New catalysts for the hetero Diels-Alder reaction

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New Catalysts for the Hetero Diels-Alder Reaction

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Abstract

Hetero Diels-Alder reactions are very important in heterocycle and natural product synthesis.[71] The imino Diels-Alder reaction provides a rapid means of construction for some highly functionalised heterocyclic rings with control of regio-, diastereo- and enantioselectivity.[72] The key to the utility of these reactions has been the progress in recent years in the activation of the imine system towards cycloaddition.

Many examples of catalytically induced Diels Alder reactions exist involving homochiral Lewis acid catalysis and olefinic dienophiles. Hetero Diels-Alder reactions involving aldehyde dienophiles have also succumbed to catalysis using homochiral Lewis acids. Similar asymmetric catalysis of imine dienophiles has remained a relatively uninvestigated area. Successful asymmetric induction in the aza Diels-Alder reaction has relied almost entirely on chiral auxiliary-based methodology. However, over the past couple of years Kobayashi and Jørgensen[73] have shown that asymmetric induction is possible with an aza diene using catalytic Lanthanide and copper based Lewis acids. Our initial objective was to find a solution to the problem of asymmetric induction in the aza Diels-Alder reaction of imino dienophiles and imino dienes with a range of silver and indium salts.

This thesis describes the synthesis of tetrahydroquinolines and tetrahydropyridine analogues using silver and indium catalysis.

Chapter 1 reviews the relevant chemistry of the aza Diels-Alder reaction and its components. That is, mechanistic aspects of the aza Diels-Alder reaction; imino dienes, 1-azadienes, 2-azadienes and N-aryl imines. Particular attention has been dedicated to imines dienophiles in asymmetric Lewis acid catalysed imino Diels-Alder reactions and Brønsted acid catalysed reactions.

The fist section of chapter 2 describes the one step synthesis of absolute *cis*-selective tetrahydroquinoline derivatives using indium catalysis form achiral imine precursors. The second section of chapter 2 describes the efficient synthesis of tetrahydropyridine analogues using silver catalysis. In the final section of chapter 2, highly active silver carborane catalysts in the production of achiral tetrahydropyridine cycloadducts are discussed.

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Abbreviations

AAS	Atomic absorption spectroscopy
Ac	Acetyl
aq	aqueous
Ar	Aryl
atm	atmosphere
(*R*)-BINAP	(*R*)-(+)-2,2'bis(diphenylphosphino)-1,1'-binapthyl
Bn	Benzyl protecting group
Bz	Benzoyl protecting group
BINOL	2,-2'-dihydroxy-1,1'-binapthyl
^{t}Bu	*tert*-Butyl
ca.	Approximately
cat.	Catalyst/Catalytic
CED	Cohesive energy density
(*R, R)*CHIRAPHOS	(2*R*,3*R)*-bis(diphenylphosphino)butane
Conc	Concentration
Conv.	Conversion
cod	1,4-Cycloctadiene
DCM	Dichloromethane
DBU	Diazobicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DFT	Density functional theory
(*R,R*)-DIOP	(4R,5R)-(-)-*O*-Isopropylidene-2,3-dihydroxy-1,4(diphenylphosphino)butane
DMAD	Dimethylacetylene dicarboxylate
DMF	N,N-Dimethyl formamide
DMSO	Dimethyl sulfoxide
dppb	1,3-Bis(diphenylphophino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DTBP	2,6-di-*t*-butylpyridine
ee	enantiomeric excess
EDG	electron donating group
eq	equivalents

Abbreviations

Et	Ethyl
EtOH	Ethanol
EV	Electron volts
EWG	electron withdrawing group
FMO	frontier molecular orbital theory
gp	group
h	Hours
HOMO	Highest occupied molecular orbital
(R)-JOSIPHOS	(R)-(-)-1-[(S)-2(Diphenylphosphino)ferrocenyl]-ethyldicyclohexylphophine
LUMO	Lowest unoccupied molecular orbital
Ln	Lanthanide
L	Ligand
Me	Methyl
MeOH	Methanol
min	minute
mmol	millimole
m	mole
M	Molar
MeCN	Acetonitrile
mp	melting point
NMDA	N-methyl-D-aspartate
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PhMe	Toluene
Ppm	parts per million
PG	protecting group
Py	Pyridine
(R)-PROPHOS	(R)-(+)-1,2-Bis(diphenylphosphino)propane
Rac	Racemic
RT	room temperature
s/c	substrate/catalyst ratio
THF	tetrahydrofuran

Abbreviations

TBDMS	Tert-butyldimethylsilyl
TBS	tributylsilyl
TMP	(1,3,5)-trimethylpiperidine
TMS	trimethylsilyl
Tol	toluene
(R)-tol-BINAP	(R)-(+)-2,2'-Bis(di-p-tolyl-phosphino)-1,1'-binapthyl
Ts	p-toluenesulfonyl
TsOH	p-toluenesulfonic acid
UV	Ultraviolet light
XS	excess

Introduction

1.1 The role of imines as viable reaction partners for hetero Diels-Alder reactions

Hetero Diels-Alder cycloaddition reactions represent a versatile synthetic methodology for the construction of a variety of heterocyclic compounds. These compounds serve as a template for the construction of many natural products.

The most predominant application of the imine in the Diels-Alder reaction is as the dienophile. A second less common variant utilises the imine function as a hetero diene. This can be expressed as either the 1-azadiene or 2-azadiene system.

Imines are readily available from their corresponding aldehyde or ketone precursors. This provides a wide range of imine dienophile substrates for a Diels-Alder reaction. The imine dienophile generally requires activation or to be used in association with an active diene.

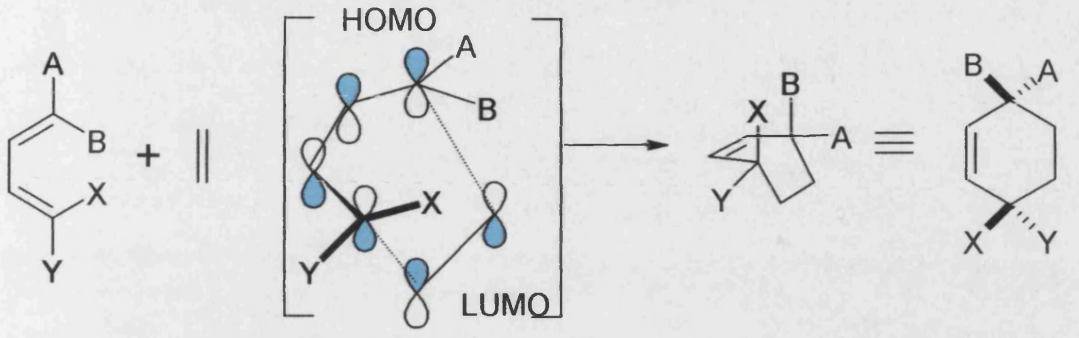
Much of the research in the area of imino Diels-Alder reactions has involved activation by Lewis acids. Many transition metal and rare earth metal salts have been investigated and have proved to be highly effective catalysts for these reactions.

1.1.1 Mechanistic aspects.

In general the Diels-Alder reaction involves three major components. The dienophile, the diene and the catalyst. In addition to increasing the rate of reaction, the catalyst often improves the regio and stereoselectivity of the cycloaddition reaction.

Generally this reaction is considered to be a concerted reaction in which both new σ bonds are formed synchronously. It should be noted at this point that evidence for a stepwise mechanism has been found and will be considered later on in the chapter. Research has demonstrated that dienophiles and dienes similar to imine dienophiles and heterodienes are most effective when the diene is electron rich and the dienophile is electron deficient. These types of reaction are generally rationalised by consideration of the interaction between the highest occupied molecular orbital

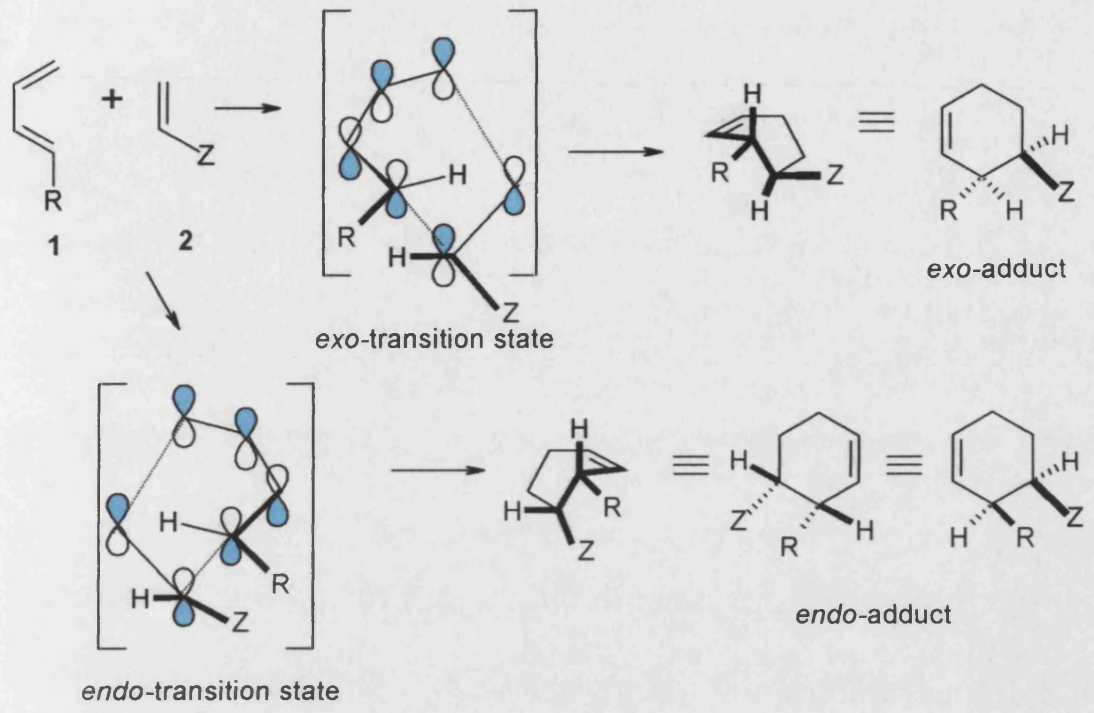
(HOMO) of the diene and the lowest unoccupied molecular orbital of the dienophile (LUMO). This is shown schematically in scheme1.



Scheme 1. Consideration of the interaction between HOMO and LUMO.

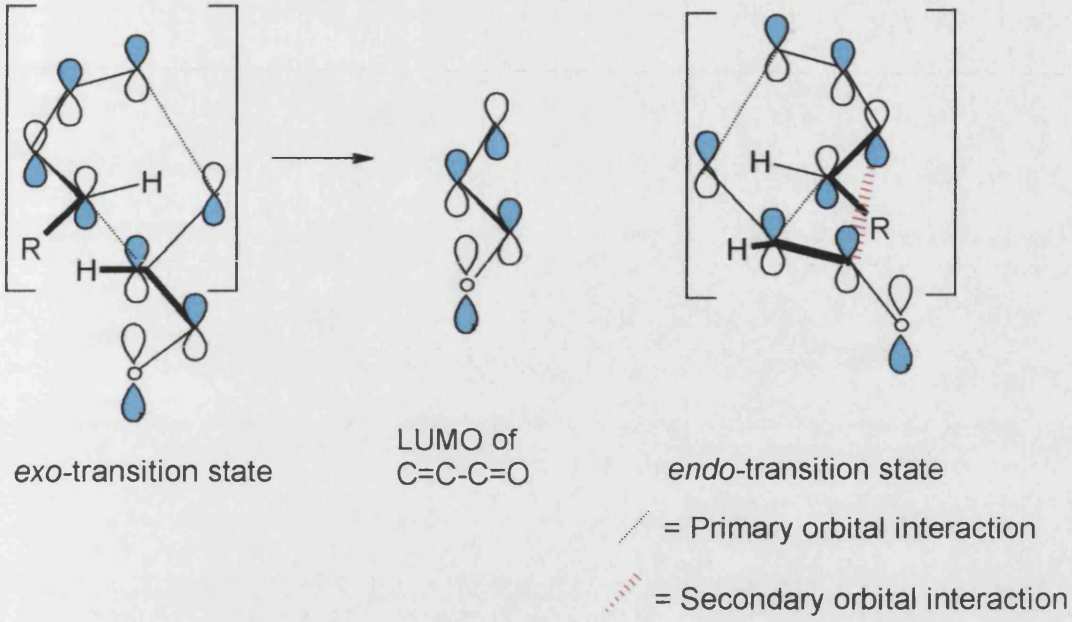
An important consequence of the mechanism is that the stereochemistry at the terminal end of the diene molecule is fixed in the cycloadduct. This has implications with the relative stereochemistries at these two centres and can be controlled predictably by choice of the diene geometry.

Many Diels-Alder reactions generate chiral centres, which are generated from the termini of the diene and dienophile. Such cases are shown in scheme 2. Here the diene **1**, has en electron donating substituent **R** and the dienophile **2**, is activated by means of an electron-withdrawing group **Z**. Assuming that the reaction precedes achirally there are two diastereoisomeric transition states which produce racemic diastereomeric products. These are known as *endo*- and *exo*-products respectively. The stereochemical result of the reaction from either face of the diene and from the same face of the dienophile is illustrated in Scheme 2.



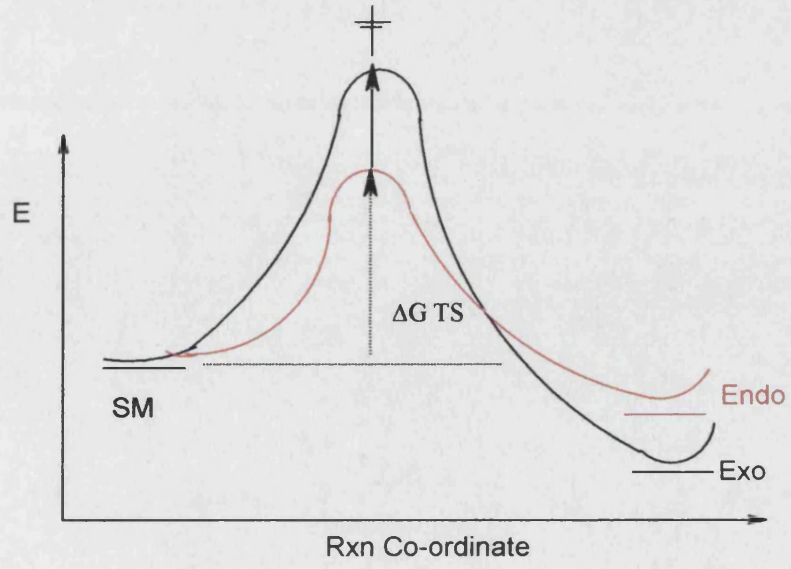
Scheme 2. Rational of *endo*- and *exo*-products.

The *exo*-transition state and *exo*-adduct usually involve less steric interactions than the corresponding *endo*-transition state. However in most cases Diels-Alder reactions under kinetic control produce predominantly the *endo*-adduct. The *endo*-adduct is usually less thermodynamically stable than the *exo*-adduct however it is formed more rapidly. This is often accounted for by citing 'secondary orbital interactions'. (Scheme 3)



Scheme 3. Secondary orbital interactions.

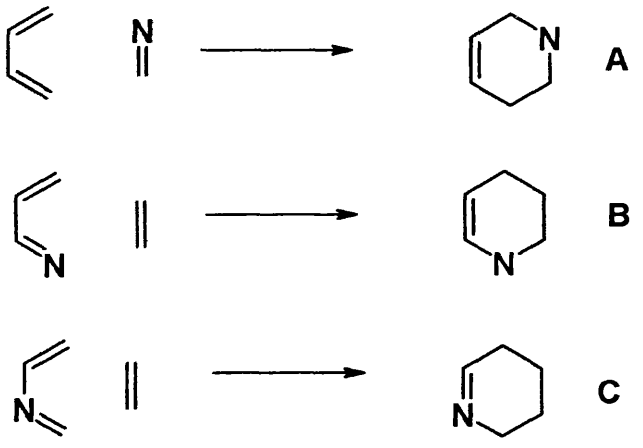
Primary orbital interaction result in bonding between the atoms involved, whereas secondary orbital interactions do not. In the case of the Diels-Alder reaction shown in scheme 2, the *endo*-transition state is thought to be stabilised (compared to the *exo*-transition state) by the secondary orbital interactions shown in scheme.3. The overall effect is to make the *endo*-adduct the major product under conditions of kinetic control, when the reaction is effectively irreversible (Scheme 4).



Scheme 4. Transition state model of *endo*-adduct the major product

1.1.2 Aza Diels-Alder mechanism.

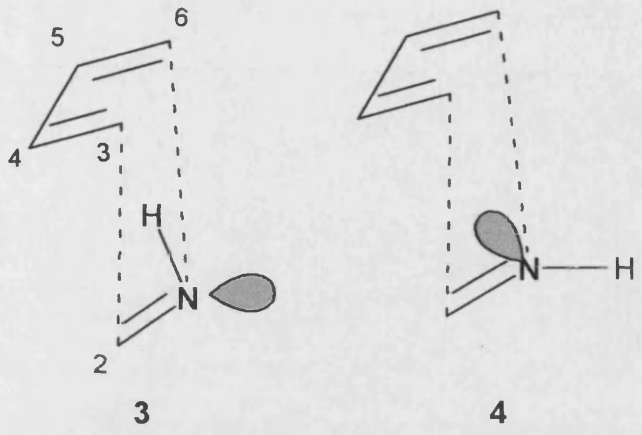
The first and most common application of the imine function in the Diels-Alder reaction is as the dienophile. The second function is found in the diene either as 1-azadiene or 2-azadiene structures. (Scheme. 5)



Scheme 5. Imine as dienophile, 1-azadiene or 2-azadiene structures.

The Diels-Alder reaction conforms to one of three $4\pi s+2\pi s$ cycloaddition types of reaction. The three types are defined as follows; firstly the 'normal' $HOMO_{diene}$-controlled reaction **A** (Scheme 5). Secondly the neutral reaction **B** and finally the 'inverse electron demand' $LUMO_{diene}$-contolled Diels-Alder reaction **C.** [1,2,3] The type of cycloaddition and their corresponding reaction rates are directly related to the magnitude of the smallest diene-dienophile HOMO-LUMO energy difference. Electronic and structural features of the reagents plus influence of catalyst determine the size of the energy difference and therefore the nature of the reaction.

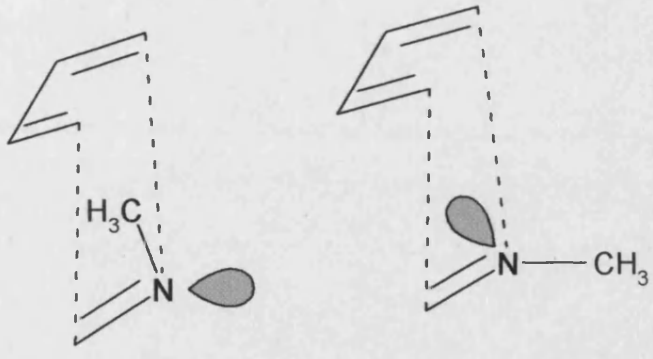
The reaction of formaldimine with butadiene has been modelled by *ab-initio* molecular orbital calculations using the 3-21G and MP2/6-31G basic sets.[4,5,6,7,8.] These experiments showed that having the nitrogen lone pair on the imine *exo* in the transition state is more stable than when they are in the *endo* orientation. The *endo*-lone pair of electrons is disfavoured due to repulsion between lone pair electrons and butadiene π-electrons (structure **3** vs. **4**, Scheme 6)



3 **4**

Scheme 6. Formaldimine and butadiene transition state structures.

In the favoured transition state, **3**, the C6-N1 bond formation is more advanced than the C2-C3 bond formation. This indicates that the dienophile HOMO/diene LUMO interaction is important. The HOMO of formaldimine has a larger co-efficient at nitrogen than at carbon. There is also a 20° twist in the C6-N1-C2-C3 dihedral angle, which is believed to be caused by the attraction between the imino hydrogen and the butadiene π-electrons at C4 and C5. This was illustrated in the modelling of *N*-methylformaldimine where the *exo*-lone pair is still the favoured conformation (structure **5** vs. **6** scheme 7)



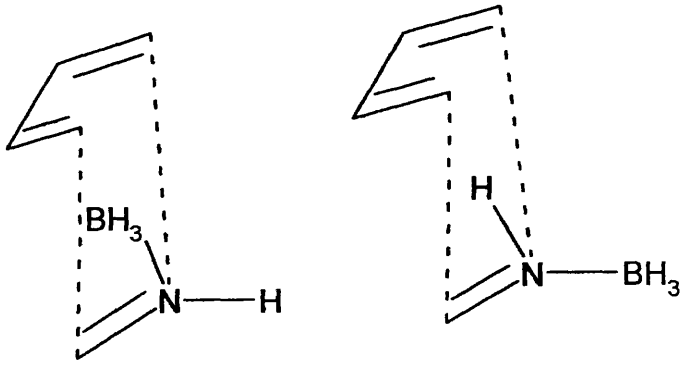
5 **6**

Scheme 7. *N*-methylformaldimine and butadiene transition state structures.

Activation of imines by electron withdrawing carbonyl and sulfonyl groups is well known. *Ab-initio* modelling shows that carbonyl groups are better activators than

sulfonyl groups. Positioning a carbonyl or sulfonyl group on either side of the imine activates the dienophile more than having a substituent on the nitrogen function.[9] An interesting conclusion of these studies is that having the sulfonyl group in the *endo*-position does not seem to stabilise the transition state through secondary overlap or electrostatic interactions therefore the *exo*-cycloaddition may be favoured. Reactions involving acylimines *endo* to the N-acyl group is the preferred orientation. When there are acyl groups on the carbon and the nitrogen, the N-acyl group generally takes the *endo* position.

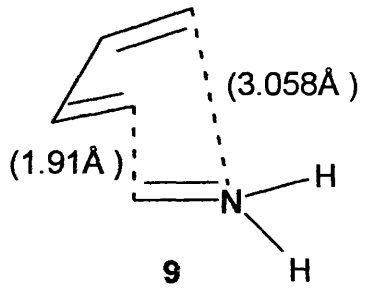
In contrast to thermal reactions, theoretical examination of the reaction between BH_3-co-ordinated formaldimine and butadiene shows that the C2-C3 bond formation is more advanced than the N1-C6 bond formation (structure **7** vs. **8**, Scheme 8)



7 **8**

Scheme 8. Transition state structures of BH_3- co-ordinated formaldimine and butadiene

Additionally the transition state energy in this model is lowered. There is an increase in asynchronicity and BH_3 in the *exo*-position is favoured. To represent the effect of a Brønsted acid, activation with the formaldiminium ion was calculated. In this case the asynchronous transition structure shows C2-C3 and N1-C6 bond lengths of 1.91 and 3.058 Å respectively, structure **9** (Scheme. 9), indicating a stepwise reaction.



9

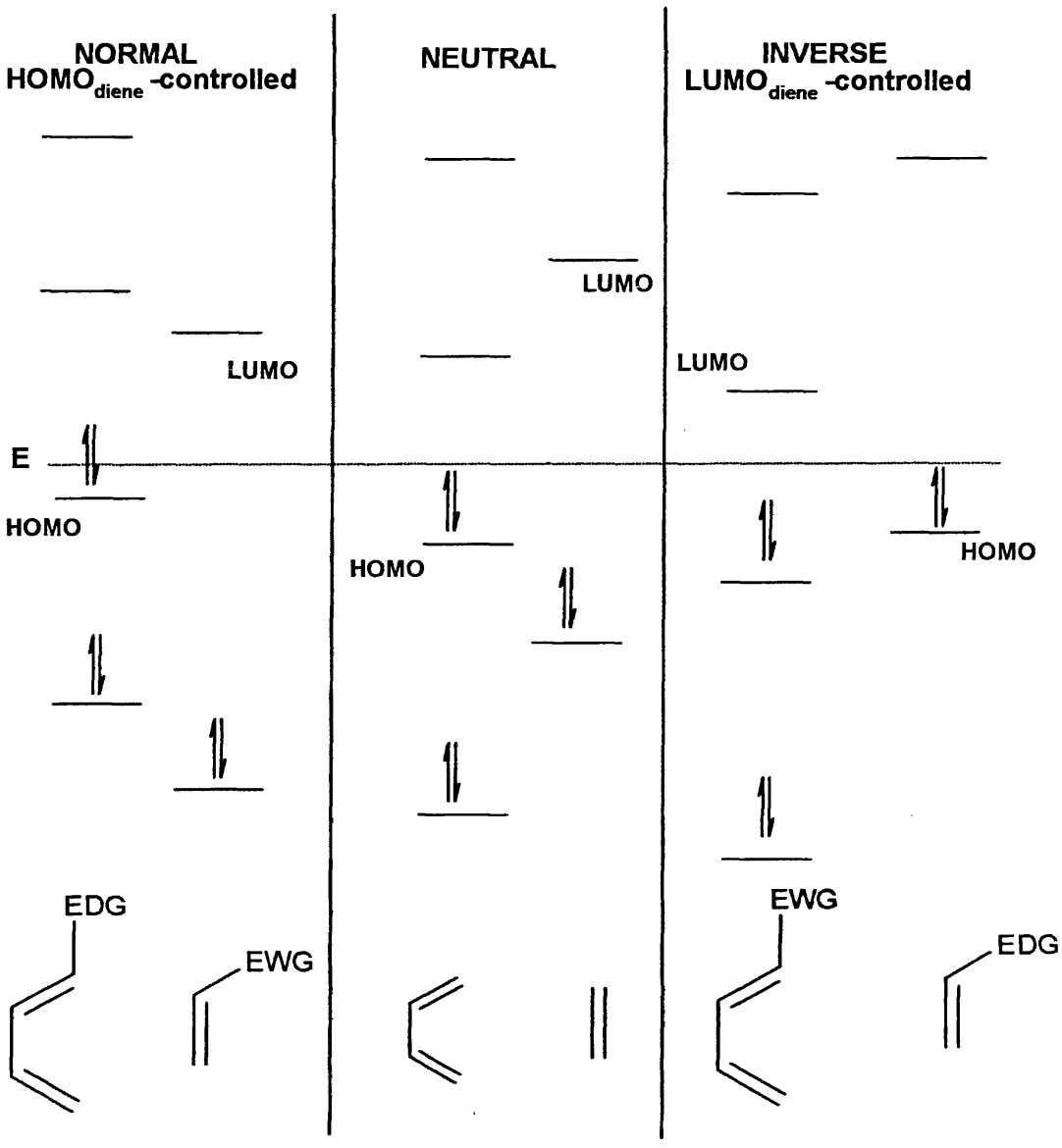
Scheme 9. Brønsted acid activation

For both types of acid activation, solvated systems were modelled and showed little difference in transition state energies or stereochemical preferences as compared to the respective gas phase reaction models.[10]

Conclusions can be drawn from the theoretical and experimental evidence that cycloaddition with imino dienophiles can be either concerted or stepwise. The stepwise mechanism involves a tandem Mannich-Michael reaction closely related to the aza Diels-Alder reaction. This will be discussed in more detail later on in this chapter.

The most commonly utilised Diels-Alder type in organic synthesis is the $HOMO_{diene}$-controlled 'normal' type in which an electron deficient dienophile is used (Scheme 10) Simple 1- and 2-aza dienes, due to their intrinsically electron deficient nature favour participation in 'inverse electron demand' $LUMO_{diene}$-contolled Diels-Alder reaction.[11,12,13] By utilising appropriate complimentary azadiene and dienophile substitution patterns however, both 'normal' $HOMO_{diene}$-controlled aza Diels-Alder reactions and 'inverse' $LUMO_{diene}$-controlled aza Diels-Alder reactions have been developed.

Computational studies in *ab-initio* STO-3G and MP2/6-31G*//MP2/6-31G* and hybrid density functional theory B3LYP/6-31G*//B3LYP/6-31G* of both 1-aza-1, 3-butadiene and 2-aza-1, 3-butadiene Diels-Alder reactions with ethylene suggest that in both cases the reactions are distinctly concerted and asynchronous.[14,15,16]

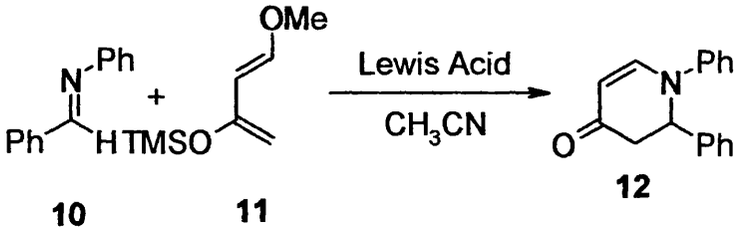


Scheme 10. 1-aza-1, 3-butadiene and 2-aza-1, 3-butadiene Diels-Alder reactions with ethylene computational study.

1.2.0 Imine dienophiles

1.2.1.1 Lewis acid catalysed imino Diels-Alder reactions.

Much of the research into imino Diels-Alder reactions has involved activation by suitable Lewis acids. Rare earth metal triflates have been thoroughly investigated under various conditions and $Yb(OTf)_3$, $Sc(OTf)_3$ and $In(OTf)_3$ are all effective. These Lewis acids can even tolerate the presence of small amounts of water[17,18,19,20,21](Scheme 11, table 1).

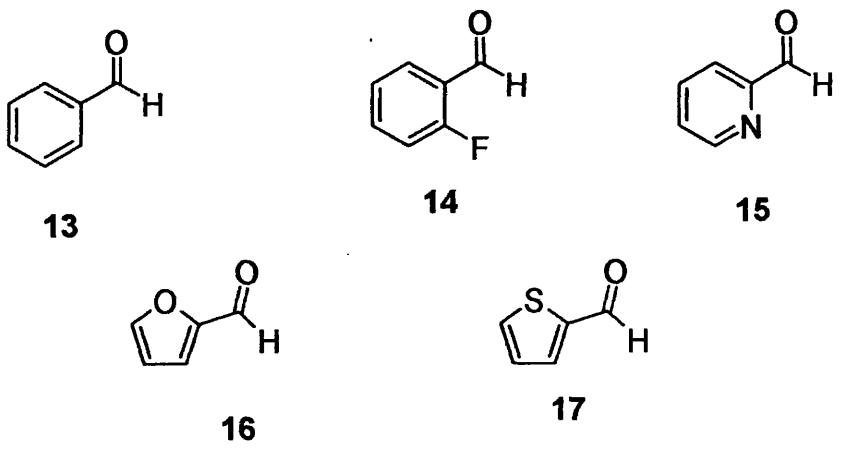


Scheme 11. Rare earth metal triflate catalysed Diels-Alder reaction

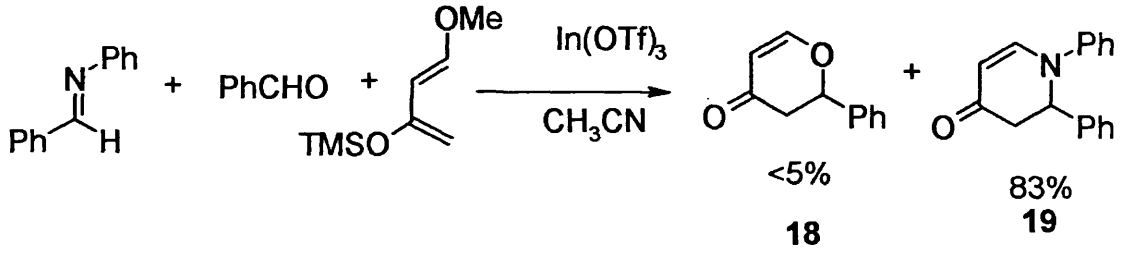
Table 1. Rare earth metal catalysts for the Diels-Alder reaction.

Entry	Lewis acid	Temp	Yield of **12**
1	$Yb(OTf)_3$,(10 mol%)	RT	93
2	$Sc(OTf)_3$, (10 mol%)	RT	99
3	$In(OTf)_3$, (0.5 mol%)	-20°C	93

These catalysts have been successfully applied to a variety of substrates. Several imines were created *in-situ* with various aldehydes with either aniline or benzylamine catalysed by $In(OTf)_3$. The yields were good, however the thiophene derivative (**17**, Scheme 12), did not react. A competition reaction between carbonyl and imino Diels-Alder reactions showed that $In(OTf)_3$ selectively catalysed the imino Diels-Alder reaction preferentially over the carbonyl precursor (scheme 13).

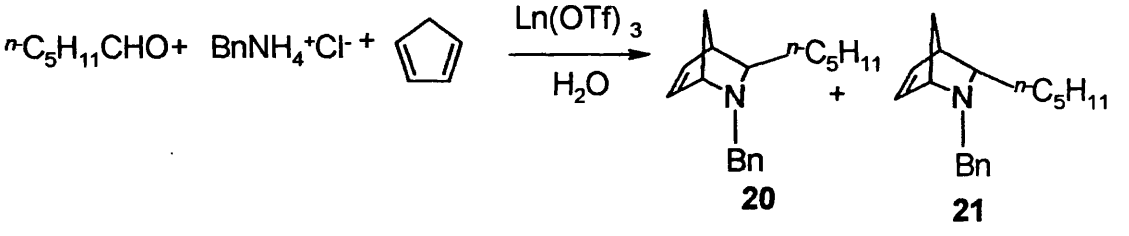


Scheme 12. Aldehydes examined in the aza-Diels-Alder reaction with $In(OTf)_3$



Scheme 13. Competition reaction between aldehyde and imine with $In(OTf)_3$

Lanthanide triflates have also been shown to catalyse aza-Diels-Alder reactions in water. (Scheme 14, Table 2). The reactions were carried out at pH 5-7 and 0.25M concentration in the presence of Lanthanide Lewis acids. Praseodymium (III) triflate, niobium (III) triflate and neodymium(III) triflate afforded the highest yields while gadolinium (III) triflate gave the lowest. Under the same conditions in 0.25M solution with magnesium chloride or lithium chloride, no catalytic effect was found. This indicates that the acceleration seen with the Lanthanides could not be attributed to salt effects.



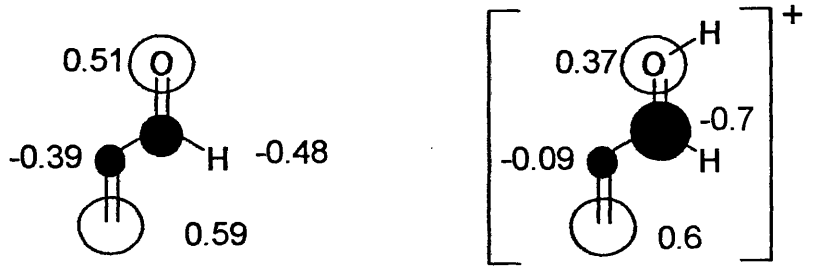
Scheme 14. Lanthanide triflates catalysed aza-Diels-Alder reactions in water.

Table 2. Aqueous aza Diels-Alder reactions in water catalysed by $Ln(OTf)_3$

Entry	$Ln(OTf)_3$	**20:21**	Yield(%)
1	-	73:27	4
2	$La(OTf)_3$	72:28	47
3	$Pr(OTf)_3$	74:26	68
4	$Nd(OTf)_3$	76:24	57
5	$Gd(OTf)_3$	73:27	19
6	$Dy(OTf)_3$	74:26	49
7	$Er(OTf)_3$	72:28	46
8	$Yb(OTf)_3$	74:26	62

1.2.1.2 Mechanism of Lewis acid activation.

Diels-Alder reactions are strongly influenced by Lewis acid catalysis. The catalyst is thought to act via co-ordination to the dienophile. This has several important effects on the LUMO of the dienophile. These are typically illustrated in the reaction of acrolein and cyclopentadiene (Scheme. 15) Acrolein is protonated, which serves as a model for a dienophile-Lewis acid complex. The energy of the dienophiles LUMO is lowered (2.5 eV to –7.0 eV) leading to a reduction of the energy gap between the HOMO of the diene and the LUMO of the dienophile. This consequently increases the rate of the reaction. The polarisation of the dienophile is also increased on co-ordination to the Lewis acid. This is represented by the orbital co-efficients, which may be loosely considered as equivalent to the relative size and phase of the p orbitals which make up the LUMO. Often a larger difference in the coefficients of the C-C double bond will increase the regio selectivity and an increase the coefficient on the carbonyl carbon, will increase secondary orbital interaction in the transition state and lead to *endo*-selectivity. Consequently with carbonyl compounds, behaviour is analogous to the corresponding imines and we can presume that secondary orbital interactions would also lead to *endo*-selectivity.



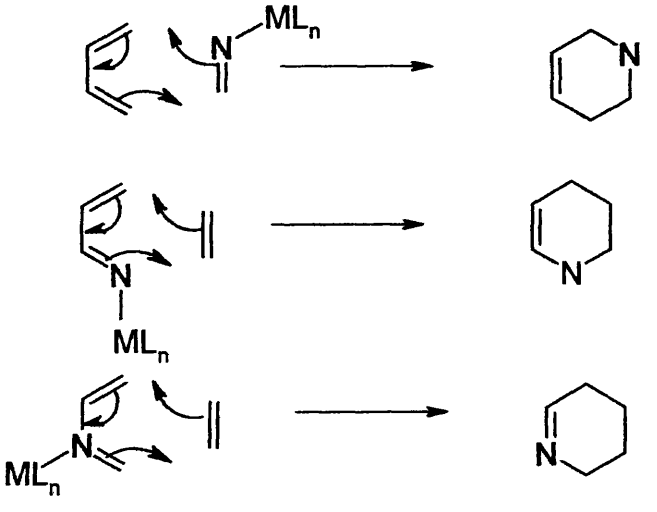
LUMO energy
2.5 eV
22

LUMO energy
-7eV
23

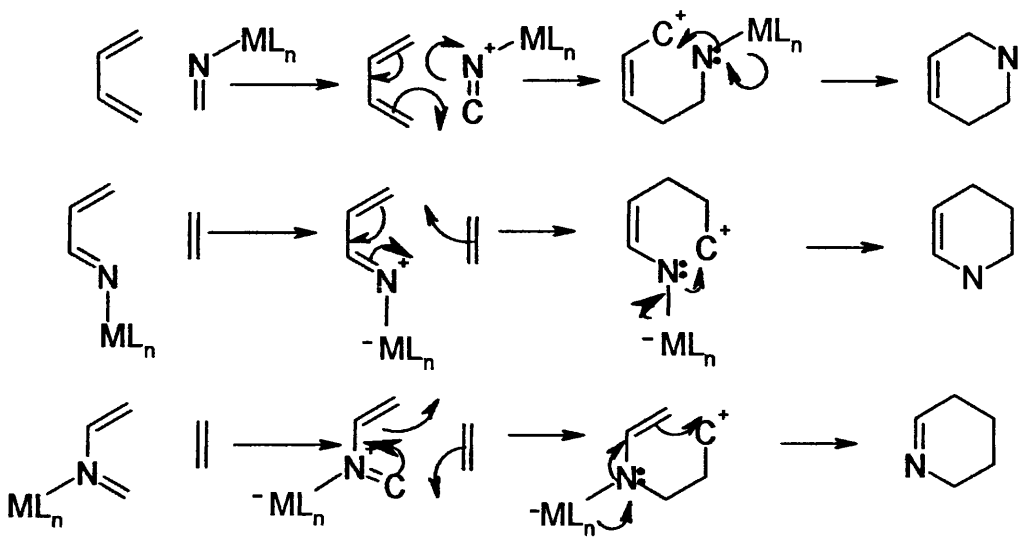
Scheme 15. Diels-Alder reaction influenced by Lewis acid catalysis

1.2.1.3 Concerted vs. stepwise mechanism.

There is still an open discussion as to whether the Diels-Alder reaction with imines undergoes cycloaddition via a concerted or stepwise mechanism (Scheme 16 vs. 17).[22]



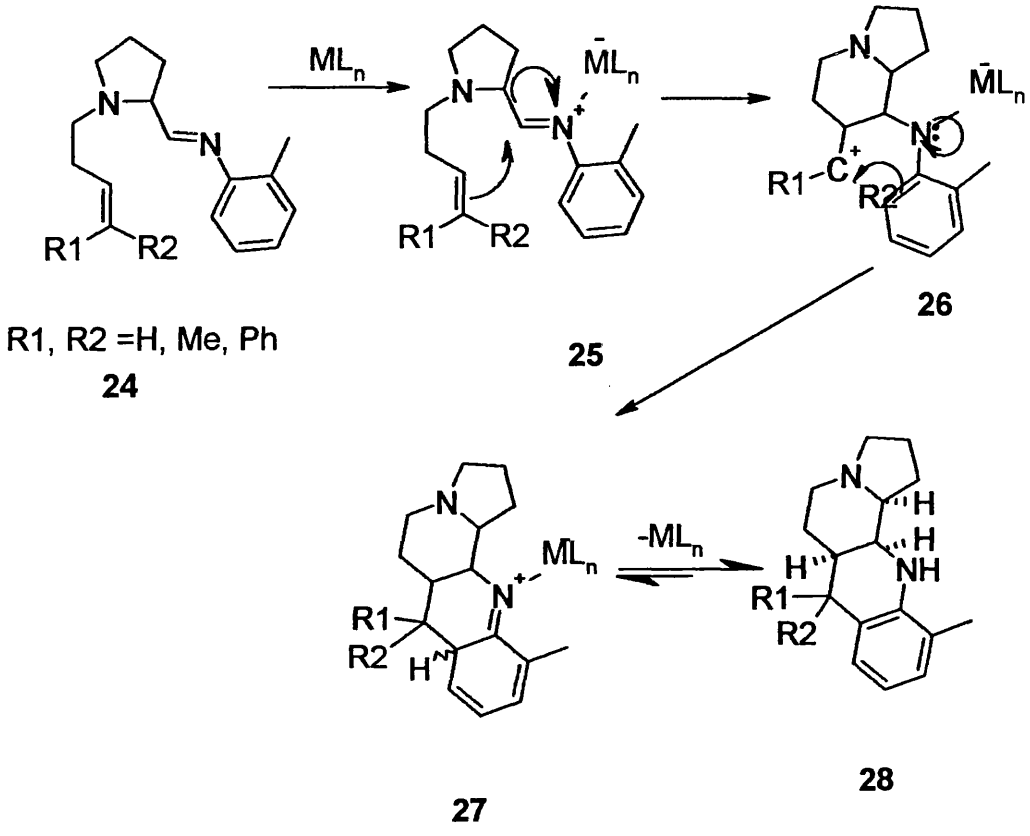
Scheme 16. Concerted mechanism



Scheme 17. Stepwise mechanism

The main focus of this reaction is in the development of an iminium cation, which rapidly undergoes cycloaddition even at very low temperatures.[23] The mechanism seems to be highly dependent on the type of heteroatom and the presence of an acid catalyst (i.e. Brønsted or Lewis acid). 1-oxabutadiene reacts in a concerted fashion as demonstrated by semi imperial calculations performed by Tietze et al.,[24] the corresponding 2-aza-1,3-butadienes display an ambivalent nature. Thermally induced intramolecular cycloadditions of imines derived from aminoisoxazole and *o*-substituted salicyladehyde is explained by a concerted mechanism although the authors stated that a stepwise pathway might be involved as well.[25] In contrast to this Mellor et al.[26] described the acid catalysed intermolecular cycloaddition of imines derived from anilines and formaldehyde with electron rich alkenes towards tetrahydroquinolines. In these systems the intermediate carbenium ion could be trapped and isolated as the corresponding tertiary alcohols.[27] Whilst investigating Lewis acid catalysis of ω-unsaturated *N*-aryl imines the authors, F. Linkert et al.[28] found that when an imine with a terminal alkene or alkyne moiety undergoes cyclisation, a tertiary carbenium ion is generated. This then undergoes a Friedel-Crafts alkylation followed by tautomerization. However for this procedure to be functional, the presence of a stabilising group (i.e. R1, R2 = Me, Ph, Scheme 18) is necessary. If the Diels-Alder mechanism is considered then the bond forming and bond breaking steps are probably asynchronous due to the polarisation by the imino nitrogen, hence a similar cation stabilising effect might be operative. However in this

study, the reactions utilising *N*-arylimines under thermal conditions in the absence of a Lewis acid did not undergo cyclisation. This confirms the stepwise mechanism of this cyclisation. Failure of the imine to undergo thermal cyclisation may be due to steric constraints present in the tetracyclic systems during Friedel-Crafts alkylation

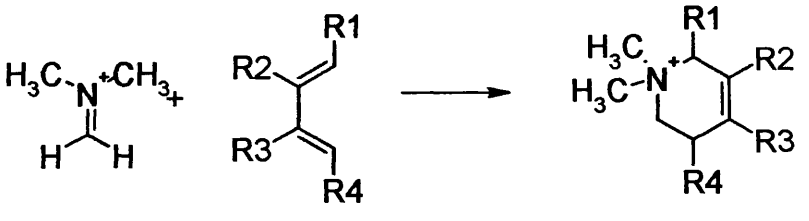


Scheme 18. Intermolecular cycloaddition of imines derived from anilines and formaldehyde

As was discussed previously in chapter **1.1.2**, in the cyclisation of formaldimine and butadiene, several transition states have been identified. Two asynchronous concerted transition states have been characterised corresponding to the *exo-* and *endo-* approaches to the lone pair of the nitrogen atoms to the Butadiene system. The formation of the C-N bond is more advanced than the C-C bond in the transition state. However for the cycloaddition between protonated formaldimine and butadiene the reaction presents a very asynchronous transition state in which the lengths of C-C and C-N are 1.91 and 3.058Å respectively (Scheme 9). Here the authors found that there are several possible intermediates associated with a stepwise mechanism. The proton in this case acts as a strong Lewis acid, which increases the electrophillic character of

the carbon atom in the protonated formaldimine and therefore the asynchronicity of the process. The inclusion of the solvent effects does not modify these findings because of the similar cationic character of both the iminium cation reactant and the transition state.[29]

Sauer and co-workers[30] have recently studied the cycloaddition between ylidene and ammonium cation using AM1 semi-empirical calculations. These authors suggest that the aza-Diels-Alder reactions of these reagents with acyclic 1,3-butadienes proceed via transition structures that closely resemble those yielding intermediate allyl cations. In only the case with cyclopentadiene do the authors conclude that the reactions take place via a pericyclic transition state. However a recent density functional theory (DFT) study for the reaction between cyclopentadiene and ammonium cation indicates that the reaction proceeds along a highly asynchronous concerted process. This was characterised by the nucleophilic attack of the cyclopentadiene on the ylidene ammonium cation instead of a pericyclic process.



29 **30** **31**

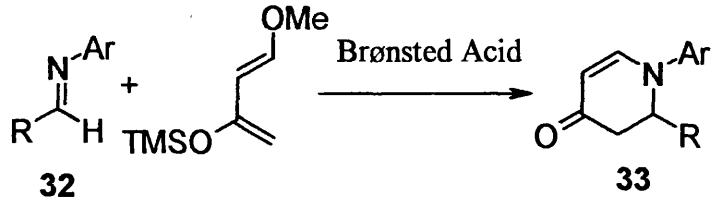
R1,R2,R3 and R4= H or CH_3

Scheme 19. Cycloaddition between ylidene and ammonium cation

Again these results conclude that the reaction proceeds along a polar stepwise mechanism. However in neutral conditions the cycloaddition proceeds via an asynchronous concerted pathway.[31]

1.2.2 Brønsted acid controlled reactions.

Brønsted acids are popular catalysts for the aza Diels Alder reaction.[32] Common acid catalysts for the cycloaddition of imines to Danishefsky's diene include HBF_4, TsOH, and CF_3CO_2H. In these reactions 0.2 equivalents of Brønsted acid and 10 equivalents of water were utilised. The reactions worked well in the presence of water and also in the presence of a surfactant sodium dodecyl sulfate/HBF_4.(Scheme. 20, Table 3)



Scheme 20. Brønsted acid catalysis

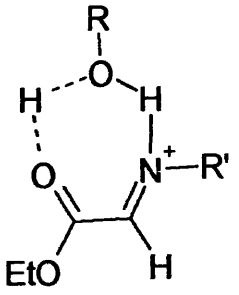
Table 3. Substituents and conditions for reaction scheme 20

Entry	R	Ar	Reaction Conditions	Yield of **33**
1	Ph	Ph	A	98
2	*p*-$NO_2C_6H_4$	Ph	A	87
3	*p*-$CH_3C_6H_4$	Ph	A	95
4	PhCH=CH	Ph	A	89
5	Ph	*p*-$CH_3OC_6H_4$	A	90
6	Ph	*p*-$CH_3OC_6H_4$	B	88
7	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	B	86
8	PhCH=CH	*p*-$CH_3OC_6H_4$	B	86
9	*c*-C_6H_{11}	*p*-$CH_3OC_6H_4$	B	75

[a] Reaction conditions A: HBF_4 (0.1 equiv.), H_2O (10 equiv.), CH_3OH, -40°C, 30 min. B: HBF_4 (0.1 equiv.), sodium dodecylsulfate (0.4equiv.), H_2O, RT, 1h.

HCl and trifluoroacetic acid have been used with cyclopentadiene and 2,3-dimethylbutadiene in DMF. Reactions with ethyl 2-(benzylimino)acetate **34** catalysed by HCl in DMF are summarised in table 4.[33] Cyclopentadiene gave good yields, cyclohexadiene gave low yields of the cyclic adduct. Regio selectivity was good for non-symmetrical dienes and the reaction was highly *cis*- selective. More importantly 0.1-1 equivalent of water gave the highest yields the reaction performed in aqueous solvent gave low yields. Replacing water with methanol afforded higher yields. From this it was proposed that water and methanol activation was due to hydrogen bonding to the imine as shown in scheme 21. The hydrogen bonding reduces rotation

of the iminium ion about the π bond and increases the effective concentration of the 2π- component. Alternatively this can stabilise the 6π-transition state.[34]

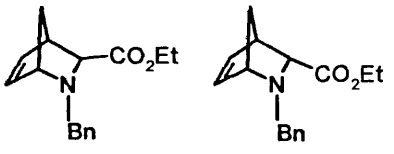
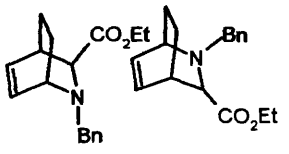
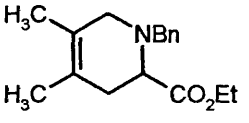
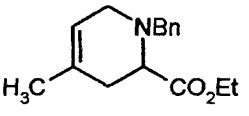
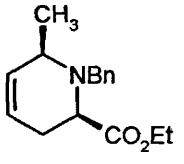
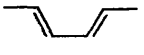
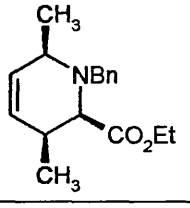


R= H, Me

34

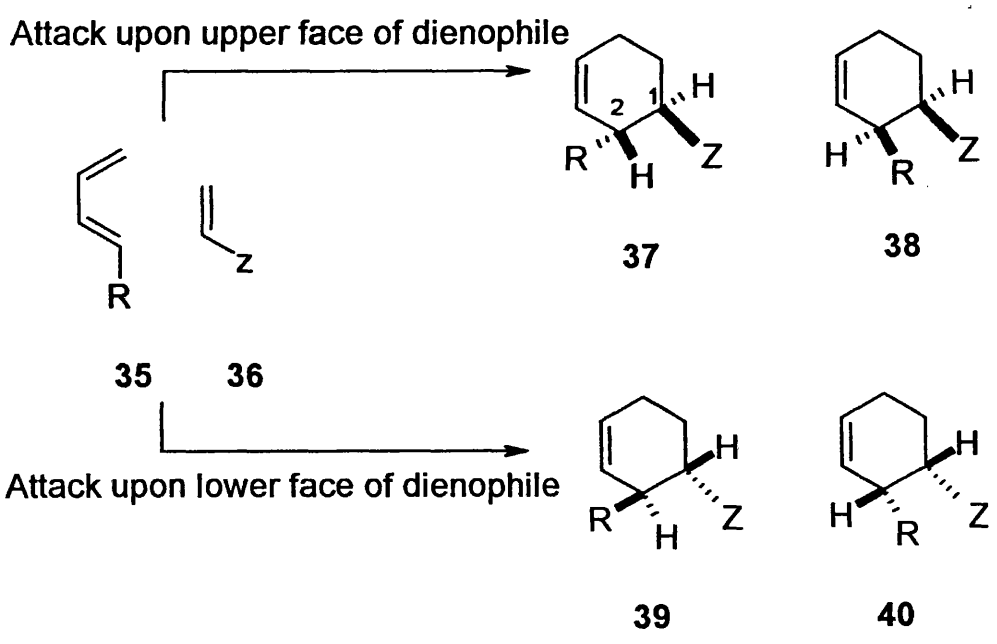
Scheme 21. Mode of catalysis with water or methanol under acidic conditions.

Table 4. HCl catalysed reactions of $PhCH_2N{=}CHCO_2Et$, **34** with various dienes

Entry	Diene	Products	Ratio (exo:endo)	Yield %
1			69:31	89
2			27:73	21
3			-	47
4			-	43
5			-	38
6			-	36

1.2.3 Stereoselective cycloaddition.

As the Diels-Alder transition state involves the diene, dienophile and catalyst if one or more of these components is chiral then asymmetric synthesis is theoretically possible. As we have seen previously, there are four possible stereoisomeric products in any typical reaction. If the precursors **35** and **36** are chiral then their products **37, 38, 39** and **40** are diastereomeric. Adducts **37** and **38** correspond to reactions from both faces of the diene on to the upper face of the dienophile. Cycloaddition products **39** and **40** arise from addition to the lower face of the dienophile. (Scheme 22)

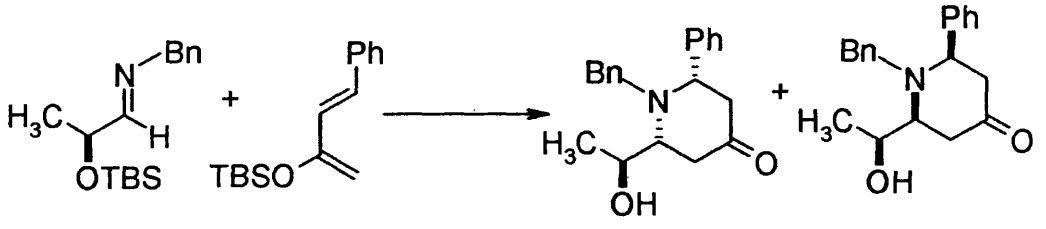


Scheme 22. Four possible stereoisomeric products

The absolute configuration at C1 depends on which face of the dienophile the diene attacks. For efficient asymmetric Diels-Alder reactions, one of the four possible cycloadducts should predominate. High facial selectivity in one of the reactions is not a guarantee of high selectivity however the *endo*-adduct usually predominates under the conditions of most enantioselective reactions and in practice high selectivity is usually achieved.

1.2.4 Imines from chiral aldehydes

Stereoselective addition of imines from chiral aldehydes has been extensively investigated.[35] These reactions are highly productive however they do require a catalyst. Cycloaddition of α-alkoxy imine **41** with diene **42** gave the best results, both in terms of selectivity and yield. For the reaction to proceed up to two equivalents of catalysts such as Et_2AlCl, TMSOTf, $Zn(OTf)_2$, $TiCl_4$ and ZnI_2 were used.[36] (Scheme 23, Table 5)



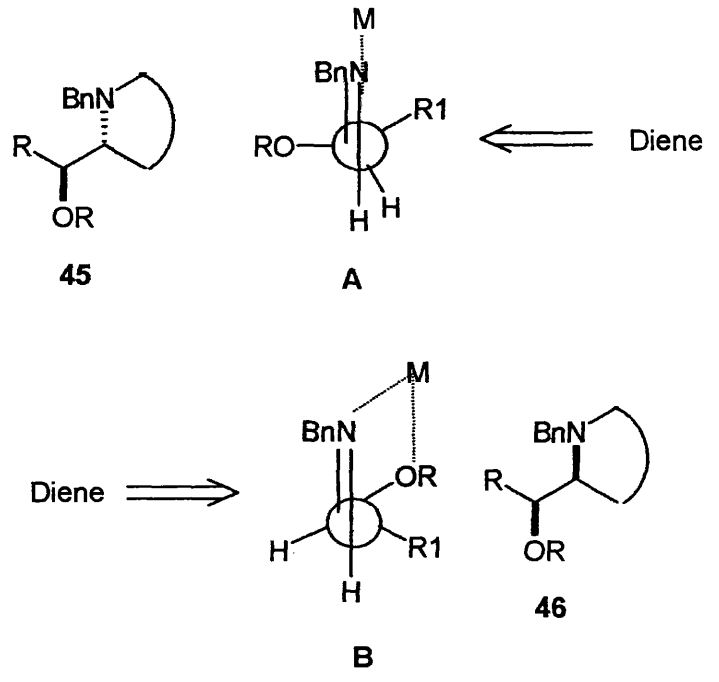
41 **42** **43** **44**

Scheme 23. Stereoselective addition of imines from chiral aldehydes

Table 5 Stereoselective addition of imines from chiral aldehydes.

Entry	Conditions	Ratio **43/44**	Yield
1	TMSOTf/PhMe	78:22	97%
2	$Zn(OTf)_2$/^{n}-hexane	89:11	93%
3	$TiCl_4$/^{i}-PrCN	<2:>98	87%

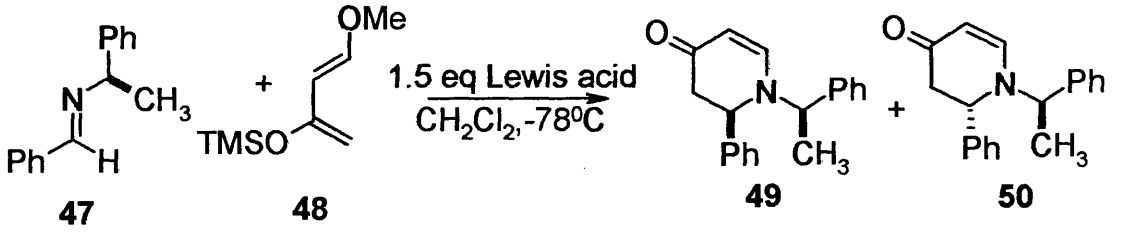
Chelation and non-chelation control models can be used to rationalise the selectivity of these reactions. Non chelation control structure **A** (Scheme 24), gives and *anti*-product **45**, in contrast chelation control structure **B**, affords the *syn*-cycloadduct **46**.



Scheme 24. Chelation and non-chelation control models

1.2.5 Imines derived from chiral amines.

Simple chiral imines can be derived from α-phenylethylamine and alkyl or aryl aldehydes. These compounds can give both high selectivities and good yields. Several Lewis acid catalysts have been used, including boron, titanium, aluminium and zinc based systems.[37] (Scheme 25, Table 6)



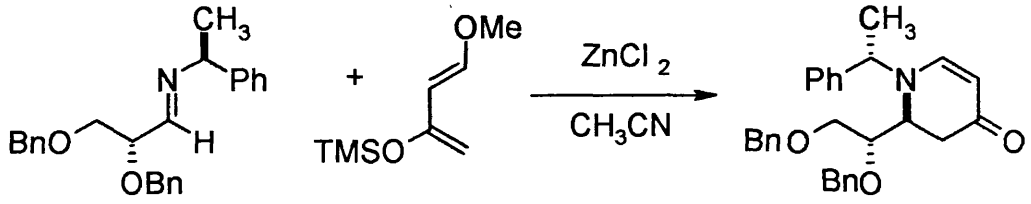
Scheme 25. Chiral imines can be derived from α-phenylethylamine

Table 6. Cycloadditions with α-phenylethylimine

Entry	Lewis Acid	**49:50**	Yield %
1	$BF_3.Et_2O$	94:6	41
2	$B(OPh)_3$	96:4	61
3	$MeAl(OPh)_3$	90:10	23
4	$ZnCl_2$	96:4	75
5	$TiCl_2(O^i\text{-}Pr)_2$	95:5	56

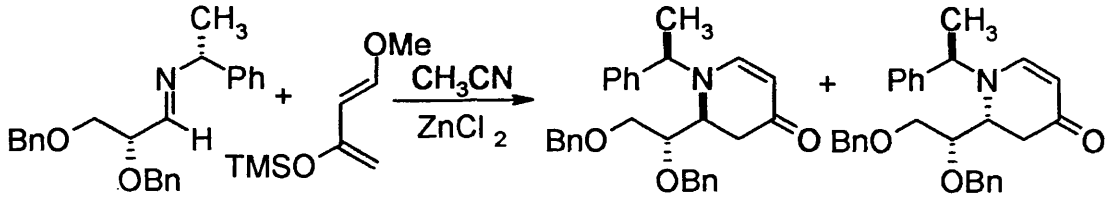
1.2.6 Double asymmetric induction. Imines derived from chiral amines and chiral aldehydes.

Imines derived from chiral phenylethylamine and dibenzyl protected glyceraldehyde were studied.[38] (Scheme. 26) when the matching auxiliary **51** was used only one stereoisomer was detected **52**. However when the mismatching auxiliary **53** was used, low selectivity of, **54, 55** was achieved (scheme 26, 27)



51 75% **52**

Scheme 26. Imines derived from chiral phenylethylamine and dibenzyl protected glyceraldehyde using the matching auxiliary



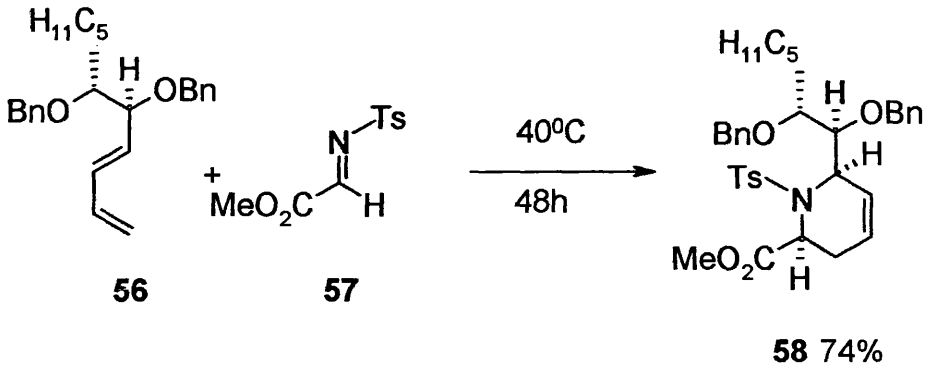
53 **54** **55**

64:35
73%

Scheme 27. Imines derived from chiral phenylethylamine and dibenzyl protected glyceraldehyde using the mismatching auxiliary

1.2.7. Chiral dienes and achiral imines.

Cycloaddition of chiral diene **56** and imine **57** only gave one detectable cycloadduct. With this type of diene the chiral centres are incorporated into the product **58** (Scheme 28).



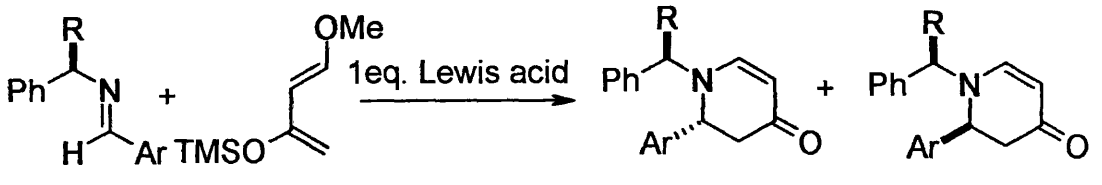
56 **57** **58** 74%

Scheme 28. Cycloaddition of chiral dienes

1.2.8 Chiral Lewis acids.

Chiral Lewis acids have proved to be the best method for stereocontrol in Diels-Alder cycloadditions.[39] Initial work relied upon stoichiometric amounts of the chiral catalyst, however more recently impressive results have been reported using catalytic amounts of the chiral reagents. The first successful results were obtained using Boron Lewis acids.[40] (scheme 29)

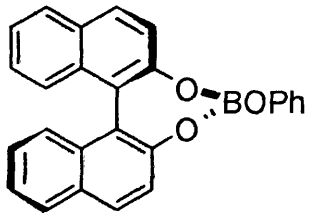
Double asymmetric induction using chiral imines gave excellent selectivities for the matching auxiliaries (*R*)-imine **59** and chiral Lewis acid (*R*)-**62**. Mismatched auxiliaries gave lower selectivities than the reaction of (*R*)-imine and achiral Lewis acid $B(OPh)_3$



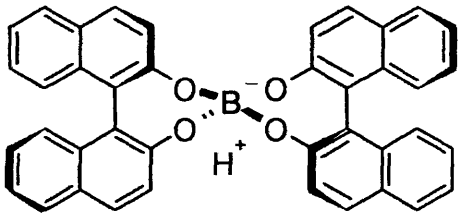
59 **61** **60**

Scheme 29. Double asymmetric induction

Table 7 shows the impressive yields and diastereoselectivities obtained with chiral Lewis acids



(R)-62



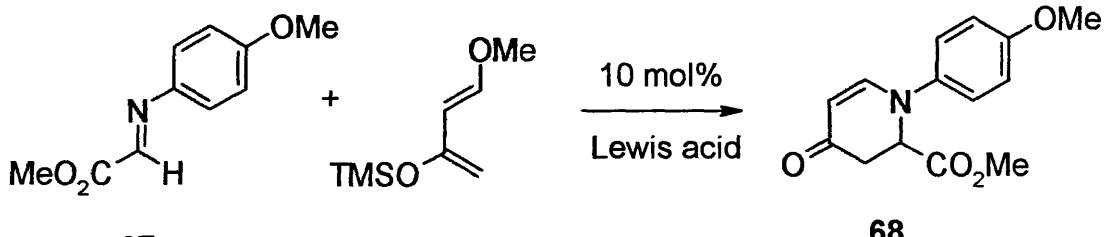
63

Scheme 30. Chiral Lewis acids for double asymmetric induction

Table 7. Diastereoselectivities obtained with chiral Lewis acids

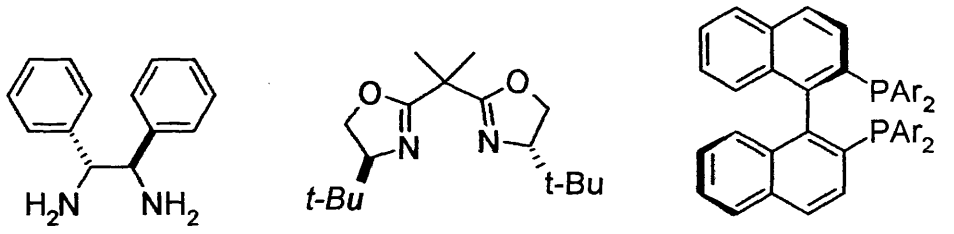
Entry	Ar	R	Lewis acid	de (%)	Yield (%)
1	Ph	H	(*R*)-62	82	75
2	*c*-Hexyl	H	(*R*)-62	76	45
3	Ph	H	$B(OPh)_3$	86	78
4	Ph	CH_3	$B(OPh)_3$	92	57
5	Ph	CH_3	(*R*)-62	98	61
6	Ph	CH_3	(*S*)-62	86	30
7	3-Pyridyl	CH_3	$B(OPh)_3$	78	53
8	3-Pyridyl	CH_3	(*R*)-62	98	63
9	3-Pyridyl	CH_3	(*S*)-62	72	35
10	*c*-Hexyl	CH_3	$B(OPh)_3$	80	40
11	*c*-Hexyl	CH_3	(*R*)-62	98	31
12	*c*-Hexyl	CH_3	(*S*)-62	78	20
13	*n*-Propyl	CH_3	$B(OPh)_3$	82	59
14	*n*-Propyl	CH_3	(*R*)-62	90	49
15	*n*-Propyl	CH_3	(*S*)-62	82	31

The importance of chiral Lewis acids is illustrated with imines derived from methyl glyoxylate and anisidine.[41] Ligands **64** and **65** derived chiral Lewis acids gave successful cycloadditions. (Scheme 31, 32).



67 68

Scheme 31. Imines derived from methyl glyoxylate and anisidine



64 65 66

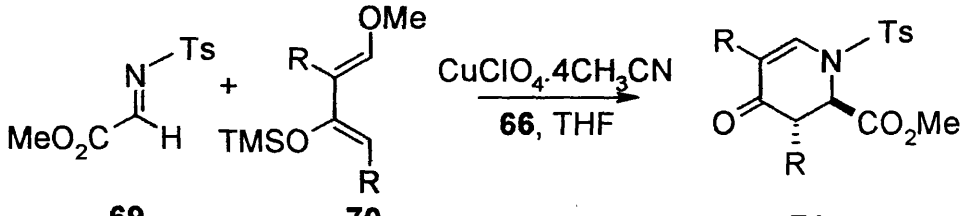
Scheme 32. Chiral Lewis acids for cycloaddition

Several Lewis acids were examined with these ligands with a further additive typically either molecular sieves or 2,6 Luitidine. (Table 8)

Table 8. Chiral Lewis acid cycloadditions with imines

Entry	Lewis acid/solvent	Ligand	Additive	ee (%)	Yield (%)
1	MgI_2/ CH_3CN	**64**	2,6-Lutidine	97	64
2	$Yb(OTf)_3$/PhMe	**64**	2,6-Lutidine	87	60
3	$Cu(OTf)_2/CH_3CN$	**64**	-	86	58
4	$FeCl_3/CH_2Cl_2$	**65**	4 Å MS	92	67

Bisphosphines gave good enantioselectivites with the tosylimine derived from methyl glyoxylate in the presence of Lewis acid $CuClO_4$ (Scheme 33).[42] High enantioselectivites were obtained with as low as 1 mol% catalyst loading. (Table 9)



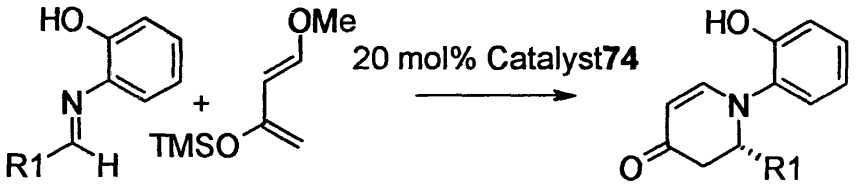
69 70 71

Scheme 33. Cycloaddition of tosylimine derived from methyl glyoxylate

Table 9. Cycloaddition reaction results scheme 33

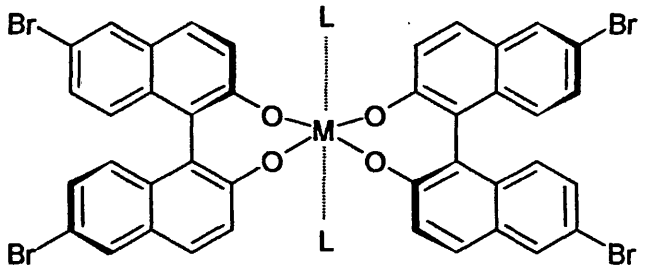
Entry	Mol%	Alkene R	ee (%)	Yield (%)
1	10	H	67	78
2	10	H	80	68
3	10	CH_3	94	67
4	5	CH_3	94	70
5	1	CH_3	96	70
6	10	CH_3	91	70

Chiral Lewis acids derived from zirconium, hafnium, and titanium with chiral binapthol also showed good enantioselectivities.[43] 2-Aminophenol **72** (scheme 34) was used as the nitrogen source of the imine. Of all the ligands screened, *N*-methyl-imidazole **74** gave the best results (Table 10).



72 **73**

Scheme 34. Cycloaddition of 2-Aminophenol



74 L=N-methylimidazole

Scheme 35. Chiral Lewis acids derived from zirconium, hafnium, and titanium with chiral binapthol

Table 10. Cycloaddition reaction results scheme 34.

Entry	R1	Metal	ee (%)	Yield (%)
1	CH_3	Zr	82	94
2	2-Thiophene	Zr	86	74
3	*c*-C_6H_{11}	Zr	81	64[a]
4	α-Napthyl	Zr	88	96
5	α-Napthyl	Hf	84	96
6	α-Napthyl	Ti	62	70

[a] 3-Amino-2-methylphenol was used.

1.3.0 Imino dienes.

1.3.1 1-Azabutadienes.

1-azadienes are unreactive towards dienophiles due to their electron deficient nature. Therefore they frequently undergo inverse electron demand Diels-Alder type reactions. Initially the electrophillic nature of the nitrogen compromised the utility of 1-azadienes as Diels-Alder dienes due to competitive self-condensation, dimerization, imine addition, and or tautomerization.[44]

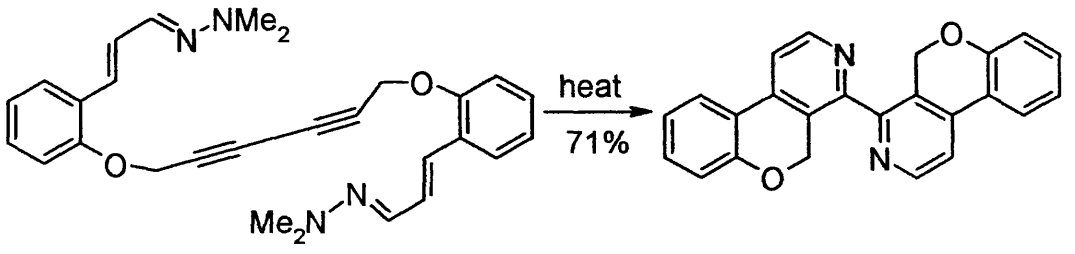
Theoretical studies of the transition state for the Diels-Alder reactions of unsubstituted 1-azabutadienes support the conclusion that the terminal nitrogen lowers the LUMO of the diene allowing an inverse electron demand type reaction.[45]

The key to a successful azadiene Diels-Alder strategy is to decrease the HOMO-LUMO energy difference by matching the azadiene to the dienophile and stabilising the transition state. To operate this aza Diels-Alder reaction effectively electron donating or withdrawing substituents are introduced onto the nitrogen atom of the diene to increase the activity with the selected dienophile.

1.3.1.1 Enhydrazones.

Introduction of electron donor groups to the imine nitrogen reverses the natural electron deficient character of 1-azadienes. Sufficient donation raises the HOMO of the azadiene and allows the reaction to proceed through the $HOMO_{diene}$-controlled pathway.

The earliest use of this chemistry was by Ghosez *et al.*[46] Here electron donor groups where positioned to facilitate a normal electron demand Diels-Alder reaction. It was shown in these reactions that the conjugative interaction between the lone pair of the amine nitrogen with the enimine system is critical to the activation. Interaction of the tertiary nitrogen lone pair with the azadiene is apparent in the yield of the intramolecular double Diels-Alder reaction of compound **76**.

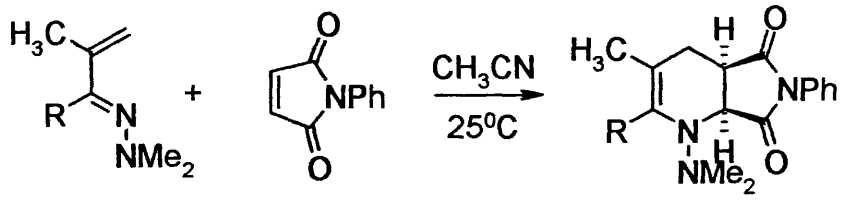


76 **77**

Scheme 36. Intramolecular double Diels-Alder reaction

Even with the enormously large influence of the electron pushing NMe_2 groups the conditions for these types of reactions are harsh. Temperatures of 100-200°C and long reaction times of 220h are not unusual. The use of additional donating groups and activated dienophiles are a necessity to obtain a useful synthetic process.

Introductions of substituent groups are used to enhance the reactivity of the azadiene. Alkyl groups in the C2 position render the azadiene useless. This is due to steric hindrance and electronic factors as the alkyl group at C2 pushes the lone pairs of the hydrazone N-Methyl out of the plane with the imine. Electron withdrawing groups at C2 are tolerated at the expense of lower reactivity. (Scheme 37)



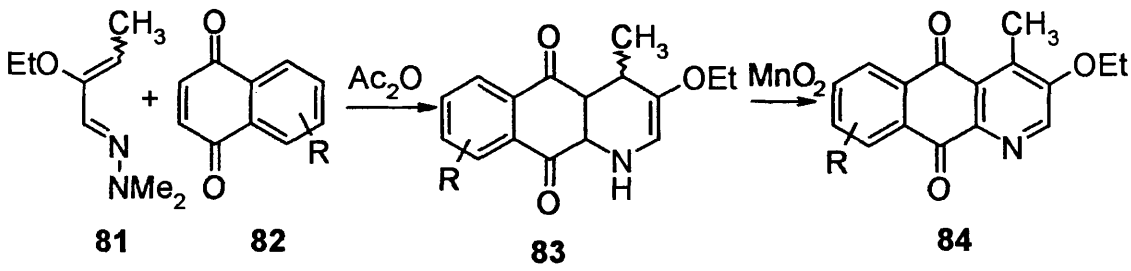
78 **79** **80**

R=H
R=CO_2Me
R=CN

R=H, 95%, 1 day
R=CO_2Me, 76%, 3 days
R=CN, 91%, 14 days

Scheme 37. Introducing substituent groups to enhance reactivity towards cycloaddition

Introduction of non-bulky electron donating substituents at C3 enhances the reaction rate for cycloadditions of 1-azadienes[47,48] This is reflected in the yields of **84** (scheme 38).

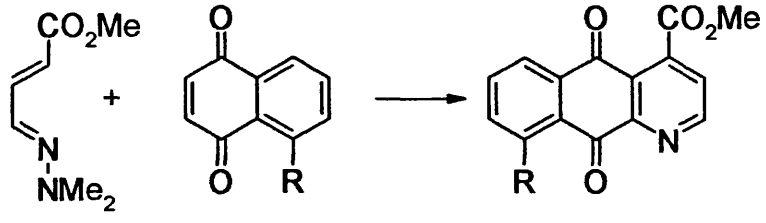


81 82 83 84

R=OH, 68%
R=OMe, 82%
R=OAc, 74%

Scheme 38. Non-bulky electron donating substituents to enhance cycloaddition

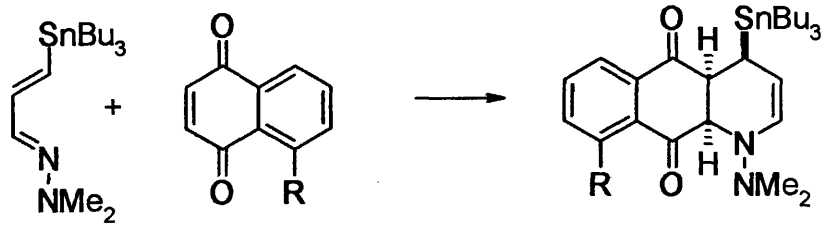
The influence of a substituent at C4 can dramatically impact the chemical yields and regio selectivity of a Diels-Alder reaction. The presence of an electron-withdrawing group results in low yields.[49] However the presence of an activating group such as tributylstannyl group (Scheme 39,40) greatly enhances reactivity with a number of dienophiles.[50]



85 86 87

R=H, 16%
R=OH, 9%

Scheme 39. Electron-withdrawing group results in low yields



88 89 90

R=H, 95%
R=OH, 100%

Scheme 40. Activating groups enhance reactivity

1.3.1.2 Enoximes and enoxime ethers.

[4+2] cycloadditions of α,β-unsaturated oximes are generally unsuccessful reactions, however several authors have reported successful reactions with these dienes.[51] The weak electron donating character of the hydroxyl group does not sufficiently reduce the HOMO-LUMO energy difference. In the few instances where successful reactions have been reported additional electron donating groups have been present on the azadiene.

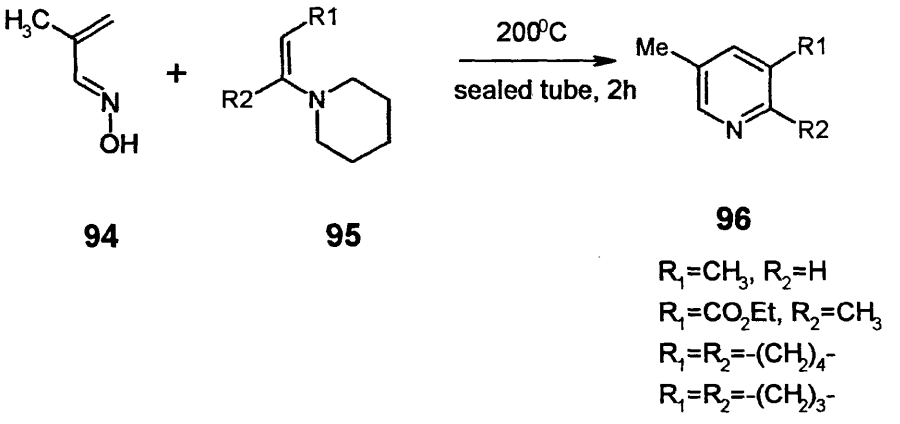
The earliest example of the cycloaddition of an oxime is illustrated in scheme 42, of 2-furfural, **91**, with electron deficient dienophiles **92** such as acrylonitrile, maleic anhydride and acrylic esters. The observed regiochemistry is consistent with FMO considerations. Diastereoselectivity was not reported (scheme 41).[52]

91 **92** **93**

R=CN, 76%

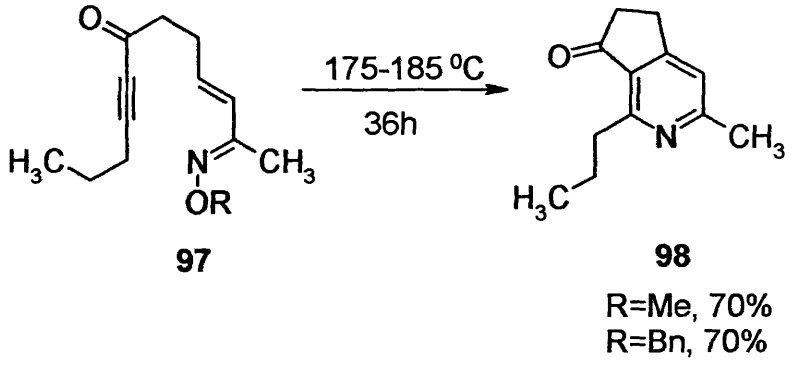
Scheme 41. Cycloaddition of an oxime

To solve the problem of low reactivity with enoxime dienes, reactions were carried out with a variety of electron rich enamines. Reaction conditions of 200°C in a sealed tube for two hours produced pyridines **96** (scheme 42).[53]



Scheme 42. Reactions of electron rich enamines

Ethers of unsaturated α,β-oximes provide sufficient electron donation to promote the normal '$HOMO_{diene}$-controlled Diels-Alder reaction. Such reactions require considerable thermal activation (Scheme 43). Other limitations of the reaction are that initial cycloaddition products are prone to oxidation through the loss of the OR functionality under the harsh reaction conditions used.[54]

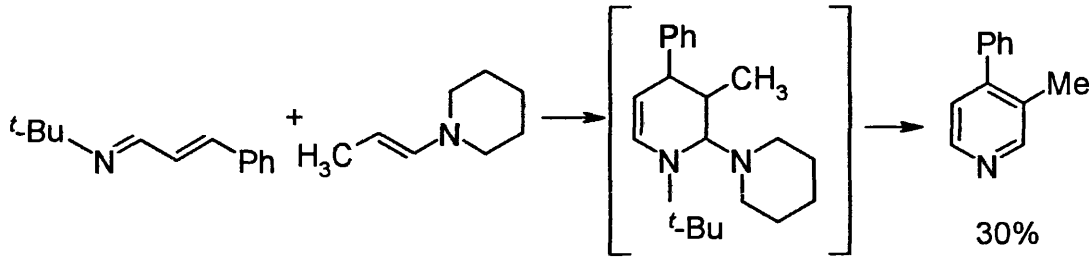


Scheme 43. Intramolecular cycloaddition using ethers of unsaturated α,β-oximes

1.3.1.3 N-alkyl enamines.

To avoid competitive self-condensation and enamine dimerization processes usually observed in the reactions involving pure isolated N-alkyl enamines, heterodiene synthesis has generally been observed *in situ*. Diels-Alder products tend to be formed in low yields even after *in situ* generation (scheme 44). As N-alkyl enamines have electron-donating properties it has been suggested that low yields of the cycloadduct

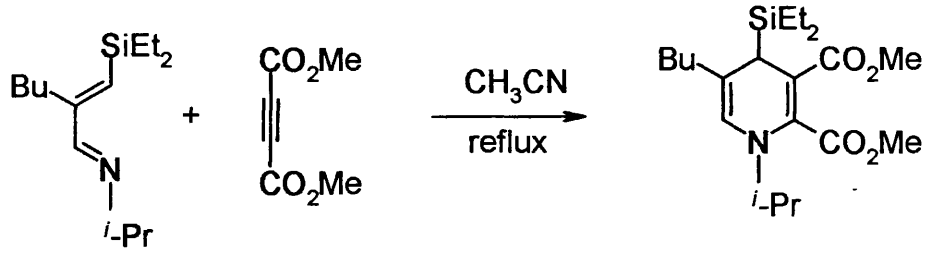
is due to an unfavourable energy barrier in $LUMO_{diene}$-controlled Diels-Alder reaction.[55]



99 **100** **101** **102**

Scheme 44. Cycloaddition reactions of N-alkyl enamines

As we have seen previously matching electronic properties of dieneophile to the diene is a useful tool with these reagents. While cycloaddition is not observed when refluxing a mixture of 4-silylated-1-azadienes with phenylethyne, 1-hexyne or 1-butyne, the more reactive dimethyl acetylene dicarboxylate does undergo Diels-Alder reaction in low to moderate yields[56] (Scheme 45). By substituting the position at C2 this can modify the electronic nature of the N-alkyl-1-azadiene to promote the cycloaddition.[57]



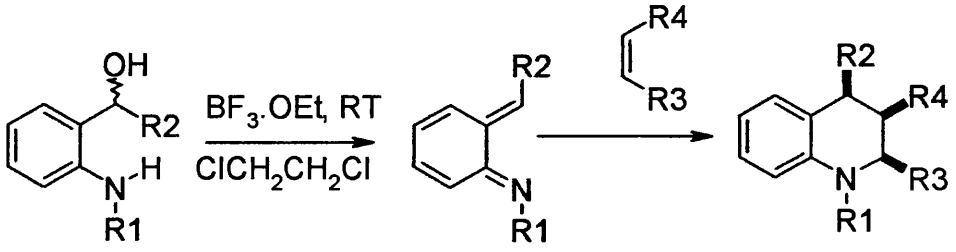
103 **104** **105**
51%

Scheme 45. Cycloaddition of 4-silylated-1-azadienes

1.3.1.4. *o*-Quinone methide imines.

Imines **107**, (scheme 46) are highly reactive intermediates. They have been used successfully in a variety of synthesises for heterocycles. Various methods exist for the production of *o*-methide imines.[58]

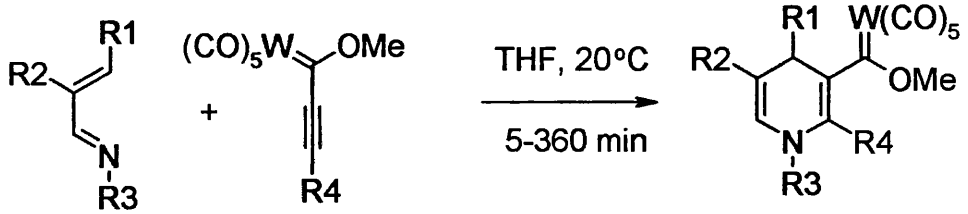
Intra-molecular and intermolecular Diels-Alder cycloadditions have been observed in the *in situ* generation of *o*-quinone by BF_3 etherate additions to *o*-amino benzyllic alcohols. The reactions were shown to be both regio and stereoselective.[59] (scheme 46).



106 **107** **108**

Scheme 46. *In situ* generation of *o*-quinone derivatives

A variety of Fischer carbene-carbodiene Diels-Alder reactions were reported by Berluenga et al. This demonstrated that alkynyl Fischer carbenes participate in [4+2] cycloadditions with N-alkyl enamines.[60] These reactions proceed at room temperature with short reaction times and in good yields compared to the typical *N*-alkyl enimine cycloadditions (scheme 47).

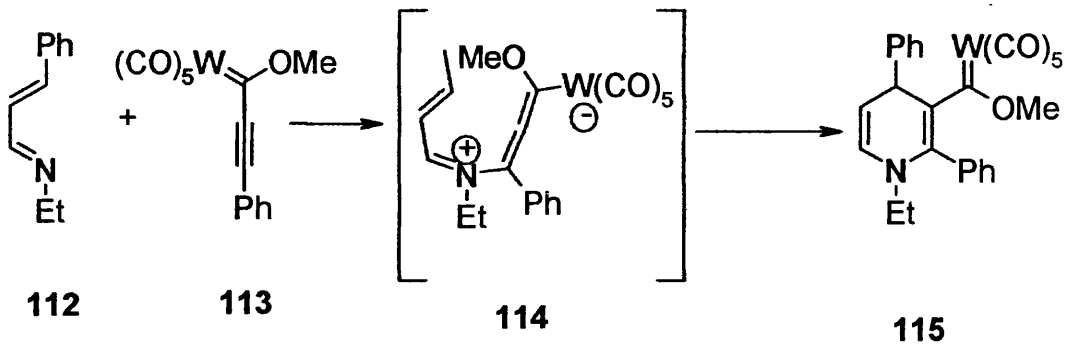


109 **110** **111**
65-95%

R_1=Ph, Me, H
R_2=H, Me
R_3=alkyl, vinyl
R_4=Ph, Me, TMS, Vinyl

Scheme 47. Typical *N*-alkyl enimine cycloadditions

Regiospecificity of the reaction can be accounted for by the formation of an allenic intermediate **114** (Scheme 48).



112 **113** **114** **115**

Scheme 48. Rationalising regiospecificity

Reductions in the HOMO-LUMO separation substantially increase the rate of the reaction. Electron withdrawing substituents to the N-1 and or C-3 positions enhance the reactivity of the 1-azadiene through an inverse electron demand pathway. *N*-acyl- and *N*-sulfonyl groups have been successfully used.

1.3.2 2-Azabutadienes.

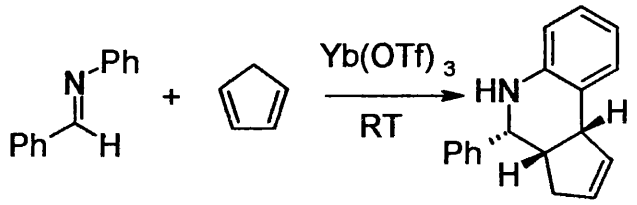
Like the 1-aza-1,3 butadienes, 2-aza-1,3 butadienes have proven themselves to be useful reagents for the Diels-Alder synthesis of pyridones, isoquinolines and pyrimidones. 2 –azabutadienes are generally more reactive than 1-aza 1,3 butadienes however their chemistry is very similar. Appropriate substitution affords either electron rich or electron deficient diene products.

A major difference between the two systems is in efficiency of Lewis acid catalysis of 2-azadiene cycloadditions. Success of these reactions relates to the identification of Lewis acid to which the functional groups complexes. This activates the dieneophile and does not irreversibly complex to the azadiene nitrogen.

1.3.2.1 N-Arylimines.

The first reports of this reaction were by Kobayashi et al.[61] During the course of a typical Diels-Alder reaction with an imine and Danishefsky's diene with lanthanide

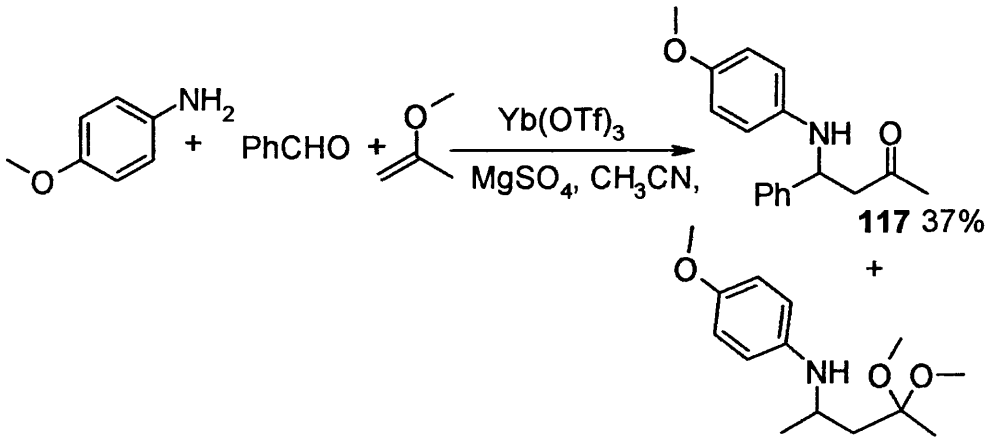
metal triflates (scheme 49), Kobayashi noticed that when the N-arylimine was reacted with cyclopentadiene the reaction proceeded more slowly under the same reaction conditions. After careful examination it was found that the reaction course had changed and had produced a tetrahydroquinoline derivative **116** which was obtained in a high yield.



116
85%

Scheme 49. Tetrahydroquinoline synthesis

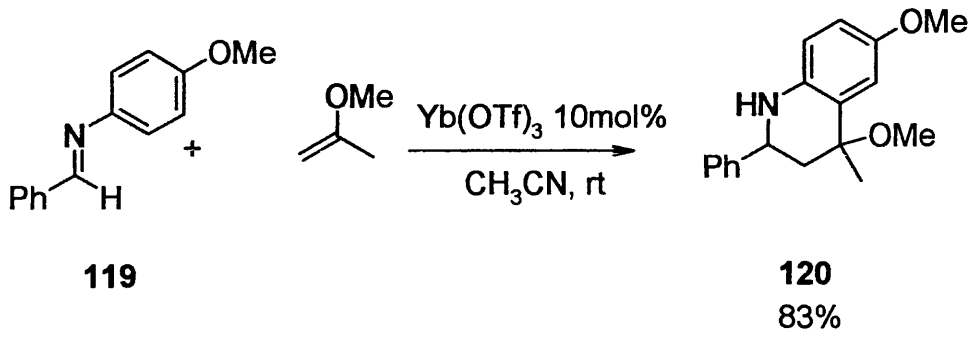
A three component coupling reaction between benzaldehyde, anisidine and 2-methoxypropene did not give the expected tetrahydroquinoline derivative but instead the β-amino ketone and its dimethylacetal. A possible mechanism was suggested (scheme 52) where the intermediate **121** was quenched with water and methanol generated *in situ* to afford **117** and **118** respectively.



117 37%
+
118 34%

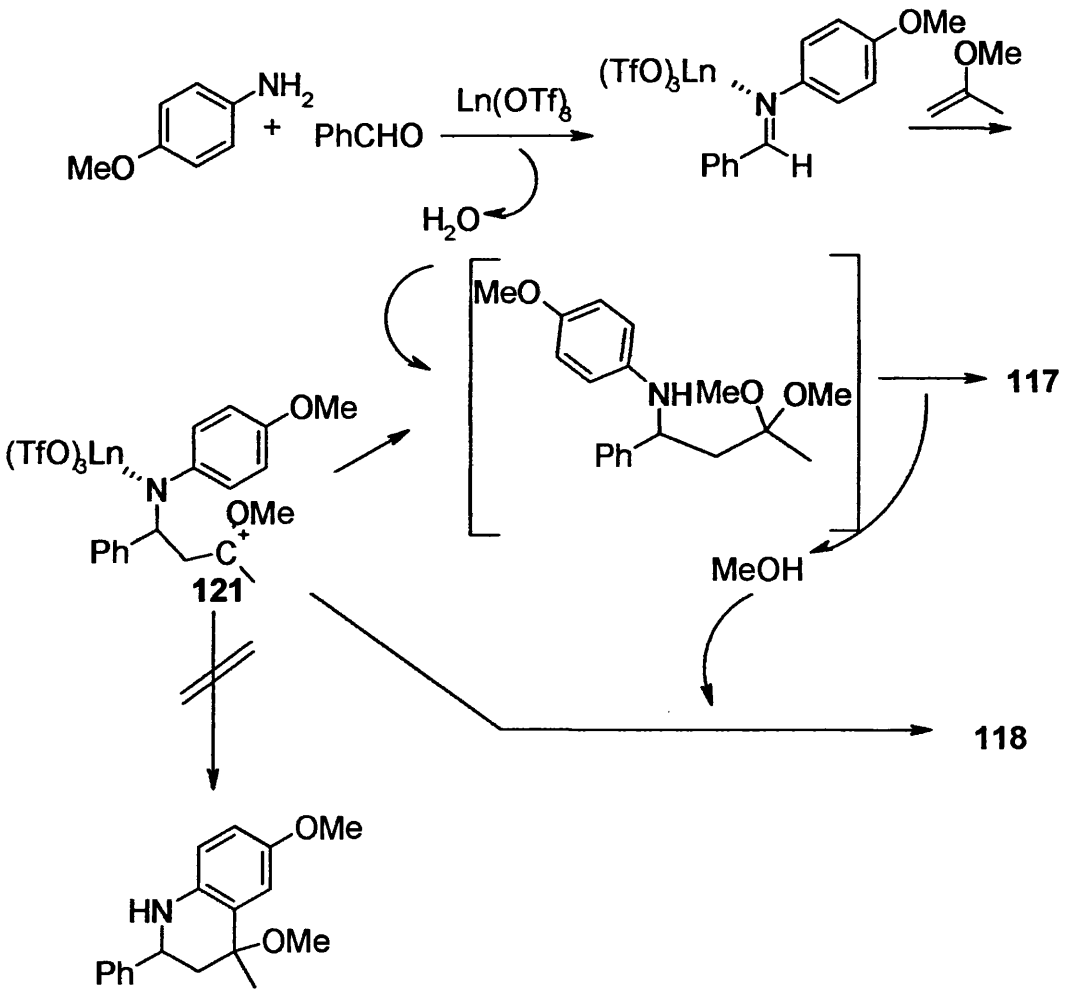
Scheme 50. β-amino ketone and dimethylacetal production

Interestingly imine **119** reacted with 2-methoxypropene to generate the tetrahydroquinoline derivative **120** in 83% yield. This suggested a stepwise mechanism for this process.



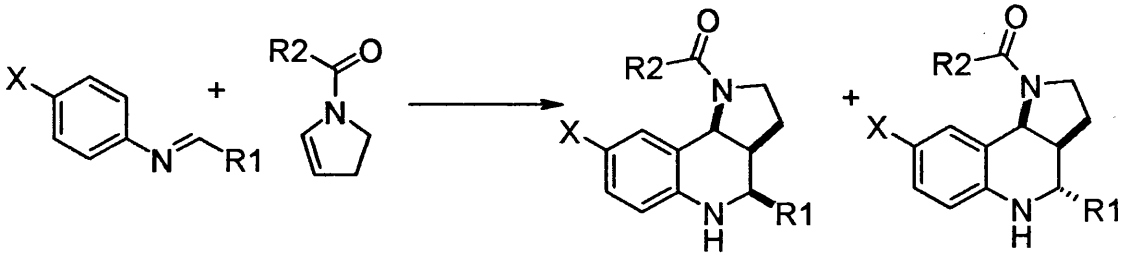
119 **120**
83%

Scheme 51. Preformed imine generation of tetrahydroquinoline derivative



Scheme 52. Proposed mechanism of β-amino ketone and dimethylacetal production

As components of independent efforts directed towards the synthesis of Martinelline, Stevenson and Batey[62] have studied the cycloaddition of N-arylimines with enamines in acetonitrile solution. In this report indium trichloride catalyses the cycloaddition of preformed N-arylimines and enamide. Dienes derived from simple aliphatic amines failed to react, however imines derived form simple glyoxylates underwent cycloaddition in low yields. Aliphatic derived amine derived N-arylimines underwent reactions in moderate yields and with *endo-exo* selectivity that did not exceed 2:1. The CBz protected enamide produced the desired cycloadduct **124** and **125** in 45% Yield in a 1:1 *endo-exo* ratio



X=OMe, R_1=CO_2Me, R_2=Et 20%
X=Me, R_1=Et, R_2=Et 31%
X=H, R_1= CH=CHPh, R_2= Et 52%
X=OMe, R_1= CO_2Et, R_2= OBn 45%

Scheme 53. Cycloaddition of N-arylimines with enamines

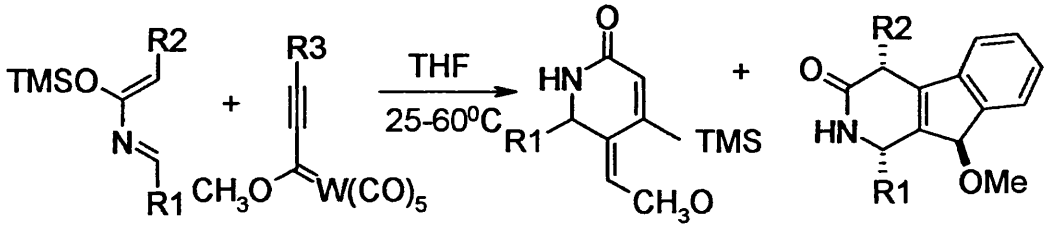
1.3.3 Mechanistic aspects

Based on semi imperial calculations of their LUMO energies and p-orbitals coefficients cationic 2-azabutadienes have been shown to be more reactive and selective than neutral analogues.[63] Empirical evidence suggests that non-concerted mechanisms play a significant sole in systems with dienophiles that stabilise the intermediate cation.[64,65] In the cycloaddition of 2-azadienes and aldehydes the Lewis acid/Brønsted catalyst lowers the dienophile LUMO increasing the charge transfer from the diene to the dienophile in the transition state. The *anti*-co-ordination if the Lewis acid to the dienophile and electrostatic interaction between the Lewis acid and the diene nitrogen lone pair are responsible for *exo*-co-ordination of the catalyst in the transition state.

1.3.3.1 Catalysed reactions.

Lewis acid catalysis has received considerable attention in promoting 2-azadiene cycloaddition.[66] Whilst Lewis acids are essential for the reaction to proceed, supra-stoichiometric quantities of the Lewis acid are often required. This is to overcome the substantial co-ordination of the acid to the nitrogen atom. In contrast sub-stoichiometric amounts of $InCl_3$ can catalyse the same reaction.[67] See chapter 1.3.2.1.

As in the case of 1-azadienes, cycloaddition of 2-azadienes with alkynl Fischer carbene complexes have been studied by Barluenga et al.[68] While 3-siloxy-2-azadiene was found to be unreactive towards methyl phenylpropiaolate after 7 days refluxing in toluene, the (trimethylsilyl)-ethynyl carbene proved reactive at room temperature. The pyridone cycloadduct was produced on 92% yield and was subsequently converted to **128** by heating to 60°C (scheme 54).

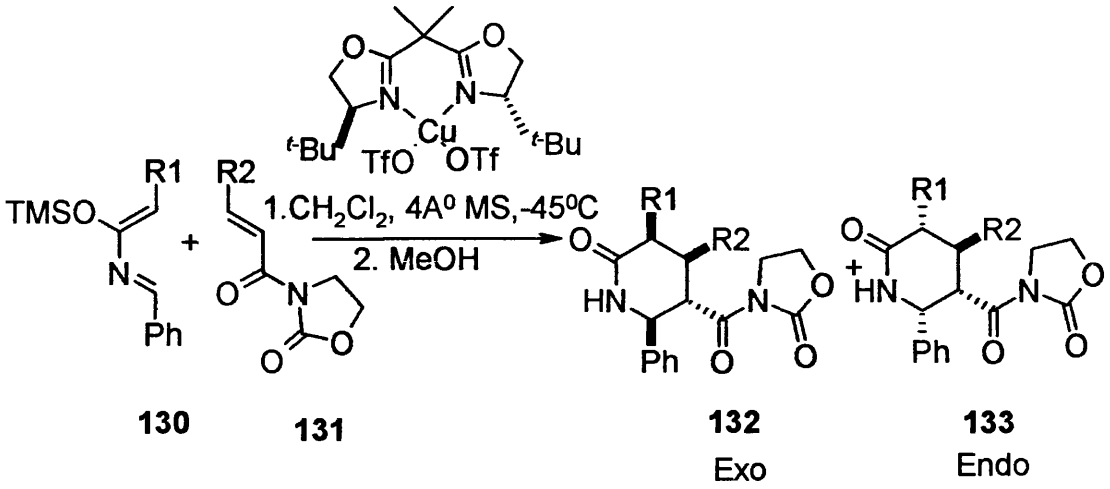


126	127	128	129
R_1=*t*-Bu, R_2=H, R_3= TMS		82%	
R_1=2-furyl, R_2=H, R_3=TMS		71%	
R_1= *t*-Bu, R_2= H, R_3=Ph		76%	
R_1=Ph, R_2=H, R_3=Ph			84%
R_1= *t*-Bu, R_2=Me, R_3=Ph.			62%

Scheme 54. 2-Azadienes cycloaddition

In an attempt to achieve asymmetric cycloaddition of 3-siloxy-2-azadienes to olefinic dienophiles, Ghosez et al.[69] Have utilised Evans's copper (II) triflate bisoxzazoline ligand complex. An advantage of this system is that the catalyst activated the dienophile with out irreversibly complexing to the heterodiene nitrogen. Increases in

diastereo, enantioselectivity and rate were reported for reactions proceeding between -45°C and room temperature (Scheme 55, Table 11).

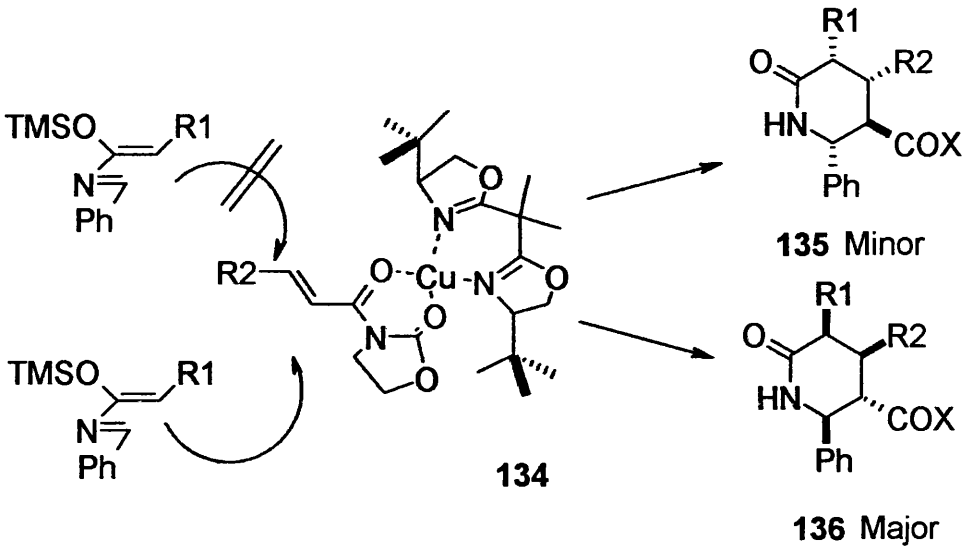


Scheme 55. Cycloaddition of 3-siloxy-2-azadienes

Table 11. Asymmetric cycloaddition of 3-siloxy-2-azadienes

Entry	R1	R2	Yield (%)	exo:endo (%)	ee (%)
1	CH_3	CH_3	80	>99:1	95
2	CH_3	H	96	>99:1	98
3	H	H	83	6:1	98

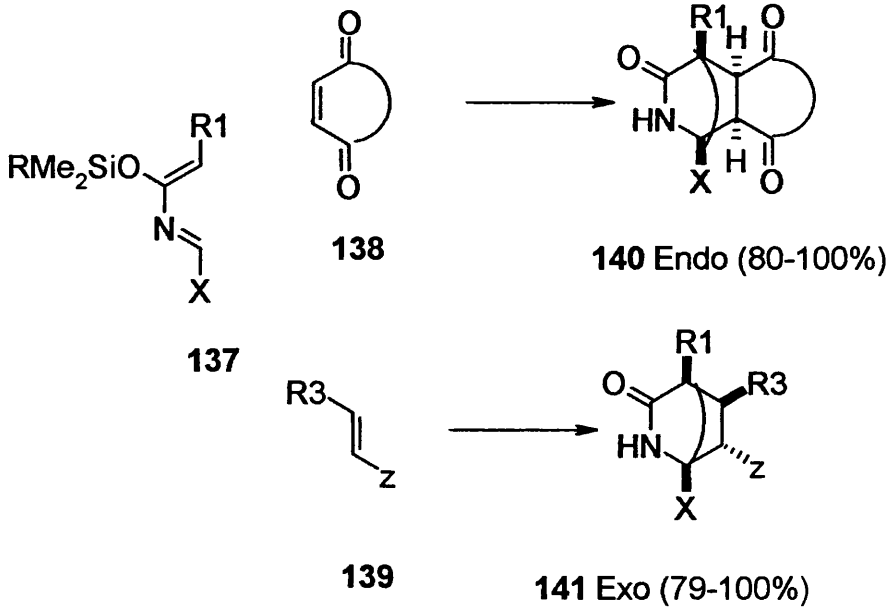
The configuration of the new stereogenic centre is accurately predicted by Evans's transition state model (Scheme 56), previously proposed for application of the identical catalyst. The predicted *exo*-selectivity was excellent with the exception of the 4-unsubstitued azadiene.



Scheme 56. Evans's transition state model

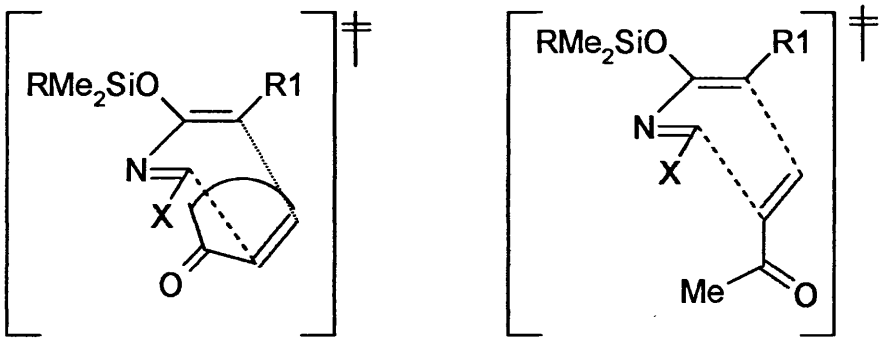
1.3.3.2. Stereoselective cycloaddition.

Cycloadditions of 2-azadienes with electron deficient olefins show interesting stereoselectivity.[70] In the reactions of cyclic dienophiles *endo*-selectivity was observed **140**, while with acyclic dienophiles display *exo*-selectivity **141** (scheme 57).



Scheme 57. cyclic dienophiles and acyclic dienophiles cyclisation

The selectivity has been attributed to the reacting conformations. The *endo*-transition state is stabilised by secondary orbital interaction. In addition lacking electrostatic repulsion between the heteroatoms would be preferred over the *exo*-transition state in reactions of cyclic dienophiles constrained to the *s*-trans conformation (Scheme 58) In the acyclic case the reaction would proceed through the *s-cis* conformation. The *exo*-transition state is preferred largely due to electrostatic repulsion between the heteroatoms. This would overcome the stabilisation due to secondary orbital interactions in the *endo*-transition state.

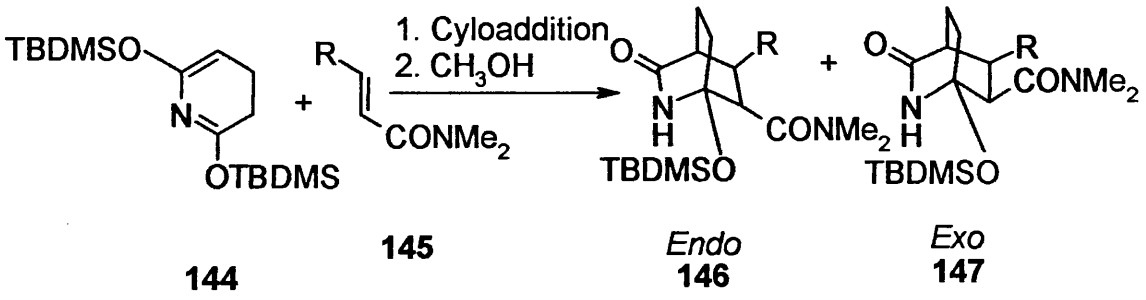


Endo-TS
Cyclic dienophiles
142

Exo-TS
Acyclic dienophiles
143

Scheme 58. Transition state models

Ghosez et al reasoned that the addition of a Lewis acid would generate an iminium ion dienophile, which would replace the electrostatic repulsion of the diene nitrogen to the carbonyl group with coulombic attraction between the diene nitrogen and a positively charged species (scheme 59). The addition of *t*-butyldimethylsiyl triflate provided the desired *endo*-product but only in the case where R=H, **145**. In 4-substituted α,β-unsaturated amides the *exo*-products were observed exclusively, as was also observed with the addition of $Eu(fod)_3$ (Table 12).



Scheme 59. 4-Substituted α,β-unsaturated amides

Table 12. Results for scheme 59

Entry	R	Conditions	endo:exo	Yield %
1	H	No Cat, benzene, heat.	15:85	53
2	H	0.1 eq. TBDMSOTf, benzene, rt.	84:16	92
3	H	0.1 eq. TBDMSOTf, CH_3CN, RT	<1:>99	40
4	H	0.1eq $Eu(fod)_3$, benzene, 80°C	<3:>97	80
5	CH_3	0.2 eq. TBDMSOTf, toluene, 60°C	<1:>99	77
6	CH_3	0.2 eq. TBDMSOTf, toluene, 60°C	<1:>99	73

1.4 References:

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Results and Discussion

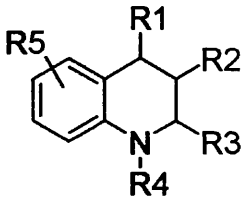
2.1 Aims and objectives

The objective of this project was to generate chiral tetrahydroquinoline cycloadducts in one step, from an achiral imine and cyclopentadiene with a chiral indium (III) catalyst. Ultimately these tetrahydroquinoline adducts could be further functionalised to generate a fast and efficient method of production for natural product templates.

2.1.1 Envisaged program of work

Initial studies would concentrate on the optimisation of a current one-step synthesis of tetrahydroquinoline cycloadducts with indium (III) chloride and indium (III) triflate. After optimisation, generation of chiral tetrahydroquinoline cycloadducts would be attempted using achiral imines and cyclopentadiene with a chiral indium (III) catalyst. Monodentate and bidentate imines would be utilised to maximise binding potential to the indium (III) cation. Finally, further functionalisation of the alkene and aromatic moieties on the cycloadducts would be attempted to generate natural product templates.

2.1.2 Standard tetrahydroquinoline synthesis



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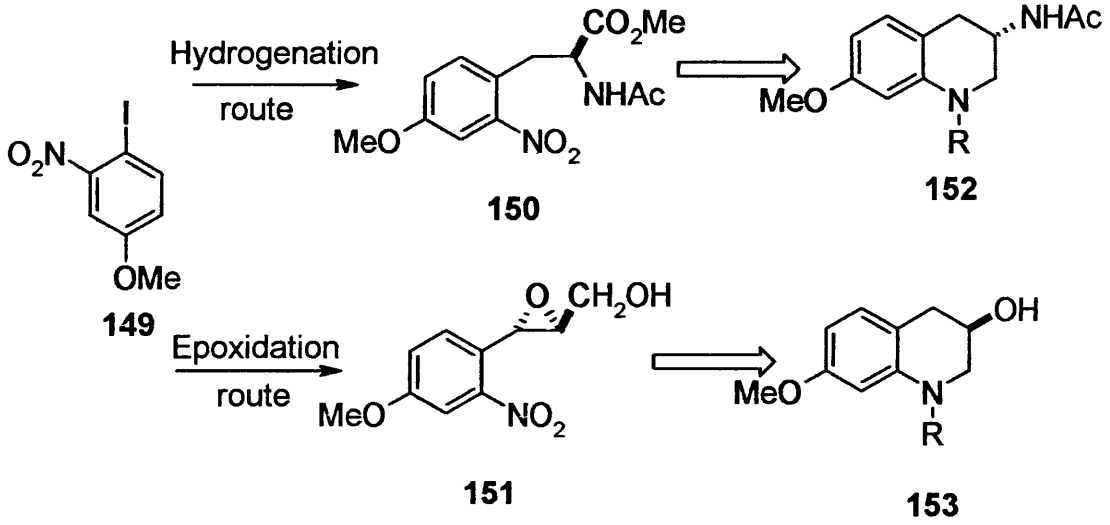
Scheme 60. Tetrahydroquinoline template

Tetrahydroquinoline derivatives (scheme 60) are an important class of natural products. Their skeletal template is found in a wide variety of biologically active pharmaceuticals. Several derivatives have been found to exhibit potent biological responses. For example analgesic, cardiovascular immnuosupressent, antitumor, antiallergenic, anticonvulsant, antiinfertitlty and NMDA antagonist activities have all been reported.[1] Derivatives of tetrahydroquinolines have also found to be pesticides, antioxidants, photosensitisers and dyes.[2] Many synthetic methods have been developed for these compounds. At present chiral tetrahydroquinoline adducts are generally synthesised using long, laborious and expensive methods.

The key steps in two popular routes to tetrahydroquinolines are enantioselective rhodium catalysed asymmetric hydrogenation and Sharpless epoxidation of *o*-nitrocinnamyl substrates. The resulting intermediates can be further transformed into tetrahydroquinoline derivatives. Starting materials are generally prepared via the Heck reaction and tetrahydroquinoline adducts can then be obtained in approximately 8 steps (scheme 61).[3]

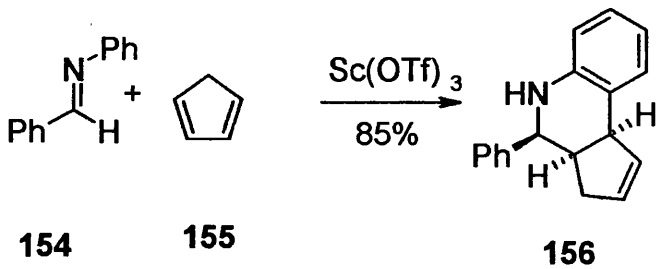


Scheme 61. Contemporary methods of tetrahydropyridine synthesis

2.1.3 Hetero Diels-Alder method.

One of the most useful synthetic methodologies for the construction of nitrogen containing six membered heterocycles is the aza Diels-Alder reaction.

As has been discussed in the introduction chapter, Kobayashi et al.[4] discovered that N-arylimines could act as hetero dienes under lanthanide metal triflates catalysis (scheme 62). During the course of a typical Diels-Alder reaction with Danishefsky's diene, Kobayashi noticed that when N-arylimines react with cyclopentadiene, the reaction proceeded more slowly than had been previously recorded. On inspection it was found that the course of the reaction had changed. Instead of producing the desired tetrahydropyridine product, a tetrahydroquinoline product was instead observed in high yield.



Scheme 62. *N*-Arylimine as a heterodiene

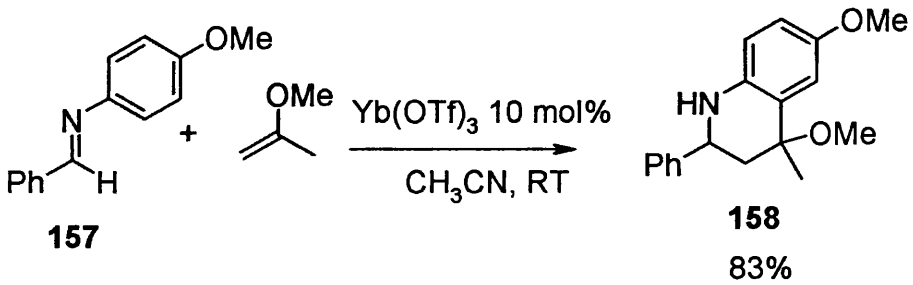
Since the pioneering work of Povarov,[5] $BF_3.OEt_2$ has been the most commonly used catalyst in this reaction. Transition metal complexes such as $Co(CO)_8$ and $Ni(CO)_4$

have been found to be effective.[6] Lanthanide triflates are very successful[7] and more recently $InCl_3$ has found its use in this reaction.[8]

Though recently much work has been devoted to the diastereoselective inverse electron demand Diels-Alder reactions, very few asymmetric methods exist for generating these tetrahydroquinoline products.[9]

Reports on the synthesis of asymmetric quinoline derivatives are limited.[10] Inverse electron demand Diels-Alder reactions can be used to synthesise quinoline derivatives where cycloaddition of electron poor 2-azadienes with an electron rich dienophile is facilitated by chiral Lewis Acid catalysis.[11] Here the reversible complexation with Lewis acids makes the 2-azadiene system more reactive in a concerted Diels-Alder process. This is due to the energy gap decrease between the LUMO of the 2-azadiene and the HOMO of the dienophile.[12]

One pot synthesis of the imine starting materials is not always practical in this reaction. It has been shown that a three component coupling reaction between benzaldehyde, anisidine and 2-methoxypropene did not give the tetrahydroquinoline derivative as expected but the β-amino ketone and its dimethylacetal. However, when the performed imine was used, the reaction affording the tetrahydroquinoline derivative was successful (scheme 63).[13]



157 **158** 83%

Scheme 63. Pre-formed imine cycloaddition with 2-methoxypropene.

Many imines are hydroscopic, difficult to purify by distillation and lack reactivity. Therefore, for these reactions to be synthetically useful we required a very effective catalyst. We chose indium salts for this reaction as they had previously shown to be successful, however there was an great opportunity to make this reaction

enantioselective with a chiral indium catalyst which would make this a novel reaction. This would simplify the current 8-step synthesis to tetrahydroquinoline cycloadducts.

Indium is in group 13 of the periodic table (scheme 64). Compounds of boron, aluminium and gallium have displayed Lewis acidity in chiral reactions. Although indium belongs to the same group as boron and aluminium, the utility of chiral indium salts has not been exploited to a greater extent largely due to its mild Lewis acid character. Indium has an ionic radius similar to scandium, another element whose chiral compounds display Lewis acidity for Hetero Diels-Alder reactions. One major advantage of indium, which would make it a good chiral catalyst, is that ligand association and dissociation is fast, which means that the reaction rate could be greatly increased. Indium is tolerant of both air and water, which makes it an ideal catalyst to work with on the bench.

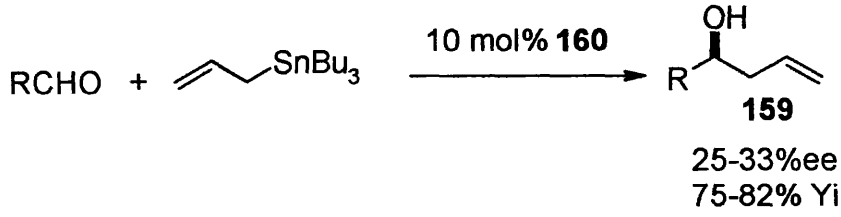
	B	
	Al	
	Ga	
Cd	**In**	Sn
Hg	Tl	Pb

Scheme 64. Group 13

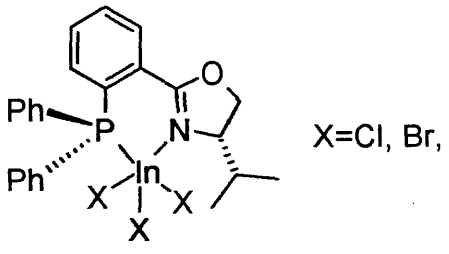
Recent years have seen an increased utility of indium reagents in synthesis. Organoindium reagents have been used in a variety of transformations including allylations, Reformatsky reactions and cyclopropanations.[14] Indium metal has also been found to be an effective reducing agent.[15] In particular indium (III) halide complexes are efficient Lewis acids and have been proven to be useful in Mukaiyama aldol reactions, Friedel-Crafts acylation and Diels-Alder cycloadditions amongst others[16]

Few examples of chiral indium complexes (scheme 66) were found in the literature. Indium salts were shown to improve the enantiomeric excesses in allyl reactions with chiral stannanes.[17] Chiral indium complexes have also been shown to improve the

enantioselectivity in the allylation reaction of allylic stannanes with aldehydes to yield chiral alcohols **159** (scheme 65).[18]



Scheme 65. Enantioselective allylation reactions under indium catalysis.



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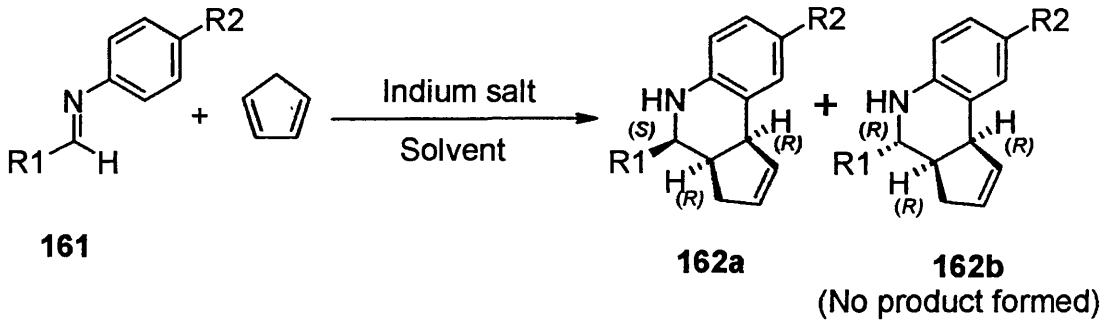
Scheme 66. Chiral indium (III) catalyst

With this literature precedent in hand we set out to generate a chiral indium catalyst for the hetero Diels-Alder reaction to generate tetrahydroquinoline cycloadducts.

2.1.4 Aza Diels-Alder reaction of imines and cyclopentadiene under indium catalysts.

Initial studies focused upon the reaction between substituted imines **161** and cyclopentadiene. Five selected imines N-[(*E*)-phenylmethylidene]aniline (R1=Ph, R2=H), 4-bromo-*N*-[(*E*)-phenylmethylidene]aniline, (R1=Ph, R2=Br), 3-methoxy-*N*-[(*E*)-phenylmethylidene]aniline (R1=Ph, R2=OMe), *N*-[(*E*)-phenylmethylidene]-3-(trifluoromethyl)aniline (R1=Ph, R2=CF_3), ethyl 2-{[3-(trifluoromethyl)phenyl]imino acetate (R1=CO_2Et, R2=CF_3) and ethyl 2-[(3-methoxyphenyl)imino] acetate (R1=CO_2Et, R2=OMe) were reacted with cyclopentadiene. The reactions were performed in dry DCM or MeCN under an inert atmosphere. Choice of Lewis acid, time and temperature were modified in order to optimise the reaction (Scheme 67, Table 13).



161 162a 162b (No product formed)

Scheme 67. Optimisation study of achiral azadienes with cyclopentadiene

Table 13. Optimisation study of scheme 67.

Entry	R1	R2	Catalyst	Temp °C	Time (Hrs)	Solvent	Yield **162a** (%)
1	Ph	H	-	RT	24	MeCN	-
2	Ph	H	$In(OTf)_3$ (10 mol%)	RT	24	MeCN	65
3	Ph	H	$In(OTf)_3$ (10 mol%)	RT	3	MeCN	40
4	Ph	H	$In(OTf)_3$ (10 mol%)	RT	1	MeCN	25
5	Ph	H	$In(OTf)_3$ (1 mol%)	RT	1	MeCN	15
6	Ph	H	$In(OTf)_3$ (10 mol%)	RT	24	DCM	95
7	Ph	H	$InCl_3$ (10 mol%)	RT	24	DCM	100
8	Ph	H	$InCl_3$ (1 mol%)	RT	24	DCM	96
9	Ph	H	$InCl_3$ (1mol%)	RT	3	DCM	61
10	Ph	Br	$InCl_3$ (1 mol%)	RT	3	DCM	100
11	Ph	Br	$InCl_3$ (1 mol%)	RT	1	DCM	99
12	Ph	H	$InCl_3$ (1 mol%)	50	3	DCM	64
13	Ph	OMe	$InCl_3$ (10 mol%)	RT	24	DCM	48
14	Ph	CF_3	$InCl_3$ (10 mol%)	RT	24	DCM	94
15	CO_2Et	CF_3	$InCl_3$ (10 mol%)	RT	24	DCM	92
16	CO_2Et	OMe	$InCl_3$ (10 mol%)	RT	24	DCM	87
17	Ph	H	Cu(I)Cl (10 mol%)	RT	24	DCM	5
18	Ph	H	$RhPF_6$(10 mol%)	RT	24	DCM	12
19	Ph	H	$Ir(PF_6$ (10 mol%)	RT	24	DCM	8
20	Ph	H	$Sc(OTf)_3$ (10mol%)	RT	24	DCM	80
21	Ph	H	$Yb(OTf)_3$ (10 mol%)	RT	24	DCM	85

This reaction was very successful with indium (III) chloride and indium (III) triflate. It can also be seen that indium demonstrated significantly enhanced reaction rates compared to other Lewis acid catalysts.

2.1.4.1 Counterion effect.

From Table 13, it can be seen that indium (III) chloride worked slightly better in this reaction than indium (III) triflate. Whilst triflates are presumed to be more weakly co-ordinating than chloride anions, triflates are renowned for being hydroscopic. Trace amounts of water in the indium (III) triflate may account for diminished reactivity. Indium (III) chloride is more robust and therefore may account for increased reactivity. Whilst there is no appreciable difference between the two catalysts, due to the inexpensiveness of indium (III) chloride in comparison with indium (III) triflate this was the catalyst of choice for future reactions.

2.1.4.2 Solvent effects.

The reactions were carried out in dry dichloromethane (DCM) and acetonitrile (MeCN). Solvents can be defined into two categories, co-ordinating solvents and non-co-ordinating solvents. Solvents such as DCM, MeCN and toluene are considered as non co-ordinating solvents, where DMSO, ethanol and ethers are considered to be co-ordinating. DCM is considered also as acidic solvents as protons in the DCM molecule are significantly more acidic than in a solvent such as acetonitrile. DCM is therefore less co-ordinating to the metal centre and more acidic than MeCN in the reaction and these property most likely accounts for increased the rate of the reaction.

2.1.4.3 Catalyst and %concentration.

The reaction was performed with other Lewis acids: Rh, Ir, Sc and Yb salts. It can be clearly seen that Indium salts perform much better than the other Lewis acids in this reaction (total conversion for indium compared to 5-85% for other Lewis acids). Catalyst loading of 10 mol% and 1 mol% with indium (III) triflate and indium (III) chloride were undertaken (100%, RT, 24h, DCM, 10 mol% $InCl_3$ compared to 96%, RT, 24h, DCM, 1 mol% $InCl_3$). We can conclude from these results that indium chloride and triflate are both as effective at 1 mol% concentration as they are at 10 mol% concentration. This has remarkably beneficial effects due to the inexpensivness of the indium salts, using less enables economically viable reactions. Lower catalyst

loading also enables lower ligand loading which has important consequences when trying to complex the metal salt to an expensive chiral ligand

2.1.4.4 Effects of increased temperature.

The reactions were performed at room temperature and 50°C. Heating the reaction to 50°C had no dramatic impact upon the reaction rate. This was very pleasing since most chiral reactions take place at lower temperatures so that absolute control over the stereochemistry is possible.

2.1.4.5 Reaction time

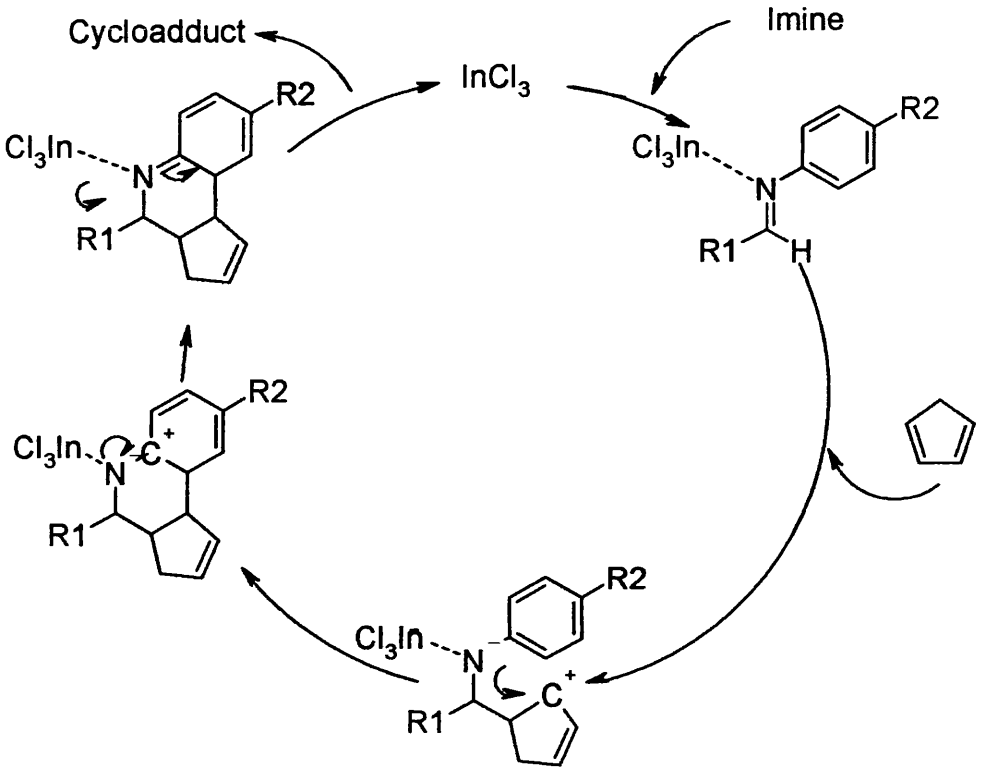
The reaction was performed for a period of twenty-four hours, three hours and one hour. It was found that longer reaction times were more productive, however most reactions had proceeded significantly after one hour.

2.1.4.6 Electronic effects

The nature of the *para* substituent R2 had a dramatic effect upon the reaction. An electron withdrawing (CF_3, Br) or neutral group (H) proved to be the best substituents. It was also shown that when an electron withdrawing substituent was placed on the α carbon of the imine, tetrahydroquinoline cycloaddition could be prepared successfully. The electron withdrawing effect upon the imine accelerates the production of the tetrahydroquinoline cycloadduct. The limitation of glyoxylate imines is their high reactivity and inherent instability. To achieve an efficient synthesis these imines were generated *in situ* from glyoxylate, and *p*-anisidine and 5 equivalents of $MgSO_4$. Once this reaction was complete the cyclopentadiene and catalyst were added and the tetrahydroquinoline cycloadduct was obtained in good to moderate yield.

2.1.5 Mechanistic aspects

A possible reaction mechanism has been proposed by Kobayashi et al.[19] based upon the HOMO and LUMO energy coefficients of protonated imines. Increased reactivity of imines with *p*-EWG'g towards electrophiles in comparison to *p*-EDG's suggested that a stepwise mechanism was occurring in this reaction (Scheme 68).



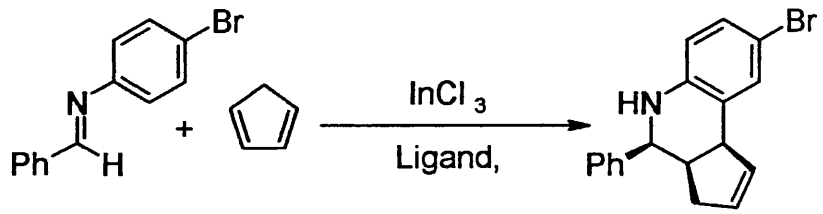
Scheme 68. Proposed mechanism of cycloaddition

A high degree of regioisomerism is observed in this reaction as only one tetrahydroquinoline product is formed. The double bond from the cyclopentadiene could be observed in the tetrahydroquinoline product as the 3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline or the 3a,4,5,9b-tetrahydro-1H-cyclopenta[c]quinoline cycloadducts. The justification as to the production of a unique regioisomer lies in the formation of a stabilised allylic carbocation transition state formation. The observed electron withdrawing group acceleration is due to a stabilised negative charge formed on the nitrogen atom. The possibility of diasteromers to form in this reaction is also of great importance. Our primary aim was try to expand the reaction to encompass an

efficient diastereoselective/enantioselective catalytic process with a chiral indium catalyst.

2.1.6 Attempted Synthesis of Chiral Tetrahydroquinoline Derivatives with Chiral Indium Catalysts.

The hetero Diels-Alder reaction was repeated with a range of diverse bidentate nitrogen, phosphorous, oxygen and hybrid oxazoline type ligands. Previously optimised conditions were used. To optimise the enantioselective catalytic reaction, time, temperature and catalyst loading were varied. 4-bromo-*N*-[(*E*)-phenylmethylidene]aniline and cyclopentadiene were the reactants of choice. This imine was selected because it was the most reactive in our initial studies. The bromine moiety also serves as a point of secondary binding capability.



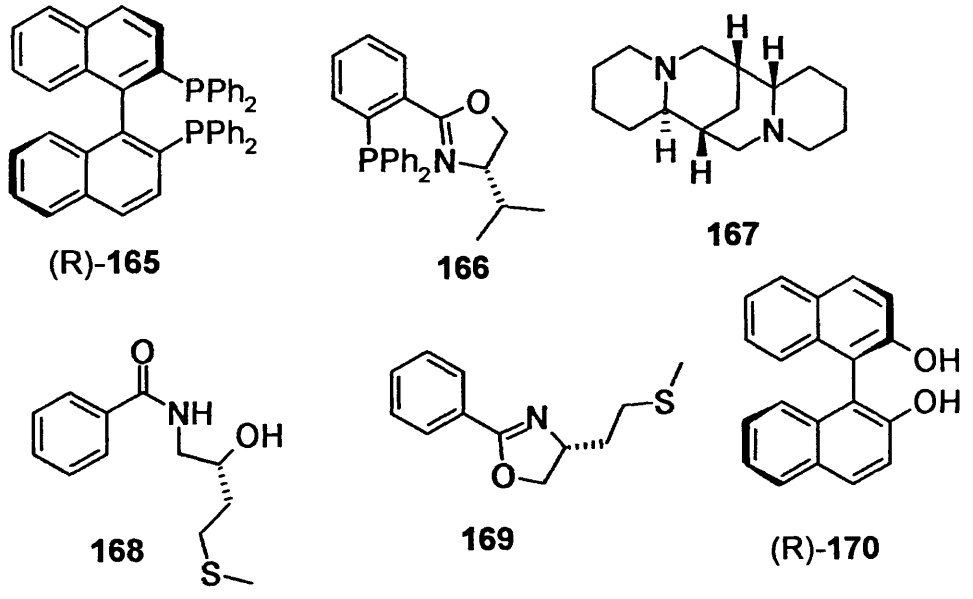
163 **164**

Scheme 69. Synthesis of 8-bromo-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline using $InCl_3$

Table 14. Asymmetric aza Diels-Alder reactions-the efficiency of the chiral ligand

Entry	Catalyst	Ligand	Temp °C	Time (Hrs)	Solvent	Yield %	ee%
1	-	-	RT	24	DCM	1	-
2	$InCl_3$ (10 mol%)	-	RT	24	MeCN	87	-
3	$InCl_3$ (10 mol%)	-	RT	24	DCM	98	-
4	$InCl_3$ (1 mol%)	-	RT	24	DCM	94	-
5	$InCl_3$ (1 mol%)	-	RT	1	DCM	95	-
6	$InCl_3$ (1 mol%)	(R)-**165**	RT	1	DCM	99	11
7	$InCl_3$ (1 mol%)	**166**	RT	1	DCM	63	11
8	$InCl_3$ (1 mol%)	**167**	RT	1	DCM	24	6
9	$InCl_3$ (1 mol%)	(S)-**165**	RT	1	DCM	98	10
10	$InCl_3$ (1 mol%)	**168**	RT	1	DCM	72	14
11	$InCl_3$ (1 mol%)	**169**	RT	1	DCM	95	12
12	$InCl_3$ (1 mol%)	**170**	RT	1	DCM	12	6
13	$InCl_3$ (1 mol%)	(R)-**165**	0	1	DCM	10	5
14	$InCl_3$ (1 mol%)	(R)-**165**	-20	1	DCM	5	7
15	$InCl_3$ (10 mol%)	(R)-**165**	0	24	DCM	17	10

The ligand and catalyst were left to complex at room temperature for one our before the reagents were added. Yields varied from total conversion to 5% conversion. Some enantioselectivity was observed albeit at low levels. The chiral ligands examined in the reaction are illustrated in scheme 70.



Scheme 70. Chiral ligands employed in the synthesis of 8-bromo-4-phenyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*c*]quinoline

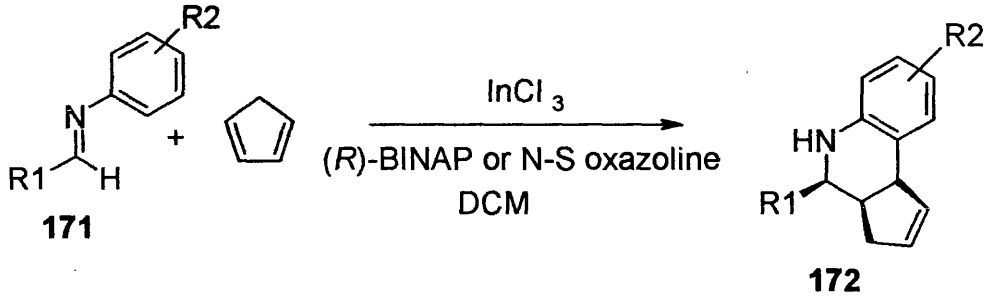
Complexing indium to chiral bis-phosphine ligands gave products in the highest yields (100%), however minimal enantioselectivity was achieved. When a hybrid bidentate phosphorous-nitrogen ligand (oxazoline) was utilised, the yield dropped from total conversion of the cycloadduct to only 63%. Again enantioselectivity was constant at 11%. We could observe the same relationship when Nitrogen-sulphur oxazoline type ligands were used. The yield of the cycloadduct being 72%. When bis-chelating nitrogen and oxygen ligands, (-) Sparteine and (R)-BINOL were employed a dramatic decrease in the yield of the reaction product resulted (24 and 12% respectively). From these three experiments we can deduce that indium has very different complexing abilities to different ligands. When Indium is bound to nitrogen and oxygen containing ligands, increased metal-ligand attachment is observed, affecting the 'Lewis acidity' of the indium, resulting in the catalyst being inhibited. Compounds with less Lewis basic electron donors such as bisoxazoline N-S and N-P ligands are therefore more successful. Co-ordination of the Lewis acid to the C=N

enhances the electophilicity of the C=N towards 'nucleophilic' attack from the otherwise unreactive diene/dienophile moiety. Successful enantioselective catalysts co-ordinate strongly enough with the nitrogen of the imine group and chiral ligand to form a compact transition state model such that the Diels-Alder reaction takes place. Ligands must also bind tightly to the metal centre to ensure effective transfer of chirality. However they must not co-ordinate to the product too strongly otherwise catalytic turnover is suppressed. It can be concluded from these experiments that with an sp^3 lone pair donor such as the nitrogen on the (-) Spartiene and the oxygen on the BINOL complex these compounds bind tightly to the indium metal centre. Sp^3 oxygen and nitrogen donors are incapable of performing as π-acceptors, therefore donation of electron density to the metal centre increases, hence the electron density increases at indium resulting in lower Lewis acidity. We can conclude from the low reactivity of the indium BINOL complex that BINOL forms a 'formal' bond to indium, suppressing catalytic activity. This is illustrated in the yield of the tetrahydroquinoline product (only 5%).

With BINAP ligands the phosphorous atoms are both π- donors and π-acceptors. Electron pairs donating from phosphorous occur in addition to back bonding into vacant *p* orbitals of the P atom. However, since we observe no real enantioselectivity we could also assume that there is no bonding at all between the P atoms on BINAP and the indium metal, which would account for the high reactivity as the metal centre is exposed. A final aspect that should be considered is that ligand association and dissociation is so fast that high reactivity would be observed but not the corresponding enantioselectivity.

Anothr possible explanation for low chiral induction was that the bromine moiety on the aromatic ring was not in a suitable position to bind effectively to the indium metal centre, if at all. It was evident that a fine balance of reactivity and binary chelating capability needed to be accomplished. With this as our objective various imines were prepared with either *ortho-* or *para-* Lewis basic functions. Imines were also prepared with the carbonyl moiety at the carbon terminus of the C=N. In previous experiments the carbonyl function of the N-aryl glyoxylate imines demonstrated substantial activating capability whilst additionally contributing as a secondary chelating group.

All reactions were carried out under an inert atmosphere in dry DCM. Modifying the chiral ligand, catalyst loading, time and temperature were the variables considered (Scheme 71, Table 15).



Scheme 71. Tetrahydroquinoline synthesis using bidentate imine precursors

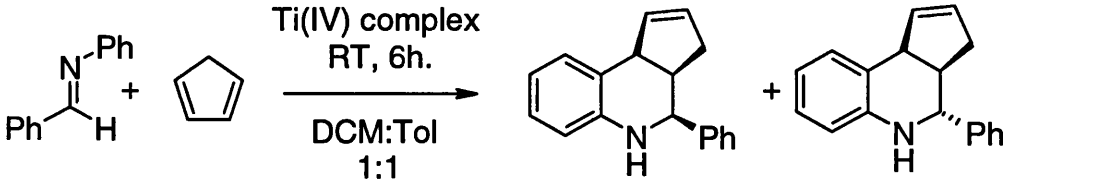
Table 15. Substituent effects upon enantioselectivity.

Entry	R1	R2	Catalyst	Ligand	Time (Hrs)	Temp °C	Yield %	Ee %
1	Ph	*o*-Br	-	-	24	RT	4	-
2	Ph	*o*-Br	$InCl_3$ 10 mol%	-	24	RT	85	-
3	Ph	*o*-Br	$InCl_3$10mol%	**(*R*)-165**	24	RT	92	7
4	Ph	*o*-Br	$InCl_3$10mol%	**(*R*)-165**	1	RT	95	4
5	Ph	*o*-Br	$InCl_3$10mol%	**(*R*)-165**	1	0	24	2
6	Ph	*o*-Br	$InCl_3$10mol%	**(*R*)-165**	1	-78	7	8
7	Ph	*o*-Br	$InCl_3$1mol%	**(*R*)-165**	1	RT	86	4
8	Ph	*o*-Br	$InCl_3$1mol%	**169**	1	RT	67	6
9	Ph	*o*-Br	$InCl_3$1mol%	**169**	1	-78	0	5
10	CO_2Et	*p*-Br	-	-	24	RT	9	-
11	CO_2Et	*p*-Br	$InCl_3$10mol%	-	24	RT	98	-
12	CO_2Et	*p*-Br	$InCl_3$10mol%	**(*R*)-165**	24	RT	94	7
13	CO_2Et	*p*-Br	$InCl_3$10mol%	**(*R*)-165**	1	-78	22	9
14	CO_2Et	*p*-Br	$InCl_3$10mol%	**169**	1	-78	16	6
15	Ph	*p*-OMe	-	-	24	RT	0	-
16	Ph	*p*-OMe	$InCl_3$10mol%	-	24	RT	71	-
17	Ph	*p*-OMe	$InCl_3$10mol%	**(*R*)-165**	24	RT	64	2
18	Ph	*p*-OMe	$InCl_3$10mol%	**(*R*)-165**	1	-78	0	5
19	Ph	*p*-OMe	$InCl_3$10mol%	**169**	1	-78	0	4
20	CO_2Et	*p*-OMe	-	-	24	RT	0	-
21	[a]CO_2Et	*p*-OMe	$InCl_3$10mol%	-	24	RT	0	-
22	Furyl	H	$InCl_3$ 10mol%	-	24	RT	0	-
23	Pyrrole	H	$InCl_3$10mol%	-	24	RT	0	-
24	CO_2Et	*p*-CF_3	$InCl_3$10mol%	-	24	RT	95	-
25	CO_2Et	*p*-CF_3	$InCl_3$10mol%	**(*R*)-165**	1	0	37	7
26	CO_2Et	*p*-CF_3	$InCl_3$10mol%	**(*R*)-165**	1	-78	12	10
27	CO_2Et	*p*-CF_3	$InCl_3$ 10mol%	**169**	1	-78	0	6

[a] imine decomposed to corresponding amine and aldehyde.

From these experiments it can be concluded that indium does not bind to BINAP or to N-S oxazoline type ligands sufficiently to induce chirality. This was shown in the low enantioselectivity that was observed in all experiments. In addition, equipping the imine with binary chelating ability does not influence the outcome of any of the reactions with chiral indium complexes. Most reactions were shown to be very successful at room temperature.

A key feature of this reaction was that all reactions were shown to be *cis*-selective. No *cis-trans* isomerization was detectable in any of the experiments. *Cis*-selectivity suggests an *endo* approach of the cyclopentadiene. This in itself is a very useful synthetic tool. This highly selective property was also observed by Varghese et al.[20] using a titanium (IV) catalyst at 35°C after 6 hours the reaction gave a 58% yield of entirely the syn adduct (scheme 72).

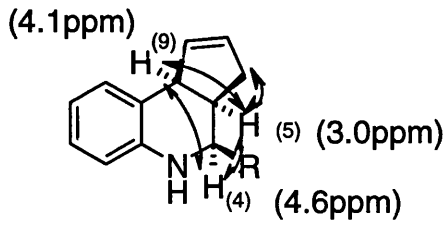


51%ee — No Product formed.

173 *Syn* — **174** *Anti*

Scheme 72a. Synthesis of *syn*-selective cycloadducts

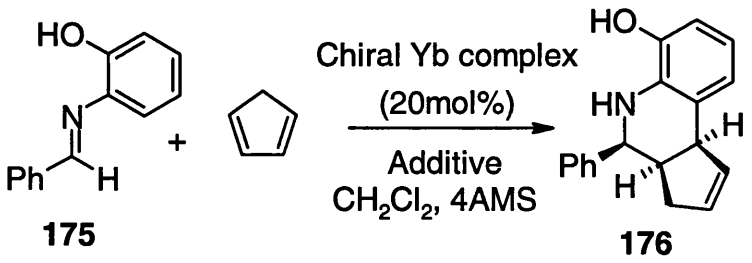
To prove that one diastereoisomer was produced exclusively, Cosy and nOe enhancement experiments were performed. Observation of nOe enhancements from the C_5 proton to both C_9 and C_4 established that all protons must be on the same side, as there would be no observed enhancement from protons of the opposite side (this was true for all irradiated protons individually). All nOe experiments showed that there was no enhancement to any aromatic protons as the aromatic ring was out of the plane. Cosy experiments showed coupling from the C_9 proton at 4.6ppm to 4.1ppm, couplings from 4.1ppm to 3.0ppm and to a CH_2 proton at position C_6. The signal at 3.0ppm showed coupling to both protons at 4.1 and 4.6ppm as well as couplings to the two CH_2 protons at C_6. There were no observed aromatic couplings to any of the protons at C_4, C_5 and C_9.



Scheme 72b. Observed nOe enhancements.

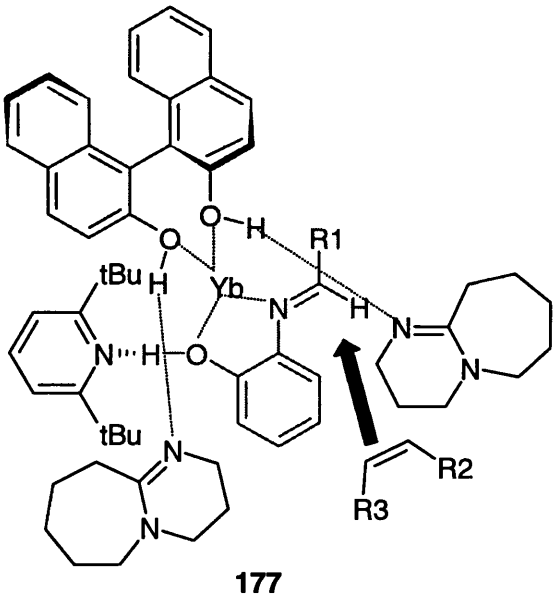
Generating an efficient enantioselective catalytic process has also proved troublesome for Kobayashi et al.[21] Lanthanide triflates had been used to generate tetrahydroquinoline products with an aza Diels-Alder reaction between imines and cyclopentadiene. In this paper Kobayashi states that in the reaction between N-benzylideneaniline and cyclopentadiene under the influence of $Yb(OTf)_3$ 20mol%, (*R*)- BINOL and an additive of TMP (1,3,5-trimethylpiperidine) the reaction proceeded smoothly in a 53% yield. However, no chiral induction was observed.

At this stage it was evident that bidentate co-ordination between substrate and a chiral Lewis acid would be necessary for a reasonable chiral induction. The reaction between N-benzylidene-2-hydroxylaniline **175** and cyclopentadiene with (*R*)-BINOL, $Yb(OTf)_3$ and additive was repeated. It was found that the reaction proceeded smoothly to afford the corresponding 8-hydroxyquinoline derivative in high yield (85%, scheme 73). The enantiomeric excess of the cis-adduct in the first trial was only 6%, however the selectivity increased when diazobicyclo[5.4.0]undec-7-ene (DBU) was added instead of TMP. It was indicated that the phenolic hydrogen of **175** (Scheme 73) would interact with DBU, which should interact with the hydrogen of (*R*)-(+)-BINOL, which decreased the selectivity. Additives were examined that interacted with the phenolic hydrogen of the imine. When 20 mol% of methylimidazole was used 91% ee of the *cis* adduct was achieved, however the chemical yield was low. Other additives were screened and high yields and selectivities were obtained when a bulky additive, 2,6-di-*t*-butylpyridine, (DTBP) was used. (*cis/trans* =99/1, 71%ee, 92%yield).



Scheme 73. Synthesis of (4*S*)-4-phenyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[*c*]quinolin-6-ol

The assumed transition state model (scheme 74) was postulated. $Yb(OTf)_3$ (*R*)-(+)-BINOL and DBU form a complex containing two hydrogen bonds. The axial chirality of (*R*)-(+)-BINOL is transferred via the hydrogen bonds to the amine moiety. The additive would interact with the phenolic hydrogen of the imine, which is fixed by bidentate co-ordination to Yb(III). As the top face is shielded by the amine the dienophiles approach from the bottom face to achieve high levels of selectivity.



Scheme 74: Assumed transition state (OTf) anions are omitted for clarity.

This chirally induced molecule is dependent on the chiral ligand as well as both base and additive and is not applicable for any imines other than N-benzylidene-2-hydroxylaniline **175**. This does not make this reaction very flexible, as only imines with phenolic hydrogens are applicable. This paper was important as it highlighted

the complexity of this reaction. This could have important implications to our reaction mechanism with Indium metal and chiral ligands.

The inclusion of additives into the reaction between 2-bromo-*N*-[(*E*)-phenylmethylidene]aniline, (an analogue of from N-benzylidene-2-hydroxylaniline), with cyclopentadiene was examined. The following results were obtained (Table 16).

Table 16. Additive effects in the aza Diels-Alder reaction between cyclopentadiene and 2-bromo-*N*-[(E)-phenylmethylidene]aniline.

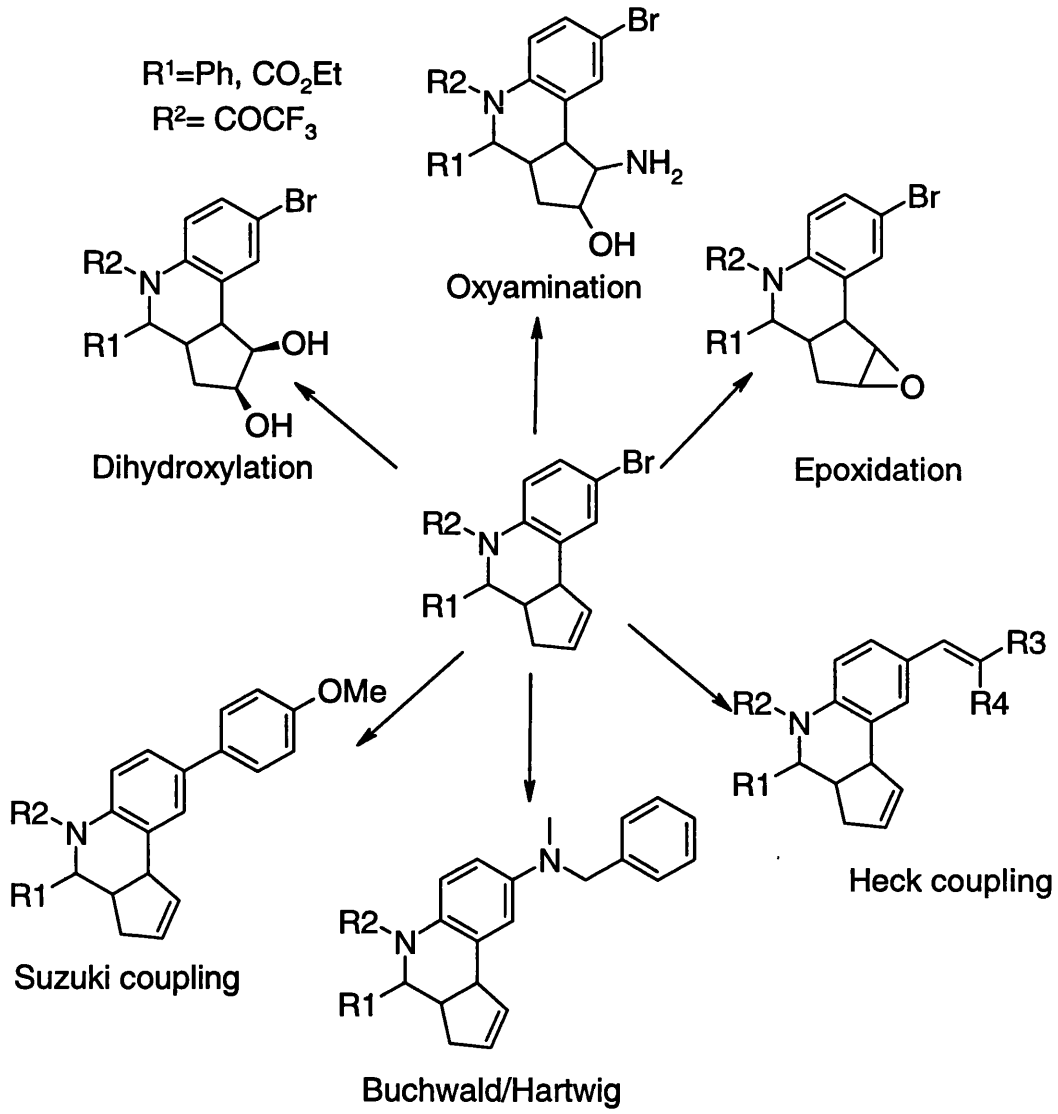
Entry	Catalyst(10 mol%)/Ligand	Temp °C	Time (Hrs)	Additive/10mol%	Yield %	ee %
1	$InCl_3$/(*R*)-**165**	RT	1	4Åsieves	89	6
2	$InCl_3$/(*R*)-**165**	RT	1	4Åsieves (XS)	83	10
3	$InCl_3$/(*R*)-**165**	RT	1	DBU, DTBP	13	3
4	$InCl_3$/(*R*)-**165**	0	6	4Åsieves	11	5
5	$InCl_3$/(*R*)-**165**	0	24	4Åsieves (XS)	26	7

It can be seen clearly from table 16 that the inclusion of additives such as molecular sieves and amine bases had little effect upon enantioselectivity in this reaction. Although disappointing, the yields remained constantly high, with short reaction times. Inclusion of the base additives actually retarded the reaction rate considerably (83% vs. 13%).

2.1.7 Tetrahydroquinoline structures as fundamental building blocks for natural product synthesis.

As previously indicated, tetrahydroquinoline cycloadducts are important skeletal templates for various natural products. The Diels-Alder methodology provides a fast and efficient way of producing these *cis*-cycloadducts in one step with an indium catalyst. By incorporating bromine into the molecule in either a *para* or *ortho* position provides an opportunity for further functionalisation of these molecules. Primarily we set out to incorporate some palladium chemistry into the synthesis of highly functionalised tetrahydroquinoline adducts. The bromine substituent enables Heck reactions, Suzuki and Buchwald-Hartwig couplings to be performed. Aromatic bromides can also be turned into Grignard reagents and used in Friedel-Crafts alkylations/acylations.

Following the protection of Nitrogen with a trifluroacetyl group, various palladium couplings, dihydroxylations, epoxide and oxyaminations were performed (scheme 75).



Scheme 75. Functionalisation of tetrahydroquinoline template

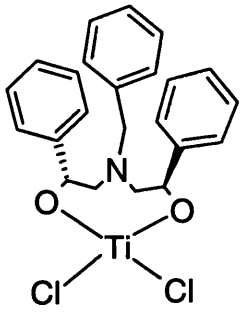
Due to time constraints, these reactions were never fully completed. With further investigation these tetrahydroquinoline templates could be utilised as a quick and efficient method for complex natural product synthesis.

2.1.8 Indium as a Chiral Catalyst?

At this stage enantioselective catalysis with indium (III) could not be achieved. The fundamental consideration as to whether indium could ever act as a chiral catalyst for

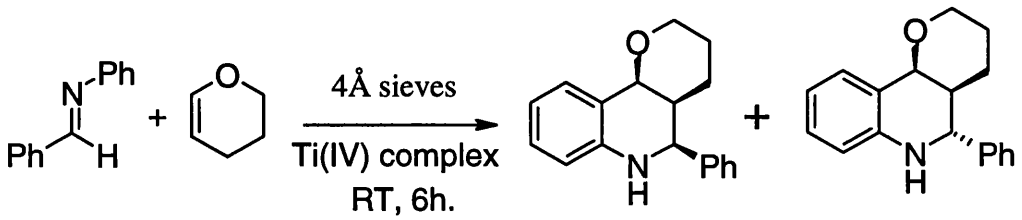
the hetero Diels-Alder reaction was questioned. Could it be that rate association and dissociation between the chiral ligand and Indium (III) anion was so fast that no transfer of chirality was possible?

The publication by Varghese et al.[22] was very revealing. The authors have generated chiral tetrahydropyridine cycloadducts in moderate yields and at times, high enantioselectivity with a Ti(IV) complex. Initial work performed on this reaction used $InCl_3$ as a catalyst. However, for enantioselective work, this group has moved away from indium to titanium based catalysts. Reacting an amino diol with titanium (di-isopropoxide) dichloride formed the desired catalyst *in-situ.* The solid was precipitated from hexane. The following reaction and results were reported using the catalyst described above (scheme 76,77 Table 17).



181

Scheme 76. Ti(IV) catalyst



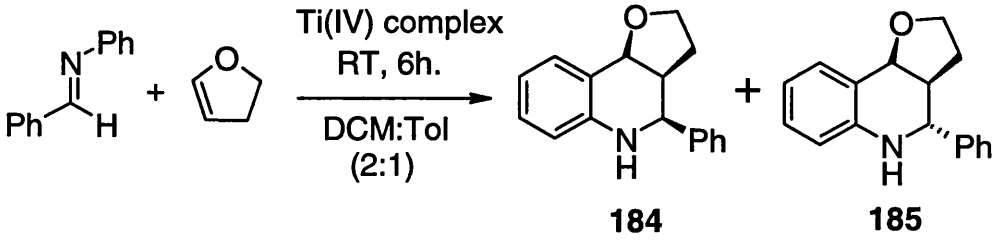
182 **183**

Scheme 77. Synthesis of tetrahydroquinoline cycloadducts with 3,4-dihydro-2*H*-pyran

Table 17. Reactions using catalyst **181**

Entry	Solvent	% Conversion	182/183	ee% 182	ee% 183
1	DCM	25	0.56	49	9
2	DCM:toluene (1:1)	43	0.54	52	13
3	DCM:toluene (2:1)	43	0.43	76	20
4	toluene	-	-	-	-

The choice of solvent was also important in this reaction. It was found that in dichloromethane the products were obtained in poor yields. With only toluene there was no reaction. The Ti(IV) catalyst also decomposed after standing for a few hours. On switching to dichloromethane/toluene mixture (2:1) there was a considerable increase in conversion and more importantly enantiomeric excess. The most important feature of this reaction is that the author's state that as the product yields was poor, Indium chloride was added to the reaction mixture. It was postulated that the Ti(IV) complex was activated by indium(III) chloride. The effect of adding an external Lewis acid on the product yield and enantiomeric excess was studied by varying the ratio of $InCl_3$/**181**. The reaction between dihydrofuran and benzylidine aniline was repeated with $InCl_3$ and 4Åsieves as additives and ee was determined (Scheme 78,Table 18).



184 **185**

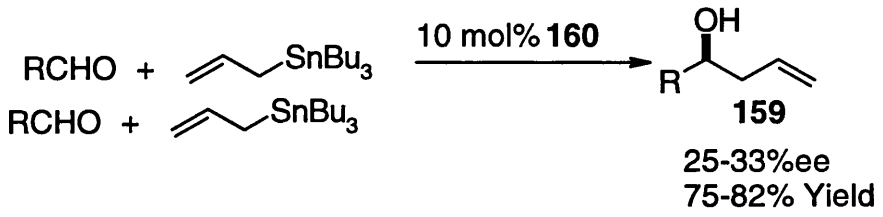
Scheme 78. Synthesis of tetrahydroquinoline cycloadducts using dihydrofuran

Table 18. Additive effects upon reaction catalysed by **181**

Entry	Additive	%Conversion	184/185	ee% 184	ee% 185
1	-	47	0.67	13	5
2	4Åsieves 10mol%	49	1.86	47	17
3	4Åsieves 20mol%	48	0.67	34	18
4	$InCl_3$ 0.5mol%	66	1.94	5	10
5	$InCl_3$ 1mol%	70	0.67	10	18
6	$InCl_3$ 1.5mol%	70	0.67	14	5

Interestingly addition of $InCl_3$, while increasing the yields of the products reduced the ee considerably. It was assumed from these results that indium and titanium act independently as catalysts rather than any to co-operative behaviour between them occurring.

The most important question raised from this paper was that the reaction studied had been performed extensivly achirally with $InCl_3$, however, the choice of enantioselective catalyst was a Ti(IV) complex. Another indication of problems with enantioselective reaction catalysed by indium was found in the literature. The chiral indium complex that has been reported to improve the enantiomeric excesses in allylation reactions with chiral stannanes[23] was never followed up by a full paper, which therefore raises the question as to why work was never continued in this area.



Scheme 79. Synthesis of chiral alcohol utilising allylic stannanes and aldehydes with chiral indium catalysis.

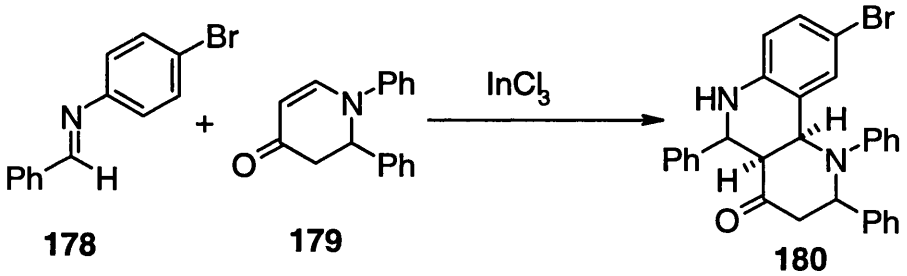
2.1.9 Summary.

Indium (III) chloride has proven to be a highly successful catalyst in the aza Diels-Alder reaction of imines with cyclopentadiene to generate a tetrahydroquinoline cycloadduct. A key feature of this reaction was that all reactions were shown to be *cis*-selective with cyclopentadiene. No *cis-trans* isomerization was observed in any of the experiments. The catalyst concentration of indium can be lowered to just 1 mol% at room temperature whilst retaining effectiveness. Most reactions are complete after only one hour to produce almost quantitatively the cycloadduct. Indium has proven to be a more successful catalyst for the inverse electron demand hetero Diels-Alder reaction than most published lanthanide Lewis acids catalysts. Enantioselective

cycloaddition was not successful. A more detailed examination of the method of indium catalysis is required before this can be achieved. Having a bromine moiety on the aromatic ring provides us with a versatile handle with which to further functionalise these molecules into highly complex natural product templates.

2.1.9.2 Future Work

A possible extension of this methodology is towards the one-pot synthesis of phenanthridinones. These compounds exhibit a wide spectrum of biological activities. The aim would be to perform a Diels-Alder reaction to generate the alkene moiety via a reaction between *a* suitable aryl imine and Danishefsky's diene with a chiral indium reagent. Once this reaction was completed additional imine would be added to produce phenanthridinones cycloadducts. The methodology to create these compounds could be a useful synthetic tool as compound libraries could potentially be produced very rapidly (scheme 80).



178 179 180

Scheme 80. One pot synthesis of phenanthridinones

2.2 Tetrahydropyridine cycloadduct synthesis, aims and objectives.

The objective of this project was to generate chiral tetrahydropyridine cycloadducts in one step from achiral imines and Danishefsky's diene via chiral silver (I) catalysis of a hetero Diels Alder reaction.

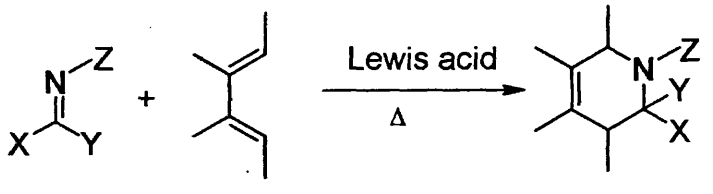
2.2.1 Envisaged Program of Work.

Initial studies would concentrate on optimising a previously reported tetrahydropyridine synthesis using silver (I) salts.[24] Various activated and unactivated imines were utilised for optimisation. After optimisation, monodentate and bidentate imines would be employed in order to maximise potential binding to the silver (I) cation. Lewis and Brønsted acid catalysis is vital for these reactions to proceed. We embarked on a program of research aimed at finding a new chiral silver catalyst for the hetero Diels-Alder reaction.

2.2.2 Imines as dienophiles.

The vast majority of work in Diels-Alder chemistry is devoted to the reaction of conjugated 1,3 dienes with suitable dienophiles. It is well known that one of the carbon atoms of the dienophile can be replaced by a heteroatom. Then the reaction with a 1, 3 conjugated diene enables a wide variety of six membered heterocyclic adducts to be produced readily and easily. Hetero Diels-Alder reactions can be thought of as either a concerted asynchronous process or a stepwise di-polar system where polar like transition states is involved.

The use of imines as the dienophillic component of [4+2] cycloaddition reactions was first reported in the literature by Alder in 1943[25] and then reviewed in 1965.[26] Not all imino compounds are effective dienophiles. Simple imines have shown to be unreactive towards cycloaddition unless exceptionally reactive dienes are utilised. Electron deficient imines however provide reliable reaction partners. N-sulfonyl, N-acyl and N-aryl imines all add to numerous 1,3-dienes to produce tetrahydropyridines in good yields. These cycloadditions are facilitated by the use of either Lewis acids or thermal activation.



186 **187** **88**

Z= SO_2Ar, COR

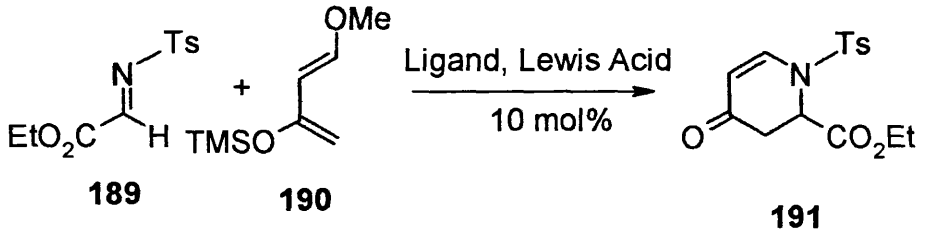
X, Y=H, CO_2R, Ar, CCl_3

Scheme 81. Imines as dienophillic components of the hetero Diels-Alder reaction

2.1 Silver Catalysts.

During a program of research directed towards the catalytic enantioselective aza Diels-Alder reaction of imines derived from ethyl glyoxylate **189** with activated dienes **190**, Jørgensen *et al.*[27] focused upon on chiral copper complexes (scheme 82). Various Lewis acid/chiral complex combinations were examined. Of these

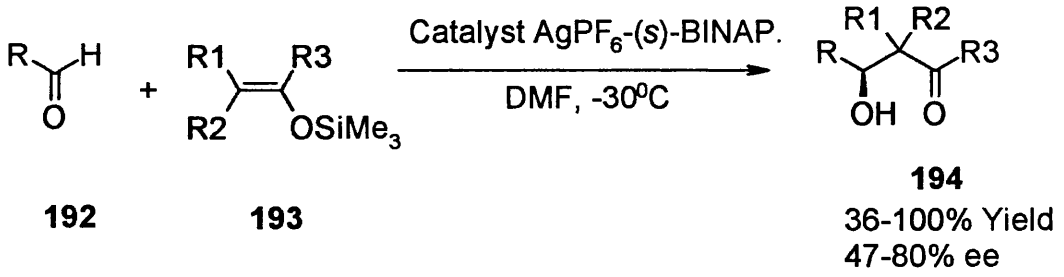
complexes, $AgSbF_6$, $AgClO_4$ and AgOTf exhibited high reactivities with 75, 90 and 85% yield respectively. Enantioselectivity of the cycloadducts was however low (33, 34 and 30% ee respectively). Nevertheless the objective with this reaction was to try to improve upon published results and further exploit the silver (I) catalysts in the hetero Diels alder reaction. Copper (II) complexes and lanthanide triflates are the catalysts of choice for enantioselective cycloaddition in the hetero Diels-Alder reaction. With this literature precedent and the fact that silver is in the same group as copper, the potential for silver to have the same affinity for the aza Diels-Alder reaction as copper (II) complexes was evident.



Scheme 82. *N*-Tosylimine cycloaddition

2.2.3.1 Silver phosphorous compound chemistry.

Cationic silver(I)-phosphine complexes have been used as effective promoters for a wide range of organic transformations including allylation, aldol, ene and glycosylation reactions. Silver catalysis in asymmetric reactions is also well documented. For example, asymmetric Aldol, Mukaiyama Aldol (scheme 83), asymmetric allylations and hetero Diels-Alder reactions have all been catalysed by silver phosphines.[28] It is well established that these reactions are catalysed with other Lewis acids such as Ti, B, Al and Sn. However many of these established catalysts are sensitive to air, water and product inhibition and are consequently used at low catalyst/substrate ratio. The use of silver phosphine complexes can provide a practical solution as many silver phophine complexes are stable in air and retain activity in the presence of the reaction product. We set out to prepare a variety of silver phosphine salts and test their efficiency in the hetero Diels-Alder reaction.



192 **193** **194**
36-100% Yield
47-80% ee

Scheme 83. Asymmetric Mukaiyama aldol reaction

2.2.4 The optimisation study of *N*-[(*E*)-phenylmethylidene]aniline with Danishefsky's diene under silver (I) phosphine catalysis.

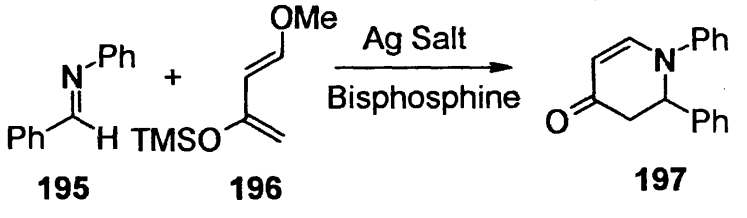
Scheme 84. Imine cycloaddition

There are few examples of asymmetric hetero Diels-Alder reactions of imines with Danishefsky's diene in the literature. Highly activated imines have been utilised with chiral Zr, Cu (I), Yb, Sc, Mg(I), Fe(II) complexes.[29] High catalysts loading of 10-20-mol% of chiral catalyst are commonly required. High ee's can be achieved, albeit at the expense of the chemical yield of the tetrahydropyridine cycloadduct.

A major explanation as to why imines have received such little attention compared to analogous aldehyde dienophillic components in hetero Diels-Alder cycloadditions is the greater Lewis basicity of imines compared to carbonyl compounds. As a consequence, the co-ordination to Lewis acids is considerably stronger leading to inhibition or decomposition of the chiral Lewis acid complexes. Initial studies required the use of stoichiometric amounts of catalyst in order to achieve high asymmetric induction. Secondly, the flexible (*E, Z*)-conformational structure of the imine C=N double bond allows more possible transition state species to exist in solution. Penultimatley imines can be unstable and some cannot be isolated limiting their utility and giving additional difficulties on accurate investigation. Finally the

tendency of enolizable imines with an α-acidic proton to form enamines is also an important consideration.

We studied the reaction between imine **195**, *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene **196** (Scheme 85). Initial studies with imine **195** showed the imine to be stable and purification of the imine was possible by recrystallisation. It was an ideal candidate to study preliminary reactions of silver (I) catalysts with Danishefsky's diene. Several silver catalysts were generated *in-situ* with bis-phosphine ligands before adding the imine and dienophile components. Silver phophine complexes are far more soluble in organic solvents than uncomplexed silver salts. Initially we studied the efficiency of silver tetrafluoroborate. All reactions were carried out on a 1mmol scale under an inert atmosphere in dry solvent. The effect of temperature, time, solvent and catalyst loading was measured. The cycloadduct, 1,2-diphenyl-2,3-dihydro-4(1*H*)-pyridinone **197**, was worked up, columned and isolated yields are shown. (Table 19)

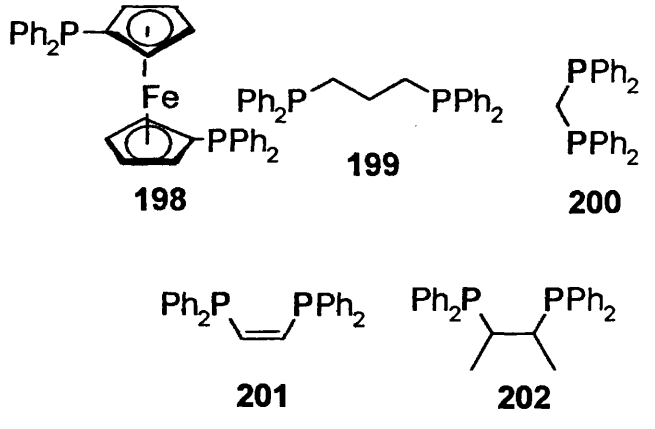


Scheme 85. Cycloaddition reaction between *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene

The achiral bis-phophine ligands that were used are illustrated in scheme 86. These include triphenyl phosphine (PPh_3), 1,1'-*Bis*-(diphenylphosphino)ferrocene **198**, (dppf), 1,3 *Bis*-(diphenylphosphino)propane **199**, (dppp), *Bis*-(diphenylphosphino)methane **200** (dppm), *Cis*-1,2 *Bis*-(diphenylphosphino)ethylene **201**, 2,3 *Bis*-(diphenylphosphino)butane **202**.

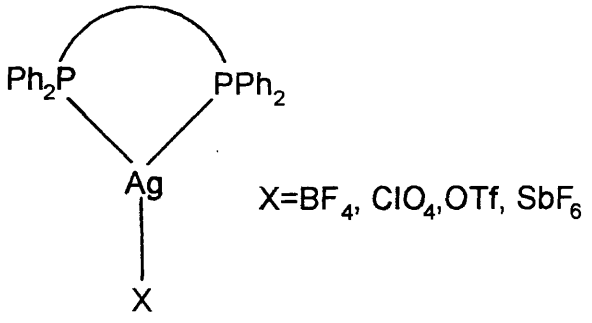
Table 19. Reaction optimisation with achiral bisphosphines.

Entry	Catalyst	% Loading	Ligand	Temp °C	Time (Hrs)	Solvent	Yield %
1	-	-	-	RT	24	MeCN	<2
2	$AgBF_4$	10 mol%	**2xPPh$_3$**	RT	24	MeCN	46
3	$AgBF_4$	10 mol%	**198**	RT	24	MeCN	17
4	$AgBF_4$	10 mol%	**199**	RT	24	MeCN	44
5	$AgBF_4$	10 mol%	**199**	RT	4	MeCN	32
6	$AgBF_4$	10 mol%	**200**	RT	24	MeCN	22
7	$AgBF_4$	10 mol%	**201**	RT	24	MeCN	43
8	$AgBF_4$	10 mol%	**202**	RT	24	MeCN	54
9	$AgBF_4$	10 mol%	**202**	RT	48	MeCN	62
10	$AgBF_4$	10 mol%	**202**	RT	48	DCM	68
11	$AgBF_4$	10 mol%	**202**	RT	4	DCM	30
12	$AgBF_4$	10 mol%	**202**	40	4	DCM	29
13	$AgBF_4$	5 mol%	**202**	RT	4	DCM	22



Scheme 86. Achiral Bisphosphines utilised.

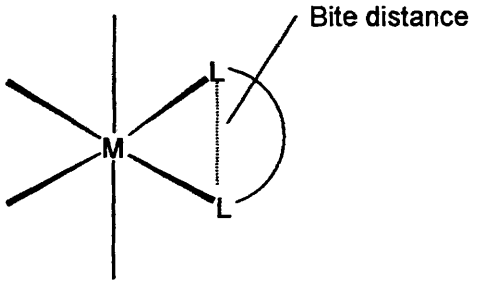
The six achiral bidentate bisphosphine ligands have slightly different bite angles. We assumed that with a bidentate ligand a trigonal planar structure would be established (Scheme 87).



203

Scheme 87. Expected trigonal planar model of silver (I) bisphosphine catalyst

The effect of different achiral bis-phophine ligands in the production of the cycloadduct **197** was examined. From the results obtained the best yields of the tetrahydropyridine product **197** was achieved with 2,3,-*bis*-(diphenylphosphino)butane **202** (68%). We reasoned that our results could be rationalised in terms of different bite angles and the length of the P-P bonds. In an octahedral complex the L-M-L angle is 90°. In some ligands, the backbone structure of the bis-chelating ligand can fold into a conformation that preserves the tetrahedral angle within the ligand yet still achieves the L-M-L angle of 90°. The degree of strain in a chelating ligand is often expressed in terms of the bite distance (scheme 88). A small ratio, provided by a more constrained fixed backbone of the chelating bis-phosphine ligand is one of the main causes of distortion from an octahedral complex towards trigonal prismatic geometry in a six co-ordinate complex.



Scheme 88. Bite distance of chiral ligand

Bisphosphine ligands possessing more flexible backbone geometries are not effective in this reaction. In contrast, ligands with a more rigid conformational geometric

backbone proved more successful. Ligands with greater bite distances were also less functional, this being similar in effect to possessing a flexible backbone.

We contemplated the outcome of changing the solvent. The reaction with 10 mol% catalyst and 2,3,-b*is*-(diphenylphosphino)butane **202,** at room temperature was undertaken with both acetonitrile and DCM. From the results, it was evident that the reaction was to some extent, more dynamic in DCM than acetonitrile (68 vs. 62% Yield). This is in accordance with the non-co-ordination properties of DCM noted on p.56.

Next the effect of changing the catalyst loading was explored. Experiments examining the use of ten and five mole percent of catalyst were used at room temperature with, 2,3,-b*is*-(diphenylphosphino)butane **202**, for four hours in DCM were investigated. It was found that with silver tetrafluoroborate, 10 mol% of catalyst loading gave an improved result (22% vs. 11%). Finally, the effect of temperature upon this reaction was probed. We observed that increasing the to 40°C had little effect on the yield of the tetrahydropyridine **197.** This was a pleasing result in view of the initial objective to create a chiral silver (I) bis-phosphine catalyst. An efficient rate of reaction at room temperature was an additional benefit, since enantioselectivity is more likely to be successful at room temperature. Although initial results demonstrated that silver tetrafluoroborate was a good catalyst for the hetero Diels-Alder reaction, it was vital that the yield of the reaction be increased if silver (I) salts were to be competitive with the copper and lanthanide catalysts of Leckta, Jørgensen and Kobayashi.[30] We examined several Ag (I) salts with the two most favourable bis-phosphine ligands, 2,3,-b*is*-(diphenylphosphino)butane **202** and two equivelents of triphenylphosphine (PPh_3) in the hetero Diels-Alder reaction, considering the variables, catalyst loading, temperature and time.

Table 20 Asymmetric aza Diels-Alder reactions with silver (I) phosphine catalysts

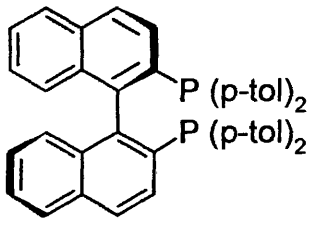
Entry	Catalyst	% Loading	Ligand	Temp °C	Time (Hrs)	Solvent	Yield %
1	Ag(OTf)	10 mol%	**202**	RT	24	DCM	92
2	$AgClO_4$	10 mol%	**202**	RT	24	DCM	89
3	$Ag(SbF_6)$	10 mol%	**202**	RT	24	DCM	76
4	Ag(OTf)	10 mol%	**2xPPh$_3$**	RT	24	DCM	89
5	$AgClO_4$	10 mol%	**2xPPh$_3$**	RT	24	DCM	72
6	$Ag(SbF_6)$	10 mol%	**2xPPh$_3$**	RT	24	DCM	78
7	Ag(OTf)	5 mol%	**202**	RT	24	DCM	87
8	Ag(OTf)	1 mol%	**202**	RT	24	DCM	62
9	Ag(OTf)	5 mol%	**202**	RT	4	DCM	89
10	Ag(OTf)	5 mol%	**202**	RT	1	DCM	75

From these reactions silver triflate clearly established itself as the best silver salt for this reaction. By changing the counterion we could dramatically influence the yield of the cycloadduct. Optimisation of the reaction gave results similar in quality to the Jørgensen, Leckta copper catalysts. At room temperature the catalyst loading could be successfully lowered to 5 mol% and the reaction times shortened to one hour without loss of reactivity.

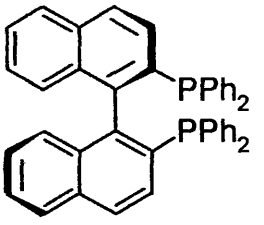
With these considerations the reaction to produce a chiral cycloadduct **197** was repeated. Application of the optimised conditions with 5 mol% silver (I) triflate, at room temperature in DCM were used to examine the effectiveness of the chiral bidentate phosphine ligands similar bite angle and distance to 2,3,-b*is*-(diphenylphosphino)butane **202.** These results are displayed in Table 21.

Table 21. Enantioselectivity under optimised reaction conditions.

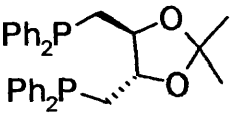
Entry	Catalyst mol%	Ligand	Time(Hrs)	Yield %	ee%
1	5	**204 (*R*)**	24	42	0
2	5	**165 *R*)**	24	90	0
3	5	**205**	24	47	0
4	5	**206**	24	21	0
5	5	**207**	24	19	0
6	5	**208**	24	85	0
7	5	**165 (*S*)**	24	88	0
8	10	**165 (*R*)**	24	92	0
9	10	**165 (*R*)**	48	95	0



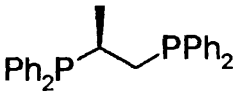
(*R*)-TOL-BINAP
204



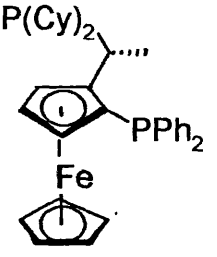
(*R*)- BINAP
165



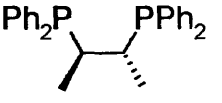
(*R, R*)-DIOP
205



(*R*)-PROPHOS
206



(*R*),(*S*)-JOSIPHO
207



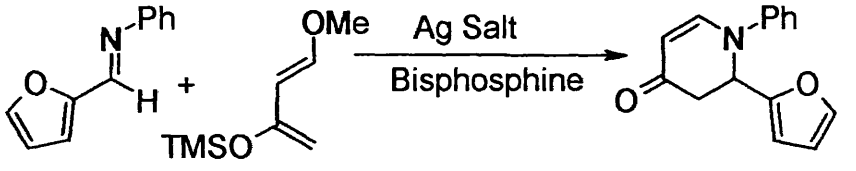
(*R, S*)-CHIRAPHOS
208

Scheme 89. Chiral bisphosphines employed in scheme 84

There was no chiral induction from any of the chiral bis phosphine ligands. Increasing the catalyst loading from 5 to 10 mol% slightly increased the reaction productivity, however no chiral tetrahydropyridine product was formed in any of the reactions.

2.2.4.1 Reactions of bidentate imines with Danishefsky's diene to maximise octahedral cationic silver (I) chiral bisphosphine binding.

A plausible explanation for chiral deficiency may have been due to utilising an imine with one binding site. To rectify this *N*-[(*E*)-2-furylmethylidene]aniline **210** was prepared. The furyl oxygen contributes as a secondary point of binding to the silver catalyst. The reactions were carried out in DCM under an inert atmosphere examining the effect of ligand, temperature and time.



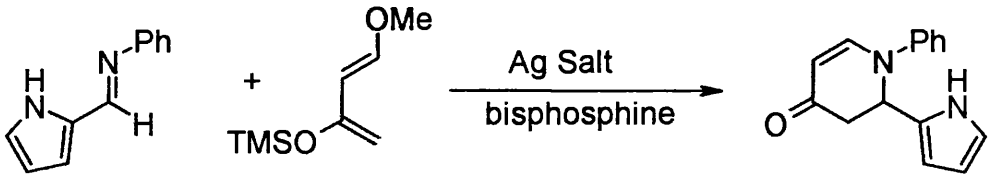
210 **211**

Scheme 90. Cycloaddition of *N*-[(*E*)-2-furylmethylidene]aniline and Danishefsky's diene

Table 22. Enantioselective cycloadditions with imine **210**

Entry	Catalyst(mol%)	Ligand	Temp °C	Time (Hrs)	Yield %	ee%
1	Ag(OTf) 10 mol%	**202**	RT	24	25	-
2	Ag(OTf) 10 mol%	**(R)-204**	RT	24	18	0
3	Ag(OTf) 10 mol%	**(R)-165**	RT	24	27	0
4	Ag(OTf) 10 mol%	**205**	RT	24	15	0
5	Ag(OTf) 10 mol%	**206**	RT	24	16	0
6	Ag(OTf) 10 mol%	**207**	RT	24	8	0
7	Ag(OTf) 10 mol%	**208**	RT	24	28	0
8	Ag(OTf) 10 mol%	**208**	0	24	14	0
9	Ag(OTf) 10 mol%	**208**	0	1	25	0
10	$AgClO_4$ 10 mol%	**208**	RT	24	26	15
11	$AgClO_4$ 10 mol%	**208**	0	24	12	9
12	$AgClO_4$ 10 mol%	**208**	0	1	7	0

It was noticeable from the results that *N*-[(*E*)-2-furylmethylidene]aniline **210** was not sufficiently activated imine to be a viable reaction partner in the hetero Diels-Alder reaction. It should be observed that a modest enantioselectivity was achieved (15%) with 10 mol% silver (I) perchlorate together with (*R*)-CHIRAPHOS **208**, both at room temperature and at 0°C. This result was encouraging. We concluded from the experiments on *N*-[(*E*)-2-furylmethylidene]aniline **210** that the oxygen function on the furyl ring may form a strong bond to the silver (I) phosphine catalyst, thus inhibiting the reaction. The reaction was repeated with a less Lewis basic pyrrole substituent and both reactivity and enantioselectivity examined. *N*-[(*E*)-1*H*-pyrrol-2-ylmethylidene]aniline **212** was prepared and utilised in the hetero Diels-Alder reaction. The effect of time, temperature and ligand were investigated.



212 **213**

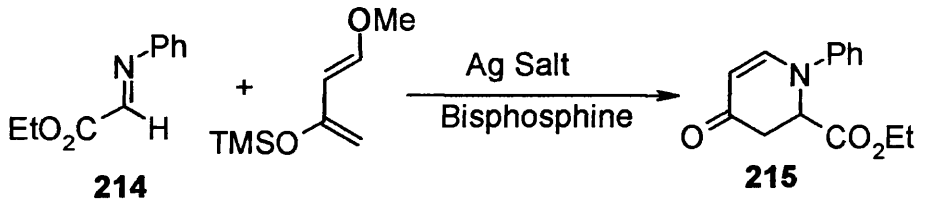
Scheme 91. Cycloaddition reaction between *N*-[(*E*)-1*H*-pyrrol-2-ylmethylidene]aniline and Danishefsky's diene

Table 23. Asymmetric cycloadditions with imine **212**

Entry	Catalyst(mol%)	Ligand	Temp °C	Time (Hrs)	Yield %	ee%
1	Ag(OTf) 10 mol%	**202**	RT	24	12	-
2	Ag(OTf) 10 mol%	**(R)-204**	RT	24	10	0
3	Ag(OTf) 10 mol%	**(R)-165**	RT	24	13	0
4	Ag(OTf) 10 mol%	**208**	RT	24	15	0
5	$AgClO_4$ 10 mol%	**208**	RT	24	17	0
6	$AgClO_4$ 10 mol%	**208**	RT	1	7	0
7	$AgClO_4$ 10 mol%	**208**	0	24	10	0

In these series of reactions we observed no chiral induction from the chiral bidentate bis-phosphine ligands. It was clear from the modest production of tetrahydropyridine product **213** that *N*-[(*E*)-1*H*-pyrrol-2-ylmethylidene]aniline **212** was also not adequately activated to test a series of ligands constructively.

From the outcome of all previous reactions it was evident that a fine balance of reactivity and binary chelating capability needs to be accomplished. With this as our objective ethyl 2-(phenylimino)acetate **214** was prepared. The ester moiety at the carbon terminus of the C=N have shown to be effective electron withdrawing substituents upon the imine in the hetero Diels-Alder reaction. Jørgensen et al.[31] has demonstrated that the ester function of imine **214** has substantial activating capability by whilst additionally contributing as a secondary chelating group. The effect of modifying the chiral bisphosphine, time and temperature was considered.



214 **215**

Scheme 92. Cycloaddition of ethyl 2-(phenylimino)acetate and Danishefsky's diene

Table 24. Asymmetric cycloadditions using imine **214**

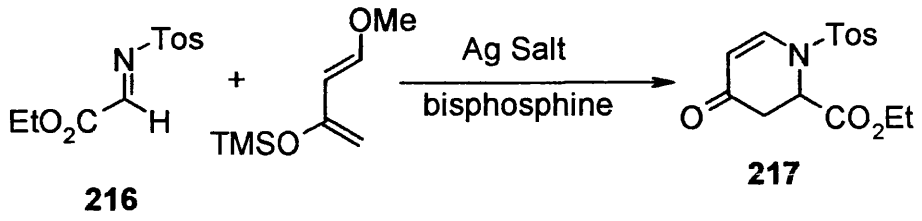
Entry	Catalyst(mol%)	Ligand	Temp °C	Time (Hrs)	Yield %	ee%
1	Ag(OTf) 10 mol%	**(R)-204**	RT	24	26	0
2	Ag(OTf) 10 mol%	**(R)-165**	RT	24	52	0
3	Ag(OTf) 10 mol%	**205**	RT	24	19	0
4	Ag(OTf) 10 mol%	**206**	RT	24	7	0
5	Ag(OTf) 10 mol%	**206**	RT	24	44	0
6	Ag(OTf) 10 mol%	**(R)-165**	RT	1	9	0
7	Ag(OTf) 10 mol%	**(R)-165**	0	24	23	0
8	Ag(OTf) 10 mol%	**(R)-165**	0	1	12	0
9	$AgClO_4$ 10 mol%	**(R)-165**	RT	24	17	0
10	$AgClO_4$ 10 mol%	**208**	RT	24	36	0
11	$AgClO_4$ 10 mol%	**208**	0	1	7	0

These reactions established that although the ester group as better able to activate the imine towards cycloaddition than the furyl and pyrrole moiety, the imine was difficult to make and purify. The presence of traces of aniline precursor could have been sufficient enough to inhibit the reaction pathway. A more highly activated imine with a secondary binding site had to be employed.

It had been shown that *N*-sulfonylimine **216** dienophile reacted rapidly with cyclopentadiene at -100°C in the absence of any catalyst.[32] Consequently we chose this imine for its exceptionally high reactivity. N-sulfonyl imine had also received much attention from Jørgensen et al.,[33] as the only α-imino ester to undergo an enantioselective hetero Diels-Alder reaction with Danishefsky's diene catalysed by several chiral copper (II) catalysts

N-sulfonyl imine was prepared using the isocyanate method of Holmes.[34] We were not able to cleanly isolate the *N*-sulfonyl imine in a pure state. The reaction between N-sulfonyl imine **216** and Danishefsky's diene with chiral silver phosphine ligands was investigated. The imine was trapped *in situ* with Danishefsky's diene to yield the

cycloadduct **217** in exceptional yields. All reactions were conducted in anhydrous DCM, under an inert atmosphere. Temperature, time and choice of chiral ligand were examined (Scheme 93).

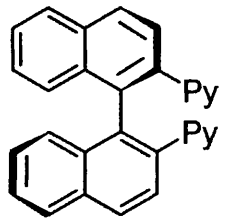


216 **217**

Scheme 93. Cycloaddition reaction of *N*-sulfonyl imine with Danishefsky's diene

Table 25. Asymmetric cycloadditions using imine **216**

Entry	Catalyst(mol%)	Ligand	Temp °C	Time (Hrs)	Yield %	ee%
1	-	-	RT	1	56	-
2	-	-	-78	1	<3	-
3	Ag(OTf) 10 mol%	-	-78	1	87	-
4	Ag(OTf) 10 mol%	**(*R*)-207**	-78	1	82	0
5	Ag(OTf) 10 mol%	**208**	-78	1	76	0
6	$AgClO_4$ 10 mol%	**(*R*)-204**	-78	1	78	0
7	$AgClO_4$ 10 mol%	**208**	-78	1	65	0
8	$AgBF_4$ 10 mol%	**(*R*)-209**	-78	1	4	0
9	$AgClO_4$ 10 mol%	**218**	-78	1	87	0
10	$AgClO_4$ 10 mol%	**218**	-78	1	98	0



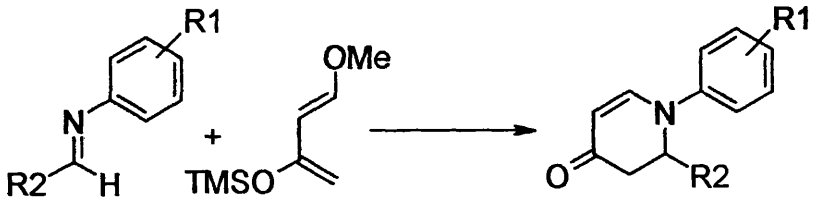
218

Scheme 94. Chiral N-containing ligand

This surprising level of thermal reactivity at room temperature clearly makes the development of new methods for the asymmetric induction of this aza Diels-Alder reaction difficult. We observed that the rate of reaction with N-Tosylimine had increased considerably with the silver catalysts at -78°C, however there still was no indication of a chiral centre being generated.

Our limited success may have been due to a number of external factors in this reaction. Firstly we could never produce the imine in sufficient purity to exclude traces of the isocyanate precursor. It could be assumed that isocyanates are capable of binding to the silver centre, therefore they could have prevented the chiral ligand from binding to the catalyst. It was at about this time that a publication by Whiting et al.[35] was discovered. In this paper the authors commented that during their studies on the development of new methods for catalysing asymmetric aza Diels-Alder reactions, they had examined the use of various methods for the generation of electron deficient imines, including imine N-Tosyl imine **216**. This paper revealed that they were unable to isolate the extremely moisture sensitive imine under the reported conditions. It was apparent that the imines could not be generated in quantitative yields under most of the conditions examined. Having achieved minimal success with respect to generating the imine, it was necessary to question whether it is actually possible to obtain asymmetric induction for the imine of type **216**. Evidently the high reactivity of the imine under thermal and catalytic conditions could be seen. It was postulated that even if a chiral Lewis acid was added to the reaction it may not result in sufficient imine activation to control the reaction outcome. The possibility also exists that this reaction is catalysed with triflic acid, which could be generated *in situ* in the presence of a small amount of water. Asymmetric induction via the addition of an external chiral Lewis acid to an imine **216** may be fortuitous given that these compounds are highly hydrolytically sensitive.

We had seen throughout the course of these reactions that the most stable imine to be productive in this hetero Diels-Alder reaction was *N*-[(*E*)-phenylmethylidene]aniline. The aromatic functionality on the nitrogen and the carbon on the C=N seemed to balance the electron withdrawing capability necessary to activate the imine without compromising imine stability. We set out to synthesise several aromatic imines with either *para* or *ortho* heteroatom substituents. These imines could be easily purified, eliminating the problem of external nucleophilic components as impurities. The imines would be sufficiently activated enough to observe the efficiency of the reaction.



Scheme 95. Cycloaddition of bidentate imines with Danishefsky's diene

We can see from the results illustrated in table 26 that by placing a para-substituent on the aromatic ring, in addition to facilitating the stability of the imine, increased the reactivity in the hetero Diels-Alder reaction to produce the tetrahydropyridine product. The introduction of *ortho*-electron withdrawing functionality induces reduced stability in contrast to the *para*-electron withdrawing substituents. Placing a weaker Lewis basic electron withdrawing substituent such as bromine in the *ortho*-position stabilises the imine and increases the productivity of the reaction. Positioning an electron withdrawing subsistent in the *para*- position rather than an electron donating substituent had a stabilising effect on the imine. Moreover, the reaction is more dynamic. However, if the electron withdrawing group is highly polarising, (such as a CF_3 group) then we observe decomposition of the imine to the corresponding amine and aldehyde. Double activation of the imine results in a very efficient reaction , unfortunately no chiral induction was detectable.

Table 26. Substituent effects.

Entry	R1	R2	Catalyst	Ligand	Temp °C	Time (Hrs)	Yield %	ee %
1	*o*-Br	Ph	-	-	RT	1	0	-
2	*o*-Br	Ph	Ag(OTf) 10 mol%	-	RT	1	82	-
3	*o*-Br	Ph	Ag(OTf) 10 mol%	**2 xPPh$_3$**	RT	1	94	-
4	*o*-Br	Ph	Ag(OTf) 10 mol%	**(R)-165**	RT	1	97	0
5	*o*-Br	Ph	Ag(OTf) 10 mol%	**(R)-165**	RT	0.25	99	0
6	*o*-Br	Ph	Ag(OTf) 10 mol%	**(R)-165**	0	1	42	0
7	*o*-Br	Ph	Ag(OTf) 1 mol%	**(R)-165**	RT	1	99	0
8	*p*-Br	Ph	-	-	RT	1	0	-
9	*p*-Br	Ph	Ag(OTf) 10 mol%	-	RT	1	87	-
10	*p*-Br	Ph	Ag(OTf) 10 mol%	**2 xPPh$_3$**	RT	1	98	-
11	*p*-Br	Ph	Ag(OTf) 10 mol%	**(R)-165**	RT	1	100	0
12	*p*-Br	Ph	Ag(OTf) 10 mol%	**(R)-165**	RT	0.25	94	0
13	*p*-Br	Ph	Ag(OTf) 10 mol%	**(R)-165**	0	1	82	0
14	*p*-Br	Ph	Ag(OTf) 1 mol%	**(R)-165**	RT	1	92	0
15	*o*-OH	Ph	-	-	RT	1	0	-
16	*o*-OH	Ph	Ag(OTf) 10 mol%	-	RT	1	54	-
17	*o*-OH	Ph	Ag(OTf) 10 mol%	**2 xPPh$_3$**	RT	1	62	0
18	*o*-OH	Ph	Ag(OTf) 10 mol%	**(R)-165**	RT	1	70	0
19	*o*-OH	Ph	Ag(OTf) 10 mol%	**(R)-165**	RT	0.25	48	0
20	*o*-OH	Ph	Ag(OTf) 10 mol%	**(R)-165**	0	1	16	0
21	*o*-OH	Ph	Ag(OTf) 1 mol%	**(R)-165**	RT	1	25	0
22	*p*-OMe	Ph	-	-	RT	1	0	-
23	*p*-OMe	Ph	Ag(OTf) 10 mol%	-	RT	1	80	-
24	*p*-OMe	Ph	Ag(OTf) 10 mol%	**2 xPPh$_3$**	RT	1	82	-
25	*p*-OMe	Ph	Ag(OTf) 10 mol%	**(R)-165**	RT	1	84	0
26	*p*-OMe	Ph	Ag(OTf) 10 mol%	**(R)-165**	RT	0.25	86	0
27	*p*-OMe	Ph	Ag(OTf) 10 mol%	**(R)-165**	0	1	72	0
28	*p*-OMe	Ph	Ag(OTf) 1 mol%	**(R)-165**	RT	1	83	0
29	*p*-CF_3	Ph	-	-	RT	1	0	-
30	*p*-CF_3[a]	Ph	Ag(OTf) 10 mol%	-	RT	1	0	-
31	*p*-OMe	CO_2Et	-	-	RT	1	0	-
32	*p*-OMe	CO_2Et	Ag(OTf) 10 mol%	-	RT	1	84	-
33	*p*-OMe	CO_2Et	Ag(OTf) 10 mol%	**2 xPPh$_3$**	RT	1	87	-
34	*p*-OMe	CO_2Et	Ag(OTf) 10 mol%	**(R)-165**	RT	1	74	0

[a] imine decomposed to 4-(trifluoromethyl)aniline starting material.

2.2.5 Summary

It was evident from the reactions performed that Silver (I) phosphine complexes are highly efficient catalysts for the hetero Diels-Alder catalyst with both activated and unactivated achiral imines.

There was no observed enantioselectivity with the silver phosphine catalysts. A more detailed look into the catalytic system was essential to understand the introduction of chirality and the cause of rate enhancement.

2.2.5.1 Future Work

A more detailed examination of the mechanism of action of the silver (I) phosphine catalyst had to be undertaken before a suitable chiral silver catalyst could be produced and utilised successfully in a hetero Diels-Alder reaction.

2.3 Silver (I) carborane catalysts-A new highly efficient catalyst for the hetero Diels-Alder reaction.

2.3.1 Aims and objectives

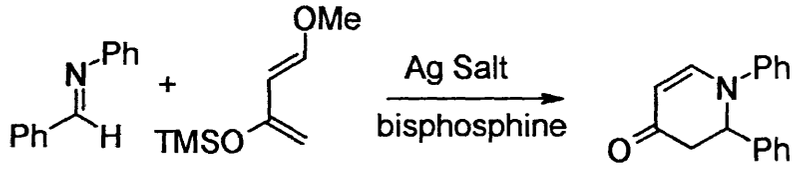
The yield of all the tetrahydropyridine cycloadducts synthesised was examined. Although silver (I) phosphine catalysts enhanced the rate of cycloadduct production, there was still significant room for improvement. It was apparent from initial results that the counterion played a significant role in the efficiency of the reaction. In collaboration with Dr. A. Weller we set out to examine Silver (I) phosphine carborane complexes as potentially new catalyst for the hetero Diels-Alder reaction.

2.3.1.1 Envisaged program of Work

Our initial reaction between *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene would be reinvestigated. The efficiency of Silver (I) phosphine carborane complexes would be measured. We assumed that we could dramatically reduce the catalyst loading of the silver (I) phosphine carborane catalyst to achieve effective catalysis in the hetero Diels-Alder reaction. The possibility of putting these catalysts on polystyrene linkers would also be considered.

2.3.2 The optimisation study of achiral *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene utilising silver (I) carborane complexes.

A substantial rate deviation was observed in the generation of tetrahydropyridine cycloadducts by swapping the counterion from BF_4^- to OTf^- (54 vs. 92%, scheme 96). We decided to focus our attention on finding new, more efficient silver (I) salt counterions, which would be more weakly co-ordinating. This would establish the silver phosphine catalyst as an effective catalytic system for the construction of the cycloadducts in the hetero Diels-Alder reaction. The reaction between *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene was utilised for this purpose.



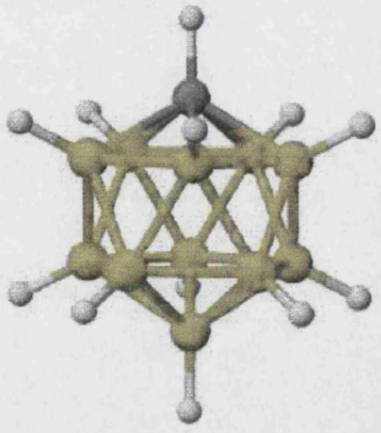
195 **197**

Scheme 96. Counterion study of reaction between *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene

Table 27. Counterion effect.

Entry	Catalyst	% Loading	Ligand	Temp °C	Time (Hrs)	Solvent	Yield %
1	Ag(OTf)	10 mol%	**196**	RT	24	DCM	92
2	$AgClO_4$	10 mol%	**196**	RT	24	DCM	89
3	$Ag(SbF_6)$	10 mol%	**196**	RT	24	DCM	36
4	$AgBF_4$	10 mol%	**196**	RT	24	DCM	54

The carborane anion is a new class of weakly co-ordinating anion that has recently been recognised. It is based on the remarkably stable boron cluster framework of monocarborane anions such as the icosohedral $CB_{11}H_{12}^-$ introduced in 1986 as a new candidate for the least co-ordinating anion.[36]



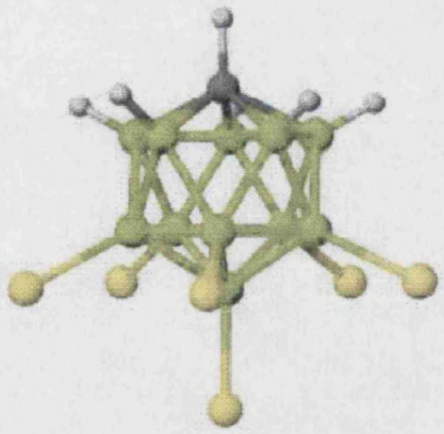
218, [*closo*-$CB_{11}H_{12}$]$^-$

Scheme 97. Carborane anion

Carboranes may be perceived as exotic species however they combine versatile functionality with unparalleled inertness. They are analogous to a 3D benzene-like structure and can be tailored to function new extremes of electrophillic and oxidative reactivity.

Commonly used Lewis acids for the hetero Diels-Alder reaction are extremely air sensitive and suffer from water and product inhibition. These catalysts are routinely used at high substrate/catalyst ratio to overcome these problems. A highly advantageous property of silver(I) phosphine carborane complexes is that they are very stable in air and retain activity in the presence of reaction product.

Two new silver (I) phosphine complexes were generated with $[CB_{11}H_{12}]^-$ and $[CB_{11}H_6Br_6]^-$. Addition of one equivalent of PPh_3 to a CH_2Cl_2 solution of $Ag[CB_{11}H_{12}]$ and $Ag[CB_{11}H_6Br_6]$ afforded the new complexes of (PPh_3) $Ag[CB_{11}H_{12}]$ **218** and (PPh_3) $Ag[CB_{11}H_6Br_6]$ **219** respectively. These compounds were crystallised successfully from CH_2Cl_2 and hexanes. Full characterisation by multinuclear NMR spectroscopy, microanalysis and X-ray crystallography was undertaken.



219, [*closo*-$CB_{11}H_6Br_6$]$^-$

Scheme 98. Hexabromocarborane anion

We investigated the reactivity of silver (I) phosphine [1-*closo*-$CB_{11}H_{12}$]$^-$ and its derivatives in the hetero Diels-Alder reaction with *N*-[(*E*)-phenylmethylidene]aniline **195** and Danishefsky's diene to affording the cycloadduct **197**. We anticipated that the carborane anions would reveal the full reactivity of silver metal in this reaction. For comparison (PPh_3)Ag(OTf), (PPh_3)Ag(ClO_4) and (PPh_3)Ag(BF_4) were used. The reactions were initially carried out at the bench on a 1 mmol scale, using only 1 mol% of catalyst at room temperature for two hours in DCM.

Table 28. Effect of carborane anions.

Entry	Catalyst/mol%	Time (Hrs)	Yield %
1	(PPh_3)Ag(OTf),/1 mol%	2	90
2	(PPh_3)Ag(ClO_4)/ 1 mol%	2	70
3	(PPh_3)Ag(BF_4)/ 1 mol%	2	35
4	(PPh_3) Ag[$CB_{11}H_{12}$]/ 1 mol%	2	99
5	(PPh_3) Ag[$CB_{11}H_6Br_6$]/ 1 mol%	2	99

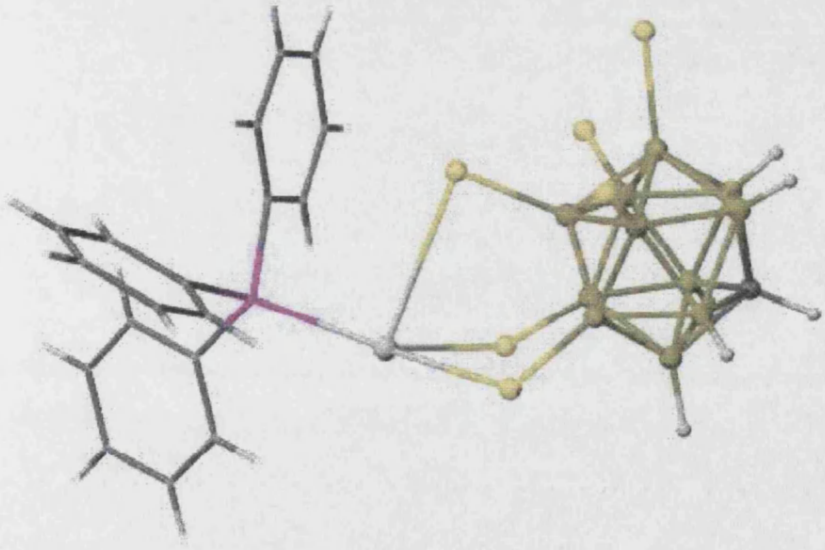
Results observed with the two carborane catalyst essentially gave quantitative yields of the cycloadduct **197**. In comparison, results with the triflate and perchlorate anion gave 70 and 90% yields respectively. The result obtained with BF_4^- counterion was however, 35% yield. Two other catalytic species were generated. The addition of another PPh_3 unit to the (PPh_3) Ag[$CB_{11}H_{12}$] **218** and (PPh_3) Ag[$CB_{11}H_6Br_6$] **219** catalysts produced two new catalysts (PPh_3)$_2$Ag[$CB_{11}H_{12}$] **220** and (PPh_3)$_2$Ag[$CB_{11}H_6Br_6$] **221**. The reaction between *N*-[(*E*)-phenylmethylidene]aniline **195** and Danishefsky's diene was repeated on the bench with these two new catalysts.

Similarly, the reactions were carried out on a 1 mmol scale with 1 mol% catalyst loading in DCM solution for 1 hour.

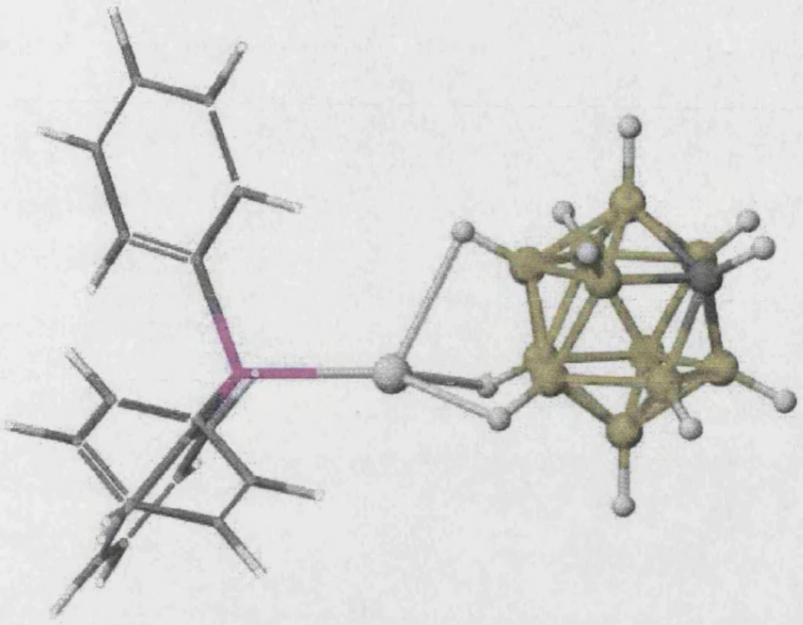
Table 29. Effect of carborane catalysis on cycloaddition.

Entry	Catalyst/mol%	Yield %
1	$(PPh_3)Ag[CB_{11}H_{12}]$	98
2	$(PPh_3)Ag[CB_{11}H_6Br_6]$	99
3	$(PPh_3)_2Ag[CB_{11}H_{12}]$	85
4	$(PPh_3)_2Ag[CB_{11}H_6Br_6]$	89

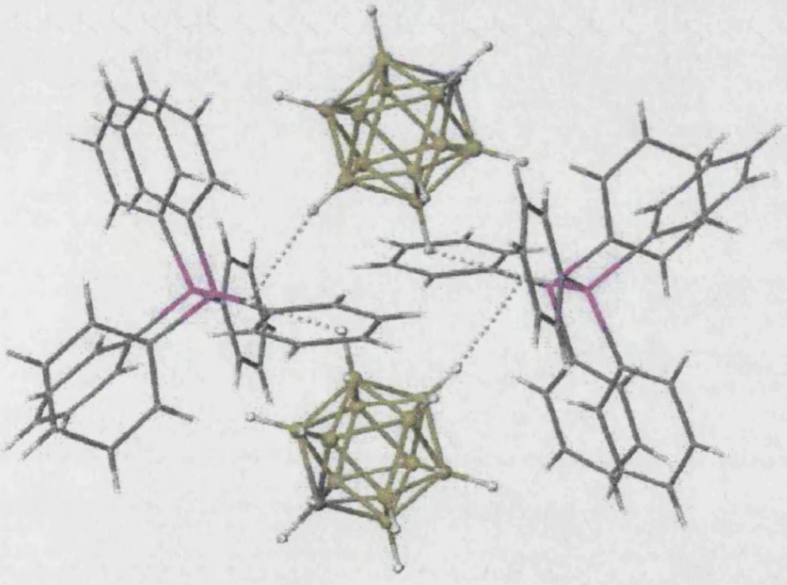
It was clear from these results that the carborane anions were efficient catalytic species for the hetero Diels-Alder reaction. Compounds **220** and **221** were fully characterised with multinuclear NMR and microanalysis, however the solid state structure of $(PPh_3)_2Ag[CB_{11}H_6Br_6]$ **221** could not be generated. The solid state structures of the three other carborane compounds were established.



Scheme 99. $Ag(PPh_3)(CB_{11}H_6Br_6)$ **218**



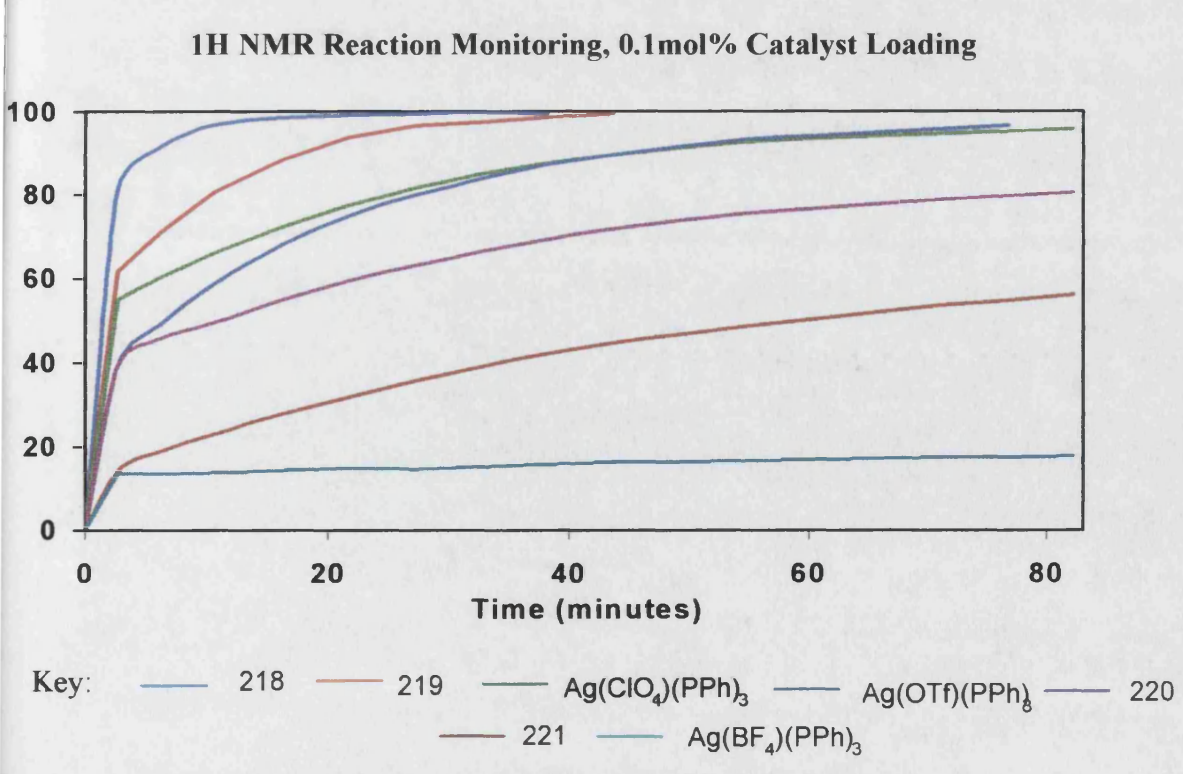
Scheme 100. $Ag(PPh_3)(CB_{11}H_{12})$ **219**



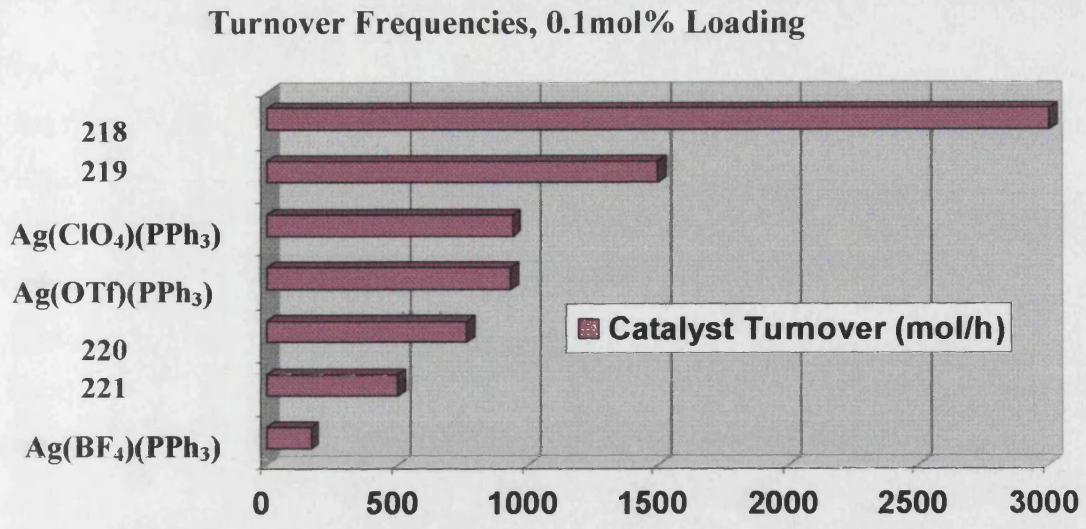
Scheme 101. $Ag(PPh_3)_2(CB_{11}H_{12})$ **220**

The remarkable activity of these catalysts could only be fully appreciated when the catalyst loading was reduced to 0.1 mol%. The reactions were monitored by NMR spectroscopy (scheme 102). The efficiency of catalyst $(PPh_3)[AgCB_{11}H_6Br_6]$ **219** for the transformation of imine to cycloadduct was particularly noticeable. Scheme 102

displays a plot of time vs. course of reaction for $(PPh_3)[AgCB_{11}H_6Br_6]$ **218**, $(PPh_3)[AgCB_{11}H_{12}]$ **219**, $(PPh_3)_2[AgCB_{11}H_6Br_6]$ **220**, $(PPh_3)_2[AgCB_{11}H_{12}]$ **221**, $Ag(OTf)(PPh_3)$, $Ag(ClO_4)(PPh_3)$, $Ag(BF_4)(PPh_3)$. It is clear from this result that complex **218** containing the halogenated carborane $[CB_{11}H_6Br_6]^-$ provides the fastest rate of catalysis. The reaction is completed in approximately 15 minutes. This gives us a catalyst turnover frequency (TOF) of *ca.* 4500mol/hour (scheme 103). Complex **219** proves to be a slower catalyst than **218.** The reaction is completed after 50 minutes while $Ag(OTF)(PPh_3)$ does not attain 100% conversion even after 80 minutes. Importantly and somewhat surprisingly we have found that water plays an especially important role in this reaction. When NMR experiments were performed in rigorously dry solvent (CD_2Cl_2, vacuum distilled from CaH_2) absolutely no catalysis occurs. Addition of a sub stoichiometric amount of water (1μl, 50 mol%) unoptimised) immediately initiates the catalysis. Silver (I) only possesses two aqueous ions, $Ag^+(aq)$ and $Ag^{2+}(aq)$. It should be noted that only Ag^+ binds to water molecules weakly.[37] The extreme potency of catalysts **218** and **219** demonstrated the marked increase in the Lewis acidic character of the silver centre. The steric bulk or reduced Lewis acidity of **220** and **221** perhaps inhibits the formation of a silver-imine complex. $Ag(PPh_3)(BF_4)$ is probably degraded by the water present to yield an oxy-borane BO_nF_{4-n}.



Scheme **102**. Plot of conversion vs. time for silver(I) phosphine catalysis



Scheme 103. Plot of catalyst turnover

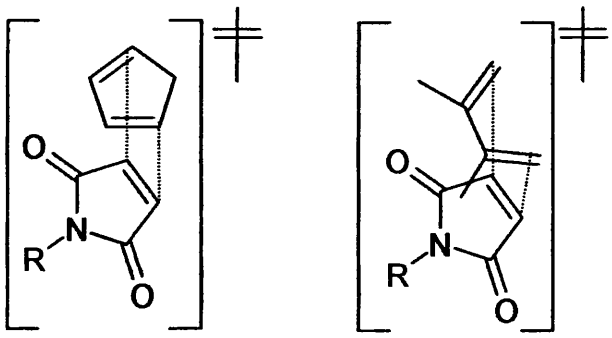
2.3.3 The Role of water in the hetero Diels-Alder reaction

Water accelerated catalysis is becoming more widely appreciated.[38] The Diels-Alder reaction normally shows modest solvent effects.[39] This indicates a small polarity change from the initial state to the activated complex. It is apparent from our initial results that there was a minor change in the rate of reaction when we changed solvent from MeCN to DCM. In 1980 Breslow discovered that Diels-Alder reactions performed in water could be subjected to huge accelerations.[40] This observation led to increasing interest by synthetic organic chemists to change their reaction solvent from an organic solvent to water. Soon it was discovered that the Claissen rearrangement, the aldol and benzoin condensations also exhibit rate enhancements in water.[41]

One explanation of water enhanced rates that should be considered is the effect of hydrophobic packing of the diene and dienophile.[42] Intramolecular Diels-Alder reactions are accelerated on addition of water thus aggregation can not be solely responsible for the aqueous acceleration observed. Alternatively, the solvents internal pressure and cohesive energy density (CED) have been used to explain rate enhancement.[43] Internal solvent pressure is thought to reflect highly distance dependant dispersion and dipole-dipole interactions within the solvent. This was proposed to influence the rate in the same way that external pressure does. Solvent polarity demonstrates significant influential factors on the increased rate of some

Diels-Alder reactions. Correlations with solvent polarity parameters are usually linear, therefore polarity alone cannot explain the aqueous acceleration. It was suggested by Engberts et al.[44] that enforced hydrophobic interactions are a major contributor to the accelerations of rates of reactions. The Diels-Alder reactions between cyclopentadiene and 2,3-dimethyl-1,3-butadiene and/or 1,3 cyclohexadiene with *N*-alkylmaleimides were studied. In this paper Diels-Alder reactions showed accelerated reaction rates in water relative to organic solvents. The authors suggested that the acceleration was due to both hydrogen bonding of water to the polarised activated complex and enforced hydrophobic interactions between the reactants. The hydrophobic interactions are essential as part of the activation process.

The authors contended that the hydrophobic part of the acceleration of the Diels-Alder reaction in water is not so much a result of a reduction of solvent accessible surface area but rather a consequence of the complete disappearance of hydrophobic character in the different groups near the reaction centre in the activated complex.

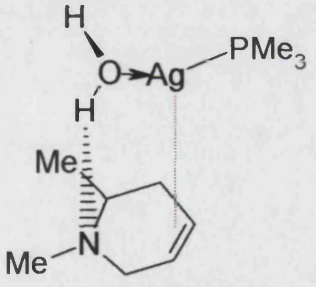


Scheme 104. Transition state models with cyclopentadiene and 2,3-dimethyl-1,3-butadiene

Lewis acid promoted reactions must generally be carried out under strictly anhydrous conditions because most Lewis acids are decomposed by water. However, Kobayashi et al. studying the effects of Lanthanide triflates in allylation, aldol reactions[45] and the hetero Diels-Alder reactions[46] found that rare earth metal triflates such as $Sc(OTf)_3$ and $Yb(OTf)_3$ and some other metal salts can be used as water stable Lewis acids for organic reactions in water containing solvents. Whilst several reactions were catalysed by these water stable Lewis acids in aqueous media, certain amounts of organic solvents such as THF and EtOH and acetonitrile needed to be combined with water to promote the reactions efficiently. This is mainly because most organic materials are insoluble in pure water. Therefore to circumvent this problem, the

authors coupled the Lewis acid-surfactant combination catalysts as Brønsted acid systems.

We can currently only speculate as to the role of water in our silver (I) phophine catalysed hetero Diels-Alder reaction. It is suggested that a Lewis assisted Brønsted acid is formed between the water and the silver. Preliminary DFT studies on the model system $[(Me_3P)Ag(MeN{=}CHMe)]^+$ suggested that a silver co-ordinated water molecule plays an important role in lowering the energy of the transition state of the silver promoted [2+4] addition of the imine to the diene. The water molecule forms a hydrogen bond with the nitrogen atom (Scheme 105). This proposed intermediate accounts for both the observed dependence upon trace amounts of water in this reaction and the strong counterion effect observed (vide infra), with both the Lewis assisted Brønsted acidity (OH---N Hydrogen bond) and the need for a vacant site (alkene co-ordination) playing important roles. Experimentally it is clear that trace amounts of water are necessary for the reaction to proceed. Reactions at the bench are probably facilitated by the presence of adventitious water.



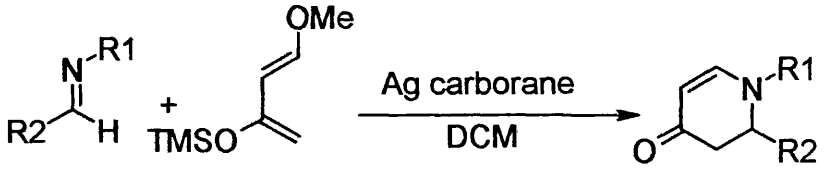
Scheme 105. Water assisted silver phosphine catalysis

The results that have been observed implicate a polarised silver-water bonded molecule as the catalytic proton source, similar to that previously reported in lanthanide catalysed aromatic electrophillic substitutions[47] and the catalytic role of co-ordinated water in certain Zeolites. This is also similar to the role that metal co-ordinated water is suggested to play in certain catalytic processes. [48] Consistent with this idea, addition of water to a mixture of imine and diene forms no product. In addition, under standard conditions the reaction was repeated in the presence of the hindered base 2,6-di-*tert*-butyl-4-methylpyridine. This base suppressed the reaction

completely. An attempted control experiment taking *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene with just 50 mol% water also resulted in no product formation.

2.3.4 Reactions of achiral imines and Danishefsky's diene to produce chiral tetrahydropyridine cycloadducts with chiral silver (I) carborane chemistry.

In previous reactions we had observed that the presence of the $[CB_{11}H_{12}]^-$ (carborane anion) and $[CB_{11}H_6Br_6]^-$ (hexabromocarborane anion) afforded superior catalysts when perchlorate, triflate and tetrafluroborate counterions were present. With these results in hand, the sluggish reactions of furyl, pyrrole and ethyl ester derived imines with the silver carborane species plus a chiral bidentate bisphosphine ligand were re-examined. We were curious to explore whether this extra activity would enable chiral induction. The reactions were performed in dry DCM with 10% unactivated 4Å molecular sieves as the water source. 10 mol% and 1 mol% of catalyst were employed with (*R*)-CHIRAPHOS **208** and (*R*)-BINAP **165** as ligands. The temperature was lowered from 25°C to -78°C and the time was varied from one hour to fifteen minutes.



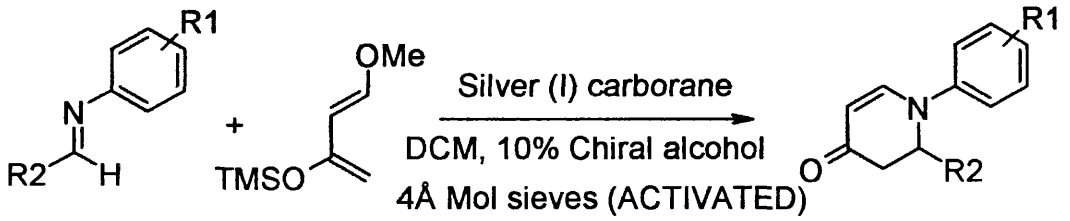
Scheme 106. Silver (I) carborane catalysis utilising bidentate imine precursors

Table 30. Asymmetric reactions of achiral imines with chiral ligands and silver carborane catalysts.

Entry	R1	R2	Cat/mol%	ligand	°C	Time (Hrs)	Yield %	ee %
1	Ph	Ph	$Ag[CB_{11}H_{12}]$/10	**208**	RT	24	100	0
2	Ph	Ph	$Ag[CB_{11}H_{12}]$/10	**208**	RT	1	100	0
3	Ph	Ph	$Ag[CB_{11}H_{12}]$/10	**208**	RT	0.25	99	0
4	Ph	Ph	$Ag[CB_{11}H_{12}]$/10	**208**	0	0.25	99	0
5	Ph	Ph	$Ag[CB_{11}H_{12}]$/1	**208**	0	0.25	96	0
6	Ph	Ph	$Ag[CB_{11}H_6Br_6]$/1	**208**	0	0.25	99	0
7	Ph	Ph	$Ag[CB_{11}H_6Br_6]$/1	**(*R*)-165**	0	0.25	99	0
8	Ph	Furyl	$Ag[CB_{11}H_{12}]$/10	**208**	RT	24	45	0
9	Ph	Furyl	$Ag[CB_{11}H_{12}]$/10	**208**	RT	1	28	0
10	Ph	Furyl	$Ag[CB_{11}H_{12}]$/10	**(*R*)-165**	RT	1	19	0
11	Ph	Furyl	$Ag[CB_{11}H_6Br_6]$/10	**(*R*)-165**	RT	1	32	0
12	Ph	Furyl	$Ag[CB_{11}H_6Br_6]$/10	**(*R*)-165**	0	24	24	0
13	Ph	CO_2Et	$Ag[CB_{11}H_{12}]$/10	**208**	RT	24	61	0
14	Ph	CO_2Et	$Ag[CB_{11}H_{12}]$/10	**(*R*)-165**	RT	24	47	0
15	Ph	CO_2Et	$Ag[CB_{11}H_6Br_6]$/10	**(*R*)-165**	0	24	38	0
16	Ph	Pyrrole	$Ag[CB_{11}H_6Br_6]$/10	**(*R*)-165**	0	24	24	0
17	Ts	CO_2Et	$Ag[CB_{11}H_6Br_6]$/10	**208**	-78	1	99	0
18	Ts	CO_2Et	$Ag[CB_{11}H_6Br_6]$/10	**(*R*)-165**	-78	1	94	0
19	Ts	CO_2Et	$Ag[CB_{11}H_6Br_6]$/10	**218**	-78	1	94	0
20	Ts	CO_2Et	$Ag[CB_{11}H_6Br_6]$/10	**(*S*)-Map**	-78	0.25	72	0

These results demonstrate that the efficiency of the rate of the formation of the tetrahydropyridine cycloadducts was increased. However we were still disappointed with the achiral nature of the reaction.

Experimentally we discovered that silver catalysts work with a substoichiometric amount of water. In our final attempt to make this reaction chirally viable we needed to introduce a chiral replacement for water. The chiral water replacement was essentially a molecule that was capable of acting like water by donating a proton to the silver metal so that it could activate the imine towards cycloaddition. Chiral alcohols were considered as suitable reagents. The following reactions were performed in dry DCM with activated 4Å molecular sieves. 10 mol% of catalyst was used to optimise the reaction. Two chiral alcohols were examined. (-) Menthol **222** and (5*R*)-5-(hydroxymethyl)-2(5*H*)-furanone **223**. The temperature and time were varied to maximise any favourable outcome.



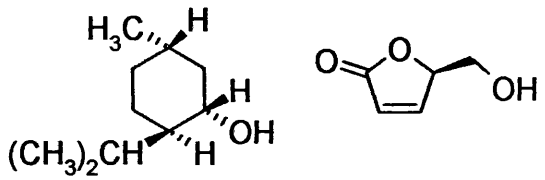
Scheme 107. Silver carborane/chiral alcohol cycloaddition

Table 31. Asymmetric induction using chiral alcohols.

Entry	R1	R2	Catalyst/10 mol%	Alcohol 10 mol%	Temp °C	Time (Hrs)	Yield %	ee %
1	H	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	RT	24	100	0
2	H	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	RT	1	100	0
3	H	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	0	1	99	0
4	H	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	-78	1	100	0
5	*o*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	RT	24	100	0
6	*o*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	RT	1	99	0
7	*o*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	0	1	99	0
8	*o*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	-78	1	98	0
9	*p*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	RT	24	100	0
10	*p*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	RT	1	100	0
11	*p*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	0	1	100	0
12	*p*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**222**	-78	1	100	0
13	H	CO_2Et	$Ag[CB_{11}H_6Br_6]$	**222**	RT	24	72	0
14	H	CO_2Et	$Ag[CB_{11}H_6Br_6]$	**222**	RT	1	68	0
15	H	CO_2Et	$Ag[CB_{11}H_6Br_6]$	**222**	0	1	7	0
16	H	CO_2Et	$Ag[CB_{11}H_6Br_6]$	**222**	-78	1	0	0
17	H	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	RT	24	100	0
18	H	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	RT	1	100	0
19	H	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	0	1	100	0
20	H	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	-78	1	100	0
21	*o*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	RT	24	100	0
22	*o*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	RT	1	98	0
23	*o*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	0	1	94	0
24	*o*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	-78	1	96	0
25	*p*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	RT	24	100	0
26	*p*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	RT	1	100	0
27	*p*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	0	1	100	0
28	*p*-Br	Ph	$Ag[CB_{11}H_6Br_6]$	**223**	-78	1	100	0
29	H	CO_2Et	$Ag[CB_{11}H_6Br_6]$	**223**	RT	24	75	0
30	H	CO_2Et	$Ag[CB_{11}H_6Br_6]$	**223**	RT	1	72	0
31	H	CO_2Et	$Ag[CB_{11}H_6Br_6]$	**223**	0	1	10	0
32	H	CO_2Et	$Ag[CB_{11}H_6Br_6]$	**223**	-78	1	0	0

The yields of the tetrahydropyridine products were outstanding however, sadly no chiral product was obtained. It was evident that a more detailed understanding as to the reaction mechanism including the involvement of and role of the bisphosphine

ligand and function of water was required before the reaction could be made asymmetric.

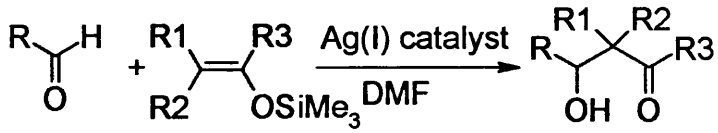


222 **223**

Scheme 108. Chiral alcohols employed in cycloaddition reactions

In the process of characterising silver (I) BINAP complexes at low temperature via ^{31}P NMR, more than one species of silver phophine complex was observed. Several separate signals were clearly visible.

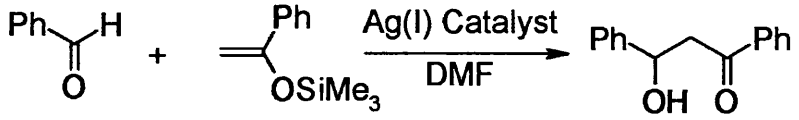
On searching through the literature that we came across an article that would explain some of our findings. Silver diphosphine complexes were noted to be effective catalysts for Mukaiyama aldol reactions in polar solvents.[49]



224 **225** **226**

Scheme 109. Mukaiyama aldol reaction with silver catalysis

The $AgPF_6$-(*S*)-BINAP cationic chiral complex displayed good activity and could afford a fairly high enantioselectivity in the reaction of aromatic aldehydes and silyl enol ethers. Conversely the AgOAc-(*S*)-BINAP system afforded the aldol product of the absolute configuration opposite to that by $AgPF_6$-(*S*)-BINAP and a very high catalytic activity was shown.



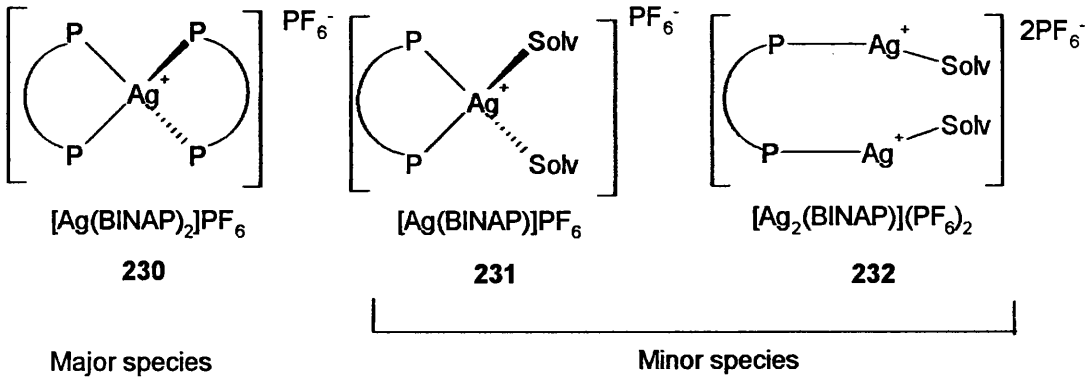
227 **228** **229**

AgPF6-(*S*)-BINAP 100% Yield, 69% ee (*S*)
AgOAc-(*S*)-BINAP 100% Yield, 11%ee (*R*)

Scheme 110. Effect of changing counterion with chiral reagent

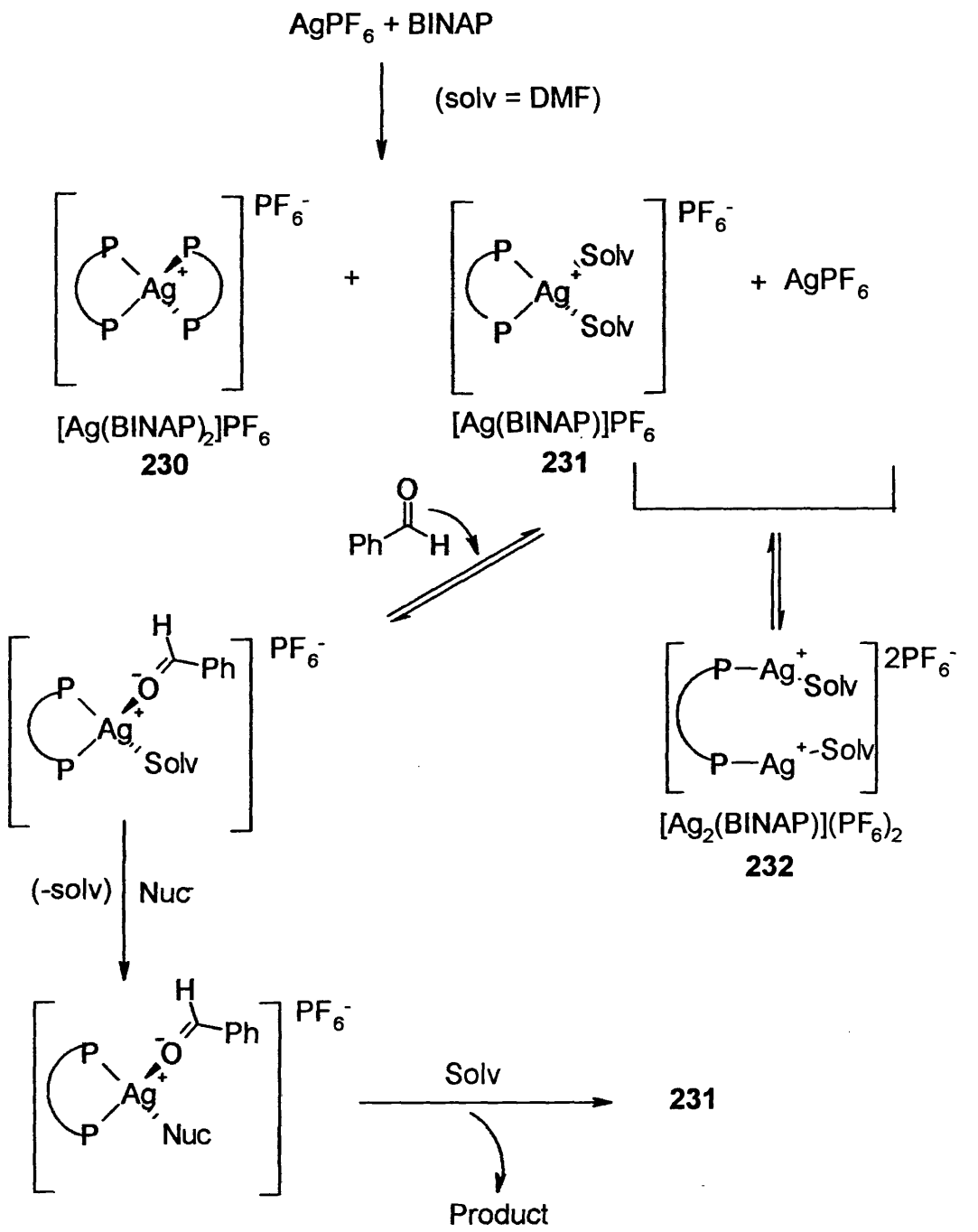
The structure and equilibrium state of Ag(I) BINAP complexes in solution were examined to better understand the reaction mechanism. The $AgPF_6$-(*S*)-BINAP complex in solution was investigated with ^{31}P-NMR. The spectra showed the $AgPF_6$-BINAP system in DMF at -50°C when BINAP and $AgPF_6$ were mixed in 1:1 ratio. Three doublet of doublet peaks were observed. The characterisation of silver (I)-monophosphine complexes in solution was performed by Muetterties and Alegranti[50] and Goel and Pilon[51]. Silver atom has two isotopes ^{107}Ag and ^{109}Ag in nature. Both of them have a nuclear spin amenable to NMR and show spin-spin coupling with the phosphorous atoms in ^{31}P NMR spectra. They reported that spin-spin coupling constant (*J*-Value) between phosphorous and silver to be dependent upon the number of co-ordinated phosphorous atoms in the silver complex. Hence the number of co-ordinated phosphorous atoms can be determined simply by measuring the *J*-value in ^{31}P NMR spectra.

The author's results showed that there were three types of silver catalyst were evident in the $AgPF_6$ system at -50°C. The major species had four co-ordinated phosphorous atoms, that is two BINAP ligands. Therefore the complexes existed as $[Ag((S)\text{-}BINAP)_2]PF_6$ **230.** The two other species were minor products in the solution. They were $[Ag((S)\text{-}BINAP)]PF_6$ **231** and $[Ag_2((S)\text{-}BINAP)_2](PF_6)_2$ **232** respectively. Even though $[Ag((S)\text{-}BINAP)_2]PF_6$ **230** was the major species among the Ag complexes in solution it could not catalyse the aldol reaction. This species is stable in solution and is not in equilibrium with the other Ag(I) species present. On raising the temperature to 25°C, ^{31}P NMR spectra revealed a sharp peak due to **230** at the same position, however the peak due to **231** and **232** disappeared, though a new broad peak was observed. This demonstrates that equilibrium exists between **231**, **232** and $AgPF_6$ in solution.



Scheme 111. Chiral bisphosphine-silver(I) species

Addition of benzaldehyde to the $AgPF_6$-BINAP solution in DMF caused a change in peak style. The peak due to **231** became broad while the addition of silyl enol ether to the $AgPF_6$-(*S*)-BINAP solution did not cause any apparent change in the spectra. Therefore [Ag((*S*)-BINAP)]PF_6 **231** is considered to interact with benzaldehyde and silyl enol ether in solution. Upon this basis the following reaction mechanism was postulated.

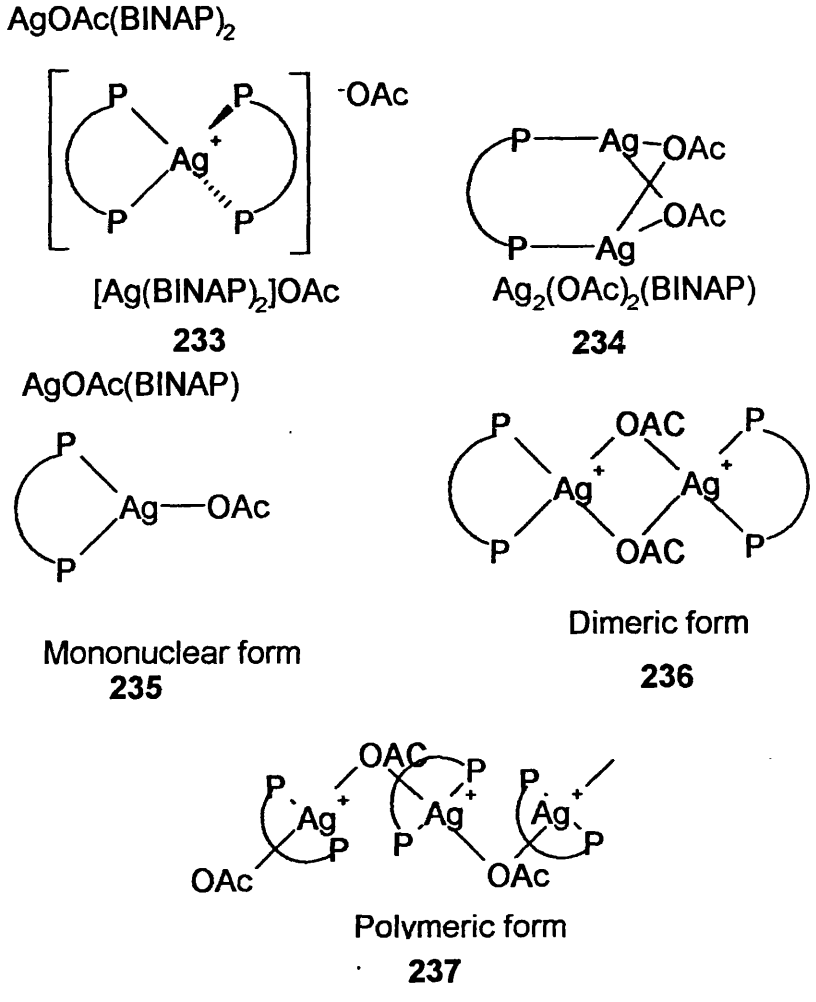


Scheme 112. Mechanism of silver (I) catalysis with chiral BINAP ligands.

The Mukaiyama Aldol reaction has also catalysed by AgOAc diphosphine complexes. Though the reaction proceeds smoothly minimal chiral enhancement was observed. The authors synthesised the AgOAc diphosphine complex responsible and characterised the structure by x-ray crystallography. The solid AgOAc-dppb complex was shown to be a binuclear complex, bridged by acetate ions and phosphorous atoms of the dppb ligand which co-ordinated to silver atoms separately. Other silver (I) complexes had also been published featuring diphosphine bridged binuclear

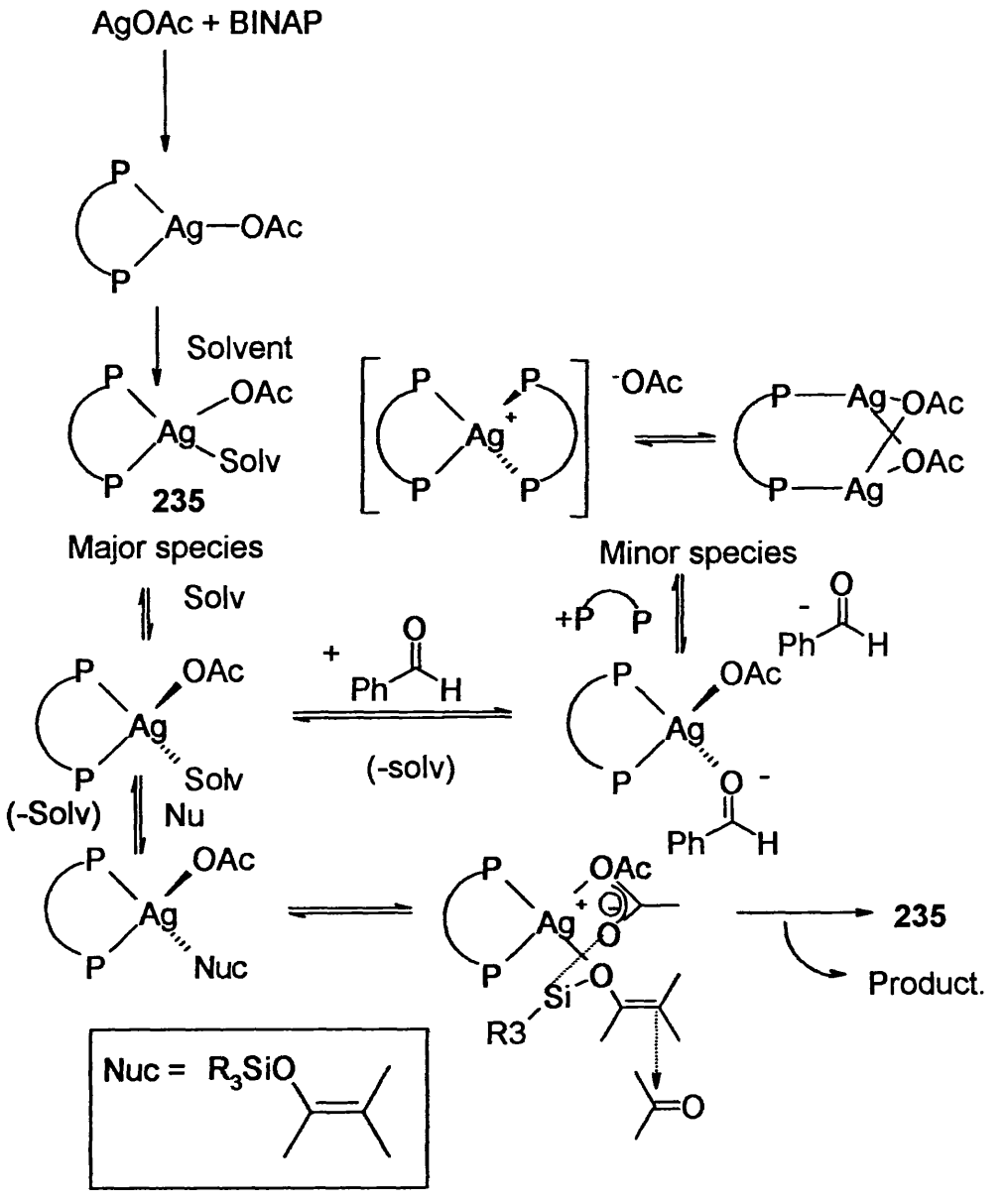
complexes.[52] Therefore the authors supposed that silver-diphosphine complexes generally form similar diphosphine bridged species in solution. Although the formation of mononuclear complexes (silver diphosphine =1:1 form) is rare, the AgOAc-(*S*)-BINAP combination forms a mononuclear system.

In DMF or THF solution $AgPF_6$-diphosphine complexes exist in equilibrium between several species. For the AgOAc-(*S*)-BINAP several species are also present in solution. At 25°C, only one doublet was observed, lowering the temperature to -50°C results in the appearance of three different peaks. Other complexes showed broad singlet or doublet peaks at 25°C and one or two sharp doublet of doublets at -50°C. These results show that these complexes are labile. At -50°C four co-ordinated phosphorous atoms are bound to the silver centre in the form of two BINAP ligands. Therefore the complex present is $Ag((S)\text{-BINAP})_2OAc$. In the $AgPF_6$ BINAP system the bis-BINAP species was the major component and proved to be extremely stable. However the $Ag((S)\text{-BINAP})_2OAc$ complex is present only as a minor species and is in equilibrium with other Ag species. In this system the major species present was a 1:1 BINAP complex. In the solid state there are three structures present, a mononuclear form **235**, a binuclear form **234**, **236** or polymeric form **237** (Scheme 113)



Scheme 113. Silver (I) BINAP (OAc) species

While the $AgPF_6$-(*S*)-BINAP system afforded reasonable high enantioselectivity in the reaction of silyl enol ether, the catalyst AgOAc-(*S*)-BINAP afforded very low enantioselectivity with an inversion of chiral induction. The reaction with the AgCl-(*S*)-BINAP catalyst also indicated the same chiral induction, though the reactivity of AgCl is much slower than that of AgOAc species. AgOAc-(*S*)-BINAP species interacts very strongly with nucleophiles with the consequence that the nucleophile is activated. The following mechanism was proposed.



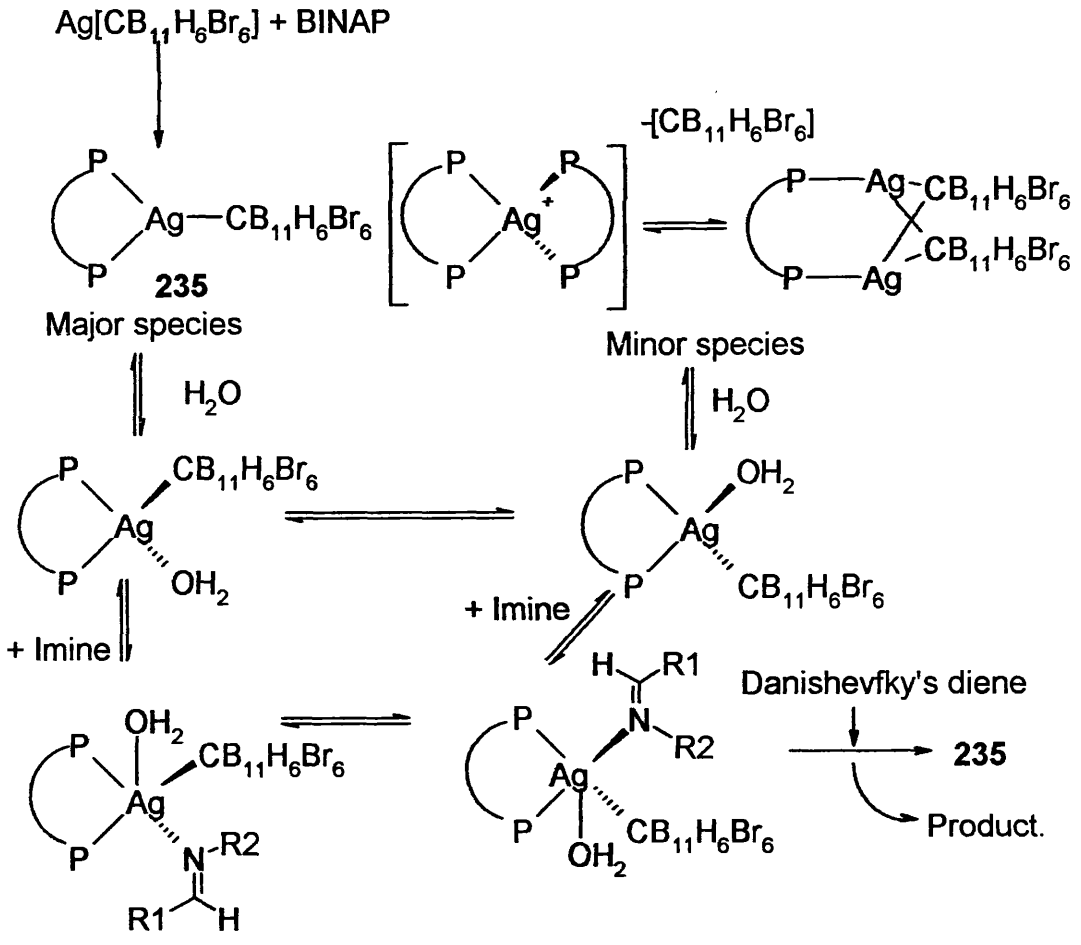
Scheme 114. Mechanism of the Mukaiyama aldol reaction with silver catalyst

The position of the equilibrium in solution is dependent upon the system.. In the $AgPF_6$ system, $[Ag(BINAP)_2]PF_6$ **230** was the major species. This species was stable and therefore inactive. $[Ag(BINAP)]PF_6$ **231**, which exists as a minor species, was the active species. The high enantioselectivity observed in the case of $AgPF_6$-BINAP is thought to result because the reaction proceeds through the six membered transition state. In the AgOAc diphosphine system the mode of co-ordination of diphosphine differs depending on the structure of the diphosphine. AgOAc-dppb formed a diphosphine bridged dimer in the solid state and in solution. AgOAc-BINAP however formed where the phosphine was bound in monomeric form in the solid state

and in solution. The 1:1 monomeric AgOAc((*S*)-BINAP) complex exists as a major species and interacts strongly with the nucleophile inducing the necessary activation. The reaction was therefore considered to proceed through an acyclic transition state by the direct attack of the Ag-nucleophile species to the substrate.

It was obvious from the Mukaiyama Aldol reaction that there are similarities to our hetero Diels-Alder experiments. We can assume that more than one type of silver BINAP species exists in solution at room temperature. The active catalyst is most probably a minor species in solution. It is apparent that the mechanism is complex rather than simple, as water plays a significant role in the activation of the silver bis-phosphine species towards catalysis. A proposed a mechanism of silver catalysis in the hetero Diels-Alder reaction of an imine with Danishefsky's diene based on the Mukaiyama aldol results is shown in scheme 115. This may help to explain lack on enantioselective induction.

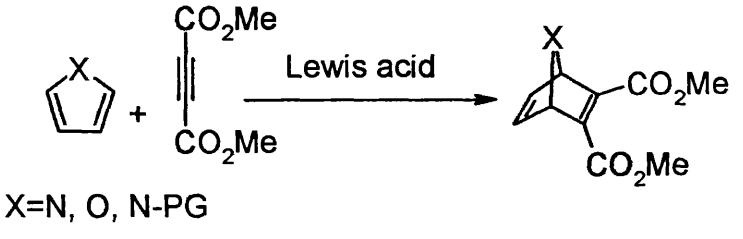
As we have already seen, $(R_3P)_2AgX$ complexes are generally dimeric with bridging ligands, but for very bulky phosphines such as $(^tBu)_3P$ linear cations $[R_3P\text{-}Ag\text{-}PR_3]^+$ are formed. Complexes with bridging bidentate phosphines tend to be dimers or tetramers with bridging phosphines. If this is our active catalyst is a polymeric species this would also explain our lack of chirality as the imine can approach the catalyst from both the top and bottom face of the polymer. The resulting product would be a mixture of both top and bottom face selective cycloadducts and the product would be a racemic mixture.



Scheme 115. Proposed equalibrium state structures for the interacton between an imine and water bound silver bisphosphine catalyst.

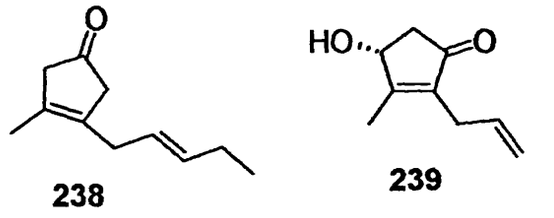
2.3.5 Influence of Lewis acids on the Diels-Alder reactions with acetylenes.

During the course of our work upon novel enantioselective catalysts in the hetero Diels-Alder reaction, we had limited success with regard to enantioselective orientation. In order to extend the application of the new and efficient Silver (I) carborane Lewis acids we decided to attempt a hetero Diels-Alder reaction between furan and pyrrole derivatives with acetylenic dienophiles.



Scheme 116. Proposed synthesis of heteronorbornadiene derivatives

Simple heterocyclic compounds such as furan, pyrrole and thiophene can be structural building blocks for the preparation of a wide variety of organic compounds through their incorporation into the skeleton of the proposed organic molecule and elimination of the heteroatom.[53] One of the simplest ways to achieve this is through the Hetero Diels-Alder reaction with the heterocycles as dienes.[54] After the cycloaddition of the Diels-Alder reaction is performed the heterocyclic ring of the bicyloadduct can be easily opened and transformed to another desirable functionality. For example furans can be opened to 1,4-dicarbonyl compounds and then closed to form a cyclopentenone ring. This framework is a crucial part of numerous natural products including *cis*-Jasmone **238**, an important perfumery constituent; the rethrolones **239**, the ester component of the insecticidal pyrethrins and most importantly the prostaglandin series **240**, mammalian hormones all contain cylopentenone rings.[55]



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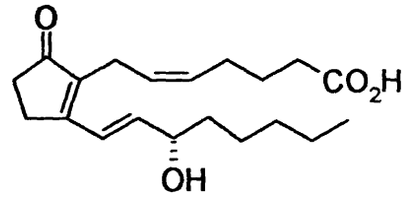
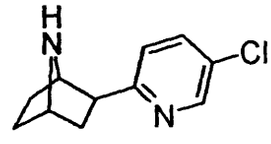


240

Scheme 117. Possible products derived from cycloaddition reactions of furans.

several important classes of alkaloid can be constructed from the hetero Diels-Alder reaction with pyrroles. Elucidation of the structure of the alkaloid 7-azabicyclo[2.2.2]heptene (Epibatidine) **241** isolated from the Ecuadorian poison frog, *Epipedobates tricolour*, caused a revival in the interest of Diels-Alder reactions featuring pyrrole as a diene.[56]



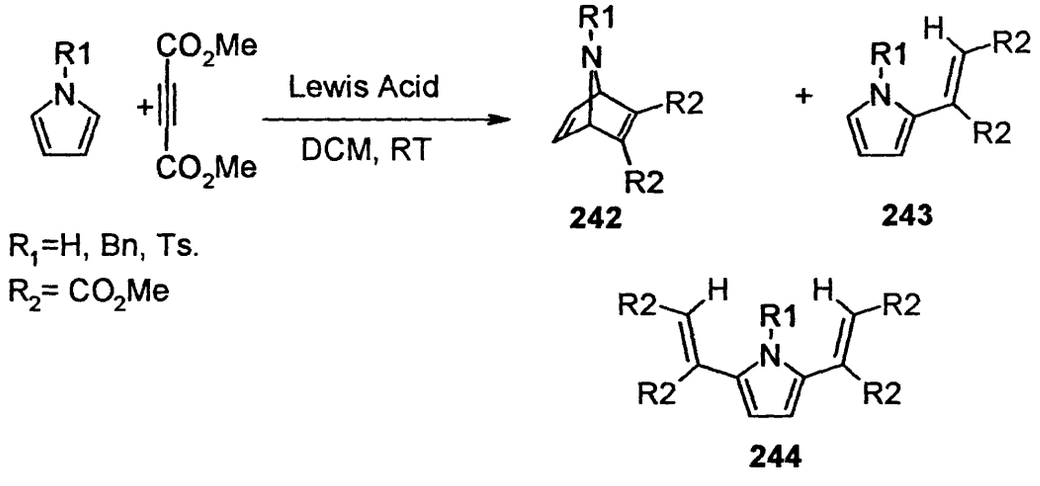
241

Scheme 118. 7-Azabicyclo[2.2.2]heptene, (-)-Epibatidine

A large number of 7-azabicylclo[2.2.1]heptane and 7-azabicylo[2.2.1]hept-2-ene derivatives have been synthesised and patented.[57] Unfortunately very few heterocyclic compounds undergo Diels-Alder reactions as dienes. The main reason for low reactivity is their high aromaticity.

In previous papers, synthesis of these heteronorbonadiene derivatives was lengthy and inefficient with very high temperatures, pressures and high catalyst loading.[58]

We examined the reaction between pyrrole derivatives and DMAD (Dimethyl acetylene dicarboxylate). All reactions were performed in anhydrous DCM solution at room temperature for 24 hours. The results obtained were fairly surprising.



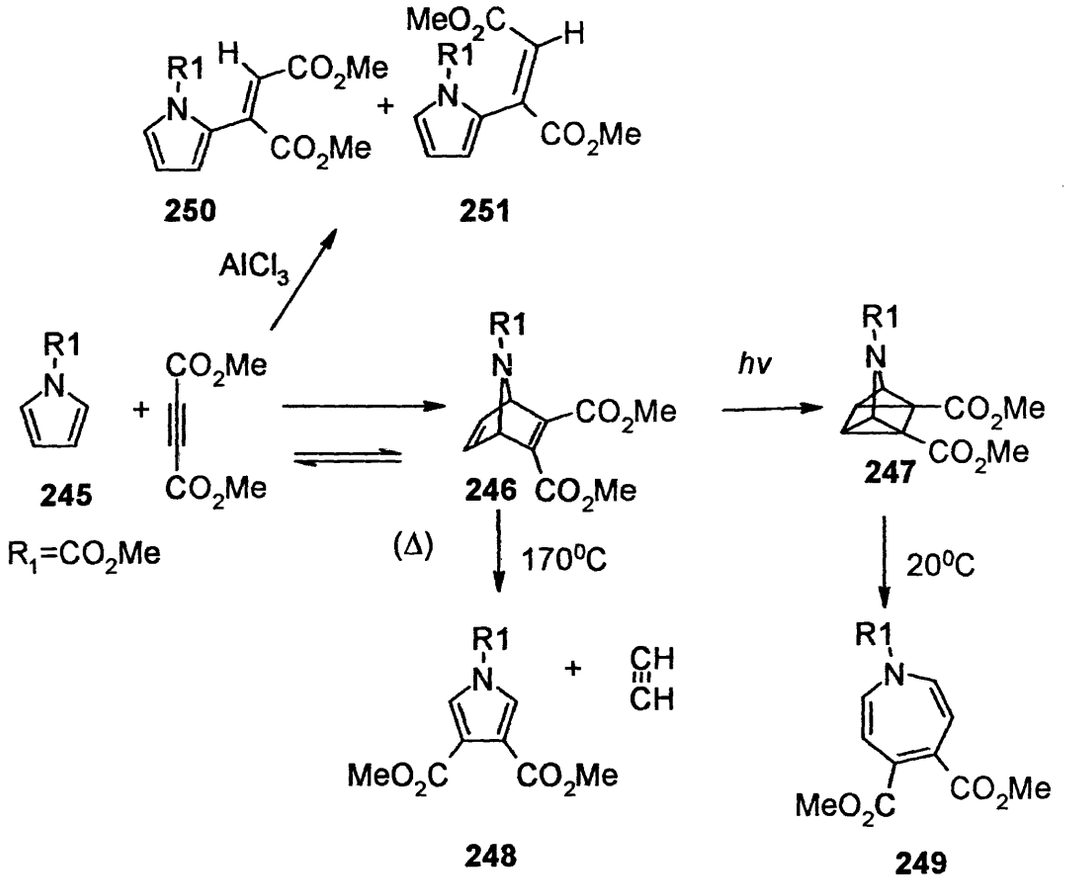
Scheme 119. Michael addition products from the attempted cycloaddition of pyrrole derivatives.

Table 31. Unexpected reactions between pyrroles and DMAD

Entry	R1	Temp	Catalyst/mol%	Yield %		
				242	**243**	**244**
1	H	RT	$Ag[CB_{11}H_6Br_6](PPh_3)$/10 mol%	4	21	-
2	H	RT	$InCl_3$/10 mol%	-	10	-
3	Bn	RT	$Ag[CB_{11}H_6Br_6](PPh_3)$/10 mol%	7	47	-
4	Bn	RT	$InCl_3$/10 mol%	3	23	12
5	Ts	RT	$Ag[CB_{11}H_6Br_6](PPh_3)$/10 mol%	-	-	-
6	Ts	RT	$InCl_3$/10 mol%	-	-	-

For this reaction the products formed were dependent upon both the substrate used and the catalyst applied. Unprotected pyrrole afforded the azanorbonadiene cycloadduct with the silver catalyst in 4% yield but with the indium catalyst no

product was detected. The main product of the two reactions proved to be the mono substituted Michael addition product **243**. With the silver catalyst the mono substituted Michael addition product was formed in 21% yield in the reaction catalysed by indium only the monsubstituted product was the only product formed (10% yield). With an electron donating functional group protecting the pyrrole nitrogen, this activated the reaction towards Michael addition with both Indium and Silver catalysts. We also observed the formation of a disubstituted compound with Indium chloride. The presence of an electron withdrawing substituent on the pyrrole inhibited the reaction completely at room temperature. It was surprising to observe that only a modest amount of the desired azanorbornadiene cycloadduct had been produced. However, until 1968 the only 7-azanorbornadiene derivatives reported were prepared at high temperatures 105-142°C, with low isolated yields of 30-45%. The first Lewis acid based synthesis and to date the only efficient Lewis acid synthesis of 7-azanorbornadienes and derivatives was reported in 1969 by Bansal, M^{c}Culloch and M^{c}Innes (scheme 120).[59] N-protected pyrroles were reacted with DMAD (Dimethyl acetylene dicarboxylate), using $AlCl_3$ catalysis. In these reactions very high quantities of Lewis acid were required (5eq). Moreover, long reaction times in sealed pressure tubes were also necessary. The following results were observed.



Scheme 120. Attempted synthesis of 7-azanorbornadienes

Table 32. Aza norbornadiene synthesis

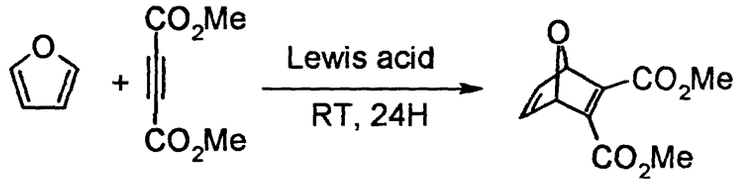
Entry	Molar eq. of catalyst	Temp. °C	Time (Hrs)	Yield %		
				250	**251**	**246**
1	1	-75	2	No reaction		
2	1	-10	4	36	36	18
3	1	25	2	34	22	34
4	1	40	0.5	30	4	54
5	3	40	1	-	19	76
6	5	40	1	-	-	93

The $AlCl_3$ promoted the reaction of **245** ($R=CO_2Me$) and DMAD in CH_2Cl_2 solution, yields variable amounts of **246**, **250** and **251** depending on the reaction conditions applied. Compounds **250** and **251** were observable products in reactions of methyl ester substituted pyrroles with DMAD. These products are formed by Michael type additions. Independent experiments established that **251** was isomerized to **250** but neither compound was interconvertable with **246** in the presence of $AlCl_3$. At Low temperatures, **250** and **251** predominate when the reactants are present in equimolar amounts. Synthesis of **246** is favoured and side reactions are minimised at higher

reaction temperatures. Increasing the Lewis acid concentration had a dramatic effect on the product composition. A threefold increase in the $AlCl_3$ concentration at 40°C not only raised the yield of **246** from 54-76% but also caused total isomerization of **251** to **250**. The yields of **246** when heated with five equivalents of catalyst increased to 93%.

It should be noted that preferential formation of **250** rather than **251** in the initial stages of the reaction implies stereospecific *cis*-addition of the diene to the triple bond of the DMAD.

We repeated this reaction with furan as the diene moiety. The reaction was undertaken at room temperature in anhydrous DCM solution, the following results being obtained.

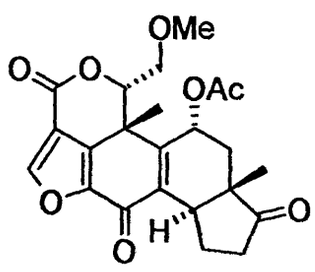


Scheme 121. cycloaddition reaction of furan and DMAD

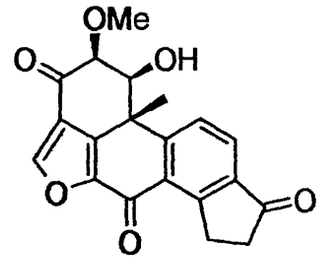
Table 33. Cycloaddition of furan as a hetero diene.

Entry	Catalyst/mol%	Yield %
1	$InCl_3$/10mol%	54
2	$Ag[CB_{11}H_6Br_6](PPh_3)$/10mol%	71

Indium chloride showed itself to be a good catalyst but the halogenated silver carborane catalyst was excellent. This reaction would be very useful in the synthesis of natural products such as Wortmannin **252** and Virdin **253**, highly oxygenated furanostroids isolated from fungal sources.[60] These compounds have received considerable attention since they function as potent inhibitors of the signalling enzyme phosphatidylinostol-3-kinase (PI-3K).[61] Excessive activity of PI-3K has been associated with certain types of cancer, prompting the development of potent and specific inhibitors.[62]



Wortmannin
252



Virdin
253

Scheme 122. Possible cycloaddition products with furan dienes.

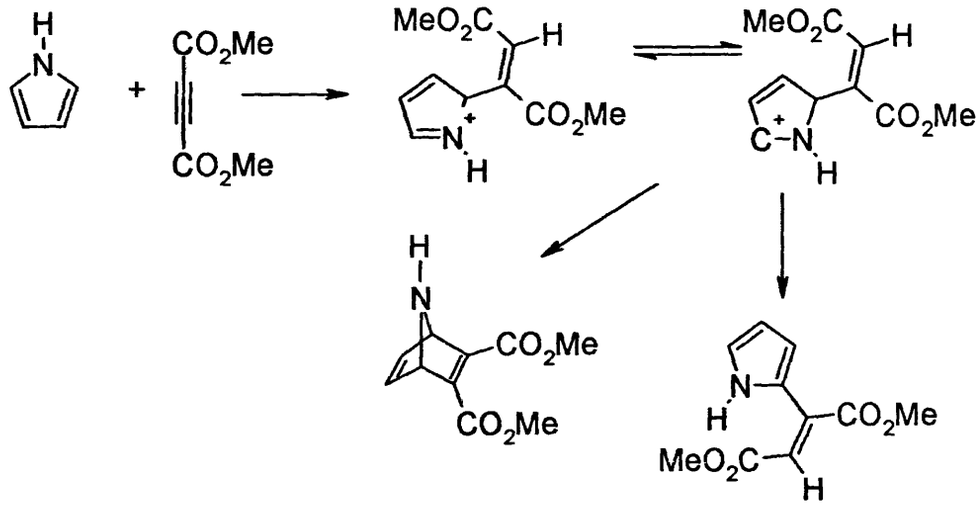
The use of Me_2AlCl was reported to have failed to produce any cycloadducts. Treatment of the furan/acetylene precursor with $Yb(OTf)_3$ in 1,4 dioxane at high temperatures produced the cycloadducts in a good yield, however temperatures of 100+°C and high pressures were necessary. This process could potentially be streamlined by application of our Indium or silver catalysts. Therefore there is considerable scope for the application of the silver catalyst in the cycloaddition reaction with heterocyclic dienes.

As considered in the introductory chapter, a normal Diels-Alder reaction considers the most important interactions between the HOMO of the Diene and the LUMO of the dienophile. In inverse Diels-Alder reactions the converse is true. It is a LUMO diene controlled reaction according to FMO energy gaps calculated by Jursic.[63] The furan and pyrrole substrates undergo HOMO diene-controlled Diels-Alder reactions similarly, thiophene with acetylene and ethylene as dienophiles are HOMO diene controlled Diels-Alder reactions. Although the energy gap between reactants was proven to be a very useful approach for the evaluation of substrates involved in pericyclic reactions it is not infallible. The major disadvantage is that it can not predict the outcome of reactions where secondary interactions between reactants in the transition state structures are important. For example, steric repulsion and secondary orbital interactions that can substantially destabilise or stabilise the corresponding transition state structure. Two possible transition state structures, *endo* or *exo*, exist for each cycloaddition reaction with furan and pyrrole derivatives. As for many Diels-Alder reactions the FMO energy change from reactants to the transition state models predicts the type of addition (either exo or *endo*) of dienophile

moiety to furan and pyrrole. Furan derivatives generally form the *exo* cycloadduct. The same explanation is used to predict pyrrole. Pyrrole has been suggested to be the more reactive of the two heterocycles, despite clear experimental evidence that furan is by far the most reactive diene for Diels-Alder reactions.

It would not be surprising to discover that furan is a better diene for the cycloaddition reaction. Furan has a lower activation energy barrier than pyrrole and formation of the thermodynamically favoured *exo*-cycloadduct is preferred. Energetically the cycloaddition of the pyrrole to the *endo* and *exo* isomeric structures is relatively similar and a mixture of products would be expected. Furan and pyrrole can be compared because they have comparable sizes, however pyrrole exhibits low reactivity towards dienophiles such as acetylene. The reason for the poor reactivity of these heterocycles towards cycloaddition is the aromaticity of the heterocycle. Disturbing the aromaticity of the pyrrole, enhances the reaction towards addition reactions. However the cycloadduct was not the major product observed in the reaction at room temperature and low catalytic loading.

In general derivatives of pyrrole do not react with low or moderately reactive dienophiles such as acetylene. There are at least two reasons, FMO energies are too low (HOMO) or too high (LUMO), and pyrrole has high aromatic character. A proposed solution to this problem is placing a substituent on the pyrrole ring that interferes with the aromatic character, therefore increasing reactivity. If pyrrole does have substituents on the nitrogen of the aromatic ring, mostly Michael type adducts are observed.



Scheme 123. Proposed mechanism of Michael addition of DMAD to pyrrole[64].

2.3.6 Summary

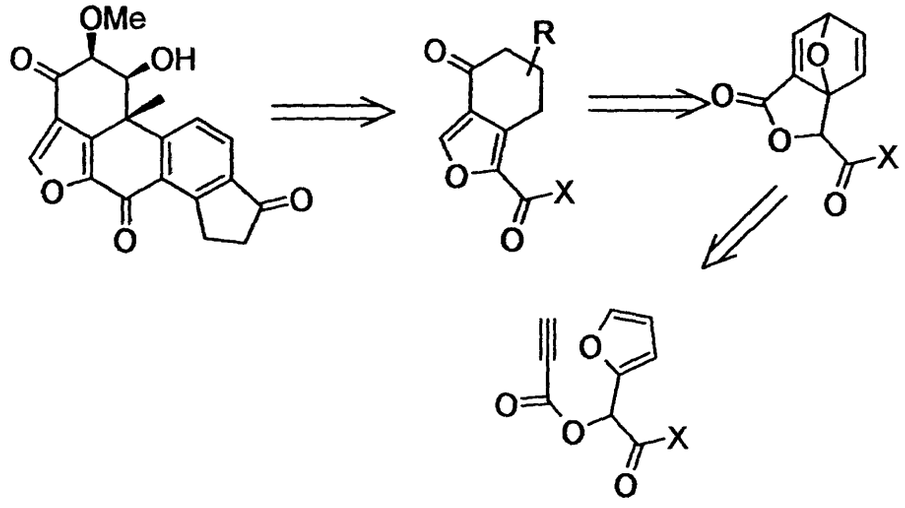
A highly efficient silver (I) phosphine carborane catalysts has been developed and shown to be a highly effective catalysts in the hetero Diels-Alder reaction (>2000 turnovers/hour). According to the classification system suggested by Kobayashi[65] the silver catalyst is an A2 Lewis acid (active, imine selective). No chiral product was observed. Water plays a significant role in the active transition state of the silver (I) catalytic system of the hetero Diels-Alder reaction. It is also assumed that the active species in solution, is a complex species involved in equilibrium.

In the Hetero Diels-Alder/Michael type reaction between furan/pyrroles and DMAD, silver (I) carborane catalysts performed to a satisfactory level of reactivity. The results obtained using silver (I) carborane species in these reactions were encouraging as previous synthesis of heterocyclic/Michael-type addition products is a laborious and expensive procedure. Utilising Silver (I) carborane catalysis could drastically effect how these compounds are synthesised in the future.

2.3.6.1 Future Work

A much more in depth study of this reaction mechanism must be undertaken before a workable chiral silver (I) phosphine based catalyst is generated. Many more chiral alcohols could be utilised in the hetero Diels-Alder reaction with silver (I) bisphosphine systems to try and enhance enantioselectivity. Silver (I) bischelating nitrogen, Nitrogen-phosphorous (Oxazoline) type ligands could also be tried in the reaction as a replacement to bischelating phosphorous ligands applied to date.

The synthesis of compounds such as Wortmannin **252** can be simplified through the sequential use of a multi-component coupling reaction followed by an intramolecular acetylene/furan Diels-Alder reaction facilitated by a Diels-Alder reaction catalysed by the silver (I) phosphine carborane catalysts (scheme 124).[66]



Scheme 124. Proposed retrosynthesis for Wortmannin utilising an intramolecular hetero Diels-Alder reaction with silver(I) carborane catalysis

2.4 Polymer supported silver catalysts.

2.4.1 Aims and objectives

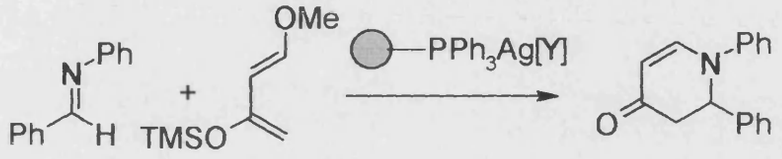
Polymer supported Lewis acids have been recently attracting significant attention since they represent one method of generating efficient, clean and reusable catalysts.[67] One major disadvantage with current polymer supported Lewis acid catalysts in synthesis are in the incorporation of the Lewis acid site onto the polymer often requires mulitstep preparation.[68] Given that one of the most popular supports is polymer bound triphenyl phosphine we were intrigued to see if the high activity and efficiency shown by complexes $[CB_{11}H_{12}]^-$ and $[CB_{11}H_6Br_6]^-$ could be transferred to a supported catalyst.

2.4.1.1 Envisaged program of work

The reaction between *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene would be repeated with polymer supported silver (I) phosphine carborane catalysts. Once the reaction was completed the catalyst would be filtered off and recycled. The efficiency of product reproducibility would be measured. Atomic absorption of the filtrate would be measured so as to determine leaching levels of the silver (I) carborane catalysts.

2.4.2 The reaction between *N*-[(*E*)-phenylmethylidene]aniline and Danishefsky's diene utilising polymer supported silver (I) catalysts.

The following reactions were performed in dry DCM on a 1 mmol scale under an inert atmosphere. Once the reactions were completed the catalyst was removed under argon and recycled. All the reactions were performed on 10 mol% supported catalyst unless otherwise indicated at room temperature for one hour.



[Y] =[$CB_{11}H_{12}$], [$CB_{11}H_6Br_6$], [OTf]

Scheme 125. Synthesis of tetrahydropyridine cycloadduct using polymer bound catalysis

Table 34. Supported silver (I) catalysed cycloaddition reactions.

Entry	Catalyst	Additive	Yield % Run 1	Yield % Run 2	Yield % Run 3
1	$AgPPh_3[CB_{11}H_{12}]$	-	99	48	12
2	$AgPPh_3[CB_{11}H_6Br_6]$	-	99	72	18
3	$AgPPh_3$[OTf]	-	90	15	12
4	$AgPPh_3[CB_{11}H_{12}]$	1µl H_2O	99	98	95
5	$AgPPh_3[CB_{11}H_6Br_6]$	1µl H_2O	99	98	98
6	$AgPPh_3$[OTf]	1µl H_2O	99	95	95
7	$AgPPh_3[CB_{11}H_6Br_6]$	10 mol% H_2O	55	-	-
8	TfOH 1mol%	-	85	-	-
9	$AgPPh_3[CB_{11}H_6Br_6]$	DTBP	0	-	-
10	$AgPPh_3[CB_{11}H_6Br_6]$	15 mol% H_2O	76	-	-
11	$AgPPh_3[CB_{11}H_6Br_6]$	20 mol% H_2O	99	-	-
12	-	20 mol% H_2O	0	-	-
13	-	50 mol% H_2O	0	-	-
14	$AgPPh_3[CB_{11}H_6Br_6]$ filtrate (supernatant)	10 mol% H_2O	4	-	-

By simply stirring a DCM solution of $Ag[CB_{11}H_{12}]$ and $Ag[CB_{11}H_6Br_6]$ and AgOTf with commercially available PPh_3 resin (Fluka) afforded a catalyst that was efficient in all three examples of the hetero Diels-Alder reaction between *N*-[(*E*)-phenylmethylidene]aniline and danishefsky's diene. All the resins were shown to be reusable over at least three catalytic runs. Low leaching levels of 0.3% Ag was also determined by AAS, while the supernatant from a freshly prepared and filtered

support catalysts afforded only trace amounts of silver (I) phosphines. When a hindered base 2,6-di-*tert*-butyl-4-methylpyridine was used in the reaction no product was observed. These supported catalysts also show a significant dependence upon the presence of water. If no water is added then the catalysts performance drops off rapidly on the second and third runs, however with 10 mol% water high yields of 95% are afforded over three consecutive cycles. Given the relatively high catalyst loading (10 mol%) used in these preliminary experiments, the counterion effects observed in the homogeneous system are not observed.

2.4.3 Summary

We have demonstrated that silver (I) phosphine complexes partnered by carborane anions based upon the $[CB_{11}H_{12}]$ framework are effective and active catalysts in a hetero Diels-Alder transformation. Water dramatically effects the observed rate of the reaction. These catalysts can be supported on a commercially available resin to give active recyclable Lewis acid catalysts

2.4.3.1 Future Work

Polymer bond Silver (I) carborane catalysts could be efficiently used to synthesis tetrahydropyridine cycloadducts achirally in the hetero Diels-Alder reaction. The Low leaching levels would allow this reaction to be performed on a large industrial scale. Once mechanistic details are fully understood to explain why these silver (I) catalysts do not achieve chiral induction in the cycloadduct, this methodology could be then encompassed into the polymer bound Lewis acid to give highly active recyclable chiral catalysis.

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Experimental

3.1 General Procedures

Commercially available solvents and reagents were obtained from Sigma-Aldrich, Lancaster Synthesis and Fischer Scientific and were used throughout without further purification; Dichloromethane and Acetonitrile were distilled from calcium hydride and stored under nitrogen. 'Petrol' refers to the fraction of petroleum ether boiling in the range of 40-60°C.

Analytical thin layer chromatography was performed on pre-coated glass-backed silica gel (Merck Kieselgel 60 F_{254}) plates and visualised under ultra-violet light (at 254nm) or by staining with vanillin or potassium permanganate. Column chromatography was carried out using Merck Kieselgel 60H silica gel.

Melting points were measured on a Büchi 535 instrument and are uncorrected. Infrared spectra were measured in the range of 4000-600 cm^{-1} using a Perkin-Elmer 1600 series FT-IR spectrophotometer, with internal calibration. Elemental analyses were performed using a Carlo Erba 1106 Elemental Analyser or an Exeter Analytical Inc CE-440 Elemental Analyser. Fast atom bombardment (FAB) and electrospray (ES) mass spectra were obtained using a Fisons VG Autospec.

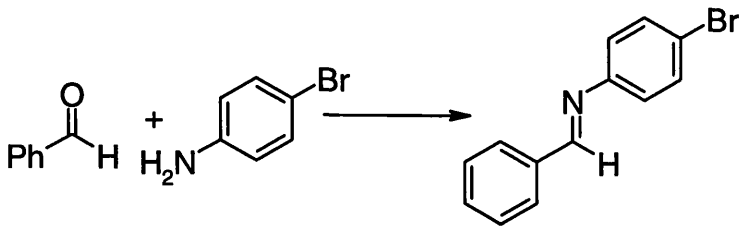
^{1}H, ^{13}C and ^{31}P spectra were recorded on either a Jeol EX-400, a Bruker 300 or a Jeol GX-270 spectrometer. Chemical shifts (δ) are expresses in parts per million (ppm), and are relative to an internal reference of residual protic solvent. The mulitplicities of the spectroscopic data are presented in the following manner: singlet (s), broad singlet (brs), doublet (d), doublet of doublets (dd) double doublet of doublets (ddd), triplet (t), triplet of doublets (td), quartet (q), or multiplet (m). Coupling constants (J) are expressed in Hz.

High performance Liquid Chromatography (HPLC) was performed on an SP thermo Separation products spectra series spectrometer and spectra physics spectrometer. Chiral columns used were Chiracel OD, AD, OJ, columns obtained from Fischer scientific supplies.

Silver analysis was performed using atomic absorption (AA) on a Varian AA-275 series spectrometer. A hollow cathode lamp provided the light source and was purchased from S+S Juniper Ltd. A silver atomic absorption standard solution (1000μg/cm^3 in 5 w/w% hydrochloric acid) was purchased from Sigma-Aldrich and diluted as necessary to provide a range of calibration standards.

Single crystal X-ray diffraction data was collected on a Nonius Kappa CCD machine. Structure determination and refinement were achieved using the SHELX suite of programs; drawings produced using ORTEX.

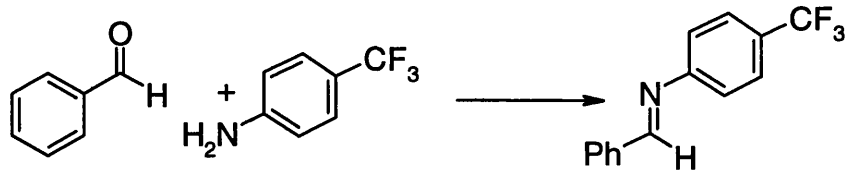
4-bromo-*N*-[(*E*)-phenylmethylidene]aniline[1] (163A)



***General Procedure for the formation of imines*:**

To a solution of 4-bromoaniline (2.5g, 14.5 mmol) in anhydrous DCM (10ml) was added to benzaldehyde (1.53g, 14.5 mmol) dropwise at 0°C, over 10 mins. To this solution was added $MgSO_4$ (5g). The solution was allowed to warm to room temperature overnight. $MgSO_4$ was filtered off and the solvent removed under vacuum. The resulting light brown solid was then purified via flash chromatography (SiO_2, 8:2 petrol/ethyl acetate). The resulting solid was further purified by recrystallisation from EtOH to yield the product as colourless needles (3.70g, 98%). mp 65-66°C (from EtOH); ν_{max}(Nujol)/cm^{-1} 1627 (C=N), 1575 (C=C), 730 (C-Br); δ_H(300MHz; $CDCl_3$) 8.42 (1 H, s, N=C*H*); 7.84-7.91 (2 H, m, Ar-*H*); 7.47-7.52 (5 H, m, Ar-*H*); 7.10 (2 H, d, *J*= 8.6, Ar-*H*); δ_C (75.5MHz, $CDCl_3$,): 161.2 (N=CH), 151.4 (=C), 136.3 (=C), 132.6 (=CH), 132.1 (=CH), 129.3 (=CH), 129.3 (=CH), 123.1 (=CH) and 119.8(=C).

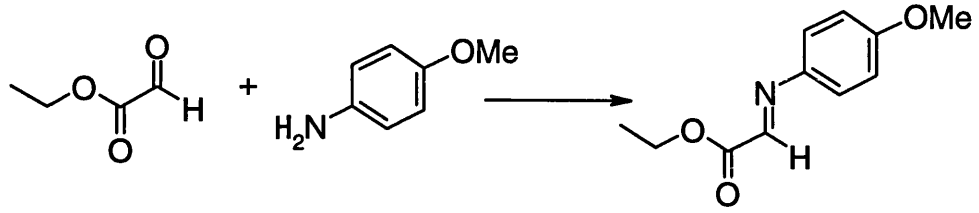
***N*-[(*E*)-phenylmethylidene]-4-(trifluoromethyl)aniline[2] (171B)**



To a solution of benzaldehyde (1g, 9.44mmol) in anhydrous DCM (10 ml) was added 4-(trifluoromethyl)aniline (1.52g, 9.44mmol) and $MgSO_4$ (5g). This solution was stirred at 50°C for 24 hrs. The $MgSO_4$ was filtered off and the solvent removed under vacuum. The resulting orange oil was distilled under vacuum (150°C, 15mmHg) to produce a white solid on cooling. The resulting solid was recrystallised from dry hexane to yield colourless needles (2.28g, 97% yield) mp 62-65°C (from hexane); ν_{max} (Nujol)/cm^{-1} 1649 (C=N), 1458 (C=C), 1168 (C-CF_3); δ_H(300MHz, $CDCl_3$); 7.70

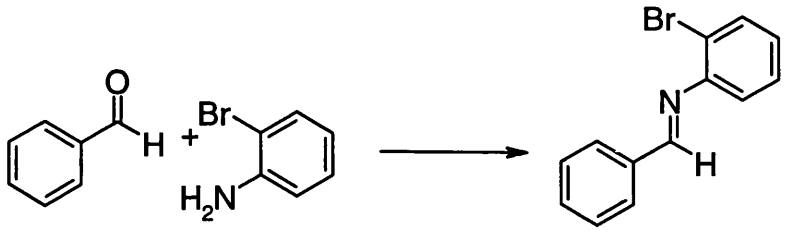
(1 H, s, N=C*H*); 7.53-7.57 (4 H, dd, *J*=1.9, 2.8, Ar-*H*); 7.32-7.36 (5 H, m, Ar-*H*); δ_C (75.5MHz, $CDCl_3$) 189.7 (N=CH), 157.6 (=C), 144.2(=CH), 135.7 (=C), 135.2 (=C), 131.2 (=CH), 130.1 (CF_3,q, *J*= 256), 129.5 (=CH), 128.2 (=CH) and 126.4 (=CH).

Ethyl 2-[(4-methoxyphenyl)imino]acetate[3] (171C)



A solution of ethyl glyoxalate (5ml, 2.58g, 25.2mmol, 50% in toluene) was heated to 110°C to crack the dimeric form. This solution was allowed to reflux at 110°C for 60mins. To this solution 4-methoxyaniline (3.10g, 24.2mmol) was added in the presence of 3Å Molecular sieves at 110°C. The reaction was left to reflux overnight at 110°C. Upon completion, $MgSO_4$ was filtered off and the solvent removed under vacuum. The resulting orange oil was distilled (200°C, 20mmHg) to afford a yellow oil, (3.54g, 73%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3417 (Aryl-H), 1703 (C=O), 1643 (C=N), 1511 (C=C), 1248 (C-O), 1182 (Me-O); δ_H (270MHz, $CDCl_3$): 7.95 (1 H, s, N=C*H*); 7.38 (2 H, dd, *J*= 2.8, 9.0, Ar-*H*,); 6.94 (2 H, d, *J*= 9.0, Ar-*H*,); 4.42 (2 H, q, *J* =6.7, CH_2,), 3.87 (3 H, s, CH_3); 1.42 (3 H, t, *J* =6.7, CH_3) δ_C (75.5MHz, $CDCl_3$,) 64.4 (N=CH), 160.2 (C=O), 148.7 (=C), 142.5 (=C), 124.7 (=CH), 115.2 (=CH), 62.9 (CH_2), 56.2 ($=OCH_3$), 14.4($=CH_3$).

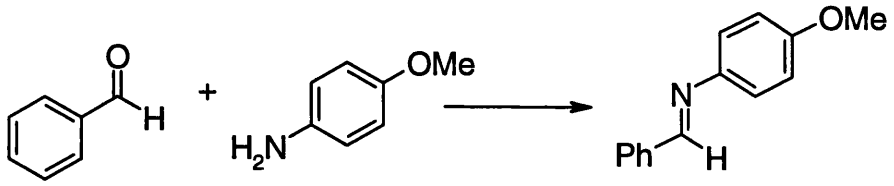
2-bromo-*N*-[(*E*)-phenylmethylidene]aniline[4] (171D)



Following the general procedure for the preparation of imines, 2-bromoaniline (14.5mmol), and benzaldehyde (14.5mmol) where mixed in the presence of $MgSO_4$. The solution was allowed to warm to room temperature overnight. The resulting yellow solid was purified by recrystallisation from hexane/ethyl acetate (9:1) to give

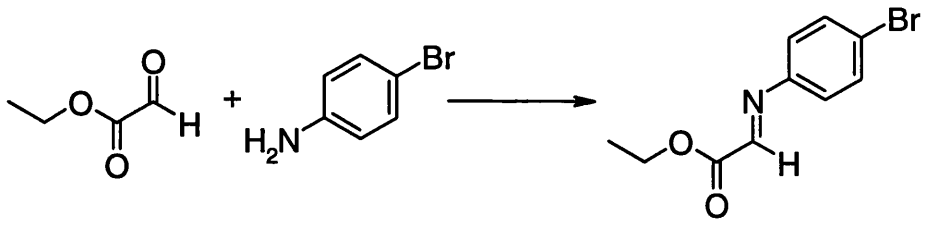
yellow needles (2.74g, 74%), mp 45°C; (from hexane/ethyl acetate). ν_{max}(Nujol)/cm^{-1} 1608 (C=N), 1487 (C=C), 782 (C-Br); δ_H(300MHz, $CDCl_3$) 8.90 (1 H, s, N=C*H*); 8.29 (1 H, dd, *J* = 2.4, 9.4, Ar-*H*); 7.66 (1 H, dd, *J* =1.2, 7.9, Ar-*H*); 7.42-7.49 (3 H, m, Ar-*H*,); 7.17-7.37 (5 H, m, Ar-*H*); δ_C(75.5 MHz, $CDCl_3$,) 160.1 (N=CH), 153.3 (=C), 136.2 (=C), 135.6 (=CH), 134.1 (=CH), 130.6 (=CH), 130.3 (=CH), 129.4 (=CH), 128.7 (=CH), 127.8 (=C), 123.2 (=CH).

4-methoxy-*N*-[(*E*)-phenylmethylidene]aniline[5] (171E)



To a solution of *p*-anisidine (5g, 40.59mmol) in anhydrous DCM (25ml) was added benzaldehyde (4.13mls, 40.59mmol) at room temperature followed by $MgSO_4$ (12g). The mixture was refluxed at 50°C overnight and allowed to cool to room temperature. Once the reaction was completed the $MgSO_4$ was filtered off and the solvent removed under vacuum. The resulting colourless powder was recrystallised from hexane to yield colourless needles (8.14g, 95%), mp 72°C (from hexane). ν_{max}(Nujol)/cm^{-1} 1603 (C=N), 1511 (C=C), 1252 (O-Me); δ_H (300MHz, $CDCl_3$) 8.29 (1 H, s, N=C*H*); 7.76 (2 H, d, *J* = 8.6, Ar-*H*,); 7.29 (2 H, t, *J* = 7.1, Ar-*H*,); 7.11 (3 H, d, *J* =8.6, Ar-*H*,); 6.89 (2 H, d, *J*= 8.6, Ar-*H*); 3.78 (3 H, s, CH_3); δ_C (75.5MHz, $CDCl_3$) 160.1 (=C), 130.9 (N=CH), 129.4 (=C), 125.9 (=C), 121.2 (=CH), 114.5 (=CH), 77.8 (=CH), 77.4 (=CH), 55.8 (=CH_3).

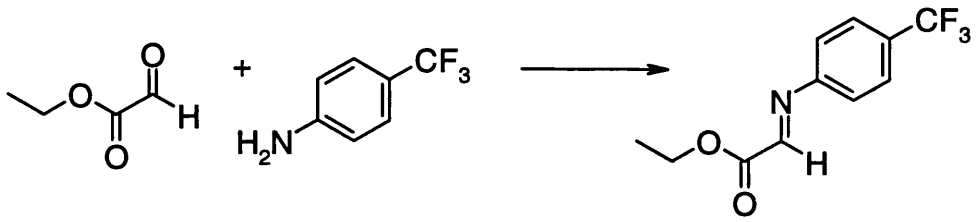
Ethyl 2-[(4-bromophenyl)imino]acetate (171F)



A solution of ethyl glyoxalate (5ml, 2.58g, 25.2mmol, 50% in toluene) was refluxed at 110°C to crack the dimeric form in Dean Stark apparatus. To this solution 4-bromoaniline (4.33g,25.2mmol) was added over a period of one hour in anhydrous

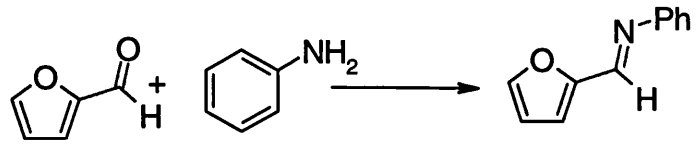
toluene (25ml). This solution was left to reflux overnight at 110°C in the presence of 3Å Molecular sieves. Once the reaction was completed the solution was allowed to cool to room temperature. The solvent was then removed under vacuum and the resulting yellow solid was recrystallised with a mixture of hexane/ethyl acetate (95:5). A yellow powder (4.01g, 62%) was finally obtained after several recrystallisations from ethanol, mp 85°C (from EtOH); ν_{max}(Nujol)/cm^{-1} 1733 (C=O), 1592 (C=N), 1493 (C=C), 817 (C-Br); δ_H(300MHz, $CDCl_3$) 7.90 (1 H, s, C*H*=N); 7,56 (2 H, d, *J*= 8.6, Ar-*H*,); 7.18 (2 H, d, *J* =8.6, Ar-*H*,); 4.44 (2 H, q, *J*= 7.1, CH_2,); 1.44 (3 H, t, *J*=7.1, CH_3,); δ_C(75.5MHz, $CDCl_3$) 164.7 (N=CH), 163.8 (C=O), 149.8 (C), 131.8 (CH), 124.9 (CH), 117.7 (C-Br), 59.9 (CH_2), 14.4 (CH_3); *m/z* (FAB+) 258.0 (100% $[MH]^+$)

Ethyl 2-{[4-(trifluoromethyl)phenyl]imino}acetate (171G)



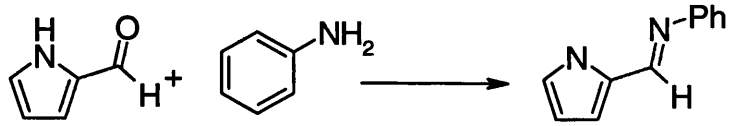
A solution of ethyl glyoxalate(2.5mls, 1.3g, 12.6mmol, 50% in Toluene) was heated to 110°C to crack the dimeric form in Dean Stark apparatus. To this solution 4-(trifluoromethyl)aniline (1.7mls, 12.6mmol) was added over a period of 30 mins in anhydrous toluene (12ml) under N_2. This solution was allowed to reflux overnight at 110°C in the presence of 3Å molecular sieves. Once the reaction was completed the solution was allowed to cool to room temperature. The solvent was then removed under vacuum and the resulting yellow solid was distilled under vacuum (200°C, 5mmHg). Yellow powder was produced (1.48g, 48%): mp 220°C (decomp); ν_{max}(Nujol)/cm^{-1} 1724 (C=O), 1617 (C=N), 1460 (C=C), 1376 (C-CF_3); δ_H(300MHz, $CDCl_3$) 7.75 (1 H, s, C*H*=N); 7.42 (2 H, m, Ar-*H*); 6.47 (2 H, d, *J* =9.2, Ar-*H*); 3.92 (2 H, m, CH_2); 0.89 (3 H, t, *J* = 6.7, CH_3); δ_C (75.5MHz, $CDCl_3$) 170.5 (C=N); 147.3 (C=O); 126.7 (C); 126.5 (CH); 121.2 (C); 113.5 (CF_3, q, *J*= 256); 113.2 (CH); 62.5 (CH_2); 13.4 (CH_3); *m/z* (FAB+) 246.0667 (54% $[MH]^+$ $C_{11}H_{10}F_3NO_2$ requires 246.0664).

_N_-[(_E_)-2-furylmethylidene]aniline[6] (210)



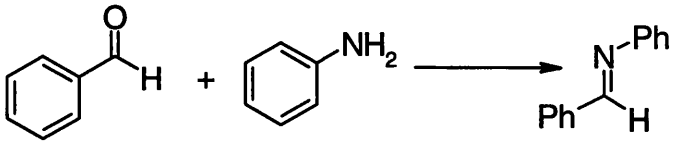
Following the general procedure for the preparation of imines, furaldehyde (2.20ml, 24.16mmol) and aniline (24.16mmol) where mixed in the presence of $MgSO_4$. The solution was allowed to warm to room temperature overnight. The resulting red solid was purified by recrystallisation from hexane/ethyl acetate (8:2) to yield red platelets (3.25g, 78%). mp 56°C (from hexane/ethyl acetate). ν_{max}(Nujol)/cm^{-1} 1629 (C=N), 1596 (C=C), 1498 (furyl); δ_H(300MHz, $CDCl_3$) 8.21 (1 H, s, C*H*=N); 7.53 (1 H, s, Ar-*H*,); 7.31 (2 H, t, *J* = 6.7, Ar-*H*); 7.15(3 H, d, *J* = 7.9, Ar-*H*); 6.87 (1 H, d, *J*= 3.3, Ar-*H*,); 6.47 (1 H, dd, *J* =1.1, 3.3, Ar-*H*,) δ_C(75.5MHz, $CDCl_3$): 171.5 (C=N); 152.4 (C); 151.7 (C); 148.1 (CH); 129.6 (CH); 127.6 (CH); 121.4 (CH); 116.7 (CH); 112.96 (CH); *m/z* (FAB+) 172.1 (100% $[MH]^+$).

_N_-[(_E_)-1_H_-pyrrol-2-ylmethylidene]aniline[7] (212)



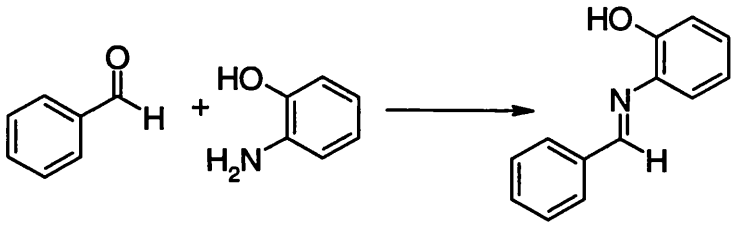
Following the general procedure for the preparation of imines, pyrrole-2-carboxaldehyde (21mmol), and aniline (21mmol), where mixed in the presence of $MgSO_4$. The solution was allowed to warm to room temperature overnight.. The resulting red solid was purified by recrystallisation from hexane/diethyl ether (8:2) to yield red platelets (1.92g, 65%). mp 95°C (from hexane); ν_{max}(Nujol)/cm^{-1} 1622 (C=N), 1583 (C=C), 1459 (Pyrrole); δ_H(300MHz, $CDCl_3$,) 10.65 (1 H, brs, N*H*); 8.15 (1 H, s, N=C*H*); 7.25 (2 H, t, *J* = 7.5, Ar-*H*,); 7.10 (3 H, d, *J* =6.7, Ar-*H*); 6.56 (1 H, dd, *J* =1.4, 2.8, Ar-*H*,); 6.50 (1 H, s, C*H*); 6.10 (1 H, dt, *J*= 2.8, 6.0 ,Ar-*H*,) δ_C (75.5MHz $CDCl_3$): 152.2 (=C), 151.0 (N=CH), 131.0 (=C), 129.7 (=CH), 125.9 (=CH), 124.5 (=CH), 121.5 (=CH), 117.8 (=CH), 110.7 (=CH).

N-[(E)-phenylmethylidene]aniline[8] (195)



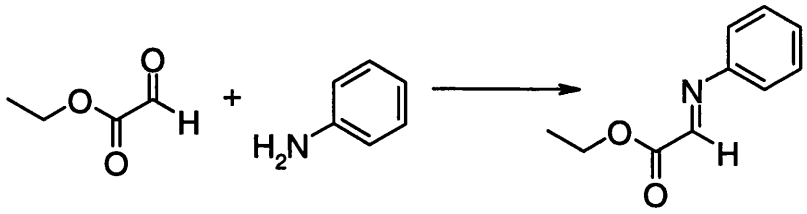
Following the general procedure for the preparation of imines, benzaldehyde, (19.67mmol) and aniline (19.67mmol) where mixed in the presence of $MgSO_4$. The solution was allowed to warm to room temperature overnight. The resulting yellow solid was purified by recrystallisation from hexane to give colourless needles (2.85g, 80%), mp 54-56°C (from hexane); ν_{max}(Nujol)/cm^{-1} 1672 (C=N), 1592 (C=C) δ_H (300MHz, $CDCl_3$) 7.87 (2 H, t, *J* =6.35, Ar-*H*,); 7.61-7.42 (5 H, m, Ar-*H*) 7.29 (3 H, d, *J*=6.7, Ar-*H*); δ_C(75.5MHz, $CDCl_3$): 160.8 (N=CH); 152.4 (C); 136.6 (C); 131.8 (CH); 129.5 (CH); 129.1 (CH); 126.3 (CH); 121.2 (CH);

2-{[(E)-phenylmethylidene]amino}phenol[9] (175)



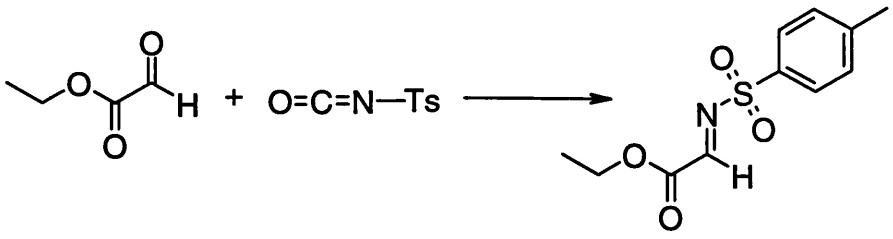
Following the general procedure for the preparation of imines, 2-Aminophenol (5ml, 49mmol), and benzaldehyde (49mmol) where mixed in the presence of $MgSO_4$. The mixture was stirred at room temperature overnight. The resulting colourless powder was recrystallised with EtOH to yield colourless needles (7.3g, 76%), mp 97°C (from ethanol). ν_{max}(Nujol)/cm^{-1} 2913 (C-OH) 1622 (C=N), 1463 (C=C); δ_H(300MHz, $CDCl_3$) 8.62 (1 H, s, N=C*H*); 7.84 (2 H, dd, *J*=2.0, 4.1, Ar-*H*); 7.41 (3 H, dd, *J*= 2.0, 4.1,, Ar-*H*); 7.13-7.25 (3 H, m, Ar-*H*,); 6.93 (1 H, dd, *J*=1.6, 9.0, Ar-*H*,); 6.84 (1 H, dt, *J* = 1.6, 9.0, Ar-*H*). δ_C(75.5MHz, $CDCl_3$) 157.5 (N=CH), 152.7 (C=O), 136.2, (N-C), 135.9 (N-C), 129.3 (=CH), 120.5 (=CH), 116.35 (=CH), 115.46 (=CH).

Ethyl 2-(phenylimino)acetate[10] (214)



A solution of ethyl glyoxalate (5mls, 2.58g, 25.2mmol, 50% in Toluene) was heated to 110°C to crack the dimeric form in Dean Stark apparatus. To this solution aniline (2.3mls, 25.2mmol) was added dropwise over an hour in anhydrous toluene (25ml). This solution was left to reflux overnight at 110°C in the presence of 3Å Molecular sieves. Once the reaction was completed the solution was allowed to cool to room temperature. The solvent was then removed under vacuum and the resulting orange solid was distilled under vacuum (250°C, 5mmHg). This solid was then recrystallised with a mixture of hexane/ethyl acetate (95:5) to afford an orange powder (2.3g, 76%) which was finally obtained after several recrystallisations with hexane/ethyl acetate, mp 180°C (decomp); ν_{max}(Nujol)/cm^{-1} 1723 (C=O), 1600 (C=N), 1458 (C=C); δ_H(300MHz $CDCl_3$) 7.84 (1 H, s, C*H*=N); 7.34 (3 H, t, *J*= 7.5, Ar-*H*); 7.25 (2 H, d, *J*= 7.5, Ar-*H*); 4.27 (2 H, q, *J*= 7.1, CH_2,); 1.34 (3 H, t, *J*= 7.5, CH_3); δ_C(75.5MHz, $CDCl_3$) 164.4 (CH), 163.8 (C=O), 150.7 (C), 128.5 (CH), 124.0 (CH), 122.5 (CH), 59.9 (CH_2), 14.4 (CH_3).

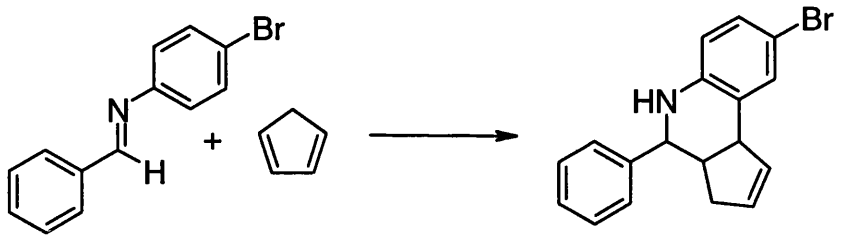
Ethyl 2-{[(4-methylphenyl)sulfonyl]imino}acetate[11] (216)



A solution of ethyl glyoxalate (5mls, 2.58g, 25.2mmol, 50% in Toluene) was heated to 110°C for 2 hours to crack the dimeric form in reflux apparatus. To this solution 4-methylbenzenesulfonyl isocyanate (3.8mls, 25.2mmol) was added dropwise, over an hour in anhydrous toluene (25ml). This mixture was allowed to reflux overnight at 110°C. This mixture was then kept at reflux, under N_2, until required. Several purification attempts were made, however the highly reactive tosyl imine was unstable and rapidly decomposed. The crude solution obtained was used crude in

future experiments. ^{1}H NMR was used to monitor the decrease of the aldehyde peak and the corresponding increase of the imine peak, which determined reaction completion. ν_{max}(Nujol)/cm^{-1} 1732 (C=N), 1597 (C=O), 1446 (C=C), 1344 (SO_2); δ_H (crude) (400MHz, $CDCl_3$,) 8.29 (1 H, s, C*H*=N); 7.86 (2 H, d, *J*= 7.6 , Ar-*H*); 7.38 (2 H, d, *J*= 7.6, Ar-*H*); 4.75 (2 H, q, *J*= 9.3, CH_2); 2.42 (3 H, s, CH_3); 1.37 (3 H, t, *J*= 9.3, CH_3,); δ_C(75.5MHz, $CDCl_3$) 166.8 (C=O); 143.5 (C=N); 143.2 (C); 138.9 (C); 129.4 (CH); 129.3 (CH); 126.9 (CH); 126.2 (CH); 63.0 (CH_2); 21.5 (CH_3); 13.6 (CH_3).

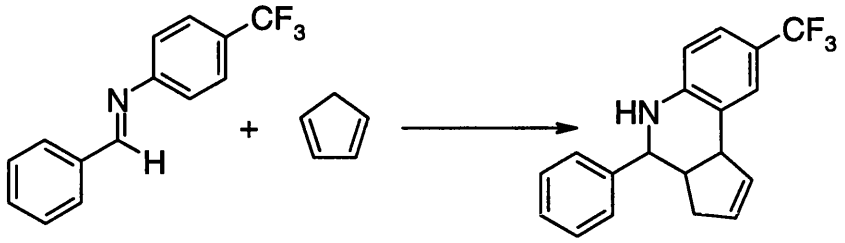
8-Bromo-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (172A)



General procedure for the production of tetrahydroquinolines.

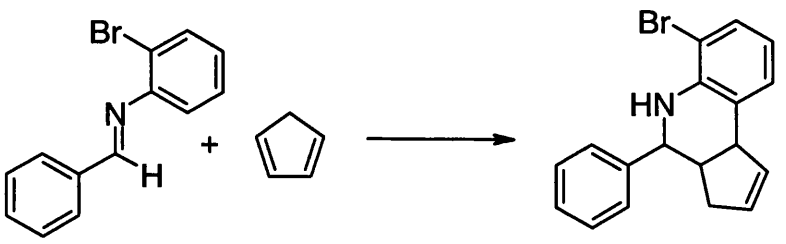
To a stirring solution of catalyst (10 mol%) and ligand (10 mol%) in anhydrous DCM (2.5ml) was added 4-bromo-*N*-[(*E*)-phenylmethylidene]aniline (0.2g, 0.77mmol) in anhydrous DCM (1ml). This solution was allowed to stir at room temperature for 15 min. To this solution, freshly cracked cyclopentadiene (0.13ml, 1.53mmol) was added dropwise in anhydrous DCM (1.5ml). Once the reaction was complete (periods off time ranging from 60 mins to 24 hours), the reaction was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with ethyl acetate (50ml). The solvent was removed under vacuum and the crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to produce a colourless white solid, which was further recrystallised from ethanol to produce colourless needles (see results and discussion for yields of tetrahydroquinoline analogue **172A**), mp 134-135°C (from EtOH). ν_{max}(Nujol)/cm^{-1} 1640 (C-NH), 1486 (C=C), 1290 (C=C) 907 (C-Br); δ_H(300MHz, $CDCl_3$) 7.50-7.06 (7 H, m, Ar-*H*); 6.52 (1 H, d, *J*=8.2, Ar-*H*); 5.81 (1 H, m, C*H*=); 5.68 (1 H, m, C*H*=); 4.62 (1 H, d, *J*= 3.0, C*H*); 4.09 (1 H, d, *J*= 8.6, C*H*); 3.78 (1 H, brs, N*H*); 3.02 (1 H, ddd, *J*=1.3, 1.9, 10.9, C*H*); 2.62 (1 H, ddd, *J*= 2.2, 7.1, 9.4, C*H*); 1.83 (1 H, ddd, *J*= 2.6, 3.9, 9.4, C*H*); δ_C(75.5MHz, $CDCl_3$) 145.0 (C); 142.7 (C); 133.8 (CH); 131.9 (CH); 131.3 (CH); 129.4 (CH); 128.9 (CH); 128.6 (CH); 127.8 (C); 126.8 (CH); 117.8 (CH); 116.0 (C-Br); 58.3 (CH); 46.6 (CH); 46.1 (CH); 31.8 (CH_2); *m/z* (FAB+) 327.0444 (95% $[MH]^+$ $C_{18}H_{16}BrN$: requires 327.0466). HPLC Chiracel AD, 98:2, (Hexane: IPA), 0.5 ml/min, Rt= 17.73, 26.76 min.

4-Phenyl-8-(trifluoromethyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (172B)



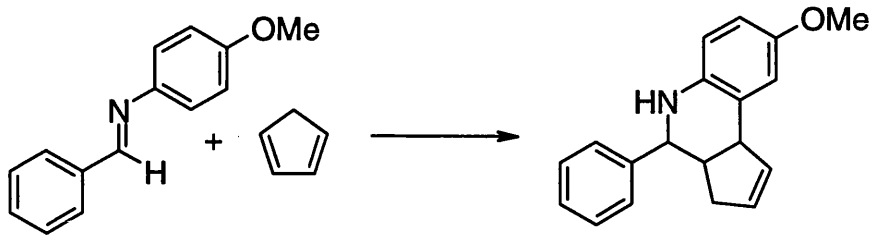
Following the general procedure for the preparation of tetrahydroquinolines, *N*-[(*E*)-phenylmethylidene]-4-(trifluoromethyl)aniline (0.80mmol) and cyclopentadiene (1.60mmol) were combined with a mixture of catalyst and ligand.. Once the reaction was completed, the reaction was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with ethyl acetate (50ml). The solvent was removed under vacuum and the crude product was then purified via flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to afford a yellow oil (see results and discussion for yields of tetrahydroquinoline analogue **172B**), ν_{max}(liquid film)/cm^{-1} 3431 (aryl-H), 1683 (C-NH), 1609 (C=C), 1494 (C=C), 1100 (C-CF_3); δ_H(300MHz, $CDCl_3$) 7.50-7.11 (7 H, m, Ar-*H*); 6.75 (1 H, d, *J*= 16.2, Ar-*H*); 6.32 (1 H, dd, *J*= 2.3, 5.6, C*H*,); 5.95 (1 H, dd, *J*= 1.8, 5.6, C*H*); 5.55 (1 H, brs, NH); 3.30 (1 H, d, *J*= 3.4, C*H*); 3.24 (1 H, m, C*H*); 2.99 (1 H, d, *J*= 1.8, C*H*); 1.83 (2 H, d, *J*= 8.6, CH_2); 1.57 (1 H, dd, *J*=1.8, 8.6, C*H*); δ_C(75.5MHz, $CDCl_3$) 145.0 (C); 142.8 (CH); 139.3 (CH); 134.9 (C); 130.7 (CH); 129.9 (CH); 129.3 (CH); 127.9 (CF_3, q, *J*= 256); 126.6 (C); 125.5 (CH); 59.8 (CH); 47.9 (CH); 47.7 (CH_2); 46.3 (CH); *m/z* (FAB+) 317.1237 (66% $[MH]^+$ $C_{19}H_{16}F_3N$: requires 317.1235) HPLC Chiracel AD, 98:2, (Hexane: IPA), 0.5 ml/min, Rt = 28.12, 32.14 min

6-bromo-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (172D)



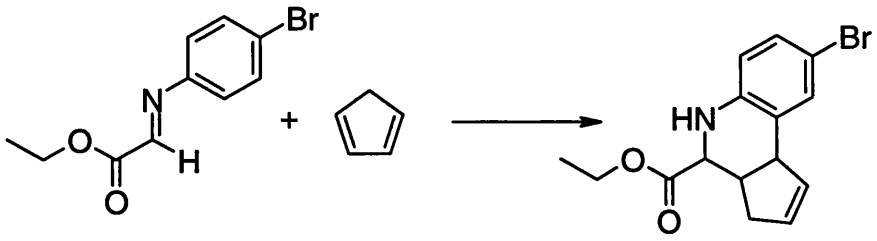
Following the general procedure for the preparation of tetrahydroquinolines, 2-bromo-*N*-[(*E*)-phenylmethylidene]aniline (0.77mmol) and cyclopentadiene (1.53mmol) were combined with a mixture of catalyst and ligand. Once the reaction was complete, it was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with ethyl acetate (50ml). The solvent was removed under vacuum and the crude product was then purified via flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to afford a yellow powder (see results and discussion for yields of tetrahydroquinoline analogue **172D**). mp 128°C (from hexane/ethyl acetate). ν_{max}(Nujol)/cm^{-1} 1625 (C-NH), 1462 (C=C), 748 (C-Br); δ_H(300MHz $CDCl_3$) 7.68 (1 H, dd, *J*=0.8, 7.9, Ar-*H*); 7.48 (2 H, m, Ar-*H*); 5.67 (1 H, m, C*H*=); 5.48 (1 H, m, C*H*=); 4.25 (1 H, d, *J*= 3.0, C*H*); 4.11 (1 H, d, *J*= 7.5, C*H*); 3.88 (1 H, brs, N*H*); 3.01 (1 H, ddd, *J*=2.5, 2.9, 9.2, C*H*); 2.62 (1 H, ddd, *J*= 3.2, 4.1, 9.4, C*H*); 1.87 (1 H, ddd, *J*= 3.6, 4.5, 9.1, C*H*); δ_C(75.5MHz, $CDCl_3$) 143.7 (C); 137.7 (C); 133.0 (CH); 128.4 (CH); 128.6 (CH); 127.3 (CH); 122.9 (CH); 118.2 (C-Br); 58.7 (CH); 47.0 (CH); 40.7 (CH_2); 40.0 (CH); *m/z* (FAB+) 327. 327.0444 (100% $[MH]^+$ $C_{18}H_{16}BrN$: requires 327.0466). HPLC Chiracel AD (99:1), (Hexane: IPA), 0.5 ml/min, Rt= 28.21, 34.22 min.

Methyl 4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinolin-8-yl ether[12] (172E)



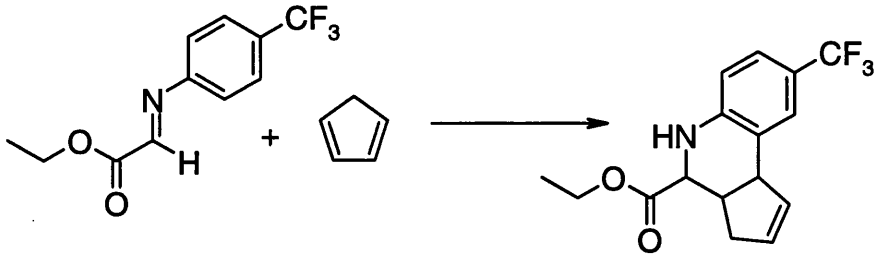
Following the general procedure for the preparation of tetrahydroquinolines, 4-methoxy-*N*-[(*E*)-phenylmethylidene]aniline (0.95mmol) and cyclopentadiene (1.90mmol) were combined with a mixture of catalyst and ligand. Once the reaction was completed, it was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with ethyl acetate (50ml). The solvent was removed under vacuum and the crude product was then purified via flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to produce white powder, (see results and discussion for yields of **172E**) mp 200°C (decomp). ν_{max}(liquid film) cm^{-1} 3384 (aryl-H), 1511 (C-OMe), 1521 (C=C), 1371 (C=C), 1257 (OMe); δ_H(400MHz, $CDCl_3$): 7.35-7.26 (5 H, m, Ar-*H*); 6.86 (1 H, dd, *J*=1.6, 3.0, Ar-*H*); 6.52 (1 H, dd, *J*= 3.2, 9.6, Ar-*H*); 6.22 (1 H, dd, *J*=1.2, 9.0, Ar-*H*); 5.83 (1 H, m, C*H*); 5.68 (1 H, m, C*H*); 4.41 (1 H, d, *J*= 3.1, C*H*); 4.08 (1 H, d, *J* = 6.7, C*H*); 3.88 (1 H, brs, N*H*); 3.65 (3 H, s, CH_3); 2.89 (1 H, ddd, *J* = 3.3, 6.7, 9.0, CH_2), 2.75 (1 H, m, C*H*); 1.85 (1 H, dd, *J*= 6.7, 12.1, CH_2); δ_C(75.5MHz, $CDCl_3$): 157.8 (C); 142.0 (C)141.1 (C); 135.7, (C) 130.6 (CH); 129.0 (CH); 128.4 (CH); 127.6 (CH); 127.4 (CH); 115.3 (CH); 113.8 (CH); 110.0 (CH); 58.9 (CH); 55.2 (CH_3); 47.0 (CH); 41.3 (CH_2); 38.9(CH); *m/z* (FAB+) 278.3 (100%, $[MH]^+$), HPLC Chiracel AD, 98:2, (Hexane: IPA), 0.5 ml/min, Rt = 14.21, 22.32 min.

Ethyl 8-bromo-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-carboxylate (172F)



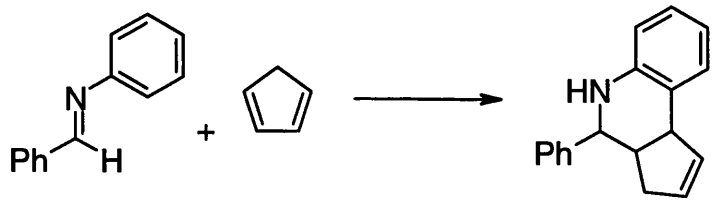
Following the general procedure for the preparation of tetrahydroquinolines, ethyl 2-[(4-bromophenyl)imino]acetate (0.78mmol) and cyclopentadiene (1.56mmol) were combined with a mixture of catalyst and ligand. Once the reaction was completed, it was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with ethyl acetate (50ml). The solvent was removed under vacuum and the crude product was then purified by flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to afford a yellow oil, (see results and discussion for yields of tetrahydroquinoline analogue **172F**) ν_{max}(liquid film)/cm^{-1} 3366 (aryl-H), 1737 (C=O), 1644 (C-NH), 1490 (C=C), 1371 (C=C), 732 (C-Br)cm^{-1}; δ_H(300MHz, $CDCl_3$): 7.11 (2 H, d, *J*= 1.5, Ar-*H*); 7.04 (1 H, dd, *J*= 1.9, 7.6, Ar-*H*); 6.50 (1 H, d, *J*= 7.6, C*H*); 5.67 (2 H, d, *J*= 7.6, C*H*); 4.21 (3 H, m, CH_2, N*H*); 4.05 (2 H, m, C*H*); 3.32 (1 H, ddd, *J*= 3.4, 5.5, C*H*); 2.41 (1 H, m, CH_2); 2.35 (1 H, ddd, *J*= 1.9, 2.9, 4.6, CH_2,); 1.32 (3H, t, *J*=7.0, CH_3); δ_C(75.5MHz, $CDCl_3$): 168.4 (C=O); 137.5 (C); 133.2 (CH); 133.0 (CH); 132.8 (CH); 128.7 (CH); 127.5 (C); 117.6 (CH); 116.3 (C); 62.6 (CH2); 61.8 (CH); 60.5 (CH); 40.8 (CH); 32.9 (CH_2); 14.5 (CH_3); *m/z* (FAB+) 323.0369, (31%, [MH]+) $C_{15}H_{16}NO_2$, requires 323.0364 HPLC Chiracel AD, 98:2, (Hexane: IPA), 0.5 ml/min, Rt = 23.90, 28.92 min.

Ethyl 8-(trifluoromethyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-4-carboxylate (172G)



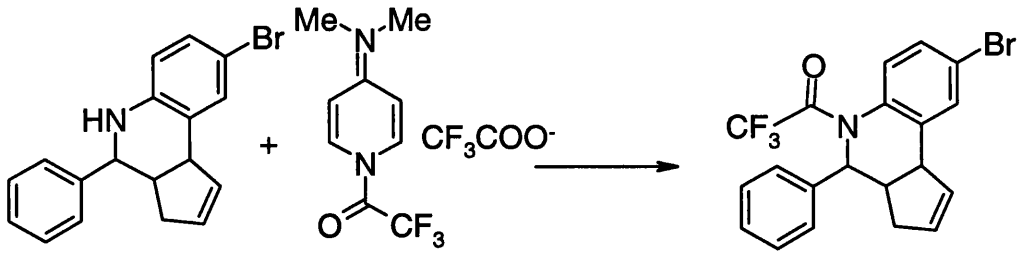
Following the general procedure for the preparation of tetrahydroquinolines, ethyl 2-{[4-(trifluoromethyl)phenyl]imino}acetate (0.81mmol) and cyclopentadiene (1.62mmol) were combined with a mixture of catalyst and ligand. Once the reaction was completed, the reaction was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with ethyl acetate (50ml). The solvent was removed under vacuum and the crude product was then purified via flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to afford a yellow powder (see results and discussion for yields of **172G**). mp: 268°C (decomp); ν_{max}(liquid film) cm^{-1} 3240 (aryl-H), 1722 (C=O) 1691 (C-NH), 1494 (C=C), 1102 (C-CF_3); δ_H(270MHz, $CDCl_3$) 7.25-7.23 (2 H, m, Ar-*H*); 6.67 (1 H, d, *J*= 11.0, Ar-*H*); 5.75 (2 H, d, *J*= 22.0, C*H*); 4.54 (1 H, brs, N*H*); 4.36 (2 H, q, *J*= 6.0, CH_2,); 4.14 (2 H, m, C*H*); 3.38 (1 H, m, C*H*); 2.40 (2 H, m, CH_2); 1.32 (3 H, t, *J*= 6.0, CH_3,) δ_C(75.5MHz, $CDCl_3$) 172.6 (C=O), 153.4 (C), 130.7 (C), 127.8 (CF_3, q, *J* = 218) 129.1 (CH), 127.2 (CH), 126.5 (CH), 125.8 (C), 116.3 (CH), 112.1 (CH), 62.3 (CH_2), 53.8 (CH), 44.0 (CH), 41.1 (CH_2), 40.1 (CH), 14.1 (CH_3); *m/z* (FAB+) 312.1136 (52%, $[MH]^+$ $C_{16}H_{16}F_3NO_2$ requires 312.1133). HPLC Chiracel OD, 95:2, (Hexane: IPA), 0.5 ml/min, Rt = 38.25, 47.12 min

4-Phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline[13] (172)



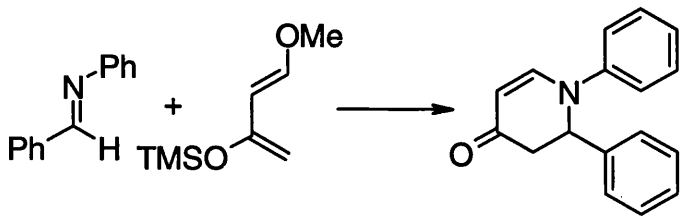
Following the general procedure for the preparation of tetrahydroquinolines, *N*-[(*E*)-phenylmethylidene]aniline (1.18mmol) and cyclopentadiene (2.36mmol) were combined with a mixture of catalyst and ligand. Once the reaction was completed the reaction was quenched with aqueous sodium hydrogen carbonate (20ml) and extracted with ethyl acetate (100ml). The solvent was removed under vacuum and the crude product was then purified via flash chromatography (SiO_2 hexane/ethyl acetate 98:2) to produce a colourless white solid, which was recrystallised using ethanol to yield colourless needles, (see results and discussion for yields of tetrahydroquinoline analogue **172**) mp 118°C (from EtOH). ν_{max}(Nujol) cm^{-1} 1612 (C-NH), 1474 (C=C); δ_H(270MHz, $CDCl_3$) 7.52- 6.92 (7 H, m, Ar-*H*); 6.73 (1 H, td, *J*= 1.1, 5.7, C*H*); 6.57 (1 H, dd, *J*= 0.9, 9.5, C*H*); 5.82 (1 H, m, C*H*); 5.61 (1 H, m, C*H*); 4.62 (1 H, d, *J*= 3.3, C*H*); 4.17 (1 H, d, *J*= 7.5, C*H*); 3.78 (1 H, brs, N*H*); 2.97 (1 H, ddd, *J*= 3.7, 5.6, 18.2, C*H*); 2.63 (1 H, m, C*H*); 1.87 (1 H, ddd, *J*=3.7, 4.5, 9.3, C*H*); δ_C(75.5MHz $CDCl_3$) 147.0 (C); 142.3 (C); 129.3 (CH); 129.0 (CH); 127.5 (CH); 126.4 (CH); 124.7 (C); 118.0 (CH); 113.9 (CH); 54.7 (CH); 51.6 (CH); 45.1 (CH); 31.1 (CH_2); HPLC Chiracel AD, 98:2, (Hexane: IPA), 0.5 ml/min, Rt = 18.23, 28.11 min.

1-(8-Bromo-4-phenyl-3,3a,4,9b-tetrahydro-cyclopenta[c]quinolin-5-yl)-2,2,2-trifluoro-ethanone



To a solution of 8-Bromo-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (6g, 0.018moles) in anhydrous THF (10 ml) was added *N*-methyl-*N*-[1-(2,2,2-trifluoroacetyl)-4(1*H*)-pyridinylidene]methanaminium 2,2,2-trifluoroacetate (8.96g, 0.027 moles) in anhydrous THF (15 ml) dropwise over a period of 30mins at 0°C under N_2. Once the reaction was completed, the DMAP by-product was filtered off and the solvent removed under vacuum. The crude product was then purified via flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to produce a colourless white powder (4.6g, 61%) which was stored under nitrogen. mp 151°C (from hexane/ethyl acetate); ν_{max}(Nujol) cm^{-1} 1724 (C=O), 1690 (C-NH), 1486 (C=C); 1150 (C-CF_3); δ_H(300MHz, $CDCl_3$) 7.57 (1 H, s, Ar-*H*); 7.26-7.09 (7 H, m, Ar-*H*); 6.83 (1 H, d, *J*=7.9, C*H*); 6.10 (1 H, m, C*H*=); 5.76 (1 H, m,C*H*=); 4.15 (1 H, m, C*H*); 3.61 (1 H, ddd, *J*= 2.9, 7.5, 9.7, C*H*); 2.68 (1 H, m, C*H*); 2.13 (1 H, ddd, *J*= 2.9, 4.2, 9.7, C*H*); δ_C(75.5MHz, $CDCl_3$): 145.2 (C=O); 142.7 (C); 136.5 (C); 133.3 (CH); 132.2 (C); 131.4 (CH); 130.8 (CH); 129.0 (CH); 128.5 (CH); 127.3 (CH); 126.3 (CH); 120.7 (CF_3, q, *J* = 256); 117.4 (CH); 115. (C-Br); 57.8 (CH); 46.1 (CH); 45.6 (CH); 31.3 (CH_2); *m/z* (FAB+) 423.0290 (100% $[MH]^+$ $C_{20}H_{15}BrF_3NO$: requires 423.0289)

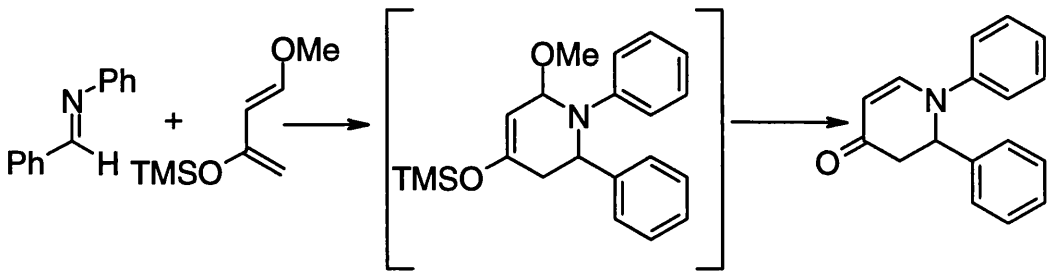
1,2-diphenyl-2,3-dihydro-4(1*H*)-pyridinone[14] (197)



General experimental procedure for catalytic studies in the production of tetrahydropyridines:

To a stirring solution of catalyst (10 mol%) and ligand (10 mol%) in dry DCM (3.5ml) was added a solution of *N*-[(*E*)-phenylmethylidene]aniline (0.200g, 1.1mmol) in DCM (1.5 ml) at room temperature. The reaction mixture was allowed to stir for 5 mins then Danishefsky's diene (0.32mls, 1.65mmol) was added dropwise. Once the reaction was completed (periods off time ranging from 60 mins to 24 hours), the reaction was quenched with aqueous sodium hydrogen carbonate (10 ml) and extracted with ethyl acetate (50 ml). The solvent was removed under vacuum and the crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow powder. (see results and discussion for yields of tetrahydropyridine analogue **197**) mp 97°C, ν_{max}(Nujol)/cm^{-1} 1734 (C=O), 1649 (C-N) 1303 (C=C); δ_H(270MHz, $CDCl_3$): 7.67 (1 H, dd, *J*=1.1, 7.6, C*H*); 6.99-7.35 (10 H, m, Ar-*H*); 5.27 (2 H, dd, *J*=1.1, 7.6, CH_2,); 3.29 (1 H, dd, *J*=7.3, 16.5, C*H*); 2.77 (1 H, ddd, *J*=1.3, 3.3, 16.5, C*H*); δ_C(75.5MHz, $CDCl_3$,): 190.0 (C=O), 148.1 (CH), 144.4 (C) , 137.7 (C), 129.3 (CH), 128.8 (CH), 127.6 (CH), 125.9 (CH), 124.2 (CH), 118.3 (CH), 102.7 (CH), 61.4 (CH), 43.3 (CH_2) *m/z* (FAB+) 250.2 (100% $[MH]^+$) HPLC Chiracel OD, 80:20, (Hexane: IPA), 0.5 ml/min, Rt = 20.37, 26.25 min.

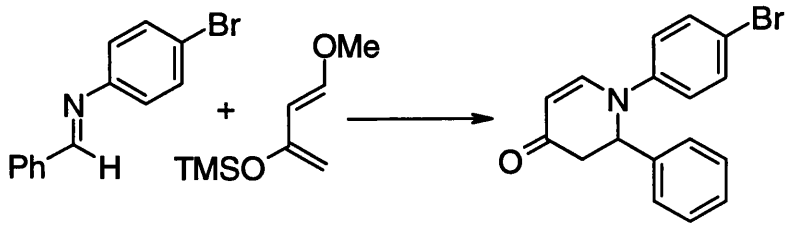
General procedure for NMR tube reactions.



Intermediate not isolated

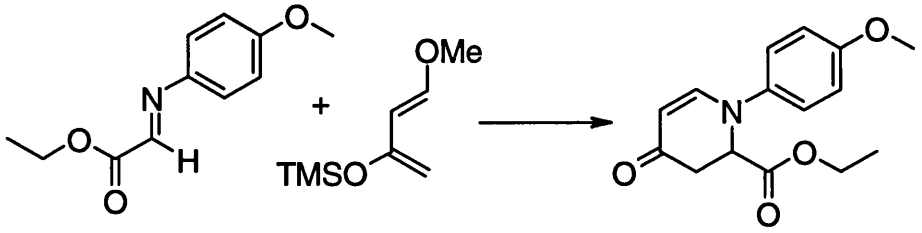
Solutions of catalysts were typically prepared by dissolving 1 mg of $Ag[CB_{11}H_{12}]$ in 1ml of CD_2Cl_2 with the use of an ultrasound bath to ensure complete catalyst dissolution. The relevant quantity of catalyst solution to give 0.1 mol% catalyst concentration (i.e. 0.00011 mmol of catalyst) was taken from this standard solution and placed in a NMR tube previously charged with *N*-benzlideneaniline (20mg, 0.11mmol). Danishefsky's diene (32µl, 0.17mmol) and water (1µl, 0.056mmol) were added to the NMR tube which was shaken vigorously before being placed in the NMR spectrometer and measurements taken at timed intervals. The disappearance of the peak at δ 8.51 ppm due to PhN=CHPh was monitored along with the growth of the peaks centred at δ 6.64 ppm and δ 5.54 (3H total of intermediate) and δ 5.27ppm (1H total, final product). A plot for each catalyst of time vs. consumption of imine and time vs. total concentration of intermediate and final product showed essentially the same profile. Repeat runs for all the catalysts tested showed the same time dependent profiles. δ_H(400MHz, CD_2Cl_2) intermediate 7.56 (1 H, d, *J*=13.0, Ar-*H*); 7.42-7.40 (2 H, m, Ar-*H*); 7.28-7.23 (1 H, m, Ar-*H*); 7.10-7.01 (3 H, m, Ar-*H*); 6.64 (1 H, m, Ar-*H*); 6.52 (2 H, m, Ar-*H*); 5.58 (1 H d, *J*=12.0, C*H*); 4.86 (1 H, q, *J*=6.0, C*H*); 4.71 (1 H, d, *J*= 6.0, C*H*); 3.68 (3 H, s, CH_3); 2.94 (2 H, dd, *J*=2.0, 6.0, CH_2); 0.14 (9 H, s, 3 x CH_3);

1-(4-bromophenyl)-2-phenyl-2,3-dihydro-4(1*H*)-pyridinone (197A)



Following the general procedure for preparation of tetrahydropyridines, 4-bromo-*N*-[(*E*)-phenylmethylidene]aniline (0.28g, 1.1mmol) and Danishefsky's diene (0.32ml, 1.65mmol) was combined with a mixture of catalyst and ligand. The crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a white powder, (see results and discussion for yields of tetrahydropyridine analogue **197A**) mp 181°C, ν_{max}(Nujol)/cm^{-1}, 1748 (C=O) 1646 (C-N), 1572 (C=C), 739 (C-Br); δ_H (300MHz, $CDCl_3$): 7.50 (1 H, dd, *J*=1.1, 9.0, C*H*); 7.27-7.09 (7 H, m, Ar-*H*); 6.76 (2 H, d, *J*=8.6, C*H*); 5.15 (2 H, m, C*H*); 3.15 (1 H, dd, *J*=7.1, 9.5, CH_2); 2.64 (1 H, ddd, *J*=0.7, 2.3, 9.5, CH_2); δ_C(75.5MHz, $CDCl_3$): 190.0 (C=O); 148.1 (CH); 144.0 (C); 137.8 (C); 132.8 (CH) 129.5 (CH); 128.4 (CH); 126.4 (CH); 120.4 (CH); 117.5 (C); 103.9 (CH); 62.0 (CH); 43.8 (CH_2) *m/z*, (FAB+) 328.0346 (100% [MH]$^+$ $C_{17}H_{14}BrNO$: requires 328.0259); HPLC Chiracel OD, 80:20, (Hexane: IPA), 1 ml/min, Rt = 20.05, 25.45 min.

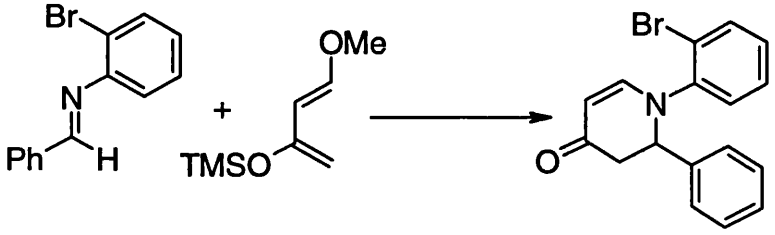
Ethyl 1-(4-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydro-2-pyridinecarboxylate[15] (197C)



Following the general procedure for preparation of tetrahydropyridines, ethyl 2-[(4-methoxyphenyl)imino]acetate (0.23g, 1.1mmol), and Danishefsky's diene (0.32ml, 1.65mmol) was combined with a mixture of catalyst and ligand. The crude product

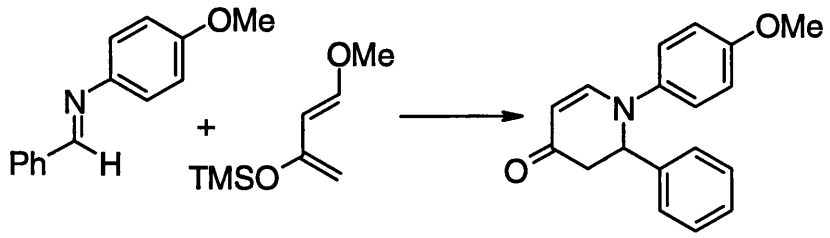
was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow oil, (see results and discussion for yields of tetrahydropyridine analogue **197C**) ν_{max}(liquid film)/cm^{-1} 3242 (Aryl-H) 1722 (C=O) 1668 (C=O), 1604 (C-N), 1512 (C=C), 1248 (O-Me); δ_H (300MHz, $CDCl_3$): 7.80 (1 H, d, *J*=8.6, C*H*); 6.68-6.94 (4 H, m, Ar-*H*); 4.14 (1 H, m, C*H*); 3.71 (2 H, q, *J*=7.1, CH_2); 2.48 (3 H, s, CH_3); 1.36 (1 H, dd, *J*=11.0, 15.9, CH_2); 1.04 (1 H, dd, *J*= 1.7, 15.9, C*H*); 0.97 (3 H, t, *J*=7.1, CH_3); δ_C(75.5MHz, $CDCl_3$) 90.3 (C=O); 173.6 (C=O); 158.8 (C); 148.9 (CH); 139.8 (C); 125.6 (CH); 113.5 (CH); 103.1 (CH); 62.6 (CH); 55.6 (CH_3); 36.7 (CH_2); 14.0 (CH_3); HPLC Chiracel OJ, 80:20 (Hexane: IPA) 1 ml/min Rt = 20.37, 27.22 min.

1-(2-bromophenyl)-2-phenyl-2,3-dihydro-4(1*H*)-pyridinone (179D)



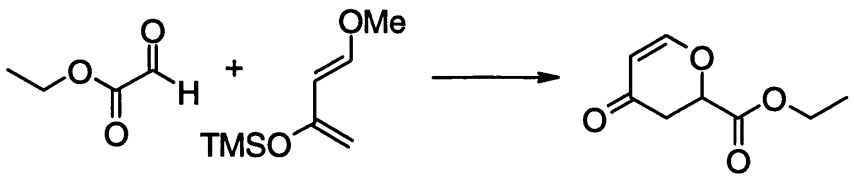
Following the general procedure for preparation of tetrahydropyridines 2-bromo-*N*-[(*Z*)-phenylmethylidene]aniline, (0.28g, 1.16mmol) and (0.32ml, 1.65mmol) Danishefsky's diene was combined with a mixture of catalyst and ligand. The crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow powder, (see results and discussion for yields of tetrahydropyridine analogue **179D**) mp 171°C; ν_{max}(Nujol) cm^{-1} 1708 (C=O), 1647 (C-N), 1576 (C=C), 757 (C-Br); δ_H(300MHz, $CDCl_3$): 7.70 (1 H, dd, *J*=0.5, 7.9, C*H*); 7.55 (1 H, dd, *J*=1.5, 7.9, Ar-*H*); 7.34-7.02 (5 H, m, Ar-*H*); 6.86 (2 H, d, *J*=7.5, C*H*); 5.52 (1 H, dd, *J*=4.0, 10.9, C*H*); 5.25 (1 H, dd, *J*=1.2, 9.0, C*H*); 3.19 (1 H, dd, *J*=7.9, 14.6, CH_2); 2.78 (1 H, ddd, *J*=1.2, 4.0, 14.6, CH_2); δ_C(75.5MHz, $CDCl_3$) 190.4 (C=O); 149.2 (CH); 144.6 (C); 137.1 (CH); 134.3 (CH); 130.0 (CH); 128.3 (CH); 128.0 (CH); 124.9 (CH); 122.1 (C-Br); 118.5 (CH); 116.4 (CH); 102.9 (CH); 61.4 (CH); 41.5 (CH_2); *m/z* (FAB+) 328.0338 (100% $[MH]^+$ $C_{17}H_{14}BrNO$: requires 328.0259). HPLC Chiracel OD, 80:20, (Hexane: IPA), 1 ml/min, Rt = 11.97, 14.77 min.

1-(4-methoxyphenyl)-2-phenyl-2,3-dihydro-4(1*H*)-pyridinone[16] (197E)



Following the general procedure for preparation of tetrahydropyridines, 4-methoxy-*N*-[(*E*)-phenylmethylidene]aniline (0.24g, 1.16mmol) and Danishefsky's diene (0.32ml, 1.65mmol) was combined with a mixture of catalyst and ligand. The crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow oil, (see results and discussion for yields of tetrahydropyridine analogue **197E**) ν_{max}(liquid film) cm^{-1} 3424 (Aryl-H) 1709 (C=O), 1645 (C-N), 1578 (C=C), 1096 (O-Me); δ_H(300MHz, $CDCl_3$): 7.58 (1 H, dd, *J*=1.2, 8.6, C*H*=); 7.22-6.94 (5 H, m, Ar-*H*); 6.76 (2 H, dd, *J*= 1.2, 8.6, C*H*); 5.19 (2 H, dd, *J*= 3.0, 7.9, C*H*); 3.70 (3 H, s, CH_3); 3.19 (1 H, dd, *J*= 7.1, 9.8, C*H*); 2.67 (1 H, ddd, *J*=0.9, 4.1, 9.8, CH_2); δ_C(75.5MHz, $CDCl_3$) 190.8 (C=O), 159.5 (C); 148.6 (CH); 145.1 (C); 130.1 (CH); 129.9 (CH); 127.75 (CH); 124.7 (CH); 119.0 (CH); 114.7 (CH); 103.1 (CH); 61.6 (CH); 55.6 (CH_2); 44.0 (CH_2): HPLC Chiracel OD, 90:10 (Hexane: IPA) 0.5 ml/min Rt = 21.51, 27.24 min

Ethyl 4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylate[17]



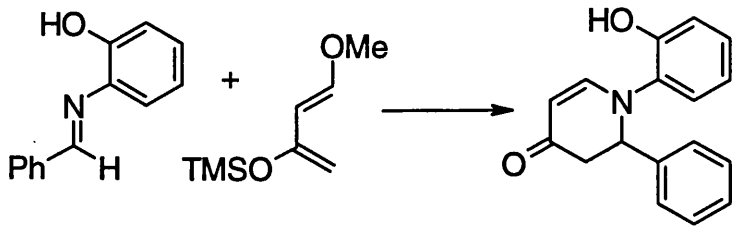
A solution of ethyl glyoxalate (5mls, 2.58g 25.2mmol, 50% in Toluene) was refluxed at 110°C to crack the dimeric form. From this solution 0.32ml was extracted (0.16g, 1.65mmol) and added to a stirring solution of catalyst (10 mol%) and ligand (10 mol%) in a solution of in DCM (1.5 ml) at room temperature. The reaction mixture was allowed to stir for 5 mins then Danishefsky's diene (0.32ml, 1.65mmol) was added dropwise. The reaction was stirred at room temperature for 24 hrs. Once the

reaction was completed it was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with ethyl acetate (50ml). The solvent was removed under vacuum and the crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product **215** (0.26g, 92%) as a yellow oil. ν_{max}(liquid film)/cm^{-1} 1742 (C=O), 1671 (C=O), δ_H(300MHz, $CDCl_3$): 5.31 (1 H, d, *J*=6.0, C*H*); 4.84 (1 H, d, *J*=6.0, C*H*); 4.13 (3 H, m, C*H*, CH_2); 2.70 (2 H, d, *J*=7.9, CH_2); 1.14 (3 H, t, *J*=7.1, CH_3); δ_C(75.5MHz, $CDCl_3$):190.0 (C=O), 168.4 (C=O),

J=6.0, C*H*); 4.84 (1 H, d, *J*=6.0, C*H*); 4.13 (3 H, m, C*H*, CH_2); 2.70 (2 H, d, *J*=7.9, CH_2); 1.14 (3 H, t, *J*=7.1, CH_3); δ_C(75.5MHz, $CDCl_3$):190.0 (C=O), 168.4 (C=O),

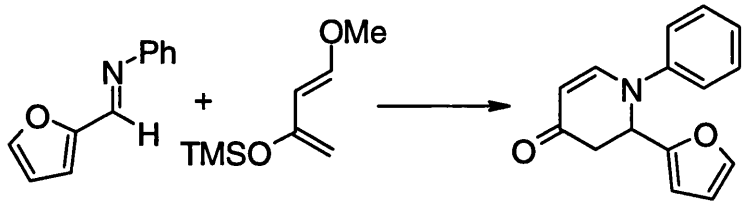
HPLC Chiracel OD, 90:10 (Hexane: IPA) 0.5 ml/min. Rt = 18.21, 22.42 min

1-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-4(1*H*)-pyridinone[18] (73)



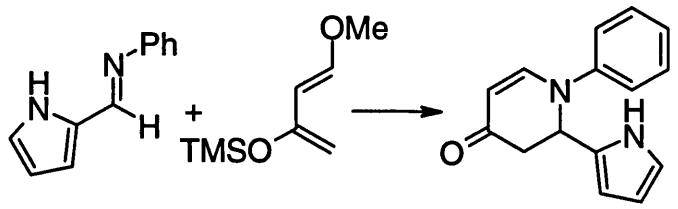
Following the general procedure for preparation of tetrahydropyridines, 2-{[(*E*)-phenylmethylidene]amino}phenol (0.21g 1.16mmol) and Danishefsky's diene (0.32ml, 1.65mmol) was combined with a mixture of catalyst and ligand. The crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow powder, (see results and discussion for yields of tetrahydropyridine analogue **75**) mp184°C, ν_{max}(liquid film)/cm^{-1} 3423 (C-OH), 1727 (C=O), 1583 (C-N), 1473 (C=C); δ_H(300MHz, $CDCl_3$): 7.99 (1 H, s, O*H*); 7.29 (1 H, d, *J*=7.9, C*H*); 7.19-7.13 (5 H, m, Ar-*H*); 6.98 (1 H dt, *J*= 2.2, 7.9, Ar-*H*); 6.82 (2 H, d, *J*=7.9, C*H*); 6.68 (1 H, dt, *J*=2.2, 7.9, C*H*); 5.18 (2 H, m, 2 x C*H*); 3.14 (1 H, dd, *J*=6.7, 10.2, CH_2); 2.81 (1 H, dd, *J*=7.1, 10.2, CH_2); δ_C(75.5MHz, $CDCl_3$) 188.8 (C=O), 151.2 (CH), 145.9 (C), 141.3 (C), 129.0 (CH), 128.5 (CH), 127.2 (CH), 125.4 (CH), 123.3 (C), 120.0 (CH), 117.9 (CH), 114.4 (CH), 103.9 (CH), 63.5 (CH), 42.2 (CH_2). HPLC was determined after converting to the corresponding benzoate, Chiracel OD, 90:10 (Hexane: IPA) 0.5 ml/min, Rt = 42.3, 45.6 min

2-(2-furyl)-1-phenyl-2,3-dihydro-4(1*H*)-pyridinone[19] (211)



Following the general procedure for preparation of tetrahydropyridines, *N*-[(*E*)-2-furylmethylidene]aniline (0.200g, 1.16mmol) and Danishefsky's diene (0.32ml, 1.65mmol) was combined with a mixture of catalyst and ligand. The crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as an orange needles, (see results and discussion for yields of tetrahydropyridine analogue **211**) mp: 103°C. ν_{max}(Nujol)/cm^{-1} 1646 (C=O); 1578 (furyl O), 1496 (C=C); δ_H(300MHz, $CDCl_3$): 7.41-7.13 (4 H, m, Ar-*H*); 7.16 (3 H, dd, *J*=7.9, 10.7, Ar-*H*); 6.28 (2 H, d, *J*=10.1, C*H*); 5.26 (2 H, dd, *J*=4.8, 7.9, C*H*); 2.88 (1 H, dd, *J*=6.0,15.2, CH_2); 2.83 (1 H, dd, *J*=2.7, 7.8, CH_2); δ_C(300MHz, $CDCl_3$) 190.7 (C=O), 150.8 (CH), 147.2 (C), 144.7 (C), 142.7 (CH), 129.8 (CH), 124.7 (CH), 119.3 (CH), 110.6 (CH), 108.7 (CH), 103.0 (CH), 56.4 (CH), 40.3 (CH_2); *m/z* (FAB+) 240.2, (100%, $[MH]^+$), HPLC Chiracel AD, 90:10 (Hexane: IPA) 0.5 ml/min, Rt =16.15, 18.23 min.

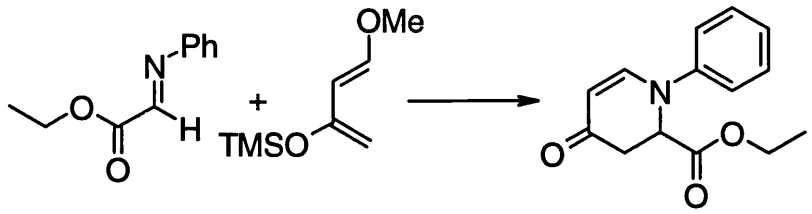
1-phenyl-2-(1*H*-pyrrol-2-yl)-2,3-dihydro-4(1*H*)-pyridinone (213)



Following the general procedure for preparation of tetrahydropyridines, *N*-[(*E*)-1*H*-pyrrol-2-ylmethylidene]aniline (0.19g, 1.16mmol) and Danishefsky's diene (0.32ml, 1.65mmol) was combined with a mixture of catalyst and ligand. The crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as an orange powder, (see results and discussion for yields of tetrahydropyridine analogue **213**) mp 142°C ν_{max}(Nujol)/cm^{-1} 1637 (C=O), 1569 (C-N), 1492 (pyrrole), 1355 (C=C); δ_H(300MHz, $CDCl_3$): 7.50 (1 H, d, *J*= 9.0, C*H*);

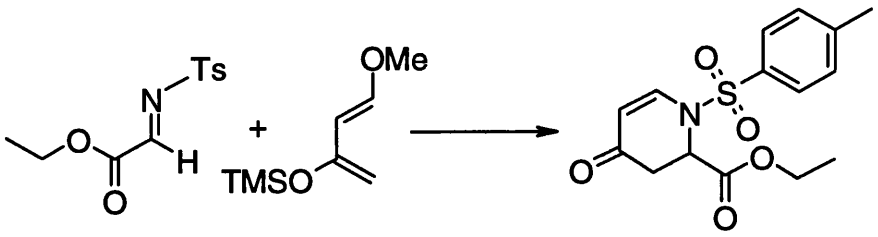
7.38 (2 H, d, *J*=7.1, Ar-*H*); 7.17 (3 H, t, *J*= 7.1, Ar-*H*); 6.68 (1 H, dd, *J*= 1.5, 2.3, Ar-*H*); 6.10 (2 H, d, *J*= 2.3, C*H*); 5.31 (2 H, dd, *J*= 7.9, 9.0, C*H*); 3.22 (1 H, dd, *J*= 6.7, 20.3, CH_2); 2.85 (1 H, ddd, *J*= 1.2, 2.3, 20.3, CH_2); δ_C(75.5MHz, $CDCl_3$) 191.6 (C=O); 148.6 (CH); 145.0 (C); 130.1 (CH); 129.0 (C); 125.2 (CH); 119.6 (CH); 118.8 (CH); 108.7 (CH); 107.9 (CH); 102.4 (CH); 56.8 (CH); 42.2 (CH); *m/z* (FAB+) 239.1174 (100% $[MH]^+$ $C_{15}H_{14}N_2O$: requires 239.1106); HPLC Chiracel AD, 85:15, (Hexane: IPA), 0.5ml/min, Rt = 29.03, 36.37 min.

Ethyl 4-oxo-1-phenyl-1,2,3,4-tetrahydro-2-pyridinecarboxylate[20] (215)



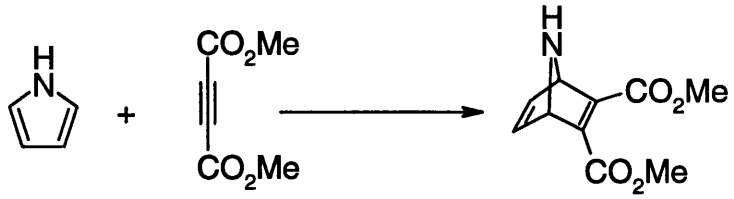
Following the general procedure for preparation of tetrahydropyridines ethyl 2-(phenylimino)acetate (0.21g, 1.16mmol)and Danishefsky's diene(0.32ml, 1.65mmol) was combined with a mixture of catalyst and ligand. The crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow oil, (see results and discussion for yields of tetrahydropyridine analogue **215**) ν_{max}(liquid film)/cm^{-1} 3380 (Aryl -H), 1734 (C=O), 1726 (C=O), 1647 (C-N), 1579 (C-N), 1499 (C=C); δ_H(300MHz, $CDCl_3$) 8.08 (1 H, dd, *J*=3.1, 8.2, C*H*) 7.57-6.99 (5 H, m, Ar-*H*); 5.04 (1 H, d, *J* = 8.2, C*H*); 5.00 (1 H, t, *J*= 6.0, C*H*); 4.04 (2 H, q, *J*=7.1, CH_2); 2.93 (1 H, dd, *J*= 7.1, 10.7, CH_2); 2.65 (1 H, dd, *J*= 6.0, 10.7, CH_2); 1.16 (3 H, t, *J* =7.1, CH_3); δ_C(400MHz, $CDCl_3$) 189.0 (C=O); 169.6 (C=O); 145.6 (CH); 141.7 (CH); 129.9 (CH); 129.5 (CH); 122.7 (CH); 114.6 (CH); 112.7 (CH); 68.9 (CH_2); 63.0 (CH_2); 51.8 (CH_2); 14.4 (CH_3); HPLC Chiracel OD, 80:20, (Hexane: IPA), 0.5ml/min, Rt = 29.22, 36.45 min.

Ethyl 1-[(4-methylphenyl)sulfonyl]-4-oxo-1,2,3,4-tetrahydro-2-pyridinecarboxylate[21] (217)



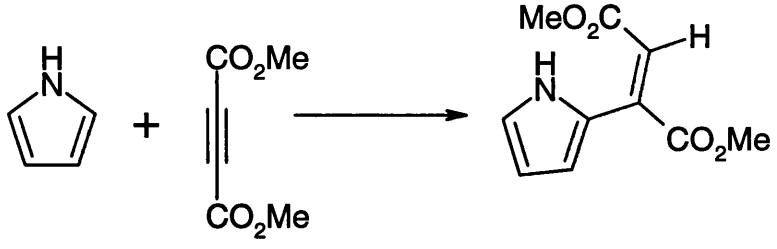
To a stirring solution of catalyst (10 mol%) and ligand (10mol%) in anhydrous DCM (5ml) was added reaction solution *N*-tosyl α-imino ester (1.83mls, approx. 2.44mmol solution of 0.02M) in dry toluene (15ml) at 110°C. The reaction mixture was allowed to stir for 5 mins then Danishefsky's diene (0.32mls, 1.65mmol) was added dropwise. Once the reaction was completed (periods off time ranging from 60 mins to 24 hours), the reaction was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with ethyl acetate (50ml). The crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow needles, (see results and discussion for yields of tetrahydropyridine analogue **217**) mp 68°C, ν_{max}(Nujol) cm^{-1} 1738 (C=O), 1663 (C=O), 1595 (C-N), 1527 (C=C), 1302 (SO_2), δ_H(400MHz, $CDCl_3$): 7.80-7.71 (3 H, m, Ar-*H*); 7.37 (1 H, d, *J*=8.2, Ar-*H*); 7.27 (1 H, t, *J*=3.0, Ar-*H*,); 5.38 (1 H, d, *J*=1.2, C*H*); 4.97 (1 H, dd, *J*=1.2, 2.2, C*H*); 4.03 (2 H m, CH_2); 2.86 (1 H, dd, *J*=1.1, 1.1, C*H*); 2.79 (1 H, d, *J*=1.1, C*H*); 2.45 (3 H, s, CH_3); 1.15 (3 H, t, *J*= 4.0, CH_3); δ_C(75.5MHz, $CDCl_3$); 189.3 (C=O); 168.0 (C=O); 145.6 (CH); 142.7 (C); 135.0 (C); 130.4 (CH); 129.7 (CH); 129.7 (CH); 127.6 (CH); 127.4 (CH); 126.5 (CH); 107.5(CH); 107.9 (CH); 62.7 (CH_2); 38.5 (CH_2); 22.0 (CH_3); 14.3 (CH_3); *m/z* (FAB+) 324.0900 (100% $[MH]^+$ $C_{15}H_{17}NO_5S$: requires 323.0827). HPLC Chiracel OD, 80:20, (Hexane: IPA), 1 ml/min, Rt = 26.98, 30.63 min.

Dimethyl 7-azabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[22] (242)



To a stirring solution of catalyst (10 mol%) in anhydrous DCM (2.5 ml) was added (0.2mls, 2.2mmol) dimethyl acetylene dicarboxylate (DMAD). This solution was allowed to stir at room temperature for 5 mins. To this solution 1*H*-pyrrole (0.10ml, 1.46mmol) was added in DCM (2.5mls) dropwise. This solution was allowed to stir at room temperature for 24 hours. Once the reaction was completed the reaction was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with DCM (50ml). Once the solvent had been removed under vacuum the crude product was purified using flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to afford the product as a yellow oil, (see results and discussion for yields of aza norbornadiene analogue **242**) ν_{max}(liquid film)/cm^{-1} 1728 (C=O), 1542 (C-N), 1424 (C=C); δ_H(300MHz, $CDCl_3$): 7.19 (2 H, s, C*H*); 5.92 (2 H, s, C*H*); 5.23 (1 H, s, N*H*); 4.06 (6 H, s, CH_3); δ_C(75.5MHz, $CDCl_3$): 163.3 (C=O); 146.7 (C); 122.0 (CH); 56.8 (CH); 51.6 (CH3);

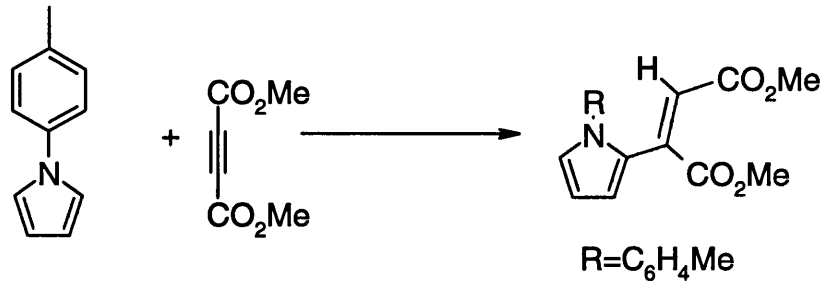
Dimethyl (*E*)-2-(1*H*-pyrrol-3-yl)-2-butenedioate[23] (243)



To a stirring solution of catalyst (10 mol%) in anhydrous DCM (2.5 ml) was added (0.2ml, 2.2mmol) dimethyl acetylene dicarboxylate (DMAD). This solution was allowed to stir at room temperature for 5 mins at room temperature. To this solution 1*H*-pyrrole (0.10ml, 1.46mmol) was added in anhydrous DCM (2.5ml). This solution was allowed to stir at room temperature for 24 hours. Once the reaction was

completed it was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with DCM (50ml). Once the solvent had been removed under vacuum, the crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow oil, (see results and discussion for yields of pyrrole analogue **243**) ν_{max}(liquid film)/cm^{-1} 1735 (C=O), 1436 (pyrrole), 1213 (C=C); δ_H(300MHz, $CDCl_3$) 6.84 (1 H, dd, *J*=1.7, 2.7, Py-*H*); 6.84 (1 H, m, Py-*H*); 6.19 (1 H dd, *J*= 2.7, 3.6, Py-*H*); 5.93 (1 H, s, C*H*); 3.86 (3 H, s, CH_3); 3.66 (3 H, s, CH_3); δ_C(75.5MHz, $CDCl_3$): 173.6 (C=O); 173.1 (C=O); 130.9 (C); 118.2 (CH); 117.3 (CH); 114.6 (C); 109.5 (CH); 108.1 (CH); 53.2 (CH3); 52.7 (CH3); *m/z* (FAB+) 210.10 (100% $[MH]^+$).

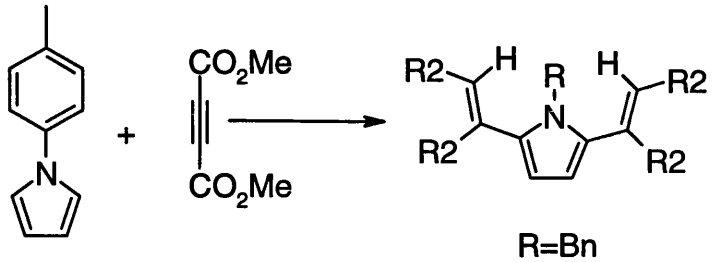
Dimethyl (*E*)-2-[1-(4-methylphenyl)-1*H*-pyrrol-3-yl]-2-butenedioate (243A)



To a stirring solution of catalyst (10 mol%) in anhydrous DCM (2.5 ml) was added (0.2ml, 2.2mmol) dimethyl acetylene dicarboxylate (DMAD). This solution was allowed to stir at room temperature for 5 mins at room temperature. To this, a solution of 1-(4-methylphenyl)-1*H*-pyrrole (0.23g, 1.46mmol) was added in DCM (2.5ml). This solution was allowed to stir at room temperature for 24 hours. Once the reaction was completed it was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with DCM (50ml). Once the solvent had been removed under vacuum the crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 95.5) to afford the product as yellow oil, (see results and discussion for yields of pyrrole analogue **243A**) ν_{max}(liquid film)/cm^{-1} 1737 (C=O), 1602 (C-N), 1515 (C=C), δ_H(300MHz, $CDCl_3$) 7.21-7.13 (4 H, m, C*H*); 6.85 (1 H, d, *J*= 3.7, Ar-*H*); 6.50 (1 H, dd, *J*= 1.5, 3.7, Py-*H*); 6.25 (1 H, dd, *J*=1.5, 3.7, Py-*H*); 5.23 (3 H, s, CH_3); 3.78 (3 H, s, CH_3); 3.56 (3 H, s, CH_3); 2.37 (3 H, s, CH_3); δ_C(75.5MHz, $CDCl_3$) 168.2 (C=O); 166.2 (C=O); 140.2 (C); 138.7 (C); 137.4 (C); 130.3 (CH); 126.5 (CH);

124.8 (C); 117.3 (Py-CH); 112.9 (Py-CH); 110.4 (Py-CH); 52.8 (CH_3); 52.0 (CH_3); 21.5 (CH_3); *m/z* (FAB+) 300.10 (100% $[MH]^+$).

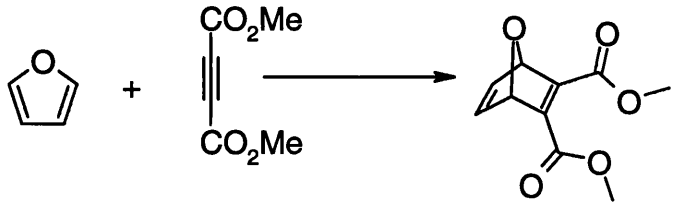
Dimethyl (*Z*)-2-[2-[(*Z*)-3-methoxy-1-(methoxycarbonyl)-3-oxo-1-propenyl]-1-(4-methylphenyl)-1*H*-pyrrol-3-yl]-2-butenedioate (239)



R=Bn
R_2 =CO_2Me

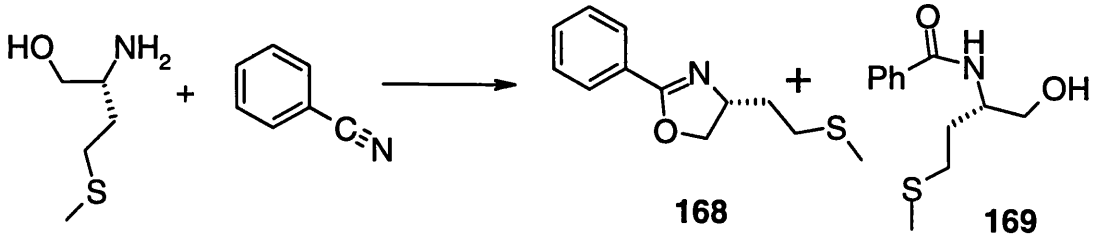
To a stirring solution of catalyst (10 mol%) in anhydrous DCM (2.5 ml) was added dimethyl acetylene dicarboxylate(0.2ml, 2.2mmol). This solution was allowed to stir at room temperature for 5 mins at room temperature. To this solution, 1-(4-methylphenyl)-1*H*-pyrrole (0.23g, 1.46mmol) was added in DCM (2.5ml). This solution was allowed to stir at room temperature for 24 hours. Once the reaction was completed it was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with DCM (50ml). Once the solvent had been removed under vacuum the crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 4:1) to afford the product as a yellow oil, (77mg, 12% yield) ν_{max}(liquid film)/cm^{-1}1726 (C=O), 1600 (C-N), 1513 (C=C); δ_H(300MHz, $CDCl_3$) 7.19 (4 H, m, Ar-*H*); 6.79 (1 H, s, C*H*); 6.48 (1 H, d, *J*= 4.1, Py-*H*); 6.24 (1 H, d, *J*= 4.1, Py-*H*); 5.17 (1 H, s, C*H*); 3.71 (3 H, s, CH_3); 3.62 (3 H, s, CH_3); 3.54 (3 H, s, CH_3); 3.45 (3 H, s, CH_3); 2.31 (3 H, s, CH_3); δ_C(75.5MHz, $CDCl_3$): 166.2 (C=O); 165.5 (C=O); 139.3 (C); 135.4 (C); 132.6 (CH); 130.2 (CH); 128.3 (CH); 116.5 (CH); 113.1 (CH); 112.7 (CH); 53.0 (CH_3); 53.0 (CH_3); 52.5 (CH_3); 52.0 (CH_3); 21.6 (CH_3); *m/z* (FAB+) 442.1500 (100% $[MH]^+$ $C_{23}H_{23}NO_8$: requires 442.1424).

Dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate[24]



To a stirring solution of catalyst (10 mol%) in 2.5 ml DCM was added dimethyl acetylene dicarboxylate (0.2ml, 2.2mmol). This solution was allowed to stir at room temperature for 5 mins at room temperature. To this solution (0.10ml, 1.46mmol) of furan was added in DCM (2.5ml). This solution was allowed to stir at room temperature for 24 hours. Once the reaction was completed it was quenched with aqueous sodium hydrogen carbonate (10ml) and extracted with DCM (50ml). Once the solvent had been removed under vacuum the crude product was purified via flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to afford the product as a yellow oil, (see results and discussion for yields of furan analogue) ν_{max}(liquid film) cm^{-1} 1731 (C=O), 1639 (C-O), 1439 (C=C); δ_H(300MHz, $CDCl_3$): 7.19 (2 H, s, C*H*); 5.61 (2 H, s, C*H*); 3.75 (6 H, s, 2 x *CH*$_3$); δ_C(75.5MHz, $CDCl_3$,): 153.4 (C=O); 143.6 (C); 140.3 (C); 85.4 (CH); 79.3 (CH); 53.6 (CH_3); 52.8 (CH_3); *m/z* (FAB+) 211.1 (35% $[MH]^+$).

***N*-[(2*R*)-2-hydroxy-5-(methylsulfanyl)pentyl]benzamide and (4*R*)-4-[2-(methylsulfanyl)ethyl]-2-phenyl-4,5-dihydro-1,3-oxazole.[25] (168, 169)**



168 **169**

In a 50cm^3 schlenk flask, zinc chloride (191 mg, 1.4mmol) was fused under high vacuum and cooled under nitrogen to room temperature. This process was repeated three times. Chlorobenzene (15 ml) was then added to it followed by benzonitrile (2.65 ml, 26mmol) and (2*R*)-1-amino-5-(methylsulfanyl)-2-pentanol (5g, 37mmol). The mixture was heated under reflux for 48hours. The solvent was removed under vacuum to produce an oily residue, which was dissolved in dichloromethane (50ml).

The solution was extracted with water (20ml) and the aqueous phase with DCM (100ml). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. The crude product was purified using flash chromatography (SiO_2 hexane/ethyl acetate 95:5) to afford the products. (4*R*)-4-[2-(methylsulfanyl)ethyl]-2-phenyl-4,5-dihydro-1,3-oxazole **168** was isolated in a 53% yield and *N*-[(2*R*)-2-hydroxy-5-(methylsulfanyl)pentyl]benzamide **169** a by-product was isolated in a 30% yield.

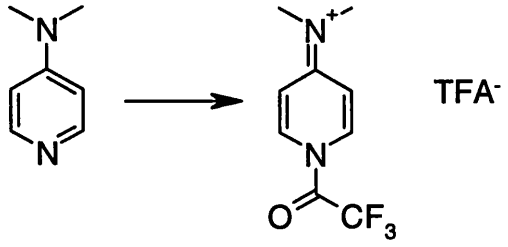
(4*R*)-4-[2-(methylsulfanyl)ethyl]-2-phenyl-4,5-dihydro-1,3-oxazole (168)

ν_{max}(liquid film) cm^{-1} 3174 (aryl-=H), 1650 (C=N), 1275 (C-S), 1050 (C-O); δ_H(300MHz, $CDCl_3$): 7.93 (2 H, dd, *J*= 1.4, 9.7, Ar-*H*,); 7.45-7.38 (3 H, m, Ar-*H*); 4.53 (1 H, d, *J*= 7.9, CH_2) 4.08 (2 H, dt, *J*=7.1, 7.5, CH_2); 2.67 (2 H, m, C*H*); 2.12 (3 H, s, CH_3); 1.23 (2 H, t, *J*=7.15, CH_2). δ_C(75.5MHz, $CDCl_3$): 159.2 (C), 131.6 (C), 130.7 (C), 128.2 (CH), 128.1 (CH), 76.0 (CH_2), 75.1 (CH), 32,2 (CH_2), 29.3 (CH_2), 15.0 (CH_3).

***N*-[(2*R*)-2-hydroxy-5-(methylsulfanyl)pentyl]benzamide (169)**

ν_{max}(liquid film) cm^{-1} 3620 (C-OH), 1710 (C=O), 1543 (C-NH), 1254 (C-S) , δ_H(, 300MHz, $CDCl_3$): 7.71 (2 H, dd, *J*= 1.5, 9.0, Ar-*H*); 7.48-7.37 (3 H, m, Ar-*H*); 6.35 (2 H, brs, NH, OH); 4.18 (1 H, m, C*H*); 3.72 (2 H, td, *J*=4.5, 7.5, CH_2); 2.56 (2 H, t, *J*=7.5, CH_2); 2.06 (3 H, s, CH_3), 1.91 (2 H, m, CH_2); δ_C(75.5MHz, $CDCl_3$):166.7 (C=O), 135.8 (C), 131.3 (CH), 128.4 (CH), 127.2 (CH), 69.4 (CH), 47.5 (CH_2), 39.4 (CH_2), 31.1 (CH_2), 15.8 (CH_3). The compound decomposed before Mass spec. analysis could be performed.

_N_-methyl-_N_-[1-(2,2,2-trifluoroacetyl)-4(1_H_)-pyridinylidene]methanaminium trifluroacetate.[26]



To a solution of DMAP (1g, 8.18mmol) in anhydrous DCM (18ml) at 0°C a solution of trifluoroacetic anhydride (1.7g, 8.18mmol) in DCM (12ml), was added dropwise under an inert atmosphere. The reaction was allowed to stir at 0°C for 30 mins until a white solid had precipitated from of solution. The solid was then filtered off under nitrogen and dried under vacuum over night. The product was formed as a white powder, (1.5g, 84% yield). mp 104°C, ν_{max}(liquid film) cm^{-1} 1720 (C=O), 1642 (C=N), 1110 (C-CF_3), δ_H(300MHz, D_2O): 7.82 (2 H, d, *J*=7.5, C*H*); 6.70 (2 H, d, *J*=7.5, C*H*); 4.69 (6 H, s, *CH*$_3$); δ_c(75.5MHz, D_2O,): 164.2 (C=O), 161.7 (C), 158.2 (C=O), 150.7 (CH), 129.6 (CF_3), 122.8 (CF_3, q, *J*= 256 Hz), 108.2 (CH), 46.46 (CH_3).

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Appendix

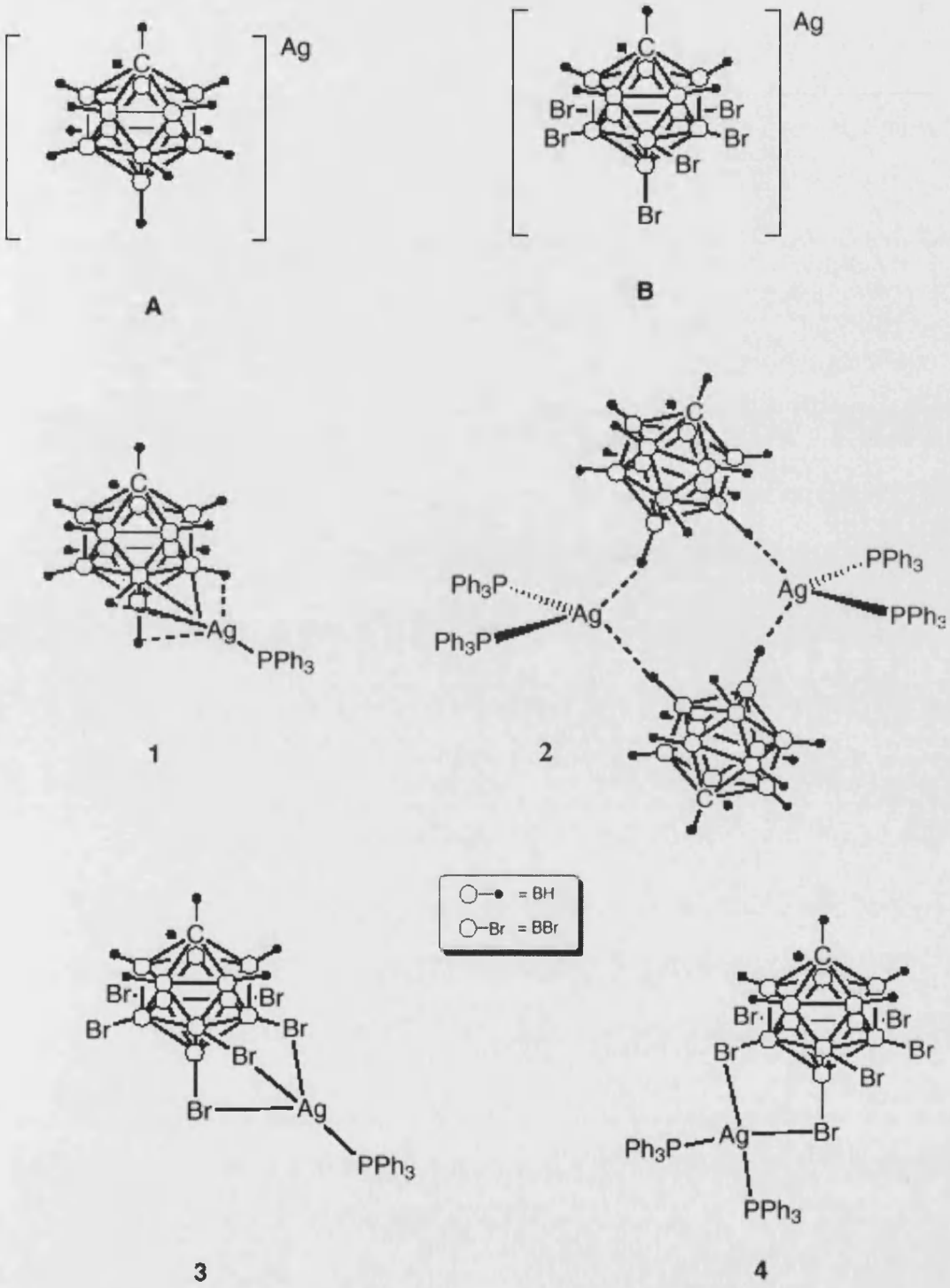

Figure 1.Crystal structures of Carborane phsophine species

Table 1. Crystal Data and structure refinement for 1,2 and 3.

	1	2	3
Empirical Formula	$C_{19}H_{27}AgB_{11}P$	$C_{74}H_{84}Ag_2B_{22}P_4$	$C_{19}H_{21}AgB_{11}Br_6P$
Formula weight	513.16	1550.85	986.57
Temperature [K]	150(2)	170(2)	150(2)
Wavelength [Å]	0.71073	0.71069	0.71073
Crystal system	Triclinic	Triclinic	Monoclinic
Space group	*P*1	*P*1	$P2_1/c$
a [Å]	10.282(2)	11.6963(2)	8.89500(10)
b [Å]	10.988(2)	13.1668(2)	24.4140(4)
c [Å]	11.302(2)	14.1393(2)	14.4170(3)
α [°]	76.22(3)	96.8860(6)	90
β [°]	75.25(3)	106.8980(7)	102.0720(10)
γ [°]	75.61(3)	110.5370(8)	90
V [Å^{-3}]	1175.7(4)	1890.30(5)	3061.60(9)
Z	2	1	4
ρ_{calcd}[mg m^{-3}]	1.450	1.362	2.140
Absorption coefficient [mm^{-1}]	0.932	0.646	8.554
F(000)	516	792	1848
Crystal size [mm]	0.20 x 0.20 x 0.10	0.25 x 0.20 x 0.17	0.10 x 0.10 x 0.05
θ range for data collection [°]	2.96 to 27.50	3.38 to 27.50	3.71 to 27.88
Reflections collected	20702	22570	23164
Indipendent reflections	5374 [*R*(int)=0.0387]	8605[*R*(int)=0.0250]	7253[*R*(int)=0.0519]
Reflections observed (>2σ)	4538	7964	5880
Max and min transmittion	0.9126 and 0.8355	1.027, 0.981	0.66 and 0.47
Data/restraints/parameters	5374/0/302	8605/2/478	7253/0/349
Goodness of fit on F^2	1.018	1.050	1.041
Final *R* indicies[I>2σ(I)]	R_1=0.0316wR_2=0.0757	R_1=0.0289wR_2=0.0738	R_1=0.0358wR_2=0.0783
R indicies (all data)	R_1=0.0417wR_2=0.0813	R_1=0.0323wR_2=0.0763	R_1=0.0521wR_2=0.0855
Largest diff.Peak and hole [eÅ^{-3}]	0.544 and -0.923	1.727 and -0.584	1.081 and -1.181

Table 2. Selected bond lengths [Å] and angles [°] for the new compounds 1-3

Compound 1			
Ag(1)–P(1)	2.3625(7)	P(1)–Ag(1)–B(7)	142.11(6)
Ag(1)–B(7)	2.619(3)	P(1)–Ag(1)–B(8)	158.23(6)
Ag(1)–B(8)	2.504(3)	P(1)–Ag(1)–B(12)	160.32(6)
Ag(1)–B(12)	2.569(3)	B(12)–Ag(1)–B(8)	41.26(8)
Ag(1)–H(7)	2.36(2)	B(12)–Ag(1)–B(7)	40.37(8)
Ag(1)–H(8)	2.14(2)	B(7)–Ag(1)–B(8)	40.98(8)
Ag(1)–H(12)	2.26(2)		
Compound 2			
Ag(1)–P(1)	2.4698(3)	Ag(1)–H(12)'	2.17(2)
Ag(1)–P(2)	2.4741(3)	Ag(1)–H(7)	2.51(2)
Ag(1)–B(7)	3.494(2)	P(1)–Ag(1)–P(2)	130.90(1)
Ag(1)–B(12)'	2.892(2)	B(7)–Ag(1)–B(12)'	72.4(6)
Compound 3			
Ag(1)–P(1)	2.4032(10)	P(1)–Ag(1)–Br(7)	117.44(3)
Ag(1)–Br(7)	2.8710(5)	P(1)–Ag(1)–Br(8)	155.55(3)
Ag(1)–Br(8)	2.6963(5)	P(1)–Ag(1)–Br(12)	93.31(3)
Ag(1)–Br(12)	3.0953(5)	P(1)–Ag(1)–Br(11)'	157.15(1)
Ag(1)–Br(11)'	3.4901(5)	Br(7)–Ag(1)–Br(8)	87.471(14)

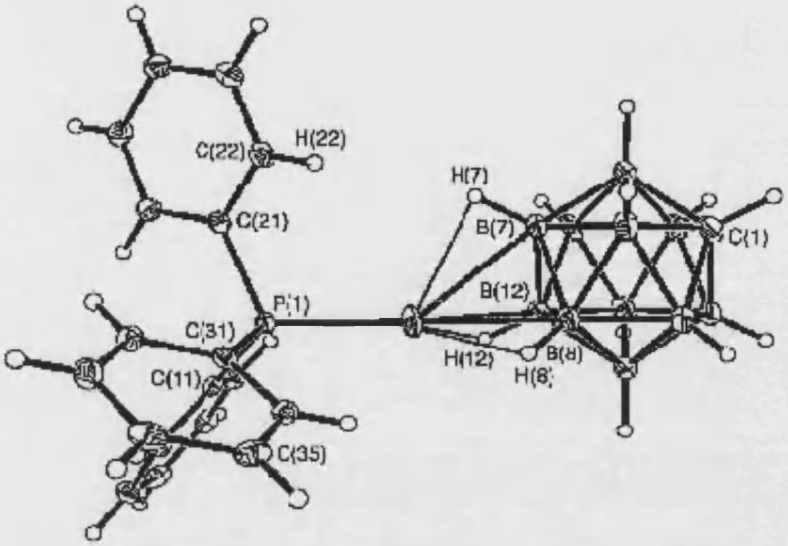

Figure 2. Molecular structure of complex **1**, showing the atom numbering schemes.

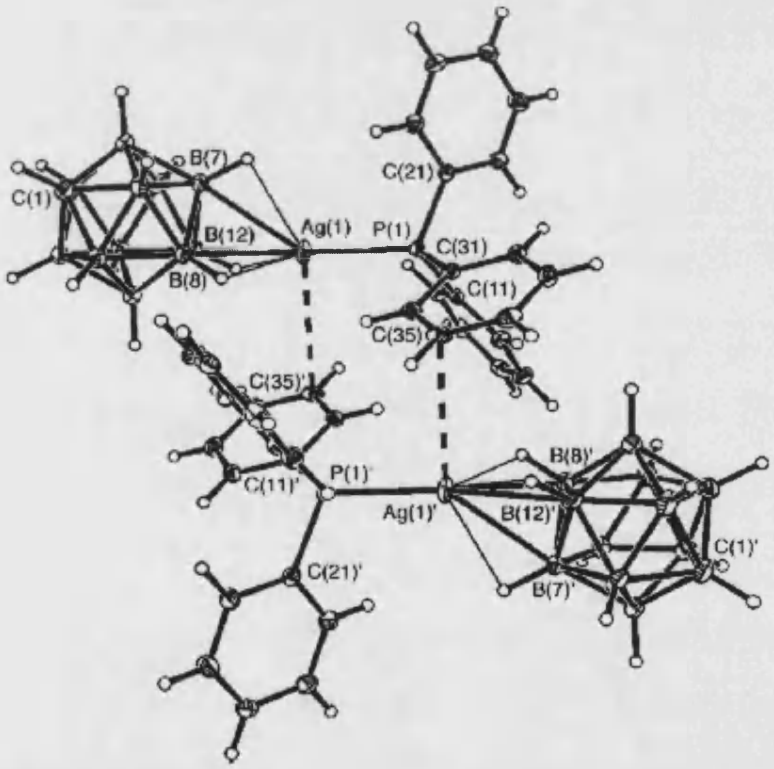

Figure 3. Dimeric unit formed in the extended lattice by Ag---C_{arene} contacts. Atomic labelling as in figure 2.

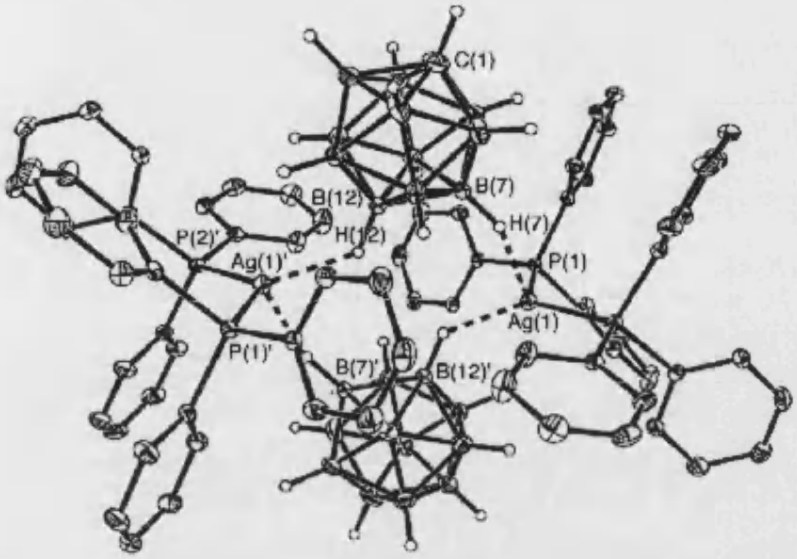

Figure 4. Molecular structure of complex **2**, showing the atom-numbering scheme.

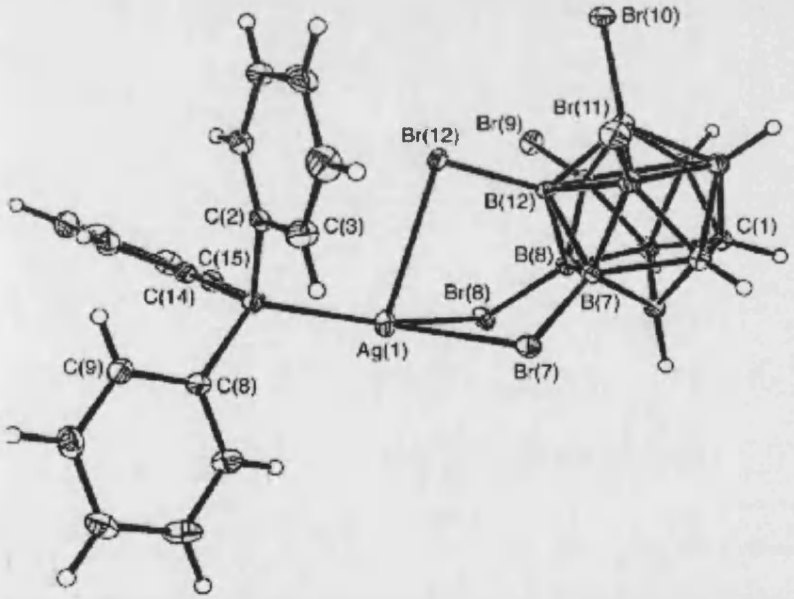

Figure 5. Molecular structure of complex **3**, showing the atom-numbering scheme

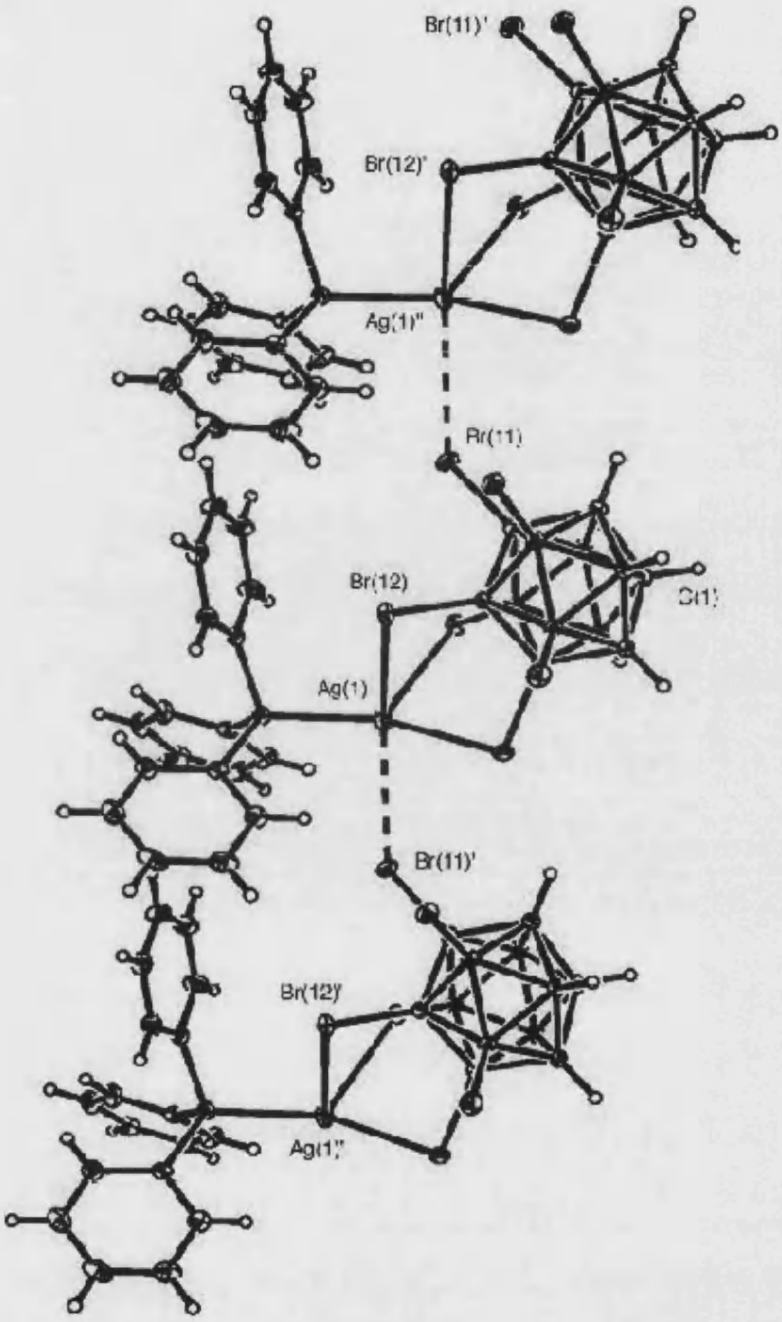

Figure 6. Extended solid state structure apparent in complex **3** showing weak axial Ag---Br interactions

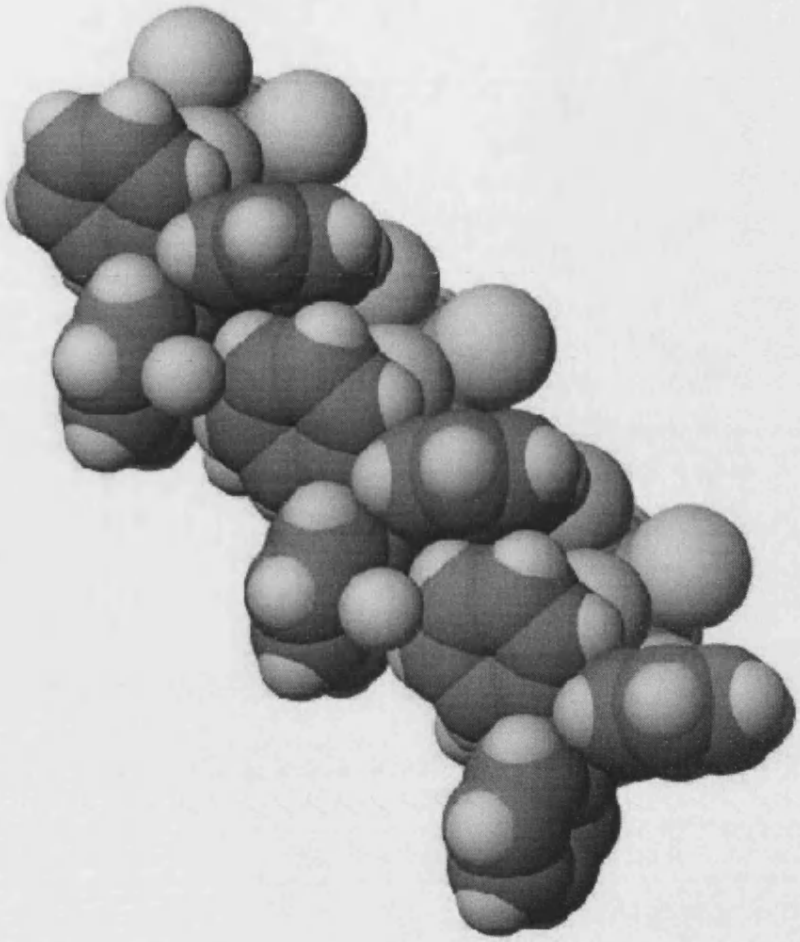

Figure 7. Extended solid state structure in complex **3** space filling diagram showing orientation of phenyl groups in the solid state.

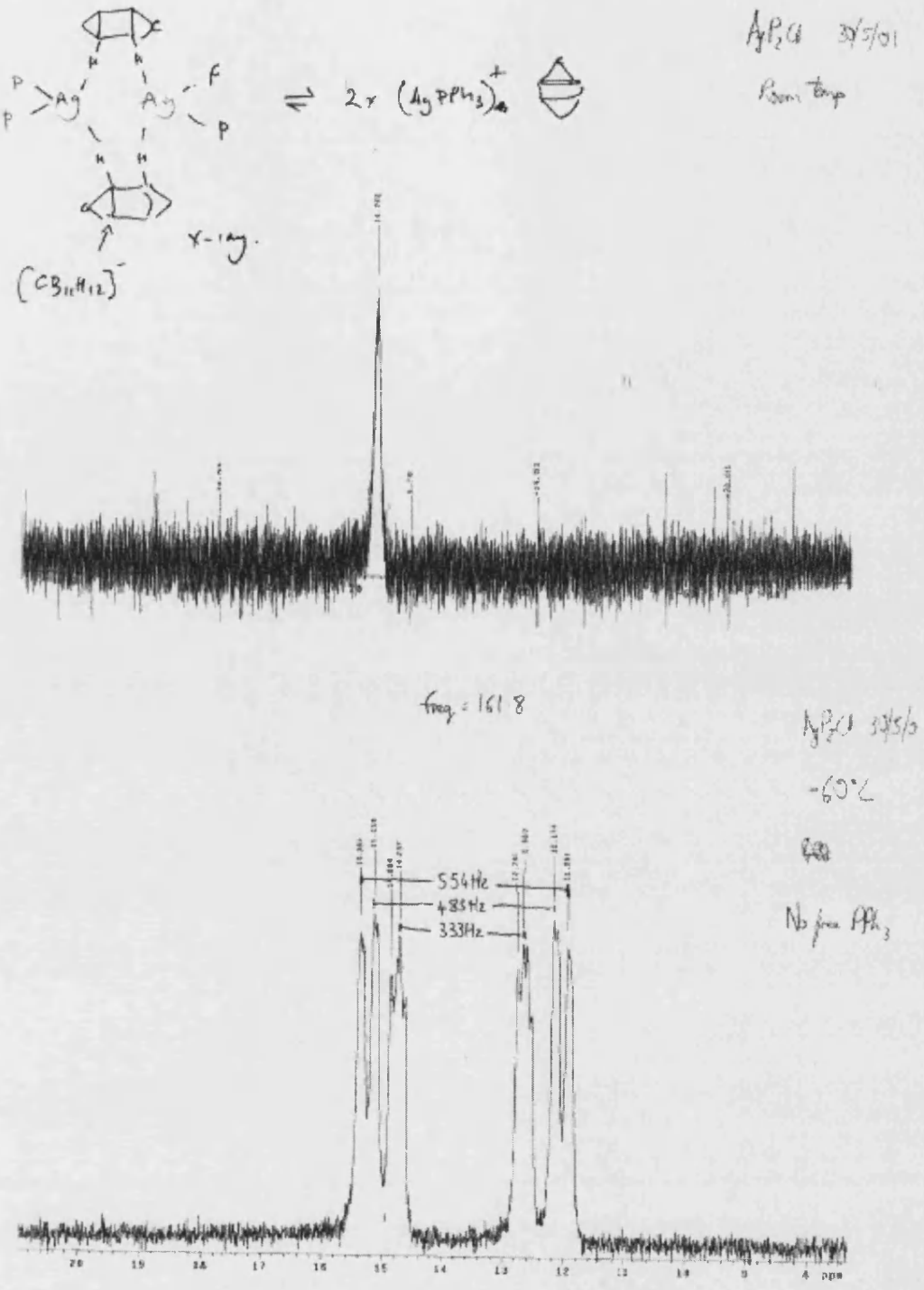

Figure 8. ^{31}P NMR spectra of silver(I) carborane BINAP complex at room tmeperture and a -60°C

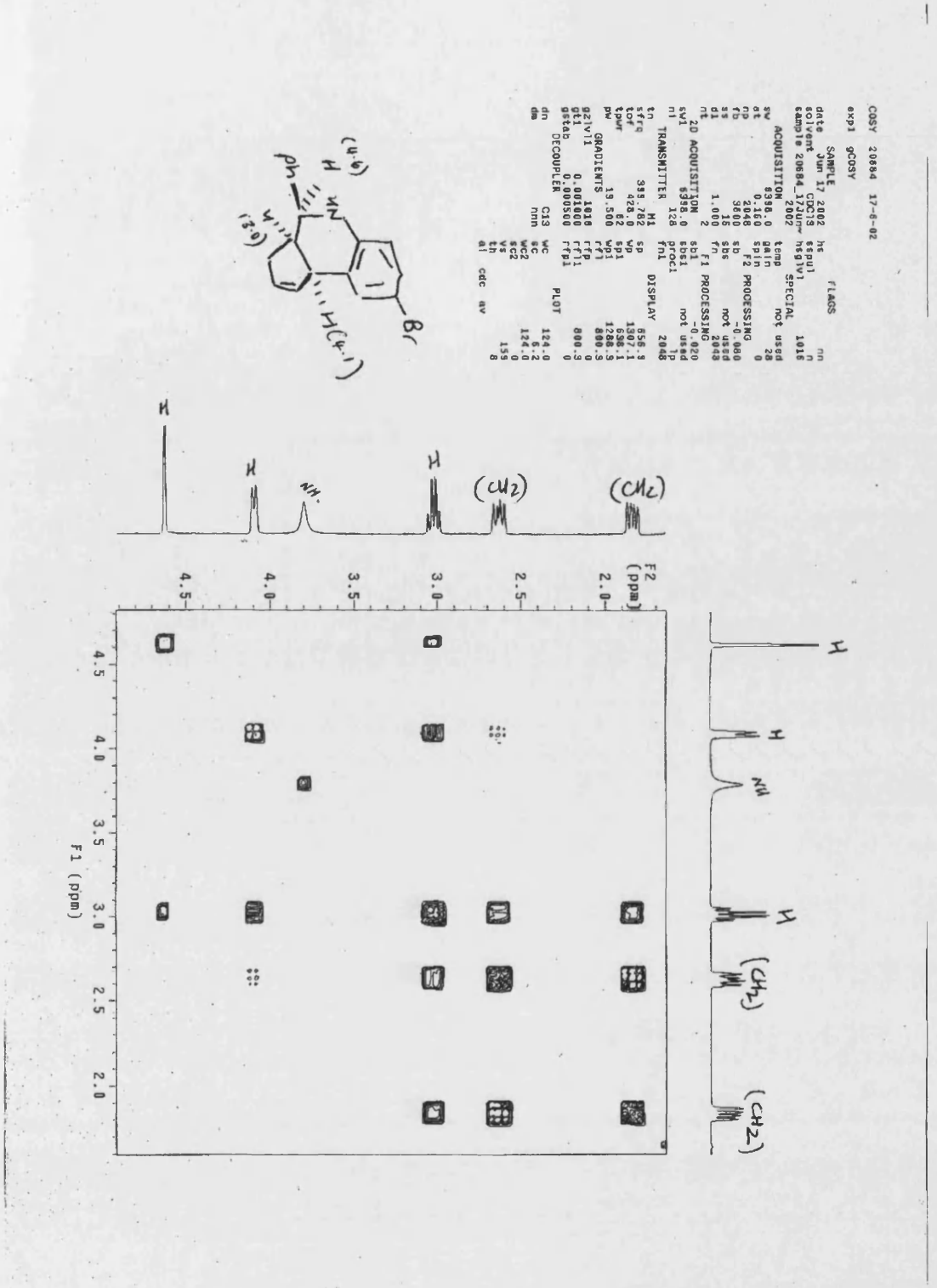

Figure 9. Cosy spectrum of compound 172A

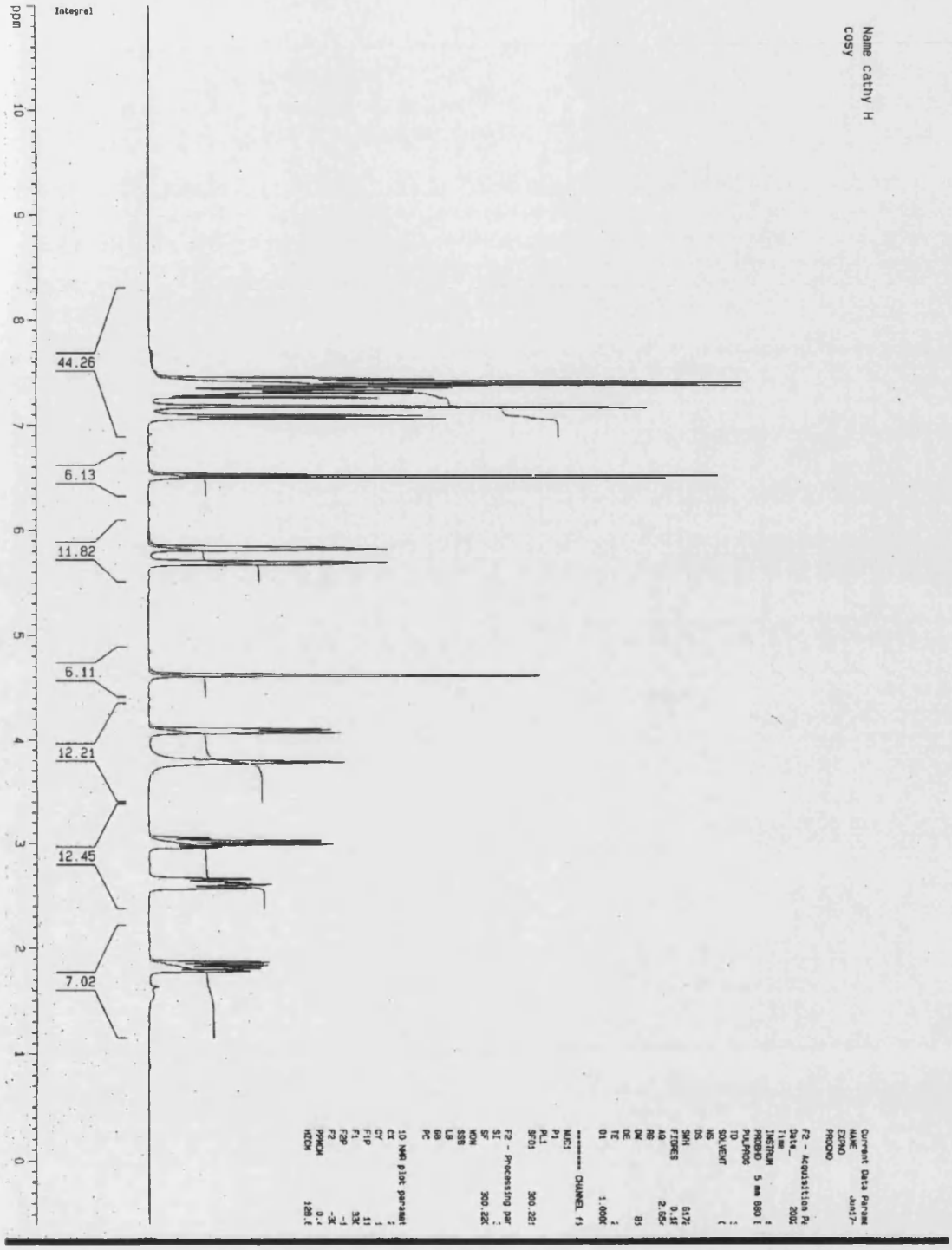

Figure 10. NMR spectrum of compound 172A

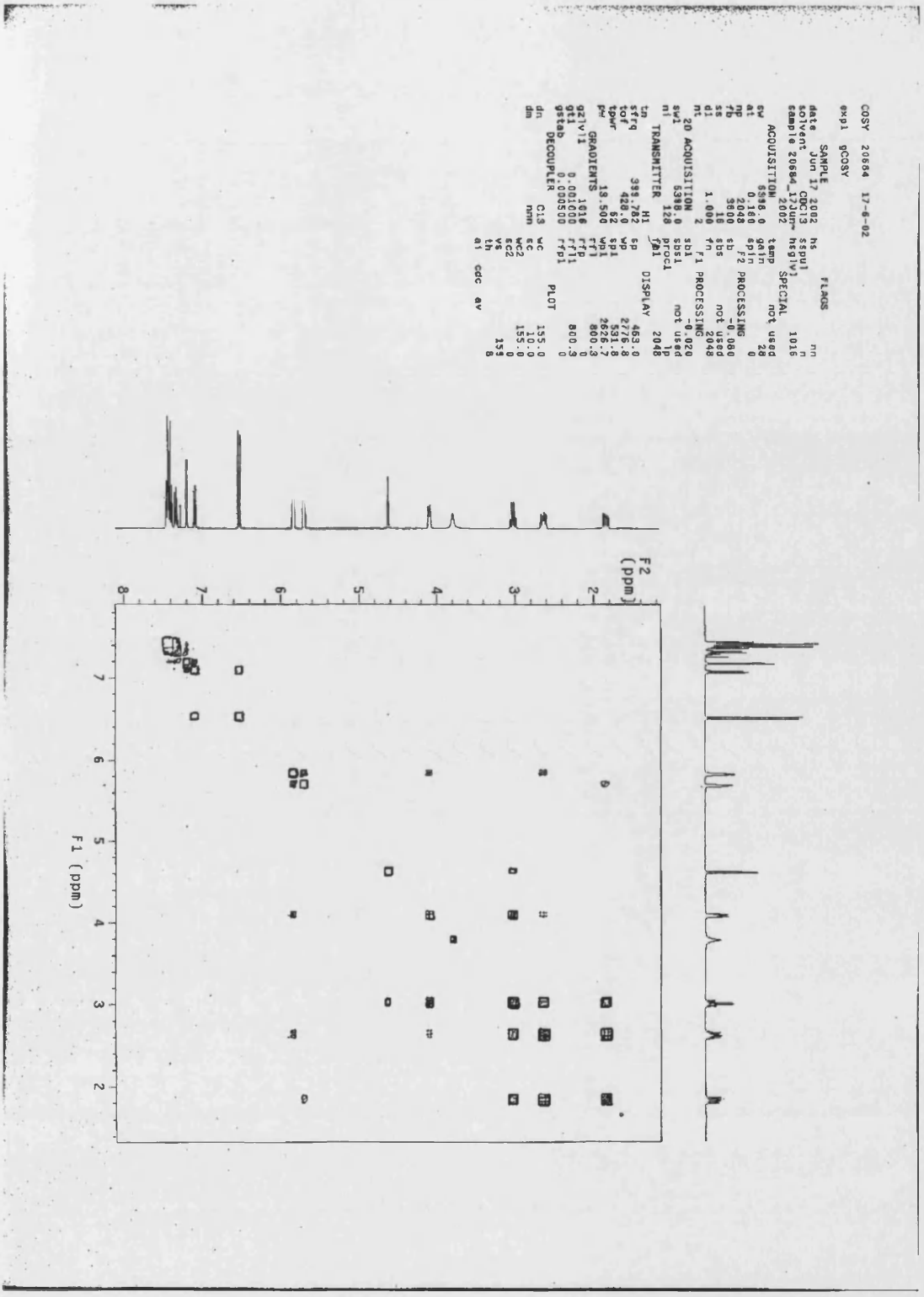

Figure 10. Full Cosy spectrum of compound 172A

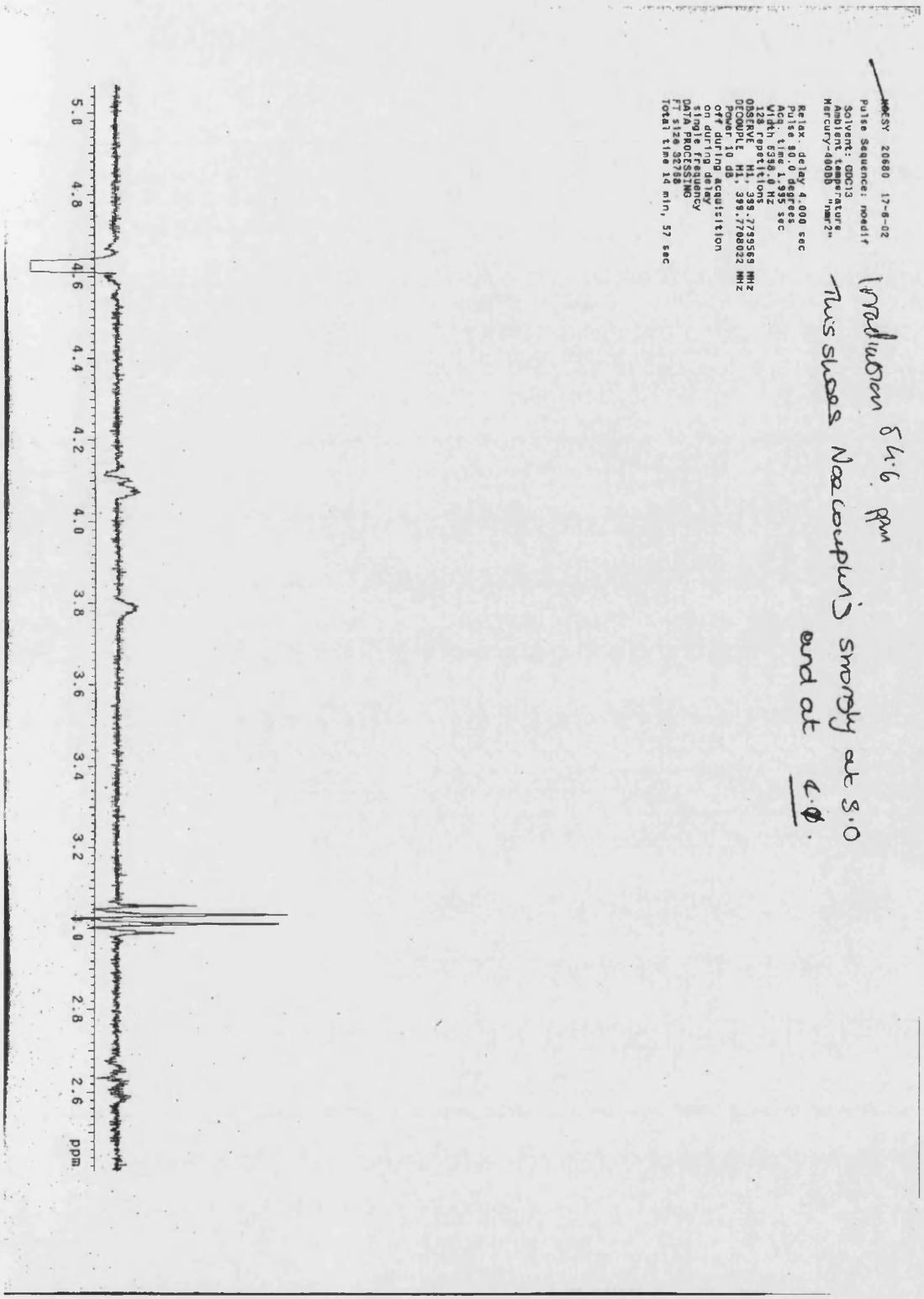

Figure 11. nOe enhancement experiment of compound 172A, irradiated at peak 4.6ppm.

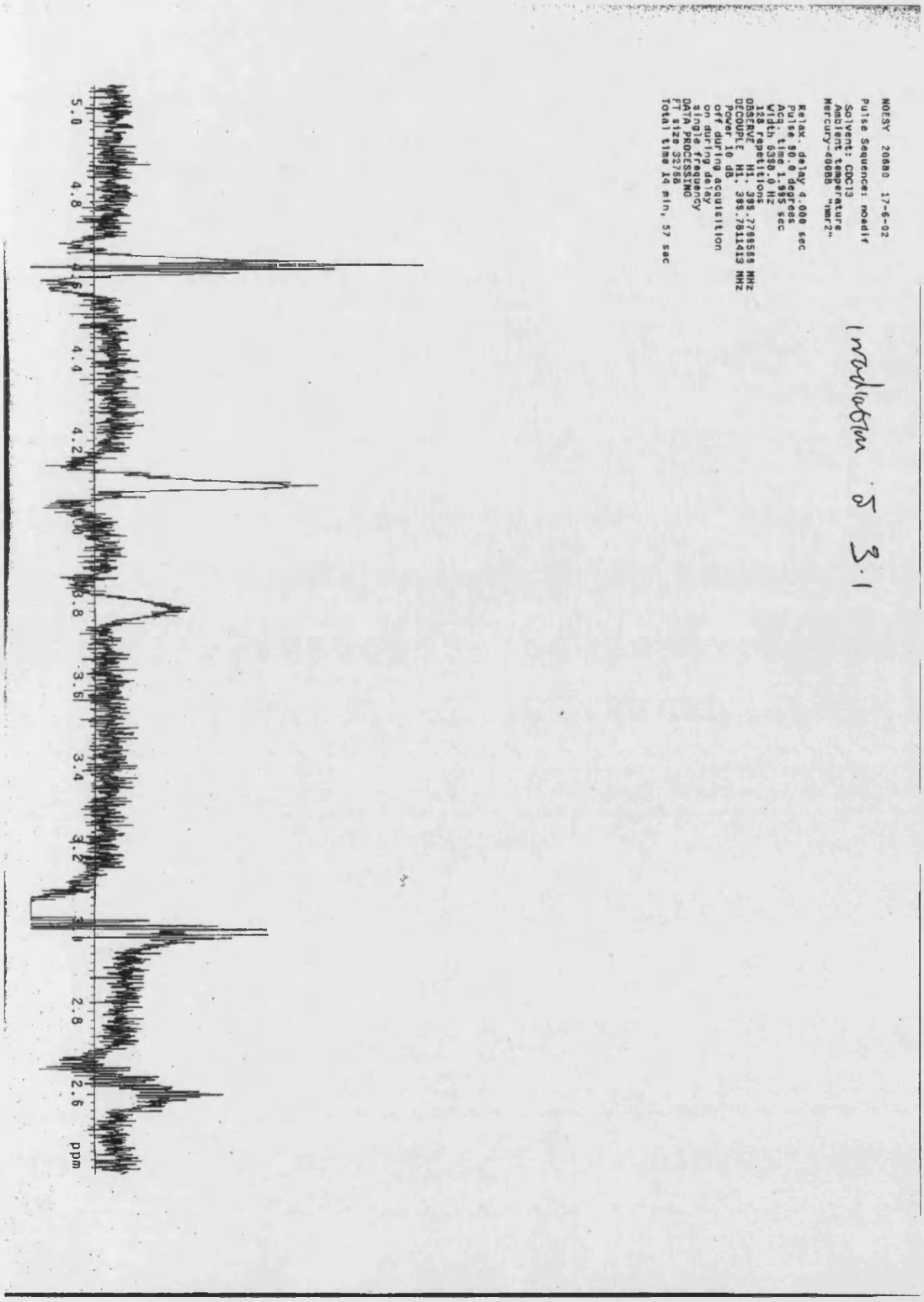

Figure 12. nOe enhancement experiment of compound 172A, irradiated at peak 3.10ppm.

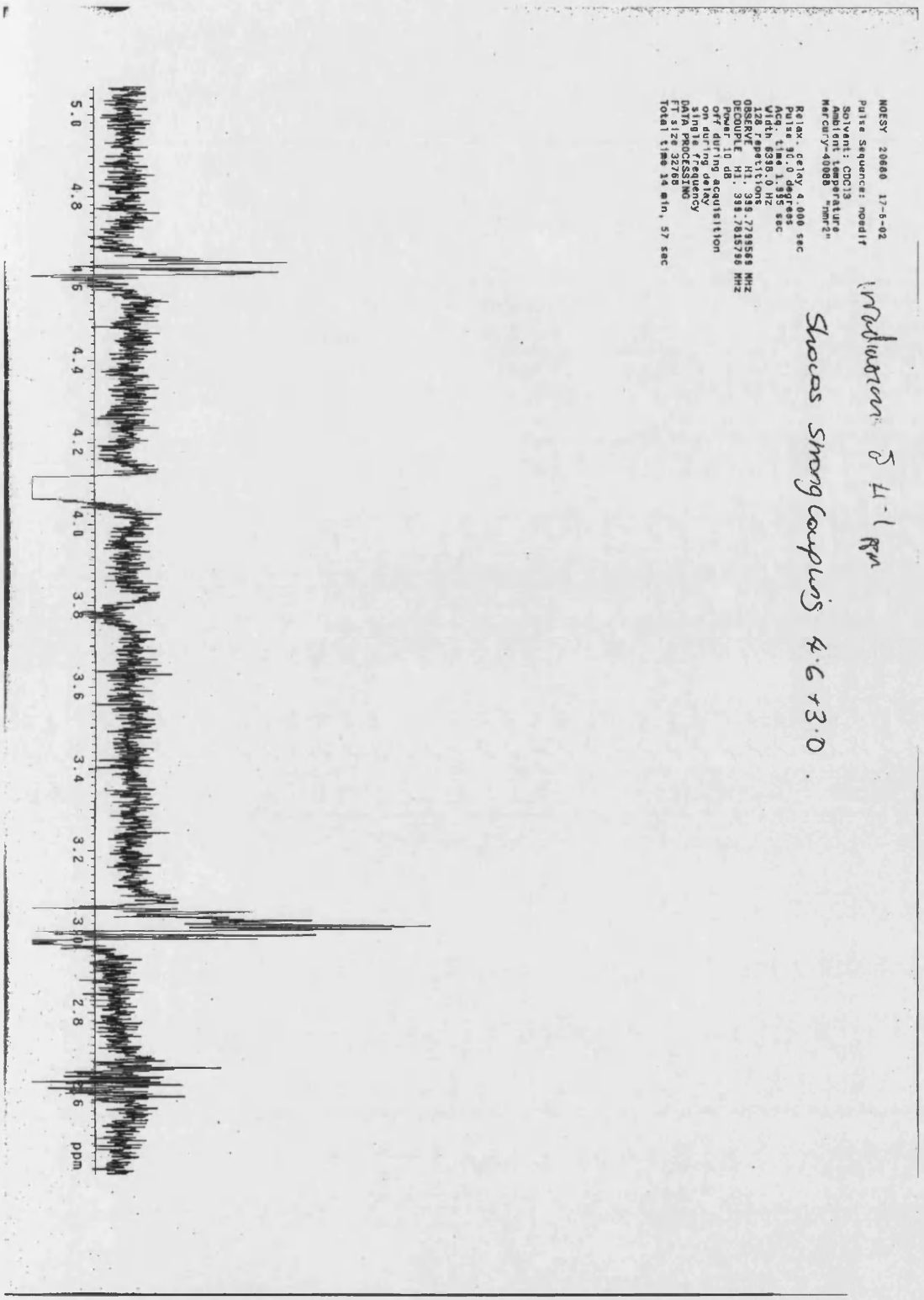

Figure 13. nOe enhancement experiment of compound 172A, irradiated at peak 4.10ppm.