STEREOSELECTIVE SYNTHESIS OF PIPERIDINES

A THESIS SUBMITTED IN PART FULFILMENT OF THE REQUIREMENTS OF THE DEGREE OF DOCTOR OF PHILOSOPHY

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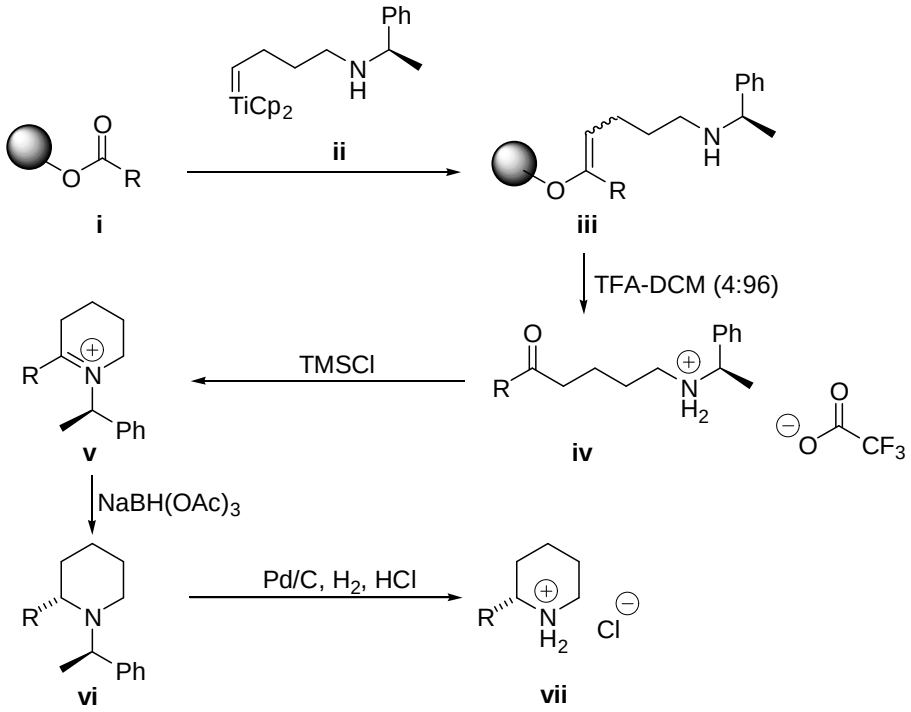
For my parents and my sister

To my father, my source of inspiration and guidance
To my mother, a loving calm steady hand on whom I can always rely
To my sister, my companion through everything

May we always be together, no matter how far apart we are.

Abstract

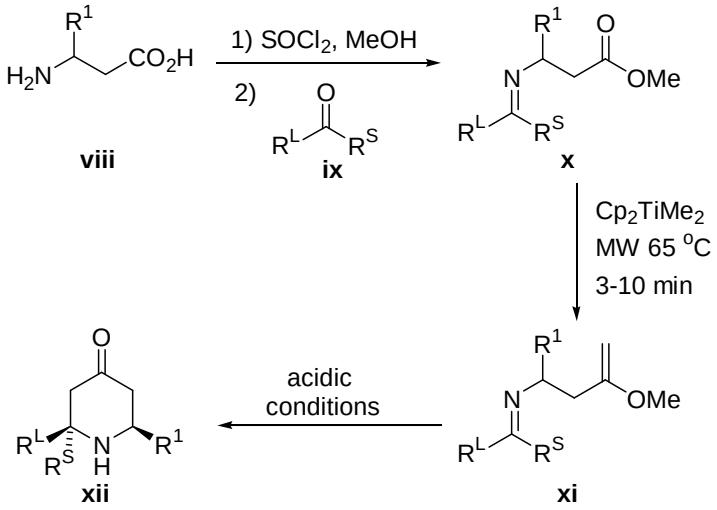
This thesis is divided into two parts. The first part describes the production of a small stereodiverse library of 2-substituted piperidines. Novel chiral titanium alkylidene reagents **ii** alkylidenated resin-bound esters **i** to give acid-labile resin-bound enol ethers **iii.** These were cleaved to give amino ketones **iv**. The switch in the nature of the resin from acid-stable to acid-labile is key to the purity of the amino ketones **iv**, as during cleavage only the acid-sensitive enol ethers **iii** are cleaved, leaving the unreacted esters **i** on the resin. The amino ketones **iv** were cyclized using TMSCl to give cyclic iminium salts **v**. Diastereoselective reduction of the iminium salts **v** with $NaBH(OAc)_3$ gave piperidines **vi** which, after cleavage of the chiral protecting group, gave the desired enantiomerically-enriched, 2-substituted piperidines **vii**.



The piperidines **vii** were produced in good overall yield, high purity, and good to excellent stereochemical purity. By switching the enantiomer of the phenylethylamine chiral protecting group used, either enantiomer of the desired piperidine could be produced at will.

The second part of the thesis describes a solution-phase route to 2,6-*syn* substituted piperidin-4-ones **xii** inspired by the Petasis-Ferrier rearrangement. Imino esters **x** derived from β-amino acids **viii** were methylenated using the Petasis reagent, dimethyltitanocene, to give imino enol ethers **xi** containing nucleophilic and electrophilic functionality in the same

molecule. The mild microwave conditions used for the methylenation gave the enol ethers **xi** in minutes. Potentially, the reaction takes advantage of selective heating of the polar Petasis reagent in a non polar solvent system so that the rate determining decomposition of the Petasis reagent is accelerated without affecting any sensitive substrate. Acidic conditions activated the imine and induced cyclization to give the desired 2,6-*syn* piperidin-4-ones **xii** in good yield and excellent diastereoselectivity. A small library of piperidinones was produced to demonstrate the method.



viii **ix** **x** **xi** **xii**

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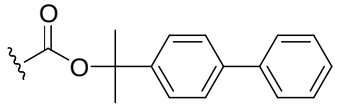
Abbreviations

Å	angstrom
Ac	acetyl
AIBN	azobisisobutyronitrile
aq	Aqueous
Ar	Aryl
atm	atmosphere
bmimPF_6	1-butyl-3-methylimidazolium hexafluorophosphate
Bn	benzyl
Boc	*tert*-butyl carbamate
Boc_2O	di-*tert*-butyldicarbonate
Bpoc	
BPS	*tert*-butyldiphenylsilyl
Bu	butyl
^{i}Bu	isobutyl
^{t}Bu	*tert*-butyl
bp	boiling point
BT	benzothiazole
^{o}C	degrees centigrade
CDA	chiral derivatizing agent
CI	chemical ionization
conc.	concentrated
Cp	cyclopentadienyl anion
Cy	cyclohexyl
d	doublet
DCM	dichloromethane
DDQ	2,3-dicyano-5,6-dichloroparabenzoquinone
DIBAL	diisobutylaluminium hydride
DOS	diversity-orientated synthesis
DMAP	4-*N*,*N*-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio

ε’	dielectric constant
ε”	dielectric loss
ee	enantiomeric excess
EI	electron impact
equiv.	equivalents
er	enantiomeric ratio
EtOAc	ethyl acetate
FAB	fast atom bombardment
GC	gas chromatography
h	hour
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IR	infrared
LDA	lithium diisopropylamide
m	multiplet
MAOS	microwave-assisted organic synthesis
mp	melting point
min	minutes
MOM	methoxymethyl
MS	molecular sieves
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Nu	nucleophile
PCC	pyridinium chlorochromate
pg	protecting group
Ph	phenyl
PhH	benzene
PhMe	toluene
PMB	paramethoxybenzyl
PSI	pounds per square inch
Py	pyridine
q	quartet

quin.	quintet
QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
RCM	ring closing metathesis
RT	room temperature
s	singlet
SASRIN	super acid sensitive resin
SPS	solid-phase synthesis
t	triplet
tanδ	loss factor
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N*, *N*, *N'*, *N'*-tetramethylethyldiamine
TMS	trimethylsilyl
p-tosic	*para*-toluenesulfonic
Ts	toluenesulfonyl

Contents

Chapter 1
Solid-Phase Chemistry

1.1 Background

First introduced as a method to streamline peptide synthesis by the late, great Merrifield[1], solid phase chemistry has grown to become a versatile and powerful method to make a wide variety of molecules. An insoluble solid support is functionalized with a linker that connects it to the substrate. Effectively, this means that the substrate can easily be separated from the reaction mixture by simple separation of the liquid and solid phases. A large excess of reagent can therefore be used to drive the reactions to completion and all unused, excess reagent can be removed by filtration and washing. Furthermore, the solid-supported substrates can be contained within porous reactors, allowing several different substrates, each contained in a different reactor, to be treated in one reaction vessel. This batch synthesis strategy means that many different products can be produced at one time in the same flask. Importantly, for industry and drug discovery, the easy workup/purification also allows solid-phase synthesis (SPS) to be easily automated. Adaptability to automation combined with batch synthesis means that libraries of thousands of compounds can be produced very quickly.

1.2 Diversity-Orientated Synthesis[2]

Diversity-orientated synthesis (DOS) involves the production of libraries of small, diverse compounds via automation and, typically, SPS. Small molecules have proven to be potent in many different areas, especially as drugs, and as tools in the investigation of biological pathways.[3] In particular, the ability to tune a compound's activity by modifying structural attributes means that small molecule probes provide unparalleled versatility in the unravelling of nature's complex workings.

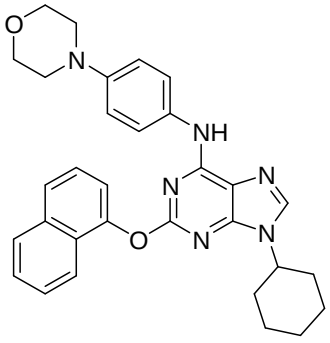
Access to large and diverse small molecule libraries is of paramount importance. Sometimes, existing knowledge of biological systems being targeted or investigated can direct the synthetic strategies, allowing for structure-based rational design. However, existing information is not always available, and even when it is, only a broad guideline is provided. Thus, even structure-based rational design must take into account a diverse and large volume of chemical space. Furthermore, to investigate fully a region of chemical space, the compounds produced must be stereodiverse. It is not enough just to construct different

scaffolds. The investigation must be deeper and take into account the different stereoisomers of each scaffold. A typical library inspired by DOS will contain thousands of compounds ideally, each existing in a unique region of chemical and stereochemical space.

DOS should not be carried out in a blind way. By incorporating information from known biologically potent compounds a DOS can be directed. Successful drugs and biology's collection of natural products populate a list of privileged structures.[4] These small but powerful molecules allow the chemist to build a library by decorating a proven foundation. Building on previous success by incorporating privileged structures allows the library to not only be large and diverse, but also significant.

The purity of each and every tested member in a DOS-inspired library must be high. Biological screening is sensitive and confidence that only one compound is being tested is necessary to be sure of the origin of observed effects. DOS requires huge numbers of compounds, and SPS provides a means to access these large numbers. Unfortunately, solid-supported intermediates cannot be purified. Thus, the reactions used in a DOS should be robust, proceeding with maximum efficiency, providing high yields and greater than 90% purity. Due to the stereospecificity of biological systems, stereochemical purity is an essential consideration in the planning of a DOS. The targets should be one enantiomer.

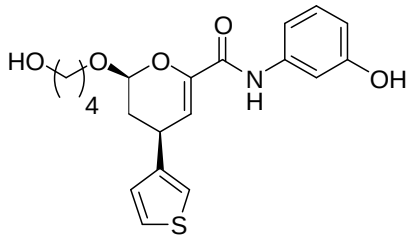
A variety of beautiful work has been accomplished in the production of DOS-inspired libraries. By using the adaptability of SPS to automation, a library of 45,140 drug-like aromatic nitrogen-containing heterocycles, such as purines and pyrimidines, was produced[5] by Schultz and co-workers, who then screened the library for the ability to influence stem cell differentiation.[6] One member in the library, purmorphamine **1**, was able to induce differentiation of mouse mesenchymal stem cells into osteoblasts, an action called osteogenesis. Other members of the library also induced various effects on stem cells, including neurogenesis, cardiomyogenesis, and dedifferentiation. Importantly, the DOS was not guided by any biological information. However, by creating a huge library, including multiple privileged structures, and covering a large volume of chemical space, Schultz and co-workers were able to discover potent small molecule stem cell differentiators.



1

Figure 1.1

Taking advantage of the ability of SPS to produce vast numbers of compounds, Schreiber *et al.* produced a 4,320 member library of dihydropyrans using a Diels-Alder cycloaddition.[7] Careful reaction planning and an excellent chiral catalyst ensured that enantiomeric excess of the final products was high, 80 to 96 % *ee*. Furthermore, by using both enantiomers of the catalyst, both enantiomers of the product could be formed separately, thus making the route stereodiverse. Purity of the final dihydropyrans that came off resin was excellent (≥ 95% pure in >75% of cases). Biological screening of the library found that one member, haptamide B **2**, showed excellent activity in affecting the transcription factor Hap3 *in vivo*.[8]



2

Figure 1.2

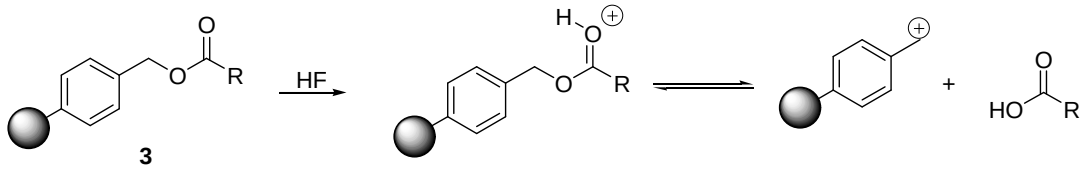
SPS and DOS are great partners in the discovery of new biologically active compounds. Only with the special characteristics of SPS, particularly the adaptability to automation, can effective DOS be achieved. By taking into consideration diversity, stereodiversity, the region of chemical space to be investigated, and by carefully planning chemically robust solid-phase routes, DOS will continue to produce important drug candidates and reveal information about biological systems.

1.3 Linkers

DOS is perhaps the greatest test of an SPS. DOS requires a variety of reactions to be compatible with potentially thousands of substrates. This means the substrate as a whole, including the solid support, must tolerate all reaction conditions used to transform specific moieties within it. The reactions, substrates and resin must be carefully chosen. The vast majority of the mass of a solid support used for SPS is typically polystyrene; however, the most important part of the solid support is the linker that "links" the substrate to the support. Different linkers have different effects on the eventual outcome of the reaction. Of particular importance are the loading conditions, the ability of the linker to tolerate a variety of reaction conditions, the cleavage conditions, and the "trace" that the linker leaves behind at the former point of attachment in the cleaved product. The linker-dependant loading conditions should allow for a wide variety of different substrates to be linked to the resin, and as with all solid-phase transformations, loading must be high yielding. Once the substrate is on resin the linker must be inert to all proposed transformations and all proposed reactants. Cleavage conditions rely on the chemical properties of the linker. These properties must allow cleavage to occur in high yield and under conditions that do not damage the product being released from resin. Finally, the trace of the point of attachment to resin should ideally be a desired functionality of the cleaved product. When taking into account the large numbers of compounds and reactants used in DOS, the ability of the linker to be transformed without affecting the substrate and vice versa is of particular concern. Thus the choice of linker is key to minimizing the negative effects, and possibly even gaining profit from SPS. There are a variety of linkers reported in the literature,[9] and the choice of which linker to use is as crucial to the success of the synthesis as any of the conditions chosen for chemical transformation.

1.4 Acid-Labile Linkers

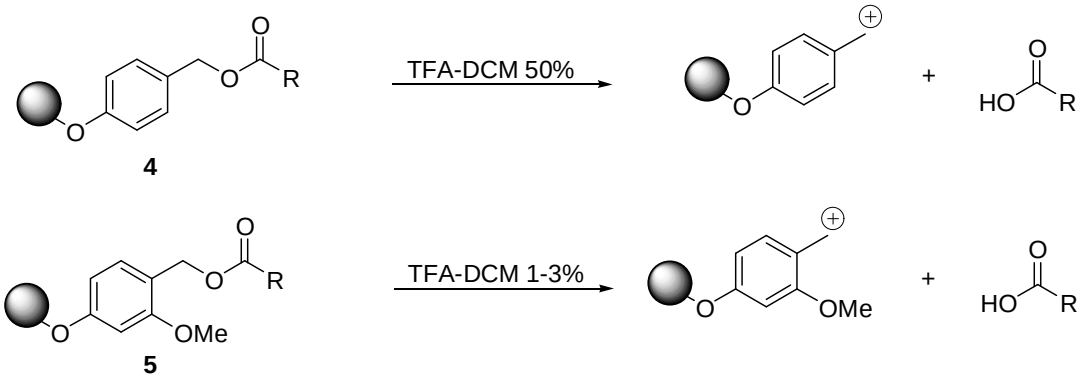
Several popular acid-labile linkers are ester-derived. The sensitivity of the linker is determined by the stability of the cation formed after cleavage in relation to the stability of the protonated ester, Scheme 1.1.



3

Scheme 1.1

When the cation is very unstable, as with Merrifield linker **3,** HF is required for cleavage. Few compounds are left unaffected by HF so linkers based on more electron-rich benzylic esters are often used to facilitate cleavage, and allow for a more diverse array of target molecules. Wang linker **4**, and the SASRIN linker **5**, are cleaved by 50% TFA in DCM, and 1-3% TFA in DCM respectively, Scheme 1.2. By using volatile acids such as TFA and HF, excess acid can be removed by simple evaporation to give the cleaved product with minimum workup.



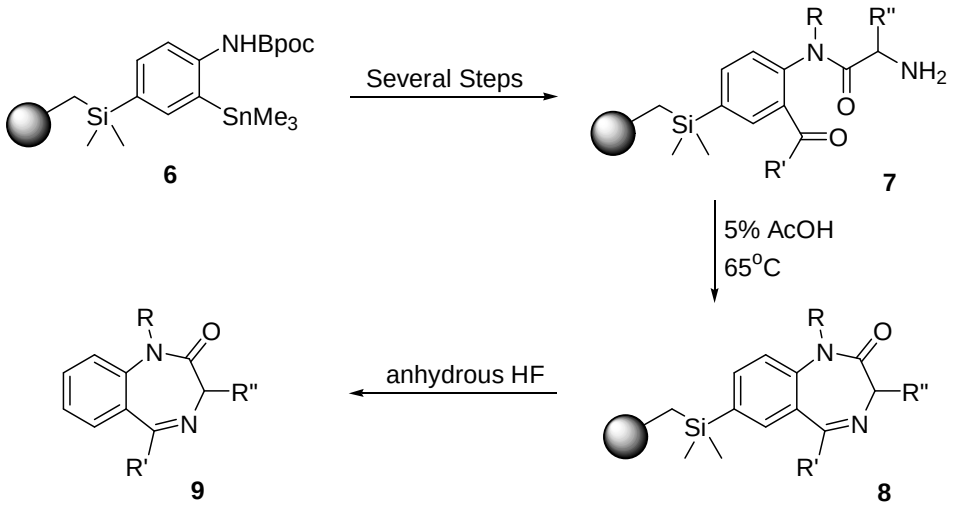
Scheme 1.2

While ester linkers are the most commonly used, amide-derived supports such as the Rink Linker[10] also exist, and these follow a similar trend to the ester linkers above. The acid-sensitive ester linkers discussed can conversely also be cleaved by using a small nucleophilic base such as NaOMe, to give the cleaved product as the methyl ester. Where this type of cleavage is undesired, a linker can be made that sterically hinders attack by nucleophiles such as a small base

1.5 Traceless Linkers[11,12]

In the ester linkers shown above the trace left at the point of attachment to resin takes the form of a carboxylic acid functional group. In a well-planned synthesis the trace could be part of the desired molecule, but this is not always the case. Sometimes it is desirable to have a linker that allows cleavage to happen such that the point of attachment is not apparent in the cleaved product. Trialkylsilanes have been used as traceless linkers since they are amenable to *ipso* substitution and can therefore be cleaved to give aromatic compounds marked only with a hydrogen atom at the former point of attachment to the resin. Furthermore, trialkylsilanes tolerate a wide variety of conditions including very basic

reagents, and transition metal catalyzed reactions. Plunkett and co-workers have used traceless linkers of this nature to make small libraries of benzodiazepines[13], Scheme 1.3.



Scheme 1.3

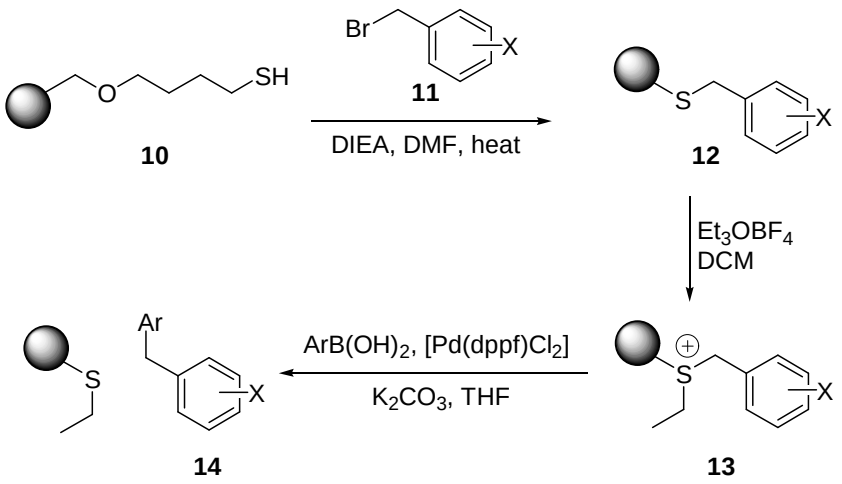
The cleavage conditions are typically harsh, and depend on the chemical nature of the linker and on the electronic properties of the aromatic ring. The *ipso* substitution is favoured by a more electron-rich environment and so the cleavage is easier for systems with electron-donating groups attached to the aromatic ring. The cleavage can be facilitated by switching from a trialkylsilane to a trialkylgermanium linker.[14] The germanium analogue of **8** is cleaved by anhydrous TFA, or elemental bromine[15] to give benzodiazepine **9**, or its 7-bromoanalogue, respectively.

1.6 Safety Catch Linkers

As stated before, linkers, substrates and reagents are chosen so that they will tolerate each other during the solid-phase portion of a synthetic route. Sometimes a targeted region of chemical space requires that reactions and substrates must be used that perturb this reactant, substrate, linker "symbiosis". In such cases a less reactive linker is needed; a linker whose lability can be turned on and off.

Safety catch linkers must undergo an activation step for their labile characteristics to be turned on. Wagner used this strategy in preparing a library of diphenylmethyl derivatives **14**,[16] Scheme 1.4. A functionalized arene **11** was linked to the support via a stable carbon-sulfur bond. The sulfur was alkylated to give the sulfonium salt **13** which was cleaved *via* a palladium catalyzed cross-coupling reaction. Interestingly, this example used the cleavage

step to introduce diversity, an example of a productive cleavage. It is important to note that, when using a safety catch linker, the resin-bound substrate must be able to tolerate not just the cleavage conditions, but the typically harsh activation conditions.

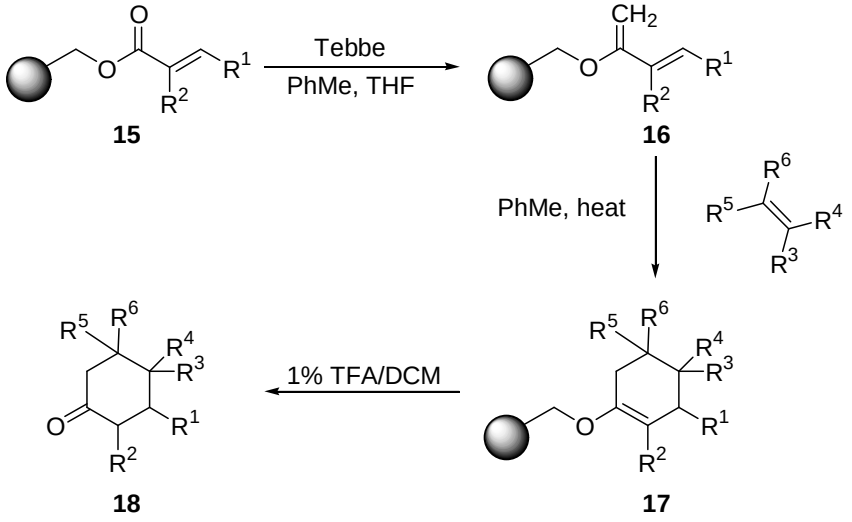


Scheme 1.4

1.7 Chameleon Catch Linkers

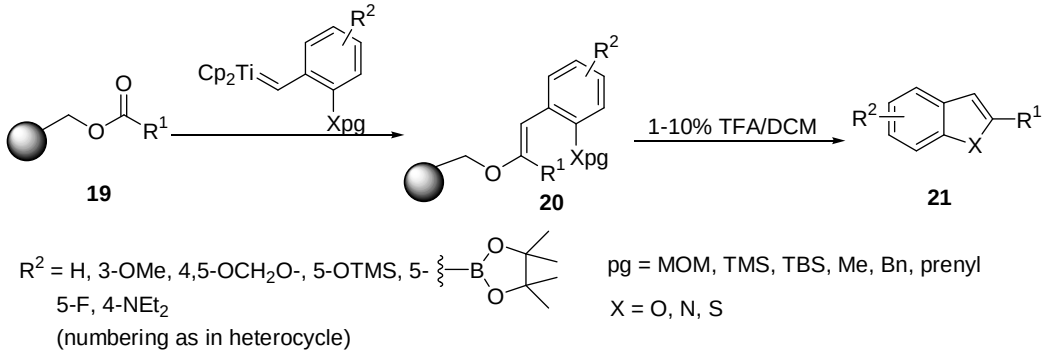
Considering the high demands of purity required by DOS, linker design inspired by purity is essential. A chameleon catch strategy switches the nature of the linker during the synthetic sequence so that it is cleaved using different conditions to the original linker. In doing so, only linker that has undergone the synthetic sequence is cleaved and all un-reacted linker is left on resin, ensuring high purity of the cleaved product. It differs from a safety catch linker in that the products can be obtained by cleaving some samples prior to switching the linker to give one set of products and cleaving some samples after switching the linker to give a different range of products. This maximizes diversity.

Barrett and co-workers revealed this method in their route to cyclohexanones,[17] Scheme 1.5. During the sequence, relatively acid-stable esters **15**, derived from Merrifield resin, were converted into acid-sensitive cyclic enol ethers **16**. Diels-Alder reactions then gave cyclic enol ethers **17**. Mild acidic cleavage conditions were then used to cleave only material derived from enol ether **16** and thus the cyclahexanones **18** were produced in high purity.



Scheme 1.5

Work within the Hartley group has exploited this elegant type of linker to provide access to a wide array of different privileged structures from the same starting esters,[18,19,20,21] Scheme 1.6. Using novel titanium carbenoids, relatively acid-stable resin-bound esters **19** are converted into acid-labile enol ethers **20**. Mildly acidic conditions then cleave the resin-bound enol ethers to give the heterocycles **21** in excellent purity. The switch in the nature of the linker is productive, as the alkylidenation adds diversity and builds the privileged structure. The heteroaromatic scaffolds can then be further decorated when R^2 is a boronate group, *via* Suzuki cross-coupling on resin. See section 3.8 for a more in depth discussion of the Hartley methodology.

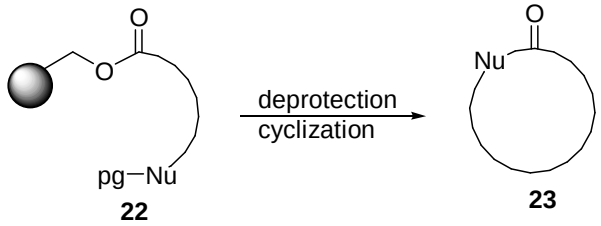


Scheme 1.6

1.8 Cyclative cleavage

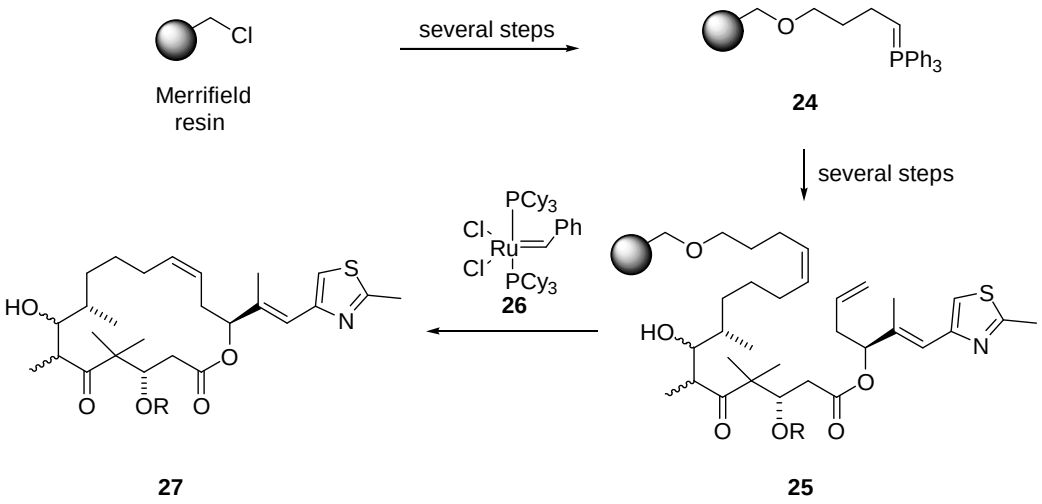
As mentioned earlier, ester-derived and amide-derived linkers can be cleaved by small nucleophiles. When the nucleophile is part of the molecule being cleaved then

cyclative cleavage occurs. A resin-bound ester containing a protected nucleophile **22** can be deprotected and then cyclized to give a range of products **23**, Scheme 1.7. This strategy has the advantage that cleavage is productive. A variety of heterocycles have been produced using this type of linker, including diketopiperazines[22], diketomorpholines[23], lactones[24], and quinolinones[25].



Scheme 1.7

Nicolaou and co-workers demonstrated another type of cyclative cleavage involving cleavage *via* ring closing metathesis (RCM), Scheme 1.8.[26] Merrifield resin could be converted into the resin-bound ylide **24**, which in turn was transformed into the diene **25**. Grubbs'1st generation catalyst[27] **26** formed the macrocycle and cleaved the product from resin in one step.



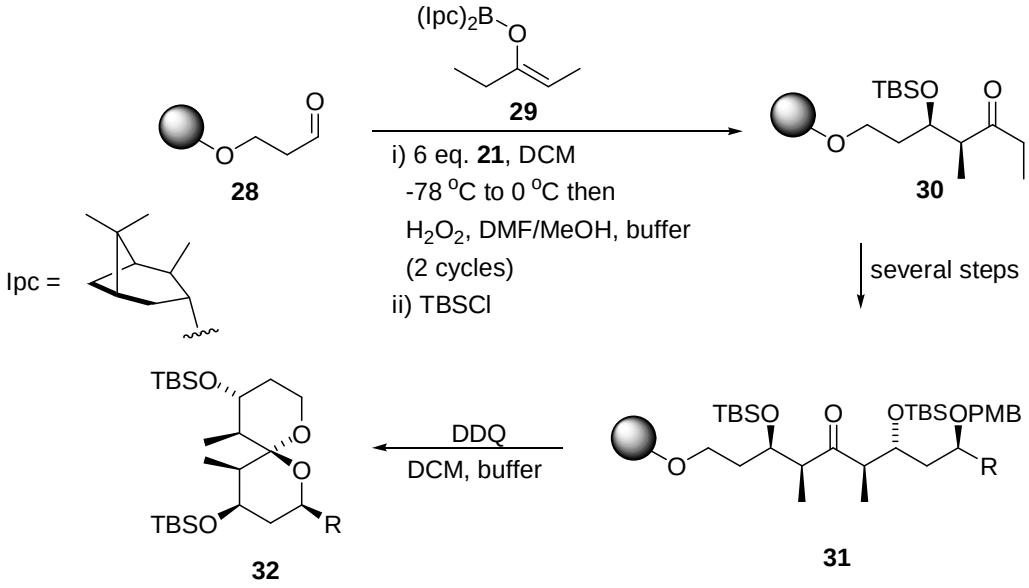
Scheme 1.8

1.9 Enantioselective Solid-Phase Synthesis

The production of stereodiverse libraries is essential for the production of selective drugs, and the complete understanding of complex biological systems. In particular, routes that allow access to a range of stereoisomers on the same scaffold are of interest.

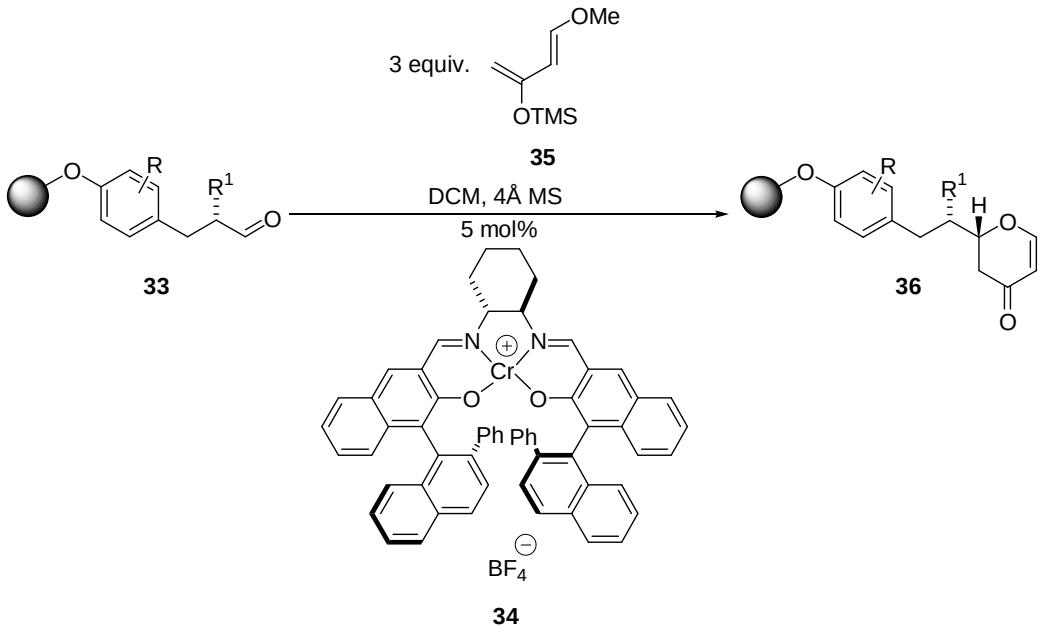
Enantioselective routes using solid phase techniques are still uncommon, but some very elegant work has been reported.[28]

The aldol reaction is a powerful tool in the stereoselective construction of carbon-carbon bonds. In the production of a library of spiroketals Waldmann and co-workers have used chiral boron enolates to perform this reaction on solid-supported aldehydes, [29] Scheme 1.9. An aldehyde linked to a polystyrene support *via* a Wang linker **28** was treated twice with the preformed boron enolate **29** to give the aldol adduct **30**. It is notable that the aldehyde must be treated twice with six equivalents of the enolate; a large excess of reagent is a common disadvantage of SPS. A further aldol reaction, followed by release and cyclization induced by cleavage of the *p*-alkoxybenzyl ether groups yielded the desired spiroketals **32** in good overall yield and high diastereoselectivity. The route proves that even demanding solution phase transformations can be used effectively in the SPS of libraries.



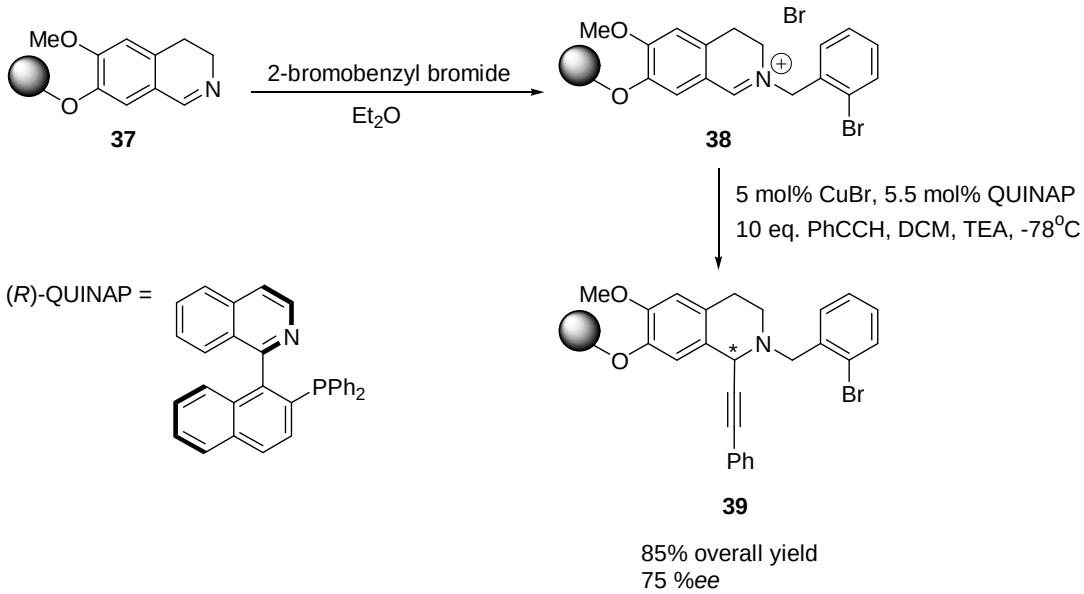
Scheme 1.9

Another powerful reaction in the production of non-racemic compounds is the Diels-Alder cycloaddition. More fine work by Waldmann demonstrated how this reaction can also be adapted to solid phase,[30] Scheme 1.10. Resin bound aldehydes **33** were treated with the Danishefsky diene **35** in the presence of the formidable chromium catalyst **34**. The cyclized product **36** could be released from resin to give the dihydropyranone in excellent enantiomeric excess (> 98% in some cases), or further functionalized via Michael addition to give a library of trisubstituted tetrahydropyranones also in good enantiomeric excess. It is notable that the high level of stereocontrol is achieved with only 5 mol% of catalyst.



Scheme 1.10

Schreiber and co-workers recently reported an enantioselective route to dihydroisoquinolines[31] using a ligand and metal system developed by Knochel,[32] Scheme 1.11. Resin-bound dihydroisoquinoline **37** was alkylated to give the imminium salt **38**. Phenyl acetylene was added to the imminium via Knochel's copper QUINAP system to give the chiral isoquinoline **39** in 84% yield and 75 % *ee*. Importantly, by using both enantiomers of QUINAP, separately, both enantiomeric series of isoquinolines could be accessed.



Scheme 1.11

1.9 Conclusion

By exploring broad swathes of chemical space, diversity orientated synthesis is proving to be an essential tool for the deciphering of biological systems. SPS is an excellent method to produce the large libraries necessary for DOS. With automation, a huge array of compounds can be made very quickly and with minimal human effort in the lab. It is important to capitalize upon these advantages, yet it is also important to respect human input. Human effort that is not necessary in the lab must be used in careful and intelligent planning and development. While producing a vast number of compounds means there are a lot of different samples to test, it does not necessarily mean that a broad range of chemical space is being investigated. For this reason a good SPS must allow for the introduction of a wide range of diversity. Furthermore, as biological systems are sensitive to the three dimensional shape and chirality of substrates, stereocontrol in the synthetic route is paramount. Several excellent examples have been discussed in this section, but the need for different, unique, stereodiverse solid phase routes is still great.

Chapter 2
Piperidines

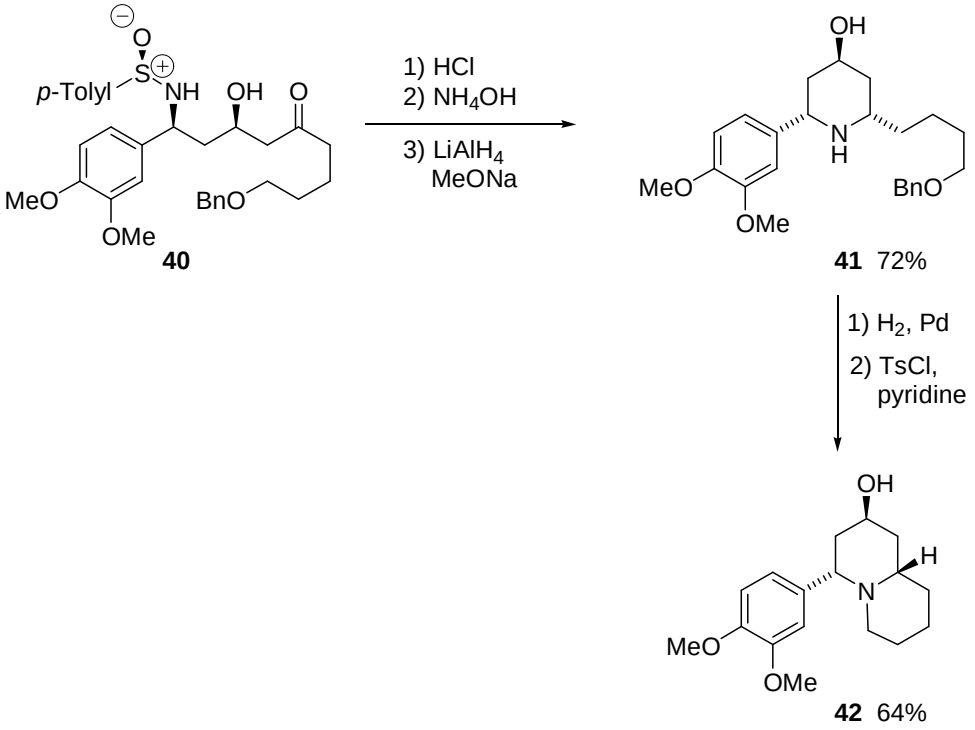
2.1 Introduction

The piperidine ring is a privileged structure,[33] exhibiting a range of biological activities. From the hemlock plant to the poison arrow frogs of South America piperidines are found in nature everywhere. Their interesting attributes as potential drugs have not been ignored; Watson and colleagues noted that over 12,000 discrete piperidine entities have been described in clinical or preclinical studies.[34] Clearly, there has been a lot of synthetic interest in this small heterocycle. Short, stereocontrolled routes are of particular interest, as three-dimensional control is imperative for the isolation of specific biological attributes.

Many different methods have been used to construct piperidines and these have been reviewed.[35] Popular strategies include reductive amination, intramolecular Michael addition, Mannich reaction, ring-closing metathesis, radical cyclization, Diels-Alder cycloaddition, and nucleophilic addition to pyridinium salts. Some recent examples and types of cyclization are discussed below, followed by a review of methods employed for the construction of piperidines on solid phase, or by post-cleavage modification.

2.2 Reductive Amination

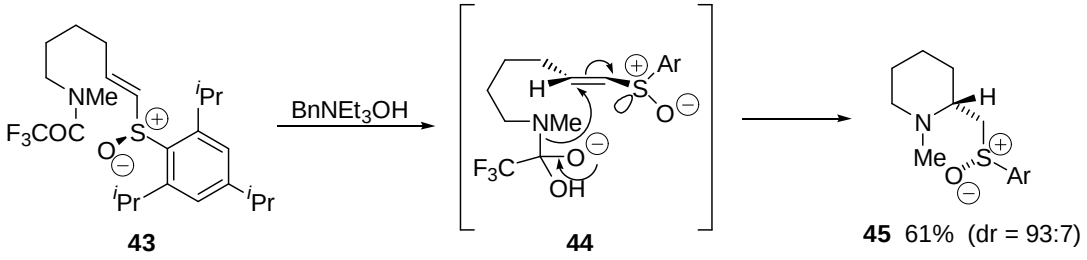
Davis and co-workers reported an elegant synthesis of lasubin II, a member of the Lythraceae family of natural products, isolated from one of the *Lagerstroemia* genus of shrubs.[36] The key reaction in the route is a reductive amination leading to the formation of a piperidine ring, Scheme 2.1. The sulfinyl group is removed from the *β*-amino alcohol **40** with HCl, neutralization causes cyclization to the imine, which is reduced with $LiAlH_4$ to give the piperidine **41** in 76% yield as a single diastereomer. Deprotection followed by tosylation causes another cyclization to give lasubin II **42**.



Scheme 2.1

2.3 Intramolecular Michael Addition

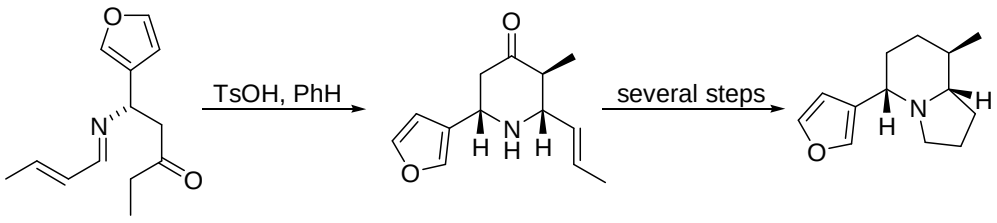
An earlier synthesis by Pyne and co-workers cyclizes vinyl sulfoxides, *via* Michael type addition, to give 2-substituted piperidines.[37] In one example, vinyl sulfoxide **43** cyclized to give predominantly piperidine **45** in good yield and excellent diastereoselectivity. Pyne proposes a likely mechanism for the transformation in which a hydroxide anion supplied by triethylbenzylammonium hydroxide attacks the carbonyl of vinyl sulfoxide **43** to give the anion **44** which would be stabilized by the electron withdrawing CF_3 group. The stereochemistry of the outcome can be explained by assuming that the anion **44** is positioned so that the electron lone pair on sulfur is *syn* coplanar with the C=C double bond, and thus the nitrogen would then attack from the opposite face to the large Ar group.



Scheme 2.2

2.4 Intramolecular Mannich Reaction

The nuphar alkaloids are a range of terpenoid alkaloids isolated from the *Nuphar* genus of aquatic plants. They exibit a range of interesting attributes such as anti-fungal, immunosuppressive, and anti-tumor activity. The core structure of the Nuphar alkaloids is a trisubstituted piperidine ring. Davis and co-workers used their intramolecular Mannich methodology to produce one of these alkaloids,[38] Scheme 2.3. The *β*-amino ketone **46** is cyclized by activation of the imine with tosic acid mono-hydrate in benzene to give the piperidine **47** in good yield as a single isomer which is taken through several more steps to give the nuphar alkaloid **48**.

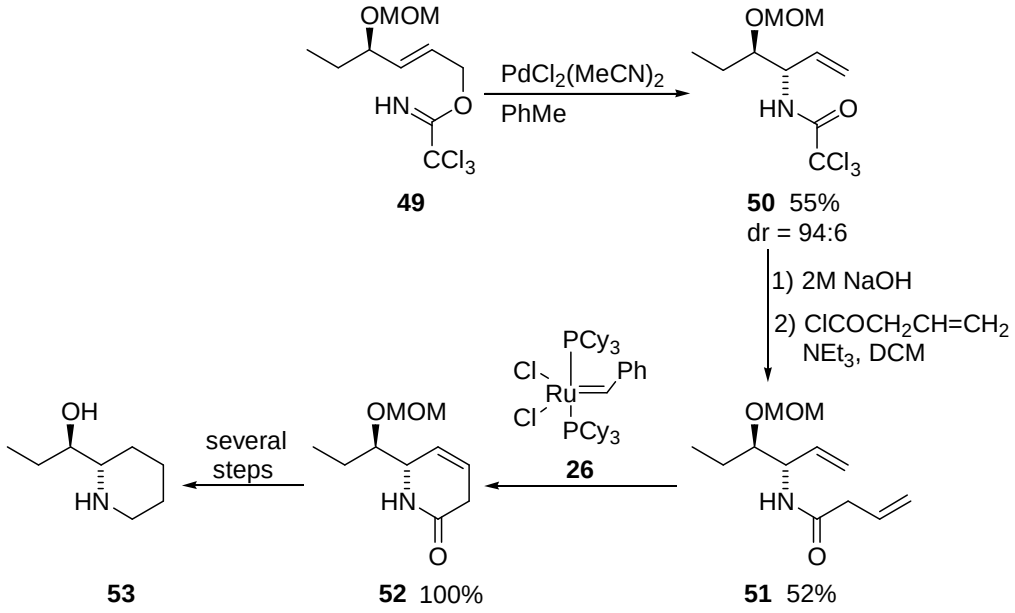


46 **47** 76% **48**

Scheme 2.3

2.5 Ring Closing Metathesis (RCM)

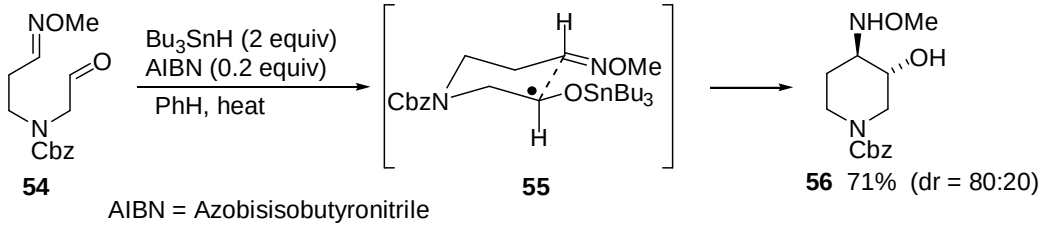
(+)-α-Conhydrine, first isolated from the seeds and leaves of *Cronium maculatum* L, is one member of the anti-viral and tumor-suppressant family of alkaloids containing the 2-(1-hydroxyalkyl) piperidine unit. Jamieson and Sutherland have used their ether-directed, stereoselective aza-Claisen rearrangement, followed by RCM, to produce this small alkaloid.[39] The trichloroacetimidate **49** underwent aza-Claisen rearrangent to provide the trichloroamide **50** in good yield and excellent diastereoselectivity. Hydrolysis of the trichloroacetate group followed by acylation gave the diene **51** which, when treated with Grubbs' 1st generation catalyst **26**, cyclized in quantitative yield to give the piperidinone **52**. Reduction of the double bond, followed by removal of the protecting group, and reduction of the lactam then gave (+)-α-conhydrine **53**.



Scheme 2.4

2.6 Radical Cyclization

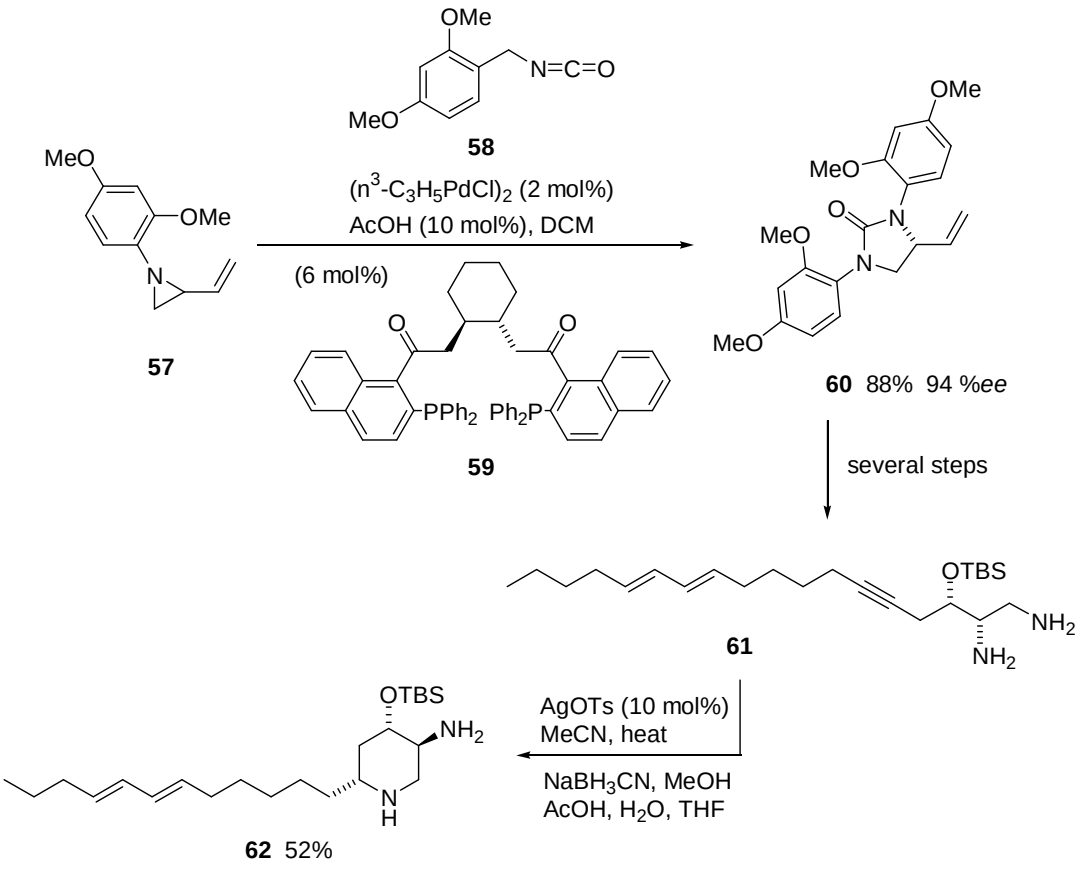
The pseudodistomins are a range of natural products whose scaffold contains a piperidine-based cyclic amino alcohol. These small alkaloids can be isolated from tunicates, also called sea squirts, such as the Ascidiacea. They exibit a range of interesting biological activities. Naito and co-workers saw the potential of a radical cyclization between the oxime ether and the aldehyde in carbamate **54** to produce the basic scaffold of a pseudodistomin type alkaloid,[40] Scheme 2.5. The major product is 3,4-*anti* piperidine **56**, which was isolated in good yield, and as an 80:20 mixture with the corresponding 3,4-*syn* compound. The proposed mechanism involves the the oxophilic stannyl radical attacking the carbonyl group of oxime **54** to make ketyl radical **55**. Naito suggests that the electronic repulsion between the oxime and the stannyloxy group lead to an *anti* configuration in the transition state **55**, and therefore predominantly the *anti* piperidine **56**. In addition, it is argued that the radical stabilizing influence of the oxygen atom in the oxime encourages 6-*exo*-*trig* cyclization, eliminating 7-*endo*-*trig* cyclization.



Scheme 2.5

2.7 Reductive Hydroamination

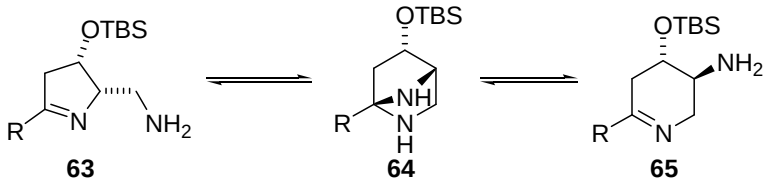
Pseudodistomin D is from the pseudodistomin family of natural products described earlier, and is found in the Okinowan sea squirt *pseudodistomina kanoko*. Along with calmodulin antagonistic activity, pseudodistomin D also exhibits potent cytotoxicity against murine leukemia, and human epidermoid carcinoma KB cells. Trost *et al*. used dynamic kinetic asymmetric cycloaddition of isocyanate **58** onto vinyl aziridine **57** to produce a chiral urea **60**, which was further manipulated to give diamine **61**,[41] Scheme 2.6. Silver tosylate induced reductive hydroamination of alkyne **61** to give the piperidine **62** in good yield as one diastereomer, and with no pyrrolidine side products. Simple deprotection of the TBS group gave pseudodistomin D.



Scheme 2.6

The lack of pyrrolidine side products and the perfect diastereoselectivity are of interest. Trost proposed that the silver ion coordinates to the alkyne causing cyclization, by the kinetically favored 5-*exo-dig* mode of cyclization to give the pyrrolidine **63**, which is in rapid equilibrium with piperidine **65** *via* bicycle **64**, Scheme 2.7. Sole formation of the

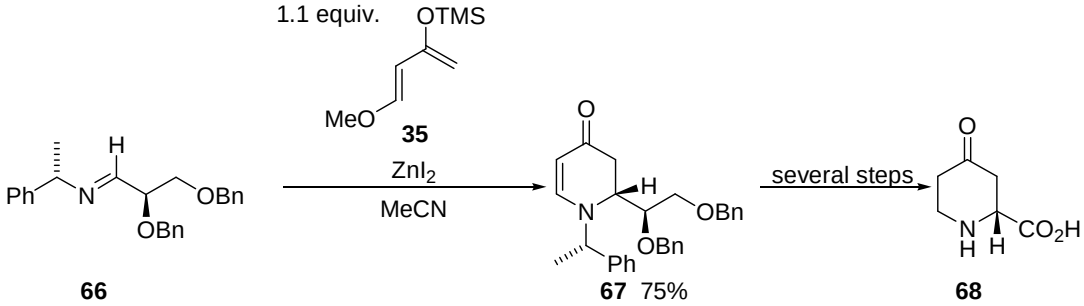
piperidine **62**, could arise because the equilibrium lies heavily to the side of **65** and hence **62** is formed by reduction of the dominant species. Another possible explanation is that due to the faster reduction rate of an sp^2 to an sp^3 carbon in a six-membered ring as compared to a five-membered ring[42] the imine **65** is preferentially reduced in the presence of imine **63**.



Scheme 2.7

2.8 Diels-Alder Cycloaddition

Pipecolic acid is a metabolite of lysine that is found in human physiological fluids, and appears to be involved in signaling in the central nervous system.[43] Diaz-de-Villegas and co-workers used an asymmetric Diels-Alder cycloaddition to form a precursor **67** to (*R*)-4-oxopipecolic acid **68**,[44] Scheme 2.8. Reaction of Danishefsky's diene **35**[45] with the chiral imine **66** in the presence of even a catalytic amount of Lewis acid gives the piperidinone **67** as a single diastereomer in good yield. However, the best results were obtained with stoichiometric amounts of zinc iodide.



Scheme 2.8

The stereoselectivity can be explained by the chelation of the zinc by the imine nitrogen atom and the oxygen atom of the closest benzyloxy group, Figure 2.1. The chiral protecting group rotates to minimize 1,3-allylic strain so that the non-coordinated *O*-benzyl group and the phenyl of the phenethyl group are matched in blocking the *si*-face. Thus, attack occurs solely from the *re*-face. When the other enantiomer of the phenethyl chiral protecting group is used, a mismatch occurs, and a mixture of diastereomers is formed.

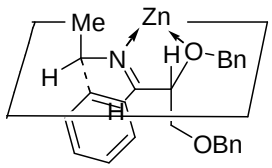
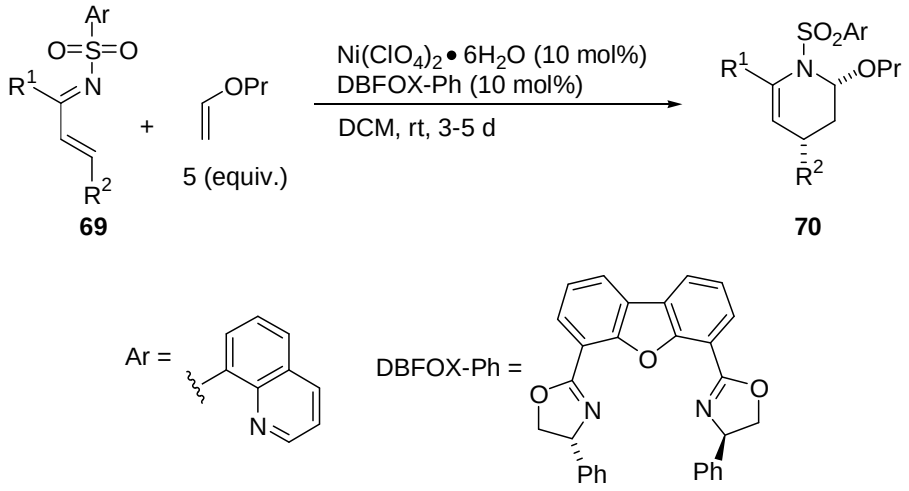


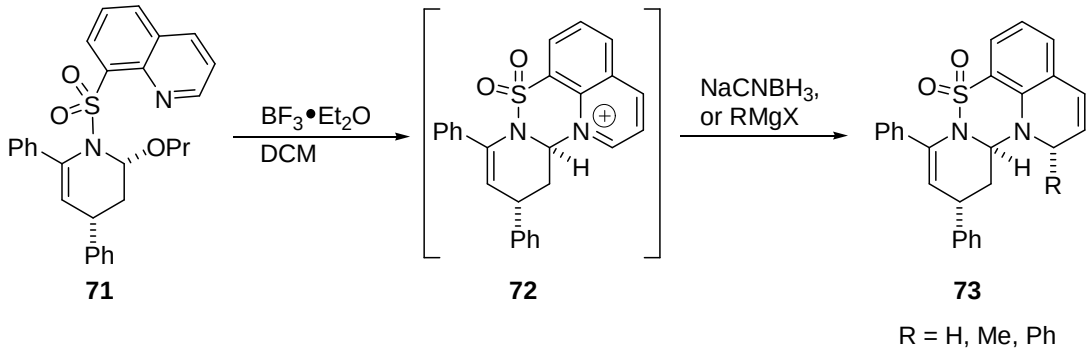
Figure 2.1

While the aza-Diels-Alder reaction has become a powerful tool in the formation of piperidines, the inverse-electron-demand Diels-Alder reaction of azadienes is far less common. However, recent work by Carretero and co-workers has highlighted just such a method.[46] Carretero used a Lewis acid and a chiral ligand to effect the cycloaddition of enol ethers, and *N*-tosylated chalcones, Scheme 2.9. The electron rich enol ether was added to the *N*-tosylimine **69** in the presence of a nickel catalyst and the chiral ligand DBFOX-Ph to give piperidine **70**. Reaction times were long, but yields were good, *endo* selectivity was excellent and enantiomeric excess ranged from 77-92%. A range of R^2 substituents was tolerated. However, substitution at the iminic carbon was limiting, with only electron-poor to electron neutral aryl groups working well, giving good yields and enantiomeric excesses between 90 and 92%.



Scheme 2.9

The resultant piperidines can then be cyclized further *via* nucleophilic displacement of the Lewis-acid-coordinated alkoxy group from hemiaminal **71** to give benzothiadiazine derivatives **73** after reduction or alkylation of intermediate quinolinium ion **72**, Scheme 2.10. Asymmetric routes to benzothiadiazines are of interest as these alkaloids have shown potential in the treatment of learning and memory disorders, and neurodegenerative disease.



Scheme 2.10

2.9 Nucleophilic Addition to Pyridinium Salts

Palinavir **74** is a potent HIV protease inhibitor with a piperidine core,[47] Figure 2.2.

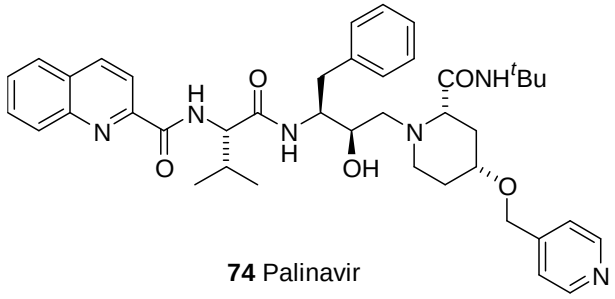
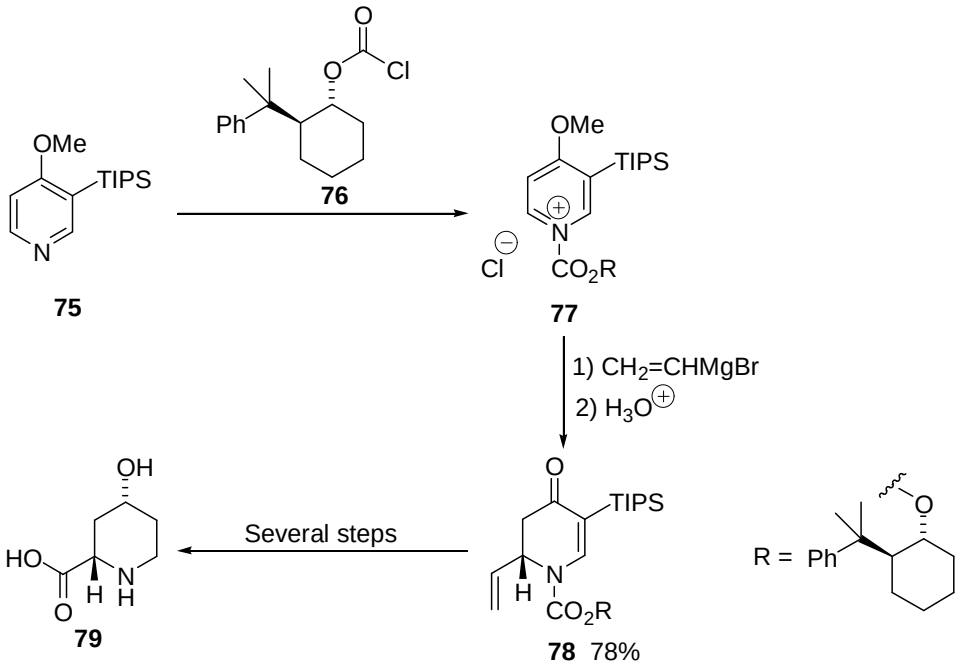


Figure 2.2

A key intermediate in the synthesis of palinavir is the piperidine (*2S,4R*)-4-hydroxypipecolic acid **79**. Brooks and Comins used a strategy involving the nucleophilic addition to a pyridinium salt to synthesize this key intermediate,[48] Scheme 2.11. Reaction of the disubstituted pyridine **75** with the chloroformate **76** gave the pyridinium salt **77**. Addition of vinylmagnesium bromide, followed by hydrolysis yielded the piperidinone **78** with a dr of 93:7. Recrystallization gave diastereomerically pure piperidinone **78** in a 78% yield. This was then converted into (*2S,4R*)-4-hydroxypipecolic acid **79** in several steps.

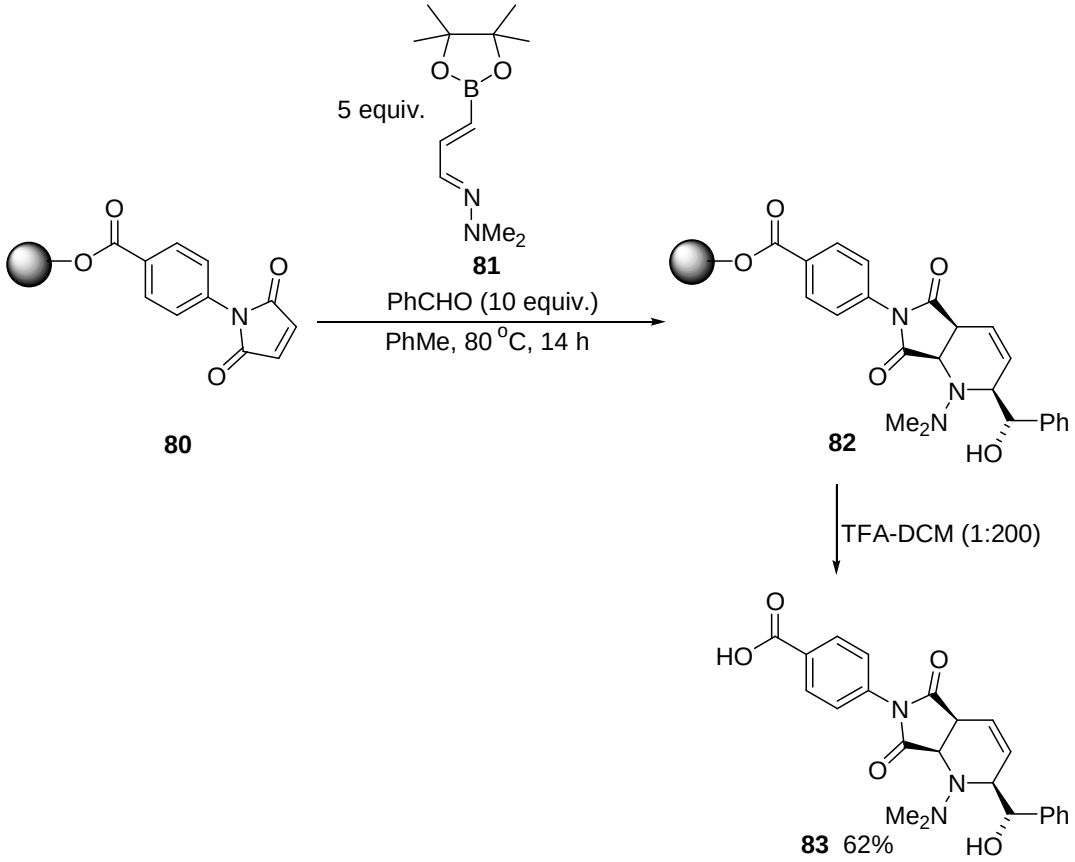


Scheme 2.11

2.10 Solid-Phase Synthesis of Piperidines

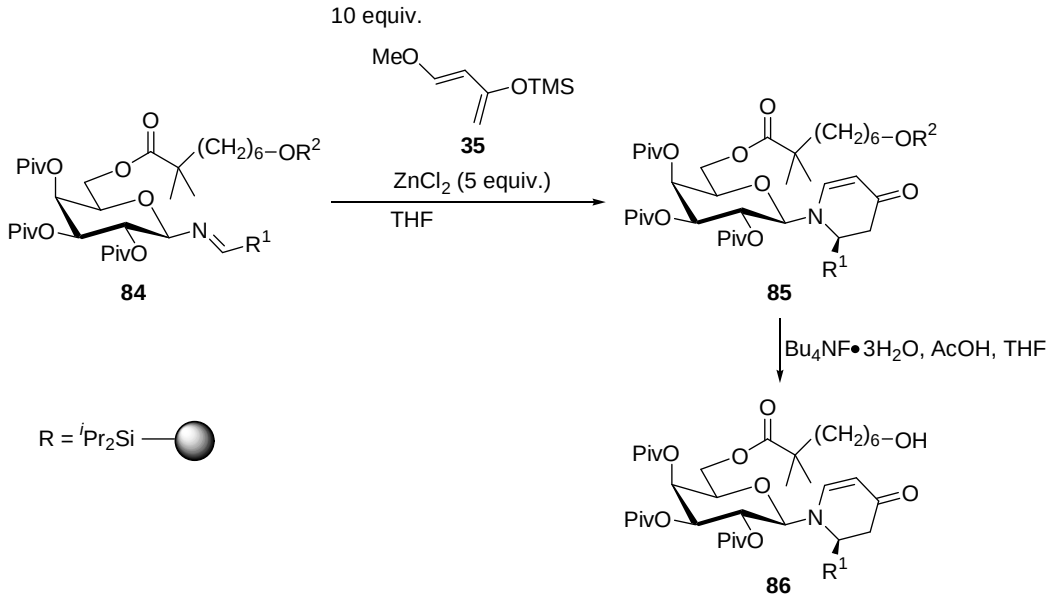
There are many different ways to make piperidines, each with their own advantages and disadvantages. However, only a select few of these methods have been adapted to solid-phase synthesis. Many solid-phase methods start with the piperidine already intact and then functionalize the piperidine. A synthetic pathway that builds the piperidine core on resin is very rare. Several methods involve the use of a Diels-Alder cycloaddition using a solid-supported reactant, but barring one other example these are the only literature methods.

Elegant work by Hall and co-workers took advantage of a novel tandem Diels-Alder cycloaddition/allylboration, to produce diverse piperidine analogues,[49] Scheme 2.12. SASRIN linked maleimides **80** were treated with diene **81**, and benzaldehyde to give the resin-bound piperidine **82**. A reaction temperature of 80 ^{o}C, and a ratio of 1:5:10 maleimide **80**/diene **81**/aldehyde was needed for the reaction to go to completion within a reasonable time, as is common with aza-diene cycloadditions. However, the reaction proceded with 100% *endo* selectivity, and release from resin with TFA-DCM (1:200) gave the piperidine **83** in good yield. While this solid phase sequence has not been broadly tested, the solution-phase analogue has been thoroughly investigated and tolerates a wide range of dienes and aldehydes.



Scheme 2.12

In the only solid-phase asymmetric synthesis of piperidines, Zech and Kunz employed a more conventional aza-Diels-Alder reaction whereby a resin-bound aza sugar, acting as a chiral auxiliary, was converted to an imine. Cycloadditon with Daneshefsky's diene **35** afforded various asymmetric piperidine analogues,[50] Scheme 2.13. Resin-bound imine **84** was treated with $ZnCl_2$, and Daneshefsky's diene **35** to yield the resin-bound piperidine **85**. This was then cleaved with tetrabutylammonium fluoride, and acetic acid in THF to give the piperidine **86**, in good yield and typically good to excellent diastereoselectivity. While the auxiliary was not removed, there is a literature procedure for its cleavage.[51] Alternatively, the resin-bound piperidine **85** could be alkylated by addition of an alkyl cuprate to give a resin-bound 2,4-disubstituted piperidinone.



Scheme 2.13

Another method developed by Rutjes, Hiemstra and co-workers relies on an acid catalyzed cyclization of a carbamate and an acetal,[52] Scheme 2.14. The resin bound carbamate **87** was treated with catalytic *p*-toluenesulfonic acid for 30 min to induce cyclization, which was followed by reaction with 1*H*-benzotriazole to give stable resin-bound piperidine **88**. Removal of the benzotriazole group with $BF_3{\cdot}OEt_2$ followed by attack with a nucleophile, and removal from resin with NaOMe, gave the piperidines **89**. Yields were typically good, though some R groups and nucleophiles gave poor results. The piperidines were produced as the 2,4-*anti* diastereomers.

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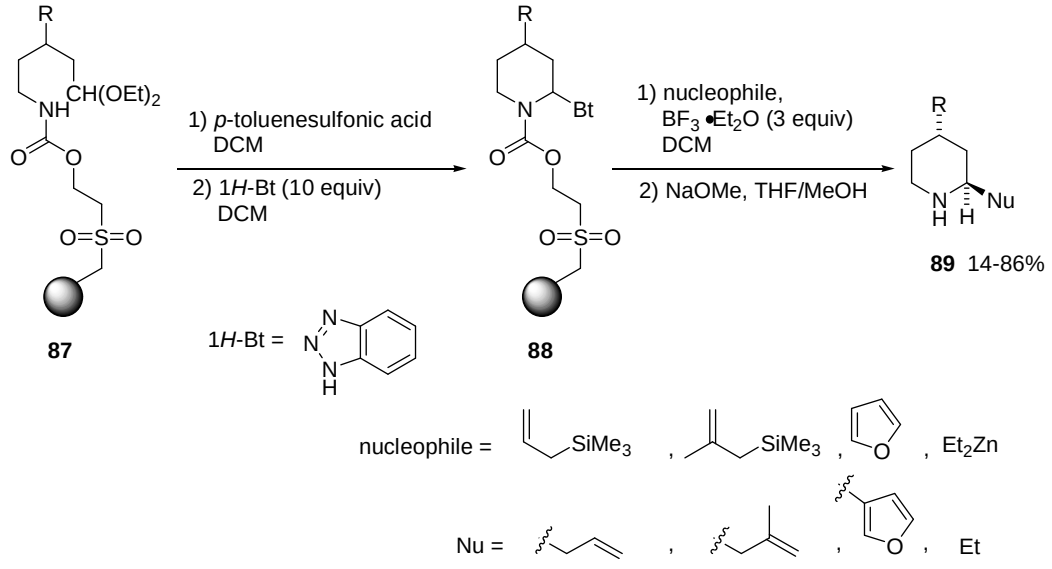


Scheme 2.14

2.11 Conclusion

Even simple piperidines show excellent biological activity, and the core structure is often seen in more complex systems. New synthetic routes to such a privileged structure are always welcome, especially when new stereogenic centers are introduced in a controlled way. Every method has its advantages and weaknesses, so each particular target will benefit from a particular method, thus the more routes available to the synthetic chemist, the better. With industrial demand for stereoselectivity, diversity, and pure amounts of compounds never higher, solid-phase stereodiverse routes to piperidines are attractive. Such methods would allow the production of large libraries of specific compounds, all distinctly different from each other.

Chapter 3
Alkenation reactions

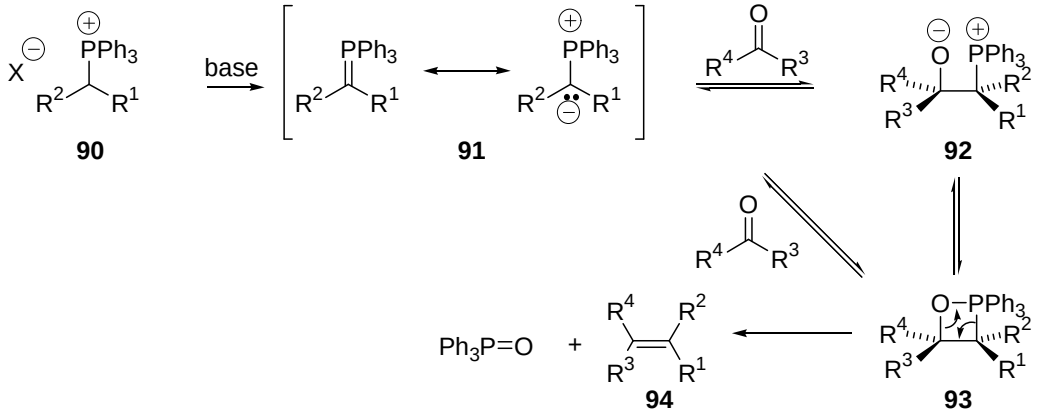
3.1 Introduction

Alkenation reactions or transformations that produce carbon-carbon double bonds are of paramount importance in organic synthesis. Not only do these reactions bring two carbons together, but due to the reactive nature of carbon-carbon double bonds further transformations are possible. Indeed the 1979 Nobel Prize was awarded to George Wittig (shared with H. C. Brown) largely due to his development of the Wittig alkenation. The most commonly used alkenation reactions are the Wittig, the Horner-Wadsworth-Emmons, and the Peterson reactions, although Julia and modified Julia reactions are becoming more popular. However, there are several titanium promoted alkenation reactions, including the Takeda and Petasis reactions that have special attributes, giving them a niche in the synthetic world.

3.2 The Wittig Reaction

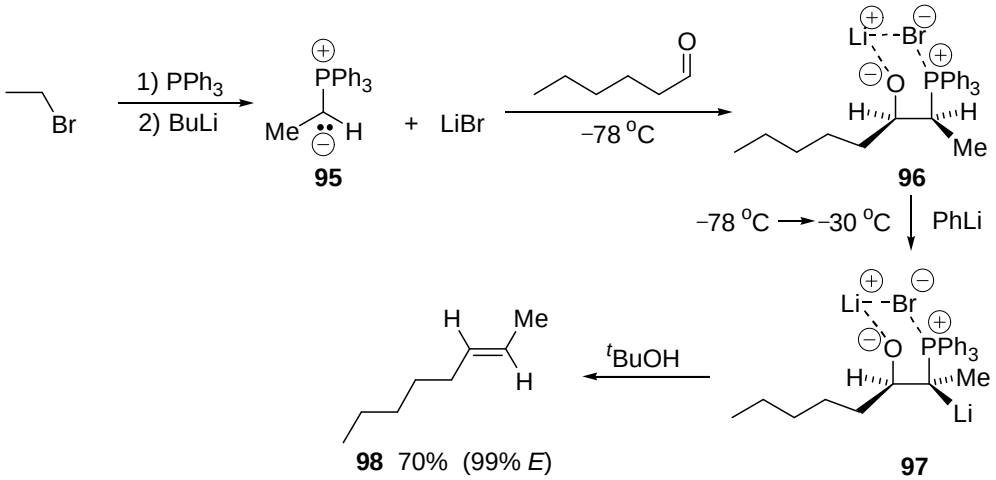
The Witttig alkenation[53,54] is particularly attractive as it requires only mild conditions, and no ambiguity exists as to the location of the double bond being formed. Before Wittig chemistry double bond formation from a carbonyl substrate was achieved through nucleophilic attack followed by elimination; rearrangement sometimes occurred and the position of the double bond formed was sometimes difficult to predict and control.

In the Wittig reaction a phosphonium salt **90** formed from the addition of PPh_3 to an alkyl halide is deprotonated with a base, usually an alkyllithium or phenyllithium, to give the resonance stabilized ylide **91**. It is thought that the ylide reacts with aldehydes or ketones to give the oxaphosphetane **93,** possibly via the betaine **92**. However, evidence for the betaine is scarce. Once the oxaphosphetane is produced, fragmentation occurs and the alkene **94** is produced together with an equivalent of triphenylphosphine oxide. The immense strength of the phosphorus oxygen double bond is the driving force of the reaction.



Scheme 3.1

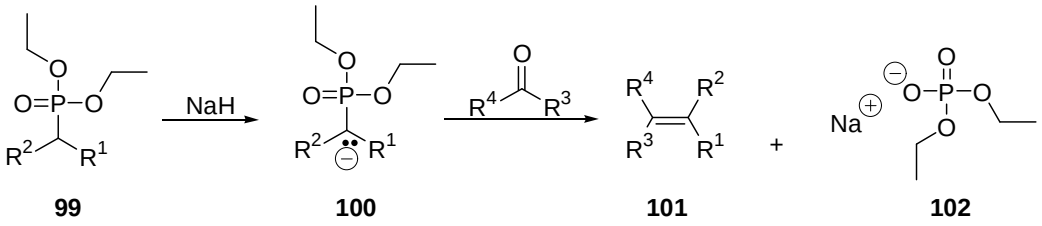
There are generally two different kinds of ylide. A stabilized ylide is produced when either R^1 or R^2 contains an electron-withdrawing group on the α-carbon atom. When such a group exists the formation of the oxaphosphetane is reversible and the thermodynamic product (the *E* isomer) is formed. If the R groups on the ylide are, instead, electron-donating, then the oxaphosphetane formation is not reversible, and the kinetic product (the *Z* isomer) is formed. The use of a lithium base slows down the elimination of triphenylphosphine oxide and therefore reduces the *Z* selectivity of the Wittig reaction when a non-stabalized ylide is used. In fact, using the Wittig-Schlosser reaction it is possible to obtain near perfect *E* selectivity,[55] Scheme 3.2. When bromoethane is treated with PPh_3 and BuLi the ylide **95** is produced together with one equivalent of LiBr. If the aldehyde is added at -78 ^oC, the LiBr slows the elimination of triphenylphosphine oxide. When the temperature is raised in the presence of PhLi the configuration of the *pseudo*-phosphetane switches to *trans*. Protonation of the *pseudo*-phosphetane with ^{t}BuOH yields the alkene **98** with 99% selectivity for the *E* geometry.



Scheme 3.2

3.3 Horner-Wadsworth-Emmons (HWE) Reaction

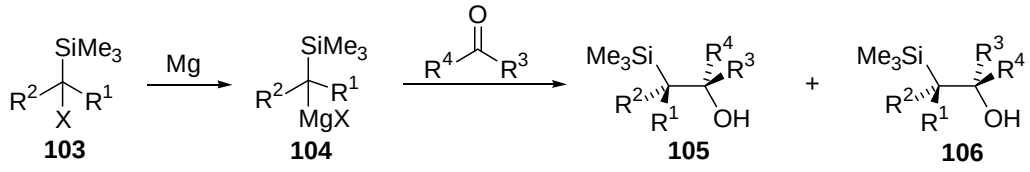
The HWE reaction[56] is a widely used variation of the Wittig reaction. A phosphonate ester **99** is used instead of a triphenylphosphonium salt. The reaction only works when either R^1, or R^2 is an electron-withdrawing group. The carbanion **100** is produced by the deprotonation of the phosphonate ester **99** with a base, Scheme 3.3; NaH is shown here but other strong bases also work. Reaction of the carbanion with an aldehyde or ketone gives the alkene **101,** *via* a mechanism similar to the Wittig reaction, and produces a water-soluble by-product **102**. The alkene is typically produced in good yield as the *E* isomer. Due to the increased reactivity of the carbanion, the method can be used to alkenate hindered ketones that would not undergo the Wittig alkenation.



Scheme 3.3

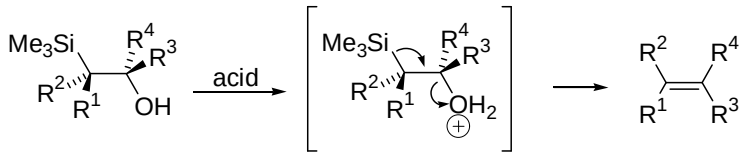
3.4 Peterson Alkenation

In what could be considered as the silicon version of the Wittig reaction, the Peterson alkenation[57] uses an α-silyl carbanion **104** to attack an aldehyde or ketone to give a mixture of diastereomeric β-hydroxyalkyltrimethylsilanes **105**, and **106**, Scheme 3.4. A Grignard type nucleophile **104** is shown but the α-silyl carbanion can take other forms as well. Each β-hydroxyalkyltrimethylsilane **105** or **106** then eliminates in a stereospecific manner dependant on acidic or basic conditions to give the alkene as either the *Z* or *E* geometric isomer.



Scheme 3.4

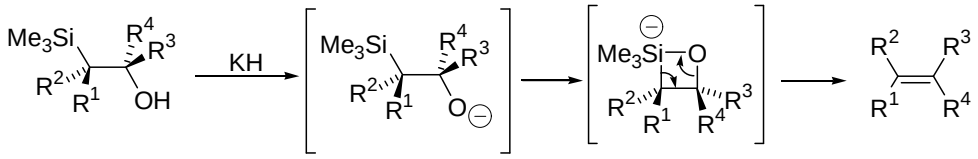
When acidic conditions are used on β-hydroxysilane **105** *anti*-elimination takes place *via* protonated intermediate **107** to give the alkene **108**, Scheme 3.5.



105 **107** **108**

Scheme 3.5

On the other hand basic conditions convert β-hydroxysilane **105** into an oxyanion **109**, which following 180° rotation around the carbon-carbon bond, forms oxasilacyclobutane **110**. Now *syn*-elimination of the oxasilacyclobutane **110** gives the other geometric isomer, alkene **111**.



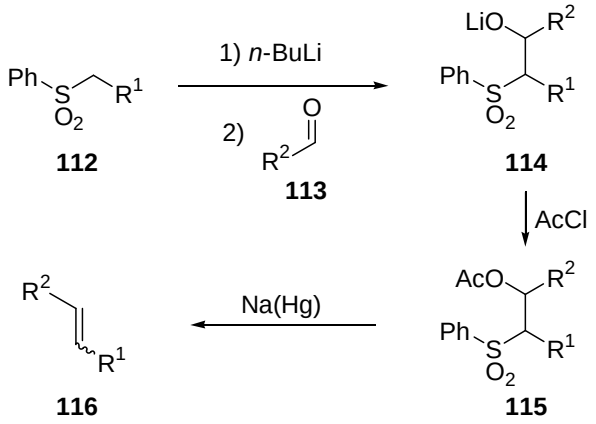
105 **109** **110** **111**

Scheme 3.6

The Peterson reaction can be used with very hindered ketones, when the Wittig reaction does not work. It has the advantage that only one geometric isomer is produced from each β-hydroxysilane, but unfortunately suffers from poor stereocontrol in the synthesis of the β-hydroxysilanes **105** and **106**.

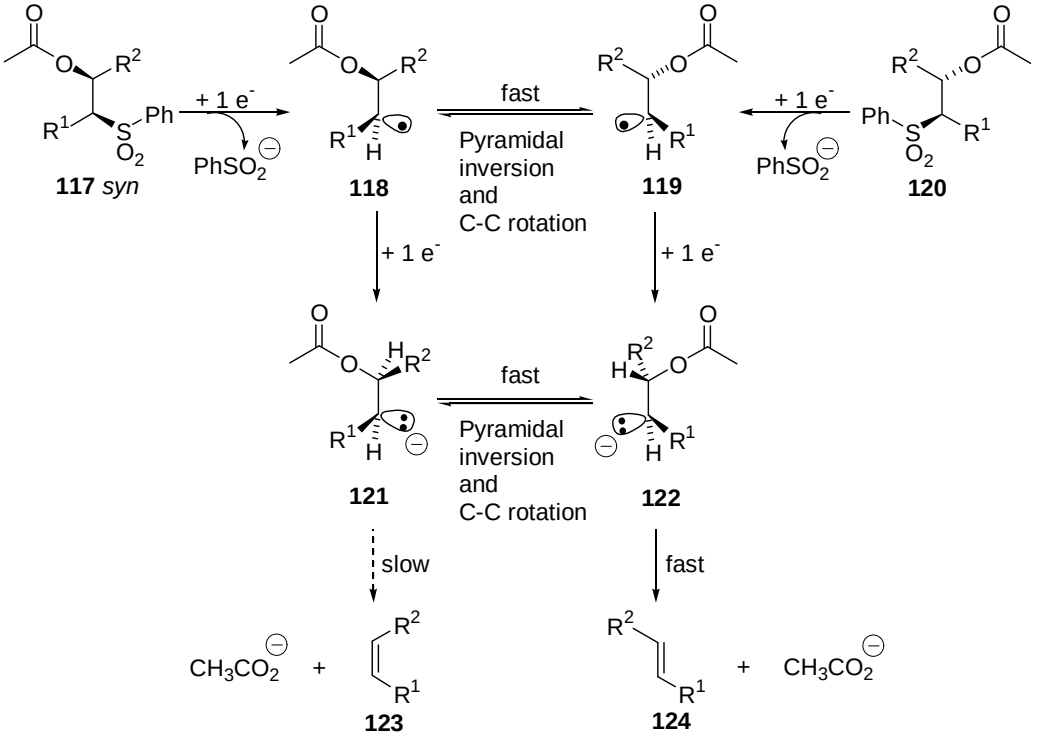
3.5 Julia Alkenation

The original Julia alkenation was developed in 1973 by Marc Julia and Jean-Marc Paris,[58] Scheme 3.7. The phenylsulfone **112** is metalated, after which addition to an aldehyde **113** affords the β-alkoxysulfone **114**. Acylation of **114** to give the β-acyloxysulfone provides a good leaving group, facilitating single-electron-donor-induced reductive elimination to give the alkene **116**. Typically the method gives high *E* selectivity. The reaction is difficult to perform, requiring 4 distinct steps. However, it has found frequent use in important synthetic schemes.



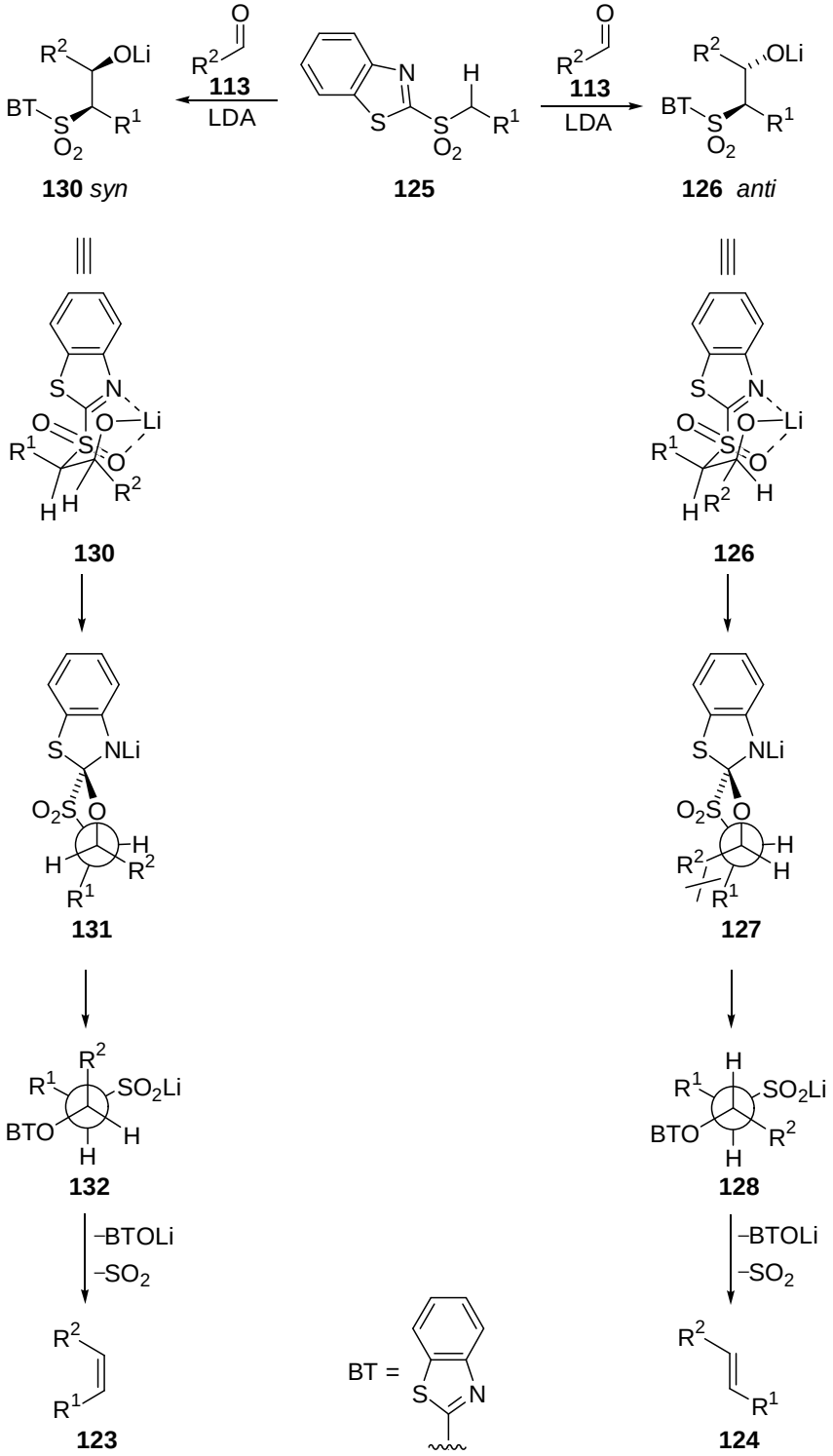
Scheme 3.7

Kocienski *et al.* showed that the reaction is stereoselective rather than stereospecific, Scheme 3.8.[59] The *E*-geometrical isomer **124** predominates regardless of which diastereomeric sulfone **117** or **120** is used, and the *E*:*Z* ratio depends on the bulk of R^1 and R^2. This is because the radicals **118** and **119**, formed by single electron transfer and loss of sulfinate, can very rapidly interconvert by pyramidal inversion. The carbanions **121** and **122** can also interconvert in this way. Presumably the rate determining step is elimination of the acylate anion and involves a product like transition-state so that steric interactions between R^1 and R^2 disfavour the formation of the *Z* geometric isomer **123**.



Scheme 3.8

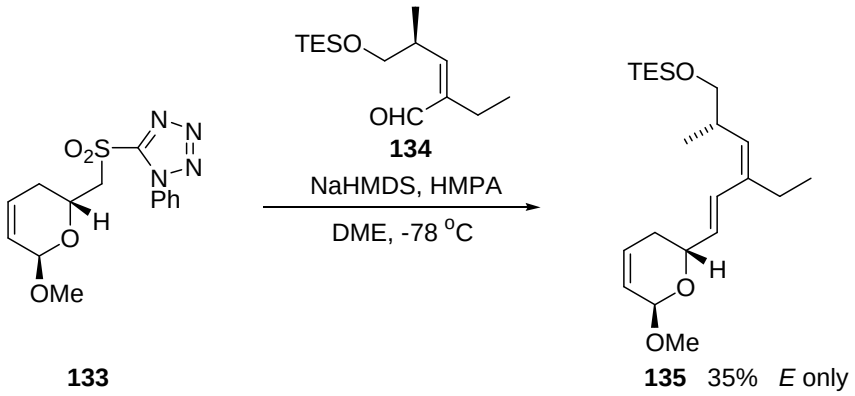
In an attempt to address the synthetic difficulties of the classical Julia alkenation, a one pot method called the modified Julia alkenation has been developed, Scheme 3.9. This method has been extensively reviewed by Blakemore.[60] Instead of a phenylsulfone **112** the modified Julia alkenation uses a heterocyclic sulfone, usually a 1-phenyl-1H-tetrazol-5-yl, or benzothiazol-2-yl sulfone **125**. The β-alkoxysulfone, **126,** or **130**, forms as before, but now there is no need for acylation as the heterocylic group is transferred via a Smiles rearrangement to the β-oxygen giving sulfinate **128** or **132**. Spontaneous elimination of sulfur dioxide and lithium benzothiazole gives the alkene **123** or **124**. While the reaction is easier to perform, stereocontrol suffers. The *anti* diastereomer **126** yields the *E* isomer **124** and the *syn* diastereomer **130** yields the Z isomer **123**. In some cases it would seem that the *syn* and *anti* diastereomers **126** and **130** can interconvert via retroaddition-addition, and so stereochemistry is not always set by the formation of the alkoxy sulfone. When unbranched aliphatic aldehydes are used the *Z* isomer is produced in moderate excess. This is possibly because during the Smiles rearrangement the *E* pathway requires the spirocylic intermediate **127** to take an eclipsed-gauche arrangement of R^1 and R^2. The spirocyclic *Z* precursor **131** does not suffer this problem. However the sulfinate salt **132** must adopt an eclipsed gauche configuration of R^1 and R^2 in order to place the eliminating groups in the antiperiplanar arrangement necessary for elimination, and this possibly hinders the formation of the Z isomer **123**.



Scheme 3.9

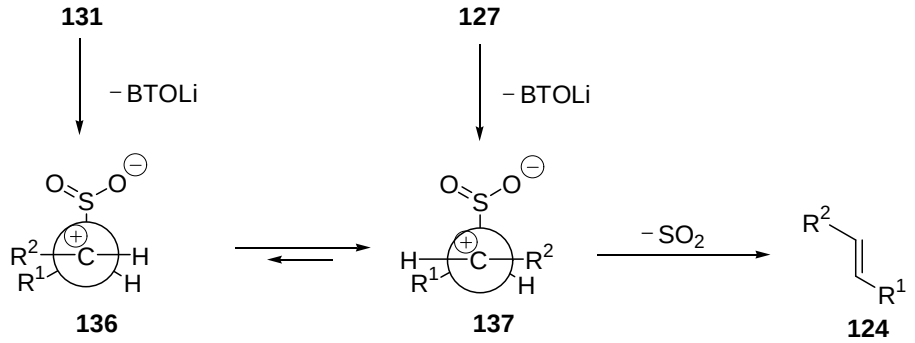
When α,β-unsaturated aldehydes, including aryl aldehydes, are used stereoselectivity improves dramatically. Smith and co-workers used a modified Julia alkenation in their total synthesis of the potent cytotoxic agent (–)-callystatin A,[61] Scheme 3.10. When sulfone **133** was metalated with NaHMDS and HMPA, the α,β-unsaturated aldehyde **134** could be added

to give the desired alkene **135** in poor yield but excellent stereoselectivity. The poor yield was a result of β-elimination of the sulfone.



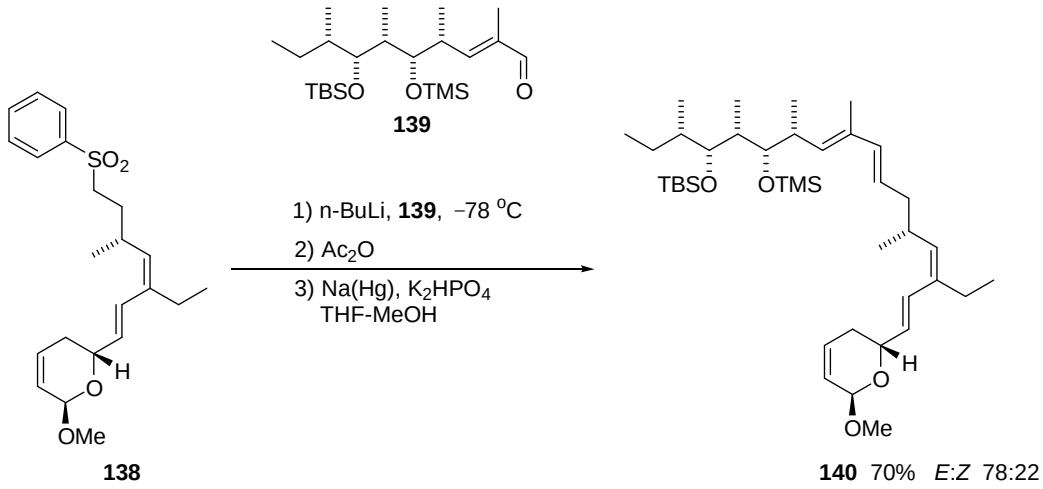
Scheme 3.10

Julia and co-workers propose that this increased stereoselectivity results from the loss of the BTOLi group from the spirocyclic precursors **127** and **131** before elimination can occur,[62] Scheme 3.11. Should this happen the zwitterionic conformers **136** and **137** would be produced. Fast equilibrium to the more stable **137** would precede loss of SO_2 to give the *E* alkene **124**. The α,β-unsaturation of R^2 helps to stabilize the positive charge thereby allowing the carbocation to be formed.



Scheme 3.11

Later in the total synthesis of (–)-callystatin A, Smith and co-workers used a conventional Julia alkenation to complete the scaffold of the target molecule,[61] Scheme 3.12. Metalation of the sulfone **138** followed by addition of the aldehyde **139**, acylation, and reductive elimination gave the desired alkene **140** in high yield and good stereoselectivity. As is demonstrated by this total synthesis, the classical and modified Julia alkenation complement each other well to give the synthetic chemist a very useful tool in the construction of alkenes.



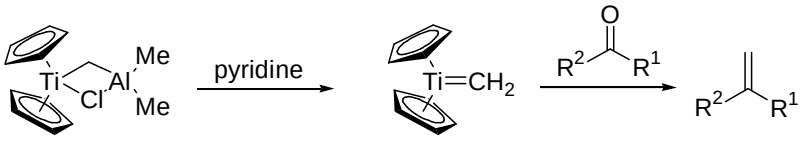
Scheme 3.12

3.5 Titanium Alkylidenes

While the Wittig-type reactions are extremely powerful and general tools in organic synthesis they suffer in cases when the carbonyl contains an acidic α-hydrogen atom, as the Wittig-type alkenations typically require strong bases. Wittig-type reactions have been known to cause epimerization of α-protons through enolate formation and even epimerize β-protons *via* retro-Michael addition. Furthermore the alkenation of carboxylic acid derivatives such as amides and esters generally is not possible using any of the above methods. To overcome these problems a range of titanium carbenoid reagents have been developed. These reagents are non basic so they do not deprotonate acidic α-protons or cause retro-Michael additions. They are also small and reactive and will, therefore, react with even hindered ketones. Most importantly they can alkylidenate carboxylic acid derivatives such as esters, and amides. These reagents and their use have been comprehensively reviewed recently,[63] but their key features will be summarized briefly.

3.6 Tebbe Methylenation

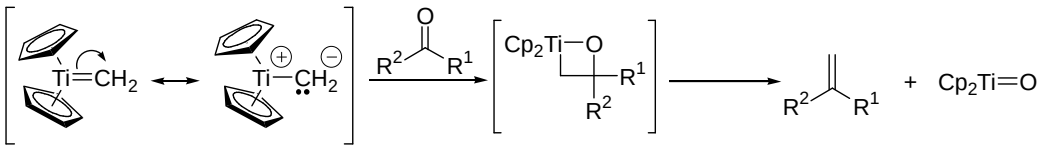
The Tebbe reagent[64] is the titanium aluminium complex **141** formed from the reaction of Cp_2TiCl_2, and $AlMe_3$ in toluene.[65] The reagent is very sensitive to air and moisture, but is nonetheless available commercially as a toluene solution. The Tebbe reagent reacts in the presence of a Lewis base, like pyridine, to give titanocene methylidene **142**, which can methylenate aldehydes, ketones, and a range of carboxylic and carbonic acid derivatives like esters, and amides, Scheme 3.13.



141 **142** **143**

Scheme 3.13

Titanocene methylidene **142** is formed *via* the base-induced elimination of $AlClMe_2$ from titanocycle **141**. This reactive species acts as a Schrock carbene; an electron deficient 16 electron titanium complex in a high oxidation state, nucleophilic at carbon and electrophilic at titanium, Scheme 3.14. The nucleophilic reagent reacts with carbonyl groups to give the alkene **143** and an equivalent of $Cp_2Ti{=}O$, *via* the decomposition of oxatitanacyclobutane **144** in a manner similar to the phosphetane in the Wittig reaction. The formation of the very strong titanium-oxygen bond gives the reaction a strong driving force.



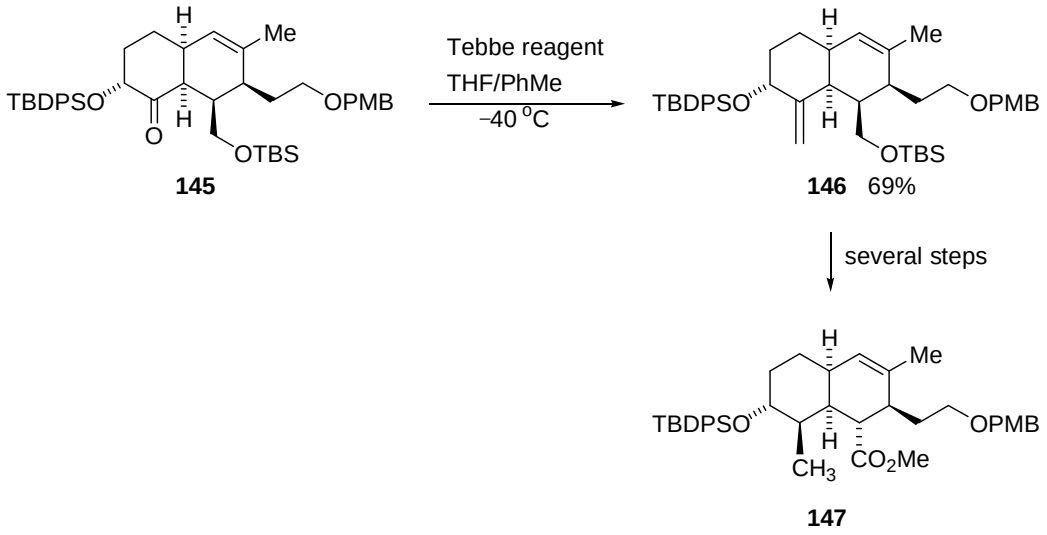
142 **144** **143**

Scheme 3.14

The main advantage of the Tebbe reagent over Wittig-like reagents is that it methylenates esters, amides, thioesters, and carbonates. The reactivity of the reagent depends on the electronics of the substrate, and therefore, due to nucleophilic nature of the Shrock carbene, the Tebbe reagent will methylenate more electrophilic carbonyls preferentially. This means that aldehydes and ketones will be methylenated in the presence of esters and amides. While the use of a Lewis base is necessary to start the reaction, only a mild Lewis base is required, and thus base sensitive groups are tolerated in the reaction. Furthermore the reaction does not require heating. Unfortunately, the reaction is limited to methylenation and due to the instability of the reagent the procedure can sometimes be tricky.

Roush and co-workers have used the Tebbe Reagent in their synthesis of the bicyclic core of HIV-1 integrase inhibitor integramycin,[66] Scheme 3.15. The *cis* fused decalin **145**, obtained from a highly stereoselective intra-molecular Diels-Alder cycloaddition, was methylenated with the Tebbe reagent at low temperature to give the desired diene **146** in 69% yield. Several transformations later and the bicyclic core of integramycin was produced. It is important to note that, despite the acid-sensitive protons α to the carbonyl, no

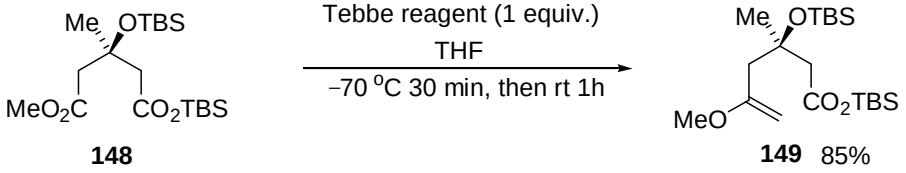
epimerization of the chiral centers occurred. This can be attributed to the mild non-basic conditions of the Tebbe methylenation.



145 **146** 69% **147**

Scheme 3.15

While electronics are the main factor in determining the reactivity of a substrate towards Tebbe methylenation, sterics also play a role. In cases where two carbonyl groups have similar electronic properties sterics will determine the regioselectivity of the reaction. Work by Steglich and co-workers demonstrates the methylenation of a methyl ester in the presence of a bulky silyl ester,[67] Scheme 3.16. Using one equivalent of Tebbe reagent and low temperature the diester **148** was selectively methylenated to provide the enol ether **149** in very good yield.



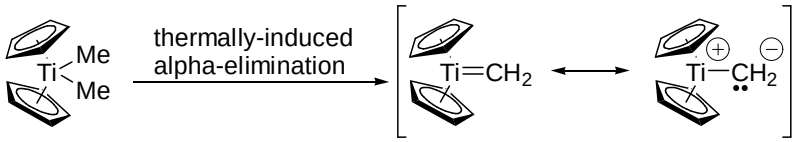
148 **149** 85%

Scheme 3.16

3.7 Petasis Reagents

The simplest Petasis reagent is dimethyltitanocene **150**.[68] It is relatively air and moisture tolerant and can be stored as a solution in a mixture of toluene and THF at low temperature for months. The reagent can be produced by the method of Payack *et al.* by the reaction of methylmagnesium chloride with titanocene dichloride;[69] this can be done on a kilogram scale.[70] Dimethyltitanocene **150** will undergo α-elimination under thermal or

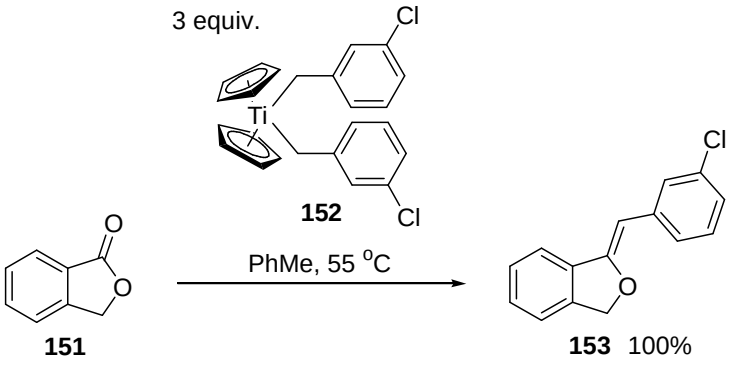
microwave conditions, Section 7.6,[71,72] to give the same Schrock carbene **142**, as is produced by the Tebbe reagent, Scheme 3.17. Meurer and co-workers have investigated the reaction mechanism for the Petasis reaction by using atmospheric pressure chemical ionization mass spectrometry to find the signals corresponding to the oxatitanocyclobutane **144**, and the products of its dissociation, which eventually lead to the desired alkene and titanocene oxide.[73]



150 **142**

Scheme 3.17

Unlike the Tebbe reagent, the Petasis reagent is not limited to methylenation. Work by Petasis and Bzowej demonstrated the use of functionalized Petasis reagents.[74] When bis(benzylic)titanocenes were heated in the presence of esters in toluene the corresponding enol ethers were produced. The particular example shown, Scheme 3.18, produced only the *Z* isomer in quantitative yield. Typically yields and *Z* to *E* selectivity were moderate to good. Unfortunately, the range of possible functionalized Petasis reagents is not broad. Only reagents that cannot undergo a fast β-elimination are effective. Otherwise this undesired β-elimination out competes the desired α-elimination, and the Schrock carbene is never generated.

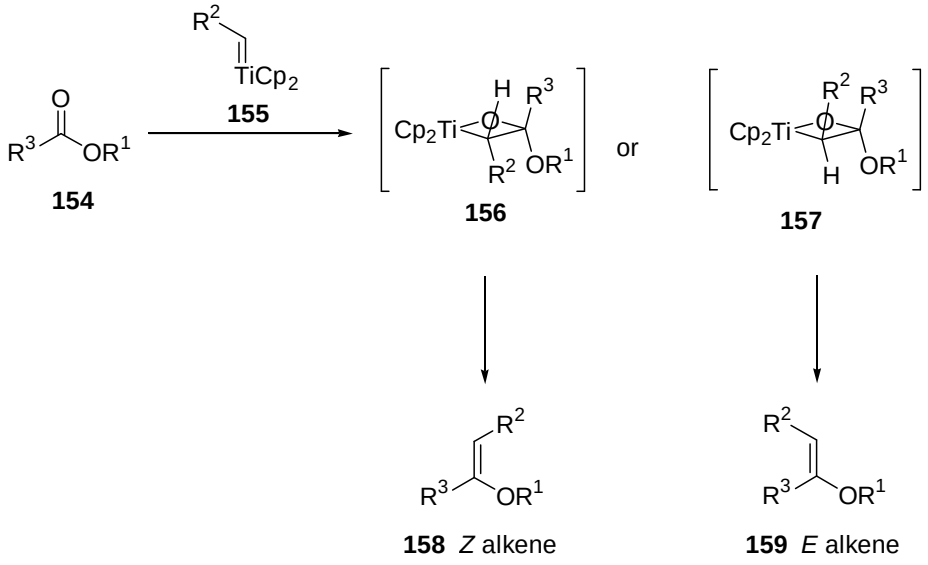


151 **152** **153** 100%

Scheme 3.18

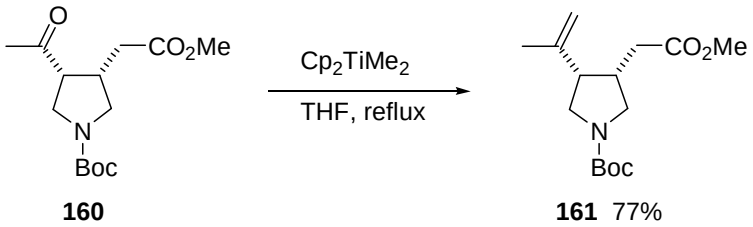
The favored geometry of the alkene can be explained by considering the two possible oxatitanacyclobutane intermediates **156** and **157**,[75] Scheme 3.19. When an ester **154** reacts with a Schrock carbene **155**, generated from a functionalized Petasis reagent, two different oxatitanacyclobutanes are possible: **156**, and **157**. Intermediate **156** will lead to the *E* alkene,

and intermediate **157** will lead to the *Z* alkene. The reaction is likely to be under kinetic control so the *E*:*Z* ratio is dependant on the relative energies of the transition states leading to **156** and **157**. The oxygen attached to R^1 acts as a spacer and thus minimizes steric interactions with the OR^1 group. So, unless R^3 is very small, intermediate **156** is favored, and the *Z* alkene is produced in preference.



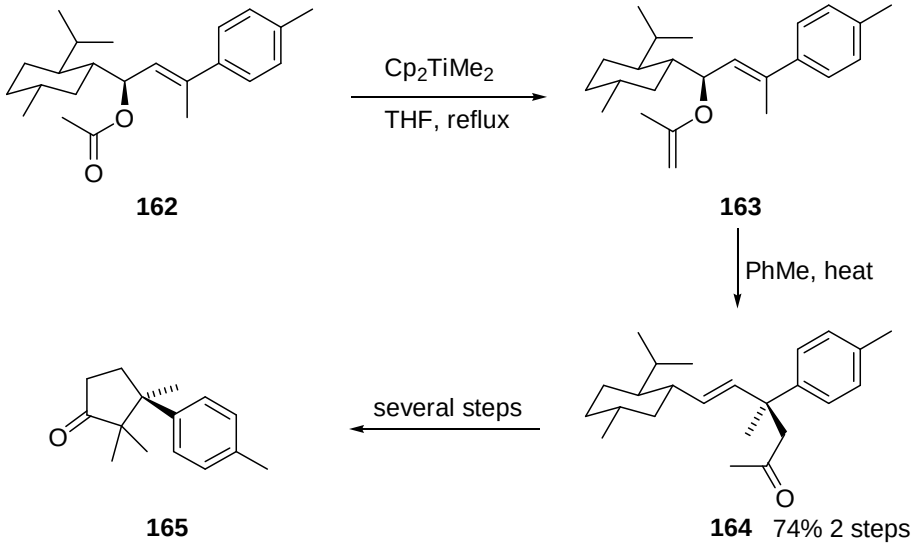
Scheme 3.19

Dimethyltitanocene has found a wide variety of uses in the literature. Its mechanism of reaction is very similar to the Tebbe alkenation, and so, due to its comparative ease of synthesis, it is used in similar situations as the Tebbe alkenation. The simple benign reaction conditions make it an attractive reagent to methylenate carbonyl groups containing acidic α-protons. In their studies towards the total synthesis of kainic acid, Parsons and co-workers used dimethyl titanocene to methylenate a ketone containing a sensitive α-chiral center, Scheme 3.20.[76] When ketone **160** was treated with the Petasis reagent in THF and heated under reflux the alkene **161** was produced in good yield, and the sensitive chirality was left untouched. The transformation also demonstrates the chemoselectivity of the reaction as the ketone is alkenated preferentially in the presence of an ester.



Scheme 3.20

The Petasis methylenation has been combined with other reactions to allow new synthetic strategies. Sigmatropic rearrangements have proved to be very powerful tools for the organic chemist. One popular strategy involves methylenation of an allylic ester to form a precursor for a Claisen rearrangement. In a paper demonstrating the utility of *p*-menthane-3-carboxaldehyde as a chiral auxiliary, Spino *et al.* used just such a strategy in the synthesis of (+)-cuparenone **165**[77], Scheme 3.21. The starting allylic ester **162** was methylenated with dimethyltitanocene to give the enol ether **163**, which was heated under reflux in toluene to give the product of the Claisen rearrangement **164** in a very good yield from ester **162** as essentially one diastereomer. Following removal of the chiral auxiliary by ozonolysis: cyclization, methylenation and hydrogenation gave (+)-cuparenone **165**.



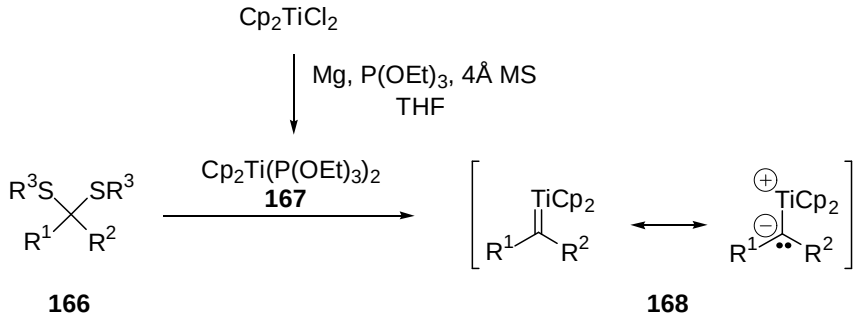
Scheme 3.21

3.8 Takeda Reagents

While Petasis reagents allow for more than just methylenation, functionalized versions of these reagents are rarely used in the literature. The award-winning group of Takeda and co-workers have produced a synthetic method that produces complex titanium alkylidenes via the reduction of thioacetals.[78] Importantly, a range of thioacetals can be used to access titanium carbenoids, notably thioacetals that contain hydrogens β to the thioacetal, and hence, after formation of the titanium reagent, β to the Schrock carbene. The titanium alkylidenes can then be used to alkylidenate aldehydes, ketones, esters, thioesters, and benzamides. The geometry of the alkene formed is governed by the same rules as for the Petasis reagents since the mechanism of reaction of the Schrock carbene is the same for both

the Takeda and the Petasis reactions. While stereoselectivity is poor or unreliable for aldehydes, ketones, and thioesters; esters and benzamides are converted to the corresponding enol ethers and enamines with good and perfect *Z* selectivity.

The reagents are generated by reduction of titanocene dichloride with magnesium in the presence of triethylphosphite to produce a low-valent titanium(II) complex **167**,[79] Scheme 3.22. The reaction is extremely water-sensitive and 4 Å molecular sieves are essential for the reaction to proceed reliably. The low-valent complex **167** reduces the thioacetal **166** to give the Schrock carbene **168**, thus oxidizing the titanium back to titanium(IV). The nature of the thioacetal **166** is important. Diphenylthioacetals, and dithianes derived from 1,3-propanedithiol are both reduced effectively, however diphenylthioacetals are slightly more reactive and generally preferable. The reaction is technically demanding, but when given careful attention, yields consistent results.



Scheme 3.22

The fact that additional functionality can be introduced with the titanium alkylidene is the key feature of the Takeda reagents. A variety of different thioacetals have been used to produce the desired Schrock carbenes, including: dithio-orthoformates **169**[80,81], triphenyltrithio-orthoformate **170**[80], 2-silyl-1-bis(phenylthio)ethanes **171**[82], benzylic and homobenzylic thioacetals **172**, **173**, **174**,[83,18,19,20,84,85] Figure 3.1. While the Takeda reaction tolerates a broad spectrum of functionality some groups cause problems in the reagent itself. Bromo and chloro groups can react with the low valent titanium(II) species **167**. Aryl chlorides are somewhat tolerated but dechlorination can occur. Unprotected amine groups generally cause problems and need to be protected so that no free hydrogen atoms exist on the amine.

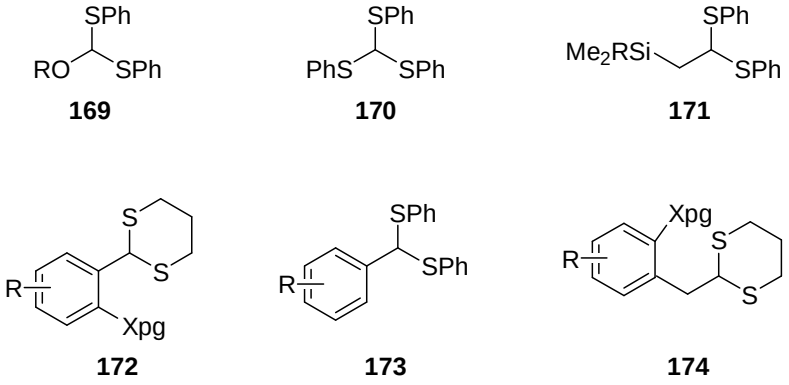
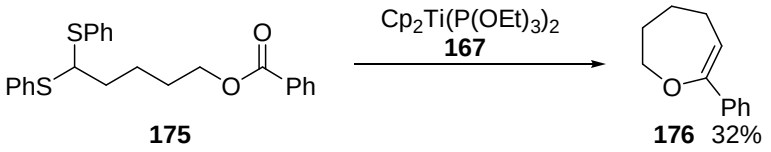


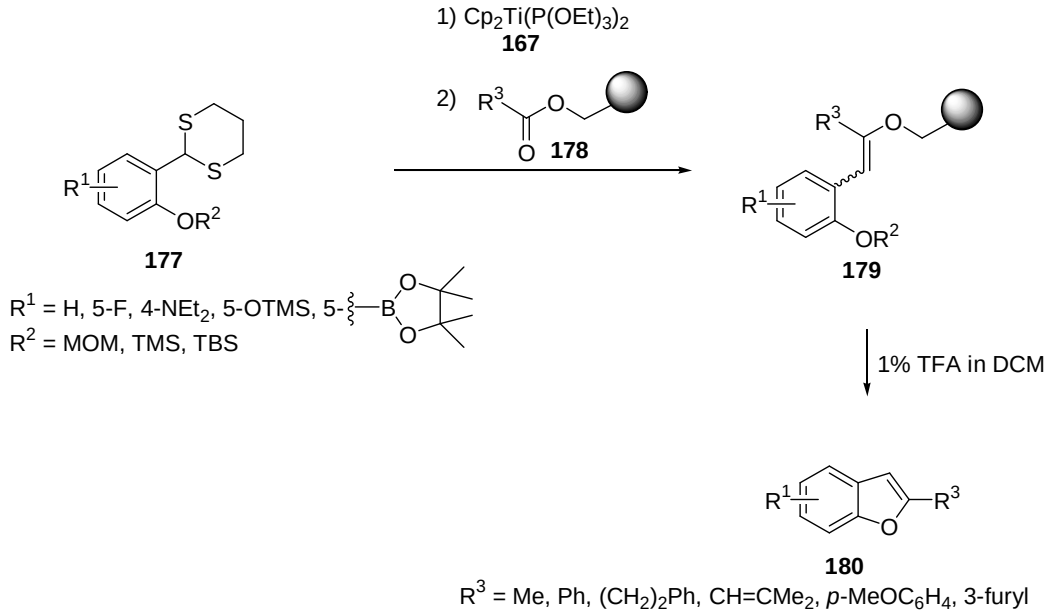
Figure 3.1

Takeda methodology has not been used in the synthesis of piperidines, but has been used to produce various heterocycles. Due to the inherent advantages of the Takeda reaction, intramolecular alkenation is possible. Takeda and co-workers have capitalized on this to produce the challenging 7 membered cyclic enol ether **176,**[86] Scheme 3.23. The thioacetal **175** was treated with low-valent titanium species **167** to provide the cyclic enol ether **176** in a modest yield. The modest yield is due in large part to competing intermolecular alkenation.



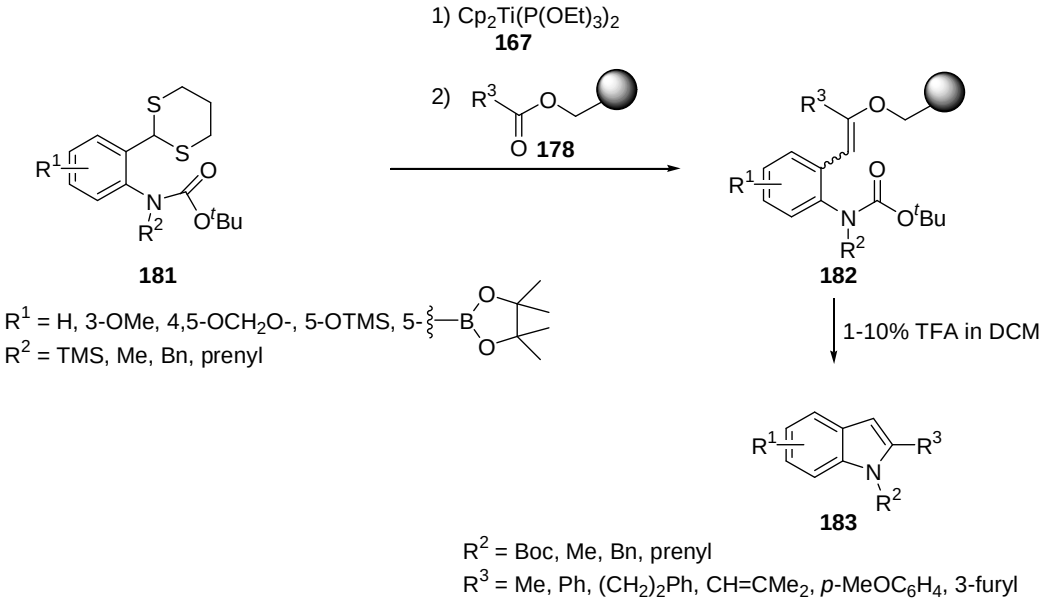
Scheme 3.23

Hartley and co-workers have used the Takeda alkenation as an integral part of their methodology towards a wide variety of aromatic heterocycles, Scheme 3.24. Originally the method was aimed at benzofuran synthesis.[18] A benzaldehyde-derived dithiane **177** is treated with the low-valent titanium complex **167** to produce a Schrock carbene that alkylidenates a Merrifield resin-bound ester **178** to give resin-bound enol ether **179**. The enol ether undergoes acid hydrolysis to cleave from resin and form the benzofuran **180**. The method exploits the functionality and reactivity of the Takeda alkenation, the ease of work up allowed by solid-phase synthesis, and the purity ensured by a chameleon catch strategy, Section 1.7. The Takeda alkenation's mild reaction conditions are especially important when the R group is a boronate group. The fact that the reactive group is tolerated means that more diversity can be introduced by means of a Suzuki cross-coupling.[19]



Scheme 3.24

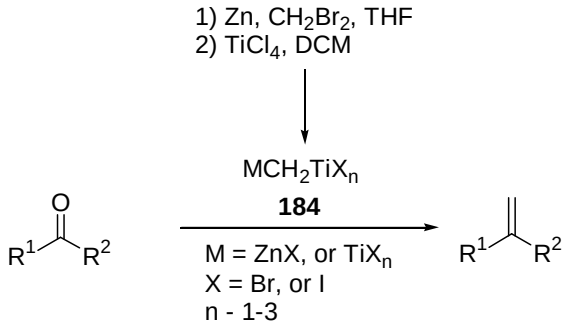
The Hartley methodology has also proven to be very adept at producing indoles, Scheme 3.25.[83] The reaction pathway is very similar to that discussed above. A benzaldehyde-derived dithiane **181** is treated with the low-valent titanium complex **167** to produce a Schrock carbene that alkylidenates a Merrifield resin-bound ester **178** to give resin-bound enol ether **182**. The choice of protecting groups is crucial and the carbamate nitrogen atom must have no free hydrogen atoms. The enol ether undergoes acid hydrolysis to cleave from resin and form the indole **183**. Once again the fact that the reactive boronate ester is tolerated means that more diversity can be introduced by means of a Suzuki cross-coupling.[21] Only indoles and benzofurans have been presented, but analogous routes give benzothiophenes[20] and quinolines.[84]



Scheme 3.25

3.9 Takai reagents

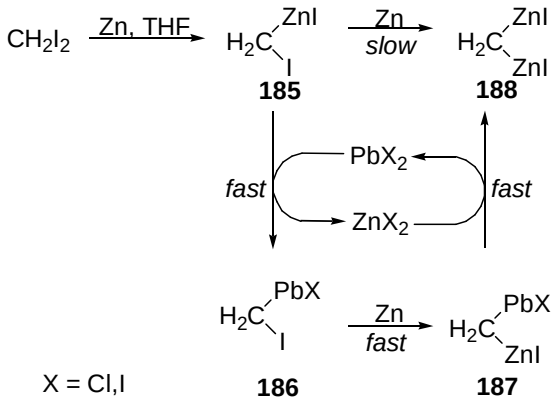
1,1-Bimetallic reagents, also called modified Takai reagents, have proved to be useful alkylidenation reagents, showing up frequently in the literature. Takai and co-workers first produced titanium bimetallics by treating dibromomethane (1.5 equiv.) and zinc dust (4.5 equiv.) in THF with $TiCl_4$ (1.1 equiv.) in DCM to give the bimetallic **184**. After stirring for 15 min, a ketone (1 equiv.) was added, which reacted with the bimetallic reagent to give alkenes,[87] Scheme 3.26.



Scheme 3.26

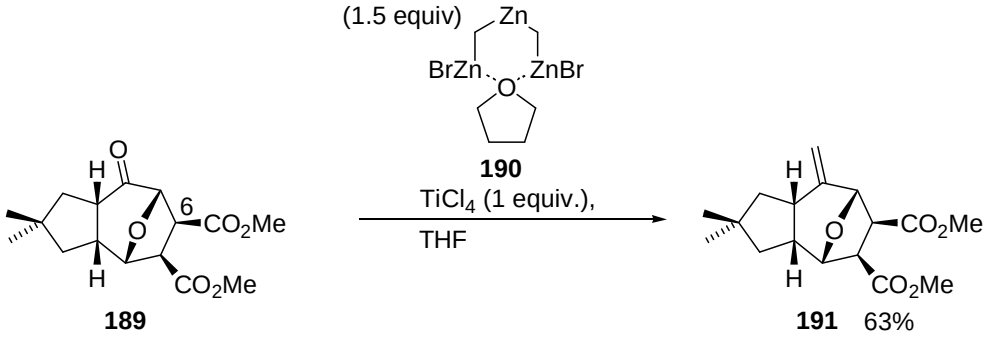
It would seem that the reaction proceeds *via* the dihaloalkane reacting with zinc dust to form a di-zink **188**, Scheme 3.25. Takai and co-workers showed that if the di-zinc **188** was preformed fewer equivalents of all reagents were necessary. The di-zinc **188** is hard to make, but its formation can be expedited with a catalytic amount of lead(II).[88] When diiodomethane

is treated with zinc dust no di-zinc **188** is produced. If a small amount of lead(II)chloride is added, the necessary di-zinc **188** is produced efficiently. The first addition of zinc to the gem dihalide is thought to be a fast addition, and the second addition a slow one. Transmetalation of monozinc **185** would give the more covalent organolead intermediate **186**. Now the second iodide is replaced quickly by zinc to give the bimetallic **187**. It is believed that replacement of the lead by zinc is fast and yields the di-zinc **188**, which undergoes transmetalation to give the titanium zinc bimetallic **184**. The pre-formed di-zinc **188** (2 equiv.), $TiCl_4$ (1 equiv.), and the ketone (1 equiv.) in THF can be stirred at RT to give the desired alkene.



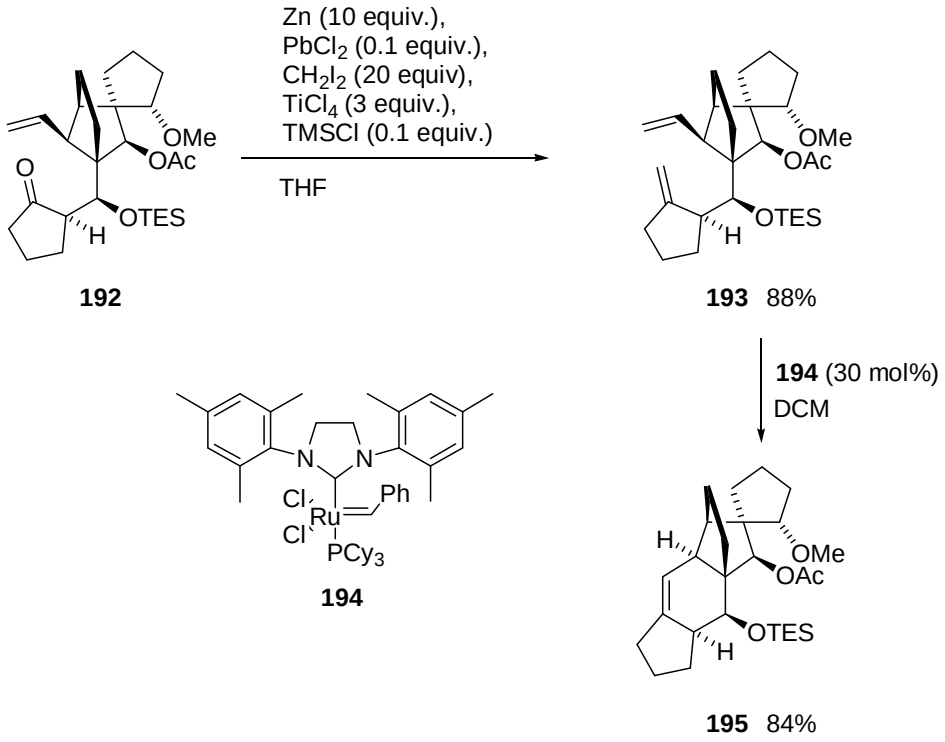
Scheme 3.26

Tochtermann and co-workers found that, alternatively to the preformed di-zinc **188**, comercially available Nysted reagent **190** will effect methylenation in the presence of $TiCl_4$, Scheme 3.27.[89] When ketone **189** was treated with Nysted reagent and $TiCl_4$ in THF, methylenation took place at room temperature to give alkene **191** in a good yield. Interestingly when the ketone **189** was treated with Wittig conditions, epimerization occurred at C-6.



Scheme 3.27

Nicolaou *et al*. used a 1,1-bimetallic reagent in their synthesis of the fused polycyclic skeleton of vannusal A, a triterpene isolated from a tropical marine ciliate,[90] Scheme 3.28. Ketone **192** was treated with zinc dust, $PbCl_2$, TMSCl, diiodomethane, and $TiCl_4$ to give the alkene **193** in very good yield. RCM using Grubbs 2nd generation catalyst **194** gave the protected fused polycycle **195**. Nicolaou *et al*. specifically chose the bimetallic reagent because of the epimerisable center α, to the ketone, and to prevent loss of the OTES group via retro Michael addition.

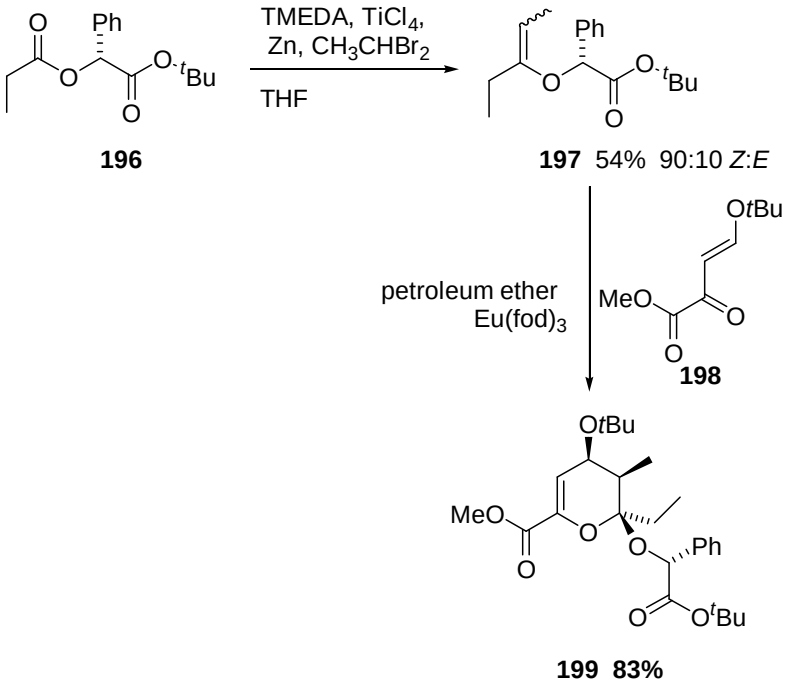


Scheme 3.28

Takai reagents are similar to 1,1-bimetallic reagents, and can incorporate diversity by allowing the use of gem-dihaloalkanes.[91,88] The method differs from that above in the use of a base, usually tetramethylethylenediamine (TMEDA). The reaction mechanism is still to be established. The reagent can be used to alkylidenate a range of carbonyl compounds including esters, amides, and thioesters. All hetero-substituted alkenes were produced with *Z*-selectivity except enamines which were produced as the *E*-isomer.

Following unsuccessful attempts *via* elimination, Dujardin and co-workers turned to Takai chemistry in their syntheis of dihydropyrans,[92] Scheme 3.29. The (*R*)-mandelic acid derivative **196** was subjected to the Takai reagent generated from 1,1-dibromoethane to produce the dieneophile **197** in modest yield. Alkenation occurred solely on the less hindered site and with good selectivity for the *Z* geometrical isomer. Alkene **197** was taken as a

mixture of geometrical isomers and subjected to europium catalyst induced Diels-Alder cycloadditon to give the dihydropyran **199** in good yield as one enantiomer. Interestingly only the *Z* isomer underwent reaction; the *E* isomer appeared to suffer overwhelming steric hindrance in the favored *endo* transition state.



196 **197** 54% 90:10 *Z*:*E* **198** **199** 83%

Scheme 3.29

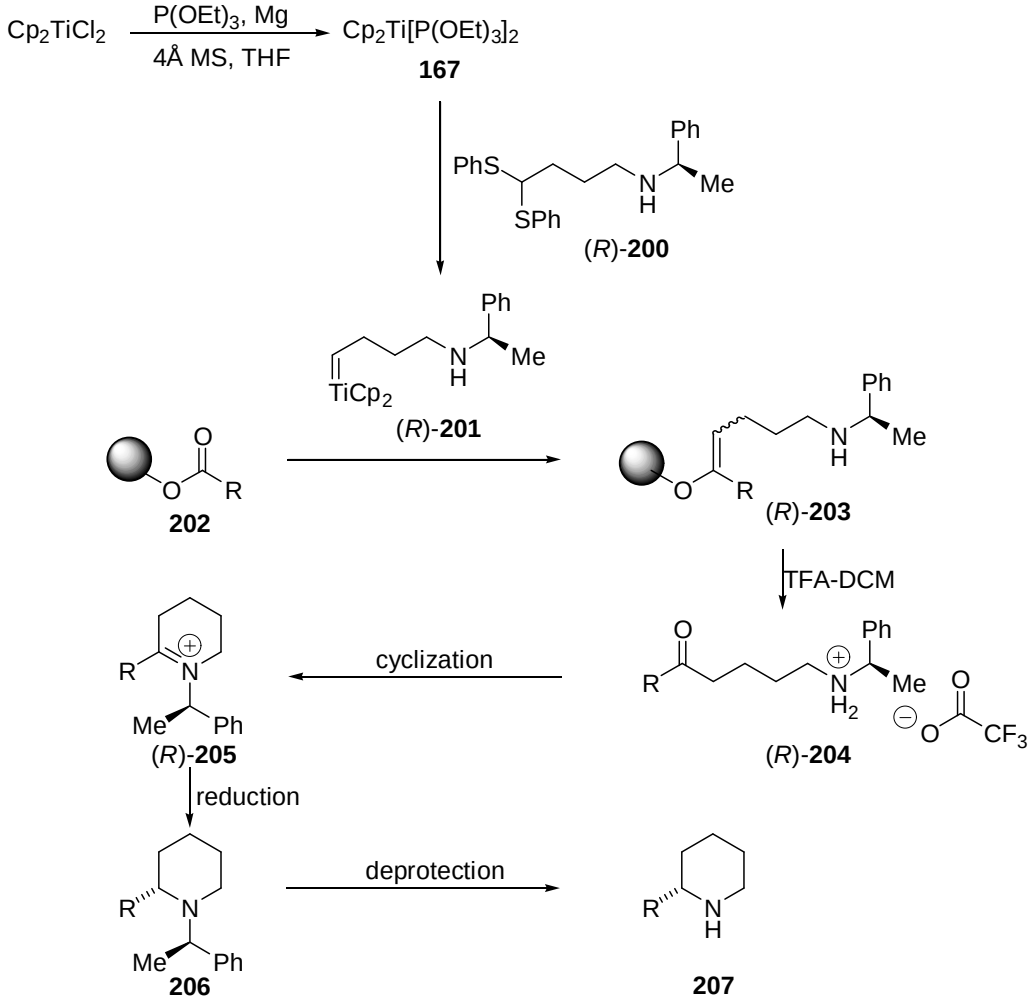
3.10 Conclusions

Whereas the Wittig-type reactions are still far more widely used, titanium-based alkylidenations have found a niche in the synthetic landscape. A range of strategies have developed that capitalize on their special qualities. The typically mild reaction conditions and reactivity allow titanium alkylidenes to be used broadly yet selectively for a multitude of synthetic situations. Most importantly where Wittig-type reagents fail to alkenate carboxylic acid derivatives, titanium carbenoids have demonstrated considerable utility in transforming esters, and amides into hetero-substituted alkenes. As shown above, access to hetero-substituted alkenes not only adds to accessible chemical space, but opens up a range of synthetic possibilities. Indeed, titanium carbenoids are used frequently by the top names in chemistry, and have proven to be an indispensable tool to the organic chemist.

Chapter 4
Previous Work

4.1 Strategy

Previous work in the Hartley group, inspired by the lack of stereodiverse solid-phase routes to piperidines, had built on the Hartley solid-phase methodology to investigate a solid-phase route to enantiomerically-enriched 2-substituted piperidines, Scheme 4.1.



Scheme 4.1

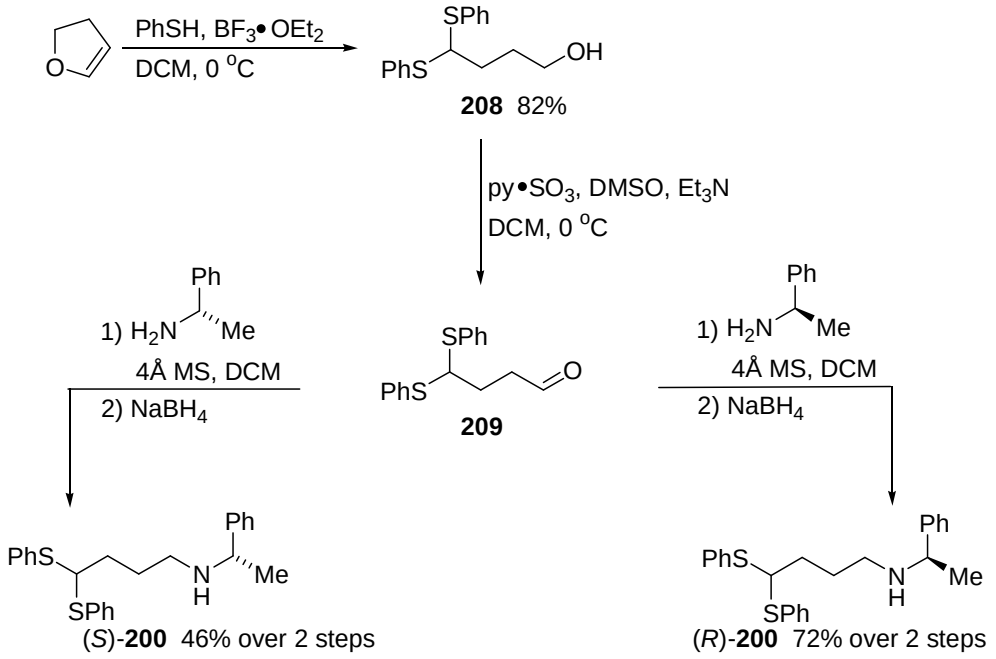
The strategy would involve the use of novel chiral titanium alkylidene **201**, generated from thioacetal **200** to produce a series of amino-ketones **204** on solid phase. The bulky chiral group would act as a protecting group during the generation of the organotitanium reagent **201**, and the alkylidenation of resin-bound esters **202**[93] to give resin-bound enol

ethers **203**. Cyclization of the amino ketones would give an iminium salt **205**. The chiral group would then control the reduction of the iminium ion **205** giving enantiomerically enriched 2-substituted piperidines **206**. No longer needed, the phenethyl chiral protecting group would be removed to give stereodiverse piperidines **207**.

Dr. Mhairi Gibson had used this strategy to produce several 2-substituted piperidines **207**, however, the reaction conditions were not optimized and the enantiomeric purity of the piperidines had not been determined.

4.2 Substrate Synthesis

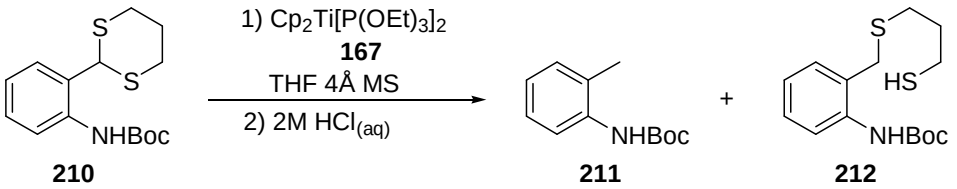
Dr. Gibson's work began with the synthesis of the thioacetal substrate **200**. The key feature of the substrate **200** was the protecting group. Using a bulky chiral group not only promised stereocontrol, but also had the potential to protect the amine during the alkylidenation. Using α-phenethylamine as a building block of the thioacetal **200** was particularly attractive as it is affordable, bulky, and readily available in both enantiomeric forms.[94] Furthermore, the benzylic nitrogen-carbon bond can be reductively cleaved, and thus the phenethyl group can easily be removed. Efforts to introduce the group using displacement were unsuccessful, however, reductive amination proved effective, Scheme 4.2. Using a method developed by Takeda and co-workers, alcohol **208** was produced from 2,3-dihydrofuran.[86] The alcohol **208** could be oxidized using a modification of the Swern conditions to give the aldehyde **209**, which underwent reductive amination with either enantiomer of α-phenethylamine to give the thioacetal substrate (*S*)-**200**, or (*R*)-**200**.



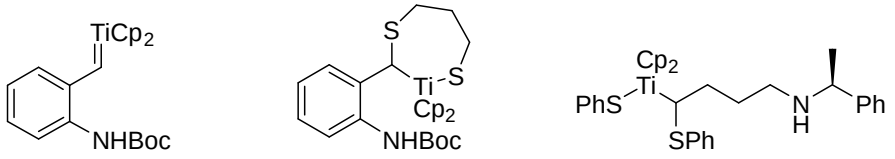
Scheme 4.2

4.3 Amino Ketone Synthesis

For the thioacetal substrate **200** to be an effective precursor it would have to be stable during the challenging solid-phase Takeda alkylidenation. Typically, amino groups complicate Takeda alkylidenations, possibly by coordination to titanium. Amino groups should contain no free protons to be successfully used as substrates for Takeda alkylidenation. Previous work within the Hartley group had shown that a dithiane **210** bearing a *tert*-butylcarbamate group was an unsuitable substrate.[83] Investigation of the substrate showed that when treated with Takeda conditions followed by an aqueous acid quench, two aromatic compounds, **211** and **212**, were isolated, Scheme 4.3. Toluidine **211** was probably formed from the desired intermediate titanium benzylidene **213**, Figure 4.1. Thiol **212** on the other hand was probably the product of monoinsertion of titanium(II) to give the titanium(IV) species **214**. Intramolecular deprotonation of the carbamate would then give the thiol **212** and prevent formation of the alkylidenating reagent **213**.



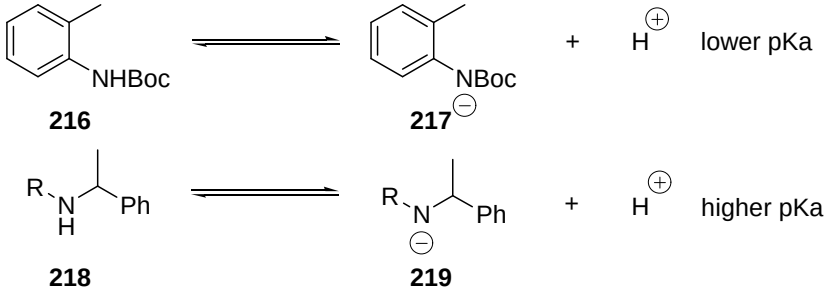
Scheme 4.3



213 **214** **215**

Figure 4.1

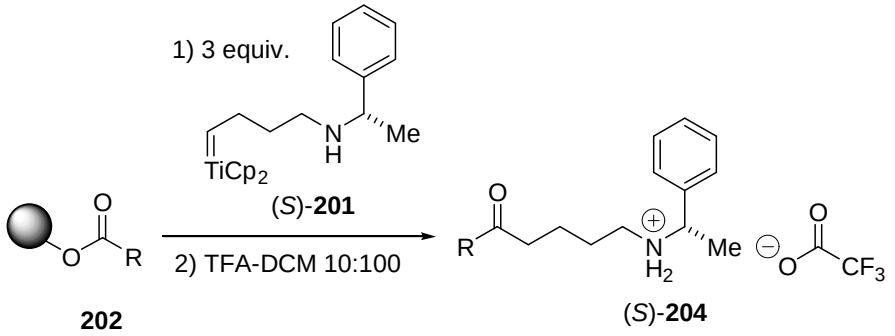
Despite these concerns, the thioacetal substrates **200** were treated with low-valent titanium reagent **167**. The reaction mixture was then added to resin-bound esters **202**. The resin was washed, and cleavage with TFA-DCM (10:90) gave the desired amino-ketones **204** in good yield and good purity. Seemingly, neither coordination of titanium, nor intramolecular deprotonation was a problem. When looking closely at titanium(IV) species **214** the molecule appears pre-arranged for proton transfer, whereas in the more flexible complex **215**, a putative intermediate in the generation of titanium alkylidine **201**, the amino and titanium groups are more separated. Furthermore, the free protons on the amino groups of complexes **214** and **215** have very different acidic qualities, Scheme 4.4. Deprotonation of aniline **216** is relatively easy due to conjugation of the resultant anion with the carbamate protecting group and the neighboring phenyl group. Secondary amine **218** is relatively difficult to deprotonate as it contains neither of these stabilizing groups. Thus intramolecular deprotonation would be significantly more difficult for complex **215** than complex **214**.



216 **217** **218** **219**

Scheme 4.4

Steric bulk of the protecting group would account for the inability of the titanium to coordinate with the amine. Dr. Gibson used the thioacetal substrate (*S*)-**200** to prepare a series of amino-ketones (*S*)-**204**, Scheme 4.5, Figure 4.2.



Scheme 4.5

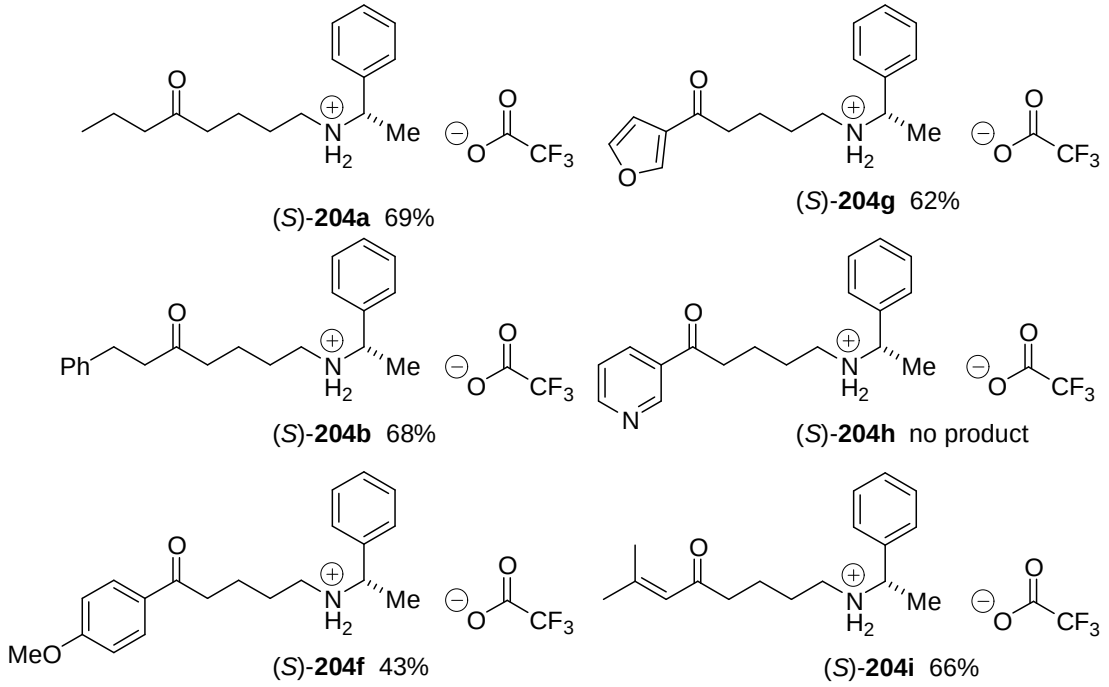


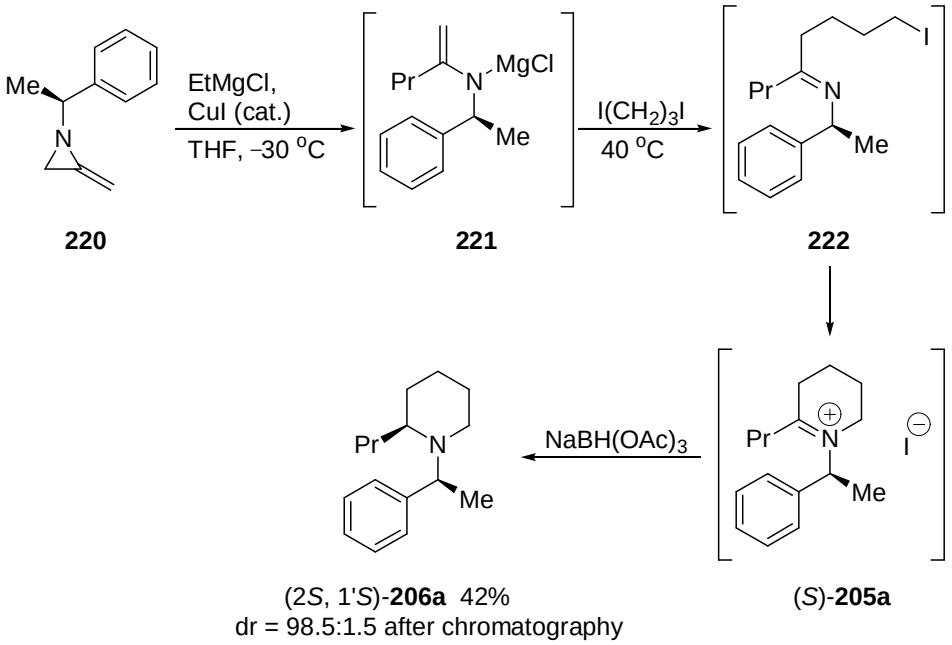
Figure 4.2 Yields of amino ketones (*S*)-**204**

The corresponding series of amino ketones (*R*)-**204** produced from thioacetal (*R*)-**200** was also prepared in similar yields. It is likely that amino ketone **200h** fails to form because the nucleophilic nitrogen atom of the pyridine ring coordinates to titanium, thus preventing formation or reaction of titanium alkylidene **201**.

4.4 Diastereoselective Cyclization *via* Reductive Amination

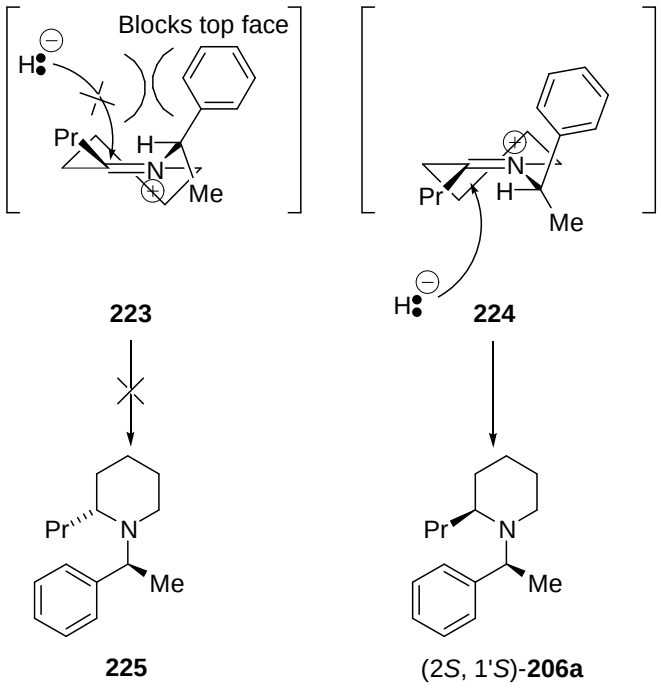
Shipman and coworkers had previously devised a method of preparing chiral 2-substituted piperidines using the α-phenethyl group to control the stereochemistry, Scheme 4.6.[95] Starting from chiral methyleneaziridines **220**, their strategy involved the opening of the aziridine with a Grignard reagent, and copper iodide to give the metalloenamine **221**.

Alkylation with 1,3-diiodopropane gave the imine **222** which cyclized to give the piperidinium salt (*S*)-**205a**. Reduction of the iminium ion with the bulky reducing agent $NaBH(OAc)_3$, gave the desired piperidine (2*S*, 1'*S*)-**206a** in moderate yield with excellent diastereoselectivity.



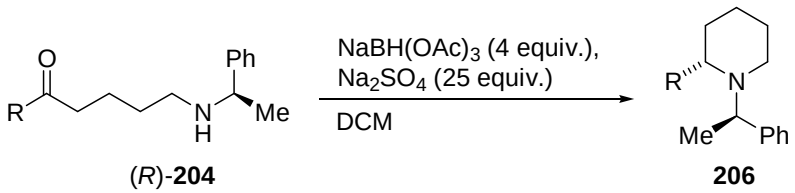
Scheme 4.6

Shipman proposed that the high level of stereocontrol can be attributed to the fact that the iminium ion (*S*)-**205a** exists in half chair conformations **223** and **224**, Scheme 4.7. The phenethyl group arranges itself so that the benzylic hydrogen atom is projected towards the propyl group, thereby minimizing 1,3-allylic strain. The hydride must attack axially to directly give a chair conformation. Therefore, the only two paths of attack available to the hydride are those shown. Hydride attack from the *Si* face of conformation **223** is blocked by the bulky phenyl group, so, formation of piperidine **225** is unlikely. On the other hand, hydride attack from the *Re* face of conformation **224** is relatively uninhibited. Thus, preferential formation of piperidine (2*S*, 1'*S*)-**206a** is ensured. A bulky reducing agent is essential due to the reliance on steric interaction with the phenethyl group. When Shipman and co-workers used $NaBH_4$ in place of $NaBH(OAc)_3$ the diastereomeric ratio in the crude mixture dropped from 95:5 to 88:12.



Scheme 4.7

Cyclization of the amino ketones **204** proved to be difficult. By using a large excess of desiccant in the presence of $NaBH(OAc)_3$ the amino-ketones **204** could be cyclized to give piperidines **206**, Scheme 4.8, Figure 4.3. Amino ketones (*R*)-**204a**, (*R*)-**204b**, and (*R*)-**204i** cyclized well. Electron-rich amino ketones (*R*)-**204f** and (*R*)-**204g** cyclized poorly. Amino ketone (*R*)-**204f** proved to be impossible to cyclize effectively, while the only way to produce piperidine (2*S*, 1'*R*)-**206g** in reasonable yield was by repeated treatment of amino ketone (*R*)-**204g** with the cyclization and reduction conditions. The (*S*) series of amino-ketones cyclized poorly, and column chromatography was necessary to purify desired piperidine **206** from uncyclized material. Clearly, the cyclization procedure was not reliable. Unfortunately, due to time constraints, the diastereomeric purity of the piperidines formed was not investigated.



Scheme 4.8

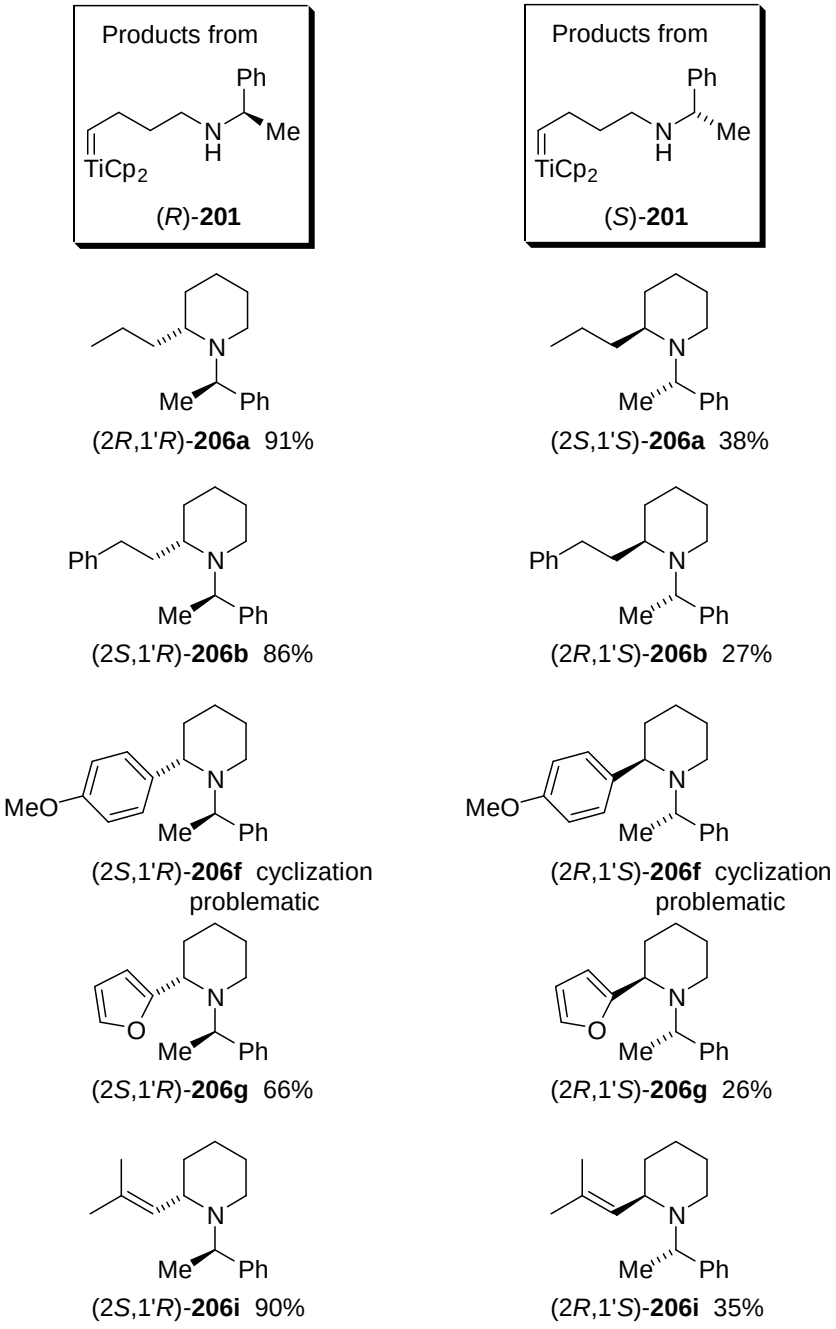
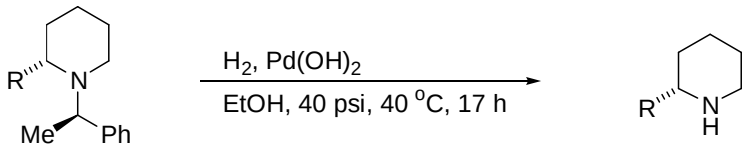


Figure 4.3 Yields of disubstituted piperidines **206**

4.5 Removal of the Chiral Protecting Group

The chiral protecting group could be removed *via* high pressure hydrogenation. Using $Pd(OH)_2$, the 2-substituted piperidines (*R*)-**207a**, and (*S*)-**207b** were produced from the *N*-protected piperidines **206**, Scheme 4.9. Unfortunately the removal of the phenethyl group was not generally applicable. In the case of (2*S*, 1'*R*)-**206g** the harsh conditions caused the *exo*cyclic and *endo*cyclic *N*-benzylic group to be cleaved giving a mixture of products. Hydrogenation of the piperidine (2*S*, 1'*R*)-**206i** removed the phenethyl group but also

reduced the alkene moiety. The deprotection of piperidines **206** derived from (*S*)-**201** was not attempted. Enantiomeric purity was not determined due to time constraints.



(2*R*,1'*R*)-**206a** R = -$(CH_2)_2$Ph
(2*S*,1'*R*)-**206b** R = -$(CH_2)_2CH_3$

(*R*)-**207a** R = -$(CH_2)_2$Ph 93%
(*S*)-**207b** R = -$(CH_2)_2CH_3$ 95%

Scheme 4.9

4.6 conclusions

The work by Dr. Gibson had shown great potential and demonstrated the viability of the method. However, even though the method was promising, there were still major concerns that needed to be addressed. Namely, the cyclization had to be less capricious, the hydrogenation had to be more general, and the enantiomeric purity of the piperidines **207** formed had to be determined. Furthermore, yields of amino ketones **204** were not always reproducible, and therefore, the alkylidenation step needed to be optimised.

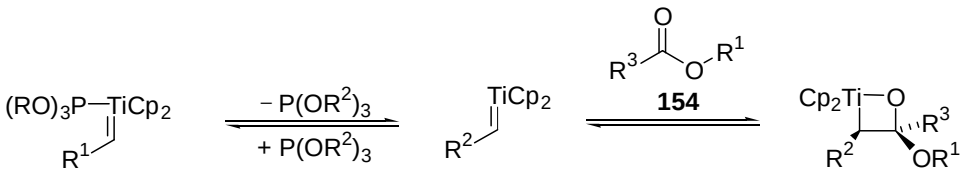
Chapter 5

Synthesis of 2-Substituted Piperidines

5.1 Improving the Solid-Phase Alkylidenation

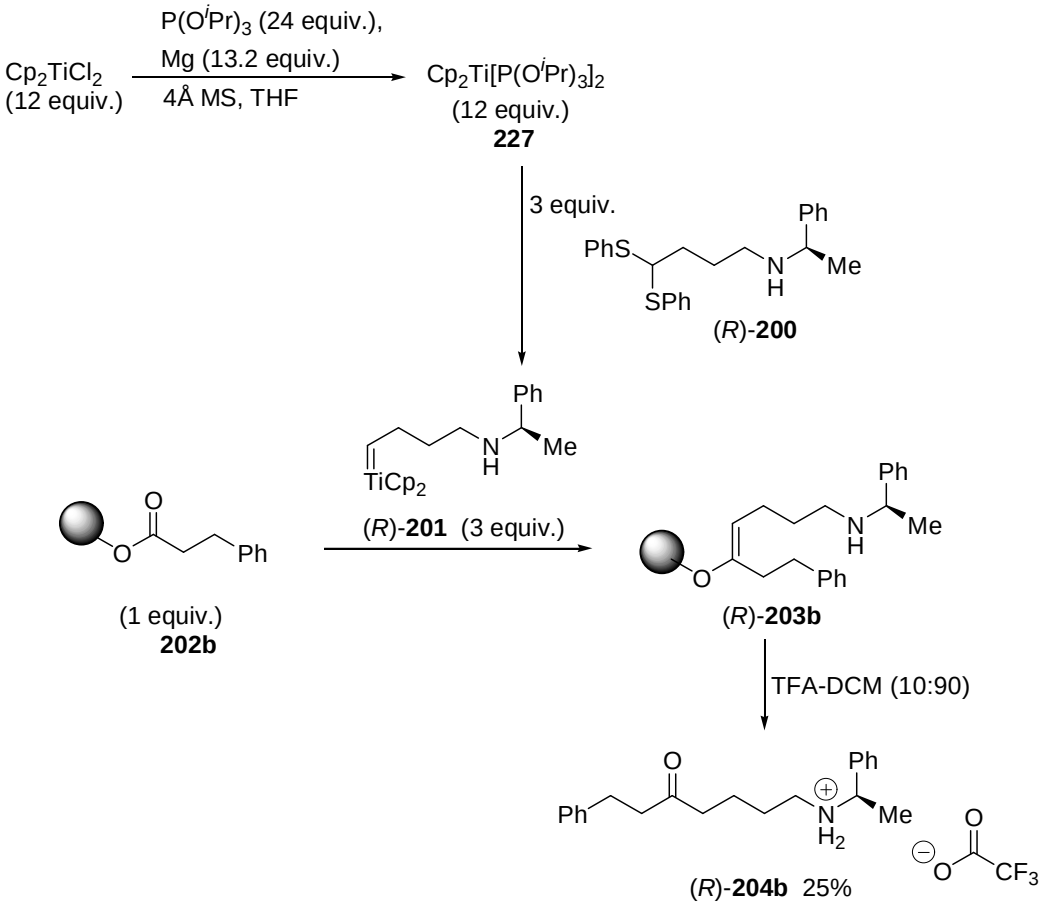
At the start of my work, SPS of amino ketones **204** had been demonstrated by Dr. Gibson, but the sequence was not yet consistently reproducible. Often, amino ketones were produced in poor yields and insufficient purity for high throughput synthesis. This necessitated optimization of the alkylidenation reaction.

The reactive organotitanium species **155** has a free coordination site, which we wish to be occupied by the carbonyl group of **154**, but could also be occupied by the triethylphosphite used in generating organotitanium reagent **155**, Scheme 5.1. We believed that by using the more bulky triisopropylphosphite in place of triethylphosphite, 18 electron complex **226** would be more likely to dissociate due to the increased sterics, and therefore aid in the formation of oxatitanacyclobutane **156**, eventually leading to the desired alkene.



Scheme 5.1

Unfortunately, the switch to triisopropylphosphite did not have an appreciable affect on the alkylidenation reaction, Scheme 5.2. When titanocene dichloride was reduced in the presence of triisopropylphosphite, a colour change from red to black was observed suggesting that the low-valent complex **227** was formed. Alkylidenation was also successful, but while the amino ketone (*R*)-**204b** was produced, the yield was poor and purity was mediocre.



Scheme 5.2

We tried several more modifications of the procedure, including: microwave irradiation of the solid phase step, different methods of reactant addition, and different reaction times for different steps of the sequence, but the results remained unsatisfactory. Finally, suspecting that trace moisture in the argon source was poisoning the reaction, we inserted a column of desiccant (CaH_2, or CaO) between the argon source and the reaction vessel, Figure 5.1.

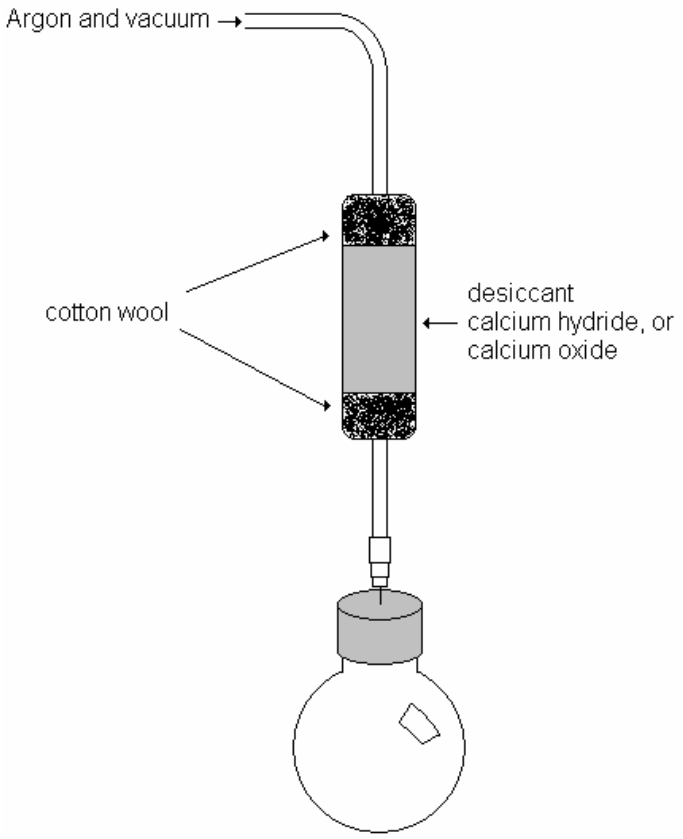
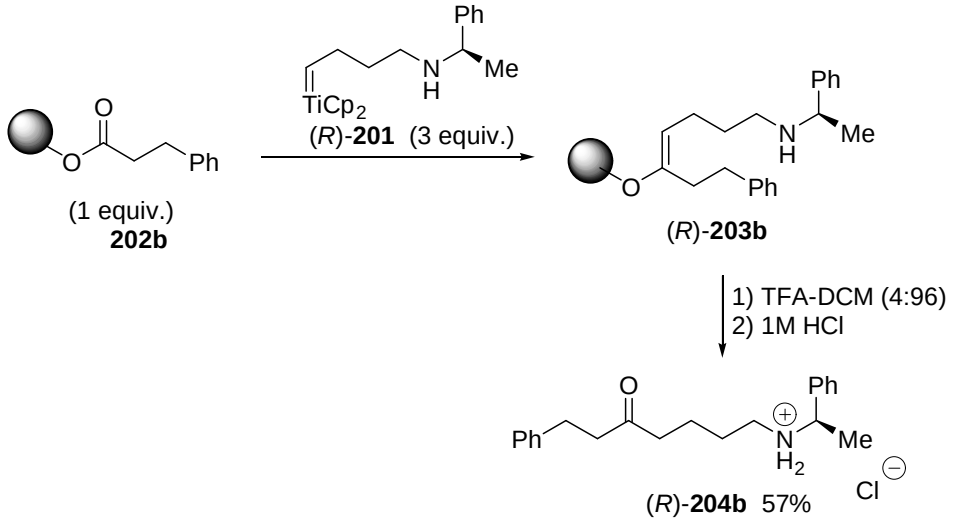


Figure 5.1

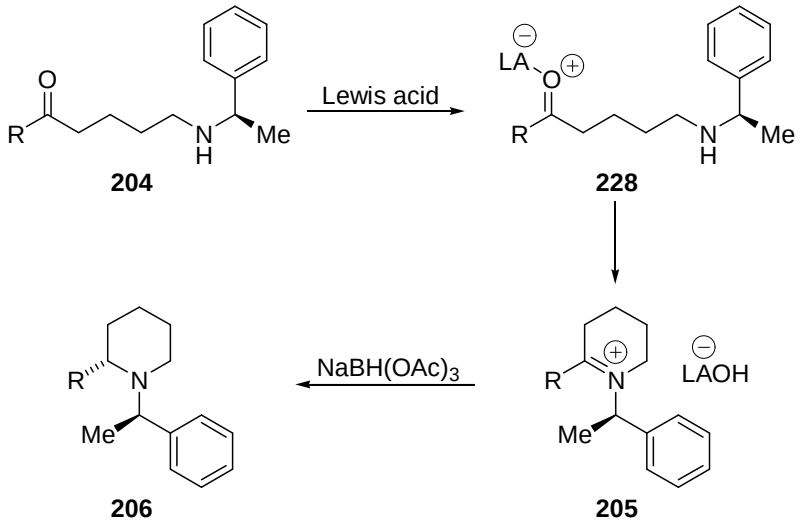
By ensuring that the all argon used in the reaction and preparation of reagents was treated in this way, the yields improved and purity was ensured, Scheme 5.3. The purity of the products could be further improved by dissolving the trifluoroacetate salt of the amino ketone (*R*)-**204b** in 1M $HCl_{(aq)}$, and extracting the product from the aqueous layer with DCM.



Scheme 5.3

5.2 A More Elegant Cyclization

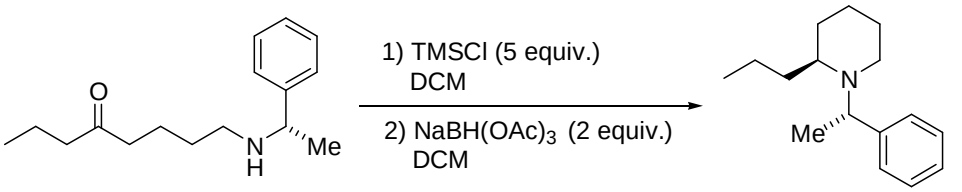
While the use of 25 equivalents of desiccant followed by $NaBH(OAc)_3$ gave the desired *N*-protected piperidines **206**, we were not satisfied with the conditions. Despite the logistics of using 25 equivalents of Na_2SO_4, the yields of *N*-protected piperidines **206** were not reliable. We envisaged that a Lewis acid could coordinate to, and thus activate, the carbonyl of amino ketone **204**, Scheme 5.4. Cyclization would then give the iminium salt **205**, which, as shown by Shipman and co-workers,[95] could be reduced by $NaBH(OAc)_3$ to give piperidines **206** in good yield and high diastereoselectivity.



204 **228** **206** **205**

Scheme 5.4

We imagined that the oxophilic Lewis acid chlorotrimethylsilane (TMSCl) should limit the coordination of the Lewis acid to the more Lewis basic nitrogen atom, encouraging oxonium ion formation and cyclization. Furthermore, the reagent would provide a chloride counterion, is volatile, and would yield only volatile side products. This would mean that before the reduction stage, any side product and any excess TMSCl could be removed *in vacuo* leaving only the pure, non-volatile piperidinium salt. The reaction was performed in a Schlenk tube to facilitate controlled evaporation. The amino ketone (*S*)-**204a** was treated with with TMSCl in DCM and then all volatile components of the reaction mixture were removed *in vacuo*, Scheme 5.5. Reduction with $NaBH(OAc)_3$ gave the desired piperidine (2*S*, 1'*S*)-**206a** in good yield and purity. Diastereomeric purity was not determined at this stage as we were unable to obtain a sample of the minor diastereomer to positively identify it in the ^1H NMR spectrum of the crude mixture.



(*S*)-**204a** (2*S*, 1'*S*)-**206a** 90%

Scheme 5.5

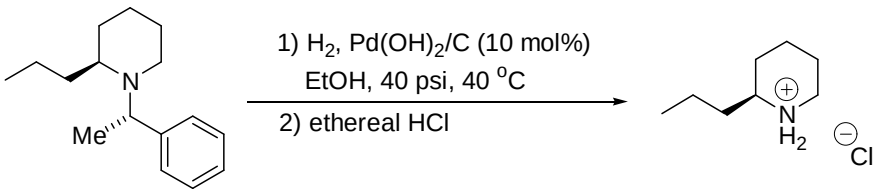
A range of different conditions and bulky reducing agents were screened to optimize the reaction, Table 5.1. The use of 5 equivalents of TMSCl was essential to drive the cyclization to completion. $NaBH(OAc)_3$ effected reduction of the iminium ion without problem above –10 ^oC, however, lower temperatures gave no product. Diisobutylaluminium hydride (DIBAL), sodium cyanoborohydride ($NaCNBH_3$), and L-Selectride all gave incomplete reaction. The best conditions used 5 equivalents of TMSCl, and 2 equivalents of $NaBH(OAc)_3$ at RT, or –10 ^oC. Following removal of the chiral phenethyl group, there was no difference in the enantiopurity of the piperidines produced from reduction at RT or at –10 ^oC, and RT was deemed more convenient.

Table 5.1 Cyclization and reduction of amino ketone (*S*)-**204a**
to give piperidine (2*S*, 1'*S*)-**206a**

equiv. TMSCl	**reducing agent (2 equiv.)**	**temperature of reduction**	**yield of piperidine** (2*S*, 1'*S*)-**206a**
2 equiv.	$NaBH(OAc)_3$	RT	66%
5 equiv.	$NaBH(OAc)_3$	RT	90%
5 equiv.	$NaBH(OAc)_3$	–78 ^oC	no product
5 equiv.	$NaBH(OAc)_3$	–40 ^oC	no product
5 equiv.	$NaBH(OAc)_3$	–10 ^oC	90%
5 equiv.	DIBAL	RT	reaction incomplete
5 equiv.	$NaCNBH_3$	RT	reaction incomplete
5 equiv.	L-Selectride	RT	reaction incomplete

5.3 Removal of the Chiral Protecting Group

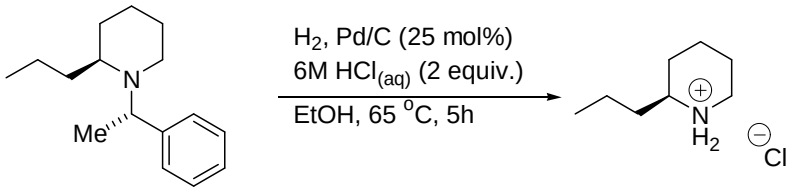
The chiral protecting group can be removed *via* high pressure hydrogenation. When the substituent at the 2-position is a simple alkyl group, the high pressure procedure gives unprotected piperidines in good yield, Scheme 5.6. However, the harsh procedure caused problems when the 2-position of the piperidine **206** was aromatic, Section 4.5.



(2*S*, 1'*S*)-**206a** (*S*)-**207a** 97%

Scheme 5.6

We investigated atmospheric pressure hydrogenolysis of the phenethyl protecting group using Pd/C. The deprotection proceeded to give the 2-substituted piperidine (*S*)-**207a** as the hydrochloride salt in excellent yield, Scheme 5.7. The addition of HCl was essential to form the hydrochloride salt and ensure that the small, potentially-volatile compound did not evaporate during workup. Most importantly, the reaction proceeded cleanly. After deprotection, pure material could be obtained by simply washing the piperidine salt **207** with EtOAc, and separating the wash from the solid product. From the solid-phase alkenation through cyclization, reduction, and deprotection, no time-intensive purification was necessary. Furthermore, the model for induction of stereochemistry, Scheme 4.7, was consistent with the absolute stereochemistry assigned by optical rotation. The piperidine (*S*)-**207a** is a natural product isolated from the hemlock plant, called (*S*)-coniine. The optical rotation (*S*)-**207a** matched that of (*S*)-coniine[96] signifying that we had produced the (*S*) enantiomer in excess.

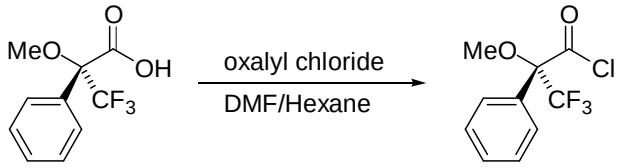


(2*S*, 1'*S*)-**206a** (*S*)-**207a** 98%

Scheme 5.7

5.4 Stereoisomeric Purity

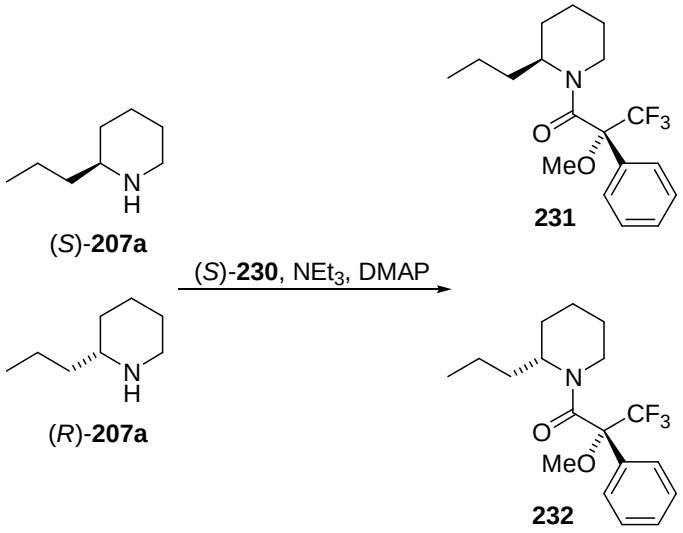
Confident in the yield and chemical purity of our synthetic route, we investigated the sterechemical purity of the final piperidines **207**. In Shipman's synthesis of (*S*)-coniine,[95] Mosher's method was used to determine enantiomeric excess.[97] Chiral derivitizing agents (CDA) are commonly used to determine enantiomeric purity, and can even be applied in the assignment of absolute configuration.[98] (*R*)-Mosher's acid (*R*)-**229** is a particularly popular CDA and, after conversion to its corresponding acid chloride (*S*)-**230**, Scheme 5.8, it can be used to make the Mosher's amide of secondary amines.



(*R*)-**229** (*S*)-**230**

Scheme 5.8

Shipman and co-workers started with an uneven mixture of enantiomers (*R*)- and (*S*)-coniine, (*R*)-**207a** and (*S*)-**207a**, respectively. From the optical rotation they knew that the (*S*) enantiomer was in excess, but they did not know by how much. Reaction of the mixture with Mosher's acid chloride (*S*)-**230** gave a diastereomeric mixture of the Mosher's amides **231** and **232**, Scheme 5.9. The enantiomeric mixture had been converted to a diastereomeric mixture and so the two compounds **231** and **232** could be differentiated by NMR spectroscopy. The fluorine atoms in the CF_3 group are shielded to different degrees in the diastereomers **231** and **232**, and appear at different shifts in the ^{19}F NMR spectrum. By integrating the peaks corresponding to the two CF_3 groups, the relative amounts of **231** and **232** in the sample were determined. Hence, the relative amounts of (*R*)-**207a** and (*S*)-**207a** in the original sample were known.

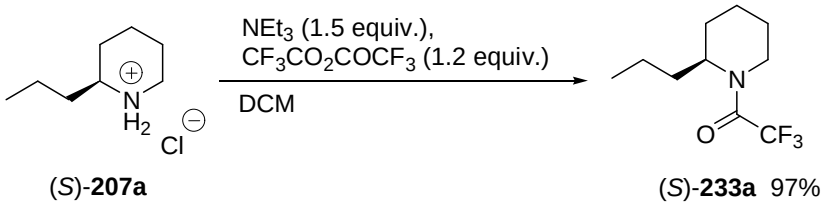


Scheme 5.9

Unfortunately in our hands the method failed. Despite separate reaction of (*S*)-**207a** with both enantiomers of Mosher's acid chloride only one identical peak was ever visible in the ^{19}F NMR spectrum. This is perhaps because the relative amount of the minor diastereomer was too small to be detected by the NMR machine, which for all its advantages is only moderately sensitive.

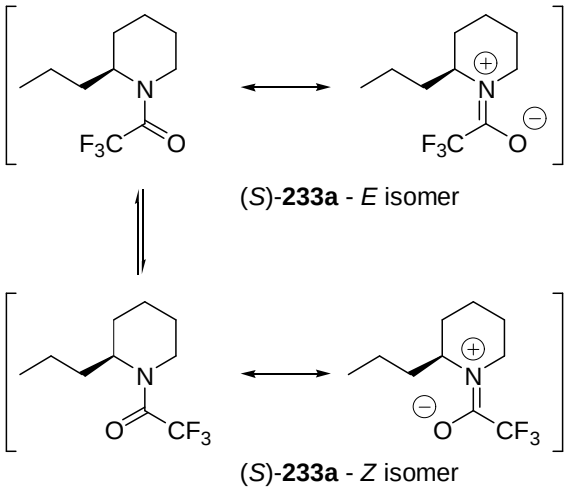
We turned our attention to chromatographic methods. Chiral gas chromatography is a very sensitive method for determination of enantiomeric purity. Low boiling points are essential when using gas chromatography (GC), so to prepare the piperidines for analytical gas chromatography, the amine group was converted into a trifluoroacetamide. Secondary amines have strong intermolecular hydrogen bonds, while tertiary amides do not have a good hydrogen bond donor. Furthermore, fluoroalkanes have only weak intermolecular interactions. This is perhaps best demonstrated by considering the boiling points of n-hexane and perfluoro-n-hexane. While perfluoro-n-hexane is much heavier than its hydrogen analogue, perfluoro-n-hexane boils at a significantly lower temperature than n-hexane.

Reaction of piperidine (*S*)-**207a** with triethylamine and trifluoroacetic anhydride gave the corresponding trifluoroacetamide (*S*)-**233a** in good yield, Scheme 5.10.



Scheme 5.10

Amide (*S*)-**233a** existed as a 2:1 mixture of geometric isomers, Scheme 5.11. As would be expected, the amide bond can rotate around its axis, but this rotation is slowed by conjugation between the nitrogen lone pair and the carbonyl group. Although this rotation allows rapid *E*-*Z* interconversion at room temperature, it is slow relative to the NMR timescale, and the two geometric isomers were well resolved in the ^{1}H NMR spectrum.

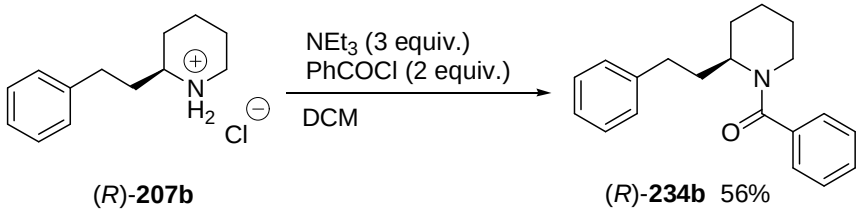


Scheme 5.11

The trifluoroacetamide (*S*)-**233a** proved to be a good candidate for chiral GC analysis. Conditions that separated the two enantiomers on a Supelco β-DEX 120 column were easily found. The analysis showed that our route had produced the piperidine (*S*)-**207a** in a very respectable 90 % ee. It is clear that with an er of 95:5, ^{19}F NMR spectroscopy did not detect the minor diastereomer in a 95:5 mixture of the Mosher's amides **231**, and **232**. As mentioned above, the enantiomeric excess of (*S*)-**233a** was identical regardless of the temperature used in the reduction of the iminium salt (*S*)-**205a**. Reduction with $NaBH(OAc)_3$ at RT and at –10 ^{o}C gave identical results.

While conversion to the trifluoroacetamide helps to make amines more suitable for analysis with GC, some compounds are just too heavy. For this reason, an alternate method was employed for the heavier piperidines, using chiral high performance liquid chromatography (HPLC), a method that can analyze large, non-volatile compounds. Reaction of the piperidine (*R*)-**207b** with benzoyl chloride and triethylamine gave the benzamide (*R*)-**234b** Scheme 5.12. Like the trifluoroacetamide (*S*)-**233a**, the benzamide (*R*)-**234b** existed as two geometrical isomers. Unfortunately, the two isomers were not well resolved by ^{1}H NMR spectroscopy at RT. To analyze the complicated spectrum, and characterize the benzamide properly, the temperature of the probe had to be changed. The probe could either be cooled to slow the rotation and thus resolve the two geometrical

isomers, or heated so that interconversion was fast on the NMR timescale. As we did not have access to a cryoprobe, heating was the only option available. When the ^{1}H NMR spectrum was obtained at 50 ^{o}C, the results were easily interpretable, and the benzamide (*R*)-**234b** could be characterized with confidence.



(*R*)-**207b** (*R*)-**234b** 56%

Scheme 5.12

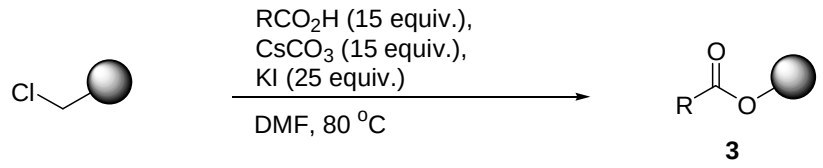
Separation and analysis of the two enantiomers (*R*)-**234b** and (*S*)-**234b** with chiral HPLC proved to be challenging. Using a Chiralcel OD-H column, the (*R*) enantiomer eluted before the (*S*) enantiomer. A simple, binary hexane-isopropanol solvent system produced peaks with large tails. When (*R*)-**234b** was in excess over (*S*)-**234b**, the peak corresponding to the minor (*S*) enantiomer was obscured by the tail of the peak corresponding to the major (*R*) enantiomer. After much experimentation with different solvent conditions, it was found that by using a more complex solvent system (hexane-isopropanol-methanol 98:1:1), the peak shape could be changed so that the peaks were well separated. This system was used when (*R*)-**234b** was in excess over the later eluting component (*S*)-**234b**. In the opposite case, when the second component (*S*)-**234b** was in excess, a binary hexane-isopropanol solvent system could be used.

Confident that we had developed conditions to analyze enantiomeric purity of the piperidines **207** produced by our solid-phase method, we aimed to demonstrate our work by developing a small library of compounds in both the (2*R*) and (2*S*) stereoisomeric forms.

5.5 Library Synthesis

We aimed to prepare a library that would demonstrate the key aspects of our method. The library should demonstrate the ability to produce diverse products by producing piperidines with varied groups at the 2-position. Both the (2*R*) and (2*S*) stereoisomeric forms of each piperidine would have to be synthesized to show that our synthetic route is stereodiverse. Both conventional and stereochemical purity of the final piperidines **207** needed to be high to demonstrate the method's applicability to diversity-orientated synthesis.

Five different resin-bound esters were prepared from Merrifield resin, Scheme 5.13, Figure 5.2. Resin **202a** was prepared from butyric acid, and allowed access to the small natural product coniine. Production of this compound would not only demonstrate the ability of the method to control stereochemistry when the group at the 2-position was small, but as discussed in section 5.3, also allowed us to confirm that our model for stereochemical induction was consistent with the absolute stereochemistry of the piperidines produced. Resin **202b** was produced from dihydrocinnamic acid, and investigated the result of steric bulk separated from the point of stereochemical induction. Resin **202c** was produced from 3-methoxybenzoic acid, and we hoped would demonstrate that the new atmospheric pressure hydrogenolysis of the chiral auxiliary tolerated 2-arylpiperidines. Enantiopure resin **202d** was prepared from (*S*)-(+)-2-methylbutyric acid and would investigate the ability of the chiral auxiliary to control diastereomeric purity in cooperation and in competition with directing effects in the substrate. Furthermore, along with resin **202c**, resin **202d** explored the effects of steric bulk adjacent to the site of stereochemical induction. Resin **202e** was prepared from (*R*)-(+)-citronellic acid, and as with resin **202d** probed the effects of existing chirality on the stereochemical outcome of the reduction. We assumed that the alkene would be reduced during removal of the auxiliary, but that this would not increase the complexity of the products.



Scheme 5.13

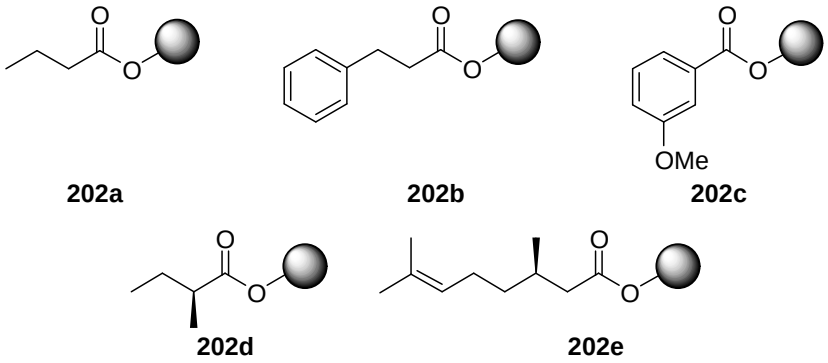
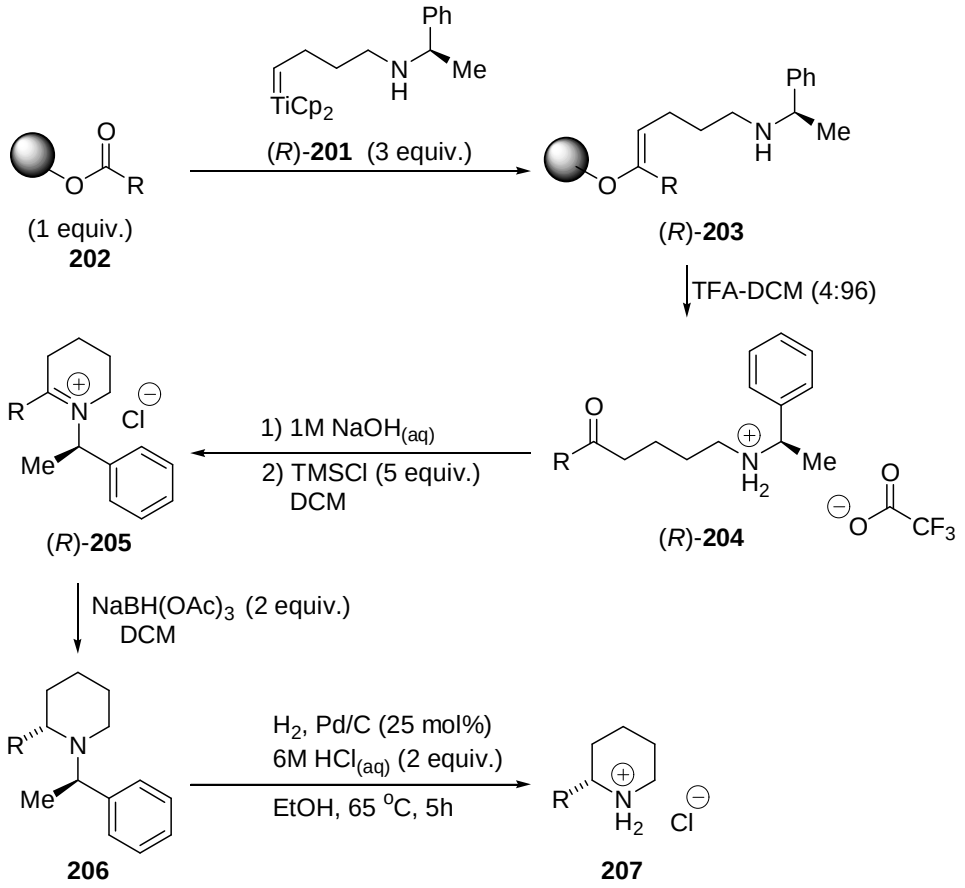


Figure 5.2 Resin-bound esters prepared for library synthesis

As the piperidines **207** were the target compounds, none of the intermediates were isolated. The synthetic scheme was followed from resin-bound ester **202** to piperidine **207**,

Scheme 5.14. The five resin-bound esters were treated with the titanium alkylidene (*R*)-**201**, generated from (R)-**200**, to make the amino ketones (*R*)-**204** *via* the resin-bound enol ethers (*R*)-**203**. Cyclization conditions gave the *N*-protected piperidines **206** which underwent hydrogenolysis to give the piperidines **207**. The route was repeated with all five resin-bound esters, but using the (*S*) enantiomer of the titanium alkylidene (*S*)-**201**. The isomeric purity of all 10 piperidines produced was determined using the methods outlined in Section 5.5. Piperidines **207a**, and **207d** were small enough to be analyzed by GC. They were converted into the corresponding trifluoroacetamides **233a**, and **233d** and stereoisomeric purity was determined by chiral GC. Piperidines **207b**, **207c**, and **207e** were converted to the corresponding benzamides **234b**, **234c**, and **234e**, and analyzed with chiral HPLC. Only benzamide (*R*)-**234b** required a complex eluent mixture. A simple binary hexane-isopropanol solvent system provided sufficient separation for all other examples analyzed by HPLC.



Scheme 5.14

All piperidines were produced in excellent chemical purity, and good overall yield (based on the original loading of the Merrifield resin) for the 5 steps from the starting resins **202**, Figure 5.3. A general similarity in the yield of the two stereoisomeric piperidines

arising from each resin-bound ester **202a-e** showed that the synthetic transformations were reliable. Efficient production of piperidine **207c** proved that aromatic substituents at C-2 of the piperidine were tolerated by the hydrogenolysis under atmospheric pressure. Clean reduction of the alkene of **206e** demonstrated that while alkenes were not tolerated by the method, a single product would likely be obtained.

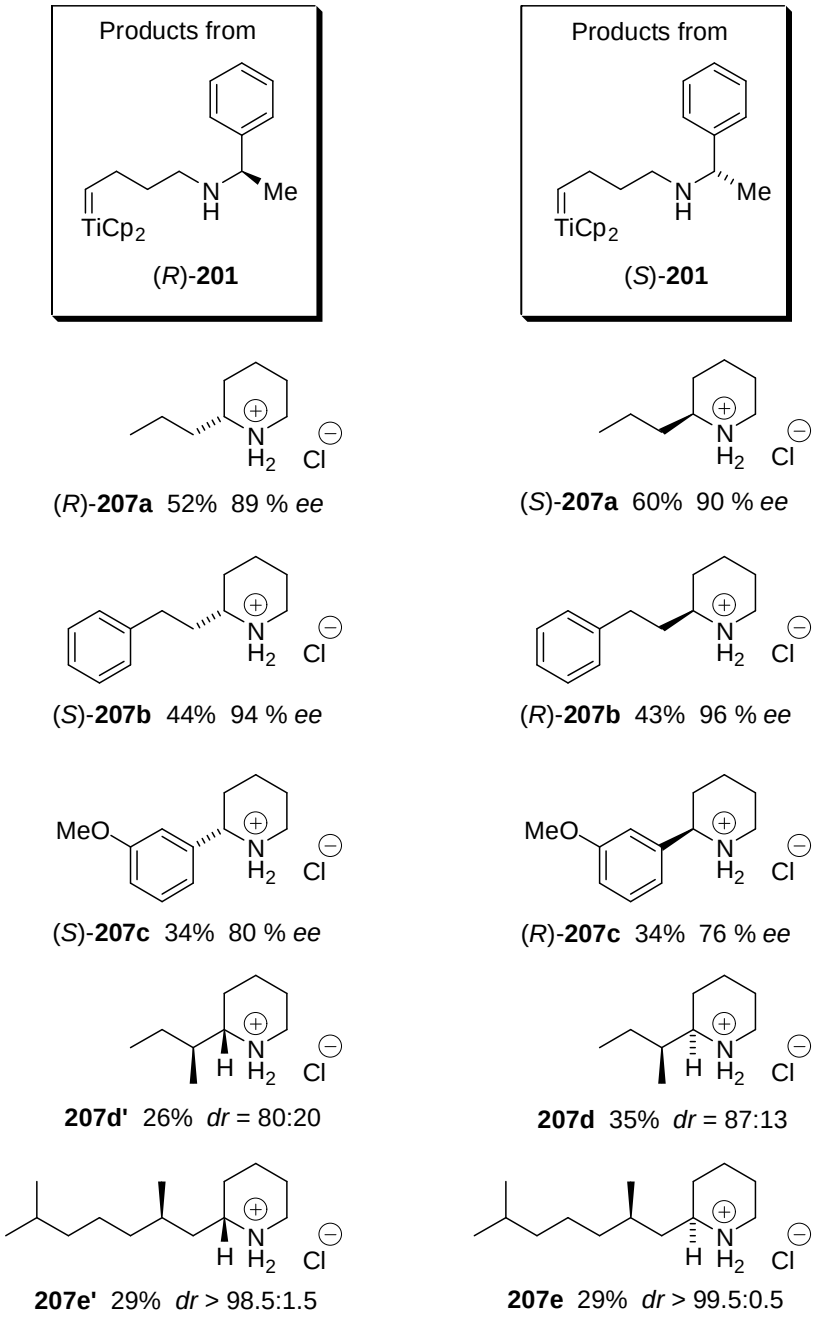
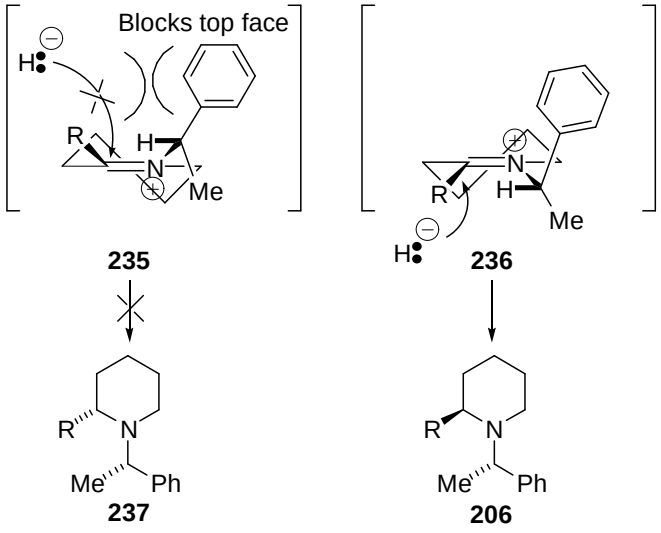


Figure 5.3 Yields of piperidines **207** from resin-bound esters **202**

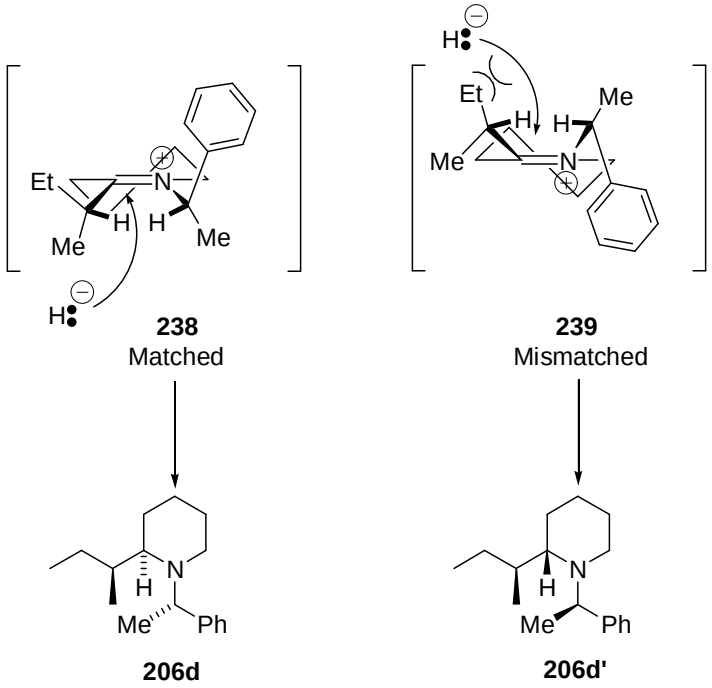
The stereoisomeric purity of the piperidines was good to excellent. The enantiomeric purity of piperidines **207a-c** produced from titanium reagents (*R*)-**201**, and (*S*)-**201** would

have been expected to be equal and opposite, and only small differences were observed. These could have arisen during reduction of the iminium ion if the conditions were slightly different, but washing of the salt of the final piperidine could also account for small changes, if homochiral material packs differently from heterochiral material (lattice energy affects solubility). Increasing steric bulk of the substituent at the 2-position appears to increase the diastereoselectivity in the reduction of the iminium ions **205**, unless the bulk is directly adjacent to the point of induction of stereochemistry. The larger the R group, the more the phenethyl group will project the small proton towards the R group to minimize 1,3-allylic strain. In doing so, the phenethyl group blocks axial attack on the half-chair conformation **235** of the ion **205** more consistently, Scheme 5.15. However, if the R group contains a large amount of steric bulk at the carbon atom adjacent to C-2 of the iminium ion, then this steric bulk will also block the reducing agent. Therefore, hindrance to attack is a result of hindrance from the phenethyl group and hindrance from the R group. The facial selectivity will be proportional to the steric hindrance to attack from one face over steric hindrance to attack from the other face. In the case of examples **205a**, **205b**, and **205c** where the R group does not contain a stereocenter, the hindrance due to the R group is equivalent on both faces. When hindrance from the R group is significant compared to the hindrance from the phenethyl group, the ratio of hindrance on the face blocked by the phenethyl group to the hindrance on the other face will be reduced, and facial selectivity will be reduced. An R group with bulk adjacent to C-2 lessens the influence of the phenethyl group, and this accounts for the lower enantiomeric purity observed for piperidine **207c**.



Scheme 5.15

Diastereomeric piperidines **207d** and **207d'** were obtained from chiral resin-bound ester **202d**, and diastereomeric piperidines **207e** and **207e'** were obtained from chiral resin-bound ester **202e**. In all cases the phenethyl group had controlled the favoured absolute configuration at C-2. The discrepancy in the diastereomeric purities in products arising from the (*R*), and (*S*) phenethyl groups is a result of matched and mismatched chiral centres, Scheme 5.16. Consider reduction of the reacting conformers **238** and **239** of diastereomeric iminium ions **205d** and **205d'**, respectively. In both cases, the R group and the phenethyl group project their hydrogen atoms inward towards each other in an effort to minimize 1,3-allylic strain. In the matched case, iminium ion **238**, the ethyl and the phenyl group from the R group and the phenethyl group, respectively, both block the upper face. When the opposite enantiomer of the phenethyl group is used, the mismatched case arises and the opposite is true. In reacting conformer **239**, the bulky substituents from the R group and the phenethyl group block opposite faces. As is evidenced from the results, the phenethyl group wins out and controls the stereochemistry of the 2-position. However, the diastereomeric purity is lower than in the matched case. The overall diastereoselectivity in both cases is low due to the bulky group adjacent to C-2 that reduces stereodifferentiation between the two faces.



Scheme 5.16

A similar effect operates in the reduction leading ultimately to piperidines **207e** and **207e'**. In both cases, the stereoselectivity is high because the R group is bulky, but there is a

CH_2 group next to C-2 of the iminium ions **205e** and **205e'**. The effect of the more distant chiral centre is weak, and matched and mismatched cases give similar diastereoselectivities.

Absolute stereochemistry of (*S*)-**207a**, and (*S*)-**207b** was assigned by comparison of their optical rotations with literature values.[96] As described earlier, these literature comparisons agreed with the predictions made by the model for stereochemical induction, Scheme 4.7. We therefore assigned the absolute stereochemistry of piperidines **207c**, **207d**, and **207e** using the model. Furthermore, all piperidines synthesized using the titanium reagent (*S*)-**201** had positive optical rotations and their trifluoroacetamides (*S*)-**233a** and (*R*)-**233d**, and benzamides (*R*)-**234b**, (*R*)-**234c** and (*R*)-**234e** eluted first on chiral GC and chiral HPLC, respectively. These consistencies in optical rotation and chromatography further confirm the assignments of absolute stereochemistry.

5.6 Conclusion

We have developed a stereodiverse route to 2-substituted piperidines. Overall yields are good (26-60%) and the stereochemistry at the 2-position can be controlled to give piperidines with high levels of isomeric purity (76-96% ee). A range of substituents can be introduced at the 2-position, though groups containing bulk separated from the site of stereochemical induction will give the best results. We imagine that this route would be useful in the production of large, diverse libraries in a DOS.

Experimental

All reactions under an inert atmosphere were carried out using oven dried or flame dried glassware. Solutions were added via syringe. THF was freshly distilled from sodium benzophenone. Dichloromethane, and triethyl phosphite were distilled from CaH_2 prior to use. Petroleum ether refers to the fraction boiling at 40-60 °C. Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The solid phase reactions were carried out in normal glassware, but with the resin (particle size = 150-300 μm diameter) contained within porous polypropylene reactors that had an internal volume of 2.4 mL, and a pore size of 74 μm. Purification by column chromatography was carried out using silica gel, mesh size 35-70 μm as the stationary phase. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz respectively. All coupling constants are measured in Hz. DEPT was used to assign the signals in the ^{13}C NMR spectra as C, CH, CH_2 or CH_3. Mass spectra (MS) were recorded on a Jeol JMS700 (MStation) spectrometer. Infra-red (IR) spectra were obtained on a Perkin-Elmer 983 spectrophotometer. A Golden Gate™ attachment that uses a type IIa diamond as a single reflection element was used in some cases so that the IR spectrum of the compound (solid or liquid) could be directly detected (thin layer) without any sample preparation. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using a AA series Automatic polarimeter. $[\alpha]_D$ values are given in units $10^{-1}degcm^2g^{-1}$.

Merrifield resin bound esters 202

Merrifield resin-bound esters were prepared following the published procedure for loading Merrifield resin.[93] Five polypropylene reactors charged with Merrifield resin [0.311 milliequiv. reactor^{-1}, 163 mg of Merrifield resin with a loading of 1.91 milliequiv. (of benzylic chloride) g^{-1}] were stirred in DMF (35 mL) straight from the bottle, with $CsCO_3$ (1.517 g, 4.66 mmol), KI (0.130 g, 7.83 mmol), and the carboxylic acid (4.65 mmol) at 80 °C for 20 h. The reactors were washed with DMF:H_2O (9:1, 2×), THF (2×), MeOH (2×), DCM (1×), and MeOH (1×) to give the desired resin bound esters contained within porous polypropylene reactors, which were dried under vacuum. The same procedure was used to prepare reactors with a loading of 0.325 milliequiv. reactor^{-1} [170 mg Merrifield resin with a loading of 1.91 milliequiv. (of benzylic chloride) g $^{-1}$].

Preparation of resin-bound enol ethers 203

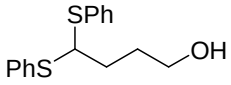
Note: any Ar used during this procedure should be passed through a column of desicant (CaH_2, or CaO) placed between the argon source and the reaction vessel.

Cp_2TiCl_2 (0.93 g, 12 equiv.), Mg (100 mg, 13.2 equiv., predried at 250 °C overnight) and freshly activated 4-Å molecular sieves (0.25 g) were twice heated, gently, by heat-gun under reduced pressure (0.3 Torr) for about 1 min, shaking the flask between heatings, and then placed under argon. Dry THF (5 mL) was added followed by dry $P(OEt)_3$ (1.3 mL, 24 equiv.). After stirring for 3 h, the thioacetal (*R*)-**200** or (*S*)-**200** (3 equiv.) in dry THF (5 mL) was added to the mixture and stirring continued for 15 min. Resin-bound ester **202** [0.311 milliequiv./reactor from Merrifield resin with a loading of 1.83 milliequiv. (chloride) g^{-1}, or 0.325 milliequiv./reactor from Merrifield resin with a loading of 1.91 milliequiv. (chloride) g^{-1}] contained in a porous polypropylene reactor and prepurged with argon was added. After 17 h the reactor was removed from the flask and washed with THF (5×) then alternately with MeOH and DCM (3×), and finally with MeOH then Et_2O. The reactor containing the resin-bound enol ether was then dried under vacuum.

Preparation of chiral piperidines 207

A reactor containing a resin-bound enol ether **203** was shaken with TFA (4%) in DCM (5 mL) for 1 h. The solution was removed and the reactor was washed with DCM (3×). The combined organics were concentrated under reduced pressure to give the salt of the intermediate amino ketone **204**, which was re-dissolved in DCM and washed (2×) with 1 M NaOH. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo to give the free base. TMSCl (5 equiv.) was added to a solution of the resulting amino ketone (0.311 mmols, or 0.325 mmols, 1 equiv.) in dry DCM (1.5 mL) under argon contained in a Schlenk tube. After stirring at RT for 6 h, solvent was carefully removed under vacuum (0.3 Torr). The resulting iminium salt was dissolved in dry DCM (1.5 mL) under argon, cooled to 0 °C and $NaBH(OAc)_3$ (2 equiv.) was added. After stirring for 18 h at RT the solution was treated with 1 M NaOH at 0 °C, washed with 1 M NaOH (3×) and then brine, dried with $MgSO_4$, and concentrated in vacuo to give a piperidine **206**. 10% Pd/C (25 mol%) was added to a solution of the disubstitued piperidine (1 equiv.) and 6 M HCl (2 equiv.) in ethanol (1.5 mL). The atmosphere was changed to H_2, and the reaction was stirred at 65 °C for 5 h. The reaction mixture was centrifuged and the supernatant liquid was decanted through a filter. Concentration *in vacuo* gave the piperidine hydrochloride salt **207** as a solid which was then washed with EtOAc.

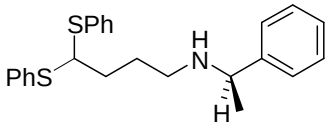
4,4-Bis-(phenylsulfanyl)-butan-1-ol[86] 208



A solution of 2,3-dihydrofuran (3.8 ml, 50 mmols, 1 equiv.) in 50 mL of DCM is cooled to 0 ^oC. Thiophenol (10.3 mL, 100 mmols, 2 equiv.), followed by borontrifluoride diethyletherate (6.35 mL, 55 mmols, 1.1 equiv.), were added to a solution of 2,3-dihydrofuran (3.8 mL, 50 mmols, 1 equiv.) in DCM (50 mL) under Ar at 0 ^oC. The reaction stirred 3.5 h at RT and was quenched with 32 mL of water. The reaction mixture was washed with 1M NaOH (4×), and satd. NaCl (1×). The organic layer was dried over $MgSO_4$ and solvent removed *in vacuo* to give the desired alcohol **208** as an oil (11.89 g, 82%). IR (thin film): 1024, 1064, 1438, 1581, 2873, 3058 cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.47 (1H, broad s, OH), 1.81-1.92 (4H, m, CH_2), 3.65 (2H, t, *J*= 6.0, C*H*$_2$OH), 4.47 (1H, t, *J*= 6.4, CHS_2), 7.25-7.37 (6H, m, H arom.), 7.47-7.51 (4H, m, H arom.). δ_C ($CDCl_3$, 100 MHz): 30.10 (CH_2), 32.30 (CH_2), 58.21 (CH), 62.29 (CH_2), 127.73 (CH), 128.91

(CH), 132.72 (CH), 134.13 (C). *m/z* (EI): 290 (M^+, 5%), 250 (10), 180 (49), 141 (80), 82 (100), 71 (100). HRMS: 290.0799. $C_{16}H_{18}OS_2$ requires (M^+) 290.0799. Data agrees with literature.[86]

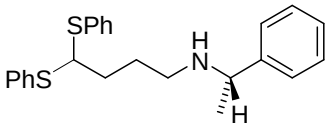
(1'*R*) *N*-[4,4-Bis(phenylsulfanyl)butyl]-*N*-[1'-phenylethyl]amine (*R*)-200



4,4-Bis(phenylsulfanyl)butan-1-ol **208** (11.92 g, 41 mmol) was dissolved in DCM (315 mL). DMSO (29 mL, 41 mmol) and triethylamine (40 mL, 28 mmol) were added. The reaction mixture was cooled to 0 °C. Sulfur trioxide pyridine complex (25.57 g, 160 mmol) was added in 3 g batches. The ice bath was removed and the mixture was stirred under Ar at RT for 20 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (120 mL). The mixture was extracted with DCM (3×) and the organic extracts were combined, washed with water (3×) then satd. NaCl (1×). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield crude 4,4-bis(phenylsulfanyl)butyraldehyde **209** as a cloudy yellow oil (11.88 g). 4Å molecular sieves (4.8 g) and half of the crude aldehyde (5.94 g, 21 mmol) were dissolved in DCM (215 mL). Enantiomerically pure (*R*)-phenylethylamine (5.7 mL, 41 mmol) was added, and the reaction mixture became cloudy. After 3 h of stirring under Ar at RT $NaBH_4$ (0.87 g, 23 mmol) was added. The mixture was stired overnight. The reaction was quenched with water (6mL), and then washed with water (3×), and satd. NaCl (1×). The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. Column chromotography (SiO_2), [petroleum ether-ethyl acetate (1:1)] followed by column chromatography (SiO_2), [eluting first with DCM-petroleum ether (4:1) to remove impurities, and then petroleum ether-ethyl acetate (1:1)] gave the desired amine (*R*)-**200** as a pale yellow oil (4.067 g, 49%). R_f [petroleum ether-ethylacetate (1:1)] 0.18. $[\alpha]_D$ +24.6 (*c* 1.21, DCM) IR (thin film): 3313 (N-H), 3058, 2958, 2925, 1581, 1479, 1450 cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.33 (3H, d, *J*= 6.6, CH_3), 1.73-1.81 (2H, m, CH_2), 1.82-1.89 (2H, m, CH_2), 2.40 (1H, dt, *J*= 11.6, 6.8, CH^AH^BN), 2.47 (1H, ddd, *J*= 11.6, 7.5, 6.2, CH^AH^BN), 3.73 (1H, q, *J*= 6.6, $CHCH_3$), 4.40 (1H, t, *J*= 6.8, CHS_2), 7.28 (11H, m, H arom.), 7.43 (4H, m, H arom.). δ_C ($CDCl_3$, 100 MHz): 24.39 (CH_3), 27.55 (CH_2), 33.58 (CH_2), 46.93 (CH_2), 58.17 (CH), 58.19 (CH), 126.51 (CH), 126.60 (CH), 126.82 (CH),

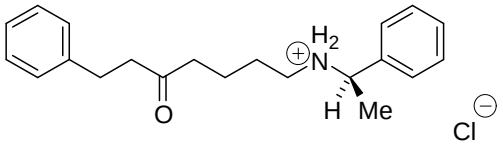
127.60 (CH), 127.63 (CH), 128.39 (CH), 128.85 (CH), 132.65 (CH), 132.70 (CH), 134.24 (C), 134.26 (C), 145.76 (C). *m/z* (EI): 393 (M^+, 58%), 284 ($M^{\bullet+}$-SPh, 100%). HRMS: 393.1586. $C_{24}H_{27}NS_2$ requires (M^+) 393.1585. Microanalysis C, 73.25; H, 6.99; N, 3.66; S, 16.09. $C_{24}H_{27}NS_2$ requires C, 73.28; H, 6.87; N, 3.56; S, 16.28

(1'*S*) *N*-(4,4-Bis-phenylsulfanylbutyl)-*N*-[1'-phenylethyl]amine (*S*)-200



In the same way, the other half of the 4,4-bis-(phenylsulfanyl)butyraldehyde **209** (5.94 g, 21 mmol) was dissolved in DCM (215 mL) and treated with enantiomerically pure (*S*)-phenylethylamine (5.7 mL, 41 mmol) to give the desired amine (*S*)-**200** as a pale yellow oil (3.8 g 46% yield). $[\alpha]_D$ –24.3 (*c* 1.08, DCM). All other data in agreement with that for (*R*)-**200**.

(1'*R*) 1-(1'-Phenylethylamino)-7-phenylheptan-3-one hydrochloride salt (*R*)-204b

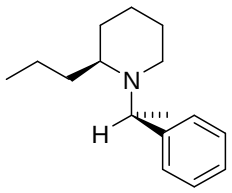


Starting with resin-bound ester **202b** (0.311 milliequiv.), following enol ether preparation using (*R*)-**200** gave the resin bound enol ether (*R*)-**203b**. The reactor containing the resin-bound enol ether (*R*)-**203b** was shaken with TFA (4%) in DCM (5 mL) for 1 h. The solution was removed and the reactor was washed with DCM (3×). The combined organics were concentrated under reduced pressure to give the amino ketone (*R*)-**204b**. The crude product was dissolved in hot 1M HCl and extracted with DCM to give the HCl salt in 57% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.51 (2H, m, CH_2), 1.81-1.90 (2H, m, CH_2), 1.88 (3H, d, *J*= 6.8, CH_3), 2.34 (2H, t, *J*= 7.2, CH_2), 2.48-2.59 (1H, m, CH^AH^{B}N), 2.58-2.68 (1H, m,

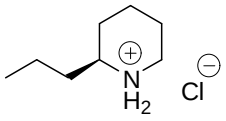
$CH^{A}H^{B}N$), 2.66 (2H, t, *J*= 7.2, CH_2), 2.83 (2H, t, *J*= 8.0, CH_2), 4.20-4.24 (1H, m, $CHCH_3$), 7.08-7.18 (3H, m, arom.), 7.23-7.28 (2H, m, arom.), 7.37-7.40 (1H, m, arom.), 7.42-7.46 (2H, m, arom.), 7.54 (2H, d *J* 7.2, arom.), 9.77 (1H, broad s, $NH^{A}H^{B}$), 10.06 (1H, broad S, $NH^{A}H^{B}$). ^{1}H NMR Consistent with, but different from data for the TFA salt. [99]

(2*S*, 1'*S*) 2-Propyl-1-(1'-phenylethyl)piperidine (2*S*, 1'*S*)-206a



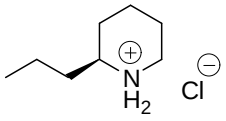
(1'*S*) 8-(1'-phenylethylamino)octan-4-one trifluoroacetic acid salt (*S*)-**204a** in DCM was washed (2×) with 1 M NaOH, dried with $MgSO_4$, filtered and concentrated *in vacuo* to give (1'*S*) 8-(1'-phenylethylamino)octan-4-one as the free base. TMSCl (1.13 mL, 8.90 mmol, 4.4 equiv.) was added to a solution of (1'*S*) 8-(1'-phenylethylamino)octan-4-one (0.499 g, 2.02 mmol, 1 equiv.) in dry DCM (10 mL) under argon contained in a Schlenk tube. After stirring at RT for 5 h, solvent was carefully removed under vacuum (0.3 Torr). The system was purged with Ar. The iminium salt was dissolved in dry DCM (10 mL), cooled to 0 °C and $NaBH(OAc)_3$ (0.856 g, 4.04 mmol, 2 equiv.) was added. After stirring under Ar for 18 h at RT the solution was treated with 1 M NaOH at 0 °C, washed with 1 M NaOH (3×), brine (1×), dried with $MgSO_4$, and concentrated in vacuo to give (2*S*, 1'*S*) 2-propyl-1-(1'-phenylethyl)piperidine (2*S*, 1'*S*)-**206a** as a deep red oil (0.423 g, 90% yield). δ_H ($CDCl_3$, 400 MHz) 0.84 (3H, t, *J*= 7.2, CH_3CH_2), 1.17 (3H, d, *J*= 6.4, CH_3CH), 1.18-1.65 (10H, m, CH_2), 2.13 (1H, m, $CH^{A}H^{B}N$), 2.28 (1H, m, $CH^{A}H^{B}N$), 2.65 (1H, m, H2), 3.92 (1H, q, *J*= 7.2, $CHCH_3$), 7.12 (1H, t, *J*= 7.2, H arom.), 7.21 (2H, m, H arom.), 7.34 (2H, d, *J* = 7.6, H arom.). ^{1}H NMR Consistent with literature data. [99]

(2*S*) 2-Propylpiperidine hydrochloride salt (*S*)-207a (prepared via high pressure hydrogenation)



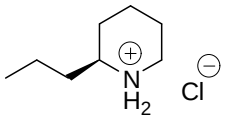
A mixture of (2*S*, 1'*S*) 2-propyl-1-(1'-phenylethyl)piperidine (2*S*, 1'*S*)-**206a** (0.189 g, 0.82 mmol, 1 equiv.), and 20% $Pd(OH)_2/C$ (0.053 g, 10 mol%) in EtOH (6 mL) was hydrogenated at 40 ^oC, and 40 PSI, for 24 h. The reaction mixture was passed through a cotton wool plug directly into saturated ethereal HCl. The solution was concentrated to yield a light brown solid. The solid was washed with hot ether to give (*S*)-**207a** as a light beige solid. (0.1295 g, 97% yield). For characterization data see **(2*S*) 2-propylpiperidine hydrochloride salt (*S*)-207a** (library synthesis)

(2*S*) 2-Propylpiperidine hydrochloride salt (*S*)-207a (prepared via atmospheric pressure hydrogenation)



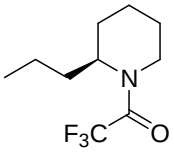
10% Pd/C (102 mg, 25 mol%) was added to a solution of (2*S*, 1'*S*) 2-propyl-1-(1'-phenylethyl)piperidine (2*S*, 1'*S*)-**206a** (92.9 mg, 0.40 mmol, 1 equiv.) and 6 M HCl (0.14 mL, 0.84 mmol, 2 equiv.) in ethanol (2 mL). The atmosphere was changed to H_2, and the reaction was stirred at 65 °C for 5 h. The reaction mixture was centrifuged and the supernatant liquid was decanted through a filter. Concentration *in vacuo* gave the piperidine as a solid which was then washed with EtOAc to give pure (2*S*) 2-propylpiperidine hydrochloride salt (*S*)-**207a** as a solid (64.5 mg, 98%). For characterization data see **(2*S*) 2-propylpiperidine hydrochloride salt (*S*)-207a** (library synthesis)

(2*S*) 2-Propylpiperidine hydrochloride salt (*S*)-207a (library synthesis)



Starting with resin-bound ester **202a** (0.325 milliequiv.), following enol ether preparation, the chiral piperidine preparation, and using thioacetal (*S*)-**200** gave (2*S*) 2-propylpiperidine hydrochloride salt (*S*)-**207a** as a solid (31.4 mg, 60% based on loading of Merrifield resin). $[\alpha]_D^{18}$ +8.1 (*c*=0.52, EtOH), $[\alpha]_D$ +19.8 (*c* 0.50, DCM). Lit:[96] $[\alpha]_D$ +6.5 (*c*=1.2, EtOH). IR (thin film): 2935, 2725, 1590, 1455 cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 0.94 (3H, t, *J*= 7.6, CH_3), 1.36-1.53 (3H, m), 1.57-2.10 (7H, m), 2.73-2.85 (1H, m, $H6^{ax}$), 2.87-2.98 (1H, m, $H6^{eq}$), 3.44 (1H, broad d, *J*=11.1, H2), 9.17 (1H, s, NH^AH^B), 9.47 (1H, s, NH^AH^B). δ_C ($CDCl_3$, 100 MHz) 13.69 (CH_3), 18.53 (CH_2), 22.14 (CH_2), 22.57 (CH_2), 28.08 (CH_2), 35.30 (CH_2), 44.71 (CH_2), 57.11 (CH). *m/z* (CI): 128 (M^+, 100%), 84 (25). HRMS: 128.1438 $C_8H_{16}N$ requires (M^+), 128.1439. ^1H NMR and ^{13}C NMR data agree with literature.[96]

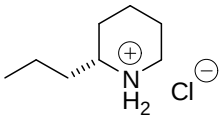
(2*S*) *N*-trifluoroacetyl-2-propylpiperidine (*S*)-233a (Determination of enantiopurity of (*S*)-**207a**)



Triethylamine in DCM (0.14 mL of a 0.37 M solution, 1.5 equiv.) was added to (2*S*) 2-propylpiperidine hydrochloride (*S*)-**207a** (5.3 mg, 32 μmol, 1 equiv.). The solution was cooled to 0 °C and trifluoroacetic anhydride in DCM (0.14 mL of a 0.30 M solution, 40 μmol, 1.2 equiv.) was added. The solution was stirred for 18 h under Ar at RT, and was washed with satd. $NaHCO_3$ (2×), 1M HCl (2×), and satd. NaCl (1×). The organic layer was dried over $MgSO_4$, and solvent removed *in vacuo* to give (2*S*) *N*-trifluoroacetyl-2-propylpiperidine (*S*)-**233a** as an oil (7.0 mg, 97%), existing as a 2:1 mixture of geometrical isomers a, and b. IR (thin film): 2954, 2876, 1686 (C=O), 1457 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.93 ($3H^a$, t *J*= 7.3, CH_3), 0.94 ($3H^b$, t *J*= 7.3, CH_3), 1.17-1.79 ($10H^{a\ \&\ b}$, m), 2.84 ($1H^b$, td *J*=13.7, 1.6, CH^AH^BN), 3.16 ($1H^a$, td *J* =13.1, 2.8, CH^AH^BN), 3.78

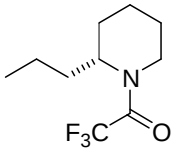
(1H[a], broad d J =13.6, CH^AH^{B}N), 3.97-4.06 (1H[b], m, H2), 4.36-4.43 (1H[b], m, CH^AH^BN), 4.66-4.73 (1H[a], m, H2). δ_C ($CDCl_3$, 100 MHz) 12.92 (CH_3)[a & b], 17.61 (CH_2)[b], 17.77 (CH_2)[a], 18.11 (CH_2)[a], 18.26 (CH_2)[b], 24.31 (CH_2)[b], 25.12 (CH_2)[a], 27.10 (CH_2)[a], 27.52 (CH_2)[b], 30.41 (CH_2)[a], 31.14 (CH_2)[b], 37.39 (CH_2)[a], 40.02 (CH_2)[b], 49.14 (CH)[a], 52.52 (CH)[b]. *m/z* (CI): 224 [$(M+H)^+$, 100%]. HRMS: 224.1264 $C_{10}H_{17}ONF_3$ requires ($M+H^+$), 224.1262. This was then used on a chiral GC (Supelco *β*-DEX 120 column, 70 °C for 2 min, then the temperature was increased at a rate of 1 °C min^{-1} to 150 °C) to show a 90 %*ee* (***t*$_S$=32.98 min**, t_R=33.57 min).

(2*R*) 2-Propylpiperidine hydrochloride salt (*R*)-207a



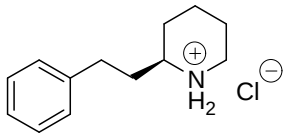
Starting with resin-bound ester **202a** (0.311 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*R*)-**200** gave (2*R*) 2-propylpiperidine hydrochloride salt (*R*)-**207a** as a solid (38.6 mg, 75% based on loading of Merrifield resin). $[\alpha]_D^{18}$ –7.3 (*c*=0.06, EtOH), $[\alpha]_D$ –20.0 (*c* 0.20, DCM). Lit:[96] $[\alpha]_D$ –7.3 (*c*=1.0, EtOH). Other data in agreement with (*S*)-**207a** and literature.[96]

(2*R*) *N*-trifluoroacetyl-2-propylpiperidine (R)-207a (Determination of enantiopurity of (*R*)-**207a**)



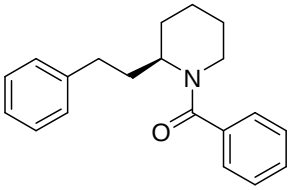
Following the same procedure as for (*S*)-**207a** above, (2*R*) 2-propylpiperidine hydrochloride (*R*)-**207a** (10.5 mg) was converted into (2*R*) *N*-trifluoroacetyl-2-propylpiperidine (*R*)-**233a** (12.1 mg, 84% - data agrees with that of other enantiomer). This was then used on a chiral GC (Supelco *β*-DEX 120 column, 70 °C for 2 min, then the temperature was increased at a rate of 1 °C min^{-1} to 150 °C) to show an 89 %*ee* (t_S=32.97 min, ***t*$_R$=33.55 min**).

(2*R*) 2-Phenylethylpiperidine hydrochloride salt (*R*)-207b



Starting with resin-bound ester **202b** (0.311 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*S*)-**200** gave (2*R*) 2-phenylethylpiperidine hydrochloride salt (*R*)-**207b** as a solid (30.1 mg, 43% based on loading of Merrifield resin). $[\alpha]_D$ +13.5 (*c* 0.38, DCM), +10.1 (*c* 0.139, MeOH) Lit:[96] $[\alpha]_D$ +11.1 (*c* 0.65, MeOH). IR (thin film): 2944, 2719, 1587, 1493, 1455 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 1.29-1.45 (1H, m), 1.63-1.78 (2H, m), 1.79-2.13 (4H, m), 2.27-2.45 (1H, m), 2.61-2.78 (3H, m), 2.80-2.95 (1H, m, CH^AH^{B}N), 3.31-3.45 (1H, m, H2), 7.13-7.37 (5H, m, H arom.), 9.30 (1H, s, NH^AH^B), 9.53 (1H, s, NH^AH^B). δ_C ($CDCl_3$, 100 MHz): 22.05 (CH_2), 22.25 (CH_2), 28.12 (CH_2), 31.09 (CH_2), 34.58 (CH_2), 44.68 (CH_2), 56.56 (CH), 126.11(CH), 128.32 (CH), 128.44 (CH), 140.04 (C). *m/z* (CI): 190 (M^+, 100%), 84 (25). HRMS: 190.1597 $C_{13}H_{20}N$ requires (M^+), 190.1596. ^{1}H NMR and ^{13}C NMR data correspond with the literature.[96]

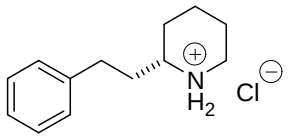
(2*R*) *N*-Benzoyl-2-phenylethylpiperidine (*R*)-234b (Determination of enantiopurity of (*R*)-**207b**)



Triethylamine (10.0 μL, 0.07 mmol, 3 equiv.) was added to (*R*)-**207b** (5.2 mg, 0.023 mmol, 1 equiv.) in DCM (0.30 mL). The solution was cooled to 0 °C and benzoyl chloride (5.0 μL, 0.05 mmol, 2 equiv.) was added. The solution stirred under Ar 18 h while warming to RT, and was then washed with water (1×). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude benzamide as a yellow oil. Column chromatography (SiO_2, Petroleum ether-EtOAc 9:1) gave (2*R*) *N*-Benzoyl-2-phenylethylpiperidine (*R*)-**234b** as a colorless oil (3.8 mg, 56 %). R_f (SiO_2, Hex-EtOAc 2:1): 0.51. IR (thin film): 2931, 1621 (C=O), 1495 cm^{-1}. δ_H ($CDCl_3$, 400 MHz, 50 °C):

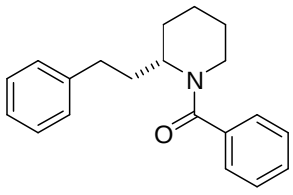
1.32-1.69 (6H, m), 1.71-1.83 (1H, m), 1.97-2.08 (1H, m), 2.41-2.61 (2H, m), 2.84-2.98 (1H, m, C*H*^{A}H^{B}N), 3.75-4.16 (1H, m, CH^{A}*H*^{B}N), 4.28-4.64 (1H, m, H2), 7.05-7.11 (2H, m, H arom.), 7.13-7.18 (3H, m, H arom.), 7.21-7.30 (5H, m, H arom.). δ_C ($CDCl_3$, 100 MHz, 50 ^{o}C): 19.28 (CH_2), 26.14 (CH_2), 28.67 (CH_2), 32.14 (CH_2), 32.89 (CH_2), 125.95 (CH), 123.65 (CH), 128.27 (CH), 128.43 (CH), 128.46 (CH), 129.14 (CH), 137.35 (C), 141.84 (C), 170.89 (C). *m/z* (EI): 293 (M^+, 20%), 188 (70), 105 (100), 77 (33). HRMS: 293.1778 $C_{20}H_{23}ON$ requires (M^+), 293.1780. Chiral HPLC (Chiralcel OD-H, hexane-isopropanol-methanol 98:1:1, 0.5mL min^{-1}) showed 96 %*ee* (***t*$_R$=55.45 min**, t_S=62.17 min).

(2*S*) 2-Phenylethylpiperidine hydrochloride salt (*S*)-207b



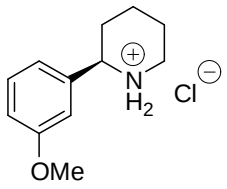
Starting with resin-bound ester **202b** (0.311 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*S*)-**200** gave (2*S*) 2-phenylethylpiperidine hydrochloride salt (*S*)-**207b** as a solid (31.2 mg, 44% based on loading of Merrifield resin). $[\alpha]_D$ –13.9 (*c* 0.47, DCM), –10.1 (*c* 0.089, MeOH). Lit:[96] $[\alpha]_D$ –11.3 (*c* 0.95, MeOH). Other data in agreement with (*R*)-**207b** and literature.[96]

(2*S*) *N*-Benzoyl-2-phenylethylpiperidine (*S*)-**234b** (Determination of enantiopurity of (*S*)-**207b**)



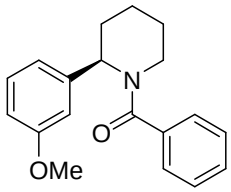
Following the same procedure as for (*R*)-**207b** above, (2*S*) 2-phenylethylpiperidine hydrochloride salt (*S*)-**207b** (6.0 mg) was converted into (2*S*) *N*-Benzoyl-2-phenylethylpiperidine (*S*)-**234b** (4.4 mg, 56% - data agrees with that of other enantiomer). Chiral HPLC (Chiralcel OD-H, hexane-isopropanol 98:2, 0.8 mL min^{-1}) showed 94 %*ee* (t_R=35.65 min, ***t*$_S$=41.27 min**).

(2*R*) 2-(3'-Methoxyphenyl)piperidine hydrochloride salt (*R)*-207c



Starting with resin-bound ester **202c** (0.325 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*S*)-**200** gave (2*R*) 2-(3'-methoxyphenyl)piperidine hydrochloride salt (*R*)-**207c** as a solid (24.9 mg, 34% based on loading of Merrifield resin). $[\alpha]_D$ +27.8 (*c* 1.32, DCM) IR (thin film): 2920, 2704, 1602, 1496 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 1.45-1.58 (1H, m), 1.68-1.77 (1H, m), 1.90-2.16 (4H, m), 2.68-2.81 (1H, m, $H6^{ax}$), 3.14 (1H, broad d, *J*=11.7, $H6^{eq}$), 3.75 (3H, s, CH_3O), 3.82-3.91 (1H, m, H2), 6.85 (1H, dd, *J*= 8.2, 2.1, H6'), 7.08 (1H, broad d, J= 7.7, H4'), 7.19-7.24 (2H, m, H2' & H5'), 9.45-9.61 (2H, m, NH_2). δ_C ($CDCl_3$, 100 MHz): 21.60 (CH_2), 23.11 (CH_2), 30.52 (CH_2), 45.63 (CH_2), 55.51 (CH_3), 61.38 (CH), 112.21 (CH), 115.87 (CH), 119.84 (CH), 129.95 (CH), 137.90 (C), 159.91 (C). *m/z* (CI): 192 (M^+, 100%). HRMS: 192.1388 $C_{12}H_{18}ON$ requires (M^+), 192.1388. Consistent with, but different from data for the racemic free base.[100]

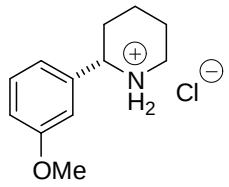
(2*R*) *N*-Benzoyl-2-(3'-methoxyphenyl)piperidine (*R*)-234c (Determination of enantiopurity of (*R*)-**207c**)



Triethylamine (18.5 μL, 130 μmol, 3 equiv.) was added to (2*R*) 2-(3'-methoxyphenyl)piperidine hydrochloride salt (*R*)-**207c** (10.0 mg, 44 μmol, 1 equiv.) in DCM (0.50 mL). The solution was cooled to 0 °C and benzoyl chloride (10.2 μL, 90 μmol, 2 equiv.) was added. The solution stirred under Ar 18 h while warming to RT, and was then washed with water (1×). The organic layer was dried over $MgSO_4$, and concentrated *in vacuo* to yield the crude benzamide as a yellow oil. Column

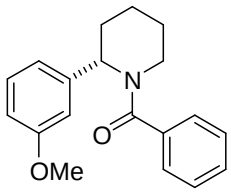
chromatography (SiO_2, Petroleum ether-EtOAc 9:1) gave (2*R*) *N*-benzoyl-2-(3'-methoxyphenyl)piperidine (*R*)-**234c** as a solid (10.1 mg, 78%). R_f (SiO_2, Hex-EtOAc 2:1): 0.45. IR (thin film): 2947, 1629 (C=O), 1490 cm^{-1}. δ_H ($CDCl_3$, 400 MHz, 50 °C): 1.59-1.72 (4H, m), 1.90-2.00 (1H, m, C3H^{A}H^B), 2.38 (1H, broad d, *J* = 14.0, C3H^{A}H^B), 2.93-3.00 (1H, m, C6H^{A}H^B), 3.82 (3H, s, CH_3O), 4.00-4.20 (1H, m, C6H^{A}H^B), 5.50-5.60 (1H, m, H2), 6.81 (1H, dd, *J*=8.2, 2.5, H6'), 6.88 (1H, broad s, H2'), 6.92 (1H, d, *J*=7.7, H4'), 7.30 (1H, t, *J*=8.0, H5'), 7.36-7.39 (3H, m, H arom.), 7.42-7.47 (2H, m, H arom.). δ_C ($CDCl_3$, 100 MHz, 50 °C): 19.85 (CH_2), 26.03 (CH_2), 28.29 (CH_2), 55.31 (CH_3), 112.00 (CH), 113.19 (CH), 119.10 (CH), 126.63 (CH), 128.50 (CH), 129.38 (CH), 129.77 (CH), 136.90 (C), 141.26 (C), 160.47 (C), 171.37 (C). *m/z* (EI): 295 (M^+, 90%), 190 (95), 105 (100), 77 (50). HRMS: 295.1570 $C_{19}H_{21}O_2N$ requires (M^+), 295.1572. Chiral HPLC (Chiralcel OD-H, hexane-isopropanol 97:3, 0.8 mL min^{-1}) showed 76 %*ee* (***t*$_R$=32.05 min**, t_S=42.25 min).

(2*S*) 2-(3'-Methoxyphenyl)piperidine hydrochloride salt (*S*)-207c



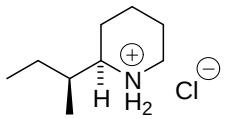
Starting with resin-bound ester **202c** (0.325 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*R*)-**200** gave (2*R*) 2-(3'-methoxyphenyl)piperidine hydrochloride salt (*S*)-**207c** as a solid (25.0 mg, 34% based on loading of Merrifield resin). $[\alpha]_D$ –24.6 (*c* 0.26 , DCM). Other data in agreement with (*R)*-**207c**.

(2*S*) 2-*N*-Benzoyl-2-(3'-methoxyphenyl)piperidine (*S*)-**234c** (Determination of enantiopurity of (*S*)-**207c**)



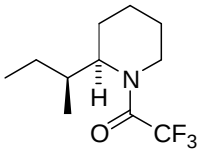
Following the same procedure as for (*R*)-**207c** above, (2*S*) 2-(3'-methoxyphenyl)piperidine hydrochloride salt (*S*)-**207c** (10.2 mg) was converted into (2*S*) *N*-Benzoyl-2-(3'-methoxyphenyl)piperidine (*S*)-**234c** (9.9 mg, 75% - data agrees with that of other enantiomer). Chiral HPLC (Chiralcel OD-H, hexane-isopropanol 97:3, 0.8 mL min^{-1}) showed 80 %*ee* (t_R=32.14 min, ***t*$_S$=41.63 min**).

(2*R*, 2'*S*) 2-[But-2'-yl]piperidine hydrochloride salt 207d



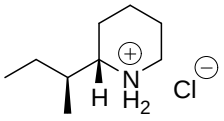
Starting with resin-bound ester **202d** (0.325 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*S*)-**200** gave (2*R*, 2'*S*) 2-[but-2'-yl]piperidine hydrochloride salt **207d** as a solid (20.2 mg, 35% based on loading of Merrifield resin). $[\alpha]_D$ +19.1 (*c* 1.15, DCM) IR (thin film): 2932, 2733, 1590, 1448 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.93 (3H, t, *J*= 7.4, C*H*$_3$CH$_2$), 1.08 (3H, d, *J*= 6.6, C*H*$_3$CH), 1.21-2.08 (9H, m) , 2.84 (2H, m, CH_2N), 3.52 (1H, broad d, *J*=12.1, H2), 8.88 (1H, s, N*H*^{A}H^B), 9.41 (1H, s, NH^A*H*^{B}). δ_C ($CDCl_3$, 100 MHz): 11.48 (CH_3), 14.10 (CH_3), 22.31 (CH_2), 22.83 (CH_2), 23.78 (CH_2), 26.21 (CH_2), 36.99 (CH), 45.73 (CH_2), 61.74 (CH). *m/z* (CI): 142 (M^+, 100%), 84 (25). HRMS: 142.1598 $C_9H_{20}N$ requires (M^+), 142.1596.

(2*R*, 2'*S*) *N*-trifluoroacetyl-2-[but-2'-yl]piperidine 233d (Determination of the diastereomeric purity of **207d**)



Triethylamine (5.9 μL, 42 μmol, 1.5 equiv.) was added to (2*R*, 2'*S*) 2-[but-2'-yl]piperidine hydrochloride salt **207d** (5.0 mg, 28 μmol, 1 equiv.) in DCM (0.25 mL). The solution was cooled to 0 °C and trifluoroacetic anhydride (4.7 μL, 34 μmol, 1.2 equiv.) was added. The solution stirred 18 h under Ar while warming to RT, and was then washed with saturated $NaHCO_3$ (2×), 1M HCl (2×), and brine (1×). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give (2*R*, 2'*S*) *N*-trifluoroacetyl-2-[but-2'-yl]piperidine **233d** as an oil (6.3 mg, 94%), existing as a 2.3:1 mixture of geometric isomers a, and b. IR (thin film): 2962, 1688 (C=O), 1455 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.87 ($3H^{a+b}$, t, *J*= 7.3, C*H*$_3$CH$_2$), 0.928 ($3H^{b}$, d *J*=6.3, C*H*$_3$CH), 0.934 ($3H^{a}$, d *J*= 6.6, C*H*$_3$CH), 0.96-1.08 ($1H^{a+b}$, m), 1.24-1.45 ($1H^{a+b}$, m), 1.46-1.78 ($5H^{a+b}$, m), 1.88-1.98 ($2H^{a+b}$, m), 2.75 ($1H^{b}$, broad t *J*=12.8, $H6^{ax}$), 3.12 ($1H^{a}$, td *J* =13.0, 1.9, $H6^{ax}$), 3.52-3.56 ($1H^{b}$, m, $H6^{eq}$), 3.78 ($1H^{b}$, broad d, *J*=13.6, $H6^{eq}$), 4.27-4.33 ($1H^{a}$, m, H2), 4.36-4.43 ($1H^{b}$, m, H2). δ_C ($CDCl_3$, 100 MHz): due to presence of the other diastereomer and geometrical isomers the carbon spectrum is too complex to analyze. *m/z* (CI): 238 [$(M+H)^+$, 100%]. HRMS: 238.1421 $C_{11}H_{19}ONF_3$ requires ($M+H^+$), 238.1419. This was then used on a chiral GC (Supelco *β*-DEX 120 column, 70 °C for 2 min, then the temperature was increased at a rate of 1 °C min^{-1} to 150 °C) to show a dr (*RS*:*SS*) = 87:13 (***t*$_{RS}$=38.32 min**, *t*$_{SS}$=40.12 min).

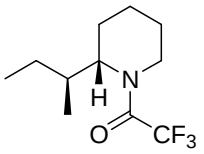
(2*S*, 2'*S*) 2-(But-2'-yl)piperidine hydrochloride salt 207d'



Starting with resin-bound ester **202d** (0.325 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*R*)-**200** gave (2*S*, 2'*S*)

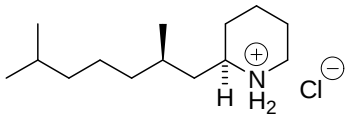
2-(but-2'-yl)piperidine hydrochloride salt **207d'** as a solid (15.0 mg, 26% based on loading of Merrifield resin). $[\alpha]_D$ –16.7 (*c* 0.27, DCM) IR (thin film): 2931, 2736, 1590, 1452 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.91 (3H, t, *J*= 7.4, C*H*$_3$CH$_2$), 1.08 (3H, d, *J*= 6.9, C*H*$_3$CH), 1.19-2.08 (9H, m), 2.73-2.92 (2H, m, CH_2N), 3.53 (1H, broad d, *J*= 12.8, H2), 8.92 (1H, s, N*H*^{A}H^B), 9.18 (1H, s, NH^A*H*^{B}). δ_C ($CDCl_3$, 100 MHz): 11.26 (CH_3), 15.64 (CH_3), 22.24 (CH_2), 22.88 (CH_2), 24.48 (CH_2), 25.46 (CH_2), 37.39 (CH), 45.84 (CH_2), 62.51 (CH). *m/z* (CI): 142 (M^+, 100%), 84 (10). HRMS: 142.1594 $C_9H_{20}N$ requires (M^+) 142.1596.

(2*S*, 2'*S*) *N*-trifluoroacetyl-2-(but-2'-yl)piperidine 233d' (Determination of the diastereomeric purity of **207d'**)



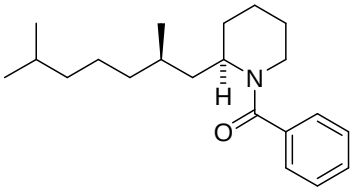
Triethylamine in DCM (0.12 mL of a 0.37 M solution, 1.5 equiv.) was added to (2*S*, 2'*S*) 2-[but-2'-yl]piperidine hydrochloride salt **207d'** (5.2 mg, 29 μmol, 1 equiv.). The solution was cooled to 0 °C and trifluoroacetic anhydride in DCM (0.12 mL of a 0.30 M solution, 1.2 equiv.) was added. The solution stirred 18 h at RT, and was washed with satd. $NaHCO_3$ (2×), 1M HCl (2×), and satd. NaCl (1×). The organic layer was dried over $MgSO_4$, and solvent removed *in vacuo* to give the (2*S*,2'*S*) *N*-trifluoroacetyl-2-(but-2'-yl)piperidine **233d'** as an oil (6.9 mg, 99%), existing as a 2.3:1 mixture of geometrical isomers a, and b. IR (thin film): 2961, 1686 (C=O), 1459, 1215, 1192, 1137, 1105 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.79 (3H^a, d *J*= 6.7, C*H*$_3$CH), 0.82 (3H^b, d *J*= 6.8, C*H*$_3$CH), 0.94 (3H^{a+b}, t *J*= 7.4, C*H*$_3$CH$_2$), 1.08-1.23 (1H^{a+b}, m), 1.24-1.29 (1H^{a+b}, m), 1.46-1.78 (4H^{a+b}, m), 1.88-1.98 (2H^{a+b}, m), 2.75 (1H^b, broad t *J*=13.6, H6^{ax}), 3.10 (1H^a, td *J* =13.9, 2.9, H6^{ax}), 3.58-3.65 (1H^b, m, H6^{eq}), 3.79 (1H^b, broad d, *J*=13.6, H6^{eq}), 4.32-4.43 (1H^{a+b}, m, H2). δ_C ($CDCl_3$, 100 MHz): due to presence of the other diastereomer and geometrical isomers the carbon spectrum is too complex to analyze. *m/z* (CI): 238 [$(M+H)^+$, 100%]. HRMS: 238.1421. $C_{11}H_{19}ONF_3$ requires ($M+H^+$), 238.1419. This was then used on a chiral GC (Supelco *β*-DEX 120 column, 70 °C for 2 min, then the temperature was increased at a rate of 1 °C min^{-1} to 150 °C) to show a dr (*RS*:*SS*) = 20/80 (t_{RS}=38.07 min, **t_{SS}=39.82 min**)

(2*R*, 2'R) 2-[2'-6'-Dimethylhept-1'-yl]piperidine hydrochloride salt 207e



Starting with resin-bound ester **202e** (0.325 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*S*)-**200** gave (2*R*, 2'*R*) 2-[2'-6'-dimethylhept-1'-yl]piperidine hydrochloride salt **207e** as a solid (23.3 mg, 29% based on loading of Merrifield resin). $[\alpha]_D$ +14.3 (*c* 0.71, DCM) IR (thin film): 2927, 2711, 1607, 1433 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.85 (3H, d, *J*= 6.6, C*H*$_3$C6'), 0.86 (3H, d, *J*= 6.6, C*H*$_3$C6'), 0.92 (3H, d, *J*= 6.4, C*H*$_3$C2'), 1.08-2.01(16 H, m), 2.73-2.87(1H, m, $H6^{ax}$), 2.94-3.04 (1H, m, $H6^{eq}$), 3.44 (1H, broad d, *J*=11.0, H2), 9.16 (1H, s, N*H*^{A}H^B), 9.42 (1H, s, NH_AH_B). δ_C ($CDCl_3$, 100 MHz) 20.04 (CH_3), 22.21 (CH_2), 22.43 (CH_2), 22.51 (CH_3), 22.71 (CH_3), 24.41(CH_2), 27.90 (CH), 28.63 (CH_2), 28.85 (CH), 36.05 (CH_2), 39.19 (CH_2), 40.91 (CH_2), 44.78 (CH_2), 55.44 (CH). *m/z* (CI): 212 (M^+, 100%), 84 (25). HRMS: 212.2379 $C_{14}H_{30}N$ requires (M^+), 212.2378.

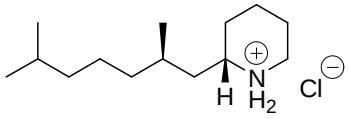
(2*R*, 2'*R*) *N*-Benzoyl-2-[2'-6'-dimethylheptyl]piperidine 234e (Determination of the diastereomeric purity of **207e**)



Triethylamine (5.7 μL, 40 μmol, 3 equiv.) was added to (2*R*, 2'*R*) 2-[2'-6'-dimethylhept-1'-yl]piperidine hydrochloride salt **207e** (3.4 mg, 14 μmol, 1 equiv.) in DCM (0.30 mL). The solution was cooled to 0 °C and benzoyl chloride (3.2 μL, 0.03 mmol, 2 equiv.) was added. The solution stirred under Ar 18 h while warming to RT, and was then washed with water (1×). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude benzamide as a yellow oil. Column chromatography [SiO_2, Petroleum ether-EtOAc (9:1)] gave (2*R*, 2'*R*) *N*-Benzoyl-2-[2'-6'-dimethylheptyl]piperidine **234e** as an oil (4.0 mg, 92%). R_f [SiO_2, Petroleum ether-EtOAc (3:1)]: 0.65. IR (thin film): 2927, 2866, 1631 (C=O) cm^{-1}. δ_H (d6 DMSO, 400

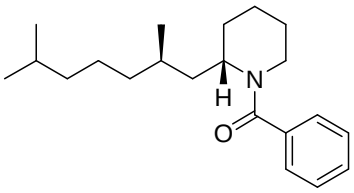
MHz, 80 °C): 0.84 (3H, d, J = 6.2, CH_3C2'), 0.91 (6H, d, J = 6.6, CH_3C6'), 1.09-1.90 (16H, m), 2.95-3.08 (1H, m, H6^{ax}, partly obscured by water peak), 3.72-3.90 (1H, m, H6^{eq}), 4.38-4.54 (1H, m, H2), 7.31-7.39 (2H, m, H arom.), 7.42-7.48 (3H, m, H arom.). δ_C ($CDCl_3$, 100 MHz, 50 ^oC): 19.33 (CH_2), 20.06, 22.57, 22.65, 24.78, 26.36, 27.99, 29.44, 29.90, 37.63, 39.38, 126.72 (CH), 128.37 (CH), 129.08 (CH), 137.51 (C), 171.03 (C). *m/z* (EI): 315 (M^+, 15%), 188 (95), 105 (100), 77 (20). HRMS: 315.2562 $C_{21}H_{33}ON$ requires (M^+), 315.2560. Chiral HPLC (Chiralcel OD-H, hexane-isopropanol 99:1, 0.8 mL min^{-1}) showed dr (*RR*:*SR*) = 99.5:0.5 (***t_{RR}*=16.28 min**, t_{SR}=19.58 min).

(2*S*, 2'R) 2-[2'-6'-Dimethylhept-1'-yl]piperidine hydrochloride salt 207e'



Starting with resin-bound ester **202e** (0.325 milliequiv.), following the enol ether preparation, the chiral piperidine preparation, and using thioacetal (*R*)-**200** gave (2*S*, 2'R) 2-[2'-6'-dimethylhept-1'-yl]piperidine hydrochloride salt **207e'** as a solid (21.2 mg, 26% based on loading of Merrifield resin). $[\alpha]_D$ –15.1 (*c* 3.18, DCM) IR (thin film): 2957, 2722, 1455 cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.841 (3H, d, J= 6.6, CH_3C6'), 0.844 (3H, d, J= 6.6, CH_3C6'), 0.87 (3H, d, J= 6.5, CH_3C2'), 1.08-2.00 (16 H, m), 2.82 (1H, m, H6^{ax}), 2.92-3.06 (1H, m, H6^{eq}), 3.45 (1H, broad d, J=11.6, H2), 9.09 (1H, s, NH^AH^B), 9.37 (1H, s, NH^AH^B). δ_C ($CDCl_3$, 100 MHz): 15.24 (CH_3), 22.25 (CH_2), 22.35 (CH_2), 22.56 (CH_3), 22.65 (CH_3), 24.62 (CH_2), 27.87 (CH), 27.93 (CH_2), 28.90 (CH), 37.75 (CH_2), 39.07 (CH_2), 40.39 (CH_2), 44.74 (CH_2), 55.52 (CH). m/z (CI): 212 (M^+, 100%). HRMS: 212.2376 $C_{14}H_{30}N$ requires (M^+), 212.2378.

(2*S*, 2'*R*) *N*-Benzoyl-2-[2'-6'-dimethylheptyl]piperidine 234e' (Determination of the diastereomeric purity of **207e'**)



Triethylamine in DCM (0.17 mL of a 0.37 M solution, 63 μmol, 1.5 equiv.) was added to **207e'** (10.3 mg, 42 μmol, 1 equiv.). The solution was cooled to 0 °C and benzoyl chloride in DCM (0.26 mL of a 0.19 M solution, 49 μmol, 1.2 equiv.) was added. The solution was stirred for 18 h at RT, and then was washed with satd. NaCl (1×). The organic layer was dried over Na_2SO_4, filtered, and solvent removed *in vacuo* to yield the crude benzamide as a yellow oil. Column chromatography [SiO_2, Petroleum ether-EtOAc 9:1] gave (2*S*, 2'*R*) *N*-Benzoyl-2-[2'-6'-dimethylheptyl]piperidine **234e'** as an oil (9.5 mg, 72%) R_f (SiO_2, Petroleum ether-EtOAc 3:1): 0.63. IR (thin film): 2926, 1625 (C=O) cm^{-1}. δ_H (d6-DMSO, 400 MHz, 80 °C): 0.84 (3H, d, *J* = 6.4, C*H*$_3$C2'), 0.90 (6H, d, *J* = 6.6, 2 × C*H*$_3$C6'), 1.05-1.74 (16H, m), 2.96-3.05 (1H, m, $H6^{ax}$, partly obscured by water peak), 3.78 - 3.93 (1H, m, $H6^{eq}$), 4.33-4.48 (1H, m, H2), 7.32-7.38 (2H, m, H arom.), 7.42-7.49 (3H, m, H arom.). δ_C ($CDCl_3$, 100 MHz, 50 °C): 19.17 (CH_2), 22.56, 22.66, 24.67 (CH_2), 28.00, 28.35 (CH_2), 37.53 (CH_2), 39.30 (CH_2), 126.60 (CH), 128.37 (CH), 129.08 (CH) m/z (EI): 315 (M^+, 15%), 188 (100), 105 (95), 77 (20), 28 (17). HRMS: 315.2562 $C_{21}H_{33}ON$ requires (M^+), 315.2565. Chiral HPLC (Chiralcel OD-H, hexane-isopropanol 99:1, 0.8mL/min) showed dr (*RR*:*SR*) = 98.5:1.5 (t_{RR}=16.19 min, $\boldsymbol{t_{SR}}$**=19.04 min**).

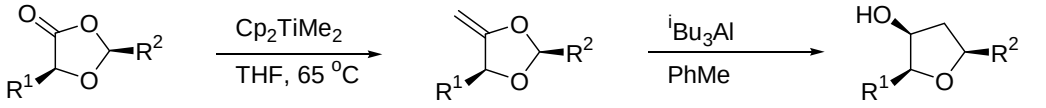
Chapter 6

Petasis-Ferrier Rearrangement

6.1 Discovery and Mechanism

Controlled rearrangements have become important transformations in organc synthesis, especially when synthetically challenging compounds can be obtained from readily synthetically available compounds. One very elegant example is the Petasis-Ferrier rearrangement. The Petasis-Ferrier rearrangement is used to produce the biologically important heterocycles, tetrahydrofurans[101] and tetrahydropyranones[102], from dioxalanones and dioxanones respectively, each available from a simple condensation reaction.

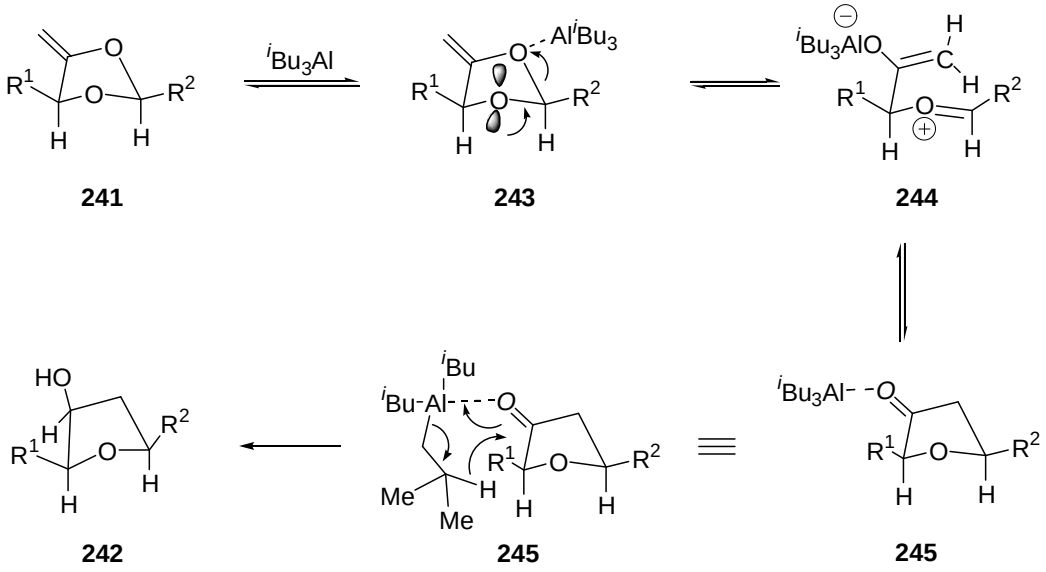
1,3 Dioxalan-4-ones **240** are synthesized *via* the straightforward condensation of α-hydroxy acids and aldehydes, Scheme 6.1. Petasis and Lu found that the dioxalanones **240** could be methylenated to give the corresponding enol ethers **241** which when treated with $^{i}Bu_3Al$ rearranged to give the tetrahydrofurans **242** with good to excellent 2,4,5-*syn* selectivity.



240 → **241** (R^1 = Me, R^2 = Ph, 55%) → **242** (R^1 = Me, R^2 = Ph, 90%, >99% *syn*)

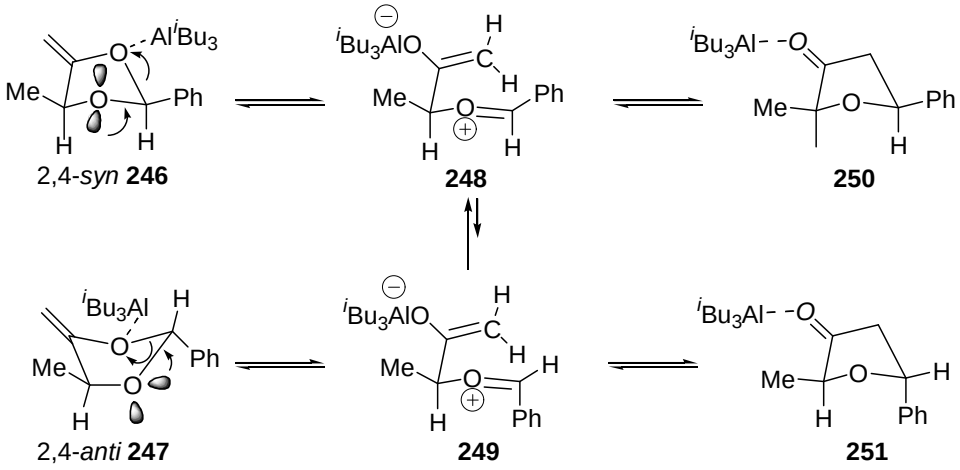
Scheme 6.1

The reaction presumably proceeds by Lewis acid activation of the system by coordination to the oxygen atom of the enol ether **241** to give the species **243**, Scheme 6.2. Following this activation, the lone pair on the oxygen atom that is antiperiplanar to the carbon-oxygen bond assists the ring to open and form the reactive aluminium enolate **244**. The oxonium ion **244** now cyclizes *via* a 5-(*enolendo*)-*endo*-*trig* mechanism to give the Lewis-acid-coordinated tetrahydrofurananone **245**. Intramolecular hydride addition from $^{i}Bu_3Al$ then gives the tetrahydrofuran **242**.



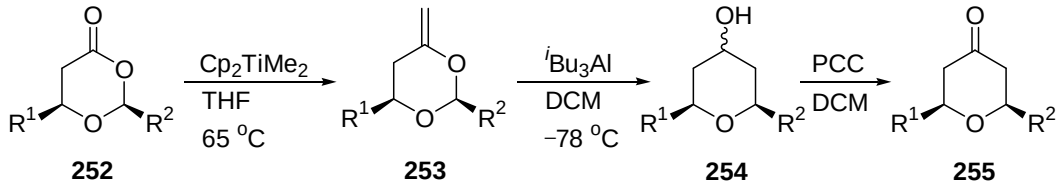
Scheme 6.2

Interestingly, even if the 2,4-*anti* diastereomer of the dioxalanone **240** is used the final tetrahydrofuran is produced in the same high *syn*:*anti* ratio as when the 2,4-*syn* dioxalanone is used. Petasis and Lu proposed explanations for this,[101] Scheme 6.3. Lewis-acid-coordinated 2,4-*syn* enol ether **246**, would likely proceed according to the mechanism proposed above to give the aluminium coordinated tetrahydrofuranone **250** and ultimately the desired tetrahydrofuran. The 2,4-*anti* diastereomer **247**, would first form *Z*-oxonium ion **249** and then isomerise to give the *E*-oxonium ion **248** which is expected to be more stable. As seen previously *E*-oxonium ion **248** would lead to the 2,5-*syn* tetrahydrofuran. It is also possible that the cyclization of the *Z*-oxonium ion **249** to the aluminium coordinated tetrahydrofuranone **251** is an equilibrium process and thus the reaction proceeds to give the thermodynamically favored 2,5-*syn* product.



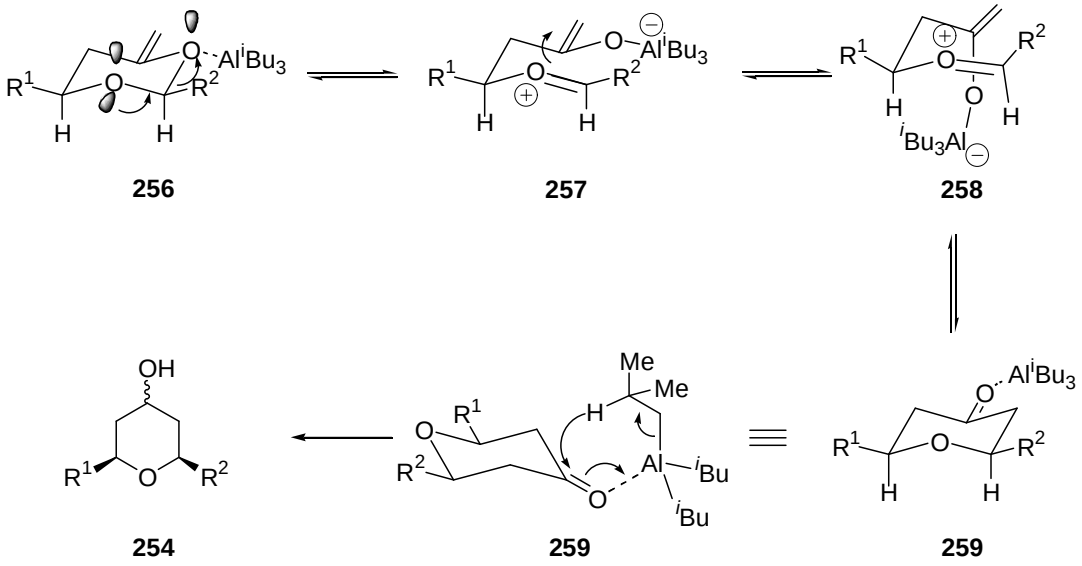
Scheme 6.3

The Petasis-Ferrier rearrangement is better known for its application to tetrahydropyranones, Scheme 6.4. Dioxanones **252** are readily available from simple condensation of β-hydroxyacids and aldehydes. Petasis methylenation of dioxanones **252** yields enol ethers **253**. Petasis and Lu found that when triisobutylaluminium was added to the enol ether **253** a mixture of epimeric 2,6-*syn* tetrahydopyranols **254** were produced. Oxidation of the epimeric alcohols **254** furnished the 2,6-*syn* tetrahydropyranones **255** in good yield.



Scheme 6.4

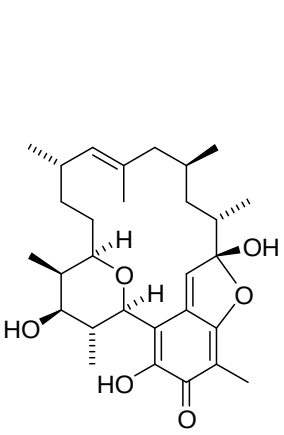
The rearrangement starts with the coordination of triisobutylaluminium to the enolic oxygen atom, Scheme 6.5. Cleavage of the adjacent carbon-oxygen bond assisted by the antiperiplanar lone pair of the other oxygen atom gives the enolate **257**. Bond rotation gives the conformation represented by enolate **258**. The R^1 group occupies the lowest energy pseudo-equatorial position in the 6-membered ring transition state leading to Lewis-acid-coordinated tetrahydropyranone **259**. Intramolecular hydride addition from the triisobutylaluminium produces the epimeric tetrahydropyranols **254**.



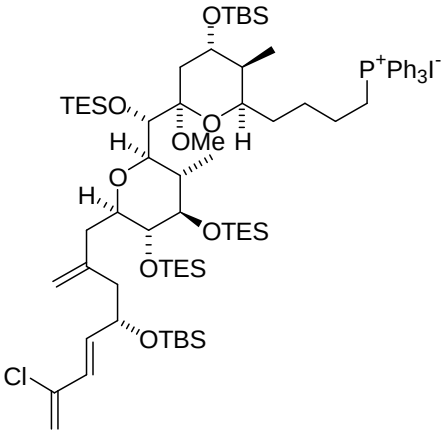
Scheme 6.5

6.2 Phorboxazole A

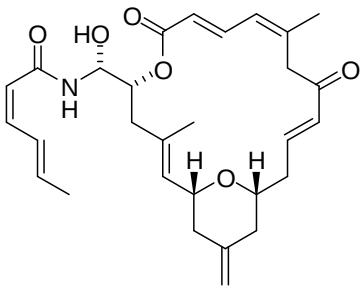
Smith *et al.* have used the Petasis-Ferrier rearrangement to produce a variety of different tetrahydropyran-containing natural products,[103,104,105,106] Figure 6.1.



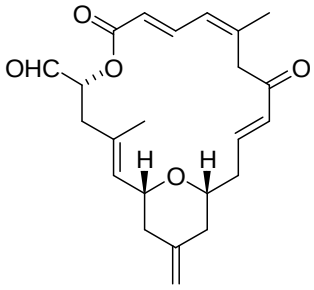
(–)-kendomycin



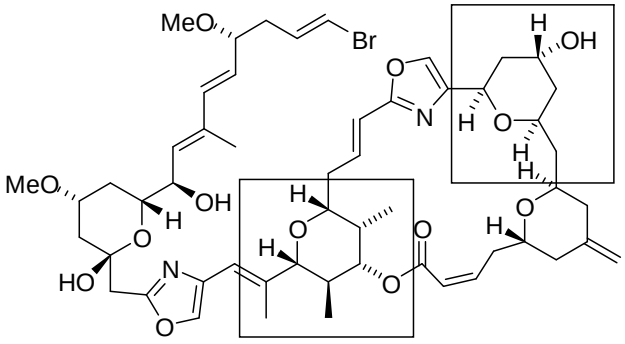
(+)-spongistatin 1 precursor



(+)-zampanolide



(+)-dactylolide

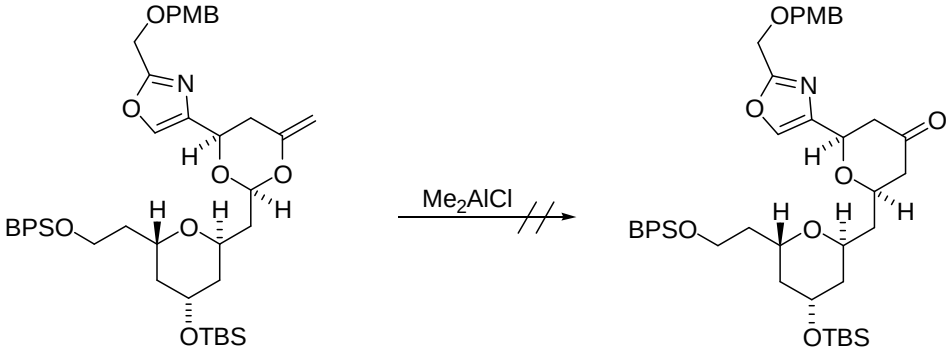


260 (+)-Phorboxazole A

Figure 6.1

In the total synthesis of (+)-phorboxazole A **260**,[106] pioneering work demonstrated the power of the Petasis-Ferrier rearrangement by using the transformation to construct the highlighted 2,6-*syn* tetrahydropyranol units.

Initially, in the synthesis of the tetrahydropyranol adjacent to the oxazole, Smith and co-workers had difficulties effecting the rearrangement. This prompted them to screen several Lewis acids on a model system not only to optimize the yield, but also to prevent the reduction of the initially formed tetrahydropyranone to epimeric alcohols, as the stereoselectivity of the reduction was not reliable. In the model system Me_2AlCl provided better yields than $^{i}Bu_3Al$ and was incapable of the undesired reduction. However, when these findings were applied to the enol ether **261** the rearrangement still failed to occur, Scheme 6.6.



261 **262**

Scheme 6.6

Smith postulated that, since the oxazole nitrogen atom is a strong Lewis base, the Lewis acid does not coordinate enough to the less Lewis basic oxygen atom of the enol ether. Smith believed that if the enol ether oxygen atom could be moved to the side of the alkene closest to the oxazole, that the Lewis acid, which is capable of di-coordination, would be able to coordinate the oxazole nitrogen and reach across to the enolic oxygen, thus allowing the rearrangement to occur, Figure 6.2.

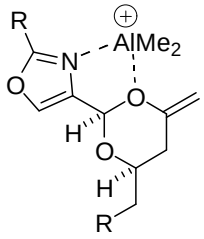
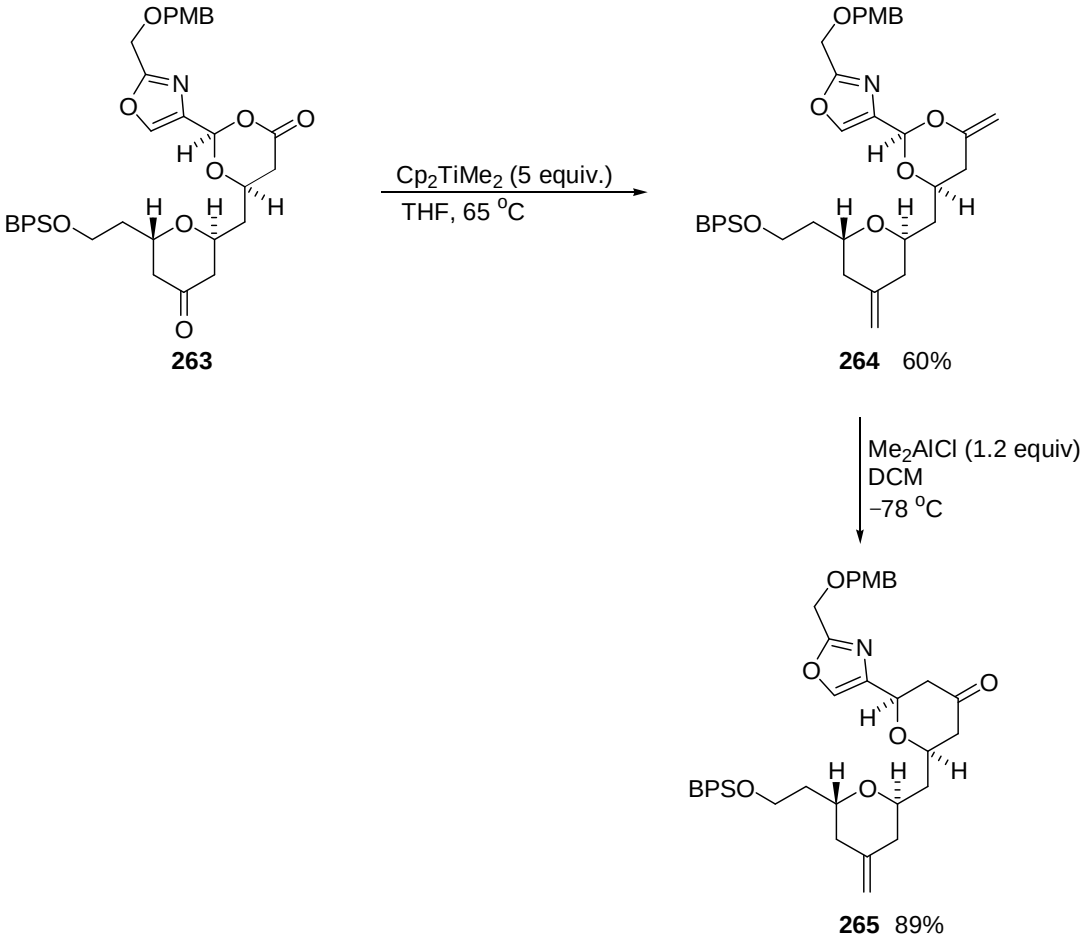


Figure 6.2

The necessary enol ether **264** was prepared from dioxanone **263** by Petasis methylenation at two sites with excess dimethyltitanocene, Scheme 6.7. Now Me_2AlCl effected the desired rearrangement at low temperature and afforded the tetrahydropyranone **265** in very good yield as a single diastereomer.



Scheme 6.7

6.3 Conclusion

Starting from dioxanones, synthetically available from a simple condensation reaction, the Petasis-Ferrier rearrangement enables the production of synthetically valuable 2,6-*syn* tetrahydropyranones. As shown above, the rearrangement has found significant use in the total synthesis of complex natural products, and can be considered a proven synthetic method. Strangely there was no nitrogen analogue of this rearrangement in the literature.

Chapter 7
Microwave-Assisted Organic Synthesis

7.1 Introduction

Microwave energy is emerging as a new source with which to heat and drive chemical transformations. Once considered a last resort to force tricky reactions, microwave irradiation is becoming an important tool for everyday synthesis and the design of experiments.[107,108] Early microwave chemistry took place in conventional kitchen appliances, but now there are a wide variety of specialized microwaves dedicated to synthesis. The extreme increases in reaction rate have attracted much attention from academics and industrialists alike.

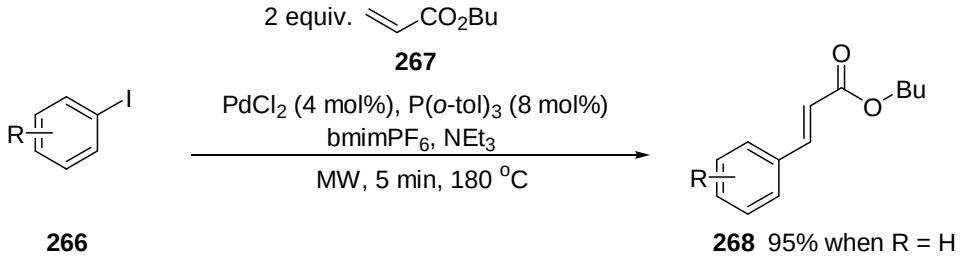
Conventional heating relies on heat transfer from a heat source, through a reaction vessel, and finally into the reaction medium. This has a host of negative effects: the exterior of the reaction is hotter than the interior, power is wasted in the heating of the exterior, and temperature is difficult to control and monitor. Microwave-assisted organic synthesis (MAOS) overcomes these problems *via* direct coupling of microwave energy to the reagents and solvents in the reaction vessel. With MAOS heating a reaction mixture is fast, efficient, and easy to control.

Applying an electromagnetic field causes dipoles or ions to align with that field. If the field oscillates then the dipoles or ions will try to reorient with the change in the field, and give off energy in the form of heat. The most efficient heating occurs when the electromagnetic field oscillates at a frequency that is slow enough for the dipoles to align with but not follow the applied electromagnetic field. Typically the frequency of chemical microwaves is 2.45 GHz. Different solvents respond to microwave irradiation to varying degrees. The two factors that are most indicative of a medium's ability to convert electromagnetic radiation into heat are the dielectric loss (ε"), and the dielectric constant (ε'). The dielectric loss describes the efficiency with which electromagnetic radiation is converted into heat. The dielectric constant describes the ability of the molecules to be polarized by the electromagnetic field. The ratio of (ε"/ε') is described as the loss factor (tanδ). A larger value of tanδ indicates a reaction medium that is more suited to MAOS. The loss factors of various solvents are summarized in table 7.1.

Table 7.1 loss factors of some standard solvents[107]

Solvent	Tanδ
Ethanol	0.941
DMSO	0.825
Methanol	0.659
DMF	0.161
Water	0.123
Acetonitrile	0.062
THF	0.047
Dichloromethane	0.042
Toluene	0.040
Hexane	0.020

Due to their very polar nature and high boiling points ionic liquids make excellent solvents for MAOS. Larhed and co-workers have used the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF_6) to perform Heck reactions,[109] Scheme 7.1. When an aryl halide **266** in the ionic solvent was treated with an acrylate **267** and standard Heck conditions, the desired cinnamic esters **268** could be obtained in only 5 minutes in high yield. This is in stark contrast to the long reaction times of several hours necessary when employing reflux conditions by conventional heating, and a conventional solvent. More challenging examples required slightly longer reaction times, but even when electron-rich aryl halides were used, reactions were finished in 45 minutes. Purification was simple as the reaction medium was completely non-volatile. Distillation isolated the product and also left the reaction medium ready for a subsequent Heck reaction. Indeed the catalytic ionic system could be recycled 5 times and still provide yields in excess of 90%, each time requiring simple distillation to separate product from reaction medium. Aside from the creative purification procedure, the high temperature made possible by a very high boiling solvent, and the ability of microwave energy to achieve this temperature are exploited to drastically shorten the reaction time for this very useful transformation.



266 **268** 95% when R = H

Scheme 7.1

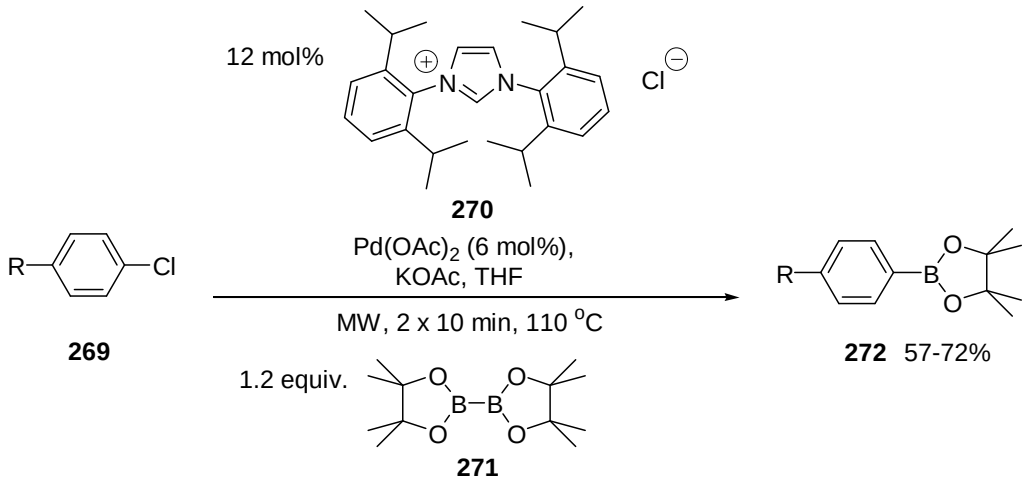
7.2 Microwave Effects:

Due to the vast increase in reaction rate sometimes observed with MAOS there is a great deal of controversy concerning the existence of a microwave effect. Some scientists believe that the rate increase is the result solely of thermal effects, that rate increase is caused by the rapidly achieved high temperatures. Others believe that the ability of the applied electromagnetic field to orientate molecules plays a part in the short reaction times.[110] The Arrhenius equation [$K = A \exp(-E_a/RT)$] is helpful in visualizing the claimed non-thermal microwave effects. The pre-exponential constant A is related to the probability of molecular impacts. The organized vibration of polar molecules at the reaction interface could plausibly effect A and increase the rate. It is also argued that the applied field can organize polar species, affecting entropy, and the activation energy. Stabilization of polar intermediates could also play a role in rate increase. If a reaction proceeds via a polar transition state the applied electromagnetic field should stabilize the polar species. When polarity increases from reactants to transition state the stabilizing effects of the applied field would decrease the activation energy of the reaction, and speed up the reaction. The reasons for the dramatic rate increase sometimes observed with MAOS will be discussed for many years to come, however, the effects of this rate increase can be enjoyed today.

7.3 Isochoric Microwave Irradiation for High Temperatures

Microwave irradiation is frequently used to heat a conventional solvent far in excess of its boiling point, by heating the reaction in a sealed tube. Fürstner and Seidel use this strategy to good effect in their route to arylboronates **272**. The Suzuki cross coupling reaction has become one of the most widely used transformations in chemistry, and many literature procedures use microwave energy to drive the reaction.[111] A microwave-assisted route to the precursor pinacol arylboronates needed for the Suzuki reaction would further streamline the technique. Fürstner's route gives pinacol boronates from aryl chlorides using a Pd-heterocyclic carbene complex,[112] Scheme 7.2. The use of aryl chlorides is significant as they are more readily available, but less reactive than their bromine and iodine analogues. No doubt the microwave technology employed plays a key role in enabling use of the less reactive chloro substrate. The catalytic system is made up of $Pd(OAc)_2$, and an *N*-heterocyclic carbene produced *in situ* by deprotonation of the imidazolium salt **270**. An aryl chloride **269** is treated twice with the catalytic system in

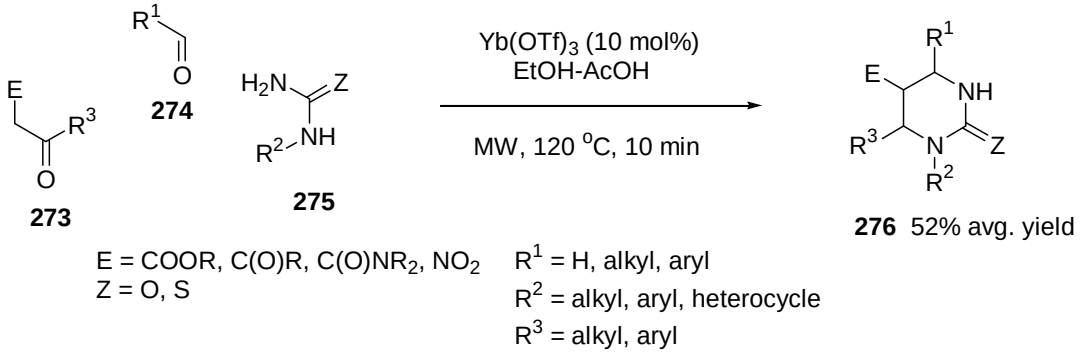
the presence of bis(pinacol)borane **271** at 110 °C for 10 minutes. After this very short 20 minute reaction time, the desired arylboronates **272** are isolated in good yield.



Scheme 7.2

7.4 Reaction Development

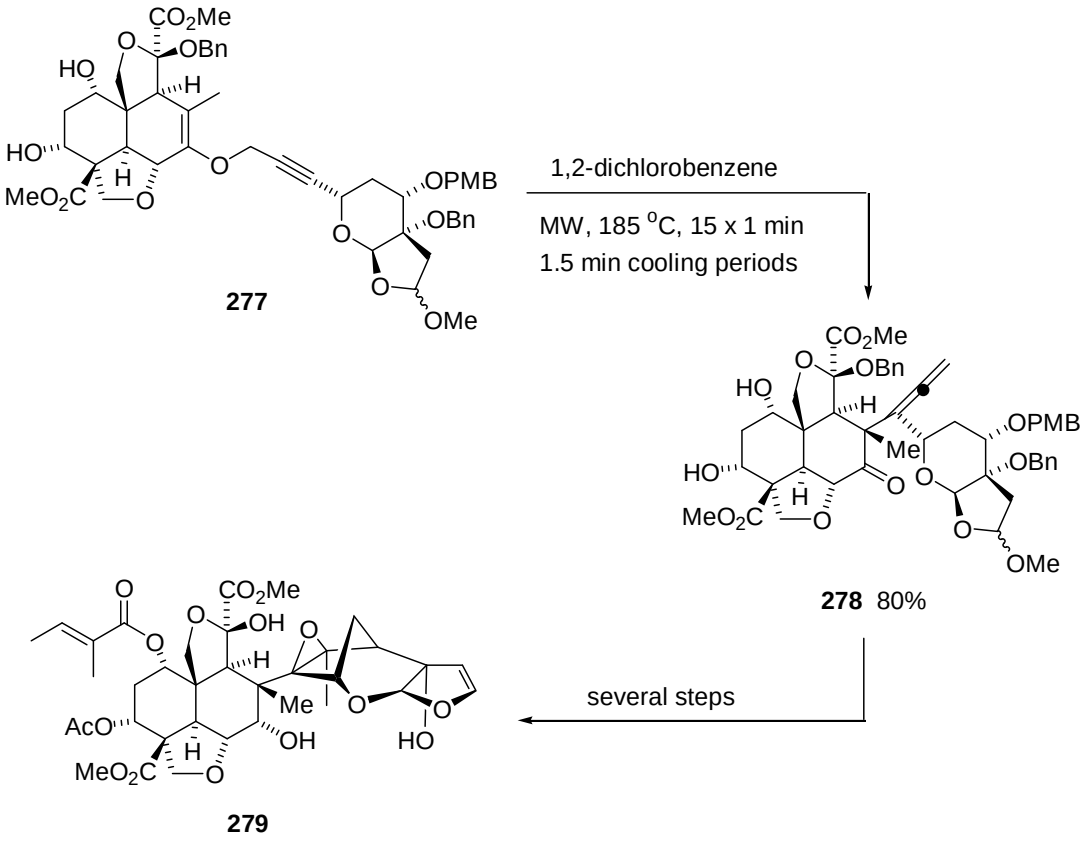
Stadler and Kappe's optimization of the Biginelli reaction demonstrates the powerful ability of microwave-assisted synthesis to speed up reaction development, Scheme 7.3.[113] Due to the very short reaction times, MAOS allows many different parameters to be tested very quickly. Furthermore, results are obtained so fast that test runs can be performed in series, not parallel. Information gained from one test run can easily provide input into the design of the next test run. Using these advantages, the catalyst, reaction temperature, and reaction time for the microwave-assisted Biginelli reaction were optimized in only a few hours of experiment time. With optimized conditions in hand, a 48 member library of dihydropyrimidines **276** was produced in good average yield and within 12 h.



Scheme 7.3

7.5 Fine Control of Reaction Temperature

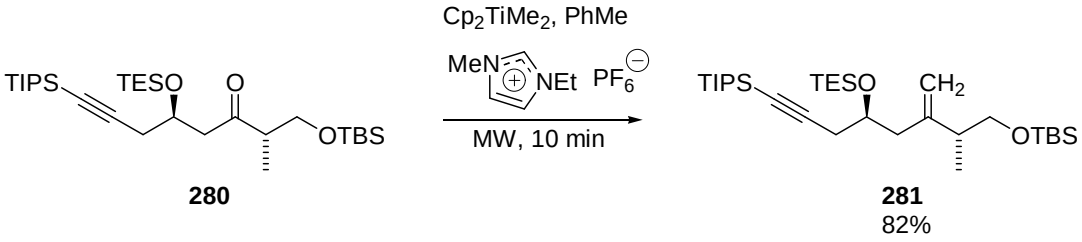
Microwave-assisted chemistry also finds itself at the forefront of natural product synthesis. Ley and co-workers have recently reported the total synthesis of azadirachtin **279**.[114] A key Claisen rearrangement is driven by microwave energy to give the allene **278** necessary for the radical cyclization that forms the core ring structure of the complex and beautiful natural product **279**, Scheme 7.4. While conventional heating failed even in the presence of Claisen rearrangement promoting Lewis acids, and after extended periods of time, microwave energy effected the desired reaction in minutes with no additive necessary. Pulsing of the microwave energy was important and prevented decomposition at the extreme temperature. Here the control made possible by microwave technology is key. Since heating only occurs in the reaction vessel, and not in the surroundings, very precise heating and cooling can be achieved with the convenience of an on-off switch. While many advantages of microwave chemistry come from the dull axe of extreme temperatures, the method also has an elegant side displayed in this beautiful total synthesis.



Scheme 7.4

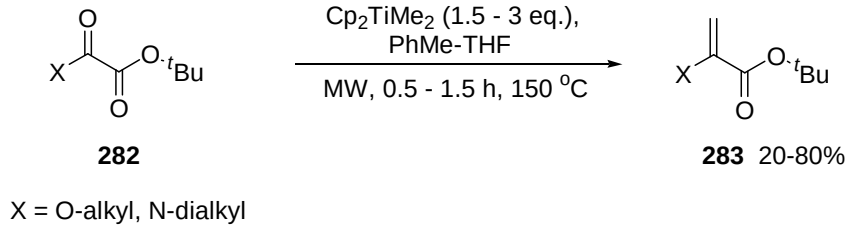
7.6 Petasis Methylenation

Two examples of microwave-assisted Petasis methylenation exist in the literature. Ley and co-workers first used the stategy to methylenate a key intermediate in the synthesis of spongistatin 1,[72] Scheme 7.5. When ketone **280** was heated conventionally at 120 ^{o}C for 3 h with dimethyltitanocene in toluene, the alkene **281** was produced in a 71% yield. However, adding a small amount of ionic liquid (1-ethyl-3-methylimidazoline hexafluorophosphate), and using microwave irradiation to heat the reaction at 160 ^{o}C for 10 min produced alkene **281** in an 82% yield. When a conventional solvent is used with a low tanδ value, achieving high temperature with microwave energy can be difficult. Ley and co-workers overcame this problem by adding the ionic liquid to the solvent which acts as a sponge for the microwave energy. Importantly, even at the extreme temperature the mild methylenating reagent leaves both chiral centres untouched, avoiding enolization or retro-Michael addition.



Scheme 7.5

More work in this area has highlighted the utility and selectivity of the microwave-assisted Petasis methylenation. Gallagher and co-workers were having trouble finding a route to pyruvate based enol ethers **283**. However, they found that microwave energy efficiently drove the Petasis reaction giving the desired products,[71] Scheme 7.6. When pyruvate-based oxalates **282** were treated with dimethyltitanocene, and heated for just 30 minutes with microwave energy, only the less hindered carbonyl was alkenated to form enol ethers **283** in good yield. Enamines could also be produced from oxalate monoamides. Conventional heating gave very poor results and even after 24 h, the reaction had failed to go to completion. In 30 min the extreme temperature achieved with microwave energy had driven the reaction entirely to completion; leaving the *tert*-butyl ester functionality completely unreacted.



282 **283** 20-80%

X = O-alkyl, N-dialkyl

Scheme 7.6

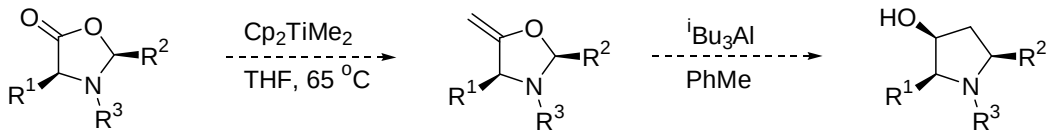
7.7 Conclusion

The advent of MAOS means that the choice of heat source has become a key variable to be considered for maximizing success in the laboratory. While microwave energy is a powerful new tool, it is not a suitable heating source for all applications, and the method suffers when it comes to scaling up. However, when compared to conventional heating in efficiency, control, and speed, microwave irradiation is a superior heat source. The speed with which information can be gathered and applied to reaction optimization is particularly impressive and significant. Every year an increasing number of microwave-assisted routes are published, and the method is gaining popularity in industry as well. As demonstrated by the microwave-assisted Petasis methylenation, some reactions benefit greatly from the special attributes of microwave energy. As with many examples, the reaction shows great promise, but has not been fully explored.

Chapter 8
β-Amino Acids to Piperidinones

8.1 Modified Petasis-Ferrier Rearrangement

We initially envisaged a nitrogen analogue of the Petasis-Ferrier rearrangement. The good yields and the excellent selectivity of the reaction, Scheme 6.1,[101] were attractive attributes and we imagined that perhaps we could produce pyrrolidines **286** *via* a similar reaction pathway, Scheme 8.1. A direct analogue would start with oxazolidinones **284** and proceed to give pyrrolidines **286** *via* enol ethers **285**.



284 **285** **286**

Scheme 8.1

An important factor in the rearrangement would be electron density around the nitrogen atom of the enol ether **285**. Only if the nitrogen atom had enough electron density to assist cleavage of the C-O bond would rearrangement occur. Although *N*-alkyl oxazolidinones proved to be too unstable or difficult to synthesize, there are several simple syntheses of amide and carbamate protected oxazolidinones in the literature.[115,116,117,118,119] However, an amide or carbamate might not have enough electron density at the nitrogen atom due to conjugation of the nitrogen lone pair with the carbonyl group, Figure 8.1.

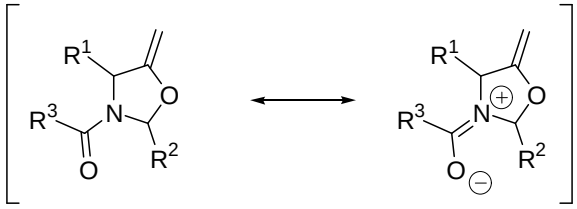
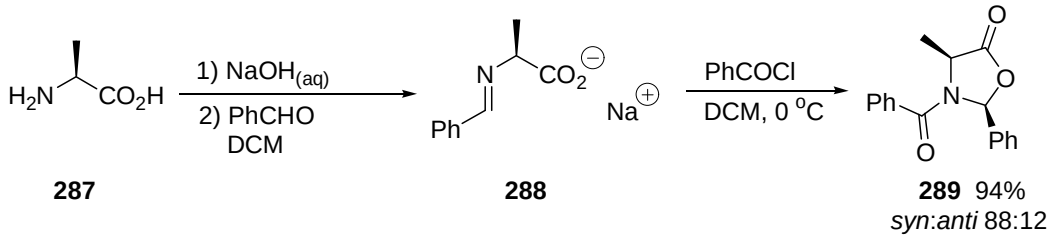


Figure 8.1

On the other hand a *tert*-butyl carbamate (Boc) protected oxazolidinone would be expected to deprotect in the acidic environment required for the Petasis-Ferrier rearrangement and thus provide the necessary electron density on the nitrogen atom.

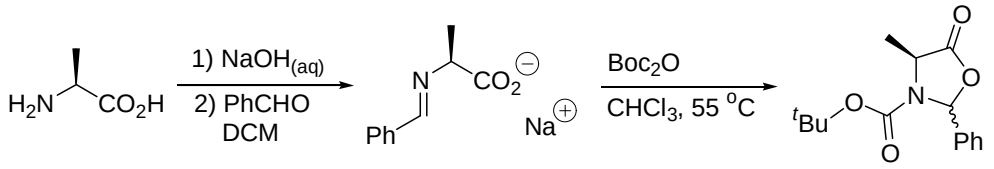
Fadel and Salaün had synthesized the *N*-benzoyl oxazolidinone **289** from alanine **287** *via* the Schiff base **288**,[120] Scheme 8.2. We thought that by using di-*tert*-butyldicarbonate (Boc_2O) in place of benzoyl chloride that we would be able to access the Boc-protected oxazolidinones.



287 **288** **289** 94%
syn:*anti* 88:12

Scheme 8.2

The synthesis of the Boc-protected oxazolidinone proved to be challenging. Boc_2O is not as reactive as an acid chloride and simply replacing benzoyl chloride with Boc_2O produced no desired product. After much experimentation it was found that by heating to 55 °C in chloroform, an appreciable amount of product **290**, presumably the 2,4-*syn* diastereomer, could be obtained, albeit in poor yield, Scheme 8.3.



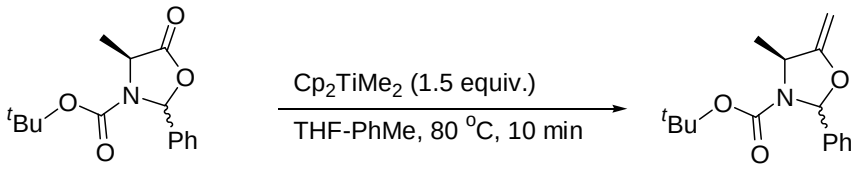
287 **288** **290** 21%

Scheme 8.3

While there are many ways to methylidenate compounds like oxazolidinone **290**, we chose to use dimethyltitanocene as it is easily produced from cheap starting materials,[69] and can be stored for long periods of time. Furthermore, the reagent breaks down to the reactive Schrock carbene by thermolysis and thus the reaction is simple to perform, requiring only heat for activation. Purification is also an attractive attribute as the titanium byproducts precipitate out of hexane. Simple filtration provides a mild workup and purification procedure that even acid-sensitive enol ethers tolerate. Furthermore, the adaptability of the reaction to microwave irradiation enables short reaction times.[71,72]

Literature procedures for microwave-assisted Petasis methylidenation call for very high temperatures and harsh reaction conditions,[71,72] Section 7.6. The solvents are

heated far in excess of their boiling points and in one example a small amount of ionic liquid is necessary to aid the absorption of microwave energy. We decided to investigate milder conditions. To our surprise, reaction of the oxazolidinone **290** with dimethyltitanocene for only 10 min at 80 °C gave the desired enol ether **291** in good yield, Scheme 8.4. While bringing the reaction to 80 °C took about 9 minutes, total reaction time was still under 20 minutes. It was later discovered that the conditions could be even milder; 10 min at 65 °C gave a slightly improved yield, 65%.

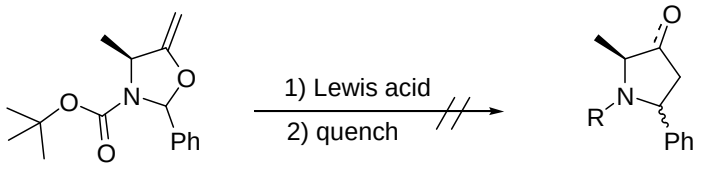


290 **291** 63%

Scheme 8.4

These findings are in stark contrast to previously reported microwave-assisted Petasis methylidenations. No additive is required, and the temperatures are equivalent to those used with conventional heating sources. This is significant, as a commonly given reason for the enhanced reaction rates seen with MAOS is the very high reaction temperature when compared to conventional heating, Section 7.2. Possibly, in this case, there is a rate enhancement due to selective absorption of the microwave energy by the titanium reagent, due to the polar metal-carbon bond. Formation of the Schrock carbene is the rate-determining step in Petasis methylenation.[121] The microwaves would pass through the relatively microwave-transparent solvents, but would interact with the titanium complex leading to α-elimination without significant heating of the bulk solvent.

Although methylenation was successful, all attempts to induce the enol ether **291** to undergo rearrangement were unsuccessful, Scheme 8.5. Trimethylsilyl chloride (TMSCl), trimethylsilyl triflate (TMSOTf), triisobutylaluminium, and dimethylaluminium chloride all failed to effect the desired transformation. Under a range of temperatures and reaction times, only the products of decomposition were ever seen.

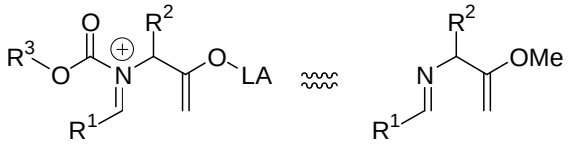


291 **292**

Scheme 8.5

8.2 A New Aproach

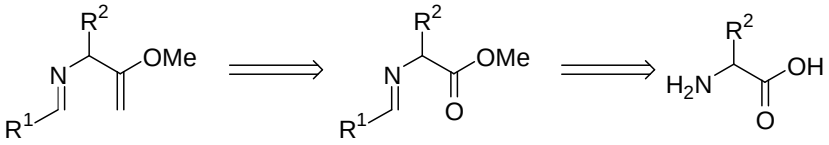
Clearly, a new approach was necessary. Believing that the carbamate failed to rearrange because the ring failed to open and produce the reactive intermediate **293**, Figure 8.2, we sought an alternative reaction that would not require a ring opening, i.e., a synthetic equivalent of the reactive intermediate **293** that would allow access to the target pyrrolidines. The important reactive groups of species **293** are the electrophilic iminium group and the nucleophilic enolate. The imino enol ether **294** contains an imine group which, after activation with an acid, would become a good electrophile, while the enol ether provides a nucleophile analogous to the enolate of bifunctional species **293**.



293 **294**

Figure 8.2

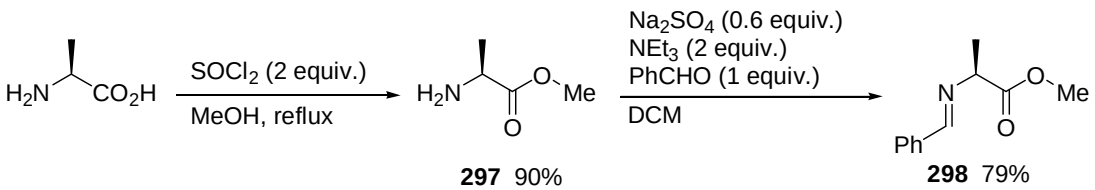
We visualized access to the imino enol ethers **294** via microwave-assisted Petasis methylenation of imino esters **295**, which are readily available from α-amino acids **296**, Scheme 8.6.



294 **295** **296**

Scheme 8.6

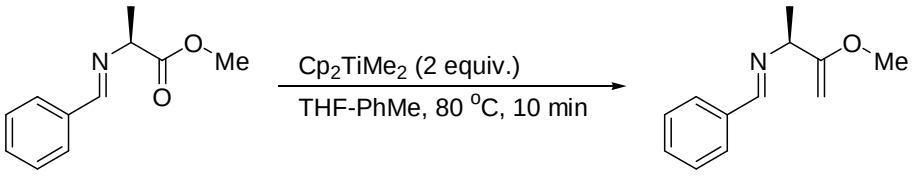
L-Alanine was esterified with $SOCl_2$ in MeOH to give α-amino ester **297** as the HCl salt in excellent yield.[122] A standard procedure taken from Roques and co-workers[123] gave the imino ester **298** in good yield from the condensation of amino ester **297** with benzaldehyde, Scheme 8.7.



297 90% **298** 79%

Scheme 8.7

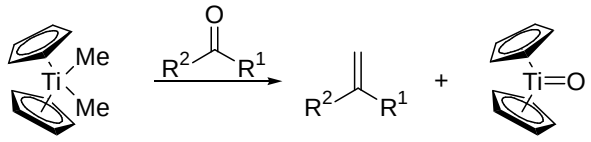
Methylenation of the imino ester **298** posed an interesting situation. While there is only one carbonyl group, the electrophilic imine could also be a target for methylenation. Furthermore, nucleophilic organometallic reagents have been shown to react selectively with the imine functionality of imino esters derived from α-amino acids.[124] Petasis methylenation proceeds *via* a Schrock carbene and, therefore, electrophilicity largely determines the reactivity of a substrate towards dimethyltitanocene. Despite these concerns, the ester group was methylenated selectively to give the enol ether **299** as a single compound, Scheme 8.8. Once again, the exceptionally mild microwave conditions effected the methylenation in only 10 minutes at 80 ^{o}C. Even milder conditions, maintaining the reaction at only 65 ^{o}C for 10 min gave an improved yield of 78%.



298 **299** 54%

Scheme 8.8

The driving force of Petasis methylenation of carbonyl groups is the formation of the strong titanium-oxygen bond in the by-product, titanocene oxide, Scheme 8.9. Reaction with the imine functionality of imino ester **298** would not produce titanocene oxide. Therefore, it seems that the strength of the titanium-oxygen bond not only ensures a good yield for the reaction, but also means dimethyltitanocene selectively reacts with carbonyls in the presence of imines.



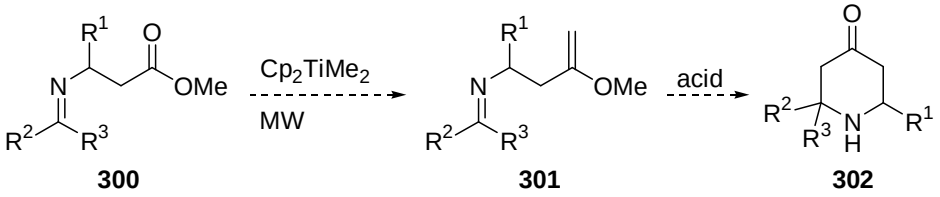
Scheme 8.9

Unfortunately, cyclization of the enol ether **299** was not successful. Once again a range of different acids and conditions failed to give the desired products. After aqueous workup, only the products of hydrolysis or decomposition were obtained. It is probable that the cyclization fails due to its very challenging nature.[125] The 5-(*enolendo*)-*endo-trig* cyclization required is rare, in fact the original Petasis-Ferrier rearrangement is one of the

few examples. We investigated the possibility of a challenging but easier 6-(*enolendo*)-*endo-trig* cyclization.

8.3 Piperidinones

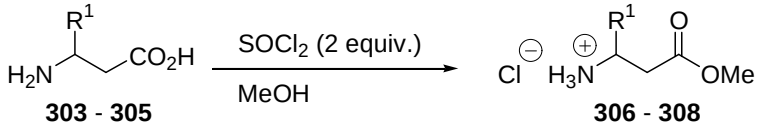
Our strategy centred on the use of a one-carbon extension; using the β-imino enol ethers **301** as the precursors to 2,4-substituted piperidin-4-ones **302**, Scheme 8.10. Thus, piperidinones **302** would be produced by the acid-induced 6-(*enolendo*)-*endo-trig* cyclization of imino enol ethers **301** theoretically available from imino esters **300**.



300 **301** **302**

Scheme 8.10

To validate and then demonstrate our proposed route to piperidinones **302**, β-amino esters **306 - 308** were prepared from β-amino acids **303 - 305**, Scheme 8.11, Table 8.1.



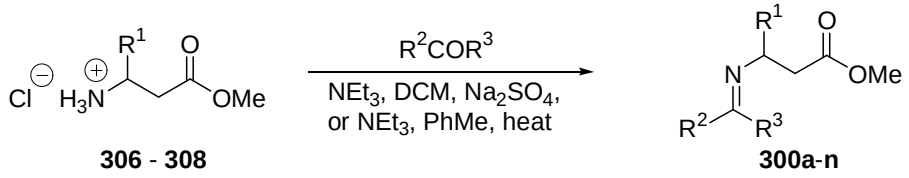
303 - 305 **306 - 308**

Scheme 8.11

Table 8.1 Yields of amino esters from β-amino acids

amino acid	amino ester	R1	Yield
303	**306**	Me	98%
304	**307**	Ph	98%
305	**308**	$PhCH_2$	100%

Condensation of the amino esters **306 - 308** with an aldehyde or ketone gave the desired imino esters **309a-n**, Scheme 8.12, in the yields shown in table 8.2.



306 - **308** **300a**-**n**

Scheme 8.12

Table 8.2 Summary of Imino Ester Synthesis

amino ester	imino ester	R^1	R^2	R^3	conditions used[a]	yield
306	**300a**	Me	Ph	H	A	75%[b]
307	**300b**	Ph	Ph	H	A	89%
307	**300c**	Ph	2,4-$(MeO)_2C_6H_3$	H	A	94%
308	**300d**	$PhCH_2$	Ph	H	A	83%
306	**300e**	Me	(*E*)-4-$MeOC_6H_4CH$=CH	H	A	87%[b]
306	**300f**	Me	2,4-$(MeO)_2C_6H_3$	H	A	61%
306	**300g**	Me	3-Br C_6H_4	H	A	58%
307	**300h**	Ph	^{t}Bu	H	B	90%
307	**300i**	Ph	Et	H	B	91%[c]
306	**300j**	Me	2-F C_6H_4	H	A	55%
307	**300k**	Ph	2-NO_2 C_6H_4	H	A	92%
307	**300l**	Ph	Pyrid-3-yl	H	A	90%
306	**300m**	Me	Ph	Me	C	74%[d]
307	**300n**	Ph	$-(CH_2)_5-$		C	73%

a) see text for details

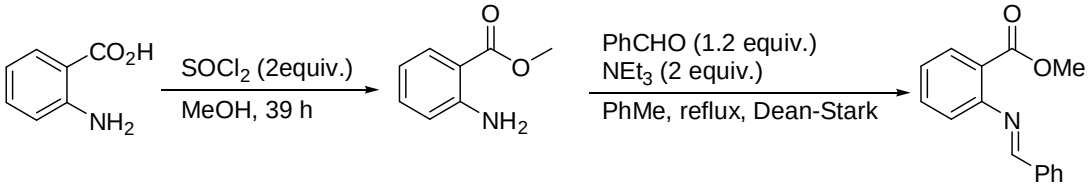
b) Yield based on aldehyde

c) **300i**:**307**:EtCHO 80:13:7; d) *E*:*Z* ratio was 93:7

Most imino esters were formed using **conditions A**, i.e., the amino ester was stirred with the aldehyde, triethylamine, and Na_2SO_4 in DCM at RT. After aqueous workup, any necessary purification was achieved by distillation. Imino esters **300h**, and **300i** were made in the same way, but could not tolerate aqueous workup or distillation, as the aliphatic imines were too unstable, and required the workup procedure outlined in **conditions B**, i.e., workup and purification involved only precipitation of triethylamine salts followed by filtration, and evaporation. While pivaldehyde-derived imino ester **300h** was isolated as pure product, propionaldehyde-derived imino ester **300i** had to be isolated as an 80:13:7 mixture of imino ester **300i**, free amino ester **307**, and propionaldehyde. An excess of easily removed volatile pivaldehyde could be used to drive the formation of **300h** to completion, however **300i** was too susceptible to the formation of enamine-derived side products, and an excess of propionaldehyde could not be used.

Ketone-derived imines **300m** and **300n** failed to form from the treatment of amino esters **306** and **307** with ketones, using Na_2SO_4 as a desiccant. The more challenging condensations required **conditions C**, i.e., the amino ester and ketone were heated at reflux with triethylamine in PhMe with azeotropic removal of water. After aqueous workup any necessary purification was achieved by distillation.

One further imino ester was prepared, Scheme 8.13. Anthranilic acid **309** was esterified with thionyl chloride in MeOH to give the amino ester **310**, and then heated to reflux with benzaldehyde and triethylamine in toluene with azeotropic removal of water to give the imino ester **311**.

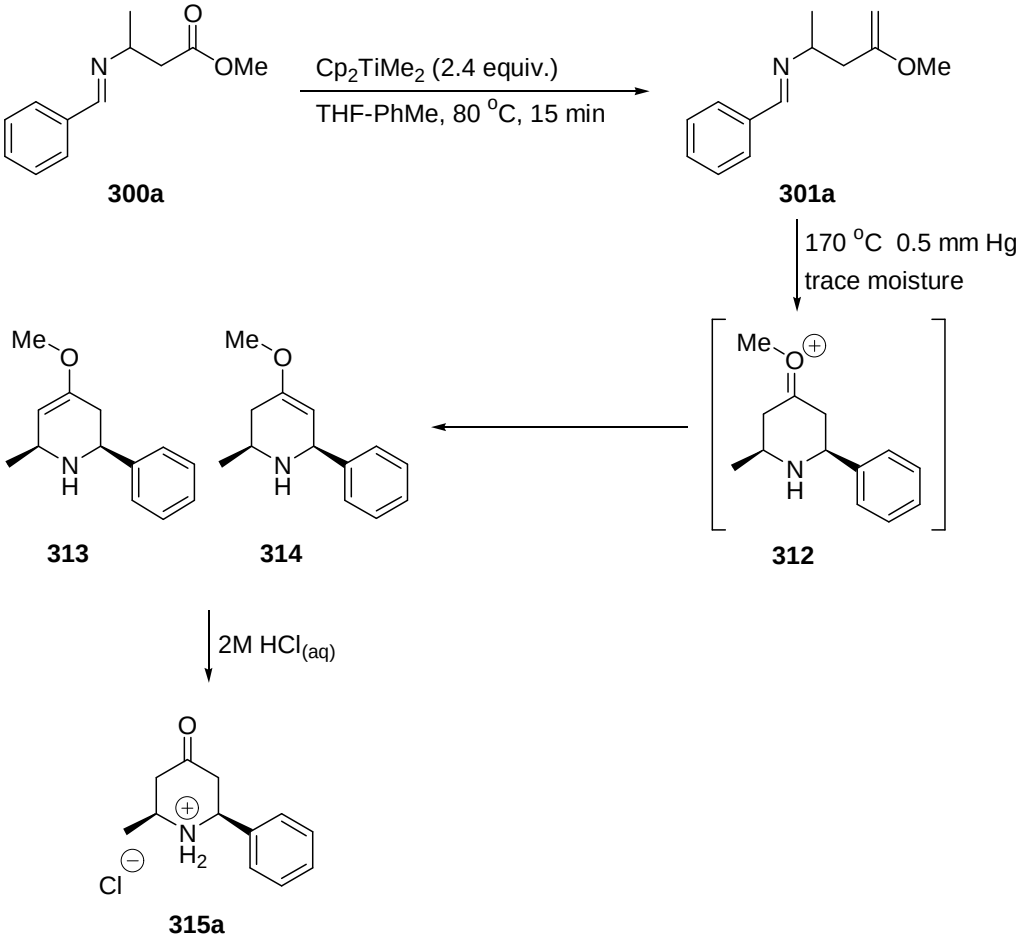


309 **310** 78% **311** 28%

Scheme 8.13

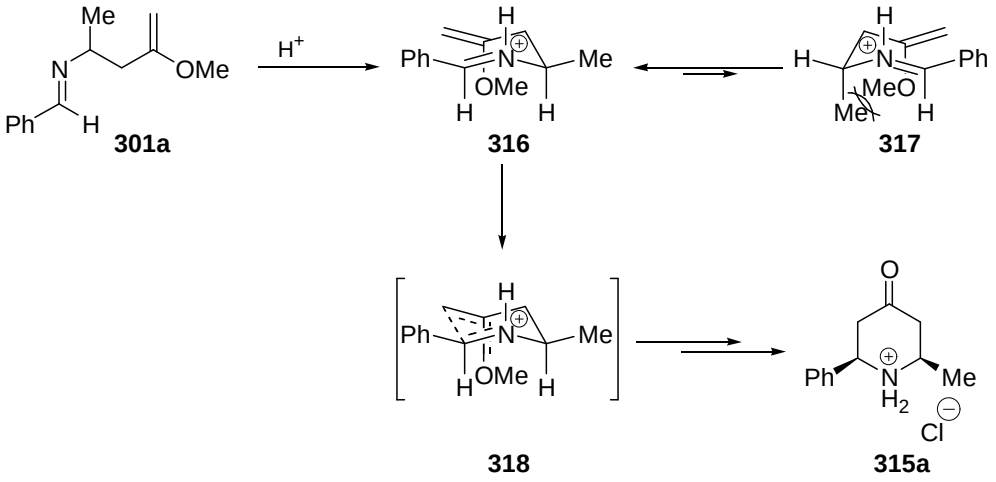
With an array of imines available, we set out to validate our route to piperidinones **302**. The methylenation of imino ester **300a** was attempted using microwave-assisted Petasis methylenation with 1.7 equivalents of dimethyltitanocene, Scheme 8.14. After reaction, analysis of the crude material by ^{1}H NMR spectroscopy revealed the appearance of two broad, overlying 1H singlets at 4.0 ppm, and an upfield shift of 0.3 ppm for the C*H*$_2$C(OMe)=CH$_2$ of the imino enol ether **301a** relative to the C*H*$_2$CO$_2$Me of the starting imino ester **300a**. These findings confirmed the presence of the desired enol ether **301a**. However, it was clear that some ester remained, and the reaction was judged to be about 75% complete. The crude material was re-treated with 0.7 equivalents of dimethyltitanocene. Importantly, the glassware used for the second treatment was not oven-dried. Following normal workup and purification, which included distillation at 170 ^{o}C, the crude material was once again analyzed by ^{1}H NMR spectroscopy. Broad singlets in the region of 3.5 to 4.0 ppm showed that several enol ethers were present, and signals farther upfield displayed peak shapes that resembled those of protons with axial and equatorial couplings in a 6-membered ring. Apparently, the enol ether **301a** had cyclized to give two cyclic enol ethers **313** and **314**. Presumably, the high temperature in the presence of trace moisture caused cyclization of imino enol ether **301a** to give the oxonium ion **312** which lost a proton α to the carbonyl group giving a mixture of the two

cyclic enol ethers **313** and **314**. Simple hydrolysis of the enol ethers with $HCl_{(aq)}$ gave the racemic piperidine as the hydrochloride salt **315a**. Interestingly, not only had we somewhat serendipitously synthesized our target molecule, but it had been made exclusively as the 2,6-*syn* diastereomer, see Section 8.4 for assignment of stereochemistry.



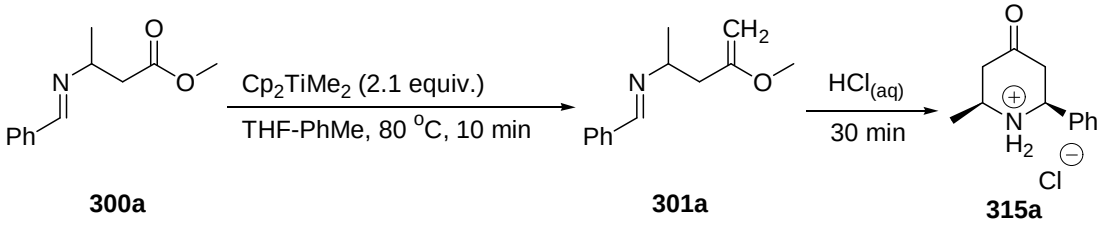
Scheme 8.14

The excellent stereoselectivity observed is probably secured by a preference for a 6-membered transition state **318**, Scheme 8.15. Acid activates the imino enol ether **301a**, which could potentially react by two chair-like conformations **316** and **317**. The low-energy conformation **316** has the R^1 group in a *pseudo*-equatorial orientation, while the *pseudo*-axial orientation of this group in conformer **317** is disfavored by 1,3-*pseudo*-diaxial interactions. The orientation of the R^2 group is set by the *E* geometry of the imine. The relative stability of conformation **316**, and the transition state **318** arising from it, results in selectivity for the 2,6-*syn* piperidinone **315a**.



Scheme 8.15

Formation of the imino enol ether **301a** was repeated in oven-dried glassware. Treatment of the crude imino enol ether **301a** with aqueous acid effected the cyclization which, following a wash with DCM and evaporation of the aqueous acid, gave 2,6-*syn* piperidinium salt **315a** in good yield from imino ester **300a**, Scheme 8.16. A range of different acid concentrations was screened, Table 8.3, with 7M $HCl_{(aq)}$ giving the best results. It is only because cyclization is so fast that aqueous acid can be used. The acid-sensitive imine and enol ether functionalities have little opportunity to undergo hydrolysis.



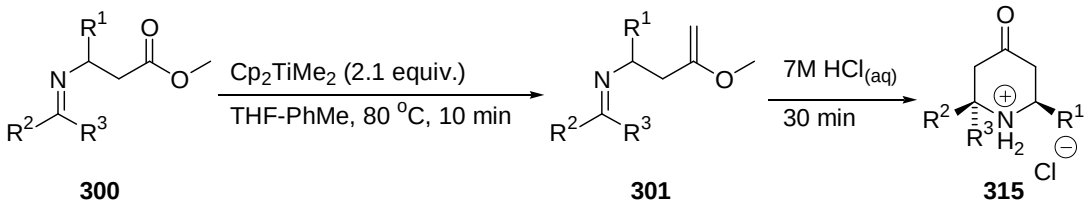
Scheme 8.16

Table 8.3 yield of piperidinium salt **315a** from imino ester **300a**

concentration of $HCl_{(aq)}$	yield of 315a
12 M	23%
9 M	59%
7 M	62%
2.4 M	59%

While the imino ester **300b** was also cleanly methylenated with dimethyltitanocene, and underwent the desired aqueous-acid-induced cyclization to give

diphenylpiperidinium salt **315b**, formation of piperidinium salts **315c** and **315m** was problematic, Scheme 8.17, Table 8.4.



300 **301** **315**

Scheme 8.17

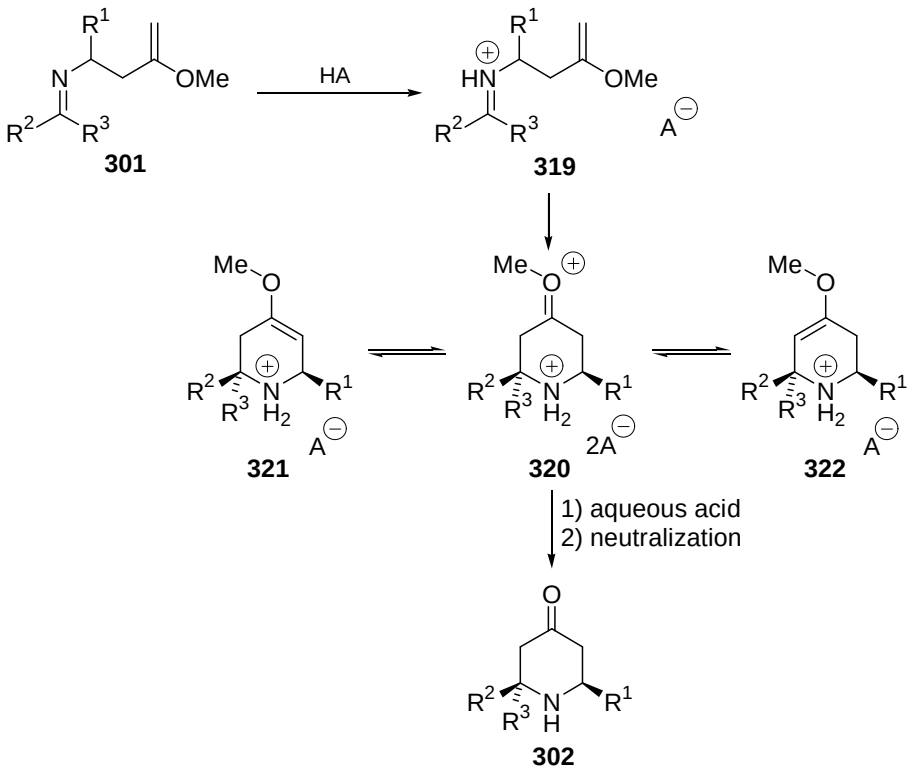
Table 8.4 Yields of piperidinones **315** from esters **300** *via* conditions from scheme 8.17

imino ester	R^1	R^2	R^3	piperidinone	yield
300a	Me	Ph	H	**315a**	62
300b	Ph	Ph	H	**315b**	62
300c	Ph	2,4-$(MeO)_2C_6H_3$	H	**315c**	no product
300m	Me	Ph	Me	**315m**	Trace

Methylenation of imino ester **300m** proceeded cleanly to give enol ether **301m**, but acidic cyclization conditions gave only a trace of piperidinium salt **315m**, isolated by crystallization out of a complex mixture. Presumably, the ketone-derived imine is too sterically hindered for rapid cyclization and hydrolysis competes. The imino ester **300c** decomposed significantly when subjected to dimethyltitanocene at 80 ^oC under microwave-irradiation, but by heating the reaction to only 65 ^oC with microwave irradiation (approximately 7 minutes) and maintaining this temperature for only 3 minutes, the methylenation could be completed without decomposition. In fact, the lower reaction temperature gave improved results in all microwave-assisted methylenations. Unfortunately, despite clean methylenation of imino ester **300c**, cyclization of enol ether **301c** was still problematic. 7M $HCl_{(aq)}$ gave only a 12% yield of the desired piperidinone salt **315c** by crystallization from a complex mixture. The electron-rich nature of the imine probably slowed the cyclization so that hydrolysis competed. The 2,4-dimethoxyphenyl group donates electron density to the imine and in doing so reduces the electrophilicity of the imine, preventing the nucleophilic enol ether from attacking quickly.

Piperidinones **315c** and **315m** were isolated by crystallization from complex mixtures, but the major products in both cases were those of imine and enol ether hydrolysis. The cyclization is fast enough to compete with hydrolysis only when electronics are favorable and the imine is not sterically hindered. We imagined that anhydrous acid would activate the imines **301** and allow cyclization to the oxonium ions **320** and the tautomeric enol ethers **321** and **322** to occur without inducing competing

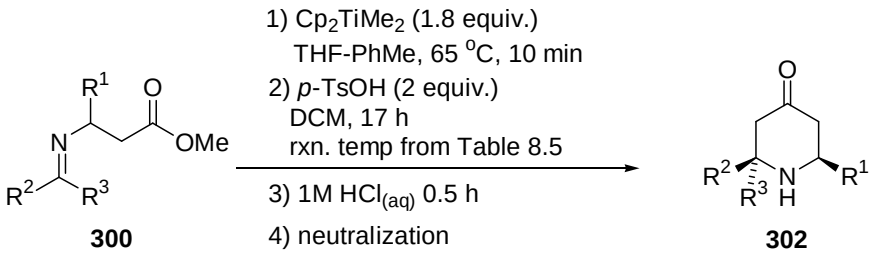
hydrolysis, Scheme 8.18. After the cyclization was complete, aqueous acid could be added to hydrolyze the oxonium ions **320** and the tautomeric enol ethers **321**, and **322** to the desired piperidinones **302**.



Scheme 8.18

Unsurprisingly, imino ester **300a** underwent microwave-assisted Petasis methylenation and was then cyclized with anhydrous *p*-toluene sulfonic acid (*p*-TsOH). After acid hydrolysis, the piperidinone **302a** was isolated in good yield as exclusively the 2,6-*syn* diastereomer, Scheme 8.19, Table 8.5. Similarly, imino ester **300d** gave a good yield of piperidinone **302d**. Methylenation and cyclization of more challenging imino ester **300c** under the new conditions gave an improved but modest yield of piperidinone **302c**. α,β-unsaturated imino ester **300e** underwent methylenation-cyclization to give piperidinone **302e** in similarly modest yield despite a higher reaction temperature for the cyclization. Following aqueous workup the ^{1}H NMR spectrum of the crude products from the cyclizations to give piperidines **302c** and **302e** showed a mixture of the desired piperidinones **302c** and **302e** and the products of imine and enol ether hydrolysis. We believe that in both cases the 17 h reaction time was not enough for the very slow cyclization, and the aqueous acid used to hydrolyze cyclized product also hydrolyzed the uncyclized imino enol ether. Despite the anhydrous conditions, the cyclization was so

slow that even without competing hydrolysis, the reaction was not viable.



Scheme 8.19

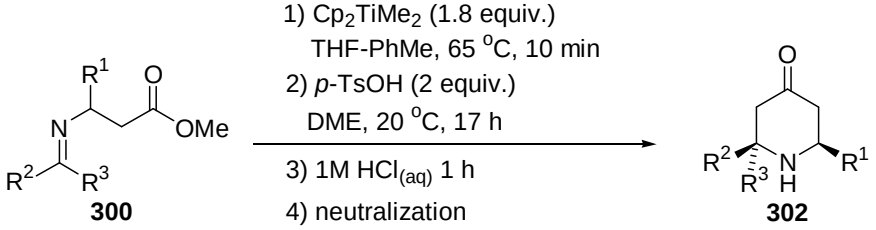
Table 8.5 Yields of piperidinones **302** from esters **300** *via* conditions from Scheme 8.19

imino ester	R^1	R^2	R^3	cyclization temperature	piperidinone	yield
300a	Me	Ph	H	20 °C	**302a**	61
300c	Ph	2,4-$(MeO)_2C_6H_3$	H	20 °C	**302c**	40[a]
300d	$PhCH_2$	Ph	H	40 °C	**302d**	61
300e	Me	(*E*)-4-$MeOC_6H_4CH$=CH	H	60 °C	**302e**	37[b]

a) During the methylenation the temperature is held at 65 °C for only 3.5 min.

b) During the methylenation the temperature is held at 65 °C for only 5 min.

Still unhappy with the cyclization conditions, we considered the role of the solvent. Activated imino enol ether **319** cyclizes to give oxonium salt **320**, Scheme 8.18. DCM is a relatively non-polar solvent and does not stabilize the oxonium ion **320** or the transition state leading to it. A more polar solvent would stabilize the transition state and encourage cyclization. Just switching from DCM to the polar dimethoxyethane (DME) improved the yield of piperidinone **302c** to a respectable 51%, Scheme 8.20, Table 8.6. Imino esters **300c**, **300f**, **300g**, **300h**, and **300i** all cyclized using *p*-TsOH in DME to give piperidines **302c**, **302f**, **302g**, **302h**, and **302i**, respectively. The yields of the reactions were all good with the exception of piperidinone **302i**. The poor yield of **302i** is due to the decomposition of the aliphatic imine of imino ester **300i** and the corresponding imino enol ether **301i** into enamine-derived side products.



Scheme 8.20

Table 8.6 Yields of piperidinones **302** from esters **300** *via* conditions from scheme 8.20

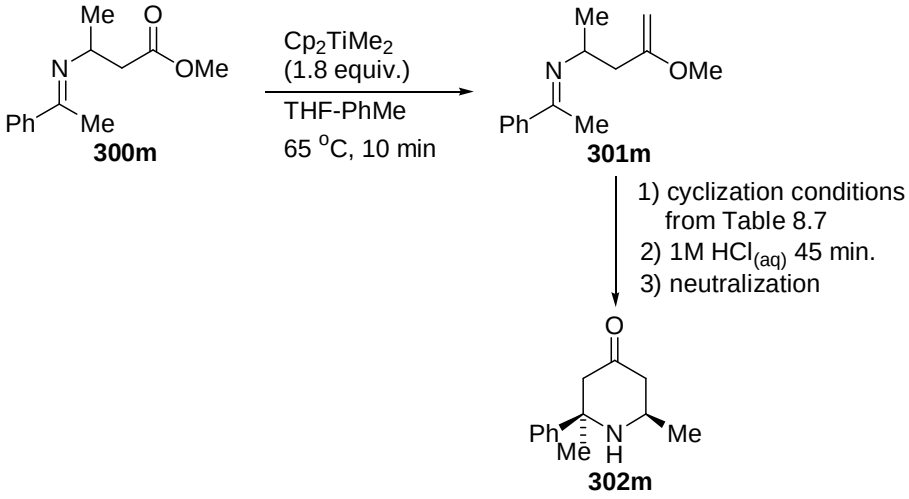
imino ester	R^1	R^2	R^3	piperidinone	yield
300c	Ph	2,4-$(MeO)_2C_6H_3$	H	**302c**	51%[a]
300f	Me	2,4-$(MeO)_2C_6H_3$	H	**302f**	58%[b]
300g	Me	3-Br C_6H_4	H	**302g**	48%
300h	Ph	^{t}Bu	H	**302h**	58%
300i	Ph	Et	H	**302i**	35%[b]
300m	Me	Ph	Me	**302m**	no product

a) During the methylenation, the temperature is held at 65 ^{o}C for only 3.5 min.

b) During the methylenation the temperature is held at 65 ^{o}C for only 2.5 min.

Even though more challenging examples were producing piperidinones in good yield, the acetophenone-derived imino ester **300m** still failed to undergo reaction to give the desired trisubstituted piperidinone, despite the improved conditions.

A range of different acids were screened in different solvents in an effort to find better conditions for the cyclization of enol ether **301m**, Scheme 8.21, Table 8.7. While most cyclization conditions gave incomplete conversion and a mixture of the *syn* and *anti* piperidinones, triisobutylaluminium in DMSO effected the cyclization in good yield and good diastereoselectivity. The use of a Lewis acid in such a polar Lewis basic solvent is unorthodox. However, the more Lewis basic imine out-competes the solvent for the attention of the Lewis acid. These unconventional conditions allowed one of the most challenging examples to successfully undergo cyclization to give the tri-substituted piperidinone in the highest yield we had yet seen, and with good 2,6-*syn* selectivity. The slightly elevated reaction temperature was used to ensure that the polar solvent did not freeze in the cold Scottish climate.



Scheme 8.21

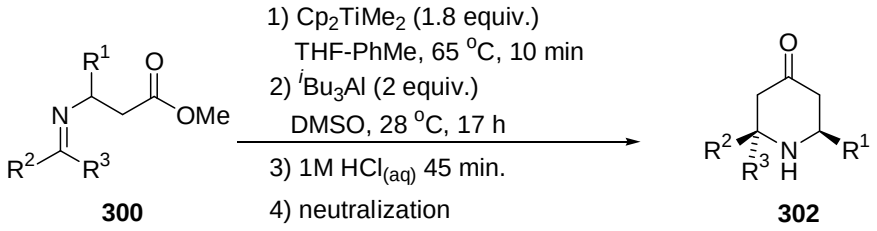
Table 8.7 Transformation of imino ester **300m** to piperidinone **302m**

solvent	acid (2 equiv.)	temperature	*syn*/*anti*	yield
DME	tosic acid	20 °C	N/A	no product
DMSO	tosic acid	28 °C	74/26	N/A
DMSO	$(Me)_2AlCl$	28 °C	63/37	N/A
DCM	$Al(iBu)_3$	-10 °C	38/62	N/A
DMSO	$Al(iBu)_3$	28 °C	89/11	69%

N/A – Not determined due to incomplete conversion

Interestingly, the use of triisobutylaluminium in DCM gave an excess of the 2,6-*anti* diastereomer. Although this result was very intriguing, the result was not investigated due to lack of time.

The new cyclization conditions proved to be superior in all cases, and a range of piperidinones was synthesized to demonstrate the method, Scheme 8.22, Table 8.8. A variety of imines cyclized well, including those from diversely-decorated aromatic aldehyes **300a**, **300b**, **300c**, and **300j**, an α,β-unsaturated aldehyde **300e**, an alkyl aryl ketone **300m**, and a dialkyl ketone **300n**, giving the spirocycle **302n**.



Scheme 8.22

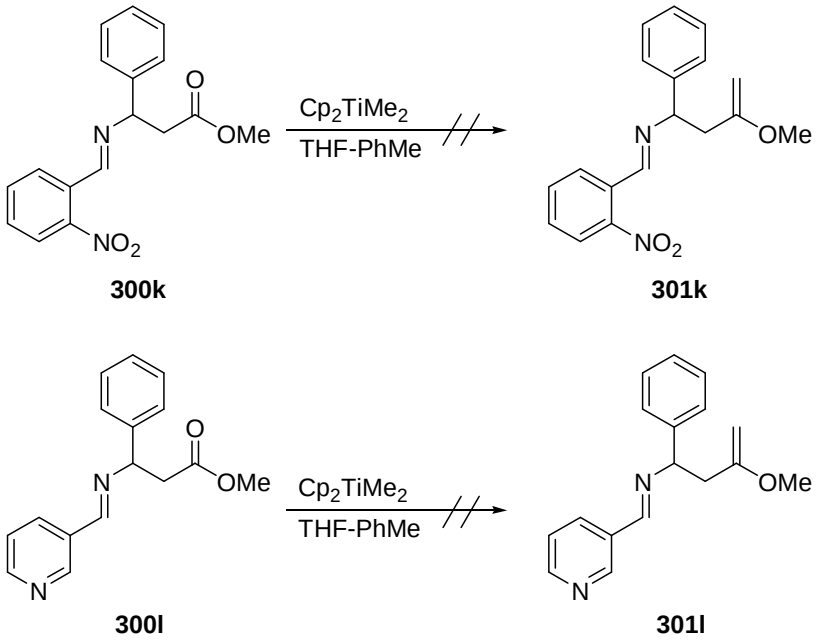
Table 8.8 Yields of piperidinones **302** from esters **300** *via* conditions from scheme 8.22

imino ester	R1	R2	R3	piperidinone	yield
300a	Me	Ph	H	**302a**	68%
300b	Ph	Ph	H	**302b**	70%
300c	Ph	2,4-$(MeO)_2C_6H_3$	H	**302c**	66%[a]
300e	Me	(*E*)-4-$MeOC_6H_4CH$=CH	H	**302e**	51%[b]
300j	Me	2-F C_6H_4	H	**302j**	64%
300m	Me	Ph	Me	**302m**	66%
300n	Ph	–$(CH_2)_5$–		**302n**	52%

a) During the methylenation the temperature is held at 65 °C for only 3.5 min.

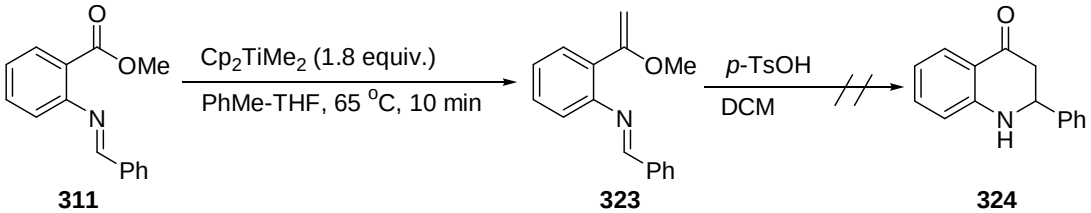
b) During the methylenation the temperature is held at 65 °C for only 3 min.

Imino esters **300k**, and **300l**, derived from aldehydes with highly electron-withdrawing 2-nitrophenyl, and 3-pyridinyl substituents, failed to undergo transformation to the corresponding piperidinones. The cyclization was not the problem in these cases. Despite extensive exploration of the methylenation reaction, only complex mixtures of products, presumably due to attack on the imine, were ever obtained, Scheme 8.23.



Scheme 8.23

Imino ester **311** could be methylenated, but cyclization of the resulting enol ether **323** failed, Scheme 8.24. Unfortunately, due to time constraints, cyclization was only tried using *p*-TsOH in DCM. It is possible that the cyclization would have proceeded had we used triisobutylaluminium in DMSO.



Scheme 8.24

8.4 Assignment of Relative Stereochemistry

The relative stereochemistry of the piperidinones was assigned via the Nuclear Overhauser Effect (NOE). For piperidines **302a**, and **302c - j**, irradiation of the protons at

either C-2 or C-6 of the piperidinones produced a signal at the other position, Figure 8.4. The NOE correlation between the protons at C-2 and C-6 are summarized in Table 8.9 and show that all the piperidinones have the 2,6-*syn* relative stereochemistry.

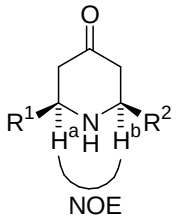


Figure 8.4

Table 8.9 NOE correlations for piperidinones **302** as shown in Figure 8.4

piperidinone	R^1	R^2	irradiated proton	NOE H^a	NOE H^b
302a	Ph	Me	H^a (3.96 ppm)		0.93%
			H^b (3.12 ppm)	0.79%	
302c	2,4-$MeOC_6H_3$	Ph	H^a (4.41 ppm)		2.07%
			H^b (4.10 ppm)	2.34%	
302d	Ph	$PhCH_2$	H^a (3.78 ppm)		1.56%
			H^b (3.15 ppm)	1.45%	
302e	(*E*)-4-$MeOC_6H_4CH$=CH	Me	H^a (3.59 ppm)		1.57%
			H^b (3.07 ppm)	1.70%	
302f	2,4-$MeOC_6H_3$	Me	H^a (4.22 ppm)		1.80%
			H^b (3.11 ppm)	1.79%	
302g	3-Br C_6H_4	Me	H^a (3.92 ppm)		1.15%
			H^b (3.10 ppm)	1.11%	
302h	^{t}Bu	Ph	H^a (2.69 ppm)		1.38%
			H^b (3.89 ppm)	1.32%	
302i	Et	Ph	H^a (2.90 ppm)		1.17%
			H^b (3.93 ppm)	1.03%	
302j	2-F C_6H_4	Me	H^a (4.31 ppm)		1.01%
			H^b (3.15 ppm)	0.95%	

This strategy was not viable for the symmetrical 2,6-diphenylpiperidinone **302b** as the protons at C-2 and C-6 are equivalent. However, our data for piperidinone **302b** matches literature data for 2,6-*syn* diphenylpiperidin-4-one.[126] The assignment of the 2,6-*syn* relative stereochemistry to piperidinone **302b** is further supported by the 2,6-*syn* relative stereochemistry of 2,6-diarylpiperidinone **302c**. Piperidinones **302b**, and **302c** are similar and one would expect both to be formed in a similar manner with the same relative stereochemistry.

Trisubstituted piperidinone **302m** displayed an NOE correlation between the proton at C-6 and the protons of the methyl group at C-2, Figure 8.5.

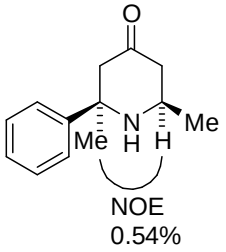
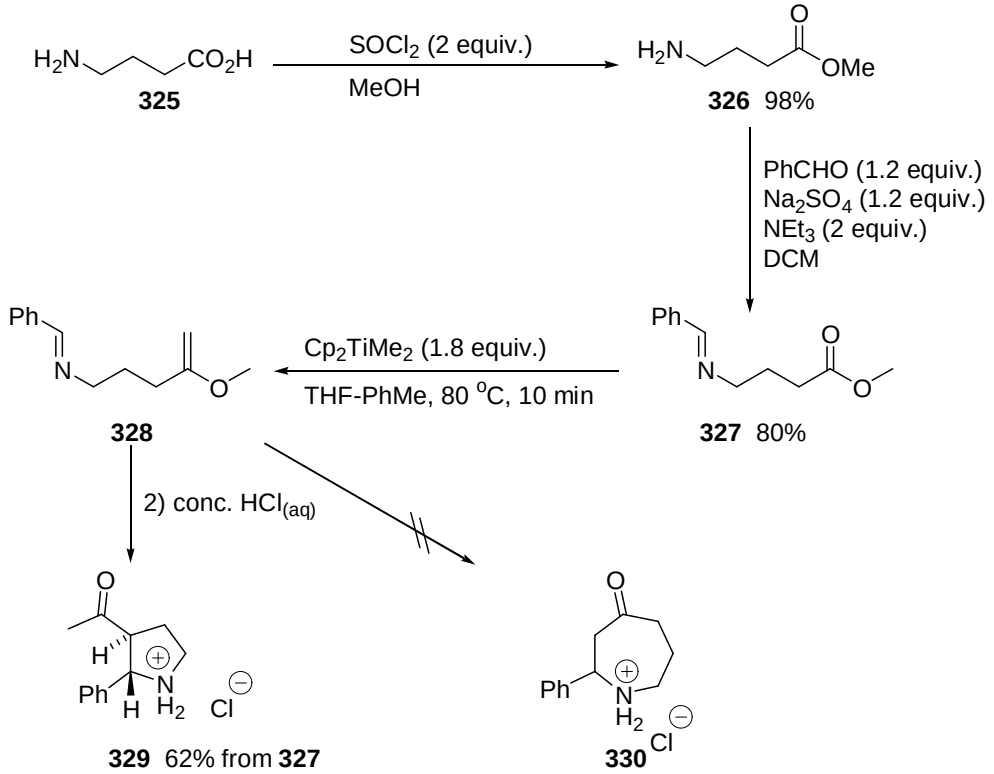


Figure 8.5

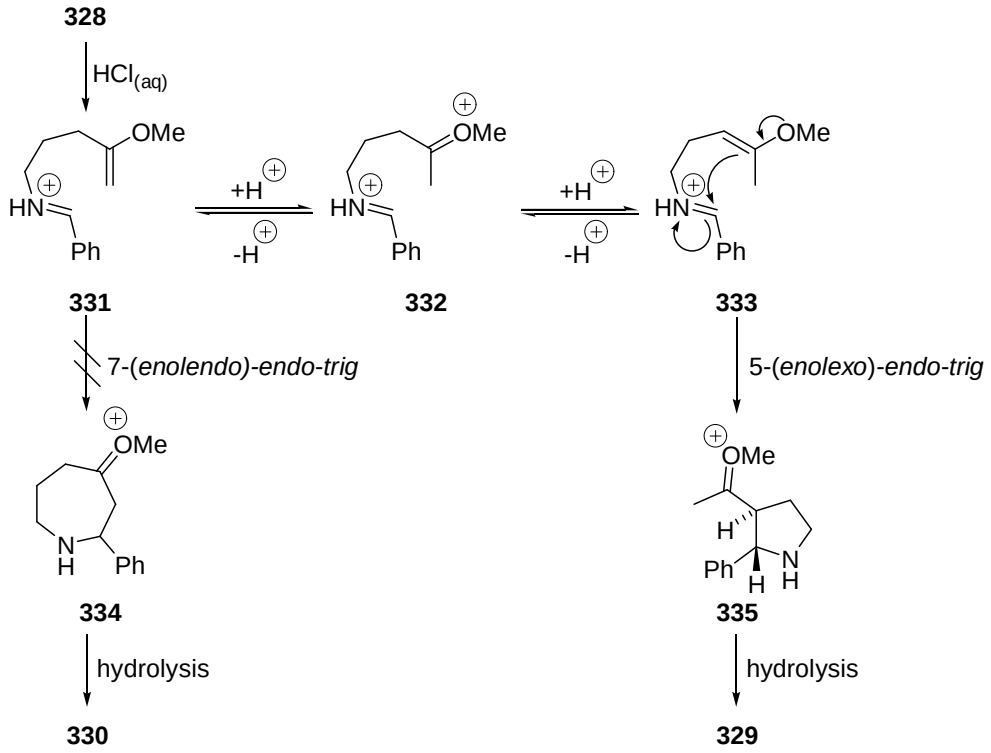
8.5 γ-Amino Acids to Pyrrolidines

During the investigation of the aqueous acid-induced cyclization, imino ester **327** was synthesized from γ-aminobutyric acid **325**, Scheme 8.25. We hoped that the imino enol ether **328** produced by microwave-assisted Petasis methylenation of imino ester **327** would cyclize under aqueous acidic conditions to give an azepine **330**. However, treatment of the imino ester **327** with dimethyltitanocene followed by aqueous acid gave the 2,3-*anti* pyrrolidine as the HCl salt **329** as a single diastereomer. The anti stereochemistry was assigned via consideration of the mechanism. However the coupling constant of 7.5 Hz observed in the ^{1}H NMR spectrum between protons at the C-2 and C-3 positions is slightly lower than seen in a related compound where the analogous coupling constant is 9.8 Hz.[127] Thus the assignment of stereochemistry is very tentative.



Scheme 8.25

We hypothesize that protonation of the imine **328** gives the iminium ion **331**, containing a terminal enol ether, Scheme 8.26. The 7-(*enolendo*)-*endo-trig* cyclization required to form the azepine **334** is slow, and so tautomerization of the iminium ion **331** *via* oxonium ion **332** to form iminium ion **333** competes. The latter then undergoes the comparatively easy 5-(*enolexo*)-*endo-trig* cyclization to give pyrrolidine **335**, which hydrolyzes to produce the corresponding ketone **329**.



Scheme 8.26

Unfortunately, very little investigation into this interesting cyclization was undertaken due to time constraints. More in depth examination of the reaction is necessary to determine whether the transformation is useful.

8.6 Conclusions

Inspired by the Petasis-Ferrier rearrangement, we have developed and thoroughly demonstrated a highly diastereoselective route to 2,6-substituted piperidin-4-ones. The key transformations are microwave-assisted Petasis methylenation and Lewis-acid-induced cyclization. The mild conditions and selectivity of the microwave-assisted methylenation are unprecedented. Using the same low temperatures as conventional

methods, we were able to obtain full conversion of esters to enol ethers in 10 min or less. The selectivity of the reagent for carbonyl groups in the presence of imines allows access to imino enol ethers containing both electrophilic and nucleophilic functionality in the same molecule. The conditions of the Lewis-acid-induced cyclization are the result of extensive optimization and the consideration of many different examples. A variety of imino esters derived from condensation with diverse aldehydes or ketones with β-amino acids should allow preparation of diverse piperidinones as single diastereomers. Since there are good methods for the asymmetric synthesis of β-amino acids,[128] the route should also allow the asymmetric synthesis of 2,6-substituted piperidinones.

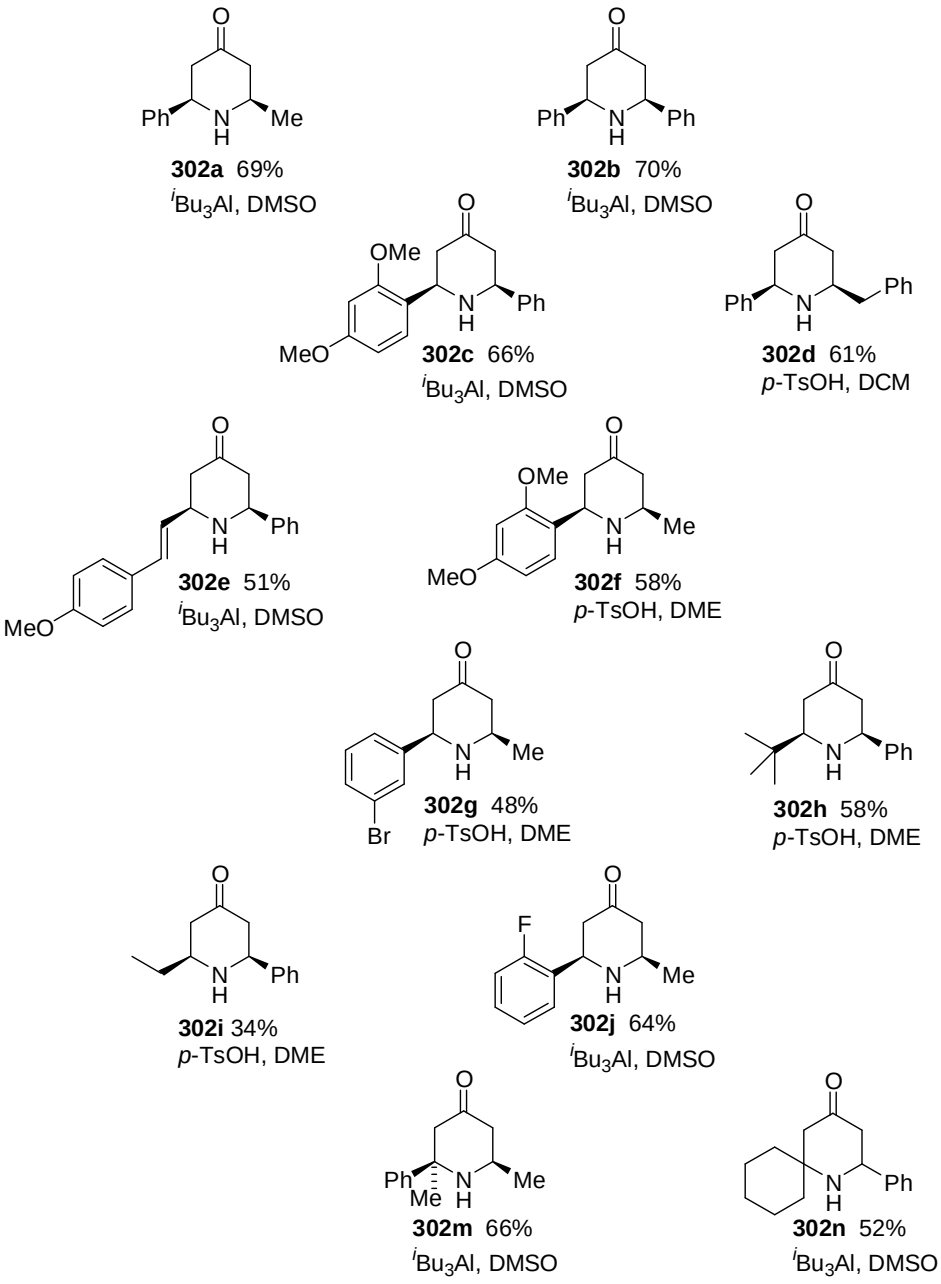


Figure 8.6 Yields of piperidines **302** and the conditions used to obtain these yields

EXPERIMENTAL

Where general procedures are given for transformations, the exact quantities used in each preparation are listed under the compound name, together with reaction times where these vary. Unless otherwise stated, all reactions were carried out using oven dried or flamedried glassware. Solutions were added via syringe unless otherwise stated. Diethyl ether, tetrahydrofuran, dichloromethane, and toluene were dried using a Puresolv© solvent drying system prior to use. DME was freshly distilled from sodium benzophenone; DMSO was dried over 4Å molecular sieves for 24 h, and then distilled from CaH_2 under reduced pressure. Petroleum ether refers to the fraction boiling at 40-60 °C. With the exception of Cp_2TiMe_2, produced via the method of Payack *et al.*[69] Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Purification by column chromatography was carried out using silica gel, mesh size 35-70 μm as the stationary phase. All distillations were carried out bulb to bulb in a Kugelrohr Apparatus. ^1H and ^{13}C NMR spectra were obtained on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz respectively. All NMR *J* values are given in Hz and are uncorrected. ^1H NMR signals of piperidinones **302** were assigned using COSY spectra. CH_3, CH_2, CH, and C in the ^{13}C NMR spectra were assigned using DEPT. Mass spectra (MS) were recorded on a Jeol JMS700 (MStation) spectrometer. Infra-red (IR) spectra were obtained on a Perkin-Elmer 983 spectrophotometer. A Golden Gate™ attachment that uses a type IIa diamond as a single reflection element was used so that the IR spectrum of each compound (solid or liquid) could be directly detected without any sample preparation.Melting points were determined on a Gallenkamp melting point apparatus.

General Esterification procedure

Thionyl chloride (2 equiv.) was added dropwise to a stirred solution of the appropriate amino-acid (1 equiv., 0.6 M) in MeOH at –10 ^{o}C under Ar. The solution was heated under reflux for 3h. After cooling to RT, all volatile compounds were removed *in vacuo* to give the crude ester. Washing the crude product with hot hexane (3×) gave the pure amino-ester as the hydrochloride salt**.**

Imine formation procedure A

Triethylamine (2 equiv.), and the desired aldehyde (0.8-1.2 equiv.) were added to a stirred suspension of an amino-ester (1 equiv., 0.3 M), and sodium sulfate (1.2 equiv.) in dry DCM under Ar at RT. After stirring for 3 h, the mixture was washed with water (2×), then satd. NaCl (1×), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Distillation yielded the pure imino ester.

Imine formation procedure C

A solution of triethylamine (2 equiv.), the desired ketone (1.2-1.5 equiv.), and the amino ester (1 equiv., 0.3 M) in dry toluene was heated at reflux under Ar with continuous removal of water by means of a Dean-Stark trap for the stated reaction time (see below). The reaction mixture was cooled to RT, washed with water (2×), and satd. NaCl (1×). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude imine. Distillation gave the pure imino ester.

Synthesis of Piperidinones 302

Although the various piperidinones were made a number of times under a variety of conditions, only one procedure is given for each piperidinone prepared, and in each case this is the procedure that gave the best yield during the studies described. The best combination is methylenation procedure B and cyclization procedure D, but this combined procedure was never used for the preparation of piperidinones **302d**, **302f**, **302g**, **302h** and **302i**.

Methylenation procedure A

A 0.96 M solution of Cp_2TiMe_2 (1.8-2.1 equiv.) in toluene-THF (1:1 by mass) was added to an imino ester (1 equiv.), and sealed in a 10 mL microwave tube under argon. This was irradiated under 100 W maximum microwave power using a CEM DISCOVERY

microwave system to raise the internal temperature to 80 ^{o}C (ca. 9 min), and the temperature maintained with microwave irradiation a further 10 min, before cooling. The resultant black solution was concentrated *in vacuo* and hexane added to precipitate most titanium-containing impurities. The hexane extract was filtered and concentrated *in vacuo* to yield the crude enol ether.

Methylenation procedure B

A 1.30 M solution of Cp_2TiMe_2 (1.8-2.1 equiv.) in toluene-THF (1:1 by mass) was added to an imino ester (1 equiv.), and sealed in a 10 mL microwave tube under argon. This was irradiated under 100 W maximum microwave power using a CEM DISCOVERY microwave system to raise the internal temperature to 65 ^{o}C (ca. 7 min), and the temperature maintained with microwave irradiation a further 2.5-10 min (the exact times and maximum internal pressures observed are included for individual transformations below), before cooling. The resultant black solution was concentrated *in vacuo* and hexane added to precipitate most titanium-containing impurities. The hexane extract was filtered and concentrated *in vacuo* to yield the crude enol ether.

Cyclization procedure A (aqueous acid)

Using non-dried glassware, 7M $HCl_{(aq)}$ (25 equiv.) was added to the crude enol ether **301** and the resulting mixture was stirred for 0.5 h. The solution was washed with DCM 5X, and the aqueous layer was concentrated *in vacuo* to give the piperidinone **315** as the hydrochloride salt.

Cyclization procedure B (*p*-tosic acid in DCM)

p-Toluene sulfonic acid (2 equiv.) was added to a stirred suspension of 4Å molecular sieves (0.3 g), and the crude enol ether **301** (1 equiv., 0.07M) in dry DCM under Ar. The solution was heated at 40 ^{o}C for 17 h, cooled to RT and quenched with 1M $HCl_{(aq)}$ (2ml). The reaction mixture stirred for a further 0.5 h, basified with $NaOH_{(aq)}$, and the solution was extracted with DCM. The organic extract was washed with satd. NaCl (1×), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude piperidinone **302**, which was purified by column chromatography.

Cyclization procedure C (*p*-tosic acid in DME)

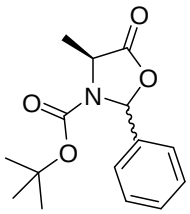
p-Toluene sulfonic acid (2 equiv.) was added to a stirred solution of crude enol ether **301** (1 equiv., 0.1 M) in dry DME, under Ar. The solution was stirred at RT for 17 h, and

concentrated *in vacuo*. The resultant residue was stirred in 1M $HCl_{(aq)}$ (10 equiv.) for 1 h. The solution was basified with $NaOH_{(aq)}$, and extracted with DCM (4×). The organic extract was washed with satd. NaCl (1×), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude piperidinone **302**, which was purified by column chromatography.

Cyclization procedure D (triisobutylaluminium in DMSO)

Triisobutylaluminium (1.0 M in Hexanes, 2 equiv.) was added to the crude enol ether **301** (1 equiv., 0.03 M) in dry DMSO, under Ar. The solution stirred at 28 ^oC for 17h, and was quenched with careful addition of 1M $HCl_{(aq)}$ (35 equiv.). The reaction mixture was stirred a further 45 min, basified with $NaOH_{(aq)}$, and extracted with EtOAc. The organic extract was washed with $NH_4Cl_{(aq)}$, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude piperidinone **302**, which was purified by column chromatography.

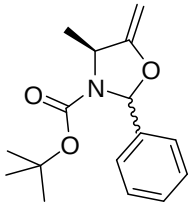
(4*S*) 4-Methyl-5-oxo-2-phenyloxazolidine-3-*tert*-butylcarbonate 290



1M NaOH (11.2 mL, 11.2 mmol, 1 equiv.) was added to L-alanine (1.000 g, 11.2 mmol, 1 equiv.). After the amino acid had fully dissolved, water was removed *in vacuo* via a Kugelrohr apparatus to leave the sodium salt. 4 Å molecular sieves (1.0 g), and benzaldehyde (1.7 mL, 16.8 mmol, 1.5 equiv.) were added to a solution of the sodium salt in DCM (11.0 mL). The solution was then heated under Ar at reflux for 5 h. The solvent was removed in vacuo to leave the Schiff base. Chloroform (17 mL), followed by di-*tert*-butyldicarbonate (4.409 g, 20.2 mmol, 1.8 equiv.) were added to the flask containing the Schiff base, and the reaction was stirred under Ar at 55 ^oC for 15 h. The turbid solution was washed with water (1×), $NaHCO_3$ (1×), $NaHSO_3$ (1×), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude oxazolidinone as a yellow oily solid. Recrystalyzation from Et_2O, in hexane gave pure (4*S*) 4-methyl-5-oxo-2-phenyloxazolidine-3-*tert*-butylcarbonate **290** as a solid (0.653 g, 21%). IR (thin film): 1778, 1685, 1399, 1365 cm^{-1}. δ_H (d6 DMSO, 400 MHz, 80 ^oC) 1.20 (9H, s, CH_3C), 1.57 (3H, d, *J*= 6.7, CH_3CH), 4.65 (1H, q, *J*= 6.7, C*H*CH_3), 6.51 (1H, s, CHC), 7.44 (5H, s, H arom.) δ_C (d6 DMSO, 100 MHz, 80 ^oC) 16.29 (CH_3), 27.68 (CH_3), 51.32 (C), 80.70

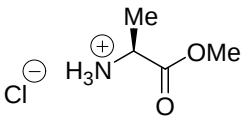
(CH), 88.98 (CH), 126.76 (CH), 128.44 (CH), 129.57 (CH), 137.80 (C), 150.69 (C), 172.34 (C). HRMS: 277.1309 $C_{15}H_{19}O_4N$, requires (M^+) 277.1314.

(4S) 4-Methyl-5-methylene-2-phenyloxazolidine-3-*tert*-butylcarbonate 291



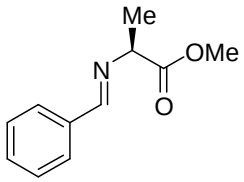
A 1.30 M solution of Cp_2TiMe_2 (0.50 mL, 0.65 mmols, 1.5 equiv.) in toluene-THF (1:1 by mass) was added to (4*S*) 4-methyl-5-oxo-2-phenyloxazolidine-3-*tert*-butylcarbonate **290** (0.1204 g, 0.43 mmol, 1 equiv.), and sealed in a 10 mL microwave tube under argon. This was irradiated under 100 W maximum microwave power using a CEM DISCOVERY synthesizer to raise the internal temperature to 65 ^oC (ca. 7 min), and the temperature maintained with microwave irradiation a further 10 min, before cooling. The resultant black solution was concentrated *in vacuo* and hexane added to precipitate most titanium-containing impurities. The hexane extract was filtered and concentrated *in vacuo* to yield the crude enol ether. Column chromatography (SiO_2, Hexane-EtOAc- NEt_3 96:6:1) gave (4S) 4-methyl-5-methylene-2-phenyloxazolidine-3-*tert*-butylcarbonate **291** as an oil (77.6 mg, 65%). R_f (SiO_2, Hexane-EtOAc-NEt_3 93:6:1): 0.65. IR (thin film): 1705, 1683, 1458 cm^{-1}. δ_H (d6 DMSO, 400 MHz, 80 ^oC) 1.17 (9H, s, CH_3C), 1.47 (3H, d, *J*= 6.1, C*H*$_3$CH), 4.05 (1H, dd, *J*= 1.2, 2.2, C*H*^{A}H^B=C), 4.24 (1H, dd, *J*= 1.5, 2.2, CH^A*H*^{B}=C), 4.67 (1H, tq, *J*= 1.3, 6.0, C*H*CH$_3$), 6.18 (1H, s, CHC), 7.27-7.34 (2H, m, H arom.), 7.34-7.39 (3H, m, H arom.) δ_C (d6 DMSO, 100 MHz, 80 ^oC) 20.23 (CH_3), 27.74 (CH_3), 53.83 (C), 79.91 (C), 80.52 (CH_2), 90.64 (CH), 126.41 (CH), 128.15 (CH), 128.83 (CH), 139.74 (C), 150.96 (C), 161.89 (C). m/z (EI): 275 (M^+, 15%), 219 (40), 202 (20), 132 (75), 104 (90), 84 (100). HRMS: 275.1523 $C_{16}H_{21}O_3N$, requires (M^+) 275.1521.

Methyl (2*S*) 2-aminopropionoate hydrochloride salt 297



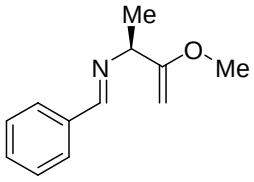
Using: thionyl chloride (1.63 ml, 22.5 mmol, 2 equiv.), L-alanine (1.000 g, 11.2 mmol, 1 equiv.), in MeOH (20.0 mL), and following the general esterification procedure gave (2*S*) methyl 2-aminopropionoate hydrochloride salt **297** as a solid (1.404 g, 90%). IR (thin film): 1740 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.72 (3H, d, *J*= 7.2, C*H*$_3$CH), 3.80 (3H, s, OCH_3), 4.23-4.33 (1H, m, CH) 8.68 (3H, broad s, NH_3). m/z (CI): 104 (M^+, 100%). HRMS: 104.0713 $C_4H_{12}O_2N$ requires (M^+), 104.0712. data in agreement with the literature.[129]

Methyl (2*S*, *E*) 2-(benzylidenamino)propionoate 298



Following general imine formation procedure A, triethylamine (1.00 ml, 7.2 mmol, 2 equiv.), benzaldehyde (0.37 ml, 3.6 mmol, 1 equiv.), (2*S*) methyl 2-aminopropionoate hydrochloride salt **297** (0.500 g, 3.6 mmol, 1 equiv.), and Na_2SO_4 (0.305 g, 2.2 mmol, 0.6 equiv.), in DCM (10 ml) gave (2*S*, *E*) methyl 2-(benzylideneamino)-propionoate **298** as an oil with no distillation necessary (542 mg, 79%). δ_H ($CDCl_3$, 400 MHz) 1.53 (3H, d, *J*= 6.8, C*H*$_3$CH), 3.75 (3H, s, OCH_3), 4.16 (1H, q, *J*= 6.8, CH), 7.38-7.47 (3H, m, H arom.), 7.75-7.80 (2H, m, H arom.), 8.32 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz) 19.42 (CH_3), 52.16 (CH_3) , 67.97 (CH), 128.45 (CH), 128.54 (CH), 131.07 (CH), 135.65 (C), 162.93 (CH), 172.95 (C). Data in agreement with the literature.[130]

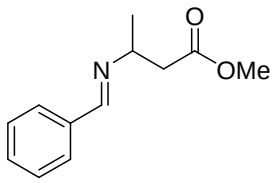
(3*S*, *E*) 2-Methoxy-3-(benzylidenamino)but-1-ene 299



Following methylenation procedure B, using a 1.30 M solution of Cp_2TiMe_2 (0.89 mL, 1.16 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (2*S*, *E*) methyl 2-(benzylideneamino)-propionoate **298** (123 mg, 0.64 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 35 psi) gave crude enol ether. Distillation

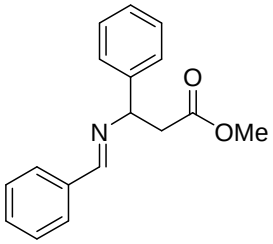
gave pure (3*S*, *E*) 2-methoxy-3-(benzylideneamino)but-1-ene **299** (95 mg, 78%). Bp 140 ^{o}C at 0.4 mm Hg. IR (thin film): 1644 (C=N), 1450, 1238 cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.43 (3H, d, *J*= 6.8, C*H*$_3$CH), 3.59 (3H, s, OCH_3), 3.94 (1H, q, *J*= 6.8, CHN), 3.93 (1H, d, *J*= 2.0, C=C*H*^{A}H^B), 4.12 (1H, d, *J*= 2.0, C=CH^A*H*^{B}), 7.28-7.37 (3H, m, H arom.), 7.67-7.72 (2H, m, H arom.), 8.22 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz) 20.68 (CH_3), 54.86 (CH_3) , 68.08 (CH), 80.67 (CH_2), 128.32 (CH), 128.47 (CH), 130.60 (CH), 136.28 (C), 160.63 (CH), 165.16 (C). m/z (CI): 190 [(M+H)$^+$, 100%]. HRMS: 190.1230 $C_{12}H_{16}ON$, requires (M+H$^+$) 190.1232.

Methyl (3*RS, E*) 3-(benzylideneamino)butanoate 300a



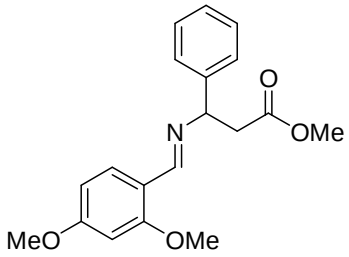
Following general imine formation procedure A, triethylamine (0.45 ml, 3.3 mmol, 2 equiv.), benzaldehyde (0.13 ml, 1.3 mmol, 0.8 equiv.), (3*RS*) methyl 3-aminobutanoate hydrochloride salt **306** (250 mg, 1.63 mmol, 1 equiv.), and Na_2SO_4 (281 mg, 1.96 mmol, 1.2 equiv.), in DCM (4.5 ml) gave (3*RS*, *E*) methyl-3-(benzylidenamino)butanoate **300a** as an oil with no distillation necessary (200 mg, 75%). IR (thin film): 1736 (C=O), 1644 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.30 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.60 (1H, dd, *J*= 5.3, 15.5, C*H*^{A}H^B), 2.69 (1H, dd, *J*= 8.1, 15.5, CH^A*H*^{B}), 3.62 (3H, s, OCH_3), 3.80-3.90 (1H, m, CHN), 7.38-7.44 (3H, m, H arom.), 7.69-7.74 (2H, m, H arom.), 8.34 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz) 22.30 (CH_3), 42.26 (CH_2), 51.43 (CH_3) , 62.68 (CH), 128.19 (CH), 128.51 (CH), 130.61 (CH), 136.14 (C), 160.38 (CH), 172.20 (C). m/z (EI): 205 (M$^+$, 15%), 132 (30), 82 (100). HRMS: 205.1101. $C_{12}H_{15}O_2N$, requires (M$^+$) 205.1103.

Methyl (3*RS, E*) 3-(benzylidenamino)-3-phenylpropionate 300b



Following imine formation procedure A, triethylamine (0.33 ml, 2.3 mmol, 2 equiv.), benzaldehyde (0.13 ml, 1.3 mmol, 1.1 equiv.), (3*RS*) methyl 3-amino-3-phenylpropionate hydrochloride salt **307** (250 mg, 1.16 mmol, 1 equiv.), and Na_2SO_4 (199 mg, 1.40 mmol, 1.2 equiv.), in DCM (5.0 ml) gave (3*RS*, *E*) methyl 3-(benzylidenamino)-3-phenylpropionate **300b** as an oil (272 mg, 89%). Bp 200 ^oC at 0.6 mm Hg. IR (thin film): 1736 (C=O), 1644 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 2.90 (1H, dd, *J*= 4.4, 15.6, C*H*^{A}H^B), 3.05 (1H, dd, *J*= 9.2, 15.6, CH^A*H*^{B}), 3.61 (3H, s, OCH_3), 4.86 (1H, dd, *J*= 9.2, 4.4, CHN), 7.21-7.44 (8H, m, H arom.), 7.73-7.79 (2H, m, H arom.), 8.44 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz) 43.09 (CH_2), 51.56 (CH_3), 70.85 (CH), 126.89 (CH), 127.36 (CH), 128.39 (CH), 128.47 (CH), 128.59 (CH), 130.76 (CH), 136.10 (C), 142.74 (CH), 161.48 (CH), 171.73 (C). m/z (EI): 267 (M^+, 80%), 208 (30%), 194 (100%), 121 (95), 104 (70). HRMS: 267.1262. $C_{17}H_{17}O_2N$, requires (M^+) 267.1259.

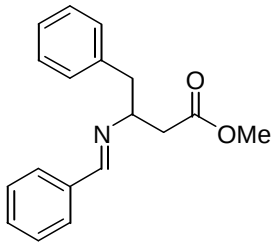
Methyl (3*RS, E*) 3-(2',4'-dimethoxybenzylidenamino)-3-phenylpropionate 300c



Following imine formation procedure A, triethylamine (0.91 ml, 6.5 mmol, 2 equiv.), (3*RS*) methyl 3-amino-3-phenylpropionate hydrochloride salt **307** (700 mg, 3.24 mmol, 1 equiv.), 2,4-dimethoxybenzaldehyde (538 mg, 3.24 mmol, 1 equiv.), and Na_2SO_4 (0.55 g, 3.9 mmol, 1.2 equiv.), in DCM (10.0 ml), gave (3*RS*, *E*) methyl 3-(2',4'-

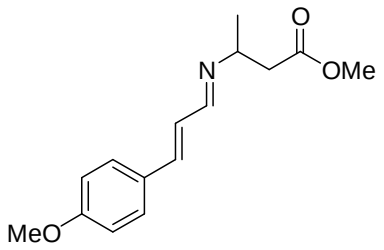
dimethoxybenzylidenamino)-3-phenylpropionate **300c** as a pale yellow solid (1.000 g, 94%). Bp 215 ^{o}C at 0.8 mm Hg. Mp 78-79 ^{o}C. IR (thin film): 1730 (C=O), 1600 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 2.90 (1H, dd, *J*= 5.1, 15.2, C*H*^{A}H^{B}), 3.00 (1H, dd, *J*= 9.0, 15.3, CH^{A}*H*^{B}), 3.61 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.82 (1H, dd, *J*= 5.1, 8.9, CHN), 6.40 (1H, d, *J*= 2.2, H3'), 6.50 (1H, dd, *J*= 2.2, 8.6, H5'), 7.21-7.28 (1H, m, H arom.), 7.29-7.36 (2H, m, H arom.), 7.42-7.46 (2H, m, H arom.), 7.96 (1H, d, *J*= 8.6, H6'), 8.71 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz) 43.41 (CH_2), 51.46 (CH_3), 55.37 (CH_3), 55.42 (CH_3), 71.18 (CH), 97.85 (CH), 105.31 (CH), 117.94 (C), 126.88 (CH), 127.11 (CH), 128.46 (CH), 128.79 (CH), 143.30 (C), 156.85 (CH), 160.20 (C), 163.11 (C), 171.76 (C). m/z (EI): 327 (M^+, 20%), 254 (100), 164 (90), 149 (60), 121 (65). HRMS: 327.1473 $C_{19}H_{21}O_4N$, requires (M^+) 327.1471.

Methyl (3*RS, E*) 3-(benzylidenamino)-4-phenylbutanoate 300d



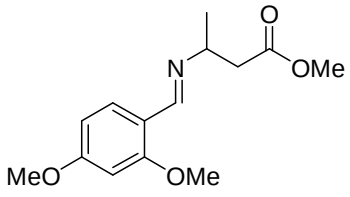
Following imine formation procedure A, triethylamine (0.31 mL, 2.2 mmol, 2 equiv.), benzaldehyde (0.12 mL, 1.2 mmol, 1.1 equiv.), (3*RS*) methyl 3-amino-4-phenylbutanoate hydrochloride salt **308** (249 mg, 1.09 mmol, 1 equiv.), and Na_2SO_4 (186 mg, 1.31 mmol, 1.2 equiv.), in DCM (4.0 mL), gave (3*RS, E*) methyl 3-(benzylidenamino)-4-phenylbutanoate **300d** as a colorless oil with no distillation necessary (253 mg, 83%). IR (thin film): 1736 (C=O), 1602 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 2.69 (1H, dd, *J*= 4.4, 15.6, C*H*^{A}H^{B}CO), 2.76 (1H, dd, *J*= 8.4, 15.6, CH^{A}*H*^{B}*CO*), 2.93 (1H, dd, *J*= 7.6, 13.2, PhC*H*^{C}H^{D}), 2.98 (1H, dd, *J*= 6.0, 13.2, PhCH^{C}*H*^{D}), 3.61 (3H, s, OCH_3), 3.86-3.94 (1H, m, CHN), 7.15-7.21 (3H, m, H arom.), 7.21-7.28 (2H, m, H arom.), 7.37-7.48 (3H, m, H arom.), 7.63-7.71 (2H, m, H arom.), 8.04 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz): 40.23 (CH_2), 42.54 (CH_2), 51.47 (CH_3), 68.94 (CH), 126.30 (CH), 128.15 (CH), 128.23 (CH), 128.45 (CH), 129.74 (CH), 130.58 (CH), 135.98 (C), 138.27 (C), 161.50 (CH), 172.18 (C). m/z (EI): 281 (M^+, 10%), 250 (20), 190 (100), 158 (50), 130 (90), 117 (30), 91 (60), 77 (20). HRMS: 281.1414 $C_{18}H_{19}O_2N$ requires (M^+), 281.1416.

Methyl (3*RS*, 1'*E*, 2'*E*) 3-[3'-(4"-methoxyphenyl)prop-2'-enylidenamino]butanoate 300e



Following imine formation procedure A, triethylamine (0.91 ml, 6.5 mmol, 2 equiv.), (3*RS*) methyl 3-amino-butanoate hydrochloride salt **306** (498 mg, 3.26 mmol, 1 equiv.), 4-methoxycinnamaldehyde (423 mg, 2.60 mmol, 0.8 equiv.), and Na_2SO_4 (0.56 g, 4.00 mmol), in DCM (10.0 ml), gave (3*RS*, 1'*E*, 2'*E*) methyl 3-[3'-(4"-methoxyphenyl)prop-2-enylidenamino]butanoate **300e** as a pale yellow oil (592 mg, 87%). Bp 190 ^oC at 0.45 mm Hg. IR (thin film): 1736 (C=O), 1635 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.25 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.53 (1H, dd, *J*= 5.2, 15.5, C*H*^{A}H^B), 2.62 (1H, dd, *J*= 8.2, 15.5, CH^A*H*^{B}), 3.63 (3H, s, OCH_3), 3.64-3.76 (1H, m, CHN), 3.81 (3H, s, OCH_3), 6.73 (1H, dd, *J*= 8.8, 15.9, H2'), 6.85-6.91 (2H, m, H arom.), 6.90 (1H, d, *J*= 16, H3'), 7.40 (2H, d, *J*= 8.9, H arom.), 8.04 (1H, d, *J* =8.8, H1'). δ_C ($CDCl_3$, 100 MHz) 22.37 (CH_3), 42.28 (CH_2), 51.41 (CH_3) , 55.26 (CH_3), 62.30 (CH), 114.20 (CH), 125.81 (CH), 128.43 (C), 138.64 (CH), 141.73 (CH), 160.42 (C), 162.31 (CH), 172.14 (C). m/z (FAB): 262 [$(M+H)^+$, 100%]. HRMS: 262.1446 $C_{15}H_{19}O_3N$, requires $(M+H)^+$ 262.1443.

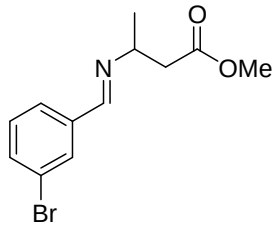
Methyl (3*RS*, *E*) 3-(2',4'-dimethoxybenzylidinamino)butanoate 300f



Following imine formation procedure A, triethylamine (0.51 mL, 3.7 mmol, 2 equiv.), (3*RS*) methyl 3-aminobutanoate hydrochloride salt **306** (278 mg, 1.81 mmol, 1 equiv.), 2,4-dimethoxybenzaldehyde (309 mg, 1.86 mmol, 1 equiv.), and Na_2SO_4 (309 mg, 2.18 mmol, 1.2 equiv.), in DCM (6.0 ml), gave (3*RS*, *E*) methyl 3-(2',4'-

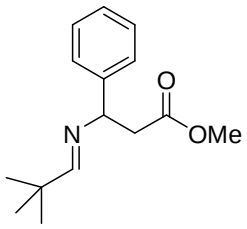
dimethoxybenzylidinamino)butanoate **300f** as an oil (291 mg, 61%). Bp 175 ^{o}C at 0.2 mm Hg. IR (thin film): 1737 (C=O), 1607 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 1.28 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.56 (1H, dd, *J*= 5.8, 15.1, C*H*^{A}H^B), 2.64 (1H, dd, *J*= 7.8, 15.1, CH^A*H*^{B}), 3.63 (3H, s, OCH_3), 3.78-3.86 (1H, m, CHN), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.42 (1H, d, *J*= 2.3, H3'), 6.49 (1H, dd, *J*= 2.3, 8.6, H5'), 7.86 (1H, d, *J*= 8.6, H6'), 8.64 (1H, s, CH=N). δ_C ($CDCl_3$, 100 MHz): 22.47 (CH_3), 42.66 (CH_2), 51.38 (CH_3), 55.41 (CH_3), 55.46 (CH_3), 62.86 (CH), 97.97 (CH), 105.27 (CH), 117.99 (C), 128.59 (CH), 155.77 (CH), 160.06 (C), 162.99 (C), 172.35 (C). m/z (EI): 265 (M$^+$, 15%), 234 (20), 192 (70), 164 (100), 149 (75), 121 (15). HRMS: 265.1313 $C_{14}H_{19}O_4N$ requires (M$^+$), 265.1314.

Methyl (3*RS*, *E*) 3-(3'-bromobenzylidenamino)butanoate 300g



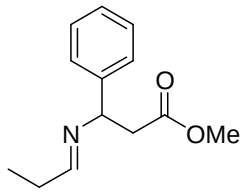
Following imine formation procedure A triethylamine (0.31 mL, 2.2 mmol, 2 equiv.), 3-bromobenzaldehyde (0.13 ml, 1.1 mmol, 1 equiv.), (3*RS*) methyl 3-aminobutanoate hydrochloride salt **306** (170 mg, 1.11 mmol, 1 equiv.), and Na_2SO_4 (309 mg, 2.18 mmol, 1.2 equiv.), DCM (6.0 ml), gave a mixture of the desired imino-ester and un-reacted 3-bromobenzaldehyde. Removal of the aldehyde by distillation (75 ^{o}C, 0.5 mmHg) gave pure (3*RS*, *E*) methyl 3-(3'-bromobenzylidenamino)butanoate **300g** as an oil (184 mg, 58%). IR (thin film): 1736 (C=O), 1644 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 1.29 (3H, d, *J*= 6.5, C*H*$_3$CH), 2.59 (1H, dd, *J*= 5.1, 15.6, C*H*^{A}H^B), 2.68 (1H, dd, *J*= 8.3, 15.6, CH^A*H*^{B}), 3.63 (3H, s, OCH_3), 3.80-3.90 (1H, m, CHN), 7.27 (1H, t, *J*= 7.8, H5'), 7.53 (1H, ddd, *J*= 1.0, 1.9, 8.0, H4'), 7.60 (1H, broad d, *J*= 7.7, H6'), 7.92 (1H, t, 1.6, H2'), 8.27 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz): 22.25 (CH_3), 42.09 (CH_2), 51.48 (CH_3), 62.58 (CH), 122.87 (C), 127.09 (CH), 130.03 (CH), 130.70 (CH), 133.50 (CH), 138.16 (C), 158.81 (CH), 172.08 (C). m/z (EI): 285 (M$^+$, 45%), 283 (M$^+$, 45%), 226 (45), 224 (45), 212 (90), 210 (100), 130 (40), 104, (65), 102 (85), 86 (70), 84 (100). HRMS: 285.0181, and 283.0207, $C_{12}H_{14}O_2N^{81}Br$ requires (M$^+$), 285.0188, and $C_{12}H_{14}O_2N^{79}Br$ requires (M$^+$), 283.0208;

Methyl (3*RS, E*) 3-(2',2'-dimethylpropylidenamino)-3-phenylbutanoate 300h



Triethylamine (0.15 mL, 1.1 mmol, 1.1 equiv.) was added to a suspension of (3*RS*) methyl 3-amino-3-phenylpropionate hydrochloride salt **307** (217 mg, 1.01 mmol, 1 equiv.), and Na_2SO_4 (170 mg, 1.20 mmol, 1.2 equiv.) in dry DCM (5.0 mL) under Ar. The suspension stirred 1 h and pivaldehyde (0.20 ml, 1.8 mmol, 1.8 equiv.) was added. The reaction mixture stirred a futher 30 min, was filtered, and concentrated *in vacuo*. The resultant residue was extracted with dry Et_2O (3×). The extracts were filtered and concentrated *in vacuo* to give (3*RS, E*) methyl 3-(2',2'-dimethylpropylidenamino)-3-phenylbutanoate **300h** as an oil (224 mg, 90 %). IR (thin film): 1740 (C=O), 1666 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 1.05 (9H, s, CH_3C), 2.77 (1H, dd, *J*= 4.5, 15.0, CH^AH^B), 2.86 (1H, dd, *J*= 9.6, 15.0, CH^AH^B), 3.63 (3H, s, OCH_3), 4.57 (1H, dd, *J*= 4.5, 9.6, CHN), 7.21-7.27 (1H, m, H arom.), 7.29-7.35 (2H, m, H arom.), 7.35-7.40 (2H, m, H arom.), 7.63 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz): 26.85 (CH_3), 36.14 (C), 43.59 (CH_2), 51.36 (CH_3), 70.57 (CH), 126.64 (CH), 127.10 (CH), 128.44 (CH), 143.14 (C), 171.68 (C=N), 172.64 (C=O). m/z (EI): 247 (M^+, 30%), 174 (40), 121 (100), 104 (50). HRMS: 247.1575 $C_{15}H_{21}O_2N$ requires (M^+), 247.1572.

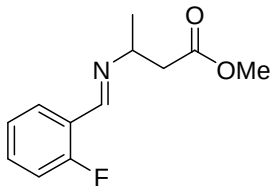
Methyl (3*RS, E*) 3-(propylidenamino)-3-phenylpropionoate 300i



In the same way as for the preparation of imine **300h**, triethylamine (0.26 mL, 1.83 mmol, 2 equiv.), (3*RS*) methyl 3-amino-3-phenylpropionate hydrochloride salt **307** (197 mg, 0.91 mmol, 1 equiv.), Na_2SO_4 (157 mg, 1.11 mmol, 1.2 equiv.), and propionaldehyde

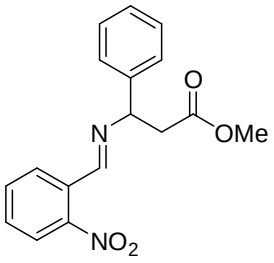
(0.073 ml, 1.01 mmol, 1.1 equiv.), in DCM (5.0 ml) gave a mixture of (3*RS*, *E*) methyl 3-(propylidenamino)-3-phenylpropionate **300i**, the starting (3*RS*) methyl 3-amino-3-phenylpropionate **307**, and propionaldehyde in a 80:13:7 ratio (183 mg, 86% imine **300i** by mass, 79% yield). δ_H ($CDCl_3$, 400 MHz): 1.07 (3H, t, *J*=7.6, C*H*$_3$CH$_2$), 2.26 (2H, dq, *J*= 4.7, 7.5, C*H*$_2$CH$_3$), 2.79 (1H, dd, *J*= 4.7, 15.4, C*H*^{A}H^B), 2.94 (1H, dd, *J*= 9.4, 15.4, CH^A*H*^{B}), 3.64 (3H, s, OCH_3), 4.59 (1H, dd, *J*= 4.7, 9.4, CHN), 7.23-7.28 (1H, m, H arom.), 7.29-7.38 (4H, m, H arom.), (1H, t, *J*= 4.8, N=CH).

Methyl (3*RS*, E) 3-(2'-fluorobenzylidenamino)butanoate 300j



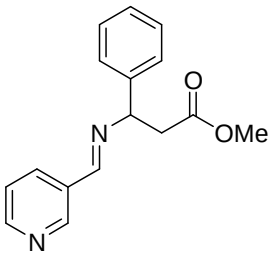
Following imine formation procedure A, triethylamine (0.68 mL, 4.9 mmol, 2 equiv.), (3*RS*) methyl 3-aminobutanoate hydrochloride salt **306** (376 mg, 2.45 mmol, 1 equiv.), 2-fluorobenzaldehyde (0.31 ml, 2.9 mmol, 1.2 equiv.), and Na_2SO_4 (422 mg, 2.97 mmol, 1.2 equiv.), in DCM (10.0 ml), gave (3*RS*, *E*) methyl 3-(2'-fluorobenzylidenamino)-butanoate **300j** as an oil (302 mg, 55%). Bp 125 ^oC at 0.5 mm Hg. IR (thin film): 1739 (C=O), 1640 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.30 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.60 (1H, dd, *J*= 5.4, 15.4, C*H*^{A}H^B), 2.68 (1H, dd, *J*= 8.1, 15.4, CH^A*H*^{B}), 3.64 (3H, s, OCH_3), 3.84-3.94 (1H, m. CHN), 7.06 (1H, broad dd, *J*= 8.7, 10.2, H3'), 7.15 (1H, broad t, *J*= 7.8, H5'), 7.35-7.41 (1H, m, H4'), 7.95 (1H, dt, *J*= 1.8, 7.5, H6'), 8.63 (1H, s). δ_C ($CDCl_3$, 100 MHz) 22.27 (CH_3), 42.27 (CH_2), 51.49 (CH_3) , 62.94 (CH), 115.70 (CH, d, *J*= 21.2), 123.79 (C, d, *J*= 9.6), 124.28 (CH, d, *J*= 3.5), 127.85 (CH, d, *J*= 2.7), 132.21 (CH, d, *J*= 8.7), 153.79 (CH, d, *J*= 4.8), 162.23 (C, d, *J*= 251.1), 172.06 (C). m/z (EI): 223 (M^+, 50%), 164 (50), 150 (100), 123 (50), 102 (60). HRMS: 223.1011. $C_{12}H_{14}O_2NF$, requires (M^+) 223.1009.

Methyl (3*RS*, *E*) 3-(2'-nitrobenzylidenamino)-3-phenylpropionoate 300k



Following imine formation procedure A, triethylamine (0.85 mL, 6.1 mmol, 2 equiv.), (3*RS*) methyl 3-amino-3-phenylpropionoate hydrochloride salt **307** (0.709 g, 3.3 mmol, 1 equiv.), 2-nitrobenzaldehyde (0.450 g, 3.0 mmol, 0.9 equiv.), and Na_2SO_4 (0.460 g, 3.3 mmol, 1 equiv.), in DCM (10.0 ml), gave (3*RS*, *E*) methyl 3-(2'-nitrobenzylidenamino)-3-phenylpropionoate **300k** as a yellow oil with no distillation necessary (0.852 g, 92%). IR (thin film): 1736 (C=O), 1636 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 2.93 (1H, dd, *J*= 4.6, 15.5, C*H*^{A}H^B), 3.08 (1H, dd, *J*= 9.4, 15.5, CH^A*H*^{B}), 3.68 (3H, s, OCH_3), 4.97 (1H, dd, *J*= 4.6, 9.4, CHN), 7.25-7.31 (1H, m, H arom.), 7.34-7.39 (2H, m, H arom.), 7.43-7.47 (2H, m, H arom.), 7.55 (1H, dt, *J*= 1.5, 7.8, H5'), 7.65 (1H, broad t, *J*= 7.5, H4'), 8.01 (1H, dd, *J*= 1.1, 8.1, H6'), 8.05 (1H, dd, *J*= 1.5, 7.7, H3'), 8.81 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz) 42.93 (CH_2), 51.77 (CH_3) , 71.01 (CH), 124.27 (CH), 126.96 (CH), 127.69 (CH), 128.78 (CH), 130.11 (CH), 130.82 (CH), 131.14 (C), 133.45 (CH), 141.86 (C), 148.87 (C), 157.58 (CH), 171.29 (C). m/z (CI): 313 [$(M+H)^+$, 100%], 163 (30), 121 (40). HRMS: 313.1190. $C_{17}H_{17}O_4N_2$, requires ($M+H^+$) 313.1188.

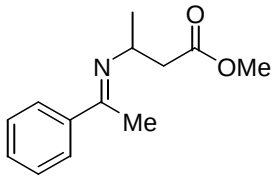
Methyl (3RS, E) 3-phenyl-3-[(pyrid-3'-yl)methylidenamino]-propionoate 300l



Following imine formation procedure A, triethylamine (0.25 mL, 1.8 mmol, 2 equiv.), (3*RS*) methyl 3-amino-3-phenylpropionoate hydrochloride salt **307** (0.198 g, 0.9 mmol, 1 equiv.), 3-pyridinecarboxaldehyde (0.10 mL, 1.0 mmol, 1.1 equiv.), and Na_2SO_4 (0.160 g, 1.1 mmol, 1.2 equiv.), in DCM (4.0 ml), gave a mixture of the desired imino-ester and

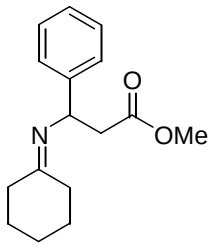
un-reacted 3-pyridinecarboxaldehyde. Removal of the aldehyde by distillation (70 ^{o}C, 0.5 mm Hg) gave pure (3RS, E) methyl 3-phenyl-3-[(pyrid-3'-yl)methylidenamino]-propionoate **300l** as an oil (0.221 g, 90%). IR (thin film): 1736 (C=O), 1644 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 2.90 (1H, dd, *J*= 4.4, 15.8, C*H*^{A}H^{B}), 3.06 (1H, dd, *J*= 9.4, 15.8, CH^{A}*H*^{B}), 3.62 (3H, s, OCH_3), 4.89 (1H, dd, *J*= 4.4, 9.4, CHN), 7.25-7.39 (4H, m, H arom.), 7.42-7.47 (2H, m, H arom.), 8.14 (1H, td, *J*= 1.9, 7.9, H4'), 8.42 (1H, s, N=CH), 8.64 (1H, dd, *J*= 1.7, 4.8, H6'), 8.88 (1H, d, *J*= 1.6, H2'). δ_C ($CDCl_3$, 100 MHz) 42.93 (CH_2), 51.64 (CH_3), 71.06 (CH), 123.58 (CH), 126.90 (CH), 127.61 (CH), 128.73 (CH), 131.64 (C), 134.86 (CH), 142.31 (C), 150.42 (CH), 151.63 (CH), 158.72 (CH), 171.59 (C). m/z (EI): 268 (M^+, 80%), 195 (85), 121 (100). HRMS: 268.1208. $C_{16}H_{16}O_2N_2$, requires (M^+) 268.1212.

Methyl (3*RS, E*) 3-(1'-phenylethylidenamino)butanoate 300m



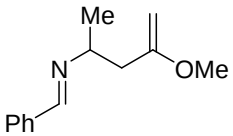
Following imine formation procedure C with a reaction time of 17 h, triethylamine (0.41 mL, 2.9 mmol, 2 equiv.), acetophenone (0.21 mL, 1.8 mmol, 1.2 equiv.), and (3*RS*) methyl 3-aminobutanoate hydrochloride salt **306** (223 mg, 1.45 mmol, 1 equiv.), in toluene (6.0 mL), gave a 93:7 mixture of (3*RS*, *E*), and (3*RS*, *Z*) methyl 3-(1'-phenylethylidenamino)butanoate **300m** as an oil (235 mg, 74%). Bp 150 ^{o}C at 0.6 mm Hg. IR (thin film): 1737 (C=O), 1635 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.22 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.29 (3H, s, CH_3C), 2.60 (1H, dd, *J*= 5.5, 15.3, C*H*^{A}H^{B}), 2.71 (1H, dd, *J*= 7.8, 15.2, CH^{A}*H*^{B}), 3.65 (3H, s, OCH_3), 4.16-4.26 (1H, m, CHN), 7.35-7.38 (3H, m, H arom.), 7.69-7.74 (2H, m, H arom.). δ_C ($CDCl_3$, 100 MHz) 15.49 (CH_3), 21.00 (CH_3), 42.83 (CH_2), 51.40 (CH_3), 53.34 (CH), 126.70 (CH), 128.17 (CH), 129.34 (CH), 141.55 (C), 164.14 (C), 172.69 (C). m/z (EI): 219 (M^+, 10%), 204 (15), 188 (15), 160 (20), 146, (100), 145 (90), 105 (60), 84 (85). HRMS: 219.1262. $C_{13}H_{17}O_2N$, requires (M^+) 219.1259.

Methyl (3*RS*) 3-(cyclohexylidenamino)-3-phenylbutanoate 300n



Following imine formation procedure C with a reaction time of 48 h, triethylamine (0.61 ml, 4.39 mmol, 2 equiv.), (3*RS*) methyl 3-amino-3-phenylpropionate hydrochloride salt **307** (472 mg, 2.19 mmol, 1 equiv.), cyclohexanone (0.34 mL, 3.3 mmol, 1.5 equiv.), in toluene (6.0 mL), gave (3*RS*) methyl 3-(cyclohexylidenamino)-3-phenylbutanoate **300n** as an oil (416 mg, 73%). Bp 190 ^{o}C at 0.4 mm Hg. IR (thin film): 1736 (C=O), 1655 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.40-1.72 (6H, m), 2.18-2.32 (3H, m), 2.39-2.48 (1H, m), 2.81 (1H, dd, *J*= 5.0, 15.2, C*H*^{A}H^{B}), 2.97 (1H, dd, *J*= 9.0, 15.2, CH^{A}*H*^{B}), 3.63 (3H, s, OCH_3), 5.09 (1H, dd, *J*= 5.0, 9.0, CHN), 7.19-7.24 (1H, m, H arom.), 7.27-7.36 (4H, m, H arom.). δ_C ($CDCl_3$, 100 MHz) 25.95 (CH_2), 26.93 (CH_2), 27.85 (CH_2), 30.02 (CH_2), 40.14 (CH_2), 43.86 (CH_2), 51.44 (CH_3), 59.40 (CH) 126.10 (CH), 126.81 (CH), 128.46 (CH), 143.54 (C), 172.19 (C=N), 174.36 (C=O). m/z (EI): 259 (M^+, 30%), 200 (15), 186 (40), 121 (50), 106 (40), 84 (100). HRMS: 259.1575. $C_{16}H_{21}O_2N$, requires (M^+) 259.1572.

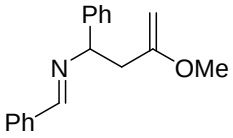
(4R*S*, *E*) 4-(Benzylidenamino)-2-methoxypent-1-ene 301a



Following methylenation procedure B, using a 1.30 M solution of Cp_2TiMe_2 (1.28 mL, 1.66 mmol, 1.9 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(benzylidenamino)butanoate **300a** (179 mg, 0.87 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 45 psi) gave crude enol ether **301a** (202 mg). δ_H ($CDCl_3$, 400 MHz) 1.28 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.32-2.37 (2H, m, CHC*H*$_2$), 3.48 (3H,

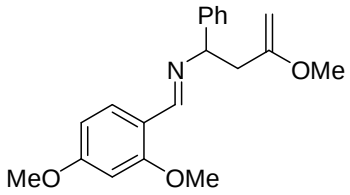
s, OCH_3), 3.55-3.63 (1H, m, CHN), 3.96-3.99 (2H, m, $C=CH_2$), 7.37-7.42 (3H, m, H arom.), 7.69-7.74 (2H, m, H arom.), 8.23 (1H, s, N=CH).

(4R*S*, *E*) 4-(Benzylidenamino)-2-methoxy-4-phenylbut-1-ene 301b



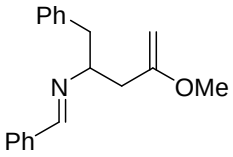
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.63 mL, 0.82 mmol, 2.1 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(benzylidenamino)-3-phenylpropionate **300b** (104.8 mg, 0.39 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 25 psi) gave crude enol ether **301b** (142.7 mg). δ_H ($CDCl_3$, 400 MHz) 2.71 (2H, d, *J* = 7.0, CHCH_2), 3.53 (3H, s, OCH_3), 3.81 (1H, d, *J* = 2.0, C=CH^AH^B), 3.88 (1H, d, J = 2.0, C=CH$^A H^B$), 4.59 (1H, t, *J*= 7.0, CHN), 7.21-7.49 (8H, m, H arom.), 7.74-7.78 (2H, m, H arom.), 8.26 (1H, s, N=CH).

(4R*S*, *E*) 4-(2',4'-dimethoxybenzylidenamino)-2-Methoxy-4-phenylbut-1-ene 301c



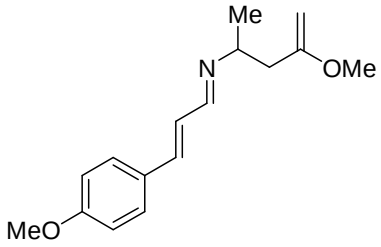
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.40 mL, 0.51 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(2',4'-dimethoxybenzylidenamino)-3-phenylpropionate **300c** (92.3 mg, 0.28 mmol, 1 equiv.) and a 3.5 min reaction time at 65 °C (maximum pressure of 24 psi) gave crude enol ether **301c** (128.9 mg). δ_H ($CDCl_3$, 400 MHz) 2.59-2.70 (2H, m, CHCH_2), 3.51 (3H, s, OCH_3), 3.78-3.87 (8H, m, 2 × OCH_3, $C=CH_2$), 4.53-4.60 (1H, m, CHN), 6.41-6.43 (1H, m, H3'), 6.50-6.54 (1H, m, H5'), 7.22-7.29 (1H, m, H arom.), 7.30-7.37 (2H, m, H arom.), 7.41-7.45 (2H, m, H arom.), 7.98-8.01 (1H, m, H6'), 8.57 (1H, s, N=CH).

(4R*S*, *E*) 4-(Benzylidenamino)-2-methoxy-5-phenylpent-1-ene 301d



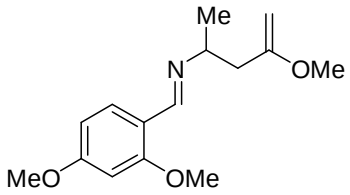
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (92 mL, 1.20 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(benzylidenamino)-4-phenylbutanoate **300d** (186.4 mg, 0.66 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 44 psi) gave crude enol ether **301d** (128.9 mg). δ_H ($CDCl_3$, 400 MHz): 2.45 (1H, dd, *J*= 8.0, 13.6, C*H*^{A}H^{B}C=), 2.52 (1H, dd, *J*= 6.0, 13.6, CH^A*H*^{B}C=), 2.91 (1H, dd, *J*= 8.4, 13.2, PhC*H*^{C}H^D), 2.99 (1H, dd, *J*= 4.8, 13.2, PhCH^C*H*^{D}), 3.48 (3H, s, OCH_3), 3.58-3.65 (1H, m, CHN), 3.89 (2H, s, C=CH_2), 7.10-7.14 (3H, m, H arom.), 7.18-7.23 (2H, m, H arom.), 7.35-7.47 (3H, m, H arom.), 7.62-7.71 (2H, m, H arom.), 7.84 (1H, s, N=CH).

(4R*S*, 1'*E*, 2'*E*) 2-Methoxy-4-[3'-(4"-methoxyphenyl)prop-2'-enylidenamino]pent-1-ene 301e



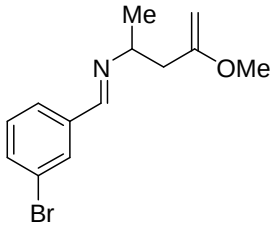
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.54 mL, 0.70 mmol, 2.0 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, 1'*E*, 2'*E*) methyl 3-[3'-(4"-Methoxyphenyl)prop-2'-enylidenamino]butanoate **300e** (91.9 mg, 0.35 mmol, 1 equiv.), and a 3 min reaction time at 65 °C (maximum pressure of 29 psi) gave crude enol ether **301e** (101.3 mg). δ_H ($CDCl_3$, 400 MHz) 1.15 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.24 (2H, d, *J*= 6.4, CHC*H*$_2$), 3.35-3.46 (1H, m, CHN), 3.43 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.80 (1H, d, *J* = 2.0, C=C*H*^{A}H^B), 3.82 (1H, d, *J* = 2.0, C=CH^A*H*^{B}), 6.67-6.88 (4H, m, H2', H3', H arom.), 7.33 (2H, d, *J*= 8.6, H arom.), 7.85 (1H, d, *J* =8.2, H1').

(4R*S*, *E*) 4-(2',4'-Dimethoxybenzylidenamino)-2-methoxypent-1-ene 301f



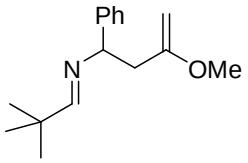
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.93 mL, 1.21 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(2',4'-dimethoxybenzylidenamino)butanoate **300f** (178.9 mg, 0.68 mmol, 1 equiv.) and a 2.5 min reaction time at 65 °C (maximum pressure of 48 psi) gave crude enol ether **301f** (198.0 mg). δ_H ($CDCl_3$, 400 MHz): 1.18 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.31 (1H, dd, *J*= 6.8, 14.0, CHC*H*^{A}H^B), 2.36 (1H, dd, *J*= 7.2, 14.0, CHCH^A*H*^{B}), 3.46 (3H, s, OCH_3), 3.61-3.68 (1H, m, CHN), 3.61 (3H, s, OCH3), 3.62 (3H, s, OCH3), 3.85 (1H, d, *J* = 2.0, C=C*H*^{A}H^B), 3.86 (1H, d, *J* = 2.0, C=CH^A*H*^{B}), 6.40 (1H, d, *J*= 2.3, H3'), 6.48 (1H, dd, *J*= 2.3, 8.6, H5'), 7.86 (1H, d, *J*= 8.6, H6'), 8.52 (1H, s, CH=N).

(4R*S*, *E*) 4-(3'-Bromobenzylidenamino)-2-methoxypent-1-ene 301g



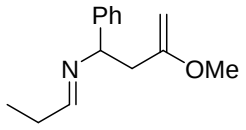
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.63 mL, 0.82 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(3'-bromobenzylidenamino)butanoate **300g** (129.6 mg, 0.46 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 33 psi) gave crude enol ether **301g** (151.4 mg). δ_H ($CDCl_3$, 400 MHz): 1.22 (3H, d, *J*= 6.6, C*H*$_3$CH), 2.31 (2H, d, *J* = 7.2, CHC*H*$_2$), 3.44 (3H, s, OCH_3), 3.68-3.75 (1H, m, CHN), 3.81 (1H, d, *J*= 2.0, C=C*H*^{A}H^B), 3.83 (1H, d, *J*= 2.0, C=CH^A*H*^{B}), 7.23-7.32 (1H, m, H5'), 7.50-7.54 (1H, m, H4'), 7.58-7.61 (1H, m, H6'), 7.90-7.93 (1H, m, H2'), 8.1 (1H, s, N=CH).

(4R*S*, *E*) 4-(2',2'-Dimethylpropylidenamino)-2-methoxy-4-phenylbut-1-ene 301h



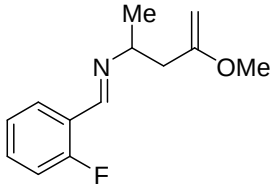
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.70 mL, 0.91 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(2',2'-dimethylpropylidenamino)-3-phenylbutanoate **300h** (125.0 mg, 0.51 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 33 psi) gave crude enol ether **301h** (158.6 mg). δ_H ($CDCl_3$, 400 MHz): 1.07 (9H, s, CH_3C), 2.50 (1H, dd, *J*= 9.2, 13.6, CHC*H*^{A}H^B), 2.58 (1H, dd, *J*= 4.4, 13.6, CHCH^A*H*^{B}), 3.52 (3H, s, OCH_3), 3.80 (1H, d, J= 2.0, C=C*H*^{A}H^B), 3.87 (1H, d, *J*= 2.0, C=CH^A*H*^{B}), 4.29 (1H, dd, *J*= 4.4, 9.2, CHN), 7.21-7.24 (1H, m, H arom.), 7.30-7.35 (2H, m, H arom.), 7.40-7.43 (2H, m, H arom.), 7.47 (1H, s, N=CH).

(4R*S*, *E*) 2-Methoxy-4-phenyl-4-(propylidenamino)but-1-ene 301i



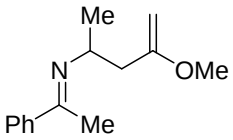
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.72 mL, 0.94 mmol, 2.1 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(propylidenamino)-3-phenylbutanoate **300i** (114.5 mg, 86% pure by mass, 0.45 mmol, 1 equiv.) and a 2.5 min reaction time at 65 °C (maximum pressure of 34 psi) gave crude enol ether **301i** (151.1 mg). No characterization was performed due to instability of the aliphatic imine.

(4R*S*, *E*) 4-(2'-Fluorobenzylidenamino)-2-methoxypent-1-ene 301j



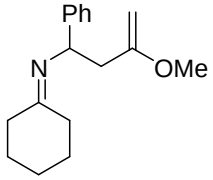
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.52 mL, 0.68 mmol, 2.0 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(2'-fluorobenzylidenamino)-butanoate **300j** (75.1 mg, 0.34 mmol, 1 equiv.), and a 10 min reaction time at 65 °C (maximum pressure of 23 psi) gave crude enol ether **301j** (100.9 mg). δ_H ($CDCl_3$, 400 MHz) 1.34 (3H, d, *J*= 6.4, C*H*$_3$CH), 2.40 (2H, d, *J*= 6.4, CHC*H*$_2$), 3.51 (3H, s, OCH_3), 3.62-3.66 (1H, m. CHN), 3.84 (1H, d, *J*= 2.0, C=C*H*^{A}H^B), 3.87 (1H, d, *J*= 2.0, C=CH^A*H*^{B}), 6.93-7.00 (1H, m, H3'), 7.04-7.07 (1H, m, H5'), 7.23-7.29 (1H, m, H4'), 7.80-7.86 (1H, m, H6'), 8.38 (1H, s, N=CH).

(4R*S*, *E*) 2-Methoxy-4-(1'-phenylethylidenamino)pent-1-ene 301m



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.94 mL, 1.22 mmol, 1.9 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(1'-phenylethylidenamino)butanoate **300m** (140.6 mg, 0.64 mmol, 1 equiv.), and a 10 min reaction time at 65 °C (maximum pressure of 42 psi) gave crude enol ether **301m** (155.7 mg). δ_H ($CDCl_3$, 400 MHz) 1.20 (3H, d, *J*= 6.2, C*H*$_3$CH), 2.21 (3H, s, CH_3C), 2.35 (1H, dd, *J*= 6.4, 13.6, CHC*H*^{A}H^B), 2.41 (1H, dd, *J*= 7.6, 13.6, CHCH^A*H*^{B}), 3.52 (3H, s, OCH_3), 3.86 (1H, d, *J* = 2.0, C=C*H*^{A}H^B), 3.88 (1H, d, J = 2.0, C=CH^A*H*^{B}), 3.92-4.01 (1H, m, CHN), 7.33-7.36 (3H, m, H arom.), 7.68-7.73 (2H, m, H arom.).

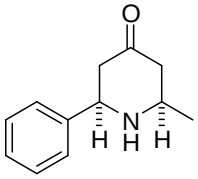
(4R*S*, *E*) 4-(cyclohexylidenamino)-2-methoxy-4-phenylbut-1-ene 301n



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.90 mL, 1.17 mmol, 2.0 equiv.) in toluene-THF (1:1 by mass) with (3*RS*) methyl 3-(cyclohexylidenamino)-3-phenylbutanoate **300n** (75.1 mg, 0.34 mmol, 1 equiv.), and a 10

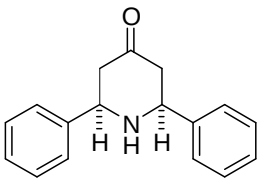
min reaction time at 65 °C (maximum pressure of 42 psi) gave crude enol ether **301n** (153.5 mg). δ_H ($CDCl_3$, 400 MHz) 1.40-1.75 (6H, m), 2.18-2.45 (4H, m), 2.55-2.66 (2H, m, CHCH_2), 3.53 (3H, s, OCH_3), 3.82 (1H, d, *J*= 2.0, C=CH^AH^B), 3.85 (1H, d, *J*= 2.0, C=CH^AH^B), 4.86 (1H, dd, *J*= 5.2, 8.0, CHN), 7.19-7.45 (5H, m, H arom.).

(2*RS*, 6*RS*) 2-Methyl-6-phenylpiperidin-4-one 302a



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (1.28 mL, 1.66 mmol, 1.9 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(benzylidenamino)-butanoate **300a** (179 mg, 0.87 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 45 psi) gave crude enol ether **301a** (202 mg). Following cyclization procedure D, triisobutylaluminium (0.62 ml, 0.62 mmol, 1.0 M in hexanes, 2 equiv.), and a portion of the crude enol ether **301a** (71.1 mg), in DMSO (10.0 ml) yielded the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (50:1)] gave (2*RS*, 6*RS*) 2-methyl-6-phenylpiperidin-4-one **302a** as a solid (39.4 mg, 68%). R_f [SiO_2, DCM-MeOH (20:1)]: 0.44. Mp 81-82 ^oC. Lit:[130] mp 65-67 ^oC. δ_H ($CDCl_3$, 400 MHz) 1.26 (3H, d, *J*= 6.2, CH_3CH), 2.23 (1H, dd, *J*= 11.6, 14.0, H3^{ax}), 2.41 (1H, broad dd, *J*= 2.8, 14.0, H3^{eq}), 2.48-2.52 (2H, m, H5), 3.12 (1H, dqd, *J*= 2.9, 6.1, 12.0, H2), 3.96 (1H, m, H6), 7.27-7.41 (5H, m, H arom.). δ_C ($CDCl_3$, 100 MHz) 22.61 (CH_3), 49.76 (CH_2), 49.89 (CH_2), 52.32 (CH), 61.02 (CH), 126.51 (CH), 127.85 (CH), 128.75 (CH) 142.58 (C), 208.93 (C). ^{1}H NMR data in agreement with the literature.[131]

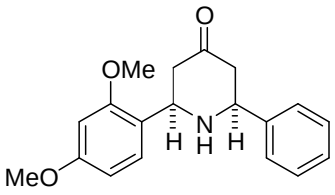
(2*RS*, 6*SR*) 2,6-Diphenylpiperidin-4-one 302b



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.63 mL, 0.82 mmol, 2.1 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-

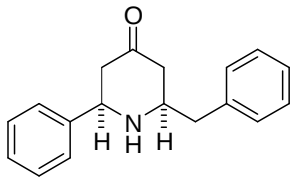
(benzylidenamino)-3-phenylpropionate **300b** (105 mg, 0.39 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 25 psi) gave crude enol ether **301b** (143 mg). Following cyclization procedure D, triisobutylaluminium (0.78 ml, 0.78 mmol, 1.0 M in hexanes, 2 equiv.), and crude enol ether **301b** (143 mg), in DMSO (13.0 ml) yielded the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (100:1)] gave (2*RS*, 6*SR*) 2,6-diphenylpiperidin-4-one **302b** as a solid (68.9 mg, 70%). R_f [SiO_2, DCM-MeOH (40/1)]: 0.31. Mp 99-100 ^oC. δ_H ($CDCl_3$, 400 MHz) 2.48-2.62 (4H, m, H3 & H5), 4.01 (2H, dd, *J*= 3.6, 10.8, H2 & H6), 7.16-7.41 (10H, m, H arom.). δ_C ($CDCl_3$, 100 MHz) 50.38 (CH_2), 61.16 (CH), 126.54 (CH), 127.93 (CH), 128.76 (CH) 142.68 (C), 208.24 (C). ^1H NMR data in agreement with the literature.[126]

(2*RS*, 6*SR*) 2-(2',4'-Dimethoxyphenyl)-6-phenylpiperidin-4-one 302c



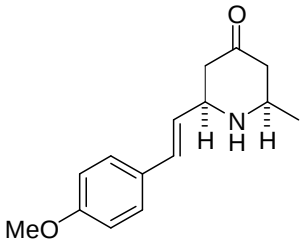
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.40 mL, 0.51 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(2',4'-dimethoxybenzylidenamino)-3-phenylpropionate **300c** (92.3 mg, 0.28 mmol, 1 equiv.) and a 3.5 min reaction time at 65 °C (maximum pressure of 24 psi) gave crude enol ether **301c** (128.9 mg). Following cyclization procedure D, triisobutylaluminium (0.56 ml, 0.56 mmol, 1.0 M in hexanes, 2 equiv.), and crude enol ether **301c** (128.9 mg), in DMSO (10.0 ml) yielded the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (50:1)] gave (2*RS*, 6*SR*) 2-(2',4'-dimethoxyphenyl)-6-phenylpiperidin-4-one **302c** as an oil (57.9 mg, 66%). R_f [SiO_2, DCM-MeOH (20:1)]: 0.70. IR (thin film): 1730 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 2.51-2.66 (4H, m, H3 & H5), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.10 (1H, dd, *J*= 5.6, 9.2, H6), 4.41 (1H, dd, *J*= 3.3, 11.5, H2), 6.46 (1H, d, *J*= 2.4, H3'), 6.52 (1H, dd, *J*= 2.4, 8.5, H5'), 7.26-7.39 (3H, m, H arom.), 7.44-7.50 (3H, m, H arom.). δ_C ($CDCl_3$, 100 MHz) 47.30 (CH_2), 49.32 (CH_2), 52.86 (CH), 54.28 (CH_3), 54.33 (CH_3), 60.13 (CH), 97.37 (CH), 103.35 (CH), 122.19 (C), 125.56 (CH), 125.90 (CH), 126.73 (CH), 127.68 (CH), 141.99 (C), 156.37 (C), 159.14 (C), 207.94 (C). m/z (EI): 311 (M^+, 75%), 192 (100), 164 (90), 149 (60), 121 (40). HRMS: 311.1523 $C_{19}H_{21}O_3N$, requires (M^+) 311.1521.

(2*RS*, 6*RS*) 2-Benzyl-6-phenylpiperidin-4-one 302d



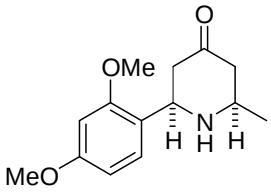
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (92 mL, 1.20 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, 3*E*) methyl 3-(benzylidenamino)-4-phenylbutanoate **300d** (186.4 mg, 0.66 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 44 psi) gave crude enol ether **301d** (128.9 mg). Following cyclization procedure B, *p*-toluene sulfonic acid (73 mg, 0.43 mmol, 2 equiv.), and crude enol ether **301d** (64.0 mg), in DCM (5.0 ml) yielded the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (50:1)] gave (2*RS*, 6*RS*) 2-benzyl-6-phenylpiperin-4-one **302d** as a colorless oil (34.5 mg, 61%). R_f [SiO_2, DCM-MeOH (20/1)]: 0.50. IR (thin film): 1714 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 2.25 (1H, dd, *J*= 11.6, 14.0, $H3^{ax}$), 2.38 (1H, dd, *J*= 2.5, 14.5, $H3^{eq}$), 2.39-2.44 (2H, m, H5), 2.73 (1H, dd, *J*= 8.2, 13.5, CH_AH_BCH), 2.81 (1H, dd, *J*= 5.0, 13.5, CH_AH_BCH), 3.15 (1H, dddd, *J*= 2.9, 5.2, 8.1, 11.3, H2), 3.74-3.82 (1H, m, H6), 7.12-7.33 (10H, m, H arom.). δ_C ($CDCl_3$, 100 MHz): 43.34 (CH_2), 48.09 (CH_2), 50.54 (CH_2), 57.82 (CH), 60.79 (CH), 126.41 (CH), 126.70 (CH), 127.78 (CH), 128.72 (CH), 128.97 (CH), 129.14 (CH), 137.63 (C), 142.64 (C), 208.46 (C). m/z (CI): 266 [$(M+H)^+$, 100%], 174.2 (15). HRMS: 266.1544 $C_{18}H_{20}ON$ requires ($M+H^+$), 266.1545.

(2*RS*, 6*RS*, *E*) 2-[2'-(4"-Methoxyphenyl)vinyl]-6-methylpiperidin-4-one 302e



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.54 mL, 0.70 mmol, 2.0 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, 1'*E*, 2'*E*) methyl 3-[3'-(4"-methoxyphenyl)prop-2'-enylidenamino]butanoate **300e** (91.9 mg, 0.35 mmol, 1 equiv.), and a 3 min reaction time at 65 °C (maximum pressure of 29 psi) gave crude enol ether **301e** (101.3 mg). Following cyclization procedure D, triisobutylaluminium (0.70 ml, 0.70 mmol, 1.0 M in hexanes, 2 equiv.), and the crude enol ether **301e** (101.3 mg), in DMSO (10.0 ml) gave the crude piperidinone. Column chromatography [SiO_2, DCM/MeOH (50/1)] gave (2*RS*, 6*RS*, *E*) 2-[2'-(4"-methoxyphenyl)vinyl]-6-methylpiperidin-4-one **302e** as an oil (44.0 mg, 51%). R_f [SiO_2, DCM/MeOH (20/1)] 0.23. IR (thin film): 1703 (C=O), 1604 (C=C) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.24 (3H, d, *J*= 6.2, C*H*$_3$CH), 2.15 (1H, broad ddd, *J*= 1.1, 11.7, 14.0, H5^{ax}), 2.33 (1H, ddd, *J*= 1.1, 11.4, 14.1, H3^{ax}), 2.34-2.37 (1H, m, H5^{eq}), 2.36 (1H, ddd, *J*= 2.1, 3.3, 14.0, H3^{eq}), 3.07 (1H, dqd, *J*= 3.0, 6.1, 11.7, H6), 3.59 (1H, dddd, *J*= 1.0, 3.4, 7.3, 11.7, H2), 3.81 (3H, s, OC*H*$_3$), 6.06 (1H, dd, *J*= 7.2, 15.8, H1'), 6.52 (1H, broad d, *J*= 15.8, H2'), 6.83-6.88 (2H, d, *J*= 8.8, H3'' & H5''), 7.28-7.33 (2H, d, *J*= 8.4, H2'' & H6''). δ_C ($CDCl_3$, 100 MHz) 22.64 (CH_3), 48.00 (CH_2), 49.77 (CH_2), 51.88 (CH), 55.27 (CH_3), 58.98 (CH), 114.04 (CH), 127.61 (CH), 128.29 (CH), 129.11 (C), 130.45 (CH), 159.42 (C), 208.53 (C). m/z (EI): 245 (M^+, 100%), 160 (70), 121 (75). HRMS: 245.1415 $C_{15}H_{19}O_2N$, requires (M^+) 245.1416.

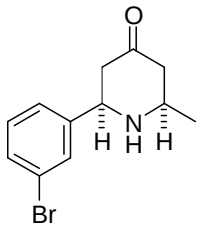
(2*RS*, 6*RS*) 2-(2', 4'-Dimethoxyphenyl)-6-methylpiperidin-4-one 302f



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.93 mL, 1.21 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(2',4'-dimethoxybenzylidenamino)butanoate **300f** (178.9 mg, 0.68 mmol, 1 equiv.) and a 2.5 min reaction time at 65 °C (maximum pressure of 48 psi) gave crude enol ether **301f** (198.0 mg). Following cyclization procedure C, *p*-toluene sulfonic acid (106 mg, 0.62 mmol, 2 equiv.), and a portion of the crude enol ether **301f** (90.9 mg), in DME (3.0 ml) yielded the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (50:1)] gave (2*RS*, 6*RS*) 2-(2', 4'-dimethoxyphenyl)-6-methylpiperidin-4-one **302f** as an oil (44.4 mg, 58%). R_f [SiO_2, DCM-MeOH (20:1)]: 0.24. IR (thin film): 1713 (C=O) cm^{-1}. δ_H

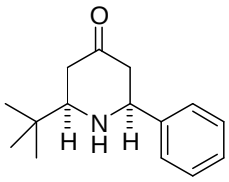
($CDCl_3$, 400 MHz): 1.22 (3H, d, *J*= 6.2, C*H*$_3$CH), 2.17 (1H, dd, *J*= 11.8, 13.9, H5^{ax}), 2.40 (1H, ddd, *J*= 1.8, 2.7, 14.0, H5^{eq}), 2.43-2.54 (2H, m, H3), 3.11 (1H, dqd, *J*= 2.9, 6.1, 12.0, H6), 3.797 (3H, s, OC*H*$_3$), 3.800 (3H, s, OC*H*$_3$), 4.22 (1H, dd, *J*= 4.1, 10.8, H2), 6.45 (1H, d, *J*= 2.4, H3'), 6.49 (1H, dd, *J*= 2.4, 8.4, H5'), 7.32 (1H, d, *J*= 8.4, H6'). δ_C ($CDCl_3$, 100 MHz): 22.72 (CH_3), 47.94 (CH_2), 49.99 (CH_2), 52.32 (CH), 54.43 (CH), 55.26 (CH_3), 55.35 (CH_3), 98.53 (CH), 104.19 (CH), 122.88 (C), 127.25 (CH), 157.45 (C), 160.09 (C), 209.73 (C). m/z (EI+): 249 ($(M)^+$, 100%), 206 (65), 192 (90), 164 (100), 149 (75), 121 (45). HRMS: 249.1362 $C_{14}H_{19}O_3N$ requires (M^+), 249.1365.

(2RS, 6RS) 2-(3'-Bromophenyl)-6-methylpiperidin-4-one 302g



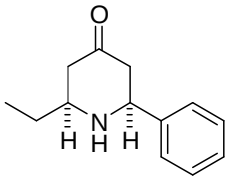
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.63 mL, 0.82 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(3'-bromobenzylidenamino)butanoate **300g** (129.6 mg, 0.46 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 33 psi) gave crude enol ether **301g** (151.4 mg). Following cyclization procedure C, *p*-toluene sulfonic acid (157 mg, 0.91 mmol, 2 equiv.), and crude enol ether **301g** (151.4 mg), in DME (5.0 ml) yielded the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (100:3)] gave (2*RS*, 6*RS*) 2-(3'-bromophenyl)-6-methylpiperidin-4-one **302g** as an oil (58.6 mg, 48%). R_f [SiO_2, DCM-MeOH (100:3)]: 0.51. IR (thin film): 1714 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 1.26 (3H, d, *J*= 6.2, C*H*$_3$CH), 2.21 (1H, ddd, *J*= 0.7, 11.7, 13.9, H5^{ax}), 2.37-2.44 (2H, m, H5^{eq}, H3^{ax}), 2.48 (1H, ddd, *J*= 2.0, 3.7, 14.0, H3^{eq}), 3.10 (1H, dqd, *J*= 3.0, 6.2, 11.6, H6), 3.92 (1H, dd, *J*= 3.7, 11.2, H2), 7.21 (1H, t, *J*= 7.8, H5'), 7.30 (1H, broad d, *J*= 7.7, H6'), 7.42 (1H, ddd, *J*= 1.2, 1.9, 7.9, H4'), 7.59 (1H, t, 1.8, H2'). δ_C ($CDCl_3$, 100 MHz): 22.58 (CH_3), 49.64 (CH_2), 49.78 (CH_2), 52.20 (CH), 60.39 (CH), 122.81 (C), 125.24 (CH), 129.59 (CH), 130.28 (CH), 130.93 (CH), 144.95 (C), 208.13 (C). m/z (EI): 269 (M^+, 15%). 267 (M^+, 15%), 212 (10), 210 (10), 184 (15), 182 (15), 85 (60), 83 (100). HRMS: 269.0239, and 267.0258, $C_{12}H_{14}ON^{81}Br$ requires (M^+), 269.0239, $C_{12}H_{14}ON^{79}Br$ requires (M^+), 267.0259.

(2*RS*, 6*SR*) 2-(1', 1'-Dimethylethyl)-6-phenylpiperidin-4-one 302h



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.70 mL, 0.91 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(2',2'-dimethylpropylidenamino)-3-phenylbutanoate **300h** (125.0 mg, 0.51 mmol, 1 equiv.) and a 10 min reaction time at 65 °C (maximum pressure of 33 psi) gave crude enol ether **301h** (158.6 mg). Following cyclization procedure C, *p*-toluene sulfonic acid (89 mg, 0.52 mmol, 2 equiv.), and a portion of the crude enol ether **301h** (80.2 mg), in DME (4.0 ml) yielded the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (50:1)] gave (2*RS*, 6*SR*) 2-(1', 1'-dimethylethyl)-6-phenylpiperidin-4-one **302h** as an oil (34.5 mg, 58 %). R_f [SiO_2, DCM-MeOH (20:1)]: 0.30. IR (thin film): 1714 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.98 (9H, s, C*H*$_3$C), 2.27 (1H, broad t, *J*= 12.6, $H3^{ax}$), 2.40-2.47 (2H, m, $H3^{eq}$ & $H5^{ax}$), 2.50 (1H, ddd, 2.0, 3.7, 13.7, $H5^{eq}$), 2.69 (1H, dd, *J*= 2.8, 11.8, H2), 3.89 (1H, dd, *J*= 3.7, 11.2, H6), 7.27-7.33 (1H, m, H arom.), 7.34-7.39 (2H, m, H arom.), 7.41-7.45 (2H, m, H arom.). δ_C ($CDCl_3$, 100 MHz): 26.18 (CH_3), 33.64 (C), 43.37 (CH_2), 50.57 (CH_2), 60.95 (CH), 65.64 (CH), 126.53 (CH), 127.73 (CH), 128.68 (CH), 143.27 (C), 210.14 (C). m/z (CI+): 232 [$(M+H)^+$, 100%], 174 (20). HRMS: 232. 1703 $C_{15}H_{22}ON$ requires $(M+H)^+$, 232.1701.

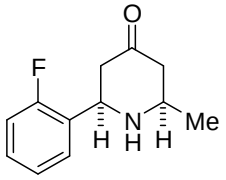
(2*SR*, 6*SR*) 2-Ethyl-6-phenylpiperidin-4-one 302i



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.72 mL, 0.94 mmol, 2.1 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, 3*E*) methyl 3-(propylidenamino)-3-phenylbutanoate **300i** (114.5 mg, 86% pure by mass, 0.45 mmol, 1 equiv.) and a 2.5 min reaction time at 65 °C (maximum pressure of 34 psi) gave crude

enol ether **301i** (151.1 mg). Following cyclization procedure C, *p*-toluene sulfonic acid (180 mg, 1.05 mmol, 2.3 equiv.), and the crude enol ether **301i** (151.1 mg), in DME (5.0 ml) yielded the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (100:3)] gave (2*SR*, 6*SR*) 2-ethyl-6-phenylpiperidin-4-one **302i** as an oil (32.4 mg, 35%). R_f [SiO_2, DCM-MeOH (20:1)]: 0.48. IR (thin film): 1714 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 0.97 (3H, t, *J*= 7.5, C*H*$_3$CH$_2$), 1.54-1.65 (2H, m, CH$_3$C*H*$_2$), 2.21 (1H, dd, *J*= 11.8, 13.7, H3^{ax}), 2.45 (1H, ddd, *J*= 1.4, 2.7, 13.9, H3^{eq}), 2.48-2.54 (2H, m, H5), 2.90 (1H, dtd, *J*= 2.8, 6.3, 11.9, H2), 3.89-3.97 (1H, m, H6), 7.27-7.32 (1H, m, H arom.), 7.32-7.43 (4H, m, H arom.). δ_C ($CDCl_3$, 100 MHz): 10.06 (CH_3), 29.74 (CH_2), 47.77 (CH_2), 50.42 (CH_2), 58.26 (CH), 61.03 (CH), 126.53 (CH), 127.82 (CH), 128.73 (CH), 142.76 (C), 208.98 (C). m/z (EI): 203 (M^+, 15%), 174 (20), 149 (20), 131 (20), 104 (20), 84 (100). HRMS: 203.1313 $C_{13}H_{17}ON$ requires (M^+), 203.1310.

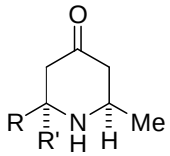
(2*RS*, 6*RS*) 2-(2'-Fluorophenyl)-6-methylpiperidin-4-one 302j



Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.52 mL, 0.68 mmol, 2.0 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(2'-fluorobenzylidenamino)-butanoate **300j** (75.1 mg, 0.34 mmol, 1 equiv.), and a 10 min reaction time at 65 °C (maximum pressure of 23 psi) gave crude enol ether **301j** (100.9 mg). Following cyclization procedure D, triisobutylaluminium (0.67 ml, 0.67 mmol, 1.0 M in hexanes, 2 equiv.), and the crude enol ether **301j** (100.9 mg), in DMSO (10.0 ml) gave the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (50:1)] gave (2*RS*, 6*RS*) 2-(2'-fluorophenyl)-6-methylpiperidin-4-one **302j** as a solid (44.8 mg, 64%). R_f (SiO_2, DCM/MeOH 50/1): 0.50. Mp 84-85 ^oC. IR (thin film): 1716 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.27 (3H, d, *J*= 6.2, C*H*$_3$CH), 2.21 (1H, ddd, *J*= 0.7, 11.7, 14.1, H5^{ax}), 2.43 (1H, ddd, *J*= 2.1, 2.8, 14.1, H5^{eq}), 2.47 (1H, ddd, *J*= 0.7, 11.6, 13.9, H3^{ax}), 2.55 (1H, ddd, *J*= 2.0, 3.5, 14.0, H3^{eq}), 3.15 (1H, dqd, *J*= 2.9, 6.2, 11.7, H6), 4.31 (1H, dd, *J*= 3.4, 11.5, H2), 7.05 (1H, ddd, *J*= 1.1, 8.2, 10.6, H3'), 7.17 (1H, dt, *J*=1.1, 7.6, H5'), 7.28 (1H, dddd, *J*= 1.8, 5.3, 7.6, 8.2. H4'), 7.54 (1H, dt, 1.7, 7.5, H6'). δ_C ($CDCl_3$, 100 MHz) 22.65 (CH_3), 48.12 (CH_2), 49.82 (CH_2) , 52.30 (CH), 53.77 (CH, d, *J*= 2.9),

115.62 (CH, d, *J*= 22.3), 124.63 (CH, d, *J*= 4.0), 127.52 (CH, d. *J*= 3.8), 129.16 (CH, d, *J*= 7.9), 129.31 (C, d, *J*= 13.5), 160.06 (C, d, *J*= 244.2), 208.36 (C). m/z (EI): 207 (M^+, 20%), 164 (15%), 149 (20%), 122 (25), 84 (100). HRMS: 207.1057 $C_{12}H_{14}ONF$, requires (M^+) 207.1059.

(2*RS*, 6*RS*) 2,6-Dimethyl-2-phenylpiperidin-4-one 302m



A) R=Ph, R'=Me

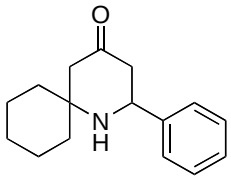
B) R=Me, R'=Ph

A:B = 89:11

Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.94 mL, 1.22 mmol, 1.9 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(1'-phenylethylidenamino)butanoate **300m** (140.6 mg, 0.64 mmol, 1 equiv.), and a 10 min reaction time at 65 °C (maximum pressure of 42 psi) gave crude enol ether **301m** (155.7 mg). Following cyclization procedure D, triisobutylaluminium (0.64 mL, 0.64 mmol, 1.0 M in hexanes, 2 equiv.), and a portion of the crude enol ether **301m** (78.1 mg), in DMSO (11.0 ml) gave an 89:11 ratio of the 2,6-*syn*, and the 2.6-*anti* 2,6-dimethyl-2-phenylpiperidin-4-one **302m** as an oil (44.8 mg, 68%) after column chromatography [SiO_2, DCM-MeOH (40:1)]. Repeated chromatography allowed samples of each diastereomer to be isolated pure. 2,6-*syn* **302m**: R_f [SiO_2, DCM-MeOH (40/1)]: 0.25. IR (thin film): 1715 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.28 (3H, d, *J*= 6.2, C*H*$_3$CH), 1.43 (3H, s, C*H*$_3$C), 2.08 (1H, ddd, *J*= 0.9, 11.4, 13.6, H5^{ax}), 2.44 (1H, ddd, *J*= 1.8, 3.2, 13.6, H5^{eq}), 2.56 (1H, broad d, *J*= 13.2, H3^{ax}), 2.63 (1H, dd, *J*= 1.8, 13.2, H3^{eq}), 3.42 (1H, dqd, *J*= 3.3, 6.2, 11.3. H6), 7.26-7.30 (1H, m, H arom.), 7.32-7.39 (2H, m, H arom.), 7.54-7.59 (2H, m, H arom.). δ_C ($CDCl_3$, 100 MHz) 23.12 (CH_3), 25.67 (CH_3), 47.27 (CH), 50.19 (CH_2), 54.08 (CH_2), 58.95 (CH), 124.65 (CH), 127.03 (CH), 128.43 (CH), 148.17 (C), 209.63 (C=O). m/z (EI): 203 (M^+, 10%), 188 (10%), 160 (5%), 149 (10%), 146 (10), 84 (100). HRMS: 203.1313 $C_{13}H_{17}ON$, requires (M^+) 203.1310. 2,6-*anti* **302m**: R_f [SiO_2, DCM-MeOH (40:1)]: 0.21. IR (thin film): 1714 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.14 (3H, d, *J*= 6.2, C*H*$_3$CH), 1.48 (3H, s, C*H*$_3$C), 2.01 (1H, broad dd, *J*= 12.2, 13.7, H5^{ax}), 2.23 (1H, ddd, *J*= 1.9, 2.9, 14.3, H5^{eq}), 2.43 (1H, broad d, *J*= 14.0, H3^{ax}), 2.67-2.77 (1H,

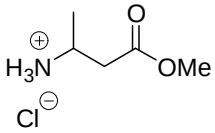
m, H6), 3.17 (1H, dd, *J*= 1.8, 14.4, $H3^{eq}$), 7.18-7.40 (5H, m, H arom.). δ_C ($CDCl_3$, 100 MHz) 25.54 (CH_3), 34.11 (CH_3), 47.15 (CH), 49.65 (CH_2), 51.67 (CH_2), 59.65 (CH), 125.90 (CH), 126.81 (CH), 128.68 (CH), 145.02 (C), 209.24 (C). m/z (CI): 204 [$(M+H)^+$, 100%]. HRMS: 204.1389 $C_{13}H_{18}ON$, requires ($M+H^+$), 204.1388.

(2*RS*) 2-Phenyl-1-aza-spiro-5,5-undecan-4-one 302n



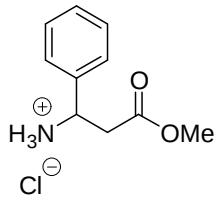
Following methylenation procedure B, a 1.30 M solution of Cp_2TiMe_2 (0.90 mL, 1.17 mmol, 2.0 equiv.) in toluene-THF (1:1 by mass) with (3*RS*) methyl 3-(cyclohexylidenamino)-3-phenylbutanoate **300n** (75.1 mg, 0.34 mmol, 1 equiv.), and a 10 min reaction time at 65 °C (maximum pressure of 42 psi) gave crude enol ether **301n** (153.5 mg). Following cyclization procedure D, triisobutylaluminium (0.48 mL, 0.48 mmol, 1.0 M in hexanes, 2 equiv.), and a portion of the crude enol ether **301n** (63.7 mg), in DMSO (8.0 ml) gave the crude piperidinone. Column chromatography [SiO_2, DCM-MeOH (40:1)] gave (2*RS*) 2-phenyl-1-aza-spiro-5,5-undecan-4-one **302n** as an oil (30.6 mg, 52%). R_f [SiO_2, DCM-MeOH (40:1)]: 0.25. IR (thin film): 1711 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.31-1.78 (10H, m, CH_2), 2.31-2.54 (4H, m H3 & H5), 4.16 (1H, dd, *J*= 4.7, 10.2, H2), 7.27-7.33 (1H, m, H arom.), 7.34-7.39 (2H, m, H arom.), 7.41-7.45 (2H, m. H arom.). δ_C ($CDCl_3$, 100 MHz) 21.50 (CH_2), 21.73 (CH_2), 25.56 (CH_2), 32.50 (CH_2), 40.32 (CH_2), 50.03 (CH_2), 53.08 (CH_2), 54.65 (CH), 55.42 (C), 126.68 (CH), 127.76 (CH), 128.70 (CH), 143.10 (C), 209.80 (C). m/z (EI): 243 (M^+, 60%), 200 (100), 187 (55), 131 (50), 104 (45), 83 (25). HRMS: 243.1624 $C_{16}H_{19}ON$, requires (M^+) 243.1623.

(3*RS*) Methyl 3-aminobutanoate, hydrochloride salt 306



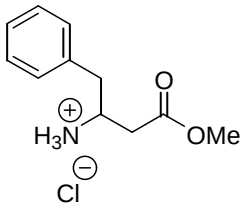
Using: thionyl chloride (2.80 ml , 38.6 mmol, 2 equiv.), (3*RS*) 3-aminobutyric acid **303** (1.98 g, 19.2 mmol, 1 equiv.), in MeOH (33.0 mL), and following the general esterification procedure gave (3*RS*) methyl 3-aminobutanoate hydrochloride salt **306** as an oil (2.90 g, 98%). IR (thin film): 1731 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.50 (3H, d, *J*= 6.5, C*H*$_3$CH), 2.75 (1H, dd, *J*= 5.7, 17.0, C*H*^{A}H^B), 2.97 (1H, dd, *J*= 6.7, 17.0, CH^A*H*^{B}), 3.73 (3H, s, OCH_3), 3.76-3.87 (1H, broad m, CHN), 8.35 (3H, broad s, NH_3). δ_C ($CDCl_3$, 100 MHz) 18.52 (CH_3), 37.99 (CH_2), 45.08 (CH) , 52.34 (CH_3), 171.10 (C). m/z (CI): 118 (M^+, 100%). HRMS: 118.0867 $C_5H_{12}O_2N$ requires (M^+), 118.0868. ^{1}H and ^{13}C NMR consistent but different with the literature NMR spectra, which used D_2O as the solvent.[132]

(3*RS*) Methyl 3-amino-3-phenylpropionate, hydrochloride salt 307



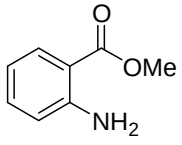
Using: thionyl chloride (3.22 ml, 44.4 mmol, 2 equiv.), (3*RS*) 3-amino-3-phenylpropionoic acid **304** (3.663 g, 22.2 mmol, 1 equiv.), in MeOH (40.0 mL) and following the general esterification procedure gave (3*RS*) Methyl 3-amino-3-phenylpropionate hydrochloride salt **307** as a solid (4.660 g, 98%). Mp 145-147 ^{o}C. IR (thin film): 1734 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 3.02 (1H, dd, *J*= 7.2, 16.8, C*H*^{A}H^B), 3.29 (1H, dd, *J*= 6.8, 16.8, CH^A*H*^{B}), 3.60 (3H, s, OCH_3), 4.65-4.78 (1H, broad m, CHN), 7.30-7.39 (3H, m, H arom.), 7.49-7.56 (2H, m, H arom.), 8.75 (3H, broad s, NH_3). δ_C ($CDCl_3$, 100 MHz) 38.37 (CH_2), 52.23 (CH) , 52.28 (CH_3), 127.55 (CH), 129.14 (CH), 129.34 (CH), 135.24 (C), 170.06 (C). m/z (CI): 180 (M^+, 100%), 163 (33), 106 (20). HRMS: 180.1024 $C_{10}H_{14}O_2N$ requires (M^+), 180.1025. Consistent with but different from data for the free base.[133]

(3*RS*) Methyl 3-amino-4-phenylbutanoate, hydrochloride salt 308



Using: thionyl chloride (0.41 mL, 5.6 mmol, 2 equiv.), (3*RS*) 3-amino-4-phenylbutyric acid **305** (500 mg, 2.8 mmol, 1 equiv.), in MeOH (5.0 mL) and following the general esterification procedure gave (3*RS*) methyl 3-amino-4-phenylbutyrate hydrochloride salt **308** as a solid (640 mg, quantitative). Mp 133-135 ^{o}C. IR (thin film): 1716 (C=O) cm^{-1}. δ_H (DMSO, 400 MHz): 2.56 (1H, dd, *J*= 5.8, 16.7, C*H*^{A}H^{B}), 2.71 (1H, dd, *J*= 6.9, 16.7, CH^{A}*H*^{B}), 2.82 (1H, dd, *J*= 8.6, 13.6, C*H*^{C}H^{D}), 3.10 (1H, dd, *J*= 5.5, 13.6, CH^{C}*H*^{D}), 3.53 (3H, s, OCH_3), 3.62-3.72 (1H, m, CHN), 7.23-7.28 (3H, m, H arom.), 7.30-7.37 (2H, m, H arom.), 8.40 (3H, s, NH_3). δ_C ($CDCl_3$, 100 MHz): 35.79 (CH_2), 37.94 (CH_2), 48.80 (CH), 51.71 (CH_3), 126.96 (CH), 128.59 (CH), 129.40 (CH), 135.92 (C), 170.10 (C=O). m/z (CI): 194 (M^+, 100%), 102 (20). HRMS: 194.1184 $C_{11}H_{16}N_1O_2$ requires (M^+), 194.1181.[134]

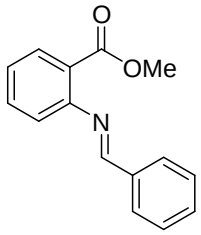
Methyl 2-aminobenzoate 310



Using: thionyl chloride (2.12 mL, 29.2 mmol, 2 equiv.), 2-aminobenzoic acid **309** (2.001 g, 14.6 mmol, 1 equiv.), in MeOH (25 mL) and following the general esterification procedure, but using a reaction time of 39 h instead of 3 h, gave the hydrochloride salt as a solid. The salt is taken up in water which is basified with 1M NaOH, and extracted with DCM. The organic layer is dried over Na_2SO_4 filtered and concentrated *in vacuo* to give methyl 2-aminobenzoate **310** as an oil (1.733 g, 78%). IR (thin film): 1694 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz): 3.86 (1H, s, OCH_3), 5.71 (2H, broad s, NH_2), 6.61-6.67 (2H, m, H arom.), 7.26 (1H, dt, *J*= 1.6, 7.7, H4), 7.85 (1H, dd, *J*= 1.6, 8.0, H6). δ_C ($CDCl_3$, 100 MHz): 51.50 (CH_3), 110.70 (C), 116.26 (CH), 116.65 (CH), 131.17 (CH), 134.06 (CH),

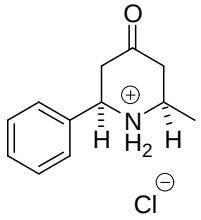
150.33 (C), 168.54 (C). m/z (EI): 151 (M^+, 80%), 119 (100). HRMS: 151.0636 $C_8H_9N_1O_2$ requires (M^+), 151.0633.

Methyl 2-(benzylidenamino)benzoate 311



Following imine formation procedure C with a 48 h reaction time, triethylamine (0.60 mL, 4.3 mmol, 2 equiv.), benzaldehyde (0.26 mL, 2.6 mmol, 1.2 equiv.), and methyl 2-aminobenzoate hydrochloride salt **310** (399 mg, 2.1 mmol, 1 equiv.), in toluene (9.0 mL), gave methyl 2-(benzylideneamino)benzoate **311** as an oil (141 mg, 28 %). Bp 180 ^oC at 0.6 mm Hg. IR (thin film): 1689, 1578 cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 3.84 (3H, s, OCH_3), 6.95 (1H, dd, *J*= 0.9, 7.9, H3), 7.23 (1H, dt, *J*= 1.0, 7.6, H5), 7.45-7.53 (4H, m, H arom.). 7.88-7.93 (3H, m, H arom.), 8.29 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz) 52.04 (CH_3), 120.21 (CH), 123.12 (C), 124.68 (CH), 128.77 (CH), 128.90 (CH), 130.72 (CH), 131.51 (CH), 132.93 (CH), 136.07 (C), 153.39 (C), 160.62 (CH), 167.14 (C). m/z (EI): 239 (M^+, 30%), 224 (100), 151 (30), 119 (35). HRMS: 239.0948. $C_{15}H_{13}O_2N$, requires (M^+) 239.0946.

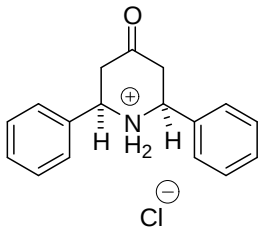
(2*RS*, 6*RS*) 2-Methyl-6-phenylpiperidin-4-one, hydrochloride salt 315a



Following methylenation procedure A, a 0.96 M solution of Cp_2TiMe_2 (0.71 mL, 0.68 mmol, 2.1 equiv.) in toluene-THF (1:1 by mass) and (3*RS*, *E*) methyl 3-(benzylidenamino)butanoate **300a** (65.4 mg, 0.32 mmol, 1 equiv.), gave crude enol ether **301a** (44.9 mg). Following cyclization procedure A, 7M $HCl_{(aq)}$ (3 ml), and a portion of

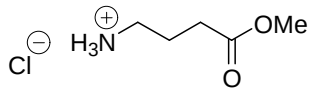
the crude enol ether **301a** (21.2 mg), gave (2*RS*, 6*RS*) 2-methyl-6-phenylpiperidin-4-one, hydrochloride salt **315a** as a brown solid (21.2 mg, 62%). Mp 191-192 ^{o}C IR (thin film): 1721 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.46 (3H, d, *J*= 6.4, CH_3), 2.53-2.58 (1H, m, H3^{eq}), 2.58-2.62 (1H, m, H5^{eq}), 2.98 (1H, dd, *J*= 12.8, 15.6, H3^{ax}), 3.21 (1H, dd, *J*= 13.6, 15.4, H5^{ax}), 3.72-3.85 (1H, broad m, H2), 4.73-4.82 (1H, broad m, H6), 7.42-7.52 (3H, m, H arom.), 7.75 (2H, d, *J*= 7.6, H arom.), 9.59-9.68 (1H, broad m, N*H*^{A}H^{B}), 10.41-10.56 (1H, broad m, NH^{A}*H*^{B}). δ_C ($CDCl_3$, 100 MHz) 18.21 (CH_3), 44.28 (CH_2), 44.42 (CH_2), 51.93 (CH), 57.98 (CH), 127.92 (CH), 128.86 (CH), 129.20 (CH) 135.95 (C), 202.60 (C). m/z (CI): 190 (M^{+}, 100%). HRMS: 190.1231 $C_{12}H_{16}ON$ requires (M^{+}), 190.1232.

(2*RS*, 6*SR*) 2,6-Diphenylpiperidin-4-one hydrochloride salt 315b



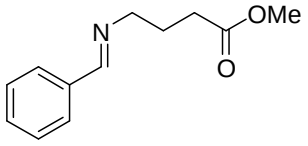
Following methylenation procedure A, a 0.96 M solution of Cp_2TiMe_2 (0.79 mL, 0.76 mmol, 1.8 equiv.) in toluene-THF (1:1 by mass) with (3*RS*, *E*) methyl 3-(benzylidenamino)-3-phenylpropionate **300b** (112.4 mg, 0.42 mmol, 1 equiv.) gave crude enol ether **301b** (110.4 mg). Following cyclization procedure A, 7M $HCl_{(aq)}$ (10 ml), and the crude enol ether **301b** (110.4 mg) gave (2*RS*, 6*SR*) 2,6-diphenylpiperidin-4-one hydrochloride salt **315b** as a beige solid (75.4 mg, 62%). Mp 215-216 ^{o}C. IR (thin film): 1725 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 2.63-2.73 (2H, broad m, H3^{eq} & 5^{eq}), 3.45-3.58 (2H, broad m, H3^{ax} & 5^{ax}), 4.92-5.01 (2H, broad m, H2 & H6), 7.38-7.48 (6H, m, H arom.), 7.80 (4H, d, *J*= 6.8, H arom.), 9.95-10.06 (1H, broad m, N*H*^{A}H^{B}), 10.71-10.84 (1H, broad m, NH^{A}*H*^{B}). δ_C ($CDCl_3$, 100 MHz) 44.33 (CH_2), 59.12 (CH), 128.35 (CH), 128.65 (CH), 129.23 (CH) 135.54 (C), 202.20 (C). m/z (CI): 252 (M^{+}, 100%). HRMS: 252.1389 $C_{17}H_{18}ON$ requires (M^{+}), 252.1388.

Methyl 4-aminobutanoate, hydrochloride salt 326



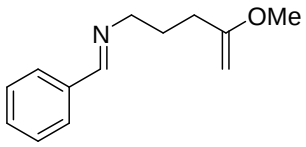
Using: thionyl chloride (3.45 mL, 47.5 mmol, 2 equiv.), 4-aminobutyric acid **325** (2.451 g, 23.8 mmol, 1 equiv.), in MeOH (45 mL) and following the general esterification procedure gave methyl 4-aminobutanoate hydrochloride salt **326** as a solid (3.567 g, 98%). IR (thin film): 1726 (C=O) cm^{-1}. δ_H (DMSO, 400 MHz): 2.13 (2H, quin., *J*= 7.3, $CH_2CH_2CH_2$), 2.53 (2H, t, *J*= 7.2, CH_2C), 3.07-3.19 (2H, m, CH_2N), 3.68 (3H, s, OCH_3), 8.19 (3H, s, NH_3). δ_C ($CDCl_3$, 100 MHz): 22.60 (CH_2), 30.94 (CH_2), 39.37 (CH_2), 51.95 (CH_3), 173.32 (C). m/z (CI): 118 (M^+, 100%). HRMS: 118.0867 $C_5H_{12}N_1O_2$ requires (M^+), 118.0868.

(*E*) Methyl 4-(benzylidenamino)butanoate 327



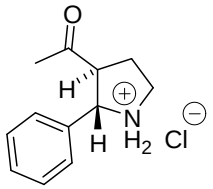
Following Imine formation procedure A, triethylamine (0.46 ml, 3.3 mmol, 2 equiv.), benzaldehyde (0.21 ml, 2.0 mmol, 1.2 equiv.), methyl 4-aminobutanoate hydrochloride salt **326** (0.254 g, 1.7 mmol, 1 equiv.), and Na_2SO_4 (0.288 g, 2.0 mmol, 1.2 equiv.), in DCM (5.0 ml) gave (*E*) methyl 4-(benzylidenamino)butanoate **327** as an oil (0.2721 g, 80%). Bp 150 ^oC at 0.6 mm Hg. IR (thin film): 1736 (C=O), 1645 (C=N) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 2.06 (2H, quin., *J*= 7.0, $CH_2CH_2CH_2$), 2.42 (2H, t, *J*= 7.2, CH_2C), 3.62 (2H, t, *J*= 6.8, CH_2N), 3.66 (3H, s, OCH_3), 7.37-7.42 (3H, m, H arom.), 7.70-7.74 (2H, m, H arom.), 8.28 (1H, s, N=CH). δ_C ($CDCl_3$, 100 MHz) 26.05 (CH_2), 31.69 (CH_2), 51.49 (CH_3) , 60.39 (CH_2), 128.04 (CH), 128.55 (CH), 130.61 (CH), 136.09 (C), 161.50 (CH), 173.89 (C). m/z (EI): 205 (M^+, 30%), 174 (85), 132 (100). HRMS: 205.1101. $C_{16}H_{16}O_2N_2$, requires (M^+) 205.1103.

(*E*) 2-Methoxy-5-(benzylidenamino)pent-1-ene 328



Following methylenation procedure B, a 0.96 M solution of Cp_2TiMe_2 (0.88 mL, 0.84 mmol, 1.8 equiv.), in toluene-THF (1:1 by mass) with (*E*) methyl 4-(benzylidenamino)butanoate **327** (96.1 mg, 0.47 mmol, 1 equiv.), and a 10 min reaction time at 65 ^oC gave crude enol ether (*E*) 2-methoxy-5-(benzylidenamino)pent-1-ene **328** (84.1 mg). δ_H ($CDCl_3$, 400 MHz) 1.91 (2H, quin., *J*= 7.2, $CH_2CH_2CH_2$), 2.18 (2H, t, *J*= 7.4, CH_2C), 3.53 (3H, s, OCH_3), 3.62 (2H, dt, *J*= 1.2, 7.2, CH_2N), 3.89 (2H, s, $C=CH_2$), 7.38-7.43 (3H, m, H arom.), 7.70-7.74 (2H, m, H arom.), 8.28 (1H, t, J= 1.2, N=CH). δ_C ($CDCl_3$, 100 MHz) 28.34 (CH_2), 32.55 (CH_2), 54.74 (CH_3) , 60.90 (CH_2), 80.60 (CH_2), 128.06 (CH), 128.60 (CH), 130.53 (CH), 136.30 (C), 161.24 (CH), 163.69 (C).

(2*SR*, 3*SR*) 1-(2'-Phenylpyrrolidin-3'-yl)ethanone, hydrochloride salt 329



Following methylenation procedure A, Cp_2TiMe_2 (0.88 mL, 0.84 mmol, 1.8 equiv.), and (*E*) methyl 4-(benzylidenamino)-butanoate **327** (96.1 mg, 0.47 mmol, 1 equiv.), gave crude enol ether **328** (84.1 mg). Using non-oven-dried glassware, conc. $HCl_{(aq)}$ (3 ml) was added to the crude enol ether and the resulting mixture was stirred for 0.5 h. The solution was washed with DCM (5X), and the aqueous layer was concentrated *in vacuo* to give (2*SR*, 3*SR*) 1-(2-phenylpyrrolidin-3-yl)ethanone hydrochloride salt **329** as a solid (25.7 mg, 62%). For characterization purposes the salt was dissolved in water, basified with $NaOH_{(aq)}$, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo* to give the free base. IR (thin film): 1708 (C=O) cm^{-1}. δ_H ($CDCl_3$, 400 MHz) 1.92-2.05 (1H, m, $CHCH^AH^B$), 2.02 (3H, s, CH_3), 2.06-2.19 (1H, m, $CHCH^AH^B$), 2.97-3.08 (2H, m, CH_2N), 3.16 (1H, ddd, *J*= 4.9, 7.5, 10.0, CHCO), 4.25 (1H, d, *J*= 7.2, CHN), 7.13-7.31 (5H, m, H arom.). δ_C ($CDCl_3$, 100 MHz) 30.00 (CH_3), 30.23 (CH_2), 46.77 (CH_2), 60.07

(CH), 65.09 (CH), 126.68 (CH), 127.35 (CH), 128.59 (CH) 143.14 (C), 209.36 (C). m/z (CI+): 190 [$(M+H)^+$, 100%]. HRMS: 190.1231. $C_{12}H_{16}ON$ requires $(M+H)^+$, 190.1232.

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