STRATEGIES FOR THE SYNTHESIS OF BENZYLTETRAHYDROISOQUINOLINE ALKALOIDS

Submitted in fulfillment of the academic requirements for the degree of

Doctor of Philosophy

in the

Faculty of Science and Agriculture
School of Chemistry

at the

University of KwaZulu-Natal
(Pietermaritzburg)

By

MOLAHLEHI SAMUEL SONOPO

Supervisor: Prof. F. R. van Heerden

March 2011

ABSTRACT

The objectives of this project were to investigate the application of new methodologies for the preparation of benzyltetrahydroisoquinoline monomers and secondly, to synthesise the bisbenzyltetrahydroisoquinoline neferine and its analogues. Neferine was isolated from the roots of *Nelumbo nucifera*. This compound has been reported to exhibit important biological activities, which include anti-arrhymia, anti-platelet aggregation, anti-thrombosis, anti-cancer as well as anti-HIV activities. Moreover, neferine showed lower cytotoxicity compared to other isoquinolines. However, the total synthesis of this compound has not been reported.

Two methodololologies based on the intramolecular hydroamination of aminostilbenes and aminoalkynes were investigated for the preparation of benzyltetrahydroisoquinolines with different oxygenation patterns. In these strategies, the aminostilbene and aminoalkyne precursors were successfully synthesised by the Heck and Sonogashira coupling reactions, respectively. The attempts to cyclise the aminostilbenes into the corresponding tetrahydroisoquinolines under base-catalysed, metal-catalysed and acid-catalysed conditions were unsuccessful. On the other hand, cyclisation of aminoalkynes into dihydroisoquinolines was achieved with the aid of titanium catalysts. Different titanium catalysts were tested for this hydroaminationation reaction. Optimum results were obtained with *bis*-(cyclopentadienyl)dimethyl titanium(IV) catalyst, albeit the yields were inconsistent when the reaction was performed on a larger scale.

Induction of the desired stereochemistry on the dihydroisoquinolines prepared by the hydroamination of aminoalkynes was attempted with the chiral BINOL phosphoric acid catalyst without success. The catalyst was prepared in good yields and high enantiomeric excess from cheap and readily-available starting materials. Had this reaction been successful, this would have been a breakthrough in the stereoselective reduction of dihydroisoquinolines as most chiral catalysts, which are currently employed are expensive, difficult to prepare and some are air and moisture-sensitive.

Although the first objectives of this project are not fully met, the results obtained in the synthesis of benzyltetrahydroisoquinolines by the hydroamination of aminostilbenes and aminoalkynes contribute greatly to the prevailing literature on the synthesis of benzyltetrahydroisoquinolines by these reactions. Presently, there is limited literature on the synthesis of benzyltetrahydroisoquinolines by these methods. Moreover, there is a need for the development of new synthetic strategies that would render benzyltetrahydroisoquinolines in minimum steps and good yields.

It was planned that, upon successful synthesis of benzyltetrahydroisoquinolines from aminostilbene and aminoalkyne precursors, these modern methodologies would be applied in the synthesis of the two benzyltetrahydroisoquinoline scaffolds of neferine. However, these routes could not be pursued due to failure to ring-close the aminostilbenes and irreproducibility of results in the preparation of dihydroisoquinolines from aminoalkynes. Therefore, classical procedures were employed for the preparation of benzylisoquinoline nuclei of neferine.

Three different synthetic routes were followed for the synthesis of neferine and its analogues. The first two methods were based on the Ullmann coupling reaction for the formation of the diaryl ether bond. The first method entailed an early construction of the ether link and late construction of the two isoquinoline rings on the ether bridge. The second method involved synthesis of the two isoquinoline nuclei, and coupling of the two units by the Ullmann reaction in the late stages of the synthesis. In the last synthetic strategy, the diaryl ether bridge was constructed by the nucleophilic aromatic substitution reaction. In all the three methods, the two isoquinoline rings were formed by the Bischler-Napieralski cyclisation reaction.

In the first route, we succeeded in preparing the two major building blocks, which were *N*-(3,4-dimethoxyphenylethyl)-4-benzyloxy-3-iodophenylacetamide and [2-(4'-hydroxy-3'-methoxyphenyl)ethyl]carbamic acid *tert*-butyl ester. The Ullmann coupling of the two compounds afforded the diphenyl ether *N*-(3,4-dimethoxyphenylethyl)-4-benzyloxy-3-(4-(3-methoxyphenoxy)ethyl-*tert*-butylcarbamate)phenylacetamide, albeit in low yields. Although *N*-(3,4-

dimethoxyphenylethyl)-4-benzyloxy-3-(4-(3-methoxyphenoxy)ethyl-*tert*-butylcarbamate)phenylacetamide was obtained in low yields, the successful formation of the diaryl ether bond from electron-rich haloacetamide and hydroxyphenethylamine is a great advancement in the synthesis of bisbenzyltetrahydroisoquinolines. In the second approach, the two benzyltetrahydroisoquinoline precursors for the Ullmann coupling reaction were successfully synthesised. These were the 7-hydroxybenzyltetrahydroisoquinoline and the 3'-iodobenzyltetrahydroisoquinoline. The Ullmann coupling reaction of the two isoquinolines did not give any fruitful results. In the last synthetic strategy, the formation of the diaryl ether bridge was based on the nucleophilic aromatic substitution reaction. In this route, we managed to synthesise the two coupling partners for the nucleophilic aromatic substitution reaction leading to *O*-methylneferine. One of the building blocks was the natural benzyltetrahydroisoquinoline, hydroxylaudanidine, and its coupling partner was *N*-[2-(4-fluoro-3-nitrophenyl)ethyl]-2-(4-methoxyphenyl)-*N*-methylacetamide. The major challenges in this route were encountered in the preparation the fluoroacetamide, which involved several low-yielding synthetic steps and tedious chromatographic purifications. The nucleophilic aromatic substitution reaction of the two precursors was attempted in vain.

Even though the total synthesis of neferine could not be accomplished, it is strongly believed that the developed synthetic routes will enable us to complete the synthesis of the targeted compound and other naturally-occurring bisbenzyltetrahydroisoquinolines. The results obtained herein represent a significant advance considering the importance of the bisbenzyltetrahydroisoquinolines as biologically active compounds.

DECLARATION

I hereby certify that this research is a result of my own investigation, which has not already been accepted in substance for any other degree and is not being in candidature for any other degree.

Signed:_____(Molahlehi S. Sonopo) Date:_____

I hereby certify that this statement is correct

Signed:_____ Professor F.R. van Heerden Date:_____
(Supervisor)

School of Chemistry
University of KwaZulu-Natal
Pietermaritzburg
January 2010

PLAGIARISM

I, *Molahlehi S. Sonopo* declare that:

1. The research reported in this thesis, except where otherwise indicated, is my original work.

2. This thesis does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other sources.

3. The thesis does not contain other persons', writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted:
    - Their words have been rewritten but the general information attributed to them has been referenced.
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Signed:_____(Molahlehi S. Sonopo) Date:_____

To my late grandmother **Selekane Emily Sonopo**

June 1928 – April 2010

AKNOWLEDGEMENTS

I would like to thank my advisor, Professor Fanie van Heerden for her constant advice, guidance, encouragement and sharing her knowledge of chemistry.

I am also grateful to Mamoalosi Selepe for her support and valuable insights towards this project.

I am also thankful to the following people:

- Professor Siegfried Drewes, Dr Anna Soares, Dr Irene Kamara and Professor Ross Robinson for their advice and valuable discussions.
- Mr. C. Grimmer for assistance with NMR experiments
- Mrs. C. Janse van Rensburg and Mr. L. Mayne for helping with mass spectroscopy.
- Mr. B. Mbhele and Mrs. I Ngubane for granting the permission to use the Infrared spectrometer.
- Mr. R. Somaru and Mr. Shaik for their technical assistance.
- My current lab mates and those who have completed for being good friends to me.

My greatest thanks go to my family for their prayers, support and patience.

I thank NRF and UKZN for financial support.

I thank the Almighty God for the gift of life, for protection and for guiding me in everything.

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ABBREVIATIONS

AcOH	acetic acid
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
BINOL	1,1'-binapthol
BOC	*tert*-butoxycarbonyl
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
BnBr	benzyl bromide
^{o}C	degree celsius
^{13}C NMR	Carbon Nuclear Magnetic Resonance
Cp	cyclopentadienyl
dba	dibenzylideneacetone
DCM	dichloromethane
DIA	diisopropyl amine
DIBAL-H	diisobutylaluminium hydride
DMAC	*N,N*-dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMG	dimethylglycine
DMSO	dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DPPF	1,1'-*bis*(diphenylphosphino)ferrocene
DtBPF	1,1'-*bis*(di-*tert*-butylphosphino)ferrocene
EDCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
Hz	hertz
^{1}H NMR	Proton Nuclear Magnetic Resonance
HRMS	High Resolution Mass Spectrometry
HOBt	hydroxybenzotriazole
IR	Infrared
LRMS	Low-Resolution Mass Spectrometry
m/z	mass/charge ratio

Me	methyl
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NEM	*N*-ethylmaleimide
NMP	*N*-methylpyrrolidine
NRF	National Research Foundation
OAc	acetate
PPA	polyphosphoric acid
i-PrBr	isopropyl bromide
rt	room temperature
TBDMSCl	tert-butyldimethylsilyl chloride
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin-Layer Chromatography
TMHD	2,2,6,6-tetramethylheptane-3,5-dione
TTN	Thallium(III) nitrate trihydrate
UV	Ultraviolet

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CHAPTER ONE

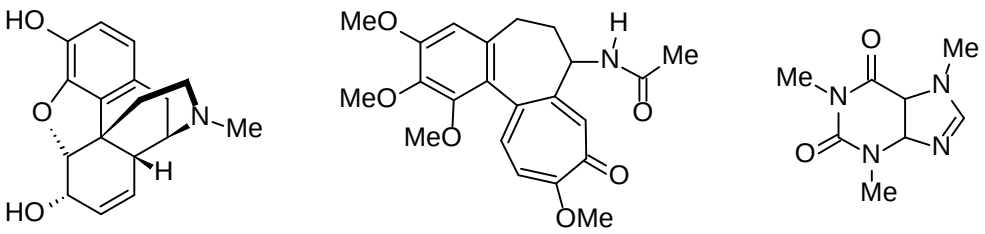
BACKGROUND AND PROJECT OVERVIEW

1.1 INTRODUCTION

One of the most diverse groups of organic compounds produced by plants is the alkaloids. The term alkaloid refers to substances that are “alkali like” in character. Generally, alkaloids are secondary metabolites that may be defined as cyclic compounds containing nitrogen in the negative oxidation state and they are of limited distribution in living organisms.[1] In the beginning, alkaloids were defined as basic nitrogen-containing compounds of either plant or animal origin, with the nitrogen atom being part of a heterocyclic system. Although the majority of the alkaloids are isolated from plants, there are other sources such as bacteria, fungi and marine animals.[2]

Many alkaloids are derived from amino acids. They include a number of bitter nitrogenous compounds, which serve to protect the plants against herbivores and pathogens. Based on their biosynthesis, alkaloids are divided into three main subgroups (Fig 1.1):[1]

- True alkaloids - they have a nitrogen-containing heterocyclic ring and are derived from amino acids, *e.g*. morphine (**1.1**).
- Proto-type alkaloids - this type does not have a nitrogen-containing heterocyclic ring and is derived from amino acids, *e.g*. colchicine (**1.2**).
- Pseudo alkaloids - they have a heterocyclic ring with nitrogen and are not derived from amino acids, *e.g*. theophylline (**1.3**).



1.1 **1.2** **1.3**

Figure 1.1. Structures of alkaloids based on biosynthetic classification.

Due to their important pharmacological effects, alkaloids are used as medications, narcotics, stimulants, and poisons. They constitute approximately 60% of drugs of plant origin that are supplied as pure compounds or crude extracts in the market. Many of these compounds are also used as scaffolds for synthetic drugs, *e.g*. atropine (**1.4**) for tropicamide (**1.5**), quinine (**1.6**) for chloroquinine (**1.7**) and cocaine (**1.8**) for procaine (**1.9**) (Fig. 1.2).[3]

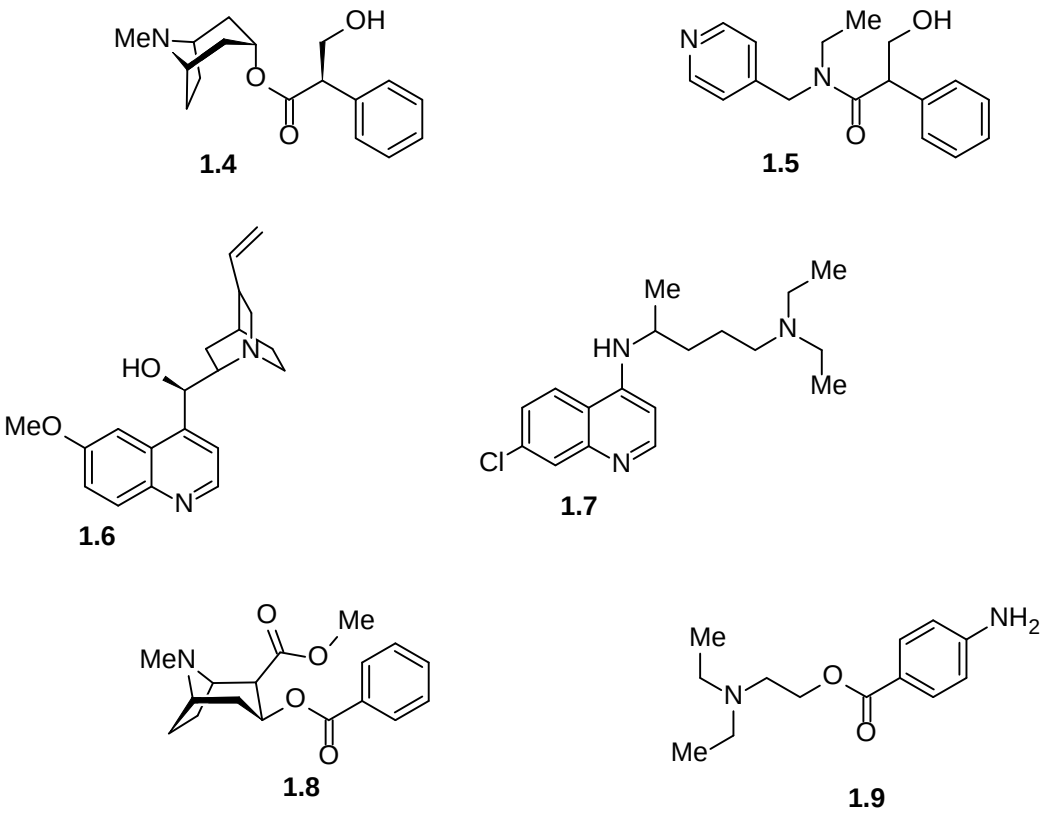
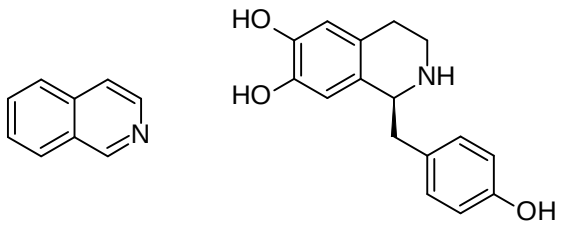


Figure 1.2. Plant alkaloids and the synthetic analogues used in the pharmaceutical industry.

The alkaloids bearing the isoquinoline scaffold (**1.10**) are important representatives of the alkaloid group. These alkaloids are present in nature in a wide range of plant families and exhibit interesting biological and pharmacological activities.[4-7] The known plant-derived isoquinolines, which are of pharmaceutical significance, include morphine and codeine, the narcotic analgesics; berberine and sanguinarine used as antimicrobials; *d*-tubocurarine, a muscle relaxant, and thalicarpine, a cytotoxin.

Isoquinolines are biosynthetically derived from 3,4-dihydroxytyramine (dopamine) and aldehydes of various origin *via* the formation of a Schiff base intermediate.[8-10] They are structurally diverse compounds, with most of them being 1-substituted derivatives, *e.g.* (*S*)-norcoclaurine (**1.11**). Sometimes isoquinolines occur as dimers (bis-isoquinolines) or oligomers.



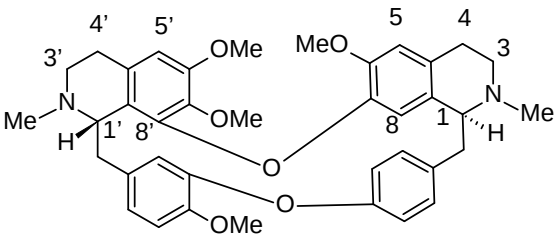
1.10 **1.11**

Figure 1.3. Structures of isoquinoline (**1.10**) and a 1-benzyltetrahydroisoquinoline (**1.11**).

Bisbenzyltetrahydroisoquinolines are another class of natural alkaloids that occur mainly in the plant families Menispermaceae, Berberidaceae, Ranunculaceae, Annonaceae, and Monimiacea.[11] Many plants that contain bisbenzyltetrahydroisoquinolines enjoy a folkloric reputation as medicines in various cultures. There are approximately 2500 bisbenzylisoquinoline alkaloids of many important structural types which are documented and known to show a variety of pharmacological activities, including antitumour, antimalarial, antifungal, antihypertensive and antihistaminic activity.[12-15]

The bisbenzyltetrahydroisoquinolines are identified as two benzyltetrahydroisoquinoline moieties joined together by one or more diaryl ether bridges, although carbon-carbon bridges or a methyleneoxy bridge may also be present.[16] Based on their biosynthesis, they are divided into three categories; the biscoclaurines, *e.g.* tetrandrine (**1.12**), the coclaurine-reticulines, *e.g.* thalibrunine (**1.13**), and the bisreticulines, *e.g.* malekulatine (**1.14**) (Fig. 1.4). The bisbenzyltetrahydroisoquinolines are further categorised based on the nature, the number and the attachment point of the bridges in the molecule. The significant differences in each alkaloid subgroup are the nature of oxygenated substituents, the degree of unsaturation in the heterocyclic ring, and the stereochemistry of the

two chiral centres at C-1 and C-1' as indicated in Fig 1.4.[16] These differences lead to the wide diversity in pharmacological activities observed within this group of molecules.[17]



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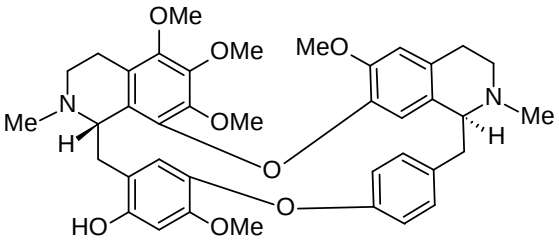

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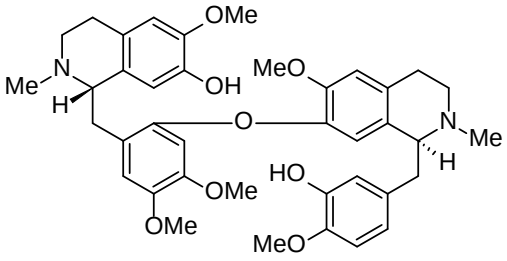

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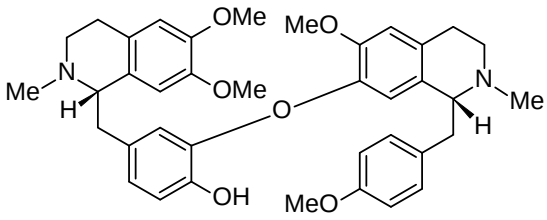
Figure 1.4. Examples of bisbenzyltetrahydroisoquinolines.

1.2 PROJECT BACKGROUND AND AIMS

The goal of this project was twofold, firstly to explore new methodologies for the preparation of benzyltetrahydroisoquinoline monomers and secondly, to synthesise the bisbenzyltetrahydroisoquinoline neferine (**1.15**) and its analogue *O*-methylneferine (**1.16**). Neferine (**1.15**) was isolated from the roots of *Nelumbo nucifera* (commonly known as lotus) along with two other analogues liensinine and isoliensinine.[18] This compound has been reported to possess extensive pharmacological effects in the cardiovascular system, *e.g.* anti-arrhymia, anti-platelet aggregation and anti-thrombosis formation. Moreover, **1.15** was reported to show potent anti-cancer and anti-HIV activities and also showed lower cytotoxicity compared to other isoquinolines.[19]



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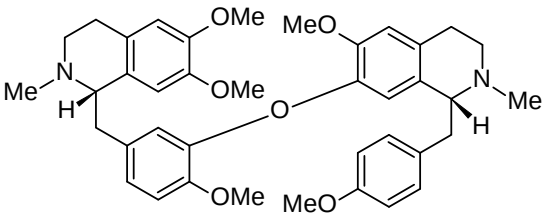

1.16

However, pharmacological and pharmaceutical studies on **1.15** are hampered by the limited supply available from its source and lack of sample purity. So far, the total synthesis of **1.15** has not been reported. Furthermore, there are only a few published papers on the synthesis of bisbenzyltetrahydroisoquinolines in general, especially those with a well-defined configuration at the chiral centres and substitution patterns present in natural products. The syntheses published on individual members of the series are lengthy and gave low yields in the diaryl ether formation, which makes the synthesis of bisbenzylisoquinolines unattractive. Inspired by these limitations, we decided to synthesise **1.15** and related analogues *via* a highly versatile method which could be employed to prepare compounds with similar structural properties and improved biological activities.

The objectives of this study were:

- To explore the application of modern synthetic methodologies in enantioselective synthesis of simple tetrahydrobenzylisoquinolines

- To develop an approach to the total synthesis of neferine (**1.15**) and its analogues.

1.3 STRUCTURE OF THIS THESIS

Following Chapter 1, this thesis consists of three other chapters. Chapter 2 examines the synthesis of benzyltetrahydroisoquinolines *via* hydroamination reactions of aminostilbenes and diarylacetylenes as intermediate precursors. This chapter also reviews different synthetic approaches to the formation of both the stilbenes and diarylacetylenes. Chapter 3 explores the scope of the traditional

synthetic methods that are used to construct benzyltetrahydroisoquinoline scaffolds and diaryl ethers. This chapter will also discuss a synthesis directed towards **1.15** and its analogues. In Chapter 4 the overall conclusions drawn from the results obtained in the study, are summarised.

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CHAPTER TWO

APPROACHES TOWARDS THE SYNTHESIS OF TETRAHYDROISOQUINOLINES BY HYDROAMINATION REACTIONS

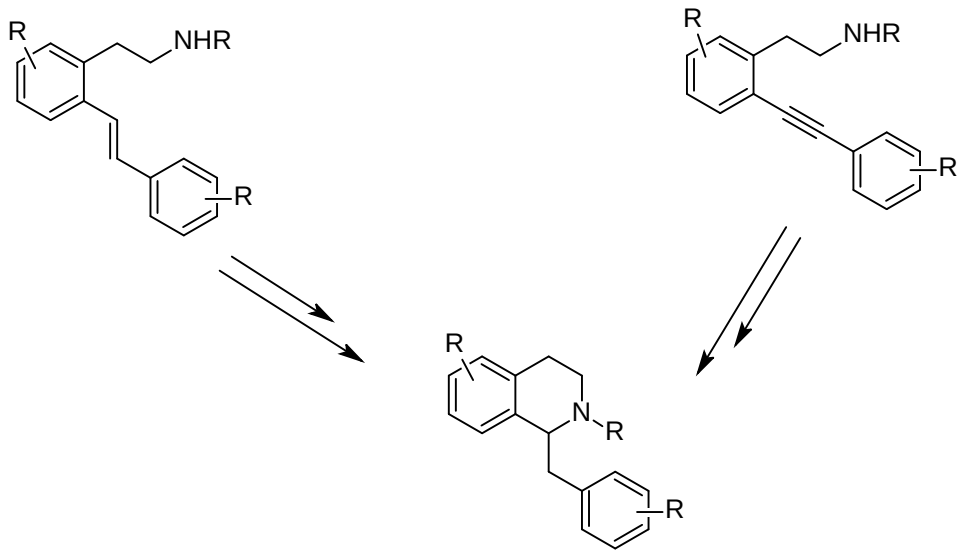
2.1 INTRODUCTION

Although the achiral syntheses of tetrahydroisoquinolines have been known for decades, their chiral syntheses have received attention only from the late 1980's.[1, 2] The primary syntheses of isoquinolines and related compounds have been studied extensively by using a variety of methods such as the Bischler-Napieralski,[1, 2] Pictet-Spengler[3, 4] and Pomeranz-Fritsch reactions (these methods will be discussed in greater detail in Chapter 3).[5] In some instances, drastic reaction conditions, tedious reaction procedures and inaccessibility of the starting materials emerged as problems in the syntheses of the benzyltetrahydroisoquinoline framework by these routes. The key step in these traditional methods involves electrophilic aromatic substitution and is often only effective with electron-rich aromatic systems.[2] Therefore, selection of appropriate synthetic precursors is of utmost importance.

The syntheses of the isoquinoline scaffold *via* α-alkylation of chiral formamidines, organolithium additions to imines followed by condensation and metal-catalysed cyclisation reactions have also been reported.[6-8] However, approaches involving asymmetric amination of carbon-carbon double bonds have received little attention.[9, 10] In addition, the asymmetric direct amination reactions of simple carbon-carbon double bonds, which are not activated by electron-withdrawing substituents, have not been investigated thoroughly.[11] Also, a literature overview indicated that there is still a need to develop methodologies to synthesise isoquinoline-type of compounds in high yields and shorter routes.

In light of the above, this Chapter reports approaches to the synthesis of the benzyltetrahydroisoquinoline framework by metal-catalysed hydroamination of functionalised aminostilbenes and aminoalkynes as the intermediate precursors

(Scheme 2.1). The different methods to synthesise stilbenes and diarylalkynes as well as methods to construct the benzyltetrahydroisoquinoline scaffold by intramolecular hydroamination reactions are reviewed in the first part of this chapter. Our results on tetrahydroisoquinoline synthesis by hydroamination of aminostilbenes and aminoalkynes will be discussed in the last section of this chapter.



Scheme 2.1. Synthesis of benzyltetrahydroisoquinolines by intramolecular hydroamination of aminostilbenes and aminoalkynes.

2.2 APPROACHES TO THE SYNTHESIS OF STILBENES – A LITERATURE OVERVIEW

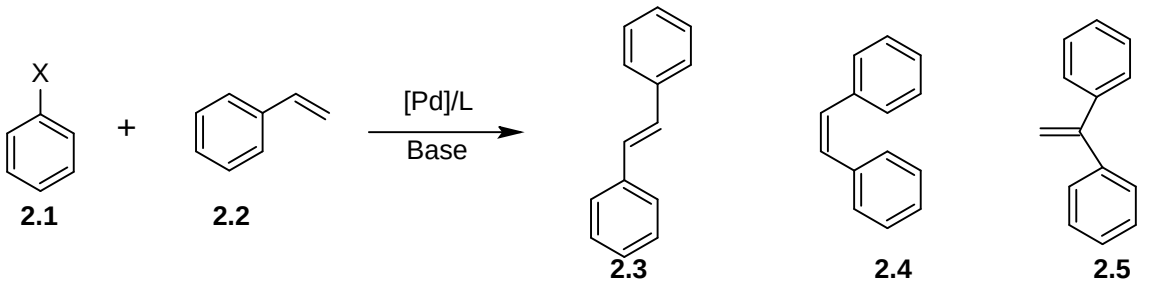
Stilbenoid-type compounds are widely distributed in nature and have become synthetic compounds of interest. Hydroxylated stilbenoids are renowned for their remarkable biological and therapeutic properties, which include antioxidant,[12, 13] radical scavenging,[13] cyclooxygenase inhibition,[14] lipid modification, platelet aggregation inhibition,[15] vasodilation, anticancer,[16] neuroprotection[17] and antiviral activity.[18]

Stilbenes are characterised by a carbon-carbon (C-C) double bond between two phenyl groups. The intra- or intermolecular formation of a C-C double bond has

always been a challenge to organic chemists, especially in the synthesis of complex natural products. Nevertheless, there are many procedures in the literature for the synthesis of alkenes that could be adopted to stilbene syntheses.[19] Methodologies such as Heck-Mizoroki,[20] Suzuki-Miyaura,[21] Wittig,[22, 23] Horner-Emmons[24] and olefin metathesis[25] are often used in the synthesis of stilbenoids. In the following subsections, only methods that involve palladium catalysis will be presented.

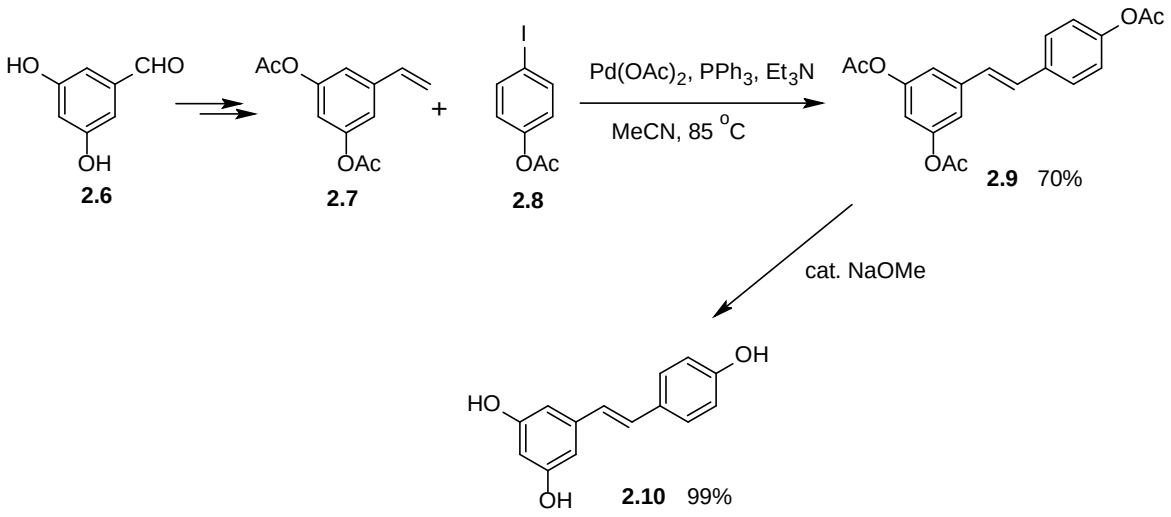
2.2.1 Palladium-Catalysed Synthesis of Stilbenes: The Heck Reaction

The palladium-catalysed C-C coupling of an aryl or vinyl halide with an activated olefin, in the presence of a base and a coordinating ligand (often a phosphine), is well known as the Heck reaction or Mizoroki-Heck reaction.[26, 27] For the development of this reaction, Heck was a co-recipient of the Nobel prize in Chemistry in 2010. The Heck coupling reaction is normally catalysed by Pd(0) or Pd(II) complexes in solution.[28, 29] Due to its chemoselectivity, this reaction is amenable to a large variety of starting materials and it serves as the major C-C coupling tool in contemporary organic chemistry. This methodology entails construction of the stilbene moiety by coupling the aryl halide **2.1** with the styrene precursor **2.2**. The three identifiable Heck products formed in this reaction, the *trans*- and *cis*-stilbenes (**2.3** and **2.4**, respectively) and the 1,1-diphenylethylene (**2.5**), can be seen in Scheme 2.2.



Scheme 2.2. The Heck reaction.

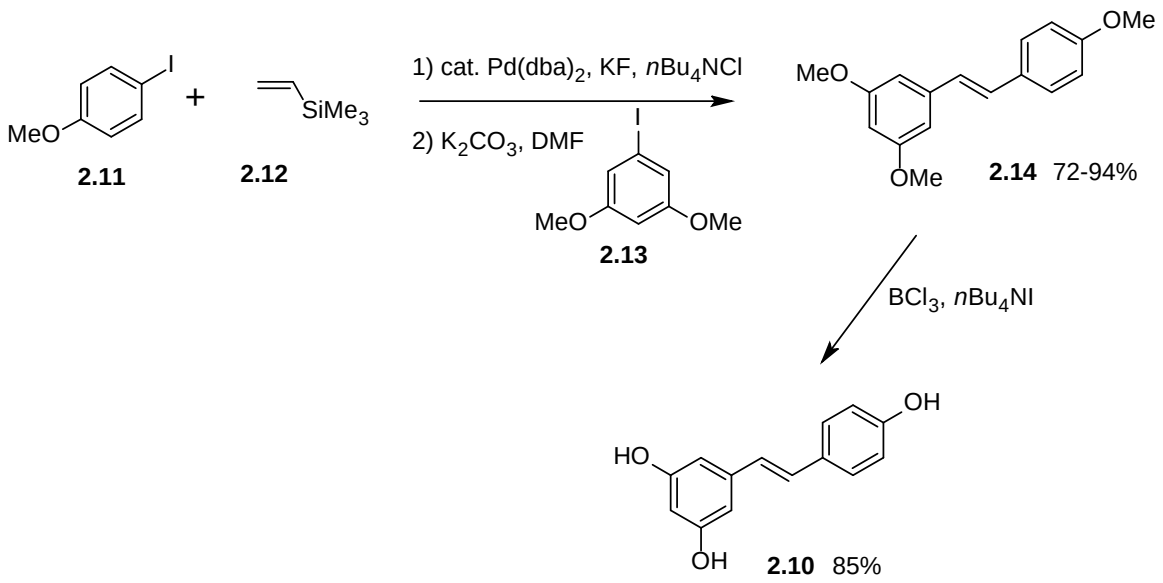
A palladium-catalysed Heck reaction of styrene **2.7** with the *para*-substituted aryl iodide **2.8** gave the corresponding 4',3,5,-triacetoxystilbene (**2.9**). Deacetylation of compound **2.9** with sodium methoxide yielded resveratrol (**2.10**) in a 99% yield. The styrene **2.7** was prepared from 3,5-dihydroxybenzaldehyde (**2.6**) (Scheme 2.3).[30]



Scheme 2.3. Palladium-catalysed Heck synthesis of resveratrol.

2.2.1.1 Heck reaction with ethene

The symmetrical *trans*-stilbene has also been prepared by coupling ethene with bromo- or iodobenzene.[31] However, not much has been published on the synthesis of stilbenes using ethene as a substrate. The major drawback associated with this procedure is the over-reaction of ethene with the aryl halide to yield the symmetrical stilbene instead of the monosubstituted alkene. Furthermore, at elevated temperatures and prolonged reaction times, ethene tends to polymerise easily. To circumvent this problem, a highly selective one-pot procedure for the synthesis of the *trans*-symmetric and non-symmetric stilbene derivatives has been reported by Jeffery and Ferber.[32] This reaction is based on two sequential Heck reactions using vinyltrimethylsilanes as the ethene equivalent (Scheme 2.4).



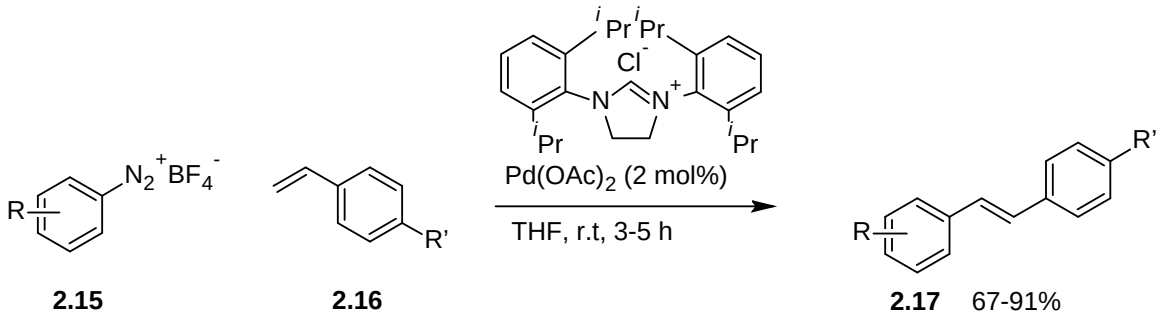
Scheme 2.4. Synthesis of resveratrol by the Heck reaction with ethene

The ethene synthesis strategy, entailing arylation of vinyltrimethylsilane (**2.12**) with 4-iodomethoxybenzene (**2.11**) as the electrophile, produced 4-methoxystyrene as the intermediate, which was successfully coupled with 1-iodo-3,5-dimethoxybenzene (**2.13**) to yield the methyl ether-protected resveratrol (**2.14**). Deprotection of the methyl ether was effected by BCl_3 to afford resveratrol in 85% yield. More recently, non-symmetrical stilbenes have been prepared using a one-pot two-step double Heck microwave procedure, whereby ethene acts as the alkene coupling partner.[33]

2.2.1.2 Aryldiazonium salts as electrophiles

Apart from the halides and the triflates, other electrophiles have found extensive use in Heck-type reactions. Among them are the aryldiazonium salts, which are even more reactive than the aryl halides.[34, 35] The advantage of this type of reaction is that it neither requires a base nor phosphine as is the case with other electrophiles. The Heck coupling reaction with a diazonium salt is fast and smooth, but requires a high loading of palladium catalyst; usually not less than 1-2 mol%.[31, 36] For instance, the stilbenes **2.17** were obtained in good yields from aryldiazonium

ions **2.15** and styrene **2.16** at room temperature with a 1:1 mixture of palladium acetate and an imidazolinium salt as catalyst (Scheme 2.5).[37]



2.15 **2.16** **2.17** 67-91%

R = H, 2-*O*Me, 4-*O*Me, 4-Br

R' = H, *O*Me

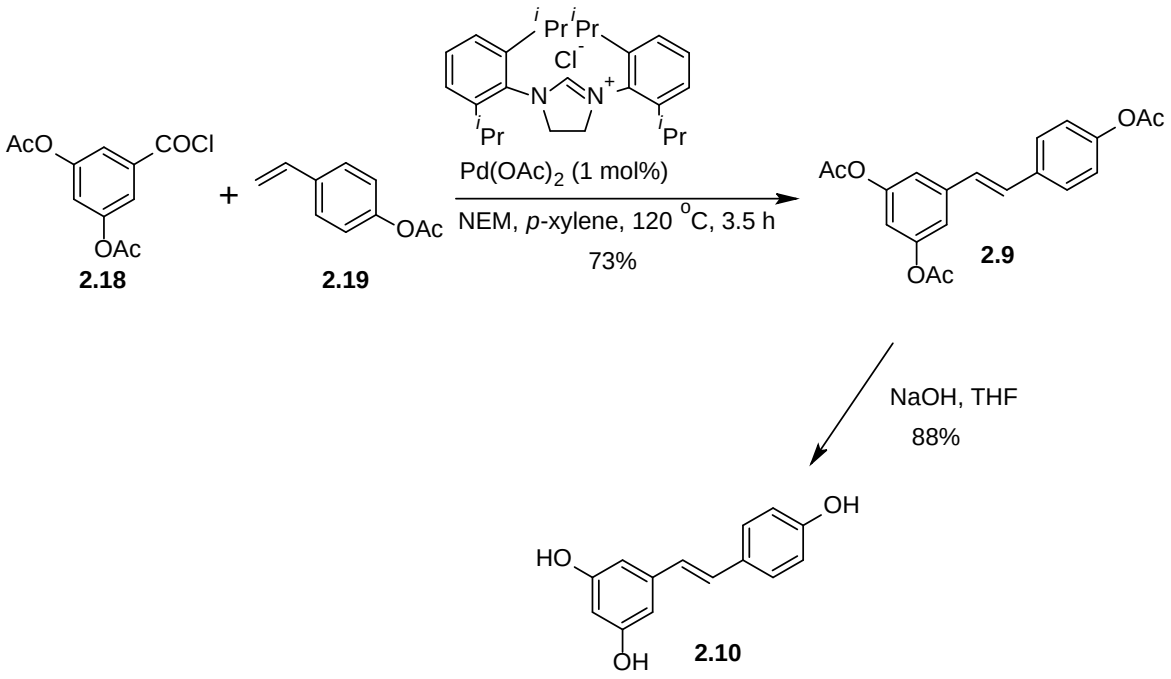
Scheme 2.5. The Heck reaction of diazonium salts with styrene.

It is anticipated that the acetate ion acts as a base to produce the active Pd(0) catalyst in this reaction. It is noteworthy that the diazonium salt used in this reaction could be generated from the *in situ* reaction of the corresponding aniline precursor, albeit the yield is reduced when compared to the use of the preformed diazonium salt.

2.2.1.3 Decarbonylative Heck reactions

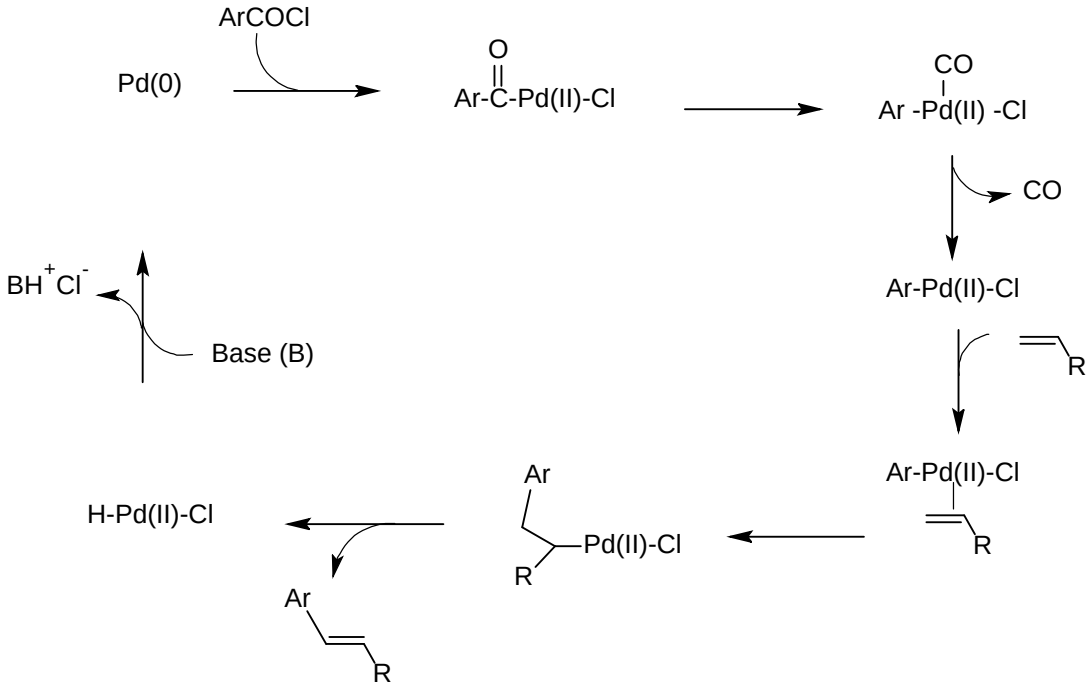
The decarbonylative Heck reaction has been known since the beginning of the 1980's. This reaction is characterised by the usage of commercially available, easy and inexpensive to prepare arylating reagents such as aroyl halides, aryl anhydrides, aryl esters and arene carboxylates. Blaser and Spencer[38] reported the palladium-catalysed arylation of alkenes with aroyl chlorides in the presence of tertiary amines in *p*-xylene to give *E*-arylation products at 130 ^{o}C. The nature of the added base is very important for the success of this reaction. For example, with aroyl chlorides bearing electron-donating substituents, *N*,*N*-dimethylbenzylamine was utilised, while *N*-ethylmorpholine was more effective only with aroyl chlorides possessing electron-withdrawing substituents. This method can also be utilised in the arylation of ethylene to produce both the styrene

and stilbene derivatives. In 2003 Andrus *et al*.[39, 40] synthesised the antioxidant resveratrol (**2.10**) *via* the decarbonylative Heck coupling reaction of **2.18** and **2.19** followed by deacetylation as shown in Scheme 2.6.



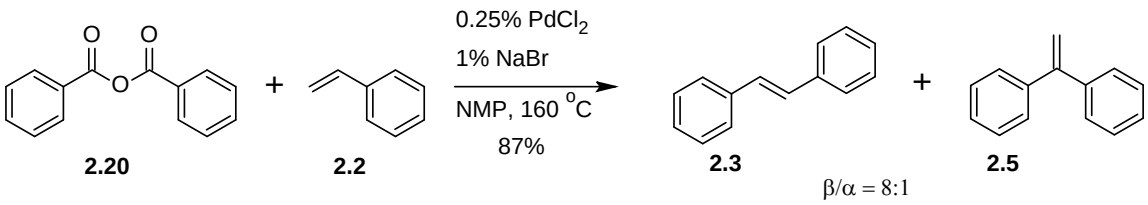
Scheme 2.6. Decarbonylative Heck reaction.

The initial step of the mechanism involves the reduction of palladium acetate to a Pd(0) species by either alkene or base. The subsequent steps are the oxidative addition to the aroyl chloride, the aryl group migration to palladium, followed by the release of carbon monoxide at high temperatures. The final steps involve alkene coordination with the resulting palladium intermediate, alkene insertion, β-hydride elimination and Pd(0) regeneration, as proposed by Heck (Scheme 2.7).[27]



Scheme 2.7. Mechanism of decarbonylative Heck reaction.

The base-free decarbonylative Heck reaction was developed by de Vries *et al.,*[41] utilising aromatic carboxylic anhydrides as arylating agents (Scheme 2.8). The aromatic carboxylic anhydride **2.20** was coupled with the styrene **2.2** at 140-190 ^{o}C in NMP in the presence of catalytic amounts of $PdCl_2$ and NaBr to afford stilbene **2.3** and diphenylethylene (**2.5**). Goossen *et al.*[41-44] developed a Heck reaction with aryl esters as the arylating agents. Palladium chloride was found to be the best precatalyst for this system and the addition of LiCl and isoquinoline improved the selectivity. In this reaction, the phosphine ligand was abandoned due to its strong coordination with the catalyst.

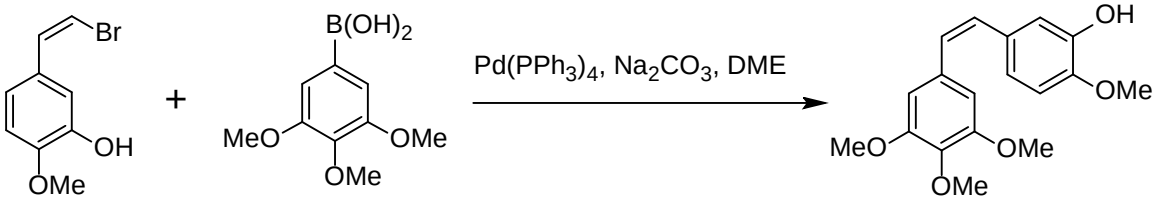


Scheme 2.8. The base-free decarbonylative Heck reaction.

2.2.2 Palladium-Catalysed Synthesis of Stilbenes: The Suzuki Coupling Reaction

The use of the Suzuki-Miyaura cross-coupling reaction of organic electrophiles such as aryldiazonium salts, halides or triflates with organoboranes as nucleophiles in the presence of a base has attracted substantial attention in the synthesis of stilbene derivatives. The groups led by Suzuki and McCague independently indicated the versatility of the Suzuki-Miyaura cross-coupling reaction of arylboronic acids with ethenyl halides to form substituted stilbenes.[21, 45] After this development, many stilbenes were synthesised with Pd(0) or Pd(II) as catalysts in the presence of a phosphine ligand.[46] For his contribution to palladium-catalysed reactions, Suzuki was also a co-recipient of the Nobel Prize in Chemistry in 2010.

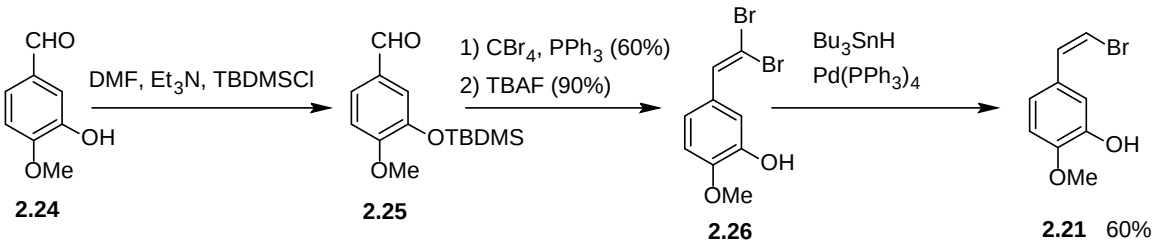
The Suzuki coupling reaction was also applied in the synthesis of combretastatin A-4 (**2.23**) with an overall *Z*-geometry.[46] The reaction involved coupling of the *Z*-vinyl halide **2.21** with the phenylboronic acid **2.22** under basic conditions using a catalytic system based on Pd(0) to afford **2.23** in good yield (Scheme 2.9).



2.21 **2.22** **2.23** 70%

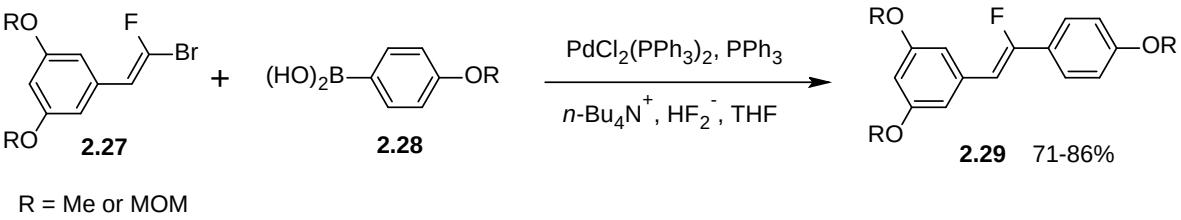
Scheme 2.9. Synthesis of combretastatin A-4 (**2.23**) by the Suzuki coupling reaction.

The *Z*-vinyl halide **2.21** was prepared from 3-hydroxy-4-methoxybenzaldehyde (**2.24**) *via* a sequence of reactions which involved a Corey-Fuchs Wittig-like procedure[47] to give the intermediate alkene **2.26.** Stereoselective reduction using Bu_3SnH and Pd(0) successfully afforded the required *Z*-vinyl halide **2.21** in a good yield as shown in Scheme 2.10.



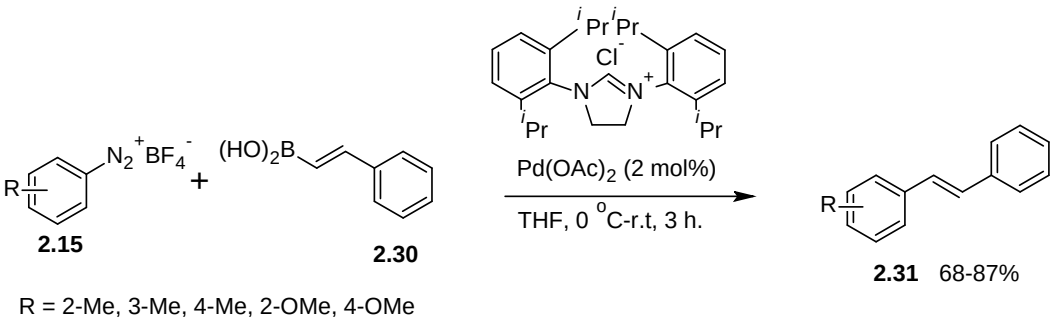
Scheme 2.10. Synthesis of *Z*-vinyl halide **2.21**.

The Suzuki-Miyaura reaction has further been extended to the synthesis of stilbenes bearing substituents such as fluorine, methyl, and phenyl on the double bond. This procedure is characterised by its stereoselectivity to yield *E*- or *Z*-stilbenes and its ability to produce stilbenes on a large scale. For example, Rolando *et al*.[48] demonstrated a general method, whereby 1-bromo-1-fluorostyrene **2.27** was coupled with phenylboronic acid **2.28**, to synthesise polyhydroxylated stilbenes **2.29**, which were monofluorinated at the central double-bond carbon atom (Scheme 2.11).



Scheme 2.11. Suzuki coupling of 1-bromo-1-fluorostyrene **2.27** with phenylboronic acid **2.28**.

The alternative approach to producing *E*-stilbenes as the major product in the Suzuki cross-coupling reaction is to use the aryldiazonium salts instead of the aryl halides.[49] This has been elegantly demonstrated in the cross coupling of the styrylboronic acid **2.30** and aryldiazonium salts **2.15** in the presence of $Pd(OAc)_2$ and an imidazolinium ligand, to give the expected stilbenes **2.31** (Scheme 2.12).[50] This reaction proceeds under mild reaction conditions to produce the desired stilbenes in moderate to high yields without any added base. Additionally, this procedure is of significance because it tolerates both electron-rich and electron-poor substituents; even though the palladium loading is very low (0.1 mol%).

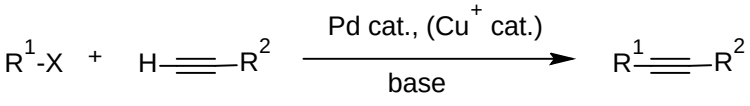


R = 2-Me, 3-Me, 4-Me, 2-OMe, 4-OMe

Scheme 2.12. Suzuki coupling reaction of the styryl boronic acid **2.30** with aryldiazonium salts **2.15**.

2.3 SYNTHETIC METHODS FOR DIARYLACETYLENES: THE SONOGASHIRA COUPLING – A LITERATURE OVERVIEW

Arylacetylenes are key building blocks in the synthesis of natural products, pharmaceuticals and organic molecular materials. In 1975, Sonogashira and Hagihara[51, 52] reported a palladium-catalysed substitution reaction used to prepare arylalkynes from aryl halides and terminal acetylenes (Scheme 2.13). Generally, the Sonogashira reaction is carried out in an organic solvent such as toluene, THF or DMF, using stoichiometric amounts of the base and a Pd(0)/Cu(I) catalytic system.



R^1 = aryl, hetaryl, vinyl

R^2 = aryl, hetaryl, alkenyl, alkyl, SiR_3

X = I, Br, Cl, OTf

Scheme 2.13. A Sonogashira coupling reaction.

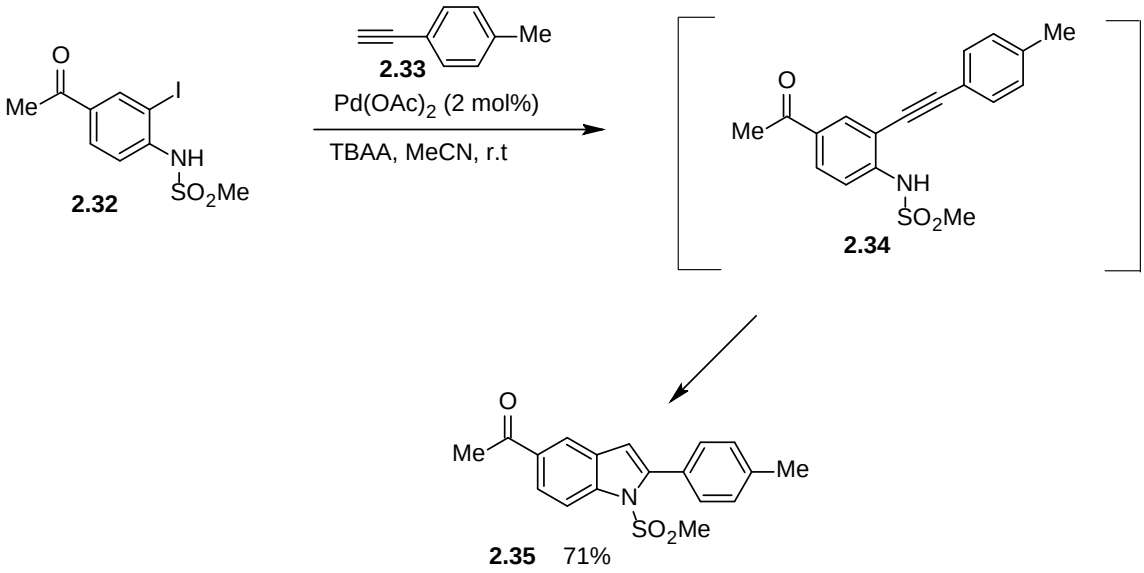
The Sonogashira coupling has been extensively modified during the last ten years. The modifications include the use of a phase-transfer agent,[53] reactions in aqueous media or without solvent, reactions in ionic liquids, palladium-free systems,[54, 55] copper-free versions,[56] and the use of promoters such as Zn, Mg, Sn

and R_4NI.[57] However, a major improvement was observed when the copper salt was eliminated. The presence of copper salts result in the *in situ* formation of some copper(I) acetylides, which can induce Glaser-type homocoupling of alkynes readily. Furthermore, copper salts are neither environmentally friendly nor easily recovered from the reactions. The palladium catalyst was unattractive due to its toxicity and high cost. The palladium-catalysed and copper-catalysed Sonogashira coupling reactions will be discussed in the following subsections.

2.3.1 Palladium-Catalysed Coupling Reactions of Aryl Halides with Terminal Acetylenes

In 1992, Genet *et al*.[58] demonstrated the first copper-free Sonogashira cross-coupling reaction of alkynes with aryl or vinyl iodides in the presence of a water-soluble Pd catalyst. Soon after these findings, Alami *et al*.[59] reported a slightly modified cross coupling of the terminal alkynes with aryl or vinyl iodides catalysed by 5% $Pd(PPh_3)_4$ in amine solvents such as pyrrolidine or piperidine. Bohm and Herrmann[60] also reported a copper-free system that resulted in an overall lower catalyst loading in their synthesis of arylalkynes and enynes. They used P(*t*-Bu)$_3$ as a co-catalyst instead of copper with their $Pd_2(dba)_3$ catalyst and reported high yields after a 20 h reaction of aryl bromides with phenylacetylene.

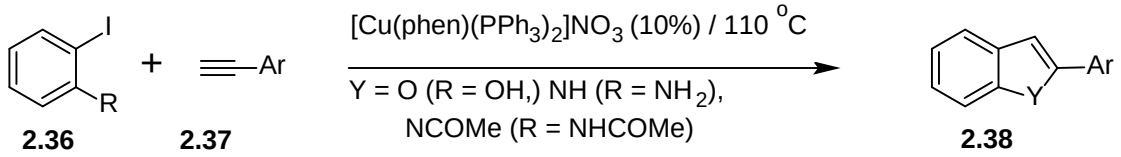
The Sonogashira coupling reaction has found major application in the synthesis of indoles. This has been well demonstrated by Palimkar *et al*.,[61] who used a ligand, copper, and amine-free one-pot cyclisation procedure to afford the corresponding indole. The reaction entailed coupling of an iodinated sulfonamide **2.32** with *p*-tolylacetylene (**2.33**) to give the indole **2.35** *via* the Sonogashira intermediate **2.34** (Scheme 2.14). The reaction took place in the presence of TBAA and $Pd(OAc)_2$ as a catalyst. The reaction time was shortened by the use of ultrasonic irradiation.



Scheme 2.14. Copper-free Sonogashira coupling reaction.

2.3.2 Copper-Catalysed Coupling of Aryl Halides with Terminal Acetylenes

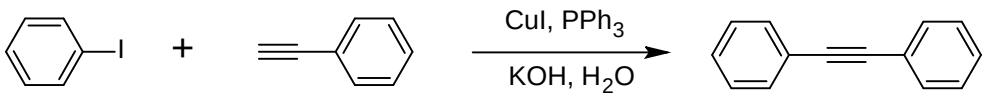
One of the major drawbacks associated with the palladium-catalysed Sonogashira reaction is the high cost of palladium. To circumvent this problem inherent to palladium catalysts, efforts have been directed to exploring new catalytic systems. This is illustrated by the development of different copper-based catalysts, which are employed as an alternative to palladium-based catalyst for the Sonogashira coupling reactions. Examples of copper-based catalysts which have successfully facilitated the coupling include CuI/PPh_3,[62] $Cu(phen)(PPh_3)Br$,[63, 64] copper nanoparticles,[65] supported copper complexes,[66, 67] CuBr/*rac*-BINOL, Cu(I)/diamine,[67] CuI/dabco,[68] $Cu(OAc)_2$/DAB-Ph,[69] $Cu[(phen)(PPh_3)_2]NO_3$,[70] Cu(I)/amino acid[71] and other copper catalysts.



Scheme 2.15. Palladium-free Sonogashira coupling reaction of indole **2.38**.

In 2005, Venkataraman *et al*.[72] reported the high efficiency of the well-defined copper-based catalytic system [Cu[(phen)(PPh_3)$_2$]NO_3] for the coupling of aryl iodides **2.36** with terminal acetylenes **2.37** to give indoles **2.38** (Scheme 2.15). It is worth noting that unlike palladium-based procedures, this reaction tolerates functional groups at the *ortho* position, making the *in situ* synthesis of benzofurans and indoles possible.

In another example, Guan *et al*.[73] demonstrated a cheap catalytic system based on CuI/PPh_3 in pure water in the presence of KOH as a base and in the absence of a ligand (Scheme 2.16). The reaction involves coupling of the aryl iodide **2.39** with terminal acetylene **2.40** to yield the corresponding diarylacetylene **2.41**. This easily handled and inexpensive system tolerates the coupling of both electron-rich and electron-poor aryl iodides with aryl and alkyl acetylenes.



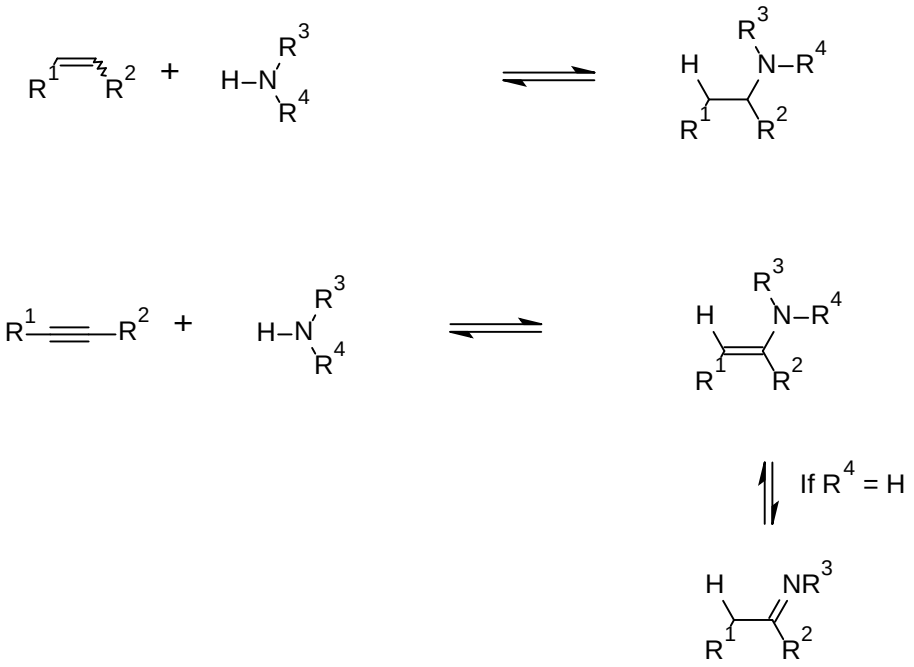
2.39 **2.40** **2.41** 87%

Scheme 2.16. Synthesis of diarylacetylene **2.41**.

2.4 INTRAMOLECULAR HYDROAMINATION OF AMINOALKENES AND AMINOALKYNES

Addition reactions play an important role in the arsenal of the synthetic organic chemist, as they are often accompanied by environmentally benign transformations. Most of addition reactions are 100% atom-economical, since both the starting materials are combined to form only one product with little or no by-products and can either be performed neat or in an innocuous solvent. Among such processes, the hydroamination of terminal, non-functionalised alkenes/alkynes have become the topic of interest only with the advent of transition metal catalysis. The hydroamination of alkenes and alkynes involves the addition of an N-H unit onto carbon-carbon multiple bonds to give the

corresponding primary, secondary and tertiary amines, as well as enamines and imines, in a single step (Scheme 2.17).[74, 75]

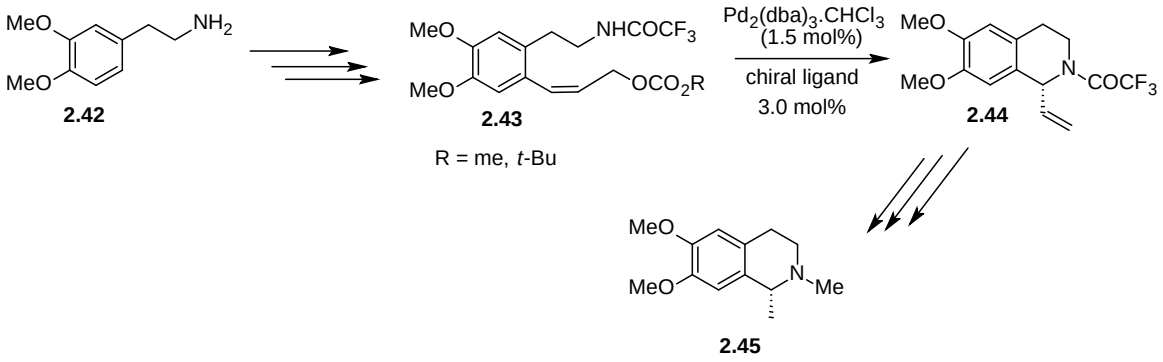


Scheme 2.17. Hydroamination of alkenes and alkynes.

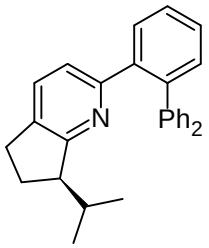
Hydroamination reactions can be catalysed by alkali metals ions (lithium,[76] potassium,[74] and sodium[74]), transition metals (iridium,[76] rhodium,[77] zirconium,[78-80] titanium[79-82] ruthenium,[83, 84] palladium,[85-87] gold,[79] and platinum[88, 89]) or lanthanide complexes (lanthanum and lutetium).[90, 91] These reactions have been used to generate small libraries of biologically interesting compounds.[92] Hydroamination reactions have been applied in the synthesis of natural products, such as isoquinoline and indole alkaloids.[92, 93]

The synthesis of the isoquinoline scaffold by hydroamination reactions was reported by Ito *et al*.[94] and Ojima *et al*.[95] The application of this method has been demonstrated by the preparation of alkyl (methyl and ethyl) as well as benzyltetrahydroisoquinoline alkaloids. For example, carnegine **2.45** was synthesised by the palladium-catalysed intramolecular asymmetric allylic amination of amines to alkenes in the presence of a chiral ligand (Scheme 2.18).[94] The key step involves cyclisation of the corresponding intermediate aminoalkenes

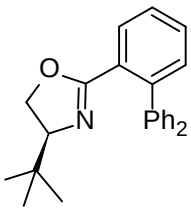
2.43 in the presence of a base, chiral ligands **2.46**, **2.47** or **2.48** and catalytic amounts of $Pd_2(dba)_3.CHCl_3$ as palladium source to yield the expected tetrahydroisoquinoline framework **2.44**. The ligands utilised in this synthesis showed low to high enantioselectivity, depending on the type of solvent and substrate used during the reaction. From **2.44**, six additional steps led to **2.45** in a 66% overall yield.



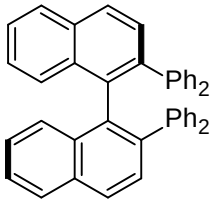
Scheme 2.18. Synthesis of carnegine by palladium-catalysed intramolecular hydroamination of aminoalkenes.



2.46

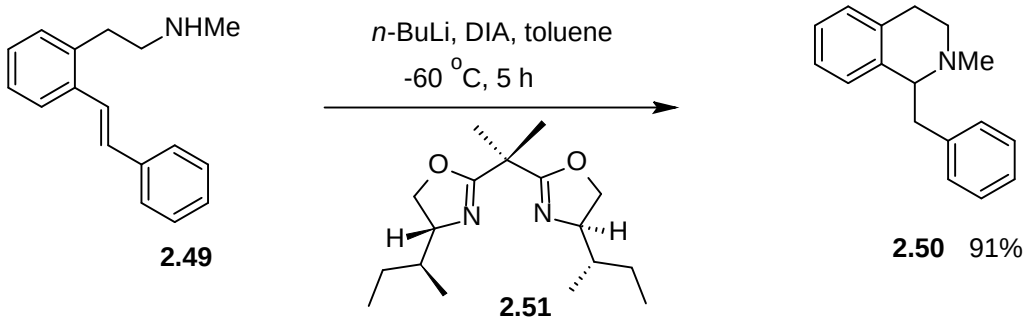


2.47



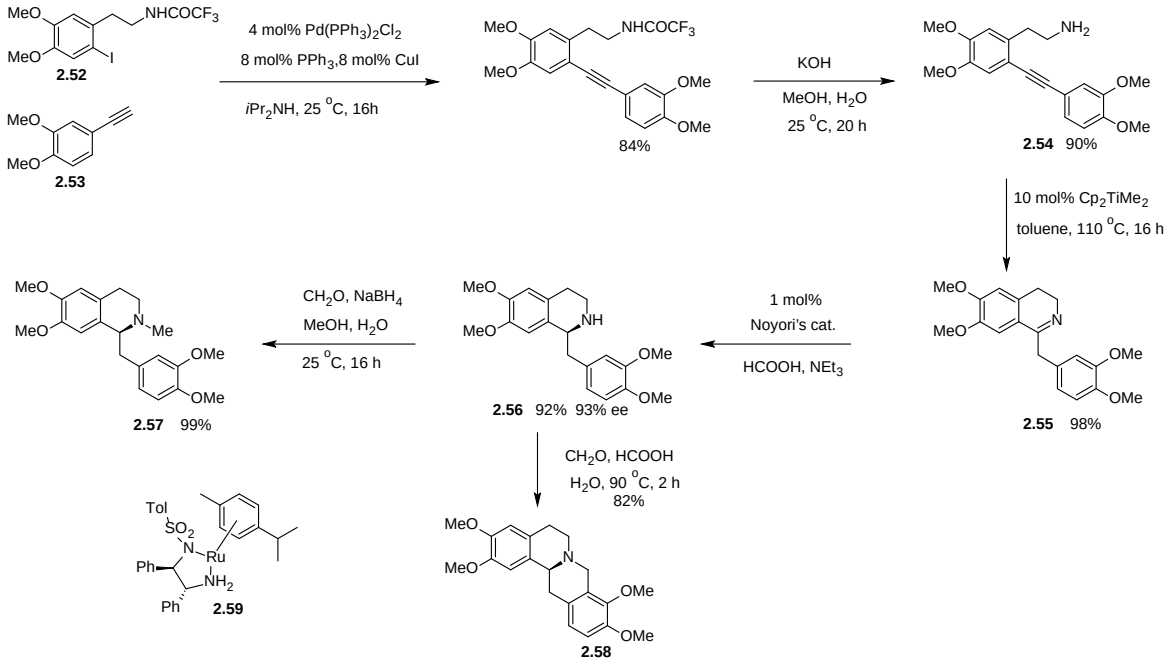
2.48

In another example, Tomioka *et al*.[96] utilised the chiral bisoxazoline ligand **2.51** in the lithium-catalysed asymmetric intramolecular hydroamination of aminostilbene **2.49** to form the benzylisoquinoline core **2.50** with enantioselectivities as high as 84% *ee* (Scheme 2.19). The reactions were performed in toluene at -60 ^{o}C to give the *endo*-cyclised product under thermodynamically controlled conditions.



Scheme 2.19. Base-catalysed hydroamination reaction.

Hydroamination reactions that are titanium catalysed have significant advantages over other process which are based on toxic (Hg, Tl) and more expensive metals (Ru, Rh, Pd, U, Th).[75, 92] Mujahidin and Doye[97] demonstrated the efficiency of a titanium-catalysed intramolecular hydroamination reaction of an amine and alkyne to form the benzyltetrahydroisoquinoline framework (Scheme 2.20). The targeted natural products were the alkaloids (*S*)-laudanosine (**2.57**) and (*S*)-xylopinine (**2.58**). The first key step in the synthesis of **2.57** and **2.58** was a Sonogashira coupling of an aryl iodide **2.52** with arylacetylene **2.53** to introduce the C1-C8a bond of the benzyltetrahydroisoquinoline scaffold. This was followed by the titanium-catalysed intramolecular hydroamination of the intermediate **2.54** to produce the imine **2.55** in a high yield. The imine **2.55** was reduced enantioselectively to the corresponding amine **2.56** according to Noyori's protocol, which utilised a ruthenium-based catalyst **2.59**. The targeted molecules **2.57** and **2.58** were obtained from the amine **2.56** by reductive methylation and the Pictet-Spengler reaction, respectively.



Scheme 2.20. Titanium-catalysed intramolecular hydroamination of aminoalkenes.

2.5 RESULTS AND DISCUSSIONS

2.5.1 Introduction

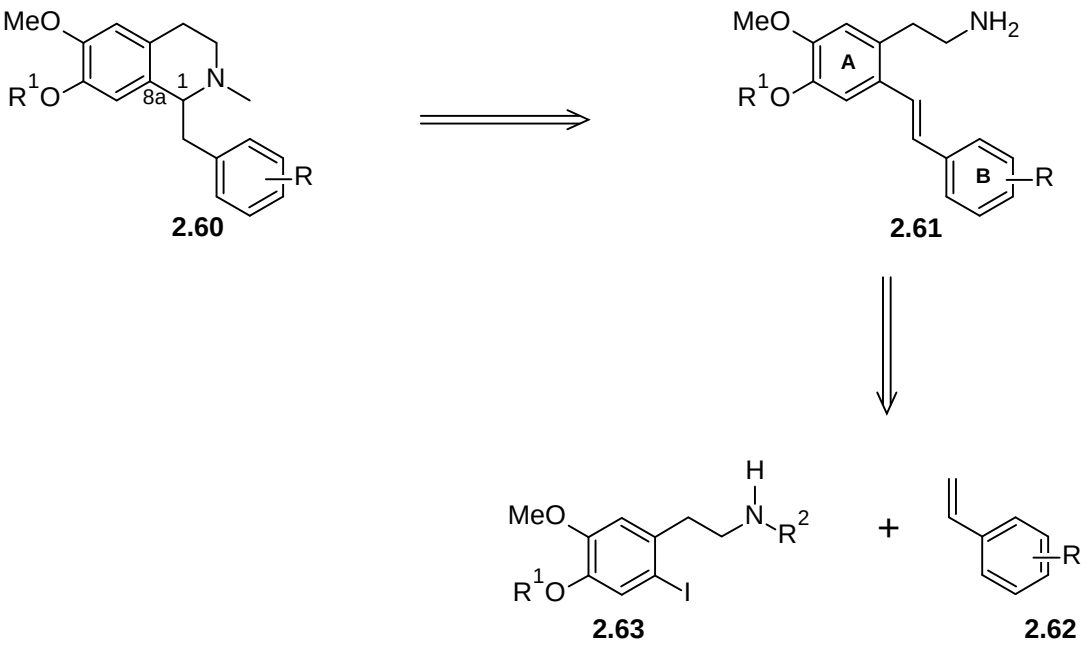
One of the primary objectives of this project was to investigate the application of modern methodologies in the synthesis of simple benzyltetrahydroisoquinolines. The synthetic methods which we explored are the hydroamination of aminostilbenes and aminoalkynes. There are limited literature reports on the synthesis of benzylisoquinolines by these methods, making the proposed study worthwhile.[96-99]

This section of the chapter presents discussions of the results obtained in the synthesis of benzyltetrahydroisoquinolines by intramolecular hydroamination of aminostilbenes and aminoalkynes. As most naturally-occurring benzyltetrahydroisoquinolines possess electron-rich substituents, we first investigated the scope of the hydroamination reaction on electron-rich aminostilbenes in the synthesis of benzyltetrahydroisoquinolines. The synthesis of

benzyltetrahydroisoquinolines by hydroamination of aminoalkynes was explored lastly.

2.5.2 Retrosynthetic Analysis

The retrosynthesis in Scheme 2.21 outlines our initial synthetic approach followed to prepare the benzyltetrahydroisoquinolines. It was envisaged that reductive coupling of the aryl iodide **2.63** and styrene **2.62** could form the aminoalkene **2.61** *via* a Heck coupling reaction. In contrast to the conventional syntheses of benzylisoquinoline alkaloids whereby the formation of the C1-C8a bond of the benzyltetrahydroisoquinoline core is usually obtained by electrophilic aromatic substitution, this bond is now formed by the Heck coupling reaction. In this approach, the proposed isoquinoline **2.60** will arise from an enantioselective intramolecular hydroamination reaction of aminoalkene **2.61**.

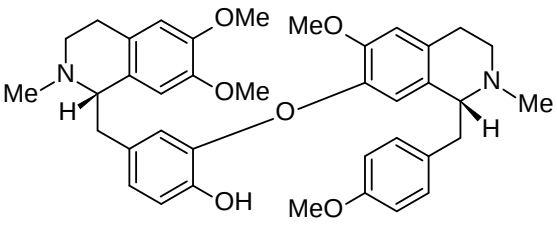


Scheme 2.21. Retrosynthesis of benzyltetrahydroisoquinoline.

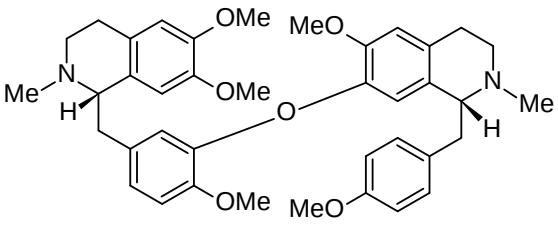
For a successful intramolecular addition of an amine onto the alkene *via* Michael-addition reaction, it would be required that the electron density on ring B of the stilbenes be reduced and the electrophilicty of the endo double bond be enhaced. This can be achieved by incorporating electron-withdrawing substituents on ring B

of the stilbenes. However, in the present case, this method was developed to be applied on the synthesis of neferine **1.15**, which possesses oxygenated substituents. Thus, it was required that R and R^1 be oxygenated substituents, in order to determine the functional group tolerance of intramolecular hydroamination of electron-rich aminostilbenes into benzyltetrahydroisoquinolines under metal-catalysed and base-catalysed conditions. There are only two references on the preparation of benzyltetrahydroisoquinolines by the intramolecular hydroamination of aminostilbenes. The first report was by the group of Tomioka in 2007 on the base-catalysed hydroamination of unsubstituted aminostilbene (Section 2.4, Scheme 2.19).[96] The second method was developed by Bourgeois et al., who utilised electron-rich aminostilbene to prepare the natural product norreticuline following a tandem Cope-type hydroamination reaction.[99]

In this study, several stilbenes were prepared from differently substituted iodophenethylamines and styrenes. The substitution patterns on the styrenes and iodophenethylamines were designed such that upon successful intramolecular hydroamination of the stilbenes, the resulting benzyltetrahydroisoquinolines could immediately be used as advanced precursors for the synthesis of the targeted bisbenzyltetrahydroisoquinolines, neferine (**1.15**) and its analogues. Therefore, a pair of styrenes, one with a *para*-hydroxy group and the other with 3,4-hydroxylation pattern were prepared to mimic the hydroxylation pattern on the benzyl scaffolds of the two benzyltetrahydroisoquinolines in neferine (**1.15**) and *O*-methylneferine (**1.16**). Similarly, in the phenethylamine **2.63**, R^1 could be a methyl group or a derivative, which would be easily cleaved to allow for formation of the ether link between the two benzyltetrahydroisoquinolines in **1.15** and **1.16**.



1.15



1.16

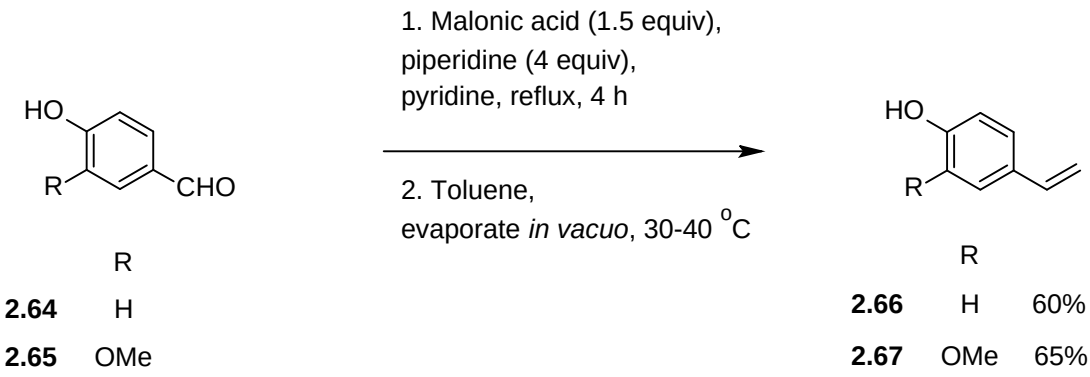
Several methods were explored for the synthesis of styrene derivatives **2.62** and phenethylamine derivatives **2.63** with the aim of optimising the yields. In the next sections, the synthesis of styrene derivatives **2.62** and phenylethylamine derivatives **2.63** will be discussed.

2.5.3 Synthesis of Vinylphenols 2.66 and 2.67

Considering the reactivity of vinyl phenols (styrenes), a protocol that would deliver these compounds using mild reaction conditions was essential. Consequently, most of the synthetic strategies used to synthesise vinyl phenols required early protection of the hydroxy group and deprotection at a later stage. Common methods followed in the preparation of vinyl phenols include the Wittig synthesis,[100] Grignard addition to benzaldehyde,[101] decarboxylation of *trans*-cinnamic acid at elevated temperatures in the presence of a metal,[102] and catalytic dehydrogenation of ethyl phenols. These procedures yield vinyl phenols in more than two steps. However, a one-step synthesis of these phenols has also been reported. Simpson *et al*.[103] synthesised vinyl phenols in a one-step procedure starting from 4-hydroxybenzaldehyde following the Knoevenagel condensation reaction under mild conditions. Sinha *et al*.[104] also reported a one-step synthesis of vinyl phenols under microwave conditions, using the Knoevenagel-Doebner reaction.

Inspired by the work done by Simpson *et al*.[103] and Sinha *et al*.,[104] we decided to synthesise vinyl phenols following their protocols. Initially, the Knoevenagel condensation was evaluated on unprotected 4-hydroxybenzaldehyde (**2.64**). In a one-pot reaction, the hydroxybenzaldehyde **2.64** was condensed with malonic acid and piperidine in the presence of pyridine to give the appropriate vinyl phenol **2.66** (Scheme 2.22). Pyridine was removed *in vacuo*, in the presence of toluene, to afford the vinyl phenol crude product. The reaction conditions were the same as those applied in the classic Knoevenagel condensation reaction. The acidic work up, which is known to give only the cinnamic acid, was avoided as water would be eliminated during the course of the reaction. It was postulated that the

Knoevenagel reaction was not reversible under these conditions. An alternative work up, which entailed removing pyridine *in vacuo* in the presence of toluene only, afforded the vinyl phenol **2.66** in a 60% yield, from 4-hydroxybenzaldehyde (**2.64**). A similar reaction starting with vanillin (**2.65**) yielded the styrene **2.67** in a 65% yield.

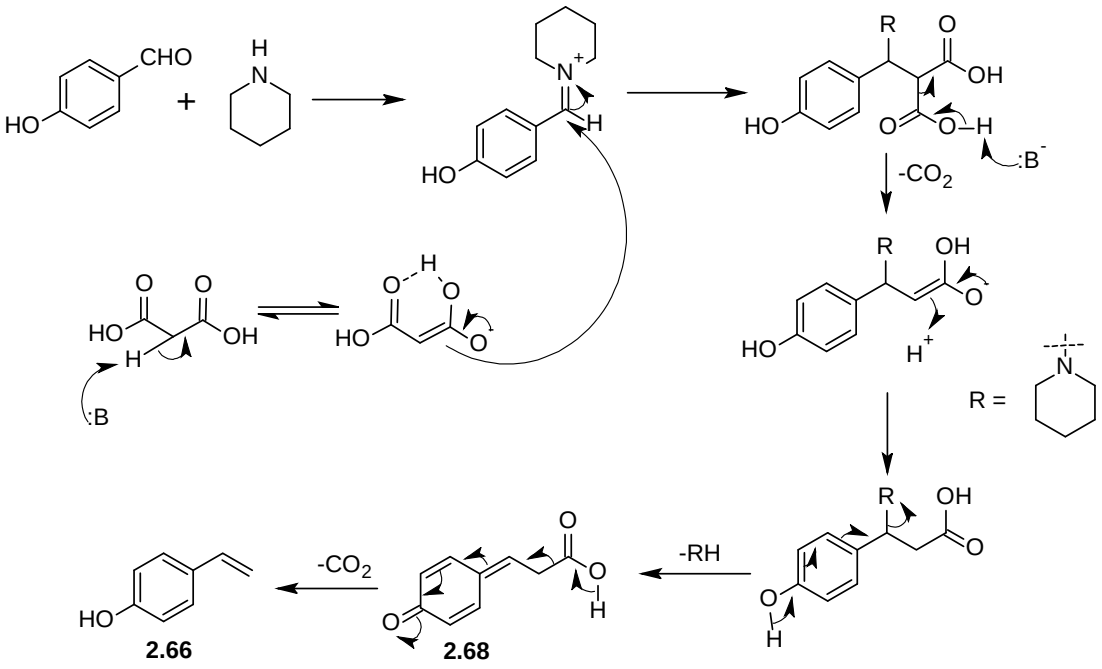


	R
2.64	H
2.65	OMe

	R	
2.66	H	60%
2.67	OMe	65%

Scheme 2.22. The classic Knoevenagel reaction.

The mechanism of the reaction is envisaged to proceed through participation of a quinone in a two-step decarboxylation to give a vinylphenol **2.66** (Scheme 2.3).[103] The initial step involves condensation of the aldehyde with piperidine to form an iminium intermediate. Concurrently, an enolate ion is generated by deprotonation of the α-carbon of malonic acid. The subsequent step is the attack of the enolate ion on the electrophilic site of the iminium ion to give the beta-amino malonate, followed by elimination of carbon dioxide. Hydrogen transfer, followed by the elimination of the amine ensures the formation of quinone methide **2.68**. The final step involves decarboxylation of the *p*-quinone methide **2.68** to afford the corresponding vinylphenol **2.66**.

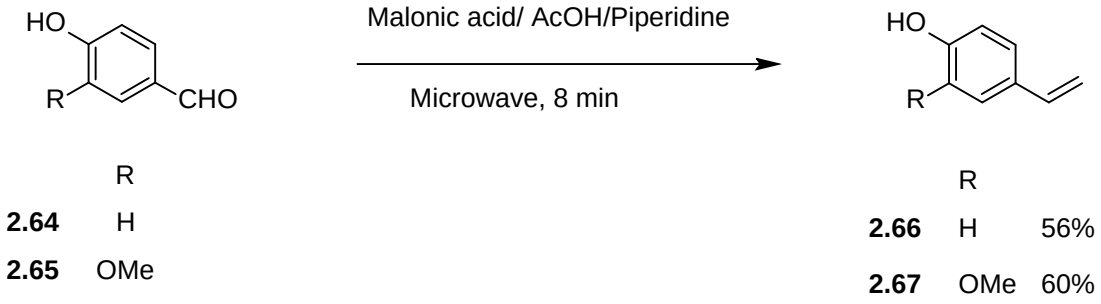


Scheme 2.23. Mechanism of the Knoevenagel condensation.

Attempts to use the *p*-methoxybenzaldehyde yielded only *trans*-cinnamic acid. This observation suggests that the 4-hydroxy substituent was essential for the one-step synthesis of vinylphenols. Although this protocol proved to be viable for the synthesis of vinylphenols, the extended reaction time which induces polymerisation is a drawback. Therefore, an alternative method which would produce the required vinylphenols in a shorter time and in good yields was devised.

The Knoevenagel-Doebner-Sinha reaction, which is an acid-catalysed reaction, was initially envisaged to proceed as a one-pot, two-step synthetic procedure. It involves condensation of the *p*-oxygenated benzaldehyde **2.64** with malonic acid, followed by decarboxylation as illustrated in Scheme 2.24.[104] Both of these steps were performed following the recommended safe method under monomide microwave irradiation. In this case, the use of acetic acid-piperidine instead of the known pyridine-piperidine combination as the condensing agent was found to be more efficient. The pyridine-piperidine combination tends to vaporise easily as this reaction is performed at elevated temperatures. The simplicity and availability of reagents, the rapid conversion and good yield of the product renders the

developed Knoevenagel-Doebner-Sinha method a useful alternative to the conventional method for the synthesis of the vinyl phenol **2.66**. Instability of the very reactive styrenes hampered the purification process, and hence the modest yields of the final products.

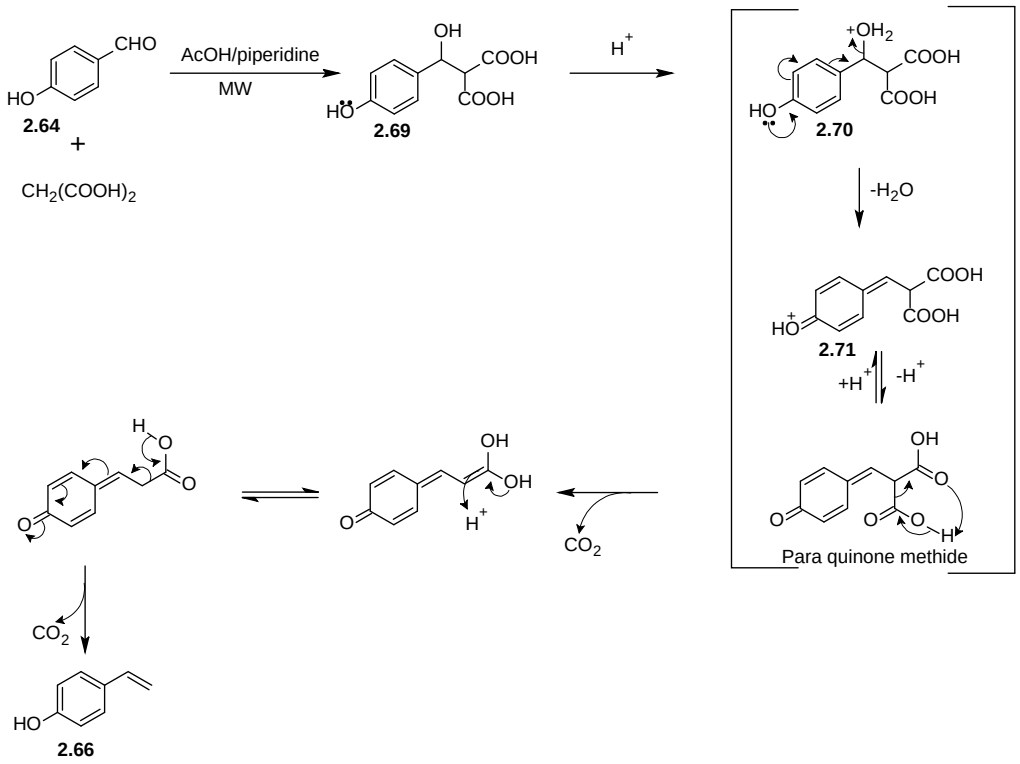


	R
2.64	H
2.65	OMe

	R	
2.66	H	56%
2.67	OMe	60%

Scheme 2.24. Knoevenagel-Doebner-Sinha reaction.

A different mechanistic pathway, where acetic acid is used in place of pyridine, was proposed. It is envisaged to proceed *via* the Hann-Lapworth mechanism.[105] Initially an enolate ion is formed from the malonic acid, which attacks the electrophilic site of the benzaldehyde to yield the alcohol intermediate **2.69**. The intermediate **2.69** is then protonated to **2.70** in an acidic medium followed by subsequent dehydration to *p*-quinone methide **2.71**. This step is followed by an early decarboxylation, hydrogen transfer and late decarboxylation to form styrene **2.66** as shown in Scheme 2.25.[105]



Scheme 2.25. Mechanism of Knoevenagel-Doebner-Sinha reaction.

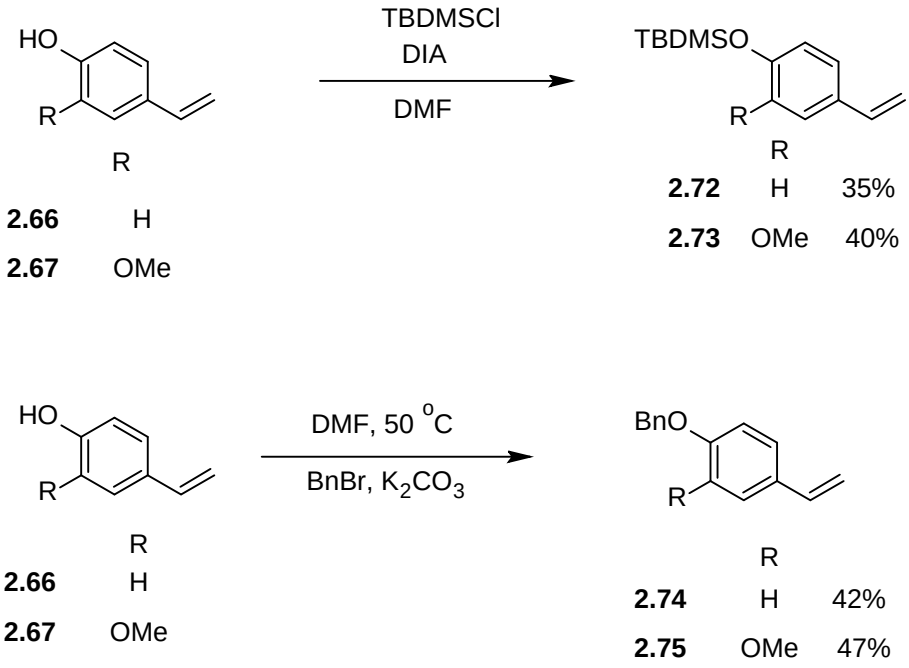
Analysis of the ^{1}H NMR spectrum of the styrene **2.66** showed the characteristic protons of a vinylic double bond at δ_H 6.62 (1H, dd, *J* = 17.5 and 11.1 Hz, C<u>H</u>=CH_2), 5.61 (1H, dd, *J* = 17.5 and 1.0 Hz, CH=C<u>H</u>$_2$) and 5.18 (1H, dd, *J* = 11.1 and 1.0 Hz, CH=C<u>H</u>$_2$). The styrene **2.67** was synthesised in a 65% yield in a similar manner as compound **2.66**.

2.5.4 Synthesis of Derivatised Styrenes

The synthesised styrenes were to be used in the Heck coupling reaction leading to aminostilbenes. As seen in the literature review, the Heck reaction is performed under basic conditions. Thus coupling hydroxystyrenes **2.66** and **2.67** with aryl iodides under Heck conditions would lead to side reactions resulting from enhanced nucleophilicity of the deprotonated hydroxy groups. For instance, an Ullmann-type reaction can occur between the free hydroxy group and an aryl iodide under palladium-catalysed conditions and will diminish the yields of the expected stilbene. Furthermore, styrenes with free hydroxy groups are prone to

polymerisation under basic conditions and at high temperatures. To circumvent these problems, it was required that the free hydroxy groups in the styrenes **2.66** and **2.67** be protected before proceeding with the next steps.

The silyl and benzyl protecting groups were used in this study due to their relative stability in the basic medium. Therefore, 4-hydroxystyrene (**2.66**) was protected as the silyl and benzyl ethers using TBDMSCl and BnBr, respectively (Scheme 2.26). DIA was used as a base instead of the usual imidazole, which requires long reaction times. The corresponding 4-*tert*-butyldimethylsilyloxystyrene **2.72** was furnished in a 35% yield. The ^{1}H NMR spectrum of **2.72** displayed the conspicuous protons at δ_H 1.04-1.05 (9H, s, C(C$\underline{H}_3$)$_3$) and δ_H 0.20-0.26 (6H, s, (Si(C$\underline{H}_3$)$_2$), confirming the presence of the silyloxy group. Using the same reaction conditions, styrene **2.73** was prepared in 40% yield. Since low yields were obtained in this protecting step, the use of another protecting group was investigated.

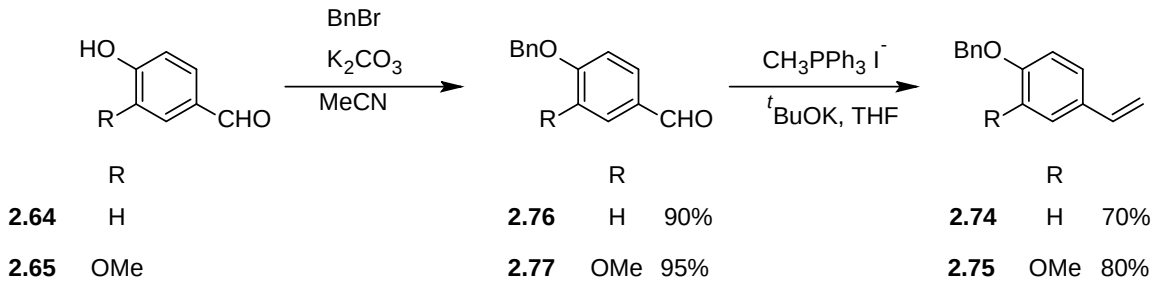


Scheme 2.26. Derivatisation of vinylphenols.

The use of BnBr instead of TBDMSCl resulted in an improvement of the yields. Therefore, benzylation of vinylphenol **2.66** was achieved by deprotonation of the hydroxy group using K_2CO_3, followed by addition of BnBr, in a typical S_N2 reaction.

The benzylated styrene **2.74** was obtained in a modest yield of 42%. The benzyl protons of compound **2.74** were observed at δ_H 7.45-7.30 and δ_H 5.10 for the aromatic protons and methylene protons, respectively, in the ^{1}H NMR spectrum. Benzyl protection of hydroxystryrene **2.67** under similar reaction conditions gave the benzylated styrene **2.75** in 47% yield.

Due to the low yields obtained in the above reactions, it was decided to try the Wittig reaction to form the alkene. The initial step entailed the synthesis of 4-benzyloxybenzaldehyde (**2.76**). Benzyloxybenzylaldehyde **2.76** was prepared in 90% yield by refluxing the mixture of benzaldehyde **2.64**, K_2CO_3 and BnBr in CH_3CN. The next step was coupling of the Wittig ylide with 4-benzyloxybenzaldehyde (**2.76**) to form styrene **2.74**. Firstly, the Wittig ylide was reacted with ^{t}BuOK to yield the highly reactive methylene species intermediate. This intermediate was subsequently reacted with **2.76** at 0 ^{o}C to furnish **2.74** in 70% yield. Using this procedure, **2.75** was also synthesised in a good yield (Scheme 2.27). This method proved to be a better one as the yields were consistent.



	R		R			R	
2.64	H	**2.76**	H	90%	**2.74**	H	70%
2.65	OMe	**2.77**	OMe	95%	**2.75**	OMe	80%

Scheme 2.27. Wittig reaction for the preparation of styrenes **2.74** and **2.75**.

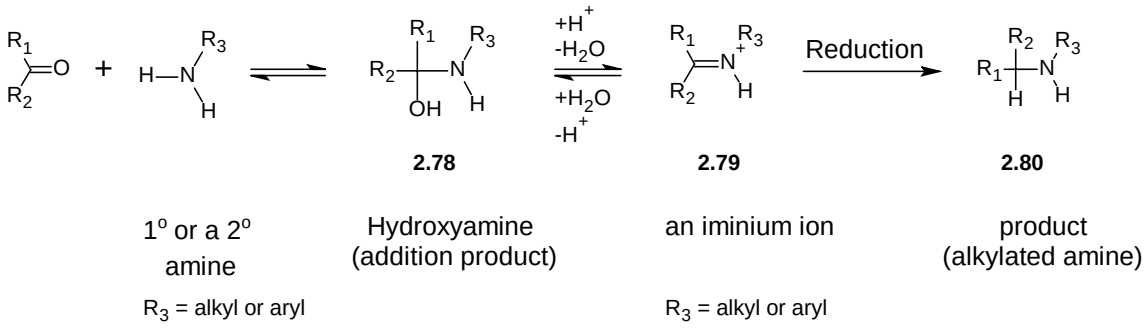
2.5.5 Synthesis of β-Phenethylamine

β-Phenethylamines are of interest to natural product scientists, not only because of the different and interesting pharmacological properties of the simple members of this family (adrenergic, sympathomimetic, anorexic, etc.), but also for their presence in a large number of skeletons of more complicated structures: phenanthrene alkaloids, aporphines, berberines. As these compounds are building

blocks of many natural products, either as the ethylamino branch or forming part of the polycyclic topologies, their synthesis is essential. Herein, their preparation by reductive amination, hydroamination and the Henry reaction is presented.

2.5.5.1 Reductive amination.

The reductive amination of aldehydes and ketones is used to prepare primary, secondary and tertiary amines. The reaction initially involves the condensation of an amine with a carbonyl compound to form the intermediate hemiaminal species **2.78**. Dehydration of **2.78** under weakly acidic to neutral conditions renders an iminium ion **2.79**, which is reduced to the desired amine **2.80** (Scheme 2.28).

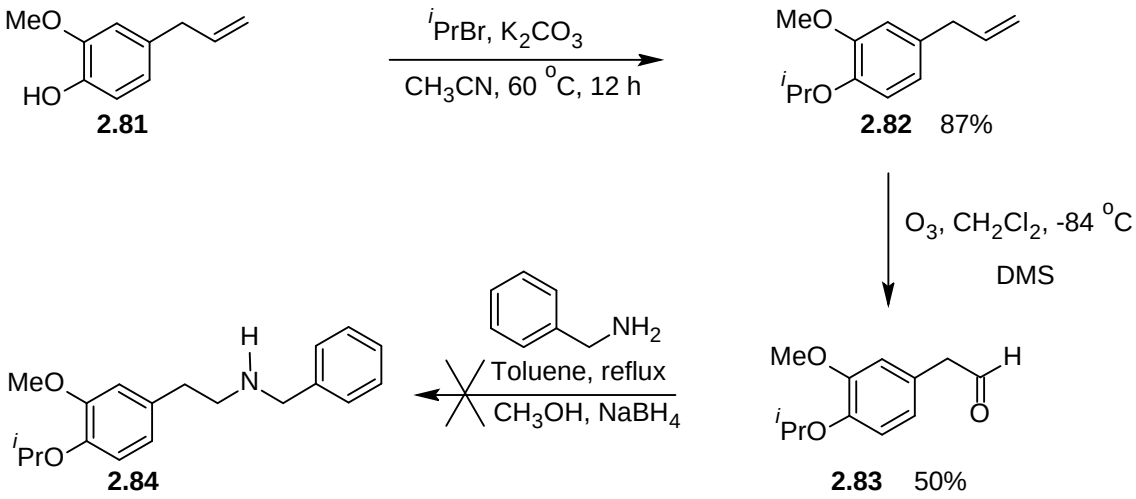


Scheme 2.28. Reductive amination reaction.

This reaction offers a variety of advantages compared to other amine syntheses. Such advantages include brevity, availability of starting substrates, and generally mild reaction conditions and in some cases, the exceptionally high functional group tolerance. The reagents which are reported to effect reductive amination include, $NaBH(OAc)_3$,[106] $ZnCl_2$-$NaBH_4$,[107] $NiCl_2$-$NaBH_4$,[108] $Ti(O^iPr)_4$-$NaBH_4$,[109] $Ti(O^iPr)_4$-polymethylhydrosiloxane,[110] Bu_3SnH,[111] Bu_2SnClH and Bu_2SnIH,[112] decaborane,[113] silica gel-$ZnBH_4$,[114] Et_3SiH-trifluoroacetic acid and[115] pyridine-BH_3.[116]

To prepare phenethylamines by reductive amination, a protocol which could deliver these compounds with high efficiency and tolerate mild reaction conditions was required. The synthesis of β-phenethylamine **2.84** commenced with the

protection of the commercially available eugenol (**2.81**) to give isopropoxy ether **2.82**. Following the protection step, an ozonolysis reaction was undertaken to furnish the desired phenylacetaldehyde **2.83**. ^{1}H NMR analysis of **2.83** showed the expected spin system in the aromatic region at δ_H 6.87 (1H, d, *J* = 8.7 Hz,) and 6.71 (2H, overlap), an aldehyde peak at 9.70 (1H, t, *J* = 2.5 Hz) and the adjacent methylene protons resonating at δ_H 3.58 (2H, d, *J* = 2.5 Hz), a confirmation that the alkene was successfully converted into an aldehyde. The presence of a diagnostic peak at δ_C 199.5 in the ^{13}C NMR spectrum further confirmed the aldehyde group in the molecule. The IR spectrum also showed the presence of a sharp band at 1722 cm^{-1}, indicative of an aldehyde functional group. The HRMS analysis showed *m/z* peak of 209.1169 $[M+H]^+$, consistent with the calculated molecular mass of 209.1168 for $C_{12}H_{17}O_3$ $[M+H]^+$, confirming the compound to be **2.83**.



Scheme 2.29. Attempted reductive amination reaction.

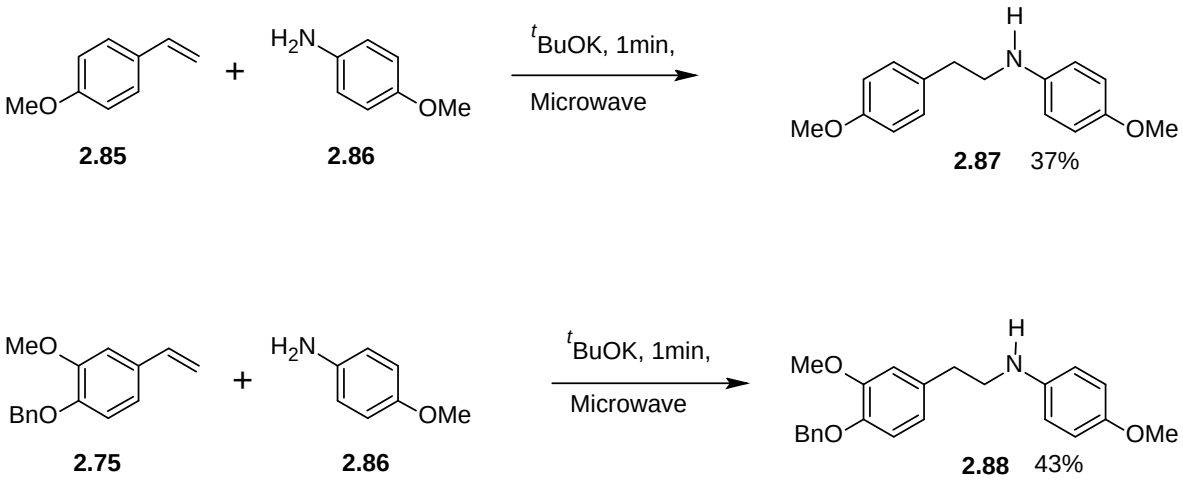
As we now had compound **2.83**, the subsequent step was to condense it with an amine through the reductive amination procedure. The reductive amination reaction was performed by refluxing benzylamine and phenylacetaldehyde in toluene and subsequent reduction with $NaBH_4$ at 0 °C in methanol. The use of benzylamine in this method was encouraged by the fact that the benzyl functional group could be easily cleaved by hydrogenolysis to render the free amine. Unfortunately, the brown mixture formed did not contain the expected

phenethylamine **2.84.** TLC analysis showed many spots that could not be separated. Attempts to characterise the mixture by NMR was unsuccessful. Repeating the reaction under milder conditions, at room temperature, also yielded the same brown mixture. The failure of this reaction was attributed to the decomposition and reactivity of phenylacetaldehyde **2.83** (Scheme 2.29). This route was abandoned and other methods for preparation of phenethylamines were explored.

2.5.5.2 Hydroamination reaction

The synthesis of phenethylamines by base-catalysed hydroamination reactions has not been investigated thoroughly. Most of the reported reactions require very harsh reaction conditions and need to be performed under pressure.[92, 117] Reports on these reactions have indicated that the reaction may not take place or it proceeds with a very low yield. However, Seijas *et al.*[118] reported the synthesis of phenethylamines in high yields by using microwave irradiation to promote the addition of aniline to styrene without heating in a solvent and also avoiding the use of a pressure vessel. One of the striking features associated with the base-catalysed reaction over that of metal-catalysed hydroamination is its high regioselectivity.

Motivated by the findings of Seijas *et al.*,[118] phenethylamine derivatives were prepared by coupling styrenes with *p*-anisidine in this study. *p*-Anisidine was used instead of aniline due to its high reactivity and ease of cleavage of the introduced *p*-methoxyphenyl group under oxidative conditions. The synthesis of phenethylamines commenced with the reaction of 4-methoxystyrene (**2.85**) with *p*-anisidine (**2.86**) to give the hydroaminated product **2.87** in a modest yield (37%) as shown in Scheme 2.30. The reaction proceeded smoothly when using stoichiometric amount of ^{t}BuOK under microwave conditions in a solvent-free medium. Starting materials were reacted in the 1:10:1 ratio of styrene, *p*-anisidine and ^{t}BuOK, respectively. In agreement with the literature precedents, the anti-Markovnikov product was obtained as the only regioisomer.



Scheme 2.30. Hydroamination of styrenes.

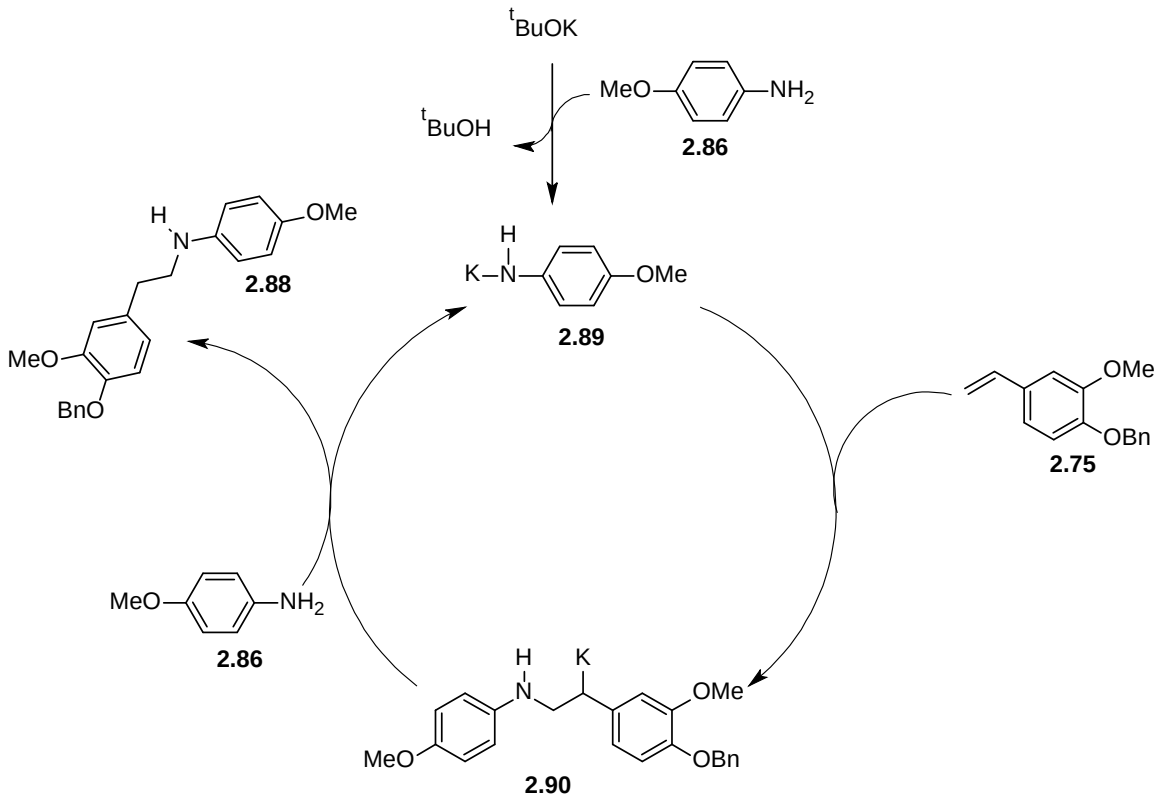
These results were supported by the ^{1}H NMR, ^{13}C NMR, IR and HRMS data. The ^{1}H NMR of compound **2.87** confirmed the presence of two AA'BB' spin system resonating at δ_H 7.11, 6.91, 6.83 and 6.81, all representing *ortho* doublets. In the spectrum, two methoxy singlets appearing at δ_H 3.79 and 3.76, were also identified. Furthermore, there were two other triplets resonating at 3.36 (J = 6.9 Hz,) and 2.95 (J = 6.9 Hz), each representing the presence of two methylene protons.

Compound **2.88** was synthesised in a similar manner from styrene **2.75** and *p*-anisidine (**2.86**). The ^{1}H NMR spectrum of compound **2.88** showed the presence of an ABX, AA'BB' spin system and the benzyloxy protons in the aromatic region. The benzyl group protons resonated at δ_H 7.46-7.31 (5H) and 5.16 (2H, s), confirming the presence of five aromatic protons and two benzylic protons, respectively. The ABX and AA'BB' spin system protons appeared at δ_H 6.87 (1H, d, J = 8.6 Hz), 6.79 (2H, d, J = 8.5 Hz), 6.76 (1H, d, J = 2.0 Hz), 6.71 (1H, dd, J = 2.0 and 8.6 Hz) and 6.60 (2H, d, J = 8.5 Hz). Two methoxy signals at 3.88 (3H, s) and 3.77 (3H, s), and two triplets at 3.37 (2H, t, J = 7.0 Hz) and 2.85 (2H, t, J = 7.0 Hz), were also present in the same spectrum.

The low yields obtained with this method were attributed to the reduced electrophilicity of the styrenes, because of the electron-donating properties of the aromatic ring, which increase the electron density of the carbon-carbon double

bond of the styrene. Therefore, the presence of the aromatic ring should considerably slow down the rate of addition of the reactive potassium amide, thus increasing the activation energy of the hydroamination process. This makes it extremely difficult for the addition reaction to take place.

Based upon these observations, a plausible mechanism for the ^{t}BuOK-catalysed hydroamination of olefins can be proposed (Scheme 2.31). The mechanism proceeds through three elementary steps. The first step involves a proton transfer from *p*-anisidine (**2.86**) to ^{t}BuOK to form **2.89** and ^{t}BuOH. In the second step, the strongly nucleophilic amide **2.89** reacts intermolecularly with styrene **2.75** to form an intermediate **2.90**. This nucleophilic attack occurs preferably in an anti-Markovnikov fashion. Finally, the carbanion **2.90** is protonated by the excess amine **2.86**, thereby releasing phenethylamine **2.88** and regenerating the potassium phenyl amide **2.89**, which initiates a new cycle.

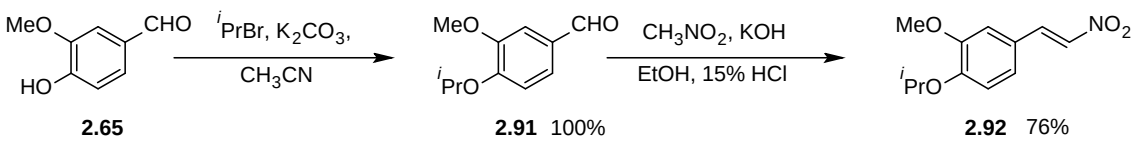


Scheme 2.31. Base-catalysed intermolecular hydroamination of alkenes.

2.5.5.3 The Henry reaction

As synthesis of phenethylamines with the base-catalysed hydroamination reaction was met with limited success, the Henry reaction, also called the nitro-aldol reaction was explored.[119-121] The Henry reaction involves formation of a carbon-carbon bond through the condensation of a nitroalkane with a carbonyl compound to give the β-nitro alcohol. Subsequent elimination of water in the presence of stoichiometric amount of a base yields the nitrostyrene.

Synthesis of the required phenethylamine commenced with the protection of the hydroxy group of 4-hydroxy-3-methoxybenzaldehyde (vanillin) (**2.65**) (Scheme 2.32) as the isopropyl ether (*i*-PrBr and K_2CO_3 in CH_3CN under reflux conditions) to afford 4-isopropoxy-3-methoxybenzaldehyde (**2.91**) in quantitative conversions. The subsequent step was to synthesise the nitrostyrene *via* Henry's method. The nitro-aldol condensation of the corresponding aldehyde with CH_3NO_2 and KOH was performed at 0 ^oC for 1 h. Thereafter, the reaction mixture was poured into a solution of 15% HCl, from which the unsaturated nitro compound precipitated out. The obtained unsaturated nitro compound was recrystallised from ethanol to afford β-nitrostyrene **2.92** as yellow crystals in 76% yield. The NMR and HRMS results confirmed the structure of compound **2.92**. The ^1H NMR spectrum of compound **2.92** displayed the two characteristic alkene signals as two doublets resonating at δ_H 7.96 and δ_H 7.52 with a coupling constant of 13.6 Hz, which indicated the *trans* configuration. The ^{13}C NMR spectrum showed 12 carbons, without an aldehyde carbon confirming that the conversion was successful. The two alkene carbons resonated at δ_C 122.6 and 135.1.



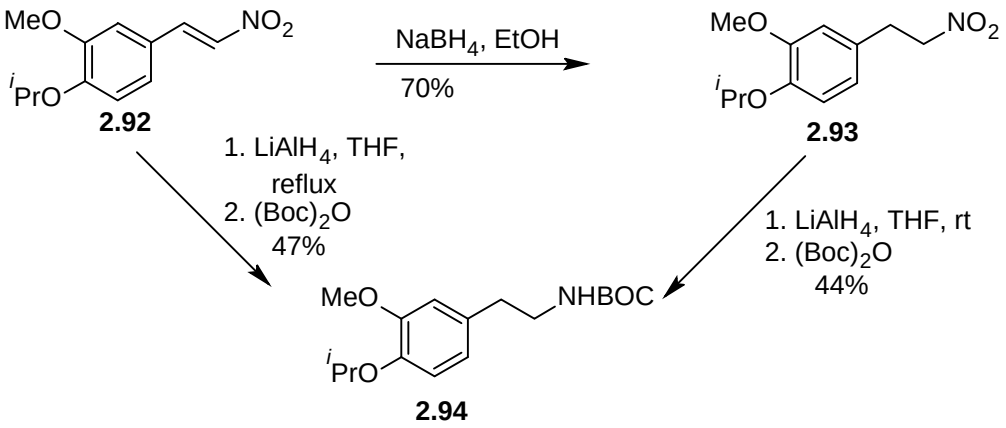
2.65 **2.91** 100% **2.92** 76%

Scheme 2.32. Synthesis of the nitrostyrene **2.92**.

Having successfully prepared the required nitrostyrene, the next step was to synthesise the phenethylamine **2.94**, which could be obtained *via* two different

routes with the nitrostyrene as the starting material (Scheme 2.33). The initial step entailed conversion of the unsaturated nitro compound into the corresponding saturated nitro compound **2.93** using sodium borohydride in ethanol at 0 ^{o}C to afford the saturated nitro compound in a 70% yield. The ^{1}H NMR spectrum of compound **2.93** did not show the alkene signals, but instead showed two triplets integrating for two protons at δ_H 3.26 and 4.59 with a coupling constant of 7.4 Hz, which were attributed to the $C\underline{H}_2C\underline{H}_2NO_2$ protons. Furthermore, absence of the two alkene carbons and appearance of two new carbons in the upfield region of the ^{13}C NMR spectrum resonating at δ_C 76.6 and 33.2, confirmed the structure. The molecular formula of compound **2.93** was confirmed by LRMS analysis to be *m/z* 239, consistent with the structure of the reduced nitro compound.

The next step was to reduce the saturated nitro compound **2.93** to phenethylamine **2.94**. Attempts to reduce the nitro group with lithium aluminium hydride in the absence of a protective group to trap the generated reactive amine were unsuccessful. Hence the reduction step was slightly modified by immediately trapping the amine with a (*t*-BOC)$_2$O group. Treatment of **2.93** with $LiAlH_4$ at room temperature for 3 h, followed by *in situ* protection of the amine with (*t*-Boc)$_2$O, yielded the protected amine, albeit in a modest yield (44%). The *in situ* protection reduced the reactivity of the free amine. The ^{1}H NMR spectrum of compound **2.94** exhibited three aromatic protons at δ_H 6.84 (1H, d, *J* = 2.0 Hz), 6.71 (1H, d, *J* = 8.7 Hz), 6.69 (1H, dd, *J* = 2.0 Hz and 8.7 Hz), a methine proton at δ_H 4.49 (1H, m, $OC\underline{H}(CH_3)_2$) and the methoxy protons at δ_H 3.86 (3H, s, OCH_3). In the same spectrum, the two methylene protons appearing at δ_H 3.36 (2H, m, $ArCH_2C\underline{H}_2NH$) and δ_H 2.75 (2H, t, *J* = 7.0 Hz, $ArC\underline{H}_2CH_2NH$) and a singlet resonance at δ_H 1.45 (9H, s, $OC(C\underline{H}_3)_3$) assigned to three equivalent methyl groups of the *tert*-butyl group, were observed. The doublet at δ_H 1.36 (3H, s, $OCH(C\underline{H}_3)_2$) is indicative of the two methyl groups of the isopropyl. The poor yield of 44% obtained from this method prompted us to seek another method to improve the phenethylamine yields.



Scheme 2.33. Synthesis of phenethylamine **2.94**.

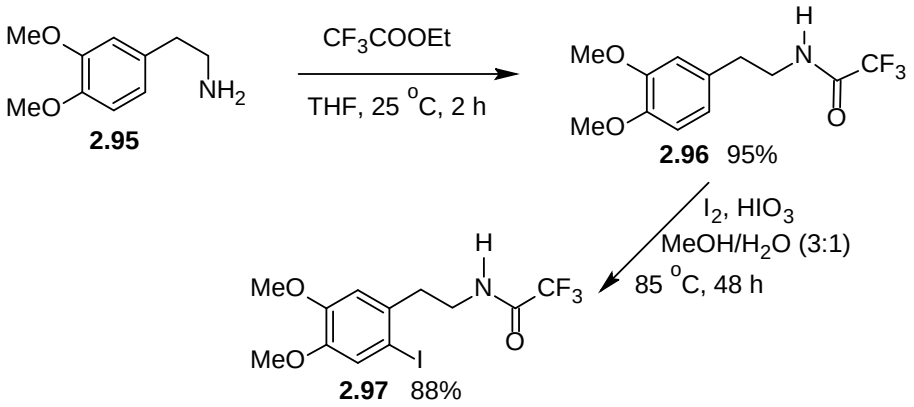
A one-step reduction reaction of the nitrostyrene **2.92** to the corresponding phenethylamine **2.94** was attempted. It is worth mentioning that in the literature it is reported that the one-step reduction of nitrostyrenes results in an inseparable mixture of products with very low yields.[122-125] Contrary to these reports, better results were observed when the unsaturated nitro compound was reacted with $LiAlH_4$ in THF at 0 ^oC. On completion of the reaction (observed by TLC), the temperature was raised to room temperature and the reaction was refluxed for 7 h in an inert atmosphere. The *in situ* protection with (*t*-Boc)$_2$O yielded the protected phenethylamine **2.94** in a 47% yield. This methodology proved to be more efficient than the first two employed in this investigation.

2.5.6 Preparation of Aryl Iodide

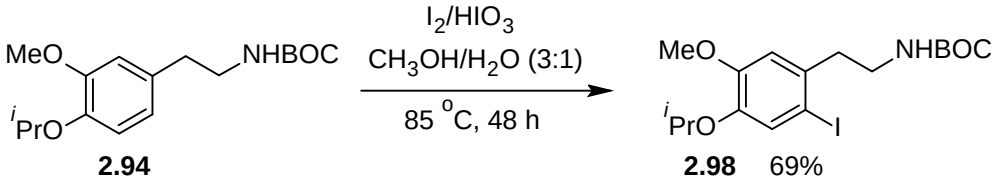
Due to their high reactivity, iodoarenes are valuable species in organic synthesis when compared to other haloarenes. They are used mostly in transition metal-catalysed reactions involving carbon-carbon bond formation.[26] Iodoarenes have many applications in the pharmacology, medicine and biochemistry fields of research. However, due to the poor electrophilic character of iodine, direct iodination of aromatic rings is difficult, and therefore requires an activating agent to produce a strongly electrophilic I^+ species.[126, 127]

The reaction of commercially available 3,4-dimethoxyphenylethylamine (**2.95**) with ethyl trifluoroacetate in THF at room temperature, as depicted in Scheme 2.34, afforded the *N*-protected trifluoroacetamide **2.96** in a 95% yield.[128] Iodination of the aromatic ring at C-6 was considered to be the next step. Initially, compound **2.96** was iodinated with I_2/CF_3COOAg in $CHCl_3$ to deliver the aryl iodide **2.97** in 92% yield. However, due to the high cost of the silver salt, an alternative method was sought. Motivated by the results reported by Shi and Ojima,[95] ICl was applied next in our synthesis. Iodination with ICl in CH_2Cl_2 for 3 - 4 h proceeded smoothly yielding the desired aryl iodide **2.96** in a 70% yield after purification. Using KI/KIO_3 as the iodinating species resulted in a low yield (50%).

Compound **2.96** was successfully iodinated with I_2/HIO_3 at 85 ^oC in a mixture of H_2O and CH_3OH to give **2.97** in an 88% yield. Compound **2.97** was obtained in its pure form after column chromatography. The amine **2.94** was also iodinated with I_2/HIO_3 to give **2.98** in a 69% yield (Scheme 2.35). As this method produced good results, it was used often in the subsequent preparations of aryl iodides, such as **2.98**.



Scheme 2.34. Preparation of aryl iodide **2.97**.



Scheme 2.35. Synthesis of *N*-BOC aryl iodide **2.98**.

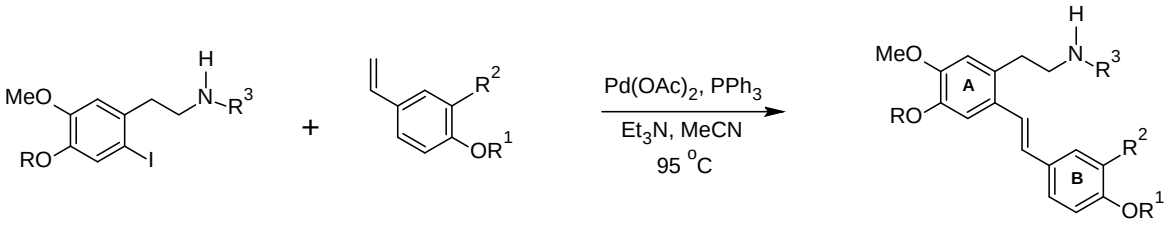
The ^{1}H NMR spectrum of the aryl iodide **2.97** displayed two singlets in the aromatic region at δ_H 7.24 (1H, s, H-3) and 6.71 (1H, s, H-6), evidence of successful iodination with the regiospecificity shown. A singlet at δ_H 6.39 (1H, br s, NHCO) of the amide and the methoxy singlets at δ_H 3.87 (3H, s, OCH_3), and 3.85 (3H, s, OCH_3) are also present in the spectrum. The two methylene protons appeared as a quartet and triplet at δ_H 3.59-3.64 (2H, q, *J* = 7.0 Hz, $ArCH_2CH_2NHC{=}O$) and δ_H 2.99 (2H, t, *J* = 7.0 Hz, $ArCH_2CH_2NHC{=}O$).

2.5.7 Palladium-Catalysed Coupling of Styrenes with Aryl Halides to Yield Aminostilbenes.

Heck demonstrated that styrenes react smoothly with aryl halides in the presence of catalytic amounts of Pd(0) or Pd(II) complexes in triethylamine under reflux conditions. This process has been the most effective way of forming carbon-carbon double bonds, *e.g*. stilbenes and many other organic compounds. In this study, six aminostilbenes (**2.99**, **2.100**, **2.101**, **2.102**, **2.103** and **2.104**), differing by hydroxylation pattern and protecting groups, were prepared *via* the Heck reaction (Table 2.1).

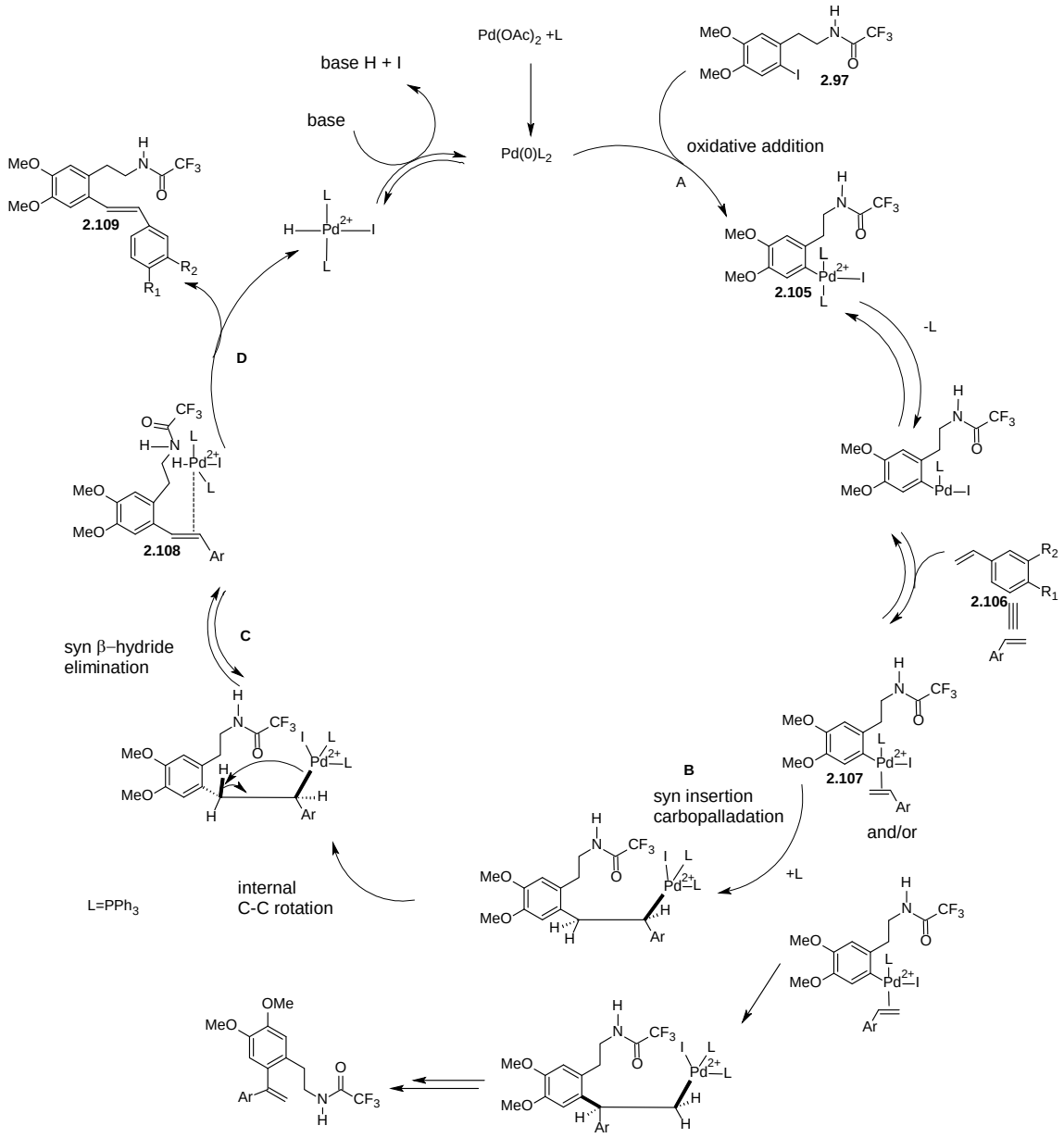
The iodophenethylamines **2.97** and **2.98** were coupled with different styrenes *via* the standard Heck[129, 130] coupling reactions as shown in Table 2.1. The reaction was catalysed by 4 mol% $Pd(OAc)_2$ and 0.5 mol% PPh_3 using Et_3N as a base at 95 ^{o}C in CH_3CN for 16 h. Following the standard workup procedure and silica gel chromatographic purification, the aminostilbenes (**2.99 2.100**, **2.101**, **2.102**, **2.103** and **2.104**) were obtained in 29-49% yields. When a polar solvent such DMF was used instead of CH_3CN in this reaction, there was no significant improvement in the yields (35-40%). Yields were dependent on the nature of oxygenation pattern and type of protecting group used on each substrate.

Table 2.1. Preparation of aminostilbenes by Heck coupling reaction of aryl iodides and styrenes.



Aryl iodide	Styrene	R	R^1	R^2	R^3	Amino stilbene	Yield%
2.97	**2.74**	Me	Bn	H	TFA	**2.99**	35
2.97	**2.75**	Me	Bn	OMe	TFA	**2.100**	30
2.97	**2.72**	Me	TBDMS	H	TFA	**2.101**	49
2.97	**2.73**	Me	TBDMS	OMe	TFA	**2.102**	33
2.97	**2.85**	Me	Me	H	TFA	**2.103**	29 - 31
2.98	**2.74**	*i*-Pr	Bn	H	BOC	**2.104**	31

Good yields compared to other derivatised styrenes were also obtained when 4-*tert*-butyldimethylsilyloxystyrene (**2.72**) was used (see Table 2.1). Low yields (29-31%) were obtained with 4-methoxystyrene (**2.84**) as the starting material. The ^{1}H NMR spectra of all the amino stilbenes showed AA'BB' or ABX spin systems for the B-rings, while only the AX spin system was observed for the A-ring. Additionally, two doublets were present in the aromatic region between δ_H 6.98 and 7.68, indicative of an alkene linkage between the two phenyl rings. The coupling constant of 16 Hz of the alkene suggests that arylation of the Heck regio- and stereoselectively favoured the *E*-product over that of the *Z*-isomer.



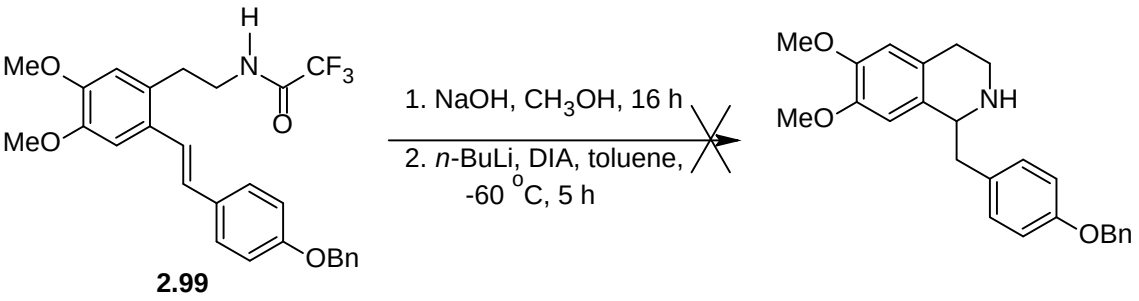
Scheme 2.36. Heck mechanism.

The presumed mechanism for the Heck catalytic cycle, using the aryl iodide **2.97**, is shown in Scheme 2.36. The reaction proceeds *via* generation of an active bis(triphenylphosphine)palladium(0) species by the reduction of palladium acetate with triphenylphosphine. Step A in the cycle involves oxidative addition of Pd(0) to the aryl iodide to give Pd(II) intermediate **2.105**, which then reacts with an alkene **2.106** to form a π-complex **2.107**. Step B envisions *syn*-addition of the alkene to the palladium-carbon bond and step C involves the formation of a new palladium-

alkene π-complex **2.108** *via* elimination of a *beta*-hydride. The next step involves dissociation of the coupled product **2.109** from complex **2.108,** followed by reductive elimination of the Pd(II) compound to regenerate the Pd(0) species.[27]

2.5.8 Attempted Intramolecular Hydroamination Cyclisation

Having successfully synthesised the aminostilbenes (**2.99**, **2.100**, **2.101**, **2.102**, **2.103** and **2.104**), which were key synthetic precursors, the following step was to synthesise the targeted benzyltetrahydroisoquinolines *via* intramolecular cyclisation. Attempts to cyclise both the *N*-protected and unprotected aminostilbenes through base- or metal-catalysed intramolecular hydroamination reactions were unsuccessful. Under a base-catalysed procedure that uses *n*-BuLi, the compound **2.99** was subjected to the intramolecular amination procedure developed by Tomioka *et al*.[96] Initially, the cyclisation reaction was attempted without adding DIA as an external protonating agent, but with catalytic amounts of *n*-BuLi. The reaction was performed at various temperatures in the presence of toluene, starting at -60 ^{o}C as described by Tomioka. Unfortunately, there was no product formed (Scheme 2.37). Repeating the reaction at higher temperatures (-50 ^{o}C, -40 ^{o}C, -20 ^{o}C, -10 ^{o}C, 0 ^{o}C) also did not produce any products.

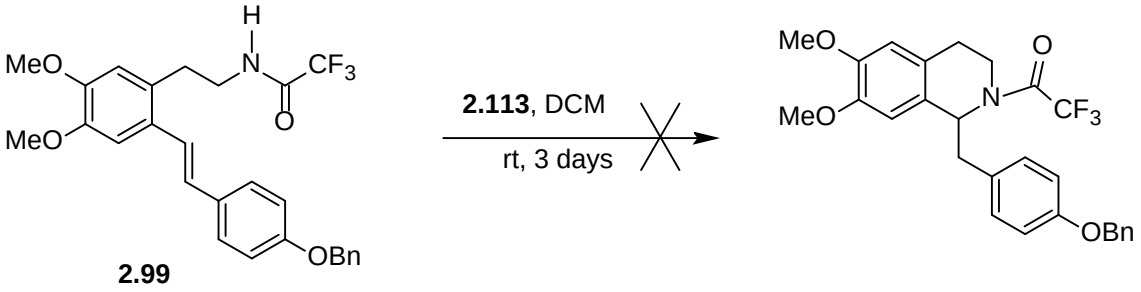


Scheme 2.37. Attempted base-catalysed intramolecular hydroamination of **2.99**.

As there was no product formation at temperatures below 0 ^{o}C, it was worthwhile attempting the reaction at higher temperatures. It was hence decided to add *n*-BuLi at room temperature and gradually increase the temperature while refluxing until 1 h of the reaction time had elapsed. Once again, no product was observed

after 6 h of reflux. Addition of DIA as an external protonating agent did not give any fruitful results either. The failure of the base-catalysed hydroamination could be attributed to the nucleophililic character of the alkene which inhibits attack by the lithium amide.

As no positive results were obtained under the base-catalysed hydroamination of aminostilbenes, a different hydroamination method was required. In this case, a procedure based on titanium metal-catalysed hydroamination reactions developed by Doye's group was adopted.[97] Consequently, the compound **2.99** was reacted at 110 ^{o}C in toluene in the presence of 20 mol% of titanium complex as catalyst using three different titanium catalysts, $Ti(NEt_2)_4$ (**2.110**), $BINOLTi(NEt_2)_2$ (**2.111**), and Cp_2TiMe_2 (**2.112**). Once again, none of them yielded the desired product with both the protected and unprotected aminostilbenes, instead decomposition of the starting materials was observed.



Scheme 2.38. Attempted metal-catalysed hydroamination cyclisation.

Having failed to achieve the desired products with the Ti-catalysts, we investigated an acid-catalysed hydroamination with a chiral catalyst, binapthylphosphoric acid (**2.113**) (Scheme 2.38). The synthesis was initiated by adding 5 mol% of **2.113** to the aminostilbene **2.99** in DCM at room temperature. After 5 h K_2CO_3 was added and the reaction was stirred for another 3 days. However, this reaction also did not furnish the required benzyltetrahydroisoquinoline. Initially, the failure of this reaction was attributed to the diminished reactivity of the *N*-protected aminostilbenes. However, efforts to use the unprotected aminostilbene did not yield positive results either.

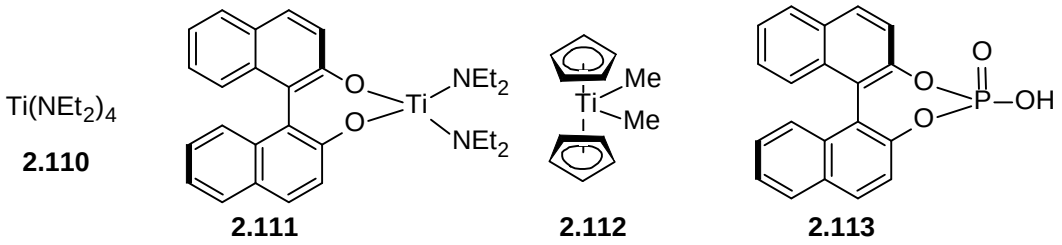


Figure 2.1. Hydroamination catalysts.

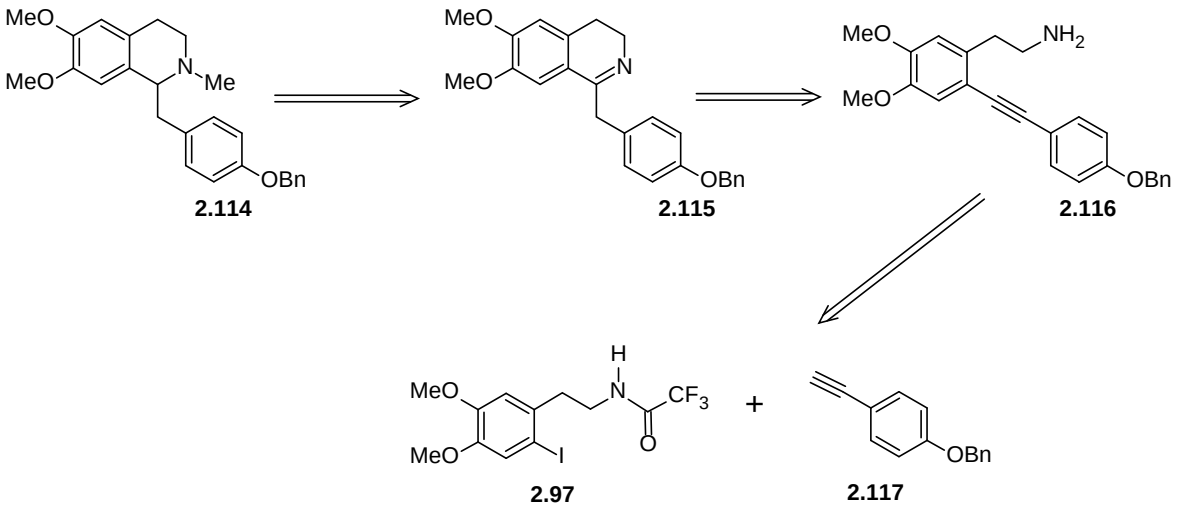
The titanium and phosphoric acid catalysts **2.110**, **2.111**, **2.112** and **2.113** used in the hydroamination reactions were synthesised in this study. The discussions on the syntheses of these catalysts will follow in section 2.5.13, with more focus on the BINOL catalysts **2.111** and **2.113**.

The unsuccessful attempts to cyclise the aminostilbenes using base- and metal-catalysed procedures demonstrate that there is still a need to develop methods, which are suitable for the hydroamination reactions of highly electron-rich substrates. From the literature, it is postulated that base-catalysed hydroamination reaction proceeds *via* formation of highly nucleophilic amide species, which undergoes addition to alkenes.[92, 117] Therefore, this reaction will require activation of the alkenes by electron-withdrawing groups. On the other hand, the titanium-catalysed hydroamination reaction follows a mechanism that involves oxidative addition of the metal to the amine, followed by insertion of the alkene onto the metal-nitrogen bond and reductive elimination.[79, 131] Since hydroamination by these methods failed, it is recommended that other synthetic strategies, which proceed via different mechanistic pathways, be investigated in the future. For instance, the reaction can be performed under palladium-catalysed or ruthenium-catalysed conditions. The two methods activate the alkene for the nucleophilic addition.[132, 133] The palladium-catalysed hydroamination is initiated by alkene insertion onto a metal complex, followed by nucleophilic attack with the amine. In the ruthenium-catalysed reaction, ruthenium coordinates to the aromatic ring to form an η^6-arene complex, thereby pulling the electron density from the alkene. This is followed by nucleophilic addition of the amine onto the alkene.[131-133]

2.5.9 Palladium-Catalysed Coupling of Acetylenes with Aryl Halides to Yield Aminoalkyne.

Failure of intramolecular ring-closure of the aminostilbenes to afford the desired benzyltetrahydroisoquinolines prompted us to investigate other routes for the preparation of the tetrahydroisoquinolines. We opted for the intramolecular hydroamination of aminoalkynes. The aminoalkynes could be obtained by Sonogashira coupling of iodophenethylamines and arylacetylenes.[95, 97, 128] The 2-iodophenethylamines were already synthesised as precursors to the stilbenes, while the arylacetylenes could be readily prepared from the styrenes.

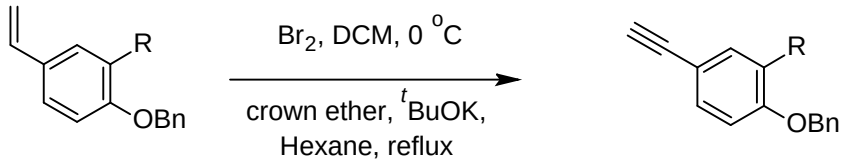
For this approach, the retrosynthetic analysis of the benzylisoquinolines is outlined in Scheme 2.40. As shown in Scheme 2.39, the first disconnection involves an enantioselective reduction of the imine **2.115** to give the benzyltetrahydroisoquinoline **2.114**. This reduction can be done by enantioselective reduction using Noyori's catalyst. The cost of this catalyst, prompted us to consider other reductive methods as well. The imine **2.115** was envisaged to arise from an intramolecular hydroamination reaction of the aminoalkyne **2.116**. Following this approach, the C1-C8a bond would hence be formed by the Sonogashira coupling between the aryl iodide **2.97** and an alkyne **2.117**.



Scheme 2.39. Retrosynthetic analysis of benzyltetrahydroisoquinoline.

2.5.10 Synthesis of Acetylene

From the previously synthesised 4-benzyloxystyrene (**2.66**), the 4-benzyloxyphenylethyne (**2.117**) was prepared in a 48% yield. The synthesis was initiated by the bromination of styrene **2.66** with bromine in CH_2Cl_2 at 0 ^oC followed by the dehydrohalogenation with ^tBuOK and 18-crown-6-ether. The ^1H NMR spectrum of compound **2.117** showed the presence of a single proton at δ_H 3.00 which indicated that the dehydrohalogenation had taken place to form arylacetylene **2.117** (Scheme 2.40). The 4-benzyloxy-3-methoxyphenylethyne (**2.118**) was also synthesised from styrene **2.67** under similar reaction conditions.

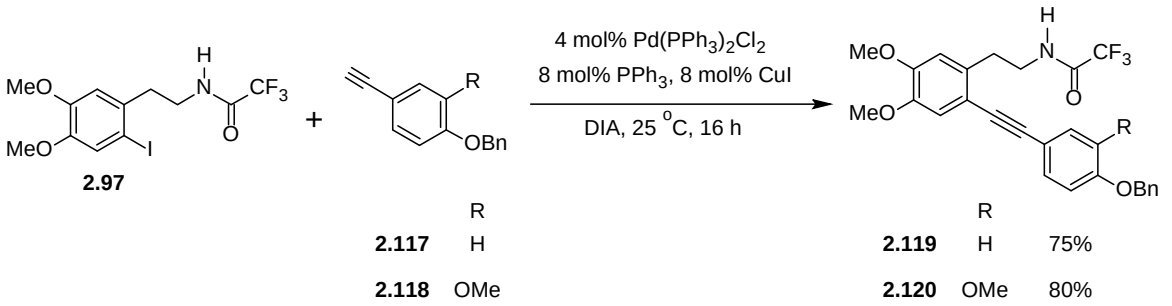


	R		R	
2.66	H	**2.117**	H	48%
2.67	OMe	**2.118**	OMe	52%

Scheme 2.40. Synthesis of arylacetylene **2.117** and **2.118**.

2.5.11 Synthesis of Aminoalkyne

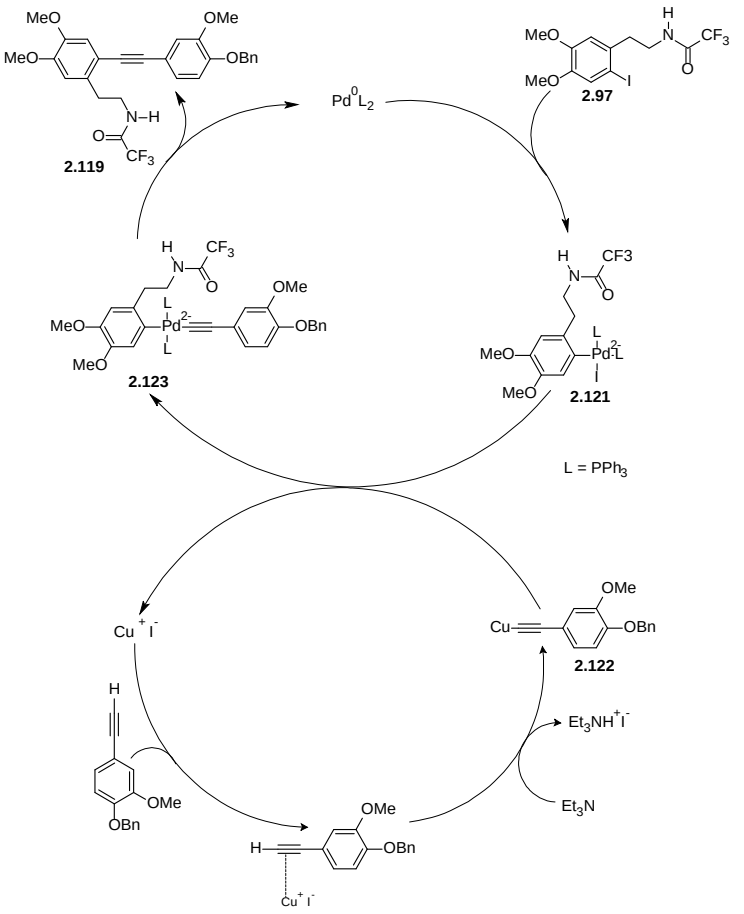
To form the C1-C8a bond in the required diarylacetylenes, a standard Sonogashira coupling procedure was performed (Scheme 2.41).[95, 97] The reaction involved coupling the aryl iodide **2.97** with acetylene **2.117** in CH_3CN in the presence of 4 mol% $Pd(PPh_3)_2Cl_2$, 8 mol% PPh_3, 8 mol% CuI, and DIA at room temperature. The diarylacetylene **2.119** was obtained in a 75% yield after chromatography. The diarylacetylene **2.120** was also prepared in 80% yield by coupling aryl iodide **2.97** and acetylene **2.118** under the same reaction conditions**.**



Scheme 2.41. Sonogashira coupling reaction.

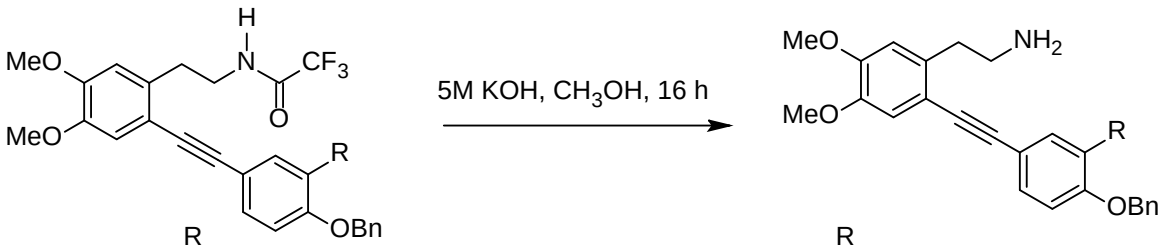
The structures of all prepared diarylacetylenes were assigned by ^{1}H NMR, ^{13}C NMR, IR and HRMS. The ^{1}H NMR of the diarylacetylene **2.119** showed disappearance of the ethynyl proton at around δ_H 3.00 owed to substitution by the phenyl ring. The molecular formula of **2.119** was confirmed by HRMS which gave 506.1552 $[M+Na]^+$, consistent with the calculated molecular mass of 506.1555 for $C_{27}H_{24}F_3NO_4Na$. The spectroscopic results of compound **2.120** were also in agreement with the assigned structure.

The mechanism for the formation of the products in the copper-cocatalysed Sonogashira reaction is believed to take place *via* two independent cycles as shown in Scheme 2.42. The Pd(0) species known as the putative active catalyst, is formed *in situ* by reduction of different Pd(II) complexes. Once the Pd(0) species is formed, it becomes involved in the oxidative addition reaction with the aryl iodide **2.97** to give the 16-electron Pd(II) intermediate **2.121**. The copper acetylide **2.122** then undergoes transmetallation with intermediate **2.121** to afford the aryl palladium complex **2.123**, which upon reductive elimination yields the coupled product **2.119** and the Pd(0) catalyst.[51]



Scheme 2.42. Mechanism of the Sonogashira reaction.

With the *N*-trifluoroacetyl diarylacetylenes in hand, the next step was base hydrolysis to give the free amine (NH_2) group. The trifluoroacetate group was cleaved by treating the aminoalkyne **2.119** with 5M solution of KOH in CH_3OH to deliver the unprotected aminoalkyne **2.124** in 77% yield (Scheme 2.43). Hydrolysis of **2.120** gave the free amine **2.125** in 80% yield.



	R		R	
2.119	H	**2.116**	H	77%
2.120	OMe	**2.124**	OMe	80%

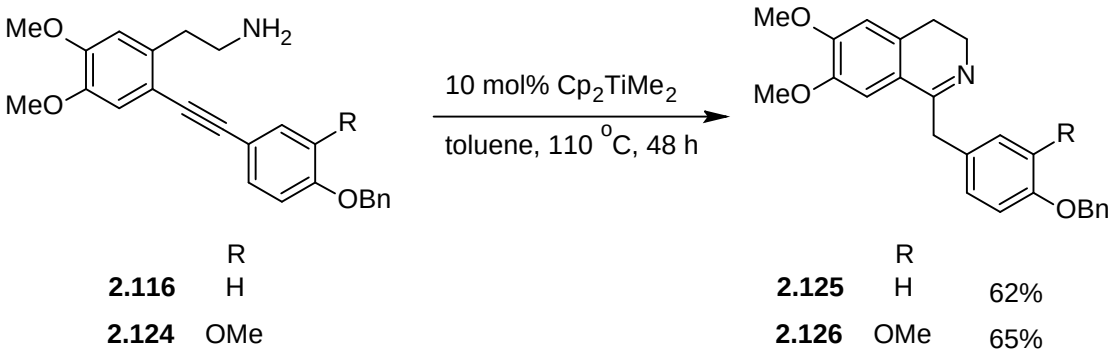
Scheme 2.43. Hydrolysis reaction.

2.5.12 Intramolecular Hydroamination

As the requisite substrates (**2.116** and **2.124**) for the intramolecular hydroamination were successfully synthesised, we were in a position to perform the intramolecular hydroamination ring cyclisation leading to dihydroisoquinolines. We followed the protocol described by Mujahidin and Doye (Scheme 2.20).[97] Initially, the intramolecular hydroamination reaction of aminoalkyne **2.124** in toluene in the presence of a catalytic amount of $Ti(NMe_2)_4$ (**2.110**) was investigated. The reaction proceeded at 110 ^oC with 5 mol% of catalyst loading, albeit the yields obtained were extremely low (ca~5-10%). No reaction was observed when the reaction was carried out at room temperature. Increasing the amount of catalyst to 30 mol% with the hope of achieving better conversion of the alkyne also did not result in any improvement of the yield. Failing to obtain satisfactory results with catalyst **2.110**, another Ti complex [$BINOLTi(NMe_2)_2$] **2.111** was examined as a catalyst. Disappointingly, switching to $BINOLTi(NMe_2)_2$ **2.111** did not improve the outcome of the cyclisation reaction, even after 5 days of reflux.

Even though Mujahidin and Doye reported high yields (98%), when Cp_2TiMe_2 (**2.112**) was used in the intramolecular hydroamination of aminoalkynes to form benzyldihydroisoquinolines, in this investigation the procedure only delivered the desired imine **2.126** in a modest yield (65%) after purification by chromatography (Scheme 2.44) (Table 2.2). It must be noted that these results were obtained after 16 h of reaction time with 10 mol% loading of Cp_2TiMe_2. Further increase of the reaction time did not result in any improvement of the yields. The aqueous workup conditions were avoided in this step, as the produced imine could easily be converted into a stable enamine under aqueous conditions.

These findings showed that the Ti-complex **2.112** exhibits better catalytic activity than the complexes **2.110** and **2.111**. An interesting phenomenon observed with these catalysts was that they showed similar cyclisation behaviour for the aminoalkynes **2.116** and **2.124**, even though their catalytic activities differed slightly.



	R		
2.116	H	**2.125**	62%
2.124	OMe	**2.126**	65%

Scheme 2.44. Intramolecular hydroamination.

Table 2.2. Alkyne hydroamination

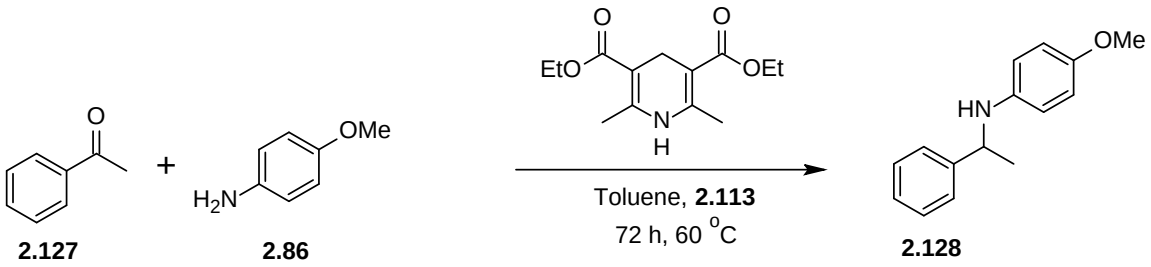
Substrate	catalyst	Time (h)	Yield %
2.116	**2.110**	16	6
2.124	**2.110**	16	10
2.116	**2.112**	48	62
2.124	**2.112**	48	65
2.116	**2.111**	72	5
2.124	**2.111**	72	8

Although the complex **2.112** seemed to be effective for the cyclisation, the low yield required that the imine **2.126** must be synthesised in large quantities in order to continue with the subsequent steps that lead to the targeted compound. It was observed that when the reaction was performed on a gram scale, the yields were inconsistent. The most likely reason for this inconsistency is the instability of the benzyldihydroisoquinolines. The long reaction times associated with the hydroamination reactions employed in this study, may result in decomposition of

the product. However, this problem may also be encountered with other methods in the preparation of dihydroisoquinolines.

Following the preparation of dihydroisoquinolines **2.125** and **2.126**, the stage was set for the enantioselective reduction. It is worth noting that the reduction could be done by employing the Noyori's catalysts. However, this reaction has been reported and furthermore, the catalysts are air and moisture sensitive, expensive and difficult to prepare. Therefore, a method which utilises Hantzsch esters as hydride source and the chiral BINOL-phosphoric acid **2.113** as a Brönsted acid was explored. The advantages of this method were that the chiral Brönsted acid could be easily synthesised from cheap and commercially available starting materials. Furthermore, this method avoids the use of toxic heavy metals. Reactions, in which the Hantzsch ester and the chiral BINOL-phoshoric acid were used to hydrogenate imines, are reported to show high degrees of enantioselectivity.[134-136] Inspired by these findings, we prepared the chiral BINOL-phosphoric acid and attempted to use it for the first time to reduce benzyldihydroisoquinolines enantioselectively.

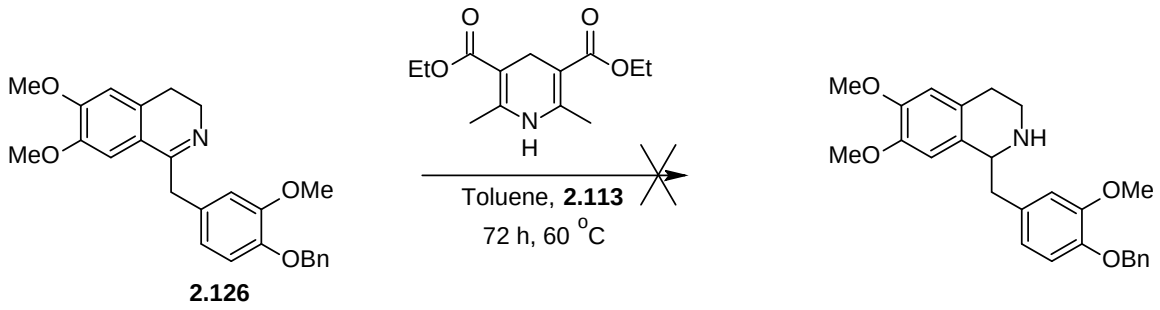
With dihydroisoquinolines **2.125** and **2.126** in hand, we then attempted the asymmetric hydrogen transfer to give the tetrahydroisoquinolines. Since the preparation of the dihydroisoquinolines involves many synthetic steps, it was decided to perform a model reaction on readily available substrates. A model reaction between compound **2.127** and **2.86** was conducted as depicted in Scheme 2.45. Condensation of the two starting materials in the presence of a phosphoric acid catalyst and Hantzsch ester proceeded successfully to give **2.128** in 60% yield. The structure of compound **2.128** was confirmed by the ^{1}H NMR analysis, which showed the expected methine proton at δ_H 4.42 (1H, q, *J* = 7.0 Hz,) and that of the methyl protons.at δ_H 1.51 (3H, d, J =7.0 Hz). Further characterisation was by ^{13}C NMR which showed the disappearance of a carbonyl carbon with the emergence of an upfield carbon at δ_C 54.5 assignable to the methine carbon.



2.127 **2.86** **2.128**

Scheme 2.45. Asymmetric hydrogen transfer: A model reaction.

Motivated by the successful synthesis of compound **2.128**, it was required that reduction be performed on the real molecule. However, after several attempts, the treatment of **2.126** with phosphoric acid catalyst and Hantzsch ester did not yield the targeted compound (Scheme 2.46). The failure of this reaction was attributed to the accumulative steric effects of the 4-benzyl substituent and the chiral BINOL-phosphoric acid. It would be worthwhile to investigate this reaction with dihydroisoquinolines with sterically less demanding substituents on C-4.



2.126

Scheme 2.46. Attempted asymmetric reduction with catalyst **2.111**.

2.5.13 Syntheses of Catalysts for Hydroamination Reactions

Titanium catalysts have been used in several instances for inter- and intramolecular hydroamination of aminoalkenes and aminoalkynes.[74, 79] However, the application of titanium catalysts in the synthesis of benzyltetrahydroisoquinolines has been demonstrated by Doye's group only, in the intramolecular hydroamination of aminoalkynes.[97] The products of the intramolecular hydroamination of aminoalkynes are benzyldihydroisoquinolines, which require further reduction to form the corresponding

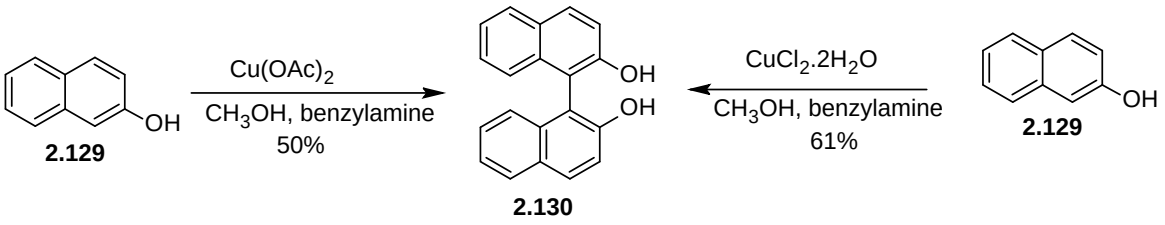
benzyltetrahydroisoquinolines. Since naturally-occurring tetrahydroisoquinolines are enantiopure compounds, it is required that the reduction of the dihydroisoquinolines must be performed in the presence of chiral catalysts to induce the desired stereochemistry at C-1.

In this study, titanium catalysts **2.110**, **2.111** and **2.112** were prepared and used in the hydroamination reactions of aminostilbenes and aminoalkynes (Sections 2.5.8 and 2.5.12). The chiral catalyst **2.111** was prepared mainly to facilitate simultaneous intramolecular hydroamination and control of stereochemistry in the synthesis of benzyltetrahydroisoquinolines from aminostilbenes. This was motivated by the fact that the metal-catalysed ring closure of aminostilbenes to tetrahydroisoquinolines has not been reported. The chiral phosphoric acid catalyst **2.113**, on the other hand, was synthesised for the enantioselective reduction of dihydroisoquinolines**,** which were prepared by the hydroamination of aminoalkynes.

The catalysts **2.110** and **2.112** were prepared according to the procedures of Bradley and Petasis, respectively.[137, 138] The syntheses of the chiral catalysts **2.111** and **2.112** are discussed in detail in the following sections. The first step involved preparation of the racemic BINOL ligand from 2-napthol (**2.129**), followed by resolution of the racemic ligand and finally coordination of the enantiopure ligand to titanium or formation of a chiral phosphoric acid for the preparation of **2.111** and **2.113**, respectively.

2.5.13.1 Synthesis of rac-BINOL

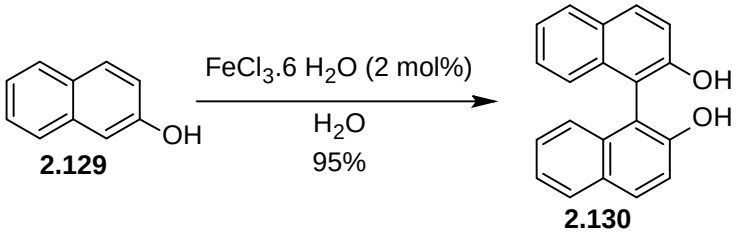
The phenolic oxidative coupling of 2-napthol (**2.129**) to yield the racemic BINOL (**2.130**), was successfully achieved using the synthetic protocols reported by Brussee *et al*.[139] and Pummerer *et al*.[140] Initially, 2-napthol was reacted with a methanolic solution of $Cu(OAc)_2$ benzylamine complex to produce 1,1'-binapthalene-2,2'-diol (BINOL, **2.130**) in a moderate yield (50%) (Scheme 2.47). The modest yield was attributed to the failure of the benzylamine and $Cu(OAc)_2$ to form a homogenous mixture.



Scheme 2.47. BINOL synthesis catalysed by Cu(II) salts.

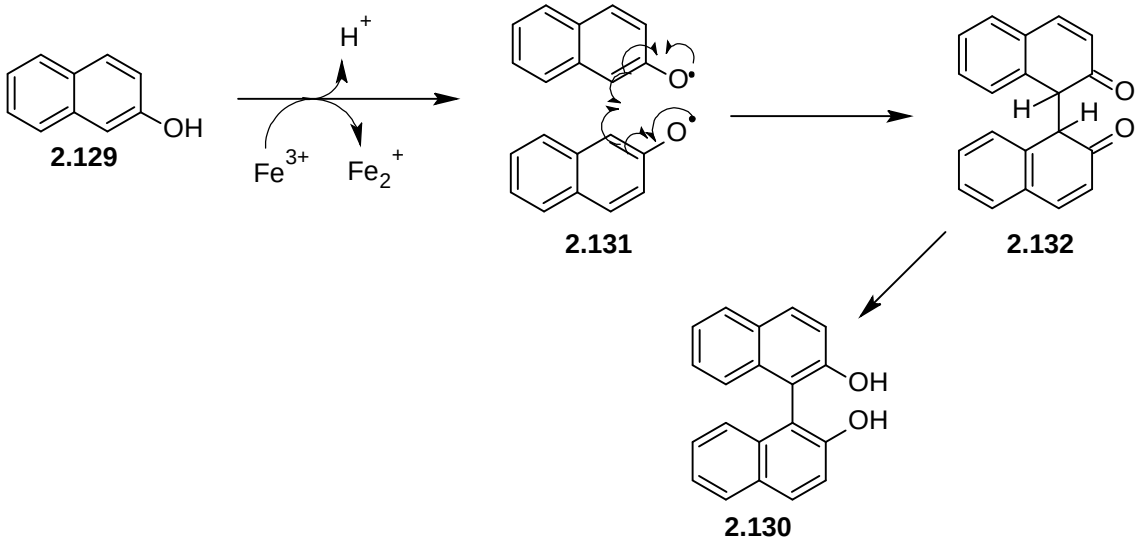
Using $CuCl_2.2H_2O$, as an alternative oxidant, the yield of the reaction was improved to 61% (Scheme 2.47). The higher yield was ascribed to the ability of the chloride ion to form a homogenous methanol solution of Cu(II)-benzylamine complex. This phenomenon was not observed with $Cu(OAc)_2$.

Failure to obtain **2.130** in quantitative yield using the protocol of Brussee *et al*.[139] prompted us to investigate the procedure of Pummerer *et al*.[140] The reaction proceeded smoothly in an aqueous Fe^{3+} solution at 50 ^{o}C in an open atmosphere for 3 h to deliver **2.130** in a 95% yield. This procedure was faster and more convenient for the synthesis of **2.130** (Scheme 2.48). The melting point, IR as well as the ^{1}H NMR data were similar to those reported in literature. [139, 140]



Scheme 2.48. Binol synthesis catalysed by Fe(III) salts.

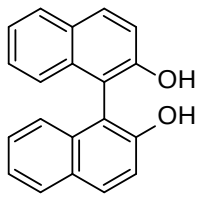
The mechanistic rationale for the formation of one molecule of **2.130** that requires 1 eq. of Fe^{3+} is shown in (Scheme 2.49). These results suggest that the radical species **2**.**131** resulting from an one-electron oxidation of **2.129** with Fe^{3+}, coupled to itself to form a new C-C bond and generate **2.132**. The final steps involve keto-enol tautomerism to regain aromaticity to form **2.130**.



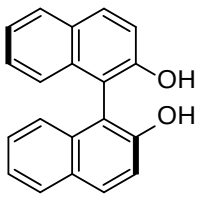
Scheme 2.49. Phenolic oxidative coupling

2.5.13.2 Synthesis of optically active BINOL

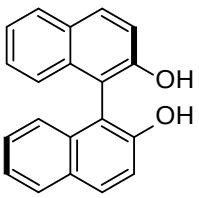
BINOL (**2.130**) was resolved into its optically active enantiomers by using (*S*)-proline **2.135**. The racemic 1,1'-bi-2-napthol (**2.130**) was reacted with borane dimethyl sulfide complex in diethyl ether at room temperature to give the intermediate **2.136.** The intermediate **2.136** was then treated with **2.135** to give the diastereomers **2.137** and **2.138** (Scheme 2.50). The diastereomers **2.137** and **2.138** were separated based on their different solubility properties. Compound **2.137** was insoluble in THF, whereas compound **2.138** was soluble in this solvent. The intermediates **2.138** and **2.139** were immediately treated separately with dilute NaOH and HCl consecutively to give the two enantiomers (*S*)-1,1'-bi-2-naphthol (**2.133**) (~91% *ee*) and (*R*)-1,1'-bi-2-naphthol (**2.134**) (~100% *ee*), respectively. Both products were optimised to their optically-pure enantiomers by "kinetic'' crystallisation. The products were obtained in about 70% overall yield.[141]



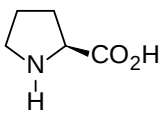
2.130



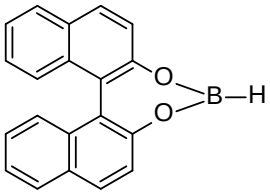
(**S**)-**BINOL 1** (**2.133**)



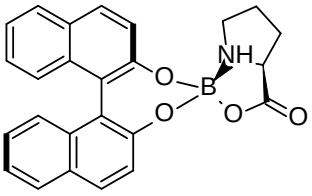
(**R**)-**BINOL 1** (**2.134**)



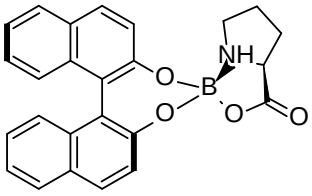
2.135



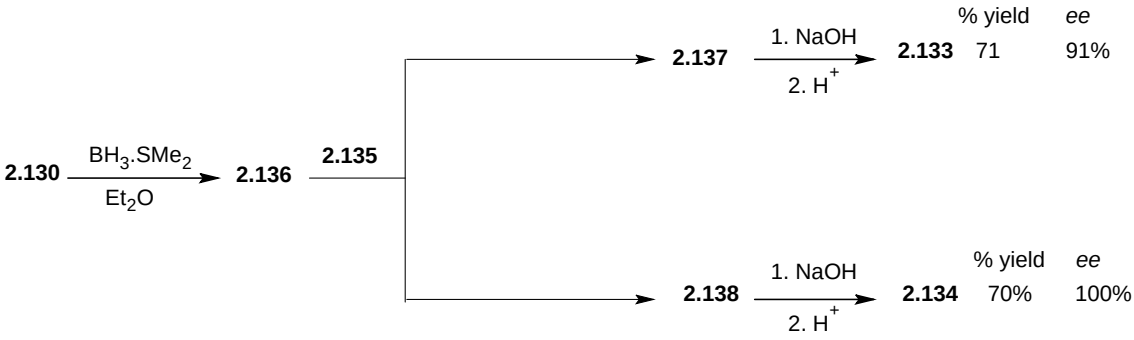
2.136



2.137



2.138



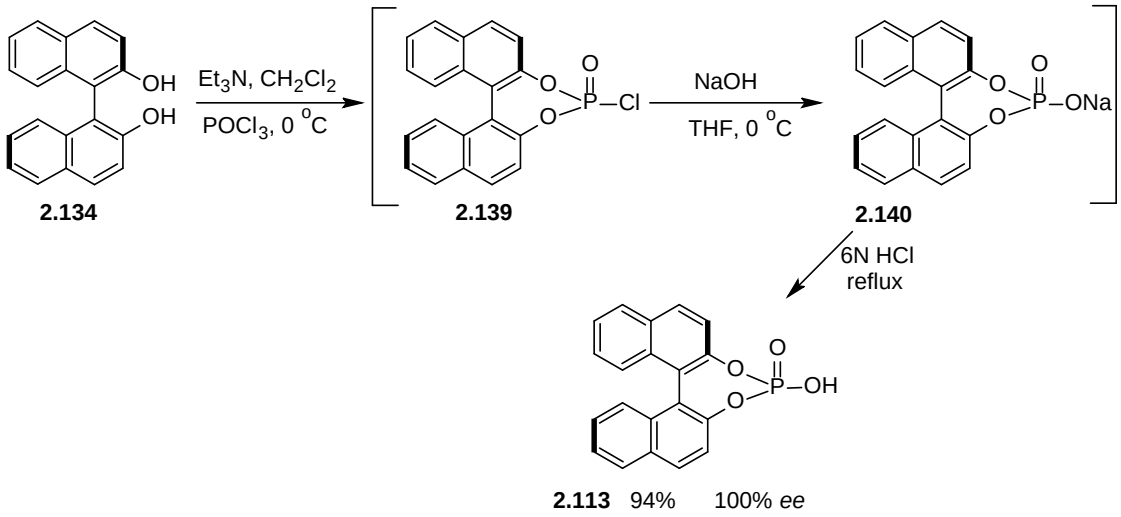
Scheme 2.50. Resolution of *r*ac-BINOL **2.130**.

2.5.13.3. Synthesis of chiral titanium and phosphoric acid catalysts

The chiral titanium catalyst **2.111** was prepared *in situ* during hydroamination reactions, by coordination of the titanium complex **2.110** with the chiral BINOL ligand **2.134**. This procedure was developed by Walsh and has been used successfully in hydroamination reactions, but the catalyst did not perform well in the present study.[142-144]

The synthesis of cyclic binaphthyl phosphoric acids from *rac*-BINOL (**2.130**) and their successful resolution *via* their cinchonine salts, was first reported by Jacques et al. in 1989.[145] The chiral phosphoric acid **2.113** was synthesised by treatment of the (*R*)-1,1'-bi-2-naphthol (**2.134**) with phosphorus oxychloride at 0 ^{o}C. The obtained 1,1'-bi-2-naphthyl-2,2'-diylphosphoryl chloride (**2.139**) was subsequently reacted with sodium hydroxide to yield chiral sodium salt **2.140**. The chiral sodium salt was treated with 6N HCl to precipitate the optically-pure (*R*)-binaphthylphosphoric acid (**2.113**) in a 94% yield and >99% *ee* (Scheme 2.51). The (*S*)-binaphthylphosphoric acid was obtained in 98% yield and 99% *ee*, with

(*S*)-BINOL **2.133** as the starting material. ^{1}H NMR data was in line with those reported in the literature.[145] The purity of the acid was confirmed by the ^{31}P NMR spectrum, which showed the presence of only one phosphorus atom.



Scheme 2.51. The preparation of (*R*)-binaphthylphosphoric acid (**2.113**).

2.6 CONCLUSION

The objective of this study was to investigate the application of modern methodologies in the synthesis of electron-rich benzyltetrahydroisoquinolines. Two synthetic routes have been explored; the intramolecular hydroamination of aminostilbenes and that of aminoalkynes. In these routes we have succeeded in synthesising the major precursors for the intramolecular hydroamination reactions, which are the aminostilbenes and aminoalkynes in moderate to good yields. These stilbenes and aminoalkynes have not been prepared previously and they may be useful as precursors in the synthesis of other natural products or biological active synthetic compounds. We have also explored different methods for the synthesis of phenethylamines, which are the starting materials for both the aminostilbenes and aminoalkynes. Of the methods studied, the Henry's reaction proved to be the most efficient method.

The attempts to cyclise the synthesised aminostilbenes into the corresponding benzyltetrahydroisoquinolines under base and metal-catalysed conditions failed after several trials. It is clear that with the current catalysts available, this reaction is not feasible with electron-rich stilbenes. However, the aminoalkynes could be successfully converted into the dihydroisoquinolines with the aid of the titanium catalysts. The enantioselective reduction of the dihydroisoquinolines with chiral phosphoric acid **2.111** was attempted without success. Although not presented in this thesis, the prepared dihydroisoquinolines can be enantioselectively reduced with Noyori's catalysts.

2.7 EXPERIMENTAL PROCEDURES

2.7.1 General Experimental Procedure

All reactions requiring inert atmosphere were performed under nitrogen in oven-dried glassware, unless otherwise stated. All solvents used for reactions and chromatography were purified and distilled prior to use. Toluene and DMF were distilled under nitrogen from sodium wire and benzophenone. Anhydrous dichloromethane, acetonitrile, tetrahydrofuran and diethyl ether were sparged with dinitrogen, and passed through an Innovative Technologies (Newburyport, MA) Pure-Solv 800 Solvent Purification System. All the required chemicals and reagents were purchased from Fluka, Sigma-Aldrich or Merck and were used without further purification. Qualitative thin-layer chromatography (TLC) was performed on pre-coated Merck aluminium sheets (silica gel 60 $PF_{254,}$ 0.25mm). After development, the plates were visualised by using UV_{254} light followed by the use of iodine, anisaldehyde or vanillin-based stains. Normal and flash chromatography were performed using Merck Kieselgel 60 (230-400 mesh) and on columns with 1 cm or 4 cm diameter. Centrifugal chromatography was performed on a Harrison Research Chromatotron Model 7924T on a glass plates coated with Merck silica gel with particle size 0.040-0.063 mm, 2-4 mm thick. The mobile phase comprised of different ratios of hexanes - ethyl acetate.

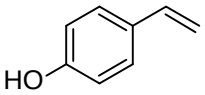
Nuclear magnetic resonance (NMR) spectra of synthesised compounds were recorded on a Bruker AVANCE DRX_{400} spectrometer and chemical shifts were referenced to the solvent shift. The solvents used more often were deuterated chloroform ($CDCl_3$, δ_H 7.26 and δ_C 77.0), and deuterated dimethyl sulfoxide [(DMSO-d_6, δ_H 2.50 and δ_C 39.43] for ^{1}H NMR and ^{13}C NMR. Chemical shifts were referenced to the solvent shifts and reported in parts per million (ppm) on the δ-scale and coupling constants were measured in Hz. Abbreviations are used as follows:

Table 2.3. Abbreviations used in describing ^{1}H NMR signal multiplicities.

Abbreviation	Signal multiplicity	Abbreviation	Signal multiplicity
s	singlet	dd	doublet of doublets
d	doublet	br	broadened
t	triplet	m	multiplet
q	quartet		

Electron impact (EI) mass spectra (MS) were obtained using a PolarisQ Thermo Finnigan GC-MS spectrometer by direct insertion technique with a 70 eV electron beam and high resolution (HR) on a VG Autospec spectrometer. Electrospray (ES) MS were recorded on a Waters Premier LCT spectrometer using nitrogen as carrier gas. IR spectra were recorded on a Perkin-Elmer FTIR spectrometer using an attenuated total reflection (ATR) method or KBr pellet.

2.7.2 4-Hydroxyphenethene (2.66)



Method A

To a solution of 4-hydroxybenzaldehyde (**2.64**) (0.61 g, 5 mmol) and malonic acid (2.08 g, 20 mmol) in pyridine (21 mL) was added piperidine (0.75 mL, 7.6 mmol). The stirred reaction solution was refluxed (115 ^{o}C) for 4 h, followed by cooling to

room temperature. To the cooled reaction mixture, toluene (40 mL) was added and the solvent was evaporated *in vacuo* at 30-40 ^{o}C. Additional toluene (20 mL) was then added and the solvent again removed *in vacuo* eliminating all traces of pyridine to afford **2.66** as a brown oil (0.36 g, 60%).

Method B

A mixture of 4-hydroxybenzaldehyde (**2.64**) (0.61 g, 5 mmol), malonic acid (2.08 g, 20 mmol), piperidine (0.50 mL, 5 mmol) and acetic acid (10 mL) was shaken well and irradiated in a focused monomode microwave system and refluxed for 5-10 minutes (150 W, 130 ^{o}C). The cooled mixture was poured into ice-cold water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with a saturated sodium chloride solution and dried over sodium sulfate. The solvent was evaporated under reduced pressure to obtain a viscous liquid, which was purified by a silica gel column chromatography using a mixture of hexanes and ethyl acetate (2:1) to provide the corresponding vinylphenol **2.66** (0.34 g, 56%).

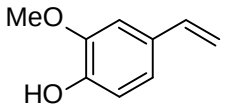
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.27 (2H, d, *J* = 8 Hz, H-2,6), 6.79 (2H, d, *J* = 8 Hz, H-3,5), 6.59 (1H, dd, *J* = 17.4 and 11.0 Hz, $\underline{H}C=CH_2$), 5.59 (1H, dd, *J* = 17.4 and 1.0 Hz, $HC=C\underline{H}_2$), 5.14 (1H, dd, *J* = 11.0 and 1.0 Hz, $HC=C\underline{H}_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 156.3 (C-4), 137.5 ($\underline{C}H=CH_2$), 131.9 (C-1), 128.9 (C-2,6), 115.6 (C-3,5), 112.5 ($C=\underline{C}H_2$)

IR ν_{max} (cm^{-1}): 3359, 3087, 2979, 1607, 1510, 1441, 1371, 1221, 991, 899, 834

LRMS-ES^{+} (*m*/*z*): [M^{+}] 120 amu.

2.7.3 4-Hydroxy-3-methoxyphenethene (2.67)



The styrene **2.67** was prepared from the 3-hydroxy-4-methoxybenzaldehyde **2.65** according to the procedures described in §2.7.2. The product was obtained as a yellow oil in 65% and 60% yields by method A and B, respectively.

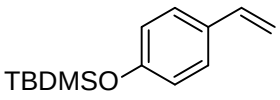
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.93 (1H, d, *J* = 2 Hz, H-2), 6.89 (1H, dd, *J* = 2, 8 Hz, H-6), 6.54 (1H, d, *J* = 8 Hz, H-5), 6.62 (1H, dd, *J* = 17.5 and 11.0 Hz, , $HC=CH_2$), 5.61 (1H, dd, *J* = 17.5 and 1.0 Hz, , $HC=CH_2$), 5.18 (1H, dd, *J* = 11.0 and 1.0 Hz, , $HC=CH_2$), 3.89 (3H, s, OCH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 146.7 (C-3), 145.7 (C-4), 136.7(C=C), 130.6 (C-1), 120.5 (C-6), 114.6 (C-5), 111.6 (C-2), 108.7 (C=C), 55,9 (OCH_3)

IR ν_{max} (cm^{-1}): 3416, 2935, 1604, 1511, 1463, 1430, 1268, 1220,1152, 1121, 1029, 989, 899, 854, 819, 773

LRMS-ES$^+$ (*m*/*z*): [M^+] 151 amu.

*2.7.4 4-*tert-*Butyldimethylsilyloxyphenethene (2.72)*



Tert-Butyldimethylsilyl chloride (1.5 g, 10 mmol) was stirred for 10 min in DMF (20 mL). To this solution DIA (1.4 mL, 10 mmol) was added dropwise and allowed to stir for 10 min. Styrene **2.66** (1.2 g, 10 mmol) was then added with further stirring

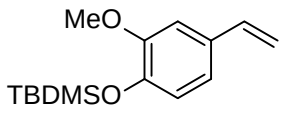
for 1 h. The reaction was quenched by addition of water (20 mL) and extracted with DCM (3 x 15 mL). The organic layers were combined, washed with water, brine and dried with anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography with a mixture of petroleum ether and diethyl ether (9:1) to give **2.72** as a brown oil (0.82 g, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.34 (2H, d, *J* = 8.4 Hz, H-2,6), 6.86 (2H, d, *J* = 8.4 Hz, H-3,5), 6.71 (1H, dd, *J* = 17.4 and 11.0 Hz, C<u>H</u>=CH_2), 5.66 (1H, dd, *J* = 17.4 and 1.0 Hz, CH=C<u>H</u>$_2$), 5.18 (1H, dd, *J* = 11.0 and 1.0 Hz, CH=C<u>H</u>$_2$), 1.05 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.26 (6H, s, (Si(C<u>H</u>$_3$)$_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 155.6 (C-4), 136.4 (<u>C</u>H=CH_2), 131.1 (C-1), 127.4 (C-2,6), 120.1 (C-3,5), 111.7 (CH=<u>C</u>H$_2$), 25.7 (C(<u>C</u>H$_3$)$_3$), 18.5 (<u>C</u>(CH$_3$)$_3$), -4.4 (Si(<u>C</u>H$_3$)$_2$)

IR ν_{max} (cm^{-1}): 2957, 2930, 2859, 1629, 1603, 1508, 1472, 1252, 1169, 1107, 988, 909, 836, 809, 778.

*2.7.5 4-*tert*-Butyldimethylsilyloxy-3-methoxyphenethene (2.73)*



Compound **2.67** was protected with TBDMSCl according to the procedure in **2.7.4** to give **2.73** as a yellow oil in 40% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.97 (1H, d, *J* = 2.0 Hz, H-2), 6.91 (1H, dd, *J* = 2.0 and 8.1 Hz, H-6), 6.84 (1H, d, *J* = 8.1 Hz, H-5), 6.68 (1H, dd, *J* = 17.5 and 11.0 Hz, C<u>H</u>=CH_2), 5.64 (1H, dd, *J* = 17.5 and 1.0 Hz, CH=C<u>H</u>$_2$), 5.17 (1H, dd, *J* = 11 and 1.0 Hz,

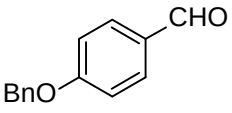
CH=C$\underline{H}_2$), 3.86 (3H, s, OCH_3), 1.04 (9H, s, C($C\underline{H}_3$)$_3$), 0.20 (6H, s, (Si($C\underline{H}_3$)$_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 151.0 (C-4), 145.2 (C-3), 136.7 (H$\underline{C}$=C), 131.6 (C-1), 120.8 (C=CH_2), 119.4 (C-6), 111.7 (C-5), 109.7 (C-2), 55.5 (OCH_3), 25.7 (C($\underline{C}H_3$)$_3$), 18.5 ($\underline{C}$(CH_3)$_3$), -4.6 (Si($\underline{C}H_3$)$_2$)

IR ν_{max} (cm^{-1}): 2955, 2930, 2857, 1600, 1575, 1508, 1464, 1277, 1234, 1156, 1126, 933, 889, 837, 779

HRMS-ES$^+$ (*m*/*z*): Found 287.1441 $[M+Na]^+$, calculated for $[C_{15}H_{24}O_2SiNa]$ 287.1443.

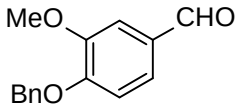
2.7.6 4-Benzyloxybenzaldehyde (2.76)



K_2CO_3 (16.3 g, 118.20 mmol) and benzyl bromide (9.85 mL, 78.80 mmol) were added to a stirred solution of 4-hydroxybenzaldehyde (**2.64**) (4.8 g, 39.40 mmol) in dry CH_3CN (20 mL) at room temperature. The reaction mixture was refluxed for 12 h after which TLC showed no starting material remaining. The product was acidified with HCl (10 mL, 3 M), extracted with ethyl acetate (3 x 20 mL) and washed with water (25 mL). The organic phase was dried under anhydrous Na_2SO_4 and purified on silica gel column using hexanes:EtOAc (8:2) solvent mixture. The product was obtained as a white solid (7.5 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.89 (1H, s, CHO), 7.84 (2H,d, *J* = 8.6 Hz, H-2′,6′), 7.47-7.32 (5H, m, $\underline{Ph}CH_2O$), 7.08 (2H, d, *J* = 8.6 Hz, H-3′,5′), 5.16 (2H, s, PhC$\underline{H}_2$O).

2.7.7 4-Benzyloxy-3-methoxybenzaldehyde (2.77)



Vanillin (**2.65**) was benzylated following the procedure in **2.7.5** to give compound **2.76** as a white solid in 95% yield. The product was recrystallised from methanol.

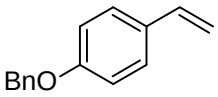
Mp: 65.5 - 66.4 ^{o}C. Lit. 64 ^{o}C - 65^{o}C[146]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.84 (1H, s, ArC<u>H</u>O) 7.45-7.32 (7H, m, H-2′, H-6′, <u>Ph</u>CH_2O-), 6.99 (1H, d, *J* = 8.3 Hz, H-5′), 5.25 (2H, s, PhC<u>H</u>$_2$O), 3.95 (3H, s, OCH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 190.9 (Ar<u>C</u>HO), 153.6 (C-4′), 150.16 (C-3′), 130.3 (C-1′) 136.3, 127.7 and 127.3 (<u>Ph</u>CH_2O), 126.5 (C-6′), 112.6 (C-2′), 109.6 (C-5), 70.9 (Ph<u>C</u>H_2O), 56.09 (OCH_3)

GC-MS *m/z*: 240 (M^+, 45), 149 (25), 121 (10), 91 (100).

2.7.8 4-Benzyloxyphenethene (2.74)



Method A

Benzyl bromide (2.4 mL, 20.4 mmol) was added to a mixture of 4-hydroxyphenethene (**2.66**) (2.0 g, 17 mmol) and K_2CO_3 (6.9 g, 49 mmol) in dry DMF (20 mL). The mixture was stirred at 50 ^{o}C for 12 h, acidified with HCl (20 mL, 0.5 M) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with water (25 mL), followed by a brine solution, dried over anhydrous

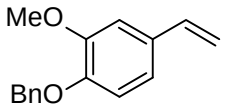
Na_2SO_4 and concentrated under vacuum to give the styrene **2.62** as cream-white solid in a 42% yield (1.5 g).

Method B

A mixture of methylphosphonium iodide (10.02 g, 24.47 mmol) and ^{t}BuOK (2.99 g, 26.67 mmol) in dry THF (30 mL) was stirred for 30 minutes. **2.76** (3.5 g, 16.51 mmol) was then added to the resulting suspension and stirring was continued for 3 h at room temperature. The reaction mixture was diluted with water and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (2 x 50 mL), brine, dried ($MgSO_4$) and concentrated. Silica gel column chromatography of crude product using hexanes:EtOAc (8:2) as eluent gave the product **2.62** (2.4 g, 70%) as colourless oil which eventually solidified to give a white solid after evaporation of the solvent.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H:	7.45-7.30 (7H, m, PhCH_2O and H-2,6), 6.94 (2H, d, *J* = 8.7 Hz, H-3,5), 6.67 (1H, dd, *J* = 17.4 and 11.0 Hz, CH=CH_2), 5.61 (1H, d, *J* = 17.4 Hz, ArCH=CH_2), 5.13 (1H, d, *J* = 11 Hz, ArCH=CH_2), 5.10 (2H, s, PhCH_2O)
^{13}C NMR (100 MHz, $CDCl_3$) δ_C:	158.6 (C-4), 136.9 (PhCH_2O), 136.2 (C-1), 130.7 (ArCH=CH_2), 128.6 (PhCH_2O), 127.9(PhCH_2O), 127.4 (PhCH_2O), 127.3 (C-2,6), 114.9 (C-3,5), 111.7 (ArCH=CH$_2$), 70.1(PhCH$_2$O)
IR ν_{max} (cm^{-1}):	3037, 1627, 1605, 1573, 1509, 1453, 1381, 1237, 1170, 1040, 1023, 996, 898, 835, 730, 695
HRMS-ES^{+} (*m*/*z*):	Found 211.1124 $[M+H]^{+}$; calculated for $C_{15}H_{15}O$ 211.1123.

2.7.9 4-Benzyloxy-3-methoxyphenethene (2.75)



Benzyloxystyrene **2.74** was prepared from **2.67** according to the procedures in **2.6.2.7**. The title compound was obtained as a yellow solid in 47% and 80% yields by method A and method B, respectively.

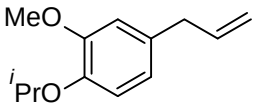
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.43 (2H, d, *J* = 8.0 Hz, PhCH_2O), 7.36 (2H, t, *J* = 8.0 Hz, PhCH_2O), 7.30 (1H, t, *J* = 8.0 Hz, PhCH_2O), 6.99 (1H, d, *J* = 2.0 Hz, H-2), 6.88 (1H, dd, *J* = 8.3 and 2.0Hz, H-6), 6.84 (1H, d, *J* = 8.3 Hz, H-5), 6.64 (1H, dd, *J* = 10.9 and 17.6 Hz, CH=CH_2), 5.61 (1H, d, *J* = 17.6 Hz, CH=CH_2), 5.16 (2H, s, PhCH_2O), 5.14 (1H, d, *J* = 17.6 Hz, CH=CH_2), 3.92 (3H, s, OCH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 149.8 (C-3), 148.2 (C-4), 137.1 (CH=CH_2), 136.5 (PhCH_2O), 131.3(C-1), 128.5 (PhCH_2O), 127.8 (PhCH_2O), 127.3 (PhCH_2O), 119.3 (C-6), 114.0 (ArCH=CH_2), 112.0 (C-5), 109.4 (C-2), 71.1 (PhCH_2O), 56.0 (OCH_3)

IR ν_{max} (cm^{-1}): 3035, 1576, 1599, 1509, 1468, 1457, 1417, 1260, 1225, 1159, 1139, 1001, 987, 892, 849, 808, 745, 695

HRMS-ES$^+$ (*m*/*z*): Found 263.1048 $[M+Na]^+$; calculated for $[C_{16}H_{16}O_2Na]$ 263.1048.

2.7.10 (4-Isopropoxy-3-methoxyphenyl)propene (2.82)

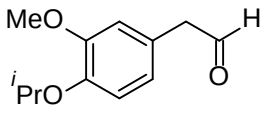


Isopropyl bromide (6.4 ml, 0.049 mmol) was added to a mixture of eugenol (**2.81**) (5 g, 41.0 mmol) and K_2CO_3 (16.9 g, 122.0 mmol) in dry CH_3CN (20 ml) and the reaction mixture was refluxed for 12 h. The reaction mixture was extracted with EtOAc (3 x 20 mL) and the organic phases were washed with water (25 mL), followed by brine solution, dried under anhydrous Na_2SO_4 and concentrated under vacuum to afford the product **2.82** (5.3 g, 87%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.84 (1H, d, *J* = 8.1 Hz, H-5), 6.72 (1H, d, *J* = 2.0 Hz, H-2), 6.69 (1H,dd, *J* = 8.6 and 2.0 Hz, H-6), 5.97 (1H, m, $ArCH_2C\underline{H}=CH_2$), 5.09 (2H, m, $ArCH_2CH=C\underline{H}_2$), 4.47 (1H, m, $OC\underline{H}(CH_3)_2$), 3.87 (3H, s, OCH_3), 3.34 (2H, d, *J* = 6.7 Hz, $ArC\underline{H}_2CH=CH_2$), 1.35 (6H, d, *J* = 6.1 Hz, $OCH(C\underline{H}_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 150.5 (C-3), 145.6 (C-4), 137.7 ($ArCH_2\underline{C}H=CH_2$), 133.3 (C-1), 120.5 (C-5), 116.4 (C-2), 115.6 (C-6), 112.7 ($ArCH_2CH=\underline{C}H_2$), 71.7 ($O\underline{C}H(CH_3)$), 55.9 ($OCH_3$), 39.9 ($Ar\underline{C}H_2CH=CH_2$), 22.2 ($OCH(\underline{C}H_3)$).

2.7.11 (4-Isopropoxy-3-methoxyphenyl)acetaldehyde (2.83)



3-(3-Methoxy-4-isopropoxyphenyl)propene (**2.82**) (1.00 g, 6.8 mmol) was dissolved in methanol (0.7 mL) and dichloromethane (16 ml) in a three–necked flask fitted with a reflux condenser and attached to an ozone generator. Two traps containing acidified 1.1 M KI solutions (110 mL acidified with 10 mL glacial acetic acid) were connected to the outlet of the three–necked flask in order to react with any unreacted ozone. The reaction mixture was cooled using a solid CO_2/acetone bath. Ozone was then bubbled through the stirred mixture for 20 min at a rate of

ca.1 mL/min. Dimethyl sulfide (5 mL) was added and the mixture was allowed to slowly warm to room temperature overnight. DCM (16 mL) was added and the volatiles were evaporated under reduced pressure to afford **2.83** as colourless oil (0.51 g, 50%).

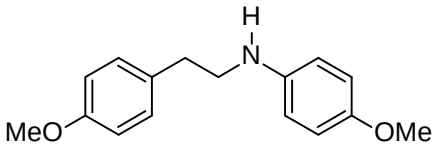
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.72 (1H, t, C<u>H</u>O), 6.88 (1H, d, *J* = 8.7 Hz, H-5), 6.73 (2H, m, H-2,6), 4.51 (1H, m, OC<u>H</u>$(CH_3)_2$), 3.84 (3H, s, OCH_3), 3.60 (2H, d, *J* = 2.7 Hz, Ar<u>C</u>H_2), 1.36 (6H, d, *J* = 7.0 Hz, OCH(<u>C</u>$H_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 199.5 (CHO), 150.8 (C-3), 146.8 (C-4), 124.6 (C-1), 121.8 (C-6), 116.4 (C-5), 113.5 (C-2), 71.6 (O<u>C</u>H$(CH_3)_2$), 55.9 (OCH_3), 50.1 (Ar<u>C</u>H_2), 22.1 (O<u>C</u>H$(CH_3)_2$)

IR ν_{max} (cm^{-1}): 2976, 2934, 1722, 1589, 1509, 1465, 1420, 1383,1373, 1259, 1231, 1136, 1107, 1034, 952, 808, 772

HRMS-ES$^+$ (*m*/*z*): Found 209.1169 $[M+H]^+$; calculated for $[C_{12}H_{17}O_3]$ 209.1168.

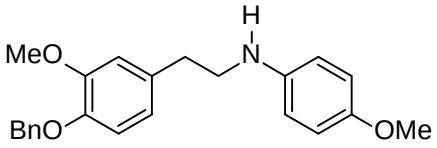
2.7.12 N-*[2-(4-Methoxyphenyl)ethyl]-4-methoxyaniline (2.87)*



A mixture of styrene **2.85** (0.13 g, 0.962 mmol), *p*-anisidine (**2.86**) (1.18 g, 9.62 mmol) and potassium *tert*-butoxide (^{t}BuOK) (0.11 g, 0.962 mmol) was heated in a domestic microwave (1000 W, 70% of total power in an open flask) until no starting styrene was observed by TLC (10 min.). The crude reaction mixture was purified by column chromatography on silica gel to give phenethylamine **2.87** in 37% (0.09 g) yield as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.13 (2H, d, *J* = 8.3 Hz, H-3,5), 6.90 (2H, d, *J* = 8.4 Hz, H-3',5'), 6.84 (2H, d, *J* = 8.3 Hz, H-2,6), 6.81 (2H, d, *J* = 8.4 Hz, H-2',6'), 3.79 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.36 (2H, t, *J* = 6.9 Hz, $ArCH_2C\underline{H}_2N$), 2.93 (2H, t, *J* = 6.9 Hz, $ArC\underline{H}_2CH_2N$).

2.7.13 **N-*[2-(4-Benzyloxy-3-methoxyphenyl)ethyl]-4-methoxyaniline (2.88)***



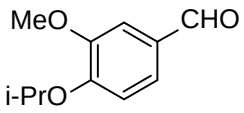
Phenethylamine **2.88** was prepared in 43% yield from styrene **2.75** and *p*-anisidine (**2.86**) according to the procedure in **2.7.12**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.49 (2H, d, *J* = 8.2 Hz, $PhCH_2O$), 7.37 (2H, t, *J* = 8.2 Hz, $PhCH_2O$), 7.32 (1H, t, *J* = 8.2 Hz, $PhCH_2O$), 6.87 (1H, d, *J* = 8.3 Hz, H-5), 6.80 (2H, d, *J* = 8.4 Hz, H-2',6'), 6.76 (1H, d, *J* = 2.0 Hz, H-2), 6.71 (1H, dd, *J* = 8.4 and 2.0 Hz, H-6), 6.59 (2H, d, *J* = 8.3 Hz, H-3',5'), 5.16 (2H, s, $PhCH_2O$), 3.88 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.36 (2H, t, *J* = 6.9 Hz, $ArCH_2C\underline{H}_2N$), 2.85 (2H, t, *J* = 6.9 Hz, $ArC\underline{H}_2CH_2N$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 152.3 (C-3), 149.8 (C-4), 142.3 (C-4´), 137.4 ($\underline{Ph}CH_2O$), 132.7 (C-1), 128.6 ($\underline{Ph}CH_2O$), 127.9 ($\underline{Ph}CH_2O$), 127.1 ($\underline{Ph}CH_2O$), 120.8 (C-6), 115.1 (C-5), 114.6 (C-2´,6´), 114.5 (C-3´,5´), 112.8 (C-2), 71.3 ($PhC\underline{H}_2O$), 56.1 (OCH_3), 55.8 (OCH_3), 46.1 ($ArCH_2\underline{C}H_2NHR$), 35.1 ($Ar\underline{C}H_2CH_2NHR$)

HRMS-ES$^+$ (*m*/*z*): Found 386.1731 $[M+Na]^+$; calculated for $[C_{23}H_{25}NO_3Na]$ 386.1732.

2.7.14 4-Isopropoxy-3-methoxybenzaldehyde (2.91)

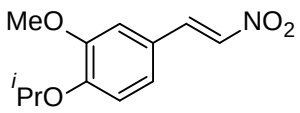


Vanillin (**2.65**) (2 g, 13.14 mmol), 2-bromopropane (19.72 mmol), and K_2CO_3 (39.44 mmol) were refluxed in CH_3CN (50 mL) for 12 h. The mixture was filtered, diluted with Et_2O (30 mL) and washed with water (20 mL). The aqueous layer was extracted with Et_2O (2 x 30 mL), the combined organic layer was washed with water (2 x 50mL) and brine (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography using hexanes:EtOAc (7:3) to afford **2.91** as a white solid in quantitative yield (2.55 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.82 (1H, s, CHO), 7.41 (2H, overlapp, H-2,6), 6.96 (1H, d, *J* = 8.0 Hz, H-5), 4.67 (1H, m, OC<u>H</u>$(CH_3)_2$), 3.89 (3H, s, OCH_3), 1.41 (6H, d, *J* = 6.1 Hz, OCH(C<u>H</u>$_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 190.7 (<u>C</u>HO), 153.1 (C-4), 150.4 (C-3), 129.8 (C-1), 126.4 (C-6), 112.9 (C-5), 109.7 (C-2), 71.3 (O<u>C</u>H$(CH_3)_2$), 55.9 (OCH_3), 21.8 (OCH(<u>C</u>H$_3)_2$).

2.7.15 E-4-Isopropoxy-3-methoxy-β-nitrophenethene (2.92)



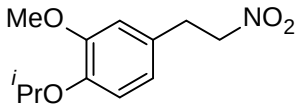
A solution of KOH (10 mL, 20%) was added to the aldehyde **2.91** (1.0 g, 5.15 mmol) and nitromethane (5 mL, 93.5 mmol) in methanol (20 mL) at 0 ^{o}C with

continuous stirring. The reaction mixture was stirred for 2 h, when TLC showed no starting material remaining. The reaction mixture was added into HCl (100 ml, 15%) to precipitate. The excess acid was removed by rinsing the precipitate with water and the product **2.92** was obtained by recrystallisation from methanol as yellow crystals (0.93 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.96 (1H, d, *J* = 13.6 Hz, C<u>H</u>=CHNO$_2$), 7.52 (1H, d, *J* = 13.6 Hz, CH=C<u>H</u>NO$_2$), 7.14 (1H, dd, *J* = 8.4 and 2.1 Hz, H-6), 7.00 (1H, d, *J* = 2.0 Hz, H-2), 6.91 (1H, d, *J* = 8.4 Hz, H-5), 4.64 (1H, m, OC<u>H</u>(CH$_3$)$_2$), 3.89 (3H, s, OCH$_3$), 1.41 (6H, d, *J* = 6.1 Hz, OCH(C<u>H</u>$_3$)$_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 151.5 (C-3), 150.5 (C-4), 139.4 (C-1), 135.1 (Ar<u>C</u>H=CHNO$_2$), 124.4 (C-6), 122.6 (ArCH=<u>C</u>HNO$_2$), 114.3 (C-5), 111.2 (C-2), 71.5 (O<u>C</u>H(CH$_3$)$_2$), 56.2 (OCH$_3$), 22.0 (O<u>C</u>H(CH$_3$)$_2$).

2.7.16 1-Isopropoxy-2-methoxy-4-(2-nitroethyl)benzene (2.93)



The unsaturated nitro compound **2.92** (0.9 g, 3.8 mmol) was dissolved in EtOH (20 mL) cooled to 0 ^{o}C, then $NaBH_4$ (0.497 g, 13.1 mmol) was added portion wise and stirred for 2 h at the same temperature. The solvent was removed under reduced pressure and the residue was quenched with saturated NH_4Cl solution and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated i*n vacuo*, and purified by chromatography to give the nitro compound **2.93** as a colourless oil in a 70% yield (0.64 g).

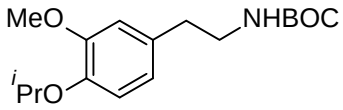
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.86 (1H, d, *J* = 8.3 Hz, Ar), 6.73 (1H, dd, *J* = 2.0 and 8.3 Hz, Ar), 6.72 (1H, d, *J* = 2.0 Hz, Ar),

4.60 (2H, t, *J* = 7.4 Hz, $ArCH_2C\underline{H}_2NO_2$), 4.49 (1H, t, *J* = $OC\underline{H}(CH_3)$), 3.85 (3H, s, OCH_3), 3.27 (2H, t, *J* = 7.4 Hz, $ArC\underline{H}_2CH_2NO_2$), 1.37 (3H, s, $OCH(C\underline{H}_3)_2$) 1.36 (3H, s, $OCH(C\underline{H}_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 151.0 (C-3), 146.0 (C-4), 128.6 (C-1), 120.7 (C-6), 116.0 (C-5), 112.5 (C-2), 71.7 ($O\underline{C}H(CH_3)$), 55.9 (OCH_3), 33.2 ($\underline{C}H_2\underline{C}H_2NO_2$), 22.1 ($OC(\underline{C}H_3)_2H$)

LRMS-ES^+ (*m*/*z*): $[M - H]^+$ 238.

2.7.17 [2-(4´-Isopropoxy-3´-methoxyphenyl)ethyl]carbamic acid tert-*butyl ester (2.94)*



Method A

To a suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in dry THF (20 mL), **2.92** (0.85 g, 3.58 mmol) was added portion-wise at 0 ^oC under nitrogen atmosphere and the mixture was refluxed for 7 h. The mixture was cooled to 0 ^oC and quenched carefully with water (5 mL) and 10% aqueous NaOH (5 mL), then $(Boc)_2O$ (0.943 g, 4.29 mmol) in THF (10 mL) was added and stirring was continued for 4 h at room temperature. On completion, the reaction mixture was filtered and washed with EtOAc, the filtrate was dried over $MgSO_4$, concentrated *in vacuo* and crude residue was purified by chromatography to give the product **2.94** (0.52 g, 47%) as a colourless oil.

Method B

To a suspension of $LiAlH_4$ (0.24 g, 6.27 mmol) in dry THF (20 mL), a solution of **2.93** (0.50 g, 2.09 mmol) in THF (5 mL) was added dropwise at 0 ^oC under

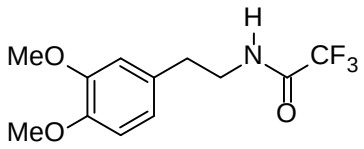
nitrogen atmosphere and the mixture was stirred at room temperature for 16 h. The mixture was cooled to 0 ^{o}C and quenched carefully with water (5 mL) and 10% aqueous NaOH (5 mL), then $(Boc)_2O$ (0.684 g, 3.13 mmol) in THF (10 mL) was added and stirring was continued for 4 h at room temperature. On completion, the reaction mixture was filtered and washed with EtOAc, the filtrate was dried over $MgSO_4$, concentrated *in vacuo* and crude residue was purified by chromatography to give the product **2.94** (0.31 g, 47%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.82 (1H, d, *J* = 8.7 Hz, H-5), 6.71 (1H, d, *J* = 8.7 Hz, H-2), 6.69 (1H, dd, *J* = 8.6 and 2.0 Hz, H-6), 4.47 (2H, m, OC<u>H</u>$(CH_3)_2$ and NH), 3.84 (s, 3H, OCH_3), 3.35 (2H, t, *J* = 7.4 Hz, $ArCH_2C\underline{H}_2N$), 2.73 (t, *J* = 7.0 Hz, 2H, $ArC\underline{H}_2CH_2N$), 1.44 (9H, s, $NCO_2C(\underline{C}H_3)_3$), 1.35 (3H, d, *J* = 6.1 Hz, $OCH(C\underline{H}_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 155.9 ($N\underline{C}O_2C(CH_3)_3$), 150.5 (C-3), 145.9 (C-4), 132.1 (C-1), 120.7 (C-6), 116.4 (C-5), 112.8 (C-2), 71.7 ($O\underline{C}H(CH_3)$), 55.9 (OCH_3), 28.4 ($C(\underline{C}H_3)_3$),18.4 ($\underline{C}(CH_3)_3$)22.1 ($OCH(\underline{C}H_3)_2$)

HRMS-ES^{+} (*m*/*z*): Found 332.1841 $[M+Na]^{+}$; calculated for $[C_{17}H_{27}NO_4Na]$ 332.1838.

2.7.18 N-*[2-(3,4-Dimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (2.96)*



Ethyl trifluoroacetate (2.88 g, 20.3 mmol) was added dropwise to a solution of homoveratrylamine (**2.95**) (3.00 g, 16.6 mmol) in THF (50 mL) at 25 ^{o}C. The mixture was stirred at 25 ^{o}C for 2 h. Evaporation of the solvent under vacuum gave the compound **2.96** (4.20 g, 95%) as a white solid.

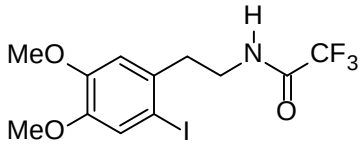
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.85 (1H, d, *J* = 8.0 Hz, H-5), 6.74 (1H, dd, *J* = 8.4 and 1.9 Hz, H-6), 6.70 (1H, d, *J* = 8.0 Hz, H-2), 6.30 (1H, brs, $\underline{H}NCOCF_3$), 3.88 (6H, s, OCH_3), 3.64-3.59 (2H, m, $ArCH_2C\underline{H}_2NHC{=}O$), 2.85 (2H, t, *J* = 7.0 Hz, $ArC\underline{H}_2CH_2NHC{=}O$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 157.8 (q, *J* = 37 Hz, C=O), 149.4 (C-4), 148.4 (C-3), 130.2 (C-1), 120.7 (C-5), 115.8 (q, *J* = 288 Hz, CF_3), 111.8 (C-2), 111.7 (C-6), 55.9 (OCH_3 x 2), 41.1 (CH_2), 34.4 (CH_2)

IR ν_{max} (cm^{-1}): 3320, 2935, 1698, 1567, 1513, 1444, 1347, 1261, 1219, 1179, 1154, 1027, 805, 772, 695

HRMS-ES$^-$ (*m*/*z*): Found 300.0821 $[M + Na]^+$; calculated for $[C_{12}H_{14}F_3NO_3Na]$ 300.0823.

*2.7.19 2,2,2-Trifluoro-*N*-[2-(2-iodo-4,5-dimethoxyphenyl)ethyl]acetamide (2.97)*



A solution of trifluoroacetamide **2.96** (2 g, 7.2 mmol), I_2 (0.73 g, 2.88 mmol), and HIO_3 (0.25 g, 1.42 mmol) in a 3:1 mixture of MeOH/H_2O (50 mL) was heated to 85 ^{o}C for 48 h. After concentration under vacuum, the residue was dissolved in CH_2Cl_2 (30 mL). The solution was washed with aqueous Na_2SO_3 (5%, 20 mL), H_2O (40 mL) and brine (40 mL). The combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification with chromatography, the aryl iodide (2.55 g, 88%) was obtained as a white solid.

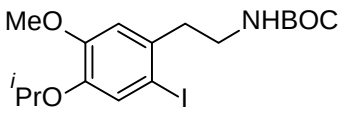
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.24 (1H, s, H-3), 6.71 (1H, s, H-6), 6.39 (1H, brs, NH), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3) 3.59-3.64 (2H, m, $ArCH_2C\underline{H}_2N$), 2.99 (2H, t, *J* = 7.0 Hz, $ArC\underline{H}_2CH_2N$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 157.1 (q, $J_{C\text{-}F}$ = 37 Hz, CF_3), 149.7 (C-4), 148.6 (C-3), 132.7 (C-1), 121.8 (C-5), 115.7 (q, $J_{C\text{-}F}$ = 288 Hz, CF_3), 112.5 (C-2), 111.66 (C-6), 55.90 (OCH_3 x 2), 41.1 (CH_2), 34,4 (CH_2)

IR ν_{max} (cm^{-1}): 3304, 2932, 1701, 1563, 1508, 1437, 1379, 1258, 1207, 1175, 1159, 1026, 774, 710

HRMS-ES$^-$ (*m*/*z*): found 425.9788 $[M+Na]^+$; Calculated for $[C_{12}H_{13}F_3INO_3Na]$ 425.9790.

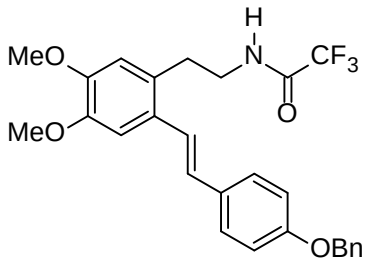
2.7.20 [2-(2´-Iodo-4´-isopropoxy-5´-methoxyphenyl)ethyl]carbamic acid tert-*butyl ester (2.98)*



Compound **2.94** was iodinated following the procedure in **2.7.19** to give iodophenethylamine **2.98** in 69% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.59 (1H, s, H-3), 6.74 (1H, s, H-6), 4.58 (1H, brs, $N\underline{H}CO$), 4.46 (1H, m, $OC\underline{H}(CH_3)_2$), 3.82 (3H, s, OCH_3), 3.33 (2H, q, *J* = 7.0 Hz, $ArCH_2C\underline{H}_2N$), 2.85 (2H, t, *J* = 7.0 Hz, $ArC\underline{H}_2CH_2N$), 1.44 (9H,s, $OC(C\underline{H}_3)_3$), 1.34 (6H, d, *J* = 6.0 Hz, $OCH(C\underline{H}_3)_2$).

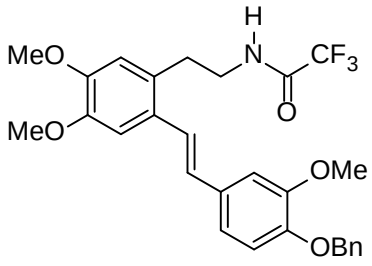
2.7.21 N-*(2-{2-[*E*-2-(4-Benzyloxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (2.99)*



To a stirred solution of aryl iodide **2.97** (0.3 g, 0.74 mmol) in acetonitrile, triethylamine (3 mL), styrene **2.74** (0.23 g, 1.09 mmol), palladium acetate (16 mg, 0.071 mmol) and triphenylphosphine (32 mg, 0.122 mmol) were added. The reaction mixture was stirred at room temperature for 1 h and then the temperature was increased to 95 ^{o}C. After 4 h of heating, a further equivalent of aryl iodide (0.3 g, 0.74 mmol) was added and stirring was further continued for 16 h. The reaction was monitored by the disappearance of styrene by TLC. The reaction mixture was quenched by addition of water (10 mL) and extracted with ethyl acetate (20 mL) and diethyl ether (3 x 20 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography and the stilbene **2.99** was obtained in a 35% yield (0.18 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.47 (2H, d, *J* = 8.5 Hz, H-2´,6´), 7.45-7.35 (m, 5H, PhCH_2O), 7.16 (1H, d, *J* = 15.9 Hz, CH=CH), 7.13 (1H, s, H-3), 6.71 (2H, d, *J* = 8.5 Hz, H-3´,5´), 6.89 (1H, d, *J* = 15.9 Hz, CH=CH), 6.65 (1H, s, H-6), 6.33 (brs, 1H, NH), 5.12 (2H, s, PhCH_2O), 3.96 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.59 (2H, m, ArCH_2CH_2N), 3.02 (2H, t, *J* = 6.7 Hz, ArCH_2CH_2N).

2.7.22 N-*(2-{2-[*E*-2-(4-Benzyloxy-3-methoxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (2.100)*

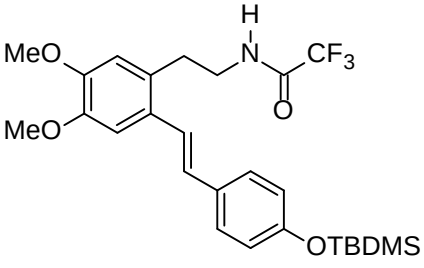


The stilbene **2.100** was synthesised in a 30% yield by the Heck reaction of aryl iodide **2.97** and styrene **2.75** according to the procedure in **2.7.21**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.45 (2H, d, *J* = 7.1 Hz, PhCH_2O), 7.37 (2H, t, *J* = 7.1 Hz, PhCH_2O), 7.32 (1H, t, *J* = 7.1 Hz, PhCH_2O), 7.22 (1H, d, *J* = 16.1 Hz, CH=CH), 7.19 (1H, d, *J* = 2.1 Hz, H-2´), 7.12 (1H, s, H-3), 6.98 (1H, dd, J = 8.4 and 2.1 Hz, H-6´), 6.87 (1H, d, *J* = 8.4 Hz, H-5´), 6.86 (1H, d, *J* = 16.1 Hz, CH=CH), 6.64 (1H, s, H-6), 6.37 (1H, br s, NH), 5.18 (2H, s, PhCH_2O), 3.98 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.56 (2H, t, *J* = 7.3 Hz, CH_2CH_2NH), 3.00 (2H, t, *J* = 7.3 Hz, CH_2CH_2NH)

HRMS-ES$^+$ (*m*/*z*): Found 538.1812 $[M+Na]^+$; calculated for $[C_{28}H_{28}F_3NO_5SiNa]$ 508.2131.

2.7.23 N-*(2-{2-[*E*-2-(4-tert-Butyldimethylsilyloxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (2.101)*



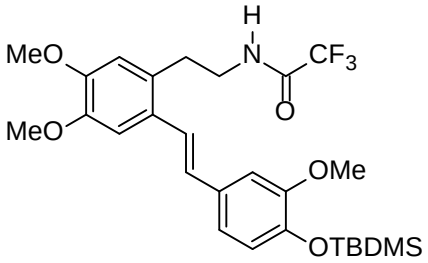
The stilbene **2.101** was synthesised in a 49% yield by the Heck reaction of aryl iodide **2.97** and styrene **2.72** according to the procedure in **2.7.21**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39 (2H, d, *J* = 8.5 Hz, H-2′,6′), 7.13 (1H, d, *J* = 16.0 Hz, C<u>H</u>=CH), 7.11 (1H, s, H-3), 6.87 (1H, d, *J* = 16.0 Hz, CH=C<u>H</u>), 6.84 (2H, d, *J* = 8.5 Hz, H-3′,5′), 6.63 (1H, s, H-6), 6.33 (1H, br s, N<u>H</u>), 3.94 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.58 (2H, q, *J* = 6.7 Hz, $ArCH_2C\underline{H}_2N$), 2.99 (2H, t, *J* = 6.7 Hz, $ArC\underline{H}_2CH_2N$), 0.99 (9H, s, $C(C\underline{H}_3)_3$), 0.22 (6H, s, $(Si(C\underline{H}_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 157.3 (q, J_{C-F} = 37 Hz, C=O), 156.6 (C-4′), 148.7 (C-5), 148.3 (C-4), 130.7 (C-1), 129.5 (C-2), 129.2 (C-1′), 127.7 (C=C), 127.6 (C-2′,6′), 122.9 (C=C), 120.4 (C-3′,5′), 115.8 (q, J_{C-F} = 288 Hz, CF_3), 113.0 (C-6), 108.9 (C-3), 56.0 (OCH_3), 55.9 (OCH_3), 40.9 ($ArCH_2\underline{C}H_2N$), 31.9 ($Ar\underline{C}H_2CH_2N$), 25.7 ($C(\underline{C}H_3)_3$),18.3 ($\underline{C}(CH_3)_3$), 4.2 ($Si(\underline{C}H_3)_2$)

HRMS-ES$^-$ (*m*/*z*): Found 508.2130 $[M-H]^-$; calculated for $[C_{26}H_{33}F_3NO_4Si]$ 508.2131.

2.7.24 N-*(2-{2-[*E*-2-(4-tert-Butyldimethylsilyloxy-3-methoxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (2.102).*

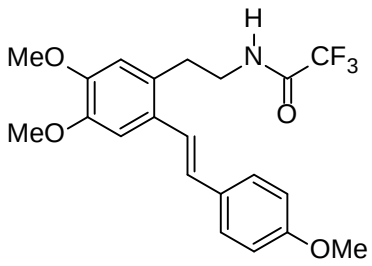


The stilbene **2.102** was synthesised by the Heck reaction of aryl iodide **2.97** and styrene **2.73** according to the procedure in **2.7.21**. The title compound was obtained in a 33% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.20 (1H, d, *J* = 16.0 Hz, CH=CH), 7.12 (1H, d, *J* = 2.0 Hz, H-2′), 7.12 (1H, s, H-3), 6.96 (1H, dd, *J* = 8.1 and 2.0 Hz, H-6′), 6.86 (1H, d, *J* = 16.0 Hz, CH=CH), 6.83 (1H, d, *J* = 8.1 Hz, H-5′), 6.63 (1H, s, H-6), 6.40 (1H, brs, N<u>H</u>COCF$_3$), 3.94 (3H, s, OCH$_3$), 3.89 (OCH$_3$), 3.88 (3H, s, OCH$_3$), 3.57 (2H, q, *J* = 7.3 Hz, ArCH$_2$C<u>H</u>$_2$N), 3.00 (2H,t, *J* = 7.3 Hz, ArC<u>H</u>$_2$CH$_2$N), 1.01 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.18 (6H, s, Si(C<u>H</u>$_3$)$_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 157.4 (q, $J_{C\text{-}F}$ = 37 Hz, C=O), 151.3 (C-3′), 148.8 (C-5), 148.3 (C-4), 145.2 (C-4′), 131.4 (C-1), 129.7 (C-1′), 129.3 (C-2), 127.7 (CH=CH), 123.0 (CH=CH), 121.0 (C-5′), 119.9 (C-6′), 115.9 (q, $J_{C\text{-}F}$ = 288 Hz, CF$_3$), 112.9 (C-6), 109.8 (C-2′), 108.9 (C-3), 56.0 (OCH$_3$), 55.9 (OCH$_3$), 55. 6 (OCH$_3$), 41.2 (ArCH$_2$<u>C</u>H$_2$N), 32.1 (Ar<u>C</u>H$_2$CH$_2$N), 25.7 ((C(<u>C</u>H$_3$)$_3$), 18.6 (<u>C</u>(CH$_3$)$_3$), -4.6 (Si(<u>C</u>H$_3$)$_2$)

*2.7.25 N-(2-{2-[***E***-2-(4-Methoxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (2.103)*



The aryl iodide **2.97** was coupled with the styrene **2.85** following the procedure in **2.7.21** to give the stilbene **2.103** in 29% yield.

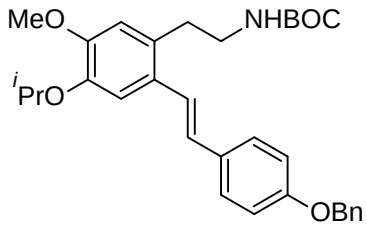
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.45 (2H, d, *J* = 8.5 Hz, H-2′,6′), 7.15 (1H, d, *J* = 15.9 Hz, C<u>H</u>=CH), 7.12 (1H, s, H-3), 6.91 (2H, d, *J* = 8.5 Hz, H-3′,5′), 6.87 (1H, d, *J* = 15.9 Hz, CH=C<u>H</u>), 6.63 (1H, s, H-6), 6.44 (brs, 1H, NH), 3.94 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.56 (2H, m, $ArCH_2C\underline{H}_2N$), 2.99 (2H, t, *J* = 6.7 Hz, $ArC\underline{H}_2CH_2N$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 159.4 (C-4′), 157.3 (q, *J* = 37 Hz, C=O), 148.9 (C-5), 148.3 (C-4), 130.2 (C-1), 129.3 (C-2), 129.2 (C-1′), 127.7 (<u>C</u>=C), 127.6 (C-2′,6′), 122.9 (C=C), 115.6 (q, *J* = 288 Hz, CF_3), 114.2 (C-3′,5′),112.9 (C-6), 108.9 (C-3), 56.0 (OCH_3), 55.9 (OCH_3), 55.3 (OCH_3), 40.9 ($ArCH_2\underline{C}H_2N$), 31.9 ($Ar\underline{C}H_2CH_2N$)

IR ν_{max} (cm^{-1}): 3303, 2940, 1697, 1607, 1513, 1277, 1254, 11771, 1104, 1024, 1004, 841, 771, 723

HRMS-ES$^+$ (*m*/*z*): Found 432.1400 $[M+Na]^+$; calculated for $[C_{21}H_{22}F_3NO_4Na]$ 431.1399.

2.7.26 (2-{2-[E-2-(4-benzyloxyphenyl)vinyl]-4-isopropoxy-5-methoxy-phenyl}ethyl)carbamic acid tert-*butyl ester (2.104)*



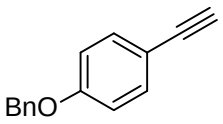
The aryl iodide **2.94** was coupled with the styrene **2.74** following the procedure in **2.7.21** to give the stilbene **2.104** in 31% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.44-7.33 (7H, m, PhH_2O and H-2′,5′), 7.19 (1H, d, *J* = 16.0 Hz, CH=CH), 7.15 (1H, s, H-2), 6.97 (2H, d, *J* = 8.2 Hz, H-3',5'), 6.81 (1H, d, *J* = 16.0 Hz, CH=CH), 6.67 (1H, s, H-5), 5.09 (2H, s, PhCH_2), 4.57 (2H, m, OC$H$$(CH_3)_2$ and NHBOC), 3.86 (3H, s, OCH_3), 3.33 (2H, q, *J* = 7.0 Hz, $ArCH_2CH_2N$), 2.89(2H, t, *J* = 7.0 Hz $ArCH_2CH_2N$), 1.42 (9H, s, $C(CH_3)_3$), 1.39 (6H, d, *J* = 6.1 Hz, $OCH(CH_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 158.5 ($NCO_2C(CH_3)$), 155.9 (C-4′), 150.2 (C-5), 146.1 (C-4), 136.9 (PhCH_2O), 130.9 (C-1), 129.9 (C-2), 129.1 (C-1′), 128.6 (PhCH_2O), 128.0 (PhCH_2O), 127.7 (C-2′,6′), 127.5 (PhCH_2O and C-6), 123.8 (CH=CH), 115.1 (C-3′,5′), 113.9 (C-3), 71.8 (OCH$(CH_3)_2$), 70.1 (Ph$C$$H_2O$) 56.0 ($OCH_3$) 28.4 ($NCO_2C(CH_3)_3$), 22.2 ($OCH(CH_3)_2$)

HRMS-ES$^+$ (*m*/*z*): Found 540.2728 $[M+Na]^+$; calculated for $[C_{32}H_{39}NO_5Na]$ 540.2726.

2.7.27 4-Benzyloxyphenylethyne (2.117)



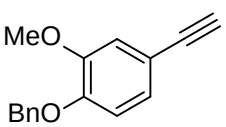
To a solution of 4-benzyloxyphenylethene (**2.66**) (0.5 g, 2.38 mmol) in DCM, bromine (0.209 g, 2.6 mmol) dissolved in DCM (15 mL) was added at 0 ^{o}C. The ice bath was removed after the complete addition of bromine and the reaction mixture was kept stirring for 1 h. The excess bromine was destroyed by addition of sodium thiosulfate (10%) solution and extracted with DCM (3 x 15 mL). The organic layer was dried, filtered and concentrated under vacuum. The crude brominated styrene was dissolved in cyclohexane and the solution was added to the suspension of ^{t}BuOK (0.8 g, 7.13 mmol) and 18-crown-ether (0.2 g, 0.76 mmol) in cyclohexane. The resultant slurry was refluxed for 2 h, then cooled to room temperature and filtered through silica. The filtrate was dried and concentrated under vacuum. The crude product was purified by flash chromatography and acetylene **2.117** was obtained as yellowish solid (0.24 g, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.44 (2H, d, *J* = 8.8 Hz, H-2,6), 7.42-7.31 (5H, m, PhCH_2O) 6.92 (2H, d, *J* = 8.8 Hz, H-3,5), 5.10 (2H, s, PhCH_2O), 3.00 (1H, s, ArC≡C<u>H</u>)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 159.2 (C-4), 136.6 (PhCH_2O), 133.6 (C-2/6), 128.6 (PhCH_2O), 127.9 (PhCH_2O), 127.5 (PhCH_2O), 114.9 (C-3/5), 114.5(C-1), 83.7 (Ar<u>C</u>≡CH), 75.9 (ArC≡<u>C</u>H), 70.1 (Ph<u>C</u>H_2O)

IR ν_{max} (cm^{-1}): 3272, 2929, 1599, 1505, 1384, 1284, 1238, 1172, 1011, 823, 759, 726, 695, 673.

2.7.28 4-Benzyloxy-3-methoxyphenylethyne (2.118)



Acetylene **2.118** was prepared from styrene **2.67** according to the procedure in **2.7.26**. The title compound was obtained in 52% yield as a yellow oil.

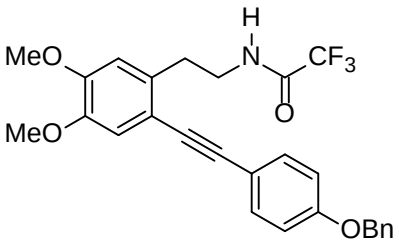
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.44 (5H, m, PhCH_2O), 7.03 (1H, dd, *J* = 8.3 and 1.8 Hz, H-6), 7.01 (1H, d, *J* = 1.8 Hz, H-2), 6.8 (1H, d, *J* = 8.3 Hz, H-5), 5.16 (2H, s, PhCH_2O), 3.88 (3H, s, OCH_3), 2.99 (1H, s, ArC≡CH)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 149.3 (C-4), 149.1 (C-3), 136.7 (PhCH_2O), 128.6 (PhCH_2O), 127.9 (PhCH_2O), 127.2 (PhCH_2O), 125.3 (C-6), 115.4 (C-2), 114.8 (C-1), 113.6 (C-5), 83.7 (ArC≡CH), 75.7 (ArC≡CH), 70.9 (PhCH_2O), 56.0 (OCH_3)

IR ν_{max} (cm^{-1}): 3269, 2932, 1593, 1506, 1455, 1375, 1319, 1255, 1232, 1134, 1030, 993, 852, 813, 747, 698

HRMS-ES$^+$ (*m*/*z*): Found 261.0891 [M+ Na]$^+$, calculated for [$C_{16}H_{16}O_2Na$] 261.0893.

2.7.29 N-*{2-[2-(4-Benzyloxyphenyl)ethynyl]-4,5-dimethoxy-phenyl]ethyl}-2,2,2-trifluoroacetamide (2.119)*



A mixture of aryl iodide **2.97** (314.5 mg, 0.78 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and CuI (1.9 mg, 0.01 mmol) was placed in a flask, and the mixture was purged with nitrogen. DIA (10 mL) was added to the mixture, and the solution was

stirred for 30 min. A solution of 4-benzyloxyphenylethyne (**2.117**) (150 mg, 0.78 mmol) in DIA (5 mL) was added to the reaction mixture via a syringe. The reaction mixture was stirred at room temperature for 16 h or until TLC indicated the completion of the reaction. Then, a saturated ammonium chloride solution was added to quench the reaction. The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$. The crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes:EtOAc, 8:2) afforded acetylene **2.119** as a yellow solid (281 mg, 75%), which was crystallised from CH_3OH as yellow needles.

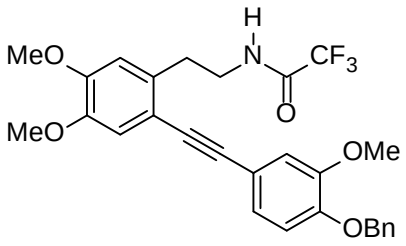
Mp: 116.5–117 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.46 (2H,d, *J* = 8.7 Hz, H-2′,6′), 7.45-7.37 (5H, m, PhCH_2O) 7.04 (1H, s, H-3), 6.98 (2H, d, *J* = 8.7 Hz, H-3′,5′), 6.71 (1H, s, H-6) 5.12 (2H, s, PhCH_2O), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.72 (2H, m, $ArCH_2CH_2N$), 3.12 (2H, t, *J* = 7.0 Hz, $ArCH_2CH_2N$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 158.8 (C-4′),157.7 (q, *J* = 37.4 Hz, C=O) 149.7 (C-5), 147.8 (C-4), 136.6 (PhCH_2O), 132.8 (C-2′,6′), 132.6 (C-1), 128.7 (PhCH_2O), 128.1 (PhCH_2O), 127.4 (PhCH_2O and C-3), 115.9 (q, J = 287 Hz, CF_3), 115.4 (C-2), 115.1 (C-3′,5′), 114.8 (C-1′), 112.2 (C-6) 92.3 (C≡C), 86.2 (C≡C), 70.05 (PhCH_2O), 56.1 (CH_3), 55.9 CH_3), 40.8 (CH_2), 33.3 (CH_2)

HRMS-ES^{+} (*m*/*z*): Found 506.1552 $[M+Na]^{+}$; Calculated for $[C_{27}H_{24}F_3NO_4Na]$ 506.1555.

2.7.30 N-*{2-[2-(4-Benzyloxy-3-methoxyphenyl)ethynyl]-4,5-dimethoxyphenyl]ethyl}-2,2,2-trifluoroacetamide (2.120)*



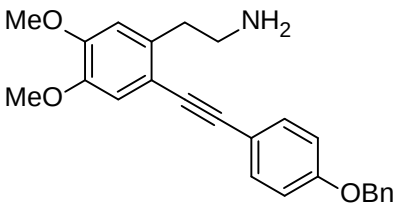
The aminoalkyne **2.120** was prepared by Sonogashira coupling of the aryl iodide **2.97** and the acetylene **2.118**, following the procedure in **2.7.28**. The title compound was obtained in 80% yields.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.46- 7.29 (5H, m, $PhCH_2$), 7.06 (1H, d, *J* = 2.0 Hz, H-2') 7.03 (1H, dd, *J* = 8.1 and 2.0 Hz, H-6'), 7.01 (1H, s, H-2), 6.86 (1H, d, *J* = 8.1 Hz, H-5'), 6.68 (1H, s, H-5), 6.48 (1H, brs, $NHCOCF_3$), 5.18 (2H, s, $PhC\underline{H_2}O$), 3.91 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.69 (2H, q, *J* = 6.8 Hz, $ArCH_2C\underline{H_2}N$), 3.08 (2H, t, *J* = 6.8 Hz, $ArC\underline{H_2}CH_2N$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 157 (q, *J* = 37Hz, C=O), 149.7 (C-4′), 149.5 (C-3′), 148.8 (C-5), 147.8 (C-4), 136.7 ($\underline{Ph}CH_2O$), 132.7 (C-1), 128.6 ($\underline{Ph}CH_2O$), 127.9 ($\underline{Ph}CH_2O$), 127.3 ($\underline{Ph}CH_2O$), 124.6 (C-6′), 118.0 (C-2′), 115.7 (C-3), 115.1 (q, *J* = 288 Hz, CF_3), 114.8 (C-1′), 114.7 (C-2), 113.8 (C-5′), 112.2 (C-6), 92.3 (C≡C), 86.1 (C≡C), 71.0 ($Ph\underline{C}H_2O$), 56.1 (2 x OCH_3), 55.9 (OCH_3), 40.9($ArCH_2\underline{C}H_2N$ $COCF_3$), 33.2 ($Ar\underline{C}H_2CH_2NCOCF_3$)

HRMS-ES$^+$ (*m*/*z*): Found 536.1659 $[M+Na]^+$; Calculated for $[C_{28}H_{26}F_3NO_5Na]$ 536.1661.

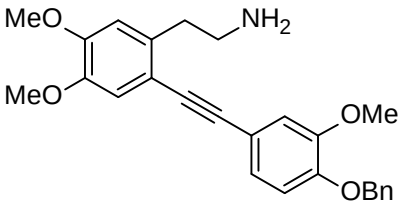
2.7.31 2-{2-[2-(4-Benzyloxyphenyl)ethynyl}-4,5-dimethoxyphenyl]ethylamine (2.116)



Aqueous KOH (5 M, 2 mL, 7.79 mmol) was added to a solution of alkyne (0.4 g, 0.827 mmol) in MeOH/THF (1:3) (20 mL) at 0 ^{o}C. The cooling bath was then removed and the mixture was stirred at 25 ^{o}C for 20 h. Then, the CH_3OH/THF were removed under vacuum and the residue was diluted with H_2O (20 mL). After extraction with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography gave the aminoalkyne as a hygroscopic yellow solid (0.246 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.45-7.38 (7H, overlap, PhCH_2O and H-2´,6´), 7.01(1H, s, H-3), 6.95 (2H, d, *J* = 8.2 Hz, 3´,5´), 6.74 (1H, s, H-6), 5.13 (2H, s, PhCH_2O), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.05 (2H, m, ArCH_2CH_2N), 2.95 (2H, t, *J* = 6.8 Hz, ArCH_2CH_2N), 1.72 (s, 2H, NH_2).

2.7.32 2-{2-[2-(4-Benzyloxy-3-methoxyphenyl)ethynyl}-4,5-dimethoxyphenyl]ethylamine (2.124)

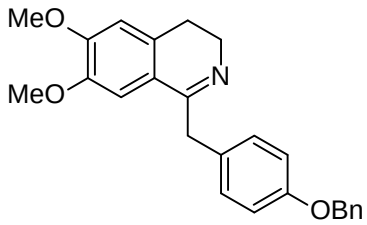


Compound **2.119** was hydrolysed according to the procedure in **2.7.30** to give the free amine **2.116** in 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.37-7.32 (5H, m, PhCH_2O), 7.05 (2H, m, H-2′,6′), 7.01 (1H, s, H-3), 6.86 (1H, d, *J* = 8.2 Hz, H-5′), 6.74 (1H, s, H-6), 5.18 (2H, s, PhCH_2O), 3.91 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.04 (2H, t, *J* = 6.8 Hz, ArCH_2CH_2N), 2.94 (2H, t, *J* = 6.8 Hz, ArCH_2CH_2N), 1.48 (2H, s, NH_2)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 149.5 (C-4′), 149.3 (C-3′), 148.6 (C-5), 147.2 (C-4), 136.8 (PhCH_2O), 135.1 (C-1), 128.6 (PhCH_2O), 127.9 (PhCH_2O), 127.3 (PhCH_2O and C-6′), 124.6 (C-2′), 116.3 (C-3), 114.9 (C-1′), 114.7 (C-2), 113.9 (C-5′), 112.4 (C-6), 91.6 (C≡C), 86.9 (C≡C), 71.0 (PhCH_2O), 56.1 (OCH_3), 56.0 (OCH_3), 55.9 (OCH_3), 42.9 (ArCH_2CH_2N), 38.6 (ArCH_2CH_2N).

2.7.33 1-[(4-Benzyloxyphenyl)methyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (2.125)



A solution of aminoalkyne **2.125** in CH_2Cl_2 (0.4 mL, c = 100 mg/mL,) was transferred to a Schlenk tube and the solvent was removed under vacuum. Then, anhydrous toluene (0.8 mL) and a solution of $Ti(Et_2N)_4$ (0.5 mL, c = 035 mol/L, in toluene, 0.20 mmol, 10 mol%) were added. The reaction mixture was heated to 110 ^{o}C for 16 h. After the obtained brown liquid had been allowed to cool to room temperature, the solvent was removed under vacuum. The purification of the

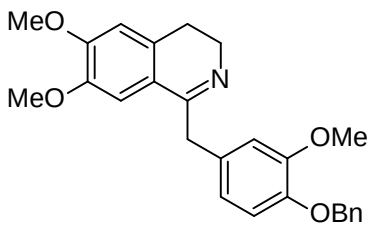
residue by flash chromatography provided the imine as a light brown solid (25 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.43-7.27 (5H, m, $PhCH_2O$),7.21 (2H, d, *J* = 8.5 Hz, H-2',6'), 6.96 (1H, s, H-8), 6.88 (2H, d, *J* = 8.2 Hz, H-3',5'), 6.65 (1H, s, H-5), 5.11 (2H, s, $PhCH_2O$), 3.98 (2H, s, H-α), 3.88 (3H, s, OCH_3) 3.73 (5H, overlap, OCH_3 and H-3), 2.64 (2H, t, *J* = 7.3 Hz, H-4).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 165.6 (C=N), 157.5 (C-4'), 150.6 (C-6), 147.3 (C-7), 137.1 ($PhCH_2O$), 131.9 (C-8a), 130.6 (C-4a), 129.6 (C-2',6'), 128.6 ($PhCH_2O$), 127.9 ($PhCH_2O$), 127.4 ($PhCH_2O$), 121.7 (C-1'), 115.1 (C-3',5'), 110.3 (C-8), 109.8 (C-5), 70.1 ($PhCH_2O$), 560 (OCH_3), 55.9 (OCH_3), 47.2 (C-3), 42.7 (C-α), 31.9 (C-4)

HRMS-ES$^+$ (*m*/*z*): Found 388.1910 $[M+ H]^+$, calculated for $[C_{25}H_{26}NO_3]$ 388.1913.

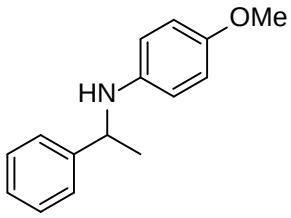
2.7.34 1-[(4-Benzyloxy-3-methoxyphenyl)methyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (2.126)



Compound **2.124** was hydroaminated according to the procedure in **2.7.32** to give the dihydroisoquinoline **2.126** in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.37-7.31 (5H, m, $PhCH_2O$), 7.09 (1H, d, *J* = 2.0 Hz, H-2´), 7.07 (1H, dd, *J* = 8.2 and 2.0 Hz, H-6´), 7.01 (1H, s, H-8), 6.87 (1H, d, *J* = 8.2 Hz, H-5´), 6.73 (1H, s, H-5), 5.19 (2H, s, $PhC\underline{H}_2O$), 3.95 (2H, s, aliph), 3.91 (9H, s, OCH_3), 3.59 (2H, q, *J* = Hz, $ArCH_2C\underline{H}_2N$), 3.03 (2H, t, *J* = 6.8 Hz, $ArCH_2C\underline{H}_2N$).

2.7.35 4-Methoxy-N-*(1-phenylethyl)aniline (2.128)*

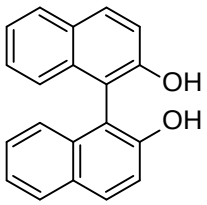


A mixture of acetophenone (**2.127**) (1.5 mmol, 0.18 g, 3.0 equiv), *p*-anisidine (**2.86**), (0.5 mmol, 0.062 g, 1.0 equiv), Hantzsch ester (0.7 mmol, 018 g, 1.4 equiv), and phosphoric acid **2.113** (5 mol%, 0.025 mmol, 0.0087 g) in toluene were stirred at 60 ^{o}C in the presence of molecular sieves 4 Å for 3 d. The solvent was removed under reduced pressure to give a brown mixture, which was purified on column chromatography to furnish the pure amine as a light brown oil in a 75% (0.068 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39-7.29 (4H, m, $\underline{Ph}CHNCH_3$), 7.25-7.20 (1H, m, $\underline{Ph}CHNCH_3$), 6.70 (2H, d, *J* = 8.8 Hz, H-2´,6´), 6.49 (2H, d, J = 8.8 Hz, H-3´,5´), 4.42 (1H, q, *J* = 6.7 Hz, $PhC\underline{H}NCH_3$), 3.70 (3H, s, OCH_3), 1.51 (3H, d, *J* = 6.7 Hz, $PhCHNC\underline{H}_3$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 152.1 (C-1), 145.3 (C-4), 128.6 (PhCHNCH$_3$), 126. 9 (PhCHNCH$_3$), 125.9 (PhCHNCH$_3$), 114.8 (C-2), 114.8 (C-3,5,6), 55.8 (OCH_3), 54.5 (PhCHNCH$_3$), 24.9 (PhCHNCH$_3$).

2.7.36 1,1′-Binaphthol (BINOL) (2.130)



Method A

2-Naphthol (**2.129**) (2.00 g, 0.014 mol) in water (150 mL) was refluxed until an oily suspension was formed. To this mixture, a solution of $FeCl_3.6H_2O$ (7.47g, 0.028 mol) in water (10 mL) was added at once. The reaction mixture was boiled further for 3 min, the hot suspension was filtered, washed with boiling water and air dried on filtered paper to yield 1,1′-binaphthol (**1.130**) as a white solid (3.8 g, 95%).

Method B

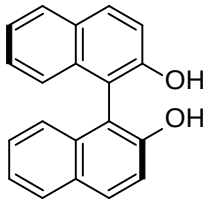
A solution of benzylamine (2.15 g, 20 mmol) in methanol (20 mL) was added to a stirred solution of $CuCl_2.2H_2O$ (1.00 g, 5 mmol) in 20 mL methanol under inert atmosphere. After 15 minutes, a solution of 2-napthol (566 mg, 3.92 mmol) in methanol (40 mL) was added and the mixture was stirred for 24 h at room temperature. The brown reaction mixture was filtered and the precipitate was washed with methanol (10 mL) and dissolved in conc. ammonia (25 mL) followed by water (50 mL). A white solid was filtered off, washed with water, dried and recrystallised from benzene to yield 1,1′-binaphthol (**2.130**) (0.67 g, 61%).

Method C

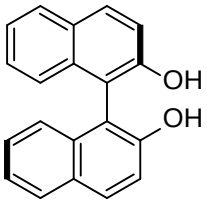
A solution of benzylamine (2.15 g, 20 mmol) in methanol (20 mL) was added to a stirred solution of $Cu(OAc)_2$ (1 g, 5 mmol) in 20 mL methanol in an inert atmosphere. After 15 minutes, a solution of 2-napthol (566 mg, 3.92 mmol) in methanol (40 mL) was added and the mixture was stirred for 24 h at room temperature. The brown reaction mixture was filtered and the precipitate was washed with methanol (10 mL) and dissolved in conc. Ammonia (25 mL) followed by water (50 mL). A white solid was filtered off, washed with water, dried and recrystallised from benzene to yield 1,1´-binaphthol (**2.130**) (0.56 g, 50%)

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ_H: 7.96 (d, *J* = 8.9 Hz, 2H, Ar), 7.89 (d, *J* = 8.9 Hz, 2H, Ar), 7.36 (d, *J* = 8.9 Hz, 2H, Ar), 7.29 (ddd, *J* = Hz, 2H, Ar), 7.22 (ddd, *J* = Hz, 2H, Ar), 7.07 (d, *J* = 8.9 Hz, 2H, Ar).

2.7.37 Resolution of 1,1´-binaphthol (2.130)



2.33



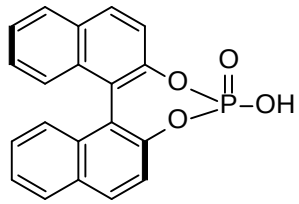
2.34

Racemic 1,1-binaphthol (**2.130**) (2.86 g, 10 mmol) and 60 mL of dry diethyl ether were added to a dry 100 L round-bottomed two-neck flask in an nitrogen atmosphere. To the flask, a solution of borane dimethyl sulfide (1.5 mL, 8.86 M) in 15 mL of diethyl ether was added dropwise with stirring. Hydrogen gas evolved in the course of the addition and the reaction temperature was maintained below 20 ^oC. After the ethereal solution was completely added, stirring was continued for an additional 3 h. The solvent and the volatile substances were removed under reduced pressure. To the residue, 50 mL of newly dried tetrahydrofuran was added and stirred to give a clear solution, which was followed by adding dry (*S*)-proline powder (15 g, 10 mmol) with constant stirring. The mixture was refluxed for

3 h to produce white precipitate, cooled to room temperature and filtered. The solid was washed with fresh THF, dried under reduced pressure to give **2.137**, which did not melt below 300 ^{o}C. Without further characterisation the solid **2.137** was treated with 20 mL of 2 N NaOH for 0.5 h while stirring, followed by adding HCl (20 mL, 2 N) and diethyl ether (40 mL). The mixture was stirred for an additional 0.5 h to give a clear two-phase solution. The organic phase was separated, dried over anhydrous sodium sulfate and filtered. The organic phase was evaporated and recrystallised from benzene to give 1.02 g of crystals of **2.131** with the m.p. 205-208 ^{o}C, $[\alpha]_D^{25}$ -35.4 (*c* 1, THF) in an overall yield of 71%.

The THF mother liquor removed from the solvolyte of **2.136** was evaporated under reduced pressure to give a yellowish solid **2.138**, which did not melt below 300 ^{o}C. The alkalification, acidification and "kinetic'' crystallisation were performed in a similar procedure as above to achieve the transparent crystals of **2.132** (1.00 g) with the m.p. 205-208 ^{o}C, $[\alpha]_D^{25}$ +35.3 (*c* 1, THF) in an overall yield of 70%.

2.7.38 Preparation of chiral phosphoric acid 2.113



Phosphorous oxychloride (0.1 mL, 1.1 mmol) was added dropwise to a solution of **2.130** (500 mg, 1.0 mmol) and Et_3N (0.3 mL, 2.1 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C. The mixture was stirred for an additional 30 min and then CH_2Cl_2 was evaporated under reduced pressure. The obtained residue was dissolved in THF (20 mL) and cooled to 0 ^{o}C, followed by addition of 15% aquoeus NaOH solution (5 mL). The reaction mixture was then stirred at room temperature for 15 min and then extracted with EtOAc (20 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness under reduced pressure to afford chiral acid **2.113** (534 mg, 91% yield).

$[\alpha]_D^{22}$	-604.0^o (*c* = 1.4, CH_3OH)
^{1}H NMR (400 MHz, $CDCl_3$) δ_H:	7.96 (1H, d, *J* = 8.8 Hz, Ar), 7.93 (1H, d, *J* = 8.2 Hz, Ar), 7.55 (1H, d, *J* = 8.8 Hz, Ar), 7.46 (1H, t, *J* = 7.4 Hz, Ar), 7.38 (1H, d, 8.6 Hz, Ar), 7.29 (1H, t, *J* = 7.2 Hz, Ar)
^{13}C NMR (100 MHz, $CDCl_3$) δ_C:	147.0 (d, *J* = 8.8 Hz, ArC), 132.3 (ArC), 131.8 (ArC), 131.2 (ArC), 128.5 (ArC), 127.1 (Ar), 126.7 (ArC), 125.7 (ArC), 121.5 (d, *J* = 2.4 Hz, ArC), 120.6 (d, *J* = 3.0 Hz, ArC)
^{31}P NMR (100 MHz, $CDCl_3$) δ_P:	4.3
HRMS-ES$^-$ (*m*/*z*):	Found 347.0488 $[M-H]^-$; calculated for $[C_{20}H_{12}O_4P]$ 347.0497.

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CHAPTER 3

APPROACHES TO THE SYNTHESES OF BISBENZYLTETRAHYDRO-ISOQUINOLINES

3.1 INTRODUCTION

Although a large number of bisbenzyltetrahydroisoquinolines have been isolated from natural sources, only limited information on their synthesis is available in the literature. The challenges associated with the synthesis of bisbenzylisoquinolines are the formation of the heterocyclic ring and the diaryl ether or biaryl bond. These problems are attributed to the coupling reaction of the highly electron-rich aryl rings (that are prone to decomposition at elevated temperatures) and also to the long and low-yielding synthetic routes.

To clearly understand and evaluate the underlying causes of the identified challenges encountered in the existing methodologies to synthesise bisbenzyltetrahydroisoquinolines and determine on new approaches needed to address those challenges, as well as possibly improve on the existing ones, we decided on conducting a literature review, the overview of which is reported herein. Also, owing to the challenges encountered in the synthesis of tetrahydroisoquinolines by intramolecular hydroamination of aminoalkenes and aminoalkynes (as discussed in Chapter 2), we decided to investigate other synthetic strategies for the tetrahydroisoquinoline moiety.

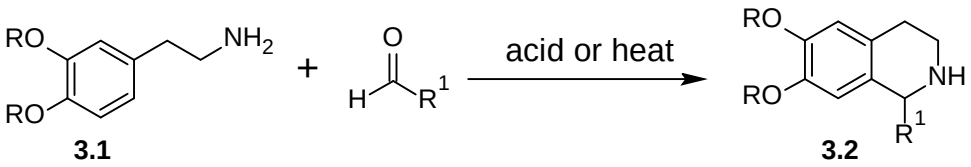
In this chapter, the traditional methods for preparing isoquinolines, the methods for the formation of the diaryl ether bond and the total syntheses of some bisbenzylisoquinolines are reviewed. The results obtained towards the total synthesis of neferine (**1.15**) and *O*-methylneferine (**1.16**) are discussed in the last section of the Chapter.

3.2 TRADITIONAL METHODS FOR THE SYNTHESIS OF TETRAHYDROISOQUINOLINES – A LITERATURE OVERVIEW

The tetrahydroisoquinoline ring is a common structural motif present in a variety of natural products and biologically active compounds. Due to their promising biological activities, efforts have been made to synthesise isoquinolines. Access to this heterocyclic system has historically involved application of the Bischler-Napieralski, Pictet-Spengler and Pomeranz-Fritsch reactions.[1-3] A brief overview of the above-mentioned strategies, with examples, is presented in the following section.

3.2.1 The Pictet-Spengler Condensation

The Pictet-Spengler condensation of the *β*-arylethylamine (**3.1**) with a carbonyl compound to form an iminium ion under acidic (protic or Lewis acid) or thermal conditions, has been of fundamental importance in the construction of the tetrahydroisoquinoline nucleus **3.2** and other related heterocyclic systems (Scheme 3.1). This reaction was first reported in 1911 by Pictet and Spengler and further extended by Decker and Becker to the condensation reaction of substituted phenethylamines with various aldehydes.[2, 4] Cyclisation is effectively achieved with aromatic compounds bearing electron-donating substituents.

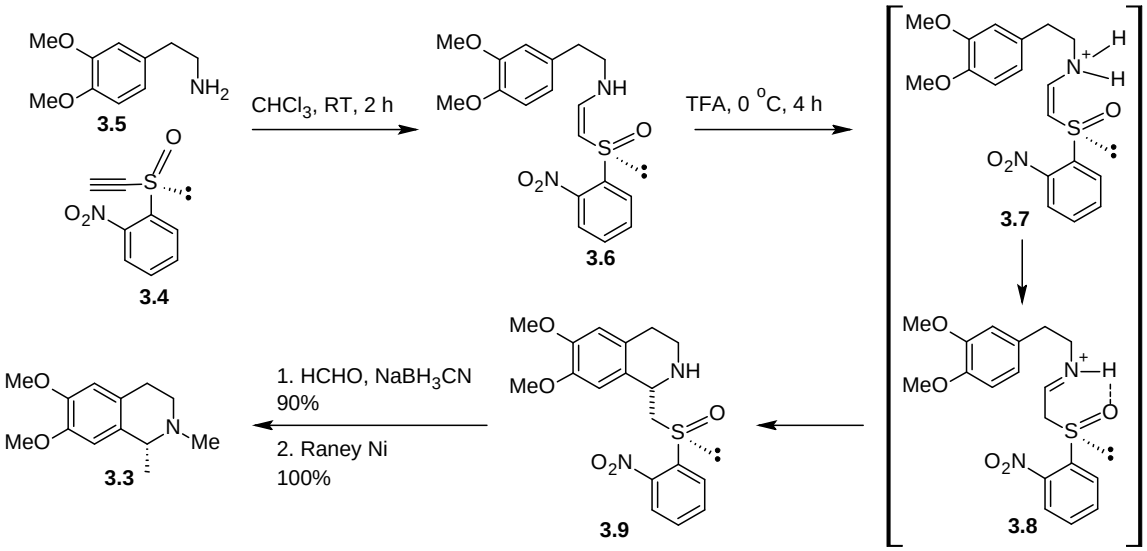


3.1 **3.2**

Scheme 3.1. The normal Pictet-Spengler approach.

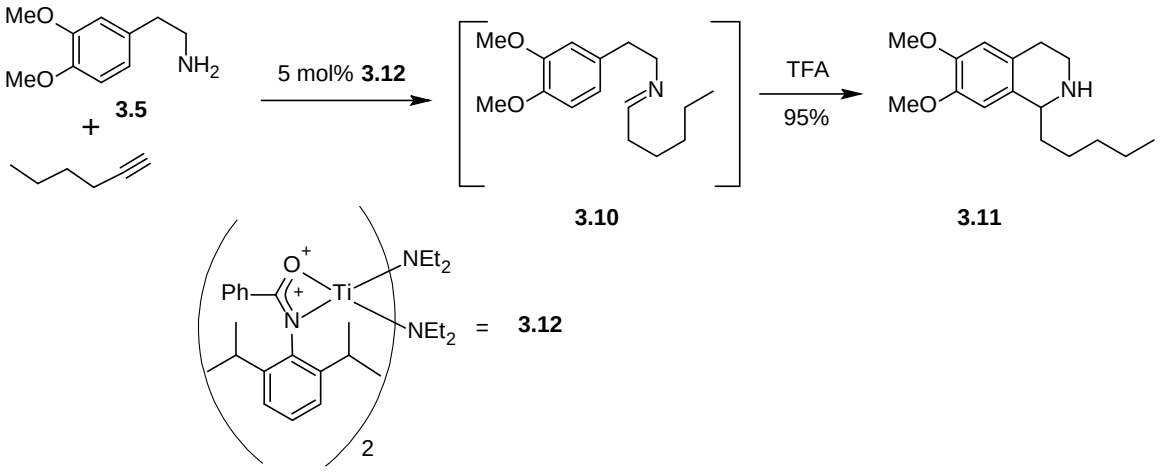
The stereoselective synthesis of tetrahydroisoquinolines by the Pictet-Spengler reaction has been accomplished by derivatisation of phenethylamines with chiral auxiliaries.[5, 6] However, this often results in the formation of two diastereomers. This lack of diastereoselectivity was addressed by Lee *et al.,*[7] when they designed the total synthesis of carnegine (**3.3**) using chiral sulfoxides, through a one-pot

Michael addition-cyclisation reaction. They reacted a chiral acetylenic sulfoxide **3.4** with 3,4-dimethoxyphenethylamine (**3.5**) and exclusively obtained the intermediate **3.9** as a single diastereomer. The reaction was performed in $CHCl_3$ with TFA to effect cyclisation. To complete the synthesis, the amine group of the intermediate **3.9** was reductively methylated, under conventional conditions, and subsequently desulfurised with Raney-nickel in water saturated with ether to give enantiomerically-pure (+)-(*R*)-carnegine (**3.3**) in a good yield (Scheme 3.2).



Scheme 3.2. The diastereoselective Pictet-Spengler synthesis of **3.3**.

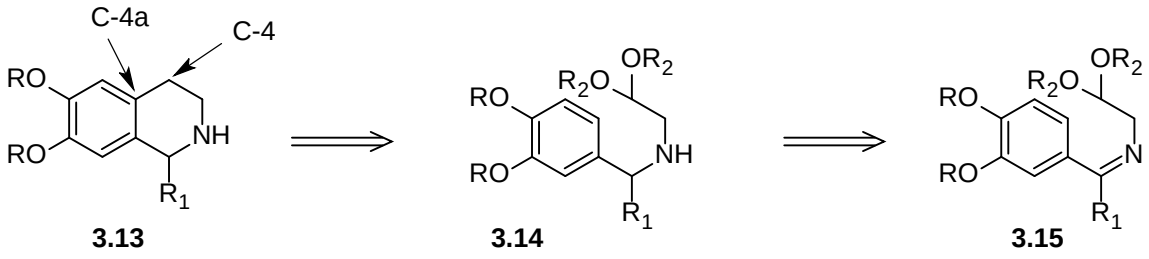
The total synthesis of isoquinolines has also been achieved by hydroamination using a modified Pictet-Spengler reaction as illustrated in Scheme 3.3. This one-pot synthesis of the isoquinoline scaffold did not employ aldehydes or ketones as substrates. However, an alkyne was regioselectively hydroaminated to provide a reactive aldimine intermediate as illustrated in Scheme 3.3. Subsequent acid-mediated cyclisation of the imine **3.10** afforded the isoquinoline **3.11** in a 95% yield as a colourless oil.[8, 9]



Scheme 3.3. The modified Pictet-Spengler reaction.

3.2.2 Pomeranz-Fritsch Synthesis

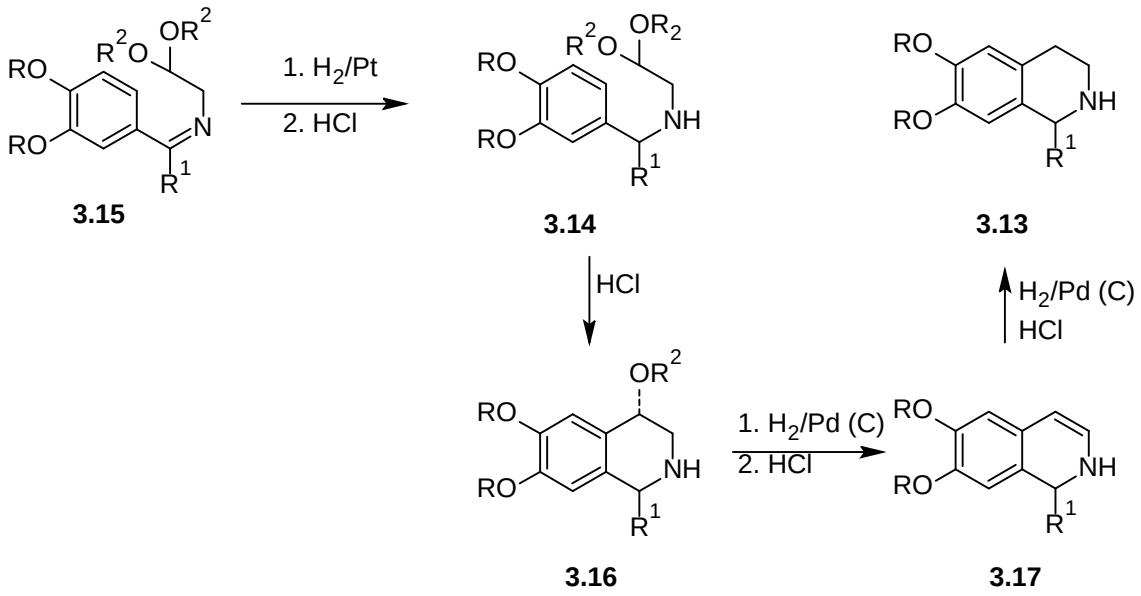
The term “Pomeranz-Fritsch isoquinoline synthesis” has been customarily applied to a variety of synthetic strategies in which the tetrahydroisoquinoline ring system was closed *via* the C4-C4a bond formation (Scheme 3.4). The Pomeranz-Fritsch reaction involves acid-catalysed cyclisation of benzylaminoacetals of the type **3.14** to give fully aromatised isoquinolines.[10] This reaction has been improved and modified in many ways.



Scheme 3.4. The Pomeranz-Fritsch reaction.

Bobbitt modified the original Pomeranz-Fritsch reaction for the synthesis of tetrahydroisoquinoline derivatives as a two-step procedure, whereby the “Pomeranz-Fritsch imines” **3.15** were hydrogenated *in situ* to the aminoacetals of type **3.14**.[1, 11, 12] The aminoacetals in turn were converted into

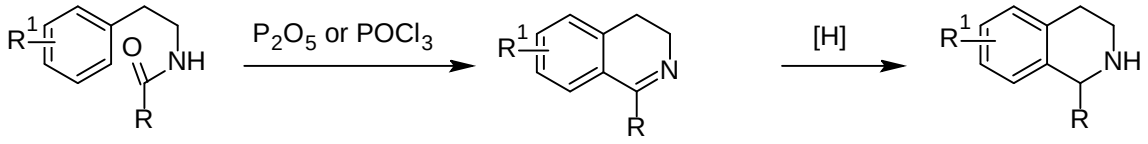
tetrahydroisoquinolines **3.13** by an acid-catalysed cyclisation-hydrogenolysis sequence. However, depending on the conditions applied, the 4-hydroxytetrahydro- and 1,2-dihydro-derivatives (**3.16** and **3.17**, respectively) could be isolated as well in some reactions (Scheme 3.5).



Scheme 3.5. The Pomeranz-Fritsch-Bobbit cyclisation.

3.2.3 The Bischler-Napieralski Reaction

Since the early 1950's, the sequential Bischler-Napieralski cyclisation/reduction approach to the asymmetric synthesis of tetrahydroisoquinoline alkaloids was the most often explored strategy. This methodology entails cyclodehydration of β-phenylethylamides **3.18** in the presence of a Lewis acid such as $POCl_3$ or P_2O_5 in an inert solvent to afford 3,4-dihydroisoquinolines **3.19**. These are subsequently reduced to the corresponding tetrahydroisoquinolines **3.20** (Scheme 3.6).[3] Under the original conditions reported for the cyclisation step of this reaction, the yields are normally very low. However, modifications using lower temperature and milder condensation reagents, such as Tf_2O, improved the yields of this reaction. The stereochemical outcome of the sequential Bischler-Napieralski cyclisation/reduction can be determined in the reduction step either by diastereoselective or enantioselective methods.



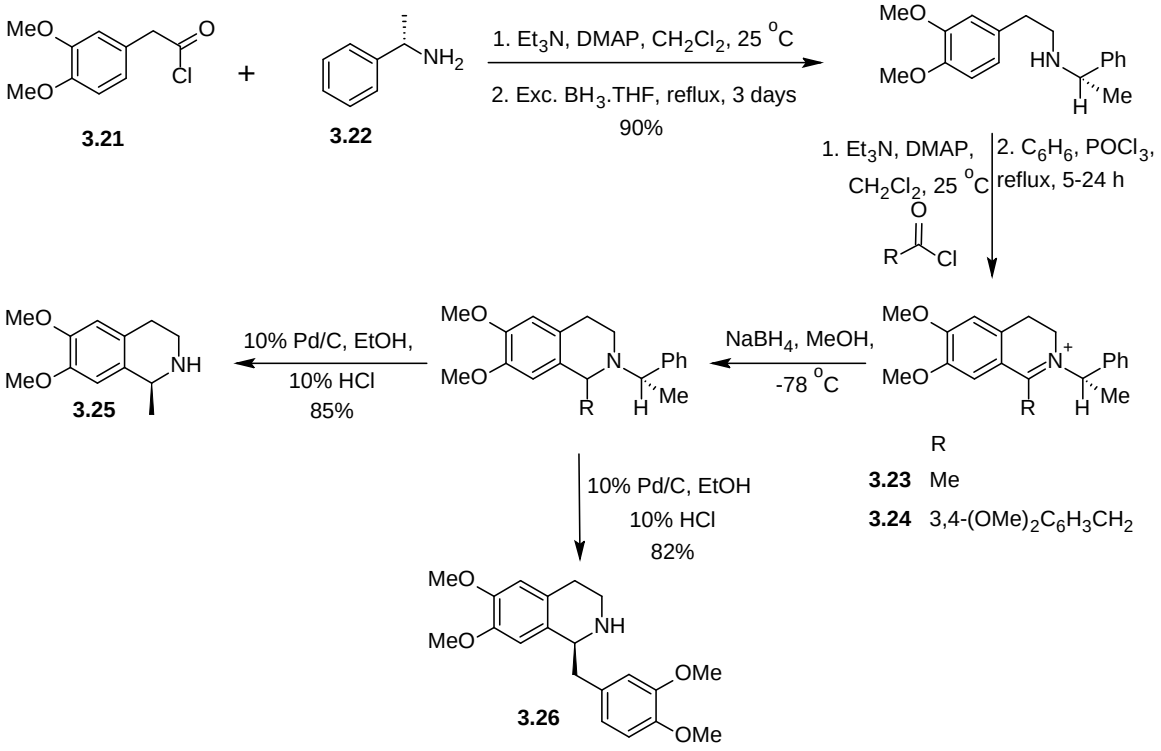
3.18 **3.19** **3.20**

R	R^1
Me, Et, Ph, Bn	OMe, OBn

Scheme 3.6. The Bischler-Napieralski reaction.

3.2.3.1 The diastereoselective syntheses

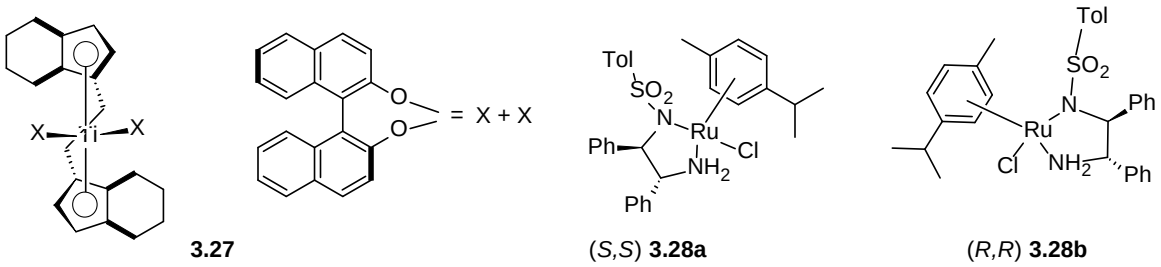
The diastereoselective syntheses of isoquinoline alkaloids by the Bischler-Napieralski cyclisation reaction have been developed with various modifications of the original procedure. Among those, is the approach where Polniaszek *et al*.[13-15] used dihydroisoquinolinium salts **3.23** and **3.24**, containing a chiral 2-methylbenzyl functionality obtained by the coupling of (*S*)-α-phenethylamine (**3.22**) and 3,4-dimethoxyphenylacetyl chloride (**3.21**), in the syntheses of (*S*)-salsolidine (**3.25**) and (*S*)-norlaudanosine (**3.26**) (Scheme 3.7). The hydride reduction of **3.23** and **3.24** with sodium borohydride resulted in formation of the targeted tetrahydroisoquinolines with excellent diastereoselectivity of 90-94%. Removal of the chiral auxiliary groups by hydrogenolysis (H_2/Pd-C) delivered **3.25** and **3.26** as optically-pure compounds in high yields of 85% and 82%, respectively.



Scheme 3.7. Synthesis of (+)- (*S*)-salsolidine (**3.25**) and (*S*)-norlaudanosine (**3.26**) by Polniaszek *et al*.[14]

3.2.3.2 Enantioselective syntheses

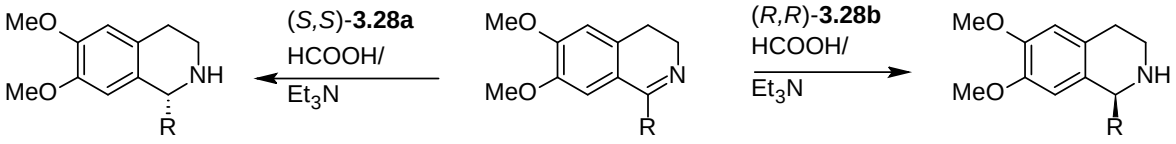
The enantioselective syntheses of tetrahydroisoquinoline scaffolds based on the Bischler-Napieralski cyclisation/reduction approach proceed *via* enantioselective reduction of prochiral 3,4-dihydroisoquinolines. For this reason, introduction of the desired chiral centres requires the use of chiral hydride reducing agents or chiral hydrogenation catalysts. Impressive synthetic results of tetrahydroisoquinolines, where chiral titanocene catalyst **3.27** was introduced to control stereoselective cyclic imines hydrogenation, with excellent enantioselectivity (95-99% *ee*) have been reported by Willoughby and Buchwald.[16, 17] The reaction displayed smooth conversion of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline to **3.25** in 85% yield.



3.27 (*S*,*S*) **3.28a** (*R*,*R*) **3.28b**

Figure 3.1. Catalysts for the enantioselective hydrogenation of imines.

Noyori and co-workers[18] reported an outstanding procedure for the asymmetric hydrogen transfer of cyclic imines in a mixture of formic acid/triethylamine, catalysed by the chiral diamine-Ru(II)-η^6 arene complexes **3.28a** and **3.28b** (Fig. 3.1). To date, this procedure has been the most frequently-used method for the enantioselective reductions of cyclic amines as it utilises the inexpensive, well-behaving formic acid/triethylamine mixture, under mild conditions. As illustrated by Noyori and co-workers,[18] this catalytic system can effectively produce several tetrahydroisoquinoline alkaloids in high yields and high *ee* values, starting from cyclic imines **3.29**. It should be emphasised that the absolute configuration of the resulting amine is totally dependent on that of the catalyst. For example, catalyst (*S,S*)-**3.28a** produced the products with (1*R*)-configuration, while catalyst (*R,R*)-**3.28b** delivered the (1*S*)-isomer as product (Scheme 3.8).



	R	*ee*
(**3.30a**)	CH_3	95%
(**3.30b**)	C_6H_5	84%
(**3.30c**)	$3,4C_6H_3(OCH_3)_2$	84%

	R	*ee*
(**3.30d**)	$3,4C_6H_3CH_2(OCH_3)_2$	84%

Scheme 3.8. The enantioselective imine reduction of dihydroisoquinolines by Noyori's procedure.

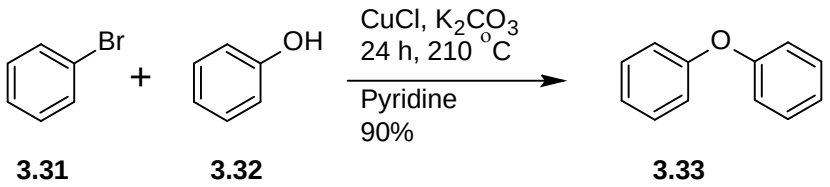
3.3 DIARYL ETHER SYNTHESIS - A LITERATURE OVERVIEW

The major challenges associated with the synthesis of bisbenzylisoquinolines are the formation of the heterocyclic ring and the diaryl ether or biaryl bond. As a result of the wide range of important biological activities exhibited by the diaryl ether class of compounds, for example, the antibiotic vancomycin and antitumoral bouvardin, many synthetic routes towards these compounds have been investigated since the 1900's. The common procedures used to prepare diaryl ethers from aryl halides and phenols are the Ullmann coupling and nucleophilic aromatic substitution reactions (S_NAr). However, harsh reaction conditions such as high temperatures (125 - 220 ºC), stoichiometric quantities of copper catalyst, strong base, formidable purification problems, and generally low to moderate yields have made the Ullmann coupling reaction unappealing. Similarly, the high cost and unavailability of the aryl fluorides made progress towards development of the nucleophilic aromatic substitution to be somehow lower. In view of these limitations, new strategies, which are efficient and environmentally-benign catalytic processes of phenols that would tolerate substitution patterns found in most naturally-occurring diaryl ethers, are still being developed. Other methods which are developed for diaryl ether synthesis include, the palladium-catalysed Buchwald-Hartwig reaction,[19, 20] coupling of phenols with arylboronic acids,[21-23] oxidative coupling and nucleophilic aromatic additions to metal-arene complexes.[24] Of the two widely employed methods for the diaryl ether synthesis, the S_NAr reaction is preferred. The subsections that follow will review the procedures for the synthesis of diaryl ethers.

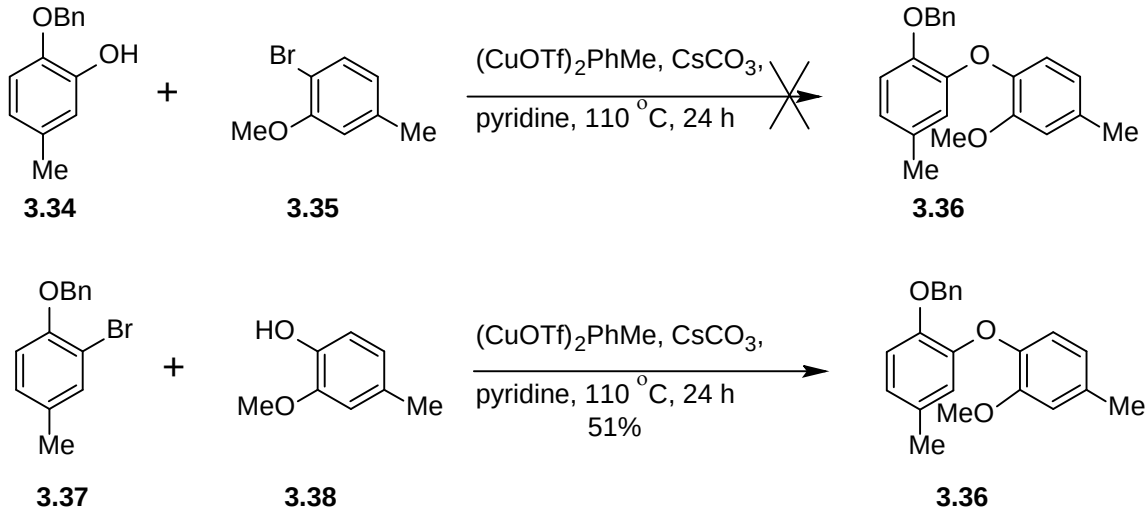
3.3.1 Ullmann Ether Synthesis

The oldest method for the synthesis of diaryl ethers is the classical Ullmann procedure. This procedure involves coupling of an aryl halide **3.31** with a phenol **3.32** in the presence of a stoichiometric amount of copper catalyst at very high temperatures to yield a diaryl ether **3.33** (Scheme 3.9).[25, 26] Despite all the limitations, it still remains the reaction of choice on large scale and industrial scale

for the construction of diaryl ether linkages. Sometimes the success of the Ullmann coupling reaction highly depends on the substitution pattern of both aryl rings. The Ullmann coupling reaction produces better results with electron-poor aryl halides than with the electron-rich aryl halides. For instance, attempts of Ullmann ether coupling between the electron-rich aryl halide **3.35** and the phenol **3.34** under the standard Ullmann reaction (in the presence of 5 mol% of $(CuOTf)_2PhMe$ and caesium carbonate in pyridine at 110 ºC) did not give the desired diaryl ether **3.36**.[27] However, under the same reaction conditions, a diaryl ether **3.36** was yielded in 51% yields when the aryl bromide **3.37** was reacted with phenol **3.38** (Scheme 3.10)**.**



Scheme 3.9. Classical Ullmann ether synthesis.



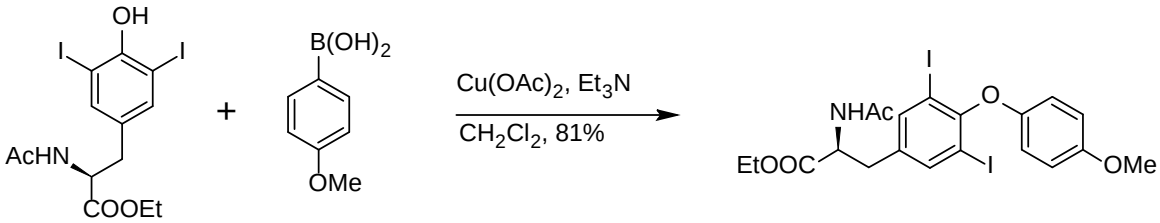
Scheme 3.10. Modified Ullmann ether synthesis.

Efforts have been made to modify the Ullmann ether coupling reactions in order to overcome the above-mentioned limitations. The two most important are: i) boronic

acid-driven diaryl ether synthesis and, ii) triazene-based diaryl ether synthesis. These methods will be discussed in this section

3.3.2 Coupling of Phenols with Arylboronic Acids

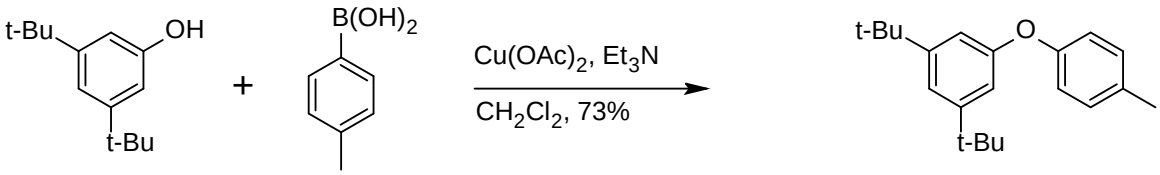
Chan, Evans and Lam reported a copper(II) catalysed synthesis of diaryl ethers under mild reaction conditions by the coupling of phenols with arylboronic acids.[21, 23, 28] The disadvantage of this method is that it requires stoichiometric amounts of a copper catalyst. However, it allows the formation of diaryl ethers at room temperature in generally high yields. Furthermore, the procedure also tolerates a wide variety of substituents on both coupling partners. This has been well demonstrated by Evans in the synthesis of diaryl ether **3.41**, an intermediate in the synthesis of *L*-thyroxine, by coupling 2,6-diiodophenol derivative **3.39** with boronic acid **3.40** (Scheme 3.11).[22]



3.39 **3.40** **3.41**

Scheme 3.11. Synthesis of *L*-thyroxine acid through boronic acid-driven ether synthesis.

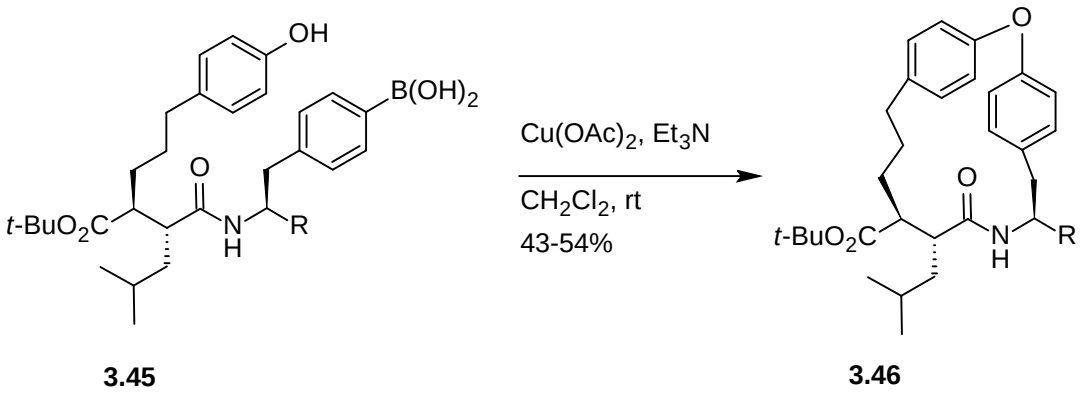
In another example, Chan utilised 3,5-di-*t*-butylphenol (**3.42**) as a coupling partner of *p*-tolylboronic acid (**3.43**) to synthesise **3.44** as shown in Scheme 3.12.[21]



3.42 **3.43** **3.44**

Scheme 3.12. An illustration of copper-catalysed boronic acid ether synthesis.

Evans and co-workers have used this method to synthesise the **F**-O-**G** ring system of teicoplanin aglycone in 80% yield and also in the synthesis of macrocyclic metalloproteinase inhibitor **3.46** from **3.45** as illustrated in Scheme 3.13.[29]

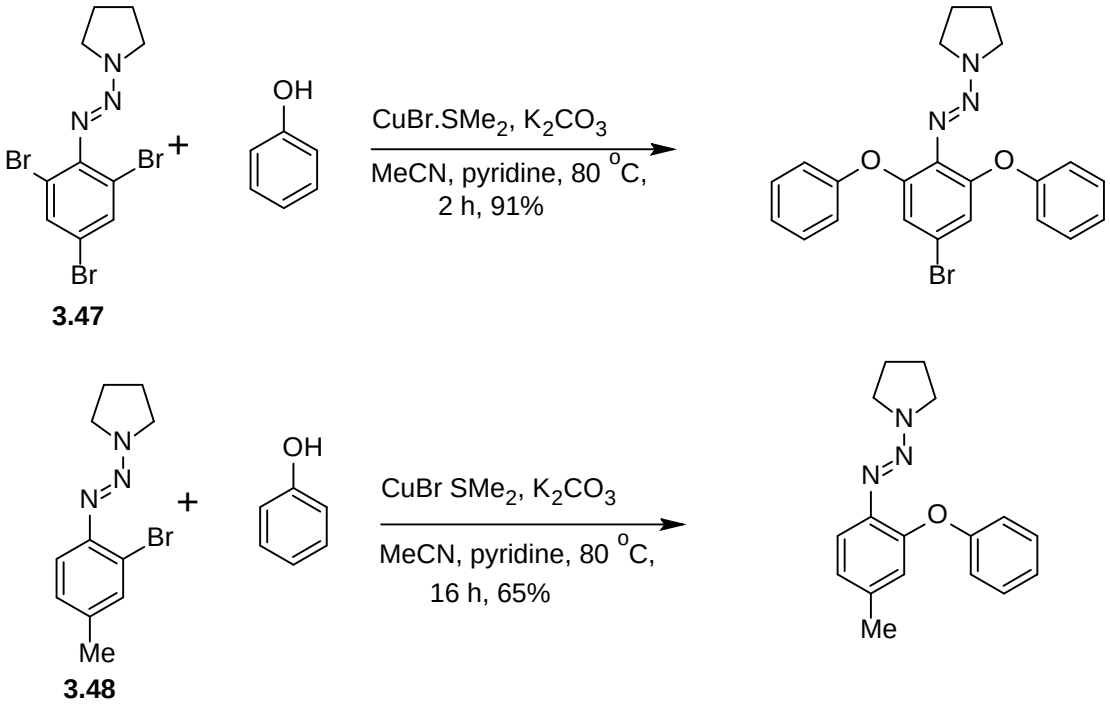


3.45 **3.46**

Scheme 3.13. Synthesis of metalloproteinase inhibitor **3.46**.

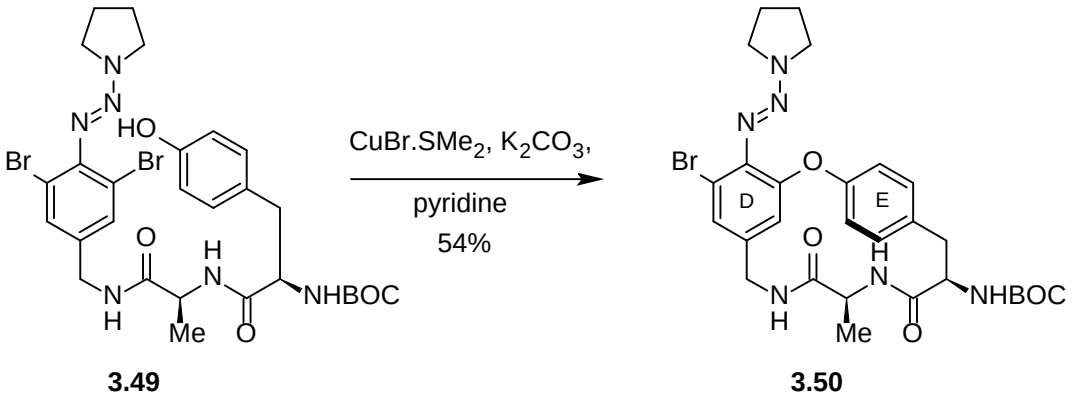
3.3.3 Triazene-Driven Diaryl Ether Synthesis

Nicolaou's group developed a triazene-biaryl ether synthesis, which is essentially a variant of the Ullmann ether synthesis.[30, 31] In this method, aryl bromides and iodides substituted with an *ortho* triazene moiety act as nucleophile acceptors. The reaction takes place under mild reaction conditions in the presence of the soluble copper complex $CuBr.SMe_2$ in refluxing acetonitrile, to give diaryl ethers in good yields. The di-*ortho*-halogenated aromatic triazenes **3.47** reacted faster than the corresponding monohalogenated aromatic triazenes **3.48** to give the expected diaryl ethers as shown in Scheme 3.14. However, *para*-halogens, if present, are not substituted.



Scheme 3.14. Triazene ether synthesis.

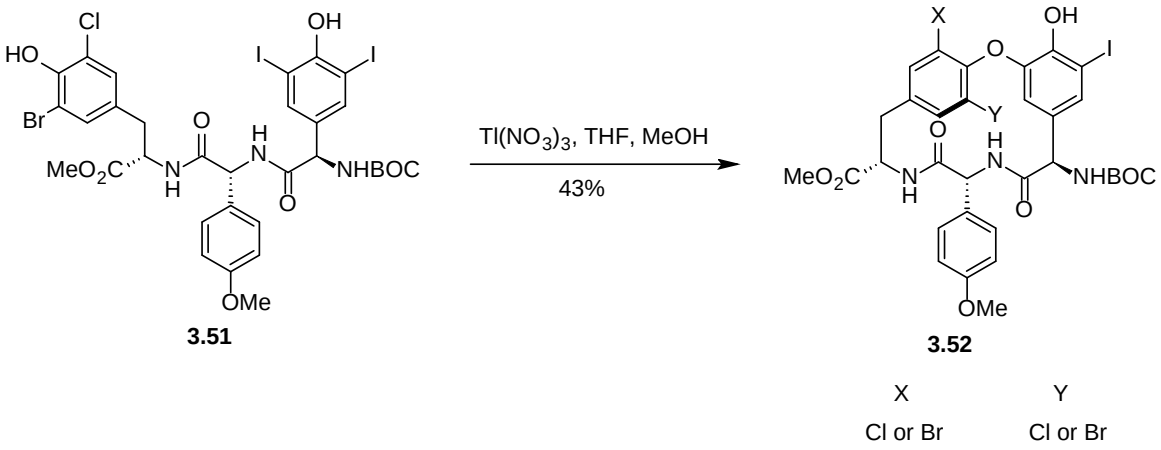
Despite not being catalytic with respect to copper complex, the absence of strong bases induces highly tolerant and selective conditions. This reaction is widely used in the macrocyclisation step of complex oligopeptide-based macrocyclic molecules involving ether linkages. This methodology was first applied by Nicolaou *et al*.[32] for the construction of **D**-O-**E** and **C**-O-**D** vancomycin model systems, and later to complete the synthesis of vancomycin. In the synthesis of a **D**-O-**E** model system, the standard triazene macrocyclisation of **3.49** afforded the desired model compound **3.50** in 54% yield (Scheme 3.15).



Scheme 3.15. Synthesis of D-O-E model system of vancomycin.

3.3.4 TTN-Promoted Oxidative Phenolic Coupling

Inspired by biosynthetic considerations, the synthesis of diaryl ethers has also been accomplished *via* the oxidative coupling of 2,6-dihalogenated phenols with thallium trinitrate (TTN).[33] Despite the fairly mild conditions applicable for complex molecular synthesis, the use of the expensive, toxic and environmentally unfriendly TTN rendered the method unattractive. Furthermore, the use of di-*ortho*-halogenated phenol as an activating agent, to control oxidative potential and regioselectivity, may be a problem to other systems; especially in the last step of selective removal of one halogen atom to give the targeted product. Scheme 3.16 illustrates the synthetic protocol of the cyclic diaryl ether **3.52** via the oxidative coupling of bis-phenol **3.51**. The cyclic diaryl ether **3.52** was unfortunately obtained as an unspecified mixture of atropisomers in 43% yield.

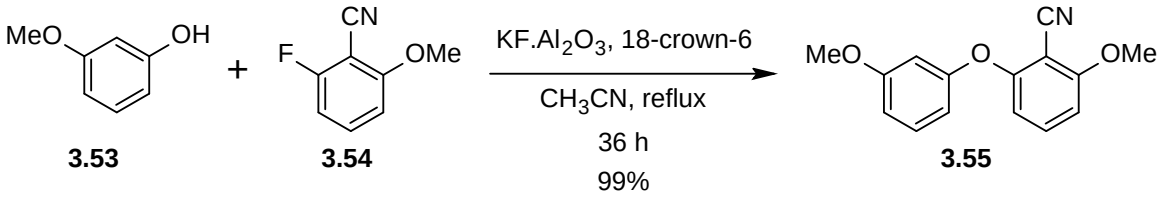


Scheme 3.16. Thallium nitrate-mediated phenolic coupling.

3.3.5 Alumina-Driven Diaryl Ether Synthesis

The intermolecular nucleophilic aromatic substitution reactions (S_NAr) for the construction of diaryl ethers using KF/Al_2O_3, in the presence of 18-crown-6 as an alternative to the copper-catalysed Ullmann ether synthesis, have been reported

by Sawyer and co-workers.[34, 35] This reaction has several advantages, which include; the use of sterically-crowded nucleophiles that are usually unreactive in Ullmann ether synthesis, and production of the desired products in high yields using both the electron-rich and electron-poor electrophiles.[36-38] However, the use of high temperatures required to drive the reaction forward, prohibit the application of this method to the synthesis of complex molecules. Moreover, in some cases it requires long reaction time (2 to 10 days). Fluorobenzonitriles and fluoronitrobenzenes are favourable substrates in this procedure as shown for the synthesis of diaryl ether **3.55** in Scheme 3.17. Phenol **3.53** was condensed with fluorobenzonitrile **3.54** to produce diaryl ether **3.55** in the presence of KF/Al_2O_3 and 18-crown-6 in refluxing acetonitrile.[34]



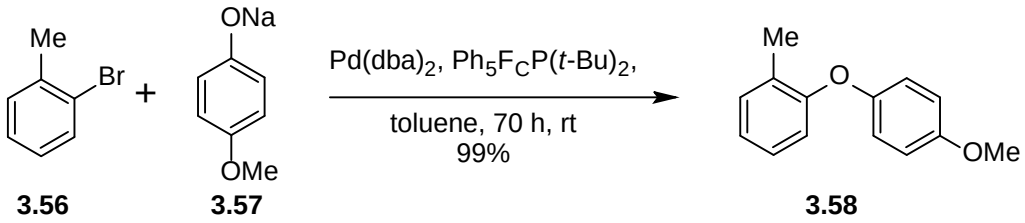
3.53 **3.54** **3.55**

Scheme 3.17. Alumina-driven ether diaryl synthesis.

3.3.6 Palladium-Catalysed Diaryl Ether Synthesis

Buchwald and Hartwig independently demonstrated the versatility of an intermolecular palladium-catalysed diaryl ether synthesis reaction from aryl halides or triflates and phenols.[20, 39] Satisfactory yields of diaryl ethers are produced using catalytic amount of palladium ions and various ligands. Examples of bulky ligands which have successfully assisted the palladium catalysts to facilitate this C-O bond coupling include (BINAP), (DPPF), $P(o\text{-tolyl})_3$ and (D^tBPF). Contrary to the copper-mediated diaryl ether coupling reactions, aryl bromides and chlorides gave higher yields than aryl iodides. The major advantage of this method is the fact that the sterically hindered *ortho*-substituted aryl halides react faster at lower temperatures than their unsubstituted equivalents and give better yields. In some instances, this reaction takes place even at room temperature.[19, 20, 40] Hartwig et al.[41, 42]

demonstrated this concept by condensing 2-bromotoluene (**3.56**) with phenoxide **3.57** in the presence of $Pd(dba)_2$ as a catalyst, using $Ph_5F_CP(t\text{-}Bu)_2$ as a ligand at room temperature for 70 h to afford the diaryl ether **3.58** in a 99% yield (Scheme 3.18).

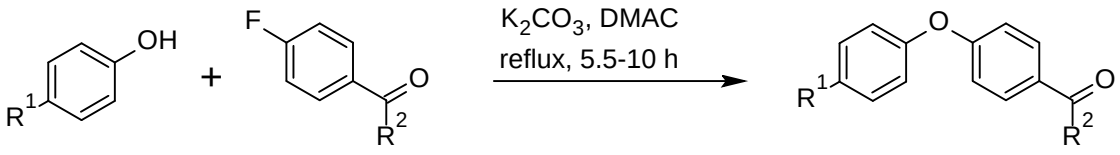


3.56 **3.57** **3.58**

Scheme 3.18. Palladium-catalysed Ullmann synthesis.

3.3.7 Nucleophilic Aromatic Substitution

The activated aryl fluorides, with electron-withdrawing groups preferably in a 1,2- or 1,4-substitution pattern easily undergo nucleophilic substitution with phenols to give diaryl ethers. A base but no catalyst is a condition required for the reaction. The electron-withdrawing groups on the electrophile that have found greater use in S_NAr include the aldehyde, nitro, nitrile and ketone groups. This is illustrated in the synthesis of the diaryl ethers **3.60** (Scheme 3.19). The *p*-fluoroacetophenone or *p*-fluorobenzaldehyde was coupled with phenols **3.59** to give the diaryl ethers **3.60** in good to high yields of 70-93%.



3.59 **3.60** 70-93%

R^1

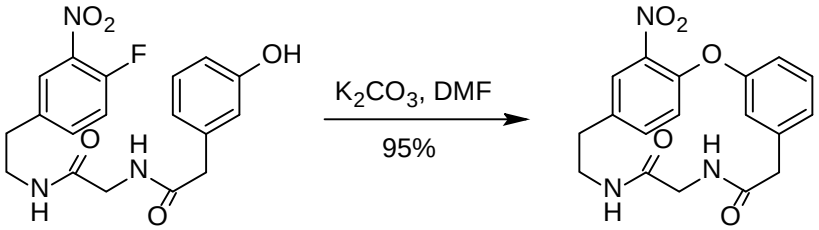
H, Cl, Br, ^{t}Bu, OMe, OPh, CO_2Et

R^2

H, Me

Scheme 3.19. Nucleophilic aromatic substitution reaction.

In 1933, Rarick reported the synthesis of diaryl ethers through nitro-activated S_NAr reaction for the first time.[43] In his work, *para*-nitrofluorobenzene was reacted with a variety of phenols to yield diaryl ethers in good yields. Years after this development, Hamilton and Beugelmans applied this method in the synthesis of macrocycles.[44, 45] Beugelmans used the nitro-activated S_NAr reaction for the synthesis of macrocycle **3.62** (Scheme 3.20).[45] The synthesis initially involved the preparation of the model compound **3.61**, which was subjected to an intramolecular nucleophilic aromatic substitution reaction to yield the macrocycle **3.62** in a 95% yield.



3.61 **3.62**

Scheme 3.20. *ortho*-Nitro-activated nucleophilic aromatic substitution.

3.3.8 Diaryl Ether Synthesis Mediated by Metal Arene Complexes

Coordination of haloarenes (unreactive towards nucleophiles) with transition metals to form η^6-complexes activates the ring towards nucleophilic attack. Metals such as Cr, Fe, Mn and Ru form stable and isolatable complexes (Figure 3.2).

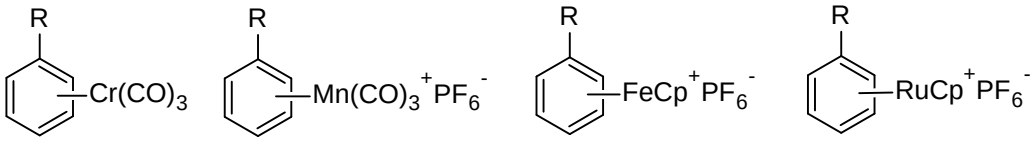
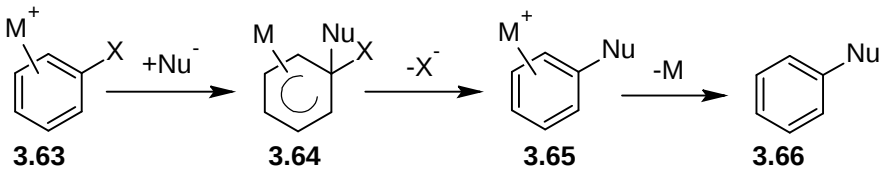


Figure 3.2. Isolatable complexes of Cr, Fe, Mn and Ru.

Initially, a metal-mediated S_NAr reaction entails an *ipso* attack of the η^6-complex **3.63** by the nucleophile to form the η^5-coordinated intermediate **3.64**. The subsequent step envisions loss of the halide ion from the intermediate **3.64** to give

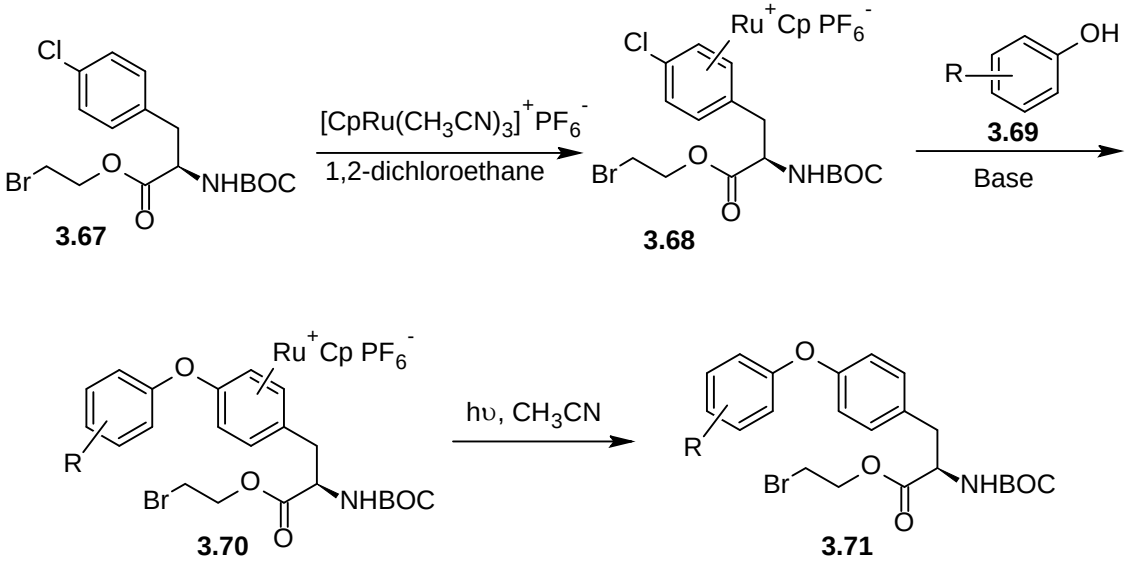
the η^6-arene metal complex **3.65**. In the last step the metal can be removed easily to afford compound **3.66** (Scheme 3.21).



3.63 **3.64** **3.65** **3.66**

Scheme 3.21. General mechanism of metal-mediated nucleophilic aromatic substitution.

Pearson and co-workers demonstrated the versatility of the metal-promoted S_NAr reactions and their applications in the synthesis of diaryl ethers.[24, 46-48] Early studies by Pearson showed that arene-manganese complexes represent promising electrophilic platforms in the S_NAr process. This later paved the way to the synthesis of cyclopentadienyl iron complexes. It was found that ruthenium complexes are superior to the latter because of the ease of preparation and handling, and a simple photolytic demetallation process. Moreover, it was observed that the ruthenium complexes can enhance the activity of the halide twice as much as that of the nitro group.[48] For example, ruthenium complex **3.68** was easily prepared in high yields by refluxing compound **3.67** with $[CpRu(CH_3CN)_3]^+PF_6^-$ in CH_2Cl_2 (Scheme 3.22). Treatment of complex **3.68** with phenol **3.69** provided compound **3.70**. Subsequent photolytic demetallation of **3.70** afforded the diaryl ether **3.71**.



Scheme 3.22. Metal-mediated nucleophilic aromatic substitution.

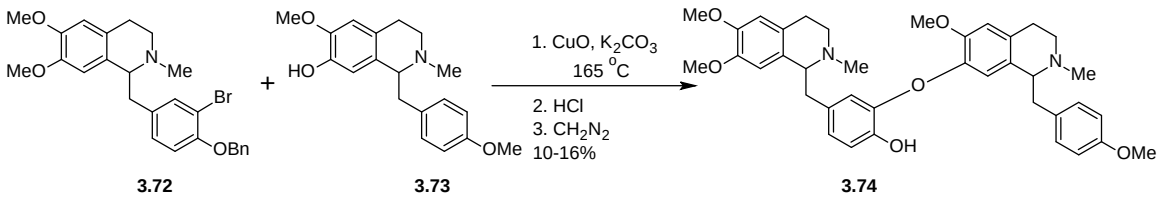
3.4. SYNTHESES OF BISBENZYLTETRAHYDROISOQUINOLINES: A LITERATURE OVERVIEW

Bisbenzyltetrahydroisoquinolines are mostly synthesised by the Bischler-Napieralski reaction for the construction of the isoquinoline nucleus. The diaryl ether bond that links two benzylisoquinolines in bisbenzyltetrahydrosoquinolines has been achieved by copper-catalysed Ullmann condensation and nucleophilic aromatic substitution reactions.[49-53] Other methods which have been developed include, palladium-catalysed Ullmann condensation[54] and electrochemical zinc-mediated procedure.[55, 56]

3.4.1. Copper-Catalysed Ullmann Coupling Reaction

Bisbenzylisoquinolines can be synthesised by the copper-catalysed Ullmann coupling of a halobenzyltetrahydroisoquinoline and a hydroxybenzyl-tetrahydroisoquinoline. However, this route often results in either low yields or no products at all.[49] Nevertheless, the major advantage associated with this route is that the two halves of the molecule can be synthesised separately as pure enantiomers before combining them in the final stage of the synthesis. The

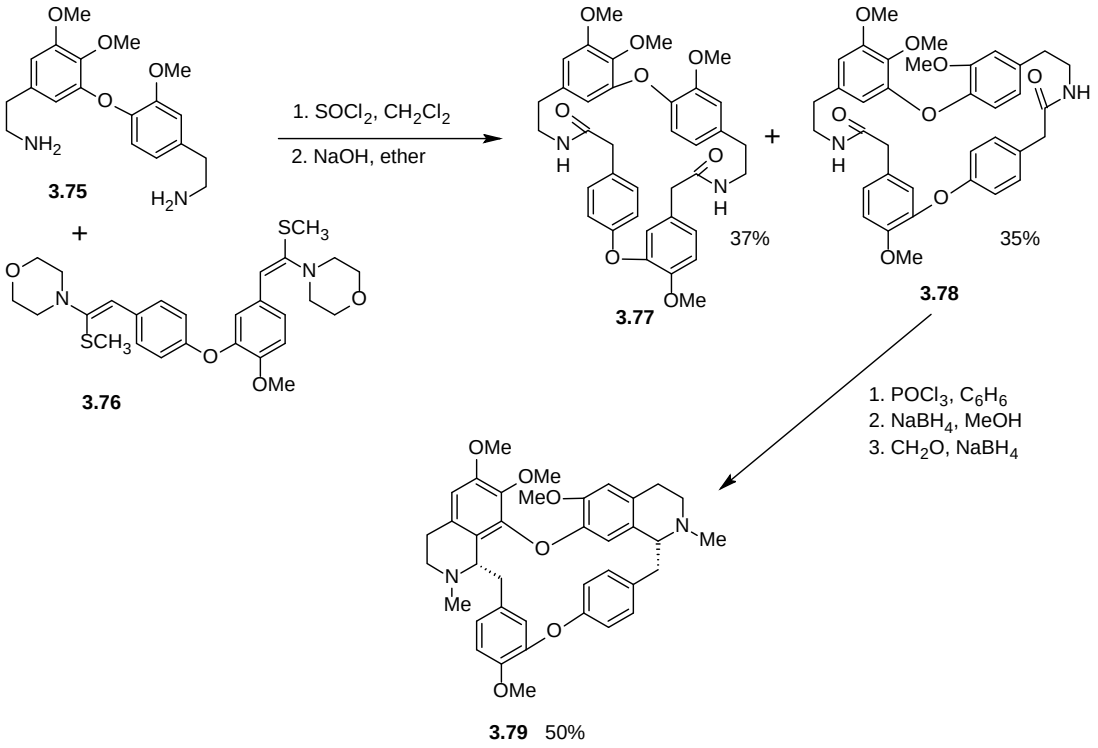
application of this route was demonstrated in the synthesis of isoliensinine (**3.74**) in Scheme 3.23. Coupling of halide **3.72** with phenol **3.73** gave **3.74** in 10-16%.[57]



3.72 **3.73** **3.74**

Scheme 3.23. Ullmann diaryl ether synthesis of isoliensinine (**3.74**).

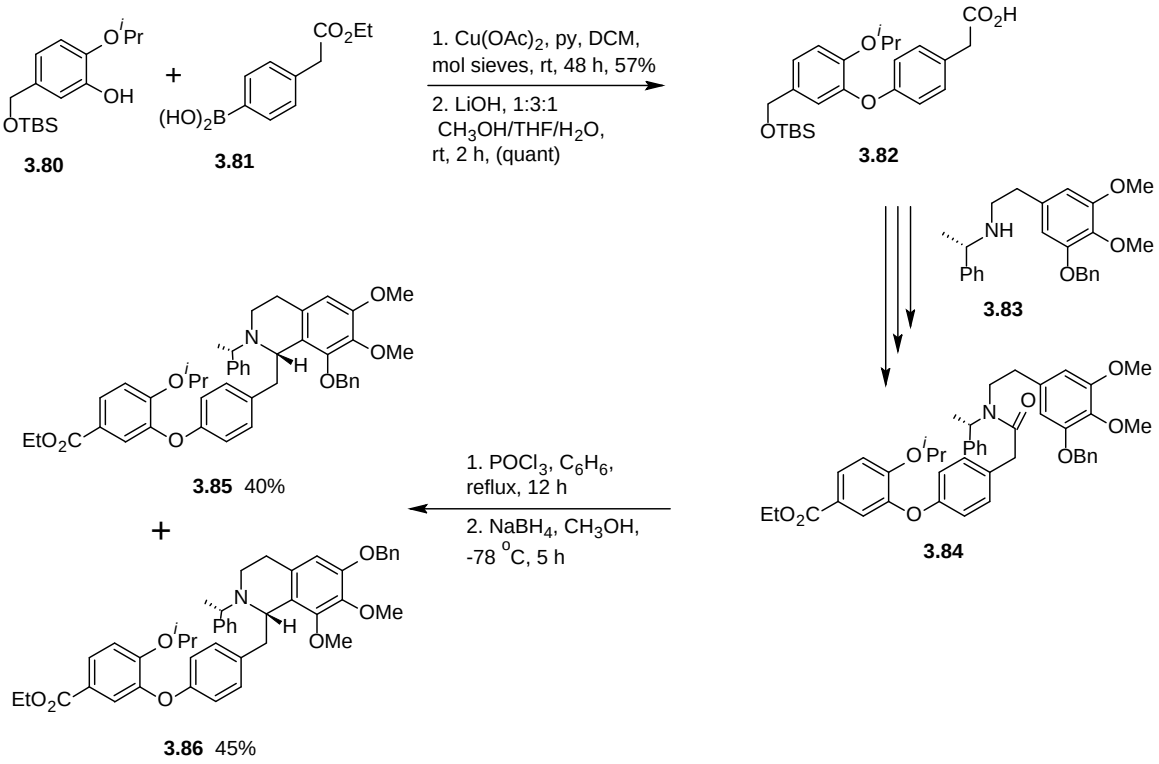
Alternatively, diaryl ether bridges can be constructed in the early stages of the synthesis, followed by building the two tetrahydroisoquinolines by either the Bischler-Napieralski or the Pictet-Spengler reactions. This concept was illustrated by Nakova and Tolkachev in the total synthesis of (±)-isotetrandrine (**3.79**) from enamino sulfides as shown in Scheme 3.24.[58] They initially prepared diaryl ethers **3.75** and **3.76** through the Ullmann coupling reaction. The two starting precursors were reacted under the Schotten-Baumann procedure to deliver the isomeric cyclobisamides **3.77** and **3.78** in 37% and 35% yields, respectively. Cyclisation of **3.78**, subsequent reduction and *N*-methylation, under reductive conditions afforded isotetrandrine in 50% yields.



Scheme 3.24. Ullmann ether synthesis of isotetrandrine (**3.79**).

3.4.2. Copper-Catalysed Ullmann reaction of Arylboronic Acid Coupled with Nucleophilic Aromatic Substitution Reactions

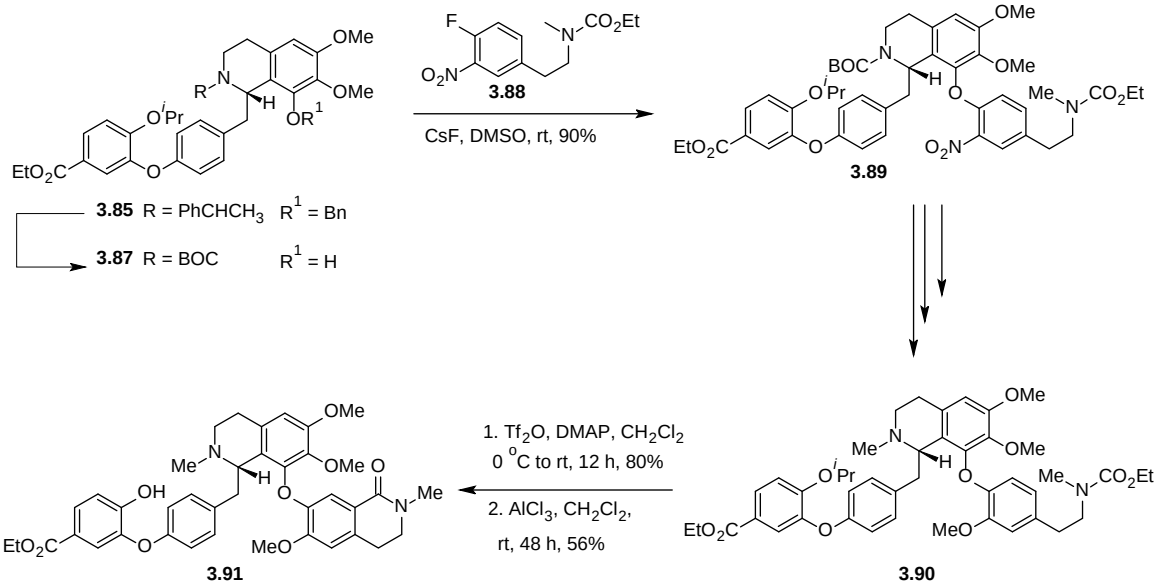
In certain instances, two methodologies have been applied for the formation of diaryl ether bridges in bisbenzylisoquinolines, which are linked by two ether bonds. For example, in 2002, a procedure which utilises both the Ullmann and nucleophilic aromatic substitution reactions to the total synthesis of (*S*)-tejedine (**3.91**), a seco-bisbenzyltetrahydroisoquinoline alkaloid was reported by Wang et al.[54] The benzylisoquinolines in (*S*)-tejedine (**3.91**) were prepared by the Bischler-Napieralski cyclisation reaction. The summarised synthetic route, which highlights the diaryl ether-forming and the isoquinoline-forming synthetic steps in the synthesis of **3.91**, is shown in Scheme 3.25 and Scheme 3.26.



3.80 **3.81** **3.82** **3.83** **3.84** **3.85** 40% **3.86** 45%

Scheme 3.25. Synthesis of **3.85** *via* boronic acid-driven Ullmann diaryl ether and Bischler-Napieralski cyclisation reactions.

The phenol **3.80** was subjected to the modified copper-catalysed coupling with boronic acid **3.81** to afford diphenyl ether **3.82.** Condensation of **3.82** with the chiral amine derivative **3.83** and functionalisation of the silyloxy group into an ester yielded the intermediate acetamide **3.84**. Bischler-Napieralski cyclisation of **3.84** with $POCl_3$, followed by reduction with $NaBH_4$, afforded the isomers **3.85** and **3.86** in 40% and 45% yields, respectively. The required regioisomer **3.85** was formed in 99% *de* (Scheme 3.25).



Scheme 3.26. Base-mediated S_NAr coupling strategy to the synthesis of (*S*)-tejedine (**3.91**).

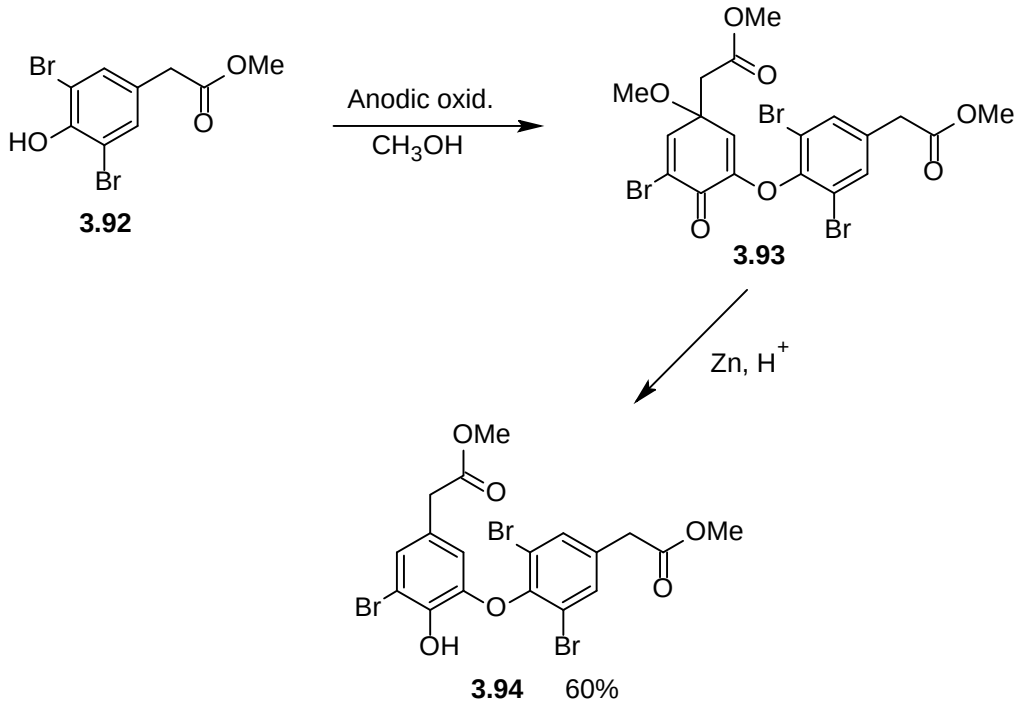
The second diphenyl ether was prepared by nucleophilic aromatic substitution of **3.87** with the nitrofluoro compound **3.88** to give **3.89** in 90% yield (Scheme 3.26).[45, 59] Conversion of the nitro group into the methoxy functionality, and *N*-methylation yielded compound **3.90**, which was activated for the final Bischler-Napieralski reaction. The penultimate step was the Bischler-Napieralski cyclisation of **3.90** using the Banwell's procedure to form the corresponding isoquinoline in a 80% yield, which upon chemoselective cleavage of the isopropyl group by $AlCl_3$ afforded (*S*)-tejedine (**3.91**).

3.4.3. Electrochemical Zinc-Mediated Procedure

A new approach to the synthesis of diaryl ethers using anodic oxidation of 2-bromo-6-chlorophenol, was reported for the first time by Yamamure and Nishiyama.[60] This method was successfully applied in the synthesis of many biologically active natural products possessing a diaryl ether bond. For example the construction of verbenachalcone, an activator of nerve growth factor from *Verbena littoralis* was by this method.[55] Very recently, Nishiyama *et al*.

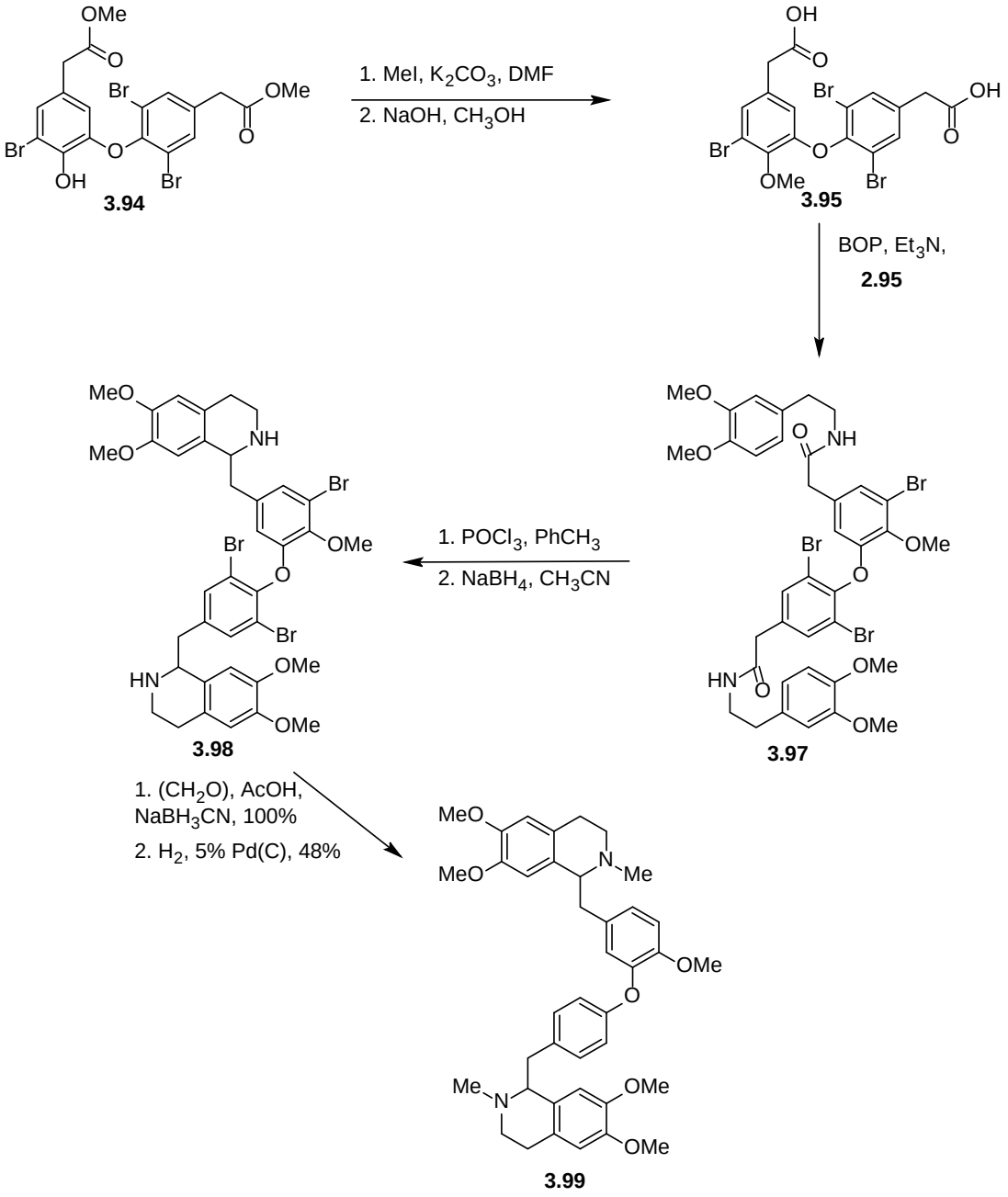
demonstrated the versatility of this procedure in the synthesis of *O*-methylthalibrine.[56]

The initial step in the synthesis of *O*-methylthalibrine involved anodic oxidation of the 2,6-dibromophenol **3.92** to effect a one-electron oxidation to give the corresponding dimer **3.93** as depicted in Scheme 3.27. Treatment of the dimer **3.93** with Zn powder in the presence of AcOH afforded the diaryl ether **3.94**.



Scheme 3.27. Phenolic oxidation approach to **3.94**.

Methyl protection of **3.94**, followed by base hydrolysis, afforded the dicarboxylic acid **3.95**. Condensation of the dicarboxylic acid with dimethoxytyramine (**2.95**) using BOP and Et_3N provided diamide **3.97**. The subsequent steps were the Bischler-Napieralski cyclisation using $POCl_3$ and reduction of the iminium salt by $NaBH_4$ to afford the corresponding bisbenzyltetrahydroisoquinoline **3.98**. *N*-methylation under reductive conditions followed by the removal of the halide by hydrogenolysis afforded *O*-methylthalibrine (**3.99**) in 48% yields (Scheme 3.28).



Scheme 3.28. Synthetic approach to *O*-methylthalibrine (**3.99**).

3.5 RESULTS AND DISCUSSIONS: SYNTHETIC STRATEGIES TOWARDS NEFERINE ANDS ITS ANALOGUES

3.5.1 Introduction

Of the numerous methods which have been developed for the construction of the ether bridge between two phenyl rings, only a few methods have been applied in

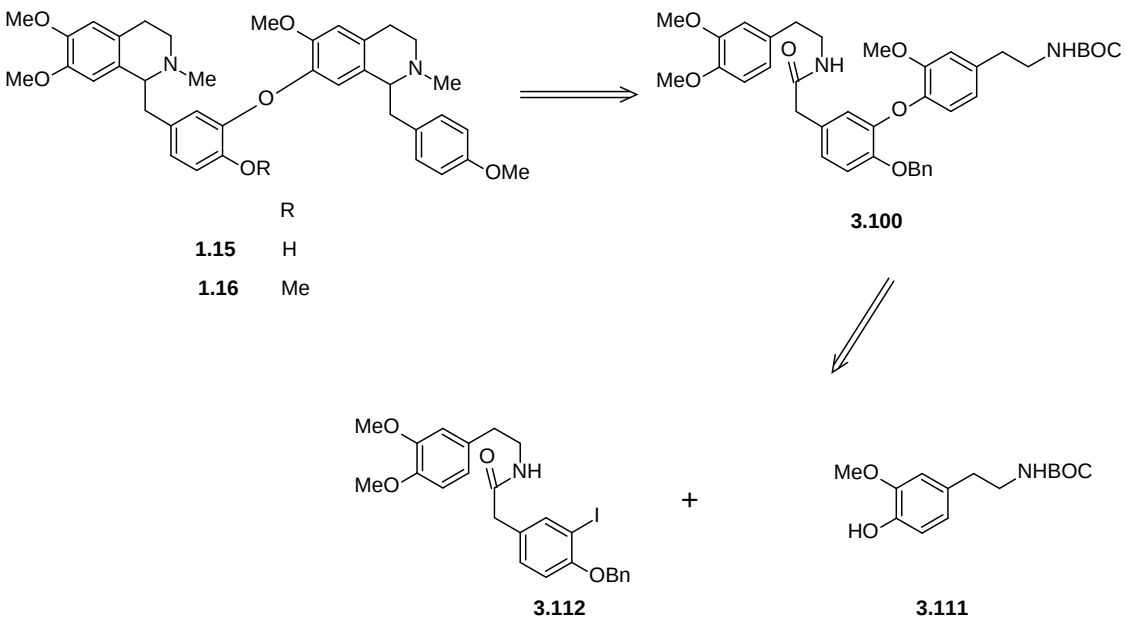
the syntheses of the bisbenzyltetrahydroisoquinolines.[22, 49, 50, 52, 54, 58, 61] The nucleophilic aromatic substitution reaction has proven to be the most efficient method for the synthesis of diaryl ethers from small substrates and large molecules alike.[50, 52-54] However, in the synthesis of naturally-occurring bisbenzyltetrahydroisoquinolines, the method becomes unattractive due to additional steps, which involve conversion of the nitro group into the desired oxygenation substituents found in these molecules.[54] Even though the Ullmann coupling reaction gives low to moderate yields, it has been used in several instances in the synthesis of the bisbenzyltetrahydroisoquinolines, mainly because it does not require additional activating substituents.These need to be removed later or converted into oxygenated substituents.[49, 57, 58, 62]

In this section, the results obtained towards the total synthesis of neferine (**1.15**) and its analogue *O*-methylneferine (**1.16**) are discussed. Three different synthetic routes were followed for the synthesis of **1.15** and **1.16**. The first two methods were based on the Ullmann coupling reaction for the formation of the diaryl ether bond. The first method entailed an early construction of the ether link and late assembly of the two isoquinoline rings on the ether bridge. The second method involved synthesis of the two isoquinoline nuclei, and coupling of the two by the Ullmann reaction in the late stages of the synthesis. In the last synthetic strategy, the diaryl ether bridge was constructed by the nucleophilic aromatic substitution reaction. In all the three methods, the two isoquinoline rings were formed by the Bischler-Napieralski cyclisation reaction.

3.5.2 The First Approach towards the Synthesis of Neferine (1.15)

The retrosynthetic analysis in Scheme 3.29 outlines the key steps towards the synthesis of neferine (**1.15**) and its methyl derivative **1.16**. The first disconnection envisaged an early Bischler-Napieralski cyclisation of the amide **3.100** and enantioselective reduction to afford to the western half of the bisbenzyltetrahydroisoquinolines **1.15** and **1.16**, followed by late construction of

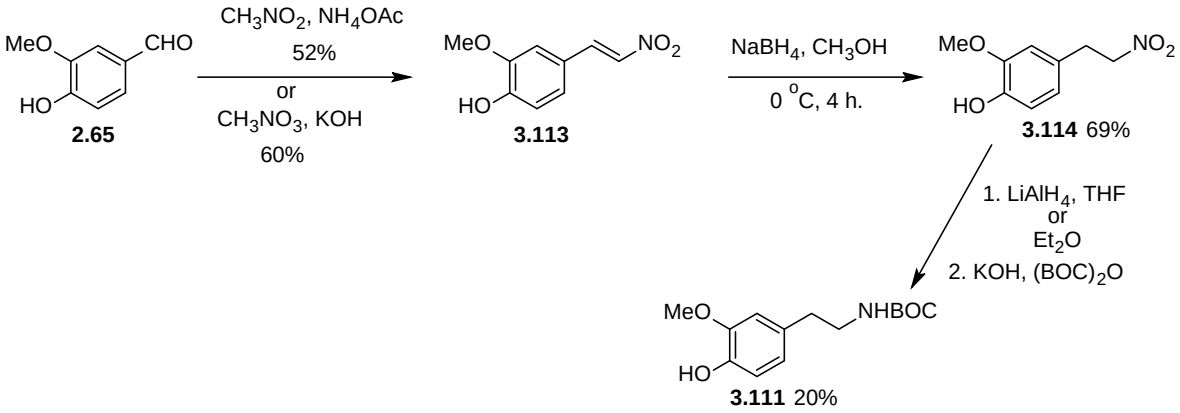
the eastern half. In turn, the intermediate **3.100** would be prepared by Ullmann diaryl ether coupling of iodinated acetamide **3.112** with phenol **3.111**.



Scheme 3.29. The first retrosynthetic strategy for neferine (**1.15**).

3.5.2.1 Synthesis of 4-hydroxyphenethylamine 3.111

The synthesis of neferine (**1.15**) in the first approach was commenced by preparing the first precursor for the Ullmann coupling reaction, the 4-hydroxyphenethylamine **3.111**. This was achieved in a series of steps starting from 4-hydroxy-3-methoxybenzaldehyde (**2.65**). Since β-phenethylamine could be easily prepared by the Henry reaction (Chapter 2), we applied the same concept to the synthesis of the phenethylamine **3.111** (Scheme 3.30). The desired nitrostyrene **3.113** was initially prepared by following the Knoevenagel method. The nitroaldol condensation of vanillin (**2.65**) with nitromethane in acetic acid and ammonium acetate or in basic medium of KOH delivered the desired product **3.113** in moderate yield of 52% and (60%), respectively. The ^{1}H NMR spectrum of **3.113** displayed the presence of 3 aromatic protons resonating at δ_H 7.16 (dd, 1H, *J* = 8.3 and 2.0 Hz), 7.02 (d, 1H, *J* = 2.0 Hz) and 6.99 (d, 1H, *J* = 8.3 Hz), one methoxy group at δ_H 3.97, two vinylic protons appearing at δ_H 7.97 (d, 1H, *J* = 14.1 Hz), 7.53 (d, 1H, *J* = 14.1 Hz), and the hydroxy group resonating at δ_H 6.06.



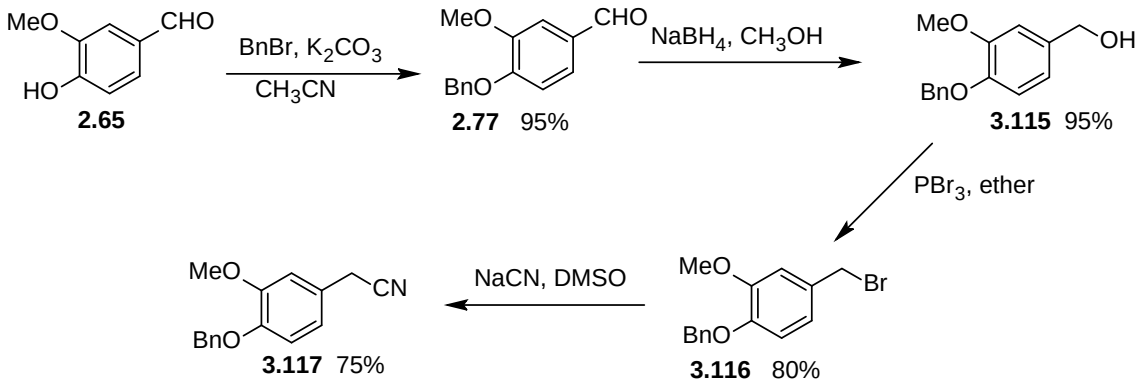
Scheme 3.30. Application of Henry reaction to the synthesis of amine **3.111**.

The next step was the one step reduction of the corresponding nitrostyrene **3.113** to the phenethylamine **3.111** using $LiAlH_4$ in THF, followed by the *in situ* protection of the produced free amine with (*t*-BOC)$_2$O. Unfortunately the expected product was not formed after several attempts. Failure to reduce **3.113** with $LiAlH_4$ prompted us to synthesise the saturated nitro compound **3.114** first. The reduction of **3.113** with $NaBH_4$ yielded the saturated nitro compound **3.114** in good yield (69%). The ^{1}H NMR of **3.114** confirmed the presence of three aromatic protons appearing at δ_H 6.85 (d, 1H, J = 8.3 Hz), 6.69 (2H, overlap), one methoxy group at δ_H 3.85 two methylene groups at δ_H 4.57 (t, 2H, *J* = 7.3 Hz) and 3.23 (t, 2H, *J* = 7.3 Hz) and the hydroxy group at δ_H 5.75.

The final reduction of the nitro group was carried out by reacting **3.114** with $LiAlH_4$ in THF followed by the addition of (*t*-BOC)$_2$O, but unfortunately the reaction did not produce good results. The amine **3.111** was obtained in 20% yields. Due to poor yields, an alternative method for the preparation of **3.111** was investigated.

The new method for the preparation of phenethylamine **3.111** proceeded through the reduction of the phenylacetonitrile **3.117** (Scheme 3.31). The initial step of the synthesis was the derivatisation of **2.65** to its benzyl ether **2.77**. The protection was performed by treating **2.65** with K_2CO_3 as a base and benzyl bromide as an alkylating agent in CH_3CN at 90 ºC. The 4-benzyloxy-3-methoxybenzaldehyde (**2.77**) was obtained in 95% yield. The subsequent step was the reduction of the aldehyde to the benzylic alcohol **3.115**. Reduction was performed in ethanol using

sodium borohydride as the reducing agent. The reduction step was followed by bromination. Different brominating reagents were employed to brominate the benzylic alcohol **3.115**.

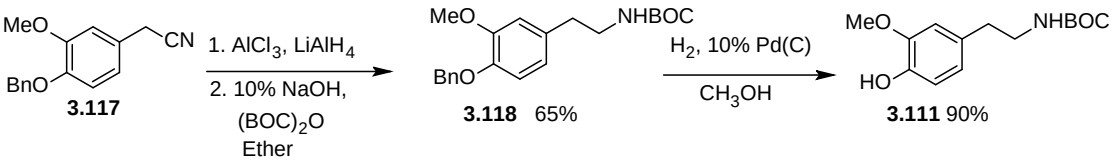


Scheme 3.31. Preparation of phenylacetonitrile **3.117**.

Initially carbon tetrabromide in THF was employed in the reaction; unfortunately, it did not give the targeted compound **3.116**. We then shifted our attention to *N*-bromosuccinamide (NBS), whereby the THF solution of the alcohol **3.115** was treated with NBS and PPh_3 at room temperature. However, the expected product was still not obtained under the latter conditions. The brominated product **3.116** was finally obtained when phosphorus tribromide (PBr_3) was used as the brominating reagent. The reaction was carried out as follows: the benzylic alcohol **3.115** was first dissolved in ether and the phosphorus tribromide solution in ether was added dropwise for 30 min and the reaction was left to stir overnight to yield compound **3.116** in 80% yield.

It should be noted that this product was very unstable upon heating and purification by silica gel column chromatography; hence it was used in the next step without any purification. The instability of this compound was believed to arise from the *para* substituent effect. Having successfully brominated the benzyl alcohol, the next step was one carbon homologation by the cyanation reaction. The benzyl bromide **3.116** was reacted with sodium cyanide in DMSO at 40 ºC for 4-6 h. The reaction neatly produced the phenylacetonitrile **3.117** as a sole product in good yield (75%).

Initial attempts to carry out the reduction reaction with $LiAlH_4$ in the presence of THF resulted in an inseparable mixture of products. Using ether instead of THF did not give positive results. At this stage it was observed that the problem was not arising from the solvents. Therefore, it was required that a stronger reducing agent be used. Inspired by the work of Nystrom, which showed that phenylacetonitriles could be reduced to the corresponding phenethylamines by activating $LiAlH_4$ with $AlCl_3$, we decided to employ the same reaction conditions for the reduction of **3.117** (Scheme 3.32).[63]



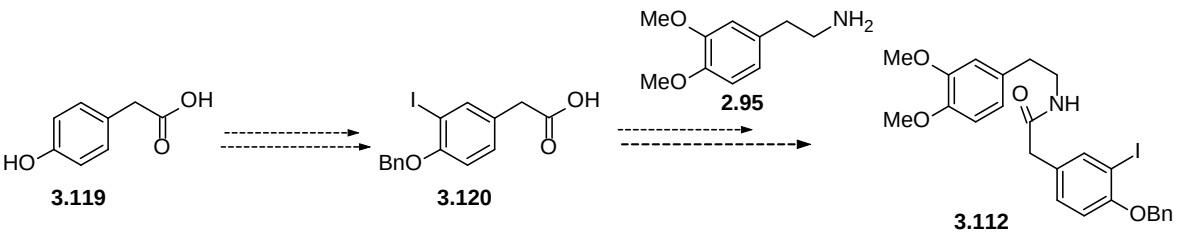
Scheme 3.32. Preparation of hydroxyphenethylamine **3.111** *via* reduction of acetonitrile.

The treatment of phenylacetonitrile **3.117** with the strong reducing agent generated from $LiAlH_4.AlCl_3$ (1:1) in ether followed by the *in situ* protection of the produced amine afforded phenethylamine **3.118** in 65% yield.[63, 64] The ^1H NMR spectrum confirmed the presence of an ABX spin system in the aromatic region at 6.84 (1H, d, J = 8.2 Hz), 6.75 (1H, d, J = 2.2 Hz) and 6.68 (1H, dd, J = 8.2 and 2.2 Hz), the five aromatic protons of the benzyl group (as multiplets) and a methoxy signal integrating for three protons at δ_H 3.81. Moreover, the NHBOC signals resonated at δ_H 1.46 (9H, s) and the broadened singlet integrating for one proton appeared at δ_H 4.56 (N<u>H</u>BOC). The two signals each integrating for two protons appearing at δ_H 3.37 and 2.74 were assignable to $CH_2C\underline{H}_2NHBOC$ and $C\underline{H}_2CH_2NHBOC$, respectively. ^{13}C NMR spectrum indicated the disappearance of a nitrile carbon and appearance of a characteristic methylene carbon resonating at δ_C 44.3 ($CH_2\underline{C}H_2NHBOC$). The cleavage of the benzyl group from phenethylamine **3.118** was accomplished in excellent yield (90%) with H_2 on 10% Pd(C) to give the requisite phenol **3.111** for the projected diaryl ether coupling.

3.5.2.2 Preparation of the iodinated acetamide 3.112

Having successfully synthesised the first coupling partner for the Ullmann condensation reaction, the interest was now projected towards the synthesis of the second coupling partner, the iodoacetamide **3.112**. From the literature, it was seen that the Ullmann coupling reactions of phenyl bromides and phenols give low to moderate yields. However, the use of aryl boronic acids or aryl iodides as coupling partners of phenols has been reported to improve yields of the Ullmann coupling reactions.[21, 22, 27, 65, 66] Thus an iodinated substrate was chosen in this study instead of the brominated one in order to take advantage of the high reactivity of the iodides.

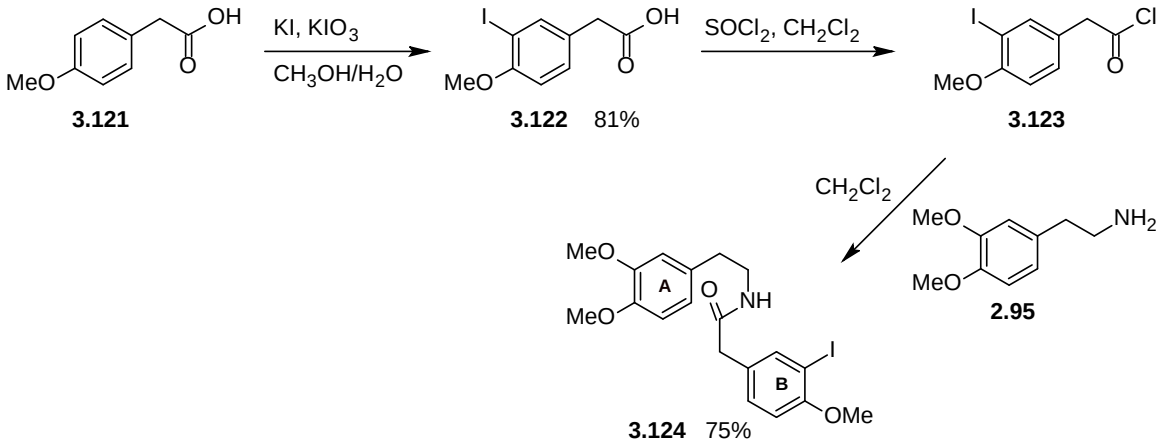
The acetamide **3.112** was planned to be prepared by coupling of iodinated phenylacetic acid **3.120** and phenethylamine **2.95** (Scheme 3.33). It was anticipated that the preparation of the iodophenylacetic acid **3.120** would present some problems as *ortho*-iodination of *para*-substituted phenols has been reported to give high yields of diiodinated products, even when mild reaction conditions are employed.[67, 68] Thus a model reaction was performed to establish the optimum conditions for the preparation of 3-iodophenylacetic acid **3.120**.



Scheme 3.33. Synthetic route for iodoacetamide **3.112**.

In the model reaction, a commercially available 4-methoxyphenylacetic acid (**3**.**121**) was used as a test compound (Scheme 3.34). The phenylacetic acid **3.121** was thus converted to the aryl iodide **3.122** under milder iodinating conditions, by reacting it with KI/KIO_3, at room temperature in a mixture of water and methanol with the slow addition of dilute HCl.[67, 68] The targeted compound **3.122** was obtained in a good yield (81%). The ^1H NMR confirmed the presence of an ABX spin system in the aromatic region, one methoxy group and one methylene group,

resonating at δ_H 3.88 (3H, s,) and 3.57 (2H, s,), respectively. The ^{13}C NMR spectrum of the compound **3.122** exhibited a signal further upfield (δ_H 85.9), which represented the iodinated aromatic carbon.

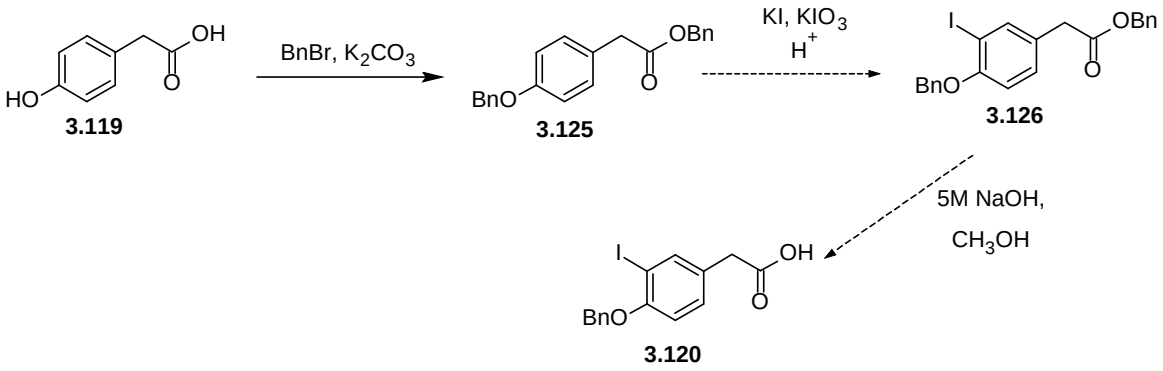


Scheme 3.34. Preparation of acetamide **3.124**.

Having successfully prepared the iodophenylacetic acid **3.122**, we decided to test the subsequent steps leading to the preparation of the acetamide. The acetamide **3.124** was prepared by conversion of **3.122** into an acid chloride **3.123** and subsequent condensation with the commercially available phenethylamine **2.95** (Scheme 3.34). The ^1H NMR spectrum of acetamide **3.124** displayed six aromatic protons resonating at δ_H 7.62 (1H, d, *J* = 2.2 Hz), 7.12 (1H, dd, *J* = 2.2 and 8.3 Hz), 6.77 (1H, d, *J* = 8.3 Hz), 6.74 (1H, d, *J* = 8.3 Hz), 6.63 (1H, d, *J* = 2.2 Hz), 6.57 (1H, dd, *J* = 2.2 and 8.3 Hz) representing the ABX spin system for both ring A and B. Additionally, the spectrum also showed the presence of three methoxy groups resonating at δ_H 3.84, 3.88 and 3.89.

Motivated by the above results, we launched the synthesis of the acetamide **3.112**. The initial step was to prepare the iodophenylacetic acid **3.120**. This was planned to be carried out by the iodination procedure employed for the synthesis of 4-methoxy-3-iodophenylacetic acid (**3.122**). The synthesis of 4-benzyloxy-3-iodophenylacetic acid (**3.120**) commenced from commercially available 4-hydroxyphenylacetic acid (**3.119**). Both the hydroxy groups of 4-hydroxyphenylacetic acid (**3.119)** were converted to the benzylated derivative

3.125 (Scheme 3.35). The next step was the iodination at the *ortho*-position to the benzyloxy group. Since KI/KIO_3 using very dilute mineral acid gave good results with 4-methoxyphenylacetic acid (**3.121**), we hoped that with **3.125**, it would still proceed smoothly to give compound **3.126**. Unfortunately it did not give us the expected results and after 24 h of reaction time only the starting material was recovered.

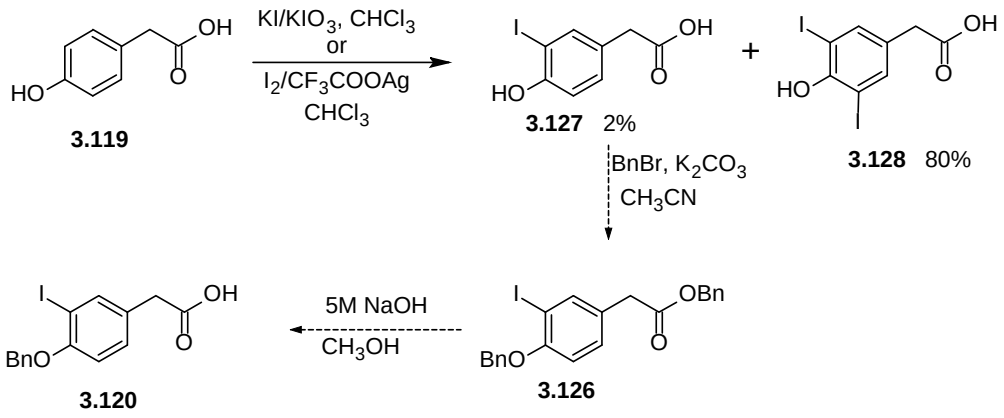


Scheme 3.35. First approach to the synthesis of iodinated phenylacetic acid **3.120**.

Switching to a different iodinating reagent did not help either. This time I_2/CF_3COOAg in the presence of $CHCl_3$ was employed as iodinating reagent.[69] Performing the reaction at high temperatures did not produce any signs of the required product. Failure of this reaction was attributed to the steric hindrance of the benzyl group, since both the incoming group (iodine) and benzyl group are large. Furthermore, the nucleophilicity of the aromatic ring was decreased by protection. Again, the silver salts generally led to iodination at the *para* position, but in this case the *para* position of the aromatic ring was blocked.

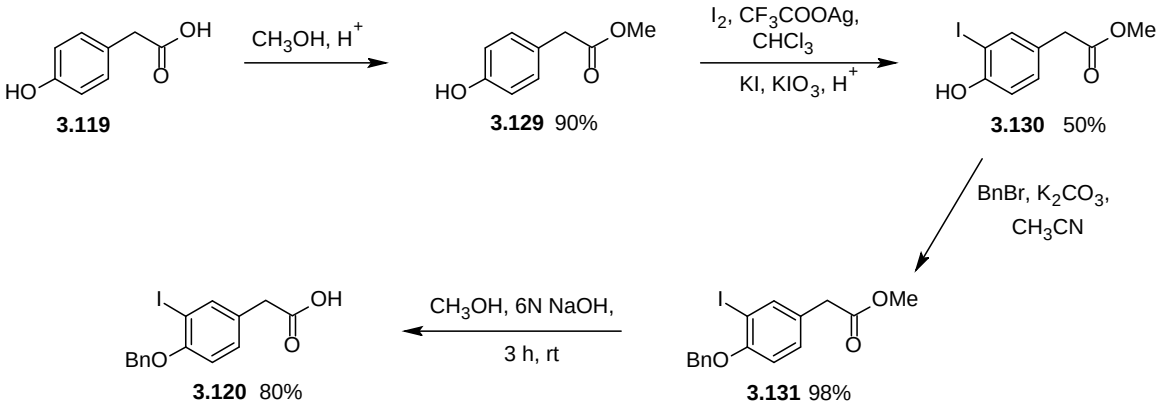
Having experienced the problems with the synthesis of 4-benzyloxy-3-iodophenylacetic acid (**3.120**) using the above synthetic route, we decided to modify the route. Instead of protecting the aromatic hydroxy group as benzyl, the acid was iodinated in its free form (Scheme 3.36). Treating 4-hydroxyphenylacetic acid (**3.119**) with KI/KIO_3 or I_2/CF_3COOAg led to the mono **3.127** and diiodinated **3.128** products with the latter being the dominant product. The monoiodinated product **3.127** was produced in 2% and 3% yields, respectively, while the

diiodinated product **3.128** was afforded in 78% and 80% yields, respectively. Lowering the temperature to 0 ^{o}C and reducing the stoichiometric amount of the iodinating reagents did not improve the results.



Scheme 3.36. Second approach to the synthesis of iodinated phenylacetic acid **3.120**.

The failure of this reaction prompted us to explore other synthetic routes. The first challenge was to selectively protect the two hydroxy groups present in the starting material as it contains a carboxylic acid and a phenol group. Therefore, in the beginning 4-hydroxyphenylacetic acid (**3.119**) was chemoselectively protected to its methyl ester following the Fischer esterification procedure (Scheme 3.37). This was executed by dissolving compound **3.119** in methanol with catalytic amount of HCl. Dean-Stark apparatus was employed to trap water which was forming during the progress of the reaction. The formation of the product **3.129** was confirmed by the ^{1}H NMR that showed the disappearance of the acid. The ^{1}H NMR showed the presence of methyl ester appearing at δ_H 3.72. With the ester **3.129** in our hands, the next step was its iodination at C-3.



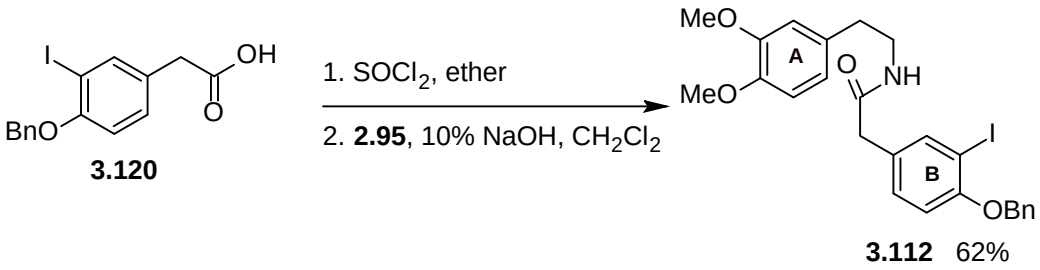
Scheme 3.37. Third approach to the synthesis of **3.120.**

The introduction of iodine was carried out following two electrophilic aromatic substitution procedures. Initially the method that utilises KI/KIO_3 in methanol with the slow addition of a mineral acid (HCl) gave two identifiable products, the monoiodinated (**3.130**) and diiodinated phenylacetates in 30% and 25% yields, respectively. Having realised that this method was not regioselective enough, another iodinating method which was hoped to be regioselective was investigated. This method was initiated by reacting 4-hydroxyphenylacetate (**3.129**) with silver trifluoroacetate and molecular iodine at room temperature for 12 h. Similarly, it gave both the mono **3.130** and diiodinated product in 50% and 25% yields, respectively.

Compound **3.131** was obtained in high yield (98%) by the benzylation of **3.131.** The reaction was carried out by treating iodophenylacetate **3.130** with benzyl bromide, whereby potassium carbonate was used as the base. This reaction was followed by ester hydrolysis with 6N sodium NaOH for 3 h at room temperature to furnish 4-benzyloxy-3-iodophenylacetic acid (**3.120**) in 80% yield.

Having successfully prepared 4-benzyloxy-3-iodophenylacetic acid (**3.120**), the next step was formation of the acetamide **3.112** (Scheme 3.38). This entailed preparation of the acid chloride as the initial step. The process involved refluxing **3.120** in the presence $SOCl_2$ in CH_2Cl_2. Following the removal of the excess thionyl chloride under vacuum, the freshly prepared acid chloride was immediately used

in the following step without further purification. The corresponding acetamide **3.112** was prepared in modest yield (62%) by dropwise addition of 3,4-dimethoxyphenethylamine (**2.95**) into a solution of the acid chloride in ether. The ^{1}H NMR spectrum of acetamide **3.112** displayed six aromatic protons resonating at δ_H 7.65 (1H, d, *J* = 2.2 Hz), 7.54-7.32 (5H, m, PhCH$_2$O), 7.09 (1H, dd, *J* = 2.2 and 8.4 Hz), 6.79 (1H, d, *J* = 8.4 Hz), 6.77 (1H, d, *J* = 8.4 Hz), 6.64 (1H, d, *J* = 2.2 Hz), 6.56 (1H, dd, *J* = 2.2 and 8.4 Hz), representing the ABX spin system for both ring A and B. The spectrum also showed the presence of two methoxy groups resonating at δ_H 3.85 and 3.89. With the iodinated acetamide **3.112** in hand, the attention was directed towards the formation of the diaryl ether bond by employing the Ullmann coupling reaction.



3.120 **3.112** 62%

Scheme 3.38. Synthesis of acetamide **3.112**.

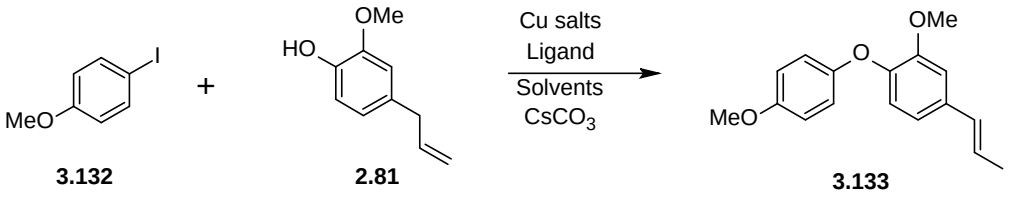
3.5.2.3 Ullmann ether coupling

Having successfully synthesised the two major precursors **3.111** and **3.112**, the next step was to couple them to form the diaryl ether bond. Initially model reactions were performed for the optimisation of the reaction conditions for the Ullmann ether coupling using phenols and aryl iodides, which bear substitution patterns similar to those in the intermediate precursors **3.111** and **3.112**. Taking advantage of the commercially available eugenol **2.81** and iodoanisole **3.132**, we decided to couple the two compounds in order to pave a way for the synthesis of the diaryl ether **3.100**, which is a requisite precursor for neferine (**1.15**).

The influence of critical reaction parameters including Cu source, ligand and solvent were investigated for the Ullmann coupling reaction. A model reaction of

eugenol **2.81** with iodoanisole **3.132** under the catalysis of CuO/pyridine at 160 ºC in toluene proceeded smoothly within 12 h to afford the corresponding diaryl ether **3.133** in 30% yield (Scheme 3.39).[28, 57] The ^{1}H NMR spectrum of compound **3.133** exhibited seven aromatic protons at δ_H 6.96 (1H, d, J = 1.7 Hz, H-2′), 6.93 (2H, d, J = 8.9 Hz, H-2,6), 6.83 (3H, overlap, H-3,5,6′), 6.77 (1H, d, J = 8.2 Hz, H-5′), two olefinic protons at δ_H 6.36 (1H, dd, J = 15.8 and 1.5 Hz, CH=CHMe) and 6.16 (1H, m, CH=CHMe). The spectrum also displayed the presence of two methoxy groups resonating at δ_H 3.87 (3H, s) and 3.78 (3H, s). Furthermore, there was a methyl resonance at δ_H 1.88 (3H, dd, J = 6.6 and 1.5 Hz) typical of a methyl group adjacent to an alkene, caused by the isomerisation of the terminal allyl double bond into a more stable alkene. The ^{13}C NMR spectrum of **3.133** showed the resonances of the internal alkene at δ_C 130.5 and 125.0 and the disappearance of the methylene carbon.

The low yields obtained in this reaction do not reflect the true efficiency of this reaction since the pioneering work by Evans *et al.*[28] showed better yields with closely related starting substrates. However, changing the ligand to DMG, the solvent to CH_3CN and the temperature, resulted in the improvement of the yield of 50%.[70] The improvement of the yield in the latter procedure was attributed to conducting the reaction at a slightly lower temperature compared to the relatively higher temperatures used in the former procedure.



3.132 **2.81** **3.133**

Scheme 3.39. The Ullmann coupling model reaction.

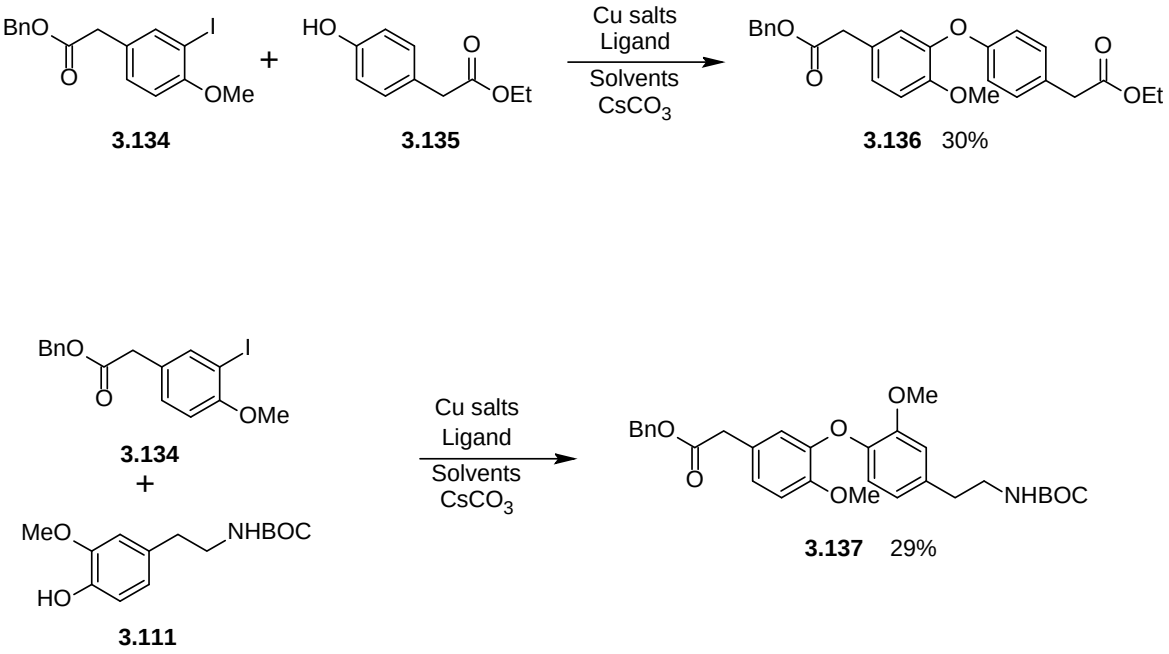
Motivated by the results reported by Song *et al.*,[66] who reported an Ullmann reaction that tolerates very delicate molecules and is fast at lower temperatures, we decided to follow their protocol in order to increase the yield of **3.133**. The use of a catalytic amount of CuCl as a copper source, TMHD as a ligand and NMP as solvent at lower temperatures (100 ^{o}C) turned out to be the best method and

produced the diaryl ether **3.133** in a 70% yield. In this reaction TMHD was used as a copper coordinator and $CsCO_3$ as the base. Surprisingly, using CuI as a copper source instead of CuCl, without altering other parameters, lowered the yield to 65%. A summary of the results obtained in coupling of eugenol (**2.81**) and iodoanisole **3.132** under different reaction conditions is given in Table 3.1.

Table 3.1. Ullmann coupling of eugenol (**2.81**) and iodoanisole **3.132** under different reaction conditions.

Entry	Cu salts	Ligand	Solvent	Temp (^oC)	Base	(Yield, %)
1	CuO	Pyridine	Toluene	160	K_2CO_3	30
2	CuO	DMG	CH_3CN	145	$CsCO_3$	50
3	CuCl	TMHD	NMP	110	$CsCO_3$	70
4	CuI	TMHD	NMP	110	$CsCO_3$	65

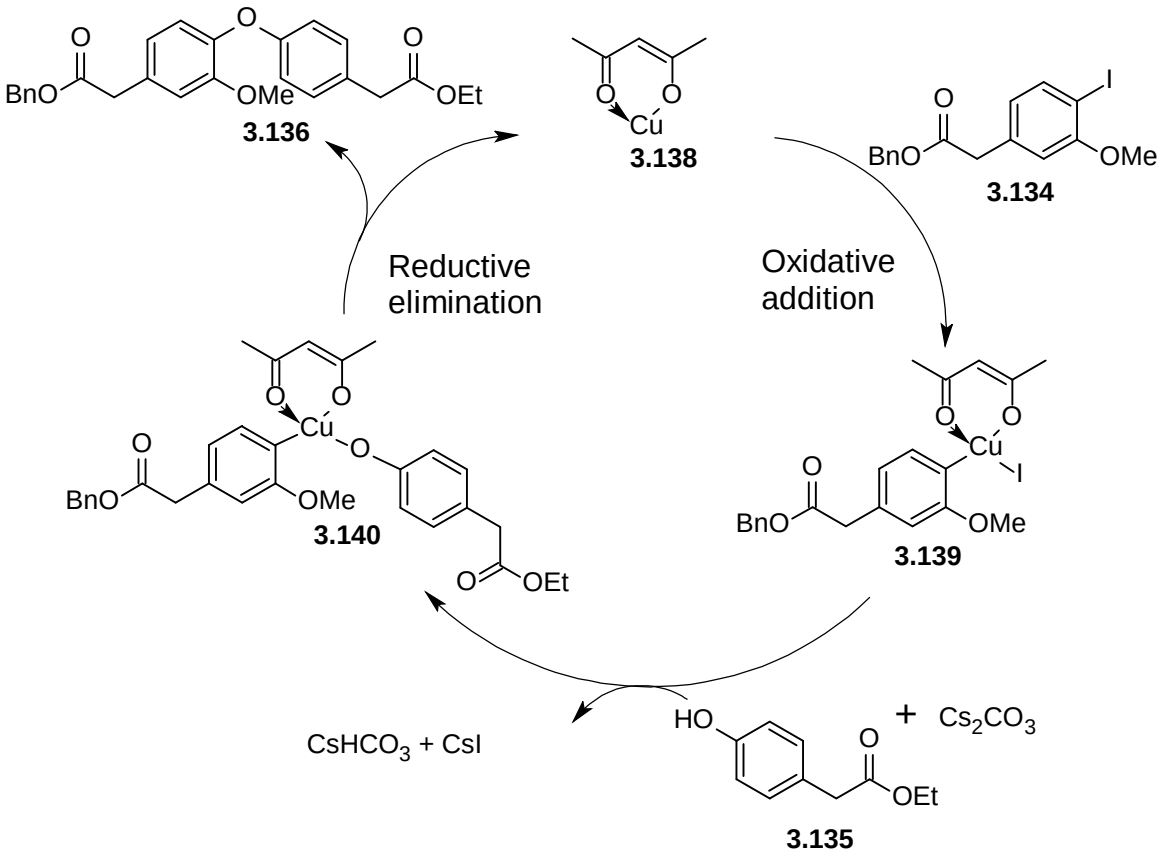
To establish the versatility of the Evans and Song procedures, other substrates were tested for the Ullmann coupling reaction (Scheme 3.40).[28, 66] The coupling of iodomethoxyphenylacetate **3.134** with ethyl 4-hydroxyphenylacetate (**3.135**) in the presence of a stoichiometric amount of CuO in toluene/pyridine with K_2CO_3 as a base afforded the corresponding diaryl ether **3.136** in a 30% yield. The ^1H NMR spectrum of **3.136** confirmed the presence of seven aromatic protons, one benzyloxy group, two methoxy groups and two singlets integrating for two protons assignable to the methylene groups. In the ^{13}C NMR spectrum the two diagnostic peaks of the esters were observed at δ_C 171.8 (COOBn) and 171.4 (COOEt), respectively. When phenol **3.111** was coupled with aryl iodide **3.134** using exactly the same reaction conditions, the diaryl ether **3.137** was formed in 28% yield. Using the optimised reaction conditions, whereby the Ullmann coupling was performed in the presence of TMHD, NMP and $CsCO_3$ also gave the diaryl ether **3.135** and **3.136** in low yields of 30% and 29%, respectively.



Scheme 3.40. Test reactions for the Ullmann coupling reaction.

The ^{1}H NMR spectrum of diaryl ether **3.137** exhibited six protons appearing at δ_H 6.99 (1H, dd, *J* = 2.2 and 8.4 Hz), 6.93 (1H, d, *J* = 8.4 Hz), 6.76 (3H, overlap), 6.66 (1H, dd, *J* = 8.2 and 1.9 Hz) representing the ABX spin system for both rings, the two methoxy groups at δ_H 3.87 and 3.84, respectively, and a benzyloxy group at 7.37-7.29 (5H, m) and 5.11 (2H, s). The spectrum also displayed the presence of three methylene groups at 3.54 (2H, s), 3.39 (2H, q) and 2.78 (2H, t, *J* = 6.9 Hz). Furthermore, the spectrum displayed the conspicuous protons for NHBOC resonating at δ_H 4.58 (1H, brs, NH) and 1.44 (9H,s).

The mechanism for the synthesis of diaryl ethers by the Ullmann coupling reaction as proposed by Buchwald is presented in Scheme 3.41.[71] The initial step of the mechanism envisions the oxidative addition of aryl iodide **3.134** with Cu species **3.138** to form the intermediate **3.139**. The phenol is then converted into a metal phenolate/cuprate-like intermediate **3.140**. Lastly, the intermediate **3.140** undergoes reductive elimination to form diaryl ether **3.136** and a Cu(I) species is regenerated.

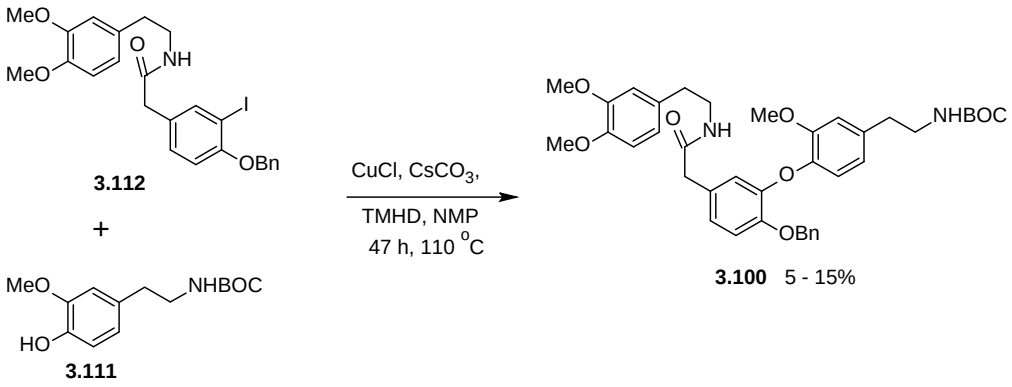


Scheme 3.41. Proposed mechanism for Ullmann diaryl ether coupling.

Having established the optimum conditions for the diaryl ether formation by the Ullmann coupling, we set out to prepare diaryl ether **3.100** as shown in Scheme 3.42. The diphenyl ether **3.100** was synthesised by coupling the iodinated acetamide **3.112** with hydroxyphenethylamine **3.111** in 5-15% yields through the modified Ullmann reaction procedure.[66, 72] Since low yields were obtained with this procedure, the classical Ullmann procedure was attempted, even though it did not produce good results with diaryl ethers **3.136** and **3.137**.[28] Similarly there was no significant improvement of the product formed. The required diphenyl ether **3.100** was obtained in only 10-15% yield.

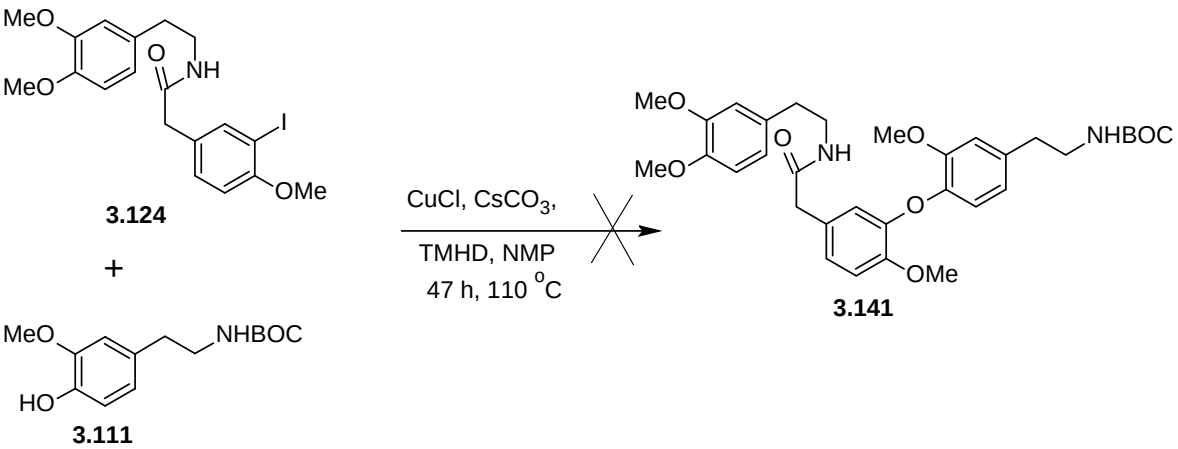
The ^{1}H NMR of compound **3.100** indicated the presence of nine aromatic protons, benzyloxy protons, three methoxy, two broad singlets which were assigned to NHBOC and $NHCOCH_2Ar$ and five methylene protons resonating at δ_H 3.49-3.67,

2.78 and 2.66. Additionally, a singlet integrating for nine protons was observed at δ_H 1.28 (BOC).



Scheme 3.42. Ullmann ether coupling of aryl iodide **3.112** and phenol **3.111**.

Even though the acetamide **3.124** was prepared as a model compound, it represents an advanced precursor for the *O*-methyl derivative of neferine **1.16**. Thus Ullmann coupling was performed between the iodoacetamide **3.124** and hydroxyphenethylamine **3.111** (Scheme 3.43). Unfortunately, this resulted in an inseparable mixture of compounds.



Scheme 3.43. Ullmann ether coupling of aryl iodide **3.124** and phenol **3.111**.

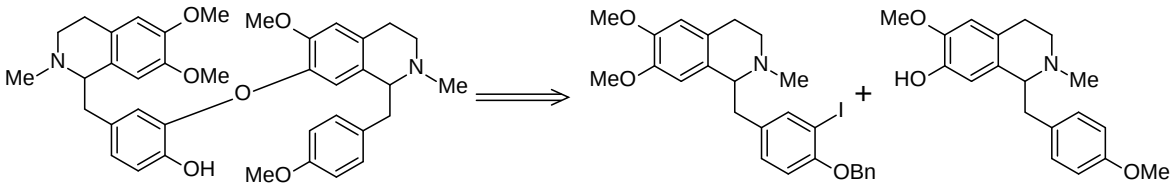
Due to the low yields obtained in the preparation of diaryl ether **3.100** and failure to prepare **3.141**, the progress towards the synthesis of neferine (**1.15**) and its analogue was hampered as more material was required in order to proceed with the remaining steps. At this stage, an alternative strategy for the synthesis of **1.15** and **1.16** was sought. The second synthetic route was designed such that some of

the advanced precursors prepared in the first route could be used. This would reduce the synthetic steps towards the target compounds. The details of the second approach towards the synthesis of neferine **1.15** are discussed in the subsequent subsection.

3.5.3 The Second Approach to the Synthesis of Neferine

The second approach to the synthesis of neferine was based on the Ullmann coupling of the two benzyltetrahydroisoquinolines, one bearing the hydroxy group at C-7 and the other one possessing the halogen atom at C-3′. Even though low yields were incurred in the Ullmann coupling stage in the first strategy, the current protocol was thought to be better than the first one as coupling would be performed as the ultimate step upon complete synthesis of the two tetrahydroisoquinolines.

The retrosynthesis of neferine through the late stage Ullmann coupling reaction is shown in Scheme 3.44. The first step would involve the Ullmann coupling of the western half iodobenzyltetrahydroisoquinoline **3.143** with the eastern half hydroxybenzyltetrahydroisoquinoline **3.142** to produce **1.15**.



1.15 **3.143** **3.142**

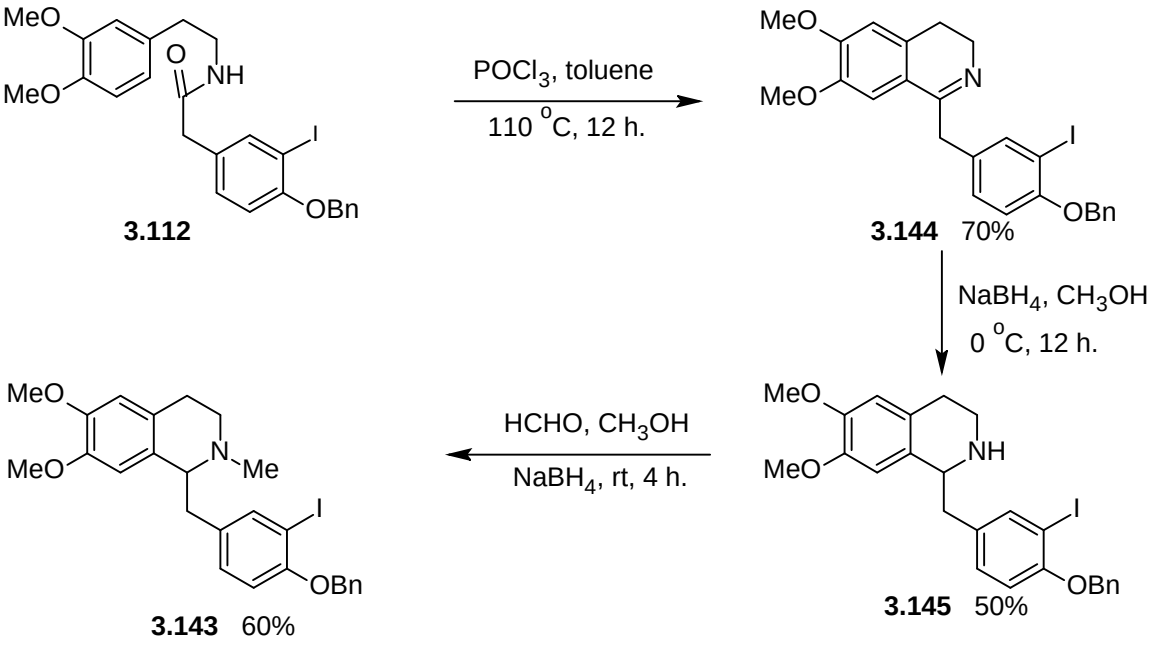
Scheme 3.44. Late stage Ullmann coupling reaction.

3.5.3.1 Synthesis of iodobenzyltetrahydroisoquinoline 3.143

The synthesis of iodobenzyltetrahydroisoquinoline **3.143** is outlined in Scheme 3.45. Since compound **3.112** was prepared previously, we took advantage of it for the preparation of **3.143**. The first step of the synthesis to **3.143** involved a

Bischler-Napieralski cyclisation. Treatment of the acetamide **3.112** with excess $POCl_3$ in toluene at 110 ^oC afforded the corresponding dihydroisoquinoline **3.144** in good yield. The ^1H NMR spectrum of **3.144** showed the expected five aromatic protons appearing at δ_H 7.79 (1H, d, *J* = 2.0 Hz), 7.30 (1H, dd, *J* = 8.0 and 2.0 Hz), 6.95 (1H, s), 6.76 (1H, d, *J* = 8.1 Hz) and 6.67 (1H, s, H-5), representing an ABX and AM spin system for rings A and B, respectively. The presence of an AM spin was a good indication that electrophilic attack has taken place to form C1-C8a. In the spectrum there were also two methoxy signals at δ_H 3.88 (3H, s), 3.77 (3H, s) and a singlet integrating for two protons at δ_H 3.94 indicative of a benzylic methylene group, present. Furthermore, there were two triplets appearing at δ_H 3.72 (2H, t, *J* = 7.5 Hz) and 2.64 (2H, t, *J* = 7.5 Hz), indicative of $CH_2C\underline{H_2}N$ and $C\underline{H_2}CH_2N$.

Due to the inherent unstable nature of dihydroisoquinolines, compound **3.144** partially decomposed after 24 h of standing at room temperature or upon purification on silica. Therefore, it was necessary to continue with the next step immediately after **3.144** was prepared. The subsequent step was the reduction of the dihydroisoquinoline **3.144** into the tetrahydroisoquinoline **3.145**. Initially, we planned an enantioselective reduction by using Noyori's chiral catalyst. Due to the high cost of the catalyst, reduction was first performed non-stereoselectively. The asymmetric reduction would be executed after all the subsequent steps leading to neferine (**1.15**) and *O*-methylneferine (**1.16**) have been carried out successfully. Thus, treatment of the methanolic solution of the imine **3.144** with $NaBH_4$ at 0 ^oC rendered the amine **3.145** in a moderate yield of 50% after column chromatographic separation. The reduction was confirmed by the appearance of a benzylic methine proton at δ_H 4.09 in the ^1H NMR spectrum. Treatment of amine **3.145** with HCHO (37%) followed by borohydride-reduction at room temperature gave *N*-methylated product **3.143** in 60% yield.



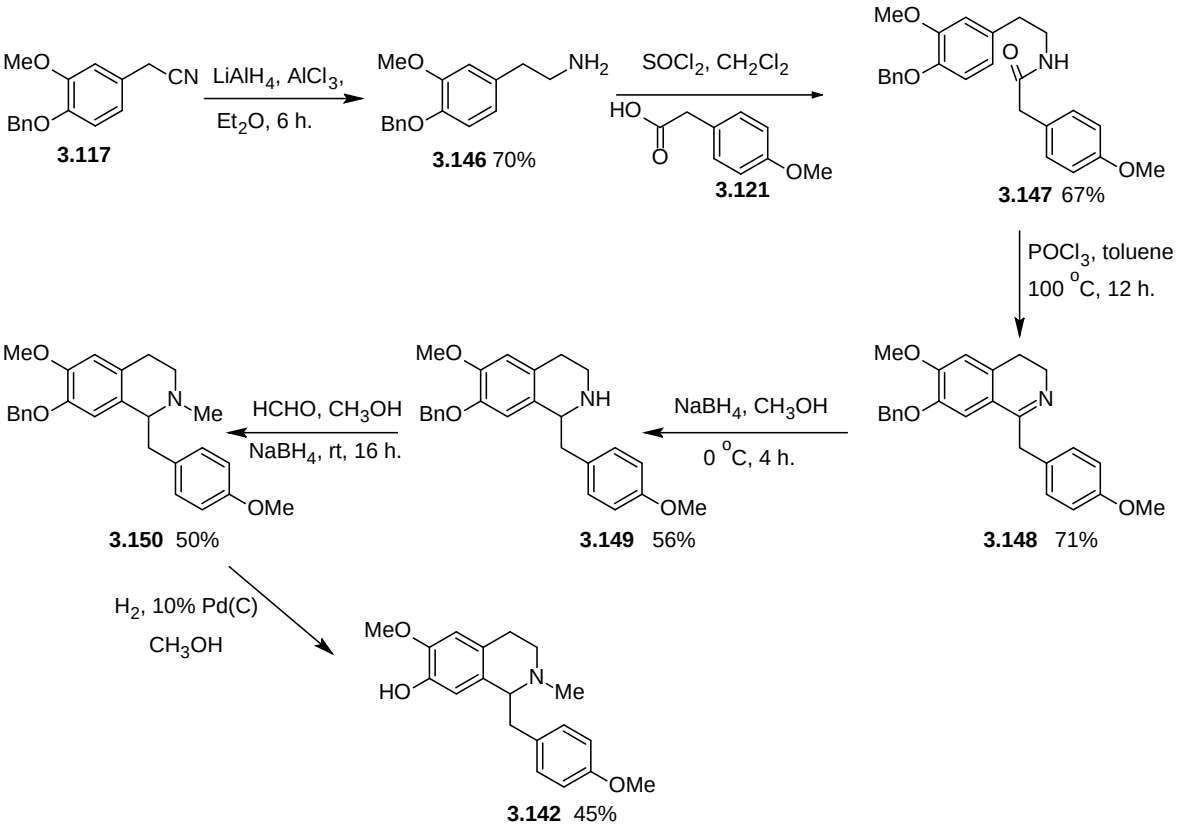
Scheme 3.45. Synthesis of iodotetrahydroisoquinoline **3.143** (precursor I).

3.5.3.2 Synthesis of hydroxybenzyltetrahydroisoquinoline 3.142

Upon the successful synthesis of aryl iodide **3.143**, attention was given to the synthesis of phenol **3.142**. The synthesis of the phenol **3.142** is summarised in Scheme 3.46. Utilising the already prepared nitrile **3.117**, the amine **3.146** was prepared in good yield by reduction of nitrile **3.117** with $LiAlH_4$ in Et_2O. The ^1H NMR spectrum of **3.146** showed the disappearance of the methylene singlet at δ_H 3.69, with the emergence of the two triplets at δ_H 2.93 and 2.68 each integrating for two protons with a coupling constant of 6.8 Hz, responsible for CH_2CH_2N. Additional to the methylene protons, another point of difference was the presence of a broad singlet at δ_H 1.75 also integrating for two protons, indicative of $CH_2CH_2N\underline{H}_2$.

Condensation of the amine **3.146** with an acid chloride generated from the reaction of 4-methoxyphenylacetic acid (**3.121**) and $SOCl_2$ following the Schotten-Baumann procedure afforded the acetamide **3.147**.[73, 74] The acetamide **3.147** was obtained in 67% yield after column chromatography. The presence of the acetamide **3.147** was confirmed by the ^1H NMR spectrum, which exhibited seven

aromatic protons at δ_H 7.07 (2H, d, *J* = 8.7 Hz), 6.81 (2H, d, *J* = 8.7 Hz), 6.72 (1H, d, *J* = 8.2 Hz), 6.62 (1H, d, *J* = 2.1 Hz) and 6.48 (1H, dd, *J* = 8.2 and 2.1 Hz). Apart from the aromatic protons, there were also two methoxy peaks resonating at δ_H 3.84 (3H, s,) and 3.79 (3H, s), two triplets at δ_H 3.43 and 2.67, the benzylic singlet at δ_H 3.46 all integrating for two protons, present. The NHCO signal appeared at δ_H 5.49 as a broad singlet. Further confirmation of **3.147** was by ^{13}C NMR, which indicated the presence of an amide carbon at δ_C 171.2. Treatment of **3.147** with $POCl_3$ in toluene at 100 ^oC under Bischler-Napieralski conditions delivered dihydroisoquinoline **3.148** in 71% yield. The ^1H NMR analyses of **3.148** showed an AA'BB' and AM spin systems in contrast to ABX and AA'BB' present in **3.147**. The disappearance of NHCO in the ^1H NMR and the emergence of AM spin system suggest that the electrophilic attack to form **3.148** has taken place.

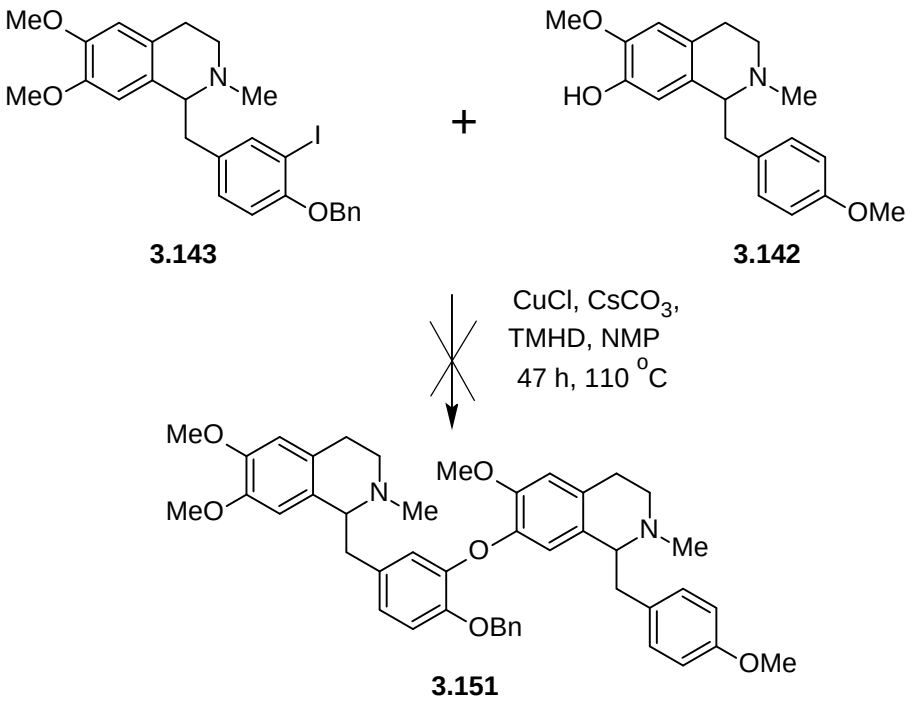


Scheme 3.46. Synthesis of hydroxytetrahydroisoquinoline **3.142**.

Reduction of the dihydroisoquinoline **3.148** with $NaBH_4$ in CH_3OH at 0 ^oC gave the amine **3.149** in modest yield (56%). The structure of **3.149** was confirmed by the presence of the C-1 methine proton at δ_H 4.07. The penultimate step was the

methylation of the N-2 atom of compound **3.149**. Condensation of the amine **3.149** with HCHO (37%) and subsequent reduction with $NaBH_4$ furnished compound **3.150** in a 50% yield. Finally, hydrogenolysis of compound **3.150** with H_2 and 10% Pd(C) delivered the phenol **3.142**.

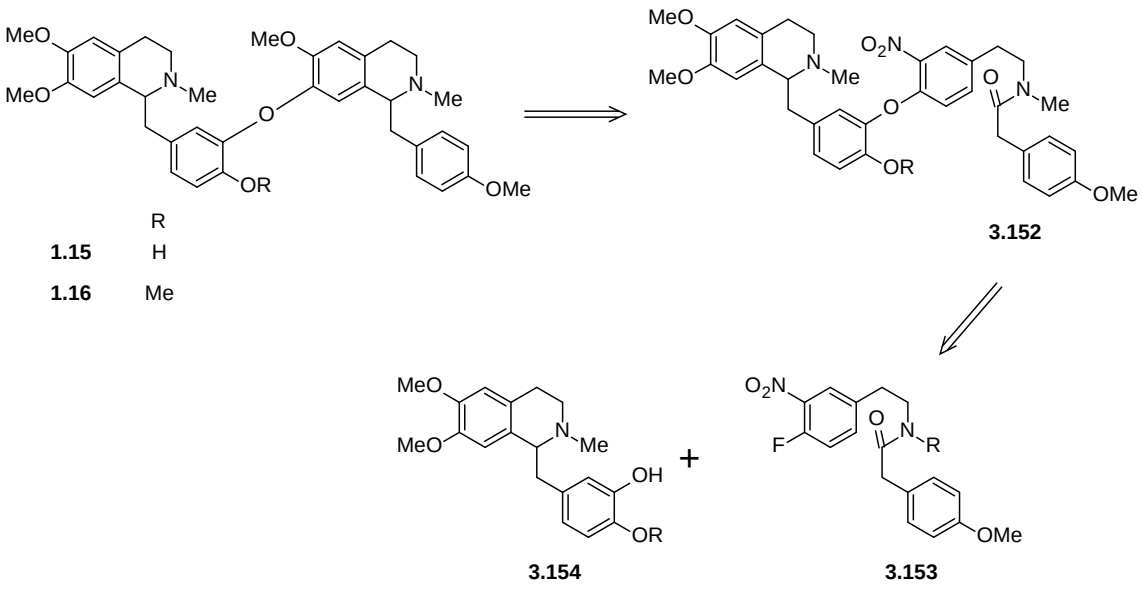
With compounds **3.142** and **3.143** in hand, we set out to synthesise compound **3.151**, which is the penultimate step to obtaining the desired compound **1.15**. The aryl iodide **3.143** and phenol **3.142** were subjected to the Ullmann coupling conditions. The initial procedure demonstrated by Evans that was followed did not deliver the desired product and neither did the procedure developed by Song *et al*., irrespective of several attempts that were made. Failure to couple the two isoquinoline rings was attributed to steric factors. Moreover, the two isoquinoline moieties were highly electron rich; a condition which does not favour the Ullmann reaction. A third approach was hence attempted.



Scheme 3.47. Attempted Ullmann coupling of benzyltetrahydroisoquinolines.

3.5.4 The Third Approach to the Synthesis of Neferine and its Analogues

The third approach to the synthesis of neferine (**1.15**) and its methyl derivative **1.16** was based on the nucleophilic aromatic substitution strategy. As shown in the retrosynthetic route (Scheme 3.48), this approach required 3'-hydroxybenzyltetrahydroisoquinoline **3.154**, and a fluorinated acetamide **3.153**, activated by the nitro group at the *ortho*-position. The key step would be the coupling of the hydroxybenzyltetrahyroisoquinoline **3.154** with the fluorinated acetamide **3.153** to afford the diaryl ether **3.152** *via* a nucleophilic aromatic substitution reaction. The second step would involve the formation of the C1-C8a bond by the Bischler-Napieralski cyclization of the diaryl ether **3.152**, which would then be followed by stereoselective reduction to yield **1.15** or **1.16**.

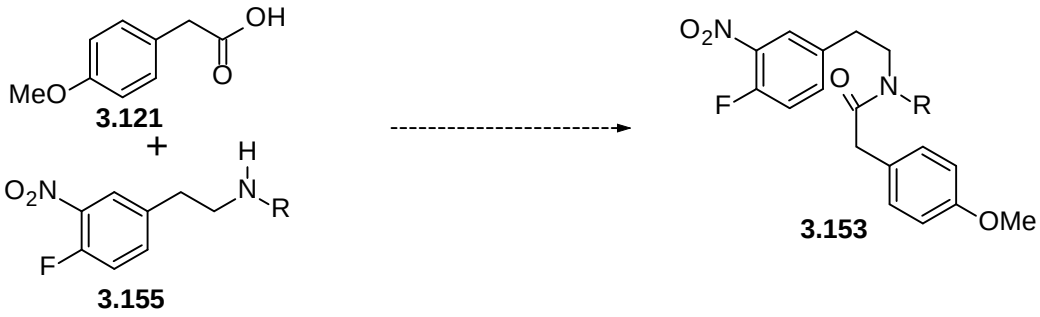


Scheme 3.48. Retrosynthesis of **1.15** and **1.16** based on *ortho*-nitro activated S_NAr.

3.5.4.1 Preparation of fluorinated acetamide.

As shown in the retrosynthesis (Scheme 3.48), a required precursor for the formation of the diaryl ether bond in the synthesis of neferine (**1.15**) and *O*-methylneferine (**1.16**) was the fluorinated acetamide **3.153**. The synthesis of

amide **3.153** was envisioned from coupling of the fluorinated phenethylamine **3.155** with the commercially available phenylacetic acid **3.121** (Scheme 3.49). However, the amine **3.155** was not commercially available and had to be prepared.

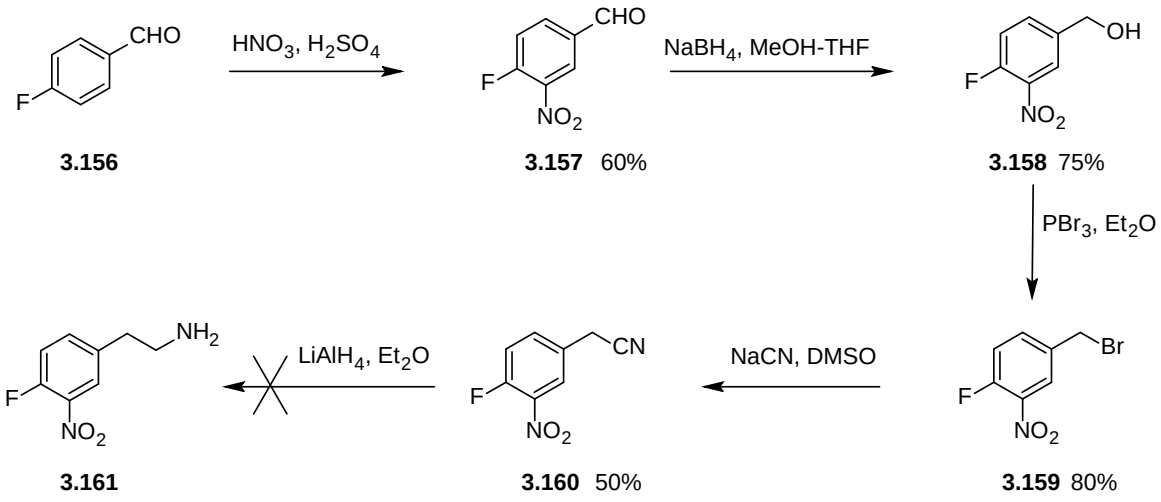


Scheme 3.49. Proposed synthesis of fluorinated acetamide.

Two synthetic routes were considered for the synthesis of phenethylamine **3.155**. The first approach was planned to proceed *via* reduction of the fluorophenylacetonitrile **3.161** as shown in Scheme 3.50.[45] The synthesis of fluorinated acetamide started from commercially available *para*-fluorobenzylaldehyde (**3.156**), which was first converted to 4-fluoro-3-nitrobenzaldehyde (**3.157**) by nitration. In this case the introduction of the nitro group served the two purposes. Firstly, it was introduced to activate the fluorine atom for the nucleophilic aromatic substitution reaction. Secondly, it needed to be transformed into the desired methoxy present in the targeted compounds **1.15** and **1.16**. Consequently, compound **3.157** was reduced to the corresponding alcohol **3.158**. The initial reduction using $NaBH_4$ in CH_3OH gave a mixture of two products which were observed from the NMR analysis in a ratio of 3:4. The reduced product was obtained as a minor product while the product formed as a result of nucleophilic aromatic substitution was a major one. Treating compound **3.157** with $NaBH_4$ in a mixture of THF/CH_3OH (9:1) neatly delivered the corresponding alcohol **3.158** in a 75% yield.

Bromination with PBr_3 afforded the corresponding benzyl bromide in good yield. Phenylacetonitrile **3.160** was formed by one carbon homologation. Thus, treating **3.159** with NaCN in DMSO produced the phenylacetonitrile **3.160** in 50% yields.

The ^{1}H NMR spectrum of compound **3.160** exhibited an ABX spin system, representing the aromatic protons resonating at δ_H 8.05 (1H, dd, *J* = 2.5 and 6.5 Hz, H-2), 7.65 (1H, m, H-6), 7.33 (1H, dd, *J* = 8.4 and 10.4 Hz, H-5), respectively. The methylene singlet was observed at 3.84 (2H, s). In the ^{13}C NMR spectrum the C-2, C-5 and C-6 appeared at δ_C 125.7 (d, *J* = 3.0 Hz,) 119.5 (d, *J* = 21.5 Hz) and 134.9 (d, *J* = 8.7 Hz), respectively. The characteristic signal of the nitrile carbon was observed at δ_C 116.3. The HRMS (ES^-) spectrum gave an m/z of 179.0254 $[M-H]^-$ in agreement with the calculated molecular mass of 179.0257 for ($C_8H_5FN_2O_2$).



3.156 **3.157** 60% **3.158** 75%

3.159 80% **3.160** 50% **3.161**

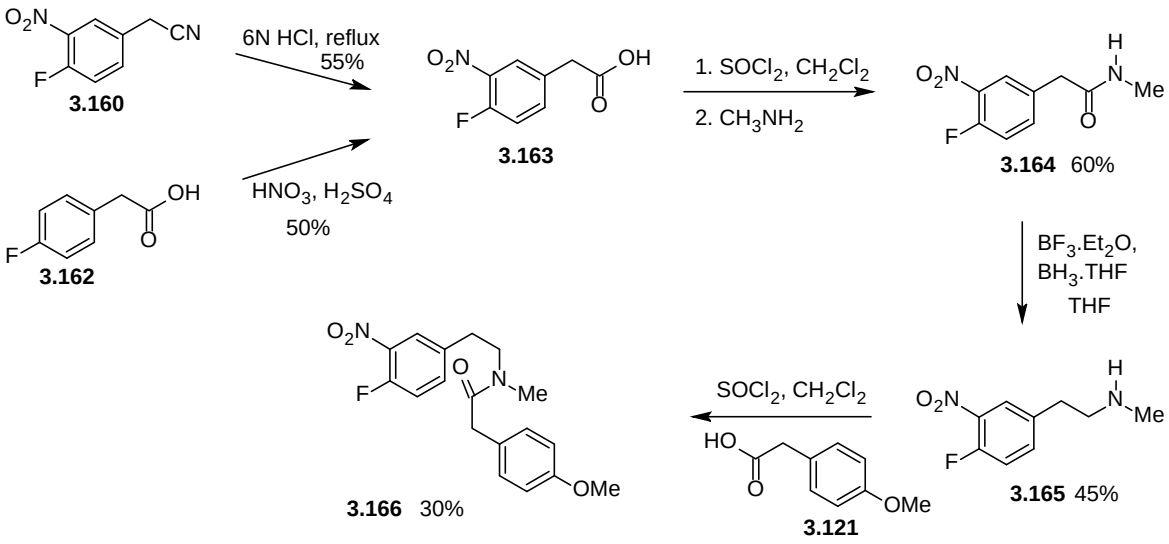
Scheme 3.50. Synthesis of the fluorinated acetamide.

The next step was the reduction of **3.160** into phenethylamine. It is worth noting that compound **3.160** possesses two functional groups that are both prone to reduction with many reducing agents. Hence chemoselective reduction of the nitrile in the presence of $LiAlH_4$ as a hydride source in Et_2O was opted for. This approach, however, did not produce the required amine **3.161**, even after several attempts. The switch to the combination of $LiAlH_4/AlCl_3$ as a hydride source also did not effect the desired reduction.

As the initial approach to prepare the amine **3.161** was unsuccessful, another route shown in Scheme 3.51 was investigated.[54] The first step entailed preparation of phenylacetic acid **3.163** by acid hydrolysis of the nitrile **3.160** to yield the acid in

a 55% yield. Base hydrolysis was avoided in this case as it could promote a nucleophilic aromatic substitution reaction.

Alternatively, the acid **3.163** was synthesised by nitration of commercially available 4-fluorophenylacetic acid (**3.162**). The synthesis of **3.163** from **3.162** was found to be more economical as it is a one step reaction, which is contrary to the five steps needed to synthesise the same compound from **3.156**. The ^{1}H NMR spectrum of **3.163** displayed the diagnostic methylene singlet at δ_H 3.73 integrating for two protons. This indicates that the nitrile group was a stronger deshielding group compared to the carboxylic acid group. The diagnostic carbonyl signal of the acid was observed at δ_C 175.2. The presence of the acid was also confirmed by IR spectroscopy, in which a characteristic peak of the OH functionality at 3340 cm^{-1} was observed as a broad band.



Scheme 3.51. The second approach to the synthesis of fluoroacetamide.

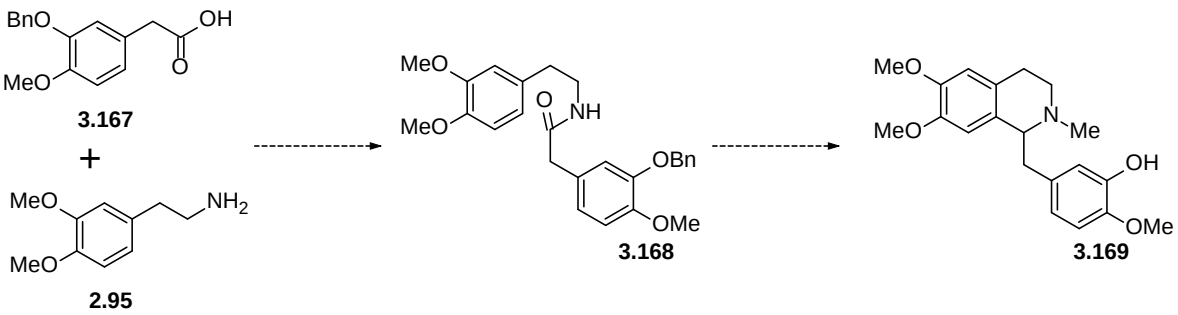
The Schotten-Baumann procedure converted the acid **3.163** into the corresponding acetamide **3.164** by first forming the acyl chloride which was immediately reacted with CH_3NH_2. The amide **3.164** was obtained in 60% yield after chromatographic purification. The reduction of amide **3.164** with BH_3.THF complex in the presence of $BF_3.Et_2O$ delivered amine **3.165** in a 45% yield.

Condensation of phenethylamine **3.165** with 4-methoxyphenylacetyl chloride formed from the reaction of **3.121** with $SOCl_2$ yielded the fluorinated acetamide

3.166 in 30% yields, after chromatographic purification. The ^{1}H NMR, ^{13}C NMR and HRMS were in agreement with the structure of **3.166**. The ^{1}H NMR spectrum of **3.166** showed the presence of seven protons, three present as an ABX spin system at δ_H 7.84 (1H, dd, *J* = 2.5 and 7.1 Hz), 7.46 (1H, ddd, *J* = 2.5, 8.5 and 11.0 Hz) and 7.17 (1H, dd, *J* = 8.5 and 11.0 Hz), whereas the other four protons were present as AA'BB' at δ_H 7.11 (2H, d, *J* = 8.7 Hz), 6.85 (2H, d, *J* = 8.7 Hz). The methoxy group appeared at δ_H 3.82 as a singlet integrating for three protons. Furthermore, the three methylene groups were present at δ_H 3.64 (2H, t, *J* = 7.1), 3.62 (2H, s,) and 2.91 (2H, t, *J* = 7.1 Hz), respectively. The methyl group resonated at δ_H 2.95 as singlet integrating for three protons. In the spectrum the methoxy group appeared at δ_H 3.82 (3H, s, OC<u>H</u>$_3$). The ^{13}C NMR showed, amongst others, the presence of the amide carbonyl at δ_C 171.5. The HRMS (ESI$^+$) analysis confirmed the molecular formula of **3.166** (Calculated for [$C_{18}H_{19}FN_2O_4Na$] 369.1227; found 369.1227 [M+Na]$^+$).

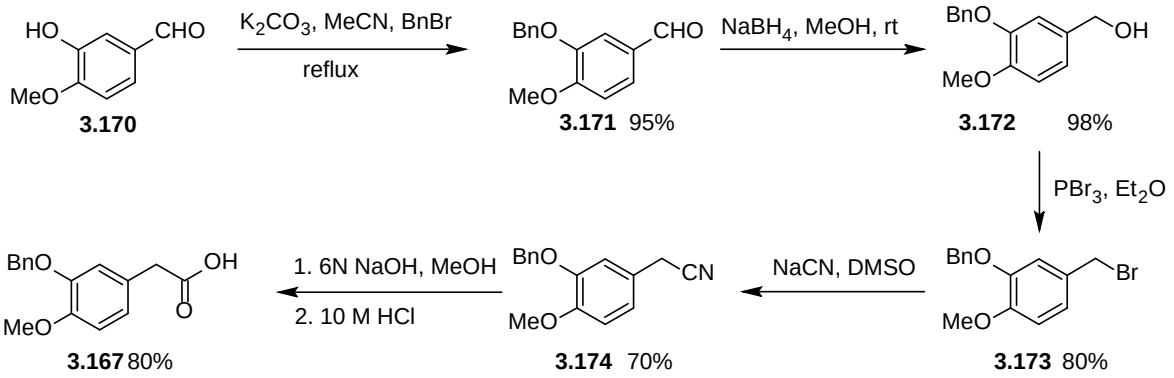
3.5.4.2 Preparation of 3'-hydroxybenzyltetrahydroisoquinoline

Having synthesised the appropriately functionalised acetamide for the nucleophilic aromatic substitution, we then focused on the preparation of its coupling partner, the 3′-hydroxybenzyltetrahydroisoquinoline. The synthesis was initiated by preparing hydroxylaudanidine **3.169**, a precursor to *O*-methylneferine **1.16**. The key steps in the synthesis of **3.169** entailed coupling of phenethylamine **2.95** and phenylacetic acid **3167** to give the acetamide **3.168**, followed by the Bischler-Napieralski cyclisation reaction as shown in Scheme 3.52.



Scheme 3.52. Synthetic pathway for hydroxylaudanidine **3.169**.

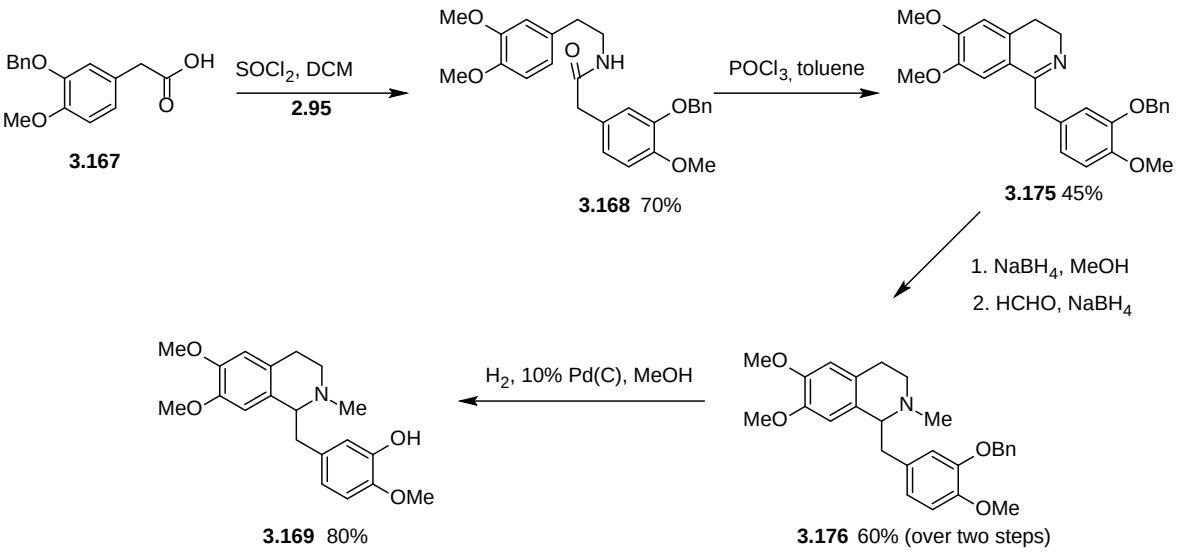
The synthesis of 3-benzyloxy-4-methoxyphenylacetic acid (**3.167**) was started from the commercially available 3-hydroxy-4-methoxybenzaldehyde (**3.170**). Initially isovanillin (**3.170**) was protected as its benzyl ether **3.171**, with BnBr being used as the alkylating reagent and K_2CO_3 as the base. Reduction of the aldehyde **3.171** to the alcohol **3.172**, and subsequent bromination proceeded smoothly to give the brominated product **3.173** in good yield. Treatment of the benzyl bromide **3.173** with sodium cyanide in DMSO rendered the phenylacetonitrile **3.174**, which was hydrolysed to give the corresponding phenylacetic acid **3.167** (Scheme 3.53).



Scheme 3.53. Preparation of phenylacetic acid **3.167**.

The structure of the acid **3.167** was confirmed by ^{1}H NMR and ^{13}C NMR. The spectrum showed amongst others the upfield shift of the benzylic protons at δ_H 3.56. Further confirmation of acid **3.167** was by ^{13}C NMR which showed the characteristic peak of the carbonyl carbon at δ_C 176.9.

Following the successful synthesis of phenylacetic acid **3.167**, the focus was then shifted to synthesis of the intermediate **3.169** (Scheme 3.54). The 3'-hydroxybenzyltetrahydroisoquinoline **3.169** was prepared in a sequence of steps from phenethylamine **2.95** and phenylacetic acid **3.167**, Scheme 3.54. The first step involved condensation of phenethylamine **2.95** with 4-methoxyphenylacetyl chloride formed from the reaction of **3.167** with $SOCl_2$ by the Schotten-Baumann amidation procedure to give the acetamide **3.168** in a 70% yield.[73, 74] The Bischler-Napieralski reaction of the acetamide **3.168** using $POCl_3$ in toluene afforded the dihydroisoquinoline **3.175** in a modest yield of 45%.



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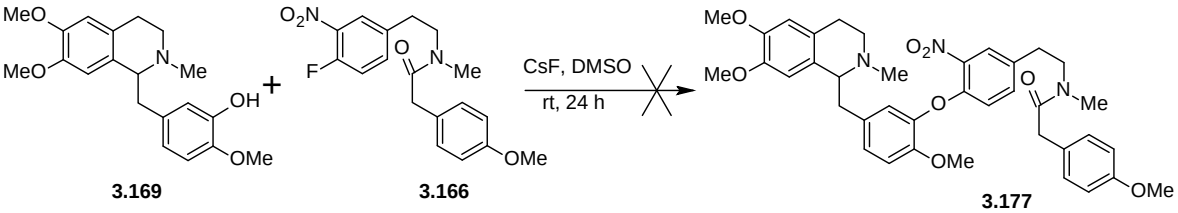
Scheme 3.54. Preparation of hydroxylaudanidine **3.169**

Compound **3.175** was unstable in the presence of silica gel and also upon leaving it at room temperature for a long period of time. The instability of the imine **3.75** might be due to the rearrangement to the enamine which would place double bond in conjugation with both rings. Therefore, compound **3.175** was used in the successive step without purification. Reduction of the imine **3.175** followed by reductive *N*-methylation gave the benzyltetrahydroisoquinoline **3.176**. The last step in the synthesis of **3.169** was the removal of the benzyl group. The catalytic hydrogenolysis of **3.176** produced compound **3.169** in 80% yield.

The structure of compound **3.169** was confirmed by NMR and HRMS data. The ^{1}H NMR spectrum of **3.169** displayed five aromatic protons compared to the ten observed in the ^{1}H NMR spectrum of **3.176**, three methoxy, an *N*-methyl group, the methine proton at 3.72 and three methylene protons resonating at δ_H 3.19, 2.83 and 2.67, respectively, appearing as multiplets. In the ^{13}C NMR spectrum were present 19 carbons, confirming that compound **3.169** does not contain the benzyloxy group. The HRMS spectrum gave *m/z* 344.1863 $[M+H]^+$ in agreement with the calculated molecular mass of 344.1862 for $C_{20}H_{26}NO_4$.

Having accomplished the synthesis of the two major precursors for the nucleophilic aromatic substitution, we attempted to couple the two as shown in Scheme 3.55. The reaction was initially performed by refluxing a DMF mixture of

3.169, **3.166** and K_2CO_3 in an inert atmosphere. This gave an inseparable mixture of compounds. At this stage, it was thought that the high temperature led to the decomposition of the starting materials. Changing the reaction conditions, by conducting the reaction at room temperature and using CsF and DMSO did not give the expected product either. However some of the fluorinated acetamide **3.166** could be recovered. Due to limited starting materials, this reaction could not be investigated further.



3.169 **3.166** **3.177**

Scheme 3.55. Attempted nucleophilc aromatic substitution.

3.6 CONCLUSION

The objective of this Chapter was to synthesise bisbenzyltetrahydroisoquinoline neferine (**1.15**) and its analogue **1.16**. In this Chapter three synthetic approaches were explored. The first two synthetic methods relied mostly on the formation of the diaryl ether bond by using the Ullmann ether coupling reaction. The third synthetic approach relied on the nucleophilic aromatic substitution reaction for the formation of the diaryl ether bridge.

In the first approach, the diaryl ether intermediate **3.100** was synthesised in low yields using both modified and classical Ullmann ether synthesis. Considering the low yields obtained in the preparation of **3.100**, and also in the synthesis of its precursor, the 4-benzyloxy-3-iodophenylacetic acid (**3.120**), it was decided that the route was not worth pursuing as there were several steps remaining in the total synthesis of the targeted compounds. Therefore, the second approach was investigated.

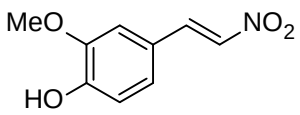
In the second approach, the synthesis of the bisbenzyltetrahydroisoquinolines **1.15** and **1.16** was planned to be accomplished by the late Ullmann coupling of hydroxybenzyltetrahydroisoquinolines and iodobenzyltetrahydroiosquinolines. The benzyltetrahydroisoquinolines **3.142** and **3.143**, which are precursors to **1.15** and **1.16**, were successfully prepared. The key step in the formation of the benzyltetrahydroisoquinolines was the Bischler-Napieralski cyclisation reaction. Compound **3.142** was prepared in six steps from phenylacetonitrile **3.117** and compound **3.143** was prepared in three steps from iodinated acetamide **3.112**. Attempts to couple **3.142** with **3.143** met with no success using the Ullmann ether synthesis. It was therefore concluded that steric factors as well as the electronic properties of the two benzylisoquinolines hampered the outcome of the Ullmann coupling reaction. Failure to couple the two benzyltetrahydroisoquinolines prompted us to consider a different approach for the formation of the diaryl ether.

In the third approach, the synthesis of the ether link was based on nucleophilic aromatic substitution. The key precursors for nucleophilic aromatic substitution were the fluorinated acetamide **3.166** and a natural product laudanidine (**3.169**).The fluorinated acetamide **3.166** was obtained in low yield using the Schotten-Baumann reaction as the key step. However, its counterpart **3.169** was prepared in moderate yields. The key step in the preparation of **3.169** was the Bischler-Napieralski cyclisation.The attempted S_NAr reaction resulted in failure.

3.7 EXPERIMENTAL PROCEDURES

General experimental procedures are given in Section 2.7.1

3.7.1 E-*3-Methoxy-4-(2-nitro-1-ethenyl)phenol (3.113)*

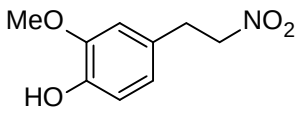


A mixture of vanillin (**2.65**) (1.00 g, 5.12 mmol), nitromethane (0.46 mL, 8.26 mmol) and ammonium acetate (0.96 g, 12.39 mmol) in acetic acid (20 mL) was

heated at 100 ^{o}C for 12 h under nitrogen atmosphere with vigorous stirring to give a homogeneous solution. The reaction mixture was cooled to room temperature when TLC showed almost complete consumption of starting material. Addition of ice yielded a yellow solid, which was washed with water several times and recrystallised in methanol/ethyl acetate. The product **3.113** was obtained in 52% (0.61 g) yield as yellow crystals.

Mp:	147-149 ^{o}C
^{1}H NMR (400 MHz, $CDCl_3$) δ_H:	7.97 (1H, d, *J* = 14.1 Hz, C<u>H</u>=CHNO_2), 7.53 (1H, d, *J* = 14.1 Hz, CH=C<u>H</u>NO_2), 7.16 (1H, dd, *J* = 8.3 and 2.0 Hz, H-6), 7.02 (1H, d, *J* = 2.0 Hz, H-2), 6.99 (1H, d, *J* = 8.3 Hz, H-5), 6.06 (1H, brs, OH), 3.97 (3H, s, OC<u>H</u>$_3$)
^{13}C NMR (100 MHz, $CDCl_3$) δ_C:	149.8 (C-3), 147.1 (C-4), 139.4 (<u>C</u>H=CHNO_2), 135.0 (CH=<u>C</u>HNO_2), 124.9 (C-1), 122.4 (C-6), 115.3 (C-5), 110.2 (C-2), 56.1 (O<u>C</u>H$_3$)
IR ν_{max}(cm^{-1}):	3467, 3114, 2930, 1627, 1602, 1518, 1486, 1473, 1432, 1384, 1355, 1288, 1248, 1210, 1193, 1159, 1127, 1020, 972, 952, 938, 855, 815
HRMS-ES^{+} (*m/z*):	Found 218.0431 $[M+Na]^{+}$; calculated for $[C_9H_9NO_4Na]$ 218.0429.

3.7.2 3-Methoxy-4-(2-nitroethyl) phenol (3.114)



The unsaturated nitro compound **3.113** (1.0 g, 5.10 mmol) was dissolved in ethanol (25 mL) cooled to 0 ^{o}C, then $NaBH_4$ (0.576 g, 15.2 mmol) was added in portions and the reaction mixture was stirred for 2 h at the same temperature. The solvent was removed under reduced pressure and the residue was quenched with

saturated NH_4Cl solution and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by chromatography to give unsaturated nitro compound **3.114** (0.7 g, 69%) as a yellow oil.

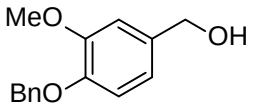
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.85 (1H, d, *J* = 8.3 Hz, H-5'), 6.69 (2H, overlap, H-2,6), 5.75 (1H, brs, OH), 4.57 (2H, t, *J* = 7.3 Hz, $CH_2C\underline{H}_2NO_2$), 3.85 (3H, s, OCH_3), 3.23 (2H, t, *J* = 7.3 Hz, $C\underline{H}_2CH_2NO_2$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 146.8 (C-3), 144.9 (C-4), 127.6 (C-1), 121.3 (C-6), 114.8 (C-5), 111.3 (C-2), 76.6 ($CH_2\underline{C}H_2NO_2$), 55.9 (OCH_3), 33.2 ($\underline{C}H_2CH_2NO_2$)

IR ν_{max}(cm^{-1}): 3499, 3011, 2940, 2846, 1613, 1550, 1517, 1453, 1433, 1379, 1272, 1237, 1209, 1154, 1125, 1033, 871, 820, 791

m/z (EI): 197 (M^+, 20), 150 (100), 91 (45).

3.7.3 4-Benzyloxy-3-methoxybenzyl alcohol (3.115)



To a solution of 4-benzyloxy-3-methoxybenzylaldehyde (**2.77**) (2.13 g, 8.81 mmol) in ethanol, $NaBH_4$ (0.99 g, 26.43 mmol) was added in portions; the mixture was stirred for 12 h at room temperature. The solvent was removed by distillation *in vacuo* and the residue was decomposed with water and extracted with ethyl acetate. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to give the benzyl alcohol **3.115** (2.10 g, 95%) as a white solid after recrystallisation from methanol.

Mp: 63-64 ^oC

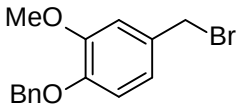
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48-7.33 (5H, m, PhCH$_2$O), 6.97 (1H, d, *J* = 2.2 Hz, H-2), 6.87 (1H, d, *J* = 8.3 Hz, H-5), 6.83 (1H, dd, *J* = 8.3 and 2.2 Hz, H-6), 5.17 (2H, s, PhCH$_2$O), 4.62 (2H, s, ArCH$_2$OH), 3.92 (3H, s, OCH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 149.9 (C-3), 147.8 (C-4), 137.1 (PhCH$_2$O), 134.3 (C-1), 128.6 (PhCH$_2$O), 127.8 (PhCH$_2$O), 127.3 (PhCH$_2$O), 119.4 (C-6'), 114.2 (C-5'), 111.1 (C-2), 71.2 (PhCH$_2$O), 65.3 (ArCH$_2$OH), 56.1 (OCH_3)

IR ν_{max}(cm^{-1}): 3360, 2932, 2874, 1597, 1513, 1448, 1260, 1237, 1135, 1032, 1005, 857

HRMS-ES$^+$ (*m/z*): Found 267.1000 $[M+Na]^+$; calculated for $[C_{15}H_{16}O_3Na]$ 267.0997.

3.7.4 4-Benzyloxy-3-methoxybenzyl bromide (3.116)



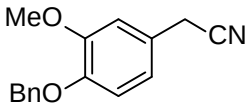
To a solution of 4-benzyloxy-3-methoxybenzyl alcohol (**3.115**) (1.0 g, 4.1 mmol) in dry ether (20 mL), PBr_3 (1.65 g, 6.1 mmol) was added. The mixture was stirred for 8 h at room temperature. The solvent was distilled off to give the expected benzyl bromide **3.116** (1.01 g, 80%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48-7.31 (5H, m, PhCH$_2$O), 6.96 (1H, d, *J* = 2.2 Hz, H-2), 6.89 (1H, dd, *J* = 8.3 and 2.2 Hz, H-6), 6.86 (1H, d, *J* = 8.3 Hz, H-5), 5.18 (2H, s, PhCH$_2$O), 4.57 (2H, s, ArCH$_2$Br), 3.93 (3H, s, OCH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 149.9 (C-3), 148.5 (C-4), 136.9 (PhCH$_2$O), 130.6 (C-1), 128.6 (PhCH$_2$O), 127.9 (PhCH$_2$O), 127.2 PhCH$_2$O), 121.1 (C-6), 113.9 (C-5), 112.4 (C-2), 71.1 (PhCH$_2$O), 56.1 (OCH$_3$), 46.6 (ArCH$_2$Br)

IR ν_{max}(cm^{-1}): 2958, 2941, 2836, 2603, 2343, 1976, 1596, 1511, 1456, 1262, 1229, 1167, 1134, 1027, 1000.

3.7.5 4-Benzyloxy-3-methoxyphenylacetonitrile (3.117)



A mixture of 4-benzyloxy-3-methoxybenzyl bromide (**3.116**) (0.58 g, 1.9 mmol), sodium cyanide (0.14 g, 2.86 mmol) in DMSO (20 mL) was heated at 40 ^{o}C for 12 h. After the addition of water (15 mL), the mixture was extracted with ether. The extract was washed with water, dried and evaporated to give the corresponding benzyl cyanide **3.117** in 75% yield (0.36 g) as a white solid, which was crystallised from EtOAc:MeOH, 9:1.

Mp: 54-55 ^{o}C

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.47-7.31 (5H, m, PhCH$_2$O), 6.88 (1H, d, *J* = 8.2 Hz, H-5), 6.86 (1H, d, *J* = 2.1 Hz, H-2), 6.80 (1H, dd, *J* = 2.1 and 8.2 Hz, H-6), 5.16 (2H, s, PhCH$_2$O), 3.92 (3H, s, OCH$_3$) 3.69 (2H, s, ArCH$_2$CN)

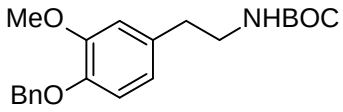
^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 150.2 (C-3), 148.0(C-4), 136.9 (PhCH$_2$O), 128.7 (PhCH$_2$O), 128.6 (PhCH$_2$O), 127.9 (PhCH$_2$O), 127.3 (C-1), 122.8 (C≡N), 120.2 (C-6), 118.0 (C-

2), 114.5 ($ArCH_2\underline{C}N$), 111.7 (C-5), 71.2 ($PhC\underline{H}_2O$), 56.1 (OCH_3), 23.2 ($Ar\underline{C}H_2CN$)

IR $\nu_{max}(cm^{-1})$: 2976, 2942, 2927, 2909, 2880, 2839, 1998, 1740, 1595, 1514, 1384, 1341, 1142

HRMS-ES$^+$ (*m/z*): Found 276.1006 $[M+Na]^+$; calculated for $[C_{16}H_{15}NO_2Na]$ 276.1000.

3.7.6 [2-(4-Benzyloxy-3-methoxyphenyl)ethyl]carbamic acid tert-*butyl ester (3.118)*

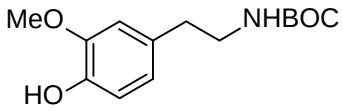


A solution of $AlCl_3$ (1.48 g, 11.1 mmol) in Et_2O (10 mL) was rapidly added to a solution of $LiAlH_4$ (0.42 g, 11.1 mmol) in Et_2O (20 mL) and the mixture was stirred at 25 ^oC for 30 min. A solution of nitrile **3.117** (2.82 g, 11.1) in Et_2O (15 mL) was then slowly added to the mixture and stirred at 25 ^oC for additional 2 h. The mixture was cooled to 0 ^oC and quenched carefully with water (10 mL), followed by 10% solution of KOH (7 mL), then $(Boc)_2O$ (2 g, 11.1mmol) in Et_2O (10 mL) was added and stirring was continued for 4 h at room temperature. On completion, the colloidal mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by chromatography (SiO_2, hexanes:EtOAc, 8:2), the carbamate **3.118** (2.6 g, 65%) was isolated as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.47-7.3 (5H, m, $Ph\underline{C}H_2O$), 6.84 (1H, d, *J* = 8.2 Hz, H-5), 6.75 (1H, d, *J* = 2.2 Hz, H-2), 6.68 (1H, dd, *J* = 8.2 and 2.2 Hz, H-6), 5.14 (2H, s, $PhC\underline{H}_2O$), 4.56 (1H, brs, $CH_2N\underline{H}CO$), 3.18 (3H, s, OCH_3), 3.37 (2H, q, *J* = 6.7 Hz, $ArCH_2C\underline{H}_2NCO$), 2.74 (2H, t, *J* = 6.7 Hz, $ArC\underline{H}_2CH_2NCO$), 1.46 (9H, s, $CO_2C(CH_3)_3$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 155.8, $\underline{C}O_2(CH_3)_3$), 149.8 (C-3), 146.9 (C-4), 137.5 ($\underline{Ph}CH_2O$), 132.3 (C-1), 128.5 ($\underline{Ph}CH_2O$), 127.8 ($\underline{Ph}CH_2O$, 127.3 ($\underline{Ph}CH_2O$, 120.7 (C-6), 114.5 (C-2), 112.8 (C-5), 71.3 ($Ph\underline{C}H_2O$), 55.9 (OCH_3), 28.4 ($CO_2C(\underline{C}H_3)_3$).

3.7.7 [2-(4-Hydroxy-3-methoxyphenyl)ethyl]carbamic acid tert-*butyl ester (3.111)*



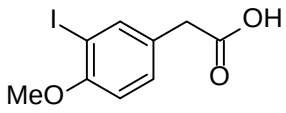
To a solution of 4-benzyloxyphenethylamine **3.118** (0.500 g, 1.39 mmol) was added palladium catalyst 10% Pd(C) (20 mg) and the mixture was degassed twice under vacuum and then replacing the vacuum by hydrogen each time. The reaction mixture was stirred at room temperature for 24 h under hydrogen gas. When the reaction was complete, the catalyst was filtered off and washed with EtOH (10 mL). The filtrate was concentrated to give a crude product which was subjected to chromatography to obtain the pure product **3.111** (0.34 g) in 90% yield as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.86 (1H,d, *J* = 7.9 Hz, H-5), 6.70 (1H, d, *J* = 1.9 Hz, H-2), 6.69 (1H, dd, *J* = 1.9 and 7.9 Hz, H-6), 5.56 (1H, brs, OH), 4.56 (1H, brs, NHCOOR), 3.89 (3H, s, OCH_3), 3.33 (2H, q, *J* = 6.3 Hz, $ArCH_2C\underline{H}_2N$), 2.74 (2H, t, *J* = 6.3 Hz, $ArC\underline{H}_2CH_2N$), 1.45 (9H, s, $COOC(C\underline{H}_3)_3$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 156.0 ($N\underline{C}O_2C(CH_3)_3$), 146.6 (C-3), 144.2 (C-4), 130.9 (C-1), 121.6 (C-6), 111.4 (C-5), 79.2 ($NCO_2\underline{C}(CH_3)_3$), 56.0 ($OCH_3$), 41.9 ($ArCH_2\underline{C}H_2N$), 36.0 ($Ar\underline{C}H_2CH_2N$)

HRMS-ES$^+$ (*m/z*): Found 290.1368 $[M+Na]^+$; calculated for $[C_{14}H_{21}O_4Na]$ 290.1368.

3.7.8 3-Iodo-4-methoxyphenylacetic acid (3.122)

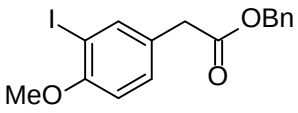


A solution of 4-methoxyphenylacetic acid (**3.121**) (1.53 g, 9.26 mmol), KI (1.03 g, 6.22 mmol) and KIO_3 (0.66 g, 3.08 mmol) was prepared in CH_3OH (5 mL) and water (30 mL). This mixture was treated at room temperature with dilute HCl (9.5 mmol) over 40 to 45 min and stirred for an additional 2-3 h, diluted with water (50 mL) and extracted with CH_2Cl_2 (25 mL x 3). The combined organic extract was washed with dilute $Na_2S_2O_3$ (5%), water, brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give compound **3.122** as a thick oil (2.17 g, 81%), which crystallized after some few min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.72 (1H, d, *J* = 2.1 Hz, H-2), 7.24 (1H, dd, *J* = 2.1 and 8.1 Hz, H-6), 6.79 (1H, d, *J* = 8.1 Hz, H-5), 3.88 (3H, s, $OC\underline{H}_3$), 3.57 (2H, s, $CO_2\ C\underline{H}_2Ar$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 176.8 ($\underline{C}OOH$), 157.8 (C-4), 140.2 (C-2), 130.5 (C-6), 127.4 (C-1), 110.9 (C-5), 86.1 (C-3), 56.5 ($O\underline{C}H_3$), 39.5 ($CO_2\ \underline{C}H_2Ar$)

3.7.9 Benzyl 3-iodo-4-methoxyphenylacetate (3.134)



Benzyl bromide (1.24 mL; 1.2 eq) was added to a mixture of 3-iodo-4-methoxyphenylacetic acid (**3.122**) (2.00 g; 8.73 mmol) and K_2CO_3 (3.62 g; 26.19 mmol) in dry DMF (20 mL) and the reaction mixture was refluxed for 12 h. The reaction mixture was basified with K_2CO_3, extracted with EtOAc (3 x 20 mL) and

the organic phases were washed with water (25 mL), followed by brine solution, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the phenylacetate **3.134** as colourless oil (2.67 g, 80%).

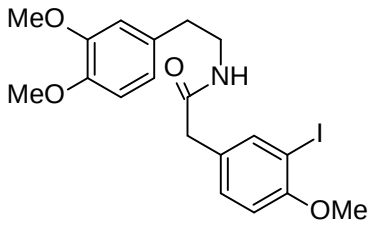
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.73 (1H, d, *J* = 2.2 Hz, H-2), 7.39-7.32 (5H, m, $\underline{Ph}CH_2O$), 7.25 (1H, dd, J = 2.2, 8.2 Hz, H-6), 6.79 (1H, d, *J* = 8.2 Hz, H-5), 5.16 (2H, s, $PhC\underline{H_2}O$), 3.88 (3H, s, OCH_3), 3.59 (2H, s, $CO_2C\underline{H_2}Ar$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 171.1 ($\underline{C}OOBn$), 157.4 (C-4), 140.1 ($\underline{Ph}CH_2O$), 135.8 (C-2), 130.2 (C-6), 128.6 ($\underline{Ph}CH_2O$, C-$\underline{1}$), 128.3 ($\underline{Ph}CH_2O$), 128.2 ($\underline{Ph}CH_2O$), $CO_2C\underline{H_2}Ar$), 110.9 (C-5′), 85.9 (C-3′), 66.8 ($PhC\underline{H_2}O$), 56.5 ($O\underline{C}H_3$), 39.7 ($CO_2\underline{C}H_2Ar$)

IR ν_{max} (cm^{-1}): 3032, 2941, 2836, 1732, 1599, 1566, 1490, 1455, 1375, 1254, 1149, 1048, 1018, 811,747, 697.

HRMS-ES$^+$ (*m/z*): Found 404.9973 $[M+Na]^+$; calculated for $[C_{16}H_{15}IO_3Na]$ 404.9964.

3.7.10 N-*(3,4-Dimethoxyphenylethyl)-3-iodo-4-methoxyphenyl acetamide (3.124)*



To a solution of 3-iodo-4-methoxyphenylacetic acid (**3.122**) (0.004 mol) in dry ether (10 mL) was added $SOCl_2$ (0.005 mol). The reaction mixture was refluxed for 1 h and cooled to room temperature. The excess $SOCl_2$ was removed on a rotary evaporator. To the crude mixture of the acyl chloride in dry ether was added 3,4-dimethoxyphenethylamine (**2.95**) (0.008 mol) dropwise. The resulting mixture was

extracted with CH_2Cl_2 (20 mL x 3), washed with K_2CO_3 solution, water, 1N HCl, brine, dried and concentrated under vacuum to afford the product **3.124** (1.36 g) in 75% yield as a white crystalline product.

Mp: 118-120 ^oC

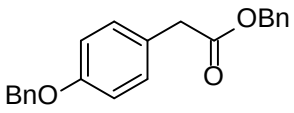
^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.62 (1H, d, *J* = 2.2 Hz, H-2′), 7.12 (1H, dd, *J* = 8.3 and 2.2 Hz, H-6′), 6.77 (1H, d, *J* = 8.3 Hz, H-5′), 6.74 (1H, d, *J* = 8.3 Hz, H-5), 6.63 (1H, d, *J* = 1.9 Hz, H-2), 6.57 (1H, dd, *J* = 1.9 and 8.3 Hz, H-6), 5.37 (1H, br s, NHCO), 3.89 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.47 (2H, q, *J* = 6.9 Hz, CH_2CH_2N), 3.43 (2H, s, $COCH_2Ar$), 2.70 (2H, t, *J* = 6.9 Hz, CH_2CH_2N)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 170.8 (NCO), 157.5 (C-4′), 149.2 (C-3), 147.8 (C-4), 140.2 (C-2′), 131.0 (C-1′), 130.5 (C-6′), 128.9 (C-1), 120.7 (C-6), 111.8 (C-5′), 111.4 (C-5), 111.2 (C-2), 86.4 (C-3′), 56.4 (OCH_3), 55.9 (OCH_3), 55.8 (OCH_3), 42.3 ($COCH_2Ar$), 40.7 (CH_2CH_2N), 35.0 (CH_2CH_2N)

IR ν_{max} (cm^{-1}): 3293, 3075, 2999, 2921, 2835, 1632, 1590, 1551, 1515, 1489, 1470, 1439,1337, 1295, 1259, 1248, 1234, 1137, 1051, 1024, 956, 813, 785

HRMS-ES$^+$ (*m/z*): Found 478.0497 $[M+Na]^+$; Calculated for $[C_{19}H_{22}INO_4Na]$ 478.0491.

3.7.11 Benzyl 4-Benzyloxyphenylacetate (3.125)



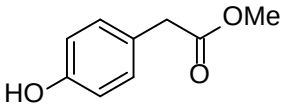
K_2CO_3 (5.52 g, 39.9 mmol) followed by BnBr (3.2 mL, 26.4 mmol) were added to a stirred solution of 4-hydroxyphenylacetic acid (**3.119**) (6.00 g, 39.40 mmol) in dry CH_3CN (20 mL). The reaction mixture was refluxed for 12 h under nitrogen after which TLC showed no starting material remaining. The product was acidified with 3 M HCl (20 mL), extracted with EtOAc (3 x 20 mL) and washed with water (25 mL) and brine (25 mL). The organic phase was dried under anhydrous $MgSO_4$ and purified on silica gel column using hexanes:EtOAc (4:6) as solvent mixture. The product **3.125** was obtained as a white solid (3.98 g, 91%).

Melting point: 65.0^{o}C - 66.5 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.36-7.50 (10H, m, PhCH_2O). 7.26 (2H, d, *J* = 8.4Hz, H-2,6); 7.00 (2H, d, *J* = 8.4 Hz, H-3,5). 5.19 (2H, s, ArCH_2COOCH_2Ph), 5.10 (2H, s, PhCH_2O), 3.66 (2H, s, ArCH_2CO)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 171.9 (ArCH_2COO), 158.0 (C-4), 137.2 (PhCH_2O), 135.9 (C-2,6), 128.6 (PhCH_2O), 127.7 (PhCH_2O), 127.3 (PhCH_2O), 126.4 (C-1), 115.0 (C-3,5), 70.2 (PhCH_2O) 66.61 (ArCH_2COOCH_2Ph), 40.5 (ArCH_2CO).

3.7.12 Methyl 4-hydroxyphenylacetate (3.129)

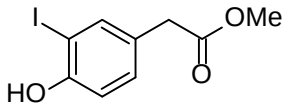


4-Hydroxyphenylacetic acid (**3.119**) (5.0 g, 117.6 mmol) was dissolved in absolute CH_3OH and conc. H_2SO_4 (0.6 mL) was added. After refluxing overnight, the solvent was evaporated to give a brown oil. The residue was dissolved in ether and washed with a saturated $NaHCO_3$ solution and brine. The organic phase was dried ($MgSO_4$) and evaporated to afford the expected phenylacetate **3.129** as a yellow oil (17.6 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.12 (2H, d, *J* = 8.2 Hz, H-3,5), 6.76 (2H, d, *J* = 8.2 Hz, H-2,6), 5.95 (1H, s, OH), 3.72 (3H, s, OCH_3), 3.58 (2H, s, Ar$\underline{C}H_2COOCH_3$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 173.1 (Ar$CH_2\underline{C}OOCH_3$), 155.1 (C-4), 130.4 (C-2,6), 125.7 (C-1), 115.6 (C-3,5), 52.2 (OCH_3), 40.3 (Ar$\underline{C}H_2COOCH_3$).

3.7.13 Methyl 4-hydroxy-3-iodophenylacetate (3.130)

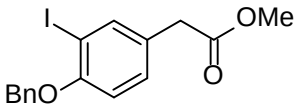


A solution of methyl 4-hydroxyphenylacetate (**3.129**) (1.54 g, 9.26 mmol), KI (1.03 g, 6.22 mmol) and KIO_3 (0.66 g, 3.08 mmol) in CH_3OH (5 mL) and water (30 mL) was prepared. This mixture was treated at room temperature with dilute HCl (9.5 mmol) over 40 to 45 min and stirred for an additional 2-3 h, diluted with water (50 mL) and extracted with CH_2Cl_2 (25 mL x 3). The combined organic extract was washed with dilute $Na_2S_2O_3$ (5%), water, brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give **3.130** as a thick oil (0.84 g, 30%), which solidified after few a min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.59 (1H, d, *J* = 1.9 Hz, H-2), 7.16 (1H, dd, *J* = 8.2 and 1.9 Hz, H-6), 6.92 (1H, d, *J* = 8.2 Hz, H-5), 5.50 (1H, s, OH), 3.72 (3H, s, OCH_3), 3.54 (2H, s, Ar$\underline{C}H_2COOCH_3$)

HRMS-ES$^+$ (*m/z*): Found 314.9491 $[M+Na]^+$; Calculated for $[C_9H_9IO_3Na]$ 314.9494.

3.7.14 Methyl 4-benzyloxy-3-iodophenylacetate (3.131)

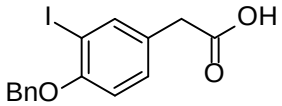


To a solution of methyl 4-hydroxy-3-iodophenylacetate (**3.130**) (3.00 g, 10.27 mmol) in acetonitrile (50 mL) were added K_2CO_3 (2.72 g, 19.66 mmol), and BnBr (3.17 g, 2.15 mL, 18.15 mmol). The mixture was heated under reflux for 6 h, then cooled and filtered to remove the solid. The solvent was evaporated at reduced pressure and the crude product dissolved in Et_2O (30 mL), washed with water (3 x 20 mL) and dried ($MgSO_4$). Further purification was carried out by column chromatography, eluting with EtOAc/hexane (1:10) to give **3.131** (3.85 g, 98%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.75 (1H, d, *J* = 1.9 Hz, H-2), 7.51-7.35 (5H, m, P<u>h</u>CH_2O), 7.21 (1H, dd, *J* = 8.2 and 1.9 Hz, H-6), 6.82 (1H, d, *J* = 8.2 Hz, H-5), 5.15 (2H, s, PhC<u>H</u>$_2$O), 3.72 (3H, s, OCH_3), 3.57 (2H, s, ArC<u>H</u>$_2$COOH)

HRMS-ES$^+$ (*m/z*): Found 404.9967 $[M+Na]^+$; calculated for $[C_{16}H_{15}IO_3Na]$ 404.9964.

3.7.15 4-Benzyloxy-3-Iodophenylacetic acid (3.120)



Aqueous KOH (5M, 5 mL, 7.78 mmol) was added to a solution of methyl 4-benzyloxy-3-iodophenylacetic acid (**3.131**) (2.00 g, 5.23 mmol) in CH_3OH (20 mL) at 0 ^{o}C. The cooling bath was then removed and the mixture was stirred at room temperature for 4 h. Then, CH_3OH was removed under vacuum and the residue was diluted with water (20 mL) and adjusted pH to 1 with concentrated HCl. The precipitate formed was collected by filtration, washed with plenty of water and then

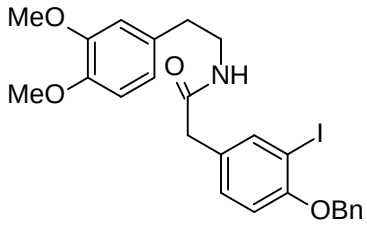
Et_2O. After drying under vacuum, **3.120** was obtained as a white solid (1.54 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.75 (1H, d, *J* = 1.9 Hz, H-2), 7.53 (5H, m, $\underline{Ph}CH_2O$), 7.21(1H, dd, *J* = 1.9 and 8.2 Hz, H-6), 6.83 (1H, d, *J* = 8.2 Hz, H-5), 5.16 (2H, s, $PhC\underline{H}_2O$), 3.57 (2H, s, $ArC\underline{H}_2COOH$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 175.9 ($\underline{C}OOH$), 158.8 (C-4), 140. 5 ($\underline{Ph}CH_2O$), 136.7 (C-2), 130.5 (C-6), 128.6 ($\underline{Ph}CH_2O$), 127.9 ($PhCH_2O$), 127.6 (C-1), 126.9 ($\underline{Ph}CH_2O$), 112.6 (C-5), 86.9 (C-3), 70.9 ($Ph\underline{C}H_2O$), 39.3 ($Ar\underline{C}H_2COOH$)

HRMS-ES$^-$ (*m/z*): Found 366.9833 $[M-H]^-$; calculated for $[C_{15}H_{12}IO_3Na]$ 366.9831.

3.7.16 N-*(3,4-dimethoxyphenylethyl)-4-benzyloxy-3-iodophenylacetamide (3.112)*



Acetamide **3.112** was prepared in 62% yield by coupling 3-iodophenylacetic acid **3.120** and 3,4-dimethoxyphenethylamine (**2.95**) following the procedure in **3.7.10**.

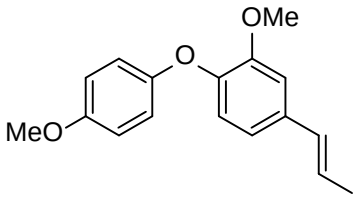
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.65 (1H, d, *J* = 2.2 Hz, H-2′), 7.54-7.32 (5H, m, $PhCH_2O$), 7.09 (1H, dd, *J* = 2.2 and 8.4 Hz, H-6′), 6.79 (1H, d, *J* = 8.4 Hz, H-5′), 6.77 (1H, d, *J* = 8.4 Hz, H-5), 6.64 (1H, d, *J* = 2.2 Hz, H-2), 6.56 (1H, dd, *J* = 2.2 and 8.4 Hz, H-6), 5.35 (1H, brs, NHCO), 5.16 (2H, s, $PhC\underline{H}_2O$), 3.86 (3H, s,

OCH_3), 3.85 (3H, s, OCH_3), 3.47 (2H, q, *J* = 6.9 Hz, $CH_2C\underline{H_2}NHCO$), 3.43 (2H, s, $ArC\underline{H_2}CO$), 2.71 (2H, t, *J* = 6.9 Hz, $C\underline{H_2}CH_2NHCO$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 170.5 ($NH\underline{C}O$), 156.6 (C-4′), 149.2 (C-3′), 147.8 (C-4′), 140.2 (C-2′), 136.4 ($\underline{Ph}CH_2O$), 130.9 (C-1′), 130.4 (C-6′), 129.2 (C-1), 128.6 ($\underline{Ph}CH_2O$), 127.9 ($\underline{Ph}CH_2O$), 126.9 ($\underline{Ph}CH_2O$), 120.6 (C-6), 118.2 (C-4), 117.3 (C-6'), 112.8 (C-5′), 111.8 (C-5), 111.4 (C-2), 87.4 (C-3′), 71.0 ($Ph\underline{C}H_2O$), 56.0 (OCH_3), 42.4 ($ArC\underline{H_2}CO$), 40.8 ($CH_2\underline{C}H_2NHCO$), 35.2 ($\underline{C}H_2CH_2NHCO$)

HRMS-ES^+ (*m/z*): Found 554.0806 $[M+Na]^+$; calculated for $[C_{25}H_{26}INO_4Na]$ 554.0804.

3.7.17 E-*2-Methoxy-1-(4-methoxyphenoxy)-4-(prop-1-en-1-yl)benzene (3.133)*



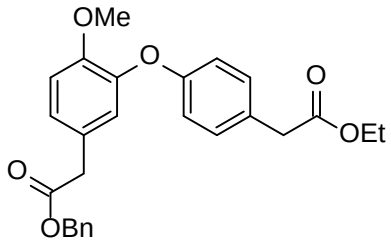
Caesium carbonate (0.773 g, 2.37 mmol), was added to the phenol **2.81** (0.300 g, 1.82 mmol) in 5 mL NMP. The slurry was degassed and the flask filled with nitrogen three times. The aryl halide **3.132** (0.21 g, 0.91 mmol) and 2,2,6,6-tetramethylheptane-3,5-dione (0.1 mmol%) were added followed by CuCl (45 mg, 0.455 mmol). The reaction mixture was degassed and the flask filled with nitrogen three times and then warmed to 120 ^oC under nitrogen. Reactions were monitored by TLC after every 30 min. When the TLC showed no starting material the reaction mixture was cooled to room temperature and diluted with 15 mL of ethyl acetate. The filtrate was washed subsequently with 15 mL 2 N HCl, 15 mL 0.6 N HCl, 15 mL 2M NaOH, 15 mL 10 % NaCl. The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was

subjected to column chromatography to obtain the pure product **3.133** as a yellow oil in 70% yield (0.172 g).

^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 6.96 (1H, d, J = 1.7 Hz, H-2′), 6.93 (2H, d, J = 8.9 Hz, H-2,6), 6.83 (3H, overlap, H-3,5,6′), 6.77 (1H, d, J = 8.2 Hz, H-5′), 6.36 (1H, dd, J = 15.8 and 1.5 Hz, CH=CHMe), 6.16 (1H, m, CH=CHMe), 3.87 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 1.88 (3H, dd, J = 6.6 and 1.5 Hz, CH=CHMe)

^{13}C NMR(400 MHz, $CDCl_3$) δ_C: 155.4 (C-4), 151.2 (C-1), 150.8 (C-3′), 145.6 (C-4′), 134.1 (C-1′), 130.5 (C$\underline{H}$=CHCH_3), 125.0 (CH=C$\underline{H}$$CH_3$), 119.3 (C-5′), 119.1 (C-2,6), 118.7 (C-6′), 114.7 (C-3,5), 109.9 (C-2′), 55.9 (OCH_3), 55.7 (OCH_3), 18.4 (CH=CH$\underline{C}H_3$).

3.7.18 Benzyl 3-[4-(2-ethoxy-2-oxoethyl)phenoxy]-4-methoxyphenylacetate (3.136)



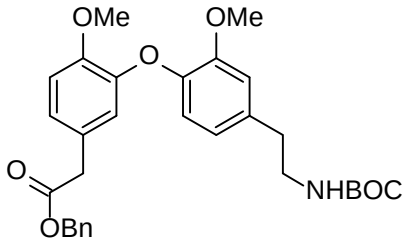
The title compound was prepared in 30% yield (yellow oil) by the Ullmann ether coupling reaction of phenol **3.135** and aryl iodide **3.134** according to the procedure in **3.7.17**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39-7.28 (5H, m $\underline{Ph}CH_2O$), 7.20 (2H, d, *J* = 8.7 Hz, H-2′,6′), 7.06 (1H, dd, *J* = 8.4 and 2.3 Hz, H-2), 6.96 (1H, d, *J* = 8.4 Hz, H-5), 6.94 (1H, d, *J* = 2.3 Hz, H-2), 6.89 (2H, d, *J* = 8.7 Hz, H-3′,5′),

5.13 (2H, s, PhC<u>H</u>$_2$O), 4.16 (2H, q, *J* = 7.0 Hz, OC<u>H</u>$_2$CH$_3$), 3.83 (3H, s, OCH$_3$), 3.58 (4H, s, overlap, ArC<u>H</u>$_2$COOR), 1.26 (3H, t, *J* = 7.0 Hz, OCH$_2$C<u>H</u>$_3$)

^{13}C NMR (400 MHz, CDCl$_3$) δ_C: 171.8 (COOBn), 171.4 (COOEt), 156.9 (C-4′), 150.6 (C-4), 144.9 (C-3), 135.8 (<u>Ph</u>CH$_2$O), 130.4 (C-1′), 128.5 (<u>Ph</u>CH$_2$O), 128.2 (P<u>h</u>CH$_2$O), 128.1 (<u>Ph</u>CH$_2$O), 126.8 (C-1), 125.6 (C-6′), 122.1 (C-6), 117.2 (C-2′), 112.9 (C-2), 66.6 (Ph<u>C</u>H$_2$O), 60.9 (OCH$_2$CH$_3$), 56.1 (OCH$_3$), 40.6 (ArCH$_2$COOBn), 40.4 (ArCH$_2$COOEt), 14.2 (OCH$_2$CH$_3$).

*3.7.19 Methyl 2-{3-[4-[2-(*tert*-butoxycarbonylamino)ethyl]-2-methoxyphenoxy]-4-methoxyphenyl}acetate (3.137)*



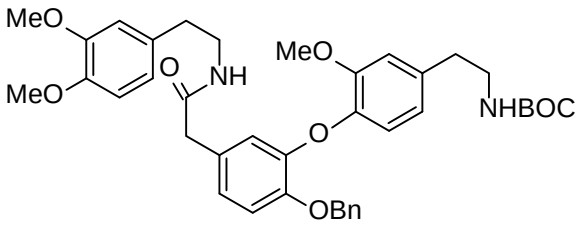
The title compound was prepared in 28-29% yield (yellow oil) by the Ullmann ether coupling reaction of phenol **3.111** and aryl iodide **3.134** according to the procedure in **3.7.17**.

^{1}H NMR (400 MHz, CDCl$_3$) δ_H: 7.37-7.29 (<u>Ph</u>CH$_2$O), 6.99 (1H, dd, *J* = 2.2 and 8.4 Hz, H-2′), 6.93 (1H, d, *J* = 8.4 Hz, H-6′), 6.76 (3H, overlap, H-5′,5,6), 6.66 (1H, dd, *J* = 1.9 and 8.2 Hz, H-2), 5.11 (2H, s, PhC<u>H</u>$_2$O), 3.87 (3H, s, OCH$_3$), 3.84 (3H, s, OCH$_3$), 3.54 (2H, s, ArC<u>H</u>$_2$COOCH$_3$), 3.39 (2H, q, *J* = 6.9 Hz, ArC<u>H</u>$_2$CH$_2$NHOCOC(CH$_3$)$_3$), 2.78 (2H, t, *J* = 6.9

Hz, ArC<u>H</u>$_2$CH$_2$NHOCOC(CH$_3$)$_3$), 1.46 (9H, s ArCH$_2$CH$_2$NHOCOC(C<u>H</u>$_3$)$_3$

HRMS-ES$^+$ (*m/z*): Found 544.2316 [M+Na]$^+$; calculated for [$C_{30}H_{35}NO_7Na$] 544.2311.

3.7.20 N-*(3,4-dimethoxyphenylethyl)-4-benzyloxy -3-(4-(3-methoxyphenoxy) ethyl* tert-*butylcarbamate)phenylacetamide (3.100)*

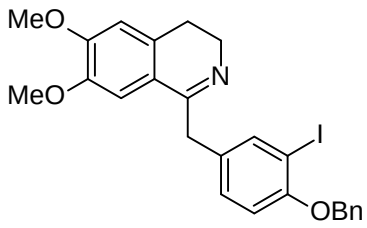


The diaryl ether **3.100** was prepared in 5-10% yield from the aryl iodide **3.112** and the phenol **3.111** according to the general procedure **3.7.17**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.33-7.29 (5H, m, Ph<u>h</u>CH$_2$O), 6.94 (1H, d, *J* = 8.4 Hz, H-5), 6.82 (1H, dd, *J* = 8.4 Hz, H-6), 6.82 (1H, d, *J* = 1.9 Hz, H-2), 6.77 (1H, d, *J* = 1.9 Hz, H-2′), 6.76 (1H, d, *J* = 8.4 Hz, H-5′), 6.73 (1H, d, *J* = 8.4 Hz, H-5′′), 6.68 (1H, dd, *J* = 1.9 and 8.4 Hz, H-2′′), 6.64 (1H, d, *J* = 1.9 Hz, H-2′), 6.54 (1H, dd, *J* = 1.9 and 8.4 Hz, H-2′′), 5.40 (1H, brs, NHCO), 5.13 (2H, s, PhCH$_2$O), 3.88 (3H, s, OCH$_3$), 3.84 (3H, s, OCH$_3$), 3.83 (3H, s, OCH$_3$), 3.49-3.67 (6H, overlap,), 2.78 (2H, t, *J* = 6.9 Hz, ArCH$_2$), 2.66 (2H, t, *J* = 6.9 Hz, ArCH$_2$CH$_2$), 1.28 (9H, s, OCOC(CH$_3$)$_3$

HRMS-ES$^+$ (*m/z*): Found 693.3147 [M+Na]$^+$; calculated for [$C_{39}H_{46}N_2O_8Na$] 693.3152.

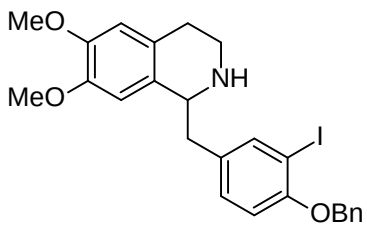
3.7.21 1-(4-Benzyloxy-3-iodobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (3.144)



Excess $POCl_3$ (0.137 mL, 1.51 mmol) was added to acetamide **3.112** (0.2 g, 0.376 mmol) (4:1 mol equivalents $POCl_3$: acetamide) in dry toluene. The resulting mixture was refluxed under a nitrogen atmosphere for 8-14 h until TLC showed no starting material remaining. The solution was cooled to room temperature and cautiously added to ice water and basified with NaOH pellets while cooling in ice water bath. It was then extracted in CH_2Cl_2 (20 mL x 3) and washed with water (40 mL x 3). The solvent was evaporated and the crude product was purified on basified silica gel column chromatography using 5%v/v Et_2NH in EtOAc as mobile phase to deliver the iodinated benzyldihydroisoquinoline **3.144** in 70% (0.14 g) yield as a brown viscous oil.

^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 7.79 (1H, d, *J* = 2.0 Hz, H-2′), 7.51-7.124 (6H, m, $PhCH_2O$ and H-6′), 6.95 (1H, s, H-8), 6.76 (1H, d, *J* = 8.1 Hz, H-5′),6.65 (1H, s, H-5), 5.09 (2H, s, $PhCH_2O$), 3.94 (2H, s, H-α), 3.88 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.72 (2H, t, *J* = 7.5 Hz, H-3), 2.64 (2H, t, *J* = 7.5 Hz, H-4).

3.7.22 1-(4-Benzyloxy-3-iodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3.145)

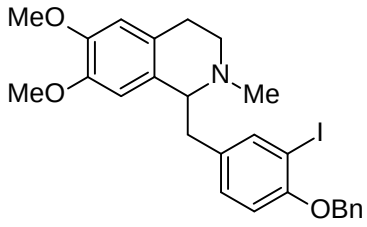


To a solution of dihydroisoquinoline **3.144** (0.20 g, 0.389 mmol) in CH_3OH at -78 ^oC was added $NaBH_4$ (58.9 mg, 1.56 mmol) in portions and stirring was continued at the same temperature for 3 h. After warming the reaction to room temperature, a solution of 10% aq. HCl (10 mL) was added dropwise, in order to decompose excess $NaBH_4$ and the resulting mixture was basified with 2 N KOH and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, brine, dried over $MgSO_4$ and evaporated *in vacuo*. The obtained residue was subjected to column chromatography eluting with EtOAc:CH_3OH (9:1) to give **3.145** in 50% yield (0.100 g) as a brown oil.

^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 7.72 (1H, d, *J* = 2.0 Hz, H-2′), 7.49 (2H, *J* = 7.7 Hz, PhCH_2O), 7.39 (2H, t, *J* = 7.7 Hz, PhCH_2O), 7.31 (1H, t, *J* = 7.7 Hz, PhCH_2O), 7.15 (1H, dd, *J* = 8.3 and 2.0 Hz, H-6′), 6.81 (1H, d, *J* = 8.3 Hz, H-5′), 6.60 (1H, s, H-8), 6.59 (1H, s, H-5), 5.13 (2H, s, PhCH_2O), 4.09 (1H, dd, *J* = 9.5 and 4.2 Hz, H-1), 3.85 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.19 (1H, m, H-3), 3.09 (1H, dd, *J* =13.8 and 4.3 Hz, H-α), 2.92 (1H, m, H-3), 2.79 (1H, q, *J* = 9.5 Hz, H-α), 2.72 (2H, m, H-4)

^{13}C NMR(100 MHz, $CDCl_3$) δ_H: 155.9 (C-4′), 147.6 (C-6), 147.1 (C-7), 140.1 (C-2′), 136.6 (PhCH_2O), 133.8 (C-1′), 130.3 (C-8a), 128.6 (PhCH_2O), 127.9 (PhCH_2O), 127.4 (C-4a), 127.0 (PhCH_2O), 112.7 (C-6′), 111.4 (C-8), 109.5 (C-5), 87.1 (C-3′), 71.0 (PhCH_2O), 56.8 (C-1), 56.0 (OCH_3), 55.9 (OCH_3), 41.5 (C-3), 40.7 (C-α), 29.4 (C-4).

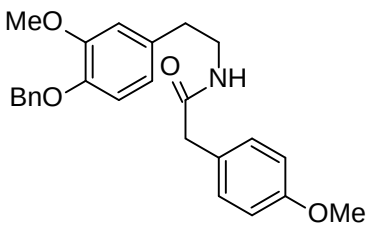
3.7.23 1-(4-Benzyloxy-3-iodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3.143)



To a solution of tetrahydroisoquinoline **3.145** (0.185 g, 0.358 mmol) in CH_3OH was added aqueous CH_2O (1.50 mL, c = 37%). After this mixture had been stirred at room temperature for 3 h, $NaBH_4$ (0.162 g, 4.29 mmol) was slowly added. The reaction mixture was stirred at room temperature for an additional 16 h. Then, saturated aqueous NH_4Cl (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 X 30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vaccum. After purification by flash chromatography (SiO_2, EtOAc/CH_3OH/Et_3N, 9:1:1), compound **3.143** (60%, 0.11 g) was isolated as a yellow solid.

^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 7.72 (1H, d, *J* = 2.0 Hz, H-2′), 7.45-7.32 (5H, PhCH_2O), 7.08 (1H, dd, *J* = 8.3 and 2.0 Hz, H-6′), 6.79 (1H, d, *J* = 8.3 Hz, H-5′), 6.60 (1H, s, H-8), 6.54 (1H, s, H-5), 5.09 (2H, s, PhCH_2O), 4.04 (1H, m, H-1), 3.84 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.15 (1H, m, H-3), 3.01 (1H, m, H-α), 2.92 (1H, m, H-3), 2.75 (1H, m, H-α), 2.69 (2H, m, H-4), 2,56 (3H, s, NCH_3).

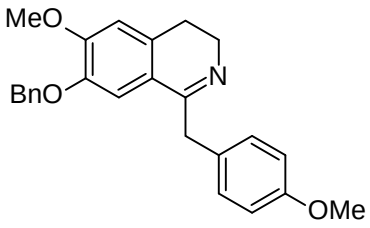
3.7.24 **N-*(4-Benzyloxy-3-methoxyphenylethyl)-4-methoxyphenyl acetamide (3.147)***



The title compound was prepared in 67% yield (white solid) by the Schotten-Baumann procedure according to the procedure in **3.7.10**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.43-7.31 (5H, m, $PhCH_2O$), 7.07 (2H, d, *J* = 8.7 Hz, H-2′,6′), 6.81 (2H, d, *J* = 8.7 Hz, H-3′,5′), 6.72 (1H, d, *J* = 8.2 Hz, H-5), 6.62 (1H, d, *J* = 2.1 Hz, H-2), 6.48 (1H, dd, *J* = 8.2 and 2.1 Hz, H-6). 5.49 (1H, brs, N<u>H</u>CO), 5.13 (2H, s, $PhCH_2O$), 3.84 (3H, s, OCH_3) and 3.79 (3H, s, OCH_3), 3.46 (2H, s, $ArCH_2C$), 3.43 (2H, t, *J* = 6.8 Hz, CH_2CH_2N), 2.67 (2H, t, J = 6.8 Hz, CH_2CH_2N.

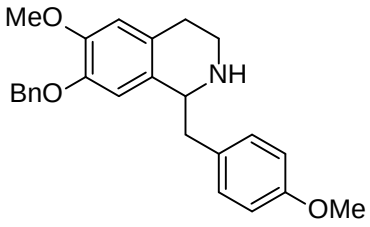
3.7.25 1-(4-Methoxybenzyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline (3.148)



The title compound was synthesised in 71% yield (yellow syrup) by Bischler-Napieralski cyclisation of acetamide **3.147** in toluene in the presence of $POCl_3$ according to the procedure in **3.7.21**.

^{1}H NMR(400 MHz, CDCl3) δ_H: 7.39 (5H, m, <u>Ph</u>CH_2O), 7.05 (2H, d, *J* = 8.4 Hz, H-2′,6′), 6.98 (1H, s, H-8), 6.76 (2H, d, *J* = 8.4 Hz, H-3′,5′), 6.66 (1H, s, H-5), 5.02 (2H, s, $PhC\underline{H_2}O$), 3.88 (3H, s, OCH_3), 3.84 (2H,s, H-α), 3.78 (3H, s, OCH_3), 3.69 (2H, t, *J* = 7.6 Hz, H-3), 2.61 (2H, t, *J* = 7.6 Hz, H-4).

3.7.26 1-(4-Methoxybenzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (3.149)

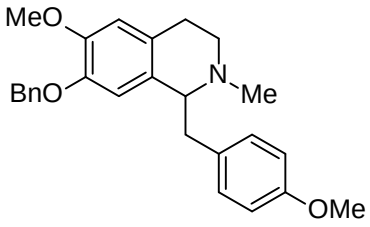


The title compound was synthesised in 56% yield (yellow syrup) by hydride reduction of **3.148** in CH_3OH in the presence of $NaBH_4$ according to the procedure in **3.7.22**.

^{1}H NMR(400 MHz, CDCl3) δ_H: 7.45 (2H, d, *J* = 7.4 Hz, PhCH$_2$O), 7.38 (2H, t, *J* = 7.4 Hz, PhCH$_2$O), 7.30 (1H, t, *J* = 7.4 Hz, PhCH$_2$O), 7.28 (2H, d, *J* = 8.4 Hz, H-2′,6′), 6.87 (2H, d, *J* = 8.4 Hz, H-3′,5′), 6.67 (1H, s, H-8), 6.63 (1H, s, H-5), 5.08 5.02 (2H, s, PhCH$_2$O), 4.07 (1H, m, H-1), 3.88 (3H, s, OCH3), 3.81 (3H, s, OCH3), 3.199 (1H, m, H-3), 3.04 (1H, dd, *J* = 13.6 and 4.4 Hz, H-α), 2.92 (1H, m, H-3), 2.83 (1H, dd, *J* = 13.6 and 9.1 Hz, H-α), 2.73 (2H, m, H-4), 2.43 (1H, brs, NH)

^{13}C NMR(100 MHz, CDCl3) δ_C: 158.2 (C-4′), 148.3 (C-6), 146.1 (C-7), 137.3 (PhCH$_2$O), 130.8 (C-1), 130.3 (C-2′,6′), 130.1 (C-8a), 128.4 (PhCH$_2$O), 127.9 (C-4a), 127.7 (PhCH$_2$O), 127.3 (PhCH$_2$O), 113.9 (C-3′,5′), 112.9 (C-8), 112.4 (C-5), 71.4 (PhCH$_2$O), 56.7 (C-1), 55.9 (OCH_3), 55.2 (OCH_3), 41.5 (C-3), 40.56 (C-α), 29.2 (C-4).

3.7.27 1-(4-Methoxybenzyl)-7-benzyloxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3.150)

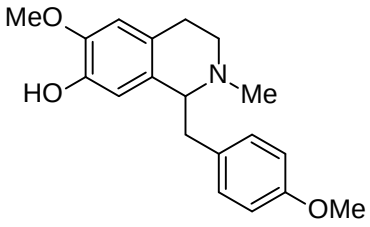


The tetrahydroisoquinoline **3.149** was *N*-methylated according to the procedure in **3.7.23** to give compound **3.150** as a yellow oil in a 50% yield.

^{1}H NMR(400 MHz, CDCl3) δ_H: 7.43-7.33 (5H, m, PhCH$_2$O), 7.20 (2H, d, *J* = 8.4 Hz, H-2′,6′), 6.81 (2H, d, *J* = 8.4 Hz, H-3′,5′), 6.66 (1H, s, H-8), 6.63 (1H, s, H-5), 5.02 (2H, s, PhCH$_2$O), 4.02 (1H, m, H-1), 3.87 (3H, s, OCH3), 3.80 (3H, s, OCH3), 3.21 (1H, m, H-3), 3.02 (1H, m, H-α), 2.92 (2H, m, H-3, H-4), 2.83 (1H, m, H-α), 2.71 (1H, m, H-4), 2.57 (3H, S, NCH$_3$)

^{13}C NMR(100 MHz, CDCl3) δ_C: 159.2 (C-4′), 148.9 (C-6), 147.1 (C-7), 137.1 (PhCH$_2$O), 130.8 (C-1), 130.3 (C-2′,6′), 130.1 (C-8a), 128.9 (PhCH$_2$O), 128.2 (C-4a), 127.5 (PhCH$_2$O), 127.0 (PhCH$_2$O), 114.2 (C-3′,5′), 113.0 (C-8), 112.9 (C-5), 71.0 (PhCH$_2$O), 57..0 (C-1), 56.2 (OCH$_3$), 55.8 (OCH$_3$), 42.3 (C-3), 41.4 (NCH$_3$), 40.7 (C-α), 30.1 (C-4).

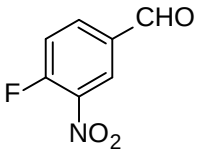
3.7.28 1-(4-Methoxybenzyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3.142)



The benzyl protecting group on **3.150** was cleaved according to the procedure in **3.7.7** to give **3.142** as a yellow oil (45%).

^{1}H NMR(400 MHz, CDCl3) δ_H: 7.18 (2H, d, *J* = 8.4 Hz, H-2′,6′), 6.80 (2H, d, *J* = 8.4 Hz, H-3′,5′), 6.64 (1H, s, H-8), 6.62 (1H, s, H-5), 3.98 (1H, m, H-1), 3.85 (3H, s, OCH3), 3.81 (3H, s, OCH3), 3.21 (1H, m, H-3), 3.12 (1H, m, H-α), 2.97 (1H, m, H-3), 2.90 (1H, m, H-4), 2.80 (1H, m, H-α), 2.65 (1H, m, H-4), 2.55 (3H, S, NCH_3).

3.7.29 4-Fluoro-3-nitrobenzaldehyde (3.157)



To a solution of 4-fluorobenzaldehyde (**3.156**) (1.77 g, 14.3 mmol) in conc. H_2SO_4 (4 mL) was added a solution of HNO_3 (1.5 mL) and sulphuric acid (1.5 mL) dropwise at 0 ^{o}C to 10 ^{o}C for 30 min. After the addition the mixture was stirred at room temperature for 10 min and poured into ice. The resulting precipitate was filtered through suction and washed with water to afford the aldehyde **3.157** as a solid (1.46 g, 60 %). Recrystallisation from ethanol gave the pure product as a white solid.

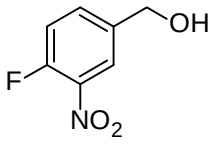
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.05 (1H, s, CHO), 8.58 (1H, dd, *J* = 2.0 and 7.2 Hz, H-2), 8.19 (1H, ddd, *J* = 2.0, 8.4 and 10.8 Hz, H-6), 7.49 (1H, dd, *J* = 8.4 and 10.8 Hz, H-5)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 188.2 (CHO), 158.8 (d, J_{C-F} = 273.9 Hz,C-4), 137.5 (C-3), 135.6 (d, J_{C-F} = 10.4 Hz, C-6), 132, 9 (d, J_{C-F} = 3.6 Hz, C-2), 127.9 (d, J_{C-F} = 1.4 Hz, C-1), 119.7 (d, J_{C-F} = 21.9 Hz, C-5)

IR ν_{max}(cm^{-1}): 3064, 2881, 1708, 1689, 1611, 1589, 1534, 1345, 1253, 1204, 1082, 923, 845, 826, 759, 712

HRMS-ES^- (*m/z*): Found 168.0096 $[M-H]^-$; calculated for $[C_7H_3FNO_3]$ 168.0097.

3.7.30 4-Fluoro-3-nitrobenzyl alcohol (3.158)



To a solution of 4-fluoro-3-nitrobenzaldehyde (**3.157**) (1.00 g, 5.91 mmol) in THF:EtOH/3:1 (10 mL), $NaBH_4$ (0.67 g, 17.7 mmol) was added in portions; the mixture was stirred for 12 h at room temperature. The solvent was distilled off and the residue was decomposed with water and extracted with EtOAc. The combined extracts were washed with water, dried with Na_2SO_4, and evaporated to give the benzyl alcohol **3.158** (0.77 g, 75%) as a white solid.

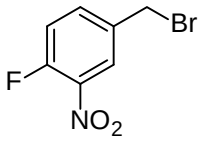
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.10 (1H, dd, *J* = 2.1 and 7.2 Hz, H-6), 7.23 (1H, ddd, *J* = 8.6 and 10.4 Hz, H-5), 4.75 (2H, s, $ArCH_2OH$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 154.6 (d, J_{C-F} = 264.4 Hz,C-4), 138.0 (d, J_{C-F} = 4.0 Hz, C-1), 137.2 (C-3), 133.6 (d, J_{C-F} = 8.9 Hz, C-6), 124.0 (dd, J_{C-F} = 2.5 and 6.2 Hz, C-2), 118.4 (ddd, J_{C-F} = 2.5, 6.6 and 21.4 Hz, C-5), 63.2 (Ar<u>C</u>H_2OH)

IR ν_{max}(cm^{-1}): 3539, 2884, 1621, 1590, 1528, 1343, 1323, 1234, 1048, 820, 758

HRMS-ES^- (*m/z*): Found 170.0252 $[M-H]^-$; calculated for $[C_7H_5FNO_3]$ 170.0253.

3.7.31 4-Fluoro-3-nitrobenzyl bromide (3.159)



To a solution of the alcohol **3.158** (1.00 g, 5.84 mmol) in dry ether (20 mL), PBr_3 (2.37 g, 8.76 mmol) was added dropwise. The mixture was stirred for 8 h at room temperature. The solvent was distilled off to give the expected benzyl bromide **3.159** (1.10 g, 80%) as a white powder.

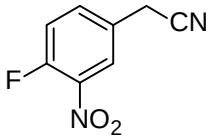
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.09 (1H, dd, *J* = 2.5 and 6.7 Hz, H-2), 7.67 (1H, ddd, *J* = 2.5, 8.6 and 10.6 Hz, H-6), 7.28 (1H, dd, *J* = 8.6 and 10.6 Hz, H-5), 4.49 (2H, s, ArCH_2Br)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 155.1 (d, J_{C-F} = 266.1 Hz,C-4), 137 (C-1), 136.0 (d, J_{C-F} = 9.0 Hz, C-6), 135.0 (d, J_{C-F} = 4.0 Hz, C-3), 126.5 (d, J_{C-F} = 3.0 Hz, C-2), 119.0 (d, J_{C-F} = 21.3 Hz, C-5), 30.3 (Ar<u>C</u>H_2Br)

IR ν_{max}(cm^{-1}): 2979, 2307, 1608, 1530, 1347, 1251, 1086, 843, 777

LRMS-ES$^+$ (*m/z):* $(M+H)^+$ 234.

3.7.32 4-Fluoro-3-nitrophenylacetonitrile (3.160)



A mixture of 4-fluoro-3-nitrobenzyl bromide (**3.159**) (0.800 g, 3.42 mmol), sodium cyanide (0.335 g, 6.84 mmol) in DMSO (5 mL) was heated at 50 ^oC for 4 h. After the addition of water (15 mL), the mixture was extracted with ether. The extract was washed with water, dried and evaporated to give the corresponding phenylacetonitrile **3.160** as a brown oil (0.31 g, 50%).

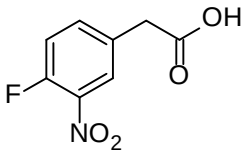
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.05 (1H, dd, *J* = 2.5 and 6.5 Hz, H-2), 7.65 (1H, m, H-6), 7.33 (1H, ddd, *J* = 2.5, 8.4 and 10.4 Hz, H-5), 3.84 (2H, s, ArC$\underline{H}_2$CN)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 155.1 (d, J_{C-F} = 168.3 Hz, C-4), 134.9 (d, J_{C-F} = 8.7 Hz, C-6), 133.9 (C-3),127.1 (d, J_{C-F} = 2.5 Hz, C-1), 125.7 (d, J_{C-F} = 3.0 Hz, C-2), 119.5 (d, J_{C-F} = 21.5 Hz, C-5), 116.3 (ArCH$_2\underline{C}$N), 22.8 (Ar$\underline{C}$H$_2$CN)

IR ν_{max} (cm^{-1}): 2961, 2255, 1625, 1533, 1500, 1349, 1250, 1138, 1090, 817

HRMS-ES$^-$ (*m/z*): Found 179.0254 $[M-H]^-$; calculated for $[C_8H_5FN_2O_2]$ 179.0257;

3.7.33 4-Fluoro-3-nitrophenylacetic acid (3.163)



4-Fluoro-3-nitrophenylacetonitrile (**3.160**) (1.50 g, 8.33 mmol) was dissolved in conc. HCl and heated under reflux for 16 h, then cooled to room temperature and was extracted with CH_2Cl_2 (4 x 30 mL). The combined extracts were washed with water, dried with Na_2SO_4, and evaporated to give the desired phenylacetic acid (0.97 g, 55%) as a white solid.

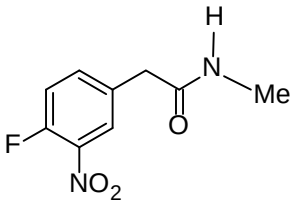
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.00 (1H, dd, *J* = 2.4 and 7.0 Hz, H-2), 7.56 (1H, ddd, *J* = 2.4, 8.5 and 10.7 Hz, H-6), 7.27 (1H, dd, *J* = 8.5 and 10.5 Hz, H-5), 3.73 (2H, s, ArC<u>H</u>$_2$COOH)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 175.2 (COOH), 154.9 (d, $J_{C\text{-}F}$ = 265.7 Hz, C-4), 136.5 (d, $J_{C\text{-}F}$ = 8.8 Hz, C-6), 132.3 (C-3), 130.2 (d, $J_{C\text{-}F}$ = 4.3 Hz, C-1), 126.9 (d, $J_{C\text{-}F}$ = 3.0 Hz, C-2), 118.7 (d, $J_{C\text{-}F}$ = 21.9 Hz, C-5), 39.4 (Ar<u>C</u>H$_2$COOH)

IR ν_{max}(cm^{-1}): 3340, 3017, 2876, 2651, 1691, 1537, 1346, 1253, 1236, 1153, 1088, 926, 843, 822, 674

HRMS-ES$^-$ (*m/z*): Found 198.0204 [M-H]$^-$; calculated for [$C_8H_5FNO_4$] 198.0203.

*3.7.34 2-(4-Fluoro-3-nitrophenyl)-*N*-methylacetamide (3.164)*



To a solution of 4-fluoro-3-nitrophenylacetic acid (**3.163**) (1.00 g, 5.00 mmol) in dry Et_2O (10 mL) was added $SOCl_2$ (7.53 mmol). The reaction mixture was refluxed for 1 h and cooled to room temperature. The excess $SOCl_2$ was removed on rotary evaporator. To the crude mixture of acid chloride in dry ether was added $MeNH_2$ (33% solution in EtOH) (10.0 mmol) dropwise. The resulting mixture was extracted with CH_2Cl_2 (20 mL x 3), washed with K_2CO_3 solution, water, 1N HCl, brine, dried and concentrated under vacuum to afford **3.164** (0.64 g, 60%) as a yellow crystalline product.

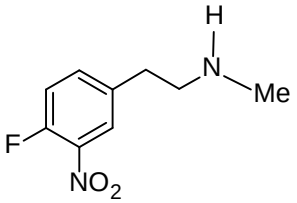
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.97 (1H, dd, *J* = 2.3 and 7.0 Hz, H-2), 7.59 (1H, ddd, *J* = 2.3, 8.6 and 10.9 Hz, H-6), 7.27 (1H, dd, *J* = 8.6 and 10.9 Hz, H-5), 5.63 (1H, br s, N<u>H</u>COCH$_3$) 3.57 (2H, s, ArC<u>H</u>$_2$CONHCH$_3$), 2.83 (2H, d, *J* = 4.7 Hz, NHCO<u>C</u>H$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 169.8 (NH<u>C</u>OCH$_3$), 154.6 (d, $J_{C\text{-}F}$ = 264.6 Hz, C-4), 136.5 (d, $J_{C\text{-}F}$ = 8.4 Hz, C-6, C-3), 132.2 (d, $J_{C\text{-}F}$ = 4.4 Hz, C-1), 126.6 (d, $J_{C\text{-}F}$ = 2.9 Hz, C-2), 118.7 (d, $J_{C\text{-}F}$ = 21.2 Hz, C-5), 42.9 (ArC<u>H</u>$_2$CONH<u>C</u>H$_3$).

IR ν_{max}(cm^{-1}): 3299, 3081, 2955, 1643, 1530, 1417, 1343, 1244, 1177,919, 673.

HRMS-ES$^-$ (*m/z*): Found 211.0517 [M-H]$^-$; calculated for [$C_9H_8FN_2O_3$] 211.0519.

*3.7.35 2-(4-Fluoro-3-nitrophenyl)-*N*-methylethanamine (3.165)*



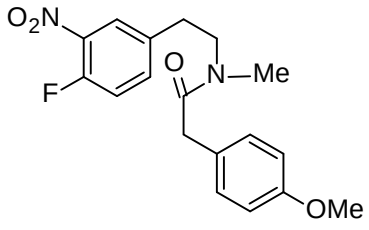
To a solution 2-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (**3.164**) (0.200 g, 0.943 mmol) in anhydrous THF (5 mL) was slowly added $BF_3.Et_2O$ complex (1.88 mmol) and 1M solution of BH_3.THF (14.1 mmol) complex at room temperature. After cooling to room temperature, the excess reagent was decomposed with 6N aq. HCl. The aqueous solution was washed with EtOAc, basified with 10% aq. KOH and extracted with CH_2Cl_2. The CH_2Cl_2 was washed with water and evaporated *in vacuo* to give pure amine **3.165** as oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.89 (1H, dd, *J* = 2.2 and 7.1 Hz, H- 2), 7.47 (1H,ddd, *J* = 2.2, 8.6, 10.9 Hz, H-6), 7.19 (1H, dd, *J* = 8.6 and 10. 9 Hz, H-5), 2.86 (4H, s, $ArC\underline{H}_2C\underline{H}_2NHC\underline{H}_3$), 2.45 (4H,s, $ArCH_2CH_2N\underline{H}C\underline{H}_3$)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 154.3 (d, $J_{C\text{-}F}$ = 263.4 Hz C-4), 137.15 (d, *J* = 3.3 Hz, C-1), 135.8 (d, $J_{C\text{-}F}$ = 8.4 Hz C-6), 133.5 (C-3),125.9 (d, $J_{C\text{-}F}$ = 2.5 Hz C-2), 118.3 (d, $J_{C\text{-}F}$ = 21 Hz, C-5), 52.4 ($Ar\underline{C}H_2CH_2NHMe$), 35.9 ($NH\underline{C}H_3$), 34.9 ($ArCH_2\underline{C}H_2NHCH_3$)

HRMS-ES$^-$ (*m/z*): Found 199.0881[M-H]$^-$; calculated for [$C_9H_{10}FN_2O_2$] 199.0883;

3.7.36 N-*[2-(4-fluoro-3-nitrophenyl)ethyl]-2-(4-methoxyphenyl)*-N-*methylacetamide (3*.166)



To a solution of 4-methoxyphenylacetic acid **3.121** (0.100 g, 0.600 mmol) in dry ether (10 mL) was added $SOCl_2$ (0.900 mmol). The reaction mixture was refluxed for 1 h and cooled to room temperature. The excess $SOCl_2$ was removed on a

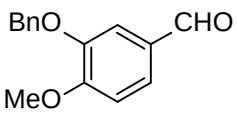
rotary evaporator. To the crude mixture of the acid chloride in dry Et_2O was added 2-(4-fluoro-3-nitrophenyl)-*N*-methylethanamine (1.200 mmol) dropwise. The resulting mixture was extracted with CH_2Cl_2 (10 mL x 3), washed with K_2CO_3 solution, water, 1N HCl, brine, dried and concentrated under vacuum to afford **3.166** (62 mg, 30%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.84 (1H, dd, *J* = 2.5 and 7.1 Hz, H-2), 7.46 (1H, ddd, *J* = 2.5, 8.5 and 11.0 Hz, H-6), 7.17 (1H, dd, *J* = 8.5 and 11.0 Hz, H-5), 7.11 (2H, d, *J* = 8.7 Hz, H-2′,6′), 6.85 (2H, d, *J* = 8.7 Hz, H-3′,5′), 3.82 (3H, s, OC$\underline{H}_3$), 3.64 (2H, t, *J* = 7.1, ArCH$_2$C$\underline{H}_2$N), 3.62 (2H, s, ArC$\underline{H}_2$C=O), 2.95 (3H, s, NC$\underline{H}_3$), 2.91 (2H, t, *J* = 7.1 Hz, ArC$\underline{H}_2$CH$_2$N).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 171.5 (NC=O), 158.6 (C-4′), 154.3 (d, $J_{C\text{-}F}$ = 263.4 Hz, C-4), 137.0 (C-3), 136.0 (d, $J_{C\text{-}F}$ = 8.4 Hz C-6), 135.9 (d, J = 4.4 Hz, C-1), 129.7 (C-3′,5′), 126.6 (C-1′), 125.9 (d, $J_{C\text{-}F}$ = 2.9 Hz, C-2), 118.4 (d, $J_{C\text{-}F}$ = 20 Hz, C-5), 114.1 (C-2′,6′), 55.3 (O$\underline{C}$H$_3$), 49.1 (ArCH$_2\underline{C}$H$_2$N), 40.3 (Ar$\underline{C}$H$_2$C=O), 36.4 (N$\underline{C}$H$_3$), 32.5 (Ar$\underline{C}$H$_2$CH$_2$N).

HRMS-ES$^+$ (*m/z*): Found 369.1227 [M+Na]$^+$; calculated for [$C_{18}H_{19}FN_2O_4Na$] 369.1227;

3.7.37 3-Benzyloxy-4-methoxybenzaldehyde (3.171)

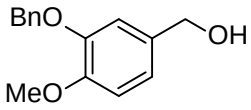


BnBr (1.56 mL; 13.14 mmol) was added to a mixture of 3-hydroxy-4-methoxybenzylaldehyde (**3.170**) (2.00 g; 13.14 mmol) and K_2CO_3 (3.62 g; 26.19 mmol) in dry CH_3CN (20 mL) and the reaction mixture was refluxed for 12 h. The reaction mixture was extracted with EtOAc (3 x 30 mL) and the organic phases

were washed with water (25 mL), followed by brine solution, dried under anhydrous Na_2SO_4 and concentrated under vacuum to give the desired benzaldehyde **3.171** as a white solid (3.12 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.83 (1H, s, C<u>H</u>O), 7.48 (2H, overlap, H-2,6), 7.43-7.31 (5H, overlap, $PhCH_2O$), 7.01 (1H, d, J = 8.4 Hz, H-5), 5.20 (2H, s, $PhCH_2O$), 3.97 (3H, s, OCH_3).

3.7.38 3-Benzyloxy-4-methoxybenzyl alcohol (3.172)



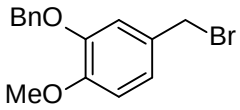
To a solution of 4-benzyloxy-3-methoxybenzylaldehyde (**3.71**) (2.13 g, 8.81 mmol) in EtOH, $NaBH_4$ (0.99 g, 26.43 mmol) was added in portions; the mixture was stirred for 12 h at room temperature. The solvent was distilled off and the residue was decomposed with water and extracted with EtOAc. The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated to give the benzyl alcohol **3.172** (2.10 g, 95%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.49-7.31 (5H, overlap, $PhCH_2O$), 6.98 (1H, d, *J* = 1.9 Hz, H-2), 6.93 (1H, dd, *J* = 1.9 and 8.0 Hz, H-6), 6.89 (1H, d, *J* = 8.0 Hz, H-5), 5.17 (2H, s, $PhCH_2O$), 4.59 (2H, s, Ar<u>C</u>H_2OH), 3.90 (3H, s, OCH_3), 1.58 (1H, s, OH)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 14.4 (C-4), 148.4 (C-3), 137.2 ($PhCH_2O$), 133.6 (C-1), 128.5 (OCH_2PH), 127.8 ($PhCH_2O$), 127.3 ($PhCH_2O$), 120.1 (C-5), 113.4 (C-6), 111.9 (C-2), 71.1 ($PhCH_2O$), 65.2 (Ar<u>C</u>H_2OH), 56.1 (OCH_3)

HRMS-ES$^+$ (*m/z*): Found 267.0993 $[M+Na]^+$; calculated for $[C_{15}H_{16}O_3Na]$ 267.0997.

3.7.39 3-Benzyloxy-4-methoxybenzyl bromide (3.173)

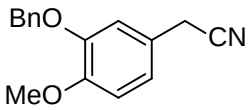


To a solution of 4-benzyloxy-3-methoxybenzyl alcohol (**3.172**) (1.0 g, 4.1 mmol) in dry Et_2O (20 mL), PBr_3 (0.730 g, 6.1 mmol) in Et_2O (10 mL) was added dropwise. The mixture was stirred for 12 h at room temperature. The pale yellow solution formed was then poured into ice water (200 mL), extracted with Et_2O (5 x 30 mL) and dried ($MgSO_4$) and the solvent removed at reduced pressure to afford **3.173** as a white solid (1.57 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.49- 7.31 (5H, overlap, PhCH_2O), 6.99 (1H, dd, *J* = 1.9 and 8.6 Hz, H-6), 6.97 (1H, d, *J* = 1.9 Hz, H-2), 6.85 (1H, d, *J* = 8.6 Hz, H-5), 5.16 (2H, s, PhCH_2O), 4.47 (2H, s, ArCH_2Br), 3.89 (3H, s, OCH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 150.0 (C-4), 148.3 (C-3), 136.7 (PhCH_2O), 130.2 (C-1), 128.6 (PhCH_2O), 127.8 (PhCH_2O), 127.5 (PhCH_2O), 122.2 (C-5), 115.0 (C-6), 111.8 (C-2), 71.2 (PhCH_2O), 56.1(OCH_3) 34.2 (ArCH_2Br).

3.7.40 3-Benzyloxy-4-methoxyphenylacetonitrile (3.174)



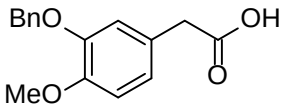
A mixture of 3-benzyloxy-4-methoxybenzyl bromide (**3.173**) (2.48 g, 8.1 mmol), sodium cyanide (0.516 g, 10.54 mmol), in DMSO (10 mL) was heated at 40 ^oC for 12 h. After the addition of water (15 mL), the mixture was extracted with Et_2O (3 X 25 mL). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Purification by column chromatography on

silica, eluting with hexanes/ethyl acetate (8:2) gave the corresponding phenylacetonitrile **3.174** as a white solid (2.93 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.49 (6H, overlap, PhCH_2O and H-5), 6.88 (2H, overlap, H-2,6), 5.16 (2H, s, PhCH_2O), 3.89 (3H, s, OCH_3), 3.65 (2H, s, ArCH_2CN)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 149.6 (C-4), 148.6 (C-3), 136.7 (PhCH_2O), 128.6 (PhCH_2O), 128.0 (PhCH_2O), 127.4 (PhCH_2O), 122.1 (C-1), 120.7 (C-5), 118.1 (CN), 113.9 (C-6), 112.3 (C-2), 71.2 (PhCH_2O), 56.1 (OCH_3), 23.1 (ArCH_2CN).

3.7.41 3-Benzyloxy-4-methoxyphenylacetic acid (3.167)



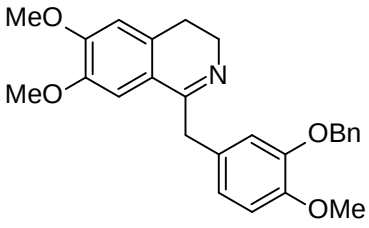
3-Benzyloxy-4-methoxyphenylacetonitrile (**3.174**) (2.4 g, 9.47 mmol) was dissolved in aqueous NaOH (2N, 90 mL) and heated to reflux for 6h, then cooled to room temperature and the pH adjusted to 1 with concentrated HCl. The precipitate formed was collected by filtration, washed with plenty of water and then diethyl ether. After drying under vacuum, **3.174** was obtained as a white solid (2.06 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48-7.31 (6H, overlap, PhCH_2O and H-5), 6.87 (2H, overlap, H-2,6), 5.15 (2H, s, PhCH_2O), 3.89 (OCH_3), 3.56 (2H, s, ArCH_2COOH)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 176.9 (COOH), 149.2 (C-4), 148.3 (C-3), 137.0 (PhCH_2O), 128.5 (PhCH_2O), 127.9 (PhCH_2O), 127.5 (PhCH_2O), 125.7 (C-1), 122.2 (C-5), 115.5 (C-6), 112.0 (C-2), 71.2 (PhCH_2O), 56.1 (OCH_3), 40.4 (ArCH_2COOH)

HRMS-ES$^+$ (*m/z*): Found 295.0936 $[M+Na]^+$; calculated for $[C_{16}H_{16}O_4Na]$ 295.0946.

3.7.42 1-(3-Benzyloxy-4-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (3.175)



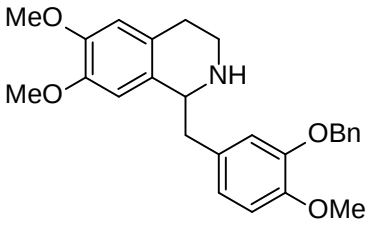
The title compound was synthesised in 70% yield (yellow syrup) by Bischler-Napieralski cyclisation of acetamide **3.168** in toluene in the presence of $POCl_3$ according to the procedure described for **3.7.21**.

^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 7.36 (2H, d, *J* = 7.4 Hz, PhCH_2O), 7.28 (2H, t, *J* = 7.4 Hz, PhCH_2O), 7.22 (1H, t, *J* = 7.4 Hz, PhCH_2O), 6.91 (1H, s, H-8), 6.86 (1H, d, *J* = 2.0 Hz, H-2´), 6.85 (1H, dd, *J* = 8.0 Hz and 2.0 Hz, H-6´), 6.78 (1H, d, *J* = 8.0 Hz, H-5´), 6.59 (1H, s H-5), 5.07 (2H, s, PhCH_2O), 3.94 (2H, s, H-α), 3.85 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.67 (5H, t, *J* = 6.7 Hz, OCH_3 and H-3), 2.57 (2H, t, J = 6.7 Hz, H-4)

^{13}C NMR(100 MHz, $CDCl_3$) δ_C: 151.7 (C-3´), 148. 5 (C-6), 148.3 (C-7), 147.3 (C-4´), 137.2 (PhCH_2O), 131.9 (C-1´), 130.2 (C-8a), 128.6 (PhCH_2O), 127.7 (PhCH_2O), 127.4 (C-4a), 127.2 (PhCH_2O), 121.3 (C-6´), 114.6 (C-2´), 112.1 (C-5´), 110.3 (C-8), 109.9 (C-7), 70.9 (PhCH_2O), 56.1 (OCH_3), 56.0 (OCH_3), 55.9 (OCH_3), 47.3 (C-α), 42.4 (C-3), 25.7 (C-4).

HRMS-ES$^+$ (*m/z*): Found 440.1840 $[M+Na]^+$; calculated for $[C_{26}H_{27}NO_4Na]$ 440.1838.

3.7.43 1-(3-Benzyloxy-4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3.178)



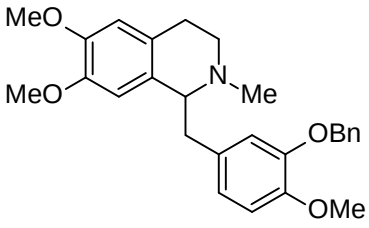
The title compound was prepared in 57% yield (brown oil) by the reduction of **3.175** in CH_3OH in the presence of $NaBH_4$ according to the procedure described in **3.7.22**.

^{1}H NMR(400 MHz, $CDCl_3$) δ_C: 7.43-7.27 (5H, m, PhCH_2O), 6.84 (1H, d, *J* = 8.0 Hz, H-5′), 6.78 (2H, overlap, H-2′,6′), 6.57 (1H, s, H-8), 6.53 (1H, s, H-5), 5.11 (2H, *J* = 3.1 Hz, PhCH_2O), 4.14 (1H, m, C-1), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.12 (2H, dd, *J* = 13.9 and 4.0 Hz, H-3), 2.86 (2H, m, H-α), 2.72 (2H, t, *J* = 5.6 Hz, H-4), 1.96 (1H, brs, NH).

^{13}C NMR(100 MHz, $CDCl_3$) δ_C: 148.6 (C-4′), 148.1 (C-3′), 147.7 (C-6), 147.2 (C-7), 137.1 (PhCH_2O), 130.6 (C-1′), 129.1 (C-8a), 128.5 (PhCH_2O), 127.8 (PhCH_2O), 127.3 (PhCH_2O), 126.8 (C-4a), 122.3 (C-6′), 115.6 (C-2′), 112.1 (C-5′), 111.8 (C-8), 109.6 (C-5), 71.0 (PhCH_2O), 56.3 (C-1), 56.1 (OCH_3), 55.9 (OCH_3), 55.9 (OCH_3), 41.7 (C-3), 40.3 (C-α), 28.6 (C-4).

HRMS-ES$^+$ (*m/z*): Found 420.2178 $[M+H]^+$; calculated for $[C_{26}H_{30}NO_4]$ 420.2175.

*3.7.44 1-(3-Benzyloxy-4-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (3.176)*



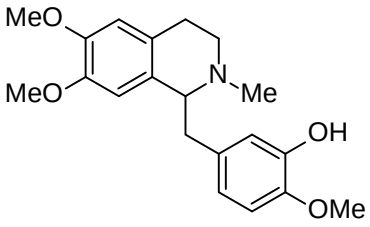
Compound **3.176** by prepared in 60% yields (yellow solid) according to the procedure in **3.7.23**.

^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 7.42-7.24 (5H, m, PhCH_2O), 6.77 (1H, d, *J* = 8.2 Hz, H-5′), 6.67 (1H, d, *J* = 2.0 Hz, H-2′), 6.60 (1H, dd, *J* = 8.2 and 2.0 Hz, H-6′), 6.54 (1H, s, H-8), 5.99 (1H, s, H-5), 5.06 (PhCH_2O), 3.84 (OCH_3), 3.83 (OCH_3), 3.63 (1H, m, H-1), 3.56 (OCH_3), 3.12 (2H, m, H-3), 2.78 (3H, m, H-4 and H-α), 2.56 (1H, m, H-4), 2.50 (3H, s, NCH_3).

^{13}C NMR(100 MHz, $CDCl_3$) δ_C: 148.2 (C-4′), 147.8 (C-3′), 147.4 (C-6), 146.5 (C-7), 137.3 (PhCH_2O), 132.2 (C-1′), 128.8 (C-8a), 128.5 (PhCH_2O), 127.7 (PhCH_2O), 127.3 (PhCH_2O), 125.8 (C-4a), 122.7 (C-6′), 116.1 (C-2′), 111.7 (C-5′), 111.2 (C-8), 111.0 (C-5), 71.1 (PhCH_2O), 64.8 (C-1), 56.1 (OCH_3), 55.8 (OCH_3), 55.6 (OCH_3), 46.9 (C-3), 42.5 (NCH_3), 40.7 (C-α), 25.4 (C-4).

HRMS-ES$^+$ (*m/z*): Found 434.2331 $[M+H]^+$; calculated for $[C_{27}H_{32}NO_4]$ 434.2331.

*3.7.45 1-(3-Hydroxy-4-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (3.169)*



The title compound was prepared in 80% yield (yellow solid) by hydrogenation of benzyltetrahydroisoquinoline **3.176** in CH_3OH according to the procedure described in **3.7.7**.

^{1}H NMR(400 MHz, $CDCl_3$) δ_H: 6.75 (1H, d, *J* = 2.0 Hz, H-2´), 6.72 (1H, d, *J* = 8.1 Hz, H-5´), 6.55 (1H, s, H-8), 6.52 (1H, dd, J = 8.1 and 2.0 Hz, H-6´), 6.04 (1H, s, H-5), 5.00 (1H, brs, OH), 3.83 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.72 (1H, q, H-1), 3.55 (3H, s, OCH_3), 3.19 (2H, m, H-3), 2.83 (2H, m, H-α), 2.67 (2H, m, H-4), 2.53 (3H, s, NCH_3).

^{13}C NMR(100 MHz, $CDCl_3$) δ_C: 147.4 (C-4´), 146.4 (C-)3´, 145.5 (C-6), 145.2 (C-7), 132.9 (C-1´), 128.7 (C-8a), 125.3 (C-4a), 121.2 (C-6´), 115.9 (C-2´), 111.2 (C-8), 111.1 (C-5), 110.5 (C-5´), 64.9 (C-1), 55.9 (OCH_3), 55.7 (OCH_3), 55.5 (OCH_3), 46.4 (C-3), 42.2 (NCH_3), 40.7 (C-α), 24.9 (C-4).

HRMS-ES$^+$ (*m/z*): Found 344.1863 $[M+H]^+$; calculated for $[C_{20}H_{26}NO_4]$ 344.1862.

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CHAPTER FOUR

GENERAL CONCLUSIONS AND FUTURE WORK

4.1 CONCLUSIONS AND FUTURE WORK

In this study, two modern methodologies for the synthesis of the tetrahydroisoquinolines were investigated. These were based on the intramolecular hydroamination reactions of the aminostilbenes and aminoalkynes. In the former protocol, electron-rich aminostilbenes of different substitution patterns were successfully prepared by the Heck reaction. The attempts to ring-close the stilbenes under base-catalysed, metal-catalysed and acid-catalysed conditions were unsuccessful. Even though the targeted benzyltetrahydroisoquinolines could not be successfully synthesised by this methodology, the results obtained in this study contribute greatly to the prevailing literature on the synthesis of benzyltetrahydroisoquinolines by the intramolecular hydroamination of aminostilbenes. Presently, this method is at an undeveloped stage, since its application has been demonstrated in two instances only.[1, 2] Therefore, further research will continue in this field in order to establish the ideal reaction conditions for this reaction and determine the functional group tolerance.

In the second approach, we succeeded in preparing the aminoalkyne precursors by the Sonogashira coupling reaction. Different titanium catalysts (**2.110**, **2.111** and **2.112**) were screened for the intramolecular hydroamination of the aminoalkynes into dihydroisoquinolines. The catalyst **2.112**, gave optimum results on a small scale synthesis. However, the results were inconsistent when reaction was performed on a larger scale.

Since naturally-occurring benzyltetrahydroisoquinolines have specified stereochemistry, it was required that the dihydroisoquinolines prepared by the

intramolecular hydroamination of aminoalkynes be reduced enantioselectively. In the present case, we opted for the chiral BINOL phosphoric acid catalyst for reduction of the benzyldihydroisoquinolines. We successfully prepared the chiral BINOL phosphoric acid catalyst **2.113**. Enantioselective reduction of the dihydroisoquinolines with the catalyst **2.113** was unsuccessful. Although the reaction failed, the low cost of starting materials, the good yielding steps and the ease of resolution of the *racemic* BINOL with readily available *S*-proline, makes this procedure ideal for enatioselective reduction of imines. Moreover, the stereoselective reduction of benzyldihydroisoquinolines by the chiral BINOL catalysts has not been reported. Therefore, it is recommended that the enantioselective reduction of dihydroisoquinolines by this catalyst be investigated further.

The second objective of this study was to synthesise the bisbenzyltetrahydroisoquinoline neferine (**1.15**) and its analogues. Neferine (**1.15**) was isolated from the roots of *Nelumbo nucifera* (commonly known as lotus) along with two other analogues liensinine and isoliensinine.[3] This compound has been reported to exhibit important pharmacological effects in the cardiovascular system, *e.g.* anti-arrhymia, anti-platelet aggregation and anti-thrombosis formation. Moreover, **1.15** was reported to show potent anti-cancer and anti-HIV activities and also showed lower cytotoxicity compared to other isoquinolines.[4]

Initially, it was planned that, upon establishment of the optimum conditions for the synthesis of benzyltetrahydroisoquinolines from aminostilbene and aminoalkyne precursors, these modern methodologies would be employed in the preparation of the two benzyltetrahydroisoquinoline scaffolds of neferine (**1.15**). However, these routes could not be pursued due to failure to ring-close the aminostilbenes and irreproducibility of results in the preparation of dihydroisoquinolines from aminoalkynes. Therefore, classical procedures were employed for the preparation of benzylisoquinoline nuclei of neferine (**1.15**).

Three different approaches leading to the synthesis neferine (**1.15**) and *O*-methylneferine **1.16** were explored. These methods were designed in such a way that they could address the long standing problems associated with the synthesis of bisbenzyltetrahydroisoquinolines. Such problems include the formation of the heterocyclic ring and the diaryl ether bond. Therefore, the Bichler-Napieralski cyclisation was the method of choice for the formation of benzyltetrahydroisoquinoline moiety. The Ullmann ether coupling reaction and nucleophilic aromatic substitution reactions were preferred methods for the formation of the biphenyl ether bond.

The first two methods were based on the Ullmann coupling reaction for the formation of the diaryl ether bond. The first method entailed an early construction of the ether link and late assembly of the two isoquinoline rings on the ether bridge. In this route, we succeeded in preparing the two major building blocks, which were the iodinated acetamide **3.112** and the hydroxyphenethylamine **3.111**. The Ullmann coupling of the two compounds afforded the the diphenyl ether **3.100**, albeit in low yields. Although **3.100** was obtained in low yields, the successful formation of the diaryl ether bond from electron-rich haloacetamide and hydroxyphenethylamine is a great advancement in the synthesis of bisbenzyltetrahydroisoquinolines. It is known that the Ullmann coupling reaction proceeds favourably if an electron-poor aryl halide is coupled with a phenol.[5-7]

The second method involved the synthesis of the two isoquinoline nuclei by the Bischler-Napieralski reaction, and coupling of the two compounds by the Ullmann reaction in the late stages of the synthesis. Here, the two benzyltetrahydroisoquinoline precursors for **1.15** were prepared successfully. However, the Ullmann coupling reaction of the two did not give any fruitful results.

In the last synthetic strategy, the formation of the diaryl ether bridge was based on the nucleophilic aromatic substitution reaction. This approach required 3’-hydroxybenzyltetrahydroisoquinoline, and a fluorinated acetamide, activated by

the nitro group at the *ortho*-position. In this route, we managed to synthesise the two coupling partners for the nucleophilic aromatic substitution reaction leading to *O*-methylneferine (**1.16**). One of the building blocks was the natural benzyltetrahydroisoquinoline, hydroxylaudanidine **3.169**, and its coupling partner was fluoroacetamide **3.153**. The major challenges in this route were encountered in the preparation the fluoroacetamide **3.153**, which involved several low-yielding synthetic steps and tedious chromatographic purifications. The nucleophilic aromatic substitution reaction of the two precursors was attempted in vain.

In conclusion, we have investigated the intramolecular hydroamination of electron-rich aminostilbenes and aminoalkynes in the synthesis of benzyltetrahydroisoquinolines. The results obtained suggest that it is more difficult to synthesise the electron-rich benzyltetrahydroisoquinolines from aminostilbenes than aminoalkynes. Because these methodologies have been developed recently, these results contribute significantly to the existing literature on the synthesis of benzyltetrahydroisoquinolines. We have also explored three different synthetic strategies for the synthesis of neferine (**1.15**) and its analogues. In all the routes, we have managed to prepared the advanced precursors for the synthesis of **1.15** and related bisbenzytetrahydroisoquinolines. It is strongly believed that the developed synthetic routes will enable us to prepare the targeted compound **1.15** and other naturally-occurring bisbenzyltetrahydroisoquinolines. Moreover, the challenges encountered in each route suggest that further research should be performed on the synthesis of bisbenzyltetrahydroisoquinolines.

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APPENDIX

Plate 1a. *^{1}H NMR spectrum of 4-hydroxyphenethene (**2.66**)*

Plate 1b. *^{1}H NMR spectrum of 4-hydroxyphenethene (**2.66**)*

Plate 2a. *^{1}H NMR spectrum of 4-hydroxy-3-methoxyphenethene (**2.67**)*

Plate 2b. *^{1}H NMR spectrum of 4-hydroxy-3-methoxyphenethene (**2.67**)*

Plate 3a. *^{1}H NMR spectrum of 4-*tert*-butyldimethylsilyloxyphenethene (**2.72**)*

Plate3b. *^{1}H NMR spectrum of 4-*tert*-butyldimethylsilyloxyphenethene (**2.72**)*

Plate 4a. *^{1}H NMR spectrum of* N*-[2-(3,4-dimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (**2.96**)*

Plate 4b. *^{13}C NMR spectrum of* N*-[2-(3,4-dimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (**2.96**)*

Plate 5. *^{1}H NMR spectrum of 2,2,2-trifluoro-*N*-[2-(2-iodo-4,5-dimethoxyphenyl)ethyl]acetamide (**2.97**)*

Plate 6a. *^{1}H NMR spectrum of* N*-(2-{2-[E-2-(4-*tert*-butyldimethylsilyloxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (**2.101**)*

Plate 6b. *^{13}C NMR spectrum of* N*-(2-{2-[*E*-2-(4-*tert*-butyldimethylsilyloxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (**2.101**)*

Plate 7. *1H NMR spectrum of* N*-(2-{2-[*E*-2-(4-benzyloxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (**2.99**)*

Plate 8a. *^{1}H NMR spectrum of (2-{2-[*E*-2-(4-benzyloxyphenyl)vinyl]-4-isopropoxy-5-methoxy-phenyl}ethyl)carbamic acid* tert*-butyl ester (**2.104**)*

Plate 8b. *^{13}C NMR of (2-{2-[*E*-2-(4-benzyloxyphenyl)vinyl]-4-isopropoxy-5-methoxy-phenyl}ethyl)carbamic acid* tert*-butyl ester (**2.104**)*

Plate 9. *^{1}H NMR spectrum of 4-benzyloxy-3-methoxyphenylethyne (**2.118**)*

Plate 10. *^{1}H NMR spectrum of* N*-{2-[2-(4-benzyloxy-3-methoxyphenyl)ethynyl]-4,5-dimethoxy-phenyl]ethyl}-2,2,2-trifluoroacetamide (**2.120**)*

Plate 11. *^{1}H NMR spectrum of 2-{2-[2-(4-benzyloxyphenyl)ethynyl]-4,5-dimethoxyphenyl}ethylamine (**2.11**)*

Plate 12. *^{1}H NMR spectrum of [2-(4'-hydroxy-3'-methoxy-phenyl)-ethyl]-carbamic acid* tert*-butyl ester (**3.111**)*

Plate 13. *^{1}H NMR spectrum of N-(3,4-dimethoxyphenylethyl) -4-benzyloxy-3-iodophenyl acetamide (**3.112**)*

Plate 14. *^{1}H NMR spectrum of* N*-(3,4-dimethoxyphenylethyl)-4-benzyloxy -3-(4-(3-methoxyphenoxy) ethyl* tert*-butylcarbamate)phenylacetamide (**3.100**)*

Plate 15. *^{1}H NMR spectrum of 1-(4-benzyloxy-3-iodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3.145**)*

Plate 16. *^{1}H NMR spectrum of 1-(4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3.149**)*

Plate 17. *^{1}H NMR spectrum of* N*-[2-(4-fluoro-3-nitrophenyl)ethyl]-2-(4-methoxyphenyl)-*N*-methylacetamide (**3.166**)*

Plate 18. *^{1}H NMR spectrum of 1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**3.169**)*

Plate 1a. *^{1}H NMR spectrum of 4-hydroxyphenethene (**2.66**)*

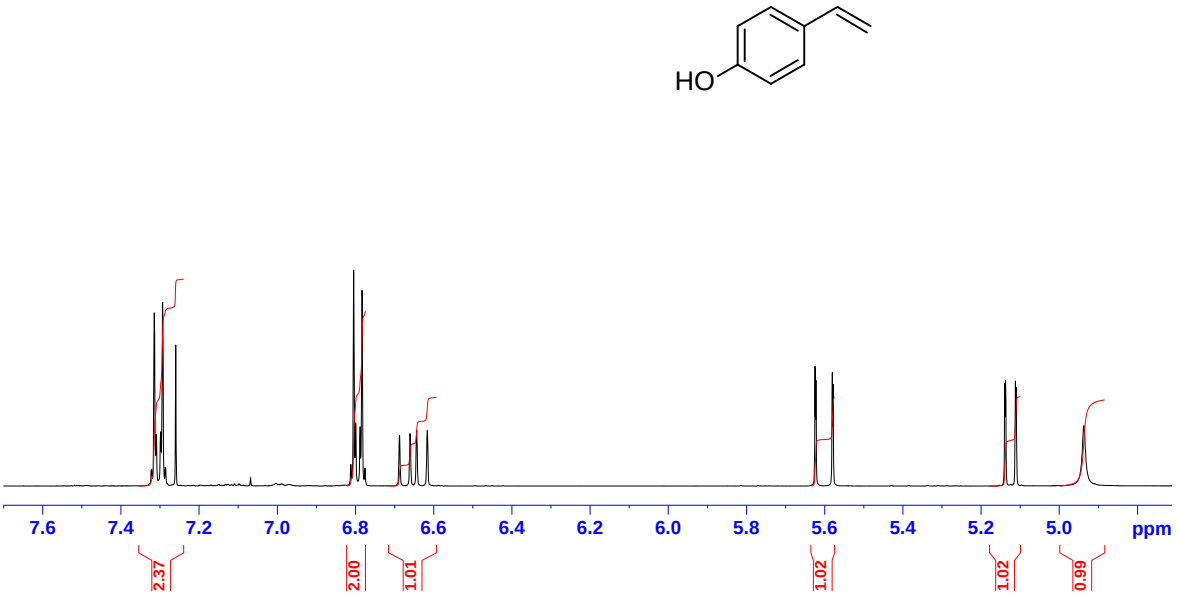


Plate 1b. *^{1}H NMR spectrum of 4-hydroxyphenethene (**2.66**)*

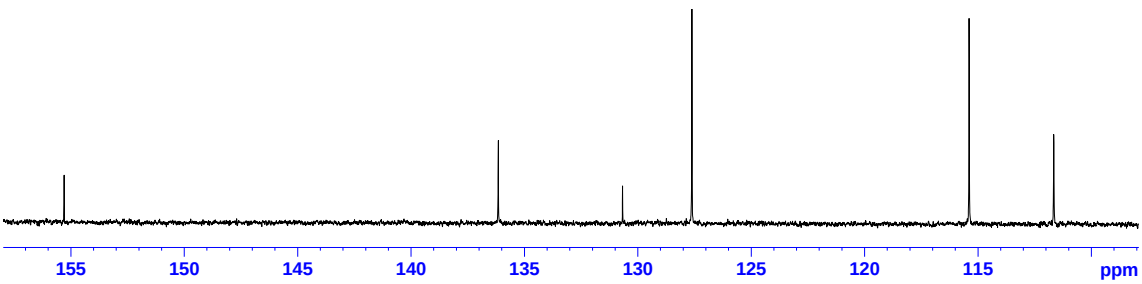


Plate 2a. *^{1}H NMR spectrum of 4-hydroxy-3-methoxyphenethene (**2.67**)*

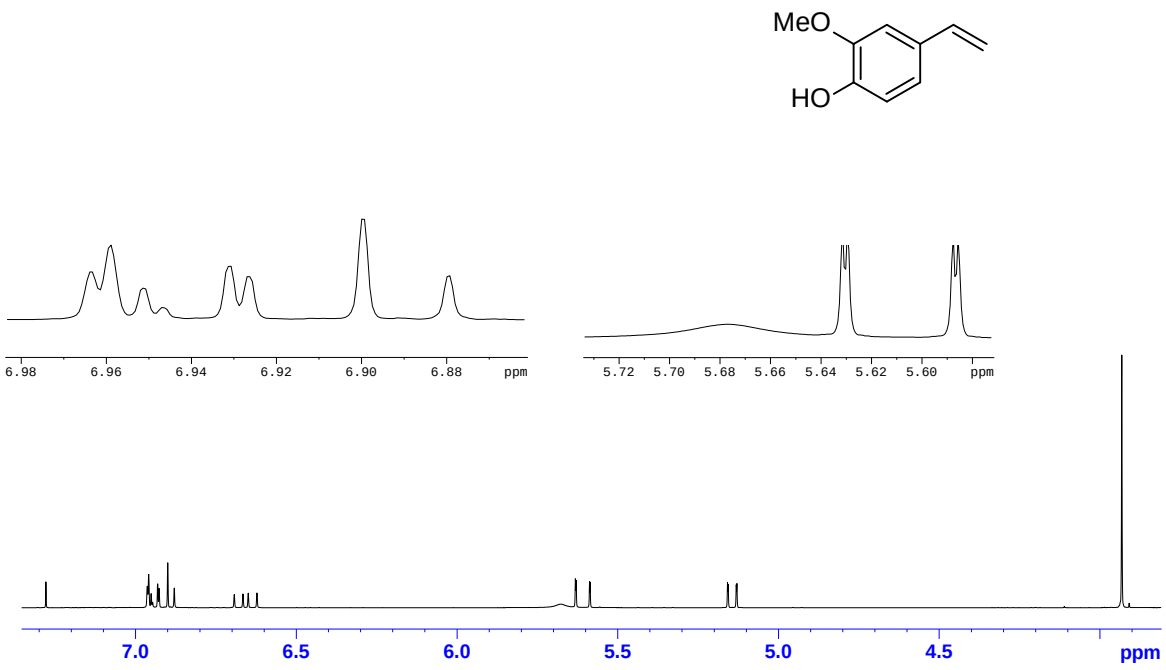


Plate 2b. *^{13}C NMR spectrum of 4-hydroxy-3-methoxyphenethene (**2.67**)*

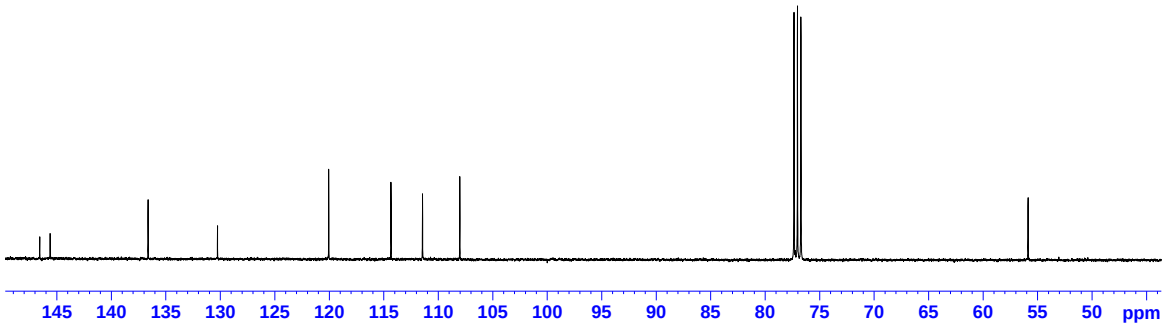


Plate 3a. *^{1}H NMR spectrum of 4-*tert*-butyldimethylsilyloxyphenethene (**2.72**)*

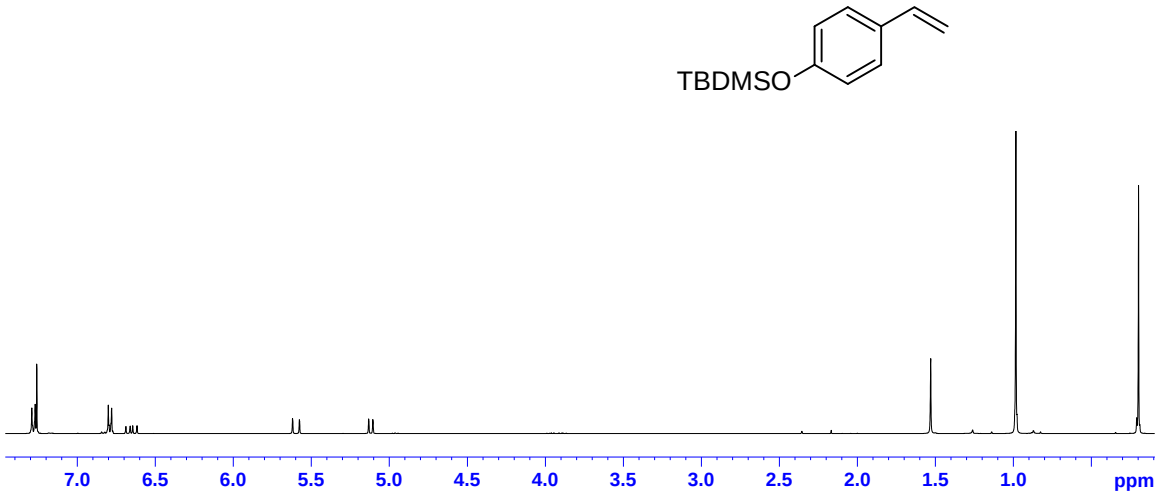


Plate3b. *^{13}C NMR spectrum of 4-*tert*-butyldimethylsilyloxyphenethene (**2.72**)*

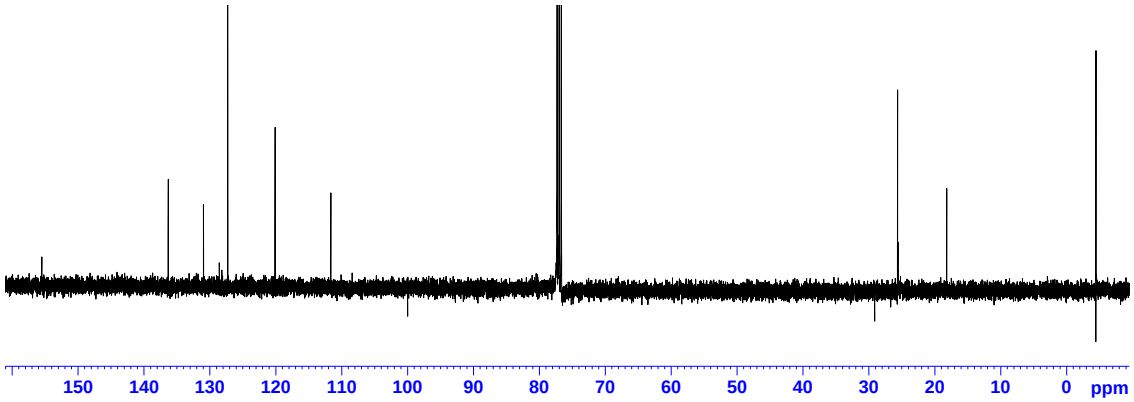


Plate 4a. *^{1}H NMR spectrum of* N-*[2-(3,4-dimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (**2.96**)*

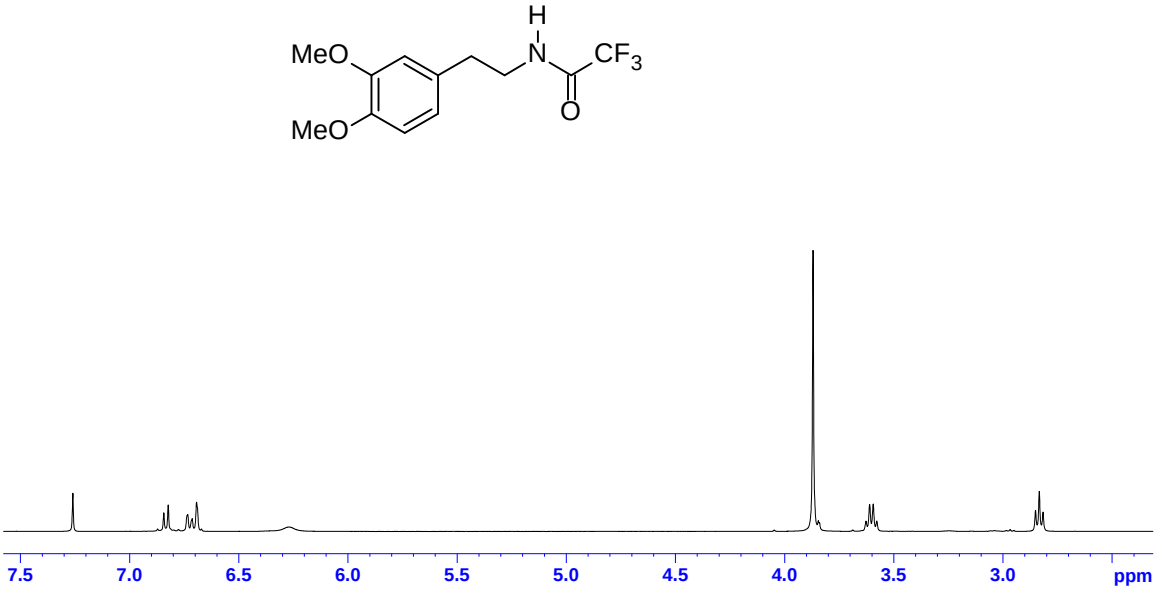


Plate 4b. *^{13}C NMR spectrum of* N-*[2-(3,4-dimethoxyphenyl)ethyl]-2,2,2-trifluoroacetamide (**2.96**)*

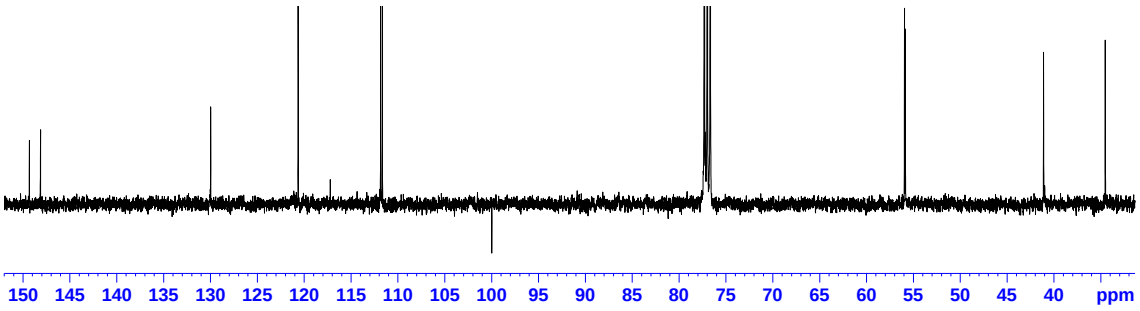
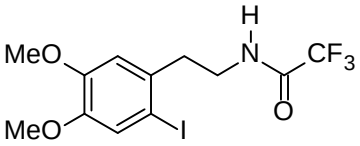


Plate 5. *^{1}H NMR spectrum of 2,2,2-trifluoro-*N*-[2-(2-iodo-4,5-dimethoxyphenyl)ethyl]acetamide (**2.97**)*



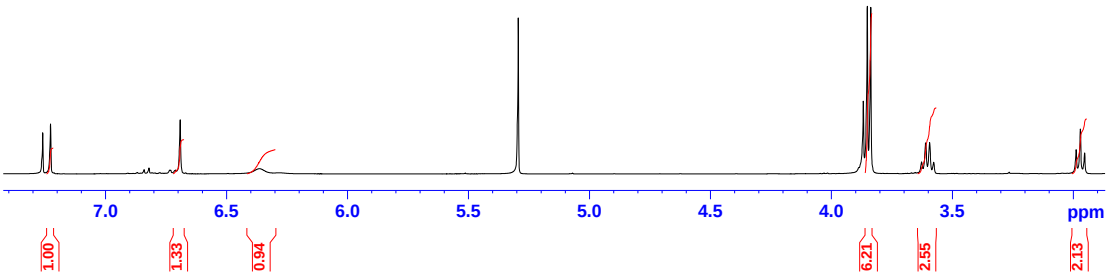


Plate 6a. *^{1}H NMR spectrum of* N-*(2-{2-[*E*-2-(4*-tert-*butyldimethylsilyloxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (**2.101**)*

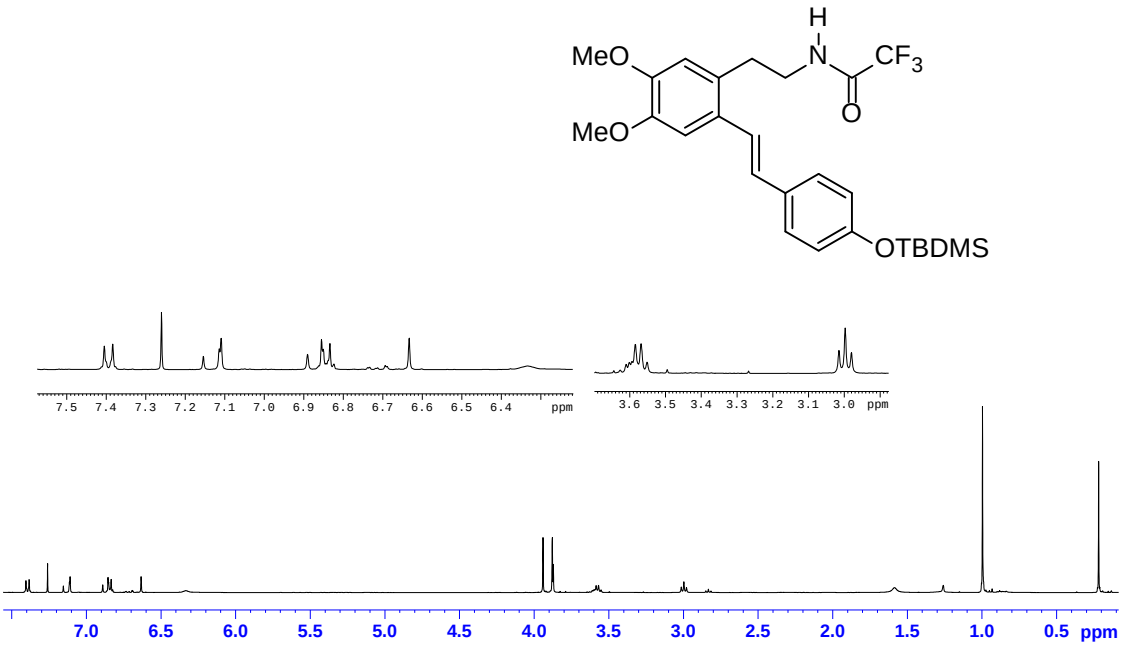


Plate 6b. *^{13}C NMR spectrum of* N-*(2-{2-[*E*-2-(4*-tert-*butyldimethylsilyloxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (**2.101**)*

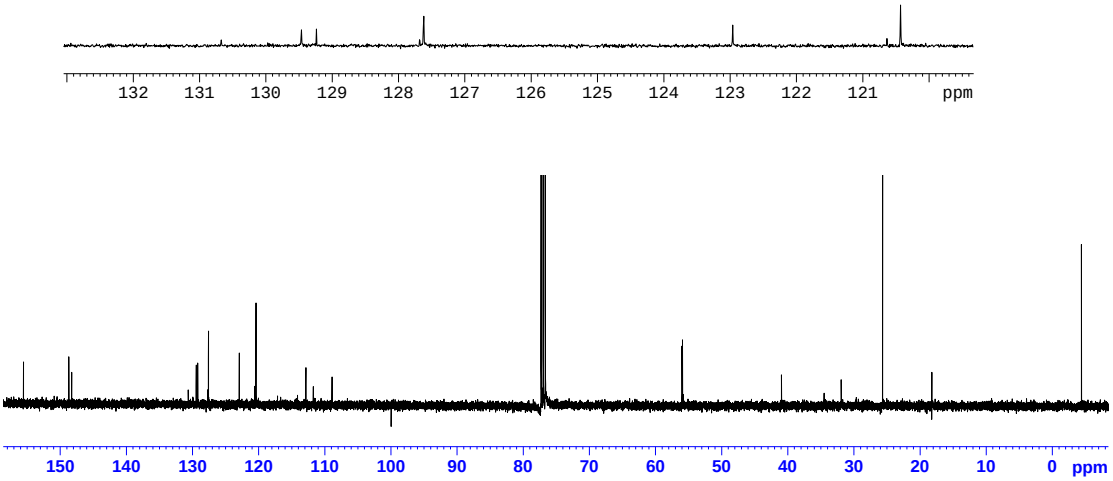


Plate 7. *1H NMR spectrum of* N-*(2-{2-[*E*-2-(4-benzyloxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)-2,2,2-trifluoroacetamide (**2.99**)*

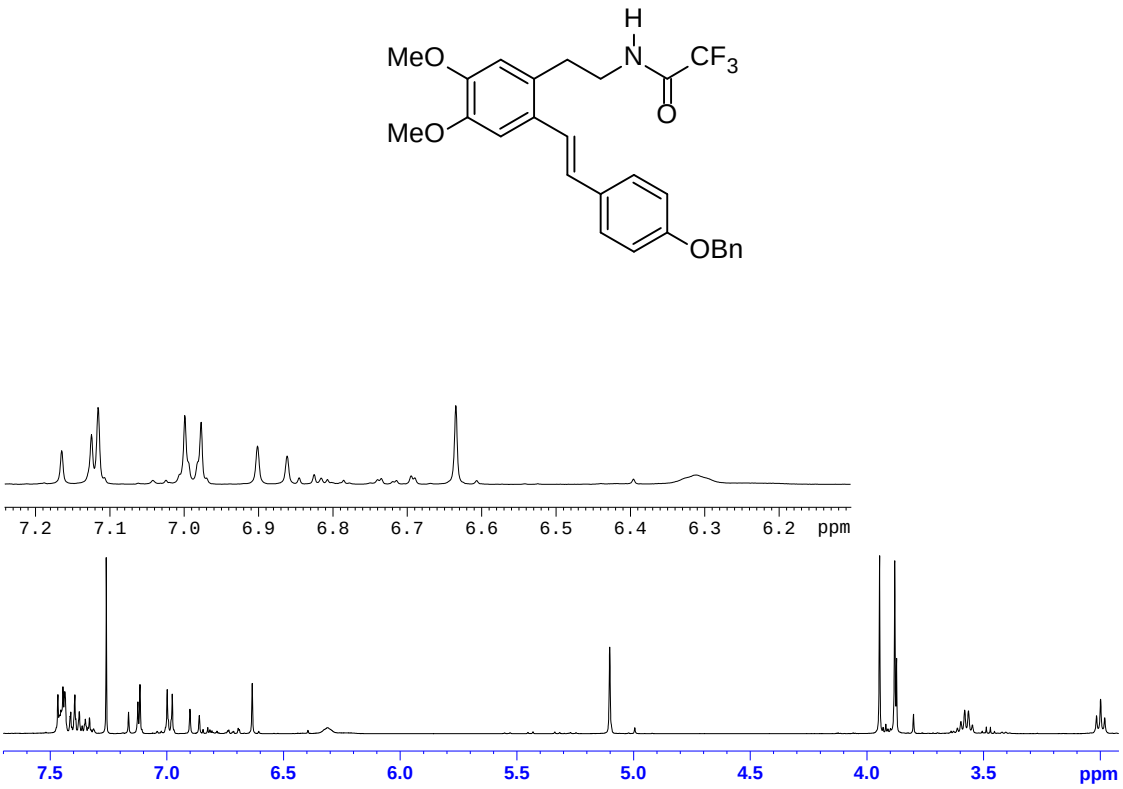


Plate 8a. *^{1}H NMR spectrum of (2-{2-[*E*-2-(4-benzyloxyphenyl)vinyl]-4-isopropoxy-5-methoxy-phenyl}ethyl)carbamic acid* tert-*butyl ester (**2.104**)*

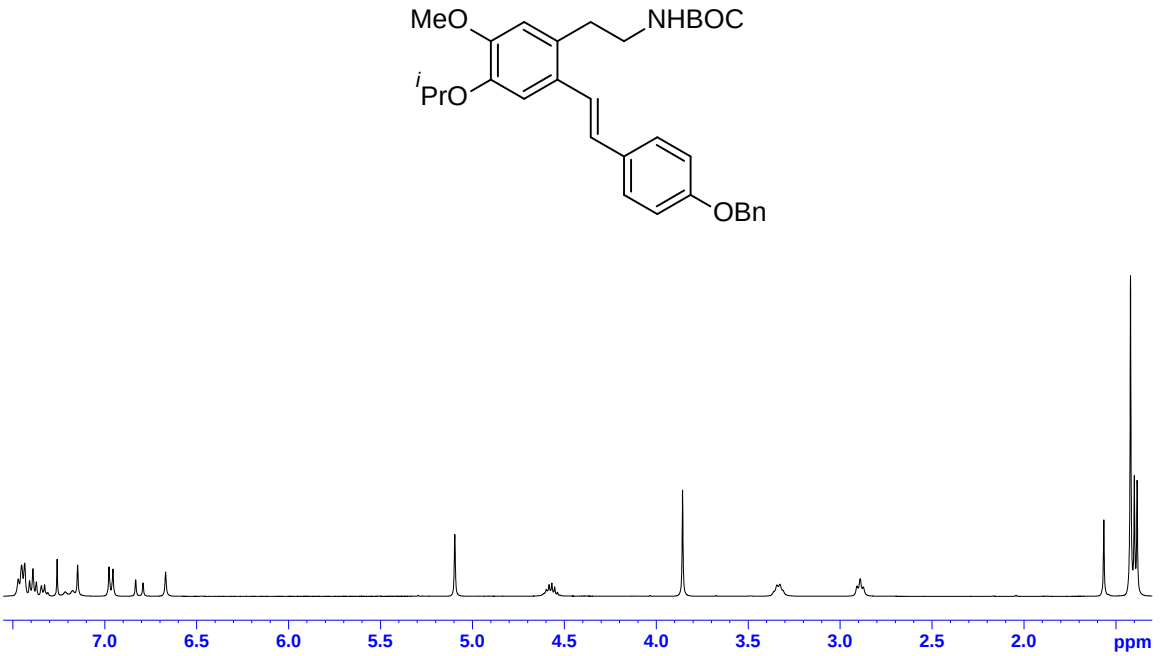


Plate 8b. *^{13}C NMR of (2-{2-[*E*-2-(4-benzyloxyphenyl)vinyl]-4-isopropoxy-5-methoxy-phenyl}ethyl)carbamic acid* tert-*butyl ester (**2.104**)*

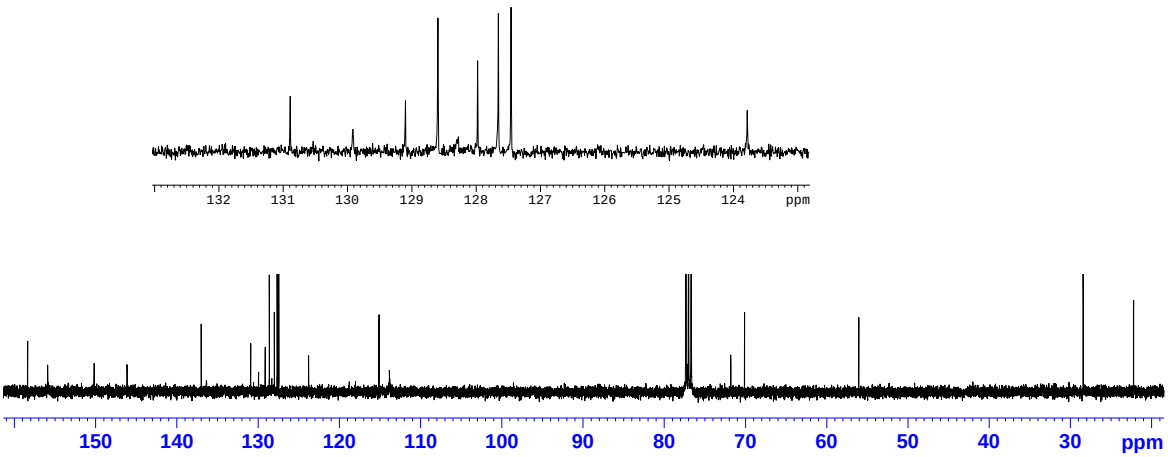


Plate 9. *^{1}H NMR spectrum of 4-benzyloxy-3-methoxyphenylethyne (**2.118**)*

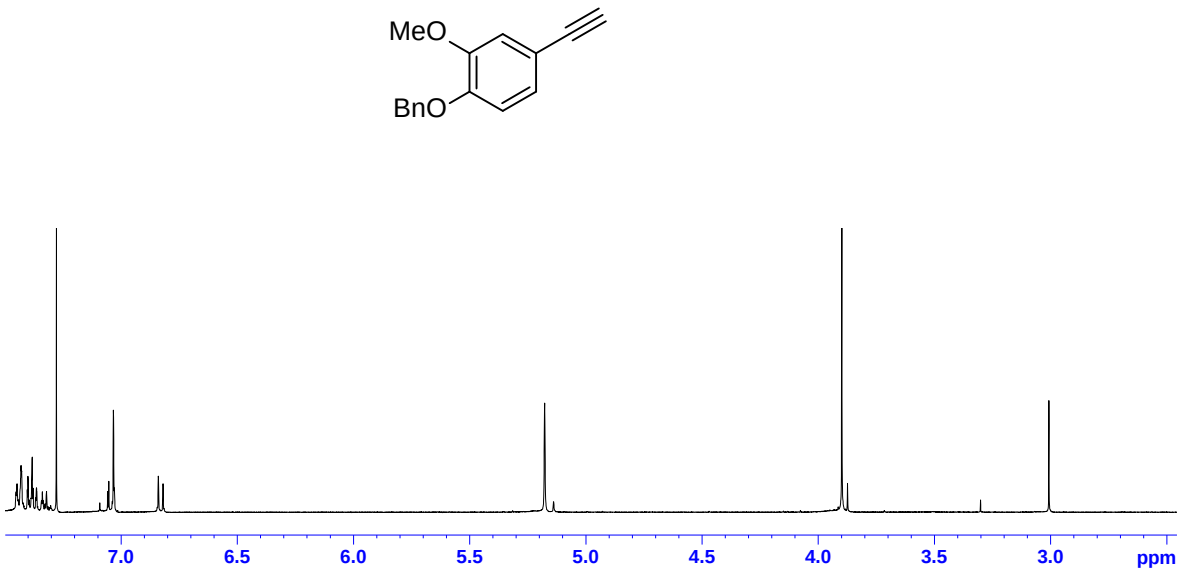


Plate 10. *^{1}H NMR spectrum of* N*-{2-[2-(4-benzyloxy-3-methoxyphenyl)ethynyl]-4,5-dimethoxy-phenyl]ethyl}-2,2,2-trifluoroacetamide (**2.120**)*

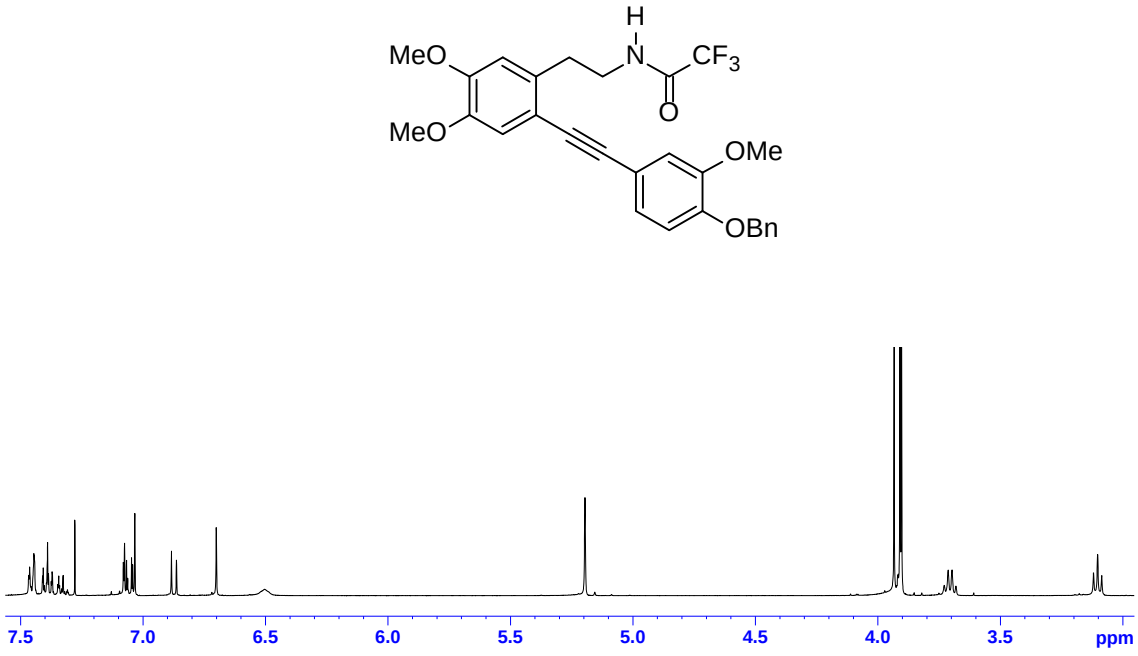


Plate 11. *^{1}H NMR spectrum of 2-{2-[2-(4-benzyloxyphenyl)ethynyl]-4,5-dimethoxyphenyl}ethylamine (**2.11**)*

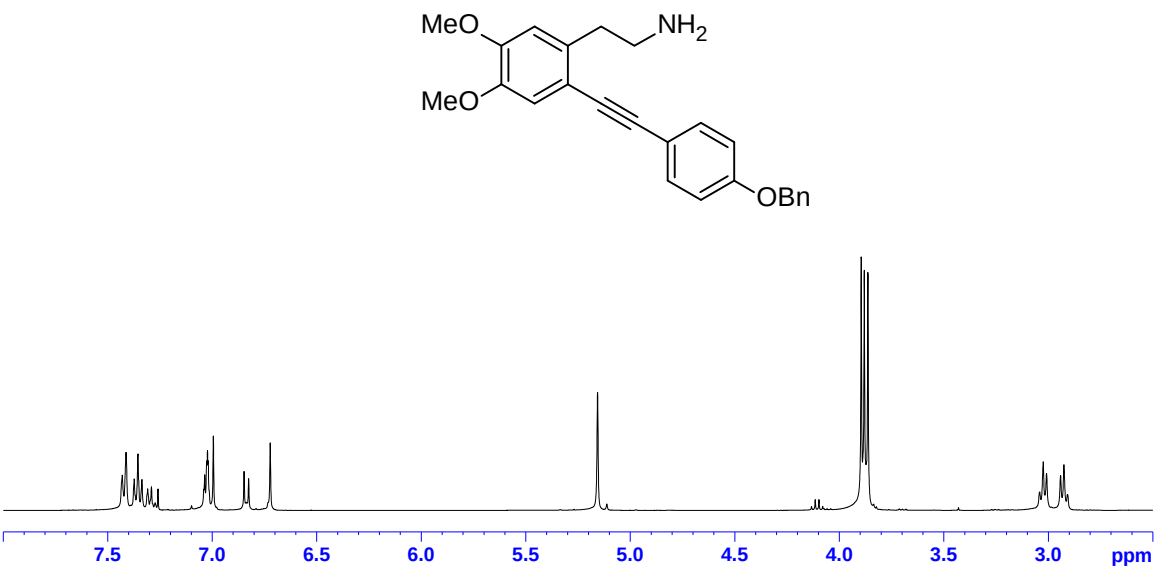


Plate 12. *^{1}H NMR spectrum of [2-(4'-hydroxy-3'-methoxy-phenyl)-ethyl]-carbamic acid* tert-*butyl ester (**3.111**)*

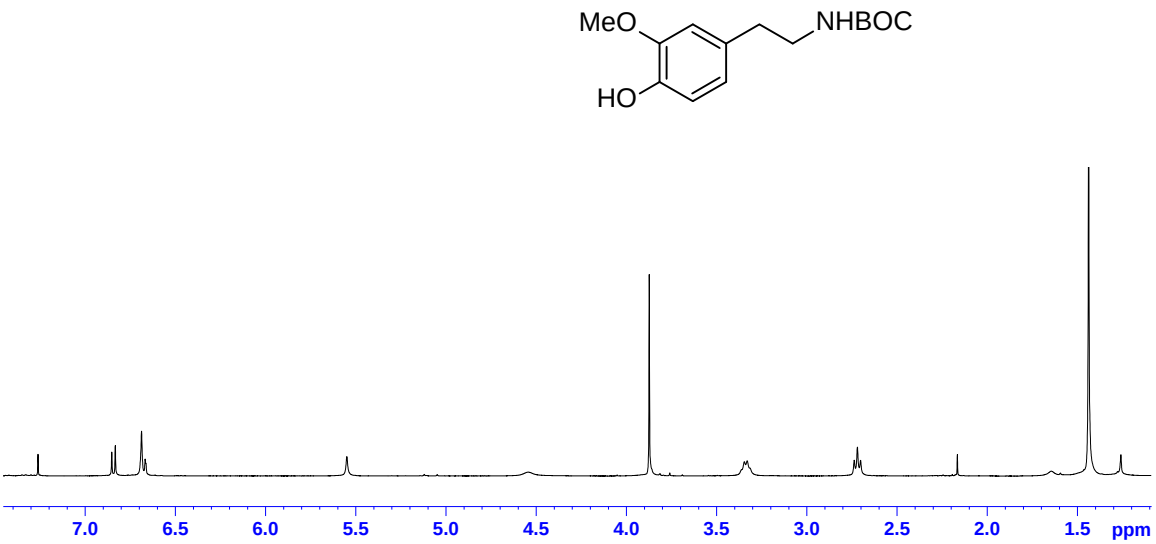


Plate 13. *^{1}H NMR spectrum of N-(3,4-dimethoxyphenylethyl) -4-benzyloxy-3-iodophenyl acetamide (**3.112**)*

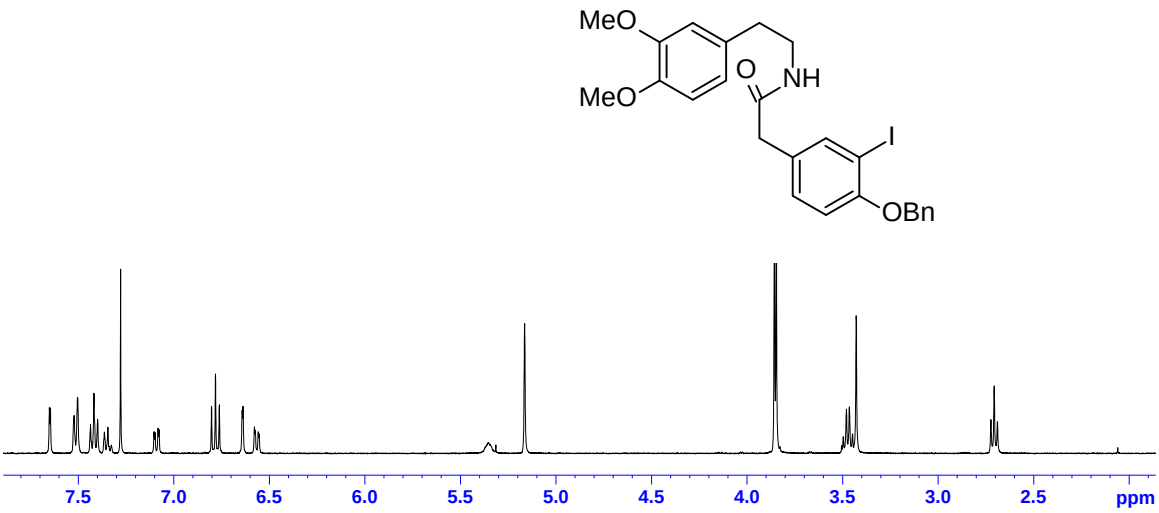


Plate 14. *^{1}H NMR spectrum of* N-*(3,4-dimethoxyphenylethyl)-4-benzyloxy -3-(4-(3-methoxyphenoxy) ethyl* tert-*butylcarbamate)phenylacetamide (**3.100**)*

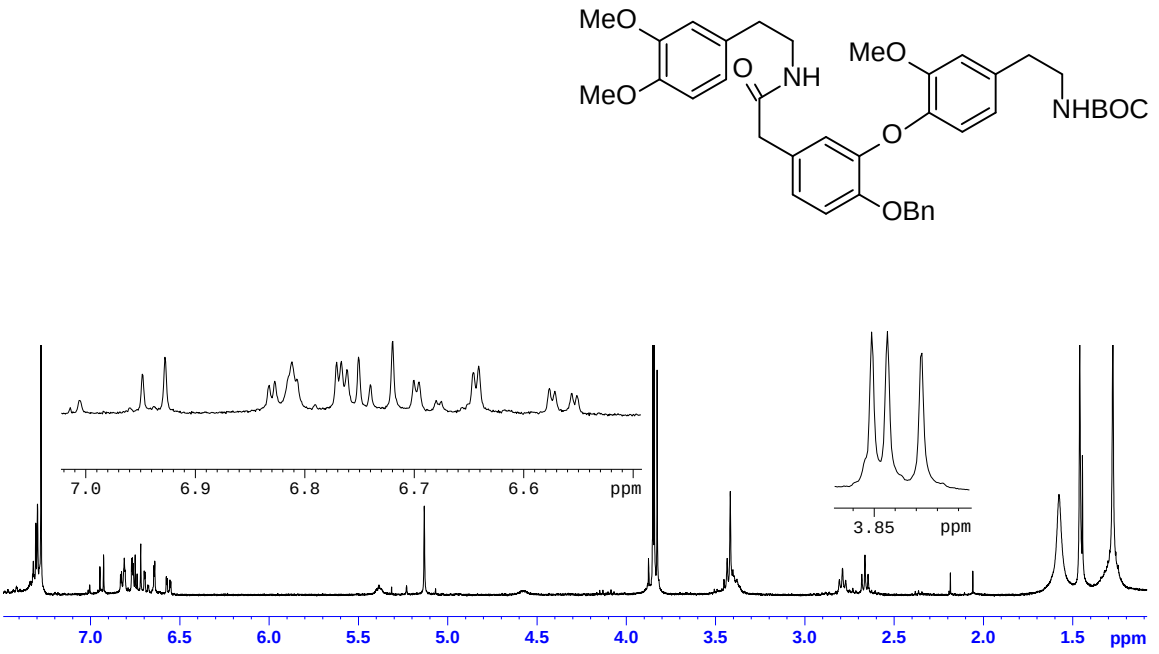


Plate 15. *^{1}H NMR spectrum of 1-(4-benzyloxy-3-iodobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3.145**)*

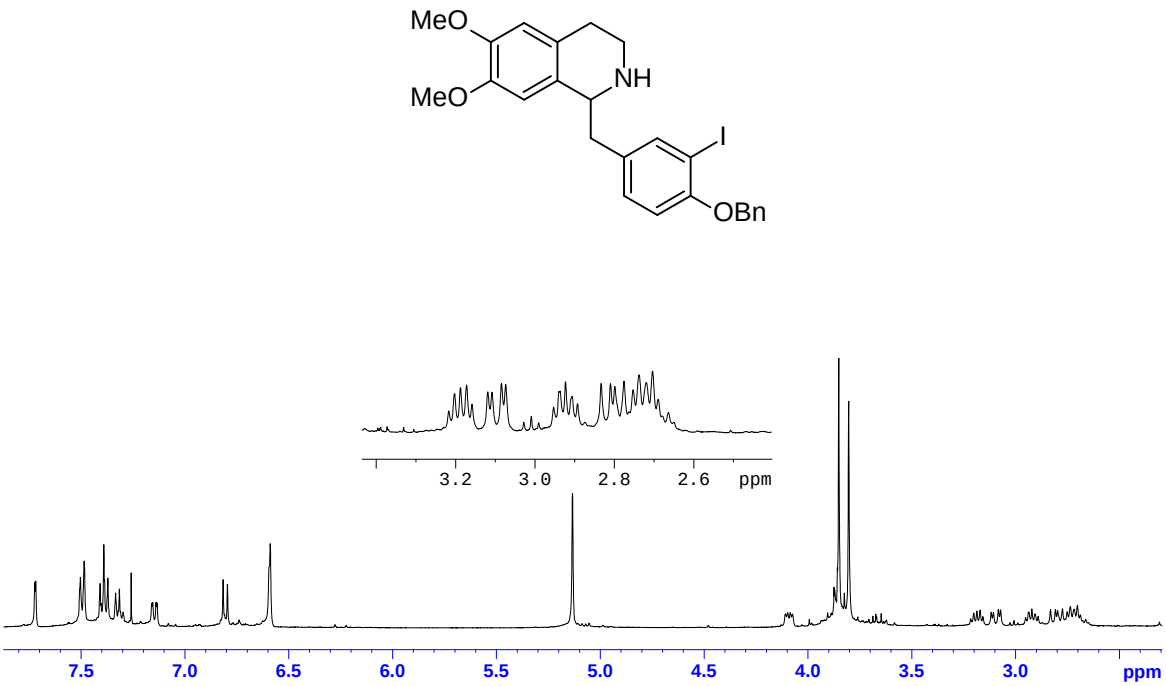


Plate 16. *^{1}H NMR spectrum of 1-(4-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3.149**)*

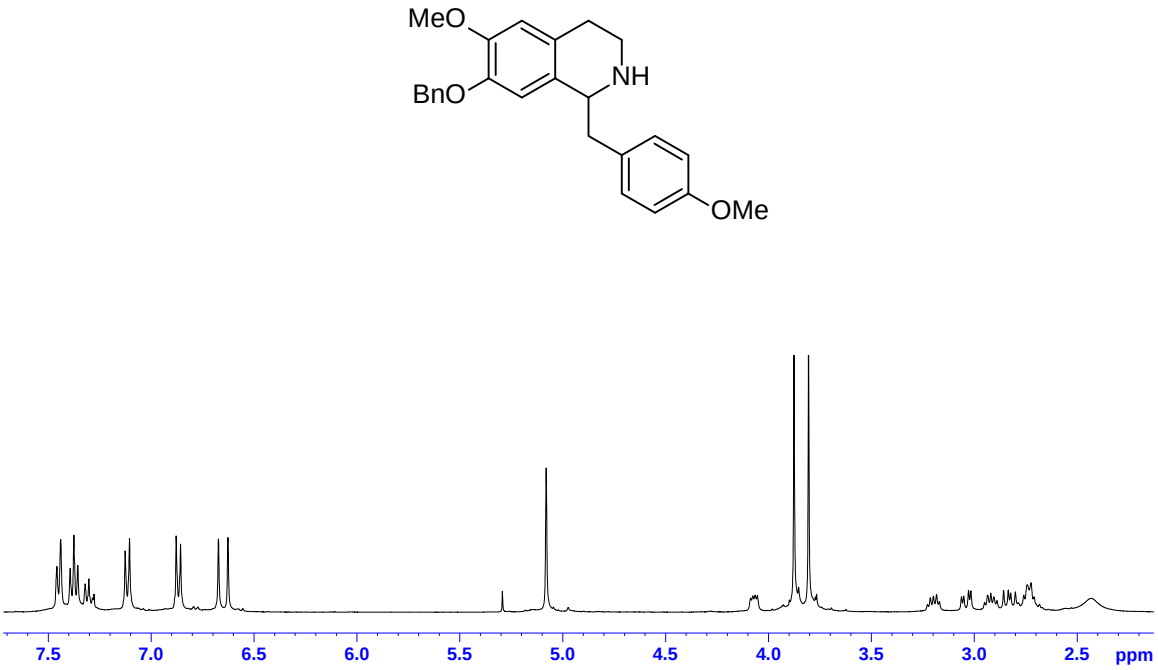


Plate 17. *^{1}H NMR spectrum of* N-*[2-(4-fluoro-3-nitrophenyl)ethyl]-2-(4-methoxyphenyl)*-N-*methylacetamide (**3.166**)*

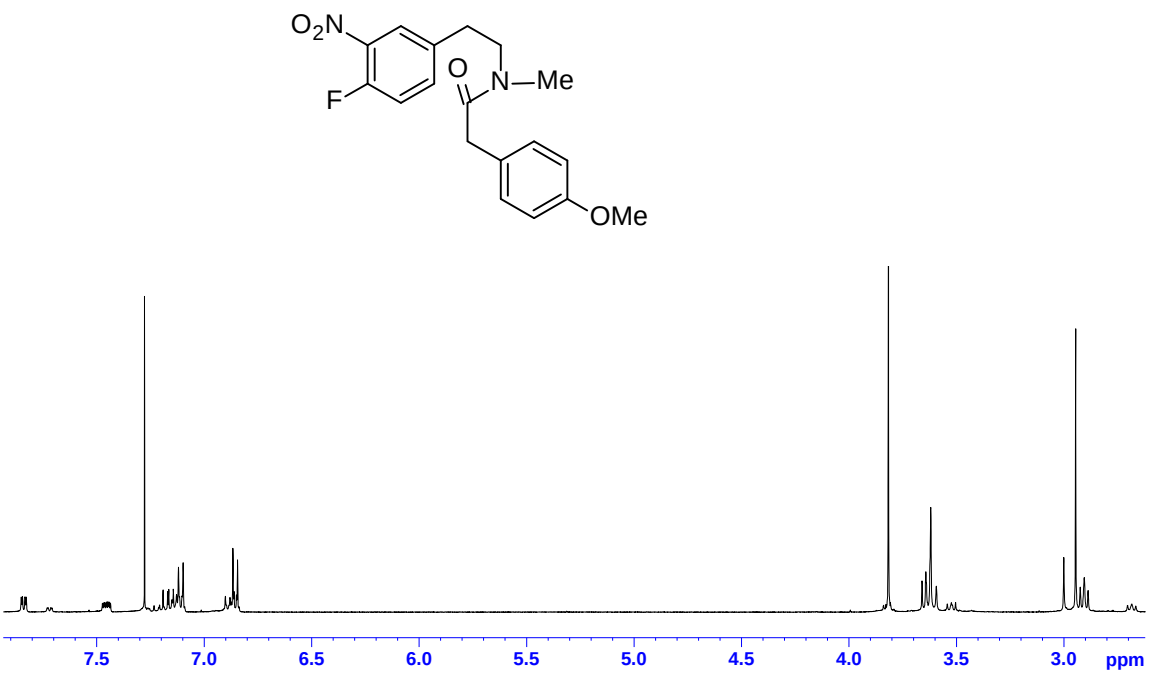


Plate18. *^{1}H NMR spectrum of 1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxy-*N-*methyl-1,2,3,4-tetrahydroisoquinoline (**3.169**)*