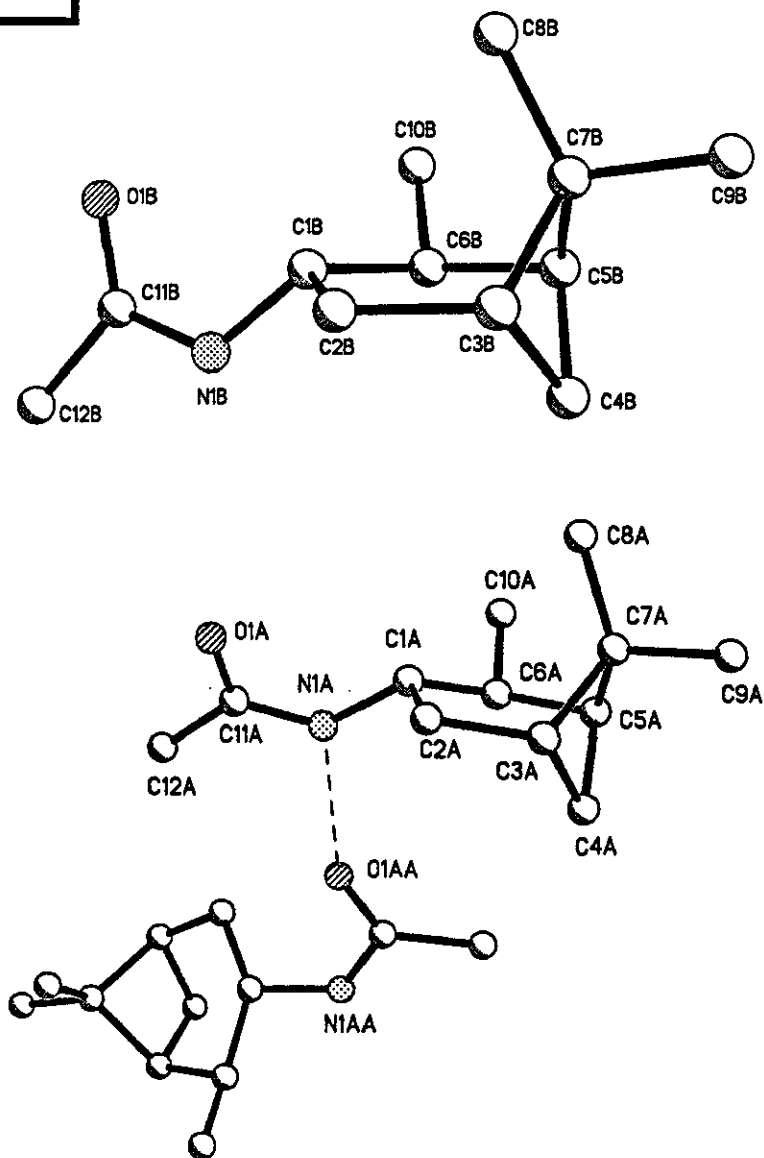
APPENDIX

8.1 X-Ray crystallography data

8.1.1 X-Ray crystallography data of *N*-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethyl-bicyclo[3.1.1]hept-3-yl]-acetamide or *N*-pinan-3-yl-acetamide, 419



419



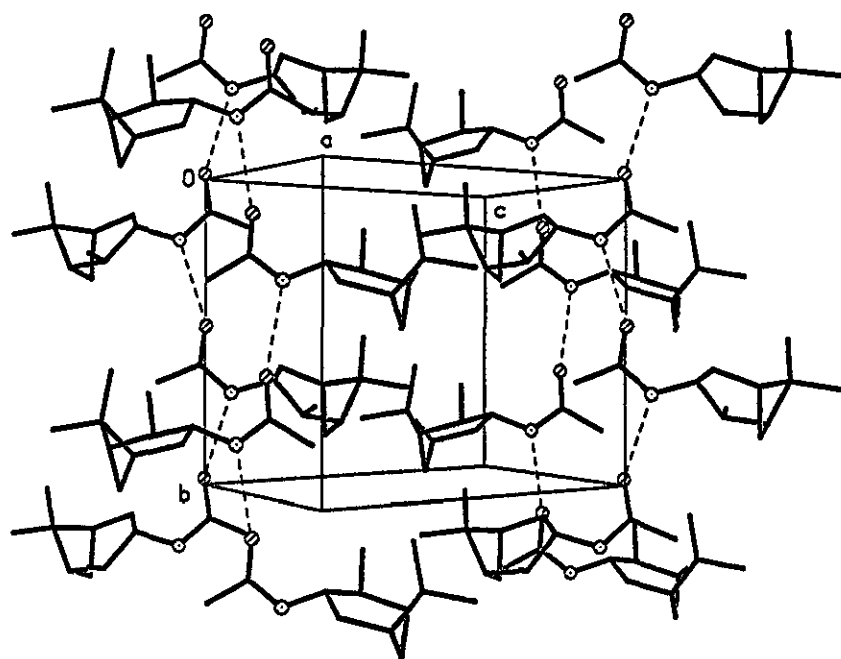
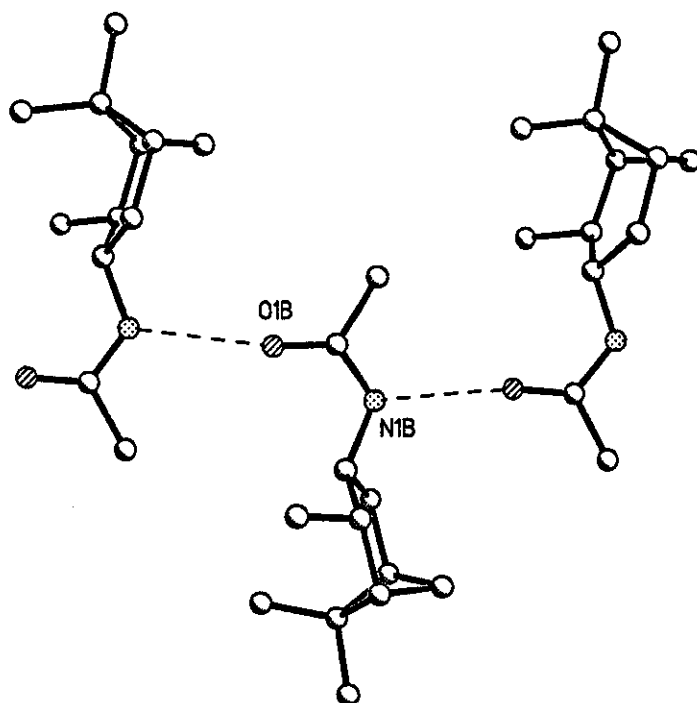


Table 1. Crystal data and structure refinement for compound **419**.

Empirical formula	$C_{12}H_{21}NO$	
Formula weight	195.30	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	$a = 10.3103(8) \text{ Å}$	$\alpha = 90^\circ$.
	$b = 9.5855(7) \text{ Å}$	$\beta = 111.0860(10)^\circ$.
	$c = 12.8702(10) \text{ Å}$	$\gamma = 90^\circ$.
Volume	$1186.79(16) \text{ Å}^3$	
Z	4	
Density (calculated)	1.093 Mg/m^3	
Absorption coefficient μ	0.068 mm^{-1}	
F(000)	432	
Crystal size	$0.42 \times 0.21 \times 0.19 \text{ mm}^3$	
θ range for data collection	1.70 to 25.00° .	
Index ranges	$-12 \leq h \leq 12$, $-11 \leq k \leq 11$, $-15 \leq l \leq 15$	
Reflections collected	8563	
Independent reflections	4088 [$R(\text{int}) = 0.0155$]	
Completeness to $\theta = 25.00^\circ$	100.0 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.000000 and 0.926250	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4088 / 1 / 255	
Goodness-of-fit on F^2	1.047	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0315$, $wR2 = 0.0745$	
R indices (all data)	$R1 = 0.0356$, $wR2 = 0.0774$	
Absolute structure parameter	0.2(10)	
Largest diff. peak and hole	0.125 and -0.119 e. Å^{-3}	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **419**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1A)	1726(1)	6562(2)	1649(1)	28(1)
C(2A)	3032(2)	6128(2)	1393(1)	34(1)
C(3A)	4376(2)	6655(2)	2252(1)	36(1)
C(4A)	4251(2)	8251(2)	2373(2)	48(1)
C(5A)	3535(2)	7909(2)	3210(1)	39(1)
C(6A)	1988(2)	7728(2)	2541(1)	32(1)
C(7A)	4392(2)	6510(2)	3469(1)	39(1)
C(9A)	5851(2)	6749(2)	4331(2)	58(1)
C(10A)	1102(2)	7507(2)	3253(1)	43(1)
N(1A)	563(1)	6985(1)	657(1)	29(1)
C(11A)	-188(2)	6066(2)	-97(1)	31(1)
O(1A)	83(1)	4803(1)	-8(1)	44(1)
C(12A)	-1407(2)	6638(2)	-1041(1)	39(1)
C(1B)	6629(2)	2874(2)	1443(1)	31(1)
C(2B)	7969(2)	3487(2)	1338(1)	36(1)
C(3B)	9060(2)	3879(2)	2449(1)	35(1)
C(4B)	8379(2)	4853(2)	3058(2)	41(1)
C(5B)	7899(2)	3520(2)	3474(1)	37(1)
C(6B)	6504(2)	3088(2)	2600(1)	32(1)
C(7B)	9199(2)	2776(2)	3370(1)	40(1)
C(8B)	9172(2)	1235(2)	3081(2)	55(1)
C(9B)	10500(2)	3046(3)	4404(2)	62(1)
C(10B)	5850(2)	1821(2)	2940(2)	52(1)
N(1B)	5407(1)	3413(1)	550(1)	31(1)
C(11B)	4357(2)	2617(2)	-92(1)	31(1)
O(1B)	4332(1)	1341(1)	12(1)	40(1)
C(12B)	3185(2)	3381(2)	-954(1)	40(1)
C(8A)	3826(2)	5188(2)	3800(1)	44(1)

Table 3. Bond lengths [Å] and angles [°] for compound **419**.

C(1A)-N(1A)	1.4594(18)	C(1B)-N(1B)	1.4610(19)
C(1A)-C(6A)	1.554(2)	C(1B)-C(2B)	1.551(2)
C(1A)-C(2A)	1.554(2)	C(1B)-C(6B)	1.553(2)
C(2A)-C(3A)	1.515(2)	C(2B)-C(3B)	1.514(2)
C(3A)-C(4A)	1.548(2)	C(3B)-C(4B)	1.541(2)
C(3A)-C(7A)	1.566(2)	C(3B)-C(7B)	1.556(2)
C(4A)-C(5A)	1.543(2)	C(4B)-C(5B)	1.535(2)
C(5A)-C(6A)	1.526(2)	C(5B)-C(6B)	1.530(2)
C(5A)-C(7A)	1.574(2)	C(5B)-C(7B)	1.566(2)
C(6A)-C(10A)	1.524(2)	C(6B)-C(10B)	1.527(2)
C(7A)-C(8A)	1.519(2)	C(7B)-C(8B)	1.521(3)
C(7A)-C(9A)	1.532(2)	C(7B)-C(9B)	1.533(2)
N(1A)-C(11A)	1.333(2)	N(1B)-C(11B)	1.3391(19)
C(11A)-O(1A)	1.2381(19)	C(11B)-O(1B)	1.2320(19)
C(11A)-C(12A)	1.503(2)	C(11B)-C(12B)	1.504(2)
N(1A)-C(1A)-C(6A)	108.44(11)	N(1B)-C(1B)-C(2B)	109.87(12)
N(1A)-C(1A)-C(2A)	113.00(11)	N(1B)-C(1B)-C(6B)	111.27(12)
C(6A)-C(1A)-C(2A)	114.54(12)	C(2B)-C(1B)-C(6B)	114.66(12)
C(3A)-C(2A)-C(1A)	113.01(12)	C(3B)-C(2B)-C(1B)	113.21(12)
C(2A)-C(3A)-C(4A)	108.40(13)	C(2B)-C(3B)-C(4B)	108.12(13)
C(2A)-C(3A)-C(7A)	112.21(12)	C(2B)-C(3B)-C(7B)	112.60(13)
C(4A)-C(3A)-C(7A)	87.62(12)	C(4B)-C(3B)-C(7B)	87.60(12)
C(5A)-C(4A)-C(3A)	86.46(12)	C(5B)-C(4B)-C(3B)	86.33(12)
C(6A)-C(5A)-C(4A)	107.23(13)	C(6B)-C(5B)-C(4B)	107.73(13)
C(6A)-C(5A)-C(7A)	114.54(13)	C(6B)-C(5B)-C(7B)	114.90(13)
C(4A)-C(5A)-C(7A)	87.50(12)	C(4B)-C(5B)-C(7B)	87.46(12)
C(10A)-C(6A)-C(5A)	114.07(13)	C(10B)-C(6B)-C(5B)	113.57(13)
C(10A)-C(6A)-C(1A)	111.22(13)	C(10B)-C(6B)-C(1B)	111.54(13)
C(5A)-C(6A)-C(1A)	111.55(12)	C(5B)-C(6B)-C(1B)	111.12(12)
C(8A)-C(7A)-C(9A)	107.36(15)	C(8B)-C(7B)-C(9B)	108.02(16)
C(8A)-C(7A)-C(3A)	119.17(14)	C(8B)-C(7B)-C(3B)	118.98(15)
C(9A)-C(7A)-C(3A)	111.44(14)	C(9B)-C(7B)-C(3B)	111.02(15)
C(8A)-C(7A)-C(5A)	121.82(13)	C(8B)-C(7B)-C(5B)	121.45(15)
C(9A)-C(7A)-C(5A)	110.85(14)	C(9B)-C(7B)-C(5B)	110.99(15)
C(3A)-C(7A)-C(5A)	84.78(12)	C(3B)-C(7B)-C(5B)	84.75(12)
C(11A)-N(1A)-C(1A)	122.18(13)	C(11B)-N(1B)-C(1B)	124.12(13)
O(1A)-C(11A)-N(1A)	121.73(14)	O(1B)-C(11B)-N(1B)	122.88(15)
O(1A)-C(11A)-C(12A)	121.80(14)	O(1B)-C(11B)-C(12B)	121.39(14)
N(1A)-C(11A)-C(12A)	116.44(14)	N(1B)-C(11B)-C(12B)	115.73(14)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **419**. The anisotropic displacement factor exponent takes the form:
 $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2hka^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1A)	33(1)	22(1)	29(1)	1(1)	11(1)	-1(1)
C(2A)	41(1)	30(1)	31(1)	1(1)	15(1)	5(1)
C(3A)	34(1)	32(1)	44(1)	0(1)	18(1)	0(1)
C(4A)	41(1)	30(1)	74(1)	-5(1)	24(1)	-9(1)
C(5A)	39(1)	34(1)	42(1)	-14(1)	12(1)	-3(1)
C(6A)	35(1)	27(1)	33(1)	-3(1)	12(1)	3(1)
C(7A)	34(1)	40(1)	40(1)	-5(1)	9(1)	3(1)
C(9A)	39(1)	71(1)	53(1)	-20(1)	4(1)	3(1)
C(10A)	40(1)	52(1)	38(1)	-5(1)	17(1)	5(1)
N(1A)	34(1)	20(1)	31(1)	2(1)	9(1)	-1(1)
C(11A)	36(1)	24(1)	36(1)	0(1)	16(1)	-3(1)
O(1A)	54(1)	25(1)	44(1)	-3(1)	8(1)	-6(1)
C(12A)	40(1)	36(1)	38(1)	-4(1)	9(1)	-2(1)
C(1B)	32(1)	25(1)	33(1)	-2(1)	8(1)	1(1)
C(2B)	34(1)	44(1)	32(1)	1(1)	15(1)	2(1)
C(3B)	30(1)	36(1)	39(1)	0(1)	13(1)	-5(1)
C(4B)	40(1)	37(1)	45(1)	-11(1)	14(1)	-9(1)
C(5B)	41(1)	44(1)	28(1)	0(1)	14(1)	-3(1)
C(6B)	34(1)	31(1)	35(1)	4(1)	15(1)	0(1)
C(7B)	34(1)	46(1)	37(1)	6(1)	9(1)	3(1)
C(8B)	49(1)	44(1)	71(1)	17(1)	19(1)	13(1)
C(9B)	42(1)	93(2)	42(1)	12(1)	4(1)	3(1)
C(10B)	48(1)	53(1)	56(1)	13(1)	22(1)	-8(1)
N(1B)	34(1)	22(1)	34(1)	0(1)	7(1)	1(1)
C(11B)	33(1)	27(1)	35(1)	-4(1)	13(1)	-1(1)
O(1B)	39(1)	25(1)	51(1)	-4(1)	10(1)	-3(1)
C(12B)	37(1)	38(1)	41(1)	-4(1)	8(1)	2(1)
C(8A)	46(1)	50(1)	34(1)	8(1)	13(1)	12(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **419**.

	x	y	z	U_{eq}
H(1A)	1415	5717	1952	34
H(2A1)	3068	5097	1361	40
H(2A2)	2947	6495	653	40
H(3A)	5242	6338	2143	43
H(4A1)	5153	8739	2705	57
H(4A2)	3642	8723	1687	57
H(5A)	3756	8568	3852	47
H(6A)	1664	8620	2125	38
H(9A1)	6246	7600	4144	87
H(9A2)	6445	5952	4330	87
H(9A3)	5795	6849	5072	87
H(10A)	126	7394	2770	64
H(10B)	1192	8317	3739	64
H(10C)	1417	6667	3710	64
H(12A)	-1416	6241	-1746	59
H(12B)	-1329	7656	-1063	59
H(12C)	-2271	6390	-931	59
H(1B)	6652	1845	1325	37
H(2B1)	8368	2793	968	43
H(2B2)	7721	4326	858	43
H(3B)	9959	4221	2413	42
H(4B1)	9047	5423	3653	49
H(4B2)	7613	5431	2557	49
H(5B)	7903	3579	4251	44
H(6B)	5852	3886	2521	39
H(8B1)	8344	1037	2424	83
H(8B2)	9147	675	3710	83
H(8B3)	10007	1001	2922	83
H(9B1)	10538	4034	4607	93
H(9B2)	11330	2802	4241	93
H(9B3)	10463	2473	5023	93
H(10D)	4967	1596	2344	77
H(10E)	5681	2033	3625	77
H(10F)	6482	1023	3067	77
H(12D)	2928	2891	-1668	60
H(12E)	3483	4332	-1037	60
H(12F)	2382	3417	-719	60

H(8A1)	2888	5005	3265	66
H(8A2)	3789	5305	4545	66
H(8A3)	4434	4401	3803	66
H(1N)	376	7959	515	40
H(2N)	5387	4398	395	40

Table 6. Torsion angles [°] for compound 419.

N(1A)-C(1A)-C(2A)-C(3A)	139.14(13)	N(1B)-C(1B)-C(2B)-C(3B)	139.66(13)
C(6A)-C(1A)-C(2A)-C(3A)	14.28(18)	C(6B)-C(1B)-C(2B)-C(3B)	13.48(19)
C(1A)-C(2A)-C(3A)-C(4A)	-53.51(17)	C(1B)-C(2B)-C(3B)-C(4B)	-53.46(17)
C(1A)-C(2A)-C(3A)-C(7A)	41.56(17)	C(1B)-C(2B)-C(3B)-C(7B)	41.62(19)
C(2A)-C(3A)-C(4A)-C(5A)	84.94(14)	C(2B)-C(3B)-C(4B)-C(5B)	85.12(14)
C(7A)-C(3A)-C(4A)-C(5A)	-27.70(12)	C(7B)-C(3B)-C(4B)-C(5B)	-27.90(12)
C(3A)-C(4A)-C(5A)-C(6A)	-87.40(14)	C(3B)-C(4B)-C(5B)-C(6B)	-87.64(13)
C(3A)-C(4A)-C(5A)-C(7A)	27.54(12)	C(3B)-C(4B)-C(5B)-C(7B)	27.72(12)
C(4A)-C(5A)-C(6A)-C(10A)	-175.00(14)	C(4B)-C(5B)-C(6B)-C(10B)	-176.20(14)
C(7A)-C(5A)-C(6A)-C(10A)	89.77(17)	C(7B)-C(5B)-C(6B)-C(10B)	88.23(17)
C(4A)-C(5A)-C(6A)-C(1A)	57.95(16)	C(4B)-C(5B)-C(6B)-C(1B)	57.08(17)
C(7A)-C(5A)-C(6A)-C(1A)	-37.28(18)	C(7B)-C(5B)-C(6B)-C(1B)	-38.50(18)
N(1A)-C(1A)-C(6A)-C(10A)	88.00(15)	N(1B)-C(1B)-C(6B)-C(10B)	91.89(16)
C(2A)-C(1A)-C(6A)-C(10A)	-144.77(13)	C(2B)-C(1B)-C(6B)-C(10B)	-142.65(14)
N(1A)-C(1A)-C(6A)-C(5A)	-143.42(13)	N(1B)-C(1B)-C(6B)-C(5B)	-140.28(13)
C(2A)-C(1A)-C(6A)-C(5A)	-16.19(18)	C(2B)-C(1B)-C(6B)-C(5B)	-14.82(18)
C(2A)-C(3A)-C(7A)-C(8A)	41.98(19)	C(2B)-C(3B)-C(7B)-C(8B)	42.0(2)
C(4A)-C(3A)-C(7A)-C(8A)	150.90(15)	C(4B)-C(3B)-C(7B)-C(8B)	150.61(16)
C(2A)-C(3A)-C(7A)-C(9A)	167.88(14)	C(2B)-C(3B)-C(7B)-C(9B)	168.24(15)
C(4A)-C(3A)-C(7A)-C(9A)	-83.20(16)	C(4B)-C(3B)-C(7B)-C(9B)	-83.12(16)
C(2A)-C(3A)-C(7A)-C(5A)	-81.75(13)	C(2B)-C(3B)-C(7B)-C(5B)	-81.27(15)
C(4A)-C(3A)-C(7A)-C(5A)	27.17(11)	C(4B)-C(3B)-C(7B)-C(5B)	27.38(12)
C(6A)-C(5A)-C(7A)-C(8A)	-40.7(2)	C(6B)-C(5B)-C(7B)-C(8B)	-40.0(2)
C(4A)-C(5A)-C(7A)-C(8A)	-148.56(16)	C(4B)-C(5B)-C(7B)-C(8B)	-148.42(16)
C(6A)-C(5A)-C(7A)-C(9A)	-168.48(14)	C(6B)-C(5B)-C(7B)-C(9B)	-168.57(15)
C(4A)-C(5A)-C(7A)-C(9A)	83.71(15)	C(4B)-C(5B)-C(7B)-C(9B)	83.04(16)
C(6A)-C(5A)-C(7A)-C(3A)	80.54(14)	C(6B)-C(5B)-C(7B)-C(3B)	80.91(14)
C(4A)-C(5A)-C(7A)-C(3A)	-27.27(11)	C(4B)-C(5B)-C(7B)-C(3B)	-27.48(12)
C(6A)-C(1A)-N(1A)-C(11A)	-158.21(13)	C(2B)-C(1B)-N(1B)-C(11B)	131.83(15)
C(2A)-C(1A)-N(1A)-C(11A)	73.69(17)	C(6B)-C(1B)-N(1B)-C(11B)	-100.08(17)
C(1A)-N(1A)-C(11A)-O(1A)	-1.7(2)	C(1B)-N(1B)-C(11B)-O(1B)	-0.5(2)
C(1A)-N(1A)-C(11A)-C(12A)	176.44(13)	C(1B)-N(1B)-C(11B)-C(12B)	179.04(13)

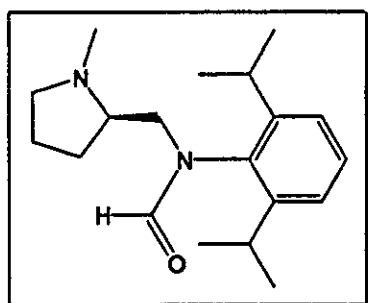
Table 7. Hydrogen bonds for compound **419** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1A)-H(1N)...O(1A)#1	0.96	1.88	2.8353(16)	171.4
N(1B)-H(2N)...O(1B)#2	0.96	1.98	2.9339(16)	168.5

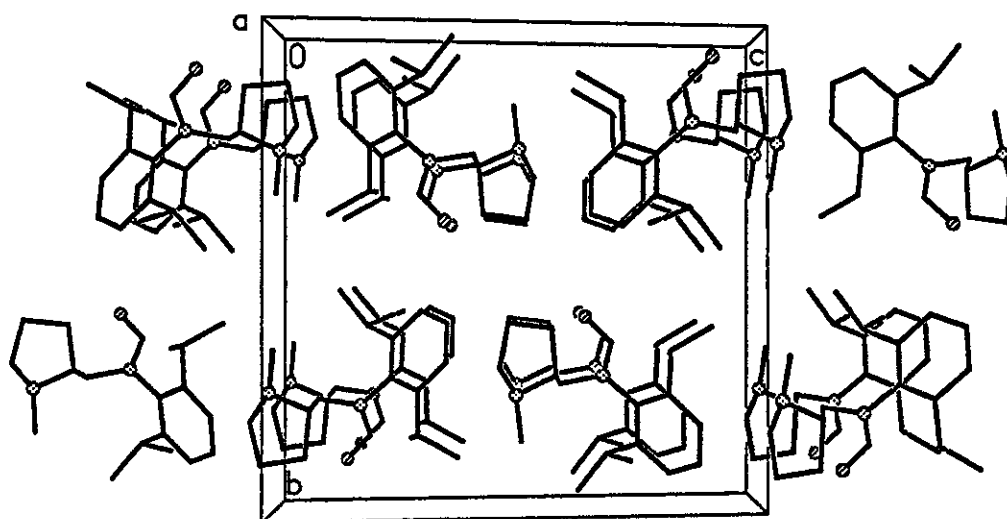
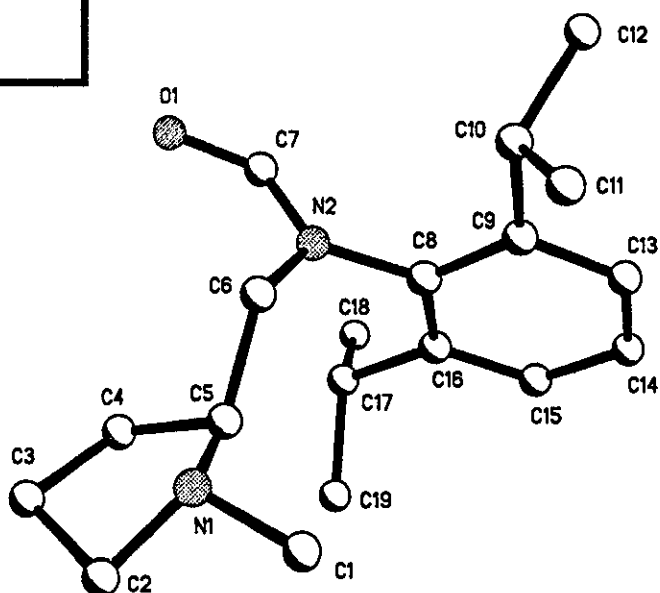
Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z #2 -x+1,y+1/2,-z

8.1.2 X-Ray crystallography data of *N*-(2,6-diisopropyl-phenyl)-*N*-[(2*S*)-1-methyl-pyrrolidin-2-ylmethyl]-formamide, 454



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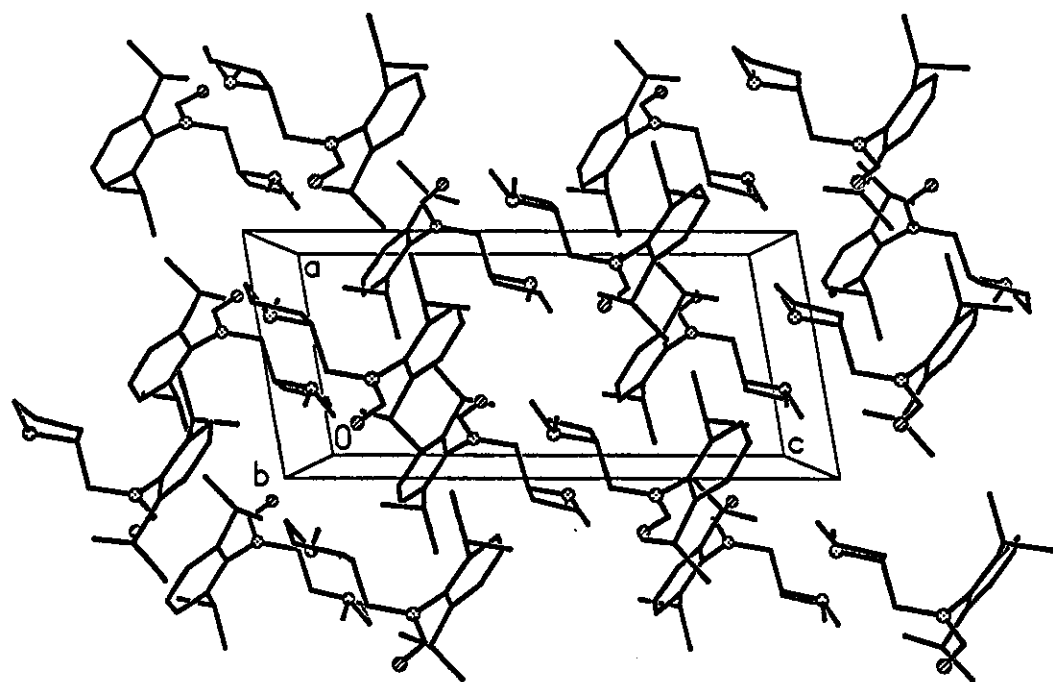


Table 1. Crystal data and structure refinement for compound **454**.

Empirical formula	$\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}$	
Formula weight	302.45	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	$a = 7.3099(10)$ Å	$\alpha = 90^\circ$.
	$b = 15.602(2)$ Å	$\beta = 100.100(2)^\circ$.
	$c = 16.195(2)$ Å	$\gamma = 90^\circ$.
Volume	$1818.4(4)$ Å ³	
Z	4	
Density (calculated)	1.105 Mg/m ³	
Absorption coefficient μ	0.068 mm ⁻¹	
F(000)	664	
Crystal size	$0.45 \times 0.43 \times 0.14$ mm ³	
Crystal description	Colourless block	
θ range for data collection	1.83 to 24.99° .	
Index ranges	$-7 \leq h \leq 8$, $-18 \leq k \leq 18$, $-19 \leq l \leq 19$	
Reflections collected	10154	
Independent reflections	3191 [$R(\text{int}) = 0.0371$]	
Completeness to $\theta = 24.99^\circ$	99.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3191 / 0 / 199	
Goodness-of-fit on F^2	1.017	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0454$, $wR2 = 0.1133$	
R indices (all data)	$R1 = 0.0789$, $wR2 = 0.1260$	
Largest diff. peak and hole	0.387 and -0.168 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **454**. U_{eq} is defined as one third of the trace of the orthogonalized U^{J} tensor.

	x	y	z	U_{eq}
C(1)	7326(3)	6636(1)	74(1)	51(1)
N(1)	6625(2)	7517(1)	-29(1)	40(1)
C(2)	7929(4)	8074(2)	-339(1)	55(1)
C(3)	7171(4)	8965(2)	-174(1)	60(1)
C(4)	6674(4)	8855(1)	686(1)	52(1)
C(5)	6270(3)	7888(1)	763(1)	31(1)
C(6)	4288(3)	7696(1)	871(1)	30(1)
N(2)	3954(2)	7845(1)	1726(1)	25(1)
C(7)	2919(3)	8509(1)	1902(1)	33(1)
O(1)	2164(2)	9038(1)	1400(1)	49(1)
C(8)	4760(3)	7256(1)	2382(1)	25(1)
C(9)	3954(3)	6440(1)	2407(1)	28(1)
C(10)	2163(3)	6187(1)	1829(1)	32(1)
C(11)	2458(3)	5439(1)	1253(1)	42(1)
C(12)	640(3)	5970(1)	2341(1)	43(1)
C(13)	4816(3)	5863(1)	3011(1)	32(1)
C(14)	6382(3)	6093(1)	3571(1)	33(1)
C(15)	7121(3)	6905(1)	3554(1)	31(1)
C(16)	6326(3)	7505(1)	2962(1)	26(1)
C(17)	7158(3)	8402(1)	2985(1)	32(1)
C(18)	6925(3)	8866(1)	3793(1)	43(1)
C(19)	9192(3)	8380(1)	2898(1)	41(1)

Table 3. Bond lengths [Å] and angles [°] for compound 454.

C(1)-N(1)	1.466(3)	C(8)-C(9)	1.407(3)
N(1)-C(2)	1.443(3)	C(9)-C(13)	1.396(3)
N(1)-C(5)	1.472(2)	C(9)-C(10)	1.521(3)
C(2)-C(3)	1.536(3)	C(10)-C(11)	1.533(3)
C(3)-C(4)	1.509(3)	C(10)-C(12)	1.537(3)
C(4)-C(5)	1.546(3)	C(13)-C(14)	1.378(3)
C(5)-C(6)	1.520(3)	C(14)-C(15)	1.380(3)
C(6)-N(2)	1.465(2)	C(15)-C(16)	1.392(2)
N(2)-C(7)	1.342(2)	C(16)-C(17)	1.524(3)
N(2)-C(8)	1.450(2)	C(17)-C(19)	1.518(3)
C(7)-O(1)	1.220(2)	C(17)-C(18)	1.530(3)
C(8)-C(16)	1.403(3)		
C(2)-N(1)-C(1)	111.44(19)	C(9)-C(8)-N(2)	118.50(16)
C(2)-N(1)-C(5)	107.08(16)	C(13)-C(9)-C(8)	117.65(18)
C(1)-N(1)-C(5)	112.44(16)	C(13)-C(9)-C(10)	119.87(17)
N(1)-C(2)-C(3)	101.80(19)	C(8)-C(9)-C(10)	122.43(16)
C(4)-C(3)-C(2)	102.13(19)	C(9)-C(10)-C(11)	111.95(17)
C(3)-C(4)-C(5)	105.43(18)	C(9)-C(10)-C(12)	110.61(16)
N(1)-C(5)-C(6)	109.88(16)	C(11)-C(10)-C(12)	110.68(16)
N(1)-C(5)-C(4)	104.35(15)	C(14)-C(13)-C(9)	120.98(18)
C(6)-C(5)-C(4)	113.68(17)	C(13)-C(14)-C(15)	120.58(18)
N(2)-C(6)-C(5)	113.43(15)	C(14)-C(15)-C(16)	120.96(18)
C(7)-N(2)-C(8)	120.38(15)	C(15)-C(16)-C(8)	117.88(17)
C(7)-N(2)-C(6)	121.12(16)	C(15)-C(16)-C(17)	119.00(17)
C(8)-N(2)-C(6)	118.50(14)	C(8)-C(16)-C(17)	123.11(16)
O(1)-C(7)-N(2)	125.94(19)	C(19)-C(17)-C(16)	111.67(16)
C(16)-C(8)-C(9)	121.89(16)	C(19)-C(17)-C(18)	110.35(17)
C(16)-C(8)-N(2)	119.60(16)	C(16)-C(17)-C(18)	110.57(16)

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **454**. The anisotropic displacement factor exponent takes the form:
 $-2 \pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	61(2)	48(2)	44(1)	-3(1)	9(1)	17(1)
N(1)	41(1)	47(1)	32(1)	-3(1)	10(1)	-2(1)
C(2)	57(2)	72(2)	41(1)	-7(1)	22(1)	-20(1)
C(3)	91(2)	44(2)	49(2)	1(1)	25(1)	-17(1)
C(4)	66(2)	42(1)	51(1)	-3(1)	24(1)	-15(1)
C(5)	35(1)	33(1)	26(1)	-1(1)	9(1)	-3(1)
C(6)	35(1)	29(1)	25(1)	-1(1)	5(1)	0(1)
N(2)	27(1)	23(1)	25(1)	-1(1)	5(1)	2(1)
C(7)	34(1)	28(1)	36(1)	0(1)	8(1)	2(1)
O(1)	56(1)	39(1)	51(1)	7(1)	9(1)	18(1)
C(8)	27(1)	26(1)	23(1)	0(1)	10(1)	4(1)
C(9)	32(1)	25(1)	28(1)	-3(1)	10(1)	0(1)
C(10)	34(1)	25(1)	37(1)	0(1)	6(1)	-4(1)
C(11)	46(2)	35(1)	45(1)	-7(1)	6(1)	-5(1)
C(12)	37(1)	41(1)	52(1)	-1(1)	11(1)	-9(1)
C(13)	39(1)	24(1)	36(1)	1(1)	12(1)	0(1)
C(14)	37(1)	33(1)	30(1)	8(1)	7(1)	8(1)
C(15)	30(1)	36(1)	26(1)	0(1)	4(1)	2(1)
C(16)	27(1)	28(1)	25(1)	-1(1)	10(1)	1(1)
C(17)	33(1)	31(1)	31(1)	3(1)	3(1)	-3(1)
C(18)	51(2)	35(1)	41(1)	-6(1)	3(1)	2(1)
C(19)	38(1)	42(1)	44(1)	0(1)	6(1)	-9(1)

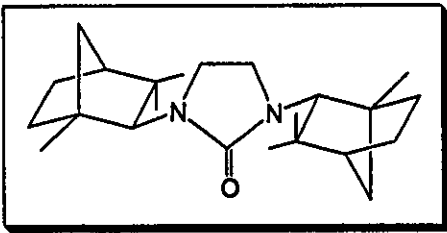
Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **454**.

	x	y	z	U_{eq}
H(1A)	6412	6274	284	77
H(1B)	8498	6629	475	77
H(1C)	7537	6416	-469	77
H(2A)	7919	7981	-944	66
H(2B)	9207	7992	-26	66
H(3A)	8128	9414	-173	72
H(3B)	6065	9111	-596	72
H(4A)	5565	9200	740	62
H(4B)	7718	9035	1126	62
H(5)	7158	7639	1243	37
H(6A)	3428	8058	478	36
H(6B)	4003	7090	720	36
H(7)	2760	8573	2468	39
H(10)	1731	6692	1467	38
H(11A)	1277	5298	890	63
H(11B)	2910	4939	1594	63
H(11C)	3374	5603	906	63
H(12A)	-502	5811	1959	64
H(12B)	402	6472	2671	64
H(12C)	1050	5491	2719	64
H(13)	4316	5303	3036	39
H(14)	6959	5688	3973	40
H(15)	8187	7057	3952	37
H(17)	6463	8733	2500	38
H(18A)	7448	9444	3793	64
H(18B)	7576	8547	4278	64
H(18C)	5601	8904	3825	64
H(19A)	9677	8966	2911	62
H(19B)	9313	8108	2365	62
H(19C)	9897	8050	3363	62

Table 6. Torsion angles [°] for compound **454**.

C(1)-N(1)-C(2)-C(3)	-165.67(17)	N(2)-C(8)-C(9)-C(13)	176.17(16)
C(5)-N(1)-C(2)-C(3)	-42.3(2)	C(16)-C(8)-C(9)-C(10)	174.71(17)
N(1)-C(2)-C(3)-C(4)	41.9(2)	N(2)-C(8)-C(9)-C(10)	-6.3(3)
C(2)-C(3)-C(4)-C(5)	-26.4(3)	C(13)-C(9)-C(10)-C(11)	-64.6(2)
C(2)-N(1)-C(5)-C(6)	147.73(18)	C(8)-C(9)-C(10)-C(11)	117.9(2)
C(1)-N(1)-C(5)-C(6)	-89.5(2)	C(13)-C(9)-C(10)-C(12)	59.3(2)
C(2)-N(1)-C(5)-C(4)	25.5(2)	C(8)-C(9)-C(10)-C(12)	-118.13(19)
C(1)-N(1)-C(5)-C(4)	148.22(19)	C(8)-C(9)-C(13)-C(14)	1.1(3)
C(3)-C(4)-C(5)-N(1)	2.0(2)	C(10)-C(9)-C(13)-C(14)	-176.44(18)
C(3)-C(4)-C(5)-C(6)	-117.7(2)	C(9)-C(13)-C(14)-C(15)	0.8(3)
N(1)-C(5)-C(6)-N(2)	165.33(15)	C(13)-C(14)-C(15)-C(16)	-1.2(3)
C(4)-C(5)-C(6)-N(2)	-78.2(2)	C(14)-C(15)-C(16)-C(8)	-0.4(3)
C(5)-C(6)-N(2)-C(7)	108.6(2)	C(14)-C(15)-C(16)-C(17)	178.18(18)
C(5)-C(6)-N(2)-C(8)	-71.7(2)	C(9)-C(8)-C(16)-C(15)	2.4(3)
C(8)-N(2)-C(7)-O(1)	-179.35(19)	N(2)-C(8)-C(16)-C(15)	-176.53(16)
C(6)-N(2)-C(7)-O(1)	0.3(3)	C(9)-C(8)-C(16)-C(17)	-176.06(17)
C(7)-N(2)-C(8)-C(16)	-76.0(2)	N(2)-C(8)-C(16)-C(17)	5.0(3)
C(6)-N(2)-C(8)-C(16)	104.34(19)	C(15)-C(16)-C(17)-C(19)	58.2(2)
C(7)-N(2)-C(8)-C(9)	105.0(2)	C(8)-C(16)-C(17)-C(19)	-123.3(2)
C(6)-N(2)-C(8)-C(9)	-74.7(2)	C(15)-C(16)-C(17)-C(18)	-65.1(2)
C(16)-C(8)-C(9)-C(13)	-2.8(3)	C(8)-C(16)-C(17)-C(18)	113.4(2)

8.1.3 X-Ray crystallography data of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolidin-2-one, 468



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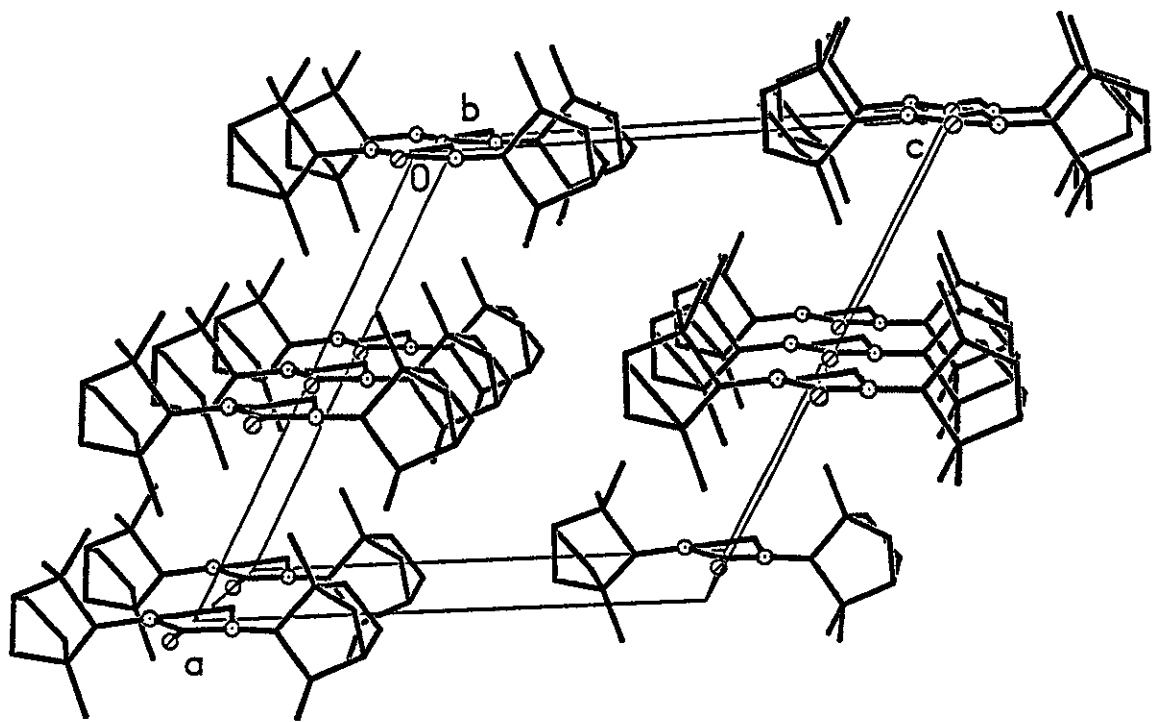
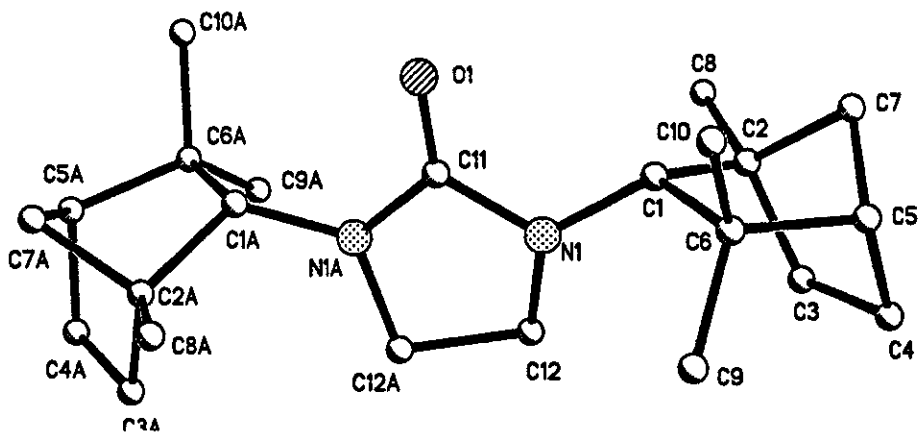


Table 1. Crystal data and structure refinement for compound **468**.

Empirical formula	$C_{11.50}H_{19}NO_{0.50}$	
Formula weight	179.28	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	$a = 13.850(4)$ Å	$\alpha = 90^\circ$.
	$b = 6.407(2)$ Å	$\beta = 120.280(3)^\circ$.
	$c = 13.724(4)$ Å	$\gamma = 90^\circ$.
Volume	$1051.6(6)$ Å ³	
Z	4	
Density (calculated)	1.132 Mg/m ³	
Absorption coefficient μ	0.068 mm ⁻¹	
F(000)	396	
Crystal size	$0.26 \times 0.36 \times 0.50$ mm ³	
θ range for data collection	1.72 to 25.00° .	
Index ranges	$-16 \leq h \leq 16$, $-7 \leq k \leq 7$, $-16 \leq l \leq 16$	
Reflections collected	3662	
Independent reflections	1779 [$R(\text{int}) = 0.0242$]	
Completeness to $\theta = 25.00^\circ$	99.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.865439	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1779 / 1 / 119	
Goodness-of-fit on F^2	1.059	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0421$, $wR2 = 0.1104$	
R indices (all data)	$R1 = 0.0451$, $wR2 = 0.1130$	
Absolute structure parameter	0(2)	
Largest diff. peak and hole	0.217 and -0.163 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **468**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
C(1)	136(2)	8605(3)	1837(2)	24(1)
C(2)	-754(2)	9349(3)	2127(2)	32(1)
C(3)	-515(2)	11598(4)	2609(2)	37(1)
C(4)	520(2)	11360(4)	3805(2)	38(1)
C(5)	839(2)	9072(3)	3835(2)	35(1)
C(6)	1265(2)	8637(3)	3004(1)	29(1)
C(7)	-333(2)	8080(4)	3223(2)	40(1)
C(8)	-1941(2)	8929(4)	1186(2)	48(1)
C(9)	2115(2)	10236(4)	3062(2)	34(1)
C(10)	1811(2)	6480(4)	3223(2)	41(1)
N(1)	151(1)	9539(2)	880(1)	25(1)
C(11)	0	8276(4)	0	24(1)
O(1)	0	6385(3)	0	36(1)
C(12)	-63(2)	11713(3)	523(1)	28(1)

Table 3. Bond lengths [Å] and angles [°] for compound **468**.

C(1)-N(1)	1.454(2)	C(5)-C(6)	1.551(3)
C(1)-C(2)	1.549(3)	C(6)-C(10)	1.531(3)
C(1)-C(6)	1.576(2)	C(6)-C(9)	1.531(3)
C(2)-C(8)	1.517(3)	N(1)-C(11)	1.379(2)
C(2)-C(7)	1.542(3)	N(1)-C(12)	1.456(2)
C(2)-C(3)	1.550(3)	C(11)-O(1)	1.211(3)
C(3)-C(4)	1.548(3)	C(11)-N(1)#1	1.379(2)
C(4)-C(5)	1.526(3)	C(12)-C(12)#1	1.530(4)
C(5)-C(7)	1.539(3)		
N(1)-C(1)-C(2)	118.78(16)	C(10)-C(6)-C(9)	107.67(18)
N(1)-C(1)-C(6)	116.98(15)	C(10)-C(6)-C(5)	110.55(16)
C(2)-C(1)-C(6)	104.20(14)	C(9)-C(6)-C(5)	114.15(17)
C(8)-C(2)-C(7)	116.85(19)	C(10)-C(6)-C(1)	109.04(15)
C(8)-C(2)-C(1)	112.79(16)	C(9)-C(6)-C(1)	113.84(15)
C(7)-C(2)-C(1)	97.44(16)	C(5)-C(6)-C(1)	101.46(15)
C(8)-C(2)-C(3)	115.79(19)	C(5)-C(7)-C(2)	95.21(16)
C(7)-C(2)-C(3)	100.35(15)	C(11)-N(1)-C(1)	118.98(15)
C(1)-C(2)-C(3)	111.65(15)	C(11)-N(1)-C(12)	110.59(14)
C(4)-C(3)-C(2)	104.19(17)	C(1)-N(1)-C(12)	127.19(14)
C(5)-C(4)-C(3)	102.93(16)	O(1)-C(11)-N(1)	125.95(11)
C(4)-C(5)-C(7)	99.83(18)	O(1)-C(11)-N(1)#1	125.95(11)
C(4)-C(5)-C(6)	111.43(16)	N(1)-C(11)-N(1)#1	108.1(2)
C(7)-C(5)-C(6)	102.25(16)	N(1)-C(12)-C(12)#1	102.42(10)

Symmetry transformations used to generate equivalent atoms:

#1 -x,y,-z

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **468**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2hka^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	30(1)	19(1)	28(1)	-1(1)	17(1)	-2(1)
C(2)	31(1)	34(1)	40(1)	-7(1)	24(1)	-10(1)
C(3)	40(1)	36(1)	49(1)	-9(1)	32(1)	-2(1)
C(4)	49(1)	38(1)	38(1)	-10(1)	31(1)	-11(1)
C(5)	45(1)	35(1)	28(1)	-2(1)	22(1)	-9(1)
C(6)	34(1)	28(1)	27(1)	2(1)	16(1)	-1(1)
C(7)	49(1)	42(1)	44(1)	-10(1)	35(1)	-15(1)
C(8)	32(1)	56(2)	59(1)	-11(1)	25(1)	-6(1)
C(9)	26(1)	39(1)	35(1)	1(1)	14(1)	-4(1)
C(10)	46(1)	35(1)	38(1)	7(1)	18(1)	7(1)
N(1)	31(1)	21(1)	24(1)	-1(1)	15(1)	0(1)
C(11)	23(1)	23(2)	27(1)	0	13(1)	0
O(1)	59(1)	20(1)	35(1)	0	29(1)	0
C(12)	33(1)	22(1)	30(1)	1(1)	16(1)	1(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **468**.

	x	y	z	U_{eq}
H(1)	-30	7094	1642	29
H(3A)	-350	12538	2139	45
H(3B)	-1160	12161	2648	45
H(4A)	1133	12295	3909	45
H(4B)	328	11666	4395	45
H(5)	1338	8516	4613	42
H(7A)	-764	8366	3605	47
H(7B)	-312	6560	3104	47
H(8A)	-2468	9433	1410	72
H(8B)	-2045	7425	1039	72
H(8C)	-2075	9657	500	72
H(9A)	1787	11637	2924	51
H(9B)	2313	9905	2488	51
H(9C)	2788	10190	3811	51
H(10A)	1282	5420	3185	62
H(10B)	2483	6456	3974	62
H(10C)	2018	6181	2652	62
H(12A)	489	12652	1114	34
H(12B)	-826	12140	332	34

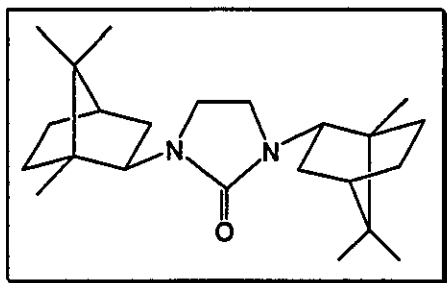
Table 6. Torsion angles [°] for compound **468**.

N(1)-C(1)-C(2)-C(8)	61.9(3)	N(1)-C(1)-C(6)-C(9)	18.5(2)
C(6)-C(1)-C(2)-C(8)	-165.76(19)	C(2)-C(1)-C(6)-C(9)	-114.78(19)
N(1)-C(1)-C(2)-C(7)	-174.77(15)	N(1)-C(1)-C(6)-C(5)	141.64(16)
C(6)-C(1)-C(2)-C(7)	-42.47(17)	C(2)-C(1)-C(6)-C(5)	8.31(19)
N(1)-C(1)-C(2)-C(3)	-70.5(2)	C(4)-C(5)-C(7)-C(2)	58.66(17)
C(6)-C(1)-C(2)-C(3)	61.82(19)	C(6)-C(5)-C(7)-C(2)	-55.99(18)
C(8)-C(2)-C(3)-C(4)	157.16(17)	C(8)-C(2)-C(7)-C(5)	179.77(19)
C(7)-C(2)-C(3)-C(4)	30.41(18)	C(1)-C(2)-C(7)-C(5)	59.51(17)
C(1)-C(2)-C(3)-C(4)	-71.95(19)	C(3)-C(2)-C(7)-C(5)	-54.20(18)
C(2)-C(3)-C(4)-C(5)	5.90(18)	C(2)-C(1)-N(1)-C(11)	-119.95(17)
C(3)-C(4)-C(5)-C(7)	-40.21(18)	C(6)-C(1)-N(1)-C(11)	113.62(16)
C(3)-C(4)-C(5)-C(6)	67.20(19)	C(2)-C(1)-N(1)-C(12)	37.7(2)
C(4)-C(5)-C(6)-C(10)	167.92(17)	C(6)-C(1)-N(1)-C(12)	-88.8(2)
C(7)-C(5)-C(6)-C(10)	-86.2(2)	C(1)-N(1)-C(11)-O(1)	-10.55(17)
C(4)-C(5)-C(6)-C(9)	46.4(2)	C(12)-N(1)-C(11)-O(1)	-171.64(9)
C(7)-C(5)-C(6)-C(9)	152.20(18)	C(1)-N(1)-C(11)-N(1)#1	169.45(17)
C(4)-C(5)-C(6)-C(1)	-76.51(18)	C(12)-N(1)-C(11)-N(1)#1	8.36(9)
C(7)-C(5)-C(6)-C(1)	29.32(19)	C(11)-N(1)-C(12)-C(12)#1	-20.3(2)
N(1)-C(1)-C(6)-C(10)	-101.69(18)	C(1)-N(1)-C(12)-C(12)#1	-179.45(17)
C(2)-C(1)-C(6)-C(10)	124.98(17)		

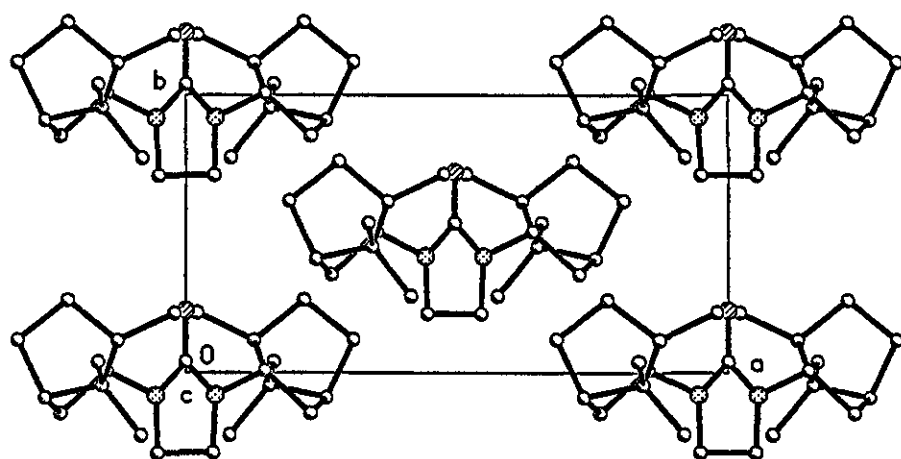
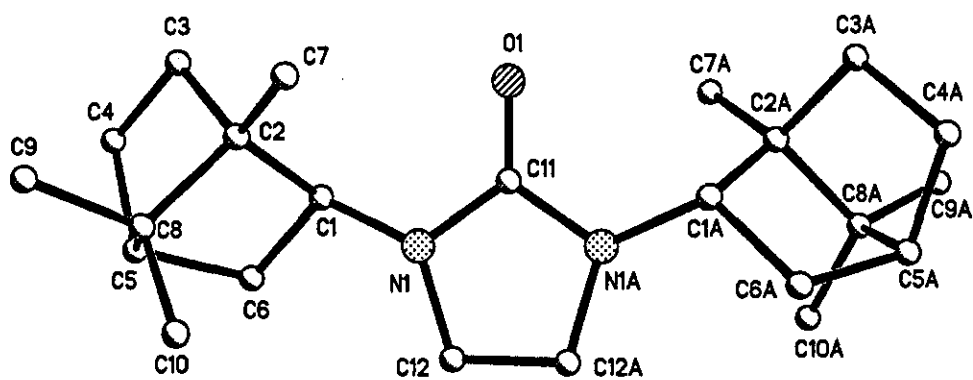
Symmetry transformations used to generate equivalent atoms:

#1 -x,y,-z

8.1.4 X-Ray crystallography data of 1,3-bis-[(1R,2R,4S)-1,7,7-trimethyl-bicyclo [2.2.1]hept-2-yl]-imidazolidin-2-one, 469



469



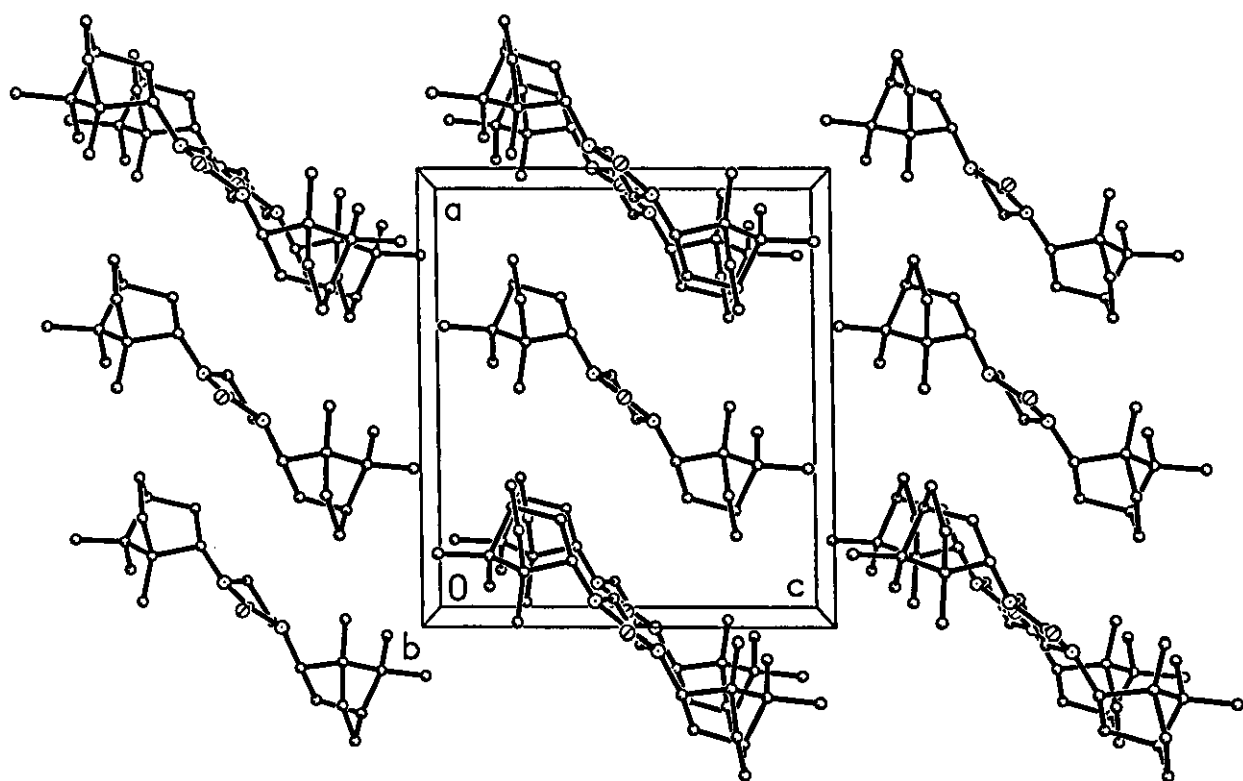


Table 1. Crystal data and structure refinement for compound **469**.

Empirical formula	$C_{23}H_{38}N_2O$	
Formula weight	358.55	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	$a = 12.9831(17)$ Å	$\alpha = 90^\circ$.
	$b = 6.6520(9)$ Å	$\beta = 90.860(2)^\circ$.
	$c = 11.7059(15)$ Å	$\gamma = 90^\circ$.
Volume	$1010.8(2)$ Å ³	
Z	2	
Density (calculated)	1.178 Mg/m ³	
Absorption coefficient μ	0.071 mm ⁻¹	
F(000)	396	
Crystal size	$0.23 \times 0.39 \times 0.62$ mm ³	
θ range for data collection	1.74 to 24.98° .	
Index ranges	$-14 \leq h \leq 15$, $-7 \leq k \leq 7$, $-13 \leq l \leq 13$	
Reflections collected	3423	
Independent reflections	1765 [$R(\text{int}) = 0.0101$]	
Completeness to $\theta = 24.98^\circ$	99.9 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.906074	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1765 / 1 / 119	
Goodness-of-fit on F^2	1.036	
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0298$, $wR2 = 0.0754$	
R indices (all data)	$R1 = 0.0304$, $wR2 = 0.0759$	
Absolute structure parameter	0.5(16)	
Largest diff. peak and hole	0.147 and -0.173 e. Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameter ($\text{\AA}^2 \times 10^3$) for compound **469**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	1448(1)	87(2)	3704(1)	22(1)
C(2)	1249(1)	1175(2)	2532(1)	22(1)
C(3)	2182(1)	2620(2)	2449(1)	28(1)
C(4)	3106(1)	1198(3)	2229(1)	29(1)
C(5)	2600(1)	-887(2)	2188(1)	24(1)
C(6)	2309(1)	-1452(2)	3417(1)	25(1)
C(7)	207(1)	2161(2)	2377(1)	27(1)
C(8)	1538(1)	-437(2)	1628(1)	22(1)
C(9)	1614(1)	401(2)	408(1)	27(1)
C(10)	805(1)	-2237(2)	1562(1)	26(1)
O(1)	0	2238(2)	5000	31(1)
C(11)	0	396(3)	5000	24(1)
N(1)	539(1)	-800(2)	4254(1)	23(1)
C(12)	503(1)	-2874(2)	4674(1)	25(1)

Table 3. Bond lengths [Å] and angles [°] for compound **469**.

C(1)-N(1)	1.4754(17)	C(5)-C(8)	1.5468(18)
C(1)-C(6)	1.5560(18)	C(8)-C(10)	1.5306(18)
C(1)-C(2)	1.5689(18)	C(8)-C(9)	1.5383(19)
C(2)-C(7)	1.5115(19)	O(1)-C(11)	1.225(3)
C(2)-C(3)	1.5504(18)	C(11)-N(1)	1.3802(16)
C(2)-C(8)	1.5567(19)	C(11)-N(1)#1	1.3802(16)
C(3)-C(4)	1.552(2)	N(1)-C(12)	1.4661(18)
C(4)-C(5)	1.535(2)	C(12)-C(12)#1	1.522(3)
C(5)-C(6)	1.5395(19)		
N(1)-C(1)-C(6)	114.40(11)	C(5)-C(6)-C(1)	103.19(10)
N(1)-C(1)-C(2)	116.30(10)	C(10)-C(8)-C(9)	106.56(11)
C(6)-C(1)-C(2)	102.96(10)	C(10)-C(8)-C(5)	114.84(12)
C(7)-C(2)-C(3)	114.93(12)	C(9)-C(8)-C(5)	113.23(10)
C(7)-C(2)-C(8)	116.19(11)	C(10)-C(8)-C(2)	114.64(10)
C(3)-C(2)-C(8)	100.83(10)	C(9)-C(8)-C(2)	113.66(11)
C(7)-C(2)-C(1)	116.17(10)	C(5)-C(8)-C(2)	93.87(10)
C(3)-C(2)-C(1)	102.85(11)	O(1)-C(11)-N(1)	125.20(8)
C(8)-C(2)-C(1)	103.79(10)	O(1)-C(11)-N(1)#1	125.20(8)
C(2)-C(3)-C(4)	103.84(11)	N(1)-C(11)-N(1)#1	109.60(16)
C(5)-C(4)-C(3)	102.95(10)	C(11)-N(1)-C(12)	108.11(11)
C(4)-C(5)-C(6)	107.60(11)	C(11)-N(1)-C(1)	117.54(11)
C(4)-C(5)-C(8)	102.54(11)	C(12)-N(1)-C(1)	123.55(11)
C(6)-C(5)-C(8)	102.33(10)	N(1)-C(12)-C(12)#1	101.57(8)

Symmetry transformations used to generate equivalent atoms: #1 -x,y,-z+1

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **469**. The anisotropic displacement factor exponent takes the form:
 $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2hka^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	22(1)	22(1)	0(1)	2(1)	-1(1)
C(2)	23(1)	21(1)	21(1)	2(1)	4(1)	0(1)
C(3)	30(1)	25(1)	27(1)	-1(1)	4(1)	-5(1)
C(4)	22(1)	39(1)	26(1)	1(1)	1(1)	-3(1)
C(5)	21(1)	29(1)	22(1)	-1(1)	2(1)	4(1)
C(6)	24(1)	27(1)	24(1)	2(1)	0(1)	3(1)
C(7)	28(1)	26(1)	26(1)	3(1)	5(1)	6(1)
C(8)	20(1)	24(1)	21(1)	0(1)	2(1)	1(1)
C(9)	28(1)	31(1)	22(1)	0(1)	2(1)	1(1)
C(10)	28(1)	25(1)	24(1)	-2(1)	0(1)	-3(1)
O(1)	41(1)	20(1)	31(1)	0	13(1)	0
C(11)	28(1)	21(1)	23(1)	0	4(1)	0
N(1)	28(1)	19(1)	21(1)	0(1)	6(1)	1(1)
C(12)	34(1)	19(1)	23(1)	2(1)	5(1)	2(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **469**.

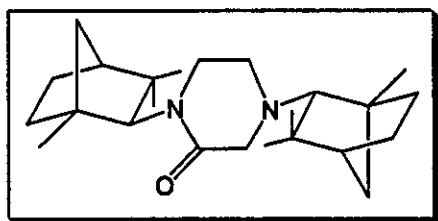
	x	y	z	U_{eq}
H(1)	1751	1097	4245	26
H(3A)	2284	3380	3169	33
H(3B)	2085	3582	1811	33
H(4A)	3440	1520	1497	35
H(4B)	3625	1283	2856	35
H(5)	3011	-1932	1784	29
H(6A)	2906	-1310	3946	30
H(6B)	2048	-2849	3455	30
H(7A)	-335	1144	2441	40
H(7B)	164	2792	1621	40
H(7C)	117	3188	2968	40
H(9A)	2078	1562	408	40
H(9B)	929	817	136	40
H(9C)	1882	-642	-99	40
H(10A)	732	-2823	2325	39
H(10B)	1083	-3249	1043	39
H(10C)	129	-1791	1277	39
H(12A)	1098	-3179	5183	30
H(12B)	483	-3852	4036	30

Table 6. Torsion angles [°] for compound **469**.

N(1)-C(1)-C(2)-C(7)	31.03(17)	C(6)-C(5)-C(8)-C(2)	55.90(12)
C(6)-C(1)-C(2)-C(7)	156.94(12)	C(7)-C(2)-C(8)-C(10)	-60.20(15)
N(1)-C(1)-C(2)-C(3)	157.47(11)	C(3)-C(2)-C(8)-C(10)	174.88(11)
C(6)-C(1)-C(2)-C(3)	-76.62(12)	C(1)-C(2)-C(8)-C(10)	68.61(13)
N(1)-C(1)-C(2)-C(8)	-97.79(12)	C(7)-C(2)-C(8)-C(9)	62.72(15)
C(6)-C(1)-C(2)-C(8)	28.12(12)	C(3)-C(2)-C(8)-C(9)	-62.21(13)
C(7)-C(2)-C(3)-C(4)	-161.70(11)	C(1)-C(2)-C(8)-C(9)	-168.47(10)
C(8)-C(2)-C(3)-C(4)	-35.93(13)	C(7)-C(2)-C(8)-C(5)	-179.82(11)
C(1)-C(2)-C(3)-C(4)	71.08(12)	C(3)-C(2)-C(8)-C(5)	55.26(12)
C(2)-C(3)-C(4)-C(5)	1.05(13)	C(1)-C(2)-C(8)-C(5)	-51.00(11)
C(3)-C(4)-C(5)-C(6)	-72.79(12)	O(1)-C(11)-N(1)-C(12)	168.88(7)
C(3)-C(4)-C(5)-C(8)	34.67(12)	N(1)#1-C(11)-N(1)-C(12)	-11.12(7)
C(4)-C(5)-C(6)-C(1)	67.07(12)	O(1)-C(11)-N(1)-C(1)	23.16(13)
C(8)-C(5)-C(6)-C(1)	-40.54(13)	N(1)#1-C(11)-N(1)-C(1)	-156.84(13)
N(1)-C(1)-C(6)-C(5)	134.36(12)	C(6)-C(1)-N(1)-C(11)	149.80(10)
C(2)-C(1)-C(6)-C(5)	7.23(13)	C(2)-C(1)-N(1)-C(11)	-90.28(14)
C(4)-C(5)-C(8)-C(10)	-175.00(11)	C(6)-C(1)-N(1)-C(12)	9.76(17)
C(6)-C(5)-C(8)-C(10)	-63.55(14)	C(2)-C(1)-N(1)-C(12)	129.68(13)
C(4)-C(5)-C(8)-C(9)	62.28(14)	C(11)-N(1)-C(12)-C(12)#1	27.37(15)
C(6)-C(5)-C(8)-C(9)	173.72(11)	C(1)-N(1)-C(12)-C(12)#1	170.55(13)
C(4)-C(5)-C(8)-C(2)	-55.55(11)		

Symmetry transformations used to generate equivalent atoms: #1 -x,y,-z+1

8.1.5 X-Ray crystallography data of 1,4-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo [2.2.1]hept-2-yl]-piperazin-2-one, 470



470

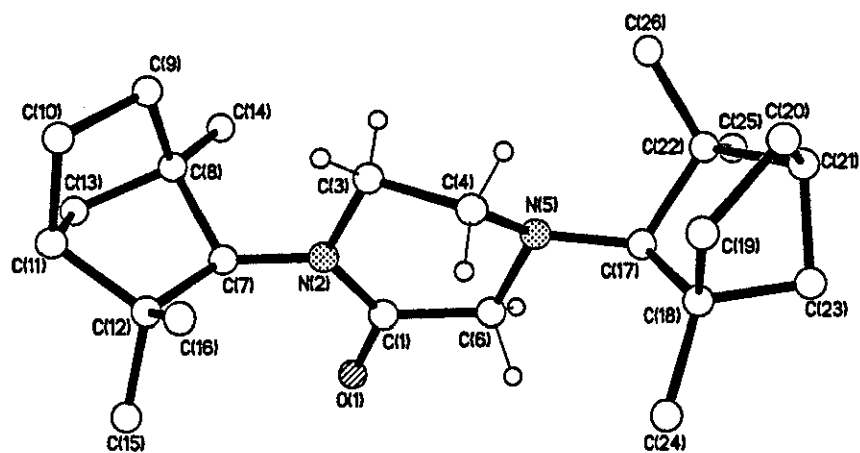


Table 1. Crystal data and structure refinement for compound **470**.

Chemical formula	$C_{24}H_{40}N_2O$	
Formula weight	372.58	
Temperature	150(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	$a = 6.5081(13)$ Å	$\alpha = 90^\circ$
	$b = 11.812(2)$ Å	$\beta = 90^\circ$
	$c = 27.375(6)$ Å	$\gamma = 90^\circ$
Cell volume	$2104.3(7)$ Å ³	
Z	4	
Calculated density	1.176 g/cm ³	
Absorption coefficient μ	0.071 mm ⁻¹	
F(000)	824	
Crystal colour and size	colourless, $0.38 \times 0.27 \times 0.09$ mm ³	
Reflections for cell refinement	5004 (θ range 2.28 to 27.30°)	
Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames	
θ range for data collection	1.88 to 25.00°	
Index ranges	$h -7$ to 7 , $k -14$ to 14 , $l -32$ to 32	
Completeness to $\theta = 25.00^\circ$	99.8 %	
Intensity decay	0%	
Reflections collected	14007	
Independent reflections	3681 ($R_{\text{int}} = 0.0705$)	
Reflections with $F^2 > 2\sigma$	3084	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.974 and 0.994	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a , b	0.0806, 6.5593	
Data / restraints / parameters	3681 / 0 / 250	
Final R indices [$F^2 > 2\sigma$]	$R1 = 0.0974$, $wR2 = 0.2399$	
R indices (all data)	$R1 = 0.1109$, $wR2 = 0.2486$	
Goodness-of-fit on F^2	1.086	
Absolute structure parameter	$-3(5)$	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.654 and -0.367 e Å ⁻³	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for compound **470**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	1.1104(6)	0.4679(4)	0.39422(16)	0.0450(12)
C(1)	0.9383(7)	0.4874(5)	0.4127(2)	0.0265(12)
N(2)	0.7667(6)	0.4969(4)	0.38544(15)	0.0220(9)
C(3)	0.5740(7)	0.5265(5)	0.41048(18)	0.0245(11)
C(4)	0.5646(7)	0.4785(5)	0.46111(18)	0.0260(12)
N(5)	0.7344(6)	0.5229(3)	0.48999(14)	0.0188(9)
C(6)	0.9296(7)	0.4909(5)	0.46722(19)	0.0282(12)
C(7)	0.7836(7)	0.4978(4)	0.33296(19)	0.0228(11)
C(8)	0.6962(8)	0.5995(5)	0.30309(19)	0.0267(12)
C(9)	0.4642(9)	0.6000(5)	0.2994(2)	0.0336(13)
C(10)	0.4122(8)	0.4999(5)	0.2658(2)	0.0354(14)
C(11)	0.6239(9)	0.4466(5)	0.2565(2)	0.0294(13)
C(12)	0.7120(8)	0.3892(5)	0.30406(19)	0.0255(12)
C(13)	0.7530(10)	0.5550(5)	0.2521(2)	0.0347(13)
C(14)	0.7912(9)	0.7125(5)	0.3181(2)	0.0332(14)
C(15)	0.8945(10)	0.3157(5)	0.2918(2)	0.0371(14)
C(16)	0.5567(9)	0.3172(5)	0.3314(2)	0.0354(14)
C(17)	0.7358(7)	0.5107(4)	0.54246(18)	0.0211(10)
C(18)	0.6628(8)	0.4000(4)	0.5688(2)	0.0236(11)
C(19)	0.4257(8)	0.3860(5)	0.5676(2)	0.0288(12)
C(20)	0.3445(8)	0.4771(5)	0.6029(2)	0.0328(13)
C(21)	0.5409(8)	0.5408(5)	0.6172(2)	0.0271(12)
C(22)	0.6272(8)	0.6076(4)	0.57318(19)	0.0256(12)
C(23)	0.6891(8)	0.4390(5)	0.6213(2)	0.0280(12)
C(24)	0.7806(9)	0.2945(4)	0.5543(2)	0.0330(13)
C(25)	0.7941(10)	0.6911(5)	0.5907(2)	0.0405(15)
C(26)	0.4713(11)	0.6754(5)	0.5441(2)	0.0420(16)

Table 3. Bond lengths [Å] and angles [°] for compound **470**.

O(1)–C(1)	1.251(6)	C(1)–N(2)	1.348(6)
C(1)–C(6)	1.493(8)	N(2)–C(7)	1.441(7)
N(2)–C(3)	1.472(6)	C(3)–C(4)	1.499(7)
C(4)–N(5)	1.457(6)	N(5)–C(17)	1.444(6)
N(5)–C(6)	1.465(6)	C(7)–C(8)	1.561(7)
C(7)–C(12)	1.577(7)	C(8)–C(9)	1.513(8)
C(8)–C(14)	1.528(7)	C(8)–C(13)	1.536(8)
C(9)–C(10)	1.535(8)	C(10)–C(11)	1.536(8)
C(11)–C(13)	1.536(8)	C(11)–C(12)	1.575(8)
C(12)–C(15)	1.509(8)	C(12)–C(16)	1.519(7)
C(17)–C(18)	1.567(7)	C(17)–C(22)	1.586(7)
C(18)–C(24)	1.516(7)	C(18)–C(23)	1.519(8)
C(18)–C(19)	1.553(7)	C(19)–C(20)	1.540(8)
C(20)–C(21)	1.534(7)	C(21)–C(22)	1.545(7)
C(21)–C(23)	1.546(7)	C(22)–C(26)	1.518(8)
C(22)–C(25)	1.544(7)		
O(1)–C(1)–N(2)	122.2(5)	O(1)–C(1)–C(6)	116.3(4)
N(2)–C(1)–C(6)	121.3(4)	C(1)–N(2)–C(7)	119.3(4)
C(1)–N(2)–C(3)	117.9(4)	C(7)–N(2)–C(3)	121.8(4)
N(2)–C(3)–C(4)	112.1(4)	N(5)–C(4)–C(3)	109.6(4)
C(17)–N(5)–C(4)	120.6(4)	C(17)–N(5)–C(6)	113.1(4)
C(4)–N(5)–C(6)	109.5(4)	N(5)–C(6)–C(1)	117.7(4)
N(2)–C(7)–C(8)	120.0(4)	N(2)–C(7)–C(12)	118.1(4)
C(8)–C(7)–C(12)	104.8(4)	C(9)–C(8)–C(14)	114.8(5)
C(9)–C(8)–C(13)	100.4(5)	C(14)–C(8)–C(13)	116.5(4)
C(9)–C(8)–C(7)	113.7(4)	C(14)–C(8)–C(7)	112.6(4)
C(13)–C(8)–C(7)	97.1(4)	C(8)–C(9)–C(10)	104.9(5)
C(9)–C(10)–C(11)	102.6(4)	C(13)–C(11)–C(10)	99.3(5)
C(13)–C(11)–C(12)	102.9(4)	C(10)–C(11)–C(12)	111.5(4)
C(15)–C(12)–C(16)	108.1(5)	C(15)–C(12)–C(11)	110.5(4)
C(16)–C(12)–C(11)	114.0(5)	C(15)–C(12)–C(7)	110.3(4)
C(16)–C(12)–C(7)	113.9(4)	C(11)–C(12)–C(7)	99.9(4)
C(11)–C(13)–C(8)	94.7(4)	N(5)–C(17)–C(18)	122.6(4)
N(5)–C(17)–C(22)	116.9(4)	C(18)–C(17)–C(22)	102.9(4)
C(24)–C(18)–C(23)	116.1(4)	C(24)–C(18)–C(19)	114.2(5)
C(23)–C(18)–C(19)	99.5(4)	C(24)–C(18)–C(17)	114.4(4)
C(23)–C(18)–C(17)	98.5(4)	C(19)–C(18)–C(17)	112.3(4)
C(20)–C(19)–C(18)	104.7(4)	C(21)–C(20)–C(19)	102.5(4)
C(20)–C(21)–C(22)	110.8(5)	C(20)–C(21)–C(23)	99.0(4)
C(22)–C(21)–C(23)	103.1(4)	C(26)–C(22)–C(25)	107.2(5)

C(26)–C(22)–C(21)	115.8(5)	C(25)–C(22)–C(21)	109.8(5)
C(26)–C(22)–C(17)	113.6(4)	C(25)–C(22)–C(17)	108.2(4)
C(21)–C(22)–C(17)	102.0(4)	C(18)–C(23)–C(21)	95.6(4)

Table 4. Anisotropic displacement parameters (\AA^2) for compound **470**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11}+\dots+2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	0.015(2)	0.060(3)	0.061(3)	0.002(2)	0.0040(18)	0.0026(19)
C(1)	0.006(2)	0.025(3)	0.049(3)	0.004(2)	0.001(2)	0.004(2)
N(2)	0.0093(18)	0.024(2)	0.033(2)	0.0020(18)	0.0027(16)	0.0076(18)
C(3)	0.008(2)	0.034(3)	0.031(3)	−0.006(2)	0.000(2)	0.007(2)
C(4)	0.010(2)	0.030(3)	0.038(3)	−0.006(2)	0.000(2)	0.005(2)
N(5)	0.0048(17)	0.018(2)	0.034(2)	−0.0036(18)	−0.0004(16)	−0.0027(16)
C(6)	0.009(2)	0.034(3)	0.042(3)	0.000(3)	−0.002(2)	0.009(2)
C(7)	0.007(2)	0.017(2)	0.045(3)	−0.005(2)	0.0026(19)	0.004(2)
C(8)	0.029(3)	0.021(3)	0.030(3)	0.002(2)	−0.003(2)	−0.011(2)
C(9)	0.026(3)	0.032(3)	0.043(3)	0.005(3)	−0.005(2)	0.009(3)
C(10)	0.020(3)	0.040(4)	0.045(3)	0.003(3)	−0.012(2)	−0.005(3)
C(11)	0.033(3)	0.024(3)	0.031(3)	−0.005(2)	−0.001(2)	0.001(2)
C(12)	0.017(3)	0.023(3)	0.036(3)	−0.003(2)	0.004(2)	−0.008(2)
C(13)	0.034(3)	0.035(3)	0.034(3)	0.008(3)	0.000(3)	−0.008(3)
C(14)	0.033(3)	0.021(3)	0.046(3)	0.000(2)	0.004(3)	−0.015(2)
C(15)	0.034(3)	0.030(3)	0.046(4)	−0.009(3)	0.005(3)	0.007(3)
C(16)	0.031(3)	0.023(3)	0.053(4)	−0.004(3)	0.000(3)	−0.009(3)
C(17)	0.009(2)	0.015(2)	0.039(3)	−0.003(2)	0.000(2)	−0.001(2)
C(18)	0.016(2)	0.017(3)	0.038(3)	0.005(2)	0.000(2)	−0.001(2)
C(19)	0.020(3)	0.027(3)	0.039(3)	0.002(2)	0.004(2)	−0.017(2)
C(20)	0.014(2)	0.033(3)	0.051(3)	−0.005(3)	0.005(2)	−0.008(2)
C(21)	0.023(3)	0.022(3)	0.036(3)	−0.003(2)	0.002(2)	0.003(2)
C(22)	0.027(3)	0.016(3)	0.033(3)	0.000(2)	0.004(2)	0.003(2)
C(23)	0.018(3)	0.025(3)	0.041(3)	0.008(2)	−0.002(2)	0.006(2)
C(24)	0.036(3)	0.020(3)	0.043(3)	0.004(2)	−0.001(3)	0.004(2)
C(25)	0.039(4)	0.027(3)	0.056(4)	−0.008(3)	0.003(3)	−0.011(3)
C(26)	0.049(4)	0.029(3)	0.047(4)	−0.003(3)	0.003(3)	0.005(3)

Table 5. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for compound **470**.

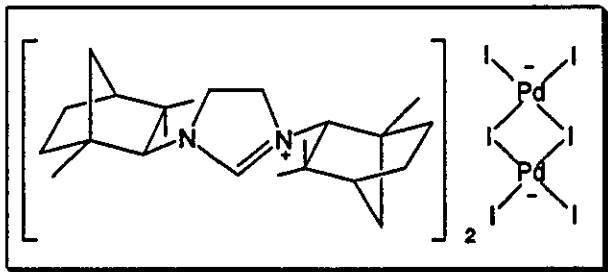
	x	y	z	U_{eq}
H(3A)	0.4564	0.4975	0.3913	0.029
H(3B)	0.5615	0.6099	0.4122	0.029
H(4A)	0.4324	0.4993	0.4766	0.031
H(4B)	0.5731	0.3949	0.4597	0.031
H(6A)	0.9680	0.4150	0.4796	0.034
H(6B)	1.0361	0.5446	0.4787	0.034
H(7)	0.9350	0.5013	0.3269	0.027
H(9A)	0.4147	0.6720	0.2851	0.040
H(9B)	0.4008	0.5899	0.3319	0.040
H(10A)	0.3484	0.5260	0.2350	0.042
H(10B)	0.3185	0.4458	0.2822	0.042
H(11)	0.6293	0.3970	0.2269	0.035
H(13A)	0.7055	0.6053	0.2255	0.042
H(13B)	0.9018	0.5394	0.2486	0.042
H(14A)	0.7386	0.7347	0.3503	0.050
H(14B)	0.7550	0.7706	0.2941	0.050
H(14C)	0.9410	0.7048	0.3197	0.050
H(15A)	0.8471	0.2466	0.2755	0.056
H(15B)	0.9675	0.2957	0.3219	0.056
H(15C)	0.9873	0.3571	0.2700	0.056
H(16A)	0.6209	0.2857	0.3608	0.053
H(16B)	0.5101	0.2553	0.3103	0.053
H(16C)	0.4388	0.3640	0.3408	0.053
H(17)	0.8842	0.5173	0.5515	0.025
H(19A)	0.3719	0.3985	0.5342	0.035
H(19B)	0.3851	0.3094	0.5786	0.035
H(20A)	0.2451	0.5279	0.5865	0.039
H(20B)	0.2783	0.4424	0.6318	0.039
H(21)	0.5282	0.5864	0.6478	0.032
H(23A)	0.8319	0.4622	0.6287	0.034
H(23B)	0.6419	0.3818	0.6452	0.034
H(24A)	0.7322	0.2301	0.5737	0.049
H(24B)	0.9276	0.3062	0.5602	0.049
H(24C)	0.7582	0.2789	0.5195	0.049
H(25A)	0.9002	0.6497	0.6088	0.061
H(25B)	0.7317	0.7481	0.6121	0.061
H(25C)	0.8564	0.7286	0.5624	0.061

H(26A)	0.5416	0.7164	0.5178	0.063
H(26B)	0.4027	0.7297	0.5657	0.063
H(26C)	0.3690	0.6241	0.5300	0.063

Table 6. Torsion angles [°] for compound **470**.

O(1)–C(1)–N(2)–C(7)	–7.5(8)	C(6)–C(1)–N(2)–C(7)	177.4(5)
O(1)–C(1)–N(2)–C(3)	–176.5(5)	C(6)–C(1)–N(2)–C(3)	8.3(7)
C(1)–N(2)–C(3)–C(4)	–33.2(6)	C(7)–N(2)–C(3)–C(4)	158.0(4)
N(2)–C(3)–C(4)–N(5)	60.2(6)	C(3)–C(4)–N(5)–C(17)	166.0(4)
C(3)–C(4)–N(5)–C(6)	–60.0(5)	C(17)–N(5)–C(6)–C(1)	173.2(4)
C(4)–N(5)–C(6)–C(1)	35.6(6)	O(1)–C(1)–C(6)–N(5)	175.0(5)
N(2)–C(1)–C(6)–N(5)	–9.6(8)	C(1)–N(2)–C(7)–C(8)	–123.0(5)
C(3)–N(2)–C(7)–C(8)	45.7(7)	C(1)–N(2)–C(7)–C(12)	107.0(5)
C(3)–N(2)–C(7)–C(12)	–84.4(6)	N(2)–C(7)–C(8)–C(9)	–74.6(6)
C(12)–C(7)–C(8)–C(9)	61.1(5)	N(2)–C(7)–C(8)–C(14)	58.1(6)
C(12)–C(7)–C(8)–C(14)	–166.3(4)	N(2)–C(7)–C(8)–C(13)	–179.3(4)
C(12)–C(7)–C(8)–C(13)	–43.6(5)	C(14)–C(8)–C(9)–C(10)	158.4(5)
C(13)–C(8)–C(9)–C(10)	32.6(6)	C(7)–C(8)–C(9)–C(10)	–70.0(6)
C(8)–C(9)–C(10)–C(11)	3.8(6)	C(9)–C(10)–C(11)–C(13)	–38.8(5)
C(9)–C(10)–C(11)–C(12)	69.2(6)	C(13)–C(11)–C(12)–C(15)	–87.1(5)
C(10)–C(11)–C(12)–C(15)	167.3(5)	C(13)–C(11)–C(12)–C(16)	151.0(5)
C(10)–C(11)–C(12)–C(16)	45.4(6)	C(13)–C(11)–C(12)–C(7)	29.1(5)
C(10)–C(11)–C(12)–C(7)	–76.5(5)	N(2)–C(7)–C(12)–C(15)	–97.9(5)
C(8)–C(7)–C(12)–C(15)	125.3(5)	N(2)–C(7)–C(12)–C(16)	23.9(6)
C(8)–C(7)–C(12)–C(16)	–112.9(5)	N(2)–C(7)–C(12)–C(11)	145.8(4)
C(8)–C(7)–C(12)–C(11)	9.0(5)	C(10)–C(11)–C(13)–C(8)	58.1(5)
C(12)–C(11)–C(13)–C(8)	–56.7(5)	C(9)–C(8)–C(13)–C(11)	–55.7(5)
C(14)–C(8)–C(13)–C(11)	179.7(5)	C(7)–C(8)–C(13)–C(11)	60.1(5)
C(4)–N(5)–C(17)–C(18)	40.1(6)	C(6)–N(5)–C(17)–C(18)	–92.3(5)
C(4)–N(5)–C(17)–C(22)	–88.4(5)	C(6)–N(5)–C(17)–C(22)	139.2(4)
N(5)–C(17)–C(18)–C(24)	58.7(6)	C(22)–C(17)–C(18)–C(24)	–167.0(5)
N(5)–C(17)–C(18)–C(23)	–177.5(4)	C(22)–C(17)–C(18)–C(23)	–43.2(5)
N(5)–C(17)–C(18)–C(19)	–73.5(6)	C(22)–C(17)–C(18)–C(19)	60.8(5)
C(24)–C(18)–C(19)–C(20)	156.4(5)	C(23)–C(18)–C(19)–C(20)	32.0(5)
C(17)–C(18)–C(19)–C(20)	–71.3(6)	C(18)–C(19)–C(20)–C(21)	4.9(6)
C(19)–C(20)–C(21)–C(22)	68.5(5)	C(19)–C(20)–C(21)–C(23)	–39.3(5)
C(20)–C(21)–C(22)–C(26)	45.9(6)	C(23)–C(21)–C(22)–C(26)	151.0(5)
C(20)–C(21)–C(22)–C(25)	167.5(4)	C(23)–C(21)–C(22)–C(25)	–87.4(5)
C(20)–C(21)–C(22)–C(17)	–77.9(5)	C(23)–C(21)–C(22)–C(17)	27.1(5)
N(5)–C(17)–C(22)–C(26)	21.5(6)	C(18)–C(17)–C(22)–C(26)	–115.9(5)
N(5)–C(17)–C(22)–C(25)	–97.4(5)	C(18)–C(17)–C(22)–C(25)	125.2(5)
N(5)–C(17)–C(22)–C(21)	146.9(4)	C(18)–C(17)–C(22)–C(21)	9.4(5)
C(24)–C(18)–C(23)–C(21)	–178.6(5)	C(19)–C(18)–C(23)–C(21)	–55.6(5)
C(17)–C(18)–C(23)–C(21)	58.9(4)	C(20)–C(21)–C(23)–C(18)	59.5(5)
C(22)–C(21)–C(23)–C(18)	–54.4(5)		

8.1.6 X-Ray crystallography data of bis-{1,3-bis-[(1R,2R,4S)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-4,5-dihydro-3H-imidazol-1-ium} diiodo-μμ'-diodo-dipalladium, 482



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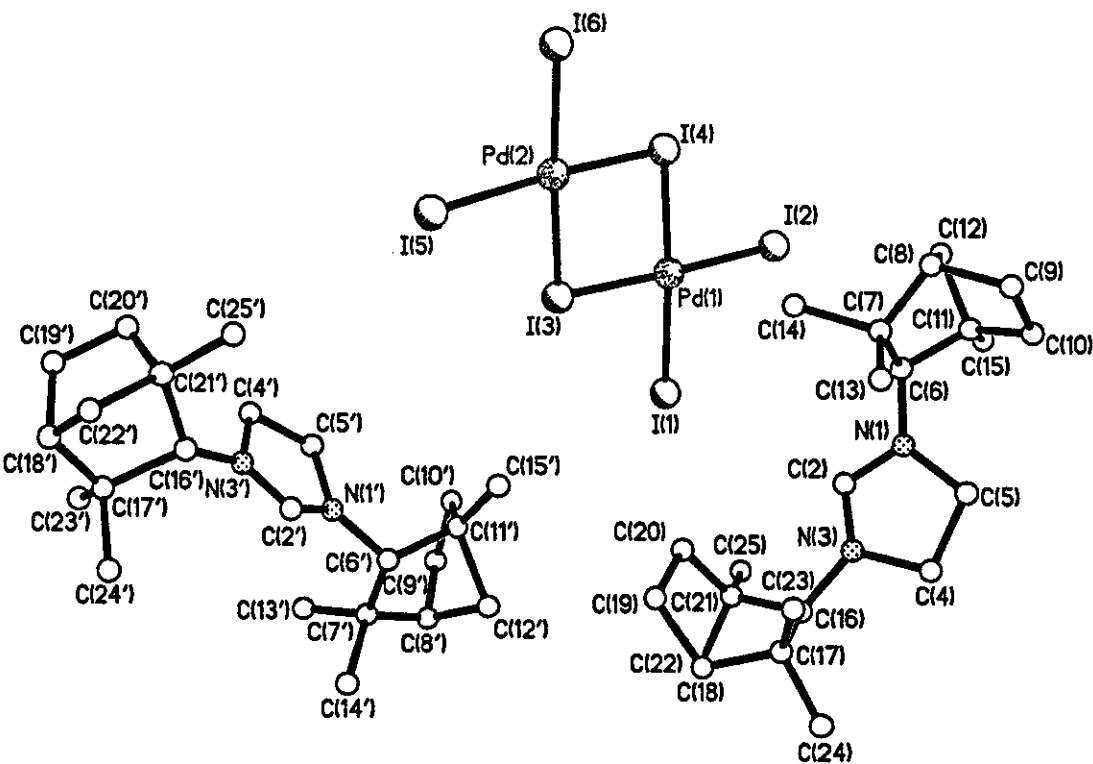


Table 1. Crystal data and structure refinement for compound **482**.

Chemical formula	$C_{46}H_{78}I_6N_4Pd_2$	
Formula weight	1661.32	
Temperature	150(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	tetragonal, $P4_1$	
Unit cell parameters	$a = 16.6972(11)$ Å	$\alpha = 90^\circ$
	$b = 16.6972(11)$ Å	$\beta = 90^\circ$
	$c = 19.9011(18)$ Å	$\gamma = 90^\circ$
Cell volume	5548.4(7) Å ³	
Z	4	
Calculated density	1.989 g/cm ³	
Absorption coefficient μ	4.020 mm ⁻¹	
F(000)	3168	
Crystal colour and size	orange, 0.38 × 0.09 × 0.07 mm ³	
Reflections for cell refinement	8784 (θ range 2.38 to 26.92°)	
Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames	
θ range for data collection	1.59 to 24.99°	
Index ranges	h -19 to 19, k -19 to 19, l -23 to 23	
Completeness to $\theta = 24.99^\circ$	100.0 %	
Intensity decay	0%	
Reflections collected	39784	
Independent reflections	9716 ($R_{int} = 0.0529$)	
Reflections with $F^2 > 2\sigma$	6237	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.310 and 0.766	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0001, 118.7748	
Data / restraints / parameters	9716 / 243 / 535	
Final R indices [$F^2 > 2\sigma$]	$R1 = 0.0634$, $wR2 = 0.1233$	
R indices (all data)	$R1 = 0.1178$, $wR2 = 0.1540$	
Goodness-of-fit on F^2	1.104	
Absolute structure parameter	0.01(7)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	1.546 and -1.352 e Å ⁻³	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for compound **482**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Pd(1)	0.01786(9)	0.59463(8)	0.49632(9)	0.0428(3)
Pd(2)	−0.08606(10)	0.39151(9)	0.50540(9)	0.0526(4)
I(1)	0.16885(9)	0.63353(9)	0.49845(12)	0.0841(6)
I(2)	−0.02809(8)	0.74340(8)	0.49457(7)	0.0560(4)
I(3)	0.05889(9)	0.44490(8)	0.49553(9)	0.0657(4)
I(4)	−0.12902(8)	0.54130(8)	0.49932(10)	0.0611(4)
I(5)	−0.02877(10)	0.24501(8)	0.50601(8)	0.0687(4)
I(6)	−0.23448(10)	0.34487(9)	0.51887(7)	0.0697(5)
N(1)	0.1106(8)	0.7430(9)	0.7533(8)	0.045(4)
C(2)	0.1718(10)	0.7038(10)	0.7266(9)	0.038(4)
N(3)	0.2349(9)	0.7021(9)	0.7637(9)	0.048(4)
C(4)	0.2278(11)	0.7565(10)	0.8223(8)	0.040(4)
C(5)	0.1363(11)	0.7814(12)	0.8175(9)	0.044(5)
C(6)	0.0305(11)	0.7395(11)	0.7247(8)	0.041(5)
C(7)	−0.0202(11)	0.6667(11)	0.7482(13)	0.057(5)
C(8)	−0.1021(10)	0.7050(12)	0.7543(11)	0.054(5)
C(9)	−0.1067(13)	0.7515(15)	0.8200(10)	0.061(6)
C(10)	−0.0505(12)	0.8217(13)	0.8056(12)	0.061(6)
C(11)	−0.0244(11)	0.8156(13)	0.7321(9)	0.050(5)
C(12)	−0.1000(12)	0.7726(14)	0.7033(10)	0.057(6)
C(13)	0.0125(12)	0.6218(12)	0.8069(10)	0.052(5)
C(14)	−0.0205(14)	0.6035(13)	0.6868(12)	0.068(7)
C(15)	0.0011(16)	0.8854(13)	0.6948(12)	0.072(7)
C(16)	0.3154(10)	0.6654(11)	0.7540(11)	0.045(5)
C(17)	0.3353(13)	0.5973(13)	0.8042(11)	0.057(6)
C(18)	0.3810(13)	0.5401(11)	0.7581(10)	0.055(5)
C(19)	0.3186(14)	0.4886(13)	0.7172(10)	0.067(7)
C(20)	0.2844(13)	0.5540(12)	0.6711(10)	0.054(5)
C(21)	0.3357(12)	0.6307(14)	0.6833(10)	0.055(6)
C(22)	0.4153(12)	0.5936(14)	0.7022(11)	0.060(6)
C(23)	0.2640(13)	0.5599(14)	0.8379(11)	0.058(6)
C(24)	0.3953(13)	0.6268(15)	0.8563(11)	0.070(7)
C(25)	0.3349(13)	0.6930(13)	0.6269(10)	0.057(5)
N(1')	0.3222(12)	0.2000(10)	0.5129(9)	0.067(4)
C(2')	0.3068(15)	0.1293(14)	0.5424(13)	0.074(6)
N(3')	0.2709(11)	0.0799(9)	0.5085(10)	0.061(4)

C(4')	0.241(2)	0.1162(17)	0.4449(17)	0.129(9)
C(5')	0.276(2)	0.2008(19)	0.4478(17)	0.126(9)
C(6')	0.3675(15)	0.2646(14)	0.5422(15)	0.081(5)
C(7')	0.4549(14)	0.2775(16)	0.5087(16)	0.085(5)
C(8')	0.4613(16)	0.3617(16)	0.5076(17)	0.092(6)
C(9')	0.418(2)	0.3977(19)	0.4513(18)	0.113(8)
C(10')	0.3288(18)	0.3827(18)	0.4741(16)	0.107(7)
C(11')	0.3273(17)	0.3474(15)	0.5401(16)	0.086(5)
C(12')	0.4126(16)	0.3942(16)	0.5674(16)	0.086(6)
C(13')	0.478(2)	0.2328(18)	0.4526(14)	0.121(11)
C(14')	0.5077(19)	0.231(2)	0.5670(15)	0.120(10)
C(15')	0.2562(15)	0.3580(15)	0.5797(16)	0.092(8)
C(16')	0.2509(15)	0.0007(13)	0.5224(17)	0.093(6)
C(17')	0.3076(13)	-0.0721(11)	0.5018(12)	0.057(4)
C(18')	0.2544(14)	-0.1397(13)	0.4959(14)	0.078(5)
C(19')	0.1966(16)	-0.1213(17)	0.4368(15)	0.087(6)
C(20')	0.1464(19)	-0.052(2)	0.4505(19)	0.123(8)
C(21')	0.1710(16)	-0.0383(15)	0.514(2)	0.105(7)
C(22')	0.198(2)	-0.1296(15)	0.5525(16)	0.108(7)
C(23')	0.352(2)	-0.064(3)	0.4368(16)	0.148(12)
C(24')	0.3752(15)	-0.075(2)	0.5520(13)	0.101(10)
C(25')	0.1031(19)	0.006(2)	0.5623(18)	0.133(11)

Table 3. Bond lengths [Å] and angles [°] for compound **482**.

Pd(1)–I(3)	2.592(2)	Pd(1)–I(2)	2.600(2)
Pd(1)–I(1)	2.604(2)	Pd(1)–I(4)	2.6098(19)
Pd(2)–I(3)	2.587(2)	Pd(2)–I(4)	2.605(2)
Pd(2)–I(6)	2.611(2)	Pd(2)–I(5)	2.627(2)
N(1)–C(2)	1.32(2)	N(1)–C(6)	1.45(2)
N(1)–C(5)	1.49(2)	C(2)–N(3)	1.29(2)
N(3)–C(4)	1.48(2)	N(3)–C(16)	1.49(2)
C(4)–C(5)	1.59(2)	C(6)–C(7)	1.55(2)
C(6)–C(11)	1.57(3)	C(7)–C(13)	1.49(3)
C(7)–C(8)	1.52(2)	C(7)–C(14)	1.62(3)
C(8)–C(12)	1.52(3)	C(8)–C(9)	1.52(3)
C(9)–C(10)	1.53(3)	C(10)–C(11)	1.53(3)
C(11)–C(15)	1.45(3)	C(11)–C(12)	1.56(3)
C(16)–C(17)	1.55(3)	C(16)–C(21)	1.56(3)
C(17)–C(23)	1.50(3)	C(17)–C(24)	1.52(3)
C(17)–C(18)	1.53(3)	C(18)–C(22)	1.54(3)
C(18)–C(19)	1.58(3)	C(19)–C(20)	1.54(3)
C(20)–C(21)	1.56(3)	C(21)–C(22)	1.51(3)
C(21)–C(25)	1.53(3)	N(1')–C(2')	1.34(3)
N(1')–C(6')	1.44(3)	N(1')–C(5')	1.51(3)
C(2')–N(3')	1.22(3)	N(3')–C(16')	1.39(3)
N(3')–C(4')	1.49(3)	C(4')–C(5')	1.53(4)
C(6')–C(11')	1.54(3)	C(6')–C(7')	1.62(4)
C(7')–C(13')	1.40(4)	C(7')–C(8')	1.41(3)
C(7')–C(14')	1.65(4)	C(8')–C(9')	1.47(4)
C(8')–C(12')	1.54(4)	C(9')–C(10')	1.57(4)
C(10')–C(11')	1.44(4)	C(11')–C(15')	1.44(3)
C(11')–C(12')	1.71(4)	C(16')–C(21')	1.49(3)
C(16')–C(17')	1.59(3)	C(17')–C(18')	1.44(3)
C(17')–C(23')	1.50(4)	C(17')–C(24')	1.51(3)
C(18')–C(22')	1.48(4)	C(18')–C(19')	1.55(4)
C(19')–C(20')	1.46(4)	C(20')–C(21')	1.36(4)
C(21')–C(25')	1.65(4)	C(21')–C(22')	1.76(4)
I(3)–Pd(1)–I(2)	177.85(8)	I(3)–Pd(1)–I(1)	89.13(7)
I(2)–Pd(1)–I(1)	92.73(6)	I(3)–Pd(1)–I(4)	85.38(6)
I(2)–Pd(1)–I(4)	92.81(7)	I(1)–Pd(1)–I(4)	174.06(8)
I(3)–Pd(2)–I(4)	85.60(6)	I(3)–Pd(2)–I(6)	176.84(9)
I(4)–Pd(2)–I(6)	91.71(8)	I(3)–Pd(2)–I(5)	88.88(7)
I(4)–Pd(2)–I(5)	174.13(9)	I(6)–Pd(2)–I(5)	93.86(7)

Pd(2)–I(3)–Pd(1)	94.85(7)	Pd(2)–I(4)–Pd(1)	94.01(6)
C(2)–N(1)–C(6)	122.2(15)	C(2)–N(1)–C(5)	109.5(14)
C(6)–N(1)–C(5)	128.1(14)	N(3)–C(2)–N(1)	114.4(16)
C(2)–N(3)–C(4)	111.8(15)	C(2)–N(3)–C(16)	132.4(17)
C(4)–N(3)–C(16)	115.1(16)	N(3)–C(4)–C(5)	100.9(13)
N(1)–C(5)–C(4)	102.6(13)	N(1)–C(6)–C(7)	114.5(16)
N(1)–C(6)–C(11)	117.8(15)	C(7)–C(6)–C(11)	106.6(14)
C(13)–C(7)–C(8)	118.7(19)	C(13)–C(7)–C(6)	115.5(17)
C(8)–C(7)–C(6)	100.7(14)	C(13)–C(7)–C(14)	105.4(15)
C(8)–C(7)–C(14)	109.5(18)	C(6)–C(7)–C(14)	106.6(17)
C(7)–C(8)–C(12)	103.9(15)	C(7)–C(8)–C(9)	109.2(19)
C(12)–C(8)–C(9)	101.3(17)	C(8)–C(9)–C(10)	101.5(16)
C(9)–C(10)–C(11)	107.6(18)	C(15)–C(11)–C(10)	121(2)
C(15)–C(11)–C(12)	114.8(18)	C(10)–C(11)–C(12)	98.7(15)
C(15)–C(11)–C(6)	115.6(16)	C(10)–C(11)–C(6)	108.1(16)
C(12)–C(11)–C(6)	93.8(15)	C(8)–C(12)–C(11)	96.6(16)
N(3)–C(16)–C(17)	114.3(15)	N(3)–C(16)–C(21)	117.7(16)
C(17)–C(16)–C(21)	105.2(16)	C(23)–C(17)–C(24)	110.7(18)
C(23)–C(17)–C(18)	113.8(19)	C(24)–C(17)–C(18)	106.3(18)
C(23)–C(17)–C(16)	115.0(18)	C(24)–C(17)–C(16)	109.9(18)
C(18)–C(17)–C(16)	100.3(15)	C(17)–C(18)–C(22)	104.9(16)
C(17)–C(18)–C(19)	108.7(18)	C(22)–C(18)–C(19)	101.0(17)
C(20)–C(19)–C(18)	99.5(17)	C(19)–C(20)–C(21)	106.7(19)
C(22)–C(21)–C(25)	117.8(18)	C(22)–C(21)–C(16)	96.8(16)
C(25)–C(21)–C(16)	114.0(17)	C(22)–C(21)–C(20)	100.7(18)
C(25)–C(21)–C(20)	116.0(18)	C(16)–C(21)–C(20)	109.1(16)
C(21)–C(22)–C(18)	95.2(16)	C(2')–N(1')–C(6')	125(2)
C(2')–N(1')–C(5')	107(2)	C(6')–N(1')–C(5')	128(2)
N(3')–C(2')–N(1')	116(2)	C(2')–N(3')–C(16')	131(2)
C(2')–N(3')–C(4')	111(2)	C(16')–N(3')–C(4')	118(2)
N(3')–C(4')–C(5')	103(2)	N(1')–C(5')–C(4')	103(2)
N(1')–C(6')–C(11')	116(2)	N(1')–C(6')–C(7')	114(2)
C(11')–C(6')–C(7')	105(2)	C(13')–C(7')–C(8')	120(3)
C(13')–C(7')–C(6')	121(3)	C(8')–C(7')–C(6')	102(2)
C(13')–C(7')–C(14')	99(2)	C(8')–C(7')–C(14')	116(2)
C(6')–C(7')–C(14')	97(2)	C(7')–C(8')–C(9')	113(3)
C(7')–C(8')–C(12')	107(2)	C(9')–C(8')–C(12')	101(2)
C(8')–C(9')–C(10')	101(2)	C(11')–C(10')–C(9')	110(3)
C(15')–C(11')–C(10')	118(3)	C(15')–C(11')–C(6')	117(2)
C(10')–C(11')–C(6')	113(2)	C(15')–C(11')–C(12')	117(2)
C(10')–C(11')–C(12')	95(2)	C(6')–C(11')–C(12')	92(2)
C(8')–C(12')–C(11')	92(2)	N(3')–C(16')–C(21')	127(2)
N(3')–C(16')–C(17')	122(2)	C(21')–C(16')–C(17')	99.8(18)

C(18')-C(17')-C(23')	108(2)	C(18')-C(17')-C(24')	120(2)
C(23')-C(17')-C(24')	102(2)	C(18')-C(17')-C(16')	104.7(19)
C(23')-C(17')-C(16')	117(3)	C(24')-C(17')-C(16')	107.2(19)
C(17')-C(18')-C(22')	104(2)	C(17')-C(18')-C(19')	107(2)
C(22')-C(18')-C(19')	99(2)	C(20')-C(19')-C(18')	112(2)
C(21')-C(20')-C(19')	98(3)	C(20')-C(21')-C(16')	116(3)
C(20')-C(21')-C(25')	114(3)	C(16')-C(21')-C(25')	111(2)
C(20')-C(21')-C(22')	110(3)	C(16')-C(21')-C(22')	96(2)
C(25')-C(21')-C(22')	108(3)	C(18')-C(22')-C(21')	86(2)

Table 4. Anisotropic displacement parameters (Å²) for compound **482**. 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
Pd(1)	0.0559(9)	0.0357(7)	0.0367(7)	0.0021(7)	-0.0089(7)	-0.0122(7)
Pd(2)	0.0803(11)	0.0464(8)	0.0310(7)	0.0011(7)	-0.0077(8)	-0.0210(8)
I(1)	0.0624(10)	0.0574(9)	0.1325(17)	-0.0093(11)	-0.0197(12)	-0.0145(7)
I(2)	0.0695(9)	0.0424(7)	0.0562(8)	0.0017(7)	0.0085(8)	-0.0034(6)
I(3)	0.0789(10)	0.0418(7)	0.0766(10)	0.0034(8)	-0.0187(9)	-0.0138(7)
I(4)	0.0602(9)	0.0512(8)	0.0719(9)	0.0046(8)	-0.0046(9)	-0.0160(7)
I(5)	0.1072(12)	0.0497(8)	0.0491(8)	0.0026(7)	-0.0033(9)	-0.0157(8)
I(6)	0.0905(12)	0.0646(9)	0.0539(9)	0.0031(7)	0.0089(8)	-0.0271(8)
N(1)	0.034(8)	0.076(11)	0.025(7)	-0.021(8)	0.000(7)	-0.003(7)
C(2)	0.037(10)	0.036(10)	0.042(10)	0.001(8)	-0.007(8)	-0.002(8)
N(3)	0.035(8)	0.049(9)	0.060(11)	0.001(8)	0.014(8)	-0.002(7)
C(4)	0.053(12)	0.036(10)	0.031(9)	-0.004(8)	-0.006(8)	-0.011(9)
C(5)	0.039(11)	0.058(13)	0.037(10)	-0.008(9)	0.003(8)	-0.004(9)
C(6)	0.044(11)	0.056(12)	0.022(9)	-0.002(8)	0.006(8)	-0.011(9)
C(7)	0.051(11)	0.049(12)	0.070(14)	0.026(12)	0.006(12)	0.004(9)
C(8)	0.031(9)	0.083(14)	0.048(12)	-0.003(12)	0.022(10)	-0.007(9)
C(9)	0.050(13)	0.096(18)	0.036(11)	0.012(11)	-0.006(9)	-0.001(12)
C(10)	0.032(11)	0.049(13)	0.103(18)	-0.013(12)	0.021(11)	0.001(10)
C(11)	0.028(10)	0.083(15)	0.039(11)	-0.003(10)	0.012(8)	0.005(9)
C(12)	0.047(13)	0.083(17)	0.042(12)	0.008(11)	0.004(9)	0.019(11)
C(13)	0.053(13)	0.056(13)	0.046(12)	0.007(10)	-0.009(10)	-0.015(10)
C(14)	0.073(17)	0.059(15)	0.073(16)	-0.020(12)	-0.001(12)	-0.013(12)
C(15)	0.092(19)	0.057(15)	0.067(15)	0.011(12)	-0.005(13)	0.033(13)
C(16)	0.035(9)	0.046(10)	0.054(12)	0.026(10)	0.003(10)	0.011(8)
C(17)	0.058(14)	0.060(14)	0.052(13)	0.012(11)	0.015(11)	0.002(11)
C(18)	0.077(14)	0.048(12)	0.039(12)	0.015(10)	-0.002(11)	0.012(10)
C(19)	0.088(17)	0.071(16)	0.043(12)	0.014(11)	0.003(11)	0.047(13)
C(20)	0.071(15)	0.041(12)	0.051(12)	-0.004(9)	0.017(11)	0.005(11)
C(21)	0.048(13)	0.070(15)	0.048(12)	0.007(11)	0.010(10)	0.011(11)
C(22)	0.043(12)	0.076(16)	0.060(14)	0.026(12)	0.005(10)	0.006(11)
C(23)	0.061(14)	0.058(14)	0.055(13)	0.004(11)	-0.008(11)	0.001(11)
C(24)	0.061(15)	0.090(18)	0.059(14)	0.015(13)	-0.016(12)	0.013(13)
C(25)	0.057(13)	0.076(15)	0.038(11)	0.008(10)	0.000(9)	0.008(11)
N(1')	0.098(11)	0.048(7)	0.056(10)	-0.002(7)	0.003(9)	-0.004(8)
C(2')	0.084(15)	0.053(10)	0.085(13)	-0.013(8)	-0.010(11)	-0.008(10)

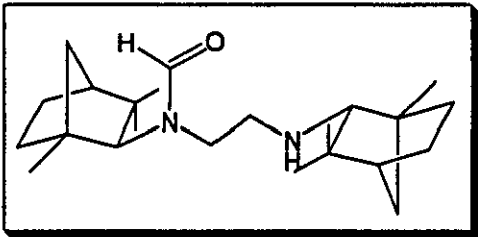
N(3')	0.083(11)	0.043(6)	0.057(9)	-0.023(7)	-0.006(9)	0.006(6)
C(4')	0.19(2)	0.071(14)	0.127(18)	0.007(12)	-0.080(16)	-0.003(15)
C(5')	0.17(2)	0.093(14)	0.114(17)	0.018(12)	-0.061(16)	-0.036(17)
C(6')	0.082(11)	0.058(8)	0.104(14)	-0.022(9)	-0.005(9)	-0.007(7)
C(7')	0.064(9)	0.089(10)	0.101(15)	-0.033(10)	-0.021(10)	0.011(8)
C(8')	0.084(10)	0.090(10)	0.101(15)	-0.014(11)	0.026(11)	-0.016(10)
C(9')	0.131(17)	0.081(15)	0.126(14)	0.022(13)	0.004(13)	-0.051(15)
C(10')	0.116(13)	0.099(16)	0.107(14)	-0.012(12)	0.025(11)	0.054(14)
C(11')	0.080(10)	0.061(9)	0.115(15)	-0.014(11)	0.022(11)	-0.002(9)
C(12')	0.072(12)	0.059(12)	0.126(13)	-0.019(12)	0.038(11)	-0.020(11)
C(13')	0.19(3)	0.097(17)	0.072(14)	0.013(13)	0.024(15)	0.07(2)
C(14')	0.102(16)	0.17(3)	0.088(15)	0.012(18)	0.007(16)	0.04(2)
C(15')	0.064(12)	0.058(15)	0.15(2)	0.003(16)	0.027(14)	-0.008(10)
C(16')	0.087(10)	0.039(7)	0.153(18)	-0.003(9)	-0.028(11)	-0.003(7)
C(17')	0.078(9)	0.042(7)	0.052(10)	-0.010(9)	-0.019(8)	-0.005(7)
C(18')	0.089(12)	0.056(8)	0.088(13)	-0.025(11)	-0.001(9)	-0.014(7)
C(19')	0.070(14)	0.074(15)	0.117(13)	-0.021(12)	-0.020(11)	-0.024(10)
C(20')	0.086(17)	0.125(19)	0.158(16)	-0.039(14)	-0.021(13)	0.003(12)
C(21')	0.074(10)	0.064(10)	0.177(19)	-0.053(12)	-0.040(13)	0.003(7)
C(22')	0.16(2)	0.046(10)	0.117(13)	-0.027(11)	0.052(14)	-0.032(10)
C(23')	0.17(3)	0.20(3)	0.072(13)	0.01(2)	0.027(15)	-0.04(2)
C(24')	0.052(13)	0.18(3)	0.076(14)	-0.060(17)	-0.010(11)	0.027(13)
C(25')	0.088(16)	0.16(3)	0.15(2)	-0.03(2)	-0.025(17)	0.033(18)

Table 5. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for compound **482**.

	x	y	z	U_{eq}
H(2)	0.1693	0.6791	0.6837	0.046
H(4A)	0.2636	0.8035	0.8180	0.048
H(4B)	0.2395	0.7283	0.8650	0.048
H(5A)	0.1054	0.7605	0.8561	0.053
H(5B)	0.1302	0.8403	0.8154	0.053
H(6)	0.0383	0.7320	0.6753	0.049
H(8)	-0.1475	0.6667	0.7475	0.065
H(9A)	-0.0875	0.7189	0.8583	0.073
H(9B)	-0.1619	0.7700	0.8292	0.073
H(10A)	-0.0033	0.8193	0.8355	0.074
H(10B)	-0.0786	0.8731	0.8135	0.074
H(12A)	-0.1485	0.8067	0.7053	0.069
H(12B)	-0.0917	0.7530	0.6569	0.069
H(13A)	0.0693	0.6101	0.7993	0.078
H(13B)	-0.0170	0.5715	0.8124	0.078
H(13C)	0.0067	0.6543	0.8476	0.078
H(14A)	0.0331	0.5804	0.6816	0.102
H(14B)	-0.0357	0.6310	0.6452	0.102
H(14C)	-0.0591	0.5607	0.6962	0.102
H(15A)	-0.0420	0.9253	0.6948	0.108
H(15B)	0.0135	0.8699	0.6485	0.108
H(15C)	0.0489	0.9082	0.7159	0.108
H(16)	0.3553	0.7089	0.7626	0.054
H(18)	0.4224	0.5074	0.7819	0.066
H(19A)	0.3449	0.4453	0.6913	0.081
H(19B)	0.2769	0.4653	0.7467	0.081
H(20A)	0.2275	0.5643	0.6820	0.065
H(20B)	0.2881	0.5372	0.6234	0.065
H(22A)	0.4541	0.6335	0.7194	0.072
H(22B)	0.4394	0.5624	0.6651	0.072
H(23A)	0.2219	0.5504	0.8045	0.087
H(23B)	0.2437	0.5961	0.8727	0.087
H(23C)	0.2798	0.5090	0.8584	0.087
H(24A)	0.3963	0.5898	0.8944	0.105
H(24B)	0.3796	0.6802	0.8719	0.105
H(24C)	0.4487	0.6295	0.8359	0.105
H(25A)	0.3630	0.7413	0.6419	0.085

H(25B)	0.2794	0.7065	0.6156	0.085
H(25C)	0.3619	0.6710	0.5872	0.085
H(2')	0.3230	0.1183	0.5872	0.089
H(4'1)	0.1818	0.1174	0.4436	0.155
H(4'2)	0.2611	0.0867	0.4051	0.155
H(5'1)	0.3115	0.2113	0.4090	0.152
H(5'2)	0.2329	0.2416	0.4487	0.152
H(6')	0.3762	0.2509	0.5906	0.097
H(8')	0.5184	0.3799	0.5090	0.110
H(9'1)	0.4296	0.3704	0.4083	0.135
H(9'2)	0.4293	0.4556	0.4469	0.135
H(10C)	0.2992	0.4341	0.4746	0.129
H(10D)	0.3020	0.3465	0.4417	0.129
H(12C)	0.4082	0.4533	0.5677	0.103
H(12D)	0.4317	0.3743	0.6114	0.103
H(13D)	0.4512	0.2534	0.4125	0.182
H(13E)	0.4639	0.1765	0.4593	0.182
H(13F)	0.5365	0.2372	0.4466	0.182
H(14D)	0.5535	0.2040	0.5461	0.179
H(14E)	0.4739	0.1910	0.5895	0.179
H(14F)	0.5269	0.2698	0.6001	0.179
H(15D)	0.2461	0.4154	0.5860	0.138
H(15E)	0.2634	0.3325	0.6236	0.138
H(15F)	0.2105	0.3336	0.5566	0.138
H(16')	0.2567	-0.0001	0.5724	0.112
H(18')	0.2815	-0.1931	0.4937	0.093
H(19C)	0.2283	-0.1113	0.3956	0.105
H(19D)	0.1621	-0.1685	0.4286	0.105
H(20C)	0.1586	-0.0065	0.4203	0.147
H(20D)	0.0886	-0.0650	0.4481	0.147
H(22C)	0.2244	-0.1236	0.5968	0.130
H(22D)	0.1548	-0.1698	0.5540	0.130
H(23D)	0.3349	-0.1064	0.4058	0.222
H(23E)	0.4098	-0.0693	0.4452	0.222
H(23F)	0.3411	-0.0116	0.4170	0.222
H(24D)	0.3535	-0.0841	0.5970	0.152
H(24E)	0.4039	-0.0234	0.5514	0.152
H(24F)	0.4122	-0.1180	0.5402	0.152
H(25D)	0.0960	0.0614	0.5477	0.200
H(25E)	0.1210	0.0049	0.6092	0.200
H(25F)	0.0521	-0.0229	0.5584	0.200

8.1.7 X-Ray crystallography data of *N*-[(1*R*,2*R*,4*S*)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl]-*N*-{2-[(1*R*,2*R*,4*S*)-1,3,3-trimethyl-bicyclo[2.2.1]hept-2-ylamino]ethyl}-formamide, 483



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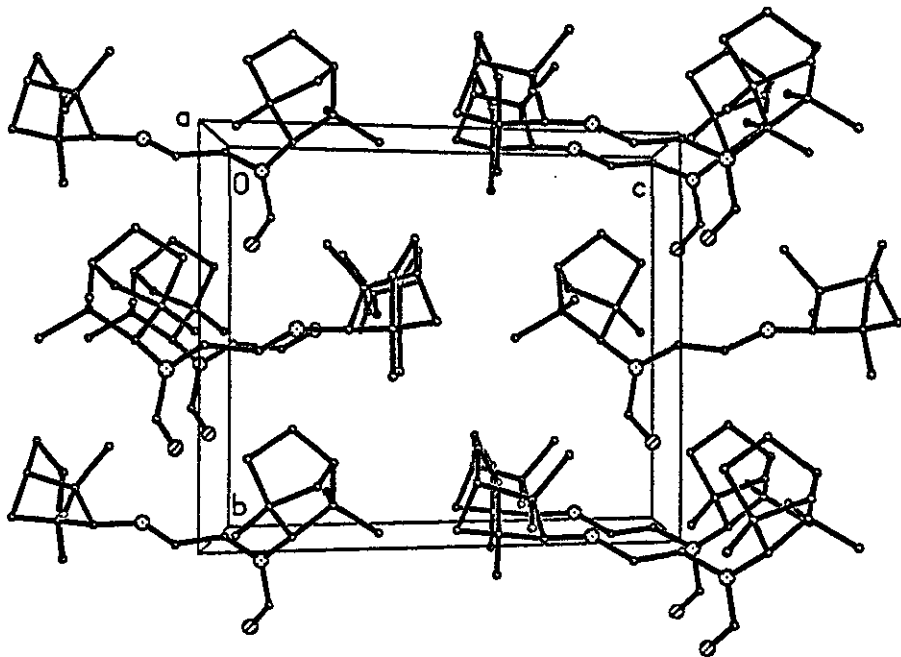
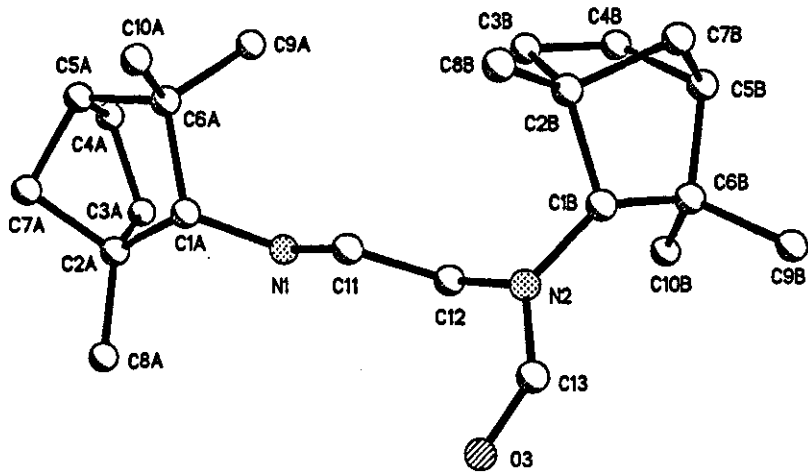


Table 1. Crystal data and structure refinement for compound **483**.

Empirical formula	$C_{23}H_{40}N_2O$	
Formula weight	360.57	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	$a = 7.6526(17)$ Å	$\alpha = 90^\circ$.
	$b = 11.086(3)$ Å	$\beta = 104.826(3)^\circ$.
	$c = 13.174(3)$ Å	$\gamma = 90^\circ$.
Volume	$1080.4(4)$ Å ³	
Z	2	
Density (calculated)	1.108 Mg/m ³	
Absorption coefficient μ	0.067 mm ⁻¹	
F(000)	400	
Crystal size	$0.62 \times 0.14 \times 0.09$ mm ³	
θ range for data collection	2.44 to 24.99° .	
Index ranges	$-9 \leq h \leq 9$, $-13 \leq k \leq 13$, $-15 \leq l \leq 15$	
Reflections collected	7424	
Independent reflections	3699 [R(int) = 0.0266]	
Completeness to $\theta = 24.99^\circ$	99.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.00000 and 0.806625	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3699 / 1 / 235	
Goodness-of-fit on F^2	1.076	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0474, wR2 = 0.1051	
R indices (all data)	R1 = 0.0592, wR2 = 0.1094	
Absolute structure parameter	0.7(19)	
Largest diff. peak and hole	0.155 and -0.185 e. Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **483**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1A)	424(3)	-177(2)	-2942(2)	31(1)
C(2A)	-1269(3)	-198(2)	-3876(2)	33(1)
C(3A)	-2232(4)	-1422(2)	-3886(2)	39(1)
C(4A)	-1050(4)	-2304(3)	-4317(2)	49(1)
C(5A)	592(4)	-1544(3)	-4350(2)	41(1)
C(6A)	1670(4)	-1184(3)	-3232(2)	45(1)
C(7A)	-368(4)	-378(2)	-4775(2)	42(1)
C(8A)	-2481(5)	886(3)	-3904(2)	53(1)
C(9A)	2017(5)	-2241(3)	-2470(3)	71(1)
C(10A)	3490(4)	-634(5)	-3279(3)	93(2)
N(1)	28(3)	-181(2)	-1913(1)	27(1)
C(11)	1458(3)	331(2)	-1084(2)	27(1)
C(12)	1014(3)	199(2)	-28(2)	24(1)
N(2)	2416(2)	743(2)	833(1)	23(1)
C(1B)	3852(3)	69(2)	1567(2)	22(1)
C(2B)	5116(3)	-788(2)	1144(2)	25(1)
C(3B)	4147(3)	-1935(2)	629(2)	28(1)
C(4B)	3759(4)	-2655(2)	1562(2)	38(1)
C(5B)	4495(3)	-1815(2)	2501(2)	31(1)
C(6B)	3294(3)	-685(2)	2456(2)	28(1)
C(7B)	6165(3)	-1308(2)	2207(2)	31(1)
C(8B)	6262(3)	-150(2)	520(2)	32(1)
C(9B)	3853(4)	14(3)	3484(2)	40(1)
C(10B)	1262(3)	-936(3)	2249(2)	40(1)
C(13)	2233(4)	1925(2)	1008(2)	30(1)
O(3)	1016(3)	2581(2)	533(1)	42(1)

Table 3. Bond lengths [Å] and angles [°] for compound **483**.

C(1A)-N(1)	1.462(3)	N(2)-C(13)	1.344(3)
C(1A)-C(2A)	1.542(3)	N(2)-C(1B)	1.468(3)
C(1A)-C(6A)	1.578(4)	C(1B)-C(2B)	1.557(3)
C(2A)-C(8A)	1.513(4)	C(1B)-C(6B)	1.584(3)
C(2A)-C(7A)	1.528(3)	C(2B)-C(8B)	1.522(3)
C(2A)-C(3A)	1.543(4)	C(2B)-C(7B)	1.537(3)
C(3A)-C(4A)	1.537(4)	C(2B)-C(3B)	1.539(3)
C(4A)-C(5A)	1.523(4)	C(3B)-C(4B)	1.557(3)
C(5A)-C(7A)	1.520(4)	C(4B)-C(5B)	1.536(3)
C(5A)-C(6A)	1.544(4)	C(5B)-C(7B)	1.533(3)
C(6A)-C(9A)	1.522(4)	C(5B)-C(6B)	1.545(3)
C(6A)-C(10A)	1.536(4)	C(6B)-C(9B)	1.525(3)
N(1)-C(11)	1.450(3)	C(6B)-C(10B)	1.534(4)
C(11)-C(12)	1.521(3)	C(13)-O(3)	1.220(3)
C(12)-N(2)	1.476(3)		
N(1)-C(1A)-C(2A)	114.11(18)	C(13)-N(2)-C(12)	116.3(2)
N(1)-C(1A)-C(6A)	120.3(2)	C(1B)-N(2)-C(12)	124.92(17)
C(2A)-C(1A)-C(6A)	103.43(19)	N(2)-C(1B)-C(2B)	120.23(17)
C(8A)-C(2A)-C(7A)	118.7(2)	N(2)-C(1B)-C(6B)	117.23(17)
C(8A)-C(2A)-C(1A)	113.1(2)	C(2B)-C(1B)-C(6B)	104.57(17)
C(7A)-C(2A)-C(1A)	99.6(2)	C(8B)-C(2B)-C(7B)	115.31(19)
C(8A)-C(2A)-C(3A)	114.2(2)	C(8B)-C(2B)-C(3B)	115.19(19)
C(7A)-C(2A)-C(3A)	100.8(2)	C(7B)-C(2B)-C(3B)	99.91(19)
C(1A)-C(2A)-C(3A)	108.8(2)	C(8B)-C(2B)-C(1B)	113.94(19)
C(4A)-C(3A)-C(2A)	103.8(2)	C(7B)-C(2B)-C(1B)	97.49(17)
C(5A)-C(4A)-C(3A)	103.1(2)	C(3B)-C(2B)-C(1B)	112.88(17)
C(7A)-C(5A)-C(4A)	99.0(2)	C(2B)-C(3B)-C(4B)	104.05(18)
C(7A)-C(5A)-C(6A)	102.8(2)	C(5B)-C(4B)-C(3B)	102.7(2)
C(4A)-C(5A)-C(6A)	111.1(2)	C(7B)-C(5B)-C(4B)	100.2(2)
C(9A)-C(6A)-C(10A)	109.0(3)	C(7B)-C(5B)-C(6B)	102.67(19)
C(9A)-C(6A)-C(5A)	113.0(3)	C(4B)-C(5B)-C(6B)	111.6(2)
C(10A)-C(6A)-C(5A)	109.5(2)	C(9B)-C(6B)-C(10B)	106.9(2)
C(9A)-C(6A)-C(1A)	113.5(2)	C(9B)-C(6B)-C(5B)	110.43(19)
C(10A)-C(6A)-C(1A)	109.8(3)	C(10B)-C(6B)-C(5B)	115.2(2)
C(5A)-C(6A)-C(1A)	101.9(2)	C(9B)-C(6B)-C(1B)	108.7(2)
C(5A)-C(7A)-C(2A)	95.58(19)	C(10B)-C(6B)-C(1B)	114.67(18)
C(11)-N(1)-C(1A)	113.69(17)	C(5B)-C(6B)-C(1B)	100.76(17)
N(1)-C(11)-C(12)	110.44(18)	C(5B)-C(7B)-C(2B)	95.32(18)
N(2)-C(12)-C(11)	111.99(17)	O(3)-C(13)-N(2)	126.3(2)
C(13)-N(2)-C(1B)	118.44(19)		

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **483**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1A)	34(1)	35(1)	27(1)	0(1)	10(1)	-10(1)
C(2A)	43(2)	29(1)	24(1)	-1(1)	4(1)	3(1)
C(3A)	32(2)	44(2)	42(2)	-12(1)	9(1)	-5(1)
C(4A)	56(2)	39(2)	53(2)	-11(1)	17(2)	-3(1)
C(5A)	42(2)	54(2)	32(2)	-7(1)	18(1)	4(1)
C(6A)	30(2)	70(2)	37(2)	-1(1)	12(1)	7(1)
C(7A)	55(2)	47(2)	25(1)	-4(1)	10(1)	-9(1)
C(8A)	76(2)	44(2)	31(2)	-2(1)	-4(2)	20(2)
C(9A)	82(2)	82(3)	49(2)	0(2)	14(2)	53(2)
C(10A)	41(2)	177(5)	67(2)	-48(3)	27(2)	-22(2)
N(1)	30(1)	32(1)	19(1)	0(1)	6(1)	-3(1)
C(11)	24(1)	30(1)	26(1)	1(1)	6(1)	-1(1)
C(12)	21(1)	26(1)	24(1)	2(1)	4(1)	-2(1)
N(2)	23(1)	22(1)	23(1)	-2(1)	5(1)	-1(1)
C(1B)	16(1)	24(1)	24(1)	-2(1)	2(1)	0(1)
C(2B)	22(1)	26(1)	26(1)	-1(1)	6(1)	1(1)
C(3B)	33(1)	26(1)	26(1)	0(1)	11(1)	1(1)
C(4B)	50(2)	28(1)	34(2)	3(1)	11(1)	-4(1)
C(5B)	35(1)	34(1)	22(1)	6(1)	4(1)	3(1)
C(6B)	25(1)	40(1)	19(1)	4(1)	3(1)	5(1)
C(7B)	26(1)	33(1)	32(1)	2(1)	1(1)	7(1)
C(8B)	27(1)	34(1)	38(1)	0(1)	11(1)	1(1)
C(9B)	45(2)	50(2)	23(1)	0(1)	9(1)	10(1)
C(10B)	33(2)	57(2)	31(1)	14(1)	12(1)	0(1)
C(13)	34(2)	27(1)	28(1)	-1(1)	9(1)	-1(1)
O(3)	46(1)	29(1)	49(1)	4(1)	6(1)	12(1)

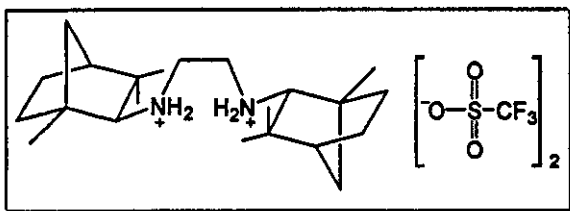
Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **483**.

	x	y	z	U_{eq}
H(1A)	1041	608	-2990	38
H(3A1)	-2286	-1656	-3169	47
H(3A2)	-3476	-1392	-4347	47
H(4A1)	-700	-3008	-3847	58
H(4A2)	-1685	-2591	-5028	58
H(5A)	1349	-1891	-4794	49
H(7A1)	-1255	-489	-5461	51
H(7A2)	483	280	-4820	51
H(8A1)	-2960	882	-3282	80
H(8A2)	-3486	853	-4538	80
H(8A3)	-1784	1627	-3911	80
H(9A1)	2695	-1961	-1775	107
H(9A2)	2719	-2860	-2722	107
H(9A3)	860	-2584	-2422	107
H(10A)	4166	-395	-2571	139
H(10B)	3276	75	-3738	139
H(10C)	4189	-1233	-3557	139
H(11A)	1608	1195	-1230	32
H(11B)	2612	-86	-1062	32
H(12A)	-162	591	-62	29
H(12B)	895	-668	122	29
H(1B)	4679	708	1958	26
H(3B1)	4929	-2404	281	33
H(3B2)	3008	-1731	104	33
H(4B1)	2447	-2799	1456	45
H(4B2)	4400	-3439	1658	45
H(5B)	4779	-2236	3195	37
H(7B1)	7031	-1945	2134	38
H(7B2)	6789	-678	2701	38
H(8B1)	7010	-742	274	49
H(8B2)	7043	445	970	49
H(8B3)	5472	261	-84	49
H(9B1)	3087	731	3441	59
H(9B2)	5119	262	3610	59
H(9B3)	3711	-500	4063	59
H(10D)	849	-1390	1593	60
H(10E)	605	-170	2191	60
H(10F)	1035	-1409	2831	60
H(13)	3137	2285	1555	35
H(1)	-198	-1027	-1776	40

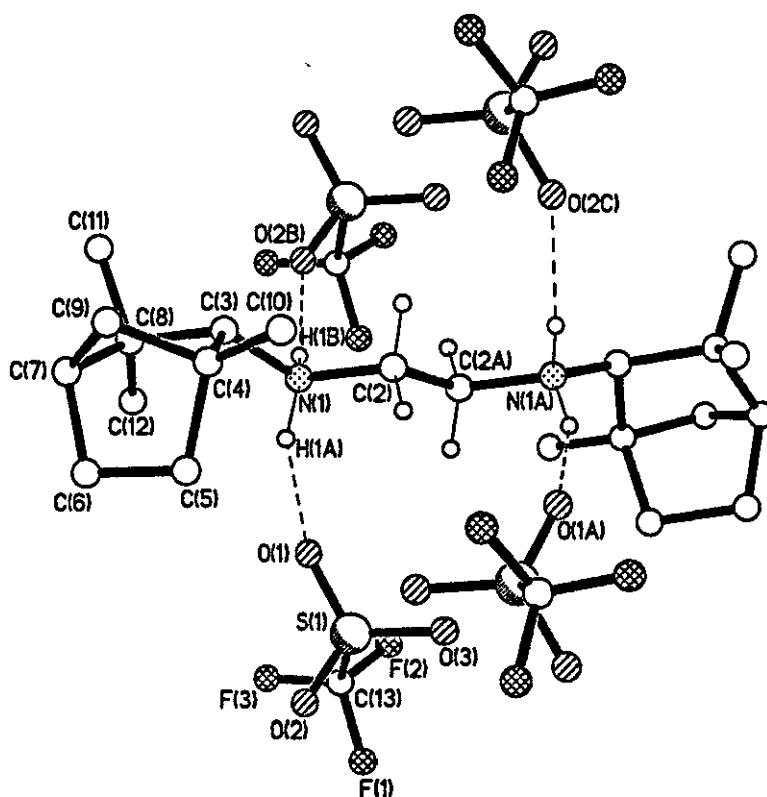
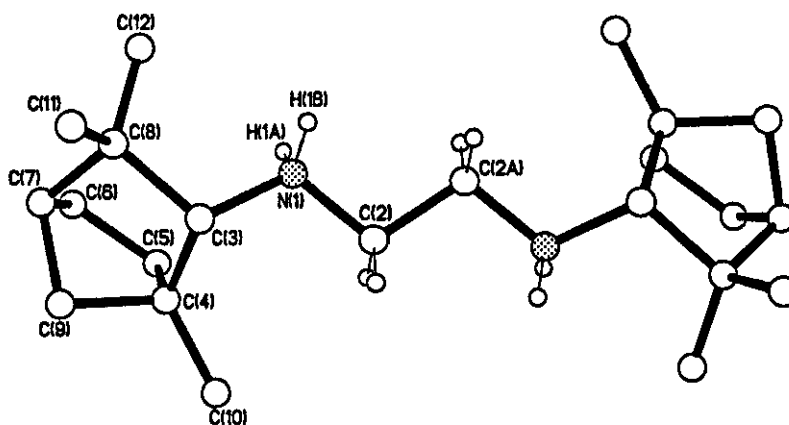
Table 6. Torsion angles [°] for compound 483.

N(1)-C(1A)-C(2A)-C(8A)	61.1(3)	C(13)-N(2)-C(1B)-C(2B)	-133.0(2)
C(6A)-C(1A)-C(2A)-C(8A)	-166.5(2)	C(12)-N(2)-C(1B)-C(2B)	54.0(3)
N(1)-C(1A)-C(2A)-C(7A)	-171.9(2)	C(13)-N(2)-C(1B)-C(6B)	98.1(2)
C(6A)-C(1A)-C(2A)-C(7A)	-39.5(2)	C(12)-N(2)-C(1B)-C(6B)	-74.9(3)
N(1)-C(1A)-C(2A)-C(3A)	-67.0(3)	N(2)-C(1B)-C(2B)-C(8B)	63.0(3)
C(6A)-C(1A)-C(2A)-C(3A)	65.5(2)	C(6B)-C(1B)-C(2B)-C(8B)	-162.70(19)
C(8A)-C(2A)-C(3A)-C(4A)	156.8(2)	N(2)-C(1B)-C(2B)-C(7B)	-175.00(19)
C(7A)-C(2A)-C(3A)-C(4A)	28.4(3)	C(6B)-C(1B)-C(2B)-C(7B)	-40.7(2)
C(1A)-C(2A)-C(3A)-C(4A)	-75.8(3)	N(2)-C(1B)-C(2B)-C(3B)	-70.9(3)
C(2A)-C(3A)-C(4A)-C(5A)	8.2(3)	C(6B)-C(1B)-C(2B)-C(3B)	63.4(2)
C(3A)-C(4A)-C(5A)-C(7A)	-42.0(3)	C(8B)-C(2B)-C(3B)-C(4B)	158.1(2)
C(3A)-C(4A)-C(5A)-C(6A)	65.5(3)	C(7B)-C(2B)-C(3B)-C(4B)	33.9(2)
C(7A)-C(5A)-C(6A)-C(9A)	152.6(2)	C(1B)-C(2B)-C(3B)-C(4B)	-68.6(2)
C(4A)-C(5A)-C(6A)-C(9A)	47.6(3)	C(2B)-C(3B)-C(4B)-C(5B)	1.8(3)
C(7A)-C(5A)-C(6A)-C(10A)	-85.7(3)	C(3B)-C(4B)-C(5B)-C(7B)	-37.1(2)
C(4A)-C(5A)-C(6A)-C(10A)	169.2(3)	C(3B)-C(4B)-C(5B)-C(6B)	71.0(3)
C(7A)-C(5A)-C(6A)-C(1A)	30.5(2)	C(7B)-C(5B)-C(6B)-C(9B)	-83.7(2)
C(4A)-C(5A)-C(6A)-C(1A)	-74.6(3)	C(4B)-C(5B)-C(6B)-C(9B)	169.8(2)
N(1)-C(1A)-C(6A)-C(9A)	12.7(3)	C(7B)-C(5B)-C(6B)-C(10B)	155.1(2)
C(2A)-C(1A)-C(6A)-C(9A)	-116.0(3)	C(4B)-C(5B)-C(6B)-C(10B)	48.6(3)
N(1)-C(1A)-C(6A)-C(10A)	-109.6(3)	C(7B)-C(5B)-C(6B)-C(1B)	31.1(2)
C(2A)-C(1A)-C(6A)-C(10A)	121.7(2)	C(4B)-C(5B)-C(6B)-C(1B)	-75.4(2)
N(1)-C(1A)-C(6A)-C(5A)	134.5(2)	N(2)-C(1B)-C(6B)-C(9B)	-101.8(2)
C(2A)-C(1A)-C(6A)-C(5A)	5.7(2)	C(2B)-C(1B)-C(6B)-C(9B)	122.3(2)
C(4A)-C(5A)-C(7A)-C(2A)	59.2(2)	N(2)-C(1B)-C(6B)-C(10B)	17.8(3)
C(6A)-C(5A)-C(7A)-C(2A)	-55.0(2)	C(2B)-C(1B)-C(6B)-C(10B)	-118.1(2)
C(8A)-C(2A)-C(7A)-C(5A)	-179.2(2)	N(2)-C(1B)-C(6B)-C(5B)	142.13(18)
C(1A)-C(2A)-C(7A)-C(5A)	57.6(2)	C(2B)-C(1B)-C(6B)-C(5B)	6.2(2)
C(3A)-C(2A)-C(7A)-C(5A)	-53.8(2)	C(4B)-C(5B)-C(7B)-C(2B)	57.9(2)
C(2A)-C(1A)-N(1)-C(11)	-155.6(2)	C(6B)-C(5B)-C(7B)-C(2B)	-57.2(2)
C(6A)-C(1A)-N(1)-C(11)	80.6(3)	C(8B)-C(2B)-C(7B)-C(5B)	179.7(2)
C(1A)-N(1)-C(11)-C(12)	-175.31(19)	C(3B)-C(2B)-C(7B)-C(5B)	-56.2(2)
N(1)-C(11)-C(12)-N(2)	-178.31(18)	C(1B)-C(2B)-C(7B)-C(5B)	58.69(19)
C(11)-C(12)-N(2)-C(13)	86.9(2)	C(1B)-N(2)-C(13)-O(3)	-172.8(2)
C(11)-C(12)-N(2)-C(1B)	-100.0(2)	C(12)-N(2)-C(13)-O(3)	0.8(3)

8.1.8 X-Ray crystallography data of 1,3-bis-[(1R,2R,4S)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]-ethyl bis-ammoniumtriflate, 500



500



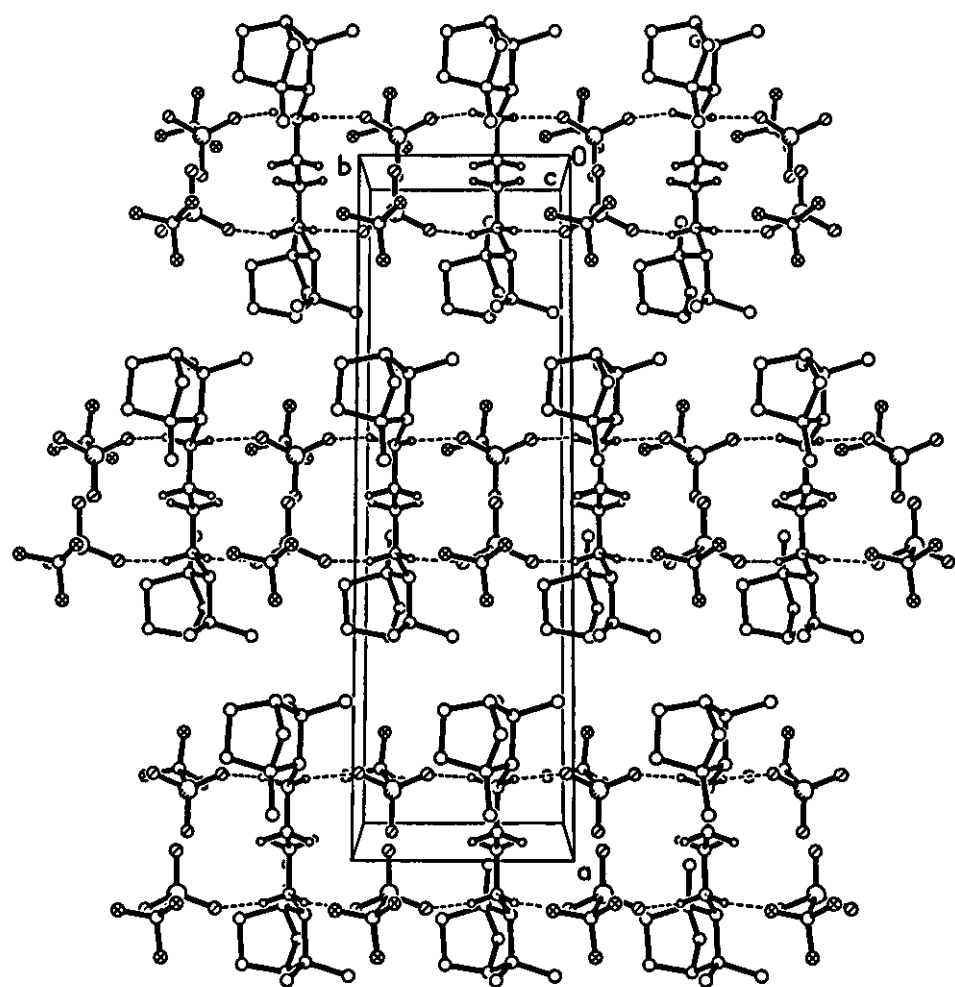


Table 1. Crystal data and structure refinement for compound 500.

Chemical formula	$C_{24}H_{42}F_6N_2O_6S_2$	
Formula weight	632.72	
Temperature	150(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	monoclinic, C2	
Unit cell parameters	$a = 22.875(3)$ Å	$\alpha = 90^\circ$
	$b = 6.9431(9)$ Å	$\beta = 99.896(2)^\circ$
	$c = 9.8184(13)$ Å	$\gamma = 90^\circ$
Cell volume	$1536.2(4)$ Å ³	
Z	2	
Calculated density	1.368 g/cm ³	
Absorption coefficient μ	0.249 mm ⁻¹	
F(000)	668	
Crystal colour and size	colourless, $0.36 \times 0.17 \times 0.09$ mm ³	
Reflections for cell refinement	2236 (θ range 2.53 to 24.38°)	
Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames	
θ range for data collection	1.81 to 26.00°	
Index ranges	h –28 to 28, k –8 to 8, l –12 to 11	
Completeness to $\theta = 26.00^\circ$	99.9 %	
Intensity decay	0%	
Reflections collected	6031	
Independent reflections	2980 ($R_{int} = 0.0217$)	
Reflections with $F^2 > 2\sigma$	2258	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.916 and 0.978	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0998, 0.9302	
Data / restraints / parameters	2980 / 125 / 222	
Final R indices [$F^2 > 2\sigma$]	$R1 = 0.0635$, $wR2 = 0.1577$	
R indices (all data)	$R1 = 0.0868$, $wR2 = 0.1790$	
Goodness-of-fit on F^2	1.078	
Absolute structure parameter	0.22(16)	
Largest and mean shift/su	0.002 and 0.000	
Largest diff. peak and hole	0.637 and –0.199 e Å ⁻³	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for compound **500**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.08130(11)	0.3372(7)	0.5741(3)	0.0453(7)
C(2)	0.01626(14)	0.3389(10)	0.5753(4)	0.0517(9)
C(3)	0.11885(18)	0.2713(6)	0.7101(5)	0.0498(10)
C(4)	0.11398(18)	0.3921(7)	0.8365(4)	0.0570(14)
C(5)	0.1318(2)	0.6024(8)	0.8104(5)	0.0636(13)
C(6)	0.1993(2)	0.5873(8)	0.8187(6)	0.0675(14)
C(7)	0.21171(18)	0.3747(9)	0.8371(4)	0.0617(15)
C(8)	0.18723(18)	0.2646(7)	0.7027(5)	0.0530(11)
C(9)	0.16958(18)	0.3259(11)	0.9326(4)	0.0642(12)
C(10)	0.0574(2)	0.3738(14)	0.8984(5)	0.089(2)
C(11)	0.2081(3)	0.0560(9)	0.7173(8)	0.0842(18)
C(12)	0.20341(18)	0.3410(13)	0.5713(5)	0.0666(11)
C(13)	0.4092(7)	0.412(3)	0.789(2)	0.128(6)
F(1)	0.4216(8)	0.586(3)	0.825(2)	0.170(7)
F(2)	0.4352(9)	0.307(4)	0.8906(16)	0.185(8)
F(3)	0.3543(6)	0.391(3)	0.780(2)	0.161(7)
C(13X)	0.4091(5)	0.326(2)	0.8009(11)	0.066(5)
F(1X)	0.4389(7)	0.444(5)	0.8908(19)	0.182(10)
F(2X)	0.4254(11)	0.158(4)	0.857(3)	0.218(11)
F(3X)	0.3547(5)	0.312(4)	0.808(2)	0.138(7)
S(1)	0.43254(4)	0.3436(2)	0.63532(9)	0.0469(3)
O(1)	0.4083(3)	0.1731(8)	0.5784(8)	0.135(3)
O(2)	0.4065(3)	0.5036(8)	0.5690(7)	0.120(2)
O(3)	0.49502(13)	0.3471(10)	0.6665(4)	0.0947(12)

Table 3. Bond lengths [Å] and angles [°] for compound **500**.

N(1)–C(2)	1.490(4)	N(1)–C(3)	1.528(5)
C(2)–C(2')	1.538(7)	C(3)–C(4)	1.518(7)
C(3)–C(8)	1.579(6)	C(4)–C(9)	1.519(6)
C(4)–C(10)	1.527(6)	C(4)–C(5)	1.549(7)
C(5)–C(6)	1.537(7)	C(6)–C(7)	1.508(8)
C(7)–C(9)	1.494(6)	C(7)–C(8)	1.544(6)
C(8)–C(12)	1.500(7)	C(8)–C(11)	1.525(7)
C(13)–F(3)	1.250(12)	C(13)–F(1)	1.277(13)
C(13)–F(2)	1.291(13)	C(13)–S(1)	1.75(2)
C(13X)–F(3X)	1.263(11)	C(13X)–F(1X)	1.309(12)
C(13X)–F(2X)	1.317(13)	C(13X)–S(1)	1.802(10)
S(1)–O(2)	1.371(5)	S(1)–O(1)	1.383(5)
S(1)–O(3)	1.409(3)		
C(2)–N(1)–C(3)	114.0(3)	N(1)–C(2)–C(2')	108.1(4)
C(4)–C(3)–N(1)	116.1(3)	C(4)–C(3)–C(8)	105.4(3)
N(1)–C(3)–C(8)	112.4(3)	C(3)–C(4)–C(9)	99.8(4)
C(3)–C(4)–C(10)	117.8(5)	C(9)–C(4)–C(10)	113.9(4)
C(3)–C(4)–C(5)	109.1(4)	C(9)–C(4)–C(5)	99.9(4)
C(10)–C(4)–C(5)	114.1(5)	C(6)–C(5)–C(4)	102.6(4)
C(7)–C(6)–C(5)	103.9(4)	C(9)–C(7)–C(6)	99.7(5)
C(9)–C(7)–C(8)	104.2(4)	C(6)–C(7)–C(8)	110.4(4)
C(12)–C(8)–C(11)	107.3(5)	C(12)–C(8)–C(7)	117.0(5)
C(11)–C(8)–C(7)	109.2(4)	C(12)–C(8)–C(3)	115.0(3)
C(11)–C(8)–C(3)	108.7(4)	C(7)–C(8)–C(3)	99.4(3)
C(7)–C(9)–C(4)	95.9(4)	F(3)–C(13)–F(1)	107.6(17)
F(3)–C(13)–F(2)	108.4(16)	F(1)–C(13)–F(2)	105.6(17)
F(3)–C(13)–S(1)	110.8(13)	F(1)–C(13)–S(1)	114.1(12)
F(2)–C(13)–S(1)	110.2(14)	F(3X)–C(13X)–F(1X)	114.5(15)
F(3X)–C(13X)–F(2X)	96.9(13)	F(1X)–C(13X)–F(2X)	101.4(16)
F(3X)–C(13X)–S(1)	120.4(11)	F(1X)–C(13X)–S(1)	111.3(12)
F(2X)–C(13X)–S(1)	109.3(10)	O(2)–S(1)–O(1)	113.0(4)
O(2)–S(1)–O(3)	115.5(4)	O(1)–S(1)–O(3)	115.0(4)
O(2)–S(1)–C(13)	91.1(8)	O(1)–S(1)–C(13)	114.8(6)
O(3)–S(1)–C(13)	104.8(6)	O(2)–S(1)–C(13X)	108.1(5)
O(1)–S(1)–C(13X)	98.3(6)	O(3)–S(1)–C(13X)	104.7(4)

Symmetry operations for equivalent atoms

' $-x, y, -z+1$

Table 4. Anisotropic displacement parameters (\AA^2) for compound 500. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11}+\dots+2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	0.0346(14)	0.0506(16)	0.0457(14)	0.000(2)	-0.0074(11)	-0.003(2)
C(2)	0.0353(18)	0.063(2)	0.051(2)	-0.007(3)	-0.0092(14)	0.000(3)
C(3)	0.037(2)	0.050(2)	0.057(3)	0.0101(18)	-0.0067(17)	-0.0011(16)
C(4)	0.039(2)	0.084(4)	0.046(2)	0.006(2)	0.0001(16)	0.001(2)
C(5)	0.067(3)	0.067(3)	0.054(3)	-0.013(2)	0.001(2)	0.005(2)
C(6)	0.056(3)	0.077(3)	0.065(3)	-0.008(3)	-0.004(2)	-0.020(3)
C(7)	0.0342(19)	0.092(5)	0.053(2)	-0.001(3)	-0.0083(15)	-0.001(2)
C(8)	0.037(2)	0.060(2)	0.058(3)	-0.001(2)	-0.0044(18)	0.0045(18)
C(9)	0.048(2)	0.086(4)	0.054(2)	0.013(3)	-0.0054(17)	0.000(3)
C(10)	0.051(3)	0.164(7)	0.051(2)	0.027(4)	0.0095(19)	0.020(4)
C(11)	0.066(3)	0.070(4)	0.112(5)	-0.007(3)	0.002(3)	0.019(3)
C(12)	0.045(2)	0.089(3)	0.066(2)	0.007(4)	0.0100(18)	0.009(3)
C(13)	0.109(9)	0.162(13)	0.114(13)	0.008(10)	0.024(9)	-0.089(10)
F(1)	0.167(12)	0.192(11)	0.165(15)	-0.130(10)	0.073(10)	-0.043(9)
F(2)	0.217(12)	0.276(18)	0.060(9)	0.023(12)	0.017(8)	-0.109(14)
F(3)	0.106(7)	0.254(19)	0.151(11)	-0.083(11)	0.100(6)	-0.067(7)
C(13X)	0.056(6)	0.122(12)	0.026(5)	0.021(7)	0.024(4)	0.011(8)
F(1X)	0.097(8)	0.37(2)	0.074(12)	-0.119(17)	-0.003(7)	-0.034(15)
F(2X)	0.254(19)	0.245(17)	0.191(18)	0.179(15)	0.138(15)	0.111(15)
F(3X)	0.050(5)	0.273(18)	0.100(7)	0.052(10)	0.036(5)	-0.025(7)
S(1)	0.0530(5)	0.0441(5)	0.0437(5)	0.0011(7)	0.0089(3)	0.0016(6)
O(1)	0.134(5)	0.087(4)	0.196(7)	-0.084(4)	0.063(5)	-0.036(4)
O(2)	0.114(4)	0.104(4)	0.143(5)	0.069(4)	0.023(4)	0.034(3)
O(3)	0.0457(17)	0.152(4)	0.087(2)	0.006(4)	0.0148(15)	0.023(3)

Table 5. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for compound **500**.

	x	y	z	U_{eq}
H(1A)	0.0930	0.4592	0.5541	0.054
H(1B)	0.0886	0.2568	0.5044	0.054
H(2A)	0.0054	0.4552	0.6239	0.062
H(2B)	0.0049	0.2238	0.6243	0.062
H(3)	0.1062	0.1374	0.7286	0.060
H(5A)	0.1122	0.6480	0.7183	0.076
H(5B)	0.1216	0.6903	0.8822	0.076
H(6A)	0.2114	0.6354	0.7327	0.081
H(6B)	0.2205	0.6615	0.8982	0.081
H(7)	0.2541	0.3442	0.8755	0.074
H(9A)	0.1773	0.4008	1.0197	0.077
H(9B)	0.1690	0.1865	0.9533	0.077
H(10A)	0.0268	0.4593	0.8488	0.133
H(10B)	0.0657	0.4101	0.9963	0.133
H(10C)	0.0433	0.2404	0.8897	0.133
H(11A)	0.1842	-0.0225	0.6456	0.126
H(11B)	0.2037	0.0073	0.8087	0.126
H(11C)	0.2499	0.0490	0.7072	0.126
H(12A)	0.1901	0.4749	0.5579	0.100
H(12B)	0.1842	0.2627	0.4932	0.100
H(12C)	0.2466	0.3353	0.5768	0.100

Table 6. Torsion angles [°] for compound **500**.

C(3)–N(1)–C(2)–C(2')	–161.0(3)	C(2)–N(1)–C(3)–C(4)	–60.5(5)
C(2)–N(1)–C(3)–C(8)	178.0(4)	N(1)–C(3)–C(4)–C(9)	–162.4(4)
C(8)–C(3)–C(4)–C(9)	–37.2(4)	N(1)–C(3)–C(4)–C(10)	73.9(6)
C(8)–C(3)–C(4)–C(10)	–160.9(4)	N(1)–C(3)–C(4)–C(5)	–58.3(5)
C(8)–C(3)–C(4)–C(5)	66.9(4)	C(3)–C(4)–C(5)–C(6)	–72.3(4)
C(9)–C(4)–C(5)–C(6)	31.7(4)	C(10)–C(4)–C(5)–C(6)	153.6(4)
C(4)–C(5)–C(6)–C(7)	4.0(5)	C(5)–C(6)–C(7)–C(9)	–39.1(4)
C(5)–C(6)–C(7)–C(8)	70.2(5)	C(9)–C(7)–C(8)–C(12)	156.1(4)
C(6)–C(7)–C(8)–C(12)	49.9(5)	C(9)–C(7)–C(8)–C(11)	–81.9(5)
C(6)–C(7)–C(8)–C(11)	171.9(4)	C(9)–C(7)–C(8)–C(3)	31.8(5)
C(6)–C(7)–C(8)–C(3)	–74.5(4)	C(4)–C(3)–C(8)–C(12)	–121.8(5)
N(1)–C(3)–C(8)–C(12)	5.7(6)	C(4)–C(3)–C(8)–C(11)	118.0(5)
N(1)–C(3)–C(8)–C(11)	–114.6(5)	C(4)–C(3)–C(8)–C(7)	4.0(4)
N(1)–C(3)–C(8)–C(7)	131.4(4)	C(6)–C(7)–C(9)–C(4)	58.8(5)
C(8)–C(7)–C(9)–C(4)	–55.3(5)	C(3)–C(4)–C(9)–C(7)	55.8(5)
C(10)–C(4)–C(9)–C(7)	–177.9(6)	C(5)–C(4)–C(9)–C(7)	–55.8(5)
F(3)–C(13)–S(1)–O(2)	71.4(13)	F(1)–C(13)–S(1)–O(2)	–50.1(14)
F(2)–C(13)–S(1)–O(2)	–168.6(12)	F(3)–C(13)–S(1)–O(1)	–44.6(15)
F(1)–C(13)–S(1)–O(1)	–166.2(13)	F(2)–C(13)–S(1)–O(1)	75.4(13)
F(3)–C(13)–S(1)–O(3)	–171.7(12)	F(1)–C(13)–S(1)–O(3)	66.7(15)
F(2)–C(13)–S(1)–O(3)	–51.8(12)	F(3)–C(13)–S(1)–C(13X)	–80(3)
F(1)–C(13)–S(1)–C(13X)	159(3)	F(2)–C(13)–S(1)–C(13X)	40(2)
F(3X)–C(13X)–S(1)–O(2)	59.0(17)	F(1X)–C(13X)–S(1)–O(2)	–79.1(16)
F(2X)–C(13X)–S(1)–O(2)	169.7(14)	F(3X)–C(13X)–S(1)–O(1)	–58.6(16)
F(1X)–C(13X)–S(1)–O(1)	163.3(15)	F(2X)–C(13X)–S(1)–O(1)	52.1(14)
F(3X)–C(13X)–S(1)–O(3)	–177.3(15)	F(1X)–C(13X)–S(1)–O(3)	44.6(15)
F(2X)–C(13X)–S(1)–O(3)	–66.6(13)	F(3X)–C(13X)–S(1)–C(13)	90(3)
F(1X)–C(13X)–S(1)–C(13)	–48(2)	F(2X)–C(13X)–S(1)–C(13)	–160(3)

Symmetry operations for equivalent atoms

' –x,y,–z+1

Table 7. Hydrogen bonds for compound **500** [Å and °].

D—H...A	d(D—H)	d(H...A)	d(D...A)	<(DHA)
N(1)—H(1A)...O(1 ["])	0.92	1.97	2.803(6)	149.6
N(1)—H(1B)...O(2 [*])	0.92	1.91	2.748(7)	150.3

Symmetry operations for equivalent atoms

["] $-x+1/2,y+1/2,-z+1$ ^{*} $-x+1/2,y-1/2,-z+1$

Table 1. Crystal data and structure refinement for compound **531**.

Chemical formula	$\text{C}_{23}\text{H}_{38}\text{N}_2\text{S}$	
Formula weight	374.61	
Temperature	150(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	$a = 6.9710(3)$ Å	$\alpha = 90^\circ$
	$b = 13.6938(5)$ Å	$\beta = 90^\circ$
	$c = 46.7186(17)$ Å	$\gamma = 90^\circ$
Cell volume	$4459.7(3)$ Å ³	
Z	8	
Calculated density	1.116 g/cm ³	
Absorption coefficient μ	0.154 mm ⁻¹	
F(000)	1648	
Crystal colour and size	colourless, $0.49 \times 0.22 \times 0.22$ mm ³	
Reflections for cell refinement	15984 (θ range 2.64 to 28.33°)	
Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames	
θ range for data collection	1.72 to 29.16°	
Index ranges	$h -9$ to 9 , $k -18$ to 18 , $l -60$ to 62	
Completeness to $\theta = 26.00^\circ$	99.9 %	
Intensity decay	0%	
Reflections collected	39776	
Independent reflections	10850 ($R_{\text{int}} = 0.0276$)	
Reflections with $F^2 > 2\sigma$	9242	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.928 and 0.967	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a , b	0.0593, 0.7860	
Data / restraints / parameters	10850 / 0 / 481	
Final R indices [$F^2 > 2\sigma$]	$R1 = 0.0447$, $wR2 = 0.1080$	
R indices (all data)	$R1 = 0.0560$, $wR2 = 0.1141$	
Goodness-of-fit on F^2	1.056	
Absolute structure parameter	$-0.04(5)$	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.302 and -0.185 e Å ⁻³	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for compound **531**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
S(1)	0.03851(7)	0.11635(5)	0.937616(12)	0.04430(15)
C(1)	0.2777(2)	0.11521(12)	0.93823(4)	0.0228(3)
N(1)	0.3936(2)	0.15940(10)	0.91878(3)	0.0256(3)
C(2)	0.5914(3)	0.12530(15)	0.92258(4)	0.0335(4)
N(2)	0.3868(2)	0.06839(11)	0.95807(3)	0.0254(3)
C(3)	0.5905(3)	0.09225(15)	0.95368(4)	0.0318(4)
C(4)	0.3205(3)	0.20692(13)	0.89297(4)	0.0264(4)
C(5)	0.3797(3)	0.16384(13)	0.86364(4)	0.0336(4)
C(6)	0.5930(3)	0.18204(18)	0.85617(5)	0.0470(5)
C(7)	0.6054(4)	0.29345(18)	0.85118(5)	0.0521(6)
C(8)	0.4010(3)	0.32808(15)	0.85758(4)	0.0424(5)
C(9)	0.3552(3)	0.32004(14)	0.89001(4)	0.0358(4)
C(10)	0.2867(4)	0.24324(15)	0.84463(4)	0.0406(5)
C(11)	0.3105(4)	0.06023(15)	0.85950(5)	0.0472(6)
C(12)	0.5079(4)	0.36097(17)	0.91004(5)	0.0538(7)
C(13)	0.1672(4)	0.37388(17)	0.89666(5)	0.0552(7)
C(14)	0.3073(3)	0.02428(12)	0.98400(4)	0.0264(4)
C(15)	0.3845(3)	0.05886(14)	1.01320(4)	0.0377(5)
C(16)	0.5929(4)	0.02555(16)	1.01909(5)	0.0455(5)
C(17)	0.5751(4)	-0.08636(17)	1.02309(5)	0.0459(5)
C(18)	0.3610(3)	-0.10598(14)	1.01768(4)	0.0380(4)
C(19)	0.3088(3)	-0.09021(13)	0.98589(4)	0.0336(4)
C(20)	0.2755(4)	-0.01500(15)	1.03201(4)	0.0441(5)
C(21)	0.3447(5)	0.16587(16)	1.01881(6)	0.0594(7)
C(22)	0.1057(4)	-0.12892(17)	0.97989(5)	0.0514(6)
C(23)	0.4446(4)	-0.13961(15)	0.96450(5)	0.0455(5)
S(2)	-0.13765(6)	0.32173(4)	0.695341(10)	0.03197(11)
C(24)	0.0985(2)	0.34066(12)	0.69107(3)	0.0234(3)
N(3)	0.2122(2)	0.39518(11)	0.70861(3)	0.0258(3)
C(25)	0.3982(3)	0.41038(14)	0.69475(4)	0.0330(4)
C(26)	0.4100(2)	0.32327(15)	0.67487(4)	0.0312(4)
N(4)	0.2070(2)	0.30376(11)	0.66936(3)	0.0247(3)
C(27)	0.1347(3)	0.45543(13)	0.73184(3)	0.0277(4)
C(28)	0.1429(3)	0.56807(14)	0.72821(4)	0.0351(4)
C(29)	0.3487(3)	0.60935(16)	0.73049(5)	0.0449(5)
C(30)	0.3988(4)	0.5961(2)	0.76256(5)	0.0554(6)
C(31)	0.2229(4)	0.54305(17)	0.77437(4)	0.0432(5)
C(32)	0.2092(4)	0.43686(16)	0.76293(4)	0.0421(5)
C(33)	0.0647(4)	0.59616(16)	0.75759(4)	0.0434(5)
C(34)	0.0318(4)	0.60338(17)	0.70223(5)	0.0512(6)
C(35)	0.0519(5)	0.38149(19)	0.77958(5)	0.0626(8)
C(36)	0.3912(4)	0.3769(2)	0.76506(5)	0.0673(8)

C(37)	0.1318(3)	0.23843(12)	0.64741(4)	0.0260(3)
C(38)	0.2321(3)	0.13861(13)	0.64295(4)	0.0339(4)
C(39)	0.4348(3)	0.14850(15)	0.62923(5)	0.0400(5)
C(40)	0.3940(3)	0.18291(18)	0.59827(4)	0.0451(5)
C(41)	0.1765(3)	0.19438(17)	0.59790(4)	0.0449(5)
C(42)	0.1095(3)	0.28236(15)	0.61635(4)	0.0341(4)
C(43)	0.1195(4)	0.10680(17)	0.61625(5)	0.0485(6)
C(44)	0.2252(5)	0.07385(17)	0.66885(5)	0.0566(7)
C(45)	0.2207(4)	0.37683(17)	0.61119(5)	0.0476(5)
C(46)	-0.1037(3)	0.3047(2)	0.61068(5)	0.0548(6)

Table 3. Bond lengths [Å] and angles [°] for compound **531**.

S(1)–C(1)	1.6677(17)	C(1)–N(1)	1.358(2)
C(1)–N(2)	1.360(2)	N(1)–C(4)	1.462(2)
N(1)–C(2)	1.467(2)	C(2)–C(3)	1.522(3)
N(2)–C(14)	1.463(2)	N(2)–C(3)	1.472(2)
C(4)–C(5)	1.548(3)	C(4)–C(9)	1.574(3)
C(5)–C(11)	1.511(3)	C(5)–C(10)	1.546(3)
C(5)–C(6)	1.548(3)	C(6)–C(7)	1.546(3)
C(7)–C(8)	1.532(3)	C(8)–C(10)	1.533(3)
C(8)–C(9)	1.552(3)	C(9)–C(12)	1.524(3)
C(9)–C(13)	1.535(3)	C(14)–C(15)	1.541(3)
C(14)–C(19)	1.570(2)	C(15)–C(21)	1.514(3)
C(15)–C(20)	1.540(3)	C(15)–C(16)	1.548(3)
C(16)–C(17)	1.549(3)	C(17)–C(18)	1.537(3)
C(18)–C(20)	1.535(3)	C(18)–C(19)	1.544(3)
C(19)–C(23)	1.534(3)	C(19)–C(22)	1.537(3)
S(2)–C(24)	1.6782(18)	C(24)–N(4)	1.362(2)
C(24)–N(3)	1.363(2)	N(3)–C(25)	1.464(2)
N(3)–C(27)	1.466(2)	C(25)–C(26)	1.514(3)
C(26)–N(4)	1.463(2)	N(4)–C(37)	1.458(2)
C(27)–C(28)	1.553(3)	C(27)–C(32)	1.563(3)
C(28)–C(34)	1.519(3)	C(28)–C(33)	1.526(3)
C(28)–C(29)	1.546(3)	C(29)–C(30)	1.549(3)
C(30)–C(31)	1.528(4)	C(31)–C(33)	1.536(3)
C(31)–C(32)	1.552(3)	C(32)–C(36)	1.514(3)
C(32)–C(35)	1.543(4)	C(37)–C(38)	1.550(3)
C(37)–C(42)	1.578(2)	C(38)–C(44)	1.501(3)
C(38)–C(43)	1.537(3)	C(38)–C(39)	1.557(3)
C(39)–C(40)	1.548(3)	C(40)–C(41)	1.525(3)
C(41)–C(43)	1.527(3)	C(41)–C(42)	1.553(3)
C(42)–C(45)	1.527(3)	C(42)–C(46)	1.540(3)
N(1)–C(1)–N(2)	109.49(14)	N(1)–C(1)–S(1)	125.39(13)
N(2)–C(1)–S(1)	125.11(13)	C(1)–N(1)–C(4)	122.88(14)
C(1)–N(1)–C(2)	109.66(13)	C(4)–N(1)–C(2)	124.69(14)
N(1)–C(2)–C(3)	101.90(14)	C(1)–N(2)–C(14)	123.21(15)
C(1)–N(2)–C(3)	109.88(14)	C(14)–N(2)–C(3)	124.92(14)
N(2)–C(3)–C(2)	101.71(14)	N(1)–C(4)–C(5)	117.88(14)
N(1)–C(4)–C(9)	117.19(15)	C(5)–C(4)–C(9)	104.87(14)
C(11)–C(5)–C(10)	116.92(18)	C(11)–C(5)–C(4)	112.71(17)
C(10)–C(5)–C(4)	97.39(15)	C(11)–C(5)–C(6)	115.42(19)
C(10)–C(5)–C(6)	99.22(17)	C(4)–C(5)–C(6)	113.22(17)
C(7)–C(6)–C(5)	104.28(19)	C(8)–C(7)–C(6)	102.95(18)
C(7)–C(8)–C(10)	99.89(19)	C(7)–C(8)–C(9)	111.11(18)
C(10)–C(8)–C(9)	102.98(17)	C(12)–C(9)–C(13)	107.19(19)
C(12)–C(9)–C(8)	115.4(2)	C(13)–C(9)–C(8)	109.81(17)
C(12)–C(9)–C(4)	114.54(16)	C(13)–C(9)–C(4)	108.89(18)
C(8)–C(9)–C(4)	100.78(15)	C(8)–C(10)–C(5)	95.06(16)
N(2)–C(14)–C(15)	118.31(15)	N(2)–C(14)–C(19)	117.14(15)

C(15)–C(14)–C(19)	104.76(15)	C(21)–C(15)–C(20)	116.5(2)
C(21)–C(15)–C(14)	112.75(18)	C(20)–C(15)–C(14)	97.53(16)
C(21)–C(15)–C(16)	115.2(2)	C(20)–C(15)–C(16)	99.68(18)
C(14)–C(15)–C(16)	113.24(17)	C(15)–C(16)–C(17)	103.75(19)
C(18)–C(17)–C(16)	103.35(18)	C(20)–C(18)–C(17)	99.41(19)

C(20)–C(18)–C(19)	102.37(16)	C(17)–C(18)–C(19)	111.26(17)
C(23)–C(19)–C(22)	107.30(18)	C(23)–C(19)–C(18)	114.79(18)
C(22)–C(19)–C(18)	110.14(17)	C(23)–C(19)–C(14)	114.07(16)
C(22)–C(19)–C(14)	109.14(17)	C(18)–C(19)–C(14)	101.25(15)
C(18)–C(20)–C(15)	95.33(16)	N(4)–C(24)–N(3)	109.14(14)
N(4)–C(24)–S(2)	125.14(13)	N(3)–C(24)–S(2)	125.72(13)
C(24)–N(3)–C(25)	109.09(14)	C(24)–N(3)–C(27)	122.60(15)
C(25)–N(3)–C(27)	125.00(15)	N(3)–C(25)–C(26)	101.99(14)
N(4)–C(26)–C(25)	101.47(14)	C(24)–N(4)–C(37)	123.47(14)
C(24)–N(4)–C(26)	109.77(13)	C(37)–N(4)–C(26)	125.69(14)
N(3)–C(27)–C(28)	117.69(15)	N(3)–C(27)–C(32)	118.27(16)
C(28)–C(27)–C(32)	104.53(15)	C(34)–C(28)–C(33)	117.14(19)
C(34)–C(28)–C(29)	114.33(19)	C(33)–C(28)–C(29)	100.22(17)
C(34)–C(28)–C(27)	112.64(17)	C(33)–C(28)–C(27)	97.99(16)
C(29)–C(28)–C(27)	112.93(17)	C(28)–C(29)–C(30)	103.48(18)
C(31)–C(30)–C(29)	102.94(19)	C(30)–C(31)–C(33)	99.60(19)
C(30)–C(31)–C(32)	111.7(2)	C(33)–C(31)–C(32)	102.94(17)
C(36)–C(32)–C(35)	107.2(2)	C(36)–C(32)–C(31)	115.7(2)
C(35)–C(32)–C(31)	109.30(19)	C(36)–C(32)–C(27)	115.31(18)
C(35)–C(32)–C(27)	108.2(2)	C(31)–C(32)–C(27)	100.82(15)
C(28)–C(33)–C(31)	94.76(17)	N(4)–C(37)–C(38)	118.25(15)
N(4)–C(37)–C(42)	116.62(14)	C(38)–C(37)–C(42)	104.90(14)
C(44)–C(38)–C(43)	118.05(19)	C(44)–C(38)–C(37)	113.48(17)
C(43)–C(38)–C(37)	97.38(17)	C(44)–C(38)–C(39)	114.4(2)
C(43)–C(38)–C(39)	98.85(16)	C(37)–C(38)–C(39)	112.84(16)
C(40)–C(39)–C(38)	104.16(17)	C(41)–C(40)–C(39)	102.98(17)
C(40)–C(41)–C(43)	99.9(2)	C(40)–C(41)–C(42)	111.89(18)
C(43)–C(41)–C(42)	102.68(16)	C(45)–C(42)–C(46)	107.14(19)
C(45)–C(42)–C(41)	114.63(18)	C(46)–C(42)–C(41)	110.40(18)
C(45)–C(42)–C(37)	114.69(16)	C(46)–C(42)–C(37)	109.20(17)
C(41)–C(42)–C(37)	100.66(15)	C(41)–C(43)–C(38)	95.76(16)

Table 4. Anisotropic displacement parameters (\AA^2) for compound **531**. 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}
S(1)	0.0182(2)	0.0630(4)	0.0517(3)	0.0183(3)	0.0012(2)	0.0029(2)
C(1)	0.0191(7)	0.0232(8)	0.0262(8)	0.0011(7)	0.0019(6)	0.0021(7)
N(1)	0.0191(7)	0.0296(7)	0.0281(7)	0.0086(6)	-0.0010(6)	0.0010(6)
C(2)	0.0192(8)	0.0420(11)	0.0392(10)	0.0163(9)	0.0013(7)	0.0021(8)
N(2)	0.0191(7)	0.0293(7)	0.0279(7)	0.0070(6)	0.0001(6)	-0.0023(6)
C(3)	0.0205(8)	0.0383(10)	0.0365(10)	0.0144(8)	-0.0024(7)	-0.0029(7)
C(4)	0.0249(9)	0.0280(9)	0.0264(8)	0.0042(7)	-0.0028(6)	0.0028(7)
C(5)	0.0444(11)	0.0285(9)	0.0279(9)	0.0023(7)	-0.0025(8)	0.0012(9)
C(6)	0.0497(13)	0.0547(13)	0.0367(11)	0.0069(10)	0.0095(9)	0.0044(11)
C(7)	0.0590(15)	0.0576(14)	0.0396(12)	0.0143(10)	0.0040(11)	-0.0132(12)
C(8)	0.0600(14)	0.0319(10)	0.0354(10)	0.0117(8)	-0.0080(10)	-0.0071(10)
C(9)	0.0505(12)	0.0250(8)	0.0318(9)	0.0038(8)	-0.0078(9)	0.0027(9)
C(10)	0.0575(14)	0.0388(11)	0.0253(9)	0.0054(8)	-0.0079(9)	-0.0023(10)
C(11)	0.0626(16)	0.0346(11)	0.0445(12)	-0.0065(9)	-0.0014(11)	0.0031(10)
C(12)	0.0800(19)	0.0339(11)	0.0475(13)	0.0034(10)	-0.0196(13)	-0.0143(12)
C(13)	0.0737(18)	0.0388(12)	0.0531(14)	0.0000(11)	-0.0057(12)	0.0234(12)
C(14)	0.0273(9)	0.0244(8)	0.0275(9)	0.0045(7)	0.0053(7)	-0.0011(7)
C(15)	0.0557(13)	0.0274(9)	0.0300(9)	-0.0034(7)	0.0019(9)	0.0027(9)
C(16)	0.0565(14)	0.0477(12)	0.0322(10)	0.0005(9)	-0.0126(10)	-0.0061(11)
C(17)	0.0537(14)	0.0480(13)	0.0360(11)	0.0135(9)	-0.0029(10)	0.0070(10)
C(18)	0.0496(12)	0.0308(9)	0.0337(10)	0.0107(8)	0.0089(9)	0.0031(9)
C(19)	0.0436(11)	0.0232(9)	0.0339(10)	0.0022(8)	0.0061(8)	-0.0032(8)
C(20)	0.0620(15)	0.0437(12)	0.0265(10)	0.0044(9)	0.0105(10)	0.0065(11)
C(21)	0.094(2)	0.0340(11)	0.0503(13)	-0.0100(10)	-0.0022(14)	0.0049(13)
C(22)	0.0572(15)	0.0410(12)	0.0560(14)	0.0065(10)	-0.0003(12)	-0.0203(11)
C(23)	0.0670(16)	0.0306(10)	0.0390(11)	-0.0046(9)	0.0111(11)	0.0035(10)
S(2)	0.0200(2)	0.0398(2)	0.0360(2)	-0.0040(2)	0.00257(18)	0.00184(19)
C(24)	0.0224(8)	0.0243(8)	0.0234(8)	0.0011(6)	-0.0012(6)	0.0011(6)
N(3)	0.0226(7)	0.0286(7)	0.0262(7)	-0.0054(6)	0.0002(6)	0.0014(6)
C(25)	0.0217(8)	0.0413(10)	0.0360(9)	-0.0134(8)	0.0011(8)	-0.0053(7)
C(26)	0.0207(8)	0.0418(10)	0.0311(9)	-0.0104(8)	0.0006(7)	-0.0001(8)
N(4)	0.0199(7)	0.0290(8)	0.0253(7)	-0.0067(6)	-0.0012(5)	-0.0013(6)
C(27)	0.0283(9)	0.0316(9)	0.0232(8)	-0.0050(7)	0.0016(7)	0.0015(8)
C(28)	0.0463(12)	0.0295(9)	0.0294(9)	-0.0053(7)	-0.0066(9)	0.0074(9)
C(29)	0.0543(13)	0.0379(11)	0.0426(11)	-0.0076(9)	0.0013(10)	-0.0082(11)
C(30)	0.0568(15)	0.0636(15)	0.0458(13)	-0.0171(11)	-0.0102(11)	-0.0088(13)
C(31)	0.0540(13)	0.0488(12)	0.0268(10)	-0.0089(9)	-0.0065(9)	0.0028(11)
C(32)	0.0583(14)	0.0405(11)	0.0274(9)	0.0008(8)	-0.0051(9)	0.0078(10)
C(33)	0.0589(14)	0.0346(11)	0.0367(11)	-0.0100(9)	0.0002(10)	0.0061(10)
C(34)	0.0736(16)	0.0428(12)	0.0370(11)	0.0009(9)	-0.0087(11)	0.0154(12)

C(35)	0.105(2)	0.0504(14)	0.0321(11)	0.0048(10)	0.0113(13)	-0.0033(15)
C(36)	0.083(2)	0.0803(19)	0.0391(12)	0.0013(12)	-0.0162(13)	0.0393(17)
C(37)	0.0245(8)	0.0283(8)	0.0254(8)	-0.0044(7)	-0.0009(7)	-0.0058(7)
C(38)	0.0440(11)	0.0256(9)	0.0321(10)	-0.0045(8)	0.0072(8)	-0.0027(8)
C(39)	0.0417(12)	0.0357(10)	0.0427(11)	-0.0104(9)	0.0065(9)	0.0024(9)
C(40)	0.0509(13)	0.0494(12)	0.0349(10)	-0.0095(10)	0.0145(9)	-0.0050(11)
C(41)	0.0515(13)	0.0568(14)	0.0264(9)	-0.0094(9)	-0.0004(9)	-0.0133(11)
C(42)	0.0371(11)	0.0403(10)	0.0250(9)	0.0018(8)	-0.0051(8)	-0.0051(9)
C(43)	0.0557(14)	0.0439(12)	0.0460(12)	-0.0178(10)	0.0076(11)	-0.0140(11)
C(44)	0.0787(19)	0.0361(12)	0.0551(15)	0.0097(11)	0.0161(13)	0.0064(12)
C(45)	0.0599(14)	0.0425(12)	0.0403(11)	0.0110(10)	-0.0058(11)	-0.0071(11)
C(46)	0.0442(13)	0.0785(18)	0.0418(12)	0.0055(12)	-0.0134(10)	0.0031(13)

Table 5. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for compound **531**.

	x	y	z	U_{eq}
H(2A)	0.6847	0.1787	0.9194	0.040
H(2B)	0.6213	0.0705	0.9095	0.040
H(3A)	0.6732	0.0343	0.9566	0.038
H(3B)	0.6329	0.1452	0.9667	0.038
H(4)	0.1780	0.1990	0.8939	0.032
H(6A)	0.6775	0.1618	0.8721	0.056
H(6B)	0.6303	0.1457	0.8387	0.056
H(7A)	0.6991	0.3241	0.8643	0.062
H(7B)	0.6422	0.3084	0.8312	0.062
H(8)	0.3692	0.3932	0.8491	0.051
H(10A)	0.3135	0.2337	0.8240	0.049
H(10B)	0.1468	0.2495	0.8478	0.049
H(11A)	0.3291	0.0409	0.8395	0.071
H(11B)	0.1739	0.0562	0.8643	0.071
H(11C)	0.3835	0.0164	0.8720	0.071
H(12A)	0.5216	0.4313	0.9067	0.081
H(12B)	0.6306	0.3284	0.9063	0.081
H(12C)	0.4696	0.3495	0.9299	0.081
H(13A)	0.1224	0.3555	0.9158	0.083
H(13B)	0.0699	0.3560	0.8824	0.083
H(13C)	0.1892	0.4445	0.8960	0.083
H(14)	0.1686	0.0429	0.9840	0.032
H(16A)	0.6443	0.0569	1.0366	0.055
H(16B)	0.6777	0.0414	1.0027	0.055
H(17A)	0.6561	−0.1218	1.0091	0.055
H(17B)	0.6124	−0.1060	1.0427	0.055
H(18)	0.3138	−0.1691	1.0258	0.046
H(20A)	0.3100	−0.0099	1.0525	0.053
H(20B)	0.1347	−0.0106	1.0296	0.053
H(21A)	0.4166	0.2058	1.0051	0.089
H(21B)	0.3848	0.1825	1.0383	0.089
H(21C)	0.2072	0.1786	1.0167	0.089
H(22A)	0.0644	−0.1076	0.9608	0.077
H(22B)	0.0169	−0.1034	0.9943	0.077
H(22C)	0.1064	−0.2004	0.9807	0.077
H(23A)	0.5756	−0.1158	0.9676	0.068
H(23B)	0.4039	−0.1241	0.9449	0.068
H(23C)	0.4411	−0.2105	0.9673	0.068
H(25A)	0.5040	0.4100	0.7089	0.040
H(25B)	0.4009	0.4726	0.6840	0.040
H(26A)	0.4795	0.3396	0.6570	0.037
H(26B)	0.4732	0.2670	0.6843	0.037

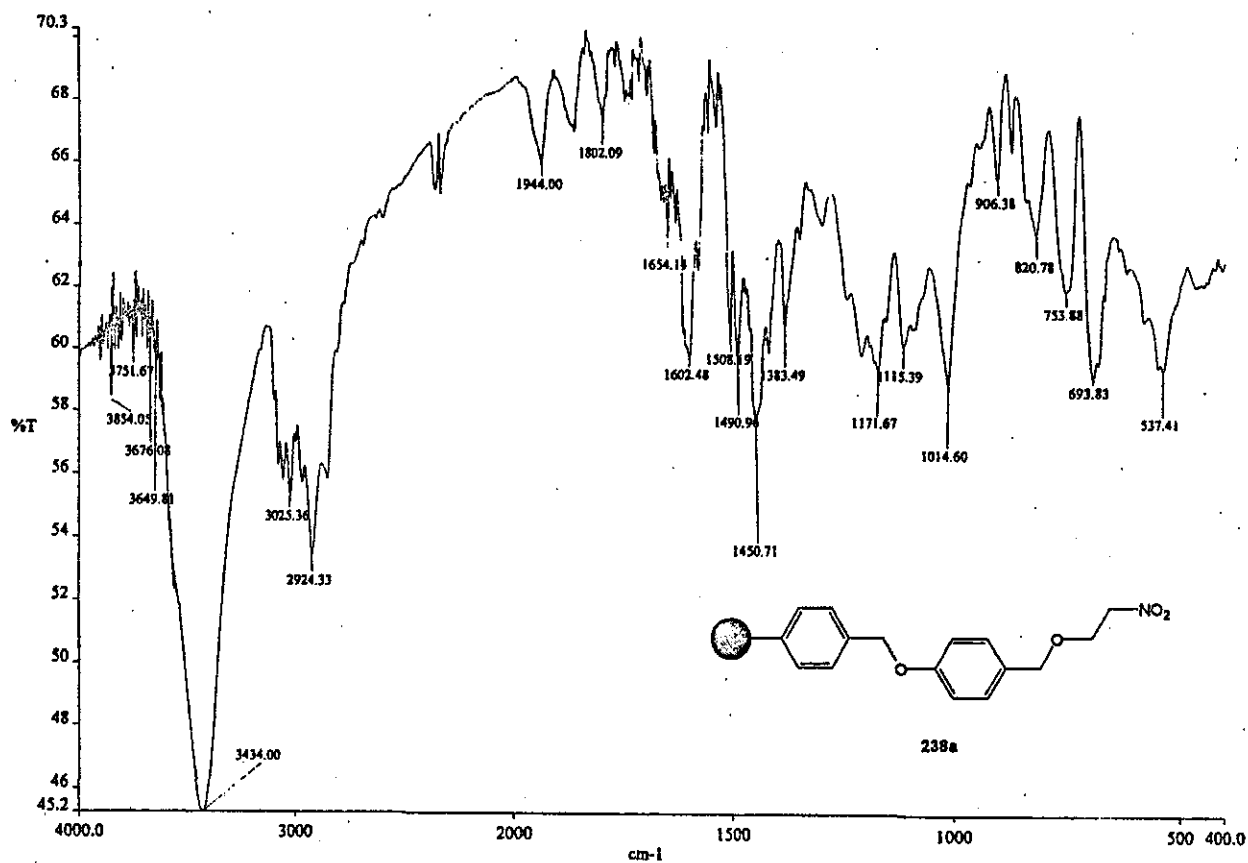
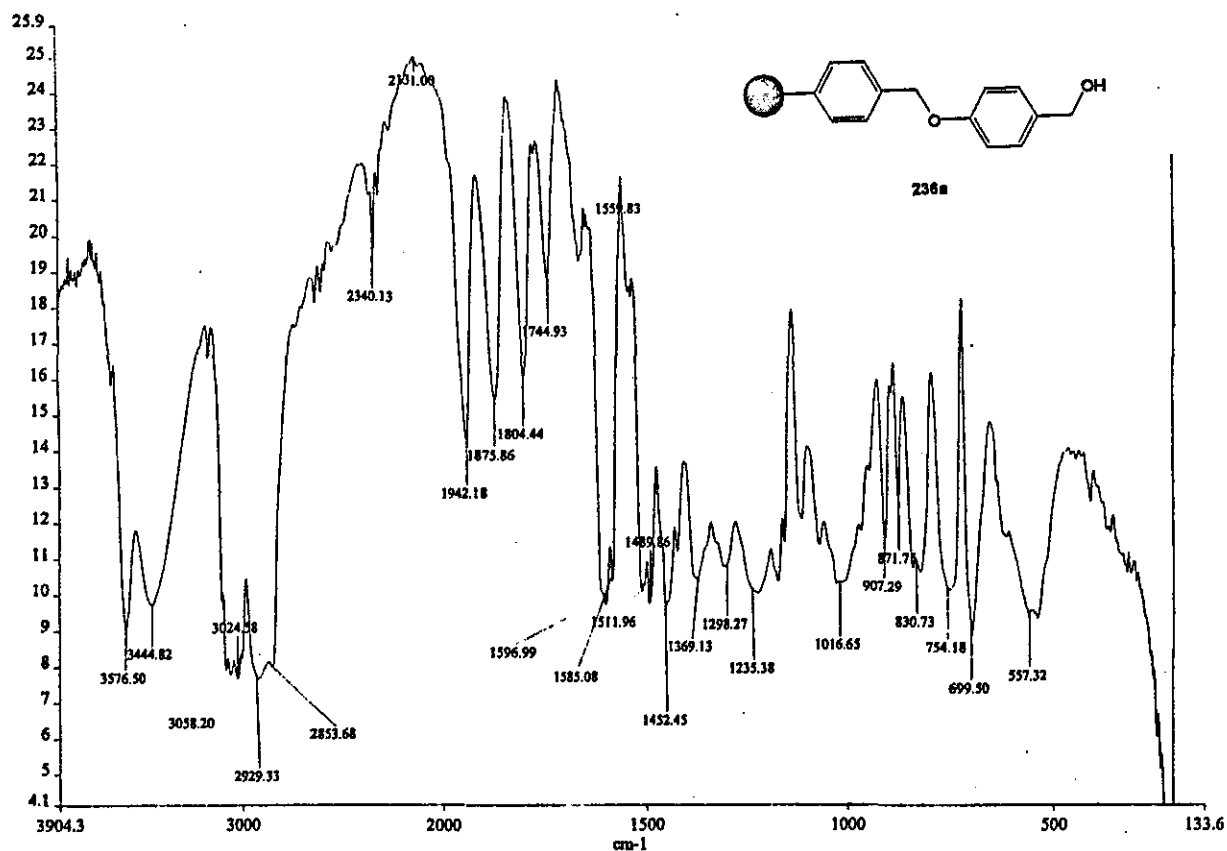
H(27)	-0.0051	0.4393	0.7325	0.033
H(29A)	0.3524	0.6791	0.7250	0.054
H(29B)	0.4385	0.5723	0.7182	0.054
H(30A)	0.5163	0.5564	0.7650	0.066
H(30B)	0.4171	0.6600	0.7721	0.066
H(31)	0.2089	0.5483	0.7956	0.052
H(33A)	-0.0646	0.5690	0.7613	0.052
H(33B)	0.0650	0.6676	0.7609	0.052
H(34A)	-0.1041	0.5867	0.7045	0.077
H(34B)	0.0825	0.5719	0.6850	0.077
H(34C)	0.0453	0.6744	0.7005	0.077
H(35A)	0.0317	0.3172	0.7708	0.094
H(35B)	-0.0679	0.4189	0.7789	0.094
H(35C)	0.0921	0.3732	0.7995	0.094
H(36A)	0.4929	0.4083	0.7539	0.101
H(36B)	0.3676	0.3112	0.7576	0.101
H(36C)	0.4310	0.3726	0.7851	0.101
H(37)	-0.0016	0.2222	0.6537	0.031
H(39A)	0.5133	0.1971	0.6397	0.048
H(39B)	0.5028	0.0850	0.6293	0.048
H(40A)	0.4586	0.2457	0.5942	0.054
H(40B)	0.4366	0.1336	0.5841	0.054
H(41)	0.1198	0.1933	0.5782	0.054
H(43A)	0.1660	0.0441	0.6083	0.058
H(43B)	-0.0204	0.1034	0.6197	0.058
H(44A)	0.2958	0.1047	0.6846	0.085
H(44B)	0.2838	0.0107	0.6643	0.085
H(44C)	0.0914	0.0639	0.6746	0.085
H(45A)	0.2075	0.3963	0.5911	0.071
H(45B)	0.3566	0.3663	0.6156	0.071
H(45C)	0.1695	0.4285	0.6235	0.071
H(46A)	-0.1502	0.3517	0.6249	0.082
H(46B)	-0.1783	0.2442	0.6121	0.082
H(46C)	-0.1181	0.3323	0.5915	0.082

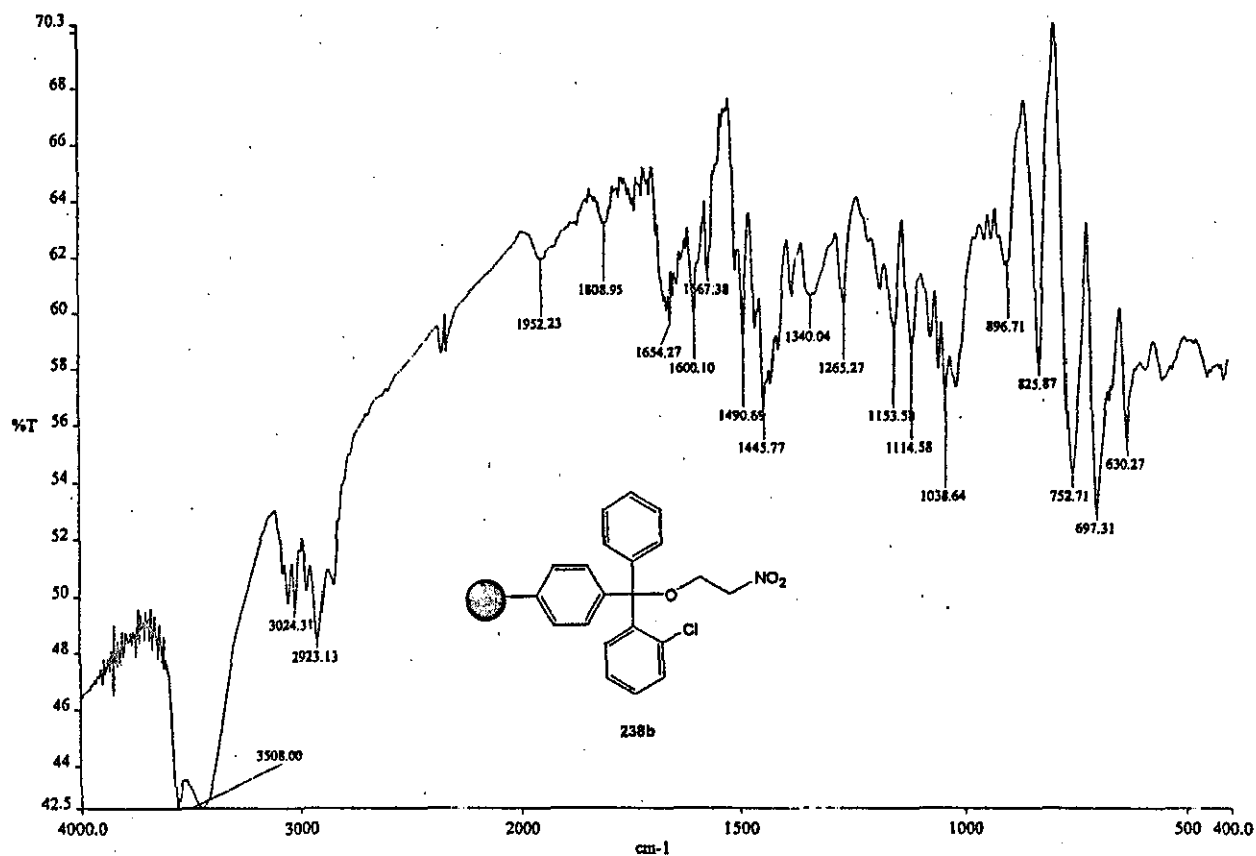
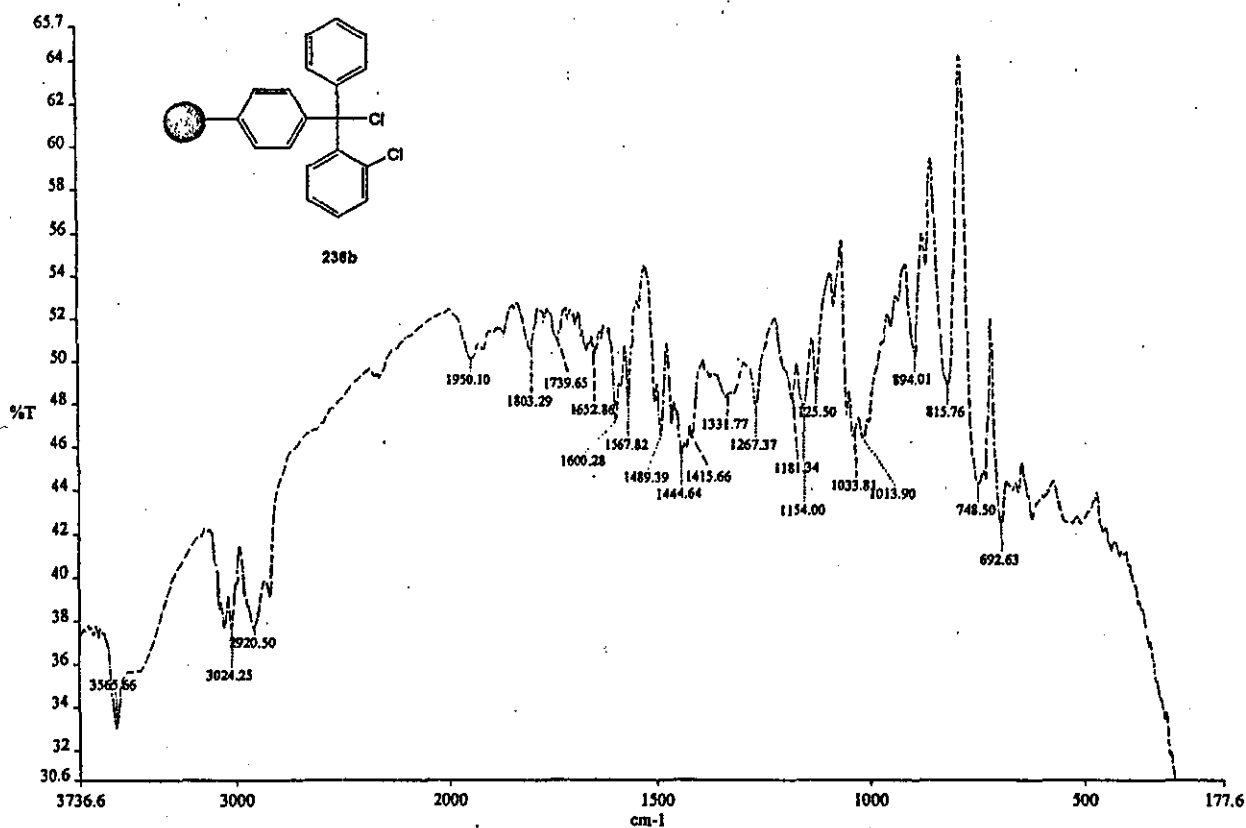
Table 6. Torsion angles [°] for compound **531**.

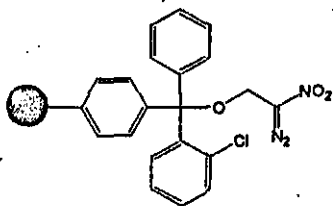
N(2)–C(1)–N(1)–C(4)	173.18(15)	S(1)–C(1)–N(1)–C(4)	–5.8(2)
N(2)–C(1)–N(1)–C(2)	11.3(2)	S(1)–C(1)–N(1)–C(2)	–167.75(15)
C(1)–N(1)–C(2)–C(3)	–23.8(2)	C(4)–N(1)–C(2)–C(3)	174.68(16)
N(1)–C(1)–N(2)–C(14)	171.80(15)	S(1)–C(1)–N(2)–C(14)	–9.2(2)
N(1)–C(1)–N(2)–C(3)	7.2(2)	S(1)–C(1)–N(2)–C(3)	–173.83(14)
C(1)–N(2)–C(3)–C(2)	–21.3(2)	C(14)–N(2)–C(3)–C(2)	174.38(16)
N(1)–C(2)–C(3)–N(2)	25.93(19)	C(1)–N(1)–C(4)–C(5)	–116.15(19)
C(2)–N(1)–C(4)–C(5)	43.0(3)	C(1)–N(1)–C(4)–C(9)	117.12(19)
C(2)–N(1)–C(4)–C(9)	–83.7(2)	N(1)–C(4)–C(5)–C(11)	62.1(2)
C(9)–C(4)–C(5)–C(11)	–165.43(17)	N(1)–C(4)–C(5)–C(10)	–174.58(16)
C(9)–C(4)–C(5)–C(10)	–42.11(19)	N(1)–C(4)–C(5)–C(6)	–71.2(2)
C(9)–C(4)–C(5)–C(6)	61.3(2)	C(11)–C(5)–C(6)–C(7)	159.40(18)
C(10)–C(5)–C(6)–C(7)	33.6(2)	C(4)–C(5)–C(6)–C(7)	–68.6(2)
C(5)–C(6)–C(7)–C(8)	2.4(2)	C(6)–C(7)–C(8)–C(10)	–38.1(2)
C(6)–C(7)–C(8)–C(9)	70.1(2)	C(7)–C(8)–C(9)–C(12)	47.3(2)
C(10)–C(8)–C(9)–C(12)	153.48(18)	C(7)–C(8)–C(9)–C(13)	168.61(19)
C(10)–C(8)–C(9)–C(13)	–85.3(2)	C(7)–C(8)–C(9)–C(4)	–76.6(2)
C(10)–C(8)–C(9)–C(4)	29.5(2)	N(1)–C(4)–C(9)–C(12)	16.5(3)
C(5)–C(4)–C(9)–C(12)	–116.4(2)	N(1)–C(4)–C(9)–C(13)	–103.49(19)
C(5)–C(4)–C(9)–C(13)	123.64(17)	N(1)–C(4)–C(9)–C(8)	141.05(17)
C(5)–C(4)–C(9)–C(8)	8.2(2)	C(7)–C(8)–C(10)–C(5)	58.64(18)
C(9)–C(8)–C(10)–C(5)	–55.9(2)	C(11)–C(5)–C(10)–C(8)	179.0(2)
C(4)–C(5)–C(10)–C(8)	58.84(18)	C(6)–C(5)–C(10)–C(8)	–56.24(19)
C(1)–N(2)–C(14)–C(15)	–122.36(19)	C(3)–N(2)–C(14)–C(15)	40.0(2)
C(1)–N(2)–C(14)–C(19)	110.7(2)	C(3)–N(2)–C(14)–C(19)	–87.0(2)
N(2)–C(14)–C(15)–C(21)	62.9(3)	C(19)–C(14)–C(15)–C(21)	–164.5(2)
N(2)–C(14)–C(15)–C(20)	–174.18(16)	C(19)–C(14)–C(15)–C(20)	–41.51(19)
N(2)–C(14)–C(15)–C(16)	–70.2(2)	C(19)–C(14)–C(15)–C(16)	62.5(2)
C(21)–C(15)–C(16)–C(17)	159.07(19)	C(20)–C(15)–C(16)–C(17)	33.5(2)
C(14)–C(15)–C(16)–C(17)	–69.1(2)	C(15)–C(16)–C(17)–C(18)	2.6(2)
C(16)–C(17)–C(18)–C(20)	–37.92(19)	C(16)–C(17)–C(18)–C(19)	69.4(2)
C(20)–C(18)–C(19)–C(23)	153.27(19)	C(17)–C(18)–C(19)–C(23)	47.9(2)
C(20)–C(18)–C(19)–C(22)	–85.5(2)	C(17)–C(18)–C(19)–C(22)	169.14(18)
C(20)–C(18)–C(19)–C(14)	29.9(2)	C(17)–C(18)–C(19)–C(14)	–75.5(2)
N(2)–C(14)–C(19)–C(23)	16.9(3)	C(15)–C(14)–C(19)–C(23)	–116.4(2)
N(2)–C(14)–C(19)–C(22)	–103.1(2)	C(15)–C(14)–C(19)–C(22)	123.59(18)
N(2)–C(14)–C(19)–C(18)	140.76(16)	C(15)–C(14)–C(19)–C(18)	7.4(2)
C(17)–C(18)–C(20)–C(15)	58.38(19)	C(19)–C(18)–C(20)–C(15)	–56.0(2)
C(21)–C(15)–C(20)–C(18)	178.9(2)	C(14)–C(15)–C(20)–C(18)	58.75(19)
C(16)–C(15)–C(20)–C(18)	–56.48(19)	N(4)–C(24)–N(3)–C(25)	11.3(2)
S(2)–C(24)–N(3)–C(25)	–168.59(14)	N(4)–C(24)–N(3)–C(27)	171.69(15)
S(2)–C(24)–N(3)–C(27)	–8.2(2)	C(24)–N(3)–C(25)–C(26)	–25.2(2)
C(27)–N(3)–C(25)–C(26)	175.03(16)	N(3)–C(25)–C(26)–N(4)	28.06(19)
N(3)–C(24)–N(4)–C(37)	177.20(15)	S(2)–C(24)–N(4)–C(37)	–2.9(2)
N(3)–C(24)–N(4)–C(26)	8.42(19)	S(2)–C(24)–N(4)–C(26)	–171.65(14)

C(25)-C(26)-N(4)-C(24)	-23.39(19)	C(25)-C(26)-N(4)-C(37)	168.15(16)
C(24)-N(3)-C(27)-C(28)	-109.5(2)	C(25)-N(3)-C(27)-C(28)	47.7(3)
C(24)-N(3)-C(27)-C(32)	123.3(2)	C(25)-N(3)-C(27)-C(32)	-79.5(2)
N(3)-C(27)-C(28)-C(34)	60.4(2)	C(32)-C(27)-C(28)-C(34)	-166.03(19)
N(3)-C(27)-C(28)-C(33)	-175.66(17)	C(32)-C(27)-C(28)-C(33)	-42.1(2)
N(3)-C(27)-C(28)-C(29)	-70.9(2)	C(32)-C(27)-C(28)-C(29)	62.6(2)
C(34)-C(28)-C(29)-C(30)	159.33(19)	C(33)-C(28)-C(29)-C(30)	33.2(2)
C(27)-C(28)-C(29)-C(30)	-70.1(2)	C(28)-C(29)-C(30)-C(31)	3.6(2)
C(29)-C(30)-C(31)-C(33)	-38.9(2)	C(29)-C(30)-C(31)-C(32)	69.3(2)
C(30)-C(31)-C(32)-C(36)	48.8(3)	C(33)-C(31)-C(32)-C(36)	154.8(2)
C(30)-C(31)-C(32)-C(35)	169.9(2)	C(33)-C(31)-C(32)-C(35)	-84.1(2)
C(30)-C(31)-C(32)-C(27)	-76.3(2)	C(33)-C(31)-C(32)-C(27)	29.7(2)
N(3)-C(27)-C(32)-C(36)	15.4(3)	C(28)-C(27)-C(32)-C(36)	-117.8(2)
N(3)-C(27)-C(32)-C(35)	-104.6(2)	C(28)-C(27)-C(32)-C(35)	122.25(19)
N(3)-C(27)-C(32)-C(31)	140.80(18)	C(28)-C(27)-C(32)-C(31)	7.6(2)
C(34)-C(28)-C(33)-C(31)	179.4(2)	C(29)-C(28)-C(33)-C(31)	-56.37(19)
C(27)-C(28)-C(33)-C(31)	58.79(19)	C(30)-C(31)-C(33)-C(28)	59.05(19)
C(32)-C(31)-C(33)-C(28)	-56.1(2)	C(24)-N(4)-C(37)-C(38)	-124.55(18)
C(26)-N(4)-C(37)-C(38)	42.4(2)	C(24)-N(4)-C(37)-C(42)	108.9(2)
C(26)-N(4)-C(37)-C(42)	-84.2(2)	N(4)-C(37)-C(38)-C(44)	61.8(2)
C(42)-C(37)-C(38)-C(44)	-166.2(2)	N(4)-C(37)-C(38)-C(43)	-173.19(16)
C(42)-C(37)-C(38)-C(43)	-41.17(18)	N(4)-C(37)-C(38)-C(39)	-70.3(2)
C(42)-C(37)-C(38)-C(39)	61.7(2)	C(44)-C(38)-C(39)-C(40)	159.35(18)
C(43)-C(38)-C(39)-C(40)	32.97(19)	C(37)-C(38)-C(39)-C(40)	-69.0(2)
C(38)-C(39)-C(40)-C(41)	2.9(2)	C(39)-C(40)-C(41)-C(43)	-38.2(2)
C(39)-C(40)-C(41)-C(42)	69.9(2)	C(40)-C(41)-C(42)-C(45)	47.4(2)
C(43)-C(41)-C(42)-C(45)	153.60(19)	C(40)-C(41)-C(42)-C(46)	168.46(19)
C(43)-C(41)-C(42)-C(46)	-85.3(2)	C(40)-C(41)-C(42)-C(37)	-76.3(2)
C(43)-C(41)-C(42)-C(37)	30.0(2)	N(4)-C(37)-C(42)-C(45)	16.6(3)
C(38)-C(37)-C(42)-C(45)	-116.31(19)	N(4)-C(37)-C(42)-C(46)	-103.6(2)
C(38)-C(37)-C(42)-C(46)	123.45(19)	N(4)-C(37)-C(42)-C(41)	140.21(17)
C(38)-C(37)-C(42)-C(41)	7.27(19)	C(40)-C(41)-C(43)-C(38)	58.98(19)
C(42)-C(41)-C(43)-C(38)	-56.3(2)	C(44)-C(38)-C(43)-C(41)	-179.7(2)
C(37)-C(38)-C(43)-C(41)	58.67(18)	C(39)-C(38)-C(43)-C(41)	-55.93(19)

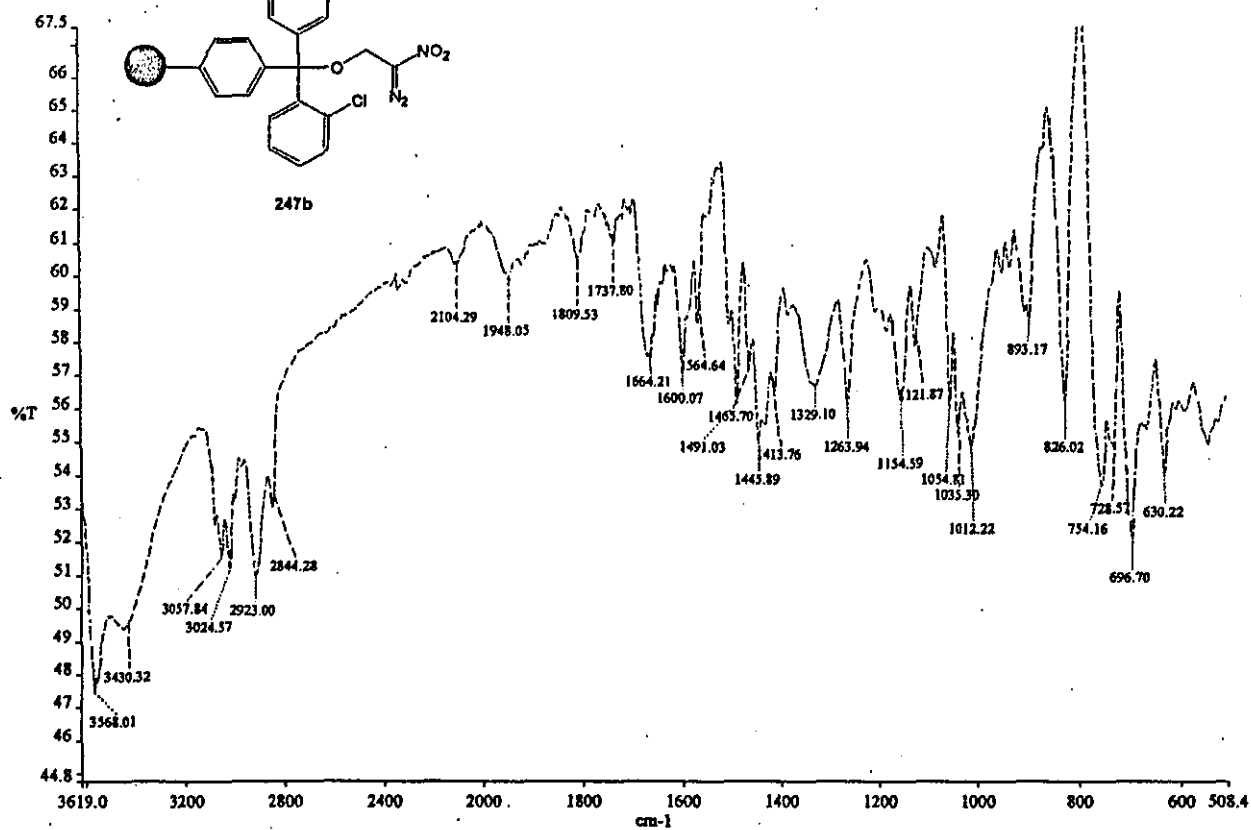
8.2 IR spectra

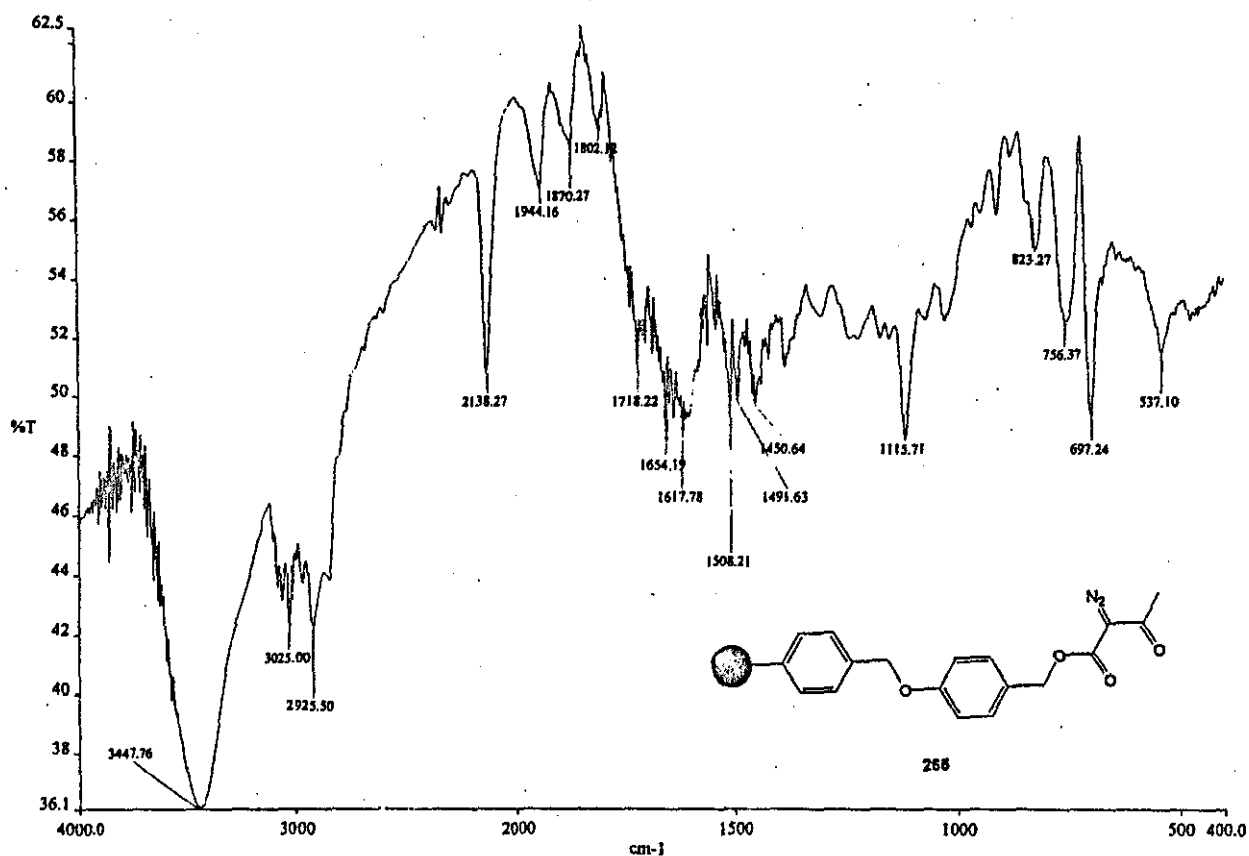
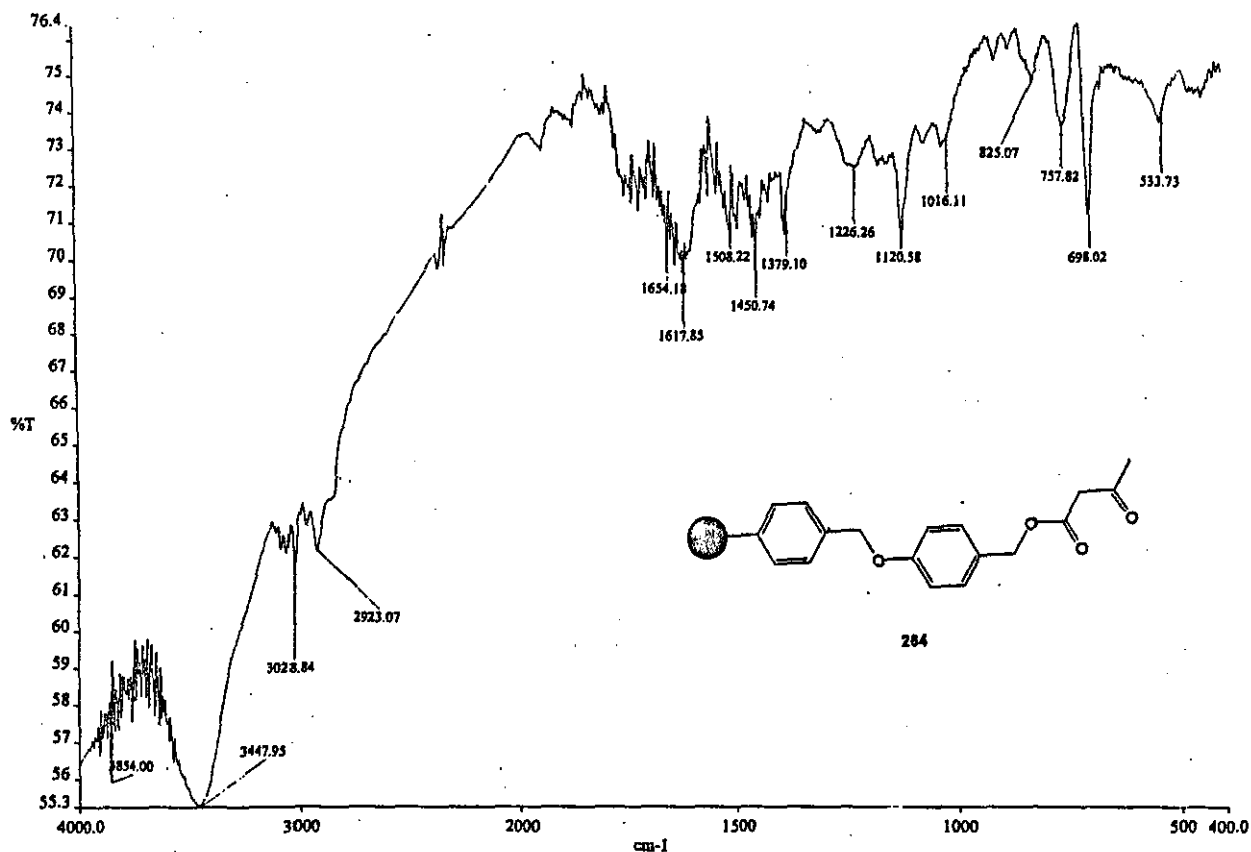


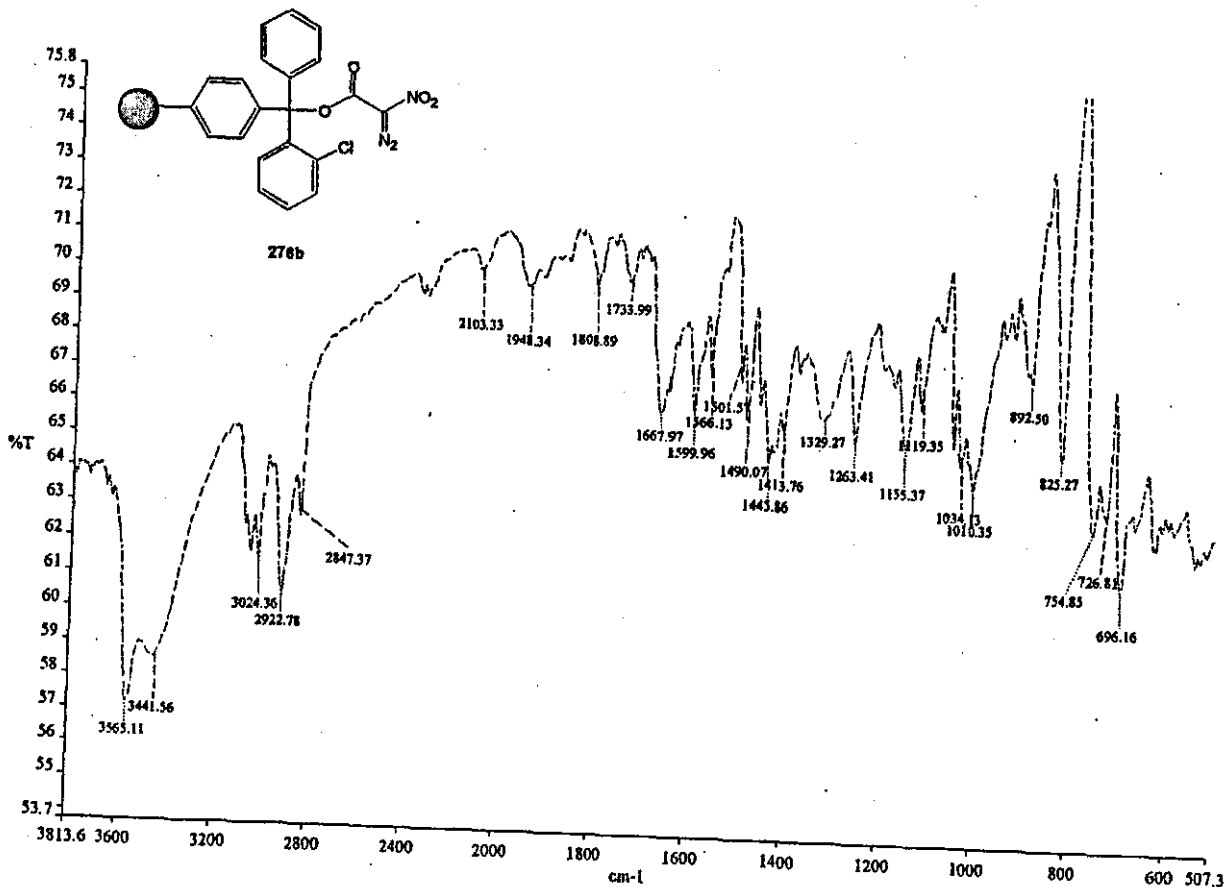
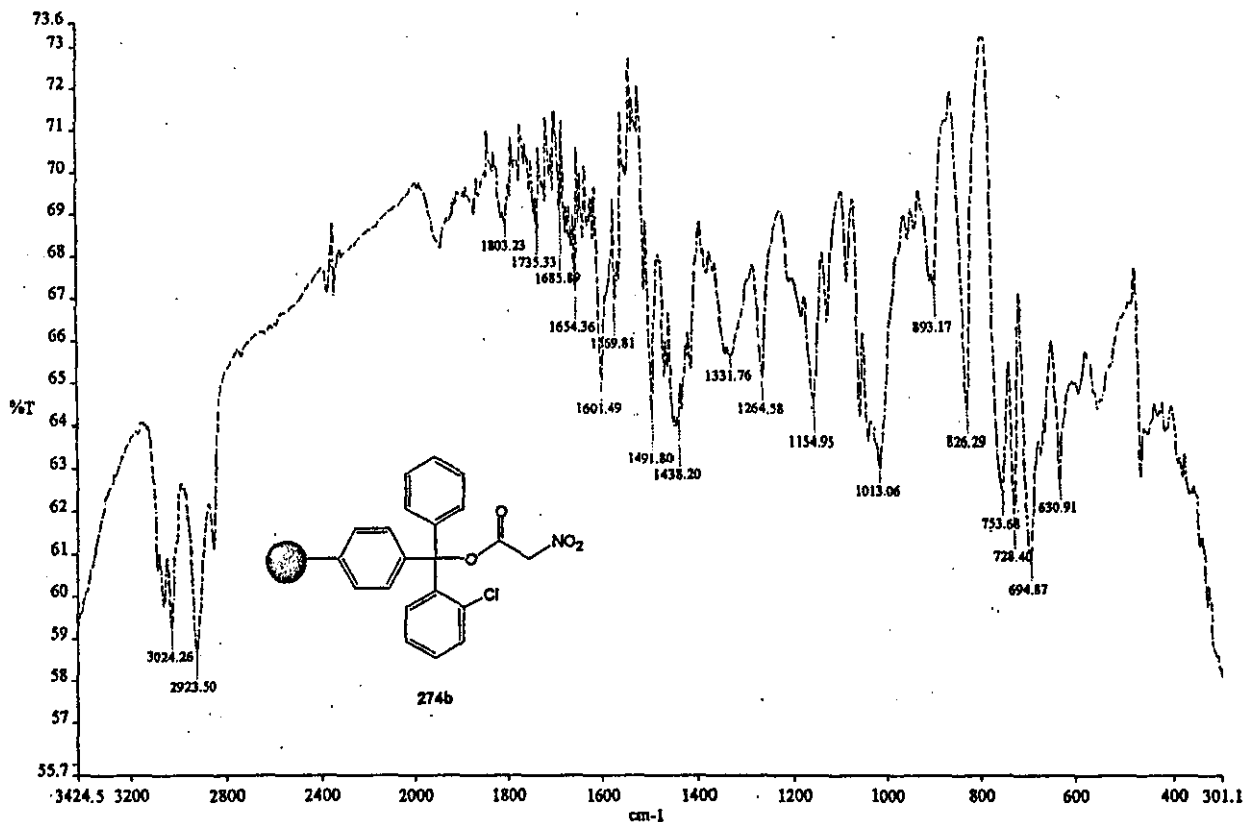




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8.3 NMR spectra

