Selective Routes to Substituted Dihydropyridones

A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in the

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by

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Hertford College

and

The Chemistry Research Laboratory

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Contents

Abstract

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Matthew J. Connolly, Hertford College and the Chemistry Research Laboratory, Hilary 2011

Introduction

The introduction provides a survey of the natural product and pharmaceutical targets accessible from dihydropyridines and dihydropyridones as well as an overview of previous work carried out towards the synthesis of these valuable intermediates. The mechanism, scope and limitations of the various approaches are covered, along with the goals of this project.

Results and Discussion

A Regioselective Route to Dihydropyridones

The regioselective addition of nucleophiles to a range of disubstituted pyridinium salts has been achieved, with selectivity determined by hard/soft factors. Certain nucleophiles can be added with complete regioselectivity to either *C*-2 or *C*-6 of these salts, depending on the conditions employed. Addition at *C*-2 allows the generation of a quaternary centre in high yield. The conditions discovered can be applied to pyridinium salts with different substitution patterns and an effective procedure has been developed for the removal of the nitrogen protecting group post reduction.

The Preparation of Enantiopure Dihydropyridones

After unsuccessful attempts to find a reagent-controlled asymmetric synthesis of dihydropyridones, a highly diastereoselective and non-chiral auxiliary based substrate-controlled procedure has been developed. By prompting an intramolecular hydride migration from a secondary silyl ether onto the pyridinium core, the corresponding dihydropyridones are available in high yield, with the diastereoselectivity being controlled by the minimization of 1,3-allylic strain between the *N*-allyl group and the hydride-bearing side chain. Thus, an enantiopure pyridyl alcohol may be converted to the corresponding dihydropyridone without loss of enantiomeric purity. Furthermore, the dihydropyridones can be easily converted to complex bicyclic systems *via* a ring closing metathesis reaction.

Experimental

Full experimental procedures and spectroscopic characterization of compounds are provided.

Acknowledgements

Firstly, I would like to thank my supervisor, Professor Tim Donohoe, for allowing me to work in his group for the past four years. His many ideas have helped me out of some very dark corners and his endless enthusiasm has inspired me greatly. Thanks are also due to my industrial supervisor, Dr Lesley Walton, for her additional help, for looking after me during my CASE placement at Lilly and for buying lunch after CASE meetings.

What errors remain in this thesis are entirely of my own devising, however, without the careful attention of my crack team of proof readers, there would be a whole lot more than I hope the reader may now find. In particular, I would like to thank Mike Tucker for the unenviable task of going through my experimental and for watching as much TV as I do, Dr Chris Jones for checking my R&D and, I believe, making me cooler by association and to Ben Pilgrim for reading my introduction and putting up with all the jokes.

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A big thank you must go to my family who have provided endless love and emotional support over the years. The weekends spent at home were an essential respite from the toils of a DPhil and helped no end. Thanks to Grandma and Grandad for teaching me to aspire to great things and for helping me to believe in myself.

Last, but certainly not least, thanks to Ida. I have been in some very dark places over the years but am now over them thanks entirely to your love, kindness and patience. All I ask is that you always remain the way you are now and, obviously, that you keep focusing “on Sailors fighting in the dance-hall…” Tusen takk, min lille dompapp! I am a very lucky man.

Declaration

This thesis, and the work it describes, is entirely my own, except where I have *either* acknowledged help from a named person *or* given a reference to a published source or thesis. Text taken directly from another source has been enclosed in quotation marks and a reference given.

Matthew James Connolly

Oxford, Hilary Term 2011

Abbreviations

[α]	specific rotation
° C	degrees Celsius
Å	Ångstrom
Ac	acetyl
ACE-Cl	1-chloroethyl chloroformate
AIBN	azo*bisiso*butyronitrile
Ar	aromatic group
ATP	adenosine triphosphate
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
ca.	*circa* (Latin: about)
CAN	ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata
cm^{-1}	wavenumbers
CNS	central nervous-system
CPC	2-(1-methyl-1-phenylethyl)-4-(2-propyl)cyclohexyl
CSA	(±)-camphor-10-sulfonic acid
Cy	cyclohexyl
DAIB	3-exo-dimethylaminoisoborneol
DBB	4,4'-di-*tert*-butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DIBALH	di-*iso*-butylaluminium hydride
dis.	disrotatory
DMAP	4-(dimethylamino)pyridine
DMB	3,4-dimethoxybenzyl
DMBA	1,3-dimethylbarbituric acid

DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
e^-	electron
E^+	generic electrophile
ee	enantiomeric excess
Eq.	equivalents
ESI	electrospray ionization
Et	ethyl
et al.	*et alii* (Latin: and others)
Fmoc	fluorenylmethyloxycarbonyl
FT	Fourier transform
g	grams
Grubbs II	Grubbs 2nd generation catalyst
h	hours
Hex	hexyl
HFIPA	1,1,1,3,3,3-hexafluoro-*iso*-propanol
HMDS	*bis*(trimethylsilyl)amide
Hoveyda-Grubbs II	Hoveyda-Grubbs 2nd generation catalyst
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
$h\nu$	photon excitement
i	iso
Ipc	di*iso*pinocampheyl
IR	infra-red (spectroscopy)
$kcalmol^{-1}$	kilocalories per mole
L	litre / generic ligand
m	milli (prefix: 10^{-3}) / metres (unit)
M	mega (prefix: 10^6) / molar (solution)
m.p.	melting point
m/z	mass to charge ratio
maj	major
Me	methyl
Mes	2,4,6-trimethylphenyl

MIB	3-exo-morpholinoisoborneol
min	minute(s) / minor
mol	moles
Ms	methanesulfonyl
MS	mass spectrometry
MTPA	α-methoxy-α-trifluoromethylphenylacetate
n	normal (unbranched)
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance (spectroscopy)
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu^-	generic nucleophile
p-	para
pH	$-\log_{10}[H^+]$
Ph	phenyl
pK_a	$-\log_{10}[K_a]$
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
rac	racemic
RCM	ring-closing metathesis
R_f	retention factor
rt	room temperature
T	temperature
t, *tert*	tertiary
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCC	*trans*-2-(α-cumyl)cyclohexanol
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
δ	chemical shift, ppm
Δ	heated at reflux
μ	micro (prefix: 10^{-6})
ν_{max}	infra-red absorption maximum, cm^{-1}

Chapter 1:
Introduction

1.1 The Piperidine Core in Natural Products

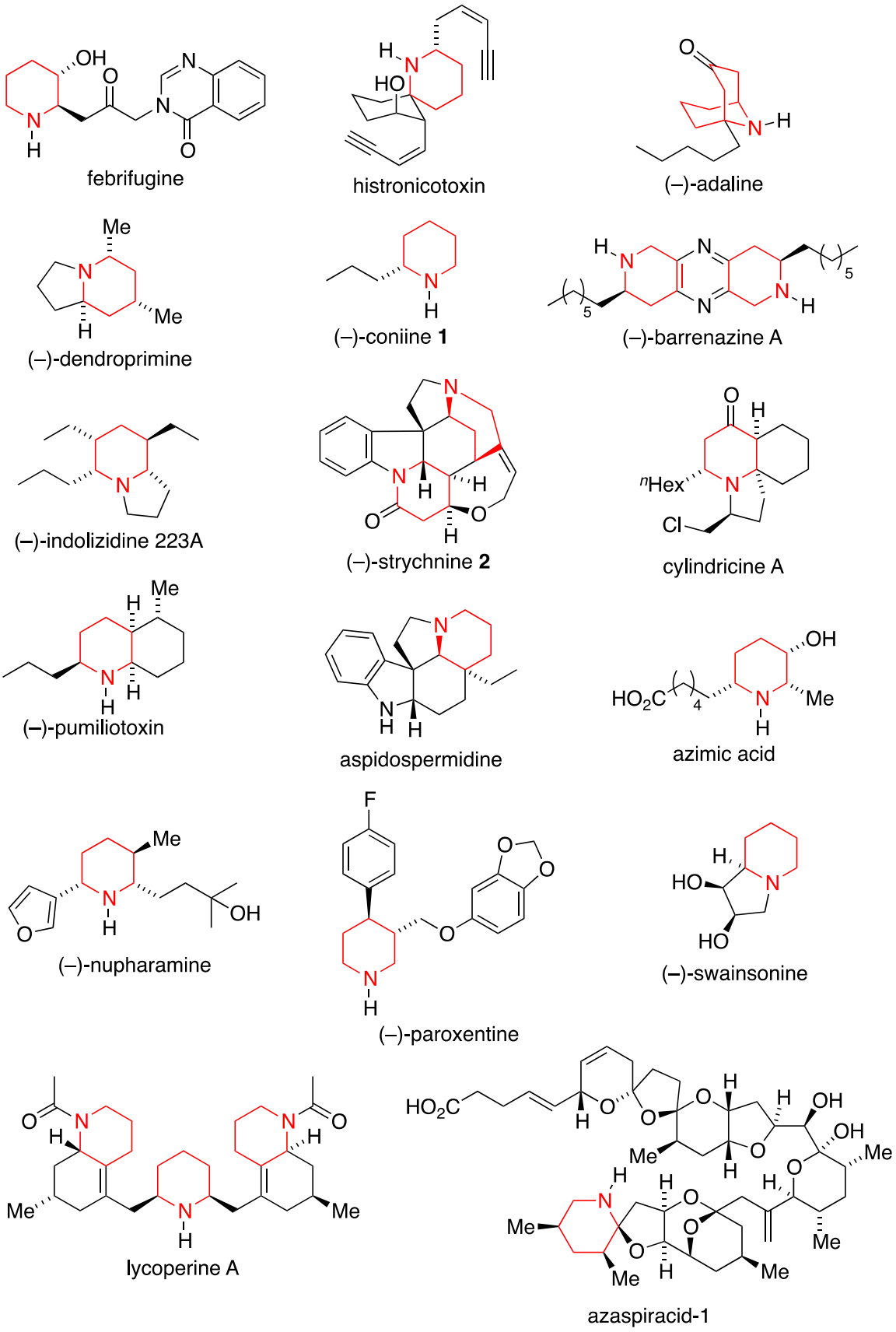
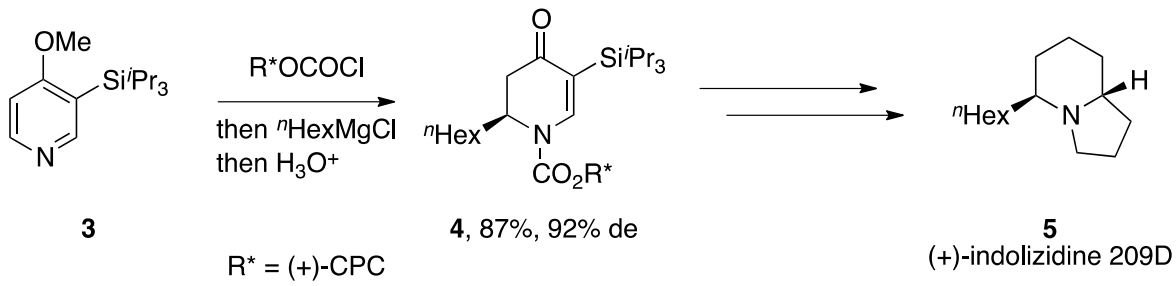


Figure 1.1: *Piperidine-containing natural products.*

The ubiquitous nature of the piperidine core in natural product chemistry can be demonstrated by a brief survey of the literature.[1-5] A vast array of different structures contain these motifs, with diversity arising from the number of substituents around the core, the identity of these substituents, their relative stereochemistry and the level of saturation (Figure 1.1). The complexity ranges from the monosubstituted hemlock alkaloid (–)-coniine **1**, to the cage-structure of (–)-strychnine **2**, of which Sir Robert Robinson remarked: *"For its molecular size, it is the most complex substance known."*[6]

The central role of the reduction of substituted pyridinium salts in the preparation of piperidine-containing natural products is clear.[7-11] Reduction of a pyridinium salt, by nucleophilic addition or other means, generates either a dihydropyridine or a dihydropyridone precursor (see Section 1.3 and 1.5). These versatile intermediates[12, 13] can be converted to substituted piperidines efficiently, by a variety of transformations.[14, 15] For example, in Comins' asymmetric synthesis of indolizidine 209D, diastereoselective addition of hexylmagnesium chloride to the chiral pyridinium salt, generated *in situ* from pyridine **3** and (1*S*, 2*R*, 4*S*)-2-(1-methyl-1-phenylethyl)-4-(2-propyl)cyclohexyl ((+)-CPC) chloroformate, provided dihydropyridone **4**. A further four transformations provided the target indolizidine **5**, in an overall yield of 35% (Scheme 1.1).[16]

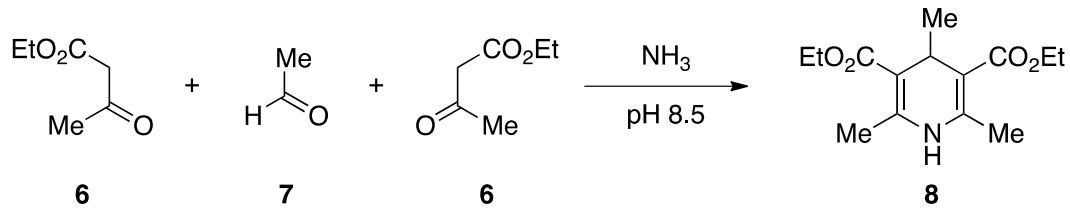


Scheme 1.1: *Utility of dihydropyridones in natural product synthesis.*

Given the crucial role played by dihydropyridines and dihydropyridones in the synthesis of substituted piperdines, their efficient and, preferably asymmetric, preparation is of great interest to synthetic organic chemists.

1.2 Dihydropyridines

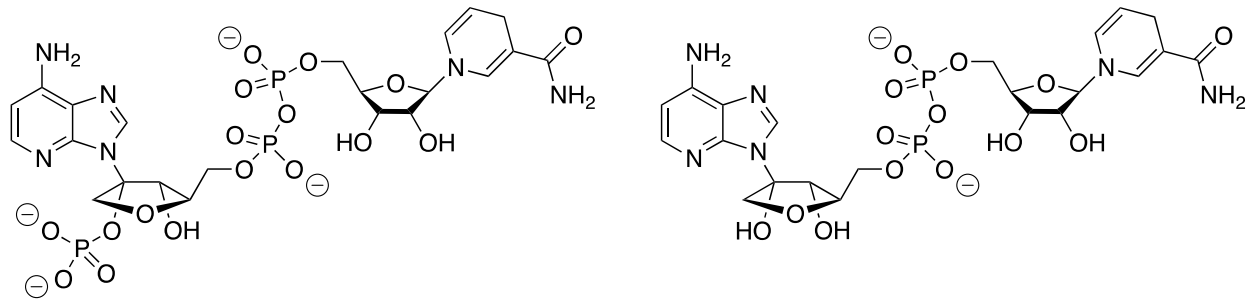
In 1882, Hantzsch reported the first isolation of a dihydropyridine, *en route* to the pyridine synthesis, which now bears his name.[17] Condensation of two equivalents of β-keto ester **6** with aldehyde **7** and ammonia provided dihydropyridine **8** (Scheme 1.2). The instability of dihydropyridines, primarily due to the ease of oxidation in air to the corresponding aromatic pyridine, necessitated the use of electron withdrawing substituents, such as esters, to facilitate isolation.



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

Scheme 1.2: *Classical Hantzsch dihydropyridine synthesis.*

The biological importance of dihydropyridines was highlighted in the 1930s, with the discovery of nicotinamide adenine dinucleotide phosphate (NADPH) **9** (Figure 1.2).[18, 19] This was shown to be a crucial reducing agent in biosynthesis, with the ability to donate a hydride to a biomolecule, leaving behind the oxidized $NADP^+$, containing a cationic pyridinium core. The closely related compound, NADH **10**, was shown to play an important role in the biosynthesis of ATP.

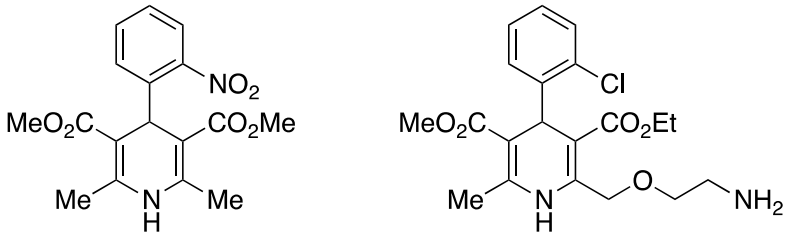


9 **10**

Figure 1.2: *NADPH **9** and NADH **10**.*

The discovery that 1,4-dihydropyridones were effective calcium channel antagonists led to extensive research into dihydropyridones from the pharmaceutical sector and they are now used for the treatment of hypertension.[20] Two successful clinical candidates were nifedipine **11** and

amlodipine **12**, both based upon the *bis*-ester motif formed in the Hantzsch dihydropyridine synthesis (Figure 1.3).



11 nifedipine **12** amlodipine

Figure 1.3: *The dihydropyridine core in pharmaceutical products.*

The important biological and medicinal properties of dihydropyridines, coupled with their utility as intermediates in natural product synthesis (see Section 1.3.3) has made dihydropyridines an important class of molecule in organic research.

1.3 The Synthesis of Dihydropyridines

The various syntheses of dihydropyridines can be classified into one of three categories:

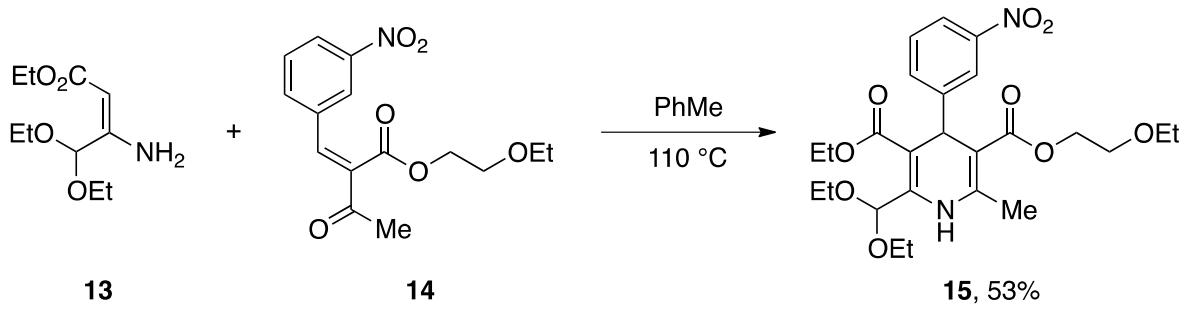
1. Ring construction.
2. Reductive processes.
3. Nucleophilic addition to pyridines or pyridinium salts.

Although nucleophilic addition to pyridines or pyridinium salts may be thought of as a sub-class of reductive processes, it will be considered separately due to the substantial volume of research in this area.

1.3.1 Ring Construction

In Hantzsch's pioneering synthesis of dihydropyridines, the products formed were necessarily C_2 symmetrical, due to the *in situ* coupling of two equivalents of the same dicarbonyl **6** with aldehyde **7** and ammonia (Scheme 1.2). Unsymmetrical dihydropyridines were accessible by a convergent route, involving pre-formation of enamine **13** and aldol product **14**. Their subsequent

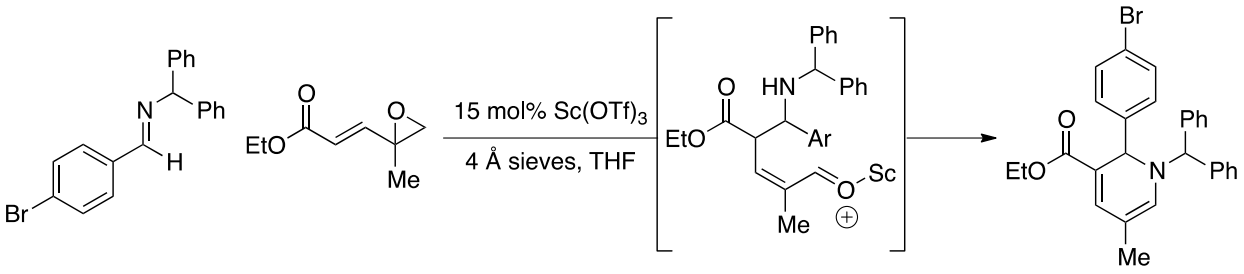
combination provided unsymmetrical dihydropyridine **15**, which was found to act as a calcium channel antagonist in animals (Scheme 1.3).[21]



13 **14** **15**, 53%

Scheme 1.3: *Hantzsch synthesis of non-symmetrical dihydropyridines.*

Lautens developed a variant of the classical dihydropyridine synthesis *via* the condensation of a 1,5-dicarbonyl with ammonia. In this vinylogous imino-aldol reaction, vinyloxirane **17** acted as a masked dienolate and scandium triflate as a Lewis acid.[22] The Lewis acid prompted rearrangement of **17**, *via* a 1,2-hydride shift, to a dienolate which, after double bond isomerization from *trans* to *cis*, underwent an aldol reaction with imine **16** to give the adduct **18**. Cyclization and subsequent dehydration gave the dihydropyridine **19** (Scheme 1.4).

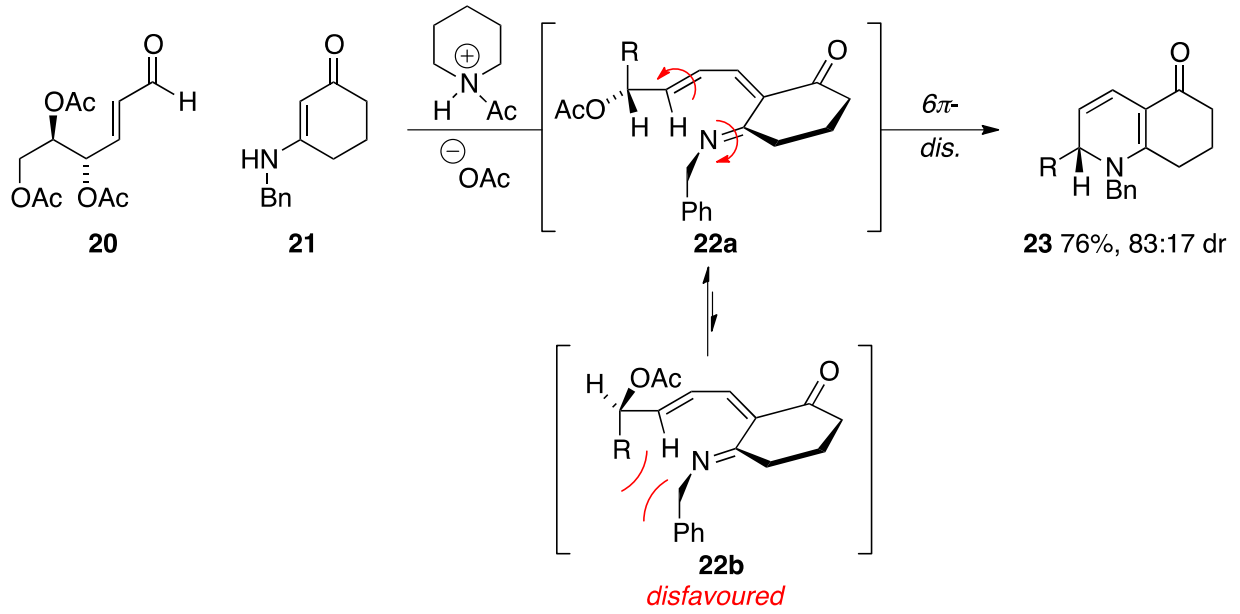


16 **17** **18** **19**

Scheme 1.4: *Lautens' synthesis of 1,2-dihydropyridines.*

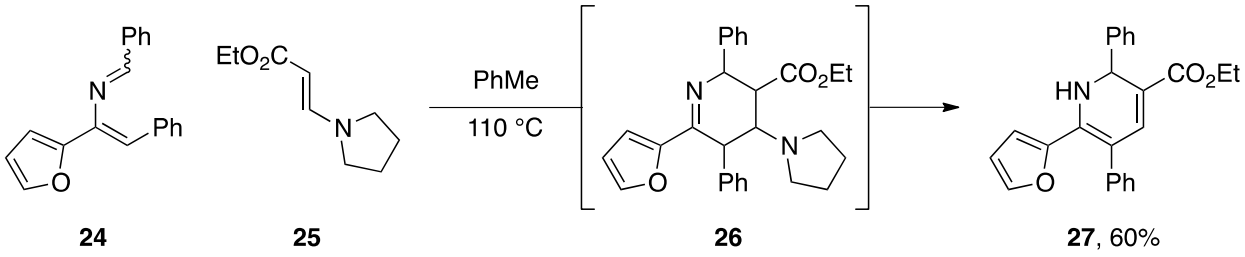
Dihydropyridines may also be accessed effectively using a pericyclic strategy. The 6π *aza*-electrocyclic ring closure of *aza*-trienes has been used to access 1,2-dihydropyridines.[23] Hsung subsequently reported an expansion of this work, involving the incorporation of a stereodefined side-chain on enal **20**, leading to a torquoselective electrocyclic ring closure, furnishing dihydropyridine **23** (Scheme 1.5).[24] The *aza*-triene could exist in two conformations with minimized allylic strain, **22a** and **22b**. Hsung proposed that **22b** was disfavoured by the remote steric interaction between the R group and the *N*-benzyl group. With *aza*-triene **22a** as the preferred conformation, the disrotatory ring closure illustrated below was favoured, as

disrotatory motion in the opposite direction would bring the R group into close contact with the *N*-benzyl group.



Scheme 1.5: *Hsung's synthesis of 1,2-dihydropyridines.*

The Diels-Alder reaction of 2-*aza*-dienes, such as **24**, with enamino ester **25** has been used by Palacios to prepare 1,2-dihydropyridines.[25] Elimination of pyrrolidine under the reaction conditions transformed the tetrahydropyridine Diels-Alder adduct **26** into dihydropyridine **27** (Scheme 1.6).

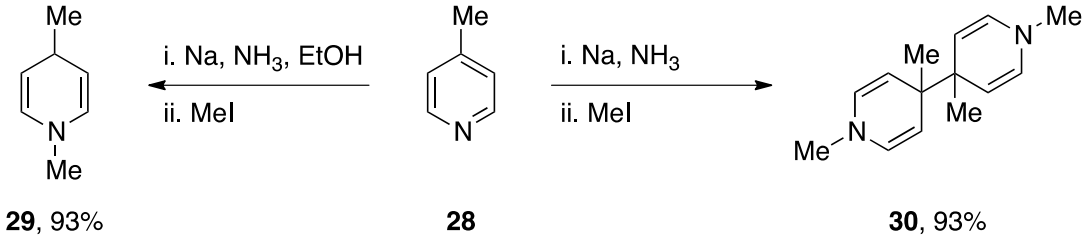


Scheme 1.6: *Palacios' synthesis of 1,2-dihydropyridines.*

1.3.2 Reductive Processes

Although reports on the use of alkali metals for the reduction of pyridines dates back to the early 20th century, only 1,5-dicarbonyl products were detected in these studies.[26-28] Birch first reported the isolation of a dihydropyridine from the dissolving metal reduction of 4-methyl substituted

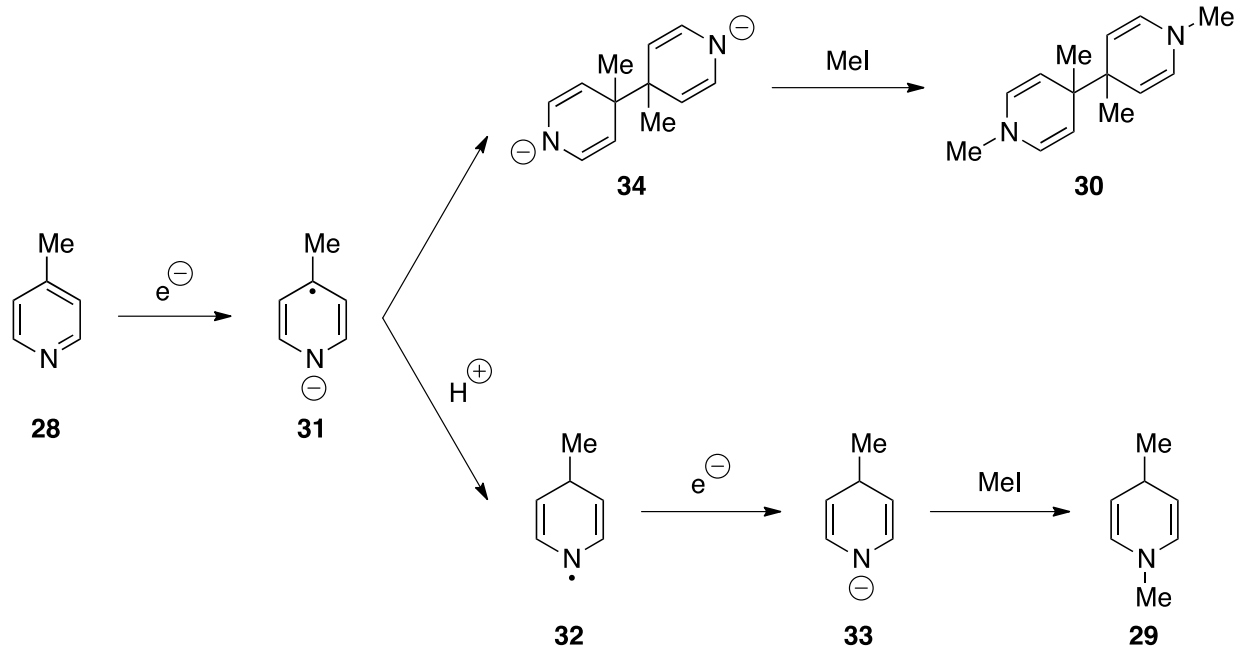
pyridine **28** in 1975.[29] If ethanol was used as a co-solvent, 1,4-dihydropyridine **29** was isolated however, in the absence of ethanol, dimer **30** was isolated instead (Scheme 1.7).



29, 93% **28** **30**, 93%

Scheme 1.7: *Birch reduction of pyridine **28**.*

The mechanism for the formation of both products first involved the addition of an electron to give radical anion **31**. In the presence of ethanol, **31** was protonated to give radical **32**, which then accepted a second electron to give anion **33**, which was subsequently quenched with methyl iodide. In the absence of ethanol, protonation of **31** could not occur and addition of a second electron to **31** was unfavourable as it would lead to a poorly stabilized dianion. Therefore, **31** dimerised to give dianion **34**, which was then trapped by the external electrophile (Scheme 1.8).

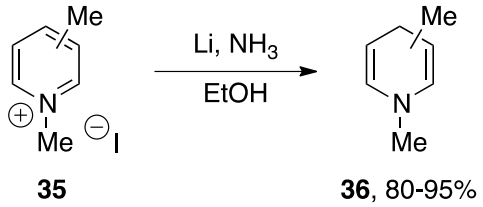


28 **31** **34** **30** **32** **33** **29**

Scheme 1.8: *Proposed mechanism for the formation of dihydropyridines **29** and **30**.*

Birch found that this reaction was not reproducible, with a mixture of 1,2- and 1,4-dihydropyridines being isolated, alongside the tetrahydropyridine and the fully saturated piperidine, due to over reduction. Boersma found that the reduction of pyridinium salt **35** was far

more consistent, giving 1,4-dihydropyridone **36** in good yield, although the products needed to be handled in an oxygen-free environment to prevent decomposition (Scheme 1.9).[30]



35 **36**, 80-95%

Scheme 1.9: *Boersma's reduction of pyridinium salt **35**.*

Donohoe hypothesized that the problems encountered during the isolation of these dihydropyridines could be addressed by increasing the electron deficiency of the ring.[31] To this end, a range of six isomeric pyridine di-esters was prepared (Figure 1.4).

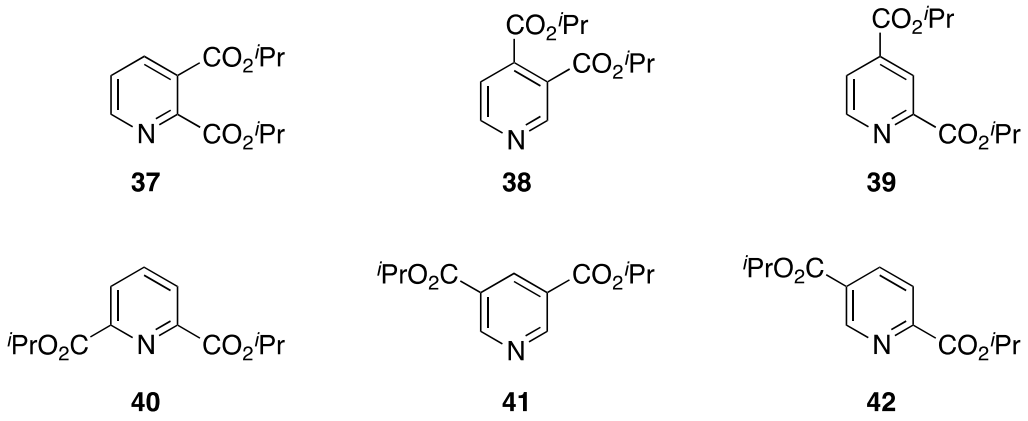
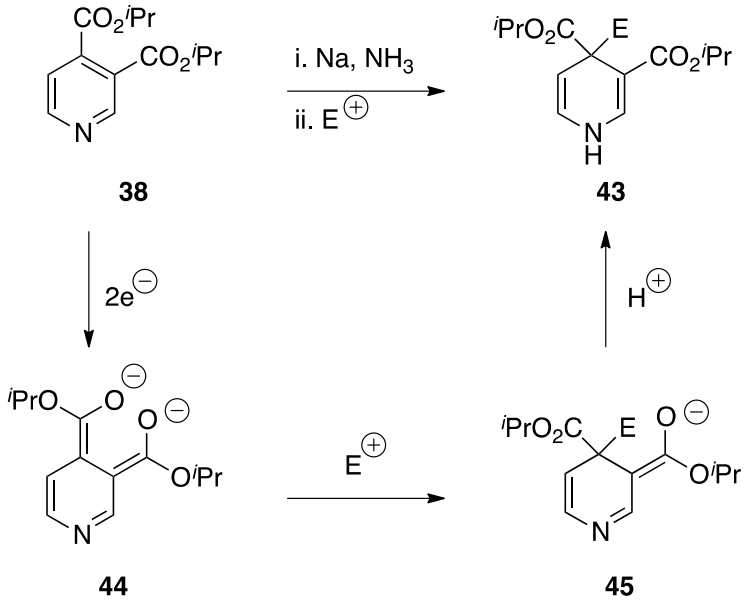


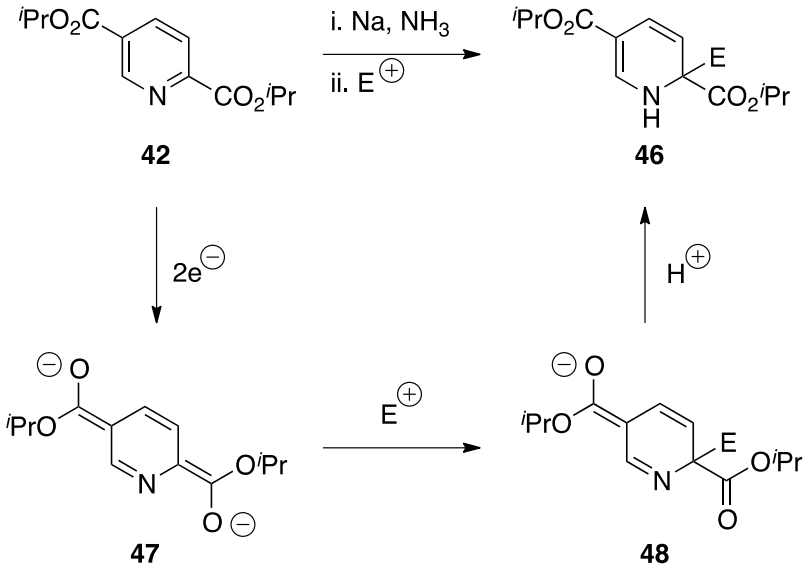
Figure 1.4: *Donohoe's range of di-esters for Birch reduction.*

Upon exposure of these pyridines to classical Birch reduction conditions, only pyridines **38** and **42** were reduced cleanly, yielding the 1,4- and 1,2-dihdropyridines **43** and **46** respectively. Analysis of the mechanism of reduction revealed that the reduction of **38** and **42** was successful because, on the addition of two electrons, a stable *bis*-enolate was formed (Scheme 1.10 and 1.11). For the 3,4-isomer **38**, the more reactive enolate was quenched first by the addition of one equivalent of electrophile, followed by subsequent protonation of the remaining enolate to provide 1,4-dihydropyridine **43** (Scheme 1.10). These products were obtained in excellent yields and a range of electrophiles could be used to trap the dianion **44**.



Scheme 1.10: *Proposed mechanism for reduction of pyridine **38**.*

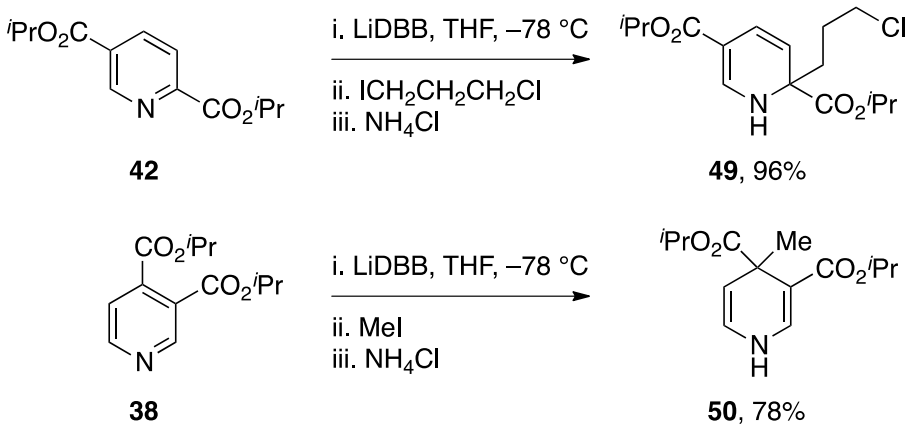
A similar mechanism could be used to explain the formation of 1,2-dihydropyridine **46**. Addition of two electrons to pyridine **42** gave the stable *bis*-enolate **47**, which was quenched in succession with an electrophile and a proton to provide dihydropyridine **46** (Scheme 1.11).



Scheme 1.11: *Proposed mechanism for reduction of pyridine **42**.*

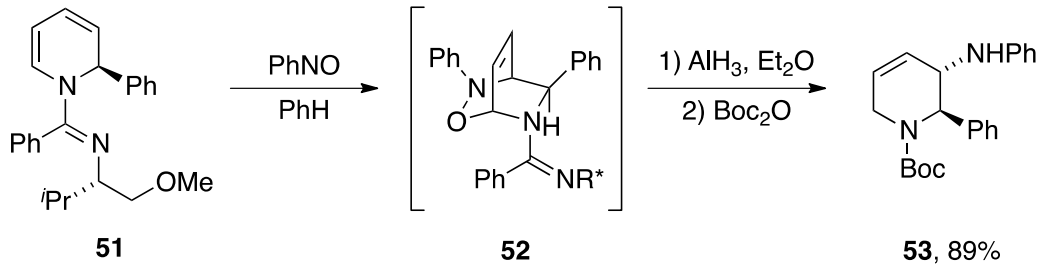
In addition, Donohoe also found that pyridines **38** and **42** were reduced in high yield using ammonia-free Birch reduction conditions, with dissolving lithium and 4,4'-di-*tert*-butylbiphenyl as the electron carrier (Scheme 1.12).[32-34] These conditions were advantageous because the use of a poorly nucleophilic aromatic radical anion, instead of the highly nucleophilic ammonia as

the electron carrier, allowed the use of electrophiles incompatible with classical Birch reduction strategies (reactive electrophiles such as benzyl iodide, enolizable aldehydes and chloroformates were consumed by the ammonia solvent prior to reaction with the desired anion).



Scheme 1.12: *Donohoe's ammonia-free Birch reduction of pyridines **38** and **42**.*

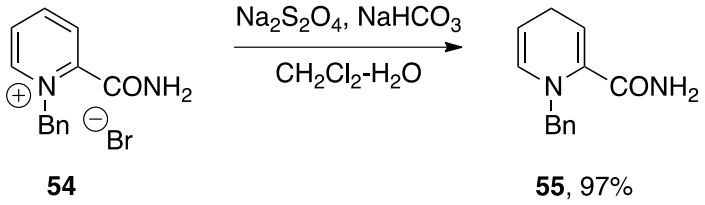
While Donohoe found that increasing the electron deficiency of dihydropyridines enhanced their stability, Charette described the stabilization of dihydropyridines, prepared using a nucleophilic addition strategy (see Section 1.3.3), using a Diels-Alder reaction with nitrosobenzene.[35] Treatment of dihydropyridine **51** with nitrosobenzene gave the [2,2,2]-bicyclo-adduct **52**. Reduction of both the N-O bond and the aminal, as well as removal of the chiral auxiliary, was achieved by treatment with alane. Subsequent protection of the secondary amine gave tetrahydropyridine **53** as a single diastereomer. The relationship between the 2- and 3-substituents of **53** was *trans*- due to the approach of nitrosobenzene from the least hindered face of dihydropyridine **51** (Scheme 1.13).



Scheme 1.13: *Charette's trapping of unstable dihydropyridine **51** by a Diels-Alder reaction.*

The use of sodium dithionite ($Na_2S_2O_4$) as a reductant is known to allow the conversion of pyridinium salts to 1,4-dihydropyridones.[36] Lavilla has exploited this methodology in his efforts

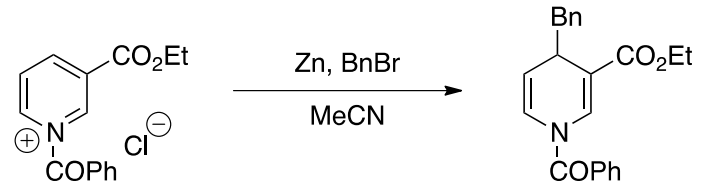
to prepare NADH analogues, such as **55** (Scheme 1.14).[37] The reduction is believed to occur through intramolecular hydride transfer from the intermediate sulfinic ester, though a single electron transfer mechanism has also been postulated.[38]



54 **55**, 97%

Scheme 1.14: *Lavilla's reduction of pyridinium salt **54**.*

Proctor utilized single electron transfer by metallic zinc for the reductive benzylation of pyridinium salt **56** (Scheme 1.15).[39] The reaction was found to selectively form the 1,4-dihydropyridine **57**, although traces of the 1,2-isomer and dimerization products were also observed. Poor yields of dihydropyridine were obtained when electrophiles other than benzyl bromide were used; reactions either did not proceed, or dimerization of the radical intermediates occurred. Furthermore, if the pyridinium salt included an alkyl group on nitrogen, rather than an acyl group, the resulting dihydropyridones were highly unstable and *in situ* hydrogenation over platinum oxide was required to reduce the core to a stable piperidine, enabling isolation.



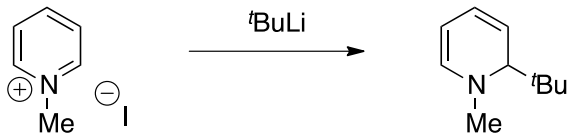
56 **57**, 68%

Scheme 1.15: *Proctor's reduction of pyridinium salt **56**.*

1.3.3 Nucleophilic Addition to Pyridines or Pyridinium Salts

The addition of organometallic reagents to both *N*-alkyl and *N*-acyl pyridinium salts is well documented in the literature. However, the regioselectivity of addition of the nucleophilic species at either the 2-position or the 4-position can complicate matters. In general, "hard" nucleophiles, such as organolithiums, favour attack at the 2-position, whereas "soft" nucleophiles, such as organocuprates, favour attack at the 4-position. It should be noted that this selectivity has been found to be highly dependent on the effects of solvent and counter-ion,

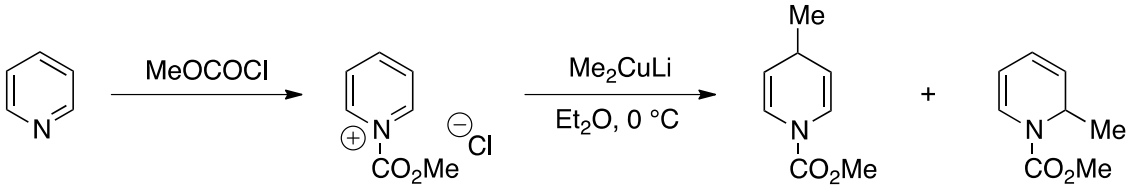
where decreased or even reversed selectivity may be observed. Francis and co-workers found that *tert*-butyllithium could be added regioselectively to *N*-methyl pyridinium salt **58**, in moderate to good yield depending on the substitution pattern, with none of the 1,4-dihydropyridine observed (Scheme 1.16).[40]



58 **59**, 80%

Scheme 1.16: *Francis' regioselective addition of* tert-*butyllithium to pyridinium salt **58**.*

Conversely, Piers found that lithium dialkyl- and diarylcuprates demonstrated good levels of selectivity on addition to *N*-acyl pyridinium salt **61**, generated *in situ* by the reaction of pyridine with methyl chloroformate, at the 4-position. A range of 1,4-dihydropyridines such as **62** were obtained in good yield (Scheme 1.17).[41]

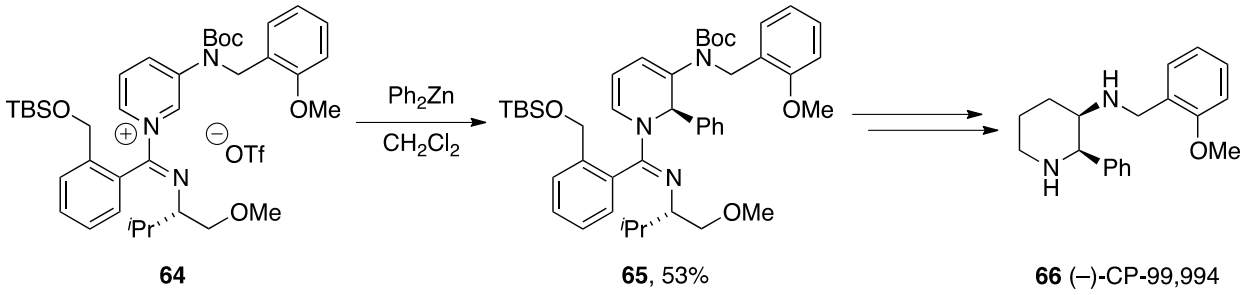


60 **61** **62** **63**

Combined yield: 81%
Ratio **62**:**63** = 98:2

Scheme 1.17: *Piers' regioselective addition to an* N-*acyl pyridinium salt.*

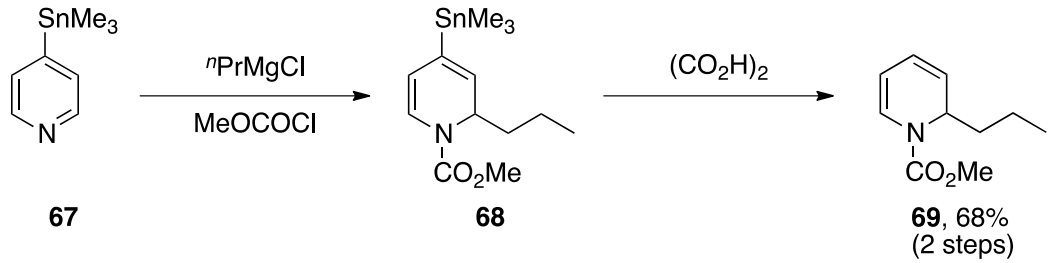
Despite the highly regioselective examples discussed above, many nucleophilic additions to pyridinium salts give mixtures of 1,2- and 1,4-dihydropyridines and predicting the regioselectivity of addition is an undisciplined area. For example, in Charette's synthesis of (–)-CP-99,994 **66**, the "soft" diphenylzinc was found to add regioselectively to pyridinium salt **64** at the 2-position, due to coordination of the organozinc reagent to the imidate nitrogen lone pair (see Section 1.5.3). The diastereoselectivity of addition was guided by the chiral auxiliary on nitrogen (Scheme 1.18).[42]



64 **65**, 53% **66** (–)-CP-99,994

Scheme 1.18: *Regioselective organozinc addition in Charette's synthesis of (–)-CP-99,994* ***66****.*

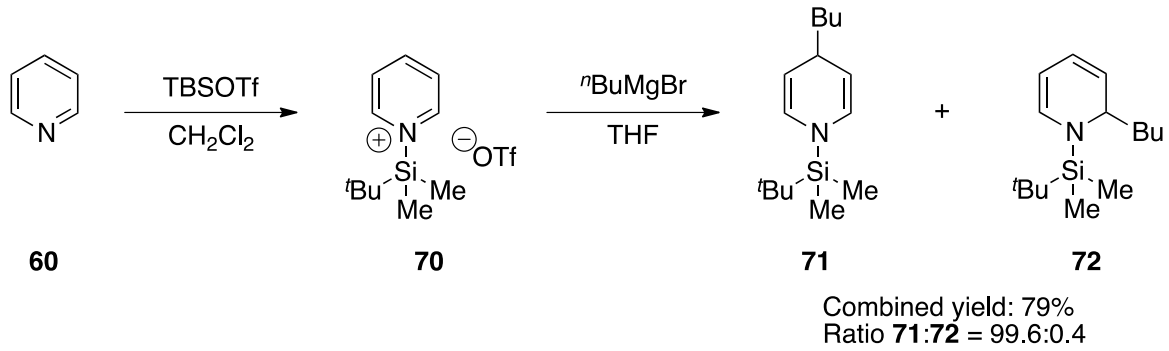
Various strategies have been developed to give exclusive reaction at either the 2- or 4- position. Comins used a trimethyltin moiety as a removable blocking group for the 4-position (Scheme 1.19).[43] The addition of propylmagnesium chloride to the 2-position of the *N*-acyl pyridinium salt, generated *in situ* by the reaction of pyridine **67** with methyl chloroformate, gave 1,2-dihydropyridine **68** as a single regioisomer. When pyridine itself was exposed to the same conditions, a mixture of 1,2- and 1,4-dihydropyridines was observed in a ratio of approximately 2:1. Subsequent destannylation was achieved by treatment of **68** with oxalic acid and dihydropyridine **69** was obtained in 68% yield over 2 steps.



67 **68** **69**, 68% (2 steps)

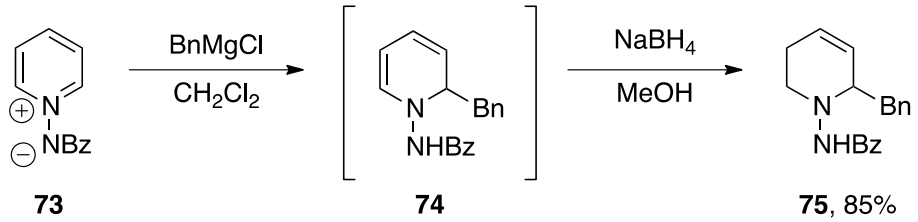
Scheme 1.19: *Comins' trimethyltin blocking group strategy.*

Akiba prepared the *N*-TBS-protected pyridinium salt **70** and found that the bulk of the silyl group disfavoured the addition of Grignard reagents at the 2-position. The 1,4-dihydropyridine **71** was formed in good yield with greater than 99% regioselectivity (Scheme 1.20).[44]



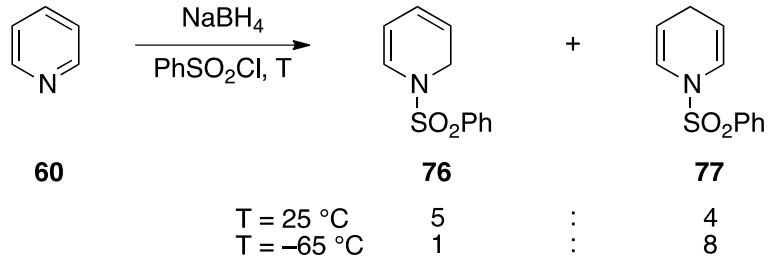
Scheme 1.20: *Akiba's* N-*TBS blocking/activating group strategy.*

Charette found that the *N*-imino group of *N*-benzoyliminopyridinium ylid **73** acted as an efficient directing group for addition of Grignard reagents at the 2-position (Scheme 1.21).[45] Even benzylmagnesium chloride, a reagent shown by Marazano to favour addition at the 4-position,[46] added to the 2-position with >95:5 regioselectivity. The dihydropyridine products were found to be highly unstable with respect to air oxidation and were reduced by methanolic sodium borohydride to the corresponding tetrahydropyridines, such as **75**.



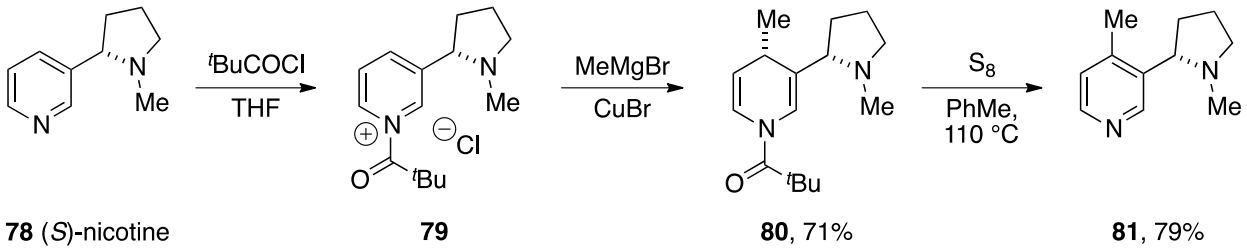
Scheme 1.21: *Charette's directing group strategy.*

The regioselectivity of hydride addition to pyridinium salts is known to be just as complex as organometallic addition, with choice of reagent, solvent and temperature exhibiting a profound effect on this selectivity. Knaus has demonstrated that, in the reduction of *N*-sulfonyl pyridinium salts, the 1,2-dihydropyridine **76** was favoured by a ratio of 5:4 at room temperature, whereas the 1,4-dihydropyridine **77** was favoured by 8:1 at –65 °C (Scheme 1.22).[47]



Scheme 1.22: *Knaus' study of the temperature dependence of hydride addition regioselectivity.*

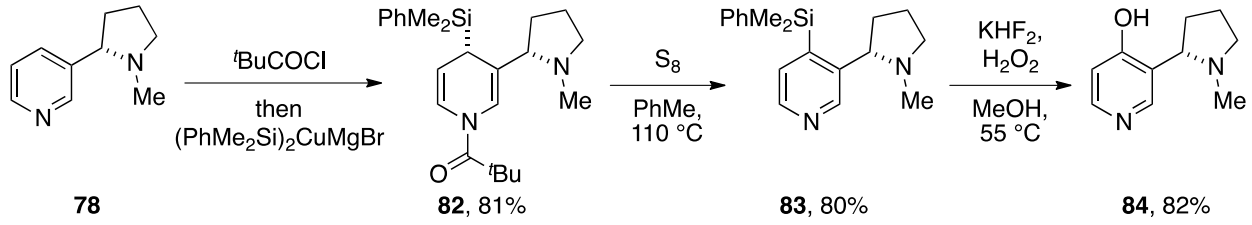
Many diastereoselective approaches to enantioenriched dihydropyridines or dihydropyridones involve the use of a chiral auxiliary on nitrogen, which both activates the pyridinium core to nucleophilic attack and controls the facial selectivity of addition (see Charette's work in Scheme 1.18 above and Section 1.5.3). However, a number of approaches have appeared in the literature using a chiral auxiliary bonded to the carbon skeleton of the pyridine ring. Nicotine **78**, the toxic and highly addictive psychoactive ingredient of tobacco,[48] has been shown to demonstrate beneficial effects on patients suffering from Parkinson's disease, anxiety, schizophrenia, ulcerative colitis and a variety of other CNS disorders.[49] Comins, in an attempt to prepare nonaddictive nicotine derivatives that still show similar health benefits, has demonstrated the highly regio- and diastereoselective addition to the *N*-acyl pyridinium salt of (*S*)-nicotine (Scheme 1.23).[50] The use of chloroformate reagents led to reaction of the pyrrolidine nitrogen with the electrophile,[51] however the more hindered, less reactive pivaloyl chloride reacted selectively with the pyridine nitogen. Addition of freshly prepared organocuprates to pyridinium salt **79** gave the corresponding dihydropyridines, such as **80**, as single regio- and diastereoisomers, with the diastereoselectivity of addition controlled by chelation of the pyrrolidine nitrogen lone pair to the organocuprate. Re-oxidation with elemental sulfur provided the 4-substituted nicotine derivative **81**.



Scheme 1.23: *Comins' preparation of 4-substituted (*S*)-nicotine derivatives.*

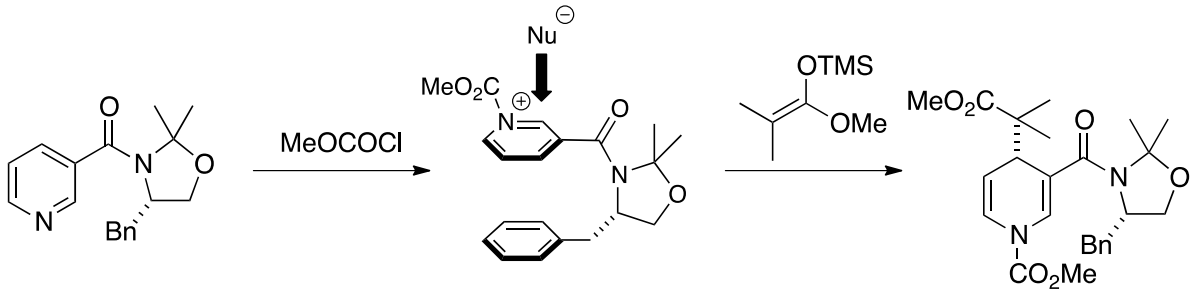
In the same study, Comins was also able to add a silicon-nucleophile to pyridinium salt **79**. After reoxidation to the nicotine derivative **83**, a Tamao-Fleming oxidation allowed the synthesis of 4-

hydroxy substituted nicotine **84** (Scheme 1.24).[52] Comins noted the potential of derivatives of pyridine **84** to undergo directed lithiation reactions, allowing further substitution of the pyridine ring.



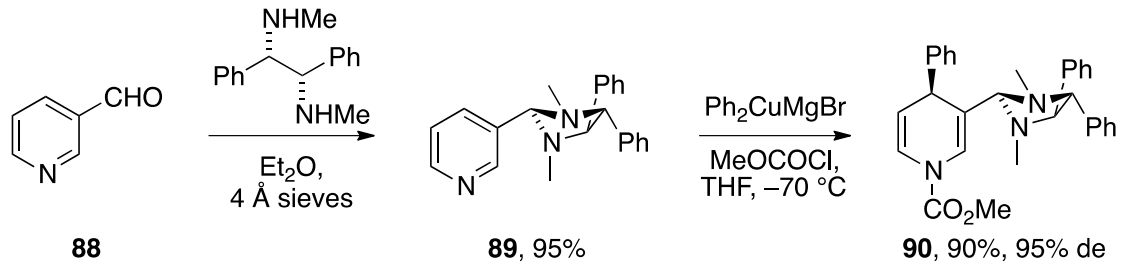
Scheme 1.24: *Comins' preparation of 4-hydroxy substituted nicotine **84**.*

In a similar study, Yamada showed that the intramolecular π-π stacking interaction between the pyridinium cation and a tethered benzyl group on pyridinium salt **86** allowed almost complete control of the diastereoselectivity of addition of silyl enol ethers (Scheme 1.25).[53] The strong π-π interaction was demonstrated by X-ray crystallography on pyridinium salt **86** and, with the aromatic ring shielding one face of the pyridinium cation, diastereoselective addition was successful. Although small amounts of the 1,6-adducts were observed, regioselectivity was generally high, favouring the 1,4-addition products.



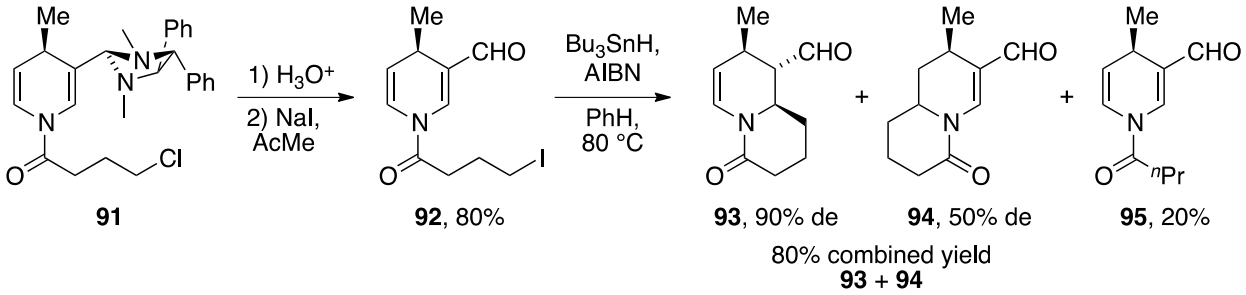
Scheme 1.25: *Yamada's diastereoselective synthesis of dihydropyridine **87**.*

Mangeney has reported the preparation of chiral aminal **89** from 3-formylpyridine **88** and the reaction of its *N*-acyl pyridinium salt with organocuprate reagents.[54] Good regioselectivity was observed for 1,4-addition, which was attributed to the soft characteristics of organocuprates (*vide supra*). Furthermore, the 1,4-dihydropyridines, such as **90**, were obtained in high diastereomeric excess (Scheme 1.26). The chiral auxiliary could then be removed by acidic hydrolysis.



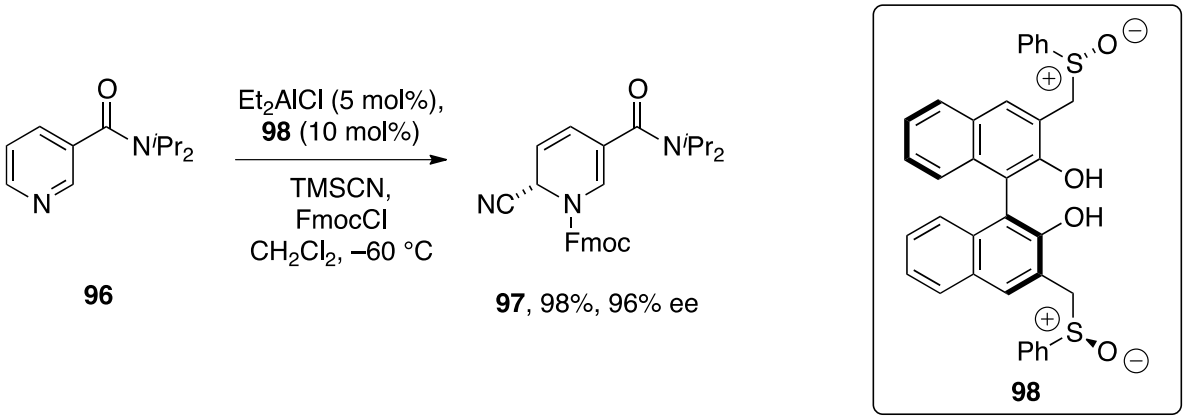
Scheme 1.26: *Mangeney's diastereoselective formation of dihydropyridine **90**.*

Mangeney has attempted to use halogenated *N*-acyl groups to induce a radical cyclization to provide bicycles, such as **93** (Scheme 1.27).[55] Although the diastereoselectivity of cyclization was promising, low regioselectivity was observed and bicycles **93** and **94** were formed in a 2:1 ratio. In addition, a significant amount of the reduced, uncyclized material **95** was also observed.



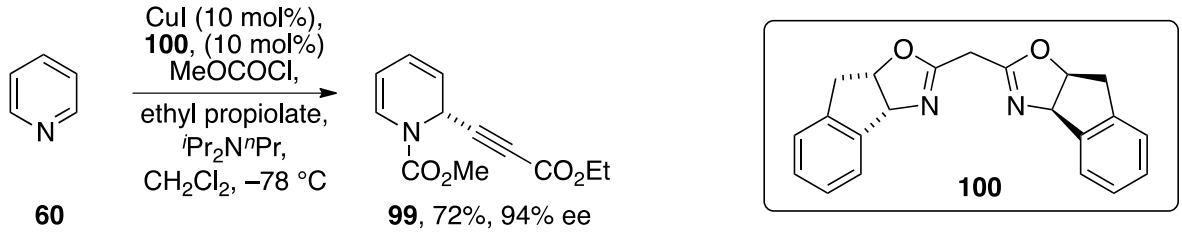
Scheme 1.27: *Mangeney's attempted diastereoselective radical cyclization.*

In 2004, Shibasaki reported the first catalytic asymmetric addition to a pyridinium salt, with all previous examples of asymmetric addition to pyridinium salts being controlled by a chiral auxiliary (see Charette's example above and Section 1.5.3). Nicotinic acid derivatives, such as **96**, were found to undergo a highly enantioselective Reissert reaction with trimethylsilyl cyanide, under the influence of the chiral catalyst generated from diethylaluminium chloride and ligand **98** (Scheme 1.28).[56] The corresponding dihydropyridines, such as **97**, were generated in excellent yield and enantiomeric excess. Shibasaki also noted that high regioselectivity was observed for addition at the 6-position, with small amounts of addition at *C*-2 and no detectable addition at *C*-4.



Scheme 1.28: *Shibasaki's asymmetric addition to nicotinic acid derivatives.*

Ma has also reported a catalytic asymmetric addition to an *N*-acyl pyridinium salt, generated *in situ* from pyridine and methyl chloroformate (Scheme 1.29).[57] The use of catalytic amounts of copper(I) iodide and chiral ligand **100** enabled the asymmetric addition of ethyl propiolate to **60** in high yield and enantioselectivity. Furthermore, complete regioselectivity for addition at the 2-position was observed; this addition of a "soft" organocuprate reagent at the 2-position highlighting the uncertainties involved in predicting the regioselectivity of addition to pyridinium salts.

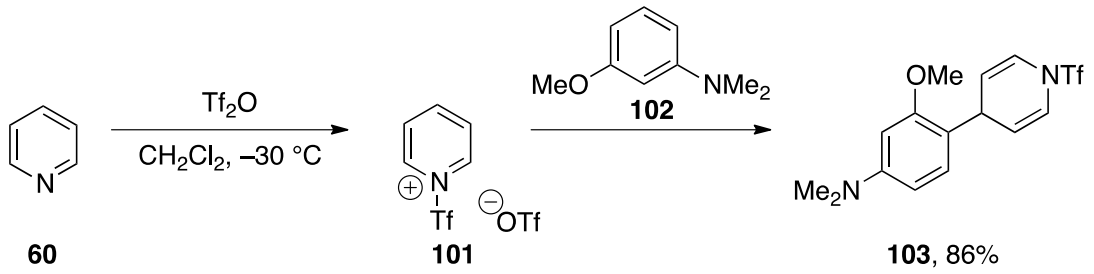


Scheme 1.29: *Ma's asymmetric addition of terminal alkynes to an* N*-acyl pyridinium salt.*

Although the work of Ma and Shibasaki represents an exciting new development in the synthesis of dihydropyridines, their methods are far from generally applicable, with small changes in the structure of the substrate or nucleophile giving much-reduced enantioselectivity or racemic products.

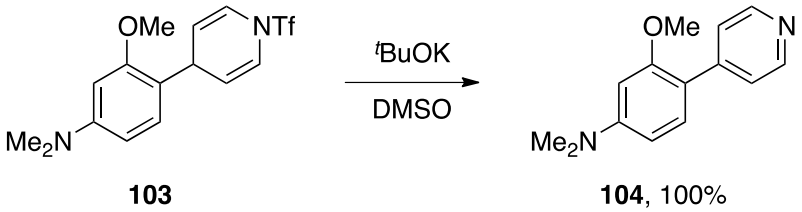
Much of the work detailed above requires the use of reactive organometallic nucleophiles, however Corey has shown that *N*-triflyl pyridinium salts, such as **101**, are sufficiently electrophilic that they may be attacked by weak nucleophiles, such as arene **102** (Scheme 1.30).[58] The high electrophilicity of the pyridinium cation of *N*-triflyl pyridinium salts was

rationalized by considering the strong electron withdrawing character of the CF_3SO_2 group and the high regioselectivity for attack at the 4-position was due to the steric shielding of the 2- and 6-positions by the *N*-sulfonyl group.



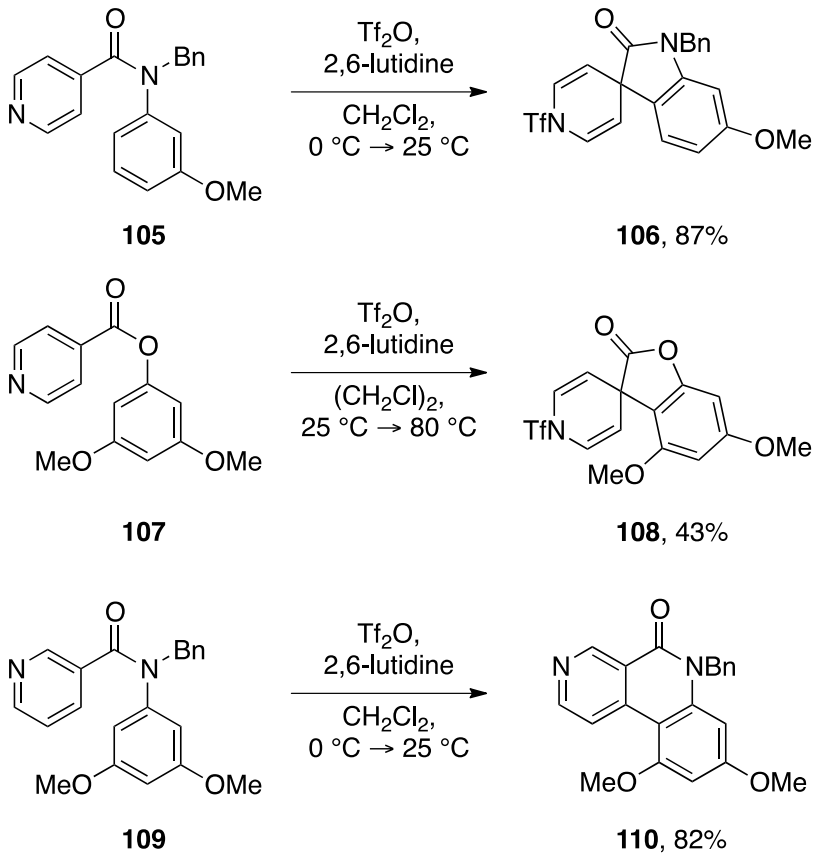
Scheme 1.30: *Corey's addition of non-activated nucleophiles to* N-*triflyl pyridinium salts.*

In addition, Corey also found that base promoted elimination of trifluoromethanesulfinic acid from dihydropyridine **103** provided the corresponding 4-arylpyridine **104** in quantitative yield.



Scheme 1.31: *Regeneration of the pyridine.*

Clayden expanded Corey's methodology to enable the preparation of spirocyclic dihydropyridines by activation of pyridine **105**, bearing a tethered latent nucleophile at the 4-position, with triflic anhydride (Scheme 1.32).[59] By using a tertiary amide linker, which favoured the reactive *cis*-conformation of the two rings,[60] and by addition of 2,6-lutidine as a base to consume the triflic acid produced as a by-product, excellent yields of the desired spirocycle **106** were obtained.



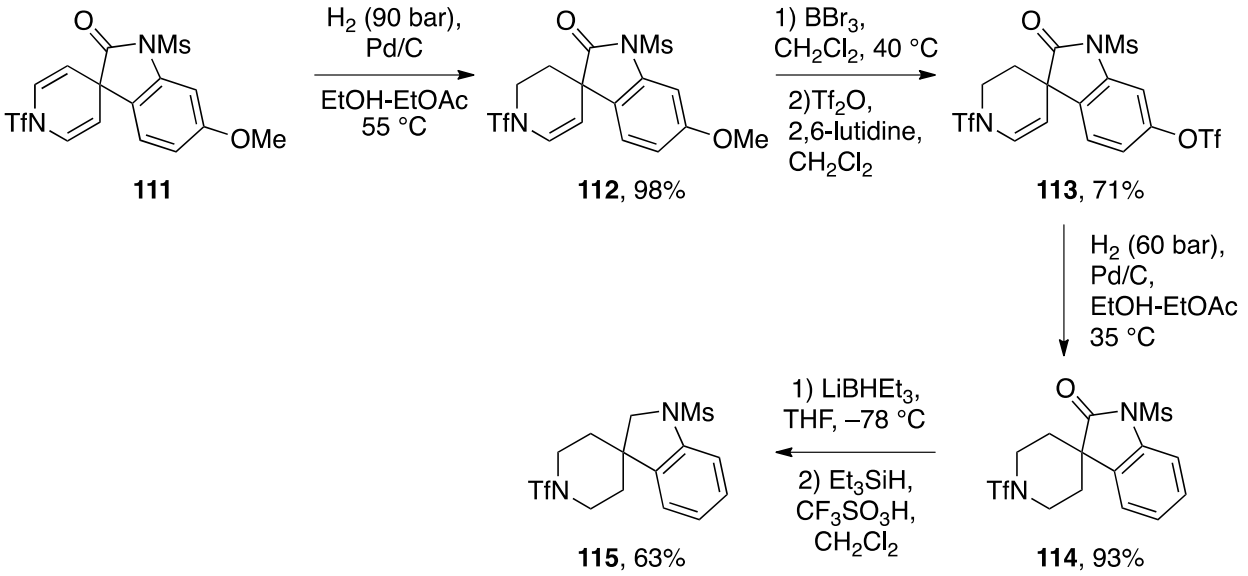
105 **106**, 87%

107 **108**, 43%

109 **110**, 82%

Scheme 1.32: *Clayden's addition of non-activated nucleophiles to* N-*triflyl pyridinium salts.*

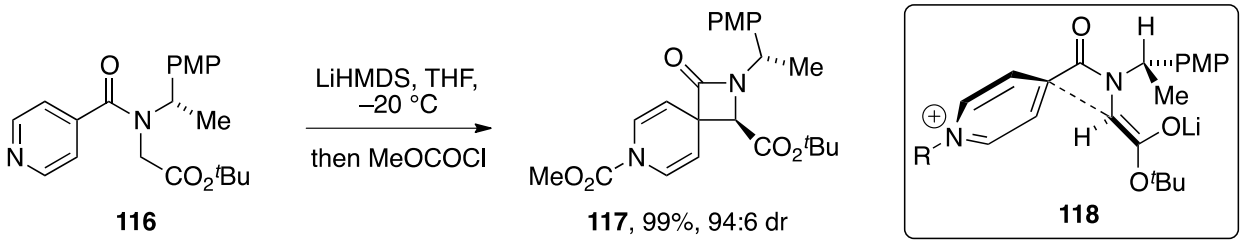
Furthermore, Clayden demonstrated that spirocyclic lactones were readily prepared by treating ester **107** to the same optimized reaction conditions, the lower yield and more forcing conditions being a result of the less favourable *cis*-conformation of the two rings. The isomeric nicotinamide **109** provided the rearomatized pyridine **110**, *via* nucleophilic attack at the 4-position of the pyridinium cation and subsequent elimination of trifluoromethylsulfinate. In addition, the synthetic utility of dihydropyridines was highlighted by preparation of spirocycle **115**, bearing an otherwise unsubstituted aromatic ring (Scheme 1.33). These structures were not accessible directly as simple phenylic tertiary amides were not sufficiently nucleophilic to cyclize in good yield.



Scheme 1.33: *Clayden's study of the synthetic utility of dihydropyridine **111**.*

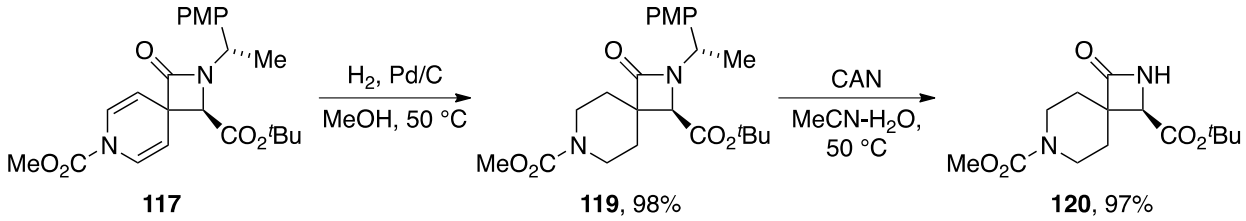
Thus, spirocyclic dihydropyridine **111** could be selectively mono-hydrogenated to enamine **112** (with the complete hydrogenation of dihydropyridine **111** to the corresponding piperidine also having been demonstrated). The aromatic methyl ether was converted to the aryl triflate **113** by a two-step deprotection-sulfonylation strategy and a combined hydrogenation-hydrogenolysis recaction gave lactam **114**. Reduction with superhydride followed by triethylsilane yielded the benzo-fused spirocyle **115**.

In a similar study, Clayden has also demonstrated that the enolates of *N*-isonicotinoyl glycine cyclized to yield spirocyclic *β*-lactams on activation of the pyridine by *N*-acylation (Scheme 1.34).[61] By use of a chiral auxiliary, a diastereoselective cyclization took place on treatment of pyridine **116** with methyl chloroformate, in the presence of lithium *bis*(trimethylsilyl)amide to generate the enolate, providing the corresponding *β*-lactam **117** in good yield and with a dr of 94:6. The high diastereoselectivity arose from the reactive conformation **118**, where the bulky *p*-methoxyphenyl group controlled the facial selectivity of addition to the pyridinium core. Claisen acylation of the enolate by methyl chloroformate, providing the corresponding *β*-diester, was minimal due to the steric crowding around the amide.



Scheme 1.34: *Clayden's diastereoselective spirolactamization.*

Hydrogenation and subsequent removal of the chiral auxiliary provided *aza*-bicyclic amino acid derivative **120** in a 94:6 er (Scheme 1.35).

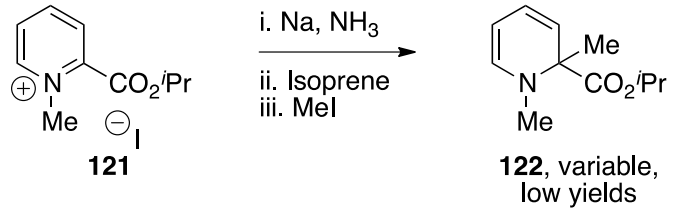


Scheme 1.35: *Clayden's preparation of* aza-*bicyclic amino acid derivatives.*

Clearly, a number of efficient routes to synthetically versatile dihydropyridines are available. However, methodology that circumvents dihydropyridine intermediates, observed to be unstable by Charette, Donohoe and Clayden above, and still provides versatile synthetic intermediates, would be desirable.

1.4 Dihydropyridones

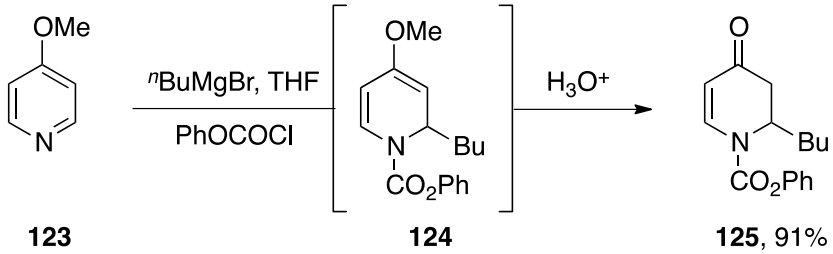
As outlined in Sections 1.2 and 1.3, dihydropyridines are known to be unstable intermediates, often being re-oxidized by air to the corresponding pyridinium species. When Donohoe reported the Birch reduction of pyridinium salt **121**, the product dihydropyridine **122**, although observable in the proton NMR spectrum of the crude product, was found to decompose rapidly in air (Scheme 1.36).[62]



Scheme 1.36: *Donohoe's findings on the instability of 1,2-dihydropyridines.*

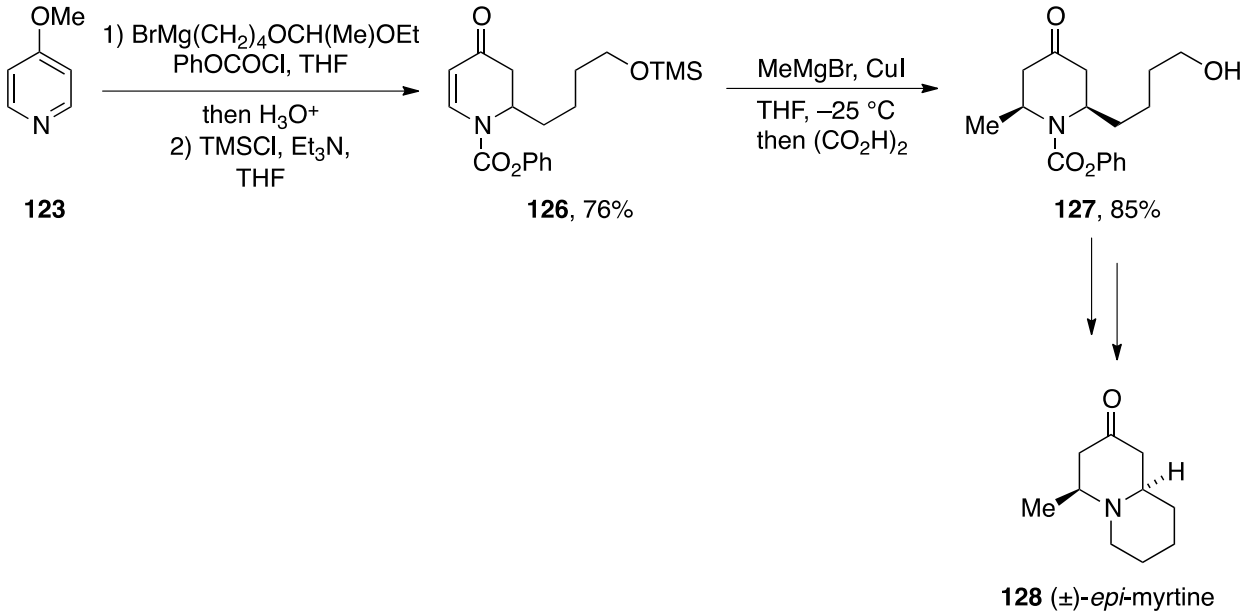
As stated in Section 1.3.2, Donohoe overcame these isolation problems by increasing the electron deficiency of the ring and therefore increasing the stability of dihydropyridines such as **43** and **46**. However, gradual decomposition of these dihydropyridines was still observed over extended time periods and the products would need to be converted to more stable materials quickly in order to maximize the efficiency of any synthesis. Also, the synthetic applications of these products were limited, due to the necessity of the 3,4- or 2,5-substitution pattern.

Comins proposed that nucleophilic addition to the *N*-acyl pyridinium salt of 4-methoxy pyridine **123**, would lead to dihydropyridine **124**. This could then be converted to the more stable dihydropyridone **125** by hydrolysis of the methyl enol ether (Scheme 1.37).[63]



Scheme 1.37: *Comins' "one-pot" preparation of dihydropyridone **125**.*

The dihydropyridone products were found to be much more stable to purification and air oxidation than dihydropyridines. In addition, the new carbonyl functionality at *C*-4 conferred greater synthetic utility to these dihydropyridones: Comins found that dihydropyridone **126** underwent a copper-catalyzed conjugate addition with methylmagnesium bromide *en route* to his synthesis of (±)-*epi*-myrtine **128** (Scheme 1.38).

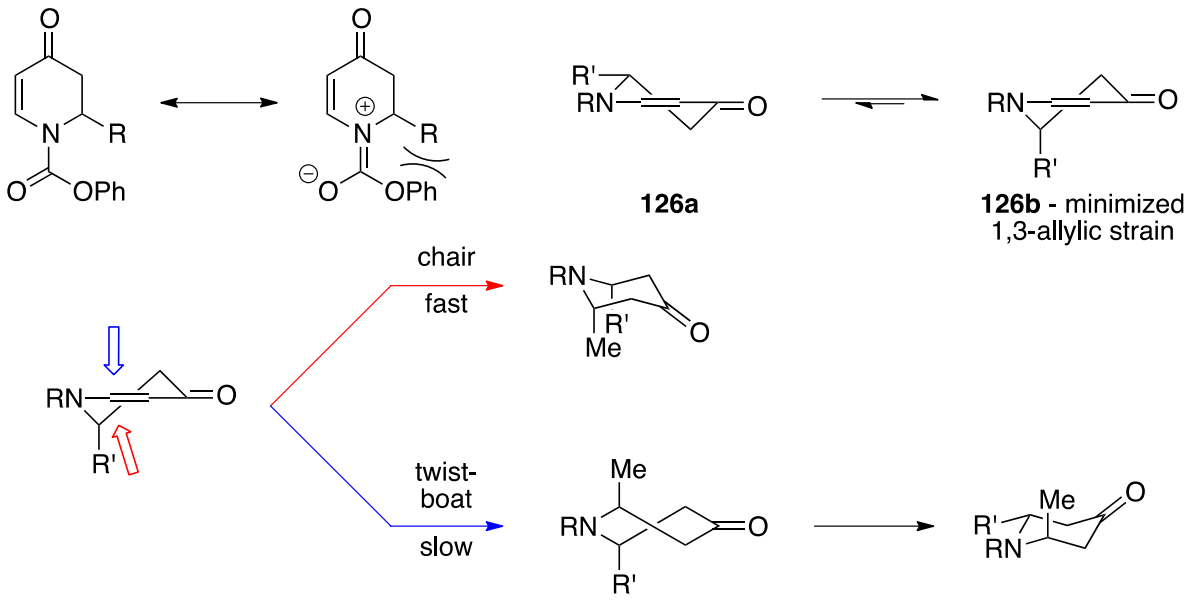


123 **126**, 76% **127**, 85%

128 (±)-*epi*-myrtine

Scheme 1.38: *The utility of dihydropyridone* ***126*** *in Comins' synthesis of* epi-*myrtine.*

Although substituents on six-membered cyclic systems usually occupy equatorial positions to minimize 1,3-diaxial interactions, Paulson and Todt have shown that the presence of a carbamate-bearing nitrogen in the ring alters the most stable conformation.[64] In order to minimize the strong 1,3-diaxial interaction between the ring substituent and the carbamate group, conformation **126b** would be adopted, with the alkyl side chain in an axial position. The diastereoselectivity of the conjugate addition was presumably, a result of the axial addition of the methyl nucleophile to the bottom face, *via* a transition state in a chair conformation.[65] Axial addition from the other face would lead to a twist-boat conformation in the transition state, which is kinetically disfavoured (Scheme 1.39).



Scheme 1.39: *Possible explanation of the diastereoselectivity of Cu-catalyzed 1,4-addition.*

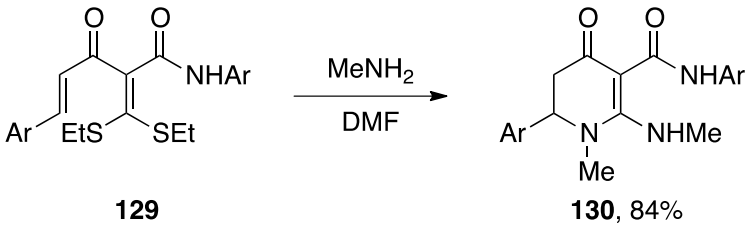
Given the high stability of dihydropyridones over dihydropyridines and their greater synthetic versatility, much recent attention has been focused on the synthesis of these valuable intermediates.

1.5 The Synthesis of Dihydropyridones

The strategies for the synthesis of dihydropyridones are, in general, much the same as for the synthesis of dihydropyridines (Section 1.3). The three main approaches, namely ring construction, reductive methods and nucleophilic addition will be dealt with individually.

1.5.1 Ring Construction

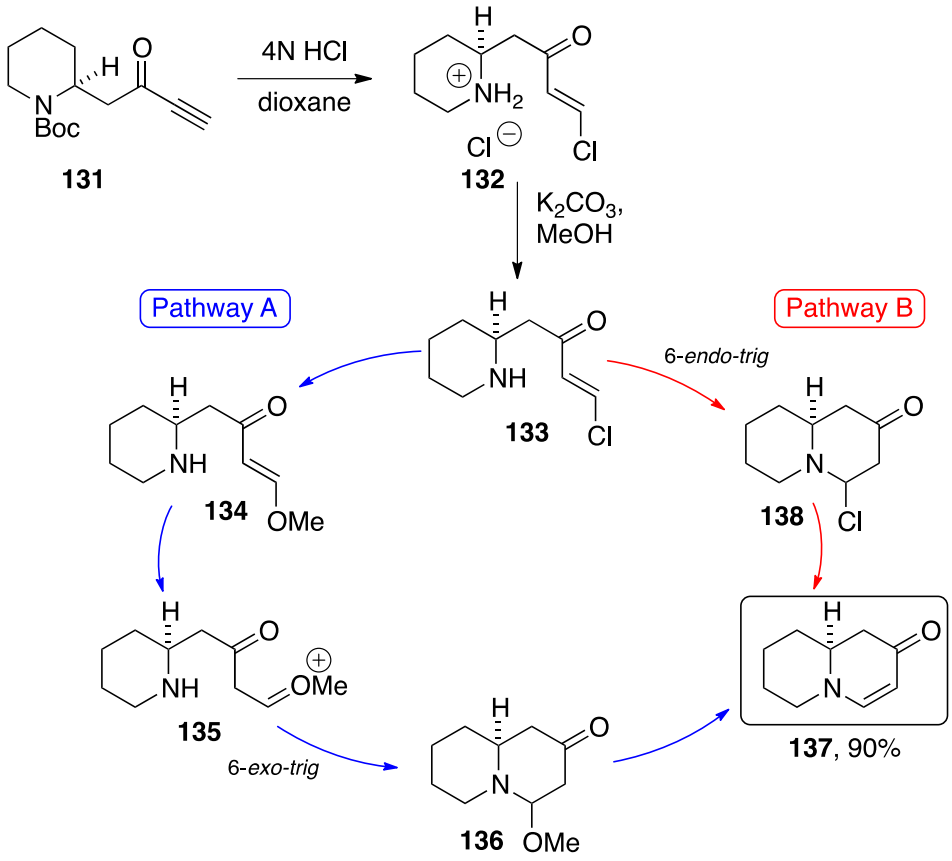
In 2005, Dong reported the double conjugate addition of primary amines to dienone **129**. The two geminal ethyl sulfide groups at the terminus of the double bond served as leaving groups and dihydropyridones, such as **130**, were obtained in good yield (Scheme 1.40).[66]



129 **130**, 84%

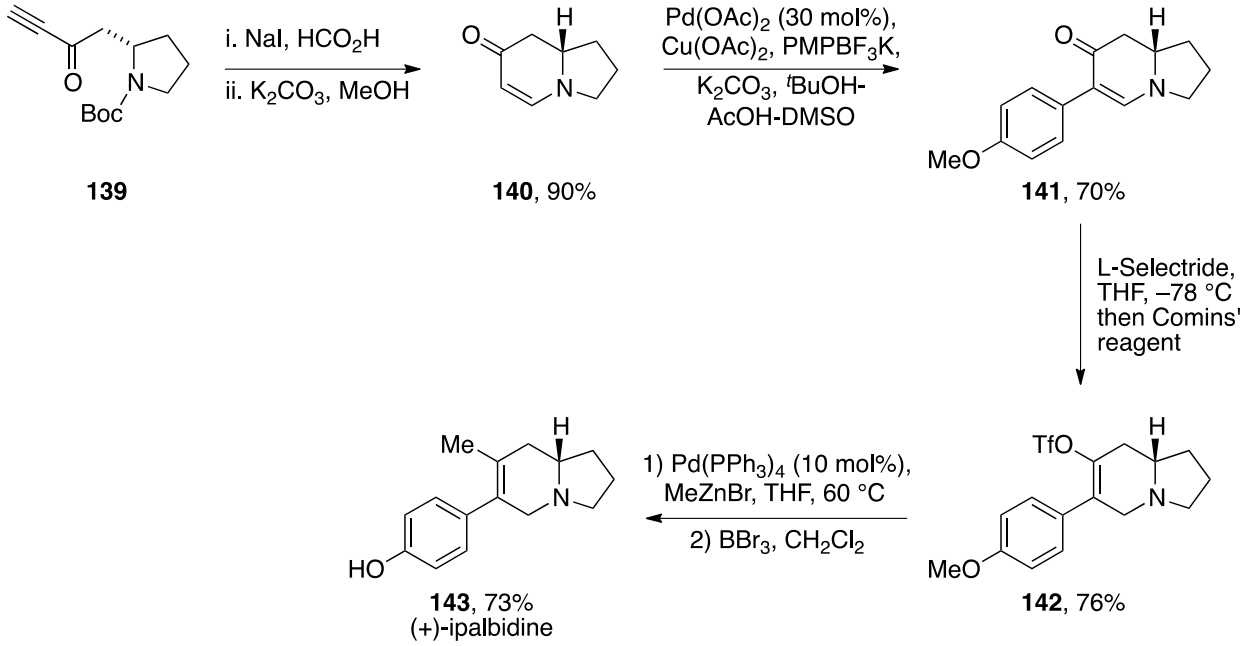
Scheme 1.40: *Dong's synthesis of dihydropyridone **130**.*

Georg found that acid-catalyzed Boc-deprotection of amino-ynone **131**, followed by treatment with potassium carbonate, provided dihydropyridone **137** as a formal 6-*endo-dig* cyclization (Scheme 1.41).[67] Although 6-*endo-dig* cyclizations are permitted by Baldwin's rules,[68] mechanistic studies showed that this reaction proceeded *via* the addition of hydrochloric acid across the alkyne, with concomitant Boc-deprotection. The authors initially proposed a mechanism involving the conjugate addition of methanol to the vinyl chloride, followed by tautomerization to oxonium intermediate **135**, 6-*exo-trig* ring closure and elimination of methanol (Pathway A). This was based on the observation that no cyclization was observed in the absence of methanol. However, NMR studies with methanol-d_4 in the second step returned no evidence of the formation of intermediates **134-136**. As a result, a different mechanistic pathway was envisaged, involving the direct 6-*endo-trig* ring closure of vinyl chloride **133** with subsequent elimination of HCl (Pathway B).[69] The importance of methanol to the reaction was therefore judged to stem from enhancing the solubility of intermediates **132**, **133** and **138**, in addition to the carbonate base, rather than any nucleophilic activity.



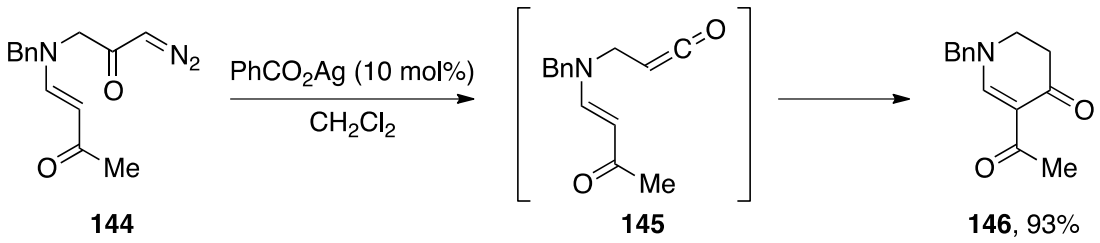
Scheme 1.41: *Georg's synthesis of dihydropyridone **137**.*

Georg has applied this methodology to the total synthesis of (+)-ipalbidine (Scheme 1.42).[70] Treatment of enantiopure amino-ynone **139**, derived from L-proline, to similar cyclization conditions provided dihydropyridone **140**. In this case, the use of sodium iodide and formic acid in the first step was analogous to the previously reported conditions of 4 N HCl, *vide supra*. Palladium-catalyzed C-H arylation, using 4-methoxyphenyl trifluoroborate, gave dihydropyridone **141**.[71] Reduction with L-Selectride and *in situ* trapping of the enolate with Comins' reagent[72] gave triflate **142**. Finally, Negishi cross-coupling and subsequent demethylation provided (+)-ipalbidine **143**.



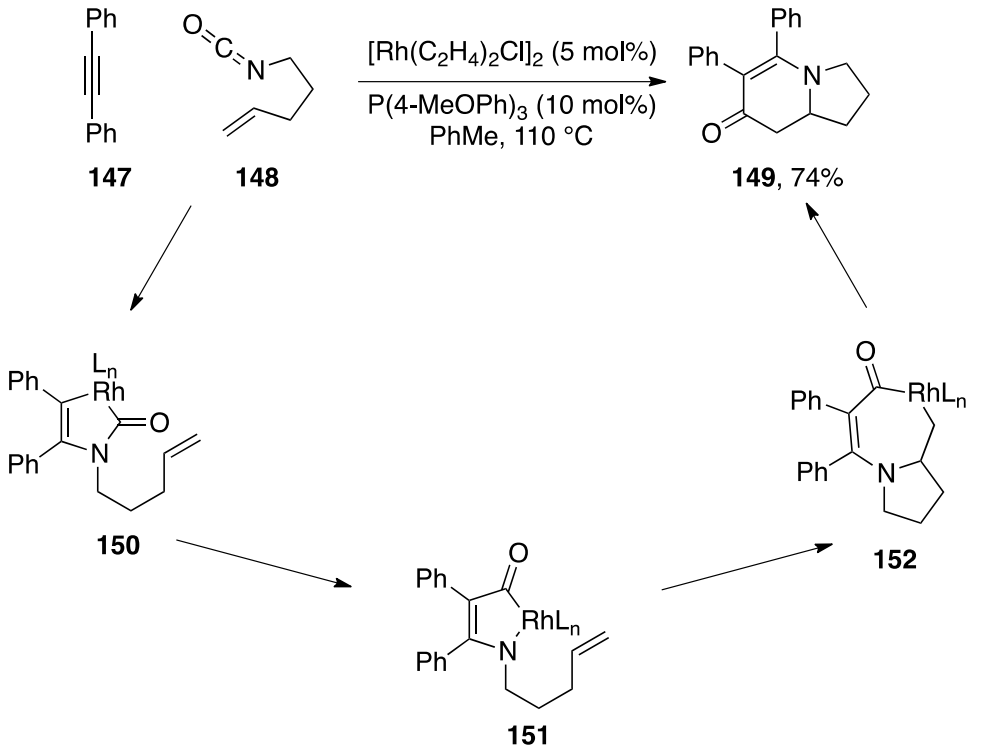
Scheme 1.42: *Georg's synthesis of (+)-ipalbidine.*

In addition to this approach, Georg also published a different ring-closing approach to dihydropyridones *via* the Wolff rearrangement, using vinylogous amides as carbon nucleophiles (Scheme 1.43).[73] When diazoketone **144** was treated with silver benzoate, a Wolff rearrangement to ketene **145** occurred, followed by 6-*exo*-*dig* cyclization to dihydropyridone **146**.



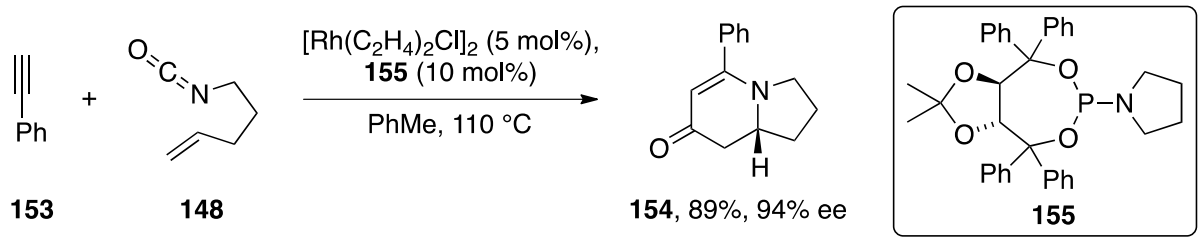
Scheme 1.43: *Georg's synthesis of dihydropyridone **146**.*

Transition metal catalysis can provide a powerful method for the formation of heterocycles.[74] One example, in the context of dihydropyridone synthesis, is the rhodium-catalyzed [2+2+2] cycloaddition of olefinic isocyanate **148** with alkyne **147**, developed by Rovis (Scheme 1.44).[75] Initial oxidative cyclization between alkyne **147**, isocyanate **148** and the catalyst gave metallacycle **150**. CO migration was followed by an olefin insertion, giving metallacycle **152** and subsequent reductive elimination provided dihydropyridone **149**.



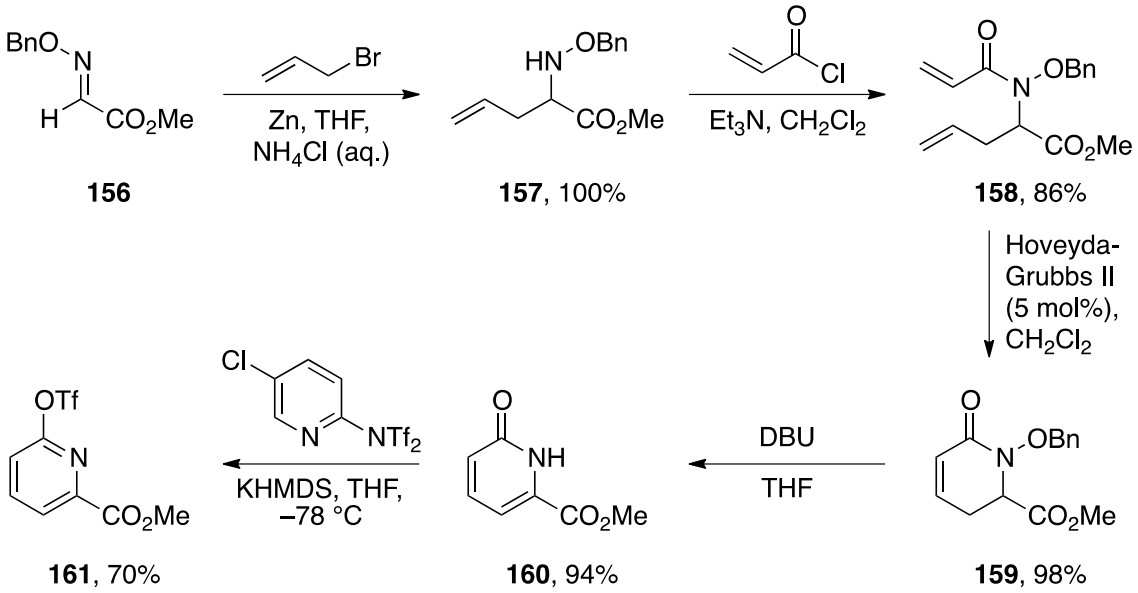
Scheme 1.44: *Rovis' synthesis of dihydropyridone **149**.*

Rovis later rendered this transformation enantioselective by the use of chiral phosphoramidite ligand **155**.[76] The corresponding dihydropyridones, such as **154**, were prepared in good yield and enantioselectivity from achiral starting materials *via* an identical mechanism (Scheme 1.45).



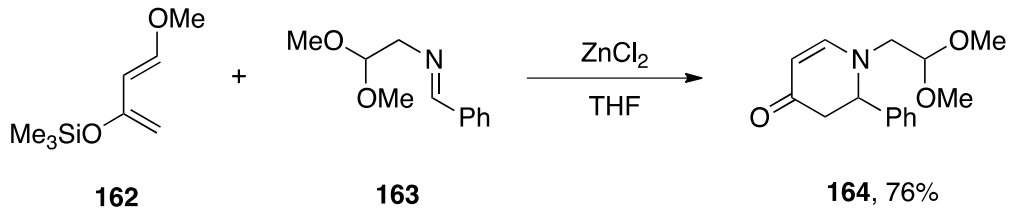
Scheme 1.45: *Rovis' enantioselective synthesis of dihydropyridone **154**.*

Donohoe has demonstrated the importance of the ring-closing metathesis (RCM) reaction to create a range of dihydro-2-pyridones *en route* to the preparation of substituted pyridines.[77] Amine **157** was produced by a zinc-mediated allylation of oxime **156**[78] and subsequent acylation with acryloyl chloride gave the metathesis precursor **158**. Treatment of **158** with Hoveyda-Grubbs 2nd generation catalyst provided the dihydropyridone **159** in 98% yield (Scheme 1.46).[79] The dihydropyridone was converted to the corresponding pyridine **161** by base-mediated elimination of benzyl alcohol and triflation using Comins' reagent.[72]



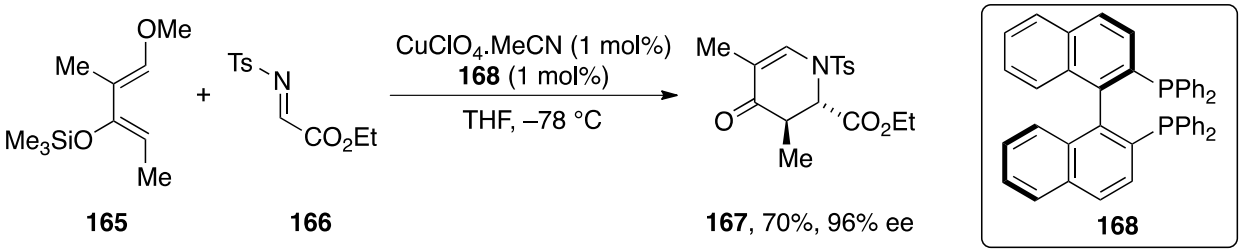
Scheme 1.46: *Donohoe's synthesis of pyridine **161**,* via *dihydropyridone **159**.*

In 1982, Danishefsky published the first general method for preparing dihydropyridones *via* an intermolecular *aza*-Diels-Alder reaction.[80] Treatment of imine **163** with Danishefsky's diene **162**,[81] using zinc chloride catalysis, allowed the preparation of dihydropyridone **164** at ambient temperature (Scheme 1.47).



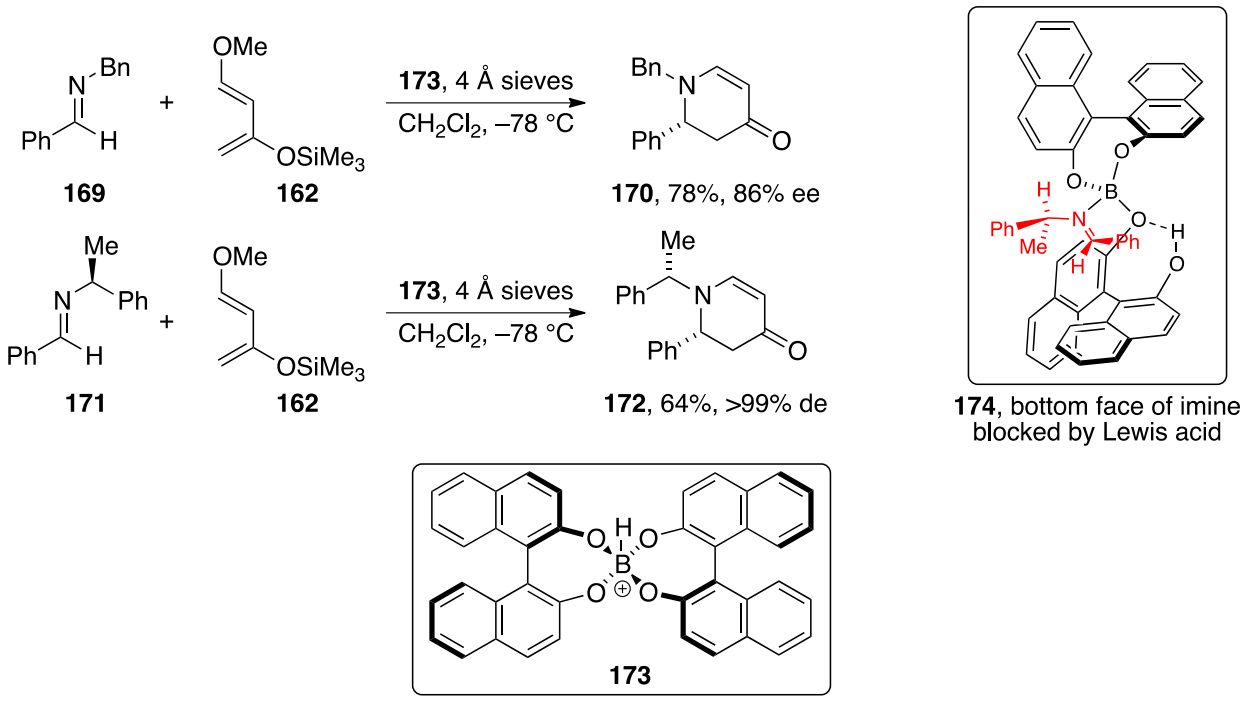
Scheme 1.47: *Danishefsky's synthesis of dihydropyridone **164**.*

Since this report, a number of catalytic enantioselective variants of this methodology have appeared in the literature. These include the zirconium-binaphthol complexes developed by Kobayashi,[82] the silver catalysts reported by Hoveyda,[83] the copper complexes of BINAP and phosphine-oxazolines described by Jørgensen[84] and the copper complexes of sulfenyl ferrocenes developed by Carretero.[85] Using Jørgensen's methodology, for example, dihydropyridone **167** could be prepared on a multi-gram scale, and in high yield and enantioselectivity, by using just 1 mol% copper catalyst (Scheme 1.48).



Scheme 1.48: *Jørgensen's synthesis of dihydropyridone **167**.*

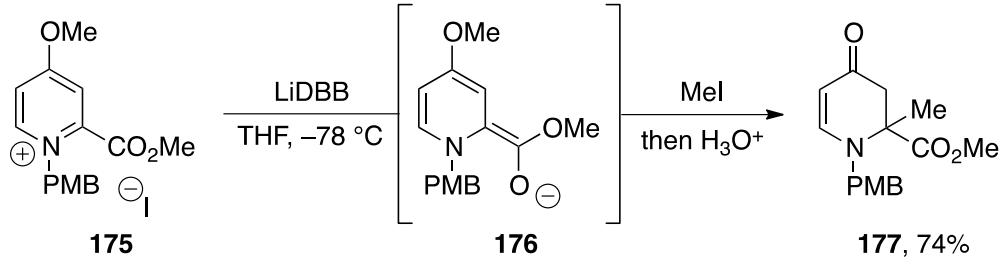
Yamamoto has reported a similar *aza*-Diels-Alder strategy to prepare dihydropyridones, using a Brønsted acid-assisted chiral Lewis acid.[86] Reaction of imine **169** with Danishefsky's diene **162** and a stoichiometric amount of acid **173** gave dihydropyridone **170** in 78% yield with an ee of 86% (Scheme 1.49). Furthermore, when the chiral imine **171** was treated to the same reaction conditions, dihydropyridone **172** was obtained in good yield, with almost complete control of diastereoselectivity. The selectivity was rationalized by consideration of the proposed complex **174** between the Lewis acid **173** and imine **171**, whereby approach of diene **162** from the bottom face was blocked by the Lewis acid.



Scheme 1.49: *Yamamoto's synthesis of dihydropyridones **170** and **172**.*

1.5.2 Reductive Processes

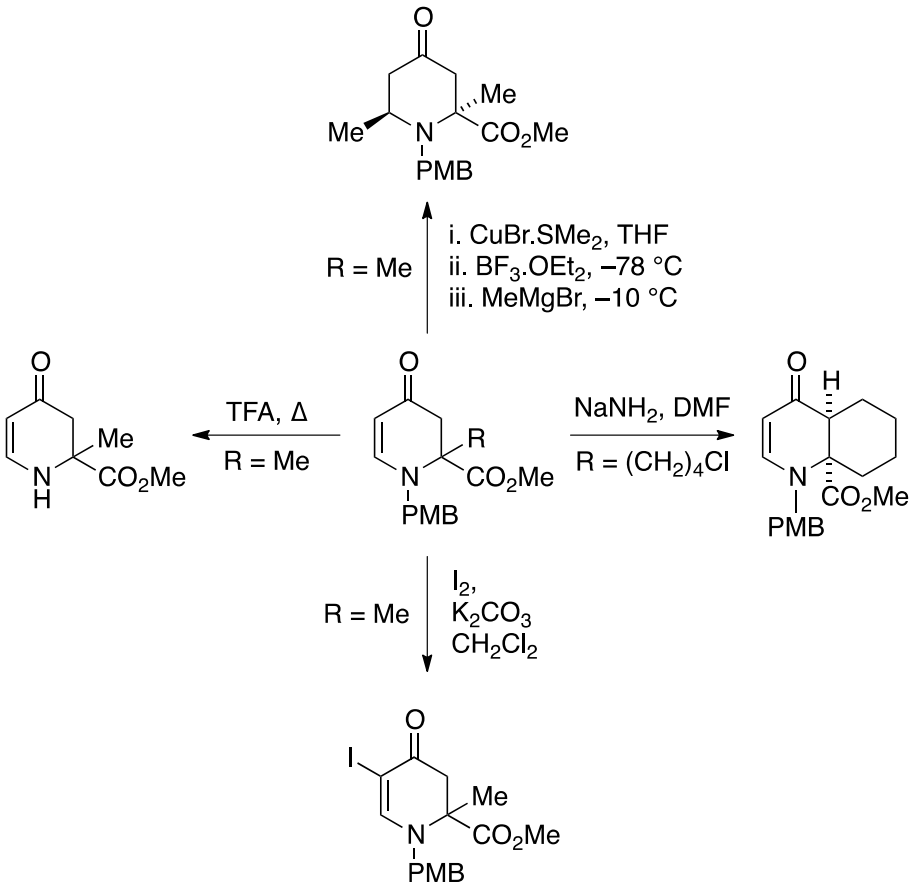
Donohoe sought to apply Comins' findings on the enhanced stability of dihydropyridones over dihydropyridines to the Birch reduction of pyridinium salts. Treatment of pyridinium salt **175** with lithium DBB solution, followed by quenching of the nascent enolate **176** with an external electrophile and subsequent enol ether hydrolysis, led to good yields of the corresponding dihydropyridones (Scheme 1.50).[13, 62] Although racemic products were obtained, Donohoe noted that this procedure provided dihydropyridones bearing a quaternary centre at *C*-2, a feat that, at the time, could not be achieved by other means.



175 **176** **177**, 74%

Scheme 1.50: *Donohoe's ammonia-free Birch reduction of pyridinium salt **175**.*

In addition, Donohoe's paper included a comprehensive study of the synthetic versatility of dihydropyridones, with manipulation of each ring position proving possible (Scheme 1.51).



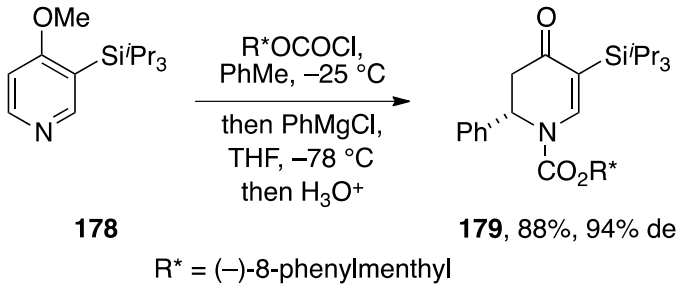
Scheme 1.51: *Donohoe's study of the synthetic utility of dihydropyridones.*

As a caveat to this work, Donohoe noted that when these reductions were performed on a larger scale than approximately 2.0 mmol, much reduced yields of dihydropyridone **177** were observed. Scale-up difficulties remained an unassailable problem in the Birch reduction of pyridinium salts and led, in part, to the inception of this project (see Section 1.6).

1.5.3 Nucleophilic Addition to Pyridinium Salts

In 1994, Comins expanded his methodology, based on nucleophilic addition to 4-methoxy-substituted pyridinium salts, to allow the preparation of enantioenriched dihydropyridones. This chiral auxiliary-controlled, diastereoselective addition of Grignard reagents utilized a combination of an (–)-8-phenylmenthol group, attached as part of the *N*-acyl group, and a triisopropylsilyl (TIPS) group in the 5-position to shield one face of the pyridinium core, leading to preferential attack of the Grignard reagent on the least hindered face (Scheme 1.52).[87] The opposite enantiomer of dihydropyridone may be prepared by use of a (+)-*trans*-2-(α-cumyl)cyclohexanol group ((+)-TCC) as the chiral auxiliary. By X-ray crystallographic analysis on the *N*-acyl pyridinium salt, Comins noted that the diastereoselectivity was primarily governed

by the π-stacking interaction between the phenyl group of the chiral auxiliary and the pyridinium core. This provided effective shielding of one face of the pyridinium cation by the chiral auxiliary, thus favouring nucleophilic attack from the opposite face. Rotation about the C-N bond of the auxiliary was inhibited by unfavourable steric interactions with the TIPS group. As a result of this, lower diastereoselectivities were observed using an (–)-8-cyclohexylmenthol-based auxiliary, or in the absence of the TIPS group.

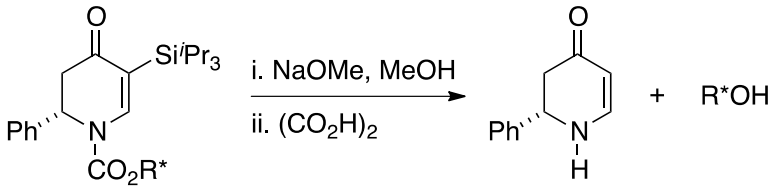


178 **179**, 88%, 94% de

R* = (–)-8-phenylmenthyl

Scheme 1.52: *Comins' diastereoselective addition to an* N*-acyl pyridinium salt.*

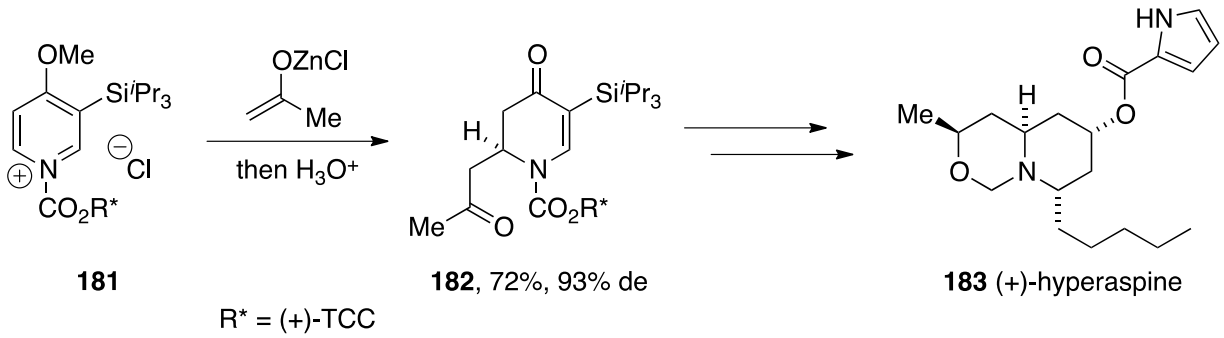
Both the chiral auxiliary and the TIPS group could be removed in a one-pot operation, involving treatment of the product dihydropyridones with a solution of sodium methoxide in methanol, before acidification with either oxalic acid or dilute aqueous hydrochloric acid solution. The chiral auxiliary could also be isolated in high yield and recycled (Scheme 1.53).



179 **180**, 88%

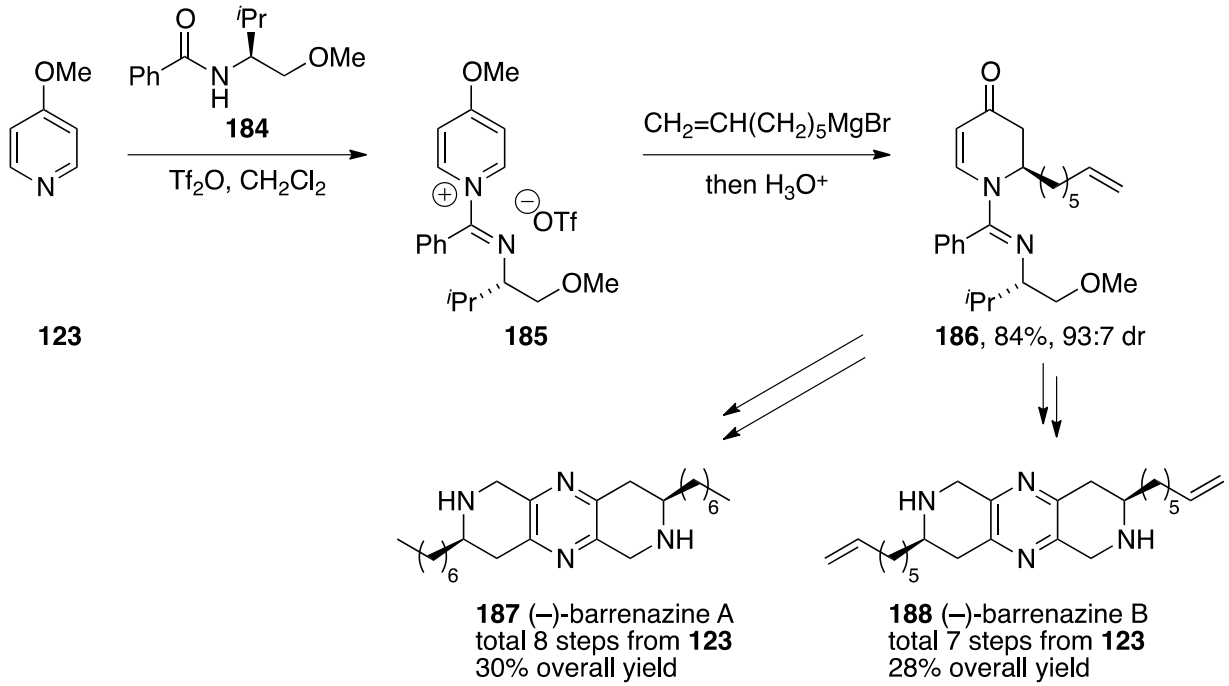
Scheme 1.53: *Liberation of dihydropyridone* ***180*** *and chiral auxiliary recycling.*

Comins applied this methodology to the synthesis of a variety of natural product targets and, in doing so, demonstrated that the scope of nucleophiles was not limited to Grignard reagents. The synthesis of (+)-hyperaspine **183** was achieved in six steps, with the key step being the diastereoselective addition of a zinc enolate to pyridinium salt **181** in a de of greater than 93%. Further elaboration led to (+)-hyperaspine **183** in an overall yield of 21% (Scheme 1.54).[88]



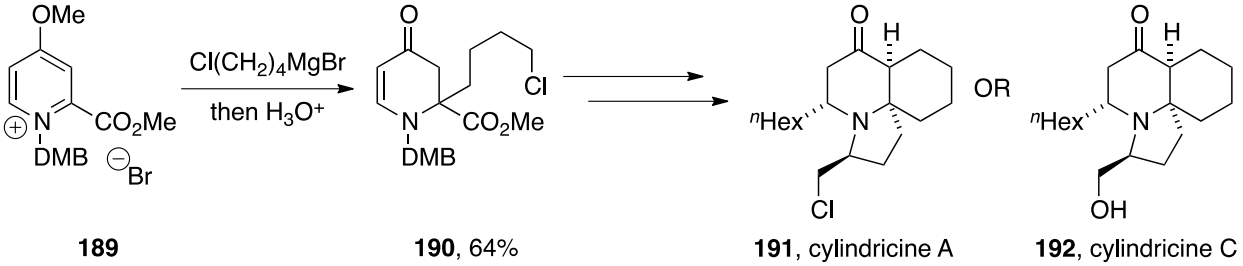
Scheme 1.54: *Utility of dihydropyridone **182** in Comins' synthesis of (+)-hyperaspine.*

A number of alternative, chiral auxiliary-based methodologies have appeared in the literature.[89-91] Charette has published an effective method for diastereoselective addition to unsubstituted or 4-methoxy-substituted pyridinium salts.[92, 93] The additional TIPS blocking group on the pyridine ring, necessary to the success of Comins' methodology, was not required and the corresponding dihydropyridines or dihydropyridones could be obtained in excellent yield and diastereomeric excess. Treatment of 4-methoxypyridine with chiral amide **184** and triflic anhydride provided pyridinium salt **185** which, Charette established by NOESY experiments, was formed selectively as the *E*-imidate. The nitrogen lone pair of the imidate acted as a directing group, by coordination to magnesium, and attack at the 6-position was suppressed by the phenyl group of the imidate (Scheme 1.55). As a result, diastereoselective attack of the Grignard reagent at the 2-position led to the corresponding dihydropyridones, such as **186**, in good yield and excellent diastereoselectivity. This methodology was applied to the synthesis of (–)-barrenazine A **187** and B **188**, *via* a dimerization strategy.



Scheme 1.55: *Charette's diastereoselective preparation of **186** and its synthetic utility.*

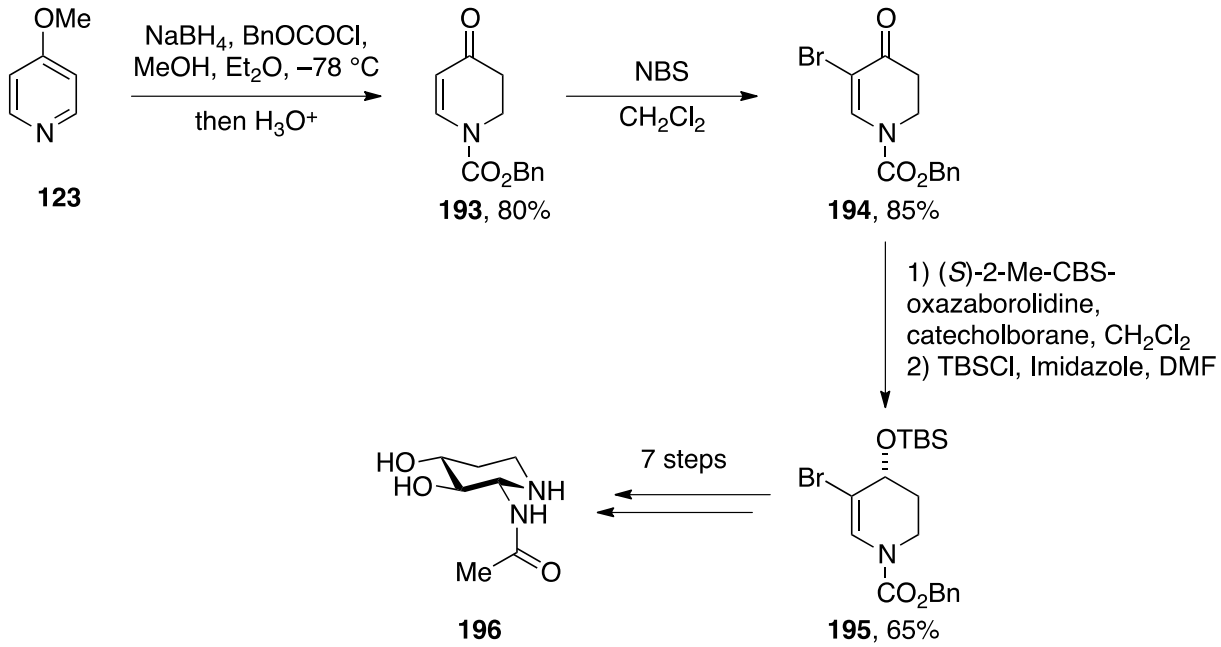
In 2010, Donohoe, utilizing results obtained during the course of this project (see Chapter 2),[94] reported the formal synthesis of (±)-cylindricine A **191** and a total synthesis of (±)-cylindricine C **192**.[95] The routes to **191** and **192** diverged at a late stage in the synthesis and therefore, a key step in the preparation of both targets was the regioselective addition of a Grignard reagent to pyridinium salt **189**, providing *C*-2 disubstituted dihydropyridone **190** (Scheme 1.56). The selective formation of a *C*-2 quaternary centre was a notable achievement as only one previous example of this, *via* nucleophilic addition to a pyridinium salt, had been reported by Charette whilst work on this project was nearing completion (see Chapter 2).[96]



Scheme 1.56: *Donohoe's use of dihydropyridone **190** in the synthesis of cylindricines A & C.*

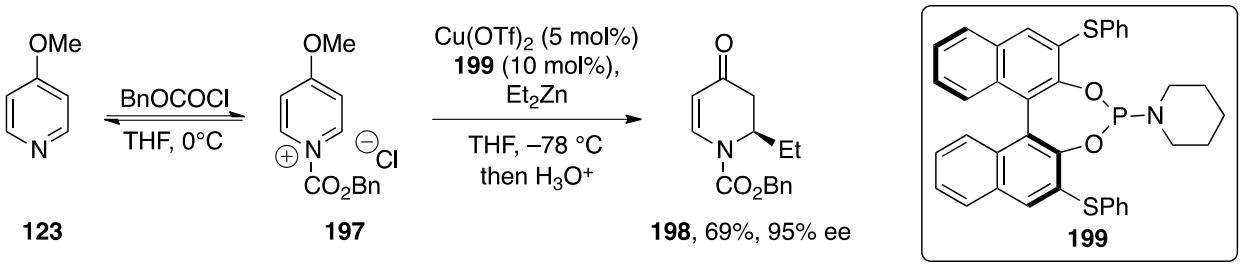
Knapp has demonstrated the addition of a hydride nucleophile to an *N*-acyl 4-methoxypyridinium salt *en route* to his asymmetric synthesis of XylNAc-isofagomine **196**, an *N*-acetylhexosaminidase inhibitor.[97] Treatment of pyridine **123** with benzyl chloroformate and

sodium borohydride in methanol, with subsequent enol ether hydrolysis, gave dihydropyridone **193** in excellent yield (Scheme 1.57). **193** was brominated in order to improve the selectivity of the subsequent enantioslective reduction, using the CBS reagent. Protection using *tert*-butyldimethylsilyl chloride gave the protected allylic alcohol **195** in good yield. A further seven steps gave the target **196** in 18% overall yield from 4 methoxypyridine **123**.



Scheme 1.57: *Knapp's hydride addition to an* N-*acyl pyridinium salt* en route *to* ***196***.

Feringa published the first catalytic, enantioselective addition of organometallic reagents (as opposed to trimethylsilyl cyanide[56] or terminal alkynes[57] discussed in Section 1.3.3) to an *N*-acyl pyridinium salt in 2009.[98] The addition of dialkylzinc reagents was catalyzed by copper triflate in the presence of chiral ligand **199**. Through careful control of the order of addition of reagents and by using an excess of benzyl chloroformate to drive forward the salt-forming equilibrium, good yields and excellent enantioselectivities were obtained for addition to 4-methoxy-substituted pyridinium salt **197** (Scheme 1.58). However, the scope of the reaction was found to be limited, with significantly reduced enantioselectivity observed for addition of di-*iso*propylzinc, and no reaction at all occurring when dimethyl- or diphenylzinc were submitted to the optimized reaction conditions.



123 **197** **198**, 69%, 95% ee **199**

Scheme 1.58: *Feringa's asymmetric addition of dialkylzincs to pyridinium salt **197**.*

1.6 Project Goals

The utility of the ammonia free Birch reduction in producing 2,2-disubstituted, quaternary dihydropyridones has been demonstrated by Donohoe (see Section 1.5.2).[13, 62] However, this procedure has subsequently been found to be irreproducible, leading to highly variable yields of dihydropyridone.[99] Given the crucial role played by dihydropyridones in the preparation of natural products containing the piperidine motif, the research described herein is centred on the finding of an alternative route to such dihydropyridones. In order to maximize the potential of any discoveries, the following points would need to be addressed:

- In addition to the lack of reproducibility associated with the Birch reduction of pyridinium salts, the reaction itself is known to be highly challenging to perform successfully, with rigorous exclusion of air and moisture being essential. A more straightforward, practical procedure would be desirable.
- The new route must be reproducible and provide dihydropyridones with high regioselectivity.
- A wide variety of ring-substituents must be installable using this methodology.
- A protecting group must be found that effectively activates the pyridine to reduction, fully satisfies the points above and is easily removable from the dihydropyridone *post* reduction.
- A means of preparing dihydropyridones as single enantiomers would be highly desirable.

Chapter 2:
A Regioselective Route to Dihydropyridones

2.1 Initial Considerations

The first major targets to be addressed in finding an alternative procedure to the Birch reduction of pyridinium salts were:

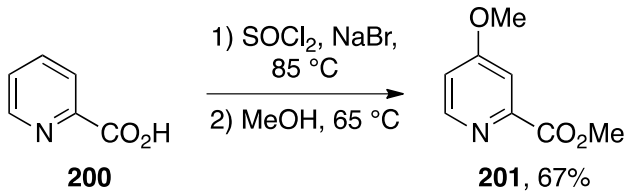
1. The discovery of appropriate reaction conditions that gave good and reproducible yields of dihydropyridone products.
2. The choice of an activating group for nitrogen that would also act as a removable protecting group *post*-reaction.

It was anticipated that the development of optimum reaction conditions (point 1) on known *N*-methyl protected pyridinium salts **209** and **212** would allow application of these conditions to new classes of pyridinium salt, synthesized through investigation of point 2.

2.2 Nucleophilic addition to *N*-Methyl Pyridinium Salts

2.2.1 Starting Material Synthesis

The synthesis of 4-methoxy substituted pyridine **201** was achieved in 67% yield in a one pot procedure from commercially available picolinic acid **200** using a procedure reported by Sundberg (Scheme 2.1).[100] The spectroscopic data obtained for **201** matched those reported in the literature. Furthermore, the reaction could be scaled up to greater than 25 g with only a minor decrease (ca. 10%) in the isolated yield of **201**.

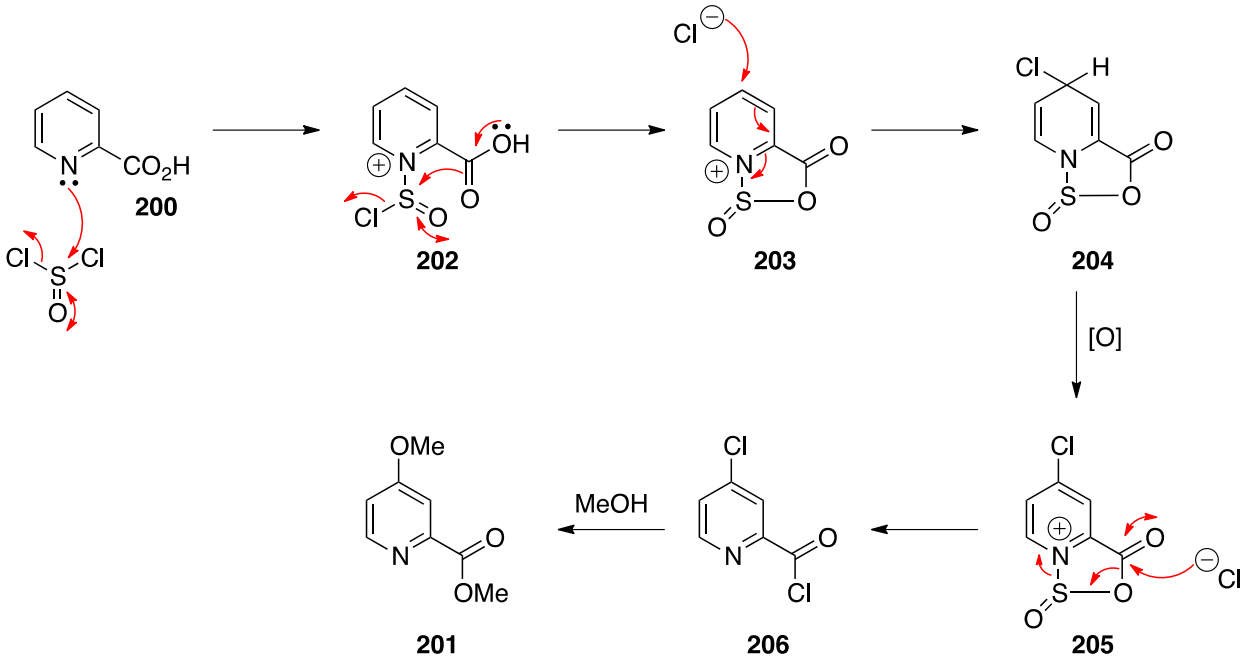


200 **201**, 67%

Scheme 2.1: *Synthesis of pyridine **201**.*

Sundberg proposed a mechanism for this procedure involving the initial attack of the nitrogen lone pair on a molecule of thionyl chloride, followed by intramolecular attack by the carboxylic acid group to furnish mixed anhydride **203**. Attack of a chloride anion at the 4- position of **203** gives 1,4-dihydropyridine **204** which undergoes an air oxidation to pyridinium intermediate **205**.

Attack of a second chloride anion at the acyl carbon of **205** leads to the extrusion of sulfur dioxide and the formation of acyl chloride **206**, which upon treatment with methanol, undergoes esterification and nucleophilic substitution of the chlorine at *C*-4 to provide the desired ester (Scheme 2.2).



Scheme 2.2: *Proposed mechanism for the conversion of **200** to **201**.*

The remaining mass from the reaction was attributed to by-products formed by the incomplete conversion of intermediates to ester **201**. These were isolated in varying amounts depending on the scale of the reaction and the length of time that each phase was run. Methyl picolinate **207** resulted from the failure of substitution by chloride at the 4-position and 4-chloro derivative **208** from nucleophilic substitution by methanol not occurring (Figure 2.1).

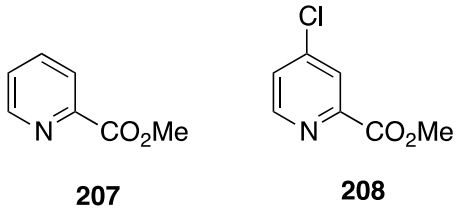
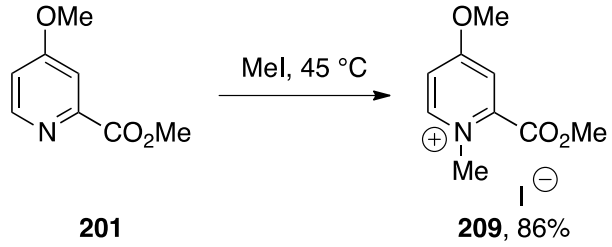


Figure 2.1: *Major by-products in the synthesis of **201**.*

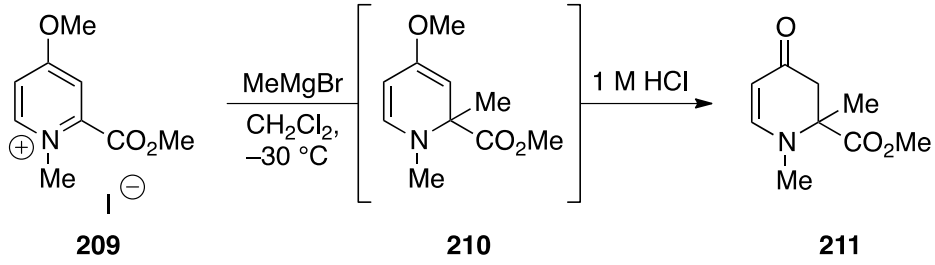
2.2.2 *N*-Methyl Pyridinium Salts

Following literature precedent, pyridine **201** was treated with methyl iodide to provide pyridinium salt **209** in 86% yield.[13] With a reliable route to **209** in hand, we began investigating the nucleophilic addition to this pyridinium salt (Scheme 2.3).



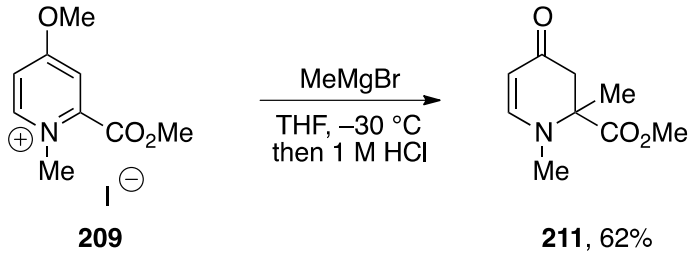
Scheme 2.3: *Formation of salt **209**.*

Following precedent from the work of Charette,[93] a solution of **209** in dichloromethane at −30 °C was treated with methylmagnesium bromide to give intermediate **210**, which was then hydrolysed *in situ* (Scheme 2.4). Dihydropyridone **211** was isolated, however yields were found to be consistently low and irreproducible. This was thought to be a consequence of the lower half-life of Grignard reagents in dichloromethane, with respect to solvents such as THF or diethyl ether.



Scheme 2.4: *Grignard addition to **209** in dichloromethane.*

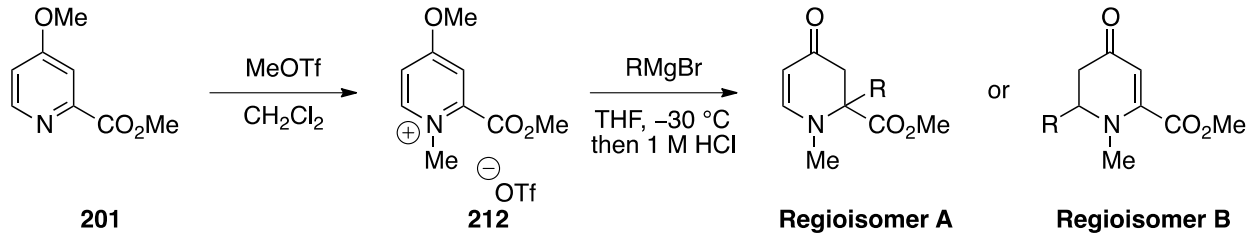
Although salt **209** appeared to have a low level of solubility in THF, it was reasoned that **209** must have some degree of solubility due to the success of the Birch reduction in this solvent.[13, 62] Consequently, the consumption of starting material would then lead to its further dissolution. Performing the same reaction in THF, with the temperature maintained at −30 °C for 16 h by use of a cryostat, led to the isolation of dihydropyridone **211** in a more encouraging 62% yield (Scheme 2.5).



209 **211**, 62%

Scheme 2.5: *Grignard addition to **209** in THF.*

At this point, it was reasoned that exchanging the counterion from iodide to trifluoromethanesulfonate may further improve this conversion, as the triflate salt was likely to be more soluble in THF than the corresponding iodide salt **209**.[101] To this end, pyridinium salt **212** was prepared in quantitative yield from pyridine **201**, following literature precedent.[62] Pleasingly, reaction of **212** with a range of Grignard reagents provided the corresponding dihydropyridones **211** and **213-217** in good to excellent yield with results found to be fully reproducible when the reactions were scaled up to 2.5 g (7.6 mmol) of substrate (Scheme 2.6, Table 2.1).



Scheme 2.6: *Formation of salt **212** and its reactivity with Grignard reagents.*

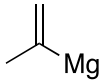
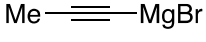
Entry	Grignard	Product	Regioisomer	Yield
1	MeMgBr	**211**	A	89%
2	EtMgBr	**213**	A	97%
3	^{n}HexMgBr	**214**	A	92%
4	^{i}BuMgBr	**215**	A	91%
5		**216**	B	69%
6		**217**	B	60%

Table 2.1: *Addition of Grignard reagents to salt **212**.*

Alkyl Grignard reagents were found to add with complete regioselectivity to the *C*-2 position of pyridinium salt **212** in excellent yield. This was a rare example of nucleophilic addition to a *C*-2 substituted pyridinium salt, generating a quaternary centre with complete control of regioselectivity.[94] The only other example was reported by Charette, shortly before this work was published.[96] While alkyl Grignard reagents added exclusively to the *C*-2 position of pyridinium salt **212** (Table 2.1, entries 1-4), it was discovered that alkenyl and alkynyl Grignard reagents added only at *C*-6 (Table 2.1, entries 5-6).[94] This complete regioselectivity was evident from studying the NMR spectrum of the crude product in each case, after aqueous work up (see Section 2.2.3).

The marked difference in regioselectivity observed for these different conditions was attributed to hard/soft factors. Harder nucleophiles were expected to react preferentially with the harder (more electron deficient due to the electron withdrawing ester group) *C*-2 centre and softer nucleophiles with the softer *C*-6 centre. The relationship between hard and soft nucleophiles and the regioselectivity of addition to pyridinium salts was discussed in Section 1.3.3 and has also been described recently by Yamaguchi.[102] However, in all previous examples, the pyridines were unsubstituted at the 2-position, meaning there were no substituent effects on the reactivity of these positions. It also seemed likely that the 4-methoxy group was acting as a blocking group for this ring position (see Comins' work, Section 1.3.3, Scheme 1.19). While these results were not explored further at this stage, some evidence in favour of this hard/soft hypothesis is presented in the discussion of addition to *N*-allyl pyridinium salts (Section 2.4).

2.2.3 Proton NMR Analysis of the *C*-2 and *C*-6 Regioisomers

The proton NMR spectra of the *C*-2 and *C*-6 regioisomers show certain characteristic differences that can be reliably utilized to determine which dihydropyridone regioisomer has been obtained. The $C(=O)CH_2$ methylene protons are diastereotopic but will differ in their overall splitting pattern depending on the presence (or absence) of neighbouring protons. For the *C*-2 addition products, the methylene protons should appear as a pair of doublets, since they are only expected to couple to each other. Conversely, in the case of *C*-6 addition, the methylene protons should appear as a pair of double doublets as they couple to each other and the proton at *C*-6 (Figure 2.2).

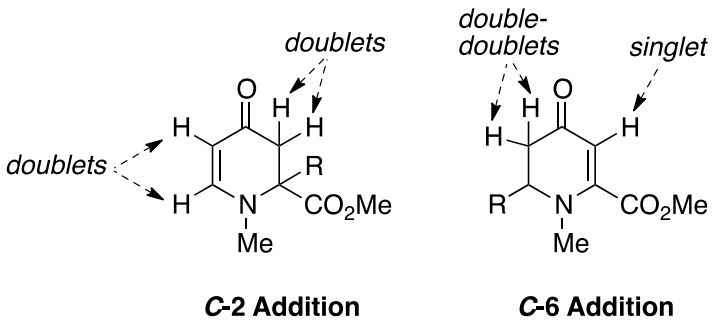


Figure 2.2: *Expected spectral coupling patterns for C-2 and C-6 addition products.*

The other characteristic difference in the proton NMR spectra of the two regioisomers is in the olefinic protons. For the *C*-2 addition product, the two olefinic protons at *C*-5 and *C*-6 were expected to appear as doublets due to coupling to each other, while the single olefinic proton at *C*-3 in the *C*-6 addition product would appear as a singlet, due to the absence of adjacent protons.

Figure 2.3 shows the NMR spectrum of dihydropyridone **211**, obtained by the addition of methylmagnesium bromide to pyridinium salt **212**. The two methylene protons can be seen as doublets at 2.87 ppm and 2.55 ppm. The more deshielded of the olefinic protons at *C*-6 appears as a doublet at 7.02 ppm and the other olefinic proton appears as a doublet at 4.97 ppm.

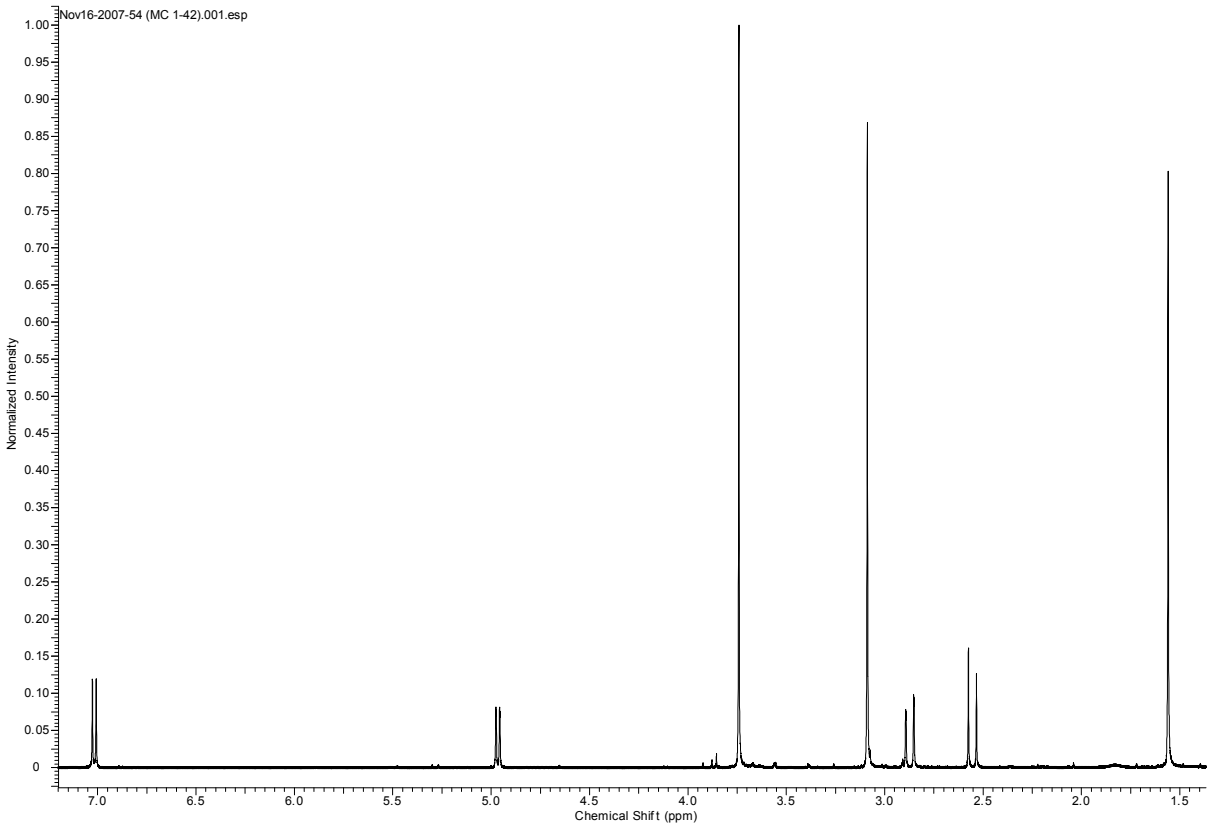


Figure 2.3: *Proton NMR spectrum of C-2 addition product **211**.*

Figure 2.4 shows the NMR spectrum of dihydropyridone **216**, obtained by the addition of *iso*propenylmagnesium bromide to pyridinium salt **212**. The two methylene protons can be seen as double doublets at 2.72 ppm and 2.53 ppm. The single olefinic proton at *C*-3 appears as a singlet at 5.22 ppm.

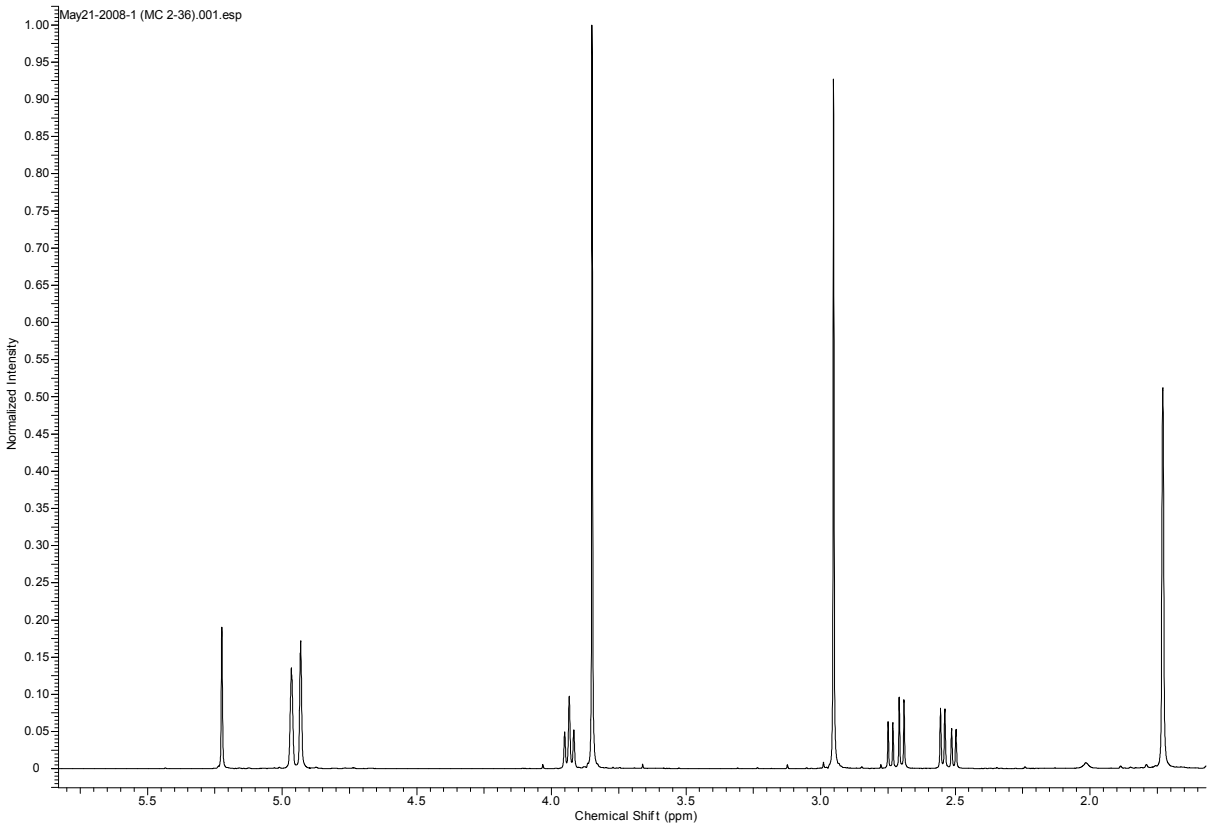


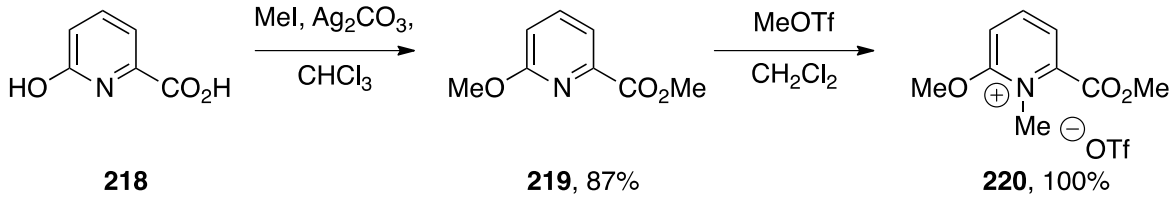
Figure 2.4: *Proton NMR spectrum of C-6 addition product **216**.*

These differences in NMR spectra were found to be general for all varieties of dihydropyridone synthesized during the course of this work and are a useful diagnostic tool for determining the identity of the regioisomer obtained.

2.2.4 Addition to 2,6-Disubstituted Pyridinium Salts

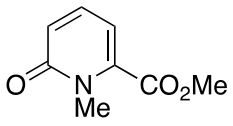
Having developed this simple, efficient and reproducible procedure, it was decided to investigate whether it could be applied to other classes of pyridinium salt that did not perform well under the ammonia-free Birch reduction conditions. The Donohoe group has previously reported the Birch reduction of pyridinium salt **220**, generated in excellent yield over two steps from commercially available 6-hydroxypicolinic acid.[62] Methylation of commercially-available 6-hydroxypicolinic acid **218** was accomplished using methyl iodide and silver carbonate as a base. If potassium carbonate was employed as a base for this reaction, the *N*-methylation product **221** was observed. It was proposed that the soft Ag^+ cation could coordinate to the soft iodine atom of methyl iodide, increasing the polarity of the carbon-iodine bond, thus creating a harder methylating agent which would preferentially react with the harder oxygen nucleophile (Figure

2.5).[103] Treatment of ester **219** with methyl triflate provided pyridinium salt **220** in quantitative yield (Scheme 2.7).



218 **219**, 87% **220**, 100%

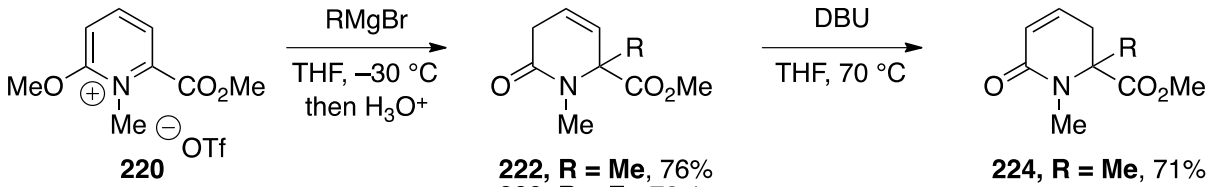
Scheme 2.7: *Preparation of pyridinium salt **220**.*



221

Figure 2.5: *Undesired N-methylation product.*

Pyridinium salt **220** did not perform well under Birch reduction conditions,[62, 103] however when **220** was subjected to the new nucleophilic conditions described in section 2.2.2, the corresponding dihydropyridones could be isolated in good yield. The olefin functionality in the product dihydropyridones **222-223** was found to lie exclusively out of conjugation with the carbonyl group, as was the case with the dihydropyridones obtained by Birch reduction. If the conjugated dihydropyridone **224** was required, it was found that treatment of **222** with DBU allowed equilibration to the thermodynamically most stable dihydropyridone **224** in 71% yield, with the remaining mass being unisomerized dihydropyridone **222** (Scheme 2.8).



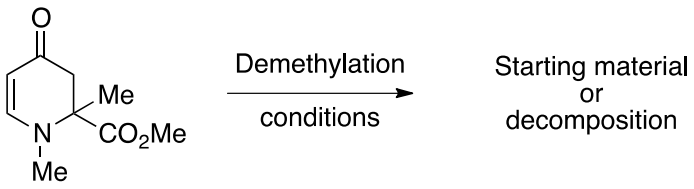
220 **222, R = Me**, 76% **223, R = Et**, 72% **224, R = Me**, 71%

Scheme 2.8: *Formation of dihydropyridones **222** and **223**, and isomerization of **222**.*

2.2.5 Removal of the *N*-Methyl Group

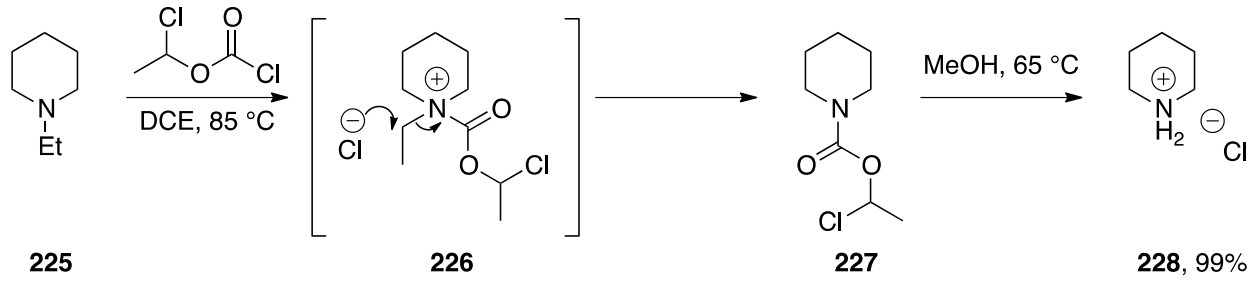
Previous work in the Donohoe group, which was centred on the ammonia free Birch reduction of pyridinium salts,[13, 62] demonstrated that the *N*-Me group could not be removed using

nucleophilic, electrophilic or oxidative procedures. Under the conditions tested (examples include boron tribromide, trifluoroacetic acid, acetic anhydride, chromium trioxide and trimethylsilyl iodide) either starting material was recovered or decomposition occurred (Scheme 2.9).[31]



Scheme 2.9: *Attempted demethylation of dihydropyridone **211**.*

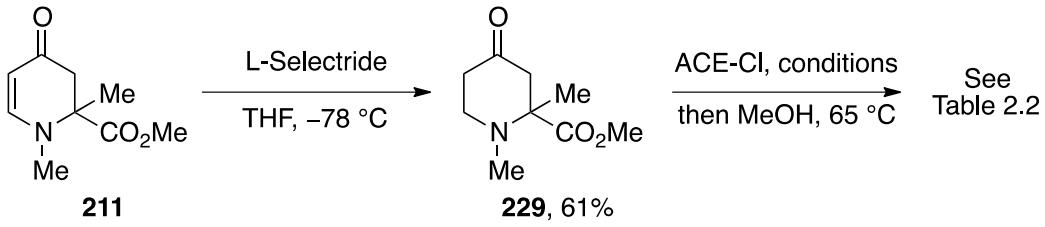
As part of this work, it was hoped that reducing dihydropyridone **211** to piperidone **229** would increase the nucleophilicity of the nitrogen lone pair by preventing its delocalization into the carbonyl moiety, and hence facilitate its reaction with electrophilic demethylating reagents. Furthermore, Olofson has reported the use of 1-chloroethyl chloroformate (ACE-Cl) as a mild means of *N*-dealkylation (Scheme 2.10).[104]



Scheme 2.10: *Olofson's dealkylation of tertiary amines.*

In this case, reaction of *N*-ethyl piperidine **225** with ACE-Cl gave ACE-piperidine **227**, which could then be converted to the secondary amine hydrochloride **228** by heating in methanol. This was in contrast to previous studies into *N*-dealkylation by chloroformates, such as vinyl chloroformate, where strong acids were required to liberate the secondary amine salt.[105]

Reduction of the vinylogous amide was achieved using L-Selectride and piperidone **229** was obtained in 61% yield. However, treatment with ACE-Cl under a variety of conditions led to either recovery of starting material, or decomposition to a complex mixture of products, inseparable by column chromatography (Scheme 2.11, Table 2.2).



Scheme 2.11: *Reduction of vinylogous amide **211** and attempted demethylation.*

Entry	Conditions	Outcome
1	DCE, Na_2CO_3, 90 °C	No reaction
2	PhMe, Na_2CO_3, 120 °C	Decomposition
3	Neat, 135 °C	Decomposition
4	Neat, 90 °C	Decomposition

Table 2.2: *Attempted demethylation of piperidone **229**.*

The failure of attempts to demethylate dihydropyridone **211** or piperidone **229** illustrated that the *N*-methyl moiety was acting as a blocking group, rather than a true protecting group. Therefore, this substrate failed to satisfy point 2, listed in the initial goals of this investigation (Section 2.1). Accordingly, an alternative activating group was sought for nitrogen that would be removable *post*-reduction.

2.3 Nucleophilic Addition to *N*-Benzylic Pyridinium Salts

2.3.1 Preliminary Considerations

From previous work on the Birch reduction of pyridinium salts, it was known that the nucleophilicity of the nitrogen lone pair of electrons on pyridine **201** was poor.[31] This lack of reactivity towards electrophiles has been attributed to two factors (Figure 2.6):

1. The steric hindrance caused by the methyl ester at *C*-2.
2. The inductive electron withdrawal by the methyl ester through the σ-bond network.

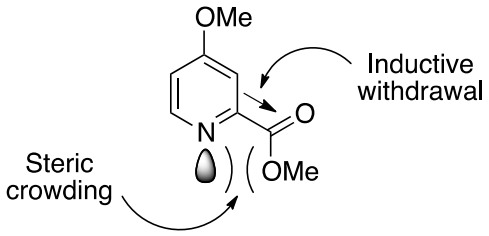
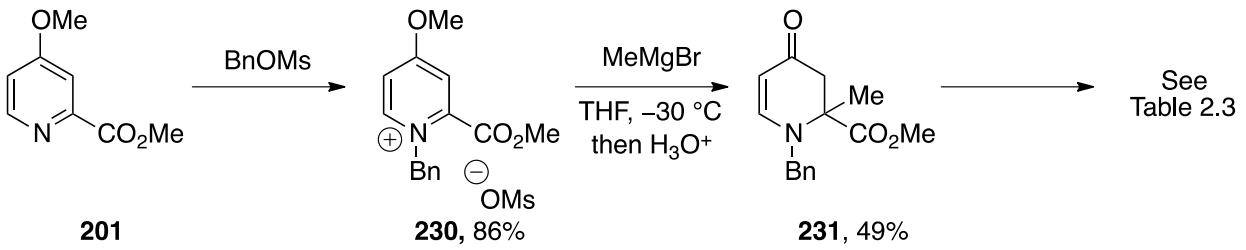


Figure 2.6: *Factors contributing to the observed low nucleophilicity of pyridine **201**.*

Consequently, this work demonstrated that pyridine **201** was unreactive towards acylation with ethyl chloroformate. Although there is a great deal of literature precedent for the formation of *N*-acyl pyridinium salts, there are very few examples of this with a substituent at *C*-2 of the pyridine.[63, 98, 106] It was also found previously that pyridine **201** was unreactive towards many alkyl iodides (such as ethyl iodide or nonyl iodide) with the exception of methyl iodide, presumably due to more facile S_N2 substitution on the less hindered electrophile.[31] The protecting group investigation detailed herein was therefore focused on alkyl mesylates or triflates or reactive benzylic halides.

2.3.2 *N*-Benzyl Pyridinium Salts

It was anticipated that deprotection of *N*-benzyl dihydropyridones may prove to be easier than for *N*-methyl dihydropyridones. Consequently, benzyl mesylate was formed by mesylation of benzyl alcohol (see Experimental) and treatment with pyridine **201** provided pyridinium salt **230** in excellent yield. However, treatment of **230** with methylmagnesium bromide and subsequent acidic hydrolysis gave only a disappointing 49% yield of dihydropyridone **231**, with the remainder of the mass being unreacted starting material. Moreover, attempts to debenzylate **231** met with failure, as starting material was recovered in all cases (Scheme 2.12, Table 2.3).



Scheme 2.12: *Formation of salt **230** and dihydropyridone **231**.*

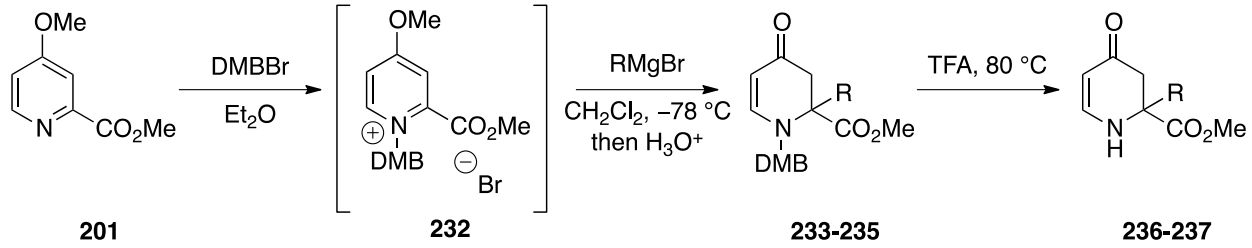
Entry	Conditions	Outcome
1	TFA, 80 °C	No reaction
2	H_2, $Pd(OH)_2/C$, MeOH	No reaction
3	CAN, 9:1 AcMe-H_2O	No reaction

Table 2.3: *Attempts to debenzylate dihydropyridone **231**.*

The low yields for dihydropyridone formation represented a failure to address point 1 of the project goals (Section 2.1) and the nonperformance of deprotection was a failure to address point 2. As a result, further studies were not pursued on this system.

2.3.3 *N*-(3,4-Dimethoxybenzyl) Pyridinium Salts

Previous work in the group has shown that *N*-(*p*-methoxybenzyl) (PMB) protected dihydropyridones can be deprotected in quantitative yield by heating in trifluoroacetic acid.[13, 107] The formation of the corresponding *N*-PMB pyridinium salt has been found to be unreliable,[99] so it was decided to investigate the reactivity of the similar *N*-(3,4-dimethoxybenzyl) (DMB) pyridinium salt **232**. The salt formed by reaction of pyridine **201** and freshly prepared DMBBr (see Experimental) was found to be very hygroscopic and insoluble in THF. It was therefore decided to carry out salt formation and subsequent Grignard addition in one pot, which furnished dihydropyridones **233-235** in reasonable yield. Accordingly, application of the conditions reported in the literature allowed the preparation of deprotected dihydropyridones **236-237** in good yield (Scheme 2.13, Table 2.4).



201 **232** **233-235** **236-237**

Scheme 2.13: *Formation of salt **232**, dihydropyridones **233-235** and dihydropyridones **236-237**.*

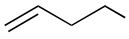
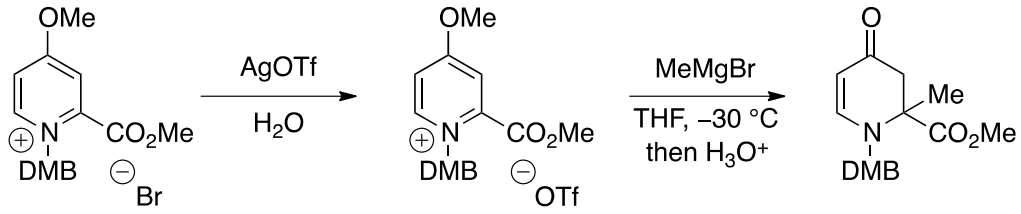
Entry	Grignard	Product	Addition Yield	Deprotection Yield
1	MeMgBr	**233**	56%	70%
2	^{n}HexMgBr	**234**	65%	82%
3		**235**	62%	Not Attempted

Table 2.4: *Addition of Grignards to **232** and subsequent deprotection.*

Unfortunately, the yields obtained for the formation of dihydropyridones **233**-**235** were found to be unreliable; a failure to address point 1 of the project goals (Section 2.1). This was attributed to the reduced stability of Grignard reagents in dichloromethane. However, it was reasoned that substituting the bromide counterion for triflate may enhance the solubility of these salts in THF (see Section 2.2.2) and, as a consequence of THF being a better solvent for Grignard additions than dichloromethane, could increase the yield of dihydropyridones and the reproducibility of the process.

Attempts to directly form the mesylate or triflate of 3,4-dimethoxybenzyl alcohol were unsuccessful, however subjecting bromide salt **232** to anion exchange conditions furnished the desired triflate salt **238** in excellent yield. Silver trifluoromethanesulfonate was chosen as the triflate source and water as the solvent for this exchange, to allow the reaction to be driven by the precipitation of silver bromide from solution.[108] The success of the anion exchange reaction was verified by the appearance of a peak at −78.4 ppm in the ^{19}F NMR spectrum, corresponding to the trifluoromethanesulfonate CF_3 group (Scheme 2.14).



232 **238**, 85% **233**, 65%

Scheme 2.14: *Anion exchange and reaction of salt **238** with Grignard reagent.*

The yields obtained for Grignard addition to salt **238** were higher than the corresponding reaction with bromide salt **232** and were more reproducible. However, the yield of dihydropyridone **233** was still significantly lower than those obtained for the addition to *N*-

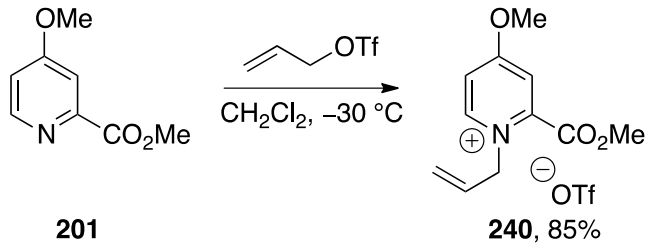
methyl salt **212** (Section 2.2.2) and it was decided to investigate an alternative activating group for nitrogen.

2.4 Nucleophilic Addition to *N*-Allyl Pyridinium Salts

2.4.1 Substrate Synthesis

The lower yields of dihydropyridones obtained from addition to pyridinium salts **232** and **238** were thought to be due, in part, to the larger steric effect of the *N*-benzyl and *N*-DMB groups, compared to *N*-methyl. Accordingly, it was proposed that an *N*-allyl group would presumably have a lower steric effect than an *N*-benzylic group and would also have greater potential for deprotection than an *N*-methyl group *post*-reduction.

Corey has reported the reaction of allyl triflate, generated *in situ* from allyl alcohol, triflic anhydride and di*iso*propylethylamine (see Experimental), with substituted pyridines to yield the corresponding *N*-allyl pyridinium salts.[109] Application of Corey's procedure to pyridine **201** furnished pyridinium salt **240** in an excellent 85% yield (Scheme 2.15).[94]



201 **240**, 85%

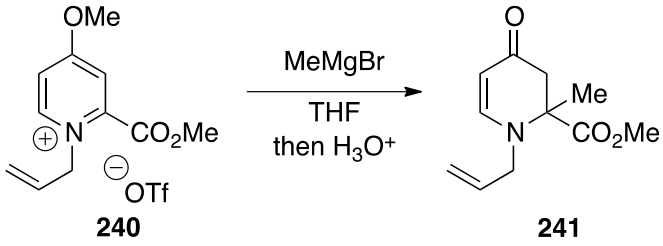
Scheme 2.15: *Formation of salt **240**.*

The formation of pyridinium salt **240** was confirmed by the downfield shift of the proton α to nitrogen to 8.86 ppm in the proton NMR spectrum and the observation of a mass ion peak at 208 in the mass spectrum, corresponding to the cationic pyridinium core.

2.4.2 Nucleophilic Addition to *N*-Allyl Pyridinium Salts[94]

Treatment of **240** with methylmagnesium bromide in THF at –30 °C, followed by acid promoted enol ether hydrolysis as before, provided dihydropyridone **241** in an encouraging 74% yield. Further optimization of these conditions allowed the yield of **241** to be increased to 86% when

the Grignard addition was carried out at −60 °C. Performing the reaction on a 2.5 g (7.0 mmol) scale did not lead to any significant decrease in the efficiency of this procedure and dihydropyridone **241** was obtained in 84% yield. This was particularly satisfactory as scale-up difficulties had proved to be a major limitation of the Birch reduction of pyridinium salts (see Section 1.5.2) and addressing this problem satisfies point 1 listed in the project goals in section 2.1 (Scheme 2.16, Table 2.5).[107]



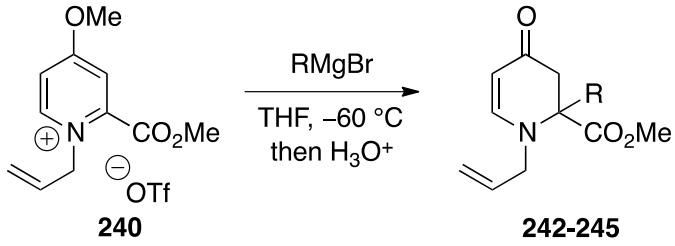
240 **241**

Scheme 2.16: *Addition of methylmagnesium bromide to salt **240**.*

Entry	Temperature	Scale	Yield
1	–30 °C	0.4 mmol	74%
2	–60 °C	0.4 mmol	86%
3	–60 °C	7.0 mmol	84%

Table 2.5: *Effect of temperature and scale-up on the isolated yield of **241**.*

With the success of methyl addition to salt **240** in hand, the generality of this procedure was tested by the addition of other Grignard reagents. Both ethyl and hexylmagnesium bromide gave the corresponding dihydropyridones in excellent yield, while *iso*-propyl and *tert*-butylmagnesium chloride gave the corresponding dihydropyridones in 76% and 50% yield respectively (Scheme 2.17, Table 2.6).



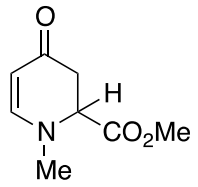
240 **242-245**

Scheme 2.17: *Addition of Grignard reagents to C-2 of salt **240**.*

Entry	Grignard	Product	Yield
1	EtMgBr	**242**	89%
2	^{n}HexMgBr	**243**	86%
3	^{i}PrMgCl	**244**	76%
4	^{t}BuMgCl	**245**	50%

Table 2.6: *Addition of Grignard reagents to C-2 of salt **240**.*

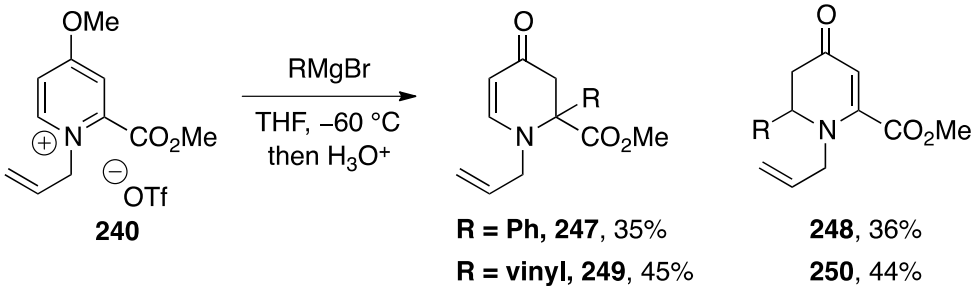
Although an increase in the bulk of the Grignard reagent led to a decrease in the yield of dihydropyridone, it is noteworthy that dihydropyridones **244** and **245** could not be synthesized by the Birch reduction route due to the poor S_N2 substitution reactions of the corresponding secondary and tertiary bromide electrophiles. Indeed, the only product that was isolated in those cases was the protonated dihydropyridone **246**, arising from elimination of HBr from the electrophile (Figure 2.7).[31]



246

Figure 2.7: *Undesired product obtained by Birch reduction of salt **209**.*

As discussed in section 2.2.2, alkyl (sp^3) Grignard reagents were found to add to *N*-methyl pyridinium salts at the *C*-2 position, whereas alkenyl (sp^2) and alkynyl (sp) Grignards were found to add at *C*-6, both with complete regioselectivity. Given that alkyl Grignards were also found to add to salt **240** at *C*-2, it was decided to investigate whether alkenyl and alkynyl Grignards also displayed similar regioselectivity to that observed with *N*-methyl salts. However, treatment of **240** with phenyl or vinylmagnesium bromide provided a 1:1 mixture of the two regioisomeric products (Scheme 2.18).



Scheme 2.18: *Addition of sp^2 Grignard reagents to salt **240**.*

This lack of regioselectivity was surprising given the total control exhibited by addition to *N*-methyl salts. It seemed possible that the *N*-allyl group could be adopting a conformation that hindered addition at *C*-6, minimizing the energy difference between *C*-2 and *C*-6 addition for sp^2 Grignard reagents.

2.4.3 Investigating Hard/Soft Nucleophiles

In order to maximize the synthetic utility of this methodology, the lack of regioselectivity displayed by sp^2 Grignard addition to pyridinium salt **240** needed to be addressed. It was thought that if the regioselectivity of addition was indeed controlled by hard/soft factors, then using a harder or softer nucleophile could introduce regioselectivity to this process (Figure 2.8).

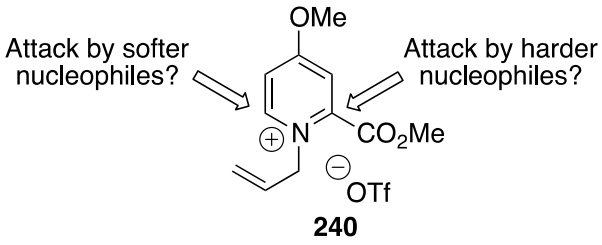
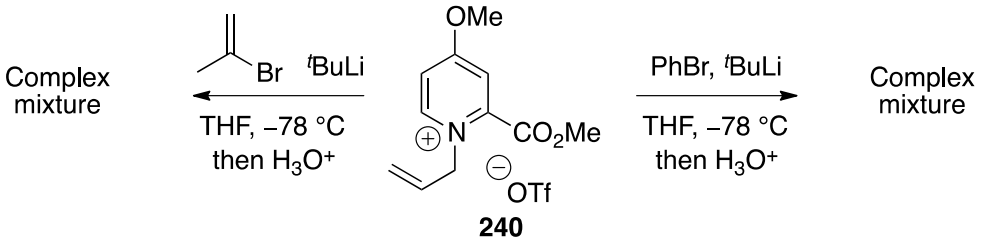


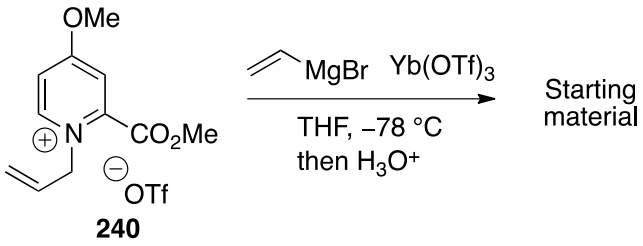
Figure 2.8: *Postulated regioselectivity preferences for hard/soft nucleophiles.*

The first investigations into this subject were centred on organolithium reagents, which are known to be harder than Grignard reagents.[110] In two separate experiments, pyridinium salt **240** was treated with phenyl lithium and isopropenyl lithium, with the organolithiums being prepared freshly from the corresponding bromide. In both cases, a complex mixture of decomposition products was observed (Scheme 2.19).



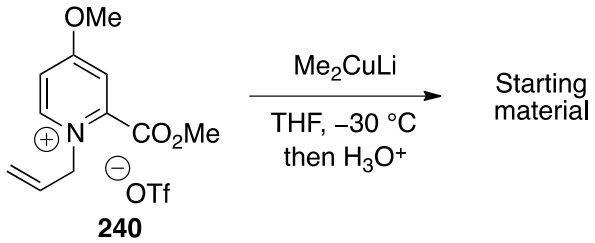
Scheme 2.19: *Attempted addition of organolithiums to salt **240**.*

Organolanthanides are another known class of hard organometallic reagents.[111] In an attempt to apply these findings, dried ytterbium(III) triflate was treated with vinylmagnesium bromide to generate an organoytterbium species. However, when a solution of pyridinium salt **240** in THF was added to this solution, only starting material was recovered (Scheme 2.20).



Scheme 2.20: *Attempted addition of organoytterbiums to salt **240**.*

At this point, attention was turned to the generation of a softer nucleophile for addition to pyridinium salt **240**. Organocuprates have received a great deal of attention for their soft characteristics.[112, 113] Treatment of pyridinium salt **240** with a freshly prepared solution of lithium dimethylcuprate provided only returned starting material (Scheme 2.21).

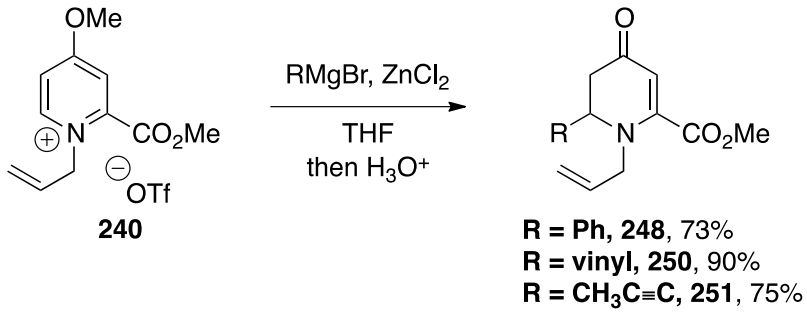


Scheme 2.21: *Attempted addition of organocuprates to salt **240**.*

Another well documented class of soft nucleophiles are organozinc species.[114] By briefly pre-mixing a solution of zinc(II) chloride and phenylmagnesium bromide, we were delighted to find only one product by analysis of TLC and the proton NMR spectrum of the crude material.[94]

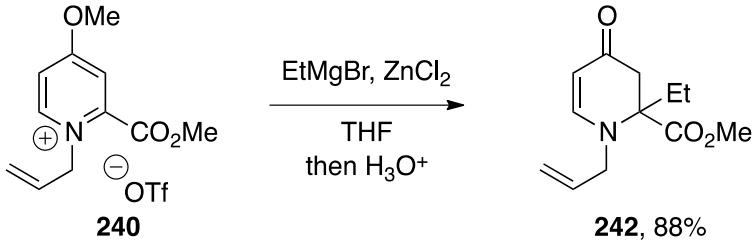
Purification allowed the compound to be characterized as dihydropyridone **248**, arising from addition at *C*-6. This regioselectivity was in agreement with the hard/soft model for addition to these pyridinium salts (Section 2.2.2), where the softer nucleophiles tend to add at the softer *C*-6 centre.

The proton NMR spectrum of **248** displayed a singlet at 5.39 ppm, corresponding to the olefinic proton at *C*-3 and a pair of double doublets at 2.93 ppm and 2.71 ppm, corresponding to the methylene group at *C*-5. These data were consistent with those typically obtained for *C*-6 addition (Section 2.2.3). Repeating this procedure using vinyl and 1-propynylmagnesium bromide gave the corresponding *C*-6 addition products **250** and **251** in excellent yields and as single regioisomers (Scheme 2.22).



Scheme 2.22: *Regioselective addition of organozincs to salt **240**.*

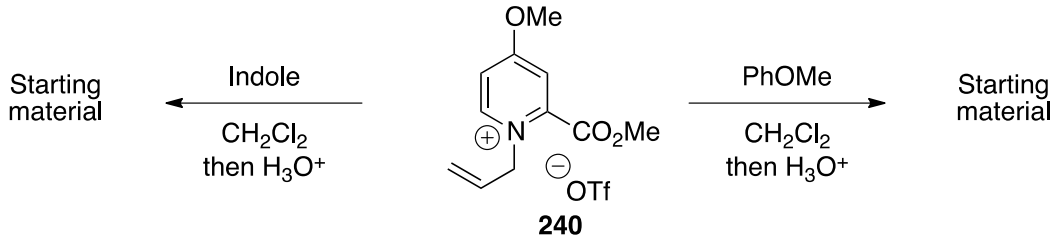
Given the profound effect of transmetallation to zinc upon the addition of sp^2 and sp Grignards to pyridinium salt **240**, it was decided to investigate whether transmetallation of alkyl (sp^3) Grignard reagents had a similar effect. However, repeating the same procedure using ethylmagnesium bromide gave the *C*-2 addition product **242** in 88% yield (compared to 89% yield of **242**, in the absence of $ZnCl_2$, section 2.4.2). The provision of the same dihydropyridone **242** that was obtained in the absence of zinc chloride demonstrates that, in this case, transmetallation does not override the preference of alkyl reagents to add at *C*-2 of pyridinium salt **240** (Scheme 2.23).



Scheme 2.23: *Formation of dihydropyridone **242** occurred as before, in the absence of $ZnCl_2$.*

2.4.4 Studies Towards the Addition of Non-organometallic Nucleophiles

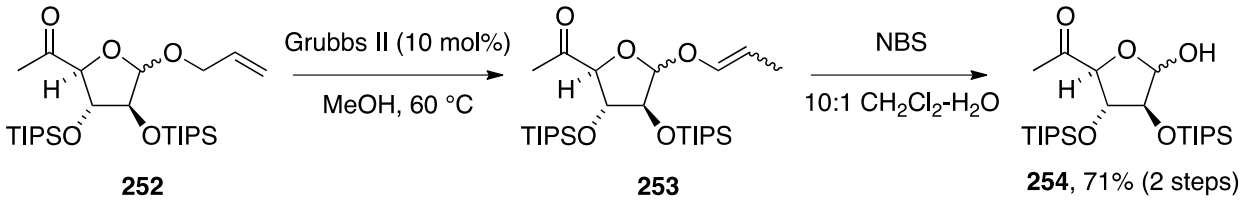
Corey and, more recently, Clayden have published work on nucleophilic addition to *N*-trifluoromethanesulfonyl pyridinium salts.[58, 59] Both authors found that these salts were sufficiently electrophilic to undergo nucleophilic addition with weak nucleophiles such as simple arenes (Section 1.3.3). If pyridinium salt **240** proved to be reactive to weaker nucleophiles such as arenes, a significant range of functionalized dihydropyridones could be generated without pre-forming an organometallic reagent. When pyridinium salt **240** was treated with either indole or anisole, using Corey's optimized procedure, only unreacted starting material was recovered. Clearly, under these conditions, salt **240** was unreactive towards "non-activated" nucleophiles (Scheme 2.24).



Scheme 2.24: *Attempted addition of unactivated nucleophles to salt **240**.*

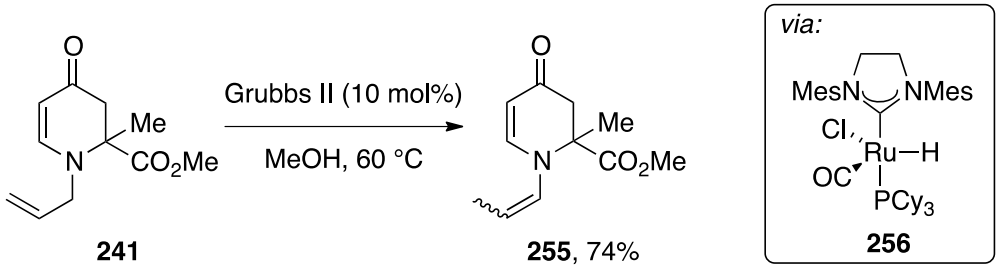
2.5 Deprotection of *N*-Allyl Dihydropyridones

In order to address point 2 listed in the project goals (Section 2.1), an efficient procedure for the removal of the *N*-allyl group from the product dihydropyridones was required. As an example of this, Donohoe has recently reported an *O*-deallylation procedure involving isomerization of the terminal double bond to generate an enol ether, followed by hydrolysis (Scheme 2.25).[115]



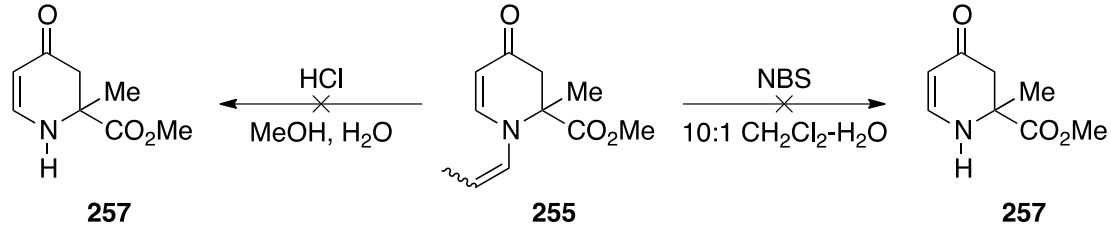
Scheme 2.25: *Excerpt from Donohoe's synthesis of (–)-hygromycin A **254**.*

Our first enquiries into deallylation of dihydropyridone **241** were focused on this method. The *N*-allyl group could easily be isomerized using Hanessian's procedure,[116] involving a "thermally-modified" Grubbs second generation catalyst, and enamine **255** was obtained in an excellent yield of 74%, as an inconsequential 4:1 mixture of *trans*-/*cis*- olefin isomers. This thermal modification is thought to involve conversion of the Grubbs 2nd generation catalyst to ruthenium hydride species **256** (Scheme 2.26). The utility of ruthenium hydride species in catalyzing terminal olefin isomerization has recently been reviewed.[117]



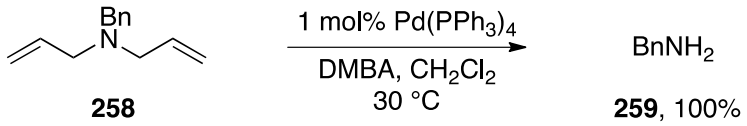
Scheme 2.26: *Terminal olefin isomerization for **241**, catalyzed by ruthenium hydride **256**.*

Attention was then focused on the hydrolysis of enamine **255** to liberate dihydropyridone **257**. Unfortunately, application of Donohoe's method, involving NBS to brominate the enamine followed by imminium ion hydrolysis, led to a complex mixture of brominated products.[115] Additionally, attempts at an acid promoted enamine hydrolysis were unsuccessful and a complex mixture of products was obtained once again (Scheme 2.27).



Scheme 2.27: *Attempted enamine hydrolysis.*

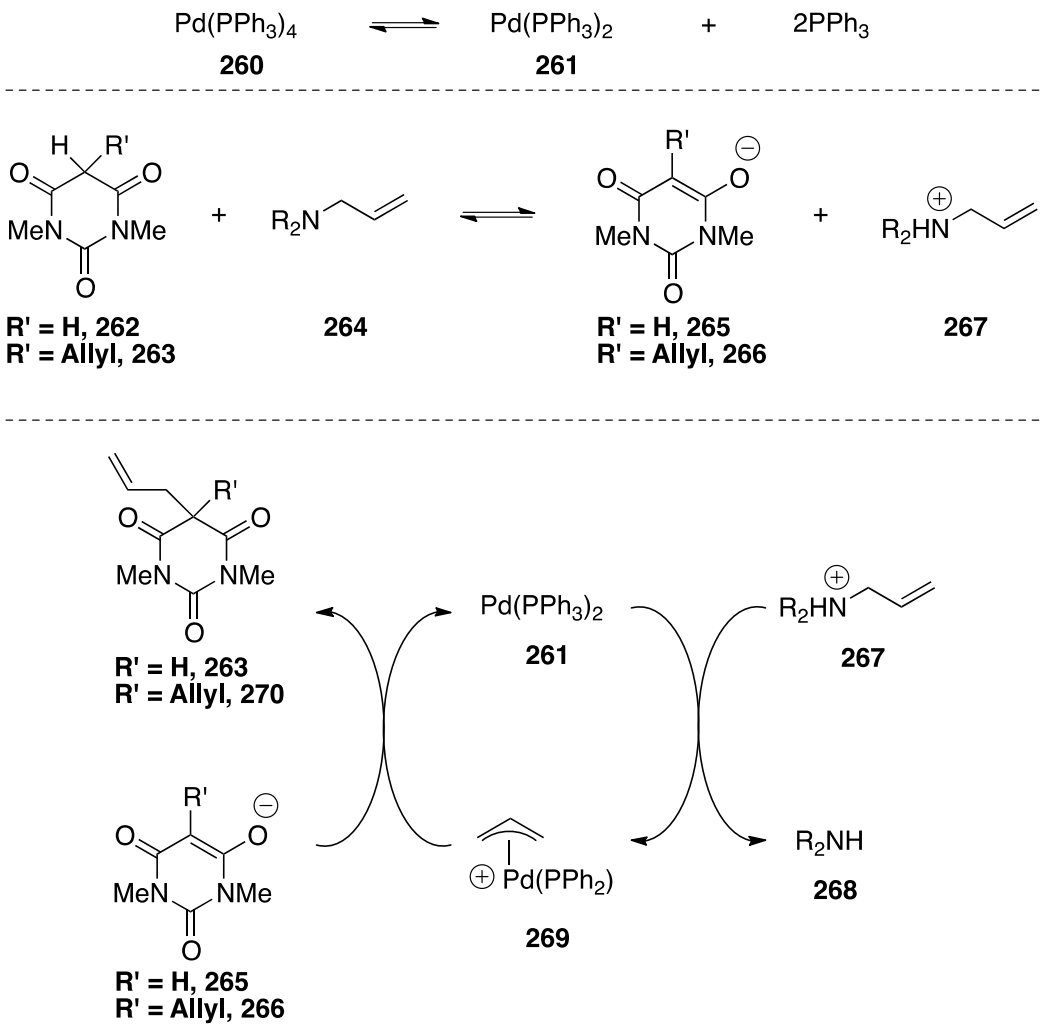
At this stage, an alternative deprotection strategy was sought. Guibé has reported an efficient, palladium catalyzed procedure for *N*-deallylation.[118] Catalyst loadings of as low as 1 mol% were found to be effective, provided that 1,3-dimethylbarbituric acid (DMBA) **262** was used as both a proton source and a scavenger for the liberated allyl group (Scheme 2.28).



258 **259**, 100%

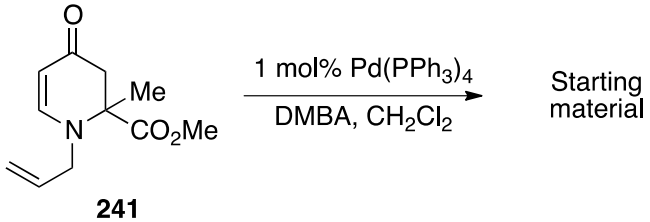
Scheme 2.28: *Guibé's N-deallylation procedure.*

Guibé proposes a mechanism for this transformation involving the reversible dissociation of two triphenylphosphine ligands from complex **260**, giving the electron deficient (14 electron) zero-valent complex **261**. Protonation of the allylic amine **264** by DMBA **262** (or by its mono-allyl derivative **263**) gives allyl ammonium species **267** along with anion **265** or **266** as part of an acid-base equilibrium. Allyl ammonium species **267** reacts with complex **261**, liberating the deallylated amine **268** and π-allyl complex **269**, which is then trapped irreversibly by anion **265** or **266** providing *C*-allylated product **263** or **270**, with concomitant regeneration of the catalytic palladium species **261**. Guibé notes that the major by-products of this reaction are recovered DMBA **262** and its di-allylated derivative **270** with mono-allyl derivative **263** only being present in small amounts. This suggests that **263** is a more efficient allyl group scavenger than DMBA itself (Scheme 2.29).[118]



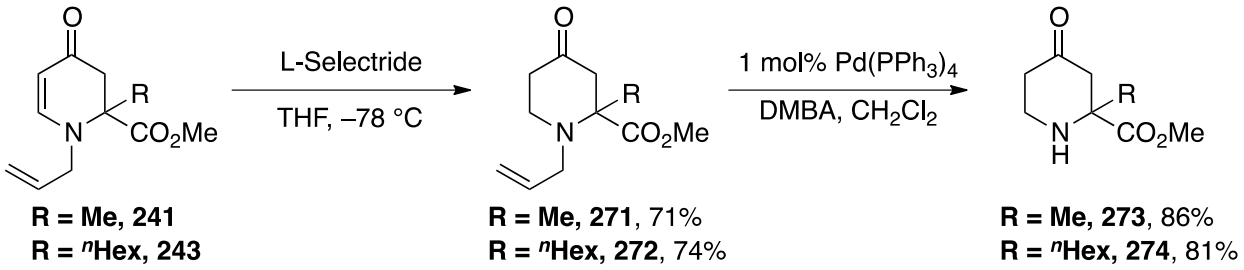
Scheme 2.29: *Postulated mechanism of Guibé's N-deallylation.*

Unfortunately, application of Guibé's procedure to dihydropyridone **241** gave only unchanged starting material. Consideration of Guibé's mechanism for this transformation revealed that protonation of the allylic nitrogen was required for the reaction to be successful. As the nitrogen atom of dihydropyridone **241** formed part of a vinylogous amide system, it seemed likely that it was insufficiently basic to be protonated by DMBA, whose pK_a (H_2O) is 4.7 (Scheme 2.30).[118]



Scheme 2.30: *Failed attempt at N-deallylation of dihydropyridone **241**.*

For this procedure to be successful, a more basic nitrogen atom was required. It was reasoned that reduction of the vinylogous amide system, by conjugate addition of either hydride or a soft organocuprate nucleophile, was likely to form part of any synthetic sequence involving dihydropyridone **241**. This reduction would leave a tertiary amine that would be more basic than the vinylogus amide nitrogen in dihydropyridone **241**. Treatment of **241** with L-Selectride (see Section 2.2.5) proceeded smoothly yielding tertiary amine **271** and subjection of **271** to Guibé's conditions provided secondary amine **273** in an excellent yield of 86%. This procedure could be repeated with dihydropyridone **243**, providing secondary amine **274** in a good yield of 60% over two steps (Scheme 2.31).



Scheme 2.31: *Reduction of vinylogous amides **241** and **243**, and their N-deallylation.*

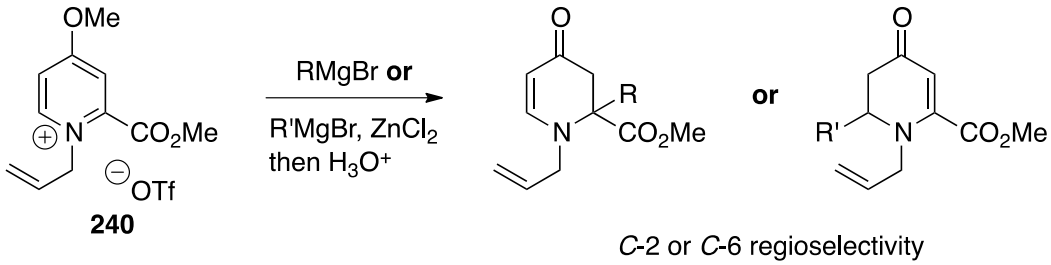
The ability to de-allylate the dihydropyridone products was a crucial advancement in the development of this methodology, allowing for further functionalization of nitrogen, if necessary, in a synthetic sequence. With both of the initial project goals satisfied (Section 2.1), it was anticipated that this methodology would be of great interest and utility to synthetic chemists.

2.6 Conclusions

Nucleophilic addition of Grignard reagents to *N*-methyl pyridinium salt **212** proceeded in good yield (60-97%) and with complete regioselectivity. However, the inability to demethylate dihydropyridones **211** and **213**-**217** necessitated an investigation of alternative activating groups for nitrogen.

When DMB was used as an activating group for nitrogen, the corresponding dihydropyridones were isolated in moderate yield and these products could be deprotected under the somewhat harsh conditions of refluxing trifluoroacetic acid. The moderate yields for dihydropyridone formation prompted an investigation of addition to *N*-allyl pyridinium salt **240**. A wide range of nucleophiles was tested and the corresponding dihydropyridones were isolated in good to

excellent yield. Where 1:1 regioisomeric mixtures were obtained, the regioselectivity of addition could be controlled by the addition of a softer organozinc nucleophile. Finally the dihydropyridones could be deprotected as part of an efficient two-step procedure. With the reduction of the vinylogous amide likely to form part of any synthetic sequence involving these intermediates, this route need not be viewed as over-convoluted (Scheme 2.32).



Scheme 2.32: *The regioselective addition of nucleophiles to pyridinium salt **240**.*

With an efficient procedure for the synthesis and de-allylation of dihydropyridones in hand, it is clear that both points 1 and 2 listed in the project goals (Section 2.1) have been addressed.

Chapter 3:
The Preparation of Enantiopure Dihydropyridones

3.1 Strategies for the Formation of Enantioenriched Dihydropyridones

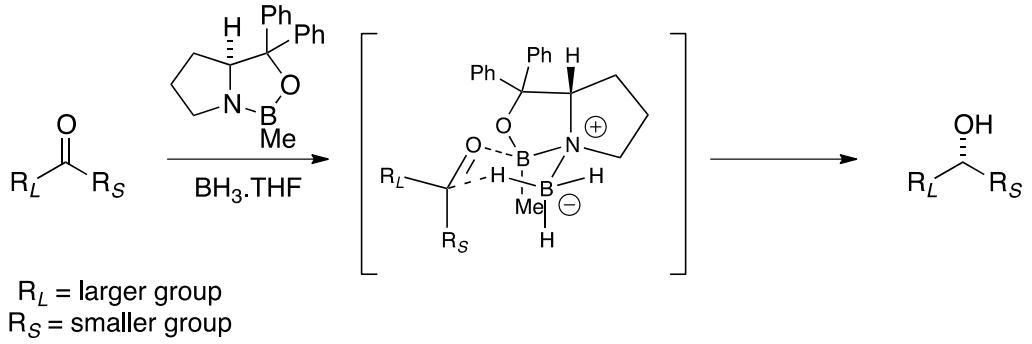
Chiral auxiliaries have proven to be a highly effective method for achieving asymmetric induction under otherwise non-enantio-differentiating reaction conditions.[119] However, the use of chiral auxiliaries in preparing chiral dihydropyridones, with high levels of diastereoselectivity, is already well documented in the literature (Section 1.5.3).[87, 93] Additionally, one of the major drawbacks to chiral auxiliary based methodology is the addition of extra steps to a synthetic sequence, involving the addition of an auxiliary to the starting material and its subsequent removal. For these reasons it was decided to attempt to find alternate means of asymmetric induction for dihydropyridone formation.

Two potential strategies for achieving this goal were reagent control and substrate control, the applications of which will be discussed individually in the coming chapter. Reagent control involves the formation of a reagent, capable of carrying out a particular reaction enantioselectively. Substrate control involves the preparation of a reaction substrate that a reagent will add to enantioselectively. Chiral auxiliaries may be thought of as a sub-class of substrate control.

Whichever method is eventually chosen to control enantioselectivity, from a synthetic viewpoint the importance of the ability to prepare products as single enantiomers is in no doubt.[119] As Donohoe has demonstrated the utility of dihydropyridones in his total synthesis of (±)-cylindricine C and formal synthesis of (±)-cylindricine A, an efficient, enantioselective route to dihydropyridones was evidently required.[95]

3.2 Reagent Control

Many transformations involving chiral reagents proceed through closed transition states, such as the six-membered, chair-like transition states involved in many enantioselective additions to aldehydes. For example, in the Corey-Bakshi-Shibata (CBS) reduction,[120] the oxygen lone pair forms a coordinate bond to the boron completing the chair. This coordination also serves to activate the carbonyl towards addition of hydride. (Scheme 3.1)

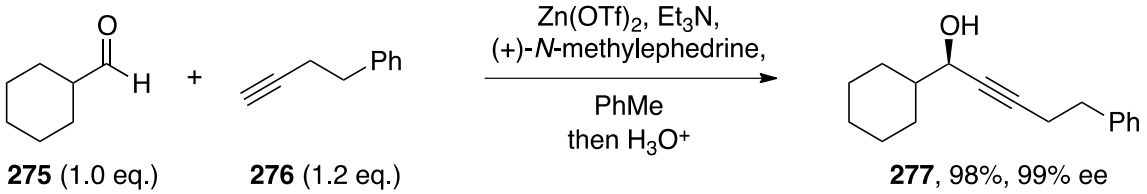


Scheme 3.1: *CBS reduction as an example of reagent control.*

In the case of pyridinium salts, coordination to a reagent *via* nitrogen was impossible, due to the lack of a lone pair of electrons on the quaternary nitrogen. However, it was felt that some work should be undertaken to determine the viability of a reagent controlled approach to enantiopure dihydropyridones.

3.2.1 Addition of Alkynyl Nucleophiles

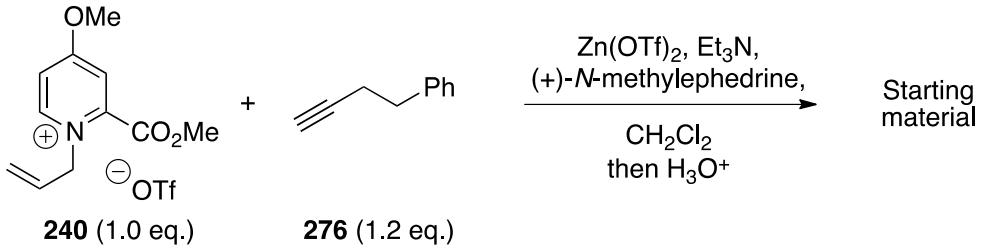
Carreira has reported the addition of a chiral organozinc species to aldehydes.[121] In the presence of zinc triflate, a tertiary amine base and *N*-methyl ephedrine as a chiral ligand for zinc, high yields and enantiomeric excesses were obtained for the addition of terminal alkynes, such as **276** to aldehydes, such as **275**. A catalytic variant of this procedure was reported by Carreira in 2001 (Scheme 3.2).[122]



Scheme 3.2: *Carreira's enantioselective addition of alkynyl-zinc reagents to aldehydes.*

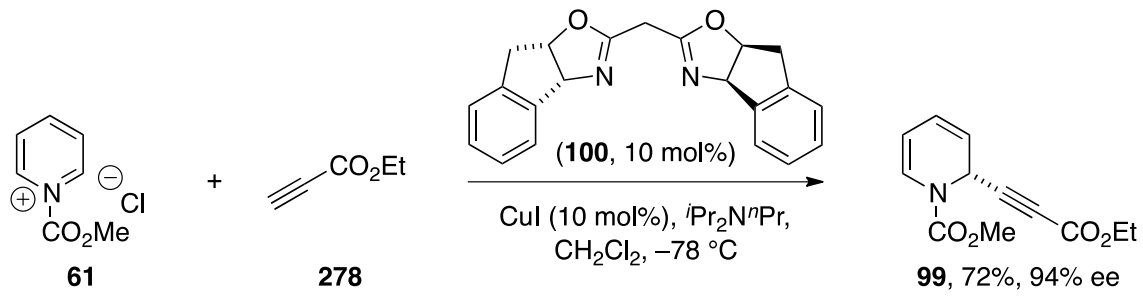
If Carreira's methodology could be successfully applied to pyridinium salt **240**, this would represent an exciting breakthrough, allowing the conversion of a flat, achiral substrate into an enantiopure product in a single step. Although Carreira found that the best enantioselectivities were obtained using toluene as a solvent, the insolubility of pyridinium salt **240** in toluene necessitated the use of dichloromethane which, Carreira reported, was only slightly detrimental to the ee of secondary alcohol **277**. Unfortunately, application of Carriera's procedure to

pyridinium salt **240** provided only returned starting material. In addition, the reaction also failed when performed without the addition of *N*-methyl ephedrine, suggesting that the zinc alkynylide species, generated *in situ*, was unreactive towards pyridinium salt **240** (Scheme 3.3).



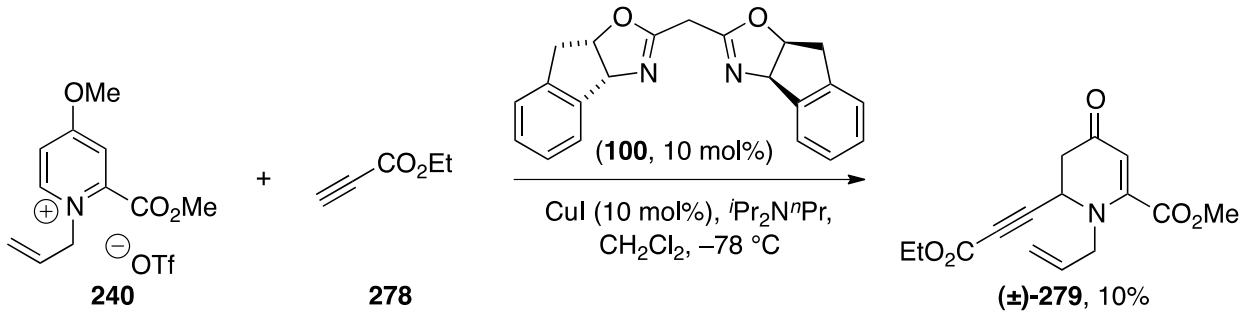
Scheme 3.3: *Attempts to apply Carreira's methodology to pyridinium salt **240**.*

In 2007, Ma published a copper catalyzed, enantioselective addition of activated terminal alkynes to *N*-acyl pyridinium salt **61**.[57] By using the bidentate *bis*-(oxazoline) ligand **100**, the corresponding dihydropyridines, such as **99**, were obtained in good yield and in up to 99% ee. However, Ma noted that small changes to both the *N*-acyl group and to the alkyne dramatically influenced the outcome of the reaction (Scheme 3.4).



Scheme 3.4: *Ma's enantioselective addition of terminal alkynes to pyridinium salts.*

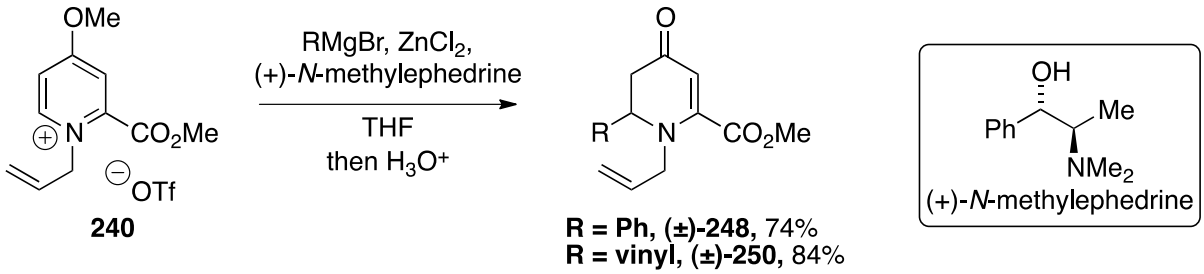
Pyridine **201** could not be *N*-acylated as **201** was known to be inert to chloroformate reagents (Section 2.3.1). However, the reactivity of pyridinium salt **240** was tested under Ma's conditions. Dihydropyridone **279** was isolated in a disappointing yield of 10%, however the *C*-6 addition product was obtained as predicted by the proposed model for addition of soft organocuprate reagents (Section 2.4.3). In addition to the low yield for this process, HPLC analysis of a sample of **279** showed that it was racemic. Due to the lack of efficiency and enantioselectivity with this method, it was not pursued further (Scheme 3.5).



Scheme 3.5: *Attempts to apply Ma's methodology to pyridinium salt **240**.*

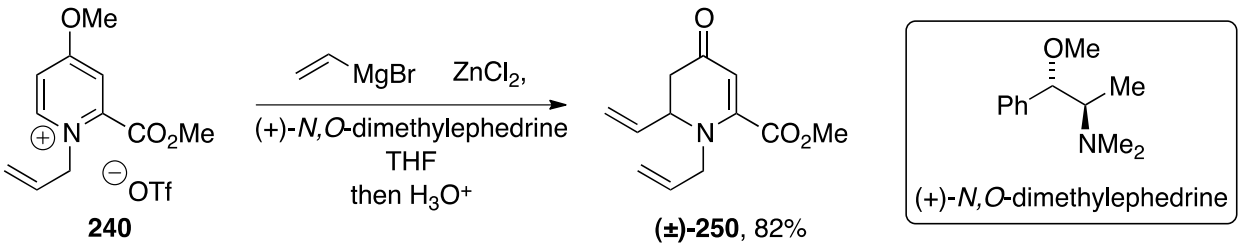
3.2.2 Addition of Other Zinc-Based Nucleophiles

Given that organozinc species have previously been shown to add to pyridinium salt **240** (Section 2.4.3), attempts were made to find a chiral ligand for these organometallic species. When (+)-*N*-methyl ephedrine was pre-mixed with the organozinc solution generated using phenyl or vinylmagnesium bromide and zinc chloride, dihydropyridones **248** and **250** were generated, as expected. Unfortunately, these samples were found to be racemic by HPLC analysis. Clearly, the chiral additive was not participating in the reaction between the organozinc species and pyridinium salt **240** (Scheme 3.6).



Scheme 3.6: *Organozinc addition with a chiral additive.*

Due to the highly basic nature of organometallic reagents, the acidic O-H proton of (+)-*N*-methyl ephedrine was removed by Williamson methylation of the alcohol. With *N,O*-dimethyl ephedrine in hand, its efficacy as a chiral additive for organozinc addition to pyridinium salt **240** was tested. Addition of a solution of **240** to the pre-mixed solution of Grignard reagent, zinc chloride and *N,O*-dimethyl ephedrine provided dihydropyridone **250** in good yield, however this sample was also found to be racemic after HPLC analysis (Scheme 3.7).



Scheme 3.7: *Organozinc addition with a chiral additive.*

In addition to the lack of asymmetric induction in these processes, stoichiometric quantities of chiral ligand would be necessary, due to the unselective background reaction between the pyridinium salt and organozinc species. Given these obstacles, an extensive screening of chiral additives was not judged to be a cost-effective pursuit and attention was focused on a different strategy.

3.2.3 Organocatalytic Addition of Nucleophiles

The organocatalytic addition of enamine nucleophiles to aldehydes, in high yield and enantioselectivity, is well documented in the literature.[123] In this process, a chiral enamine is formed *in situ* by condensation of an aldehyde with a chiral amine. Two amines suited to this purpose have been reported by Hayashi and MacMillan (Figure 3.1).[124, 125]

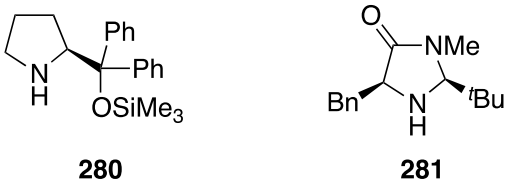
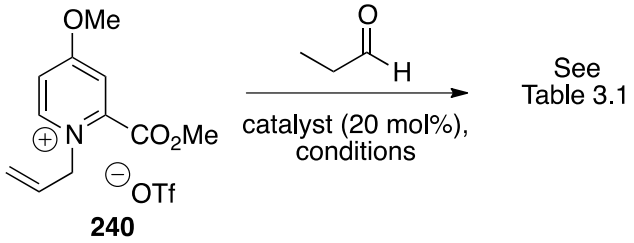


Figure 3.1: *Chiral amines for enamine catalysis.*

It was hoped that the enamine formed by condensation of one of the catalysts **280** or **281** with a simple aldehyde, such as propionaldehyde, could add to pyridinium salt **240** in similarly high yield and enantioselectivity. Unfortunately, no reaction was observed under any of the conditions investigated, including strong heating (Scheme 3.8, Table 3.1). On reflection, this seemed to be in line with the findings of Section 2.4.4, where unactivated (non-organometallic) nucleophiles were not reactive enough to add to salt **240**.



Scheme 3.8: *Attempted organocatalytic addition to pyridinium salt **240**.*

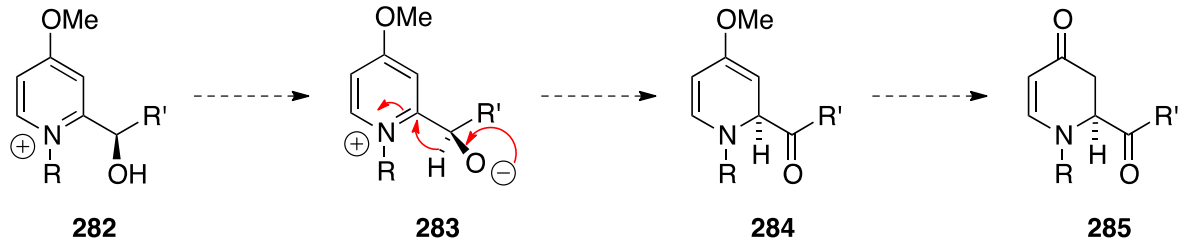
Entry	Catalyst	Conditions	Outcome
1	**280**	CH_2Cl_2, rt	No reaction
2	**280**	DMF, 100 °C	No reaction
3	**281**	TFA (20 mol%), CH_2Cl_2, rt	No reaction
4	**281**	TFA (20 mol%), DMF, 100 °C	No reaction

Table 3.1: *Attempted organocatalytic addition to pyridinium salt **240**.*

3.3 Substrate Control

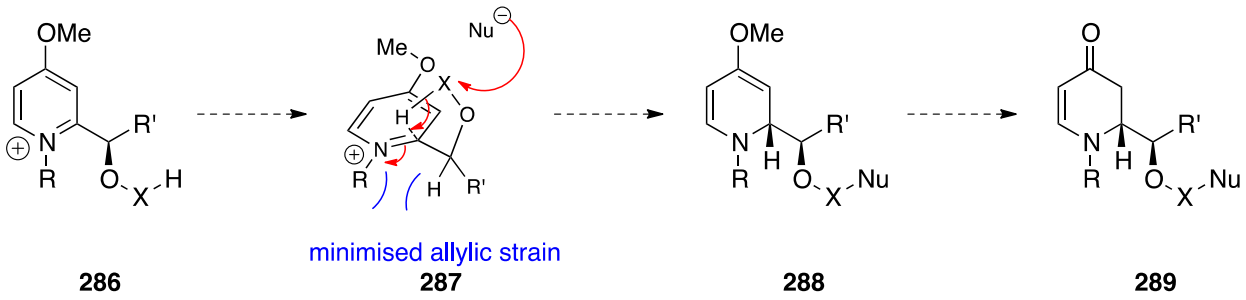
Due to the failures of a reagent-controlled route to enantiopure dihydropyridones, attention was switched to a substrate-controlled route. For the reasons outlined in section 3.1, a chiral auxiliary approach was deemed undesirable. However, installing a stereogenic centre that could both control the diastereoselectivity of addition to the pyridinium nucleus and form an integral part of the required building blocks in later synthetic steps would be highly desirable.

To this end, two potential strategies were proposed; both of which would require the preparation of the chiral pyridinium salt **282**. The first route would focus on a base-promoted [1,2]-hydride migration onto the pyridinium nucleus. There is limited literature precedent for a process such as this, whereby the hydride would be delivered from the same face as it originated from, due to orbital requirements. (Scheme 3.9).[126]



Scheme 3.9: *Proposed [1,2]-hydride migration strategy.*

The second route would involve tethering a hydride source to the chiral secondary alcohol **282** and inducing a hydride migration onto the pyridinium nucleus. The utility of dialkyl silyl ethers as a hydride donor has been demonstrated in the literature, so this was proposed as a viable substrate for investigation.[127, 128] The diastereoselectivity of hydride addition to the pyridinium nucleus would be controlled by 1,3-allylic strain between the *N*-allyl group and the chiral secondary alcohol, the most favourable conformation being depicted in Scheme 3.10. It is also noteworthy that the product dihydropyridones **289** would contain two contiguous stereocentres.

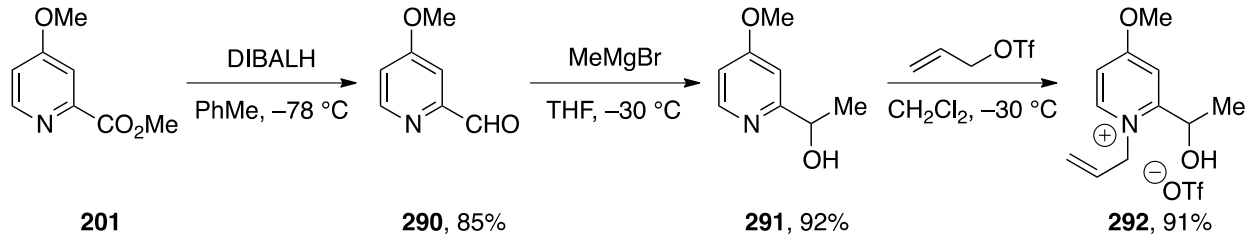


Scheme 3.10: *Proposed hydride migration strategy, controlled by 1,3-allylic strain.*

3.3.1 Substrate Synthesis

Owing to cost considerations, it was decided to optimize reaction conditions on racemic material before applying any findings to enantiopure substrates. A short route to pyridinium salt **292** was therefore envisioned: pyridine **201** was converted to the commercially available, although expensive, aldehyde **290** in 85% yield. This could be verified by the appearance of the 1 H singlet at 10.00 ppm in the proton NMR spectrum. Aldehyde **290** was considered the starting point for this methodology investigation due to its commercial availability, although it could be easily prepared from cheaper material. Addition of methylmagnesium bromide to **290** gave the secondary alcohol **291** and *N*-allylation provided the corresponding pyridinium salt **292** in 84% yield over two steps. Although significant regioselectivity in favour of *N*-allylation over *O*-

allylation of pyridine **291** was observed, small amounts of di-allylated product were obtained. This could be minimized by reducing the amount of allyl triflate to 1.2 equivalents, down from 1.5 equivalents, used for the formation of salt **240** (Scheme 3.11).

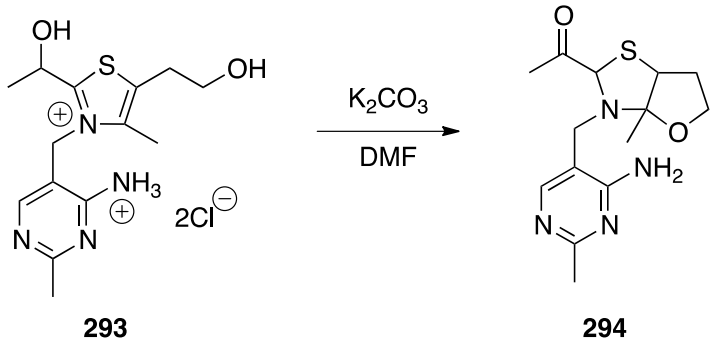


Scheme 3.11: *Synthesis of pyridinium salt **292**.*

The formation of the correct pyridinium salt **292** was confirmed by a downfield shift to 8.61 ppm of the proton α to nitrogen and the observation of a mass ion peak at 194 in the mass spectrum, corresponding to the cationic pyridinium core.

3.3.2 Attempts to Promote a [1,2]-Hydride Migration

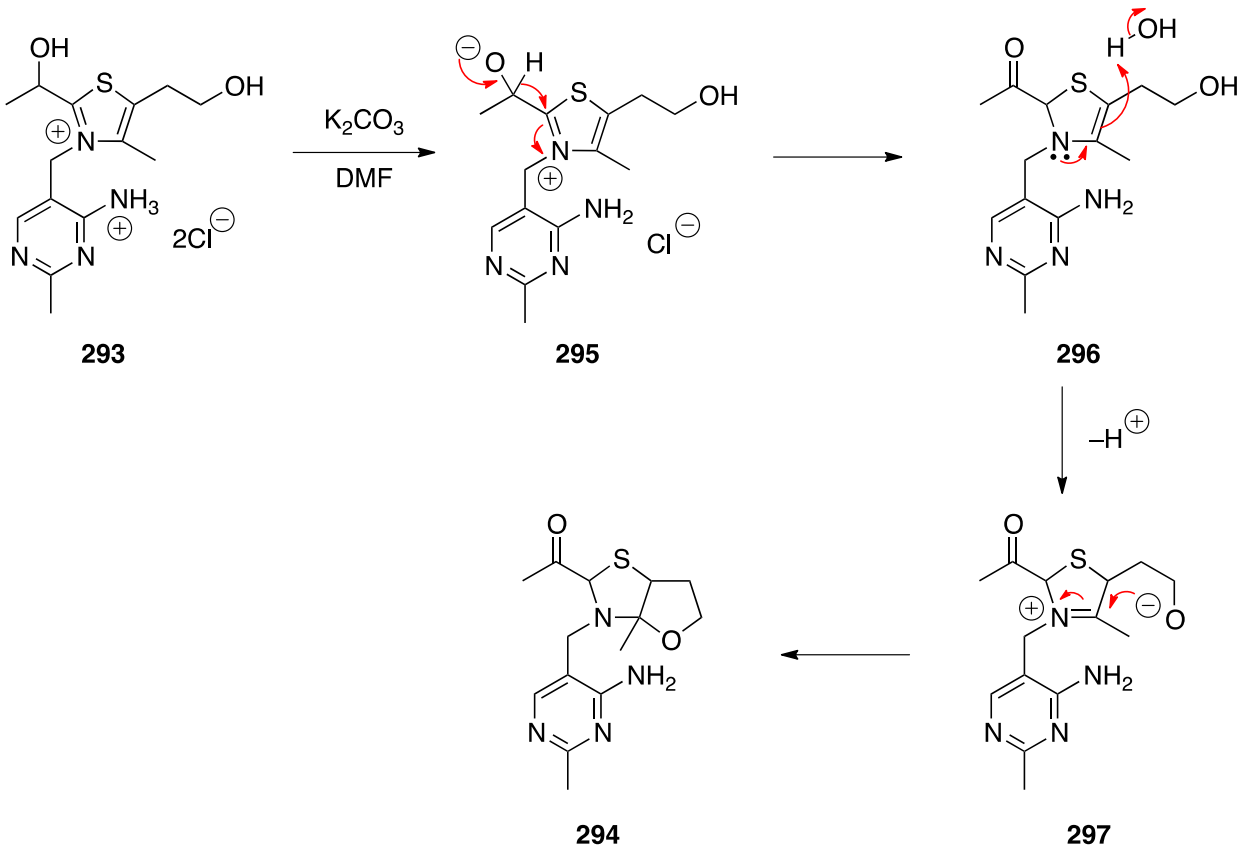
With an efficient, reliable route to pyridinium salt **292** in hand, attention was turned to promoting the 1,2-hydride migration onto the pyridinium nucleus. To this end, the work of Risinger seemed appropriate who, in 1978, reported an improvement to the procedure of Takamizawa *et al.* for the preparation of heterocycle **294** (Scheme 3.12).[126, 129]



Scheme 3.12: *Risinger's preparation of heterocycle **294**.*

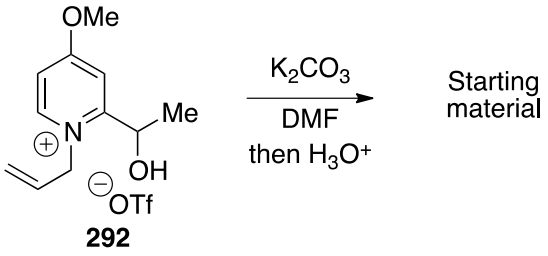
The likely mechanism for this procedure first involved *N*- and *O*-deprotonation when salt **293** was treated with potassium carbonate. The subsequent 1,2-hydride migration was promoted by the formation of the ketone in intermediate **296**, from alkoxide **295**. Enamine-imminium

tautomerization gave intermediate **297** and ring closure provided the observed product **294** (Scheme 3.13).



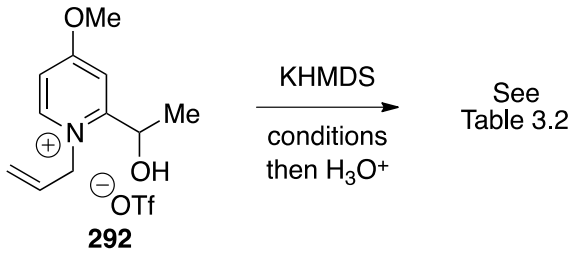
Scheme 3.13: *Proposed mechanism for formation of **294**, including 1,2-hydride migration.*

If this procedure could be successfully applied to pyridinium salt **292**, this would represent a significant achievement in the quest for enantiopure dihydropyridones. However, subjection of pyridinium salt **292** to Risinger's conditions resulted only in returned starting material (Scheme 3.14).



Scheme 3.14: *Attempt to apply Risinger's conditions to pyridinium salt **292**.*

Further investigations into a base-promoted hydride migration involved treatment of pyridinium salt **292** with potassium *bis*(trimethylsilyl)amide. However, only starting material was observed, even after allowing the reaction mixture to warm to room temperature. It was proposed that formation of the "naked" alkoxide, rather than the potassium salt, could increase the reactivity of this system. However, treatment of salt **292** with potassium *bis*(trimethylsilyl)amide and 18-crown-6, to sequester the K^+ cation,[130] also resulted in the isolation of unreacted starting material (Scheme 3.15).



Scheme 3.15: *Further attempts to promote 1,2-hydride migration.*

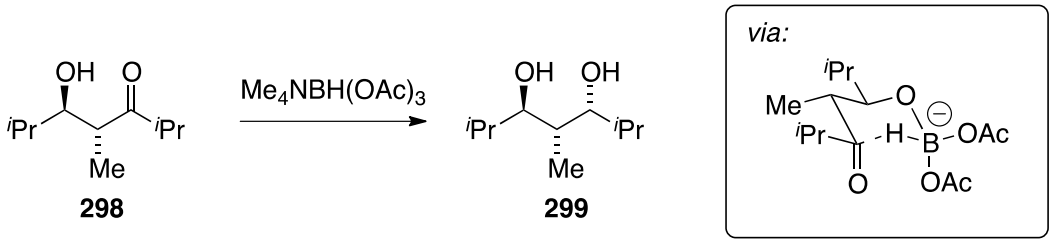
Entry	Conditions	Outcome
1	THF, –78 °C	No reaction
2	THF, –78 °C → rt	No reaction
3	THF, 18-crown-6, –78 °C → rt	No reaction

Table 3.2: *Further attempts to promote 1,2-hydride migration.*

The outcome of these investigations was the realization that pyridinium salt **292** seemed to be unreactive towards a base-induced 1,2 hydride migration. Accordingly, attention then turned to the use of a tethered hydride source for diastereoselective reduction of the pyridinium nucleus.

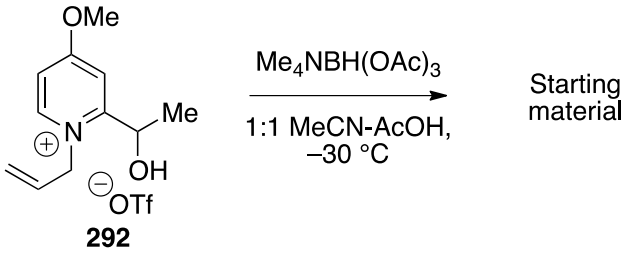
3.3.3 Reduction Using a Tethered Hydride Source

Since its discovery by Evans, tetramethylammonium triacetoxyborohydride has become a powerful reagent for the conversion of β-hydroxy ketones, such as **298**, to the corresponding *anti*-1,3-diols.[131] The triacetoxyborohydride first becomes tethered to the free alcohol, promoting an intramolecular delivery of hydride to the carbonyl (Scheme 3.16).



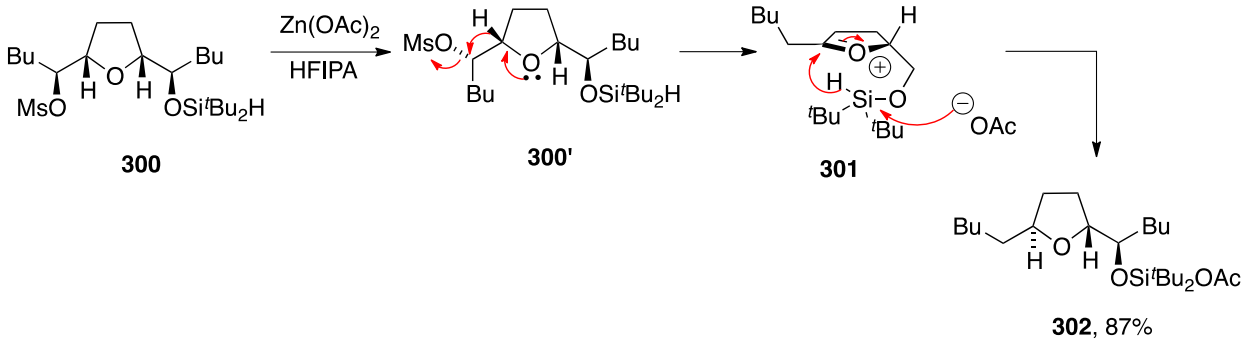
Scheme 3.16: *Stereoselective reduction of β-hydroxy ketones using triacetoxyborohydride.*

It was hoped that a similar reduction would occur if triacetoxyborohydride could be tethered to the free alcohol of pyridinium salt **292**. However, subjection of **292** to Evans' optimized conditions resulted only in the recovery of unchanged **292**.



Scheme 3.17: *Attempt to apply Evans' conditions to pyridinium salt **292**.*

Donohoe has recently reported the utility of di-*tert*-butylsilyl ethers, such as **300**, for the intramolecular donation of hydride onto an oxonium ion **301**, generated by 1,2-hydride migration involving mesylate **300**. The corresponding *trans*-THFs were isolated in excellent yield and this procedure has also been applied to the total synthesis of (+)-sylvaticin (Scheme 3.18).[127, 128]

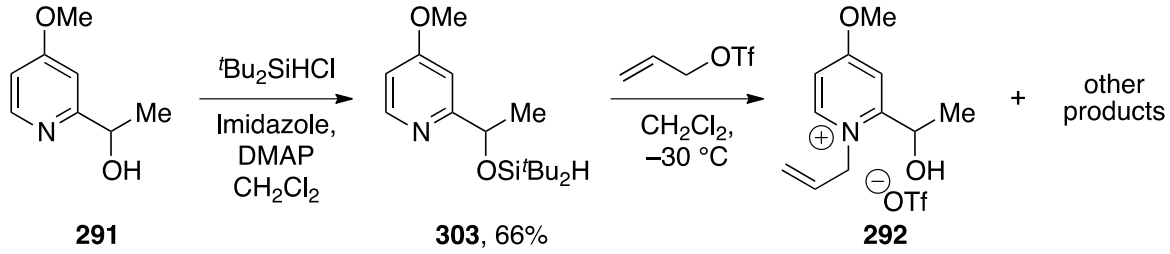


Scheme 3.18: *Donohoe's use of di-*tert*-butylsilyl ethers as intramolecular hydride donors.*

The 1,2-hydride migration promoted displacement of the mesylate group, which was given additional assistance by coordination to the Lewis acidic Zn^{2+}. The crucial intramolecular

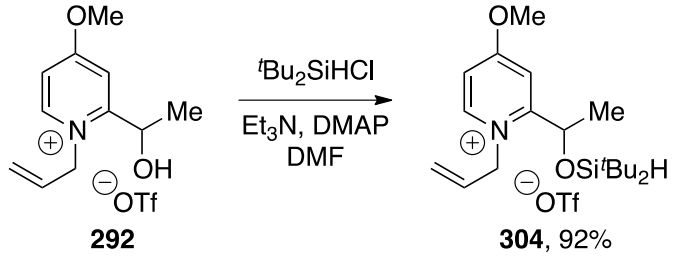
hydride migration was, in turn, promoted by attack of acetate on silicon. If these conditions could be adapted for use with pyridinium salt **304** *vide infra*, it would represent the advent of a novel route to dihydropyridones with two contiguous stereocentres.

Silylation of pyridine **291** proceeded smoothly, under standard conditions, to yield pyridine **303**. However, subsequent attempts to form the corresponding pyridinium salt **304** resulted in a complex mixture of products, predominantly pyridinium salt **292**, resulting from de-silylation under the reaction conditions, presumably due to the presence of small quantities of triflic acid (Scheme 3.19).



Scheme 3.19: *Failed attempt to form silylated pyridinium salt **304**.*

As a result of these observations, it was proposed that the silylation and salt formation steps could be reversed. Treatment of pyridine **291** with allyl triflate (Section 3.3.1) provided pyridinium salt **292** and subsequent reaction with di-*tert*-butylchlorosilane provided the desired pyridinium salt **304** in 92% yield (Scheme 3.20).

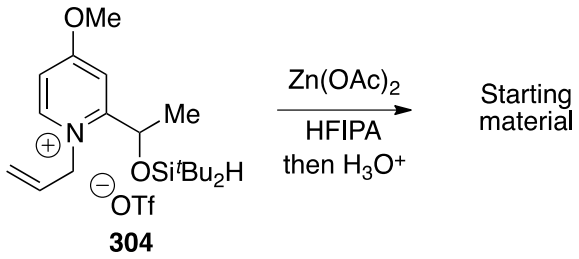


Scheme 3.20: *Formation of pyridinium salt **304**.*

The silylation of pyridinium salt **292** was confirmed by the appearance of two 9 H singlets at 1.08 ppm and 0.92 ppm in the proton NMR spectrum, corresponding to the two *tert*-butyl groups, plus the appearance of a 1 H singlet at 4.10 ppm, due to the Si*H* proton. Furthermore, the O-H stretch at 3405 cm^{-1} was replaced by an Si-H stretch at 2090 cm^{-1} in the IR spectrum and a

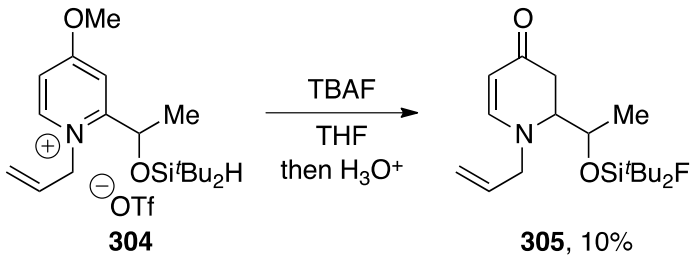
mass ion peak was observed at 336 in the mass spectrum, corresponding to the cationic pyridinium core.

With a high-yielding route to pyridinium salt **304** in hand, investigations into the key hydride migration step began. Subjection of pyridinium salt **304** to Donohoe's optimized conditions for the formation of *trans*-THFs resulted only in returned starting material (Scheme 3.21).[127]



Scheme 3.21: *Application of Donohoe's conditions to pyridinium salt **304**.*

The lack of reactivity of pyridinium salt **304** with zinc acetate was, on reflection, unsurprising, given the differences between the two systems. An alternative nucleophile to attack the silicon atom of salt **304** and promote hydride migration was therefore sought. The fluoride anion is a well-known nucleophile for silicon, with tetrabutylammonium fluoride (TBAF) a common source due to its high solubility in organic solvents. Treatment of **304** with 1.0 equivalent of TBAF in THF, followed by acidic enol ether hydrolysis, provided a 10% yield of the desired dihydropyridone **305**, as well as 85% yield of the de-silylated product **292** (Scheme 3.22).



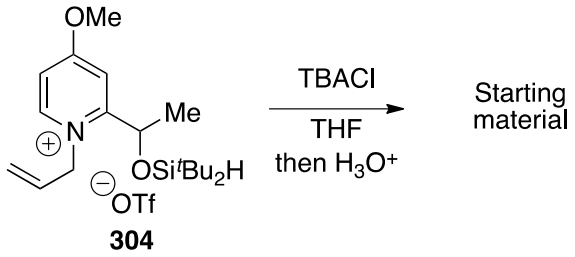
Scheme 3.22: *Formation of dihydropyridone **305**.*

The identity of dihydropyridone **305** was verified by proton NMR analysis, with the 1 H doublets at 7.29 ppm (corresponding to the NC*H*=CH proton) and at 4.89 ppm (corresponding to the NCH=C*H* proton) indicating addition of the hydride at *C*-2 (Section 2.2.3). Although significant optimization of the reaction conditions was necessary to improve the yield of this

process to a synthetically useful level, the formation of dihydropyridone **305** proved that this was indeed a viable reaction.

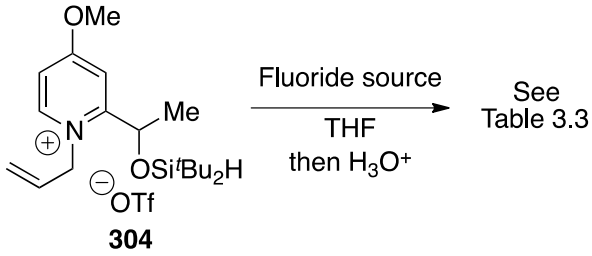
3.3.4 Optimization of Reaction Conditions

In order to maximize the efficiency of this procedure, a number of reaction conditions would need to be optimized. Initial studies in this area were focused on the nucleophile to attack silicon and promote a hydride shift. Firstly, the nature of the nucleophile was tested, with tetrabutylammonium fluoride being replaced by tetrabutylammonium chloride (TBACl), under the same reaction conditions. By analysis of the proton NMR spectrum of the crude reaction mixture, only starting material **304** was observed. This enhanced reactivity of TBAF over TBACl was rationalized by considering the high bond enthalpy of a Si-F bond (129.3 $kcalmol^{-1}$), over a Si-Cl bond (85.7 $kcalmol^{-1}$) (Scheme 3.23).[132]



Scheme 3.23: *Attempts to induce hydride migration using TBACl.*

With fluoride identified as the nucleophile of choice, the next task was to determine the optimum source of fluoride for this reaction. In addition to TBAF (10% yield of **305**, section 3.3.3), cesium fluoride and *tris*(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) were tested. In the case of TASF, only the desilylation product **292** was observed. When the reaction was attempted with cesium fluoride, traces of dihydropyridone **305** were observed in the proton NMR spectrum of the crude product, alongside the major desilylation product **292**. Due to the lower conversion of **304** to **305** using CsF, and the predicted lower solvent tolerance of this highly ionic compound, it was judged that TBAF would be the best source of fluoride for this investigation (Scheme 3.24, Table 3.3).

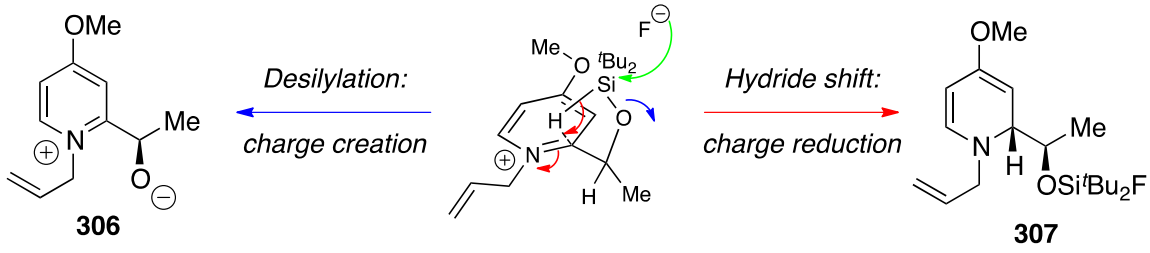


Scheme 3.24: *Investigation of alternative fluoride sources.*

Entry	Fluoride Source	Outcome
1	TBAF	10% yield of **305**
2	TASF	Desilylation to **292**
3	CsF	Traces of **305**

Table 3.3: *Investigation of alternative fluoride sources.*

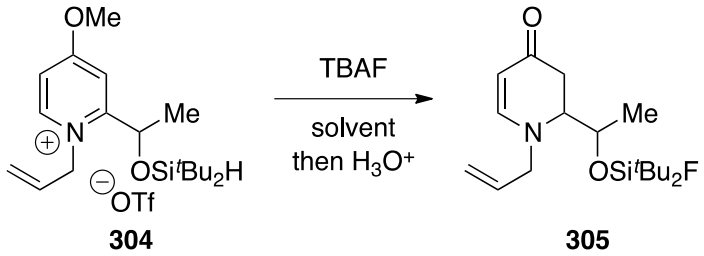
Attention was then turned to the optimization of the reaction solvent. A consideration of the likely mechanism of the hydride shift reaction versus desilylation is provided in Scheme 3.25.



Scheme 3.25: *Likely mechanisms of desilylation and hydride shift.*

In the case of desilylation, attack of fluoride at silicon generates an "ate-complex" and subsequent cleavage of the Si-O bond provides the oxy-anion **306**. Hence, charge is created in the transition state for this process. Conversely, in the case of hydride shift, the formation of the "ate-complex" is followed by hydride shift onto the pyridinium core, with conversion of the cationic, quaternary nitrogen to a neutral, tertiary nitrogen atom in compound **307** (Scheme 3.25). Hence, charge is neutralized in the transition state for this process. Therefore, it was hypothesized that the use of a less polar solvent than THF may promote hydride shift over desilylation.

Pyridinium salt **304** proved to be insoluble in pentane or cyclohexane, however when the reaction was attempted in toluene or benzene, dihydropyridone **305** was obtained in much improved yields of 32% and 34% respectively. As the difference in yield attributable to the use of either benzene or toluene was insignificant, toluene was chosen as the optimum reaction solvent due to its lower toxicity (Scheme 3.26, Table 3.4).



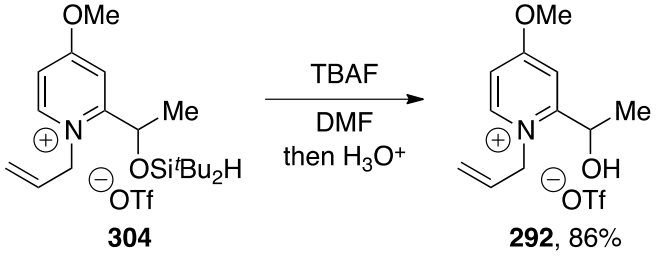
304 **305**

Scheme 3.26: *The effect of solvent on the formation of dihydropyridone **305**.*

Entry	Solvent	Yield of 305
1	THF	10%
2	Pentane	**304** insoluble
3	Cyclohexane	**304** insoluble
4	PhMe	32%
5	PhH	34%

Table 3.4: *The effect of solvent on the formation of dihydropyridone **305**.*

To provide further support for the solvent-dependence hypothesis, the reaction was also conducted using the highly polar DMF as a solvent. In this instance, only pyridinium salt **292** was isolated in 86% yield, validating the hypothesis that generation of an alkoxide on desilylation would be favoured by more polar solvents, *vide supra* (Scheme 3.27).



304 **292**, 86%

Scheme 3.27: *Further evidence of the dependence of reactivity on solvent.*

It seemed possible that increasing the reaction temperature could increase the yield of the desired dihydropyridone **305**. However, heating too much would lead to more freedom of rotation of the hydride bearing side chain and therefore overcome the diastereocontrol conferred by allylic strain arguments (Figure 3.2).

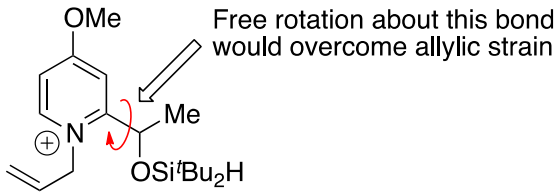
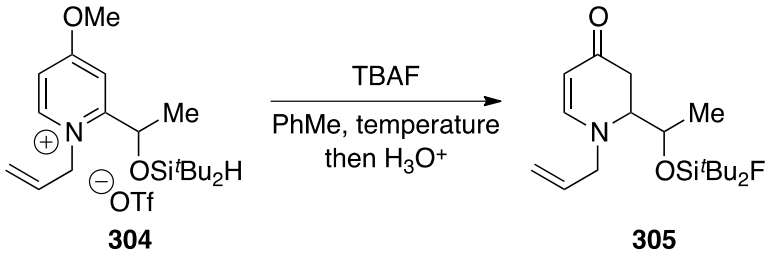


Figure 3.2: *Possible break-down of allylic strain control, upon heating.*

Heating a solution of pyridinium salt **304** in toluene to 50 °C prior to addition of TBAF gave dihydropyridone **305** in a much improved yield of 52%. Analysis of the proton NMR spectrum of the crude product showed that the dr of **305** was 8:1. Conducting a similar experiment at 80 °C gave dihydropyridone **305** in a modestly increased yield of 57%, but in a much reduced dr of 4:1. Accordingly, a reaction temperature of 50 °C was judged to be a good compromise between increased yield and decreased diastereoselectivity as the temperature was increased (Scheme 3.28, Table 3.5).



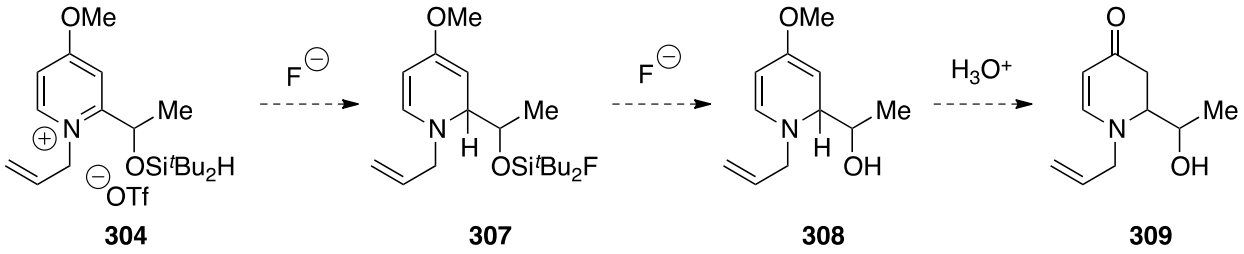
Scheme 3.28: *Optimization of reaction temperature.*

Entry	Temperature	Yield	dr
1	50 °C	52%	8:1
2	80 °C	57%	4:1

Table 3.5: *Optimization of reaction temperature.*

In many optimization experiments, a polar product was encountered by TLC analysis of the reaction mixture, which was judged to be the desilylated product **309**. Unfortunately, **309** was

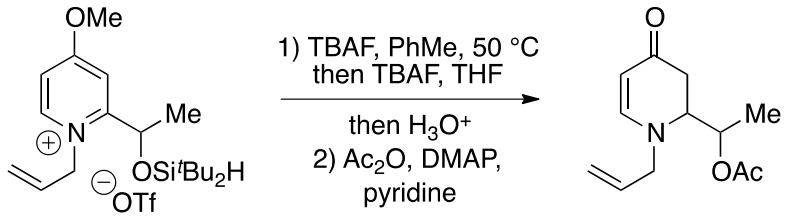
too polar to separate from tetrabutylammonium-containing residues by column chromatography. However, it seemed likely that the yield of dihydropyridone **305** was being eroded by complete desilylation after hydride shift, resulting in the formation of dihydropyridone **309**. It was, therefore, decided to attempt a complete desilylation of intermediate **307** to provide dihydropyridone **309** as a single product and, in doing so, improve the yield of isolated dihydropyridone (Scheme 3.29).



304 **307** **308** **309**

Scheme 3.29: *Possible route for the formation of dihydropyridone **309**.*

The complete consumption of intermediate **307** proved challenging, with a large excess of TBAF and extended reaction times required to prevent traces of dihydropyridone **305** remaining in the crude reaction mixture. However, this goal was eventually achieved by the addition of a further 3.0 eq. of TBAF after the hydride shift had been given sufficient time to occur, and leaving the reaction to stir for a further 16 h at room temperature. The isolation of the very polar dihydropyridone **309** could be aided by acetylation of the crude secondary alcohol, under standard conditions, and dihydropyridone **310** was isolated in a gratifying 85% yield, as an 8:1 mixture of diastereomers (Scheme 3.30).[133]



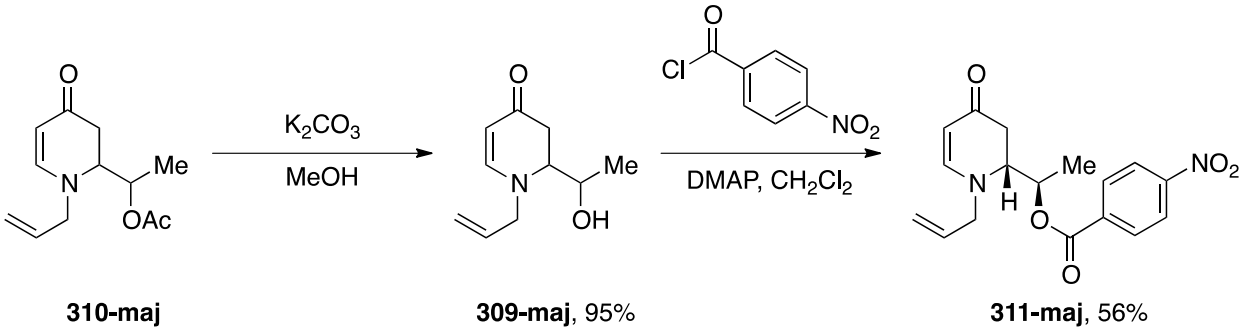
304 **310**, 85%, 8:1 dr

Scheme 3.30: *Optimized conditions to generate dihydropyridone **310**.*

The identity of dihydropyridone **310** was confirmed by analysis of the proton NMR spectrum, where doublets at 7.31 ppm and 4.90 ppm were characteristic of addition of hydride at *C*-2, and the triplet at 3.75 ppm corresponded to the newly installed proton at *C*-2 (all data given for major

diastereomer). Furthermore, a stretching vibration at 1738 cm^{-1} was observed in the IR spectrum, corresponding to the ester carbonyl, and a mass ion peak at 246 corresponded to the $M+Na^+$ ion.

The next task was to determine the identity of the major diastereomer of dihydropyridone **310**. Fortunately, these diastereomers were separable by column chromatography and a diastereomerically pure sample of **310-maj** was subjected to a two-step transesterification. Treatment of dihydropyridone **310-maj** with potassium carbonate in methanol provided alcohol **309-maj**, which was re-esterified with *p*-nitrobenzoyl chloride to give the highly crystalline dihydropyridone **311-maj**. It should be noted that treatment of the crude "hydride shift" reaction mixture with *p*-nitrobenzoyl chloride did provide dihydropyridone **311**, however the two diastereomers were inseparable by column chromatography. The X-ray crystal structure of the diastereomerically pure sample of **311-maj** demonstrated that the relationship between the newly installed *C*-2 proton and the oxygen-containing substituent on the side chain was *syn*. This was in agreement with the model for a diastereoselective hydride shift (Scheme 3.10), providing experimental support for the hypothesis (Scheme 3.31, Figure 3.3).



Scheme 3.31: *Formation of dihydropyridone **311-maj**.*

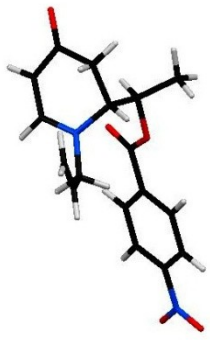
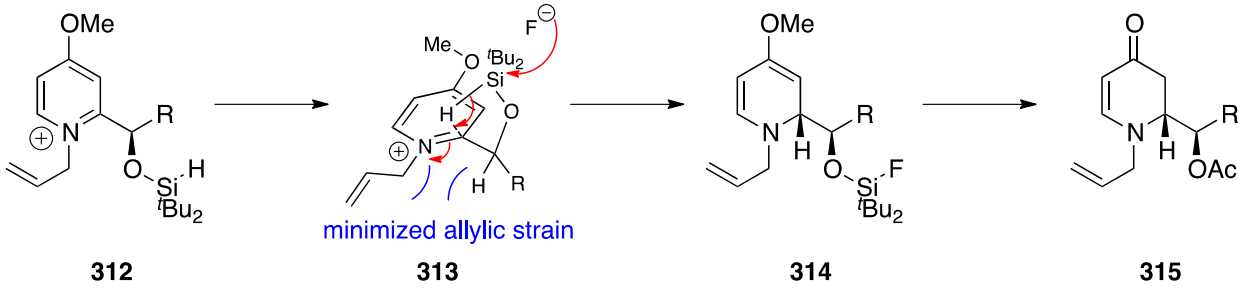


Figure 3.3: *X-ray crystal structure of dihydropyridone **311-maj**, demonstrating the* syn-*relationship between the* C*-2 proton and the oxygen-containing substituent.*

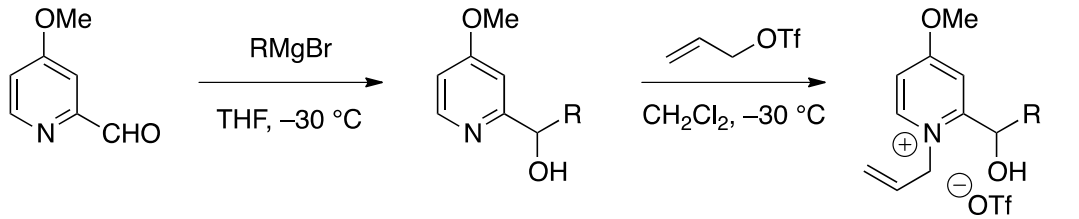
3.3.5 Substrate Scope[133]

The next phase of the investigation was to explore the reactivity of different substrates under the optimized reaction conditions, as a wide variety of different pyridines could be generated by variation of the Grignard reagent used to add to aldehyde **290**. According to our model for allylic strain controlled, diastereoselective hydride migration (Scheme 3.10), more bulky side chains should improve the diastereoselectivity of hydride migration, due to increased allylic strain between the *N*-allyl group and the side chain (Scheme 3.32).



Scheme 3.32: *Model for 1,3-allylic strain controlled diastereoselective hydride migration.*

Addition of a variety of Grignard reagents to aldehyde **290** proceeded smoothly giving the corresponding secondary alcohols **316-321** in 65-98% yield. These pyridines could be *N*-allylated, as before, to provide the corresponding pyridinium salts **322-327**, also in good yield (Scheme 3.33).



290

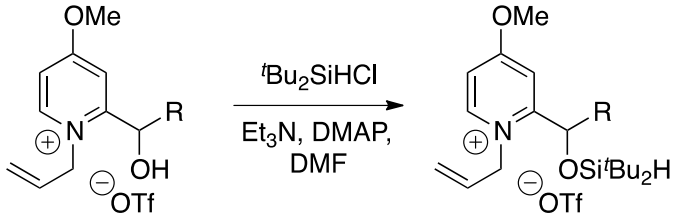
R = *n*Hex, 316, 80%
R = Allyl, 317, 79%
R = Vinyl, 318, 71%
R = Bn, 319, 75%
R = Ph, 320, 98%
R = *i*Pr, 321, 65%

R = *n*Hex, 322, 88%
R = Allyl, 323, 83%
R = Vinyl, 324, 72%
R = Bn, 325, 80%
R = Ph, 326, 80%
R = *i*Pr, 327, 81%

Scheme 3.33: *Formation of pyridinium salts **322-327**.*

All pyridines **316-321** and pyridinium salts **322-327** gave spectral data consistent with their structures, with the primary features of the pyridine ring present and differing only according to

the structure of the side chain. Pyridinium salts **322-326** could then be silylated, as before, to provide the hydride shift precursors **328-332** in good yield (Scheme 3.34).

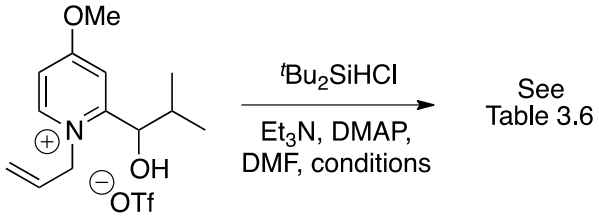


R = ^{n}Hex, 322
R = Allyl, 323
R = Vinyl, 324
R = Bn, 325
R = Ph, 326

R = ^{n}Hex, 328, 75%
R = Allyl, 329, 79%
R = Vinyl, 330, 74%
R = Bn, 331, 73%
R = Ph, 332, 69%

Scheme 3.34: *Formation of pyridinium salts **328-332**.*

When pyridinium salt **327** was exposed to the standard silylation conditions, only starting material was recovered. It seemed likely that this was due to the increased steric bulk of the *iso*-propyl side chain providing too much hindrance for effective silylation of the secondary alcohol. In a separate experiment, heating the reaction mixture to 60 °C again provided returned starting material, with some gradual decomposition observed when the reaction was left for extended periods. Heating the reaction mixture to 120 °C resulted in complete decomposition of the starting material (Scheme 3.35).



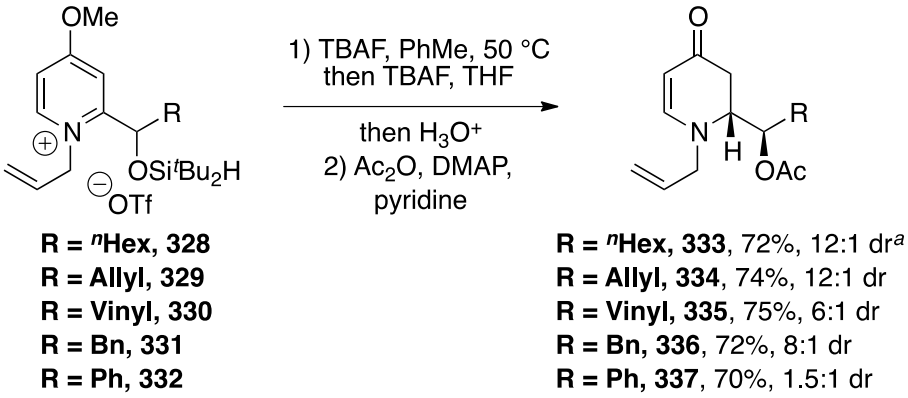
327

Scheme 3.35: *Attempts to silylate pyridinium salt **327**.*

Entry	Temperature	Outcome
1	rt	No reaction
2	60 °C	No reaction, gradual decomposition
3	120 °C	Decomposition

Table 3.6: *Attempts to silylate pyridinium salt **327**.*

It was apparent that bulkier side chains, such as *iso*-propyl, preclude silylation of the secondary alcohol and therefore, testing the diastereoselectivity of the corresponding hydride shift reaction. However, pyridinium salts **328-332** could easily be prepared and the next task was to submit each of these to the optimized conditions for hydride migration (Scheme 3.36).



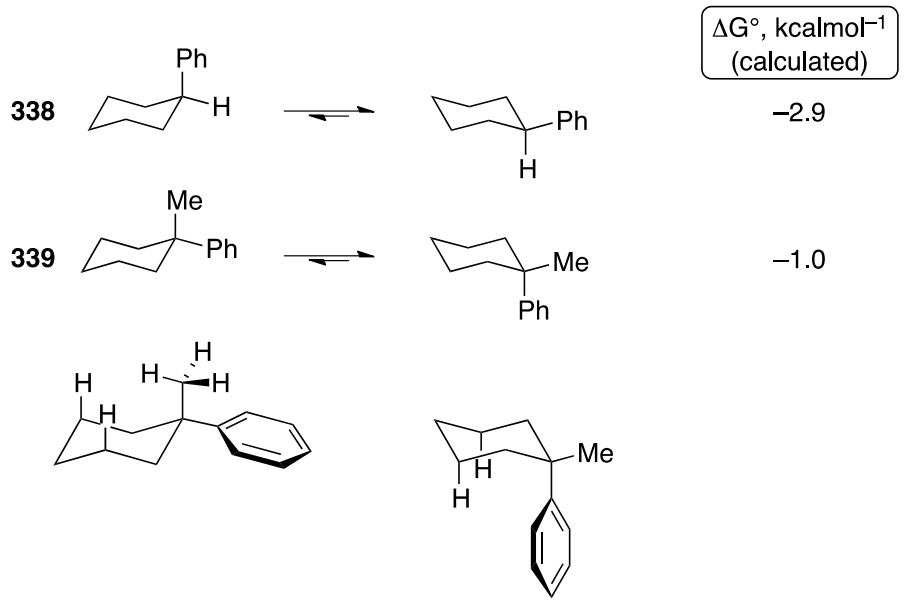
Scheme 3.36: *Formation of Dihydropyridones **333-337**.*

[a.] *Isolated as the free secondary alcohol, without acetylation.*

In all cases, the corresponding dihydropyridones **333-337** could be isolated in good yields, ranging from 70% to 75% with the relative stereochemistry of the major diastereoisomer assigned by analogy with dihydropyridone **311**. The key spectral data of the dihydropyridone core was present in all cases, indicating hydride addition at *C*-2 (see Section 2.2.3), and the spectra differed only according to the structures of the side chains. Dihydropyridone **333** was found to be significantly apolar to isolate cleanly without resorting to acetylation of the secondary alcohol. The diastereoselectivity of the hydride shift was found to mirror the perceived steric bulk of the side chains in most cases. The hexyl and allyl substituted dihydropyridones **333** and **334** were formed with higher diastereoselectivity than the methyl substituted product **310**, owing to their greater steric bulk. Vinyl substituted dihydropyridone **335** was formed with lower diastereoselectivity than **310** for the same reason (the A-values for methyl and vinyl groups are 1.70 and 1.35 respectively, demonstrating the lower steric effect of the vinyl moiety).[134]

The low diastereoselectivity displayed in the formation of phenyl substituted dihydropyridone **337** was initially surprising, given the high A-value of 3.0 for phenyl groups. However, the steric effect of a phenyl group has been found to depend greatly on its spatial orientation. Wiberg and co-workers have found that phenylcyclohexane **338** exhibits a strong conformational preference for an equatorial phenyl group. Conversely, 1-methyl-1-phenylcyclohexane **339**

exhibits a preference for the conformer with an axial phenyl group and an equatorial methyl group.[135] The authors calculated that this observable difference was due to differing rotational arrangements of the phenyl group in phenylcyclohexane and 1-methyl-1-phenylcyclohexane providing a varying steric contribution. If the phenyl group was axial in 1-methyl-1-phenylcyclohexane, the "face-on" interaction of the phenyl group with the axial cyclohexane protons was smaller than the 1,3-diaxial interactions of these protons with the methyl group (Scheme 3.37).



Scheme 3.37: *Wiberg's calculated gas phase free energy changes for conformational flipping.*

Applying the findings of Wiberg to the formation of dihydropyridone **337**, it seemed likely that the phenyl group was adopting a "face-on" rotational arrangement with the *N*-allyl group and therefore, exhibiting a very low facial directing effect due to the reduced 1,3-allylic strain (Figure 3.4).

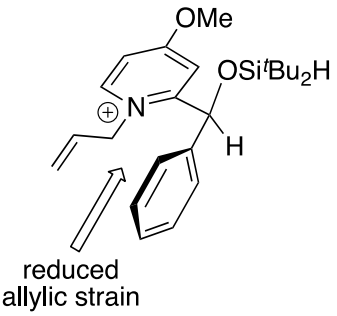
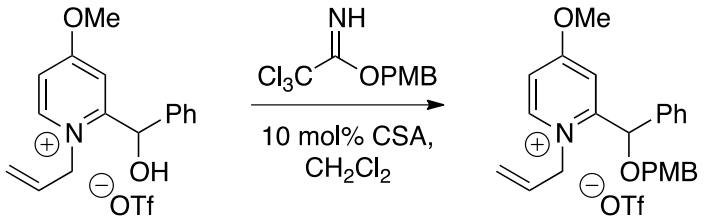


Figure 3.4: *Proposed "face-on" interaction between the phenyl and* N*-allyl groups.*

3.3.6 Mechanistic Investigations

Given the high diastereoselectivity of the hydride shift reaction (Schemes 3.30 and 3.36) and that the identity of the major diastereomer was accurately predicted by our model for this transformation (Scheme 3.32), an intramolecular mechanism seemed most likely. However, it was decided that further evidence for the possible intramolecular nature of this mechanism should be obtained.

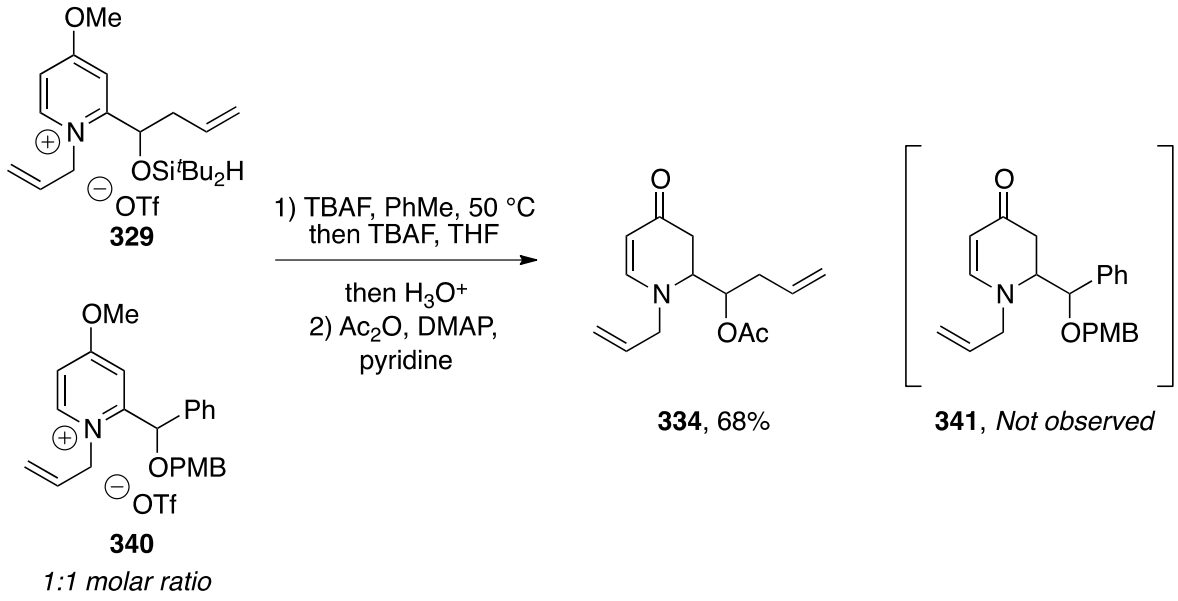
To this end, a competition experiment was devised. Pyridinium salt **326** was converted to its *p*-methoxybenzyl ether **340** in good yield by treatment with the corresponding trichloroacetimmidate and catalytic camphorsulfonic acid (Scheme 3.38).[136]



326 **340**, 70%

Scheme 3.38: *Formation of pyridinium salt **340**.*

The formation of pyridinium salt **340** was confirmed by the detection of a mass ion peak at 376 in the mass spectrum, corresponding to the cationic pyridinium core. Equimolar amounts of pyridinium salts **329** and **340** were then subjected to the optimized hydride shift reaction conditions (Section 3.3.4). If the mechanism was indeed intramolecular, pyridinium salt **329** would be converted to dihydropyridone **334** in the usual way whereas pyridinium salt **340** should be unreactive (Scheme 3.39).

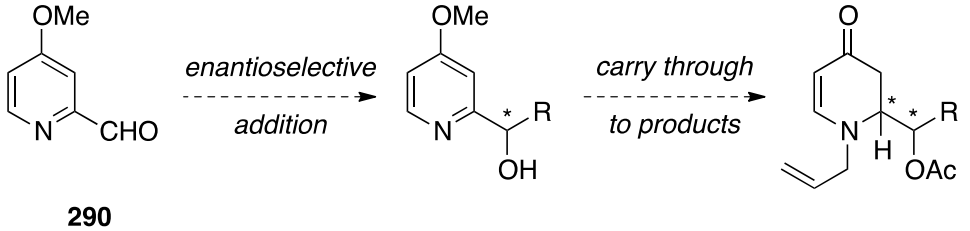


Scheme 3.39: *Competition experiment leading to dihydropyridone **334** and not **341**.*

Gratifyingly, after conducting this experiment, the only dihydropyridone obtained was **334**, as expected, in 68% yield with respect to the amount of salt **329** subjected to the reaction conditions. Dihydropyridone **341**, which would have resulted from an intermolecular hydride shift, was not observed in the proton NMR spectrum of the crude product and the unreacted pyridinium salt **340** was presumably removed during aqueous work up.

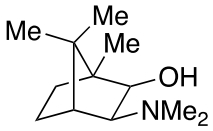
3.3.7 The Synthesis of Enantioenriched Dihydropyridones

As discussed in Section 3.1, the aim of this methodology was the synthesis of enantioenriched dihydropyridones from an achiral starting material. It follows that the next step for the highly diastereoselective methodology described herein would be to apply it to an enantiopure sample of pyridinium salt, and investigate whether the pre-installed chirality was carried through efficiently to the products. The enantiopure pyridinium salt could be derived from an asymmetric addition to aldehyde **290** (Scheme 3.40).



Scheme 3.40: *Proposed route to enantioenriched dihydropyridones.*

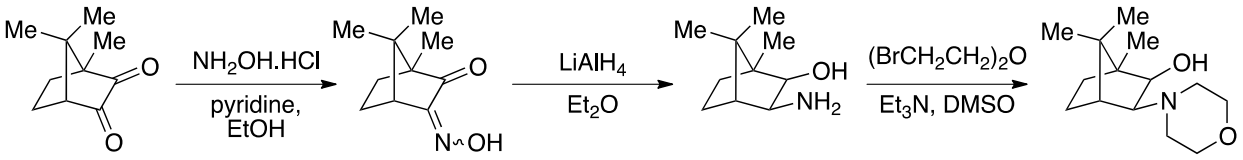
Initial efforts focused on the addition of a dialkylzinc reagent to aldehyde **290**, catalyzed by an enantiopure β-amino alcohol. The research into this area has been catalogued in review articles and 3-exo-dimethylaminoisoborneol (DAIB) **342**, developed by Noyori and co-workers, has received considerable attention (Figure 3.5).[137, 138]



342

Figure 3.5: *DAIB.*

Recently, Nugent has reported that 3-exo-morpholinoisoborneol (MIB) **346** can be used as an effective substitute for DAIB which, despite its utility as an asymmetric ligand for organozinc addition, is difficult to prepare and is also somewhat unstable. In contrast, MIB is a stable crystalline solid, which was prepared in three steps from (1*S*)-(+)-camphorquinone **343**, according to literature precedent (Scheme 3.41).[139]



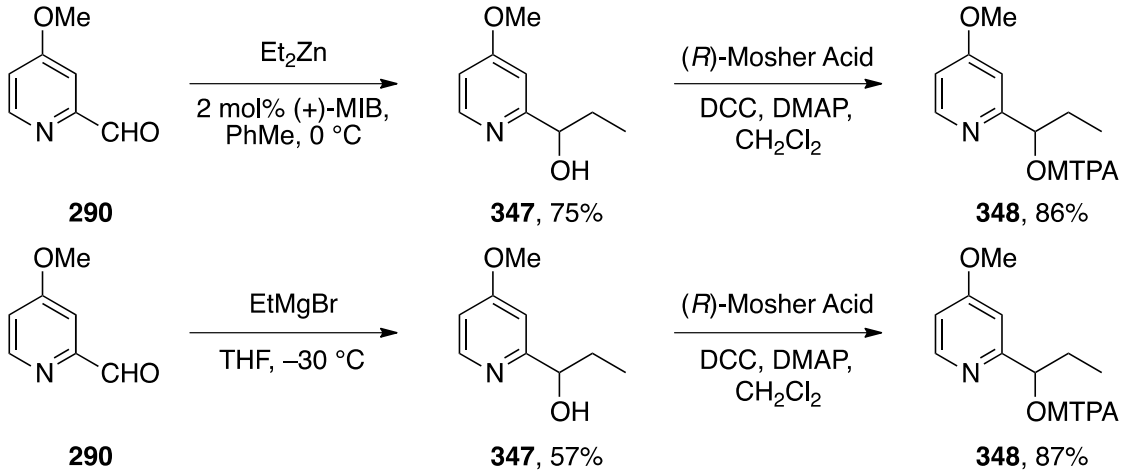
343 | **344**, 68% | **345** | **346**, 57% (2 steps)

Scheme 3.41: *Preparation of (+)-MIB **346**.*

Oxime **344** was formed from the condensation of hydroxylamine with the less hindered carbonyl of (1*S*)-(+)-camphorquinone **343**. Subsequent lithium aluminium hydride reduction proceeded with addition of hydride from the less hindered *endo*-face, to provide amino alcohol **345**. Treatment with *bis*-(2-bromoethyl)ether provided (+)-MIB **346**, which was recrystallized from hexane. The spectroscopic properties of **346** matched those reported in the literature.[139]

With ligand **346** in hand, attention was turned to its application to organozinc addition to aldehyde **290**. Treatment of **290** with diethylzinc and a catalytic amount of **346** provided alcohol **347** in 75% yield. A racemic standard of alcohol **347** was also prepared by addition of ethylmagnesium bromide to aldehyde **290**. Conversion of the organozinc addition product and its

racemic standard to the corresponding Mosher esters was achieved under standard conditions. Analysis of the proton and ^{19}F NMR spectra for organozinc addition product **348** revealed that the sample of alcohol **347** was racemic, due to the two diastereomeric singlets at –71.2 ppm and –71.4 ppm in the ^{19}F NMR spectrum, integrating to equal intensity (Scheme 3.42).



Scheme 3.42: *Analysis of the enantioselectivity of diethylzinc addition to aldehyde **290**.*

Clearly, either aldehyde **290** or the product alcohol **347** (or conceivably, a combination of both) was acting as a competing ligand for zinc and catalyzing the addition to aldehyde **290** in an unselective manner (Figure 3.6). A review of the examples of asymmetric organozinc additions reported in the literature demonstrated that there are no examples of pyridine-2-carboxaldehydes being used successfully in this transformation. It was therefore decided to switch to an alternative strategy for the synthesis of enantiopure pyridyl alcohols.

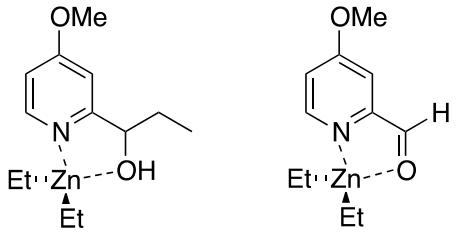
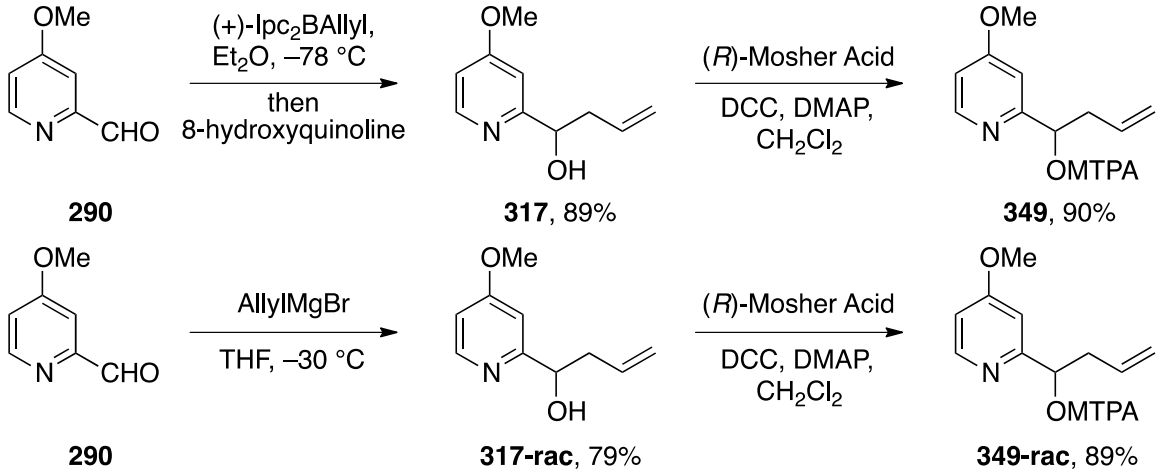


Figure 3.6: *Possible coordination of alcohol **347** and aldehyde **290** to diethylzinc.*

The asymmetric allylation of aldehydes using allyl-boron reagents has received a great deal of attention in the literature, with seminal contributions from the groups of Brown and Roush.[140, 141] As these organoboron reagents allow only monodentate coordination to boron, it was felt that these may enable the asymmetric allylation of aldehyde **290**.

Treatment of aldehyde **290** with a solution of commercially available (+)-*B*-allyldiisopinocampheylborane ((+)-$Ipc_2BAllyl$) provided the borinate intermediate, which was cleaved by treatment with 8-hydroxyquinoline to give alcohol **317** in 89% yield.[142] A racemic sample of alcohol **317-rac** was also prepared as discussed in Scheme 3.33. Conversion of both the racemic alcohol **317-rac** and its counterpart **317**, prepared by Brown allylation, to their corresponding Mosher esters **349-rac** and **349**, was achieved in good yield under standard conditions (Scheme 3.43).



Scheme 3.43: *Analysis of the enantioselectivity of allylation of aldehyde **290**.*

Analysis of the ^{19}F NMR spectrum of **349-rac** showed a pair of diastereomeric singlets at –71.2 ppm and –71.4 ppm. These singlets both appeared in the ^{19}F NMR spectrum of **349**, however their ratio was 1:25, indicating that the ee of alcohol **317** was 92% (Appendix 2).

Hoye has recently published details of how to determine the absolute stereochemistry of a chiral secondary alcohol using Mosher's esters.[143] By using this Mosher ester analysis, the absolute configuration of an enantiopure secondary alcohol may be determined by preparation of each of the diastereomeric *R*- and *S*-Mosher esters and comparison of the chemical shifts of analogous protons. The foundation of this analysis lies in the empirically based (and validated) conformation of Mosher esters whereby the ester adopts the usual *trans*- arrangement about the O-CO bond and both the trifluoromethyl group of the MTPA moiety and the methine C-H bond of the secondary alcohol are *syn*-coplanar with the carbonyl group (Figure 3.7).[144]

S-Mosher Ester *R*-Mosher Ester

Figure 3.7: *Favoured conformations of Mosher esters and anisotropic shielding effects.*

The phenyl group of the MTPA moiety exhibits an anisotropic magnetic shielding effect on protons located above or below the ring, resulting in an upfield shift (*ie.* more shielding) for spatially proximal protons (Figure 3.7). By determining the difference in chemical shifts for the analogous protons in both the *R*- and *S*-Mosher esters and with a reliable assignment of the secondary alcohol's proton signals, the absolute configuration of the secondary alcohol may be deduced.

These results could be applied to alcohol **317** with a minor modification. Samples of the *R*-Mosher esters derived from racemic alcohol **317-rac** and its enantiopure counterpart **317** were readily available. The *R*-Mosher ester **349-rac** displayed doubling of the signals due to protons on the pyridine ring and on the allyl side chain, with intensities of 1:1. Specifically, the NC*H* proton appeared as a pair of doublets at 8.43 ppm and at 8.37 ppm. The NCHC*H* proton appeared as a pair of double doublets at 6.76 ppm and 6.72 ppm, while the C(CHOMTPA)C*H* proton appeared as a pair of doublets at 6.86 ppm and 6.63 ppm. The C*H*=CH_2 proton of the allyl group gave a pair of double double triplets at 5.79 ppm and 5.67 ppm (Figure 3.8).

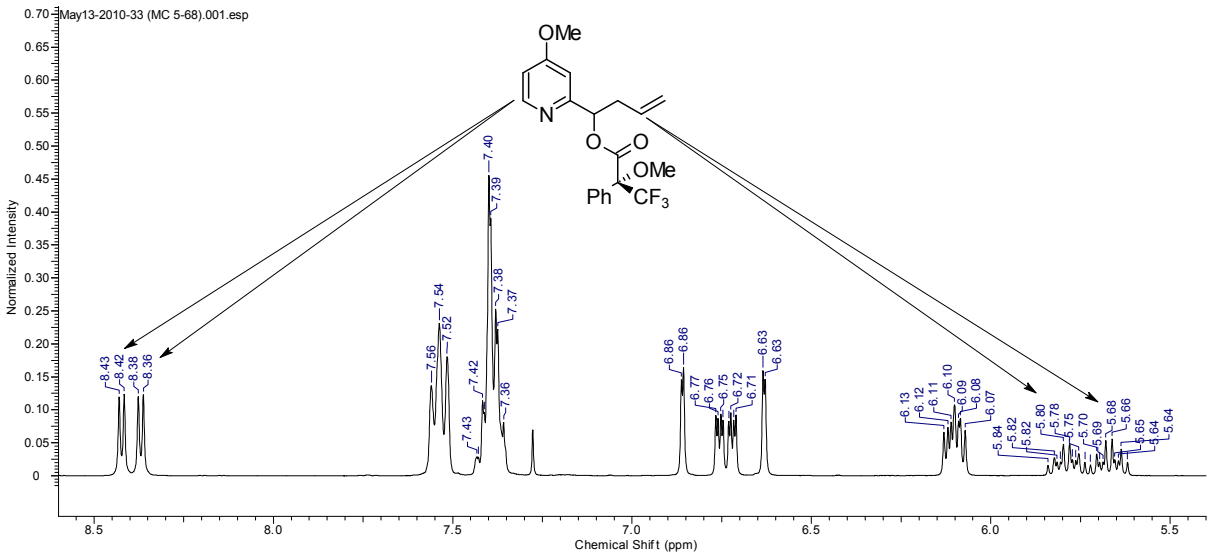


Figure 3.8: *Excerpt from proton NMR spectrum of Mosher ester **349-rac**.*

Inspection of the proton NMR spectrum of Mosher ester **349** revealed that the major peaks, corresponding to the major diastereomer, included a doublet at 8.43 ppm (NC*H*), a doublet at 6.86 ppm (C(CHOMTPA)C*H*) and a double doublet at 6.76 ppm (NCHC*H*). Furthermore, the C*H*=CH_2 proton appeared as a double double triplet at 5.67 ppm (Figure 3.9).

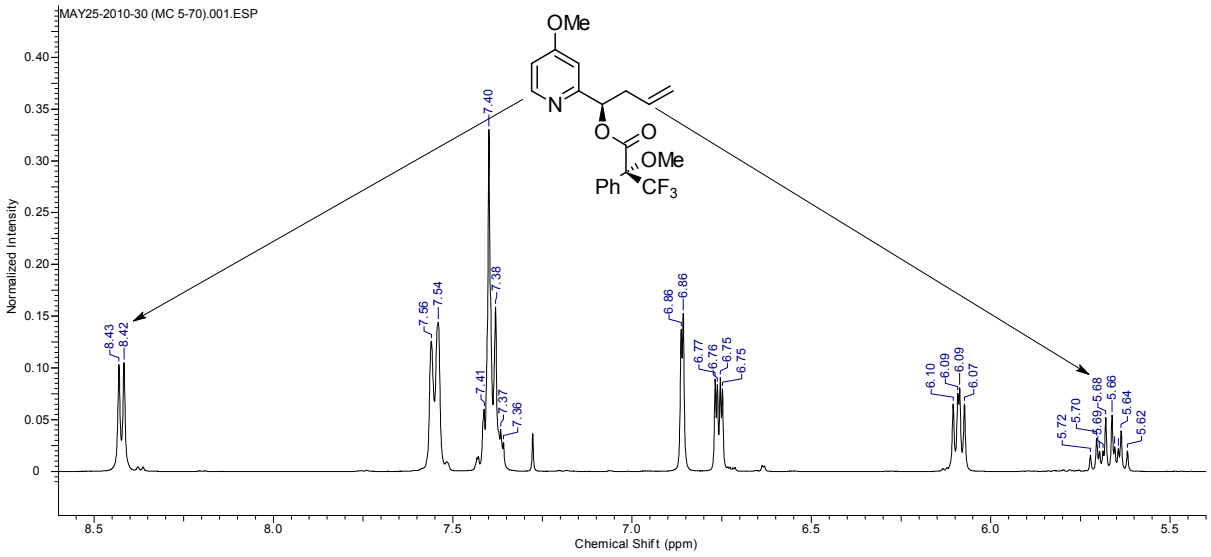
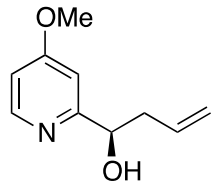


Figure 3.9: *Excerpt from proton NMR spectrum of Mosher ester **349**.*

Clearly, the major diastereomer of **349** displayed the comparatively deshielded pyridyl group and the comparatively more shielded allyl group. Application of the major conformation of Mosher esters, discussed by Hoye (Figure 3.7), to these results indicated an *R*- configuration of

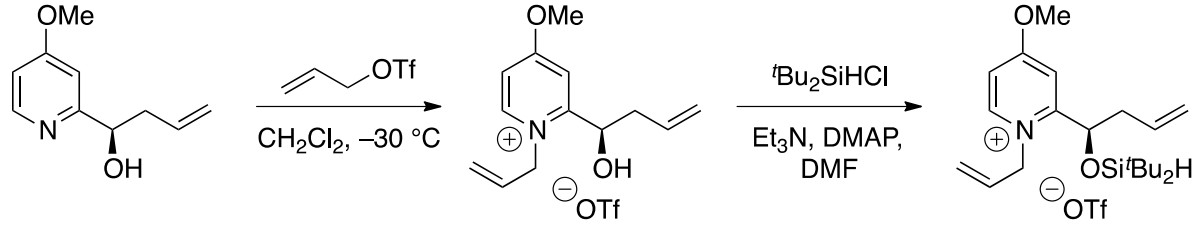
the secondary alcohol. This result was in line with the findings of Brown, reported in the literature (Figure 3.10).[140]



317

Figure 3.10: *Absolute stereochemistry of the major enantiomer, obtained by Brown allylation.*

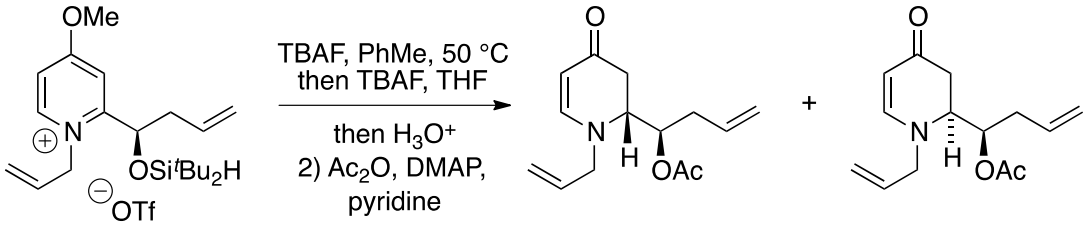
Once the ee of alcohol **317** and the absolute configuration of the major enantiomer had been determined, the remainder of the material was converted to pyridinium salt **329**, using the methods described in Section 3.3.5. Thus, allylation of pyridine **317** proceeded in 72% yield and subsequent silylation afforded the hydride shift precursor **329** in 70% yield (Scheme 3.44).



317 **323**, 72% **329**, 70%

Scheme 3.44: *Formation of pyridinium salt **329**.*

Submitting pyridinium salt **329** to the optimized conditions for the hydride shift reaction provided dihydropyridone **334** in 73% yield. The proton NMR spectrum of **334** displayed all the characteristic signals for these compounds, including the multiplet at 3.66-3.62 ppm corresponding to the newly installed proton at *C*-2 and the doublets at 6.95 ppm and 4.95 ppm, characteristic of hydride addition at *C*-2 (Scheme 3.45).

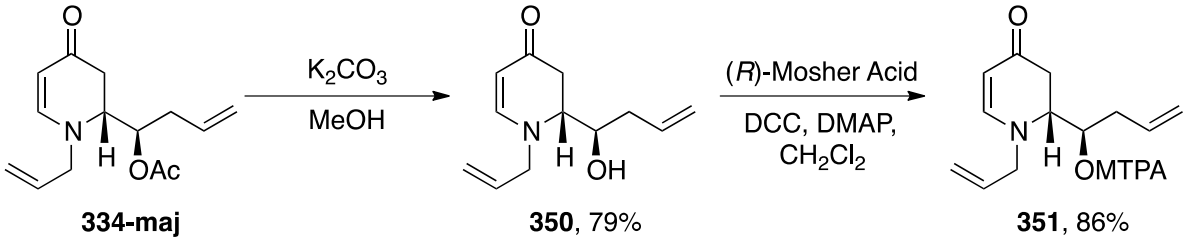


329 **334-maj** **334-min**

73%, 12:1 dr

Scheme 3.45: *Formation of dihydropyridone diastereomers **334-maj** and **334-min**.*

The diastereomers were separated at this stage by further column chromatography and the major diastereomer was then de-acetylated using potassium carbonate in methanol, to provide alcohol **350**. *R*-Mosher ester **351** was formed by DCC-mediated coupling of alcohol **350** and *R*-Mosher acid. In addition, the *R*-Mosher ester **351-rac** was prepared in an identical two-step procedure from **334-maj-rac** (Scheme 3.46).



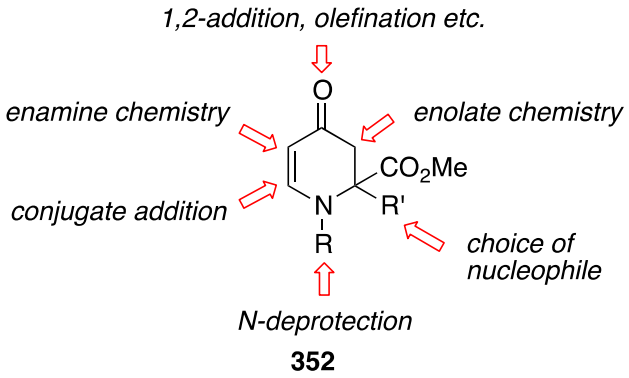
334-maj **350**, 79% **351**, 86%

Scheme 3.46: *Formation of Mosher Ester **351**.*

Analysis of the ^{19}F NMR spectrum of **351-rac** revealed a pair of diastereomeric singlets at –70.8 ppm and –70.9 ppm with a relative intensity of 1:1, as expected. Subsequent inspection of the ^{19}F NMR spectrum of **351** revealed that the relative intensity of the same two peaks was 25:1, corresponding to an ee of 92% for the major diastereomer **334-maj**. As no erosion of enantiopurity was observed using this methodology, this result clearly demonstrated the viability of this novel hydride shift methodology for the construction of enantioenriched dihydropyridones, such as **334**.

3.4 The Synthetic Utility of Dihydropyridones

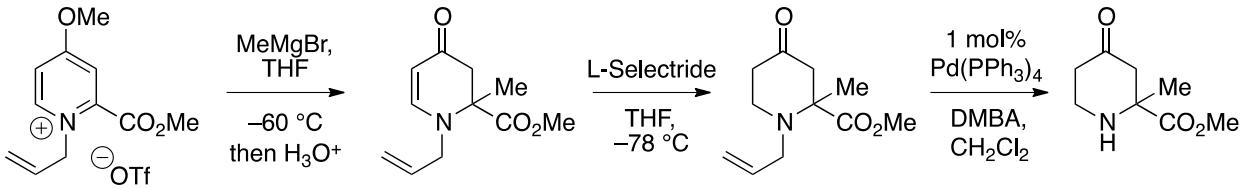
For the methodology developed as part of this project to be of use to synthetic organic chemists, the dihydropyridones created were required to be versatile intermediates, stable to a variety of reaction conditions. Comins and Donohoe have previously demonstrated the use of *N*-acyl and *N*-benzylic pyridinium salts in synthesis (Section 1.5.3).[88, 95] In particular, Donohoe has demonstrated the reactivity of each ring position of the generic dihydropyridone **352** (Figure 3.11).[13]



352

Figure 3.11: *Donohoe's study of the reactivity of dihydropyridones.*

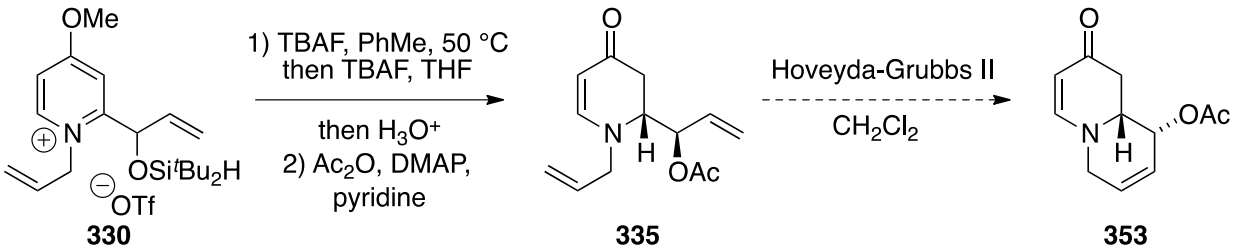
In addition to Donohoe's comprehensive study of the reactivity of dihydropyridones, it has been discovered, as part of this project, that a wide variety of nucleophiles may be added regioselectively to either *C*-2 or *C*-6 of the corresponding pyridinium salts. Furthermore, conjugate addition of nucleophiles was possible at *C*-6 of *N*-allyl dihydropyridones **241** and **243**. Subsequent *N*-deallylation, using palladium catalysis, proceeded in good yield (Section 2.5, Scheme 3.47).[94]



240 **241**, 86% **271**, 71% **273**, 86%

Scheme 3.47: *Formation of dihydropyridone **241** and its reactivity.*

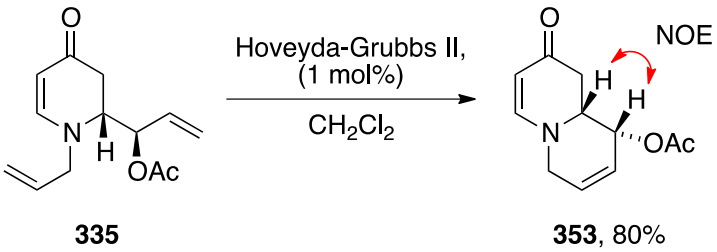
The hydride shift methodology described herein has allowed the reliable synthesis of a range of dihydropyridones, including **334** and **335**, in high yield (Section 3.3.5).[133] It was postulated that a ring closing metathesis reaction between the alkene-containing side chain and the *N*-allyl group of dihydropyridones **334** and **335** could furnish the corresponding bicyclic systems. If successful, this transformation would allow the facile creation of complex skeletons, found in a variety of natural product targets. Furthermore, the *N*-allyl group would be incorporated as an integral part of these bicyclic structures, meaning that it need not be thought of as a protecting group, but as an essential synthetic building block. If this were considered alongside the *N*-allyl group being an essential activating group for the corresponding pyridine, the overall atom economy of this methodology would be greatly improved (Scheme 3.48).[145]



Scheme 3.48: *Formation of dihydropyridone **335** and proposed RCM strategy.*

3.4.1 Construction of Bicyclic Systems

The major diastereomers of dihydropyridones **334** and **335** were isolated in their pure forms by column chromatography of the crude diastereomeric mixtures obtained from the hydride shift reaction (Section 3.3.5). Treatment of dihydropyridone **335** with the Hoveyda-Grubbs 2nd generation catalyst[79] in dry, degassed dichloromethane, provided the corresponding 6,6-bicycle **353** in an excellent yield of 80% (Scheme 3.49).[133]

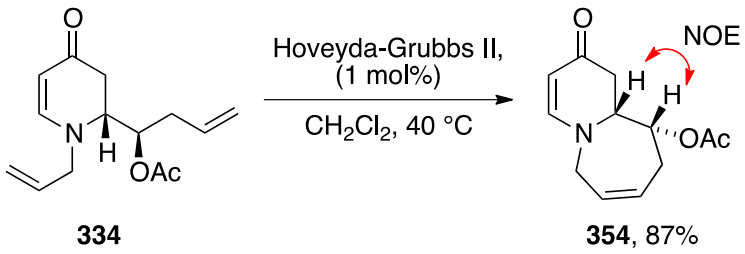


Scheme 3.49: *Formation of bicycle **353**.*

The success of this reaction was verified by the proton NMR spectrum of **353**, where the signals at 5.85 ppm, 5.73 ppm and the multiplet at 5.39-5.29 ppm, integrating to six protons in total for dihydropyridone **335** were replaced by a multiplet, integrating to two protons, at 6.04-6.03 ppm corresponding to the olefinic protons. Furthermore, peaks at 222 and 244 in the mass spectrum corresponded to the M+H$^+$ and M+Na$^+$ ions respectively. In addition, an NOE enhancement of the C*H*OAc signal was observed on irradiation of the NC*H*CHOAc proton at 3.82 ppm and *vice versa*, providing additional confirmation of the diastereoselectivity observed in Section 3.3.4 (Appendix 2).

Application of the same conditions to dihydropyridone **334** resulted in the incomplete consumption of starting material, presumably due to the greater loss of configurational entropy on formation of the 7-membered ring than for the 6-membered ring. However, it was

subsequently found that heating the reaction solvent at reflux enabled the complete consumption of starting material and the 6,7-bicycle **354** was isolated in an excellent yield of 87% (Scheme 3.50).[133]

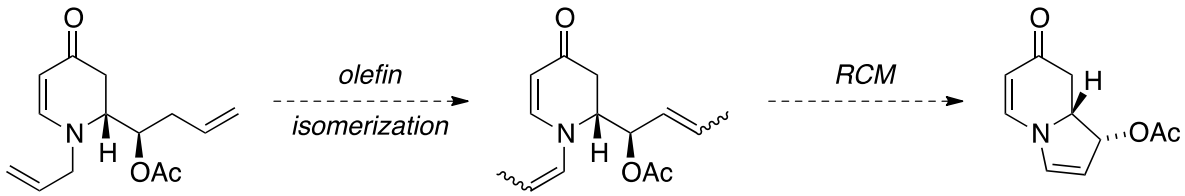


334 **354**, 87%

Scheme 3.50: *Formation of bicycle **354**.*

In a similar way to bicycle **353**, mutual NOE enhancements between the C*H*OAc and NC*H*CHOAc proton signals of **354** confirmed the observed diastereoselectivity of the hydride shift reaction (Section 3.3.4, Appendix 2).

It was proposed that a 6,5 ring system could be formed by the isomerization of both double bonds of dihydropyridone **334**, prior to ring closing metathesis. The use of catalytic amounts of ruthenium hydride complexes in terminal olefin isomerization has been reviewed and Hanessian's method has been successfully applied to dihydropyridone **241**, during the course of this investigation (Section 2.5).[116, 117] However, there are no reports of a double isomerization of terminal olefins by ruthenium hydride species in the literature (Scheme 3.51).

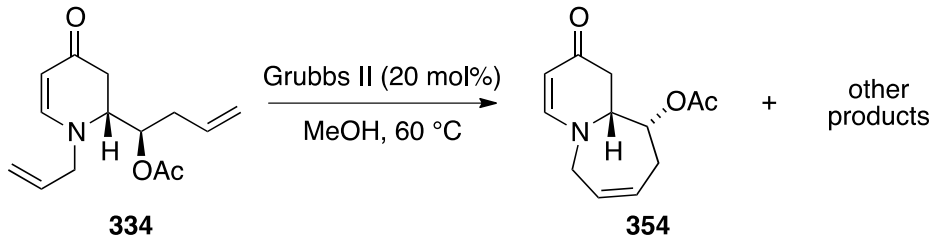


334 **355** **356**

Scheme 3.51: *Proposed route to 6,5 bicyclic system **356**.*

Undeterred, Hanessian's method was applied to dihydropyridone **334**, however a complex mixture of products was obtained. Analysis of the proton NMR spectrum of the crude reaction mixture revealed the major product to be bicycle **354**, presumably formed by ring closing metathesis, catalyzed by undecomposed Grubbs 2nd generation catalyst. Allowing a longer time for catalyst decomposition prior to the addition of starting material made little difference to the

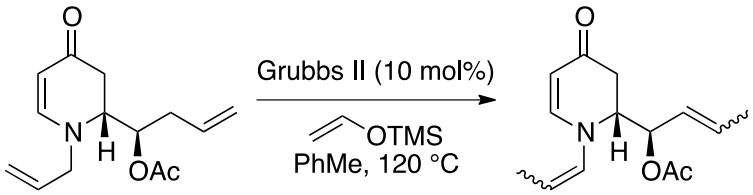
outcome as a complex mixture, of which bicycle **354** was the major constituent, was obtained in all cases (Scheme 3.52).



334 **354**

Scheme 3.52: *Application of Hanessian's method for terminal olefin isomerization.*

Nishida has reported an alternative procedure for terminal double bond isomerization, involving pre-mixing of Grubbs 2nd generation catalyst with vinyloxytrimethylsilane to generate the ruthenium hydride species.[146] In addition, lower catalyst loadings may be used with Nishida's method, although an excess of vinyloxytrimethylsilane is required. Treatment of Grubbs 2nd generation catalyst with vinyloxytrimethysilane in toluene, and subsequent heating, resulted in a colour change from purple-red to bright yellow, characteristic of the ruthenium hydride species **256**, within 5 minutes.[116] Addition of a solution of dihydropyridone **334** in toluene to this mixture resulted in the complete conversion of **334** to a single product, as judged by TLC analysis. Purification of the crude mixture by column chromatography allowed the identification of this product as dihydropyridone **355**, the result of a double terminal olefin isomerization (Scheme 3.53).



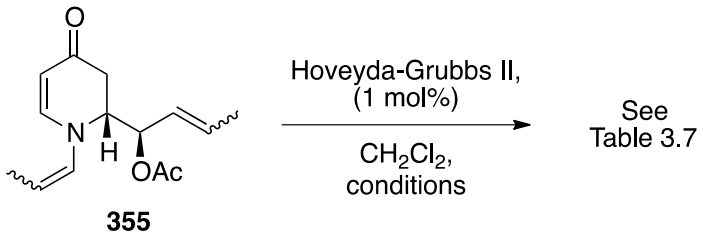
334 **355**, 97%

Scheme 3.53: *Double terminal olefin isomerization.*

Dihydropyridone **355** was obtained as an inseparable mixture of geometric double bond isomers, however the success of this double isomerization could be judged by analysis of the proton NMR spectrum due to the appearance of a pair of doublets at 1.57 ppm and 1.50 ppm, corresponding to the two terminal methyl groups. Furthermore, the ^{13}C DEPT 135 edited spectrum displayed only

one signal due to a methylene carbon, compared to five in the unisomerized starting material **334**.

Subjection of dihydropyridone **355** to the metathesis conditions, successful for dihydropyridone **335**, resulted in the recovery of unchanged starting material. If the reaction solvent was heated at reflux, gradual decomposition of the starting material was evident with no conversion to the desired bicycle **356** (Scheme 3.54, Table 3.7).

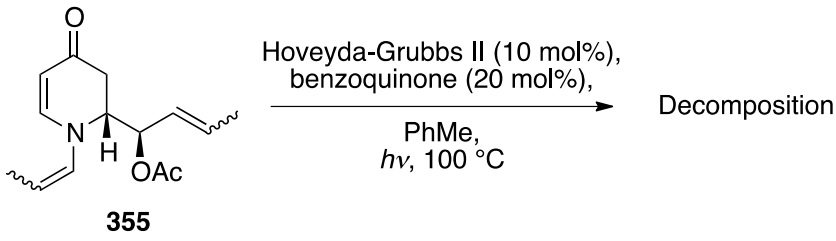


Scheme 3.54: *Attempts to induce RCM.*

Entry	Temperature	Outcome
1	rt	No reaction
2	40 °C	Starting material, some decomposition

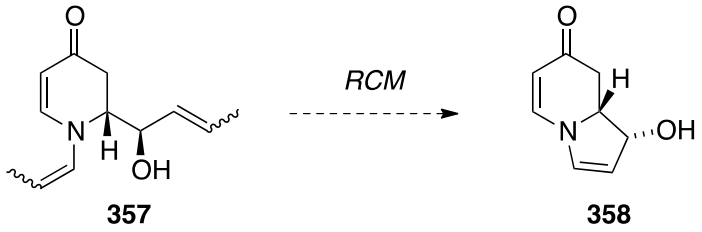
Table 3.7: *Attempts to induce RCM.*

Since its discovery by Kiddle, the accelerating effect of microwave irradiation on metathesis reactions has received considerable interest.[147] However, the use of microwave irradiation, in the presence of benzoquinone to re-oxidize any ruthenium hydride species formed,[148] was also unsuccessful with total decomposition of the starting material **355** to an insoluble, black powder (Scheme 3.55).



Scheme 3.55: *Attempted microwave-accelerated RCM.*

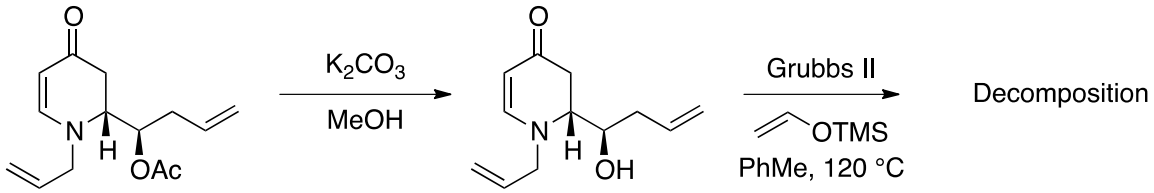
These results were unsurprising considering Hoye's finding that protected allylic alcohols were deactivated towards ring closing metathesis.[149] However, in the same paper, Hoye demonstrated that free allylic alcohols were greatly activated towards ring closing metathesis. Accordingly, it was proposed that ring closing metathesis on substrate **357** could furnish the desired 6,5-bicyclic system **358** (Scheme 3.56).



357 **358**

Scheme 3.56: *Proposed route to bicycle **358**.*

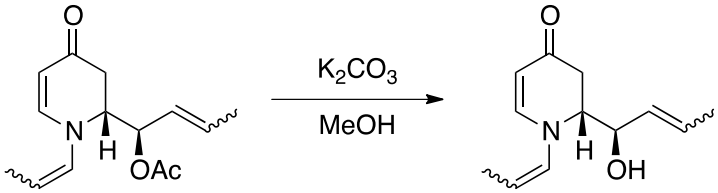
Treatment of dihydropyridone **334** with potassium carbonate in methanol provided the corresponding homoallylic alcohol **350** in a good yield of 86%. When alcohol **350** was subjected to Nishida's isomerization conditions, decomposition occurred. Clearly, an unprotected alcohol was undesirable when attempting the ruthenium-catalyzed isomerization of terminal olefins (Scheme 3.57).



334 **350**, 86%

Scheme 3.57: *Attempted isomerization of dihydropyridone **350**.*

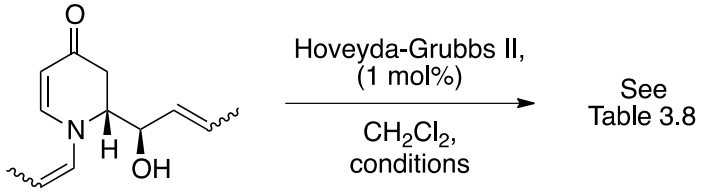
As the double isomerization of dihydropyridone **334** was known to be a viable transformation, it was proposed that alcohol **357** could be formed by standard deacetylation of dihydropyridone **355**. Treatment of **355** with potassium carbonate in methanol gave alcohol **357** in 80% yield (Scheme 3.58).



355 **357**, 80%

Scheme 3.58: *Formation of dihydropyridone **357**.*

Unfortunately, when alcohol **357** was treated with Hoveyda-Grubbs 2nd generation catalyst, only unchanged starting material was recovered. In addition, no reaction was observed when the reaction solvent was heated at reflux and unchanged starting material was observed in the proton NMR spectrum of the crude reaction mixture (Scheme 3.59, Table 3.8).



357

Scheme 3.59: *Attempted RCM on dihydropyridone **357**.*

Entry	Temperature	Outcome
1	rt	No reaction
2	40 °C	No reaction

Table 3.8: *Attempted RCM on dihydropyridone **357**.*

In spite of the success in the preparation of 6,6- and 6,7-bicyclic systems, it seemed likely that the 6,5-system was too strained to be created by this method.

3.5 Conclusions

At the outset of this investigation, the most widely utilized method for preparing enantioenriched dihydropyridones involved the addition of a nucleophile to a pyridinium salt, activated using a chiral auxiliary on nitrogen.[87, 93] The addition of a catalytically generated chiral nucleophile to pyridinium salts was an extremely under-developed part of the literature with only the methods of Shibasaki[56] and Ma[57] having been reported when work on this project began in September 2007 (the work of Feringa was published while the experimental work for this thesis was being carried out).[98] Although efforts to utilize reagent control to prepare enantioenriched dihydropyridones were unsuccessful, a non-auxiliary based method of substrate control has been demonstrated, involving a high yielding, regio- and diastereoselective hydride shift onto a pyridinium salt. This transformation was subsequently found to proceed without erosion of enantiomeric purity from the enantiopure pyridyl alcohol **317**.[133]

The synthetic advantages of this non-chiral auxiliary based method became apparent when it was found that the *N*-allyl group, used initially to activate the pyridine nucleus to nucleophilic addition, could be utilized as an essential part of complex bicyclic structures using ring closing metathesis. The fact that the *N*-allyl group need no longer be thought of as a mere protecting group demonstrated the increased atom economy of this methodology and, it is believed, will make this work of significant interest to the synthetic community.

Chapter 4:
Experimental

4.1 General Experimental Techniques

THF, CH_2Cl_2 and diethyl ether were dried prior to use by alumina column. Triethylamine was dried by stirring over and distilling from calcium hydride and was stored over calcium hydride granules. Reagents obtained from Acros, Aldrich, Avocado, Fluka and Lancaster fine chemicals suppliers were used directly as supplied or following purification according to procedures described by Perrin and Armarego.[150] All non-aqueous reactions were carried out under an atmosphere of argon using oven- or flame- dried glassware.

Flash column chromatography was carried out according to the method of Still[151] using silica gel 60 (0.040-0.063 mm) (Merck) using head pressure by means of head bellows. Thin layer chromatography was performed on commercially available pre-coated glass-backed plates (Merck silica Kieselgel $60F_{254}$). Spots were made visible either by the quenching of UV fluorescence or by staining with a potassium permanganate or vanillin solution.

^{1}H NMR spectra were recorded on a Bruker AVANCE AV400 (400 MHz) spectrometer and referenced to $SiMe_4$ as an internal standard. Signal positions were recorded in δ ppm with the abbreviations s, d, t, q, qu, sept, br, app and m denoting singlet, doublet, triplet, quartet, quintet, septet, broad, apparent and multiplet respectively. ^{13}C NMR spectra were recorded on the same spectrometer listed above at 100 MHz and were referenced in the same way. All NMR chemical shifts are quoted in ppm. All coupling constants, *J*, are quoted in Hz.

Infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Spectra were analysed as thin films between NaCl plates. Only structurally important peaks are quoted. Absorption maxima (ν_{max}) are recorded in wavenumbers (cm^{-1}) and refer to stretching vibrations unless otherwise stated.

Mass spectra (*m/z*) under the conditions of electrospray ionisation (ESI) were recorded on a Fisons Platform II. Accurate mass (HRMS) data were recorded under conditions of ESI on a Brucker MicroTof (resolution = 10 000 FWHM) using a lock-spray source. The lock-mass used for calibration was tetraoctylammonium bromide in positive ion and sodium dodecyl sulfate in negative ion. Relative intensities of assignable peaks observed are quoted as a percentage value.

Melting points were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

"Petrol" refers to the fraction boiling in the range 30-40 ºC unless otherwise stated. "Ether" refers to diethyl ether.

4.2 General Procedures

General Procedure A: Grignard Addition to a THF-soluble Pyridinium Salt

Grignard reagent (1.5 eq.) was added dropwise to a stirred solution of pyridinium salt (1.0 eq.) in THF (3 mL per 0.40 mmol substrate) at –30 ºC and left stirring at this temperature for 16 h (temperature maintained by use of a cryostat.) An aqueous solution of HCl (1 M, 5 mL per 0.40 mmol substrate) was added and the biphasic system was allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with CH_2Cl_2 (10 mL) and then extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product, which was then purified as specified.

General Procedure B: Grignard Addition to a non-THF-soluble Pyridinium Salt

4-(Bromomethyl)-1,2-dimethoxybenzene, **361** (1.0 eq.) was added to a stirred solution of pyridine **4** (1.0 eq.) in ether (0.8 M) and the resulting mixture was left stirring for 3 h. The solvent was removed under a steady flow of nitrogen and the residue was dissolved in CH_2Cl_2 (3 mL per 0.40 mmol substrate). The resulting solution was cooled to –78 ºC using a cryostat, Grignard reagent (2.5 eq.) was added dropwise and the mixture was left stirring at this temperature for 16 h. An aqueous solution of HCl (1 M, 5 mL per 0.40 mmol substrate) was added and the biphasic system was allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with CH_2Cl_2 (10 mL) and then extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product, which was then purified as specified.

General Procedure C: Organozinc Addition to a Pyridinium Salt

Grignard Reagent (4.0 eq.) was added dropwise to a stirred solution of $ZnCl_2$ (1 M solution in ether, 2.0 eq.) in THF (3 mL per 0.40 mmol substrate) at room temperature and left stirring for 10 mins. A solution of pyridinium salt (1.0 eq.) in THF was added dropwise and the resulting mixture was left stirring for 16 h. An aqueous solution of HCl (1 M, 5 mL per 0.40 mmol

substrate) was added and the mixture was stirred for 1 h, before being diluted with CH_2Cl_2 (10 mL) and then extracted with CH_2Cl_2 (5 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to give the crude product, which was then purified as specified.

General Procedure D: Grignard Addition to an Aldehyde

Grignard Reagent (2.0 eq.) was added dropwise to a stirred solution of aldehyde (1.0 eq.) in THF (10 mL per 1.00 mmol substrate) at –30 ºC and the resulting solution was stirred at this temperature for 3 h. A saturated, aqueous solution of NH_4Cl was added and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated to give the crude product, which was then purified as specified.

General Procedure E: Formation of an *N*-Allyl Pyridinium Salt

A solution of allyl alcohol (1.2 eq.) and *N*,*N*-diisopropylethylamine (1.2 eq.) in CH_2Cl_2 (1 mL per 1.0 mmol substrate) was added dropwise to a solution of trifluoromethanesulfonic anhydride (1.2 eq.) in CH_2Cl_2 (1 mL per 1.0 mmol substrate) at –30 °C and stirred for 5 mins. The solution was warmed to 0 °C and stirred for a further 5 mins before re-cooling to –30 °C. Ether (3 mL per mmol substrate) was added to precipitate the ammonium salts. The resulting mixture was filtered through celite® into a stirred solution of pyridine (1.0 eq.) in CH_2Cl_2 (10 mL per mmol substrate) at –30 °C and the reaction mixture was allowed to warm to room temperature over a period of 4 h. The solvent was removed *in vacuo* and the residue was purified as specified.

General Procedure F: Silylation of an *N*-Allyl Pyridinium Salt

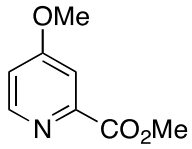
Di-*tert*-butylchlorosilane (2.0 eq.) was added dropwise to a stirred solution of pyridinium salt (1.0 eq.), triethylamine (3.0 eq.) and 4-(dimethylamino)pyridine (3.0 eq.) in DMF (2 mL per mmol substrate) and the resulting solution was left to stir for 16 h. The reaction was then diluted with CH_2Cl_2 (3 mL per mmol substrate) and an aqueous solution of HCl (2 M, 3 mL per mmol substrate) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed successively with saturated, aqueous LiCl solution (3 × 30 mL), water (30 mL) and brine (30 mL). The combined organic layers were then dried over Na_2SO_4, filtered and concentrated to give the crude product, which was then purified as specified.

General Procedure G: Hydride Migration

A solution of pyridinium salt (1.0 eq.) in toluene (25 mL per 1.0 mmol substrate) was heated to 50 °C. Tetrabutylammonium fluoride solution (1.0 M in THF, 1.0 eq.) was added and the resulting solution was left to stir at this temperature for 2 h. The reaction mixture was cooled to room temperature before the addition of THF (25 mL per mmol substrate) and then further tetrabutylammonium fluoride solution (1.0 M in THF, 3.0 eq.). The resulting solution was left to stir at room temperature for 16 h before an aqueous solution of HCl (2 M, 25 mL per mmol substrate) was added. The biphasic mixture was left to stir for 1 h before the aqueous phase was neutralized with $NaHCO_3$. The aqueous phase was then extracted with ethyl acetate, or ^{n}butanol, in the case of substrate **304** (4 × 30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude residue was re-dissolved in pyridine (5 mL per 1.0 mmol substrate) before the addition of 4-(dimethylamino)pyridine (0.5 eq.) and acetic anhydride (3 mL per mmol substrate). The resulting solution was left to stir for 16 h before being neutralized with 2 M aqueous HCl solution. The aqueous phase was then extracted with ethyl acetate, or ^{n}butanol, in the case of substrate **304** (4 × 30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude residue was then purified as specified.

4.3 Experimental Details

Methyl 4-methoxypicolinate, 201[13]

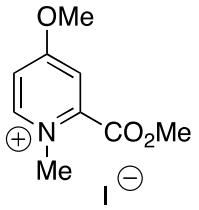


Picolinic acid **3** (15.704 g, 0.128 mol) and sodium bromide (1.313 g, 12.8 mmol) were dissolved in thionyl chloride (110 mL) and the resulting mixture was heated to 90 ºC for 30 h with vigorous stirring. The mixture was then concentrated *in vacuo* and the residue cooled to 0 ºC. Methanol (50 mL) was added cautiously and the resulting mixture was heated to 70 ºC for 36 h. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (100 mL). Sodium carbonate (20.280 g, 0.191 mol) was added and the mixture was stirred for 3 h before the addition of H_2O (100 mL). The mixture was then extracted with CH_2Cl_2 (5 × 75 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 9:1 ether-petrol → ether) to yield *pyridine **201*** (9.835 g, 58.9 mmol, 46%) as brown needles.

R_f 0.21 (ether); **m.p.** 47-49 °C (lit. 48-50 °C)[13]; **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.55-8.54 (1 H, m, NC*H*), 7.68-7.67 (1 H, m, $(CO_2Me)CCH$), 6.99-6.97 (1 H, m, NCHC*H*), 4.01 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.5 (CO_2Me), 165.8 ($NCCO_2Me$), 150.9 (NCH), 149.5 (*C*OMe), 113.2 (NCH*C*H), 111.1 ($(CO_2Me)CCH$), 55.6 (OCH_3), 53.0 (OCH_3).

All data were in agreement with those previously reported.[13]

4-Methoxy-2-(methoxycarbonyl)-1-methylpyridinium iodide, 209[13]

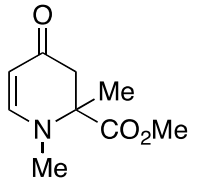


Pyridine **201** (0.503 g, 3.01 mmol) was dissolved in iodomethane (10 mL) and the resulting solution was heated to 45 ºC for 16 h. The reaction mixture was allowed to cool to room temperature before the addition of ether (20 mL). The resulting precipitate was filtered and washed with ether (3 × 10 mL) before being dried under high vacuum to furnish *pyridinium salt **209*** (0.800 g, 2.59 mmol, 86%) as a pale yellow powder.

R_f 0.35 (1:9 methanol-CH_2Cl_2); **m.p.** 112-114 °C (lit. 113-115 °C)[13]; **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 9.64-9.62 (1 H, m, NC*H*), 7.89-7.86 (2 H, m, NCHC*H*, $(CO_2Me)CCH$), 4.58 (3 H, s, NCH_3), 4.24 (3 H, s, OCH_3), 4.09 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.5 (CO_2Me), 159.5 ($NCCO_2Me$), 152.2 (NCH), 142.9 (*C*OMe), 118.0 ($(CO_2Me)CCH$), 114.6 (NCH*C*H), 59.3 (OCH_3), 54.9 (OCH_3), 48.0 (NCH_3).

All data were in agreement with those previously reported.[13]

Methyl 1,2-dimethyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 211[13]



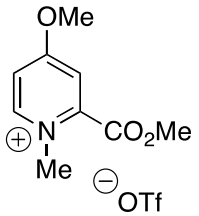
Pyridinium salt **209** (0.063 g, 0.205 mmol) was subjected to general procedure A, using methylmagnesium bromide (1.4 M solution in 3:1 toluene-THF) as the Grignard reagent. Flash column chromatography (SiO_2, ethyl acetate) gave *dihydropyridone **211*** (0.023 g, 0.128 mmol, 62%) as cubes.

Pyridinium salt **212** (0.268 g, 0.809 mmol) was subjected to general procedure A, using methylmagnesium bromide (1.4 M solution in 3:1 toluene-THF) as the Grignard reagent. Flash column chromatography (SiO_2, ethyl acetate) gave *dihydropyridone **211*** (0.132 g, 0.721 mmol, 89%) as cubes.

R_f 0.12 (ethyl acetate); **m.p.** 106-108 °C (lit. 107-110 °C)[13]; **IR ν_{max}** (thin film/cm^{-1}) 1732 (ester C=O), 1629 (C=O), 1583 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.02 (1 H, d, *J* 7.7, NC*H*), 4.97 (1H, dd, *J* 7.7, 0.9, NCHC*H*), 3.74 (3 H, s, CO_2CH_3), 3.09 (3 H, s, NCH_3), 2.87 (1 H, dd, *J* 16.4, 0.9, $COCH_AH_B$), 2.55, (1 H, d, *J* 16.4, $COCH_AH_B$), 1.56 (3 H, s, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.0 (*C*=O), 172.8 (CO_2Me), 155.5 (N*C*H), 98.9 (NCH*C*H), 64.7 (quaternary N*C*), 52.9 (CO_2CH_3), 46.4 ($COCH_2$), 39.1 (NCH_3), 22.2 (CH_3); **MS *m/z*** (ESI^+) 184 (75%, $M+H^+$), 206 (80%, $M+Na^+$), 389 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_9H_{13}NNaO_3$ requires $M+Na^+$ 206.0788, found 206.0791 (–1.40 ppm).

All data were in agreement with those previously reported.[13]

4-Methoxy-2-(methoxycarbonyl)-1-methylpyridinium trifluoromethanesulfonate, 212[62]

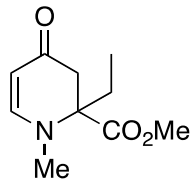


Methyl trifluoromethanesulfonate (0.400 mL, 3.53 mmol) was added dropwise to a stirred solution of pyridine **201** (0.536 g, 3.21 mmol) in CH_2Cl_2 (5 mL) at 0 ºC. The mixture was allowed to warm to room temperature and left stirring for 16 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 1:99 → 2:23 methanol-CH_2Cl_2) to give *pyridinium salt **212*** (1.063 g, 3.21 mmol, 100%) as a pale brown solid.

R_f 0.35 (1:9 methanol-CH_2Cl_2); **m.p.** 68-70 °C (lit. 69-71 °C)[62]; **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.89 (1 H, d, *J* 7.2, NC*H*), 7.85 (1 H, d, *J* 3.1, (CO_2Me)CC*H*), 7.61 (1 H, dd, *J* 7.2, 3.1, NCHC*H*), 4.41 (3 H, s, NCH_3), 4.16 (3 H, s, OCH_3), 4.05 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.7 (CO_2Me), 159.6 (N*C*CO_2Me), 151.4 (N*C*H), 143.3 (*C*OMe), 122.1 (Tf *C*F_3), 117.5 ((CO_2Me)C*C*H), 114.3 (NCH*C*H), 58.6, 54.6 (2 × OCH_3), 47.2 (NCH_3); **^{19}F NMR δ_F** (377 MHz, $CDCl_3$) –78.6 (Tf CF_3).

All data were in agreement with those previously reported.[62]

Methyl 2-ethyl-1-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 213[13]

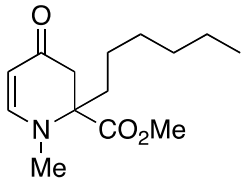


Pyridinium salt **212** (0.107 g, 0.324 mmol) was subjected to general procedure A, using ethylmagnesium bromide (3.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, ethyl acetate) gave *dihydropyridone **213*** (0.062 g, 0.316 mmol, 97%) as an oil.

R_f 0.26 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1735 (ester C=O), 1637 (C=O), 1586 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.00 (1 H, d, *J* 7.6, NC*H*), 4.90 (1 H, d, *J* 7.6, NCHC*H*), 3.69 (3 H, s, OC*H*$_3$), 3.07 (3 H, s, NC*H*$_3$), 2.69 (1 H, d, *J* 16.3, COC*H*$_A$H$_B$), 2.63 (1 H, d, *J* 16.3, COCH$_A$*H*$_B$), 1.90 (2 H, q, *J* 7.5, C*H*$_2$CH$_3$), 0.97 (3 H, t, *J* 7.5, CH$_2$C*H*$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.6 (*C*=O), 173.0 (*C*O$_2$Me), 156.3 (N*C*H), 98.8 (NCH*C*H), 68.2 (quaternary N*C*), 52.7 (CO$_2$*C*H$_3$), 42.1 (CO*C*H$_2$), 39.0 (N*C*H$_3$), 27.6 (*C*H$_2$CH$_3$), 8.2 (CH$_2$*C*H$_3$); **MS *m/z*** (ESI$^+$) 198 (60%, M+H$^+$), 220 (40%, M+Na$^+$), 395 (50%, 2M+H$^+$), 417 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{10}H_{15}NNaO_3$ requires *M*+*Na*$^+$ 220.0944, found 220.0946 (–0.93 ppm).

All data were in agreement with those previously reported.[13]

Methyl 2-hexyl-1-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 214

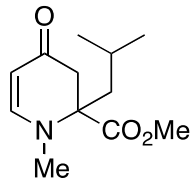


Pyridinium salt **212** (0.110 g, 0.331 mmol) was subjected to general procedure A, using hexylmagnesium bromide (2.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, ethyl acetate) gave *dihydropyridone **214*** (0.082 g, 0.323 mmol, 92%) as an oil.

R_f 0.53 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1736 (ester C=O), 1640 (C=O), 1588 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.00 (1 H, d, *J* 7.7, NC*H*), 4.93 (1 H, d, *J* 7.7, NCHC*H*), 3.71 (3 H, s, CO$_2$C*H*$_3$), 3.09 (3 H, s, NC*H*$_3$), 2.74 (1 H, d, *J* 16.3, COC*H*$_A$H$_B$), 2.67 (1 H, d, *J* 16.3, COCH$_A$*H*$_B$), 1.89-1.79 (2 H, m, C(CO$_2$Me)C*H*$_2$CH$_2$), 1.36-1.29 (8 H, m, 4 × C*H*$_2$), 0.88 (3 H, t, *J* 6.8, C*H*$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.6 (*C*=O), 173.0 (*C*O$_2$Me), 156.2 (N*C*H), 98.9 (NCH*C*H), 68.0 (quaternary N*C*), 52.7 (CO$_2$*C*H$_3$), 42.8 (CO*C*H$_2$), 39.1 (N*C*H$_3$), 34.7, 31.5, 29.4, 23.7, 22.5 (5 × *C*H$_2$), 14.0 (*C*H$_3$); **MS *m/z*** (ESI$^+$) 254 (90%, M+H$^+$), 276 (30%, M+Na$^+$), 317

(90%, M+MeCN+Na^+), 507 (100%, 2M+H^+), 529 (90%, 2M+Na^+); **HRMS** (ESI^+) $C_{14}H_{23}NNaO_3$ requires $M+Na^+$ 276.1570, found 276.1570 (+0.12 ppm).

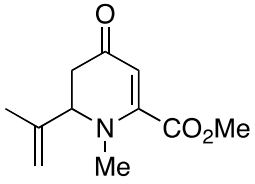
Methyl 2-isobutyl-1-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 215



Pyridinium salt **212** (0.109 g, 0.328 mmol) was subjected to general procedure A, using isobutylmagnesium bromide (2.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, ethyl acetate) gave *dihydropyridone* ***215*** (0.067 g, 0.299 mmol, 91%) as oil.

R_f 0.32 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1735 (ester C=O), 1650 (C=O), 1588 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.94 (1 H, d, *J* 7.6, NC*H*), 4.88 (1 H, d, *J* 7.6, NCHC*H*), 3.67 (3 H, s, OCH_3), 3.08 (3 H, s, NCH_3), 2.78 (1 H, d, *J* 16.2, COC$H_A$$H_B$), 2.62 (1 H, d, *J* 16.2, COC$H_A$$H_B$), 1.86-1.72 (3 H, m, $(CH_3)_2CHCH_2$), 0.97 (3 H, d, *J* 5.7, CH_3), 0.90 (3 H, d, *J* 5.7, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.6 (*C*=O), 172.7 (*C*O_2Me), 155.7 (N*C*H), 98.7 (NCH*C*H), 67.8 (quaternary N*C*), 52.7 (CO_2CH_3), 43.1 (CO*C*H_2), 42.8 ($(CH_3)_2CHCH_2$), 39.4 (N*C*H_3), 24.1 (*C*H_3), 23.8 ($(CH_3)_2CHCH_2$), 23.8 (*C*H_3); **MS *m/z*** (ESI^+) 226 (85%, M+H^+), 289 (20%, M+MeCN+Na^+), 451 (95%, 2M+H^+), 473 (100%, 2M+Na^+); **HRMS** (ESI^+) $C_{12}H_{20}NO_3$ requires $M+H^+$ 226.1438, found 226.1437 (+0.40 ppm).

Methyl 1-methyl-4-oxo-6-(prop-1-en-2-yl)-1,4,5,6-tetrahydropyridine-2-carboxylate, 216

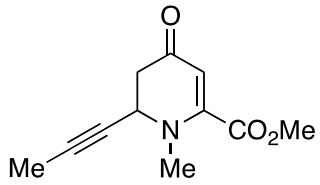


Pyridinium salt **212** (0.103 g, 0.311 mmol) was subjected to general procedure A, using isopropenylmagnesium bromide (0.5 M solution in THF) as the Grignard reagent. Flash column chromatography (SiO_2, 3:2 ethyl acetate-petrol) gave *dihydropyridone* ***216*** (0.045 g, 0.215 mmol, 69%) as an oil.

R_f 0.48 (ethyl aetate); **IR ν_{max}** (thin film/cm^{-1}) 1737 (ester C=O), 1647 (C=O), 1566 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 5.22 (1 H, s, (CO_2Me)CC*H*), 4.95 (2 H, d, *J* 14.3, C=CH_2), 3.93 (1 H, t, *J* 7.0, NC*H*), 3.85 (3 H, s, OCH_3), 2.95 (3 H, s, NCH_3), 2.72 (1 H, dd, *J* 16.6, 7.0, COC$H_A$$H_B$), 2.53 (1 H, dd, *J* 16.6, 7.0, COC$H_A$$H_B$), 1.73 (3 H, s, C$H_3$); **^{13}C NMR δ_C** (100 MHz,

$CDCl_3$) 191.2 (*C*=O), 164.6 (*C*O_2Me), 153.9 (quaternary N*C*), 139.9 (*C*=CH_2), 114.7 (C=*C*H_2), 100.2 ((CO_2Me)C*C*H), 66.2 (N*C*H), 52.9 (CO_2*C*H_3), 39.5 (CO*C*H_2), 38.4 (N*C*H_3), 18.4 (*C*H_3); **MS *m/z*** (ESI$^+$) 210 (70%, M+H$^+$), 419 (80%, 2M+H$^+$), 441 (100%, 2M+Na$^+$), 650 (50%, 3M+Na$^+$); **HRMS** (ESI$^+$) $C_{11}H_{15}NNaO_3$ requires $M+Na^+$ 232.0944, found 232.0945 (–0.45 ppm).

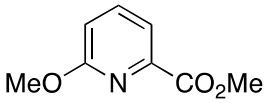
Methyl 1-methyl-4-oxo-6-(prop-1-ynyl)-1,4,5,6-tetrahydropyridine-2-carboxylate, 217



Pyridinium salt **212** (0.093 g, 0.280 mmol) was subjected to general procedure A, using 1-propynylmagnesium bromide (0.5 M solution in THF) as the Grignard reagent. Flash column chromatography (SiO_2, 7:3 ethyl acetate-petrol) gave *dihydropyridone **217*** (0.035 g, 0.168 mmol, 60%) as an oil.

R_f 0.65 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 2254 (C≡C), 1737 (ester C=O), 1650 (C=O), 1563 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 5.42 (1 H, s, (CO_2Me)CC*H*), 4.28-4.23 (1 H, m, NC*H*), 3.85 (3 H, s, CO_2C*H*$_3$), 3.10 (3 H, s, NC*H*$_3$), 2.75 (1 H, dd, *J* 16.2, 6.2, COC*H*$_A$H$_B$), 2.54 (1 H, dd, *J* 16.2, 5.2, COCH$_A$*H*$_B$), 1.81 (3 H, d, *J* 2.3, C*H*$_3$C≡C); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 191.2 (*C*=O), 164.4 (*C*O_2Me), 152.6 (N*C*CO_2Me), 102.2 ((CO_2Me)C*C*H), 82.3 (*C*≡C), 73.9 (C≡*C*), 53.0 (N*C*H), 52.9 (CO_2*C*H_3), 41.9 (CO*C*H_2), 38.6 (N*C*H_3), 3.6 (*C*H_3C≡C); **MS *m/z*** (ESI$^+$) 208 (75%, M+H$^+$), 271 (80%, M+MeCN+Na$^+$), 437 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{11}H_{14}NO_3$ requires $M+H^+$ 208.0968, found 208.0968 (–0.08 ppm).

Methyl 6-methoxypicolinate, 219[152]



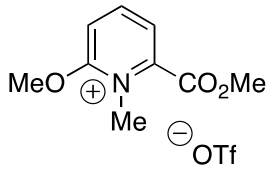
A suspension of 6-hydroxypicolinic acid **218** (0.806 g, 5.79 mmol), silver carbonate (4.793 g, 17.4 mmol) and methyl iodide (2.886 mL, 46.4 mmol) in chloroform (32 mL) was heated at 65 °C for 16 h in the dark. The reaction mixture was filtered through a plug of silica and the filtrate concentrated *in vacuo*. Flash column chromatography (SiO_2, 1:19 ethyl acetate-petrol) furnished *pyridine **219*** (0.839 g, 5.02 mmol, 87%) as colourless cubes.

R_f 0.57 (1:4 ethyl acetate-petrol); **m.p.** 35-36 °C (lit. 37-39 °C)[152]; **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.73-7.66 (2 H, m, Ar*H*), 6.94-6.92 (1 H, m, Ar*H*), 4.02 (3 H, s, OC*H*$_3$), 3.96 (3 H, s,

OC*H*$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 165.7 (*C*O_2Me), 163.9 (*C*OMe), 145.4 (*C*(CO_2Me)), 139.0, 118.7, 115.3 (3 × Ar*C*), 53.7, 52.7 (2 × O*C*H_3).

All data were in agreement with those previously reported.[152]

2-Methoxy-6-(methoxycarbonyl)-1-methylpyridinium trifluoromethanesulfonate, 220[62]

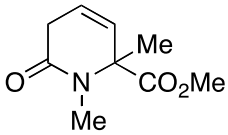


Methyl trifluoromethanesulfonate (0.412 mL, 3.64 mmol) was added dropwise to a stirred solution of pyridine **219** (0.553 g, 3.31 mmol) in CH_2Cl_2 (6 mL) at 0 ºC. The mixture was allowed to warm to room temperature and left stirring for 16 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 1:99 → 2:23 methanol-CH_2Cl_2) to give *pyridinium salt **220*** (1.093 g, 3.31 mmol, 100%) as an oil.

R_f 0.39 (1:9 methanol-CH_2Cl_2); **^{1}H NMR δ_H** (400 MHz, CD_3OD) 8.57 (1 H, dd, *J* 8.9, 7.8, CHC*H*CH), 8.02 (1 H, dd, *J* 7.8, 1.1, C*H*CHCH), 7.93 (1 H, dd, *J* 8.9, 1.1, CHCHC*H*), 4.41 (3 H, s, NC*H*$_3$), 4.18 (3 H, s, OC*H*$_3$), 4.08 (3 H, s, OC*H*$_3$); **^{13}C NMR δ_C** (100 MHz, CD_3OD) 162.6 (*C*O_2Me), 160.8 (N*C*CO_2Me), 147.6 (CH*C*HCH), 142.0 (*C*OMe), 122.1 (Tf *C*F_3), 121.2, 114.5 (2 × *C*H), 59.9 (N*C*H_3), 53.9, 38.0 (2 × O*C*H_3); **^{19}F NMR δ_F** (377 MHz, CD_3OD) –80.1 (Tf C*F*$_3$).

All data were in agreement with those previously reported.[62]

Methyl 1,2-dimethyl-6-oxo-1,2,5,6-tetrahydropyridine-2-carboxylate, 222[62]



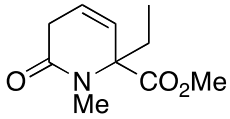
Pyridinium salt **220** (0.059 g, 0.179 mmol) was subjected to general procedure A, using methylmagnesium bromide (1.4 M solution in 3:1 toluene-THF) as the Grignard reagent. Flash column chromatography (SiO_2, ethyl acetate) gave *dihydropyridone **222*** (0.025 g, 0.137 mmol, 76%) as an oil.

R_f 0.25 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1734 (ester C=O), 1653 (amide C=O); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 5.82 (1 H, dt, *J* 10.1, 3.5, CH_2C*H*=CH), 5.57 (1 H, dt, *J* 10.1, 2.1, CH_2CH=C*H*), 3.70 (3 H, s, OC*H*$_3$), 2.99-2.95 (2 H, m, C*H*$_2$CH=CH), 2.86 (3 H, s, NC*H*$_3$), 1.59 (3 H, s, C*H*$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 172.0 (*C*O_2Me), 167.8 (amide *C*=O), 126.3 (CH_2CH=*C*H), 123.9 (CH_2*C*H=CH), 66.4 (quaternary N*C*), 53.0 (CO_2*C*H_3), 31.3 (*C*H_2CH=CH),

30.4 (N*C*H$_3$), 23.9 (*C*H$_3$); **MS *m/z*** (ESI$^+$) 184 (50%, M+H$^+$), 247 (70%, M+MeCN+Na$^+$), 367 (35%, 2M+H$^+$), 389 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_9H_{14}NO_3$ requires *M*+*H*$^+$ 184.0968, found 184.0970 (–0.92 ppm).

All data were in agreement with those previously reported.[62]

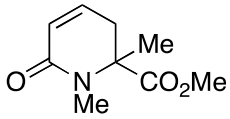
Methyl 2-ethyl-1-methyl-6-oxo-1,2,5,6-tetrahydropyridine-2-carboxylate, 223



Pyridinium salt **220** (0.110 g, 0.331 mmol) was subjected to general procedure A, using ethylmagnesium bromide (3.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, 2:3 → 4:1 ethyl acetate-^{i}hexane) gave *dihydropyridone* ***223*** (0.047 g, 0.239 mmol, 72%) as an oil.

R$_f$ 0.31 (ethyl acetate); **IR ν$_{max}$** (thin film/cm^{-1}) 1731 (ester C=O), 1653 (amide C=O); **^{1}H NMR δ$_H$** (400 MHz, $CDCl_3$) 5.94-5.89 (1 H, m, CH$_2$C*H*=CH), 5.45-5.41 (1 H, m, CH$_2$CH=C*H*), 3.69 (3 H, s, OC*H$_3$*), 3.03-2.90 (2 H, m, C*H$_2$*CH=CH), 2.80 (3 H, s, NC*H$_3$*), 2.08-1.89 (2 H, m, C*H$_2$*CH$_3$), 0.76 (3 H, dt, *J* 7.3, 4.6, CH$_2$C*H$_3$*); **^{13}C NMR δ$_C$** (100 MHz, $CDCl_3$) 172.0 (*C*O$_2$Me), 168.4 (amide *C*=O), 125.6 (CH$_2$CH=*C*H), 124.6 (CH$_2$*C*H=CH), 70.4 (quaternary N*C*), 52.9 (CO$_2$*C*H$_3$), 31.3 (*C*H$_2$CH=CH), 29.9 (N*C*H$_3$), 27.4 (*C*H$_2$CH$_3$), 6.9 (CH$_2$*C*H$_3$); **MS *m/z*** (ESI$^+$) 198 (10%, M+H$^+$), 220 (40%, M+Na$^+$), 395 (50%, 2M+H$^+$), 417 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{10}H_{15}NO_3$ requires *M*+*Na*$^+$ 220.0944, found 220.0943.

Methyl 1,2-dimethyl-6-oxo-1,2,3,6-tetrahydropyridine-2-carboxylate, 224

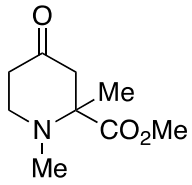


1,8-Diazabicyclo[5.4.0]undec-7-ene (0.109 mL, 0.731 mmol) was added to a stirred solution of dihydropyridone **222** (0.045 g, 0.244 mmol) in THF (5 mL) and the resulting mixture heated to 70 °C for 16 h. The mixture was allowed to cool to room temperature and water (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:1 → 7:3 ethyl acetate-^{i}hexane) furnished *conjugated dihydropyridone* ***224*** (0.032 g, 0.175 mmol, 71%) as an oil, along with recovered dihydropyridone **222** (0.005 g, 0.027 mmol, 11%).

R$_f$ 0.30 (ethyl acetate); **IR ν$_{max}$** (thin film/cm^{-1}) 1741 (ester C=O), 1669 (C=C), 1618 (amide C=O); **^{1}H NMR δ$_H$** (400 MHz, $CDCl_3$) 6.43-6.37 (1 H, m, CH$_2$C*H*=CH), 5.94-5.90 (1 H, m,

$CH_2CH{=}CH$), 3.68 (3 H, s, OCH_3), 2.97 (3 H, s, NCH_3), 2.88-2.81 (1 H, m, $CH_AH_BCH{=}CH$), 2.47-2.40 (1 H, m, $CH_AH_BCH{=}CH$), 1.56 (3 H, s, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 174.2 (CO_2Me), 165.6 (amide $C{=}O$), 136.5 ($CH_2CH{=}CH$), 125.5 ($CH_2CH{=}CH$), 63.1 (quaternary NC), 52.8 (CO_2CH_3), 35.9 ($CH_2CH{=}CH$), 28.5 (NCH_3), 24.0 (CH_3); **MS *m/z*** (ESI^+) 184 (15%, $M+H^+$), 206 (45%, $M+Na^+$), 242 (10%, $M+MeCN+NH_4^+$), 367 (40%, $2M+H^+$), 389 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_9H_{13}NO_3$ requires $M+Na^+$ 206.0788, found 206.0785 (+1.10 ppm).

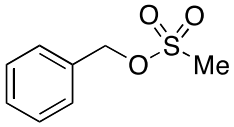
Methyl 1,2-dimethyl-4-oxopiperidine-2-carboxylate, 229



L-Selectride® (1.0 M solution in THF, 0.620 mL, 0.620 mmol) was added dropwise to a stirred solution of dihydropyridone **211** (0.113 g, 0.620 mmol) in THF (10 mL) at –78 °C and the resulting mixture was stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of a saturated, aqueous solution of NH_4Cl (10 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (SiO_2, 1:9 acetone-ether) furnished *piperidone **229*** (0.069 g, 0.373 mmol, 61%) as an oil.

R_f 0.62 (1:1 acetone-petrol); **IR ν_{max}** (thin film/cm^{-1}) 1737 (ester C=O), 1725 (C=O); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 3.69 (3 H, s, OCH_3), 2.97 (1 H, ddd, *J* 12.1, 6.9, 3.5, NCH_AH_B), 2.76 (1 H, ddd, *J* 12.1, 9.9, 4.7, NCH_AH_B), 2.59 (1 H, dd, *J* 14.8, 2.0, $(CO_2Me)CCH_AH_B$), 2.55-2.46 (1 H, m, $NCH_2CH_AH_B$), 2.41 (3 H, s, NCH_3), 2.39-2.36 (1 H, m, $NCH_2CH_AH_B$), 2.30 (1 H, dd, *J* 14.8, 1.1, $(CO_2Me)CCH_AH_B$), 1.37 (3 H, s, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 206.6 ($C{=}O$), 171.9 (CO_2Me), 64.7 (quaternary NC), 51.7 (CO_2CH_3), 50.6 (NCH_2), 50.1 ($(CO_2Me)CCH_2$), 40.2 (NCH_2CH_2), 38.5 (NCH_3), 22.5 (CH_3); **MS *m/z*** (ESI^+) 186 (75%, $M+H^+$), 393 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_9H_{15}NNaO_3$ requires $M+Na^+$ 208.0944, found 208.0945 (–0.44 ppm).

Benzyl methanesulfonate, 359[153]



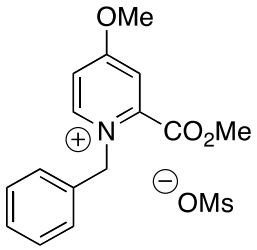
Methanesulfonic anhydride (0.604 g, 3.47 mmol) was added to a stirred solution of benzyl alcohol (0.239 mL, 2.31 mmol) and triethylamine (0.644 mL, 4.62 mmol) in CH_2Cl_2 (23 mL) at 0 °C. The mixture was allowed to warm to room temperature and left stirring for 90 mins. The

reaction mixture was diluted with CH_2Cl_2 (25 mL), and washed sequentially with H_2O (25 mL), aqueous HCl solution (1 M, 25 mL) and brine (25 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to yield *benzyl methanesulfonate* ***359*** (0.418 g, 2.25 mmol, 97%) as an oil which was used without further purification.

R_f 0.12 (1:4 ether-petrol); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.44-7.41 (5 H, m, Ar*H*), 5.26 (2 H, s, PhCH_2), 2.92 (3 H, s, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 133.4 (quaternary Ar*C*), 129.4, 128.9, 128.9 (5 × Ar*C*), 71.6 (Ph*C*H_2), 38.4 (*C*H_3).

All data were in agreement with those previously reported.[153]

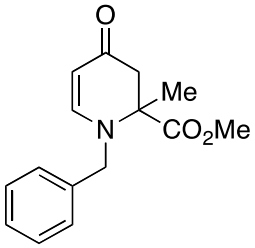
1-Benzyl-4-methoxy-2-(methoxycarbonyl)pyridinium methanesulfonate, 230



Pyridine **201** (0.100 g, 0.599 mmol) was added to stirred benzyl methanesulfonate **359** (0.339 g, 1.82 mmol) and the resulting mixture was left stirring for 16 h, after which time the mixture was purified by flash column chromatography (SiO_2, 2:23 methanol-CH_2Cl_2) to furnish *pyridinium salt* ***230*** (0.181 g, 0.513 mmol, 86%) as an oil.

R_f 0.30 (1:9 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 1745 (C=O), 1333, 1199 (SO_2); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 9.57 (1 H, d, *J* 7.2, NC*H*), 7.78 (1 H, dd, *J* 7.2, 3.1, NCHC*H*), 7.72 (1 H, d, *J* 3.1, (CO_2Me)CC*H*), 7.26-7.13 (5 H, m, Ar*H*), 5.98 (2 H, s, PhCH_2), 4.10 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 2.60 (3 H, s, Ms SO_2CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.8 (*C*O_2Me), 160.0 (N*C*CO_2Me), 151.9 (N*C*H), 143.4 (*C*OMe), 133.5 (quaternary Ar*C*), 129.3, 129.2, 128.2 (5 × Ar*C*), 117.5 ((CO_2Me)*C*CH), 114.7 (NCH*C*H), 61.0 (Ph*C*H_2), 58.9, 54.6 (2 × O*C*H_3), 39.5 (Ms SO_2*C*H_3); **MS *m/z*** (ESI$^+$) 258 (100%, M^+); **HRMS** (ESI$^+$) Cation $[C_{15}H_{16}NO_3]^+$ requires M^+ 258.1125, found 258.1121 (+1.61 ppm).

Methyl 1-benzyl-2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 231[62]

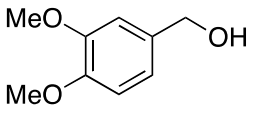


Pyridinium salt **230** (0.135 g, 0.383 mmol) was subjected to general procedure A, using methylmagnesium bromide (1.4 M solution in 3:1 toluene-THF) as the Grignard reagent. Flash column chromatography (SiO_2, 3:1 ethyl acetate-petrol) gave *dihydropyridone* ***231*** (0.049 g, 0.188 mmol, 49%) as an oil.

R_f 0.54 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1737 (ester C=O), 1645 (C=O), 1589 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.40-7.29 (5 H, m, Ar*H*), 7.02 (1 H, d, *J* 7.8, NC*H*), 5.03 (1 H, d, *J* 7.8, NCHC*H*), 4.56 (1 H, d, *J* 15.7, PhC$H_A$$H_B$), 4.44 (1 H, d, *J* 15.7, PhC$H_A$$H_B$), 3.73 (3 H, s, CO_2CH_3), 2.93 (1 H, d, *J* 16.5, COC$H_A$$H_B$), 2.64 (1 H, d, *J* 16.5, COC$H_A$$H_B$), 1.51 (3 H, s, C$H_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.1 (*C*=O), 173.3 (*C*O_2Me), 154.7 (N*C*H), 137.4 (quaternary Ar*C*), 129.0, 128.0, 127.4 (5 × Ar*C*), 100.0 (NCH*C*H), 65.8 (quaternary N*C*), 55.0 (Ph*C*H_2), 53.0 (CO_2CH_3), 47.0 (CO*C*H_2), 22.6 (*C*H_3); **MS *m/z*** (ESI^+) 260 (70%, $M+H^+$), 323 (20%, $M+MeCN+Na^+$), 519 (100%, $2M+H^+$), 541 (95%, $2M+Na^+$); **HRMS** (ESI^+) $C_{15}H_{17}NNaO_3$ requires $M+Na^+$ 282.1101, found 282.1099 (+0.49 ppm).

All data were in agreement with those previously reported.[62]

(3,4-Dimethoxyphenyl)methanol, 360[154]

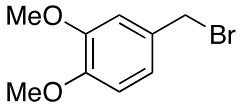


Sodium borohydride (2.288 g, 60.5 mmol) was added to a stirred solution of 3,4-dimethoxybenzaldehyde (10.05 g, 60.5 mmol) in pre-mixed THF (50 mL) and H_2O (1.5 mL) at 0 °C and left for 5 mins. The reaction mixture was diluted with ether (100 mL), quenched with H_2O (100 mL) and extracted with ether (3 × 75 mL). The combined organic extracts were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated to yield *alcohol* ***360*** (10.16 g, 60.5 mmol, 100%) as an oil, which was used without further purification.

R_f 0.51 (ether); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.93-6.82 (3 H, m, Ar*H*), 4.61 (2 H, s, CH_2OH), 3.88 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 1.93 (1 H, br s, O*H*); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 149.0, 148.5, 133.6 (3 × quaternary Ar*C*), 119.4, 111.0, 110.4 (3 × Ar*C*), 65.2 (*C*H_2OH), 55.9, 55.8 (2 × O*C*H_3).

All data were in agreement with those previously reported.[154]

4-(Bromomethyl)-1,2-dimethoxybenzene, 361[155]

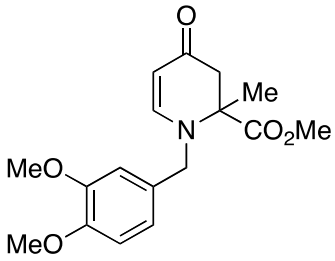


A solution of phosphorous tribromide (2.272 mL, 24.2 mmol) in ether (5 mL) was added dropwise to a stirred solution of alcohol **360** (10.154 g, 60.4 mmol) in ether (25 mL) at 0 °C and left for 1 h. The reaction mixture was then washed with brine (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL) before being dried over $MgSO_4$, filtered and concentrated to yield *bromide **361*** (13.052 g, 56.5 mmol, 93%) as white plates which were used without further purification.

R_f 0.80 (ether); **m.p.** 48-50 °C (lit. 52-53 °C)[155]; **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.97-6.80 (3 H, m, Ar*H*), 4.51 (2 H, s, CH_2Br), 3.90 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 149.2, 149.1, 130.2 (3 × quaternary Ar*C*), 121.6, 112.0, 111.0 (3 × Ar*C*), 55.9, 55.9 (2 × O*C*H_3), 34.4 (*C*H_2Br).

All data were in agreement with those previously reported.[155]

Methyl 1-(3,4-dimethoxybenzyl)-2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 233

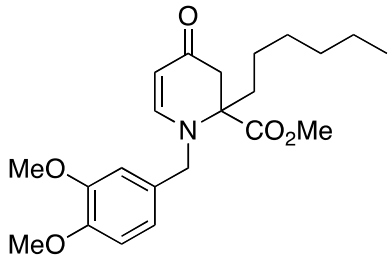


Pyridine **201** (0.224 g, 1.34 mmol) was subjected to general procedure B, using methylmagnesium bromide (1.4 M solution in 3:1 toluene-THF) as the Grignard reagent. Flash column chromatography (SiO_2, 7:3 ethyl acetate-petrol) gave *dihydropyridone **233*** (0.239 g, 0.749 mmol, 56%) as an oil.

Pyridinium salt **238** (0.094 g, 0.200 mmol) was subjected to general procedure A, using methylmagnesium bromide (1.4 M solution in 3:1 toluene-THF) as the Grignard reagent. Flash column chromatography (SiO_2, 7:3 ethyl acetate-petrol) gave *dihydropyridone **233*** (0.042 g, 0.132 mmol, 65%) as an oil.

R_f 0.43 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1737 (ester C=O), 1644 (C=O), 1586 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.99 (1 H, d, *J* 7.9, NC*H*), 6.87-6.82 (2 H, m, Ar*H*), 6.79 (1 H, s, Ar*H*), 5.00 (1 H, d, *J* 7.9, NCHC*H*), 4.47 (1 H, d, *J* 15.3, NC$H_A$$H_B$), 4.36 (1 H, d, *J* 15.3, NCH$_A$$H_B$), 3.87 (6 H, s, 2 × OC$H_3$), 3.74 (3 H, s, CO_2CH_3), 2.93 (1 H, d, *J* 16.5, COC$H_A$$H_B$), 2.61 (1 H, d, *J* 16.5, COCH$_A$$H_B$), 1.53 (3 H, s, C$H_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.0 (*C*=O), 173.3 (*C*O_2Me), 154.3 (N*C*H), 149.4, 148.8, 129.4 (3 × quaternary Ar*C*), 120.1, 111.3, 110.7 (3 × Ar*C*), 99.7 (NCH*C*H), 65.8 (quaternary N*C*), 55.9 (2 × O*C*H_3), 54.7 (N*C*H_2), 53.0 (CO_2CH_3), 47.0 (CO*C*H_2), 22.4 (*C*H_3); **MS *m/z*** (ESI^+) 320 (70%, $M+H^+$), 383 (20%, $M+MeCN+Na^+$), 639 (100%, $2M+H^+$), 661 (75%, $2M+Na^+$); **HRMS** (ESI^+) $C_{17}H_{21}NNaO_5$ requires $M+Na^+$ 342.1312, found 342.1311 (+0.30 ppm).

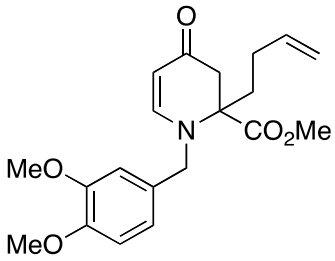
Methyl 1-(3,4-dimethoxybenzyl)-2-hexyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 234



Pyridine **201** (0.242 g, 1.45 mmol) was subjected to general procedure B, using hexylmagnesium bromide (2.0 M solution ether) as the Grignard reagent. Flash column chromatography (SiO_2, 3:2 ethyl acetate-petrol) gave *dihydropyridone **234*** (0.366 g, 0.942 mmol, 65%) as an oil.

R_f 0.68 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1734 (ester C=O), 1640 (C=O), 1587 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.96 (1 H, d, *J* 7.9, NC*H*), 6.87 (2 H, s, Ar*H*), 6.81 (1 H, s, Ar*H*), 4.98 (1 H, d, *J* 7.9, NCHC*H*), 4.50 (1 H, d, *J* 14.8, NC$H_A$$H_B$), 4.39 (1 H, d, *J* 14.8, NCH$_A$$H_B$), 3.89 (6 H, s, 2 × OC$H_3$), 3.74 (3 H, s, CO_2CH_3), 2.88 (1 H, d, *J* 16.3, COC$H_A$$H_B$), 2.73 (1 H, d, *J* 16.3, COCH$_A$$H_B$), 2.00-1.86 (2 H, m, C($CO_2$Me)C$H_2$$CH_2$), 1.39-1.19 (8 H, m, 4 × CH_2), 0.88-0.84 (3 H, m, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.6 (*C*=O), 173.3 (*C*O_2Me), 154.2 (N*C*H), 149.4, 148.9, 129.0 (3 × quaternary Ar*C*), 120.7, 111.3, 111.1 (3 × Ar*C*), 99.8 (NCH*C*H), 69.1 (quaternary N*C*), 55.9, 55.9 (2 × O*C*H_3), 53.7 (N*C*H_2), 52.8 (CO_2CH_3), 43.6 (CO*C*H_2), 34.8, 31.5, 29.4, 23.8, 22.5 (5 × *C*H_2), 14.0 (*C*H_3); **MS *m/z*** (ESI^+) 390 (40%, $M+H^+$), 779 (100%, $2M+H^+$), 801 (10%, $2M+Na^+$); **HRMS** (ESI^+) $C_{22}H_{32}NO_5$ requires $M+H^+$ 390.2275, found 390.2277 (–0.42 ppm).

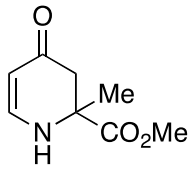
Methyl 2-(but-3-enyl)-1-(3,4-dimethoxybenzyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 235



Pyridine **201** (0.258 g, 1.54 mmol) was subjected to general procedure B, using 1-butenylmagnesium bromide (prepared fresh from 4-bromo-1-butene (0.313 mL, 3.09 mmol), Mg (0.094 g, 3.86 mmol) and 1,2-dibromoethane (0.005 mL, 0.058 mmol) in THF (1.5 mL)) as the Grignard reagent. Flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol → ethyl acetate) gave *dihydropyridone **235*** (0.342 g, 0.953 mmol, 62%) as an oil.

R_f 0.52 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1735 (ester C=O), 1647 (C=O), 1587 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.96 (1 H, d, *J* 7.9, NC*H*), 6.85 (2 H, s, Ar*H*), 6.79 (1 H, s, Ar*H*), 5.75-5.64 (1 H, m, CH_2CH=CH_2), 4.99-4.94 (3 H, m, CH_2CH=CH_2, NCHC*H*), 4.48 (1 H, d, *J* 14.8, NC$H_A$$H_B$), 4.37 (1 H, d, *J* 14.8, NC$H_A$$H_B$), 3.86 (6 H, s, 2 × OC$H_3$), 3.72 (3 H, s, CO_2CH_3), 2.89 (1 H, d, *J* 16.3, COC$H_A$$H_B$), 2.70 (1 H, d, *J* 16.3, COC$H_A$$H_B$), 2.15-1.95 (4 H, m, C$H_2CH_2$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.2 (*C*=O), 172.9 (*C*O_2Me), 154.2 (N*C*H), 149.3, 148.8 (2 × quaternary Ar*C*), 136.4 (CH_2*C*H=CH_2), 128.9 (quaternary Ar*C*), 120.6 (Ar*C*), 115.8 (CH_2CH=*C*H_2), 111.0, 110.8 (2 × Ar*C*), 99.9 (NCH*C*H), 68.8 (quaternary N*C*), 55.9, 55.9 (2 × O*C*H_3), 53.8 (N*C*H_2), 52.9 (CO_2*C*H_3), 43.5 (CO*C*H_2), 33.8, 28.0 (2 × *C*H_2); **MS *m/z*** (ESI^+) 360 (50%, $M+H^+$), 719 (100%, $2M+H^+$), 741 (50%, $2M+Na^+$); **HRMS** (ESI^+) $C_{20}H_{26}NO_5$ requires $M+H^+$ 360.1805, found 360.1803 (+0.63 ppm).

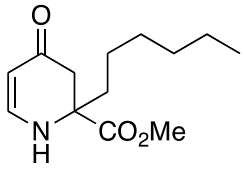
Methyl 2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 236



Dihydropyridone **233** (0.111 g, 0.347 mmol) was dissolved in trifluoroacetic acid (5 mL) and the resulting solution was heated to 80 °C for 16 h. The volatiles were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (5 mL). K_2CO_3 (0.096 g, 0.694 mmol) was added and the resulting mixture was stirred for 16 h before being filtered and concentrated. Flash column chromatography (SiO_2, ethyl acetate) yielded *dihydropyridone **236*** (0.041 g, 0.244 mmol, 70%) as an oil.

R_f 0.21 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3254 (N-H), 1735 (ester C=O), 1627 (C=O), 1577 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.16 (1 H, dd, *J* 7.5, 6.5, NC*H*), 5.51 (1 H, br s, N*H*), 5.05 (1 H, dd, *J* 7.5, 1.1, NCHC*H*), 3.78 (3 H, s, OCH_3), 2.90 (1 H, d, *J* 16.5, COCH_AH$_B$), 2.58 (1 H, d, *J* 16.5, COCH$_A$$H_B$), 1.52 (3 H, s, C$H_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.8 (*C*=O), 174.2 (*C*O_2Me), 149.5 (N*C*H), 99.6 (NCH*C*H), 60.3 (quaternary N*C*), 53.1 (CO_2CH_3), 44.8 (CO*C*H_2), 23.9 (*C*H_3); **MS *m/z*** (ESI$^+$) 170 (50 %, M+H$^+$), 192 (15%, M+Na$^+$), 233 (40%, M+MeCN+Na$^+$), 339 (100%, 2M+H$^+$), 361 (50%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_8H_{11}NNaO_3$ requires $M+Na^+$ 192.0631, found 192.0628 (+1.85 ppm).

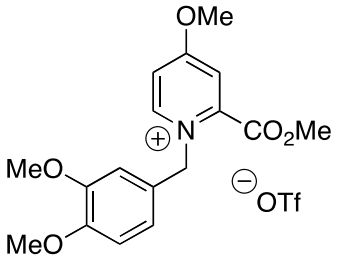
Methyl 2-hexyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 237



Dihydropyridone **234** (0.143 g, 0.366 mmol) was dissolved in trifluoroacetic acid (10 mL) and the resulting solution was heated to 80 °C for 16 h. The volatiles were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL). K_2CO_3 (0.101 g, 0.733 mmol) was added and the resulting mixture was stirred for 16 h before being filtered and concentrated. Flash column chromatography (SiO_2, 7:3 ethyl acetate-petrol) yielded *dihydropyridone **237*** (0.072 g, 0.300 mmol, 82%) as an oil.

R_f 0.51 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3253 (N-H), 1738 (ester C=O), 1631 (C=O), 1585 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.15 (1 H, dd, *J* 7.5, 6.4, NC*H*), 5.68 (1 H, br d, *J* 6.4, N*H*), 5.00 (1 H, d, *J* 7.5, NCHC*H*), 3.75 (3 H, s, OCH_3), 2.86 (1 H, d, *J* 16.3, COCH_AH$_B$), 2.59 (1 H, d, *J* 16.3, COCH$_A$$H_B$), 1.97-1.90 (1 H, m, C($CO_2$Me)C$H_AH_BCH_2$), 1.73-1.66 (1 H, m, C($CO_2$Me)CH$_A$$H_BCH_2$), 1.29-1.16 (8 H, m, 4 × CH_2), 0.85 (3 H, t, *J* 6.9, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.9 (*C*=O), 173.7 (*C*O_2Me), 149.6 (N*C*H), 99.3 (NCH*C*H), 63.5 (quaternary N*C*), 52.9 (CO_2CH_3), 43.6 (CO*C*H_2), 36.3, 31.4, 29.0, 23.7, 22.4 (5 × *C*H_2), 14.0 (*C*H_3); **MS *m/z*** (ESI$^+$) 240 (70%, M+H$^+$), 303 (30%, M+MeCN+Na$^+$), 479 (100%, 2M+H$^+$), 501 (80%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{13}H_{22}NO_3$ requires $M+H^+$ 240.1594, found 240.1595 (–0.46 ppm).

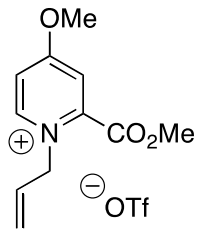
1-(3,4-Dimethoxybenzyl)-4-methoxy-2-(methoxycarbonyl)pyridinium trifluoromethanesulfonate, 238



4-(Bromomethyl)-1,2-dimethoxybenzene, **361** (0.341 g, 1.48 mmol) was added to a stirred solution of pyridine **201** (0.247 g, 1.48 mmol) in ether (2 mL) and the resulting mixture was left stirring for 3 h. The solvent was removed under a steady flow of nitrogen and the residue was dissolved in H_2O (10 mL). A solution of silver trifluoromethanesulfonate (0.380 g, 1.48 mmol) in H_2O (5 mL) was added dropwise and the resulting solution was stirred at 0 °C for 10 mins. The mixture was then filtered and concentrated to yield *pyridinium salt* ***238*** (0.586 g, 1.25 mmol, 85%) as an oil.

R_f 0.30 (1:9 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 1746 (C=O); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 9.01 (1 H, d, *J* 7.3, NC*H*), 7.76 (1 H, d, *J* 3.1, (CO_2Me)CC*H*), 7.57 (1 H, dd, *J* 7.3, 3.1, NCHC*H*), 6.91-6.90 (1 H, m, Ar*H*), 6.83-6.78 (2 H, m, Ar*H*), 5.84 (2 H, s, NCH_2), 4.13 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.8 (*C*O_2Me), 160.1 (N*C*CO_2Me), 150.0 (quaternary Ar*C*), 149.8 (N*C*H), 149.6 (quaternary Ar*C*), 143.7 (*C*OMe), 125.1 (quaternary Ar*C*), 122.3 (Tf *C*F_3), 121.8 (Ar*C*), 117.3 ((CO2Me)C*C*H), 114.5 (NCH*C*H), 111.8, 111.3 (2 × Ar*C*), 61.2 (N*C*H_2), 58.7, 56.1, 55.9, 54.7 (4 × O*C*H_3); **^{19}F NMR δ_F** (377 MHz, $CDCl_3$) –78.4 (Tf C*F*$_3$); **MS *m/z*** (ESI^+) 318 (100%, M^+); **HRMS** (ESI^+) Cation $[C_{17}H_{20}NO_5]^+$ requires M^+ 318.1336, found 318.1333 (+0.87 ppm).

1-Allyl-4-methoxy-2-(methoxycarbonyl)pyridinium trifluoromethanesulfonate, 240

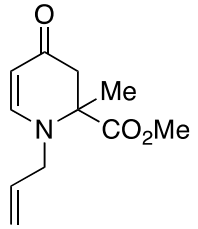


A solution of allyl alcohol (0.339 mL, 4.93 mmol) and *N*,*N*-diisopropylethylamine (0.858 mL, 4.93 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of trifluoromethanesulfonic anhydride (0.829 mL, 4.93 mmol) in CH_2Cl_2 (2 mL) at –30 °C and stirred for 5 mins. The solution was warmed to 0 °C and stirred for a further 5 mins before re-cooling to –30 °C. Ether (5 mL) was added to precipitate the ammonium salts. The resulting mixture was filtered through

celite® into a stirred solution of pyridine **201** (0.549 g, 3.29 mmol) in CH_2Cl_2 (15 mL) at –50 °C and the reaction mixture was allowed to warm to room temperature over a period of 4 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 1:99 → 3:97 → 1:19 methanol-CH_2Cl_2) to yield *pyridinium salt* ***240*** (0.998 g, 2.79 mmol, 85%) as cubes.

R_f 0.41 (1:9 methanol-CH_2Cl_2); **m.p.** 45-48 °C; **IR ν_{max}** (thin film/cm^{-1}) 1749 (C=O), 1633 (C=C); **^{1}H NMR δ_H** (400 MHz, CD_3OD) 8.86 (1 H, d, *J* 7.2, NC*H*), 8.00 (1 H, d, *J* 3.1, $(CO_2Me)CCH$), 7.72 (1 H, dd, *J* 7.2, 3.1, NCHC*H*), 6.20-6.10 (1 H, m, $CH_2CH{=}CH_2$), 5.46-5.35 (4 H, m, $CH_2CH{=}CH_2$), 4.23 (3 H, s, OCH_3), 4.07 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, CD_3OD) 172.9 (CO_2Me), 160.4 ($NCCO_2Me$), 149.6 (NCH), 144.5 (COMe), 131.6 ($CH_2CH{=}CH_2$), 122.4 (Tf CF_3), 121.0 ($CH_2CH{=}CH_2$), 117.2 ($(CO_2Me)CCH$), 114.5 (NCHCH), 60.6 ($CH_2CH{=}CH_2$), 58.3, 54.1 (2 × OCH_3); **^{19}F NMR δ_F** (377 MHz, CD_3OD) –80.1 (Tf CF_3) **MS *m/z*** (ESI^+) 208 (100%, M^+); **HRMS** (ESI^+) Cation $[C_{11}H_{14}NO_3]^+$ requires M^+ 208.0968, found 208.0967 (+0.64 ppm).

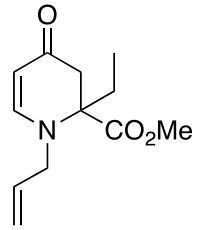
Methyl 1-allyl-2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 241



Pyridinium salt **240** (0.143 g, 0.399 mmol) was subjected to general procedure A, using methylmagnesium bromide (1.4 M solution in 3:1 toluene-THF) as the Grignard reagent and at a temperature of –60 °C. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) gave *dihydropyridone* ***241*** (0.072 g, 0.343 mmol, 86%) as an oil.

R_f 0.49 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1737 (ester C=O), 1644 (C=O), 1586 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.01 (1 H, d, *J* 7.7, NC*H*), 5.90-5.81 (1 H, m, $CH_2CH{=}CH_2$), 5.27-5.21 (2 H, m, $CH_2CH{=}CH_2$), 4.97 (1 H, d, *J* 7.7, NCHC*H*), 3.96-3.77 (2 H, m, $CH_2CH{=}CH_2$), 3.69 (3 H, s, OCH_3), 2.85 (1 H, d, *J* 16.4, $COCH_AH_B$), 2.55 (1 H, d, *J* 16.4, $COCH_AH_B$), 1.52 (3 H, s, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.0 (C=O), 173.2 (CO_2Me), 154.1 (NCH), 134.3 ($CH_2CH{=}CH_2$), 118.4 ($CH_2CH{=}CH_2$), 99.4 (NCHCH), 65.4 (quaternary NC), 53.5 ($CH_2CH{=}CH_2$), 52.9 (CO_2CH_3), 46.8 ($COCH_2$), 22.2 (CH_3); **MS *m/z*** (ESI^+) 210 (65%, $M+H^+$), 232 (15%, $M+Na^+$), 273 (60%, $M+MeCN+Na^+$), 419 (50%, $2M+H^+$), 441 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{11}H_{16}NO_3$ requires $M+H^+$ 210.1125, found 210.1126 (–0.56 ppm).

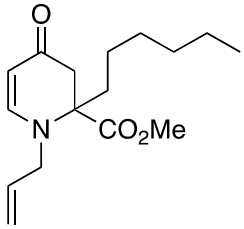
Methyl 1-allyl-2-ethyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 242



Pyridinium salt **240** (0.124 g, 0.348 mmol) was subjected to general procedure A, using ethylmagnesium bromide (3.0 M solution in ether) as the Grignard reagent and at a temperature of –60 °C. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) gave *dihydropyridone* ***242*** (0.069 g, 0.309 mmol, 89%) as an oil.

R_f 0.57 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1735 (ester C=O), 1644 (C=O), 1586 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.03 (1 H, d, *J* 7.9, NC*H*), 5.90-5.80 (1 H, m, CH_2CH=CH_2), 5.28-5.23 (2 H, m, CH_2CH=CH_2), 4.96 (1 H, d, *J* 7.9, NCHC*H*), 3.93 (1 H, dd, *J* 15.8, 5.3, NC$H_A$$H_B$), 3.80 (1 H, dd, *J* 15.8, 6.6, NC$H_A$$H_B$), 3.68 (3 H, s, OC$H_3$), 2.75 (1 H, d, *J* 16.3, COC$H_A$$H_B$), 2.64 (1 H, d, *J* 16.3, COC$H_A$$H_B$), 1.93 (2 H, dq, *J* 7.3, 4.7, C$H_2$$CH_3$), 0.94 (3 H, t, *J* 7.3, CH_2CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.5 (*C*=O), 173.2 (*C*O_2Me), 154.1 (NCH), 134.1 (CH_2*C*H=CH_2), 119.0 (CH_2CH=*C*H_2), 99.6 (NCH*C*H), 69.0 (quaternary N*C*), 52.7 (CO_2*C*H_3), 52.4 (N*C*H_2), 42.9 (CO*C*H_2), 27.6 (*C*H_2CH_3), 8.2 (CH_2*C*H_3); **MS *m/z*** (ESI^+) 224 (50%, $M+H^+$), 246 (40%, $M+Na^+$), 287 (65%, M+MeCN+Na^+), 469 (100%, 2M+Na^+); **HRMS** (ESI^+) $C_{12}H_{18}NO_3$ requires $M+H^+$ 224.1281, found 224.1281 (+0.02 ppm).

Methyl 1-allyl-2-hexyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 243

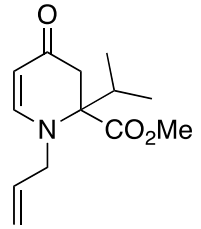


Pyridinium salt **240** (0.144 g, 0.402 mmol) was subjected to general procedure A, using hexylmagnesium bromide (2.0 M solution in ether) as the Grignard reagent and at a temperature of –60 °C. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) gave *dihydropyridone* ***243*** (0.097 g, 0.348 mmol, 86%) as an oil.

R_f 0.74 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1737 (ester C=O), 1652 (C=O), 1590 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.05 (1 H, d, *J* 7.8, NC*H*), 5.93-5.83 (1 H, m, CH_2CH=CH_2), 5.33-5.27 (2 H, m, CH_2CH=CH_2), 5.01 (1 H, d, *J* 7.8, NCHC*H*), 3.98-3.80 (2 H, m, C$H_2$$CH$=$CH_2$), 3.72 (3 H, s, OC$H_3$), 2.81 (1 H, d, *J* 16.3, COC$H_A$$H_B$), 2.69 (1 H, d, *J* 16.3, COC$H_A$$H_B$), 1.90-

1.86 (2 H, m, C(CO_2Me)C$H_2$$CH_2$), 1.39-1.23 (8 H, m, 4 × CH_2), 0.87 (3 H, t, *J* 6.6, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.6 (*C*=O), 173.4 (*C*O_2Me), 154.0 (N*C*H), 134.1 (CH_2*C*H=CH_2), 119.1 (CH_2CH=*C*H_2), 99.6 (NCH*C*H), 68.8 (quaternary N*C*), 52.8 (CO_2*C*H_3), 52.5 (N*C*H_2), 43.5 (CO*C*H_2), 34.8, 31.5, 29.4, 23.6, 22.5 (5 × *C*H_2), 14.0 (*C*H_3); **MS *m/z*** (ESI^+) 280 (70%, $M+H^+$), 302 (20%, $M+Na^+$), 343 (30%, $M+MeCN+Na^+$), 559 (20%, $2M+H^+$), 581 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{16}H_{26}NO_3$ requires $M+H^+$ 280.1907, found 280.1907 (+0.20 ppm).

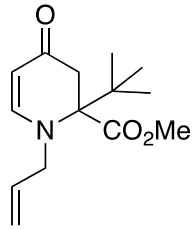
Methyl 1-allyl-2-isopropyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 244



Pyridinium salt **240** (0.148 g, 0.413 mmol) was subjected to general procedure A, using *iso*-propylmagnesium chloride (2.0 M solution in ether) as the Grignard reagent and at a temperature of –60 °C. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) gave *dihydropyridone **244*** (0.074 g, 0.312 mmol, 76%) as plates.

R_f 0.63 (ethyl acetate); **m.p.** 69-71 °C; **IR ν_{max}** (thin film/cm^{-1}) 1728 (ester C=O), 1650 (C=O), 1594 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.99 (1 H, d, *J* 7.9, NC*H*), 5.86-5.76 (1 H, m, CH_2C*H*=CH_2), 5.29-5.24 (2 H, m, CH_2CH=CH_2), 4.94 (1 H, dd, *J* 7.9, 1.2, NCHC*H*), 4.00 (1 H, ddt, *J* 15.5, 5.2, 1.5, NC$H_A$$H_B$), 3.78 (1 H, ddt, *J* 15.5, 7.2, 1.3, NC$H_A$$H_B$), 3.67 (3 H, s, OC$H_3$), 2.67 (1 H, dd, *J* 16.2, 1.2, COC$H_A$$H_B$), 2.52 (1 H, d, *J* 16.2, COC$H_A$$H_B$), 2.47 (1 H, sept, *J* 6.8, Me_2C*H*), 0.97 (3 H, d, *J* 6.8, (CH_3)CH(CH_3)), 0.84 (3 H, d, *J* 6.8, (CH_3)CH(CH_3)); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 191.2 (*C*=O), 172.9 (*C*O_2Me), 153.4 (N*C*H), 134.0 (CH_2*C*H=CH_2), 119.5 (CH_2CH=*C*H_2), 99.6 (NCH*C*H), 71.7 (quaternary N*C*), 52.4 (CO_2*C*H_3), 51.1 (N*C*H_2), 37.7 (CO*C*H_2), 30.9 (Me_2*C*H), 17.2 ((CH_3)$_2$CH); **MS *m/z*** (ESI^+) 238 (30%, $M+H^+$), 301 (20%, $M+MeCN+Na^+$), 475 (70%, $2M+H^+$), 497 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{13}H_{19}NO_3$ requires $M+H^+$ 238.1438, found 238.1437 (+ 0.41 ppm).

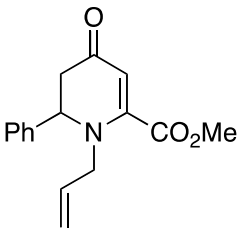
Methyl 1-allyl-2-*tert*-butyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate, 245



Pyridinium salt **240** (0.145 g, 0.406 mmol) was subjected to general procedure A, using *tert*-butylmagnesium chloride (2.0 M solution in ether) as the Grignard reagent and at a temperature of –60 °C. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) gave *dihydropyridone* ***245*** (0.051 g, 0.203 mmol, 50%) as an oil.

R_f 0.68 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1727 (ester C=O), 1651 (C=O), 1593 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.06 (1 H, d, *J* 8.0, NC*H*), 5.95-5.85 (1 H, m, CH_2CH=CH_2), 5.31-5.26 (2 H, m, CH_2CH=CH_2), 5.00 (1 H, d, *J* 8.0, NCHC*H*), 4.16-4.10 (1 H, m, NCH_AH_B), 3.99 (1 H, ddt, *J* 15.5, 5.5, 1.7, NCH_AH_B), 3.74 (3 H, s, OCH_3), 3.08 (1 H, d, *J* 16.6, COCH_AH_B), 2.76 (1 H, d, *J* 16.6, $COCH_AH_B$), 1.16 (9 H, s, C(CH_3)$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.3 (*C*=O), 172.2 (*C*O_2Me), 154.8 (N*C*H), 134.5 (CH_2CH=CH_2), 119.1 (CH_2CH=CH_2), 99.1 (NCH*C*H), 74.9 (quaternary N*C*), 55.9 (NCH_2), 52.4 (CO_2CH_3), 42.4 (COCH_2), 39.6 (quaternary *C*Me_3), 27.8 (C(*C*H_3)$_3$); **MS *m/z*** (ESI^+) 252 (35%, $M+H^+$), 315 (40%, $M+MeCN+Na^+$), 503 (80%, $2M+H^+$), 525 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{14}H_{22}NO_3$ requires $M+H^+$ 252.1594, found 252.1596 (–0.55 ppm).

Methyl 1-allyl-4-oxo-6-phenyl-1,4,5,6-tetrahydropyridine-2-carboxylate, 248

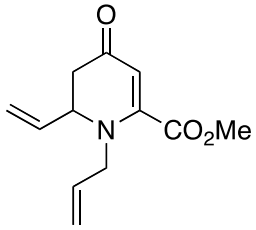


Pyridinium salt **240** (0.110 g, 0.307 mmol) was subjected to general procedure C, using phenylmagnesium bromide (1.0 M solution in THF) as the Grignard reagent. Flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol) gave *dihydropyridone* ***248*** (0.061 g, 0.224 mmol, 73%) as an oil.

R_f 0.77 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1734 (ester C=O), 1650 (C=O), 1559 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.37-7.27 (5 H, m, Ar*H*), 5.79 (1 H, dddd, *J* 17.2, 10.3, 7.0, 5.0, CH_2CH=CH_2), 5.39 (1 H, s, (CO_2Me)CC*H*), 5.20 (1 H, dd, *J* 10.3, 1.3, *cis*-CH=C*H*H), 5.12 (1 H, dd, *J* 17.2, 1.3, *trans*-CH=CH*H*), 4.71 (1 H, t, *J* 6.8, NC*H*), 4.20 (1 H, ddt, *J* 16.3, 5.0, 1.3,

NCH_AH$_B$), 3.87 (3 H, s, OCH_3), 3.58-3.52 (1 H, m, NCH$_A$$H_B$), 2.93 (1 H, dd, *J* 16.6, 6.8, COCH_AH$_B$), 2.71 (1 H, dd, *J* 16.6, 6.8, COCH$_A$$H_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.9 (*C*=O), 164.7 (*C*O_2Me), 153.6 (N*C*CO_2Me), 138.0 (quaternary Ar*C*), 133.1 (CH_2*C*H=CH_2), 129.1, 128.3, 126.7 (5 × Ar*C*), 118.8 (CH_2CH=*C*H_2), 102.1 ((CO_2Me)C*C*H), 61.2 (N*C*H), 53.0 (N*C*H_2), 53.0 (CO_2*C*H_3), 43.2 (CO*C*H_2); **MS *m/z*** (ESI$^+$) 272 (70%, M+H$^+$), 335 (75%, M+MeCN+Na$^+$), 543 (90%, 2M+H$^+$), 565 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{16}H_{17}NNaO_3$ requires *M*+*Na*$^+$ 294.1101, found 294.1107 (–2.05 ppm).

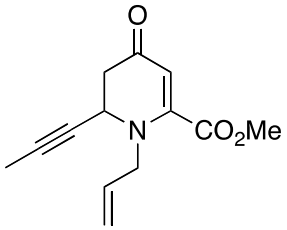
Methyl 1-allyl-4-oxo-6-phenyl-1,4,5,6-tetrahydropyridine-2-carboxylate, 250



Pyridinium salt **240** (0.126 g, 0.352 mmol) was subjected to general procedure C, using vinylmagnesium bromide (0.7 M solution in THF) as the Grignard reagent. Flash column chromatography (SiO_2, 7:3 ethyl acetate-petrol) gave *dihydropyridone* ***250*** (0.070 g, 0.317 mmol, 90%) as an oil.

R_f 0.74 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1734 (ester C=O), 1645 (C=O), 1557 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 5.89-5.78 (2 H, m, CH_2C*H*=CH_2, CHC*H*=CH_2), 5.30 (1 H, s, (CO_2Me)CC*H*), 5.27-5.19 (4 H, m, CH_2CH=CH_2, CHCH=CH_2), 4.16 (1 H, ddt, *J* 16.2, 5.0, 1.6, NCH_AH$_B$), 4.12-4.06 (1 H, m, NC*H*), 3.83 (3 H, s, OCH_3), 3.73 (1 H, ddt, *J* 16.2, 6.9, 1.1, NCH$_A$$H_B$), 2.78 (1 H, dd, *J* 16.4, 6.7, COCH_AH$_B$), 2.42 (1 H, dd, *J* 16.4, 4.5, COCH$_A$$H_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 191.2 (*C*=O), 164.6 (*C*O_2Me), 152.1 (N*C*CO_2Me), 133.5, 132.5 (2 × *C*H=CH_2), 118.5, 118.3 (2 × CH=*C*H_2), 101.2 ((CO_2Me)C*C*H), 60.2 (N*C*H), 53.1 (N*C*H_2), 52.9 (CO_2*C*H_3), 40.6 (CO*C*H_2); **MS *m/z*** (ESI$^+$) 222 (35%, M+H$^+$), 285 (70%, M+MeCN+Na$^+$), 443 (40%, 2M+H$^+$), 465 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{12}H_{16}NO_3$ requires *M*+*H*$^+$ 222.1125, found 222.1125 (–0.04 ppm).

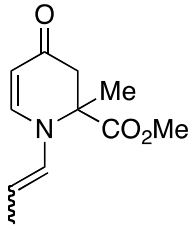
Methyl 1-allyl-4-oxo-6-(prop-1-ynyl)-1,4,5,6-tetrahydropyridine-2-carboxylate, 251



Pyridinium salt **240** (0.101 g, 0.283 mmol) was subjected to general procedure C, using 1-propynylmagnesium bromide (0.5 M solution in THF) as the Grignard reagent. Flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol) gave *dihydropyridone* ***251*** (0.049 g, 0.210 mmol, 75%) as an oil.

R_f 0.79 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 2248 (C≡C), 1735 (ester C=O), 1652 (C=O), 1558 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 5.87 (1 H, dddd, *J* 17.3, 10.1, 7.4, 4.6, CH_2CH=CH_2), 5.42 (1 H, s, $(CO_2Me)CCH$), 5.27-5.21 (2 H, m, CH_2CH=CH_2), 4.37-4.33 (1 H, m, NC*H*), 4.15 (1 H, ddt, *J* 15.9, 4.6, 1.6, NCH_AH_B), 3.92 (1 H, dd, *J* 15.9, 7.4, NCH_AH_B), 3.82 (3 H, s, OCH_3), 2.70 (1 H, dd, *J* 16.2, 6.1, $COCH_AH_B$), 2.52 (1 H, dd, *J* 16.2, 5.0, $COCH_AH_B$), 1.79 (3 H, d, *J* 2.2, CH_3C≡C); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 191.2 (*C*=O), 164.4 (CO_2Me), 151.9 ($NCCO_2Me$), 133.3 (CH_2CH=CH_2), 118.8 (CH_2CH=CH_2), 102.4 ($(CO_2Me)CCH$), 82.1 (*C*≡C), 74.2 (C≡*C*), 53.3 (NCH_2), 52.9 (CO_2CH_3), 49.9 (N*C*H), 41.8 ($COCH_2$), 3.6 (CH_3C≡C); **MS *m/z*** (ESI^+) 234 (55%, $M+H^+$), 297 (70%, $M+MeCN+Na^+$), 467 (95%, $2M+H^+$), 489 (100%, $2M+Na^+$), 722 (20%, $3M+Na^+$); **HRMS** (ESI^+) $C_{13}H_{16}NO_3$ requires $M+H^+$ 234.1125, found 234.1121 (+1.75 ppm).

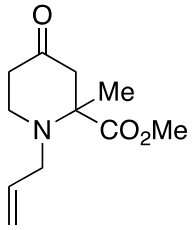
Methyl 2-methyl-4-oxo-1-(prop-1-enyl)-1,2,3,4-tetrahydropyridine-2-carboxylate, 255



Grubbs 2nd generation catalyst (0.020 g, 0.024 mmol) was added to a stirred solution of dihydropyridone **241** (0.050 g, 0.24 mmol) in undistilled, reagent grade methanol (3 mL) and the reaction mixture heated to 60 °C for 16 h. The mixture was allowed to cool to room temperature and concentrated *in vacuo* to give the crude residue. Flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol) yielded *enamine* ***255*** (0.037 g, 0.177 mmol, 74 %) as an oil and as a 4:1 mixture of *trans*-/*cis*- olefin isomers, which were not separated.

R_f 0.66 (ethyl aetate); **IR ν_{max}** (thin film/cm^{-1}) 1739 (ester C=O), 1651 (C=O), 1581 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.18 (0.8 H, d, *J* 7.8, NC*H*), 6.98 (0.2 H, d, *J* 7.8, NC*H*), 6.20-6.14 (1 H, m, NC*H*=CHCH$_3$), 5.38 (1 H, dq, *J* 13.3, 6.7, NCH=C*H*CH$_3$), 5.06 (0.2 H, dd, *J* 7.8, 0.9, NCHC*H*), 5.05 (0.8 H, dd, *J* 7.8, 0.9, NCHC*H*), 3.74 (2.4 H, s, OC*H*$_3$), 3.73 (0.6 H, s, OC*H*$_3$), 2.95 (0.2 H, dd, *J* 16.5, 0.9, COC*H*$_A$H$_B$), 2.91 (0.8 H, dd, *J* 16.5, 0.9, COC*H*$_A$H$_B$), 2.62 (0.2 H, d, *J* 16.5, COCH$_A$*H*$_B$), 2.57 (0.8 H, d, *J* 16.5, COCH$_A$*H*$_B$), 1.74 (0.6 H, dd, *J* 6.7, 1.7, NCH=CHC*H*$_3$), 1.72 (2.4 H, dd, *J* 6.7, 1.7, NCH=CHC*H*$_3$), 1.55 (2.4 H, s, C*H*$_3$), 1.50 (0.6 H, s, C*H*$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.4 (*C*=O), 172.9 (*C*O$_2$Me), 153.2, 150.3 (N*C*H), 130.5, 130.4 (N*C*H=CHCH$_3$), 120.8, 115.1 (NCH=*C*HCH$_3$), 100.8, 100.0 (NCH*C*H), 64.5, 64.4 (quaternary N*C*), 53.1, 53.0 (CO$_2$*C*H$_3$), 46.7, 46.3 (CO*C*H$_2$), 23.3, 22.7 (*C*H$_3$), 15.0, 12.1 (NCH=CH*C*H$_3$); **MS *m/z*** (ESI$^+$) 210 (65%, M+H$^+$), 232 (10%, M+Na$^+$), 273 (55%, M+MeCN+Na$^+$), 419 (65%, 2M+H$^+$), 441 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{11}H_{16}NO_3$ requires *M*+*H*$^+$ 210.1125, found 210.1119 (+2.70 ppm).

Methyl 1-allyl-2-methyl-4-oxopiperidine-2-carboxylate, 271

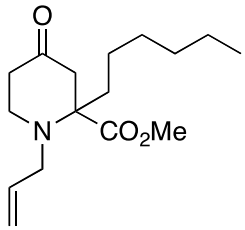


L-Selectride (1.0 M solution in THF, 0.191 mL, 0.191 mmol) was added dropwise to a stirred solution of dihydropyridone **241** (0.040 g, 0.191 mmol) in THF (5 mL) at –78 °C and the resulting mixture was stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of a saturated, aqueous solution of NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (SiO_2, 2:3 ethyl acetate-petrol) furnished *piperidone **271*** (0.028 g, 0.136 mmol, 71 %) as an oil.

R_f 0.79 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1737 (ester C=O), 1727 (C=O), 1642 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 5.82 (1 H, dddd, *J* 17.2, 10.0, 7.5, 4.7, CH$_2$C*H*=CH$_2$), 5.23 (1 H, dd, *J* 17.2, 1.1, *trans*-CH=C*H*H), 5.15 (1 H, dd, *J* 10.0, 1.1, *cis*-CH=CH*H*), 3.71 (3 H, s, OC*H*$_3$), 3.61-3.56 (1 H, m, NC*H*$_A$H$_B$CH=CH$_2$), 3.09 (1 H, ddd, *J* 12.3, 6.6, 3.6, NC*H*$_A$H$_B$CH$_2$), 2.84 (1 H, dd, *J* 14.5, 7.5, NCH$_A$*H*$_B$CH=CH$_2$), 2.67-2.59 (2 H, m, NCH$_A$*H*$_B$CH$_2$, NCH$_2$C*H*$_A$H$_B$), 2.50-2.33 (3 H, m, NCH$_2$CH$_A$*H*$_B$, C(CO$_2$Me)C*H*$_2$), 1.42 (3 H, s, C*H*$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 207.0 (*C*=O), 172.6 (*C*O$_2$Me), 136.2 (*C*H=CH$_2$), 117.2 (CH=*C*H$_2$), 64.9 (quaternary N*C*), 53.2 (*C*H$_2$CH=CH$_2$), 51.7 (CO$_2$*C*H$_3$), 50.7 (NCH$_2$*C*H$_2$), 46.4 (N*C*H$_2$CH$_2$), 40.5 (C(CO$_2$Me)*C*H$_2$), 23.1

(CH_3); **MS *m/z*** (ESI^+) 212 (90%, $M+H^+$), 275 (100%, M+MeCN+Na^+), 423 (10%, $2M+H^+$), 445 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{11}H_{17}NNaO_3$ requires $M+Na^+$ 234.1101, found 234.1099 (+0.88 ppm).

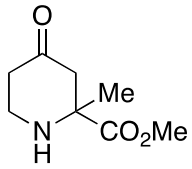
Methyl 1-allyl-2-hexyl-4-oxopiperidine-2-carboxylate, 272



L-Selectride (1.0 M solution in THF, 0.252 mL, 0.252 mmol) was added dropwise to a stirred solution of dihydropyridone **243** (0.074 g, 0.266 mmol) in THF (5 mL) at –78 °C and the resulting mixture was stirred at this temperature for 1 h. The reaction was quenched by dropwise addition of a saturated, aqueous solution of NH_4Cl (5 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Flash column chromatography (SiO_2, 3:7 ethyl acetate-petrol) furnished *piperidone **272*** (0.055 g, 0.196 mmol, 74 %) as an oil.

R_f 0.81 (3:7 ethyl acetate-petrol); **IR ν_{max}** (thin film/cm^{-1}) 1734 (ester C=O), 1642 (C=O); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 5.84-5.75 (1 H, m, CH_2CH=CH_2), 5.22 (1 H, d, *J* 17.1, *trans*-CH=C*H*H), 5.14 (1 H, d, *J* 10.1, *cis*-CH=CH*H*), 3.70-3.64 (1 H, m, NCH_AH_B), 3.69 (3 H, s, OCH_3), 3.21-3.11 (1 H, m, $NCH_AH_BCH_2$), 2.75 (1 H, dd, *J* 14.8, 7.8, NCH_AH_B), 2.59 (1 H, d, *J* 14.9, $C(CO_2Me)CH_AH_B$), 2.49-2.29 (4 H, m, $NCH_AH_BCH_2$, $C(CO_2Me)CH_AH_B$, NCH_2CH_2), 1.87-1.69 (2 H, m, $NC(CO_2Me)CH_2CH_2$), 1.44-1.13 (8 H, m, 4 × CH_2), 0.87 (3 H, t, *J* 6.4, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 207.6 (*C*=O), 172.4 (CO_2Me), 136.2 (CH_2CH=CH_2), 116.9 (CH_2CH=CH_2), 67.8 (quaternary N*C*), 52.3 (NCH_2CH=CH_2), 51.4 (CO_2CH_3), 47.2 ($C(CO_2Me)CH_2$), 46.3 (NCH_2CH_2), 40.3 (NCH_2CH_2), 36.0, 31.6, 29.5, 22.9, 22.5 (5 × CH_2), 14.0 (CH_3); **MS *m/z*** (ESI^+) 282 (35%, $M+H^+$), 340 (85%, M+MeCN+NH_4^+), 563 (100%, $2M+H^+$); **HRMS** (ESI^+) $C_{16}H_{27}NNaO_3$ requires $M+Na^+$ 304.1883, found 304.1181 (+0.70 ppm).

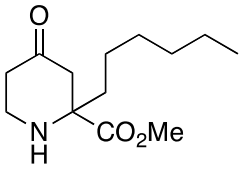
Methyl 2-methyl-4-oxopiperidine-2-carboxylate, 273



Tetrakis(triphenylphosphine)palladium(0) (0.001 g, 0.957 μmol) was added to a stirred solution of piperidone **271** (0.020 g, 0.0957 mmol) and 1,3-dimethylbarbituric acid (0.045 g, 0.287 mmol) in CH_2Cl_2 (1 mL). The reaction flask was wrapped in aluminium foil and the mixture left stirring for 16 h. An aqueous solution of HCl (1 M, 2 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (5 mL). The aqueous phase was then basified using a saturated, aqueous solution of K_2CO_3 (4 mL) and was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to furnish *piperidone **273*** (0.014 g, 0.0819 mmol, 86%) as an oil.

R_f 0.14 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3419 (N-H), 1729 (C=O); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 3.73 (3 H, s, OCH_3), 3.22 (1 H, ddd, *J* 12.3, 6.7, 3.5, NC$H_A$$H_B$), 2.93 (1 H, ddd, *J* 12.3, 10.7, 4.1, NCH$_A$$H_B$) 2.82 (1 H, dd, *J* 14.6, 1.8, C(CO_2Me)C$H_A$$H_B$), 2.50-2.41 (1 H, m, NCH$_2$C$H_A$$H_B$), 2.37-2.30 (2 H, m, NCH$_2$CH$_A$$H_B$, C($CO_2$Me)CH$_A$$H_B$), 1.94 (1 H, br s, N*H*), 1.42 (3 H, s, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 207.0 (*C*=O), 175.3 (*C*O_2Me), 62.0 (quaternary N*C*), 52.4 (CO_2CH_3), 49.7 (C(CO_2Me)*C*H_2), 41.9 (N*C*H_2), 40.8 (NCH$_2$*C*H_2), 26.5 (*C*H_3); **MS *m/z*** (ESI$^+$) 172 (100%, M+H$^+$); **HRMS** (ESI$^+$) $C_8H_{14}NO_3$ requires $M+H^+$ 172.0968, found 172.0968 (+0.05 ppm).

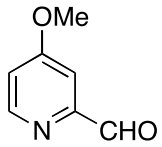
Methyl 2-hexyl-4-oxopiperidine-2-carboxylate, 274



Tetrakis(triphenylphosphine)palladium(0) (0.001 g, 1.06 μmol) was added to a stirred solution of piperidone **272** (0.030 g, 0.106 mmol) and 1,3-dimethylbarbituric acid (0.050 g, 0.319 mmol) in CH_2Cl_2 (1 mL). The reaction flask was wrapped in aluminium foil and the mixture left stirring for 16 h. An aqueous solution of HCl (1 M, 2 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (5 mL). The aqueous phase was then basified using a saturated, aqueous solution of K_2CO_3 (4 mL) and was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to furnish *piperidone **274*** (0.021 g, 0.086 mmol, 81%) as an oil.

R_f 0.31 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3340 (N-H), 1729 (C=O); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 3.73 (3 H, s, OCH_3), 3.18 (1 H, ddd, *J* 12.3, 6.6, 3.6, NHCH_AH$_B$), 2.93 (1 H, ddd, *J* 12.3, 10.3, 4.1, NHCH$_A$$H_B$), 2.83 (1 H, dd, *J* 14.6, 1.8, C(CO_2Me)CH_AH$_B$), 2.50-2.41 (1 H, m, NHCH_2CH_AH$_B$), 2.36-2.30 (1 H, m, NHCH_2CH$_A$$H_B$), 2.34 (1 H, d, *J* 14.6, C(CO_2Me)CH$_A$$H_B$), 2.20 (1 H, br s, N*H*) 1.75-1.63 (2 H, m, C(CO_2Me)CH_2CH_2), 1.30-1.23 (8 H, m, 4 × CH_2), 0.87 (3 H, t, *J* 6.9, CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 207.2 (*C*=O), 175.0 (*C*O_2Me), 65.3 (quaternary N*C*), 52.3 (CO_2*C*H_3), 48.2 (C(CO_2Me)*C*H_2), 41.7 (N*C*H_2), 41.2 (NCH_2*C*H_2), 39.7, 31.5, 29.3, 23.3, 22.5 (5 × *C*H_2), 14.0 (*C*H_3); **MS *m/z*** (ESI^+) 264 (100%, M+Na^+); **HRMS** (ESI^+) $C_{13}H_{23}NNaO_3$ requires $M+Na^+$ 264.1570, found 264.1573 (–1.20 ppm).

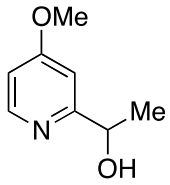
4-Methoxypicolinaldehyde, 290



Diisobutylaluminium hydride (1.0 M solution in hexane, 14.14 mL, 14.1 mmol) was added to a stirred solution of pyridine **201** (2.147 g, 12.9 mmol) in toluene (50 mL) at –78 ºC and the resulting mixture stirred for 2 h. Methanol (10 mL) was added and the solution was allowed to warm to room temperature before saturated, aqueous potassium sodium tartrate solution (25 mL) was added. The aqueous phase was extracted with ethyl acetate (5 × 25 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol) yielding *aldehyde* ***290*** (1.499 g, 10.9 mmol, 85%) as a pale yellow solid.

R_f 0.70 (ethyl acetate); **m.p.** 28-30 °C; **IR ν_{max}** (thin film/cm^{-1}) 1712 (C=O); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 10.00 (1 H, s, C(=O)*H*), 8.56 (1 H, d, *J* 5.7, NC*H*), 7.44 (1 H, d, *J* 2.6, (CHO)CC*H*), 7.00 (1 H, dd, *J* 5.7, 2.6, NCHC*H*), 3.89 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 193.3 (*C*(=O)H), 166.5 (*C*OMe), 154.6 (*C*CHO), 151.2 (N*C*H), 114.5 (CHO)C*C*H), 106.7 (NCH*C*H), 55.6 (O*C*H_3); **MS *m/z*** (FI^+) 137 (100%, M^+); **HRMS** (FI^+) $C_7H_7NO_2$ requires M^+ 137.047, found 137.0482 (+3.8 ppm).

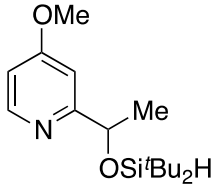
1-(4-Methoxypyridin-2-yl)ethanol, 291



Aldehyde **290** (0.654 g, 4.77 mmol) was subjected to general procedure D, using methylmagnesium bromide (3.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, ethyl acetate) gave *alcohol* ***291*** (0.670 g, 4.38 mmol, 92%) as a colourless solid.

R_f 0.30 (ethyl acetate); **m.p.** 85-87 °C; **IR ν_{max}** (thin film/cm^{-1}) 3172 (O-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.35 (1 H, d, *J* 5.8, NC*H*), 6.80 (1 H, d, *J* 2.3, C(CH(OH))C*H*), 6.73 (1 H, dd, *J* 5.8, 2.3, NCHC*H*), 4.84 (1 H, q, *J* 6.6, C*H*OH), 4.08 (1 H, br s, O*H*), 3.86 (3 H, s, OCH_3), 1.50 (3 H, d, *J* 6.6, CH(OH)CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.4 (*C*OMe), 165.1 (*C*CHOH), 149.3 (N*C*H), 108.8 (NCH*C*H), 105.3 (C(CH(OH))*C*H), 69.0 (*C*HOH), 55.2 (O*C*H_3), 24.2 (CH(OH)*C*H_3); **MS *m/z*** (ESI^+) 154 (30%, $M+H^+$), 176 (40%, $M+Na^+$), 329 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_8H_{11}NO_2$ requires $M+Na^+$ 176.0682, found 176.0676 (+3.4 ppm).

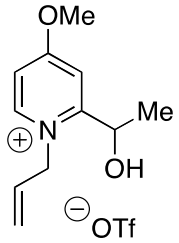
2-(1-((Di-*tert*-butylsilyl)oxy)ethyl)-4-methoxypyridine, 303



Pyridine **291** (0.336 g, 2.20 mmol) was subjected to general procedure F. Flash column chromatography (SiO_2, 3:17 ethyl acetate-petrol) provided *pyridine* ***303*** (0.428 g, 1.45 mmol, 66%) as an oil.

R_f 0.78 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 2099 (Si-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.33 (1 H, d, *J* 5.7, NC*H*), 7.14 (1 H, d, *J* 2.7, C(CHOSi)C*H*), 6.69 (1 H, dd, *J* 5.7, 2.7, NCHC*H*), 5.01 (1 H, q, *J* 6.4, C*H*OSi), 4.14 (1 H, s, Si*H*), 3.86 (3 H, s, OCH_3), 1.50 (3 H, d, *J* 6.4, CH(OSi)CH_3), 1.08 (9 H, s, SiC(CH_3)$_3$), 0.94 (9 H, s, SiC(CH_3)$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 167.3 (*C*OMe), 166.4 (*C*CHOSi), 149.7 (N*C*H), 108.3 (NCH*C*H), 105.1 (C(CHOSi)*C*H), 74.9 (*C*HOSi), 55.0 (O*C*H_3), 27.4, 27.2 (2 × SiC(*C*H_3)$_3$), 24.8 (CH(OSi)*C*H_3), 20.3, 19.6 (2 × Si*C*(CH$_3$)$_3$); **MS *m/z*** (ESI^+) 296 (95%, $M+H^+$), 318 (10%, $M+Na^+$), 613 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{16}H_{29}NO_2Si$ requires $M+H^+$ 296.2040, found 296.2043 (–0.9 ppm).

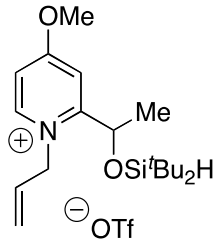
1-Allyl-2-(1-hydroxyethyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 292



Alcohol **291** (0.325 g, 2.12 mmol) was subjected to general procedure E. Flash column chromatography (SiO_2, 1:49 → 3:97 → 1:24 methanol-CH_2Cl_2) provided *pyridinium salt **292*** (0.660 g, 1.92 mmol, 91%) as an oil.

R_f 0.15 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 3405 (O-H); **^{1}H NMR δ_H** (400 MHz, CD_3OD) 8.61 (1 H, d, *J* 7.2, NC*H*), 7.66 (1 H, d, *J* 3.0, C(CH(OH))C*H*), 7.49 (1 H, dd, *J* 7.2, 3.0, NCHC*H*), 6.20-6.10 (1 H, m, CH_2CH=CH_2), 5.45 (1 H, d, *J* 10.4, *cis*- CH=C*H*H), 5.24-5.12 (4 H, m, NCH_2, C*H*OH, *trans*- CH=CH*H*), 4.18 (3 H, s, OCH_3), 1.59 (3 H, d, *J* 6.6, CH(OH)CH_3); **^{13}C NMR δ_C** (100 MHz, CD_3OD) 172.5 (*C*OMe), 163.4 (*C*CHOH), 147.5 (N*C*H), 131.7 (*C*H=CH_2), 119.4 (CH=*C*H_2), 112.5 (NCH*C*H), 110.9 (C(CH(OH))*C*H), 64.8 (*C*HOH), 57.6 (NCH_2), 57.5 (OCH_3), 22.3 (CH(OH)CH_3); **MS *m/z*** (ESI^+) 194 (100%, M^+); **HRMS** (ESI^+) Cation $[C_{11}H_{16}NO_2]^+$ requires M^+ 194.1176, found 194.1176 (–0.1 ppm).

1-Allyl-2-(1-((di-*tert*-butylsilyl)oxy)ethyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 304



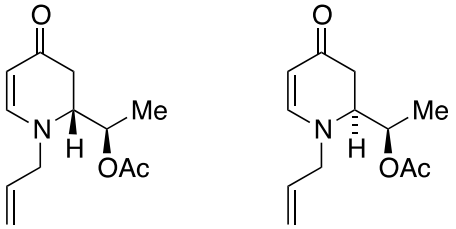
Pyridinium salt **292** (0.450 g, 1.31 mmol) was subjected to general procedure F. Flash column chromatography (SiO_2, 3:97 → 1:24 methanol-CH_2Cl_2) yielded *pyridinium salt **304*** (0.582 g, 1.20 mmol, 92%) as an off-white solid.

R_f 0.35 (2:23 methanol-CH_2Cl_2); **m.p.** 92-94 °C; **IR ν_{max}** (thin film/cm^{-1}) 2090 (Si-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.83-8.81 (1 H, m, NC*H*), 7.52-7.50 (2 H, m, NCHC*H*, C(CH(OSi))C*H*), 6.09-5.99 (1 H, m, C*H*=CH_2), 5.44 (1 H, d, *J* 10.5, *cis*- CH=C*H*H), 5.31-5.25 (1 H, m, NCH_AH_B), 5.21 (1 H, q, *J* 6.3, C*H*OSi), 5.13 (1 H, d, *J* 17.0, *trans*- CH=CH*H*), 5.04 (1 H, dd, *J* 16.5, 5.6, NCH_AH_B), 4.15 (3 H, s, OCH_3), 4.10 (1 H, s, Si*H*), 1.64 (3 H, d, *J* 6.3, CH(OSi)CH_3), 1.08 (9 H, s, SiC(CH_3)$_3$), 0.92 (9 H, s, SiC(CH_3)$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.8 (*C*OMe), 161.6 (*C*CHOSi), 148.9 (N*C*H), 130.4 (*C*H=CH_2), 120.8 (CH=*C*H_2), 112.1 (NCH*C*H), 111.7

(C(CH(OSi))*C*H), 69.5 (C*H*OSi), 57.9 (N*C*H$_2$), 57.8 (O*C*H$_3$), 27.2, 27.1 (2 × C(*C*H$_3$)$_3$), 24.6 (CH(OSi)*C*H$_3$), 20.1, 19.6 (2 × *C*(CH$_3$)$_3$); **MS *m/z*** (ESI$^+$) 336 (100%, M$^+$); **HRMS** (ESI$^+$) Cation $[C_{19}H_{34}NO_2Si]^+$ requires M^+ 336.2353, found 236.2351 (+0.7 ppm).

(*R)-1-((*R**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)ethyl acetate, 305-maj**

(*R)-1-((*S**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)ethyl acetate, 305-min**



310-maj **310-min**

Pyridinium salt **304** (0.079 g, 0.163 mmol) was subjected to general procedure G. Flash column chromatography (SiO_2, 3:1 ethyl acetate-petrol) furnished *dihydropyridones* ***310-maj*** *and* ***310-min*** (0.031 g, 0.139 mmol, 85%) as an oil and as an 8:1 mixture of diastereoisomers with **310-maj** being the major product.

Diastereoisomer ***310-maj***:

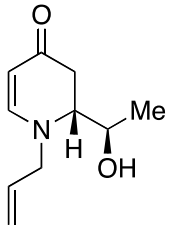
R$_f$ 0.77 (1:1 acetone-ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1738 (ester C=O), 1639 (C=O), 1587 (C=C); **^{1}H NMR δ_H** (400 MHz, CD_3OD) 7.31 (1 H, d, *J* 7.5, NC*H*=CH), 5.96 (1 H, ddt, *J* 16.4, 10.3, 6.1, CH_2CH=CH_2), 5.38-5.26 (3 H, m, C*H*OAc, CH_2CH=CH_2), 4.90 (1 H, d, *J* 7.5, NCH=C*H*), 4.07-4.05 (2 H, m, NCH_2), 3.75 (1 H, t, *J* 7.8, NC*H*CHOAc), 2.91 (1 H, dd, *J* 17.3, 7.8, COCH_AH$_B$), 2.38 (1 H, d, *J* 17.3, COCH$_A$$H_B$), 2.06 (3 H, s, COC$H_3$), 1.25 (3 H, d, *J* 6.5, CH(OAc)CH_3); **^{13}C NMR δ_C** (100 MHz, CD_3OD) 191.6 (*C*=O), 170.8 (O*C*(O)CH$_3$), 155.4 (N*C*H=CH), 133.9 (CH_2*C*H=CH_2), 118.1 (CH_2CH=*C*H$_2$), 96.2 (NCH=*C*H), 69.0 (*C*HOAc), 58.7 (N*C*HCHOAc), 58.1 (N*C*H$_2$), 35.5 (CO*C*H$_2$), 20.1 (CO*C*H$_3$), 15.6 (CH(OAc)*C*H$_3$); **MS *m/z*** (ESI$^+$) 224 (30%, M+H$^+$), 246 (100%, M+Na$^+$), 447 (20%, 2M+H$^+$), 469 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{12}H_{17}NNaO_3$ requires M+Na^+ 246.1101, found 246.1103 (– 0.9 ppm).

Diastereoisomer ***310-min***:

R$_f$ 0.68 (1:1 acetone-ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1738 (ester C=O), 1639 (C=O), 1587 (C=C); **^{1}H NMR δ_H** (400 MHz, CD_3OD) 7.27 (1 H, d, *J* 7.4, NC*H*=CH), 6.00-5.91 (1 H, m, C*H*=CH_2), 5.38-5.28 (CH=CH_2, C*H*OAc), 4.82 (1 H, d, *J* 7.4, NCH=C*H*), 4.04-4.01 (2 H, m, NCH_2), 3.70-3.67 (1 H, m, NC*H*CHOAc), 2.84 (1 H, dd, *J* 17.1, 7.9, COCH_AH$_B$), 2.55 (1 H, d, *J* 17.1, COCH$_A$$H_B$), 2.00 (3 H, s, COC$H_3$), 1.24 (3 H, d, *J* 6.6, CH(OAc)CH_3); **^{13}C NMR δ_C** (100 MHz, CD_3OD) 191.6 (*C*=O), 170.7 (O*C*OCH$_3$), 155.3 (N*C*H=CH), 133.9 (CH_2*C*H=CH_2), 118.1 (CH_2CH=*C*H$_2$), 96.2 (NCH=*C*H), 68.9 (*C*HOAc), 58.7 (N*C*HCHOAc), 58.5 (N*C*H$_2$), 35.5

($CO\mathit{C}H_2$), 20.1 ($CO\mathit{C}H_3$), 15.6 ($CH(OAc)\mathit{C}H_3$); **MS *m/z*** (ESI^+) 224 (30%, $M+H^+$), 246 (100%, $M+Na^+$); **HRMS** (ESI^+) $C_{12}H_{17}NNaO_3$ requires $M+Na^+$ 246.1101, found 246.1102 (–0.5 ppm).

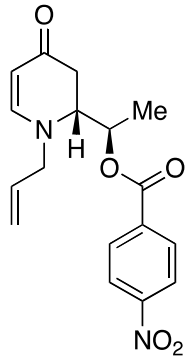
(*R)-1-Allyl-2-((*R**)-1-hydroxyethyl)-2,3-dihydropyridin-4(1H)-one, 309**



Potassium carbonate (0.113 g, 0.815 mmol) was added to a stirred solution of dihydropyridone **310-maj** (0.073 g, 0.326 mmol) in wet, reagent grade methanol (8 mL) and the resulting solution was left to stir at room temperature for 2 h. The reaction mixture was then diluted with ethyl acetate (10 mL) and quenched with water (10 mL). The aqueous phase was extracted with *n*-butanol (5 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:3 acetone-ethyl acetate) gave *alcohol **309*** (0.056 g, 0.311 mmol, 95%) as an oil.

R_f 0.45 (1:1 acetone-ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3356 (O-H), 1625 (C=O), 1582 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.01 (1 H, d, *J* 7.3, $NC\mathit{H}$=CH), 5.90-5.81 (1 H, m, $CH_2C\mathit{H}$=CH_2), 5.30-5.24 (2 H, m, CH_2CH=$C\mathit{H}_2$), 4.85 (1 H, d, *J* 7.3, NCH=C*H*), 4.28-4.21 (1 H, m, C*H*OH), 4.14 (1 H, dd, *J* 15.9, 6.6, $NC\mathit{H}_AH_B$), 3.99-3.94 (1 H, m, $NCH_A\mathit{H}_B$), 3.46 (1 H, br s, O*H*), 3.35 (1 H, t, *J* 7.7, NC*H*CHOH), 2.77 (1 H, dd, *J* 16.9, 7.7, $COC\mathit{H}_AH_B$), 2.32 (1 H, d, *J* 16.9, $COCH_A\mathit{H}_B$), 1.18 (3 H, d, *J* 6.3, $C\mathit{H}_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.4 (*C*=O), 153.0 (N*C*H=CH), 133.8 ($CH_2\mathit{C}H$=CH_2), 118.3 (CH_2CH=$\mathit{C}H_2$), 96.6 (NCH=*C*H), 65.5 (*C*HOH), 62.1 (N*C*HCHOH), 58.9 (NCH_2), 36.7 ($CO\mathit{C}H_2$), 20.2 ($\mathit{C}H_3$); **MS *m/z*** (ESI^+) 204 (40%, $M+Na^+$), 385 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{10}H_{15}NNaO_3$ requires $M+Na^+$ 204.0995, found 204.0993 (+0.8 ppm).

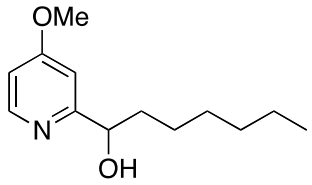
(*R)-1-((*R**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)ethyl 4-nitrobenzoate, 311**



4-Nitrobenzoyl chloride (0.105 g, 0.567 mmol) was added to a stirred solution of dihydropyridone **309** (0.051 g, 0.283 mmol) and 4-dimethylaminopyridine (0.087 g, 0.709 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was stirred at this temperature for 16 h. Brine (5 mL) was added and the aqueous layer was extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) yielded *ester **311*** (0.053 g, 0.159 mmol, 56%) as off-white prisms.

R_f 0.50 (ethyl acetate); **m.p.** 115-117 °C; **IR ν_{max}** (thin film/cm^{-1}) 1724 (ester C=O), 1639 (C=O), 1588 (C=C), 1527 (O-N=O asymm.), 1350 (O-N=O symm.); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.31 (2 H, d, *J* 8.7, Ar*H*), 8.19 (2 H, d, *J* 8.7, Ar*H*), 6.99 (1 H, d, *J* 7.5, NC*H*=CH), 5.85 (1 H, dddd, *J* 16.7, 10.4, 6.5, 5.1, C*H*=CH_2), 5.58 (1 H, qu, *J* 6.5, C*H*OCOAr), 5.35-5.30 (2 H, m, CH=CH_2), 5.00 (1 H, d, *J* 7.5, NCH=C*H*), 3.97 (1 H, dd, *J* 15.7, 6.5, NC$H_A$$H_B$), 3.89 (1 H, dd, *J* 15.7, 5.1, NC$H_A$$H_B$), 3.77 (1 H, t, *J* 8.1, NC*H*CHOCOAr), 2.90 (1 H, dd, *J* 17.2, 8.1, COC$H_A$$H_B$), 2.53 (1 H, d, *J* 17.2, COC$H_A$$H_B$), 1.43 (3 H, d, *J* 6.5, CH(OCOAr)CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 189.5 (*C*=O), 163.8 (CHO*C*OAr), 152.3 (N*C*H=CH), 150.7 (quaternary Ar*C*), 135.1 (quaternary Ar*C*), 133.0 (*C*H=CH_2), 130.7 (2 × Ar*C*H), 123.7 (2 × Ar*C*H), 119.1 (CH=*C*H_2), 98.1 (NCH=*C*H), 71.0 (*C*HOCOAr), 58.6 (N*C*HCHOCOAr), 57.7 (N*C*H_2), 36.1 (CO*C*H_2), 16.3 (*C*H_3); **MS *m/z*** (ESI$^+$) 331 (35%, M+H$^+$), 353 (65%, M+Na$^+$), 661 (20%, 2M+H$^+$), 683 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{17}H_{18}N_2O_5$ requires *M*+*Na*$^+$ 353.1108, found 353.1104 (+1.2 ppm).

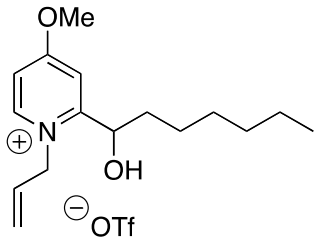
1-(4-Methoxypyridin-2-yl)heptan-1-ol, 316



Aldehyde **290** (0.190 g, 1.38 mmol) was subjected to general procedure D, using hexylmagnesium bromide (2.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol) gave *alcohol **316*** (0.247 g, 1.11 mmol, 80%) as an oil.

R_f 0.44 (1:1 ethyl acetate-petrol); **IR ν_{max}** (thin film/cm^{-1}) 3204 (O-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.34 (1 H, d, *J* 5.6, NC*H*), 6.78 (1 H, d, *J* 1.8, C(CH(OH))C*H*), 6.73 (1 H, dd, *J* 5.6, 1.8, NCHC*H*), 4.68 (1 H, dd, *J* 7.6, 4.5, C*H*OH), 3.95 (1 H, br s, O*H*), 3.86 (3 H, s, OCH_3), 1.84-1.76 (1 H, m, CH(OH)CH_AH$_B$), 1.72-1.63 (1 H, m, CH(OH)CH$_A$$H_B$), 1.45-1.28 (8 H, m, (C$H_2$)$_4CH_3$), 0.89-0.85 (3 H, m, CH$_2CH_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.3 (*C*OMe), 164.4 (*C*CHOH), 149.3 (N*C*H), 108.8 (NCH*C*H), 105.8 (C(CH(OH))*C*H), 73.0 (*C*HOH), 55.2 (O*C*H$_3$), 38.6, 31.8, 29.3, 25.3, 22.6 (5 × *C*H$_2$), 14.1 (CH$_2$*C*H$_3$); **MS *m/z*** (ESI$^+$) 224 (80%, M+H$^+$), 246 (50%, M+Na$^+$), 469 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{13}H_{21}NO_2$ requires *M*+*Na*$^+$ 246.1465, found 246.1462 (+0.87 ppm).

1-Allyl-2-(1-hydroxyheptyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 322

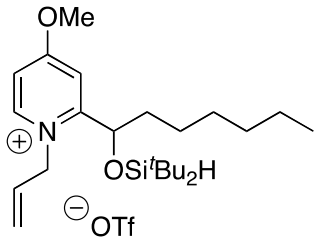


Alcohol **316** (0.398 g, 1.78 mmol) was subjected to general procedure E. Flash column chromatography (SiO_2, 1:49 → 3:97 → 1:24 methanol-CH_2Cl_2) provided *pyridinium salt **322*** (0.649 g, 1.57 mmol, 88%) as an oil.

R_f 0.31 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 3409 (O-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.38 (1 H, d, *J* 7.2, NC*H*), 7.58 (1 H, d, *J* 3.0, C(CHOH)C*H*), 7.24 (1 H, dd, *J* 7.2, 3.0, NCHC*H*), 6.03 (1 H, ddt, *J* 16.5, 11.0, 5.5, CH$_2$C*H*=CH$_2$), 5.47 (1 H, d, *J* 10.3, *cis*-CH=C*H*H), 5.28 (1 H, d, *J* 17.0, *trans*-CH=CH*H*), 5.13 (1 H, dd, *J* 16.0, 6.1, NCH_AH$_B$), 5.07-4.99 (2 H, m, C*H*OH, NCH$_A$$H_B$), 4.11 (3 H, s, OC$H_3$), 1.78-1.55 (3 H, m, O*H*, CH(OH)CH_2), 1.35-1.22 (8 H, m, (CH_2)$_4$CH$_3$), 0.88 (3 H, t, *J* 6.9, CH$_2$CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.4 (*C*OMe), 163.7 (*C*CHOH), 145.9 (N*C*H), 130.3 (*C*H=CH$_2$), 121.8 (CH=*C*H$_2$), 113.0 (NCH*C*H), 111.0

(C(CH(OH))*C*H), 68.8 (*C*HOH), 57.7 (O*C*H$_3$), 57.5 (N*C*H$_2$), 36.7, 31.6, 28.8, 25.7, 22.5 (5 × C*H$_2$*), 12.5 (CH$_2$*C*H$_3$); **MS *m/z*** (ESI$^+$) 264 (100%, M$^+$); **HRMS** (ESI$^+$) Cation $[C_{16}H_{26}NO_2]^+$ requires M^+ 264.1958, found 264.1959 (–0.51 ppm).

1-Allyl-2-(1-((di-*tert*-butylsilyl)oxy)heptyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 328

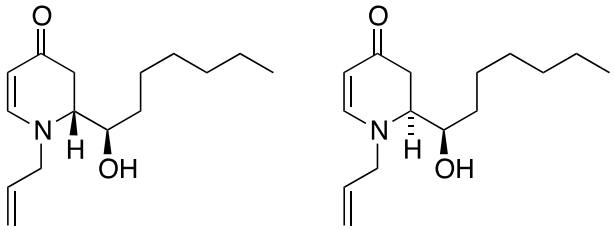


Pyridinium salt **322** (0.598 g, 1.45 mmol) was subjected to general procedure F. Flash column chromatography (SiO_2, 3:97 → 1:24 methanol-CH_2Cl_2) yielded *pyridinium salt **328*** (0.602 g, 1.09 mmol, 75%) as an oil.

R$_f$ 0.53 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 2101 (Si-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.93 (1 H, d, *J* 7.2, NC*H*), 7.58 (1 H, dd, *J* 7.2, 2.9, NCHC*H*), 7.42 (1 H, d, *J* 2.9, C(CHOSi)C*H*), 6.02 (1 H, ddt, *J* 16.2, 10.6, 5.4, C*H*=CH$_2$), 5.47 (1 H, d, *J* 10.6, *cis*-CH=C*H*H), 5.31-5.26 (1 H, m, NCH_AH$_B$), 5.22 (1 H, d, *J* 17.5, *trans*-CH=CH*H*), 5.13 (1 H, t, *J* 5.0, C*H*OSi), 5.03 (1 H, dd, *J* 16.2, 5.4, NCH$_A$*H$_B$*), 4.15 (3 H, s, OC*H$_3$*), 4.11 (1 H, s, Si*H*), 1.95-1.79 (2 H, m, CH(OSi)C*H$_2$*), 1.44-1.27 (8 H, m, (C*H$_2$*)$_4$CH$_3$), 1.09 (9 H, s, SiC(C*H$_3$*)$_3$), 0.90 (9 H, s, SiC(C*H$_3$*)$_3$), 0.88 (3 H, t, *J* 7.0, CH$_2$C*H$_3$*); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.3 (*C*OMe), 159.9 (*C*CHOSi), 149.5 (N*C*H), 130.2 (*C*H=CH$_2$), 121.4 (CH=*C*H$_2$), 112.9 (C(CH(OSi))*C*H), 111.9 (NCH*C*H), 73.1 (*C*HOSi), 58.0 (O*C*H$_3$), 57.8 (N*C*H$_2$), 37.7, 31.5, 28.8 (3 × *C*H$_2$), 27.3, 27.2 (2 × C(*C*H$_3$)$_3$), 24.3, 22.5 (2 × *C*H$_2$), 20.3, 20.0 (2 × *C*(CH$_3$)$_3$), 13.9 (CH$_2$*C*H$_3$); **MS *m/z*** (ESI$^+$) 406 (100%, M$^+$); **HRMS** (ESI$^+$) Cation $[C_{24}H_{44}NO_2Si]^+$ requires M^+ 406.3136, found 406.3139 (–0.82 ppm).

(*R)-1-Allyl-2-((*R**)-1-hydroxyheptyl)-2,3-dihydropyridin-4(1H)-one, 333-maj**

(*S)-1-Allyl-2-((*R**)-1-hydroxyheptyl)-2,3-dihydropyridin-4(1H)-one, 333-min**



333-maj **333-min**

Pyridinium salt **328** (0.136 g, 0.245 mmol) was subjected to general procedure G. Flash column chromatography (SiO_2, 13:7 ethyl acetate-petrol) furnished *dihydropyridones **333-maj** and **333-min*** (0.044 g, 0.176 mmol, 72%) as an oil and as a 12:1 mixture of diastereoisomers with **333-maj** being the major product.

*Diastereoisomer **333-maj***:

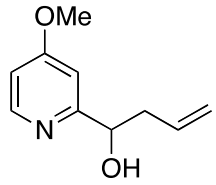
R_f 0.40 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3416 (O-H); **^{1}H NMR δ_H** (400 MHz, CD_3OD) 7.34 (1 H, d, *J* 6.9, NC*H*=CH), 6.01-5.91 (1 H, m, C*H*=CH_2), 5.34 (1 H, d, *J* 17.2, *trans*-CH=C*H*H), 5.30 (1 H, d, *J* 10.2, *cis*-CH=CH*H*), 4.87 (1 H, d, *J* 6.9, NCH=C*H*), 4.17 (1 H, dd, *J* 15.7, 6.7, NC$H_A$$H_B$), 4.09 (1 H, dd, *J* 15.7, 5.0, NC$H_A$$H_B$), 3.99 (1 H, t, *J* 7.9, C*H*OH), 3.49 (1 H, t, *J* 7.8, NC*H*CHOH), 2.84 (1 H, dd, *J* 17.2, 7.8, COC$H_A$$H_B$), 2.38 (1 H, d, *J* 17.2, COC$H_A$$H_B$), 1.56-1.53 (2 H, m, CH(OH)CH_2), 1.37-1.27 (8 H, m, (CH_2)$_4$$CH_3$), 0.93-0.90 (3 H, m, CH_2CH_3); **^{13}C NMR δ_C** (100 MHz, CD_3OD) 191.8 (*C*=O), 155.6 (N*C*H=CH), 134.2 (*C*H=CH_2), 117.8 (CH=*C*H_2), 95.4 (NCH=*C*H), 69.0 (*C*HOH), 61.2 (N*C*HCHOH), 59.0 (N*C*H_2), 35.8 (CO*C*H_2), 32.9, 31.9, 29.3, 25.6, 22.7 (5 × *C*H_2), 13.4 (CH_2*C*H_3); **MS *m/z*** (ESI^+) 252 (75%, M+H^+), 274 (80%, M+Na^+), 503 (40%, 2M+H^+), 525 (100%, 2M+Na^+); **HRMS** (ESI^+) $C_{15}H_{25}NO_2$ requires *M*+Na^+ 274.1778, found 274.1779 (–0.63 ppm).

*Diastereoisomer **333-min***:

R_f 0.36 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3415 (O-H); **^{1}H NMR δ_H** (400 MHz, CD_3OD) 7.35 (1 H, d, *J* 7.4, NC*H*=CH), 5.97 (1 H, dddd, *J* 16.8, 10.2, 6.6, 5.2, C*H*=CH_2), 5.34 (1 H, dd, *J* 17.2, 1.4, *trans*-CH=C*H*H), 5.29 (1 H, dd, *J* 10.1, 1.2, *cis*-CH=CH*H*), 4.87 (1 H, d, *J* 7.4, NCH=C*H*), 4.16 (1 H, dd, *J* 15.8, 6.7, NC$H_A$$H_B$), 4.11-4.04 (1 H, m, NC$H_A$$H_B$), 3.99 (1 H, t, *J* 7.7, C*H*OH), 3.49 (1 H, t, *J* 7.8, NC*H*CHOH), 2.72 (1 H, dd, *J* 17.1, 7.9, COC$H_A$$H_B$), 2.60 (1 H, dd, *J* 17.1, 4.3, COC$H_A$$H_B$), 1.56-1.50 (2 H, m, CH(OH)CH_2), 1.36-1.26 (8 H, m, (CH_2)$_4$$CH_3$), 0.91 (3 H, t, *J* 6.9, CH_2CH_3); **^{13}C NMR δ_C** (100 MHz, CD_3OD) 191.8 (*C*=O), 155.5 (N*C*H=CH), 134.2 (*C*H=CH_2), 117.8 (CH=*C*H_2), 95.4 (NCH=*C*H), 69.0 (*C*HOH), 61.1 (N*C*HCHOH), 59.0 (N*C*H_2), 35.8 (CO*C*H_2), 32.9, 31.9, 29.3, 25.6, 22.7 (5 × *C*H_2), 13.4 (CH_2*C*H_3); **MS *m/z*** (ESI^+)

252 (70%, M+H$^+$), 274 (75%, M+Na$^+$), 503 (35%, 2M+H$^+$), 525 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{15}H_{25}NO_2$ requires *M*+*Na*$^+$ 274.1778, found 274.1779 (–0.62 ppm).

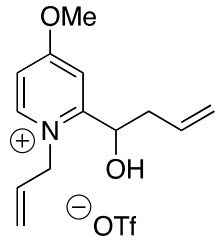
1-(4-Methoxypyridin-2-yl)but-3-en-1-ol, 317-rac



Aldehyde **290** (0.491 g, 3.59 mmol) was subjected to general procedure D, using allylmagnesium bromide (1.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) gave *alcohol **317-rac*** (0.510 g, 2.85 mmol, 79%) as an oil.

R$_f$ 0.34 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3207 (O-H), 1601 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.36 (1 H, d, *J* 5.8, NC*H*), 6.83 (1 H, d, *J* 2.3, C(CHOH)C*H*), 6.74 (1 H, dd, *J* 5.8, 2.3, NCHC*H*), 5.85 (1 H, ddt, *J* 17.4, 10.3, 7.0, C*H*=CH$_2$), 5.15-5.10 (2 H, m, CH=C*H*$_2$), 4.76 (1 H, dd, *J* 7.3, 4.7, C*H*OH), 3.86 (3 H, s, OC*H*$_3$), 3.84 (1 H, br s, O*H*), 2.67-2.60 (1 H, m, CH(OH)C*H*$_A$H$_B$), 2.51-2.44 (1 H, m, CH(OH)CH$_A$*H*$_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.3 (*C*OMe), 163.5 (*C*CHOH), 149.5 (NC*H*), 134.2 (*C*H=CH$_2$), 118.0 (CH=*C*H$_2$), 108.9 (NCH*C*H), 105.9 (C(CH(OH))*C*H), 72.3 (*C*HOH), 55.2 (O*C*H$_3$), 42.9 (CH(OH)*C*H$_2$); **MS *m/z*** (ESI$^+$) 180 (60%, M+H$^+$), 202 (100%, M+Na$^+$); **HRMS** (ESI$^+$) $C_{10}H_{13}NO_2$ requires *M*+*H*$^+$ 180.1019, found 180.1019 (+0.1 ppm).

1-Allyl-2-(1-hydroxybut-3-en-1-yl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 323-rac

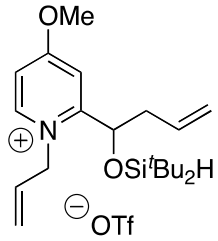


Alcohol **317-rac** (0.462 g, 2.58 mmol) was subjected to general procedure E. Flash column chromatography (SiO_2, 1:49 → 3:97 methanol-CH_2Cl_2) provided *pyridinium salt **323-rac*** (0.789 g, 2.12 mmol, 83%) as an oil.

R$_f$ 0.26 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 3387 (O-H), 1639 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.41 (1 H, d, *J* 7.2, NC*H*), 7.57 (1 H, d, *J* 3.1, C(CHOH)C*H*), 7.26 (1 H, dd, *J* 7.2, 3.1, NCHC*H*), 6.04 (1 H, ddt, *J* 16.8, 10.6, 5.5, NCH$_2$C*H*=CH$_2$), 5.85 (1 H, ddt, *J* 17.2,

10.4, 7.1, CH(OH)CH_2C*H*=CH_2), 5.47 (1 H, d, *J* 10.6, *cis*-NCH_2CH=C*H*H), 5.27 (1 H, d, *J* 16.8, *trans*-NCH_2CH=CH*H*), 5.19-5.01 (5 H, m, C*H*OH, NCH_2, CH(OH)CH_2CH=CH_2), 4.12 (3 H, s, OCH_3), 2.57 (2 H, app t, *J* 6.6, CH(OH)CH_2); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.3 (*C*OMe), 162.3 (*C*CHOH), 146.2 (N*C*H), 132.1 (*C*H=CH_2), 130.3 (*C*H=CH_2), 121.9 (NCH_2CH=*C*H_2), 119.3 (CH(OH)CH_2CH=*C*H_2), 113.0 (NCH*C*H), 111.5 (C(CHOH)*C*H), 68.3 (*C*HOH), 57.8 (O*C*H_3), 57.7 (N*C*H_2), 40.6 (CH(OH)*C*H_2); **MS *m/z*** (ESI$^+$) 220 (100%, M^+); **HRMS** (ESI$^+$) Cation $[C_{13}H_{18}NO_2]^+$ requires M^+ 220.1332, found 220.1331 (+0.7 ppm).

1-Allyl-2-(1-((di-*tert*-butylsilyl)oxy)but-3-en-1-yl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 329-rac

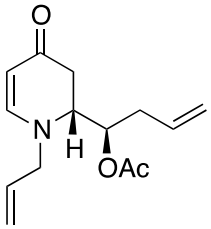


Pyridinium salt **323-rac** (0.214 g, 0.580 mmol) was subjected to general procedure F. Flash column chromatography (SiO_2, 1:49 methanol-CH_2Cl_2) yielded *pyridinium salt* ***329-rac*** (0.233 g, 0.455 mmol, 79%) as an oil.

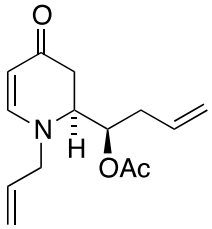
R_f 0.41 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 2103 (Si-H), 1638 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.88 (1 H, d, *J* 7.2, NC*H*), 7.55 (1 H, dd, *J* 7.2, 2.5, NCHC*H*), 7.40 (1 H, d, *J* 2.5, C(CHOSi)C*H*), 6.08-5.98 (1 H, m, NCH_2C*H*=CH_2), 5.80-5.70 (1 H, m, CH(OSi)CH_2C*H*=CH_2), 5.47 (1 H, d, *J* 10.3 *cis*-NCH_2CH=C*H*H), 5.30-5.04 (6 H, m, C*H*OSi, NCH_2, *trans*-NCH_2CH=CH*H*, CH(OSi)CH_2CH=CH_2), 4.15 (3 H, s, OCH_3), 4.12 (1 H, s, Si*H*), 2.79-2.72 (1 H, m, CH(OSi)C$H_A$$H_B$), 2.68-2.61 (1 H, m, CH(OSi)C$H_A$$H_B$), 1.09 (9 H, s, SiC(C$H_3$)$_3$), 0.91 (9 H, s, SiC(C$H_3$)$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.2 (*C*OMe), 159.2 (*C*CHOSi), 149.2 (N*C*H), 130.3 (*C*H=CH_2), 130.1 (*C*H=CH_2), 121.3 (NCH_2CH=*C*H_2), 121.1 (CH(OSi)CH_2CH=*C*H_2), 113.3 (C(CHOSi)*C*H), 112.0 (NCH*C*H), 72.7 (*C*HOSi), 58.1 (O*C*H_3), 58.0 (N*C*H_2), 41.9 (CH(OSi)*C*H_2), 27.3, 27.1 (2 × SiC(*C*H_3)$_3$), 20.2, 20.0 (2 × Si*C*(CH$_3$)$_3$); **MS *m/z*** (ESI$^+$) 362 (100%, M^+); **HRMS** (ESI$^+$) Cation $[C_{21}H_{36}NO_2Si]^+$ requires M^+ 362.2510, found 365.2509 (+0.1 ppm).

(*R)-1-((*R**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)but-3-en-1-yl acetate, 334-maj-rac**

(*R)-1-((*S**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)but-3-en-1-yl acetate, 334-min-rac**



334-maj-rac



334-min-rac

Pyridinium salt **329-rac** (0.194 g, 0.379 mmol) was subjected to general procedure G. Flash column chromatography (SiO_2, 3:2 ethyl acetate-petrol) furnished *dihydropyridones **334-maj-rac** and **334-min-rac*** (0.070 g, 0.281 mmol, 74%) as an oil and as a 12:1 mixture of diastereoisomers with **334-maj-rac** being the major product.

*Diastereoisomer **334-maj-rac***:

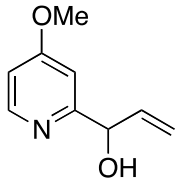
R_f 0.55 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1739 (ester C=O), 1638 (C=O), 1584 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.95 (1 H, dd, *J* 7.6, 1.0, NC*H*=CH), 5.84 (1 H, dddd, *J* 16.9, 10.3, 6.5, 5.0, NCH_2CH=CH_2), 5.69 (1 H, dddd, *J* 16.7, 10.4, 8.1, 5.9, $CH(OAc)CH_2CH$=CH_2), 5.35-5.28 (3 H, m, C*H*OAc, NCH_2CH=CH_2), 5.12-5.07 (2 H, m, $CH(OAc)CH_2CH$=CH_2), 4.95 (1 H, dd, *J* 7.6, 1.0, NCH=C*H*), 3.94 (1 H, ddt, *J* 15.6, 6.3, 1.0, NC$H_A$$H_B$), 3.87 (1 H, ddt, *J* 15.6, 4.8, 1.5, NCH_AH_B), 3.66-3.62 (1 H, m, NC*H*CHOAc), 2.81 (1 H, dd, *J* 16.9, 8.1, COC$H_A$$H_B$), 2.51-2.41 (2 H, m, $COCH_AH_B$, $CH(OAc)CH_AH_B$), 2.32-2.24 (1 H, m, $CH(OAc)CH_AH_B$), 2.05 (3 H, s, COCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 189.6 (*C*=O), 170.1 ($OC(O)CH_3$), 152.3 (N*C*H=CH), 133.2 (NCH_2CH=CH_2), 132.4 ($CH(OAc)CH_2CH$=CH_2), 118.9 (NCH_2CH=CH_2), 118.6 ($CH(OAc)CH_2CH$=CH_2), 97.9 (NCH=*C*H), 71.0 (*C*HOAc), 57.7 (N*C*HCHOAc), 57.5 (NCH_2), 36.0 ($COCH_2$), 34.6 ($CH(OAc)CH_2$), 21.0 ($COCH_3$); **MS *m/z*** (ESI^+) 250 (30%, $M+H^+$), 272 (95%, $M+Na^+$), 521 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{14}H_{19}NO_3$ requires $M+Na^+$ 272.1257, found 272.1257 (+0.2 ppm).

*Diastereoisomer **334-min-rac***:

R_f 0.46 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1739 (ester C=O), 1637 (C=O), 1585 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.89 (1 H, d, *J* 7.7, NC*H*=CH), 5.89-5.78 (1 H, m, NCH_2CH=CH_2), 5.73-5.61 (1 H, m, $CH(OAc)CH_2CH$=CH_2), 5.36-5.27 (3 H, m, C*H*OAc, NCH_2CH=CH_2), 5.14-5.07 (2 H, m, $CH(OAc)CH_2CH$=CH_2), 4.83 (1 H, d, *J* 7.7, NCH=C*H*), 3.93-3.84 (2 H, m, NCH_2), 3.59-3.55 (1 H, m, NC*H*CHOAc), 2.83 (1 H, dd, *J* 16.8, 8.7, COC$H_A$$H_B$), 2.63-2.58 (1 H, m, $COCH_AH_B$), 2.45-2.22 (2 H, m, $CH(OAc)CH_2$), 1.97 (3 H, s, COCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.0 (*C*=O), 170.8 ($OC(O)CH_3$), 153.1 (N*C*H=CH), 132.9 (NCH_2CH=CH_2),

132.4 (CH(OAc)CH_2*C*H=CH_2), 119.3 (NCH_2CH=*C*H_2), 118.9 (CH(OAc)CH_2CH=*C*H_2), 96.5 (NCH=*C*H), 72.5 (*C*HOAc), 57.5 (N*C*HCHOAc), 56.3 (N*C*H_2), 35.0 (CO*C*H_2), 34.9 (CH(OAc)*C*H_2), 21.0 (CO*C*H_3); **MS *m/z*** (ESI$^+$) 250 (35%, M+H$^+$), 272 (90%, M+Na$^+$), 521 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{14}H_{19}NO_3$ requires *M*+*Na*$^+$ 272.1257, found 272.1257 (+0.2 ppm).

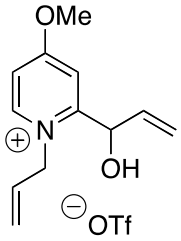
1-(4-Methoxypyridin-2-yl)prop-2-en-1-ol, 318



Aldehyde **290** (0.493 g, 3.60 mmol) was subjected to general procedure D, using vinylmagnesium bromide (1.0 M solution in THF) as the Grignard reagent. Flash column chromatography (SiO_2, 9:1 ethyl acetate-petrol) gave *alcohol **318*** (0.421 g, 2.55 mmol, 71%) as an oil.

R_f 0.29 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3205 (O-H), 1593 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.36 (1 H, d, *J* 5.8, NC*H*), 6.81 (1 H, d, *J* 2.5, C(CHOH)C*H*), 6.75 (1 H, dd, *J* 5.8, 2.5, NCHC*H*), 5.97 (1 H, ddd, *J* 17.0, 10.2, 6.7, C*H*=CH_2), 5.46 (1 H, d, *J* 17.0, *trans*-CH=C*H*H), 5.25 (1 H, d, *J* 10.2, *cis*-CH=CH*H*), 5.13 (1 H, d, *J* 6.7, C*H*OH), 3.86 (3 H, s, OC*H*$_3$), 3.61 (1 H, br s, O*H*); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.5 (*C*OMe), 162.0 (*C*CHOH), 149.2 (N*C*H), 139.4 (*C*H=CH_2), 116.5 (CH=*C*H_2), 109.3 (NCH*C*H), 106.2 (C(CHOH)*C*H), 74.3 (*C*HOH), 55.2 (O*C*H_3); **MS *m/z*** (ESI$^+$) 166 (10%, M+H$^+$), 188 (65%, M+Na$^+$), 353 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_9H_{11}NO_2$ requires *M*+*H*$^+$ 166.0863, found 166.0864 (–1.0 ppm).

1-Allyl-2-(1-hydroxyallyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 324

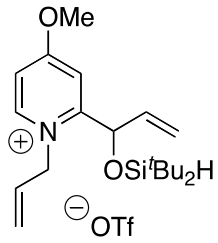


Alcohol **318** (0.401 g, 2.43 mmol) was subjected to general procedure E. Flash column chromatography (SiO_2, 1:49 → 3:97 methanol-CH_2Cl_2) provided *pyridinium salt **324*** (0.625 g, 1.76 mmol, 72%) as an oil.

R_f 0.13 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 3375 (O-H), 1638 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.45 (1 H, d, *J* 7.3, NC*H*), 7.55 (1 H, d, *J* 3.0, C(CHOH)C*H*), 7.30 (1 H, dd,

J 7.3, 3.0, NCHC*H*), 6.06-5.96 (2 H, m, NCH_2CH=CH_2, $CH(OH)CH$=CH_2), 5.61 (1 H, d, *J* 5.0, C*H*OH), 5.46-5.42 (3 H, m, *cis*-NCH_2CH=C*H*H, $CH(OH)CH$=CH_2), 5.30 (1 H, d, *J* 17.2, *trans*-NCH_2CH=CH*H*), 5.15 (1 H, dd, *J* 15.7, 5.8, NCH_AH_B), 5.05 (1 H, dd, *J* 15.7, 5.8, NCH_AH_B), 4.45 (1 H, br s, O*H*), 4.11 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.6 (*C*OMe), 160.0 (*C*CHOH), 146.6 (N*C*H), 134.7 (NCH_2CH=CH_2), 130.2 ($CH(OH)CH$=CH_2), 122.1 (NCH_2CH=CH_2), 119.7 ($CH(OH)CH$=CH_2), 113.1 (NCH*C*H), 112.3 (C(CHOH)*C*H), 69.8 (*C*HOH), 57.9 (OCH_3), 57.7 (NCH_2); **MS *m/z*** (ESI^+) 206 (100%, M^+); **HRMS** (ESI^+) Cation $[C_{12}H_{16}NO_2]^+$ requires M^+ 206.1176, found 206.1176 (–0.2 ppm).

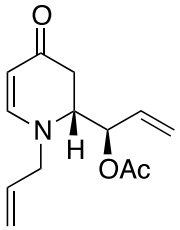
1-Allyl-2-(1-((di-*tert*-butylsilyl)oxy)allyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 330



Pyridinium salt **324** (0.317 g, 0.893 mmol) was subjected to general procedure F. Flash column chromatography (SiO_2, 1:49 → 3:97 methanol-CH_2Cl_2) yielded *pyridinium salt **330*** (0.329 g, 0.662 mmol, 74%) as an oil

R_f 0.31 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 2103 (Si-H), 1637 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 9.24 (1 H, d, *J* 7.1, NC*H*), 7.68 (1 H, dd, *J* 7.1, 2.8, NCHC*H*), 7.54 (1 H, d, *J* 2.8, C(CHOSi)C*H*), 6.09-5.99 (1 H, m, NCH_2CH=CH_2), 5.88 (1 H, ddd, *J* 17.2, 10.4, 6.8, $CH(OSi)CH$=CH_2), 5.51-5.39 (5 H, m, NCH_AH_B, $CH(OSi)CH$=CH_2, NCH_2CH=CH_AH_B), 5.18-5.08 (2 H, m, NCH_AH_B, NCH_2CH=CH_AH_B), 4.17 (3 H, s, OCH_3), 4.10 (1 H, s, Si*H*), 1.04 (9 H, s, $SiC(CH_3)_3$), 0.92 (9 H, s, $SiC(CH_3)_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.7 (*C*OMe), 157.9 (*C*CHOSi), 150.0 (N*C*H), 134.9 (NCH_2CH=CH_2), 130.4 ($CH(OSi)CH$=CH_2), 121.2 (NCH_2CH=CH_2), 120.9 ($CH(OSi)CH$=CH_2), 112.9 (C(CHOSi)*C*H), 112.3 (NCH*C*H), 74.4 (*C*HOSi), 58.2 (OCH_3), 57.8 (NCH_2), 27.2, 27.1 (2 × $SiC(CH_3)_3$), 20.2, 19.8 (2 × $SiC(CH_3)_3$); **MS *m/z*** (ESI^+) 348 (100%, M^+); **HRMS** (ESI^+) Cation $[C_{20}H_{34}NO_2Si]^+$ requires M^+ 348.2353, found 348.2352 (+0.3 ppm).

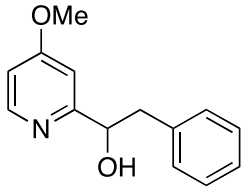
(*R)-1-((*R**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)allyl acetate, 335**



Pyridinium salt **330** (0.596 g, 1.20 mmol) was subjected to general procedure G. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) furnished a 6:1 diastereomeric mixture of *dihydropyridones* (0.210 g, 0.90 mmol, 75%) as an oil with **335** being the major product.

R_f 0.34 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1741 (ester C=O), 1641 (C=O), 1586 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.94 (1 H, d, *J* 7.6, NC*H*=CH), 5.85 (1 H, dddd, *J* 16.9, 10.1, 6.5, 5.0, NCH_2CH=CH_2), 5.73 (1 H, ddd, *J* 17.3, 10.3, 7.0, CH(OAc)C*H*=CH_2), 5.61 (1 H, t, *J* 7.0, C*H*OAc), 5.39-5.29 (4 H, m, NCH_2CH=CH_2, CH(OAc)CH=CH_2), 4.95 (1 H, d, *J* 7.6, NCH=C*H*), 4.03-3.97 (1 H, m, NC$H_A$$H_B$), 3.93-3.87 (1 H, m, NCH_AH_B), 3.65-3.61 (1 H, m, NC*H*CHOAc), 2.75 (1 H, dd, *J* 16.9, 7.8, COC$H_A$$H_B$), 2.43 (1 H, d, *J* 16.9, $COCH_AH_B$), 2.08 (3 H, s, COCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 189.4 (*C*=O), 169.5 (O*C*(O)CH_3), 152.0 (N*C*H=CH), 133.2 (NCH_2CH=CH_2), 131.7 (CH(OAc)*C*H=CH_2), 120.8 (NCH_2CH=CH_2), 118.9 (CH(OAc)CH=CH_2), 98.4 (NCH=*C*H), 72.9 (*C*HOAc), 58.1 (N*C*HCHOAc), 57.9 (NCH_2), 36.1 ($COCH_2$), 21.1 ($COCH_3$); **MS *m/z*** (ESI^+) 236 (40%, $M+H^+$), 258 (60%, $M+Na^+$), 493 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{13}H_{17}NO_3$ requires $M+Na^+$ 258.1101, found 258.1101 (+0.1 ppm).

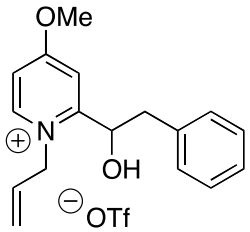
1-(4-Methoxypyridin-2-yl)-2-phenylethanol, 319



Magnesium turnings (0.248 g, 10.22 mmol) were added to a stirred solution of benzyl bromide (0.972 mL, 8.18 mmol) in THF (15 mL) at 0 ºC. 1,2-Dibromoethane (2 drops) was then added and the resulting suspension was stirred at 0 ºC for 90 mins. The entirety of the resulting solution was taken up in a syringe and added to a stirred solution of aldehyde **290** (0.560 g, 4.09 mmol) in THF (15 mL) at –30 ºC . The resulting solution was left stirring at this temperature for 4 h before saturated aqueous NH_4Cl (10 mL) and water (5 mL) were added. The aqueous phase was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol) gave *alcohol **319*** (0.702 g, 3.07 mmol, 75%) as a white solid.

R_f 0.56 (ethyl acetate); **m.p.** 103-105 °C; **IR ν_{max}** (thin film/cm^{-1}) 3266 (O-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.35 (1 H, d, *J* 5.8, NC*H*), 7.31-7.18 (5 H, m, Ar*H*), 6.73 (1 H, dd, *J* 5.8, 2.4, NCHC*H*), 6.61 (1 H, d, *J* 2.4, C(CHOH)C*H*), 4.92 (1 H, dd, *J* 7.5, 5.5, C*H*OH), 3.90 (1 H, br s, O*H*), 3.78 (3 H, s, OCH_3), 3.10 (1 H, dd, *J* 13.6, 5.5, PhCH_AH$_B$), 3.04 (1 H, dd, *J* 13.6, 7.5, PhCH$_A$$H_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.1 (*C*OMe), 163.2 (*C*CHOH), 149.3 (N*C*H), 137.8 (quaternary Ar*C*), 129.6, 128.4, 126.5 (5 × Ar*C*H), 109.3 (NCH*C*H), 106.1 (C(CHOH)*C*H), 74.2 (*C*HOH), 55.2 (O*C*H$_3$), 45.1 (Ph*C*H$_2$); **MS *m/z*** (ESI$^+$) 230 (70%, M+H$^+$), 252 (100%, M+Na$^+$), 481 (95%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{14}H_{15}NO_2$ requires $M+H^+$ 230.1176, found 230.1175 (+0.2 ppm).

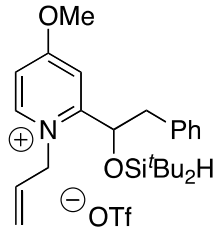
1-Allyl-2-(1-hydroxy-2-phenylethyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 325



Alcohol **319** (0.454 g, 1.98 mmol) was subjected to general procedure E. Flash column chromatography (SiO_2, 1:49 → 3:97 methanol-CH_2Cl_2) provided *pyridinium salt* ***325*** (0.666 g, 1.59 mmol, 80%) as an oil.

R_f 0.21 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 3386 (O-H), 1638 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.27 (1 H, d, *J* 7.1, NC*H*), 7.45 (1 H, d, *J* 3.1, C(CHOH)C*H*), 7.28-7.21 (3 H, m, Ar*H*), 7.18 (1 H, dd, *J* 7.1, 3.1, NCHC*H*), 7.11-7.09 (2 H, m, Ar*H*), 5.85 (1 H, ddt, *J* 16.8, 10.4, 5.8, C*H*=CH$_2$), 5.40 (1 H, d, *J* 10.4, *cis*-CH=C*H*H), 5.33 (1 H, t, *J* 6.0, C*H*OH), 5.18 (1 H, d, *J* 16.8, *trans*-CH=CH*H*), 4.83-4.81 (2 H, m, NCH_2), 3.99 (3 H, s, OCH_3), 3.95 (1 H, br s, O*H*), 3.17 (1 H, dd, *J* 13.9, 7.0, PhCH_AH$_B$), 3.07 (1 H, dd, *J* 13.9, 6.0, PhCH$_A$$H_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.1 (*C*OMe), 162.3 (*C*CHOH), 145.6 (N*C*H), 135.5 (quaternary Ar*C*), 129.9, 129.5, 128.7 (5 × Ar*C*H), 127.3 (*C*H=CH$_2$), 122.2 (CH=*C*H$_2$), 113.2 (NCH*C*H), 111.6 (C(CHOH)*C*H), 69.5 (*C*HOH), 57.7 (O*C*H$_3$), 57.6 (N*C*H$_2$), 43.0 (Ph*C*H$_2$); **MS *m/z*** (ESI$^+$) 270 (100%, M$^+$); **HRMS** (ESI$^+$) Cation $[C_{17}H_{20}NO_2]^+$ requires M^+ 270.1489, found 270.1489 (–0.1 ppm).

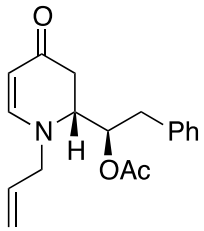
1-Allyl-2-(1-((di-*tert*-butylsilyl)oxy)-2-phenylethyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 331



Pyridinium salt **325** (0.535 g, 1.28 mmol) was subjected to general procedure F. Flash column chromatography (SiO_2, 1:49 methanol-CH_2Cl_2) yielded *pyridinium salt* ***331*** (0.523 g, 0.932 mmol, 73%) as an off-white solid.

R_f 0.34 (2:23 methanol-CH_2Cl_2); **m.p.** 71-73 °C; **IR ν_{max}** (thin film/cm^{-1}) 2101 (Si-H), 1635 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.79 (1 H, d, *J* 7.1, NC*H*), 7.54 (1 H, dd, *J* NCHC*H*), 7.29-7.26 (3 H, m, Ar*H*), 7.17 (1 H, d, *J* 3.0, C(CHOSi)C*H*), 7.00-6.97 (2 H, m, Ar*H*), 5.94-5.84 (1 H, m, C*H*=CH_2), 5.43 (1 H, d, *J* 10.6, *cis*-CH=C*H*H), 5.35 (1 H, t, *J* 6.6, C*H*OH), 5.14 (1 H, d, *J* 17.2, *trans*-CH=CH*H*), 4.94-4.89 (1 H, m, NC$H_A$$H_B$), 4.68-4.63 (1 H, m, NC$H_A$$H_B$), 4.03 (4 H, s, OC$H_3$, Si*H*), 3.28 (1 H, dd, *J* 13.8, 5.3, PhC$H_A$$H_B$), 3.18 (1 H, dd, *J* 13.8, 6.9, PhC$H_A$$H_B$), 1.04 (9 H, s, SiC(C$H_3$)$_3$), 0.91 (9 H, s, SiC(C$H_3$)$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.0 (*C*OMe), 159.5 (*C*CHOH), 148.6 (N*C*H), 133.8 (quaternary Ar*C*), 130.0, 129.7, 129.0 (5 × Ar*C*H), 127.9 (C*H*=CH_2), 121.6 (CH=*C*H_2), 113.3 (C(CHOH)*C*H), 112.7 (NCH*C*H), 73.9 (*C*HOSi), 57.9 (O*C*H_3), 57.9 (N*C*H_2), 45.0 (Ph*C*H_2), 27.3, 27.2 (2 × SiC(*C*H_3)$_3$), 20.2, 20.0 (2 × Si*C*$(CH_3)_3$); **MS *m/z*** (ESI$^+$) 412 (100%, M^+); **HRMS** (ESI$^+$) Cation $[C_{25}H_{38}NO_2Si]^+$ requires M^+ 412.2666, found 412.2666 (+0.1 ppm).

(*R)-1-((*R**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)-2-phenylethyl acetate, 336**

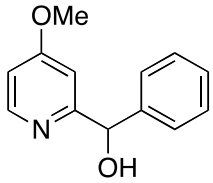


Pyridinium salt **331** (0.347 g, 0.619 mmol) was subjected to general procedure G. Flash column chromatography (SiO_2, 7:3 ethyl acetate-petrol) furnished an 8:1 diastereomeric mixture of *dihydropyridones* (0.134 g, 0.448 mmol, 72%) as an oil with **336** being the major product.

R_f 0.42 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1739 (ester C=O), 1638 (C=O), 1584 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.27-7.12 (5 H, m, Ar*H*), 6.96 (1 H, d, *J* 7.4, NC*H*=CH), 5.87-5.78 (1 H, m, C*H*=CH_2), 5.46-5.42 (1 H, m, C*H*OAc), 5.31-5.26 (2 H, m, CH=CH_2), 4.96 (1 H, d, *J*

7.4, NCH=C*H*), 3.98-3.84 (2 H, m, NCH_2), 3.67 (1 H, t, *J* 7.0, NC*H*CHOAc), 3.03 (1 H, d, *J* 14.4, PhCH_AH$_B$), 2.87-2.73 (2 H, m, PhCH$_A$$H_B$, COC$H_AH_B$), 2.56 (1 H, d, *J* 17.2, COCH$_A$$H_B$), 1.91 (3 H, s, COC$H_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 189.6 (*C*=O), 169.8 (O*C*(O)CH_3), 152.4 (N*C*H=CH), 136.5 (quaternary Ar*C*), 133.1 (*C*H=CH_2), 129.2, 128.4, 126.7 (5 × Ar*C*H), 119.1 (CH=*C*H_2), 97.9 (NCH=*C*H), 72.4 (*C*HOAc), 57.5 (NC*H*CHOAc), 57.5 (N*C*H_2), 36.1 (CO*C*H_2), 36.0 (Ph*C*H_2), 14.2 (CO*C*H_3); **MS *m/z*** (ESI$^+$) 300 (15%, M+H$^+$), 322 (75%, M+Na$^+$), 621 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{18}H_{21}NO_3$ requires *M*+*Na*$^+$ 322.1414, found 322.1406 (+2.5 ppm).

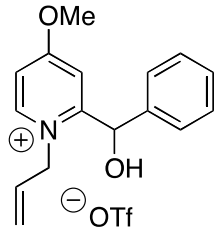
(4-Methoxypyridin-2-yl)(phenyl)methanol, 320



Aldehyde **290** (0.550 g, 4.01 mmol) was subjected to general procedure D, using phenylmagnesium bromide (1.0 M solution in THF) as the Grignard reagent. Flash column chromatography (SiO_2, 3:2 ethyl acetate-petrol) gave *alcohol **320*** (0.844 g, 3.92 mmol, 98%) as an oil.

R_f 0.58 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3170 (O-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.38 (1 H, d, *J* 5.7, NC*H*), 7.40-7.26 (5 H, m, Ar*H*), 6.73 (1 H, dd, *J* 5.7, 2.5, NCHC*H*), 6.67 (1 H, d, *J* 2.5, C(CHOH)C*H*), 5.71 (1 H, s, C*H*OH), 4.35 (1 H, br s, O*H*), 3.78 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.4 (*C*OMe), 162.9 (*C*CHOH), 148.9 (N*C*H), 143.1 (quaternary Ar*C*), 128.6, 127.8, 127.0 (5 × Ar*C*H), 109.2 (NCH*C*H), 106.8 (C(CHOH)*C*H), 75.0 (*C*HOH), 55.2 (O*C*H_3); **MS *m/z*** (ESI$^+$) 216 (45%, M+H$^+$), 238 (95%, M+Na$^+$), 453 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{13}H_{13}NO_2$ requires *M*+*H*$^+$ 216.1019, found 216.1019 (+0.0 ppm).

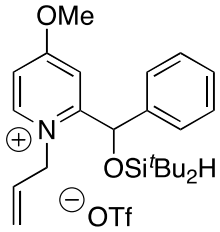
1-Allyl-2-(hydroxy(phenyl)methyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 326



Alcohol **320** (0.773 g, 3.59 mmol) was subjected to general procedure E. Flash column chromatography (SiO_2, 1:49 → 3:97 → 1:24 methanol-CH_2Cl_2) provided *pyridinium salt* ***326*** (1.047 g, 2.59 mmol, 80%) as an oil.

R_f 0.11 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 3357 (O-H), 1638 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.38 (1 H, d, *J* 7.1, NC*H*), 7.64 (1 H, d, *J* 3.0, C(CHOH)C*H*), 7.39-7.24 (6 H, m, Ar*H*, NCHC*H*), 6.19 (1 H, s, C*H*OH), 5.60 (1 H, ddt, *J* 16.6, 10.3, 5.9, C*H*=CH_2), 5.27 (1 H, d, *J* 10.3, *cis*-CH=C*H*H), 5.15 (1 H, d, *J* 16.6, *trans*-CH-CH*H*), 4.90-4.80 (2 H, m, NCH_2), 4.23 (1 H, br s, O*H*), 4.09 (3 H, s, OCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.5 (*C*OMe), 160.4 (*C*CHOH), 146.9 (N*C*H), 137.7 (quaternary Ar*C*), 129.6, 129.3, 129.2 (5 × ArC*H*), 127.2 (*C*H=CH_2), 122.3 (CH=*C*H_2), 113.0 (NCH*C*H), 113.0 (C(CHOH)*C*H), 71.5 (*C*HOH), 57.9 (O*C*H_3), 57.6 (N*C*H_2); **MS *m/z*** (ESI^+) 256 (100%, M^+); **HRMS** (ESI^+) Cation $[C_{16}H_{18}NO_2]^+$ requires M^+ 256.1332, found 256.1335 (–1.0 ppm).

1-Allyl-2-(((di-*tert*-butylsilyl)oxy)(phenyl)methyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 332

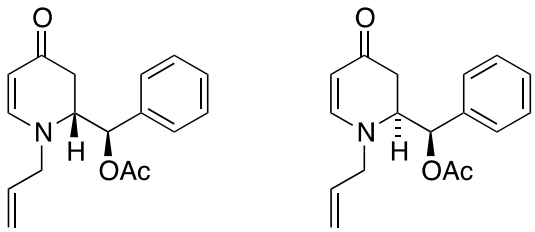


Pyridinium salt **326** (0.808 g, 1.99 mmol) was subjected to general procedure F. Flash column chromatography (SiO_2, 1:49 methanol-CH_2Cl_2) yielded *pyridinium salt* ***332*** (0.752 g, 1.37 mmol, 69%) as an oil.

R_f 0.24 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 2110 (Si-H), 1636 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.98 (1 H, d, *J* 7.1, NC*H*), 7.87 (1 H, d, *J* 3.0, C(CHOSi)C*H*), 7.64 (1 H, dd, *J* 7.1, 3.0, NCHC*H*), 7.44-7.37 (3 H, m, Ar*H*), 7.23-7.21 (2 H, m, Ar*H*), 6.04 (1 H, s, C*H*OSi), 5.67-5.58 (1 H, m, C*H*=CH_2), 5.32 (1 H, *J* 11.0, *cis*-CH=C*H*H), 5.07 (1 H, d, *J* 17.1, *trans*-CH=CH*H*), 5.03-4.98 (1 H, m, NC$H_A$$H_B$), 4.85 (1 H, dd, *J* 16.4, 6.2, NCH$_A$$H_B$), 4.21 (3 H,

s, OC*H*$_3$), 4.09 (1 H, s, Si*H*), 0.97 (9 H, s, SiC(C*H*$_3$)$_3$), 0.79 (9 H, s, SiC(C*H*$_3$)$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.8 (*C*OMe), 158.5 (*C*CHOSi), 149.9 (N*C*H), 136.7 (quaternary Ar*C*), 130.1, 129.7, 129.6 (5 × Ar*C*H), 128.0 (*C*H=CH$_2$), 121.1 (CH=*C*H$_2$), 113.0 (C(CHOSi)*C*H), 112.0 (NCH*C*H), 75.7 (*C*HOSi), 58.2 (O*C*H$_3$), 57.6 (N*C*H$_2$), 27.0, 26.8 (2 × SiC(*C*H$_3$)$_3$), 20.4, 19.5 (2 × Si*C*(CH$_3$)$_3$); **MS *m/z*** (ESI$^+$) 398 (100%, M$^+$); **HRMS** (ESI$^+$) Cation $[C_{24}H_{36}NO_2Si]^+$ requires M^+ 398.2510, found 398.2510 (–0.1 ppm).

(*R)-((*R**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)(phenyl)methyl acetate, 337-maj**
(*R)-((*S**)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)(phenyl)methyl acetate, 337-min**



337-maj **337-min**

Pyridinium salt **332** (0.464 g, 0.848 mmol) was subjected to general procedure G. Flash column chromatography (SiO_2, 13:7 ethyl acetate-petrol) furnished *dihydropyridones **337-maj** and **337-min*** (0.169 g, 0.593 mmol, 70%) as an oil and as a 1.5:1 mixture of diastereoisomers with **337-maj** being the major product. Further flash column chromatography (SiO_2, 13:7 ethyl acetate-petrol) provided *dihydropyridone **337-maj*** (0.099 g, 0.347 mmol) as a pale yellow solid and *dihydropyridone **337-min*** (0.067 g, 0.237 mmol) as a pale yellow oil.

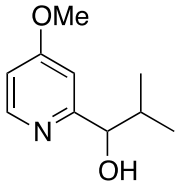
*Diastereoisomer **337-maj***:

R$_f$ 0.38 (ethyl acetate); **m.p.** 120-122 °C; **IR ν_{max}** (thin film/cm^{-1}) 1742 (ester C=O), 1638 (C=O), 1583 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.37-7.27 (5 H, m, Ar*H*), 6.97 (1 H, d, *J* 7.5, NC*H*=CH), 6.13 (1 H, d, *J* 9.1, C*H*OAc), 5.87 (1 H, dddd, *J* 17.0, 10.4, 6.6, 4.9, C*H*=CH$_2$), 5.34-5.28 (2 H, m, CH=C*H*$_2$), 4.99 (1 H, d, *J* 7.5, NCH=C*H*), 4.02 (1 H, m, NC*H*$_A$H$_B$), 3.94 (1 H, dd, *J* 15.9, 4.9, NCH$_A$*H*$_B$), 3.83-3.78 (1 H, m, NC*H*CHOAc), 2.64 (1 H, dd, *J* 17.0, 7.5, COC*H*$_A$H$_B$), 2.07 (3 H, s, COC*H*$_3$), 1.97 (1 H, d, *J* 17.0, COCH$_A$*H*$_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 189.3 (*C*=O), 169.4 (O*C*(O)CH$_3$), 151.7 (N*C*H=CH), 136.6 (quaternary Ar*C*), 133.5 (*C*H=CH$_2$), 128.8, 128.8, 127.2 (5 × Ar*C*H), 118.6 (CH=*C*H$_2$), 98.6 (NCH=*C*H), 74.1 (*C*HOAc), 59.8 (N*C*HCHOAc), 58.6 (N*C*H$_2$), 36.7 (CO*C*H$_2$), 21.2 (CO*C*H$_3$); **MS *m/z*** (ESI$^+$) 286 (70%, M+H$^+$), 308 (80%, M+Na$^+$), 593 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{17}H_{19}NO_3$ requires $M+Na^+$ 308.1257, found 308.1254 (+1.1 ppm).

*Diastereoisomer **337-min***:

R_f 0.33 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1745 (ester C=O), 1639 (C=O), 1590 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.42-7.27 (5 H, m, Ar*H*), 6.92 (1 H, d, *J* 7.6, NC*H*=CH), 6.21 (1 H, d, *J* 5.3, C*H*OAc), 5.77 (1 H, dddd, *J* 17.1, 10.1, 7.0, 4.8, C*H*=CH_2), 5.30-5.18 (2 H, m, CH=CH_2), 4.94 (1 H, d, *J* 7.6, NCH=C*H*), 3.74-3.70 (1 H, m, NC$H_A$$H_B$), 3.54-3.42 (2 H, m, NCH$_A$$H_B$, NC*H*CHOAc), 2.70 (1 H, dd, *J* 16.9, 7.8, COC$H_A$$H_B$), 2.62-2.57 (1 H, m, COCH$_A$$H_B$), 2.09 (3 H, s, COC$H_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.0 (*C*=O), 169.9 (O*C*(O)CH_3), 152.5 (N*C*H=CH), 137.1 (quaternary Ar*C*), 133.0 (*C*H=CH_2), 129.1, 128.7, 126.4 (5 × Ar*C*H), 119.2 (CH=*C*H_2), 97.6 (NCH=*C*H), 72.9 (*C*HOAc), 60.2 (N*C*HCHOAc), 57.0 (N*C*H_2), 35.4 (CO*C*H_2), 21.1 (CO*C*H_3); **MS *m/z*** (ESI^+) 286 (25%, $M+H^+$), 308 (50%, $M+Na^+$), 593 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{17}H_{19}NO_3$ requires $M+Na^+$ 308.1257, found 308.1255 (+0.7 ppm).

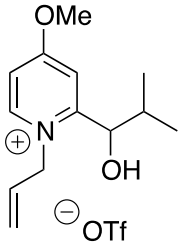
1-(4-Methoxypyridin-2-yl)-2-methylpropan-1-ol, 321



Aldehyde **290** (0.562 g, 4.10 mmol) was subjected to general procedure D, using isopropylmagnesium chloride (2.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, 3:1 ethyl acetate-petrol) gave *alcohol **321*** (0.483 g, 2.67 mmol, 65%) as an oil.

R_f 0.41 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3207 (O-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.36 (1 H, d, *J* 6.6, NC*H*), 6.75-6.74 (2 H, m, NCHC*H*, C(CHOH)C*H*), 4.50 (1 H, d, *J* 4.3, C*H*OH), 4.18 (1 H, br s, O*H*), 3.87 (3 H, s, OCH_3), 2.07-1.99 (1 H, m, C*H*$(CH_3)_2$), 1.02 (3 H, d, *J* 6.9, CHCH_3), 0.81 (3 H, d, *J* 6.9, CHCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.1 (*C*OMe), 163.2 (*C*CHOH), 149.1 (N*C*H), 108.8 (NCH*C*H), 106.5 (C(CHOH)*C*H), 77.3 (*C*HOH), 55.2 (O*C*H_3), 35.1 (*C*H$(CH_3)_2$), 19.5, 16.0 (2 × CH*C*H_3); **MS *m/z*** (ESI^+) 182 (40%, $M+H^+$), 204 (45%, $M+Na^+$), 385 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{10}H_{15}NO_2$ requires $M+Na^+$ 204.0995, found 204.0996 (–0.6 ppm).

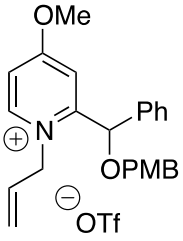
1-Allyl-2-(1-hydroxy-2-methylpropyl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 327



Alcohol **321** (0.462 g, 2.55 mmol) was subjected to general procedure E. Flash column chromatography (SiO_2, 1:49 → 3:97 methanol-CH_2Cl_2) provided *pyridinium salt **327*** (0.773 g, 2.08 mmol, 81%) as an oil.

R_f 0.23 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.39 (1 H, d, *J* 7.4, NC*H*), 7.52-7.51 (1 H, m, C(CHOH)C*H*), 7.28-7.25 (1 H, m, NCHC*H*), 6.09-6.00 (1 H, m, C*H*=CH_2), 5.48 (1 H, d, *J* 10.3, *cis*-CH=C*H*H), 5.30 (1 H, d, *J* 17.1, *trans*-CH=CH*H*), 5.10-5.08 (2 H, m, NCH_2), 4.87 (1 H, d, *J* 5.8, C*H*OH), 4.12 (3 H, s, OCH_3), 3.20 (1 H, br s, O*H*), 2.06-1.97 (1 H, m, C*H*$(CH_3)_2$), 1.01-0.98 (6 H, m, CH(CH_3)$_2$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.0 (*C*OMe), 158.7 (*C*CHOH), 146.1 (N*C*H), 130.4 (C*H*=CH_2), 122.0 (CH=*C*H_2), 112.9 (NCH*C*H), 112.2 (C(CHOH)*C*H), 73.7 (*C*HOH), 57.8 (O*C*H_3), 57.5 (N*C*H_2), 33.1 (*C*H$(CH_3)_2$), 19.7, 16.6 (2 × CH*C*H_3); **MS *m/z*** (ESI$^+$) 222 (100%, M^+); **HRMS** (ESI$^+$) Cation $[C_{13}H_{20}NO_2]^+$ requires M^+ 222.1489, found 222.1490 (–0.77 ppm).

1-Allyl-4-methoxy-2-(((4-methoxybenzyl)oxy)(phenyl)methyl)pyridin-1-ium trifluoromethanesulfonate, 340

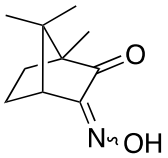


4-Methoxybenzyl trichloroacetimidate (0.104 mL, 0.502 mmol) was added to a stirred solution of pyridinium salt **326** (0.102 g, 0.251 mmol) and (±)-10-camphorsulfonic acid (0.006 g, 0.025 mmol) in CH_2Cl_2 and the resulting solution was left to stir at rt for 16 h. The solvent was removed *in vacuo* and the residue was purified by flask column chromatography (SiO_2, 1:49 → 3:97 methanol-CH_2Cl_2) to give *pyridinium salt **340*** (0.092 g, 0.176 mmol, 70%) as an oil.

R_f 0.19 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 1640 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.71 (1 H, d, *J* 7.3, NC*H*), 7.49-7.44 (3 H, m, NCHC*H*, 2 × Ar*H*), 7.40 (1 H, d, *J* 3.1, C(CHOPMB)C*H*), 7.30-7.27 (3 H, m, 3 × Ar*H*), 7.23 (2 H, d, *J* 8.7, 2 × PMB-Ar*H*), 6.90 (2 H,

d, *J* 8.7, 2 × PMB-Ar*H*), 5.81 (1 H, s, C*H*OPMB), 5.63-5.54 (1 H, m, C*H*=CH_2), 5.26 (1 H, d, *J* 10.4, *cis*-CH=C*H*H), 5.07 (1 H, d, *J* 17.1, *trans*-CH=CH*H*), 4.90-4.89 (2 H, m, NCH_2), 4.61 (1 H, d, *J* 11.5, OC$H_A$$H_B$), 4.52 (1 H, d, *J* 11.5, OC$H_A$$H_B$), 4.09 (3 H, s, OC$H_3$), 3.82 (3 H, s, PMB-OC$H_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.5 (*C*OMe), 159.9 (*C*CHOPMB), 156.9 (quaternary Ar*C*), 149.0 (N*C*H), 143.0 (quaternary Ar*C*), 134.9 (quaternary Ar*C*), 130.3 (*C*H=CH_2), 129.9, 129.8, 129.7, 128.0 (Ar*C*H), 121.8 (CH=*C*H_2), 114.2 (NCH*C*H), 114.2 (Ar*C*H), 112.0 (C(CHOPMB)*C*H), 76.7 (*C*HOPMB), 71.4 (O*C*H_2), 58.0 (O*C*H_3), 57.8 (N*C*H_2), 55.3 (PMB-O*C*H_3); **MS *m/z*** (ESI$^+$) 376 (100%, M^+); **HRMS** (ESI$^+$) Cation $[C_{24}H_{26}NO_3]^+$ requires M^+ 376.1907, found 376.1893 (+3.8 ppm).

(1*S*,4*R*)-3-(Hydroxyimino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, 344[156]

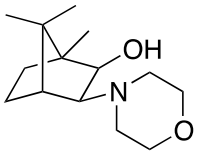


Hydroxylamine hydrochloride (0.548 g, 7.89 mmol) was added to a stirred solution of (1*S*)-(+)-camphorquinone **343** (1.009 g, 6.07 mmol) in ethanol (25 mL) and pyridine (4 mL) and the resulting solution was stirred at rt for 30 mins. The ethanol was removed *in vacuo* and the resulting solution was diluted with a 1:1 mixture of hexane and ethyl acetate (30 mL). This solution was washed successively with 1 M HCl (30 mL), water (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting solid was taken up in heptane (7 mL) and heated to reflux for 2 mins and then cooled to rt. The mixture was filtered and the filter cake was dried under high vacuum to yield *oxime **344*** (0.747 g, 4.13 mmol, 68%) as an off-white solid and as a mixture of *cis*- and *trans*- oxime isomers.

m.p. 147-149 °C (lit. 148-151 °C)[156]; **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 9.06 (1 H, br s, O*H*), 3.28 (1 H, d, *J* 4.4, C*H*C(NOH)), 2.17-2.01 (1 H, m, C(NOH)CHC$H_A$$H_B$), 1.88-1.75 (1 H, m, C(NOH)CHCH_2C$H_A$$H_B$), 1.64-1.53 (2 H, m, C(NOH)CHC$H_A$$H_BCH_A$$H_B$), 1.04 (3 H, s, C$H_3$), 1.01 (3 H, s, C$H_3$), 0.89 (3 H, s, C$H_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 204.3 (*C*=O), 159.8 (*C*=NOH), 58.5 (*C*(Me)C=O), 46.6 (*C*HC=NOH), 44.9 (*C*Me_2), 30.7 (C(NOH)CHCH_2CH_2), 23.8 (C(NOH)CH*C*H_2), 20.7 (*C*H_3), 17.6 (*C*H_3), 8.9 (*C*H_3).

All data were in agreement with those previously reported.[156]

(1*S*,2*R*,3*S*,4*R*)-1,7,7-Trimethyl-3-morpholinobicyclo[2.2.1]heptan-2-ol, 346[139]



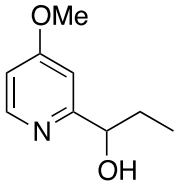
Lithium aluminium hydride (0.431 g, 11.36 mmol) was suspended in ether (25 mL) in a dry two-necked round-bottom flask, fitted with a reflux condenser and a pressure-equalised dropping funnel charged with a solution of oxime **344** (0.686 g, 3.79 mmol) in ether (15 mL). The reaction mixture was cooled to 0 °C and the solution of **344** was then added dropwise over a period of 20 mins. The reaction mixture was heated to reflux for 90 mins and then re-cooled to 0 °C. Saturated aqueous Na_2SO_4 (10 mL) was added with care and the white, granular precipitate was removed by filtration through a pad of celite. The filter cake was washed with chloroform (3 × 15 mL) and the combined filtrate and washings were dried over Na_2SO_4, filtered and concentrated to furnish 0.559 g of crude amino alcohol **345** which was used without further purification.

Bis-(2-bromoethyl) ether (0.925 mL, 3.83 mmol) was added to a stirred solution of crude amino alcohol **345** (0.540 g, 3.19 mmol) and triethylamine (1.34 mL, 9.57 mmol) in DMSO (4 mL) and the resulting solution was stirred at rt for 72 h. The reaction mixture was then diluted with ether (10 mL) and the organic layer was washed with 1 M HCl (3 × 10 mL). The aqueous layer was then basified with 1 M NaOH (40 mL) and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:3 → 3:7 ether-petrol) yielded a white solid, which was recrystalised from hexane to give *(+)-MIB **346*** (0.4351 g, 1.82 mmol, 57%) as a white crystalline solid.

m.p. 63-65 °C (lit. 65-67 °C)[139]; **^{1}H NMR δ_H** (400 MHz, C_6D_6) 4.06 (1 H, br s, O*H*), 3.56 (1 H, d, *J* 7.2, C*H*OH), 3.49 (4 H, br s, O(CH_2)$_2$), 2.40 (2 H, br s, NCH_2), 2.21 (2 H, br s, NCH_2), 2.18 (2 H, d, *J* 7.2, C*H*N(CH$_2$)$_2$), 1.77 (1 H, d, *J* 4.8, C*H*CHN(CH$_2$)$_2$), 1.62 (1 H, tt, *J* 12.0, 4.8, CH_AH$_B$CHCHN), 1.43 (1 H, td, *J* 12.4, 3.8, CH_AH$_B$CH$_2$CHCHN), 1.26 (3 H, s, CH_3), 1.15 (3 H, s, CH_3), 1.01-0.95 (1 H, m, CH$_A$$H_B$CHCHN), 0.87-0.80 (1 H, m, CH$_A$$H_BCH_2$CHCHN), 0.80 (3 H, s, C$H_3$); **^{13}C NMR δ_C** (100 MHz, C_6D_6) 78.9 (*C*HOH), 73.3 (*C*HN(CH$_2$)$_2$), 66.8 (O(*C*H$_2$)$_2$), 49.5 (*C*(Me)CCOH), 46.6 (*C*Me$_2$), 45.2 (*C*HCHN(CH$_2$)$_2$), 32.5 (*C*H$_2$CHCHN), 27.9 (*C*H$_2$CH$_2$CHCHN), 22.1 (*C*H$_3$), 21.0 (*C*H$_3$), 11.9 (*C*H$_3$). One ^{13}C resonance (N(*C*H$_2$)$_2$) is too broad to observe at rt.[139]

All data were in agreement with those previously reported.[139]

1-(4-Methoxypyridin-2-yl)propan-1-ol, 347



Method 1:

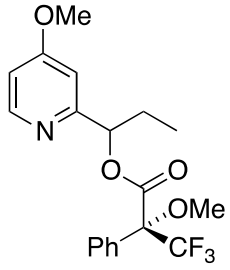
Aldehyde **290** (0.157 g, 1.15 mmol) was subjected to general procedure D, using ethylmagnesium bromide (3.0 M solution in ether) as the Grignard reagent. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) gave *alcohol **347*** (0.109 g, 0.652 mmol, 57%) as an oil.

Method 2:

Diethyl zinc (1.0 M solution in hexane, 1.60 mL, 1.60 mmol) was added to a stirred solution of aldehyde **290** (0.110 g, 0.801 mmol) and (+)-MIB **346** (0.004 g, 0.016 mmol) in toluene (5 mL) at 0 °C and the resulting solution was stirred at this temperature for 3 h. A saturated solution of $NaHCO_3$ (10 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) provided *alcohol **347*** (0.099 g, 0.592 mmol, 75%) as an oil.

R_f 0.31 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3205 (O-H); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.35 (1 H, d, *J* 5.8, NC*H*), 6.78 (1 H, d, *J* 2.5, C(CHOH)C*H*), 6.74 (1 H, dd, *J* 5.8, 2.5, NCHC*H*), 4.64 (1 H, dd, *J* 7.1, 4.6, C*H*OH), 3.91 (1 H, br s, O*H*), 3.86 (3 H, s, OCH_3), 1.93-1.83 (1 H, m, $CH_3CH_AH_B$), 1.77-1.66 (1 H, m, $CH_3CH_AH_B$), 0.96 (3 H, t, *J* 7.5 (CH_2CH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.2 (*C*OMe), 164.0 (*C*CHOH), 149.3 (N*C*H), 108.8 (NCH*C*H), 105.8 (C(CHOH)*C*H), 73.9 (*C*HOH), 55.2 (O*C*H_3), 31.3 (CH_2CH_3), 9.4 (CH_2CH_3); **MS *m/z*** (ESI^+) 168 (40%, $M+H^+$), 190 (60%, $M+Na^+$), 357 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_9H_{13}NO_2$ requires $M+Na^+$ 190.0838, found 190.0838 (+0.1 ppm).

(2*R*)-1-(4-Methoxypyridin-2-yl)propyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 348



Experiment 1:

(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (0.053 g, 0.227 mmol) was added to a stirred solution of alcohol **347** [prepared by method 1, above] (0.025 g, 0.151 mmol), *N,N'*-dicyclohexylcarbodiimide (0.047 g, 0.227 mmol) and 4-(dimethylamino)pyridine (0.009 g, 0.076 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was allowed to stir for 16 h. Water (5 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 3:7 ethyl acetate-petrol) provided *ester **348*** (0.051 g, 0.132 mmol, 87%) as an oil.

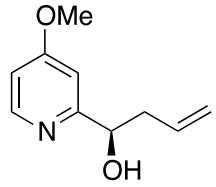
Experiment 2:

(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (0.066 g, 0.282 mmol) was added to a stirred solution of alcohol **347** [prepared by method 2, above] (0.027 g, 0.161 mmol), *N,N'*-dicyclohexylcarbodiimide (0.058 g, 0.282 mmol) and 4-(dimethylamino)pyridine (0.010 g, 0.081 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was allowed to stir for 16 h. Water (5 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:3 ethyl acetate-petrol) provided *ester **348*** (0.053 g, 0.138 mmol, 86%) as an oil.

R_f 0.81 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1746 (C=O); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.42 (0.5 H, d, *J* 5.7, NC*H*), 8.37 (0.5 H, d, *J* 5.7, NC*H*), 7.57-7.50 (2 H, m, Ar*H*), 7.43-7.36 (3 H, m, Ar*H*), 6.84 (0.5 H, d, *J* 2.2, C(CHOMTPA)C*H*), 6.75 (0.5 H, dd, *J* 5.7, 2.2, NCHC*H*), 6.72 (0.5 H, dd, *J* 5.7, 2.2, NCHC*H*), 6.63 (0.5 H, d, *J* 2.2, C(CHOMTPA)C*H*), 5.98-5.94 (1 H, m, C*H*OMTPA), 3.81 (1.5 H, s, OC*H*$_3$), 3.71 (1.5 H, s, OC*H*$_3$), 3.60 (3 H, s, OC*H*$_3$), 3.55 (3 H, s, OC*H*$_3$), 2.09-1.99 (2 H, m, C*H*$_2$CH$_3$), 0.96 (1.5 H, t, *J* 7.4, CH$_2$C*H*$_3$), 0.87 (1.5 H, t, *J* 7.4, CH$_2$C*H*$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.3 (O*C*(O)CPh), 165.9, 165.8 (*C*OMe), 160.3, 160.0 (*C*CHOMTPA), 150.5, 150.3 (N*C*H), 132.1, 132.1 (quaternary Ar*C*), 129.6, 128.4, 127.6, 127.4 (5 × Ar*C*H), 123.4 (q, $J_{C\text{-}F}$ 288, *C*F$_3$), 109.4, 109.2 (NCH*C*H), 107.0, 105.9 (C(CHOMTPA)*C*H), 80.2, 80.2 (*C*HOMTPA), 55.6, 55.4 (O*C*H$_3$), 55.1, 55.0 (O*C*H$_3$), 28.0, 27.8 (*C*H$_2$CH$_3$), 9.5, 9.2 (CH$_2$*C*H$_3$); **^{19}F NMR δ_F** (377 MHz, $CDCl_3$) –71.2, –71.4 (C*F*$_3$) [ratio 1:1,

347 was racemic]; **MS *m/z*** (ESI^+) 384 (75%, $M+H^+$), 406 (75%, $M+Na^+$), 789 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{19}H_{20}F_3NO_4$ requires $M+Na^+$ 406.1237, found 406.1239 (–0.5 ppm).

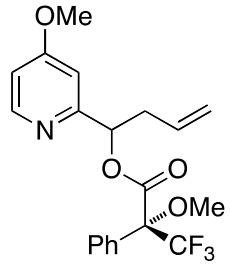
(*R*)-1-(4-Methoxypyridin-2-yl)but-3-en-1-ol, 317



(+)-Ipc_2B(allyl)borane solution (1.0 M in pentane, 1.82 mL, 1.82 mmol) was added dropwise to a stirred solution of aldehyde **290** (0.250 g, 1.82 mmol) in ether at –78 ºC and the resulting mixture was stirred at this temperature for 3 h. The reaction mixture was concentrated *in vacuo* and the residue taken up in methanol. 8-Hydroxyquinoline (0.264 g, 1.82 mmol) was added and the resulting solution was heated to 70 ºC for 18 h. A further portion of 8-hydroxyquinoline (0.264 g, 1.82 mmol) was added and the mixture was left stirring at 70 ºC for a further 20 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 3:2 ethyl acetate-petrol) to yield *alcohol **317*** (0.292 g, 1.63 mmol, 89%) as an oil.

R_f 0.34 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3207 (O-H), 1601 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.36 (1 H, d, *J* 5.8, NC*H*), 6.83 (1 H, d, *J* 2.3, C(CHOH)C*H*), 6.74 (1 H, dd, *J* 5.8, 2.3, NCHC*H*), 5.85 (1 H, ddt, *J* 17.4, 10.3, 7.0, C*H*=CH_2), 5.15-5.10 (2 H, m, CH=CH_2), 4.76 (1 H, dd, *J* 7.3, 4.7, C*H*OH), 3.86 (3 H, s, OCH_3), 3.84 (1 H, br s, O*H*), 2.67-2.60 (1 H, m, CH(OH)C$H_A$$H_B$), 2.51-2.44 (1 H, m, CH(OH)C$H_A$$H_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.3 (*C*OMe), 163.5 (*C*CHOH), 149.5 (N*C*H), 134.2 (*C*H=CH_2), 118.0 (CH=*C*H_2), 108.9 (NCH*C*H), 105.9 (C(CH(OH))*C*H), 72.3 (*C*HOH), 55.2 (O*C*H_3), 42.9 (CH(OH)*C*H_2); **MS *m/z*** (ESI^+) 180 (60%, $M+H^+$), 202 (100%, $M+Na^+$); **HRMS** (ESI^+) $C_{10}H_{13}NO_2$ requires $M+H^+$ 180.1019, found 180.1018 (+0.5 ppm); $[\alpha]_D^{25}$ +76.2 (*c* 1.0, $CHCl_3$).

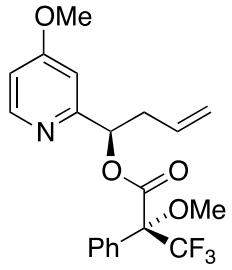
(2*R*)-1-(4-Methoxypyridin-2-yl)but-3-en-1-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 349-rac



(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (0.057 g, 0.243 mmol) was added to a stirred solution of alcohol **317-rac** (0.025 g, 0.139 mmol), *N,N'*-dicyclohexylcarbodiimide (0.050 g, 0.243 mmol) and 4-(dimethylamino)pyridine (0.008 g, 0.070 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was allowed to stir for 16 h. Water (5 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:4 ethyl acetate-petrol) provided *ester **349-rac*** (0.049 g, 0.124 mmol, 89%) as an oil.

R_f 0.72 (1:1 ethyl acetate-petrol); **IR ν_{max}** (thin film/cm^{-1}) 1745 (C=O), 1602 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.43 (0.5 H, d, *J* 5.7, NC*H*), 8.37 (0.5 H, d, *J* 5.7, NC*H*), 7.56-7.52 (2 H, m, Ar*H*), 7.43-7.36 (3 H, m, Ar*H*), 6.86 (0.5 H, d, *J* 2.2, C(CHOMTPA)C*H*), 6.76 (0.5 H, dd, *J* 5.7, 2.2, NCHC*H*), 6.72 (0.5 H, dd, *J* 5.7, 2.2, NCHC*H*), 6.63 (0.5 H, d, *J* 2.2, C(CHOMTPA)C*H*), 6.13-6.07 (1 H, m, C*H*OMTPA), 5.79 (0.5 H, ddt, *J* 17.1, 10.1, 7.0, C*H*=CH_2), 5.67 (0.5 H, ddt, *J* 17.1, 10.1, 7.0, C*H*=CH_2), 5.15-5.01 (2 H, m, CH=CH_2), 3.81 (1.5 H, s, OCH_3), 3.71 (1.5 H, s, OCH_3), 3.60 (1.5 H, s, OCH_3), 3.53 (1.5 H, s, OCH_3), 2.87-2.72 (2 H, m, CH_2CH=CH_2); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.4 (O*C*(O)CPh), 165.8, 165.7 (*C*OMe), 159.8, 159.5 (*C*CHOMTPA), 150.5, 150.2 (NCH), 132.7, 132.3 (*C*H=CH_2), 132.0 (quaternary Ar*C*), 129.6, 128.3, 127.6, (5 × Ar*C*H), 123.3 (q, $J_{C\text{-}F}$ 287, *C*F_3), 118.8, 118.7 (CH=*C*H_2), 109.5, 109.3 (NCH*C*H), 107.1, 106.0 (C(CHOMTPA)*C*H), 84.5 (CO*C*(Ph)(OMe)(CF_3)), 78.1, 78.0 (*C*HOMTPA), 55.7, 55.5, 55.1, 55.0 (2 × O*C*H_3), 39.2, 39.0 (*C*H_2CH=CH_2); **^{19}F NMR δ_F** (377 MHz, $CDCl_3$) –71.2, –71.4 (C*F*$_3$) [ratio 1:1]; **MS *m/z*** (ESI^+) 396 (45%, $M+H^+$), 418 (80%, $M+Na^+$), 813 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{20}H_{20}F_3NO_4$ requires $M+Na^+$ 418.1237, found 418.1235 (+0.5 ppm).

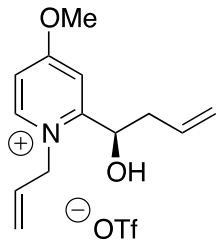
(*R*)-(*R*)-1-(4-Methoxypyridin-2-yl)but-3-en-1-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 349



(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (0.070 g, 0.300 mmol) was added to a stirred solution of alcohol **317** (0.031 g, 0.172 mmol), *N,N'*-dicyclohexylcarbodiimide (0.062 g, 0.300 mmol) and 4-(dimethylamino)pyridine (0.010 g, 0.086 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was allowed to stir for 16 h. Water (5 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:4 ethyl acetate-petrol) provided *ester **349*** (0.061 g, 0.154 mmol, 90%) as an oil.

R_f 0.72 (1:1 ethyl acetate-petrol); **IR ν_{max}** (thin film/cm^{-1}) 1745 (C=O), 1602 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.43 (1 H, d, *J* 5.7, NC*H*), 7.56-7.54 (2 H, m, Ar*H*), 7.41-7.36 (3 H, m, Ar*H*), 6.86 (1 H, d, *J* 2.2, C(CHOMTPA)C*H*), 6.76 (1 H, dd, *J* 5.7, 2.2, NCHC*H*), 6.09 (1 H, dd, *J* 7.3, 5.3, C*H*OMTPA), 5.67 (1 H, ddt, *J* 17.1, 10.1, 7.0, C*H*=CH_2), 5.06-5.01 (2 H, m, CH=CH_2), 3.81 (3 H, s, OCH_3), 3.53 (3 H, s, OCH_3), 2.83-2.72 (2 H, m, CH_2CH=CH_2); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 166.4 (O*C*(O)CPh), 165.8 (*C*OMe), 159.5 (*C*CHOMTPA), 150.5 (N*C*H), 132.3 (*C*H=CH_2), 132.0 (quaternary Ar*C*), 129.6, 128.3, 127.6 (5 × Ar*C*H), 123.3 (q, J_{C-F} 287, *C*F_3), 118.8 (CH=*C*H_2), 109.3 (NCH*C*H), 107.1 (C(CHOMTPA)*C*H), 84.5 (CO*C*(Ph)(OMe)(CF_3)), 78.0 (*C*HOMTPA), 55.5, 55.1 (2 × O*C*H_3), 39.0 (*C*H_2CH=CH_2); **^{19}F NMR δ_F** (377 MHz, $CDCl_3$) –71.2, –71.4 (C*F*$_3$) [ratio 1:25, ee of **317** is 92%]; **MS *m/z*** (ESI^+) 396 (45%, M+H^+), 418 (80%, M+Na^+), 813 (100%, 2M+Na^+); **HRMS** (ESI^+) $C_{20}H_{20}F_3NO_4$ requires *M*+Na^+ 418.1237, found 418.1236 (+0.3 ppm).

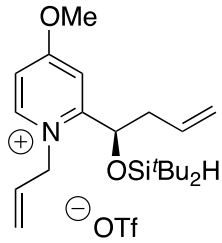
(*R*)-1-Allyl-2-(1-hydroxybut-3-en-1-yl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 323



Alcohol **317** (0.290 g, 1.62 mmol) was subjected to general procedure E. Flash column chromatography (SiO_2, 1:49 → 3:97 methanol-CH_2Cl_2) provided *pyridinium salt* ***323*** (0.428 g, 1.16 mmol, 72%) as an oil.

R_f 0.26 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 3387 (O-H), 1639 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.41 (1 H, d, *J* 7.2, NC*H*), 7.57 (1 H, d, *J* 3.1, C(CHOH)C*H*), 7.26 (1 H, dd, *J* 7.2, 3.1, NCHC*H*), 6.04 (1 H, ddt, *J* 16.8, 10.6, 5.5, NCH_2CH=CH_2), 5.85 (1 H, ddt, *J* 17.2, 10.4, 7.1, $CH(OH)CH_2CH$=CH_2), 5.47 (1 H, d, *J* 10.6, *cis*-NCH_2CH=C*H*H), 5.27 (1 H, d, *J* 16.8, *trans*-NCH_2CH=CH*H*), 5.19-5.01 (5 H, m, C*H*OH, NCH_2, $CH(OH)CH_2CH$=CH_2), 4.12 (3 H, s, OCH_3), 2.57 (2 H, app t, *J* 6.6, $CH(OH)CH_2$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.3 (*C*OMe), 162.3 (*C*CHOH), 146.2 (N*C*H), 132.1 (*C*H=CH_2), 130.3 (*C*H=CH_2), 121.9 (NCH_2CH=*C*H_2), 119.3 ($CH(OH)CH_2CH$=*C*H_2), 113.0 (NCH*C*H), 111.5 (C(CHOH)*C*H), 68.3 (*C*HOH), 57.8 (OCH_3), 57.7 (NCH_2), 40.6 ($CH(OH)CH_2$); **MS *m/z*** (ESI^+) 220 (100%, M^+); **HRMS** (ESI^+) Cation $[C_{13}H_{18}NO_2]^+$ requires M^+ 220.1332, found 220.1332 (+0.2 ppm); $[\alpha]_D^{21}$ +26.2 (*c* 1.0, $CHCl_3$).

(*R*)-1-Allyl-2-(1-((di-*tert*-butylsilyl)oxy)but-3-en-1-yl)-4-methoxypyridin-1-ium trifluoromethanesulfonate, 329

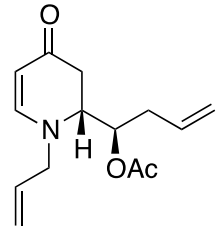


Pyridinium salt **323** (0.214 g, 0.580 mmol) was subjected to general procedure F. Flash column chromatography (SiO_2, 1:49 methanol-CH_2Cl_2) yielded *pyridinium salt* ***329*** (0.393 g, 0.770 mmol, 70%) as an oil.

R_f 0.41 (2:23 methanol-CH_2Cl_2); **IR ν_{max}** (thin film/cm^{-1}) 2103 (Si-H), 1638 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 8.88 (1 H, d, *J* 7.2, NC*H*), 7.55 (1 H, dd, *J* 7.2, 2.5, NCHC*H*), 7.40 (1 H, d, *J* 2.5, C(CHOSi)C*H*), 6.08-5.98 (1 H, m, NCH_2CH=CH_2), 5.80-5.70 (1 H, m,

CH(OSi)CH_2C*H*=CH_2), 5.47 (1 H, d, *J* 10.3 *cis*-NCH_2CH=C*H*H), 5.30-5.04 (6 H, m, C*H*OSi, NCH_2, *trans*-NCH_2CH=CH*H*, CH(OSi)CH_2CH=CH_2), 4.15 (3 H, s, OCH_3), 4.12 (1 H, s, Si*H*), 2.79-2.72 (1 H, m, CH(OSi)C$H_A$$H_B$), 2.68-2.61 (1 H, m, CH(OSi)$CH_A$$H_B$), 1.09 (9 H, s, SiC(C$H_3$)$_3$), 0.91 (9 H, s, SiC(C$H_3$)$_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 171.2 (*C*OMe), 159.2 (*C*CHOSi), 149.2 (N*C*H), 130.3 (*C*H=CH_2), 130.1 (*C*H=CH_2), 121.3 (NCH_2CH=*C*H_2), 121.1 (CH(OSi)CH_2CH=*C*H_2), 113.3 (C(CHOSi)*C*H), 112.0 (NCH*C*H), 72.7 (*C*HOSi), 58.1 (OCH_3), 58.0 (NCH_2), 41.9 (CH(OSi)*C*H_2), 27.3, 27.1 (2 × SiC(*C*H_3)$_3$), 20.2, 20.0 (2 × Si*C*$(CH_3)_3$); **MS *m/z*** (ESI^+) 362 (100%, M^+); **HRMS** (ESI^+) Cation $[C_{21}H_{36}NO_2Si]^+$ requires M^+ 362.2510, found 365.2509 (+0.1 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ –3.6 (*c* 1.0, $CHCl_3$).

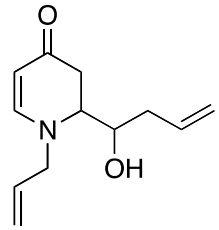
(*R*)-1-((*R*)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)but-3-en-1-yl acetate, 334



Pyridinium salt **329** (0.348 g, 0.682 mmol) was subjected to general procedure G. Flash column chromatography (SiO_2, 7:3 ethyl acetate-petrol) furnished a 12:1 diastereomeric mixture of *dihydropyridones* (0.124 g, 0.498 mmol, 73%) as an oil with **334** being the major product. Further flash column chromatography (SiO_2, 3:2 ethyl acetate-petrol) provided *dihydropyridone **334*** (0.105 g, 0.422 mmol) as an oil.

R_f 0.55 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1739 (ester C=O), 1638 (C=O), 1584 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.95 (1 H, dd, *J* 7.6, 1.0, NC*H*=CH), 5.84 (1 H, dddd, *J* 16.9, 10.3, 6.5, 5.0, NCH_2C*H*=CH_2), 5.69 (1 H, dddd, *J* 16.7, 10.4, 8.1, 5.9, CH(OAc)CH_2C*H*=CH_2), 5.35-5.28 (3 H, m, C*H*OAc, NCH_2CH=CH_2), 5.12-5.07 (2 H, m, CH(OAc)CH_2CH=CH_2), 4.95 (1 H, dd, *J* 7.6, 1.0, NCH=C*H*), 3.94 (1 H, ddt, *J* 15.6, 6.3, 1.0, N$CH_A$$H_B$), 3.87 (1 H, ddt, *J* 15.6, 4.8, 1.5, $NCH_A$$H_B$), 3.66-3.62 (1 H, m, NC*H*CHOAc), 2.81 (1 H, dd, *J* 16.9, 8.1, CO$CH_A$$H_B$), 2.51-2.41 (2 H, m, $COCH_A$$H_B$, CH(OAc)C$H_A$$H_B$), 2.32-2.24 (1 H, m, CH(OAc)$CH_A$$H_B$), 2.05 (3 H, s, CO$CH_3$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 189.6 (*C*=O), 170.1 (OC(O)CH_3), 152.3 (N*C*H=CH), 133.2 (NCH_2*C*H=CH_2), 132.4 (CH(OAc)CH_2*C*H=CH_2), 118.9 (NCH_2CH=*C*H_2), 118.6 (CH(OAc)CH_2CH=*C*H_2), 97.9 (NCH=*C*H), 71.0 (*C*HOAc), 57.7 (N*C*HCHOAc), 57.5 (NCH_2), 36.0 (CO*C*H_2), 34.6 (CH(OAc)*C*H_2), 21.0 (CO*C*H_3); **MS *m/z*** (ESI^+) 250 (30%, $M+H^+$), 272 (95%, $M+Na^+$), 521 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{14}H_{19}NO_3$ requires $M+Na^+$ 272.1257, found 272.1256 (+0.5 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +50.1 (*c* 1.0, $CHCl_3$).

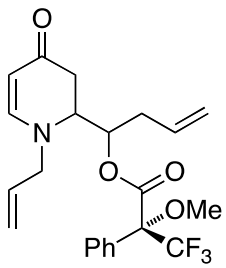
1-Allyl-2-(1-hydroxybut-3-en-1-yl)-2,3-dihydropyridin-4(1H)-one, 350-rac



Potassium carbonate (0.035 g, 0.256 mmol) was added to a stirred solution of dihydropyridone **334-maj-rac** (0.026 g, 0.102 mmol) in wet, reagent grade methanol (5 mL) and the resulting solution was left to stir at room temperature for 2 h. The reaction mixture was then diluted with ethyl acetate (10 mL) and quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (5 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, ethyl acetate) gave *alcohol* ***350-rac*** (0.018 g, 0.088 mmol, 86%) as an oil.

R_f 0.47 (1:1 acetone-ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3347 (O-H), 1624 (C=O), 1581 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.03 (1 H, d, *J* 7.5, NC*H*=CH), 5.92-5.73 (2 H, m, NCH_2CH=CH_2, $CH(OH)CH_2CH$=CH_2), 5.32-5.26 (2 H, m, NCH_2CH=CH_2), 5.20-5.15 (2 H, m, $CH(OH)CH_2CH$=CH_2), 4.90 (1 H, d, *J* 7.5, NCH=C*H*), 4.17-4.10 (2 H, m, C*H*OH, NCH_AH_B), 3.99-3.94 (1 H, m, NCH_AH_B), 3.45 (1 H, t, *J* 7.8, NC*H*CHOH), 2.81 (1 H, dd, *J* 17.0, 7.8, $COCH_AH_B$), 2.45-2.40 (1 H, m, $CH(OH)CH_AH_B$), 2.37 (1 H, d, *J* 17.0, $COCH_AH_B$), 2.30 (1 H, br s, O*H*), 2.08 (1 H, dt, *J* 14.2, 8.6, $CH(OH)CH_AH_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.1 (*C*=O), 152.7 (N*C*H=CH), 133.8 (NCH_2CH=CH_2), 133.4 ($CH(OH)CH_2CH$=CH_2), 119.5 ($CH(OH)CH_2CH$=CH_2), 118.4 (NCH_2CH=CH_2), 96.9 (NCH=*C*H), 68.1 (*C*HOH), 60.5 (N*C*HCHOH), 58.9 (NCH_2), 38.1 ($CH(OH)CH_2CH$=CH_2), 36.7 ($COCH_2$); **MS *m/z*** (ESI^+) 208 (20%, $M+H^+$), 230 (65%, $M+Na^+$), 437 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{12}H_{17}NO_2$ requires $M+Na^+$ 230.1151, found 230.1151 (+0.2 ppm).

(2*R*)-1-(1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)but-3-en-1-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 351-rac

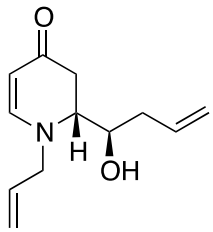


(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (0.035 g, 0.150 mmol) was added to a stirred solution of alcohol **350-rac** (0.018 g, 0.086 mmol), *N,N'*-dicyclohexylcarbodiimide

(0.031 g, 0.150 mmol) and 4-(dimethylamino)pyridine (0.005 g, 0.043 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was allowed to stir for 16 h. Water (5 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol) provided *ester* ***351-rac*** (0.032 g, 0.076 mmol, 89%) as an oil.

R_f 0.58 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1748 (ester C=O), 1643 (C=O), 1588 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.53-7.37 (5 H, m, Ar*H*), 6.89 (0.5 H, d, *J* 7.6, {NC*H*=CH} diastereomer A), 6.68 (0.5 H, d, *J* 7.6, {NC*H*=CH} diastereomer B), 5.81-5.52 (2 H, m, 2 × C*H*=CH_2), 5.50-5.46 (1 H, m, C*H*OMTPA), 5.26-5.02 (4 H, m, 2 × CH=CH_2), 4.95 (0.5 H, d, *J* 7.6, {NCH=C*H*} diastereomer A), 4.90 (0.5 H, d, *J* 7.6, {NCH=C*H*} diastereomer B), 3.76-3.49 (2.5 H, m, NC*H*CHOMTPA, NC$H_A$$H_B$, {NCH$_A$$H_B$} diastereomer A), 3.58 (1.5 H, s, {OCH_3} diastereomer B), 3.44 (1.5 H, s, {OCH_3} diastereomer A), 3.18-3.13 (0.5 H, m, {NCH$_A$$H_B$} diastereomer B), 2.78 (0.5 H, dd, *J* 17.2, 7.8, {COCH_AH$_B$} diastereomer A), 2.68 (0.5 H, dd, *J* 17.2, 7.8, {COCH_AH$_B$} diastereomer B), 2.64-2.57 (1 H, m, CH(OMTPA)CH_AH$_B$), 2.41-2.25 (2 H, m, COCH$_A$$H_B$, CH(OMTPA)CH$_A$$H_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 189.2 (*C*=O), 166.1 (O*C*(O)CPh), 152.1, 152.0 (N*C*H=CH), 133.3, 133.2 (*C*H=CH_2), 132.2 (quaternary Ar*C*), 131.7, 131.2 (*C*H=CH_2), 129.9, 129.8, 128.6, 128.4, 127.7, 127.1 (5 × Ar*C*H), 119.5, 119.5, 118.9, 118.6 (2 × CH=*C*H_2), 98.0, 97.8 (NCH=*C*H), 73.2, 72.9 (*C*HOMTPA), 57.7, 57.5 (N*C*H_2), 56.5, 56.4 (N*C*HCHOMTPA), 55.9 (O*C*H_3), 55.2 (O*C*H_3), 35.8, 35.7 (CO*C*H_2), 34.4, 34.2 (CH(OMTPA)*C*H_2); **^{19}F NMR δ_F** (377 MHz, $CDCl_3$) –70.8, –70.9 (CF_3) [ratio 1:1]; **MS *m/z*** (ESI$^+$) 424 (25%, M+H$^+$), 446 (70%, M+Na$^+$), 847 (40%, 2M+H$^+$), 869 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{22}H_{24}F_3NO_4$ requires *M*+*H*$^+$ 424.1730, found 424.1733 (–0.8 ppm).

(*R*)-1-Allyl-2-((*R*)-1-hydroxybut-3-en-1-yl)-2,3-dihydropyridin-4(1H)-one, 350

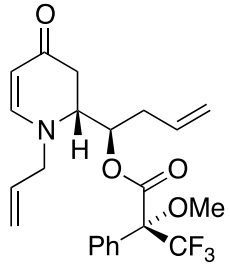


Potassium carbonate (0.036 g, 0.261 mmol) was added to a stirred solution of dihydropyridone **334-maj** (0.026 g, 0.104 mmol) in wet, reagent grade methanol (5 mL) and the resulting solution was left to stir at room temperature for 2 h. The reaction mixture was then diluted with ethyl acetate (10 mL) and quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (5 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and

concentrated. Flash column chromatography (SiO_2, ethyl acetate) gave *alcohol* ***350*** (0.017 g, 0.082 mmol, 79%) as an oil.

R_f 0.47 (1:1 acetone-ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3347 (O-H), 1624 (C=O), 1581 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.03 (1 H, d, *J* 7.5, NC*H*=CH), 5.92-5.73 (2 H, m, NCH_2CH=CH_2, $CH(OH)CH_2CH$=CH_2), 5.32-5.26 (2 H, m, NCH_2CH=CH_2), 5.20-5.15 (2 H, m, $CH(OH)CH_2CH$=CH_2), 4.90 (1 H, d, *J* 7.5, NCH=C*H*), 4.17-4.10 (2 H, m, C*H*OH, NCH_AH_B), 3.99-3.94 (1 H, m, NCH_AH_B), 3.45 (1 H, t, *J* 7.8, NC*H*CHOH), 2.81 (1 H, dd, *J* 17.0, 7.8, $COCH_AH_B$), 2.45-2.40 (1 H, m, $CH(OH)CH_AH_B$), 2.37 (1 H, d, *J* 17.0, $COCH_AH_B$), 2.30 (1 H, br s, O*H*), 2.08 (1 H, dt, *J* 14.2, 8.6, $CH(OH)CH_AH_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.1 (*C*=O), 152.7 (N*C*H=CH), 133.8 (NCH_2CH=CH_2), 133.4 ($CH(OH)CH_2CH$=CH_2), 119.5 ($CH(OH)CH_2CH$=CH_2), 118.4 (NCH_2CH=CH_2), 96.9 (NCH=*C*H), 68.1 (*C*HOH), 60.5 (N*C*HCHOH), 58.9 (NCH_2), 38.1 ($CH(OH)CH_2CH$=CH_2), 36.7 ($COCH_2$); **MS *m/z*** (ESI^+) 208 (20%, $M+H^+$), 230 (65%, $M+Na^+$), 437 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{12}H_{17}NO_2$ requires $M+Na^+$ 230.1151, found 230.1151 (+0.2 ppm); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +58.1 (*c* 0.8, $CHCl_3$).

(*R*)-(*R*)-1-((*R*)-1-Allyl-4-oxo-1,2,3,4-tetrahydropyridin-2-yl)but-3-en-1-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, 351

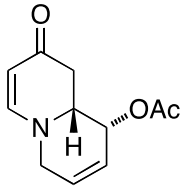


(*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (0.030 g, 0.129 mmol) was added to a stirred solution of alcohol **350** (0.015 g, 0.074 mmol), *N,N'*-dicyclohexylcarbodiimide (0.027 g, 0.129 mmol) and 4-(dimethylamino)pyridine (0.004 g, 0.037 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was allowed to stir for 16 h. Water (5 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 1:1 ethyl acetate-petrol) provided *ester* ***351*** (0.027 g, 0.064 mmol, 86%) as an oil.

R_f 0.58 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1748 (ester C=O), 1643 (C=O), 1588 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 7.49-7.40 (5 H, m, Ar*H*), 6.89 (1 H, d, *J* 7.6, NC*H*=CH), 5.77 (1 H, dddd, *J* 17.1, 10.3, 6.8, 4.8, NCH_2CH=CH_2), 5.58 (1 H, dddd, *J* 17.9, 9.6, 8.3, 5.8, $CH(OMTPA)CH_2CH$=CH_2), 5.49 (1 H, dt, *J* 7.6, 3.3, C*H*OMTPA), 5.27-5.20 (2 H, m, NCH_2CH=CH_2), 5.06-5.02 (2 H, m, $CH(OMTPA)CH_2CH$=CH_2), 4.95 (1 H, d, *J* 7.6, NCH=C*H*),

3.74 (1 H, dd, *J* 15.9, 6.8, NCH_AH$_B$), 3.66 (1 H, t, *J* 7.6, NC*H*CHOMTPA), 3.62-3.56 (1 H, m, NCH$_A$$H_B$), 3.44 (3 H, s, OC$H_3$), 2.78 (1 H, dd, *J* 17.2, 7.6, COCH_AH$_B$), 2.63-2.57 (1 H, m, CH(OMTPA)CH_AH$_B$), 2.41-2.30 (2 H, m, COCH$_A$$H_B$, CH(OMTPA)CH$_A$$H_B$); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 189.2 (*C*=O), 166.1 (O*C*(O)CPh), 152.1 (N*C*H=CH), 133.2 (NCH$_2$*C*H=CH$_2$), 131.2 (CH(OMTPA)CH$_2$*C*H=CH$_2$), 129.9, 128.6, 127.7 (5 × Ar*C*H), 119.5 (CH(OMTPA)CH$_2$CH=*C*H$_2$), 118.9 (NCH$_2$CH=*C*H$_2$), 98.0 (NCH=*C*H), 73.2 (*C*HOMTPA), 57.7 (N*C*H$_2$), 56.5 (N*C*HCHOMTPA), 55.2 (O*C*H$_3$), 35.8 (CO*C*H$_2$), 34.2 (CH(OMTPA)*C*H$_2$); **^{19}F NMR δ_F** (377 MHz, $CDCl_3$) –70.8, –70.9 (CF_3) [ratio 25:1, ee of **334-maj** is 92%]; **MS *m/z*** (ESI$^+$) 424 (25%, M+H$^+$), 446 (60%, M+Na$^+$), 847 (70%, 2M+H$^+$), 869 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{22}H_{24}F_3NO_4$ requires *M*+*Na*$^+$ 446.1550, found 446.1547 (+0.6 ppm); $[\alpha]_D^{25}$ +69.6 (*c* 1.0, $CHCl_3$).

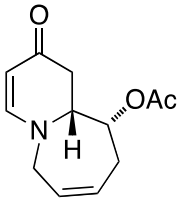
(1*R,9a*R**)-8-Oxo-4,8,9,9a-tetrahydro-1H-quinolizin-1-yl acetate, 353**



Hoveyda-Grubbs 2nd generation catalyst (0.0013 g, 0.002 mmol) was added to a stirred solution of dihydropyridone **335** (0.024 g, 0.102 mmol) in dry, degassed CH_2Cl_2 and the resulting solution was left to stir for 16 h. The solvent was then removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, ethyl acetate) to furnish *bicycle **353*** (0.017 g, 0.082 mmol, 80%) as an oil.

R_f 0.20 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1732 (ester C=O), 1644 (C=O), 1590 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.96 (1 H, d, *J* 7.9, NC*H*=CH), 6.04-6.03 (2 H, m, CH(OAc)C*H*=C*H*), 5.19-5.16 (1 H, m, C*H*OAc), 5.02 (1 H, d, *J* 7.9, NCH=C*H*), 3.89-3.88 (2 H, m, NCH_2), 3.82 (1 H, td, *J* 8.5, 3.0, NC*H*CHOAc), 2.69-2.58 (2 H, m, COCH_2), 2.06 (3 H, s, COCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 191.2 (*C*=O), 170.5 (O*C*(O)CH$_3$), 153.6 (N*C*H=CH), 129.3 (*C*H=CH), 123.7 (CH=*C*H), 99.5 (NCH=*C*H), 67.7 (*C*HOAc), 56.0 (N*C*HCHOAc), 50.9 (N*C*H$_2$), 37.2 (CO*C*H$_2$), 20.8 (CO*C*H$_3$); **MS *m/z*** (ESI$^+$) 208 (40%, M+H$^+$), 230 (80%, M+Na$^+$), 437 (100%, 2M+Na$^+$); **HRMS** (ESI$^+$) $C_{11}H_{13}NO_3$ requires *M*+*Na*$^+$ 230.0788, found 230.0789 (–0.6 ppm).

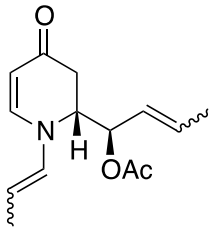
(10*R,10a*R**)-2-Oxo-1,2,6,9,10,10a-hexahydropyrido[1,2-a]azepin-10-yl acetate, 354**



Hoveyda-Grubbs 2nd generation catalyst (0.0027 g, 0.004 mmol) was added to a stirred solution of dihydropyridone **334-maj** (0.054 g, 0.217 mmol) in dry, degassed CH_2Cl_2 and the resulting solution was heated to 40 ºC and left to stir for 16 h. The solvent was then removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, ethyl acetate) to furnish *bicycle **354*** (0.042 g, 0.187 mmol, 87%) as an oil.

R_f 0.27 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1730 (ester C=O), 1630 (C=O), 1568 (C=C); **^{1}H NMR δ_H** (400 MHz, $CDCl_3$) 6.98 (1 H, d, *J* 7.5, NC*H*=CH), 5.77-5.65 (2 H, m, CH_2CH=C*H*), 5.28 (1 H, m, C*H*OAc), 4.88 (1 H, d, *J* 7.5, NCH=C*H*), 4.13-4.07 (1 H, m, NCH_AH_B), 4.01 (1 H, td, *J* 7.1, 4.9, NC*H*CHOAc), 3.94-3.88 (1 H, m, NCH_AH_B), 2.77-2.68 (2 H, m, CH(OAc)CH_AH_B, COCH_AH_B), 2.41-2.31 (2 H, m, CH(OAc)CH_AH_B, $COCH_AH_B$), 2.02 (3 H, s, COCH_3); **^{13}C NMR δ_C** (100 MHz, $CDCl_3$) 190.8 (*C*=O), 170.3 (O*C*(O)CH_3), 153.6 (N*C*H=CH), 127.6 (*C*H=CH), 126.9 (CH=*C*H), 97.6 (NCH=*C*H), 73.0 (*C*HOAc), 58.5 (N*C*HCHOAc), 54.6 (NCH_2), 36.6 ($COCH_2$), 29.8 (CH(OAc)CH_2), 20.8 ($COCH_3$); **MS *m/z*** (ESI^+) 222 (40%, $M+H^+$), 244 (75%, $M+Na^+$), 465 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{12}H_{15}NO_3$ requires $M+H^+$ 222.1125, found 222.1125 (–0.1 ppm).

(*R)-1-((*R**)-4-Oxo-1-(prop-1-en-1-yl)-1,2,3,4-tetrahydropyridin-2-yl)but-2-en-1-yl acetate, 355**

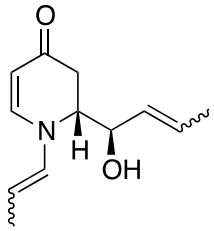


Grubbs 2nd generation catalyst (0.008 g, 0.009 mmol) was added to a stirred solution of vinyloxytrimethylsilane (0.270 mL, 1.81 mmol) in toluene (5 mL) and the resulting solution was heated to 120 ºC and left to stir at this temperature for 20 mins. A solution of dihydropyridone **334-maj** (0.023 g, 0.090 mmol) in toluene (2 mL) was then added and the resulting solution was left stirring at the same temperature for 6 h. The mixture was allowed to cool to room temperature and the volatiles were removed *in vacuo*. Flash column chromatography (SiO_2, 1:1

ethyl acetate-petrol) yielded *dihydropyridone* ***355*** (0.022 g, 0.088 mmol, 97%) as an oil and as an inseparable mixture of geometric isomers.

R_f 0.59 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 1741 (ester C=O), 1646 (C=O), 1589 (C=C); **^{1}H NMR δ_H** (400 MHz, C_6D_6) *Major geometric isomer:* 6.38 (1 H, d, *J* 7.6, NC*H*=CH), 5.88 (1 H, t, *J* 7.6, C*H*OAc), 5.71-5.65 (1 H, m, CH(OAc)CH=C*H*), 5.63-5.60 (1 H, m, NCH=C*H*CH_3), 5.37 (1 H, dd, *J* 15.1, 8.0, CH(OAc)C*H*=CH), 5.23 (1 H, d, *J* 7.6 NCH=C*H*), 4.93-4.86 (1 H, m, NCH=C*H*CH_3), 3.64 (1 H, t, *J* 7.1, NC*H*CHOAc), 2.58 (1 H, d, *J* 16.9, $COCH_AH_B$), 2.48 (1 H, dd, *J* 16.9, 7.5, $COCH_AH_B$), 1.70 (3 H, s, $COCH_3$), 1.57 (3 H, d, *J* 6.6, NCH=CHCH_3), 1.50 (3 H, d, *J* 6.6, CH(OAc)CH=CHCH_3); **^{13}C NMR δ_C** (100 MHz, C_6D_6) *Major geometric isomer:* 188.9 (*C*=O), 168.9 (O*C*(O)CH_3), 146.4 (N*C*H=CH), 133.0 (NCH=*C*HCH_3), 132.7 (CH(OAc)CH=*C*H), 125.3 (CH(OAc)*C*H=CH), 102.9 (N*C*H=CHCH_3), 101.3 (NCH=*C*H), 72.1 (*C*HOAc), 57.3 (N*C*HCHOAc), 36.0 ($COCH_2$), 20.5 ($COCH_3$), 17.7 (CH(OAc)CH=CHCH_3), 14.9 (NCH=CHCH_3); **MS *m/z*** (ESI^+) 250 (20 %, $M+H^+$), 272 (70%, $M+Na^+$), 313 (60%, $M+MeCN+Na^+$), 521 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{14}H_{19}NO_3$ requires $M+Na^+$ 272.1257, found 272.1255 (+0.6 ppm).

(*R)-2-((*R**)-1-Hydroxybut-2-en-1-yl)-1-(prop-1-en-1-yl)-2,3-dihydropyridin-4(1H)-one, 357**



Potassium carbonate (0.031 g, 0.221 mmol) was added to a stirred solution of dihydropyridone **355** (0.022 g, 0.088 mmol) in wet, reagent grade methanol (5 mL) and the resulting solution was left to stir at room temperature for 2 h. The reaction mixture was then diluted with ethyl acetate (10 mL) and quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (5 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2, 4:1 ethyl acetate-petrol) gave *alcohol* ***357*** (0.015 g, 0.071 mmol, 80%) as an oil and as an inseparable mixture of geometric isomers.

R_f 0.40 (ethyl acetate); **IR ν_{max}** (thin film/cm^{-1}) 3358 (O-H), 1671 (C=C), 1635 (C=C), 1585 (C=O); **^{1}H NMR δ_H** (400 MHz, C_6D_6) *Major geometric isomer:* 6.51 (1 H, d, *J* 7.7, NC*H*=CH), 5.83-5.79 (1 H, m, NC*H*=CHCH_3), 5.69-5.63 (1 H, m, CH(OH)CH=C*H*CH_3), 5.49-5.43 (1 H, m, CH(OH)C*H*=CHCH_3), 5.18 (1 H, d, *J* 7.7, NCH=C*H*), 4.84-4.76 (1 H, m, NCH=C*H*CH_3), 4.47 (1 H, t, *J* 7.1, C*H*OH), 3.62 (1 H, t, *J* 7.5, NC*H*CHOH), 2.88 (1 H, br s, O*H*), 2.74 (1 H, d, *J*

16.9, $COCH_AH_B$), 2.54 (1 H, dd, *J* 16.9, 7.5, $COCH_AH_B$), 1.62 (3 H, d, *J* 7.2, $CH(OH)CH{=}CHCH_3$), 1.57 (3 H, d, *J* 6.7, $NCH{=}CHCH_3$); **^{13}C NMR** δ_C (100 MHz, C_6D_6) *Major geometric isomer:* 190.5 (*C*=O), 146.7 (N*C*H=CH), 133.8 ($NCH{=}CHCH_3$), 130.2 ($CH(OH)CH{=}CHCH_3$), 129.4 ($CH(OH)CH{=}CHCH_3$), 103.7 ($NCH{=}CHCH_3$), 100.5 (NCH=*C*H), 70.6 (*C*HOH), 60.0 (N*C*HCHOH), 35.8 ($COCH_2$), 17.4 ($CH(OH)CH{=}CHCH_3$), 14.9 ($NCH{=}CHCH_3$); **MS *m/z*** (ESI^+) 230 (75%, $M+Na^+$), 437 (100%, $2M+Na^+$); **HRMS** (ESI^+) $C_{12}H_{17}NO_2$ requires $M+Na^+$ 230.1151, found 230.1152 (–0.4 ppm).

Appendix 1:
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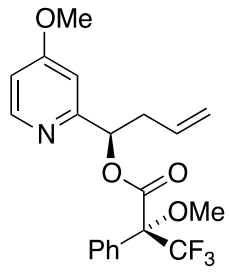
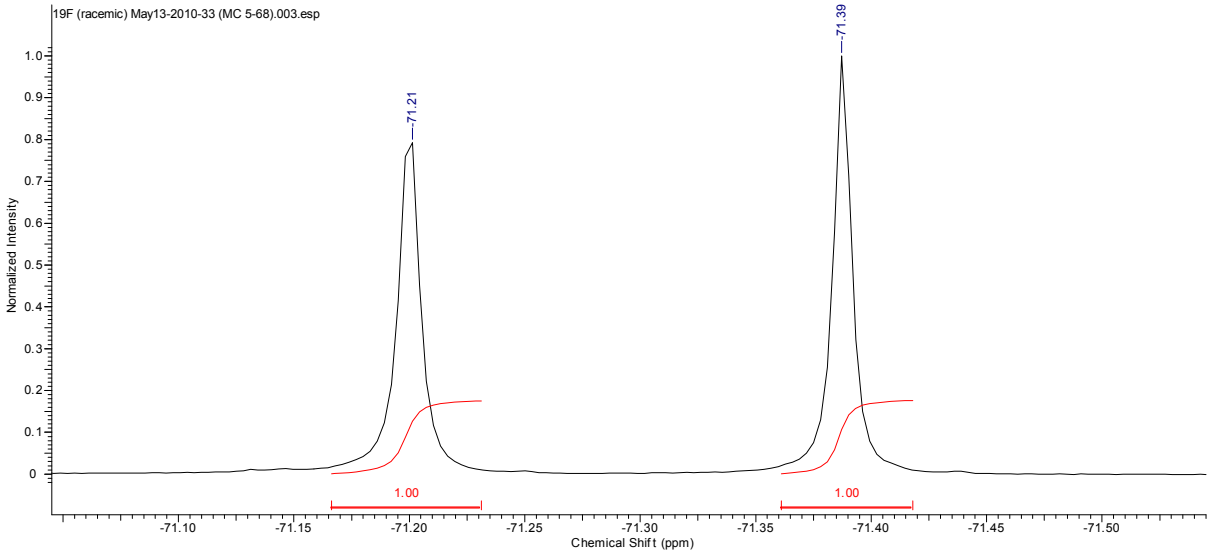
Appendix 2:
NMR Data

^{19}F NMR spectra of Mosher esters 349-rac and 349



349-rac



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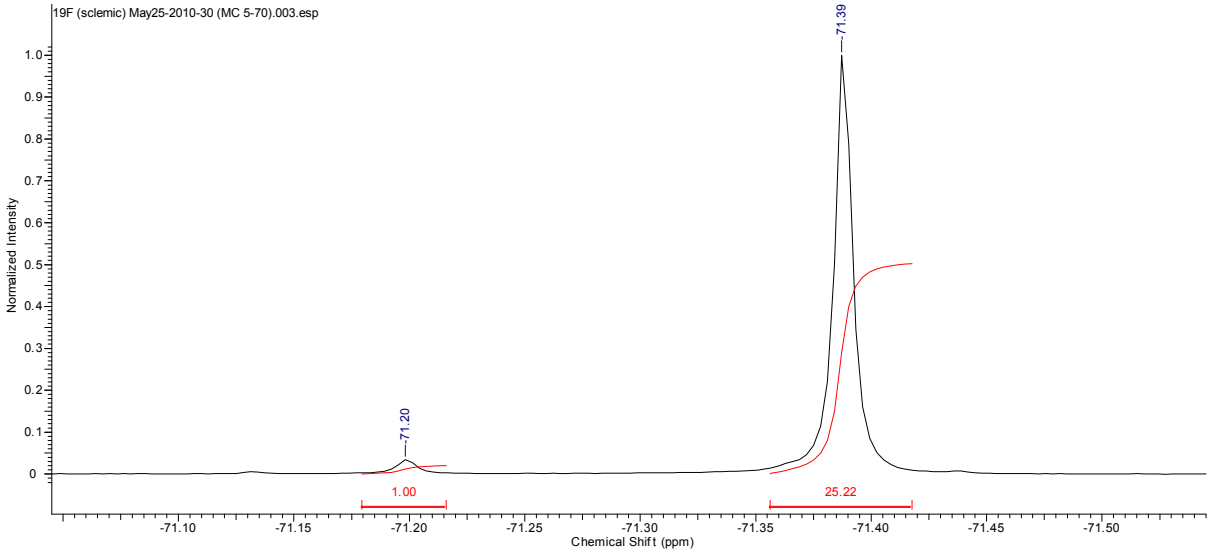
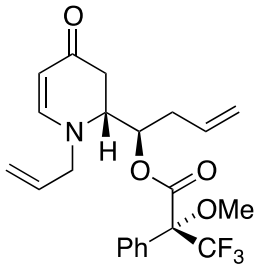
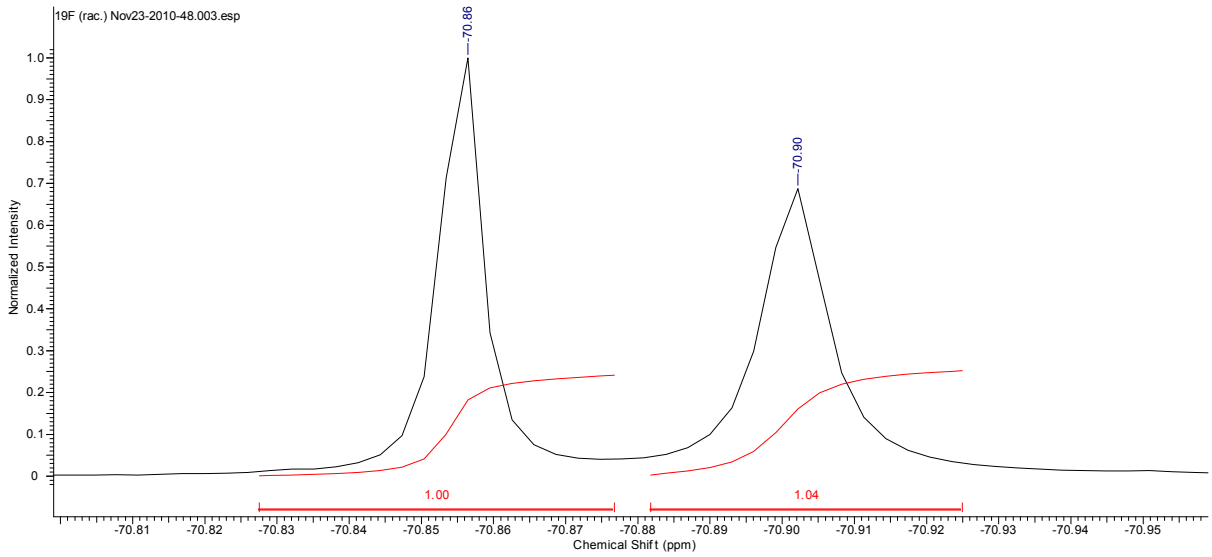


ee of alcohol **317** is 92%

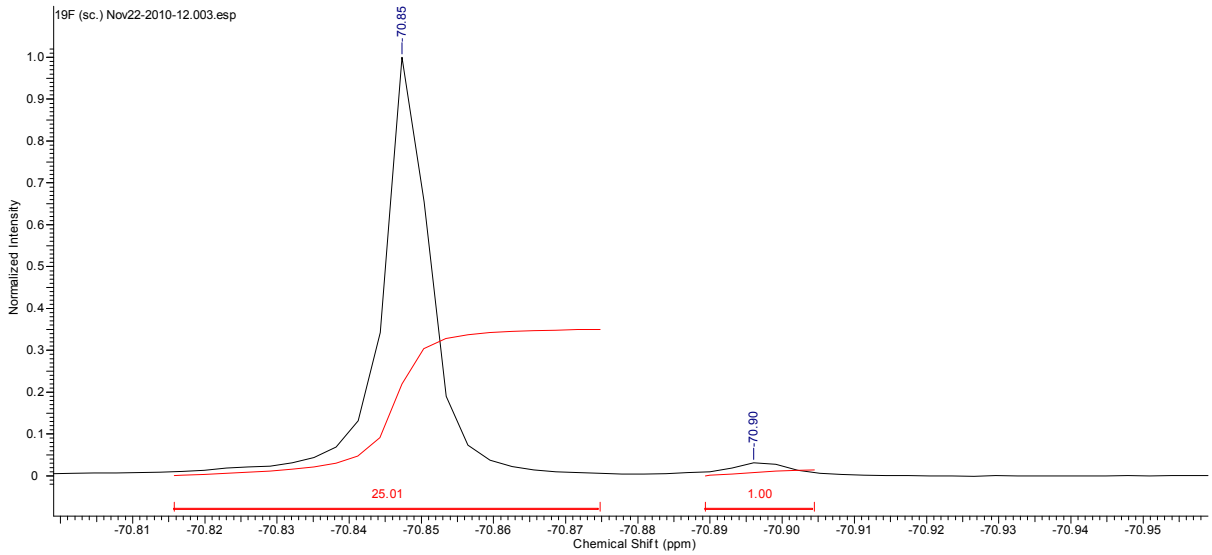
^{19}F NMR spectra of Mosher esters 351-rac and 351



351-rac

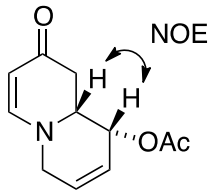


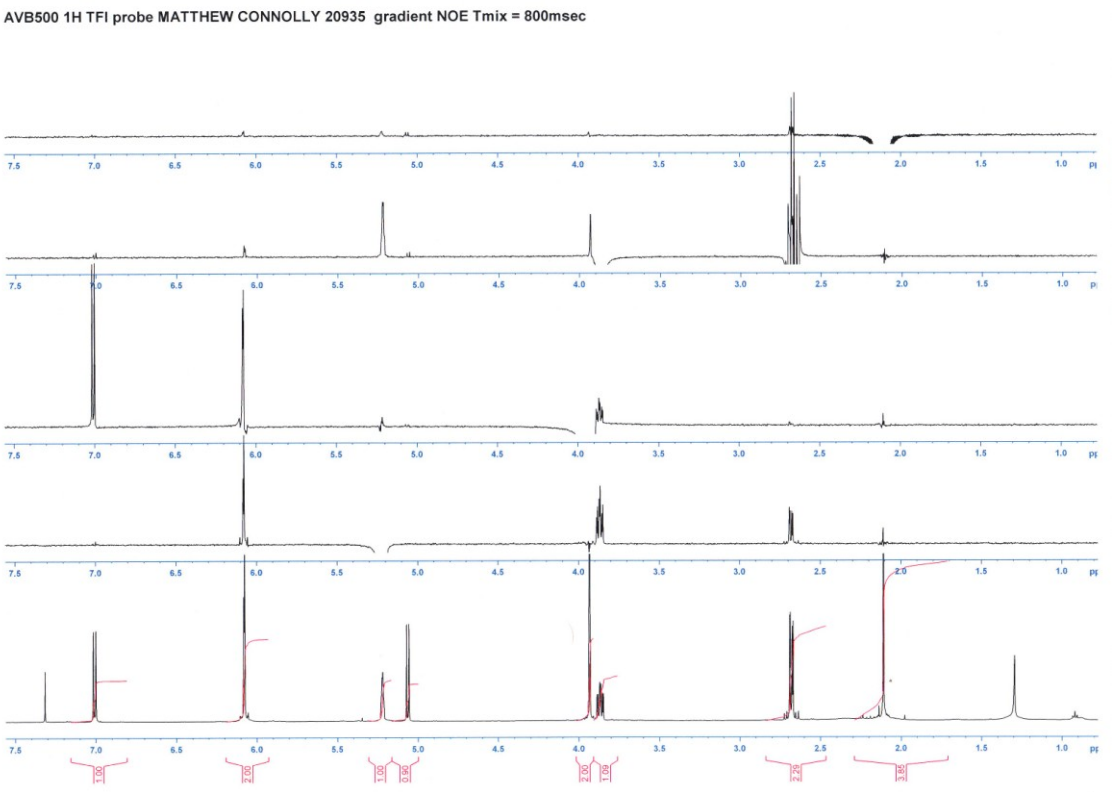
351



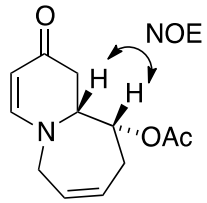
ee of dihydropyridone **334-maj** is 92%

^{1}H NMR NOE data (500 MHz, $CDCl_3$) for compound 353

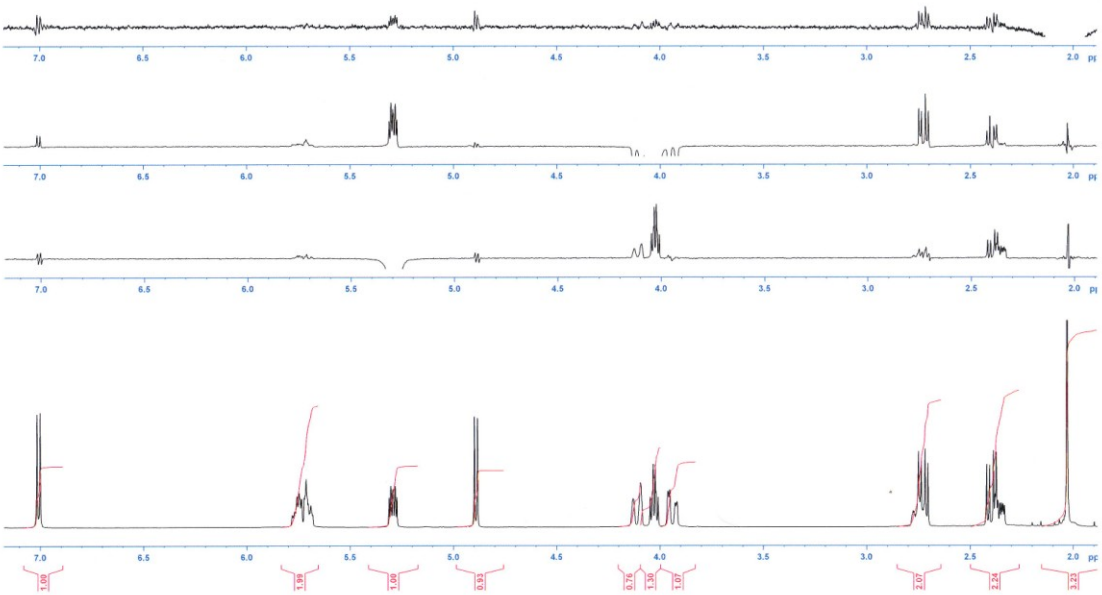




^{1}H NMR NOE data (500 MHz, $CDCl_3$) for compound 354



AVB500 1H TFI probe MATTHEW CONNOLLY 1569 30/11/10 gradient NOE Tmix = 800msec



Appendix 3:
X-Ray Crystallographic Data