Divergent rhodium catalysed cycloisomerisation of substituted 1,6-dienes: determination of the factors controlling the reaction pathways.

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Y los sueños…

sueños son.

(C. de la Barca)

Abstract

The cycloisomerisation of dienes is of high interest as it involves the formal rearrangement of hydrogen atoms and it presents very good atom economy. Unfortunately, the diastereoselectivity of this process has hitherto not been successfully controlled. Herein, the first example of highly diastereoselective rhodium-catalysed cycloisomerisation of substituted 1,6-dienes triggered by C-H activation is described and an overview of the metal-catalysed cycloisomerisation of 1,6-dienes is depicted.

A cationic rhodium catalyst cycloisomerises a 1,6-octadiene bearing a vinylpyridine moiety to a mixture of isomers in a highly diastereoselective fashion. The mechanism of the reaction, which was elucidated by the results of the D-labelling experiments, is examined. It is observed that the product selectivity can be improved by controlling the competition between the second migratory insertion and the 1,2-insertion and the competition between the reductive elimination and the β-hydride elimination respectively.

The control of the reductive elimination *versus* the β-hydride elimination has been achieved after an extensive phosphine ligand screening. The use of large phosphines as ligands favours the reductive elimination, while small phosphines promote the formation of the β-hydride elimination product. A careful monitoring of the reaction shows the transient character of the β-hydride elimination product which can get converted into the reductive elimination product under specific conditions.

The enhancement of the second migratory insertion is examined by modifying the steric and the electronic characteristics of the substrate in different positions and, overall, the tendency observed previously in the cycloisomerisation of the benchmark substrate is maintained.

The stepwise syntheses of the fourteen tested substrates, and the unambiguous identification of the products, are also reported.

Acknowledgements

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Abbreviations

$\tilde{\nu}$ wavenumber

∂ chemical shift

θ cone angle

ν frequency

2D two dimensional

3D three dimensional

APT Attached Proton Test

AVG. Average

cod cyclooctadiene

coe cyclooctene

Conf. Configuration

Conv. Conversión

Conven. Conventional

COSY correlation spectroscopy

Cp Cyclopentadienyl

CPD Composite Pulse Decoupling

DCE dichloroethane

DCM dichloromethane

de diastereomeric excess

DEG diethyleneglycol

DG Directing group

DIBAL-H Diisobutylaluminum hydride

DMF dimethyl formamide

DMSO dimethyl sulfoxide

DOL 2-methyl-1,3-dioxolane

dr diastereoisomeric ratio

ee enantiomeric excess

equiv. equivalent

et al. et alias

Et_2O Diethyl Ether

EtOAc Ethyl Acetate

EtOH Ethanol

FCC Flash Column Chromatography

GB Gaussian maximal position

HMBC Heteronuclear Multiple Bond Correlation

HRMS High Resolution Mass Specrometry

HSQC Heteronuclear single quantum coherence spectroscopy

Hz Hertz

i-PrOH isopropanol

LB Line broadening

LiHMDS Lithium bis(trimethylsilyl)amide

M molarity

m multiplet

m.b. mass balance

MeCN Acetonitrile

MHz MegaHertz

mmol millimole

MS Mass Spectrometry

MW microwave

n.d. non determined

NaHMDS Sodium bis(trimethylsilyl)amide

n-BuLi *n*-buthyllithium

NMR Nuclear Magnetic Ressonance

NOE Nuclear overhausser effect

NOESY Nuclear Overhauser Effect SpectroscopY

PE petroleum ether

phen Phenantroline

ppm parts per million

Prod. Product

q quartet

RCM Ring closing metathesis

rt room temperature

s,a syn,anti

s,s syn,syn

Std. Dev. Standard Deviation

Subs. Substrate

TBAF tetra-butylammonium fluoride

TBAI tetra-butyl ammonium iodide

TBSCl *tert*-Butyldimethylsilyl chloride

TEP Tolman Electronic Parameter

Trig: Trigonal systems

THF tetrahydrofuran

Tol *para*-tolyl

Tosyl Toluene sulfonic

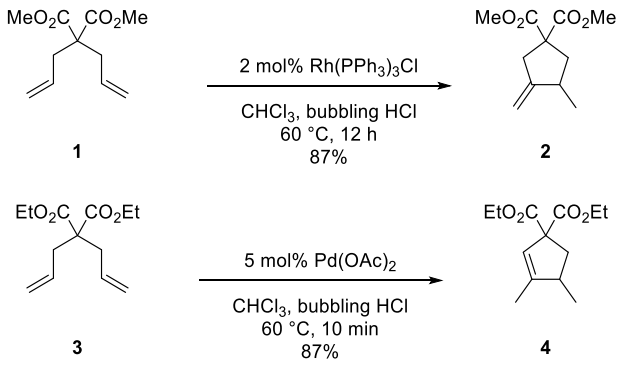
vs. versus

w/w weight/weight

Chapter 1 : Cycloisomerisation of 1,6-dienes

The metal-catalysed cycloisomerisation of 1,n-dienes and 1,n-enynes is a great approach for the formation of carbocycles. These reactions present an excellent atom economy and afford products with a high degree of structural complexity. In this regard, the cyclisation of 1,n-enynes has been extendedly studied and it can be easily applied in total synthesis.[1] The different reactivity of the olefin moiety and the alkyne group towards the catalyst has enabled the development of very regio- and stereoselective reactions. In contrast, the cycloisomerisation of 1,n-dienes presents more difficulties.[2-4] The similar reactivity of the two alkene moieties is usually translated into a loss of selectivity. Despite of all the disadvantages, several advances have been made.

In 1984, Grigg *et al*. described the cycloisomerisation of dimethyl 2,2-diallylmalonate **1** to methylene cyclopentane **2** using Wilkinson's catalyst in chloroform (Scheme 1.1).[5] They also described the cycloisomerisation of diethyl 2,2-diallylmalonate **3** to the corresponding cyclopentene **4** under similar conditions with palladium acetate as catalyst in very good yield.



Scheme 1.1: Cycloisomerisation of malonates described by Grigg in 1984.

The work by Grigg is one of the first examples of cycloisomerisation of 1,6-dienes described in the literature.[6,7] Previously, in 1971, Malone *et al*. reported a rhodium-catalysed cyclisation of diallyl ether.[8] Since then, several groups have been studying the reaction features. These studies proved that late transition metal complexes are the most suitable catalysts for this reaction. However, few reactions have been completed using early transition metals like titanium. Most studies showed that the cycloisomerisation of 1,6-dienes can afford up to three different isomers for the most simple symmetric substrate **A** (Figure 1.1).

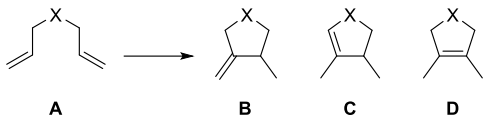


*Figure 1.1: The most common products of the cycloisomerisation of benchmark substrate **A**.*

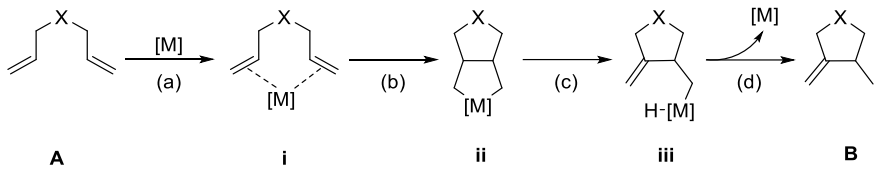
Methylene cyclopentane **B** is the kinetic product, while the two cyclopentenes **C** and **D** are the more thermodynamically stable isomers. As opposed to the cycloisomerisation of 1,6-enynes, the control of the product selectivity has been a difficult issue to solve. The similar characteristics of the two olefins in **A** make it difficult to differentiate them. This is especially important when substrate **A** is substituted in one of the alkene moieties. In that case, up to five different isomers can be observed.[9] Fortunately, several groups have managed to tune the reaction conditions and obtain each of the isomers selectively. Several mechanisms have been proven to operate during the course of the reaction. Herein, only the most common ones will be discussed: oxidative cyclometallation and intermolecular addition of metal hydride, also known as hydrometallation. Moreover, few examples of cycloisomerisation triggered by C-H activation are reported. Therefore, in this chapter, a brief description of the metal-catalysed cycloisomerisation of 1,6-dienes is intended. Longer or shorter chains or cycloisomerisation by other methods like ionic liquids or Lewis acids are not described here.[10,11] Moreover, examples with oxygen or nitrogen atom in the tether are not included, even though they are usually benchmark substrates for this reaction. Only substrates **A** where X = CHR or CR_2, will be discussed as they are the most closely related to the substrates described in the following chapters. Reactions that involve the formation of six-membered ring products are not reported for the same reason. Specifically, we focus on the cycloisomerisation of substituted 1,6-dienes, 1,6-octadienes and 2,7-nonadienes, as well as on examples for which the diastereoselectivity and enantioselectivity of the reaction was reported.

1.1. Oxidative cyclometallation

Zirconium complexes can promote the cyclisation of 1,6-dienes, but a stoichiometric amount of an electrophile is required to close the catalytic cycle.[12] In contrast, titanium and ruthenium complexes fully catalyse the cycloisomerisation of 1,6-dienes without using a stoichiometric additive. As described in the following sections, two different oxidative cyclometallation mechanisms have been reported. While titanium catalysts follows the classical mechanism (Section 1.1.1), ruthenium catalysts need a source of hydrides (Section 1.1.2).

1.1.1 Classical oxidative cyclometallation

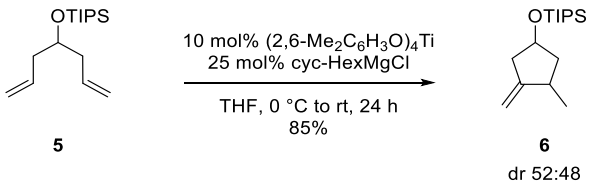
Four elementary steps define the classical oxidative cycloisomerisation mechanism. (Scheme 1.2).



Scheme 1.2: Classical mechanism of the oxidative cycloisomerisation.

In the first step, the metal catalyst coordinates with both olefin moieties of substrate **A** to form intermediate **i** (a). Then, this intermediate undergoes oxidative cyclometallation (b), giving its name to this general mechanism, to form the fused metallacycle **ii**. Following step b, intermediate **iii** is obtained by β-hydride elimination of **ii** (c). Finally, reductive elimination (d) affords methylene cyclopentane **B**. This mechanism can explain the high product selectivity for kinetic product **B** instead of the more thermodynamically stable cyclopentenes **C** and **D**. These two products cannot be directly obtained from intermediates **ii** and **iii**. In fact, they could only be obtained from the isomerisation of methylene cyclopentane **B** and a metal-hydride complex is usually required for that process.

Similar to zirconocenes, titanocene complexes usually require stoichiometric amount of a Grignard reagent to drive the reaction to completion. Nevertheless, in 2000, Livinghouse and Okamoto developed the first cycloisomerisation reaction of dienes using catalytic amounts of both the titanium alkoxide species and the Grignard reagent (Scheme 1.3).[13]



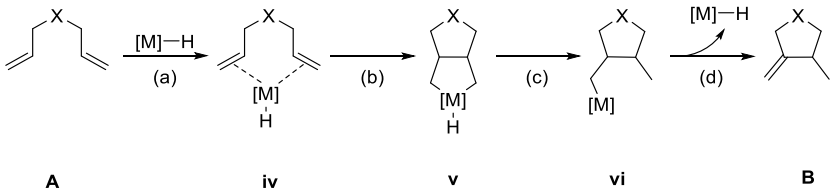
*Scheme 1.3: Titanium-catalysed cyclomerisation of diene **5**.*

Silylated alcohol **5** is cyclised into the methylene cyclopentane **6** in good yield and very mild conditions. Unfortunately, the authors observed a very poor diastereomeric ratio which was slightly improved to 60:40 by an elongation of the tether by including a silicon atom in position 4. An excellent

diastereoisomeric ratio was only observed for the cycloisomerisation of 1,7-octadienes which afforded a six-membered ring. The lack of reactivity observed for a 1,6-diene bearing a phenyl group on the terminal carbon of one of the olefins convinced the authors that the cycloisomerisation of substituted 1,6-dienes was not possible under those conditions. However other substituents were not tested.

1.1.2 Oxidative cyclometallation bearing a metal hydride catalyst

Ruthenium complexes are well-known for catalysing the ring closing metathesis (RCM) of 1,n-dienes. However, cycloisomerised 1,6-dienes can be obtained as secondary products of this reaction.[14] This and other studies positioned the ruthenium catalysts as one of the best options for the cycloisomerisation of dienes into methylene cyclopentane derivatives. The mechanistic and deuterium labelling studies carried out on the reaction showed that a ruthenium-hydride complex is the active catalyst of the transformation. The presence of the metal hydride changes the classical oxidative cyclometallation mechanism to the one described in Scheme 1.4, which has been proved by D-labelling experiments.

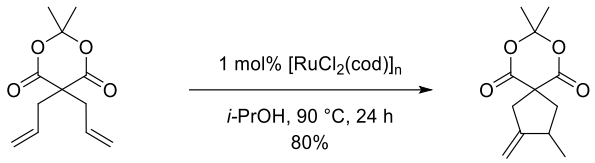


Scheme 1.4: Mechanism of the oxidative cyclomerisation requiring a metal-hydride catalyst.

Similar to the mechanism described in Scheme 1.2, the metal-hydride complex first coordinates to the olefin moieties of substrate **A** to form intermediate **iv** (Scheme 1.4, a). Then, it undergoes oxidative cyclometallation (b) to form the fused metallacycle **v**. At that stage, the mechanism differs from the classical one (Scheme 1.2). Intermediate **v** undergoes reductive elimination (c) and then β-hydride elimination (d) to form methylene cyclopentane **B**. Contrary to the previously described mechanism, the reductive elimination needs to occur first, as the complex is already a hydrido metal species after cycloisomerisation.

In the early 2000s, Itoh *et al*. carried out an extensive study on the optimal conditions of the reaction with different ruthenium complexes.[15,16] Surprisingly, they observed that oligomeric and partially insoluble $[RuCl_2(cod)]_n$ gave the best results. More soluble complexes afforded better yields to the detriment of the purity of the product. Further studies showed that the reaction needed to be carried out in an alcoholic solvent like ethanol or isopropanol. The oxidation of these solvents into carbonyls

provided the metal hydrides species needed for further reaction. Therefore, *tert*-butanol, which lacks hydrogens in the β-position, was not an appropriate solvent for the reaction. Traces of the more thermodynamically stable cyclopentenes were observed after long reaction times. This indicates that the Ru-H complex can very slowly catalyse the isomerisation from cyclopentane **B** into **C** and **D**. The system tolerated various functional groups like ketone, tosyl and nitriles and the corresponding methylene cyclopentane was always obtained in excellent purity (Scheme 1.5).



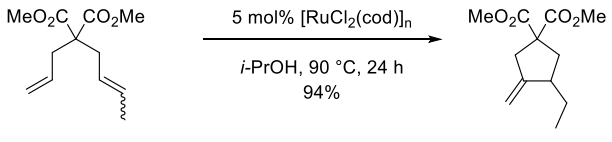
7 **8**

*Scheme 1.5: Ruthenium-catalysed cycloisomerisation of diene **7**.*

For example, cyclic diester **7** was transformed into the spiro compound **8** in high yield and 100% product selectivity. The double substitution in position 4 of the heptadiene was crucial for the reaction to proceed. Allyl ether, silicon-based tethers and 1,7-octadienes could not be cyclised. This indicates that the Thorpe-Ingold effect influences positively the reaction.[17]

1.1.2.1 M-H oxidative cyclometallation of substituted dienes

The substitution on the terminal carbon of one olefin moiety was also studied (Scheme 1.6).[15] The cycloisomerisation of 1,6-octadienes was achieved in excellent yields under the reaction conditions. Nevertheless, a higher catalyst loading was needed.

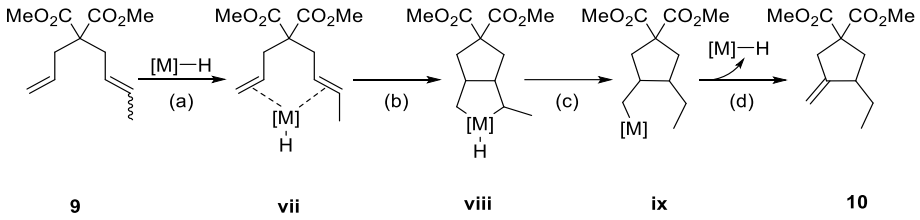


9 **10**

Subs.	Conf.	Yield	Purity
9a	**E/Z 3:1**	94%	77%
9b	**Z**	95%	63%

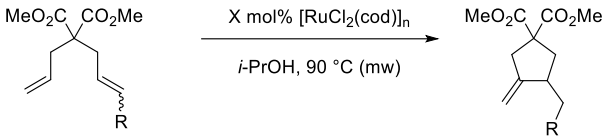
*Scheme 1.6: Ruthenium-catalysed cycloisomerisation of substituted dienes **9**.*

Substrates **9**, either as a *trans*-enriched mixture of isomers (**9a**) or as a pure *cis* substrate (**9b**) were transformed into the corresponding cyclopentanes **10** in excellent yields. However, the purity was 77 and 63%, respectively. Therefore, the geometry of the double bond affected considerably the product selectivity. In the same manner, the replacement of the methyl group on the olefin in **9** with a trimethylsilyl group improved the selectivity towards the *exo*-methylenecyclopentane product. The formation of a terminal olefin instead of the more thermodynamically stable tri-substituted olefin can be explained by the mechanism depicted in Scheme 1.7. After coordination (a) and oxidative cyclisation (b), reductive C-H elimination (c) occurs to give the more stable primary organometallic intermediate **ix**. It can then undergo β-hydride elimination (d) to yield product **10** (Scheme 1.7).



Scheme 1.7: Evidence of the formation of the less hindered exo-methylenecyclopentane by the oxidative cyclometallation requiring a metal-hydride.

The long reaction times and the moderate product selectivity for some substrates pushed Fairlamb *et al*. to continue studying the ruthenium-catalysed cycloisomerisation conditions.[18] By using microwave dielectric heating instead of conventional heating, they managed to reduce the reaction times down to a few minutes. This is the first example of microwave-assisted cycloisomerisation of 1,6-dienes. The microwave heating was suitable for all the 1,6-heptadienes tested and for some cyclic and substituted substrates. For simple diallylmalonate **1** and for 1,6-octadiene **9a**, the reaction was completed after 15 and 60 minutes respectively (Scheme 1.8).



Subs.	Prod.	R	mol% [Ru]	Time (min)	%Yield	%Purity
1	**2**	**H**	1	15	98	98
9a	**10**	**Me**	10	60	96	94

Scheme 1.8: Comparison of the ruthenium-catalysed cycloisomerisation of the naked and methyl substituted malonates.

In addition, the purity was increased significantly under these conditions. For example, product **10** was obtained 94% pure in contrast to the less than 80% selectivity observed for the conventional heating. In general, higher yields were also obtained.

Unfortunately, none of these conditions were suitable to cycloisomerise more complicated substrates (Figure 1.2). Substrates **11**, **12** and **13** were fully recovered after being tested under Itoh´s conditions. Disubstituted diene **11** and substrate **12**, which contained two internal olefins, remained untouched in the microwave-assisted reaction, while malonate **13** was not tested.

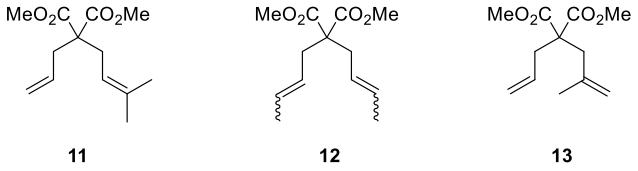
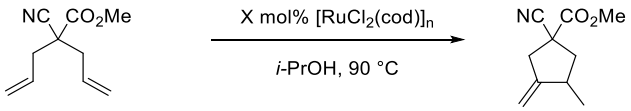


*Figure 1.2: Unreactive methyl substituted malonates **11**, **12** and **13**.*

1.1.2.2 M-H oxidative cyclometallation of prochiral substrates

In order to apply the reaction conditions in total synthesis, the diastereoselectivity needs to be perfectly established. Several groups have tried to improve the diasteroisomeric ratio in the cycloisomerisation of 1,6-dienes, but the control is usually poor. Both Itoh and Fairlamb tested their conditions on prochiral substrates (**Error! Reference source not found.**Scheme 1.9).[15,18]

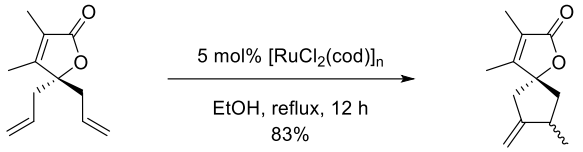


14 **15**

Heating	mol% [Ru]	Time (h)	%Yield	dr
Conven.	5	24	93	2.8:1
MW	0.5	0.5	97	3.1:1

*Scheme 1.9: Comparison of the ruthenium-catalysed cycloisomerisation of pro-stereogenic substrate **14** induced by conventional or microwave heating.*

When diene **14** was converted into *exo*-methylene cyclopentane **15** by conventional heating, the diastereomer ratio was 2.8 to 1. Other diastereoselective examples were reported, but the dr was significantly lower. The results were slightly improved when **14** was cycloisomerised using the MW heating. In this case, both the reaction time and the catalyst loading were reduced. However, a similar dr of 3.1 to 1 was obtained for this reaction. This indicates that the diastereoselectivity of the reaction in the oxidative cyclometallation mechanism is controlled by the substrate. This fact was proven by Parrain *et al*. in 2003 (Scheme 1.10). [19]



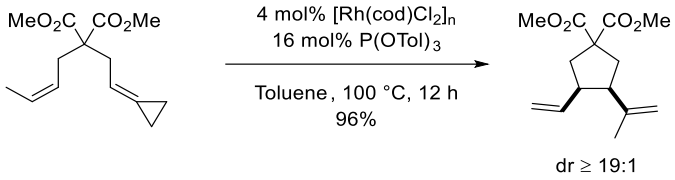
dr 95:5

16 **17**

Scheme 1.10: Highly diastereogenic ruthenium-catalysed cycloisomerisation induced by the rigidity of the substrate.

Symmetric cyclic substituents in position 4 of the diene afforded the corresponding cyclopentane product in good yields by both conventional and microwave heating. In this specific example, the substitution with butyrolactone provided the substrate with a prostereogenic centre. An increase of the rigidity of the lactone moiety gradually improved the diastereoselectivity of the reaction. An exceptional diastereomer ratio of 95:5 was obtained when the lactone was insaturated and doubly substituted (Scheme 1.10). In that case, spirolactone **17** was recovered in 83% yield.

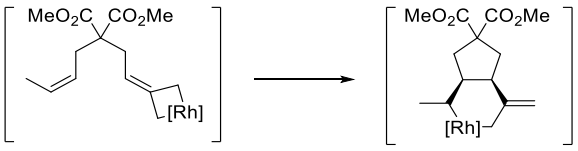
Finally, an interesting example was reported by P. Andrew Evans and Phillip A. Inglesby. The alkenylidenecylopropane **18** was cycloisomerised into *exo*-methylene cyclopentane **19** in an outstanding diastereoselective fashion (Scheme 1.11).[20]



18 **19**

Scheme 1.11: Highly diastereogenic rhodium-catalysed cycloisomerisation.

The reaction goes through a modified oxidative cyclometallation mechanism. The rhodium-phosphite complex triggers first C-C activation of the cyclopropane moiety before the oxidative cyclometallation step (Scheme 1.12). The unconventional nature of the substitution contributes to the formation of a six-membered ring fused metallacycle intermediate (**xi**) instead of the usual five-membered ring. This method was successfully applied in the total synthesis of kainic acid.

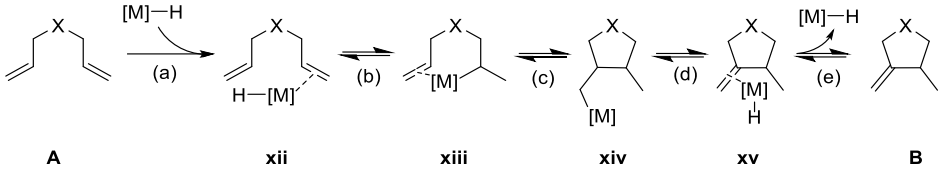


x **xi**

Scheme 1.12: Intermediates of the modified cyclometallation mechanism described by Evans and Inglesby.

1.2 Intermolecular addition of a metal hydride

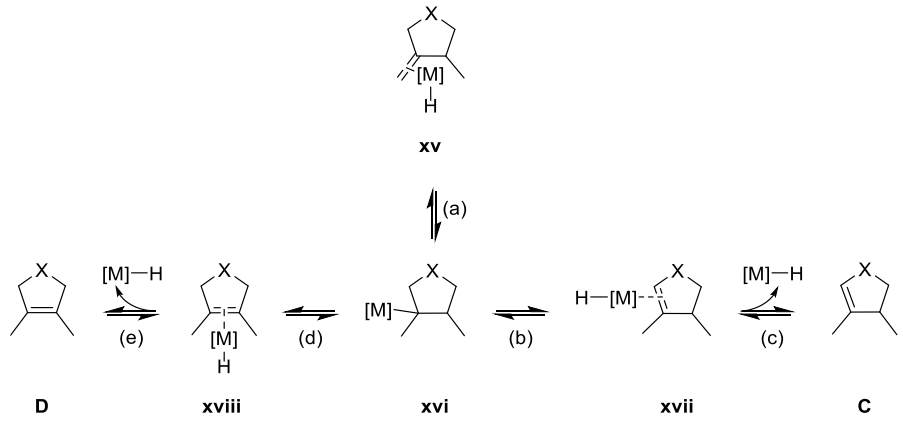
In contrast to the oxidative cyclometallation mechanism (Section 1.1), the intermolecular addition of a metal hydride can produce the three expected isomers **B**, **C** and **D**. Still, several groups have achieved excellent product selectivity. The reaction mechanism can be divided in two different sections: the formation of the kinetic product **B** (Scheme 1.13) and the generation of the more thermodynamically stable products **C** and **D** (Scheme 1.14).



*Scheme 1.13: Mechanism of the cycloisomerisation by intermolecular addition of metal hydride to form exo-methylenecyclopentane **B**.*

The formation of *exo*-methylene product **B** can be described in 5 steps. In the first stage of the reaction, the metal-hydride catalyst is bound by one of the olefins of the substrate (a). Then, the olefin is inserted in a 2,1-fashion and forms intermediate **xiii**. A second insertion occurs and the cyclisation (c) takes place. Finally, the catalyst undergoes β-hydride elimination (d) and decoordination of the recovered metal-hydride catalyst (e) affords the final product **B**. Several studies have proven that this last step is clearly reversible and that **B** can isomerise to **C** and **D**.

Cyclopentane **xv** can be obtained by β-hydride elimination of **xiv** (d) or by coordination of the metal hydride with kinetic product **B** (e). The hydrometallation of intermediate **xv** in a 2,1-fashion leads to the formation of the two cyclopentenes (Scheme 1.14).

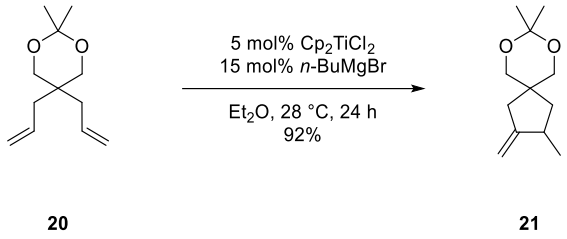


*Scheme 1.14: Mechanism of the isomerisation of intermediate **xv** to form cyclopentenes **B** and **C** by the intermolecular addition of metal hydride.*

Thus from intermediate **xvi**, two possible β-hydride eliminations can occur in different positions. Step b affords intermediate **xvii** that, after catalyst decoordination (c), leads to product **C**. On the contrary, the β-hydride elimination in the opposite carbon (d) forms the symmetrical intermediate **xviii**. Then, the most stable thermodynamic cyclopentene **D** is obtained.

1.2.1 Kinetic control

As mentioned in section 1.2.1, the control of the product selectivity in the hydrometallation mechanism is more complicated. Nickel is the most common metal in the cycloisomerisation of 1,6-dienes by hydrometallation under kinetic control. However a titanium based catalyst has also been described.[21] In that reaction, Livinghouse and Okamoto obtained the *exo*-methylene cyclopentanes in good to excellent yields by using a catalytic amount of Cp_2TiCl_2 and Grignard reagent (Scheme 1.15).

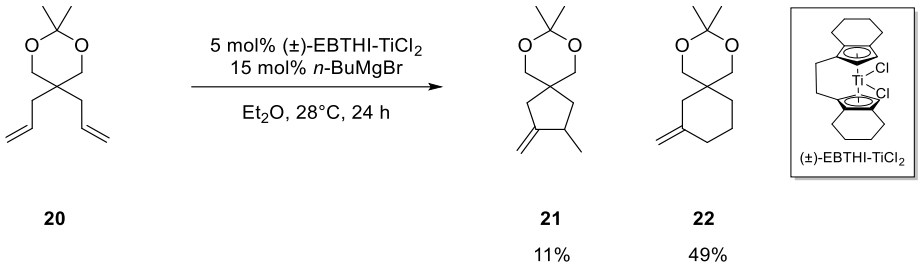


20 **21**

*Scheme 1.15: Cycloisomerisation of diene **20** using Cp_2TiCl_2 as a precatalyst.*

Few months before, they had already reported a similar titanium catalyst for this transformation (Scheme 1.3).[13] In that case, the oxidative cyclometallation dictated the mechanism of the reaction. However, the isomerisation of the terminal olefin bonds of some substrates, as well as the formation of high amounts of the thermodynamic product **C** are a definitive evidence of the involvement of metal-hydride species in the mechanism of the reaction described in this section.

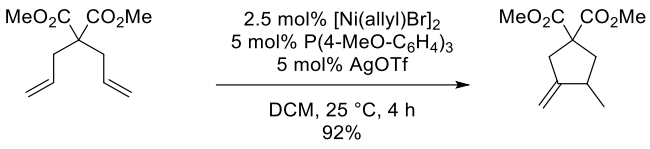
Under Livinghouse and Okamoto conditions, diene **20** was cycloisomerised into product **21** in excellent yield (Scheme 1.15). However, the substitution of one of the olefin moieties of substrate **20** with a phenyl group blocked the cyclisation process. Although other substrates with simpler and less bulky substituents were not tested, the authors claimed that terminal substituted dienes were unreactive. The substitution of the quaternary carbon for a silicon based tether only promoted the isomerisation of both terminal olefins. This shows that this catalyst is sensitive to the geometry of the substrate. The modification of the catalyst geometry also affected the outcome of the reaction. When (±)-EBTHI-$TiCl_2$ was used as a pre-catalyst for the cycloisomerisation of substrate **20**, the head-to-tail six-membered ring was the predominant product (Scheme 1.16).



20 **21** 11% **22** 49%

*Scheme 1.16: Cycloisomerisation of diene **20** using (±)-EBTHI-TiCl$_2$ as a precatalyst.*

After studying the nickel-catalysed hydrovinylation of vinylarenes, RajanBabu and Radetich decided to apply similar reaction conditions in the cycloisomerisation of 1,6-dienes (Scheme 1.17).[22,23]

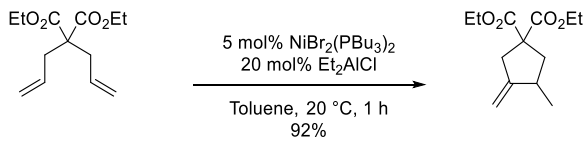


1 **2**

*Scheme 1.17: Nickel-catalysed cycloisomerisation of malonate **1** into the kinetic exo-methylene cyclopentane product.*

The reaction of the diallyl malonate **1** with 5 mol% of the cationic nickel catalyst afforded cyclopentane **2** in 92% yield after few hours, but traces of the internal olefin product were also observed. Substrates bearing a heteroatom were cyclised in only moderate yields.

Few years later, Kotora *et al*. reported a new nickel catalyst for this transformation (Scheme 1.18).[24] Previously, they had studied the deallylation of malonates catalysed by a nickel-phosphine complex that required two equivalents of an organoaluminium reagent.[25]



3 **23**

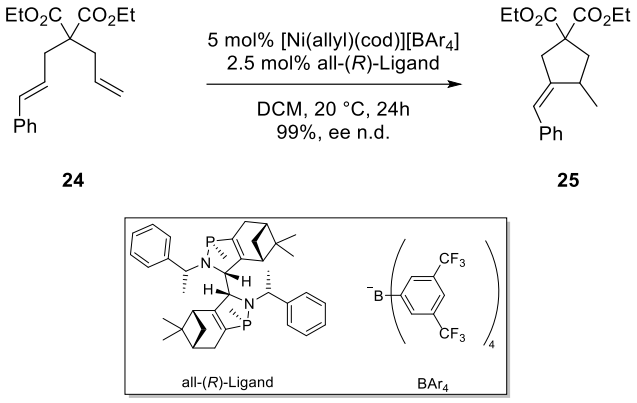
*Scheme 1.18: Nickel-catalysed cycloisomerisation of malonate **3** into the kinetic exo-methylene cyclopentane product.*

They proposed that, by reducing the amount of Et$_3$Al to catalytic quantities, the nickel procatalyst is transformed into the active nickel-hydride complex which catalyses the cycloisomerisation. Two

different catalytic systems were tested. In general, the combination of $NiBr_2(PPh_3)_2$ and Et_3Al is much less selective and efficient than $NiBr_2(PBu_3)_2$ and Et_2AlCl. For example, diallyl ethylmalonate **3** was transformed with $NiBr_2(PBu_3)_2$ and Et_2AlCl into *exo*-methylenecyclopentane **23** in 92% yield after 1 hour (Scheme 1.18). On the contrary, when the reaction was carried out with $NiBr_2(PPh_3)_2$ and Et_3Al, the product **23** was only obtained in 37% yield after 36 hours.

1.2.1.1 Kinetic control conditions in substituted 1,6-dienes

In 2008, Leitner *et al*. reported the selective cycloisomerisation of substituted 1,6-dienes towards the formation of the kinetic product (Scheme 1.19).[26]

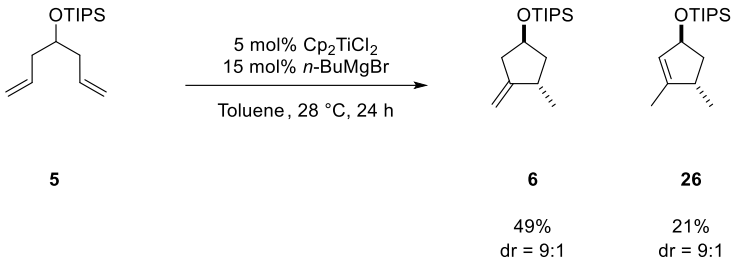


*Scheme 1.19: Nickel-catalysed cycloisomerisation of the phenyl-substituted malonate **24**.*

The cationic nickel-azaphospholene catalyst afforded the cycloisomerisation of **24** in excellent yield and selectivity. The reaction tolerated both electron-donating and electron-withdrawing substituents in the aromatic ring, albeit to the detriment of the selectivity or the conversion. It is noteworthy that only product **25** that contains an *exo*-substituted olefin was formed.

1.2.1.2 Kinetic control conditions in prochiral substrates

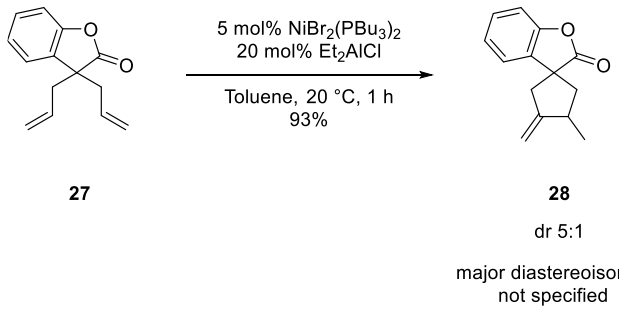
Livinghouse and Okamoto reported the titanium-catalysed reaction of only one prochiral substrate (Scheme 1.20).[21]



*Scheme 1.20: Titanium-catalysed cycloisomerisation of prochiral diene **5**.*

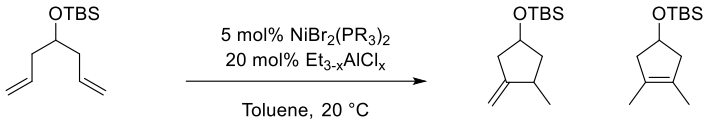
The procatalyst Cp_2TiCl_2 induced a better diastereomer ratio than the alkoxide-titanium complex (dr = 5:1, Scheme 1.3). However, it was to the detriment of the product selectivity and the overall yield. Product **26** bearing an internal olefin was obtained in 21% yield, while the desired *exo*-methylene cyclopentane **6** was only obtained in 49% yield.

The diastereoselectivity was also poor for the nickel-catalysed reaction described by Kotora *et al*. (Scheme 1.21).[24]



*Scheme 1.21: Nickel-catalysed cycloisomerisation of prochiral diene **27**.*

The spirolactone **28** was obtained in 93% yield, but only in a 5:1 diastereoisomeric ratio. Contrary to the reaction catalysed by $[RuCl_2(cod)]_n$ (Scheme 1.10) where the diastereoselectivity depended on the substrate, the rigidity of the substituent in position 4 did not affect the diastereomeric ratio of the product obtained in this reaction (Scheme 1.21 and Scheme 1.22), as both product **28** and **30** where obtained in a dr = 5:1 when using Et_2AlCl as a co-catalyst.



29 **30** **31**

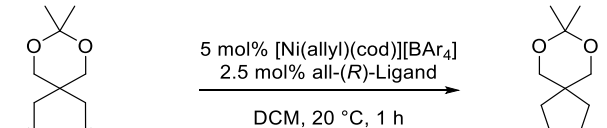
R	$Et_{3-x}AlCl_x$	Time (h)	30 (%)	30 (dr)	31 (%)
Bu	Et_2AlCl	1	51	5:1	44
Ph	Et_3Al	3	71	3:2	0

*Scheme 1.22: Comparison of the nickel-catalysed cycloisomerisation of prochiral diene **29** using two different aluminium co-catalysts.*

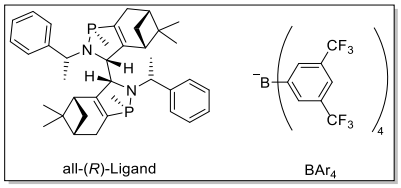
Unfortunately, the cycloisomerisation of substrate **29** under those conditions showed very poor product selectivity and isomer **30** was obtained in 51% yield, while cyclopentene **31** was recovered in 44% yield. Lower diastereoisomeric ratio but better product selectivity was observed when triethylaluminium was used as a co-catalyst and triphenylphosphine as a ligand.

1.2.1.3 Kinetic control conditions in asymmetric cycloisomerisations

The cycloisomerisation of 1,6-dienes has not been extensively studied. In this regard, Leitner *et al.* have optimised the reaction conditions to obtain good to excellent enantioselectivity.[27,28] In 2008, they reported the enantioselective cycloisomerisation of 1,6-dienes catalysed by a cationic chiral nickel-complex (Scheme 1.23).[26] Substrate **20** was transformed into the kinetic product **21** in 87% product selectivity and 86% enantioselectivity.

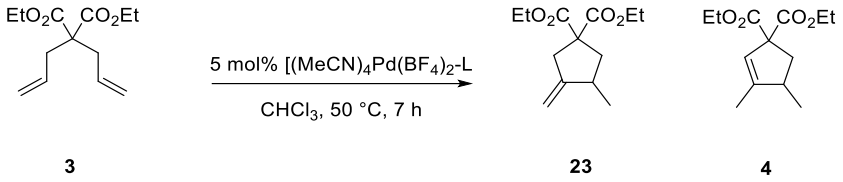


20 **21**



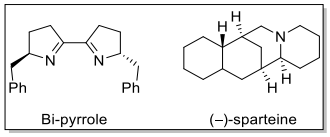
*Scheme 1.23: Chiral control of the nickel-catalysed cycloisomerisation of diene **20**.*

Ten years before, in 1998, Heumann and Moukhliss had reported the asymmetric cycloisomerisation of the *di*-allyl malonates (Scheme 1.24).[29,30]



3 **23** **4**

L	%conv.	23 (%)	23 (ee)	4 (%)	4 (ee)
Bi-pyrrole	46	38	60	8	23
(−)-sparteine	51	27	60	24	37

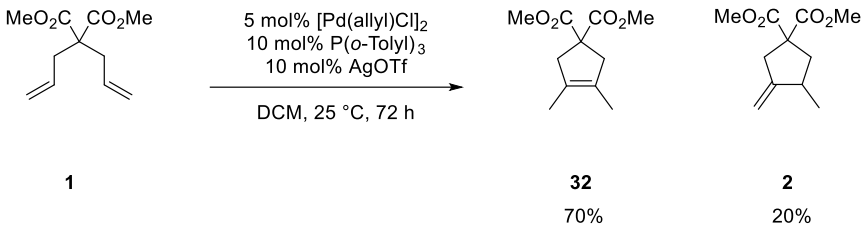


*Scheme 1.24: Asymmetric palladium-catalysed cycloisomerisation of malonate **3** using two different chiral ligands.*

In that case, both the kinetic (**23**) and the thermodynamic product (**4**) were obtained. Similar conversion was observed when using *bi*-pyrrole or the (−)-sparteine as a ligand. In contrast, the product selectivity and the enantioselecetivity of the reaction were clearly affected by the use of one or another. The enantiomeric excess of the *exo*-methylene product **23** was 60% under both reaction conditions, while the thermodynamic product **4** was obtained in lower enantiomeric excess. The replacement of the "dicationic" palladium catalyst for a Pd^{+} complex diminished the enantioselectivity of the reaction.

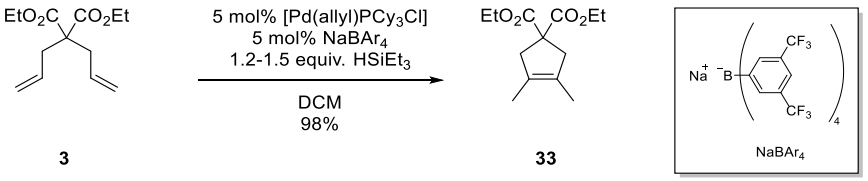
1.2.2 Thermodynamic control

Selective cycloisomerisation of 1,6-dienes towards the most thermodynamically stable cyclopentenes has only been possible with palladium catalysts. Allyl-palladium complexes usually form the symmetric cyclopentene **D** while more coordinating ligands afford the unsymmetric isomer **C**. In 1997, RajanBabu and Radetich reported the cycloisomerisation of diallyl malonate **1** preferentially to product **32** (Scheme 1.25).



*Scheme 1.25: Thermodynamic control of the palladium-catalysed cycloisomerisation of malonate **1**.*

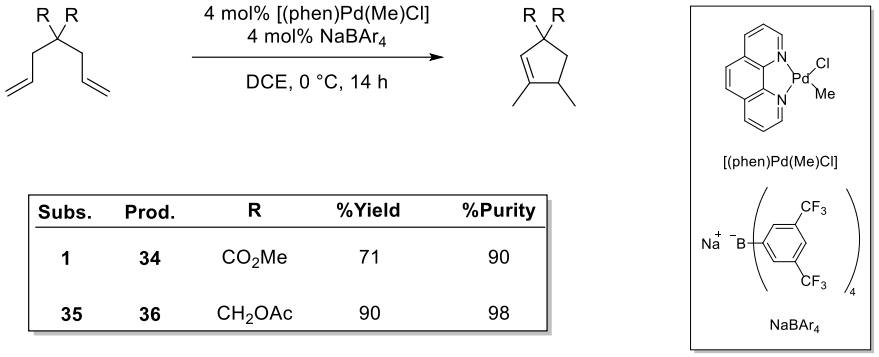
A very long reaction time was required and 20% of *exo*-methylene cyclopentane **2** was also obtained.[23] Contrary to nickel catalysts, palladium complexes isomerise the olefin in the *exo* position to form the more stable *endo* isomers. The conditions were improved in the following years. In 2000, Widenhoefer and Kisanga reported an extensive study of the reaction.[31] They observed that the addition of one equivalent of triethylsilane was essential to have a complete product selectivity in this reaction (Scheme 1.26).



*Scheme 1.26: Selective formation of symmetric cyclopentene **33** using $HSiEt_3$ as an additive in the palladium-catalysed cycloisomerisation.*

Malonate **3** was transformed in 98% yield to cyclopentene **33** by a cationic palladium catalyst. Although the role of the silane additive is not completely clear, perfect control of the product selectivity was obtained. The authors assumed two different purposes for the triethylsilane. The first role is to activate the palladium procatalyst, probably by hydride donation. The induction period observed during the kinetic studies supported the hypothesis. On its second role, the silane would stabilise the cationic palladium complex and would also facilitate the isomerisation of the *exo*-methylene cyclopentane **23** to the final product.

One year later, the same group inverted the product selectivity. When a phenantroline molecule replaced the allyl ligand in the palladium complex, the formation of 1,5-dimethylcyclopentenes was favoured (Scheme 1.27).[9]

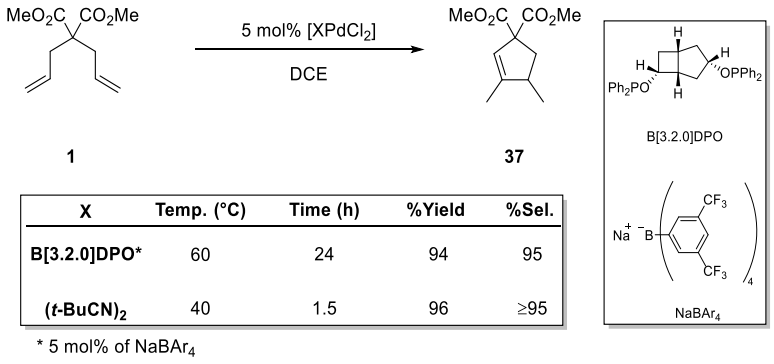


Subs.	Prod.	R	%Yield	%Purity
1	**34**	CO_2Me	71	90
35	**36**	CH_2OAc	90	98

Scheme 1.27: Selective formation of unsymmetric cyclopentenes using phenantroline as a ligand in the Palladium-catalysed cycloisomerisation.

The procatalyst [(phen)Pd(Me)Cl] promoted the cycloisomerisation of substrates **1** and **35** to the corresponding 1,5-dimethylcyclopentenes in good yield and excellent purity. However, increasing the temperature of the reaction diminished considerably the product selectivity. The authors also reported the cycloisomerisation of 1,5-dienes. Harsher conditions but shorter reaction times were required for this transformation. The activation of the palladium procatalyst produced 5% of a methylated secondary product.

Fairlamb *et al*. and Lloyd-Jones *et al*. achieved similar results with bidentate phosphinite B[3.2.0]DPO and nitrile ligands in the following years (Scheme 1.28).[32-35]



1 **37**

X	Temp. (°C)	Time (h)	%Yield	%Sel.
B[3.2.0]DPO*	60	24	94	95
(*t*-BuCN)$_2$	40	1.5	96	≥95

* 5 mol% of $NaBAr_4$

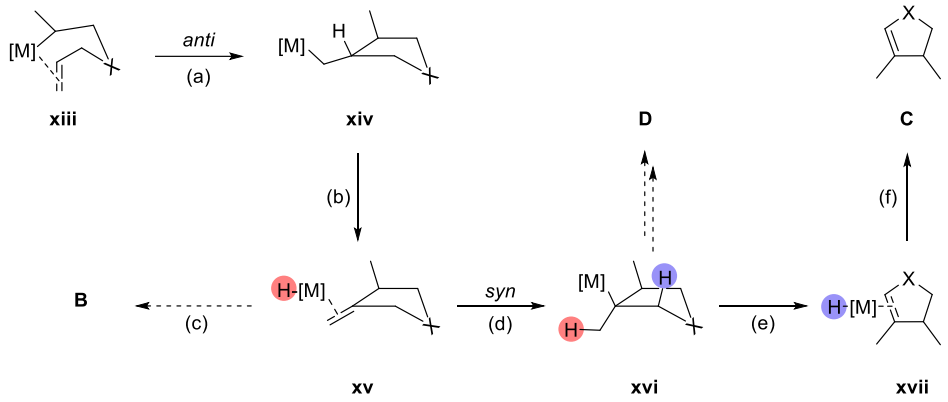
*Scheme 1.28: Selective formation of unsymmetric cyclopentenes using B[3.2.0.]DPO or (t-BuCN)$_2$ as ligands in the palladium-catalysed cycloisomerisation of malonate **1**.*

The cationic palladium (II) complex catalyses the cycloisomerisation of diallyl malonate **1** into 1,5-dimethylcyclopentene **37** in 95% product selectivity in 24 hours. The remaining 5% corresponds to the 1,2-dimethylcyclopentene **32** (see Scheme 1.25). An optimisation of the reaction conditions showed that the nature of the counter ion affected notably the regioselectivity. More coordinating BF_4 anion

raised the selectivity towards isomer **37**. Unfortunately, the efficiency of the reaction dropped considerably. In contrast, an increase of the amount of $NaBAr_4$ salt diminished the selectivity.

Neutral [(*t*-BuCN)$_2$PdCl$_2$] catalysed the same reaction in excellent yield and selectivity in only one hour at 40 °C. The acetonitrile-palladium complex was also very efficient. However, it showed slightly lower selectivity. In contrast to the bidentate phosphinite catalyst and contrary to general opinion, the cationic complex formed by halide abstraction was less active.

Kinetic studies carried out in the three systems ([(phen)Pd(Me)Cl], B[3.2.0]DPO and (*t*-BuCN)$_2$PdCl$_2$) showed that the kinetic *exo*-methylene cyclopentane was not formed. Moreover, when this product was reacted with the nitrile catalyst, there was no appreciable conversion into the cyclopentene isomers. These observations and the evidence from the deuterium labelling experiments moved the groups to propose a reaction mechanism to justify the product selectivity (Scheme 1.29).[9,33,35,36]



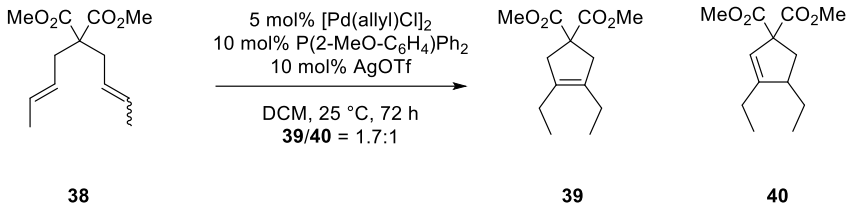
*Scheme 1.29: Mechanism of the formation of the unsymmetric cyclopentene **C** when using strong coordinating ligands.*

The olefin of intermediate **xiii** undergoes 1,2-insertion in an *anti* fashion (a). This places the hydrogen on the tertiary carbon atom in *syn* relationship to the methyl group. Then, β-hydride elimination (b) forms intermediate **xv**. The lack of product **B** in the reaction mixture showed that dissociation of the metal-hydride (c) is not possible under these reaction conditions. Hence, the olefin is reinserted into the metal-hydride complex in a *syn* fashion (d). The metal complex is now attached to the tertiary carbon atom (intermediate **xvi**). The insertion to give the opposite diastereoisomer with the metal and the methyl group in an *anti* relationship is not possible as the metal-hydride complex is never dissociated from **xv**. Intermediate **xvi** has only one available hydrogen in *syn*-coplanar position (H in purple) to undergo β-hydride elimination (e). Thus, only intermediate **xvii** is formed. Dissociation and recovery of the active catalyst (f) afford the final product **C**.

Lloyd-Jones proposed that the strong coordinating character of the nitrile ligand was responsible for the stability of intermediate **xv**.[35] The precise geometry of the phosphinite ligand under the given conditions would justify the product selectivity in that specific system. Interestingly, in 2014, Guo *et al*. reported the same selectivity when $[Pd(allyl)Cl]_2$ catalysed the cycloisomerisation of diallyl malonates under irradiation of UV light.[37] Nevertheless, the yields were only low to moderate.

1.2.2.1 Thermodynamic control conditions in substituted 1,6-dienes

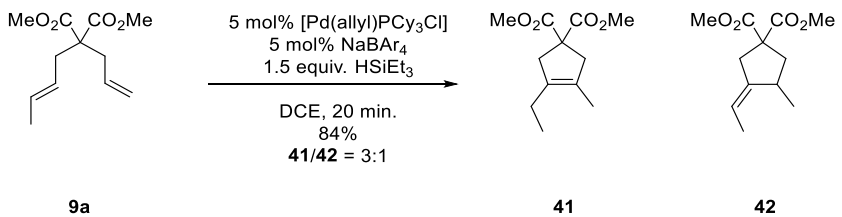
The substitution of one or both olefin moieties of the 1,6-diene substrates decreased the product selectivity considerably. When substrate **38** reacted with a cationic allyl-palladium catalyst, the expected cyclopentene **39** was only obtained in a product selectivity of 1.7:1, while 1,5-diethyl cyclopentene **40** was obtained as a secondary product (Scheme 1.30).[23]



*Scheme 1.30: Palladium-catalysed cycloisomerisation of 2,7-nonadiene **38** under thermodynamic control conditions.*

It is noteworthy that the kinetic *exo*-ethylene cyclopentane isomer was not formed. The similar steric hindrance of both intermediates and products is probably the reason for the low product selectivity of this cycloisomerisation. Moreover, longer reaction times were required for the completion of the reaction.

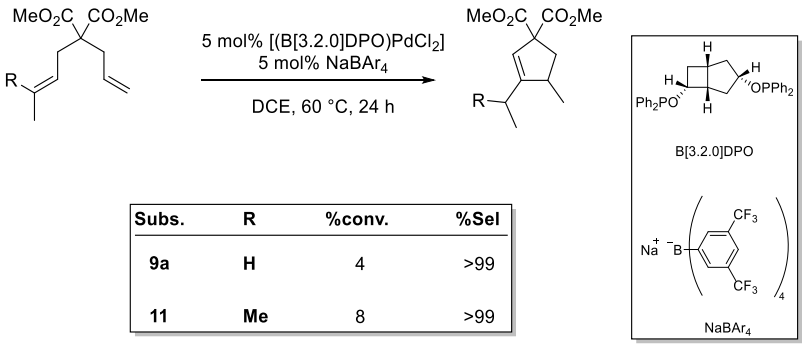
The addition of 1.5 equivalents of $HSiEt_3$ as described by Widenhoefer improved the product ratio (Scheme 1.31).[31] However, the kinetic *exo*-ethylene cyclopentane was still an important side product of the reaction.



Scheme 1.31: Palladium-catalysed cycloisomerisation of methyl substituted malonate 9a under thermodynamic control conditions using $HSiEt_3$ as an additive.

As expected, longer reaction times and higher reaction temperature reduced the product selectivity, but they did not affect the combined yield. The selectivity was raised to 6:1 when an excess of 4 equivalents was used and a maximum of 31:1 was obtained with 8 equivalents of triethylsilane. In contrast to the oxidative cyclometallation (Scheme 1.6 and Scheme 1.8), the symmetric cyclopentene **41** was obtained as the major product. The reaction mechanisms can explain the difference observed. In this case, the addition of the metal-hydride occurs selectively to the less hindered olefin. Therefore, the reductive elimination takes place to form the substituted alkene.

The phosphinite-palladium complex developed by Fairlamb *et al*. catalysed the cycloisomerisation of the methyl substituted diallyl malonates **9a** and **11** to the corresponding 1,5-cyclopentenes in excellent selectivity (Scheme 1.32).[32] However, the conversion was extremely low.

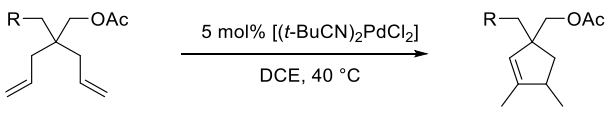


Subs.	R	%conv.	%Sel
9a	**H**	4	>99
11	**Me**	8	>99

Scheme 1.32: Palladium-catalysed cycloisomerisation of methyl substituted malonates under thermodynamic control conditions using B[3.2.0]DPO as a ligand.

1.2.2.2 Thermodynamic control conditions of prochiral substrates

Lloyd-Jones and co-workers tested the cycloisomerisation of prochiral substrates (Scheme 1.33). [34]



43 **44**

Subs.	R	Time (h)	%Yield	%de
43a	**OBn**	3	96	5
43b	**OH**	1	82	17

*Scheme 1.33: Palladium-catalysed cycloisomerisation of prochiral substrate **43** under thermodynamic control conditions using t-BuCN as a ligand.*

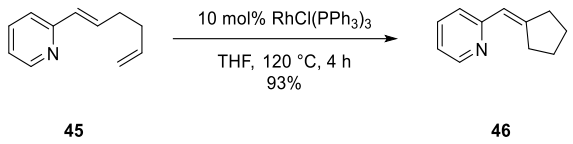
Product **44a** was obtained in excellent yield after 3 hours. However, extremely poor diastereoselectivity was observed. The substitution of the benzyl moiety for an alcohol accelerated the rate of the reaction and improved slightly the diastereoisomeric excess at the expense of the yield. The alcohol group probably coordinated with the metal catalyst and directed the cycloisomerisation.

1.3 C-H activation

The cycloisomerisation of dienes triggered by C-H activation is less common. However, the pioneer work by Murai showed the effectiveness of the reaction.[38-40] More recent examples were described by Dong during the course of this thesis.

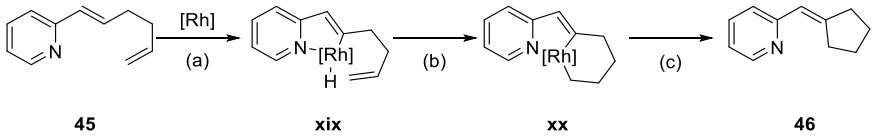
1.3.1 Murai cycloisomerisation of 1,5 and 1,6-dienes

In 1996, Murai *et*. *al* presented the cycloisomerisation of 1,5 and 1,6-dienes triggered by C-H activation. 1-(2-pyridyl)-1,5-diene (**45**) was converted into product **46** in 93% yield in 4 hours (Scheme 1.34).[38,39]



Scheme 1.34: Rhodium-catalysed cycloisomerisation of 1,5-dienes described by Murai.

The optimisation of the reaction conditions showed Wilkinson´s complex as the most efficient catalyst for this transformation. High product selectivity was observed and neither the terminal olefin nor the vinyl bond were isomerised. Then, the authors proposed a plausible reaction mechanism (Scheme 1.35).

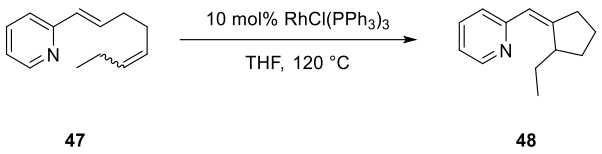


*Scheme 1.35: Mechanism of the rhodium-catalysed cycloisomerisation of 1,5-diene **45**.*

First of all, the rhodium complex coordinates with the pyridine nitrogen atom. This complexation places the catalyst next to the vinyl carbon-hydrogen bond which is activated and undergoes an oxidative addition (a). The formation of a five-membered ring metallacycle stabilises the intermediate

xix. Then, the terminal olefin undergoes 1,2-insertion (b) to form the fused six-membered ring **xx**. Finally, the reductive elimination (c) releases product **46** and liberates the active catalyst.

The applicability of the reaction conditions was tested in other 1,n-diene substrates. Internal olefins and 1,6-dienes were also suitable substrates. Cycloisomerisation of substrate **47** afforded product **48** in high yields (Scheme 1.36)

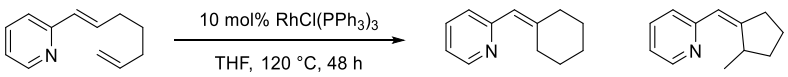


47 **48**

Conf.	Time (h)	% Yield
trans	38	86
cis	3	84

Scheme 1.36: Rhodium-catalysed cycloisomerisation of substituted 1,5-dienes.

However, the configuration of the alkene affected significantly the catalyst efficiency. When the *cis* olefin **47** was tested, product **48** was obtained after 3 hours. On the contrary, the *trans*-isomer **47** reacted much slower and only after 38 hours the reaction reached completion. This agrees with the tendency usually observed. The reaction conditions were also tested with 1,6-dienes (Scheme 1.37).

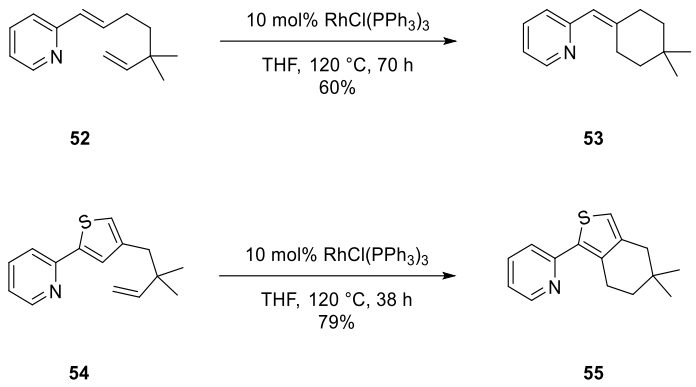


49 **50** 33% **51** 47%

Scheme 1.37: Rhodium-catalysed cycloisomerisation of 1,6-dienes.

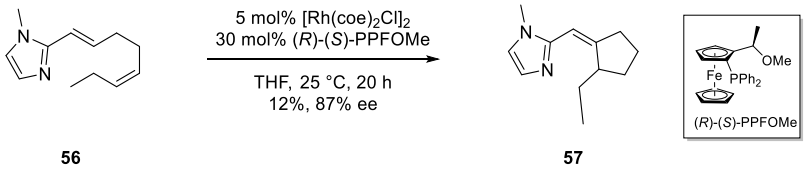
The addition of an extra methylene to the alkyl chain decreased the control of the product selectivity. Cyclohexane **50** was obtained in 33% isolated yield, but the major product was the methyl-substituted cyclopentane **51** which was obtained in 47% yield. The former is formed by the previously described 1,2-insertion of the terminal olefin into the Rh-H bond formed after the C-H activation. On the contrary, product **51** is formed by the 2,1-insertion of the olefin. The two corresponding metallacycles

intermediates are very close in energy, thus, the regioisomeric ratio is especially low. The authors circumvented this issue by adding a *gem*-dimethyl substituent near the terminal olefin in substrate **52** (Scheme 1.38). In that case, only product **53** was observed. Moreover, the authors observed that the reaction was also possible with a substrate containing an aromatic C-H bond (**54**) which convinced them that the mechanism is triggered by C-H activation (Scheme 1.38).



Scheme 1.38: Rhodium-catalysed cycloisomerisation in strained and aromatic substrates.

Later on, the same group reported the asymmetric version of this reaction (Scheme 1.39).[40] A modified ferrocene-rhodium complex catalysed the cycloisomerisation or 1-(2-pyridyl)-1,5-dienes with low enantiomeric excess. The substitution of the pyridine group by an imidazole improved the ee up to 87% at room temperature.

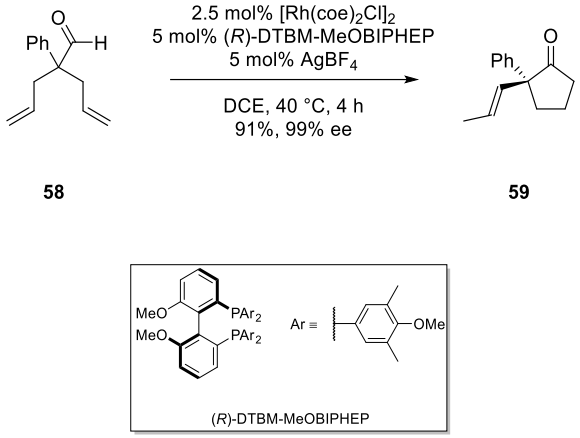


Scheme 1.39: Asymmetric rhodium-catalysed cycloisomerisation of 1,5-dienes.

1.3.2 Dong cycloisomerisation of 1,6-dienes

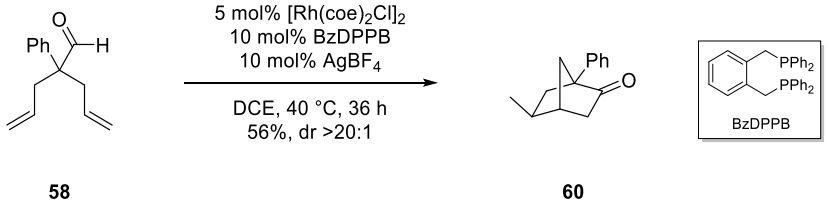
Contrary to the work done by Murai, Dong *et al*. presented the cycloisomerisation of 1,6-dienes bearing an aldehyde as a directing group. They described the enantioselective hydroacylation of 1,6-

dienes catalysed by $[Rh(coe)_2Cl]_2$ and an enantiopure bidentate phosphine to obtain cyclopentanones in an excellent enantiomeric excess (Scheme 1.40). [41]



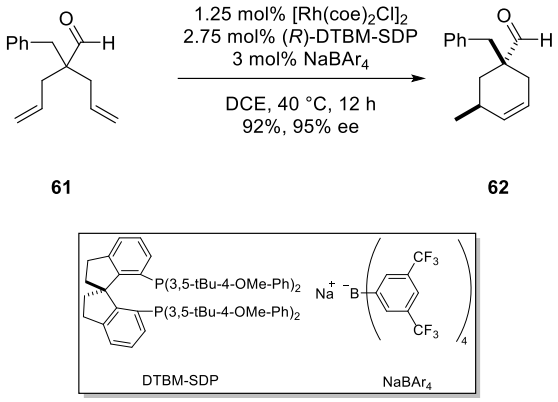
Scheme 1.40: Asymmetric rhodium-catalysed cycloisomerisation of 1,6-dienes described by Dong.

Few months earlier Stephanie Yip and Christophe Aïssa reported a similar reaction.[42] However, Dong observed that the replacement of the ligand for a simpler phosphine afforded norbornanone **60** as the major isomer (Scheme 1.41).[41] In the Aïssa group, the cycloisomerisation of 1,6-dienes triggered by C-H activation of the aldehyde group was obtained with comparable results.[43] This work was reported after the publication of the cycloisomerisation of 1,6-dienes that will be discussed in the next chapter.[44]



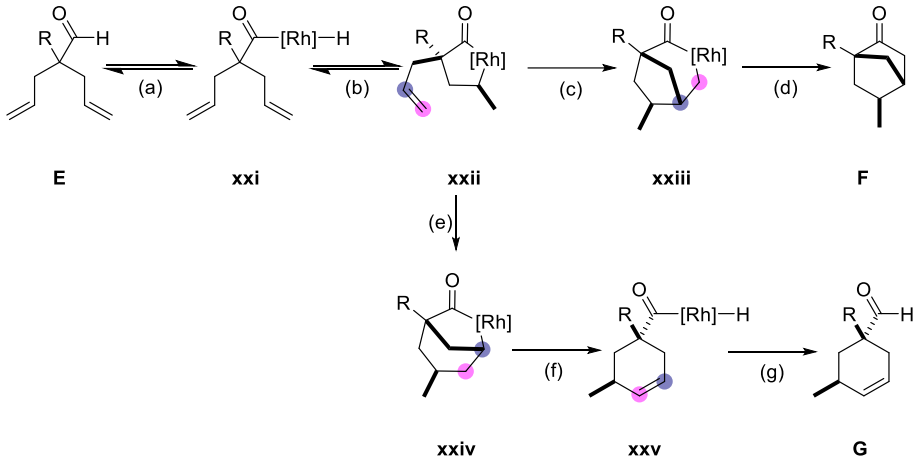
*Scheme 1.41: Rhodium-catalysed cycloisomerisation of 1,6-dienes to form norbornanone **60**.*

Further studies showed that cyclohexenes can also be obtained under the specific catalytic conditions (Scheme 1.42).[45] When using the chiral bidentate phosphine (*R*)-DTBM-SDP as a ligand, diene **61** was converted into cyclohexene **62** in excellent yield and enantiomeric excess. This is the first described cycloisomerisation of 1,6-dienes that affords a methyl-substituted cyclohexene. Both the endocyclic olefin and the carbonyl group of the group can be easily functionalised.



*Scheme 1.42: Rhodium-catalysed cycloisomerisation of 1,6-dienes to form cyclohexene **62**.*

A divergent mechanism was proposed for the cycloisomerisation of both the norbornanone and the cyclohexene products (Scheme 1.43).[45]



Scheme 1.43: Mechanism of the rhodium-catalysed cycloisomerisation of 1,6-dienes triggered by C-H activation to form the norbornanone and the cyclohexene products described by Dong.

In the first stage of the reaction, substrate **E** undergoes C-H activation (a). Then, a first migratory insertion of one olefin moiety forms intermediate **xxii**. When using BzDPPB as the ligand, the second olefin moiety is inserted in a 1,2-fashion (c) to form intermediate **xxiii**. After reductive elimination (d), norbornanone **F** is obtained. In contrast, the 2,1-insertion of the olefin moiety in intermediate **xxii** produces the seven-membered ring metallacycle **xxiv** which can undergo β-hydride elimination (f) to obtain intermediate **xxv**. The final reductive elimination forms the aldehyde **G**.

1.4 Conclusion

To conclude, the cycloisomerisation of dienes is still a growing field. Its ideal atom economy and the usually accessible starting materials make it the perfect reaction for potential application in the total

synthesis of pharmaceutical and natural products. The strong understanding of the main reaction mechanisms; oxidative cyclometallation and intermolecular addition of a metal-hydride, has enabled the researchers to control the product selectivity. What is more, it has made possible to switch from one product to the other by only changing the reaction conditions. Nevertheless, the observed poor diastereoselectivity of the reaction as a consequence of the undistinguishable faces of the intermediates is still an issue to be solved. The elongation of the carbon chain by substituting the terminal carbon of the alkene has presented as well some other problems. The similar features of the two alkene moieties prevent them to be differentiated affecting negatively to the product selectivity. As shown by Murai, Dong and Aïssa, the introduction of directing groups in the substrate and, therefore, the facilitation of the C-H activation process might be the solution to these issues.

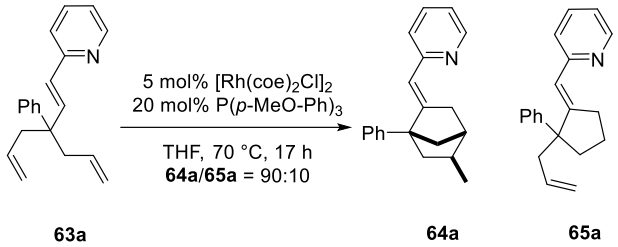
1.5. Aims of the thesis

Following the ideas described in this chapter, the first diastereoselective domino cycloisomerisation of substituted 1,6-dienes is presented herein. An extensive understanding of the reaction mechanism has been achieved by deuterium-labelling and monitoring experiments. The main objective of the project is to develop a new reaction that enables us to create carbocyclic structures with high degree of complexity in a selective fashion by the cycloisomerisation of substituted 1,6-dienes. It also pursues to comprehend the implications of having different substituents in the original molecule. Finally, it seeks to understand the cycloisomerisation factors that need to be controlled in order to have complete diastereoselectivity and product selectivity, so that the reaction could then be applied in organic synthesis. In order to accomplish this last objective, further studies should be done. Contrary to most of the examples presented in this chapter, long syntheses were required to obtain the initial substrates. This does not agree with the excellent atom economy of the cycloisomerisation process shown in the previous sections. However, this project does not claim to be atomically economic, but it seeks to understand this specific cycloisomerisation. Overall, it examines the limitations of the catalytic system.

Chapter 2 : Cycloisomerisation of vinylpyridine substituted 1,6-dienes triggered by C-H activation

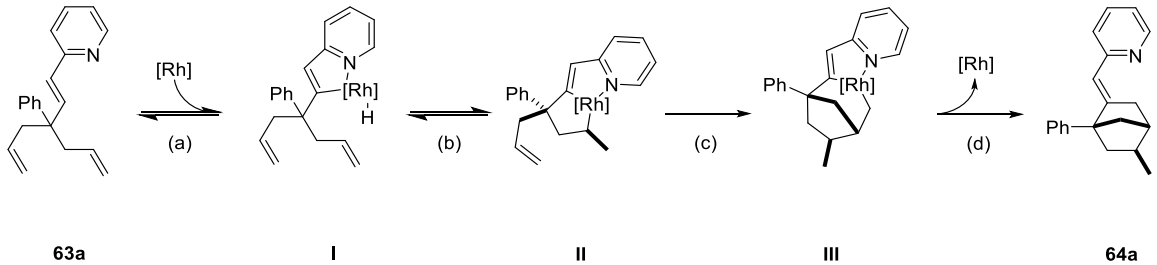
2.1 Introduction

In 2014, the Aïssa group reported the highly stereoselective cycloisomerisation of 1,6-heptadienes triggered by C-H activation of an olefin.[44] Treatment of substrate **63a** with a rhodium catalyst afforded a mixture of norbornane **64a** and cyclopentane **65a** in a 9:1 ratio (Scheme 2.1).



Scheme 2.1: Previous work by the group. Rhodium-catalysed cycloisomerisation of symmetric phenyl vinylpyridine substituted 1,6-dienes.

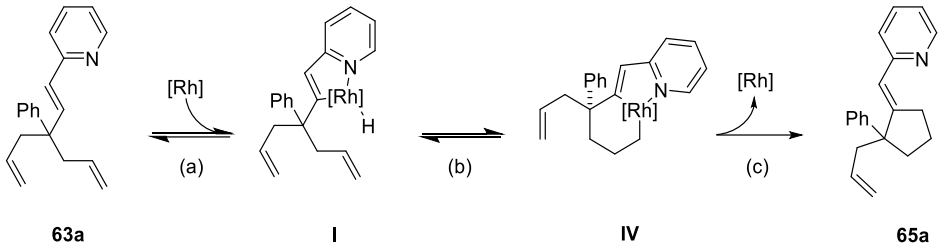
This transformation produced a new molecule with great complexity from the prochiral substrate **63a**. In fact, **64a** was obtained as only one diastereomer while three very well defined stereocentres were formed. The formation of **64a** can be explained by the following reaction mechanism (Scheme 2.2).



*Scheme 2.2: Proposed mechanism of the rhodium-catalysed cycloisomerisation of substrate **63a** to form substituted norbornane **64a**.*

In the first step, the active catalyst coordinates to the nitrogen atom of the pyridine moiety. This first coordination positions the catalyst next to the vinylic C-H bond which undergoes oxidative addition (a). At this stage of the reaction, a first migratory insertion (b) occurs to form the five-membered

metallacycle **II** in a diastereoselective fashion. Following the empirical rules about cyclisation reported by Baldwin in 1976, this intermediate was expected, as it can be described as a favoured 5-E*xo-Trig* cyclisation.[46] Then, the second migratory insertion (c) of the alkene affords intermediate **III**. Finally, the reductive elimination (d) provides compound **64a**. Unfortunately, the undesired product **65a** was also obtained and the mixture could not be separated by common methods. This compound, analogue to those described by Murai in the mid-90s (Section 1.3.1), is the product of a 1,2-insertion (Scheme 2.3).[38]



*Scheme 2.3: Proposed mechanism of the rhodium-catalysed cycloisomerisation of substrate **63a** to form cyclopentane **65a**.*

As described previously, the rhodium catalyst first coordinates to the molecule through the nitrogen atom and forms **I** after C-H activation (a). Then, a 1,2-migratory insertion (b) takes place to give the six-membered metallacycle **IV** which provides the five-membered ring **65a** after reductive elimination (c). Intermediate **IV** is the consequence of the favoured 6-*Endo-Trig* cyclisation.[46] However, in a competing environment of 5-*Exo-Trig vs*. 6-*Endo-Trig*, the latest is usually less favoured, which could explain the difference in product ratio. In order to improve the product selectivity towards the formation of **64a**, some methods were tested. An increase of the reaction temperature from 70 to 90 °C enhanced the selectivity towards cyclopentane **65a**. But, the addition of $^{-}BF_4$ (as $AgBF_4$) to form a cationic catalyst *in situ* by halide abstraction increased the selectivity up to 98:2 for norbornane **64a**. Other sources of cationic rhodium were less effective. The final optimised conditions are shown in Figure 2.1 and were applied to several examples.

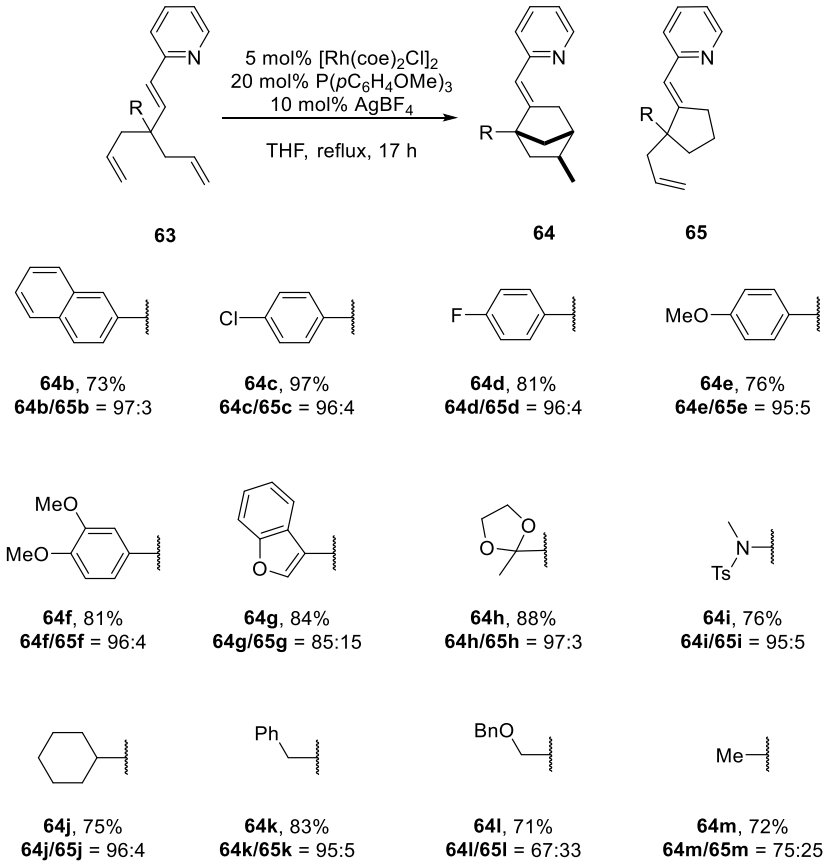
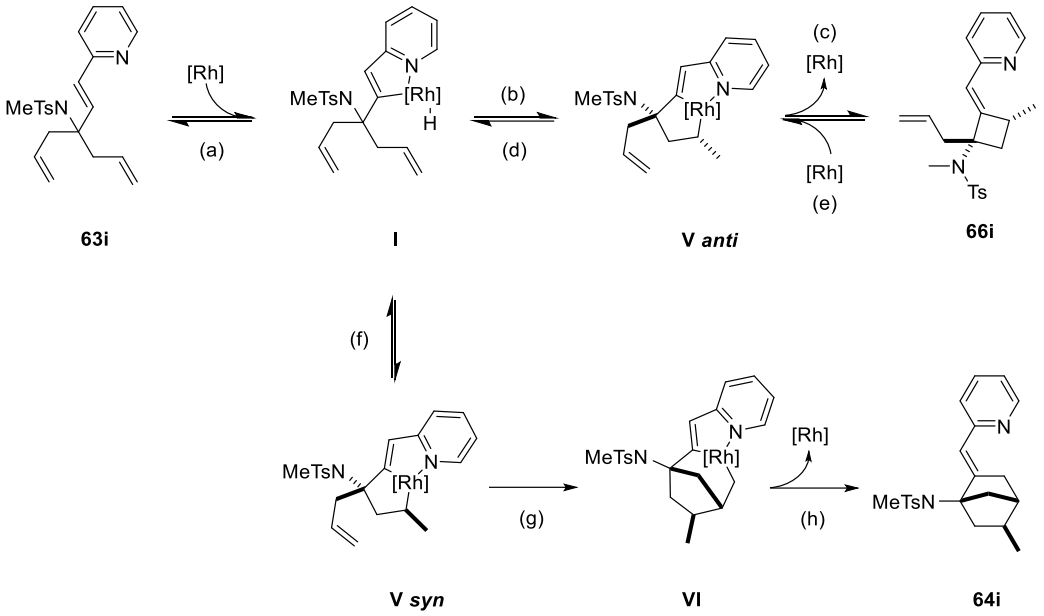


*Figure 2.1: Previous work by the group showed the efficient cycloisomerisation of substrates **63b** to **63m**.*

In all examples, the products were obtained in good to excellent yields and diastereomeric ratio greater than 20:1. Neither electron-donating (**63e**, **63f**) nor electron-withdrawing (**63c** and **63d**) substituents on the phenyl ring affected the product selectivity. Reaction with large substituents such as cyclohexyl (**63j**), acetal (**63h**), tosyl amine (**63i**) and benzyl (**63k**) provided the desired product **63** in product selectivities over 95:5. However, less bulky substituents such as a benzyl ether (**63l**) or a methyl group (**63m**) reduced the product selectivity to around 3:1. This suggests that the Thorpe-Ingold effect accelerates the second migratory insertion from **II** to **III**.[17] The decreased selectivity observed with the bulky benzofuran substituent (**63g**) indicates that electronic effects might also play a small role in the reaction.

The excellent diastereoselectivity could be further explained when a four-membered ring intermediate (**66i**) was isolated (Scheme 2.4).



*Scheme 2.4: Proposed mechanism for the rhodium-catalysed cycloisomerisation of diene **63i** to form the four-membered ring **66i** and the substituted norbornane **64i**.*

In this case, after the oxidative addition (a), the 2,1-migratory insertion of the alkene moiety (b) produces the stereoisomer **V *anti***. In this intermediate, the allyl moiety and the methyl group are in *anti* which prevents the second migratory insertion from occurring, because the allyl moiety is far from the Rh centre (Figure 2.2, b). Thus, the reaction can only undergo the reductive elimination (c). Nevertheless, all the steps in the process are reversible. Hence, product **66i** can then undergo a C-C activation (e) followed by β-hydride elimination (d) to form the intermediate **I**. Then, this intermediate can cycloisomerise into norbornane **64i** by forming the intermediates **V *syn*** and **VI**. The Rhodium centre is more accessible for the allyl in the **V *syn*** intermediate, therefore the 1,2-insertion can take place and intermediate **VI** can be formed (Figure 2.2, a). It is noteworthy that the first migratory insertion is not a diastereoselective step and that the *anti* intermediate is formed. This is probably because the formation of both **V *syn*** and **V *anti*** corresponds to a favoured 5-*Exo*-*Trig* cyclisation.[46] However, the reversibility of the process explains the excellent diastereoselectivity observed in the reaction.

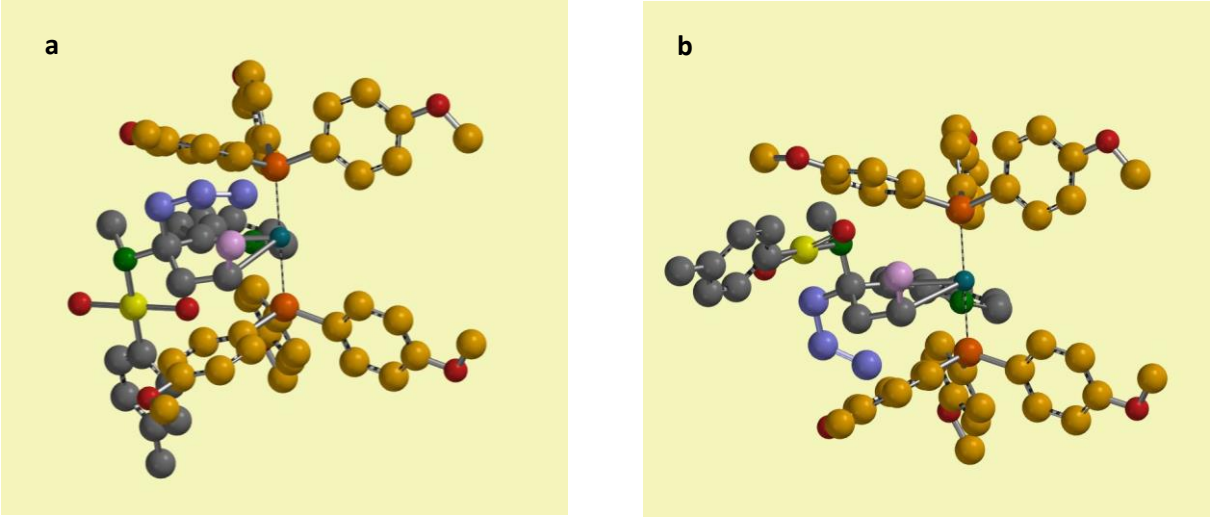


*Figure 2.2: Proposed 3D structures of intermediates **V**. The two phosphines expected to be connected to the Rhodium are highlighted in orange. The structures were designed with Spartan '16. a) Intermediate **V syn**, the Rhodium centre (blue) is accessible to the allyl moiety (purple) which is in syn to the methyl (pink). b) Intermediate **V anti**, the allyl moiety (purple) is too far from the Rhodium centre (blue) for the second migratory insertion to take place.*

2.2 Cycloisomerisation of substituted 1,6-dienes

After all these results were brought to light, the goal was to study the influence of a substitution on the reaction. For that purpose, some substituted 1,6-dienes were synthesised and tested. The effect of the different substitutions could provide us some insights on the reaction mechanism.

2.2.1 Synthesis of substrates 66a to 66d

In order to study the effect of the substitution on the reaction, four methyl substituted 1,6-dienes (**67a-d**) were synthesised (Figure 2.3).

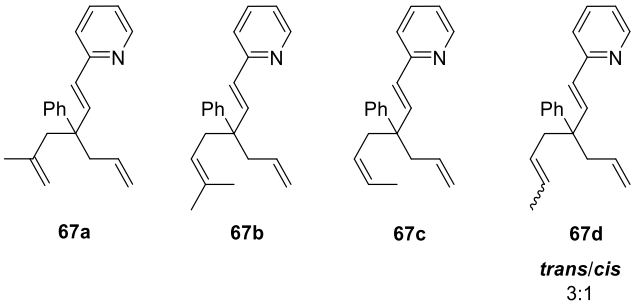
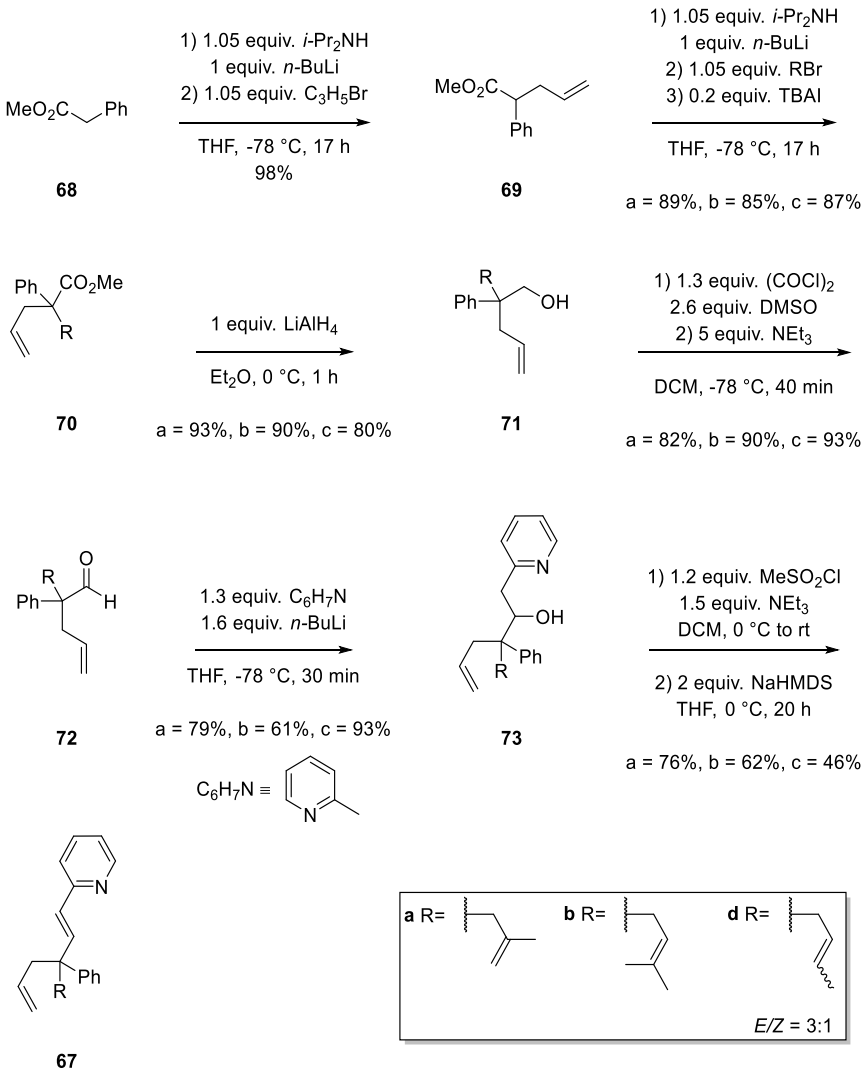


*Figure 2.3: Methyl substituted 1,6-dienes **67a** to **67d**.*

Methyl substitution was chosen because it is synthetically simple. However, other substituents were planned to be introduced depending on the results given by these substrates. The substrates **67a**, **67b**

and **67d** were synthesised in 7 steps following the procedure previously optimised by the group (Scheme 2.5).[43] The substrate **67d** was synthesised originally as a mixture of *trans* and *cis* regioisomers in an approximately 3:1 ratio.

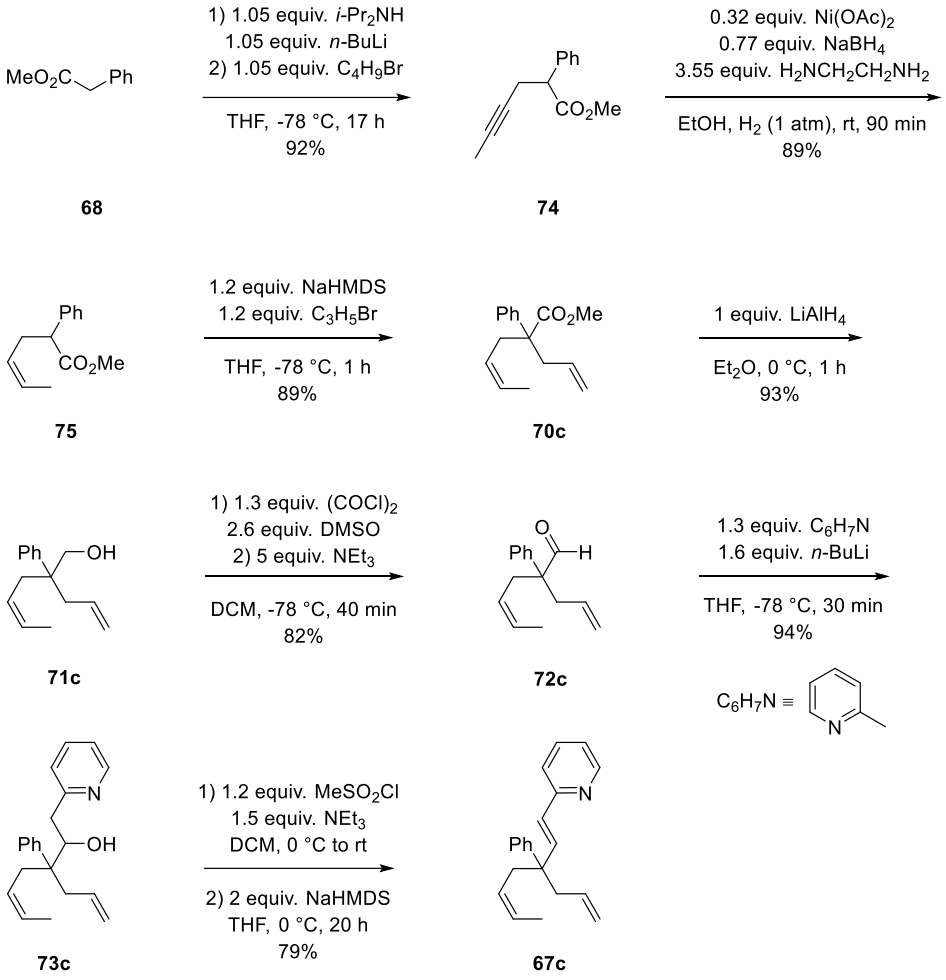


*Scheme 2.5: Synthesis of substrates **67a**, **67b** and **67d**.*

Methyl phenyl acetate **68** was allylated using allyl bromide as the electrophile in excellent yield. A second allylation introduced the substituted alkene to form **70** in good yields. Then, the ester moiety was reduced to the alcohol with $LiAlH_4$ in around one hour with very good yields. Intermediate **71** was oxidised to the aldehyde by a Swern reaction and the corresponding intermediate **72** was reacted with α-lithiated methylpyridine to form the two diastereoisomers of the secondary alcohol **73** in high yields. Although these two isomers could be separated, only a fast filtration to remove the impurities was

done. Intermediate **73** was then mesylated and then allowed to undergo elimination by treatment with 2 equivalents of NaHMDS to provide the final substrate **67** in moderate to good yields.

Although monosubstitution on the terminal carbon of the alkene was already covered by substrate **67d**, it was decided to synthesise pure *cis* substituted substrate **677c** in order to see the influence of the configuration of the substrate (Scheme 2.6).



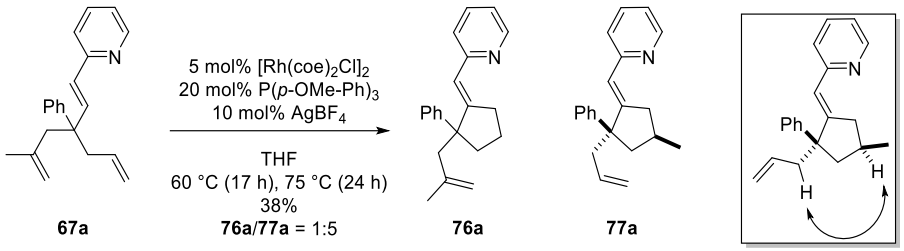
*Scheme 2.6: Synthesis of substrate **67c**.*

Propargylation was carried out instead of allylation in the first step of the synthetic path. Then, colloidal P-2 Nickel was formed *in situ* by reduction of the nickel acetate which catalysed the reduction of alkyne **74** into the *cis* olefin **75** in excellent yields and stereoselectivity.[47-49] Addition of ethylenediamine avoids over reduction by the competitive binding of the catalyst vacant sites.[50] The unsubstituted allyl group was then introduced by treating the ester **75** with NaHMDS and allyl bromide, and intermediate **70c** was obtained in good to excellent yields. The next steps are identical to those

that have been previously described. First, the ester **70c** was reduced to the alcohol **71c**, which was transformed into the aldehyde **72c** by a Swern oxidation. At that stage, α-lithiated methylpyridine was introduced to form the secondary alcohol **73c** which provided the desired vinylpyridine substrate **67c** after mesylation and elimination in good yields.

2.2.2 Results for the cycloisomerisation of substrates 67a-67d.

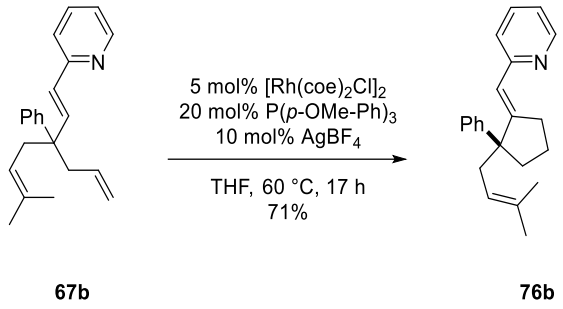
Substrates **67a** and **67b** showed very poor conversion after 17 hours at 60 °C (Scheme 2.7). Hence, the reaction was then tested at either 75 °C or 90 °C. As expected, the conversion improved, but the product of the 1,2-migratory insertion was mostly observed.



*Scheme 2.7: Cycloisomerisation of substrate **67a**. The selective NOESY showed the conformation of **77a**.*

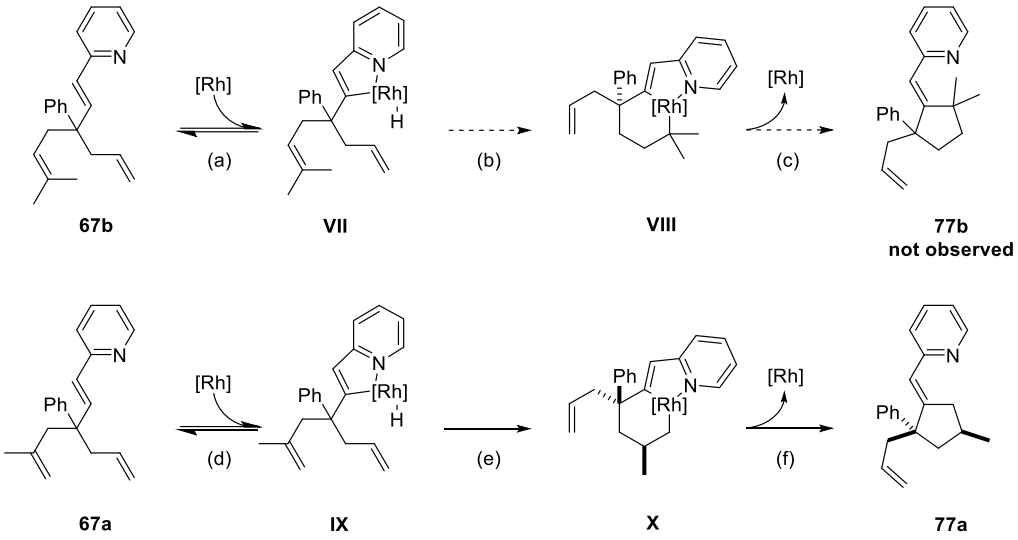
The internally substituted allyl **67a** afforded two different cyclopentanes in a 5:1 ratio. As it was expected, the product of the 1,2-migratory insertion of the unsubstituted alkene **76a** was obtained under the reaction conditions. However, the 1,2-migratory insertion of the substituted alkene moiety afforded *anti* **77a** as the major product. The relative configuration was proven by 2D NOESY, selective NOESY and complementary NMR experiments.

When the substrate **67b** was treated at 60 °C only the cyclopentane **76b** was obtained (Scheme 2.8). However, when the temperature was increased to 90 °C, the reaction almost reached completion but a complex mixture of products was observed.



*Scheme 2.8: Cycloisomerisation of substrate **67b**.*

The diverse results for these two substrates can be explained with the difference in steric hindrance in the intermediates of the reaction (Scheme 2.9).

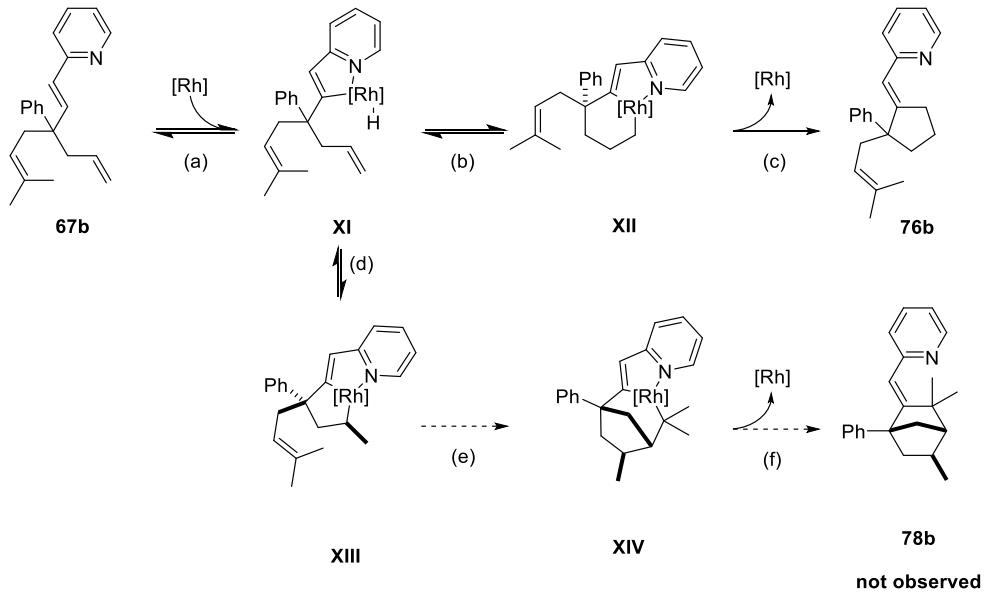


*Scheme 2.9: Proposed mechanistic comparison of the formation of cyclopentanes **77a** and **77b** (not observed).*

The hypothesis is that after C-H activation (a) and 1,2-migratory insertion (b), the six-membered metallacycle **VIII** would be sterically hindered. The formation of this intermediate is likely to be prevented by the steric repulsion between the two methyl groups and the ligands around the metal. Therefore, product **77b** cannot be formed. On the contrary, the internal substitution on **67a** does not prevent the rhodium catalyst from being inserted (e) and after reductive elimination (f), product **77a** is obtained. The small steric difference between the two alkene moieties in substrate **67a** can explain the lack of regioselectivity and the formation of a mixture of **76a** and **77a**.

Although the results afforded by these two substrates were not promising, they could already provide some insights about the reaction. In both cases, the substitution of one olefin decreased the reaction

rate as compared to the reaction of unsubstituted 1,6-diene **63a**. The steric hindrance introduced by the disubstitution in **67b** might prevent the second migratory insertion to occur and yield the desired norbornane (Scheme 2.10).



*Scheme 2.10: Proposed mechanism of the formation of cyclopentane **76b** and norbornane **78b** (not observed).*

The next step of the study was to test the 1,6-octadienes **67c** and **67d**. The proposed hypothesis suggested that the cycloisomerisation of substrate **67c** would afford the *syn,syn* norbornane **78** where the two methyls are in the same plane as the methylene bridge, while the substrate **67d** would be preferentially transformed into the *syn,anti* isomer where the methyl in *alpha* to the vinylpyridine is in the opposite direction (Figure 2.4).

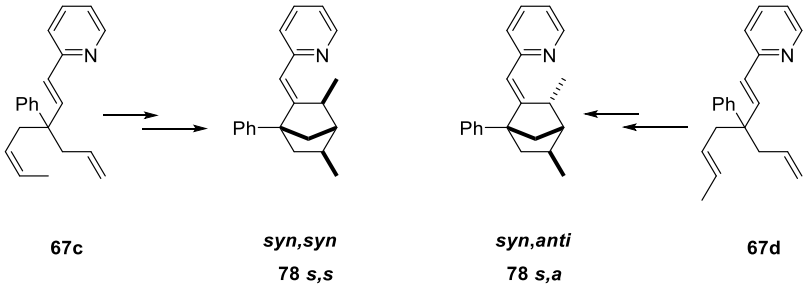
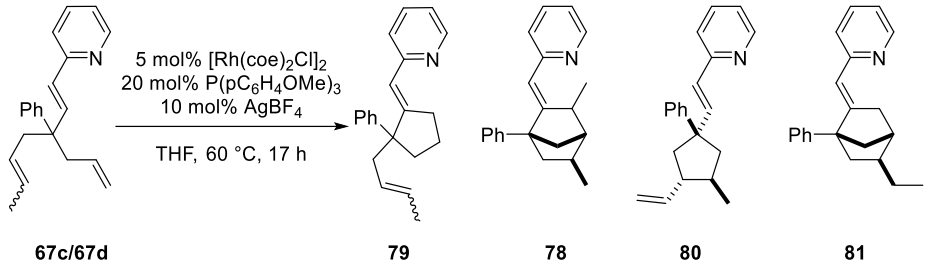


*Figure 2.4: Hypothesised transformation of **67c** and **67d** into **78 s,s** and **78 s,a** respectively*

When **67c** and **66d** were allowed to react under the optimised conditions, the full conversion was reached after 17 hours (Table 2.1).

*Table 2.1: Results of the cycloisomerisation of substrates **67c** and **67d** under the conditions previously optimised by the group.*



Entry	Isomer	79 (*cis*/*trans*)	78 (*s,s*/*s,a*)	80	81
1*	**67d (E/Z 3:1)**	20 (5:15)	26 (20:6)	52	2
2	**67c (E/Z 0:1)**	20 (12:8)	15 (12:3)	52 (38%)[a]	13

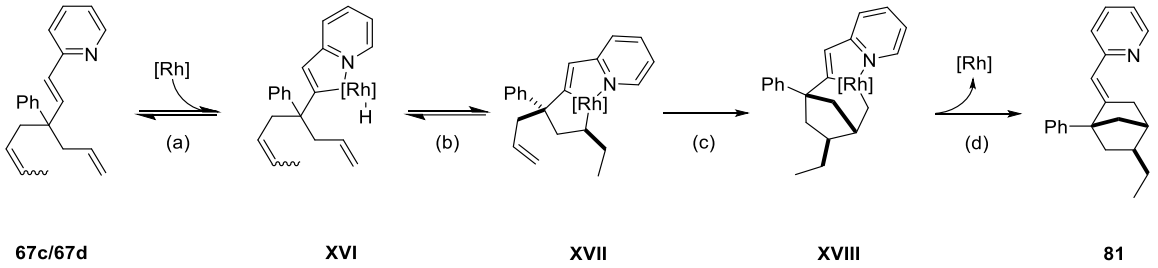
*Standard: 3,5-dimethoxybenzene. a) Isolated yield is between parentheses.

Compound **67d** was converted into a mixture of products in 77% yield, in a reaction carried out by Daniel J. Tetlow (Entry 1). Unfortunately, the excellent product selectivity obtained with prochiral substrates **63** was not reproduced here, as the cyclopentane **79** was obtained in 20% yield. The regioisomeric ratio was 3:1, similar to the one initially observed for the starting material **67d**. However, norbornane **78** was afforded as a mixture of isomers in a 3:1 ratio, *syn*,*syn* **78** being the predominant isomer. Surprisingly, a new cyclopentane **80** was obtained as the major product. Reaction with substrate **67c** afforded a similar mixture (Entry 2). As expected, the norbornane **78** ***s,s*** and the cyclopentane **79** were observed. Even if starting from pure *cis* substrate **67c**, the product of 1,2-migratory insertion **79** was obtained as a mixture of *E-Z* regioisomers in an approximately 1.5:1 ratio. This indicates that isomerisation of the internal alkene occurred during the reaction, while the terminal alkene remained apparently untouched. Compound **78** was also obtained as a mixture of isomers. The probable isomerisation of the starting material can explain the poor diastereoselectivity observed for this product. Once again, the new cylopentane **80** was obtained as the major product. It is noteworthy to report that both **67c** and **67d** afforded the same very well defined diastereoisomer **80** which evidences the high diastereoselectivity of the reaction for this product. Nevertheless, the mechanism of its formation was still an open question.

As discussed in the previous chapter, 1,6-diene can lead to this type of product either by oxidative cyclometallation or by reversible addition of metal-hydride. However, this is the first described

example where the allyl substituted cyclopentane is obtained in high diastereoselectivity. Few of these products were successfully isolated from the reaction carried out with **67c** (Entry 2). The polarity of the isomers is very similar and the separation of the products only afforded the clean products in very low yield. Fractions containing a mixture of products were also obtained.

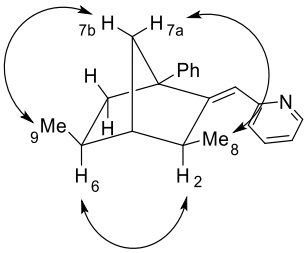
A fifth product was observed in small amount. Norbornane **81** is the product of two migratory insertions, where the most substituted alkene undergoes the first migratory insertion (b). The bulkiness provided by the substitution decelerates the first migratory insertion, favouring the less hindered alkene to react first (Scheme 2.11).



*Scheme 2.11: Proposed mechanism of the formation of norbornane **81**.*

2.2.3 Identification of products

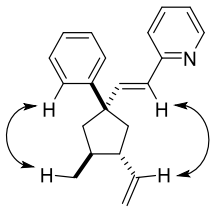
The stereochemistry for both **78** ***s,s*** and **80** was elucidated by NOESY and selective NOESY NMR experiments. In the norbornane **78** ***s,s***, the experiments show the correlations of the methyl groups 9 and 8 with the methylene protons H-7b and H-7a respectively, as well as between protons 6 and 2 (Figure 2.5).



78*s,s*

*Figure 2.5: Space correlations of norbornane **78 s,s** observed with NOESY and selective NOESY NMR experiments.*

For cyclopentane **80**, the phenyl protons correlated with the methyl, while the vinyl proton correlated with the alkene (Figure 2.6). That positioned the phenyl and the methyl on the same face of the molecule while the vinylpyridine and the alkene were in the opposite one.



80

*Figure 2.6: Space correlations of cyclopentane **80** observed with NOESY and selective NOESY NMR experiments.*

Norbornane **81** could be only isolated in a mixture with cyclopentane **79**. However, full characterisation was still possible. Several experiments including COSY, HSQC and HMBC were carried out to fully identify the norbornane **81** (Figure 2.7). The ethyl protons (9) as long as protons 2a and 2b were key to elucidate the structure. Unfortunately, a high peak of water overlaps with the signals of protons 9.

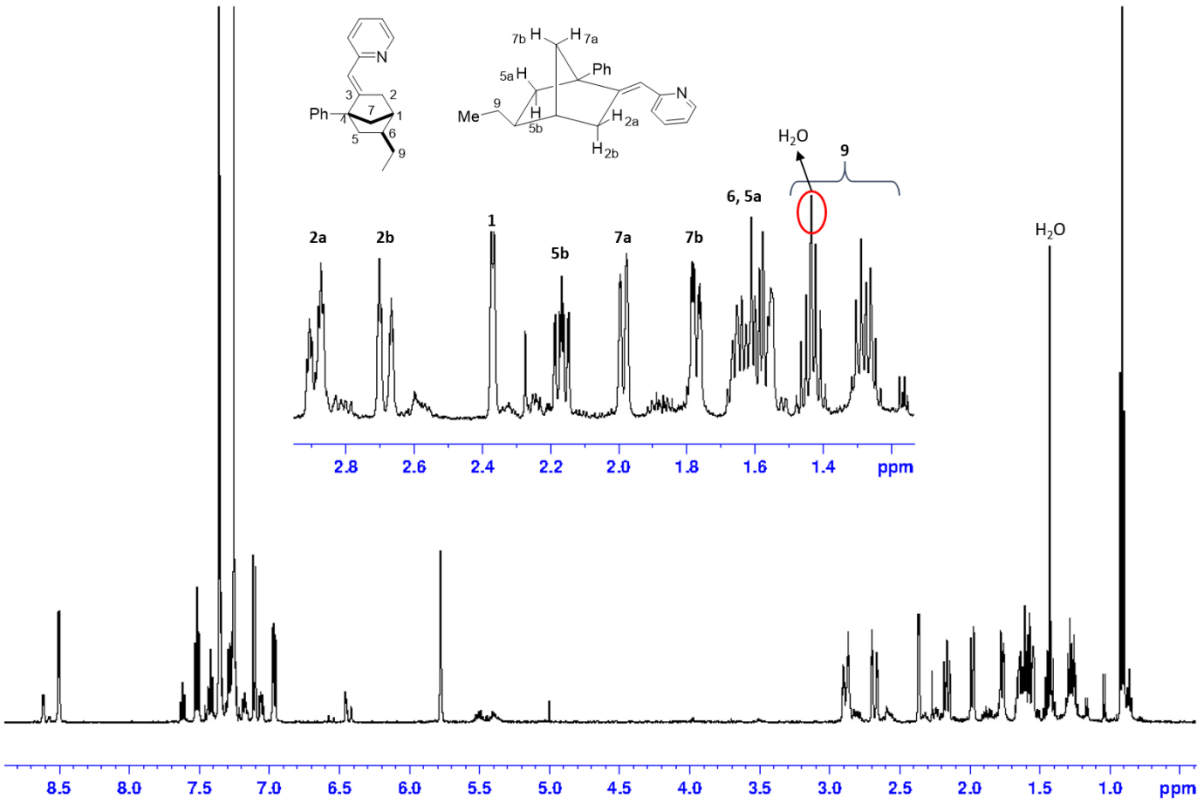


*Figure 2.7: ^{1}H NMR spectrum of norbornane **81** in a mixture with cyclopentane **79**.*

2.2.3.1 Identification of *syn,anti* norbornane 78 by the *gamma gauche* effect

In order to elucidate the stereochemistry of product **78 *s,a***, some NMR experiments were carried out. Unfortunately, the most characteristic ^{1}H NMR peaks overlapped in the spectrum (Figure 2.8).

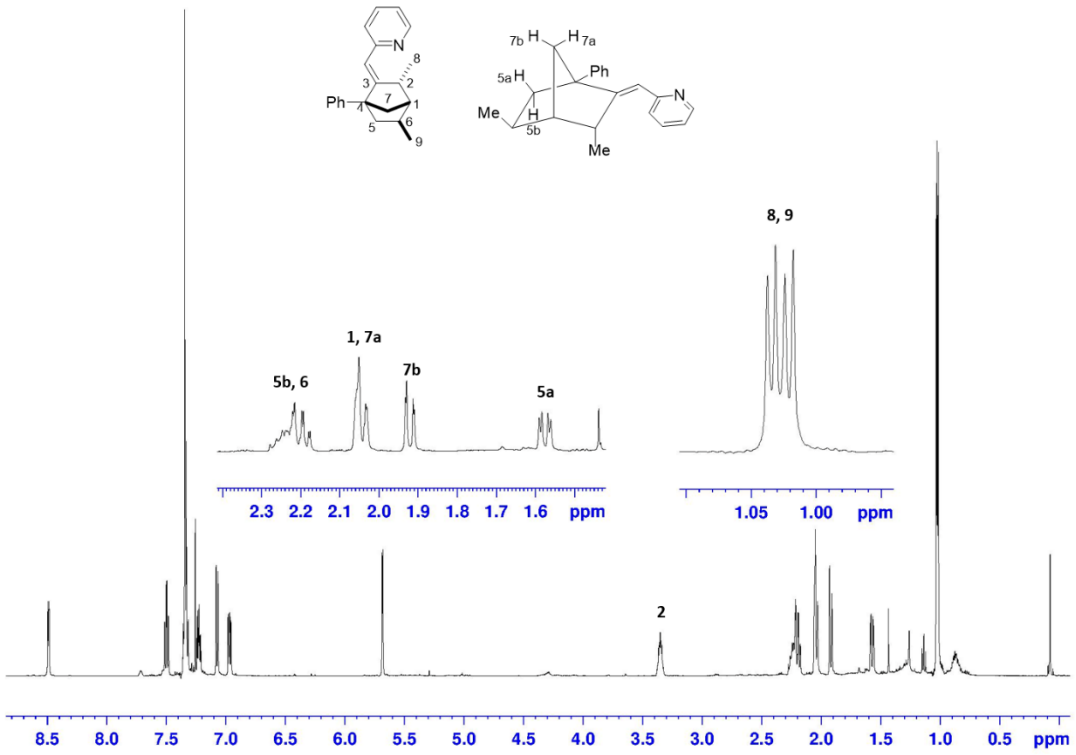
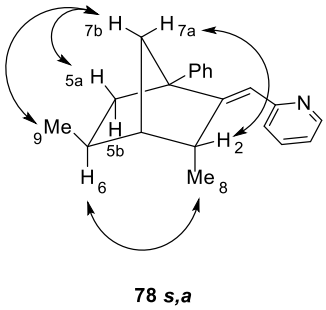


*Figure 2.8: ^{1}H NMR spectrum of norbornane **78 s,a**.*

Methyl groups 8 and 9 appeared as two contiguous doublets. While protons 1 and 7a overlapped as an undefined multiplet. Finally, methylene proton 5b and methine proton 6 also appeared overlapped. The NOESY spectrum could be expected to indicate a correlation between proton 2 and 7a, proton 7b and methyl 9 as well as between methyl 8 and proton 6 and protons 7b and 5a (Figure 2.9).



78 *s,a*

*Figure 2.9: Expected space correlations of norbornane **78 s,a**.*

However, the overlap of the signals prevented us from reaching unambiguous conclusions about the stereochemistry.

The main concern was to differentiate the methyl groups 8 and 9. A selective NOESY experiment confirmed that the doublets of the methyl groups were overlapped and not contiguously placed (Figure 2.10, a). A further study on the NMR technique showed that the overlapped peaks could be separated under special circumstances. For that purpose, product **78 *s,a*** was analysed by ^{1}H NMR under different conditions (Figure 2.10, b).

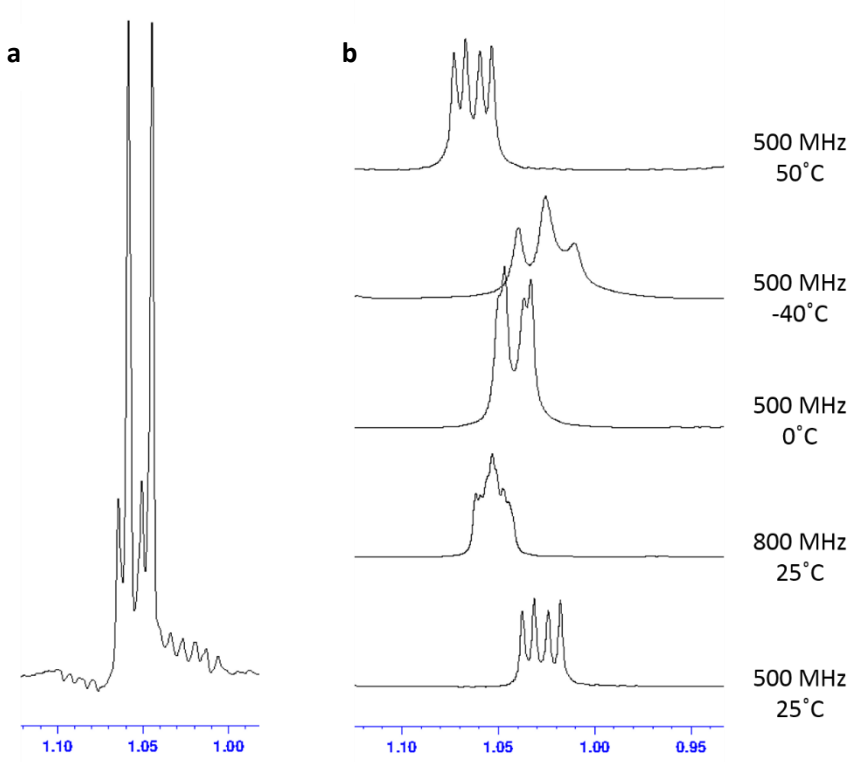


*Figure 2.10: a) Detail of the selective NOESY spectrum of norbornane **78 s,a** that shows the overlapping of the two methyl signals. b) Detail of the ^{1}H NMR spectrum of the methyls of norbornane **78 s,a** at different temperatures.*

The sample was measured in an 800 MHz NMR with poor results. Usually, the higher is the magnetic field, the better the resolution is. However, in this case, the methyl signals collapsed forming an undefined multiplet. Then, the sample was measured in a 500 Hz NMR at different temperatures. At low temperature, the molecule conformations can be blocked. This affects the chemical shifts by either shielding or deshielding the signals. There is no defined correlation between the temperature of the experiment and the shielding or the deshielding of the peaks. When the NMR experiment was carried out at 0 °C, the signals collapsed to form two overlapped doublets. When the temperature was lower down to -40 °C, the peak lost the resolution completely. Hence, it was decided to try the experiment at higher temperature. An increase of temperature facilitates the exchange between conformations and it homogenises the sample. In that case, the peaks should become more defined. Indeed, the two doublets became separated, but not enough to be completely assigned.

Therefore, in order to clearly distinguish the stereochemistry of product **78** ***s,a*** a new approach was attempted. As discussed previously, the elucidation of product **78** ***s,s*** was completed by the combination of several methods. Consequently, a broad comparison between the two products could provide the insights for the correct stereochemical assignment.

First of all, the carbon spectra was assigned unambiguously for both products (Figure 2.11 and Figure 2.12). HSQC, COSY, NOESY and selective NOESY experiments were carried out in order to unambiguously assign the peaks. The signals allowing to differentiate the two diastereoisomers appear on the aliphatic region only which is the one assigned in the following figures.

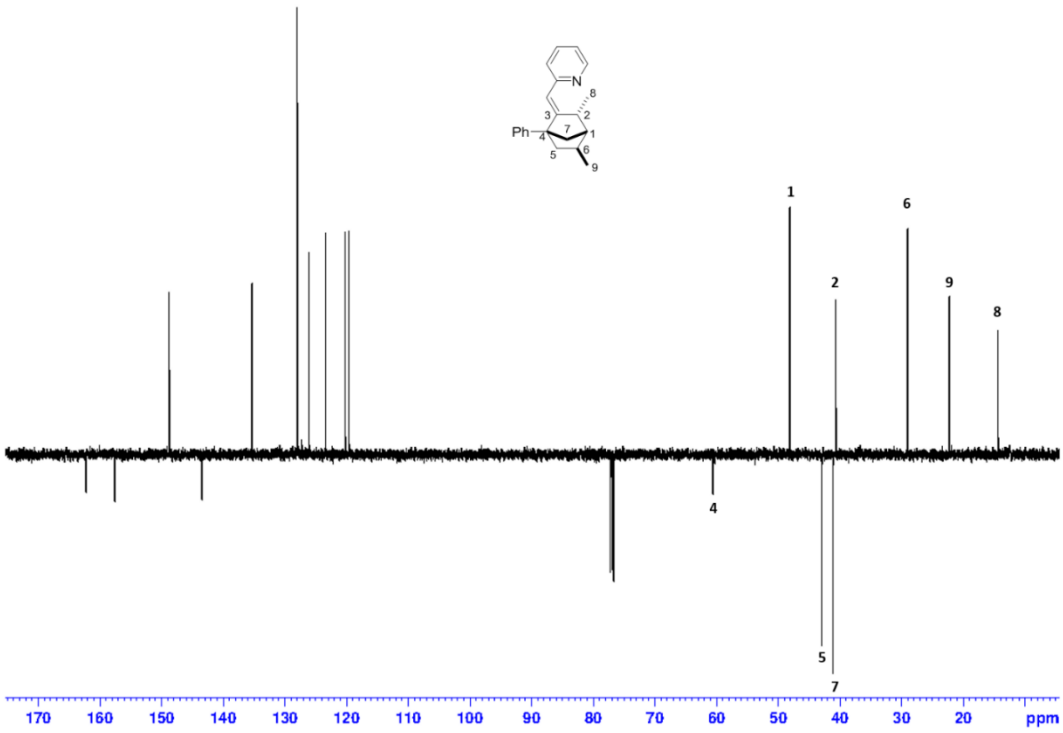


*Figure 2.11: ^{13}C APT spectrum of norbornane **78 s,a**.*

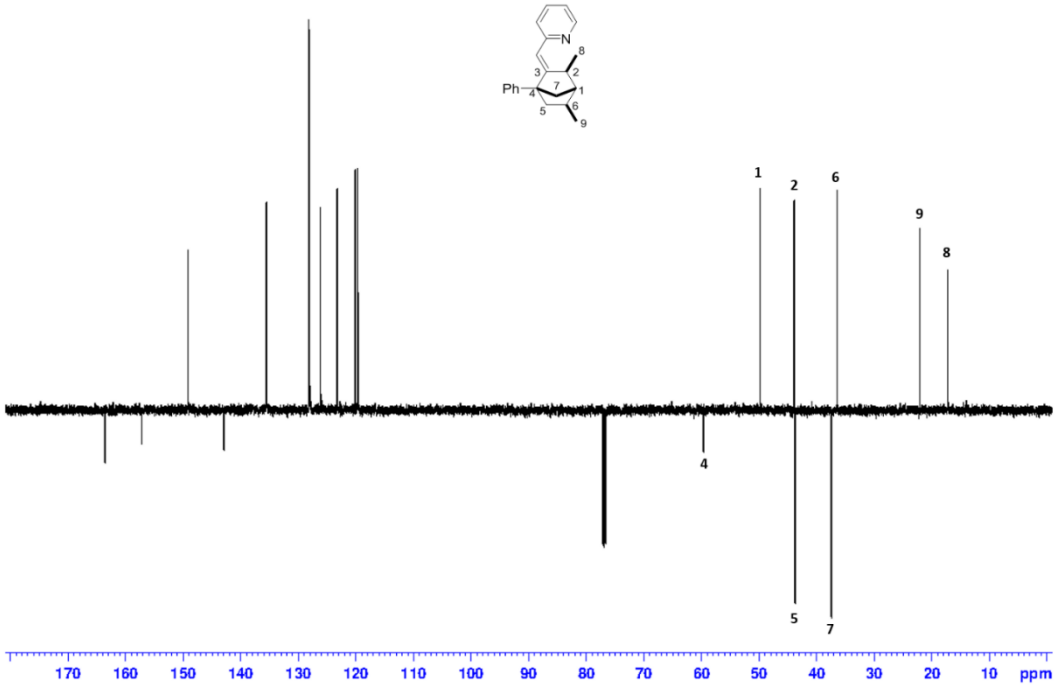
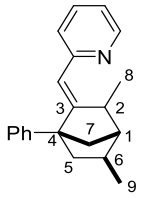
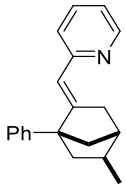


*Figure 2.12: ^{13}C APT spectrum of norbornane **78 s,s**.*

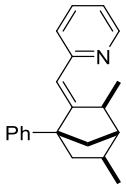
Comparison of Figure 2.11 and Figure 2.12 showed that both norbornanes present a similar pattern. However, the chemical shifts are clearly affected by the stereochemistry of the product. Table 2.2 summarises the most characteristic chemical shifts for products **78 *s,s*** and **78 *s,a***.

*Table 2.2: Comparison of the ^{13}C chemical shifts of norbornanes **64a**, **78 s,s** and **78 s,a**.*

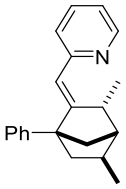




64a



78 *s,s*



78 *s,a*

	^{13}C chemical shift (ppm)			
Isomer	**C-6**	**C-7**	**C-8**	**C-9**
64a	42.6	41.2	----------	22.3
78 *s,s*	36.5	37.5	17.3	22.1
78 *s,a*	29.1	41.2	14.4	22.3

The effect of the methyl substitution on the chemical shift of the ^{13}C nuclei in a norbornane has been previously studied. In 2004, Kleinpeter and Seidl showed that the NMR spectra is directly related to the stereochemistry of the product.[51] They reported that the carbon nucleus in *gamma* to the substituent is further up field in the *endo* isomer compared to the *exo* isomer. The same tendency can be observed in norbornanes **78 *s,s*** and **78 *s,a*** (Table 2.3). Carbon nucleus 6, which is in *gamma* to methyl group 8, is shielded 7 ppm in the **78 *s,a*** isomer compare to norbornane **78 *s,s***. But, the same carbon nucleus is moved upfield if both *syn*,*syn* and *syn*,*anti* diastereoisomers are compared with the unsubstituted norbornane **64**. In contrast, C-7 is clearly downshifted 4 ppm in only the *syn*,*syn* diastereoisomer. Actually, a similar tendency was also reported by Kleinpeter and Seidl.[51] In that case, bridge carbon nucleus in the *endo* norbornane isomer was moved down field respect to the *exo* diastereoisomer. The chemical shift of the methyl 9 remains the same for all the three molecules. Some steric interactions are the responsible for the small shift in the methyl 8. As reported by Kleinpeter and Seidl, the steric hindrance between methylene 7 and methyl 8 in the *syn*,*syn* diastereoisomer moves the chemical shift of 8 to lower values.[51]

The tendency observed in the carbon NMR confirmed unambiguously the formation of *syn*,*anti* norbornane **78**. Moreover, this results could also be supported by the comparison of the ^{1}H NMR spectra (Figure 2.13)

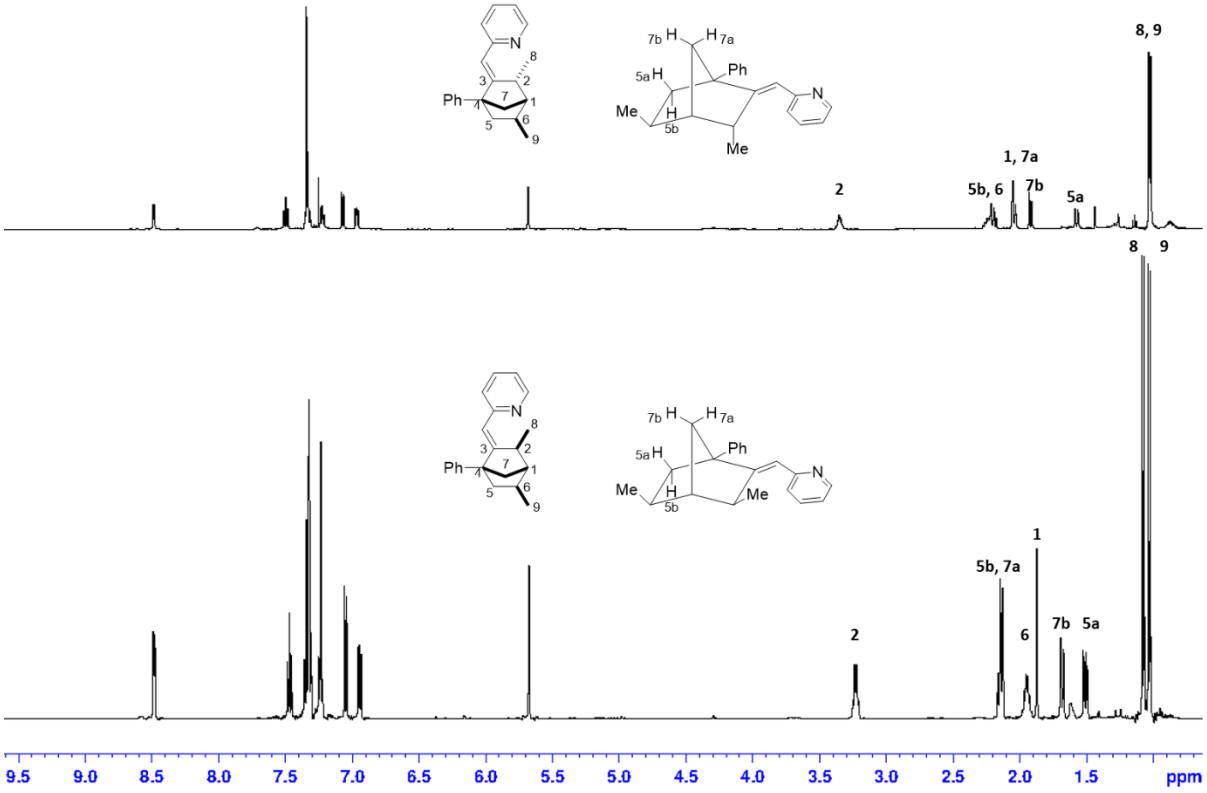
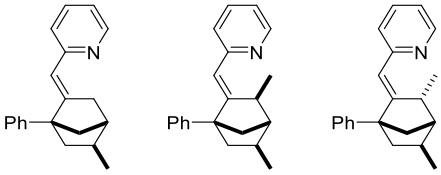
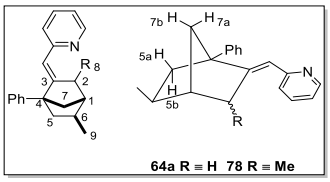


*Figure 2.13: Comparison of ^{1}H NMR spectra of norbornanes **78 s,a** and **78 s,s**. The aliphatic region in detail is shown in Figure 2.14.*

As in the carbon spectra previously discussed, ^{1}H NMR spectra presented similar patterns for both norbornanes. Nevertheless, very specific changes can also be observed. As shown in Figure 2.13, protons 7 are closer in the *syn,anti* isomer than in the *syn,syn* isomer. While proton 1 is more deshielded in the *syn*,*anti* isomer than in the *syn*,*syn* isomer. These and other trends are summarised in Table 2.3.

*Table 2.3: Comparison of the ^{1}H chemical shifts of norbornanes **64a**, **78 s,s** and **78 s,a**.*





	^{1}H chemical shift (ppm)					
Isomer	**H-1**	**H-2**	**H-7a**	**H-7b**	**H-8**	**H-9**
64a	2.23	2.67/2.86	1.97	1.82	----------	1.02
78 *s,s*	1.87	3.23	2.15	1.68	1.08	1.03
78 *s,a*	2.07	3.37	2.06	1.94	1.04	1.05

The ^{1}H NMR experiments were carried out in $CDCl_3$ at 25°C.

In 1992, Fisher and Gradwell assigned unambiguously the proton chemical shifts for 2-*endo*- and 2-*exo*-methylnorbornane.[52] They observed that H-7b, the furthest proton from the methyl substituent, is slightly deshielded for the *endo* isomer. This is due to the rigidity of the molecule that promotes a big W-coupling with H-2 which in norbornane derivatives it usually corresponds to ^{4}J = 2-3.5 Hz.[53-56] The same tendency can be observed for norbornanes **78 *s,s*** and **78 *s,a***. As described in Table 2.3, H-7b for product **78 *s,a*** is deshielded 0.26 ppm with respect to norbornane **78 *s,s***. A similar tendency can be also observed for proton 1. Comparing **78 *s,a*** and **78 *s,s***, this proton is slightly shifted upfield in norbornane **78 *s,s***. The steric interactions around H-1 can explain the difference in chemical shift for this situation. As described by Abraham *et al*. the protons closer to the incorporated substituent experience a shielding effect.[57] In order to compensate this effect, H-7a is moved downfield in what is known as the push-pull effect. The trend observed for proton 2 by Fisher and Gradwell is achieved in the concerned norbornane in a lesser extent. On the contrary, chemical shift for the methyl 8 is not affected by the stereochemistry of the reaction probably because of the effect of the other substituents present in the molecule.

Although both products have very similar patterns, it is noteworthy that some peaks in **78 *s,s*** and **78 *s,a*** present different multiplicity (Figure 2.14).

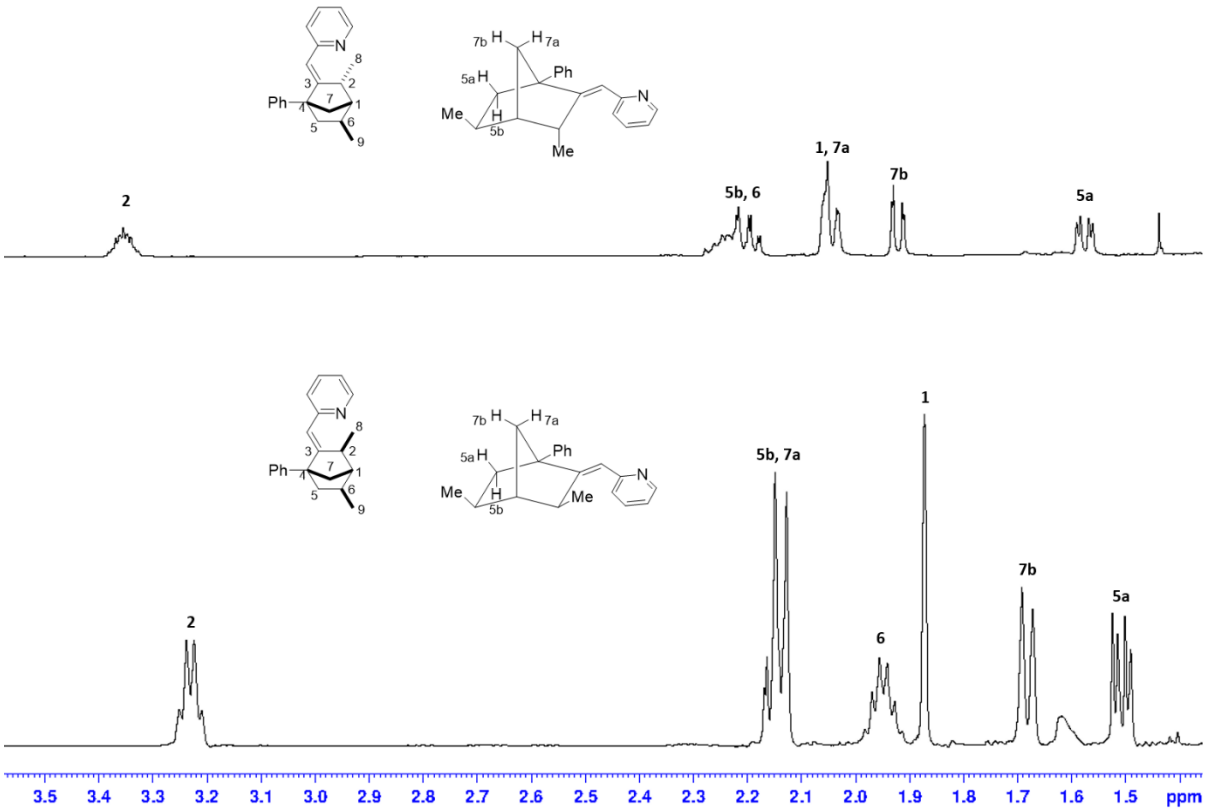


*Figure 2.14: Detail of the comparison of ^{1}H NMR spectra of norbornanes **78 s,a** and **78 s,s**. The full spectra are shown in Figure 2.13.*

For instance, proton 2 is observed as a quadruplet for the *syn*,*syn* diastereoisomer while it appears as a complicated multiplet for the *syn*,*anti* isomer. Apparently, proton 2 of norbornane **78 *s,s*** only couples with methyl 8 (^{3}J = 7.0 Hz). However, when improving the resolution by applying the Lorentz-Gaussian transformation[i], a long-range coupling can also be observed which would correspond to the coupling of H-2 with H-1 and H-7b (^{3,4}J = 2.2 Hz) as a false triplet.[58] The same technique applied on the ^{1}H NMR spectra of norbornane **78 *s,a*** shows the coupling of H-2 with H-8 (^{3}J = 6.9 Hz), H-1 (^{3}J = 4.6 Hz) and H-6 (^{4}J = 2.4 Hz)[i]. Two main differences can be extracted from these data. First, the long-range W-coupling between H-2 and H-7b is only possible in the *syn*,*syn* diastereoisomer and the coupling constant falls into the expected values.[53-56] Second, while for **78 *s,s***, $^{3}J_{H1\text{-}H2}$ = 2.2 Hz, the same coupling constant appears as 4.6 Hz for the *syn*,*anti* diastereoisomer. This phenomenon which was firstly described by Karplus in 1963, is due to the difference of the dihedral angle between H-1—C-1—C-2—H-2 on the two diastereoisomers.[59] A simulation of the three dimensional structures showed that protons 2 and 1

[i] Lorentz-Gauss transformation parameters: Line broadening (LB) = -2 Hz; Gaussian maximal position (GB) = 0.1

present a dihedral angle of around 75° in norbornane **78** ***s,s*** whilst **78** ***s,a*** presents a dihedral angle of 45°. This 30° difference already affects the proton-proton coupling. This effect is also clear for proton 1. The signal for proton 1 in the norbornane **78** ***s,s*** spectrum appears as a very sharp singlet. On the contrary, although it is overlapped with the signal of proton 7a, the short signal afforded for proton 1 in the **78** ***s,a*** spectrum indicates that some coupling is involved.

Hence, both the carbon and the proton NMR spectroscopic analysis prove the configuration of product **78** ***s,a*** by comparison with **78** ***s,s***.

2.3 Formation of cyclopentane 80

Formation of analogues of product **80** from 1,6-dienes in the presence of metal catalyst have always been observed and rationalised by two main mechanisms, namely oxidative cyclisation and addition of metal-hydride (Chapter 1). Therefore, the first hypothesis was that the vinylpyridine moiety might not be required for the reaction to happen. In order to verify this hypothesis, few substrates were synthesised (see section 6.2.15) and tested under the cycloisomerisation conditions (Figure 2.15).

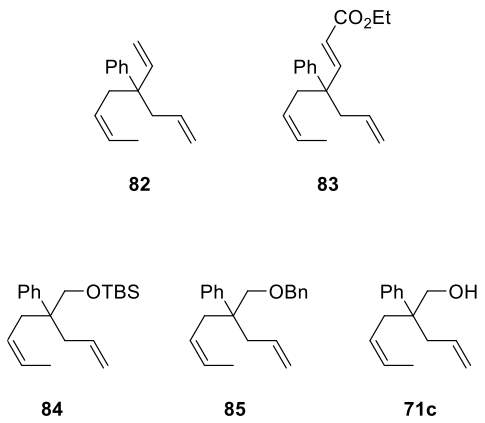


Figure 2.15: Substrates tested to understand the role of the vinylpyridine in the cycloisomerisation.

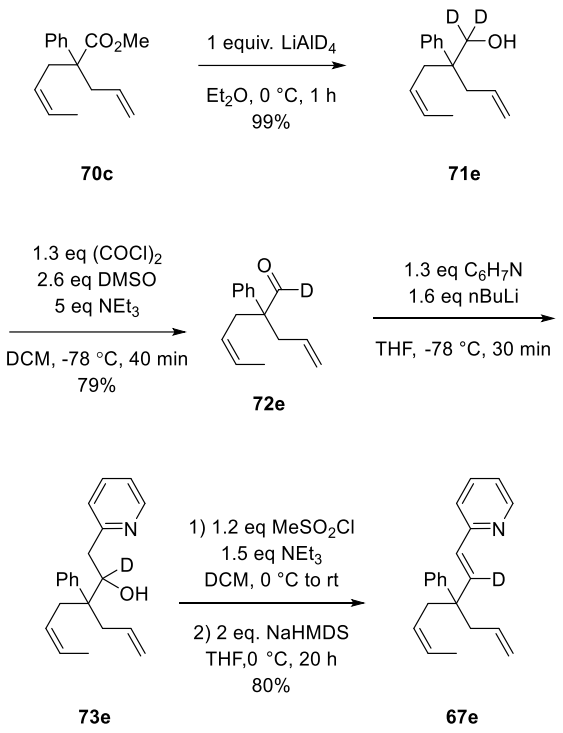
After 17 hours at 60°C, none of the substrates reacted as expected. Substrate **82** led to a complex mixture, but no cyclopentane was apparently formed. On the contrary, no reaction was observed for substrate **83**. Isomerisation of the internal double bond was seen for substrates **84** and **85** and transfer of the terminal olefin was observed for substrate **71c**. Hence, the results of these few experiments manifest that the vinylpyridine plays an essential role on the cycloisomerisation.

2.4 Deuterium-labelling studies

With those results in hand, it was decided to carry out some mechanistic studies. Therefore, **67e** was synthesised and deuterium incorporation was analysed.

2.4.1 Synthesis of deuterated 67e

Following the synthesis of substrate **66e** described in Scheme 2.6, the deuterium was incorporated during the reduction step by using 99% pure $LiAlD_4$ (Scheme 2.12).

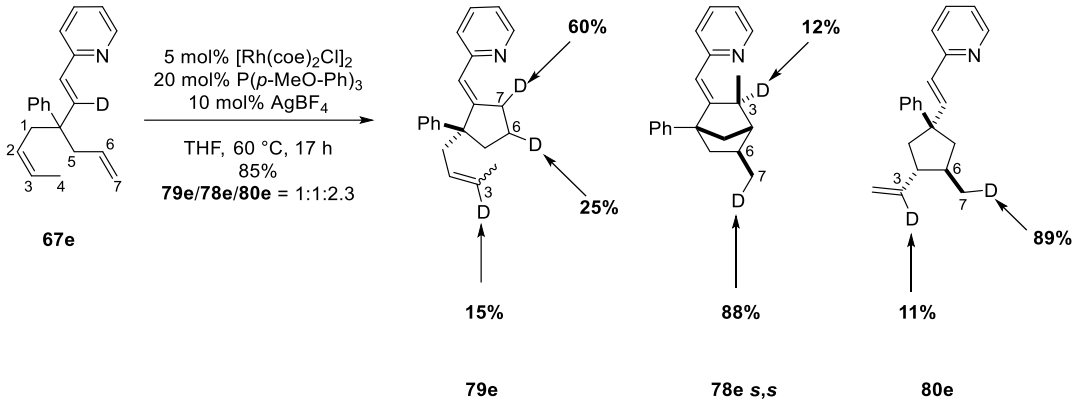


*Scheme 2.12: Synthesis of the deuterated substrate **67e**.*

Intermediate **71e** was obtained in excellent yield and with >99% deuterium incorporation on the vinlypyridine bond. The scrambling of the deuterium was not observed during these synthesis. Yields were comparable to those obtained in the synthesis of **67c** (Scheme 2.6).

2.4.2 Results

This reaction was carried out by Daniel J. Tetlow.

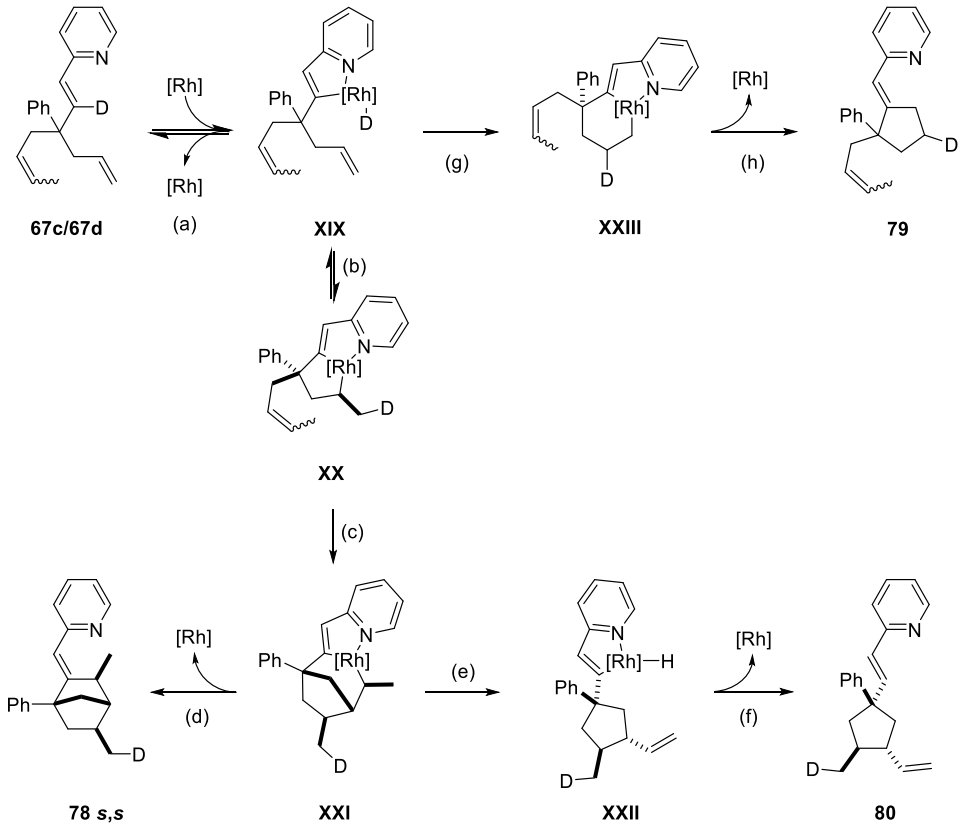


*Scheme 2.13: Cycloisomerisation of the deuterated substrate **67e**. The deuterium incorporation is expressed as the percentage of molecules that contain the deuterium in a given position and it was calculated by a combination of ^{1}H and ^{2}H NMR without using a standard.*

Under the optimised conditions, only traces of products **78e *s,a*** and **81** were observed. As their isolation was not feasible, only products **79e**, **78e *s,s*** and **80** were studied. The deuterium ratios were calculated by ^{1}H and ^{2}H NMR (Scheme 2.13). The results of these experiments showed that there was no solvent exchange, as 100% deuterium was incorporated into the products. The absence of deuterium scrambling indicates that the reaction is intramolecular. Product **79e** presented the deuterium atoms in three different positions (C-3, C-6 and C-7). As it was hypothesised before, the incorporation of deuterium at C-3 shows that the substituted alkene is isomerised during the reaction. In addition, the presence of deuterium on the carbon 7 agrees with the mechanism proposed previously. The 25% incorporation at C-6 could be explained by the reversibility of the first 2,1-migratory insertion. For **78e *s,s***, 88% deuterium was incorporated at the methyl position C-7. On the contrary, the remaining 12% was placed on carbon 3. Following the mechanism proposed earlier (Scheme 2.2), the terminal alkene would undergo first 2,1-migratory insertion, which explains the high deuterium incorporation on the methyl. Product **80e** presented an 89% incorporation at the methyl C-7, while only 11% was incorporated into the vinylic position (C-3). Moreover, products **78e *s,s*** and **80** both afforded approximately 90% incorporation at the methyl position which indicated that their mechanism was common at the first stage..

2.5 Proposed mechanism

The similar deuterium incorporation in both cyclopentane **80e** and **78e *s,s*** suggests that these two products share a common intermediate (Scheme 2.14).



*Scheme 2.14: Proposed mechanism for the formation of products **78 s,s**, **79** and **80** by cycloisomerisation of substrates **67c** and **67d**. The deuterium is transferred on the first migratory insertion. The reversibility of the elementary steps and the isomerisation of the internal alkene explains the deuterium incorporation in the products.*

This proposed mechanism agrees with the one previously suggested by the Aïssa group (Scheme 2.2). Initially, the nitrogen atom of the pyridine moiety coordinates the rhodium catalyst. The presence of the directing group is essential for the reaction to occur, as it supported by the experiments in section 2.3. Once the substrate is strongly coordinated, it undergoes C-H activation (a) to form intermediate **XIX**. The terminal alkene undergoes 2,1-migratory insertion (b) and the five-membered metallacycle **XX** is obtained. This step is reversible as the incorporation of deuterium in two different carbons of cyclopentane **79** can only be explained by this hypothesis. After the first 2,1-migratory insertion, the intermediate can experience a second migratory insertion (c) to the form seven-membered ring **XXI**. At this stage, the mechanism can bifurcate. On the one hand, the expected reductive elimination (d) generates norbornane **78**. On the other hand, a β-hydride elimination (e) can form the hydrido-

rhodium intermediate **XXII** that, after reductive C-H elimination, (f) provides cyclopentane **80**. The cycloisomerisation reaction under these conditions proved not only to be stereoselective, but also very regioselective, as the catalyst can differentiate the two alkenes present in the substrate. This statement can be evidenced by the fact that **81** was obtained only as a minor product. As previously mentioned, the cyclopentane **79** was observed as a mixture of diastereoisomers. The presence of deuterium on the internal alkene in all products, the traces of product **81** and the proved reversibility of 2,1-migratory insertion might suggest that the isomerisation of the internal olefin occurs on the first stage of the reaction. In contrast, the lack of deuterium incorporation in the position 6 of both the norbornane **78** and the cyclopentane **80** (Scheme 2.13) indicates the that the 1,2-insertion is irreversible. According to these results, the mechanism of formation of cyclopentane **79** agrees with the one already described in Scheme 2.3.

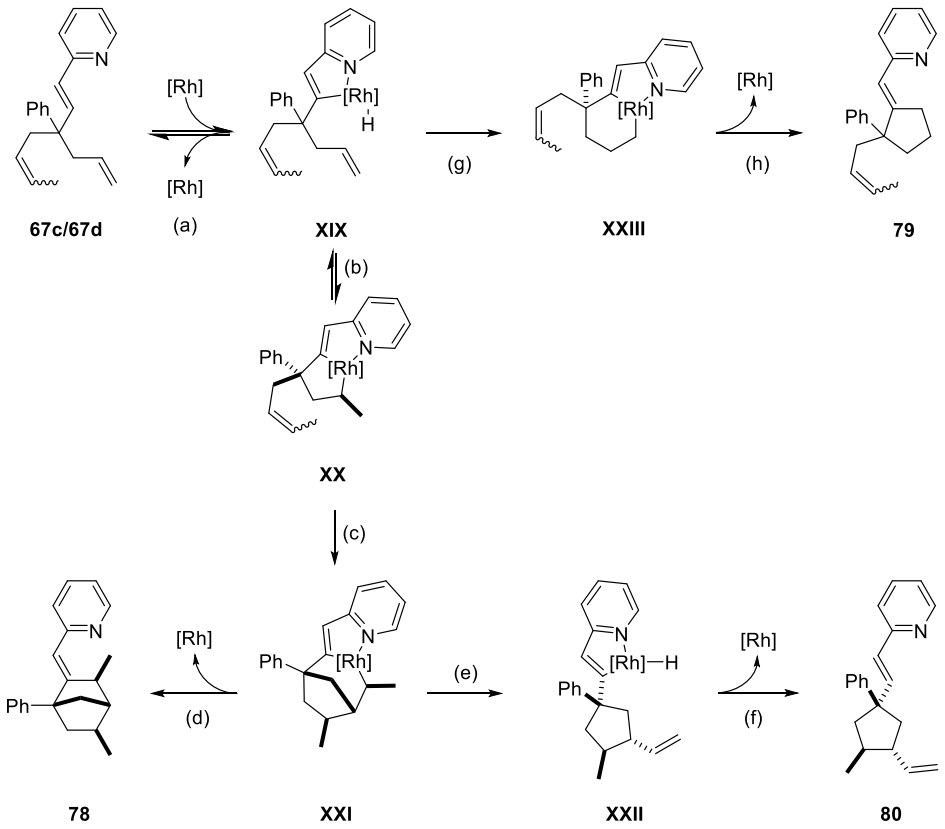
2.6 Conclusion

The cycloisomerisation of the prochiral substrates **63** affords norbornanes **64** in good yields and in a diastereoselective manner. The introduction of the methyl substituents in one olefin of the substrate diminishes considerably the product selectivity. Substrates **67a** and **67b** bearing one methyl at the internal carbon and two methyls at the terminal carbon of the olefin require high temperature and long reaction times, respectively. The undesired cyclopentanes **76a**, **76b** and **77a** accounted for the majority of the mass balance for both reactions. Five different isomers were obtained for the cycloisomerisation of substrates **67c** and **67d** which are mono-substituted on the terminal carbon of one alkene moiety. The desired norbornane **78** was obtained as an enriched *syn*,*syn* mixture of diastereoisomers. Common NMR experiments were used to elucidate the structure of **78 *s,s***. However, the overlapping of the peaks in the NMR spectra for **78 *s,a*** prevented the unambiguous assignment of the atoms of the molecule. Thus, the structure elucidation of **78 *s,a*** was accomplished by comparison with **78 *s,s*** and the study of the *gamma gauche* effect. Surprisingly, the cyclopentane **80** was obtained as the major product for both reactions in a diastereoselective fashion. This is the first time that a substituted cyclopentane is obtained as a single well-defined diastereoisomer by cycloisomerisation of a 1,6-diene. The tests of several substrates in which the pyridine moiety had been replaced by other functional groups showed that a nitrogen directing group is needed for the reaction to take place. Finally, some deuterium studies were carried out and the mechanism was revealed. The similar deuterium incorporation in the three main products (**78 *s,s***, **80** and **81**) demonstrated that the naked alkene undergoes first migratory insertion. Moreover, it proved that the cyclopentane **80** and the norbornane **78** share the common intermediate **XXI**. This seven-membered ring metallacycle can undergo either β-hydride elimination to form **80** or the expected reductive elimination to obtain **78**. The control of those elementary steps is discussed in the next chapters.

Chapter 3 : Optimisation of the reaction pathways

3.1 Introduction

The discovery of the common intermediate in the formation of cyclopentane **80** and norbornane **78** ***s,s*** was a great surprise. As previously mentioned, **80** is the first example of product formation of similar cyclopentanes by C-H activation. However, very poor product selectivity was observed in this reaction. Therefore, at this stage, the main goal was to obtain selectively either **80** or **78** ***s,s*** by tuning the reaction conditions to control the relative rates of reductive elimination (a) and β-hydride elimination (b) from intermediate **XXI** (Scheme 3.1). At the same time the conditions that accelerate the second migratory insertion (c) and prevent the formation of product **79** were expected to be found. The optimisation carried out previously by the group on substrates **63** showed that neither bidentate phosphines nor monodentate phosphites were effective on the second migratory insertion. As well, no reaction was observed when N-heterocyclic carbenes were used as a ligand.[43] Therefore, the optimisation was focused on monodentate phosphines only. The phosphine ratio, the temperature, the solvent and the concentration were also screened.

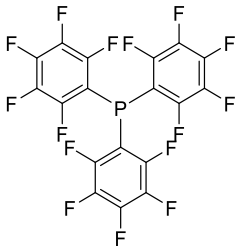


*Scheme 3.1: Proposed mechanism for the formation of products **78**, **79** and **80**..*

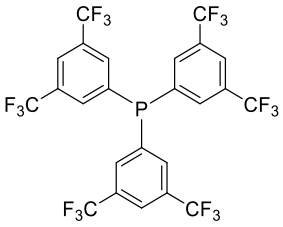
3.2 Optimisation of the reaction conditions

3.2.1 Optimisation of the ligand sphere

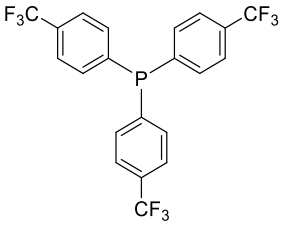
The β-hydride elimination step consists in the formation of an alkene by abstraction of a hydrogen from the molecule by the metal. As the metal acquires some electronic density in the process, this step is favoured when the metal core tends to be electron-poor. Moreover, a coordination site on the metal is required to accommodate the hydrogen atom and to promote the formation of the olefin moiety. Hence, a logical step in the optimisation of β-hydride elimination pathway is both to use electron-poor phosphines and reduce the amount of phosphine introduced in the reaction. On the contrary, reductive elimination is favoured by more bulky phosphines. Figure 3.1 and Figure 3.2 presents the tested phosphines, their Tolman cone angles (θ) and Tolman Electronic Parameters ($\tilde{\nu}$ in cm^{-1}).[60-63]



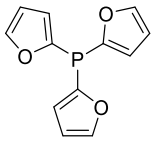
$P(C_6F_5)_3$
$\tilde{\nu}$ = 2090.9 cm^{-1}
θ = 184°



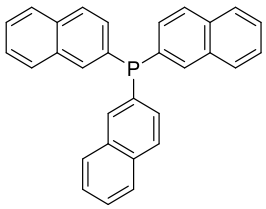
$P(3,5\text{-}CF_3\text{-}Ph)_3$
θ = 165°



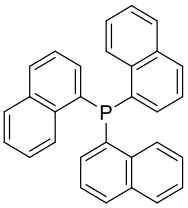
$P(4\text{-}CF_3\text{-}Ph)_3$
θ = 145°



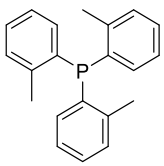
$P(2\text{-furyl})_3$
$\tilde{\nu}$ = 2078.4 cm^{-1}
θ = 133°



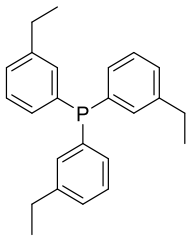
$P(2\text{-naphthyl})_3$



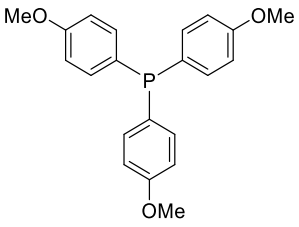
$P(1\text{-naphthyl})_3$



$P(o\text{-tolyl})_3$
$\tilde{\nu}$ = 2066.6 cm^{-1}
θ = 194°



$P(m\text{-Et-Ph})_3$
θ = 145°



$P(4\text{-MeO-Ph})_3$
$\tilde{\nu}$ = 2066.1 cm^{-1}
θ = 145°

Figure 3.1: Phosphines tested in the optimisation of the ligand sphere. All the parameters were extracted from references 60 and 61, except θ of $P(3,5\text{-}CF_3\text{-}Ph)_3$ and θ of $P(m\text{-}Et\text{-}Ph)_3$ which are approximations extracted from reference 62 and, θ and $\tilde{\nu}$ of $P(2\text{-furyl})_3$ which were obtained from reference 63.

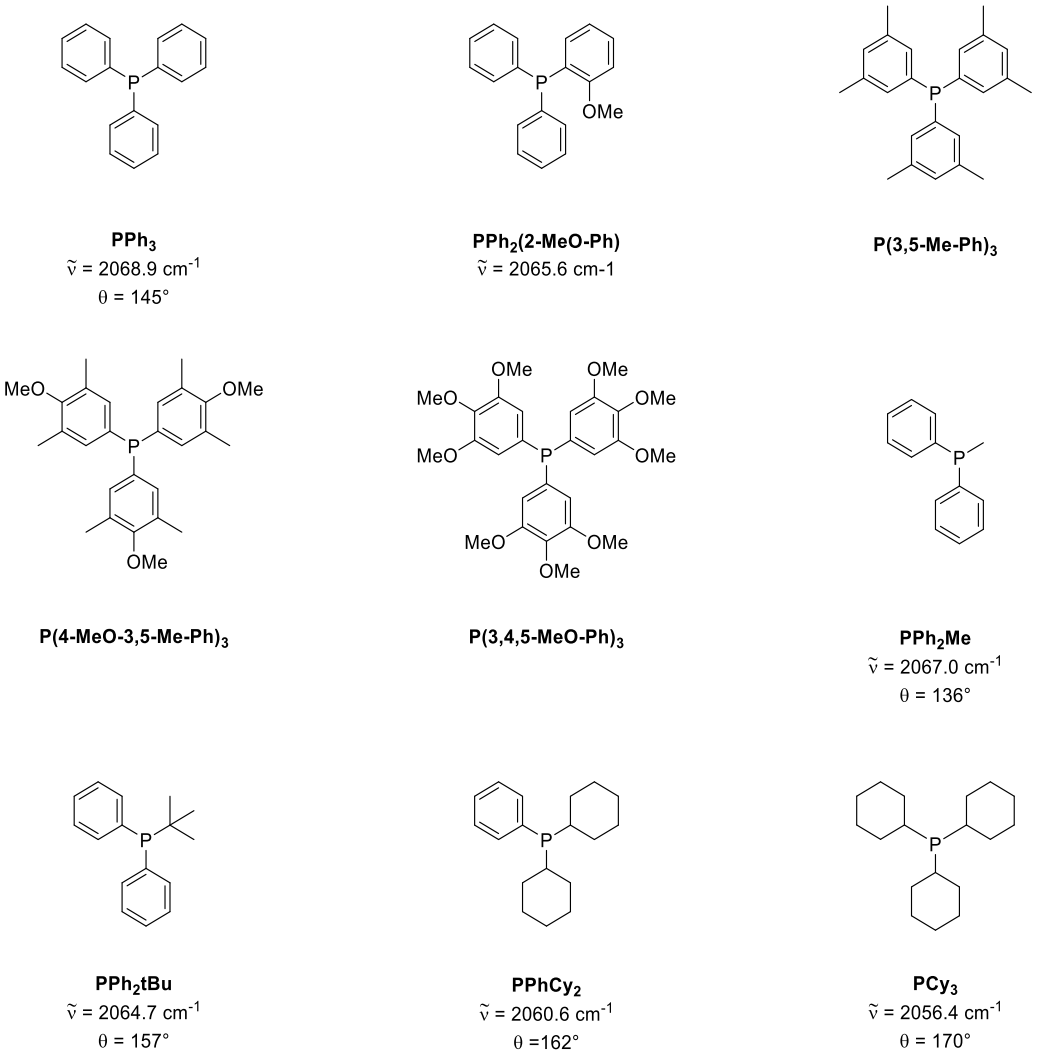
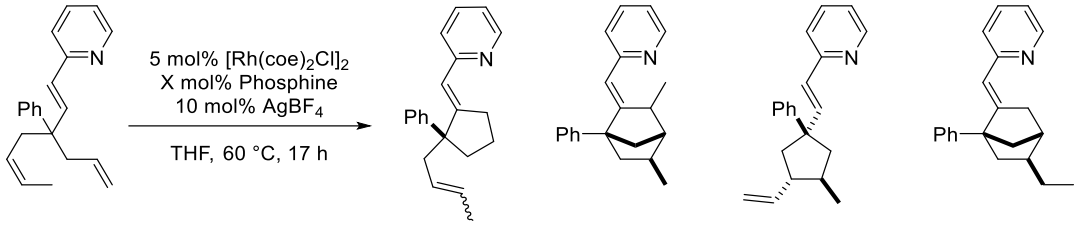


Figure 3.2: Phosphines tested in the optimisation of the ligand sphere. All the parameters were obtained from references 60 and 61.

The Tolman Electronic Parameter (TEP), expressed as a wavenumber ($\tilde{\nu}$ in cm^{-1}), corresponds to the carbonyl band of the in the $Ni(CO)_3L$ complex, where L is the studied phosphine. A big wavenumber suggests an electron-withdrawing ability of the phosphine, while small ν indicates that the ligand is electron-donating. The cone angle (θ) illustrates the size of the phosphine and its steric hindrance in the metal complex. It has been suggested that this two parameters are not completely precise and new parameters have been reported over the last years.[64] However, they are still widely used in the prediction of the catalytic behaviour. Unfortunately, the parameters of few of phosphines described herein are not reported in the literature, but a clear tendency in their application can be observed.

Taking this into account, the reaction of *cis*-substrate **67c** was examined using 10 mol%, 20 mol% or 30 mol% of the selected phosphines (Table 3.1). The conversion and product selectivity was calculated by NMR using 2,4-benzaldehyde or 2-chlorobenzaldehyde as the NMR standard.

*Table 3.1: Phosphine optimisation of the cycloisomerisation of substrate **67c**.*



67c **79** **78** **80** **81**

Entry*	Phosphine (mol%)	Conversion	79 (*cis*/*trans*)	78 (*s,s*/*s,a*)	80	81
1	**P(*p*-MeO-Ph)$_3$ (10)**	29	16 (10:6)	0	10	3
2	**P(C$_6$F$_5$)$_3$ (10)**	28	2 (2:0)	0	0	0
3	**P(3,5-CF$_3$-Ph)$_3$ (10)**	77	19 (15:4)	14 (14:0)	42	2
4	**P(4-CF$_3$-Ph)$_3$ (10)**	100	22 (16:6)	10 (9:1)	64	5
5	**P(2-furyl)$_3$ (10)**	78	14 (7:7)	0	63	0
6[a]	**P(2-furyl)$_3$ (10)**[a]	100	15 (8:7)	3 (3:0)	73	6
7[b]	**P(2-furyl)$_3$ (20)**	100	22 (11:11)	6 (6:0)	73	0
8[c]	**P(1-naphthyl)$_3$ (10)**	20	9 (7:2)	0	0	0
9	**P(2-naphthyl)$_3$ (10)**	100	19 (12:7)	16 (13:3)	56	9
10	**P(2-naphthyl)$_3$ (20)**	100	16 (11:5)	29 (27:2)	46	9
11	**P(*o*-tolyl)$_3$ (10)**	5	5 (n.d.)	0	0	0
12	**P(*m*-Et-Ph)$_3$ (10)**	100	20 (11:9)	31 (28:3)	40	11
13	**P(*m*-Et-Ph)$_3$ (20)**	31	10 (6:4)	4 (4:0)	8	11
14[b]	**PPh$_3$ (10)**	100	16 (10:6)	17 (13:4)	63	5
15[b]	**PPh$_2$(2-MeO-Ph) (10)**	4	4 (4:0)	0	0	0

16	**P(3,5-Me-Ph)$_3$ (10)**	100	18 (12:6)	31 (27:4)	43	8
17	**P(4-MeO-3,5-Me-Ph)$_3$ (10)**	100	17 (13:4)	42 (38:4)	30	10
18[b]	**P(4-MeO-3,5-Me-Ph)$_3$ (20)**	100	17 (10:7)	48 (38:10)	19	6
19[d]	**P(3,4,5-MeO-Ph)$_3$ (10)**	95	19 (9:10)	17 (8:9)	42	10
20[b]	**PPh$_2$Me (10)**	40	12 (5:7)	0	8	16
21[b]	**PPh$_2$tBu (10)**	100	22 (19:3)	44 (35:9)	32	1
22[b]	**PPh$_2$tBu (20)**	100	20 (17:3)	70 (59:11)	0	4
23[b]	**PPh$_2$tBu (30)**	100	27 (23:4)	70 (65:5)	0	3
24[b]	**PPhCy$_2$ (10)**	100	33 (27:6)	20 (14:6)	38	2
25[b]	**PPhCy$_2$ (20)**	96	36 (32:4)	30 (23:7)	24	5
26[b]	**PCy$_3$ (10)**	18	13 (10:3)	0	0	0

*Unless noted, standard:2,4-dichlorbenzaldehyde. In entries 4, 16 and 17 the standard was 4-dichlorobenzaldehyde. Entries 8, 9, 10 and 12 did not have a standard. In entry 11, 3,5-dimethoxybenzene was used. a) 72h reaction. b) 24h reaction. c) 95% mass balance identified. d) 20h reaction

Preliminary results for substrates **67c** and **67d** showed that product **79** appeared as a mixture of *cis* and *trans* isomers. The first hypothesis was that isomerisation of the starting material occurred. This was confirmed in reactions that did not reach full conversion, as the ^{1}H NMR clearly shows the formation of the *trans* isomer **67d**. Hence, as stated in Chapter 2, the formation of **78** ***s,a*** could then arise from an early isomerisation of the substrate.

Extremely electron-poor phosphines proved to be unsuitable for the reaction as they only afforded low conversion and poor product selectivity (Entries 2 and 3). The bulkiness provided by P(3,5-CF_3-Ph)$_3$ could explain the formation of product **78** in 14% yield. This can be proven by the results of P(4-CF_3-Ph)$_3$ (Entry 4). With this less bulky but still electron-poor phosphine, the amount of **78** was reduced to 10%. The extreme bulkiness of P(C_6F_5)$_3$ would justify the poor conversion reported in entry 1. When P(2-furyl)$_3$ was tried, only 78% conversion was observed after 17 hours (Entry 5). Nevertheless, **80** was obtained in a 63% yield and the conditions blocked completely the reductive elimination from intermediate **XXI**. Full conversion was reached after 24 hours reaction with excellent results (Entry 6).

Only traces of products **81** and **78** were observed, while the amount of **79** remained low. Despite increasing the amount of phosphine, results for P(2-furyl)$_3$ remained similar after 17 hours reaction (Entry 7). In this case, full conversion was observed but to the detriment of the selectivity as cyclopentane **79** was observed in 22% yield.

The configuration of the phosphine proved to be important. The apparently bulky P(1-naphthyl)$_3$ only reached 20% conversion (Entry 8). On the contrary, the lineal P(2-naphthyl)$_3$ afforded completion after 17 hours (Entry 9). Unfortunately, 16 % of norbornane **78** was still present in the reaction. The selectivity towards cyclopentane **80** was worsened slightly by the increase of the phosphine ratio (Entry 10). However, formation of **79** was not affected. The extremely bulky P(*o*-tolyl)$_3$ (θ = 194˚) did not promote any reaction (Entry 11). However, the introduction of substituents in *meta* position, which are less sterically hindered, promoted the cycloisomerisation reaction (Entries 12 and 13). Unfortunately, the product selectivity was not great. PPh_3 afforded similar results to P(4-OMe-Ph)$_3$ which is expected as these two phosphines look identical when compared by the Tolman Parameters (Entry 14). Cyclopentane **80** was obtained in 63% while desired product **78** was only obtained in 17% as a mixture of *syn*,*syn* and *syn*,*anti* isomers. A slightly more electron-donating but bigger *ortho* substituted phosphine PPh_2(2-MeO-Ph) only afforded 4% conversion towards product **79** (Entry 15). This situation was previously described with P(*o*-tolyl)$_3$ (Entry 11). Surprisingly, it only required one *ortho*-substituted phenyl group on the phosphorus atom to stop the migratory insertion.

As hypothesised, progress to apparently bulkier and electron-donating phosphines promoted the reductive elimination (Entries 16 to 19). Using methoxy substituted xylyl phosphine, 42% of norbornane was obtained (Entry 17). Only a small difference was observed when increasing the phosphine ratio to 20% (Entry 18). Methyl substitution afforded better results than methoxy substitution (Entries 18 and 19). Nevertheless, selectivity towards cyclopentane **79** remained constant for the three phosphines. Substitution of one aryl group for a methyl group reduced the selectivity of the reaction dramatically (Entry 20). Only 40% conversion was obtained and norbornane **78** was not present in the product mixture. In fact, norbornane **81** was the major product. In that case, first migratory insertion is favoured for the substituted alkene. This correlates with the previous data shown, this small phosphine (θ = 136˚) creates a space around the metal which might help the migratory insertion of the substituted olefin. However, when an aryl group was substituted for a *tert*-butyl group, the reaction reached full conversion after 24 hours and a selectivity of 1.4:1 (**78**/**80**) was achieved (Entry 21). The bulkiness afforded by the *tert*-butyl moiety is key for the reaction to occur. Moreover, when using PPh_2tBu, only small amount of the *trans* and *anti* isomers was observed which might have indicated that isomerisation of the starting material was almost stopped. These good results stimulated further studies with this phosphine.

As previously stated, reductive elimination can be accelerated by the excess of ligand that brings the two substituents together. Thus, the reaction was tested with 0.2 equivalents of PPh_2tBu (Entry 23). To our delight, cyclopentane **80** was not observed in the reaction mixture. Furthermore, norbornane **78** was obtained in 70% and only 11% as the *syn*,*anti* isomer. An increase of the amount of phosphine did not affect the formation of cyclopentane **79** which was obtained in 20% yield. However, when 0.3 equivalents of PPh_2tBu were used the amount of product of the single migratory insertion increased slightly (Entry 23). Moreover, the diastereoselectivity of norbornane **78** was slightly affected. Taking into account that **79** *trans* was obtained in the same ratio for both 20 and 30% PPh_2tBu, the difference in diastereoselectivity for norbornane **78** suggests that the diastereoseletivity is controlled by the sterics around the metal sphere.

Bulkier phosphines ($\theta > 160^{\circ}$) decreased the product selectivity (Entries 24 to 26). But it was not affected by the use of either 10 mol% or 20 mol% of $PPhCy_2$. The coordination of a second phosphine with the rhodium might be hindered by the large size of the phosphine. In addition, when a larger phosphine was tested, the conversion dropped to 18% (Entry 26). The size of PCy_3 hinders the catalyst and might prevent the substrate from undergoing C-H activation. It is noteworthy that the larger the ligand is, the more favoured is the formation of the product of the single migratory insertion. Nevertheless, this is not greatly affected by the equivalents of phosphine in the reaction. Overall, a small range of phosphine size is effective in the selective cycloisomerisation of the substituted 1,6-dienes. While the use of small ligands results in poor conversion, the introduction of too bulky phosphines derive in a loss of product selectivity.

At this stage, isolated yields were obtained for the reactions of the two best phosphines (Table 3.2).

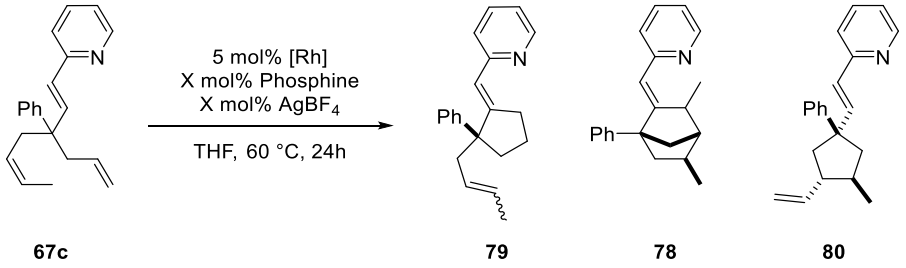
*Table 3.2: Isolated yields of the β-hydride elimination and the reductive elimination products under the optimised reaction conditions for substrate **67c**.*

Entry	Phosphine (mol%)	Product	Yield (%)
1	**$P(2\text{-furyl})_3$ (10)**	**80**	45
2	**PPh_2tBu (20)**	**78 *s,s***	24

In both cases, isolation was carried out by flash column chromatography using a mixture of pentane and ethyl acetate as eluent. The isomers presented an extremely similar polarity. It is one of the reasons why the isolated yield was low compared to the one observed by NMR. Moreover, some material could still remained coordinated to the catalyst. Even after very fast filtrations through a small silica column chromatography with a high polarity eluent, around 20% of the mass balance was lost.

3.2.2 Optimisation of the catalyst

*Table 3.3: Catalyst optimisation of the cycloisomerisation of substrate **67c**.*



67c **79** **78** **80**

Entry	Catalyst	Phosphine (mol%)	$AgBF_4$ (mol%)	Conversion
1[a]	**$[Rh(CO)_2Cl]_2$**	None	0	0
2	**$[Rh(CO)_2Cl]_2$**	$P(2\text{-furyl})_3$ (10)	10	0
3	**$[Rh(CO)_2Cl]_2$**	PPh_2tBu (20)	10	6
4	**$[Rh(CO)_2Cl]_2$**	$P(2\text{-furyl})_3$ (10)	0	0
5	**$[Rh(CO)_2Cl]_2$**	PPh_2tBu (20)	0	0
6[a]	**$[Rh(coe)_2Cl]_2$**	P(*p*-MeO-Ph)$_3$ (20)	0	21
7[a]	**$[Rh(coe)_2Cl]_2$**	None	10	12

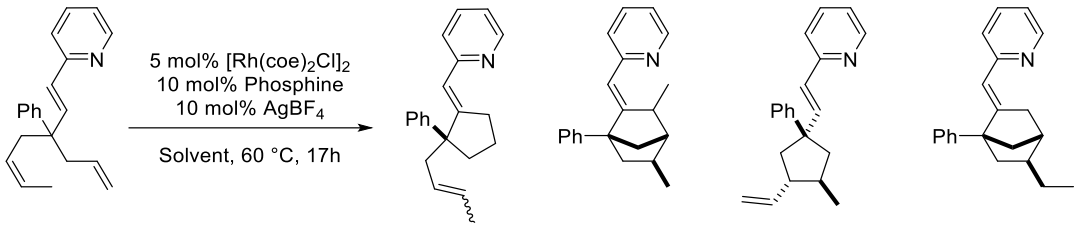
a) 17h reaction

First, substrate **67c** was reacted with rhodium carbonyl chloride (I) at 60°C and no conversion was observed (Table 3.3, Entry 1). When the same rhodium source was tried with both the phosphine and $AgBF_4$, either none or sluggish conversion was obtained (Entries 2 and 3). It is noteworthy, that the small conversion did not correspond to any of the already characterised product. The removal of the silver from the reaction mixture did not afford any conversion (Entries 4 and 5). These five entries suggest that rhodium carbonyl chloride (I) is not a suitable rhodium source for this reaction. Then, the reaction was tested with $[Rh(coe)_2]Cl_2$ (Entries 6 and 7). When the silver was not present in the reaction mixture, only 21% conversion was observed. This indicates that formation of the monomeric cationic catalyst is key for the reaction to occur. If the reaction was lacking the phosphine acting as a ligand, only 12% conversion was obtained. Therefore, the presence of the ligand is also a requirement in this reaction.

3.2.3 Optimisation of solvent and concentration

A screening of solvents was then carried out with some of the previously tested phosphines (Table 3.4).

*Table 3.4: Solvent optimisation of the cycloisomerisation of substrate **67c**.*



67c **79** **78** **80** **81**

Entry*	Phosphine	Solvent	Conversion	79 (cis/trans)	78 (*s,s/s,a*)	80	81
1	**P(4-CF_3-Ph)$_3$**	CH_3NO_2	100	22 (14:8)	13 (6:7)	58	7
2[a]	**P(2-naphthyl)$_3$**	1,2-DCE	74	17 (10:7)	8 (3:5)	42	7
3[a]	**P(2-naphthyl)$_3$**	Acetone	67	13 (9:4)	5 (2:3)	46	4
4[a]	**P(2-naphthyl)$_3$**	*i*-PrOH	100	16 (10:6)	14 (8:6)	60	10
5[b]	**P(4-CF_3-Ph)$_3$**	MeCN	13	0	2	9	2
6[b]	**P(2-naphthyl)$_3$**[c]	THF	71	20 (11:9)	7 (0:7)	38	6
7[b]	**P(4-CF_3-Ph)$_3$**[c]	THF	100	21 (15:6)	25 (22:3)	53	6
8[b]	**P(2-furyl)$_3$**[c]	THF	100	17 (9:8)	4 (4:0)	68	4
9[b]	**P(2-furyl)$_3$**[d]	THF	52	14 (8:6)	0	31	7

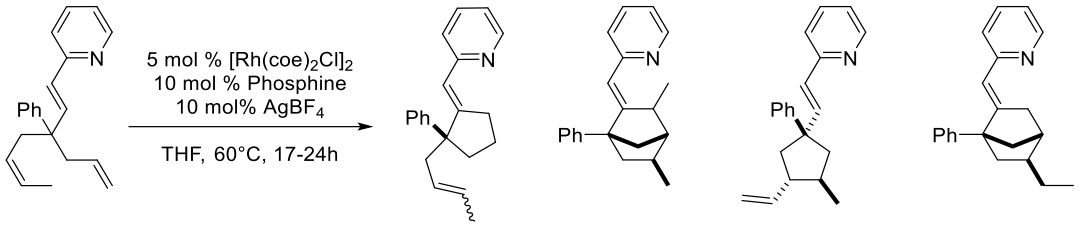
* Unless noted, the standard that was used was 2,4-dichlorobenzaldehyde. a) 4-chlorobenzaldehyde. b) 72 hours reaction. c) 1equiv of MeCN compared to rhodium. d) 2 equiv MeCN compared to rhodium.

The use of nitromethane as a solvent did not affect the product selectivity (Entry 1). 1,2-dichloroethane enhanced slightly the product selectivity towards cyclopentane **80** , but the conversion was reduced to 74% (Entry 2). When the reaction was carried out in acetone, the conversion of the cycloisomerisation dropped to 67% (Entry 3). But, when *i*PrOH was used as a solvent the product

selectivity was not significantly altered compared to the reaction in THF (Entry 4). In contrast, when acetonitrile and P(4-CF_3-Ph)$_3$ were used instead, only low conversion was observed (Entry 5). Surprisingly, the product of single migratory insertion **79** was not apparently obtained. Although, the low conversion might have hidden the characteristic signals in the ^{1}H NMR of the crude mixture. Then, some acetonitrile was accurately added to the THF and its influence was checked. The addition of 0.1 equivalents of MeCN decelerated the reaction when using P(2-naphthyl)$_3$ as the ligand (Entry 6). In this case, the MeCN did not block the formation of cyclopentane **79**. The same phenomenon occurred for both P(4-CF_3-Ph)$_3$ and P(2-furyl)$_3$ as cyclopentane **79** was obtained in the same ratio as without MeCN. The addition of 0.2 equivalents of acetonitrile decelerated the rate of the reaction and only 52% conversion was observed (Entry 9). Hence, it can be concluded that addition of acetonitrile does not improve the product selectivity and that THF was still the best solvent.

The effect of concentration was then tested for some of the more selective phosphines (Table 3.5).

*Table 3.5: Concentration optimisation of the cycloisomerisation of substrate **67c**.*



67c **79** **78** **80** **81**

Entry*	Phosphine	Concentration	Conversion	79 (*cis*/*trans*)	78 (*s,s*/*s,a*)	80	81
1	**P(2-furyl)$_3$**	0.05 M	70	17 (12:5)	2 (2:0)	50	1
2	**P(2-furyl)$_3$**[b]	0.05 M	100	18 (8:10)	2 (2:0)	77	3
3	**P(4-CF$_3$-Ph)$_3$**	0.05 M	100	21 (16:5)	12 (10:2)	63	4
4	**P(2-naphthyl)$_3$**	0.05 M	100	18 (11:7)	18 (15:3)	56	8
5	**P(2-furyl)$_3$**[a]	0.2 M	80	11 (6:5)	traces	53	4
6	**P(4-CF$_3$-Ph)$_3$**[a]	0.2 M	75	14 (10:4)	5 (5:0)	38	4
7	**P(2-Naphthyl)$_3$**[a]	0.2 M	56	9 (6:3)	4 (2:2)	40	0

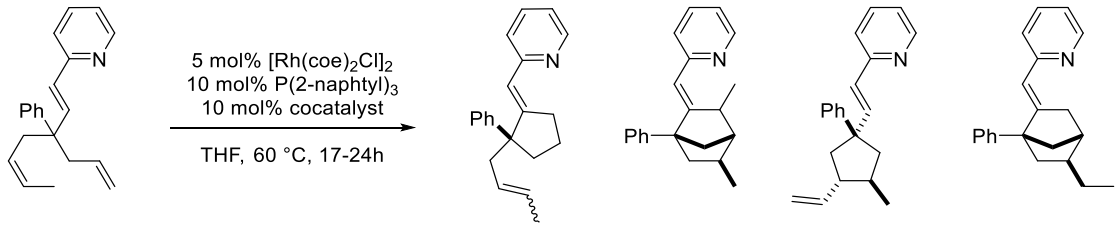
*Standard:2,4-dichlorobenzaldehyde. a) 48 h reaction. b) 30 mg scale reaction

Comparing to the results in Table 3.1, a decrease of concentration from 0.1 M to 0.05 M did not affect the reaction rate or the product selectivity (Entries 1 to 4). When the reaction was carried out using P(2-furyl)$_3$ as a ligand, the cycloisomerisation reached completion in 48 hours. An increase of the concentration from 0.1 M to 0.2 M did not alter the product selectivity (Entries 5-7). However, the conversion dropped significantly. Thus, it can be suggested that the concentration is not an important factor on the product selectivity.

3.2.4 Optimisation of the co-catalyst

The addition of silver salts keeps the catalyst cationic by breaking the Rh-Cl bonds of the pre-catalyst. In that case, the different characteristics of the counter ion might affect the course of the reaction. Herein, a very small screening for silver salt co-catalysts is described (Table 3.6).

*Table 3.6: Co-catalyst optimisation of the cycloisomerisation of substrate **67c**.*



Entry*	Co-catalyst	Conversion	79 (*cis*/*trans*)	78 (*s,s*/*s,a*)	80	81
1	**NaBArF**[a]	100	19 (11:9)	17 (12:5)	55	9
2	**$AgPF_6$**	100	15 (10:5)	19 (14:5)	56	10
3[b]	**$AgBF_4$**	23	5 (3:2)	0	7	3

*Unless noted, standard: 4-dichlorobenzaldehyde. a) Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. b) 10 mol% $P(2\text{-furyl})_3$, 20 mol% $AgBF_4$, 24h reaction. Standard: 2,4-dichlorobenzaldehyde. Only 15% of mass balance respect to substrate **67c** was identified.

The use of 10 mol% of $AgPF_6$ or NaBArF did not affect the product selectivity (Entries 1 and 2). In contrast, when 20 mol% of $AgBF_4$ was used as a co-catalyst, the conversion dropped to 23% and only 15% of the mass balance was identified (Entry 3).

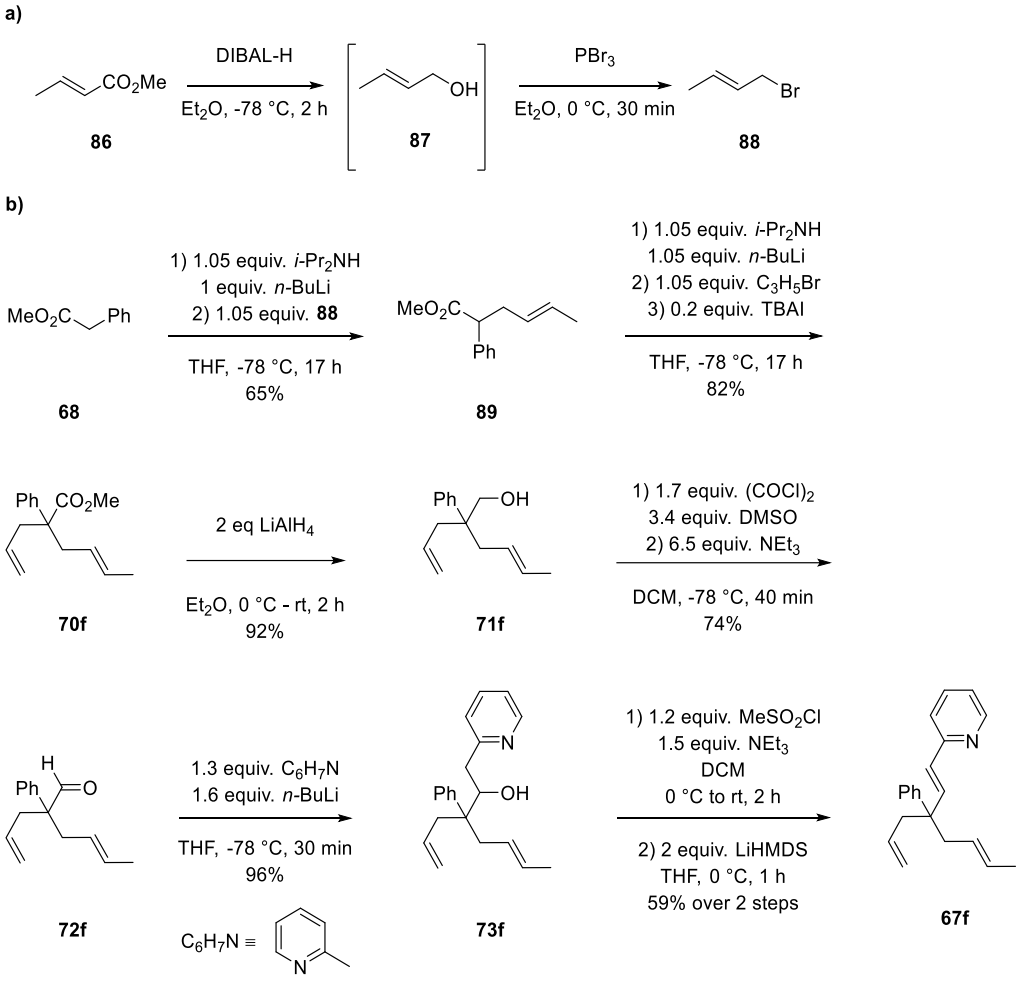
As it can be observed, the small solvent and co-catalyst optimisation did not improve the product selectivity or the reaction rate. Thus, PPh_2tBu and $P(2\text{-furyl})_3$ were determined as the best phosphines for the reductive elimination and the β-hydride elimination pathways respectively. Both reactions were carried out in THF using 0.1 equivalents of $AgBF_4$ as co-catalyst.

3.3 Influence of the substrate configuration

Preliminary results reported in chapter 2 showed that configuration of the starting material was an important factor on the reaction, especially for the diastereoselectivity of product **78**. Therefore, **67f** was synthesised as pure *trans*-isomer to study this factor.

3.3.1 Synthesis of substrate 67f

The synthesis of isomerically-pure substrate **67f** was carried out in 8 steps (Scheme 3.2).



*Scheme 3.2: Synthesis of substrate **67f**. a) Synthesis of crotyl bromide **88**. b) Synthesis of substrate **67f**.*

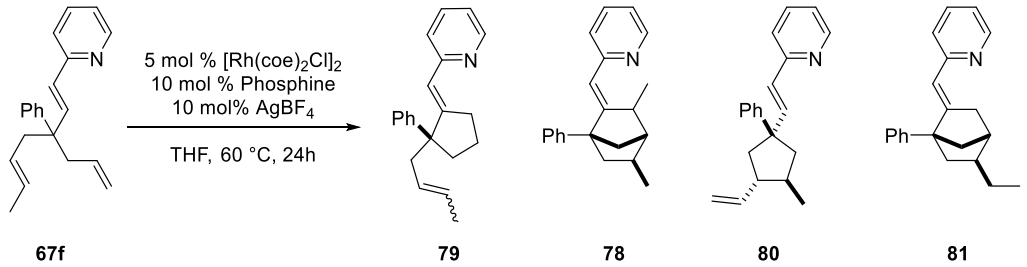
Commercially available crotyl ester **86** was reduced to crotyl alcohol **87** with DIBAL-H at -78 ˚C for two hours (Scheme 3.2, a). Addition of the reagent had to be extremely slow to avoid epimerisation. For the same reason, the temperature control was very important in this step. Intermediate **87** is very volatile. Therefore, the reaction was quenched, but the solvent was not removed. Then, the temperature was increased to 0 ˚C and phosphorus tribromide was added. The reaction was controlled by ^{1}H NMR using aliquots. Once the reaction was over, it was quenched with brine and extracted with diethylether. The mixture was then concentrated under vacuum at low temperature to avoid epimerisation. Crotyl bromide **88** was then used without further purification. The next reaction steps were the same as those previously described in chapter 2 (Scheme 3.2, b). First, methyl phenyl acetate

68 was allylated with intermediate **88**. Substrate **89** was only obtained in 65% yield. This is probably due to the low accuracy in the weighting of the previously made allyl bromide **88**. A second allylation provided intermediate **70f** in good yield. Then, reduction to the alcohol was carried out using two equivalents of lithium aluminium hydride. Intermediate **71f** was obtained in excellent yields and no purification was required. Compound **71f** was then oxidised to the aldehyde by a Swern reaction which provided intermediate **72f** in 74% yield. The α-lithiated methyl pyridine was added to the aldehyde **72f** to provide the secondary alcohol **73f** as two different diastereoisomers in excellent yield. Finally, **73f** was mesylated and consecutively eliminated to form isomerically pure substrate **67f**.

3.3.2 Results

Substrate **67f** was submitted to few cycloisomerisation conditions to study the role of the substrate configuration. The results of these reactions are shown in Table 3.7.

*Table 3.7: Phosphine optimisation of the cycloisomerisation of substrate **67f**.*



Entry*	Phosphine	79 (*cis*/*trans*)	78 (*s,s*/*s,a*)	80	81
1[a]	**P(2-furyl)$_3$**	13 (3:10)	0	82	5
2[b]	**P(2-furyl)$_3$**	18 (5:13)	0	82	0
3	**P(2-naphthyl)$_3$**	16 (3:13)	20 (6:14)	59	5
4	**P(4-CF$_3$-Ph)$_3$**	14 (2:12)	26 (13:13)	57	3
5	**P(4-MeO-3,5-Me-Ph)$_3$**	20 (4:16)	32 (8:24)	45	3
6	**PPh$_2$tBu**	17 (2:15)	78 (17:61)	0	5
7[b]	**PPh$_2$tBu**	17 (2:15)	84 (14:70)	0	0

*Standard: 2,4-dichlorobenzaldehyde. a) 72 hours. b) 20 mol% P(2-furyl)$_3$

The product selectivity was comparable to the one presented for isomer **67f** in Table 3.1. Therefore, it was not apparently affected by the configuration of the substrate. The optimised conditions for the *β*-hydride elimination afforded cyclopentane **80** in 82% (Entry 1). As previously presented, when moving to more electron-donating and bulky phosphines, the product of reductive elimination **78** increased slowly until it became the major product under the optimised conditions, with complete suppression of the formation of **80** (Entry 7). The isomeric ratio of product **79** suggested that isomerisation of the substrate in the reaction was not as important as for *cis* isomer **67f**. From *cis* **67c**, cyclopentane **79** was obtained in approximately 1:1 *cis*/*trans* ratio when using the more electron-withdrawing phosphines. In contrast, *trans* **67f** led to cyclopentane **79** in a 3:1 *trans*/*cis* ratio. The difference of *cis*/*trans* ratio slowly increased with the electron-donating power and the bulkiness of the phosphine. It is noteworthy that this increase is not translated to the isomeric ratio of norbornane **78**. As it was predicted, **78** ***s,a*** is the major of two isomers but, the isomeric difference is much smaller than for product **79**. Remarkably, while the *trans*/*cis* ratio of **79** was 6:1 when P(4-CF_3-Ph)$_3$ was used, the *syn*,*syn*/*syn*,*anti* ratio of **78** was close to 1:1. These outstanding results might suggest that an unknown mechanism is taking place in the process.

The configuration of the substrate did indeed affect the diastereomer ratio for both **79** and **80**. However, product selectivity remained similar for substrates **67c** and **67f**. Hence, P(2-furyl)$_3$ and PPh_2tBu were again the optimal phosphines for the reaction. The products of these reactions were isolated (Table 3.8).

*Table 3.8: Isolated yields of the β-hydride elimination and the reductive elimination products under the optimised reaction conditions for substrate **67f**.*

Entry	Phosphine (mol%)	Product	Yield (%)
1	**P(2-furyl)$_3$ (10)**	**80**	44%
2	**PPh_2tBu (20)**	**78**	35%

3.4 Reaction monitoring studies by NMR spectroscopic analysis.

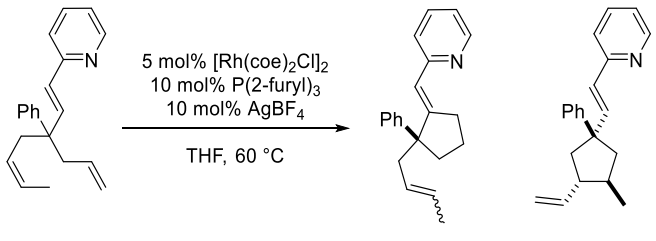
In order to understand the outcome of the reaction, monitoring studies were carried out under the optimal conditions for both **67c** and **67f**. The goal was not only to understand the reaction mechanism, but also to elucidate the rate of appearance of the different products. For that purpose, four reactions were set up individually but simultaneously and each was stopped after a specific time. Each reaction was then checked by NMR. An alternative monitoring experiment was carried by removing aliquots

from the same reaction every few hours, but the conversion was worse. In that case, it is likely that some oxygen was added every time the flask was open, and that the results were affected.

3.4.1 Monitoring of the reaction conditions favouring the β-hydride elimination

First, the studies were carried out on substrate **67c** in a 24 hours period. Following the cycloisomerisation procedure (see Chapter 6), four reactions were prepared at the same time and stopped after 1, 4, 8 or 24 hours respectively. This monitoring procedure was repeated three times, the yields obtained were transformed into concentration (M) and the average (AVG.) and the standard deviation (Std. Dev.) were calculated for each point (see Section 6.4). The initial theoretical concentration was considered the fifth point of data. Products **78** and **80** were obtained in less than 5% yield during the course of the reaction. Therefore, the results on these two norbornanes are not included in the plot. In contrast, the isomerisation of **67c** into **67f** could be observed. The results obtained at different given times show that the reaction is very sensitive to small changes (see Section 6.4). However, they are reproducible when the reaction is completed. Several factors could be the cause of the sensitivity. First, errors likely occurred during the weighting of such small amounts of material. Second, a small change on the temperature of the reaction or on the speed of the stirring might change significantly the metal complex at a given time. Moreover, the catalyst might change during the course of the reaction which might explain the reproducibility of product distribution at completion. In this regard, all those results were removed from the dataset and the averages and standard deviations were calculated again (Table 3.9 and Table 3.10).

*Table 3.9: Average concentration of organic species of the cycloisomerisation of substrate **67c** favouring the β-hydride elimination at given times.*



67c **79** **80**

Time (h)	67c	67f	80	79*cis*	79*trans*	79
0	0.099	0.000	0.000	0.000	0.000	0.000
1	0.078	0.010	0.004	0.001	0.000	0.001
4	0.057	0.023	0.020	0.003	0.001	0.003
8	0.009	0.010	0.058	0.006	0.005	0.011
24	0.000	0.000	0.075	0.011	0.007	0.019

*Table 3.10: Standard deviation of the concentration of organic species of the cycloisomerisation of substrate **67c** favouring the β-hydride elimination at given times.*

Time (h)	67c	67f	80	79*cis*	79*trans*	79
0	0.000	0.000	0.000	0.000	0.000	0.000
1	0.005	0.002	0.002	0.001	0.000	0.001
4	0.009	0.000	0.010	0.001	0.001	0.001
8	0.001	0.000	0.008	0.000	0.002	0.002
24	0.000	0.000	0.002	0.001	0.000	0.002

In this case, most of the standard deviations are less than 0.005. Only the three results that are marked in red in Table 3.15 have larger standard deviation. The results as the average of the concentration and its standard deviation for each point were plotted (Figure 3.3).

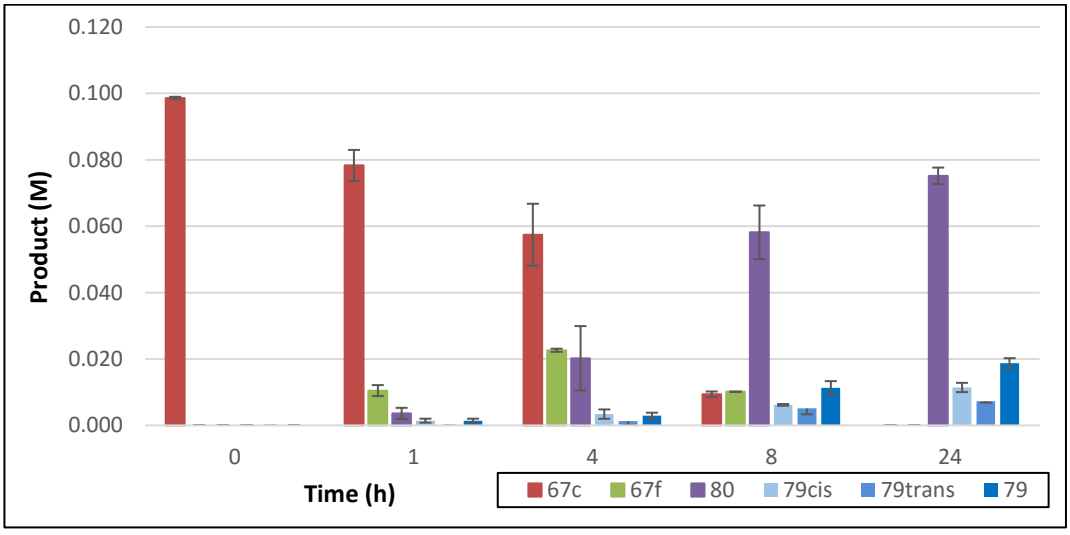


*Figure 3.3: Average of the consumption of substrate **67c** and formation of products **78**, **79** and **80** and intermediate **67f** in a 24-hour period under the optimised conditions that favour the β-hydride elimination. The error bar shows the standard deviation of the experiments.*

The decay of the starting material **67c** is observed, while the amount of its *trans* isomer **67f** peaks at 4 hours. Products **80** and **79** appear very early in the reaction and their growth is constant during the length of the process. None of the products apparently plateaus after certain time. This could indicate that neither **79** nor **80** hinders the formation of the other products. More importantly, it hinders the control of the product selectivity by tuning the reaction time. The isomerisation of the starting material

promotes the formation of **79** *trans*. This product appears after 4 hours of reaction and is constantly formed. A lined-scatter plot shows the different tendencies (Figure 3.4).

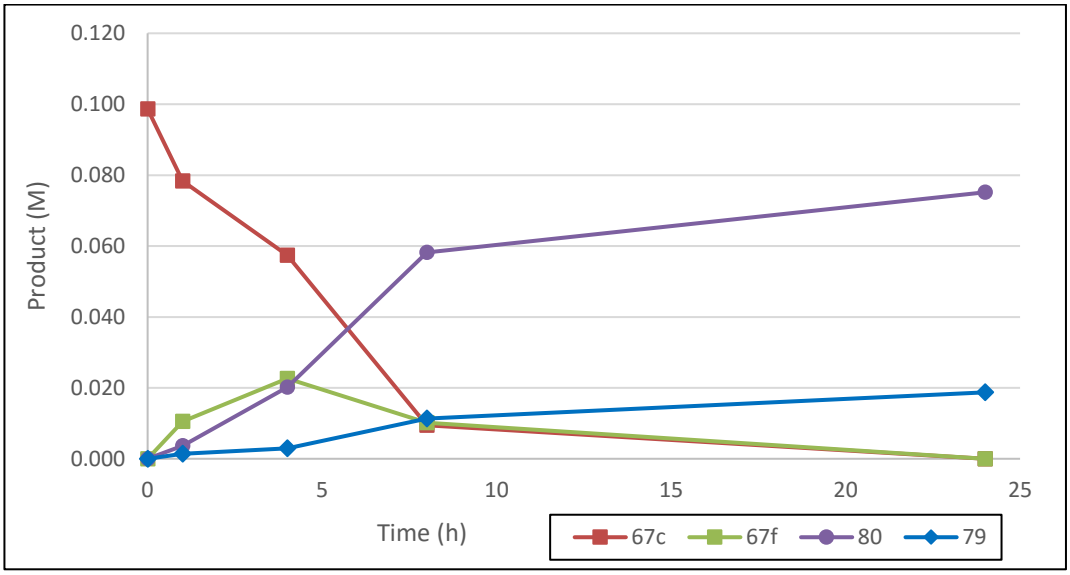


*Figure 3.4: Average of the consumption of substrate **67c** and the formation of products **78**, **79** and **80** and intermediate **67f** in a 24-hour period under the optimised conditions that favour the β-hydride elimination.*

The curve of the consumption of substrate **67c** indicates that the cycloisomerisation follows zero order kinetics for most of the reaction. In this case, the system is under saturation kinetics. This means that the catalyst is saturated with substrate and that the concentration of the substrate in the reaction medium does not affect the reaction rate.

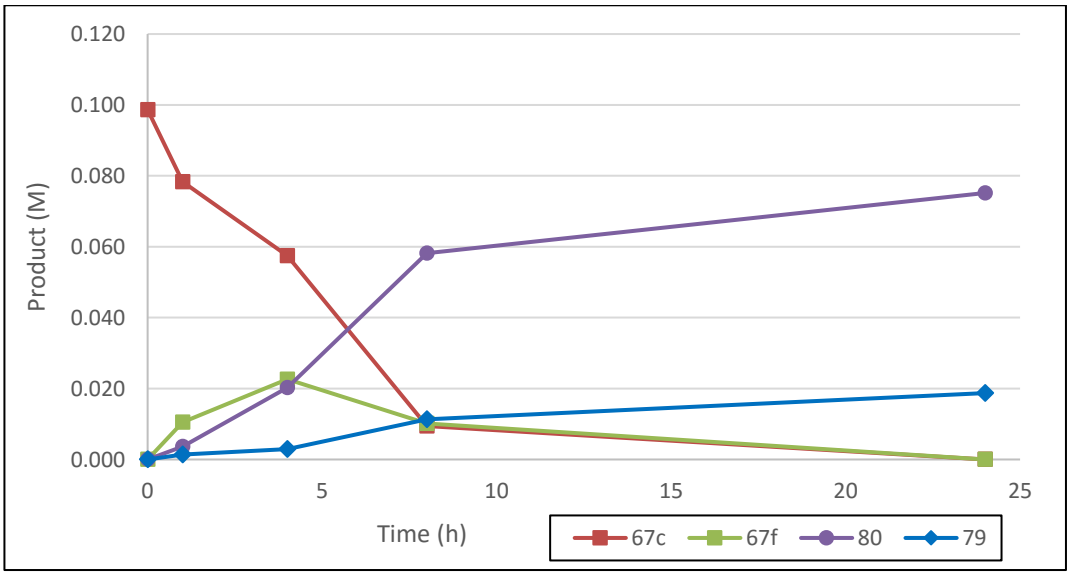
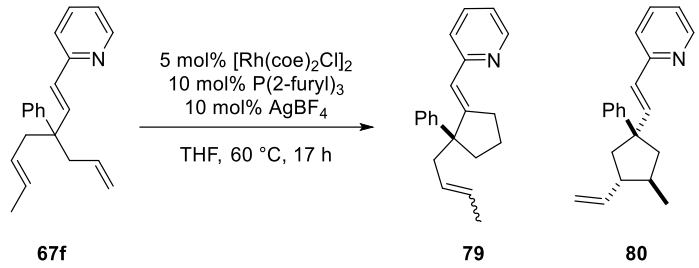


*Figure 3.5: Average of the formation of cyclopentane **79** and itemisation into **79cis** and **79trans** under the optimised conditions that favour the β-hydride elimination.*

As previously discussed, **79** *cis* was already observed after 1 hour of reaction (Figure 3.5). On the contrary, **79** *trans* did not appear until few hours later. Despite the fast isomerisation of the substrate, the small concentration of isomer **67f** in the reaction mixture could explain the lack of **79** *trans*. The almost perfectly linear dependence for both isomers might suggest that there was no isomerisation of the internal bond of product **79**.

In order to understand the importance of the substrate configuration, the same monitoring experiments were done with isomer **67f** (Table 3.11). Even though the reaction of substrate **67c** was proved to be very sensitive, a clear tendency was observed. Therefore, it was decided to conduct the monitoring experiments only once for substrate **67f**.

*Table 3.11: Concentration of organic species of the cycloisomerisation of substrate **67f** favouring the β-hydride elimination at given times.*



Time (h)	67c	67f	80	79*cis*	79*trans*	79
0	0.000	0.099	0.000	0.000	0.000	0.000
1	0.003	0.073	0.006	0.000	0.001	0.001
4	0.013	0.063	0.019	0.000	0.003	0.003
8	**0.012**	**0.056**	**0.025**	**0.001**	**0.004**	**0.005**
24	0.003	0.004	0.075	0.002	0.012	0.014

Comparing the results for the monitoring of *cis*-substrate **67c**, the consumption of substrates **67f** and **67c** are equivalent. The formation of cyclopentanes **79** and **80** also appears to follow the same pattern. As expected, smaller amount of isomerised substrate **67c** and cyclopentane product **79*cis*** are observed. This is because the isomerisation process is under thermodynamic control favouring the formation of the *trans* olefin. Unfortunately, it is evident that the point at t = 8 hours is out of the expected range since the results are strangely similar to those at t = 4 hours. As mentioned before, the extreme sensitivity of the reaction can affect the results.

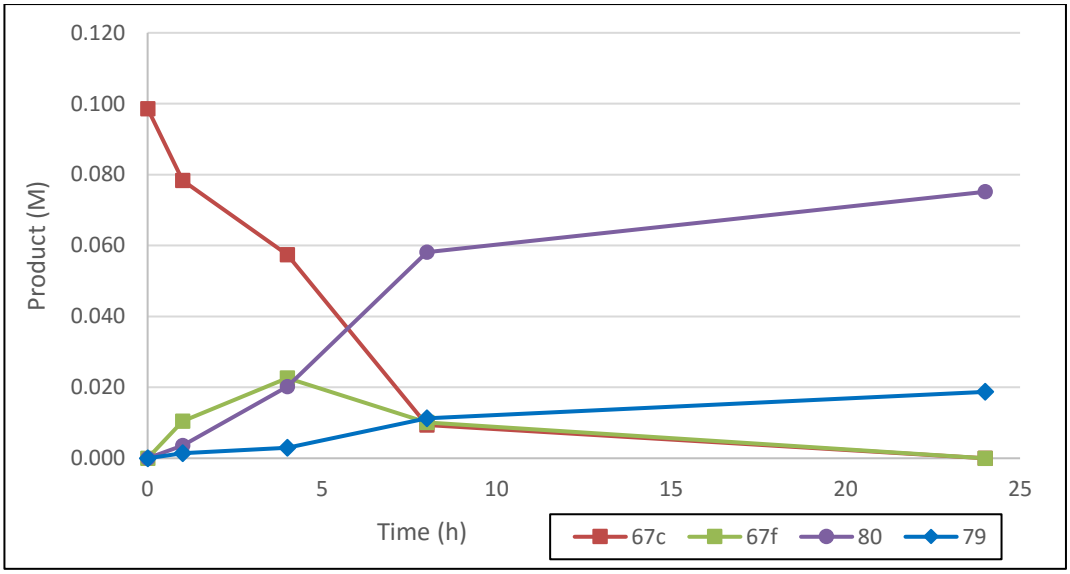


*Figure 3.6: Consumption of substrate **67f** and formation of products **78**, **79** and **80** and intermediate **67c** under the optimised conditions that favour the β-hydride elimination*

It appears that the configuration of the substrate does not affect the order of the reaction. Nevertheless, it is a major influence on the isomerisation (Figure 3.6). This process is an equilibrium between species **67c** and **67f** which is under thermodynamic control. Under these conditions, the formation of **67f**, the most thermodynamically stable isomer, is slightly favoured. The production of both cyclopentanes **80** and **79** are linear and constant over time.

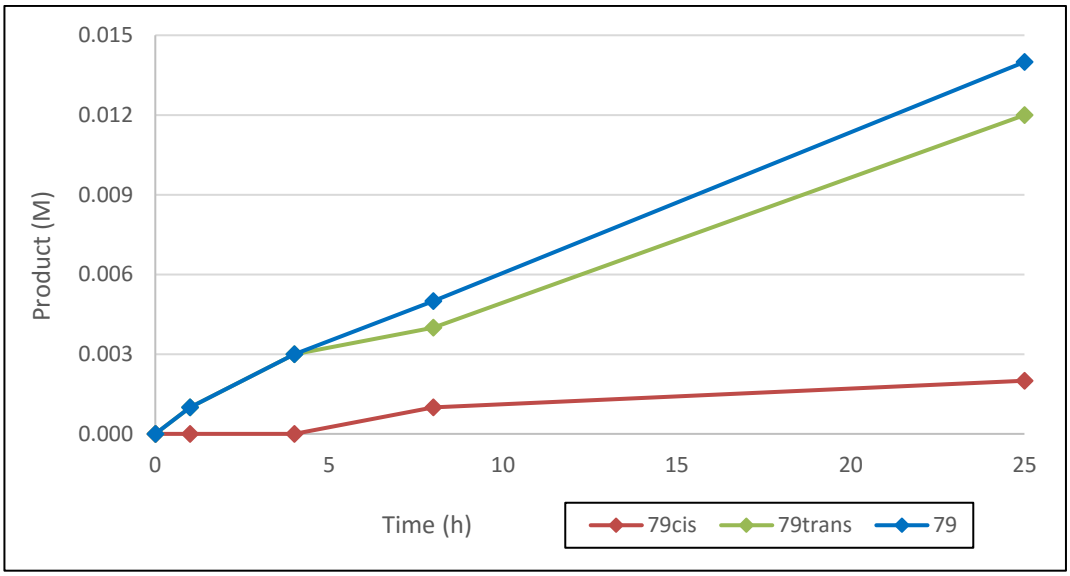
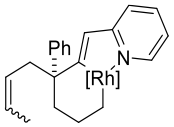


*Figure 3.7: Formation of cyclopentane **79** and itemisation into **79cis** and **79trans** under the optimised conditions that favour the β-hydride elimination.*

The lower degree of isomerisation of the *trans* double bond of **67f** in the reaction is reflected in the configuration of the products. In this case, a smaller amount of isomerised product **79*cis*** is obtained (Figure 3.7). Nevertheless, the total amount of product **79** is similar in both reactions. The rate of formation of **79** from the non-isomerised substrate (**79*cis*** from **67c** and **79*trans*** from **67f**) is also similar in both experiments. This is expected as only the terminal olefin undergoes 1,2-insertion. Therefore, it is hypothesised that the substituted alkene moiety does not participate in the metallacycle **XXIII** by coordination (Figure 3.8).



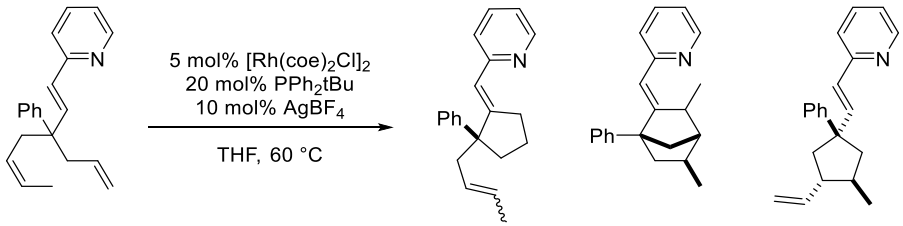
XXIII

*Figure 3.8: Intermediate metallacycle **XXIII**.*

3.4.2 Monitoring of the reaction conditions favouring the reductive elimination

Monitoring studies were also carried out for substrate **67c** under the optimal cycloisomerisation conditions to obtain norbornane **78** in which the reductive elimination is favoured over the β-hydride elimination (Table 3.12, Figure 3.9, Figure 3.10 and Figure 3.11). As mentioned in section 3.4.1, norbornane **81** was obtained in a maximum of 5% yield. Therefore, it has been omitted from the reaction plot.

*Table 3.12: Concentration of organic species of the cycloisomerisation of substrate **67c** favouring the reductive elimination at given times.*



67c **79** **78** **80**

Time (h)	67c	78 *s,s*	78 *s,a*	78	80	79*cis*	79*trans*	79
0	0.098	0.000	0.000	**0.000**	0.000	0.000	0.000	**0.000**
1	0.074	0.006	0.000	**0.006**	0.015	0.005	0.000	**0.005**
4	0.034	0.020	0.000	**0.020**	0.023	0.011	0.000	**0.011**
8	0.000	0.053	0.007	**0.060**	0.010	0.018	0.002	**0.020**
24	0.000	0.058	0.011	**0.068**	0.000	0.017	0.003	**0.020**

At first sight, more products were obtained. This was quite shocking as only cyclopentane **79** and norbornane **78** were expected to be formed. Contrary to the reaction with 10 mol% of P(2-furyl)$_3$, the isomerised substrate **67f** was not obtained at any reaction time. However, the most surprising result was to find that the β-hydride elimination product **80** was produced at the early stages of the reaction and then consumed.

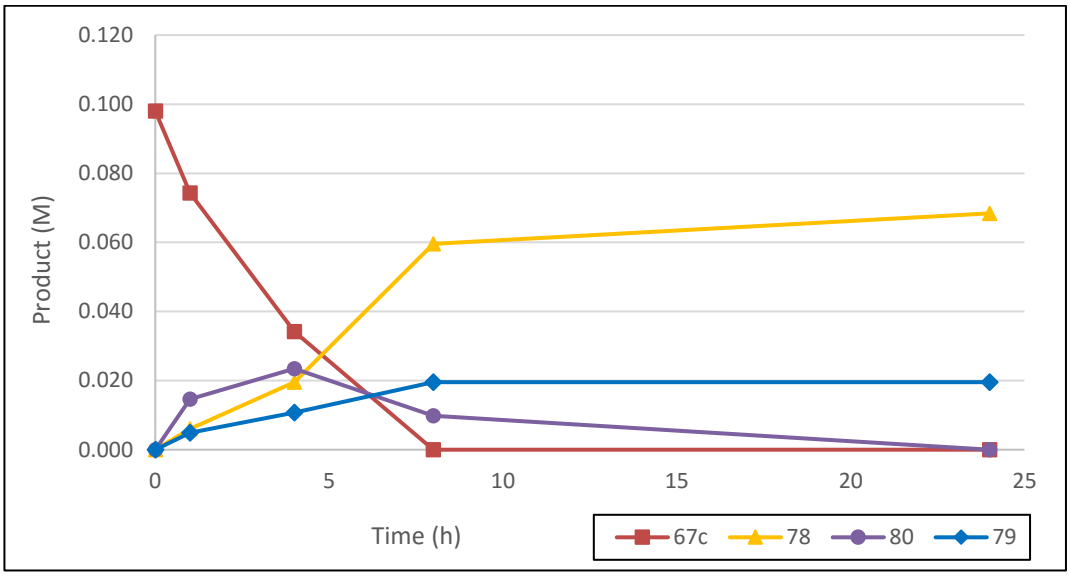


*Figure 3.9: Consumption of substrate **67c** and formation of products **78**, **79** and **79** and intermediate **67f** under the optimised conditions that favour the reductive elimination.*

The decay of substrate **67c** shows that reaction is under saturation kinetics and that if follows a 0 dependence order with respect to the substrate. It is clear that the consumption of the substrate **67c** is faster under these conditions than when 10 mol% P(2-furyl)$_3$ was used as the ligand. However, the formation of cyclopentane **79** is not apparently affected by the ligand. The isomerisation of **67c** into **67f** is not observed, but cyclopentane **80** is produced rapidly at the very beginning of the reaction and its concentration reaches the maximum around 4 hours. Then, it is slowly consumed. The rate of formation of norbornane **78** changes at t = 8 hours. A fast formation is observed on the first stage of the reaction followed by a decrease in rate. The concentration of cyclopentane **79** reaches the maximum at t = 8 hours too.

Then, a comparison of the formation of **78 *s*,*s*** and **78 *s*,*a*** was done (Figure 3.10).

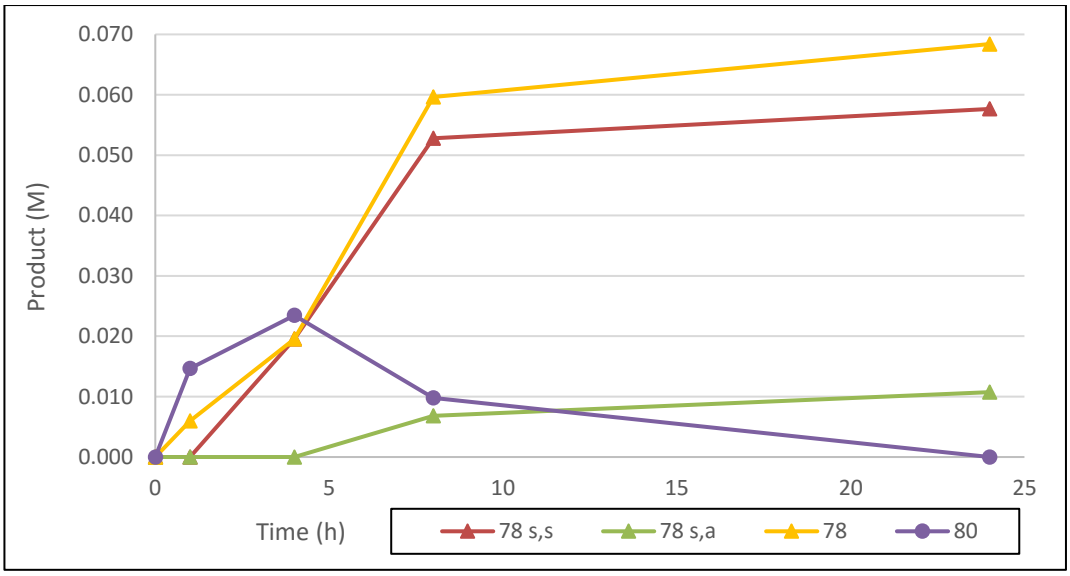


*Figure 3.10: Formation of products **80** and **78** and itemisation into **78 s,s** and **78 s,a** under the optimised conditions that favour the reductive elimination.*

The isomerisation of the *cis* double bond of the starting material was not observed at any time of the experiment. Nevertheless, some norbornane **78 *s*,*a*** was obtained after 8 hours. In that case, **67f** might have been formed in an untraceable concentration. An equilibrium between **78 *s*,*s*** and **78 *s*,*a*** was considered. This would indicate that the reductive elimination step from intermediate **XXI** is reversible. However, some control experiments denied this possibility (Section 3.4.3). In fact, the **79*cis*/79*trans*** ratio is very similar to **78 *s*,*s*/78 *s*,*a***, 5.67 and 5.3 respectively. This could suggest that **78 *s*,*a*** and **79*trans*** come from the same isomerisation process. The formation and consumption of cyclopentane **80** was intriguing. This transformation implies that the β-hydride elimination and the subsequent reductive elimination from intermediate **XXI** are reversible. The rate of formation of norbornane **78** apparently changes at t = 8 hours. At that time, substrate **67c** was totally consumed. It is noteworthy that the consumption of cyclopentane **70** is noticeable from t = 4h. Therefore, it is suggested that product **80** is transformed into norbornane **78** under these reaction conditions. While the optimisation results of the previous sections (Section 3.2.1) suggested that the β-hydride elimination and the reductive elimination steps were competitive, these monitoring studies show that cyclopentane **80** is indeed a transient intermediate when 20 mol% PPh_2tBu is used.

Moreover, the monitoring of the formation of cyclopentane **79** confirms this hypothesis (Figure 3.11).

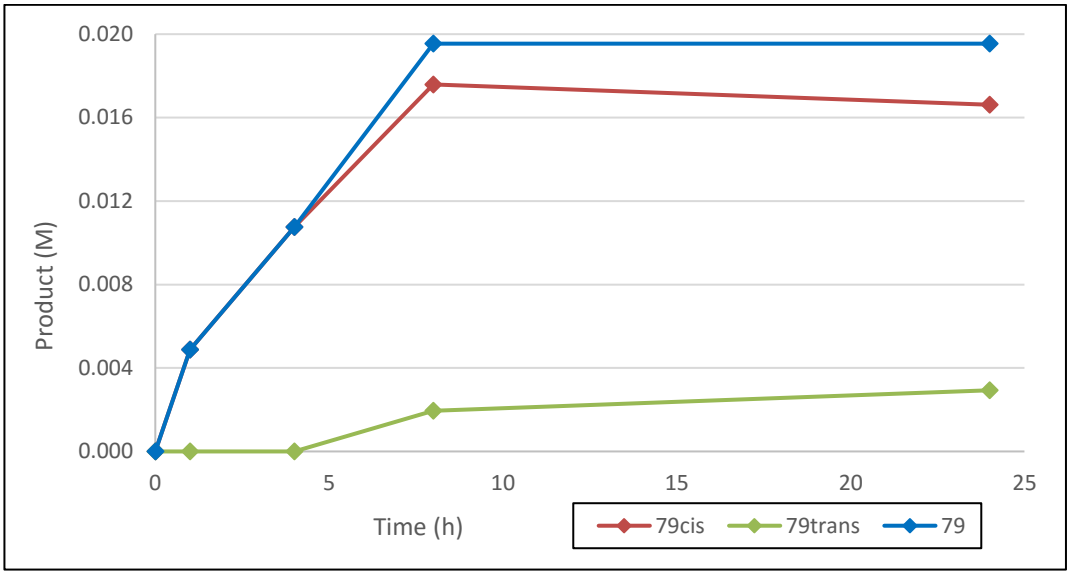
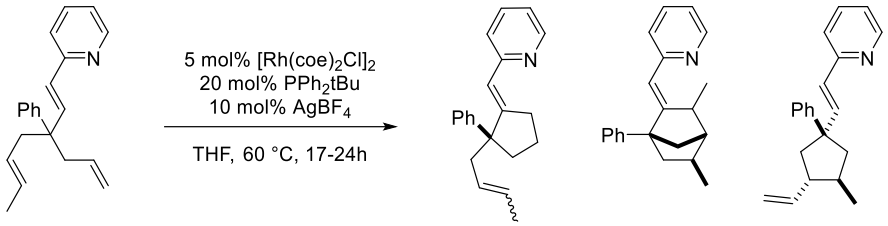


*Figure 3.11: Formation of cycloopentane **79** and separation into **79cis** and **79trans** under the optimised conditions that favour the reductive elimination.*

The amount of cyclopentane **79** reaches the maximum after 8 hours of reaction. Then, the concentration of this product remains constant at 0.020 M. At that time, all the substrate **67c** has been already consumed. These results confirmed that cyclopentane **79** can only be directly obtained from substrate **67c** and that cyclopentane **80** is only transformed into norbornane **78**. Isomer **79*trans*** is not observed until t = 8 hours and it probably starts to form between t = 4 hours and t = 8 hours. From some control experiments, it was observed that this product does not get isomerised under the reaction conditions. Therefore, epimerisation of the starting material **67c** might occur in an untraceable manner which might explain the low concentration of **79*trans*** in the system. The data shows that after 8 hours, the formation of **79*cis*** decays slightly, while the concentration of **79*trans*** increases almost imperceptibly. These two results fall inside the error limits. Hence, it can be considered that the formation of both **79*cis*** and **79*trans*** isomers stops at t = 8 hours.

The same monitoring studies were carried out with substrate **67f** (Table 3.13).

*Table 3.13: Concentration of organic species of the cycloisomerisation of substrate **67f** favouring the reductive elimination at given times.*



67f **79** **78** **80**

Time (h)	67f	78 *s,s*	78 *s,a*	78	80	79*cis*	79*trans*	79
0	0.097	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	0.080	0.000	0.008	0.008	0.006	0.000	0.002	0.002
4	**0.003**	**0.009**	**0.063**	**0.072**	**0.006**	**0.000**	**0.015**	**0.015**
8	0.000	0.010	0.056	0.066	0.012	0.002	0.015	0.017
24	0.000	0.016	0.058	0.074	0.006	0.002	0.015	0.017

The consumption of substrate **67f** catalysed under these conditions is faster than when 10 mol% P(2-furyl)$_3$ was used as the ligand. Moreover, it is apparently faster than the conversion of substrate **67c** under the same conditions. This would mean that the configuration of the starting material is important in this reaction. However, the point at t = 4 hours appears to be out of the expected limits. For example, the concentration of norbornane **78** is higher than at t = 8 hours. Therefore, it is probable that the reaction rate is similar for both substrates. As it was previously observed in the last monitoring, the isomerised substrate **67c** is not detected and cyclopentane **80** is formed and consumed during the length of the reaction. In this case, the maximum concentration of cyclopentane **80** is 0.012 M. This fact suggests that a smaller amount of product **70** is formed compared to the previous reaction. The amounts of cyclopentane **79** and norbornane **78** as a combination of regio- and diastereoisomers are comparable to the ones of the previous monitoring.

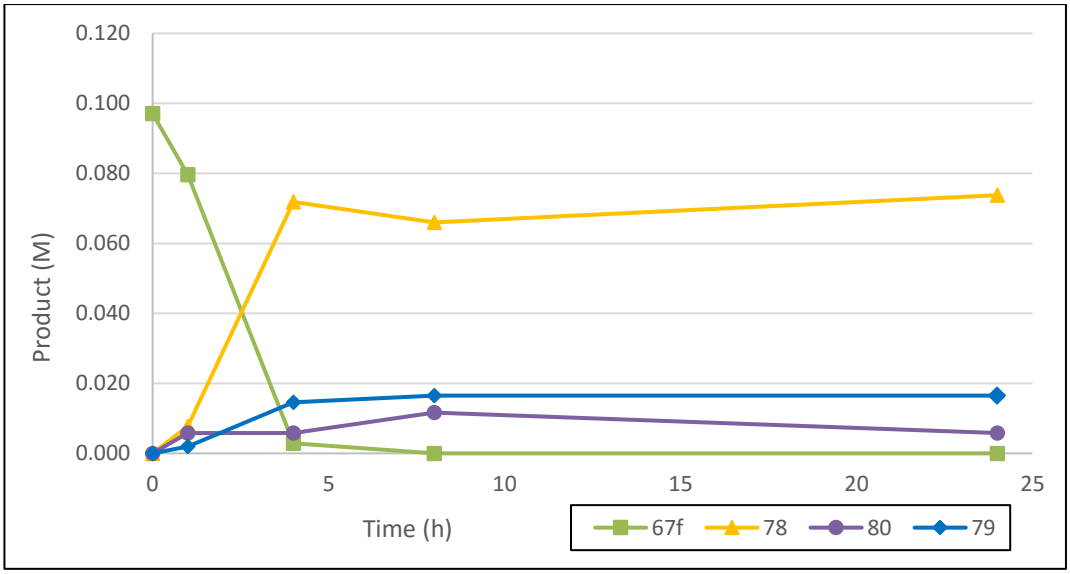


*Figure 3.12: Consumption of substrate **67f** and formation of products **78**, **79** and **80** and intermediate **67c** under the optimised conditions that favour the reductive elimination.*

The apparently fast consumption of substrate **67f** and the lack of more data points prevents us from reaching a conclusion about the reaction rate (Figure 3.12). However, considering the previous monitored reactions, it is likely that the system is under saturation kinetics and that the decay of the substrate is zero order. As it was previously observed for the reaction with substrate **67c**, the concentration of cyclopentane **79** reaches its maximum at t = 8 hours. In the same way, cyclopentane **80** is formed early on the reaction and then, totally consumed.

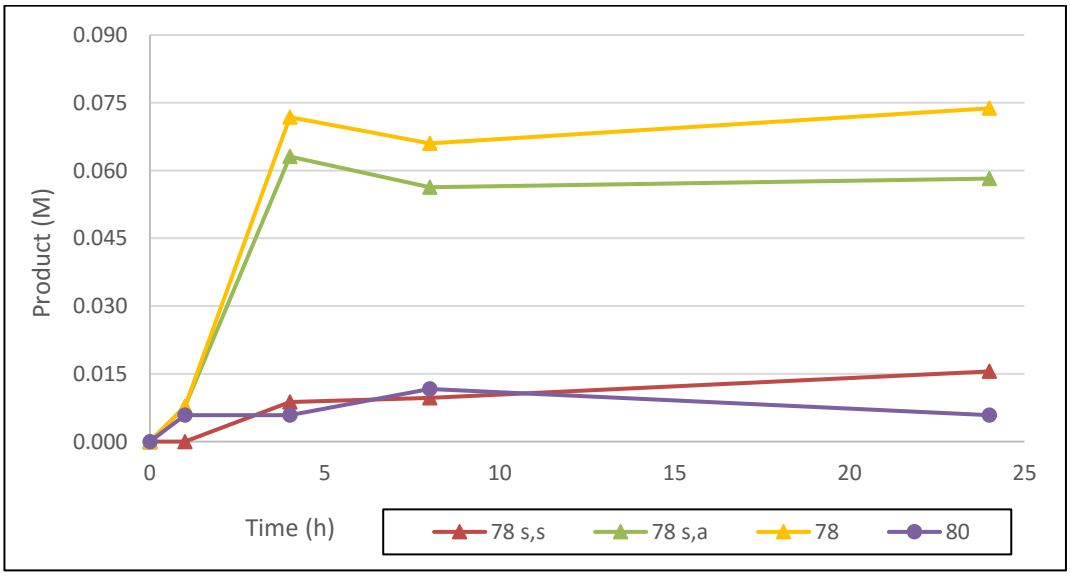


*Figure 3.13: Formation of products **80** and **78** and itemisation into **78 s,s** and **78 s,a** under the optimised conditions that favour the reductive elimination.*

The formation of the *syn*,*anti* norbornane happens in the first 8 hours of reaction (Figure 3.13). Then, it stops. On the contrary, the amount of norbornane **78** ***s*,*s*** is formed slowly before t = 8 h and then, the reaction rate apparently increases slightly. It is noteworthy that the slope of the decay of cyclopentane **80** from t = 8 hours to t = 24 hours is similar to the slope of formation of norbornane **78** ***s*,*s***, but of different sign. This would confirm the hypothesis that was stated previously: the transformation of cyclopentane **80** to norbornane **78** ***s*,*s*** is diastereoselective under the given conditions. Moreover, comparing the isomeric rations, **78** ***s*,*a***/**78** ***s*,*s*** = 3.6, while **79*trans***/**79*cis*** = 7.5. This definitely shows that norbornane **78** ***s*,*s*** is mainly formed from the recycling of cyclopentane **80**.

Then, the rate of formation of cyclopentane **79** in the reaction was compared (Figure 3.14).

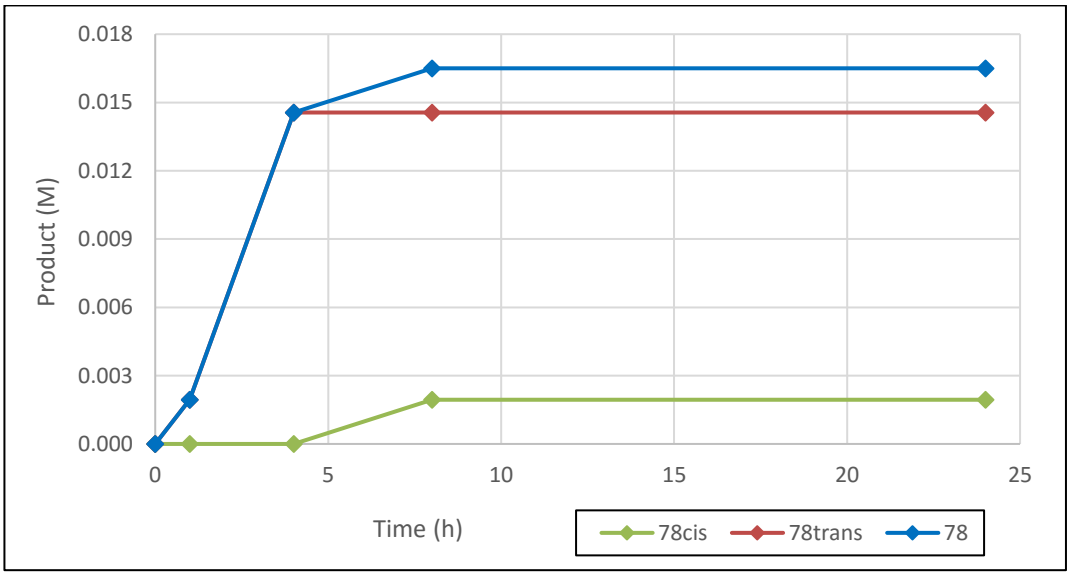


*Figure 3.14: Formation of cycloopentane **79** and separation into **79cis** and **79trans** under the optimised conditions that favour the reductive elimination.*

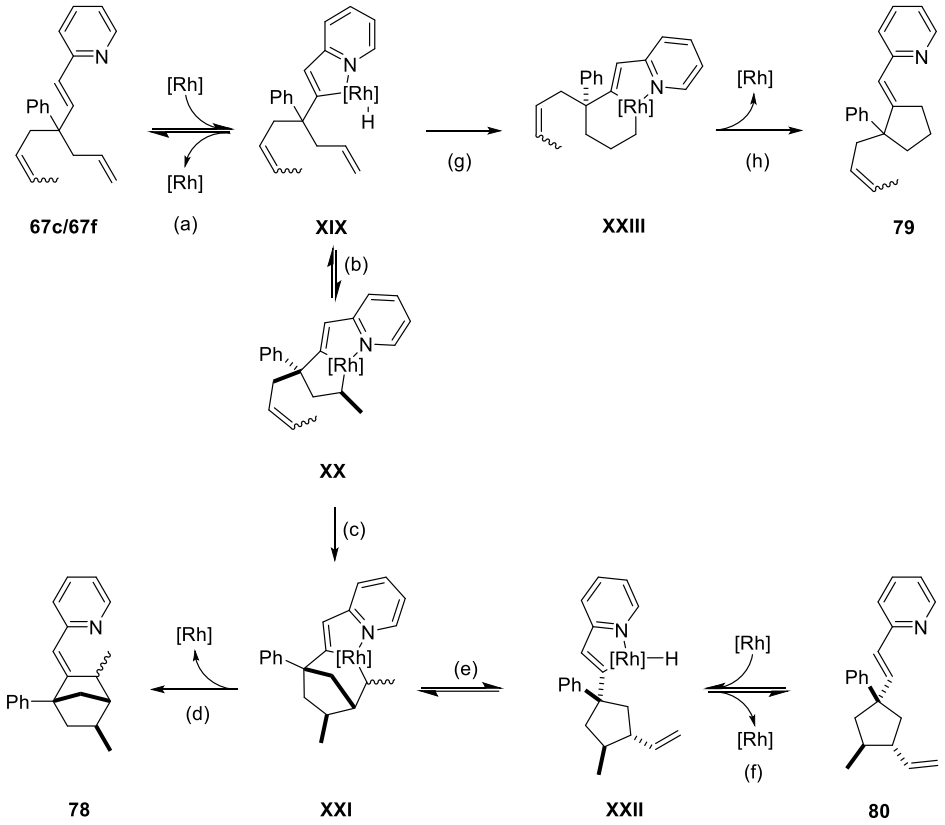
As it has been described for the reaction with **67c**, the formation of cyclopentane **79** stops after full consumption of substrate **67f**. In the same way, product **79*cis*** appears after few hours of reaction. As for the previous substrate, it is proposed that **79*cis*** is formed from the traces of the isomerised **67f** formed.

3.4.3 A revaluation of the reaction mechanism

Some conclusions can be drawn from the monitoring studies carried out under the different reaction conditions. Firstly, under the optimal β-hydride elimination conditions (10 mol% P(2-furyl)$_3$) the substituted double bond of substrate is significantly isomerised. Accordingly, the configuration of the starting material does not affect the course of the reaction and only the cyclopentanes **79** and **80** are

formed. Secondly, under the optimal conditions to obtain norbornane **78** selectively (20 mol% PPh_2tBu), this isomerisation is not so prominent. Thirdly, under these same conditions, cyclopentane **80** acts as a transient intermediate. Fourthly, the recycling process of cyclopentane **80** looks highly diastereoselective towards the *syn,syn* isomer. Finally, the technique that has been used to monitor the reaction presents some limitations, especially the low reproducibility at the first stage of the reaction. A more precise technique, which depends less on the human error and that provides more points, would be useful to extract some more accurate conclusions.

Therefore, the mechanism presented in Chapter 2 can be updated to the following one (Scheme 3.3).



*Scheme 3.3: Proposed updated mechanism for the formation of products **78**, **79** and **80** by cycloisomerisation of substrate **67c** or **67f**.*

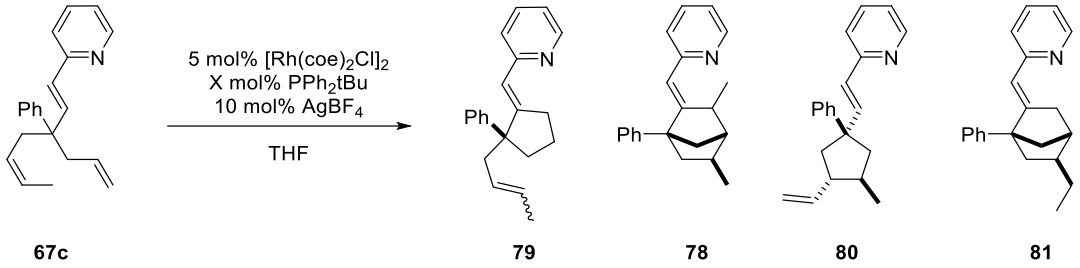
In that case, when using PPh_2tBu, cyclopentane **80** would undergo C-H activation (f) to form intermediate **XXII**. Then, migratory insertion (e) of the rhodium catalyst would occur to obtain intermediate **XXI**. Finally, this intermediate would undergo irreversible reductive elimination to form norbornane **78**. The results of these monitoring studies suggest that formation of **80** and **78** from intermediate **XXI** is a typical example of kinetic (**80**) *versus* thermodynamic (**78**) control. Moreover, this hypothesis is supported by ongoing computational studies.

3.5 Control experiments

3.5.1 The influence of the temperature on the product selectivity

The results presented in section 3.4 suggested that the reaction was a typical kinetic *vs.* thermodynamic control directed by the ligand effect. As previously observed, only traces of norbornane **78** were afforded with P(2-furyl)$_3$. This suggests that reductive elimination is not possible with that phosphine. Therefore, experiments to understand the control of the selectivity were only carried out with PPh$_2$tBu (Table 3.19).

*Table 3.14: Product distribution of the cycloisomerisation of substrate **67c** favouring the reductive elimination at given temperatures.*



67c **79** **78** **80** **81**

Entry*	Phosphine (mol%)	Temperature (˚C)	Time (h)	Conversion	79 (*cis/trans*)	78 (*s,s/s,a*)	80	81
1	**PPh$_2$tBu (20)**	25	118	44	7 (7:0)	15 (15:0)	20	3
2	**PPh$_2$tBu (20)**	40	49	100	21 (>10:1)	50 (50:0)	25	4
3	**PPh$_2$tBu (10)**	60	45	100	21 (18:3)	46 (40:6)	33	0
4[a]	**PPh$_2$tBu (10)**	60-90	48	100	22 (16:5)	77 (56:22)	0	0

* Standard: 2,4-dichlorobenzaldehyde. a) The reaction was carried out at 60°C for 24 hours. Then, the temperature was increased to 90°C and it was left for other 24 hours.

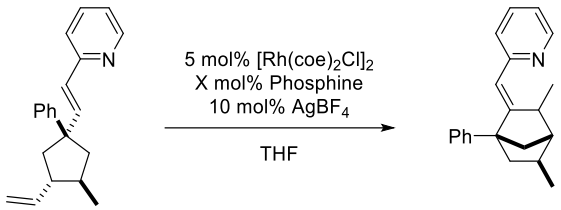
When the reaction was performed at room temperature during five days, 44% conversion was observed (Entry 1). It is noteworthy that all the expected products were obtained. When the temperature was increased to 40°C, the reaction was completed after 49 hours (Entry 2). Cyclopentane **79** was already obtained in 21%. This percentage is similar to the one observed at 60°C (see Section 3.2). Therefore, it suggests that formation of the 1,2-migratory insertion product cannot be controlled by the temperature. Previous data suggested that 2 equivalents of PPh$_2$tBu respect to rhodium were necessary for the reaction to be selective. For that purpose, a reaction using only 10% phosphine was carried out (Entry 3). Indeed, after 45 hours, only 46% of norbornane **78** was observed while a 33% of

cyclopentane **80** still remained. This results suggests that recycling of β-hydride elimination product is accelerated by the presence of two phosphines. The optimisation carried out previously on the symmetrical substrate **63** showed that the amount of product of single migratory insertion was enhanced at high temperature. Moreover, as shown in section 3.4, the formation of cyclopentane **79** after the starting material was totally consumed (t = 8 h). Therefore, a new experiment using 10% PPh_2tBu was designed (Entry 4). In that case, the reaction was carried out at 60°C during 24 hours and then, the temperature was raised to 90 °C. The system was left stirring for another 24 hours. The goal of this experiment was to prove that a higher energy could promote the recycling of cyclopentane **80** into norbornane **78** using 10% PPh_2tBu, whilst avoiding the increase of product **79**. The hypothesis was correct. Cyclopentane **80** was not obtained under those conditions and norbornane **78** was formed in a similar ratio as with 20% at 60°C. Unfortunately, lower diastereoselectivity was observed.

3.5.2 Examination of the transient character of cyclopentane 80

In order to prove the transient character of cyclopentane **80**, the product was used as substrate for some control experiments (Table 3.20).

*Table 3.15: Recycling of product **80** into **78**.*



80 **78**

Entry*	Phosphine (mol%)	Temperature (˚C)	Time (h)	Conversion (%)	78 (*s,s*/*s,a*)
1	**P(2-furyl)$_3$ (10)**[a]	60	24	20	0:2
2	**P(2-furyl)$_3$ (10)**	90	24	36	29:7
3	**P(2-furyl)$_3$ (20)**	90	24	18	9:9
4	**PPh$_2$tBu (10)**	60	24	12	n.d.
5	**PPh$_2$tBu (20)**	60	17	100	90:10
6	**PPh$_2$tBu (20)**[b]	60	24	100	77:12

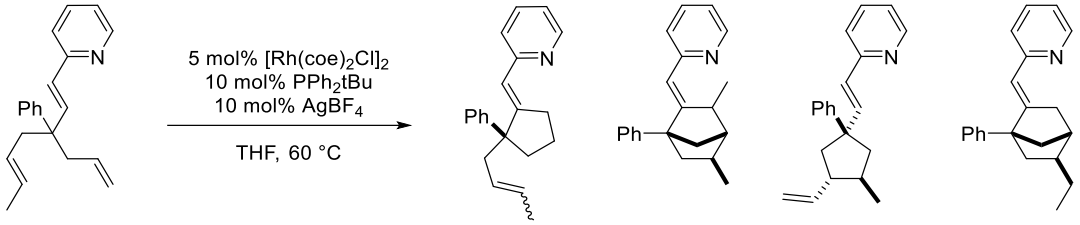
*Standard: 2,4-dichlorobenzaldehyde. a) Contaminated with 2% of **78 *s,a***. 18% of the mass balance was not identified. b) Starting material was contaminated with traces of **78 *s,a*** and **67**.

As expected, cyclopentane **80** could only be transformed into norbornane **78**. This indicates that the β-hydride elimination is reversible. Therefore, products **79** and **81** as well as substrates **67c** or **67f** should not be observed in the reaction mixture. Although, the results afforded by the optimisation experiments showed that P(2-furyl)$_3$ could not transform cyclopentane **80** into **78** at 60°C, a reaction was tested with 10% P(2-furyl)$_3$ (Entry 1). As expected, only small conversion was observed and **78** was formed in less than 2% yield. Therefore, the following reactions were tested at 90°C (Entries 2 and 3). At that temperature, using 10% phosphine only led to 36% conversion after 24 hours. This proves that using P(2-furyl)$_3$ can promote the reductive elimination but that more energy is required than when using PPh$_2$tBu. When the phosphine ratio was increased to 20%, only 18% conversion towards **78** was

observed. Surprisingly, the diastereoselectivity dropped from 4:1 to 1:1 (*syn,syn*/*syn,anti*). This indicates that the coordination of the two phosphines might prevent one of the steps (C-H activation, insertion or reductive elimination). Moreover, the coordination of two phosphines on the metal probably diminishes the diastereoselectivity. Then, the reaction was carried out with 10% PPh_2tBu (Entry 4). After 24 hours, only 12% conversion was observed. Unfortunately, the diastereoisomeric ratio could not be determined. However, when the 20 mol% PPh_2tBu was used, the reaction was completed after 17 hours (Entry 5). As previously hypothesised, this transformation is quite diastereoselective. A diastereisomeric ratio of 9:1 was observed towards the formation of the *syn,syn* isomer. This proves that 2 phosphines per atom of rhodium are required for the recycling of **80** to occur. That is either the C-H activation, the olefin insertion or the reductive elimination need the second phosphine. During the optimisation reaction, it has been shown that product **78** was obtained when using 10% PPh_2tBu (Table 3.1, Entry 21). Therefore, it is supposed that reductive elimination is not prevented by the decrease of phosphine ratio and that C-H activation is possible under these conditions. This might be suggested by the ease of C-H activation on substrates **67c** and **67d**. Thus, an educated guess would be that the step requiring two PPh_2tBu would be the olefin insertion. Surprisingly, this is totally opposite to the results observed for $P(2\text{-furyl})_3$ (Entries 2 and 3). The difference in electronegativity and sterics probably condition some of the elementary steps of the reaction. When the reaction was tested with substrate **80** being contaminated with mixture **67c** and **67f** in 28%, the diastereoselectivity dropped to 7 to 1 (Entry 6). This correlates with the previous observations.

In section 3.3.2, a high product selectivity towards norbornane **78** was obtained when the cycloisomerisation reaction of substrate **67f** was catalysed using 10 mol% of PPh_2tBu as a ligand (Table 3.7, Entry 6). Thus, it was surprising that this catalyst could not recycle the cyclopentane **80** into the norbornane **78** when **80** was used as the starting material (Table 3.20, Entry 4). In order to better understand this process, some further control experiments were carried out (Table 3.21).

*Table 3.16: Control experiments of the power of PPh_2tBu in the cycloisomerisation of substrate **67f**.*



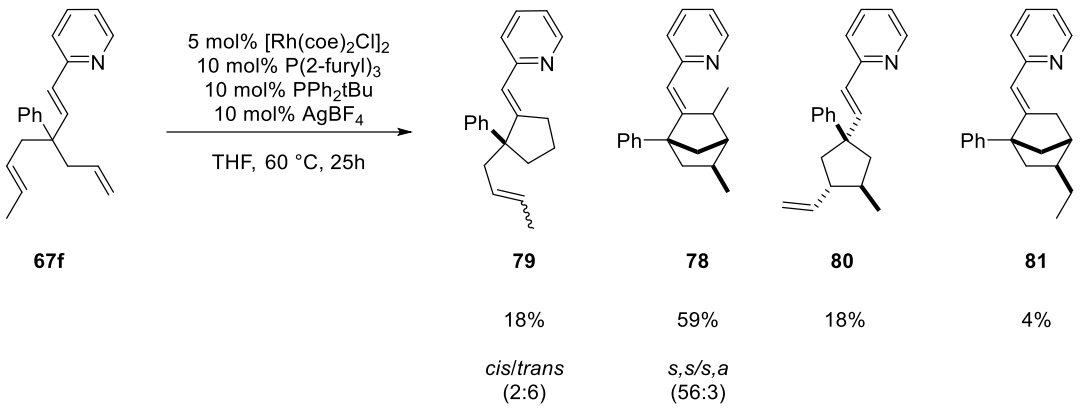
67f **79** **78** **80** **81**

Entry*	Time (h)	Conversion (%)	79 (*cis*/*trans*)	78 (*s,s/s,a*)	80	m.b.
1	24	100	18 (16:2)	70 (14:56)	8	100
2	24	100	17 (15:2)	78 (17:61)	0	100
3	2	19	4 (0:4)	7 (0:7)	9	100
4	6	66	9 (0:9)	33 (0:33)	17	98

*Standard:2,4-dichlorobenzaldehyde

When the substrate was subjected to a 24-hours reaction, norbornane **78** was obtained in over 70% yield (Entries 1 and 2). In that case, only traces of cyclopentane **80** were obtained. In contrast, shorter reaction times afforded cyclopentane **80** in identical or higher yield (Entries 3 and 4). This suggests that, under these reaction conditions, the cyclopentane **80** can be converted into norbornane **78**. The opposite results obtained when treating diene **67f** or cyclopentane **80** might be due to a difference in the nature of the catalyst under the different conditions.

3.5.3 The influence of using two different phosphines simultaneously



Scheme 3.4

In this experiment, both of the optimal phosphines in 10% ratio each were mixed together. After 25 hours, 59% of norbornane **78** was obtained, while only 18% of cyclopentane **79** was observed. Comparing these results to the ones afforded by 10% PPh_2tBu in 24 hours (Table 3.1, Entry 21), recycling of cyclopentane **80** is more favourable under these conditions. This, in fact, correlates to the observations previously discussed; the bulkiness provided by two phosphines accelerates the reductive elimination pathway. However, as $P(2\text{-furyl})_3$ is much smaller than PPh_2tBu, the recycling is not completed after one day. Interestingly, cyclopentane **79** is less present in this mixture. The results, for this specific product are much similar to the ones afforded by 10 mol% $P(2\text{-furyl})_3$, which can indicate that the first migratory insertion is favoured by this phosphine.

3.6 Conclusions

The selective formation of cyclopentane **80** and norbornane **78** was achieved after the ligand optimisation. Norbornane **78** was obtained as an enriched mixture of diastereoisomers when 20 mol% of the bulky PPh_2tBu was used a ligand. On the contrary, the small $P(2\text{-furyl})_3$ promoted the cycloisomerisation towards cyclopentane **80**. The monitoring studies demonstrated that under the optimal conditions for the reductive elimination pathway, the cyclopentane **80** is a transient intermediate of the reaction. The control experiments with product **80** as the starting material showed total conversion when 20 mol% of PPh_2tBu was used as a ligand. The *syn,syn* norbornane was obtained as the major diasteroisomer in a dr of 9:1. Further control experiments implied that the catalyst might be different when the reaction is done with the cyclopentane **80** as a substrate than with the diene **67**. Moreover, these studies showed that the differentiation of cyclopentane **80** and norbornane **78** is under kinetic *vs*. thermodynamic control.

As it was previously discussed in Chapter 2, the formation of cyclopentane **80** is diastereoconvergent as only one diastereoisomer is obtained independently of the configuration of the starting material. On the contrary, the formation of norbornane **78** can be considered diastereospecific. This isomerisation clearly observed in the presence of the Rh-P(2-furyl)$_3$ catalyst would explain the moderate diastereoselectivity. The isolation of the products was problematic and only moderate isolated yields were obtained.

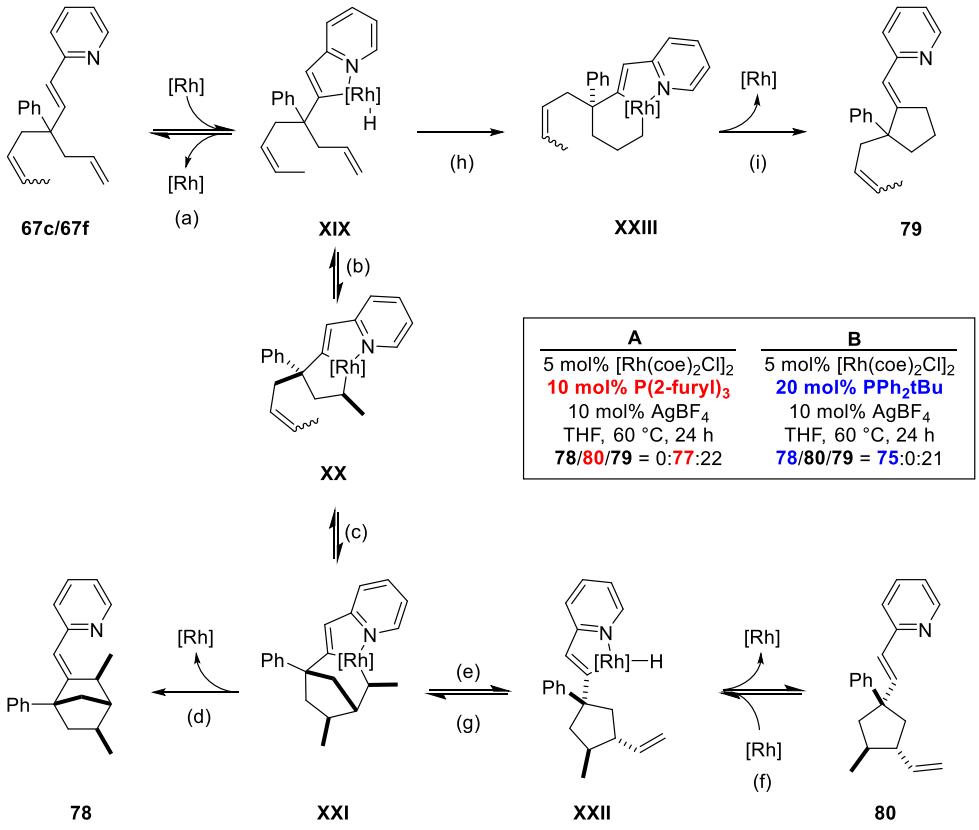
By monitoring the reaction under both sets of conditions, preliminary results of the reaction kinetics were obtained. These studies show that the cycloisomerisation follows the catalytic kinetics similar to which Michaelis and Menten described for enzymes.[65,66] In the reported case, it is considered that the catalyst gets saturated with the starting material and that the reaction is then zero order in substrate. The four different experiments carried out also show that the neither the use of different phosphines nor the configuration of the alkene apparently affect the kinetics of the reaction.

Unfortunately, the formation of cyclopentane **79** is not stopped under the studied conditions. An average of 20% yield is always observed for this product. Therefore, a new approach has to be designed to inhibit its formation.

Chapter 4 : Influence of the modifications of the substrate

4.1 Introduction

In Chapter 3, the optimisation for the control of the rates of reductive elimination *versus* β-hydride elimination was discussed. It was observed that the use of P(2-furyl)$_3$ as a ligand favours the β-hydride elimination (e) and prevents the reductive elimination (d) to occur (Scheme 4.1). In contrast, the rhodium-PPh$_2$tBu catalyst can catalyse both pathways. However, it was also observed that the product of the β-hydride elimination **79** can act as a transient intermediate which can then be recycled into the norbornane **77** in the presence of the Rh-PPh$_2$tBu catalyst (Scheme 4.1, f and g). However, with both catalysts the amount of cyclopentane **78** obtained from the 1,2-insertion (h) was still important (Scheme 4.1).



*Scheme 4.1: Proposed mechanism for the formation of products **78**, **79** and **80** by cycloisomerisation of substrate **67c** or **67f**. **A**: Optimised conditions that favour the β-hydride elimination. **B**: Optimised conditions that favour the reductive elimination and that recycle the β-hydride elimination product (**80**) into the reductive elimination product (**78**).*

Following these ideas, in this chapter two different aspects of the reaction are discussed. First of all, the aim was to study the reproducibility of the results observed in different substrates. And secondly, the objective was to accelerate the second migratory insertion and suppress the formation of **79** by taking other factors into account. The elucidation of the structure of the products previously described in section 2.2.2.1 was key for the identification of the molecules described in this chapter. *Syn,syn* and *syn,anti* norbornanes described herein have the same characteristic ^{1}H NMR pattern already showed in Chapter 2. The characteristic peaks for cyclopentanes **79** and **80** were also very clear (Figure 4.1).

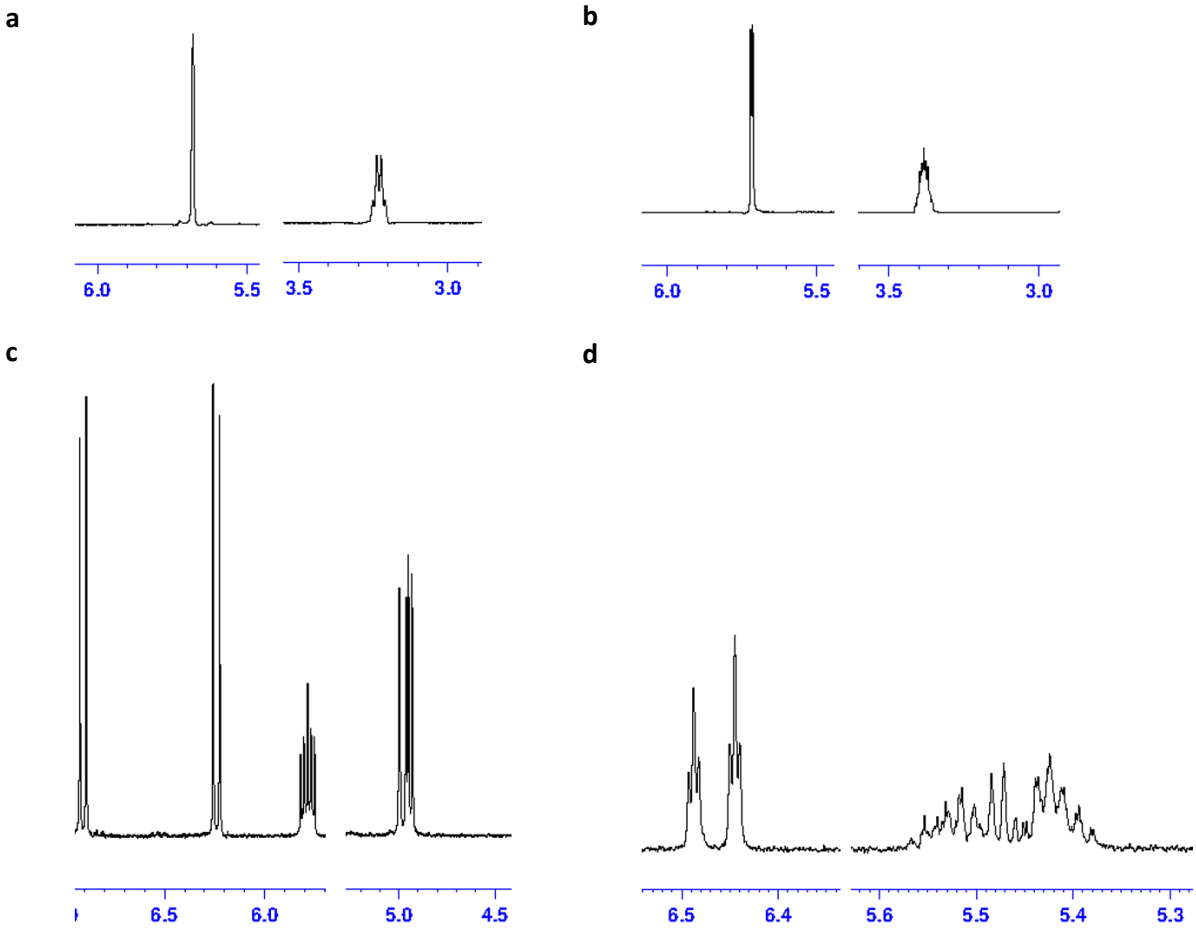


*Figure 4.1: ^{1}H NMR of products **78 s,s**, **78 s,a**, **80** and **79**. a) Detail of the characteristic olefinic and methine signals of product **78 s,s**. b) Detail of the characteristic olefinic and methine signals of product **78 s,a**. c) Detail of the characteristic olefinic signals of product **80**. d) Detail of the characteristic olefinic signals of product **79**.*

The norbornane **78*s, s*** presents two main characteristic peaks (Figure 4.1, a). A very well defined singlet appears around 5.7 ppm. However, the most characteristic signal corresponds to a quartet at 3.2 ppm. Similar peaks can be observed for norbornane **78*s, a*** (Figure 4.1, b). As discussed previously, these two signals are more complex. In this case, a doublet with a small coupling constant is present at 5.7 ppm

and a multiplet at 3.4 ppm. The cyclopentane **80** has the most characteristic peaks in the olefin region of the spectrum (Figure 4.1, c). First of all, two doublets appear between 6.0 and 7.0 ppm and they correspond to the olefinic protons of the vinyl-pyridine moiety. Then, two multiplets integrating for 1 and 2 protons respectively appear between 5.0 and 6.0 ppm and correspond to the terminal alkene of the molecule. Cyclopentane **79**, which is presented in the figure as a *cis*/*trans* mixture, has two triplets for the olefinic protons of the vinyl-pyridine around 6.45 ppm and a broad multiplet for the other olefinic protons between 5.3 and 5.6 ppm (Figure 4.1, d).

4.2 The effect of the substituent at the quaternary carbon atom

It was reasoned that a larger substituent should accelerate the 2,1-insertion of the olefin moiety in intermediate **XXII** to form the metallacycle **XXI** (Scheme 4.1, g). As postulated by Richard Beesley, Christopher Ingold and Jocelyn Thorpe in 1915, the increase of steric bulkiness in a quaternary carbon would bring two of the geminal substituents in close proximity.[17] Therefore, the second migratory insertion (**XX** to **XXI**, c) should be also accelerated (Scheme 4.1, c). By doing so, a decreased of the amount of cyclopentane **79** in favour of more cyclopentane **80** and norbornane **78** was expected. However, the same effect could also accelerate the reconversion of **XXII** into **XXI** (g), which would affect the **78**/**80** product ratio. Finally, the replacement of the phenyl group in **67** with a larger substituent could also prevent the insertion of the catalyst into the vinylic C-H bond of **67** and **80**.

Three different substrates were synthesised (Figure 4.2).

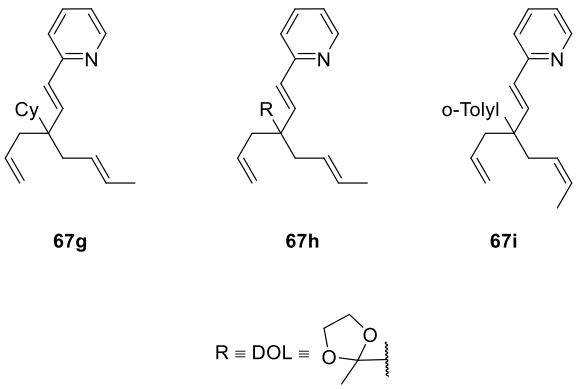
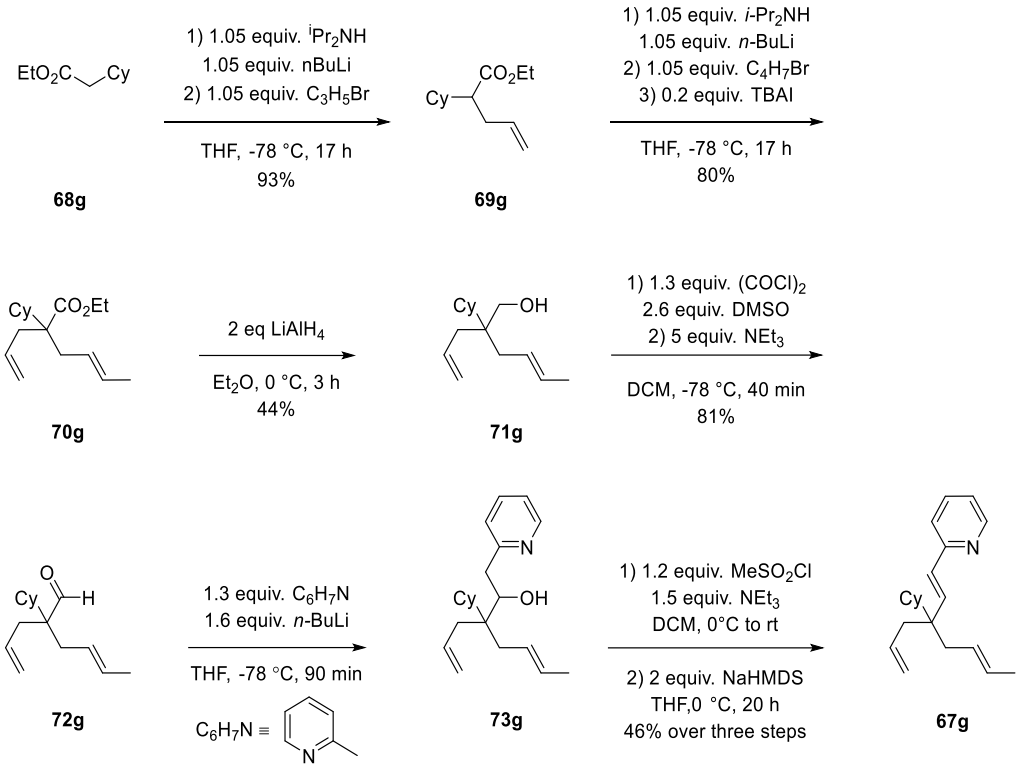


*Figure 4.2: Substrates **67g** to **67i**.*

4.2.1 Synthesis of substrates 67g to 67i

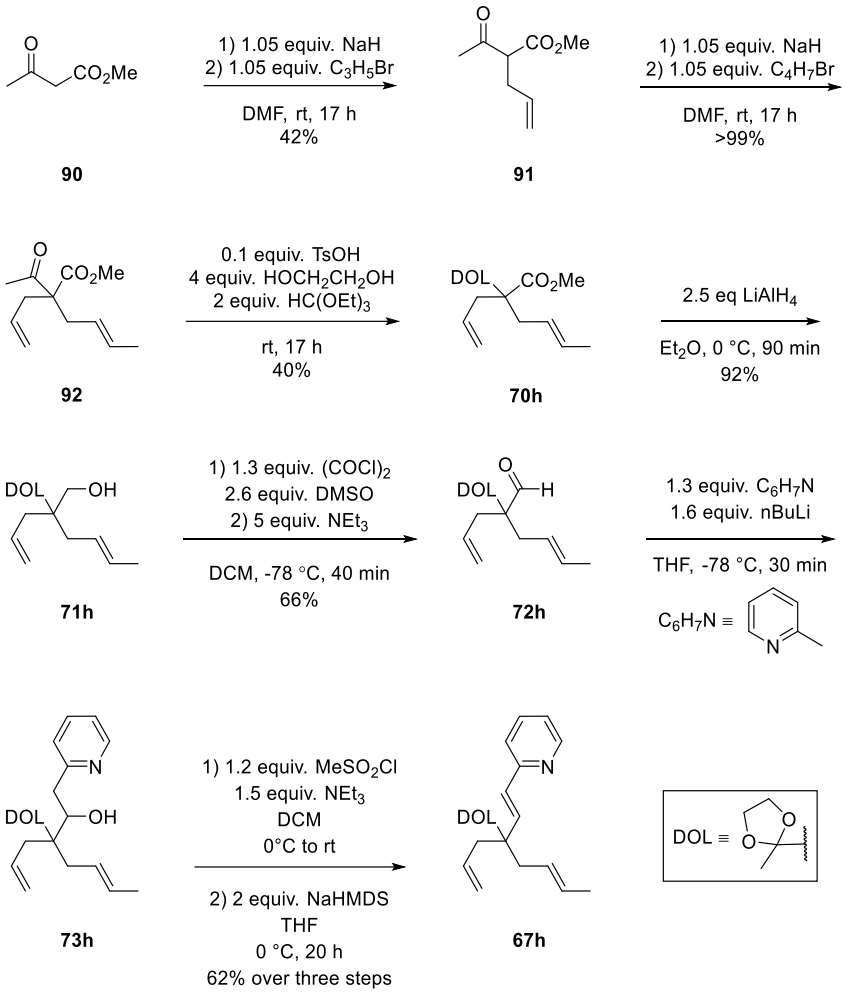
The syntheses of the products are described in the following schemes. The synthesis of substrate **67g** was started with the allylation in excellent yield of commercially available methyl cyclohexylacetate **68g** (Scheme 4.2).



*Scheme 4.2: Synthesis of substrate **67g**.*

Then, a second allylation was carried out using crotyl bromide to obtain intermediate **70g** in good yield. After that, reduction of the ester moiety was accomplished with lithium aluminium hydride. For this reaction, two equivalents of $LiAlH_4$ were used for the reaction to reach completion. Intermediate **71g** was then oxidised in 81% yield. The aldehyde was then reacted with the α-lithiated methylpyridine to form **73g**. Then, secondary alcohol **73g**, which was obtained as a mixture of diastereoisomers, was mesylated in few hours. Finally, the sulfonate moiety was eliminated with sodium bis(trimethylsilyl)amide to afford substrate **67g** in 46% yield over three steps, which was formed as an enriched mixture of *E*-isomer. An unknown impurity which could not be separated was carried through the synthesis from compound **70g**.

The synthesis of substrate **67h** was completed in 8 steps (Scheme 4.3). In line with the syntheses previously described. Only the protection of the ketone moiety in the third step has not been already discussed.

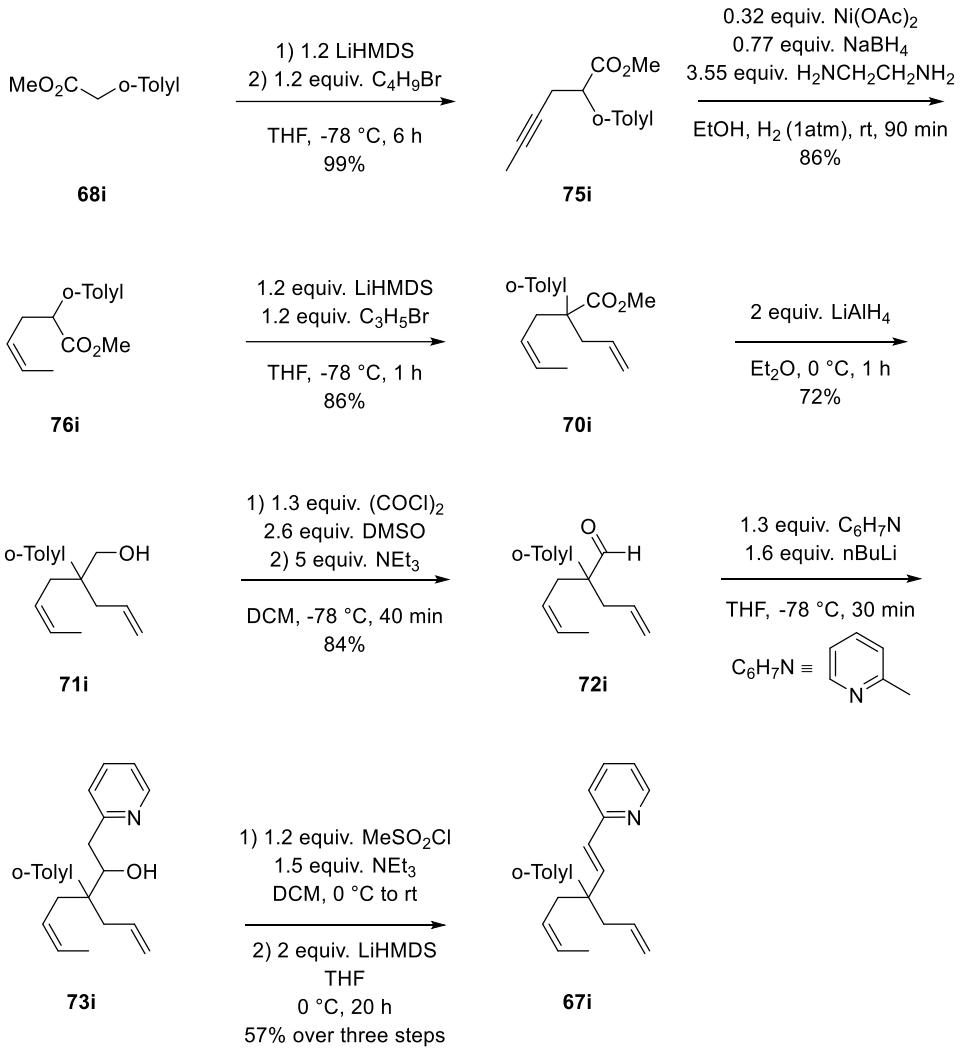


*Scheme 4.3: Synthesis of substrate **67h**.*

Methyl acetoacetate was allylated in a 42%, besides some *bis*-allylated product. The separation between products was especially difficult and only 42% of intermediate **91** was recovered clean. Once the two products were separated, the synthesis was carried through with the mono-substituted intermediate (**91**) which underwent a second allylation under the same conditions to obtain intermediate **92** in excellent yield. At that stage, the ketone moiety was transformed into the dioxolane group. In spite of carrying the reaction out several times to reach completion, some starting material was still unreacted. The excess of water and the little power of the dehydrating agent $HC(OEt)_3$ might explain the poor performance of this reaction. Then, the usual lithal reduction of the intermediate **70h** afforded the alcohol **71h** in excellent yields. A Swern reaction was then carried out and the aldehyde **72h** was obtained in moderate yields. In this case, two consecutive oxidations were required for the reaction to be completed. Finally, the introduction of the vinylpyridine moiety was achieved after three consecutive steps: addition of α-lithiated methylpyridine, conversion of the alcohol into a good leaving

group and elimination. Substrate **67h** was obtained as the *trans*-isomer, but an unknown impurity which could not be separated was carried through the sequence since the synthesis of compound **70h**.

Substrate **67i** was synthesised as a pure *cis* isomer applying the already described synthesis ().



*Scheme 4.4. Synthesis of substrate **67i**.*

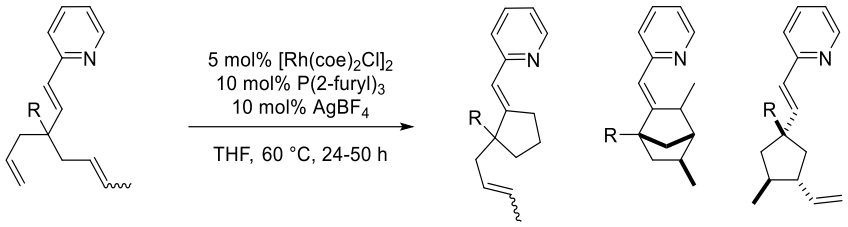
First of all, the propargylation of the ester **68i** was carried out at low temperature in excellent yields. The alkyne was then reduced to the pure *cis* olefin using the method described by Brown. After that, the allylation of the intermediate **76i** afforded ester **70i** in 86% yield. The reduction with $LiAlH_4$ of the intermediate **70i** provided the correspondent alcohol which was submitted to a Swern oxidation to obtain **72i** in good yields. Finally, 2-picoline was α-lithiated to attack the aldehyde. This step introduced the pyridine moiety into the molecule. The secondary alcohol **73i** was mesylated and consecutively eliminated using two equivalents of LiHMDS to obtain substrate **67i** in 57% yield after three steps.

4.2.2 Results

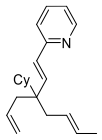
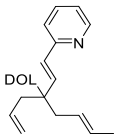
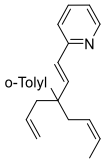
The influence of the substituent is summarised in section 4.2.2.1 for the β-hydride elimination conditions and in section 4.2.2.2 for the optimal reductive elimination conditions. Norbornane **81** could not be identified and isolated. Therefore, it has been removed from the table.

4.2.2.1 Examination of the reaction conditions that favour the β-hydride elimination

*Table 4.1: Cycloisomerisation of substituted substrates **67g-i** favouring the β-hydride elimination.*



67 **79** **78** **80**

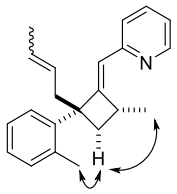
Entry*	Substrate	Time (h)	Conversion (%)	79 (*cis*/*trans*)	78 (*s,s*/*s,a*)	80[a]	m.b. [b]
1	 **67g**	24	100	13 (2:11)	8 (3:5)	77	97
2	 **67h**	24	89	15 (5:10)	traces	60	89
3	 **67i**	24	88	8 (3:5)	0	54	88
4		49	100	4 (n.d.)	8 (n.d.)	73 (50%)	93

*Standard: 2,4-dicholorbenzaldehyde, 1 equivalent. a) The isolated yields of the major isomer of cyclopentane **80** are between parentheses. b) m.b = mass balance

When the reaction was carried out with P(2-furyl)$_3$, the expected product **80g** was obtained in 77% yield, which is a comparable result to those of the reactions conducted with **67c** and **67f**. Unfortunately, the cyclopentane **79g** was also obtained in 13% yield (Entry 1). A total of 10% yield of the combined *syn,syn* and *syn,anti* diastereoisomers of **78g** was obtained under these conditions. Hence, the reaction with substrate **67g** follows the trend observed on substrate **67c** and **67f**. The rhodium-P(2-furyl)$_3$ catalysts favours the β-hydride elimination of intermediate **XXII** over the reductive elimination.

The optimised conditions for β-hydride elimination were also tested with the dioxolane substituted substrate **67h** and 89% conversion was observed (Entry 2). This indicates that the reaction rate might be slightly slower when comparing those of substrates **67c** and **67f**. When using P(2-furyl)$_3$ as a ligand, cyclopentane **80h** was obtained in a 60% yield while only traces of norbornane **78h** were present in the reaction mixture. Unfortunately, 1,2-insertion product **79h** was obtained in 15% yield. These results show that the replacement of the phenyl moiety for the dioxolane group did not affect the course of the reaction.

Finally, the reaction was carried out with *ortho*-tolyl substituted substrate **67i** and only 88% conversion was observed after 24 hours (Entry 3). Cyclopentane **80i** was obtained in 54% yield and surprisingly only 8% of the starting material was converted into the 1,2-insertion product **79i**. However, the four-membered ring **93i** was obtained in 26% yield as a mixture of three different isomers. This product could not be completely separated from cyclopentane **79i**. While the structure of the major isomer of **66i** was identified with ^{1}H, ^{13}C and COSY, the configuration was elucidated by NOESY (Figure 4.3).

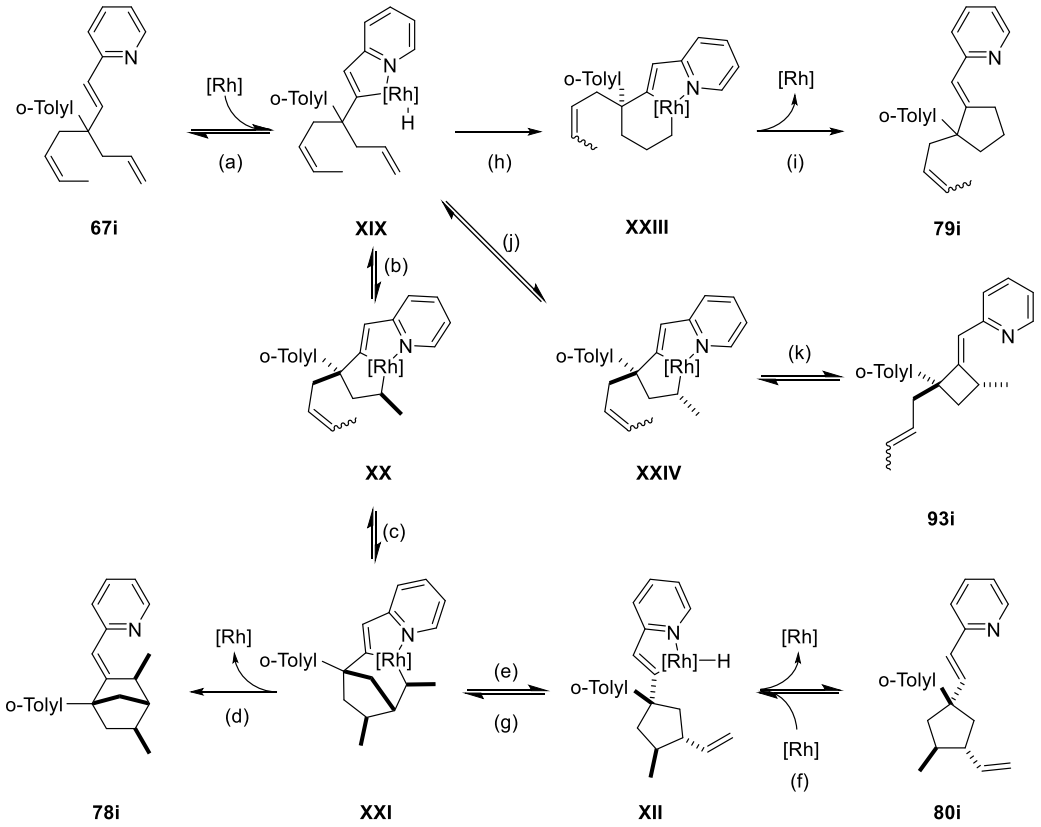


92i

*Figure 4.3: Space correlations of cyclobutane **93i** observed with NOESY and selective NOESY NMR experiments.*

As discussed in Chapter 2, a similar product was already described by Daniel J. Tetlow for substrate **63i** (Scheme 2.4). The four-membered ring **93i** is the product of the reductive elimination (k) of intermediate **XXVI** (Scheme 4.5). This five-membered ring metallacycle is formed by the migratory insertion of the terminal olefin (j). However, the configuration of this intermediate does not allow the migratory insertion of the substituted olefin to occur. The reversibility of these two steps (j, k) permits to recycle product **67i** into intermediate **XIX** which can then undergo 2,1-insertion to give **XX** (b) or the

1,2-insertion to intermediate **XXIII**. The formation of this intermediate shows that the diastereoselectivity is determined by the ability of **XX** to undergo migratory insertion to give **XXI**, whereas **XXIV** cannot.

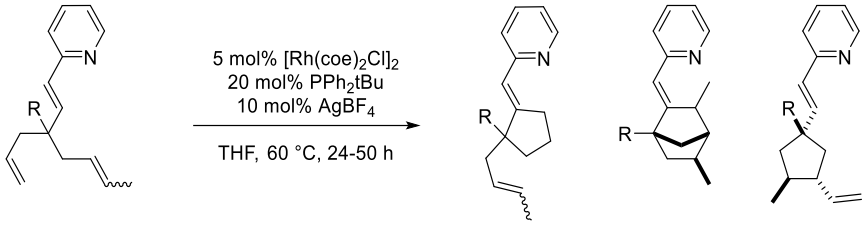


*Scheme 4.5: Proposed mechanism for the formation of products **78i, 79i, 80i** and **93i**.*

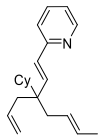
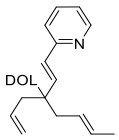
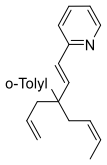
Although the low yield of cyclopentane **79i** was a promising result, we were cautious, as the presence of both the four-membered ring product and the unreacted starting material could increase the yield of product **79** after longer reaction times. Therefore, the reaction was then left for 48 hours (Entry 4). To our delight, total conversion was observed and the four-membered ring was obtained in only 7% yield. But, the most gratifying result was that the formation of cyclopentane **79i** remained limited to only 4%.

4.2.2.2 Examination of the reaction conditions that favour the reductive elimination

*Table 4.2: Cycloisomerisation of substituted substrates **67g-i** favouring the reductive elimination.*



67 79 78 80

Entry*	Substrate	Time (h)	Conversion (%)	79 (*cis*/*trans*)	78 (*s,s*/*s,a*)[a]	80	m.b. [b]
1	 **67g**	24	100	18 (0:18)	68 (8:60) (17%)	14	100
2	 **67h**	24	100	17 (4:13)	46 (13:33)	34	97
3		48	100	20 (7:13)	33 (10:23)	35	87
4	 **67i**	24	100	10 (4:6)	68 (57:11)	16	94
5		48	100	10 (6:4)	69 (59:10) (40%)	6	85

*Standard: 2,4-dicholorbenzaldehyde, 1 equivalent. a) The isolated yields of the major isomer of norbornane **78** are between parentheses. b) m.b. = mass balance

Under the conditions optimised to favour the formation of the norbornane derivatives **78**, the 1,2-insertion product **79g** was obtained in 18% as a single isomer (Table 4.2) Norbornane **78g** was obtained in 68% yield and cyclopentane, **80g** in 14% yield. The monitoring studies discussed in the previous chapter showed that cyclopentane **80** is normally quickly recycled to norbornane **78 *s,s*** when 20 mol% of PPh_2tBu is used. Thus, the presence of remaining **80g** in this reaction might indicate that the steric

hindrance provided by the cyclohexyl moiety could disfavour some steps of the recycling process. Although the product selectivity is clearly diminished with substrate **67g**, this substrate follows the same tendency observed for substrates **67c** and **67f** (R = Ph).

Then, the dioxolane substituted substrate **67h** was tested and the reaction was completed in 24 hours (Entry 2). Unfortunately, poor product distribution was observed for this substrate. The β-hydride elimination product **80h** was obtained in 34% yield, while **78h** was obtained in a combined 46% yield. Then, in order to study the conversion of **80h** into **78h**, the reaction was left for 48 hours (Entry 3). Nevertheless, cyclopentane **80h** was still obtained in a high yield and therefore only poorly recycled into norbornane **78h**. The 1,2-insertion product **79h** was still obtained in approximately 17%. It is noteworthy that the ratio of *syn,syn* and *syn,anti* diastereoisomers is similar to the *cis*-*trans* ratio of the cyclopentane **79**. As the control experiments in section 3.5.3 showed that conversion of cyclopentane **80** is highly selective to the *syn,syn* diastereoisomer, the similarity between the ratios of norbornane **78h** and the cyclopentane **79h** might indicate that the recycling of cyclopentane **80h** cannot occur. As it was discussed in the previous chapter, the consumption of the substrate is faster when 20 mol% of PPh_2tBu is used as a ligand than when the Rh-P(2-furyl)$_3$ complex catalyses the cycloisomerisation reaction.

After 24 hours, **78i** was obtained in a combined yield of 68%, while cyclopentane **80i** was only obtained in 16% yield (Entry 4). Longer reaction times did not apparently improve the formation of the norbornane products as **78i** was obtained in 69% yield (Entry 5). However, the yield of cyclopentane **80i** dropped to 6%. It is noteworthy that the completely identified mass balance for this reaction at 48h was of 85% and of 94% at 24h. Therefore, it could be considered that the cyclopentane **80i** might be recycled into an unknown product or reaction intermediate. In this case, the four-membered ring intermediate **93i** was not observed. In agreement with the monitoring studies of substrate **67c** and **67f** (Section 3.4), the reaction with the Rh-PPh_2tBu catalyst is faster than when 10 mol% of P(2-furyl)$_3$ is used as a ligand. It was pleasant to observe that the amount of cyclopentane **79i** was still low. Surprisingly, both *cis* and *trans* isomers were obtained in an approximate 1:1 ratio.

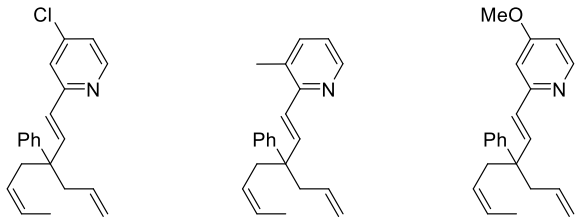
4.2.2.3 Comments on the effect of the substituent in the quaternary carbon

Overall, the cycloisomerisation reaction was not considerably affected by the replacement of the phenyl for bulkier substituents. The reaction rates were similar to the ones observed for substrates **67c** and **67f** and described in Chapter 3. Only substrate **67i**, bearing the *o*-tolyl group required longer reaction times. In this regard, the reactions done with the Rh-PPh_2tBu catalyst were faster than the ones catalysed with Rh-P(2-furyl)$_3$ as observed before. Under the conditions optimised to favour the formation of the cyclopentane **80**, the product selectivity matches the one observed in the previous

chapter for substrates **67c** and **67i**. In that case, the norbornane derivatives were only detected as traces. In contrast, the product selectivity was clearly diminished under the optimised conditions promoting the reductive elimination pathway. It has been previously suggested that an increase of the bulkiness in the stereogenic centre of the substrate might facilitate the recycling process from cyclopentane **80** to norbornane **78**. However, a significant amount of the β-hydride elimination product was obtained from all the substrates after 24 hours and longer reaction times did not modify the selectivity. This is especially remarkable for substrate **67h** containing a ketal group. In this case, the **78**/**80** ratio is around 1:1. This means that the rates of β-hydride elimination and reductive elimination are similar and that the recycling process is not taking place. It was proposed that the second migratory insertion would be accelerated respect to the 1,2-insertion conducting to the cyclopentane **79**. However, the amount of cyclopentane **79** obtained remained similar except for the *o*-tolyl substituent.

4.3 The effect of the directing group

In the mechanism presented in Chapter 2, it was suggested that the nitrogen atom of the pyridine moiety coordinates to the rhodium catalyst in all the intermediate of the catalytic cycle. *Azo*-compounds are the most commonly used directing groups. The flexibility on the number of substituents on the nitrogen atom and the simple control of its basicity allows to precisely tune the coordination of the directing group.[67,68] The hypothesis was that the second migratory insertion might be accelerated under these conditions. In addition, the introduction of a methyl group in the position 3 of the pyridine moiety might fix the conformation of the substrate and favour the nitrogen-rhodium coordination. For that purpose, three different substrates were synthesised (Figure 4.4).

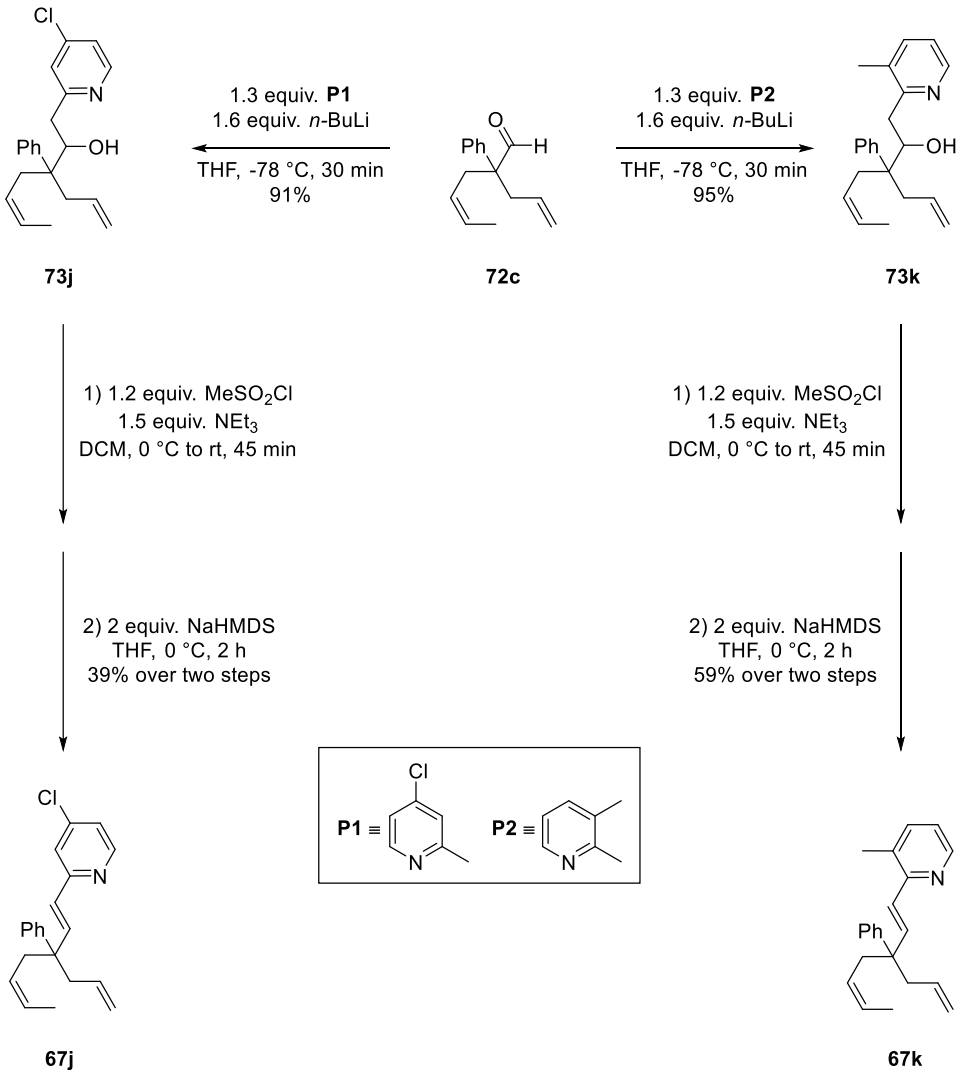


67j **67k** **67l**

*Figure 4.4: Substrate **67j** to **67l**.*

4.3.1 Synthesis of substrates 67j to 67l

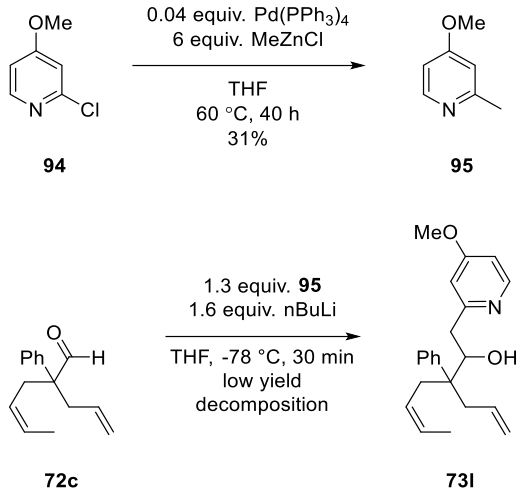
Substrates **67j**, **67k**, and **67l** were synthesised as the pure *cis* isomer from the intermediate **72c** whose synthesis has been already discussed in Chapter 2 (Scheme 4.6 to Scheme 4.8).



*Scheme 4.6: Synthesis of substrates **67j** and **67k**.*

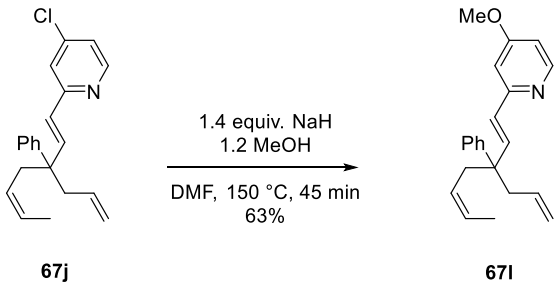
For the syntheses of substrate **67j** and **67k**, the desired 2-picolines **P1** and **P2** were commercially available. Then, the corresponding 2-methylpyridines were α-lithiated and directly used in the reaction to form either secondary alcohol **73j** or **73k** in excellent yields. The intermediates were mesylated and the leaving group eliminated to obtain substrates **67j** and **67k** in moderate yields. Some decomposition was observed for the elimination step of the synthesis of substrate **67k**. In addition, intermediate **73j** was not fully converted to the substrate **67j** under the optimised reaction conditions.

The synthesis of substrate **67l** was a little bit more elaborated. 4-methoxy-2-picoline **95** could not be obtained from a commercial source. For that reason, the first synthetic approach was to transform 2-chloro-4-methoxy-pyridine **94** into 4-methoxy-2-picoline **95** (Scheme 4.7).



*Scheme 4.7: Initial of intermediate **73l**.*

The Negishi reaction of substrate **94** afforded the picoline **95** in very low yield. Then, intermediate **95** was used to form compound **73l**. The secondary alcohol **73l** was obtained in very low yield and decomposition was the major product of the reaction. Thus, a second approach was designed (Scheme 4.8). In that case, the already synthesised substrate **67l** was used as starting material.



*Scheme 4.8: Final synthesis of substrate **67l**. Transformation of substrate **67j** into substrate **67l** by Negishi reaction.*

For the transformation of **67j** into **67l**, several reactions were tested with moderate results. The reaction with the commercially available NaOMe in methanol at room temperature was very slow. When the system was taken to 150˚C, the reaction was not accelerated and no completion was observed after four days. Moreover, a lot of decomposition was observed. Nevertheless, when the sodium methoxide was prepared *in situ* with dry methanol and sodium hydride in DMF the reaction reached completion after 45 min at 150°C. Purification by flash column chromatography using a mixture of pentane and ethyl acetate as the eluent afforded the desired substrate **67l** in 63% yield.

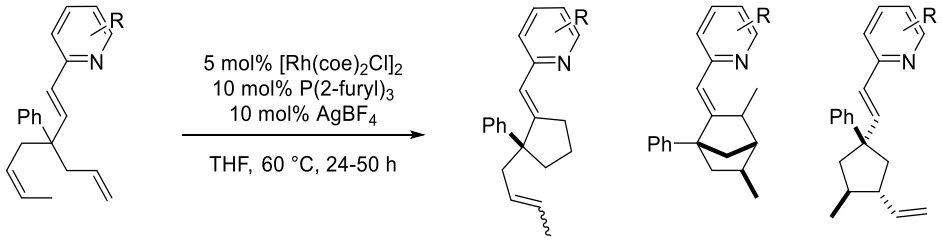
4.3.2 Results

It has been reported that the modification of the electrondensity of the catalyst affects the rates of the catalytic reactions.[69,70] While an electron-poor metal core usually accelerates the reductive elimination, the electron-rich catalyst favours the oxidative addition of the substrates.[71] In this regard, it is proposed that the introduction of either a chlorine atom or a methoxy group in the position 4 of the pyridine moiety will probably modify the rates of the catalytic steps which will be translated in a change of the selectivity. Moreover, it is suggested that the electron-withdrawing group will probably accelerate the second migratory insertion from intermediate **XX** to intermediate **XXI**.[69] Thus, the amount of 1,2-insertion product should decrease. In addition, it is suggested that the introduction of a methyl group in the position 3 of the pyridine moiety would orient the N-Rh towards the C-H vinyl bond. Hence, it would promote the coordination of the nitrogen atom with the metal catalyst which should also increase the reaction rate.

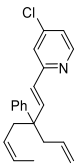
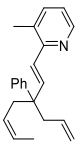
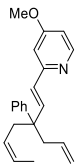
4.3.2.1 Examination of the reaction conditions that favour the β-hydride elimination

Substrates **67j**, **67k** and **67l** were tested under the optimised conditions to favour the formation of cyclopentane **80** (Table 4.3).

*Table 4.3: Cycloisomerisation of substituted substrates **67j-l** favouring the β-hydride elimination.*



67 **79** **78** **80**

Entry*	Substrate	Time (h)	Conversion	79 (*cis*/*trans*)	78 (*s,s*/*s,a*)	80[a]	m.b.
1	 **67j**	43	92	19 (9:10)	7(n.d.)	64	97
2		15	93	15 (6:9)	9 (n.d.)	69 (42%)	100
3	**67k**	24	100	16 (5:11)	10 (9:1)	71 (36%)	96
4		24	45	18 (13:5)	0	27	100
5	**67l**	50	100	35 (23:12)	0	63 (37%)	99

*Standard: 2,4-dichlorobenzaldehyde, 1 equivalent. a) The yield of the cyclopentane **80** is between parentheses

After 24 hours, the 4-chloropyridine substrate **67j** was only poorly converted. The reaction almost reached completion in 48 hours (Entry 1). The major product was the cyclopentane **80j**, whilst the norbornane **78j** was obtained in 7% yield. This agrees with the previous results and it indicates that using the small tri(2-furyl)phosphine favours the β-hydride elimination process. Unfortunately, the cyclopentane **79j** was also obtained in 19% yield as an equimolar mixture of *cis* and *trans* isomers. This result is similar to those obtained in the reactions of substrates **67c** and **67f**. This follows the tendency already observed on the previous reactions that the use of P(2-furyl)$_3$ as a ligand catalyses the isomerisation of the substrate.

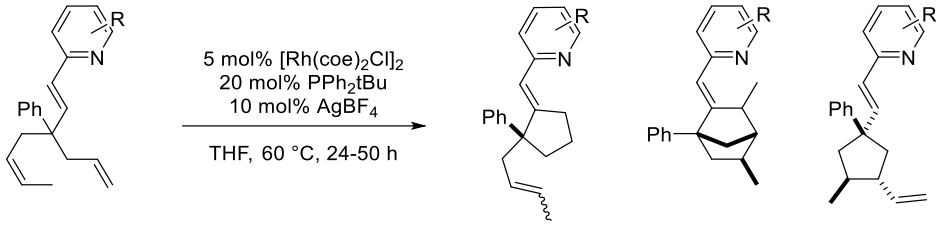
After an overnight reaction, 93% of the substrate **67k** was consumed (Entry 2), whereas the same reaction with unsubstituted substrate **67c** only reached 78% conversion (Table 3.1, Entry 7). Under these conditions, cyclopentane **80k** was obtained in 69% yield. Unfortunately, norbornane **78k**, as a mixture of diastereoisomers, was also obtained in 9% yield, while the cyclopentane **79k** was obtained in 15% yield which is similar to the amount of **79** obtained under the same reaction conditions (Table 3.1, Entry 6). Longer reaction time did not affect the product selectivity (Entry 3).

After 24 hours, less than 50% of substrate **67l** was converted and only two products were obtained (Entry 4). The amount of cyclopentane **79l** was impressively high for the low conversion. When the reaction was stopped after 50 hours, full conversion was reached (Entry 5). In that case, the expected compound **80l** was obtained in 63% yield, while the cyclopentane **79l** was obtained in 35% yield. Surprisingly, the diastereoisomeric ratio for this product was not close to 1:1. It is possible that an electron-rich metal core might disfavour the epimserisation of the internal olefin. Under these reaction conditions, the norbornane **78l** was not obtained.

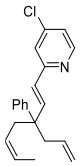
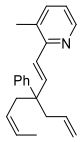
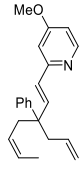
4.3.2.2 Examination of the reaction conditions that favour the reductive elimination

The cycloisomerisation of substrates **67j**, **67k** and **67l** was done with the Rh-PPh_2tBu catalyst (Table 4.4).

*Table 4.4: Cycloisomerisation of substituted substrates **67j-l** favouring the reductive elimination.*

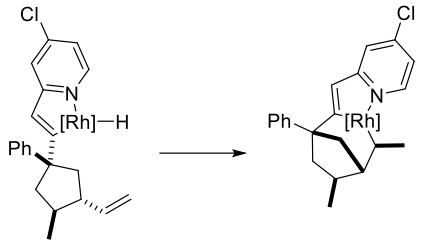


67 **79** **78** **80**

Entry*	Substrate	Time (h)	Conversion	79 (*cis/trans*)[a]	78 (*s,s/s,a*)[a]	80[a]	m.b.
1	 **67j**	24	72	10 (10:0)	32 (26:6)	25	95
2		24	84	16 (13:3)	34 (24:10)	33	100
3		43	100	16 (14:2)	45 (36:9) (27%)	35 (28%)	97
4	 **67k**	24	100	13 (10:3)	82 (68: 14)	0	95
5	 **67l**	24	100	37 (30:7)	37 (32:5) (17%)	26 (16%)	100
6		50	100	31 (25:6) (17%)	60 (52:8) (32%)	0	99

*Standard: 2,4-dichlorobenzaldehyde, 1 equivalent. a) Between parentheses, there is the isolated yield of the products

The electron-withdrawing substrate **67j** was not fully converted in 24h, but both cyclopentane **80j** and norbornane **78j** were obtained under the reaction conditions (Entries 1 and 2). In order to test the transient character of product **80j**, a reaction with substrate **67j** was running for 43 hours (Entry 3). Surprisingly, cyclopentane **80j** was still obtained in 35% yield. In absence of further data regarding longer reaction times, it is proposed that the recycling process was either decelerated greatly or not possible at all. Therefore, it would indicate that the conversion of **80** into **78** is not possible with an electron-poor metal centre. An educated guess would be that it is the insertion from intermediate **XXII** to intermediate **XXI** which is more likely to be affected by the electronic changes, as the C-H activation is the first step of the cycloisomerisation reaction (Scheme 4.9).



XXII **XXI**

*Scheme 4.9: Blocked insertion of the rhodium catalyst into the alkene bond of intermediate **XXII** to form intermerdiate **XXI**.*

Moreover, the monitoring studies described in chapter 3 showed that the conversion of **80** into **78** is highly selective towards the *syn,syn* diastereoisomer. Assuming this, it is possible that the recycling process of product **80j** does not take place here, as the ratio of *syn,syn vs*. *syn,anti* is only around 3 to 1. Cyclopentane **79j** was obtained in around 16% after full conversion of the starting material (Entry 3). Same as with other substrates, the isomerisation of the internal olefin of substrate **67j** is less efficiently catalysed with the rhodium-PPh_2tBu catalyst than with rhodium-$P(2\text{-furyl})_3$.

The reaction with substrate **67k** reached completion in 24 hours (Entry 4). Under the reaction conditions, the cyclopentane **79k** was obtained in 16% yield with an isomeric ratio of around 3 to 1, whilst cyclopentante **80k** was not observed. Major product **78k**, as a mixture of diastereoisomers, was obtained in a combined yield of 82%. This is highest selectivity for the substrates tested under these reaction conditions. The big difference in the diastereoisomeric ratio (dr = 5:1, *syn,syn*/*syn,anti*) compared to the diastereoisomeric ratio of cyclopentane **79k** (dr = 3.3, *cis*/*trans*) implies that the recycling process takes places for this reaction. These results are similar to the ones obtained with substrate **67c** (Table 3.1, Entry 24).

Contrary to the reaction of substrate **67l** with Rh-P(2-furyl)$_3$, the cycloisomerisation of **67l** was completed in 24 hours (Entry 5). This follows the tendency previously observed in chapter 3 where we discussed that the reaction using PPh_2tBu as the ligand is usually faster (Section 3.4). In this case, the product selectivity for the reaction with substrate **67l** was extremely poor. Cyclopentane **79l** was obtained in over 30% yield. It has been previously observed that the characteristics of the different phosphines do not apparently affect the rates of 1,2-insertion and the second migratory insertion (Section 3.2.1). In this specific case, when the reaction was carried out with 10 mol% of P(2-furyl)$_3$, a similar amount of cyclopentane **79l** was obtained after reaction completion (Table 4.4, Entry 6). The product ratio between norbornane **78l** and **80l** was 1.5:1. However, the reaction carried out with tri(2-furyl)phosphine proved to be very slow for this particular substrate. Therefore, substrate **67l** was submitted to a 50-hour reaction to improve the product selectivity and to test the transient character of product **80l** (Entry 6). To our delight, the hypothesis proved to be right and the yield of **77l** was increased to 60%, while cyclopentane **80l** was not obtained.

4.3.2.3 Comments on the effect of the directing group

Overall, the product selectivity of this reaction is clearly affected by the electronegativity of the pyridine substituent. While, the introduction of these different substituents did not affect the competition of the reductive elimination *vs*. the β-hydride elimination when using P(2-furyl)$_3$ as a ligand, the **78**/**80** ratio was clearly diminished when PPh_2tBu was used instead. This is especially evident on substrate **67j** that contains a chlorine group. Initially, it had been proposed that the introduction of an electron-withdrawing group would accelerate the reductive elimination from intermediate **XXI** to form the norbornane **78j**. However, under those conditions, the cyclopentane **80j** was obtain in over 30% yield after reaction completion. Moreover, the electron-poor environment apparently blocked the recycling process of cyclopentane **80j** to the norbornane **78j**. In contrast, the introduction of an electron-donating group in the position 4 of the pyridine moiety did not affect the transformation of the cyclopentane **80l** into the norbornane **78l**. Unfortunately, very poor product selectivity was observed for this reaction. This is consistent with the studies on the anti-Markovnikov hydroamination of alkenes that showed that the energy barrier between the Markovnikov and anti-Markovnikov intermediates is lower when the catalyst is electron-rich.[72] However, using the electron-poor substrate **67j** did not reduce the amount of cyclopentane **79** obtained. It is noteworthy that the electronically opposite substrates **67j** and **67l** react at a similar rate.

In addition, it had been suggested that the introduction of the methyl group on the position 3 of the pyridine moiety would accelerate the C-H activation. In this aspect, the completion of the reaction of

67k with Rh-P(2-furyl)$_3$ in 15 hours confirms this hypothesis. However, the product selectivity was identical to the one observed for the unsubstituted substrates **67c** and **67f**.

4.4 The influence of alkene substitution

The results discussed in section 2.2.2 showed that the substitution of one of the olefin moieties is a major influence on the cycloisomerisation reaction. In order to keep studying the effect of the substituents, the substrates **96a**, **95b** and **97** were synthesised (Figure 4.5). Substrates **96a** and **96b** are substituted by an ether and an ester respectively in the terminal carbon of the olefin moiety. In this case, the β-hydride elimination process is not possible. Hence, for these substrates only the products of the reductive elimination and the 1,2-insertion are expected. Substrate **97** has two methyl substituted *cis*-olefins. The results presented in both Chapter 2 and Chapter 3 showed that only the terminal alkene can undergo 1,2-insertion, while the presence of norbornane 81 indicates that the substituted alkene can slowly undergo 2,1-insertion. On the contrary, the second migratory insertion is mostly accomplished by the methyl substituted alkene. Therefore, the hypothesis is that the presence of the two substituted olefins would hamper the 1,2-insertion and prevent the formation of the undesired cyclopentane **79**. Moreover, in this section we have decided to revaluate the first substrates **67a** and **67b** under the optimised conditions (Figure 4.5).

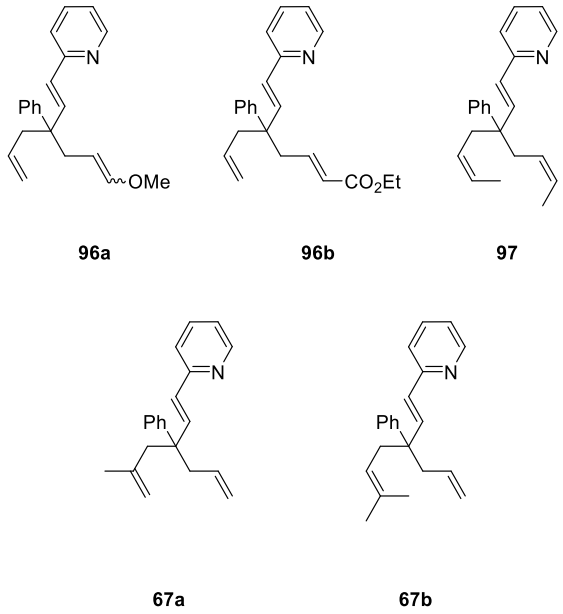


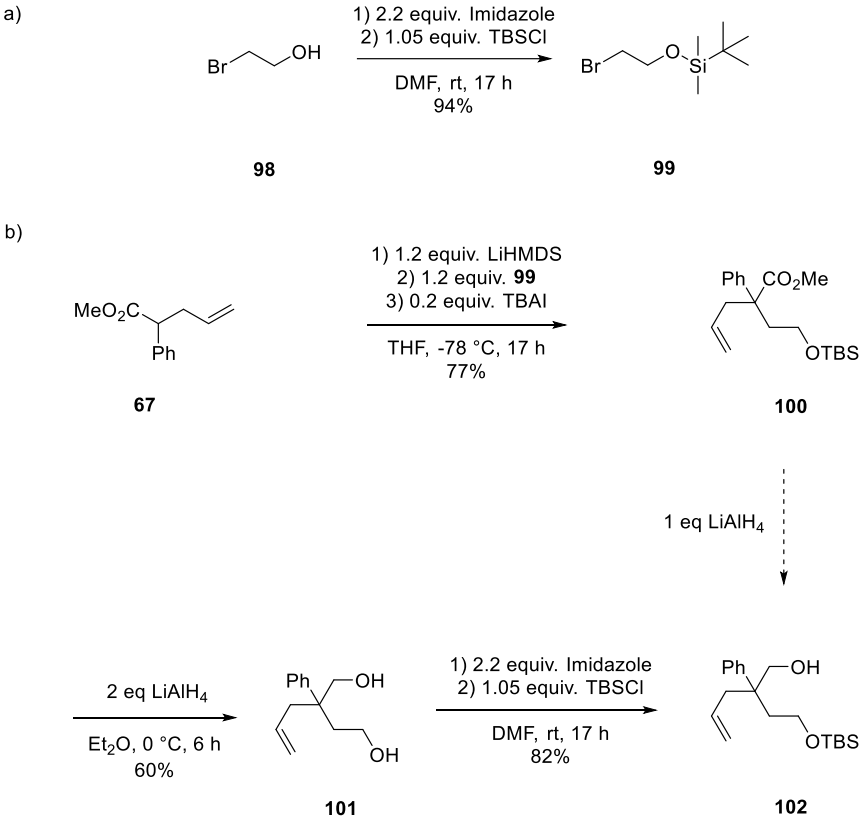
*Figure 4.5: Substrates **96a**, **96b**, **97**, **67a** and **67b**.*

4.4.1 Synthesis of substrates

The syntheses of the substrates followed two different approaches. On the one hand, the synthesis of ether **96a** and ester **96b** starts with the alkylation reaction and it diverges on the last step of the route. On the other hand, the pure *cis bis*-allylated substrate **97** was synthesised in a similar way to substrate **67c**.

4.4.1.1 Synthesis of substrates 96a and 96b

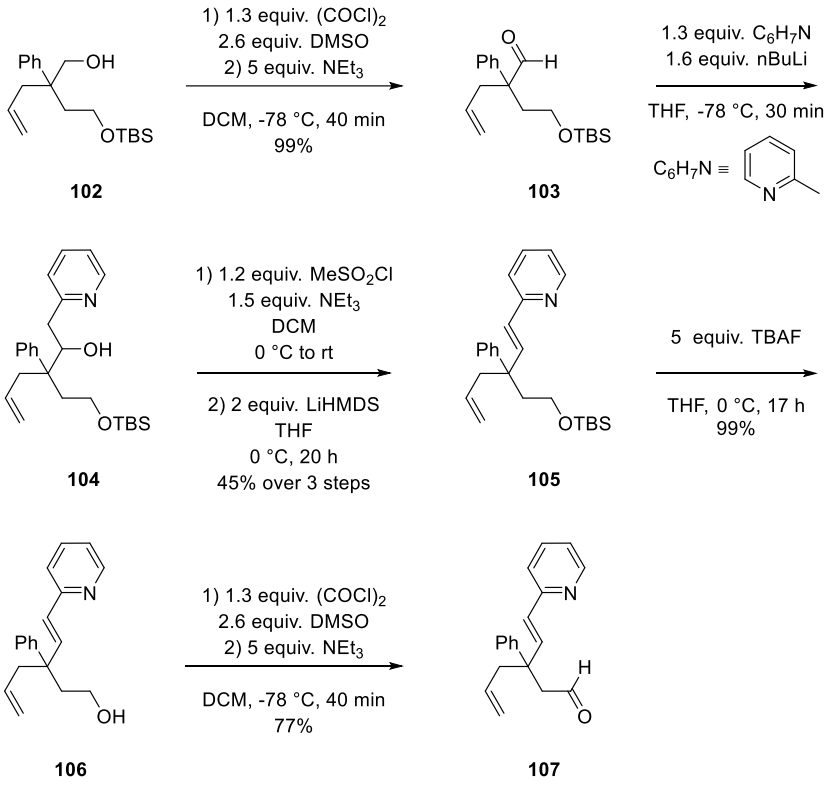
The syntheses of substrates of **96a** and **96b** were carried out in 10 steps (Scheme 4.10 and Scheme 4.11). The first 4 steps are described in Scheme 4.10.



*Scheme 4.10: Synthesis of intermediate **102**. a) Synthesis of intermediate **99**. b) Synthesis of intermediate **102**.*

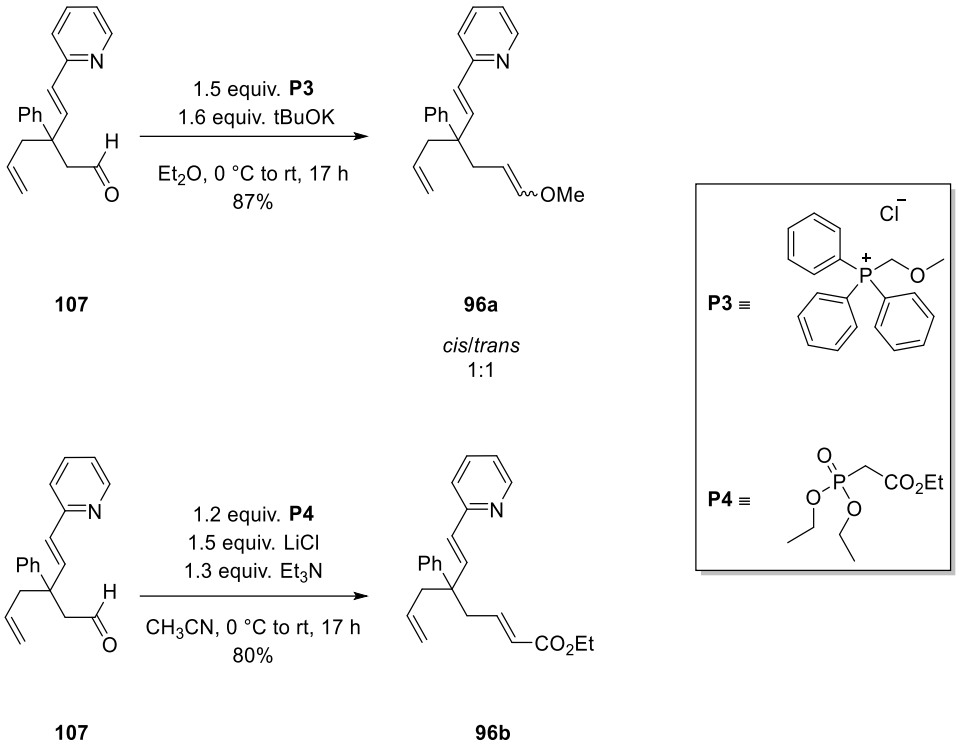
The protection of the commercially available 2-bromoethanol **98** was performed in excellent yields using imidazole and *tert*-butyldimethylsilyl chloride in excellent yield (a). The intermediate **99** did not require any purification and it was used directly from the crude. Then, the product **69**, which was already described in Scheme 2.5, was alkylated using substrate **99** as the alkylating agent (b). The reduction of **100** with lithium aluminium hydride did not afford compound **102** as expected, but the deprotected substrate **102**.[73,74] Less than one equivalent of lithium aluminium hydride would have been required to reduce the ester moiety. However, after few hours, the reaction did not reach

completion. Hence, two equivalents were added in portions throughout few hours period to obtain diol **101** in 60% yield. Several temperatures as well as reaction times were examined to obtain **102** from intermediate **100** without success. Therefore, compound **101** was protected with *tert*-butyldimethylsilyl to afford product **102** in good yield. The mono protection of the less hindered alcohol was achieved without any difficulty and the di-protection was not observed. The synthesis was continued in a similar way to the one already described in Chapter 2 (Scheme 4.11).



*Scheme 4.11: Synthesis of intermediate **107**.*

The intermediate **102** was oxidised with a Swern reaction to obtain product **103** in quantitative yield. Then, α-lithiated 2-methylpyridine was prepared by reacting 2-picoline and n-BuLi. After few minutes, aldehyde **102** was added to the reaction mixture to afford alcohol **104** as a mixture of diastereoisomers. The secondary alcohol **104** was mesylated and consecutively eliminated with lithium bis(trimethylsilyl)amide to afford **105** in 45% yield after 3 steps. Then, this intermediate was deprotected to provide alcohol **106** in quantitative yield. At that point, a second Swern reaction was carried out to obtain intermediate **107** in 77% yield**.** The aldehyde was then used in two different reactions (Scheme 4.12).

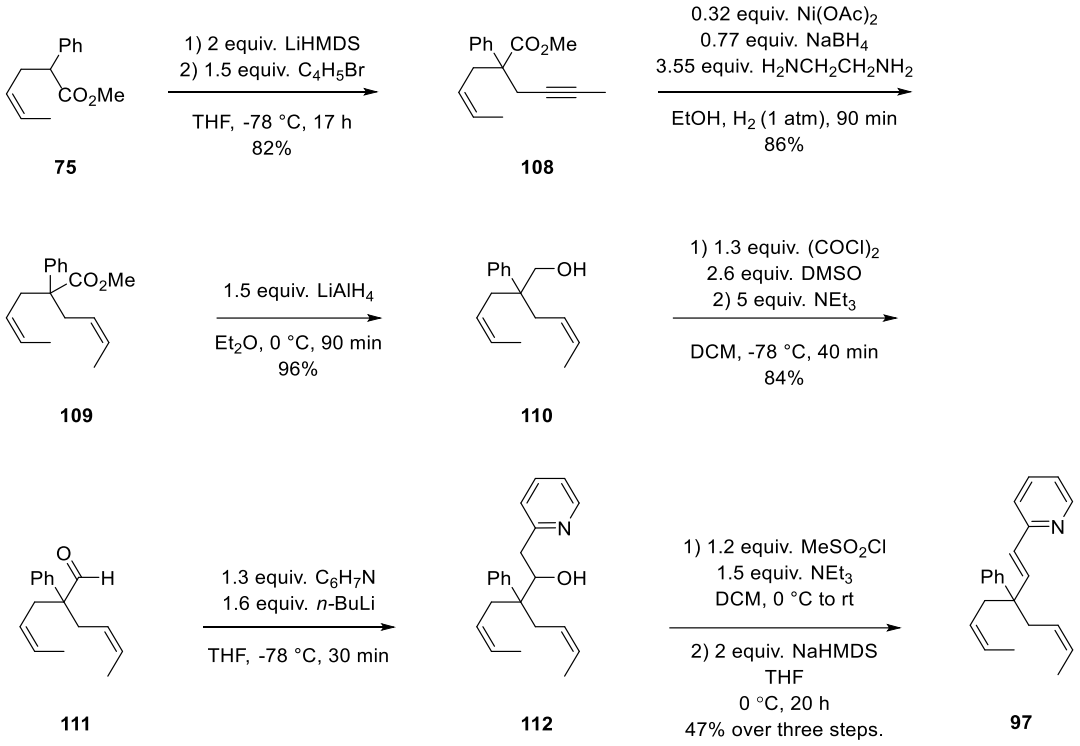


*Scheme 4.12: Synthesis of substrates **96a** and **96b**.*

Substrate **96a** was obtained as a mixture of *cis* and *trans* isomers in 87% using a Wittig reaction. Substrate **96b**, synthesised by Yasmin Reviriot, was obtained as a pure *trans* isomer in 80% by the Horner-Wadsworth-Emmons procedure.

4.4.1.2 Synthesis of substrate 97

Pure *cis bis*-allylated substrate **97** was synthesised in a similar way as substrate **67c** (Scheme 4.13)



*Scheme 4.13: Synthesis of substrate **97**.*

Substrate **75**, whose synthesis was already described in Scheme 2.6, was propargylated in good yields. In order to reach completion, the reaction needed to be carried out twice. The presence of the internal olefin might hinder the introduction of the propargyl. Then, intermediate **108** was reduced using the heterogeneous method discussed previously. As described by H. C. Brown, the catalyst tolerated the presence of the olefin moiety and it only decelerated the reaction.[47-49] The decrease of the reaction rate was expected, as the alkene moiety can bind to the nickel catalyst and block some of the reactive sites. However, the reaction completion was only reached after two consecutive reductions. Then, the intermediate **109** was reduced with lithium aluminium hydride in excellent yields to obtain product **110**. The alcohol was then oxidised to the aldehyde by a Swern reaction in good yields. Finally, α-lithiated methylpyridine was introduced to form secondary alcohol **112** which after mesylation and elimination afforded substrate **97** in 47% yield after three steps.

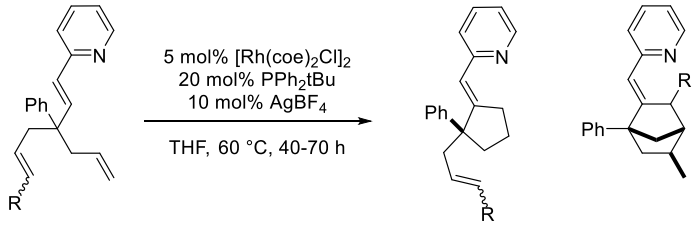
4.4.2 Results

The substitution on the terminal carbon of the olefin moiety with the methoxy group (**96a**) or the methyl carboxylate (**96b**) prevents the β-hydride elimination process. Hence, these substrates were only tested with the optimised conditions for the selective formation of the norbornane product. On the contrary, substrate **97** was submitted to both conditions. It is proposed that 1,2-insertion would be disfavoured by the presence of the methyl groups in the terminal carbon of the olefin moieties.

4.4.2.1 Enhancing the reductive elimination process

In this section, it is intended to compare the effect of the different electrondensity in the substrate on the 1,2-insertion and the second migratory insertion (Table 4.5). Previously, it has been proved that P(2-furyl)$_3$ only catalyses the reductive elimination poorly. Therefore, the following reactions were only carried out with PPh_2tBu.

*Table 4.5: Cycloisomerisation of substrates **96** under the optimised conditions that favour the reductive elimination.*



96 **113** **114**

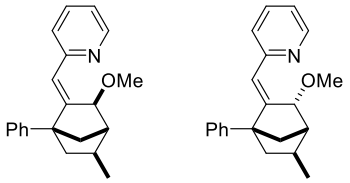
Entry*	Substrate	R	Time (h)	Conversion	113 (*cis*/*trans*)	114 (*s*,*s*/*s*,*a*)	m. b.
1	**96a**	OMe	42	100	25 (13:12)	71 (24:47)	96
2	**96b**	CO_2Et	69	100	27 (0:27)	73 (46:27)	100

*Standard: 2,4-dichlorobenzaldehyde.

The cycloisomerisation of the electron-donating substrate **96a** reached completion in 42 hours (Entry 1). As expected, this substrate was cycloisomerised into cyclopentane **113a** and norbornane **114a** in 25 and 71% yield respectively, both as a mixture of isomers. The equimolar stereoisomeric ratio of product **113a** correlates to the one of the starting material. In contrast, the norbornane **114a** was obtained in a 1:2 diastereoisomeric ratio which is opposite to the one it has been previously observed for substrates **67** (Section 3.2.1 and Section 3.3.2). It is suggested that the epimerisation occurs after

the first migratory insertion through an unstudied mechanism. The two norbornane products were isolated clean in 32 and 37% yield respectively (Table 4.6).

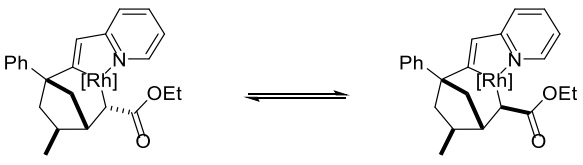
*Table 4.6: Isolated yields of products **114a s,s** and **114a s,a**.*



114a *s,s* **114a *s,a***

114a (*s,s*) (%)	114a (*s,a*) (%)
32	37

The reaction with substrate **96b** was only finished after 69 hours (Entry 2) This agrees with the previous studies already discussed in this chapter which showed that electron-withdrawing substrates decelerated the reaction greatly (Section 4.3.2.2). After the reaction reached completion, norbornane **114b** was obtained as a mixture of *syn,syn* and *syn,anti* diastereoisomers in a combined yield of 73%, while the undesired cyclopentane **113b** was obtained in 27% as a single isomer. Contrary to the results of substrate **96a**, the diastereoselectivity of this reaction was favoured towards the *syn,syn* norbornane **114b**. Taking into account that the isomerisation of the internal olefin does not take place for the substrate, as it can be deduced from the lack of isomerisation of product **113b**, the diastereospecificity is lost after the second migratory insertion. One plausible mechanism for this process is the formation of an enolate intermediate which derives in the *cis* isomer as the most stable form (Scheme 4.14).



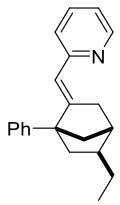
XXV **XXVI**

*Scheme 4.14: Mechanism of the reversible isomerisation of intermediates **XXV** and **XXVI**.*

Albeit it was pleasant to see that the substitution other than methyl in the terminal carbon of the olefin moiety was tolerated by the reaction, the product selectivity was a surprising result. In both cycloisomerisations, the cyclopentane **113** was obtained in around 25% yield. This indicates that neither an electron-withdrawing substituent nor an electron-donating one affects the competition between the 1,2-insertion and the second migratory insertion. Studies by Okamoto and Halpern on the 1,2-insertion of *para*-styrenes in a Rh(III)-H bond showed that the presence of electron-withdrawing substituents enhanced the coordination of the rhodium with the alkene moiety but decelerated the rate of insertion, while the substitution with electron-donating groups has completely the opposite effect.[69,75] Overall, the reaction rates were identical. This could be translated into our system and explain the product selectivity observed.

4.4.2.2 Cycloisomerisation on *bis*-methyl allylated substrate 97

The results obtained by both substrates **67c** and **67f** along with the substituted substrates presented herein showed that 1,2-insertion was unlikely to occur with the substituted alkene. However, the traces of product **81** obtained indicated that the internal olefin can undergo first migratory insertion, even though in a difficult fashion (Figure 4.6).

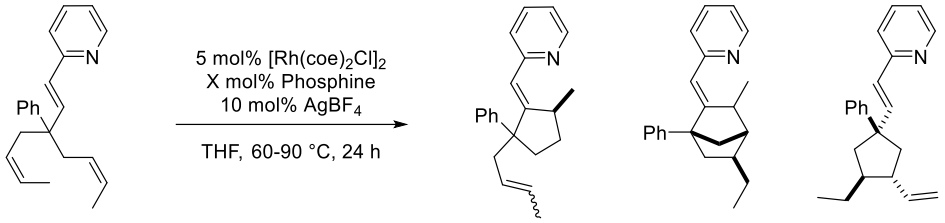


81

*Figure 4.6: Norbornane **81**.*

Therefore, the symmetric substrate **97**, which is monosubstituted in both olefins, was synthesised and submitted to the cycloisomerisation reaction conditions (Table 4.7).

*Table 4.7: Cycloisomerisation of substrate **97**.*



97 **115** **116** **117**

Entry*	Phosphine (mol%)	T (˚C)	Conversion	115 (*cis*/*trans*)	116 (*s,s*/*s,a*)	117	m.b.
1	**P(2-furyl)$_3$ (10)**	60	29	17 (n.d.)	0	12	100
2	**PPh$_2$tBu (20)**	60	50	11 (7:4)	24 (12:12)	10	95
3	**PPh$_2$tBu (20)**	90	100	65 (49:16)	10 (0:10)	19	95

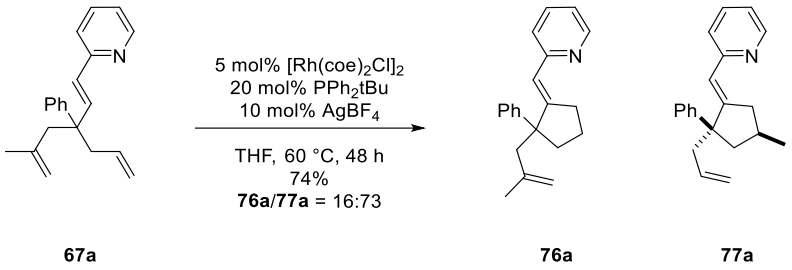
*Standard: 2,4-dichlorobenzaldehyde.

When the substrate **97** was submitted to the optimal conditions for the β-hydride elimination process, only a sluggish reaction was observed after 24 hours (Entry 1). As it was expected, the norbornane **116** was not obtained and cyclopentane **117** was obtained in 12%. Surprisingly, 7% yield of cyclopentane **115** was also recovered. Then, the substrate was reacted with [Rh(coe)$_2$Cl]$_2$ and 20 mol% of PPh$_2$tBu at 60°C for 24 hours (Entry 2). In that case, the reaction reached only 50% conversion and norbornane **116** was obtained in 24% yield. Unfortunately, the product selectivity dropped considerably for this reaction, as 10 and 11% yield was obtained for cyclopentanes **117** and **115** respectively. An attempt to avoid the difficulties of the first migratory insertion was carried out by increasing the reaction temperature (Entry 3). The reaction did reach completion under these conditions, but the yield of cyclopentane **115** rose to 65%. In this regard, the same effect of the temperature on product selectivity was previously reported by Kelvin Ho for substrates **63**.[43] The steric hindrance created by the methyl on the terminal carbon of the olefin hinders the first migratory insertion. Therefore, the rate of the reaction decreases. It is noteworthy that the 1,2-insertion is more favourable than the 2,1-insertion.

4.4.2.3 The re-examination of previous results (67a, 67b)

After studying the influence of the olefin substitution in both the product distribution and diastereoselectivity, it was decided to review the results on substrates **67a** and **67b** (Scheme 4.15 and

Table 4.8). Substrate **67a**, which cannot undergo β-hydride elimination, was only submitted under the optimal conditions for the formation of the norbornane (Scheme 4.15).

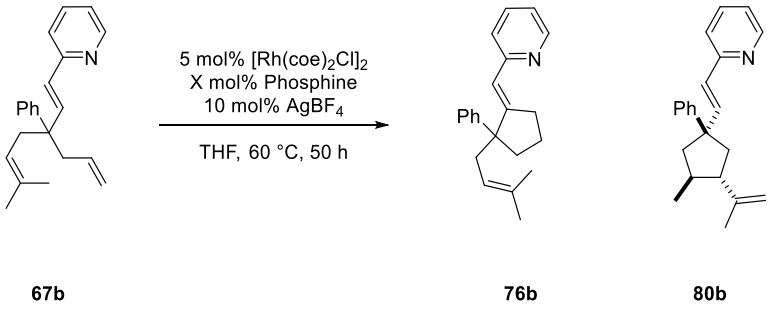


*Scheme 4.15: Cycloisomerisation of substrate **67a** using the optimised conditions that favour the reductive elimination.*

The reaction was only completed after two days. However, the results obtained under these conditions were similar to those presented in chapter 2. The cyclopentanes **76a** and **77a** were obtained in isomeric ratio of 1:4.5. The product selectivity remained similar to that observed for the reaction with Rh-P(*p*MeOC_6H_4)$_3$ catalyst. Therefore, it could be considered that the phosphine does not have a role on the product distribution of this reaction. As previously discussed, the methyl on the internal carbon of the olefin probably hinders the second migratory insertion. In contrast, it facilitates the 1,2-insertion to obtain cyclopentane **77a**.

Substrate **67b** presents a double substitution in the terminal carbon of one olefin and it was submitted to the optimal conditions for the formation of cyclopentane **80** and norbornane **78** respectively (Table 4.8).

*Table 4.8: Cycloisomerisation of substrate **67b** under the optimised conditions.*

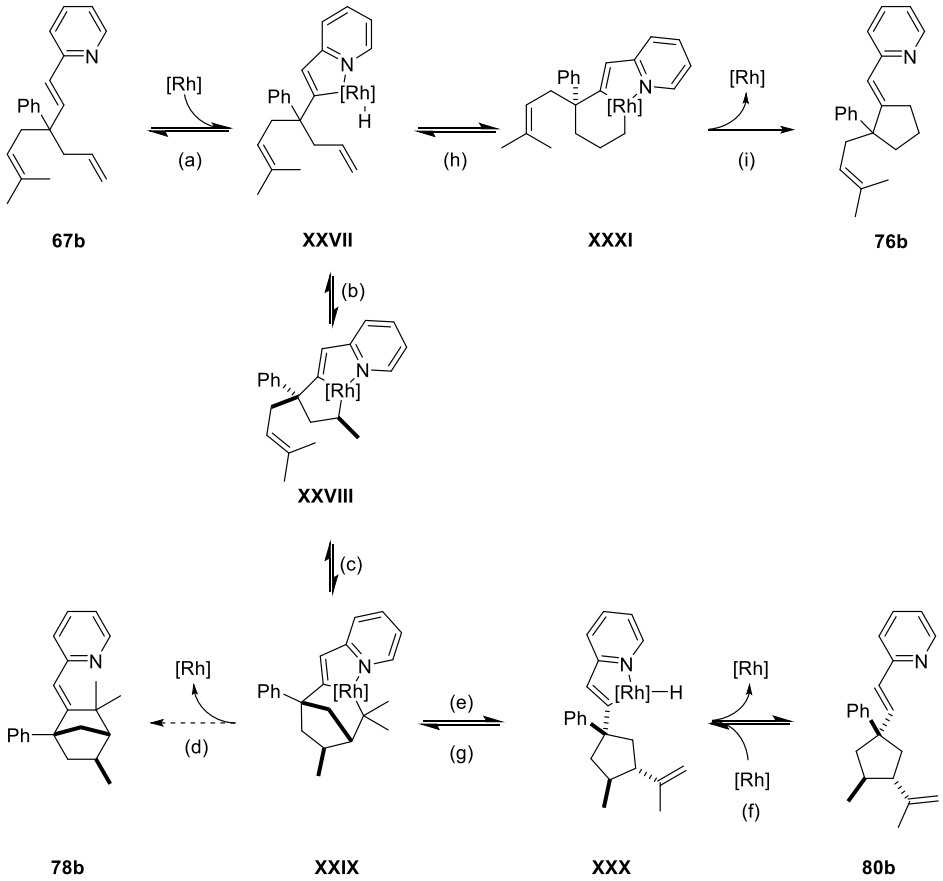


67b **76b** **80b**

Entry*	Phosphine (mol%)	Conversion	76b	80b
1	**P(2-furyl)$_3$ (10)**	22	8	4
2	**PPh$_2$tBu (20)**	79	50	12

*Standard: 2,4-dichlorobenzaldehyde

After 50 hours of reaction with P(2-furyl)$_3$, only 22% conversion was observed (Entry 1). However, only traces of cyclopentane **80b** were obtained. This shows that, although slow, first and second migratory insertion are possible with this substrate using the small tri(2-furyl)phosphine as the ligand. Cyclopentane **76b** was obtained as the major product. Better conversion was achieved when the reaction was catalysed by Rh-PPh$_2$tBu catalyst, but only 12% yield of cyclopentane **80b** was obtained (Entry 2). The steric hindrance that the *gem*-dimethyl group provides to the complex probably hinders the second migratory insertion. The lack of norbornane **78b** in both reactions indicates that, although the second migratory is possible, the reductive elimination (d) from intermediate **XXIX** cannot take place (Scheme 4.16).



*Scheme 4.16: Proposed mechanism for the formation of products **76b** and **80b** by cycloisomerisation of substrate **67b**. The high steric hindrance blocs the formation of product **78b**.*

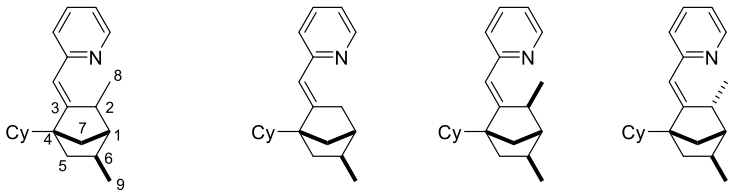
4.5 Identification of products 78g to 78l and 114a and 114b

The separation of the isomers was extremely difficult and some of them could not be isolated. However, some of the norbornanes whose ^{13}C NMR have been analysed to determine their stereochemistry was isolated. In that case, the ^{13}C spectra are compared to the carbon spectrum of the corresponding norbornane **64** and the *gamma gauche* effect is discussed.

4.5.1 Identification of norbornanes 78g to 78l

The norbornane **64j** was synthesised and characterised by Daniel J. Tetlow.[44] Table 4.9 shows the comparison of the characteristic ^{13}C NMR peaks of **64j** and the *syn,syn* and *syn,anti* isomers for norbornane **78g**.

*Table 4.9: Comparison of the ^{13}C chemical shifts of norbornanes **64j**, **78g s,s** and **78g s,a**.*



64j **78g s,s** **78g s,a**

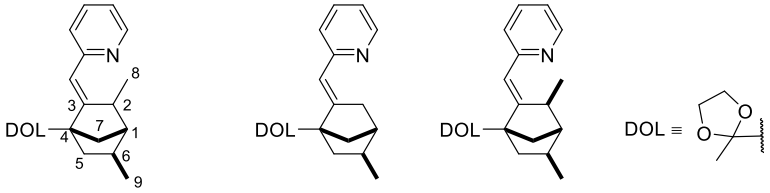
	^{13}C chemical shift (ppm)			
Isomer	**C-6**	**C-7**	**C-8**	**C-9**
64j	35.6	36.1	----------	22.3
78g *s,s*	36.1	31.8	16.5	22.1
78g *s,a*	28.5	36.5	14.7	22.4

As it has been previously discussed in Section 2.2.2.1.1, the studies by Kleinpeter and Seidl show that the carbon in a *gamma* position respect to the methyl group 8 is affected by the different environment created by the stereogenic centre in the diastereoisomers.[51] The chemical shift of that carbon nucleus is usually moved upfield for both the *endo* and *exo* diastereoisomers, while the difference is more pronounced for the *anti* isomer. In this case, the C-6 is clearly shielded for **78g *s,a***. In contrast, the chemical shift for the same carbon nucleus in the *syn,syn* diastereoisomer remains similar to that on the unsubstituted norbornane **64j**. They also reported that the signal for methylene from the bridge (C-7) is normally moved to lower chemical shifts in the spectrum of the *exo* isomer. In this case, the signal of norbornane **78g *s,s*** is clearly moved upfield, while the chemical shift for the *syn,anti* diastereoisomer is similar that on the unsubstituted norbornane **64j**. The chemical shift for the methyl

group 9 is not affected by the configuration of the molecule and the signal for the methyl group 8 is slightly deshielded for the *syn,syn* isomer.

For the reaction with substrate **67h**, only **78h *s,s*** could be fully isolated and characterised (Table 4.10). The norbornane **64h** was synthesised and characterised by Kelvin Ho.[43,44]

*Table 4.10: Comparison of the ^{13}C chemical shifts of norbornanes **64h**, **78h s,s**.*



64h **78h *s,s***

	^{13}C chemical shift (ppm)			
Isomer	**C-6**	**C-7**	**C-8**	**C-9**
64h	35.8	38.7	----------	22.1
78h *s,s*	36.2	34.6	16.8	22.1

Overall, the ^{13}C NMR characteristic peaks for product **78h *s,s*** followed the tendency described by Kleinpeter and Seidl. The chemical shift for the methyl group 9 is identical to that on norbornane **64h**, while the 16.8 ppm chemical shift is similar to other signals of methyl groups in that position. The carbon in the position 7 is deshielded slightly respect to the same signal in the norbornane **64h** Surprisingly, the chemical shift for the carbon nucleus 6 is identical for both **64h** and **78h *s,s***.

The identification of the norbornane **78i** was a little bit more delicate. The presumably restricted rotation between carbon 4 and the o-tolyl moiety was translated into very broad signals in the aliphatic region for the *syn,syn* disatereoisomer on the ^{1}H NMR (Figure 4.7) In addition, none of the aliphatic peaks were observed when using the APT experiment. The ^{13}C spectrum was then obtained with the more sensitive ^{13}CPD NMR experiment and very small signals could be observed. It is noteworthy that the other products obtained in this reaction presented very clear spectra with very well defined and sharp peaks. It is especially remarkable the clear spectrum of the opposite diastereoisomer **78i *s,a***. The rigid structure of the molecule might complicate the rotation of the bond between C-4 and the *o*-tolyl moiety. For the **78i *s,a*** the *exo* face is probably more open and the rotation less restricted.

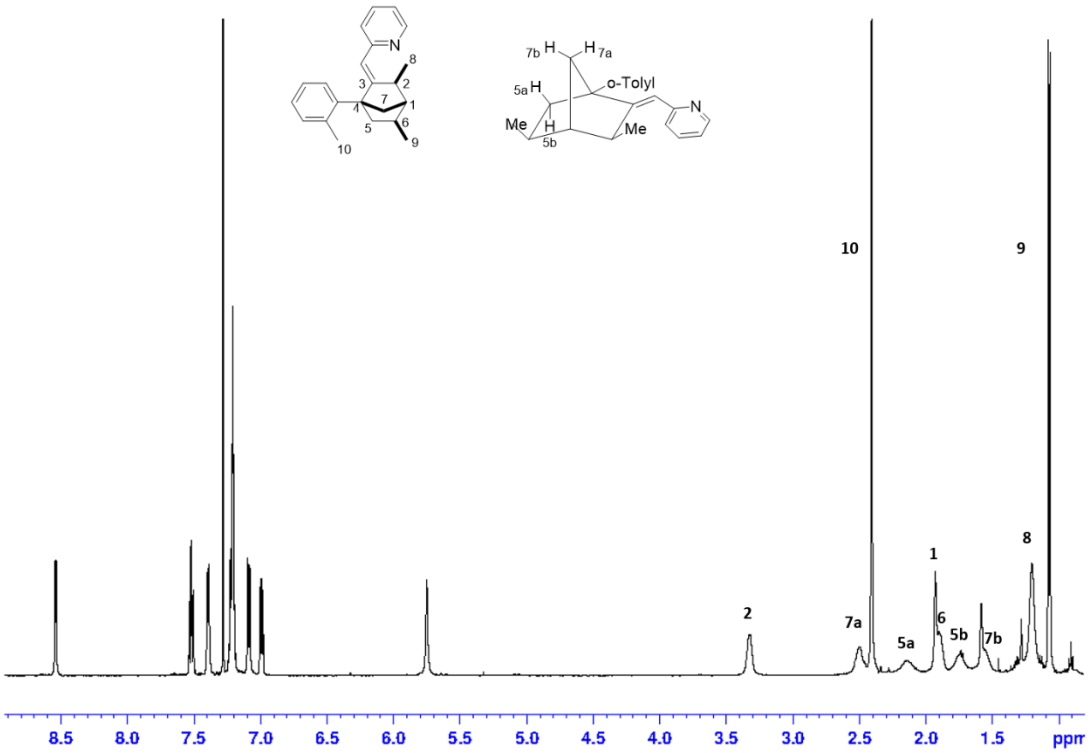
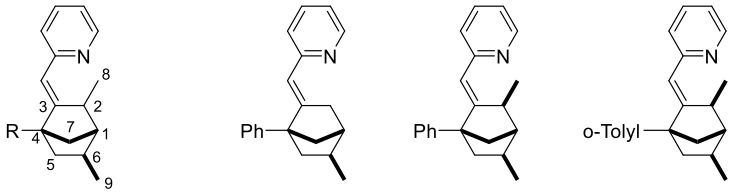


*Figure 4.7: ^{1}H NMR spectrum of norbornane **78i s,s**. The aliphatic region is not very well defined due to the hindered rotation.*

As the *o*-tolyl analogue of **64** was not synthesised previously by the group, a comparison of the *syn,syn* isomers **78i** with the phenyl substituted norbornane **64a** and norbornane **78** is made (Table 4.11).

*Table 4.11: Comparison of the ^{13}C chemical shifts of norbornanes **64a**, **78 s,s** and **78i s,s**.*



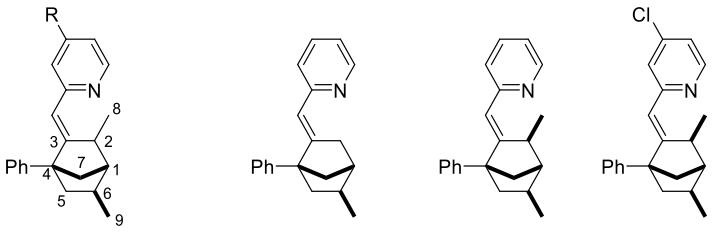
64a **78 *s,s*** **78i *s,s***

	^{13}C chemical shift (ppm)			
Isomer	**C-6**	**C-7**	**C-8**	**C-9**
64a	42.6	41.2	----------	22.3
78 *s,s*	36.5	37.5	17.3	22.1
78i *s,s*	36.2	34.6	17.2	22.2

The carbon nucleus C-6 in *gamma* to the methyl group 8 is shifted to upper fields by 6 ppms and its signal is identical to that on norbornane **78**. In contrast, the shielding of C-7 respect to **64a** is much more pronounced in **78i** than in the **78**. As expected, the signals of the carbon nuclei 8 and 9 are the same to their analogues in the norbornane **78**. It is noteworthy that two reversed tendencies can be observed depending on the substituent in C-4. When the carbon is substituted by an electron-acceptor group, the signal for the C-6 nucleus does not move upfield as it could be expected. On the contrary, when the carbon 4 is substituted by an electron-donor group, the signal of the C-6 follows the expected trend and the chemical shift exactly matches that of **78 *s,s*** but the signal of the C-7 is moved to lower chemical shifts in a much greater extent.

The chlorine substituted isomer of **64** was not synthesised, therefore the *syn,syn* isomer was only compared to the original norbornane **64a** and to its methyl analogue **78 *s,s*** (Table 4.12).

*Table 4.12: Comparison of the 13C chemical shifts of norbornanes **64a**, **78 s,s** and **78j s,s**.*



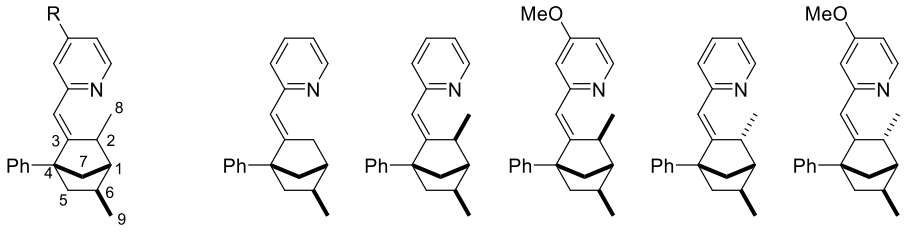
64a **78 *s,s*** **78j *s,s***

	^{13}C chemical shift (ppm)			
Isomer	**C-6**	**C-7**	**C-8**	**C-9**
64a	42.6	41.2	----------	22.3
78 *s,s*	36.5	37.5	17.3	22.1
78j *s,s*	36.4	37.5	17.2	22.1

The signal for the carbon nuclei 6 and 7 are moved upfield compared to the unsubstituted norbornane **64a**. In both cases, the chemical shifts of the characteristic carbon nuclei of compound **78j *s,s*** are identical to those of norbornane **78 *s,s***.

Finally, the two norbornanes which are MeO-substituted in the position 4 of the pyridine moiety **78l** are compared with their unsubstituted analogues **78** (Table 4.13).

*Table 4.13: Comparison of the ^{13}C chemical shifts of norbornanes **64a**, **78 s,s**, **78l s,s**, **78 s,a** and **78l s,a**.*



64a | **78 *s,s*** | **78l *s,s*** | **78 *s,a*** | **78l *s,a***

	^{13}C chemical shift (ppm)			
Isomer	**C-6**	**C-7**	**C-8**	**C-9**
64a	42.6	41.2	----------	22.3
78 *s,s*	36.5	37.5	17.3	22.1
78l *s,s*	36.5	37.4	17.3	22.2
78 *s,a*	29.1	41.2	14.4	22.3
78l *s,a*	29.1	40.7	14.4	22.1

The tendency observed in the previous products is repeated for norbornane **78l**. The methyl substitution in the position 3 of the pyridine moiety does not affect any of the chemical shifts of the characteristic carbon nuclei. Thus, all the signals are identical to those of the unsubstituted analogue **78**.

4.5.2 Identification of the norbornanes 114a and 114b

The introduction of a substituent different than methyl in the carbon 2 of norbornane **114** changed the ^{1}H NMR spectra pattern of these norbornanes. Therefore, identification by the analogy method was not possible for these products and more exhaustive studies were needed to completely differentiate the diastereoisomers. Fortunately, both *syn,syn* and *syn,anti* norbornanes **114b** presented a well-defined proton NMR spectrum which facilitated the discrimination of the diastereosiomers (Figure 4.8 and Figure 4.10).

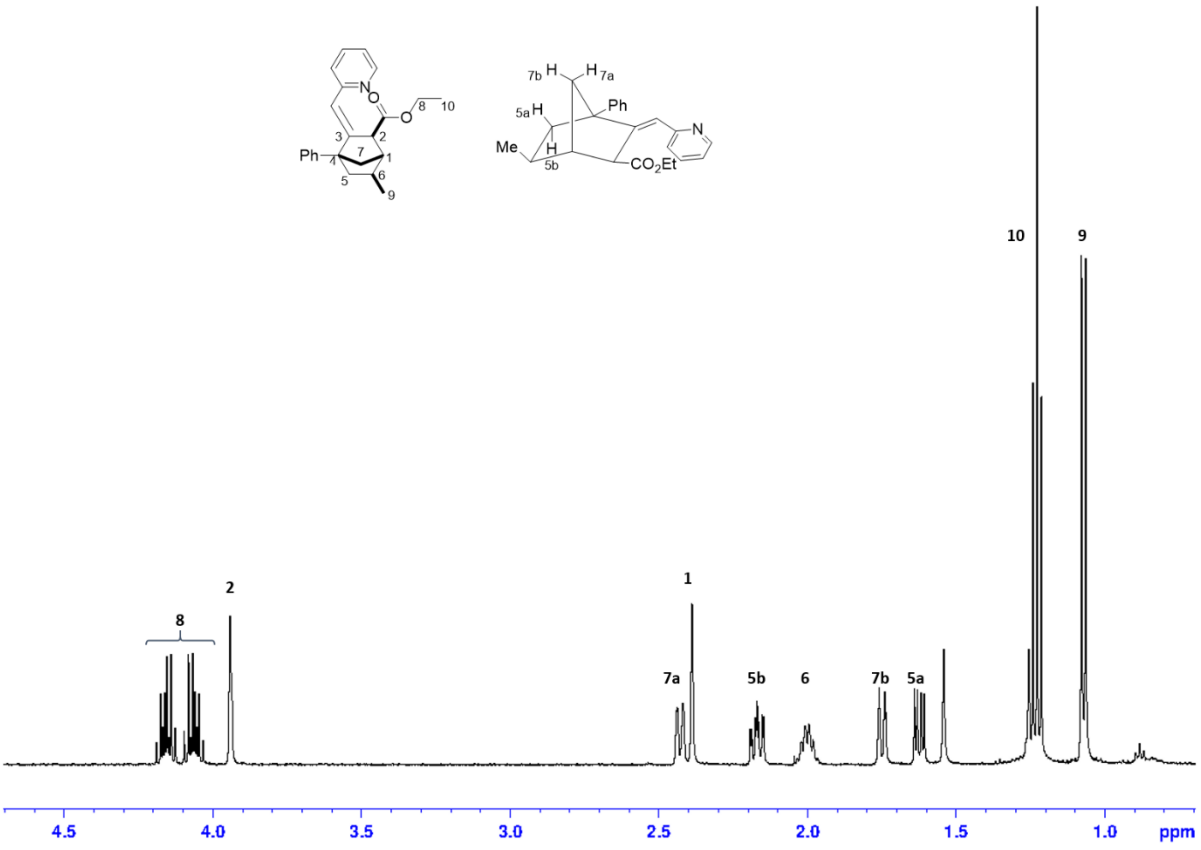


*Figure 4.8: ^{1}H NMR spectrum of norbornane **114b s,s**.*

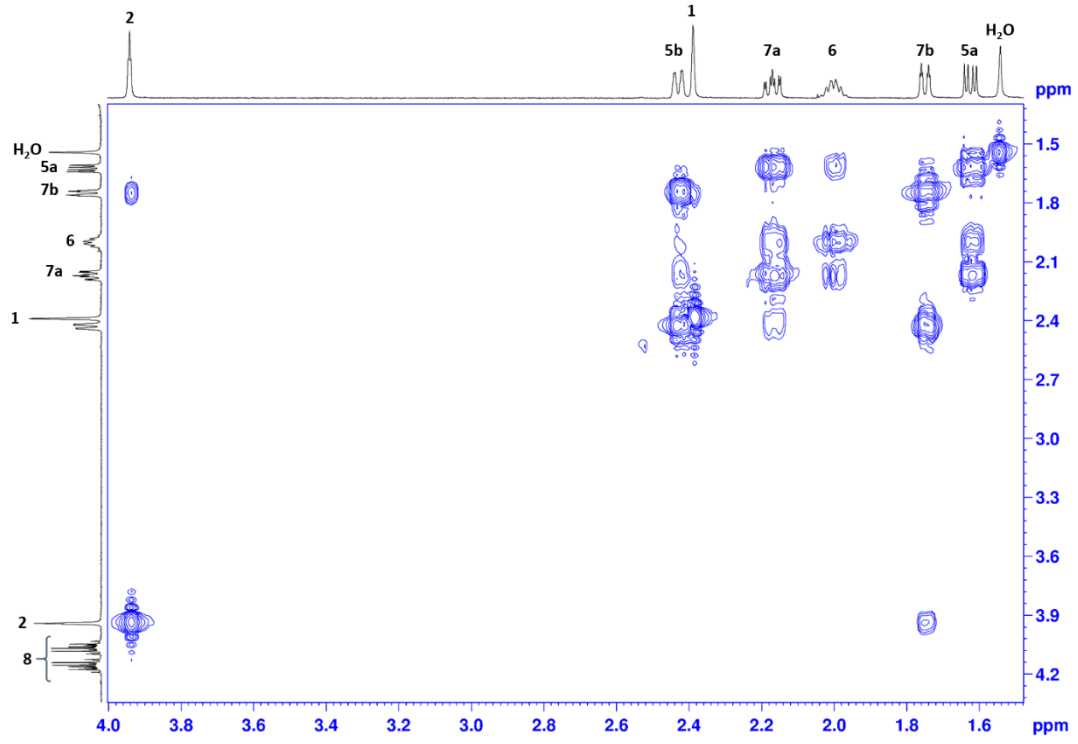


*Figure 4.9: Detail of the COSY spectrum of norbornane **114b s,s**.*

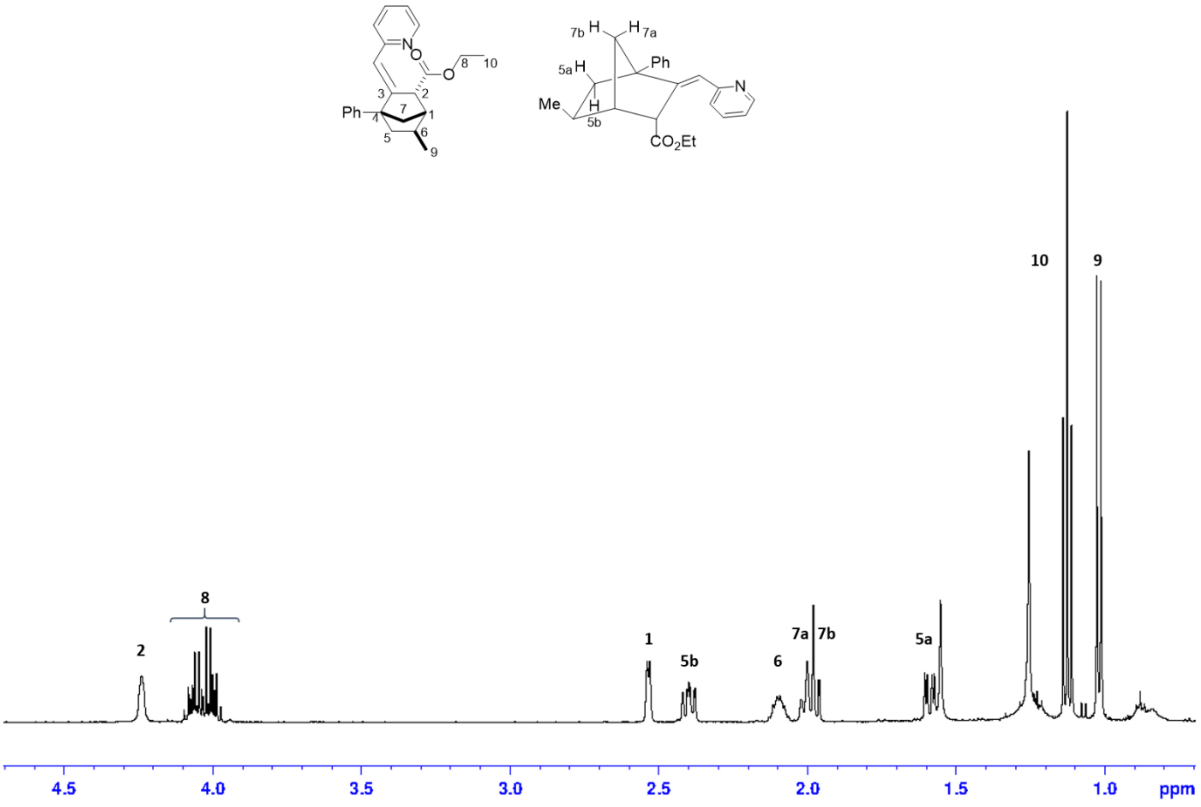


*Figure 4.10: ^{1}H NMR spectrum of norbornane **114b s,a**.*

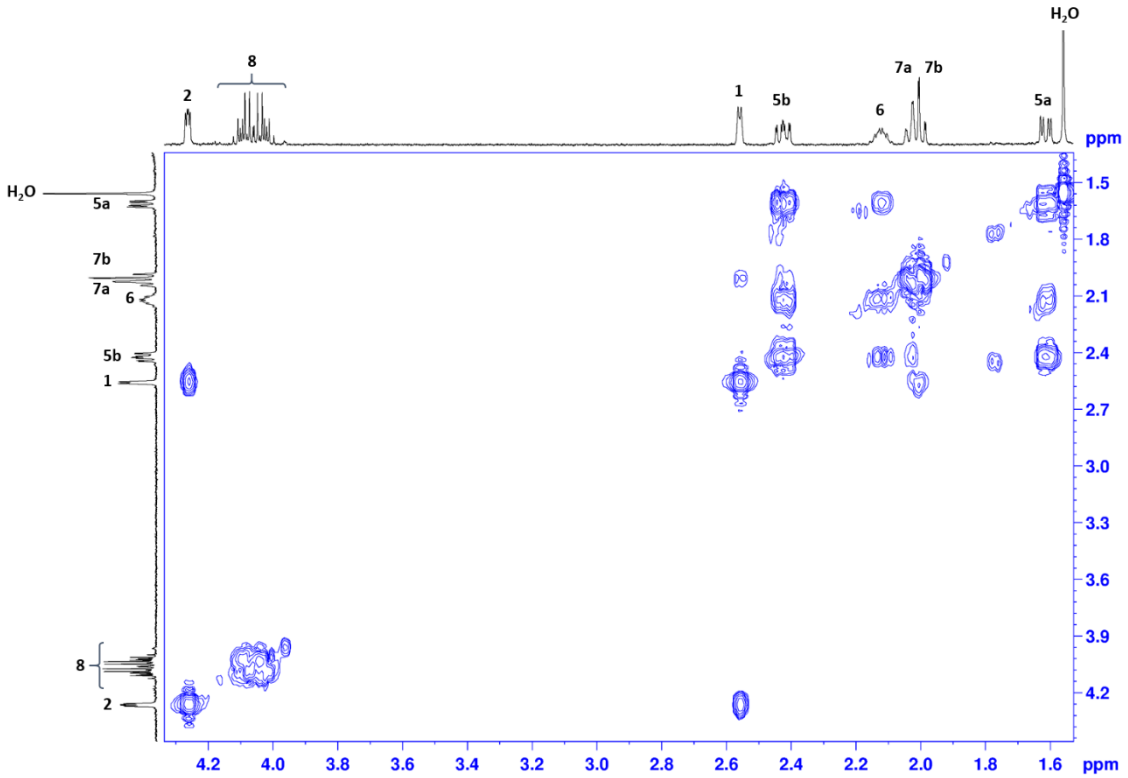


*Figure 4.11: Detail of the COSY spectrum of norbornane **114b s,a**.*

Different NMR experiments including ^{13}C, COSY and HSQC were carried out to distinguish both the protons and the carbons of the molecule. Proton 7b was differentiated from proton 7a because it presents a very strong W-coupling with proton 2 for the *syn,syn* diastereoisomer (^{4}J = 2.18 Hz)[ii]. This results in a correlation in the COSY NMR experience (Figure 4.9). A weaker interaction between these two protons can be also appreciated for the *syn,anti* diastereoisomer (Figure 4.11). However, the coupling constant is too small be calculated in the proton spectrum. Although this W-coupling is lost for the *endo* isomer, the rigidity of the molecule enhances other long distance H-H interactions. Protons 5a and 5b were identified following a similar process. The geometry of the molecule facilitates the W-coupling between H-7a and H-5b in both diastereoisomers (**114b *s,s***: ^{4}J = 2.6 Hz; **114b *s,a***: ^{4}J = 2.1 Hz).[ii] This interaction is clearly appreciated in the COSY spectra. It is noteworthy that methylene 8 has two diastereotopic protons and it can be really appreciated in the *syn,syn* ^{1}H NMR spectrum (Figure 4.8). Then, NOESY experiments were run to differentiate the configuration of both **114a** and **114b**.

The most distinctive NOESY correlation to distinguish the *endo* from the *exo* substituted norbornane corresponds to the one between proton 2 and protons 7 (Figure 4.8). The *syn,anti* isomer presents a clear interaction between these protons as they are very close in space. On the contrary, the position of proton 2 far from methylene 7 in the *syn,syn* diastereoisomer prevents the interaction. Consequently, no correlation can be appreciated in the NOESY spectrum.

Unfortunately, the identification of the two diastereoisomers of the norbornanes **114a** was more complicated. As it was previously observed with the norbornane **78 *s,a***, the key signals to distinguish the two isomers overlapped in both ^{1}H NMR spectra. This prevented the isomers from being discriminated by the NOESY experiment. Therefore, other identification approaches were tested to clearly identify the methoxy substituted norbornanes. To start with, some proton NMR experiments were carried out at low temperature (Figure 4.12 and Figure 4.13). This approach was previously tried with the *syn,anti* isomer norbornane **78 *s,a*** with bad results. However, the definition of the signals and the clear separation between the methyl moieties encourage us to try again.

[ii] The coupling constants were calculated after applying the Lorentz-Gauss transformation with the following parameters: Line broadening (LB) = -2 Hz; Gaussian maximal position (GB) = 0.1

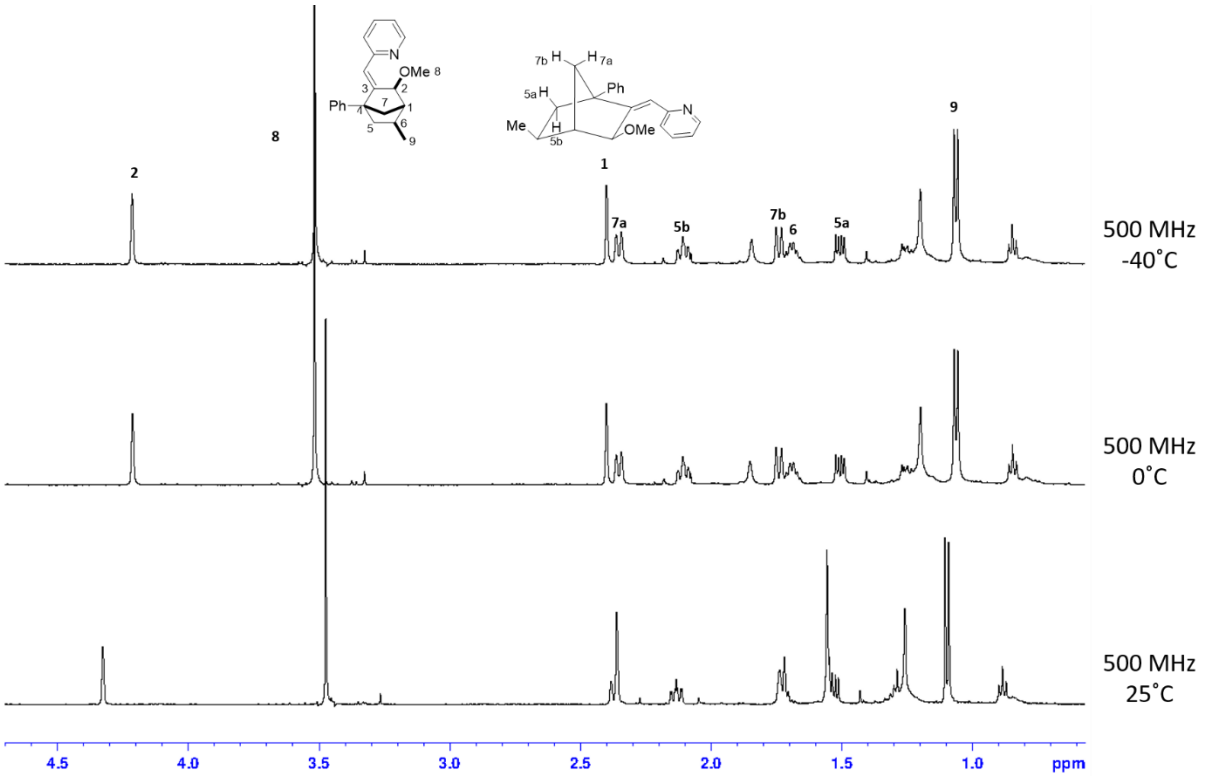


*Figure 4.12: Comparison of ^{1}H NMR spectra of norbornane **114a s,s** at different temperatures.*

When the temperature of the spectrometer was set up at 0°C, the signals of the *syn,syn* norbornane **114a** clearly separated (Figure 4.12). While protons 1 and 7a appeared as an undefined multiplet at 25˚C, the experiment at 0˚C showed them as a singlet and a doublet respectively. The same situation can be observed for protons 7b and 6. Lowing the temperature down to -40°C did not improve the signal's resolution.

The same approach was then carried out with the *syn,anti* isomer with similar results (Figure 4.13). While protons 1 and 6 are clearly overlapped at 25˚C, lowing the temperature to either 0˚ or -10˚C separated the two set of signals. In this case, lowing the temperature and the high resolution of the experiment allows us to observe the hyperfine coupling of different signals. Proton 1 appears as a doublet and proton 2 as a complicated triplet. This collides with the signals of the *syn,syn* isomer which are shown as thick singlets even at low temperature.

Improving the resolution of the protons in both diastereoisomers was a promising result, as carrying either a NOESY or a selective NOESY experiment at low temperature would have showed the key interactions. Unfortunately, the results of these experiments were not conclusive.

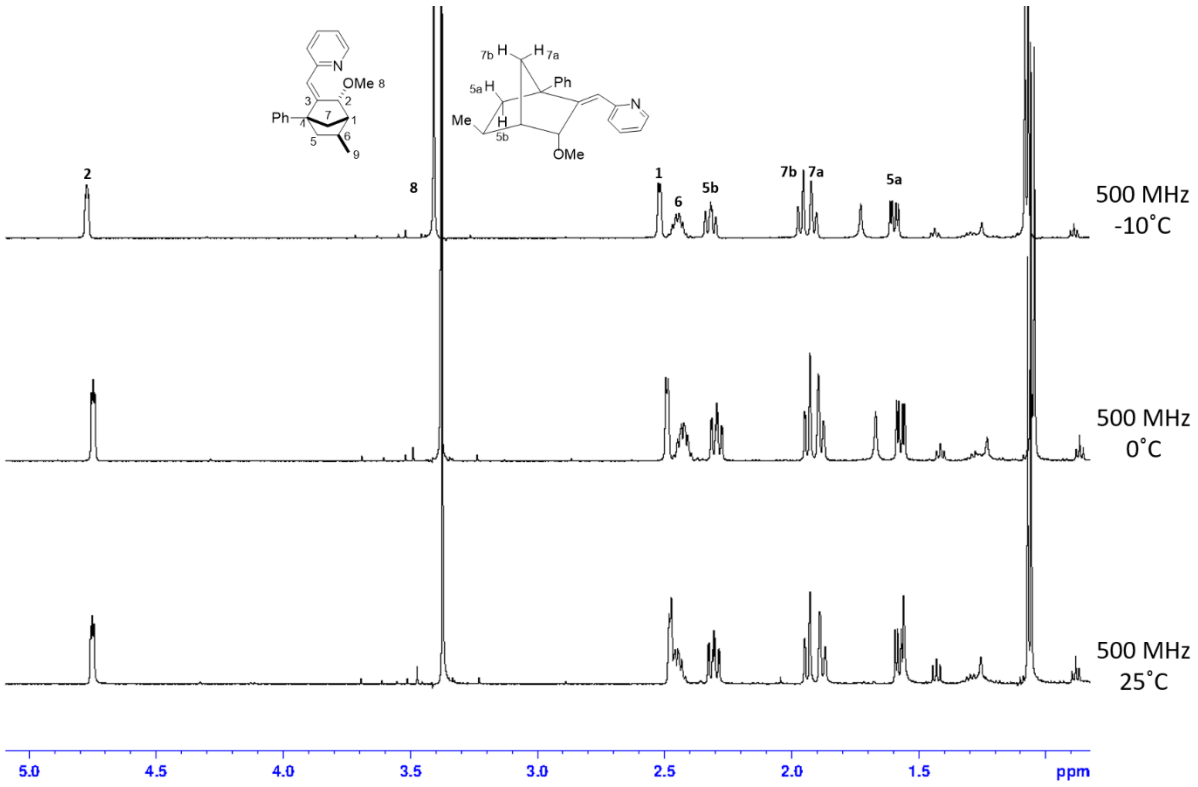
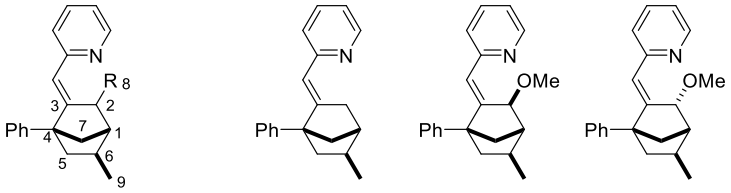


*Figure 4.13: Comparison of ^{1}H NMR spectra of norbornanes **114a s,a** at different temperatures.*

Therefore, a new approach was needed for the identification of the methoxy substituted norbornanes **114a**. First, the carbon spectra was assigned unambiguously by a combination of ^{1}H, ^{13}C, COSY, HSQC and HMBC NMR experiments. Then, following the approach of the characterisation carried out for product **78 *s,a***, the most characteristic chemical shifts of the carbon atoms were analysed and the *gamma gauche* effect was taken into consideration (Table 4.14).

*Table 4.14: Comparison of the ^{13}C chemical shifts of norbornanes **64a**, **114a s,s** and **114a s,a**.*



64a R ≡ H
114a R ≡ OMe

64a

114a
s,s

114a
s,a

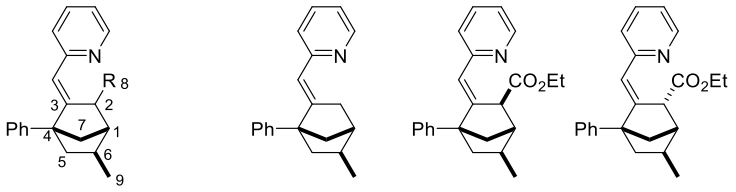
	^{13}C chemical shift (ppm)			
Isomer	**C-6**	**C-7**	**C-8**	**C-9**
64a	42.6	41.2	----------	22.3
114a *s,s*	31.3	38.3	56.6	21.7
114a *s,a*	27.0	37.2	56.6	21.7

In this case, compared to the unsubstituted norbornane **64a**, the C-6 of both the *endo* and the *exo* diastereoisomers is moved downfield. However, the *syn,anti* diastereoisomer is few ppms more shielded. This agrees with the data reported by Kleinpeter and Seidl and that it has been previously discussed in section 2.2.2.1.[51] On the contrary, the presence of the methoxy substituent either in the *endo* or the *exo* position does not really affect the chemical shift of the C-9. This situation was already seen for the norbornanes **78 *s,s*** and **78 *s,a***. The rigidity of the molecule and the long distance between methyl 9 and the methoxy substituent 8 prevents the interaction between the two moieties. Consequently, this is reflected in both diastereoisomers having the same chemical shift. When the norbornane had a methyl substituent in carbon 2 (products **78 *s,s*** and **78 *s,a***), the *syn,syn* isomer presented a slightly deshielded chemical shift (Table 2.2). For the methoxy substituted norbornanes, both diastereoisomers showed the exact chemical shift. This can be explained by the electronic effects of the oxygen atom. In both cases, the oxygen isolates the methyl from the rest of the molecule, diminishing the effect of the steric interactions in the methyl 8. However, the most surprising data was afforded by methylene 7. Both the *endo* and the *exo* diastereoisomers are shielded compare to norbornane **63**. This agrees with the data reported for norbornanes **78 *s,s*** and **78 *s,a***. In that case, the *exo* diastereoisomer was 4 ppm more shielded, while for products **114a** the *syn,syn* diastereoisomer is slightly moved up field. The steric effects described by Kleinpeter and Seidl are less important than the electronic effects of the methoxy substituent. It is widely known that presence of an

electronegative atom in a molecule deshields its surrounding atoms in the ^{13}C NMR spectra. Therefore, the proximity between the methylene 7 and the methoxy moiety could electronically affect the chemical shift of the C-7 in the *syn,syn* diastereoisomer.

Although the ester substituted norbornanes **114b** were already identified and characterised, the study of the effect of the electron-withdrawing group in the *gamma gauche* interactions was also interesting (Table 4.15). Moreover, the comparison of the characteristic ^{13}C shifts could confirm the identification carried out with the NOESY experiments.

*Table 4.15: Comparison of the ^{13}C chemical shifts of norbornanes **64a**, **114b s,s** and **114b s,a**.*



64a R ≡ H
114b R ≡ CO_2Et

64a

114b
s,s

114b
s,a

	^{13}C chemical shift (ppm)			
Isomer	**C-6**	**C-7**	**C-8**	**C-9**
64a	42.6	41.2	----------	22.3
114b *s,s*	36.7	39.2	173.1	22.0
114b *s,a*	31.6	40.9	172.0	22.0

In this case, both methine 6 and methylene 7 followed the tendency observed in the methyl substituted norbornanes **78 *s,s*** and **78 *s,a***. Both diastereoisomers were moved upfield compare to the unsubstituted norbornane **64a**. Furthermore, the *syn,anti* diastereoisomer **114b** is slightly more deshielded than its *syn,syn* counterpart. This shows that the steric effects are more important than the possible electronic effects of the ester moiety. As described for the methoxy substituted norbornanes **114a**, the chemical shift of the carbon 8, which corresponds is not affected by the configuration of the molecule.

Although an unambiguous identification of the diastereoisomers could not be done by analogy with the previously identified norbornanes **78 *s,s*** and **78 *s,a***, a closer look to the different ^{1}H NMR spectra

showed some similarities between the isomers (Figure 4.12 and Figure 4.13). To start with, the *syn,anti* isomers presented the methylene protons 7 very close to 2 ppm with a clear roof effect for the substituted norbornanes **114a** and **114b**. It is noteworthy that both protons present different multiplicity. While proton 7a appears as doublet, proton 7b has a hyperfine coupling with proton 2 that is translated in the signal splitting as a doublet of doublets. Moreover, the proton 2 of the *endo* diastereoisomers appears as a complex doublet for norbornanes **114a** and **114b**, and as a multiplet for methyl substituted norbornane **78 *s,a***. On the contrary, the H-2 signal of the *exo* substituted norbornanes is much simpler. This proton appears as a singlet for both *syn,syn* **114a** and **114b** norbornanes, and it is coupled with methyl 8 looking like a quartet for methyl substituted norbornane **78 *s,s***. This situation was previously discussed in section 2.2.2.1 and it can be explained by the Karplus law. A 3D simulation carried out on the different diastereoisomers showed that the *syn,syn* norbornanes presented a dihedral angle between H-1 and H-2 of approximate 70˚, while the dihedral angle of the *syn,anti* isomers was close to 50˚. Obviously, the multiplicity of H-1 is also affected. As it is expected, this proton appears as a singlet in the *exo* isomer spectrum and as a small doublet for the *endo* isomer ^{1}H NMR. This clear pattern on the ^{1}H NMR spectra can be used to identify similar molecules in a future.

4.6 Conclusions

The competition of the reductive elimination *versus* the *β*-hydride elimination was examined and discussed in chapter 3. However, after the optimisation of the reaction conditions, the product of the 1,2-insertion was still formed in high yields. It was hypothesised that either the introduction of bulky substituents in the C-4 of the diene or the modification of the electronical environment of the metal centre would improve the product selectivity towards the formation of the norbornane **78** and the cyclopentane **80** under the specific reaction conditions. Thus, substrates bearing different steric and electronic substituents in different positions of the compound were synthesised and examined.

It was suggested that the replacement of the phenyl group for larger substituents would enhance the Thorpe-Ingold effect and accelerate the second migratory insertion from intermediate **XX** to **XXI**. Unfortunately, the cycloisomerisation of substrates **67g** and **67h**, bearing a cyclohexyl group and a 1,3-dioxolane group respectively, afforded the 1,2-insertion product **79** in around 20% yield independently of the reaction conditions. In this regard, the introduction of these substituents decreased the **80**/**78** selectivity when 20 mol% of PPh_2tBu was used as a ligand. In addition, the recycling of the cyclopentane **80** into the norbornane **78** was stopped under those conditions. In contrast, the replacement of the phenyl group for the *ortho*-tolyl group accelerated the second migratory insertion and reduced the amount of cyclopentane **79** formed.

In a second approach, the effect of the electrondensity in the metal centre was examined. Thus, substrates **67j** and **67l** containing an electron-poor and an electron-rich substituent in the position 4 of the pyridine moiety were synthesised. In this regard, the cycloisomerisation of the electron-poor substrate **67j** afforded the cyclopentane **79j** in comparable yields to those of the neutral substrate **67f**. However, the **78j**/**80j** ratio was diminished when the reaction was carried out with 20 mol% of PPh_2tBu as the ligand. In addition, cyclopentane **80j** could not be recycled under those reaction conditions. In contrast, the introduction of the electron-donating methoxy group favoured the reductive elimination over the β-hydride elimination, but it also favoured the formation of the 1,2-insertion product. The introduction of a methyl group in the position 3 of the pyridine moiety resulted in a similar product distribution to that observed for the cycloisomerisation of substrate **67c**.

The cycloisomerisation of the substrates which contain substituents lacking hydrogens in a β-position was also examined. Surprisingly, the reaction with both the electron-poor and electron-donating substrates resulted in a similar product distribution. This indicated that electronic properties of the olefin moiety did not influence the second migratory insertion.

It was expected that the cycloisomerisation of a *bis*-methyl allylated substrate would promote the second migratory insertion over the 1,2-insertion. However, the 1,2-insertion product was obtained as the major compound. In addition, the reaction proved to be very slow and higher temperatures were required to reach the reaction completion. The results of **67a** and **67b** were re-examined. The second migratory insertion was only possible in substrate **67b** which contained a *gem*-dimethyl group. However, the reduction elimination from the seven-membered ring metallacycle was not possible and only the β-hydride elimination product was obtained in low yields. The 1,2-insertion products were obtained in high yields for both substrates. Thus, the 1,2-insertion was favoured by the increase of the steric hindrance in the olefin moiety.

Finally, the characteristic ^{13}C NMR spectra of the norbornane diastereoisomers were compared with the unsubstituted norbornane and the *gamma gauche* effect enabled the identification of each diastereoisomer. In this regard, the shielding by gamma gauche effect was observed for all the distinctive carbons. The introduction of the substituent on the pyridine moiety did not affect the chemical shift of the carbon nuclei.

Chapter 5 : Conclusions

A cationic rhodium catalyst cycloisomerised a 1,6-octadiene bearing a vinylpyridine moiety to a mixture of isomers in a highly diastereoselective fashion. The mechanism of the reaction, which was elucidated by the results of the D-labelling experiments, showed that the seven-membered ring intremediate could undergo either β-hydride elimination or reductive elimination to form a diastereoselective cyclopentane and a norbornane respectively as the major products of the reaction. In contrast, the undesired side product was the result of the 1,2-insertion of the unsubstituted olefin.

The control of the reductive elimination and the β-hydride elimination was achieved after an extensive phosphine screening. When 20 mol% PPh_2tBu was used as the ligand, the norbornane was obtained in over 70% selectivity. The β-hydride elimination was favoured when 10 mol% $P(2\text{-furyl})_3$ was used as the ligand and the cyclopentane was obtained in over 70% NMR yield. This screening showed that the phosphine had no influence on the control of the second migratory insertion *vs*. the 1,2-insertion. The configuration of the starting material proved to be an important factor on the *syn,syn*/*syn,anti* ratio of the norbornane. In contrast, the cyclopentane was obtained as only one diastereoisomer regardless of the configuration of the starting material.

A careful NMR monitoring of the reaction showed the isomerisation of the substrate before being consumed when 10 mol% of $P(2\text{-furyl})_3$ was used as the ligand. This phenomenon was stopped when the reaction was carried out with 20 mol% PPh_2tBu instead. Under those conditions, the cyclopentane was formed and then transformed into the norbornane. Further control experiments examined the transient character of the cyclopentane which could only be converted when PPh_2tBu was used as a ligand. These results showed that the cyclopentane was the kinetic product, while the formation of the norbornane was done under thermodynamic control.

The enhancement of the second migratory insertion was examined by modifying the steric and electronic characteristics of the substrate. The introduction of either the cyclohexyl or the 2-methyl-1,3-dioxolane at the quaternary carbon atom of the diene did not improve the product selectivity and the results using 10 mol% $P(2\text{-furyl})_3$ as a ligand where comparable to those of the benchmark substrate. In contrast, when the reaction was carried out under the conditions that favoured the reductive elimination, the excellent product selectivity was diminished. The preliminary results suggested that the transformation of the cyclopentane into the norbornane was hindered. The 1,2-insertion was minimised to the detriment of the reaction rate when *ortho*-tolyl substituent was

introduced at the quaternary carbon atom of the diene. In that case, the control of the reductive elimination and the β-hydride elimination was not affected.

In the second approach to improve the product distribution, the modification of the electronic environment of the metal catalyst did not accelerate the second migratory insertion. As a matter of fact, the 1,2-insertion was clearly enhanced when an electron-donating substituent was introduced in the position 4 of the pyridine moiety. The conversion of the cyclopentane into the norbornane was not affected by the electron-rich environment, but it was halted by the introduction of an electron-withdrawing group in the position 4 of the pyridine moiety. The methyl substitution in the position 3 of the pyridine moiety resulted in the acceleration of the reaction rate without affecting the product distribution.

The substitution of the alkene moiety was also examined. The introduction of electronically opposite substituents in the terminal carbon of the olefin lacking electrons in the β-position resulted in the formation of the corresponding norbornane and the 1,2-insertion in a similar product distribution. More sterically demanding substrates favoured the formation of the 1,2-insertion product.

Overall, the cycloisomerisation of substituted 1,6-dienes resulted in the formation of a mixture of isomers, whose product selectivity was partially controlled by modifying the catalytic sphere. Unfortunately, the efforts to stop the 1,2-insertion from occurring did not succeed. The conditions favouring the β-hydride elimination yielded a highly diastereoselective cyclopentane. The norbornane, as an enriched mixture of *syn,syn* and *syn,anti* isomers was obtained under the reductive elimination conditions. The introduction of substituents in different positions of the diene could diminish the product distribution.

Chapter 6 : Experimental section

6.1 General considerations

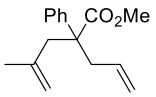
Unless otherwise noted, all the reactions were monitored by thin layer chromatography (TLC) which were performed on Merck F254 precoated silica gel plates (250 μm thickness). They were revealed by UV light and *p*−anysaldehyde or $KMnO_4$ solution. All the products were purified by flash column chromatography (FCC) which was performed using Sigma−Aldrich Silica Gel 60 Å (230−400 mesh). Better isolation of products was accomplished by preparatory thin layer chromatography (PrepTLC) either in glass precoated F254 plate, 0.25 mm thick or in Merck glass precoated F254 plate, 0.5 mm thick. Celite® 545 was purchased from Alfa Aesar. Solvents for extraction and FCC were technical grade. The FCC eluents are reported as volume/volume mixtures.

^{1}H NMR and ^{13}C NMR were recorded on Bruker AV 500 MHz NMR spectrometer in $CDCl_3$ and the residual protium was set to 7.26 ppm for ^{1}H NMR and to 77.00 ppm for ^{13}C NMR. Data is reported in the following order: chemical shift in ppm (δ) (multiplicity; which is indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J* in Hz); integration). Infrared spectra (IR) were obtained on a Perkin-Elmer Spectrum 100 series FTIR spectrophotometer. The wavenumber ($\tilde{\nu}$) of the peaks are reported in cm^{-1} with the following relative intensities: s (strong), m (medium) and w (weak); broad peaks (br) are also reported. High resolution mass spectrometry (HRMS) and elemental analysis were recorded by the Analytical Services of the University of Liverpool. Two different methods were used in HRMS: chemical ionisiation (CI) was done in a Trio−1000 or Agilent QTOF 7200 mass spectrometers while positive electrospray (ES+) was done in micromass LCT mass spectrometer

All starting materials were purchased from Acros, Sigma−Aldrich, Alfa Aesar, Fluorochem or Strem chemical companies and used without further purification. Unless otherwise noted, all the solvents were purchased from Fisher and used without further purification.

6.2 Synthesis of substrates

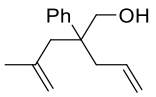
6.2.1 Synthesis of compounds a



70a

Diisopropylamine (8.4 mmol, 1.2 mL) was dissolved in THF (10 mL) in a 3−neck round−bottom flask under N_2. At 0 °C, *n*−BuLi (6.9 mmol, 2.75 mL, 2.5 M in hexanes) was added dropwise via syringe. After 15 minutes stirring at that temperature, compound **69** (5.7 mmol, 1 g) in THF (5 mL) was added at −78 °C. After 45 minutes stirring at that temperature, 2-methylallyl bromide (8.8 mmol, 0.9 mL) was added neat and the mixture was stirred for 20 min before adding Bu_4NI (430 mg, 0.2 mmol) After stirring overnight at room temperature, the mixture was quenched with a saturated solution of NH_4Cl and extracted three times with ethyl acetate. The organic layers were combined and washed with water and brine then before drying over $MgSO_4$. After filtration and concentration at reduced pressure, purification by flash chromatography (PE:Et_2O = 45:1) gave **70a** as a colourless oil (1.2 g, 89%).

Compound 70a Colourless oil (1.2 g, 89%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.37−7.29 (m, 2H), 7.29−7.20 (m, 3H), 5.62−5.48 (m, 1H), 5.07−4.99 (m, 2H), 4.84 (s, 1H), 4.68 (s, 1H), 3.63 (s, 3H), 2.93−2.79 (m, 3H), 2.74 (d, *J* = 14.1 Hz, 1H), 1.40 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 175.9, 142.3, 141.6, 133.7, 128.3 (2C), 126.8, 126.5 (2C), 118.6, 115.5, 53.3, 51.9, 42.4, 38.7, 23.8; **IR (neat):** $\tilde{\nu}$ = 3077 (w), 2950 (w), 1729 (s), 1641 (w), 1599 (w), 1583 (w), 1498 (w), 1446 (m), 1376 (w), 1327 (w), 1273 (w), 1262 (w), 1238 (w), 1203 (s), 1135 (w), 1080 (w), 1067 (w), 1053 (w), 1034 (w), 991 (w), 915 (m), 896 (m), 858 (w), 824 (w), 802 (w), 771 (w), 734 (w), 698 (s) cm^{-1}; **MS (CI):** 245 [M + H] (100%), 262 [M + NH_4] (42%); **elemental analysis** (%) calcd for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 77.82, H 8.33.

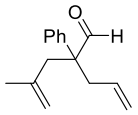


71a

$LiAlH_4$ (2.5 mmol, 100 mg) was dissolved in Et_2O (17 mL) in a three−neck round−bottom flask under N_2. At 0 °C, **70a** (5 mmol, 1.2 g) in Et_2O was added via cannula. After 20 minutes stirring at room temperature, $LiAlH_4$ (2.5 mmol, 100 mg) was added at 0 °C. After 30 minutes stirring at room temperature, an aqueous the reaction mixture was quenched with saturated solution of Na_2SO_4 at 0

°C. The mixture was filtered over Celite to remove the white precipitate and it was concentrated at reduced pressure. **71a** was obtained as a colourless oil (1g, 93%).

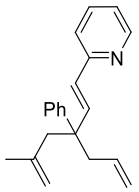
Compound 71a Colourless oil (1 g, 93%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.37−7.31 (m, 4H), 7.24−7.19 (m, 1H), 5.75−5.64 (m, 1H), 5.12 (d, *J* = 17.2, 1H), 5.02 (d, *J* = 10.1, 1H), 4.79−4.76 (m, 1H), 4.63 (s, 1H), 3.88 (d, *J* = 6.5 Hz, 2H), 2.64 (ddt, *J* = 14.6, 6.6, 1.3 Hz, 1H), 2.53 (dd, *J* = 14.1, 7.8 Hz, 1H), 2.45 (s, 2H), 1.41 (t, *J* = 6.6 Hz, 1H (OH)), 1.31 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 143.9, 142.9, 134.8, 128.3 (2C), 126.8 (2C), 126.2, 117.9, 114.6, 67.0, 45.6, 44.7, 40.2, 24.4; **IR (neat):** $\tilde{\nu}$ = 3443 (w, br), 3073 (w), 3024 (w), 2921 (w), 1801 (w), 1639 (w), 1600 (w), 1580 (w), 1499 (w), 1445 (m), 1375 (w), 1331 (w), 1138 (w), 1137 (w), 1033 (m), 1049 (m), 1023 (m), 1000 (w), 970 (w), 914 (m), 894 (m), 849 (w), 769 (w), 748 (w), 699 (s) cm^{-1}; **MS (CI):** 234 [M + NH_4] (100%), 217 [M + H] (17%); **elemental analysis** (%) calcd for $C_{15}H_{20}O$: C 83.28, H 9.32; found: C 83.26, H 9.52.



72a

Oxalyl chloride (10 mmol, 0.8 mL) was dissolved in DCM (20 mL) in a three−neck round−bottom flask under N_2. At −78 °C, dimethyl sulfoxide (5 mmol, 0.4 mL) in DCM (4 mL) was added *via* cannula. After 15 minutes of stirring at that temperature, **71a** (4 mmol, 820 mg) in DCM (4 mL) was added *via* cannula. After 30 minutes stirring, NEt_3 (19 mmol, 3 mL) was rapidly added and the mixture was stirring for 10 minutes at room temperature. An aqueous saturated solution of NH_4Cl was to the reaction mixture and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with water and brine before drying over $MgSO_4$. After filtration and concentration at reduced pressure, purification by flash chromatography (PE:EtOAC = 90:1) gave **72a** as a colourless oil

Compound 72a Colourless oil (595 mg, 73%); **^{1}H NMR** (500 MHz, $CDCl_3$): 9.56 (s, 1H), 7.41−7.35 (m, 2H), 7.32−7.27 (m, 1H), 7.25−7.20 (m, 2H); 5.63−5.53 (m, 1H), 5.11−5.02 (m, 2H), 4.84 (s, 1H), 4.66 (s, 1H), 2.82 (dd, *J* = 14.4, 7.0 Hz, 1H), 2.78−2.66 (m, 3H), 1.42 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 202.0, 141.0, 138.1, 133.0, 128.7 (2C), 127.8 (2C), 127.4, 119.0, 115.6, 56.8, 40.6, 36.6, 24.3; **IR (neat):** $\tilde{\nu}$ = 3077 (w), 3026 (w), 2979 (w), 2945 (w), 2803 (w), 2713 (w), 1809 (w), 1721 (s), 1641 (w), 1599 (w), 1582 (w), 1495 (w), 1446 (m), 1377 (w), 1316 (w), 1284 (w), 1231 (w), 1158 (w), 1090 (w), 1030 (w), 995 (w), 918 (m), 896 (m), 836 (w), 810 (w), 761 (w), 699 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{15}H_{18}O$ + H): 215.1430; found: 215.1439.



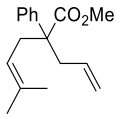
67a

2−picoline (3.6 mmol, 0.34 mL) was dissolved in THF (9 mL) in a three−neck round−bottom flask under N_2. At −78 °C, *n*-BuLi (4 mmol, 2 mL, 2.5 M in hexanes) was added dropwise *via* syringe. After 15 minutes stirring at that temperature, **72a** (2.7 mmol, 0.6 g) in THF (5 mL) was added to the mixture which was allowed to warm up to room temperature and it was stirring overnight. The reaction mixture was quenched with an aqueous saturated solution of $NaHCO_3$ at 0 °C and extracted three times with EtOAc. The combined organic layers were washed with water and brine before drying over $MgSO_4$. The mixture was filtered over a cotton plug and concentrated at reduced pressure. Purification by flash chromatography (PE:EtOAc = 10:1 → 6:1) gave **73a** as a yellow oil. Compound **73a** (1.6 mmol, 500 mg) was dissolved in DCM (3 mL) in a three−neck round−bottom flask at N_2. At 0 °C, NEt_3 (2.4 mmol, 0.34 mL) was added neat and the mixture was stirring for 5 minutes before methanesulfonyl chloride (2 mmol, 0.15 mL) in DCM (1 mL) was added *via* cannula. After stirring overnight at room temperature, the reaction mixture was quenched with an aqueous saturated solution of $NaHCO_3$ and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with water and brine before drying over $MgSO_4$. The mixture was filtered over a cotton plug and concentrated at reduced pressure to obtain and orange oil which was dissolved in THF (0.65 mL) at 0 °C. NaHMDS (3.2 mmol, 3.2 mL, 1 M in THF) was added *via* syringe at that temperature. The reaction mixture was stirring for one hour and then, it was quenched with an aqueous saturated solution of $NaHCO_3$. The mixture was extracted three times with EtOAc and the combined organic layers were washed with water and brine before drying over $MgSO_4$. The mixture was filtered over a cotton plug and concentrated at reduced pressure. Purification by flash column chromatography (PE:EtOAc = 20:1) afforded **67a** as a colourless oil (331 mg, 76%).

Compound 67a Yellow oil (331 mg, 76%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.55 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.39−7.34 (m, 2H), 7.34−7.27 (m, 3H), 7.22−7.17 (m, 1H), 7.11 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.92 (d, *J* = 16.3 Hz, 1H), 6.56 (d, *J* = 16.4 Hz, 1H), 5.74−5.63 (m, 1H), 5.10−5.04 (m, 1H), 5.04−5.00 (m, 1H), 4.84−4.81 (m, 1H), 4.65 (s, 1H), 2.79 (d, *J* = 6.93 Hz, 2H), 2.73 (d, *J* = 13.6, 1H), 2.65 (d, *J* = 13.4, 1H) 1.39 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.1, 149.5, 145.0, 142.31, 142.28, 136.3, 134.9, 128.3, 128.0, 127.6, 126.1, 121.7, 120.9, 117.8, 115.2, 46.9, 46.1, 41.7, 24.8; **IR (neat):** $\tilde{\nu}$ = 3074 (w), 3005 (w), 2976 (w), 2926 (w), 1949 (w), 1737 (w), 1640 (w), 1585 (s), 1563 (m), 1494 (w), 1469 (m), 1445 (m), 1429 (s), 1374 (w), 1327 (w), 1304 (w), 1239 (w), 1189 (w), 1149 (w), 1117 (w),

1090 (w), 1049 (w), 1033 (w), 990 (m), 894 (s), 763 (s), 751 (m), 699 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{23}N$ + H): 290.1903; found: 290.1901.

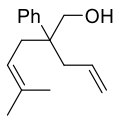
6.2.2 Synthesis of compounds b



70b

Substrate **70b** was synthesised following the procedure for the synthesis substrate **70a** except that 3-methylcrotyl bromide was used and that purification by FCC (PE:Et_2O = 44:1).

Compound 70b Colourless oil (789 mg, 85 %); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.32−7.29 (m, 2H), 7.26−7.22 (m, 3H), 5.55−5.46 (m, 1H), 5.09−5.01 (d, *J* = 12.8 Hz, 2H), 4.89 (t, *J* = 6.7 Hz, 1H), 3.63 (s, 3H), 2.80−2.70 (m, 3H), 2.64 (dd, *J* = 14.4, 6.7 Hz, 1H), 1.65 (s, 3H), 1.52 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 175.8, 142.1, 134.7, 133.6, 128.2 (2C), 126.7 (2C), 126.4, 118.6, 118.3, 54.1, 51.9, 39.2, 33.0, 26.0, 17.9; **IR (neat):** $\tilde{\nu}$ = 3062 (w), 2950 (w), 2917 (w), 2858 (w), 1730 (s), 1673 (w), 1641 (w), 1600 (w), 1583 (w), 1497 (w), 1446 (m), 1377 (w), 1321 (w), 1273 (w), 1215 (s), 1173 (m), 1138 (w), 1115 (w), 1077 (w), 1061 (w), 1035 (w), 996 (w), 916 (m), 892 (w), 852 (w), 773 (w), 762 (w), 737 (m), 698 (s) cm^{-1}; **HRMS (ES+):** calcd for ($C_{17}H_{22}O_2$ +Na): 281.1517; found 281.1519; **elemental analysis** (%) calc for $C_{17}H_{22}O_2$: C 79.03, H 8.58; found: 78.87, 8.69.

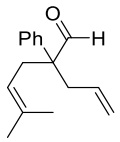


71b

Substrate **71b** was synthesised following the procedure for the synthesis of substrate **71a**.

Compound 71b Colourless oil (588 mg, 90%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.38−7.32 (m, 4H), 7.25−7.20 (m, 1H), 5.69−5.59 (m, 1H), 5.07 (d, *J* = 16.9 Hz, 1H), 5.04−4.97 (m, 2H), 3.79 (d, *J* = 6.6 Hz, 2H), 2.55 (ddt, *J* = 14.0, 7.2, 1.2 Hz, 1H), 2.51−2.43 (m, 2H), 2.39 (dd, *J* = 14.8, 7.0 Hz, 1H), 1.65 (d, *J* = 1.0 Hz, 3H), 1.60 (s, 3H), 1.28 (t, *J* = 6.6 Hz, 1H (OH)); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 143.8, 134.7, 134.1, 128.3 (2C), 126.9 (2C), 126.1, 119.6, 117.6, 68.2, 46.4, 39.8, 33.7, 26.0, 18.0; **IR (neat):** $\tilde{\nu}$ = 3402 (w, br), 3059 (w), 2975 (w), 2914 (w), 1671 (w), 1638 (w), 1601 (w), 1580 (w), 1498 (w), 1445 (m), 1376 (w), 1321 (w), 1111 (w), 1046 (m), 999 (w), 913 (m), 867 (w), 829 (w), 782 (w), 763 (m), 739 (w), 697 (s), 664 (w) cm^{-1};

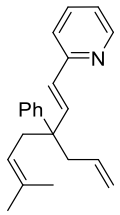
MS (CI): 248 [M + NH_4] (100%), 231 [M + H] (3%); **elemental analysis** (%) calcd for $C_{16}H_{22}O$: C 83.43, H 9.63; found: C 83.17, H 9.77.



72b

Substrate **72b** was synthesised following the procedure for the synthesis of substrate **72a** except that purification was done by FCC (PE:EtOAc = 75:1)

Compound 72b Colourless oil (349 mg, 90%); **^{1}H NMR** (500 MHz, $CDCl_3$): 9.52 (s, 1H), 7.41−7.38 (m, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 2H), 5.56−5.47 (m, 1H), 5.07−4.99 (m, 2H), 4.95 (tt, *J* = 7.2, 1.4 Hz, 1H), 2.72−2.65 (m, 3H), 2.61 (dd, *J* = 15.0, 7.2 Hz, 1H), 1.56 (s, 3H), 1.54 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 202.4, 138.4, 135.0, 133.1, 128.7 (2C), 127.7 (2C), 127.3, 118.5, 117.9, 57.6, 37.1, 30.7, 25.9, 18.0; **IR (neat):** $\tilde{\nu}$ = 3062 (w), 2979 (w), 2915 (w), 2858 (w), 2711 (w), 2257 (w), 1722 (s), 1640 (w), 1599 (w), 1582 (w), 1496 (w), 1446 (m), 1377 (w), 1264 (w), 1242 (w), 1205 (w), 1111 (w), 1029 (w), 997 (w), 913 (m), 880 (w), 855 (w), 760 (m), 732 (m), 698 (s) cm^{-1}; **MS (CI):** 246 [M + NH_4] (100%), 229 [M + H] (4%); **elemental analysis** (%) calcd for $C_{16}H_{20}O$: C 84.16, H 8.83; found: C 85.37, H 9.21.



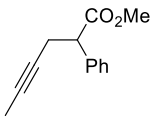
67b

Substrate **67b** was synthesised following the procedure for the synthesis of substrate **67a** except purification was done by FCC (PE:EtOAc = 15:1 → 8:1).

Compound 67b Yellow oil (73 mg, 62%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.55 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.61 (td, *J* = 7.7, 1.7 Hz, 1H), 7.36−7.28 (m, 5H), 7.20 (t, *J* = 7.1 Hz, 1H), 7.11 (ddd, *J* = 7.7, 4.9, 0.9 Hz, 1H), 6.86 (d, *J* = 16.4 Hz, 1H), 6.54 (d, *J* = 16.3 Hz, 1H), 5.68−5.58 (m, 1H), 5.06−4.97 (m, 3H), 2.68 (d, *J* = 7.1 Hz, 2H), 2.60 (d, *J* = 7.0 Hz, 2H), 1.63 (s, 3H), 1.52 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.2, 149.4, 145.0, 142.2, 136.4, 134.8, 133.7, 128.6, 128.0 (2C), 127.6 (2C), 126.0, 121.7, 120.9, 119.8, 117.6, 47.6, 42.2, 36.1, 26.0, 18.1; **IR (neat):** $\tilde{\nu}$ = 3058 (w), 2977 (w), 2913 (w), 2856 (w), 1949 (w), 1740 (w), 1647 (w), 1585 (m), 1563 (w), 1495 (w), 1468 (m), 1445 (m), 1429 (m), 1376 (w), 1322 (w), 1305 (w), 1262 (w), 1241 (w), 1191 (w), 1149 (w), 1089 (w), 1049 (w), 1033 (w), 990 (m), 979 (m), 913 (m), 854 (w),

761 (m), 742 (m), 698 (s) cm^{-1}; **HRMS (ES+):** calcd for ($C_{22}H_{25}N$ + H): 304.2065; found: 204.2067; **elemental analysis** (%) calcd for $C_{22}H_{25}N$: C 87.08, H 8.30 N 4.62; found: C 86.09, H 8.58, N 4.22.

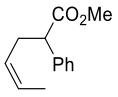
6.2.3 Synthesis of compounds c



74

Diisopropylamine (10 mmol, 1.4 mL) was dissolved in THF (20 mL) in a 3−neck round−bottom flask under N_2. At 0 °C, *n*-BuLi (10 mmol, 3.9 mL, 2.5 M in hexanes) was added dropwise via syringe. After 15 minutes stirring at that temperature, methyl 2−phenylent−4−enoate (9 mmol, 1.4 g) in THF (10 mL) was added at −78 °C. After 45 minutes stirring at that temperature, propargyl bromide (10 mmol, 0.8 mL) was added neat. After stirring overnight at room temperature, the mixture was quenched with a saturated solution of NH_4Cl and extracted three times with ethyl acetate. The organic layers were combined and washed with water and brine then before drying over $MgSO_4$. After filtration and concentration at reduced pressure, purification by flash chromatography (PE:Et_2O = 30:1) gave **73** as a colourless oil (1.3 g, 92%).

Compound 74 Colourless oil (1.3 g, 92%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.36−7.27 (m, 5H), 3.76 (dd, *J* = 8.5, 6.8 Hz, 1H), 3.69 (s, 3H), 2.86 (ddq, *J* = 16.5, 8.5, 2.5 Hz, 1H), 2.59−2.51 (m, 1H), 1.73 (t, *J* = 2.4 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 173.3, 137.9, 128.7 (2C), 127.7 (2C), 127.6, 76.1, 52.2, 51.3, 41.2, 23.4, 3.5; **IR (neat):** $\tilde{\nu}$ = 3065 (w), 3031 (w), 2952 (w), 2920 (w), 2845 (w), 1734 (s), 1603 (w), 1585 (w), 1496 (w), 1455 (m), 1435 (m), 1350 (w), 1314 (w), 1293 (w), 1269 (m), 1226 (m), 1197 (m), 1162 (s), 1079 (w), 1056 (w), 1031 (w), 1005 (w), 988 (w), 961 (w), 927 (w), 879 (w), 837 (w), 812 (w), 788 (w), 765 (w), 727 (m), 697 (s) cm^{-1}; **MS (CI):** 220 [M + NH_4] (100%), 203 (21%); **elemental analysis** (%) calcd for $C_{13}H_{14}O_2$: C 77.20, H 6.98; found: C 77.29, H 7.07.

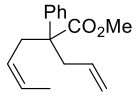


75

$Ni(OAc)_2$•$5H_2O$ (2 mmol, 0.4 g) was dissolved in EtOH (2 mL) in a three-neck round-bottom flask and the mixture was purged with H_2 (1 atm). Then, a freshly prepared solution of $NaBH_4$ (4 mmol, 0.16 g) in EtOH (4 mL) was added *via* syringe and the mixture was stirring for 10 minutes. Ethylenediamine (19 mmol, 1.3 mL) was added neat to the mixture which was left stirring for further 5 minutes. Then, a solution of **73** (5.4 mmol, 1.1 g) in EtOH (54 mL) was added to the mixture. After 90 minutes of stirring,

the mixture was filtered and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 45:1) afforded **75** (988 mg, 89%).

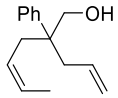
Compound 75 Colourless oil (988 mg, 89%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.34−7.29 (m, 4H), 7.34−7.24 (m, 1H), 5.53−5.46 (m, 1H), 5.32−5.25 (m, 1H), 3.66 (s, 3H), 3.58 (t, *J* = 7.8 Hz, 1H), 2.87−2.78 (m, 1H), 2.55−2.48 (m, 1H), 1.57 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 174.1, 138.7, 128.5 (2C), 127.9 (2C), 127.2, 126.7, 126.3, 51.9, 51.5, 30.9, 12.8; **IR (neat):** $\tilde{\nu}$ = 3018 (w), 2951 (w), 1735 (s), 1602 (w), 1495 (w), 1454 (m), 1435 (m), 1405 (w), 1337 (w), 1270 (m), 1222 (m), 1193 (m), 1162 (s), 1107 (w), 1075 (w), 1033 (w), 929 (w), 842 (w), 773 (w), 733 (w), 699 (m) cm^{-1}; **MS (CI):** 222 [M + NH_4] (100%), 205 [M + H] (41%); **elemental analysis** (%) calcd for $C_{13}H_{16}O_2$: C 76.44, H 7.90; found: C 76.81, H 8.09.



70c

Compound **75** (4.4 mmol, 0.9 g) was dissolved in THF (9 mL) in a three-neck round-bottom flask under N_2. At −78 ˚C, LiHMDS (5.2 mmol, 0.8 g) was added in one portion. The mixture was stirring at this temperature for 20 minutes before adding allyl bromide (5.2 mmol, 0.5 mL) *via* syringe. The mixture was then stirring at room temperature for one hour. The mixture was quenched with a saturated solution of NH_4Cl and it was extracted three times with Et_2O. The organic layers were combined and washed with water and brine before drying over $MgSO_4$. The mixture was filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 10:1 → 5:1) afforded **70c** (914 mg, 89%).

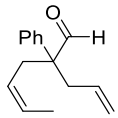
Compound 70c Colourless oil (914 mg, 89%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.37−7.29 (m, 2H), 7.29−7.22 (m, 3H), 5.59−5.46 (m, 2H), 5.19−5.11 (m, 1H), 5.05 (d, *J* = 5.1 Hz, 1H), 5.02 (s, 1H), 3.64 (s, 3H), 2.88−2.65 (m, 4H), 1.53 (d, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 175.8, 141.9, 133.6, 128.3 (2C), 127.1, 126.8, 126.4 (2C), 124.7, 118.5, 54.0, 52.0, 39.1, 31.9, 13.1; **IR (neat):** $\tilde{\nu}$ = 3063 (w), 3021 (w), 2980 (w), 2950 (w), 1730 (s), 1641 (w), 1600 (w), 1583 (w), 1497 (w), 1445 (w), 1372 (w), 1321 (w), 1275 (w), 1242 (w), 1205 (s), 1137 (w), 1036 (w), 997 (w), 917 (m), 847 (w), 802 (w), 779 (w), 736 (w), 698 (s), 671 (w) cm^{-1}; **MS (CI):** 245 [M + H] (100%), 262 [M + NH_4] (33%); **elemental analysis** (%) calcd for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found C: 78.83, H 8.41.



71c

Substrate **71c** was synthesised following the procedure for the synthesis of substrate **71a**.

Compound 71c Colourless oil (726 mg, 93%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.39−7.33 (m, 4H), 7.25−7.20 (m, 1H), 5.71−5.61 (m, 1H), 5.56−5.48 (m, 1H), 5.29−5.21 (m, 1H), 5.09 (d, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 3.80 (d, *J* = 6.6 Hz, 2H), 2.55 (dd, *J* = 14.1, 7.2 Hz, 1H), 2.52−2.40 (m, 3H), 1.58 (d, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 6.61 Hz, 1H (OH)); **^{13}C NMR** (125.77 MHz, $CDCl_3$):143.6, 134.6, 128.4 (2C), 126.9 (2C), 126.5, 126.2, 125.7, 117.8, 68.1, 46.3, 39.7, 32.4, 13.1; **IR (neat):** $\tilde{\nu}$ = 3412 (w, br), 3060 (w), 3019 (w), 2977 (w), 2919 (w), 1638 (w), 1600 (w), 1580 (w), 1498 (w), 1445 (m), 1406 (w), 1371 (w), 1323 (w), 1045 (m), 1000 (w), 984 (w), 914 (m), 865 (w), 769 (w), 750 (w), 699 (s) cm^{-1}; **MS (CI):** 234 [M + NH_4] (100%), 217 [M + H] (5%); **elemental analysis** (%) calcd for $C_{15}H_{20}O$: C 83.28, H 9.32; found: C 83.55, H 9.59.

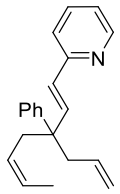


72c

Substrate **72c** was synthesised following the procedure for the synthesis of substrate **72a** except that purification was done by FCC (PE:EtOAc = 75:1).

Compound 72c Colourless oil (568 mg, 82%); **^{1}H NMR** (500 MHz, $CDCl_3$): 9.52 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.28 (tt, *J* = 7.4 Hz, 1H), 7.22−7.19 (m, 2H), 5.57−5.48 (m, 2H), 5.26−5.18 (m, 1H), 5.10−5.02 (m, 2H), 2.75−2.60 (m, 4H), 1.53 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$):202.1, 138.2, 132.9, 128.8 (2C), 127.6 (2C), 127.4 (2C)[iii], 124.0, 118.8, 57.4, 36.9, 29.5, 13.1; **IR (neat):** $\tilde{\nu}$ = 3062 (w), 3022 (w), 2979 (w), 2919 (w), 2804 (w), 2711 (w), 1723 (s), 1640 (w), 1599 (w), 1582 (w), 1496 (w), 1446 (m), 1417 (w), 1384 (w), 1310 (w), 1079 (w), 1033 (w), 997 (w), 918 (m), 873 (w), 839 (w), 756 (m), 699 (s) cm^{-1}; **MS (CI):** 232 [M + NH_4] (100%), 215 [M + H] (5%); **elemental analysis** (%) calcd for $C_{15}H_{18}O$: C 84.07, H 8.47; found: C 84.09, H 8.55.

[iii] Two non−equivalent carbon nuclei corresponding to the proton at 7.28 ppm (phenyl) and the proton at 5.57 ppm (olefin).

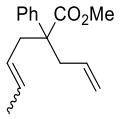


67c

Substrate **67c** was synthesised following the procedure for the synthesis of substrate **67a** except that purification was done by FCC (PE:EtOAc = 10:1).

Compound 67c Yellow oil (765 mg, 79%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.55 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.38−7.33 (m, 2H), 7.33−7.28 (m, 3H), 7.23−7.18 (m, 1H), 7.11 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.88 (d, *J* = 16.3 Hz, 1H), 6.56 (d, *J* = 16.3 Hz, 1H), 5.70−5.59 (m, 1H), 5.53−5.45 (m, 1H), 5.33−5.25 (m, 1H), 5.08−4.98 (m, 2H), 2.70 (d, *J* = 7.1 Hz, 2H), 2.67 (d, *J* = 6.7 Hz, 2H), 1.57−1.53 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.1, 149.4, 144.9, 142.0, 136.3, 134.7, 128.6, 128.1, 127.5, 126.1, 125.9, 121.7, 120.9, 117.7, 47.4, 42.2, 34.8, 13.2; **IR (neat):** $\tilde{\nu}$ = 3059 (w), 3020 (w), 2977 (w), 2916 (w), 2857 (w), 1948 (w), 1647 (w), 1585 (m), 1563 (w), 1495 (w), 1469 (m), 1445 (w), 1429 (m), 1370 (w), 1322 (w), 1255 (w), 1190 (w), 1149 (w), 1049 (w), 1034 (w), 990 (m), 979 (m), 913 (m), 842 (w), 815 (w), 764 (m), 699 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{23}N$ + H): 290.1903; found: 290.1902; **elemental analysis** (%) calcd for $C_{21}H_{23}N$: C 87.15, H 8.01, N 4.84; found: C 83.22, H 7.68, N 4.45.

6.2.4 Synthesis of compounds d

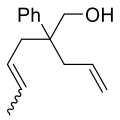


70d

Substrate **70d** was synthesised following the procedure for the synthesis of substrate **70a** except that purification was done by FCC (PE:EtOAc = 45:1).

Compound 70d This compound was obtain as *trans*:*cis* mixture in 3:1 ratio. Only the signals corresponding to the *trans* isomer are listed below. Colourless oil (1.2 g, 87%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.39−7.32 (m, 2H), 7.28−7.22 (m, 3H), 5.54−5.44 (m, 2H), 5.18−5.10 (m, 1H), 5.06−5.00 (m, 2H), 3.64 (s, 3H), 2.80−2.72 (m, 3H), 2.73-2.65 (m, 1H), 1.60 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 175.4, 141.8, 133.3, 129.0, 128.1 (2C), 126.6, 126.2 (2C), 125.4, 118.2, 53.6, 51.7, 38.8, 37.4, 18.0; **IR (neat):** $\tilde{\nu}$ = 3063 (w), 3026 (w), 2981 (w), 2950 (w), 1730 (s), 1640 (w), 1600 (w), 1583 (w), 1498 (w), 1444 (m), 1378 (w), 1320 (w), 1296 (w), 1264 (w), 1240 (w), 1205 (s), 1137 m), 1070 (w), 1035 (w), 997

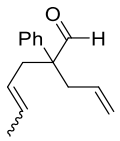
(w), 969 (m), 943 (w), 916 (m), 846 (w), 778 (w), 758 (w), 736 (w), 698 (s) cm^{-1}; **MS (CI):** 262 [M + NH_4] (100%), 245 [M + H] (79%); **elemental analysis** (%) calcd for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 79.95, H 8.41.



71d

Substrate **71d** was synthesised following the procedure for the synthesis of substrate **71a** except that the product was purified by FCC (PE:EtOAc = 15:1).

Compound 71d This compound was obtain as *trans*:*cis* mixture in 3:1 ratio. Only the signals corresponding to the *trans* isomer are listed below. Colourless oil (549 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.38−7.32 (m, 4H), 7.25−7.20 (m, 1H), 5.70−5.58 (m, 1H), 5.56−5.47 (m, 1H), 5.31−5.23 (m, 1H), 5.07 (d *J* = 16.8 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 3.79 (d, *J* = 6.7 Hz, 1H), 2.62−2.48 (m, 2H), 2.48−2.36 (m, 2H), 1.62 (d, *J* = 6.2Hz, 3H), 1.27 (t, *J* = 6.7 Hz, 1H (OH)); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 143.7, 134.5, 128.4, 126.9, 126.5, 126.2, 67.9, 46.0, 39.7, 38.2, 18.1; **IR (neat):** $\tilde{\nu}$ = 3411 (w, br), 3060 (w), 3025 (w), 2917 (w), 2856 (w), 1735 (w), 1638 (w), 1601 (w), 1581 (w), 1498 (w), 1445 (m), 1415 (w), 1377 (w), 1338 (w), 1260 (w), 1140 (w), 1044 (m), 1000 (m), 970 (m), 913 (m), 860 (w), 804 (w), 764 (w), 697 (s) cm^{-1}; **MS (CI):** 234 [M + NH_4] (100%), 217 [M + H] (1%); **elemental analysis** (%) calcd for $C_{15}H_{20}O$: C 83.28, H 9.32; found: C 83.80, H 9.42.

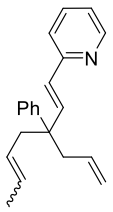


72d

Substrate **72d** was synthesised following the procedure for the synthesis of substrate **72a** except that the product was purified by FCC (PE:EtOAc = 75:1).

Compound 72d This compound was obtain as a *trans*:*cis* mixture in 3:1 ratio Only the *trans* isomer is reported.. Colourless oil (313 mg, 93%); **^{1}H NMR** (500 MHz, $CDCl_3$): 9.52 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.32−7.27 (m, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 5.60−5.46 (m, 2H), 5.24−5.15 (m, 1H), 5.10−5.01 (m, 2H), 2.77−2.60 (m, 4H), 1.63 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 202.0, 138.1, 132.8, 129.4, 128.6 (2C), 127.5 (2C), 127.2 (2C), 124.7, 118.5, 56.8, 36.7, 35.2, 17.9; **IR (neat):** $\tilde{\nu}$ = 3061 (w), 3026 (w), 2979 (w),

2918 (w), 2855 (w), 2710 (w), 1722 (s), 1640 (w), 1599 (w), 1582 (w), 1496 (w), 1446 (m), 1418 (w), 1379 (w), 1337 (w), 1192 (w), 1077 (w), 1034 (w), 997 (w), 968 (m), 916 (m), 865 (w), 844 (w), 759 (m), 734 (w), 698 (s) cm^{-1}; **MS (CI):** 232 [M + NH_4] (100%), 215 [M + H] (6%); **elemental analysis** (%) calcd for $C_{15}H_{18}O$: C 84.07, H 8.47; found: C 84.35, H 8.56.

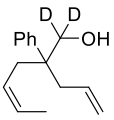


67d

Substrate **67d** was synthesised following the procedure for the synthesis of substrate **67a** except that the product was purified by FCC (PE:EtOAc = 75:1).

Compound 67d This compound was obtain as a *trans*:*cis* mixture in 3:1 ratio. Only the trans isomer is reported. Yellow oil (39 mg, 46%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.55 (d, *J* = 4.5 Hz, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.37−7.28 (m, 5H), 7.23−7.18 (m, 1H), 7.13−7.09 (m, 1H), 6.84 (d, *J* = 16.3 Hz, 1H), 6.53 (d, *J* = 16.3 Hz, 1H), 5.67−5.57 (m, 1H), 5.50−5.42 (m, 1H), 5.32−5.19 (m, 1H), 5.08−4.96 (m, 2H), 2.67(d, *J* = 6.9 Hz, 2H), 2.62 (d, *J* = 7.0 Hz, 2H), 1.60 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.1, 149.4, 145.0, 142.1, 136.4, 128.6, 128.4, 128.0 (2C), 127.5 (2C), 126.5, 126.1, 126.1, 121.7, 120.9, 117.6, 46.9, 41.8, 40.7, 18.1; **IR (neat):** $\tilde{\nu}$ = 3024 (w), 2915 (w), 1646 (w), 1585 (s), 1563 (m), 1494 (w), 1468 (m), 1444 (m), 1429 (s), 1377 (w), 1304 (w), 1148 (w), 1033 (w), 970 (s), 912 (s), 855 (w), 760 (s), 739 (m), 699 (s), 620 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{21}H_{23}N$ + H): 290.1909; found: 290.1907.

6.2.5 Synthesis of compounds e

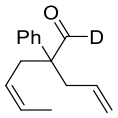


71e

$LiAlD_4$ (0.4 mmol, 17 mg) was dissolved in Et_2O (2.7 mL) in a three−neck round−bottom flask under N_2. At 0 °C, **70a** (0.8 mmol, 190 mg) in Et_2O was added via cannula. After 20 minutes stirring at room temperature, $LiAlD_4$ (0.4 mmol, 17 mg) was added at 0 °C. After 30 minutes stirring at room temperature, an aqueous the reaction mixture was quenched with saturated solution of Na_2SO_4 at 0

°C. The mixture was filtered over Celite to remove the white precipitate and it was concentrated at reduced pressure. **71e** was obtained as a colourless oil (174 mg, 99%).

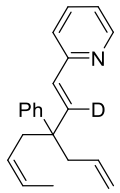
Compound 71e Colourless oil (174 mg, 99%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.40−7.30 (m, 4H), 7.25−7.19 (m, 1H), 5.72−5.60 (m, 1H), 5.56−5.47 (m, 1H), 5.31−5.21 (m, 1H), 5.08 (d, *J* = 17.1 Hz, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 2.57 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.54−2.42 (m, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.25−1.21 (s, 1H (OH)); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 143.7, 134.5, 128.3 (2C), 126.8 (2C), 126.2, 126.1, 125.7, 117.6, 67.1 (quin, *J* = 21.6 Hz), 46.0, 39.5, 32.3, 13.0; **IR (neat):** $\tilde{\nu}$ = 3407 (w, br), 3060 (w), 3020 (w), 2977 (w), 2918 (w), 2857 (w), 2206 (w), 2096 (w), 1638 (w), 1600 (w), 1497 (w), 1445 (m), 1406 (w), 1371 (w), 1286 (w), 1145 (w), 1102 (m), 1032 (w), 1000 (w), 975 (m), 913 (m), 840 (w), 808 (w), 759 (m), 698 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{15}H_{18}D_2O$ + NH_4): 236.1978; found: 236.1975.



72e

Substrate **72e** was synthesised following the procedure for the synthesis of substrates **72a** except that purification was done by FCC (PE:EtOAc = 10:1).

Compound 72e (131 mg, 79%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.42−7.35 (m, 2H), 7.34−7.27 (m, 1H), 7.24−7.20 (m, 2H), 5.62−5.48 (m, 2H), 5.26−5.16 (m, 1H), 5.09−5.01 (m, 2H), 2.78−2.61 (m, 4H), 1.55 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 201.8, (t, *J* = 26.7 Hz), 138.3, 132.9, 128.8 (2C), 127.7 (2C), 127.4, 127.3, 124.0, 118.7, 57.2, 37.0, 29.7, 13.0; **IR (neat):** $\tilde{\nu}$ = 3078 (w), 3022 (w), 2979 (w), 2920 (w), 2858 (w), 2058 (w), 1710 (s), 1640 (w), 1599 (w), 1582 (w), 1496 (w), 1446 (w), 1417 (w), 1371 (w), 1309 (w), 1077 (w), 1032 (w), 996 (w), 917 (m), 833 (w), 751 (w), 698 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{15}H_{17}DO$ + H): 216.1499; found: 216.1501.

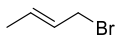


67e

Substrate **67e** was synthesised following the procedure for the synthesis of substrate **67a** except that purification was done by FCC (PE:EtOAc = 45:1).

Compound 67e Yellow oil (70.4 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.55 (d, *J* = 3.9 Hz, 1H), 7.60 (td, *J* = 7.7, 1.5 Hz, 1H), 7.36−7.4 (m, 2H), 7.34−7.28 (m, 3H), 7.24−7.17 (m, 1H), 7.14−7.07 (m, 1H), 6.58−6.52 (m, 1H), 5.71−5.59 (m, 1H), 5.55−5.43 (m, 1H), 5.33−5.24 (m, 1H), 5.09−4.97 (m, 2H), 2.70 (d, *J* = 7.0 Hz, 2H), 2.67 (d, *J* = 6.8 Hz, 2H) 1.57 (d *J* = 9.0 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.2, 149.5, 145.0, 141.6 (t, *J* = 23.3 Hz), 136.4, 134.7, 128.7, 128.1 (2C), 127.6 (2C), 126.1, 126.0, 121.7, 120.9, 117.7, 47.3, 42.3, 34.9, 13.2; **IR (neat):** $\tilde{\nu}$ = 3059 (w), 3020 (w), 2977 (w), 2917 (w), 2856 (w), 1952 (w), 1637 (w), 1585 (m), 1562 (m), 1494 (w), 1468 (m), 1445 (m), 1428 (m), 1370 (w), 1321 (w), 1190 (w), 1149 (w), 1097 (w), 1049 (w), 1030 (w), 994 (w), 911 (m), 778 (w), 744 (m), 699 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{22}DN$ + H): 291.1966; found: 291.1976.

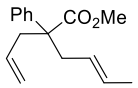
6.2.6 Synthesis of compounds f



88

Methyl crotonate (10 mmol, 1 g) was dissolved in Et_2O (20 mL) in a three-neck round-bottom flask. At −78˚C, Dibal−H (20 mmol, 20 mL, 1 M in hexanes) was added dropwise very slowly. The mixture was stirring for 2 hours at that temperature. The reaction mixture was quenched at 0˚C with water (0.5 mL). After few minutes of stirring NaOH (0.5 mL, 3M) was added slowly. Then, a new volume of water (1 mL) was added. The mixture was stirred strongly until a white precipitate was formed. It was dried over $MgSO_4$ and filtered. The precipitate was washed with Et_2O several times. The filtrate was cooled down to 0˚C and put under N_2. Then, PBr_3 (75 mmol, 0.7 mL) was added slowly. The reaction was stirring for 30 minutes. Then, the mixture was quenched with an aqueous saturated solution of NaCl. Then, the two layers were separated and the organic phase was dried over $MgSO_4$ and filtered over a cotton plug. The crude was carefully concentrated and used immediately in the next reaction.

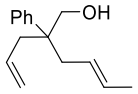
Compound 88. This compound was obtain in a solution of Et_2O. Some impurities can be observed. Orange solution (1 g, 78%); **^{1}H NMR** (500 MHz, $CDCl_3$): 5.86−5.74 (m, 1H), 5.74−5.62 (m, 1H), 3.95 (d, *J* = 7.4 Hz, 1H), 3.82−3.77 (m, 1H).[iv]



70f

Compound **69** (2 mmol, 400 mg) was dissolved in THF (4 mL) in a three-neck round-bottom flask under N_2. At −78 ˚C, LiHMDS (5.2 mmol, 0.8 g) was added in one portion. The mixture was stirring at this temperature for 45 minutes before compound **88** (3 mmol, 0.5 g, 5 M in Et_2O) *via* syringe. The mixture was then stirring at −78 ˚C for 30 min before adding Bu_4NI (0.4 mmol, 145 mg). The reaction mixture was stirring at room temperature for 3 hours. The mixture was quenched with a saturated solution of NH_4Cl and it was extracted three times with Et_2O. The organic layers were combined and washed with water and brine before drying over $MgSO_4$. The mixture was filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 70:1) afforded **70f** (914 mg, 89%).

Compound 70f Colourless oil (440 mg, 92% after two steps); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.36−7.30 (m, 2H), 7.26−7.21 (m, 3H), 5.55−5.43 (m, 2H), 5.20−5.10 (m, 1H), 5.08−4.99 (m, 2H), 3.64 (s, 3H), 2.82−2.71 (m, H), 2.71−2.63 (m, 1H), 1.62 (dd, *J* = 6.4, 1.4 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 175.5, 141.9, 133.4, 129.1, 128.4, 128.2 (2C), 127.0, 126.6, 126.3 (2C), 125.5, 118.3, 53.7, 51.8, 38.9, 37.5, 17.9; **IR (neat):** $\tilde{\nu}$ = 3062 (w), 3026 (w), 2949 (w), 2359 (w), 2009 (w), 1730 (s), 1640 (w), 1599 (w), 1497 (w), 1444 (m), 1378 (w), 1295 (w), 1263 (w), 1205 (s), 1137 (m), 1069 (w), 1035 (m), 997 (w), 969 (m), 942 (w), 916 (m), 844 (w), 776 (w), 735 (m), 699 (s), 635 (w), 589 (w), 578 (w), 565 (w), 557 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{16}H_{20}O_2$ + H): 245.1536; found: 245.1536.

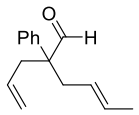


71f

Substrate **71f** was synthesised following the procedure for the synthesis of substrate **71a** except that 3 equivalents of $LiAlH_4$ were used.

[iv] The spectrum is in agreement with the one reported in the literature: Sigma-Aldrich (Spectral data were obtained from Advanced Chemistry Development, Inc.)

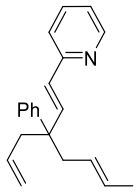
Compound 71f Colourless oil (371 mg, 95%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.38−7.37 (m, 4H), 7.26−7.20 (m, 1H), 5.69−5.57 (m, 1H), 5.56−5.47 (m, 1H), 5.32−5.23 (m, 1H), 5.12−5.00 (m, 2H), 3.79 (d, *J* = 6.7 Hz, 2H), 2.55−2.36 (m, 4H), 1.64−1.59 (m, 3H), 1.28 (t, *J* = 6.6 Hz, 1H (OH)); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 143.7, 134.5, 128.4 (2C), 128.3, 126.9 (2C), 126.5, 126.1, 117.6, 67.9, 45.9, 39.7, 38.2, 18.0; **IR (neat):** $\tilde{\nu}$ = 3406 (w, br), 3060 (w), 3025 (w), 2917 (w), 1831 (w), 1638 (w), 1600 (w), 1498 (w), 1444 (m), 1415 (w), 1377 (w), 1338 (w), 1140 (w), 1044 (m), 998 (m), 970 (s), 912 (s), 861 (w), 762 (w), 733 (w), 698 (s), 665 (w), 620 (w), 609 (w), 592 (w), 578 (w), 569 (w), 562 (w), 553 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{15}H_{20}O$ + NH_4): 234.1582; found: 234.1855.



72f

Substrate **72f** was synthesised following the procedure for the synthesis of substrate **72a** except FCC (PE:EtOAc = 100:1).

Compound 72f Colourless oil (314 mg, 91%); **^{1}H NMR** (500 MHz, $CDCl_3$): 9.52 (s, 1H), 7.42−7.36 (m, 2H), 7.32−7.27 (m, 1H), 7.24−7.18 (m, 2H), 5.58−5.46 (m, 2H), 5.24−5.15 (m, 1H), 5.08−5.01 (m, 2H), 2.74−2.58 (m, 4H), 1.64−1.58 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$):202.2, 138.2, 132.9, 132.6, 129.6, 128.7 (2C), 127.6 (2C), 127.3, 124.8, 118.6, 57.0, 36.9, 35.4, 18.0; **IR (neat):** $\tilde{\nu}$ = 3061 (w), 3026 (w), 2917 (w), 2854 (w), 2709 (w), 1723 (s), 1640 (w), 1598 (w), 1581 (w), 1495 (w), 1445 (m), 1379 (w), 1336 (w), 1075 (w), 1033 (w), 996 (w), 968 (m), 917 (m), 863 (w), 846 (w), 759 (m), 699 (s), 650 (w), 614 (w), 587 (w), 577 (w), 559 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{15}H_{18}O$ + NH_4): 232.1696; found: 232.1696.

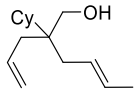


67f

Substrate **67f** was synthesised following the procedure for the synthesis of substrate **67a** except that NaHMDS, as a freshly prepared solution, was used and that FCC (Pentane/EtOAc = 100:1 → 50:1).

Compound 67f Appearance (315 mg, 81% over three steps); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.57−8.53 (m, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.36−7.28 (m, 5H), 7.23−7.16 (m, 1H), 7.11 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H), 6.85 (d, *J* = 16.3 Hz, 1H), 6.53 (d, *J* = 16.3 Hz, 1H), 5.69−5.58 (m, 1H), 5.51−5.41 (m, 1H), 5.30−5.20 (m, 1H), 5.07−4.97 (m, 2H), 2.68 (d, *J* = 7.1 Hz, 2H), 2.62 (d, *J* = 7.1 Hz, 1H), 1.60 (dd, *J* = 6.4, 1.5 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.2, 149.5, 145.0, 142.1, 136.4, 134.6, 128.6, 128.4, 128.0 (2C), 127.5 (2C), 126.6, 126.1, 121.7, 120.9, 117.6, 47.0, 41.9, 40.8, 18.0; **IR (neat):** $\tilde{\nu}$ = 3026 (w), 2915 (w), 1645 (w), 1585 (m), 1563 (m), 1494 (w), 1468 (m), 1444 (m), 1429 (s), 1377 (w), 1304 (w), 1148 (w), 1033 (w), 970 (s), 912 (s), 855 (w), 760 (s), 740 (m), 700 (s), 621 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{21}H_{23}N$ + H): 290.1909; found: 290.1911; **elemental analysis** (%) calcd for $C_{21}H_{23}N$: C 87.15, H 8.01, N 4.84; found: C 88.05, H 8.19, N 4.72.

6.2.7 Synthesis of compounds g

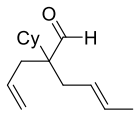


71g

Diisopropylamine (9.3 mmol, 1.3 mL) was dissolved in THF (20 mL) in a 3−neck round−bottom flask under N_2. At 0 °C, *n*-BuLi (9.3 mmol, 3.7 mL, 2.5 M in hexanes) was added dropwise via syringe. After 15 minutes stirring at that temperature, methyl 2−cyclohexylpent−4−enoate (8.8 mmol, 1.5 g) in THF (10 mL) was added at −78 °C. After 45 minutes stirring at that temperature, allyl bromide (9.3 mmol, 0.8 mL) was added neat and the mixture was stirred overnight at room temperature. The mixture was quenched with a saturated solution of NH_4Cl and extracted three times with diethyl ether. The organic layers were combined and washed with water and brine before drying over $MgSO_4$. After filtration and concentration at reduced pressure, purification by flash chromatography (PE:EtOAc = 40:1) gave **69g**. Diisopropylamine (8.5 mmol, 1.2 mL) was dissolved in THF (20 mL) in a 3−neck round−bottom flask under N_2. At 0 °C, *n*-BuLi (8.5 mmol, 3.4 mL, 2.5 M in hexanes) was added dropwise via syringe. After 15 minutes stirring at that temperature, compound **69g** (8 mmol, 1.7 g) in THF (10 mL) was added at −78 °C. After 45 minutes stirring at that temperature, crotyl bromide (8.5 mmol, 0.9 mL) was added neat and the mixture was stirred overnight at room temperature. The mixture was quenched with a saturated solution of NH_4Cl and extracted three times with diethyl ether. The organic layers were combined and washed with water and brine before drying over $MgSO_4$. After filtration and concentration at reduced pressure, purification by flash chromatography (PE:EtOAc = 100:1) gave **70g**. $LiAlH_4$ (3.5 mmol, 135 mg) was dissolved in Et_2O (22 mL) in a three−neck round−bottom flask under N_2. At 0 °C, **70g** (7.1 mmol, 1.9 g) in Et_2O (11 mL) was added via cannula. After 20 minutes stirring at room

temperature, $LiAlH_4$ (3.5 mmol, 135 mg) was added at 0 °C. After 30 minutes stirring at room temperature, a third portion of $LiAlH_4$ (7.1 mmol, 270 mg) was added. After 2 hours, an aqueous the reaction mixture was quenched with saturated solution of Na_2SO_4 at 0 °C. The mixture was filtered over Celite to remove the white precipitate and it was concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 45:1 → 20:1) afforded **71g** as a colourless oil (675 mg, 38%).

Compound 71g Colourless oil (675 mg, 38% over three steps); **^{1}H NMR** (500 MHz, $CDCl_3$):[v] 5.97−5.87 (m, 1H), 5.60−5.47 (m, 2H), 5.11−5.03 (m, 2H), 3.52 (d, *J* = 6.46 Hz, 2H), 2.20−1.98 (m, 4H), 1.82−1.70 (m, 4H), 1.67 (d, *J* = 4.6 Hz, 3H), 1.46−1.35 (m, 1H), 1.29−1.02 (m, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 136.1, 128.0, 127.6, 117.0, 116.9, 67.8, 43.0, 41.9, 38.0, 36.6, 27.3, 26.8, 18.1; **IR (neat):** $\tilde{\nu}$ = 3378 (w, br), 3073 (w), 2920 (s), 2851 (s), 1637 (w), 1447 (m), 1376 (w), 1268 (w), 1041 (m), 1018 (m), 993 (m), 968 (w), 909 (w), 863 (w), 843 (w), 811 (w), 734 (m), 652 (w), 613 (w), 593 (w), 584 (w), 570 (w), 551 (w), 539 (w), 529 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{15}H_{26}O$ + H): 223.2056; found: 223.2066.



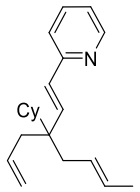
72g

Substrate **72g** was synthesised following the procedure for the synthesis of substrate **72a** except FCC (PE:EtOAc = 60:1).

Compound 72g Colourless oil (487 mg, 82%); **^{1}H NMR** (500 MHz, $CDCl_3$):[vi] 9.56 (s, 1H), 5.80−5.70 (m, 1H), 5.53−5.44 (m, 1H), 5.38−5.29 (m, 1H), 5.11−5.03 (m, 2H), 2.44−2.17 (m, 5H), 1.82 (1.71 (m, 5H), 1.70−1.63 (m, 4H), 1.63−1.55 (m, 2H), 1.28−1.01 (m, 7H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 207.1, 134.0, 128.7, 125.8, 117.9, 54.1, 41.7, 34.6, 33.5, 27.6, 27.5, 27.0, 27.0, 26.5, 18.0; **IR (neat):** $\tilde{\nu}$ = 3076 (w),2925 (s), 2853 (m), 2707 (w), 2255 (w), 1720 (s), 1638 (w), 1448 (m), 1377 (w), 1272 (w), 995 (w), 968 (m), 912 (s), 874 (w), 843 (w), 810 (w), 732 (s), 648 (w), 609 (w), 568 (w), 562 (w), 553 (w), 532 (w), 526 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{15}H_{25}O$ + H): 221.1900; found: 221.1903.

[v] The NMR show some impurities. **^{1}H NMR**: 3.54 (d, *J* = 6.40 Hz, 2H), 1.65 (d, *J* = 5.1 Hz, 3H). **^{13}C NMR**: 127.0, 125.8, 117.0, 43.4, 42.0, 38.1, 30.3, 27.43, 17.37, 12.9.

[vi] The NMR showed some impurities which could not be removed. **^{1}H NMR**: 9.57 (s). **^{13}C NMR**: 207.0, 133.9, 126.5, 125.0, 65.8, 41.7, 34.6, 27.74, 27.66, 15.2.

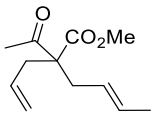


67g

Substrate **67g** was synthesised following the procedure for the synthesis of substrate **67a** except that NaHMDS, as a freshly prepared solution, was used and that FCC (Pentane/EtOAc = 30:1 → 20:1).

Compound 67g Colourless oil (305 mg, 51% over three steps); **^{1}H NMR** (500 MHz, $CDCl_3$):[vii] 8.54 (d, *J* = 4.6 Hz, 1H), 7.64−7.56 (m, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.08 (dd, *J* = 7.4 Hz, 7.2 Hz, 1H), 6.68 (d, *J* = 16.4 Hz, 1H), 6.36 (d, *J* = 16.4 Hz, 1H), 5.86−5.76 (m, 1H), 5.56−5.37 (m, 2H), 5.10−5.01 (m, 2H), 2.43−2.17 (m, 4H), 1.81 (d, *J* = 11.7 Hz, 2H), 1.73 (d, *J* = 12.8 Hz, 2H), 1.66 (d, *J* = 5.9 Hz, 3H), 1.45−1.35 (m, 1H), 1.24−0.96 (m, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.3, 149.4, 140.8, 136.3, 128.9, 127.6, 127.2, 121.5, 120.9, 117.0, 44.5, 44.2, 38.5, 37.0, 27.3, 27.3, 27.1, 26.9, 18.1; **IR (neat):** $\tilde{\nu}$ = 2922 (s), 2851 (m), 1645 (w), 1585 (s), 1563 (m), 1469 (m), 1448 (m), 1429 (s), 1376 (w), 1307 (w), 1148 (w), 1049 (w), 696 (s), 910 (s), 853 (w), 767 (m), 734 (s), 643 (w), 622 (w), 575 (w), 568 (w), 556 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{21}H_{29}N$ + H): 296.2374; found: 296.2378; **elemental analysis** (%) calcd for $C_{21}H_{29}N$: C 85.37, H 9.89, N 4.74; found: C 84.43, H 9.84, N 4.42.

6.2.8 Synthesis of compounds h



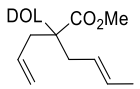
91

Methyl acetoacetate (12.9 mmol, 1.4 mL) was dissolved in DMF (65 mL) in a 3−neck round−bottom flask under N_2. At 0 °C, NaH (13.6 mmol, 542 mg, 60% w/w dispersion in mineral oil) and allyl bromide (13.6 mmol, 1.2 mL) were added neat. After stirring overnight at room temperature, the reaction mixture was diluted with Et_2O at 0 ˚C and quenched slowly with water. The organic layer was washed four times with water and once with brine. The mixture was dried over $MgSO_4$. After filtration over cotton plug and concentration at reduced pressure, purification by FCC (PE:EtOAc = 20:1) afforded componund **91**. This compound was dissolved in DMF (30 mL) in a three-neck round-bottom flask under N_2. At 0 ˚C, NaH (6 mmol, 240 mg, 60% w/w dipersion in mineral oil) and crotyl bromide (6 mmol,

[vii] The NMR showed some impurities which could not be removed. **^{1}H NMR**: 6.69 (d, *J* = 16.3 Hz), 6.38 (d, *J* = 16.4 Hz), 1.62 (d, *J* = 5.9 Hz, 3H). **^{13}C NMR**: 135.3, 126.5, 125.4, 117.1, 44.3, 31.2, 27.53, 27.46.

0.6 mL) were added neat. After stirring overnight at room temperture, the reaction mixture was diluted with Et_2O at 0 ˚C and quenched slowly with water. The organic layer was washed four times with water and once with brine. The mixture was dried over $MgSO_4$, filtered over cotton plug and concentrated at reduced pressure.

Compound 91 Colourless oil (1.30 g, 48% over two steps); **^{1}H NMR** (500 MHz, $CDCl_3$):[viii] 5.65−5.56 (m, 2H), 5.56−5.55 (m, 1H), 5.23−5.15 (m, 1H), 5.13−5.04 (m, 3H), 3.72 (s, 3H), 2.70−2.48 (m, 6H), 2.11 (s, 3H), 1.66−1.63 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 204.2, 172.2, 132.4, 129.9, 124.3, 119.0, 63.6, 52.3, 36.0, 34.9, 27.0, 18.0; **HRMS (CI):** calcd for ($C_{12}H_{18}O_3$ + H): 211.1329; found: 211.1332.



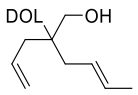
70h

Compound **91** (5.9 mmol, 1.23 g), ethyleneglycol (23.4 mmol, 2.2 mL) and ethyl orthoformate (11.6 mmol, 1.9 mL) were mixed in a three-neck round-bottom flask under N_2. TsOH•H_2O (0.6 mmol, 115 mg) was added to the mixture *via* syringe and it was stirring overnight at room temperature. The reaction mixture was quenched with an aqueous solution of $NaHCO_3$ and extracted three times with Et_2O. The organic layers were combined and wash with water and brine. The mixture was dried over $MgSO_4$, filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 20:1) afforded 69h (610 mg, 41%).

Compound 70h Colourless oil (610 mg, 41%); **^{1}H NMR** (500 MHz, $CDCl_3$):[ix] 5.94−5.82 (m, 1H), 5.54−5.37 (m, 2H), 5.10−4.97 (m, 3H), 3.98−3.87 (m, 5H), 3.72−3.69 (m, 3H), 2.62−2.48 (m, 4H), 2.48−2.39 (m, 1H), 1.66−1.63 (m, 3H), 1.36 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 173.9, 135.4, 128.0, 127.1, 116.7, 64.76, 64.75, 51.8, 35.9, 34.7, 28.9, 21.6, 18.0; **IR (neat):** $\tilde{\nu}$ = 3075 (w), 2983 (w), 2950 (w), 2886 (w), 1724 (s), 1638 (w), 1435 (m), 1376 (m), 1271 (m), 1250 (m), 1196 (m), 1132 (m), 1105 (m), 1038 (s), 997 (m), 970 (m), 950 (m), 912 (m), 835 (w), 765 (w), 730 (w), 704 (w), 661 (w), 605 (w), 583 (w), 573 (w), 556 (w), 546 (w), 540 (w), 526 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{15}H_{22}O_4$ + H): 255.1591; found: 255.1602 (5.21%); caldc for ($C_4H_7O_2$): 81.0446; found: 87.0454 (100%).

[viii] The NMR showed some impurities which could not be removed. **^{1}H NMR**: 3.73 (s), 2.12 (s), 1.63−1.59 (m). **^{13}C NMR**: 132.37, 128.0, 119.07, 52.33, 36.1, 29.0, 26.91.

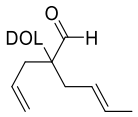
[ix] The NMR showed some impurities which could not be removed. **^{1}H NMR**: 1.63−1.60 (m), 1.37 (s). **^{13}C NMR**: 135.3, 135.0, 126.3, 125.4, 117.2, 116.9, 111.6, 64.8, 57.8, 51.79, 36.0, 23.8, 21.5, 13.0



71h

Substrate **71h** was synthesised following the procedure for the synthesis of substrate **71a**.

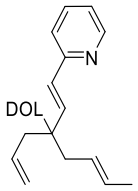
Compound 71h Colourless oil (345 mg, 92%); **^{1}H NMR** (500 MHz, $CDCl_3$):[x] 6.00−5.90 (m, 1H), 5.63−5.42 (m, 2H), 5.12−5.00 (m, 2H), 4.02−3.90 (m, 4H), 3.61−3.45 (m, 2H), 3.14−3.08 (m, 1H(OH)), 2.29−2.07 (m, 4H), 1.64 (dd, *J* = 5.9, 1.0 Hz, 3H), 1.31 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 135.3, 127.9, 127.1, 116.9, 66.0, 64.39, 64.37, 64.3, 48.0, 35.1, 33.4, 20.0, 18.1; **IR (neat):** $\tilde{\nu}$ = 3532 (w, br), 3074 (w), 2936 (w), 2885 (w), 1725 (w), 1637 (w), 1436 (w) 1376 (w), 1334 (w), 1270 (w), 1201 (m), 1126 (m), 1095 (m), 1075 (m), 1035 (s), 970 (m), 949 (m), 910 (m), 872 (m), 766 (w), 668 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{12}H_{20}O_2$ + H): 197.2; found: 197.2 (100%); calcd for ($C_{13}H_{22}O_3$ + H) 227.2; found: 227.2.



72h

Substrate **72h** was synthesised following the procedure for the synthesis of substrate **72a** except that purification was done by FCC (PE:EtOAc = 35:1).

Compound 72h Colourless oil (231 mg, 37%); **^{1}H NMR** (500 MHz, $CDCl_3$):[xi], 9.66 (s, 1H), 5.88−5.73 (m, 1H), 5.59−5.44 (m, 1H), 5.44−5.29 (m, 1H), 5.12−5.00 (s, 2H), 4.03−3.90 (m, 4H), 2.57−2.34 (m, 4H), 1.67−1.61 (m, 3H), 1.26 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 205.3, 134.2, 128.7, 125.7, 117.3, 64.67, 64.65, 59.6, 33.4, 32.1, 26.1, 21.4, 18.0.



67h

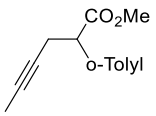
[x] The NMR showed some impurities which could not be removed. **^{1}H NMR**: 1.62 (d, *J* = 6.30 Hz), 1.32 (s). **^{13}C NMR**: 135.26, 126.3, 125.6, 117.1, 114.8, 35.0, 27.7, 19.95.

[xi] The NMR showed some impurities which could not be removed. **^{1}H NMR**: 9.69 (s, 1H), 1.27 (s, 3H). **^{13}C NMR**: 205.0, 134.1, 126.3, 124.9, 117.8, 117.5, 111.9, 21.3, 13.0.

Substrate **67h** was synthesised following the procedure for the synthesis of substrate **67a** except that NaHMDS, as a freshly prepared solution, was used and that FCC (Pentane/EtOAc = 5:1 → 2:1).

Compound 67h Colourless oil (367 mg, 45% after three steps); **^{1}H NMR** (500 MHz, $CDCl_3$):[xii] 8.57−8.52 (m, 1H), 7.63−7.57 (m, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.11−7.07 (m, 1H), 6.81 (d, *J* = 16.6 Hz, 1H), 6.67 (d, *J* = 16.6 Hz), 5.98−5.86 (m, 1H), 5.61−5.41 (m, 2H), 5.10−4.97 (m, 2H), 4.00−3.88 (m, 4H), 2.58−2.34 (m, 4H), 1.64−1.60 (m, 3H), 1.29 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.3, 149.4, 139.5, 136.2, 135.8, 130.0, 127.5, 127.1, 121.6, 120.8, 116.1, 113.2, 64.83, 64.77, 64.7, 50.7, 36.7, 35.3, 21.1, 18.0; **IR (neat):** $\tilde{\nu}$ = 3073 (w), 2980 (w), 2936 (w), 2881 (w), 1836 (w), 1647 (w), 1585 (m), 1563 (m), 1469 (m), 1429 (m), 1372 (m), 1305 (w), 1197 (s), 1149 (m), 1099 (m), 1086 (m), 1069 (m), 1034 (s), 990 (m), 970 (m), 950 (m), 908 (s), 852 (w), 764 (m), 732 (m) cm^{-1}; **HRMS (ES+):** calcd for ($C_{19}H_{25}NO_2$ + H): 300.1964; found: 300.1959; **elemental analysis** (%) calcd for $C_{19}H_{22}NO_2$: C 76.22, H 8.42, N 4.68; found: C 76.18, H 8.54, N 4.46.

6.2.9 Synthesis of compounds i



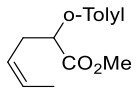
74i

Methyl *o*-tolylacetate (2.4 mmol, 400 mg) was dissolved in THF (5 mL) in a three-neck round-bottom flask under N_2. At −78 ˚C, LiHMDS (2.9 mmol, 490 mg) was added in one portion. The mixture was stirring at this temperature for 20 minutes before adding propargyl bromide (2.9 mmol, 0.3 mL) *via* syringe. The mixture was then stirring at room temperature for six hours. The mixture was quenched with a saturated solution of NH_4Cl and it was extracted three times with Et_2O. The organic layers were combined and washed with water and brine before drying over $MgSO_4$. The mixture was filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 70:1 → 60:1) afforded **74i** (550 mg, 91%).

Compound 74i Colourless oil (550 mg, 91%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.27−7.13 (m, 4H), 4.05 (dd, *J* = 8.6, 6.6 Hz, 1H), 3.68 (s, 3H), 2.94−2.85 (m, 1H), 2.54−2.45 (m, 1H), 2.42 (s, 3H), 1.72 (t, *J* = 2.5 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 173.6, 136.6, 136.2, 130.5, 127.3, 126.4, 76.9, 76.3, 52.1, 46.7, 23.0, 19.8, 3.5; **IR (neat):** $\tilde{\nu}$ = 3022 (w), 2952 (w), 2919 (w), 1734 (s), 1603 (w), 1493 (w), 1462 (w), 1434 (m), 1380 (w), 1346 (w), 1296 (w), 1269 (w), 1223 (m), 1191 (m), 1161 (s), 1106 (w), 1054 (w), 986 (w), 960

[xii] The NMR showed some impurities which could not be removed. **^{1}H NMR**: 6.83 (d, *J* = 16.6 Hz), 6.52 (d, *J* = 16.6 Hz), 1.30 (s). **^{13}C NMR**: 139.4, 135.7, 135.5, 130.1, 126.8, 124.8, 116.5, 116.3, 36.7, 29.2, 21.05

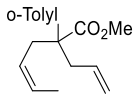
(w), 916 (w), 835 (w), 805 (w), 756 (m), 738 (m), 663 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{14}H_{16}O_2$ + H): 217.1223; found: 217.1231.



75i

Substrate **75i** was synthesised following the procedure for the synthesis of substrate **75** except that purification was done by FCC (PE:EtOAc = 60:1).

Compound 75i Colourless oil (467 mg, 88%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.33, (d, *J* = 7.4 Hz, 1H), 7.21−7.12 (m, 3H), 5.54−5.44 (m, 1H), 5.36−5.26 (m, 1H), 3.86 (dd, *J* = 8.2, 7.2 Hz, 1H), 3.65 (s, 3H), 2.90−2.77 (m, 1H), 2.52−2.42 (m, 1H), 2.38 (s, 3H), 1.60−1.58 (m, 3H); **^{13}C NMR**[xiii] (125.77 MHz, $CDCl_3$): 137.3, 136.1, 130.4, 127.0, 126.9, 126.8, 126.4, 126.2, 51.9, 46.8, 30.5, 19.8, 12.8; **IR (neat):** $\tilde{\nu}$ = 3019 (w), 2951 (w), 1733 (s), 1604 (w), 1492 (w), 1462 (w), 1434 (m), 1404 (w), 1341 (w), 1292 (w), 1268 (w), 1212 (m), 1179 (m), 1158 (s), 1116 (w), 1052 (w), 1020 (w), 993 (w), 911 (w), 843 (w), 805 (w), 759 (m), 733 (s), 707 (m) cm^{-1}; **HRMS (CI):** calcd for ($C_{14}H_{18}O_2$ + H): 219.1380; found: 219.1386.

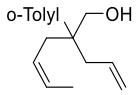


70i

Substrate **70i** was synthesised following the procedure for the synthesis of substrate **70c** except that purification was done by FCC (PE:EtOAc = 60:1).

Compound 70i Colourless oil (461 mg, 84%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.29−7.23 (m,1H), 7.22−7.11 9m, 3H), 5.59−5.44 (m, 2H), 5.18−5.09 (m, 1H), 5.08−4.99 (m, 2H), 3.65 (s, 3H), 2.90−2.66 (m, 4H), 2.22 (s, 3H), 1.55−1.49 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$):[xiv] 176.5, 139.9, 136.1, 133.6, 132.0, 127.2, 126.86, 126.82, 125.6, 124.5, 53.3, 51.9, 38.9, 31.5, 20.3, 12.9; **IR (neat):** $\tilde{\nu}$ = 3019 (w), 2948 (w), 1730 (s), 1639 (w), 1489 (w), 1433 (m), 1319 (w), 1259 (w), 1210 (s), 1125 (m), 1042 (w), 993 (w), 917 (m), 855 (w), 809 (w), 790 (w), 767 (w), 739 (m), 726 (m), 706 (w), 663 (w), 632 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{17}H_{22}O$ + H): 259.1693; found: 259.1687.

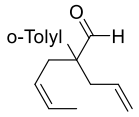
[xiii] Carbon peak corresponding to the ester moiety could not be observed in the NMR.
[xiv] 127.0, 126.7, 125.5, 60.7, 30.3 ppm were also observed



71i

Substrate **71i** was synthesised following the procedure for the synthesis of substrate **71a** except that 2 equivalents of $LiAlH_4$ were used and that FCC (PE:EtOAc = 60:1).

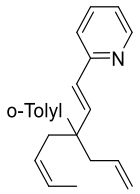
Compound 71i Colourless oil (281 mg, 72%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.34−7.09 (m, 4H), 5.67−5.57 (m, 1H), 5.53−5.45 (m, 1H), 5.24−5.17 (m, 1H), 5.13, 5.05 (m, 1H), 5.19−4.96 (m, 1H), 4.01−3.92 (m, 2H), 2.77−2.70 (m, 1H), 2.68−2.56 (m, 3H), 2.55 (s, 3H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.44−1.38 (m, 1H (OH)); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 140.6, 136.5, 135.2, 133.2, 128.7, 126.4, 126.3, 126.2, 125.9, 117.3, 67.2, 47.7, 39.6, 32.3, 23.5, 13.0; **IR (neat):** $\tilde{\nu}$ = 3417 (w, br), 3061 (w), 3016 (w), 2919 (w), 1833 (w), 1638 (w), 1600 (w), 1450 (w), 1405 (w), 1371 (w), 1296 (w), 1251 (w), 1167 (w), 1034 (m), 997 (m), 980 (m), 855 (w), 797 (w), 763 (m), 729 (s), 687 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{16}H_{22}O + NH_4$): 248.2009; found: 248.2020.



72i

Substrate **72i** was synthesised following the procedure for the synthesis of substrate **72a** except that purification was done by FCC (PE:EtOAc = 70:1).

Compound 72i Colourless oil (235 mg, 83%); **^{1}H NMR** (500 MHz, $CDCl_3$): 9.67 (s, 1H), 7.34−7.29 (m, 1H), 7.28−7.16 (m, 3H), 5.58−5.48 (m, 2H), 5.24−5.17 (m, 1H), 5.09−5.01 (m, 2H), 2.82−2.61 (m, 4H), 2.25 (s, 3H), 1.55−1.50 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 204.3, 136.7, 136.7, 132.9, 132.5, 128.2, 127.6, 127.4, 126.1, 123.9, 118.7, 57.5, 36.6, 29.5, 21.3, 13.0; **IR (neat):** $\tilde{\nu}$ = 3075 (w), 3019 (w), 2978 (w), 2921 (w), 2710 (w), 1721 (s), 1639 (w), 1602 (w), 1488 (w), 1443 (w), 1417 (w), 1382 (w), 1293 (w), 1233 (w), 1117 (w), 1061 (w), 1031 (w), 996 (s), 916 (m), 875 (w), 797 (w), 758 (m), 724 (m), 689 (m) cm^{-1}; **HRMS (CI):** calcd for ($C_{16}H_{20}O + NH_4$): 246.1852; found: 246.1857.

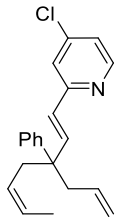


67i

Substrate **67i** was synthesised following the procedure for the synthesis of substrate **67a** except that LiHMDS, as a freshly prepared solution, was used and that FCC (Pentane/EtOAc = 100:1 → 60:1).

Compound 67i Colourless oil (170 mg, 60% over three steps); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.56−8.52 (m, 1H), 7.59 (td, *J* = 7.7, 1.9 Hz, 1H), 7.37−7.34 (m 1H), 7.28−7.23 (m, 1H), 7.21−7.06 (m, 4H), 6.93 (d, *J* = 16.4 Hz, 1H), 6.40 (d, *J* = 16.4 Hz, 1H), 5.68−5.57 (m, 1H), 5.53−5.45 (m, 1H), 5.31−5.24 (m, 1H), 5.09−5.02 (m, 1H), 5.02−4.98 (m, 1H), 2.89−2.68 (m, 4H), 2.39 (s, 3H), 1.58−1.54 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.1, 149.5, 142.8, 142.6, 137.3, 136.3, 134.8, 132.7, 128.4, 127.8, 126.4, 126.1 (2C), 125.4, 121.6, 120.8, 117.6, 47.7, 41.6, 34.3, 23.0, 13.2; **IR (neat):** $\tilde{\nu}$ = 3072 (w), 3015 (w), 2976 (w), 2929 (w), 2203 (w), 1962 (w), 1833 (w), 1644 (w), 1585 (s), 1562 (m), 1487 (w), 1468 (s), 1428 (s), 1319 (w), 1148 (w), 1091 (w), 1091 (w), 1049 (w), 1032 (w), 990 (m), 979 (s), 912 (s), 852 (w), 798 (w), 764 (s), 730 (s), 690 (w), 659 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{22}H_{25}N$ + H): 304.2060; found: 304.2071; **elemental analysis** (%) calcd for $C_{22}H_{25}N$: C 87.08, H 8.30, N 4.62; found: C 88.06, H 8.56, N 4.54.

6.2.10 Synthesis of compound j



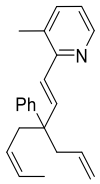
67j

Substrate **67j** was synthesised following the procedure for the synthesis of substrate **67a** except that LiHMDS, as a freshly prepared solution, was used and that FCC (Pentane/EtOAc = 100:1 → 45:1).

Compound 67j Yellow oil (135 mg, 39%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.43 (d, *J* = 5.3 Hz, 1H), 7.36−7.28 (m, 5H), 7.24−7.19 (m, 1H), 7.12 (dd, *J* = 5.3, 2.0 Hz, 1H), 6.92 (d, *J* = 16.4 Hz, 1H), 6.50 (d, *J* = 16.9 Hz, 1H), 5.68−5.58 (m, 1H), 5.54−5.46 (m, 1H), 5.31−5.23 (m, 1H), 5.09−4.99 (m, 2H), 2.69 (d, *J* = 7.1 Hz, 2H), 2.66 (d, *J* = 6.5 Hz, 2H), 1.57−1.53 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 157.7, 150.3, 144.6, 144.3, 143.7, 134.4, 128.1 (2C), 127.7, 127.5 (2C), 126.31, 126.25, 125.7, 121.9, 121.2, 117.9, 47.5, 42.2, 34.8, 13.2; **IR (neat):** $\tilde{\nu}$ = 3020 (w), 2977 (w), 2916 (w), 2856 (w), 1646 (w), 1597 (w), 1570 (s),

1494 (w), 1460 (w), 1444 (m), 1381 (w), 1299 (w), 1251 (w), 1234 (w), 1101 (w), 1033 (w), 980 (m), 913 (m), 878 (w), 818 (m), 763 (w), 735 (w), 698 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{23}ClN$ + H): 324.1514; found: 324.1522; **elemental analysis** (%) calcd for $C_{21}H_{23}ClN$: C 77.88, H 6.85, N 4.32; found: C 78.30, H 7.04, N 4.11.

6.2.11 Synthesis of compound k

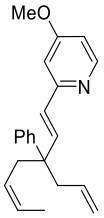


67k

Substrate **67k** was synthesised following the procedure for the synthesis of substrate **67a** except that a commercially available solution of LiHMDS was used. Purification by FCC (Pentane/EtOAc =40:1 → 20:1) afforded **67k** (708 mg, 56%).

Compound 67k Yellow oil (708 mg, 56% over three steps); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.41 (d, *J* = 4.6 Hz, 1H), 7.44−7.34 (m, 3H), 7.34−7.28 (m, 2H), 7.23−7.16 (m, 1H), 7.08 (d, *J* = 15.9 Hz, 1H), 7.02 (dd, *J* = 7.6, 4.7 Hz, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 5.73−5.61 (m, 1H), 5.54−5.45 (m, 1H), 5.36−5.27 (m, 1H), 5.11−4.99 (m, 2H), 2.77−2.62. (m, 4H), 2.33 (s, 3H), 1.59−1.53 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 153.8, 147.0, 145.2, 142.7, 138.0, 134.9, 130.1, 128.0 (2C), 127.6 (2C), 126.2, 126.0, 125.9, 125.0, 121.7, 117.5, 47.6, 42.7, 35.2, 18.9, 13.2; **IR (neat):** $\tilde{\nu}$ = 3058 (w), 3020 (w), 2977 (w), 2917 (w), 2218 (w), 1832 (w), 1640 (w), 1599 (w), 1583 (w), 1563 (w), 1494 (w), 1464 (w), 1145 (m), 1421 (m), 1381 (w), 1370 (w), 1318 (w), 1165 (w), 1103 (w), 1034 (w), 983 (w), 907 (s), 784 (m), 757 (w), 729 (s), 698 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{22}H_{25}N$ + H): 304.2060; found: 304.2071; **elemental analysis** (%) calc for $C_{22}H_{25}N$: C 87.08, H 8.30, N 4.62; found: C 86.75, H 8.05, N 4.35.

6.2.12 Synthesis of compound l

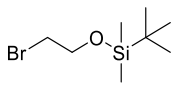


67l

NaH (1.29 mmol, 51 mg, 60% w/w in mineral oil) was dissolved in DMF (0.9 mL) in a J-Young schlenk flask. At 0 ˚C, dry MeOH (1.1 mmol, 0.04 mL) was added *via* syringe. The mixture was stirring for 5 minutes at room temperature before a solution of **67j** (0.92 mmol, 280 mg) in DMF (0.9 mL) was added. The mixture was heated to 150 ˚C and it was stirring at that temperature for 45 minutes. The reaction mixture was quenched with an aqueous saturated solution of NH_4Cl and extracted three times with Et_2O. The organic layers were combined and washed four times with water and once with brine. The mixture was dried over $MgSO_4$, filtered over cotton plug and concentrated at reduced pressure. Purification by FCC (Pentane/EtOAc = 15:1) afforde **67l** (185 mg, 63%).

Compound 67l Colourless oil (185 mg, 63%); **^{1}H NMR** (500 MHz, $CDCl_3$):[xv] 8.37 (d, *J* = 5.7 Hz, 1H), 7.4−7.28 (m, 4H), 7.24−7.18 (m, 1H), 6.86 (d, *J* = 16.3 Hz, 1H), 6.81 (d, *J* = 2.5 Hz, 1H), 6.66 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.50 (d, *J* = 16.3 Hz, 1H), 5.69−5.59 (m, 1H), 5.53−5.45 (m, 1H), 5.33−5.25 (m, 1H), 5.08−4.99 (m, 2H), 3.84 (s, 3H), 2.70 (d, *J* = 7.1 Hz, 2H), 2.66 (d, *J* = 6.9 Hz, 2H), 1.56−1.53 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 166.1, 157.8, 150.7, 144.9, 142.0, 134.7, 128.7, 128.1 (2C), 127.6 (2C), 126.1 (2C), 125.9, 117.7, 108.1, 106.8, 55.0, 47.4, 42.2, 34.8, 13.2; **IR (neat):** $\tilde{\nu}$ = 3017 (w), 2974 (w), 2936 (w), 2856 (w), 1647 (w), 1588 (s), 1562 (s), 1472 (m), 1444 (m), 1415 (w), 1370 (w), 1301 (m), 1266 (w), 1190 (w), 1155 (w), 1114 (w), 1038 (m), 990 (w), 915 (w), 872 (w), 827 (w), 793 (w), 769 (w), 737 (w), 719 (w), 701 (m) cm^{-1}; **HRMS (ES+):** calcd for ($C_{22}H_{25}NO$ + H): 320.2014; found: 320.2006; **elemental analysis** (%) calcd for $C_{22}H_{25}NO$: C 82.72, H 7.89, N 4.38; found: C 84.88, H 9.02, N 2.98.

6.2.13 Synthesis of substrate 96a

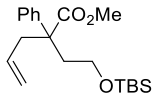


99

Tert-butyldimethylsilyl chloride (36.8 mmol, 5.54 g) and imidazole (77 mmol, 7.6 g) were dissolved in DMF (45 mL) in a three-neck round-bottom flask. The mixture was stirring at room temperature for 5 minutes before adding 2-bromoethanol (35 mmol, 2.5 mL) in DMF (25 mL). The mixture was then stirring for 2 hours and washed four times with water and once with brine. It was concentrated at reduced pressure and used without further purification.

[xv] EtOAc and some impurities can be observed in the ^{1}H NMR.

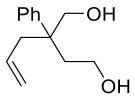
Compound 99 Brown oil (7.8 g, 94%); **^{1}H NMR** (500 MHz, $CDCl_3$): 3.89 (t, *J* = 6.6 Hz, 2H), 3.60 (*J* = 6.6 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6 H).[xvi]



100

Compound **69** (18.6 mmol, 3.5 g) was dissolved in THF (30 mL) in a three-neck round-bottom flask under N_2. At −78 ˚C, LiHMDS (22 mmol, 3.7 g) was added in one portion. The mixture was stirring at this temperature for 20 minutes before adding substrate **99** (22 mmol, 5.2 g) in THF (7 mL) *via* cannula. The mixture was then stirring at room temperature for one hour before Bu_4NI (3.7 mmol, 1 g) was added. The mixture was stirring overnight. It was then quenched with a saturated solution of NH_4Cl and it was extracted three times with Et_2O. The organic layers were combined and washed with water and brine before drying over $MgSO_4$. The mixture was filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 25:1) afforded **100** (914 mg, 89%).

Compound 100 Oil (5.8 g, 90% over two steps); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.36−7.29 (m, 2H), 7.28−7.21 (m, 3H), 5.61−5.50 (m, 1H), 5.10−5.00 (m, 2H), 3.64 (s, 3H), 3.61−3.55 (m, 1H), 3.51−3.44 (m, 1H), 2.87−2.77 (m, 2H), 2.38−2.29 (m, 1H), 2.27−2.19 (m, 1H), 0.86 (s, 9H), 0.001 (s, 3), −0.004 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 175.6, 141.9, 133.6, 128.4 (2C), 126.8, 126.3 (2C), 118.4, 59.6, 52.4, 52.0, 39.8, 36.9, 25.9 (3C), 18.3, −5.4 (2C); **IR (neat):** $\tilde{\nu}$ = 3063 (w), 2952 (w), 2929 (w), 2885 (w), 2857 (w), 1731 (s), 1640 (w), 1600 (w), 1497 (w), 1471 (w), 1462 (w), 1446 (w), 1434 (w), 1389 (w), 1361 (w), 1320 (w), 1252 (m), 1212 (m), 1092 (s), 1033 (w), 1003 (w), 969 (w), 915 (m), 834 (s), 811 (w), 774 (s), 733 (s), 698 (s), 662 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{20}H_{32}O_3Si$ + Na): 371.2018; found: 371.2009.



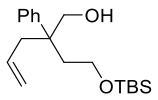
101

$LiAlH_4$ (3.8 mmol, 138 mg) was dissolved in Et_2O (48 mL) in a three−neck round−bottom flask under N_2. At 0 °C, **100** (14.5 mmol, 5 g) in Et_2O was added via cannula. After 20 minutes stirring at room

[xvi] The spectrum is in agreement with the one reported in the literature: Messerle, B. A; Vuong, K. Q. *Organometallics*, **2007**, *26*, 3031.

temperature, $LiAlH_4$ (3.6 mmol, 138 mg) was added at 0 °C. After 30 minutes stirring at room temperature, another portion of $LiAlH_4$ (3.6 mmol, 138 mg) was added at 0 ˚C. The mixture was stirring at room temperature for 30 minutes before adding more $LiAlH_4$ (3.6 mmol, 138 mg). Two more equivalents of LiAlH4 were added in the course of 2 hours. After 3 hours of stirring, the reaction mixture was quenched with saturated solution of Na_2SO_4 at 0 °C. The mixture was filtered over Celite to remove the white precipitate and it was concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 20:1 → 1:1) afforded **71a** as a white solid (1.8 g, 60%).

Compound 101 White solid (1.81 g, 60%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.39−7.29 (m, 3H), 7.28−7.19 (m, 2H), 5.59−5.48 (m, 1H), 5.04 (d, *J* = 17.1 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.83 (d, *J* = 11.6 Hz, 1H), 3.78−3.70 (m, 1H), 3.66−3.58 (m, 1H), 2.54−2.41 (m, 2H), 2.19−2.11 (m, 1H), 2.05−1.95 (m, 1H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 143.5, 134.1, 128.4 (2C), 126.7 (2C), 126.1, 117.7, 67.6, 58.7, 45.3, 42.3, 39.1; **IR (neat):** $\tilde{\nu}$ = 3220 (m, br), 3067 (w), 2951 (w), 2892 (w), 1638 (w), 1599 (w), 1497 (w), 1446 (m), 1383 (w), 1313 (w), 1265 (w), 1144 (w), 1115 (w), 1071 (w), 1043 (s), 1028 (s), 1016 (s), 998 (s) 947 (w), 916 (s), 861 (w), 783 (w), 763 (m), 698 (s), 672 (m), 621 (w), 607 (w), 599 (w), 587 (w), 581 (w), 563 (w), 553 (m), 542 (w), 528 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{13}H_{16}O$ + NH_4): 206.1539; found: 206.1545.

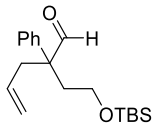


102

Substrate **102** was synthesised following the procedure for the synthesis of substrate **99** except that it was purified by FCC (PE:EtOAc = 20:1 → 10:1).

Compound 102 Colourless oil (2.29 g, 82%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.37−7.26 (m, 4H), 7.24−7.18 (m, 1H), 5.24−5.41 (m, 1H), 5.04−5.00 (m, 1H), 5.00−4.92 (m, 1H), 3.95 (dd, *J* = 11.9, 7.1 Hz, 1H), 3.77 (dd, *J* = 11.7, 7.35 Hz, 1H), 3.74−3.68 (m, 1H), 3.59−3.52 (m, 1H), 3.91 (t, *J* = 7.2 Hz, 1H(OH)), 2.47 (d, *J* = 7.3 Hz, 1H), 2.11 (ddd, *J* = 15.0, 6.5, 3.5 Hz, 1H), 1.95 (ddd, *J* = 15.1, 8.0, 3.7 Hz, 1H), 0.88 (s, 9H), 0.04 (s, 3H) 0.02 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 143.9, 134.4, 128.3 (2C), 126.9 (2C), 126.0, 117.6, 67.3, 59.8, 45.6, 42.7, 39.3, 25.8 (3C), 18.1, −5.60, −5.61; **IR (neat):** $\tilde{\nu}$ = 2409 (w, br), 3061 (w), 2952 (w), 2928 (w), 2883 (w), 2856 (w), 2160 (w), 2075 (w), 1638 (w), 1601 (w), 1498 (w), 1471 (w), 1445 (w), 1389 (w), 1361 (w), 1254 (m), 1079 (m), 1048 (m), 1031 (m), 1002 (w), 938 (w), 913 (w), 867 (w), 835 (s), 776 (m), 734 (w), 699 (s), 665 (w), 630 (w), 612 (w), 587 (w), 576 (w), 563 (w), 556 (w), 551

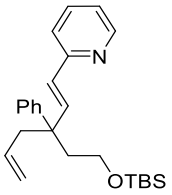
(w), 540 (m), 530 (m), 517 (m), 506 (s) cm^{-1}; **HRMS (ES+):** calcd for ($C_{19}H_{32}O_2Si$ + Na): 343.2069; found: 343.2063.



103

Substrate **103** was synthesised following the general procedure for the synthesis of substrate **72a** except that no purification was required.

Compound 103 Colourless oil (978 mg, 99%); **^{1}H NMR** (500 MHz, $CDCl_3$): 9.49 (s, 1H), 7.41−7.34 (m, 2H), 7.30−7.23 (m, 3H), 5.54−5.43 (m, 1H), 5.07−4.97 (m, 2H), 3.69−3.57 (m, 2H), 2.82 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.67 (dd, *J* = 14.6, 8.2 Hz, 1H), 2.35−2.27 (m, 1H), 2.21−2.13 (m, 1H), 0.86 (s, 9H), 0.01 (s, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 201.1, 138.0, 133.2, 128.7 (2C), 127.6 (2C), 127.3, 118.3, 58.9, 55.6, 37.2, 35.1, 25.8 (3C), 18.2, −5.66, −5.58; **IR (neat):** $\tilde{\nu}$ = 3063 (w), 2951 (w), 2929 (w), 2883 (w), 2857 (w), 2711 (w), 2602 (w), 2531 (w), 2255 (w), 1978 (w), 1955 (w), 1722 (m), 1640 (w), 1599 (w), 1495 (w), 1472 (m), 1445 (w), 1397 (w), 1362 (w), 1253 (m), 1172 (w), 1094 (m), 1035 (w), 1005 (w), 966 (w), 915 (w), 876 (w), 834 (s), 808 (s), 774 (s), 760 (m), 733 (w), 698 (s), 665 (w), 645 (w), 625 (w), 615 (w), 593 (w), 583 (w), 579 (w), 563 (w), 558 (w), 549 (w), 537 (w), 530 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{19}H_{30}O_2Si$ + Na): 341.1913; found: 341.1903.

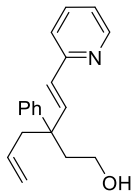


105

Substrate **105** was synthesised following the procedure for the synthesis of substrate **67a** except that LiHMDS was used as a freshly prepared 1 M solution and that the compound was purified by FCC (PE:EtOAc = 10:1 → 3:1)

Compound 105 Colourless oil (605 mg, 25% over three steps); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.57−8.52 (m, 1H), 7.61 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.37−7.28 (m, 5H), 7.23−7.18 (m, 1H), 7.11 (ddd, *J* = 7.5, 4.9, 1.1 Hz), 6.85 (d, *J* = 16.2 Hz, 1H), 6.56 (d, *J* = 16.2 Hz, 1H), 5.71−5.60 (m, 1H), 5.10−5.00 (m, 2H), 3.62−3.51

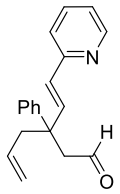
(m, 2H), 2.76−2.69 (m, 2H), 2.25−2.13 (m, 2H), 0.84 (s, 9H), −0.026 (s, 3H), −0.028 (s, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.0, 149.5, 144.9, 141.9, 136.4, 134.5, 128.4, 128.2 (2C), 127.2 (2C), 126.2, 121.8, 121.1, 117.7, 59.8, 46.1, 42.6, 40.1, 25.9 (3C), 18.3, −5.28, −5.29; **IR (neat):** $\tilde{\nu}$ = 3060 (w), 2952 (w), 2928 (w), 2883 (w), 2855 (w), 2205 (w), 1834 (w), 1646 (w), 1586 (m), 1564 (w), 1494 (w), 1470 (m), 1445 (w), 1429 (w), 1389 (w), 1360 (w), 1304 (w), 1253 (m), 1188 (w), 1148 (w), 1087 (s), 991 (w), 979 (w), 910 (m), 835 (s), 813 (s), 774 (s), 732 (s), 699 (s), 664 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{25}H_{35}NOSi$ + H): 394.2566; found: 394.2559.



106

Compound **105** (1.5 mmol, 600 mg) was dissolved in THF (10 mL) in a three−neck round−bottom flask under N_2. At 0 °C, Bu_4NF (1.8 mmol, 0.6 g) was added *via* syringe. The mixture was stirring for 1 hour before more Bu_4NF (5 mmol, 5 mL, 1 M in THF) was added. The mixture was stirring overnight at room temperature, quenched with brine and extracted three times with Et_2O. The mixture was filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 2:1) afforded **106** as a colourless oil (438 mg, 99%).

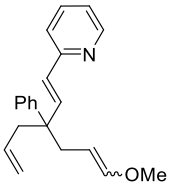
Compound 106 Colourless oil (438 mg, 99%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.56−8.50 (m, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.38−7.27 (m, 5H), 7.24−7.18 (m, 1H), 7.11 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 1H), 6.88 (d, *J* = 16.3 Hz, 1H), 6.56 (d, *J* = 16.3 Hz, 1H), 5.69−5.57 (m, 1H), 5.11−5.00 (m, 2H), 3.68−3.56 (m, 2H), 2.72 (d, *J* = 7.1 Hz, 2H), 2.30−2.17 (m, 2H), 1.80 (s, 1H (OH), br); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 155.8, 149.4, 144.7, 141.7, 136.5, 134.2, 128.4, 128.3 (2C), 127.1 (2C), 126.3, 121.9, 121.2, 117.9, 59.3, 46.1, 42.8, 40.2; **IR (neat):** $\tilde{\nu}$ = 3296 (w, br), 3058 (w), 2937 (w), 2243 (w), 2139 (w), 2049 (w), 1980 (w), 1645 (w), 1587 (m), 1564 (m), 1494 (w), 1470 (m), 1445 (m), 1430 (m), 1327 (w), 1151 (w), 1031 (m), 994 (m), 979 (m), 908 (s), 762 (m), 730 (s), 700 (s), 645 (m), 627 (w), 592 (w), 573 (w), 561 (w), 551 (w), 538 (w), 530 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{19}H_{21}NO$ + H): 280.1701; found: 280.1694.



107

Substrate **107** was synthesised following the procedure for the synthesis of substrate **72a** except that purification was done by FCC (PE:EtOAc = 4:1).

Compound 107 Colourless oil (268 mg, 68%); **^{1}H NMR** (500 MHz, $CDCl_3$): 9.64 (t, *J* = 2.7 Hz, 1H), 8.58−8.54 (m, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.41−7.32 (m, 4H), 7.30−7.22 (m, 2H), 7.14 (ddd, *J* = 8.0, 4.8, 1.1 Hz, 1H), 7.05 (d, *J* = 16.2 Hz, 1H), 6.54 (d, *J* = 16.2 Hz, 1H), 5.68−5.56 (m, 1H), 5.14−5.06 (m, 1H), 2.97 (d, *J* = 2.7 Hz, 2H), 2.86−2.77 (m, 2H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 202.4, 155.1, 149.6, 143.5, 139.9, 136.5, 133.3, 129.4, 128.6 (2C), 127.0 (2C), 126.9, 122.2, 121.6, 119.1, 50.2, 45.6, 43.9; **IR (neat):** $\tilde{\nu}$ = 3058 (w), 3005 (w), 2977 (w), 2912 (w), 2835 (w), 2743 (w), 2212 (w), 2007 (w), 1949 (w), 1717 (s), 1640 (w), 1584 (s), 1563 (m), 1494 (m), 1469 (m), 1445 (m), 1430 (m), 1324 (w), 1149 (w), 1066 (w), 1050 (w), 1030 (w), 991 (m), 917 (m), 860 (w), 763 (s), 733 (s), 700 (w), 644 (w), 620 (w), 588 (w), 578 (w), 565 (w), 554 (w), 545 (w), 537 (m), 526 (m) cm^{-1}; **HRMS (ES+):** calcd for ($C_{19}H_{19}NO$ + Na): 300.1364; found: 300.1363.

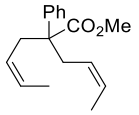


96a

(Methoxymethyl)triphenylphosphonium chloride (2.4 mmol, 0.82 mL) was dissolved in THF (1.2 mL) in a three-neck round-bottom flask under N_2. At 0 ˚C, a freshly prepared solution of NaHMDS (2.0 mmol, 0.37 g) in THF (1.8 mL) was added *via* cannula. The mixture was stirring for 5 minutes at that temperature before compound **107** (0.6 mmol, 0.1 mL) in THF (0.5 mL) was added. The reaction mixture was stirring overnight at room temperature. It was then diluted in Et_2O and quenched with an aqueous solution of NH_4Cl. The mixture was dried over $MgSO_4$, filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (Pentane/EtOAc = 4:1) afforded **96a** (162 mg, 87%) as a mixture of *cis*:*trans* isomers.

Compound 96a As a mixture of *trans*:*cis* in a 1:1.15 ratio. Colourless oil (162 mg, 87%) Only the peaks for the *trans* isomer are reported;[xvii] **^{1}H NMR** (500 MHz, $CDCl_3$): 8.57−8.53 (m, 2H), 7.64−7.59 (m, 2H), 7.39−7.28 (m, 14H), 7.24−7.17 (m, 2H), 7.15−7.08 (m, 2H), 6.92−6.85 (m, 2H), 6.60−6.53 (m, 2H), 5.86 (dt, *J* = 6.3, 1.5 Hz, 1H), 5.72−5.58 (m, 2H), 5.10−4.97 (m, 4H), 4.27−4.20 (m, 1H), 3.54 (s, 3H), 2.75−2.66 (m, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.2, 156.0, 149.31, 149.27, 147.5, 145.0, 144.9, 142.2, 142.1, 136.51, 136.45, 134.7, 134.6, 133.8, 133.6, 128.7, 128.6, 128.5, 128.4, 128.1 (2C), 128.0 (2C), 127.6 (2C), 127.5 (2C), 126.1, 126.0, 121.8, 121.7, 121.0, 121.0, 117.7, 117.5, 102.2, 56.0, 59.4, 47.4, 47.1, 41.5, 31.9; **IR (neat):** $\tilde{\nu}$ = 3056 (w), 3002 (w), 2930 (w), 2853 (w), 2202 (w), 2047 (w), 1968 (w), 1827 (w), 1650 (m), 1584 (m), 1563 (m), 1494 (w), 1468 (m), 1444 (m), 1429 (m), 1389 (w), 1324 (w), 1204 (w), 1254 (w), 1208 (m), 1147 (w), 1131 (w), 1106 (s), 1049 (w), 1032 (w), 979 (m), 913 (m), 855 (w), 803 (w), 763 (m), 742 (m), 699 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{23}NO$ + H): 306.1852; found: 306.1858; **elemental analysis** (%) calcd for $C_{21}H_{23}NO$: C 82.58, H 7.59, N 4.59; found: C 82.48, H 7.78, N 3.74.

6.2.14 Synthesis of substrate 97



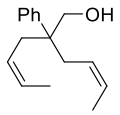
109

Compound **75** (2.5 mmol, 500 mg) was dissolved in THF (5 mL) in a three-neck round-bottom flask under N_2. At −78 ˚C, NaHMDS (3.7 mmol, 670 mg) was added in one portion. The mixture was stirring at this temperature for 30 minutes before adding 1-bromo-2-butyne (3.7 mmol, 0.3 mL) *via* syringe. The mixture was then stirring overnight at room temperature. The mixture was quenched with a saturated solution of NH_4Cl and it was extracted three times with Et_2O. The organic layers were combined and washed with water and brine before drying over $MgSO_4$. The mixture was filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 15:1) afforded **108**. $Ni(OAc)_2 \bullet 5H_2O$ (0.7 mmol, 180 mg) was dissolved in EtOH (3 mL) in a three-neck round-bottom flask and the mixture was purged with H_2 (1 atm). Then, a freshly prepared solution of $NaBH_4$ (1.6 mmol, 610 mg) in EtOH (9 mL) was added *via* syringe and the mixture was stirring for 10 minutes. Ethylenediamine (7.3 mmol, 0.5 mL) was added neat to the mixture which was left stirring for further 5 minutes. Then, a solution of **108** (2.1 mmol, 528 mg) in EtOH (9 mL) was added to the mixture. After

[xvii] Peaks for the *cis* isomer. **^{1}H NMR**: 6.24 (d, *J* = 12.5 Hz, 1H), 4.51 (dt, J = 12.6, 7.6 Hz, 1H), 3.42 (s, 3H), 2.57-2.52 (m, 2H). **^{13}C NMR**: 149.0, 98.0, 56.0, 36.0

90 minutes of stirring, the mixture was filtered and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 5:1) afforded **109** (457 mg, 84%).

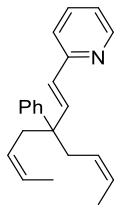
Compound 109 Colourless oil (457.5 mg, 84% over two steps); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.36−7.29 (m, 2H), 7.29−7.22 (m, 4H), 5.56−5.48 (m, 2H), 5.20−5.13 (m, 2H), 3.64 (s, 3H), 2.84 (dd, *J* = 14.5, 7.8 Hz, 2H), 2.70 (dd, *J* = 14.5, 6.7 Hz, 2H), 1.55−1.51 (m, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 176.0, 142.2, 128.3 (2C), 127.1 (2C), 126.7, 126.5 (2C), 125.0 (2C). 54.1, 52.0, 32.1 (2C), 12.9 (2C); **IR (neat):** $\tilde{\nu}$ = 3020 (w), 2949 (w), 2919 (w), 2859 (w), 1731 (s), 1656 (w), 1599 (w), 1497 (w), 1446 (m), 1407 (w), 1371 (w), 1316 (w), 1257 (m), 1203 (s), 1123 (m), 1050 (m), 1015 (w), 983 (w), 924 (w), 855 (w), 804 (w), 779 (w), 699 (s), 665 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{17}H_{22}O_2$ + H): 259.1693; found: 259.1705.



110

Substrate **110** was synthesised following the procedure for the synthesis of substrate **71a**.

Compound 110 Oil (351 mg, 79%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.40−7.31 (m, 4H), 7.25−7.20 (m, 1H), 5.57−5.48 (m, 2H), 5.31−5.23 (m, 2H), 3.81 (d, *J* = 6.4 Hz, 2H), 2.58−2.44 (m, 4H), 1.63−1.59 (m, 6H), 1.28 (t, *J* = 6.5 Hz, 1H (OH)); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 143.9, 128.4 (2C), 127.0 (2C), 126.4 (2C), 126.2, 126.0 (2C), 68.3, 46.6, 32.6 (2C), 13.0 (2C); **IR (neat):** $\tilde{\nu}$ = 3430 (w, br), 3058 (w), 3019 (w), 2918 (w), 1943 (w), 1655 (w), 1600 (w), 1580 (w), 1498 (w), 1445 (m), 1406 (w), 1371 (w), 1319 (w), 1120 (w), 1135 (w), 2034 (m), 1004 (w), 988 (w), 944 (w), 911 (w), 843 (w), 769 (w), 752 (w), 698 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{16}H_{22}O$ + NH_4): 248.2009; found: 248.2016.

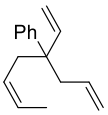


112

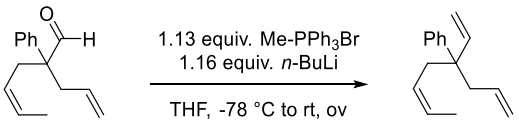
Substrate **112** was synthesised following the procedure for the synthesis of substrate **66a** except that purification was done by FCC (Pentane/EtOAc = 15:1).

Compound 112 Colourless oil (195 mg, 41% over 4 steps); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.57−8.53 (m, 1H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1H), 7.39−7.35 (m, 2H), 7.33−7.28 (m, 3H), 7.22−7.18 (m, 1H), 7.10 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 6.89 (d, *J* = 16.3 Hz, 1H), 6.57 (d, *J* = 16.3 Hz, 1H), 5.54−5.44 (m, 2H), 5.35−5.25 (m, 2H), 2.68 (d, *J* = 7.2 Hz, 4H), 1.28−1.52 (m, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.2, 149.4, 145.1, 142.1, 136.3, 128.3, 128.0 (2C), 127.6 (2C), 126.2 (2C), 126.0 (3C), 121.7, 120.8, 47.8, 35.1 (2C), 13.1 (2C); **IR (neat):** $\tilde{\nu}$ = 3020 (w), 2917 (w), 2857 (w), 1951 (w), 1738 (w), 1648 (w), 1585 (m), 1563 (w), 1495 (w), 1469 (m), 1445 (w), 1429 (m), 1405 (w), 1371 (w), 1306 (w), 1239 (m), 1149 (w), 1090 (w), 1047 (w), 979 (s), 930 (w), 846 (w), 766 (m), 699 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{22}H_{25}N$ + H): 304.2060; found: 304.2065.

6.2.15 Synthesis of compounds 82-85



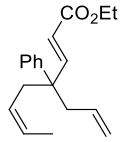
82



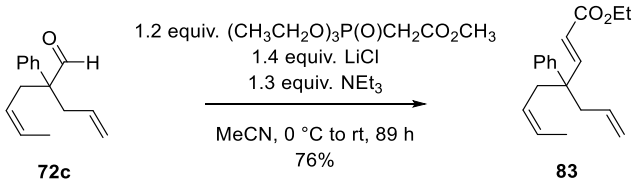
72c **82**

Methyltriphenylphosphonium bromide (1.36 mmol, 486 mg) was dissolved in THF (4 mL) in a three-neck round-bottom flask under N_2. At −78 ˚C, *n*-BuLi (1.4 mmol, 0.5 mL, 2.5 M in hexanes) was added dropwise. Compound **72c** (1.2 mmol, 260 mg) in THF (8 mL) was cannulated to the mixture. After stirring overnight at room temperature, the reaction mixture was quenched with NH_4Cl and extracted three times with Et_2O. The organic layer was washed three times with water and once with brine. The mixture was dried over $MgSO_4$, filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE) afforded compound **82** (161 mg, 61%).

Compound 82 Colourless oil (161 mg, 61%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.34−7.27 (m, 2H), 7.23−7.17 (m, 1H), 5.99 (dd, *J* = 17.6, 10.9, 1H), 5.66−5.55 (m, 1H), 5.52−5.42 (m, 1H), 5.29−5.19 (m, 2H), 2.60−2.42 (m, 4H), 1.56−1.50 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 145.1, 145.0, 134.9, 127.9, 127.5, 126.2, 125.9, 125.7, 117.3, 113.1, 47.5, 42.0, 34.4, 13.1; **IR (neat):** $\tilde{\nu}$ = 3080 (w), 3021 (w), 2978 (w), 2917 (w), 2858 (w), 1830 (w), 1638 (w), 1600 (w), 1494 (w), 1445 (m), 1407 (w), 1370 (w), 1301 (w), 1189 (w), 1082 (w), 1034 (w), 998 (m), 913 (s), 841 (w), 767 (w), 749 (m), 698 (s), 674 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{16}H_{20}$ + H): 213.1638; found: 213.1642.



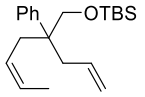
83



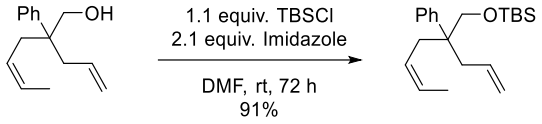
72c **83**

LiCl (0.66 mmol, 25 mg) was dissolved in MeCN (0.3 mL) in a J-Young schlenk flask at room temperature. At that temperature, triethyl phosphonoacetate (0.55 mmol, 0.11 mL) was added neat to the mixture. At 0 ˚C, NEt_3 (0.60 mmol, 0.08 mL) was added to the mixture *via* syringe. After 10 minutes of stirring, **71c** (0.46 mmol, 0.08 mL) in THF (0.36 mL) was cannulated. The reaction mixture was stirring for 89 hours, quenched with 5% HCl and the aqueous phase was extracted three times with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc → 100:1) afforded substrate 82 (100 mg, 76%).

Compound 83 Colourless oil (100 mg, 76%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.36−7.29 (m, 2H), 7.28−7.19 (m, 3H), 7.12 (d, *J* = 16.1 Hz, 1H), 5.88 (d, *J* = 16.2 Hz, 1H), 5.61−5.45 (m, 2H), 5.25−5.15 (m, 1H), 5.08−4.98 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 166.8, 154.8, 143.4, 133.8, 128.2, 127.4, 126.7, 126.5, 125.1, 120.1, 118.4, 118.2, 60.3, 47.6, 41.7, 34.3, 14.2, 13.1; **IR (neat):** $\tilde{\nu}$ = 3062 (w), 3021 (w), 2979 (w), 2932 (w), 1716 (s), 1646 (m), 1600 (w), 1496 (w), 1445 (w), 1405 (w), 1391 (w), 1366 (w), 1310 (m), 1266 (m), 1179 (s), 1095 (w), 1035 (m), 993 (m), 916 (m), 862 (w), 810 (w), 763 (w), 699 (s), 616 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{19}H_{24}O_2$ + H): 285.1849; found: 285.1854.



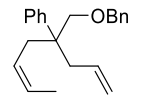
84



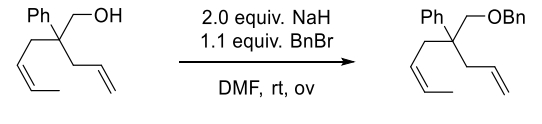
71c **84**

Tert-butyldimethylsilyl chloride (1.0 mmol, 146 mg) and imidazole (1.9 mmol, 132 mg) were dissolved in DMF (1.1 mL) in a three-neck round-bottom flask. The mixture was stirring at room temperature for 5 minutes before adding compound **71c** (0.9 mmol, 190 mg) in DMF (0.5 mL). The mixture was then stirring for 72 hours. Et_2O was added to the reaction mixture. It was then washed four times with water and once with brine. The mixture was concentrated at reduced pressure and purified by FCC (PE).

Compound 84 Colourless oil (266 mg, 91%); **^{1}H NMR** (500 MHz, $CDCl_3$): 7.32−7.26 (m, 4H), 7.20−7.14 (m, 1H), 5.61−5.50 (m, 1H), 5.48−5.39 (m, 1H), 5.20−5.13 (m, 1H), 5.05−4.92 (m, 2H), 3.73 (s, 2H), 2.57−2.40 (m, 4H), 1.58−1.54 (m, 3H), 0.86 (s, 9H), −0.04 (d, *J* = 2.1 Hz, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$):144.6, 134.9, 127.8, 126.9, 125.7, 117.2, 66.6m 45.9, 40.1, 33.0, 29.7 (grease), 25.8, 18.2, 13.1, −5.7; **IR (neat):** $\tilde{\nu}$ = 3060 (w), 3020 (w), 2954 (m), 2927 (m), 2856 (m), 1639 (w), 1602 (w), 1498 (w), 1471 (w), 1463 (w), 1445 (w), 1405 (w), 1388 (w), 1361 (w), 1330 (w), 1252 (m), 1188 (w), 1091 (m), 1036 (w), 1004 (w), 992 (w), 938 (w), 913 (w), 834 (s), 814 (w), 773 (s), 735 (w), 696 (s), 669 (w), 619 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{21}H_{34}OSi$ + Na): 353.2277; found: 353.2275.



84



71c **85**

NaH (1.8 mmol, 80 mg, 60% w/w suspension in mineral oil) was dissolved in DMF (0.9 mL) in a three-neck round-bottom flask under N_2. Compound 70c (0.9 mmol, 0.2 mL) in DMF (0.4 mL) was cannulated to the mixture. After 2 hours of stirring, benzyl bromide (1 mmol, 0.10 mL) and Bu_4NI (0.6 mmol, 210 mg) were added to the mixture. After stirring overnight at room temperature, the reaction was

quenched with water and it was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered over a cotton plug and concentrated at reduced pressure. Purification by FCC (PE:EtOAc = 90:1) afforded compound **85**.

Compound 85 Colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$): 7.36−7.27 (m, 9H), 7.22−7.16 (m, 1H), 5.60−5.49 (m, 1H), 5.49−5.40 (m, 1H), 5.20−5.10 (m, 1H), 5.05−4.91 (m, 2H), 4.50 (s, 2H), 3.63 (d, *J* = 1.2 Hz, 2H), 2.62−2.52 (m, 3H), 2.45 (dd, *J* = 14.6, 6.9 Hz, 1H), 1.58−1.52 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 144.5, 138.7, 134.7, 128.2, 128.0, 127.4, 127.7, 126.1, 126.0, 125.8, 117.4, 73.8, 73.2, 45.2, 41.1, 33.9, 13.0; **IR (neat):** $\tilde{\nu}$ = 3062 (w), 3020 (w), 2915 (w), 2856 (w), 1946 (w), 1638 (w), 1601 (w), 1497 (w), 1477 (w), 1445 (w), 1405 (w), 1362 (w), 1307 (w), 1260 (w), 1204 (w), 1096 (m), 1028 (w), 998 (w), 913 (m), 768 (w), 734 (m), 696 (s), 657 (w), 618 (w); **HRMS (CI):** calcd for ($C_{22}H_{26}$o + H): 324.2322; found: 324.2335.

6.2.16 Synthesis of $[Rh(coe)Cl_2]_2$

$RhCl_3 \bullet xH_2O$ (0.95 mmol, 203 mg) was dissolved with a predegassed, by argon bubbling, 4 to 1 mixture of isopropanol and water in a schlenk bomb under N_2.The solution was left stirring for ten minutes at room temperature. Then, *cis*−cyclooctene (4.89 mmol, 0.64 mL) was added neat to the system which was stirring strongly for 20 minutes at room temperature before warming it up to 80˚C. The reaction was stopped after 3 hours. The solid was filtrated and wash with cold PE.

The precatalyst $[Rh(coe)_2Cl]_2$ was characterised by elemental analysis. Theoretical C 53.57, H 7.87

Entry	Reference	C	H	% Yield
1	KHO−Rh−A	52.23	7.62	Prepared by
2	KHO−Rh−B	47.55	6.81	Kelvin Ho
3	MPN−02−014	51.62	7.63	−−−−−−−−−
4	MPN−02−049	52.84	7.72	28
5	MPN−02−129	53.20	7.81	44
6	MPN−03−078	53.47	7.85	33
7	MPN−04−131	53.28	7.88	−−−−−−−−
8	MPN−05−115	52.55	7.66	26
9	MPN−06−080	53.03	7.72	31
10	MPN−07−011	53.25	7.74	26
11	MPN−08−018	52.25	7.66	34

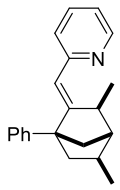
6.3 Characterisation of products

General procedure for the cycloisomerisation

The THF used in this reaction was either distilled over sodium or dried using a PureSolv drying system with alumina columns and the THF was used fresh. No differences were observed between the two methods.

$[Rh(coe)_2Cl]_2$ (0.003 mmol, 2.5 mg) and P(2-furyl)$_3$ (0.007 mmol, 3.2 mg) were added to a flame-dried J-Young Schlenk flask in the glovebox. THF was added (0.2 mL) and the mixture was stirred for 10 minutes. $AgBF_4$ (1.3 mg, 0.007 mmol) in THF (0.1 mL) was added via syringe and the mixture was stirring for 10 minutes. Then, substrate **67c** (20 mg, 0.069 mmol) in THF (0.39 mmol) was added *via* cannula. The flask was sealed and heated at 60 ˚C. After 24 hours, the reaction mixture was cooled to room temperature, filtered over a plug of silica (washing with DCM) and concentrated at reduced temperature. Purification by FCC (Pentane:EtOAc = 100:1 → 50:1).

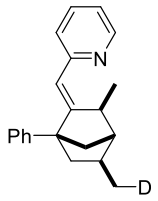
6.3.1 Characterisation of *syn,syn* norbornanes



78

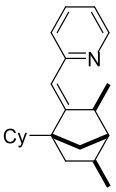
Compound 78 Colourless oil (4.7 mg, 24%); **^{1}H NMR** (500 MHz, $CDCl_3$):[xviii] 8.54−8.48 (m, 1H), 7.50 (td, *J* = 7.7, 1.9 Hz, 1H), 7.41−7.31 (m, 4H), 7.29−7.23 (m, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 7.00−6.95 (m, 1H), 5.70 (s, 1H), 3.25 (q, *J* = 6.9 Hz, 1H), 2.20−2.12 (m, 2H), 2.02−1.92 (m, 1H), 1.89 (s, 1H), 1.70 (d, *J* = 10.0 Hz, 1H), 1.53 (dd, *J* = 11.8, 4.9, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 163.5, 157.2, 149.1, 142.8, 135.6, 128.3, 128.1, 126.2, 123.3, 120.2, 119.8, 59.7, 49.9, 43.9, 43.8, 37.5, 36.5, 22.2, 17.3; **IR (neat):** $\tilde{\nu}$ = 3058 (w), 2953 (m), 2865 (w), 1945 (w), 1735 (w), 1652 (m), 1602 (w), 1584 (s), 1560 (w), 1496 (w), 1471 (s), 1445 (m), 1426 (s), 1374 (w), 1346 (w), 1311 (w), 1254 (w), 1236 (w), 1218 (w), 1171 (w), 1148 (w), 1118 (w), 1096 (w), 1063 (w), 1035 (w), 1008 (w), 991 (w), 946 (w), 931 (w), 903 (w), 890 (w), 865 (w), 817 (w), 778 (w), 763 (m), 753 (m), 741 (m), 698 (s), 675 (w), 657 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{23}N$ + H): 290.1903; found: 290.1909.

[xviii] The underlined chemical shifts correspond to the irradiated protons on the selective NOESY experiment.



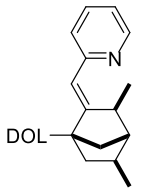
78e

Compound 78e Compound prepared by Daniel *J*. Tetlow. Colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): 8.53−8.48 (m, 1H), 7.50 (td, *J* = 7.7, 1.9 Hz, 1H), 7.40−7.31 (m, 4H), 7.28−7.24 (m, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.97 (ddd, *J* = 7.5 Hz, 1H), 5.69 (d, *J* = 1.9 Hz, 1H), 3.24 (q, *J* = 7.0 Hz, 1H), 2.21−2.12 (m, 2H), 2.00−1.91 (m, 1H), 1.89 (s, 0.9H), 1.73−1.66 (m, 1H), 1.59−1.48 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.04−1.00 (m, 2H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 163.5, 157.1, 149.1, 142.8, 135.6, 128.3, 128.1, 126.2, 123.3, 120.2, 119.7, 59.7, 49.8, 49.8, 43.8, 43.8, 37.4, 36.4, 22.2, 21.8 (t, *J* = 19.2 Hz), 17.3; **IR (neat):** $\tilde{\nu}$ = 3058 (w), 2923 (m), 2856 (w), 2170 (w), 1734 (w), 1651 (m), 1584 (s), 1559 (w), 1496 (w), 1471 (s), 1445 (m), 1426 (s), 1374 (w), 1316 (w), 1260 (w), 1234 (w), 1218 (w), 1147 (w), 1093 (w), 1057 (w), 1033 (w), 991 (w), 943 (w), 928 (w), 890 (w), 865 (w), 801 (w), 777 (w), 762 (m), 752 (m), 740 (m), 698 (s), 671 (w), 656 (w) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{22}DN$ + H): 291.1966; found: 291.1975.



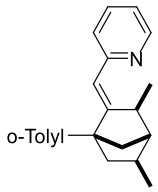
78g

Compound 78g Colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$): 8.58−8.52 (m, 1H), 7.57 (td, *J* = 7.7, 1.9 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.00 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 6.20 (d, *J* = 1.5 Hz, 1H), 3.12 (q, *J* = 6.9 Hz, 1H), 1.99−1.89 (m, 2H), 1.86−1.67 (m, 5H), 1.66 (s, 1H), 1.46−1.40 (m, 1H), 1.40−1.24 (m, 3H), 1.23−0.97 (m, 5H), 0.97−0.92 (m, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 161.3, 157.7, 149.1, 135.7, 123.0, 120.0, 117.9, 58.6, 49.1, 44.5, 41.6, 37.3, 36.0, 31.7, 29.7, 29.2, 27.1, 26.9, 22.1, 16.5.



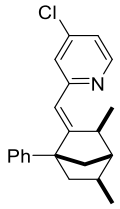
78h

Compound 78h Colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$): 8.55 (d, *J* = 3.9 Hz, 1H), 7.55 (td, *J* = 7.7, 1.8 Hz, 1H), 7.25−7.22 (m, 1H), 7.02−6.97 (m, 1H), 6.76−6.72 (m, 1H), 4.09−3.88 (m, 4H), 3.22 (q, *J* = 6.9 Hz, 1H), 1.84−1.74 (m, 1H), 1.70 (s, 1H), 1.67−1.57 (m, 3H), 1.48 (s, 3H), 1.38 (dd, *J* = 11.7, 5.1 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 157.8, 157.6, 149.1, 135.6, 123.6, 120.4, 120.1, 110.9, 65.3, 64.4, 63.1, 49.5, 44.5, 39.2, 36.2, 34.6, 29.7 (grease), 22.1, 21.7, 16.8; **HRMS (CI):** calcd for ($C_{19}H_{25}NO_2$ + H): 300.1958; found: 300.1966.



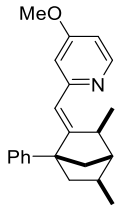
78i

Compound 78i Colourless oil (8.0 mg, 40%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.56−8.48 (m, 1H), 7.50 (td, *J* = 7.7, 1.8, 1H), 7.40−7.34 (m, 1H), 7.24−7.15 (m, 3H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.00−6.95 (m, 1H), 5.73 (s, 1H), 3.30 (s, 1H), 2.48 (s, 1H, br), 2.38 (s, 3H), 2.26−1.96 (s, 1H, br), 1.96−1.80 (s, 2H, br), 1.80−1.64 (s, 1H, br), 1.63−1.45 (s, 1H, br), 1.18 (s, 3H, br), 1.05 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 161.3, 157,2, 149.1, 140.4, 137.6, 135.7, 131.8, 129.3, 126.6, 125.7, 123.2, 120.1, 118.6, 59.9, 50.5, 45.7, 44.4, 35.6, 35.2, 22.2 (2C), 17.2; **HRMS (CI):** calcd for ($C_{22}H_{25}N$ + H): 304.2060; found: 304.2057.



78j

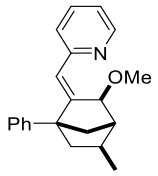
Compound 78j This product was obtained as mixture of **77j**:**78j** (4.2:1)[xix]. Colourless oil (3.5 mg, 27%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.40 (d, *J* = 5.3 Hz, 1H), 7.42−7.27 (m, 5H), 7.05 (d, *J* = 1.9 Hz, 1H), 6.99 (dd, *J* = 5.3, 2.0 Hz, 1H), 5.62 (d, *J* = 1.9 Hz, 1H), 3.25 (qt, *J* = 6.9, 2.0 Hz, 1H), 2.20−2.09 (m, 2H), 2.00−1.92 (m, 1H), 1.90 (s, 1H), 1.70 (dt, *J* = 10.1, 1.8, 1H), 1.59−1.53 (m, 1H), 1.53 (dd, *J* = 11.7, 5.1 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 165.8, 158.6, 149.9, 143.6, 142.5, 128.20 (2C), 128.18 (2C), 126.4, 123.4, 120.4, 59.9, 49.8, 44.0, 43.7, 37.4, 36.4, 22.1, 17.2; **HRMS (CI):** calcd for ($C_{21}H_{22}ClN$ + H): 324.1514; found: 324.1517.



78l

Compound 78l Colourles oil (8.9 mg, 37%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.32 (d, *J* = 5.8 Hz, 1H), 7.41−7.31 (m, 4H), 7.29−7.24 (m, 1H), 6.60 (d, *J* = 2.5 Hz, 1H), 6.55 (dd, *J* = 5.7, 2,5 Hz, 1H), 5.65 (d, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 3.24 (q, *J* = 6.9 Hz, 1H), 2.20−2.12 (m, 2H), 2.01−1.92 (m, 1H), 1.88 (s, 1H), 1.72−1.67 (m, 1H), 1.52 (dd, *J* = 11.6, 5.7 Hz, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 165.6, 163.6, 158.7, 150.2, 142.8, 128.3 (2C), 128.1 (2C), 126.2, 119.8, 108.9, 107.0, 59.7, 54.9, 49.8, 43.9, 43.8, 37.4, 36.5, 22.2, 17.3; **HRMS (CI):** calcd for ($C_{22}H_{25}NO$ + H): 320.2009; found: 320.2018.

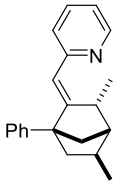
[xix] **^{1}H NMR**, only product **79j** is reported. Carbon peaks corresponding to **79j** are reported here. **^{13}C NMR**: 158.7, 150.0, 145.9, 128.1, 127.12, 127.05, 126.9, 126.0, 125.9, 122.2, 120.6, 118.6, 56.4, 37.7, 37.3, 32.5, 22.1, 13.0



114a

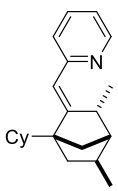
Compound 114a Yellow crystals (6.23 mg, 32%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.51 (d, *J* = 4.9 Hz, 1H), 7.59−7.54 (m, 1H), 7.41−7.31 (m, 5H), 7.28−7.22 (m, 1H), 7.03 (dd, *J* = 7.3, 4.9 Hz, 1H), 5.98 (s, 1H), 4.33 (s, 1H), 3.47 (s, 3H), 2.40−2.34 (m, 2H), 2.17−2.10 (m, 1H), 1.76−1.68 (m, 2H), 1.57−1.50 (m, 2H), 1.09 (d, *J* = 7.0, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.7, 156.2, 149.1, 142.0, 135.9, 128.3 (2C), 128.2 (2C), 126.4, 125.8, 123.2, 121.1, 84.0, 57.8, 56.6, 45.2, 44.0, 38.2, 31.3, 21.7; **HRMS (CI):** calcd for ($C_{21}H_{23}NO$ + H): 306.1852; found: 306.1856.

6.3.2 Characterisation of *syn*,*anti* norbornanes



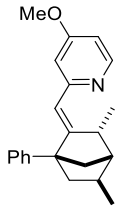
78

Compound 78 Colourless oil (7.2 mg, 35%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.52−8.47 (m, 1H), 7.53−7.47 (m, 1H), 7.38−7.30 (m, 4H), 7.25−7.20 (m, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.96 (ddd, *J* = 7 .5, 4.9 Hz, 1 Hz, 1H), 5.69 (d, *J* = 2.8 Hz, 1H), 3.39−3.31 (m, 1H), 2.31−2.13 (m, 2H), 2.11−2.02 (m, 2H), 1.92 (dd, *J* = 9.7, 1.5 Hz, 1H), 1.58 (dd, *J* = 11.2, 3.5, 1H), 1.05−1.00 (m, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 162.3, 157.7, 148.8, 143.5, 135.4, 128.1, 128.1, 126.2, 123.5, 120.3, 119.7, 60.6. 48.2, 43.0, 41.2, 40.7, 29.1, 22.3, 14.4; **IR (neat):** $\tilde{\nu}$ = 3058 (w), 2957 (m), 2940 (m), 2866 (m), 1728 (w), 1656 (m), 1602 (w), 1584 (m), 1557 (m), 1495 (m), 1470 (m), 1444 (m), 1425 (m), 1370 (w), 1347 (w), 1312 (w), 1281 (w), 1245 (w), 1183 (w), 1148 (w), 1104 (w), 1088 (w), 1068 (w), 1056 (w), 1036 (w), 1009 (w), 990 (w), 948 (w), 934 (w), 889 (m), 878 (w), 867 (w), 852 (m), 784 (m), 761 (m), 745 (s), 698 (s), 666 (m), 649 (w), 622 (w); **HRMS (CI):** calcd for ($C_{21}H_{23}N$ + H): 290.1903; found: 290.1906.



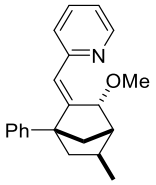
78g

Compound 78g Colourless oil (3.3 mg, 16%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.56−8.51 (m, 1H), 7.59−7.54 (m, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.04−6.99 (m, 1H), 6.26 (d, *J* = 3.0 Hz, 1H), 3.09−3.00 (m, 1H), 2.05−1.90 (m, 3H), 1.85−1.76 (m, 2H), 1.76−1.64 (m, 3H), 1.54−1.51 (m, 1H), 1.45−0.96 (m, 1H), 0.94 (d *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 160.1, 158.3, 148.9, 135.5, 123.6, 120.2, 117.8, 59.4, 48.0, 41.8, 40.4, 38.6, 36.4, 29.6, 29.2, 28.4, 27.1, 27.1, 26.8, 22.4, 14.7.



78l

Compound 78l This product was obtained as mixture of **78l**:**79l** (1:2)[xx] Colourless oil (2.2 mg, 11%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.31 (d, *J* = 5.7 Hz, 1H), 6.60 (d, *J* = 2.56 Hz, 1H), 6.54 (d, *J* = 5.7, 2.5 Hz, 1H), 5.63 (d, *J* = 2.9 Hz, 1H), 3.78 (s, 3H), 3.38 (m, 1H), 2.21−2.15 (m, 2H), 2.08−2.00 (m, 2H), 1.93−1.89 (m, 1H), 1.05−1.00 (m, 6H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 128.1, 126.2, 109.1, 107.3, 54.9, 48.2, 41.2, 40.7, 29.1, 22.3, 14.4.



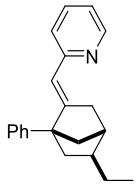
114a

Compound 114a Oil (7.3 mg, 37%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.51−8.46 (m, 1H), 7.54 (td, *J* = 7.7, 1.8 Hz, 1H), 7.29 (m, 4H), 7.29−7.22 (m, 2H), 7.02−6.97 (m, 1H), 5.88 (d, *J* = 2.4 Hz, 1H), 4.77−4.73 (m, 1H), 3.38 (s, 3H), 2.50−2.41 (m, 2H), 2.34−2.28 (m, 1H), 1.94 (dd, *J* = 10.3, 1.7 Hz, 1H), 1.88 (d, *J* = 10.4 Hz, 1H), 1.61−1.54 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.2, 155.0, 148.8,

[xx] **^{1}H NMR**, only product **78l** is reported. Carbon peaks corresponding to **79l** are reported here. **^{13}C NMR**: 150.4, 128.1, 127.1, 125.9, 125.7, 123.4, 119.7, 106.9, 55.0, 37.6, 37.5, 32.2, 22.4, 13.1. Some quaternary carbons could not be observed.

142.5, 135.4, 128.2 (2C), 128.0 (2C), 126.5, 123.6, 123.5, 120.7, 81.8, 59.2, 56.6, 44.4, 43.5, 37.2, 27.0, 21.7.

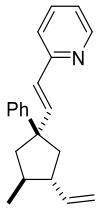
6.3.3 Characterisation of norbornane 81



81

Compound 81. This product was obtained as mixture of **81**:**79** (3:1);[xxi] **^{1}H NMR** (500 MHz, $CDCl_3$): 8.52−8.48 (m, 1H), 7.55−7.49 (m, 1H), 7.47−7.26 (m, 5H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.97 (ddd, *J* = 4.9, 4.2, 1 Hz, 1H), 5.80−5.76 (m, 1H), 2.94−2.84 (m, 1H), 2.73−2.64 (m, 1H), 2.37 (d, *J* = 4.2 Hz, 1H), 2.20−2.13 (m, 1H), 2.01−1.96 (m, 1H), 1.80−1.74 (m, 1H), 1.70−1.53 (m, 3H), 1.48−1.39 (m, 1H), 1.33−1.22 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 158.4, 157.6, 149.2, 149.1, 142.8, 135.9, 135.8, 135.7, 128.19 (2C), 128.15 (2C), 128.1, 128.0, 127.8, 127.8, 127.2, 127.1, 127.0, 126.6, 126.3, 125.9, 125.8, 125.7, 125.5, 123.4, 123.3, 122.8, 122.6, 120.5, 120.1, 120.0, 59.2, 44.3, 43.6, 43.5, 42.6, 41.8, 41.7, 41.2, 41.1, 40.9, 40.5, 40.4, 37.7, 37.6, 37.5, 37.2, 36.4, 32.4, 32.2, 31.9, 30.3, 29.5, 27.4, 23.4, 22.5, 22.4, 22.3, 18.0, 14.1, 13.1, 12.3.

6.3.4 Characterisation of cyclopentanes 80.



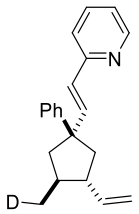
80

Compound 80 Colourless oil (9.3 mg, 45%); **^{1}H NMR** (500 MHz, $CDCl_3$):[xxii] 8.53−8.47 (m, 1H), 7.57 (td, *J* = 7.7, 1.8 Hz, 1H), 7.38−7.28 (m, 4H), 7.23−7.17 (m, 2H), 7.07 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1H), 6.93 (d, *J* =

[xxi] Only the peaks of compound **81** are reported for ^{1}H NMR. All the peaks that were observed are reported for ^{13}C NMR.

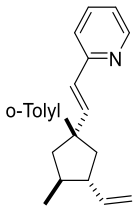
[xxii] The underlined chemical shifts correspond to the irradiated protons on the selective NOESY experiment.

15.9 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 5.86−5.75 (m, 1H), 5.05−4.93 (m, 2H), 2.58−2.49 (m, 1H), 2.49−2.42 (m, 1H), 2.24−2.12 (m, 2H), 2.03−1.93 (m, 1H), 1.93−1.84 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.0, 149.4, 148.2, 144.9, 142.1, 136.4, 128.2, 127.0, 126.3, 125.9, 121.6, 121.3, 114.0, 52.0, 51.8, 47.4, 44.5, 39.4, 18.0; **IR (neat):** $\tilde{\nu}$ = 3061 (w), 2953 (m), 2924 (m), 2868 (m), 1731 (w), 1641 (m), 1585 (s), 1563 (m), 1494 (w), 1469 (m), 1446 (m), 1429 (m), 1375 (w), 1306 (w), 1148 (w), 1090 (w), 1049 (w), 1033 (w), 991 (m), 977 (m), 910 (m), 757 (m), 741 (m), 700 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{23}N$ + H): 290.1903; found: 290.1908.



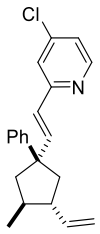
80e

Compound 80e Colourless oil (3.8 mg, 18%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.53−8.47 (m, 1H), 7.57 (td, *J* = 7.7, 1.8 Hz, 1H), 7.38−7.28 (m, 4H), 7.23−7.16 (m, 2H), 7.07 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 6.93 (d, *J* = 16.0 Hz, 1H), 6.26 (d, *J* = 15.9 Hz, 1H), 5.85−5.76 (m, 0.88H), 5.05−4.93 (m, 2H), 2.57−2.49 (m, 1H), 2.49−2.43 (m, 1H), 2.24−2.13 (m, 2H), 2.03−1.93 (m, 1H), 1.91−1.85 (m, 1H), 1.04−0.96 (m, 2.28H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.1, 149.4, 149.3, 148.8, 148.2, 145.0, 142.1, 136.3, 135.5, 128.3, 128.3, 128.1, 128.1, 127.4. 127.0, 126.9, 126.8, 126.4, 126.2, 126.1, 125.9, 123.5, 123.4, 121.6, 121.3, 121.3, 121.2, 114.0, 113.8, 52.0, 51.8, 51.7, 47.4, 44.6, 44.6, 39.4, 39.4, 39.4, 18.0, 17.8 (t, *J* = 19.2 Hz); **IR (neat):** $\tilde{\nu}$ = 3058 (w), 2923 (m), 2860 (m), 2164 (w), 1726 (w), 1641 (m), 1585 (s), 1563 (m), 1494 (w), 1469 (m), 1446 (m), 1429 (m), 1282 (w), 1148 (w), 1091 (w), 1049 (w), 1033 (w), 991 (m), 977 (m), 910 (m), 844 (w), 757 (m), 742 (m), 700 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{22}DN$ + H): 291.1966; found: 291.1956.



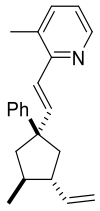
80h

Compound 80h Oil (9.9 mg, 50%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.53−8.48 (m, 1H), 7.55 (d, *J* = 7.7, 1.8 Hz, 1H), 7.41−7.37 (m, 1H), 7.22−7.11 (m, 4H), 7.06 (ddd, *J* = 7.5, 4.8, 1.0 *J* = 1H), 6.96 (d, *J* = 16.0, Hz, 1H), 6.14 (d, *J* = 15.9 Hz, 1H), 5.91−5.81 (m, 1H), 5.06−4.97 (m, 2H), 2.45 (dd, *J* = 14.0, 9.4 Hz, 1H), 2.41−2.34 (m, 1H), 2.33−2.25 (m, 4H), 2.20−2.09 (m, 1H), 2.04−1.92 (m, 2H), 1.60−1.52 (m, 1H), 1.00 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 156.1, 149.4, 146.1, 144.3, 141.9, 137.3, 136.3, 132.1, 126.8, 126.3, 126.1, 125.6, 121.6, 121.3, 114.2, 52.0, 51.9, 49.3, 44.3, 38.6, 22.3, 17.7; **HRMS (CI):** calcd for ($C_{22}H_{25}N$ + H): 304.2060; found: 304.2063.



80j

Compound 80j Colourless oil (3.7 mg, 28%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.39 (d, *J* = 5.3 Hz, 1H), 7.36−7.28 (m, 4H), 7.24−7.17 (m, 2H), 7.08 (dd, *J* = 5.2, 1.8 Hz, 1H), 6.96 (d, *J* = 15.8 Hz, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 5.84−5.75 (m, 1H), 5.06−4.93 (m, 2H), 2.60−2.48 (m, 1H), 2.45 (dd, *J* = 12.1, 5.9 Hz, 1H), 2.25−2.12 (m, 2H), 2.09−1.93 (m, 1H), 1.93−1.85 (m, 1H), 1.01 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$):[xxiii] 157.6, 150.2, 147.8, 146.7, 144.3, 141.9, 128.3, 127.0, 126.0, 125.4, 121.8, 121.5, 120.5, 114.1, 52.1, 51.7, 47.3, 45.5, 39.4, 18.0; **HRMS (CI):** calcd for ($C_{21}H_{22}ClN$ + H): 324.1514; found: 324.1520.

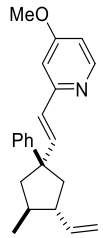


80k

Compound 80k Oil (8.5 mg, 42%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.38 (d, *J* = 3.8 Hz, 1H), 7.43−7.28 (m, 4H), 7.23−7.16 (m, 1H), 7.12 (d, *J* = 15.5 Hz, 1H), 7.01 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.34 (d, *J* = 15.5 Hz, 1H), 5.89−5.78 (m, 1H), 5.06−5.00 (m, 1H), 5.00−4.94 (m, 1H), 2.56−2.51 (m, 1H), 2.51−2.44 (m, 1H), 2.29−2.14 (m, 5H), 2.07−1.96 (m, 1H), 1.95−1.88 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125.77 MHz,

[xxiii] Some small impurities could be observed. ^{13}C NMR: 128.13, 128.06, 126.3, 48.1, 41.1, 29.1

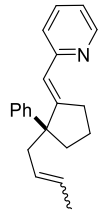
$CDCl_3$):[xxiv] 153.6, 148.2, 146.5, 142.1, 138.4, 130.3, 128.2 (2C), 128.16, 128.06 (2C), 127.1, 125.8, 122.3, 121.6, 114.0, 52.4, 51.7, 47.6, 44.5, 39.3, 29.7 (grease), 18.8, 18.1; **IR (neat):** $\tilde{\nu}$ = 3058 (w), 2951 (w), 2925 (w), 2867 (w), 1639 (w), 1599. (w), 1582 (m), 1562 (w), 1494 (w), 1462 (w), 1445 (m), 1421 9m), 1375 (w), 1296 (w), 1217 (w), 1165 (w), 1101 (w), 1033 (w), 979 (m) 908 (m), 847 (w), 783 (m), 763 (m), 698 (s), 670 (w) cm^{-1}; **HRMS (ES+):** calcd for ($C_{22}H_{26}N$ + H): 304.2065; found: 304.2060.



80l

Compound 80l Colourless oil (8.9 mg, 37%); **^{1}H NMR** (500 MHz, $CDCl_3$): 8.33 (d, *J* = 5.7 Hz, 1H), 7.37−7.28 (m, 4H), 7.22−7.16 (m, 1H), 6.92 (d, *J* = 16.0 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.62 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.20 (d, *J* = 15.8 Hz, 1H), 5.86−8.75 (m, 1H), 5.04−4.93 (m, 2H), 3.82 (s, 3H), 2.57−2.48 (m, 1H), 2.45 (dd, *J* = 12.3, 6.3 Hz, 1H), 2.23−2.13 (m, 2H), 2.06−1.93 (m, 1H), 1.93−1.84 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 1H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 166.1, 157.7, 150.6, 148.2, 145.1, 142.0, 128.2 (2C), 127.0 (2C), 126.4, 125.9, 114.0, 108.0, 107.2, 55.0, 52.0, 51.8, 47.4, 44.6, 39.4, 18.0; **HRMS (CI):** calcd for ($C_{22}H_{25}NO$ + H): 320.2009; found: 320.2010.

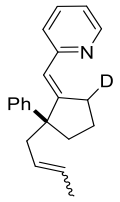
6.3.5 Characterisation of cyclopentanes 79 and analogues



79

[xxiv] The quaternary carbon of the pyridine moiety was not be observed. Peaks corresponding to small impurities are reported here. ^{13}C NMR: 49.7, 37.5, 17.4.

Compound 79 As a mixture of *trans*:*cis* isomers in 1.2:1 ratio.[xxv] Colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$): 8.63−8.59 (m, 1H), 7.63 (td, *J* =7.7, 1.9 Hz, 1H), 7.46−7.38 (m, 2H), 7.33−7.26 (m, 3H), 7.21−7.15 (m, 1H), 7.07 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 6.46 (t, *J* = 2.6 Hz, 1H), 5.57−5.34 (m, 2H), 2.91−2.84 (m, 2H), 2.84−2.77 (m, 1H), 2.61−2.54 (m, 1H), 2.28−2.20 (m, 1H), 1.93−1.83 (m, 1H), 1.82−1.71 (m, 1H), 1.58−1.54 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 157.4, 156.4, 149.2, 146.5, 146.2, 135.8, 128.1, 128.0, 127.8, 127.8, 127.2, 127.1, 125.9, 125.8, 125.7, 123.4, 123.3, 120.4, 56.1, 43.6, 37.68, 32.4, 32.2, 22.5, 18.0; **IR (neat):** $\tilde{\nu}$ = 3055 (w), 3021 (w), 2954 (m), 2920 (m), 2853 (w), 1943 (w), 1731 (w), 1647 (w), 1584 (m), 1558 (w), 1492 (w), 1471 (m), 1444 (m), 1427 (m), 1376 (w), 1286 (w), 1219 (w), 1149 (w), 1092 (w), 1048 (w), 1031 (w), 969 (w), 930 (w), 890 (w), 864 (w), 758 (m), 741 (m), 700 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{23}N$ + H): 290.1903; found: 290.1909 (100%), $C_{17}H_{16}N$: 234.1281 (57.8%).

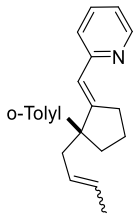


79e

Compound 79e As a mixture of *trans* and *cis* isomers in 1 to 1 ratio. Colourless oil; **^{1}H NMR** (500 MHz, $CDCl_3$):[xxvi] 8.64−8.59 (m, 1H), 7.63 (td, *J* = 7.7, 1.8 Hz, 1H), 7.46−7.39 (m, 2H), 7.34−7.27 (m, 3H), 7.22−7.15 (m, 1H), 7.07 (ddd, *J* = 7.4, 4.9, 0.9 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 5.55−5.34 (m, 2H), 2.92−2.84 (m, 1.3H), 2.72−2.65 (m, 1H), 2.64−2.53 (m, 1H), 2.22−2.15 (m, 1H), 1.93−1.82 (m, 1H), 1.82−1.71 (m, 1H), 1.62 (dd, *J* = 6.1, 1.0 Hz, 2H); **IR (neat):** $\tilde{\nu}$ = 2922 (m), 1732 (w), 1647 (w), 1584 (m), 1558 (w), 1492 (w), 1470 (m), 1427 (m), 1261 (w), 1148 (w), 1031 (w), 968 (w), 890 (w), 741 (m), 699 (s) cm^{-1}; **HRMS (CI):** calcd for ($C_{21}H_{22}DN$ + H): 291.1966; found: 291.1969 (100%), $C_{17}H_{15}DN$: 235.1342 (48.97%).

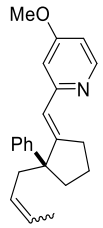
[xxv] Only the *trans* isomer is reported. The following identified peaks correspond to the *cis* isomer. ^{1}H NMR: 6.42 (t, J = 2.6 Hz, 1H), 2.68 (dd, J = 14.3, 7.3 Hz, 1H), 2.20-2.15 (m, 1H), 1.63-1.60 (m, 3H). ^{13}C NMR: 37.68, 37.5, 13.1.

[xxvi] Only the *trans* isomer is reported. The following identified peaks correspond to the *cis* isomer. ^{1}H NMR: 6.46 (d, *J* = 2.4 Hz, 1H), 2.84−2.77 (m, 1H), 2.22−2.15 (m, 1H), 1.57 (d, *J* = 6.0 Hz, 2H).



79i

Compound 79i As a mixture of *cis*:*trans* isomers in 1.7 :1 ratio. Colourless oil (1.7 mg, 7%); **^{1}H NMR** (500 MHz, $CDCl_3$):[xxvii] 8.58 (ddd, *J* = 4.9, 1.8, 0.8 Hz, 1H), 7.58 (td, *J* = 7.7, 1.9 Hz, 1H), 7.48−7.43 (m, 1H), 7.22−7.10 (m, 4H), 7.03 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 6.12 (t, *J* = 2.6 Hz, 1H), 5.59−5.50 (m, 2H), 3.16−2.95 (m, 2H), 2.86−2.79 (m, 1H), 2.75−2.64 (m, 1H), 2.35−2.30 (m, 3H), 1.96−1.80 (m, 4H), 1.67−1.62 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 157.4, 156.4, 149.2, 146.5, 146.2, 135.8, 128.1, 128.0, 127.8, 127.8, 127.2, 127.1, 125.9, 125.8, 125.7, 123.4, 123.3, 120.4, 43.6, 56.1, 37.7, 37.5, 32.4, 32.2, 22.5, 13.1; **HRMS (CI):** calcd for ($C_{22}H_{25}N$ + H): 304.2060; found: 304.2061.

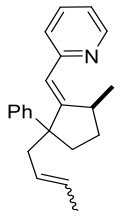


79l

Compound 79l Compound **79l** was obtain as a *cis:trans* mixture (5.2:1) Colourless oil (3.4 mg, 17%);[xxviii] **^{1}H NMR** (500 MHz, $CDCl_3$): 8.43 (d, *J* = 5.7 Hz, 1H), 7.45−7.39 (m, 2H), 7.32−7.27 (m, 2H), 7.21−7.15 (m, 2H), 6.82 (d, *J* = 2.3 Hz, 1H), 6.64 (dd, *J* = 5.7, 2.5 Hz, 1H), 6.42 (t, *J* = 2.5 Hz, 1H), 3.85 (s, 3H), 2.95−2.84 (m, 2H), 2.80 (dd, *J* = 15.0, 7.6 Hz, 1H), 2.66 (d, *J* = 15.1, 6.4 Hz, 1H), 2.25 (ddd, *J* = 12.6, 6.6, 3.4 Hz, 1H), 1.92−1.82 (m, 1H), 1.82−1.73 (m, 1H), 1.66−1.58 (m, 1H), 1.58−1.53 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 165.7, 158.9, 156.5, 150.4, 146.1, 128.1 (2C), 127.2, 127.1 (2C), 125.9, 125.7, 123.4, 109.2, 106.9, 56.2, 55.0, 37.6, 37.5, 32.2, 22.4, 13.1; **HRMS (CI):** calcd for ($C_{22}H_{25}NO$ + H): 320.2009; found: 320.2016.

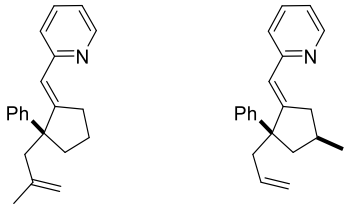
[xxvii] Only the *cis* isomer is reported. The following identified peaks correspond to the *trans* isomer. ^{1}H NMR: 6.07 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR: 37.6, 43.6, 18.0

[xxviii] Only the *cis* isomer is reported. The following identified peaks correspond to the *trans* isomer. ^{1}H NMR: 7.38−7.33 (m, 2H), 6.37 (t, *J* = 2.5 Hz, 1H), 2.67 (d, *J* = 14.4, 7.2 Hz, 1H), 2.22−2.15 (m, 1H). ^{13}C NMR: 127.81, 127.78, 127.1, 125.8, 43.6, 32.4, 18.0.



115

Compound 115 Compound **115** was obtain as mixture of *trans:cis* (3.4:1). Colourless oil (13.5 mg, 67%); **^{1}H NMR** (500 MHz, $CDCl_3$):[xxix] 8.63−8.59 (m, 1H), 7.66−7.58 (m, 1H), 7.51−7.41 (m, 2H), 7.33−7.27 (m, 3H), 7.22−7.15 (m, 1H), 7.06 (ddd, *J* = 7.3, 4.9, 1.0 Hz, 1H), 6.35 (d, *J* = 2.0 Hz, 1H), 5.57−5.33 (m, 2H), 3.74−3.64 (m, 1H), 2.64−2.5 (m, 2H), 2.41−2.25 (m, 1H), 2.04−1.91 (m, 1H), 1.91−1.82 (m, 1H), 1.61 (d, *J* = 5.1 Hz, 3H), 1.39−1.28 (m, 1H), 0.95−0.94 (m, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$):[xxx] 161.0, 157.1, 149.2, 146.6, 135.8, 128.0, 127.8, 127.7, 127.3, 127.2, 125.8, 125.7, 123.6, 123.6, 123.4, 120.5, 56.3, 45.0, 37.2, 36.2, 31.2, 29.7, 20.1, 18.0; **HRMS (CI):** calcd for ($C_{22}H_{25}N$ + H): 304.2060; found: 304.2059.



76a **77a**

Compounds 76a and 77a (**77a**/**76a** = 4.5:1) Colourless oil (15 mg, 74%);[xxxi] **^{1}H NMR** (500 MHz, $CDCl_3$):[xxxii] 8.63−8.56 (m, 1H), 7.67−7.56 (m, 1H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.33−7.27 (m, 2H), 7.21−7.15 (m, 2H), 7.09−7.01 (m, 1H), 6.17−6.15 (m, 1H), 5.90−5.78 (m, 1H), 5.15−5.00 (m, 2H), 3.37 (dd, *J* = 17.6, 6.8 Hz, 1H), 2.93−2.67 (m, 2H), 2.47−2.36 (m, 1H), 2.32−2.19 (m, 2H), 1.82−1.71 (m, 1H), 1.10 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 157.7, 157.4, 149.2, 148.1, 135.8, 135.7, 128.1, 127.2, 125.7, 124.1, 123.4, 122.9, 117.3, 56.1, 48.8, 44.4, 41.9, 32.1, 20.4; **HRMS (CI):** calcd for ($C_{21}H_{23}N$ + H): 290.1903; found: 290.1906.

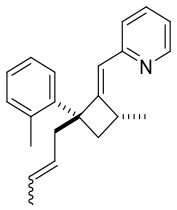
6.3.6 Characterisation of compound 93i

[xxix] Only the *trans* isomer is reported. The following identified peaks correspond to the *cis* isomer. 6.4 (d, *J* = 2.1 Hz, 1H), 2.71 (dd, *J* = 14.8, 7.5 Hz, 1H), 1.52 (d, *J* = 6.5 Hz, 3H).

[xxx] Minor isomer: 128.0, 125.5, 123.3, 38.7, 37.0, 36.1, 31.2

[xxxi] Only the peaks corresponding to isomer **77a** are reported. The following peaks correspond to **76a**. ^{1}H NMR: 6.58 (t, *J* = 2.5 Hz, 1 H), 4.58 (s, 1 H), 4.77 (s, 1 H), 2.59 (d, *J* = 13.6 Hz, 1H), 1.93−1.84 (m, 1H), 1.47 (s, 3 H). ^{13}C NMR: 157.3, 156.9, 149.2, 143.3, 135.83, 128.0, 125.9, 123.3, 120.5, 114.5, 55.6, 49.0, 36.9, 31.6, 24.7, 22.3.

[xxxii] The underlined chemical shifts correspond to the irradiated protons on the selective NOESY experiment.

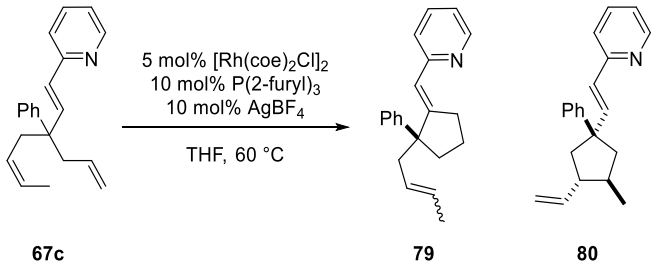


93i

Compound 93i Compound **93i** was obtain as mixture of isomers. Colourless Oil;[xxxiii] **^{1}H NMR** (500 MHz, $CDCl_3$): 8.61−8.57 (m, 1H), 7.64 (ddd, *J* = 14.3, 7.6, 1.7 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.20−7.09 (m, 4H), 7.07 (ddd, *J* = 7.5, 4.8, 1.5 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 5.58−5.49 (m, 1H), 5.49−5.40 (m, 1H), 3.48−3.36 (m, 1H); **^{13}C NMR** (125.77 MHz, $CDCl_3$): 159.2, 156.4, 149.5, 144.6, 136.0, 135.1, 132.0, 127.2, 127.0, 126.17, 126.08, 125.3, 125.0, 122.4 (2C), 120.7, 53.8, 39.1, 37.1, 35.5, 20.6, 19.3, 13.2.

6.4 Tables of the monitoring of the reaction conditions favouring the β-hydride elimination

The reaction of **67c** under the optimised conditions favouring the β-hydride elimination was repeated three times (Figure 6.1). For each independent experiment, the concentration of each intermediate and product was obtained. Below, there are all the concentrations of all the intermediates and products at given times (t = 0, 1, 4, 8, 24 h) and their average and standard deviations. The numbers highlighted in red correspond to those which were visibly out of the expected range and that were removed on the calculation of the corrected averaged and standard deviation (see Section 3.4.1, Table 3.9 and Table 3.10)



67c **79** **80**

*Figure 6.1: Conditions for the cycloisomerisation of **67c** favouring the β-hydride elimination.*

The concentration at t = 0 hour is an estimation calculated from the initial concentration of the reactions at t = 1 hour (Table 6.1). That is the reason why there is a small difference of molarity of substrate **67c** between experiments.

[xxxiii] Only the major isomer is reported. A quaternary carbon peak could not be recorded in the NMR spectra. The following peaks correspond to the minor isomers. ^{1}H NMR: 6.66 (d, *J* = 2.3 Hz, 1H), 6.62 (d, *J* = 2.3 Hz, 1H). ^{13}C NMR: 135.8, 132.8, 131.99, 128.5, 128.14, 128.07, 127.9, 125.9, 125.7, 125.5, 125.2, 125.1, 123.33, 123.28, 120.6, 120.2, 117.5, 43.2, 38.7, 37.7, 36.5, 36.2, 35.3, 29.7, 23.6.

*Table 6.1: Concentrations of organic species of the cycloisomerisation of substrate **67c** favouring the β-hydride elimination at t = 0 hour for three independent experiments.*

	67c	67f	80	79*cis*	79*trans*	79
Experiment 1	0.098	0.000	0.000	0.000	0.000	0.000
Experiment 2	0.099	0.000	0.000	0.000	0.000	0.000
Experiment 3	0.099	0.000	0.000	0.000	0.000	0.000
Average	0.099	0.000	0.000	0.000	0.000	0.000
Stand. Dev.	0.000	0.000	0.000	0.000	0.000	0.000

*Table 6.2: Concentrations of organic species of the cycloisomerisation of substrate **67c** favouring the β-hydride elimination at t = 1 hour for three independent experiments*

	67c	67f	80	79*cis*	79*trans*	79
Experiment 1	0.083	0.012	0.002	0.001	0.000	0.001
Experiment 2	0.074	0.009	0.003	0.001	0.000	0.001
Experiment 3	**0.060**	**0.031**	0.006	0.002	0.000	0.002
Average	0.072	0.017	0.004	0.001	0.000	0.001
Stand. Dev.	0.010	0.010	0.002	0.001	0.000	0.001

*Table 6.3: Concentrations of organic species of the cycloisomerisation of substrate **67c** favouring the β-hydride elimination at t = 4 hours for three independent experiments.*

	67c	67f	80	79*cis*	79*trans*	79
Experiment 1	0.057	0.023	**0.004**	0.002	0.000	0.002
Experiment 2	0.057	0.022	0.011	0.003	0.001	0.004
Experiment 3	**0.038**	0.023	**0.030**	0.005	0.003	**0.008**
Average	0.051	0.023	0.015	0.003	0.001	0.005
Stand. Dev.	0.009	0.000	0.011	0.001	0.001	0.003

The concentration of cyclopentane **80** is variable for the three experiments and the standard deviation is considerably high. But, when calculating the corrected average (Section 3.4.1, Table 3.9), it was decided to remove the result from experiment 1 as the concentration is similar to the one observed for t = 1 hour.

*Table 6.4: Concentrations of organic species of the cycloisomerisation of substrate **67c** favouring the β-hydride elimination at t = 8 hours for three independent experiments*

	67c	67f	80	79*cis*	79*trans*	79
Experiment 1	**0.030**	**0.024**	**0.033**	0.006	0.003	0.009
Experiment 2	0.010	0.010	0.050	0.006	0.005	0.011
Experiment 3	0.009	0.010	0.066	0.007	0.007	0.014
Average	0.016	0.015	0.050	0.006	0.005	0.011
Stand. Dev.	0.010	0.006	0.013	0.000	0.002	0.002

*Table 6.5: Concentrations of organic species of the cycloisomerisation of substrate **67c** favouring the β-hydride elimination at t = 24 hours for three independent experiments.*

	67c	67f	80	79*cis*	79*trans*	79
Experiment 1	0.000	0.000	0.073	0.010	0.007	0.017
Experiment 2	0.000	0.000	0.074	0.013	0.007	0.020
Experiment 3	0.000	0.000	0.079	0.011	0.008	0.019
Average	0.000	0.000	0.075	0.011	0.007	0.019
Stand. Dev.	0.000	0.000	0.002	0.001	0.000	0.002

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