A generic parallel combinatorial approach to Chiral Lewis acid catalyst discovery: application to the aza-Diels-Alder reaction

Jay, David Alexander

A Generic Parallel Combinatorial Approach to Chiral Lewis Acid Catalyst Discovery: Application to the Aza-Diels-Alder Reaction

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David Alexander Jay

Department of Chemistry

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No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification at this or any other university, or other institute of learning.

To Mum and Dad

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Abstract

A generic parallel combinatorial method was used in order to attempt to develop new asymmetric processes for the aza-Diels-Alder reaction. Initially, an *N-para*-methoxyphenyl glyoxylate derived imine and its reactions with a variety of dienes was examined. Several new adducts were obtained, which included both "normal" and "inverse" electron-demand aza-Diels-Alder products, and an acyclic product. These results strongly suggested the intervention of a stepwise addition-cyclisation mode of the reaction of diene with the imine.

Later, new *N*-phosphorus imines were examined as dienophile substrates for aza-Diels-Alder reactions. The results of the reactions between these imines and a variety of dienes showed a reduced level of imine reactivity when compared to the *N-para*-methoxyphenyl *C*-carboxylate-derived system. Several new products were obtained and the results indicated a stepwise reaction process was in operation, due to the formation of other di-dehydro-piperidinone or acyclic ketone or aldehyde derivatives. In this study, the first apparent *N*-phosphonyl imino-Diels-Alder reaction on such systems has been recorded. Screening reactions with different Lewis acids and chiral ligands produced no asymmetric induction, however, this system proved to be unreliable for monitoring by HPLC due to the presence of both cyclic and acyclic products.

Glossary

A summary of abbreviations:

Ac	: Acetyl
AcOH	: Acetic acid
Ar	: Aryl
BINAP	: 2,2'-bis(diphenylphosphanyl)-1,1'-binapthyl
Binapthol	: 1,1'–Bi–2–napthol
BINOL	: see Binapthol
Bn	: Benzyl
Boc	: ^{t}Butoxycarbonyl
Br – BINOL	: 6,6'–Dibromo–1,1'–bi–2–napthol
^{t}Bu	: 2-(2-methylpropyl)
^{t}BuOMe	: ^{t}Butyl methyl ether
Cat.	: Catalyst
CD	: Circular Dichroism
CI	: Chemical Ionisation
CONJ	: Conjugating Group
DBU	: 1,8-Diazabicyclo[5.4.0.]undec-7-ene
DCM	: Dichloromethane
DEPT	: Distortionless Enhancement through Polarisation Transfer
DFT	: Density Functional Theory
DMAP	: 4–Dimethylaminopyridine
DMF	: *N*,*N*,-Dimethyl formamide
DMI	: 1,2-Dimethylimidazole
DMP	: 2,6-Dimethylpyridine
DTBMP	: 2,6-Di-*tert*-butyl-4-methylpyridine
DTBP	: 2,6-Di-*tert*-butyl-pyridine
EDG	: Electron Donating Group
e.e.	: Enantiomeric Excess
EI	: Electron Ionisation
ES	: Electro-spray Ionisation
Et	: Ethyl
Et_3N	: Triethylamine
EWG	: Electron Withdrawing Group

eV	: Electron Volt
FAB	: Fast Atom Bombardment
FMO	: Frontier Molecular Orbital
Fur	: 2-Furyl
GC	: Gas Chromatography
GLC	: Gas-Liquid Chromatography
HIV	: Human Immuno-deficiency Virus
HOMO	: Highest Occupied Molecular Orbital
HPLC	: High Performance Liquid Chromatography
IPA	: Isopropyl alcohol
IR	: Infra Red
L	: Ligand
LUMO	: Lowest Unoccupied Molecular Orbital
Me	: Methyl
MeCN	: Acetonitrile
MeOH	: Methanol
Mol	: Mole
m.p.	: Melting Point
MS	: Molecular Sieves
Nap	: Napthyl
NBS	: *N*-bromosuccinimide
NMI	: *N*–Methylimidazole
NMR	: Nuclear Magnetic Resonance
OTf	: see Triflate
Ph	: Phenyl
PMA	: Phosphomolybdic acid
PMP	: *p*-methoxyphenyl
^{i}Pr	: 2-propyl
^{n}Pr / Pr	: 1-propyl
RT	: Room Temperature
T	: Temperature
TBAF	: Tetrabutylammonium fluoride
TBDMS	: ^{t}Butyldimethylsilyl
TFA	: 1,1,1-Trifluoroacetic acid
THF	: Tetrahydrofuran

TLC	:	Thin Layer Chromatography
TMS	:	Trimethylsilyl
TMSO	:	Trimethylsilyloxy
Tol	:	Toluene
Tol-BINAP	:	2,2'-bis(di-*p*-tolylphosphanyl)-1,1'-binapthyl
Triflate	:	Trifluoromethanesulfonate
Ts / Tosyl	:	*p*-Toluenesulfonyl
T-S	:	Transition State
UV	:	Ultra Violet
Xylyl	:	Dimethylphenyl

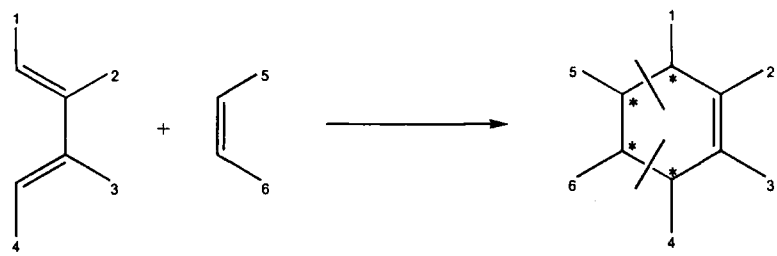
Chapter One

Introduction

1.1 Diels-Alder Reaction

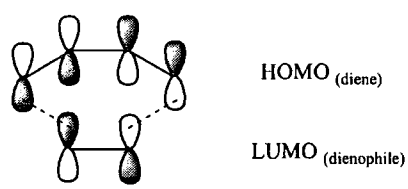
Search almost any organic chemistry textbook and there will be a section on the Diels-Alder reaction. After its discovery in 1928 by Otto Diels and Kurt Alder, research into this area, particularly by Woodward and Hoffman in the 1960s and 70s, has unearthed a much greater understanding into the way in which the reaction works. The product (certainly in the all-carbon Diels-Alder reaction) regio- and stereochemistry can largely be predicted by employing Frontier Molecular Orbital (FMO) theory.[1] It is generally accepted as being the most powerful way of constructing six-membered rings, creating two new C-C bonds and up to four new chiral centres at the binding sites of the diene and dienophile (Equation 1).

Equation 1



In the normal electron demand cycloaddition, the orbital interactions of consideration are that of the HOMO of the diene, and the LUMO of the dienophile. This is exemplified in the reaction between butadiene and ethene (Figure 1).

Figure 1



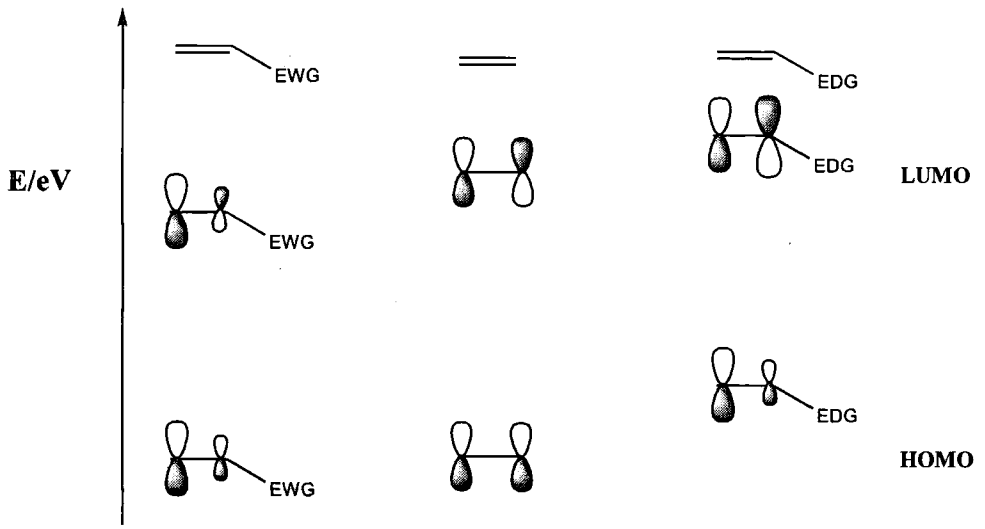
The symmetry of orbitals in the HOMO of butadiene, and the LUMO of ethene are identical. The reaction is said to be "symmetry allowed". If the signs of the orbitals are opposite, the reaction is symmetry forbidden. Maximum stability in the transition state is found when terminal atoms in both HOMO $_{(diene)}$ and LUMO $_{(dienophile)}$ interact. In symmetry allowed reactions, a four-centre transition state is stabilised more than a two-centre transition state. In symmetry forbidden reactions, the opposite is true.

1.2 Substituent Effects and Product Prediction

1.2.1 Rate of reaction

Substituents on the alkene and diene have a dramatic effect on the rate of reaction, and the stereochemistry of the product formed. If a carbon atom has a substituent other than hydrogen, a change in the energy of the HOMO and LUMO and the magnitude of their coefficients occurs (Figure 2). This can be a decrease in energy or an increase depending on the nature of the substituent. Electron withdrawing groups have the effect of lowering the orbital energy of both the HOMO and LUMO, whilst simultaneously lowering the magnitude of the orbital coefficients. The greater impact is felt by the LUMO. It should also be noted that atoms closest to the electron-withdrawing group experience the largest diminution in orbital coefficient magnitude. Electron donating groups, on the other hand, increase the energies of the HOMO and LUMO – the greater impact being felt on the HOMO. The magnitudes of the orbital coefficients of the HOMO are decreased proximal to the electron donating group, whilst the distal orbitals remain larger. In the case of the LUMO, the proximal orbital has greater coefficient magnitude than the distal.

Figure 2

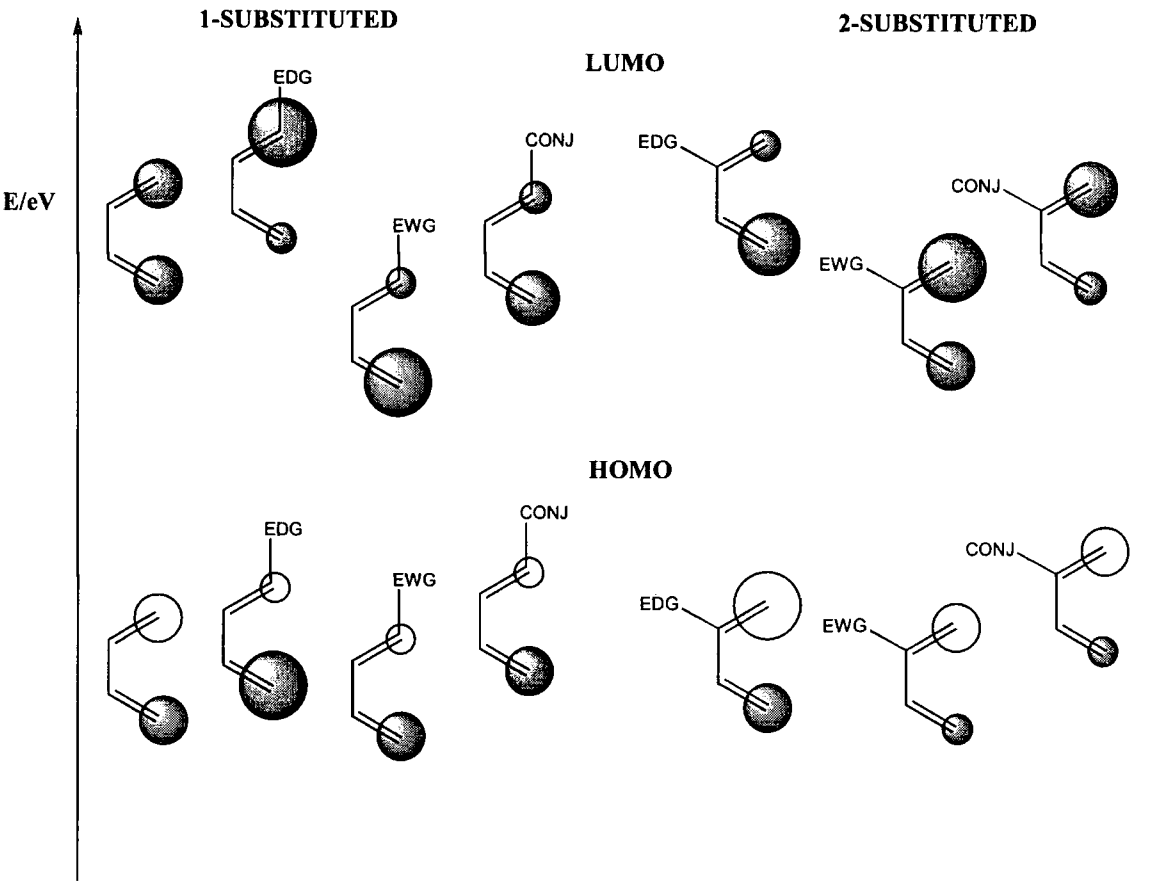


EWG = ELECTRON WITHDRAWING GROUP
EDG = ELECTRON DONATING GROUP

In the case of styrene (CH_2=CHPh) and other alkenes with added conjugation, there is an increase in the energy of the HOMO and a decrease in the energy of the LUMO with respect to ethene. Also, the magnitude of the orbital coefficients is lowered, with the proximal atom experiencing the greater reduction. The effect is similar to that of an electron-withdrawing group, with the exception that the HOMO increases in energy (relative to ethene). 1,3-Butadiene can be treated in this way. Obviously all the atomic orbitals should be considered, yet, in the Diels-Alder reaction, it is only the terminal orbitals that interact with the dienophile in bonding. This is where the majority of electron density is found, due to the electron withdrawing effect and the symmetry of the molecule.

The substituents on butadiene have a similar effect to that on ethene (Figure 3). EWGs lower frontier orbital energies, whilst EDGs increase them. Adding extra conjugation to the system also has an impact. In addition, there is the question of regiochemical control. Substituents can be placed on either C_1 or C_2 and the position of the substituent does have some bearing of the severity of the effects on the FMOs.

Figure 3



CONJ = CONJUGATING SUBSTITUENT (e.g. Ph)

With EDGs, the energies of both the HOMO and LUMO are raised relative to butadiene. C_1 substitution has a greater overall effect on the FMOs than the equivalent C_2 substituted system. The magnitude of the HOMO orbital coefficients is larger distal in C_1, and proximal in C_2 substituted butadienes. LUMO coefficients are larger proximal to C_1 substituted, and distal to C_2 substituted. In the case of EWG's, the HOMO and LUMO energies are lowered with respect to butadiene; C_1 substitution having a greater effect than C_2. The orbital coefficients are larger at the distal position in C_1 substituted dienes for both HOMO and LUMO. In C_2 substituted dienes, greater orbital coefficient magnitude is observed at the proximal position of both HOMO and LUMO. Conjugation increases the energy of the HOMO and lowers that of the LUMO. The orbital coefficients of the HOMO and LUMO are larger distal to C_1 substituted, and larger proximal to C_2 substituted.

The efficiency of the Diels-Alder reaction is a product of the difference in energy between the HOMO and LUMO of the reactants. A smaller energy gap leads to a faster reaction. Therefore, in the normal electron demand case, it is advantageous to have an electron donating group on the diene (to increase the HOMO energy) and an electron withdrawing group on the dienophile (to lower the energy of the LUMO). Of course, in the case of inverse electron demand (HOMO $_{(diene)}$, LUMO $_{(dienophile)}$), the opposite is true.

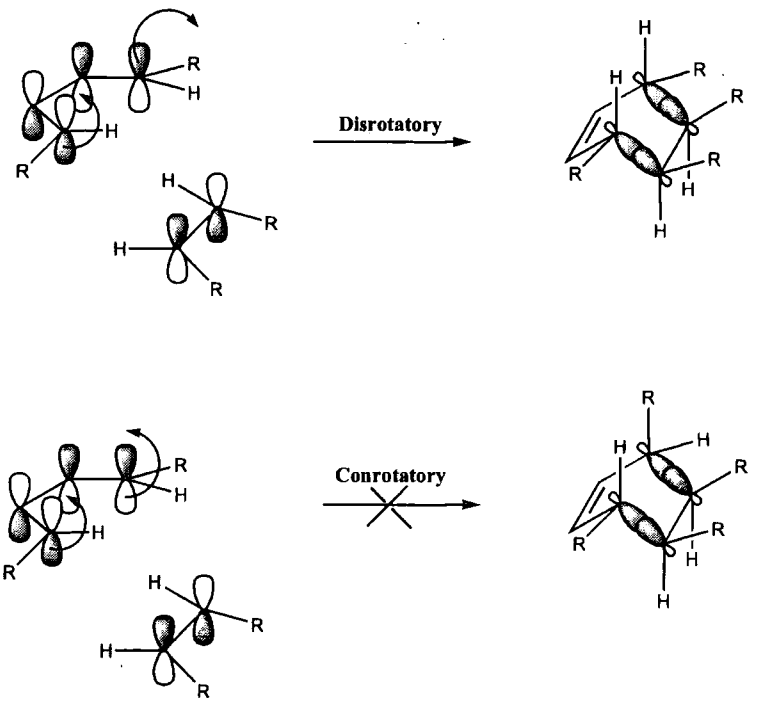
1.2.2 The *Cis*-Principle

The relative stereochemistry of both diene and dienophile are retained in the cycloadduct (Figure 4). This observation has been termed the "*cis*-principle". Again, this facet of the Diels-Alder reaction can be explained using Frontier Molecular Orbital theory.

The terms **conrotatory** and **disrotatory** are prescribed to the motion of the frontier orbitals to achieve the greatest overlap. Conrotatory is where the orbitals move in the same direction (*i.e.* both clockwise, or both anticlockwise). Disrotatory is where the orbitals move in opposite directions.

In the normal Diels-Alder reaction (as can be seen below), this motion has to be disrotatory to allow orbitals of the same sign to overlap. This enables prediction of the stereochemistry in the cycloadduct. *Trans*, *trans* dienes give a cycloadduct where the substituents are *syn* relative to each other. *Cis*, *trans* dienes give the cycloadduct where the substituents are *anti* relative to one another.

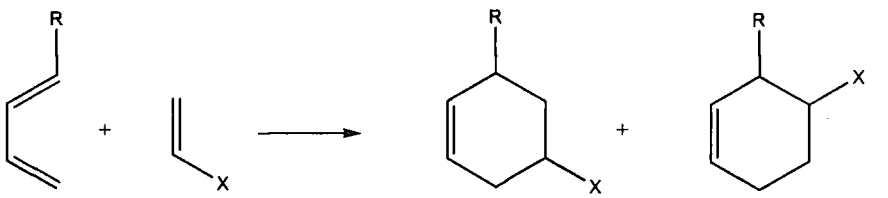
Figure 4



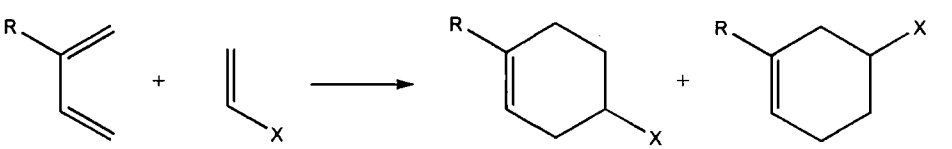
1.2.3 The Ortho Effect

Following on from the *cis*-principle, it can be seen that the cycloadduct could have different regioisomers (Equation 2 & 3). Ordinarily, the Diels-Alder reaction is remarkably selective and this depends on the nature of the diene and the alkene. Again, it can be rationalised using FMO theory.

Equation 2

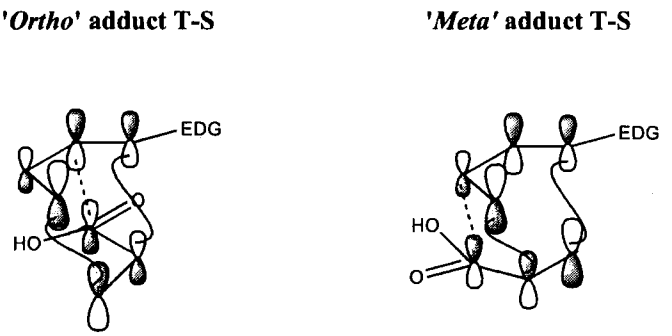


Equation 3



It is the magnitude of the orbital coefficients that dictates the regiochemistry. Similar to the relative rate of reaction being determined by the difference between the energies of the HOMO and the LUMO, the magnitude of coefficients affects the orientation of the reactive orbitals. Large-large / small-small interactions are greater than having large-small / small-large. A small difference in magnitude means better overlap between orbitals (of the same sign). This is where secondary orbital interactions may have a role. In a substituted butadiene, the magnitude of the C_2 and C_3 orbitals can be markedly different. This will affect the relative orientation of reactants (and thus stability) in the transition state (Figure 5).

Figure 5



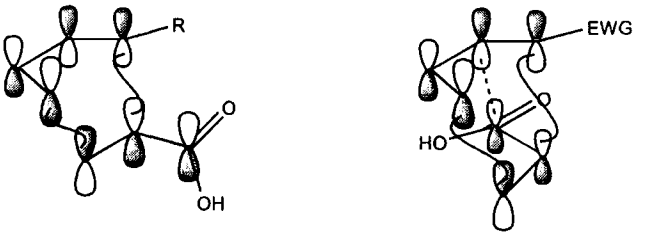
There is a tendency to form the "*ortho*" transition state in the Diels-Alder reaction. The reason for this is greater overlap between the HOMO of C_2 of the diene and the LUMO of the carbonyl carbon in the above example, relative to that of the HOMO of C_3 in the diene and the LUMO of the carbonyl carbon.

1.2.4 The *Endo* Rule

Secondary orbital interactions also have influence over *endo* / *exo* selectivity (Figure 6). The fact that these interactions exist means that there is a strong drive for a stabilised *endo*-transition state. Although thermodynamically the *endo*-adduct is less stable than *exo* (due to steric effects), the increased stability of the transition state means it is kinetically preferred.

Figure 6

***Exo*-adduct T-S** ***Endo*-adduct T-S**



1.3 Asymmetric Diels-Alder Reaction

The all-carbon (homo) Diels-Alder reaction can be extrapolated into the hetero-Diels-Alder reaction. Since many natural product targets contain functionalities such as cyclic ethers, thio-ethers and amines, a process that constructs such systems in a single cycloaddition reaction is particularly attractive. Thus, carbonyl, nitroso, nitrile and imine functionalities have all been used in hetero-Diels-Alder reactions to rapidly build up the corresponding heterocyclic frameworks. In addition, the presence of a heteroatom, often in the dienophile component, provides further potential for the use of Brønsted or Lewis acid catalysts, *i.e.* these acids can coordinate to the heteroatom, lowering the energies of both HOMO and LUMO (on either the dienophile or diene component), and thus the activation energy.

Whilst the "*endo*-rule", "*ortho*-effect" and the "*cis*-principle" can be applied to ensure a frequently high degree of diastereoselectivity in the reaction through secondary orbital interactions, these principles do not address the control of absolute stereochemistry. There is no way for there to be facial bias in an intermolecular Diels-Alder reaction, without the introduction of a source of chirality into the process. Methods by which this can be done include the addition of a chiral centre onto the diene or dienophile, or preferably the application of a chiral Lewis acid catalyst.

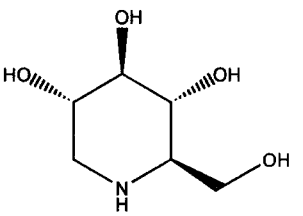
Auxiliary based methods offer a good approach to stereoselective transformations. They have been proven to afford high levels of asymmetric induction in a broad range of different reaction classes. However, the drawbacks when compared to a chiral catalyst based method are several-fold. Firstly, catalytic methods require a sub-stoichiometric amount of reagent to execute the transformation, and this is done in one step. In auxiliary based methods, the auxiliary must be attached, and subsequently

removed from the substrate. This involves more reaction steps, which often leads to lower overall yields, more waste and longer waiting periods for the final product. This in turn, can often lead to greater expense.

1.4 Piperidine Alkaloids and the Diels-Alder Approach

The biological activity of the various piperidine ring derivatives is well known. One such example is the natural product 1-deoxynojirimycin **1** (Figure 7).[2] This aza-sugar and its derivatives have a range of biological activities, including, antidiabetic, anticancer and anti-HIV I and II properties.

Figure 7



1

This type of piperidine structure is ideally suited to construction *via* the aza-Diels-Alder reaction. One way to construct the 6-membered ring fragment could utilise an imine as a dienophile, plus a diene, or conversely using an imine as a diene to react with a dienophile. Although the imino-Diels-Alder reaction has been known for some time,[3] it is only in recent years that major advances have been made in developing catalytic asymmetric versions.[4] There are now a few examples of truly catalytic asymmetric imino-Diels-Alder processes in the literature, unlike the myriad examples of aldehyde dienophile Diels-Alder reactions. The reasons for this are several-fold: firstly, there is poorer electrophilicity in imines compared with aldehydes, and hence there is lower reactivity of the C=N bond *versus* the C=O bond; secondly, some imines are highly susceptible to hydrolysis, which creates problems in synthesis and purification, making imines less easy to study; thirdly, there are a greater number of solution conformations possible for imines, due to the potential for the existence of both *cis*- and *trans*-isomers; finally, a problem lies in the Lewis basicity of the nitrogen atom of imino dienophiles, which is more Lewis basic than the corresponding carbonyl system. It is therefore more likely to have strong coordination to whatever Lewis acid is present, resulting in a slowing or stopping of the reaction. In addition, the product of the reaction is basic and

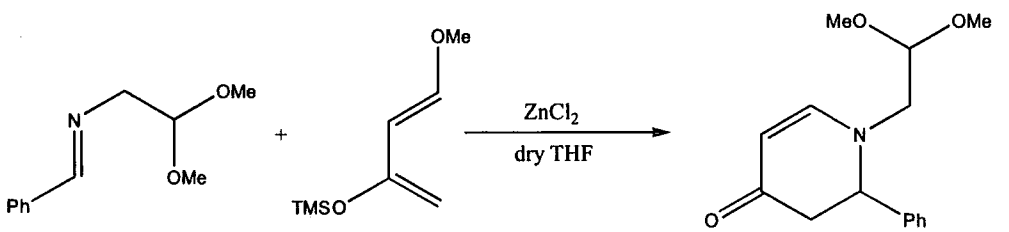
can therefore exert a similar effect, preventing catalyst release. These effects can result in catalyst inhibition, which may necessitate the use of a stoichiometric amount of Lewis acid. Hence, there are numerous examples of asymmetric imino-dienophile Diels-Alder reactions using either imines or dienes with chiral auxiliary functions attached,[4] but there are very few examples of chiral Lewis acid catalysed processes.

1.5 Imine Activation and the Homogeneous Imino-Dienophile Diels-Alder Reaction

Catalysts are widely used in chemical synthesis, often allowing reactions to progress under much milder conditions, producing higher yields and greater selectivities. Generally speaking, in the case of imines, catalysts are required for activation of the imine in order to react with a diene in Diels-Alder processes. Exceptions include the use of iminium salts and intramolecular additions.[5]

Danishefsky *et al.* published the first Lewis acid catalysed ($ZnCl_2$) cycloaddition using imines with the reactive diene **3** back in 1982.[6] The best result (product isolated in 76% yield with 4.2 eq. of diene) is shown below (Equation 4). These reactions were performed with use of a stoichiometric amount of the Lewis acid in anhydrous THF under an inert atmosphere.

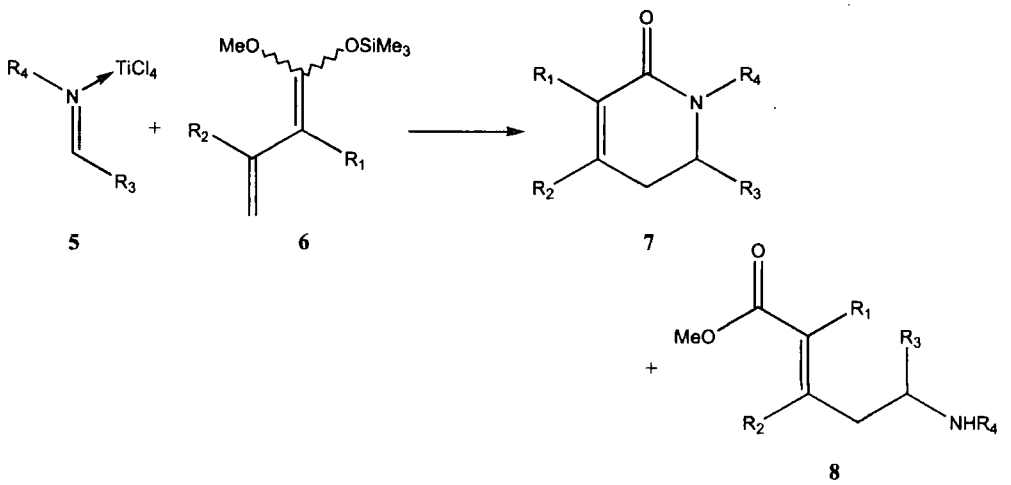
Equation 4



2 3 4

Ojima also noted that imines would produce cycloadducts and acyclic products in titanium(IV) chloride catalysed reactions of vinyl ketene silyl acetals (Equation 5).[7]

Equation 5

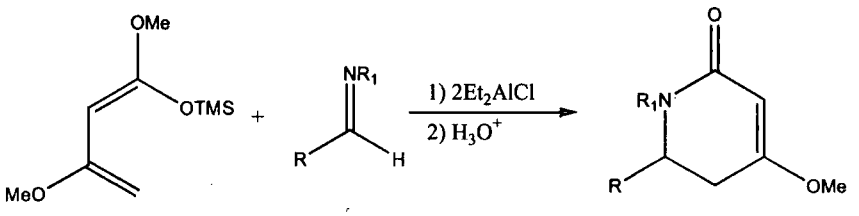


5 **6** **7** **8**

He proposed that the two products observed in Equation 5 arose by a common intermediate. Evidence existed from GC monitoring of the reaction mixture; the acyclic product could be seen to disappear at the same rate that cyclic material was forming. Also, a reaction that gave *exclusively the cyclic* product (R_1 = H, R_2 = Me, R_3 = Ph, R_4 = CH_2Ph), when quenched at room temperature, afforded four times more *acyclic* material than cyclic when the quench was performed below –50 °C, regardless of reaction time.

A year later, Midland and co-workers published results using a variety of unactivated imines **10** with the highly reactive 1,3-dimethoxy-1-(trimethylsilyloxy)-1,3-butadiene **9** (Equation 6, Table 1).[8] They found that stronger Lewis acids such as Et_2AlCl were needed to effect high yields.

Equation 6



9 **10** **11**

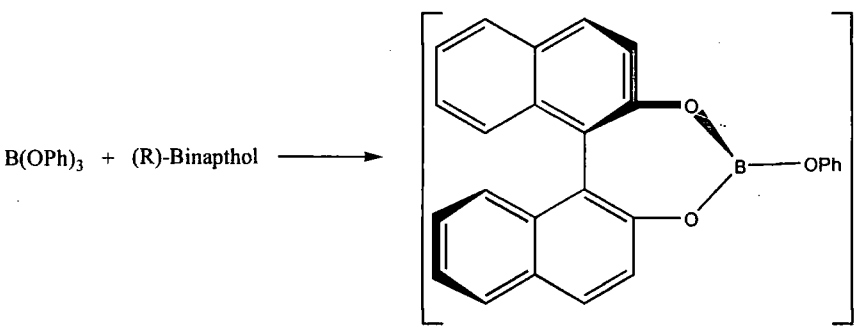
Table 1. Table showing the yields of cycloadducts **11** from the Diels-Alder reaction of diene **9** and various imines, catalysed by Et_2AlCl.

Entry	R	R_1	Yield (%)
a	Ph	Me	82
b	Ph	^{n}Pr	65
c	Ph	CH_2TMS	80
d	Ph	Bn	73
e	^{i}Pr	^{n}Pr	62
f	^{i}Pr	Bn	68

This publication also illustrated one of the earliest examples of an asymmetric reaction of an unactivated imine. The asymmetry, however, was auxiliary induced.

In 1993, work from Yamamoto's laboratory showed one of the earliest examples of a chiral Lewis acid complex in an enantioselective imino-Diels-Alder reaction.[9] They developed chiral boron complexes (Equation 7) constructed *in situ* from triphenyl borate and (*R*) or (*S*) - BINOL in a 1:1 ratio.

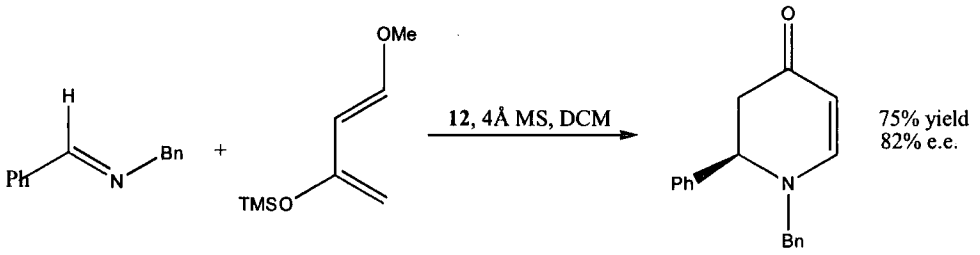
Equation 7



12

In a subsequent reaction with imine **10d** and Danishefsky's diene **3** (Equation 8), the catalyst **12** was used in a stoichiometric amount in DCM with 4Å MS at –78 °C for 5 hours to afford product **13** in 75 % yield and with 82 % enantiomeric excess.

Equation 8



10d **3** **13**

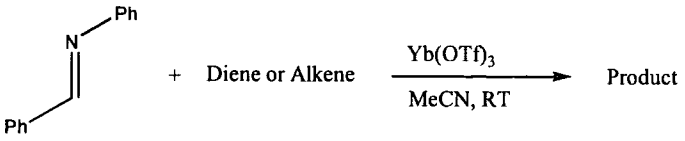
The product was formed in good yield with high e.e., however, the importance of the choice of Lewis acid was illustrated on further investigation. Different Lewis acids were combined with BINOL to reveal varying degrees of success (Table 2).

Table 2. Table showing the effect of Lewis acid on yield and e.e. on the reaction detailed in Equation 8.

Entry	Lewis Acid	Yield (%)	e.e. (%)
a	BH_3	62	72
b	$TiCl_2(O^iPr)_2$	20	17
c	Me_3Al	15	12
d	Me_2Zn	0	-
e	$PhB(OH)_2$	15	30
f	$B(OMe)_3$	42	72
g	$B(OPh)_3$	75	82
h	$B(O\text{-}2\text{-}PhMe)_3$	76	84
i	$B(O\text{-}3,5\text{-}Xylyl)_3$	75	86

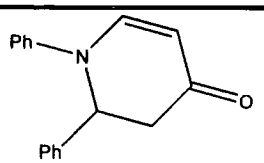
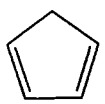
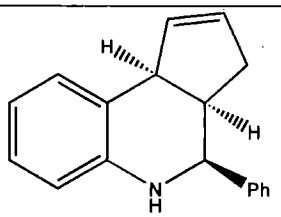
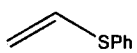
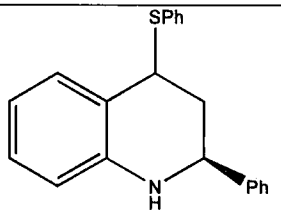
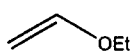
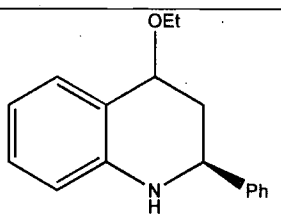
Although successful in introducing asymmetry, these catalyst systems were not truly catalytic, which prompted further investigations into new catalytic Lewis acid catalysed aza-Diels-Alder reactions. The first breakthrough was made by Kobayashi's group in 1995.[10] They found that lanthanide triflates would catalyse imino-Diels-Alder reactions with loadings as low as 5 mol %. Although the reactions were achiral, it uncovered the potential for using truly catalytic amounts of Lewis acid in these reactions. In a typical reaction, 10 mol % $Yb(OTf)_3$ was used to catalyse the reaction between **14** and a variety of dienes and alkenes. It was interesting to note that different kinds of product arose depending on the choice of reaction partner (Equation 9, Table 3).

Equation 9



14

Table 3. Table showing the products obtained and yields for the reaction detailed in Equation 9.

Entry	Diene or Alkene	Product	Yield (%)
a	**3**	 **15**	80
b	 **16**	 **17**	56
c	 **18**	 **19**	70
d	 **20**	 **21**	60

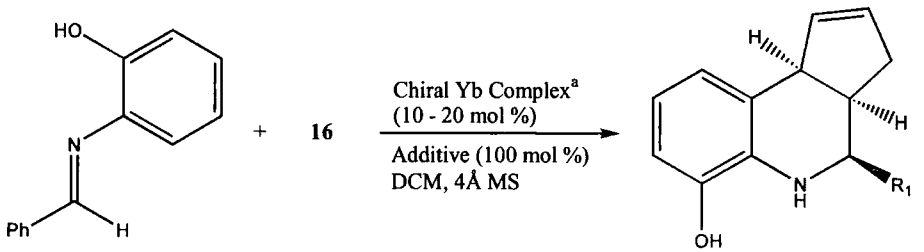
Danishefsky's diene **3** reacts with imine **14** as a diene, however, cyclopentadiene **16**, reacts as a dienophile and the imine as an aza-diene. This was further exemplified by reaction with electron rich alkenes **18** and **20**.

By 1996, Kobayashi had used lanthanide(III) triflates to perform asymmetric aza-Diels-Alder reactions.[11] A chiral ytterbium complex was prepared from $Yb(OTf)_3$, (*R*)-(+)-BINOL and 1,3,5-trimethylpiperidine (TMP), and used in the reaction of *N*-

benzylideneaniline **14** with cyclopentadiene **16** to produce tetrahydroquinoline **17** in 53 % yield, but with no asymmetric induction.

It was decided that bidentate chelation of the imine substrate to the chiral Lewis acid catalyst would be needed to generate any selectivity. This turned out to be a useful observation and further experimentation (Equation 10, Table 4) using imine **22** gave a maximum e.e. of 91 % (Entry c). The best overall result was 92 % yield and 71 % e.e. (Entry h).

Equation 10



22 **23**

Table 4. Table showing the effect of different bases and temperature on the reaction shown in Equation 10.

Entry	Additive[b] (mol %)	Temp (°C)	Yield (%)	*cis* / *trans*	e.e. of *cis* (%)
a	____	0	71	98 / 2	62
b	____	-15 to 0	48	99 / 1	68
c	NMI (20)	-15 to 0	21	98 / 2	91
d	DTBP (20)	0	49	95 / 5	31
e	DTBP (100)	0	67	99 / 1	61
f	DMP (100)	0	14	98 / 2	56
g	DTBMP (100)	-15	82	>99 / 1	70
h	DTBP (100)	-15	92	>99 / 1	71

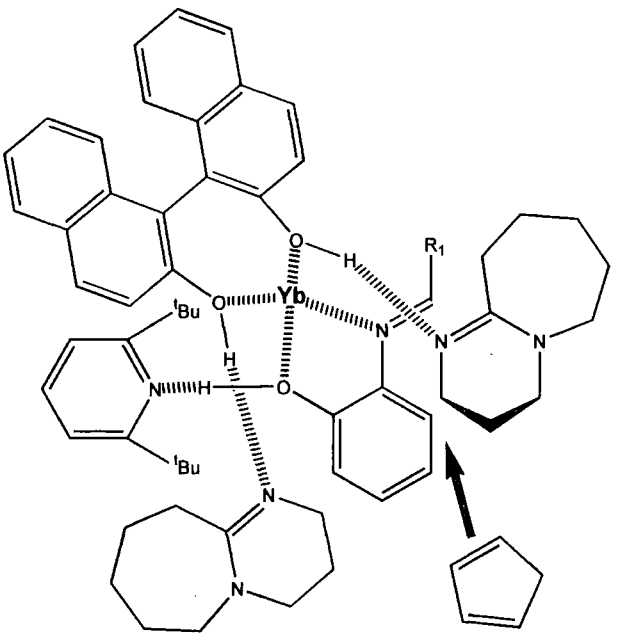
[a] Prepared from $Yb(OTf)_3$, (*R*)-(+)-BINOL and DBU.

[b] NMI = *N*-methylimidazole. DTBP = 2,6-di-*t*-butyl-pyridine. DMP = 2,6-dimethylpyridine. DTBMP = 2,6-di-*t*-butyl-4-methylpyridine

During this process the base was changed from TMP to DBU and the selectivity increased from 6 % to 68 % e.e. This was rationalised in terms of DBU interacting with

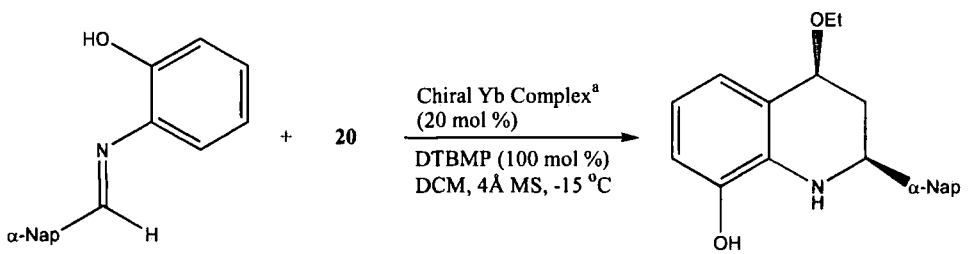
the phenolic hydrogen on **22**, in addition to interacting with the BINOL hydroxyl groups. This might feasibly lower selectivity, and addition of 20 mol % of NMI increased selectivity to 91 % e.e. (Table 4, Entry c) of the *cis*-adduct (Figure 8 shows the proposed transition state of the reaction. Triflate anions are excluded for clarity). Note how the DBU molecules are blocking attack of the iminophile. By interaction with (*R*)-BINOL, they are placed in such a position as to shield the top face of the imine.

Figure 8



The yield in that case was poor (21 %), however, the most impressive result came from the reaction between a 1-naphthaldehyde derived imine **24** and ethyl vinylether **20** to give **25** in 74 % yield and 91 % e.e. (Equation 11) with >99 : 1 *cis* : *trans* selectivity.

Equation 11



24

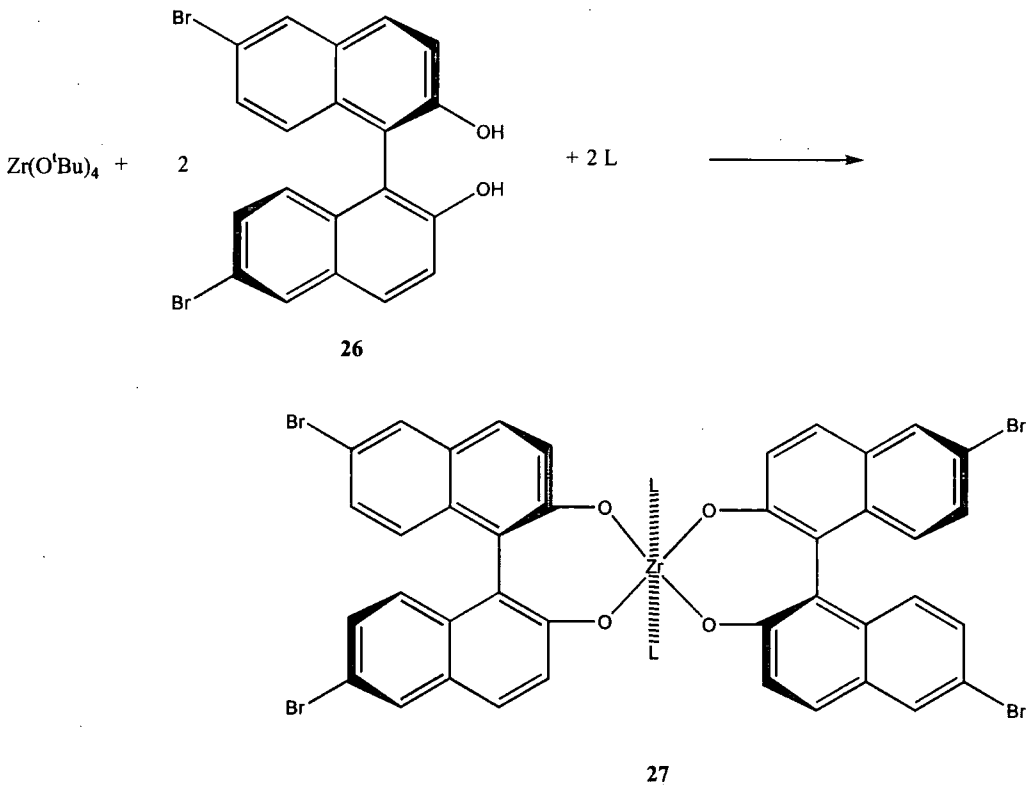
25

cis >99 / 1 *trans*
74 % yield
91 % e.e. (*cis*)

This paper, whilst not detailing reactions of imino-dienophiles, displayed the importance of additives on the outcome of the reaction. More importantly, they showed that asymmetric catalytic aza-Diels-Alder processes were indeed possible, albeit involving activation of the aza-diene (A recent review of the importance of additives and co-catalysts in asymmetric synthesis has been published.[12]).

In 1998, Kobayashi's group reported the use of a chiral zirconium catalyst in the first enantioselective imino-dienophile Diels-Alder reaction.[13] The catalyst was prepared (Equation 12) from $Zr(O^tBu)_4$, (*R*)-6,6'-dibromo-1,1'-binapthol [(R)-Br-BINOL] **26** and a ligand (L). The reactions were between various aromatic aldehyde-derived *N*-aryl imines and Danishefsky's diene.

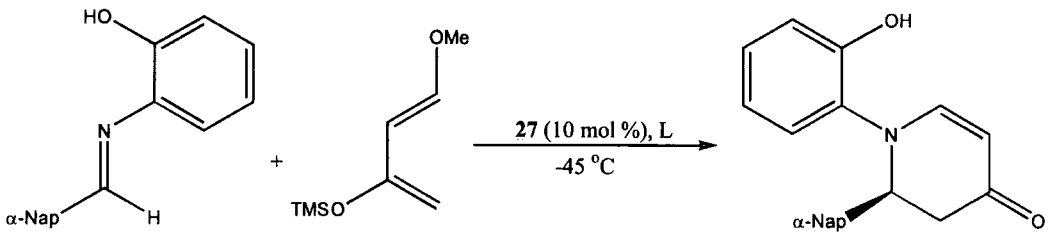
Equation 12



L = Ligand

It was found that the ligand (Figure 9) and solvent used, markedly affected the yield and enantioselectivities of the reaction outlined below (Equation 13). Table 5 details the group's findings.

Equation 13



24 3 28

Table 5. Table showing the effect of solvent and ligand on the level of asymmetric induction produced by catalyst **27** in the reaction outlined in Equation 13.

Ligand[a]	**Solvent**	**Yield (%)**	**e.e. (%)**
NMI[b]	DCM	74	40
NMI	1. benzene 2. DCM[c]	81	61
NMI	1. benzene 2. DCM[c]	83[d]	41
NMI	1. Toluene 2. DCM[c]	81	71
NMI	Toluene	86	82
DMI[e]	Toluene	76	59
29	Toluene	28	24
30	Toluene	86	50
31	Toluene	81	46
-	Toluene	65	10[f]

[a] 30 mol%, unless noted otherwise.

[b] NMI = 1-Methylimidazole.

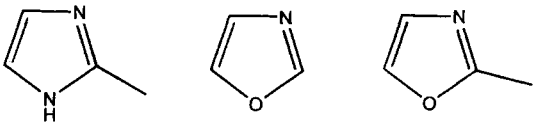
[c] chiral catalyst constructed in solvent 1, solvent evaporated under reduced pressure, and reaction carried out in solvent 2.

[d] Reaction with 4-*tert*-butoxy-2-trimethylsilyloxy-1,3-butadiene as diene component

[e] DMI = 1,2-dimethylimidazole (20 mol %)

[f] Reverse enantioselectivity

Figure 9

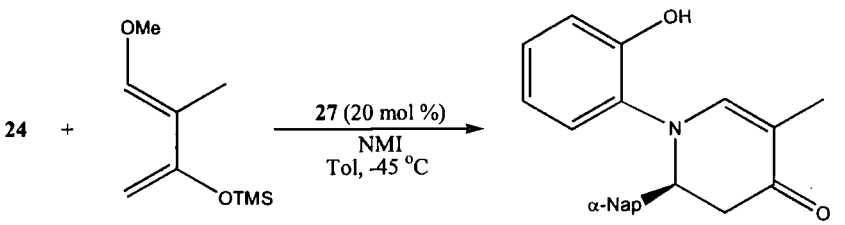


29 **30** **31**

Other Group 4 metals (Ti and Hf) were also used in the reaction above (Equation 13) and the catalysts were prepared in the same way. It was found that at 10 mol % hafnium(IV) gave slightly better yields than the equivalent zirconium(IV)-mediated reaction, but lower e.e. There was no difference in yield, but there was a slight decrease in e.e. at 20 mol %. Titanium(IV) produced significantly lower yield and e.e., regardless of catalyst loading.

The most successful reactions were those shown below (Equation 14), in which **33** was obtained in 93 % yield with an e.e. of 93 %. The absolute configuration of the cycloadduct was tentatively assigned as (*S*), on the basis of previous results.[14]

Equation 14



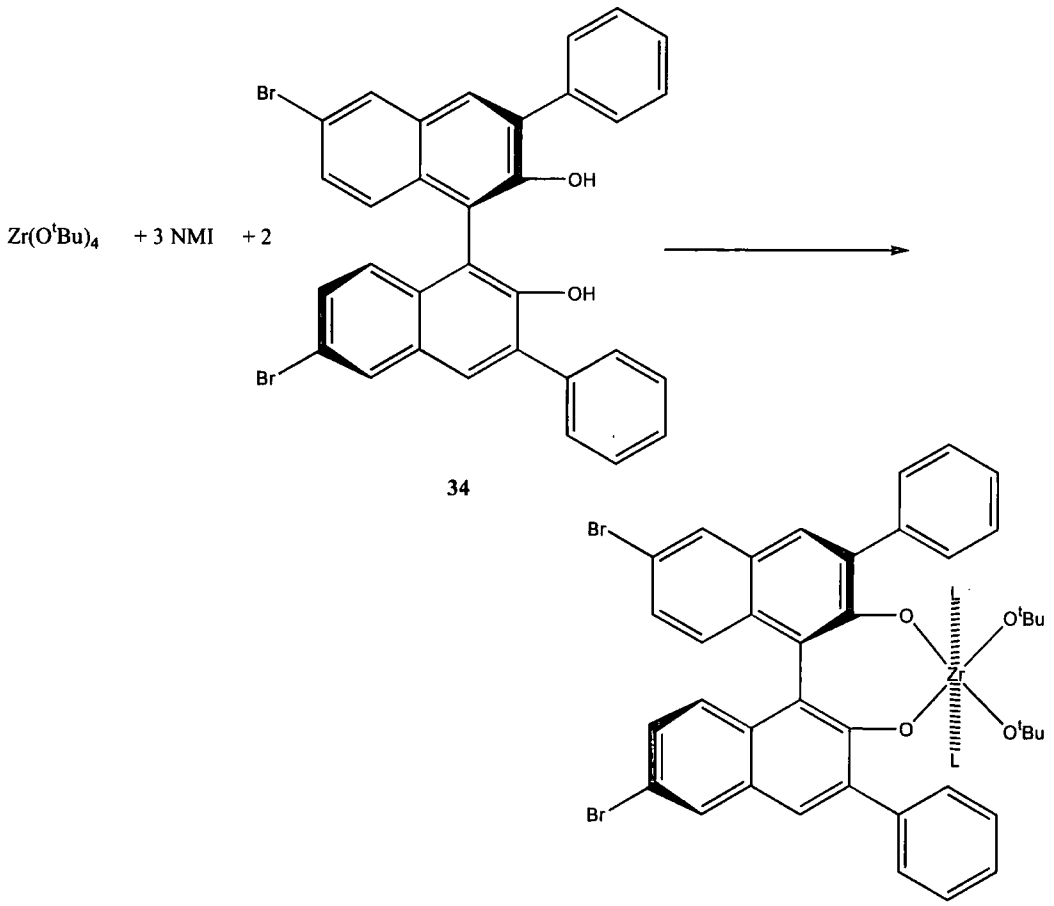
32 **33**

The presence of the *o*-phenol is imperative in order to generate high enantioselectivity. In all cases (even where OH is replaced with OMe), where there is no *ortho*-phenol function, the degree of asymmetric induction was much diminished

A year later, Kobayashi *et al.* also reported that modification of the catalyst, without interfering with the inherent chirality of the catalyst [still an (R)–BINOL derivative], could alter enantiofacial selectivity.[15] They noted that placing phenyl groups at the 3 and 3` positions of (*R*)-Br-BINOL **34** generated a new catalyst **35**, which when reacted with $Zr(O^tBu)_4$ and NMI (Equation 15) resulted in similarly high selectivities as reported earlier,[13] but the sense of induction changed. Using the reaction in Equation 16, and altering temperature, solvent and additive (in this case molecular sieves), they

demonstrated not only how enantiofacial selectivity could be altered, but also highlighted the effect of the additive on the yield and level of asymmetric induction of the reaction (see Table 6).

Equation 15



Equation 16

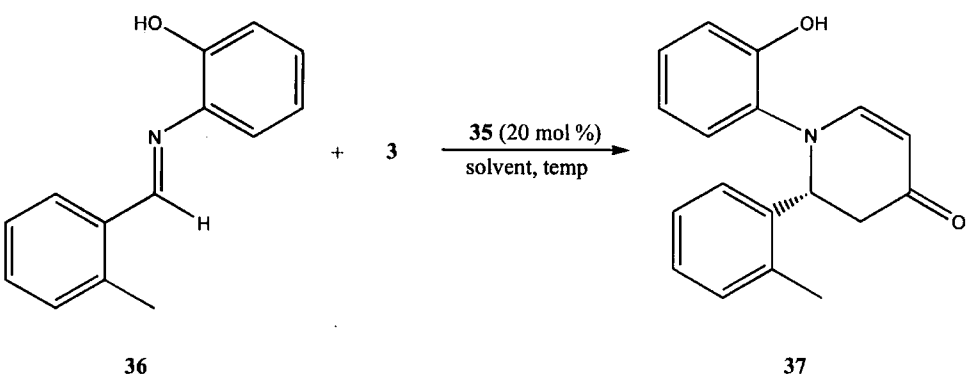


Table 6. Table showing the effect of molecular sieves and temperature on the yield and e.e. of products, as described in the reaction shown in Equation 16.

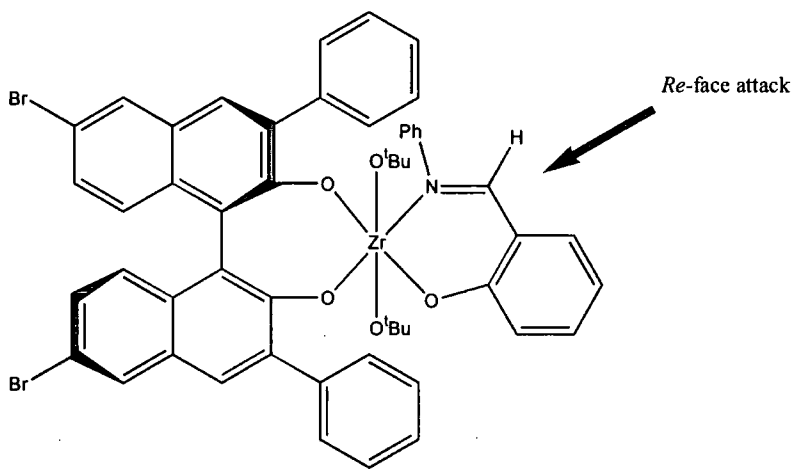
Entry	Solvent	Temp (°C)	MS	Yield (%)	e.e. (%)
a	Tol	-45	none	66	84
b	Tol	-45	none	83	82 (S)[a]
c	Tol	0	none	45	57
d	Tol	0	3Å MS	80	90
e	Tol	0	4Å MS	76	89
f	Tol	0	5Å MS	77	89
g	Tol	-45	3Å MS	54	77
h	Tol	23	3Å MS	96	88
i	Benzene	23	3Å MS	93	91

[a] Catalyst **27** used.

There is an obvious enhancement of both the yield and e.e. in the presence of molecular sieves, but this is dependant upon temperature. Indeed, the best result came with a change of solvent and when the reaction was performed at 23 °C (Table 6 Entry i).

The switch in facial selectivity was explained by the model shown in Figure 10. It is suggested that the ^{t}butoxy groups occupy the axial positions, and one of the phenyl groups covers one side of the imine, which leaves approach from one face much more favourable. In this case, using (*R*)-BINOL derivative **35**, it is the *Re*-face that is exposed (**38**).

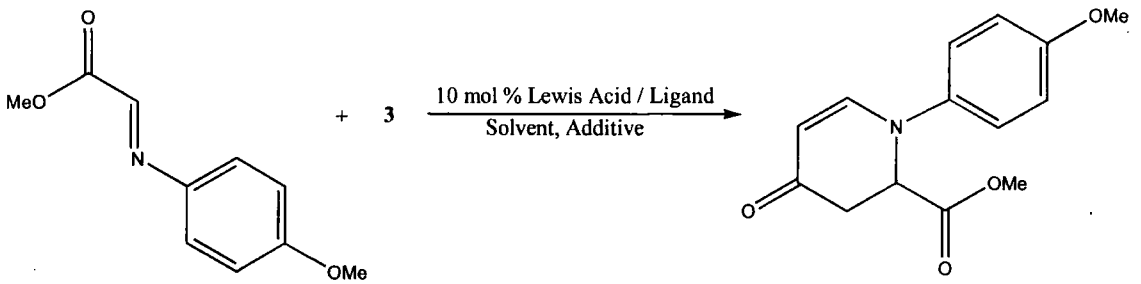
Figure 10



38

Concurrent with Kobayashi's publication on the enantioselective imino-dienophile aza-Diels-Alder reaction, Whiting reported several chiral catalysts for imino-dienophile Diels-Alder reactions.[16] The approach adopted in developing this catalyst was of a parallel combinatorial nature. This was achieved with 144 reactions being carried out in one week, and each was screened for approximate yield and e.e. by chiral HPLC. The model reaction was that of imine **39** and Danishefsky's diene **3** (Equation 17).

Equation 17



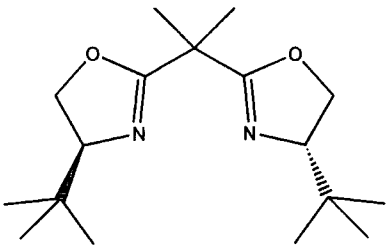
39 **40**

They found that hard Lewis acids such as BF_3, $TiCl_4$ and $EtAlCl_2$ did not catalyse the reaction, however, slightly softer ytterbium(III) triflate was successful. Various combinations of Lewis acids, chiral ligands (Figure 11), additives and solvents were screened in parallel. The results were detailed in a table, and the best are shown here in Table 7.

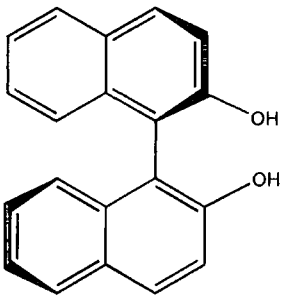
Table 7. Table showing the yield and e.e. of certain catalysts applied in the reaction outlined in Equation 17.

Lewis acid	Ligand	Additive	Solvent	Yield (%)	e.e. (%)
MgI_2	**43**	2,6-lutidine	MeCN	64	97
$Yb(OTf)_3$	**43**	2,6-lutidine	Tol	60	87
$Cu(OTf)_2$	**43**	None	MeCN	58	86
$FeCl_3$	**41**	4Å MS	DCM	67	92

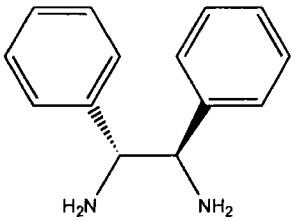
Figure 11



41



42



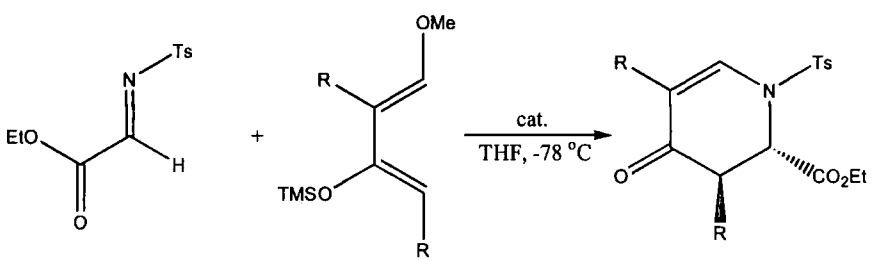
43

Each chiral ligand was found to produce the same sense of absolute stereochemistry. This obviously has mechanistic implications into the asymmetric induction process.

This method of catalyst discovery proved to be rapid, and successful. For this reason, a parallel combinatorial approach appears to be a good strategy to employ for developing new asymmetric catalytic processes.

About the same time, advances in the field of imino-Diels-Alder reactions were also made by Jørgensen *et al.*[17] In this work, an array of glyoxylate derived imines with various *N*-protecting groups was prepared. A range of Lewis acids were then used, ranging from zinc(II) and copper(I) and copper(II) triflates, through to palladium(II) and rubidium(I) tetrafluoroantimonates, with varying degrees of success. A small range of chiral ligands, namely bis-oxazoline and BINAP-type ligands, were also used. The greatest successes were born out of an ethyl glyoxylate and *p*-toluenesulfonamide (Equation 18, Table 8) derived imine **44**, using a copper(I), (*R*)-BINAP **48a** or a copper(I) and (*R*)-Tol-BINAP **48b** chiral Lewis acid complex (Figure 12).

Equation 18



44

3: R = H
45: R = Me

46: R = H
trans-**47**: R = Me

Table 8. Table showing the effect of chiral ligand and catalyst loading on the yield and e.e. of reactions described in Equation 18.

Entry	Catalyst	Load (mol %)	Diene	Yield[a] (%)	e.e.[b] (%)
a	**48a**/$CuClO_4$.4MeCN	10	**3**	78	67
b	**48b**/$CuClO_4$.4MeCN	10	**3**	68	80
c	**48b**/$CuClO_4$.4MeCN	10	**45**	67	94
d	**48b**/$CuClO_4$.4MeCN	5	**45**	70[c]	94
e	**48b**/$CuClO_4$.4MeCN	1	**45**	70[c]	96
f[d]	**48b**/$CuClO_4$.4MeCN	10	**45**	70	81

[a] Total yield of isolated products.

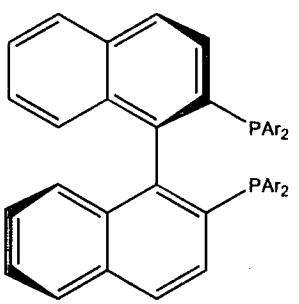
[b] Determined by HPLC using a Chiralpak-AD column.

[c] Diastereoselective ratio = 10 : 1.

[d] T = 20 °C.

An excellent result of 70 % yield and 96 % e.e. (Table 8, entry e) was achieved with an impressive 1 mol % catalyst loading. Note also, that the reactions were highly diastereoselective. This suggests that copper(I) is an efficient activator of imines in aza-Diels-Alder reactions.

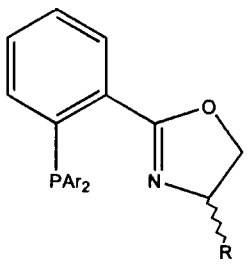
Figure 12



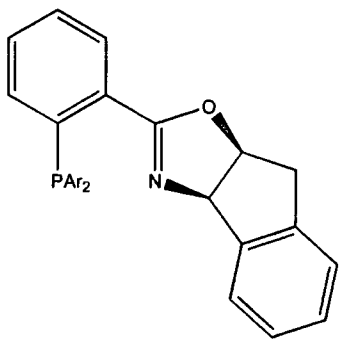
48a: Ar = Ph
48b: Ar = Tol

In 2000, Jørgensen and co-workers published the full paper of their findings.[18] This showed further examples of aza-Diels-Alder reactions of *N*-Tosyl imine **44** with Danishefsky's diene **3**, catalysed by $CuClO_4$ and chiral phosphanyl oxazoline ligands (Figure 13).

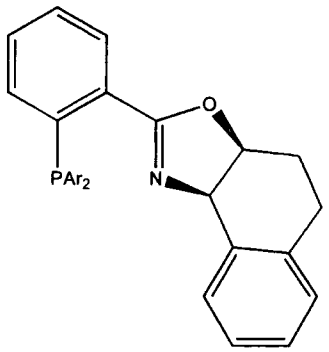
Figure 13



49a: Ar = Ph, R = Ph (R)
49b: Ar = Ph, R = ^{i}Pr (S)
49c: Ar = Ph, R = ^{t}Bu (S)
49d: Ar = *p*-Tol, R = ^{t}Bu (S)



49e: (3aR, 9bS), Ar = Ph
49f: (3aR, 9bS), Ar = *p*-Tol
49g: (3aR, 9bS), Ar = 2,4-xylene



49h: (3aR, 9bS), Ar = Ph
49i: (3aR, 9bS), Ar = *p*-Tol
49j: (3aR, 9bS), Ar = 2,4-xylene

Reactions were performed with a 10 mol % catalyst loading in DCM and THF at –78 °C for between 15 and 20 hours (*c.f.* Equation 18, R = H). It was found that in all cases, the combinations of copper(I) with these chiral ligands, catalysed the reaction to give high yields of **46**. Solvent played an important role in the level of asymmetric induction and in the yield of the reaction (Table 9). The use of **48b** in DCM as solvent gave an 89 % yield, but a rather poor 26 % e.e. of **46**. On changing the solvent to THF, however, the yield lowered to 80 %, but the e.e. rose by over three times to 78 %. It was also noted that other solvents could be used, but MeCN, DMF, toluene, Et_2O, ^{t}BuOMe and benzenetrifluoride all gave lower e.e.s.

Table 9. Table showing the effect of solvent on the yield and e.e. of products of the reaction detailed in Equation 18.

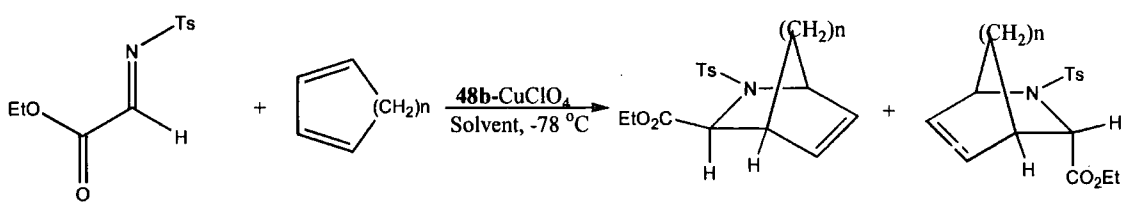
Entry	Ligand	Yield[a] / e.e.[b] (%) (THF)	Yield[a] / e.e.[b] (%) (DCM)
a	**48a**	78/67 (S)	85/10 (S)
b	**48b**	80/79 (S)	89/26 (S)
c	(R)-**49a**	93/27 (R)	90/29 (R)
d	(S)-**49b**	97/77 (S)	73/71 (S)
e	(S)-**49c**	82/87 (S)	96/77 (S)
f	(S)-**49d**	74/87 (S)	91/77 (S)
g	(3aR, 9bS)-**49e**	94/61 (R)	81/62 (R)
h	(3aR, 9bS)-**49f**	97/62 (R)	93/62 (R)
i	(3aR, 9bS)-**49g**	97/79 (R)	94/53 (R)
j	(3aR, 9bS)-**49h**	49/80 (R)	92/75 (R)
k	(3aR, 9bS)-**49i**	66/81 (R)	77/86 (R)
l	(3aR, 9bS)-**49j**	90/66 (R)	70/45 (R)

[a] Isolated yield.

[b] e.e. determined by HPLC using a Chiralpak AD column.

Reactions of **44** with cyclopentadiene **16** and cyclohexadiene **50** also gave aza-Diels-Alder products in good yields with good selectivities, but the best results were obtained with **48b** and $CuClO_4$ (Equation 19, Table 10). The reactions, in all cases, produced the *exo*-diastereoisomer as the major component, and again, a solvent effect was observed. Perhaps predictably, cyclohexadiene did not perform quite as well as the more reactive cyclopentadiene.

Equation 19



44

16: n = 1
50: n = 2

exo-**51**: n = 1
exo-**52**: n = 2

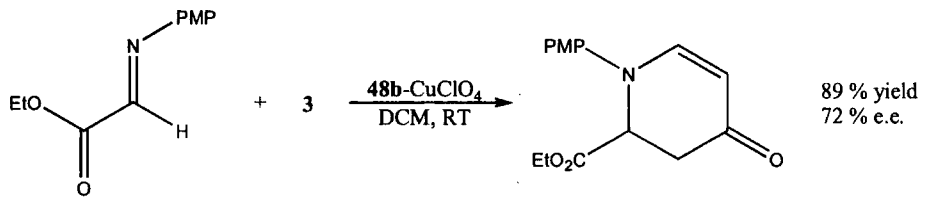
endo-**51**: n = 1
endo-**52**: n = 2

Table 10. Table showing the effect of solvent on yield and e.e. of both *endo* and *exo* isomers in the reaction described in Equation 19.

Entry	Load (mol %)	Solvent	Yield / e.e. (%) (*exo*)	Yield / e.e. (%) (*endo*)
a	10	THF	88/60 (n = 1)	9/99 (n = 1)
b	10	DCM	85/83 (n = 1)	7/83 (n = 1)
c	10	THF	31/91 (n = 2)	6/40 (n = 2)
d	10	DCM	52/95 (n = 2)	7/37 (n = 2)

This paper showed how the *N*-protecting group can influence the course of reaction. It was found that by swapping the Ts group for a *p*-methoxyphenyl (PMP) group, the absolute stereochemistry of the product changed from (*S*) (in **46**) to (*R*) (Equation 20). The authors suggested that this can be attributed to different binding modes of the imine to the chiral Lewis acid complex, however, the mechanistic aspects will be discussed fully in Chapter 2.

Equation 20



53 54

1.6 Parallel Combinatorial Approach to Chiral Lewis Acid Development

Combinatorial chemistry was something of a buzz-term throughout the nineties. It was particularly applied to the field of pharmaceuticals, as a rapid way of synthesising compound libraries for subsequent biological screening. Such practises however, can also be applied quite readily to homogeneous enantioselective catalyst discovery,[16,19,20,21] and this subject has been reviewed in recent years.[19a,b] There are many methods for screening reaction progress, and depending upon finances, time and the particular constraints of the project, there are pros and cons for each. The utility lies in the quantity of reactions that can be performed and monitored in any given reaction set. In this way, a screen can be performed on a wide range of potential catalysts without too much consideration of the intricacies of why these catalysts should be used.

In the field of catalysis, and particularly a relatively unexplored field, such as the enantioselective catalytic imino-dienophile aza-Diels-Alder reaction, that kind of flexibility can be essential for significant progress to be made. In performing a screen of many different candidate catalysts, a profile can be built, upon which further libraries can be constructed with rather more thoughtful reasoning. This process deliberately introduces diversity into the discovery process, and (as has been seen time and time again), that can become invaluable for progress. It is an evolutionary route utilising human, rather than natural selection. Of course, the assay used (in this case, the aza-Diels-Alder reaction) is important, as is the screening method. In drug discovery, the screening process was so efficient by the early 90s, that efforts became dependent on the speed of drug candidate synthesis! In catalysis, both fields of rapid screening and rapid synthesis had to be cultivated in parallel. This is so because, until very recently, neither of these fields had been practised in catalyst development.

The first priority in the screening of catalysts is the detection of activity. There are a range of methods available to perform this screening. Chromatographic techniques such as chiral HPLC[16] and chiral GLC are obvious candidates. The advantages lie in the ability to accurately determine both conversion and enantioselectivity, coupled with the ease of automation of such techniques. These techniques, however, are not without their limitations. Fast run times of chiral HPLC systems are often in excess of 10 minutes, meaning that only 144 reactions could be screened per instrument per day. This short-fall has been overcome in some assays by overlaying runs where long enantiomer resolution times were found.

An alternative is to couple an HPLC machine to a detector system capable of distinguishing between enantiomers. Generally, chromatography is faster when enantioseparation is not required. By using circular dichroism (CD) or optical rotation as a detection method, many more runs per day can be performed due to the faster elution times.[19c]

UV-visible spectroscopy has been used to avoid the limitations of serial chromatography. Plate-readers can measure the absorbance of light through a 96 (or more) well-plate, and clever techniques were used to adopt this instrument to enantioselective screening. Reetz used UV-visible spectroscopy to evolve an enzyme capable of resolving racemic *p*-nitrophenol esters by enantioselective hydrolysis.[19d]

Mutagenesis was carried out on the parent enzyme, and a library of around 1000 new enzymes were used in the screens. This technology involved isolating the two enantiomers of the ester, exposing enantiopure samples to the array of enzymes, and measuring the relative rates for hydrolysis of *R* and *S* enantiomers by absorbance of the nitrophenol over time. After four rounds of mutagenesis, the e.e. had increased from 2 to 81 %. Due to the sheer number of reactions screened (around 4000!), HPLC or GC would have been wholly inappropriate. Such a method is particularly useful for enzyme catalysed reactions which are highly specific in terms of product formation, and involve use of enantiopure substrates rather than the production of enantiomixtures of products from achiral substrates.

Fluorescence has also been used to assay large numbers of reactions.[19e] By linking a fluorescent pH sensor to beads containing peptide based acetylation catalysts, Miller and co-workers produced a simple acid sensitive indicator for reaction rate. It was found that beads containing non-reactive catalysts remained dark, whilst those beads with an active catalyst present fluoresced when viewed under a fluorescent microscope. Manual selection of the brightest beads was followed by washing, and subjection to a kinetic resolution involving racemic secondary alcohols. The beads with the highest selectivity were deconvoluted by Edman degradation, resynthesised and subject to the reaction conditions. The obvious pit-fall of this technique is in the requirement for an appropriate by-product, and a solid-support.

Chiral capilliary electrophoresis has been used to determine e.e.,[19f] in which it was found that good correlations existed (all within 4%) between the data obtained and the data gathered using chiral GLC.

IR thermography has also been used in high throughput screening.[20] In this technique, the heat produced in a reaction is measured. Whilst this is a good indicator of catalyst activity, the measure of e.e. can only be achieved in a manner analogous to that using UV-visible spectroscopy. That is, in kinetic resolution type experiments where both enantiomers of a substrate are screened separately and together to assess relative rates of reaction.

Mass spectrometry has also been used to assess e.e.[19g] This technology involves synthesis of enantiomers containing a different isotope in each (pseudoenantiomers).

These pseudoenantiomers can be resolved by an enantioselective transformation, and the degree of e.e. accurately measured by integration of the resulting spectrum which will show the two products by their different masses. Again, this method is more suitable toward kinetic resolution procedures.

In summary, it has been shown that there are a wide variety of techniques available to assess the e.e. of reactions in a high throughput screen. The best technique to use depends on the assay, the funding available to the project, and the particular requirements of what data is needed. Whilst chiral HPLC has its limitations, it is a technique that is simple to use and given the constraints of this particular project, is ideally suited to the kinds of numbers of reactions that will be dealt with in any given reaction screen. Therefore, chiral HPLC will be used in the screening reactions of this project.

Once a technique has been established for screening catalyst activity, the screening process can begin. It should then be possible to generate libraries that grow gradually more refined until catalysts are optimised.

1.7 Concluding Remarks

The imino-dienophile aza-Diels-Alder reaction exhibits obvious utility for piperidine type alkaloid intermediate synthesis. Whilst some impressive asymmetric catalytic versions of the reaction have been developed, there is still a great deal of scope for further elaboration of the versatility of such processes.

Chapter Two

Results and Discussion

2.1 Project Aims

The purpose of this project was to discover and develop new catalysts in the aza-Diels-Alder reaction. A strategy must be employed in order for the project to have direction. It was one of the aims of this project that the method for catalyst discovery was generic, and could be applied to any reaction where asymmetric catalysis is required. As mentioned in Chapter One, there is evidence to suggest that employing parallel, combinatorial methods allows the rapid development of such catalytic systems. With this in mind, the approach to the project was broken down into several stages:

The first stage was that of reaction location. A preliminary screen was to be carried out of imines and dienes, with a broad range of Lewis acids, solvents, chiral ligands and additives, which was expected give an indication of the types of systems for which chiral catalysts could be developed. These model systems would ideally be unreactive at some temperature between –20 °C and room temperature in the absence of a catalyst, but it should then be possible to catalyse the reaction at or below that temperature. It would then be necessary to ascertain what catalyst types work for a particular reaction. It was expected that variables such as Lewis acidity (hard through to soft) and solvent polarity (polar / non-polar) would probably be the most important variables at this stage of the process. Successful "hits" from this stage would be ascertained by the degree of conversion of the imine (monitored by TLC) to product, taking into account the speed of the reaction and that these screening reactions would be done on small scale.

The second step would then involve scale-up of "hit" reactions from the first stage, and would also include isolation and characterisation of the products obtained. Once the identity of the various products was confirmed, HPLC conditions would then be developed in order to assess the enantiomeric purity of those products obtained in subsequent reaction screens, where a chiral source was present. Indeed, chiral HPLC would be used as the method of screening the reactions in the ensuing reaction sets. Other details, such as the stability of products, would also be assessed at this stage.

The third stage would involve the actual catalyst discovery process using more focused libraries consisting of chiral ligands, Lewis acids, different solvents and different additives (molecular sieves, bases etc.). The choices made would be based on the information gained from each previous screen, gradually honing in until better catalytic systems are developed. Included under this heading is reaction optimisation, where yield and e.e. are optimised, based on the same parallel combinatorial approach.

Finally, it was expected that some mechanistic insights could be made into the different catalytic reactions developed.

For this particular project, the aim was to use these general diversity-based catalyst development methods to look for new efficient asymmetric catalysts for aza-Diels-Alder reactions. As discussed in the Introduction, the aza-Diels-Alder reaction plays an important role in the synthesis of useful nitrogen-containing heterocycles,[3,4] which have utility for the synthesis of piperidine and indolizidine alkaloids.[22-29] The immediate aims of this project were therefore to develop new efficient asymmetric catalysts for a wider range of diene-dienophile combinations than had been previously shown to be susceptible to asymmetric catalysis.

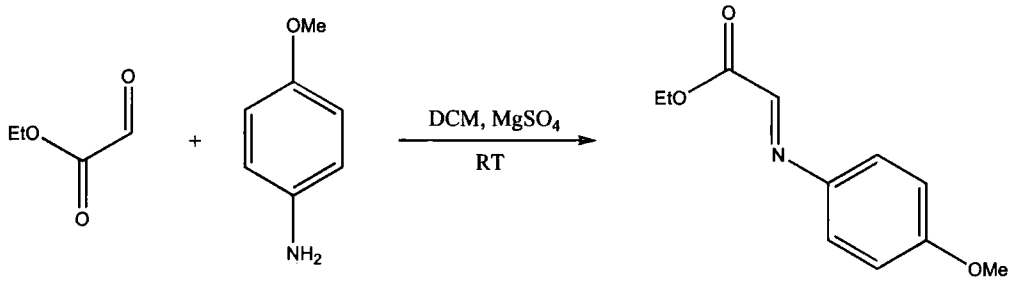
2.2 Choice of Imine

The first problem in a diversity based catalyst search is a suitable choice of reactants to be combined. In particular, it was felt that certain requirements had to be met with regard to the imine. Firstly, it had to have a suitable *N*-protecting group, *i.e.* relatively easy to deprotect after the Diels-Alder transformation, or at a later stage in any subsequent synthesis. The reactivity had to be suitable towards different dienes that one might wish to react with, *i.e.* slow or no reactivity at ambient temperature under thermal reaction conditions alone, but reactive in the presence of different Lewis acid catalysts. Ideally, the imine employed would be also be cheap and easy to synthesise, of course, the resulting Diels-Alder adducts should be useful synthetic intermediates.

With these factors in mind, the first imine produced was the *N*-*p*-methoxyphenyl (PMP) protected system **53**. This protecting group had already been used in the Whiting group,[16] and seemed to be a good place to start since it fulfilled the above criteria. The only change made from previous studies, was that the methyl ester version **39** was

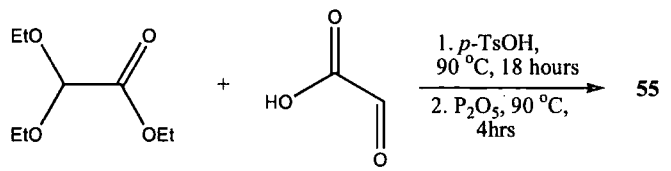
exchanged for the slightly more stable ethyl ester. This imine **53** was readily prepared in 79 % yield from a condensation reaction between ethyl glyoxylate **55** (prepared according to Equation 22 in 81 % yield),[30] and *p*-anisidine **56** (Equation 21) performed in DCM over $MgSO_4$ at ambient temperature, followed by purification by Kugelrohr distillation.

Equation 21



55 **56** **53**

Equation 22

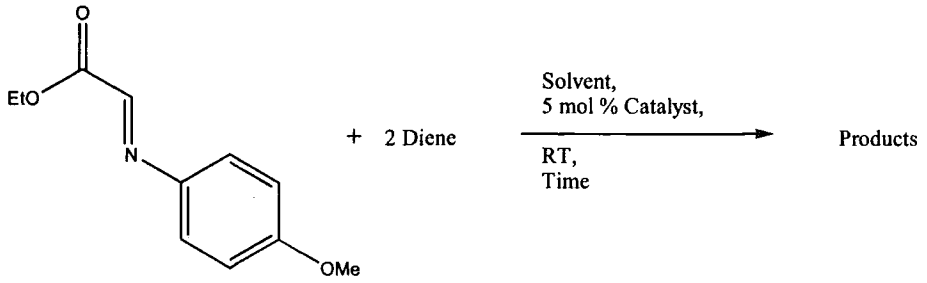


57 **58**

2.3 The Diversity Approach

The next stage was to select a range of suitable dienes to react with imine **53**. The purpose of this stage was to establish the level of reactivity of the imine **53** with a range of dienes, *i.e.* to find out which classes of dienes were reactive and which were not, under Lewis acid catalysed conditions. The dienes chosen were to be reacted with a broad range of Lewis acids (hard to soft) and in both polar and a non-polar solvents, as part of a series of reaction screens, *i.e.* following our generic approach described in Section 2.1. The general reaction scheme followed is detailed in Equation 23, with the corresponding results outlined in Table 11. This table shows the length of time it took for the imine to be consumed (see also Figure 14).

Equation 23



53

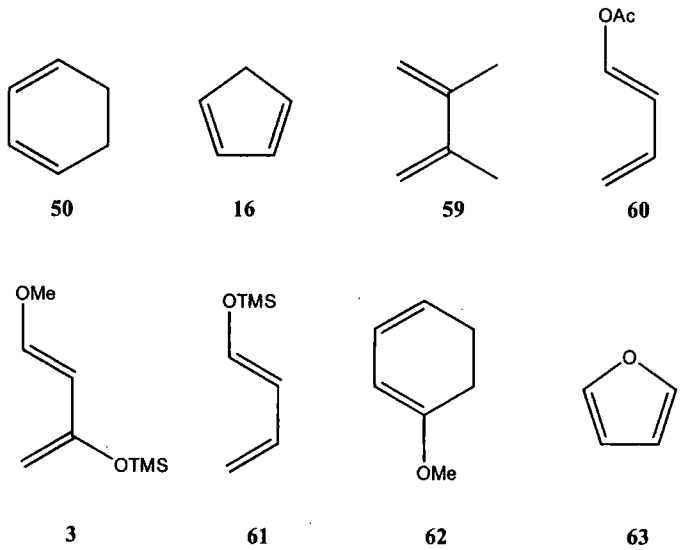
Table 11. Table showing the length of time (hours) it took for imine **53** to be consumed in the presence of different dienes, according to Equation 23.

		Diene							
Solvent	**Lewis acid**	**50**	**16**	**59**	**60**	**3**	**61**	**62**	**63**
MeCN	None	-[a]	-	-	-	-	-	-	-
	$Cu(OTf)_2$	-	1	-	2	1	1	1	-
	$Yb(OTf)_3$	-	1	-	2	1	1	1	-
	$Co(acac)_3$	-	-	-	-	-	-	-	-
Toluene	None	-	-	-	-	-	-	-	-
	$Cu(OTf)_2$	-	1	-	16	1	1	1	-
	$Yb(OTf)_3$	-	1	-	16	1	1	1	-
	$Co(acac)_3$	-	-	-	-	-	-	-	-

[a] imine consumption not complete within 24 hours

The experiments in the screening processes throughout the project were all initiated in generally the same manner. Firstly, the Lewis acid and (where appropriate) chiral ligand were mixed together. Usually, these were added as concentrated solutions in an appropriate solvent (*i.e.* a solvent capable of solvating the reagent). On occasion, the solvent for a particular reagent would be different to the reaction solvent, however this was avoided wherever possible. After stirring the two for approximately ten minutes, a solution of imine in the reaction solvent was added. This was left for a further five minutes after which, the neat diene appropriate to the reaction was added. In this particular screen, reactions were checked by TLC for consumption of imine.

Figure 14



50 **16** **59** **60**

3 **61** **62** **63**

For this initial screen, just two solvents were chosen, one polar and one non-polar solvent, *i.e.* acetonitrile and toluene. These were combined with a small range of three Lewis acids, starting with a relatively soft Cu(II) system, going to a harder Yb(III) and finally using a harder Co(III) system. These Lewis acids were chosen in order to gain a preliminary understanding of which Lewis acid type was ideally matched to which diene-imine combinations and would therefore be focused upon more closely in later screens. For comparison, these Lewis acid catalysed reactions were also carried out in the absence of Lewis acid to act as a reference. All the reactions were performed using 20 mgs of imine **53**, and were initially monitored by TLC for consumption of imine. To ensure that all the imine **53** was converted through to product, two equivalents of diene were used and all reactions were performed in open vessels, *i.e.* in air. The results of these experiments are summarised in Table 11.

From examination of Table 11, some conclusions could be drawn from this initial screening process. Firstly, and perhaps most obvious, was that all the reactions did not proceed efficiently in the absence of a catalyst, nor did they proceed in the presence of cobalt(III) acetylacetonate; the cobalt(III) system was therefore a poor catalyst for such imine cycloaddition reactions. This was perceived as good news in the sense that it meant that the competing uncatalysed reaction was essentially irrelevant in all screening reactions carried out. [This is contrary to the findings of Ding and co-workers[31] who found that reaction between Danishefsky's diene **3** and benzylidene aniline imine **14** (Section 1.5, Equation 9 and Table 3, Entry a) in MeCN at room temperature without, either a Lewis or Brønsted acid catalyst, furnished cycloadduct **15** in >99 % yield after

2 hours! Whilst some product formation was observed in this screen after 24 hours (detected by TLC), the reaction was very slow in the absence of a catalyst, and imine consumption was not complete]. Moreover, it could be inferred from these results that the type of Lewis acid best suited to these types of transformations would be of the softer to medium type.

The second major finding from Table 11, was that the polar solvent (MeCN) appeared to allow the reactions to proceed faster, at least in some cases. In the reaction between acetoxybutadiene **60** and imine **53** using both $Yb(OTf)_3$ and $Cu(OTf)_2$ as catalyst, complete consumption of imine **53** was observed within 2 hours in MeCN. However, the reactions in toluene had not run to completion within 4 hours, and were subsequently allowed to stir overnight. This could be attributable either to the solubility of the metal complex (although metal / ligand complexes of the imine **53** tend to be soluble in most solvents), or to the intervention of a stepwise or highly polar transition state being involved in the reaction, which would be more stabilised in polar solvents.

The third major finding from Table 11, was that it appeared that the choice of diene was also important. The trend of reactivity was almost what one would have predicted, *i.e.* unactivated (less electron rich) dienes **50**, **59**, and **63** were very sluggish and produced long reaction times. Complete conversion of the imine was not observed within a 24 hour period, which contrasted with the known reactive dienes cyclopentadiene **16**, Danishefsky's diene **3**, and the other activated dienes, silyloxybutadiene **61** and methoxycyclohexadiene **62**. Intermediate reactivity was observed in the reaction with acetoxybutadiene **60**, which if the electron releasing power of an acetate over a methoxy or trimethylsilyloxy group is considered, does not seem an unreasonable observation. It was in this latter reaction, between imine **53** and diene **60**, that the reaction accelerating solvent effect of acetonitrile was observed.

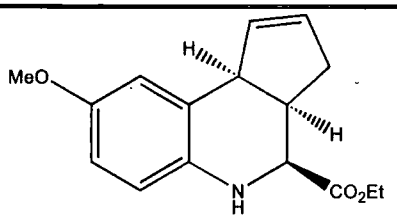
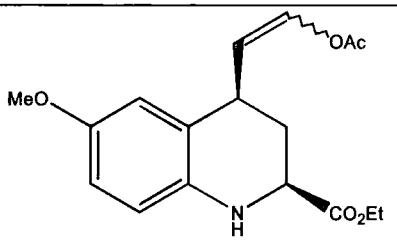
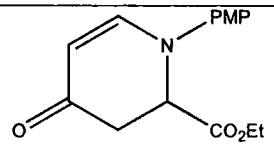
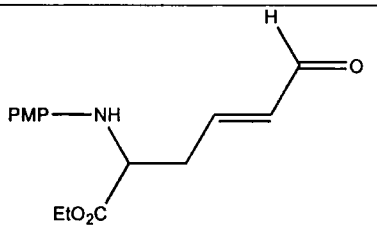
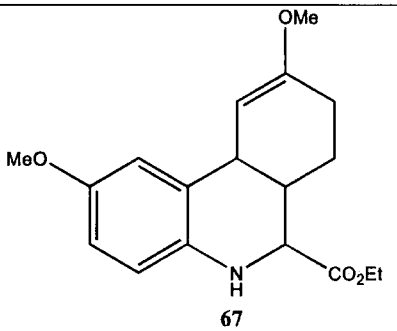
With the first set of screening experiments complete, it was then necessary to scale-up and isolate the products formed from the 'hit' reactions, *i.e.* those which resulted in complete consumption of imine **53** according to TLC. Since the catalyst which appeared to be most generally effective was ytterbium(III) triflate, this salt was chosen as the Lewis acid catalyst and the reactions were performed in what was believed to be dry solvent (MeCN), at ambient temperature and under argon. The reactions were carried out using much the same procedure as the screening experiments, but on larger

scale. Imine **53** (200 mg) was added to a stirred solution of 5 mol % $Yb(OTf)_3$ in MeCN (5 ml) under argon. Diene (1.5 equivalents) was added, and the reaction monitored (TLC) for consumption of imine **53**. Generally, the reactions were left for between 1 and 3 hours depending on the diene. When no imine remained, brine was added to quench. After extraction into EtOAc and washing with brine, the combined extracts were dried over $MgSO_4$ and evaporated to yield crude products. The products were purified by silica gel chromatography and characterised by NMR, IR, mass spectrometry and accurate mass. The different products that were isolated from the various reaction mixtures involving the imine **53** are summarised in Table 12.[32]

Table 12 shows that reactions involving cyclopentadiene **16**, 1-acetoxybutadiene **60** and 1-methoxycyclohexadiene **62** all gave the "inverse-electron-demand" products, *i.e.* tetrahydroquinoline derivatives **64**, **65**, and **67** respectively (entries a, b and e). Danishefsky's diene **3** on the other hand (entry c), gave the "normal electron-demand" Diels-Alder adduct **54**. Interestingly, 1-(trimethylsilyloxy)butadiene **61** gave an acyclic product **66** (entry d).

Some adducts listed in Table 12 were extremely difficult to purify due to instability problems, and with the exception of the Danishefsky's diene adduct **54**, all of the remaining adducts (see Table 12) were found to be unstable in air. Even solutions of the purified compounds rapidly began to darken in colour upon standing. It was clear that there was an unidentified oxidative process occurring, resulting in a complex mixture of products in nearly all cases. Indeed, the TLC of all the reaction mixtures (except that of cyclopentadiene **16** and Danishefsky's diene **3**), showed a complex mixture of products. It was immediately clear after isolation of each of the main products from this first stage of screening experiments, that simple Diels-Alder adducts were not being uniformly isolated. It was therefore necessary to carry out a series of experiments, both practical and spectroscopic in order to identify the actual structure of each of the screening products. The structures which are shown in Table 12, are the result of a long series of experiments and findings that are fully documented in the following sections, where, in each case, evidence for the individual structure assignment of each compound is presented. In retrospect, the various spectroscopic data for each compound can be assigned to even the more problematic adducts without difficulty, but, most of the conclusive evidence for the structure of each of the products was obtained by the preparation of often more stable derivatives of these rather unstable adducts.

Table 12. Table showing the products obtained from the reactions outlined in Equation 23 between imine **53** and various dienes.

Entry	Diene	Product	Isolated Yield (%)
a	**16**	 **64**	81
b	**60**	 **65**	61
c	**3**	 **54**	65
d	**61**	 **66**	59
e	**62**	 **67**	57

There are many reports of the use of *N*-aryl imines acting as dienes in Lewis acid catalysed inverse-electron-demand Diels-Alder reactions.[10,11,33-44] However, at the time that these experiments were carried out, it was expected that the imine would react as a dienophile with electron rich dienes, not as a diene. The first evidence of such reversed reactivity came from the isolation of the cyclopentadiene adduct **64**. The structural data

obtained was close to that reported in related literature compounds.[35] IR data showed the ester carbonyl at 1720 cm^{-1}, which was a change from the 1740 cm^{-1} in the starting imine **53**, and the disappearance of the imine C=N stretching frequency at 1710 cm^{-1}. The 4H AB quartet at δ 7.20 of the aromatic ring in the ^1H NMR of the starting material had disappeared, and a 3H multiplet at δ 6.58 - 6.64 had appeared in the product. An exchangeable proton at δ 4.01 had also appeared, indicating the presence of an N-H, whilst the imine N=CH proton at δ 7.94 had disappeared as expected. Two alkene protons were identified, each as 1H multiplets at δ 5.65 - 5.71 and δ 5.72 - 5.78 respectively. The stereochemistry of the adduct **64** was assigned based on literature precedent,[38,39] and was supported by a small coupling constant (3.5 Hz) for the protons at the chiral centre alpha to nitrogen, and the adjacent bridgehead proton. It was also proven by X-ray crystallographic analysis of the acetamide derivative (*vide infra*). Notably, the product was isolated as a single diastereoisomer.

2.4 A Concerted or Stepwise Mechanism?

2.4.1 Occam's Razor[45]

"Pluralitas non est ponenda sine neccesitate" or "Entities should not be multiplied unnecessarily." is a principle attributed to the 14th century logician and Franciscan friar, William of Occam (or Ockham). The principle is frequently used in science where it has been translated to read "when you have two competing theories which make exactly the same predictions, the one that is simpler is the better.".

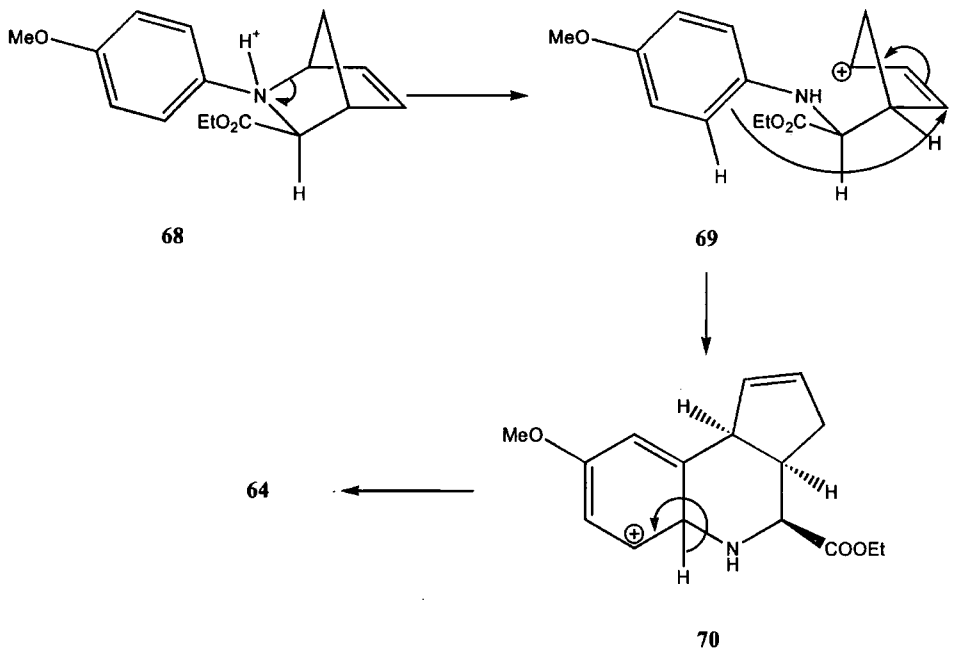
2.4.2 Normal-Electron-Demand or Inverse-Electron Demand?

The first compounds in Table 12 that were fully characterised were the cyclopentadiene adduct **64**, the Danishefsky's diene adduct **54** and the 1-trimethylsilyloxybutadiene adduct **66**. Hence, because it was initially thought that all products were derived from reaction of the imine **53** with each of the dienes under a normal electron-demand Diels-Alder cycloaddition processes it was necessary to determine how structure **64** might have been derived. The Danishefsky's diene addition product **54** could be certainly explained by a "normal-electron-demand" pathway. Indeed, it was a compound whose structure had been confirmed by others,[18] as well as in our own group.[16] It was initially

proposed therefore that product **64** could have arisen by a normal aza-Diels-Alder reaction, followed by a rearrangement, perhaps as outlined in Scheme 1.

The protonated adduct **68** could ring open, alleviating ring-strain, to provide the allylic cation **69**. Aryl cyclisation, double bond migration, and re-aromatisation would then give the observed tetrahydroquinoline adduct **64**. The stereochemistry observed in the product can also be explained by this mechanism, assuming the *exo*-Diels-Alder adduct is the major product.

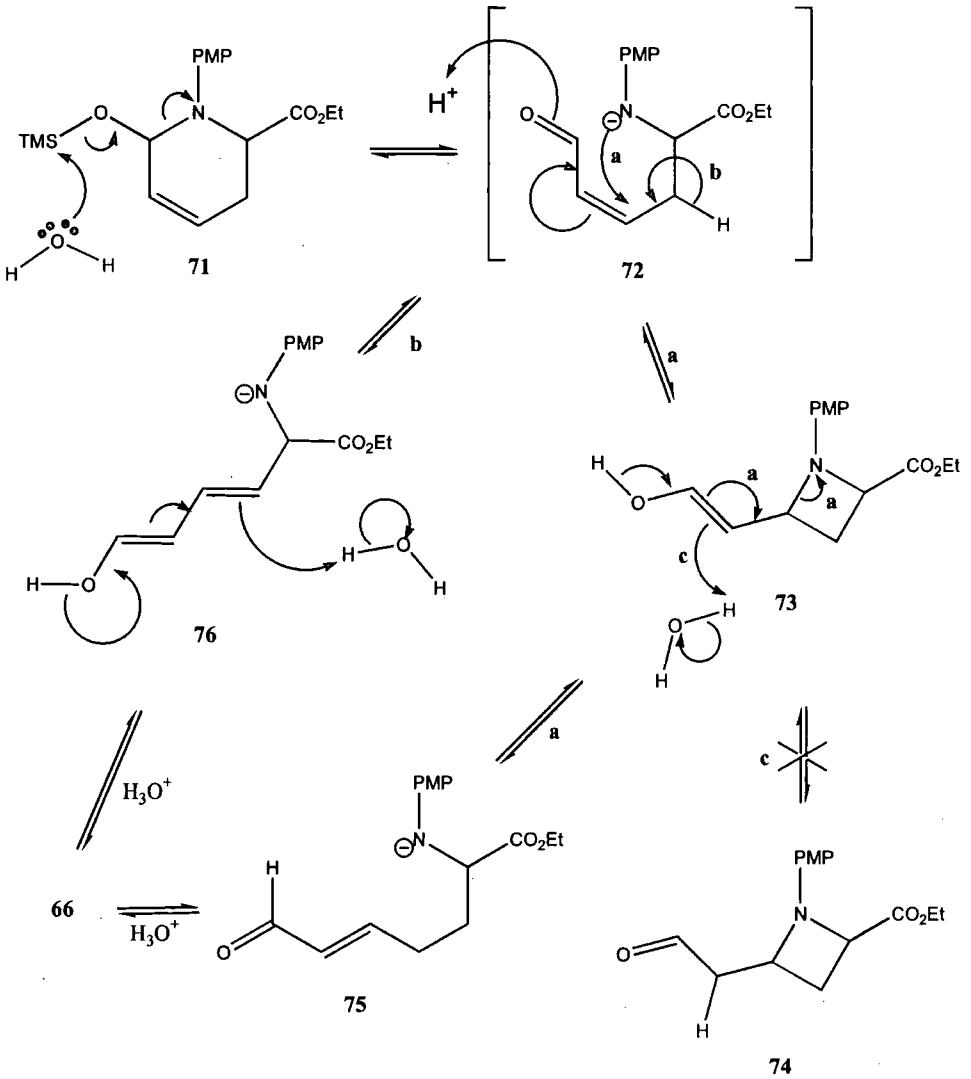
Scheme 1



The acyclic product **66** was relatively easy to identify by its spectroscopic data. IR indicated that the ester carbonyl was now at 1730 cm^{-1}, from 1720 cm^{-1} in the starting imine. An absorbance at 1690 cm^{-1} showed the presence of an aldehyde which was confirmed in the ^1H NMR as a doublet at δ 9.51. A doublet at δ 4.03 which exchanged with D_2O showed the presence of the NH. An AB quartet at δ 6.70 showed that the aromatic ring was still *para*-disubstituted, although the signal was more upfield than that of the imine precursor. The two olefinic protons were identified as (1) a triplet of doublets at δ 6.85 with a *trans* coupling of 15.9 Hz, and the triplet being produced by two 7.3 Hz couplings to the neighbouring CH_2 unit, and (2) a double doublet at δ 6.19 with the same *trans* coupling constant, and a 7.9 Hz coupling to the aldehyde proton.

It seemed reasonable that the acyclic compound **66** (Table 12) could have been derived from ring opening of the normal-electron-demand Diels-Alder adduct **71**, *via* the process shown in Scheme 2. This involves cleavage of the carbon – nitrogen bond to provide ring-opened product **72**. Enolisation through either proton or Lewis acid binding to the aldehyde (pathway b) could result in the thermodynamically favoured *E*-olefin, which, after tautomerisation would furnish the acyclic product **66**. An alternative pathway (pathway a), involves an intramolecular Michael addition by the nitrogen atom in **72**, which would also allow double-bond isomerisation. It would then be expected that a retro-Michael addition could take place to give the (now *trans*) product **75**. Protonation of the resulting aniline would furnish the acyclic product **66**. The fact that no *Z*-olefin was observed suggests that this theory may be less likely, but certainly not inconceivable. Also, the fact that none of the cyclic amine **74** has been isolated (this does not categorically infer that it was not formed), makes this pathway seem less probable.

Scheme 2

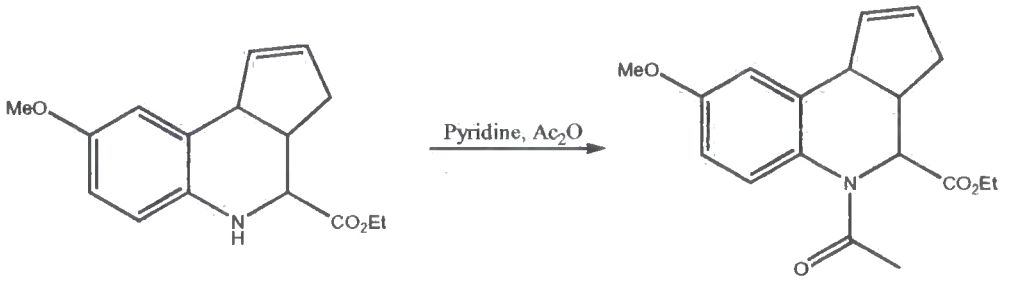


The adducts produced in the reactions with imine **53**, and ultimately the manner in which the imine reacted, became more readily understood whilst attempting to characterise products **66** and **64**. It was extremely difficult to gather the characterisation data of the initial adducts due to their instability, and was theorised that the source of instability lay in the anilinic nitrogen atom. These are known to readily undergo oxidation processes (one need only look at the colour and consistency of *p*-anisidine prior to recrystallisation for evidence!). By making the *N*-acetamide, it was hoped that these instability problems would be counteracted, and the resulting derivatives would be more stable and easier to characterise. However, efforts were still being made to gather full characterisation data of the initial adducts. To accomplish this, it was necessary to repeat the experiments, purify the products and gather the necessary spectroscopic data, before the decomposition / oxidation process occurred (on occasion, removal of the last

traces of EtOAc from the columned material, resulted in the vibrant yellow oil turning black in seconds!).

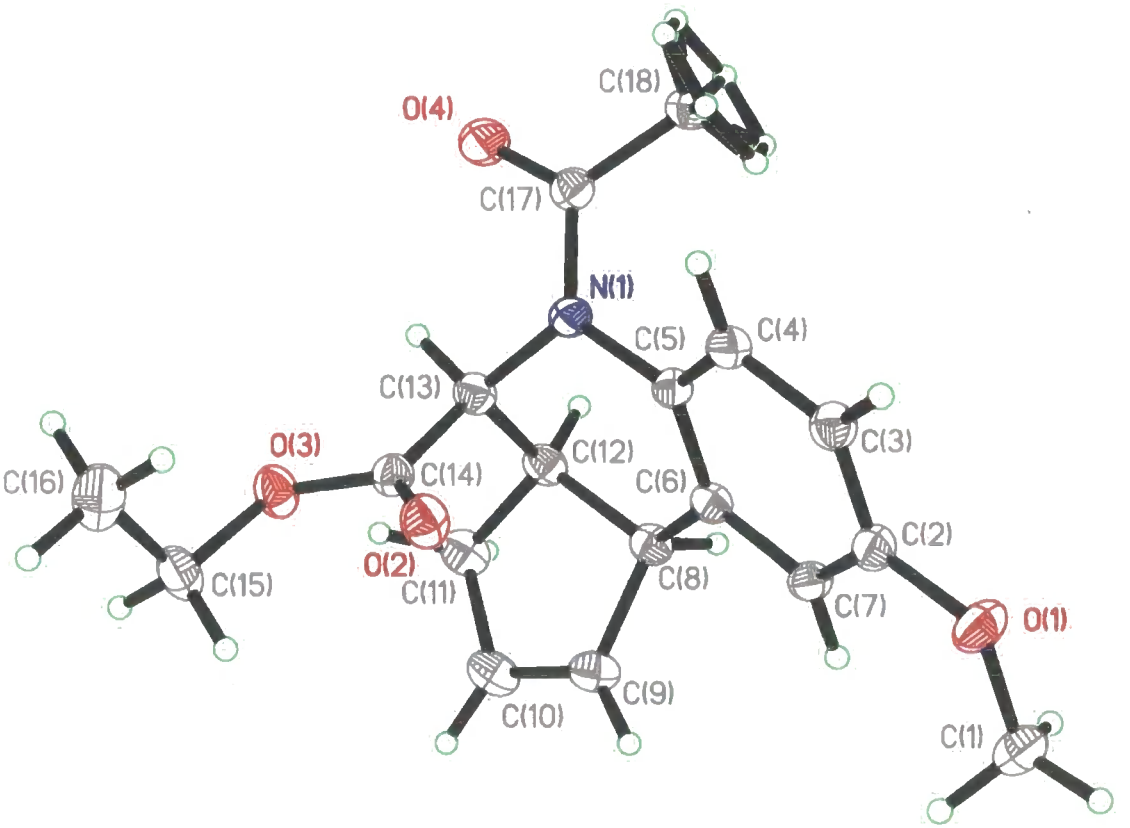
All acetylations could be done in one pot by simply removing the solvent from the cycloaddition reaction *in vacuo* and adding pyridine and acetic anhydride. The acetylation product of the cyclopentadiene adduct **77** was isolated in 72 % yield as a colourless solid (Equation 24) and the crystal structure was determined by X-ray diffraction (Figure 15) (see also Appendix 1).

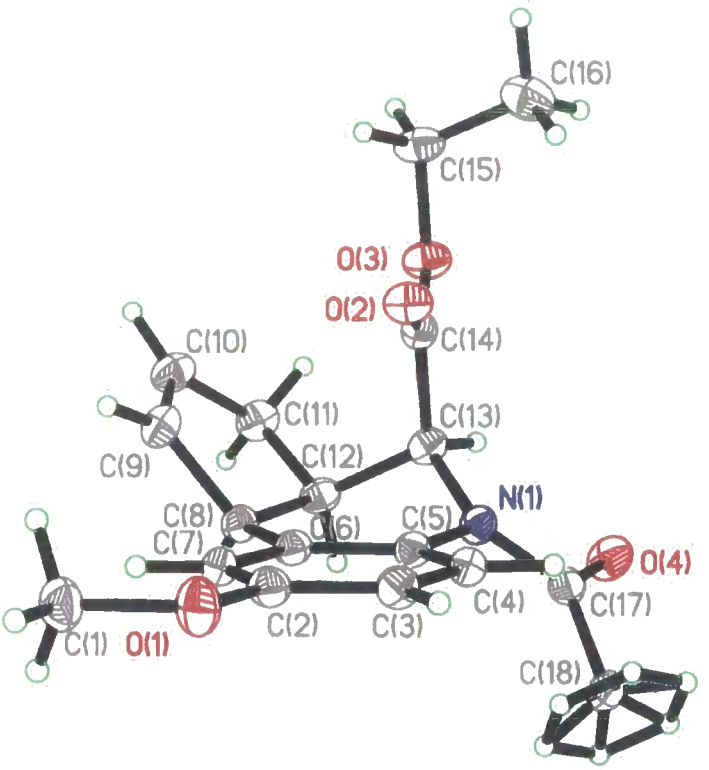
Equation 24



64 77

Figure 15

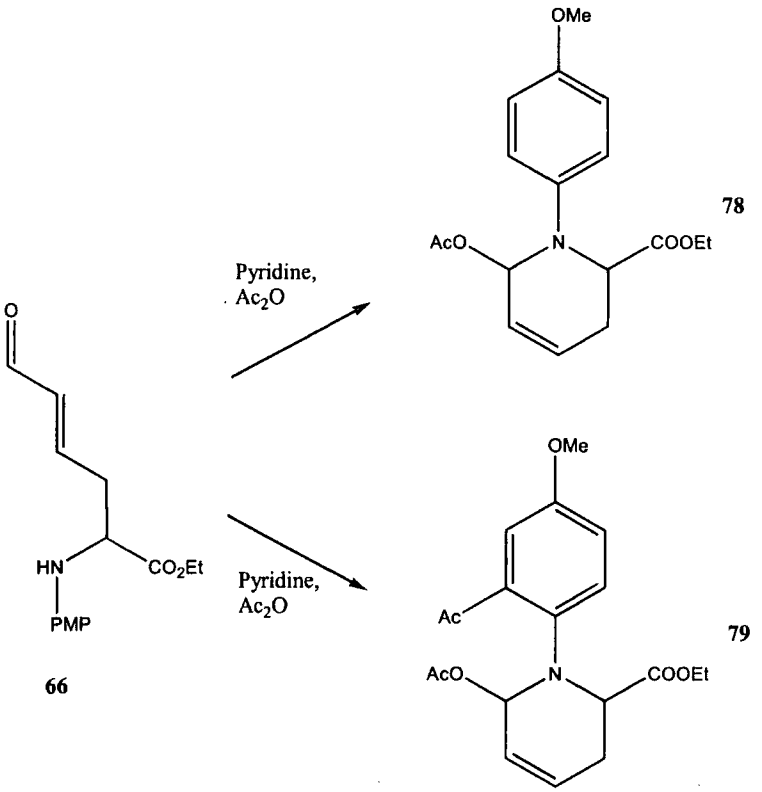




Looking at structure **77** along the tetrahydroquinoline axis, it is clear that the ethyl ester and the *cis*-fused cyclopentene ring are *syn*-coplanar. The acetamide is placed away from the congestion on the other side of the ring, which is considerably flattened. This is a result of both the aromatic ring (and therefore hybridisation of the carbon atoms), and the cyclopentene ring, both of which lock the nitrogen-containing ring into a flattened geometry.

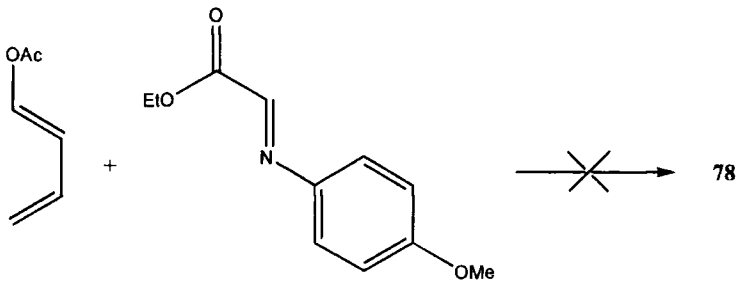
The acyclic compound **66**, when exposed to the same acetylation conditions, gave a result that was not expected. The compound had reacted (the ^{1}H, ^{13}C, IR and mass spectroscopic data had all changed), but the perplexing issue was the appearance of not one, but two new acetate functions. The expected product **78** (Scheme 3) could not have contained two acetates. Also, the benzene ring had become tri-substituted. It first was thought that some kind of Friedel-Crafts acylation had taken place to give **79**. At the time, scepticism surrounded this hypothesis however, and therefore a new one was sought. The answer came from analysis of the acetoxybutadiene adduct, whose structure had been incorrectly assigned up to this point.

Scheme 3



On first inspection of the characterisation data, it appeared that 1-acetoxybutadiene had given the normal Diels-Alder adduct **78** [*i.é.* the expected product of acetylation of **66** (Scheme 3)], even though certain pieces of the data did not fully support this assignment. The ^{1}H NMR spectrum was not clean, and there were traces of something else (unknown) on the baseline. It was obvious therefore, that this compound was not completely pure. The traces of impurity were initially attributed to oxidation and / or decomposition. The first problem was the aromatic ring. Although on first inspection of the ^{1}H NMR spectrum, it appeared that there was an AB quartet at δ 6.64, it became obvious from the expansions that it was not. Also, the integration was between three and four protons, but knowing impurities were present, it was difficult to say with authority what the multiplicity and correct integrals were. Furthermore, the product of acetylation was the same as that of **66** by ^{1}H and ^{13}C NMR. Serendipity, and a failed hydrogenation experiment, allowed completion of the puzzle.

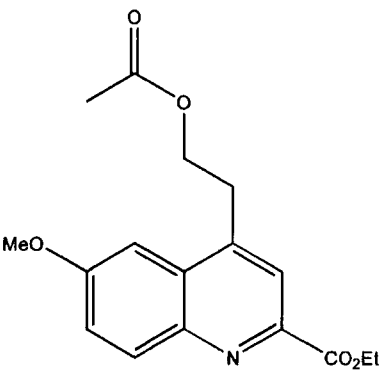
Equation 25



60 **53**

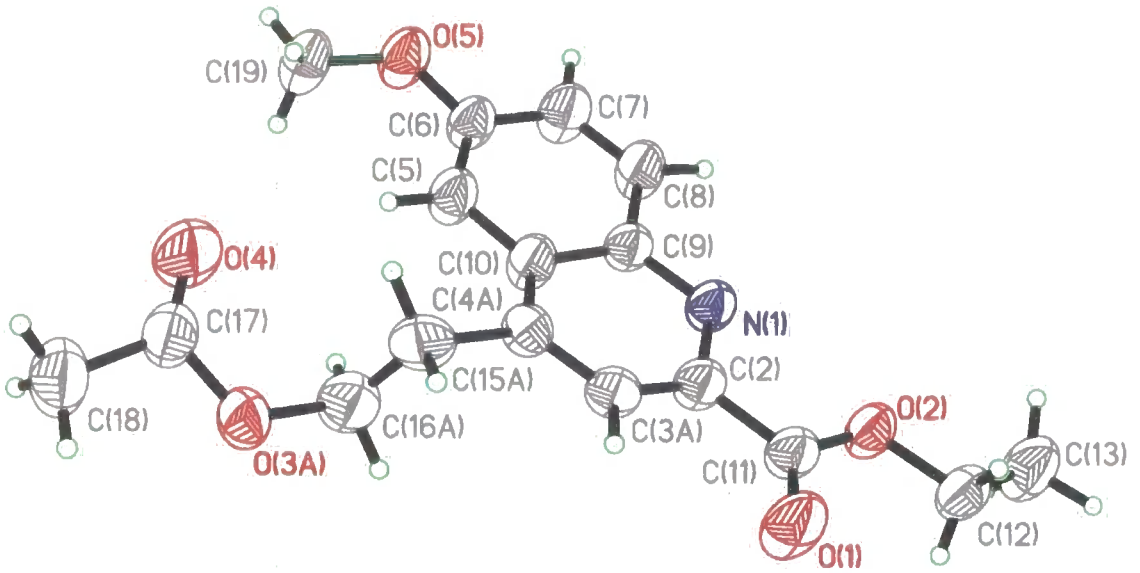
The crude reaction mixture of the acetoxybutadiene reaction was evaporated, redissolved in EtOAc, palladium on carbon was added, and the reaction vessel was reacted with hydrogen overnight. After silica gel chromatography, the compound **80** was isolated in 62 % yield (Figure 16). The elucidation of this structure suddenly explained, what was happening in these previous aza-Diels-Alder reactions. The structure of compound **80** was confirmed by X-ray crystallography (Figure 17) (see Appendix 2).

Figure 16



80

Figure 17

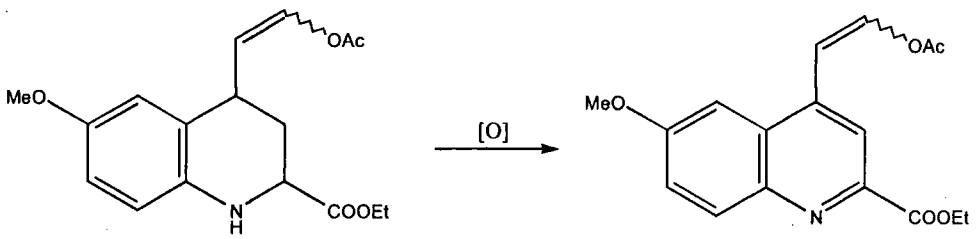


The precursor to structure **80** must therefore have been tetrahydroquinoline **65**, since the hydrogenation had been accompanied by a de-hydrogenation of the ring system to furnish the quinoline (probably due to incomplete hydrogen saturation of the atmosphere), leaving only the alkene to be reduced. The conclusive evidence was obtained by a PCC oxidation of the crude reaction mixture of acetoxybutadiene **60** and imine **53**, which gave **81** as an approximately 3 : 1 mixture of *E*- and *Z*-olefins, respectively, in 51 % overall yield (Equation 26). Note that the acetoxybutadiene starting material used was a mixture of *E*- and *Z*-olefins (1.6 : 1 respectively, as determined by ^{1}H NMR). Again, serendipity played its role in uncovering how facile the oxidation of initial adduct **65** to quinoline **81** is. On changing the source of silica gel used to perform column chromatography, it was found that it had now become impossible to isolate pure **65**, but instead, **81** was isolated in 32 % yield. Some of the mass loss was due to the fact that the **65** is faster moving on the column than **81**, and would invariably have come off the column and started to oxidise, resulting in an impure sample. This time, the ratio of *E*- to *Z*-olefins was 6 : 1, respectively. A final experiment was carried out by taking the crude cycloaddition reaction mixture, and after solvent removal, re-dissolving in chloroform and heating to 50 °C in air for 1 hour. Quinoline **81** was isolated as an approximately 4 : 1 mixture of *E*- and *Z*-olefins in 83 % yield. The half-life of adduct **65** in EtOAc at room temperature was found to be approximately 3 days (as determined by ^{1}H NMR).

The fact that the ratio of *E*- to *Z*-olefin in the product of acetoxybutadiene **60** and imine **53** varies from reaction to reaction, (and is different to the alkene ratio in the starting diene), may suggest that the reaction is not concerted.

To establish the link between **80** and **81** a hydrogenation was carried out on a pure sample of **81**. Reduced product **80** was isolated after silica gel column chromatography, as a white crystalline solid in 86 % yield.

Equation 26



65 **81**

With the knowledge of the structure of the various derivatives of **65**, re-analysis of the spectroscopic data for the original acetoxybutadiene adduct revealed that the impurities were not the result of oxidation. Rather, they could be tentatively assigned as being the *cis*-alkenyl acetate with a *syn*-configuration around the tetrahydroquinoline ring (19 % with respect to the major diastereoisomer), and the diastereoisomer with an *anti*-configuration around the tetrahydroquinoline and a *trans*-alkenyl acetate (17 % with respect to the major product). This assignment could be made on the analysis of the ^{1}H NMR spectrum of the mixture.

The IR spectrum of the major component showed absorbances at 1750 and 1730 cm^{-1}, corresponding to the ethyl ester and acetoxy carbonyl stretches respectively. The ethyl ester carbonyl at 1720 in the starting material was no longer present. The imine proton of the starting material had disappeared in the ^{1}H NMR spectrum, and an exchangeable proton at δ 4.21 was found in the product, indicating the presence of the NH. A 3H multiplet between δ 6.57 – 6.71 indicated that the *para*-disubstituted benzene ring in the starting material had become tri-substituted. Also, a 3H singlet at δ 2.18 indicated the presence of an acetyl group.

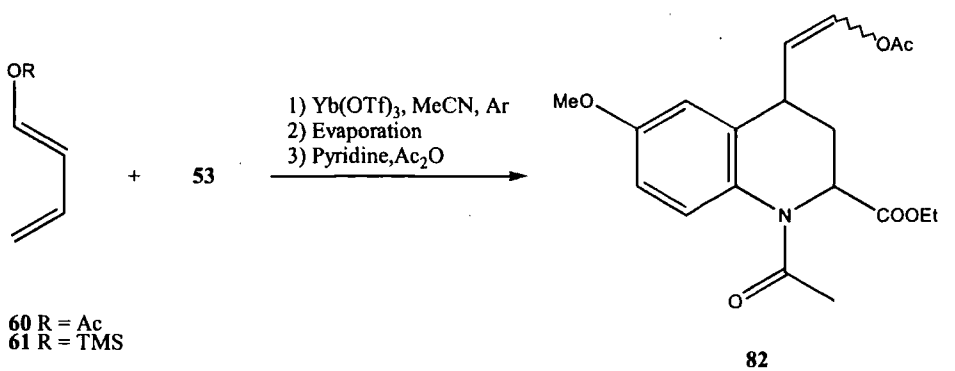
The stereochemistry of the major diastereoisomer was assigned according to a similar structure reported in the literature,[41] and was indicated by the coupling constants for the

methylene protons. Both protons (situated at δ 1.81 and δ 2.41) had a geminal coupling of 12.5 Hz. The proton at δ 1.81 was a triplet of doublets, the triplet being produced by an 11.0 Hz coupling, indicative of two *trans*-couplings across the ring. The proton at δ 2.41 was assigned as a double double doublet, with couplings of 3.5 and 5.5 Hz, in addition to the geminal coupling. These small couplings indicate a *cis*-arrangement with the protons on neighbouring carbon atoms. This must make the vinyl acetate and the ethyl ester groups *syn* to one another across the ring, since if they were *anti*, one large coupling and one small coupling would be expected for each of the methylene protons.

The assignment of the minor stereoisomers was based on what are believed to be the two olefinic protons of each. For the *cis*-product with the same configuration across the ring as the major product, a double doublet at δ 4.91 with 6.5 and 9.0 Hz coupling constants, and a doublet at δ 6.81 with a 9.0 Hz coupling constant were observed. For the component with the opposite configuration, but with a *trans*-olefin, a double doublet at δ 5.56 with 8.5 and 12.6 Hz coupling constants and a doublet at δ 7.09 with a 12.6 Hz coupling constant were used in the assignment.

Having established that the Diels-Alder product of acetoxybutadiene **60** and imine **53** was of the "inverse-electron-demand" type, and given that the products arising from exposure to the acetylation conditions were the same in both cases, it became clear that, in the acetylation of trimethylsilyloxybutadiene adduct **66** (Equation 27), the acyclic material did not cyclise as would be expected (*i.e.* by an *N*-cyclisation pathway). Rather, it had cyclised on the benzene ring and doubly acetylated to give **82**. What complicated matters further was that **66** could no longer be identified in the crude product of the reaction between **61** and **53** (*i.e.* there was no aldehyde signal in the ^{1}H NMR).

Equation 27



60 R = Ac
61 R = TMS

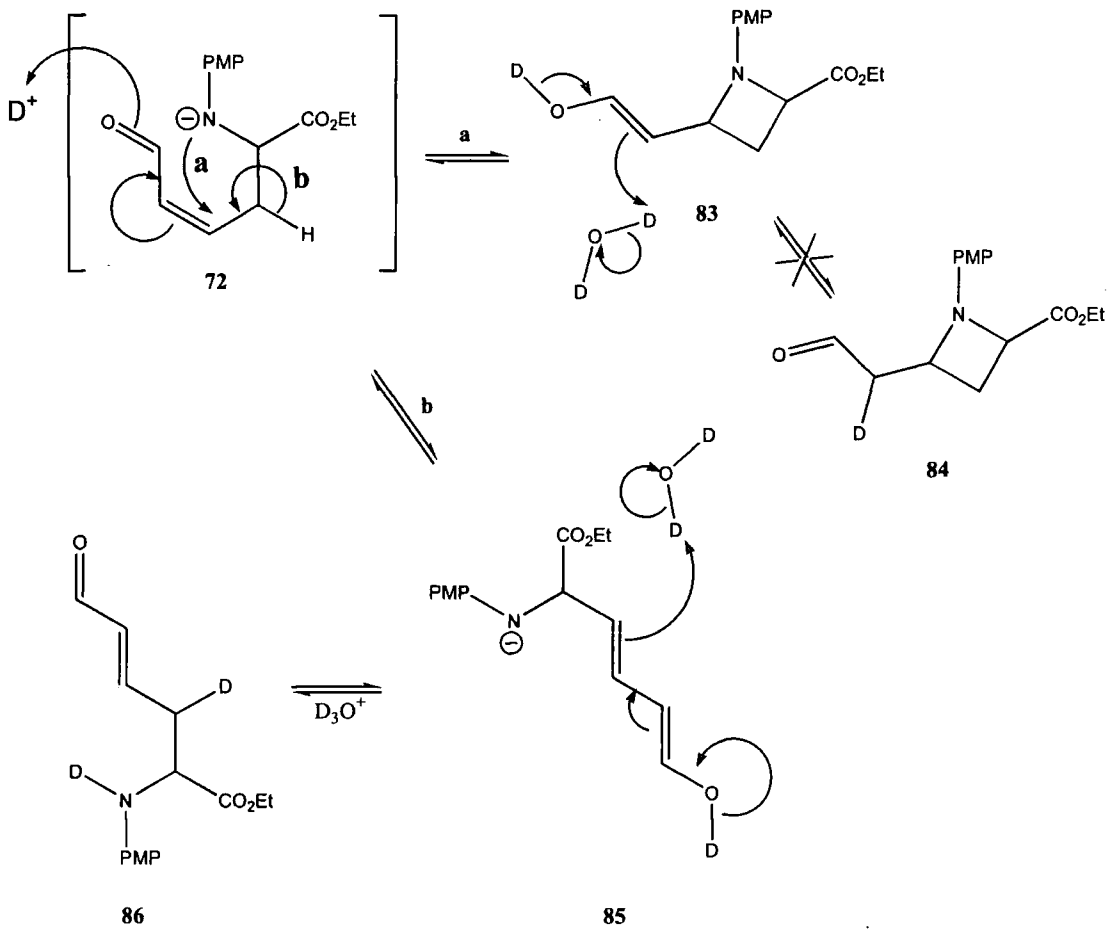
82

2.4.3 The Effect of Water in the Reaction

Seemingly, there had been no changes to the manner in which the reactions were carried out. The same bottles of reagents and the same batch of had been used, and the reactions were allowed to stir in an inert atmosphere for the same length of time. The only change (other than glassware and stirrer beads) had been the solvent source. The stock of "dry" acetonitrile that had been used in the early reactions had run out. This prompted the rigorous drying of a new batch, and since this new batch had been used in other experiments with no detrimental effect, the connection was not made until the reaction was performed with non-dried acetonitrile, fresh from the supplier, but straight from the bottle. Suddenly, the appearance of a doublet at 9.5 ppm in the ^{1}H NMR of the crude product began to occur again. Taking the newly dried MeCN and carrying out the reaction using the normal approach, but with the addition of one equivalent of water, it was found that the doublet re-appeared again. Since the reaction had an aqueous work-up after consumption of starting materials, it became evident that water was needed *in situ* to produce aldehyde **66**.

Next, the addition of D_2O into the reaction mixture, in place of water, was attempted in order to check for deuterium incorporation into the carbon skeleton. It was anticipated that, following either of the mechanisms outlined in Scheme 2, some deuterium may be incorporated into the CH_2 beta to nitrogen, as outlined in Scheme 4. However, no deuterium incorporation was observed showing that an intermediate such as **72** (Scheme 4) is highly unlikely to be involved in the formation of open-chain product **66**.

Scheme 4



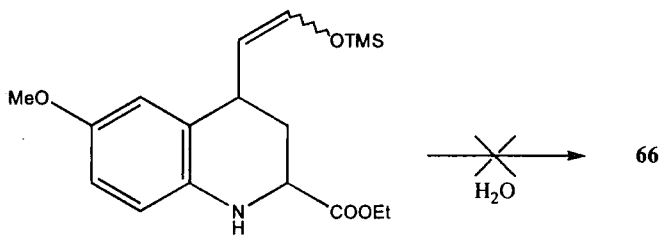
However, it could be argued that TMS-OTf or TfOH could be an active catalyst in this reaction, and that Yb(III) was not the active catalyst. This theory was tested by using 5 mol % TMS-OTf under the same reaction conditions (trimethylsilyloxybutadiene **61** and imine **53** in MeCN), both with and without water (hence TfOH would be produced in aqueous conditions). A complex mixture of products was observed by TLC and ^{1}H NMR The aldehyde was not observed in either the aqueous or anhydrous case, clearly implicating Yb(III) as being vital in the reaction to produce compound **66**.

2.4.4 A More Simple Solution?

The results of the above reactions prompted further consideration of the mechanism involved in these "cycloaddition" reactions. Obviously, the imine was not behaving solely as an imino-dienophile as originally expected. Hence, to explain the observed products, it was originally thought that perhaps several different reaction mechanisms were operating in the presence of different dienes. These are: 1) normal-electron-demand imino-dienophile Diels-Alder reaction (as with Danishefsky's diene, Table 12,

Entry c); 2) inverse-electron-demand Diels-Alder reaction (where the imine acts as a diene, Table 12, Entries a, b and e); and 3) Mannich-like process, whereby the diene adds *via* a nucleophilic addition pathway (Table 12, Entry d). Having suggested that 1-trimethylsilyloxybutadiene **61** does not undergo a normal electron-demand Diels-Alder reaction with imine **53** (water is needed *in situ* to produce the acyclic product, and no deuterium incorporation was observed when D_2O was used in place of H_2O), and on the basis that it was extremely unlikely that the inverse-electron-demand product **87** would undergo hydrolysis of the bridgehead C-C bond (Equation 28) to give **66**, it became apparent that the products could all perhaps be explained by a single reaction mechanism, as outlined in Scheme 5.

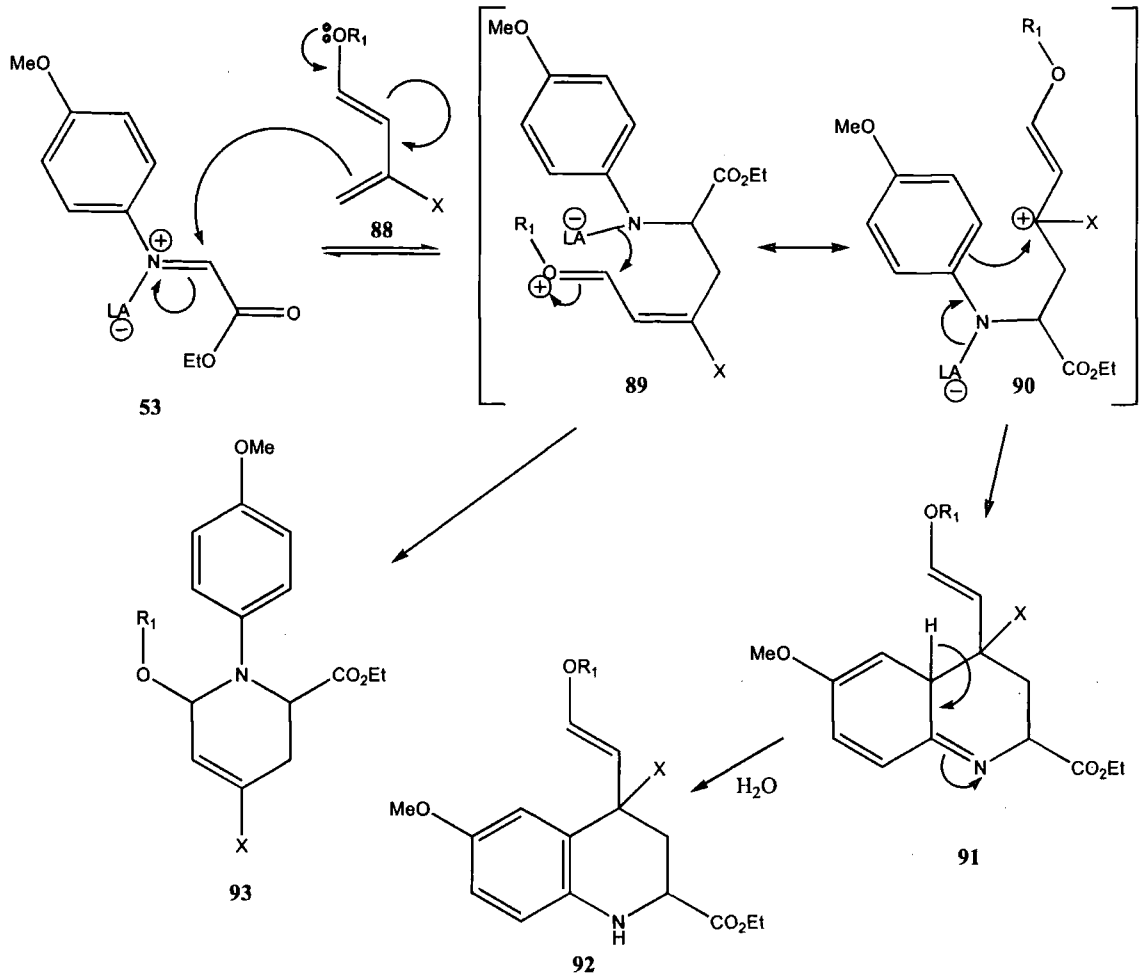
Equation 28



87

For the purposes of illustration of the generality of this mechanism, a generic 1-oxygenated butadiene is used (Scheme 5). The first step is the Lewis acid activation of the imine, followed by nucleophilic addition of the 1-oxygenated diene, to furnish a zwitterionic intermediate **89**, common to all the reactions. This is in resonance with the alternative structure **90**. Examining these two resonance forms (**89** and **90**), it can be seen that there are two possible modes of cyclisation: 1) that onto nitrogen **93**; or 2) a Friedel-Crafts type cyclisation onto the benzene ring to give **91**. In this later case, re-aromatisation produces the observed tetrahydroquinolines. The particular preference for each of the cyclisation pathways can be explained by the nature of the substituent X. Where the substituent is hydrogen, there is a propensity for aryl ring-cyclisation to occur. In the case of Danishefsky's diene (X = OTMS), the much bulkier silyl enol ether substituent could inhibit this pathway, forcing *N*-cyclisation to proceed. Obviously, β-elimination of methanol then produces the observed adduct **54**.

Scheme 5



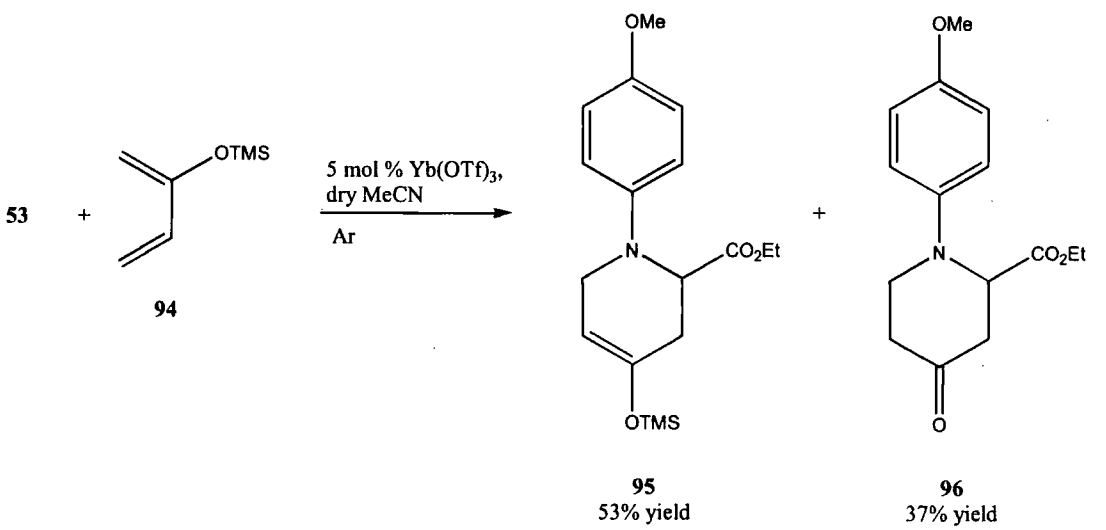
Hence, it can be justified that in the case of 1-trimethylsilyloxybutadiene, the addition of water to the reaction mixture quenches the intermediate, *i.e.* of the type **89**, and the acyclic product is observed. Proof would be obtained if the corresponding tetrahydroquinoline could be isolated when the reaction is carried out in anhydrous conditions. Although this product has not been isolated, comparison of the crude ^{1}H NMR of the 1-trimethylsilyloxybutadiene reaction, executed under dry conditions, with the ^{1}H NMR of the isolated 1-acetoxybutadiene adduct **65**, shows a distinct correlation in size, shape and chemical shift of certain signals (see Appendix 3), perhaps indicating that it probably is formed, but is extremely difficult to isolate.

With this in mind, it was decided to investigate the reaction between the 2-substituted diene, 2-(trimethylsilyloxy)-1,3-butadiene **94** and imine **53** (Equation 29),[46] under the usual reaction conditions, *i.e.* with 5 mol % $Yb(OTf)_3$ in MeCN at room temperature. This reaction was carried out both under anhydrous and aqueous conditions (non-dried MeCN), and this was worked-up by simply adsorbing the crude reaction mixture onto

silica gel and eluting. The only difference in the results between the anhydrous and aqueous reactions was a reduction in yield when water was present, presumably due to diene hydrolysis.

Two new products were obtained from each of these reactions, *i.e.* **95** and **96**, with these being isolated in 53 and 37 % yields respectively from the anhydrous reaction (Equation 29).

Equation 29



Importantly, no acyclic product was isolated in either reaction, but this could be due simply to the fact that the cyclic form is more stable than the acyclic form. The possibility still exists for **95** to be produced in a normal-electron-demand Diels-Alder reaction, however, the observed results can also be explained by the stepwise addition-cyclisation mechanism. No tetrahydroquinoline-type structure was observed in the reaction product of **53** and **94**, and this fact could also be explained by the presence of the bulky OTMS group, effectively blocking formation of the six-membered ring if aryl ring-cyclisation were to take place. Product **96** must arise from hydrolysis of compound **95** on the column, although **95** is apparently fairly water and dilute aqueous acid stable. It is, however, rapidly converted through to ketone **96** using wet TBAF, as determined by a ^{1}H NMR experiment. Thus, exposure of a $CDCl_3$ solution of trimethylsilyl enol ether **95** to excess TBAF produces solely the ketone **96**.

Compound **95** could be identified readily: in the IR spectrum, the ester carbonyl appeared at 1735 cm^{-1}; the ^{1}H NMR showed a 4H singlet for the aromatic protons at δ

6.63, a characteristic upfield shift from the starting material; the TMS group appeared as a 9H singlet at δ 0.00 and the olefinic proton could be found as a multiplet at δ 4.71 – 4.76; ^{13}C NMR showed the presence of two olefinic carbon atoms at δ 101.2 for the CH, and δ 146.0 for the C-OTMS carbon atom; and the two ring CH_2 units were located by DEPT at δ 32.3 and δ 44.4.

Compound **96** showed a broad IR absorbance at 1729 cm^{-1} which is due to both the ester and ketone carbonyl stretches. ^{1}H NMR showed a 4H AB quartet at δ 6.83 indicating a *para*-disubstituted benzene ring. The methoxy protons appeared as a singlet at δ 3.71 and three CH_2 units were found at 39.3, δ 41.4 and δ 44.8 in the ^{13}C and DEPT NMR spectra. The ketone carbon atom could be seen at δ 205.3, whilst the chiral carbon appeared at δ 60.2.

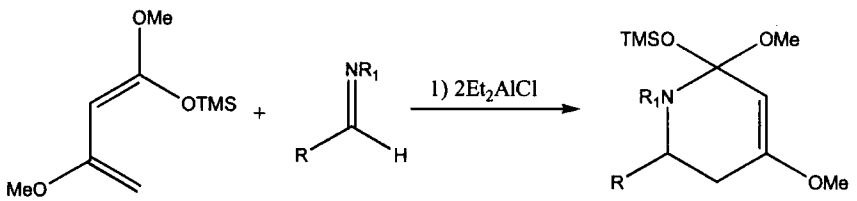
The most problematic of the adducts to purify and characterise was the methoxycyclohexadiene adduct **67**. It was estimated that the purity of the material isolated was in the region of 80 – 90 %, based on the ^{1}H NMR spectrum. It was clear from TLC of the crude product, that the isolation of a pure product would be challenging, because it was difficult to discern spots from the streak created by elution of the reaction mixture. Efforts were made to sharpen the TLC resolution, including the addition of a small amount of triethylamine to the elution solvent, the use of various solvent mixtures and the use of alumina instead of silica gel. All were unsuccessful. In addition, it is noteworthy that 1-methoxycyclohexa-1,3-diene is sold as technical grade (65 %), and it is possible that other products could well have derived from the constituent elements of the remaining 35 % (presumably mono-alkenes and 1,4 dienes) reacting with the imine **53**. Couple this with the stability problems inherent in the tetrahydroquinoline derivatives, and there is a substantial task to purify each of the products cleanly. However, the spectroscopic data for the crude reaction product showed that it was certainly different to the starting material, and it was obvious that the structure was not the normal-electron-demand product. The first piece of evidence that pointed to this was the appearance of only one olefinic C-H in the ^{1}H NMR (located at δ 5.14), and confirmed by ^{13}C NMR (located at δ 95.3). Also, the aromatic ring had become tri-substituted. Inspection of the ^{1}H NMR revealed three protons located at δ 6.56, δ 6.64 and δ 6.79, each integrating for 1H, which corresponds to the aromatic hydrogen atoms. Two methoxy singlets were found at δ 3.60 and δ 3.75, showing the presence of the aryl and olefinic OMe groups. ^{13}C NMR showed the correct number of

carbon atoms and the DEPT spectrum indicated the correct number of quaternary, methylene and methyl / methine carbon atoms. IR showed the presence of the ester function as a signal at 1720 cm^{-1}, an NH stretch at 3380 and the Me-O-C stretching frequencies at 2840 and 2820 cm^{-1}, indicating the aryl-methoxy group and the alkenyl-methoxy group respectively.

There has been considerable discussion and perhaps dispute over the mechanism of the imino-Diels-Alder reaction over the years in the chemical literature. In his original paper,[6] Danishefsky deferred any discussion of the mechanism. Ojima's study[7] concluded that the cycloaddition went through a common, acyclic intermediate, although the authors conceded that further mechanistic investigations were needed.

The Midland group stated evidence for a pericyclic mechanism in their reactions with Brassard's diene **9**.[8] They isolated the cyclic intermediate **97** as a single diastereoisomer (Equation 30) and implicated a normal Diels-Alder reaction as the rationale.

Equation 30

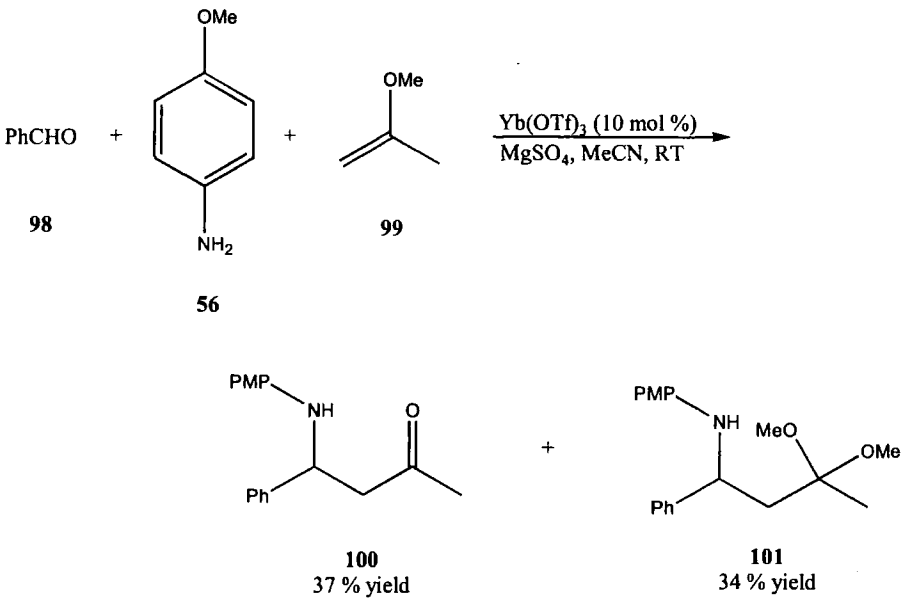


9 **10** **97**

In fact, there are myriad examples that suggest a concerted (if sometimes asynchronous) mechanism could be operating in these types of reactions. Equally, there are myriad examples that state a stepwise mechanism is the probable mode of operation.

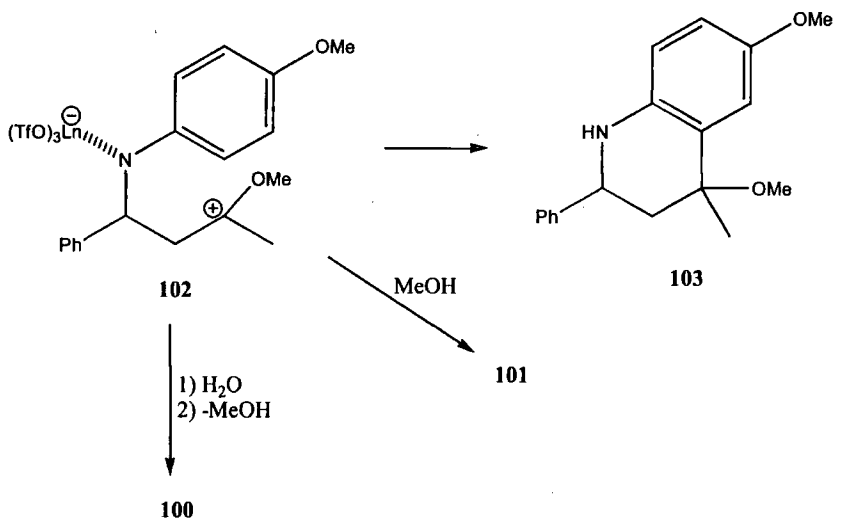
In Kobayashi's work,[10] a stepwise mechanism was suggested following the results outlined in Section 1.5 involving imine **14** and a variety of dienes and activated mono-alkenes (Equation 9, Table 3). In a study based on the three component coupling reaction between *p*-anisidine **56**, benzaldehyde **98** and 2-methoxypropene **99** (Equation 31) it was found that significant amounts of by-products could be isolated, when compared with the analogous reaction using the pure imine under anhydrous conditions.

Equation 31



They proposed an intermediate **102** (Scheme 6),[10] equivalent to the one proposed above, from which it is easy to see where the products **100** and **101** arise, in addition to the tetrahydroquinoline **103**.

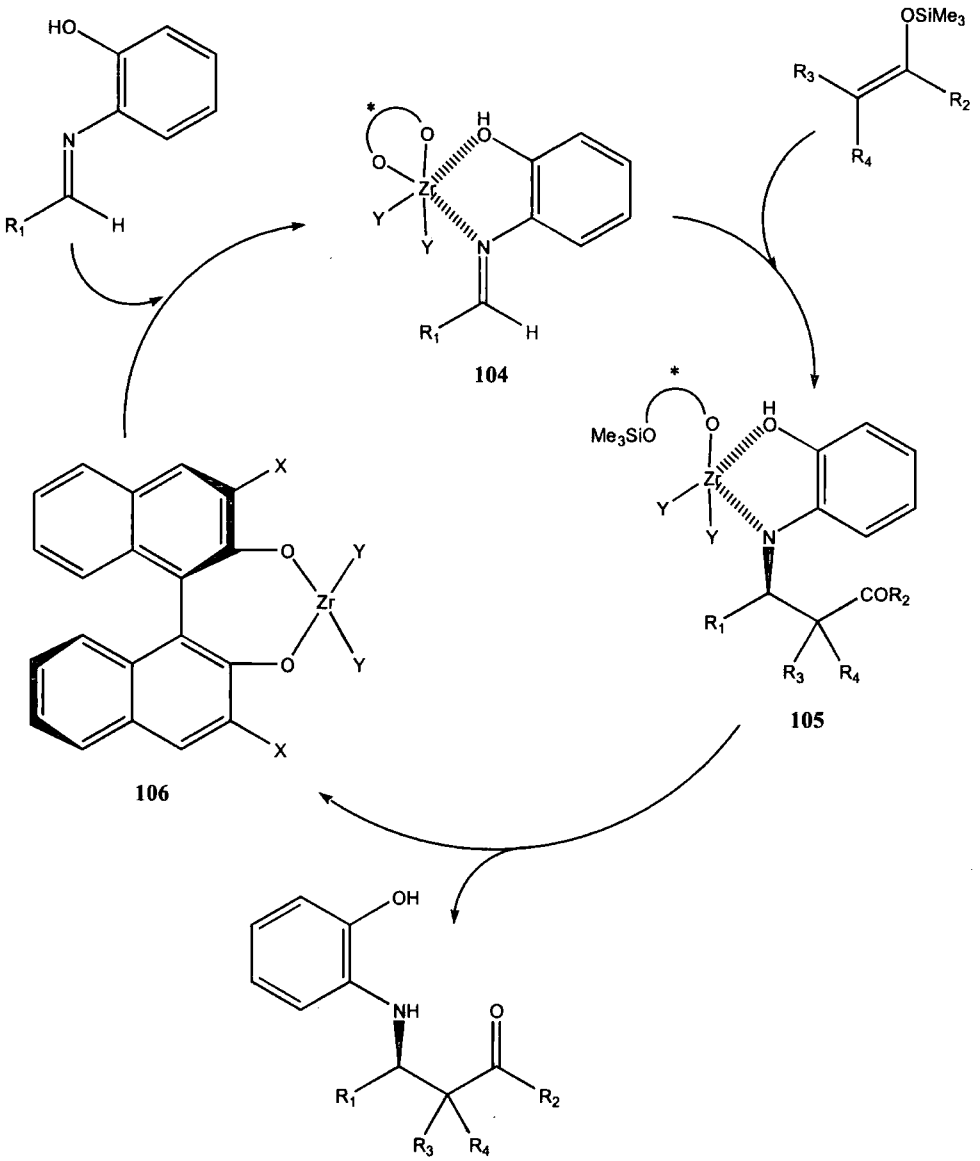
Scheme 6



In later work on the asymmetric Mannich reaction,[47] Kobayashi *et al.* showed that a catalytic cycle could be drawn upon, based on the believed catalytic cycle in Mukaiyama aldol reactions, to explain the observed results. However, it was found in the study that an alcohol (PrOH) or water was required to free the catalyst (Scheme 7, transition from **105** to **106**), yet amazingly, neither PrOH or water had been drawn in the catalytic cycle! It could be argued that the alcohol, or water, attacks the metal centre

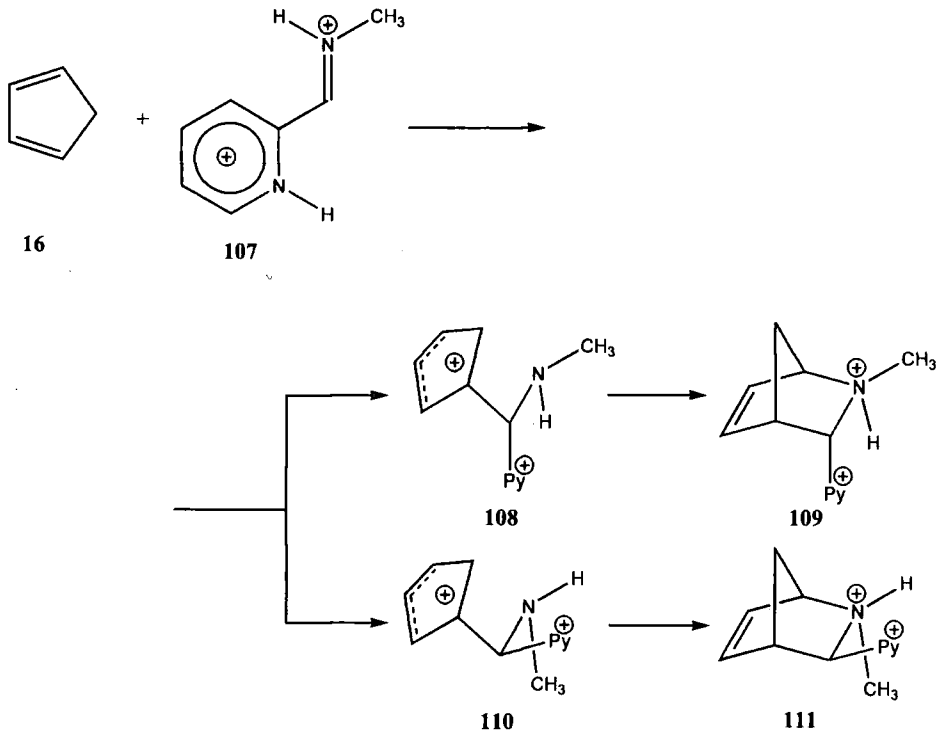
before the silicon transfer to the BINOL derivative **105**. This could in turn reduce the affinity of the substrate for the catalyst, allowing silicon to migrate to either the nitrogen atom, or the phenolic oxygen atom. If the former were the case, the isolated product could be explained by the transfer of silicon onto oxygen to give the stronger O-Si bond. Regardless of which process operates, the use of a source of PrOH or water to produce acyclic products when (*vide supra*) using slightly different substrates under anhydrous conditions produces aza-Diels-Alder products, certainly indicates that there is a fine balance between the conditions needed to produce either Mannich-type or Diels-Alder-type products. Indeed, this adds more weight to the idea of an essentially similar mechanistic pathway operating in the case of diene **61** and imine **53**. It appears that on occasion, intermediates of the type **89** and **102** can be trapped by nucleophiles, although the exact mechanism behind this obviously needs a great deal more study in order to elucidate exactly what process is operating, and whether there are slightly different reactions occurring in each case.

Scheme 7



Recently, molecular modelling studies by Domingo and co-workers have added strength to the idea of a stepwise mechanism in related reactions.[48] Although based on proton activation of imines (hence, a strong Lewis acid effect), they concluded that a reaction between cyclopentadiene **16** and protonated *N*-methylpyridine-2-carboxaldehyde imine **107**, proceeded by a stepwise mechanism (Scheme 8), according to theoretical calculations.

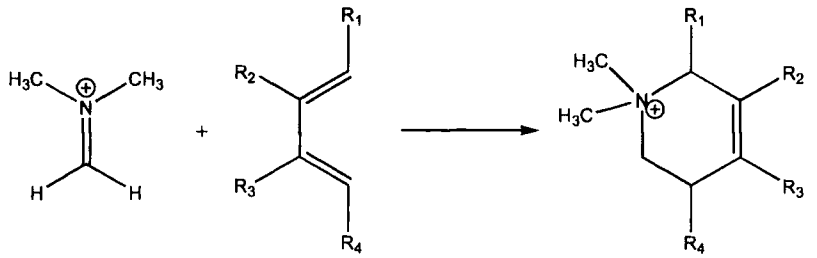
Scheme 8



This study showed that the *exo*-intermediate **110** is 0.4 kcal / mol more favourable than its *endo*-equivalent **108**. Despite the slightly exothermic formation of **110**, the second (cyclisation) step was found to favour rapid transformation to **111**. In addition, in the acyclic intermediates **108** and **110**, it was found that the newly formed C-C bond lengths were 1.569 and 1.552 Å respectively, whilst the (about to form bonds) C-N distances were 3.662 and 3.793 Å respectively. The imine carbon, and the cyclopentadiene carbon involved in the first bond formation, were found to be completely pyramidalised at this intermediate point, whilst the data corresponding to the three carbon atoms of the allylic cation were found to have bond lengths of about 1.4 Å and were planar in arrangement. It was also found that the H-N-CH_3 bond angle was 111°, corresponding to a sp^3-hybridised nitrogen. This evidence is consistent with a charge transfer brought about by nucleophilic attack of cyclopentadiene **16** on iminium ion **107**.

The above study was conducted after previous studies by Sauer *et al.*,[49] who experimentally and theoretically studied the reaction between ylidene ammonium cation **112** and several substituted butadienes **113** (Equation 32).

Equation 32



112 **113** **114**

This group proposed that the aza-Diels-Alder reaction of the two partners **112** and **113**, proceed *via* transition structures very close to those yielding allyl cations. In the reaction of the same ammonium cation **112** and cyclopentadiene, they found the process to be occurring along a pericyclic pathway. A more recent Density Functional Theory (DFT) study of the same reaction of **112** and cyclopentadiene by Domingo,[50] concluded that the reaction "takes place along a highly asynchronous concerted process characterised by the nucleophilic attack of the cyclopentadiene on the ylidene ammonium cation (**112**) instead of a pericyclic process".

Amidst the number of examples in the relatively recent literature on imino-Diels-Alder reaction (whether they be; imino-dienophiles, 1- or 2-iminodienes, intramolecular or intermolecular reactions), there are still comparatively few that make bold assessments of the mechanism involved in the reactions studied.[41,51-53] In fact there are many examples that suggest a concerted (if sometimes asynchronous) mechanism,[5,8,22,23,37,42-44,54] and equally, there are many that state a stepwise mechanism is the probable mode of operation.[24-27,32,55,56] Some papers conclude that more than one mechanism is in operation.[18,40,57] The problem is certainly complex. In studies where more than one mechanism is implicated, the likelihood is that a stepwise mechanism is in operation and that two different fates can await the common intermediate. Undoubtedly, on sifting through the literature, there are some common assumptions made where apparently Diels-Alder products are observed and a diene and dienophile reaction system is operating. To take one example, whilst not speculating on the mechanism of the reaction, Andersson[39] states how "when imines derived from aromatic amines are used in the Diels-Alder reaction, the imine turns to act as a diene instead of a dienophile". The fact that this is clearly not the case has already been discussed. Even if the reaction were concerted, the aromatic-amine-derived imine reacts with some dienes as a dienophile. Perhaps the accepted language used in the current literature is partially to

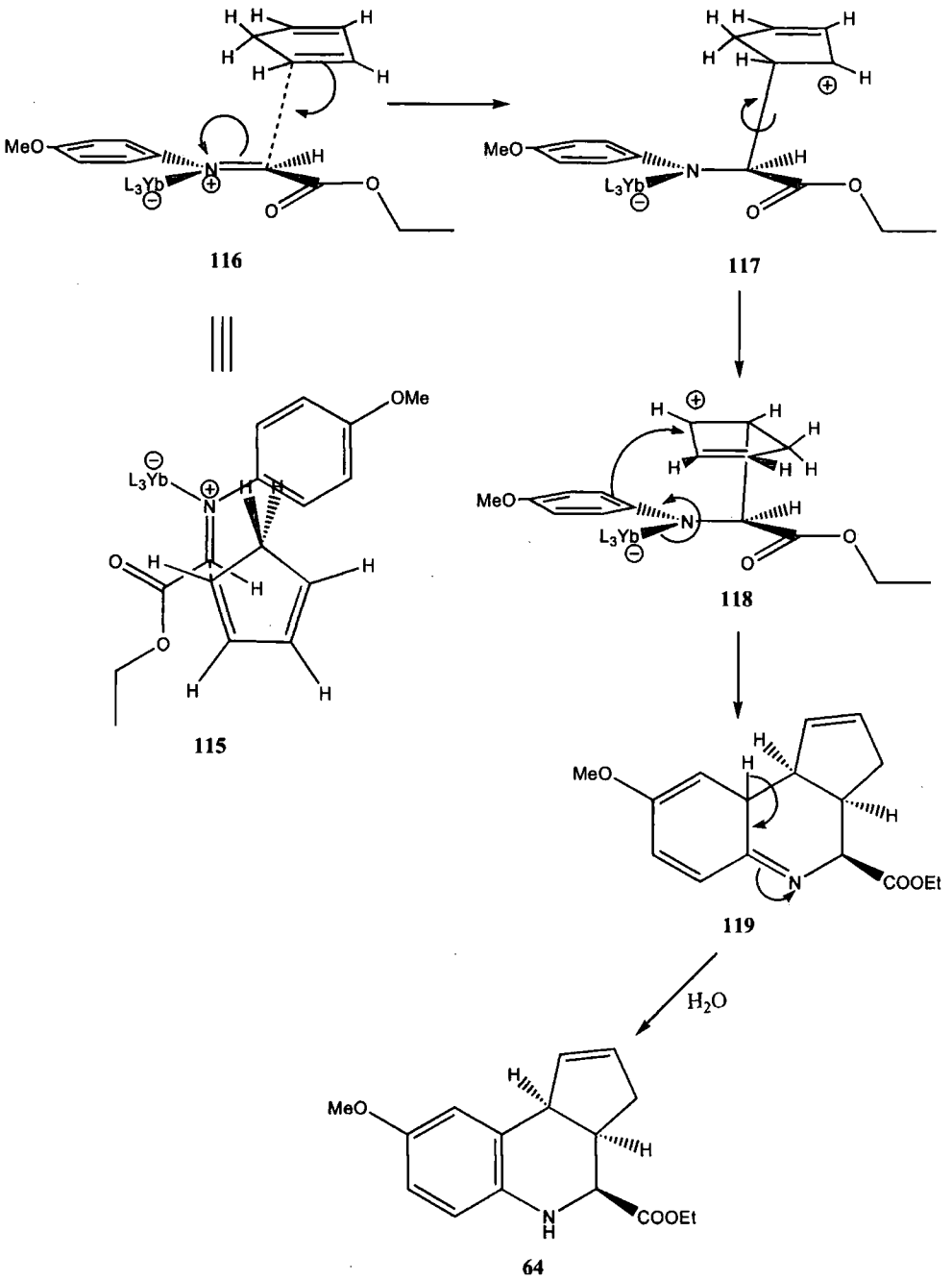
blame. Most papers make mention of "aza-Diels-Alder" processes, and the use of this term with descriptions such as "*endo*" and "*exo*" can easily bring to mind the rules associated with the all-carbon Diels-Alder reaction. Such expressions clearly relate to the structure of the products isolated, and not necessarily the mechanism by which they are derived. Quite simply, whilst the experimentally observed results can, in many cases, be explained by using the same rules governing Diels-Alder reactions, the use of imines (if not carbonyl functionalities) brings greater complexity to the reaction mechanism.

In light of the computational studies by Domingo *et al.*,[48,50] and the fact that only one diastereoisomer is observed in the reaction between cyclopentadiene **16** and imine **53**, some consideration was given as to how this might arise in a stepwise reaction. In product **64**, the bridgehead protons have to be *syn* due the massive ring strain involved in forming a 5,6-fused ring system. Therefore, the stereochemistry of the chiral centre next to the aromatic ring is predetermined by the manner in which the addition of cyclopentadiene to the imine occurs. Consequently, the stereochemistry of the molecule is set up by the initial nucleophilic attack step. This is diastereoselective however, with the ethyl ester being *syn* to the cyclopentene ring in the product. Shown in Scheme 9 is the first draft of the proposed manner of cyclopentadiene attack on the imine **53**.

Of course, there is no bias to influence whether the nucleophile (cyclopentadiene) attacks the *Re*- or *Si*- face of the imine. This is irrelevant, because the transition state from attack at the opposite face is enantiomeric and will still result in the *syn*-product being formed, but with the opposite absolute stereochemistry.

From the "ate"-complex **116**, the nucleophile approaches from the least hindered path, as shown by **115** and **116**. Essentially, the nitrogen end of the imine is blocked by the large ytterbium complex, and the *p*-methoxyphenyl group (which of course can rotate about the C-N axis. Note: it is drawn flat for visualisation purposes). The logical approach is from the side of the imine hydrogen (see **115**), to accommodate a Bürgi-Dunitz approach trajectory, since the opposite side is blocked by the freely rotating ethyl ester.

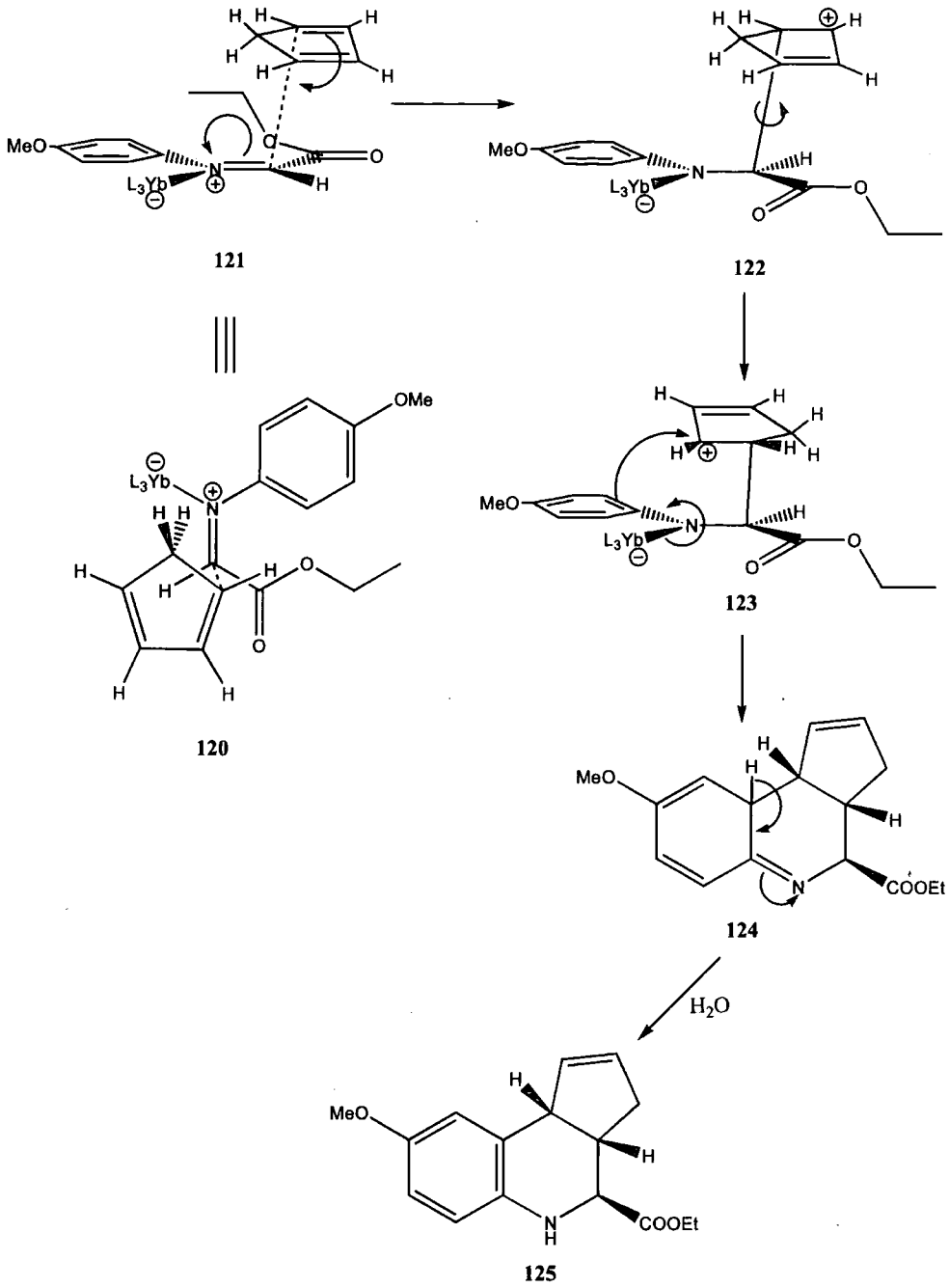
Scheme 9



The nucleophile then attacks the imine to form the intermediate complex **117**. Rotation about the newly formed C-C bond (to give **118**) exposes the allylic cation to the aromatic ring, where cyclisation occurs. Re-aromatisation and aqueous work-up subsequently give the cycloadduct **64** with the correct relative configuration.

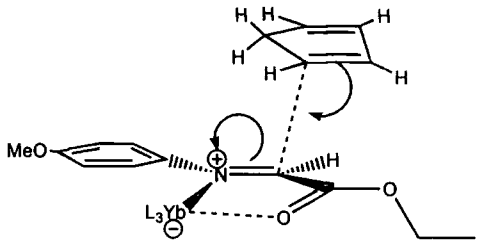
Of course this model relies on the fact that the imine **53** has the *E*-stereochemistry. Were the imine to react in a *cis*-conformation, the stereochemistry of the product would be incorrect compared to that observed (Scheme 10).

Scheme 10

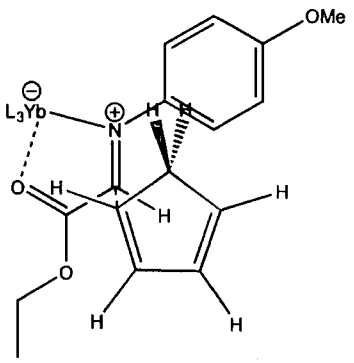


In that case, it may be more likely to consider bidentate chelation to ytterbium through the imine nitrogen and the ester carbonyl (see **126** and **127**, Figure 18). This would essentially lock the imine in the *trans*-configuration.

Figure 18



127

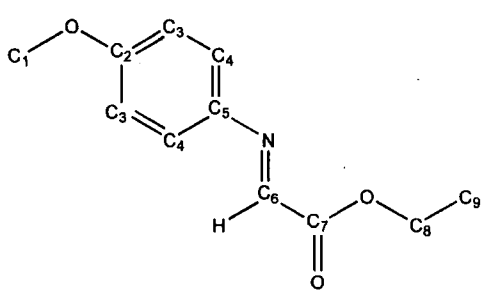


126

It was felt that binding experiments should be undertaken to attempt to understand how binding of the imine **53** to ytterbium(III) might be occurring. To achieve this; ^{13}C NMR experiments were performed with varying catalyst loadings with respect to the imine **53**. It was envisaged that by increasing the catalyst loading, the ^{13}C NMR signals would perhaps shift differentially indicating sites of binding to ytterbium(III).

Firstly, a ^{13}C NMR of imine **53** was run on its own in d_3-MeCN. Next, samples with 1, 5, 10, 20, 40, 60, and 100 mol % of $Yb(OTf)_3$, were run under identical conditions. The chemical shifts in relation to the corresponding carbon atoms of the uncomplexed imine are outlined in Table 13, as depicted by the numbering system in Figure 19.

Figure 19



53

Table 13. Table showing the ^{13}C NMR chemical shift values of the carbon atoms of imine **53** at various loadings of $Yb(OTf)_3$ in a d_3-acetonitrile solvent.

	Chemical Shift (δ)								
Catalyst Loading (mol %)	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9
0	54.9	160.1	114.2	123.2	141.0	148.2	163.1	61.0	13.2
1	54.9	160.1	114.2	123.2	141.0	148.3	163.1	61.0	13.2
5	54.9	160.1	114.2	123.3	141.0	148.2	163.2	61.0	13.1
10	54.9	160.1	114.3	123.4	*[a]	148.1	163.2	61.1	13.1
20	54.9	160.0	114.3	123.5	*	148.1	163.2	61.1	13.1
40	54.9	159.9	114.4	123.9	*	*	*	61.3	13.0
60	54.9	159.7	114.5	124.0	*	*	*	*	13.0
100	54.7	159.5	114.4	124.0	*	*	*	*	*

[a] * = Peak disappeared

At 1 mol %, some observations were noted. Firstly, none of the chemical shifts had moved (except the imine carbon, C_6, which had moved 0.1 ppm to δ 148.3). However, the relative intensities had all diminished somewhat, and as the amount of Yb(III) was increased the most noticeable effect was that observed for the imine carbon C_6. The diminution of the signal intensities continued through 5 and 10 mol % ytterbium(III). At 10 mol %, the aromatic C-H's *ortho* to nitrogen (C_4) showed an appreciable loss in intensity relative to the C_3, signals when compared to lower catalyst loadings. The C_5 peak had completely disappeared from the spectrum at this point.

At 20 mol %, most of the peaks had virtually disappeared from the ^{13}C spectrum; in fact, the most interesting data was now extracted from the DEPT spectrum. The ester CH_2 (C_8) and aromatic CH (C_4) had diminished considerably, and the ester CH_3 (C_9) was beginning to lower in intensity relative to methoxy carbon C_1 and aromatic carbons C_3.

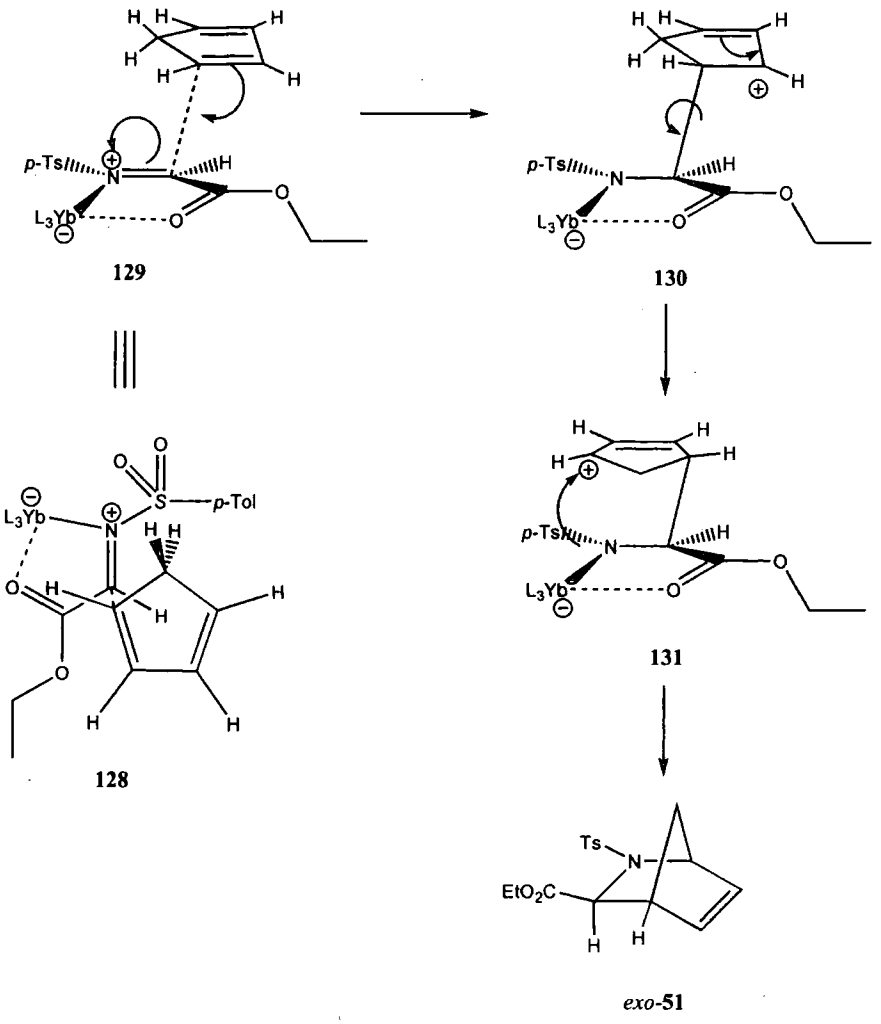
By 60 mol%, all peaks had disappeared except C_1, C_2, C_3, C_4 and C_9. C_2 and C_9 were barely visible by this point. C_4 had moved to δ 124.0, C_2 had moved to δ 159.7, and C_9 had moved to δ 13.0.

This evidence suggests primarily, that the strongest binding interaction exists between ytterbium(III) and the imine nitrogen atom. However, the fact that the ester carbonyl and ethyl units disappear at higher catalyst loadings suggests that binding at the ester carbonyl is also occurring, adding strength to the model proposed by structure **127** (Figure 17) (*vida supra*).

This seems a plausible argument, and certainly explains the outcome of the various experiments carried out. Moreover, it explains the observed preference for *exo*-products in other imino-Diels-Alder reactions with cyclopentadiene. Taking for example the reaction performed by Jørgensen, from Section 1.5 (Equation 19),[18] it can be seen that by using a bidentate (metal-substrate) complex (where the metal is bound to the ester carbonyl and the imine nitrogen), the formation of the major *exo*-products can be explained, by a process similar to that outlined in Scheme 9 (see Scheme 11).

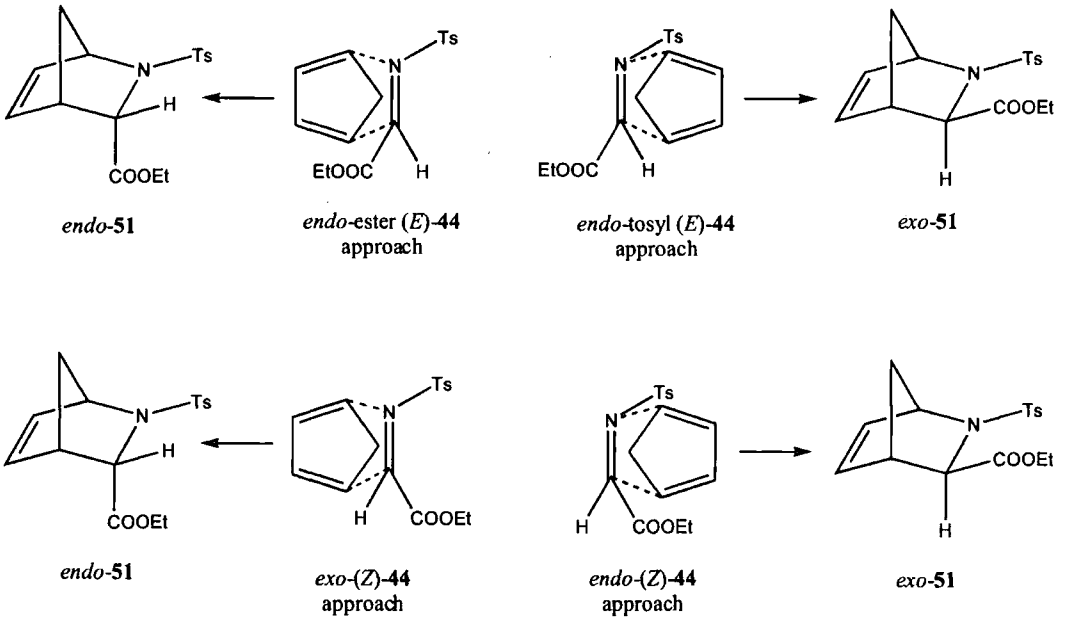
Thus, the first step is the same as that in Scheme 9, although in this case, the nucleophilic addition is followed by a rearrangement of the allylic cation, and rotation about the newly formed C-C bond **130** to give **131**. Cyclisation then occurs at nitrogen (as there is no carbon atom available to cyclise as is the case with the *p*-anisidine derived imine **53**) to give the product **51**. In fact, the cyclisation step could occur by nucleophilic attack of the nitrogen atom to the double bond, which would then quench the charge on the cation. The outcome would be the same in either case. Since there is no chiral ligand present, a racemate would be produced.

Scheme 11



Jørgensen presented a different view, based upon the possible concerted Diels-Alder *endo-* / *exo*-transition pathways that could operate (Scheme 12). These essentially would give the same predictions as the model in Scheme 10, but in the context of a concerted reaction mechanism. He stated that the major *exo*-products could be due to: 1) the reaction of the *E*-imine and the diene approaching *endo-* relative to the tosyl group; or 2) that *endo*-**51** is in equilibrium with *exo*-**51** *via* a retro-Diels-Alder reaction, favouring the thermodynamically more stable *exo*-product. However, on testing the latter hypothesis by exposing the *endo*-adduct to the reaction conditions, under which *exo*-**51** is formed, no trace of *exo*-**51** was found and *endo*-**51** was recovered, indicating that no retro-Diels-Alder reaction occurred. He concluded that the former hypothesis was therefore in operation.

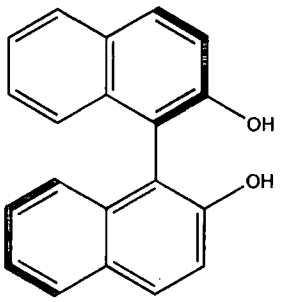
Scheme 12



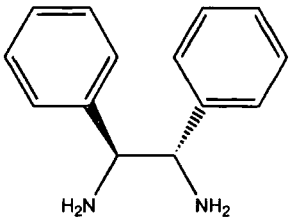
2.5 Asymmetric Screening I

Having characterised the products produced in the initial screening experiments involving imine **53**, the process of performing asymmetric screens began. In order to carry out these screens, a method of assaying the success of individual reactions was required. Chiral HPLC was chosen to do this, as it is a relatively simple method, and can be automated with ease. It was decided to first pursue asymmetric induction in the cyclopentadiene reaction with imine **53** (Table 12, Entry a). A clean sample of cycloadduct **61** was placed in a HPLC vial, diluted with HPLC grade ethyl acetate, and the sample was passed through a Chiralpak AD and a Chiralcel OD column, using 5 %, 10 %, and 20 % IPA in hexane each at 1 ml per minute. The best resolution was found on the AD column with 10 % IPA as eluent. The retention time of the two enantiomers was found to be 11.07 and 14.20 minutes. A reaction screen was then carried out involving two, twenty reaction arrays. The Lewis acids chosen were copper(II), ytterbium(III) and scandium(III) triflates, iron(III) chloride and magnesium(II) iodide. The chiral ligands used are shown in Figure 20. All reactions (see Table 14) were performed in acetonitrile or toluene.

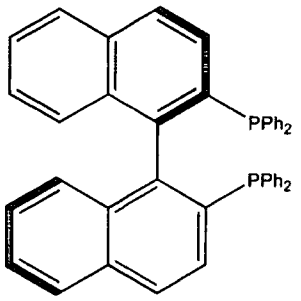
Figure 20



42



43



48a

Table 14. Table showing the combinations of Lewis acid and chiral ligand in the first asymmetric screen of the reaction between cyclopentadiene **16** and imine **53** (Equation 33).

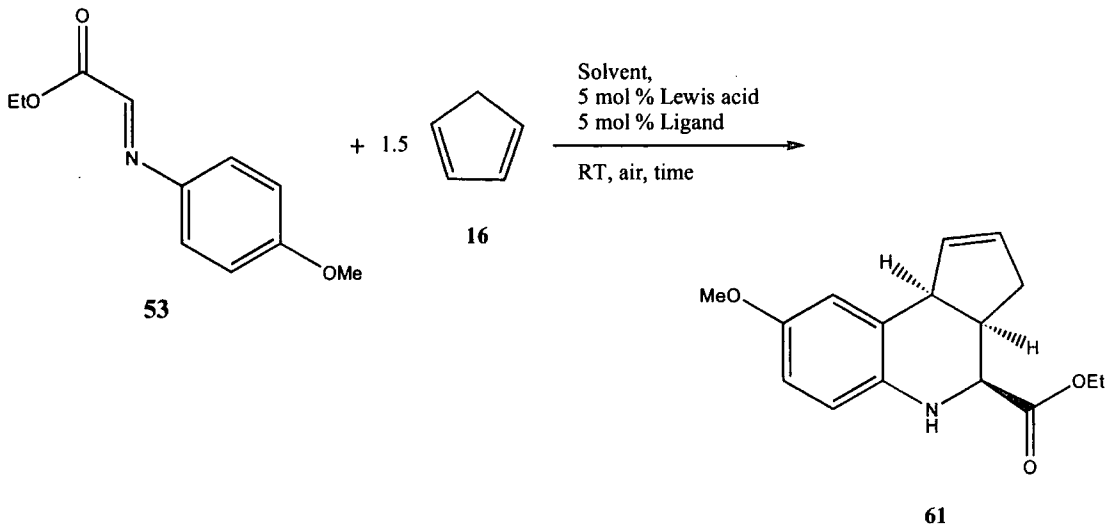
		Lewis acid				
Solvent	**Ligand**	$Cu(OTf)_2$	$Yb(OTf)_3$	$Sc(OTf)_3$	$FeCl_3$	MgI_2
MeCN	-[a]	1[b]	2	3	4	5
	42	6	7	8	9	10
	43	11	12	13	14	15
	48a	16	17	18	19	20
Tol	-	21	22	23	24	25
	42	26	27	28	29	30
	43	31	32	33	34	35
	48a	36	37	38	39	40

[a] No chiral ligand used

[b] Numbers used to itemise each reaction.

As with the initial screen, solutions of all the reagents were prepared and aliquots were placed in the corresponding reaction vessels. All reactions were carried out in air in small sample vials with screw caps. The reactions were carried out following the stoichiometries detailed in Equation 33, on a 20 mg imine scale.

Equation 33



Lewis acids and chiral ligands were added together and agitated periodically over 30 minutes (no stirrer beads small enough for the vessels were available). Next, imine **53** was added to each vessel, and again, agitated periodically over a 30 minute period. Finally, cyclopentadiene was added, the reactions shaken and allowed to stand for 1 hour, with periodic shaking. TLCs of the reactions were taken, and all [except for those where MgI_2 was the Lewis acid (Table 14, reactions 5, 10, 15, 20, 25, 30, 35 and 40)] showed consumption of the imine. It was noted that the TLC of the reactions in toluene were streakier than those conducted in acetonitrile (this mirrors the findings in the initial screen). The reactions were worked-up by adding 1 ml of saturated brine to each reaction and shaking. Next, EtOAc (1 ml) was added, and the biphasic mixture was shaken and allowed to separate. The organic layer was removed by glass pipette, passed through a short plug of silica gel (approximately 2 cm deep in a Pasteur pipette) and placed into HPLC vials. These were then diluted with HPLC grade EtOAc, the samples placed in the HPLC autosampler and passed down the chiral AD column.

Disappointingly, almost all the reactions gave a single, slightly broader peak. In a small number of reactions, this peak could be seen to overlap (about 50 % resolution) with the enantiomer at 11.07 minutes (see Appendix 4), making the integration (and hence the assessment of e.e.) impossible. Other experiments failed to show any of the peaks corresponding to the cycloadduct, only the single new peak was observed. The origin of this new peak is unknown, however, it is believed that due to the fact that the reactions were done in air, and the length of time the samples had to wait in order to be

examined by chiral HPLC, oxidation of the tetrahydroquinoline ring to the quinoline has probably occurred, removing the chiral centres and resulting in a single major peak. An example chromatogram can be seen in Appendix 4, where the overlap of the new peak impairs accurate integration of the faster moving enantiomer. The oxidation product was never intentionally made and isolated, hence a comparison of the chromatograms of the oxidation product and the cycloadduct **61** was never made.

It was therefore decided that the screening should be done on the acetamide derivative **77** instead, since this was considered to be more stable, and should survive standing whilst waiting for HPLC analysis. This would mean that, rather than using the brine work-up procedure adopted previously, the quench should be performed by adding pyridine and acetic anhydride. Although in principle this seemed like a prudent decision, in practice, it was considerably more frustrating.

A pure sample of **77** was passed down the chiral AD column and after testing several different methods, it was found that the best separation was achieved by using 5 % IPA in hexane at a flow rate of 0.5 ml per minute. Unfortunately, this did not give baseline resolution of the enantiomers, and the retention times of the two peaks were at 41.52 and 44.38 minutes. These are rather long retention times, especially considering that the HPLC method was chosen as a means of high throughput screening! However, until this situation was resolved, it was decided to utilise the time to perform the asymmetric reaction screens regardless. After all, the *N*-acetyl compounds were stable, so meaningful data could be obtained, despite waiting longer than desired for the results.

The same set of reagents was used as in the previous asymmetric screen, with the exception of MgI_2, which was replaced with CuBr. The reactions carried out are shown in Table 15 and relate to Equation 34.

The reactions were monitored by TLC for consumption of imine. Within 2 hours, all reactions, except those catalysed by CuBr, were complete (no imine remained). At this point, three equivalents of pyridine and acetic anhydride were added to the reaction mixtures, and these were left overnight.

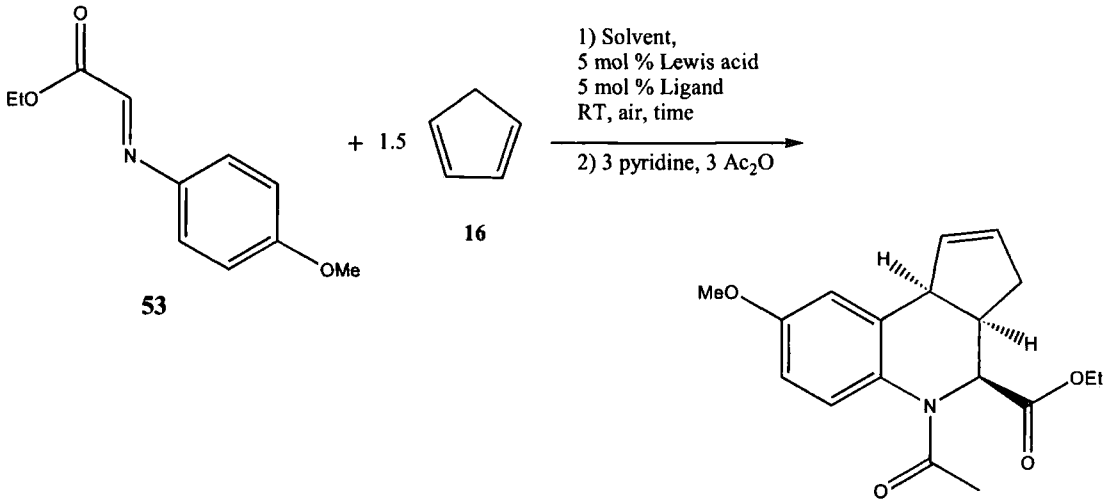
Table 15. Table showing the combinations of Lewis acid and chiral ligand used in an asymmetric screen according to Equation 34.

		Lewis acid				
Solvent	**Ligand**	$Cu(OTf)_2$	$Yb(OTf)_3$	$Sc(OTf)_3$	$FeCl_3$	CuBr
MeCN	-[a]	1[b]	2	3	4	5
	42	6	7	8	9	10
	43	11	12	13	14	15
	48a	16	17	18	19	20
Tol	-	21	22	23	24	25
	42	26	27	28	29	30
	43	31	32	33	34	35
	48a	36	37	38	39	40

[a] No chiral ligand used

[b] Numbers used to itemise each reaction.

Equation 34



Due to the presence of excess acetic acid and pyridine in the reaction mixtures, it was necessary to carry out a different work-up, since pyridine and acetic acid could be deleterious to the chiral column. This was achieved by using a three component pipette column as follows: after plugging with cotton wool, a layer of silica gel (approximately 1 cm deep) was added, then a layer of $CuSO_4$ (about 1 cm deep), to complex out the pyridine, and finally a layer of K_2CO_3 (about 1 cm deep), to neutralise the acetic acid was added to a pipette. A test reaction was used to assess the ability of this type of

column system to remove the excess reagents. After passing down the column, evaporation of the sample *in vacuo* and checking the NMR of the sample, it became clear that the acetylation was not working well. Only a small amount of acylated product could be detected by ^{1}H NMR.

A further three equivalents of pyridine and acetic anhydride were added to each of the reaction mixtures and left for another 24 hours. One of the remaining reactions was then exposed to the three component column, and ^{1}H NMR of the resulting sample still showed that there was much more un-acetylated product than acetylated. This therefore made the problems with the HPLC conditions irrelevant. Hence it was decided that further experiments needed to be performed in order to check the feasibility of a pyridine and acetic anhydride work-up. On preparative scale, the acetylations were carried out in solvent proportion, *i.e.* therefore, excess reagents. Small scale reactions (*i.e.* those that were being performed in the reaction screens), were used to test this new work-up procedure.

Acetyl chloride-triethylamine, and pyridine-acetic anhydride combinations were tested. It was found that acetyl chloride-triethylamine mixtures outperformed the acetic anhydride-pyridine combinations. A small screen was undertaken to check if 3, 6, or 10 equivalents of pyridine-Ac_2O, or Et_3N-AcCl was preferred for effecting this transformation. The screen showed that 3 and 6 equivalents were ineffective in all cases, an it was deemed that this would make the screen impossible on a large number of targets (removal of the excess reagents would be near impossible without an aqueous work-up). These procedures certainly did not lend themselves to high-throughput screening, and therefore it was decided that this particular reaction was not suitable for the development of a general method for chiral Lewis acid catalyst discovery using parallel, combinatorial techniques.

2.6 *N*-Protecting Groups

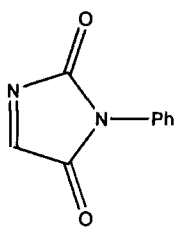
2.6.1 *N*-Acyl Groups

The frustrations encountered with the amines obtained in the initial screen, with reference to their ability to be used in a high throughput screen, rapidly began to manifest the idea that a change in *N*-protecting group strategy was required. It seemed

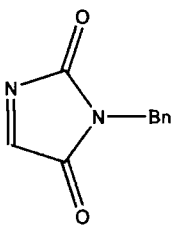
that all the instability problems lay with the presence of an anilinic nitrogen atom. This was halting the progress of the real aims of the project and so it was decided that a new imine should be sought. The criteria for selection were still very much the same, *i.e.* that it should be easy to construct the imine, it should be relatively cheap, should be able to be used in imino-dienophile aza-Diels-Alder reactions, and finally, that the *N*-protecting group should be relatively easy to cleave.

Originally, ideas for the kind of imine to be used were drafted, without consideration of the synthesis thereof. Some of the more relevant structures are shown in Figure 21. Of particular interest was the formyl group **135**, which had been shown to have interesting Lewis acid binding properties in enantioselective reactions of aldehydes[58] and there was further scope if cyclic imines were to be employed, such as **132** – **134**.

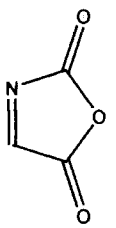
Figure 21



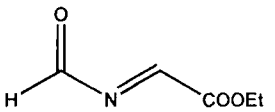
132



133



134

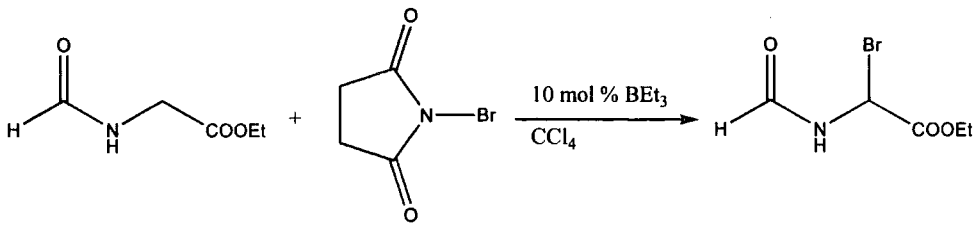


135

It was imagined that all of the above imines may be produced by bromination of the carbon alpha to nitrogen in a parent amide or hydantoin, generating the corresponding imine by elimination. The theory was tested with the attempted synthesis of the potentially glycine derived imine **135**.

Starting with commercially available *N*-formylglycine ethyl ester **136** (Equation 35), the first attempt to perform a radical bromination was carried out using triethylborane as radical initiator and NBS. This reaction however proved unsuccessful; only starting material was recovered from the reaction. Consequently, it was decided to initiate the same reaction photochemically.

Equation 35



136 **137** **138**

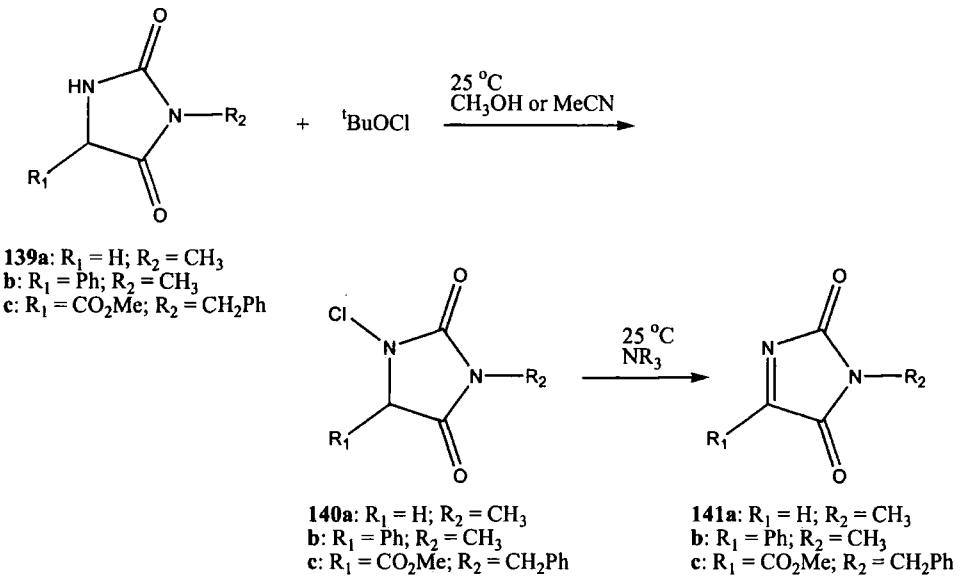
Using a 300 watt sunlamp, the amino-ester **136** and NBS **137** in CCl_4 were stirred at 70 °C under nitrogen for 3 hours, after which the irradiation was stopped and the reaction allowed to cool to room temperature. The resulting mixture was filtered, a small sample of the filtrate was evaporated, and the ^1H NMR spectrum was recorded. A rather complex mixture of products was observed, some of which may have been the brominated product **138**, and perhaps the desired imine **135** (signals in the 7 - 8 ppm range). However, it was apparent that the reaction was not suitable for the intended purpose. Primarily, it was considered that clean reactions were vital to the project, particularly with less stable imines. Any nitrogen (other than that of the imine) present in the asymmetric reactions had the potential to extinguish any asymmetric induction by binding to the Lewis acid in place of the chiral substrate, resulting in a competing, non-asymmetric reaction. The effects could even have been more far reaching, with the nitrogen source completely inhibiting the Lewis acid action. Therefore, if the imine was not stable enough to be produced and purified, it had to be constructed cleanly using alternative methods. Having checked the literature for examples of *N*-formyl imines, it became obvious that there would be problems. There are very few examples, whereas *N*-acetyl imines are much more commonplace. Clearly there are good reasons why *N*-formyl systems are largely absent, and construction and handling problems are probably amongst them.

Subsequently, efforts directed towards the construction of cyclic imines. Practically all of the early work reported on these types of systems has come from the laboratory of Ben-Ishai.[59-65] However, as this work was due to commence, a paper by Evnin *et al.* suggested that the compounds **132** and **133** would not be isolable.[66] Their approach to such systems was through the corresponding *N*-chloro derivatives **140** (Scheme 13).

This group found that, de-hydrohydantoins with R_1 = H were unstable and that they had to be produced *in situ*, which concurs with the work of Ben-Ishai. Evnin *et al.* stated

that the carbon substituent significantly influenced the stability of the imine. It was found that **141b** was isolable, thermally stable and still relatively reactive in cycloaddition reactions. However, **141c** and **141a** were progressively less stable. They concluded that both steric and electronic factors influence this reactivity and stability; with bulky substituents, or those capable of conjugation, de-activating the imine to nucleophilic attack.

Scheme 13



139a: $R_1 = H$; $R_2 = CH_3$
b: $R_1 = Ph$; $R_2 = CH_3$
c: $R_1 = CO_2Me$; $R_2 = CH_2Ph$

140a: $R_1 = H$; $R_2 = CH_3$
b: $R_1 = Ph$; $R_2 = CH_3$
c: $R_1 = CO_2Me$; $R_2 = CH_2Ph$

141a: $R_1 = H$; $R_2 = CH_3$
b: $R_1 = Ph$; $R_2 = CH_3$
c: $R_1 = CO_2Me$; $R_2 = CH_2Ph$

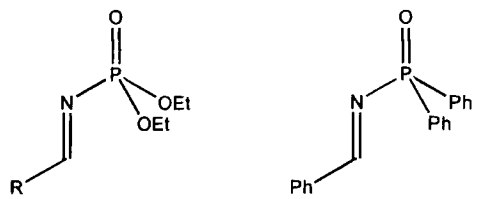
This meant that work on these systems was not really viable. It was important to have a hydrogen atom attached to the carbon terminal of the imine double bond in order to construct the 1-deoxynojirimycin-related analogues in the future.

2.6.2 Phosphorus Protecting Groups

Given that another avenue had been blocked by inherent stability problems of the above imines, thought was given to other types of protecting groups which might be used for imine *N*-protection and activation. A literature search suggested a type of imine which had not previously been considered. Although *N*-sulfonyl imines had been explored in aza-Diels-Alder chemistry, there were no examples of their *N*-phosphorus counterparts being used for identical reactions. Several examples of phosphorus protecting groups attached to imines were uncovered however, and it was the development of these imines that was pursued in the final section of this project.

Two likely types of *N*-phosphorus protecting group were identified (Figure 22): the phosphoramidate derived systems **142** and the phosphinate derived system **143**.

Figure 22



142a: R = Ph
b: R = 2-Fur
c: R = CO_2Et

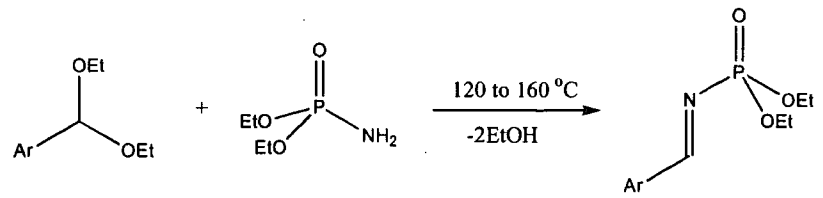
143

Compounds with the *N*-phosphinyl protecting group (of the type **143**) have been shown to undergo nucleophilic additions to the imine.[67] More recently, asymmetric diethylzinc additions to imines of this type have been reported,[68-70] as have catalytic asymmetric nitro-Mannich-type reactions.[71] Given the findings of the apparent stepwise nature of the imino-Diels-Alder reaction of *N*-aryl imines, and the similarity in electronic withdrawing nature compared to (for example) *N*-tosyl imines, it seemed reasonable that such *N*-phosphorus protected imines may undergo similar aza-Diels-Alder reactions.

Three imines were therefore made. These were **142a**, **142b** and **143**. The procedures adopted for the preparation of each may prove to be fairly general, meaning that different functional groups could be used at the carbon terminus of the imine in future.

Phosphoramidate derived imines **142a** and **142b** are simple to make; using the procedure of Zwierzak,[72,73] **142a** and **142b** were made in 71 and 83 % yield respectively (Equation 36). The diethyl acetals of the corresponding aromatic aldehydes were heated, neat, with diethyl phosphoramidate in a distillation apparatus, from 120 to 160 °C. Two equivalents of ethanol are distilled off and the resulting residue was purified by Kugelrohr distillation under high vacuum (*ca.* 45 mmHg). The highest boiling fractions were the analytically pure imine in each case, whose data agreed with the literature.[73]

Equation 36



144a: Ar = Ph
b: Ar = 2-Fur

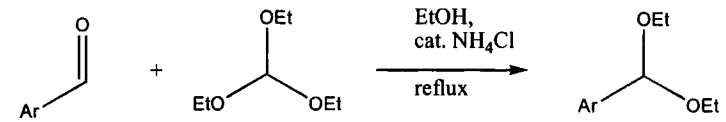
145

142a: Ar = Ph
b: Ar = 2-Fur

The importance of maintaining constant high vacuum for the purification of imines **142a** and **142b**, was illustrated when insufficient vacuum grease was applied to the joints during one particular distillation. The imine rapidly decomposed to unknown products, resulting in impure imine and in much lower yield.

The corresponding diethyl acetals **144** were prepared (Equation 37) according to the procedure of Zwierzak,[73] and both **144a** and **144b** were obtained in high yield (89 and 86 % respectively).

Equation 37



98: Ar = Ph
146: Ar = 2-Fur

147

144a: Ar = Ph
b: Ar = 2-Fur

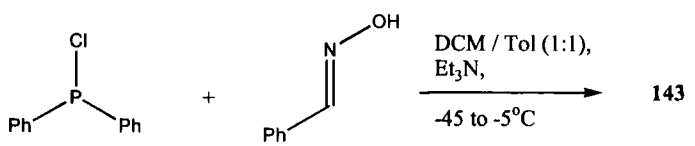
One diagnostic piece of evidence for the production of these imines is the large, 32 Hz, coupling constant of the imine hydrogen to ^{31}P, observed in the ^{1}H NMR. The spectroscopic data of the diethyl acetals also agreed with those in the literature.[74,75]

It was hoped that the corresponding glyoxylate derived imine **142c** could be made in an analogous manner, however, heating the commercially available diethoxyethyl acetate **57** to 180 °C with diethylphosphoramidate **145** only resulted in charring of the reaction mixture, and the observation of starting materials in the ^{1}H NMR spectrum. A further experiment was carried out; using the freshly prepared glyoxylate **55** and heating with the phosphoramidate **145** to 130 °C, in the presence of a heaped spatula of $MgSO_4$, a colour change was observed. After cooling of the reaction mixture, analysis of the ^{1}H NMR spectrum showed that the starting materials were no longer present, but what remained was never purified. A tiny peak appeared at around δ 8.00 in the ^{1}H NMR

spectrum, which may have been an imine hydrogen atom, but it is believed that only the first addition had occurred to produce the corresponding hemi-aminal, and the elimination reaction was much less facile. Since this was turning into a more taxing problem than expected, it was abandoned in order to continue with those experiments that did work.

The phosphinyl imine **143** was produced according to the procedure of Stec[67] (Equation 38).

Equation 38



148 **149**

The mechanism of the reaction shown in Equation 38 is thought to proceed through an initial addition step, which is followed by a radical rearrangement from a P(III) to a P(V), species to give the desired imine.[76] After recrystallisation, the imine **143** was obtained as a white powder in 73 % yield. A similar 32 Hz coupling of the imine proton to ^{31}P was observed in the ^{1}H NMR as with imines **144**.

It was found that the recrystallisation of **143** was difficult on occasion. The imine can hydrolyse to give benzaldehyde and (presumably) the corresponding phoshinic amide, leaving an impure imine. As discussed previously, the availability of other, achiral ligands in the reaction mixture is wholly undesirable. For this reason, efforts were concentrated on the phosphoramidate derived imines **142**, since they were easier to handle, *i.e.* they dissolved in a greater number of solvents and were easier to re-purify if the situation arose.

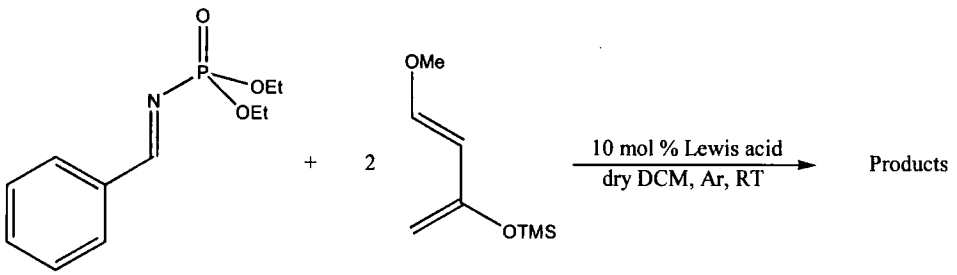
2.7 Testing the Reactivity of Imines 142a and 142b

It was unknown at this point, exactly what kind of Lewis acid would facilitate the cycloaddition of dienes with imines **142**. The rate of reaction with different dienes in the absence of a catalyst was also unknown. A small screen was performed to find out

if in fact these imines were viable candidates for use in Diels-Alder reactions where the aim was to develop catalytic asymmetric processes.

Danishefsky's diene **3** was the only diene used in this initial screen. The justification for this was that if this highly reactive diene did not react, then it was highly unlikely that any other would. The *C*-phenyl imine **142a** was used in this preliminary screen, and three Lewis acids were chosen to catalyse the reaction. These were, $TiCl_4$ (a hard Lewis acid), $ZnCl_2$ (slightly softer; this was chosen as it was used to catalyse the diethyl zinc additions, and therefore it seemed reasonable that there would be some success with this particular Lewis acid), and $CuOTf.C_6H_6$ (a soft Lewis acid). The reactions were carried out as shown in Equation 39 and the results are tabulated in Table 16.

Equation 39



142a **3**

Table 16. Table showing if imine **142b** had been consumed within 24 hours according to the reaction in Equation 39.

Lewis acid	Imine consumed?
None	no
$TiCl_4$	no
$ZnCl_2$	no[a]
$CuOTf.C_6H_6$	yes

[a] TLC indicated product formation, but incomplete consumption of imine.

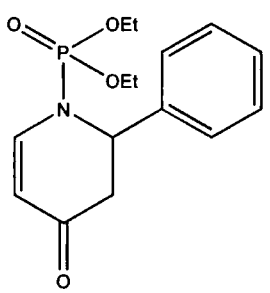
It was hoped that any products derived from these reactions would be isolated immediately and hence, they were performed on a 200 mg of imine scale. Two equivalents of diene were used to ensure no imine remained, and reactions were monitored by TLC for consumption of imine. Within 15 minutes, the imine **142a** had been consumed in the reaction with Cu(I). This was not known at the time however, as

an unidentified product which co-eluted with the imine was produced in the reaction, and only after later experimentation was it revealed that the use of a vanillin stain could allow the two components to be distinguished (the impurity stains yellow, the imine does not stain). $ZnCl_2$ also facilitated the reaction, but the reaction was slower, which may be due to some product inhibition of the catalyst. After 24 hours, imine was still present.

It appeared that $TiCl_4$ did not induce the reaction at all. Although after 15 minutes, it looked as though some product had formed (by TLC), at 17 hours there was no product, yet no imine left. It seemed that the Lewis acid was causing decomposition of the product, and possibly of the imine. Overall, these results indicated that softer Lewis acids would be more suitable for these types of reaction.

The Cu(I) catalysed reaction was worked up by adding 5 % HCl to quench, and purification by silica gel chromatography. In the first attempt at this reaction, it is suspected that most of the product was lost, due to a high affinity with the silica gel and neat EtOAc was required to elute any product. However, the product **150** (Figure 23) was isolated in 16 % yield as a pale orange oil. This was later improved to 54 %, although it is suspected that some material was still left on the column since no other products could be observed by crude NMR, and mass recoveries for the reaction were high .

Figure 23



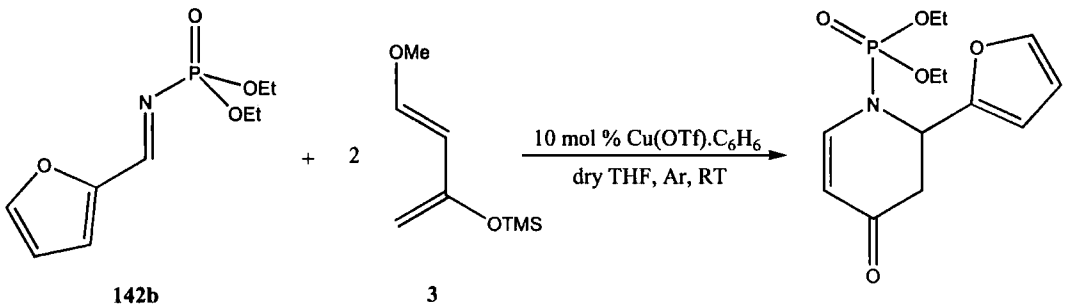
150

The isolation of adduct **150** was an exciting result, since to the best of our knowledge, this is the first example of an imino-Diels-Alder reaction using a phosphorus protected imine.

The IR spectrum of **150** showed the presence of the unsaturated ketone carbonyl as a stretch at 1666 cm^{-1}. The P=O could be also be identified as two peaks at 1291 and 1271 cm^{-1}, with the corresponding P-OEt at 1091 and 1019 cm^{-1}. ^{1}H and ^{13}C NMR data clarified the structure. Most notably, in the ^{1}H NMR, the imine CH signal at δ 9.10 had disappeared. The ethyl ester CH_3 at δ 1.37 in the starting material had become two signals in the product (diastereotopic) at δ 1.00 and δ 1.26. The proton attached to the chiral carbon centre was seen as a triplet at δ 5.14. The two olefinic protons were found at δ 5.33 and δ 7.54 and coupled at 8.0 Hz indicating a *cis*-double bond. ^{13}C NMR indicated the carbonyl carbon at δ 191.0 and DEPT indicated a CH_2 at δ 42.4 in addition to the phosphoramidate CH_2 carbons at δ 63.9. ^{31}P NMR showed a signal at δ 2.96 which is a significant deviation from the δ 8.30 observed in the starting imine.

With the evidence that CuOTf.C_6H_6 was activating the imine **142a** suitably to undergo Diels-Alder reaction with diene **3**, it was believed that its analogue **142b** would be activated in a similar manner towards Danishefsky's diene **3**. The reaction was performed in dry THF on this occasion, because there were problems at the time with the DCM still usually employed (Equation 40). Once again, a parallel reaction was carried out with no Lewis acid as a control experiment, to ascertain that reaction did not occur at room temperature in the absence of a Lewis acid. Indeed, that was found to be the case.

Equation 40



142b **3** **151**

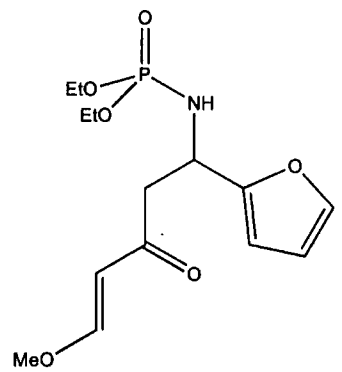
The reaction shown in Equation 40 was quenched using 5 % HCl and after work-up the crude product was purified by silica gel chromatography. The desired cycloadduct **151** was obtained in 38 % yield as a pale yellow oil.

IR spectroscopy showed that **151** had a carbonyl stretch at 1665 cm^{-1}, indicating the unsaturated ketone. The phosphorus protecting group was detected by absorbances at

1289 and 1274 cm^{-1} (P=O), and 1048 and 1019 cm^{-1} (P-OEt). The absence of the imine CH at δ 8.81 in the ^{1}H NMR indicated that the imine was no longer present. The phosphoramidate CH_3 signals were at δ 1.24 and δ 1.27 (3H each). The proton attached to the chiral carbon centre was seen as a triplet at δ 5.24. Similar to cycloadduct **150**, two olefinic protons were detected at δ 5.30 and δ 7.24 and were found to have an 8.0 Hz *cis* coupling constant, whilst the three furan CHs could be found at δ 6.21, δ 6.23 and δ 7.27 (*o*-, *m*-, *p*- respectively), a change from δ 6.59, δ 7.20 and δ 7.68 in the parent compound. ^{13}C and DEPT data confirmed a quaternary carbon at δ 191.6 indicating the cyclic ketone. A methylene carbon was found at δ 39.9, and the phosphoramidate CH_2s appeared at δ 64.2. ^{31}P NMR showed a signal at δ 2.56 rather than the δ 8.79 observed in the starting imine. This is a similar value to that obtained in the phenyl imine cycloadduct **150**, indicating a similar chemical environment.

The problems of the low yield obtained of this compound prompted an investigation into different work-up procedures. Rather than using an aqueous work-up, it was hoped that the yield could be improved by adsorption of the crude reaction mixture straight onto silica gel and eluting without further manipulations. This theory was tested and the outcome was not as expected. Rather than obtaining the cycloadduct **151**, a new product was isolated in 82 % yield. Although not characterised fully (no mass spectral data on a pure sample), it is believed that this new product was the nucleophilic addition product **152** (Figure 24).

Figure 24



152

It seemed that the work-up was important in dictating the structure of the product obtained and the yield. Therefore, switching to using 1 % TFA in DCM to quench the reaction, adsorbing straight onto silica gel and eluting, the cycloadduct **151** was

obtained as the sole product, with an increased yield of 50 %. However, it was later found that this quench was unreliable, and on occasion appeared to destroy the product (presumably by hydrolysis of the phosphoramidate and perhaps the furan). It is thought that the lower yield obtained when using an aqueous work-up is probably due to washing out of the intermediate **152** into the acidic aqueous layer.

Attempts to isolate the analogous acyclic intermediate **152** in the same reaction with the phenyl imine **142a** using a silica gel mediated work-up were unsuccessful.

Absorbances of 1246 and 1231 (P=O), and 1031 cm^{-1} (P-O) were observed in the IR spectrum of **152**, which showed the presence of the phosphoramidate group. A strong absorbance at 1620 cm^{-1} showed the presence of ketone carbonyl, probably hydrogen bonded to the N-H, whilst a peak at 3257 cm^{-1} indicated the N-H stretch. The proton NMR indicated the correct number and arrangement of protons for the given structure **152**. The methoxy singlet was plainly visible at δ 3.63 and a multiplet between δ 3.72 and 4.08 which integrated as 5H was assigned as the phosphoramidate CH_2s, and the NH. The chiral CH was found as a multiplet at δ 4.64 – 4.77 and the two olefinic hydrogen atoms appeared at δ 5.52 and δ 7.56 with a 12.8 Hz coupling constant. ^{13}C and DEPT spectra showed the requisite number of carbon atoms and the correct number of methylene carbons (found at δ 45.7, δ 62.4 and δ 62.5). The ketone carbon atom was situated at δ 196.6 and the methoxy carbon appeared at δ 57.6. ^{31}P NMR showed a signal at δ 8.12 indicating a new chemical environment for phosphorus. Mass spectral data of a pure sample was not obtained, however, evidence was found in an impure sample of cycloadduct **151**, where the molecular ion of **152** plus sodium was found *m/z* 354 using electrospray.

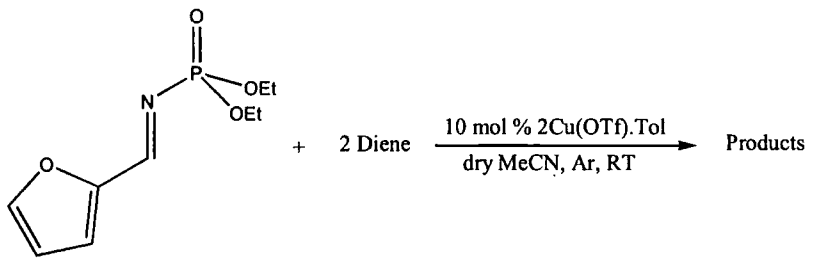
2.8 Reactivity with Other Dienes

In order to find out how many other dienes would react with the *N*-phosphonyl imines **142a** and **142b**. Several reactions were carried out on the furyl imine **142b** as an initial example substrate. This imine was concentrated on primarily because it was believed that intermediates with a *C*-furyl substituent would have greater scope for manipulations in future reactions. Also, it was rationalised that, assuming the products were either of the nucleophilic addition or cycloaddition type involving only the imine function and

the diene, the reactions would give analogous products when reacted with the *C*-phenyl imine **142a**.

The reactions were carried out on a 200 mg imine scale using copper(I) triflate as catalyst. The reactions were all performed in dry MeCN as outlined in Equation 41 and Table 17.

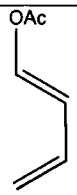
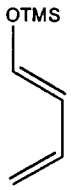
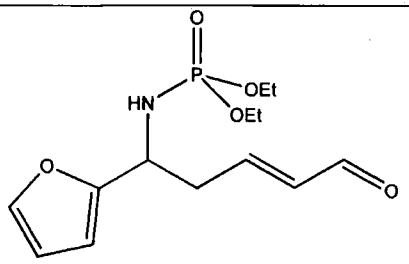
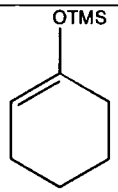
Equation 41



142b

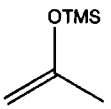
The results in Table 17, suggested that the imine was rather un-reactive towards less electron rich dienes, as only diene **61** showed any sign of reaction. Silyl enol ether **153** was initially included in the test reactions in an attempt to see if the straight forward nucleophilic addition compound could be obtained using this class of imine. With hindsight, perhaps it would have been instructive to have also included a silyl enol ether such as **155** (Figure 25), which might be expected to have similar reactivity to diene **61**. It was surprising that neither cyclopentadiene **16** nor acetoxybutadiene **60** reacted at all (no evidence for reaction occurred by TLC; the imine remained present and no new spots were detected).

Table 17. Table showing the products obtained in the reaction between imine **142b** and various electron rich species as detailed by Equation 41.

Entry	Diene	Product	Yield (%)
a	 **16**	—[a]	—
b	 **60**	—	—
c	 **61**	 **154**	33
d	 **153**	—	—

[a] No reaction occurred

Figure 25



155

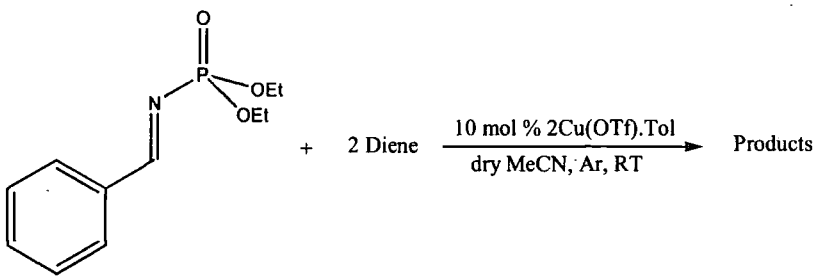
It was, however, interesting to note that the product derived from 1-trimethylsilyloxybutadiene, *i.e.* **154** was acyclic. The low yield of the product obtained seemed to be commonplace with this particular imine. It is not known at what stage the reaction yields diminished, *i.e.* in the reaction itself, during work-up, or on the column. However, the results of the furyl imine **142b** have proven consistently irreproducible when compared to the reactions of their sister compound **142a**. It is highly likely that the source of the problem lies in the chemical reactivity *versus* stability of the furyl

group, rather than any bearing that the furyl substituent might have on the electronic and steric properties of the imine.

In the IR spectrum of **154**, the α,β-unsaturated aldehyde was confirmed by absorbances at 1690 cm^{-1} (C=O) and 1639 cm^{-1} (C=C). Characteristic peaks were observed at 1235 cm^{-1} (P=O), 1057 cm^{-1} (P-OEt) and 1030 cm^{-1} (P-OEt) indicating that the phosphorus protecting group was intact. ^{1}H NMR showed the phosphoramidate CH_3 groups at δ 1.18 and δ 1.23. The NH was found as a broad triplet at δ 3.38 (exchanged with D_2O) and the aldehyde proton appeared as a double doublet at δ 9.40. The two alkene protons appeared at δ 6.08 and δ 6.71 with a 15.6 Hz typical *trans*- coupling constant. ^{13}C and DEPT NMR indicated methylene carbons at δ 38.1 ($NCH\underline{C}H_2$) and δ 61.5 and δ 61.6 (phosphoramidate) and the aldehyde was further confirmed by a resonance at δ 192.6 (CHO). ^{31}P NMR showed a signal at δ 7.86, which is a similar chemical shift to that in the proposed acyclic intermediate **152**.

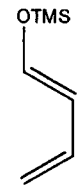
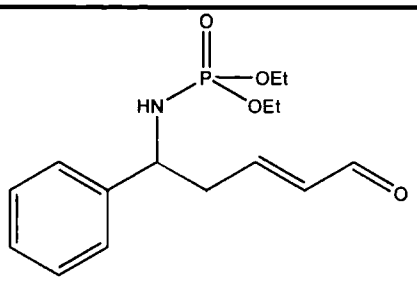
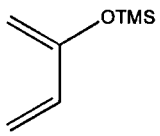
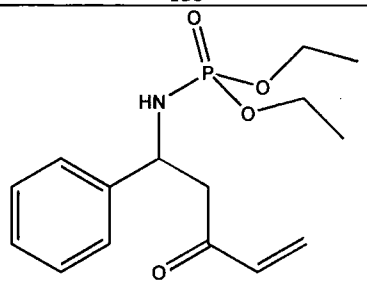
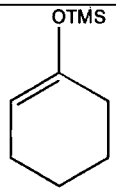
Considering the problematic nature of the products obtained from the furyl imine **142b** in terms of isolated yield, the decision was made to attempt further exploratory reactions using the phenyl imine **142a**, whose products had been produced in higher yield (albeit still moderate) and whose reactions were seemingly more predictable. The same silyl enol ether **153** was used, as were the silyl dienol ethers 1- and 2-trimethylsilyloxybutadiene (*i.e.* **61** and **94** respectively). The reactions are as detailed in Equation 42 and the results are shown in Table 18.

Equation 42



142a

Table 18. Table showing the outcome of reactions of imine **142a** with various dienes as depicted by Equation 42.

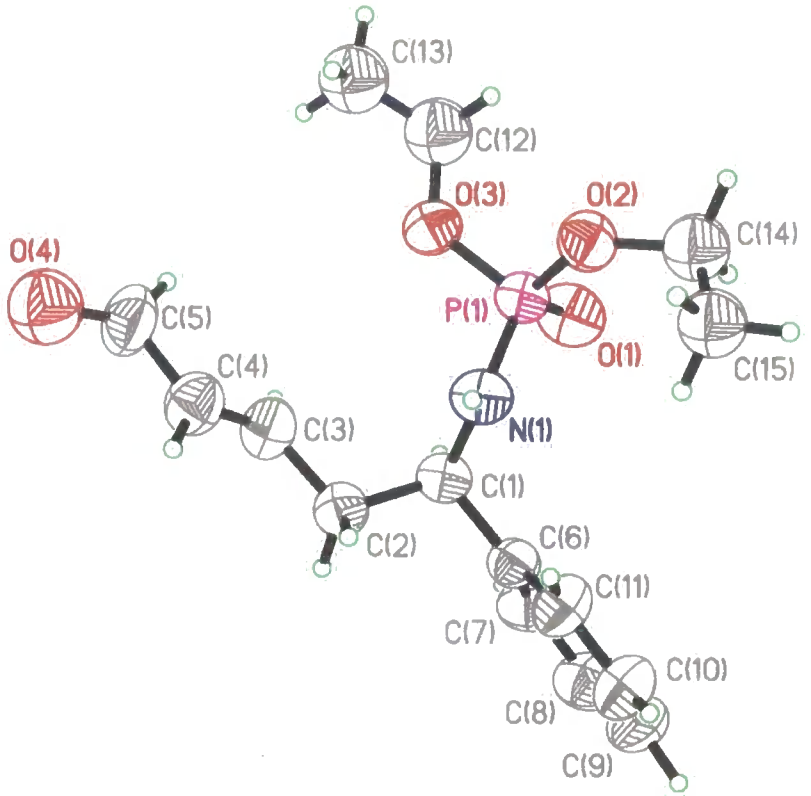
Entry	Diene	Product	Yield (%)
a	 **61**	 **156**	46
b[a]	 **94**	 **157**	61
c	 **153**	[b] —	—

[a] 100 mol % $BF_3.OEt_2$ used as catalyst

[b] No reaction

The silyl enol ether **153** did not react with imine **142a**, however, both dienol ethers **61** and **94** did react. The product **156** mirrored the reaction found with the furyl imine **142b**. The rather poor yield was in part due to the need for a recrystallisation of the columned crude material to afford completely pure, white crystalline **156**. The structure was confirmed by X-ray crystallography and is shown in Figure 26 (see also Appendix 5).

Figure 26



The spectroscopic data for **156** was comparable to that obtained for **154**. IR showed the α,β-unsaturated aldehyde as absorbances at 1684 cm^{-1} (C=O), and 1613 cm^{-1} (C=C). The P=O was situated at 1225 cm^{-1} and the P-OEt frequencies were observed at 1059 and 1030 cm^{-1}. Proton NMR data showed the labile NH as a broad triplet at δ 3.57 (exchanged with D_2O) and the aldehyde CHO proton at 9.44 as a double doublet. The phosphoramidate CH_3 groups were detected at δ 1.08 and δ 1.28 and the *trans*-alkene protons were located at δ 6.12 and δ 6.74 with a 15.6 Hz coupling constant. ^{13}C and DEPT NMR showed the presence of methylene carbons at δ 42.1 ($NCH\underline{C}H_2$) and δ 62.6 and δ 62.7 (phosphoramidate). The aldehyde was further confirmed by the resonance at δ 193.9 (CHO). ^{31}P NMR showed a signal at δ 8.07, which is a similar chemical shift observed in the furyl analogue **154**.

In the reaction leading to **157**, $BF_3.OEt_2$ (100 mol%) was used as catalyst. This arose due to a desire to test the previous findings with $TiCl_4$. It was presumed up to this point that hard Lewis acids would not catalyse these types of reactions using this class of imine, because the mode of complexation may not actually activate the C=N bond (it might be expected that the harder Lewis acids would bind solely to the P=O oxygen, which is a harder Lewis base than nitrogen, and this would not cause sufficient

activation). This was based on the findings of the earlier screen with $TiCl_4$, where it was believed that the imine was not being consumed *vide supra*. BF_3 was used in the experiment to check this theory. The reaction was that detailed in Table 18 (Entry b), and with a 20 mol % catalyst loading, it was imagined that perhaps a stoichiometric reaction would occur, but no catalysis would take place. TLC of the reaction mixture after 24 hours indicated product formation, but still the presence of imine. The reaction was allowed to stir for a further 24 hours, but still imine was observed by TLC. After a further 48 hours, the TLC still showed imine was present. When the catalyst loading was increased to 100 mol %, and the reaction stirred overnight, the following day, TLC indicated the complete consumption of imine. This suggests that the product does inhibit the catalytic cycle as expected.

It is noteworthy that in the analogous reaction with the PMP-protected imine **53** and diene **94**, cyclic products was formed. The acyclic adduct **157** may not cyclise as the phosphoramidate nitrogen is much less nucleophilic than the anilinic nitrogen atom in **95**.

IR spectroscopy of product **157** showed the ketone carbonyl stretch at 1679 cm^{-1}, and the C=C at 1639 cm^{-1}. The phosphoramidate was detected by absorbances at 1247 cm^{-1} (P=O), 1224 cm^{-1} (P=O), 1059 cm^{-1} (P-OEt) and 1030 cm^{-1} (P-OEt). ^1H NMR showed the phosphoramidate CH_3 at δ 1.02 and 1.22. The NH was observed as an exchangeable proton at δ 3.77, and the three olefinic protons could be found at δ 5.75, δ 6.10 and δ 6.21. The vinyl group could be ascertained by a geminal coupling of 18.0 Hz, and a 10.5 Hz *cis*-coupling. The aromatic hydrogen atoms appeared as a 5H multiplet at δ 7.14 – 7.29. The ketone carbon atom appeared at δ 197.4 in the ^{13}C NMR and the DEPT spectrum showed the methylene ($NHCH_2$) at δ 46.1. The chiral carbon centre appeared at δ 51.3, and ^{31}P NMR showed a peak at δ 8.18.

2.9 Asymmetric Screening II

At the same time that the above work was being undertaken, catalytic screening was also being investigated in the reaction between furyl imine **142b** and Danishefsky's diene **3** (Equation 40). Reactions were being performed in arrays of 24. All were carried out under argon, using dry solvents, and the format followed was as described before. Stock solutions of all the materials used were prepared, and aliquots were

placed into the corresponding reaction vessels. Reactions were carried on a 20 mg imine scale, with 2 equivalents of diene, 10 mol % Lewis acid and 11 mol % chiral ligand (Equation 43). The chiral ligands used can be seen in Figure 27.

Equation 43

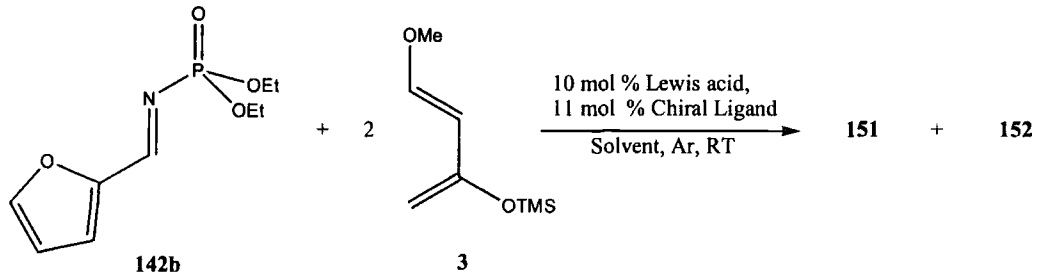
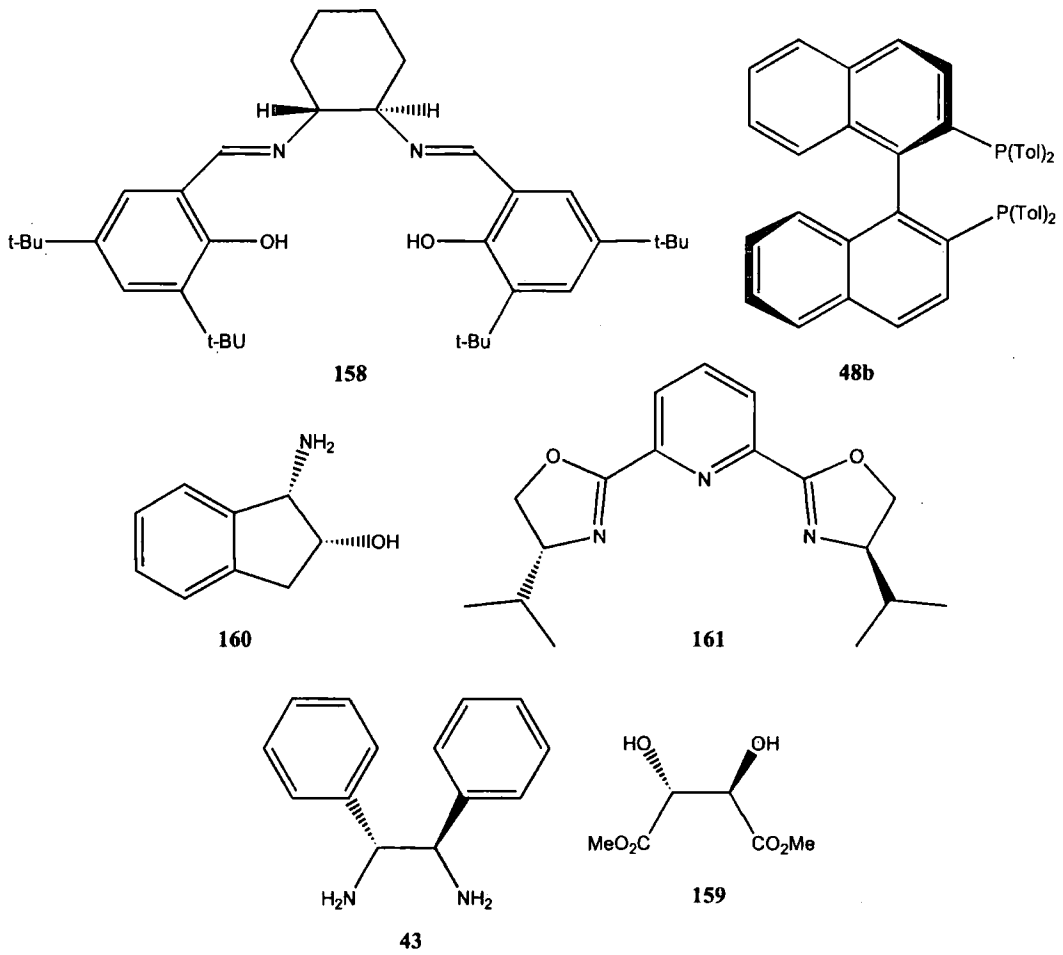


Figure 27



HPLC conditions were developed on the pure cycloadduct **151**, and it was found that the AD column with 10 % EtOH in hexane running at 1 ml per minute gave suitable enantiomer separation. The results of these screening experiments are shown in Table 19.

There were a multitude of problems in the screening of these reactions. In the final analysis, it was due to the problems associated with the furyl imine **142b** and particularly in the reaction with Danishefsky's diene **3**. The first reaction screen (Table 19, Reaction Screen 1) was performed with molecular sieves in the reaction vessels to ensure the reactions were free from water. This proved to be problematic for a number of reasons; the first was that it was impossible to take the TLCs of the reactions, since the molecular sieves clogged the capillary tubes, which meant that either the reactions were exposed to air to accommodate thicker capillaries, or they had to be left sealed and the TLC could not be taken. Consequently, all the reactions where sieves were present were arbitrarily left for 48 hours. The second problem was that the processing of the reactions was made more difficult by the presence of sieves. Water could not be used to quench the reactions. It was hoped that by performing an aqueous work-up, the problem of both acyclic **152** and cyclic products **151** being produced would be overcome (no acyclic material was isolated previously when an aqueous work-up was employed and the crude product was much cleaner). In the end, the reaction mixtures were filtered through a short plug of silica gel directly into HPLC vials and diluted ready for analysis.

Finally, the HPLC chromatograms of these reactions were of generally poor quality. There was a complex mixture of compounds in many of the chromatograms, which unfortunately meant the data was not particularly reliable. A typical chromatogram can be seen in Appendix 6. Perhaps the most important conclusion from this preliminary screen was not to employ molecular sieves if at all possible. This lesson was taken onboard in subsequent screening experiments.

Table 19. Table showing the reaction conditions and calculated e.e. for the screening experiments detailed in Equation 43.

Reaction Screen	Reaction #	Imine	Diene	Lewis acid	Ligand	Solvent	Sieves[a]	Reaction Quality[b]	$\sum^{c}$	B. C.[d]	Problem?[e]
1	1	**142b**	**3**	None	None	DCM	Y	P	-85.65	N	Y1
1	2	**142b**	**3**	None	**41**	DCM	Y	P	9.93	N	Y1
1	3	**142b**	**3**	None	**48b**	DCM	Y	P	-50.15	Y	Y2
1	4	**142b**	**3**	None	**43**	DCM	Y	P	5.88	N	Y3
1	5	**142b**	**3**	Cu(OTf).Tol	None	DCM	Y	P	-9.35	Y	Y3
1	6	**142b**	**3**	Cu(OTf).Tol	**41**	DCM	Y	P	-7.29	N	Y2&Y3
1	7	**142b**	**3**	Cu(OTf).Tol	**48b**	DCM	Y	P	-3.36	N	Y2&Y3
1	8	**142b**	**3**	Cu(OTf).Tol	**43**	DCM	Y	P	-82.74	Y	Y3
1	9	**142b**	**3**	$Cu(OTf)_2$	None	DCM	Y	P	-[f]	-	Y4
1	10	**142b**	**3**	$Cu(OTf)_2$	**41**	DCM	Y	P	-	-	Y4
1	11	**142b**	**3**	$Cu(OTf)_2$	**48b**	DCM	Y	P	-60.04	N	Y3
1	12	**142b**	**3**	$Cu(OTf)_2$	**43**	DCM	Y	P	100.00	N	Y3
1	13	**142b**	**3**	$Yb(OTf)_3$	None	DCM	Y	P	-	-	N
1	14	**142b**	**3**	$Yb(OTf)_3$	**41**	DCM	Y	P	32.40	N	Y3
1	15	**142b**	**3**	$Yb(OTf)_3$	**48b**	DCM	Y	P	19.31	N	Y3
1	16	**142b**	**3**	$Yb(OTf)_3$	**43**	DCM	Y	P	24.36	Y	Y3
1	17	**142b**	**3**	$Sn(OTf)_2$	None	DCM	Y	P	3.54	N	Y3

Reaction Screen	Reaction #	Imine	Diene	Lewis acid	Ligand	Solvent	Sieves[a]	Reaction Quality[b]	$\sum^{c}$	B. C.[d]	Problem?[e]
1	18	**142b**	**3**	$Sn(OTf)_2$	**41**	DCM	Y	P	-87.88	Y	Y2&Y3
1	19	**142b**	**3**	$Sn(OTf)_2$	**48b**	DCM	Y	P	0.90	N	Y2&Y3
1	20	**142b**	**3**	$Sn(OTf)_2$	**43**	DCM	Y	P	-17.05	N	Y3
1	21	**142b**	**3**	$Zn(OTf)_2$	None	DCM	Y	P	2.92	Y	Y3
1	22	**142b**	**3**	$Zn(OTf)_2$	**41**	DCM	Y	P	-8.78	N	Y3
1	23	**142b**	**3**	$Zn(OTf)_2$	**48b**	DCM	Y	P	-99.56	N	N
1	24	**142b**	**3**	$Zn(OTf)_2$	**43**	DCM	Y	P	-7.28	N	Y3
2	1	**142b**	**3**	$Mg(ClO_4)_2$	None	MeCN	N	G	-8.41	N	N
2	2	**142b**	**3**	$AgClO_4$	None	MeCN	N	G	-10.47	N	Y1
2	3	**142b**	**3**	$AgBF_4$	None	MeCN	N	P	-19.67	N	N
2	4	**142b**	**3**	$CuClO_4.4MeCN$[g]	None	MeCN	N	P	-50.89	N	N
2	5	**142b**	**3**	$Mg(ClO_4)_2$	**161**	MeCN	N	P	-19.08	N	N
2	6	**142b**	**3**	$AgClO_4$	**161**	MeCN	N	P	-17.91	N	Y1
2	7	**142b**	**3**	$AgBF_4$	**161**	MeCN	N	M	-18.47	N	N
2	8	**142b**	**3**	$CuClO_4.4MeCN$	**161**	MeCN	N	P	-4.83	N	Y1
2	9	**142b**	**3**	$Mg(ClO_4)_2$	**48b**	MeCN	N	G	-11.26	N	N
2	10	**142b**	**3**	$AgClO_4$	**48b**	MeCN	N	G	-18.86	N	Y1
2	11	**142b**	**3**	$AgBF_4$	**48b**	MeCN	N	G	-24.15	N	N

Reaction Screen	Reaction #	Imine	Diene	Lewis acid	Ligand	Solvent	Sieves[a]	Reaction Quality[b]	$\sum^{c}$	B. C.[d]	Problem?[e]
2	12	**142b**	**3**	$CuClO_4.4MeCN$	**48b**	MeCN	N	M	-8.43	N	N
2	13	**142b**	**3**	$Mg(ClO_4)_2$	**160**	MeCN	N	G	3.88	N	N
2	14	**142b**	**3**	$AgClO_4$	**160**	MeCN	N	M	-15.74	N	Y1
2	15	**142b**	**3**	$AgBF_4$	**160**	MeCN	N	G	-13.78	N	N
2	16	**142b**	**3**	$CuClO_4.4MeCN$	**160**	MeCN	N	P	-6.22	N	Y1
2	17	**142b**	**3**	$Mg(ClO_4)_2$	**158**	MeCN	N	M	-13.22	N	N
2	18	**142b**	**3**	$AgClO_4$	**158**	MeCN	N	M	-15.96	N	N
2	19	**142b**	**3**	$AgBF_4$	**158**	MeCN	N	M	-15.29	N	N
2	20	**142b**	**3**	$CuClO_4.4MeCN$	**158**	MeCN	N	M	11.93	N	Y1
2	21	**142b**	**3**	$Mg(ClO_4)_2$	**43**	MeCN	N	M	-15.87	N	N
2	22	**142b**	**3**	$AgClO_4$	**43**	MeCN	N	G	-18.24	N	N
2	23	**142b**	**3**	$AgBF_4$	**43**	MeCN	N	G	-16.47	N	N
2	24	**142b**	**3**	$CuClO_4.4MeCN$	**43**	MeCN	N	G	-6.15	N	N
3	1	**142b**	**3**	Cu(OTf).Tol	None	DCM	N	P	-97.26	N	Y1
3	2	**142b**	**3**	Cu(OTf).Tol	**43**	DCM	N	P	-21.45	N	Y1
3	3	**142b**	**3**	Cu(OTf).Tol	**48b**	DCM	N	P	100.00	N	N
3	4	**142b**	**3**	Cu(OTf).Tol	**161**	DCM	N	P	-	-	N
3	5	**142b**	**3**	$Cu(OTf)_2$	None	DCM	N	M	-20.35	N	Y1

Reaction Screen	Reaction #	Imine	Diene	Lewis acid	Ligand	Solvent	Sieves[a]	Reaction Quality[b]	$\sum^{c}$	B. C.[d]	Problem?[e]
3	6	**142b**	**3**	$Cu(OTf)_2$	**43**	DCM	N	M	8.83	N	N
3	7	**142b**	**3**	$Cu(OTf)_2$	**48b**	DCM	N	M	-15.84	N	N
3	8	**142b**	**3**	$Cu(OTf)_2$	**161**	DCM	N	M	-8.13	Y	N
3	9	**142b**	**3**	$Yb(OTf)_3$	None	DCM	N	G	-17.04	N	Y1
3	10	**142b**	**3**	$Yb(OTf)_3$	**43**	DCM	N	M	-17.50	N	N
3	11	**142b**	**3**	$Yb(OTf)_3$	**48b**	DCM	N	M	-8.30	Y	N
3	12	**142b**	**3**	$Yb(OTf)_3$	**161**	DCM	N	P	-	-	N
3	13	**142b**	**3**	$Sn(OTf)_2$	None	DCM	N	M	-23.68	N	Y1
3	14	**142b**	**3**	$Sn(OTf)_2$	**43**	DCM	N	P	-	-	N
3	15	**142b**	**3**	$Sn(OTf)_2$	**48b**	DCM	N	P	-	-	N
3	16	**142b**	**3**	$Sn(OTf)_2$	**161**	DCM	N	P	-	-	N
3	17	**142b**	**3**	$Zn(OTf)_2$	None	DCM	N	M	-25.57	N	Y1
3	18	**142b**	**3**	$Zn(OTf)_2$	**43**	DCM	N	G	-20.34	N	N
3	19	**142b**	**3**	$Zn(OTf)_2$	**48b**	DCM	N	M	-6.13	Y	N
3	20	**142b**	**3**	$Zn(OTf)_2$	**161**	DCM	N	P	-	N	N
3	21	**142b**	**3**	None	None	DCM	N	P	-	-	N
3	22	**142b**	**3**	None	**43**	DCM	N	P	-	-	N
3	23	**142b**	**3**	None	**48b**	DCM	N	P	-	-	N

Reaction Screen	Reaction #	Imine	Diene	Lewis acid	Ligand	Solvent	Sieves[a]	Reaction Quality[b]	$\sum$[c]	B. C.[d]	Problem?[e]
3	24	**142b**	**3**	None	**161**	DCM	N	P	-	-	N
4	1	**142b**	**3**	Cu(OTf).Tol	**159**	MeCN	N	G	-17.75	N	Y1
4	2	**142b**	**3**	Cu(OTf).Tol	**160**	MeCN	N	G	-9.06	N	Y1
4	3	**142b**	**3**	Cu(OTf).Tol	**158**	MeCN	N	G	-19.49	N	Y1
4	4	**142b**	**3**	Cu(OTf).Tol	**43**	MeCN	N	P	-18.16	N	Y1
4	5	**142b**	**3**	$Cu(OTf)_2$	**159**	MeCN	N	M	-4.61	N	Y1
4	6	**142b**	**3**	$Cu(OTf)_2$	**160**	MeCN	N	G	-17.42	N	Y1
4	7	**142b**	**3**	$Cu(OTf)_2$	**158**	MeCN	N	M	-22.52	N	Y1
4	8	**142b**	**3**	$Cu(OTf)_2$	**43**	MeCN	N	G	-17.72	N	Y1
4	9	**142b**	**3**	$Yb(OTf)_3$	**159**	MeCN	N	M	-47.81	N	Y1
4	10	**142b**	**3**	$Yb(OTf)_3$	**160**	MeCN	N	G	-19.70	N	Y1
4	11	**142b**	**3**	$Yb(OTf)_3$	**158**	MeCN	N	M	-17.68	N	Y1
4	12	**142b**	**3**	$Yb(OTf)_3$	**43**	MeCN	N	P	-22.78	N	Y1
4	13	**142b**	**3**	$Sn(OTf)_2$	**159**	MeCN	N	M	-64.29	N	Y1
4	14	**142b**	**3**	$Sn(OTf)_2$	**160**	MeCN	N	G	-99.27	N	Y1
4	15	**142b**	**3**	$Sn(OTf)_2$	**158**	MeCN	N	M	-36.64	N	Y1
4	16	**142b**	**3**	$Sn(OTf)_2$	**43**	MeCN	N	M	-54.85	N	Y1
4	17	**142b**	**3**	$Zn(OTf)_2$	**159**	MeCN	N	G	-18.95	N	Y1

Reaction Screen	Reaction #	Imine	Diene	Lewis acid	Ligand	Solvent	Sieves[a]	Reaction Quality[b]	$\sum$[c]	B. C.[d]	Problem?[e]
4	18	**142b**	**3**	$Zn(OTf)_2$	**160**	MeCN	N	G	-19.84	N	Y1
4	19	**142b**	**3**	$Zn(OTf)_2$	**158**	MeCN	N	M	-25.10	N	Y1
4	20	**142b**	**3**	$Zn(OTf)_2$	**43**	MeCN	N	G	-18.50	N	Y1
4	21	**142b**	**3**	$ZnCl_2$	**159**	MeCN	N	G	-19.69	N	Y1
4	22	**142b**	**3**	$ZnCl_2$	**160**	MeCN	N	P	-12.14	N	Y1
4	23	**142b**	**3**	$ZnCl_2$	**158**	MeCN	N	M	-20.05	N	Y1
4	24	**142b**	**3**	$ZnCl_2$	**43**	MeCN	N	P	-16.50	N	Y1

[a] 4 Å molecular sieves used in the reaction: Y = Yes, N = No.

[b] G = Good, M = Moderate, P = Poor (generally, poor reactions had no product, or were a complex mixture of products). Example chromatograms can be found in Appendix 7.

[c] $\sum$ = (Peak area1 – Peak area2) / (Peak area1 + Peak area2)

[d] Baseline Correction. Computer introduced an artificial baseline which subsequently affected e.e. calculations slightly.

[e] Y1 = Mixture of **151** and **152**; Y2 = Peak integrated as if more than one peak - totals added together; Y3 = Difficult to discern product peaks from impurities; Y4 = Sample too concentrated to integrate.

[f] No product in chromatogram.

[g] Prepared according to the literature.[77]

In the second screen of the reaction of imine **142b** with diene **3** to give product **151** (Table 19, Reaction Screen 2), no molecular sieves were used for the reasons discussed. The reactions were worked up by adding 5 % HCl and EtOAc to the reaction mixtures. The organic layers were removed by pipette and filtered through a plug of silica gel directly into the HPLC vial. In the chromatograms (see Appendix 7 for a typical example), the enantiomers did not separate properly. One clean looking (by HPLC) sample was evaporated and the ^{1}H NMR spectrum obtained. It showed only the acyclic compound **152** and not the cyclic **151**! A new HPLC method therefore was developed using this sample, *i.e.* using compound **152** for HPLC screening. This time, 8 % EtOH in hexane at 1.5 ml per minute on the AD column brought about separation of the enantiomers of **152**. As the data was only meant to be a rough guide to the level of asymmetric induction at this point (scale-up of reactions would be needed to validate any e.e. followed by isolation and subsequent HPLC of pure material) the HPLC data was roughly interpreted and the next screen was carried out.

In Reaction Screen 3 (Table 19, Reaction Screen 3), a new work-up was developed. This was based on a three component pipette column. At the bottom of the column was a 1 cm deep plug of silica gel, which was topped by approximately 1 cm of $MgSO_4$ and finally about 1 cm of wet amberlite. The wet amberlite was intended to perform the same task as the aqueous HCl had accomplished previously when using an aqueous work-up. The $MgSO_4$ served to remove the moisture from the solvent picked up on passing through the wet amberlite and the silica gel was to ensure that all metal traces had been removed. HPLC was then performed using the new method, however, enantiomer separation was still not occurring. It was believed that the new conditions were not separating the cycloadduct **151**, and that this was now present in the majority of reaction mixtures as the main component. Again, an example sample was evaporated and the ^{1}H NMR spectrum obtained, but the NMR spectrum indicated that acyclic material was the major compound in the HPLC sample!

The samples from the previous screens had been kept, and the first sample (the one that the new HPLC method had been developed on) had all been used. Hence, a sample with an equivalent chromatogram was found and the HPLC run using the new conditions. It gave enantioseparation as expected for compound **152**. The sample was evaporated, and the ^{1}H NMR recorded. This time, the compound was the cycloadduct **151**. It transpired therefore, that on standing, the intermediate acyclic compound **152**

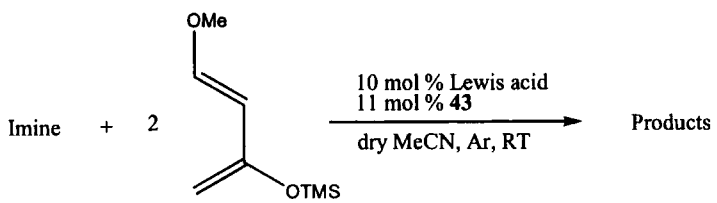
cyclises to give **151**. It also appears that one enantiomer of the cyclic material **151**, and one of the acyclic material **152** overlap in the HPLC chromatogram. Under the HPLC conditions used, both enantiomers of the acyclic compound **152** also overlap with one another, making the situation rather complex in terms of accurate assessment of the reaction outcome. The data thus obtained could be viewed as highly unreliable because the integrations are not on sole peaks with baseline resolution. It did appear that in the majority of cases, acyclic product **152** appeared rather than cyclic compound **151**.

A fourth and final screen was carried out using the same work-up protocol as for Reaction Screen 3. In order to check that the e.e. calculated from the chromatograms was real and reproducible, two reactions were scaled-up. These were using $Yb(OTf)_3$ and $Sn(OTf)_2$ (10 mol %) with dimethyl-D-tartrate **43** (11 mol %) in dry MeCN under argon. The reactions were checked using the phenyl imine **142a** also. The results obtained are outlined in Table 20.

Table 20. Table showing the results of the reactions as detailed in Equation 44.

Entry	Imine	Lewis acid	Product	Yield (%)	e.e. (%)
a	**142a**	$Yb(OTf)_3$	**150**	54	0
b	**142a**	$Sn(OTf)_2$	**150**	53	0
c	**142b**	$Yb(OTf)_3$	**151**	11	0
d	**142b**	$Sn(OTf)_2$	**151**	34	0

Equation 44



3

The reactions were given the usual aqueous work-up, and as a result, only cyclic compounds **150** and **151** were obtained. Zero e.e. was obtained in all reactions, suggesting that the screening process needed to be refined and improved asymmetric catalysts identified. With hindsight, more meaningful data could almost certainly have been obtained by simply using imine **142a** rather than **142b**. The reactions are more reliable, reproducible and generally cleaner.

2.10 Concluding Remarks

The imino-dienophile Diels-Alder reaction is one of the most synthetically useful reactions for making nitrogen containing heterocycles. There are many reasons why there are few truly catalytic asymmetric processes for aza-Diels-Alder reactions in the literature, but the root of the problem lies in the presence of the nitrogen atom and the number of possible isomers of the imine C=N bond. Developing such systems is therefore no trivial task. A diversity approach would seem to be ideally suited to tackling this challenge, since it allows a broad range of possibilities to be explored in a comparatively short timescale. However, the diversity approach itself is not without its own challenges. Working with extremely small quantities of chemicals is a testing exercise in itself. The problems associated with working on small scales were compounded in this project, by the instability of the initially isolated products, and compounded further by problems of removing excess reagents from crude reaction mixtures. This inhibited the high throughput technique being developed as an integral part of the project. Later on in the project, the reaction screening was impaired by the unreliability of the reactions at producing a single product reliably. This highlights the importance of the first stage of the generic approach, *i.e.* reaction location. Choosing the right reaction at the outset has a knock-on effect to the rest of the screening process. In the case of this project, this was clouded on occasion, by the desire to be able to isolate what was seen as the more useful intermediates. This halted progress by digressions into problem solving, which after all, is the nature of a research project.

However, several new reactions have been developed and a new mechanistic insight has been gained into their derivation; hopefully these results will re-open the literature debate on the predominant mechanism operating in the aza-Diels-Alder reactions. In addition, for the first time, an imino-dienophile Diels-Alder reaction has been developed (although un-optimised) where the imine is protected by a phosphorus functional group. Of course, in the case of Danishefsky's diene, the reaction will be called an aza-Diels-Alder reaction, because overall, that is what is observed. In reality, on the basis of the isolation of the intermediate addition product **152** and the formation of only acyclic products with other dienes, it seems that these processes are also stepwise. The formation of acyclic products is probably due to the lack of nucleophilicity of the phosphorus protected nitrogen atom. It is apparent that these imines only react with highly activated dienes. There are many more of these types of dienes in the literature

and as yet only three have been tested. The recent finding of boron Lewis acids activating these imines to attack by dienes is perhaps an important one. It seems that both hard and soft Lewis acids activate these imines and certainly more experimentation is needed to elucidate the details of that activation process. More work is required in developing catalytic versions of these processes, followed by new asymmetric processes. A lack of asymmetric induction in these processes was unfortunate, however, the reactions were new, and very little work in this area has been done to date.

Chapter Three

Future Work

There is a great deal of work yet to be undertaken in this area. The dienyl additions to *N*-phosphoryl imines present the greatest scope for new developments. This chemistry is relatively untouched and the Diels-Alder reactions of these imines are unknown. Where there are asymmetric addition reactions on similar imines reported in the literature, it seems reasonable that there can, and should be, asymmetric cycloaddition reactions on these types of systems. The exploratory work to examine this area more fully has only just begun and much of the asymmetric work completed was on an unreliable system, due to the competing formation of both cyclic and acyclic products. Repetition of this work on more stable systems, *e.g.* *C*-phenyl, may offer more encouragement in the future. The chemistry in this thesis should open the door to other potentially more profitable projects based on the same guidelines as this one. Many of the problems associated with this kind of work have been uncovered in the development of the chemistry herein and the lessons learned can be passed on.

Chapter Four

Experimental

5.1 General Procedures

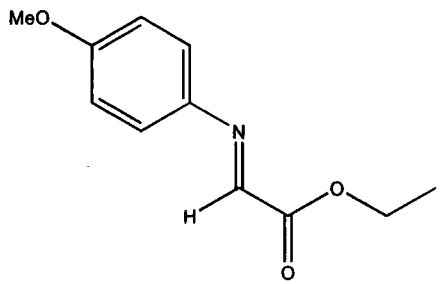
^{1}H NMR spectra were recorded on Bruker AC200, AC300 and AC400 instruments and on Varian 200, 300 and 500 model spectrometers at frequencies of 200-500MHz in d-chloroform unless otherwise stated. ^{13}C NMR spectra were recorded on the same instruments at 75.5, 100 or 125MHz. Chemical shifts are expressed as parts per million downfield from the internal standard tetramethyl silane. EI (70 eV) and CI mass spectra were performed on Kratos MS25, Micromass Autospec or Finnigan MAT XP 95 spectrometers. ES mass spectra were recorded on Finnigan MAT 900 XLT and Micromass Autospec spectrometers. FAB spectra were recorded on a Kratos MS50 using meta nitrobenzyl alcohol matrix; high resolution spectra were obtained from either Kratos Concept IS, Finnigan MAT 900 XLT or Micromass Autospec spectrometers. IR-spectra were recorded on a Perkin-Elmer 298 spectrometer. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. HPLC were recorded using a Shimadzu Class VP HPLC system, or a Gilson HPLC system, both with a UV detector set at 254 nm. Column chromatography was performed under medium pressure with Fluka silica gel (pore size 60Å). TLC was performed on Fluka silica gel aluminium backed plates. Visualisation of TLC plates was effected using UV radiation at 254 nm and 365 nm, and by PMA or Vanillin stain.

All glassware used in anhydrous reactions was first dried with a heat-gun and cooled under a stream of argon. All extracted solvents were first dried with $MgSO_4$. Evaporation was effected at ca. 20 mmHg using a Buchi rotary evaporator and water bath, followed by evaporation to dryness under high vacuum.

All solvents used were either distilled over sodium-benzophenone ketyl (THF) or calcium hydride (DCM, petroleum ether, ethyl acetate and toluene) and stored under an argon atmosphere. Acetonitrile was pre-dried over P_2O_5, re-distilled from K_2CO_3 and stored under argon over 4Å molecular sieves.

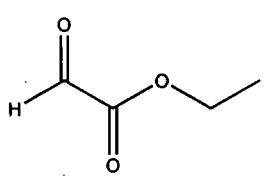
All reagents used were purchased from Fluka, Lancaster Synthesis or Aldrich Chemical Co. and used as received. Dicyclopentadiene was cracked using a fractional distillation apparatus to afford the monomer and used immediately. *p*-Anisidine was recrystallised prior to use from distilled water.

5.2 Specific Procedures



Ethyl 2-[(4-methoxyphenyl)imino]acetate 53

Ethyl glyoxalate **55** (8.16 g, 79.95 mmol) was added to a stirred solution of *p*-anisidine **56** (9.85 g, 79.95 mmol) in dry DCM (300 ml) with $MgSO_4$ at room temperature. After stirring for 8 hours, the $MgSO_4$ was removed by filtration, and the filtrate was concentrated *in vacuo* to yield crude (4-methoxyphenylimino) acetic acid ethyl ester **53** as an orange / brown oil which was purified by Kugelrohr distillation to yield a bright yellow oil (13.07 g, 79 %); ν_{max} (neat)/cm^{-1} *inter alia* 1740 (C=O), 1710 (C=N); δ_H (300 MHz; $CDCl_3$) 1.40 (3H, t, *J* 7.2, $C\underline{H}_3$), 3.83 (3H, s, $OC\underline{H}_3$), 4.41 (2H, q, *J* 7.2, $C\underline{H}_2CH_3$), 6.93 (2H, d, *J* 9.1, ArC<u>H</u>), 7.36 (2H, d, *J* 9.1, ArC<u>H</u>), 7.94 (1H, s, <u>H</u>C=N); δ_C (75.5 MHz; $CDCl_3$) 13.2 ($OCH_2\underline{C}H_3$), 54.9 (ArC-O<u>C</u>H_3), 61.0 ($OC\underline{H}_2CH_3$), 114.2 (*m*-Ar<u>C</u>), 123.2 (*o*-Ar<u>C</u>), 141.0 (Ar<u>C</u>-N), 148.2 (N<u>C</u>H), 160.1 (Ar<u>C</u>-OCH_3), 163.1 (C=O); *m/z* (FAB) 208 (MH^+), 134 (100 %, MH^+ - CO_2Et). $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.32; N, 6.76; Found: C, 63.45: H, 5.95: N, 6.85 %.



Ethyl glyoxylate 55

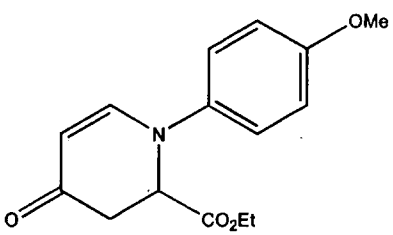
Ethyl diethoxyacetate **57** (50.88 g, 0.29 mol), glyoxylic acid monohydrate **58** (26.58 g, 0.29 mol) and *p*-toluenesulfonic acid monohydrate (400 mg) were heated at 90 °C for 27h. The resulting solution was cooled to –10 °C and stirred vigorously during addition

of phosphorus pentoxide (36 g) (portion wise). The mixture was then heated at 90 - 100 °C for an additional 2 hours. Distillation at reduced pressure (ca. 20mmHg) afforded ethyl glyoxylate **55** (23.87 g, 81 %) as a pale yellow mobile liquid as described in the literature.[30]

General Procedure for Reaction Screens[a]

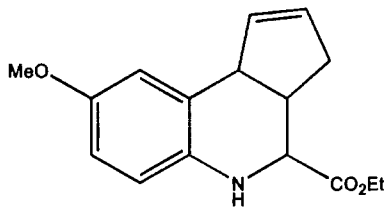
A solution of imine (20 mg, 0.097 mmol) in dry reaction solvent (1.5 ml) was added to stirred, pre-made solutions of Lewis acid (0.010 mmol) and chiral ligand (0.011 mmol) (each added to all of the reaction vessels as a concentrated solution in an appropriate dry solvent), which had been stirring for approximately 10 minutes at room temperature under argon. After a further 10 minutes, neat diene (0.194 mmol) was added to the reactions and they were monitored by TLC (generally hexane 1 : 1 EtOAC) for consumption of imine. When the imine had been completely consumed or after 48 hours (whichever was sooner), the reactions were worked-up.

[a] See Chapter 2 for specific details of quantities and work-up procedures.



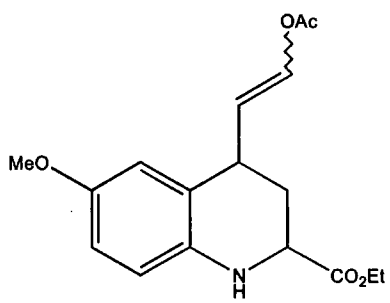
Ethyl 1-(4-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydro-2-pyridinecarboxylate 54

Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of $Yb(OTf)_3$ (30 mg, 0.05 mmol) in dry MeCN (5 ml) under argon. Danishefsky's diene **3** (1.45 mmol) was added at room temperature, and stirred for 3 hours. After quenching with brine, extraction with ethyl acetate (3 x 20 ml), and washing with brine (3 x 20 ml), the extract was dried and evaporated to afford crude adduct as a yellow / brown oil. Chromatography [petroleum ether (40 - 60) : ethyl acetate, 1 : 1 as the eluent] yielded **54** (173 mg, 65 %) as a yellow oil whose data agreed with the literature.[18]



Ethyl 8-methoxy-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-carboxylate 64

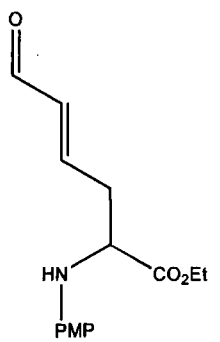
Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of $Yb(OTf)_3$ (30 mg, 0.05 mmol) in dry MeCN (5 ml) under argon. Diene **16** (1.45 mmol) was added at room temperature, and stirred for 3 hours. After quenching with brine, extraction with ethyl acetate (3 x 20 ml), and washing with brine (3 x 20 ml), the extract was dried and evaporated to afford crude adduct as a light brown oil. Chromatography [petroleum ether(40 - 60) : ethyl acetate, 3:1 as the eluent] yielded **64** (0.214 g, 81 %) as an off white solid; ν_{max} (neat)/cm^{-1} *inter alia* 3330 (NH), 1720 (COOEt); δ_H (300 MHz; $CDCl_3$) 1.35 (3H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 2.36 (1H, unsymm. tdd, *J* 2.0, 9.0 and 16.5, HC=CHC$\underline{H}$H), 2.51 (1H, unsymm. qdd, *J* 2.5, 8.5 and 16.5, HC=CHCH$\underline{H}$), 3.30 – 3.39 (1H, m, =CHCH_2C$\underline{H}$), 3.77 (3H, s, $OC\underline{H}_3$), 4.01 (1H, bs, N$\underline{H}$, *exchanges with* D_2O), 4.06 (1H, d, *J* 3.5, C$\underline{H}$-N), 4.09 (1H, qd, *J* 1.5 and 9.5, CHC=CHC$\underline{H}$), 4.21 – 4.39 (2H, m, $OC\underline{H}_2CH_3$), 5.65 – 5.71 (1H, m, C$\underline{H}$=CH), 5.72 – 5.78 (1H, m, CH=C$\underline{H}$), 6.58 – 6.64 (3H, m, ArC$\underline{H}$); δ_C (75.5 MHz; $CDCl_3$) 14.7 ($\underline{C}H_3$), 33.0 (HC=CH$\underline{C}H_2$), 40.9 (HC=CH$\underline{C}$H), 47.3 (=CHC$H_2\underline{C}$H), 56.0 (N$\underline{C}$H), 57.4 ($O\underline{C}H_3$), 61.5 ($O\underline{C}H_2$), 112.8 (Ar$\underline{C}$H), 114.3 (Ar$\underline{C}$H), 117.1 (Ar$\underline{C}$H), 127.6 (Ar$\underline{C}$-CH), 130.4 (HC=$\underline{C}$HCH$_2$), 134.3 (H$\underline{C}$=CHCH$_2$), 138.2 (Ar$\underline{C}$-N), 153.5 (Ar$\underline{C}$-O), 172.4 ($\underline{C}OOCH_2$); *m/z* (ES^+) 274.1429 (100 %, MH^+, $C_{16}H_{20}NO_3$ requires 274.1443), 200 ($MH^+ - HCO_2Et$).



Ethyl 4-[(*E/Z*)-2-(acetyloxy)ethenyl]-6-methoxy-1,2,3,4-tetrahydro-2-quinolinecarboxylate 65

Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of $Yb(OTf)_3$ (30 mg, 0.05 mmol) in dry MeCN (5 ml) under argon. Diene **60** (1.45 mmol) was added at room temperature, and stirred for 3 hours. After quenching with brine, extraction with ethyl

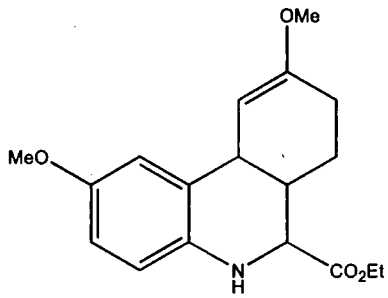
acetate (3 x 20 ml), and washing with brine (3 x 20 ml), the extract was dried and evaporated to afford crude adduct as a light brown oil. Chromatography [petroleum ether (40 - 60) : ethyl acetate, 3:1 as the eluent] yielded a mixture of *cis* and *trans* vinyl acetates (approx. 1 : 6 respectively) with a *syn* arrangement around the tetrahydroquinoline ring, and the *anti* diastereoisomer with a *trans* vinyl acetate [approx. 1 : 5 with respect to the major (*syn* / *trans*) diastereoisomer] **65** (0.188 g, 61 %) as a yellow oil; (Major *E*-diastereoisomer only) ν_{max} (neat)/cm^{-1} *inter alia* 1750 (EtOC=O), 1730 (CH_3C=O), 1620 (C=C); δ_H (300 MHz; $CDCl_3$) 1.33 (3H, t, *J* 7.0, CH_3), 1.81 (1H, td, *J* 11.0 and 12.5, NHCHC<u>H</u>H), 2.18 (3H, s, CH_3CO), 2.41 (1H, ddd, *J* 3.5, 5.5 and 12.5, NHCHCH<u>H</u>), 3.59 (1H, dt, *J* 5.5 and 10.6, AcOCH=CHC<u>H</u>), 3.74 (3H, s, OCH_3), 4.06 (1H, dd, *J* 2.5 and 11.5 C<u>H</u>CO_2Et), 4.21 (1H, bs, NH, *Exchanges with* D_2O), 4.26 (2H, q, *J* 7.2, O<u>C</u>H_2CH_3), 5.40 (1H, dd, *J* 10.5 and 12.5 C<u>H</u>=CHOAc), 6.57 – 6.71 (3H, m, ArCH), 7.32 (1H, d, *J* 12.5, CH=C<u>H</u>OAc); δ_C (100.6 MHz; $CDCl_3$) 13.2 (OCH$_2$<u>C</u>H$_3$), 19.7 (C(O)<u>C</u>H$_3$), 32.1 (NCH<u>C</u>H$_2$), 35.4 (HC=CH<u>C</u>H), 52.9 (N<u>C</u>HCH$_2$), 54.8 (O<u>C</u>H$_3$), 60.4 (O<u>C</u>H$_2$CH$_3$), 112.7 (Ar<u>C</u>H), 113.1 (Ar<u>C</u>H), 115.0 (HC=<u>C</u>HCH), 116.1 (Ar<u>C</u>H), 122.7 (Ar<u>C</u>C), 135.9 (Ar<u>C</u>N), 136.1 (H<u>C</u>=CHCH), 151.3 (Ar<u>C</u>O), 167.1 (<u>C</u>(O)CH$_3$), 171.6 (<u>C</u>O$_2$Et); *m/z* (ES$^+$) 320.1507 (100 %, MH$^+$, $C_{17}H_{22}NO_5$ requires 320.1511), 278 (MH$^+$ – H_2CCO).



<u>Ethyl (*E*)-2-(4-methoxyanilino)-6-oxohex-4-enoate 66</u>

Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of Yb(OTf)$_3$ (30 mg, 0.05 mmol) in wet MeCN (5 ml) under argon. Diene **61** (1.45 mmol) was added at room temperature, and stirred for 3 hours. After quenching with brine, extraction with ethyl acetate (3 x 20 ml), and washing with brine (3 x 20 ml), the extract was dried and evaporated to afford crude adduct as a red / brown oil. Chromatography [petroleum ether (40 - 60) : ethyl acetate, 3:1 as the eluent] yielded **66** (0.158 g, 59 %) as a yellow oil; ν_{max} (neat)/cm^{-1} *inter alia* 3330 (NH), 1730 (COOEt), 1690 (CHO); δ_H (300 MHz;

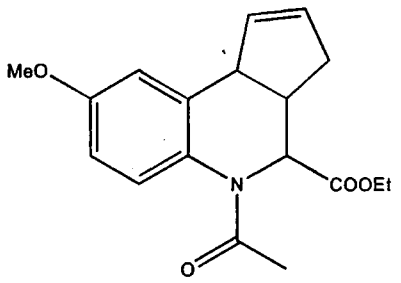
$CDCl_3$) 1.24 (3H, t, *J* 7.2, CH_3), 1.63 – 1.74 (1H, m, NHC<u>H</u>CO), 2.71 – 2.92 (2H, m, HC=CHC<u>H</u>$_2$), 3.74 (3H, s, OC<u>H</u>$_3$), 4.03 (1H, d, *J* 3.8, N<u>H</u>, *exchanges with* D_2O), 4.15 – 4.25 (2H, m, OC<u>H</u>$_2$CH$_3$), 6.19 (1H, dd, *J* 7.9 and 15.9, CHOC<u>H</u>=CH), 6.62 (2H, d, *J* 9.1, ArCH), 6.78 (2H, d, *J* 9.1, ArCH), 6.85 (1H, td, *J* 7.3 and 15.9, CHOCH=C<u>H</u>), 9.51 (1H, d, *J* 7.9, CHO); δ_C (75.5 MHz; $CDCl_3$) 14.6 (CH_3), 36.2 (=CH<u>C</u>H$_2$), 56.2 (OCH_3), 57.1 (NCH), 62.0 (O<u>C</u>H$_2$), 115.3 (Ar<u>C</u>H), 115.8 (Ar<u>C</u>H), 135.8 (<u>C</u>HCHO), 140.4 (Ar<u>C</u>-N), 152.4 (=<u>C</u>HCH$_2$), 153.5 (Ar<u>C</u>-O), 173.1 (<u>C</u>O$_2$Et), 193.8 (<u>C</u>HO); *m/z* (ES^+) 278.1393 (100 %, MH^+, $C_{15}H_{20}NO_4$ requires 278.1392), 260 ($MH^+ - H_2O$), 232 (MH^+ – EtOH).



<u>Ethyl 2-methoxy-5,6,6a,7,8,10a-hexahydro-6-phenanthridinecarboxylate 67</u>

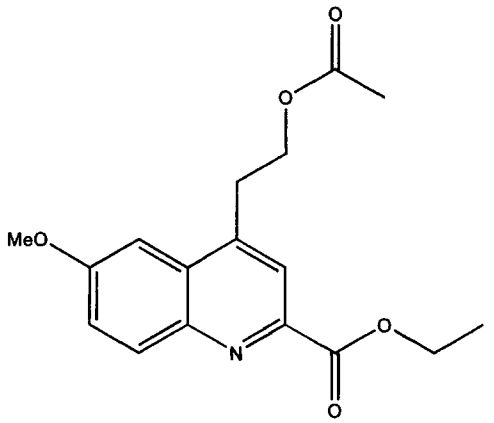
Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of $Yb(OTf)_3$ (30 mg, 0.05 mmol) in dry MeCN (5 ml) under argon. Diene **62** (1.45 mmol) was added at room temperature, and stirred for 3 hours. After quenching with brine, extraction with ethyl acetate (3 x 20 ml), and washing with brine (3 x 20 ml), the extract was dried and evaporated to afford crude adduct as a light brown oil. Chromatography [petroleum ether (40 - 60) : ethyl acetate, 3:1 as the eluent] yielded **67** (0.175 g, 57 %) in approximately 80 – 90 % purity, as a yellow oil; ν_{max} (neat)/cm^{-1} 3380 (NH), 2840 (Ar-OCH_3), 2820 (HC=C-OCH_3), 1710 (COOEt), 1660 (C=C), 1230 (C-O), 1060 (=C-O-CH_3); δ_H (300 MHz; $CDCl_3$) 1.34 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 1.40 - 1.49 (1H, m, CH_2), 1.62 (1H, qd, *J* 6.1 and 12.8, CH), 2.07 (1H, br dd, *J* 5.8 and 15.4, CH_2), 2.19 - 2.34 (1H, m, CH_2), 2.41 – 2.49 (1H, m, CH), 3.60 (3H, s, <u>H</u>$_3$CO-C=CH), 3.75 (3H, s, <u>H</u>$_3$CO-Ar), 3.70 – 3.76 (1H, m, CH_2), 4.04 – 4.25 (1H, br s, NH), 4.15 (1H, d, *J* 2.7, NCH), 4.23 – 4.36 (2H, m, OC<u>H</u>$_2$CH$_3$), 5.14 (1H, br d, *J* 6.1, MeO-C=C<u>H</u>), 6.56 (1H, unsymm. d, *J* 8.6, ArC<u>H</u>), 6.64 (1H, unsymm. dd, *J* 2.4 and 8.7, ArC<u>H</u>), 6.79 (1H, unsymm. d, *J* 2.4, ArC<u>H</u>); δ_C (100.6 MHz; $CDCl_3$) 14.7 ($OCH_2\underline{C}H_3$), 28.0 (MeO-C<u>C</u>H$_2$), 35.2 (NCH<u>C</u>H), 35.7 (NCHCH<u>C</u>H), 54.7 (N<u>C</u>H), 56.1 (H$_3$<u>C</u>O-C=C), 57.8 (H$_3$<u>C</u>O-Ar), 61.7 (O<u>C</u>H$_2$CH$_3$), 95.3 (MeO-C=<u>C</u>H), 113.1 (Ar<u>C</u>H), 115.1 (Ar<u>C</u>H), 116.2 (Ar<u>C</u>H), 126.5

(Ar<u>C</u>-C), 135.8 (MeO-<u>C</u>=CH), 152.9 (Ar<u>C</u>-N), 156.3 (Ar<u>C</u>-O), 172.6 (<u>C</u>OOCH$_2$); *m/z* (ES$^+$) 615 (2M + H$^+$) 318.174 (100%, MH$^+$, $C_{18}H_{24}NO_4$ requires 318.1705).



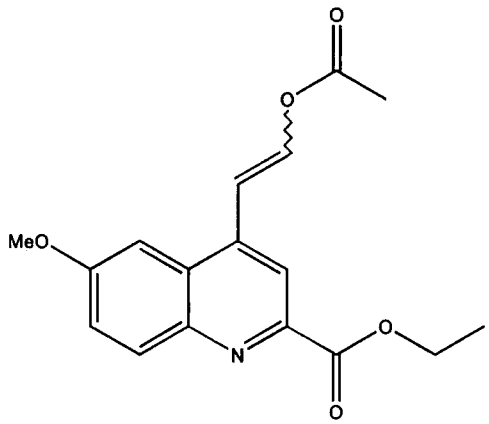
<u>Ethyl 5-acetyl-8-methoxy-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-carboxylate 77</u>

Pyridine (1 ml) and acetic anhydride (1 ml) were added to **64** (0.111 g, 0.41mmol) under argon. After 16h, the reaction was cooled to 0 °C, quenched with water (5 ml), extracted with EtOAc (2 x 20 ml), washed with 5 % HCl (2 x 20 ml), water (2 x 20 ml), dried and evaporated to yield a dark brown oil. Silica gel chromatography [petroleum ether (40 – 60) : EtOAc, 1 : 1 as eluent] yielded **77** (219 mg, 72 %) as a white crystalline solid; m.p. 109 °C; ν_{max} (neat)/cm^{-1} *inter alia* 1730 (COOEt), 1660 (NC=O), 1650 (C=C); δ_H (300 MHz; $CDCl_3$) 1.12 (3H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$), 2.21 (3H, s, COC<u>H</u>$_3$), 2.51 – 2.69 (2H, m, HC=CHC<u>H</u>$_2$), 3.2 (1H, ddd, *J* 4.9, 7.3 and 12.4, =CHCH$_2$C<u>H</u>), 3.81 (3H, s, OC<u>H</u>$_3$), 3.84 – 3.91 (1H, m, HC=CHC<u>H</u>), 3.92 – 4.02 (2H, m, OC<u>H</u>$_2$CH$_3$), 5.52 (1H, d, *J* 7.9, NC<u>H</u>), 5.76 – 5.82 (1H, m, <u>H</u>C=CH), 5.85 – 5.90 (1H, m, HC=C<u>H</u>), 6.75 – 6.81 (2H, m, ArCH), 7.09 (1H, d, *J* 8.3, ArC<u>H</u>CN); δ_C (75.5 MHz; $CDCl_3$) 14.4 (CH$_3$), 22.9 (CO<u>C</u>H$_3$), 35.6 (HC=CH<u>C</u>H$_2$), 41.5 (HC=CH<u>C</u>H), 46.3 (=CHCH$_2$<u>C</u>H), 54.8 (N<u>C</u>H), 55.8 (O<u>C</u>H$_3$), 61.1 (O<u>C</u>H$_2$), 112.1 (Ar<u>C</u>H), 113.4 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 131.7 (Ar<u>C</u>-CH), 131.8 (HC=<u>C</u>HCH$_2$), 132.9 (HC=<u>C</u>HCH$_2$), 134.7 (Ar<u>C</u>-N), 157.6 (Ar<u>C</u>-O), 170.1 (N<u>C</u>OCH$_3$) 170.3 (<u>C</u>OOCH$_2$); *m/z* (EI) 316 (100 %, MH$^+$), 274 (MH$^+$ – COCH$_2$), 200 (MH$^+$ – CH$_3$CONCHCO$_2$Et). $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44; Found C, 68.44; H, 6.80; N, 4.50 %.



4-[2-(acetyloxy)ethyl]-6-methoxy-2-quinolinyl propionate 80

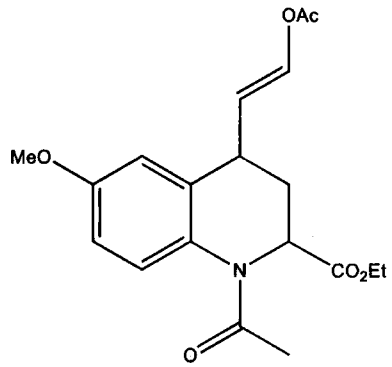
To a flask charged with 10 % palladium on activated carbon (5 mg, 0.005 mmol) and ethyl acetate (15 ml) was added **81** (15 mg, 0.05 mmol). The flask was evacuated and purged with hydrogen three times, then stirred overnight under a positive pressure of hydrogen. Filtration of the reaction mixture through celite followed by evaporation *in vacuo* gave a crude pale yellow oil which was purified by column chromatography [petroleum ether (40 – 60) : EtOAc, 3 : 1 as eluent] to give **80** (13 mg, 86 %) as a white crystalline solid; m.p. 110 – 112 °C; ν_{max} (neat)/cm^{-1} *inter alia* 1730 ($H_3CC{=}O$), 1710 (EtOC=O); δ_H (300 MHz; $CDCl_3$) 1.50 (3H, t, *J* 7.2, $C\underline{H}_3CH_2O$), 2.08 [3H, s, $C(O)C\underline{H}_3$], 3.43 (2H, t, *J* 7.4, $C\underline{H}_2CH_2OAc$), 4.03 (3H, s, $OC\underline{H}_3$), 4.47 (2H, t, *J* 7.4, $CH_2C\underline{H}_2OAc$), 4.55 (2H, q, *J* 7.2, $OC\underline{H}_2CH_3$), 7.43 [1H, s, ArC(5)H], 7.46 [1H, dd, *J* 2.6 and 8.4, ArC(7)H], 8.06 [1H, s, ArC(3)H], 8.22 [1H, dd, *J* 1.1 and 8.4, ArC(8)H]; δ_C (75.5 MHz; $CDCl_3$) 14.8 ($OCH_2\underline{C}H_3$), 21.4 ($\underline{C}H_3COO$), 32.3 ($\underline{C}H_2CH_2OAc$), 56.2 ($O\underline{C}H_3$), 62.5 ($NCH\underline{C}H_2$), 54.3 ($N\underline{C}HCH_2$), 56.0 ($\underline{C}H_3O$), 62.5 ($O\underline{C}H_2CH_3$), 63.5 ($CH_2\underline{C}H_2OAc$) 101.5 [Ar<u>C</u>(5)-H], 122.3 [Ar<u>C</u>(3)H], 123.3 [Ar<u>C</u>(7)H], 130.5 [Ar<u>C</u>(4)], 133.6 [ArC(8)H], 143.3 [Ar<u>C</u>(4a)], 144.3 [Ar<u>C</u>(8a)], 145.8 [Ar<u>C</u>(2)], 160.1 [Ar<u>C</u>(6)], 166.1 ($CH_3\underline{C}OO$), 171.5 ($\underline{C}OOCH_2$); *m/z* (ES^+) 318.1344 (100 %, MH^+, $C_{17}H_{20}NO_5$ requires 318.1341), 320 ($MH^+ - CH_2CO$), 316 ($MH^+ - C_2H_5OH$).



4-[(E/Z)-2-(acetyloxy)ethenyl]-6-methoxy-2-quinolinyl propionate 81

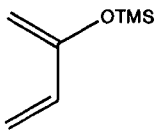
Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of $Yb(OTf)_3$ (30 mg, 0.05 mmol) in dry MeCN (5 ml) under argon. Diene **60** (1.45 mmol) was added at room temperature, and stirred for 3 hours. MeCN was removed *in vacuo*, and the residue redissolved in chloroform (10 ml). This was then stirred at room temperature in an air atmosphere for 7 days. Solvent removal was followed by silica gel chromatography (hexane : ethyl acetate gradient) to yield a mixture of *E* and *Z* diastereoisomers (approximately 4 : 1 respectively) of **81** (255 mg, 83 %) as a bright yellow powder; m.p. 124 – 130 °C; ν_{max} (neat)/cm^{-1} *inter alia* 1760 (H_3CC=O), 1710 (EtOC=O), 1645 (C=C-OAc); δ_H (300 MHz; $CDCl_3$) 1.51 (4.11H, t, *J* 7.2, $OC\underline{H}_3CH_2$, both), 2.26 (1.11H, s, $C\underline{H}_3COO$, minor), 2.30 (3H, s, $C\underline{H}_3COO$, major), 3.98 (1.11H, s, $OC\underline{H}_3$, minor), 3.99 (3H, s, $OC\underline{H}_3$, major), 4.57 (2.74H, q, *J* 7.2, $CH_3C\underline{H}_2O$, both), 6.31 (0.37H, d, *J* 7.3, C<u>H</u>=CH-OAc, minor), 6.98 (1H, d, *J* 12.6, C<u>H</u>=CH-OAc, major), 7.24 [1.37H, unsymm. d, *J* 2.7, ArC(5)<u>H</u>, both], 7.44 [1.37H, dd, *J* 2.7 and 9.4, ArC(7)<u>H</u>, both], 7.69 (0.34H, d, *J* 7.3, CH=C<u>H</u>-OAc, minor), 8.10 (1H, unsymm. d, *J* 12.7, CH=C<u>H</u>-OAc, major), 8.19 [1H, s, ArC(3)<u>H</u>, major], 8.22 [1H, d, *J* 9.4, ArC(8)<u>H</u>, major], 8.23 [0.37H, d, *J* 9.4, ArC(8)<u>H</u>, minor], 8.52 [0.37H, s, ArC(3)<u>H</u>, minor]; δ_C (75.5 MHz; $CDCl_3$) 14.8 ($OCH_2C\underline{H}_3$, both), 21.1 [OC(O)$C\underline{H}_3$, major], 21.2 [OC(O)$C\underline{H}_3$, minor], 56.1 ($OC\underline{H}_3$, both), 62.5 ($OC\underline{H}_2CH_3$, minor), 62.6 ($OC\underline{H}_2CH_3$, major), 101.5 [Ar<u>C</u>(5)H, major], 101.7 [Ar<u>C</u>(5)H, minor], 106.6 (AcOCH=<u>C</u>H, minor), 110.3 (AcOCH=<u>C</u>H, major), 118.4 [Ar<u>C</u>(7)H, major], 122.2 [Ar<u>C</u>(7)H, minor], 123.2 [Ar<u>C</u>(3)H, minor], 123.4 [Ar<u>C</u>(3)H, major], 129.1 [Ar<u>C</u>(4a)C, minor], 129.2 [Ar<u>C</u>(4a)C, major], 133.4 [Ar<u>C</u>(8)H, both], 138.3 (AcO<u>C</u>H=CH, minor), 138.4 [Ar<u>C</u>(4)C, minor], 138.6 [Ar<u>C</u>(4)C, minor], 139.9 [Ar<u>C</u>(4)C, major], 140.8 (AcO<u>C</u>H=CH, major), 144.5 [Ar<u>C</u>(2)C, major], 144.6 [Ar<u>C</u>(2)C, minor], 145.8 [Ar<u>C</u>(8a)N, minor], 145.9 [Ar<u>C</u>(8a)N, major], 159.9 [Ar<u>C</u>(6)O, both], 166.0 [$CH_3\underline{C}$(O)O, major] 166.2 [$CH_3\underline{C}$(O)O, minor], 167.8 ($EtO_2\underline{C}$, minor), 167.9 ($EtO_2\underline{C}$, major); *m/z* (ES^+) 316 (100 %, MH^+),

255 [$MH^+ - CH_3CO(OH_2)$]; $C_{17}H_{17}NO_5$ requires C, 64.75; H, 5.43; N, 4.44; Found C, 64.35; H, 5.53; N, 4.55 %.



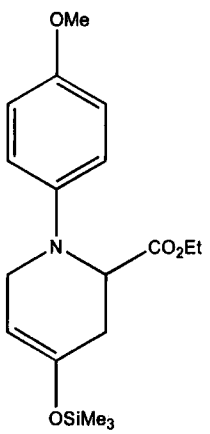
Ethyl 1-acetyl-4-[(*E/Z*)-2-(acetyloxy)ethenyl]-6-methoxy-1,2,3,4-tetrahydro-2-quinolinecarboxylate 82

Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of $Yb(OTf)_3$ (30 mg, 0.05 mmol) in dry MeCN (5 ml) under argon. Diene **60** (1.45 mmol) was added at room temperature, and stirred for 3 hours. Solvent was evaporated *in vacuo*, and pyridine (2 ml) and acetic anhydride (2 ml) were added at room temperature under an argon atmosphere. The reaction was stirred overnight, after which the reaction was cooled to 0 °C, quenched with water (5 ml), extracted with EtOAc (2 x 30 ml), washed with 5 % HCl (2 x 30 ml), saturated sodium bicarbonate (3 x 50 ml), brine (2 x 30 ml), dried ($MgSO_4$) and evaporated to yield a dark brown oil. Silica gel chromatography [petroleum ether (40 – 60) : EtOAc, 3 : 1 as eluent] yielded **82** (139 mg, 40 %) as a light brown oil; ν_{max} (neat)/cm^{-1} *inter alia* 1750 (O=C, AcO and EtO_2C), 1660 (C=C and NC=O); δ_H (300 MHz; $CDCl_3$) 1.25 (3H, t, *J* 7.0, $C\underline{H}_3CH_2O$), 1.60 (1H, dt, *J* 10.0 and 12.6 NCHC$\underline{H}$H), 2.19 (3H, s, $C\underline{H}_3CON$), 2.20 (3H, s, $C\underline{H}_3COO$), 2.64 (1H, ddd, *J* 4.0, 9.5 and 13.1, NCHCH$\underline{H}$), 3.23 (1H, ddd, *J* 4.0, 9.0, 13.0 C$\underline{H}$CH=CHO), 3.83 (3H, s, $OC\underline{H}_3$), 4.09 – 4.21 (2H, m, $CH_3C\underline{H}_2O$), 5.26 (1H, t, *J* 9.5, NC$\underline{H}$), 5.55 (1H, dd, *J* 9.5 and 12.5, C$\underline{H}$CH=CHO), 6.73 (1H, d, *J* 3.0, ArC$\underline{H}$), 6.83 (1H, dd, *J* 3.0 and 8.5, ArC$\underline{H}$), 7.16 (1H, d, *J* 8.5, ArC$\underline{H}$), 7.34 (1H, d, *J* 12.5, AcOC$\underline{H}$=); δ_C (75.5 MHz; $CDCl_3$) 14.5 ($OCH_2\underline{C}H_3$), 21.1 ($\underline{C}H_3COO$), 22.8 ($\underline{C}H_3CON$), 35.5 (Ar$\underline{C}$HCH=), 36.0 (NCH$\underline{C}H_2$), 54.3 (N$\underline{C}HCH_2$), 56.0 ($\underline{C}H_3O$), 61.6 ($O\underline{C}H_2CH_3$) , 111.6 (Ar$\underline{C}$H), 112.0 (Ar$\underline{C}$H), 113.2 (AcOCH=$\underline{C}$H), 126.8 (Ar$\underline{C}$H), 130.7 (Ar$\underline{C}$-N), 138.2 (AcO$\underline{C}$=CH), 139.0 (Ar$\underline{C}$-C), 158.0 (Ar$\underline{C}$-O), 168.3 ($CH_3\underline{C}OO$), 170.6 [N$\underline{C}$(O)CH_3], 171.9 ($\underline{C}OOCH_2$); *m/z* (ES^+) 362.1595 (100 %, MH^+, $C_{19}H_{24}NO_6$ requires 362.1604), 320 ($MH^+ - CH_2CO$), 316 ($MH^+ - C_2H_5OH$).



2-Trimethylsilyloxy-1,3-butadiene 94

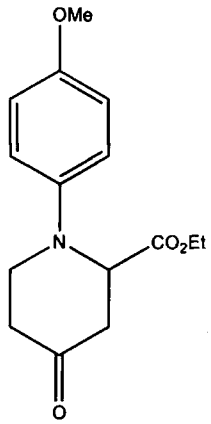
n-BuLi (1.55M, 19.50 ml) was cautiously added to a stirred solution of diispropylamine (5.08 ml, 35.95 mmol) in anhydrous THF (50 ml) under argon at -78 °C. A solution of methyl vinyl ketone (2.50 ml, 30.03 mmol) was added dropwise over about 20 minutes at -78 °C, after which the mixture was stirred for a further 20 minutes at this temperature. TMS-Cl (4.60 ml, 36.24 mmol) was added cautiously to quench, and the mixture allowed to warm to room temperature. After overnight stirring, the mixture was poured into ether (100 ml) and washed with sat. ammonium chloride (3 x 40 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give crude product as a yellow liquid. Kugelrohr distillation gave the desired diene **94** (1.86 g, 43.6 %) as a colourless liquid as described in the literature.[46]



Ethyl-1-(4-methoxyphenyl)-4-[(trimethylsilyl)oxy]-1,2,3,6-tetrahydro-2-pyridinecarboxylate 95

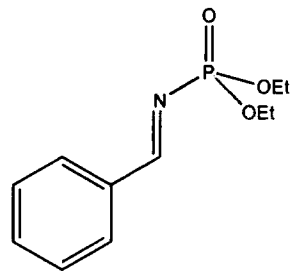
Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of $Yb(OTf)_3$ (30 mg, 0.05 mmol) in dry MeCN (5 ml) under argon. Diene **94** (1.45 mmol) was added at room temperature, and stirred overnight. The reaction mixture was adsorbed onto silica gel and purified by column chromatography (hexane : ethyl acetate gradient) to yield **95** (175 mg, 53 %) as a white crystalline solid; m.p. 69 – 70 °C; ν_{max} (neat)/cm^{-1} *inter alia* 1735 (COOEt), 1685 (C=C), 1257 ($SiMe_3$); δ_H (200 MHz; $CDCl_3$) 0.00 [9H, s, $Si(C\underline{H}_3)_3$], 0.97 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 2.30 (1H, unsymm. dd, *J* 1.6 and 16.8, NCHC$\underline{H}$H), 2.46 – 2.64 (1H, m, NCHCH$\underline{H}$), 3.55 (3H, s, $OC\underline{H}_3$), 3.58 – 3.65 (1H, m, NC$\underline{H}$H), 3.65 – 3.72 (1H, q, *J* 2.4, NCH$\underline{H}$), 3.78 – 3.98 (2H, m, $OC\underline{H}_2CH_3$), 4.33 – 4.39

(1H, dd, *J* 2.2 and 6.6 NCHCHH), 4.71 – 4.76 (1H, m, CH=COSiMe$_3$), 6.63 (4H, s, ArCH); δ_C (100.6 MHz; $CDCl_3$) 0.0 [Si(CH_3)$_3$], 13.9 (OCH_2CH_3), 32.3 ($NCHCH_2$), 44.4 (NCH_2), 55.3 (OCH_3), 56.8 ($NCHCH_2$), 60.4 (OCH_2CH_3), 101.2 (CH=C), 114.2 (ArCH), 116.1 (ArCH), 143.5 (ArC-N), 146.0 (CH=C-OTMS), 152.6 (ArC-O). 171.9 (CO_2Et); *m/z* (ES^+) 721 (2M + Na^+), 372 (100 %, MNa^+). $C_{18}H_{27}NO_4$ requires C, 61.86; H, 7.79; N, 4.01; Found C, 68.89; H, 7.83; N, 3.96 %.



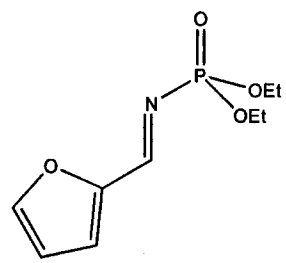
Ethyl 1-(4-methoxyphenyl)-4-oxo-2-piperidinecarboxylate 96

Imine **53** (0.20 g, 0.97 mmol) was added to a stirred solution of Yb(OTf)$_3$ (30 mg, 0.05 mmol) in dry MeCN (5 ml) under argon. Diene **94** (1.45 mmol) was added at room temperature, and stirred overnight. The reaction mixture was adsorbed onto silica gel and purified by column chromatography (hexane : ethyl acetate gradient) to yield **96** (98 mg, 37 %) as a yellow oil; ν_{max} (neat)/cm^{-1} *inter alia* 1729 (2 x C=O); δ_H (300 MHz; $CDCl_3$) 1.09 (3H, t, *J* 7.2, OCH_2CH_3), 2.52 – 2.61 (2H, m, NCH_2CH_2), 2.62 – 2.71 (1H, m, NCHCHH), 2.80 (1H, unsymm. dd, *J* 6.6 and 15.0, NCH_2CHH), 3.47 – 3.56 (1H, unsymm. dd, *J* 5.0 and 11.9, NCHH), 3.58 – 3.65 (1H, m, NCHH), 3.71 (1H, s, OCH_3), 4.04 (2H, q, *J* 7.2, OCH_2CH_3), 4.46 – 4.52 (1H, m, $NCHCH_2$), 6.73 – 6.82 (2H, unsymm. d, *J* 9.0, ArCH), 6.85 – 6.90 (2H, unsymm. d, *J* 9.0, ArCH); δ_C (100.6 MHz; $CDCl_3$) 13.1 (OCH_2CH_3), 39.3 (NCH_2CH_2), 41.4 ($NCHCH_2$), 44.8 (NCH_2CH_2), 54.6 (OCH_3), 60.2 (OCH_2CH_3), 60.5 ($NCHCH_2$), 113.5 (ArCH), 117.9 (ArCH), 142.3 (ArC-N), 153.3 (ArC-O). 170.1 (CO_2Et), 205.3 (C=O); *m/z* (ES^+) 300.1240 (100 %, MNa^+, $C_{15}H_{19}NO_4Na$ requires 300.1212).



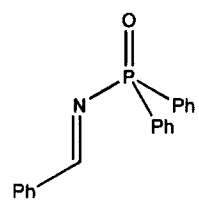
N-Benzylidene-diethylphosphonamide 142a

Diethyl phosphoramidate **145** (6.120 g, 0.040 mol) and benzaldehyde diethyl acetal **144a** (9.360 g, 0.052 mol) were heated to 120 °C in distillation apparatus. The temperature was increased to 160 °C over about 45 minutes, during which time ethanol distilled off. The residue was purified by Kugelrohr distillation under high vacuum to give pure **142a** (the highest boiling fraction, 6.844 g, 71 %) as a colourless liquid whose data agreed with the literature.[73]



N-(2-furylmethylidene)-diethylphosphonamide 142b

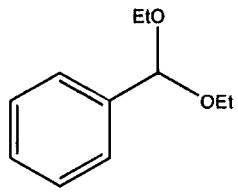
Diethyl phosphoramidate **145** (6.120 g, 0.040 mol) and 2-furaldehyde diethyl acetal **144b** (9.360 g, 0.052 mol) were heated to 120 °C in distillation apparatus. The temperature was increased to 160 °C over about 45 minutes, during which time ethanol distilled off. The residue was purified by Kugelrohr distillation under high vacuum to give pure **142b** (the highest boiling fraction, 7.785 g, 83 %) as a bright yellow liquid whose data agreed with the literature.[73]



N-Benzylidenediphenylphosphinamide 143

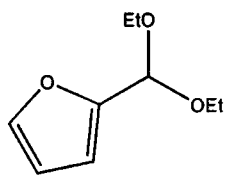
To a solution of benzaldoxime **149** (9.2 g, 0.075 mol) and triethylamine (7.6 g, 0.075 mol) in DCM : toluene (1 : 1, 160 ml) a solution of chlorodiphenylphosphine **148** (16.5

g, 0.075 mol) in DCM (20 ml) was added dropwise at -45 to -40 °C. The cooling bath was not removed until the temperature inside the reaction vessel was at -20 °C. At this point the bath was removed and the reaction mixture allowed to warm to -5 °C. The precipitated triethylamine hydrochloride was filtered off, the filtrate dried ($MgSO_4$), re-filtered and the solvents removed *in vacuo*. Recrystallisation of the resulting solid reside (DCM / hexane) gave **143** as a white powder (13.5 g, 73 %) whose data agreed with the literature;[R51] δ_H (250 MHz; $CDCl_3$) 7.40 – 7.63 (10H, m, *p*-ArC<u>H</u>), 7.94 – 8.05 (5H, m, CH-ArC<u>H</u>), 9.33 (1H, d, *J* 32.0, N=C<u>H</u>).



<u>Benzaldehyde diethyl acetal 144a</u>

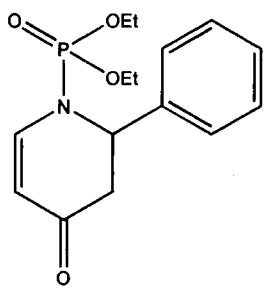
Benzaldehyde **146a** (50 ml, 0.60 mol), triethyl orthoformate **147** (110 ml, 0.66 mol) absolute ethanol (105 ml, 1.8 mol) and a catalytic amount of ammonium chloride (1.50 g, 0.03 mol) were heated at reflux for 1 hour under argon. Ethanol was distilled off, and, after cooling to room temperature, DCM (160 ml) was added. The DCM layer was washed with water (1 x 50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give crude acetal as a dark yellow liquid. Distillation under reduced pressure gave pure **144a** (91.218 g, 89 %) as a colourless liquid as reported in the literature.[74]



<u>2-Furaldehyde diethyl acetal 144b</u>

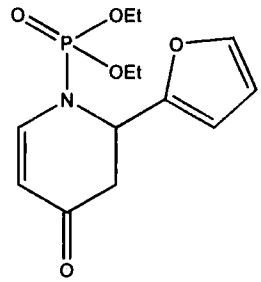
2-Furaldehyde **146b** (16.58 ml, 0.20 mol), triethyl orthoformate **147** (36.58 ml, 0.22 mol) absolute ethanol (35 ml, 0.60 mol) and a catalytic amount of ammonium chloride (0.50 g, 9.40 mmol) were heated at reflux for 2h under argon. Ethanol was distilled off, and, after cooling to room temperature, DCM (60 ml) was added. The DCM layer was washed with water (1 x 20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give crude acetal as a dark yellow liquid. Distillation through a vigreaux column at reduced pressure gave pure **144b** (29.154 g, 86 %) as a colourless liquid as reported in the

literature;[75] δ_C (100.6 MHz; $CDCl_3$) 15.2 ($OCH_2\underline{C}H_3$), 61.3 ($O\underline{C}H_2CH_3$), 96.4 (Ar$\underline{C}$CH), 108.1 (*o*-Ar$\underline{C}$H), 110.1 (*m*-Ar$\underline{C}$H), 142.4 (*p*-Ar$\underline{C}$H), 152.0 (Ar$\underline{C}$C)



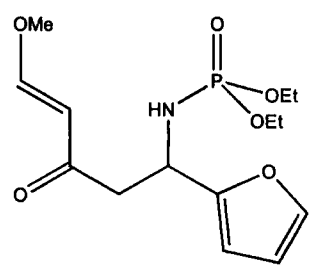
Diethyl 4-oxo-2-phenyl-3,4-dihydropyridin-1(2*H*)-ylphosphonate 150

Danishefsky's diene **3** (0.32 ml, 1.66 mmol), was added to a stirred solution of imine **142a** (0.20 g, 0.83 mmol) and $Yb(OTf)_3$ (45 mg, 0.073 mmol) in dry MeCN (5 ml) under argon at room temperature. The reaction was allowed to stir for 16 hours after which, 5 % aqueous HCl (2 ml) was added to quench, followed by water (15 ml). Ethyl acetate (30 ml) was added and the phases separated. The aqueous phase was extracted with EtOAc (3 x 30 ml), and the combined organic layers washed with brine (3 x 30 ml), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The crude was adsorbed onto silica gel and eluted with hexane/ethyl acetate (gradient elution), after which, evaporation gave **150** (139 mg, 54 %) as a pale orange oil; ν_{max} (neat)/ cm^{-1} *inter alia* 1666 (C=O), 1601 (C=C), 1291 (P=O), 1271 (P=O), 1091 (P-O), 1019 (P-O); δ_H (200 MHz; $CDCl_3$) 1.00 (3H, dt, *J* 1.0 and 7.0, $OCH_2C\underline{H}_3$), 1.26 (3H, dt, *J* 1.0 and 7.0, $OCH_2C\underline{H}_3$), 2.55 – 2.70 (1H, m, NCHC$\underline{H}$H), 3.06 (1H, unsymm. dd, *J* 7.6 and 16.4, NHCHCH$\underline{H}$), 3.54 – 3.76 (1H, m, $OC\underline{H}_2CH_3$), 3.85 – 4.12 (3H, m, $OC\underline{H}_2CH_3$), 5.14 (1H, t, *J* 6.8, NC$\underline{H}CH_2$), 5.33 (1H, ddd, *J* 1.0, 2.8 and 8.0, NC$\underline{H}$=CH), 7.16 – 7.30 (5H, m, ArC$\underline{H}$), 7.54 (1H, ddd, *J* 1.0, 7.2 and 8.0, NHCH=C$\underline{H}$); δ_P (81.0 MHz; $CDCl_3$) 2.96; δ_C (62.9 MHz; $CDCl_3$) 15.6 (d, *J* 7.0, $OCH_2\underline{C}H_3$), 16.1 (d, *J* 7.0, $OCH_2\underline{C}H_3$), 42.4 (d, *J* 5.1, NCH$\underline{C}H_2$), 56.8 (d, *J* 3.3, N$\underline{C}HCH_2$), 63.9 (d, *J* 9.4, $O\underline{C}H_2CH_3$), 63.9 (d, *J* 9.4, $O\underline{C}H_2CH_3$), 106.9 (d, *J* 9.7, NCH=$\underline{C}$H), 126.3 (*o*-Ar$\underline{C}$H), 128.0 (*p*-Ar$\underline{C}$H), 128.7 (*m*-Ar$\underline{C}$H), 139.2 (Ar$\underline{C}$C), 146.7 (d, *J* 6.5, N$\underline{C}$H=CH), 191.0 ($\underline{C}$=O); *m/z* (ES^+) 332.1056 (100 %, MNa^+, $C_{15}H_{20}NO_4PNa$ requires 332.1028), 641 ($2M + Na^+$).



Diethyl 4-oxo-2-(2-furyl)-3,4-dihydropyridin-1(2*H*)-ylphosphonate 151

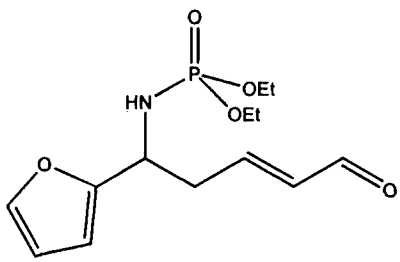
Danishefsky's diene **3** (0.34 ml, 1.66 mmol), was added to a stirred solution of imine **142b** (0.20 g, 0.83 mmol) and Cu(OTf).C_6H_6 (0.083 mmol) in dry THF (5 ml) under argon at room temperature. The reaction was allowed to stir for 16 hours after which, 1 % TFA in DCM (2 ml) was added to quench, followed by evaporation of the solvents *in vacuo*. The crude was adsorbed onto silica gel and eluted with hexane/ethyl acetate (gradient elution), after which, evaporation gave **151** (129 mg, 50 %) as a pale yellow oil; ν_{max} (neat)/ cm^{-1} *inter alia* 1665 (C=O), 1598 (C=C), 1289 (P=O), 1274 (P=O), 1048 (P-O), 1019 (P-O); δ_H (400 MHz; $CDCl_3$) 1.24 (3H, dt, *J* 0.8 and 7.2, $OCH_2C\underline{H}_3$), 1.27 (3H, dt, *J* 0.8 and 7.2, $OCH_2C\underline{H}_3$), 2.69 (1H, unsymm. d, *J* 16.4, NCHC$\underline{H}$H), 2.92 (1H, unsymm. dd, *J* 6.8 and 16.4, NCHCH$\underline{H}$), 5.24 (1H, t, *J* 6.0, NC$\underline{H}$), 5.30 (1H, dd, *J* 2.8 and 8.0, NC$\underline{H}$=CH), 6.21 (1H, unsymm. d, *J* 3.2, *o*-ArC$\underline{H}$), 6.23 (1H, unsymm. dd, *J* 1.6 and 3.2, *m*-ArC$\underline{H}$), 7.24 (1H, dd, *J* 1.2 and 8.0, NCH=C$\underline{H}$), 7.27 (1H, unsymm. dd, *J* 0.8 and 1.6, *p*-ArC$\underline{H}$); δ_P (81.0 MHz; $CDCl_3$) 2.56; δ_C (100.6 MHz; $CDCl_3$) 16.1 (d, *J* 7.0, $OCH_2\underline{C}H_3$), 16.3 (d, *J* 7.0, $OCH_2\underline{C}H_3$), 39.9 (d, *J* 4.2, NCH$\underline{C}H_2$), 51.3 (d, *J* 3.4, N$\underline{C}$HCH$_2$), 64.2 (d, *J* 5.4, O$\underline{C}H_2CH_3$), 64.2 (d, *J* 9.4, O$\underline{C}H_2CH_3$), 107.1 (d, *J* 9.2, NCH=$\underline{C}$H), 108.6 (*o*-Ar$\underline{C}$H), 110.6 (*m*-Ar$\underline{C}$H), 142.6 (*p*-Ar$\underline{C}$H), 145.4 (d, *J* 5.7, N$\underline{C}$H=CH), 151.7 (Ar$\underline{C}$C), 191.6 ($\underline{C}$=O); *m/z* (ES^+) 621.1800 (100 %, 2M + Na^+, $C_{26}H_{36}N_2O_{10}P_2Na$ requires 621.1743), 322 (MNa^+).



Diethyl 1-(2-furyl)-5-methoxy-3-oxo-4-pentenylphosphonamide 152

Danishefsky's diene **3** (0.34 ml, 1.66 mmol), was added to a stirred solution of imine **142b** (0.20 g, 0.83 mmol) and Cu(OTf).C_6H_6 (0.083 mmol) in dry THF (5 ml) under argon at room temperature. The reaction was allowed to stir for 16 hours after which,

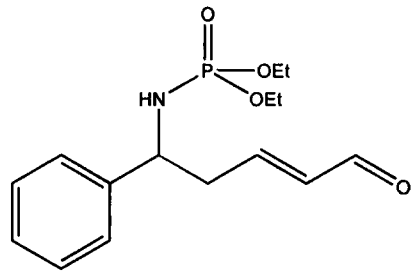
silica gel was added and the solvent removed *in vacuo*. Column chromatography (hexane/ethyl acetate gradient) gave **152** (99 mg, 38 %) as a brown oil; ν_{max} (neat)/ cm^{-1} *inter alia* 3257 (N-H), 1620 (C=O), 1592 (C=C), 1246 (P=O), 1231 (P=O), 1031 (P-O); δ_H (300 MHz; $CDCl_3$) 1.17 – 1.34 (6H, m, $OCH_2C\underline{H}_3$), 2.94 (1H, unsymm. dd, *J* 6.0 and 16.2, NHCHC$\underline{H}$H), 3.08 (1H, unsymm. dd, *J* 5.7 and 16.2, NHCHCH$\underline{H}$), 3.63 (3H, s, $OC\underline{H}_3$), 3.72 – 4.08 (5H, m, $OC\underline{H}_2CH_3$ and N$\underline{H}$), 4.64 – 4.77 (1H, m, NHC$\underline{H}$), 5.52 (1H, d, *J* 12.8, C(O)C$\underline{H}$=CH), 6.17 – 6.22 (1H, m, *o*-ArC$\underline{H}$), 6.24 – 6.29 (1H, m, *m*-ArC$\underline{H}$), 7.26 – 7.31 (1H, m, *p*-ArC$\underline{H}$), 7.56 (1H, d, *J* 12.8, MeOC$\underline{H}$=CH); δ_P (81.0 MHz; $CDCl_3$) 8.12; δ_C (62.9 MHz; $CDCl_3$) 16.0 (t, *J* 7.2, $OCH_2\underline{C}H_3$), 45.7 (d, *J*, 4.7, NHCH$\underline{C}H_2$), 46.6 (NH$\underline{C}$H), 57.6 ($O\underline{C}H_3$). 62.4 (d, *J* 8.3, $O\underline{C}H_2CH_3$), 62.5 (d, *J* 8.3, $O\underline{C}H_2CH_3$), 105.7 (MeOCH=$\underline{C}$H), 106.0 (*o*-Ar$\underline{C}$H), 110.3 (*m*-Ar$\underline{C}$H), 141.5 (*p*-Ar$\underline{C}$H), 155.1 (d, *J* 5.1, Ar$\underline{C}$C), 163.4 (MeO$\underline{C}$H=CH), 196.6 ($\underline{C}$=O).



Diethyl (*E*)-1-(2-furyl)-5-oxo-3-pentenylphosphonamide 154

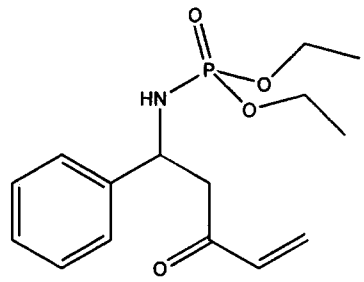
CuOTf.Tol (41 mg, 0.08 mmol) was added to a stirred solution of imine **142b** (0.20 g, 0.83 mmol) in dry MeCN (5 ml) under argon. Diene **61** (1.45 mmol) was added at room temperature causing the reaction mixture to turn from a green suspension to a slightly opaque yellow solution within minutes. After stirring for 3 hours 30 minutes, 1% TFA in DCM (2.5 ml) was added and the whole evaporated *in vacuo* to afford crude product as an orange oil. Silica gel chromatography (hexane : EtOAc gradient) gave the product **154** as a brown oil (86 mg, 33 %); ν_{max} (neat)/cm^{-1} *inter alia* 1690 (C=O), 1639 (C=C), 1235 (P=O), 1057 (P-OEt), 1030 (P-OEt); δ_H (400 MHz; $CDCl_3$) 1.18 (1H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 1.23 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 2.80 (2H, t, *J* 7.2, NHCHC$\underline{H}_2$), 3.38 (1H, bt, *J* 10.6, N$\underline{H}$, *exchanges with* D_2O), 3.79 – 3.90 (1H, m, $OC\underline{H}_2CH_3$), 3.90 – 4.02 (3H, m, $OC\underline{H}_2CH_3$), 4.36 – 4.46 (1H, m, NHC$\underline{H}$), 6.08 (1H, ddd, *J* 0.8, 7.6 and 15.6, =C$\underline{H}$CHO), 6.16 (unsymm. dd, *J* 0.4 and 3.2, *o*-ArC$\underline{H}$), 6.25 (unsymm. ddd, *J* 0.4, 2.0 and 3.2, *m*-ArCH), 6.71 (1H, td, *J* 7.2 and 15.6, C$\underline{H}$=CHCHO), 7.29 – 7.30 (1H, m, *p*-ArC$\underline{H}$), 9.40 (1H, dd, *J* 0.8 and 7.6, C$\underline{H}$O); δ_p (81.0 MHz; $CDCl_3$) 7.86; δ_C (100.6 MHz; $CDCl_3$) 15.1 (d, *J* 6.9, $OCH_2\underline{C}H_3$), 15.2 (d, *J* 6.9, $OCH_2\underline{C}H_3$), 38.1 (d, *J* 5.3, NHCH$\underline{C}H_2$), 47.8

(NHCH), 61.5 (d, *J* 10.5, OCH_2CH_3), 61.6 (d, *J* 10.5, OCH_2CH_3), 105.3 (*o*-ArCH), 109.3 (*m*-ArCH), 134.3 (=CHCHO), 141.1 (*p*-ArCH), 151.9 (CH=CHCHO), 153.4 (d, *J* 5.3, ArCC), 192.6 (CHO); *m/z* (ES^+) 625 (2M + Na^+), 324.0970 (100 %, MNa^+, $C_{13}H_{20}NO_5PNa$ requires 324.0977).



Diethyl (*E*)-5-oxo-1-phenyl-3-pentenylphosphonamide 156

CuOTf.Tol (39 mg, 0.08 mmol) was added to a stirred solution of imine **142a** (0.20 g, 0.83 mmol) in dry MeCN (5 ml) under argon. Diene **61** (1.45 mmol) was added at room temperature causing the reaction mixture to turn from a green suspension to a yellow homogeneous solution within a minute. After overnight stirring, 5% HCl (2 ml), and brine (15 ml) were added, followed by DCM (30 ml) and the phases separated. The aqueous phase was extracted three times with DCM, and the combined organic extracts washed once with brine, dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford crude product as a brown oil. Silica gel chromatography (hexane : EtOAc gradient) afforded a pale yellow oil which formed crystals on standing overnight. Recrystallisation from Et_2O/hexane gave the product **156** as a white crystalline solid (120 mg, 46 %); m.p. 89 °C; ν_{max} (neat)/cm^{-1} *inter alia* 1684 (C=O), 1613 (C=C), 1225 (P=O), 1059 (P-OEt), 1030 (P-OEt); δ_H (500 MHz; $CDCl_3$) 1.08 (3H, dt, *J* 0.8 and 7.2, OCH_2CH_3), 1.28 (3H, dt, *J* 0.8 and 7.2, OCH_2CH_3), 2.73 – 2.87 (2H, m, $NHCHCH_2$), 3.57 (1H, bt, *J* 10.2, NH, *exchanges with D_2O*), 3.62 – 3.73 (1H, m, OCH_2CH_3), 3.86 – 3.96 (1H, m, OCH_2CH_3), 3.96 – 4.06 (2H, m, OCH_2CH_3), 4.30 – 4.39 (1H, m, NHCH), 6.12 (1H, ddd, *J* 1.2, 8.0 and 15.6, =CHCHO), 6.74 (1H, dtd, *J* 0.8, 7.2 and 15.6, CH=CHCHO), 7.24 – 7.37 (5H, m, ArCH), 9.44 (1H, dd, *J* 1.0 and 8.0, CHO); δ_p (161.9 MHz; $CDCl_3$) 8.07; δ_C (100.6 MHz; $CDCl_3$) 16.1 (d, *J* 7.1, OCH_2CH_3), 16.4 (d, *J* 7.1, OCH_2CH_3), 42.1 (d, *J* 6.9, $NHCHCH_2$), 55.3 (NHCH), 62.6 (d, *J* 20.3, OCH_2CH_3), 62.7 (d, *J* 20.3, OCH_2CH_3), 126.3 (*o*-ArCH), 128.0 (*p*-ArCH), 129.0 (*m*-ArCH), 135.4 (=CHCHO), 142.7 (d, *J* 3.9, ArCC), 153.7 (CH=CHCHO), 193.9 (CHO); *m/z* (ES^+) 645 (2M + Na^+), 334 (100 %, MNa^+). $C_{15}H_{22}NO_4P$ requires C, 57.87; H, 7.12; N, 4.50; Found C, 57.80; H, 7.14; N, 4.51 %.



Diethyl 3-oxo-1-phenyl-4-pentenylphosphonamide 157

$BF_3.OEt_2$ (0.1 ml, 0.80 mmol) was added to a stirred solution of imine **142a** (0.20 g, 0.83 mmol) in dry MeCN (5 ml) under argon. Diene **94** (1.45 mmol) was added at room temperature and stirred overnight, during which time the reaction mixture had changed from colourless to yellow. Brine (15 ml) and EtOAc (30 ml) were added, and the two separated. The aqueous phase was extracted three times with EtOAc, and the combined organic extracts dried ($MgSO_4$) and evaporated to dryness *in vacuo* to afford crude product as a light orange oil. Silica gel chromatography (hexane : EtOAc gradient) afforded the product **157** (158 mg, 61 %) as a colourless oil which formed white crystals on standing overnight; m.p. 43-55°C; ν_{max} (neat)/cm^{-1} *inter alia* 1679 (C=O), 1639 (C=C), 1247 (P=O), 1224 (P=O), 1059 (P-OEt), 1030 (P-OEt); δ_H (500 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.0, $C\underline{H}_3CH_2O$), 1.22 (3H, t, *J* 7.0, $C\underline{H}_3CH_2O$), 2.98 (1H, unsymm. dd, *J* 6.0 and 16.5, NHCHC$\underline{H}$H), 3.12 (1H, unsymm. dd, *J* 6.0 and 16.5, NHCHCH$\underline{H}$), 3.60 - 3.69 (1H, m, $CH_3C\underline{H}_2O$), 3.77 (1H, bt, *J* 10.0, N$\underline{H}$, *exchanges with* D_2O), 3.81 - 4.00 (3H, m, $CH_3C\underline{H}_2O$), 4.59 - 4.66 (1H, m, NHC$\underline{H}$CHH), 5.75 [1H, unsymm. dd, *J* 10.5, C(O)CH=C$\underline{H}$H], 6.10 [1H, unsymm. dd, *J* 18.0, C(O)CH=CH$\underline{H}$], 6.21 [1H, unsymm. dd, *J* 10.5 and 18.0, C(O)C$\underline{H}$=CHH], 7.14 - 7.29 (5H, m, ArC$\underline{H}$); δ_p (81.0 MHz; $CDCl_3$) 8.18; δ_C (100.6 MHz; $CDCl_3$) 14.9 (d, *J* 7.0, $OCH_2\underline{C}H_3$), 15.2 (d, *J* 7.0, $OCH_2\underline{C}H_3$), 46.1 (d, *J* 7.0, NHCH$\underline{C}H_2$), 51.3 (NH$\underline{C}HCH_2$), 61.3 (d, *J* 21.0, $O\underline{C}H_2CH_3$), 61.4 (d, *J* 21.0, $O\underline{C}H_2CH_3$), 125.3 (*o*-Ar$\underline{C}$H), 126.4 (*p*-Ar$\underline{C}$H), 127.5 (*m*-Ar$\underline{C}$H), 128.0 [C(O)$\underline{C}$H=CH_2], 135.6 [C(O)CH=$\underline{C}H_2$], 141.7 (d, *J* 4.0, Ar$\underline{C}$C), 197.4 ($\underline{C}$=O); *m/z* (ES^+) 645 (2M + Na^+), 334 (100 %, MNa^+), 242 (MNa^+ - 2EtOH). $C_{15}H_{22}NO_4P$ requires C, 57.87; H, 7.12; N, 4.50; Found C, 58.13; H, 7.12; N, 4.21 %.

Tetrakis(acetonitrile) copper(I) perchlorate

Copper(I) oxide (4.0 g, 28 mmol), acetonitrile (80 ml) and 2 molar $HClO_{4(aq)}$ (30 ml), were heated to 100 °C under argon, with stirring, behind a blast screen. When the red copper oxide was no longer visible, heating was stopped, and the reaction mixture allowed to cool under an argon atmosphere. After cooling to 0 °C, the newly formed white solid was filtered under a stream of argon, and the crystals dried under vacuum to give 7.481 g (55 %) of tetrakis(acetonitrile) copper(I) perchlorate as a white powdery solid which was stored under argon in the freezer.[77]

Appendices

Appendix 1

Crystallographic data for compound 77

Table 7. Crystal data and structure refinement for 02srv184.

Identification code	02srv184	
Empirical formula	C18 H21 N O4	
Formula weight	315.36	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.2885(4) Å	α= 67.610(2)°.
	b = 9.7175(4) Å	β= 83.860(2)°.
	c = 10.1841(5) Å	γ = 66.887(2)°.
Volume	780.73(6) $Å^3$	
Z	2	
Density (calculated)	1.341 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	336	
Crystal size	0.3 x 0.08 x 0.06 mm^3	
Theta range for data collection	2.17 to 30.01°.	
Index ranges	-11<=h<=13, -12<=k<=13, -14<=l<=14	
Reflections collected	7014	
Independent reflections	4517 [R(int) = 0.0248]	
Completeness to theta = 30.01°	99.0 %	
Absorption correction	None	
Max. and min. transmission	. and .	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4517 / 0 / 209	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0490, wR2 = 0.1329	
R indices (all data)	R1 = 0.0735, wR2 = 0.1433	
Largest diff. peak and hole	0.478 and -0.282 $e.Å^{-3}$	

Table 8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 02srv184. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4904(1)	3294(1)	11818(1)	28(1)
O(2)	8416(1)	2510(1)	7219(1)	26(1)
O(3)	8836(1)	1865(1)	5278(1)	27(1)
N(1)	8328(1)	-588(1)	8792(1)	20(1)
O(4)	9965(1)	-2909(1)	8560(1)	31(1)
C(5)	7413(2)	355(2)	9601(1)	19(1)
C(7)	5002(2)	2385(2)	9869(2)	20(1)
C(6)	5877(2)	1396(2)	9127(1)	19(1)
C(3)	7207(2)	1311(2)	11506(2)	22(1)
C(4)	8080(2)	339(2)	10778(2)	20(1)
C(12)	6253(2)	503(2)	6978(2)	22(1)
C(2)	5663(2)	2347(2)	11052(2)	21(1)
C(8)	5146(2)	1517(2)	7808(2)	21(1)
C(14)	8417(2)	1658(2)	6619(1)	21(1)
C(13)	7983(2)	184(2)	7249(1)	21(1)
C(17)	9229(2)	-2210(2)	9343(2)	22(1)
C(18)	9283(2)	-3124(2)	10922(2)	24(1)
C(11)	5654(2)	1484(2)	5405(2)	27(1)
C(9)	4528(2)	3193(2)	6671(2)	26(1)
C(15)	9271(2)	3250(2)	4525(2)	30(1)
C(1)	3324(2)	4400(2)	11371(2)	29(1)
C(10)	4800(2)	3171(2)	5379(2)	29(1)
C(16)	10949(2)	2873(2)	4870(2)	37(1)

Table 9. Bond lengths [Å] and angles [°] for 02srv184.

O(1)-C(2)	1.3687(16)	C(9)-H(9A)	0.9500
O(1)-C(1)	1.4304(18)	C(15)-C(16)	1.502(2)
O(2)-C(14)	1.2026(17)	C(15)-H(15A)	0.9900
O(3)-C(14)	1.3398(17)	C(15)-H(15B)	0.9900
O(3)-C(15)	1.4618(18)	C(1)-H(1A)	0.9800
N(1)-C(17)	1.3753(17)	C(1)-H(1B)	0.9800
N(1)-C(5)	1.4331(17)	C(1)-H(1C)	0.9800
N(1)-C(13)	1.4685(18)	C(10)-H(10A)	0.9500
O(4)-C(17)	1.2235(17)	C(16)-H(16A)	0.9800
C(5)-C(6)	1.3911(19)	C(16)-H(16B)	0.9800
C(5)-C(4)	1.3988(19)	C(16)-H(16C)	0.9800
C(7)-C(2)	1.391(2)		
C(7)-C(6)	1.4016(19)	C(2)-O(1)-C(1)	117.78(11)
C(7)-H(7A)	0.9500	C(14)-O(3)-C(15)	116.12(11)
C(6)-C(8)	1.5140(19)	C(17)-N(1)-C(5)	125.44(11)
C(3)-C(4)	1.3793(19)	C(17)-N(1)-C(13)	117.85(11)
C(3)-C(2)	1.3922(19)	C(5)-N(1)-C(13)	115.30(11)
C(3)-H(3A)	0.9500	C(6)-C(5)-C(4)	120.04(12)
C(4)-H(4A)	0.9500	C(6)-C(5)-N(1)	118.72(12)
C(12)-C(11)	1.547(2)	C(4)-C(5)-N(1)	121.03(12)
C(12)-C(13)	1.547(2)	C(2)-C(7)-C(6)	120.68(12)
C(12)-C(8)	1.5476(19)	C(2)-C(7)-H(7A)	119.7
C(12)-H(12A)	1.0000	C(6)-C(7)-H(7A)	119.7
C(8)-C(9)	1.5147(19)	C(5)-C(6)-C(7)	119.04(12)
C(8)-H(8A)	1.0000	C(5)-C(6)-C(8)	121.55(12)
C(14)-C(13)	1.524(2)	C(7)-C(6)-C(8)	119.39(12)
C(13)-H(13A)	1.0000	C(4)-C(3)-C(2)	120.09(13)
C(17)-C(18)	1.507(2)	C(4)-C(3)-H(3A)	120.0
C(18)-H(18A)	0.9756	C(2)-C(3)-H(3A)	120.0
C(18)-H(18B)	0.9756	C(3)-C(4)-C(5)	120.47(13)
C(18)-H(18C)	0.9756	C(3)-C(4)-H(4A)	119.8
C(18)-H(18D)	0.9756	C(5)-C(4)-H(4A)	119.8
C(18)-H(18E)	0.9756	C(11)-C(12)-C(13)	113.79(12)
C(18)-H(18F)	0.9756	C(11)-C(12)-C(8)	104.77(11)
C(11)-C(10)	1.506(2)	C(13)-C(12)-C(8)	111.03(11)
C(11)-H(11A)	0.9900	C(11)-C(12)-H(12A)	109.0
C(11)-H(11B)	0.9900	C(13)-C(12)-H(12A)	109.0
C(9)-C(10)	1.320(2)	C(8)-C(12)-H(12A)	109.0

O(1)-C(2)-C(7)	124.42(12)	C(17)-C(18)-H(18F)	109.5
O(1)-C(2)-C(3)	115.92(12)	H(18A)-C(18)-H(18F)	56.3
C(7)-C(2)-C(3)	119.65(13)	H(18B)-C(18)-H(18F)	56.3
C(6)-C(8)-C(9)	114.64(11)	H(18C)-C(18)-H(18F)	141.1
C(6)-C(8)-C(12)	115.57(11)	H(18D)-C(18)-H(18F)	109.5
C(9)-C(8)-C(12)	102.39(11)	H(18E)-C(18)-H(18F)	109.5
C(6)-C(8)-H(8A)	107.9	C(10)-C(11)-C(12)	102.88(12)
C(9)-C(8)-H(8A)	107.9	C(10)-C(11)-H(11A)	111.2
C(12)-C(8)-H(8A)	107.9	C(12)-C(11)-H(11A)	111.2
O(2)-C(14)-O(3)	123.99(13)	C(10)-C(11)-H(11B)	111.2
O(2)-C(14)-C(13)	126.16(13)	C(12)-C(11)-H(11B)	111.2
O(3)-C(14)-C(13)	109.83(11)	H(11A)-C(11)-H(11B)	109.1
N(1)-C(13)-C(14)	111.14(11)	C(10)-C(9)-C(8)	112.07(13)
N(1)-C(13)-C(12)	107.52(11)	C(10)-C(9)-H(9A)	124.0
C(14)-C(13)-C(12)	115.32(11)	C(8)-C(9)-H(9A)	124.0
N(1)-C(13)-H(13A)	107.5	O(3)-C(15)-C(16)	111.56(13)
C(14)-C(13)-H(13A)	107.5	O(3)-C(15)-H(15A)	109.3
C(12)-C(13)-H(13A)	107.5	C(16)-C(15)-H(15A)	109.3
O(4)-C(17)-N(1)	120.46(13)	O(3)-C(15)-H(15B)	109.3
O(4)-C(17)-C(18)	120.29(13)	C(16)-C(15)-H(15B)	109.3
N(1)-C(17)-C(18)	119.25(12)	H(15A)-C(15)-H(15B)	108.0
C(17)-C(18)-H(18A)	109.5	O(1)-C(1)-H(1A)	109.5
C(17)-C(18)-H(18B)	109.5	O(1)-C(1)-H(1B)	109.5
H(18A)-C(18)-H(18B)	109.5	H(1A)-C(1)-H(1B)	109.5
C(17)-C(18)-H(18C)	109.5	O(1)-C(1)-H(1C)	109.5
H(18A)-C(18)-H(18C)	109.5	H(1A)-C(1)-H(1C)	109.5
H(18B)-C(18)-H(18C)	109.5	H(1B)-C(1)-H(1C)	109.5
C(17)-C(18)-H(18D)	109.5	C(9)-C(10)-C(11)	111.92(13)
H(18A)-C(18)-H(18D)	141.1	C(9)-C(10)-H(10A)	124.0
H(18B)-C(18)-H(18D)	56.3	C(11)-C(10)-H(10A)	124.0
H(18C)-C(18)-H(18D)	56.3	C(15)-C(16)-H(16A)	109.5
C(17)-C(18)-H(18E)	109.5	C(15)-C(16)-H(16B)	109.5
H(18A)-C(18)-H(18E)	56.3	H(16A)-C(16)-H(16B)	109.5
H(18B)-C(18)-H(18E)	141.1	C(15)-C(16)-H(16C)	109.5
H(18C)-C(18)-H(18E)	56.3	H(16A)-C(16)-H(16C)	109.5
H(18D)-C(18)-H(18E)	109.5	H(16B)-C(16)-H(16C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 10. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 02srv184. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	29(1)	29(1)	-18(1)	1(1)	-3(1)
O(2)	33(1)	27(1)	23(1)	-12(1)	5(1)	-14(1)
O(3)	38(1)	27(1)	20(1)	-11(1)	8(1)	-16(1)
N(1)	22(1)	18(1)	19(1)	-8(1)	2(1)	-5(1)
O(4)	37(1)	21(1)	29(1)	-12(1)	6(1)	-6(1)
C(5)	20(1)	16(1)	20(1)	-6(1)	3(1)	-6(1)
C(7)	18(1)	18(1)	23(1)	-6(1)	1(1)	-5(1)
C(6)	20(1)	18(1)	19(1)	-6(1)	1(1)	-8(1)
C(3)	23(1)	23(1)	20(1)	-8(1)	1(1)	-9(1)
C(4)	19(1)	19(1)	20(1)	-6(1)	1(1)	-6(1)
C(12)	28(1)	19(1)	21(1)	-7(1)	0(1)	-11(1)
C(2)	23(1)	20(1)	22(1)	-9(1)	5(1)	-8(1)
C(8)	21(1)	21(1)	21(1)	-6(1)	-1(1)	-9(1)
C(14)	20(1)	22(1)	19(1)	-8(1)	1(1)	-6(1)
C(13)	26(1)	20(1)	18(1)	-8(1)	1(1)	-8(1)
C(17)	21(1)	20(1)	25(1)	-9(1)	2(1)	-8(1)
C(18)	25(1)	19(1)	23(1)	-6(1)	-1(1)	-6(1)
C(11)	33(1)	28(1)	23(1)	-9(1)	-3(1)	-13(1)
C(9)	28(1)	21(1)	26(1)	-7(1)	-5(1)	-6(1)
C(15)	42(1)	26(1)	22(1)	-8(1)	8(1)	-18(1)
C(1)	24(1)	26(1)	35(1)	-15(1)	4(1)	-4(1)
C(10)	34(1)	26(1)	25(1)	-5(1)	-5(1)	-13(1)
C(16)	40(1)	41(1)	40(1)	-21(1)	13(1)	-22(1)

Table 11. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 02srv184.

	x	y	z	U(eq)
H(7A)	3947	3089	9562	25
H(3A)	7661	1274	12318	26
H(4A)	9141	-347	11079	24
H(12A)	6129	-551	7294	27
H(8A)	4249	1158	8102	26
H(13A)	8652	-610	6816	26
H(18A)	9968(9)	-4252(14)	11145(3)	36
H(18B)	8230(13)	-3048(2)	11218(4)	36
H(18C)	9688(5)	-2662(6)	11424(7)	36
H(18D)	8622(8)	-2390(9)	11380(6)	36
H(18E)	10360(14)	-3594(6)	11307(5)	36
H(18F)	8902(5)	-3979(11)	11101(3)	36
H(11A)	6535	1423	4762	32
H(11B)	4938	1096	5129	32
H(9A)	4006	4149	6866	31
H(15A)	8579	4168	4792	35
H(15B)	9114	3572	3488	35
H(1A)	2922	4999	12006	43
H(1B)	2672	3803	11405	43
H(1C)	3297	5155	10396	43
H(10A)	4493	4107	4533	34
H(16A)	11201	3824	4349	56
H(16B)	11637	1977	4591	56
H(16C)	11102	2573	5894	56

Appendix 2

Crystallographic data for compound 80

Table 1. Crystal data and structure refinement for aw07b.

Identification code	a	
Empirical formula	C17 H19 N O5	
Formula weight	317.33	
Temperature	293(2) K	
Wavelength	1.54078 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 7.959(14) Å	α= 90°.
	b = 16.440(14) Å	β= 90°.
	c = 12.342(13) Å	γ = 90°.
Volume	1615(4) $Å^3$	
Z	4	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.801 mm^{-1}	
F(000)	672	
Crystal size	0.40 x 0.40 x 0.40 mm^3	
Theta range for data collection	4.48 to 60.70°.	
Index ranges	-5<=h<=8, -18<=k<=18, -13<=l<=13	
Reflections collected	5069	
Independent reflections	2397 [R(int) = 0.0652]	
Completeness to theta = 60.70°	98.1 %	
Absorption correction	None	
Max. and min. transmission	0.7400 and 0.7400	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2397 / 0 / 299	
Goodness-of-fit on F^2	1.025	
Final R indices [I>2sigma(I)]	R1 = 0.0540, wR2 = 0.1273	
R indices (all data)	R1 = 0.0849, wR2 = 0.1463	
Extinction coefficient	0.0384(17)	
Largest diff. peak and hole	0.225 and -0.251 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for aw07b. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	9527(2)	6277(1)	5331(2)	90(1)
O(2)	7501(2)	7154(1)	5741(1)	55(1)
O(3A)	7440(4)	2198(2)	5546(2)	65(1)
O(4)	5529(2)	1764(1)	6743(1)	85(1)
O(5)	1182(2)	3647(1)	7972(1)	65(1)
N(1)	5589(2)	5965(1)	6502(1)	50(1)
C(2)	6997(2)	5755(1)	6032(2)	52(1)
C(3A)	7639(5)	4969(2)	6107(3)	53(1)
C(4A)	6696(5)	4340(2)	6459(3)	49(1)
C(5)	3805(2)	3930(1)	7082(2)	59(1)
C(6)	2355(2)	4159(1)	7561(2)	52(1)
C(7)	1959(3)	4984(1)	7658(2)	70(1)
C(8)	3028(2)	5564(1)	7321(2)	65(1)
C(9)	4560(2)	5352(1)	6831(1)	47(1)
C(10)	4945(2)	4520(1)	6702(2)	57(1)
C(11)	8147(2)	6412(1)	5670(2)	56(1)
C(12)	8591(3)	7817(1)	5436(2)	65(1)
C(13)	7609(3)	8576(1)	5401(2)	80(1)
C(15A)	7389(5)	3455(3)	6483(3)	58(1)
C(16A)	6724(6)	3036(3)	5531(4)	70(1)
C(17)	6757(3)	1624(1)	6216(2)	66(1)
C(18)	7380(3)	815(1)	5893(2)	84(1)
C(19)	1496(3)	2799(1)	7906(2)	69(1)
O(3B)	8008(3)	2189(2)	6160(2)	49(1)
C(3B)	7300(5)	4935(2)	5637(3)	43(1)
C(4B)	6251(4)	4317(2)	5928(3)	37(1)
C(15B)	6646(5)	3471(2)	5616(3)	41(1)
C(16B)	7609(5)	2981(2)	6486(3)	47(1)

Table 3. Bond lengths [Å] and angles [°] for aw07b.

O(1)-C(11)	1.196(3)	C(3A)-C(2)-C(3B)	26.0(2)
O(2)-C(11)	1.327(2)	N(1)-C(2)-C(11)	118.05(17)
O(2)-C(12)	1.443(3)	C(3A)-C(2)-C(11)	117.9(2)
O(3A)-C(17)	1.367(3)	C(3B)-C(2)-C(11)	118.1(2)
O(3A)-C(16A)	1.491(5)	C(4A)-C(3A)-C(2)	121.9(3)
O(4)-C(17)	1.197(3)	C(3A)-C(4A)-C(10)	116.3(3)
O(5)-C(6)	1.356(2)	C(3A)-C(4A)-C(15A)	121.7(3)
O(5)-C(19)	1.419(3)	C(10)-C(4A)-C(15A)	121.7(3)
N(1)-C(2)	1.308(3)	C(6)-C(5)-C(10)	120.27(19)
N(1)-C(9)	1.360(2)	C(5)-C(6)-O(5)	125.38(18)
C(2)-C(3A)	1.392(4)	C(5)-C(6)-C(7)	120.09(17)
C(2)-C(3B)	1.454(5)	O(5)-C(6)-C(7)	114.54(17)
C(2)-C(11)	1.484(3)	C(8)-C(7)-C(6)	121.3(2)
C(3A)-C(4A)	1.350(6)	C(7)-C(8)-C(9)	120.40(19)
C(4A)-C(10)	1.456(5)	N(1)-C(9)-C(8)	117.86(17)
C(4A)-C(15A)	1.556(6)	N(1)-C(9)-C(10)	123.58(17)
C(5)-C(6)	1.350(3)	C(8)-C(9)-C(10)	118.56(16)
C(5)-C(10)	1.409(3)	C(5)-C(10)-C(9)	119.33(18)
C(6)-C(7)	1.397(3)	C(5)-C(10)-C(4B)	121.5(2)
C(7)-C(8)	1.344(3)	C(9)-C(10)-C(4B)	116.9(2)
C(8)-C(9)	1.405(3)	C(5)-C(10)-C(4A)	123.1(2)
C(9)-C(10)	1.411(3)	C(9)-C(10)-C(4A)	115.4(2)
C(10)-C(4B)	1.450(4)	C(4B)-C(10)-C(4A)	29.74(17)
C(12)-C(13)	1.472(3)	O(1)-C(11)-O(2)	123.34(18)
C(15A)-C(16A)	1.462(6)	O(1)-C(11)-C(2)	122.42(19)
C(17)-O(3B)	1.364(3)	O(2)-C(11)-C(2)	114.23(17)
C(17)-C(18)	1.474(3)	O(2)-C(12)-C(13)	109.2(2)
O(3B)-C(16B)	1.399(4)	C(16A)-C(15A)-C(4A)	107.3(4)
C(3B)-C(4B)	1.363(6)	C(15A)-C(16A)-O(3A)	106.7(4)
C(4B)-C(15B)	1.476(5)	O(4)-C(17)-O(3B)	119.6(2)
C(15B)-C(16B)	1.546(5)	O(4)-C(17)-O(3A)	121.4(2)
		O(3B)-C(17)-O(3A)	37.68(15)
C(11)-O(2)-C(12)	116.39(17)	O(4)-C(17)-C(18)	126.5(2)
C(17)-O(3A)-C(16A)	119.6(3)	O(3B)-C(17)-C(18)	110.8(2)
C(6)-O(5)-C(19)	117.86(16)	O(3A)-C(17)-C(18)	109.0(2)
C(2)-N(1)-C(9)	116.97(16)	C(17)-O(3B)-C(16B)	117.0(3)
N(1)-C(2)-C(3A)	122.0(2)	C(4B)-C(3B)-C(2)	120.1(3)
N(1)-C(2)-C(3B)	122.3(2)	C(3B)-C(4B)-C(10)	116.2(3)

C(3B)-C(4B)-C(15B)	120.2(3)	C(4B)-C(15B)-C(16B)	114.5(3)
C(10)-C(4B)-C(15B)	122.7(3)	O(3B)-C(16B)-C(15B)	113.4(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for aw07b. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	62(1)	61(1)	147(1)	2(1)	54(1)	2(1)
O(2)	47(1)	43(1)	76(1)	4(1)	17(1)	-3(1)
O(3A)	64(2)	42(1)	88(2)	-5(1)	26(2)	5(1)
O(4)	68(1)	77(1)	110(1)	2(1)	32(1)	-10(1)
O(5)	50(1)	49(1)	96(1)	6(1)	22(1)	-6(1)
N(1)	46(1)	41(1)	64(1)	1(1)	15(1)	0(1)
C(2)	46(1)	45(1)	66(1)	2(1)	17(1)	3(1)
C(3A)	44(2)	49(2)	67(3)	-4(2)	21(2)	6(2)
C(4A)	47(2)	38(2)	62(2)	0(2)	13(2)	13(2)
C(5)	55(1)	40(1)	84(1)	4(1)	22(1)	4(1)
C(6)	42(1)	45(1)	68(1)	5(1)	9(1)	-4(1)
C(7)	51(1)	52(1)	106(2)	2(1)	33(1)	3(1)
C(8)	55(1)	40(1)	101(2)	-2(1)	32(1)	5(1)
C(9)	43(1)	42(1)	55(1)	1(1)	11(1)	1(1)
C(10)	48(1)	38(1)	83(1)	2(1)	24(1)	5(1)
C(11)	49(1)	48(1)	70(1)	1(1)	20(1)	2(1)
C(12)	62(1)	54(1)	81(1)	2(1)	24(1)	-11(1)
C(13)	83(2)	50(1)	106(2)	18(1)	23(1)	0(1)
C(15A)	44(2)	70(3)	61(2)	1(2)	10(2)	4(2)
C(16A)	67(2)	64(3)	78(3)	3(2)	14(2)	4(2)
C(17)	65(1)	49(1)	83(1)	1(1)	12(1)	-4(1)
C(18)	94(2)	51(1)	107(2)	3(1)	7(2)	4(1)
C(19)	61(1)	49(1)	96(2)	12(1)	9(1)	-8(1)
O(3B)	40(1)	41(1)	64(2)	6(1)	0(1)	7(1)
C(3B)	46(2)	46(2)	37(2)	-5(2)	9(2)	5(2)
C(4B)	38(2)	41(2)	33(2)	0(2)	-3(2)	3(2)
C(15B)	43(2)	36(2)	43(2)	-2(2)	6(2)	3(2)
C(16B)	49(2)	30(2)	64(2)	-2(2)	1(2)	7(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for aw07b.

	x	y	z	U(eq)
H(3A)	8750	4876	5909	64
H(15A)	8608	3460	6464	70
H(15B)	7031	3181	7140	70
H(16A)	7055	3318	4874	83
H(16B)	5507	3015	5560	83
H(18A)	8390	876	5475	126
H(18B)	6543	545	5464	126
H(18C)	7614	498	6529	126
H(18D)	6641	404	6170	126
H(18E)	8488	735	6181	126
H(18F)	7418	781	5117	126
H(5)	4040(30)	3396(14)	7031(17)	79(7)
H(7)	940(30)	5101(14)	8069(18)	97(8)
H(8)	2810(30)	6149(13)	7328(16)	72(6)
H(12B)	9000(30)	7659(13)	4819(15)	66(6)
H(12A)	9490(30)	7829(14)	6066(19)	98(8)
H(13C)	8260(30)	9046(14)	5207(18)	84(7)
H(13B)	6800(40)	8451(18)	4790(30)	144(12)
H(13A)	6990(40)	8636(16)	6050(20)	110(9)
H(19B)	2470(30)	2613(14)	8256(16)	78(7)
H(19C)	580(30)	2532(17)	8180(18)	95(8)
H(19A)	1670(30)	2626(15)	7193(18)	83(7)
H(3B)	8210	4832	5185	52
H(15C)	7311	3481	4958	49
H(15D)	5604	3191	5454	49
H(16C)	8640	3267	6663	57
H(16D)	6932	2955	7138	57

Table 6. Torsion angles [°] for aw07b.

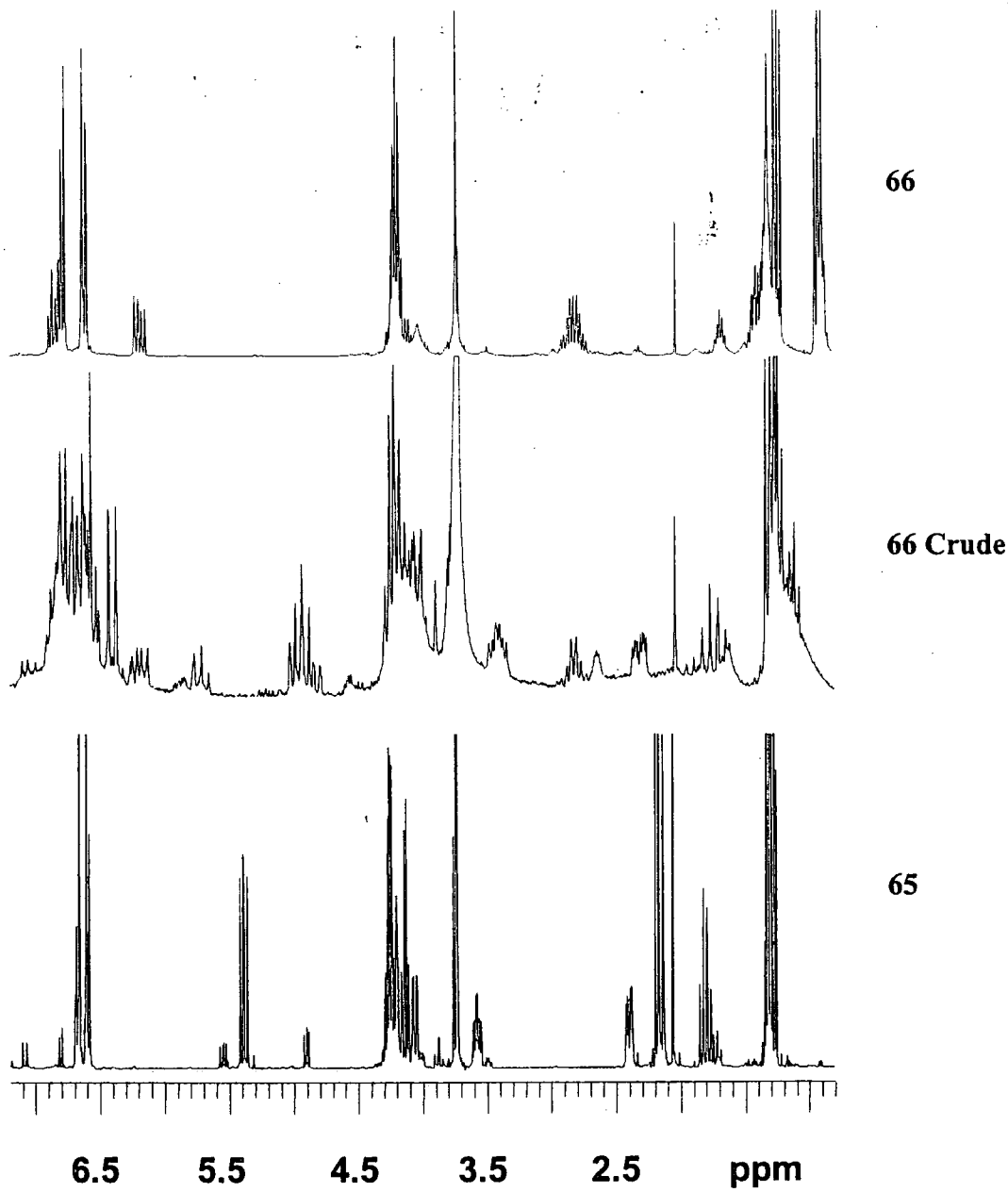
C(9)-N(1)-C(2)-C(3A)	-16.3(3)
C(9)-N(1)-C(2)-C(3B)	14.5(3)
C(9)-N(1)-C(2)-C(11)	-179.67(17)
N(1)-C(2)-C(3A)-C(4A)	14.7(5)
C(3B)-C(2)-C(3A)-C(4A)	-84.5(7)
C(11)-C(2)-C(3A)-C(4A)	178.0(3)
C(2)-C(3A)-C(4A)-C(10)	3.1(6)
C(2)-C(3A)-C(4A)-C(15A)	176.7(3)
C(10)-C(5)-C(6)-O(5)	-178.81(19)
C(10)-C(5)-C(6)-C(7)	1.7(3)
C(19)-O(5)-C(6)-C(5)	0.6(3)
C(19)-O(5)-C(6)-C(7)	-179.9(2)
C(5)-C(6)-C(7)-C(8)	-2.8(4)
O(5)-C(6)-C(7)-C(8)	177.7(2)
C(6)-C(7)-C(8)-C(9)	1.9(4)
C(2)-N(1)-C(9)-C(8)	-178.98(18)
C(2)-N(1)-C(9)-C(10)	0.7(3)
C(7)-C(8)-C(9)-N(1)	179.7(2)
C(7)-C(8)-C(9)-C(10)	0.0(3)
C(6)-C(5)-C(10)-C(9)	0.2(3)
C(6)-C(5)-C(10)-C(4B)	-162.3(2)
C(6)-C(5)-C(10)-C(4A)	162.4(3)
N(1)-C(9)-C(10)-C(5)	179.30(18)
C(8)-C(9)-C(10)-C(5)	-1.0(3)
N(1)-C(9)-C(10)-C(4B)	-17.4(3)
C(8)-C(9)-C(10)-C(4B)	162.3(2)
N(1)-C(9)-C(10)-C(4A)	15.8(3)
C(8)-C(9)-C(10)-C(4A)	-164.5(2)
C(3A)-C(4A)-C(10)-C(5)	-179.7(3)
C(15A)-C(4A)-C(10)-C(5)	6.7(5)
C(3A)-C(4A)-C(10)-C(9)	-16.8(4)
C(15A)-C(4A)-C(10)-C(9)	169.6(3)
C(3A)-C(4A)-C(10)-C(4B)	83.6(5)
C(15A)-C(4A)-C(10)-C(4B)	-90.0(5)
C(12)-O(2)-C(11)-O(1)	-3.2(3)
C(12)-O(2)-C(11)-C(2)	177.76(17)
N(1)-C(2)-C(11)-O(1)	172.5(2)
C(3A)-C(2)-C(11)-O(1)	8.5(4)

C(3B)-C(2)-C(11)-O(1)	-21.0(3)
N(1)-C(2)-C(11)-O(2)	-8.5(3)
C(3A)-C(2)-C(11)-O(2)	-172.5(2)
C(3B)-C(2)-C(11)-O(2)	158.0(2)
C(11)-O(2)-C(12)-C(13)	171.39(19)
C(3A)-C(4A)-C(15A)-C(16A)	-100.5(5)
C(10)-C(4A)-C(15A)-C(16A)	72.8(5)
C(4A)-C(15A)-C(16A)-O(3A)	178.3(3)
C(17)-O(3A)-C(16A)-C(15A)	79.0(4)
C(16A)-O(3A)-C(17)-O(4)	4.7(4)
C(16A)-O(3A)-C(17)-O(3B)	-94.2(4)
C(16A)-O(3A)-C(17)-C(18)	166.0(3)
O(4)-C(17)-O(3B)-C(16B)	-16.2(4)
O(3A)-C(17)-O(3B)-C(16B)	88.0(3)
C(18)-C(17)-O(3B)-C(16B)	-177.6(3)
N(1)-C(2)-C(3B)-C(4B)	-12.6(5)
C(3A)-C(2)-C(3B)-C(4B)	84.9(6)
C(11)-C(2)-C(3B)-C(4B)	-178.5(3)
C(2)-C(3B)-C(4B)-C(10)	-4.7(5)
C(2)-C(3B)-C(4B)-C(15B)	-174.1(3)
C(5)-C(10)-C(4B)-C(3B)	-178.8(3)
C(9)-C(10)-C(4B)-C(3B)	18.3(4)
C(4A)-C(10)-C(4B)-C(3B)	-76.2(5)
C(5)-C(10)-C(4B)-C(15B)	-9.7(4)
C(9)-C(10)-C(4B)-C(15B)	-172.6(3)
C(4A)-C(10)-C(4B)-C(15B)	92.9(5)
C(3B)-C(4B)-C(15B)-C(16B)	94.3(4)
C(10)-C(4B)-C(15B)-C(16B)	-74.3(4)
C(17)-O(3B)-C(16B)-C(15B)	-79.3(4)
C(4B)-C(15B)-C(16B)-O(3B)	-178.4(3)

Symmetry transformations used to generate equivalent atoms:

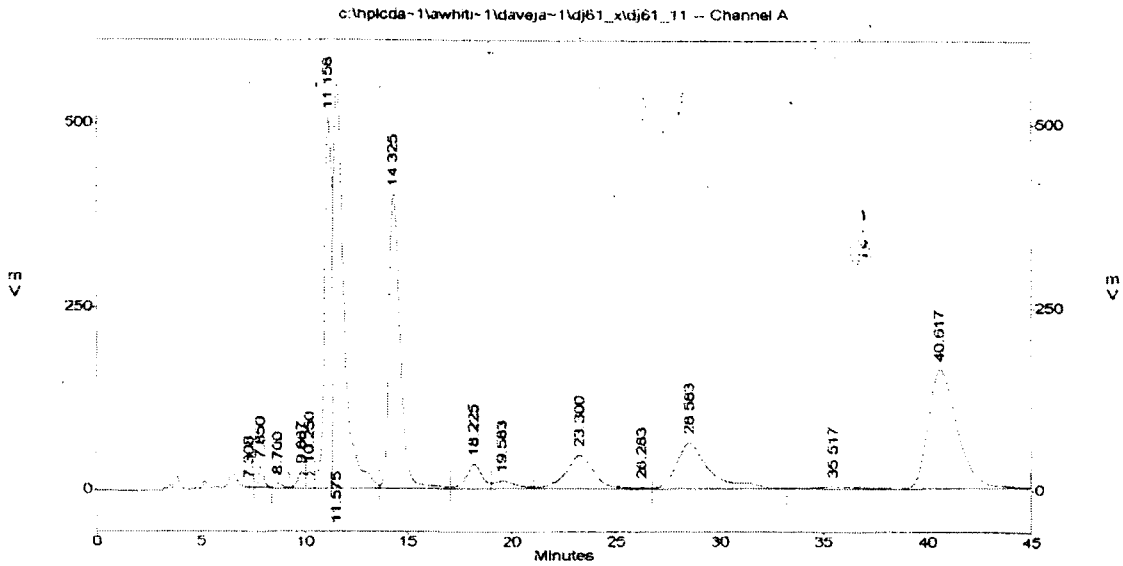
Appendix 3

Comparison of the ^{1}H NMR spectra of compounds 66 (top), crude reaction mixture of 66 (middle) and 65 (bottom)



Appendix 4

Typical example of a chromatogram where one enantiomer is obscured by the impurity found in the reaction screen as detailed in Table 14.



Channel A Results

Pk No.	Ret. Time	Peak Area	Area %
1	7.31	5094	0.01
2	7.85	502812	0.64
3	8.70	154843	0.20
4	9.87	553767	0.70
5	10.25	493802	0.62
6	11.16	12203371	15.41
7	11.57	19915316	25.15
8	14.32	15265734	19.28
9	18.23	1777330	2.24
10	19.58	777872	0.98
11	23.30	4240686	5.36
12	26.28	77334	0.10
13	28.58	6943873	8.77
14	35.52	422368	0.53
15	40.62	15837204	20.00
Totals :		79171408	100.00

Appendix 5

Crystallographic data for compound 156

Table 1. Crystal data and structure refinement for 02srv203.

Identification code	s203	
Empirical formula	C_{15} H_{22} N O_4 P	
Formula weight	311.31	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 5.2493(2) Å	□= 90°.
	b = 32.851(9) Å	□= 102.27(1)°.
	c = 9.9222(3) Å	□ = 90°.
Volume	1672.0(1) $Å^3$	
Z	4	
Density (calculated)	1.237 Mg/m^3	
Absorption coefficient	0.178 mm^{-1}	
F(000)	664	
Crystal size	0.24 x 0.14 x 0.06 mm^3	
Theta range for data collection	2.19 to 27.49°.	
Index ranges	-6<=h<=6, -42<=k<=42, -12<=l<=12	
Reflections collected	13662	
Independent reflections	3836 [R(int) = 0.0749]	
Completeness to theta = 27.49°	99.9 %	
Absorption correction	None	
Max. and min. transmission	0.9894 and 0.9584	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3836 / 0 / 233	
Goodness-of-fit on F^2	1.085	
Final R indices [I>2sigma(I)]	R1 = 0.0682, wR2 = 0.1806	
R indices (all data)	R1 = 0.1206, wR2 = 0.1960	
Largest diff. peak and hole	0.452 and -0.295 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 02srv203. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
P(1)	4038(2)	1087(1)	3892(1)	50(1)
O(1)	1829(4)	999(1)	4535(3)	75(1)
O(2)	4674(4)	750(1)	2898(2)	64(1)
O(3)	3583(5)	1463(1)	2910(2)	75(1)
O(4)	10260(17)	2736(3)	3151(9)	101(3)
O(4')	9582(17)	2699(3)	2809(9)	95(3)
N(1)	6707(5)	1173(1)	4979(3)	53(1)
C(1)	6800(6)	1382(1)	6294(3)	50(1)
C(2)	8727(7)	1735(1)	6465(4)	57(1)
C(3)	8073(8)	2041(1)	5344(4)	63(1)
C(4)	9593(8)	2231(1)	4688(4)	69(1)
C(5)	8623(10)	2522(1)	3617(4)	84(1)
C(6)	7374(6)	1098(1)	7515(3)	53(1)
C(7)	6023(8)	1124(2)	8555(4)	72(1)
C(8)	6577(11)	872(2)	9689(4)	90(2)
C(9)	8476(10)	590(2)	9818(4)	85(1)
C(10)	9851(10)	560(1)	8812(5)	85(1)
C(11)	9341(8)	807(1)	7662(4)	67(1)
C(14)	4436(17)	317(3)	3006(11)	80(3)
C(15)	7160(16)	171(3)	3654(9)	80(2)
C(14')	5030(20)	343(3)	3648(12)	99(3)
C(15')	6200(20)	53(3)	2900(12)	107(3)
C(12)	1630(20)	1491(3)	1715(11)	91(3)
C(13)	1840(20)	1818(3)	888(11)	94(3)
C(12')	829(16)	1497(3)	2025(8)	61(2)
C(13')	820(20)	1817(4)	1024(11)	97(3)

Table 7. Hydrogen bonds for 02srv203 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(1)#1	0.73(3)	2.15(3)	2.873(3)	170(3)

Symmetry transformations used to generate equivalent atoms: #1 x+1,y,z

Table 3. Bond lengths [Å] and angles [°] for 02srv203.

P(1)-O(1)	1.467(2)	O(4')-C(5)	1.187(9)	C(7)-C(8)	1.377(6)
P(1)-O(3)	1.559(2)	N(1)-C(1)	1.466(4)	C(8)-C(9)	1.348(7)
P(1)-O(2)	1.566(2)	C(1)-C(6)	1.508(4)	C(9)-C(10)	1.354(6)
P(1)-N(1)	1.601(3)	C(1)-C(2)	1.525(5)	C(10)-C(11)	1.380(6)
O(2)-C(14)	1.436(10)	C(2)-C(3)	1.483(5)	C(14)-C(15)	1.515(12)
O(2)-C(14')	1.523(11)	C(3)-C(4)	1.292(5)	C(14')-C(15')	1.426(14)
O(3)-C(12)	1.397(11)	C(4)-C(5)	1.440(5)	C(12)-C(13)	1.370(14)
O(3)-C(12')	1.528(8)	C(6)-C(7)	1.374(4)	C(12')-C(13')	1.448(14)
O(4)-C(5)	1.271(10)	C(6)-C(11)	1.392(5)		

O(1)-P(1)-O(3)	113.49(15)	C(4)-C(3)-C(2)	129.4(4)
O(1)-P(1)-O(2)	115.31(14)	C(3)-C(4)-C(5)	122.2(4)
O(3)-P(1)-O(2)	101.04(13)	O(4')-C(5)-O(4)	20.9(6)
O(1)-P(1)-N(1)	113.67(14)	O(4')-C(5)-C(4)	133.7(6)
O(3)-P(1)-N(1)	106.10(14)	O(4)-C(5)-C(4)	118.4(6)
O(2)-P(1)-N(1)	106.04(14)	C(7)-C(6)-C(11)	117.0(3)
C(14)-O(2)-C(14')	25.3(5)	C(7)-C(6)-C(1)	121.2(3)
C(14)-O(2)-P(1)	128.4(4)	C(11)-C(6)-C(1)	121.8(3)
C(14')-O(2)-P(1)	109.5(4)	C(6)-C(7)-C(8)	121.5(5)
C(12)-O(3)-C(12')	21.9(5)	C(9)-C(8)-C(7)	121.0(4)
C(12)-O(3)-P(1)	124.7(5)	C(8)-C(9)-C(10)	118.6(4)
C(12')-O(3)-P(1)	114.6(3)	C(9)-C(10)-C(11)	121.8(5)
C(1)-N(1)-P(1)	122.8(2)	C(10)-C(11)-C(6)	120.0(4)
N(1)-C(1)-C(6)	112.8(3)	O(2)-C(14)-C(15)	104.8(7)
N(1)-C(1)-C(2)	110.5(3)	C(15')-C(14')-O(2)	110.8(8)
C(6)-C(1)-C(2)	111.6(3)	C(13)-C(12)-O(3)	114.9(9)
C(3)-C(2)-C(1)	112.9(3)	C(13')-C(12')-O(3)	108.1(7)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 02srv203. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	46(1)	57(1)	48(1)	-3(1)	12(1)	1(1)
O(1)	49(1)	104(2)	78(2)	-10(1)	28(1)	-4(1)
O(2)	74(2)	59(2)	62(1)	-6(1)	21(1)	2(1)
O(3)	82(2)	64(2)	68(2)	9(1)	-9(1)	4(1)
N(1)	39(1)	73(2)	51(2)	-3(1)	20(1)	3(1)
C(1)	46(2)	59(2)	47(2)	-4(2)	13(1)	3(1)
C(2)	58(2)	57(2)	56(2)	-1(2)	15(2)	-1(2)
C(3)	55(2)	60(2)	76(2)	9(2)	17(2)	4(2)
C(4)	67(2)	71(3)	72(2)	8(2)	20(2)	-1(2)
C(5)	104(3)	70(3)	85(3)	14(2)	38(3)	-14(2)
C(6)	53(2)	60(2)	45(2)	1(2)	13(1)	-8(2)
C(7)	69(2)	98(3)	51(2)	1(2)	20(2)	3(2)
C(8)	89(3)	130(4)	55(3)	3(3)	26(2)	-20(3)
C(9)	102(3)	90(3)	59(3)	25(2)	10(2)	-22(3)
C(10)	95(3)	66(3)	88(3)	16(2)	7(3)	10(2)
C(11)	74(2)	65(2)	66(2)	11(2)	24(2)	7(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 02srv203.

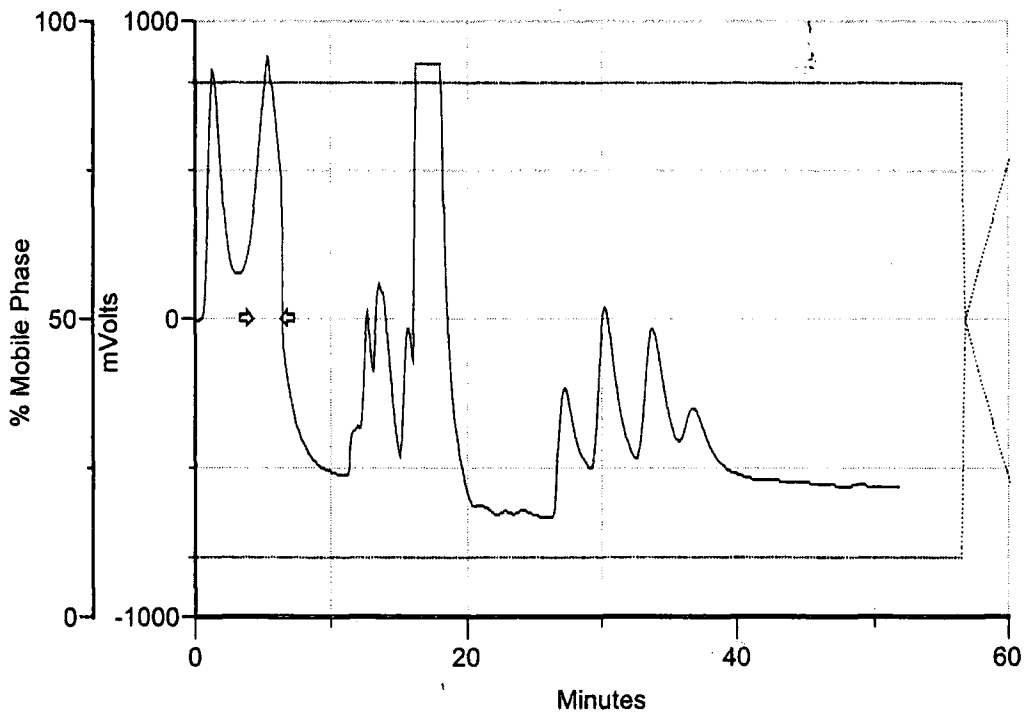
Atom	x	y	z	U(eq)
H(14A)	3822	193	2084	96
H(14B)	3196	246	3594	96
H(15A)	7156	-126	3746	120
H(15B)	7722	295	4567	120
H(15C)	8363	250	3068	120
H(14C)	6138	380	4579	119
H(14D)	3307	241	3758	119
H(15D)	6336	-210	3378	160
H(15E)	7940	147	2838	160
H(15F)	5120	22	1970	160
H(1N)	7960(60)	1141(9)	4780(30)	41(9)
H(1)	5100(70)	1493(10)	6280(30)	68(10)
H(21)	10480(70)	1602(11)	6480(30)	75(10)
H(22)	8830(60)	1861(10)	7420(30)	61(9)
H(3)	6510(80)	2103(12)	5200(40)	89(14)
H(4)	11460(90)	2210(13)	5000(40)	102(14)
H(5)	6320(110)	2506(15)	3400(50)	140(18)
H(7)	4790(80)	1315(13)	8530(40)	86(13)
H(8)	5510(90)	886(14)	10180(50)	107(16)
H(9)	9000(60)	418(10)	10650(30)	62(9)
H(10)	11120(70)	408(12)	8830(40)	68(12)
H(11)	10220(70)	795(12)	6990(40)	87(13)
H(12A)	1644	1238	1171	109
H(12D)	-81	1505	1985	109
H(13A)	376	1817	89	141
H(13B)	3483	1799	572	141
H(13C)	1813	2070	1411	141
H(12B)	309	1235	1549	73
H(12C)	-425	1561	2612	73
H(13D)	-932	1846	450	145
H(13E)	2050	1749	439	145
H(13F)	1352	2074	1505	145

Table 6. Torsion angles [°] for 02srv203.

O(1)-P(1)-O(2)-C(14)	-34.4(5)	C(3)-C(4)-C(5)-O(4)	170.5(6)
O(3)-P(1)-O(2)-C(14)	-157.2(5)	N(1)-C(1)-C(6)-C(7)	-136.6(3)
N(1)-P(1)-O(2)-C(14)	92.3(5)	C(2)-C(1)-C(6)-C(7)	98.3(4)
O(1)-P(1)-O(2)-C(14')	-53.7(5)	N(1)-C(1)-C(6)-C(11)	45.5(4)
O(3)-P(1)-O(2)-C(14')	-176.5(5)	C(2)-C(1)-C(6)-C(11)	-79.6(4)
N(1)-P(1)-O(2)-C(14')	73.0(5)	C(11)-C(6)-C(7)-C(8)	-0.4(6)
O(1)-P(1)-O(3)-C(12)	-62.2(6)	C(1)-C(6)-C(7)-C(8)	-178.4(4)
O(2)-P(1)-O(3)-C(12)	61.8(6)	C(6)-C(7)-C(8)-C(9)	0.0(7)
N(1)-P(1)-O(3)-C(12)	172.2(6)	C(7)-C(8)-C(9)-C(10)	0.5(7)
O(1)-P(1)-O(3)-C(12')	-39.8(4)	C(8)-C(9)-C(10)-C(11)	-0.7(7)
O(2)-P(1)-O(3)-C(12')	84.3(4)	C(9)-C(10)-C(11)-C(6)	0.3(7)
N(1)-P(1)-O(3)-C(12')	-165.3(4)	C(7)-C(6)-C(11)-C(10)	0.2(6)
O(1)-P(1)-N(1)-C(1)	-34.9(3)	C(1)-C(6)-C(11)-C(10)	178.3(4)
O(3)-P(1)-N(1)-C(1)	90.5(3)	C(14')-O(2)-C(14)-C(15)	-51.1(12)
O(2)-P(1)-N(1)-C(1)	-162.6(2)	P(1)-O(2)-C(14)-C(15)	-98.0(7)
P(1)-N(1)-C(1)-C(6)	106.4(3)	C(14)-O(2)-C(14')-C(15')	51.1(12)
P(1)-N(1)-C(1)-C(2)	-127.9(3)	P(1)-O(2)-C(14')-C(15')	-166.3(8)
N(1)-C(1)-C(2)-C(3)	58.9(4)	C(12')-O(3)-C(12)-C(13)	122(2)
C(6)-C(1)-C(2)-C(3)	-174.7(3)	P(1)-O(3)-C(12)-C(13)	-169.7(7)
C(1)-C(2)-C(3)-C(4)	-138.1(4)	C(12)-O(3)-C(12')-C(13')	-48.4(16)
C(2)-C(3)-C(4)-C(5)	-179.9(4)	P(1)-O(3)-C(12')-C(13')	-170.9(6)
C(3)-C(4)-C(5)-O(4')	-171.7(8)		

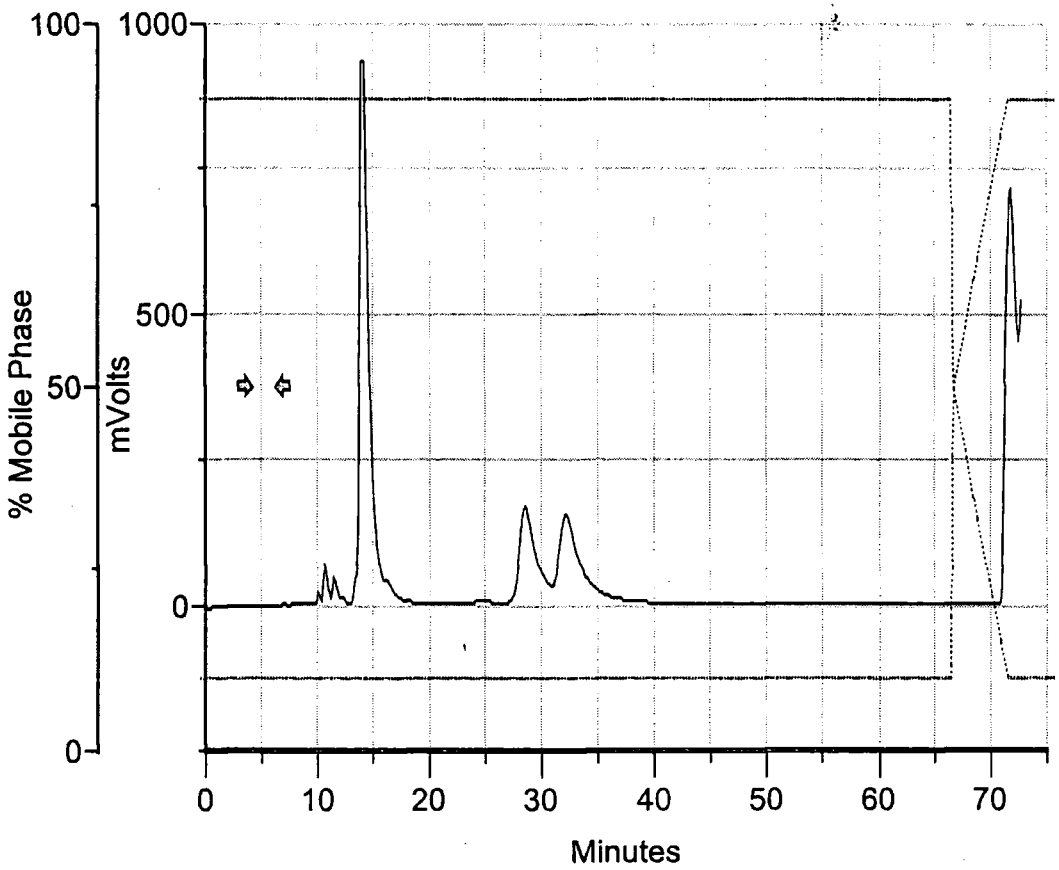
Appendix 6

Typical example of a poor quality chromatogram obtained in reaction screen one (Table 19) where molecular sieves were used in the reaction.



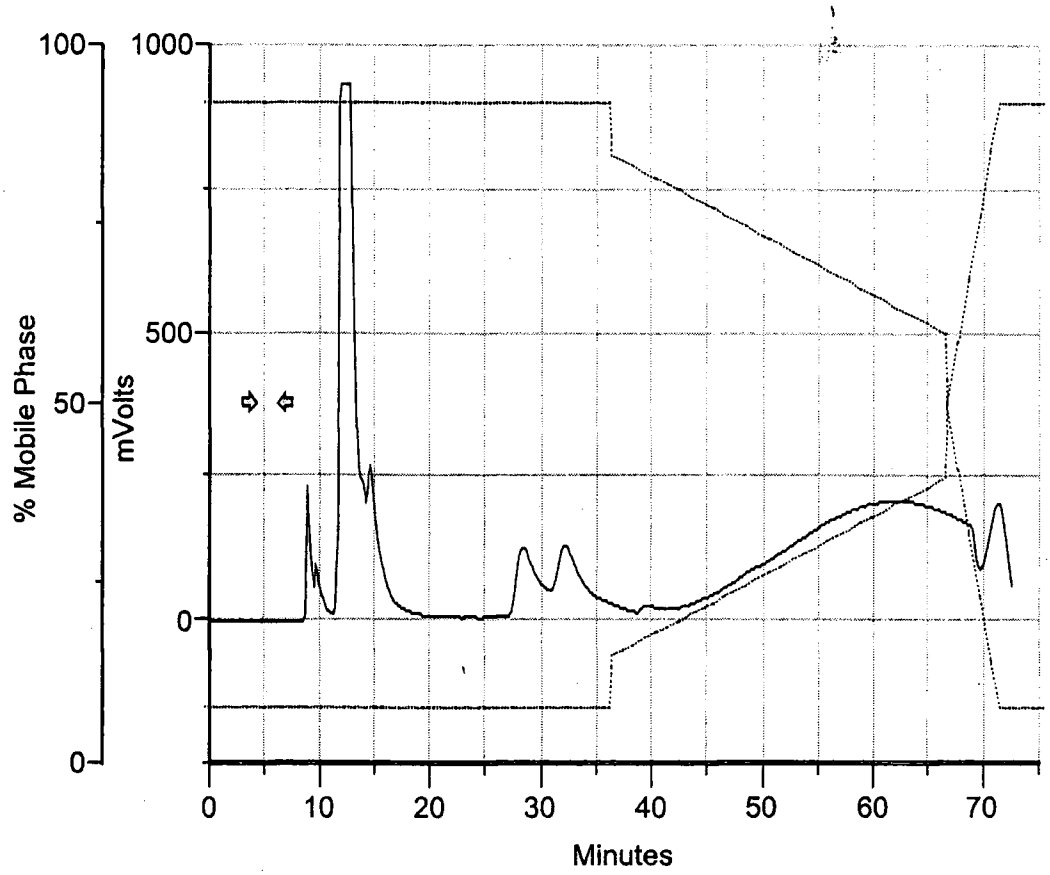
Appendix 7

Typical example of a good quality reaction (designated "G") obtained in the reaction screens in Table 19



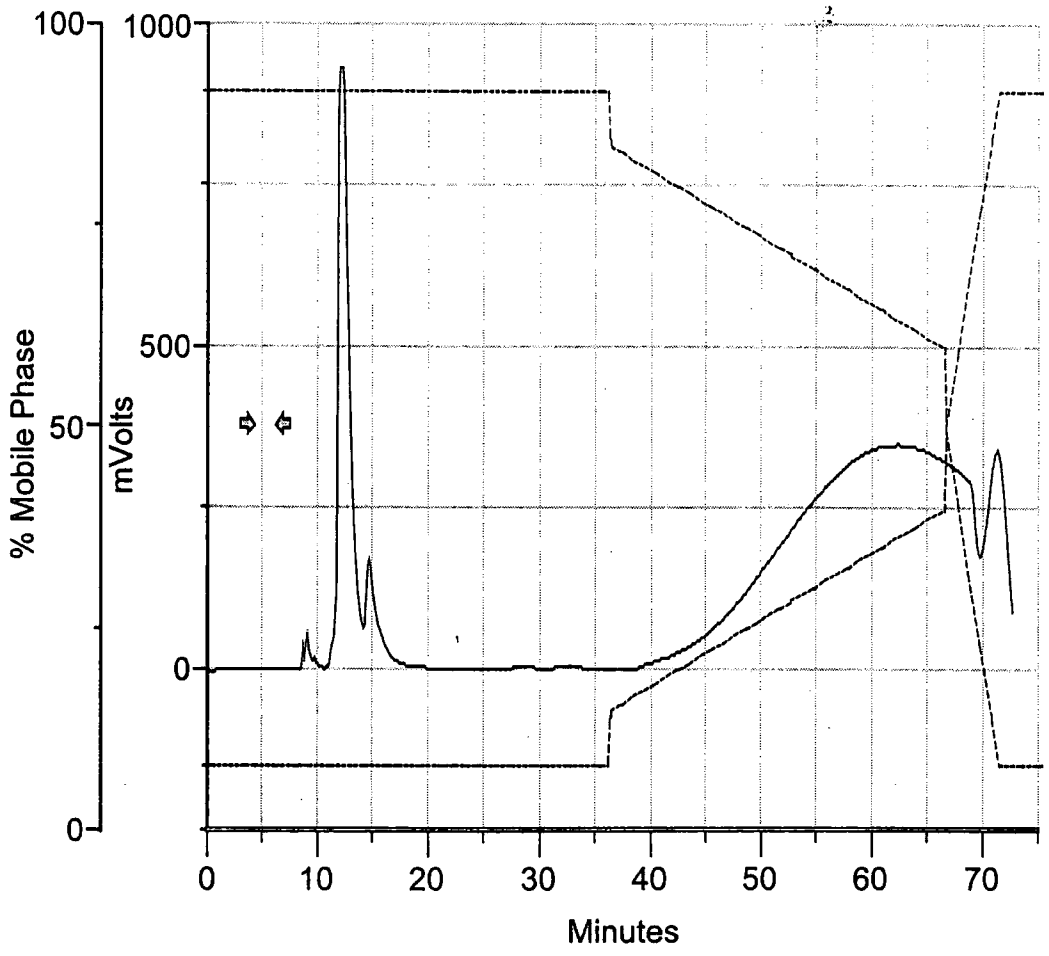
Appendix 7

Typical example of a moderate quality reaction (designated "M") obtained in the reaction screens in Table 19



Appendix 7

Typical example of a poor quality reaction (designated "P") obtained in the reaction screens in Table 19



Chapter Six

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