The synthesis of novel nitrogen containing heterocycles

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The Synthesis of Novel Nitrogen Containing Heterocycles

A thesis submitted in (partial) fulfillment
of the requirements for the award of the degree

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By

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THESIS CERTIFICATION

I, Arife Yazici, hereby declare that all material in this thesis, submitted in partial fulfillment of the requirements of the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.

Arife YAZICI

Date:

To my husband and son.

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2. Jury, Jasmine C.; Swamy, Nalivela K.; Yazici, Arife; Willis, Anthony C.; Pyne, Stephen G. "Metal-Catalyzed Cycloisomaerization Reactions of *cis*-4-Hydroxy-5-alkynylpyrrolidinones and *cis*-Hydroxy-6-alkynylpiperidinones : Synthesis of Furo[3,2-*b*]pyrroles and Furo[3,2-*b*]pyridines" *Journal of Organic Chemistry* **2009**, *74*, 5523-5527.

3. Yazici, Arife; Pyne, Stephen G. "Intermolecular Addition Reactions of *N*-Acyliminium Ions (Part 1)" *Synthesis* **2009**, 339-368.

4. Yazici, Arife; Pyne, Stephen G. "Intermolecular Addition Reactions of *N*-Acyliminium Ions (Part 2)" *Synthesis* **2009**, 513-541.

5. Pyne, Stephen G.; Au, Christopher W. G.; Davis, Andrew S.; Morgan, Ian R.; Ritthiwigrom, Thunwadee; Yazici, Arife. "Exploiting the borono-Mannich reaction in bioactive alkaloid synthesis" *Pure and Applied Chemistry* **2008**, *80*, 751-762.

6. Morgan, Ian R.; Yazici, Arife; Pyne, Stephen G. "Diastereoselective Ritter Reactions of Chiral Cyclic *N*-Acyliminium Ions: Synthesis of Pyrido- and Pyrrolo[2,3-*d*]oxazoles and 4-Hydroxy-5-*N*-acylaminopyrrolidines and 5-Hydroxy-6-*N*-acylaminopiperidines" *Journal of Organic Chemistry* **2008**, *73*, 2943-2946.

7. Morgan, Ian R.; Yazici, Arife; Pyne, Stephen G. "Diastereoselective borono-Mannich reactions on cyclic *N*-acyliminium ions" *Tetrahedron* **2008**, *64*, 1409-1419.

ABSTRACT

This thesis reports on the development of new methods for the synthesis of functionalized pyrrolidines. These compounds are of important since they are the common ring structure that forms the bicyclic, heterocyclic core structure of the pyrrolizidine, indolizidine and *Stemona* alkaloids.

In Chapter 2 we report our efforts to develop a general method for preparing 4-hydroxy-5-substituted pyrrolidin-2-ones from the borono-Mannich reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones with boronic acids in the presence of $BF_3.Et_2O$. The 4,5-dihydroxypyrrolidin-2-one gave in two cases 4,5-*cis* adducts with very high *cis* selectivity but in relatively low yields, while the 4-benzyloxy-5-hydroxypyrrolidin-2-one gave 4,5-*trans* adducts with good *trans* selectivity and in good to moderate yields. Unfortunately the desired dienyl 4,5-*cis* adduct, required for the synthesis of the *Stemona* alkaloids, could only be obtained in the low yield of 33%. A RCM reaction of this compound gave the desired pyrrolo[1,2-*a*]azepine in 72% yield.

In Chapter 2 we also report the formation of a novel, Ritter reaction product, a pyrrolo[3,2-*b*]oxazole as an unwanted side product in the borono-Mannich reaction when acetonitrile was used as a solvent.

In Chapter 3 we describe an efficient synthesis of pyrrolo[3,2-*b*]oxazoles from the Ritter reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones with nitriles in the presence of $BF_3.Et_2O$. When 4-benzyloxy-5-hydroxypyrrolidin-2-one was used as the substrate the corresponding pyrrolo[3,2-*b*]oxazoles were formed along with the corresponding *N*-benzyl amides, which were formed from the Ritter reactions of benzyl cation and the nitrile. The isolation of these amide compounds were consistent with our proposed reaction mechanism. Two of the pyrrolo[3,2-*d*]oxazole compounds were hydrolyzed to novel 5-acylaminopyrrolidinones.

In Chapter 4 we report the metal-catalyzed cycloisomerization reactions of 3-hydroxy-2-alkynylpyrrolidine which was obtained from the borono-Mannich reaction of 2,3-dihydroxypyrrolidine and potassium phenylethynyltrifluoroborate. The cycloisomerization reaction of this pyrrolidine afforded a 2,5-disubstituted furan when Ag(I), Au(I) or Pd(II)/Cu(I) were used as a catalyst. While 3-halo-2,5-disubstituted furans were synthesized from the corresponding CuCl or CuBr

mediated reactions. Novel 3-iodo, 3-phenyl and 3-cyano susbstituted furo[3,2-*b*]pyrroles were synthesized from the reactions of the 3-hydroxy-2-alkynylpyrrolidine with CuI, CuCN and PhI/$Pd(dba)_2$, respectively.

In Chapter 5 a novel method for the synthesis of 3-cyanoindoles is reported. This method showed good tolerance to electron-donating and electron withdrawing substituents on the starting *ortho*-alkynylaniline and allowed 3-cyanoindoles to be obtained in a single step. While the method of Wang provides 3-bromo and 3-chloro indoles in one step from *ortho*-alkynylanilines this method has not been extended to make 3-cyanoindoles. Future studies could involve the examination of Wang`s conditions using $CuCN/O_2$ instead of $CuBr_2$ or $CuCl_2$ to prepare 3-cyanoindoles.

ABBREVIATIONS

$[\alpha]_D$	Specific Rotation
Ac	Acetyl
Ac_2O	Acetic anhydride
amu	Atomic mass unit
ArC	Aromatic carbon
ArCH	Aromatic methine
Bu	Butyl
Bn	Benzyl
br. s	Broad singlet
CAN	Cerium ammonium nitrate
Cbz	Benzyloxycarbonyl
C_6D_6	Deuterated benzene
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
CH_3NO_2	Nitromethane
COSY	Correlation spectroscopy
d	Day
d	Doublet (NMR)
δ	Chemical shift
dd	Doublet of doublets (NMR)
DCE	1,2-Dichloroethane
DEPT	Distortionless enhancement by polarization transfer
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
de	Diastereomeric excess
dr	Diastereomeric ratio
ee	Enantiomeric excess
EE	Ethoxyethyl
eq	Molar equivalents
Et_2O	Diethylether

EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour
HMBC	Heteronuclear multiple bond correlation
HREIMS	High resolution electron impact mass spectrometry
HRESIMS	High resolution electrospray ionization mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
IR	Infrared spectroscopy
J	Coupling constant (NMR)
Lit.	Literature
LREIMS	Low resolution electron impact mass spectrometry
LRESIMS	Low resolution electrospray ionization mass spectrometry
m	Multiplet (NMR)
MeOH	Methanol
min	Minutes
MOM	Methoxymethyl
Mp	Melting point
NIS	*N*-Iodosuccinimide
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser enhancement spectroscopy
ϕ	Dihedral angle
Ph	Phenyl
PMB	*p*-Methoxybenzyl
ppm	Parts per million (NMR)
q	Quartet (NMR)
RCM	Ring closing metathesis
R_f	Retardation factor
rt	Room temperature
s	Singlet (NMR)
sat.	Saturated
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl

td	Triplet of doublets
t	Triplet
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-Tetramethylethylenediamine
TMS	Tetramethylsilane

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1. INTRODUCTION

1.1. Definition of Alkaloids

Meissner first proposed the word "alkaloid" in 1819.[1] He described alkaloids as plant-derived substances that react like alkalis. His definition was put forward at a time when only few plant bases were known.[1,2] In 1896 Guareschi described the alkaloids as basic organic compounds whether obtained from animal or plant materials, or prepared artificially. His definition is synonymous with organic base or organic alkali. In 1910 Winterstein and Trier described alkaloids as compounds with nitrogen atoms bound in a heterocyclic fashion, with a greater or lesser degree of basic character, marked physiological effects, complicated molecular structure, which are found in plants, and, with a few exceptions, are characteristic for particular plant families, genera or species.[1,2] Another definition was made by Stoll in 1953 which described alkaloids as nitrogen-containing bases of vegetable origin. In 1983, Pelletier described alkaloids as cyclic organic compounds containing nitrogen in a negative oxidation state which are of limited distribution among living organisms. Although many definitions of alkaloids have been made, none of them are fully satisfactory. For instance, it is clear that not all alkaloids are heterocyclic or even cyclic and they are not necessarily physiologically active. Moreover, it is now accepted that the occurrence of alkaloids is not restricted to plants. It is obvious that alkaloids are most commonly found in plants but they are also found in animals. Hydroxylated tyrosine or tryptamine derivatives are the most common alkaloids found in mammals. Thus alkaloids occur in all types of living organisms. In view of all this information the general definition may be "Alkaloids are nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character".[1]

1.2. History of Alkaloids

Humans have been using alkaloids as drugs, medicines, teas and poisons for 4000 years. They used plants which contained arrow poisons in hunting or in dealing with enemies. These poisons are still in use in Africa and South America. Alkaloids that were isolated from arrow poison have been used in the treatment of glaucoma and myasthenia gravis, as a muscle relaxant in anesthesia and as an antihypertensive.[3] The first crude drug was from the opium poppy, which had been used for its

analgesic and narcotic properties for centuries. In 1805 Serturner isolated morphine from opium. Between the years 1817 and 1820 many biologically active compounds were isolated from plants, including styrchnine, emetine, brucine, caffeine, quinine, cinchocine and colchicine. This pioneering work formed the cornerstone of all that has occurred in alkaloid chemistry to the present.[4] The number of alkaloids that had been isolated and identified was 200 in 1939 and by 1989, 10,000 alkaloids were known. Currently there are over 27000 known alkaloids.[5,6]

1.3. Classification of Alkaloids

Alkaloids can be classified according to the nature of the nitrogen atom or according to their biogenetic origins. They have been classified into four groups according to the nature of the nitrogen atom (**Figure 1.1**).[7] These four groups include:

1. Secondary or tertiary amines which are protonated and therefore hydrophilic at pH < 7.0, and lipophilic at pH > 8.0. e.g., atropine **1**;
2. Quarternary amino compounds which are very polar and charged at all pH values. e.g., berberine **2**;
3. Neutral amino compounds which include the amide-type alkaloids. e.g., colchicine **3**;
4. *N*-oxides, which are generally highly soluble in water, the pyrrolizidine group of alkaloids being rich in this alkaloid type. e.g., indicine *N*-oxide **4**.

Alkaloids can also be classified into four groups according to their biogenetic origins (**Figure 1.2**).[7] These four groups include:

1. Alkaloids derived from amino acids. e.g., morphine **5**, ornithine, arginine, lysine, histidine and phenylalanine;
2. Purine alkaloids. e.g., caffeine **6** and xanthine;
3. Aminated terpenes. e.g., aconitine **7** and the triterpene solanine;
4. Polyketide alkaloids. e.g., coniine **8** and the coccinellines.

The number of new alkaloids continues to increase as more insect and marine organisms are investigated.

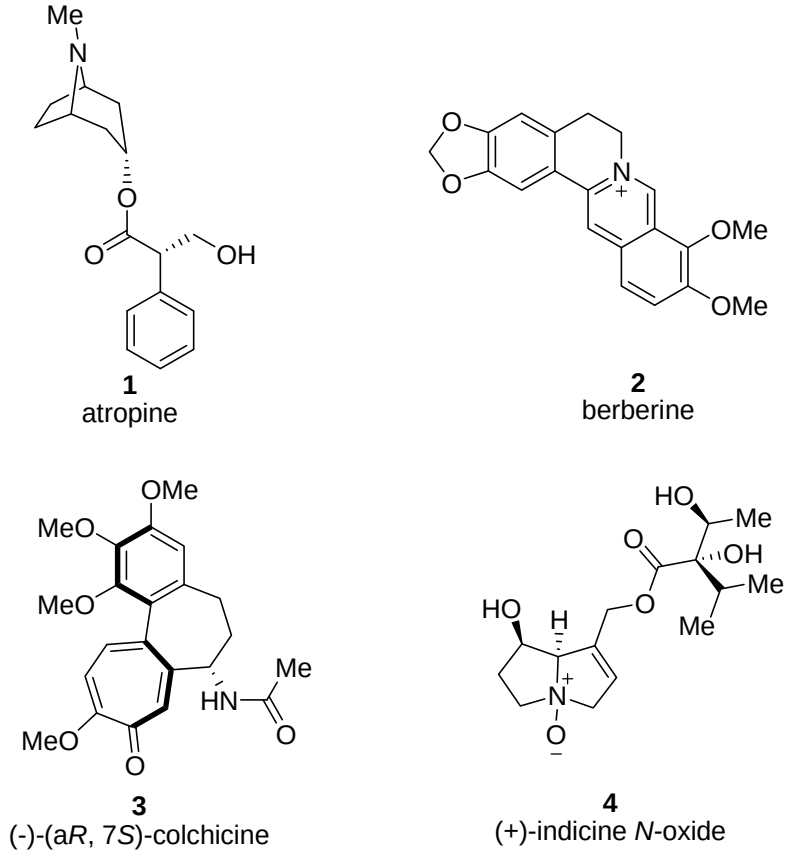


Figure 1.1. Structures of atropine **1**, berberine **2**, colchicine **3** and indicine *N*-oxide **4**.

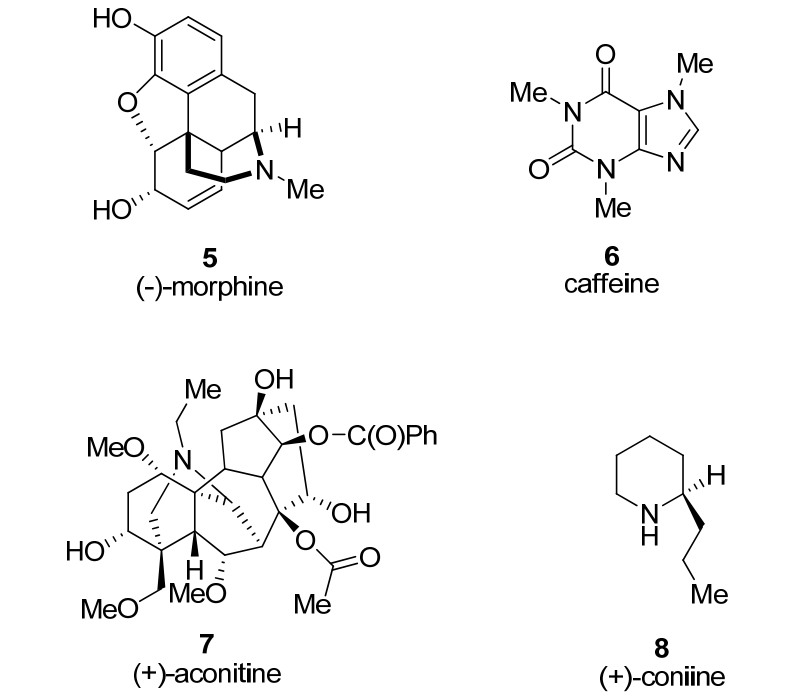
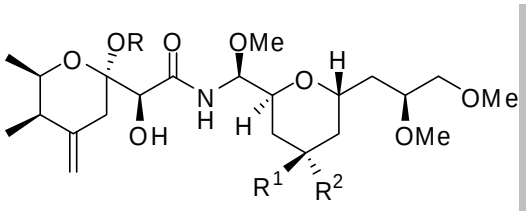


Figure 1.2. Structures of morphine **5**, caffeine **6**, aconitine **7** and coniine **8**.

1.4. Occurrence and Distribution of Alkaloids

In the past the major source of alkaloids were flowering plants, the *Angiospermea*. In recent years a large number of alkaloids have been isolated from animals, insects, marine organisms, microorganisms and lower plants. Alkaloids in animals can act as defensive compounds or as chemical signals. A powerful cytotoxin, pederin **9** was isolated from the genus *Paederus* (**Figure 1.3**). It is toxic when digested and causes dermatoxic wounds when it is applied to the skin of animals. Two close derivatives, pseudopederin **10** and pederone **11** were also isolated from the same genus (**Figure 1.3**).[7,8]



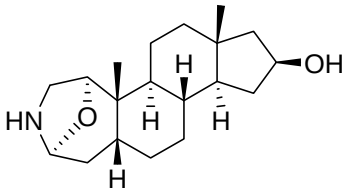
9 R = Me, R^1 = H, R^2 = OH
10 R = H, R^1 = H, R^2 = OH
11 R = Me, R^1 = R^2 = O

Please see print copy for image

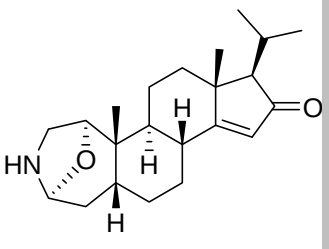
Paederus (picture taken from Wikipedia)[9]

Figure 1.3. Structures of pederin **9**, pederone **10** and pseudopederin **11** and a photo of the *Paederus*.

Salamanders are known to be toxic. The alpine salamander toxins have been found to be the steroidal alkaloids, samandarine **12** and samandenone **13** (**Figure 1.4**).[10]



12
Samandarine



13
Samandenone

Please see print copy for image

Alpine salamander
(picture taken from Wikipedia)[11]

Figure 1.4. Structures of samandarine **12** and samandenone **13** and a photo of the alpine salamander.

While there are a large number of different structural classes of alkaloids this Chapter will only discuss the alkaloid classes that are relevant to this thesis.

1.5. Pyrrolizidine Alkaloids

Pyrrolizine alkaloids are a diverse class of naturally occurring compounds. Over 350 pyrrolizidine alkaloids have been isolated from more than 6000 plant species belonging to *Boraginaceae*, *Leguminoseae* and *Asteraceae* families.[7,12] The main groups of pyrrolizidine alkaloids are based on necines. They are mono or diesters of the 1-hydroxymethyl-7-hydroxy-1,2-dehydropyrrolizine structure. They may have 1, 2 or 3 hydroxyl groups and 1 or 2 double bonds. Typical alkaloids are retrocine **14**, rosmarine **15** and monocrotaline **16** that were isolated from the *Senecio* genus (**Figure 1.5**).

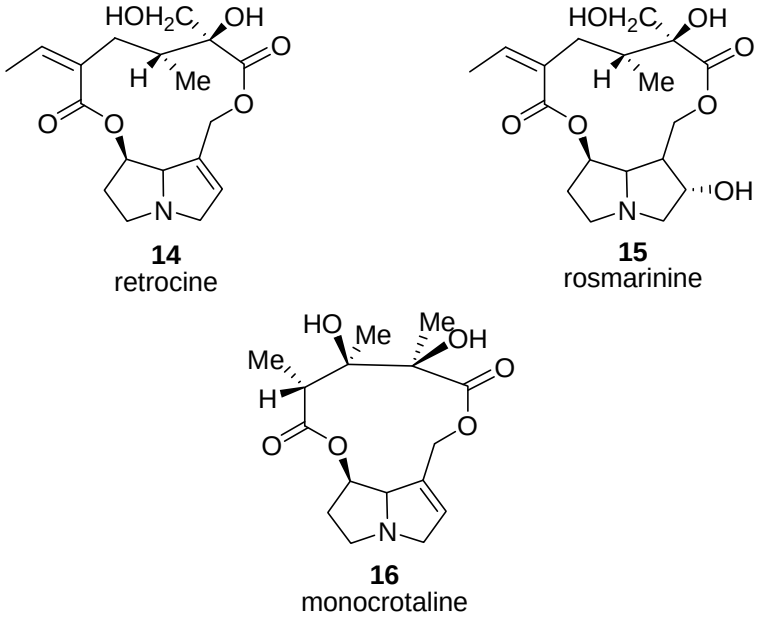


Figure 1.5. Structures of retrocine **14**, rosmarinine **15** and monocrotaline **16**.

More recently several 3-hydroxymethylpyrrolizidines alkaloids have been isolated. In 1988, the polyhydroxylated pyrrolizidine alkaloid alexine **17** was isolated from the pods of the legume *Alexa leiopetala* (**Figure 1.6**).[13] It was the first example of a pyrrolizidine alkaloid having a carbon substituent at the C-3 position.[14,15] At about the same time australine **18** was isolated from the seeds of *Castanospermum australe* (**Figure 1.7**), which was found to be 7-*epi*-alexine by X-ray crystallographic analysis.[16] Later, 1-*epi*-australine **19**, 3-*epi*-australine **20** and 7-*epi*-australine **21**

(**Figure 1.6**) were isolated from the same plant. The structures of 1-*epi*-australine **19** and 3-*epi*-australine **20** were also identified by X-ray crystallographic analysis.[17-19] The structure of 7-*epi*-australine **21** was assigned based on NMR spectroscopic studies. The synthesis of australine **18** and 7-*epi*-australine **21** and extensive studies on both natural and synthetic australine **18** isomers elucidated that the natural product reported as 7-*epi*-australine **21** was actually australine. As a result, 7-*epi*-australine **21** has not yet been found as a natural product. These polyhydroxylated pyrrolizidine alkaloids are of medicinal chemistry interest as they are inhibitors of glycosidases.[7]

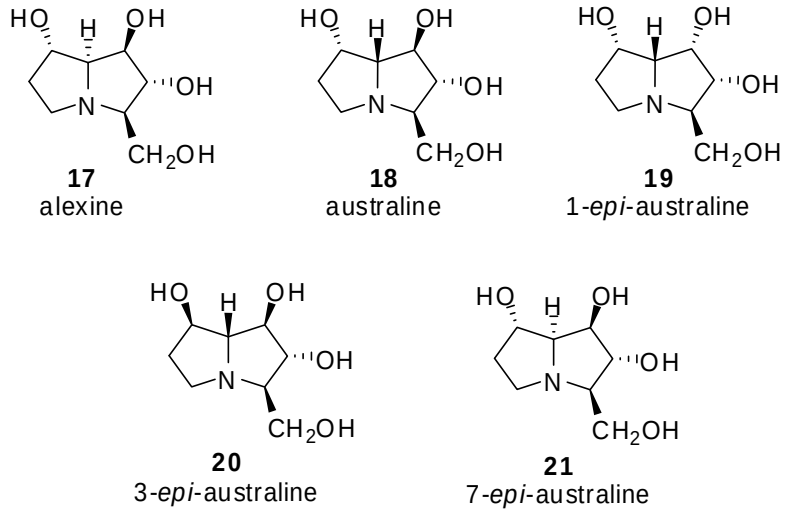


Figure 1.6. Pyrrolizidine alkaloids from legumes **17-21**.

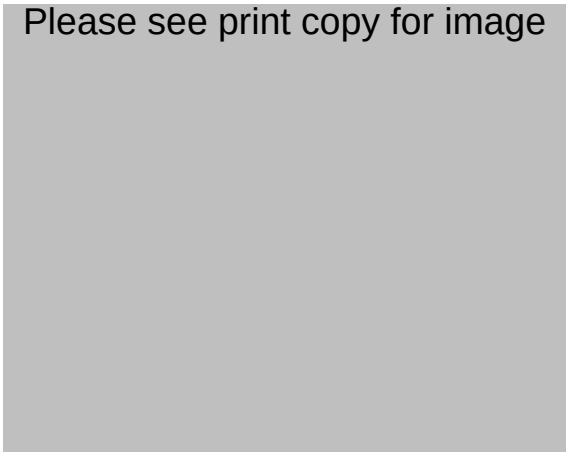


Figure 1.7. The seeds of *Castanospermum australe* (picture taken from Wikipedia).[20]

Alexine and the australines have also been isolated from two small genera of *Leguminose (Castanospermum and Alexia)*. It was initially thought that the occurrence of polyhydroxylated 3-hydroxypyrrolizidine alkaloids would be restricted. However, many such alkaloids were found from a different family, *Hyacinhaceae*. In 1999, several new pyrrolizidine alkaloids were isolated from this family and named as hyacinthacines. Hyacinthacines B_1 **22** and B_2 **23** (**Figure 1.9**) were isolated from the immature fruits and stalks of *Hyacinthoides non-scripta* (**Figure 1.8**) and hyacinthacine C_1 **24** (**Figure 1.9**) was isolated from the bulbs of *Scilla campanulata* (**Figure 1.8**).[21] Four novel hyacinthacines, A_1 **25**, A_2 **26**, A_3 **27** and B_3 **28** (**Figure 1.9**) were isolated from the bulbs of *Muscari armeniacum* (**Figure 1.8**).[22] Seven new hyacinthacines, A_4 **29**, A_5 **30**, A_6 **31**, A_7 **32**, B_4 **33**, B_5 **34**, and B_6 **35** (**Figure 1.9**), were found from the GC-MS analysis of extract of *S. sibirica* (**Figure 1.8**).[23] Many of these species are common as garden plants, for example "bluebells" (*Hyacinthoides non-scripta*) (**Figure 1.8**).

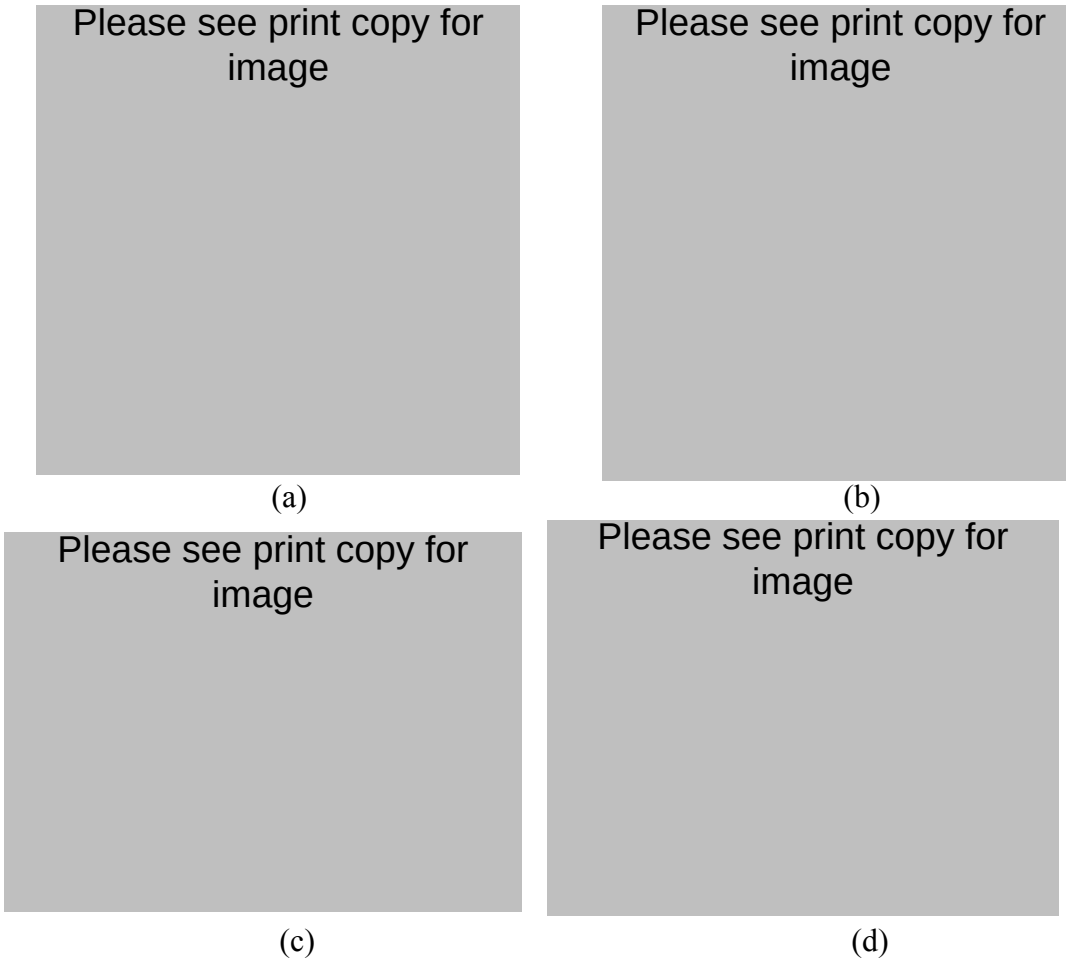


Figure 1.8. a) *Hyacinthoides non-scripta* (bluebells)[24] b) *Scilla campanulata*[25] c) *Muscari armeniacum*[26] d) *Scilla sibirica*[27] (pictures taken from Wikipedia).

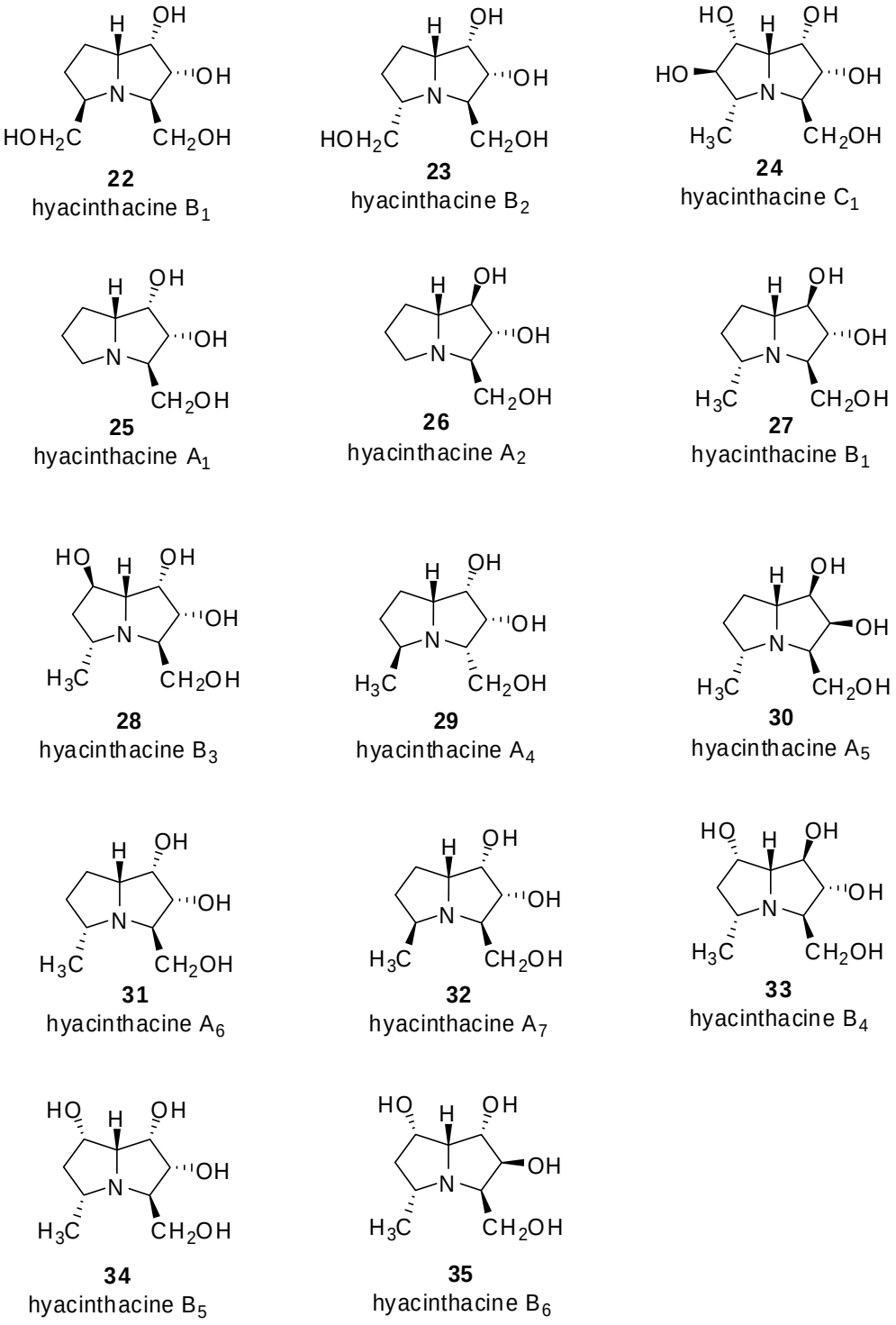


Figure 1.9. Structures of hyacinthacines **22-35**.

1.6. Indolizidine Alkaloids

Indolizidine alkaloids have a fused 5- and 6-membered ring. Over 170 indolizidine alkaloids have been isolated from a diverse group of organisms. They are also known to occur in frogs, toads and orchidaceae species.[28,29] Like the polyhydroxylated

pyrrolizidine alkaloids, the polyhydroxylated indolizidine alkaloids also are known to inhibit glycosidases.[7] The polyhydroxylated indolizidine alkaloid swainsonine **36** (**Figure 1.10**), was detected in two members of the genus *Ipomoea* which were *I. sericophylla* and *I. riedelli*. Mezher reported the first total synthesis of swainsonine and confirmed its absolute configuration in 1984.[30] The polyhydroxylated indolizidine alkaloid, castanospermine **37**, was isolated from the immature seeds of *Castanospermum australe* (**Figure 1.7**) in 1981 (**Figure 1.10**).[31] Four indolizidine alkaloids, 6-*epi*-castanospermine **38**, 7-deoxy-6-*epi*-castanospermine **39**, 6,7-di*epi*-castanospermine **40** and 6,8-di*epi*-castanospermine **41** (**Figure 1.10**) were also isolated from the seeds of the same plant.[32] Lentiginosine **42** and 2-*epi*-lentiginosine **43** (**Figure 1.10**) were found in the leaves of *Astragalus lentiginosus* (**Figure 1.11**). These two indolizidine alkaloids were shown to be biosynthesized from (1*R*)-1-hydroxyindolizidine by hydroxylation at C-2.[33]

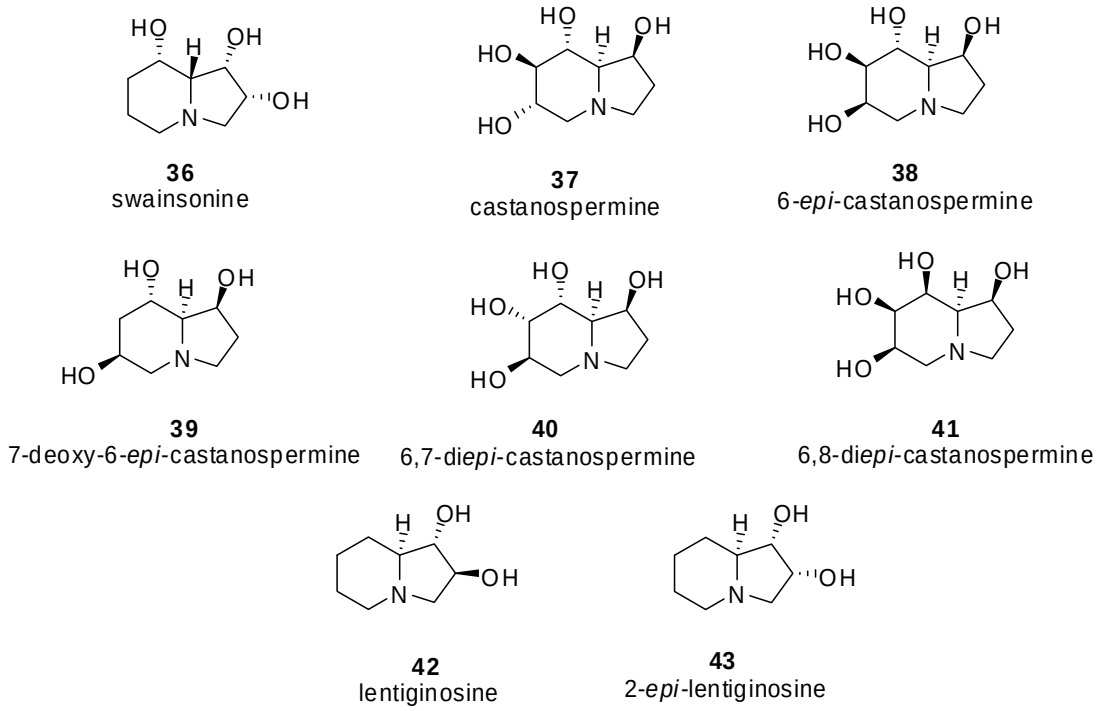


Figure 1.10. Structures of polyhydroxylated indolizidine alkaloids **36-43**.

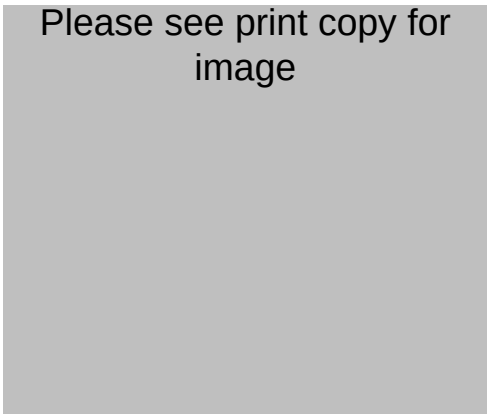


Figure 1.11. *Astragalus lentiginosus* (picture taken from Wikipedia)[34]

1.7. *Stemona* Alkaloids

The *Stemona* alkaloids have been isolated from the monocotyledonous family *Stemonaceae*. The *Stemonaceae* comprises three genera, *Croomia*, *Stemona*, and *Stichoneuron*, mainly distributed in China, Japan and South-East Asia. *Stemona* is the largest genus with 25 species and can be easily distinguished by tetramerous flowers. Many of the *Stemona* alkaloids have biological and insecticidal activities. The tuberous roots and herbal extracts of *S. japonica*, *S. sessilifolia* and *S. tuberosa* have been used in Chinese, Japanese and Vietnamese traditional medicine for the treatment of respiratory diseases and have also been used against *Enteric helminths* and ectoparasites on humans.[35,36] The roots of these plants are also widely used as insecticides and for medicinal purposes. In Thailand the roots of *S. cutisii* are used to protect pepper plants against insects.[35,36]

In 1973 only seven *Stemona* alkaloids had been described with a defined structure. In 2000 Pilli and Ferreira listed 42 structures which they separated into five structural groups.[36] In the meantime the number of *Stemona* alkaloids has been nearly doubled, now containing 82 derivatives. Among these alkaloids only four alkaloids had been isolated from the *Croomia* and *Stichoneuron* species, all the other derivatives were isolated from the *Stemona* species.[36] Based on structural considerations and their species of origin the *Stemona* alkaloids have more recently been classified into three skeletal types, the stichoneurine-, protostemonine-, and croomine-type alkaloids (**Figure 1.12**). The three groups can be distinguished by different carbon chains attached to C-9 of the pyrrolo[1,2-*a*]azepine nucleus.[36] The *croomine* type **A** contains four carbon atoms forming a lactone ring directly attached to C-9 in a spiro system. The *stichoneurine* **B** and *protostemonine* **C** type contain eight carbon atoms forming

a terminal lactone, but differ in their branching patterns. The genera *Croomia* and *Stichoneuron* produce only croomine and stichoneurine derivatives, respectively while the genus *Stemona* produces all three types of alkaloids.[37]

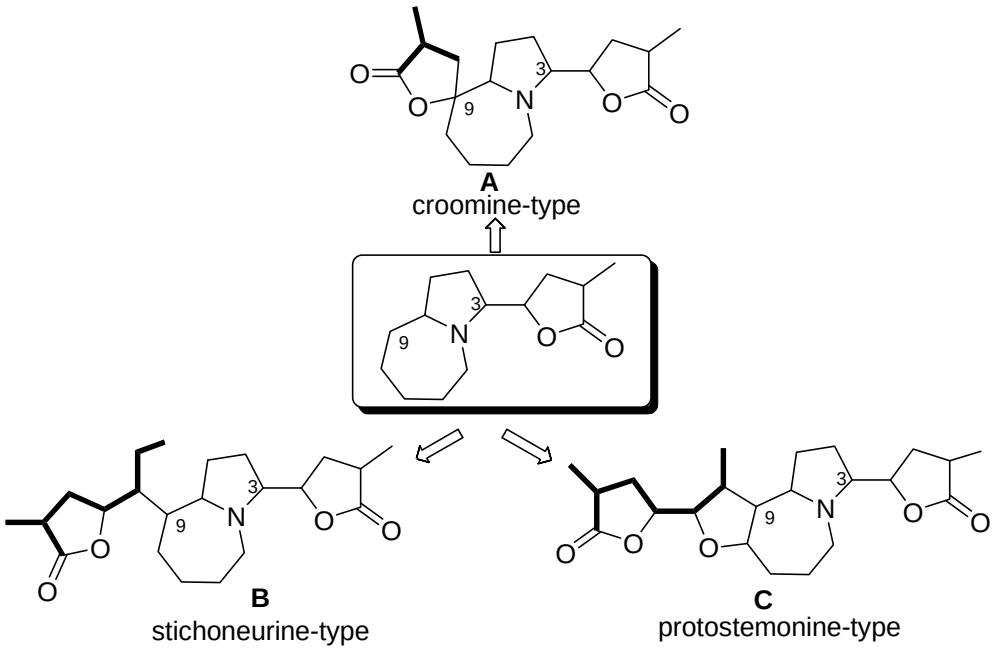


Figure 1.12. Classification of *Stemona* alkaloids.

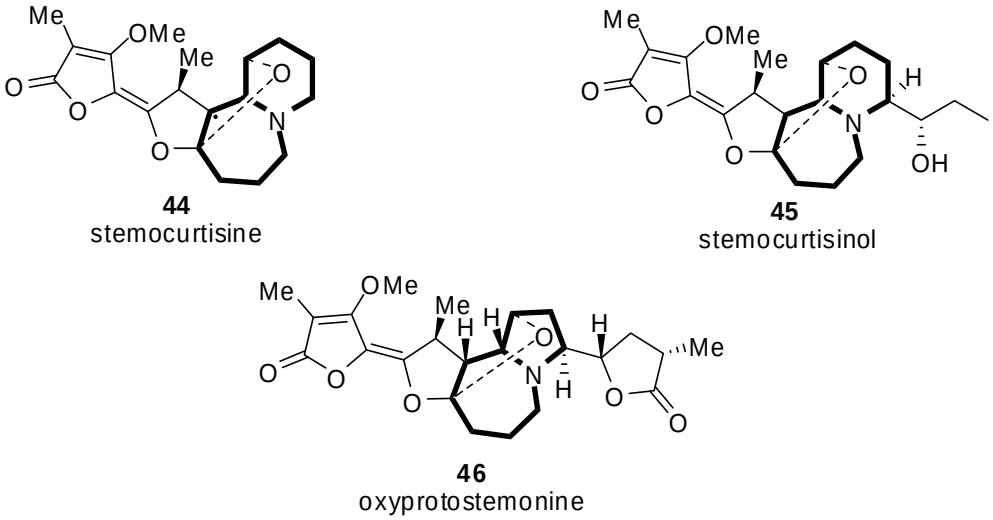


Figure 1.13. Structures of stemocurtisine **44**, stemocurtisinol **45** and oxyprotostemonine **46**.

The *Stemona* alkaloids were first thought to be based upon a pyrrolo[1,2-*a*]azepine core. In 2003 Pyne[38] isolated a new *Stemona* alkaloid stemocurtisine **44** which was based on a pyrrido[1,2-*a*]azepine core, a new structural type of *Stemona* alkaloid.

After one year the same group isolated two more alkaloids, stemocurtisinol **45** and oxyprotostemonine **46**, from the roots of the same plant. Stemocurtisinol **45** is based upon a pyrrido[1,2-*a*]azepine core, while oxyprotostemonine **46** is based upon a pyrrolo[1,2-α]azepine core (**Figure 1.13**). These alkaloids showed good larvicidal activity on malaria carrying mosquito larvae.[39]

1.8. Alkaloids having a Furo[3,2-*b*]pyrrole Nucleus

The furo[3,2-*b*]pyrrole nucleus is a common motif in a relatively small number of biologically active natural products for example lucilactene **47**, 13α-lucilactaene, fusarin A **48** and D, UCS1025A **49** and B (**Figure 1.14**). Lucilactaene **47** was isolated from a strain of fungi from the genus *Fusarium* in 2001 by Osada.[40] It was found to inhibit the cell-cycle in p53-transfected cancer cells. p53 is the tumour suppressor gene which controls cell cycle progression.[41] It plays a critical role in apoptosis and in DNA repair. In many human tumours this gene is mutated and inactive.[42] Fusarin A **48** and D were isolated from *Fusarium moniliforme* in 1992.[43] The alkaloids UCS1025A **49** and B were discovered in the fermentation broth of the fungus *Acremonium* species. UCS1025A exhibited antimicrobial activity and antiproliferative activity against human tumour cell lines.[44]

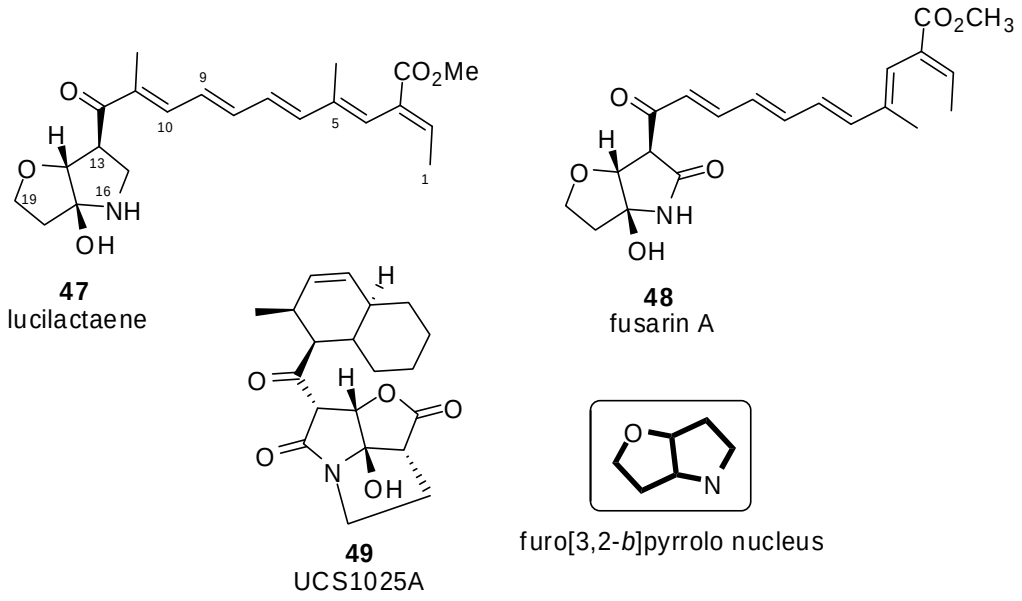
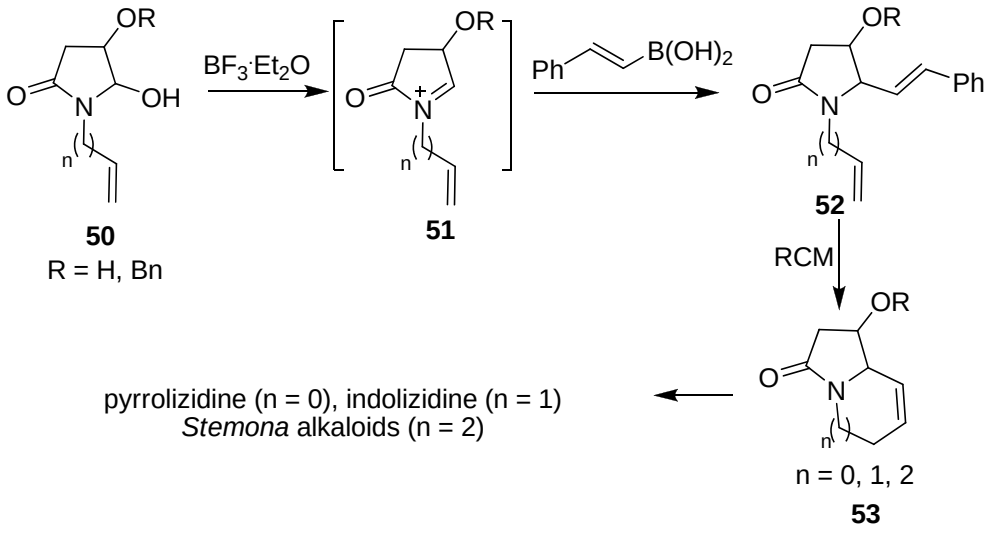


Figure 1.14. Structures of lucilactaene **47**, fusarin A **48** and UCS1025A **49**.

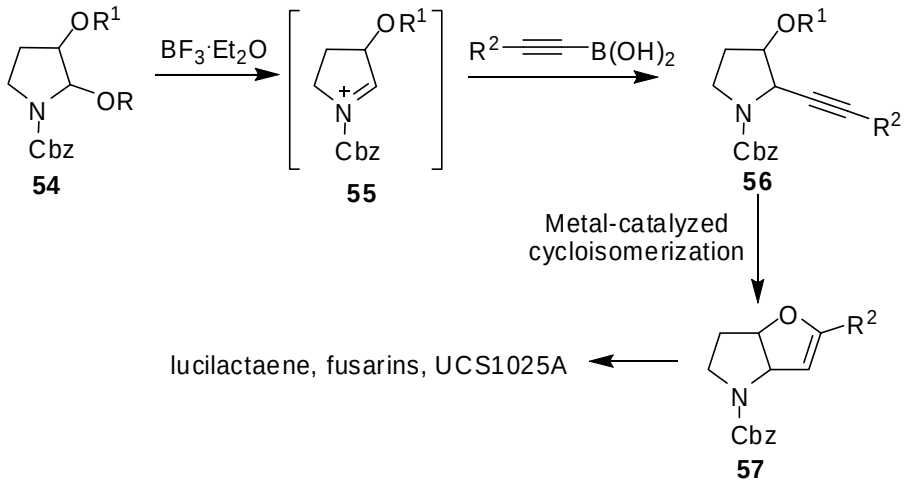
1.9. Aims of the Project

The synthesis of pyrrolizidine, indolizidine and *Stemona* alkaloids are very desirable for structure-activity relationship studies since many of them are biologically active compounds. In this project we aimed to developed a common synthetic method to obtain the bicyclic heterocyclic core structures of the pyrrolizidine, indolizidine and *Stemona* alkaloids. In our synthetic approach (**Scheme 1.1**) these bicyclic cores (**53**) would be obtained from the ring closing metathesis (RCM) reactions of the *N*-alkenyl-5-styrylpyrrolidinones **52**. The 4-benzyloxy or 4-hydroxy-5-alkenylpyrrolidines **52** would be obtained from the borono-Mannich reaction of 4-benzyloxy or 4-hydroxy-5-hydroxypyrrolidinone **50** and styrenylboronic acid.



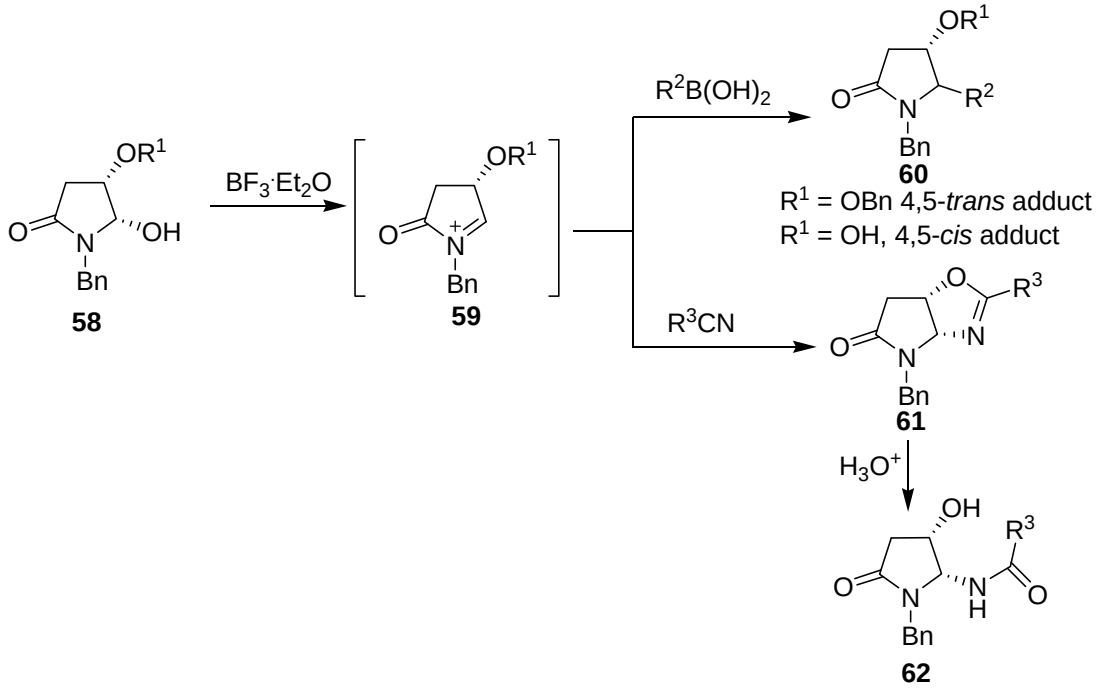
Scheme 1.1. Proposed synthesis of pyrrolidine based alkaloids.

We also aimed to synthesize the furo[3,2-*b*]pyrroles **57** using a similar initial strategy. This heterocyclic core structure could be obtained from the metal catalysed cycloisomerization reactions of 2-alkynyl-3-hydroxypyrrolidines **56**. The 2-alkynyl-3-hydroxypyrrolidines **56** could be obtained from the borono-Mannich reaction of 2,3-dihydroxypyrrolidine **54** and an alkynylboronic acids (**Scheme 1.2**). These borono-Mannich reactions would be expected to proceed through the *N*-acyliminium ion intermediates **51** and **55,** respectively. As part of this PhD project two comprehensive review articles on the intermolecular reactions of *N*-acyliminium ions were written and published in *Synthesis* in 2009.[45,46] These review articles are included as Appendices 1 and 2 of this thesis.



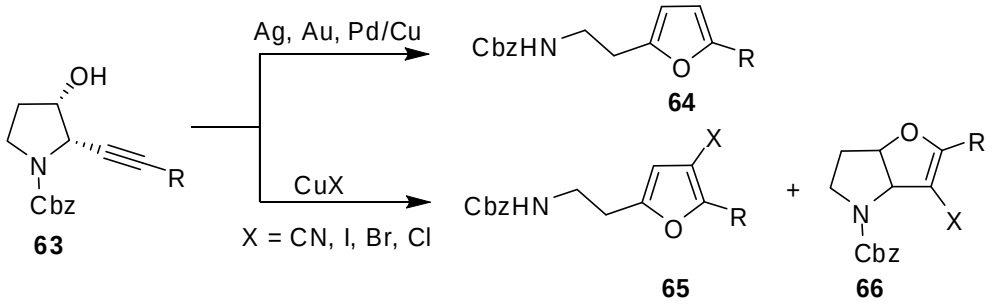
Scheme 1.2. Proposed synthesis of the furo[3,2-*b*]pyrroles **57**.

The results and discussion section of this thesis is divided into four chapters, Chapters 2-5. In Chapter 2 the reactions of *in situ* generated *N*-acyliminium ions **59** with organoboron compounds (borono-Mannich reaction) are reported in terms of product yields and diastereoselectivities. The RCM reaction of a *N*-alkenyl 5-styrylpyrrolidine was also examined. In Chapter 3, the reactions of *N*-acyliminium ions with nitriles (Ritter reaction) are documented along with the hydrolysis reactions of the adducts **61** to give novel 4-hydroxy-5-acylaminopyrrolidinones **62** (**Scheme 1.3**).



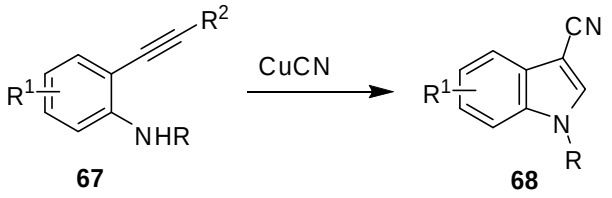
Scheme 1.3. General Scheme for Chapters 2 and 3.

In Chapter 4, the metal-catalyzed cycloisomerization reactions and copper-mediated cyclization-cyanation and cyclization-halogenation reactions of the 4-hydroxy-5-alkynylpyrrolidines **63** are reported (**Scheme 1.4**).



Scheme 1.4. General Scheme for Chapter 4.

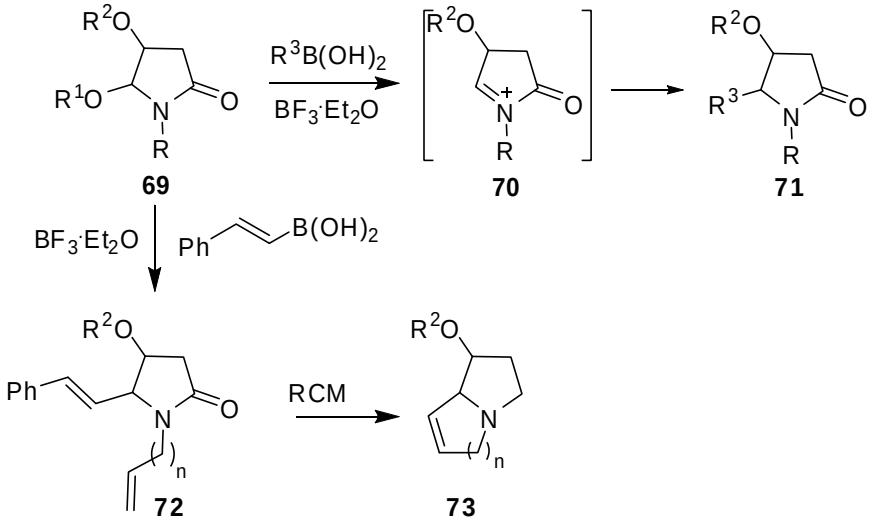
In Chapter 5 the results of the copper mediated cyclization-cyanation reactions of 2-alkynylanilines **66** are described (**Scheme 1.5**).



Scheme 1.5. General Scheme for Chapter 5.

2. DIASTEREOSELECTIVE BORONO MANNICH REACTIONS OF PYRROLIDINONES

In this Chapter we report our efforts to develop a general method for preparing 4-hydroxy-5-substituted pyrrolidin-2-ones **71** from the reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones **69** with boronic acids (**Scheme 2.1**). For the specific synthesis of our target molecules we required these reactions to be highly diastereoselective in favour of either the 4,5-*cis* or 4,5-*trans* adducts. In the case of *Stemona* alkaloid synthesis we specifically required a synthesis of the 4,5-*cis* isomer **72** (n = 3).

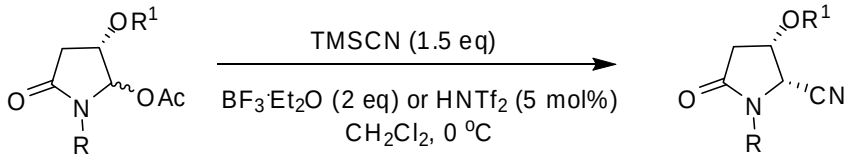


Scheme 2.1. Retrosynthetic analysis for 2-alkyl-3-hydroxypyrrolidines.

O-Protected-4-hydroxy-5-substituted pyrrolidinones, have been synthesized from the Lewis acid-catalyzed reactions of 5-hydroxy, 5-acetoxy, 5-benzyloxy or 5-methoxy pyrrolidinones with nucleophiles.[45,46] The nucleophiles can be organosilyl compounds, electron rich aromatics, organostannanes, organometallic reagents or active methylene compounds. These reactions proceeds through an *N*-acyliminium ion intermediate which is generated in situ using a Lewis ($BF_3.Et_2O$ in our studies) or protic acid. For recent reviews see Appendices 1 and 2.

The reactions of 5-acetoxypyrrolidin-2-ones **74**-**76** with trimethylsilyl cyanide in the presence of $BF_3.Et_2O$ afforded the 4-substituted-5-cyanopyrrolidinones **77** in 70-98% yields (**Scheme 2.2**).[47,48] The pyrrolidinones **74** and **76** furnished the 4,5-*cis*

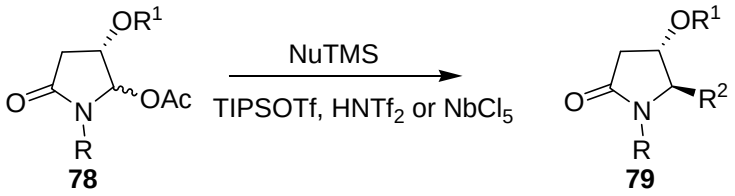
products (*cis* : *trans* = 73: 27 and 66 : 34, respectively) while the pyrrolidinone **75** gave the 4,5-*trans* product with a *trans* : *cis* ratio of 61 : 39. Treatment of the *N*-substituted-5-acetoxypyrrolidin-2-ones **78** with silicon based nucleophiles under the catalysis of TIPSOTf, $HNTf_2$, or $NbCl_5$ yielded the 4,5-*trans* pyrrolidinones **79** with high diastereselectivities (**Scheme 2.3**).[48-53] Interestingly, treatment of the *N*-unsubstituted 4-OTBS-5-methoxypyrrolidinone **80** with organosilyl compounds afforded the 4,5-*cis* adducts **81** in yields of 26-89% (**Scheme 2.4**).[50]



74 R = Bn, R^1 = Ac
75 R = PMB, R^1 = Ac
76 R = PMB, R^1 = TBS

77
70-98%

Scheme 2.2. Reactions of pyrrolidinones **74-76** with TMSCN.



78

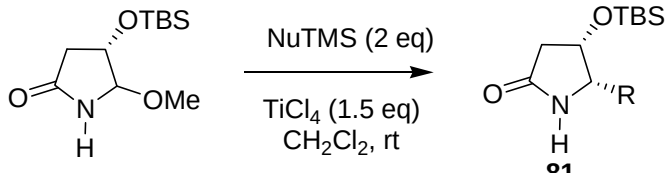
R = Bn, PMB, allyl
R^1 = Ac, TBS

79

55-95%
trans : *cis* = 99 : 1 - 60 : 40

NuTMS	R^2
CH_2=C(Ph)(OTMS)	-CH_2COPh
CH_2=C(*t*Bu)(OTMS)	-CH_2CO*t*Bu
CH_2=CHCH_2TMS	-CH_2CH=CH_2
$(Me)_2$C=C(OMe)(OTMS)	-C$(Me)_2CO_2$Me

Scheme 2.3. Reactions of pyrrolidinones **78** with organosilyl compounds.



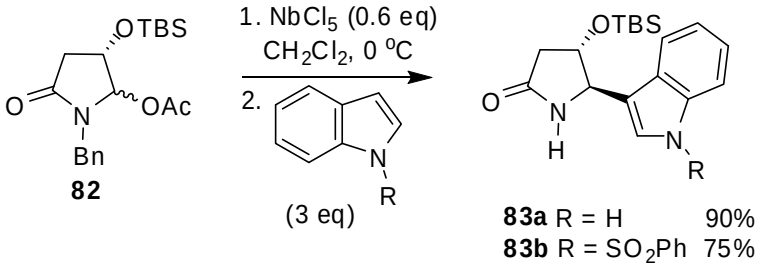
80

81
26-89%
cis : *trans* = 79 : 21 - 91 : 9

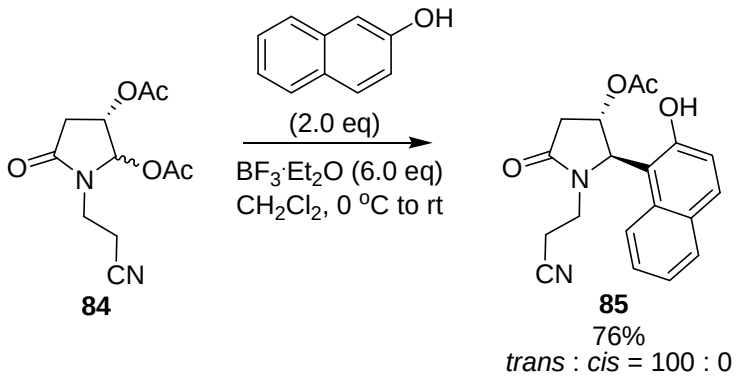
NuTMS	R
(EtO)(TMSO)C=CH(CO_2Et)	-CH(CO_2Et)CO_2Et
Me(TMSO)C=CH(CO_2Me)	-CH(CO_2Me)COMe
H_2C=CHCH_2TMS	-CH_2CH=CH_2

Scheme 2.4. Synthesis of 4,5-*cis* pyrrolidinones **81**.

Reactions of the pyrrolidinones **82** and **84** with electron-rich aromatics such as indoles and 2-naphthol also gave the 4,5-*trans* pyrrolidinone products. Treatment of pyrrolidinone **82** with indoles furnished the 4,5-*trans* adducts **83a** and **83b** in respective yields of 90% and 75%, with diastereomeric ratios of 86 : 14 and 94 : 16, respectively (**Scheme 2.5**).[49] The reaction of pyrrolidinone **84** with 2-naphthol gave the 4,5-*trans* product **85** exclusively in 76% yield (**Scheme 2.6**).[54]

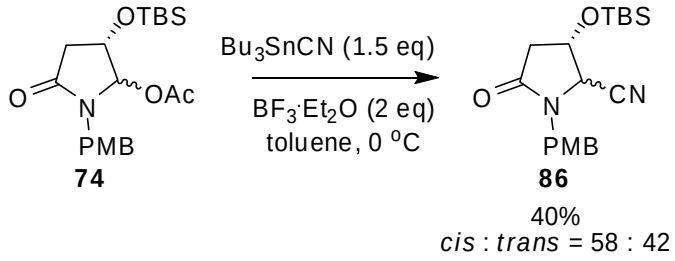


Scheme 2.5. Reactions of **82** with indoles.

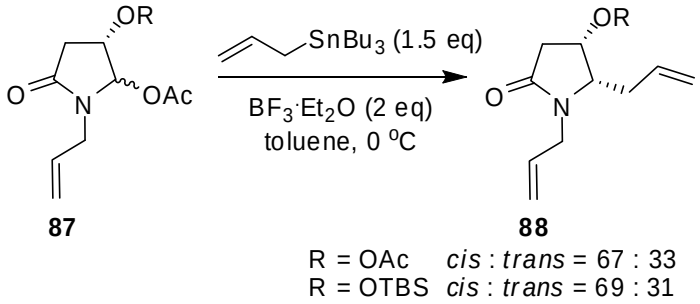


Scheme 2.6. Reaction of **84** with 2-naphthol.

Treatment of the pyrrolidinone **74** with tributylstannane cyanide furnished the 4,5-*cis* adduct **86** as the major product (**Scheme 2.7**).[47] While, treatment of *N*-allyl-4,5-diacetoxypyrrolidinone **87** with allyltributylstannane in the presence of magnesium bromide gave a 67 : 33 diastereomeric mixture of *cis* and *trans* products **88**. Its 4-OTBS analogue gave a mixture of *cis* and *trans* allylated products in a ratio of 69 : 31, respectively (**Scheme 2.8**).[55,56]

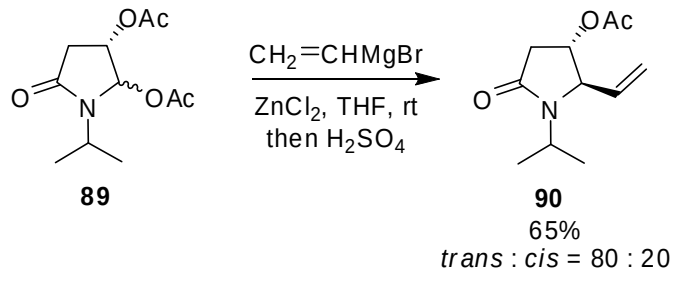


Scheme 2.7. Reaction of pyrrolidinone **74** with tributylstannane cyanide.

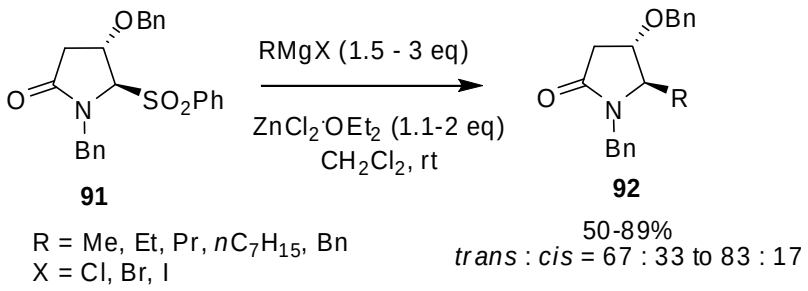


Scheme 2.8. Reactions of pyrrolidinones **87** with allyltributyltin.

The 4,5-*trans* pyrrolidinones have also been synthesized *via* the reaction of 5-acetoxy and 5-phenylsulfonyl pyrrolidinones with Grignard reagents. Treatment of 4,5-diacetoxy-*N*-isopropylpyrrolidin-2-one **89** with vinylmagnesium bromide and $ZnCl_2$ yielded a 80 : 20 mixture of the *trans* and *cis* isomers of the 4-acetoxy-5-vinylpyrrolidinone **90** in 65% yield (**Scheme 2.9**).[57] The zinc chloride-diethyl ether complex promoted reaction of 4-benzyloxy-5-phenylsulfonylpyrrolidinone **91** with Grignard reageants led to the formation of the 4,5-*trans* products **92** in yields of 50-89% (**Scheme 2.10**).[58]



Scheme 2.9. Reaction of **89** with vinylmagnesium bromide.



Scheme 2.10. Reactions of **91** with Grignard reagents.

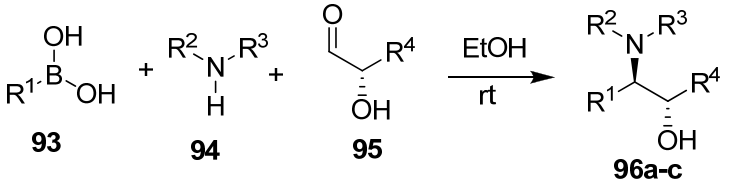
Although many methods have been developed for the synthesis of 4,5-disubstituted pyrrolidinones, most of them provided mixtures of 4,5-*trans* and 4,5-*cis* pyrrolidinones with variable diastereoselectivities. Thus the diastereoslective synthesis of 4,5-*cis* and 4,5-*trans* pyrrolidinones still remains an important topic to study. As mentioned earlier in this Chapter the 4,5-*cis* isomer of **72** (**Scheme 2.1**) was required for our *Stemona* alkaloids synthesis.

2.1. The Borono-Mannich Reaction

In 1998, Petasis[59] reported a Mannich-type condensation reaction involving boronic acids (**93**), primary or secondary amines (**94**) and α-hydroxy aldehydes (**95**). These reactions were quite remarkable in terms of their high *anti*-diastereoselectivity and enantioselectivity. Using boronic acids was important since they do not react with aldehydes, but effectively trap the more reactive iminium intermediates formed in these reactions and have good air and water stability.[60] Reactions of several organoboron compounds were examined and they all worked well (**Table 2.1**). In particular, reactions of phenylvinylboronic acid, *p*-methoxyphenylboronic acid and *N*-Boc-1*H*-pyrrol-2-yl-boronic acid afforded the corresponding Mannich adducts **96a-c** in 84%, 63% and 86% yields, respectively. All products were obtained with very high diastereoselectivity (>99% de) and enantiopurities.

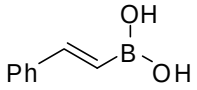
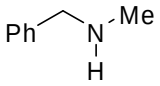
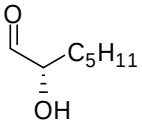
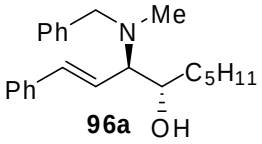
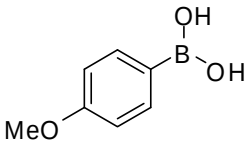
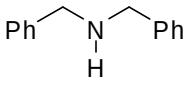
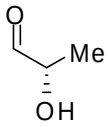
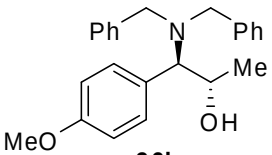
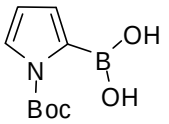
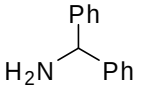
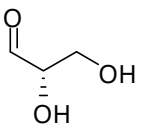
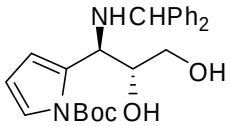
The mechanism of borono-Mannich reaction is not fully understood. The proposed mechanism involves formation of iminium ion intermediate **97**, formation of boronate complex **98**, and then intramolecular delivery of the nucleophile (R^1) to form the product **96** (**Scheme 2.11**).[61]

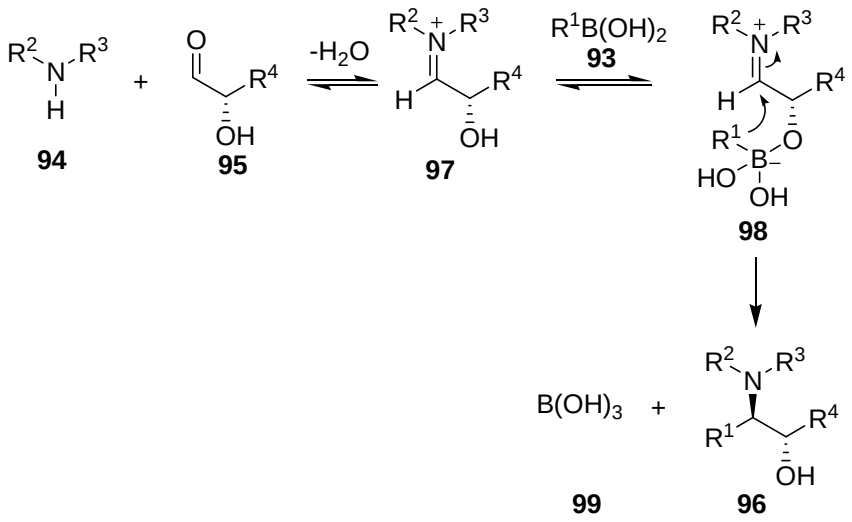
Table 2.1. Selected results from Petasis`s paper[59].



93 **94** **95** **96a-c**

>99%de, >95%ee

Boronic acid	Amine	Aldehyde	Product	Yield% (de)
			 **96a**	84 (>99%)
			 **96b**	63% (>99%)
			 **96c**	86% (>99%)

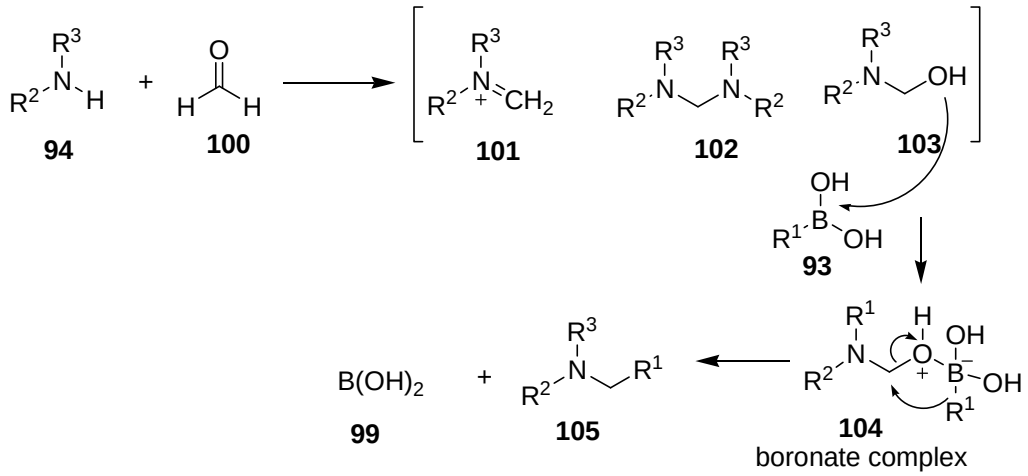


94 **95** **97** **98** **99** **96**

Scheme 2.11. Proposed mechanism of the borono-Mannich reaction.

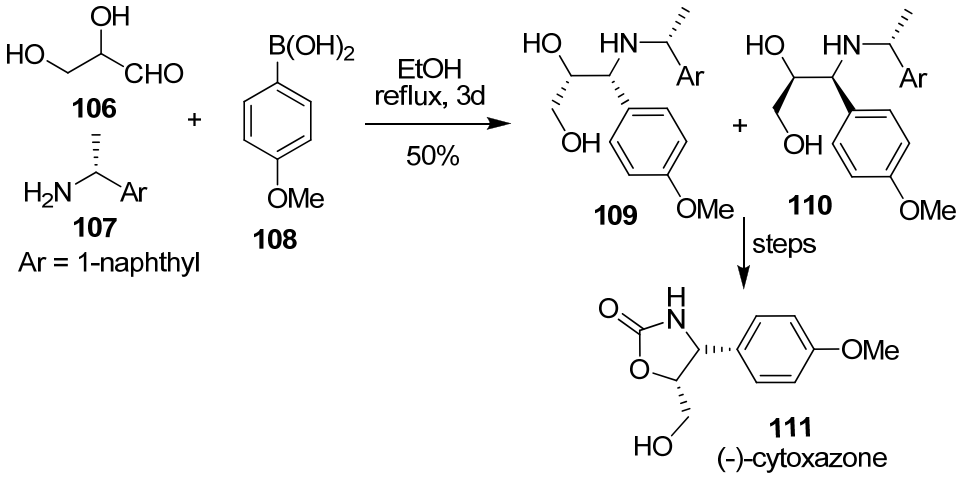
For the Petasis reaction with formaldehyde an alternative mechanism was proposed.[62] Three possible intermediates, the iminium salt **101**, the aminal **102** and the semiaminal **103**, can be formed from the mixing of the amine and formaldehyde (**Scheme 2.12**). It has been suggested that the reaction proceeds through semiaminal

103, where the hydroxyl group forms a boronate complex **104** with boronic acid **93**. Subsequent intermolecular transfer of the nucleophile (R^1) provides the product **105** (**Scheme 2.12**).



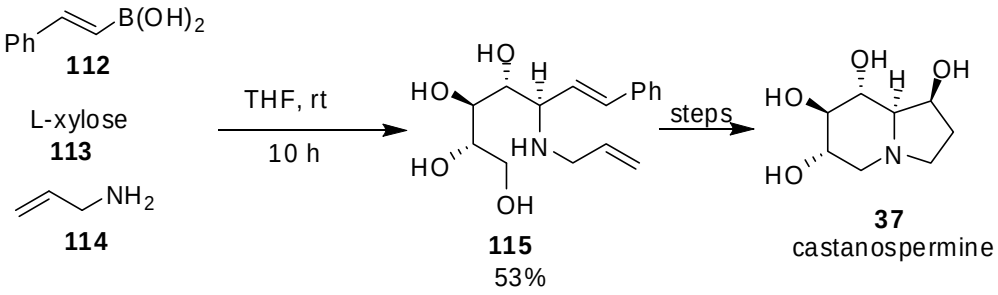
Scheme 2.12. Alternative proposed mechanism of the borono-Mannich reaction.

The borono-Mannich reaction has been widely used in the total synthesis of natural products and related biologically active compounds. The total synthesis of (-)-cytoxazone **111**, which is a novel cytokine modulator, was accomplished by Sugiyama in 2004 (**Scheme 2.13**).[63] The precursor 3-amino-1,2-propanediols **109** and **110** were synthesised by a borono-Mannich reaction of DL-glyceraldehyde **106**, (*R*)-1-(1-naphthyl)ethylamine **107** and 4-methoxyphenylboronic **108**. The diols **109** and **110** were obtained as a 1 : 1 mixture in 50% yield.



Scheme 2.13. Synthesis of (-)-cytoxazone.

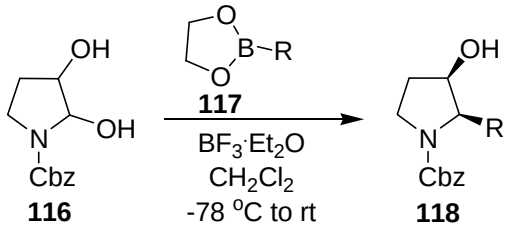
Pyne[64] reported the total synthesis of castanospermine **37**, which is a potent inhibitor of several glycosidases and has potential for the treatment of viral infections and cancer, using the borono-Mannich reaction (**Scheme 2.14**). The precursor **115** was synthesised from the borono-Mannich reaction of (*E*)-styrene boronic acid **112**, L-xylose **113** and allylamine **114**. The amino-tetraol **115** was obtained in 53% yield. The same group reported the total synthesis of uniflorine A from the diastereomer of **115** which was obtained from the borono-Mannich reaction of D-xylose, allylamine and (*E*)-styrene boronic acid.[65]

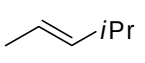
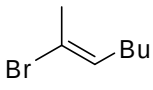
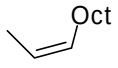
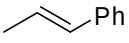
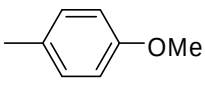
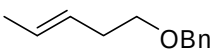


Scheme 2.14. Synthesis of castanospermine.

Batey[66] expanded the Petasis reaction to cyclic *N*-acyliminium ions. Racemic 2,3-dihydroxypyrrolidine **116** was treated with alkenyl- and arylboronic acids and esters **117** in the presence of $BF_3.Et_2O$ to give the racemic *cis*-2,3-substituted pyrrolidines **118** (**Table 2.2**).

Table 2.2. Selected results from Batey`s paper.[66]



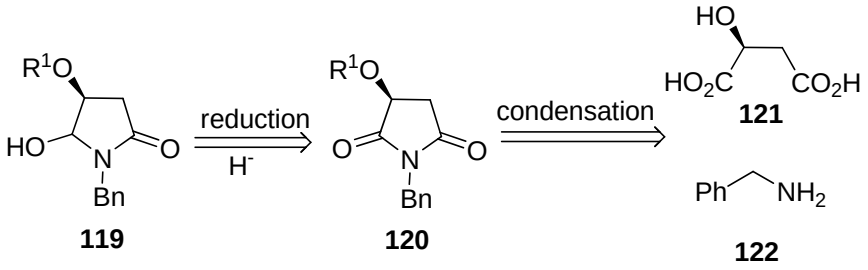
R	Yield%	R	Yield%
	91		98
	80		64
	83		81

Although these reactions were highly diastereoselective they did not extend these studies to enantiomerically enriched cyclic hemi-aminals having an *endo*-cyclic *N*-acyl group that were of interest to this project.

2.2. Borono-Mannich Reaction of Pyrrolidinones

2.2.1. Borono-Mannich Reaction of (4*S*)-1-Benzyl-4,5-dihydroxypyrrolidin-2-one

O-Protected-4-hydroxy-5-hydroxypyrrolidinones **119** can be obtained from a regioselective reduction of the corresponding succinimide **120** with $NaBH_4$.[58] Succinimide **120** can be constructed by a condensation reaction of commercially available L-malic acid **121** and benzylamine **122** (**Scheme 2.15**).

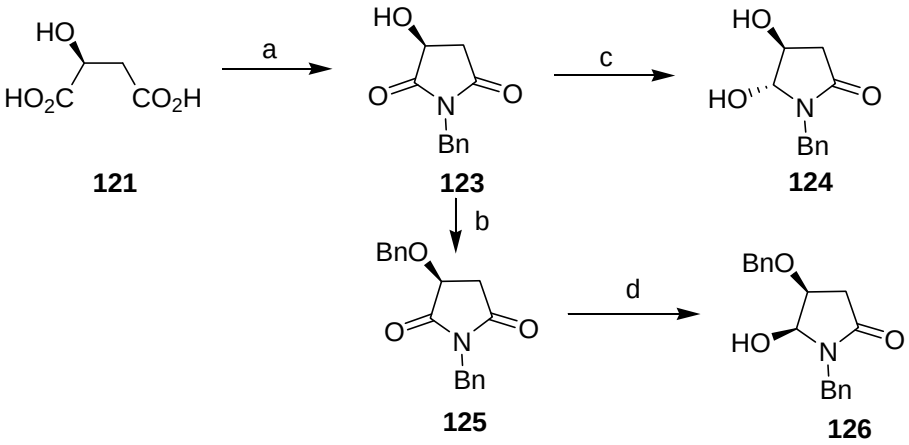


119 **120** **121** **122**

Scheme 2.15. Retrosynthetic analysis for **119**.

4,5-Dihydroxypyrrolidin-2-one **124** and the 4-benzyloxypyrrolidin-2-one **126** were chosen as precursors to study the borono-Mannich reaction (**Scheme 2.16**). Compound **124** was easily prepared in two steps from L-malic acid **121** and benzylamine **122**. A mixture of L-malic **121** and benzylamine **122** (1.2 eq.) were heated at reflux temperature in xylene for 2 h to give the known succinimide **123**[67] in 80% yield. The succinimide was treated with $NaBH_4$ (5.0 eq.) in CH_2Cl_2/EtOH (1 : 1) at -40 ^oC for 30 min to afford the 4,5-dihydroxypyrrolidinone **124** in 72% yield as a 92 : 8 mixture of diastereomers. This compound has not been reported in the literature. The ^1H NMR spectrum of the major diastereomer showed a very small $J_{4,5}$ coupling constant, $J_{4,5}$ = 1.0 Hz, which was consistent with the 4,5-*trans*-stereochemistry.[68-70] However obtaining the $J_{4,5}$ coupling constant for the minor isomer proved difficult because of overlapping signals. Similarly, pyrrolidinone **126** was prepared in two steps from **123**. Succinimide **123** was reacted with BnBr (3.0 eq.) in the presence of Ag_2O (3.0 eq.) in Et_2O at rt for 2 d to yield the known

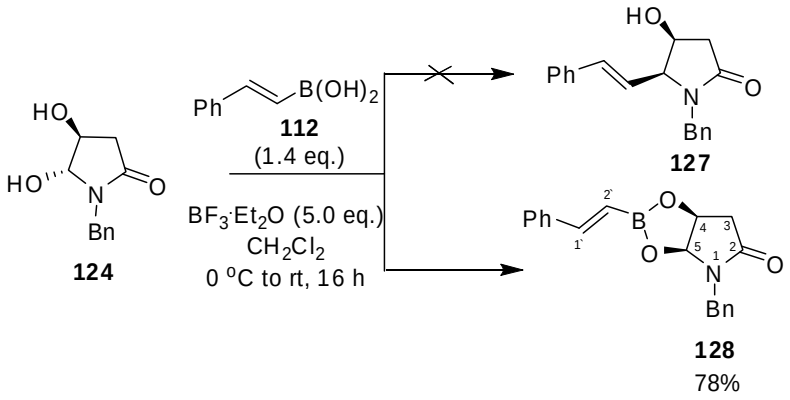
benzylated succinimide **125**[67] in 78% yield. Succinimide **125** was reduced to the corresponding known hemi-aminal **126**[58] in 70% yield using the same reduction conditions that were used for the synthesis of **124**. Compound **126** was obtained as a single *cis* isomer ($J_{4,5}$ = 6.5 Hz).



Reagents and conditions: a) $PhCH_2NH_2$ (1.1 eq.), xylene, reflux, 2 h; 80% b) BnBr (3.0 eq.), Ag_2O (3.0 eq.), Et_2O, 2 d; 78% c) $NaBH_4$ (5.0 eq.) CH_2Cl_2/EtOH : 1 : 1, -40^oC, 30 min. 72% d) $NaBH_4$ (5.0 eq.) CH_2Cl_2/EtOH : 1 : 1, -40^oC, 30 min. 70%.

Scheme 2.16. Synthesis of **124** and **126**.

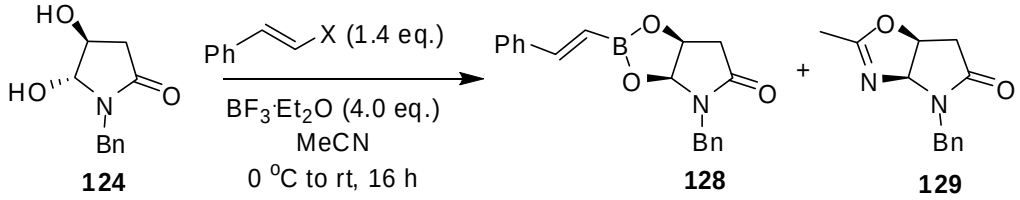
We first examined the borono-Mannich reactions of the 4-hydroxypyrrolidinone **124**. Treatment of **124** with (*E*)-2-styrylboronic acid **112** (1.4 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_2Cl_2 at -78^oC to 0 ^oC according to Batey`s[66] reaction conditions resulted in the recovery of only unreacted starting material **124**. Increasing the temperature from 0 ^oC to rt did not give the desired 5-hydroxy-4-styrylpyrrolidinone **127**, instead it gave the cyclic boronate ester **128 (Scheme 2.17**). The ^1H NMR spectrum of **128** showed two vinyl proton resonances at 7.42 and 6.14 ppm, both as a doublet, with a *J* value of 18.5 Hz. The pyrrolidine ring protons resonated at 5.59 (1H, d, *J* = 6.0 Hz, H5), 4.93 (1H, dd, *J* = 6.0, 7.0 Hz, H4), 2.83 (1H, dd, *J* = 7.0, 18.0 Hz, H3) and 2.71 (1H, d, *J* = 18.0 Hz, H3) ppm which was consistent with the structure of **128**. The vinyl carbon signals appeared at 129.4 (C2`) and 127.2 (C1`) ppm in the ^{13}C NMR spectrum. The pyrrolidine ring carbons resonated at 171.2 (C2), 89.4 (C5), 73.1 (C4) and 38.1 (C3) ppm. The low resolution (EI) mass spectrum of **128** showed a molecular ion peak at 319 amu while a high resolution (HREIMS) mass spectrometric analysis confirmed the molecular formula to be $C_{19}H_{18}BNO_3$.



Scheme 2.17. Formation of boronate complex **128**.

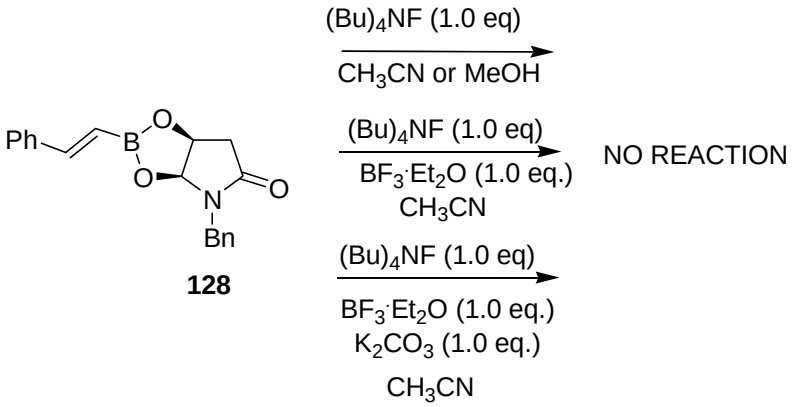
Repeating this reaction with 5.0 equivalents of (*E*)-2-styrylboronic acid **112** and 4.0 equivalents of $BF_3.Et_2O$ in CH_2Cl_2 at 0 ^oC to rt again gave the boronate ester **128** in 78% yield. Using EtOAc, THF, $CHCl_3$, DMF or DCE as a solvent in the reaction of **124** with (*E*)-2-styrylboronic (1.4 eq.) acid and $BF_3.Et_2O$ (5.0 eq.) resulted in only the formation of boronate complex **128**. However, performing this reaction in CH_3CN yielded two products which were the boronate ester **128** (52%) and the novel Ritter reaction product **129** (21%) (**Table 2.3**, Entry 1). The Ritter product is a result of the reaction of the cyclic *N*-acyliminium ion intermediate with CH_3CN. The Ritter reactions of the *N*-acyl iminium ion intermediates formed from **124** and **126** will be the subject of Chapter 3 of this thesis. The use of potassium (*E*)-styryltrifluoroborate (1.4 eq.) in this reaction resulted in the formation of **128** and **129** in 62% and 23% yields (**Table 2.3**, Entry 2), respectively. Treatment of **124** with (*E*)-2-styryl-1,3,2-dioxoborolane under the same experimental conditions also afforded the products **128** (58%) and **129** (20%) (**Table 2.3,** Entry 3).

Table 2.3. Yields of boronate ester **128** and Ritter product **129**.



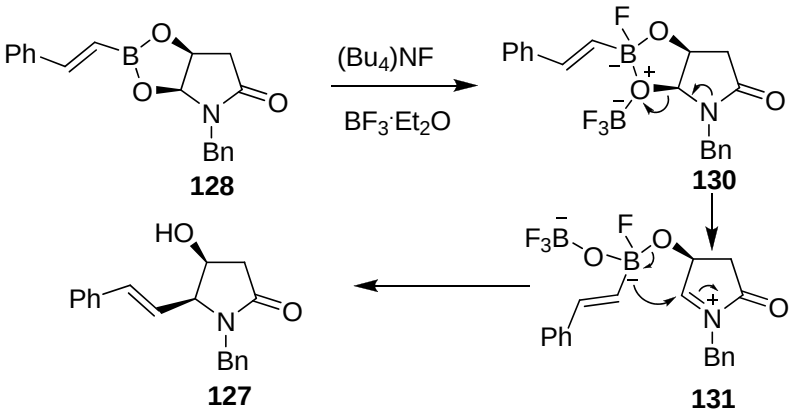
Entry	X	Yield% of 128	Yield% of 129
1	$B(OH)_2$	52	21
2	BF_3K	62	23
3	$BO(CH_2)_2O$	58	20

We then attempted to synthesize the desired 5-hydroxy-4-styrylpyrrolidinone **127** from the boronate complex **128**. Treatment of **128** with $(Bu_4)NF$ (1.0 eq.) in CH_3CN or MeOH, with or without $BF_3.Et_2O$ (1.0 eq.), with $BF_3.Et_2O$ (1.0 eq.) and K_2CO_3 (1.0 eq.) at rt for 2 d were unsuccessful (**Scheme 2.18**). In all attempts only the boronate complex **128** was recovered. It was found to be a very stable molecule.



Scheme 2.18. Attempts to synthesize 5-styrylpyrrolidine **128** from boronate complex.

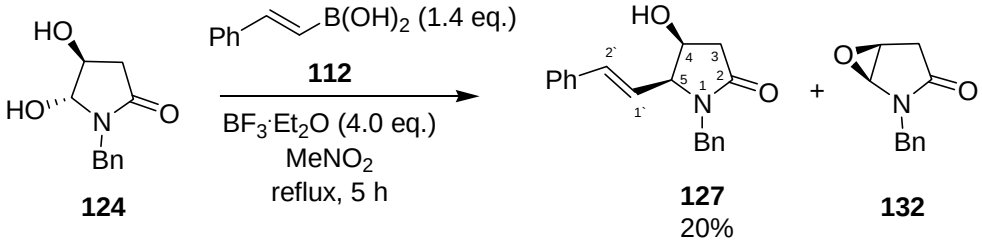
It was anticipated that the intermediate **130** could be formed in the above reactions which would give the *N*-acyliminium ion intermediate **131** which could lead the desired product **127**. (**Scheme 2.19**).



Scheme 2.19. Proposed mechanism for the synthesis of **127** from **128**.

The Mannich reaction was then performed in CH_3NO_2, since **124** is only slightly soluble in CH_2Cl_2, EtOAc, THF, CH_3Cl, DMF, DCE and forms the Ritter product **129** in CH_3CN. The pyrrolidinone **124** was unreactive when reacted with (*E*)-2-

styrylboronic acid **112** (1.4 eq.) or (1.4 eq. or 4.0 eq.) in CH_3NO_2 at rt. Treatment of **124** with **112** (1.4 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_3NO_2 at reflux temperature gave a compound that was tentatively assigned as the epoxide **132** and the desired addition product the 5-hydroxy-4-styrylpyrrolidinone **127** in a ratio of 70 : 30 respectively, from ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Purification of the crude reaction mixture by column chromatography gave **127** in 20% yield with a high diastereoselectivity (dr = 91 : 9) **(Scheme 2.20**). The diastereomeric ratio was measured from the integrals for the C*H*$_2$Ph signals (4.93 ppm for major isomer, 5.05 ppm for minor isomer) of both isomers. The epoxide **132** could not be isolated by column chromatography suggesting that it was a relatively unstable molecule. Repeating the same reaction with (*E*)-2-styryl-1,3,2-dioxoborolane gave similar results. The stereochemistry of **127** and related products will be discussed in a later section of this Chapter.



Scheme 2.20. Synthesis of **127** and **132**.

In the ^{1}H NMR spectrum of **127** signals for the vinylic protons H1` and H2` were observed at 6.51 (1H, d, *J* = 16.5 Hz) and 6.15 (1H, dd, *J* = 8.5, 16.5 Hz) ppm, respectively (**Figure 2.1**). The H4 and H5 protons of the pyrrolidine ring resonated at 4.43 (1H, ddd, *J* = 3.5, 6.0, 7.0 Hz) and 4.10 (1H, dd, *J* = 6.0, 8.5 Hz) ppm, respectively. The peaks at 2.73 (1H, dd, *J* = 7.0, 17.5 Hz) and 2.54 (1H, dd, *J* = 3.5, 17.5 Hz) ppm were assigned to H3α and H3β, respectively based upon the magnitute of their coupling constants to H4α. The ^{13}C NMR spectrum also confirmed the structure. It showed a resonance at 172.9 ppm corresponding to the C2 carbonyl group. The signals for the vinylic carbons C2` and C1` were observed at 136.3 and 123.3 ppm, respectively. The pyrrolidine ring carbons C3, C4 and C5 showed resonances at 39.9, 67.5 and 65.2 ppm, respectively. The IR spectrum was also in good agreement with the structure showing a broad peak at 3334 cm^{-1} for the O-H stretch and a sharp peak at 1669 cm^{-1} for the C=O stretch. The LREIMS and

HREIMS analysis of **127** confirmed its molecular weigth at 293 amu and the molecular formula as $C_{19}H_{19}NO_2$, respectively.

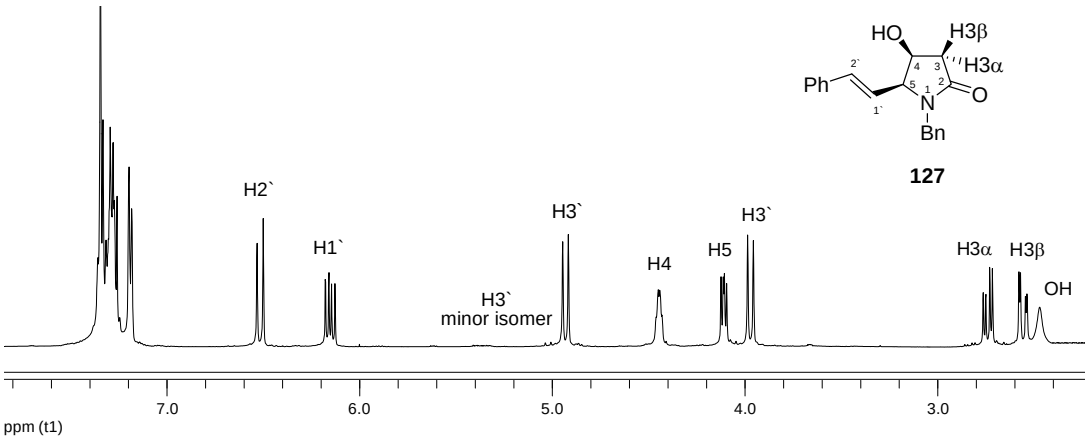
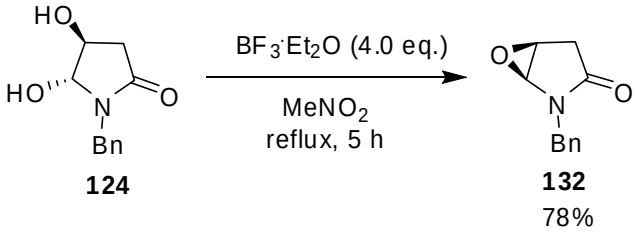


Figure 2.1. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **127**.

The epoxide **132** was unstable on silica gel. After a number of failed attempts to purify it by column chromatography, it was decided to synthesise it by the treatment of **124** with $BF_3.Et_2O$ (4.0 eq.) in CH_3NO_2 at reflux temperature (**Scheme 2.21**). TLC analysis of the reaction showed complete consumption of starting material after 5 h. The ^{1}H NMR spectrum (**Figure 2.2**) of the crude product showed a relatively pure compound had been formed. The structure of **132** was assigned from its NMR, IR and HREIMS analysis. Its ^{1}H NMR spectrum showed the typical splitting patern of the diastereotopic H3 protons at 2.85 (1H, dd, J = 8.0, 18.5 Hz) and 2.68 (1H, d, J = 18.5 Hz) ppm. The methine protons H5 and H4 resonated at 5.41 (1H, d, J = 7.0 Hz) and 4.89 (1H, dd, J = 7.0, 8.0 Hz) ppm, respectively. The LREIMS spectrum of **132** showed a molecular ion peak at 189 amu and its molecular formula was found to be $C_{11}H_{11}NO_2$ from HREIMS analysis.



Scheme 2.21. Synthesis of epoxide **132**.

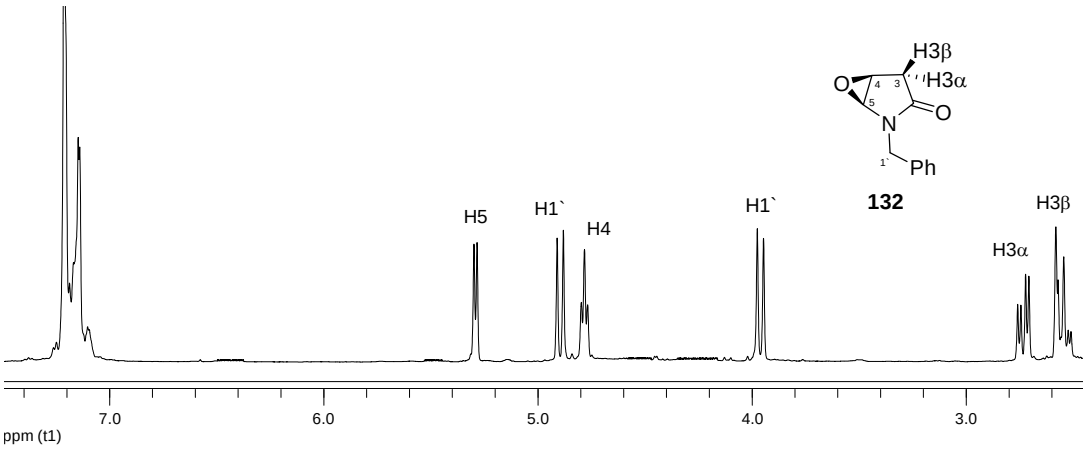
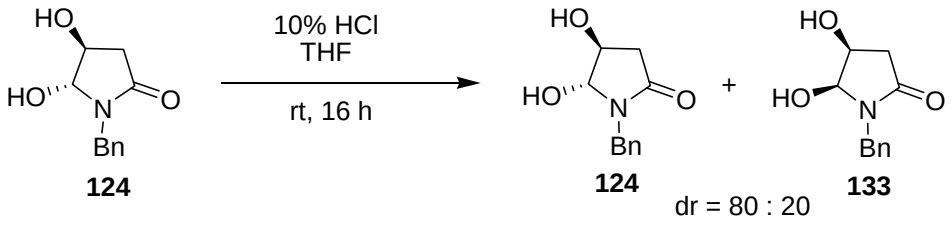


Figure 2.2. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **132** without purification.

However, the ^{1}H and ^{13}C NMR spectra of the epoxide **132** were similar to that of pyrrolidine **124**. Their molecular weights are not same but there was an 18 amu difference which could be the result of loss of a water molecule in the EI mass spectrum. In order to make sure that epoxide **132** was not the C-5 epimer of **124**, compound **124** was epimerized by treating it with 10% HCl/THF at rt for 16 h to give a 80 : 20 mixture of the C-5 epimers that could not be separated by TLC (**Scheme 2.22**). ^{1}H and ^{13}C NMR spectra of **132** and the minor epimer of **124** were different (**Table 2.4**). The H4 proton signal appeared in the ^{1}H NMR spectrum of **132** at 4.89 ppm while that of the epimer of **124** appeared at 4.24 ppm. The H3α and H3β proton signals of the epoxide **132** appeared at 2.85 (dd, J = 8.0, 18.5 Hz) and 2.68 (1H, d, J = 18.5) ppm, respectively while those of the of epimer of **124** appeared at 2.62 (dd, J = 6.5, 17.5 Hz) and 2.42 (dd, J = 2.5, 17.7 Hz) ppm, respectively. The IR spectrum of **132** did not show any peak around 3300 cm^{-1} that would corresponds to a O-H stretch. It was clear that the product **132** was not the C-5 epimer of **124**.

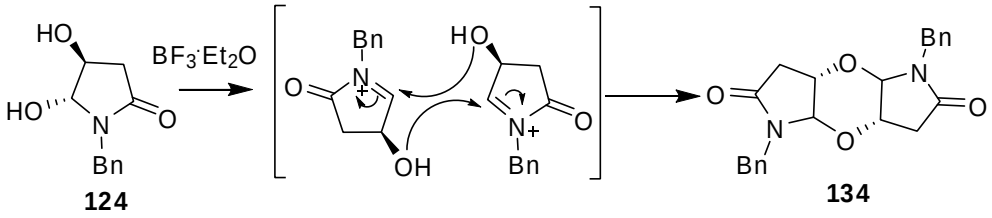


Scheme 2.22. Epimerization of **124**.

Table 2.4. Comparison of selected ^{1}H NMR chemical shifts of **132** and **133**.

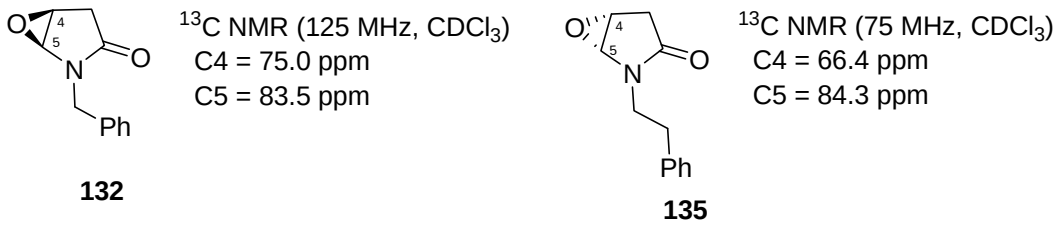
Compound	^{1}H NMR chemical shifts		
	H4	$H3_a$	$H3_b$
132	4.89 (t, *J* = 7.0 Hz)	2.85 (dd, *J* = 8.0, 18.5 Hz)	2.68 (d, *J* = 18.5 Hz)
133	4.24 (app q. *J* = 6.0 Hz)	2.62 (dd, *J* = 7.0, 16.5 Hz)	2.42 (dd, *J* = 5.5, 16.5 Hz)

Another possible product from the reaction of **124** with $BF_3.Et_2O$ (**Scheme 2.21**) was the dimer **134** of the pyrrolidinone **124** (**Scheme 2.23).** However the mass spectrum of **132** did not show any peak at 378 amu for this possible dimer. Further, the *N*-PMB analogue of **134** was synthesized by one of the Pyne group members and was purified by column chromatography. This compound showed a clear molecular ion for the dimer structure in the ESI mass spectrum.



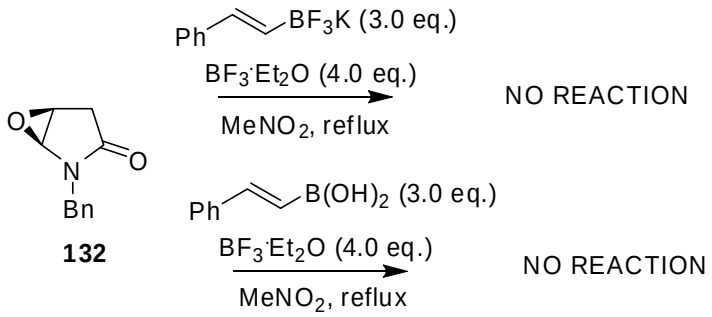
Scheme 2.23. Formation of the dimer **134**.

The *N*-phenethyl analogue of **132**, the compound **135** was prepared by Hwang.[71] The C4 and C5 carbon resonances of **135** were observed at 66.4 and 84.3 ppm, respectively. The ^{13}C NMR spectrum of **132** showed the C4 carbon signal much further downfield at 75.0 ppm, (**Scheme 2.24**). The ^{13}C NMR chemical shift for C4 in **132** was thus not consistent with an epoxide structure and therefore the structure of **132** is not certain.



Scheme 2.24. Comparison of the C4 and C5 ^{13}C NMR chemical shifts of **132** and **135**.

Further, treatment of **132** with (*E*)-2-styrylboronic acid (3.0 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_3NO_2 or potassium (*E*)-styryltrifluoroborate (3.0 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_3NO_2 at 80 ^oC for 16 h did not give a reaction product (**Scheme 2.25**). These results also lead us to doubt the proposed epoxide structure of **132**.

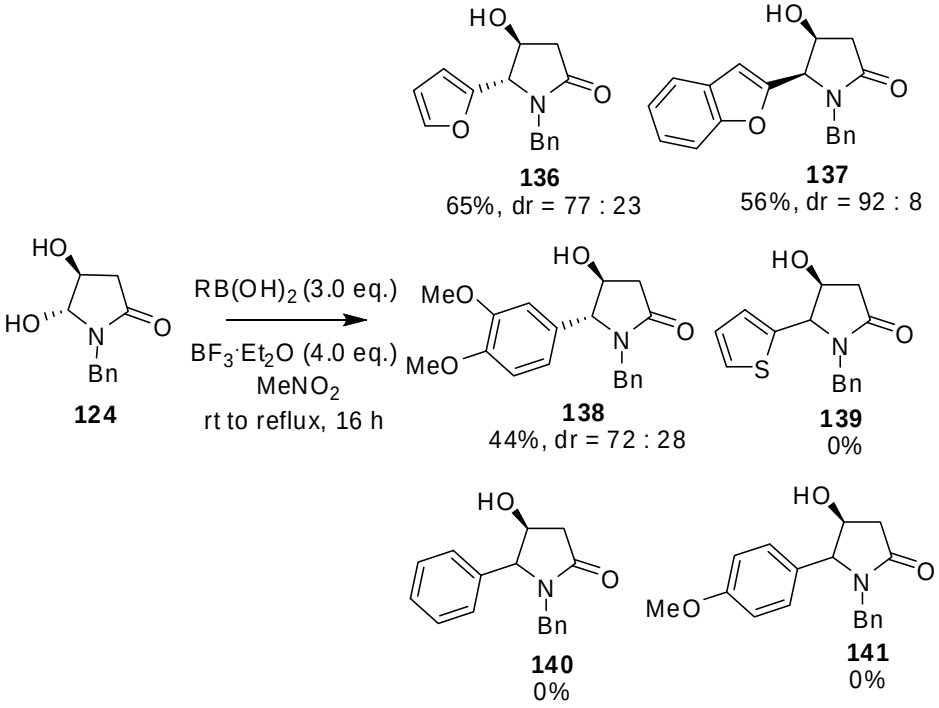


Scheme 2.25. Reactions of epoxide **132**.

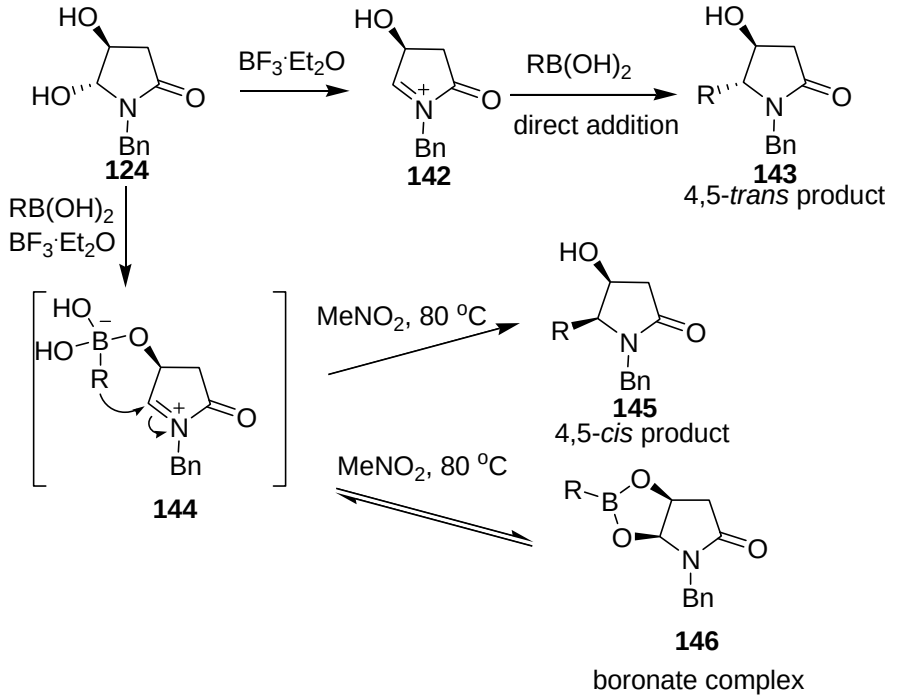
We also examined the borono-Mannich reaction of the pyrrolidinone **124** with aryl boronic acids. Six boronic acids were chosen and the reactions of these boronic acids with pyrrolidinone **124** which were performed under the optimized conditions using $MeNO_2$ as a solvent with heating at reflux. The electron-rich aromatic boronic acids; 2-furylboronic acid, 2-benzofurylboronic acid and 3,4-dimethoxyphenylboronic acids gave addition products **136**, **137** and **138**, respectively (**Scheme 2.26**). Phenyl boronic acid, 4-methoxyphenylboronic acid, and 2-thienylboronic acids did not give any of the desired products. We found that 2-benzofurylboronic acid afford the 4,5-*cis* adduct **137** in 56% yield with a 92 : 8 distereomeric ratio. 2-Furyl and 3,4-dimethoxyphenylboronic acids however gave the 4,5-*trans* adducts **136** and **138** in 65% and 44% yields, respectively with diastereomeric ratios of 77 : 23 and 72 : 28, respectively (**Scheme 2.26**). The stereochemistry of the adducts **127**, **136**, **137**, and **138** will be discussed in a later section of this Chapter.

Although the exact mechanism of the borono-Mannich reaction is not known, the proposed mechanism in the literature[62,72,73] for reactions involving acyclic *N*-acyliminium ions suggested the possible involvement of the boronate complex **144** in the above reactions of **124**. Formation of the 4,5-*cis* pyrrolidinones **127** and **137** can be rationalized as arising from the boronate intermediate **144** followed by the intramolecular delivery of the carbon nucleophile to the same face of the iminium ion. While the stereochemical outcomes of products **136** and **138** suggests direct

addition of the boronic acid to the cyclic iminium ion had occurred, *anti* to the C-4 substituent. While the boronate intermediate **146**, analogous to **128**, may have formed in these reactions, its formation may be reversible under these reaction conditions (**Scheme 2.27**).



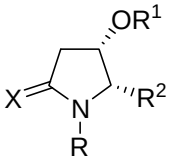
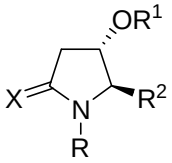
Scheme 2.26. Results of Borono-Mannich reactions of **124**.



Scheme 2.27. Formation of *cis* and *trans* pyrrolidinones and boronate complex.

The stereochemistry assigned to the adducts **127** and **136-138** was based on the magnitute of $J_{4,5}$. In the literature, $J_{4,5}$ for 4,5-*cis* pyrrolidines **147** is typically between 5.5-7.5 Hz and that for 4,5-*trans* pyrrolidines **148** is typically between 0-2 Hz (**Table 2.5**).[68-70]

Table 2.5. Selected $J_{4,5}$ values for *cis* and *trans* pyrrolidines from the literature.[68-70]

Compound	X	R	R^1	R^2	$J_{4,5}$ Hz
 **147**	O	PMB	TBDMS	CN	6.0
	H_2	CO_2Me	H	Allyl	5.5
	O	H	TBDMS	Allyl	5.7
	O	H	TBDMS	$CH_2C(CH_2)CH_2Cl$	5.8
 **148**	O	PMB	TBDMS	CN	2.0
	H_2	CO_2Me	H	Allyl	2.0
	O	H	TBDMS	$OCH_2C(CH_3)CH_2$	1.0

We found that $J_{4,5}$ for the major diastereomer of adducts **127** (**Scheme 2.20**) and **137 (Scheme 2.25)** was 6.0 Hz and 7.0 Hz, respectively which is consistent with the 4,5-*cis* stereochemistry, while that of adducts **136** and **138** (**Scheme 2.26**) was 2.0 Hz and 2.5 Hz, respectively which suggested the 4,5-*trans* stereochemistry. The $J_{4,5}$ values of the minor *cis* isomers of adducts **136** and **138** were 7.0 Hz and 5.5 Hz, respectively and that of **127** and **137** were both 2.5 Hz which was also consistent with their proposed stereochemistries (**Table 2.6**).

Table 2.6. $J_{4,5}$ values of pyrrolidinones.

Compound no	$J_{4,5}$ (Hz) of major isomer	$J_{4,5}$ (Hz) of minor isomer
127	6.0	2.5
136	2.0	7.0
137	7.0	2.5
138	2.5	5.5

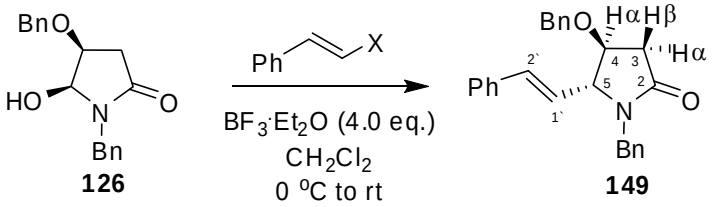
2.2.2. Borono-Mannich Reaction of (4*S*)-1-Benzyl-4-benzyloxy-5-hydroxypyrrolidin-2-one

The borono-Mannich reaction of the 4-*O*-benzyl pyrrolidinone **126** with (*E*)-2-styrylboronic acid was then investigated. When **126** was treated with 1.4 equivalents of (*E*)-2-styrylboronic acid **112** and $BF_3.Et_2O$ (4.0 eq.) in CH_2Cl_2 at -78 ^oC to 0 ^oC, under Batey`s conditions, no reaction was observed (**Table 2.8**, Entry 1). However increasing the temperature to 0 ^oC afforded the 4,5-*trans* pyrrolidinone adduct **149** in 12% yield and good diastereoselectivity (dr = 90 : 10) (**Table 2.8**, Entry 2). Performing this reaction at 0 ^oC to rt gave the adduct **149** in 34% yield (**Table 2.8**, Entry 3). Increasing the molar equivalents of **112** to 3.0 resulted in formation of the addition product **149** in 47% yield (**Table 2.8**, Entry 4). The pyrrolidinone **126** was treated with 1.4 equivalents of the more nucleophilic potassium (*E*)-styryltrifluoroborate in CH_2Cl_2 at 0 ^oC to rt to afford the product **149** in 30% yield (**Table 2.8**, entry 5). Increasing the amount of potassium (*E*)-styryltrifluoroborate to 3.0 equivalents gave the adduct **149** in 58% yield (**Table 2.8**, Entry 6). (*E*)-2-styryl-1,3,2-dioxoborolane was also used as a nucleophilic partner but it gave lower yields of **149** than potassium (*E*)-styryltrifluoroborate. Treatment of **126** with 1.4 equivalents of (*E*)-2-styryl-1,3,2-dioxoborolane and $BF_3.Et_2O$ (4.0 eq.) yielded the adduct **149** in 32% yield. The product **149** was obtained in 39% yield from the reaction of **126** with 3.0 equivalents of (*E*)-2-styryl-1,3,2-dioxoborolane and $BF_3.Et_2O$ (4.0 eq.) (**Table 2.8**, Entries 7 and 8).

The 4,5-stereochemistry assigned to **149** was again based on the magnitute of $J_{4,5}$. In the ^1H NMR spectrum of **149**, the signal of the H5 proton was a doublet with a *J* value of 8.0 Hz which is the coupling constant between H5 and the adjacent vinyl proton H1`. The H4 proton appeared as a doublet with a *J* value of 7.2 Hz which is the coupling constant between H4 and H3α. The coupling constant between the protons 4 and 5 was therefore 0 Hz which indicated the 4,5-*trans* stereochemistry. For further examination of its stereochemistry, **149** was subjected to a debenzylation reaction (**Scheme 2.28**). Compound **149** was reacted with BBr_3 (4.0 eq.) in CH_2Cl_2 at 0 ^oC for 10 min. to give the corresponding debenzylated product **150** in 90% yield. The ^1H and ^{13}C NMR spectra of **150** were identical to the minor isomer that was formed from the reaction of **124** and (*E*)-2-styrylboronic acid **112** (**Scheme 2.20**).

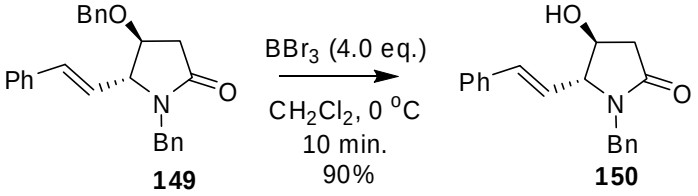
The $J_{4,5}$ value of the debenzylated product **150** was 2.5 Hz, consistent with its assigned *trans* stereochemistry.

Table 2.7. Optimization of borono-Mannich reaction of **126**.



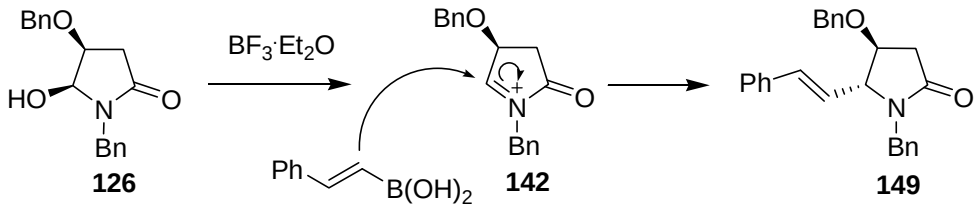
Entry	X	Eq. of Organoboron Compounds	Temperature	Yield%	dr[a] *trans* : *cis*
1	$B(OH)_2$	1.4	-78 °C to 0 °C	0	-
2	$B(OH)_2$	1.4	0 °C	12	90 : 10
3	$B(OH)_2$	1.4	0 °C to rt	34	94 : 6
4	$B(OH)_2$	3.0	0 °C to rt	47	91 : 9
5	BF_3K	1.4	0 °C to rt	30	95 : 5
6	BF_3K	3.0	0 °C to rt	58	92 : 8
7	$B(OCH_2)_2$	1.4	0 °C to rt	32	98 : 2
8	$B(OCH_2)_2$	3.0	0 °C to rt	39	96 : 4

[a] Ratios were obtained from the ^1H NMR analysis of the crude reaction mixture.



Scheme 2.28. Debenzylation of **149**.

Formation of the 4,5-*trans* isomer **149** indicated the direct addition of the organoboron compound to the cyclic *N*-acyliminium ion intermediate (**Scheme 2.29**). Since there is large benzyl protecting group on the β face of the *N*-acyliminium ion intermediate, the nucleophile prefers to attack from the α face of the molecule which resulted in the formation of 4,5-*trans* product.

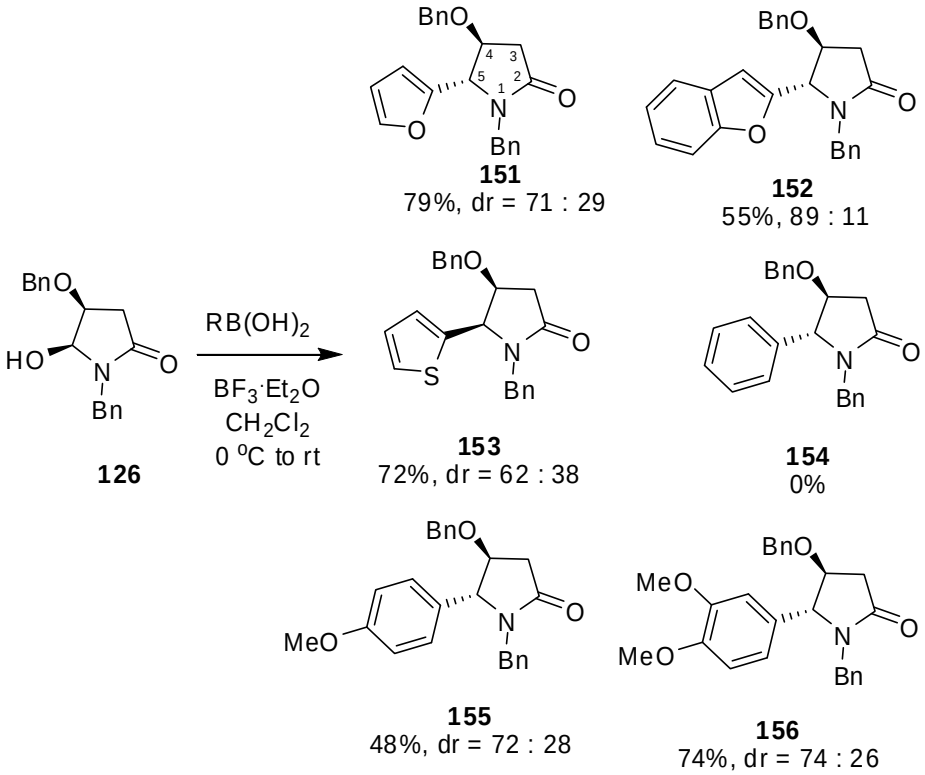


Scheme 2.29. Mechanism of formation of *trans* product.

In order to generalize the borono-Mannich reaction, **126** was treated with six different aryl boronic acids (**Scheme 2.30**). Compound **126** was treated with 3.0 equivalents of boronic acid and 4.0 equivalents of $BF_3.Et_2O$ in CH_2Cl_2 at 0 ^oC to rt for 16 h (**Table 2.8**). The electron-rich aromatic boronic acids; 2-furyl and 2-benzofurylboronic acid gave the corresponding addition products **151** and **152** in yields of 79% and 55%, respectively, with good *trans* distereoselectivities, while 2-thienylboronic acid afforded the unexpected 4,5-*cis* product **153** in 72% yield with a distereomeric ratio of *cis* : *trans* = 62 : 38. In contrast, phenylboronic acid did not react with **126**, while its more electron-rich analogues, 4-methoxyphenylboronic acid and 3,4-dimethoxyphenyl boronic acid afforded the corresponding adducts **155** and **156** with respective yields of 48% and 74%, and good 4,5-*trans* diastereoselectivities (**Table 2.8**). The stereochemical outcomes of these reactions were based on the magnitute of $J_{4,5}$ which was typically 1.5-2.5 Hz for the *trans* isomers and 6.0-7.5 Hz for the corresponding *cis* isomers, consistent with the literature examples (**Table 2.8**).[68-70]

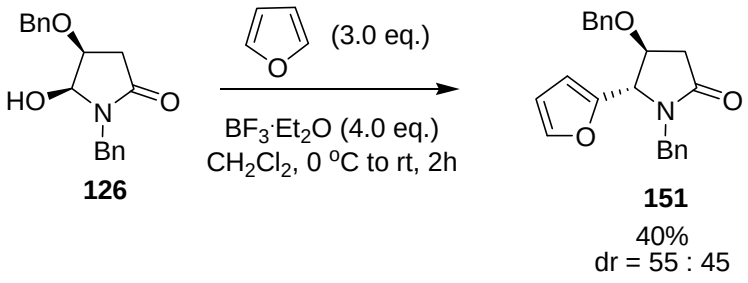
Table 2.8. $J_{4,5}$ values of products of Borono-Mannich reaction of **126**.

Compound no	$J_{4,5}$ (Hz) of major isomer	$J_{4,5}$ (Hz) of minor isomer
151	1.5	7.5
152	2.0	7.5
153	7.0	2.0
155	2.5	6.5
156	2.5	7.0



Scheme 2.30. Borono-Mannich adducts of **126**.

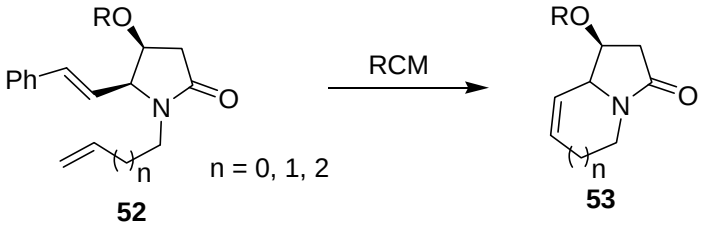
The adduct **151** was also prepared from the reaction of **126** with furan (3.0 eq.) in the presence of $BF_3.Et_2O$ (4.0 eq.) in CH_2Cl_2 at 0 °C to rt for 2 h in 40% yield (**Scheme 2.31**). The yield and diastereoselectivity of this reaction were lower than those of the reaction of **126** with 2-furylboronic acid.



Scheme 2.31. Alternative synthesis of **151**.

2.2.3. Borono-Mannich Reaction of (4*S*)-4,5-Dihydroxy-1-(pent-4-enyl)pyrrolidin-2-one

As part of this project we planned to make 5-styrylpyrrolidinones of the type general **52** which could serve as valuable precursors for the total synthesis of pyrrolizidine, indolizidine and *Stemona* alkaloids, through the RCM reaction (**Scheme 2.32**).

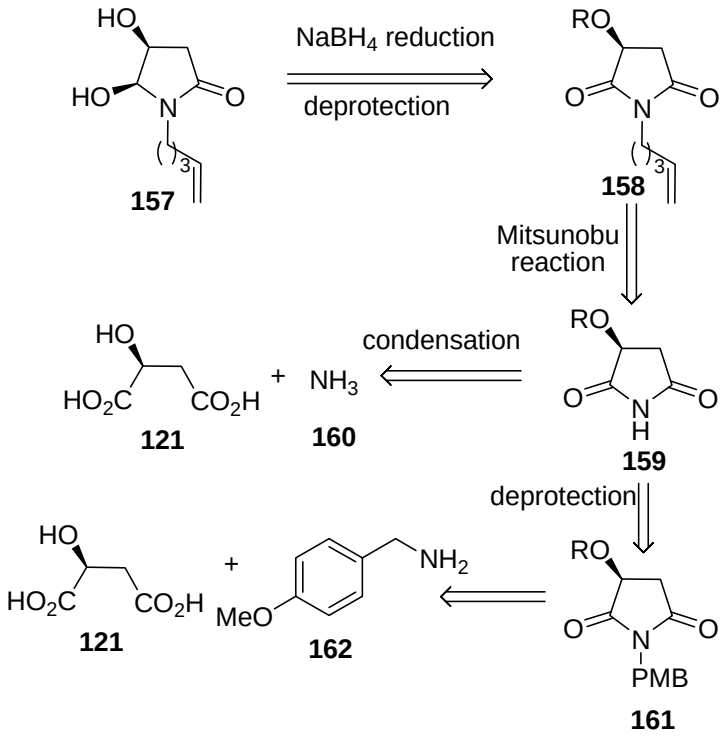


52 **53**

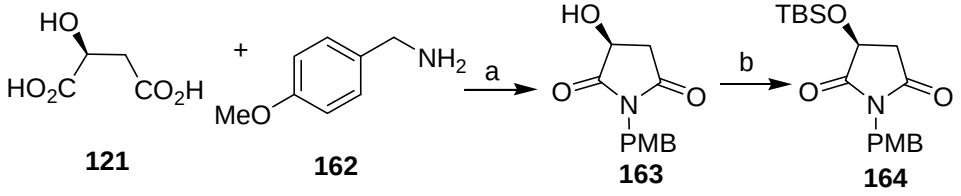
Scheme 2.32. RCM reaction of **52**.

After studying the borono-Mannich reactions of pyrrolidinone **124** and **126**, we focused on the reaction of the *N*-pentenyl analogue of pyrrolidinone **124** with the aim of constructing the common pyrrolo[1,2-*a*]azepine core of *Stemona* alkaloids. Pyrrolidinone **157** could be obtained from the succinimide **159** in three steps (**Scheme 2.33**). The succinimide **159** could be synthesised in two different ways. The first way was the deprotection of the *N*-PMB derivative of succinimide **161** which could be obtained from the condensation reaction of L-malic acid and *p*-methoxybenzylamine. The second way for obtaining **159** was directly from the condensation of L-malic acid **121** and ammonia gas **160**.

The first method was used for the synthesis of succinimide **159**, to avoid the toxicity and handling problems of ammonia gas. The condensation reaction of *p*-methoxybenzylamine and L-malic acid was performed in xylene at reflux temperature for 2 h to give the succinimide **163** in 84% yield (**Scheme 2.34**). Before the deprotection of the PMB group the hydroxyl of **163** was protected to avoid formation of a very polar molecule. The succinimide **163** was treated with TBSCl (1.5 eq.), imidazole (1.2 eq.) and DMAP (0.1 eq.) in THF at 0 ^{o}C to rt for 16 h to give the protected product **164** in 90% yield (**Scheme 2.34**).



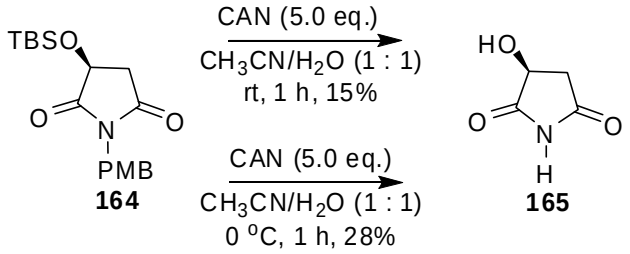
Scheme 2.33. Retrosynthetic analysis for *N*-pentenyl derivative **157**.



Reagents and conditions: a) xylene, reflux, 2 h, 84%; b) TBSCl (1.5 eq.), imidazole (1.2 eq.), DMAP (0.1 eq.), THF, 0 ^{o}C to rt, 16 h, 90%.

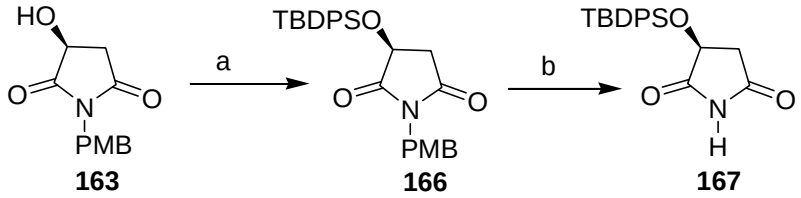
Scheme 2.34. Synthesis of **164**.

The reaction of **164** with cerium ammonium nitrate (CAN) (5.0 eq.) in CH_3CN/H_2O (1 : 1) at rt for 1 h afforded the product **165** in only 15% yield (**Scheme 2.35**). Both the PMB and the TBS groups had been cleaved under the oxidative reaction conditions. After 1 h of reaction TLC analysis showed a number of new product spots. Repeating this reaction at 0 ^{o}C gave the product **165** in an increased yield of 28%. As the TBS group was unstable in the deprotection reaction with CAN, DDQ was used as a deprotection agent. Treatment of succinimide **164** with DDQ (1.2 eq.) in CH_2Cl_2/H_2O (20 : 1) at rt for 16 h did not give any product and only unreacted starting material was recovered.



Scheme 2.35. Deprotection reaction of **164**.

We then decided to protect the hydroxyl group with the more stable TBDPS protecting group. The succinimide **163** was treated with TBDPSCl (1.5 eq.), imidazole (1.2 eq.) and DMAP (0.1 eq.) in THF at 0 ^{o}C to rt for 16 h to give the silylated product **166** in 92% yield. Treatment of **166** with CAN (5.0 eq.) in CH_3CN/H_2O (1 : 1) at rt for 1 h afforded the desired product **167** in 40% yield (**Scheme 2.36**).



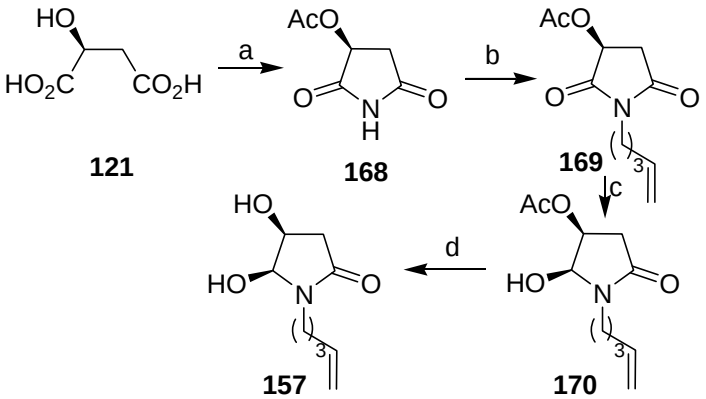
Reagents and conditions: a) TBDPSCl (1.5 eq.), imidazole (1.2 eq.), DMAP (0.1 eq.), THF, 0 ^{o}C to rt, 16 h, 92%; b) CAN (5.0 eq.), CH_3CN/H_2O (1 : 1), rt, 1 h, 40%.

Scheme 2.36. Synthesis of **167**.

Although we obtained the desired product **167**, the overall yield for its synthesis was not satisfactory. The purification of the product **167** was very difficult due to an impurity that had nearly the same R_f value as that of **167**, so that the column chromatography of the reaction mixture had to be done very carefully. Because of these problems we decided to synthesize the succinimide **159** directly from the condensation reaction of L-malic acid and ammonia. A suspension of L-malic acid in acetyl chloride was heated at reflux for 1.5 h, after removal of all volatiles the residue was treated with gaseous ammonia for 30 min and then the residue was treated with acetyl chloride at reflux temperature to afford the succinimide **159** in 56% yield (**Scheme 2.37**). The succinimide **159** reacted under Mitsunobu reaction conditions with 4-penten-1-ol (1.0 eq.), PPh_3 (1.0 eq.), DIAD (1.0 eq.) in THF at 0 ^{o}C to rt for 1 h to give *N*-pentenyl succinimide **168** in 81% yield. The *N*-pentenyl succinimide was treated with $NaBH_4$ (5.0 eq.) in MeOH/ CH_2Cl_2 (1 : 1) at 0 ^{o}C for

1.5 h to give the hemi-aminal **170** in 62% yield and as single isomer. $J_{4,5}$ was 6.5 Hz, indicative of the 4,5-*cis* stereochemistry. Deacetylation of **170** with K_2CO_3 in MeOH at rt for 2 h afforded the diol **157** in 67% yield (**Scheme 2.37**).

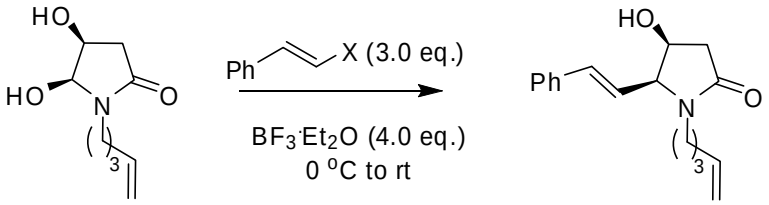
We next examined the borono-Mannich reaction of **157** with (*E*)-2-styrylboronic acid. Since **157** was soluble in CH_2Cl_2, unlike **124**, these reactions were performed in CH_2Cl_2. The reaction of **157** with (*E*)-2-styrylboronic acid (3.0 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_2Cl_2 at 0 ^oC to rt yielded the desired addition product **171** in only 15% yield (**Table 2.9**, Entry 1). After 2 h of reaction, TLC analysis shows consumption of starting material and a new less polar spot which was the adduct **171**. Increasing the polarity of the TLC solvent system to CH_2Cl_2/MeOH (1 : 1) did not raise any new spots from the baseline. An analysis of the ^1H NMR spectrum of the crude reaction mixture showed mainly the desired product and did not provide a reason for the low yield. Treatment of **157** with potassium (*E*)-styryltrifluoroborate under the same experimental conditions afforded adduct **171** in an slightly increased yield of 21% (**Table 2.9**, Entry 2). Product **171** was obtained in 33% yield from the reaction of **157** with (*E*)-2-styrylboronic acid (3.0 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_3CN (**Table 2.9**, Entry 3). The ^1H NMR spectrum of the crude reaction mixture showed methyl protons of the corresponding Ritter product at 2.01 ppm as a singlet. The ratio of **171** to the Ritter product was about 90 : 10.



Reagents and conditions: a) i.Acetyl chloride, ii. NH_3, iii. Acetyl chloride, 56%; b) 4-penten-1-ol, PPh_3, DIAD, THF, 0 ^oC to rt, 81%; c) $NaBH_4$ (5.0 eq.), MeOH/CH_2Cl_2 (1:1), 0 ^oC, 62%; d) K_2CO_3 (0.5 eq.), MeOH, rt, 67%.

Scheme 2.37. Synthesis of **157**.

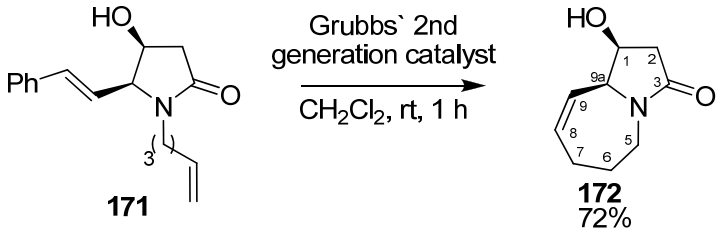
Table 2.9. Results of borono-Mannich reaction of **157**.



Entry	X	Solvent	Yield%	dr[a] *cis* : *trans*
1	$B(OH)_2$	CH_2Cl_2	15	90 : 10
2	BF_3K	CH_2Cl_2	21	92 : 8
3	$B(OH)_2$	CH_3CN	33	90 : 10

[a] Ratios were obtained from the ^{1}H NMR analysis of the crude reaction mixture.

With the adduct **171** in hand we decided to perform the ring closing metathesis reaction to obtain the corresponding pyrrolo[1,2-*a*]azepine **172**. Adduct **171** was treated with Grubbs` second generation catalyst (13% mol) in CH_2Cl_2 at rt for 1 h to give the pyrrolo[1,2-*a*] azepine **172** in 72% yield. This bicyclic structure is common to the *Stemona* alkaloids.



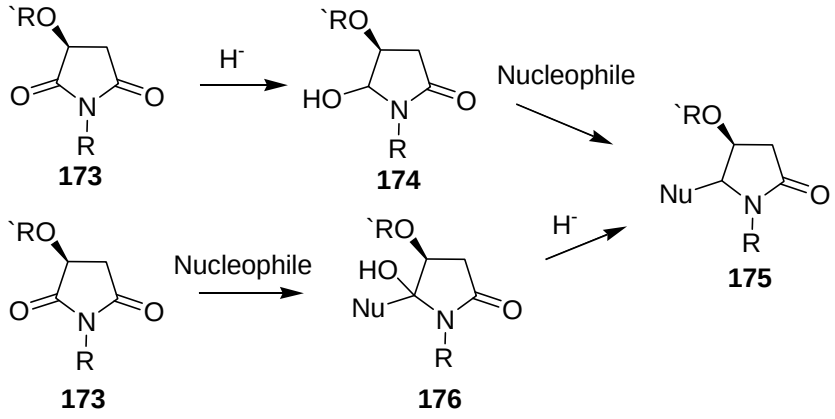
Scheme 2.38. RCM reaction of **171**.

The ^{1}H NMR spectrum of **172** showed signals for the H8, H9, H9a and H1 methine protons at 6.04-6.02 (1H, m), 5.64 (1H, d, J = 10.5 Hz), 4.40 (1H, br. s) and 4.38 (1H, br. s) ppm, respectively. The coupling constant $J_{8,9}$ of 10.5 Hz was consistent with the expected *cis* alkene geometry in **172**. The diastereotopic pairs of methylene protons resonated at 4.12 (1H, dt, J = 5.6, 13.8 Hz) and 2.95 (1H, dt, J = 6.6, 13.8 Hz) ppm for H5, at 2.61 (1H, dd, J = 5.4, 16.5 Hz) and 2.45 (1H, dd, J = 3.3, 16.5 Hz) ppm for H2, at 2.39-2.36 (1H, m) and 2.24-2.16 (1H, m) ppm for H7, while those of H6 resonated at 1.84 (2H, m) ppm. The ^{13}C NMR spectrum was also consistent with the structure of **172**. It showed methine resonances at 172.3 (C3), 134.3 (C8), 123.9 (C9) and 67.0 ppm (C9a). The four methylene carbons C2, C5, C6

and C7 were observed at 39.9, 41.2, 26.9 and 26.0 ppm, respectively. The IR spectrum was also in good agreement with the structure showing an O-H stretch at 3359 cm^{-1} and a C=O stretch at 1662 cm^{-1}. The HREIMS analysis showed its molecular formula to be $C_{17}H_{21}NO_2$, which is consistent with the structure of **172**.

2.3. Grignard Reaction of Succinimide 125

Since 5-styrylpyrrolidinone type compounds were important for our synthetic projects (**Scheme 2.32**), we decided to try a different method to prepare this type of compound in higher yield and diastereoselctivities. These compounds can in principle be synthesized from the corresponding succinimide in two ways (**Scheme 2.39**). The first way is reduction of the succinimides to the hemi-aminals **174** and then the addition of nucleophiles as we have discussed earlier in this Chapter. The second way is the addition of the nucleophiles to succinimides first and then reduction. We thus studied the potential of this second method.



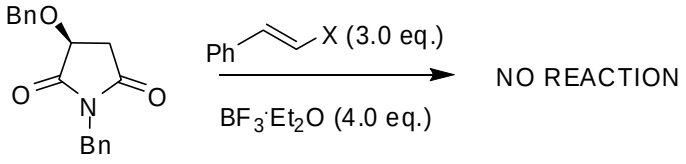
Scheme 2.39. Two ways for the reparation of 5-substituted pyrrolidines.

Succinimide **125** was found to be unreactive when it was treated with organoboron compounds (**Table 2.10**). The reactions of **125** (*E*)-2-styrylboronic acid and potassium (*E*)-styryltrifluoroborate were tried under different reaction conditions and none of them provided the addition product and only the starting material was recovered. Treatment of **125** with (*E*)-2-styrylboronic acid (3.0 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_2Cl_2 at rt gave only succinimide **125** (**Table 2.10**, Entry 1). Repeating this reaction at 40 ^oC only afford the starting material (**Table 2.10**, Entry 2). Attempts to get the addition product from the reaction of **125** and more nucleophilic, potassium (*E*)-styryltrifluoroborate (3.0 eq.), in the presence of $BF_3.Et_2O$ (4.0 eq.) in

CH_2Cl_2 failed, and only the starting material was recovered (**Table 2.10**, Entry 3). Increasing the temperature of the reaction of **125** with potassium (*E*)-styryltrifluoroborate (3.0 eq.) in the presence of $BF_3.Et_2O$ (4.0 eq.) to 40 ^oC did not give any of the desired product either (**Table 2.10**, Entry 4). Performing the reaction of **125** with potassium (*E*)-styryltrifluoroborate (3.0 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_3CN at 60 ^oC did not give any product (**Table 2.10**, Entry 5).

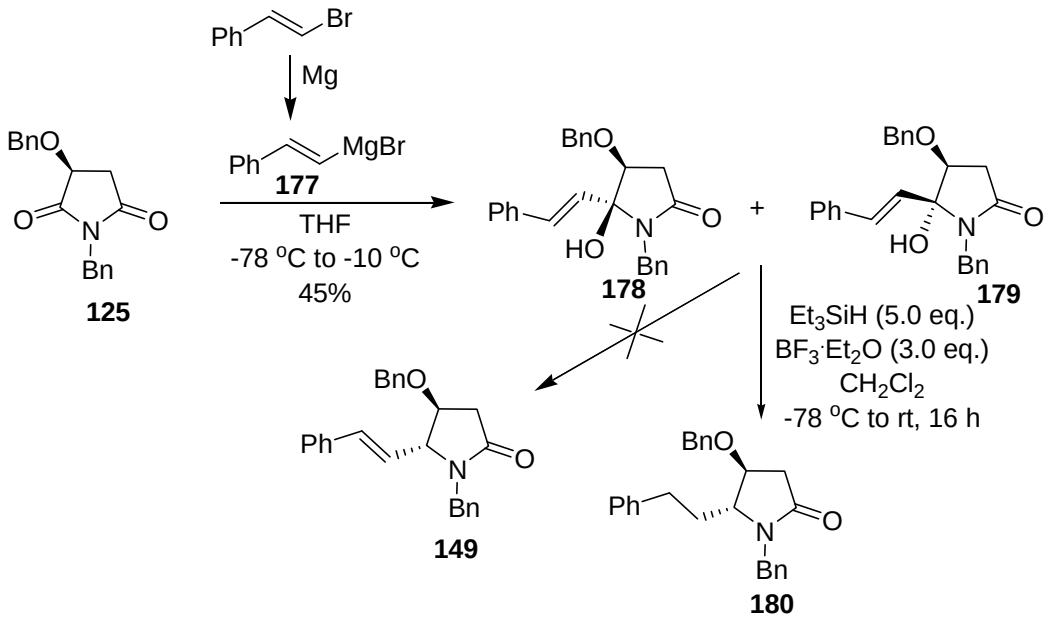
We then decided to try the reaction of the corresponding Grignard reagent with the succinimide **125 (Scheme 2.40**). Since phenylvinylmagnesium bromide **177** is not commercially available, it was synthesized from the reaction of phenylvinyl bromide and magnesium turmings in THF at 40 ^oC for 1 h.[74] Freshly prepared phenylvinylmagnesium bromide was treated with succinimide **125** in THF at -78 ^oC to -10 ^oC for 4 h to afford a diastereomeric mixture of the tertiary carbinols **178** and **179** in 45% yield with a diastereomeric ratio of 58 : 42 (not necessarily respectively). This isomeric mixture could not be separated by column chromatography. Reduction of this mixture with Et_3SiH (5.0 eq.) and $BF_3.Et_2O$ (4.0 eq.) in CH_2Cl_2 at -78 ^oC to rt for 16 h provided the *trans*-5-(2-phenylethyl)-2-pyrrolidinone **180** and not the desired 5-styrylpyrrolidinone product **149** (**Scheme 2.40**).

Table 2.10. Results of treatment of **125** with organoboron compounds.



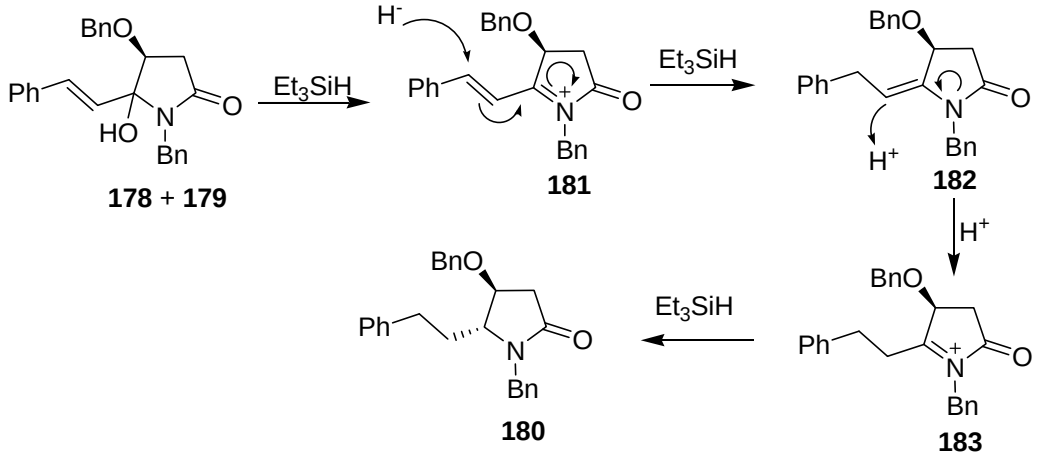
125

Entry	X	Solvent	Temperature	Yield%
1	$B(OH)_2$	CH_2Cl_2	rt	0
2	$B(OH)_2$	CH_2Cl_2	40 ^oC	0
3	BF_3K	CH_2Cl_2	rt	0
4	BF_3K	CH_2Cl_2	40 ^oC	0
5	BF_3K	CH_3CN	60 ^oC	0



Scheme 2.40. Result of reaction of **125** with phenylvinylmagnesium bromide.

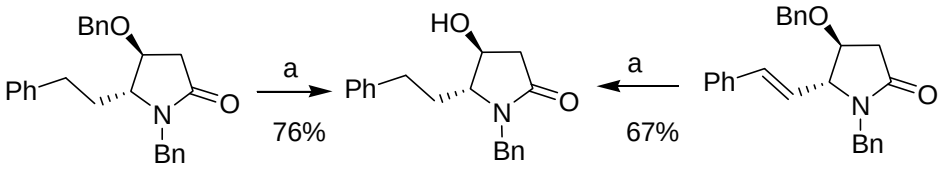
The observed product **180** suggested that after formation of the *N*-acyliminium ion intermediate **181** that 1,4-addition of hydride takes place to give the *N*-acyl enamine **182**. Protonolysis of this intermediate **182** then gives iminium ion **183** and further reduction of this intermediate yielded the 4,5-*trans* product **180** (**Scheme 2.41**). The proton source may have arisen from adventitious water in the reaction mixture after reaction with $BF_3.Et_2O$.



Scheme 2.41. Proposed mechanism for the formation of **180**.

In the ^{1}H NMR spectrum of **180**, the signal of the H4 proton appeared at 3.93 ppm as a doublet with $J_{3,4}$ = 6.5 Hz and the signal of the H5 proton appeared at 3.52 ppm as

a broad doublet with a *J* value of 8.5 Hz which is the coupling constant between H5 and adjacent CH_2 protons. The coupling constant between the H4 and H5 protons was therefore calculated as 0 Hz which indicated the 4,5-*trans* stereochemistry. In order to further prove the stereochemistry of **180**, it was subjected to a debenzylation reaction. Product **180** reacted with $PdCl_2$ (0.8 eq.) in MeOH under a H_2 atmosphere for 1 h at rt to afford the debenzylated product **184** in 76% yield (**Scheme 2.42**). The product **149**, from the reaction of **126** and (*E*)-2-styrylboronic acid **(Table 2.7**), was also subjected to the same debenzylation reaction conditions to afford the product **184** in 67% yield. The ^{1}H and ^{13}C NMR spectra of these two products were identical which confirmed that the stereochemistry of product **180** was 4,5-*trans*.



180 **184** **149**

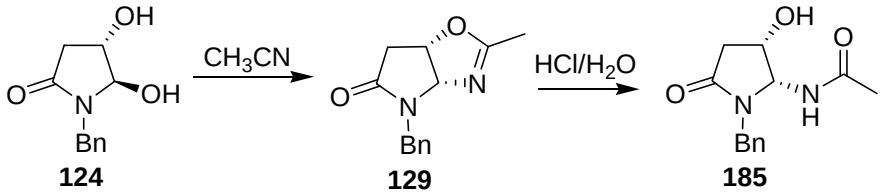
Reagents and conditions: a) $PdCl_2$ (0.8 eq.), H_2, MeOH, 1 h.

Scheme 2.42. Debenzylation of **180** and **149**.

In conclusion, the 4,5-disubstituted pyrrolidinones were synthesized in a diastereoselective manner from the borono-Mannich reaction of 4-hydroxy and 4-benzyloxy-5-hydroxypyrrolidin-2-ones. The 4,5-dihydroxypyrrolidin-2-one gave the 4,5-*cis* adducts **127** and **137** with very high *cis* selectivity but in relatively low yields, while the 4-benzyloxy-5-hydroxypyrrolidin-2-one gave the 4,5-*trans* adducts with good *trans* selectivity and in moderate to good yields. Unfortunately the desired dienyl 4,5-*cis* adduct **171**, required for the synthesis of the *Stemona* alkaloids could only be obtained in a low yield of 33%. A RCM reaction of **171** gave the desired pyrrolo[1,2-*a*]azepine **172** in 72% yield.

3. DIASTEREOSELECTIVE RITTER REACTIONS OF PYRROLIDINONES

In Chapter 2 we reported the formation of the novel Ritter product **129** as an unwanted side product in the reaction of **124** with (*E*)-2-styrylboronic acid **122** when acetonitrile was used as a solvent. We decided to examine the scope and utility of this interesting reaction. In principle the Ritter product **129** could be hydrolysed to give the 2-acylaminopyrrolidinones **185** (**Scheme 3.1**). 2-Acylaminopyrrolidines are common motifs of the natural products odorine **186** and odorinol **187** (**Figure 3.1**).



Scheme 3.1. Synthetic pathway to **185**.

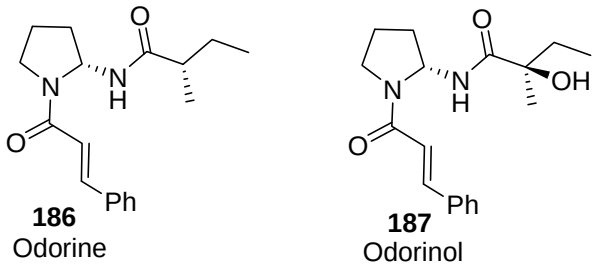
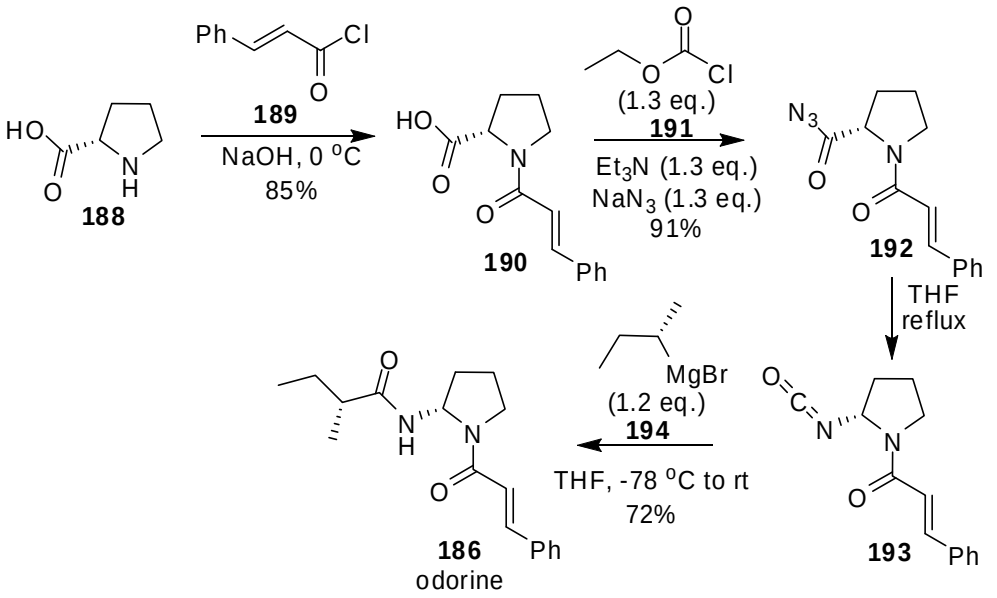


Figure 3.1. Structures of odorine **186** and odorinol **187**.

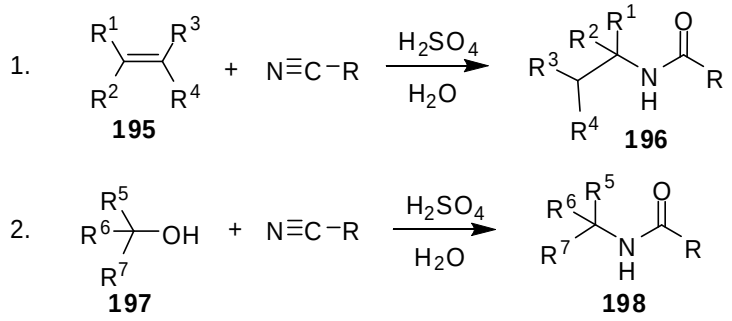
The first and unique synthesis of the odorine **186** and odorinol **187** was reported by Babidge[75] in 1980. Their synthesis started with the acylation of L-proline **188** with 3-phenylpropanoyl chloride **189** to give amide **190**. Then compound **190** was treated with ethyl chloroformate **191**, followed by triethylamine and sodium azide to afford the corresponding acyl azide **192** which rearranged to form the isocyanate **193** on heating in THF. Addition of 2-(*S*)-butylmagnesium bromide **194** to **193** yielded odorine **186** in 72% yield (**Scheme 3.2**). From the optical rotations of natural and synthetic samples of odorine **186**, it was discovered that they were enantiomers. This indicated the absolute configuration of **186** was as shown in **Figure 3.1**. A similar strategy was used in the synthesis of the enantiomer of odorinol **187**.



Scheme 3.2. Synthesis of odorine **186**.

3.1. The Ritter Reaction

In 1948, Ritter[76,77] reported that the reaction of nitriles with alkenes **195** or tertiary alcohols **197** under acidic conditions gave amides **196** and **198** (**Scheme 3.3**). The use of hydrogen cyanide as a nitrile component resulted in the formation of *N-tert*-alkyl formamides. In general, the Ritter reaction is the reaction of nitriles and carbocations to form *N*-alkyl carboxamides. The carbocations can be generated from tertiary, secondary or benzylic alcohols, alkenes or alkyl halides. The nitrile substituent (R) can be a primary, secondary or tertiary alkyl, alkenyl, alkynyl, aryl or heteroaryl substituent.



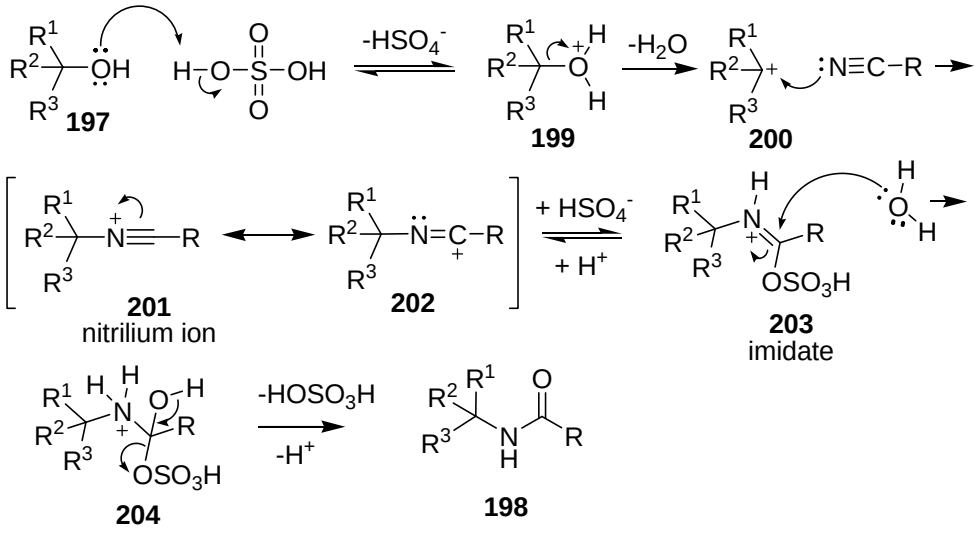
Scheme 3.3. Ritter reactions of alkenes **195** and alcohols **197**.

Treatment of 2-methylpent-2-ene **195a** with acetonitrile, H_2SO_4 and H_2O gave the corresponding acetamide **196a** in 75% yield (**Table 3.1**, Entry 1).[76] Reaction of 2-methylbut-2-ene **195b** with acrylonitrile and 2-(3-nitrophenyl)acetonitrile afforded

their respective amide adducts **196b** and **196c** in yields of 75% and 89%, respectively (**Table 3.1**, Entries 2 and 3). Treatment of 2-phenylpropan-2-ol with sodium cyanide, H_2SO_4 and H_2O yielded the formamide **198a** in 61% yield (**Table 3.1**, Entry 4).

Table 3.1. Results of the Ritter reaction of alkenes **195** and alcohols **197**.[76]

Entry	Alkene or Alcohol	Nitrile	Product	Yield%
1	$(H_3C)_2C{=}CHC_2H_5$ **195a**	CH_3CN	$C_3H_7(H_3C)_2C{-}NH{-}C(=O){-}CH_3$ **196a**	75
2	$C_2H_5(H_3C)C{=}CH_2$ **195b**	$H_2C{=}CHCN$	$C_2H_5(H_3C)_2C{-}NH{-}C(=O){-}CH{=}CH_2$ **196b**	75
3	$C_2H_5(H_3C)C{=}CH_2$ **195c**	*p*-$NO_2C_6H_4CH_2CN$	$C_2H_5(H_3C)_2C{-}NH{-}C(=O){-}CH_2C_6H_4NO_2$ **196c**	89
4	$PhC(CH_3)_2OH$ **197a**	NaCN	Ph, CH_3, H_3C, NH, C(=O), H **198a**	61

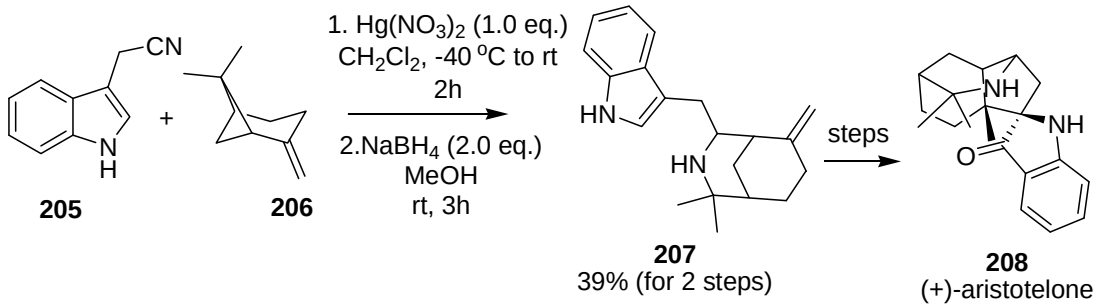


Scheme 3.4. Mechanism of the Ritter reaction.

In the mechanism of the Ritter reaction (**Scheme 3.4**) the hydroxyl group of the alcohol **197** is first protonated and then cleavage of the C-O bond of the cationic intermediate **199** generates the carbocation **200**. The nitrile attacks the cation **200** to form a resonance stabilized nitrilium ion **201**. The nitrilium ion **201** reacts with the

conjugate base of the acid to form an imidate **203**. Finally, hydrolysis of the imidate intermediate yields the observed *N*-alkyl carboxamide **198**.[77]

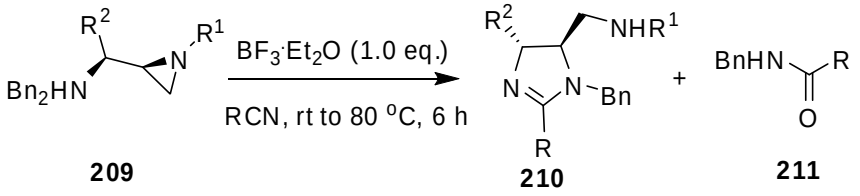
Since its discovery the Ritter reaction has been widely used in the total synthesis of natural products and alkaloids. In 1993, Heathcock[78] reported the Ritter reaction of 3-indoleacetonitrile **205** and (1*S*)-(-)-*β*-pinene **206** in the sythesis of (+)-aristotelone **208** (**Scheme 3.5**). The Ritter reaction of **205** with **206** in the presence of $Hg(NO_3)_2$ in CH_2Cl_2 at -40 ^oC to rt for 2 h gave an imine intermediate which was reduced to the corresponding amine product **207** by $NaBH_4$.



Scheme 3.5. Ritter reaction of **205** and **206**.

Concellon[79] reported the preparation of enantiopure tetrasubstituted imidazoles **210** through the Ritter reaction of enantiopure 2-(1-aminoalkyl)aziridines **209** with nitriles (**Table 3.2**). These reactions were highly regio- and enantio-selective.

Table 3.2. Synthesis of imidazoles.

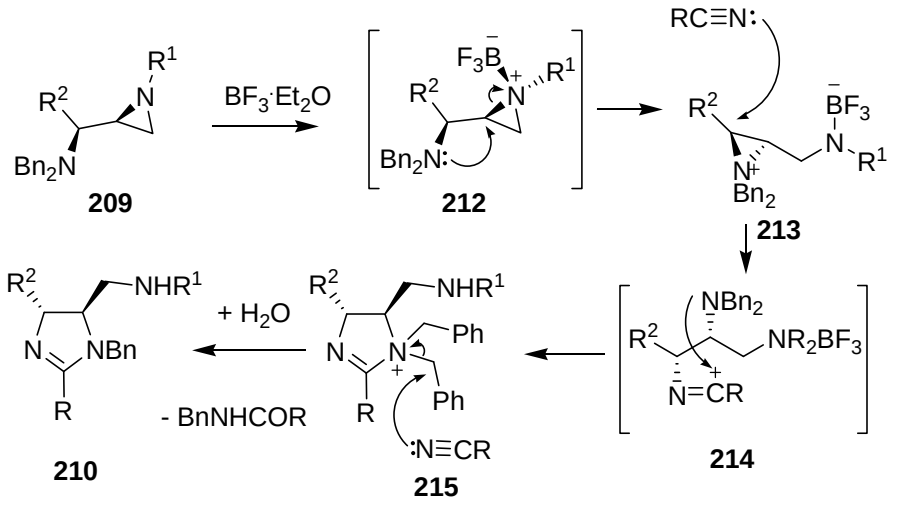


209 **210** **211**

R	R^1	R^2	Yield% of 210
Me	Bn	*i*Bu	45
*i*Pr	Bn	Bn	61
Ph	Bn	$BnOCH_2$	55
$MeOCH_2$	Allyl	*i*Bu	58

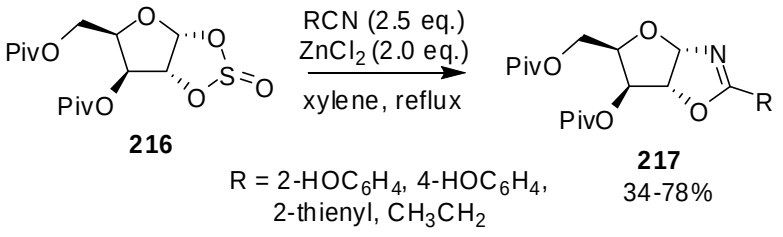
The suggested mechanism (**Scheme 3.6**) involves selective coordination of the Lewis acid to the aziridine ring nitrogen, then intramolecular nuclephilic attack of the dibenzylamino group at C-2 of the ring to form the aziridinium ion **213**. Ring opening of intermediate **213** takes place with inversion of configuration by an attack

of the nitrile molecule. *N*-cyclization of the resulting intermediate **214** afforded the cyclic *N*-acyliminium ion intermediate **215**. Debenzylation of **215** and hydrolysis gave the observed imidazole **210**.



Scheme 3.6. Proposed mechanism for the formation of imidazoles **210**.

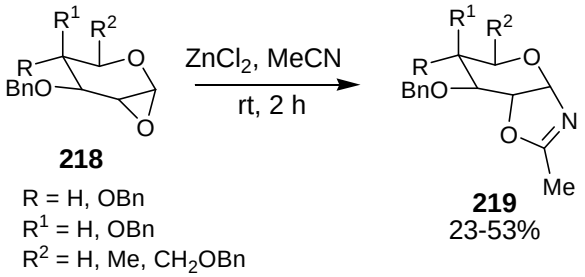
2-Oxazolines were prepared from the Ritter reaction of cyclic sulfites by Batoux[80] in 2009. The reaction of 1,2-cyclic sulfites **216** with nitriles in the presence of Lewis acids in xylene at reflux temperature furnished the corresponding 2-oxazoles **217** in moderate yields (**Scheme 3.7**). While the reaction of *o*- and *p*-hydroxybenzonitriles provided the Ritter adducts in 57% and 78% yield, respectively, *m*-hydroxybenzonitrile did not give any product. 2-Cyanothiophene and propionitrile furnished the corresponding oxazoles in respective yields of 34% and 50%.



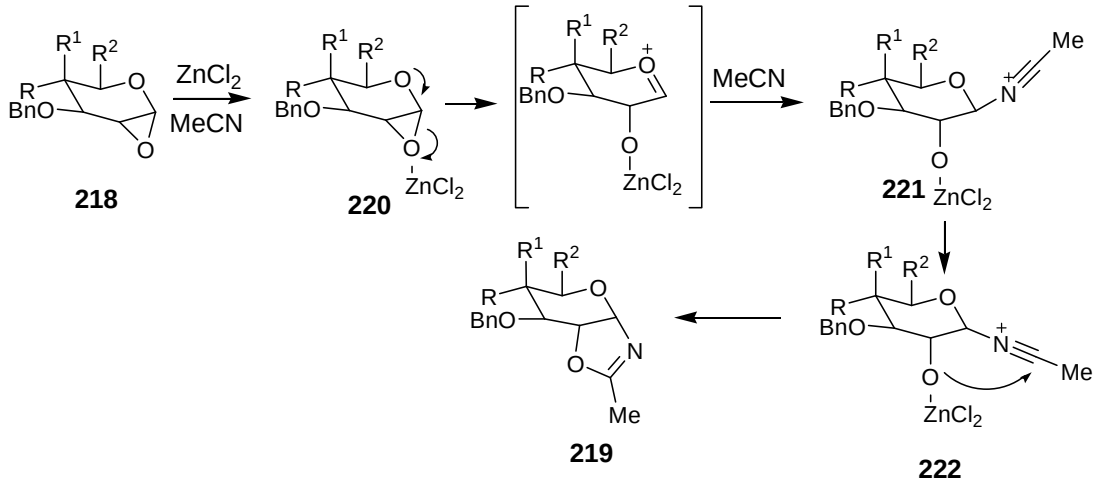
Scheme 3.7. Synthesis of 2-oxazoles **217**.

In 1991, Danishefsky[81] reported Ritter-like reactions of 1,2-anhydropyranose derivatives **218**. Treatment of 1,2-anhydropyranose compounds **218** with CH_3CN and $ZnCl_2$ afforded the corresponding oxazolines **219** in yields of 23-53% (**Scheme 3.8**).

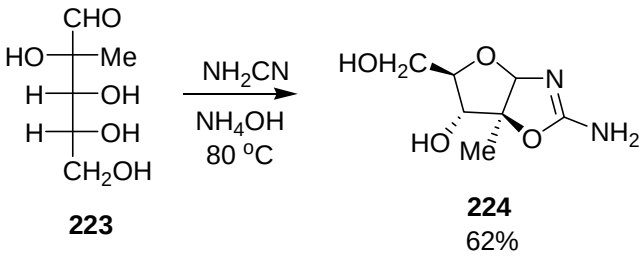
They suggested that a S_N1 type opening of the epoxide ring resulted in the equatorial anomeric intermediate **221**. Inversion of this intermediate to the axial anomeric intermediate **222** followed by intramolecular attack of oxygen gave the oxazolines **219** (**Scheme 3.9**).



Scheme 3.8. Synthesis of oxazolines **219**.



Scheme 3.9. Proposed mechanism for the formation of oxazolines **219**.



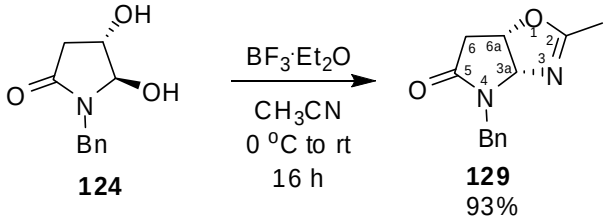
Scheme 3.10. The Holy reaction of arabinose **223** with cyanamide.

Jenkinson[82] demonstrated the Holy reaction of 2-*C*-methyl arabinose **223** to form the oxazoline **224** in 62% yield by treatment with cyanamide and ammonium hydroxide at 80 ^{o}C (**Scheme 3.10**).

3.1.1. Ritter Reactions of (4*S*)-1-Benzyl-4,5-dihydroxypyrrolidin-2-one

With the aim of preparing the pyrrolo[2,3-*d*]oxazole **129** in good yield, the pyrrolidinone **124** was first treated with 2.0 mol equivalents of $BF_3.Et_2O$ in CH_3CN at 0 ^{o}C to rt for 16 h. This reaction provided the pyrrolo[2,3-*d*]oxazole **129** in 88% yield (**Table 3.3**, Entry 1). The use of 3.0 or 4.0 mol. equivalents of $BF_3.Et_2O$ under the same experimental conditions afforded the oxazole **129** in slightly enhanced yields of 93% and 91%, respectively (**Table 3.3**, Entries 2 and 3). Increasing the amount of $BF_3.Et_2O$ above 3.0 mol equivalents did not cause much of a difference in the yield of the reaction, thus we decided to use 3.0 mol. equivalents of $BF_3.Et_2O$ in future reactions. The effects of the concentration of **124** on the yield of **129** was also investigated. Repeating the reaction at 0.05 M and 0.2 M concentrations gave the desired product **129** in 90% and 91% yields, respectively (**Table 3.3**, Entries 4 and 5). The molar equivalents of $BF_3.Et_2O$ and the concentration of **129** did not have much of an affect on the yield of this reaction.

Table 3.3. Results of reaction of **124** with CH_3CN.



124 **129** 93%

Entry	Eq. of $BF_3.Et_2O$	Concentration of **124**	Yield% of **129**
1	2.0	0.1M	88
2	3.0	0.1M	93
3	4.0	0.1M	91
4	3.0	0.05M	90
5	3.0	0.2M	91

The structure of **129** was confirmed from NMR spectroscopic analysis. In the ^{1}H NMR spectrum of **129** (**Figure 3.2**) the diastereotopic H6 protons resonated at 2.85

(1H, dd, J = 7.5, 18.5 Hz) and 2.69 (1H, d, J = 18.5 Hz) ppm. The coupling constants for $J_{6\alpha,6\beta}$ was 18.5 Hz, $J_{6\beta,6a}$ was 7.5 Hz and $J_{6\alpha,6a}$ was 0 Hz. H6a resonated at 4.90 (1H, t, J = 7.5 Hz) ppm, while H3a resonated more downfield at 5.38 (1H, d, J = 7.5 Hz) ppm. $J_{3a,6a}$ was 7.5 Hz. The dihedral angles calculated from molecular modelling studies using Spartan 04 (AMI) of **129** were consistent with the observed J values. The dihedral angles (ϕ) calculated for H6α and H6a was 96.6 ^{o}, indicative of a very small coupling constant (**Figure 3.4**), consistent with the observed 0 Hz coupling. The dihedral angle calculated for H6β and H6a was -28.6 ^{o}, indicative of a relatively large coupling constant consistent with that observed (7.5 Hz). The methyl protons were observed at 2.03 ppm as a singlet. The ^{13}C NMR spectrum of **129** (**Figure 3.3**) was also consistent with the structure. The carbonyl carbon resonated at 170.7 ppm, while the quaternary carbon C2 resonated at 168.8 ppm. The DEPT spectrum of **129** showed two methine carbon resonances at 83.2 and 74.4 ppm corresponding to the C3a and C6a carbons, respectively and two methylene carbon signals at 44.2 and 37.5 ppm corresponding to C1` and C6, respectively. The methyl carbon resonance was observed at 14.1 ppm in the ^{13}C NMR spectrum. The LREIMS spectrum of **129** showed a molecular ion peak at 230 amu. Its molecular formula was found to be $C_{13}H_{14}N_2O_2$ from HREIMS analysis which was consistent with the structure of **129**. The C=O bond stretch was observed at 1680 cm^{-1} in its IR spectrum.

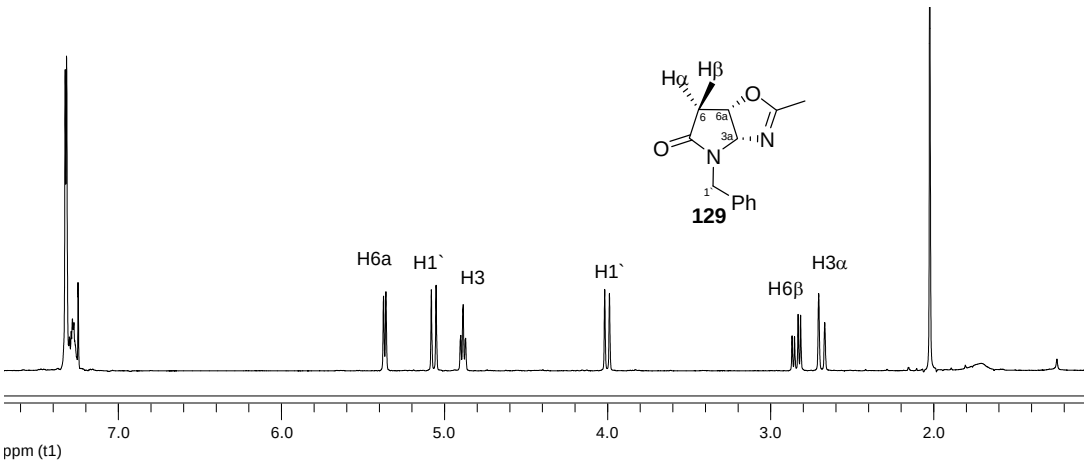


Figure 3.2. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **129**.

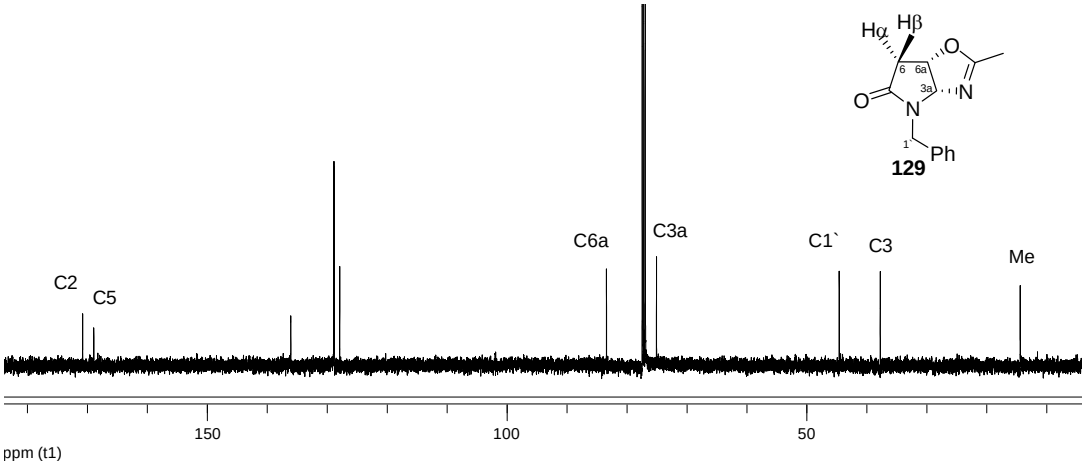


Figure 3.3. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **129**.

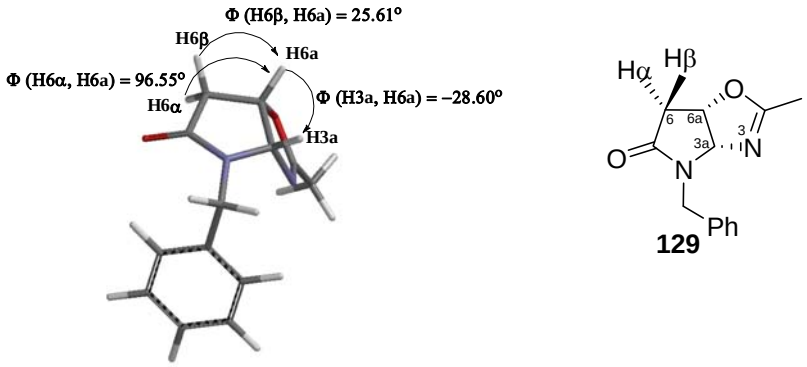
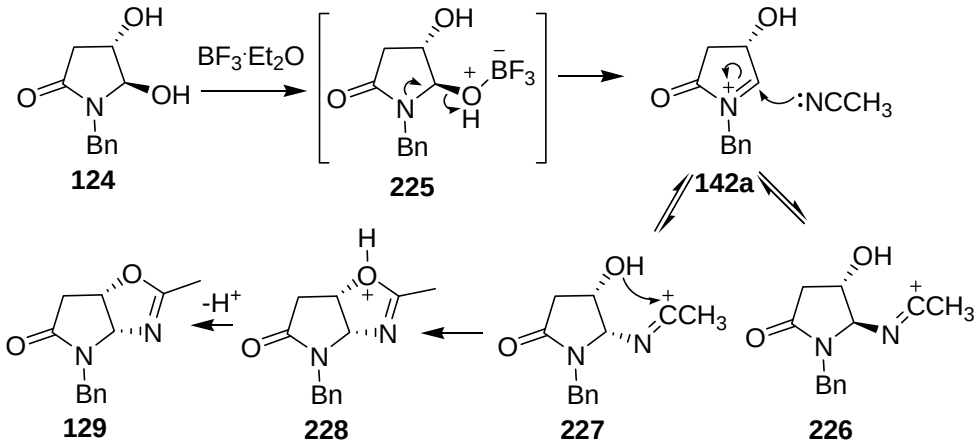


Figure 3.4. Calculated dihedral angles of **129** using Spartan 04 (AMI).

The reaction of **124** with CH_3CN was remarkable for providing the Ritter adduct **129** in high yield and total diastereoselectivity. The ^1H NMR spectrum of **129** showed only one diastereoisomer. This result was unexpected since *N*-acyliminium ions can be attacked by nucleophiles from either face which results in the formation of both diastereomers. To explain the high yield and diastereoselectivity of the reaction, we suggested that the attack of nitriles to the *N*-acyliminium ion was reversible[81-83] and gave a mixture of 4,5-*trans* pyrrolidinone **226** and 4,5-*cis* pyrrolidinone **227** isomers. The 4,5-*cis* pyrrolidinone **227** cyclises to the oxazolidine cationic intermediate **228** more rapidly resulting in the formation of only the *cis* isomer. Deprotonation of the intermediate **228** gives the observed oxazolidine **129** (**Scheme 3.11**). Consistent with this hypothesis were the calculated heats of formation of the *cis* and *trans* isomers of **129** using Spartan 04 (AMI). The heat of formation of the *cis* isomer was -14.4 kcal/mol, while that of the *trans* isomer was 24.3 kcal/mol. The *cis* isomer, whose

heat of formation was 38.7 kcal/mol less than *trans* isomer, was predicted to be thermodynamically much more stable.



Scheme 3.11. Proposed mechanism for the formation of **129**.

A 2D NOESY experiment on **129** also confirmed its *cis* stereochemistry. The protons H3a and H6a showed a cross peak which indicates a *cis* relation between these two protons (**Figure 3.5**). There were also cross peaks observed between the protons H6a and H6β and the protons H6β and H6α.

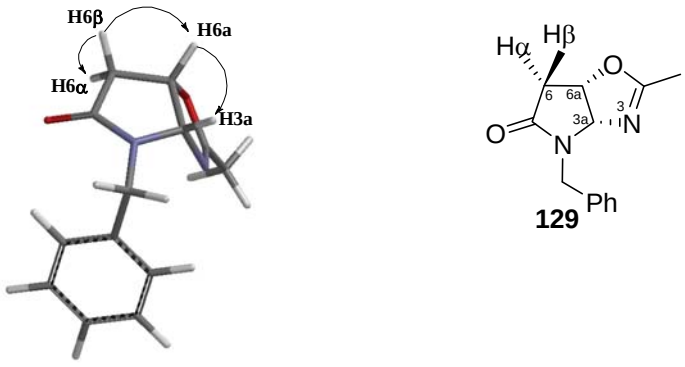
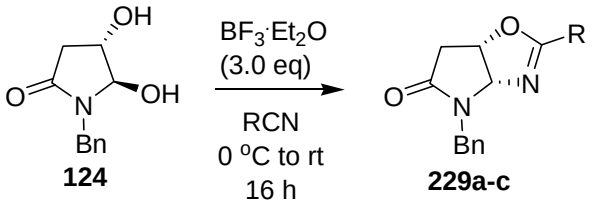


Figure 3.5. The observed NOE correlations of **129**.

Next the pyrrolidinone **124** was treated with isopropylnitrile under the same reaction conditions to give the corresponding pyrrolo[2,3-*d*]oxazole **229a** in 90% yield as one isomer (**Table 3.4**, Entry 1). Aromatic nitriles were also tried in this reaction and they also worked well. The reaction of **124** with benzonitrile provided the desired Ritter product **229b** in 86% yield, while that of 3,4-dimethoxybenzonitrile furnished the desired adduct **229c** in 91% yield (**Table 3.4**, Entries 2 and 3). All reactions

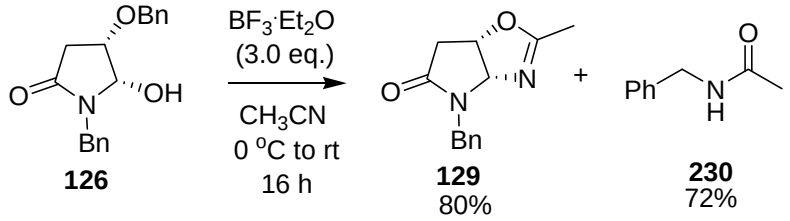
worked well without the formation of any detectible side products. Their TLC analysis showed only one spot which was the product. Their ^{1}H and ^{13}C NMR spectra were consistent with their structures. LREIMS analysis confirmed the structures of compounds **229a-c** possessing molecular ions consistent with their structures at, 258, 292 and 352 amu, respectively.

Table 3.4. Ritter reactions of **124**.



Entry	Compound no	R	Yield%
1	**229a**	$(CH_3)_3CH$	90
2	**229b**	Ph	86
3	**229c**	3,4-$MeOC_6H_4$	91

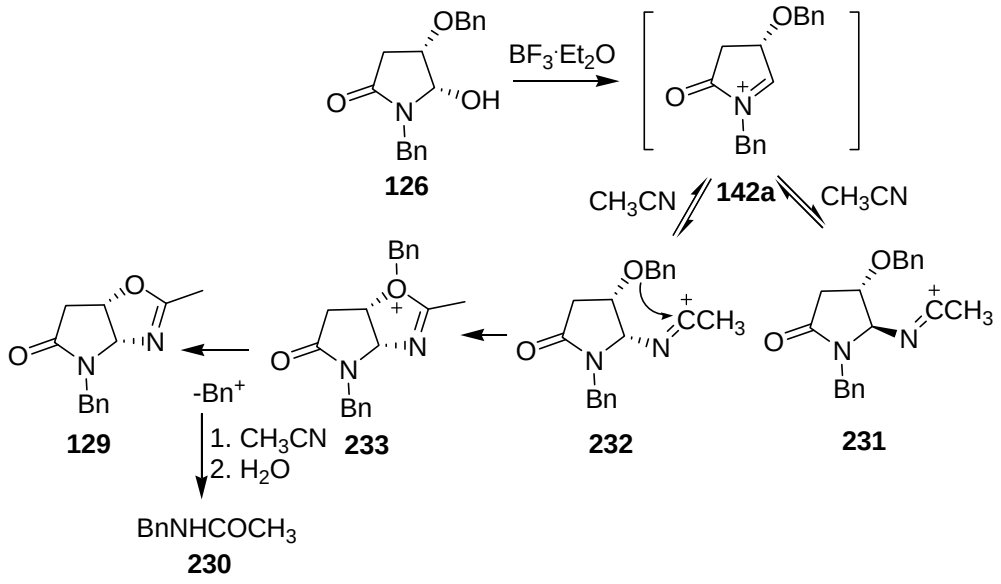
After having very high yields and diastereoselectivities from the Ritter reactions of **124**, we decided to investigate the Ritter reactions of pyrrolidinone **126**. The pyrrolidinone **126** was first treated with CH_3CN in the presence of $BF_3.Et_2O$ (3.0 eq.) to afford the Ritter product **129** in 80% yield as one isomer and the known compound *N*-benzylacetamide **230** in 72% yield (**Scheme 3.12**). The ^{1}H and ^{13}C NMR spectra of the Ritter product **129** was identical to that of the product that was obtained from the reaction of diol **124** with CH_3CN (**Table 3.3**). Amide **230** was identified from a comparison of its NMR spectra with that reported in the literature.[84]



Scheme 3.12. Reaction of **126** with CH_3CN.

The proposed mechanism (**Scheme 3.13**) for the Ritter reaction of **126** is similar to that proposed for the reaction of **124** with CH_3CN (**Scheme 3.11**) except for the

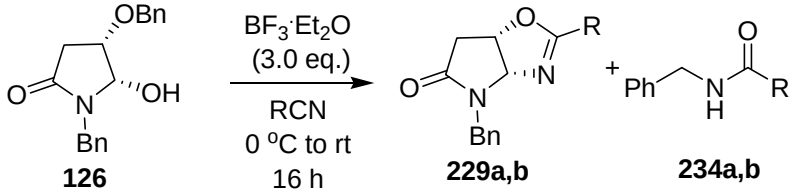
deprotonation step. In this case, instead of deprotonation of cation intermediate **233**, debenzylation occured and the benzyl cation underwent a Ritter reaction with CH_3CN to yield *N*-benzylacetamide **230** after an aqueous work up.



Scheme 3.13. Proposed mechanism for the Ritter reaction of **129** and formation of **230**.

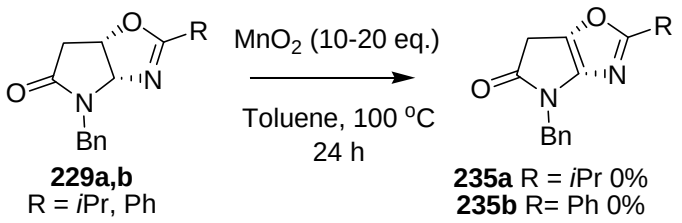
The reaction of **126** with isopropylnitrile and benzonitrile under the same experimental conditions yielded the corresponding oxazoles **229a** and **229b** in 87% and 80% yields, respectively and the known amide products *N*-benzylisobutylamide **234a**[85] and *N*-benzylbenzamide **234b**[86] in 77% and 63% yield, respectively (**Table 3.5**, Entries 1 and 2). The ^{1}H and ^{13}C NMR spectra of **229a** and **229b** were identical to those of the products that were obtained from the reactions of **124** with isopropylnitrile and benzonitrile, respectively.

Table 3.5. Results of Ritter reaction of **126**.



Entry	R	Yield% of 229	Yield% of 234
1	$(CH_3)_2CH$	87	77
2	Ph	80	63

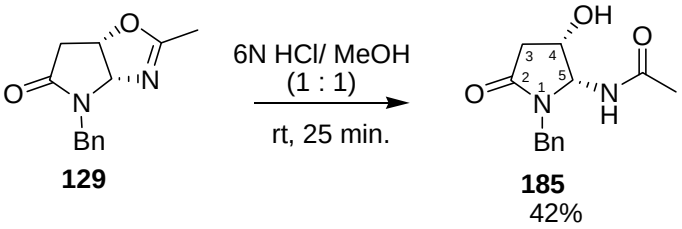
We attempted to oxidize products **229a** and **229b** with MnO_2 (10 or 20 eq.) in toluene with heating at 100 ^oC for 24 h (**Scheme 3.14**). These oxidation reactions did not give the desired oxazole products **235a,b** and only unreacted starting material was recovered.



Scheme 3.14. Attempted oxidation reactions of **229a** and **229b**.

3.2. Hydrolysis of Pyrrolo[2,3-*d*]oxazoles

Next the pyrrolo[2,3-*d*]oxazoles **129** and **229a** were converted to the 2-acylaminopyrrolidinones through acidic hydrolysis. The Ritter product **129** was treated with 6N HCl in MeOH at rt for 25 min to give the corresponding 2-acylaminopyrrolidinone **185** in 42% yield (**Scheme 3.15**).



Scheme 3.15. Acidic hydrolysis of **129**.

The product **185** was identified from analysis of its ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum showed a signal at 5.55 (1H, d, J = 6.5 Hz) ppm, corresponding to the H5 proton, and at 4.39 (1H, app. br. q, J = 6.5 Hz) ppm corresponding to the H4 proton. The $J_{4,5}$ value of 6.5 Hz indicated the *cis* 4,5-stereochemistry. The signals for the diastereotopic hydrogens H3 appeared at 2.68 (1H, dd, J = 6.5, 17.5 Hz) and 2.46 (1H, dd, J = 4.5, 17.5 Hz) ppm. The methyl protons resonated at 1.88 ppm as a singlet. However the signals of the NH and OH protons could not be observed in the ^1H NMR spectrum of **185** (**Figure 3.6**) due to rapid exchange with the NMR solvent CD_3OD. However, a broad peak at 3318 cm^{-1} in its IR spectrum clearly indicated the

existence of these groups. The ^{13}C NMR spectrum was also consistent with the structure of **185** and showed resonances at 174.9 and 173.9 ppm for the two carbonyl carbons.

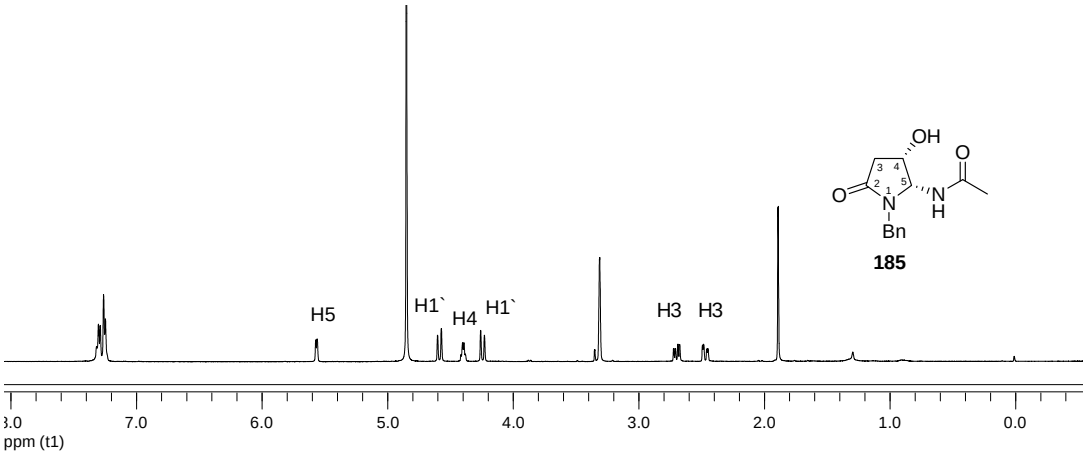
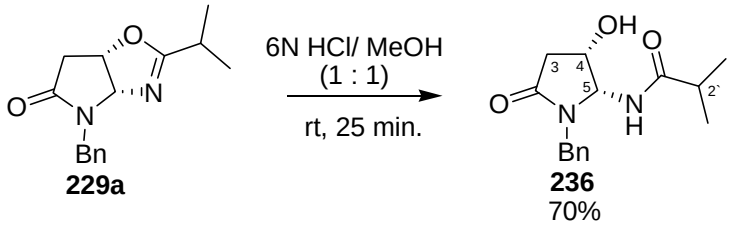


Figure 3.6. ^{1}H NMR (500 MHz, CD_3OD) spectrum of **185**.

When the oxazole **229a** was subjected to the same acid hydrolysis reaction conditions the corresponding 2-acylaminopyrrolidinone **236** was obtained in 70% yield (**Scheme 3.16**).



Scheme 3.16. Acidic hydrolysis of **229a**.

In this case, the product was soluble in $CDCl_3$ and the NH and OH proton signals of **238** were observed at 6.40 (1H, d, J = 9.0 Hz) and 3.87 (1H, d, J = 4.5 Hz) ppm, respectively in the ^{1}H NMR spectrum (**Figure 3.7**). The methine protons H5 and H4 resonated at 5.58 (1H, dd, J = 5.5, 9.0 Hz) and 4.36 (1H, br. t, J = 5.5 Hz) ppm, respectively. $J_{4,5}$ was 5.5 Hz, indicative of a *cis* relation between H4 and H5. The ^{13}C NMR spectrum was also consistent with the structure of **236** and it showed signals at 177.9 and 172.3 ppm corresponding to two carbonyl carbons. The DEPT spectrum showed three methine carbon signals at 66.2, 65.1 and 35.5 ppm corresponding to

C5, C4 and C2`, respectively and two methylene carbon resonances at 44.2 and 39.1 ppm corresponding to CH_2Ph and C3, respectively. The signals for the diastereotopic methyl carbons were observed at 19.2 and 19.1 ppm. The IR spectrum of **236** also confirmed the structure showing a broad peak at 3291 cm^{-1} for the N-H and O-H stretches and two sharp peaks at 1663 and 1649 cm^{-1} for the two C=O stretches.

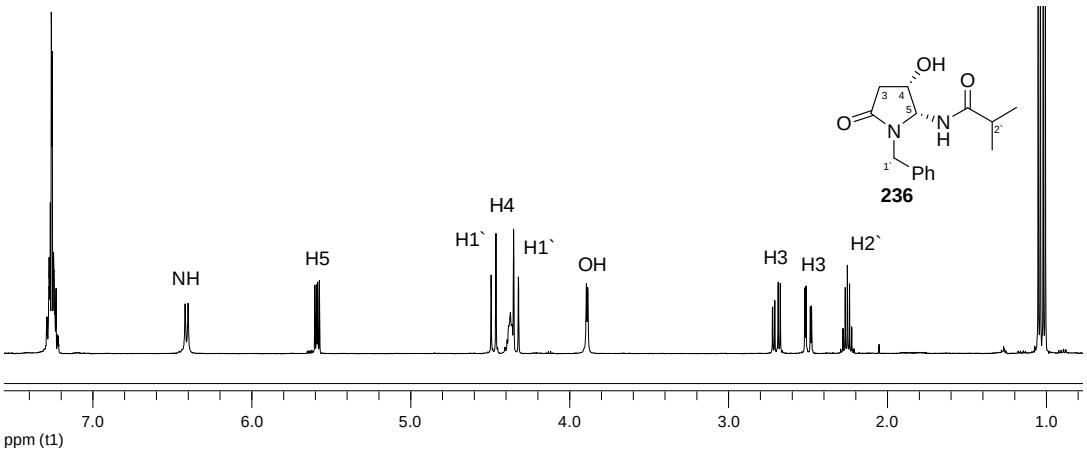
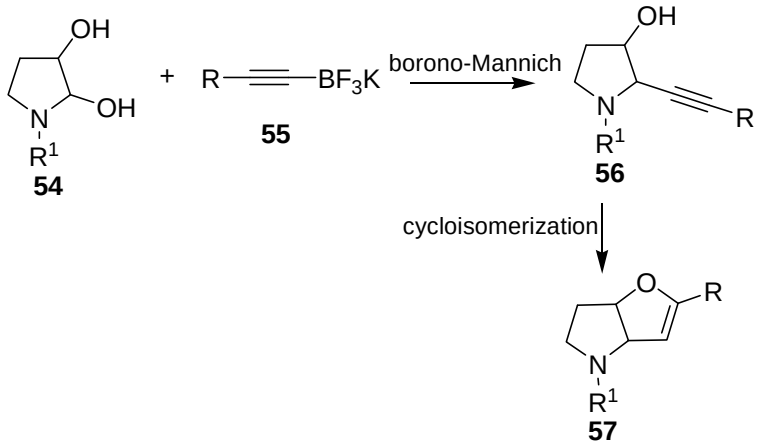


Figure 3.7. ^1H NMR (500 MHz, $CDCl_3$) spectrum of **236**.

In conclusion, a high yielding and diastereoselective method has been developed to prepare chiral pyrrolo[3,2-*d*]oxazoles using the Ritter reaction of 5-hydroxy or 5-benzyloxy-4-hydroxypyrrolidin-2-one with nitriles in the presence of $BF_3.Et_2O$. When the 4-benzyloxy-5-hydroxypyrrolidin-2-one substrate was used the corresponding *N*-benzyl amides were isolated from the Ritter reactions of benzyl cation and the nitrile. The isolation of these compounds were consistent with our proposed reaction mechanism. Two of the pyrrolo[3,2-*d*]oxazoles compounds were hydrolyzed to the novel 5-acylaminopyrrolidinones, **185** and **236**.

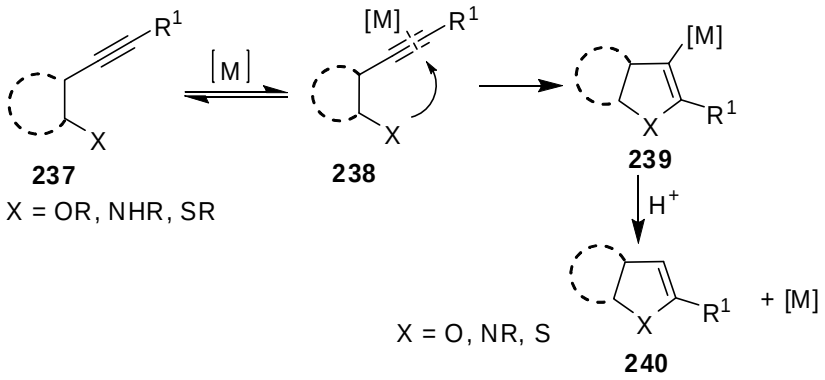
4. METAL CATALYZED CYCLOISOMERIZATION REACTIONS AND COPPER MEDIATED CYCLIZATION-HALOGENATION AND CYCLIZATION-CYANATION REACTIONS OF 2-ALKYNYL-3-HYDROXY PYRROLIDINES

In Chapter 2 we reported the borono-Mannich reactions of pyrrolidines, having an *endo*-cyclic *N*-acyl group, with alkenyl and aryl boronic acids and borates. In this Chapter we focused on the borono-Mannich reaction of pyrrolidines **54**, having an *exo*-cyclic *N*-acyl group, with alkynyl boronates **55** and the metal-catalyzed cycloisomerization reactions of the borono-Mannich adducts **56** (**Scheme 4.1**). These adducts **56** can in principle be cyclised to novel furo[3,2-*b*]pyrroles **57** which is the common heterocyclic nucleus of the biologically active alkaloids, lucilactaene,[40] 13α-lucilactaene[87] **47**, UCS1025A **49** and fusarin A **48** which were discussed in Chapter 1, Section 1.8.



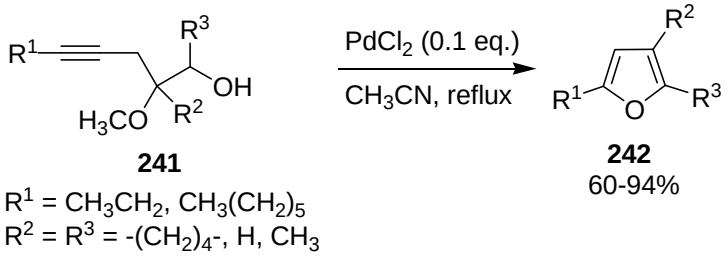
Scheme 4.1. Proposed sythesis of furo[3,2-*b*]pyrroles **57**.

Metal-catalysed cycloisomerization of alkynes is a well known method for the construction of heterocyclic systems. Pd(II), Pt(II), Ag(I), $Ru(CO)_{12}$, Au(I), Au(III), Cu(I) and Zn(II) salts have been used as catalyst in the cyclization reactions of alkynes.[88-97] These transformations involve the fast and reversible complexation of the alkyne by the metal salt [M]. The resulting electrophilic alkyne complex **238** is reactive towards nucleophiles. Intramolecular nucleophilic attack on the alkyne complex results in the formation of the heterocyclic intermediate **239**. Protonolysis of **239** gives the cycloisomerization product **240** and releases the metal catalyst [M] (**Scheme 4.2**).

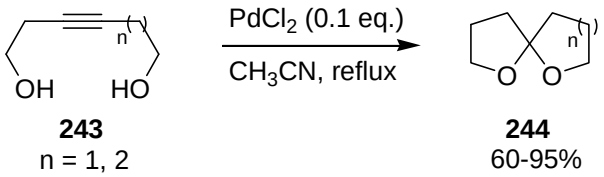


Scheme 4.2. Mechanism of metal-catalyzed cycloisomerization reactions of alkynes **237**.

The metal-catalyzed cyclization of alkynes bearing an oxygen nucleophile is a powerful method for the construction of various oxygen-containing heterocycles. Utimoto[98] first reported the Pd(II)-catalyzed cyclization of 2-methoxy-3-alkyn-1-ols **241** to 2,3,5-trisubstituted furans **242** in good yields (**Scheme 4.3**). Treatment of alkynediols **243** with Pd(II) under the same experimental conditions gave spirocyclic acetals **244** through intramolecular addition of two hydroxyl groups to the internal alkyne (**Scheme 4.4**).



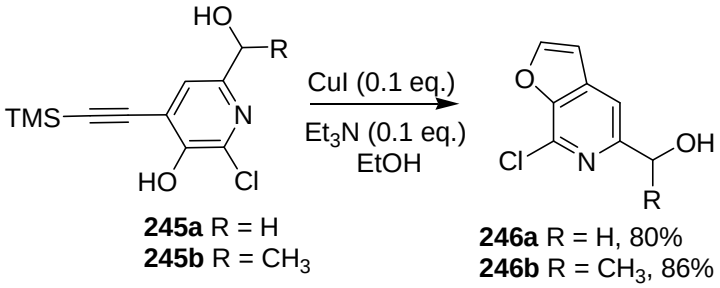
Scheme 4.3. Utimoto`s synthesis of furans **242**.



Scheme 4.4. Synthesis of **244**.

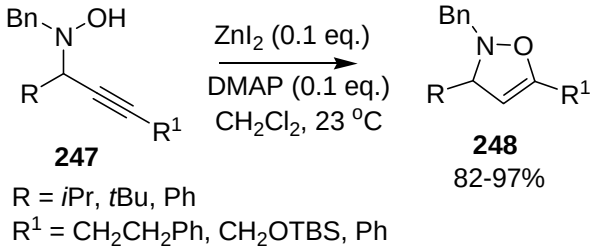
The furopyridines **246a,b** were obtained from the cyclization reactions of 4-acetylenic pyridines **245a,b** in the presence of CuI (**Scheme 4.5**).[99] The TMS group did not survive under the reaction conditions. Cyclization of **245a** produced the

corresponding furopyridine **246a** in 80% yield, while **245b** afforded the furopyridine **246b** in 86% yield.



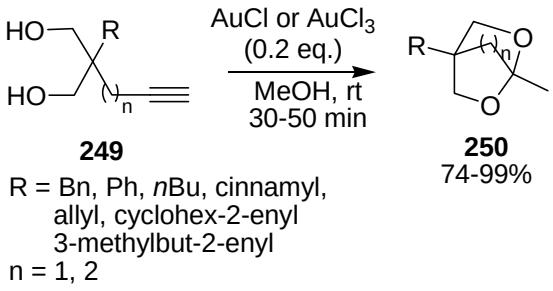
Scheme 4.5. Synthesis of furopyridines **246a** and **246b**.

Carreira[100] used ZnI_2 as a catalyst in the cyclization of *N*-hydroxylamines **247** to 2,3-dihydroisoxazoles **248** (**Scheme 4.6**). Treatment of *N*-hydroxylamines with ZnI_2 (0.1 eq.) and DMAP (0.1 eq.) in CH_2Cl_2 furnished the cyclic products in yields of 82-97%. However, using other Lewis acids ($BF_3.Et_2O$, $AlCl_3$, $Cu(OTf)_2$, $Mg(OTf)_2$ and $Sn(OTf)_2$) together with DMAP in the same reaction did not provide the desired 2,3-dihydroisoxazoles.



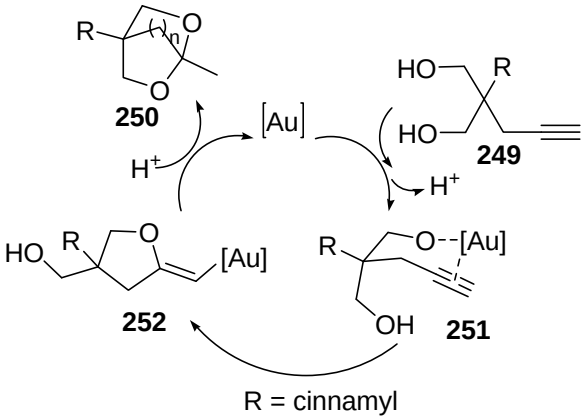
Scheme 4.6. Synthesis of 2,3-dihydroisoxazoles **248**.

Genet[101] reported the cyclization of *bis*-homopropargylic diols **249** under gold catalysis. The reactions of homopropargylic diols **249** with AuCl or $AuCl_3$ provided easy access to the strained bicyclic ketals **250** under mild conditions (**Scheme 4.7**). The reaction did not give any of the bicyclic ketal product in the absence of the metal. In most cases the reaction had completed in 30 min, the longest reaction time was 50 min.



Scheme 4.7. Preparation of bicyclic ketals **250**.

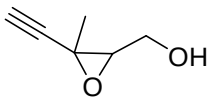
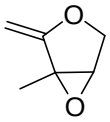
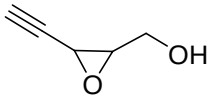
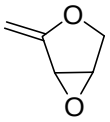
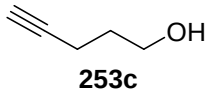
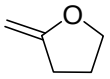
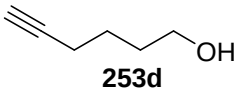
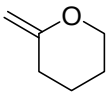
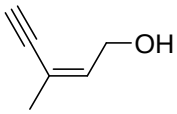
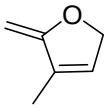
In a plausible mechanism for this reaction the Au catalyst forms the complex **251** with the triple bond (**Scheme 4.8**). The coordination to triple bond enchances the electrophilicity of the alkyne, which allows the addition of one alcohol to the triple bond. Protonolysis of the enol vinylgold intermediate **252** leads to an enol ether, which then undergoes a second intramolecular addition of the alcohol group to provide the product **250**.



Scheme 4.8. Proposed mechanism for the formation of bicyclic ketals **250**.

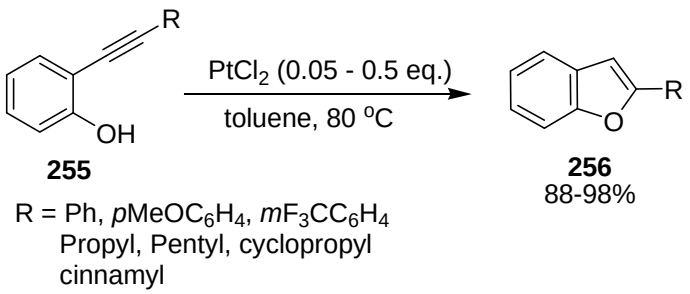
Silver has also found to be effective catalyst in the cycloisomerization of alkynols. 2-Methylene–oxolanes were prepared from the reaction of acetylenic alcohols **243a-e** with Ag_2CO_3. A catalytic amount of Ag_2CO_3 was enough for cyclic substrates **253a,b**, in which the two reacting parts of the molecule were close together (**Table 4.1**, Entries 1 and 2), while other substrates **253c-e** needed stoichiometric amounts of Ag_2CO_3 (**Table 4.1**, Entries 3, 4 and 5).[102]

Table 4.1. Synthesis of 2-methylene-oxolanes **254a-e**.

Entry	Alkynol 253	Amount of Ag_2CO_3	Product 254	Yield%
1	 **253a**	10 mol %[a]	 **254a**	99
2	 **253b**	10 mol%[a]	 **254b**	90
3	 **253c**	100 mol%[b]	 **254c**	90
4	 **253d**	100 mol%[b]	 **254d**	90
5	 **253e**	100 mol%[c]	 **254e**	95

a) Reactions were performed in benzene at 80 °C for 1 h, b) Reactions were performed in C_6D_6 at 80 °C for 6 h. c) Reaction was performed in C_6D_6 at 20 °C for 2 h.

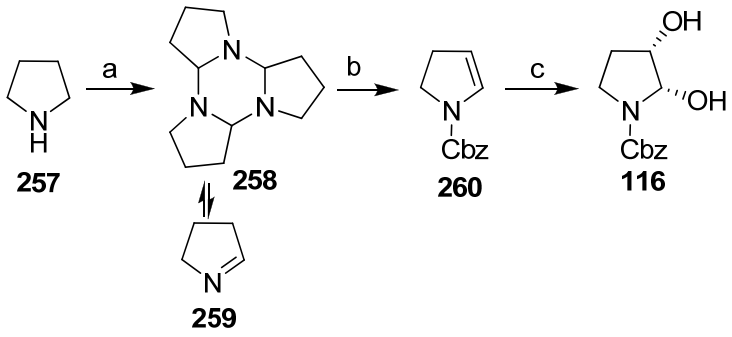
Fürstner[103] showed $PtCl_2$ was an effective catalyst in the cycloisomerization reactions of *ortho*-alkynylphenols **255**. Treatment of *ortho*-alkynylphenols **255** with $PtCl_2$ in toluene at 80 °C furnished the 2-subtituted benzofurans **256** in yields of 88-98% (**Scheme 4.9**).



Scheme 4.9. Synthesis of 2-substituted benzofurans **256**.

4.1. Borono-Mannich Reactions of Benzyl 2,3-Dihyroxypyrrolidine-1-carboxylate

The two components of the borono-Mannich reaction were not commercially available. The *N*-acyliminium ion precursor, benzyl 2,3-dihyroxypyrrolidine-1-carboxylate[66] **116**, was prepared in three steps from pyrrolidine **257** following a known procedure (**Scheme 4.10**). The first step was the silver(I)-catalyzed oxidation of pyrrolidine **257** to the 1-pyrrolidine trimer **258** with $Na_2S_2O_8$ in water.[104] The second step was the *N*-acylation of trimer with CbzCl in THF to give **260.**[105] The third step was the dihydroxylation of double bond with $K_2OsO_4{\cdot}2H_2O$ to give **116**.[106] Although the first step looked simple we had many problems in making the trimer. A suspension of pyrrolidine, NaOH, $AgNO_3$ in water was treated with aqueous solution of $Na_2S_2O_8$ below 10 ^oC as indicated in the literature. Since the temperature of the reaction after adding the $Na_2S_2O_8$ was not mentioned, the reaction mixture was first stirred at rt which did not give the desired oxidation product. The reaction was also performed at 10 ^oC or 0 ^oC but none of these reactions gave the desired trimer. However the use of a fresh bottle of $Na_2S_2O_8$ and stirring the reaction mixture at rt furnished the trimer **258** in 50% yield. The freshness of the $Na_2S_2O_8$ was found to be crucial in this reaction. The freshly prepared trimer **258** was subjected to a *N*-acylation reaction with CbzCl in the presence of Et_3N. A 0.1 M THF solution of the trimer was distilled into a flask precooled to -78 ^oC and then was treated with Et_3N and CbzCl to afford the desired *N*-Cbz pyrrolidine **260** in 60% yield. The dihydroxylation of the double bond of **260** worked smoothly to give the desired diol **116** in 85% yield as a single isomer.

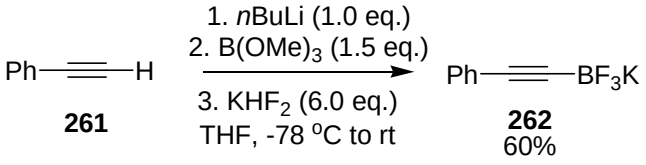


Reagents and conditions: a) $Na_2S_2O_8$ (1.0 eq), $AgNO_3$ (5.0 eq.), NaOH (2.0 eq.), H_2O, 10 ^oC to rt, 50%; b) CbzCl (3.0 eq.), Et_3N (3.0 eq.), THF, -78 ^oC to rt, 60%; c) $K_2OsO_4{\cdot}2H_2O$ (0.05 eq.), NMO (2.0 eq.), $(CH_3)_2CO/H_2O$ (3 : 2), rt, 85%.

Scheme 4.10. Synthesis of diol **116**.

It should be noted that compound **116** is racemic and therefore all chiral derivatives or products arising from this compound are also racemic. In many cases these chiral derivatives or products are drawn as a single enantiomers, this is to show the relative configuration of the molecule.

The other component of the borono-Mannich reaction, potassium phenylethynyltrifluoroboronate **262**, was synthesized from the reaction of phenylacetylene **261** with *n*BuLi followed by treatment of the corresponding lithium acetylide with trimethylborate. Treatment of the resulting boronate ester with KHF_2 provided the potassium phenylethynyltrifluoroborate **262** in 60% yield (**Scheme 4.11**).[107,108]

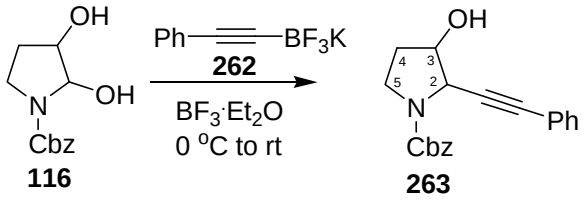


Scheme 4.11. Synthesis of **262**.

Having both components of the reaction in hand, the borono-Mannich reaction of **116** and **262** was performed in CH_2Cl_2 with 3.0 mol equivalents of **262** and 4.0 mol equivalents of $BF_3.Et_2O$ at 0 ^oC to rt for 16 h. The desired product was obtained in 46% yield with a diastereomeric ratio of 64 : 36 (**Table 4.2**, Entry 1). These isomers could be separated by column chromatography. Although we obtained the desired addition product the yield of the reaction was not satisfactory. The amounts of the trifluoroborate component and the Lewis acid component in the borono-Mannich reaction were increased to 5 mol equivalents which furnished the desired product in 50% yield (**Table 4.2**, Entry 2). In order to increase the yield of the desired product the reaction was repeated in $MeNO_2$ and $CHCl_3$ which provided the desired adduct in respective yields of 39% and 52% (**Table 4.2**, Entries 3 and 4). The use of CH_3CN as a solvent in the reaction was expected to give low yields, since it can react with the *N*-acyliminium ion intermediate to give the Ritter product. However, the borono-Mannich adduct **263** was obtained in a very high yield of 89% as a 73 : 27 diastereomeric mixture (**Table 4.2**, Entry 5). The ^1H NMR spectrum of the crude reaction mixture did not show any signals that could be related to the possible Ritter product. The isomers of **263** could be separated by column chromatography. The ^1H

and ^{13}C NMR spectra of the individual isomers were in good agreement with their structures. In the ^{1}H NMR spectrum of the major product, the H3 proton resonated at 4.85 (1H, br. s) ppm, while the H2 proton resonated at 4.41-4.32 (1H, m) ppm. The same methine protons, H3 and H2 of the minor isomer resonated at 4.66 (1H, s) and 4.50 (1H, br. s) ppm, respectively. The alkyne carbons of the minor isomer showed signals at 86.3 and 84.2 ppm, while those of the major isomer appeared at 87.2 and 84.0 ppm in ^{13}C NMR spectra. The IR spectrum of the major isomer showed a broad peak at 3421 cm^{-1} corresponding to the O-H stretch, a sharp band at 2245 cm^{-1} corresponding to the C≡C stretch and a sharp peak at 1685 cm^{-1} corresponding to the C=O stretch. Similarly the IR spectrum of the minor isomer showed bands at 3477, 2287 and 1680 cm^{-1} corresponding to the O-H, C≡C and C=O stretches, respectively.

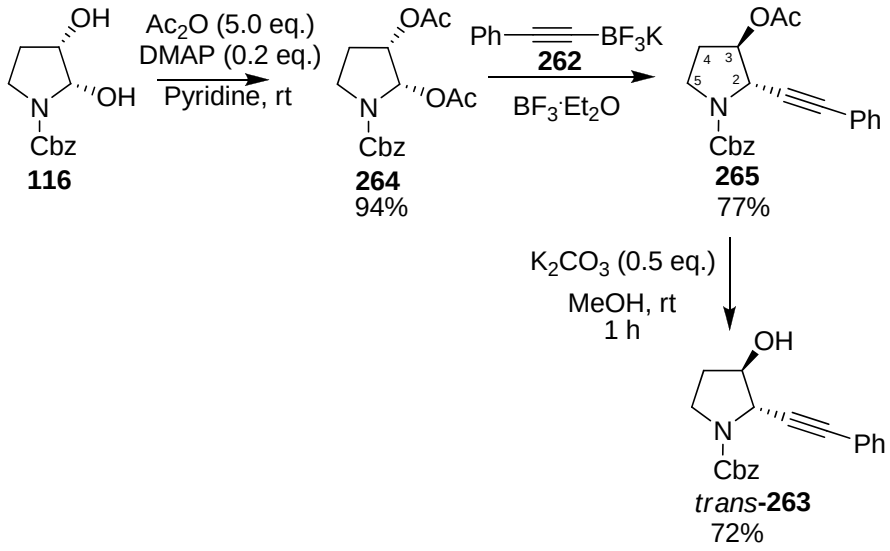
Table 4.2. Optimization of borono-Mannich reaction of **116** and **262**.



Entry	Equivalents of 262	Equivalents of $BF_3.Et_2O$	Solvent	Yield% of 263
1	3	4	CH_2Cl_2	46
2	5	5	CH_2Cl_2	50
3	3	4	CH_3NO_2	39
4	3	4	$CHCl_3$	52
5	3	4	CH_3CN	89

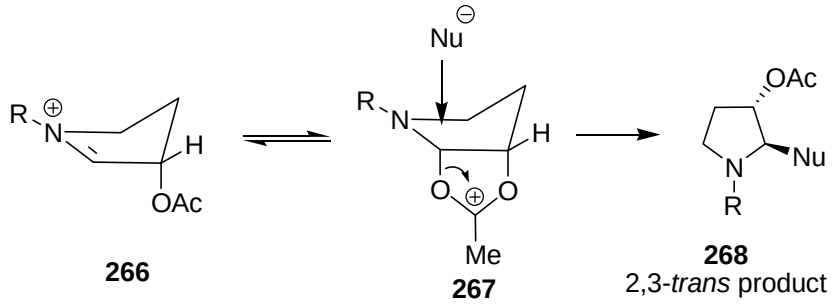
Obtaining **263** as a diastereomeric mixture was unexpected since 2,3-*cis* pyrrolidines was obtained exclusively from the borono-Mannich reaction of **116** with alkenyl or aryl boronates in the literature.[66] Although these isomers of **263** could be separated by column chromatography the signals in the ^{1}H NMR spectrum were broad due to rotamers making the measurement of $J_{2,3}$ difficult. The stereochemistry of these isomers was not clear from NMR spectroscopic analysis. To help determine the stereochemistry, the diacetate derivative of **116** was synthesized and subjected to a borono-Mannich reaction with the same organotrifluoroboronate **262**. The diol **116** was treated with Ac_2O and DMAP in pyridine at rt to give the 2,3-diacetate pyrrolidine **264** in 94% yield. The diacetate **264** was reacted with **262** under the optimized conditions to give the 2,3-*trans* adduct **265** exclusively in 77% yield

(**Scheme 4.12**). For this compound $J_{2,3}$ was found to be 0 Hz from its ^{1}H NMR spectrum which was consistent with the 2,3-*trans* stereochemistry. The methine protons H2 and H3 of the pyrolidine ring of **265** resonated at 4.74 (1H, s) and 5.20 (1H, s) ppm, respectively. The methyl protons resonated at 2.06 (3H, s) ppm. The carbonyl carbon of the acetate group resonated at 170.2 ppm, while that of the Cbz group was at 154.4 ppm. The methyl carbon signal was observed at 21.0 ppm in the ^{13}C NMR spectrum. The adduct **265** was then subjected to a deacetylation reaction by treatment with K_2CO_3 in MeOH at rt to provide the 2,3-*trans* adduct *trans*-**263** in 72% yield (**Scheme 4.12**). The ^{1}H and ^{13}C NMR spectra of *trans*-**263** was identical to that of minor isomer of **263**. It was thus concluded that the major isomer from the reaction of **116** and **262** was the 2,3-*cis* pyrrolidine and the minor isomer was the 2,3-*trans* pyrrolidine.



Scheme 4.12. Synthesis of racemic *trans*-**263**.

The high *trans* selectivity of acetate derivatives can be explained by neighbouring-group participation of the acetate group to give a bridged bicyclic cationic intermediate **267** and then S_N2-like attack of the nucleophile on this intermediate would provide the *trans* adduct **268** (**Scheme 4.13**).[46]

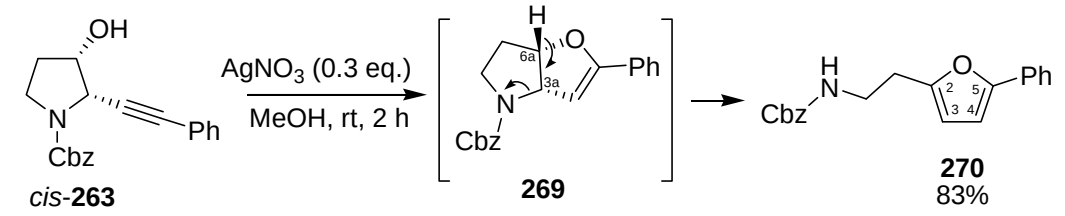


266 **267** **268**
2,3-*trans* product

Scheme 4.13. Formation of the 2,3-*trans* product **268**.

4.2. Metal-Catalyzed Cycloisomerization Reactions of the 2,3-*cis* Pyrrolidine

As mentioned previously the cycloisomerization of alkynols have been performed under the catalysis of a range of metal salts. Salts of the metal cations Ag(I), Pd(II)/Cu(I) and Au(I) were chosen as a catalyst in this project. The 2,3-*cis* pyrrolidine *cis*-**263** was treated with 30 mol% of $AgNO_3$ in methanol at rt for 2 h.[109] The reaction afforded the 2,5-disubstituted furan **270** in a yield of 83% but not the expected furo[3,2-*b*]pyrrole structure **269** (**Scheme 4.14**). It was suggested that the desired bicyclic structure **269** was formed in the reaction first and then underwent a ring opening reaction to form furan **270**. The structure of **270** was clearly identified by the presence of resonances in the ^{13}C NMR spectrum (**Figure 4.2**) corresponding to the C3 and C4 carbons which appeared at 108.7 and 105.7 ppm, respectively. These chemical shifts are typical for the C3 and C4 carbons of furans.[110] The chemical shifts of the C3a and C6a carbons in the desired bicyclic structure **269** were expected to appear between 70-80 ppm. The resonance at 4.92 (1H, br. s) ppm in the ^1H NMR spectrum of **270** (**Figure 4.1**) corresponding to NH proton and was also consistent with the structure of **270**. The H3 and H4 protons resonated at 6.13 (1H, d, J = 3.5 Hz) and 6.54 (1H, d, J = 3.5 Hz) ppm, respectively with a vicinal coupling constant of 3.5 Hz, typical values for $J_{3,4}$ of furans.[110] Furthermore the methylene protons H1` and H2` appeared as a triplet and broad quartet, respectively, consistent with a ring-opened structure. The existence of the N-H and C=O bonds were supported by two bands at 3246 and 1695cm^{-1}, respectively in the IR spectrum. LRESIMS analysis of the compound confirmed the molecular weight of **270** possessing a molecular ion consistent with the structure at 322 amu. The molecular formula of the compound was found to be $C_{20}H_{19}NO_3$ from HRESIMS analysis.



Scheme 4.14. Synthesis of 2,5-disubstituted furan **270**.

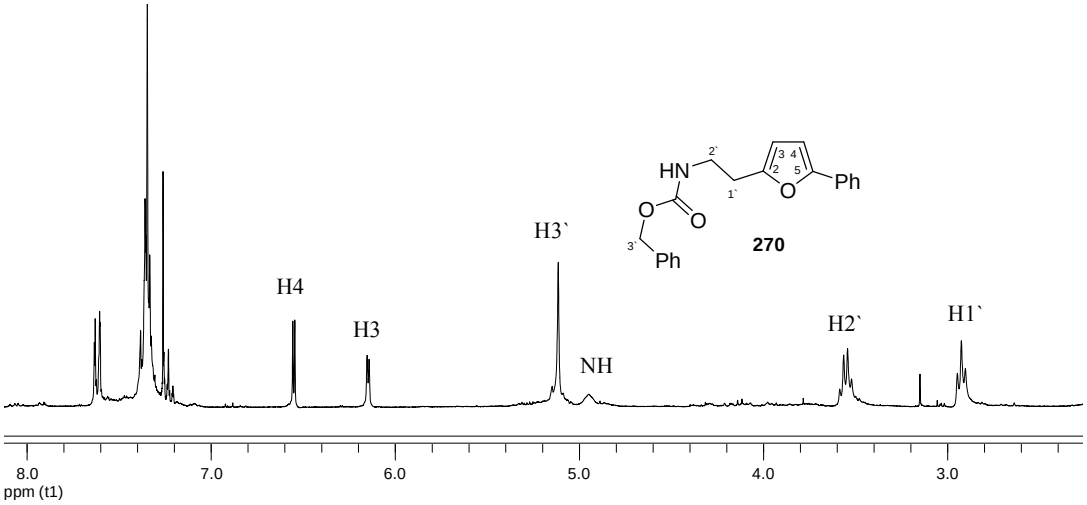


Figure 4.1. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **270**.

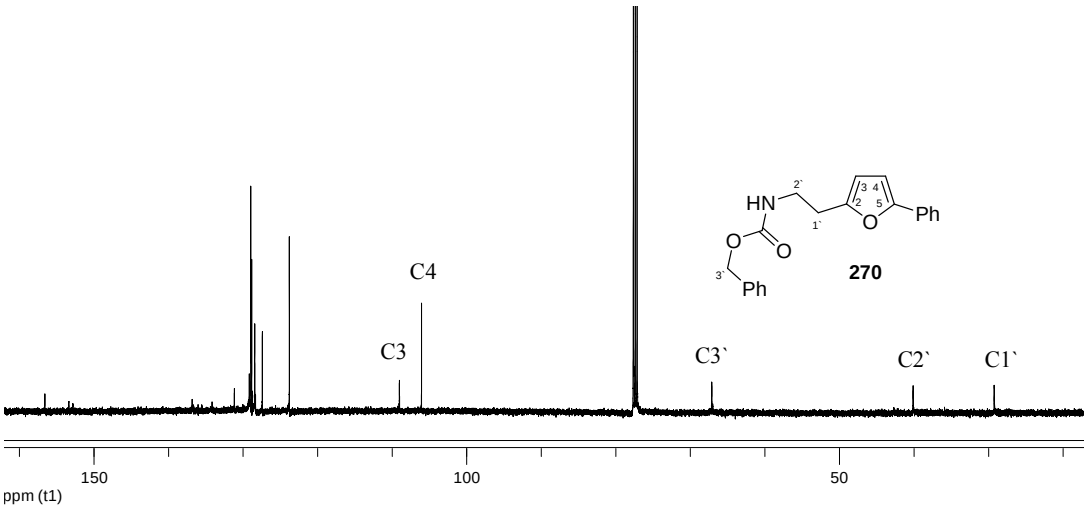
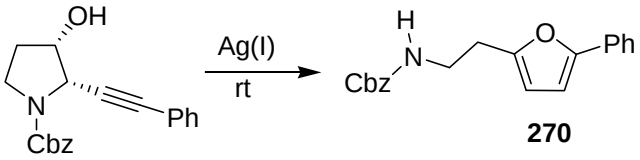


Figure 4.2. ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **270**.

Performing the cycloisomerisation reaction of *cis*-**263** under the catalysis of $AgNO_3$ in DMF at rt for 5 h produced the **270** in 63% yield (**Table 4.3**, Entry 2). When 10 mol % of $AgNO_3$ and MeOH was used, **270** was isolated in 75% yield after 10 h at rt (**Table 4.3**, Entry 3). However while the reaction worked well with the lower load of

catalyst, it needed a longer reaction time for completion. The use of 30 mol % of AgF or Ag_2O as catalyst afforded **270** in 71% and 75% yields, respectively (**Table 4.3**, Entries 4 and 5). Although AgF[102] and Ag_2O were effective catalysts for this transformation, they needed longer reaction times than $AgNO_3$.

Table 4.3. Cycloisomerization of *cis*-**263** with Ag(I).

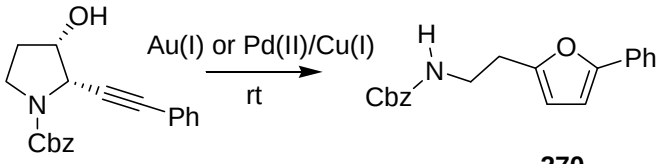


cis-**263** **270**

Entry	Catalyst (mol %)	Solvent	Time	Yield % of 270
1	$AgNO_3$ (30)	MeOH	2 h	83
2	$AgNO_3$ (30)	DMF	5 h	63
3	$AgNO_3$ (10)	MeOH	10 h	75
4	AgF (30)	MeOH	7 h	71
5	Ag_2O (30)	MeOH	8 h	75

We then tried $Au(Ph_3P)Cl$ catalysed reactions of *cis*-**263**. At first the reaction was performed with 30 mol % of $Au(Ph_3P)Cl$ in MeOH at rt for 8 h.[90] Furan **270** was obtained in 87% yield (**Table 4.4**, Entry 1). Although this reaction was slower than that catalyzed by $AgNO_3$, it provided the product in a higher yield than Ag(I). Encouraged by this result and aiming to get a similar yield with a lower load of catalyst, the reaction was repeated with 10 mol % and 5 mol % of $Au(Ph_3P)Cl$ which furnished **270** in 74% and 60% yields, respectively (**Table 4.4**, Entries 2 and 3). The yields of these reactions were good, even with 10 mol% and 5 mol % of catalyst, but the reaction times were 21 h and 3 d, respectively. When 1 mol % of catalyst was used the reaction had not gone to completion even after 5 d. Column chromatography of the reaction mixture yielded **270** in only 22% yield and starting material was isolated in 49% yield. Performing the reaction in DMF with 30 mol % of $Au(Ph_3P)Cl$ at rt for 24 h gave **270** in 70% yield (**Table 4.4**, Entry 4). The use of $PdCl_2(PPh_3)$ (4 mol%) and CuI (5 mol%) as a catalyst system in MeOH at rt for 8 h afforded **270** in 69% yield (**Table 4.4**, Entry 5).[93] Performing this reaction in DMF lowered the yield to 43% (**Table 4.4**, Entry 6). The order of catalyst reactivity in these transformation was found to be Ag(I) > Au(I) > Pd(II)/Cu(I).

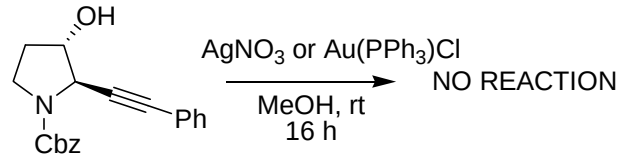
Table 4.4. Cycloisomerization of *cis*-**263** with Au(I) or Pd(II)/Cu(I) catalysts.



cis-**263** **270**

Entry	Catalyst (mol %)	Solvent	Time	Yield % of 270
1	$Au(Ph_3P)Cl$ (30)	MeOH	8 h	87
2	$Au(Ph_3P)Cl$ (10)	MeOH	21 h	74
3	$Au(Ph_3P)Cl$ (5)	MeOH	3 d	60
4	$Au(Ph_3P)Cl$ (30)	DMF	10 h	70
5	$PdCl_2(PPh_3)$ (4)/CuI (5)	MeOH	8 h	69
6	$PdCl_2(PPh_3)$ (4)/CuI (5)	DMF	12 h	43

The cycloisomerization of *trans*-**263** was also investigated. In an initial attempt *trans*-**263** was treated with 30 mol % of $AgNO_3$ in MeOH at rt for 16 h which resulted in only the recovery of unreacted *trans*-**263** quantitatively (**Scheme 4.15**). The use of $Au(Ph_3P)Cl$ (30 mol%) did not give any product, *trans*-**263** was isolated quantitatively. Performing the reaction in DMF with 30 mol % of $AgNO_3$ at 80 ^oC yielded only the starting material.

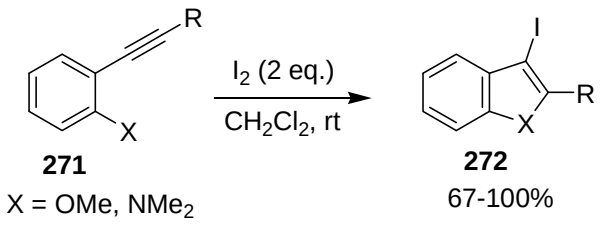


trans-**263**

Scheme 4.15. Results of the treatment of *trans*-**263** with Ag(I) or Au(I).

4.3. Copper Mediated Cyclization-Halogenation and Cyclization-Cyanation Reactions of 2,3-*cis* Pyrrolidine

It is known that cyclization-iodination reactions of alkynols can be achieved by using the electrophilic iodinating agents, I_2, NIS, $I(coll)_2PF_6$ and ICl with or without a base. For example Larock[111] reported the synthesis of iodo benzofurans and iodo indoles from the electrophilic cyclizations of 2-alkynyl phenols and anilines with I_2 (**Scheme 4.16**).

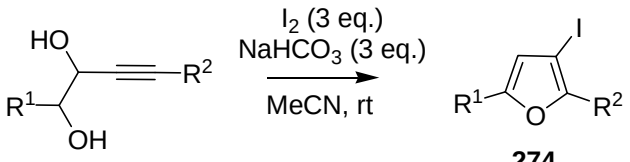


271
X = OMe, NMe_2

272
67-100%

Scheme 4.16. Synthesis of 3-iodobenzofurans and indoles.

Knight[112] reported the cyclization of alk-3-yn-1,2-diols **273** with I_2 in the presence of $NaHCO_3$ to furnished *β*-iodofurans **274** in good yields (**Scheme 4.17**).

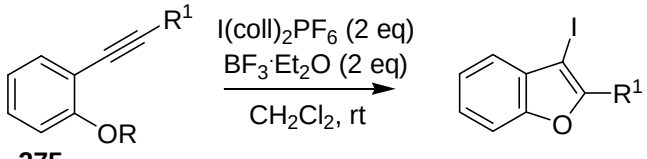


273
R^1 = Me, Ph, CO_2Me
R^2 = Bu, Ph

274
70-95%

Scheme 4.17. Synthesis of iodofurans **274**.

Okitsu[113] showed the synthesis of 3-iodobenzofurans **276** *via* cyclization of 2-alkynyl-1-(1-ethoxyethoxy)benzenes **275** in the presence of $I(coll)_2PF_6$. They found that using $BF_3.Et_2O$ as an additive in the reaction enhanced the reactions rate to give **276** in quantitative yield within 10 min. The iodocyclization reaction worked well with the different substrates to give the 3-iodo-2-substitutedbenzofurans in 70-100% yields (**Scheme 4.18**).



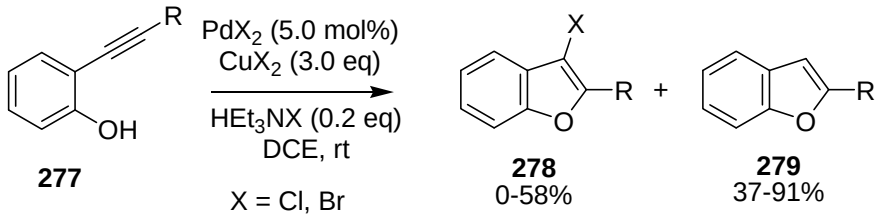
275
R = EE, MOM, THP
R^1 = Ph, *n*Bu, *t*Bu, 2-thienyl, 3-thienyl cyclohexenyl, Bn, $(CH_2)_4OTBS$

276
70-100%

Scheme 4.18. Synthesis of 3-iodobenzofurans **276**.

Cyclization-chlorination and cyclization-bromination reactions of 2-alkynyl phenols were reported by Li.[114] The 2-alkynyl phenols **277** were treated with PdX_2/CuX_2 in

the presence of HEt_3NX in DCE at rt to afford a mixture of 3-halo-2-substituted benzofurans **278** and 2-substituted benzofurans **279** (**Scheme 4.19**). In the presence of PdX_2, 2-substituted benzofurans **279** were obtained in good yields whereas in the presence of PdX_2/CuX_2 and HEt_3NI, 2-substituted-3-halobenzofurans **278** were obtained as the major products.

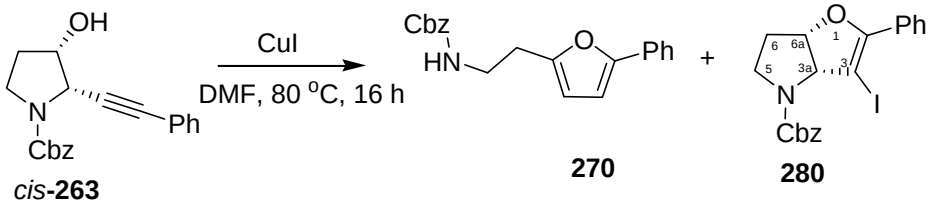


Scheme 4.19. Synthesis of 3-halo-2-substituted benzofurans.

We then tested the Cu(I) salts as a catalyst in the cycloisomerization reaction of **263**. The reaction of *cis*-**263** with 30 mol % of CuI in MeOH at rt did not proceed, *cis*-**263** was recovered quantitatively. However, performing the reaction at 80 ^oC in DMF with with 1 mol equivalent of CuI under a nitrogen atmosphere furnished products **270** and **280** in 55% and 20% yields, respectively (**Table 4.5**, Entry 1). The product **280** was an important compound since it could potentially be a useful intermediate in many palladium-catalyzed processes, like the Sonogashira,[115] Suzuki,[116] and Heck coupling reactions.[117] The structure of **280** was identified from its ^1H and ^{13}C NMR spectra. The ^{13}C NMR spectrum showed a resonance at 83.3 ppm, corresponding to C3a, at 71.7 ppm corresponding to C6a, and at 56.6 ppm corresponding to C3 which was consistent with the structure **280**. The ^1H NMR spectrum (**Figure 4.3**) showed peak broadening due to carbamate rotamers. It showed a resonances at 5.46 (1H, br. s) and 5.33 (1H, s) ppm, corresponding to H3a and H6a, respectively. The IR analysis showed a C=O stretch at 1701 cm^{-1}, but did not show any peak corresponding to a NH stretch which was consistent with the bicyclic structure. LREIMS analysis confirmed the identity of the compound, possessing molecular ions consistent with the structure at 447 amu. With the aim of getting only the iodocyclic product **280**, the reaction was performed with 3.0 mol equivalents of CuI under the same experimental conditions. The products **270** and **280** were obtained again but in a ratio of 25 : 75 and in respective yields of 19% and 52% (**Table 4.5**, Entry 2). However, **280** was isolated as the only product in 65% yield, when 6 mol equivalents

of CuI were used (**Table 4.5**, Entry 3). An attempt to synthesize **280** from the reaction of *cis*-**263** with a catalytic amount of CuI (10 mol %) and LiI (1.5 eq.) failed. The starting material was recovered quantitatively.

Table 4.5. Synthesis of **270** and **280**.



cis-**263** **270** **280**

Entry	Equivalents of CuI	270 : 280[a]	Yield% of 270	Yield% of 280
1	1	77 : 23	55	20
2	3	25 : 75	19	52
3	6	0 : 100	0	65

[a] From ^{1}H NMR analysis of the crude reaction mixture.

The proposed mechanism for the formation of products **270** and **280** involves the coordination of copper to the triple bond to form intermediate **281** and then formation of the organometallic intermediate **282** by nucleophilic attack of oxygen. Protonation of this intermediate gives the bicyclic structure **269** which then underwent an elimination reaction to the 2,5-disubstituted furan **270**. Oxidation of the Cu(I) intermediate **282** to the Cu(II) intermediate **283** by oxygen or by a disproportionation reaction of Cu(I) and then reductive elimination would account for the formation of the iodocyclic product **280** (**Scheme 4.20**).

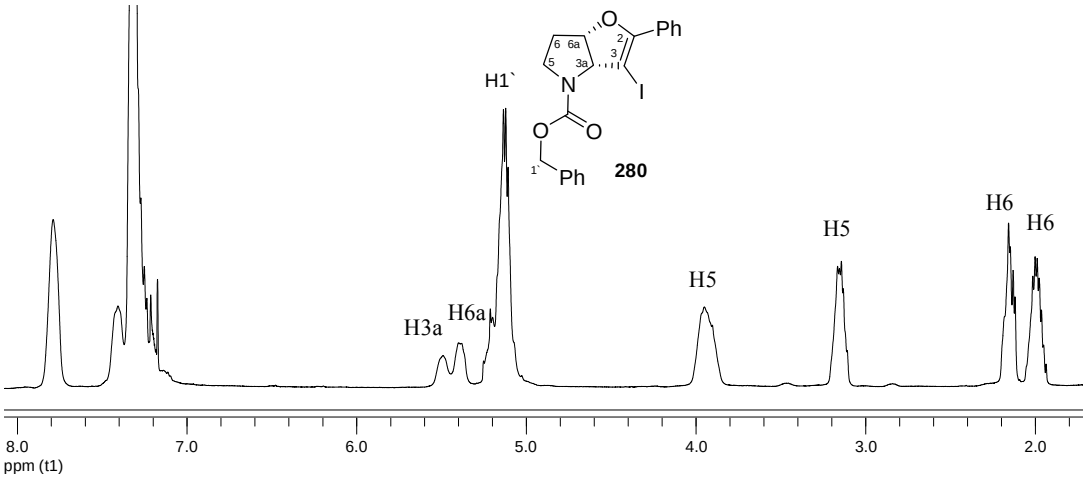
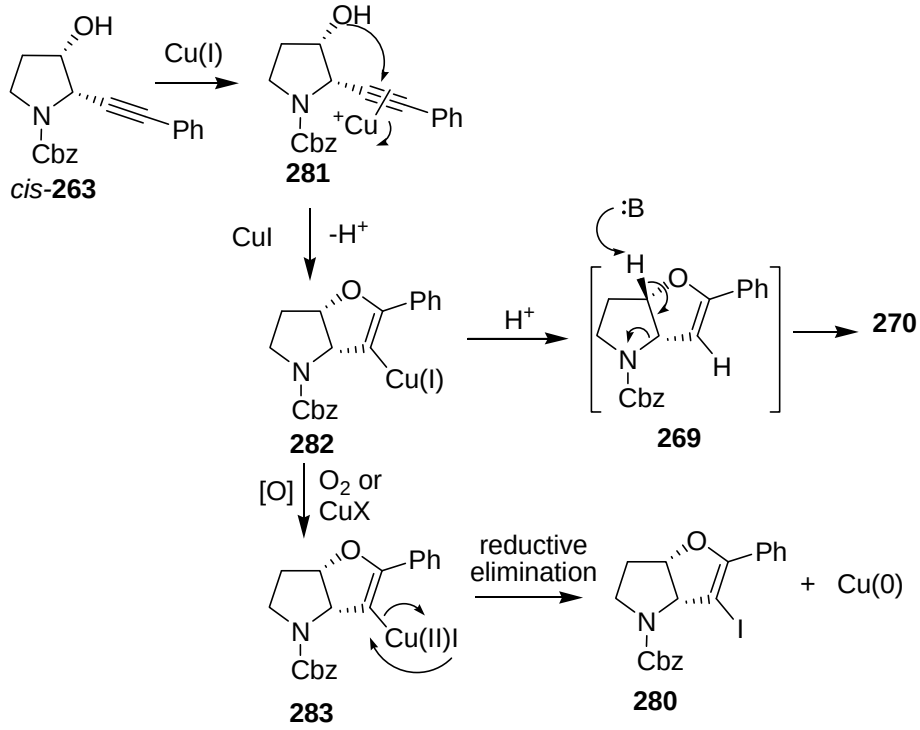
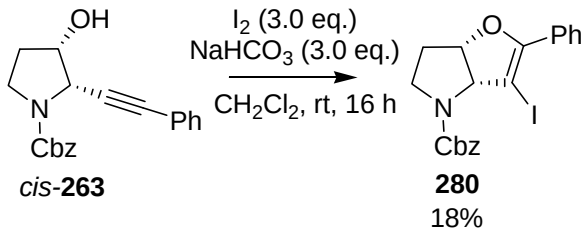


Figure 4.3. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **280**.

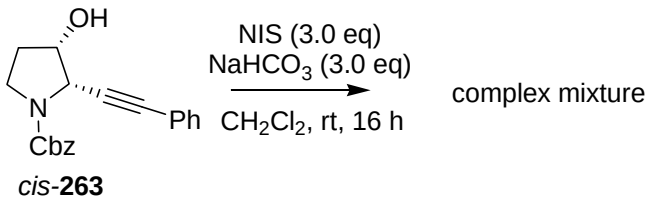


Scheme 4.20. The proposed mechanism for the formation of **270** and **280**.

We also attempted to make the iodocyclic product **280** *via* a cyclization-iodination reaction of *cis*-**263**. Treatment of *cis*-**263** with I_2 (3.0 eq.) and $NaHCO_3$ (3.0 eq.) gave the product **270** in a yield of only 18% (**Scheme 4.21**). The LREIMS analysis of the crude reaction mixture showed molecular ion peaks of the product **280** 447 amu. It also showed a molecular ion peak at 575 amu which was the molecular weight of the diodide product, that formed from the addition of the iodine to the triple bond. The reaction of *cis*-**263** with NIS (3.0 eq.) and $NaHCO_3$ (3.0 eq.) however produced a complex mixture of products (**Scheme 4.22**).

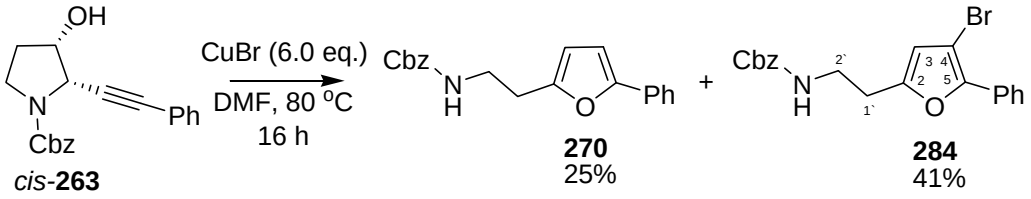


Scheme 4.21. Reaction of *cis*-**263** with I_2 and $NaHCO_3$.



Scheme 4.22. Reaction of *cis*-**263** with NIS.

After investigating CuI as catalyst in this reaction we turned our focus on CuBr and CuCl with the aim of preparing the chloro and bromo substituted bicyclic structures. Thus *cis*-**263** was treated with CuBr under the optimized conditions. The reaction did not give the desired bromobicyclic product instead it gave a 75 : 25 mixture of the 3-bromo furan **284** and the furan **270** in respective yields of 41% and 25% (**Scheme 4.23**). The structure of the bromo furan **284** was identified from its NMR spectroscopic analysis. The signal for the methine proton H3 was observed at 6.23 (1H, s) ppm, while that of the NH proton was observed at 4.91 (1H, br. s) ppm in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum confirmed the structure of **284** and showed signals at 113.1 and 96.4 ppm, corresponding to the C3 and C4 carbons, respectively. The HMBC spectrum of **284** showed a cross peak between the methylene protons H1` and the methine carbon C3, which confirmed that the bromo was at the C4 position of the furan. LREIMS spectrum showed two molecular ion peaks at 401 and 403 amu for the two bromine isotopes of ^{79}Br and ^{81}Br, respectively.



Scheme 4.23. Reaction of *cis*-**263** with CuBr.

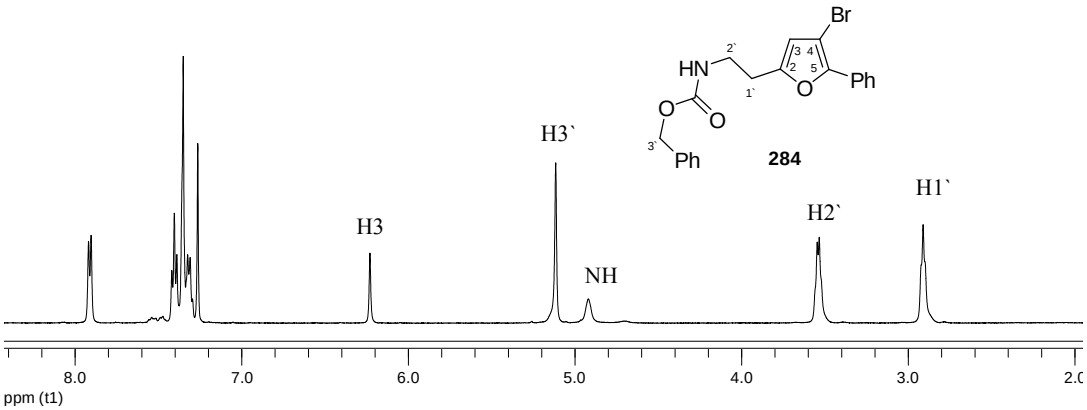
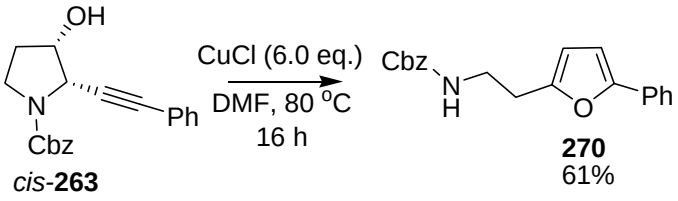


Figure 4.4. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **284**.

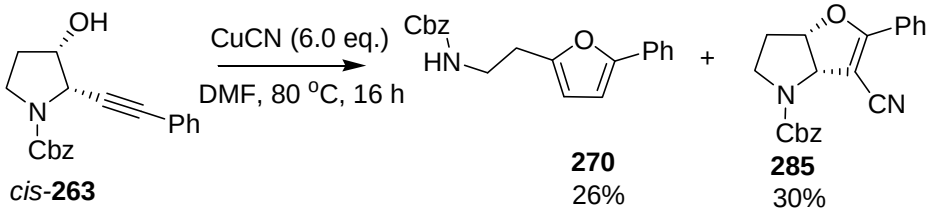
When *cis*-**263** was allowed to react with CuCl under the same experimental conditions, furan **270** was obtained exclusively in a yield of 61% (**Scheme 4.24**). The reactions of *cis*-**263** with CuBr and CuCl were repeated twice under the same experimental conditions and the results did not change. The use of CuBr resulted in the formation of a mixture of **270** and **284**, while the use of CuCl resulted in the formation of **270**. Thus CuI was found to be most effective catalyst in the cyclization-halogenation reactions of *cis*-**263**.



Scheme 4.24. Reaction of *cis*-**263** with CuCl.

We next focused on the reaction of *cis*-**263** with CuCN, with the aim of getting a 3-cyano substituted furo[3,2-*b*]pyrrole. Thus *cis*-**263** was treated with CuCN in DMF to furnished a mixture of **270** and **285** in respective yields of 26% and 30% (**Scheme 4.25**). The result of this reaction was significant since cyclization-cyanation reactions are not known. However the yield of **285** needed to be increased if this reaction could be of synthetic utility. NMR spectroscopic analysis of **285** was in good agreement with the structure. In the ^{13}C NMR spectrum of the **285** the CN carbon resonance appeared at 82.6 ppm and the methine carbons C3a and C6a appeared at 87.1 and 65.1 ppm, respectively. The IR spectrum of **285** showed the C≡N and C=O

bond stretches at 2202 and 1708 cm^{-1}, respectively. HREIMS analysis showed the molecular formula to be $C_{21}H_{19}N_2O_3$ consistent with the structure.



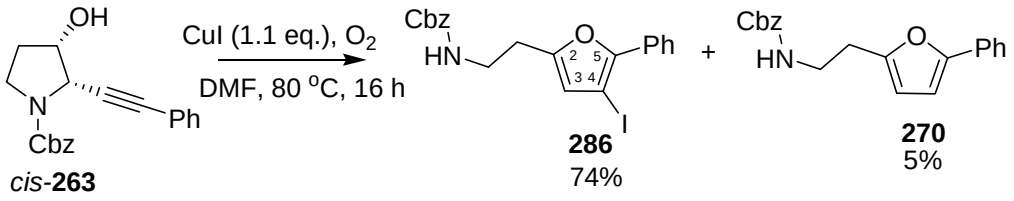
cis-**263**

270 26%

285 30%

Scheme 4.25. Reaction of *cis*-**263** with CuCN.

The halo and cyano substituted products were assumed to form *via* a reductive elimination pathway of a RCu(II)X intermediate **283** as mentioned in **Scheme 4.20**. Presumably if we could oxidize the Cu(I) intermediate to the Cu(II) intermediate *in situ* we can increase the yield of these products using less amounts of copper salts. For this reason we decided to performed these reactions under an oxygen atmosphere. We first examine the reaction of *cis*-**263** with 1.1 mol equivalents of CuI in DMF at 80 °C for 16 h which yielded the iodofuran **286** in 74% yield and **270** in 5% yield (**Scheme 4.26**). The relative ratio of these compounds was 91 : 9 from ^1H NMR analysis of the crude reaction mixture. The iodofuran **286** was identified by the presence of resonances, in its ^1H NMR spectrum corresponding to a furan methine group and a NH, which appeared as a singlet resonance at 6.27 ppm and a broad singlet resonance at 4.90 ppm, respectively. The ^{13}C NMR spectrum of **286** also confirmed the structure and showed a resonance at 117.6 ppm corresponding to the furan methine carbon, at 61.4 ppm corresponding to C4. The IR spectrum showed N-H and C=O stretches at 3367 and 1683 cm^{-1}, respectively. HREIMS analysis confirmed its molecular formula to be $C_{20}H_{18}NO_3I$, consistent with the structure.



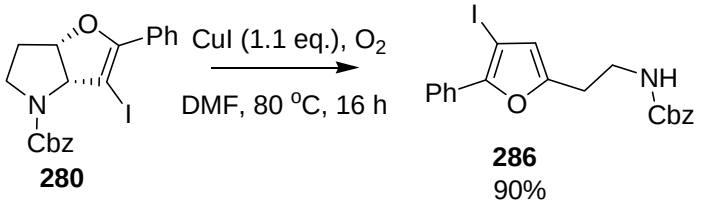
cis-**263**

286 74%

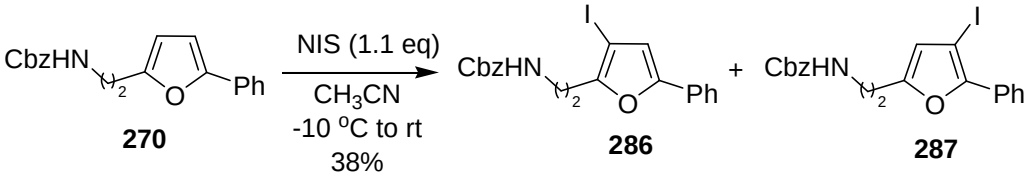
270 5%

Scheme 4.26. Reaction of *cis*-**263** with CuI under an O_2 atmosphere.

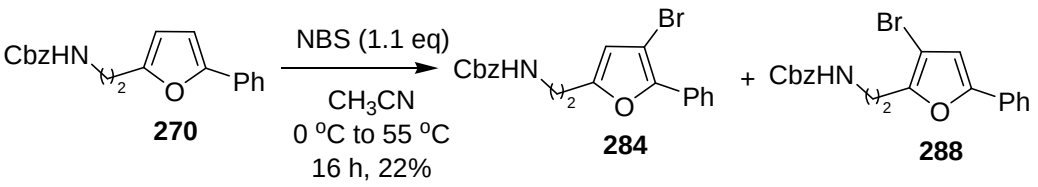
In order to prove that the iodofuran **286** is formed from the ring opening reaction of iodo bicyclic structure **280**, and not from the iodination reaction of **270,** compound **286** was treated with CuI (1.1 eq.) in DMF under an O_2 atmosphere for 16 h. The iodofuran **286** was isolated in 90% yield (**Scheme 4.27**). However, treatment of **270** with CuI under the same experimental conditions resulted in recovery of **270**. So it was clear that in the reaction the bicyclic structure **280** was formed first and then underwent a ring opening reaction to yield the iodofuran **286**. We suspect that Cu(II)O is formed from the reaction between Cu(I) and O_2 which acts as a base to catalyse the ring-opening reaction of **280** to **286**. Further evidence for the above mechanism in the formation of **286** came from the treatment of **270** with NIS in CH_3CN at -10 ^oC to rt for 16 h which provided a 1 : 1 mixture of the 3-iodofuran **286** and the 4-iodofuran **287** in 36% yield (**Scheme 4.28**). Separation of these isomers could not be achieved due to the same R_f values of these products. The ^1H NMR analysis of the crude reaction mixture showed the methine proton resonances of **286** and **287** at 6.27 (1H, s) and 6.23 (1H, s), and two NH proton signals at 4.90 (1H, br. s) and 4.40 (1H, br. s) ppm, respectively. The LREIMS spectrum of the crude mixture showed a molecular ion peak at 447 amu, consistent with the structures. Treatment of **270** with NBS in CH_3CN at 0 ^oC to 55 ^oC for 16 h gave a 1 : 1 mixture of 4-bromofuran **284** and 3-bromofurans **288** in overall 22% yield (**Scheme 4.29**).



Scheme 4.27. Reaction of **280** with CuI.



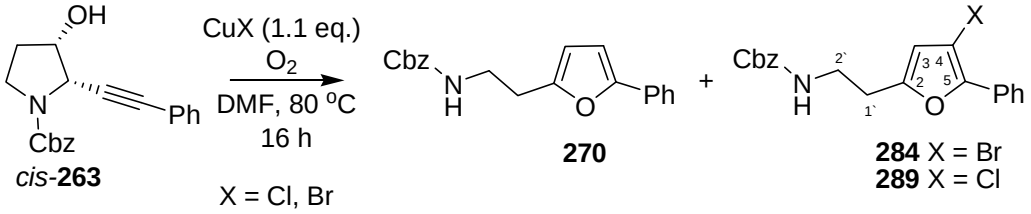
Scheme 4.28. Treatment of **270** with NIS.



Scheme 4.29. Treatment of **270** with NBS.

Under similar conditions the reaction of *cis*-**263** with CuBr afforded the 3-bromofuran **284** and the non-brominated furan **270** in a ratio of 95 : 5 and in 68% and 5% yields, respectively (**Table 4.6**, Entry 1). When CuCl was used as a catalyst 3-chlorofuran **289** and **270** were isolated in respective yields of 78% and 5% (**Table 4.6**, Entry 2) and in a ratio of 90 : 10. The structure of furan **289** was clear from its NMR spectroscopic analysis. The ^{1}H NMR spectrum showed a signal at 6.17 (1H, s) ppm corresponding to the furan methine proton and a signal at 4.92 (1H, br. s) ppm corresponding to the NH proton. The furan methine carbon resonance was observed at 111.0 ppm while that of C4 was observed at 124.7 ppm in the ^{13}C NMR spectrum.

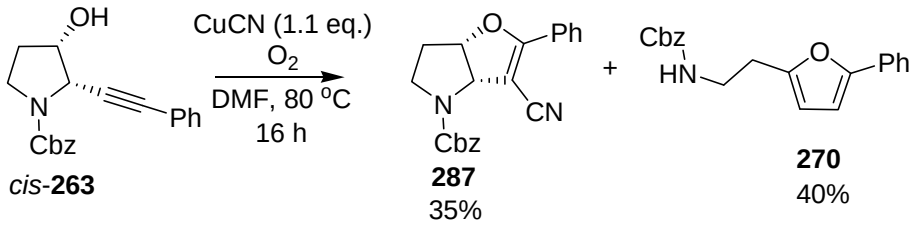
Table 4.6. Reactions of *cis*-**263** with copper salts under O_2 atmosphere.



Entry	X	Yield% of 270	Yield% of 284 or 289
1	Br	5	68
2	Cl	5	78

The reaction of *cis*-**263** with CuCN afforded a 35 : 65 mixture of products which were separated by column chromatography to give **285** and **270** in yields of 35% and 40%, respectively (**Scheme 4.30**). Interestingly the use of CuX (X = I, Cl, Br) furnished the halofurans products which were formed from the ring opening of the corresponding bicyclic products, while the CuCN catalyzed reaction yielded the cyano substituted bicyclic product **287**. Product **287** was stable under the reaction conditions and did not give a ring-opened (furan) product. As a result the cyclisation-halogenation and cyclization-cyanation reactions of pyrrolidine *cis*-**263** provided the halo- and cyano- substituted products in higher yields when these reactions were

performed under an oxygen atmosphere, consistent with the proposed reductive elimination mechanism (**Scheme 4.20**).



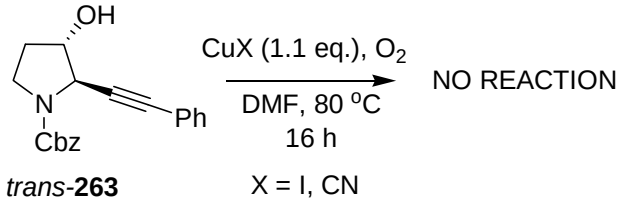
cis-**263**

287
35%

270
40%

Scheme 4.30. Reaction of *cis*-**263** with CuCN under O_2 atmosphere.

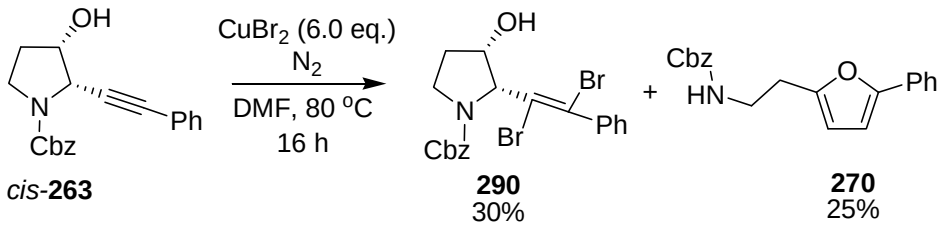
The cyclization-iodination and cyclization-cyanation reactions of 2,3-*trans* pyrrolidine *trans*-**263** were also tested. Compound *trans*-**263** was treated with 1.1 mol equivalents of CuX (X = I, CN) in DMF at 80 ^oC for 16 h under an O_2 atmosphere. None of these attempts worked, in all cases *trans*-**263** was recovered quantitatively (**Scheme 4.31**).



trans-**263**

Scheme 4.31. Treatment of *trans*-**263** with CuI and CuCN.

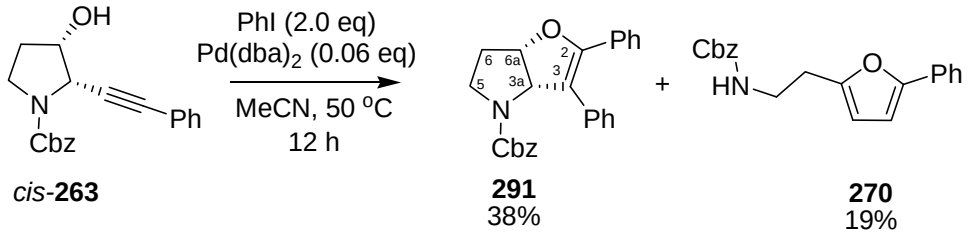
Since Cu(II) salts have been used in cyclization-halogenation reactions in the literature, *cis*-**362** was treated with 6 mol equivalents of $CuBr_2$.[118] The reaction gave two products **290** and **270** in respective yields of 30% and 25% (**Scheme 4.32**). The structure of the dibromo product **290** was confirmed from NMR spectroscopic analysis. The quarternary carbons C1` and C2` resonated at 111.6 and 115.0 ppm, respectively. The IR spectrum was confirmed the structure showing a broad peak at 3326 cm^{-1} corresponding to the O-H stretch, and a sharp peak at 1710 cm^{-1} corresponding to the C=O stretch. The mass spectrometric analysis showed three molecular ion peaks at 479, 481 and 483 amu for the bromine isotopic peaks which was consistent with the structure.



cis-**263** **290** 30% **270** 25%

Scheme 4.32. Reaction of *cis*-**263** with $CuBr_2$.

In order to investigate the synthetic potential of the metal-catalyzed cycloisomerizations of *cis*-**263**, the tandem palladium-catalyzed cycloisomerization-cross coupling reaction[119] of *cis*-**263** was studied. Treatment of *cis*-**263** with PhI, $Pd(dba)_2$ and K_2CO_3 in CH_3CN at 50 °C for 12 h gave the arylated product **291** and **270** in yields of 38% and 19%, respectively (**Scheme 4.33**). Unlike the bromo and chloro substituted furo[3,2-*b*]pyrroles, but like the iodo derivative **280** and CN derivative **287**, product **291** did not undergo a ring opening reaction to form a diphenyl substituted furan. Compound **291** was stable under the reaction conditions. The structure of **291** was established by its NMR spectroscopic studies. The signals for the methine protons H3a and H6a were observed at the respective chemical shifts of 5.24 (1H, br. s) and 5.67 (1H, br. d, J = 5.5 Hz) ppm. The methine carbons of **291**, C3a and C6a, resonated at 82.4 and 69.6 ppm, respectively. The chemical shifts of these carbons were typical of a furo[3,2-*b*]pyrrole structure. The C=O stretch was observed at 1701 cm^{-1} in its IR spectrum. The HREIMS analysis revealed the molecular formula $C_{26}H_{23}NO_3$ which was consistent with the structure. We assume that product **291** arises *via* a reductive elimination mechanism on an intermediate analogus to **283** in **Scheme 4.20**, in which the Cu(II)I species is replaced by a PhPd(II) species.



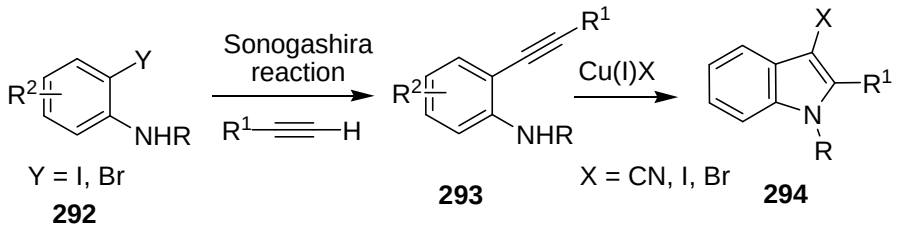
cis-**263** **291** 38% **270** 19%

Scheme 4.33. Tandem cyclization-cross coupling reaction of *cis*-**263**.

In conclusion, methods for the synthesis of novel 3-halo-2,5-substituted furans and 3-cyano, 3-iodo and 3-phenyl substituted furo[3,2-*b*]pyrroles have been developed.

5. COPPER MEDIATED CYCLIZATION-CYANATION REACTIONS OF *ORTHO*-ALKYNYLANILINES

In Chapter 4 we reported novel copper mediated cyclization-halogenation and cyclization-cyanation reactions of a 2-alkynyl-3-hydroxypyrrolidine. In this Chapter we applied this methodology to *ortho*-alkynylanilines with the aim of synthesizing 3-functionalized-2-substituted indoles. The indole ring is a key structural feature of a vast number of biologically active natural and unnatural compounds. Thus the synthesis and functionalization of the indole ring has been the object of many researchers. We aimed to synthesize 3-halo and 3-cyano indoles **294** from the cyclization-halogenation and cyclization-cyanation reactions of *ortho*-alkynylanilines. The *ortho*-alkynylanilines **293** could be obtained from the Sonagoshira[115] coupling reaction of *ortho*-haloanilines **292** and terminal alkynes (**Scheme 5.1**).

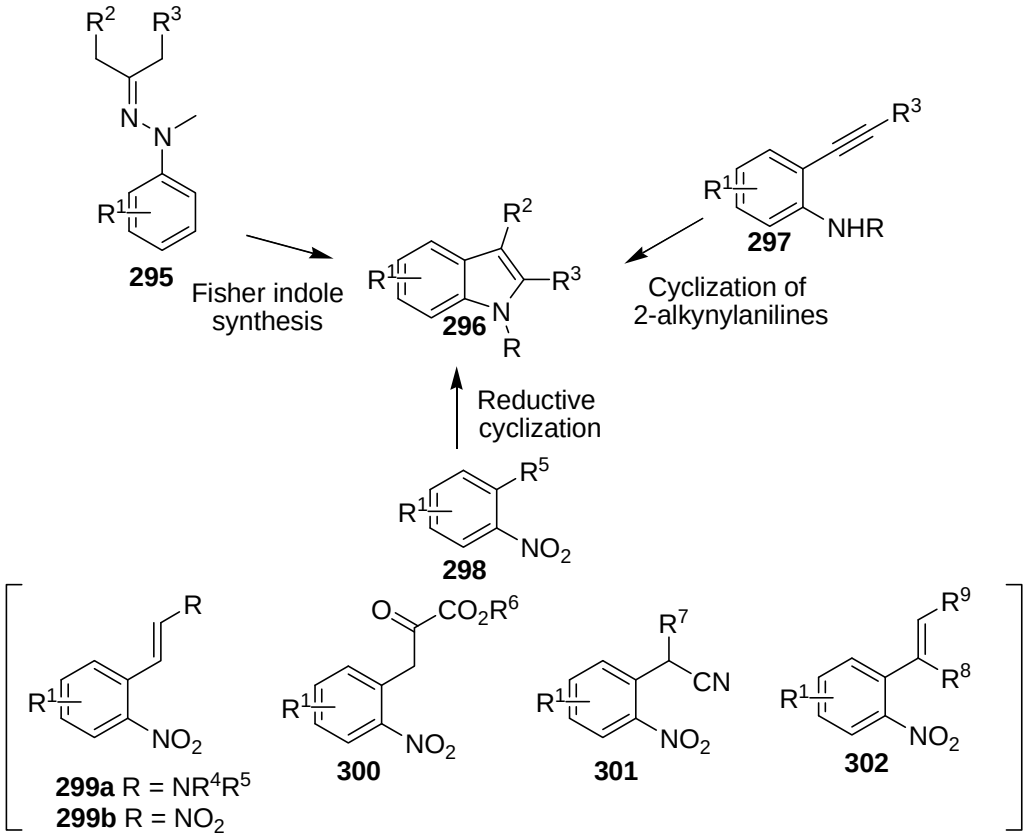


Scheme 5.1. Proposed synthesis of 3-halo and 3-cyano indoles **294**.

5.1. Synthesis of Indoles

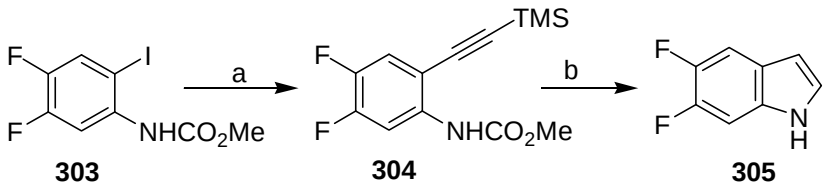
The Fisher indole synthesis, reductive cyclizations of aromatic nitro compounds and cyclization of *ortho*-alkynylanilines are the most common methods to construct the indole ring (**Scheme 5.2**).[120,121] The Fisher indole synthesis is the construction of the indole ring by heating arylhydrazones of ketone or aldehydes **295** in the presence of a protic acid or a Lewis acid. Reductive cyclization of aromatic nitro compunds **298** has been accomplished by catalytic hydrogenation over Pd/C, Pt/C or a combination of Raney nickel and hydrazine.[122,123] Precursors for the reductive cyclization reactions to indoles can be *β*-amino-*ortho*-styrenes **299a**, *ortho*-*β*-nitrostyrenes **299b**, *ortho*-nitrobenzylcarbonyls **300**, *ortho*-nitrophenylacetonitriles **301** or *ortho*-nitrostyrenes **302**.[120] In this Chapter we will focus on the cyclization of *ortho*-alkynylanilines **297** to form the indole ring. The synthesis of indoles *via* cyclization

of *ortho*-alkynyl anilines usually involves two steps. The first step is the Sonogashira cross-coupling of *ortho*-halo-anilines or 2-carboxamidoaryl triflates with the terminal alkynes. The second step is the cyclization of *ortho*-alkynylanilines in the presence of metal alkoxides, Pd(II) salts or iodine. Although Pd(II)[121] salts are the most common catalysts in this cyclization reactions platinum,[124] molybdenum,[125] iridium,[126] rhodium,[127] zinc,[128,129] mercury[130] and indium[131,132] salts have also been used.



Scheme 5.2. Three methods for the synthesis of indole ring.

Wang[118] reported the synthesis of 5,6-difluoroindole from the cyclization of the *ortho*-alkynylaniline **304** (**Scheme 5.3**). The Sonogashira coupling of **303** with trimethylsilylacetylene in the presence of $Pd(OAc)_2$ and $(o\text{-tolyl})_3P$ in Et_3N afforded the alkyne **304** in 94% yield. Treatment of **304** with EtONa at 70 ^oC for 14 h yielded the 5,6-difluoroindole **305** in a yield of 82%.

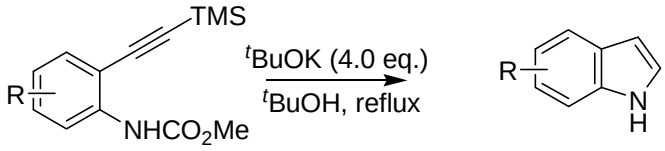


303 **304** **305**

Reagents and conditions : a) $Pd(OAc)_2$ (1.5 mol%), (*o*-tolyl)$_3$P (2 mol%), Et_3N, TMSacetylene, rt, 16 h, 94%; b) EtONa, EtOH, 70 ^oC, 14 h, 82%.

Scheme 5.3. Synthesis of 5,6-difluoroindole **305**.

Indole derivatives containing oxygen-bearing substituents, such as hydroxyl, alkoxy, or acyloxy group, at the benzene moiety are present in a number of physiologically active substances. Sakamato[133] developed a strategy for synthesizing indoles with these substituents. The cyclization of *ortho*-alkynylanilines **306** in the presence of ^{t}BuOK furnished indoles **307** in 70-79% yields (**Scheme 5.4**). The TMS and CO_2Me groups did not survive under the cyclization reaction conditions.



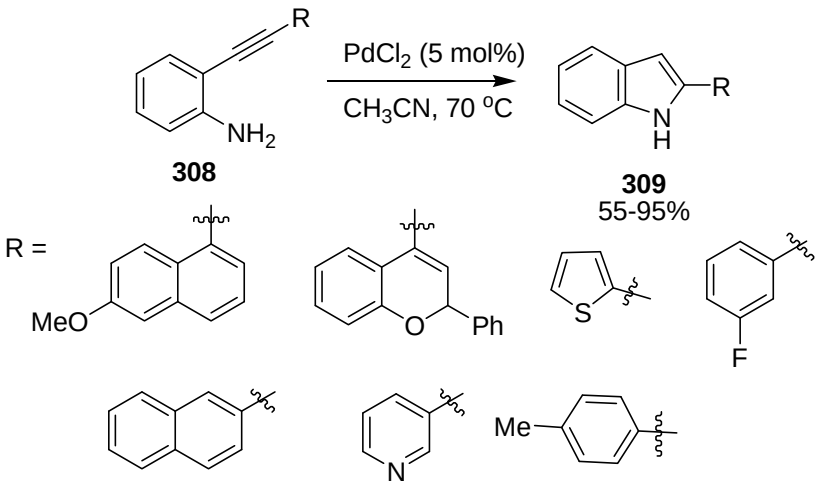
306 **307**
70-79%

R = 4-OMe, 5-OMe, 7-OMe
5-OTIPS, 6-OTIPS, 7-OTIPS

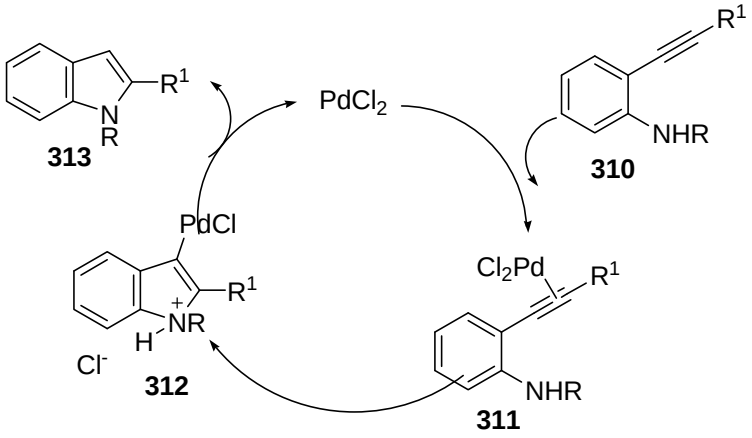
Scheme 5.4. Synthesis of oxygen-bearing substituted indoles **307**.

2-Substituted indoles **309** have been synthesized from the $PdCl_2$ catalyzed cycloisomerization reaction of alkynylanilines **308**. Treatment of **308** with $PdCl_2$ (5 mol%) in CH_3CN at 70 ^oC provided 2-arylindoles **309** in 55-95% yields (**Scheme 5.5**). The method is very useful for making the free NH-2-substituted indoles.[134]

The proposed mechanism (**Scheme 5.6**) of the palladium-catalyzed cyclization of alkynylanilines involves the coordination of palladium(II) to the triple bond of **310** to form a π-alkyne-palladium complex **311**. Intramolecular nucleophilic attack of the nitrogen to the activated triple bond forms the σ-indolylpalladium complex **312**. Protonation of this intermediate at C-3 with loss of palladium(II) gives the indole product **313**.[134]

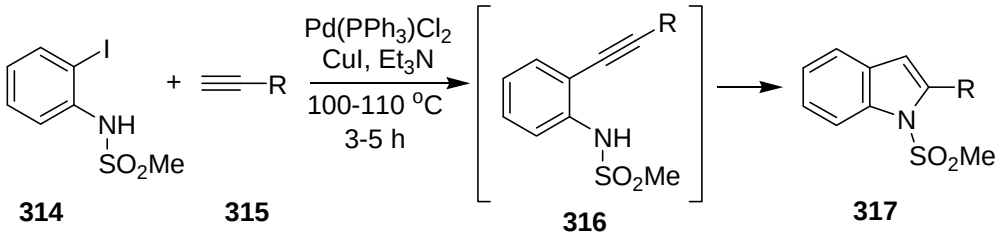


Scheme 5.5. Synthesis of 2-substituted-NH-indoles **309**.



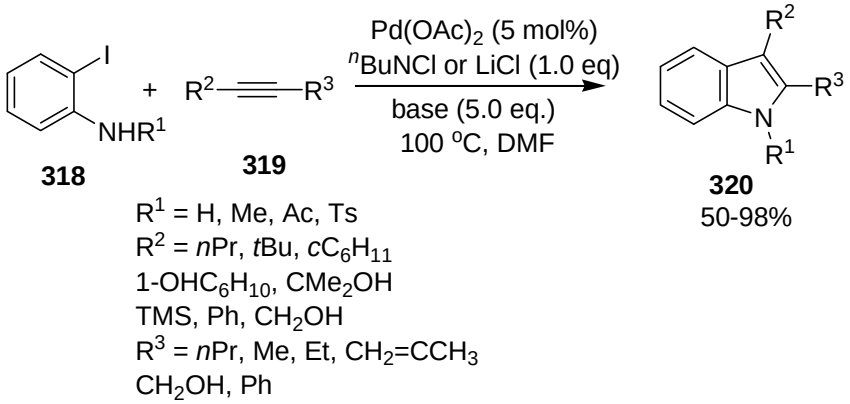
Scheme 5.6. The proposed mechanism of Pd(II)-catalyzed cyclization of 2-alkynylanilines.

The synthesis of indoles *via* cyclization of *ortho*-alkynylaniline derivatives usually requires two steps. However, a one-pot synthesis of indoles from *ortho*-iodoanilines **314** and terminal alkynes **315** under Sonogashira reaction conditions was reported (**Scheme 5.7**). Yamanaka[135] observed that treatment of terminal alkynes with *ortho*-iodo-*N*-mesylanilidines **314** in the presence of $Pd(PPh)_3Cl_2$ and CuI in Et_3N afforded directly indole products **317**. In control experiments the indole product was observed when 2-trimethylsilylethynyl-*N*-mesylanilidine was heated with $Pd(PPh)_3Cl_2$ and CuI, however no indole product was observed using only Et_3N and DMF.



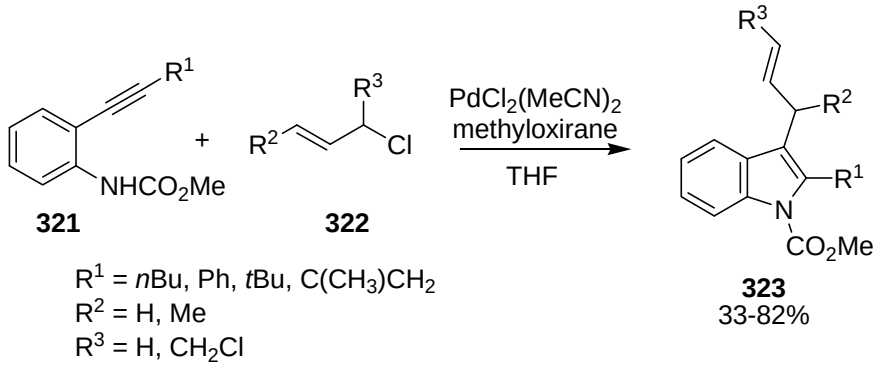
Scheme 5.7. One-pot synthesis of indoles.

Another one-pot procedure for the synthesis of highly substituted indoles was reported by Larock.[136,137] The palladium catalyzed reaction of *ortho*-iodoaniline derivatives **318** with internal alkynes **319** furnished the complex indoles **320** in a single step (**Scheme 5.8**). This is an important method for synthesizing complex indoles since both starting materials can possess considerable functionality. The reaction is regioselective and always provides 2,3-disubstituted indoles, where the more sterically hindered group of the alkyne occupies the 2 position of the indole.



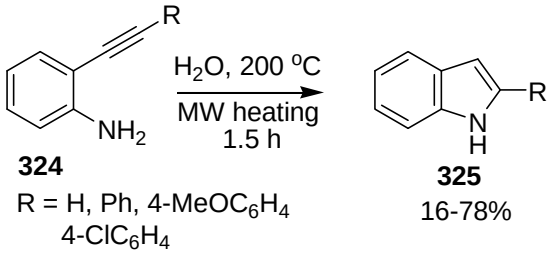
Scheme 5.8. One-pot synthesis of 2,3-disubstituted indoles **320**.

Utimoto[138] described the reaction of *ortho*-alkynyl-*N*-methoxycarbonylanilidines **321** with allylic chlorides **322** in the presence of a palladium catalyst (**Scheme 5.9**). While the reaction occurred under mild conditions with *N*-methoxycarbonylanilides, the unprotected amino group or the acetamido derivative gave low yields. It was also found that the use of the proton scavenger, methyloxirane, was essential. In the mechanism of this palladium catalyzed cyclization (**Scheme 5.6**), a σ-indolylpalladium intermediate **312** forms and undergoes protonolysis to form 2-substituted indoles. Trapping of this intermediate by allylic chlorides afforded the 2-alkenyl-3-substituted indoles **323**.



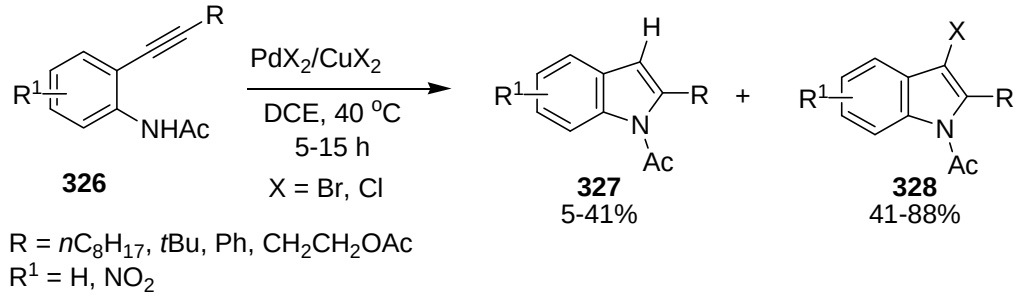
Scheme 5.9. Palladium catalyzed reactions of **321** with **322**.

Ribecai[139] recently reported the microwave assisted cyclization of *ortho*-alkynylanilines to form indoles in the absence of added catalyst, acids or bases (**Scheme 5.10**). They synthesized indole and 2-substituted indoles **325** by heating 2-alkynylanilines **324** in water using a microwave reactor. The use of organic solvents resulted in only 1-3% yields of indole products while the use of a 75 : 25 mixture of organic solvent and water gave slightly increased yields of 3-10%.

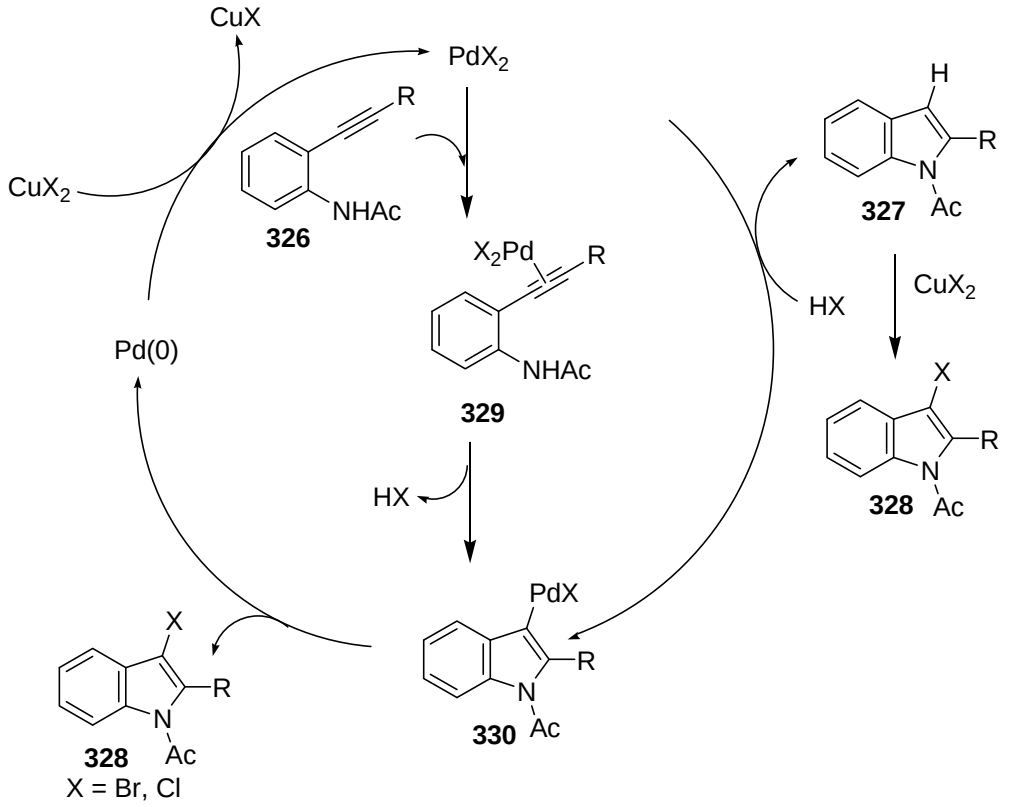


Scheme 5.10. Microwave-assisted synthesis of indoles.

Wang[140] demonstrated the direct synthesis of 3-halo-2-substitutedindoles **328** from the treatment of *N*-acetyl-2-alkynylanilines **326** with bromo or chloro salts of Pd(II)/Cu(II) in DCE at 40 °C for 5 h. The reaction of **326** with $PdBr_2$ or $PdCl_2$ (5 mol%) and $CuBr_2$ or $CuCl_2$ (5 mol%) afforded products **327** and **328** in moderate to good yields (**Scheme 5.11**). They found that *N*-unprotected and *N*-benzyl protected alkynylanilines did not give any of the desired products.



Scheme 5.11. Synthesis of 3-haloindoles.



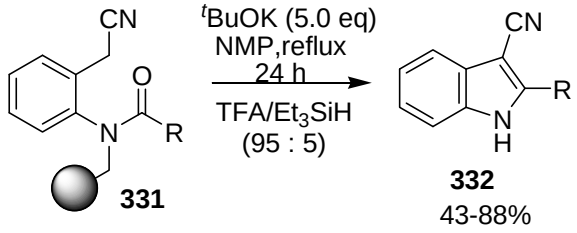
Scheme 5.12. The proposed mechanism for the formation of 3-haloindoles **328**.

The proposed mechanism[140] (**Scheme 5.12**) starts with coordination of the palladium species to the triple bond of **326** to form intermediate **329** and then intramolecular nucleophilic attack of nitrogen results in the formation of indolylpalladium complex **330**. Protonation of this intermediate gives the product **327**. Reductive elimination of **330** gives the product **328** and Pd(0). The Pd(II) catalyst is regenerated from the redox reaction of the Pd(0) with CuX_2. The 2-substituted indole **327** can also provide halogenated indoles **328** *via* halogenation with CuX_2. In control experiments, **326** was treated with $PdBr_2$ (1.0 eq) in DCE at 40 °C to give a mixture of products **327**

and **328** in 21% and 75% yields, respectively. However treatment of **327** with $CuBr_2$ in DCE at 40 ^oC afforded the haloindole **328** in 58% yield.

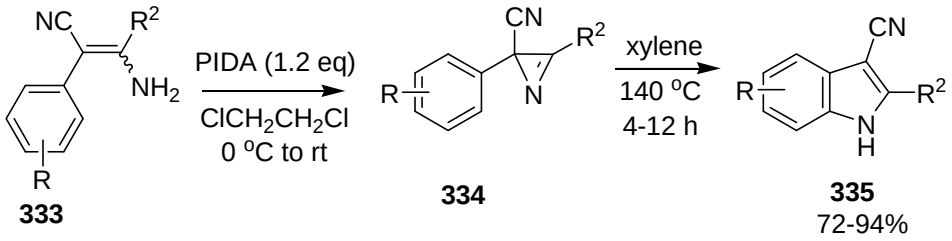
5.2. Synthesis of 3-Cyanoindoles

3-Cyanoindoles have been synthesized from the solid phase Madelung indole synthesis.[141] The *ortho*-substituted anilines were first attached to a resin using reductive amination and then the resin-bound aniline was acylated. Cyclization of **331** in the presence of ^{t}BuOK furnished the 3-cyano-2-substituted indoles **332** in 43-88% yields (**Scheme 5.13**). The products were quantitatively removed from the resin by treatment with TFA/Et_3SiH (95 : 5).



Scheme 5.13. Solid phase synthesis of 3-cyano indoles.

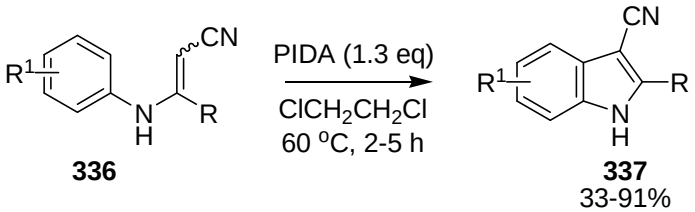
Zhao[142] synthesized 3-cyano indoles *via* thermolysis of 2-aryl-2*H*-aziridines **334**. Heating **334** in xylene at 140 ^oC for 4-12 h yielded 3-cyano 2-substituted indoles **335** in yields of 72-94%. They prepared **334** from the enamine derivatives **333** *via* oxidative cyclization using phenyliodine(III) diacetate (PIDA).



Scheme 5.14. Synthesis of 3-cyanoindoles from 2-aryl-2H-aziridines.

Zhao[143] synthesized 3-cyanoindoles also from *N*-aryl enamines *via* PIDA-mediated oxidative C-C bond formation. Treatment of *N*-aryl enamines **336** with PIDA (1.3 eq.) in DCE at 60 ^oC gave 3-cyano-2-substituted indoles **337** in 33-91% yields

(**Scheme 5.15**). The use of phenyliodine(III) bis(trifluoroacetate) (PIFA) resulted in the formation of indoles **337** in moderate yields (40-55%). The reaction has good functional group tolerance and allowed for the formation of 2-alkyl or 2-aryl indoles in good yields.

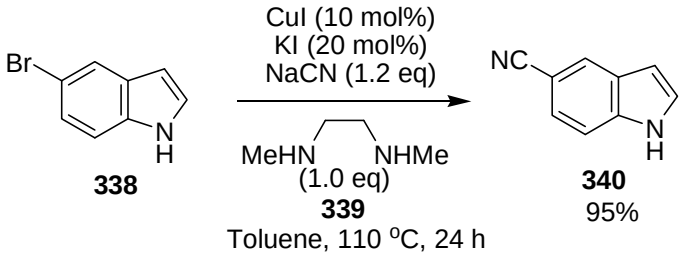


336 **337** 33-91%

R = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, Me, *i*Pr, *i*Bu, CO_2Et
R^1 = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 3,4-MeC_6H_3, 3,4-$MeOC_6H_3$
2-MeC_6H_4, 3-FC_6H_4

Scheme 5.15. PIDA-mediated synthesis of 3-cyanoindoles **337**.

Reaction of arylhalides with CuCN to form arylcyanides is known as the Rosenmund-van Braun reaction. Although the reaction showed good tolerance to functional groups, it needs high temperatures (150-280 °C) which has limited its applications.[144] Buchwald reported a modified version of the Rosenmund-van Braun reaction which worked under relatively mild conditions. They synthesized 5-cyanoindole **340** from the corresponding bromide **338** upon treatment with CuI, KI, NaCN and diamine ligand **339** at 110 °C for 24 h (**Scheme 5.16**).[145]



338 **339** **340** 95%

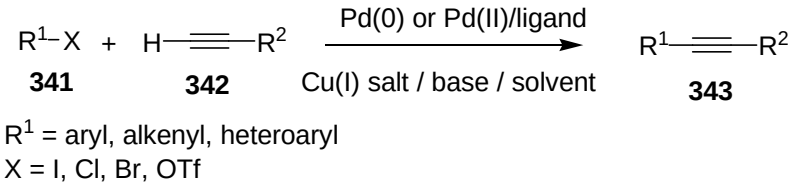
Scheme 5.16. Synthesis of 5-cyanoindole.

5.3. Preparation of *ortho*-Alkynylaniline Derivatives *via* the Sonogashira Reaction

5.3.1. The Sonogashira Reaction

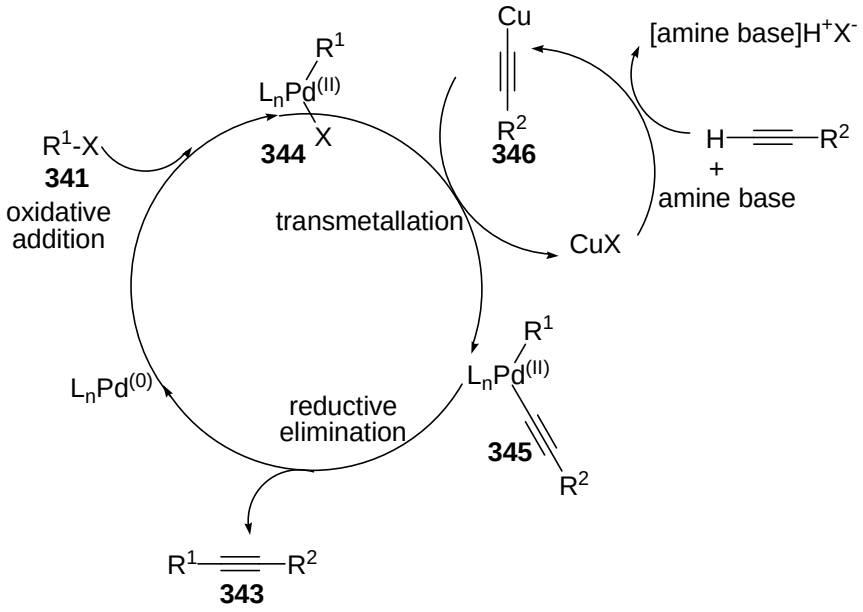
The Sonogashira[115] reaction is a cross coupling of terminal alkynes **342** with vinyl or aryl halides **341** (**Scheme 5.17**). A palladium complex and a halide salt of copper(I)

is used as a catalyst. An organic base usually serves as the solvent, however occasionally a co-solvent is used or an inorganic base. Palladium catalysts can be $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$, the copper(I) salt can be CuI or CuBr. The palladium complex activates the organic halides *via* oxidative addition to the carbon halogen bond. Copper(I) halides activates the terminal alkyne by forming a copper(I) acetylide in the presence of the base.[146]



Scheme 5.17. The Sonogashira reaction.

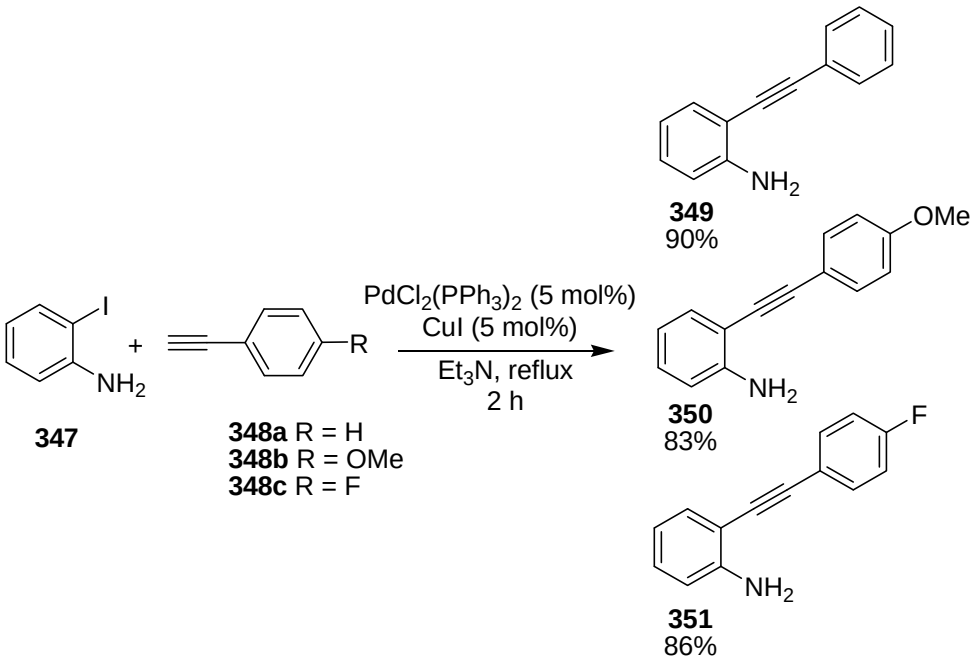
The mechanism (**Scheme 5.18**) of the Sonogashira reaction involves oxidative addition of a Pd(0) species to the aryl or vinyl halides (R^1-X) to give $R^1Pd(II)XLn$ **344** and then transmetallation by the copper(I) acetylide to give **345**. Reductive elimination then affords the coupled product **343** and regenerates the Pd(0) catalyst.[146]



Scheme 5.18. The mechanism of the Sonogashira coupling reaction.

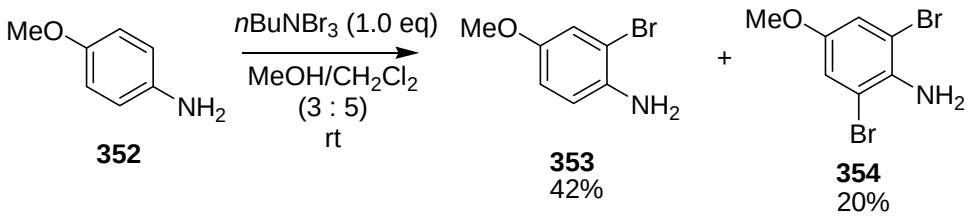
5.3.2. Sonogashira Reactions of *ortho*-Iodoaniline Derivatives

The Sonogashira reaction of aniline derivatives is well established in the literature.[146] In order to investigate the scope of cyclization-cyanation reaction we decided to synthesize *ortho*-alkynylanilines that have electron donating or electron withdrawing groups on the aniline component or on the alkyne component. We chose $PdCl_2(PPh_3)_2$ and CuI as a catalyst and Et_3N as a base and solvent. At first we decided to investigate the Sonogashira reactions of 2-iodoaniline with phenylacetylene and its derivatives having electron-donating or electron withdrawing substituents. 2-Iodoaniline **347** was treated with phenylacetylene **348a** in the presence of $PdCl_2(PPh_3)$ (5 mol%) and CuI (5 mol%) in Et_3N at reflux temperature for 2 h. The reaction afforded the desired known[129] alkynylaniline **349** in a high yield of 90% (**Scheme 5.19**). The NMR spectroscopic data of **349** were identical to the published data.[129] The LREIMS spectrum showed a molecular ion peak at 194 amu, consistent with the structure. The reaction of 2-iodoaniline with 4-ethynylanisole **348b** under the same experimental conditions yielded the desired known[147] alkynylaniline **350** in 83% yield (**Scheme 5.19**). The methoxy protons resonated at 3.80 (3H, s) ppm, while the NH proton appeared at 4.21 (2H, br. s) ppm in the ^{1}H NMR spectrum of **450**. The alkyne carbons resonated at 94.5 ppm and 84.4 ppm, while the methoxy carbon resonated at 55.2 ppm in the ^{13}C NMR spectrum of **350**. Treatment of 2-iodoaniline **347** with 1-ethynyl-4-fluorobenzene **348c** in the presence of $PdCl_2(PPh_3)_2$ and CuI in Et_3N furnished the desired adduct **351** in 86% yield (**Scheme 5.19**). The structure of **351** was clear from its NMR, IR and MS analyses. The aromatic protons *ortho* to the F-substituent resonated at 7.48 (2H, dd, J = 5.5, 8.5 Hz) ppm and showed a ^{1}H-^{19}F coupling constant of 5.5 Hz. While the *meta* protons resonated at 6.72-6.69 (2H, m) ppm. The ^{13}C-^{19}F coupling constants of the aromatic *ortho* and *meta* methine carbons and the quarternary *para* carbon to F were 22.0 Hz, 8.5 Hz and 3.7 Hz, respectively and they resonated at 115.6, 133.3 and 119.3 ppm, respectively. The *ipso* carbon resonated at 162.4 (d, J = 247 Hz) ppm. The alkyne carbons appeared at 93.5 ppm and 85.5 ppm in the ^{13}C NMR spectrum of **351**. The molecular formula was found to be $C_{14}H_{11}NF$ from the HREIMS analysis, consistent with the structure.



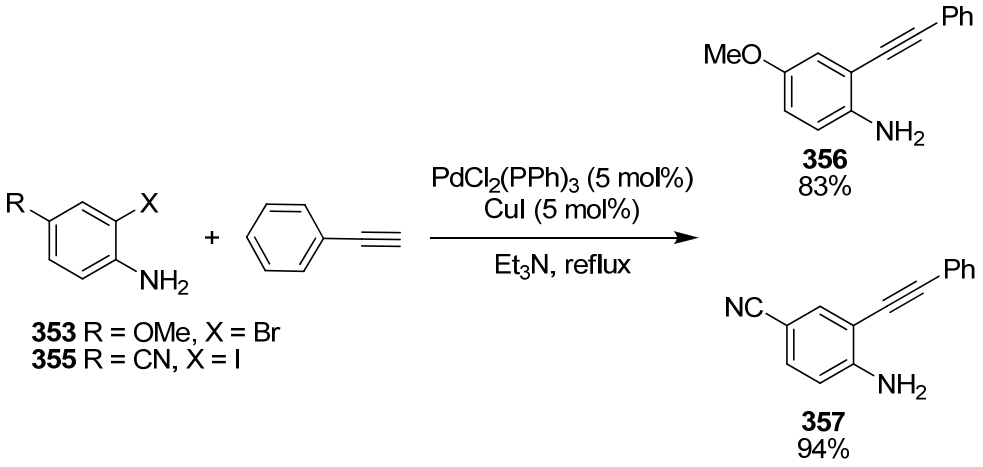
Scheme 5.19. Sonogashira reaction of *ortho*-iodoaniline **347**.

After investigating the Sonogashira reaction of *ortho*-iodoaniline, we decided to study the Sonogashira reactions of aniline derivatives having an electron donating or electron withdrawing substituents, with phenylacetylene. Cyano and methoxy groups were chosen as substituents on the aniline ring. Since anilines with electron donating group substituents were not commercially available we decided to synthesize 2-iodo or 2-bromo-4-methoxyaniline from *p*-anisidine **352**. The reaction of **352** with Br_2 in acetic acid resulted in the formation of a complex mixture.[148] The desired 2-bromo-4-methoxyaniline **353** however was successfully synthesized from the reaction of **352** with nBu$_4$NBr$_3$ (**Scheme 5.20**).[149,150] The reaction afforded the products **353** and **354** in respective yields of 42% and 20%. The starting material **352** was also recovered from this reaction in 20% yield.



Scheme 5.20. Synthesis of 2-bromo-4-methoxyaniline **353**.

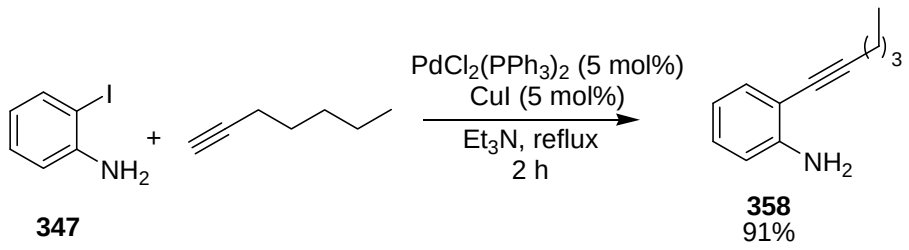
The 2-bromo-4-methoxyaniline **353** was subjected to a Sonogashira reaction under the optimised conditions. This reaction furnished the desired alkynylaniline **356** in 83% yield (**Scheme 5.21**). The ^{1}H and ^{13}C NMR spectra of **356** confirmed the structure. The NH_2 protons resonated at 4.0 (2H, br. s) ppm, while the methoxy protons resonated at 3.75 (3H, s) ppm in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum alkyne carbon signals were observed at 94.6 and 85.9 ppm, while the methoxy carbon resonated at 55.8 ppm. The Sonogashira reaction of 4-cyano-2-iodoaniline **355** with phenylacetylene under the same experimental conditions gave the known[131] alkynylaniline **357** in a high yield of 94% (**Scheme 5.21**). The NMR analysis confirmed the structure of **357**. The ^{1}H NMR spectrum showed a resonance for the NH_2 protons at 4.81 (2H ,br. s) ppm. The ^{13}C NMR spectrum showed signals at 96.1 and 83.3 ppm corresponding to the alkyne carbons and at 100.0 ppm corresponding to CN carbon. The IR spectrum was also consistent with the structure. It showed a broad band at 3467 cm^{-1} corresponding to the NH stretch and a sharp peak at 2215 cm^{-1} corresponding to the C≡N stretch. HREIMS analysis confirmed its molecular formula to be $C_{15}H_{10}N_2$.



Scheme 5.21. Sonogashira reactions of **353** and **355**.

The Sonogashira reaction of 2-iodoaniline **347** with the aliphatic alkyne, 1-heptyne, was also studied. Compound **347** was treated with 1-heptyne under the optimised reaction conditions to afford the desired adduct **358** in 91% yield (**Scheme 5.22**). The structure of **358** was identified from its NMR spectroscopic analysis. The methylene protons were observed at 1.47-1.30 (4H, m), 1.65-1.57 (2H, m) and 2.45 (2H, m)

ppm, while the methyl protons were observed at 0.92 (3H, t, J = 7.0 Hz) ppm. The NH_2 protons resonated at 4.15 (2H, br. s) ppm. In the ^{13}C NMR spectrum the methylene carbon signals were observed at 31.1, 28.6, 22.2 and 19.5 ppm while that of the methyl carbon was observed at 13.9 ppm. The alkyne carbon resonances appeared at 108.9 and 95.7 ppm. HREIMS analysis revealed its molecular formula to be $C_{13}H_{17}N$, consistent with the structure.

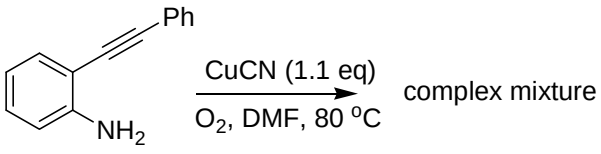


347 **358** 91%

Scheme 5.22. The Sonogashira reaction of 2-iodoaniline **347** and 1-heptyne.

5.4. Protection Reactions of *ortho*-Alkynylanilines

Metal-catalyzed cyclization reactions of *ortho*-alkynylanilines are usually performed with *N*-protected aniline derivatives since most of the methods cannot deal with the *N*-unprotected anilines. When *ortho*-alkynylaniline **349** was subjected to cyclization-cyanation reaction with CuCN (1.1 eq.) in DMF at 80 ^oC for 16 h, it produced a very polar complex mixture (**Scheme 5.23**). We decided to protect nitrogen of the **349** with Ts and TFA groups which have commonly been used in similar reactions.[120,121]

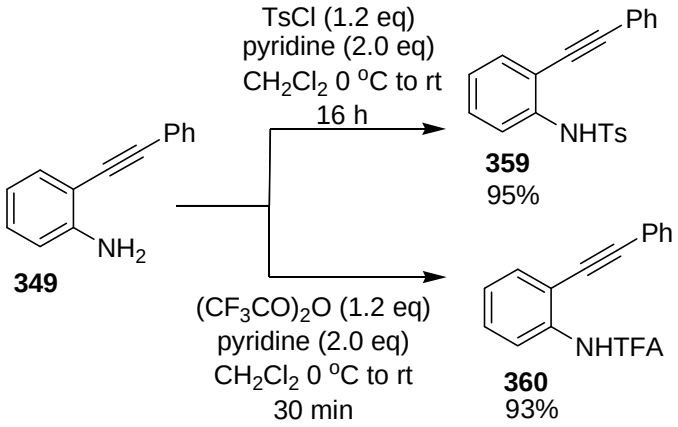


349

Scheme 5.23. Treatment of **349** with CuCN.

Compound **349** was treated with TsCl (1.2 eq) and pyridine (2.0 eq) in CH_2Cl_2 at 0 ^oC to rt for 16 h to give the desired sulfonamide **359** in a high yield of 95% (**Scheme 5.24**). The ^1H and ^{13}C NMR spectra of **359** was in good agreement with the structure. The methyl protons resonated at 2.31 (3H, s) ppm while the methyl carbon resonated at 21.4 ppm. The alkyne carbon signals were observed at 96.0 and 83.6 ppm in the

^{13}C NMR spectrum. The N-H and C≡C bond stretches were observed at 3267 and 2366 cm^{-1}, respectively in the IR spectrum. Similarly the reaction of **349** with $(CF_3CO)_2O$ (1.2 eq) and pyridine (2.0 eq) under the same experimental conditions provided the trifluoroacetamide **360** in 93% (**Scheme 5.24**). The ^{1}H NMR spectrum of **360** was consistent with its desired structure and showed a resonance at 8.90 (1H, br. s) ppm corresponding to the NH proton. The carbonyl carbon was observed at 154.4 ppm as a quartet with a ^{13}C-^{19}F coupling constant of 37.6 Hz, while the CF_3 was observed at 115.8 ppm as a quartet with a coupling constant of 287.6 Hz in the ^{13}C NMR spectrum. The alkyne carbons resonated at 98.0 and 82.8 ppm. The N-H and C≡C bond stretches were observed at 3344 and 2366 cm^{-1}, respectively in the IR spectrum.

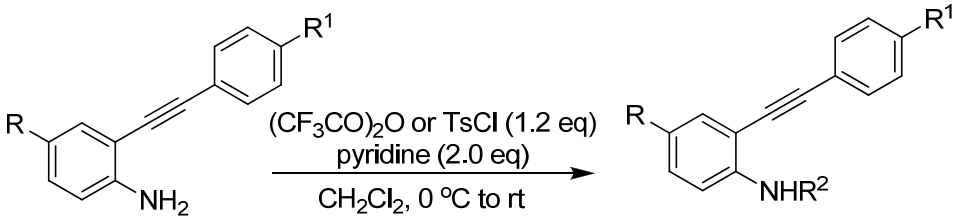


Scheme 5.24. The reaction of **349** with TsCl and $(CF_3CO)_2O$.

The *ortho*-alkynylaniline derivatives **350**, **351**, **356** and **357** were also subjected to *N*-protection reactions under the same experimental conditions. These protection reactions worked smoothly and yielded the desired products in high yields. When the alkynylanilines **350**, **351**, **356** and **357** were treated with $(CF_3CO)_2O$/pyridine the desired products **361-365** were obtained in yields of 96%, 96%, 90% and 91%, respectively (**Table 5.1**, Entries 1,2,3 and 4). Their structures were confirmed by NMR analysis. The carbonyl carbon resonances of products **361-365** were observed at 154.3 (q, J = 37.3 Hz), 154.6 (q, J = 37.8 Hz), 154.3 (q, J = 36.6 Hz) and 154.7 (q, J = 37.7 Hz) ppm, respectively in their ^{13}C NMR spectra, while the CF_3 carbon resonated at 114.3 (q, J = 287.5 Hz), 115.9 (q, J = 287.7 Hz), 115.8 (q, J = 287.5 Hz) and 115.4 (q, J = 287.5 Hz) ppm, respectively. MS analysis of compunds **361-365**

revealed molecular ions 319, 307, 319 and 314 amu, respectively consistent with their structures. Although the *N*-protection reaction of **357** with $(CF_3CO)_2O$ worked well and provided the product **364** in 91% yield, the tosylation reaction of **357** gave unsatisfactory results at rt for 16 h. However heating the reaction mixture at 40 ^oC for 6 h afforded the tosylated product **365** in 57% yield (**Table 5.1**, Entry 5) and unreacted aniline **357** in 25% yield. The structure of **365** was clearly identified by the presence of resonances, in both the ^1H and ^{13}C NMR spectra, corresponding to the tosyl methyl group, which were observed at 2.94 (3H, s) and 21.5 ppm. LREIMS analysis also confirmed the identity of the compound with a molecular ion consistent with the structure at 372 amu.

Table 5.1. Results of protection of *ortho*-alkynylanilines.



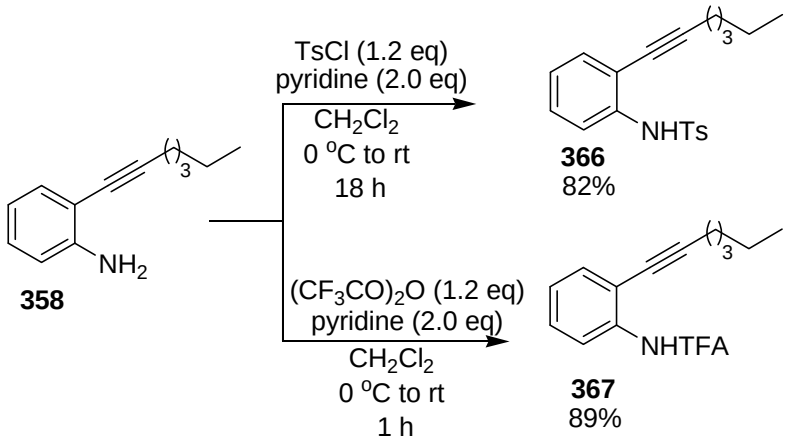
350 R = H, R^1 = OMe
351 R =H, R^1 = F
356 R = OMe, R^1 = H
357 R = CN, R^1 =H

361-365

Entry	Compound no	R	R^1	R^2	Yield%
1	**361**	H	OMe	TFA	96
2	**362**	H	F	TFA	96
3	**363**	OMe	H	TFA	90
4	**364**	CN	H	TFA	91
5	**365**	CN	H	Ts	57[a]

[a] Reaction was performed at 40 ^oC.

The *N*-Ts and *N*-TFA derivatives of 2-heptynylaniline **358** were also prepared. Treatment of **358** with TsCl and pyridine at 0 ^oC to rt for 18 h afforded the desired product **366** in a yield of 82% (**Scheme 5.25**). The structure of **366** was identified from its NMR and MS analysis. The *N*-TFA derivative of **367** was prepared upon treatment with $(CF_3CO)_2O$ and pyridine in CH_2Cl_2 at 0 ^oC to rt for 1 h (**Scheme 5.25**). The desired product **367** was isolated in a high yield of 89%.



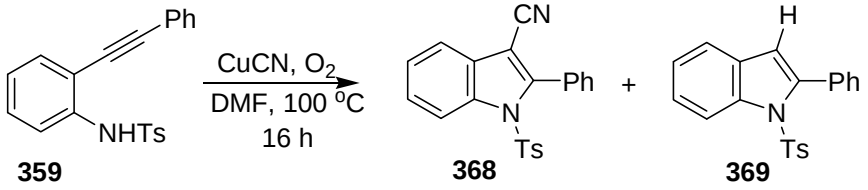
Scheme 5.25. Reaction of **357** with TsCl and $(CF_3CO)_2O$.

5.5. Cyclization-Cyanation Reactions of *ortho*-Alkynylanilines

After preparing the precusors for the cyclization-cyanation reactions, the reaction of *ortho*-alkynylaniline **359** with CuCN was performed. Treatment of **359** with CuCN (1.1 eq) in DMF at 100 ^oC under an oxygen atmosphere gave a 58 : 42 mixture of the cyanated indole **368** and the 3-unsubstituted indole **369** in respective yields of 41% and 34% (**Table 5.2**, Entry 1). The indole **369** is a known compound and its NMR data were the same as those in the literature.[85] The ^1H NMR spectrum (**Figure 5.2**) showed resonances at 6.54 (1H, s) ppm, corresponding to methine proton H3 and at 2.28 (3H, s) ppm, corresponding to the methyl protons. The 3-cyano indole **368** was identified from its NMR spectroscopic analysis. The ^1H and ^{13}C NMR spectra were in good agreement with the structure. The signal for the methine proton at the C3 position was not observed in the ^1H NMR spectrum of **368**, while the methyl protons resonated at 2.33 (3H, s) ppm (**Figure 5.1**). The CN carbon resonated at 96.7 ppm, and the methyl carbon resonated at 21.6 ppm in the ^{13}C NMR spectrum. The presence of cyano group was also confirmed by the sharp band in the IR spectrum at 2230 cm^{-1}. HREIMS analysis confirmed its molecular formula to be $C_{22}H_{16}N_2O_2S$. The reaction was repeated with 2.2 mol equivalents of CuCN under the same reaction conditions with the aim of obtaining only 3-cyanoindole. The reaction afforded products **368** and **369** in 48% and 26% yields, respectively. ^1H NMR analysis of the crude mixture showed **368** and **369** in a ratio of 74 : 26, respectively (**Table 5.2**, Entry 2). The yield and ratio of 3-cyanoindole **368** over **369** was increased by increasing the amount of CuCN. The use of 3.0 mol equivalents of

CuCN in the same reaction resulted in the formation of a 97 : 3 mixture of products **368** and **369** which were isolated in 74% and 3% yield, respectively (**Table 5.2**, Entry 3). The ratios were determined by measuring the integrals of the methyl proton signals for both products in the ^{1}H NMR spectrum of the crude reaction mixture.

Table 5.2. Optimization of cyclization-cyanation reaction of **359**.



359 **368** **369**

Entry	Equivalents of CuCN	Yield% of 368	Yield% of 369	368 : 369[a]
1	1.1	41	34	58 : 42
2	2.2	48	26	74 : 26
3	3.0	74	3	98 : 2

[a] Ratios were obtained from the ^{1}H NMR spectrum of the crude reaction mixture.

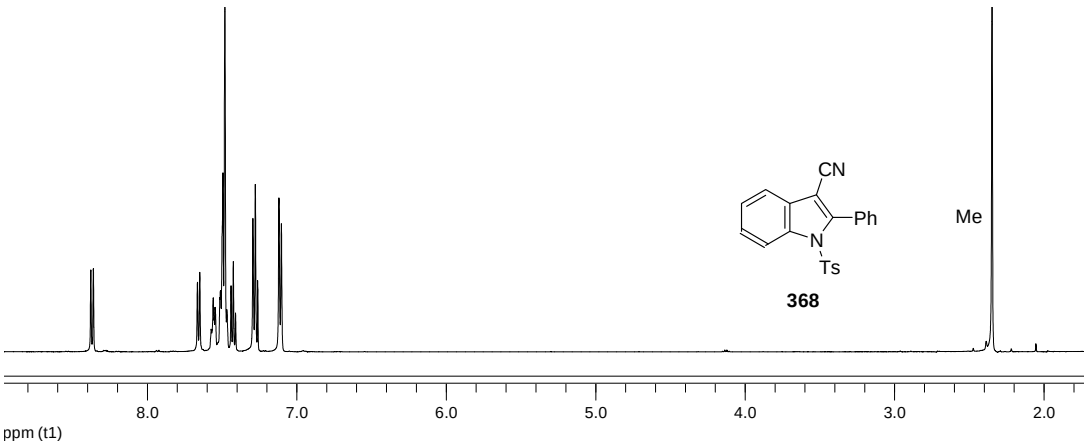


Figure 5.1. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **368**.

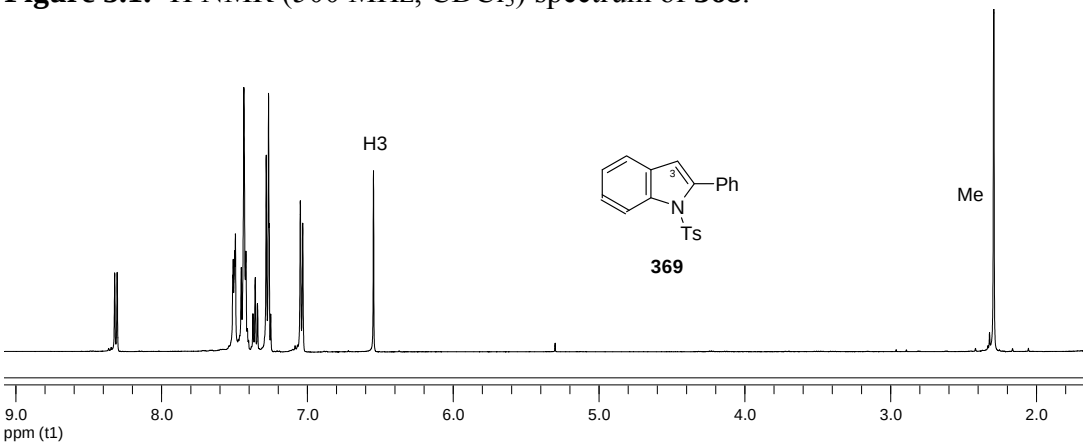
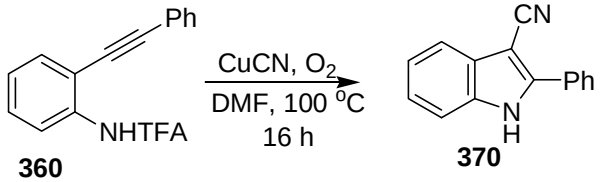


Figure 5.2. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **369**.

Next, the TFA protected aniline derivative **360** was subjected to the same reaction under the optimized experimental conditions (3.0 eq. of CuCN). The reaction yielded the 3-cyanoindole **370** exclusively in a high yield of 80% (**Table 5.3**, Entry 1). The TFA group did not survive under the reaction conditions. The ^{1}H NMR spectrum of **370** confirmed the structure by showing a resonance at 11.5 (1H, br. s) ppm corresponding to the NH proton. The ^{13}C NMR spectrum was also confirmed the structure by showing a resonance at 83.7 ppm corresponding to the CN carbon. The DEPT experiment showed 5 quarternary aromatic carbons at 145.5, 136.6, 130.7, 129.7 and 117.1 ppm, and seven aromatic methine carbons at 130.6, 130.1, 127.8, 124.8, 122.9, 119.4 and 113.2 ppm. The IR spectrum possessed bands at 3221 and 2217 cm^{-1}, corresponding to the N-H and C≡N stretches. LRESIMS analysis showed a $[M + H]^{+}$ ion at 219 amu, consistent with the structure. The reaction was repeated with 1.1 and 2.2 mol equivalents of CuCN in order to find the optimum amount of CuCN. The use of 1.1 equivalents of CuCN resulted in formation of **370** exclusively in a yield of 69% while the use of 2.2 equivalents of CuCN gave the product **370** in 55% yield exclusively (**Table 5.3**, Entries 2 and 3). The use of 3.0 equivalents of CuCN provided the best results for both tosyl and TFA derivatives.

Table 5.3. Optimizaton of cyclization-cyanation reaction of **360**.

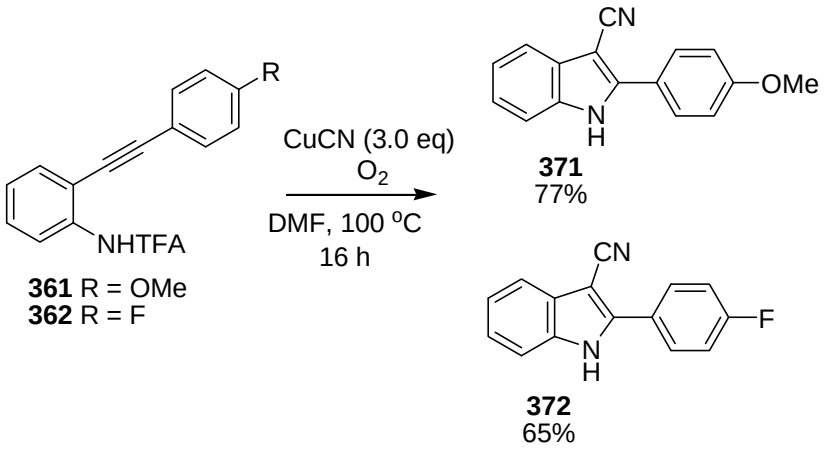


360 **370**

Entry	Equivalents of CuCN	Yield% of 370
1	3.0	80
2	1.1	55
3	2.2	69

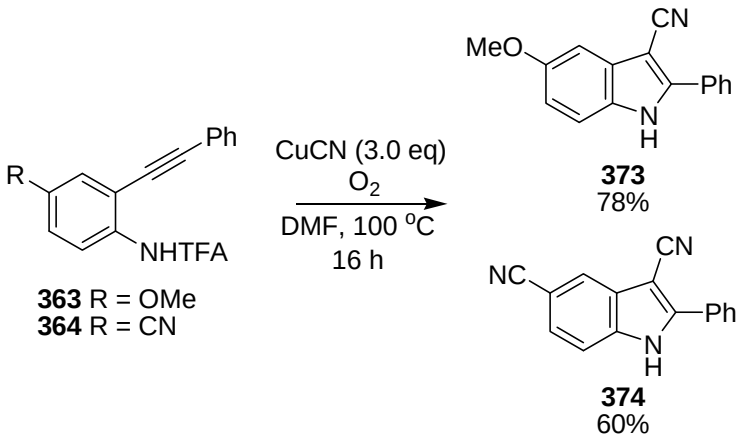
The cyclization-cyanation reactions of **361** and **362** using 3.0 equivalents of CuCN afforded the desired 3-cyanoindoles **371** and **372** in respective yields of 77% and 65% (**Scheme 5.26**). The ^{1}H NMR spectrum of **371** was consistent with the desired structure and showed the NH proton peak at 11.4 (1H, br. s) ppm and the methoxy protons at 3.89 (3H, s) ppm. The CN carbon resonated at 81.9 ppm in the ^{13}C NMR spectrum. The N-H and C≡N bond stretches were observed in the IR spectrum of **371** at 3257 cm^{-1} and 2212 cm^{-1}, respectively. Further the HREIMS analysis revealed its

molecular formula as $C_{16}H_{12}N_2O$. The ^{1}H NMR spectrum of **372** showed a resonance for the NH proton at 11.5 (1H, br. s) ppm. In the ^{13}C NMR spectrum the CN carbon was observed at 83.7 ppm. The quarternary aromatic *ipso* carbon (CF) resonated at 164.2 (d, $J_{C,F}$ = 247.6 Hz) ppm, while the aromatic methine carbons at the *ortho* and *meta* position to fluorine resonated at 130.2 (d, $J_{C,F}$ = 8.5 Hz) and 116.9 (d, $J_{C,F}$ = 7.1 Hz) ppm, respectively. The quarternary aromatic carbon *para* to the fluorine substituent was observed at 116.5 (d, $J_{C,F}$ = 3.1 Hz) ppm. The IR spectrum confirmed the structure by showing bands at 3257 cm^{-1}, corresponding to N-H bond stretch, and 2213 cm^{-1} corresponding to the C≡N bond stretch. Thus the cyanation-cyclization reactions tolerated well the electron donating and electron withdrawing substituents on the phenyl ring of the alkyne.



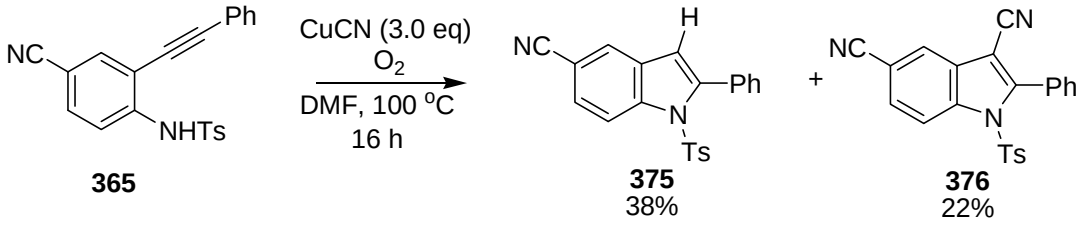
Scheme 5.26. Cyclization-cyanation reactions of **361** and **362**.

After obtaining encouraging results from the cyclization–cyanation reaction of **361** and **362**, the *ortho*-alkynylanilines **363** and **364** were subjected to the the same reaction under the same experimental conditions. The desired 3-cyanoindoles **373** and **374** were obtained in 78% and 60% yield, respectively (**Scheme 5.27**). The ^{1}H and ^{13}C NMR spectroscopic and MS data were in good agreement with the structures. As a result the cyclization-cyanation reaction worked equally well with both electron donating or electron withdrawing substituents on both phenyl rings of the 2-alkynylanilines.



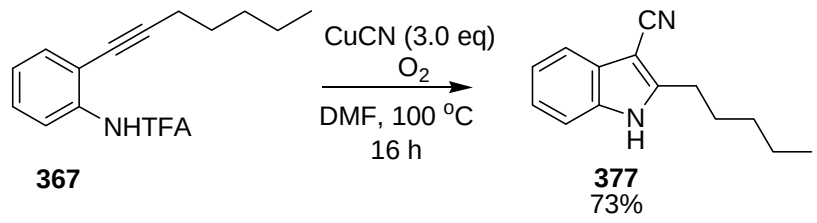
Scheme 5.27. Cyclization-cyanation reactions of **363** and **364**.

Although the *N*-TFA derivative of 4-cyano-2-alkynylaniline **364** afforded the cyanoindole **374** exclusively, the *N*-Ts analogue of the same precursor gave a mixture of indole and 3-cyanoindole. Treatment of **365** with CuCN under the same experimental conditions furnished a 60 : 40 mixture of products **375** and **376** in 38% and 22% yields, respectively (**Scheme 5.28**). The H3 and methyl protons appeared at 6.56 (1H, s) and 2.31 (3H, s) ppm, respectively in the ^{1}H NMR spectrum of **375**. The cyano carbon and methyl carbon resonances appeared at 107.6 and 21.6 ppm, respectively in the ^{13}C NMR spectrum. The IR spectrum of **375** showed the C≡N bond stretch at 2223 cm^{-1}, while the HREIMS analysis revealed the molecular formula $C_{22}H_{17}N_2O_2S$, consistent with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **376** was also in good agreement with the proposed structure. The methyl protons resonated at 2.36 (3H, s) ppm, while its carbon resonated at 21.6 ppm. The cyano carbon signals were observed at 109.1 and 96.0 ppm in the ^{13}C NMR spectrum. The HRESIMS analysis confirmed molecular formula of **376** as $C_{23}H_{16}N_3O_2S$.



Scheme 5.28. Cyclization-cyanation reaction of **365**.

The cyclization-cyanation reactions of *ortho*-heptynylaniline derivatives were also studied. 3-Cyano-2-pentylindole **377** was synthesized from the reaction of **367** with CuCN (3.0 eq) under the optimized reaction conditions in 73% yield (**Scheme 5.29**). The ^{1}H NMR spectrum of **377** showed resonances at 8.70 (1H, br. s) ppm corresponding to the NH, and at 2.94 (2H, t, *J* = 7.0 Hz), 1.80-1.78 (2H, m) and 1.38-1.35 (4H, m) ppm corresponding to methylene protons, and at 0.90 (3H, t, *J* = 7.0 Hz) ppm corresponding to methyl protons of the pentyl side chain. The ^{13}C NMR spectrum showed a signal at 84.7 ppm corresponding to the CN carbon. The DEPT spectrum showed four methylene carbons at 31.1, 28.7, 27.5 and 22.2 ppm and a methyl carbon at 13.8 ppm, consistent with the structure of **377**. The C≡N bond stretch was observed at 2208 cm^{-1} in the IR spectrum. The HRESIMS analysis also confirmed the structure of **377** by revealing the molecular formula as $C_{14}H_{17}N_2$.

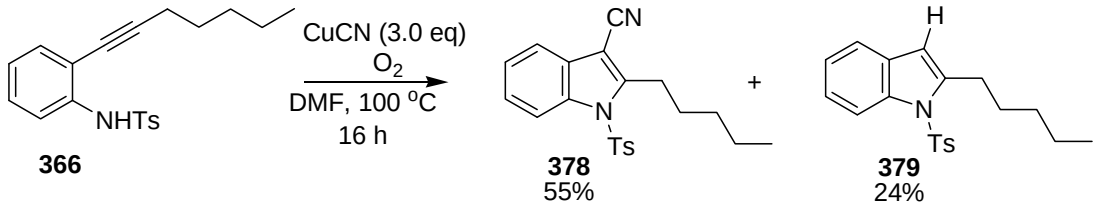


367 **377** 73%

Scheme 5.29. Synthesis of 3-cyano-2-pentylindole **375**.

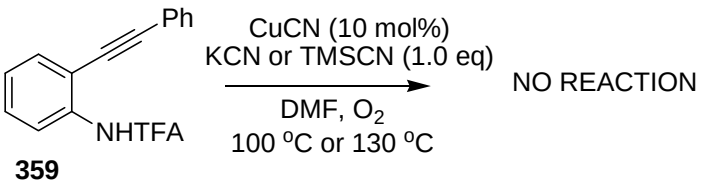
While the cyclization-cyanation reaction of **367** provided the 3-cyano-2-pentylindole **377** exclusively, the *N*-Ts analogue **366** afforded two products. The reaction of **366** furnished a 70 : 30 mixture of products **378** and **379** that were separated by column chromatography in respective yields of 55% and 24% (**Scheme 5.30**). The structures of **378** and **379** were identified from their NMR spectroscopic analysis. For **378** the methylene protons resonated at 3.20 (2H, t, *J* = 7.0 Hz), 1.82-1.77 (2H, m) and 1.43 (4H, m) ppm while the methyl protons resonated at 2.37 (3H, s) and 0.91 (3H, t, *J* = 7.0 Hz) ppm in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum showed the CN carbon signal at 94.5 ppm. The DEPT spectrum confirmed the structure of **378** by showing four methylene carbon resonances at 31.4, 30.4, 28.5 and 22.2 ppm, and two methyl carbon signals at 21.6 and 13.9 ppm. Further the IR spectrum showed a band at 2228 cm^{-1} corresponding to the C≡N group. The ^{1}H NMR spectrum of **379** confirmed the structure and showed the diagnostic H3 proton resonance at 6.37 (1H, s) ppm. It was concluded that the *N*-Ts derivatives of anilines provided mixtures of

indole and cyanoindole products while the *N*-TFA derivatives afforded the 3-cyanoindole products exclusively. The cyclization-cyanation was useful for making both 2-aryl or 2-alkyl-3-cyanoindoles.



Scheme 5.30. Reaction of **366** with CuCN.

An attempt to obtained the cyanoindole from the reaction of **359** with a catalytic amount of CuCN and a cheap cyanide source failed. The *ortho*-alkynylaniline **359** was treated with CuCN (10 mol%) and KCN (3.0 eq) and TMEDA (1.0 eq) in DMF at 100 ^{o}C under an oxygen atmosphere. After 16 h the TLC analysis showed only starting material (**Scheme 5.31**). The reaction temperature was increased to 130 ^{o}C and the reaction mixture was stirred at this temperature for 6 h which resulted in only recovery of unreacted starting material. It was thought that the poor solubility of KCN in DMF might be a problem and for this reason TMSCN was next used as a cyanide source. The use of TMSCN (1.0 eq.) under the same experimental conditions resulted in only quantitative recovery of the unreacted starting material (**Scheme 5.31**).

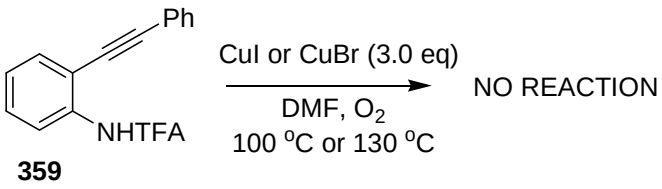


Scheme 5.31. Attempts to synthesize 3-cyanoindole by using 10 mol% of CuCN.

5.5.1. Attempts to Synthesise 3-Haloindoles

Unexpectedly the copper mediated cyclization-halogenation reactions of 2-alkynylanilines did not work. Treatment of **359** with CuI (3.0 eq) in DMF at 100 ^{o}C or 130 ^{o}C under an oxygen atmosphere did not give any of the desired 3-iodoindole,

the unreacted starting material was recovered (**Scheme 5.32**). The use of CuBr (3.0 eq) under the same experimental conditions did not change the result, only unreacted **359** was recovered.



359

Scheme 5.32. Attempts to make 3-haloindoles.

In conclusion, a novel method for the synthesis of 3-cyanoindoles have been developed. This method showed good tolerance to electron-donating and electron withdrawing substituents and allowed 3-cyanoindoles to be obtained in a single step. While the method of Wang[140] (**Scheme 5.11**) provides 3-bromo and 3-chloro indoles in one step from *ortho*-alkynylanilines this method has not been extended to make 3-cyanoindoles. Future studies could involve the examination of Wang`s conditions using $CuCN/O_2$ instead of $CuBr_2$ or $CuCl_2$ to prepare 3-cyanoindoles.

6. CONCLUSIONS

The development of new methods for the synthesis of functionalized pyrrolidines is of important since they are the common ring structure that forms the bicyclic, heterocyclic core structure of the pyrrolizidine, indolizidine and *Stemona* alkaloids.

In Chapter 2 we reported our efforts to develop a general method for preparing 4-hydroxy-5-substituted pyrrolidin-2-ones **71** from the borono-Mannich reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones **69** with boronic acids. The 4,5-dihydroxypyrrolidin-2-one **124** gave the 4,5-*cis* adducts **127** and **137** with very high *cis* selectivity but in relatively low yields, while the 4-benzyloxy-5-hydroxypyrrolidin-2-one gave the 4,5-*trans* adducts with good *trans* selectivity and in good to moderate yields. Unfortunately the desired dienyl 4,5-*cis* adduct **171**, required for the synthesis of the *Stemona* alkaloids, could only be obtained in the low yield of 33%. A RCM reaction of **171** gave the desired pyrrolo[1,2-*a*]azepine **172** in 72% yield.

In Chapter 2 we also reported the formation of the novel Ritter reaction product, a pyrrolo[3,2-*b*]oxazole **129**, as an unwanted side product in the reaction of **124** with (*E*)-2-styrylboronic acid **122** when acetonitrile was used as a solvent.

In Chapter 3 we described an efficient synthesis of pyrrolo[3,2-*b*]oxazoles from the Ritter reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones with nitriles in the presence of $BF_3.Et_2O$. When 4-benzyloxy-5-hydroxypyrrolidin-2-one was used as the substrate the corresponding pyrrolo[3,2-*b*]oxazoles were formed along with the corresponding *N*-benzyl amides, which were formed from the Ritter reactions of benzyl cation and the nitrile. The isolation of these amide compounds were consistent with our proposed reaction mechanism. Two of the pyrrolo[3,2-*d*]oxazole compounds were hydrolyzed to the novel 5-acylaminopyrrolidinones **185** and **236**.

In Chapter 4 we reported the metal-catalyzed cycloisomerization reactions of 3-hydroxy-2-alkynylpyrrolidine **263** which was obtained from the borono-Mannich reaction of 2,3-dihydroxypyrrolidine **116** and potassium phenylethynyltrifluoroborate **262**. The cycloisomerization reaction of the pyrrolidine *cis*-**263** afforded the 2,5-disubstituted furan **270** when Ag(I), Au(I) or Pd(II)/Cu(I) were used as a catalyst. While 3-halo-2,5-disubstituted furans were synthesized from the CuCl or CuBr

mediated reactions of pyrrolidine **116**. Novel 3-iodo, 3-phenyl and 3-cyano substituted furo[3,2-*b*]pyrroles were synthesized from the reactions of **116** with CuI, CuCN and PhI/Pd(dba)$_2$, respectively.

In Chapter 5 a novel method for the synthesis of 3-cyanoindoles was developed. This method showed good tolerance to electron-donating and electron withdrawing substituents on the starting *ortho*-alkynylaniline and allowed 3-cyanoindoles to be obtained in a single step. While the method of Wang (**Scheme 5.11**) provides 3-bromo and 3-chloro indoles in one step from *ortho*-alkynylanilines this method has not been extended to make 3-cyanoindoles. Future studies could involve the examination of Wang`s conditions using CuCN/O_2 instead of $CuBr_2$ or $CuCl_2$ to prepare 3-cyanoindoles.

7. EXPERIMENTAL

7.1. General Experimental

7.1.1. Reaction Conditions

All reactions were performed in an oven dried glassware under an atmosphere of nitrogen, unless otherwise stated. Reactions were monitored by thin-layer chromatographic analysis.

Anhydrous CH_2Cl_2 and MeOH were obtained from Sigma-Aldrich Chemical Co. Anhydrous THF was obtained by distillation from sodium wire/benzophenone. "Evaporation" refers to the removal of solvent under reduced pressure using a rotary evaporator and then the removal of the last traces of solvent under high vacuum. "Dried" refers to the drying of organic extracts over $MgSO_4$ or Na_2SO_4. Commercial substances were used without further purification. Petrol refers to the hydrocarbon fraction of bp 45-55 ^oC.

7.1.2. Nuclear Magnetic Resonance (NMR) Spectroscopy

^1H and ^{13}C NMR spectra were recorded on a Varian Inova NMR Spectrometer (^1H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or Varian Unity-300 (^1H NMR at 300 MHz, ^{13}C NMR at 75 MHz) instruments. $CDCl_3$ (internal reference at δ 7.26 for ^1H NMR and δ 77.00 for ^{13}C NMR) was used as the NMR solvent unless otherwise stated. The following abbreviations were used; s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, br = broad. NMR assigments were based on COSY, HSQC, HMBC and DEPT experiments.

7.1.3. Chromatography

TLC analyses were performed using aluminium backed Merck silica gel TLC plates. Compounds were detected under a 254 nm ultraviolet lamp if applicaple, or by staining with an acidified aqueous solution of ammonium molybdate and cerium(IV) sulphate, followed by development with a 1400 W heat gun. Flash column chromatography was performed using Merck silica gel (40 – 63 μm) packed by the slurry method.

7.1.4. Melting Points

Melting points were obtained using a Gallenkamp MF-370 capillary tube melting point apparatus and are uncorrected.

7.1.5. Polarimetry

Optical rotations were measured using a 1 cm cell, in a Jasco DIP-370 digital polarimeter. Specific rotations were calculated by using the average value of 10 optical rotation measurements.

7.1.6. Mass Spectrometry

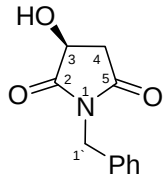
Low-resolution mass spectra were obtained on a Shimadzu GC mass spectrometer (EI) or Waters LCZ single quadropole (ESI). High-reslotion mass spectra (exact masses) were obtained on a VG Autospec mass spectrometer (EI) or a Waters QTOF (ESI). HRMS were obtained in lieu of elemental analysis and ^{1}H and ^{13}C NMR spectroscopy were used as the criteria for purity.

7.1.7. Infrared Spectrometry

Infrared spectra were obtained as neat samples on a Smart Omni-Sampler Avator ESP Nicolet-Brand.

7.2. Experimental for Chapter 2

(*S*)-1-Benzyl-3-hydroxypyrrolidine-2,5-dione (123)



123

To a suspension of L-malic acid (5.00 g, 37.2 mmol) in xylene (250 mL) in a Dean-Stark and condenser equipped round bottom flask was added benzylamine (3.99 g, 37.2 mmol) at rt. The resulting suspension was heated at reflux temperature for 2 h, then xylene was removed *in vacuo*. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title compound (6.10 g, 80%) as a white solid.

R_f : 0.53 (1 : 1, EtOAc/petrol).

Mp 100-102 ^{o}C (Lit[67] Mp = 101-102 ^{o}C).

$[\alpha]_D^{23}$ +16.8^{o} (*c* 0.23, $CHCl_3$) (Lit.[67] $[\alpha]_D^{25}$ +75.4 ^{o} (*c* 4.4, $CHCl_3$)).

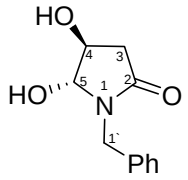
^{1}H NMR δ 7.33-7.22 (5H, m, ArH), 4.61 (2H, s, H1`), 4.58-4.54 (1H, m, H3), 4.38 (1H, br. s, OH), 3.01 (1H, dd, *J* = 8.0, 18.0 Hz, H4), 2.65 (1H, dd, *J* = 5.0, 18.0 Hz, H4).

^{13}C NMR δ 173.8 (CO), 172.1 (CO), 135.2 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.0 (ArCH), 69.4 (C3), 42.3 (C1`), 37.2 (C4).

^{1}H and ^{13}C NMR data matched the published data.

EIMS *m/z* 205 (M^+, 70%).

(4*S*)-1-Benzyl-4,5-dihydroxypyrrolidin-2-one (124)



124

(*S*)-1-Benzyl-3-hydroxypyrrolidine-2,5-dione (1.00 g, 4.87 mmol) was dissolved in a mixture of EtOH and CH_2Cl_2 (40 mL, 1 : 1), and the solution was cooled to -20 ^{o}C. $NaBH_4$ (0.92 g, 24.3 mmol) was added portionwise and the resulting suspension was stirred at -20 ^{o}C for 30 min. The mixture was poured into a saturated aqueous solution of $NaHCO_3$ (30 mL) and was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by column chromatography (increasing polarity from 1 : 1, EtOAc/petrol to EtOAc) to give the title compound (0.725 g, 72%, dr = 92 : 8) as a white solid.

R_f : 0.22 (1 : 1, EtOAc/petrol).

Mp 109-111 ^{o}C.

$[\alpha]_D^{23}$ +19.2^{o} (*c* 0.21, MeOH).

υ_{max}/cm^{-1} 3477, 1644, 1449, 1332, 1178, 1081.

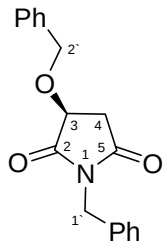
^{1}H NMR δ (CD_3OD) 7.32-7.24 (5H, m, ArH), 4.85 (1H, d, *J* = 15.5 Hz, H1'), 4.76 (1H, br d, *J* = 1.5 Hz, H5), 4.12 (1H, dd, *J* = 1.5, 6.5 Hz, H4), 4.08 (1H, d, *J* = 15.5 Hz, H1'), 2.86 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.22 (1H, dd, *J* = 1.5, 17.0 Hz, H3).

^{13}C NMR δ (CD_3OD) 175.7 (C2), 137.6 (ArC), 129.6 (ArCH), 128.9 (ArCH), 128.4 (ArCH), 90.1 (C4), 72.3 (C5), 43.9 (C1`), 39.3 (C3).

EIMS *m/z* 207 (M^+, 75%).

HREIMS calculated for $C_{11}H_{13}NO_3$ (M^+), 207.0895, found 207.0902.

(*S*)-1-Benzyl-3-(benzyloxy)pyrrolidine-2,5-dione (125)



125

The alcohol **123** (2.00 g, 9.75 mmol) was dissolved in Et_2O (100 mL) and then BnBr (5.0 g, 29.2 mmol) and Ag_2O (6.76 g, 29.2 mmol) were added. The resulting suspension was stirred at rt for 2 d in the dark. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 2, EtOAc/petrol) to give the title product (2.24 g, 78%) as a pale yellow solid.

R_f : 0.46 (1 : 2, EtOAc/petrol).

Mp 74-76 ^oC (Lit.[67] Mp 76-77.5 ^oC).

$[\alpha]_D^{23}$ +23.6^o (*c* 0.18, $CHCl_3$) (Lit.[67] $[\alpha]_D^{25}$ + 34.7 ^{o} (*c* 0.7, $CHCl_3$)).

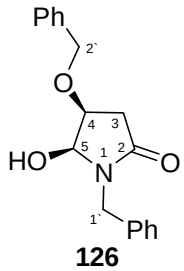
^{1}H NMR δ 7.38-7.30 (10H, m, ArH), 4.98 (1H, d, *J* = 11.5 Hz, H2`), 4.78 (1H, d, *J* = 11.5 Hz, H2`), 4.67 (2H, s, H1`), 4.37-4.34 (1H, m, H3), 2.94 (1H, dd, *J* = 8.0, 18.0 Hz, H4), 2.66 (1H, dd, *J* = 4.5, 18.5 Hz, H4).

^{13}C NMR δ 175.8 (CO), 173.9 (CO), 136.8 (ArC), 135.6 (ArC), 129.0 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 73.2 (C2`), 72.3 (C3), 42.4 (C1`), 36.5 (C4).

^{1}H and ^{13}C NMR data matched the published data.

EIMS *m/z* 295 (M^+, 65%).

(4*S*,5*S*)-1-Benzyl-4-(benzyloxy)-5-hydroxypyrrolidin-2-one (126)



126

Prepared in a similar fashion to **124** above, from **125** (0.70 g, 2.5 mmol) and $NaBH_4$ (0.47 g, 12.6 mmol) in CH_2Cl_2/EtOH (30 mL, 1 : 1) with stirring at -20 ^oC for 30 min. The crude product was purified by column chromatography (1 : 2, EtOAc/petrol) to give the title product (0.51 g, 70%, dr = 100 : 0) as a white solid.

R_f : 0.37 (1 : 2, EtOAc/petrol).

Mp 130-132 ^oC (Lit.[58] Mp 130-130.5 ^oC).

$[\alpha]_D^{23}$ +37.1^o (*c* 0.17, $CHCl_3$) (Lit.[58] $[\alpha]_D^{24}$ + 20.6 ^{o} (*c* 1.2, $CHCl_3$)).

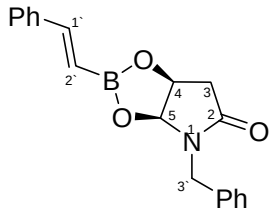
^{1}H NMR δ 7.36-7.28 (10H, m, ArH), 4.98 (1H, dd, *J* = 6.5, 7.5 Hz, H5), 4.90 (1H, d, *J* = 14.5 Hz, H1`), 4.61 (1H, d, *J* = 11.5 Hz, H2`), 4.56 (1H, d, *J* = 11.5 Hz, H2`), 4.16 (1H, d, *J* = 14.5 Hz, H1`), 4.10 (1H, dd, *J* = 6.5, 7.0 Hz, H4), 3.50 (1H, br. s, OH), 2.59 (2H, d, *J* = 7.0 Hz, H3).

^{13}C NMR δ 171.0 (C2), 136.5 (ArC), 136.3 (ArC), 128.6 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.3 (ArCH), 127.9 (ArCH), 127.5 (ArCH), 81.1 (C5), 72.1 (C2`), 71.7 (C4), 43.4 (C1`), 35.9 (C3).

^{1}H and ^{13}C NMR data matched the published data.

EIMS *m/z* 297 (M^+ 100%).

(3a*S*, 6a*S*, *E*)-1-Benzyl-5-styryl-hexahydroborolo[3,4-*b*]pyrrol-2(1*H*)-one (128)



128

To a solution of **124** (0.10 g, 0.482 mmol) and *trans*-styrylboronic acid (0.214 g, 1.45 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 ^{o}C under N_2, was added dropwise $BF_3{\cdot}OEt_2$ (0.273 g, 1.927 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated $NaHCO_3$ solution (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The title product was obtained without further purification (0.113 g, 78%).

R_f : 0.34 (1 : 1, EtOAc/petrol).

$[\alpha]_D^{25}$ +48.3^{o} (*c* 0.32, $CHCl_3$).

υ_{max}/cm^{-1} 1685, 1449, 1367, 1065.

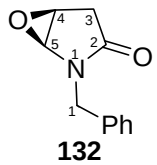
^{1}H NMR δ 7.42 (1H, d, *J* = 18.5 Hz, H2'), 7.35-7.20 (10H, m, ArH), 6.14 (1H, d, *J* = 18.5 Hz, H1'), 5.59 (1H, d, *J* = 6.0 Hz, H5), 5.02 (1H, d, *J* = 14.5 Hz, H3'), 4.93 (1H, dd, *J* = 6.0, 7.0 Hz, H4), 4.15 (1H, d, *J* = 14.5 Hz, H3'), 2.83 (1H, dd, *J* = 7.0, 18.0 Hz, H3), 2.71 (1H, d, *J* = 18.0 Hz, H3).

^{13}C NMR δ 171.2 (C2), 136.9 (ArC), 135.6 (ArC), 129.4 (C2'), 128.7 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128. 4 (ArCH), 128.3 (ArCH), 127.8 (ArCH), 127.2 (C1'), 89.4 (C5), 73.1 (C4), 43.9 (C3'), 38.1 (C3).

EIMS *m/z* 319 (M^+, 100%).

HREIMS calculated for $C_{19}H_{18}BNO_3$ (M^+) 319.1379, found 319.1376.

(1*S*, 5*S*)-2-Benzyl-6-oxa-2-aza-bicyclo[3.1.0]hexan-3-one (132)



132

To a solution of **124** (0.10 g, 0.482 mmol) in nitromethane (5 mL), at 0 ^{o}C was added $BF_3{\cdot}OEt_2$ (0.273 g, 1.93 mmol). The mixture was stirred at 80 ^{o}C for 5 h. A saturated solution of $NaHCO_3$ (5 mL) was added, and aqueous layer was extracted with dichloromethane (3 x 10 mL).

The combined extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The title compound was unstable to silica gel and was obtained as an oil without further purification (0.071 g, 78%).

R_f : 0.31 (EtOAc).

$[\alpha]_D^{24}$ +53.7° (*c* 0.42, $CHCl_3$).

υ_{max}/cm^{-1} 1690, 1449, 1362, 1214, 1081, 1019.

^{1}H NMR δ 7.33-7.22 (5H, m, ArH), 5.41 (1H, d, *J* = 7.0 Hz, H5), 5.03 (1H, d, *J* = 14.5 Hz, H1'), 4.89 (1H, dd, *J* = 7.0, 8.0 Hz, H4), 4.07 (1H, d, *J* = 14.5 Hz, H1'), 2.85 (1H, dd, *J* = 8.0, 18.5 Hz, H3), 2.68 (1H, d, *J* = 18.5 Hz, H3).

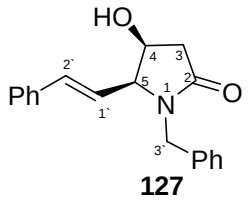
^{13}C NMR δ 171.1 (C2), 136.2 (ArC), 128.9 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 83.5 (C5), 75.0 (C4), 44.7 (C1'), 37.7 (C3).

EIMS *m/z* 189 (M^+, 75%).

HREIMS calculated for $C_{11}H_{11}NO_2$ (M^+) 189.0789, found 189.0783.

General Procedure for Borono-Mannich Reaction of 124 and Preparation of (4*S*, 5*S*, *E*)-1-Benzyl-4-hydroxy-5-styrylpyrrolidin-2-one (127)

To a solution of **124** (0.10 g, 0.482 mmol) in anhydrous $MeNO_2$ (5 mL), at 0 °C was added *trans*-styrylboronic acid (0.214 g, 1.4 mmol) and then $BF_3{\cdot}OEt_2$ (0.273 g, 1.93 mmol). The mixture was stirred at 80 °C for 16 h. A saturated aqueous solution of $NaHCO_3$ (5 mL) was added, and aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title compound (0.027 g, 20%, dr = 91 : 9) as a white solid,



127

R_f : 0.32 (1 : 1, EtOAc/petrol).

Mp 128-130 °C.

υ_{max}/cm^{-1} 3334, 1669, 1444, 1426, 1262, 1176, 1071.

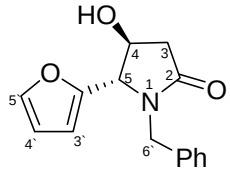
^{1}H NMR δ (major *cis* isomer) 7.35-7.18 (10H, m, ArH), 6.51 (1H, d, *J* = 16.5 Hz, H2'), 6.15 (1H, dd, *J* = 8.5, 16.5 Hz, H1'), 4.93 (1H, d, *J* = 15.5 Hz, H3'), 4.43 (1H, ddd, *J* = 3.5, 6.0, 7.0 Hz, H4), 4.10 (1H, dd, *J* = 6.0, 8.5 Hz, H5), 3.96 (1H, d, *J* = 15.5 Hz, H3'), 2.73 (1H, dd, *J* = 7.0, 17.5 Hz, H3), 2.54 (1H, dd, *J* = 3.5, 17.5 Hz, H3), 2.45 (1H, br.s, OH).

^{13}C NMR δ (major *cis* isomer) 172.9 (C2), 136.5 (ArC), 136.3 (C2'), 135.7 (ArC), 128.6 (ArCH), 128.6 (ArCH), 128.4 (ArCH) , 128.3 (ArCH), 127.4 (ArCH), 126.6 (ArCH), 123.3 (C1'), 67.5 (C4), 65.2 (C5), 44.3 (C3'), 39.9 (C3).

EIMS *m/z* 293 (M^+, 100%).

HREIMS calculated for $C_{19}H_{19}NO_2$ (M^+) 293.1417, found 293.1415.

(4*S*, 5*S*)-1-Benzyl-5-(furan-2-yl)-4-hydroxypyrrolidin-2-one (136)



136

Prepared using the general method above, from **124** (0.150 g, 0.725 mmol), 2-furanboronic acid (0.243 g, 2.17 mmol), $MeNO_2$ (5.0 mL) and $BF_3{\cdot}OEt_2$ (0.411 g, 2.90 mmol), except that the reaction mixture was warmed to rt and stirred for 16 h. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title compound (0.126 g, 65%, dr = 77 : 23) as an oil.

R_f : 0.53 (1:1, EtOAc/petrol).

υ_{max}/cm^{-1} 3365, 1669, 1447, 1253, 1149, 1070, 1012.

^{1}H NMR δ (major *trans* isomer) 7.38 (1H, d, *J* = 1.5 Hz, H5'), 7.30-7.17 (5H, m, ArH), 6.34 (1H, dd, *J* = 1.5, 3.0 Hz, H4'), 6.21 (1H, d, *J* = 3.0 Hz, H3'), 4.92 (1H, d, *J* = 15.5 Hz, H6'), 4.42 (1H, ddd, *J* = 2.0, 2,5, 6.0 Hz, H4), 4.31 (1H, d, *J* = 2.0 Hz, H5), 3.58 (1H, d, *J* = 15.5 Hz, H6'), 3.00 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.48 (1H, dd, *J* = 2.5, 17.0 Hz, H3).

^{13}C NMR δ (major *trans* isomer) 172.9 (C2), 150.1 (C2`), 143.5 (C5`), 135.8 (ArC), 128.7 (ArCH), 128.3 (ArCH), 128.0 (ArCH), 110.3 (C4'), 109.0 (C3'), 69.5 (C4), 63.9 (C5), 44.2 (C6'), 39.8 (C3).

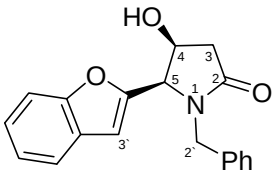
^{1}H NMR δ (minor *cis* isomer) 7.46 (1H, d, *J* = 1.5 Hz, H5'), 7.30-7.17 (5H, m, ArH), 6.42 (1H, dd, *J* = 1.5, 3.0 Hz, H4'), 6.17 (1H, d, *J* = 3.0 Hz, H3'), 4.98 (1H, d, *J* = 15.0 Hz, H6'), 4.57 (1H, d, *J* = 7.0 Hz, H5), 4.53 (1H, ddd, *J* = 7.5, 7.0, 2.5 Hz, H4), 3.60 (1H, d, *J* = 15.0 Hz, H6'), 2.70 (1H, dd, *J* = 7.5, 17.0 Hz, H3), 2.65 (1H, dd, *J* = 2.5, 17.0 Hz, H3).

^{13}C NMR δ (minor *cis* isomer) 172.5 (C2), 148.3 (C2`), 135.7 (ArC), 128.7 (ArCH), 128.5 (ArCH), 128.0 (ArCH), 127.6 (C5'), 111.1 (C4'), 110.5 (C3'), 66.9 (C4), 59.8 (C5), 44.6 (C6'), 39.1 (C3).

EIMS *m/z* 257 (M^+, 100%).

HREIMS calculated for $C_{15}H_{15}NO_3$ (M^+) 257.1049, found 257.1049.

(4*S*, 5*R*)-5-(Benzofuran-2-yl)-1-benzyl-4-hydroxypyrrolidin-2-one (137)



137

Prepared using the general method above, from **124** (0.05 g, 0.241 mmol), 2-benzofuranboronic acid (0.117 g, 0.724 mmol), $MeNO_2$ (3.0 mL) and $BF_3{\cdot}OEt_2$ (0.137 g, 0.966 mmol). The crude product was purified by column chromatography (Et_2O) to give the title compound (0.041 g, 56%, dr = 92 : 8) as an oil.

R_f : 0.47 (Et_2O).

υ_{max}/cm^{-1} 3308, 1670, 1454, 1417, 1355, 1306, 1255, 1167, 1108, 1086.

^{1}H NMR δ (major *cis* isomer) 7.51 (1H, d, *J* = 8.0 Hz, ArH), 7.41 (1H, d, *J* = 8.0 Hz, ArH), 7.54-7.29 (6H, m, ArH), 7.08 (1H, d, *J* = 8.0 Hz, ArH), 6.64 (1H, s, H3'), 5.06 (1H, d, *J* = 15.0 Hz, H2'), 4.64 (1H, d, *J* = 7.0 Hz, H5), 4.57 (1H, app br. q, *J ca* 7 Hz, H4), 3.61 (1H, d, *J* = 15.0 Hz, H2'), 2.76-2.74 (2H, m, H3).

^{13}C NMR δ (major *cis* isomer) 172.5 (C2), 155.3 (ArC), 151.3 (ArC), 135.7 (ArC), 128.4 (ArCH), 128.2 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 124.8 (ArC), 123.1 (ArCH), 121.2 (ArCH), 111.5 (ArCH), 107.7 (C3'), 67.0 (C4), 60.2 (C5), 44.5 (C2'), 39.1 (C3).

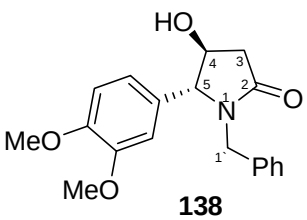
^{1}H NMR δ (minor *trans* isomer) 7.54 (1H, d, *J* = 8.0 Hz, ArH), 7.42 (1H, d, *J* = 8.0 Hz, ArH), 7.36-7.14 (7H, m, ArH), 6.58 (1H, s, H3'), 5.12 (1H, d, *J* = 15.0 Hz, H2'), 4.57 (1H, br. dd, *J* = 7.0, 2.5 Hz, H4), 4.48 (1H, s, H5), 3.71 (1H, d, *J* = 15.0 Hz, H2'), 3.07 (1H, dd, *J* = 7.0, 17.5 Hz, H3), 2.52 (1H, dd, *J* = 2.5, 17.5 Hz, H3).

^{13}C NMR δ (minor *trans* isomer) 172.8 (C2), 155.2 (ArC), 152.6 (ArC), 135.7 (ArC), 128.6 (ArCH), 128.1 (ArCH), 127.6 (ArCH), 125.5 (ArC), 124.8 (ArCH), 123.1 (ArCH), 121.1 (ArCH), 111.4 (ArCH), 105.9 (C3'), 69.6 (C4), 64.3 (C5), 44.4 (C2'), 39.9 (C3).

EIMS *m/z* 307 (M^+, 100%).

HREIMS calculated for $C_{19}H_{17}NO_3$ (M^+) 307.1208, found 307.1207.

(4*S*, 5*R*)-1-Benzyl-5-(3,4-dimethoxyphenyl)-4-hydroxypyrrolidin-2-one (138)



138

Prepared using the general method above, from **124** (0.05 g, 0.241 mmol), 3,4-dimethoxyphenylboronic acid (0.132 g, 0.724 mmol) and $BF_3{\cdot}OEt_2$ (0.137 g, 0.966 mmol). The desired product (0.035 g, 44%, dr = 72 : 28) was obtained

as an oil after purification by column chromatography (EtOAc).

R_f : 0.23 (EtOAc).

υ_{max}/cm^{-1} 3352, 1699, 1505, 1463, 1272, 1257, 1149, 1016.

^1H NMR δ (major *trans* isomer) 7.28-7.21 (5H, m, ArH), 7.02 (1H, s, ArH), 6.89 (1H, d, *J* = 8.0 Hz, ArH), 6.72 (1H, d, *J* = 8.0 Hz, ArH), 4.88 (1H, d, *J* = 2.5 Hz, H5), 4.82 (1H, d, *J* = 14.5 Hz, H1'), 4.23 (1H, br. dd, *J* = 2.5, 6.5 Hz, H4), 4.10 (1H, d, *J* = 14.5 Hz, H1'), 3.89 (3H, s, OMe), 3.80 (3H, s, OMe), 2.58 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.46 (1H, d, *J* = 17.0 Hz, H3).

^{13}C NMR δ (major *trans* isomer) 172.4 (C2), 149.3 (ArC), 147.9 (ArC), 136.0 (ArC), 128.6 (ArC), 128.5 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 125.2 (ArCH), 121.0 (ArCH), 111.6 (ArCH), 81.8 (C4), 65.13 (C5), 55.8 (OMe), 43.2 (C1'), 38.3 (C3).

^1H NMR δ (minor *cis* isomer) 7.28-7.21 (5H, m, ArH), 6.99 (1H, s, ArH), 6.86 (1H, d, *J* = 8.0 Hz, ArH), 6.70 (1H, d, *J* = 8.0 Hz, ArH), 5.06 (1H, d, *J* = 14.5 Hz, H1'), 4.47 (1H, d, *J* = 5.5 Hz, H5), 4.43-4.45 (1H, br.m H4), 3.87 (3H, s, OMe), 3.77 (3H, s, OMe), 3.63 (1H, d, *J* = 14.5 Hz, H1'), 2.70 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.54 (1H, d, *J* = 17.0 Hz, H3).

^{13}C NMR δ (minor *cis* isomer) 174.1 (C2), 149.2 (ArC), 147.8 (ArC), 135.7 (ArC), 128.6 (ArC), 128.4 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 125.2 (ArCH), 121.0 (ArCH), 111.6 (ArCH), 66.7 (C5), 66.3 (C4), 55.9 (OMe), 44.6 (C1'), 39.5 (C3).

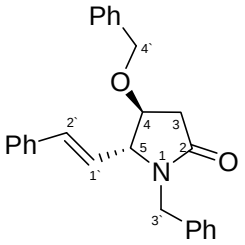
EIMS *m/z* 327 (M^+, 100%).

HREIMS calculated for $C_{19}H_{21}NO_4$ (M^+) 327.1470, found 327.1468.

General Procedure for Borono-Mannich Reaction of 126 and Preparation of (4*S*, 5*R*, *E*)-1-Benzyl-4-(benzyloxy)-5-styrylpyrrolidin-2-one (149)

To a solution of **126** (0.150 g, 0.504 mmol) and potassium (*E*)-2-styryltrifluoroborate (0.315 g, 1.49 mmol) in dry CH_2Cl_2 (5 mL) at 0 ^oC under N_2, was added dropwise $BF_3{\cdot}OEt_2$ (0.286 g, 2.06 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated $NaHCO_3$ solution (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give the title compound (0.113 g, 58%, dr = 92 : 8) as an oil.

R_f : 0.32 (1 : 2, EtOAc/petrol).



149

υ_{max}/cm^{-1} 1692, 1495, 1451, 1261, 1096, 1071, 1028.

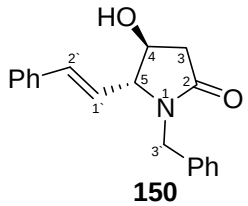
^{1}H NMR δ (major *trans* isomer) 7.58-7.15 (15H, m, ArH), 6.45 (1H, d, *J* = 15.7 Hz, H2'), 5.91 (1H, dd, *J* = 15.7, 8.0 Hz, H1'), 5.07 (1H, d, *J* = 14.7 Hz, H3'), 4.50 (2H, s, H4'), 4.10 (1H, d, *J* = 7.2 Hz, H4), 3.99 (1H, d, *J* = 8.0 Hz, H5), 3.91 (1H, d, *J* = 14.7 Hz, H3'), 2.82 (1H, dd, *J* = 7.2, 17.5 Hz, H3), 2.58 (1H, d, *J* = 17.5 Hz, H3).

^{13}C NMR δ (major *trans* isomer) 172.4 (C2), 137.3 (ArC), 136.2 (ArC), 135.7 (ArC), 133.9 (C2`), 128.7 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.8, (ArCH) 127.6 (ArCH), 127.4 (ArCH), 126.5 (ArCH), 125.6 (C1`), 77.0 (C5), 71.2 (C4), 65.9 (C4`), 44.0 (C3`), 37.2 (C3).

EIMS *m/z* 383 (M^+, 80%).

HREIMS calculated for $C_{26}H_{25}NO_2$ (M^+) 383.1881, found 383.1885.

(4*S*, 5*R*, *E*)-1-Benzyl-4-hydroxy-5-styrylpyrrolidin-2-one (150)



150

To a solution of **127** (0.080 g, 0.208 mmol) in CH_2Cl_2 (10 mL) at 0 ^{o}C under N_2, was added dropwise BBr_3 (0.209 g, 0.835 mmol). The mixture was stirred for 10 min, and then water (15 mL) and saturated aqueous $NaHCO_3$ solution (5mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (increasing polarity from 1 : 1, EtOAc/petrol to EtOAc) to give the title compound (0.055 g, 90%) as an oil.

R_f : 0.62 (EtOAc).

υ_{max}/cm^{-1} 3334, 1664, 1511, 1449, 1253, 1058.

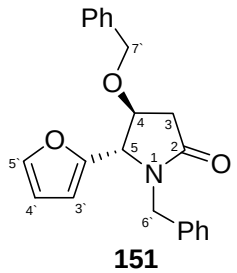
^{1}H NMR δ 7.32-7.21 (10H, m, ArH), 6.47 (1H, d, *J* = 15.5 Hz, H2'), 5.90 (1H, dd, *J* = 8.5, 15.5 Hz, H1'), 4.90 (1H, d, *J* = 15.0 Hz, H3'), 4.23 (1H, br. dd, *J* = 6.5, 2.5 Hz, H4), 3.94 (1H, d, *J* = 15.0 Hz, H3'), 3.92 (1H, d, *J* = 8.5 Hz, H5), 2.84 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.63 (1H, br. s., OH), 2.45 (1H, dd, *J* = 2.5, 17.0 Hz, H3).

^{13}C NMR δ 172.6 (C2), 136.2 (ArC), 135.6 (C2') , 134.2 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.5 (ArCH), 126.5 (ArCH), 125.09 (C1'), 70.6 (C4), 68.9 (C5), 44.2 (C3'), 39.4 (C3).

EIMS *m/z* 293 (M^+, 100%).

HREIMS calculated for $C_{19}H_{19}NO_2$ (M^+), 293.1415; found 293.1409.

(4*S*, 5*R*)-1-Benzyl-4-(benzyloxy)-5-(furan-2-yl)pyrrolidin-2-one (151)



151

Method A. Prepared using the general method above, from **126** (0.150 g, 0.504 mmol), 2-furanboronic acid (0.169 g, 1.51 mmol), $BF_3{\cdot}OEt_2$ (0.286 g, 2.06 mmol) and CH_2Cl_2 (5 mL). The desired product (0.140 g, 79%, dr = 71 : 29) was obtained as an oil after purification by column chromatography (1 : 3, EtOAc/petrol). R_f : 0.44 (1 : 3, EtOAc/petrol).

Method B. To a solution of **126** (0.10 g, 0.336 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC under N_2 was added furan (0.068 g, 1.00 mmol) and then $BF_3{\cdot}OEt_2$ (0.168 g, 1.34 mmol). The reaction mixture was stirred at rt for 2 h. Saturated aqueous $NaHCO_3$ solution (5 mL) was added and aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The desired product (0.045 g, 40%, dr = 55 : 45) was obtained as an oil after purification by column chromatography (1 : 3, EtOAc/petrol).

R_f : 0.44 (1 : 3, EtOAc/petrol).

υ_{max}/cm^{-1} 1673, 1452, 1263, 1154, 1072, 1027.

^1H NMR δ (major *trans* isomer) 7.35 (1H, d, *J* = 1.2 Hz, H5'), 7.29-7.05 (10H, m, ArH), 6.32 (1H, dd, *J* = 1.2, 3.2 Hz, H4'), 6.16 (1H, d, *J* = 3.2 Hz, H3'), 5.07 (1H, d, *J* = 15.0 Hz, H6'), 4.51 (1H, d, *J* = 1.5 Hz, H5), 4.45 (2H, s, H7'), 4.24-4.20 (1H, m, H4), 3.64 (1H, d, *J* = 15.0 Hz, H6'), 2.93 (1H, dd, *J* = 7.0, 17.5 Hz, H3), 2.59 (1H, dd, *J* = 2.5, 17.5 Hz, H3).

^{13}C NMR δ (major *trans* isomer) 172.4 (C2), 150.3 (C2'), 143.0 (C5'), 137.1 (ArC), 135.7 (ArC), 128.4 (ArCH), 128.2 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.4 (ArC), 127.3 (ArCH), 110.2 (C3'), 108.6 (C4'), 76.1 (C4), 71.0 (C7'), 60.85 (C5), 44.0 (C6'), 37.3 (C3).

^1H NMR δ (minor *cis* isomer) 7.45 (1H, d, *J* = 1.2 Hz, H5'), 7.29-7.05 (10H, m, ArH), 6.38 (1H, dd, *J* = 1.2, 3.0 Hz, H4'), 6.29 (1H, d, *J* = 3.0 Hz, H3'), 5.07 (1H, d, *J* = 14.7 Hz, H6'), 4.67 (1H, d, *J* = 7.5 Hz, H5), 4.32 (2H, s, H7'), 4.30-4.28 (1H, m, H4), 3.58 (1H, d, *J* = 14.7 Hz, H6'), 2.84 (1H, dd, *J* = 8.5, 16.5 Hz, H3), 2.71 (1H, dd, *J* = 2.5, 16.5 Hz, H3).

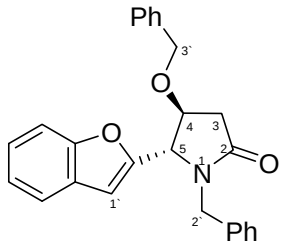
^{13}C NMR δ (minor *cis* isomer) 171.8 (C2), 148.8 (C2'), 143.0 (C5'), 137.0 (ArC), 135.9 (ArC), 128.4 (ArCH), 128.2 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.5

(ArCH), 127.3 (ArCH), 110.3 (C3'), 110.2 (C4'), 73.2 (C4), 71.4 (C7'), 57.8 (C5), 44.3 (C6'), 36.6 (C3).

EIMS *m/z* 347 (M^+, 100%).

HREIMS calculated for $C_{22}H_{21}NO_3$ (M^+) 347.4078, found 347.4079.

(4*S*, 5*R*)-5-(Benzofuran-2-yl)-1-benzyl-4-(benzyloxy)pyrrolidin-2-one (152)



152

Prepared using the general method above, from **126** (0.10 g, 0.336 mmol), benzofuranboronic acid (0.163 g, 1.0 mmol), $BF_3{\cdot}OEt_2$ (0.190 g, 1.34 mmol) and CH_2Cl_2 (5 mL). The desired product (0.110 g, 55%, dr = 89 : 11) was obtained as an oil after purification by column chromatography (1 : 3, EtOAc/petrol).

R_f : 0.47 (1 : 2, EtOAc/petrol).

υ_{max}/cm^{-1} 1684, 1454, 1417, 1253, 1109, 1093.

^{1}H NMR δ (major *trans* isomer) 7.53 (1H, d, *J* = 8.0 Hz, ArH), 7.42 (1H, d, *J* = 8.0 Hz, ArH), 7.28-7.18 (12H, m, ArH), 6.55 (1H, s, H1'), 5.15 (1H, d, *J* = 15.2 Hz, H2'), 4.63 (1H, d, *J* = 2.0 Hz, H5), 4.49 (2H, s, H3'), 4.30-4.28 (1H, m, H4), 3.71 (1H, d, *J* = 15.2 Hz, H2'), 3.01 (1H, dd, *J* = 7.0, 17.2 Hz, H3), 2.65 (1H, dd, *J* = 2.5, 17.2 Hz, H3).

^{13}C NMR δ (major *trans* isomer) 172.6 (C2), 155.1 (ArC), 137.0 (ArC), 135.6 (ArC), 128.5 (ArCH), 128.3 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 124.7 (ArC), 127.1 (ArCH), 123.0 (ArCH), 121.0 (ArCH), 111.3 (ArCH), 105.4 (C1'), 76.1 (C4), 71.2 (C3'), 61.3 (C5), 44.2 (C2'), 37.4 (C3).

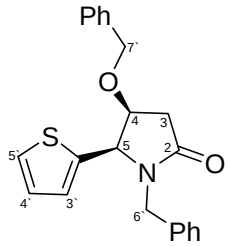
^{1}H NMR δ (minor *cis* isomer) 7.56 (1H, d, *J* = 8.0 Hz, ArH), 7.48 (1H, d, *J* = 8.0 Hz, ArH), 7.29-7.02 (12H, m, ArH), 6.67 (1H, s, H1'), 5.16 (1H, d, *J* = 15.0 Hz, H2'), 4.78 (1H, d, *J* = 7.5 Hz, H5), 4.49 (1H, d, *J* = 12.0 Hz, H3'), 4.43-4.39 (1H, m, H4), 4.39 (1H, d, *J* = 12.0 Hz, H3'), 3.65 (1H, d, *J* = 15.0 Hz, H2'), 2.93 (1H, dd, *J* = 8.0, 16.5 Hz, H3), 2.76 (1H, dd, *J* = 8.0, 16.5 Hz, H3).

^{13}C NMR δ (minor *cis* isomer) 172.0 (C2), 155.3 (ArC), 137.0 (ArC), 135.9 (ArC), 128.7 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.7 (ArC), 127.5 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 124.5 (ArC), 122.9 (ArCH), 120.9 (ArCH), 111.5 (ArCH), 107.1 (C1'), 73.4 (C4), 71.8 (C3'), 58.3 (C5), 44.5 (C2'), 36.6 (C3).

EIMS *m/z*: 397 (M^+, 75%).

HREIMS calculated for $C_{26}H_{23}NO_3$ (M^+) 397.1676, found 397.1677.

(4*S*, 5*R*)-1-Benzyl-4-(benzyloxy)-5-(2-thienyl)pyrrolidin-2-one (153)



153

Prepared using the general method above, from **126** (0.10 g, 0.336 mmol), 2-thiopheneboronic acid (0.127 g, 1.0 mmol), $BF_3{\cdot}OEt_2$ (0.190 g, 1.34 mmol) and CH_2Cl_2 (5 mL). The desired product (0.088 g, 72%, dr = 62 : 38) was obtained as an oil after purification by column chromatography (1 : 4, EtOAc/petrol). R_f : 0.33 (1 : 3, EtOAc/petrol).

υ_{max}/cm^{-1} 1685, 1451, 1434, 1269, 1111, 1072.

^{1}H NMR δ (major *cis* isomer) 7.29-7.22 (9H, m, ArH), 7.13 (1H, d, *J* = 7.0 Hz, ArH), 7.03 (2H, m, H5', H4'), 6.95 (1H, d, *J* = 3.5 Hz, H3'), 5.13 (1H, d, *J* = 15.0 Hz, H6'), 4.89 (1H, d, *J* = 7.0 Hz, H5), 4.33 (1H, d, *J* = 12.0 Hz, H7'), 4.33-4.29 (1H, m, H4), 4.28 (1H, d, *J* = 12.0 Hz, H7'), 3.58 (1H, d, *J* = 15.0 Hz, H6'), 2.79 (1H, dd, *J* = 7.5, 17.5 Hz, H3), 2.72 (1H, dd, *J* = 7.5, 17.5 Hz, H3).

^{13}C NMR δ (major *cis* isomer) 171.1 (C2), 140.5 (C2`), 137.7 (ArC), 136.0 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.4 (C5'), 126.8 (C4'), 126.4 (C3'), 73.3 (C4), 71.7 (C6'), 60.2 (C5), 44.1 (C7'), 36.8 (C3).

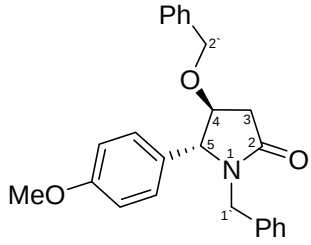
^{1}H NMR δ (minor *trans* isomer) 7.39-7.12 (10H, m, ArH), 7.03 (1H, m, H5'), 6.98 (1H, dd, *J* = 3.2, 4.7 Hz, H4'), 6.84 (1H, d, *J* = 3.2 Hz, H3'), 5.17 (1H, d, *J* = 15.5 Hz, H6'), 4.72 (1H, d, *J* = 2.0 Hz, H5), 4.47 (2H, s, H7'), 4.11-4.07 (1H, m, H4), 3.65 (1H, d, *J*=15.5 Hz, H6'), 2.93 (1H, dd, *J* = 7.0, 17.5 Hz, H3), 2.59 (1H, dd, *J* = 2.5, 17.5 Hz, H3).

^{13}C NMR δ (minor *trans* isomer) 172.3 (C2), 141.6 (C2'), 137.1 (ArC), 135.7 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 127.1 (C5'), 125.9 (C4'), 125.7 (C3'), 79.5 (C4), 71.3 (C6'), 63.0 (C5), 44.0 (C7'), 37.0 (C3).

EIMS *m/z* 363 (M^+, 100%).

HREIMS calculated for $C_{22}H_{21}NO_2S$ (M^+) 363.1296, found 363.1293.

(4*S*, 5*R*)-1-Benzyl-4-(benzyloxy)-5-(4-methoxyphenyl)pyrrolidin-2-one (155)



155

Prepared using the general method above, from **126** (0.10 g, 0.336 mmol), *p*-methoxyphenylboronic acid (0.214 g, 1.00 mmol), $BF_3{\cdot}OEt_2$ (0.190 g, 1.34 mmol), and CH_2Cl_2 (5 mL). The desired product (0.063 g, 48%, dr = 72 : 28) was obtained as an oil after purification by column chromatography (1 : 3, EtOAc/petrol).

R_f : 0.42 (1 : 3, EtOAc/petrol).

υ_{max}/cm^{-1} 1690, 1512, 1442, 1408, 1248, 1175, 1072.

^{1}H NMR δ (major *trans* isomer) 7.29-7.12 (10H, m, ArH), 7.00 (2H, d, *J* = 8.0 Hz, ArH), 6.89 (2H, d, *J* = 8.0 Hz, ArH), 5.10 (1H, d, *J* = 15.0 Hz, H1'), 4.37 (2H, s, H2'), 4.34 (1H, d, *J* = 2.5 Hz, H5), 3.90-3.87 (1H, m, H4), 3.74 (3H, s, OMe), 3.44 (1H, d, *J* = 15.0 Hz, H1'), 2.87 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.60 (1H, dd, *J* = 2.5, 17.0 Hz, H3).

^{13}C NMR δ (major *trans* isomer) 172.9 (C2), 159.5 (ArC), 137.3 (ArC), 135.8 (ArC), 128.5 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.4 (ArC), 127.3 (ArCH), 127.1 (ArCH), 114.4 (ArCH), 79.4 (C4), 71.1 (C5), 67.0 (C2'), 55.2 (OMe), 43.9 (C1'), 37.2 (C3).

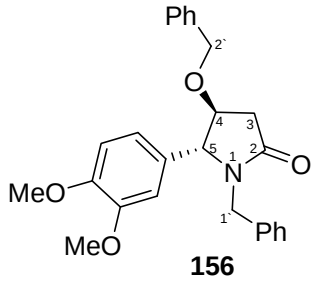
^{1}H NMR δ (minor *cis* isomer) 7.28-7.12 (14H, m, ArH), 7.10 (2H, d, *J* = 8.5 Hz, ArH), 6.93 (2H, d, *J* = 8.5 Hz, ArH), 5.15 (1H, d, *J* = 14.5 Hz, H1'), 4.53 (1H, d, *J* = 6.5 Hz, H5), 4.25-4.23 (1H, m, H4), 4.17 (1H, d, *J* = 12.0 Hz, H2'), 4.12 (1H, d, *J* = 12.0 Hz, H2'), 3.76 (3H, s, OMe), 3.48 (1H, d, *J* = 14.5 Hz, H1'), 2.73 (2H, m, H3).

^{13}C NMR δ (minor *cis* isomer) 172.6 (C2), 159.6 (ArC), 137.2 (ArC), 136.0 (ArC), 129.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.7 (ArC), 127.4 (ArCH), 127.1 (ArCH), 113.8 (ArCH), 73.5 (C4), 71.6 (C5), 64.4 (C2'), 55.2 (OMe), 44.1 (C1'), 37.6 (C3).

EIMS *m/z* 387 (M^+,100%).

HREIMS calculated for $C_{25}H_{25}NO_3$ (M^+) 387.1833, found 387.1834.

(4*S*, 5*R*)-1-Benzyl-4-(benzyloxy)-5-(3,4-dimethoxyphenyl)pyrrolidin-2-one (156)



156

Prepared using the general method above, from **126** (0.10 g, 0.336 mmol), 3,4-dimethoxyphenylboronic acid (0.182 g, 1.0 mmol), $BF_3{\cdot}OEt_2$ (0.190 g, 1.34 mmol), and CH_2Cl_2 (5 mL). The desired product (0.103 g, 74%, dr = 74 : 26) was obtained as an oil after purification by column chromatography (1 : 2, EtOAc/petrol).

R_f : 0.47 (1 : 3, EtOAc/petrol).

υ_{max}/cm^{-1} 1689, 1515, 1453, 1413, 1260, 1237, 1139, 1072, 1026.

^{1}H NMR δ (major trans isomer) 7.28-7.12 (10H, m, ArH), 6.85 (1H, d, *J* = 8.0 Hz, ArH), 6.66 (1H, dd, *J* = 2.0, 7.7 Hz, ArH), 6.48 (1H, d, *J* = 2.0 Hz, ArH), 5.14 (1H, d, *J* = 15.5 Hz, H1'), 4.45 (2H, s, H2'), 4.40 (1H, d, *J* = 2.5 Hz, H5), 4.00-3.97 (1H, m, H4), 3.88 (3H, s, OMe), 3.79 (3H, s, OMe), 3.58 (1H, d, *J* = 15.5 Hz, H1'), 2.88 (1H, dd, *J* = 7.0, 17.0 Hz, H3), 2.60 (1H, dd, *J* = 3.5, 17.0 Hz, H3).

^{13}C NMR δ (major trans isomer) 172.7 (C2), 149.4 (ArC), 148.8 (ArC), 137.2 (ArC), 135.8 (ArC), 134.9 (ArC), 128.3 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 128.0 (ArCH), 127.4 (ArCH), 127.4 (ArCH), 118.9 (ArCH), 111.3 (ArCH), 109.3 (ArCH), 79.1 (C4), 71.0 (C2'), 67.3 (C5), 55.7 (OMe), 43.9 (C1'), 37.0 (C3).

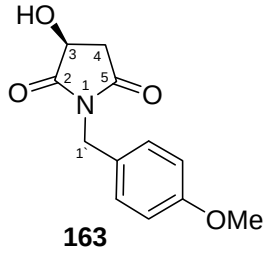
^{1}H NMR δ (minor cis isomer) 7.28-7.12 (10H, m, ArH), 6.87 (1H, d, *J* = 8.0 Hz, ArH), 6.72 (1H, d, *J* = 8.0 Hz, ArH), 6.71 (1H, s, ArH), 5.10 (1H, d, *J* = 15.0 Hz, H1'), 4.51(1H, d, *J* = 7.0 Hz, H5), 4.22-4.20 (1H, m, H4), 4.19 (1H, d, *J* = 11.5 Hz, H2'), 4.08 (1H, d, *J* = 11.5 Hz, H2'), 3.91 (3H, s, OMe), 3.78 (1H, d, *J* = 15.0 Hz, H1'), 3.73 (3H, s, OMe), 2,73 (2H, m, H3).

^{13}C NMR δ (minor cis isomer) 172.8 (C2), 149.5 (ArC), 148.9 (ArC), 137.3 (ArC), 136.0 (ArC), 128.3 (ArC), 128.0 (ArCH), 127.6 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 127.1 (ArCH), 126.6 (ArCH), 121.2 (ArCH), 111.9 (ArCH), 110.6 (ArCH), 73.6 (C4), 71.5 (C2'), 64.9 (C5), 55.6 (OMe), 44.1 (C1'), 37.7 (C3).

EIMS *m/z* 417 (M^+, 80%).

HREIMS calculated for $C_{26}H_{27}NO_4$ (M^+) 417.1941, found 417.1940.

(*S*)-3-Hydroxy-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (163)



163

Prepared in a similar fashion to **123** above, using L-malic acid (2.00 g, 15 mmol), *p*-methoxybenzylamine (2.04 g, 15 mmol) and xylene (150 mL) with stirring at reflux temperature for 2 h. The crude product was purified by column chromatography (2 : 1, EtOAc/petrol) to give the title compound as a light yellow solid (2.96 g, 84%).

R_f : 0.52 (2 : 1, EtOAc/petrol).

Mp 108-110 ^oC.

$[\alpha]_D^{24}$ +24.5^o (*c* 0.28, $CHCl_3$).

υ_{max}/cm^{-1} 3441, 1685, 1513, 1431, 1408, 1302, 1247, 1177, 1105, 1025, 928.

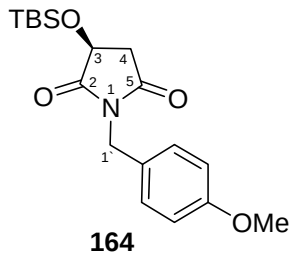
^1H NMR δ 7.30 (2H, d, *J* = 8.0 Hz, ArH), 6.82 (2H, d, *J* = 8.0 Hz, ArCH), 4.61-4.58 (3H, m, H3, H1`), 3.77 (3H, s, OMe), 3.03 (1H, dd, *J* = 8.5, 18.5 Hz, H4), 2.65 (1H, dd, *J* = 2.5, 18.5 Hz, H4).

^{13}C NMR δ 178.0 (CO), 173.8 (CO), 159.4 (ArC), 130.3 (ArCH), 127.4 (ArC), 114.0 (ArCH), 66.9 (C3), 55.2 (OMe), 41.9 (C1`), 37.1 (C4).

EIMS *m/z* 235 (M^+, 100%).

HREIMS calculated for $C_{12}H_{13}NO_4$ (M^+) 235.0809, found 235.1204.

(*S*)-3-(tert-Butyldimethylsilyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (164)[47]



164

To a solution of **163** (2.0 g, 8.50 mmol), imidazole (0.69 g, 10.2 mmol) and DMAP (0.10 g, 0.85 mmol) in THF (100 mL) at 0 ^oC were added TBSCl (3.37 g, 12.76 mmol). The reaction mixture was allowed to warmed to rt and was stirred at this temperarure for 16 h. Saturated aqueous solution of $NaHCO_3$ (40 mL) was added and aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title product as a colorless oil (2.66 g, 90%).

R_f : 0.83 (1 : 2, EtOAc/petrol).

$[\alpha]_D^{23}$ +22.9^o (*c* 0.11, $CHCl_3$) (Lit. value not reported).

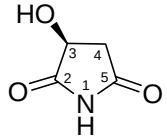
^{1}H NMR δ 7.31 (2H, d, *J* = 8.5 Hz, ArH), 6.81 (2H, d, *J* = 8.5 Hz, ArH), 4.57 (2H, s, C1`), 4.55-4.53 (1H, m, H3), 3.70 (3H, s, OMe), 2.96 (1H, dd, *J* = 7.5, 18.0 Hz, H4), 2.57 (1H, dd, *J* = 4.5, 18.0 Hz, H4), 0.89 (9H, s, (C*H*$_3$)$_3$C), 0.16 (6H, s, (CH$_3$)$_2$Si).

^{13}C NMR δ 176.3 (CO), 173.9 (CO), 159.3 (ArC), 130.4 (ArC), 127.9 (ArCH), 113.9 (ArCH), 67.9 (C3), 55.2 (OMe), 41.7 (C1`), 38.8 (C4), 25.6 (C(*C*H$_3$)$_3$), 18.2 *C*(CH$_3$)$_3$), -4.7 (*C*H$_3$)$_2$Si), -5.3 (*C*H$_3$)$_2$Si).

^{1}H and ^{13}C NMR data matched with the published data.

ESIMS *m/z* 350 (M + H^{+}, 100%).

(*S*)-3-Hydroxypyrrolidine-2,5-dione (165)



165

To a solution of **165** (0.50 g, 1.43 mmol) in CH$_3$CN/H$_2$O (20 mL, 1 : 1) at 0 ^{o}C was added CAN (3.9 g, 7.15 mmol). The reaction mixture was stirred at 0 ^{o}C for 1 h. EtOAc (20 mL) and water (10 mL) were added and aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc) to give the title product as a white solid (0.046 g, 28%).

Mp 93-94 ^{o}C (Lit.[151] Mp 95 ^{o}C).

$[\alpha]_D^{23}$ +19.6^{o} (*c* 0.20, CHCl$_3$) (Lit. Value not reported).

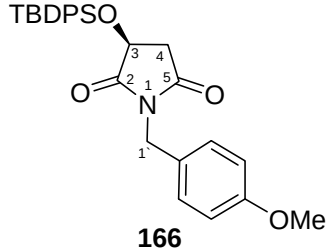
R$_f$: 0.33 (EtOAc).

^{1}H NMR δ (CD$_3$OD) 10.9 (1H, br. s, NH), 4.80 (1H, br. s, OH), 4.59-4.57 (1H, m, H3), 3.02 (1H, dd, *J* = 6.0, 17.5 Hz, H4), 2.52 (1H, dd, *J* = 2.5, 17.5 Hz, H4).

^{13}C NMR δ (CD$_3$OD) 180.1 (CO), 176.7 (CO), 68.0 (C3), 38.6 (C4).

^{1}H and ^{13}C NMR data matched with the published data.

(*S*)-3-(*tert*-Butyldiphenylsilyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (166)



166

Prepared in a similar fashion to **164** above from **163** (1.0 g, 4.25 mmol), imidazole (0.347 g, 5.1 mmol), DMAP (0.05 g, 0.42 mmol) and TBDPSCl (1.75 g, 6.38 mmol) with stirring at rt for 16 h. The crude product was purified by column chromatography (1 : 6, EtOAc/petrol) to give the title product (2.21 g, 92%) as a colorless oil.

R_f : 0.68 (1 : 6, EtOAc/petrol).

$[\alpha]_D^{23}$ +28.7° (*c* 0.15, $CHCl_3$).

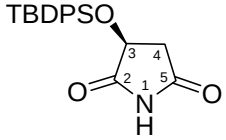
^{1}H NMR δ 7.84 (2H, d, *J* = 7.5 Hz, ArH), 7.69 (2H, d, *J* = 7.5 Hz, ArH), 7.46-7.33 (8H, m, ArH), 6.83 (2H, d, *J* = 8.5 Hz, ArH), 4.58 (2H, s, C1`), 4.54-4.52 (1H, m, C3), 2.63 (1H, dd, *J* = 8.0, 18.0 Hz, H4), 2.57 (1H, dd, *J* = 5.0, 18.0 Hz, H4), 1.13 (9H, s, (CH_3)$_3$C).

^{1}H NMR δ 175.8 (CO), 173.5 (CO), 159.2 (ArC), 135.8 (ArCH), 135.6 (ArCH), 132.7 (ArC), 131.8 (ArC), 130.3 (ArCH), 130.1 (ArCH), 130.0 (ArC), 127.8 (ArCH), 127.7 (ArCH), 113.8 (ArCH), 68.3 (C3), 55.1 (OMe), 41.6 (C1`), 38.6 (C4), 26.6 (C(*C*H_3)$_3$), 19.1 (*C*(CH$_3$)$_3$).

ESIMS *m/z* 474 (M + H^+, 30%).

HRESIMS calculated for $C_{28}H_{32}NO_4Si$ (M + H^+) 474.1582, found 474.1566.

(*S*)-3-(*tert*-Butyldiphenylsilyloxy)pyrrolidine-2,5-dione (167)



167

Prepared in a similar fashion to **165** above from **166** (0.69 g, 1.47 mmol), CAN (4.02 g, 7.34 mmol) and CH_3CN/H_2O (50 mL, 1 : 1) with stirring at rt for 1 h. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title product (0.20 g, 40%) as a colorless oil.

R_f : 0.68 (1 : 6, EtOAc/petrol).

$[\alpha]_D^{23}$ +47.1° (*c* 0.25, $CHCl_3$).

υ_{max}/cm^{-1} 3242, 1716, 1475, 1429, 1337, 1183, 1112, 840.

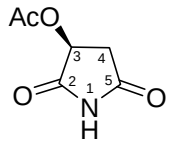
^{1}H NMR δ 8.99 (1H, br. s, NH), 7.83 (2H, d, *J* = 6.5 Hz, ArH), 7.71 (2H, d, *J* = 6.5 Hz, ArH), 7.48-7.41 (6H, m, ArH), 4.60-4.57 (1H, m, H3), 2.69-2.64 (2H, m, H4), 1.14 (9H, (CH_3)$_3$C).

^{13}C NMR δ 176.8 (CO), 174.3 (CO), 135.9 (ArCH), 135.6 (ArCH), 132.6 (ArC), 131.7 (ArC), 130.1 (ArCH), 130.1 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 69.2 (C3), 39.6 (C4), 26.6 (C(*C*H_3)$_3$), 19.0 (*C*(CH$_3$)$_3$).

ESIMS *m/z* 353 (M + H^+, 100%).

HRESIMS calculated for $C_{20}H_{24}NO_3Si$ (M + H^+) 353.1579, found 353.1596.

(*S*)-2,5-Dioxopyrrolidin-3-yl acetate (168)



168

A suspension of L-malic acid (4.0 g, 29.8 mmol) in acetyl chloride (15 mL) was heated at reflux temperature for 1.5 h and then all volatiles were removed *in vacuo*. The resulting yellow oil was diluted with THF (25 mL) and treated with a stream of gaseous ammonia over 10 min. to give a white solid. Acetyl chloride (15 mL) was added to the white solid and the mixture was heated at reflux temperature for 2 h. The crude product was purified by column chromatography (2 : 1, EtOAc/petrol) to give the title compound as a light yellow solid (2.62 g, 56%).

R_f : 0.47 (2 : 1, EtOAc/petrol).

Mp 112-115 ^oC (Lit.[152] Mp 112-114 ^oC).

$[\alpha]_D^{23}$ +31.3^o (*c* 0.18, $CHCl_3$) (Lit.[152] $[\alpha]_D^{25}$ +48.0 ^{o} (*c* 2.2, MeOH)).

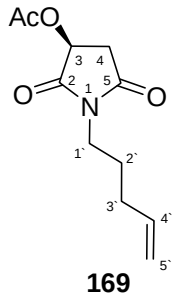
^{1}H NMR δ 8.88 (1H, br. s, NH), 5.47 (1H, dd, *J* = 5.0, 9.0 Hz, H3), 3.19 (1H, dd, *J* = 8.5, 18.5 Hz, H4), 2.74 (1H, dd, *J* = 5.5, 18.5 Hz, H4), 2.17 (CH_3).

^{13}C NMR δ 173.6 (CO), 173.1 (CO), 170.0 (CO), 68.6 (C3), 37.0 (C4), 20.6 (CH_3).

^{1}H and ^{13}C NMR data matched with the published data.

EIMS *m/z* 157 (M^+, 100%).

(*R*)-2,5-Dioxo-1-(pent-4-enyl)pyrrolidin-3-yl acetate (169)



169

A solution of **168** (0.500 g, 3.18 mmol), 4-penten-1-ol (0.275 g, 3.18 mmol) and PPh_3 (0.835 g, 3.18 mmol) at 0 ^oC was treated with DIAD (0.640 g, 3.18 mmol) over 5 min. The resulting reaction mixture was warmed to rt and stirred for 1 h. The solvent was removed and the crude residue was purified by column chromatography (1 : 1, EtOAc/petrol) to give title product (0.571 g, 81%) as an oil.

R_f : 0.57 (1 : 1, EtOAc/petrol).

$[\alpha]_D^{25}$ +36.9^o (c 0.15, $CHCl_3$).

υ_{max}/cm^{-1} 1751, 1709, 1439, 1403, 1372, 1250, 1223, 1054, 1045, 912.

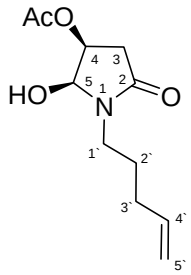
^{1}H NMR δ 5.83-5.74 (1H, m, H4`), 5.41 (1H, dd, *J* = 4.5, 8.5 Hz, H3), 5.05 (1H, dd, *J* = 1.5, 17.0 Hz, H5`), 4.99 (1H, d, *J* = 10.5 Hz, H5`), 3.56 (2H, t, *J* = 7.0 Hz, H1`), 3.14 (1H, dd, *J* = 8.5, 18.5 Hz, H4), 2.66 (1H, dd, *J* = 4.5, 18.5 Hz), 2.16 (3H, s, CH_3), 2.08 (2H, q, *J* = 7.0 Hz, H3`), 1.71 (2H, pentet, *J* = 7.0 Hz, H2`).

^{13}C NMR δ 173.4 (CO), 173.1 (CO), 169.8 (CO), 137.0 (C4`), 115.4 (C5`), 67.4 (C3), 38.7 (C1`), 35.6 (C4), 30.8 (C3`), 26.4 (C2`), 20.5 (CH_3).

EIMS *m/z* 225 (M^+, 80%).

HREIMS calculated for $C_{11}H_{15}NO_4$ (M^+) 225.1856, found 225.1885.

(*S*)-2-Hydroxy-5-oxo-1-(pent-4-enyl)pyrrolidin-3-yl acetate (170)



170

To a solution of **169** (0.300 g, 1.33 mmol) MeOH/CH_2Cl_2 (15 mL, 1 : 1) at 0 ^oC was added $NaBH_4$ (0.252 g, 6.66 mmol) portionwise and then the mixture was stirred at this temperature for 1.5 h. An aqueous solution of $NaHCO_3$ (15 mL) was added and the aqueous layer was extracted with EtOAc (3 x 15 mL). The crude extracts were dried ($MgSO_4$), filtered and concentrated under *vacuo*. The crude product was purified by column chromatograpy (EtOAc) to give the title product (0.183 g, 62%, dr = 90 : 10) as an oil.

R_f : 0.22 (1 : 1, EtOAc/petrol).

$[\alpha]_D^{22}$ +34.1^o (c 0.17, $CHCl_3$).

υ_{max}/cm^{-1} 3356, 2914, 1708, 1450, 1390, 1273, 1050, 1038, 942.

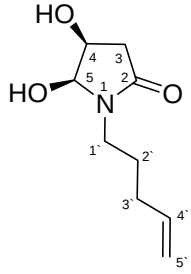
^{1}H NMR δ (major isomer) 5.82-5.76 (1H, m, C4`), 5.31 (1H, d, *J* = 7.0 Hz, H5), 5.15 (1H, dd, *J* = 6.5, 7.0 Hz, H4), 5.10 (1H, dd, *J* = 1.5, 17.0 Hz, H5`), 4.98 (1H, d, *J* = 10.5 Hz, H5`), 4.46 (1H, br. s, OH), 3.49-3.45 (1H, m, H1`), 3.20-3.16 (1H, m, H1`), 2.65-2.59 (2H, m, H3), 2.13 (3H, s, $CH_3$), 2.08-2.04 (2H, m, H3`), 1.70-1.64 (2H, m, H2`).

^{13}C NMR δ (major isomer) 171.0 (C2), 170.6 (CO), 137.4 (C5`), 115.1 (C4`), 81.5 (C5), 69.9 (C4), 39.8 (C1`), 38.6 (C3), 30.9 (C3`), 26.7 (C2`), 20.6 (CH_3).

EIMS *m/z* 227 (M^+ 50%).

HREIMS calculated for $C_{11}H_{17}NO_4$ (M^+) 227.1148, found 227.1157.

(*S*)-4,5-Dihyroxy-1-(pent-4-enyl)pyrrolidin-2-one (157)



157

To a solution of **170** (0.200 g, 0.88 mmol) in MeOH (10 mL) was added K_2CO_3 (0.060 g, 0.44 mmol) and the mixture was stirred at rt for 2h. MeOH was removed under vacuo. The crude porduct was purified by column chromatography (5% MeOH in EtOAc) to give the desired product (0.108 g, 67%) as an oil.

R_f : 0.20 (EtOAc).

$[\alpha]_D^{23}$ +29.3° (c 0.12, $CHCl_3$).

υ_{max}/cm^{-1} 3329, 2960, 1664, 1465, 1413, 1259, 1081, 1016, 799.

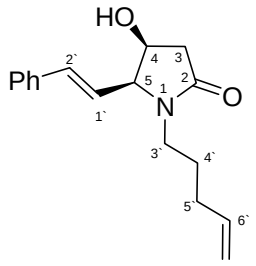
^{1}H NMR δ 5.83-5.76 (1H, m, H4`), 5.09-4.97 (2H, m, H5`), 4.35 (1H, dd, *J* = 6.5, 7.0 Hz, H4), 4.21-4.17 (1H, d, *J* = 7.0 Hz, H5), 3.50-3.42 (1H, m, H1`), 3.22-3.13 (1H, m, H1`), 2.83 (1H, dd, *J* = 6.5, 17.5 Hz, H3), 2.24 (1H, dd, *J* = 2.0, 17.5 Hz, H3), 2.09-2.04 (2H, m, H3`), 1.73-1.60 (1H, m, H2`).

^{13}C NMR δ 173.7 (C2), 137.5 (C5`), 115.3 (C4`), 82.9 (C5), 71.8 (C4), 39.7 (C1`), 38.5 (C3), 31.0 (C3`), 26.7 (C2`).

EIMS *m/z* 185 (M^+ 70%).

HREIMS calculated for $C_9H_{15}NO_3$ (M^+) 185.1044, found 185.1038.

(4*S*,5*S*,*E*)-4-Hydroxy-1-(pent-4-enyl)-5-styrylpyrrolidin-2-one (171)



171

To a suspension of **157** (0.100 g, 0.54 mmol) and phenylvinylboronic acid (0.240 g, 1.62 mmol) in CH_3CN (5 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ dropwise. The resulting reaction mixture was warmed to rt and stirred at this temperature for 2 h. An aqueous solution of $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL), dried ($MgSO_4$), filtered and concentrated under *vacuo*. The crude product was purified by column chromatograpy (1 : 1, EtOAc/petrol) to give the title product (0.048 g, 33%) as an oil.

R_f : 0.36 (EtOAc).

$[\alpha]_D^{25}$ +27.7° (c 0.16, $CHCl_3$).

υ_{max}/cm^{-1} 3349, 2924, 1667, 1449, 1424, 1367, 1255, 1965, 994, 917.

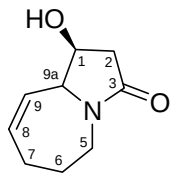
^{1}H NMR δ 7.44-7.26 (5H, m, ArH), 6.68 (1H, d, *J* = 16.0 Hz, H2`), 6.21 (1H, dd, *J* = 8.5, 16.0 Hz, H1`), 5.79-5.72 (1H, m, H6`), 5.05-4.93 (2H, m, H7`), 4.50 (1H, br. d, *J* = 6.0 Hz, H4), 4.26 (1H, dd, *J* = 6.0, 8.5 Hz, H5), 3.61-3.55 (1H, m, H3`), 2.98-2.92 (1H, m, H3`), 2.70 (1H, dd, *J* = 6.5, 17.0 Hz, H3), 2.47 (1H, dd, *J* = 3.5, 17.0 Hz, H3), 2.08-1.99 (2H, m, H5`), 1.67-1.54 (2H, m, H4`).

^{13}C NMR δ 172.8 (C2), 137.5 (C7`), 136.1 (C2`), 135.6 (ArC), 128.7 (ArCH), 128.4 (ArCH), 126.7 (ArCH), 123.4 (C1`), 115.0 (C6`), 67.8 (C4), 65.9 (C5), 40.2 (C3`), 40.0 (C3), 30.9 (C5`), 26.5 (C4`).

EIMS *m/z* 271 (M^+ 65%).

HREIMS calculated for $C_{17}H_{21}NO_2$ (M^+) 271.1564, found 271.1572.

(1*S*,*Z*)-1-Hydroxy-5,6,7,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-3(2*H*)-one (172)



172

To a solution of **171** (0.010 g, 0.037 mmol) in CH_2Cl_2 (10 mL) at rt was added Grubb`s second generation catalyst (0.004 g, 0.004 mmol). The reaction mixture was stirred at rt for 1 h. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (2 : 1, EtOAc/petrol) to give the desired product (72%) as a colorless oil.

R_f : 0.34 (2 : 1, EtOAc/petrol).

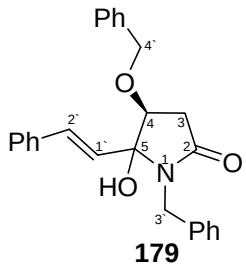
$[\alpha]_D^{26}$ +33.5^o (c 0.24, $CHCl_3$).

υ_{max}/cm^{-1} 3359, 2934, 1662, 1444, 1316, 1260, 1101, 1070.

^{1}H NMR δ 6.04-6.02 (1H, m, H8), 5.64 (1H, d, *J* = 10.5 Hz, H9), 4.40 (1H, br. s, H9a), 4.38 (1H, br. s, H1), 4.12 (1H, dt, *J* = 5.6, 13.8 Hz, H5), 2.95 (1H, dt, *J* = 6.6, 13.8 Hz, H5), 2.61 (1H, dd, *J* = 5.4, 16.5 Hz, H2), 2.45 (1H, dd, *J* = 3.3, 16.5 Hz), 2.39-2.36 (1H, m, H7), 2.24-2.16 (1H, m, H7), 1.99 (1H, br. s. OH), 1.88-1.80 (2H, m, H6).

^{13}C NMR δ 172.3 (C3), 134.3 (C8), 123.9 (C9), 67.0 (C9a), 64.4 (C1), 41.2 (C5), 39.9 (C2), 26.9 (C6), 26.0 (C7).

(4*S*)-1-Benzyl-4-(benzyloxy)-5-hydroxy-5-styrylpyrrolidin-2-one (179)



179

Magnesium turnings (0.302 g, 12.6 mmol) were stirred overnight under N_2, and anhydrous THF (5 mL) was then added to the flask. Neat *trans*-*β*-bromostyrene (0.461 g, 2.52 mmol) was added dropwise at rt. The reaction mixture was stirred at 40 ^{o}C for 1 h. The pyrrolidine-2,5-dione **125** (0.50 g, 1.68 mmol) was dissolved in dry THF (10 mL) and the solution was cooled to -78 ^{o}C. 2-Phenylvinylmagnesium bromide was then transferred to the solution *via* syringe. The reaction mixture was stirred at -78 ^{o}C for 4 h, and then warmed slowly to -10 ^{o}C. Saturated aqueous NH_4Cl solution (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by

column chromatography (1 : 1, EtOAc/petrol) to give the title compound as an oil (0.306 g, 45%, dr = 58 : 42).

R_f : 0.54 (1 : 1, EtOAc/petrol).

^{1}H NMR δ (major diastereomer) 7.31-7.17 (15H, m, ArH), 6.79 (1H, d, *J* = 16.0 Hz, H2'), 5.86 (1H, d, *J* = 16.0 Hz, H1'), 4.60 (2H, s, H4'), 4.85 (1H, d, *J* = 15.0 Hz, H3'), 4.42 (1H, d, *J* = 15.0 Hz, H3'), 4.03 (1H, br. s, OH), 4.00-3.98 (1H, m, H4), 2.70 (1H, dd, *J* = 7.0, 17.0 Hz, H3), 2.58 (1H, dd, *J* = 4.5, 17.0 Hz, H3).

^{13}C NMR δ (major diastereomer) 171.6 (C2), 138.3 (ArC), 135.3 (ArC), 132.4 (C2'), 128.5 (ArC), 128. 4 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.3 (ArCH), 126.8 (ArCH), 126.7 (C1'), 90.5 (C5), 77.2 (C4), 72.3 (C4'), 43.0 (C3'), 35.5 (C3).

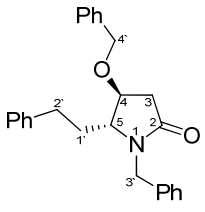
^{1}H NMR δ (minor diastereomer) 7.30-7.19 (15H, m, ArH), 6.85 (1H, d, *J* = 16.5 Hz, H2'), 6.25 (1H, d, *J* = 16.5 Hz, H1'), 4.57-4.49 (3H, m, H4', H3'), 4.31 (1H, d, *J* = 15.0 Hz, H3'), 3.99-3.96 (1H, m, H4), 2.87 (1H, dd, *J* = 6.5, 17.5 Hz, H3), 2.52 (1H, dd, *J* = 3.0, 17.5 Hz, H3).

^{13}C NMR δ (minor diastereomer) 173.1 (C2), 138.1 (ArC), 137.3 (ArC), 135.7 (C2'), 128.5 (ArC), 128.5 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 127.3 (ArCH), 126.8 (C1'), 93.7 (C5), 81.7 (C4), 72.1 (C4'), 42.8 (C3'), 36.6 (C3).

EIMS *m/z* 399 (M^+, 100%).

HREIMS calculated for $C_{26}H_{25}NO_3$ (M^+) 399.1834, found 399.1819.

(4*S*, 5*R*)-1-Benzyl-4-(benzyloxy)-5-phenethylpyrrolidin-2-one (180)



180

To a solution of **179** (0.98 g, 2.45 mmol) in CH_2Cl_2 (7 mL) at -78 ^{o}C, was added dropwise Et_3SiH (1.42 g, 12.25 mmol) and then $BF_3{\cdot}OEt_2$ (1.03 g, 7.35 mmol). The mixture was stirred at -78 ^{o}C for 6 h and then allowed to warm slowly to rt and stirred overnight. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (increasing polarity from 1:1, EtOAc/petrol to EtOAc) to give the title compound as an oil (0.781 g, 83%, dr = 91 : 9).

R_f : 0.26 (1 : 1, EtOAc/petrol).

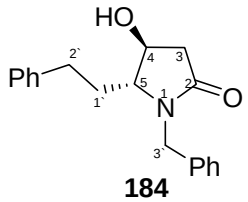
^{1}H NMR δ 7.32-7.02 (15H, m, ArH), 4.9 (1H, d, *J* = 15.5 Hz, H3'), 4.45 (1H, d, *J* = 11.5 Hz, H4'), 4.36 (1H, d, *J* = 11.5 Hz, H4'), 3.97 (1H, d, *J* = 15.5 Hz, H3'), 3.93 (1H, d, *J* = 6.5 Hz, H4), 3.52 (1H, br. d, *J* = 8.5 Hz, H5), 2.74 (1H, dd, *J* = 6.5, 17.5 Hz, H3), 2.55-2.52 (2H, m, H3, H1'), 2.48-2.45 (1H, m, H1'), 1.94-1.93 (1H, m, H2'), 1.67-1.69 (1H, m, H2').

^{13}C NMR δ 172.5 (C2), 140.5 (ArC), 137.3 (ArC), 136.0 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 127.4 (ArCH), 126.1 (ArCH), 76.7 (C4), 70.5 (C4'), 62.8 (C5), 44.1 (C3'), 37.2 (C3), 32.2 (C3), 31.0 (C1').

EIMS *m/z* 385 (M^+, 100%).

HREIMS calculated for $C_{26}H_{27}NO_2$ (M^+) 385.2041, found 385.2039.

(4*S*, 5*R*)-1-Benzyl-4-hydroxy-5-phenethylpyrrolidin-2-one (184)



184

To a solution of **181** (0.050 g, 0.130 mmol) in MeOH (3 mL), was added $PdCl_2$ (0.018 g, 0.10 mmol). The mixture was stirred at rt under an atmosphere of H_2 for 1 h, then the flask was flushed with N_2 before the mixture was filtered through a pad of celite and the solids were washed with MeOH (2 x 10 mL). The filtrate was evaporated *in vacuo*, the crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title product as an oil (0.030 g, 76%).

R_f : 0.19 (1 : 1, EtOAc/petrol).

υ_{max}/cm^{-1} 3359, 1663, 1474, 1451, 1244, 1081.

^{1}H NMR δ 7.26-7.04 (10H, m, ArH), 4.94 (1H, d, *J* = 15.0 Hz, H3'), 4.21 (1H, d, *J* = 6.0 Hz, H4), 3.99 (1H, d, *J* = 15.0 Hz, H3'), 3.35 (1H, br. d, *J* = 7.0 Hz, H5), 2.80 (1H, dd, *J* = 6.0, 17.5 Hz, H3), 2.64-2.62 (1H, m, H1'), 2.53-2.50 (1H, m, H1'), 2.39 (1H, d, *J* = 17.5 Hz, H3), 1.95-1.52 (1H, m, H2'), 1.63-1.60 (1H, m, H2').

^{13}C NMR δ 171.9 (C2), 141.0 (ArC), 136.4 (ArC), 128.9 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 127.8 (ArCH), 126.4 (ArCH), 69.3 (C4), 66.4 (C5), 44.6 (C3'), 40.4 (C3), 32.4 (C2'), 31.4 (C1').

EIMS *m/z* 295 (M^+, 80%).

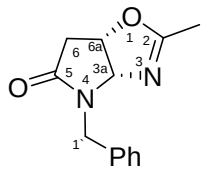
HREIMS calculated for $C_{19}H_{21}NO_2$ (M^+) 295.1572, found 295.1556.

EIMS *m/z* 167 (M^+ 100%).

HREIMS calculated for $C_{17}H_{21}NO_2$ (M^+) 167.0946, found 167.0954.

7.3. Experimental for Chapter 3

General Method for Ritter Reaction of 124 and Preparation of (3a*R*, 6a*S*)-4-Benzyl-2-methyl-6,6a-dihydro-3a*H*-pyrrolo[2,3-*d*]oxazol-5(4*H*)-one (129)



129

To a suspension of diol **124** (0.10 g, 0.483 mmol) in acetonitrile (3 mL) at 0 ^oC was added dropwise $BF_3.Et_2O$ (0.192 g, 1.35 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc) to give the title compound (0.103 g, 93%) as a colorless waxy solid.

R_f: 0.22 (EtOAc).

$[\alpha]_D^{23}$ + 21.0 (*c* 0.19, $CHCl_3$).

υ_{max}/cm^{-1} 1680, 1433, 1308, 1227, 1065, 1024.

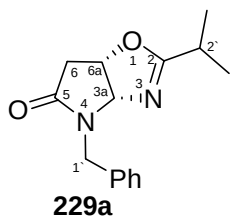
^1H NMR δ 7.34-7.32 (5H, m, ArH), 5.38 (1H, d, *J* = 7.5 Hz, H3a), 5.07 (1H, d, *J* = 14.5 Hz, H1`), 4.90 (1H, td, *J* = 2.0, 7.5 Hz, H6a), 4.02 (1H, d, *J* = 14.5 Hz, H1`), 2.85 (1H, dd, *J* = 7.5, 18.5 Hz, H6), 2.69 (1H, d, *J* = 18.5 Hz, H6), 2.03 (3H, s, Me).

^{13}C NMR δ 170.7 (C5), 168.8 (C2), 135.9 (ArC), 128.7 (ArCH), 128.6 (ArCH), 127.7 (ArCH), 83.2 (C3a), 74.4 (C6a), 44.3 (C1`), 37.5 (C6), 14.1 (CH_3).

EIMS *m/z* 230 (M^+, 100%).

HREIMS calculated for $C_{13}H_{14}N_2O_2$ (M^+) 230.1055, found 230.1057.

(3a*R*, 6a*R*)-4-Benzyl-2-isoproyl-3a,4,6,6a-tetrahydropyrrolo[2,3-*d*]oxazol-5-one (229a)



229a

The title compound was prepared following the general method described above using **124** (0.10 g, 0.483 mmol), isopropylnitrile (3 mL), and $BF_3.Et_2O$ (0.192 g, 1.35 mmol). The desired product (0.112 g, 90%) was obtained as a white solid after purification by column chromatography (Et_2O).

R_f: 0.49 (Et_2O).

Mp 43-45 ^{o}C.

$[\alpha]_D^{23}$ +45.4^{o} (*c* 0.11, $CHCl_3$).

υ_{max}/cm^{-1} 1683, 1639, 1430, 1234, 1120, 1027.

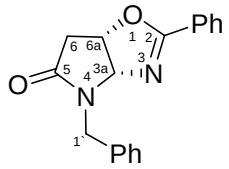
^{1}H NMR δ 7.22-7.09 (5H, m, ArH), 5.42 (1H, d, *J* = 7.5 Hz, H3a), 4.99 (1H, d, *J* = 14.5 Hz, H1`), 4.89 (1H, td, *J* = 1.5, 7.5 Hz, H6a), 4.12 (1H, d, *J* = 14.5 Hz, H1`), 2.85 (1H, dd, *J* = 7.5, 18.5 Hz, H6), 2.67 (1H, d, *J* = 18.5 Hz, H6), 2.55-2.63 (1H, septet, *J* = 7.0 Hz, H2`), 1.19 (6H, d, *J* = 7.0 Hz, 2 x CH_3).

^{13}C NMR δ 175.7 (C5), 170.8 (C2), 136.1 (ArC), 128.5 (ArCH), 128.5 (ArCH), 127.6 (ArCH), 83.3 (C3a), 74.5 (C6a), 44.4 (C1`), 37.4 (C6), 28.2 (C2`), 19.4 (CH_3), 19.3(CH_3).

EIMS *m/z* 258 (M^+, 75%).

HREIMS calculated for $C_{15}H_{18}N_2O_2$ (M^+) 258.1368, found 258.1373.

(3a*R*, 6a*S*)-4-Benzyl-2-phenyl-6,6a-dihydro-3a*H*-pyrrolo[2,3-*d*]oxazol-5(4*H*)-one (229b)



229b

The title compound was prepared following the general method described above using **124** (0.10 g, 0.483 mmol), benzonitrile (3 mL), and $BF_3.Et_2O$ (0.192 g, 1.35 mmol). The desired product (0.121 g, 86%) was obtained as a white solid after purification by column chromatography (Et_2O).

R_f : 0.43 (Et_2O).

Mp 96-98 ^{o}C.

$[\alpha]_D^{23}$ +2.46^{o} (*c* 15.0, $CHCl_3$).

υ_{max}/cm^{-1} 1676, 1638, 1428, 1403, 1356, 1234, 1154, 1089.

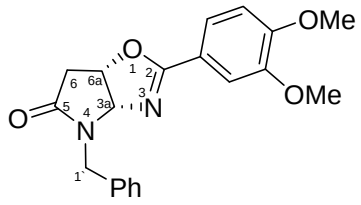
^{1}H NMR δ 7.93 (2H, d, *J* = 8.5 Hz, ArH), 7.51-7.27 (8H, m, ArH), 5.60 (1H, d, *J* = 7.5 Hz, H3a), 5.07 (1H, td, *J* = 2.0, 7.5 Hz, H6a), 5.03 (1H, d, *J* = 14.5 Hz, H1`), 4.16 (1H, d, *J* = 14.5, H1`), 2.91 (1H, dd, *J* = 7.5, 18.5 Hz, H6), 2.79 (1H, d, *J* = 18.5 Hz, H6).

^{13}C NMR δ 170.6 (C5), 166.9 (C2), 136.1 (ArC), 132.2 (ArC), 127.8 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 127.6 (ArCH), 126.7 (ArCH), 83.6 (C3a), 75.0 (C6a), 44.5 (C1`), 37.5 (C6).

EIMS *m/z* 292 (M^+, 70%).

HREIMS calculated for $C_{18}H_{16}N_2O_2$ (M^+) 292.1211, found 292.1204.

(3a*R*, 6a*S*)-4-Benzyl-2-(3,4-dimethoxyphenyl)-6,6a-dihydro-3aH-pyrrolo[2,3-*d*]oxazol-5(4H)-one (229c)



299c

The title compound was prepared following the general method described above using **124** (0.10 g, 0.483 mmol), 3,4-dimethoxybenzonitrile (0.164 g, 1.00 mmol), $BF_3.Et_2O$ (0.192 g, 1.35 mmol), and nitromethane (3 mL) as solvent. The desired product (0.154 g, 91%) was obtained as a white solid after purification by column chromatography (Et_2O).

R_f : 0.28 (Et_2O).

Mp 147-149 ^oC.

$[\alpha]_D^{23}$ +76.7^o (*c* 0.36, MeOH).

υ_{max}/cm^{-1} 1687, 1634, 1516, 1375, 1216, 1135, 1005.

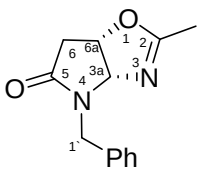
^1H NMR δ 7.52-7.27 (7H, m, ArH), 6.86 (1H, d, *J* = 8.5 Hz, ArH), 5.60 (1H, d, *J* = 7.5 Hz, H3a), 5.07 (1H, td, *J* = 2.0, 7.5 Hz, H6a), 5.01 (1H, d, *J* = 15.0 Hz, H1`), 4.21 (1H, d, *J* = 15.0 Hz, H1`), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 2.90 (1H, dd, *J* = 7.5, 17.5 Hz, H6), 2.80 (1H, d, *J* = 17.5 Hz, H6).

^{13}C NMR δ 170.7 (C5), 166.7 (C2), 152.4 (ArC), 148.6 (ArC), 136.2 (ArC), 128.6 (ArC), 128.6 (ArCH), 128.5 (ArCH), 127.6 (ArCH), 125.4 (ArCH), 122.3 (ArCH), 111.0 (ArCH), 83.7 (C3a), 75.0 (C6a), 55.9 (OCH_3), 55.7 ,(OCH_3) 44.5 (C1`), 37.5 (C6).

EIMS *m/z* 352 (M^+, 65%).

HREIMS calculated for $C_{20}H_{20}N_2O_4$ (M^+) 352.1423, found 352.1417.

General Method for Ritter Reaction of 126 and Preparation of (3a*R*, 6a*S*)-4-Benzyl-2-methyl-6,6a-dihydro-3a*H*-pyrrolo[2,3-*d*]oxazol-5(4*H*)-one (129)



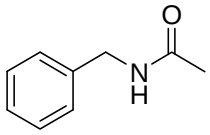
129

To a suspension of diol **126** (0.10 g, 0.483 mmol) in acetonitrile (3 mL) at 0 ^oC was added dropwise $BF_3.Et_2O$ (0.192 g, 1.35 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified

by column chromatography (EtOAc) to give compounds **129** (0.088 g, 80%) as a colorless waxy solid and **230** (0.052 g, 72%) as a colorless solid.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **129** prepared from diol **124**.

***N*-Benzylacetamide (230)**



230

R_f: 0.53 (Et_2O).

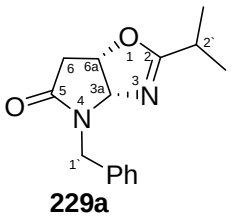
Mp 59-61 ^oC (Lit.[153] Mp 61-62^oC)

^1H NMR δ 7.26-7.35 (5H, m, ArH), 5.90 (1H, br. s, NH), 4.41 (2H, d, J = 5.7 Hz, CH_2Ph), 2.01 (3H, s, Me).

^{13}C NMR δ 169.6, 137.9, 128.3, 127.5, 43.5, 23.0.

^1H and ^{13}C NMR data matched with the published data.

(3a*R*, 6a*R*)-4-Benzyl-2-isopropyl-3a,4,6,6a-tetrahydropyrrolo[2,3-*d*]oxazol-5-one (229a)

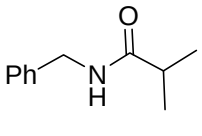


229a

The title compound was prepared following the general method described above using **126** (0.09 g, 0.30 mmol), isopropylnitrile (3 mL), and $BF_3.Et_2O$ (0.173 g, 1.22 mmol). The crude product was purified by column chromatography (Et_2O) to give the title compound (0.068 g, 87%) and *N*-benzylisobutyramide **234a** (0.041 g, 77 %) both as a white solid. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **229b** prepared from diol **124**.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **229b** prepared from diol **124**.

***N*- Benzylisobutyramide (234a)**



234a

R_f: 0.68 (Et_2O).

Mp 73-75 ^oC (Lit. [85] Mp 75-76^oC)

^1H NMR δ 7.32-7.25 (5H, m, ArH), 5.86 (1H, br s, NH), 4.22 (2H, d, J = 5.5 Hz, CH_2Ph), 2.41-2.34 (1H, septet, J = 7.0 Hz,

$CH(CH_3)_2$, 1.17 (6H, d, *J* = 7.0 Hz, 2xMe).

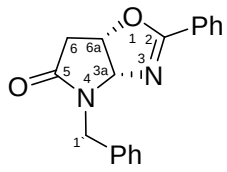
^{13}C NMR δ 176.7, 138.5, 128.6, 127.3, 43.3, 35.6, 19.5.

^{1}H and ^{13}C NMR data matched with the published data.

EIMS *m/z* 177 (M^+, 100%).

HREIMS calculated for $C_{11}H_{15}NO$ (M^+) 177.1153, found 177.1157.

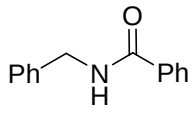
(3a*R*, 6a*S*)-4-Benzyl-2-phenyl-6,6a-dihydro-3a*H*-pyrrolo[2,3-*d*]oxazol-5(4*H*)-one (229b)



229b

The title compound was prepared following the general method described above using **126** (0.10 g, 0.33 mmol), benzonitrile (3 mL), and $BF_3.Et_2O$ (0.190 g, 1.34 mmol). The crude product was purified by column chromatography (Et_2O) to give the title compound (0.079 g, 80%) and *N*-benzylbenzamide **234b** (0.045 g, 63 %) both as a white solid. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **229b** prepared from diol **124**.

***N*-Benzylbenzamide (234b)**



234b

Yield : 0.045 g (63%).

R_f : 0.72 (Et_2O).

Mp 99-101°C, (Lit. [86] Mp 103-105°C)

^{1}H NMR δ 7.78 (2H, d, *J* = 7.5 Hz, ArH), 7.49-7.24 (8H, m, ArH), 6.62 (1H, br s, NH), 4.61 (2H, d, *J* = 5.5 Hz, CH_2Ph).

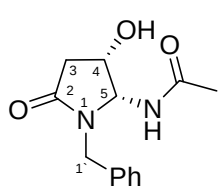
^{13}C NMR δ 167.3, 138.1, 134.3, 131.4, 128.6, 128.4, 127.8, 127.5, 126.9, 44.02.

^{1}H and ^{13}C NMR data matched with the published data.

EIMS *m/z* 211 (M^+, 100%).

HREIMS calculated for $C_{14}H_{13}NO$ (M^+) 211.0997, found 211.1000.

***N*-((2*R*, 3*S*)-1-Benzyl-3-hydroxy-5-oxopyrrolidin-2-yl)acetamide (185)**



185

To a solution of oxazoline **129** (0.020 g, 0.086 mmol) in MeOH (1 mL) at rt was added dropwise 6N HCl (1 mL). The reaction mixture was stirred at rt for 25 min. and concentrated *in vacuo*, then diluted with water (5 mL), basidified with solid $NaHCO_3$ to

pH = 9. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4) filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (5% MeOH in EtOAc) to give the title compound (0.009 g, 42%) as a white solid.

R_f : 0.24 (5% MeOH in EtOAc).

Mp 190-193 ^oC.

$[\alpha]_D^{23}$ -160 (*c* 0.075 MeOH).

υ_{max}/cm^{-1} 3318, 1577, 1653, 1541, 1446, 1434, 1378, 1275, 1157.

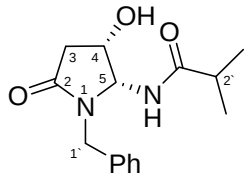
^1H NMR δ (CD_3OD) 7.31-7.24 (5H, m, ArH), 5.55 (1H, d, *J* = 6.5 Hz, H5), 4.57 (1H, d, *J* = 15.0 Hz, H1`), 4.39 (1H, br q, *J* = 6.5 Hz, H4), 4.23 (1H, d, *J* = 15.0 Hz, H1`), 2.68 (1H, dd, *J* = 6.5, 17.5 Hz, H3), 2.46 (1H, dd, *J* = 2.0, 17.5 Hz, H3), 1.88 (3H, s, Me).

^{13}C NMR δ (CD_3OD) 174.9 (CO), 173.9 (CO), 138.2 (ArC), 129.5 (ArCH), 129.1 (ArCH), 128.5 (ArCH), 67.6 (C5), 65.8 (C4), 45.0 (C1`), 39.6 C3), 22.6 (Me).

EIMS *m/z* 248 (M^+, 45%).

HREIMS calculated for $C_{13}H_{16}N_2O_3$ (M^+) 248.1160, found 248.1158.

_N_-((2_R_, 3_S_)-1-Benzyl-3-hydroxy-5-oxopyrrolidin-2-yl)isobutyramide (236)



236

The title compound was prepared in a similar fashion to **185,** from oxazoline **229a** (0.020g, 0.077 mmol). The desired product (0.015 g, 70%) was obtained as a white solid after purification by column chromatography (5% MeOH in EtOAc).

R_f : 0.53 (5% MeOH in EtOAc).

Mp 161-163 ^oC.

$[\alpha]_D^{23}$ -65.3^o (*c* 0.49, MeOH).

υ_{max}/cm^{-1} 3291, 1663, 1649, 1536, 1425, 1182, 1070.

^1H NMR δ 7.28-7.22 (5H, m, ArH), 6.40 (1H, d, *J* = 9.0 Hz, NH), 5.58 (1H, dd, *J* = 5.5, 9.0 Hz, H5), 4.47 (1H, d, *J* = 15.0 Hz, C1`), 4.34-4.39 (1H, br t, *J* = 5.5 Hz, H4), 4.33 (1H, d, *J* = 15.0 Hz, H1`), 3.87 (1H, d, *J* = 4.5 Hz, OH), 2.69 (1H, dd, *J* = 7.0, 17.5 Hz, H3), 2.48 (1H, dd, *J* = 4.0, 17.5 Hz, H3), 2.20-2.28 (1H, septet, *J* = 7.0 Hz, H2`), 1.03 (3H, d, *J* = 7.0 Hz, Me), 1.00 (3H, d, *J* = 7.0 Hz, Me).

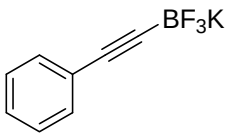
^{13}C NMR δ 177.9 (CO), 172.3 (CO), 137.0 (ArC), 128.5 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 66.2 (C5), 65.1 (C4), 44.2 (C1`), 39.1 (C3), 35.5 (C2`), 19.2 (Me), 19.1 (Me).

ESIMS *m/z* 315 ($M+K^+$, 100%).

HRESIMS calculated for $C_{15}H_{20}N_2O_3$ $(M+K)^+$ 315.1111, found 315.1124.

7.4. Experimental for Chapter 4

Potassium Styryltrifluoroborate (262)[107,108]



262

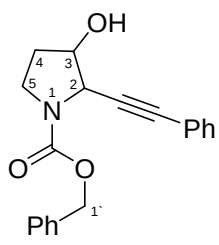
A solution of phenylacetylene (5.0 g, 49.0 mmol) in dry THF (150 mL) was cooled to -78 ^{o}C. *n*BuLi (2.5 M in hexane, 19.6 mL, 49.0 mmol) was added dropwise, and the solution was stirred for 1 h at this temperature. Trimethylborate (7.57 g, 73.5 mmol) was then added dropwise at -78 ^{o}C. The solution was stirred at this temperature for 1 h and then it was allowed to warm to -20 ^{o}C for 1 h. A saturated aqueous solution of KHF_2 (26.5 g, 0.29 mol) was then added. The resulting mixture was allowed to stir at -20 ^{o}C for 1 h and then it was allowed to warmed to rt for 1 h. The solvent was removed, and the resulting white solid was dried under high vacuum for 2 h. The solid was then washed with hot acetone. The resulting organic solution was filtered and the solvent was removed to give the title compound (6.11 g, 60%) as a white solid.

R_f : 0.15 (1 : 1, EtOAc/petrol)

^{1}H NMR δ 7.32-7.22 (4H, m, ArH), 7.20-7.17 (1H, m, ArH).

^{1}H and ^{13}C NMR data matched with the published data.

(±)-(2*S*,3*S*)-Benzyl 3-hydroxy-2-(phenylethynyl)pyrrolidine-1-carboxylate (*cis*-263) and (±)-(2*R*,3*S*)-Benzyl 3-hydroxy-2-(phenylethynyl)pyrrolidine-1-carboxylate (*trans*-263)



263

A solution of benzyl 2,3-dihydroxypyrrolidine-1-carboxylate **116**[3] (0.15 g, 0.63 mmol) and potassium phenylacetylenetrifluoroborate (0.26 g, 1.27 mmol) in MeCN (10 mL) maintained at 0 ^{o}C under a nitrogen atmosphere was treated dropwise with $BF_3{\cdot}OEt_2$ (0.36 g,

2.53 mmol). The resulting reaction mixture was stirred for 2 h, then treated with $NaHCO_3$ (15 mL of a saturated aqueous solution). The separated aqueous layer was extracted with Et_2O (3 x 15 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give *trans*-**263** (48 mg, 24%) and *cis*-**263** (133 mg, 65%) both as a pale yellow oils.

Data for *trans*-**263**

R_f : 0.55 (1 : 1, EtOAc/petrol)

υ_{max}/ cm^{-1} 3477, 2287, 2900, 1680, 1406, 1393, 1228, 1074.

^1H NMR δ (major rotamer)7.40–7.26 (10H, m, ArH), 5.32 (1H, d, *J* = 12.5 Hz, H1`), 5.90 (1H, d, *J* = 12.5 Hz, H1`), 4.66 (1H, s, H3), 4.50 (1H, br s, H2), 3.67 (2H, br s, H5), 2.32 (1H, br s, H4), 1.98 (1H, br s, H4).

^{13}C NMR δ (major rotamer) 154.9 (CO), 136.7 (ArC), 131.6 (ArC), 128.3 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 127.4 (ArCH), 86.3 (*C*≡C), 84.2 (C≡*C*), 77.20 (C3), 66.9 (C1`), 57.4 (C2), 44.1 (C5), 31.7 (C4).

ESIMS *m/z* 322 ($M + H^+$, 100%)

HRESIMS calculated for $C_{20}H_{20}NO_3$ ($M + H^+$) 322.1443, found 322.1501.

Data for *cis*-**263**

R_f : 0.50 (1 : 1, EtOAc/petrol).

υ_{max}/ cm^{-1} 3421, 2245, 1685, 1415, 1356, 1209, 1110, 1050.

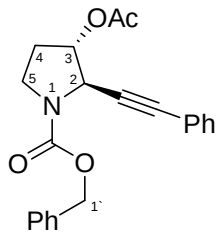
^1H NMR δ (major rotamer) 7.38–7.29 (10H, m, ArH), 5.14 (2H, s, H1`), 4.85 (1H, br s, H3), 4.41–4.32 (1H, m, H2), 3.68–3.48 (1H, m, H5), 3.56–3.48 (1H, m, H5), 2.38 (1H, d, *J* = 10 Hz, OH), 2.18–2.00 (2H, m, H4).

^{13}C NMR δ (major rotamer) 154.6 (CO), 136.6 (ArC), 131.9 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 122.0 (ArCH), 87.2 (*C*≡C), 84.0 (C≡*C*), 71.8 (C2), 67.1 (C1`), 54.3 (C3), 43.8 (C5), 31.6 (C4).

ESIMS *m/z* 322 ($M + H^+$, 100%).

HRESIMS calculated for $C_{20}H_{19}NO_3$ ($M + H^+$) 322.1443, found 322.1511.

(±)-(2*R*, 3*S*)-Benzyl 3-acetoxy-2-(phenylethynyl)pyrrolidine-1-carboxylate (265)



265

Compound **265** was prepared in a similar fashion to phenyl alkyne **263**, using benzyl 2,3-diacetoxypyrrolidine-1-carboxylate **264**[7] (57 mg, 0.19 mmol), potassium phenylacetylenetrifluoroborate (115 mg, 0.56 mmol), $BF_3{\cdot}OEt_2$ (105 mg, 0.74 mmol) and CH_2Cl_2 (10 mL), with stirring at 0 ^oC for 1 h then at rt for 16 h. Column chromatography of the crude product (1 : 3, EtOAc/petrol) afforded the title compound (51 mg, 77%) as a colorless oil.

R_f : 0.5 (1 : 3, EtOAc/petrol).

υ_{max}/ cm^{-1} 2929, 1740, 1705, 1411, 1356, 1236, 1200, 1113, 1050.

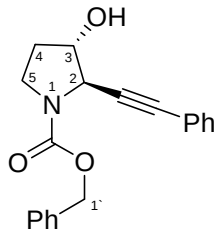
^1H NMR δ (major rotamer) 7.41–7.25 (10H, m, ArH), 5.33 (2H, s, H1`), 5.20 (1H, s, H3), 4.74 (1H, s, H2), 3.75–3.67 (1H, m, H4), 3.63–3.55 (1H, m, H4), 2.48–2.40 (1H, m, H5), 2.06 (4H, br s, overlapping signals from Me and H5).

^{13}C NMR δ (major rotamer) 170.2 (CO), 154.4 (CO), 136.6 (ArC), 131.8 (ArC), 128.5 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.5 (ArCH), 122.2 (ArCH), 85.1 (C2), 66.9 (C1`), 54.9 (C3), 44.2 (C5), 30.8 (C4), 21.0 (CH_3).

ESIMS *m/z* 364 ($M + H^+$, 100%).

HRESIMS calculated for $C_{22}H_{21}NO_4$ ($M + H^+$) 364.1555, found, 364.1549.

(±)-(2*R*,3*S*)-Benzyl 3-hydroxy-2-(phenylethynyl)pyrrolidine-1-carboxylate (*trans*-263)

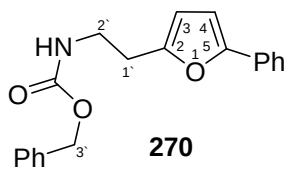


265

To a solution of 265 (0.100 g, 0.275 mmol) in MeOH (5 mL) at rt was added K_2CO_3 (0.018 g, 0.137 mmol) and the reaction mixture was stirred for 1 h. Water (10 mL) and EtOAc (10 mL) were added and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography to give the title compound (0.064 g, 72%) as a pale yellow oil.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound *trans*-**263** prepared from **116** and **262**.

Benzyl 2-(5-phenylfuran-2-yl) ethylcarbamate (270)



270

Method A. A solution of *cis*-**263** (25 mg, 0.08 mmol) in MeOH (2 mL) under a nitrogen atmosphere at rt was treated with $AgNO_3$ (4 mg, 0.02 mmol). The resulting mixture was stirred for 2 h then water (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography of the resulting residue (1 : 1, EtOAc/petrol) afforded the title compound **270** (20 mg, 83%) as a colorless oil.

R_f : 0.6 (1 : 1, EtOAc/petrol).

υ_{max}/ cm^{-1} 3246, 1695, 1428, 1350, 1234, 1075.

^{1}H NMR δ (major rotamer) 7.63 (1H, d, *J* = 8.5 Hz, ArH), 7.33 – 7.21 (10H, m, ArH), 6.54 (1H, d, *J* = 3.5 Hz, H4), 6.13 (1H, d, *J* = 3.5 Hz, H3), 5.11 (2H, s, H3`), 4.92 (1H, br. s, NH), 3.55 (2H, dd, *J* = 13.0 and 6.5 Hz, H2`), 2.91 (2H, t, *J* = 6.5 Hz, H1`).

^{13}C NMR δ (major rotamer) 156.3 (CO), 153.0 (ArC), 152.5 (ArC), 132.5 (ArC), 130.8 (ArC), 128.8 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 127.0 (ArCH), 123.4 (ArCH), 108.7 (C3), 105.7 (C4), 66.7 (C3`), 39.7 (C2`), 28.8 (C1`).

ESIMS *m/z* 322 ($M + H^+$, 33%), 344 ($M + Na^+$, 100%).

HRESIMS calculated for $C_{20}H_{19}NO_3$ ($M + H^+$) 322.1443, found 322.1486.

Method B. A magnetically stirred solution of *cis*-**263** (10 mg, 0.03 mmol) in MeOH (2 mL) maintained under a nitrogen atmosphere at rt was treated with $Au(PPh_3)Cl_2$ (5 mg, 9.3 μmol). The resulting mixture was stirred for 8 h then water (5 mL) was added, and the separated aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography of the resulting residue (1:1, EtOAc/petrol) and concentration of the relevant extracts (R_f 0.6 in 1:1 EtOAc/petrol) afforded the title compound **270** (9 mg, 87%) as a colorless oil.

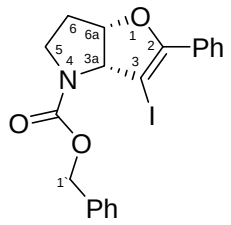
The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **270** prepared by Method A.

Method C. A solution of *cis*-**263** (20 mg, 0.06 mmol) in MeOH (3 mL) maintained under a nitrogen atmosphere at rt was treated with $PdCl_2(PPh_3)_2$ (2 mg, 0.02 mmol) and CuI (1 mg, 3.1 μmol). The resulting mixture was stirred for 8 h then water (5 mL) was added, and the separated aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography of the resulting residue (1:1, EtOAc/petrol) and concentration of the relevant extracts (R_f 0.6 in 1:1 EtOAc/petrol) afforded the title compound **270** (14 mg, 69%) as a colorless oil.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **270** prepared by Method A.

General Method for the Cyclization Halogenation and Cyclization Cyanation Reactions of *cis*-263 under Nitrogen Atmosphere and Preparation of Benzyl 3-iodo-2-phenyl-6,6a-dihydro-3a*H*-furo[3,2-*b*]pyrrole-4(5*H*)-carboxylate (280)

To a suspension of CuI (0.077 g, 0.411 mmol), in DMF (4 mL) was added *cis*-**263** (0.022 g, 0.068 mmol) and the resulting mixture was heated to 80 ^oC for 16 h under a nitrogen atmosphere. After the reaction mixture was cooled to rt, water (10 mL) was added and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude product. Column chromatography (CH_2Cl_2) of the crude residue furnished the title product (0.020 g, 65%) as a light pink oil.



280

R_f : 0.79 (CH_2Cl_2).

υ_{max}/cm^{-1} 1701, 1414, 1362, 1212, 1096, 1072.

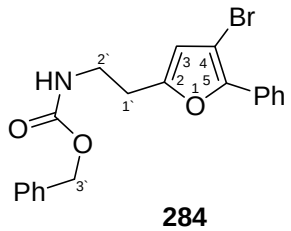
^1H NMR δ (major rotamer) 7.85 (2H, br. s, ArH), 7.46-7.25 (8H, m, ArH), 5.46 (1H, br. s, H6a), 5.22 (1H, s, H3a), 5.18 (2H, s, H1`), 3.99 (1H, br. s, H5), 3.21 (1H, ddd, *J* = 9.5, 9.5, 19.5, Hz, H5), 2.22 (1H, dd, *J* = 9.5, 19.5 Hz, H6), 2.07 (1H, m, H6).

^{13}C NMR δ (major rotamer) 155.3 (CO), 129.8 (ArC), 129.7 (ArC), 129.3 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 83.3 (C3a), 71.7 (C6a), 67.2 (C1`), 56.5 (C6), 42.8 (C6), 33.1 (C5).

EIMS *m/z* 447 (M^+, 40%).

HREIMS calculated for $C_{20}H_{18}NO_3I$ ($M^{+\cdot}$) 447.0331, found 447.0318

Benzyl 2-(4-bromo-5-phenylfuran-2-yl)ethylcarbamate (284)



284

Prepared using the general procedure above, from *cis*-**263** (0.020 g, 0.062 mmol), CuBr (0.053 g, 0.373 mmol) and DMF (2 mL). Column chromatography (1 : 5, EtOAc/petrol) of the crude product yielded compound **284** (0.010 g, 41%) as a colorless oil, and compound **270** (0.006 g, 25%) as a colorless oil.

R_f: 0.60 (1 : 5, EtOAc/petrol).

υ_{max}/cm^{-1} 1708, 1395, 1240, 1083, 1072.

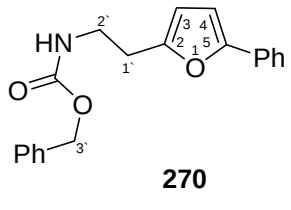
^{1}H NMR δ 7.91 (2H, d, *J* = 7.5 Hz, ArH), 7.42-726 (8H, m, ArH), 6.23 (1H, s, H3), 5.2 (2H, s, H3`), 4.91 (1H, br. s, NH), 3.53 (2H, br. d, *J* = 6.0 Hz, H2`), 2.90 (2H, br. s, H1`).

^{13}C NMR δ 156.3 (CO), 152. 6 (ArC), 148.0 (ArC), 136.4 (ArC), 134.3 (ArC), 129.7 (ArC), 128.5 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 125.2 (ArCH), 113.1 (C3), 96.4 (C4), 66.8 (C3`), 39.4 (C2`), 28.7 (C1`).

EIMS *m/z* 401 (M^+, ^{79}Br, 50%), 403 (M^+, ^{81}Br, 50%).

HREIMS calculated for $C_{20}H_{18}NO_3{}^{79}Br$ (M^+) 401.0449, found 401.0438.

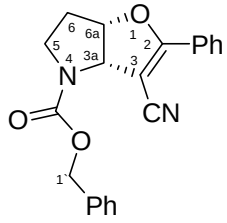
Benzyl 2-(5-phenylfuran-2-yl) ethylcarbamate (270)



270

Prepared using the general procedure above, from *cis*-**263** (0.020 g, 0.062 mmol), CuCl (0.053 g, 0.373 mmol) and DMF (2 mL). Column chromatography (1 : 5, EtOAc/petrol) of the crude product yielded compound **270** (0.012 g, 61%) as a colorless oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **270** prepared by Method A.

Benzyl 3-cyano-2-phenyl-6,6a-dihydro-3a*H*-furo[3,2-*b*]pyrrole-4(5*H*)-carboxylate (285)



285

Prepared using the general procedure above, from *cis*-**263** (0.025 g, 0.078 mmol), CuCN (0.042 g, 0.468 mmol) and DMF (2 mL). Column chromatography (1 : 1, EtOAc/petrol) of the crude product yielded compound **285** (0.0079 g, 30%) and compound **270** (0.012 g, 25%) both as colorless oils.

R_f: 0.60 (1 : 1, EtOAc/petrol).

υ_{max}/cm^{-1} 2202, 1708, 1614, 1414, 1364, 1224, 1103.

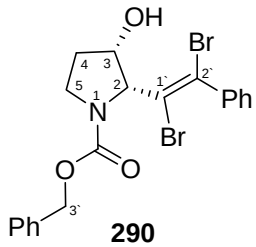
^{1}H NMR δ (major rotamer) 7.96 (2H, d, *J* = 7.5 Hz, ArH), 7.51-7.33 (8H, m, ArH), 5.42-5.35 (3H, m, H3a, H6a, H1`), 5.08 (1H, d, *J* = 12 Hz, H1`), 3.97 (1H, t, *J* = 12 Hz, H5), 3.28 (1H, ddd, *J* =5.5, 12, 17.5 Hz, H5), 2.32 (1H, dd, *J* = 5.5, 12 Hz, H6), 2.16 (1H, m, H6).

^{13}C NMR δ (major rotamer) 169.5 (CO), 153.7 (C5), 136.3 (ArC), 132.1 (ArC), 129.9 (ArC), 128.8 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 116.8 (ArCH), 87.1 (C6a), 82.6 (CN), 67.6 (C1`), 65.1 (C3a), 43.0 (C2), 31.7 (C3).

ESIMS *m/z* 347 ($M + H^+$, 100%.)

HRESIMS calculated for $C_{21}H_{19}N_2O_3$ ($M + H^+$) 347.1396, found 347.1475.

(2*R*, 3*S*)-Benzyl 2-((*E*)-1,2-dibromo-2-phenylvinyl)-3-hydroxypyrrolidine-1-carboxylate (290)



290

Prepared in a similar fashion to **270** above, from *cis*-**263** (0.020 g, 0.078 mmol), $CuBr_2$ (0.104 g, 0.468 mmol) and DMF (2 mL). Column chromatography (1 : 1, EtOAc/petrol) of the crude product yielded compound **290** as a colorless oil (0.0079 g, 30%) and compound **270** as a colorless oil (0.012 g, 25%).

R_f: 0.60 (1 : 1, EtOAc/petrol)

υ_{max}/cm^{-1} 3326, 1710, 1548, 1409, 1327.

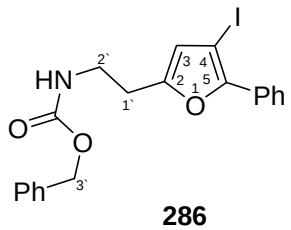
^{1}H NMR δ (major rotamer) 7.76-7.75 (2H, m, ArH), 7.45- 7.27 (8H, m, ArH), 5.27-5.13 (3H, m, H3`, H2,), 4.99 (1H, app. br. t, *J* = 7.0 Hz, H3), 3.88-3.80 (1H, m, H5), 3.67-3.60 (1H, m, H5), 2.13-2.0 (2H, m, H4).

^{13}C NMR δ (major rotamer) 167.0 (CO), 147.2 (ArC), 134.6 (ArC), 129.5 (ArCH), 128.7 (ArCH), 128.0 (ArCH), 127.6 (ArCH), 127.0 (ArCH), 126.9 (ArCH), 115.0 (C2`), 111.6 (C1`), 80.3 (C3), 74.4 (C2), 67.5 (C3`), 46.9 (C4), 29.1 (C5).

ESIMS *m/z* 479 (M + H^+, $^{79}Br_2$, 30%), 481 (M+H^+, $^{79}Br^{81}Br$, 50%), 483 (M+H^+, $^{81}Br_2$, 30%).

HRESIMS calculated for $C_{20}H_{20}NO_3{}^{79}Br_2$ (M + H^+) 479.9810, found 479.9656.

General Method for the Cyclization-Halogenation and Cyclization-Cyanation Reaction of *cis*-263 under Oxygen Atmosphere and Preparation of Benzyl 2-(4-iodo-5-phenylfuran-2-yl)ethylcarbamate (286)



286

To a solution of *cis*-**263** (0.040g, 0.125 mmol) in DMF (1.5 mL) under an oxygen atmosphere (balloon) was added CuI (0.026 g, 0.173 mmol) and the reaction vessel was placed in a pre-heated oil bath at 100 ^oC. The reaction mixture was stirred at this temperature for 16 h. H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the title compound (0.041 g, 74%) as a pink oil.

R_f: 0.52 (1 : 2, EtOAc/petrol)

υ_{max}/cm^{-1} 3367, 1683, 1532, 1459, 1274, 1108.

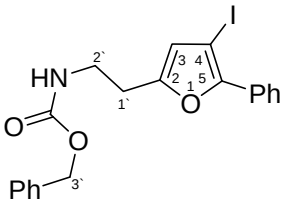
^{1}H NMR δ 7.92 (1H, d, *J* = 8.0 MHz, ArH), 7.40-7.31 (8H, m, ArH), 7.25 (1H, d, *J* = 2.0 MHz, ArH), 6.27 (1H, s, H3), 5.10 (2H, s, H3`), 4.90 (1H, br. s, NH), 3.54 (2H, dd, *J* = 7.0, 13.0 MHz, H2`), 2.90 (2H, t, *J* = 7.0 MHz, H1`).

^{13}C NMR δ 156.4 (CO), 151.6 (ArC), 136.4 (ArC), 130.3 (ArC), 128.7 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 127.8 (ArC), 127.1 (ArC), 126.2 (ArCH), 117.6 (C3), 67.0 (CH_2Ph), 61.4 (C4), 39.6 (C2`), 28.8 (C1`).

EIMS *m/z* 447 (M^+,50%);

HREIMS calculated for $C_{20}H_{18}NO_3I$ ($M^{+\cdot}$) 447.0320, found 447.0331.

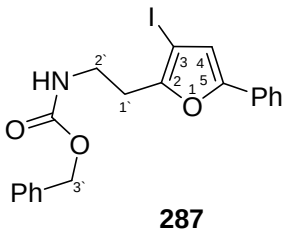
Benzyl 2-(4-iodo-5-phenylfuran-2-yl)ethylcarbamate (286)



286

Prepared using the general procedure above, from **280** (0.030 g, 0.067 mmol), CuI (0.013 g, 0.074 mmol) and DMF (2 mL). Column chromatography (1 : 2, EtOAc/petrol) of the crude product yielded the title compound (0.026 g, 90%) as a colorless oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **286** prepared from *cis*-**263**.

Benzyl 2-(3-iodo-5-phenylfuran-2-yl)ethylcarbamate (287)

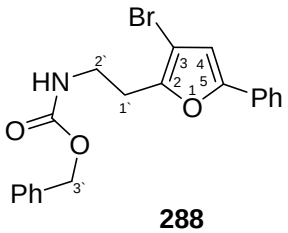


287

To a solution of **270** (0.025 g, 0.078 mmol) in CH_3CN (2 mL) at -10 ^oC was added NIS (0.019 g, 0.086 mmol). The resulting mixture was stirred at rt for 16 h. Water (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give a 1 : 1 mixture of the compounds **286** and **287** (0.029 g, 38%) as pale yellow oil.

Data for **287:** ^{1}H NMR δ 7.94-7.24 (10H, m, ArH), 6.23 (1H, s, H4), 5.19 (2H, s, H3`), 4.40 (1H, br. s, NH), 3.62 (2H, t, *J* = 7.0 Hz, H2`), 3.00 (2H, t, *J* = 7.0 Hz, H1`).

Benzyl 2-(3-bromo-5-phenylfuran-2-yl)ethylcarbamate (288)

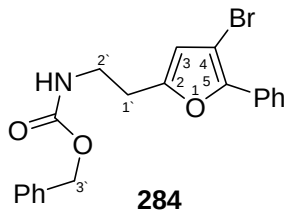


288

Prepared in a similar fashion to **287** using **270** (0.030, 0.077 mmol), CH_3CN (2 mL) and NBS (0.015 g, 0.085 mmol). Column chromatography (1 : 2, EtOAc/petrol) of the crude product yielded a 1 : 1 mixture of compounds **284** and **288** (0.007 g, 22%) as a colorless oil.

Data for **288:** ^{1}H NMR δ 7.97-7.28 (10H, m, ArH), 6.16 (1H, s, H4), 5.19 (2H, s, H3`), 3.66 (2H, t, *J* = 6.0 Hz, H2`), 2.98 (2H, t, *J* = 6.0 Hz, H1`).

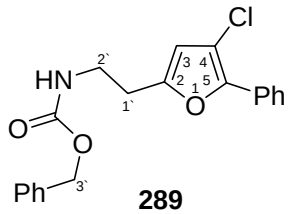
Benzyl 2-(4-bromo-5-phenylfuran-2-yl)ethylcarbamate (284)



284

Prepared using the general procedure above, from *cis*-**263** (0.040 g, 0.125 mmol), CuBr (0.020 g, 0.137 mmol) and DMF (2 mL). Column chromatography (1 : 2, EtOAc/petrol) of the crude product yielded the title compound (0.035 g, 68%) as a colorless oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **284** prepared by the general method for cyclization-halogenation and cyclization-cyanation reaction under N_2 atmosphere.

Benzyl 2-(4-chloro-5-phenylfuran-2-yl)ethylcarbamate (289)



289

Prepared using the general procedure above, from *cis*-**263** (0.040 g, 0.125 mmol), CuCl (0.014 g, 0.137 mmol) and DMF (1.5 mL). Column chromatography (1 : 2, EtOAc/petrol) of the crude product yielded compound **289** (0.035 g, 78%) as a colorless oil.

υ_{max}/cm^{-1} 3359, 1685, 1598, 1526, 1444, 1413, 1265.

R_f: 0.44 (1 : 2, EtOAc/petrol)

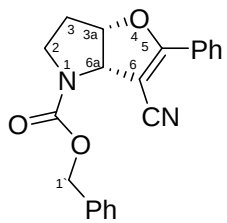
^{1}H NMR δ 7.86 (2H, d, *J* = 8.0 Hz, ArH), 7.41-7.25 (8H, m, ArH), 6.17 (1H, s, H3), 5.10 (2H, s, H3`), 4.92 (1H, br. s, NH), 3.52 (2H, dd, *J* = 5.5, 12 Hz, H2`), 2.88 (2H, t, *J* = 5.5 Hz, H1`).

^{13}C NMR δ 156.2 (CO), 151.5 (ArC), 146.4 (ArC), 136.4 (ArC), 129.8 (ArC), 129.4 (ArCH), 128.5 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.5 (ArCH), 124.7 (C4), 111.0 (C3), 66.7 (C3`), 39.3 (C2`) 28.7 (C1`).

EIMS *m/z* 355 (M^+, ^{35}Cl, 30%).

HREIMS calculated for $C_{20}H_{18}NO_3{}^{35}Cl$ (M^+) 355.0969, found 355.0975.

Benzyl 3-cyano-2-phenyl-6,6a-dihydro-3a*H*-furo[3,2-*b*]pyrrole-4(5*H*)-carboxylate (285)

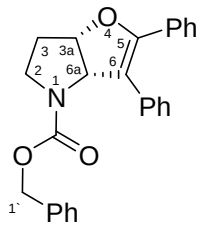


285

Prepared using the general procedure above, from *cis*-**263** (0.040 g, 0.125 mmol), CuCN (0.013 g, 0.137 mmol) and DMF (2 mL). Column chromatography (1 : 3, EtOAc/petrol) of the crude product yielded compound **285** (0.015 g, 35%) and compound

270 (0.017g, 40%) both as colorless oils. The spectral data derived from the materials prepared as described above were in good agreement with those obtained from the sample of compound **285** and **270** prepared by the general method for cyclization-halogenation and cyclization-cyanation reaction under N_2 atmosphere.

(±)-(3a*S*, 6a*S*)-Benzyl 2,3-diphenyl-6,6a-dihydro-3a*H*-furo[3,2-*b*]pyrrole-4(5*H*)-carboxylate (291)



291

A solution of iodobenzene (51 mg, 0.25 mmol), 2,2'-bipyridine (2 mg, 12.5 μmol), and K_2CO_3 (0.050 g, 0.5 mmol) in CH_3CN (5 mL) maintained under a nitrogen atmosphere at 50 ^oC was treated with $Pd_2(dba)_3$ (6 mg, 6.25 μmol). The resulting mixture was stirred for 1 h, before being treated with a solution of compound *cis*-**263** (20 mg, 0.06 mmol) in CH_3CN (2 mL). After being stirred for a further 24 h, the reaction mixture solvent was removed *in vacuo* and the resulting residue was filtered through a short plug of silica gel using EtOAc. The filtrate was concentrated under reduced pressure and the resulting crude material was purified using column chromatography (1 : 1, EtOAc/petrol) to afford two extracts, A and B. Concentration of fraction A gave biphenyl compound **291** (9 mg, 38%) as a colorless oil. Concentration of fraction B (R_f 0.6 in 1:1 EtOAc/petrol) gave compound **270** (8 mg, 19%) as a colorless oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound **270** previously prepared.

Data for **291**:

R_f : 0.7 (1 : 1, EtOAc/petrol)

υ_{max}/ cm^{-1}1706, 1593, 1516, 1448, 1260, 1217, 1101, 1026.

^1H NMR δ (major rotamer) 7.31–7.24 (5H, m, ArH), 5.67 (1H, br d, *J* 5.5 Hz, H6a), 5.24 (1H, br s, H3a), 4.94 (1H, d, *J* 12.0 Hz, H1`), 4.50 (1H, d, *J* 12.0 Hz, H1`), 4.10 (1H, br s, H2), 3.33 (1H, br s, H2), 2.24 (1H, br s, H3), 2.10 (1H, br s, H3).

^{13}C NMR δ (major rotamer) 154.1 (CO), 136.4 (ArC), 134.4 (ArC), 129.7 (ArC), 129.2 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 127.1 (ArCH), 126.8 (ArCH), 82.4 (C3a), 69.6 (C6a), 66.8 (C1`), 42.9 (C3), 33.4 (C2).

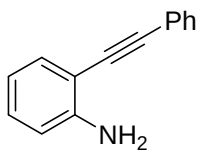
ESIMS *m/z* 398 ($M + H^+$, 100%).

HRESIMS calculated for $C_{26}H_{23}NO_3$ (M + H^+) 398.1756, found 398.1767.

7.5. Experimental for Chapter 5

General Method for Preparation of *2*-alkynylanilines via the Sonogashira Reaction of 2-Iodoaniline Derivatives: Preparation of 2-(Phenylethynyl)benzeneamine (349)

To a solution of 2-iodoaniline (0.500 g, 2.28 mmol) in Et_3N (8 mL) under a nitrogen atmosphere were added $PdCl_2(PPh_3)_2$ (0.079 g, 0.11 mmol) and CuI (0.022 g, 0.11 mmol) and the reaction mixture was stirred for 15 min at reflux temperature. Phenylacetylene (0.256 g, 2.51 mmol) was added to the mixture. The reaction mixture was stirred and heated at reflux and was monitored by TLC. After 2 h, H_2O (20 mL) was added and the aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 10, EtOAc/petrol) to give the title compound (0.391 g, 90%) as a white solid.



349

R_f : 0.38 (1 : 8 EtOAc/petrol).

Mp 85-87 °C (Lit.[129] Mp 85.5-86 °C).

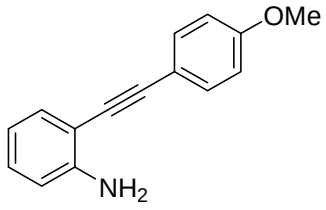
ν_{max}/cm^{-1} 3487, 3370, 2202, 1612, 1495, 1438, 1454, 1313, 1260, 1152, 748.

^1H NMR δ 7.54-7.51 (2H, m, ArH), 7.38-7.33 (4H, m, ArH), 7.14 (1H, td, *J* = 1.5, 7.5 Hz, ArH), 6.74-6.69 (2H, m, ArH), 4.28 (2H, br. s, NH_2).

ESIMS *m/z* 194 (M + H^+, 100%).

HRESIMS calculated for $C_{14}H_{11}N$ (M + H^+) 194.0892, found 194.0880.

2-((4-Methoxyphenyl)ethynyl)benzeneamine (350)[147]



350

Following the general method, a solution of 2-iodoaniline (0.500 g, 2.28 mmol), $PdCl_2(PPh_3)_2$ (0.160 g, 0.22 mmol), CuI (0.043 g, 0.22 mmol) and 4-ethynylanisole (0.36 g, 2.74 mmol) in Et_3N (20 mL) was heated at reflux for 2 h. The crude product was purified by column chromatography (1 : 6, EtOAc/petrol) to give the title compound (0.382 g, 83%) as a yellow oil.

R_f : 0.34 (1 : 6 EtOAc/petrol)

ν_{max}/cm-^{1} 3487, 3226, 3385, 2361, 1609, 1506, 1449, 1245, 1174, 1026, 833.

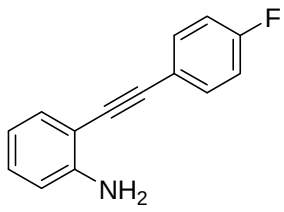
1H NMR δ 7.45 (2H, d, J = 9 Hz, ArH), 7.34 (1H, d, J = 5.5 Hz, ArH), 7.10 (1H, t, J = 5.5 Hz, ArH), 6.86 (2H, d, *J* = 9.0 Hz, ArH), 6.71- 6.68 (2H, m ,ArH), 4.21 (2H, br. s, NH_2), 3.80 (3H, s, CH_3O).

13C NMR δ 159.5 (ArC), 147.5 (ArC), 132.8 (ArCH), 131.9 (ArCH), 129.3 (ArCH), 117.9 (ArCH), 115.3 (ArC), 114.2 (ArCH), 113.9 (ArCH), 108.2 (ArC), 94.5 (*C*≡C), 84.4 (C≡*C*), 55.2 (CH_3O).

ESIMS *m/z* 224 (M + H^+, 100%).

HREIMS calculated. for $C_{15}H_{14}NO$ (M + H^+) 224.1065, found 224,1075.

2-((4-Fluorophenyl)ethynyl)benzeneamine (351)



351

Following the general method, a solution of 2-iodoaniline (0.500 g, 2.28 mmol), $PdCl_2(PPh_3)_2$ (0.160 g, 0.22 mmol), CuI (0.043 g, 0.22 mmol) and 1-ethynyl-4-fluorobenzene (0.330 g, 2.74 mmol) in Et_3N (20 mL) was heated at reflux for 1.5 h. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give the title compound (0.405 g, 86%) as an orange solid.

R_f : 0.52 (1 : 4, EtOAc/petrol)

Mp 79-81 ^{o}C

ν_{max}/cm^{-1} 2361, 2340, 1613,1504, 1448, 1454, 1306, 1220, 1155, 840.

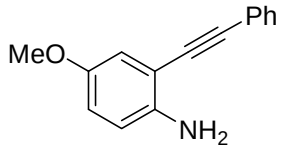
^{1}H NMR δ 7.48 (2H, dd, *J* = 5.5, 8.5 Hz, ArH), 7.34 (1H, dd, *J* = 1.5, 8.0 Hz, ArH), 7.12 (1H, dt, *J* = 1.5, 8.0 Hz, ArH), 7.02 (2H, t, *J* = 8.0 Hz, ArH), 6.72-6.69 (2H, m, ArH), 4.23 (2H, br. s, NH_2)

^{13}C NMR δ 162.4 (ArC, d, *J* = 247 Hz), 147.7 (ArC), 133.3 (ArCH, d, *J* = 8.5 Hz), 132.0 (ArCH), 129.7 (ArCH), 119.3 (ArC, d, *J* = 3.7 Hz), 117.9 (ArCH), 115.6 (ArCH, d, *J* = 22.0 Hz), 114.3 (ArCH), 107.6 (ArC), 93.5 (*C*≡C), 85.5 (C≡*C*).

ESIMS *m/z* 212 (M + H^+, 100%).

HRESIMS calculated. for $C_{14}H_{11}NF$ (M + H^+) 212.0864, found 212.0876.

4-Methoxy-2-(phenylethynyl)benzeneamine (356)



356

Following the general method, a solution of 2-bromo-4-methoxyaniline (0.500 g , 2.05 mmol), $PdCl_2(PPh_3)_2$ (0.154 g, 0.22 mmol), CuI (0.041 g, 0.22 mmol) and phenylacetylene (0.273 g, 2.67 mmol) in Et_3N (20 mL) was heated at reflux for 6 h. The crude product was purified by column chromatography (1 : 6, EtOAc/petrol) to give the title compound (0.382 g, 83%) as a yellow oil.

R_f : 0.37 (1 : 6, EtOAc/petrol)

ν_{max}/cm^{-1} 3298, 2361, 1700, 1613, 1541, 1424, 1275, 1186, 1040, 912.

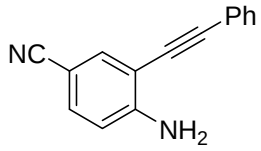
^1H NMR δ 7.53 (2H, d, *J* = 6.0 Hz, ArH), 7.35 (3H, d, *J* = 6.0 Hz, ArH), 6.92 (1H, d, *J* = 2.5 Hz, ArH), 6.78 (1H, dd, *J* = 2.5, 8.5 Hz, ArH), 6.68 (1H, d, *J* = 8.5 Hz, ArH), 4.00 (2H, br. s, NH_2), 3.75 (3H, s, CH_3O).

^{13}C NMR δ 151.9 (ArC), 141.9 (ArC), 131.4 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 123.1 (ArC), 117.4 (ArCH), 115.9 (ArCH), 115.8 (ArCH), 108.6 (ArC), 94.6 (*C*≡C), 85.9 (C≡*C*), 55.8 (CH_3O).

EIMS *m/z* 223 (M^+, 100%).

HREIMS calculated. for $C_{15}H_{13}NO$ (M^+) 223.0998, found 223.0997.

4-Amino-3-(phenylethynyl)benzonitrile (357)



357

Following the general method, a solution of 4-cyano-2-iodoaniline (0.500 g, 2.05 mmol), $PdCl_2(PPh_3)_2$ (0.070 g, 0.10 mmol), CuI (0.019 g, 0.10 mmol) and phenylacetylene (0.230 g, 2.25 mmol) in Et_3N (20 mL) was heated at reflux for 2 h. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.439 g, 94%) as a brown solid.

R_f : 0.41 (1 : 3, EtOAc/petrol)

Mp 106-108 ^oC (Lit.[131] Mp 107-108 ^oC)

ν_{max}/cm^{-1} 3467, 3353, 2215, 11627, 1620, 1503, 1337, 1270, 1029. 821.

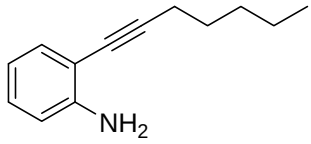
^1H NMR δ 7.61 (1H, s, ArH), 7.51 (2H, t, *J* = 3.5 Hz, ArH), 7.37-7.34 (4H, m, ArH), 6.70 (1H, d, *J* = 8.5 Hz, ArH), 4.81 (2H, br. s, NH_2).

^{13}C NMR δ 150.9 (ArC), 136.2 (ArCH), 133.1 (ArCH), 131.1 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 122.2 (ArC), 119.3 (ArC), 113.9 (ArCH), 108.1 (ArC), 100.0 (CN), 96.1 (*C*≡C), 83.3 (C≡*C*).

EIMS *m/z* 314 (M^+, 30%).

HREIMS calculated. for $C_{15}H_{10}N_2$ (M^+) 218.0843, found 218.0843.

2-(Hept-1-ynyl)benzeneamine (358)



358

Following the general method, a solution of 2-iodoaniline (0.300 g, 1.37 mmol), $PdCl_2(PPh_3)_2$ (0.048 g, 0.069 mmol), CuI (0.013 g, 0.069 mmol) and heptyne (0.154 g, 1.50 mmol) in Et_3N (20 mL) was heated at reflux for 4 h. The crude product was purified by column chromatography (1 : 10, EtOAc/petrol) to give the title compound (0.232 g, 91%) as a yellow oil.

R_f : 0.38 (1 : 7, EtOAc/petrol).

ν_{max}/cm^{-1} 3375, 2955, 2929, 2852, 1690, 1603, 1495, 1455, 1306, 1157, 748.

^{1}H NMR δ (300 MHz) 7.23 (1H, dd, *J* = 1.5, 8.0 Hz, ArH), 7.09-7.04 (1H, m, ArH), 6.68-6.62 (2H, m, ArH), 4.15 (2H, br. s, NH_2) 2.45 (2H, t, *J* = 7.0 Hz, CH_2), 1.65-1.57 (2H, m, CH_2), 1.47-1.30 (4H, m, 2 x CH_2), 0.920 (3H, t, *J* = 7.0 Hz, CH_3).

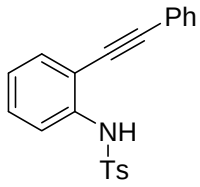
^{13}C NMR δ (75 MHz) 147.5 (ArC), 131.9 (ArCH), 128.7 (ArCH), 127.7 (ArC), 117.8 (ArCH), 114.1 (ArCH), 108.9 (*C*≡C), 95.7 (C≡*C*), 31.1 (CH_2), 28.6 (CH_2), 22.2 (CH_2), 19.5 (CH_2), 13.9 (CH_3).

EIMS *m/z* 187 (M^+, 80%).

HREIMS calculated. for $C_{13}H_{17}N$ (M^+) 187.1353, found 187.1361.

General Procedure for the Protection Reactions of Anilines : 2-Ethynylaniline derivative (1.03 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and the solution was cooled to 0 ^{o}C. Pyridine (2.07 mmol) and tosyl chloride (1.23 mmol) or trifluoroacetic anhydride (1.23 mmol) were then added. The reaction mixture was warmed to rt and then stirred at this temperature until TLC analysis shows consumption of starting material. H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography.

4-Methyl-*N*-(2-(phenylethynyl)phenyl)benzenesulfonamide (359)



359

Following the above general procedure, 2-phenylethynylaniline (0.200 g, 1.03 mmol), CH_2Cl_2 (8 mL), pyridine (0.164 g, 2.07 mmol) and tosyl chloride (0.236 g, 1.23 mmol) were stirred for 15 h. The crude product was purified by column chromatography (1 : 8, EtOAc/petrol) to give the title compound (0.340 g, 95%) as a colorless solid.

R_f : 0.52 (1 : 2, EtOAc/petrol)

Mp 110-112 ^oC (Lit.[129] Mp 111-112 ^oC).

ν_{max}/cm^{-1} 3267, 2366, 1603, 1501, 1338, 1334, 1167, 1091, 917, 814.

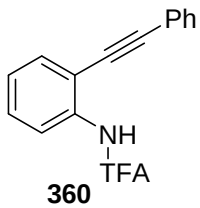
^1H NMR δ 7.66 (2H, d, *J* = 8.0 Hz, ArH), 7.62 (1H, d, *J* = 8.0 Hz, ArH), 7.46-7.45 (2H, m, ArH), 7.37 (3H, m, ArH), 7.27 (1H, t, *J* = 8.0 Hz, ArH), 7.23 (1H, br. s, ArH), 7.15 (2H, d, *J* = 8.0 Hz, ArH), 7.04 (1H, t, *J* = 8.0 Hz, ArH), 2.31 (3H, s, CH_3).

^{13}C NMR δ 143.9 (ArC), 137.4 (ArC), 136.0 (ArC), 131.9 (ArCH), 131.4 (ArCH), 129.5 (ArCH), 128.9 (ArCH), 128.4 (ArCH), 127.1 (ArCH), 124.5 (ArCH), 121.9 (ArC), 120.3 (ArCH), 114.5 (ArC), 96.0 (*C*≡C), 83.6 (C≡*C*), 21.4 (CH_3).

ESIMS *m/z* 348 ($M + H^+$, 75%).

HRESIMS calculated. for $C_{21}H_{18}NO_2S$ ($M + H^+$) 348.1074, found 348.1058.

2,2,2,-Trifluoro-*N*-(2-(phenylethynyl)phenyl)acetamide (360)



360

Following the above general procedure, 2-phenylethynylaniline (0.300 g, 1.55 mmol), CH_2Cl_2 (10 mL), pyridine (0.245 g, 3.10 mmol) and trifluoroacetic anhydride (0.390 g, 1.86 mmol) were stirred for 0.5 h. The crude product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the title compound (0.414 g, 93%) as a white solid.

R_f : 0.47 (1 : 3, EtOAc/petrol).

Mp 95-96 ^oC (Lit.[129] Mp 96-97 ^oC)

ν_{max}/cm^{-1} 3344, 2366, 1711, 1588, 1541, 1501, 1449, 1280, 1184, 1280, 1157, 767.

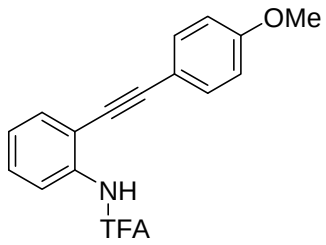
^1H NMR δ 8.90 (1H, br. s, NH), 8.38-8.36 (1H, m, ArH), 7.57-7.52 (2H, m, ArH), 7.43-7.40 (3H, m, ArH), 7.25-7.20 (1H, m, ArH).

^{13}C NMR δ 154.4 (CO, q, *J* = 37.6 Hz), 136.0 (ArC), 131.4 (ArCH), 129.8 (ArCH), 129.9 (ArCH), 128.6 (ArCH), 125.5 (ArCH), 121.6 (ArC), 119.5 (ArCH), 115.8 (CF_3, q, *J* = 287.6 Hz), 113.4 (ArC), 98.0 (*C*≡C), 82.8 (C≡*C*).

EIMS *m/z* 289 (M^+, 100%).

HREIMS calculated. for $C_{16}H_{10}NOF_3$ (M^+) 289.0718, found 289.0732.

2,2,2-Trifluoro-*N*-(2((4-methoxyphenyl)ethynyl)acetamide (361)



361

Following the above general procedure, 2-((4-methoxyphenyl)ethynyl)benzeneamine (0.100 g, 0.45 mmol), CH_2Cl_2 (5 mL), pyridine (0.072 g, 0.90 mmol) and trifluoroacetic anhydride (0.113 g, 0.54 mmol) were stirred for 2 h. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.135 g, 96%) as a white solid.

R_f : 0.48 (1 : 3, EtOAc/petrol).

Mp 99-101 ^{o}C.

ν_{max}/cm-^{1} 3300, 2356, 2330, 1713, 1511, 1291, 1239, 1191, 1166, 1159, 828.

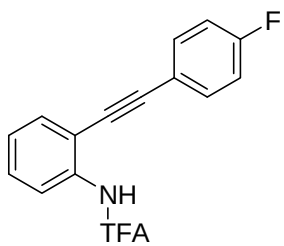
^{1}H NMR δ 8.90 (1H, br. s, NH), 8.36 (1H, d, *J* = 7.0 Hz, ArH), 7.54 (1H, dd, *J* = 1.5, 7.0 Hz, ArH), 7.46 (2H, dt, *J* = 2.0, 8.5 Hz, ArH), 7.39 (1H, ddd, *J* = 1.5, 7.0, 8.5 Hz, ArH), 7.20 (1H, ddd, *J* = 1.5, 7.0, 8.5 Hz, ArH), 6.92 (2H, dt, *J* = 2.0, 8.5 Hz, ArH), 3.85 (3H, s, CH_3O).

^{13}C NMR δ 160.4 (ArC), 154.3 (CO, q, *J* = 37.3 Hz), 135.8 (ArC), 133.0 (ArCH), 131.4 (ArCH), 129.4 (ArCH), 125.4 (ArCH), 119.5 (ArCH), 114.3 (ArCH), 113.8 (ArC), 113.6 (ArC), 98.2 (*C*≡C), 81.7 (C≡*C*), 55.3 (CH_3O).

ESIMS *m/z* 319 (M + H^+, 100%).

HRESIMS calculated. for $C_{17}H_{12}NO_2F_3$ (M + H^+) 319.0825, found 319.0820.

2,2,2-Trifluoro-*N*-(2-((4-fluorophenyl)ethynyl)phenyl)acetamide (362)



362

Following the above general procedure, 2-((4-fluorophenyl)ethynyl)benzeneamine (0.100 g, 0.48 mmol), CH_2Cl_2 (5 mL), pyridine (0.076 g, 0.96 mmol) and trifluoroacetic anhydride (0.121 g, 0.58 mmol) were stirred for 1 h. The crude product was purified by column

chromatography (1 : 5, EtOAc/petrol) to give the title compound (0.140 g, 96%) as a light yellow solid.

R_f : 0.61 (1 : 5, EtOAc/petrol).

Mp 79-81 ^oC.

ν_{max}/cm^{-1} 3300, 2361, 1335, 1710, 1509, 1233, 1187, 1173, 1166, 1156, 836.

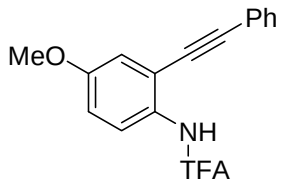
^1H NMR δ 8.83 (1H, br. s, NH), 8.35 (1H, d, *J* = 8.5Hz, ArH), 7.55 (1H, d, *J* = 8.0 Hz, ArH), 7.52-7.49 (2H, dd, *J* = 2.5, 8.0 Hz, ArH), 7.41 (1H, t, *J* = 7.5 Hz, ArH), 7.21 (1H, t, *J* = 7.5 Hz, 7.09 (2H, t, *J* = 8.5 Hz, ArH).

^{13}C NMR δ 163.0 (ArC, d, *J* = 250.6 Hz), 154.6 (CO, q, *J* = 37.8 Hz), 136.0 (ArC), 133.4 (ArCH, d *J* = 8.7 Hz), 131.6 (ArCH), 129.9 (ArCH), 125.5 (ArCH), 119.6 (ArCH), 117.8 (ArC, d, *J* = 3.2 Hz), 116.1 (ArCH, d, *J* = 22.2 Hz), 115.9 (CF_3, q, *J* = 287.7 Hz) 113.3 (ArC), 96.8 (*C*≡C), 82.6 (C≡*C*).

EIMS *m/z* 307 (M^+, 100%).

HREIMS calculated. for $C_{16}H_9NOF_4$ (M^+) 307.0626, found 307.0620.

2,2,2-Trifluoro-*N*-(4-methoxy-2-(phenylethynyl)phenyl)acetamide (363)



363

Following the above general procedure, 4-methoxy-2-(phenylethynyl)benzeneamine (0.100 g, 0.45 mmol), CH_2Cl_2 (5 mL), pyridine (0.071 g, 0.90 mmol) and trifluoroacetic anhydride (0.113 g, 0.54 mmol) were stirred for 1 h. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.129 g, 90%) as a white solid.

R_f : 0.47 (1 : 3, EtOAc/petrol)

Mp 120-122 ^oC.

ν_{max}/cm^{-1} 3446, 2945, 1603, 1500, 1285, 1226, 1036, 819.

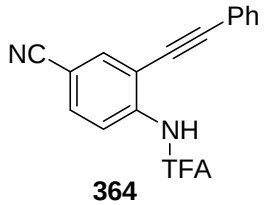
^1H NMR δ 8.71 (1H, br. s, NH), 8.24 (1H, d, *J* = 9.0 Hz, ArH), 7.53-7.51 (2H, m, ArH), 7.40-7.38 (3H, m, ArH), 7.06 (1H, d, *J* = 3.0 Hz, ArH), 6.94 (1H, dd, *J* = 3.0, 9.0 Hz, ArH), 3.82 (3H, s, CH_3O).

^{13}C NMR δ 156.7 (ArC), 154.3 (CO, q, *J* = 36.6 Hz), 131.4 (ArCH), 129.5 (ArC), 129.3 (ArCH), 128.6 (ArCH), 121.6 (ArC), 121.2 (ArCH), 116.2 (ArCH), 115.8 (CF_3, q, *J* = 287.5 Hz), 115.7 (ArCH) 114.8 (ArC), 97.6 (*C*≡C), 82.9 (C≡*C*), 55.5 (CH_3O).

EIMS *m/z* 319 (M^+, 100%).

HREIMS calculated. for $C_{17}H_{12}NO_2F_3$ (M^+) 319.0814, found 319.0820.

***N*-(4-Cyano-2-(phenylethynyl)phenyl)-2,2,2-trifluoroacetamide (364)**



364

Following the above general procedure, 4-amino-3-(phenylethynyl)benzonitrile (0.150 g, 0.65 mmol), CH_2Cl_2 (5 mL), pyridine (0.061 g, 0.78 mmol) and trifluoroacetic anhydride (0.165 g, 0.78 mmol) were stirred for 1 h. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give the title compound (0.195 g, 91%) as a white solid.

R_f : 0.37 (1 : 4, EtOAc/petrol).

Mp 115-117 ^oC.

ν_{max}/cm^{-1} 3259, 2366, 2233, 1731, 1716,1530, 1485, 1413, 1288, 1190, 1156, 1142, 886.

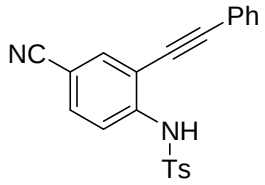
^1H NMR δ 9.00 (1H, br. s, NH), 8.54 (1H, d, *J* = 9.0 Hz, ArH), 7.86 (1H, d, *J* = 1.5 Hz, ArH), 7.69 (1H, dd, *J* = 1.5, 9.0 Hz, ArH), 7.53 (2H, m, ArH), 7.44 (3H, m, ArH)

^{13}C NMR δ 154.7 (CO, q, *J* = 37.7 Hz), 139.3 (ArC), 135.1 (ArCH), 133.2 (ArCH), 131.6 (ArCH), 130.07 (ArCH), 128.8 (ArC), 120.6 (ArC), 119.8 (ArCH), 117.4 (ArCH), 115.4 (CF_3, q, *J* = 287.5 Hz), 114.5 (ArC), 109.3 (CN), 100.3 (*C*≡C), 80.6 (C≡*C*).

EIMS *m/z* 314 (M^+, 100%).

HREIMS calculated. for $C_{17}H_9N_2OF_3$ (M^+) 314.0672, found 314.0666.

***N*-(4-Cyano-2-(phenylethynyl)phenyl)-4-methylbenzenesulfonamide (365)**



365

Following the above general procedure, 4-amino-3-(phenylethynyl)benzonitrile (0.200 g, 0.872 mmol), CH_2Cl_2 (5 mL), pyridine (0.137 g, 1.74 mmol) and tosyl chloride (0.199 g ,1.04 mmol) were stirred at 40 ^oC for 6 h. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.190 g, 57%) as a yellow solid.

R_f : 0.38 (1 : 3, EtOAc/petrol).

Mp 93-95 ^oC.

ν_{max}/cm^{-1} 3257, 2233, 1598, 1496, 1408, 1347, 1291, 1167, 1090, 894.

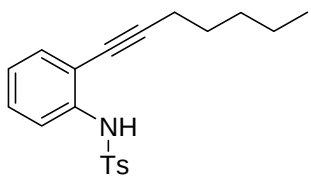
^{1}H NMR δ 7.66 (2H, d, *J* = 8.0 Hz, ArH), 7.57 (2H, t, *J* = 7.0 Hz, ArH), 7.49 (1H, br. s, ArH), 7.43 (3H, m, ArH), 7.33 (2H, dd, *J* = 9.0, 16.5 Hz, ArH), 7.17 (2H, d, *J* = 8.0 Hz, ArH), 2.94 (3H, s, CH_3);

^{13}C NMR δ 144.8 (ArC), 141.2 (ArC), 135.6 (ArC), 135.5 (ArCH), 132.8 (ArCH), 131.7 (ArCH), 129.9 (ArCH), 129.7 (ArCH), 128.6 (ArCH), 127.1 (ArCH), 126.9 (ArC), 120.9 (ArC), 118.3 (ArCH), 114.2 (ArC), 107.5 (CN), 98.5 (*C*≡C), 81.3 (C≡*C*), 21.5 (CH_3).

EIMS *m/z* 372 (M^+, 100%).

HREIMS calculated. for $C_{22}H_{16}N_2O_2S$ (M^+) 372.0933, found 372.0932.

_N_-(2-(Hept-1-ynyl)phenyl)-4-methylbenzenesulfonamide (366)



366

Following the above general procedure, 2-(hept-1-ynyl)benzeneamine (0.150 g, 0.80 mmol), CH_2Cl_2 (5 mL), pyridine (0.126 g, 1.6 mmol) and tosyl chloride (0.183 g ,0.96 mmol) were stirred for 18 h. The crude product was purified by column chromatography (1 : 6, EtOAc/petrol) to give the title compound (0.224 g, 82%) as a yellow oil.

R_f : 0.24 (1 : 6, EtOAc/petrol)

ν_{max}/cm^{-1} 2965, 2924, 1603, 1490, 1398, 1342, 1259, 1166, 1091, 1017, 795

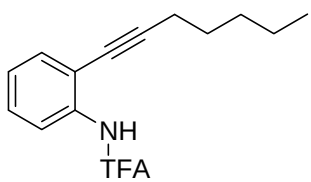
^{1}H NMR δ 7.69-7.62 (3H, m, ArH), 7.24-7.18 (4H, m, ArH), 6.98- 6.95 (1H, m, ArH), 2.40 (2H, t, *J* = 7.0 Hz, CH_2), 2.35 (3H, s, CH_3), 1.62-1.57 (2H, m, CH_2), 1.43-1.36 (4H, m, 2 x CH_2), 0.94 (3H, t, *J* = 7.0 Hz, CH_3)

^{13}C NMR δ 143.8 (ArC), 137.4 (ArC), 131.8 (ArCH), 129.5 (ArCH), 128.6 (ArCH), 127.1(ArCH), 124.0 (ArC), 119.2 (ArCH), 115.7 (ArCH), 114.8 (ArC), 97.8 (*C*≡C), 75.2 (C≡*C*), 31.0 (CH_2), 28.2 (CH_2), 22.1 (CH_2), 21.4 (CH_2), 19.4 (CH_3), 13.8 (CH_3).

EIMS *m/z* 341 (M^+, 40%).

HREIMS calculated. for $C_{20}H_{23}NO_2S$ (M^+) 341.1455, found 341.1449.

2,2,2-Trifluoro-_N_-(2-(hept-1-ynyl)phenyl)acetamide (367)



367

Following the above general procedure, 2-(hept-1-ynyl)benzeneamine (0.150 g, 0.80 mmol), CH_2Cl_2 (5 mL), pyridine (0.126 g, 1.6 mmol) and trifluoroacetic anhydride (0.076 g ,0.96 mmol) were stirred for 1 h. The crude

product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the title compound (0.228 g, 89%) as a yellow oil.

R_f : 0.64 (1 : 5, EtOAc/petrol).

ν_{max}/cm^{-1} 3370, 2955, 2934, 2361, 2335, 1746, 1588, 1541, 1454, 1296, 1260, 1149, 1101, 1015.

^1H NMR δ 8.82 (1H, br. s, NH), 8.33 (1H, d, *J* = 8.0 Hz, ArH), 7.42 (1H, d, *J* = 8.0 Hz, ArH), 7.34 (1H, t, *J* = 8.0 Hz, ArH), 7.20-7.12 (1H, m, ArH).

^{13}C NMR δ 154.2 (CO, q, *J* = 37.1 Hz), 146.7 (ArC), 136.1 (ArCH), 131.6 (ArCH), 129.0 (ArCH), 125.2 (ArCH), 119.2 (ArC), 115.7 (CF_3, q, *J* = 287.6 Hz), 99.7 (*C*≡C), 74.6 (C≡*C*), 31.0 (CH_2), 28.2 (CH_2), 22.1 (CH_2), 19.4 (CH_2), 13.8 (CH_3).

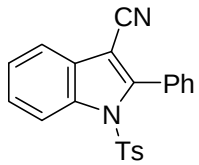
ESIMS *m/z* 283 ($M + H^+$, 100%).

HRESIMS calculated. for $C_{15}H_{16}NOF_3$ ($M + H^+$) 283.1431, found 283.1184.

General Procedure for the Preparation of Indoles

To a solution of the 2-ethynylaniline derivative (0.30 mmol) in anhydrous DMF (4 mL) under an oxygen atmosphere (balloon) was added CuCN (0.90 mmol) and the reaction vessel was placed in a pre-heated oil bath at 100 ^oC. The reaction mixture was stirred at this temperature for 16 h. Two different work-up procedures were followed.Work-up procedure A: H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography. Work-up procedure B: The solvent was removed *in vacuo* at 60 ^oC. The crude residue was purified by column chromatography.

2-Phenyl-1-(4-methylbenzenesulfonyl)-1*H*-indole-3-carbonitrile (368)



368

Using the general indole preparation procedure above, 4-methyl-*N*-(2-(phenylethynyl)phenyl)benzenesulfonamide (0.100 g, 0.288 mmol), DMF (4 mL) and CuCN (0.080 g, 0.86 mmol) were stirred at 100 ^oC for 16 h. Work-up procedure A was applied. The crude product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the compound **368** (0.080 g, 74%) as a white solid and compound **369** (0.003 g , 3%) as a colorless solid.

Data for **368**;

R_f : 0.35 (1 : 5, EtOAc/petrol).

Mp 148-150 ^oC.

ν_{max}/cm^{-1} 2361, 1342, 2230, 1451, 1375, 1197, 1178.

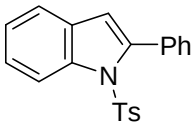
^1H NMR δ 8.36 (1H, d, *J* = 8.5 Hz, ArH), 7.65 (1H, d, *J* = 7.5 Hz, ArH), 7.55-754 (1H, m, ArH), 7.51-7.46 (5H, m, ArH), 7.42 (1H, t, *J* = 7.5 Hz, ArH), 7.28 (2H, d, *J* = 8.0 Hz, ArH), 7.10 (2H, d, *J* = 8.0 Hz, ArH), 2.33 (3H, s, CH_3).

^{13}C NMR δ 148.6 (ArC),145.8 (ArC), 136.4 (ArC), 134.6 (ArC), 130.9 (ArCH), 130.5 (ArCH), 129.7 (ArCH), 128.3 (ArC), 127.9 (ArCH), 127.8 (ArC), 126.9 (ArCH), 126.6 (ArCH), 125.3 (ArCH), 119.6 (ArCH), 116.3 (ArCH), 113.9 (ArC), 96.7 (CN), 21.6 (CH_3).

EIMS *m/z* 372 (M^+, 65%).

HREIMS calculated. for $C_{22}H_{16}N_2O_2S$ (M^+) 372.0935 found 372.0932.

2-Phenyl-1-(4-methylbenzenesulfonyl)-1*H*-indole1 (369)



369

R_f : 0.52 (1 : 3, EtOAc/petrol).

Mp 144-146 ^oC (Lit.[85] Mp 146-148 ^oC).

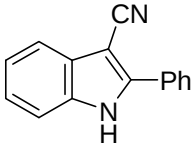
ν_{max}/cm^{-1} 1598, 1449, 1367, 1306, 1167, 1060, 978, 809.

^1H NMR δ 8.31 (1H, d, *J* = 8.5 Hz, ArH), 7.50-7.48 (2H, m, ArH), 7.43 (4H, m, ArH), 7.35 (1H, t, *J* = 7.5 Hz, ArH), 7.27-7.24 (3H, m, ArH), 7.03 (2H, d, *J* = 8.5 Hz, ArH), 6.54 (1H, s, ArH), 2.28 (3H, s, CH_3).

ESIMS *m/z* 348 ($M + H^+$, 100%).

HRESIMS calculated. for $C_{21}H_{18}NO_2S$ ($M + H^+$) 348.1042, found 348.1058.

2-Phenyl-1*H*-indole-3-carbonitrile (370)



370

Using the general indole preparation procedure above, 2,2,2,-trifluoro-*N*-(2-(phenylethynyl)phenyl)acetamide (0.100 g, 0.34 mmol), DMF (4 mL), and CuCN (0.093 g, 1.02 mmol) were stirred at 100 ^oC for 16 h. Work-up procedure A was applied. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.059 g, 80%) as a white solid.

R_f : 0.22 (1 : 3, EtOAc/petrol).

Mp 224-226 ^oC.

ν_{max}/cm^{-1} 3221, 2361, 2335, 2217, 1654, 1490, 1451, 1424, 1250, 732.

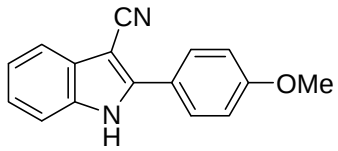
^1H NMR δ (d_6-acetone) 11.5 (1H, br. s, NH), 8.05-8.02 (2H, m, ArH), 7.71-7.68 (1H, m, ArH), 7.61-7.56 (4H, m, ArH), 7.35-7.26 (2H, m, ArH).

^{13}C NMR δ (d_6-acetone) 145.5 (ArC), 136.6 (ArC), 130.7 (ArC), 130.6 (ArCH), 130.1 (ArCH), 129.7 (ArC), 127.8 (ArCH), 124.8 (ArCH), 122.9 (ArCH), 119.4 (ArCH), 117.1 (ArC), 113.2 (ArCH), 83.7 (CN).

ESIMS *m/z* 219 ($M + H^+$, 100%).

HREIMS calculated. for $C_{15}H_{10}N_2$ ($M + H^+$) 219.0846, found 219.0843.

2-(4-Methoxyphenyl)-1*H*-indole-3-carbonitrile (371)



371

Using the general indole preparation procedure above, **361** (0.100 g, 0.32 mmol), DMF (4 mL), and CuCN (0.086 g, 0.95 mmol) were stirred at 100 °C for 16 h. Work-up procedure B was applied. The crude product was purified by column chromatography (EtOAc) to give the title compound (0.061 g, 77%) as a white solid.

R_f : 0.15 (3 : 1, EtOAc/petrol).

Mp 99-101 °C.

ν_{max}/cm^{-1} 3257, 2212, 1613, 1499, 1446, 1255, 1245, 1173, 1040, 836.

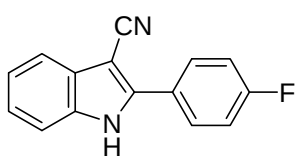
^1H NMR δ (d_6-acetone) 11.4 (1H, br. s, NH), 7.99 (2H, d, *J* = 8.5 Hz, ArH), 7.67 (1H, d, *J* = 7.5 Hz, ArH), 7.53 (1H, d, *J* = 7.5 Hz, ArH), 7.30-7.24 (2H, m, ArH), 7.15 (2H, d, *J* = 8.5 Hz, ArH), 3.89 (3H, s, CH_3O).

^{13}C NMR δ (d_6-acetone) 161.3 (ArC), 145.1 (ArC), 135.8 (ArC), 129.1 (ArC), 128.7 (ArCH) 123.8 (ArCH), 122.4 (ArC), 122.1 (ArCH), 118.6 (ArCH), 116.8 (ArC), 114.9 (ArCH), 112.3 (ArCH), 81.9 (CN), 55.2 (CH_3O).

EIMS *m/z* 248 (M^+, 80%).

HREIMS calculated. for $C_{16}H_{12}N_2O$ (M^+) 248.0943, found 248.0949.

2-(4-Fluorophenyl)-1*H*-indole-3-carbonitrile (372)



372

Using the general indole preparation procedure above, **362** (0.080 g, 0.26 mmol), DMF (3 mL), CuCN (0.072 g, 0.79 mmol) were stirred at 100 °C for 16 h. Work-up procedure B was applied. The crude product was purified by column

chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.041 g, 65%) as a white solid.

R_f : 0.26 (1 : 3, EtOAc/petrol).

Mp 239-241 ^oC.

ν_{max}/cm^{-1} 3257, 2213, 1675, 1613, 1498, 1448, 1241, 1173, 830.

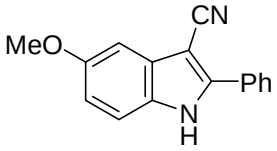
^1H NMR δ (d_6-acetone) 11.5 (1H, br. s, NH), 8.08-8.06 (2H, m, ArH), 7.69 (1H, d, *J* = 7.5 Hz, ArH), 7.56 (1H, d, *J* = 7.5 Hz, ArH), 7.39-7.34 (2H, m. ArH), 7.32-7.27 (2H, m, ArH).

^{13}C NMR δ (d_6-acetone) 164.2 (ArC, d, *J* = 247.6 Hz), 144.5 (ArC), 136.6 (ArC), 130.2 (ArCH, d, *J* = 8.5 Hz), 129.5 (ArC), 127.3 (ArC), 124.9 (ArCH), 122.9 (ArCH), 119.4 (ArCH), 116.9 (ArCH, d, *J* = 7.1 Hz), 116.5 (ArC, d, *J* = 3.1 Hz), 113.1 (ArCH), 83.7 (CN).

EIMS *m/z* 236 (M^+, 100%).

HREIMS calculated. for $C_{15}H_9N_2F$ (M^+) 236.0760, found 236.0749.

5-Methoxy-2-phenyl-1*H*-indole-3-carbonitrile (373)



373

Using the general indole preparation procedure above, 2,2,2-trifluoro-*N*-(4-methoxy-2-(phenylethynyl)phenyl)acetamide (0.100 g, 0.32 mmol), DMF (4 mL), CuCN (0.086 g, 0.95 mmol) were stirred at 100 ^oC for 16 h at 130 ^oC. Work-up procedure B was applied. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.062 g, 78%) as a white solid.

R_f : 0.35 (1 : 3, EtOAc/petrol).

Mp 120-122 ^oC.

ν_{max}/cm^{-1} 3216, 2965, 2909, 2358, 2341, 2217, 1685, 1652, 1558, 1540, 1456, 1055, 752;

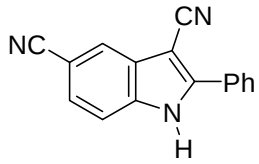
^1H NMR δ (d_6-acetone) 11.4 (1H, br. s, NH), 8.01 (2H, d, *J* = 7.0 Hz, ArH), 5.95 (2H, t, *J* = 7.0 Hz, ArH), 7.53 (1H, d, *J* = 7.0 Hz, ArH), 7.46 (1H, d, *J* = 8.5 Hz, ArH), 7.16 (1H, s, ArH), 6.94 (1H, d, *J* = 8.5 Hz, ArH), 3.90 (3H, s, CH_3O);

^{13}C NMR δ (d_6-acetone) 156.7 (ArC), 145.1 (ArC), 131.2 (ArC), 130.5 (ArC), 130.3 (ArCH), 130.2 (ArCH), 129.8 (ArCH), 127.3 (ArCH), 117.1 (ArC), 115.1 (ArCH), 113.8 (ArC), 100.4 (ArCH), 83.2 (CN), 55.6 (CH_3O).

EIMS *m/z* 248 (M^+, 100%).

HREIMS calculated. for $C_{16}H_{12}N_2O$ (M^+) 248.0938, found 248.0949.

Phenyl-1*H*-indole-3,5-dicarbonitrile (374)



374

Using the general indole preparation procedure above, **364** (0.070 g, 0.21 mmol), DMF (3 mL), CuCN (0.059 g, 0.64 mmol) were stirred at 100 ^oC for 16 h. Work-up procedure B was applied. The crude product was purified by column chromatography (2 : 1, EtOAc/petrol) to give the title compound (0.031 g, 60%) as a white solid.

R_f : 0.64 (EtOAc).

Mp 265-267 ^oC.

ν_{max}/cm^{-1} 3231, 2360, 2335, 2224, 1685, 1654, 1475, 1449, 1367, 1255, 1070, 906.

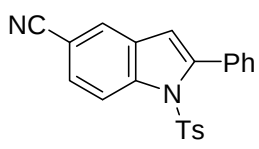
^1H NMR δ (d_6-acetone) 12.1 (1H, br. s, NH), 8.13 (1H, d, *J* = 1.5 Hz, ArH), 8.06 (2H, dd, *J* = 1.5, 7.0 Hz, ArH), 7.76 (1H, d, *J* = 7.0 Hz, ArH), 7.68-7.59 (4H, m, ArH).

^{13}C NMR δ (d_6-acetone) 147.8 (ArC), 138.0 (ArC), 131.1 (ArCH), 130.0 (ArCH), 129.4 (ArC), 129.0 (ArC), 127.8 (ArCH), 127.4 (ArCH), 124.3 (ArCH), 119.7 (ArC), 115.7 (ArC), 114.2 (ArCH), 106.0 (CN), 84.1 (CN).

EIMS *m/z* 243 (M^+, 100%).

HREIMS calculated. for $C_{16}H_9N_3$ (M^+) 243.0813, found 243.0796.

2-Phenyl-1-(4-methylbenzenesulfonyl)-1*H*-indole-5-carbonitrile (375)



375

Using the general indole preparation procedure above, *N*-(4-cyano-2-(phenylethynyl)phenyl)-4-methylbenzenesulfonamide (0.100 g, 0.26 mmol), DMF (4 mL) and CuCN (0.072 g, 0.78 mmol) were stirred at 100 ^oC for 16 h. Work-up procedure A was applied. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give the compound **375** (0.037 g, 38%) and compound **376** (0.023 g, 22%) both as white solids.

Data for **375:**

R_f : 0.34 (1 : 4, EtOAc/petrol).

Mp 78-80 ^oC.

ν_{max}/cm^{-1} 2970, 2361, 1340, 2223, 1654, 1375, 1173, 1091, 1081, 756.

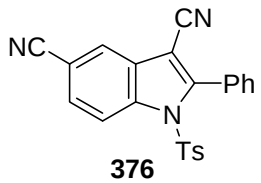
^1H NMR δ 8.42 (1H, d, *J* = 8.0 Hz, ArH), 7.70 (1H, s, ArH), 7.60 (1H, dd, *J* = 1.5, 8.0 Hz, ArH), 7.45-7.42 (5H, m, ArH), 7.24 (2H, d, *J* = 7.0 Hz, ArH), 7.07 (2H, d, *J* = 7.0 Hz, ArH), 6.56 (1H, s, ArH), 2.31 (3H, s, CH_3).

^{13}C NMR δ 145.3 (ArC), 144.1 (ArC), 139.8 (ArC), 134.5 (ArC), 130.5 (ArCH), 129.5 (ArCH), 129.2 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 126.9 (ArCH), 125.3 (ArCH), 123.5 (ArC), 119.2 (ArC), 117.0 (ArCH), 111.9 (ArCH), 107.6 (CN), 21.6 (CH_3).

ESIMS *m/z* 373 ($M + H^+$, 100%).

HRESIMS calculated. for $C_{22}H_{17}N_2O_2S$ ($M + H^+$) 373.1018, found 373.1011.

2-Phenyl-1-(4-methylbenzenesulfonyl)-1*H*-indole-3,5-dicarbonitrile (376)



376

R_f : 0.32 (1 : 4, EtOAc/petrol).

Mp 131-133 °C.

ν_{max}/cm^{-1} 2228, 1598, 1465, 1378, 1260, 1378, 1260, 1175, 1091, 819.

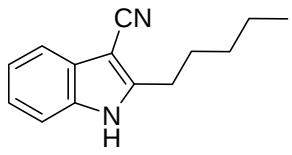
^1H NMR δ 8.50 (1H, d, *J* = 8.5 Hz, ArH), 7.99 (1H, s, ArH), 7.59 (1H, t, *J* = 7.0 Hz, ArH), 7.74 (1H, d, *J* = 8.5 Hz, ArH), 7.49 (2H, t, *J* = 7.0 Hz, ArH), 7.42 (2H, d, *J* = 7.0 Hz, ArH), 7.25 (2H, d, *J* = 8.0 Hz, ArH), 7.14 (2H, d, *J* = 8.0 Hz, ArH), 2.36 (3H, s, CH_3).

^{13}C NMR δ 150.6 (ArC), 146.6 (ArC), 138.0 (ArC), 134.1 (ArC), 131.3 (ArCH), 130.2 (ArCH), 129.6 (ArCH), 128.3 (ArCH), 127.7 (ArC), 127.3 (ArCH), 124.4 (ArCH), 118.2 (ArC), 117.4 (ArCH), 112.7 (ArC), 109.1 (CN), 96.0 (CN), 21.6 (CH_3).

ESIMS *m/z* 398 ($M + H^+$, 100%).

HRESIMS calculated. for $C_{23}H_{16}N_3O_2S$ ($M + H^+$) 398.0944, found 398.0963.

2-Pentyl-1*H*-indole-3-carbonitrile (377)



377

Using the general indole preparation procedure above, 2,2,2-trifluoro-*N*-(2-(hept-1-ynyl)phenyl)acetamide (0.100 g, 0.32 mmol), DMF (4 mL), CuCN (0.088 g, 0.96 mmol) were stirred at 100 °C for 16 h. Work-up procedure A was

applied. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.050 g, 73%) as a white solid.

R_f : 0.31 (1 : 3, EtOAc/petrol).

Mp 49-51 ^oC.

ν_{max}/cm^{-1} 3262, 2955, 2929, 2858, 2208, 1557, 1490, 1452, 1332, 1239, 742.

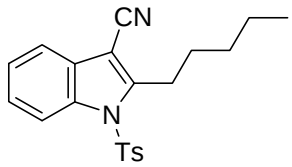
^1H NMR δ 8.70 (1H, br. s, NH), 7.65 (1H, d, *J* = 8.5 Hz, ArH), 7.38 (1H, d, *J* = 8.5 Hz, ArH), 7.25-7.22 (2H, m, ArH), 2.94 (2H, t, *J* = 7.0 Hz, CH_2), 1.80-1.78 (2H, m, CH_2), 1.38-1.35 (4H, m, 2 x CH_2), 0.90 (3H, t, *J* = 7.0 Hz, CH_3).

^{13}C NMR δ 149.3 (ArC), 134.5 (ArC), 127.6 (ArC), 123.3 (ArCH), 121.9 (ArCH), 118.9 (ArCH), 116.4 (ArC), 111.3 (ArCH), 84.7 (CN), 31.1 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 22.2 (CH_2), 13.8 (CH_3).

ESIMS *m/z* 213 ($M + H^+$, 100%).

HRESIMS calculated. for $C_{14}H_{17}N_2$ ($M + H^+$) 213.1360, found 213.1392.

2-Pentyl-1-(4-methylbenzenesulfonyl)-1*H*-indole-3-carbonitrile (378)



378

Using the general indole preparation procedure above, *N*-(2-(hept-1-ynyl)phenyl)-4-methylbenzenesulfonamide (0.0.080g, 0.23 mmol), DMF (3 mL), CuCN (0.063 g, 0.69 mmol) were stirred at 100 ^oC for 16 h. Work-up procedure A was applied. The crude product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the compound **378** (0.046 g, 55%) as a colorless oil and compound **379** (0.019 g, 24%) as a white solid with a ratio of **378** : **379** = 70 : 30.

Data for **378**

R_f : 0.42 (1 : 5, EtOAc/petrol).

ν_{max}/cm^{-1} 2955, 2924, 2863, 2228, 1598, 1451, 1384, 1191, 1178, 1155, 1098, 969.

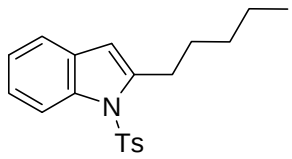
^1H NMR δ 8.17 (1H, d, *J* = 8.5 Hz, ArH), 7.65 (1H, d, *J* = 8.5 Hz, ArH), 7.58 (1H, d, *J* = 8.0 Hz, ArH) 7.39-7.33 (2H, m, ArH), 7.25 (3H, d, *J* = 8.0 Hz, ArH), 3.20 (2H, t, *J* = 7.5 Hz, CH_2), 2.37 (3H, s, CH_3), 1.82-1.77 (2H, m, CH_2), 1.43-1.35 (4H, m, 2 x CH_2), 0.91 (3H, t, *J* = 7.5 Hz, CH_3).

^{13}C NMR δ 151.4 (ArC), 145.9 (ArC), 135.6 (ArC), 135.3 (ArC), 130.2 (ArCH), 127.2 (ArC), 126.4 (ArCH), 125.7 (ArCH), 124.8 (ArCH), 119.1 (ArCH), 115.1 (ArCH), 114.1 (ArC), 94.5 (CN), 31.4 (CH_2), 30.4 (CH_2), 28.5 (CH_2), 22.2 (CH_2), 21.6 (CH_3), 13.9 (CH_3).

ESIMS *m/z* 367 ($M + H^+$, 100%).

HRESIMS calculated. for $C_{21}H_{23}N_2O_2S$ ($M + H^+$) 367.1470, found 367.1480.

2-Pentyl-1-(4-methylbenzenesulfonyl)-1*H*-indole (379)



379

R_f : 0.55 (1 : 5, EtOAc/petrol).

Mp 57-59 ^oC.

ν_{max}/cm^{-1} 2955, 2924, 2356, 2330, 1444, 1369, 1224, 1170, 1139, 1092, 1060, 804.

^1H NMR δ 8.16 (1H, d, *J* = 8.0 Hz, ArH), 7.61 (2H, d, *J* = 8.0 Hz, ArH), 7.39 (1H, d, *J* = 8.0 Hz, ArH), 7.25-7.16 (4H, m, ArH), 2.97 (2H, t, *J* = 7.5 Hz, CH_2), 2.32 (3H, s, CH_3), 1.75-1.72 (2H, m, CH_2), 1.39-1.35 (4H, m, 2 x CH_2), 0.91 (3H, t, *J* = 7.5 Hz, CH_3).

^{13}C NMR δ 144.2 (ArC), 142.5 (ArC), 137.1 (ArC), 136.2 (ArC), 129.7 (ArCH), 126.6 (ArCH), 126.2 (ArC), 123.7 (ArCH), 123.4 (ArCH), 119.9 (ArCH), 114.7 (ArCH), 108.5 (ArCH), 31.5 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 14.0 (CH_3).

EIMS *m/z* 341 (M^+, 50%).

HREIMS calculated. for $C_{20}H_{23}NO_2S$ (M^+) 341.1451, found 341.1449.

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APPENDIX 1: INTERMOLECULAR ADDITION REACTIONS OF *N*-ACYLIMINIUM IONS (PART I)

Intermolecular Addition Reactions of *N*-Acyliminium Ions (Part I)[1]

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Abstract: This review highlights the advances in the literature up to July 2008 on the intermolecular reactions of acyclic and cyclic *N*-acyliminium ions. This is an update of an earlier review in 2000 on this topic and does not include intramolecular addition reactions to *N*-acyliminium ions which was recently reviewed. This review is presented in two parts, with the first part dealing with acyclic and pyrrolidinone-based *N*-acyliminium ions. Part II continues with other five-membered heterocyclic derivatives and higher systems.

Key words: *N*-acyliminium ion, nucleophilic addition, cycloaddition, aromatic electrophilic substitution, radical addition, peptides, pyrrolidines, piperidines

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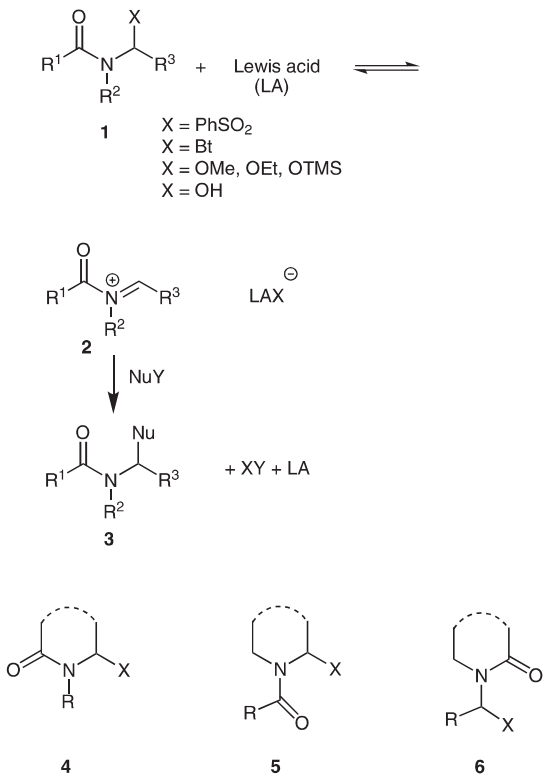
1 Introduction

This review highlights the advances in the literature up to July 2008 on the intermolecular reactions of acyclic and cyclic *N*-acyliminium ions. This is an update of an earlier review in 2000[2] on this topic and does not include intramolecular addition reactions to *N*-acyliminium ions which was recently reviewed.[3] A review article on addition reactions to related, but less reactive, *N*-acylimines has also been recently published.[4]

The highly reactive nature of *N*-acyliminium ions require that they are generated in situ usually in the presence of the other reactive, electron-rich, nucleophilic partner (NuY, Y = metal, SiR_3, SnR_3, etc.). In general these intermediates are generated from more stable and isolatable α-substituted *N*-acylamines of the type **1** by treatment with a Lewis acid or sometimes a protic acid (Scheme 1). The reaction of **2** with a nucleophilic species (NuY) then gives α-substituted *N*-acylamine **3**. Compounds **1**–**3** can be acyclic systems or R^1 and R^2, R^2 and R^3, R^1 and R^3 can be taken together to form part of a ring system as shown in the general structures **4**, **5**, and **6**.

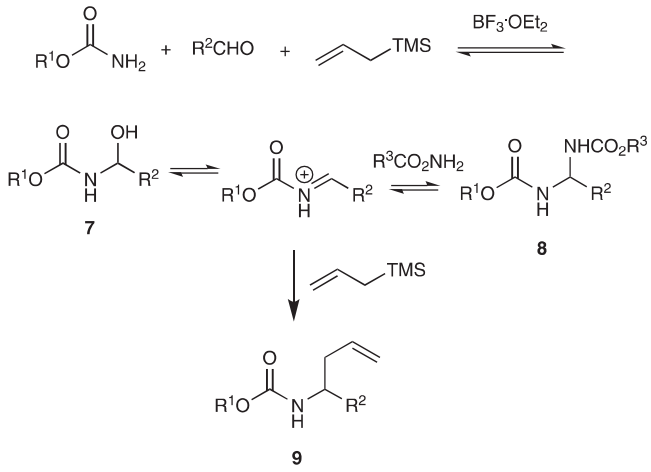
Compounds like **1** (X = OH and $NHCO_2R$) are most likely formed in situ from the Lewis acid promoted three-component, one-pot coupling reactions of carbamates, aldehydes (or acetals) and silyl nucleophiles or electron-rich aromatic nucleophiles (Scheme 2).[5,6]

N-Acyliminium ions like **11** can also be generated in dichloromethane solution, in the absence of nucleophiles, by the electrochemical oxidation of *N*-trimethylsilylmethyl carbamates like **10** (Scheme 3). These intermediates have been characterised spectroscopically and were sub-

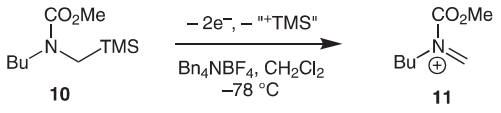


Scheme 1

sequently treated with nucleophiles or dipolarophiles to give addition products.[7–9]



Scheme 2



Scheme 3

2 Acyclic *N*-Acyliminium Ions

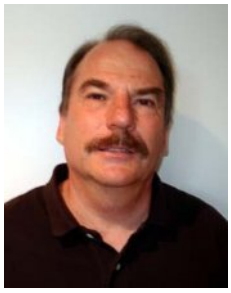
2.1 Synthesis of Acyclic *N*-Acyliminium Ion Precursors

Acyclic *N*-acyliminium precursors of the type **1** are generally synthesised from the coupling of an amide or carbamate with an aldehyde in the presence of HX or MX.[4,10]

α-Sulfonyl-*N*-alkyl amides and α-sulfonyl-*N*-alkyl carbamates **12** are useful precursors of acyclic *N*-acylimini-

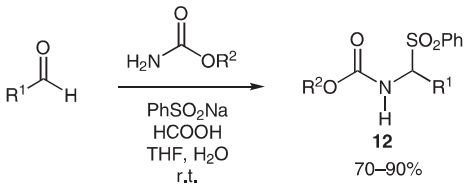
Biographical Sketches

Arife Yazici obtained her MSc degree in chemistry at Hacettepe University-Ankara (Turkey) in 2005. She is currently doing her PhD studies with Professor Stephen Pyne at the University of Wollongong. Her area of study is the total synthesis of Stemona alkaloids.



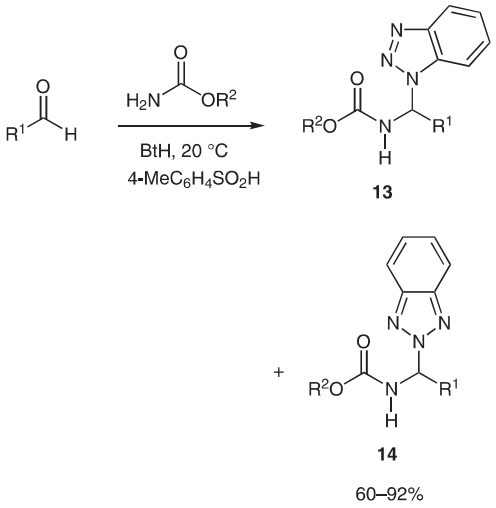
Stephen G. Pyne is a Professor of Chemistry at the University of Wollongong (UOW) and Chair of the Division of Organic Chemistry of the Royal Australian Chemical Institute. He obtained his BSc (Hons) degree at the University of Adelaide with Dr. Ralf Massey-Westrop and his PhD degree with Professor Lew Mander (Australian National University) in 1979. After post-doctoral positions with Professor Phil Fuchs (Purdue) and Professor E. J. Corey (Harvard), he was appointed as a lecturer at UOW in 1985. His research interests include the total synthesis of bioactive alkaloids, natural products chemistry, drug design and synthesis, and fullerene chemistry.

um ions since they are often stable solids. They can be prepared by the coupling reaction of amides or carbamates with an aldehyde in the presence of benzenesulfinic acid or its salt (Scheme 4).[11–13]



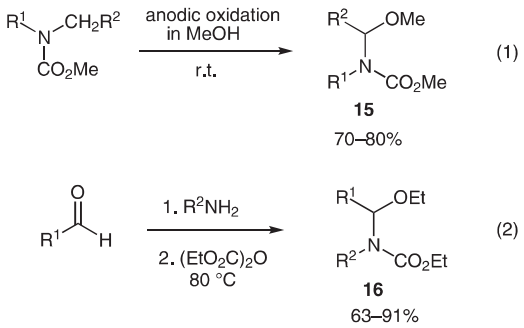
Scheme 4

α-Carbamylalkylbenzotriazole derivatives **13** and **14** can be prepared from the coupling of carbamates, benzotriazole and aldehydes (Scheme 5). These benzotriazole adducts are usually formed as a mixture of 1-yl **13** and 2-yl **14** isomers. These regioisomers, however, are both readily converted into the same *N*-acyliminium ion.[6,14,15]



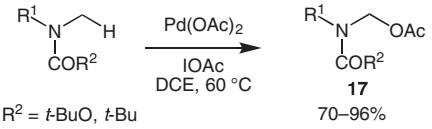
Scheme 5

α-Alkoxycarbamates **15** and **16** can be obtained from the electrochemical oxidation of carbamates in methanolic solution[16] (Scheme 6, equation 1) or from the reaction of primary amines with aldehydes, followed by reaction with diethyl pyrocarbonate (Scheme 6, equation 2).[17,18]



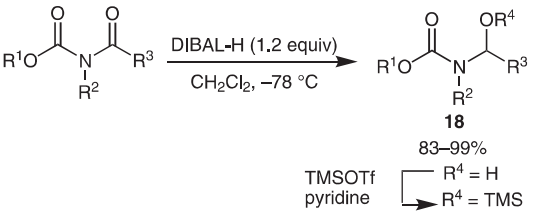
Scheme 6

α-Acetoxycarbamate and amide derivatives **17** can be synthesised from the corresponding *N*-methylcarbamates and amides by palladium-catalysed oxidation (Scheme 7).[19]



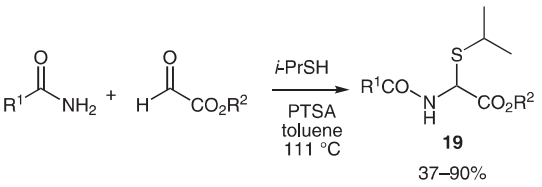
Scheme 7

α-Hydroxycarbamate derivatives **18** can be prepared by the partial reduction of imides using diisobutylaluminium hydride (Scheme 8). Although other reducing agents, such as sodium borohydride, are effective for the reduction of cyclic imides, only diisobutylaluminium hydride was effective for acyclic imides.[20,21]



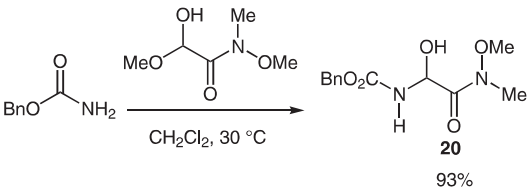
Scheme 8

α-Alkylthiocarbamates **19** can be synthesised from the three-component condensation of amides or carbamates with isopropylmercaptan and glyoxylic acid or its ester derivatives (Scheme 9).[22]



Scheme 9

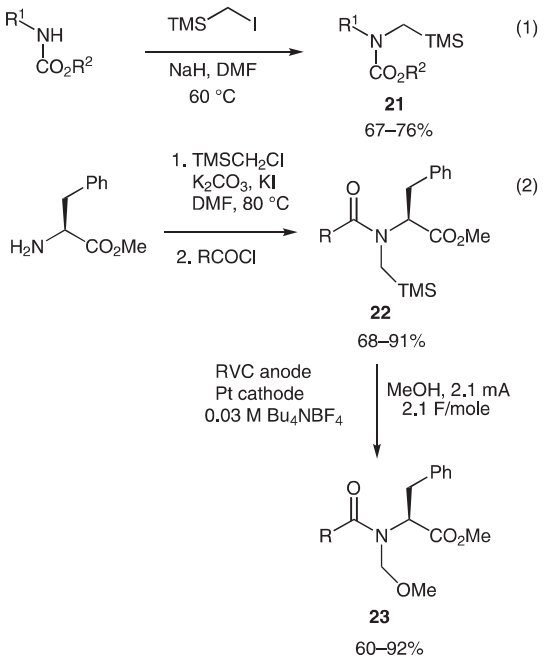
Weinreb amide derivatives **20** can be obtained from the condensation of carbamates with the corresponding hemiacetal (Scheme 10).[23]



Scheme 10

Carbamates **21**, having a *N*-silylmethyl substituent, can be easily synthesised from the reaction of carbamates with α-silylalkyl iodides under basic conditions (Scheme 11,

equation 1). They can be used to generate *N*-acyliminium ions by anodic oxidation (Scheme 3).[7–9] Alternatively, these compounds can be prepared by N-alkylation of amines with α-silylalkyl chlorides and then N-acylation of the resulting *N*-silylmethylamine (Scheme 11, equation 2). The *N*-trimethylsilylmethyl amides **22** can be converted into *N*-methoxymethyl carbamates **23** upon anodic oxidation in methanol or by oxidation with ceric ammonium nitrate (see Scheme 18).[24]



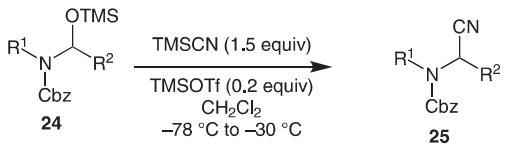
Scheme 11

2.2 Reactions of Acyclic *N*-Acyliminium Ions

2.2.1 Reactions with Nucleophiles

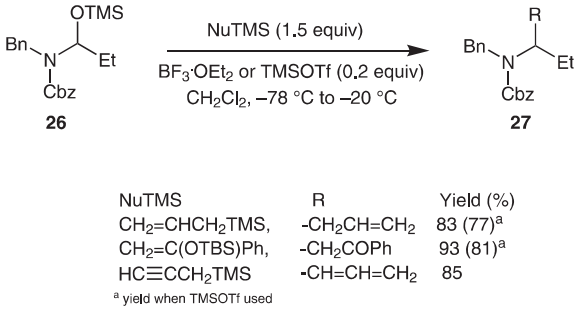
2.2.1.1 Silicon-Based Nucleophiles

Allylsilanes and silyl enol ethers constitute the largest class of silicon-based nucleophiles that have been treated with in situ generated *N*-acyliminium ions. The α-trimethylsilyloxy carbamates **24** reacted with trimethylsilyl cyanide in the presence of trimethylsilyl triflate (0.2 equiv) at –78 °C to –20 °C to give nitriles **25** in high yields (Scheme 12).[20]



Scheme 12

In a limited study the α-trimethylsilyloxy carbamate **26** gave products **27** upon treatment with three different silicon-based nucleophiles (Scheme 13).[20]



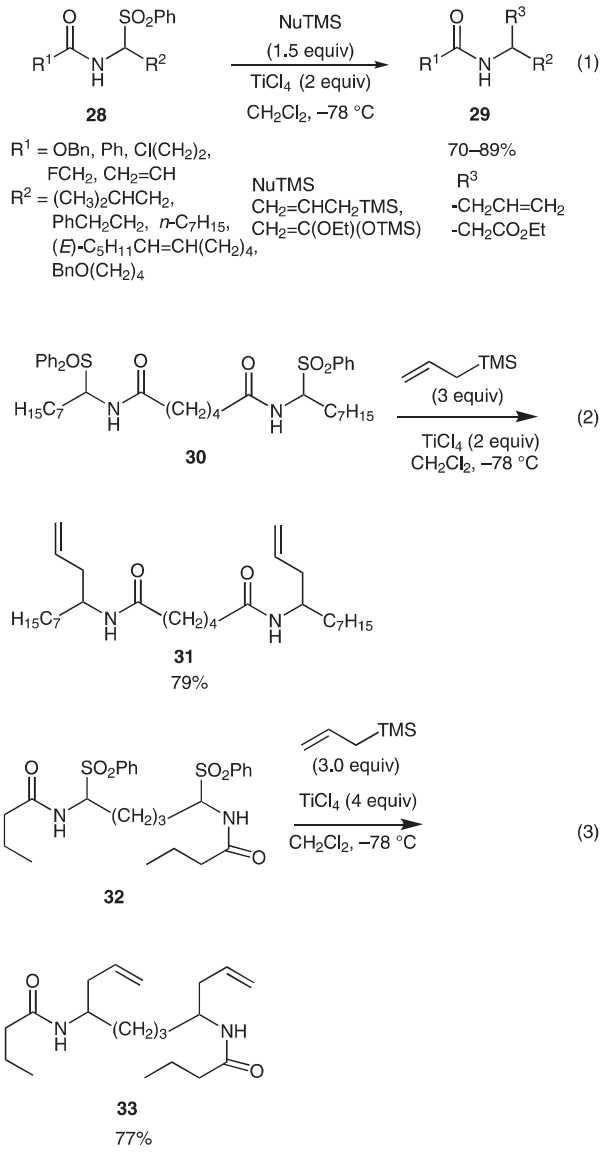
Scheme 13

The α-amido sulfones **28** reacted with silicon nucleophiles (1.5 equiv) in the presence of titanium(IV) chloride (2 equiv) to give adducts **29** in 70–89% yields. Halogen-containing substrates were also efficient in the allylation reaction (Scheme 14, equation 1). The bisamido sulfones **30** and **32** were treated with allyltrimethylsilane under the same reaction conditions to give the corresponding bisallylated products **31** and **33** in good yields (Scheme 14, equations 2 and 3).[10]

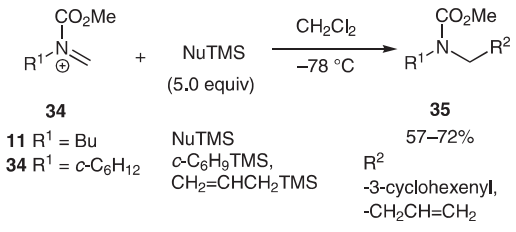
The *N*-acyliminium ions **11** and **34**, which were generated by electrochemical oxidation from the corresponding *N*-silylmethylcarbamates (Scheme 3), reacted with allyltrimethylsilane and 3-trimethylsilylcyclohexene to give the corresponding adducts **35** in 57–72% yields (Scheme 15).[9]

The one-pot three-component coupling reaction of *N*-acyliminium ion **11** with enamine **36** and silicon nucleophiles afforded products **39** in 52–68% yields. The *N*-acyliminium ion **11** first reacted with the enamine **36** to form the new cationic species **37**. The resulting cation, which was assumed to be an equilibrium mixture of **37** and **38**, was then treated with nucleophiles to give the products **39** as diastereomeric mixtures. The major *trans* isomer most likely was a result of attack on the iminium **37** from the face *anti* to the ring C-3 substituent or from an S_N2-like attack on the bridged cationic intermediate pyrrolidine **38**. The reaction of the *N*-acyliminium ion **11** with six-membered-ring analogues of enamine **36** and allyltrimethylsilane gave the corresponding six-membered analogues of product **39** in 62% yield and with a *trans*/*cis* ratio of 91:9. Treatment of the *N*-cyclohexyl analogue of the *N*-butyl *N*-acyliminium ion **11** with allyltrimethylsilane afforded the corresponding *N*-cyclohexyl analogue of **39** in 70% yield and with a diastereomeric ratio of 91:9.[25] The analogous *tert*-butyl carbamate of **36** gave the *tert*-butyl analogue of **39** in the same yield and with the same *trans*/*cis* diastereoselectivity (Scheme 16).[26]

The use of vinyl sulfide **40** as an olefinic component in the three-component coupling reaction of the *N*-acyliminium ion **11** and silicon nucleophiles gave the products **41** in 56–75% yields (Scheme 17).[25]

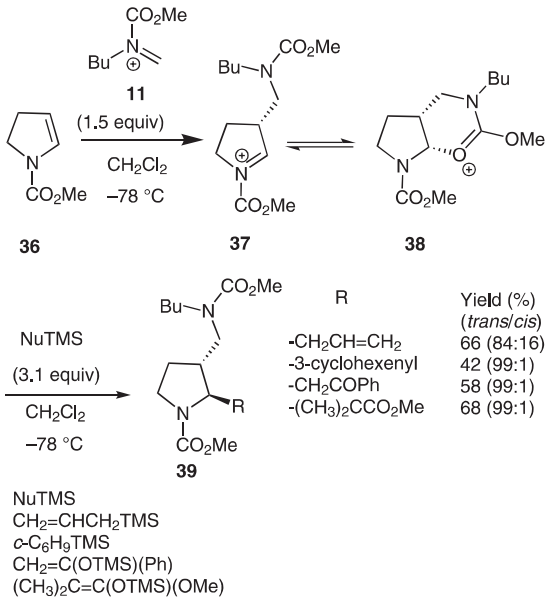


Scheme 14

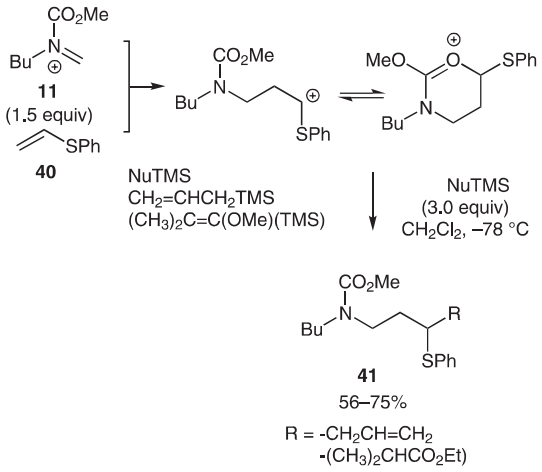


Scheme 15

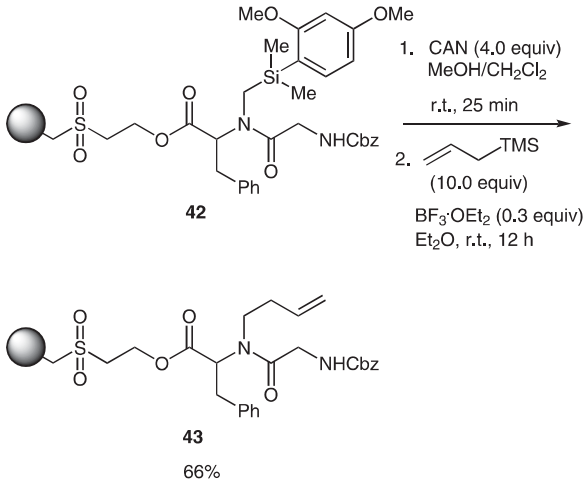
An *N*-acyliminium ion was selectively generated in the polymer-supported dipeptide **42** by oxidation of the *N*-silylmethyl group with ceric ammonium nitrate in methanol. The resulting *N*-methoxymethyl carbamate reacted with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give the polymer-supported allylated product **43**. The yield of **43** was determined to be 66% yield (Scheme 18).[24,27]



Scheme 16

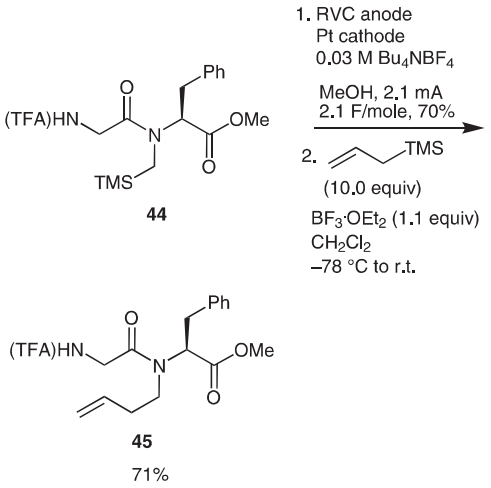


Scheme 17



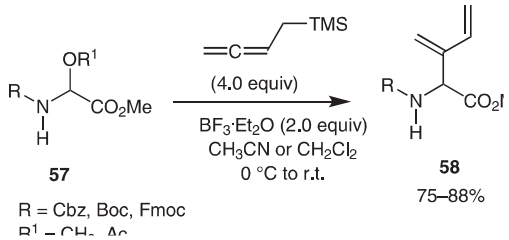
Scheme 18

Similarly, anodic oxidation of the trimethylsilyl group in peptide **44** gave the corresponding *N*-methoxymethyl carbamate, which was treated with allyltrimethylsilane and boron trifluoride–diethyl ether complex to give product **45** (Scheme 19).[24,28]



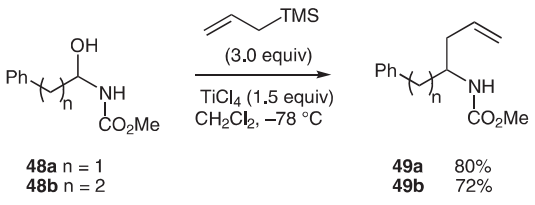
Scheme 19

The reaction of the α-benzotriazole carbamate **46** with allyltrimethylsilane gave the allylated product **47** in 80% yield (Scheme 20). The analogous reactions of **46** with buta-2,3-dienylsilane and (furan-2-yloxy)trimethylsilane were less efficient and gave the corresponding adducts **47** in 53% and 51% yields, respectively.[6]



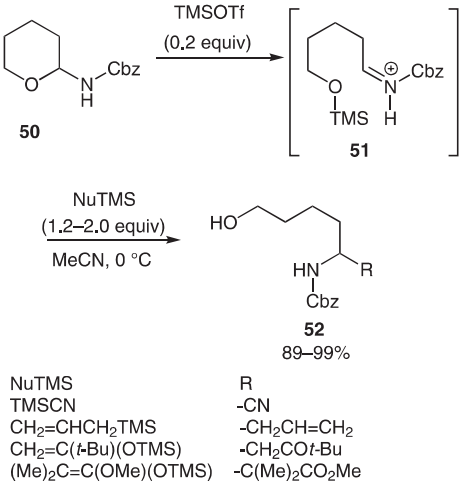
Scheme 20

The reaction of the α-hydroxy carbamates **48a** and **48b** with allyltrimethylsilane in the presence of titanium(IV) chloride provided the corresponding allylated products **49a** and **49b** in 80% and 72% yields, respectively (Scheme 21).[21]



Scheme 21

The Lewis acid catalysed reactions of the *N*,*O*-acetals **50** and **53** gave the corresponding ring-opened acyclic *N*-acyliminium ions **51**. These reacted smoothly with allyltrimethylsilane, trimethylsilyl cyanide, and ketene silyl acetals to afford the adducts **52** (Scheme 22) and the diastereomeric products **54** and **55** (Scheme 23) in good yields.[29]



Scheme 22

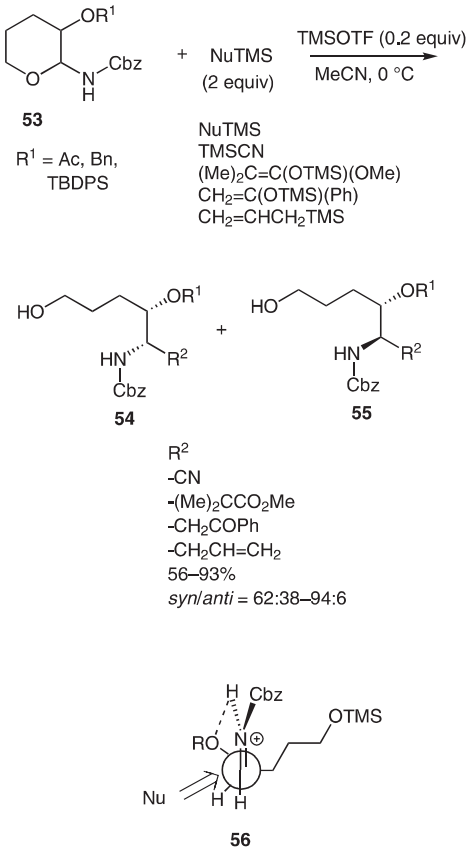
High *syn* selectivity was observed in the adducts from the reactions of the 3-benzyloxycarbonyl acetal **53**. A hydrogen-bonded transition-state model **56**, involving hydrogen-bonding between the proton bound to the iminium nitrogen and the α-oxygen substituent group, was proposed. The nucleophile preferentially attacked from the less-hindered face of the iminium ion (from the side of the α-hydrogen) to give the *syn* product (Scheme 23).[29] The *syn*/*anti* ratio did not vary dramatically with the nature of R^1 in **53**.

Allenylmethylsilane reacted with the α-methoxy and α-acetoxy carbamates **57** in the presence of boron trifluoride–diethyl ether complex to give dienes **58** in 75–88% yields (Scheme 24).[30]

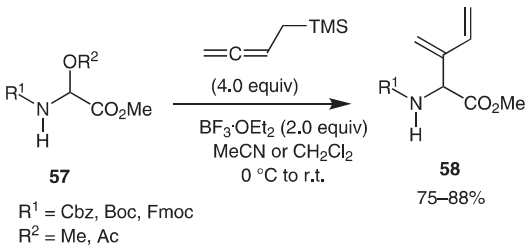
The one-pot reaction of carbamates **59** with aldehydes or their acetals and silyl nucleophiles in the presence of boron trifluoride–diethyl ether complex gave adducts **60** in yields ranging from 5% to 92% (Scheme 25). In the same study, treatment of carbamate **59** (R^1 = Bn) with vinyl acetate and benzaldehyde in the presence of a catalytic amount of scandium(III) triflate provided product **60** in 28% yield. The reaction did not work with boron trifluoride–diethyl ether complex.[6]

The (benzylsulfonyl)ethyl and (benzylsulfinyl)ethyl carbamates **61a** and **61b** underwent one-pot reactions with aldehydes or their acetals and allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to afford products **62** in 45–89% yields (Scheme 26).[6]

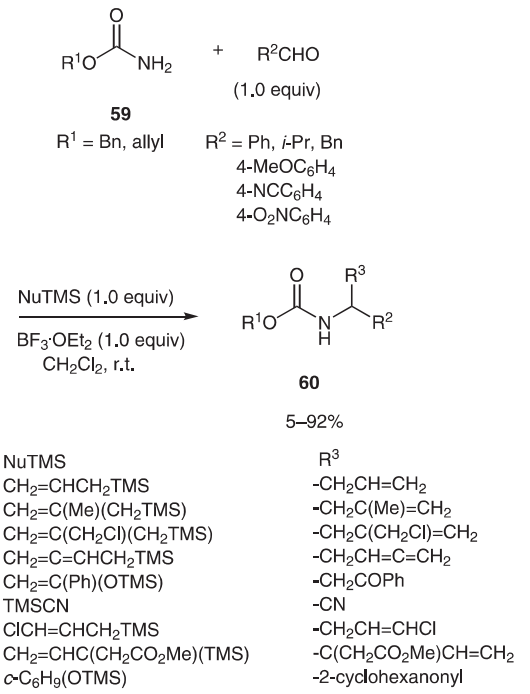
Similarly, the reaction of carbamate **63** with diethyl acetal **64** and allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex afforded a mixture of the



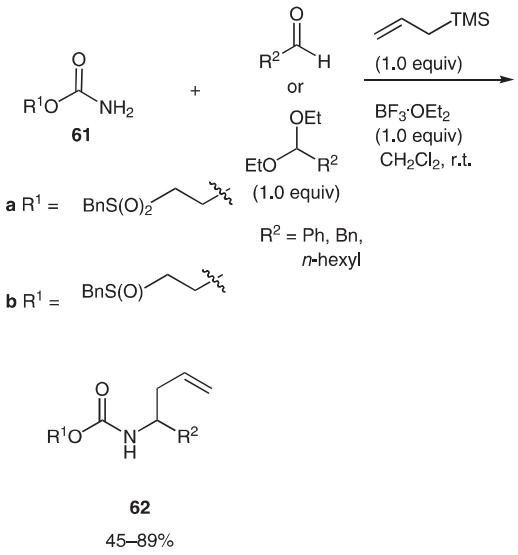
Scheme 23



Scheme 24



Scheme 25



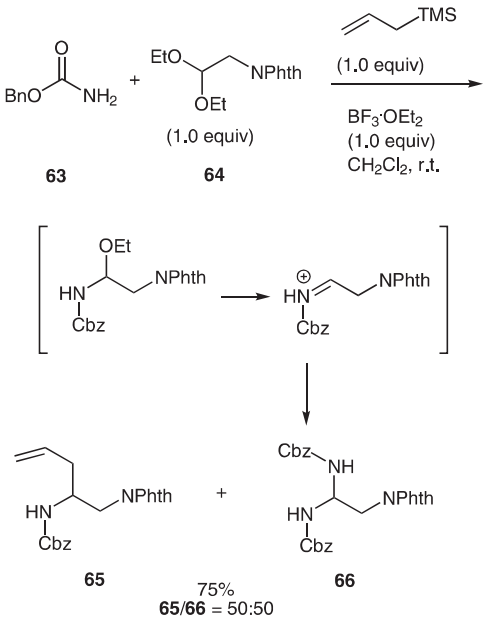
Scheme 26

desired allylated product **65** and the bis-carbamate **66** in 75% yield (Scheme 27). Treatment of **66** with allyltrimethylsilane and boron trifluoride–diethyl ether complex resulted in a 6:4 mixture of compounds **65** and **66**.[6]

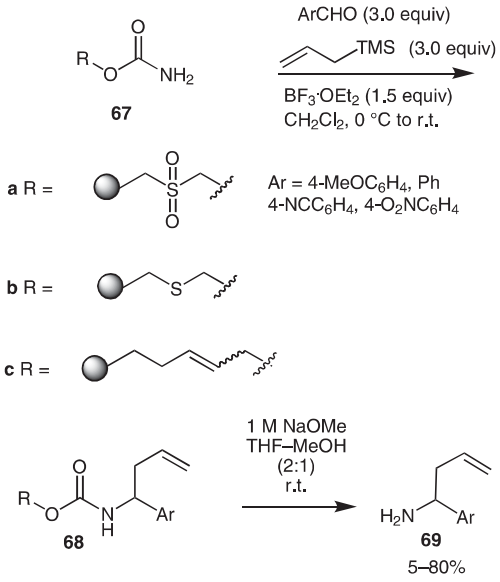
Treatment of resin-bound **67a** with aromatic aldehydes and allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the corresponding allylated products **69** in a range of yields, <5% to 80%, after base-promoted cleavage from the resin (Scheme 28). Use of 4-methoxybenzaldehyde and benzaldehyde resulted in 79% and 80% yields of **69**, respectively, while the use of benzaldehydes having electron-withdrawing groups, 4-cyanobenzaldehyde and 4-nitrobenzaldehyde, gave poor yields of **69** (< 5% and 39%, respectively). The three-component, one-pot reactions of compounds **67b** and **67c** with benzaldehyde and allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex gave the corresponding allylated products **69** in 83% and 57% yields, respectively, after cleavage from the resin.[5]

In a similar study, the one-pot reaction of resin-bound **67a** with aldehydes or their acetals and silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex provided products **70** in 3–80% yields, after cleavage from the resin (Scheme 29).[6]

The reaction of Weinreb amide **71** with allyltrimethylsilane under boron trifluoride–diethyl ether complex catalysis gave product **72** in 89% yield (Scheme 30).[23]



Scheme 27

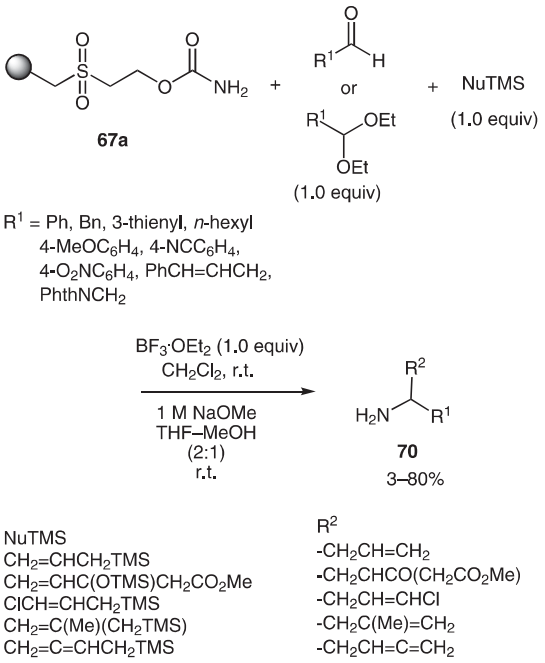


Scheme 28

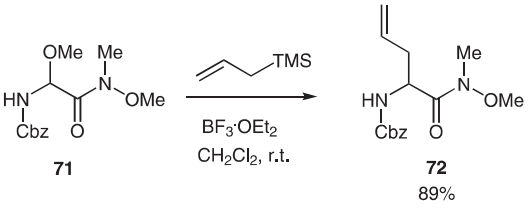
The reaction of immobilised α-benzotriazole carbamates **73a** and **73b** with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the desired allylated products **74a** and **74b** in 71% and 36% yields, respectively, after cleavage from the resin by sodium methoxide (Scheme 31).[6]

Tin(IV) chloride mediated allylation reaction of oxazolidinone **75** with allyltrimethylsilane provided product **76** in 78% yield (Scheme 32).[31]

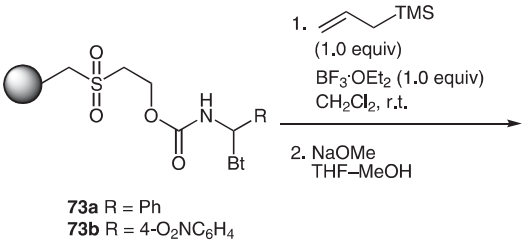
The reactions of oxazolidinone **77** with silicon nucleophiles under boron trifluoride–diethyl ether complex catalysis led to the formation of the desired products **78** in 85–94% yields (Scheme 33).[32]

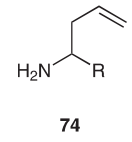


Scheme 29

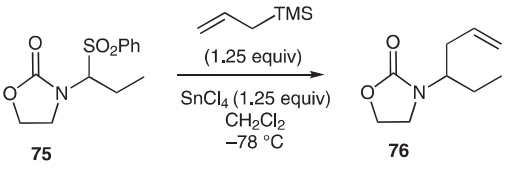


Scheme 30

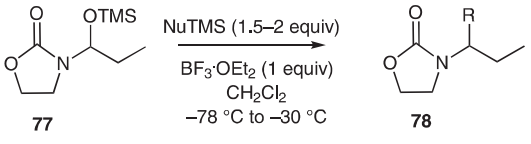




Scheme 31



Scheme 32

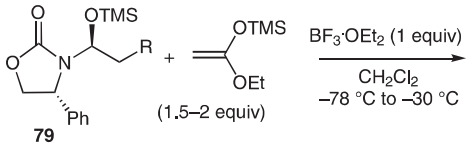


77 78

NuTMS	R	Yield (%)
CH_2=C(OTBS)(OEt)	-CH_2CO_2Et	94
CH_2=$CHCH_2$TMS	-CH_2CH=CH_2	85
CH_2=C(OTMS)(Ph)	-CH_2COPh	89

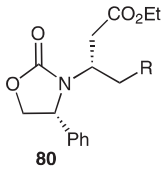
Scheme 33

The boron trifluoride–diethyl ether complex catalysed reaction of chiral oxazolidinones **79** with CH_2=C(OTMS)(OEt) yielded products **80** in yields of 47–99% with very high diastereoselectivity (dr = 91:9 to 96:4) (Scheme 34).[32]



79

R = Me, Et, Bu,
CH_2CH_2CH=CH_2
$CH_2(CH_2)_7CH_3$
CH_2CH_2Ph

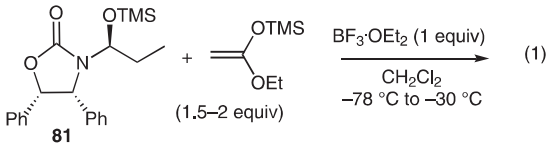


80

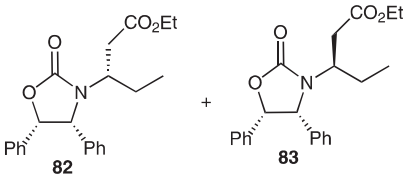
47–99%
cis/*trans* = 91:9 to 96:4

Scheme 34

The oxazolidinone **81** reacted with CH_2=C(OTMS)(OEt) in the presence of boron trifluoride–diethyl ether complex and provided the products **82** and **83** in a ratio of 95:5 (Scheme 35, equation 1); while the reaction of diastereomer **84** of the oxazolidinone **81** under the same reaction conditions yielded product **82** and **83** in a ratio of 6:94 (Scheme 35, equation 2).[32]

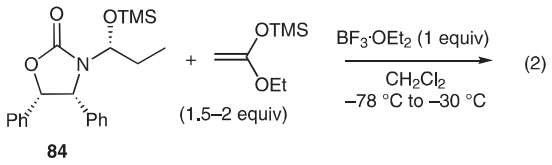


81

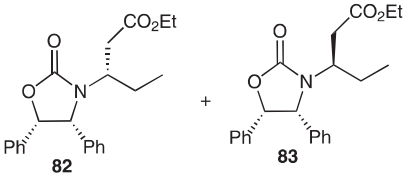


82 83

82/**83** = 95:5



84

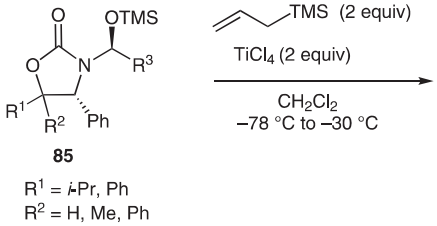


82 83

82/**83** = 6:94

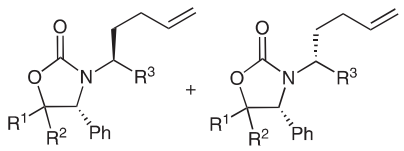
Scheme 35

The oxazolidinone **85** was treated with allyltrimethylsilane in the presence of titanium(IV) chloride to provide adducts **86** and **87** in yields of 46–93%, in favour of product **86** (Scheme 36).[33]



85

R^1 = *i*-Pr, Ph
R^2 = H, Me, Ph
R^3 = Et, *i*-Bu,
i-Pr, $PhCH_2CH_2$,
n-C_7H_{15}, $Cl(CH_2)_5$,
CH_2=$CH(CH_2)_7$



86 87

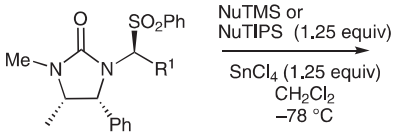
46–93%
cis/*trans* = 55:45 to 95:5

Scheme 36

Treatment of the imidazolidinones **88** with silicon nucleophiles under tin(IV) chloride catalysis led to the formation of adducts **89** and **90** in yields of 30–80% (Scheme 37).[31]

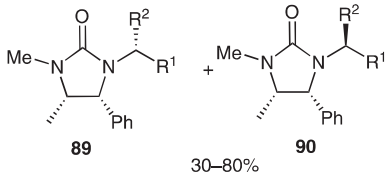
2.2.1.2 Aromatic Nucleophiles

The reaction of the *N*-acyliminium ion **11** with substituted benzenes and heteroaromatic compounds afforded the corresponding monoalkylated and dialkylated products **91–94** (Scheme 38). The use of a conventional batch reactor resulted in the formation of both mono- and dialkylated products, except in the cases of toluene, 1,4-dimethylbenzene and 1,3,5-trimethylbenzene, where the monoalkylated products **91** were obtained exclusively, in yields of 62–69%. When the reactions were performed in a micromixer-type reactor, however, only the monoalky-



88

R^1 = EtCHO, $Ph(CH_2)_2CHO$
$(Me)_2CHCH_2CHO$
n-$C_7H_{15}CHO$, $BnO(CH_2)CHO$,
$C_5H_{11}CH{=}CH(CH_2)_2CHO$

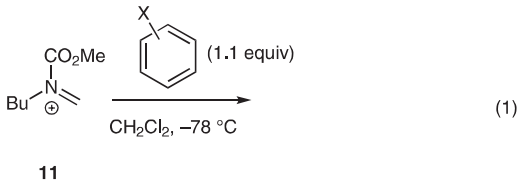


89 90

30–80%
89/**90** = 60:40 to 97:3

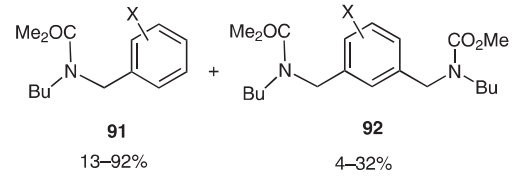
NuTMS	R^2
$CH_2{=}C(OTBS)(OEt)$	$-CH_2CO_2Et$
$CH_2{=}CHCH_2TMS$	$-CH_2CH{=}CH_2$
$CH_2{=}C(OTMS)(Ph)$	$-CH_2COPh$
$CH_2{=}C(OTIPS)(OEt)$	$-CH_2CO_2Et$

Scheme 37



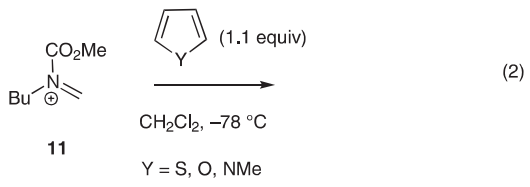
11

ArX
MePh, 1,4-$(Me)_2C_6H_4$, 1,3,5-$(Me)_3C_6H_3$,
MeOPh, 1,2-$(MeO)_2C_6H_4$, 1,3,5-$(MeO)_3C_6H_3$



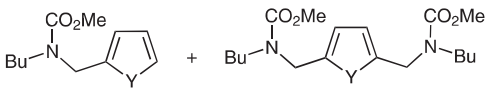
91 92

13–92% 4–32%



11

Y = S, O, NMe



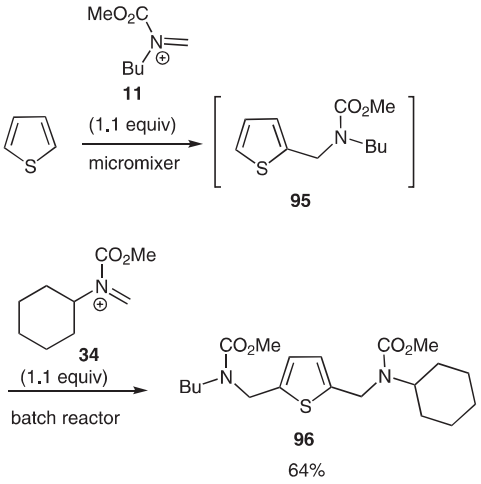
93 94

11–84% 5–28%

Scheme 38

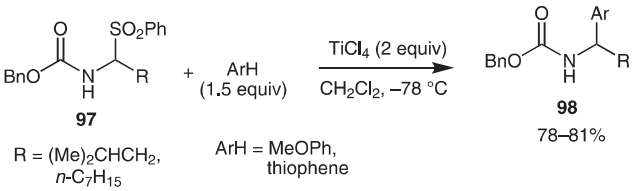
lated products **91** and **93** were obtained, in 26–92% and 39–84% yields, respectively.[9]

The above method, using a micromixer together with pregenerated *N*-acyliminium ions, has been extended to the selective introduction of two different alkyl groups onto aromatic compounds (Scheme 39). Monoalkylation of thiophene was carried out in a micromixer, and the product **95** was directly treated with a different *N*-acyliminium ion **34**, to give the dialkylated product **96** in 64% yield.[9]



Scheme 39

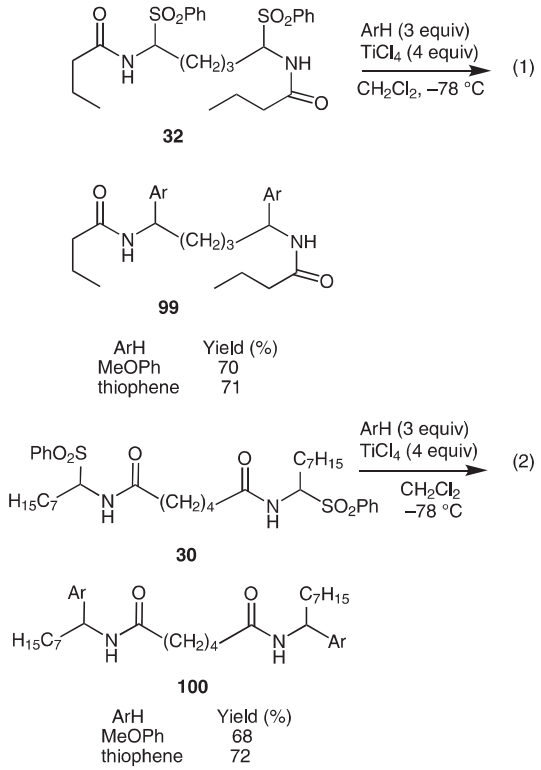
The α-amido sulfones **97** gave the corresponding arylated adducts **98** in good yields when treated with electron-rich aromatic compounds in the presence of titanium(IV) chloride (Scheme 40).[10]



Scheme 40

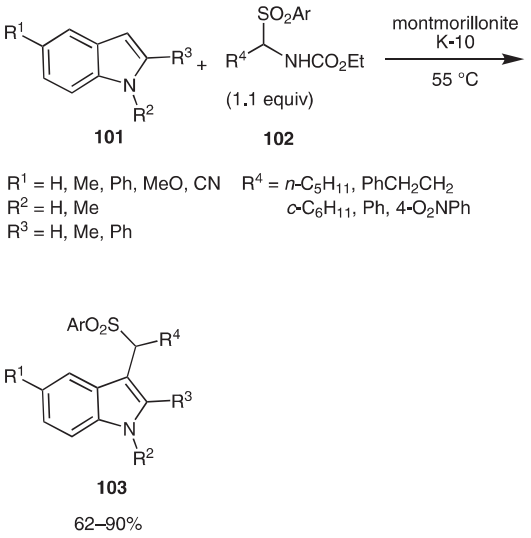
Treatment of bisamido sulfones **32** and **30** with aromatic compounds (1.5 equiv) in the presence of titanium(IV) chloride (2 equiv) resulted in poor yields of monoarylated products due to the formation of bisarylated products and side products. Bisarylation took place efficiently when excess amounts of the aromatic nucleophiles (3 equiv) and titanium(IV) chloride (4 equiv) were used (Scheme 41).[10]

The α-amido sulfones **102** reacted with indoles **101** in the presence of montmorillonite K-10 without solvent to give the 3-substituted indole derivatives **103** (Scheme 42). Unexpectedly, these products retained the toluenesulfonyl group of **102**, instead of its carbamoyl group. The formation of these products **103** has been explained by the mechanism shown in Scheme 43. The *N*-acyliminium ion

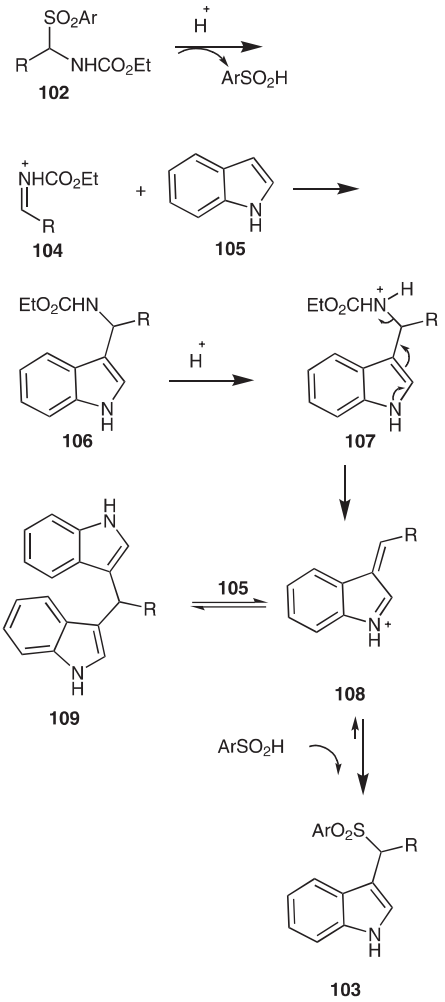


Scheme 41

104 forms from the α-amido sulfone under acidic conditions. The indole **105** attacks the *N*-acyliminium ion **104** to form the expected product **106**, which is then protonated and eliminates the carbamate group. The resulting iminium ion **108** can react with another molecule of indole to give the bisindole **109**, or with the arenesulfinic acid to give the observed product **103**. Since the formation of the bisindole is reversible and product **103** is more stable than the bisindole, the reaction favours the formation of **103**.[34]

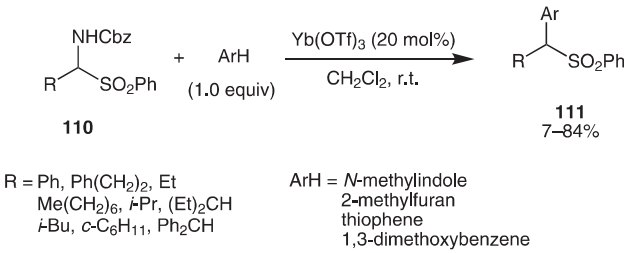


Scheme 42



Scheme 43

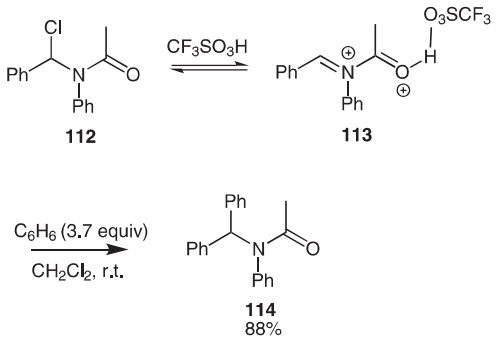
The α-amido sulfones **110** gave products **111** when they were treated with 1,2,4-trimethoxybenzene in the presence of ytterbium(III) triflate at room temperature (Scheme 44). Heteroaromatic compounds gave lower yields of adducts than electron-rich benzene derivatives, which might be the result of formation of a deactivating complex between the heteroaromatic compounds and the Lewis acid.[35]



Scheme 44

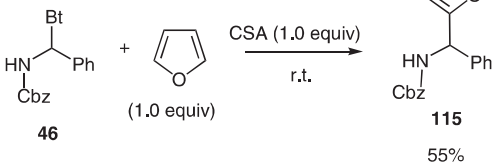
Trifluoromethanesulfonic acid catalysed the reaction of α-chloro amide **112** with benzene and gave the benzhydril

product **114** in 88% yield (Scheme 45).[33] Evidence for the dicationic intermediate **113** has been reported.[36]



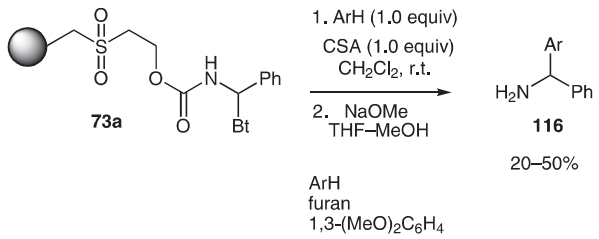
Scheme 45

Treatment of the α-benzotriazole carbamate **46** with furan in the presence of camphorsulfonic acid monohydrate afforded product **115** in 55% yield (Scheme 46).[6]



Scheme 46

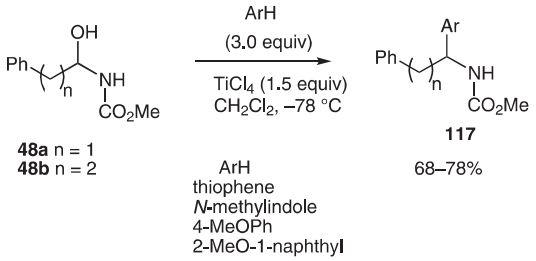
In the same study, the reaction of immobilised α-benzotriazole carbamate **73a** with furan and 1,3-dimethoxybenzene in the presence of camphorsulfonic acid gave products **116** in 50% and 20% yields, respectively, after cleavage from the resin (Scheme 47).[6]



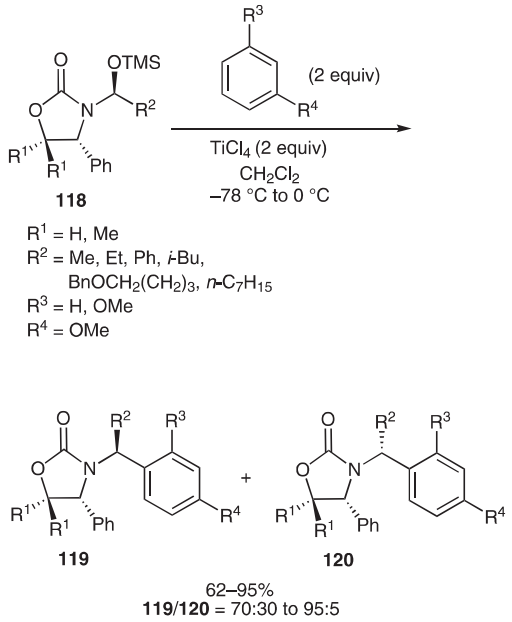
Scheme 47

Treatment of the α-hydroxy carbamates **48a** and **48b** with aromatic nucleophiles under titanium(IV) chloride catalysis afforded the desired arylated products **117** in yields ranging from 68% to 78% (Scheme 48).[21]

The oxazolidinones **118** reacted with methoxybenzene and 1,3-dimethoxybenzene in the presence of titanium(IV) chloride to afford the corresponding adducts **119** and **120** in 62–95% yields (Scheme 49).[37]



Scheme 48



Scheme 49

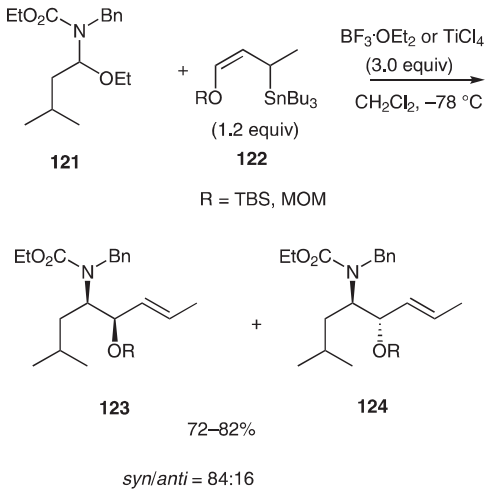
2.2.1.3 Organostannanes

Racemic allylic stannanes **122** reacted with *N*-acyliminium ions derived from α-ethoxy carbamate **121** to give the racemic adducts **123** and **124** in good to excellent yields, and with good diastereoselectivities (Scheme 50).[17,18]

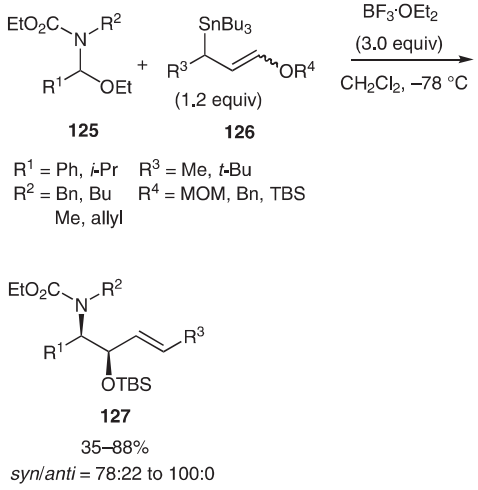
The racemic (*E*)-γ-OTBS derivative of allylic stannane **126** gave only the racemic *syn* adduct **127** from its reaction with α-ethoxy carbamates **125**. The *E*- or *Z*-geometry of the stannane and the nature of the substituents on the iminium ion did not affect the *syn* preference of the reaction (Scheme 51).[17]

The *N*-(2-methoxyphenyl) carbamates **128**, however, underwent highly diastereoselective reactions (dr > 95:5) with the enantiomerically enriched (*S*)-γ-silyloxyallylic stannane **129** to give the *syn* products **130** (Scheme 52). The reason for this enhanced diastereoselectivity, apparently due to the presence of the 2-methoxy group, was not clear.[18]

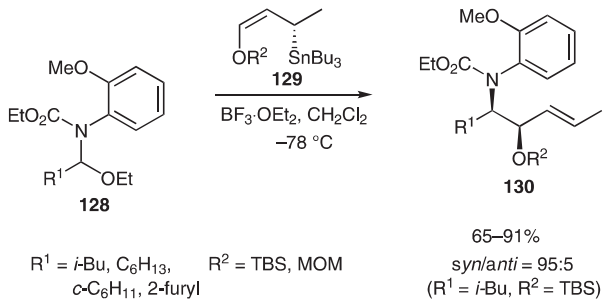
The boron trifluoride–diethyl ether complex promoted reaction of (*R*)-**131** and (*S*)-**132** gave the *syn*,*anti* adduct **133** as the exclusive product (the matched case) while the corresponding reaction of (*S*)-**131** and (*S*)-**132** gave a 60:40



Scheme 50

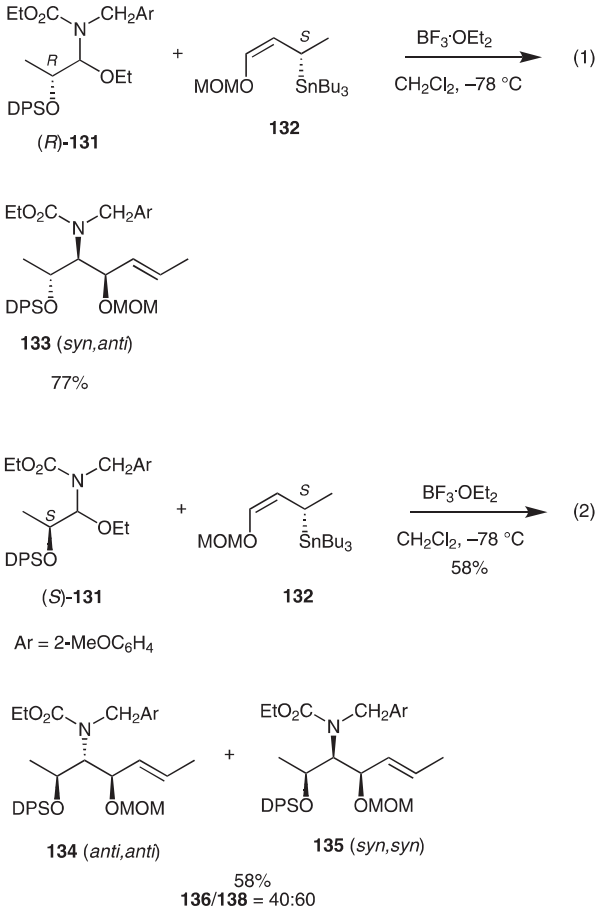


Scheme 51



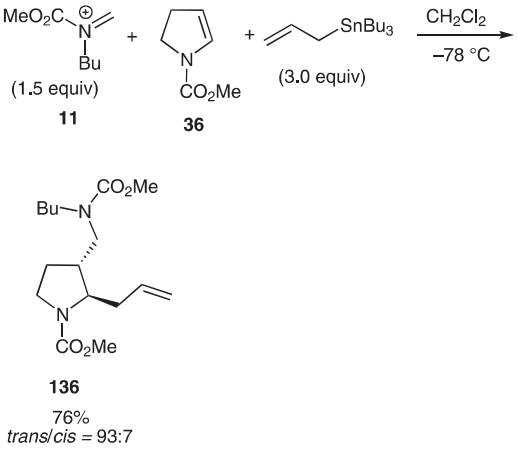
Scheme 52

mixture of diastereomers **134** and **135** (mismatched pair) (Scheme 53).[18]



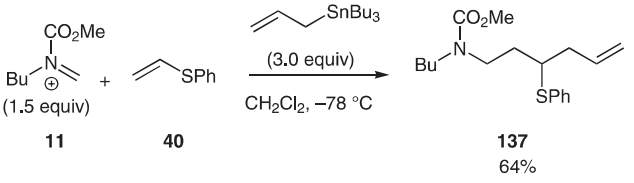
Scheme 53

The reaction of the *N*-acyliminium ion **11** with allyltributylstannane and enamine **36** led to the formation of product **136** in a yield of 76% (*trans*/*cis* = 93:7) (Scheme 54).[25]



Scheme 54

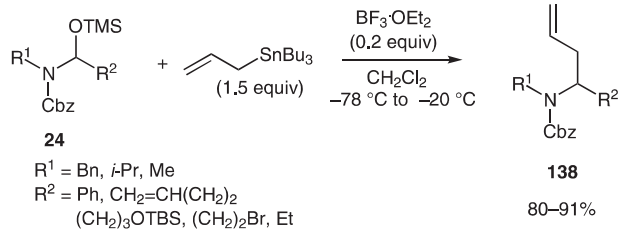
In the same study, the three-component coupling reaction of the *N*-acyliminium ion **11** with vinyl phenyl sulfide **40** and allyltributylstannane provided the corresponding product **137** in 64% yield (Scheme 55).[25]



11 40 137
64%

Scheme 55

Treatment of α-silyloxycarbamates **24** with allyltributylstannane in the presence of boron trifluoride–diethyl ether complex provided the desired adducts **138** in yields of 80–91% (Scheme 56).[20]

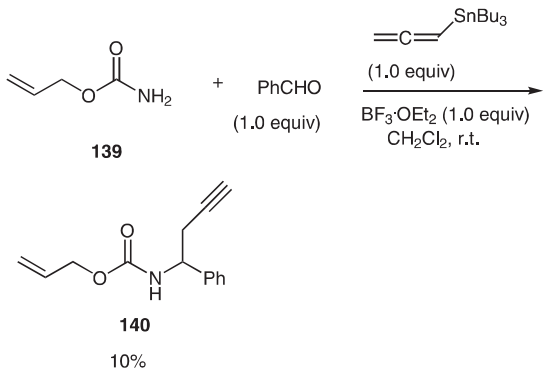


24
R1 = Bn, *i*-Pr, Me
R2 = Ph, CH_2=CH$(CH_2)_2$
$(CH_2)_3$OTBS, $(CH_2)_2$Br, Et

138
80–91%

Scheme 56

The one-pot reaction of allyl carbamate **139** with benzaldehyde and an allenylstannane nucleophile in the presence of boron trifluoride–diethyl ether complex gave the alkyne product **140** in only 10% yield (Scheme 57).[6]



Scheme 57

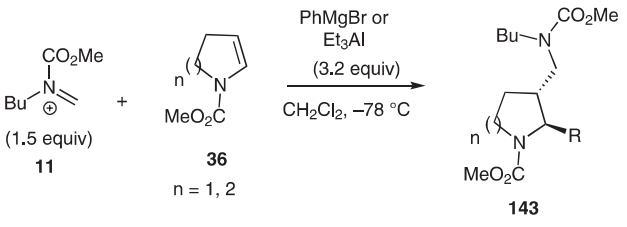
2.2.1.4 Organometallic Reagents

The *N*-acyliminium ion **141**, generated from the corresponding carbamate by electrochemical oxidation (Scheme 3), was treated with phenylmagnesium bromide to give the desired adduct **142** in 72% yield (Scheme 58).[38]

141 142
72%

Scheme 58

Phenylmagnesium bromide and triethylaluminium each gave the corresponding three-component coupling products **143**, with good diastereoselectivity, when they were added to a solution of **37** and **38** (Scheme 16), formed in situ from the reaction of **11** and **36** (Scheme 59).[25]



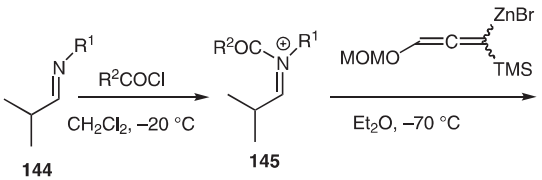
11 36
n = 1, 2

143

R	Yield (%) (*trans*/*cis*)
Ph (n = 1)	51 (88:12)
Et (n = 1)	61 (89:11)
Ph (n = 2)	46 (98:2)
Et (n = 2)	71 (61:39)

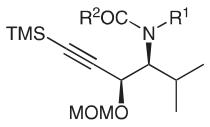
Scheme 59

A 3-alkoxyallenylzinc reagent reacted with the *N*-acyliminium ion **145**, which was generated in situ from the treatment of the imine **144** with acyl chlorides, to provide products **146** in yields of 31–96% and with *syn*/*anti* ratios of 61:39 to 74:26 (Scheme 60).[39]



144 145

R1 = PMB, allyl, Pr, Cy
R2 = Me, Ph

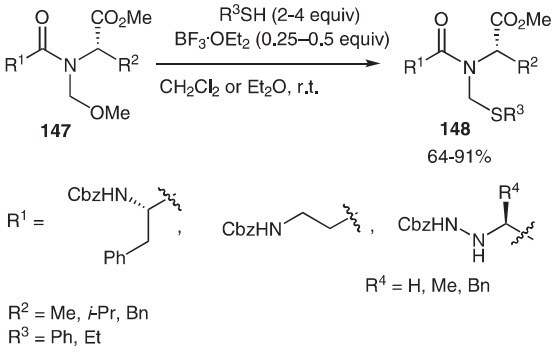


146
31–96%
syn/*anti* = 61:39–74:26

Scheme 60

2.2.1.5 Thiols

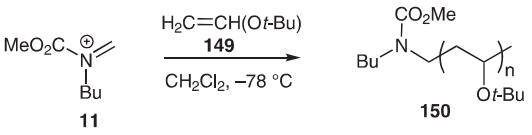
Treatment of *N*-methoxymethyl dipeptides **147** with thiol nucleophiles afforded thiol-substituted dipeptides **148** in 64–91% yields (Scheme 61).[24]



Scheme 61

2.2.1.6 Alkenes

Generation of *N*-acyliminium ions by low-temperature electrochemical oxidation and the use of a micromixer system were successfully applied to the synthesis of polymers of *tert*-butyl vinyl ether **150** (Scheme 62). The method allowed for the control of molecular-weight distribution.[40]



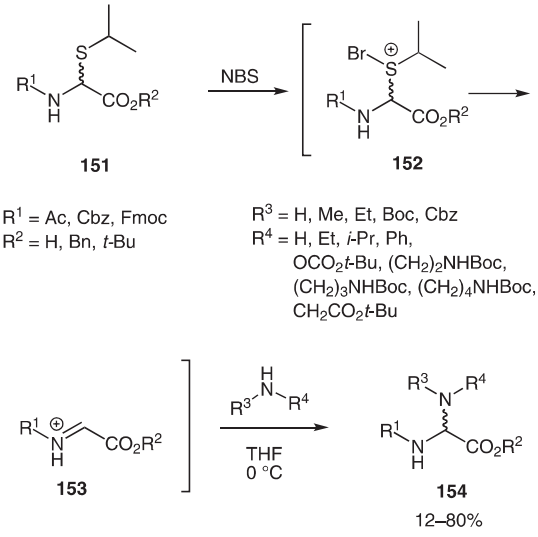
Scheme 62

2.2.1.7 Nitrogen Nucleophiles

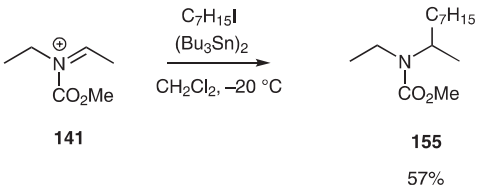
Treatment of the α-isopropylthioglycine derivative **151** with *N*-bromosuccinimide provided bromosulfonium salt **152** which formed the corresponding *N*-acyliminium ion **153**. This intermediate underwent reaction with amines, amides and carbamates to afford products **154** in yields ranging from 12% to 80% (Scheme 63).[22]

2.2.1.8 Alkyl Radicals

The *N*-acyliminium ion **141**, generated from the corresponding carbamate by low-temperature electrochemical oxidation, was treated with heptyl iodide in the presence of hexabutyldistannane to afford product **155** in 57% yield (Scheme 64). Decreasing the rate of addition of the distannane had increased the yield from 31% to 57%.[41,42]



Scheme 63



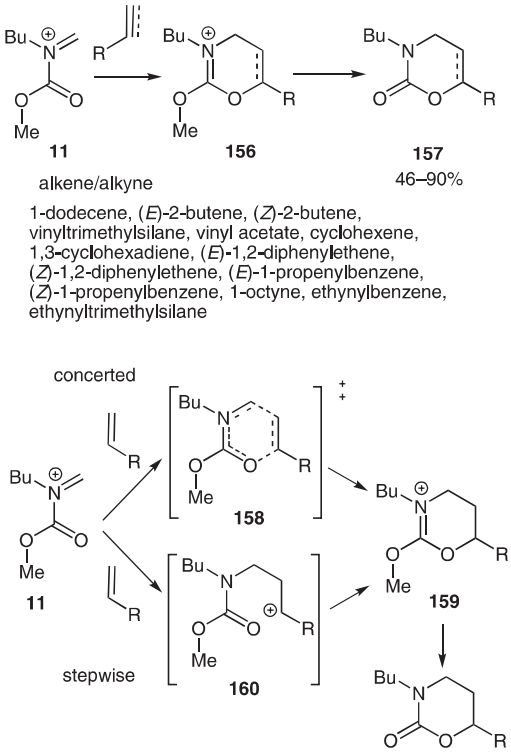
Scheme 64

2.2.2 Cycloaddition Reactions

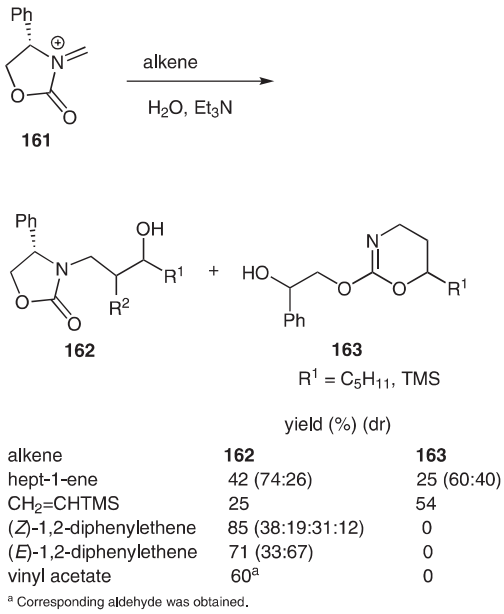
The *N*-acyliminium ion **11** underwent smooth [4+2]-cycloaddition reactions with various alkenes and alkynes (Scheme 65). (*E*)-But-2-ene, (*E*)-1,2-diphenylethene and (*Z*)-propenylbenzene each gave the corresponding *trans* cycloadduct exclusively in 68%, 87%, and 88% yields, respectively, while (*Z*)-but-2-ene gave the *cis* cycloadduct exclusively. These results were consistent with a concerted reaction mechanism. The loss of stereoselectivity in the reaction of (*Z*)-1,2-diphenylethene (*trans*/*cis* = 45:55) and (*E*)-propenylbenzene (*trans*/*cis* = 44:56) suggested a stepwise mechanism in which bond rotation competed with cyclisation in the intermediate **160**. It was concluded that the stereospecificity of the reactions of alkyl-substituted alkenes was consistent with a concerted mechanism, while that observed with aryl-substituted alkenes was consistent with a stepwise mechanism.[8,43]

2.2.3 Cationic Carbohydroxylation Reactions

Alkenes underwent cationic carbohydroxylation reaction with the *N*-acyliminium ion **161** to afford products **162** and **163** in combined yields of 60–85% (Scheme 66). The reaction of electrochemically generated **161** with hept-1-ene in the presence of water and triethylamine gave products **162** and **163** in 42% (dr = 74:26) and 25% (dr = 60:40) yields, respectively, while the reaction of vi-



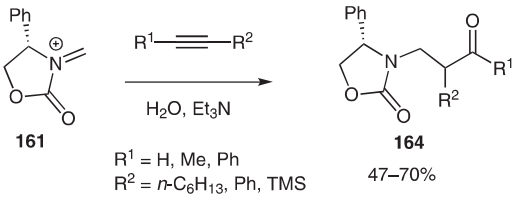
Scheme 65



Scheme 66

nyltrimethylsilane with **161** afforded products **162** and **163** in 25% and 54% yields, respectively. The reactions of (*Z*)-1,2-diphenylethene and (*E*)-1,2-diphenylethene with **161** afforded the **162**-type products exclusively in 85% and 71% yields, respectively. The corresponding ketone of product **162** was obtained in 60% yield from the reaction of **161** with vinyl acetate under the same reaction conditions.[44]

The *N*-acyliminium ion **161** reacted with alkynes in water and triethylamine to give the corresponding cationic carbohydroxylation products **164** in yields of 47–70% (Scheme 67).[44]

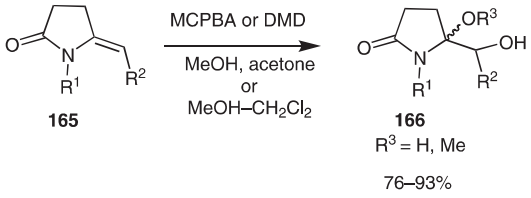


Scheme 67

3 Cyclic *N*-Acyliminium Ions

3.1 Synthesis of Cyclic *N*-Acyliminium Ion Precursors

Earlier methods for the synthesis of these precursors were reported in the previous review.[2] 5-Alkoxypyrrolidinones **166** were synthesised from the oxidation reactions of 5-alkylidenepyrrolidinones **165** with *m*-chloroperoxybenzoic acid or dimethyldioxirane (DMD) (Scheme 68).[45]

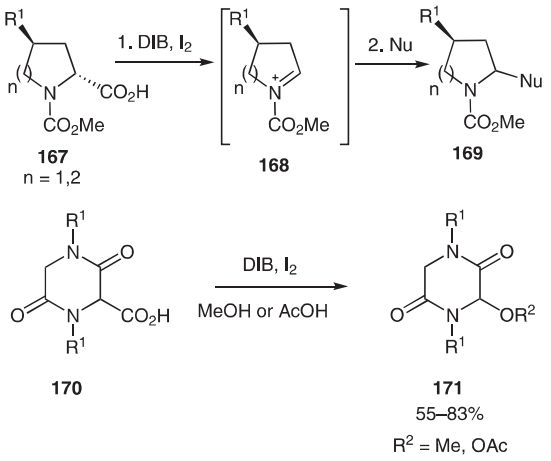


Scheme 68

3.1.1 Preparation of Iminium Ions in situ by Anodic Oxidation

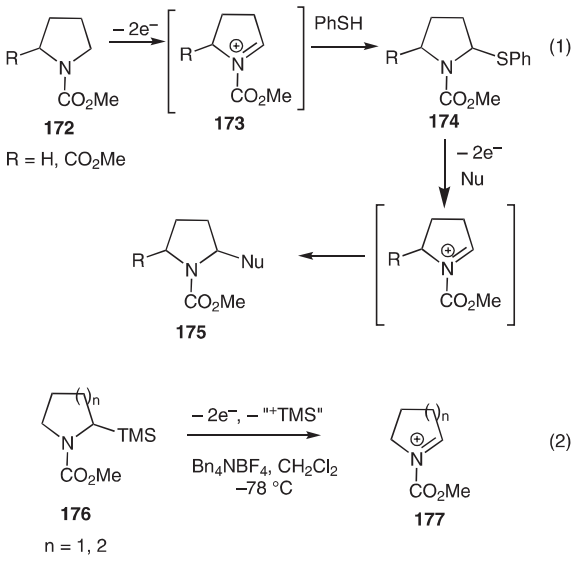
Five-membered-ring *N*-acyliminium ions like **168** can be generated in situ by a one-pot radical decarboxylation–oxidation process using (diacetoxyiodo)benzene (DIB) and iodine. Decarboxylation–oxidation of **167** first formed the *N*-acyliminium ion **168** in situ, then addition of a nucleophile gave addition products **169** (Scheme 69).[46,47] This one-pot decarboxylation–oxidation–nucleophilic addition reaction can be used for the preparation of α-functionalised piperazinediones. Treatment of piperazinedione **170** with (diacetoxyiodo)benzene and iodine in methanol or acetic acid provided the corresponding α-methoxy or α-acetoxy diketopiperazines **171** in 55–83% yields.[48]

Anodic oxidation of compounds **172** in a 1 M lithium perchlorate/nitromethane electrolyte solution in the presence of 50 mM acetic acid generated the *N*-acyliminium ions **173**, which were trapped with thiophenol to give 2-phenylsulfanyl derivatives **174**. Subsequent oxidation of these 2-phenylsulfanyl derivatives also gave rise to the corresponding *N*-acyliminium ions which, when generated in the presence of a nucleophile, gave the expected adducts **175** (Scheme 70, equation 1).[49] The *N*-acyliminium



Scheme 69

ions **177** (R = H) can also be formed by low-temperature oxidation of the corresponding carbamates **176** in dichloromethane solution in the absence of nucleophiles (Scheme 70, equation 2).[38,41,42,50]



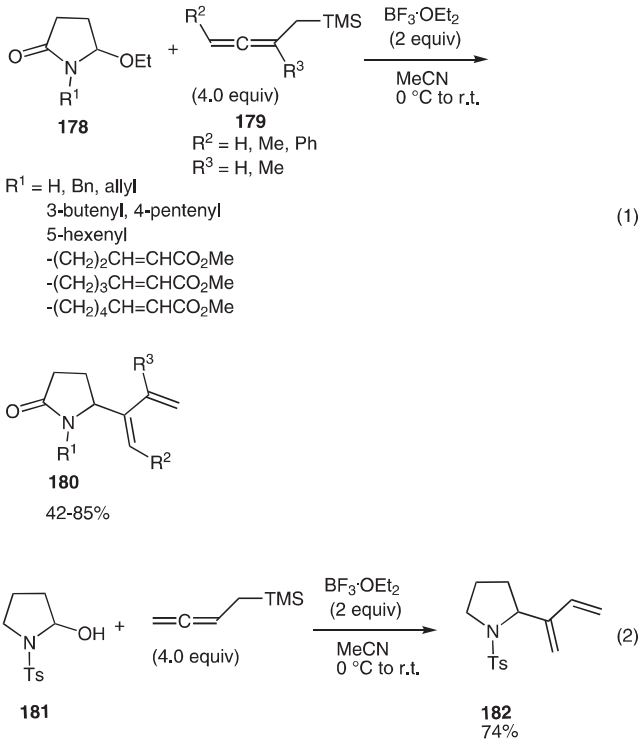
Scheme 70

3.2 Five-Membered-Ring *N*-Acyliminium Ions

3.2.1 Reactions of Pyrrolidinone-Based *N*-Acyliminium Ions with Nucleophiles

3.2.1.1 Silicon-Based Nucleophiles

Allenylmethylsilanes **179** react with 5-ethoxypyrrolidinones **178** in the presence of boron trifluoride–diethyl ether complex in acetonitrile to give the corresponding dienes **180** (Scheme 71, equation 1). Reaction of allenylmethylsilane (**179**, $R^2 = R^3 = H$) with **178** gave 5-substituted pyrrolidinone products in 42–74% yields. Substituted allenylsilanes **179** resulted in formation of products **180** in yields of 65–85%. Product **180** with $R^1 = H$, $R^2 = Me$, $R^3 = H$ was obtained as the pure *E*-isomer, while product **180** with $R^1 = H$, $R^2 = Ph$, $R^3 = H$ was obtained as a 1:1 mixture of isomers. Treatment of the 5-hydroxypyrrolidinone **181** with allenylmethylsilane under the same reaction conditions provided product **182** in 74% yield (Scheme 71, equation 2).[30a]

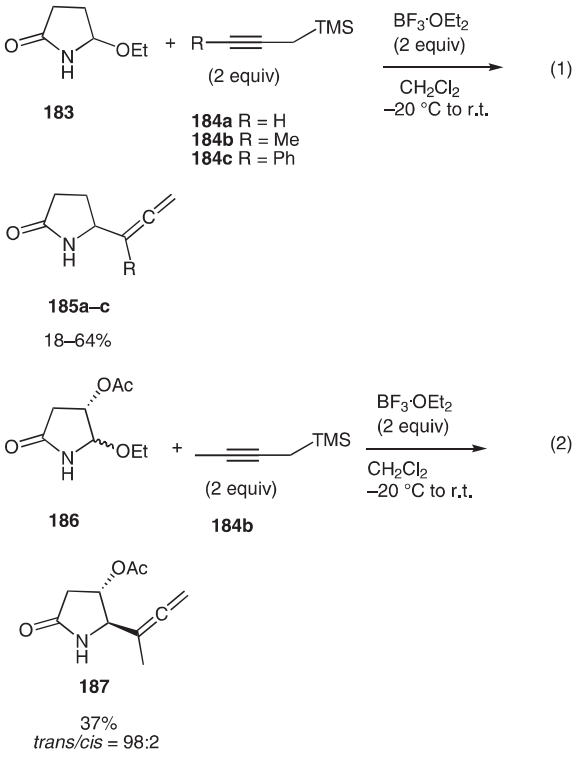


Scheme 71

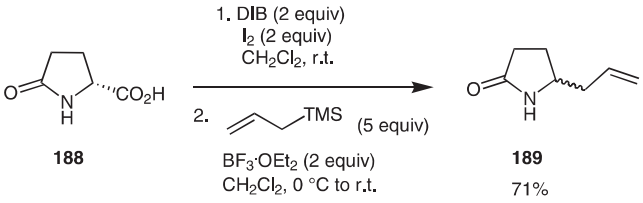
The reaction of 5-ethoxypyrrolidinone **183** with propargylsilanes **184a–c** led to the formation of the 5-allenylpyrrolidinones **185a–c**. Propargyltrimethylsilane (**184a**) and but-2-ynyltrimethylsilane (**184b**) gave allenyl products **185a** and **185b** in 55% and 64% yields, respectively, while phenyl-substituted propargylsilane **184c** gave **128c** in 18% yield (Scheme 72, equation 1). The reaction of 4-acetoxy-5-ethoxypyrrolidinone **186** with propargylsilane **184b** under the same reaction conditions afforded the corresponding product **187** in 37% yield and with very high *trans* selectivity (*trans*/*cis* = 98:2) (Scheme 72, equation 2).[51]

The *N*-acyliminium ion generated from **188** was trapped with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give allylated product **189** in 71% yield (Scheme 73).[46]

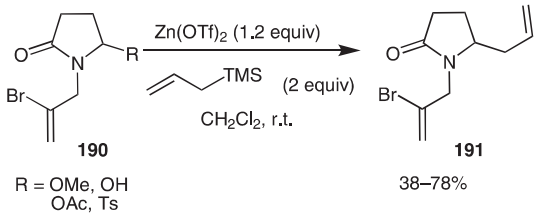
The zinc triflate catalysed reaction of allyltrimethylsilane with the 5-hydroxy-, 5-methoxy-, 5-acetoxy- and 5-sulfonylpyrrolidinones **190** afforded 5-allylated products **191** in moderate to good yields (Scheme 74). The 5-methoxypyrrolidinone derivative of **190** (R = OMe) underwent an addition reaction with a silyl enol ether [CH_2=C(OTMS)(Ph)] to give the desired product in 69% yield.[52]



Scheme 72

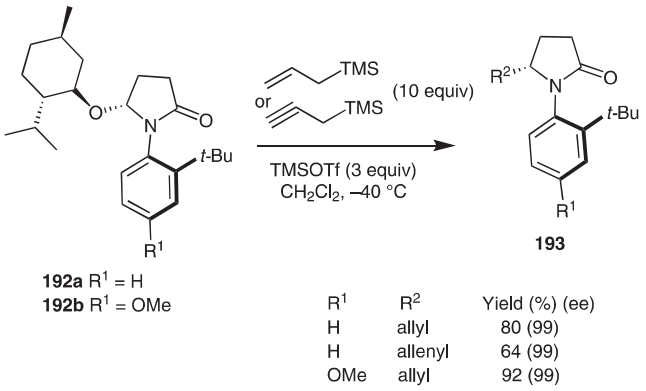


Scheme 73



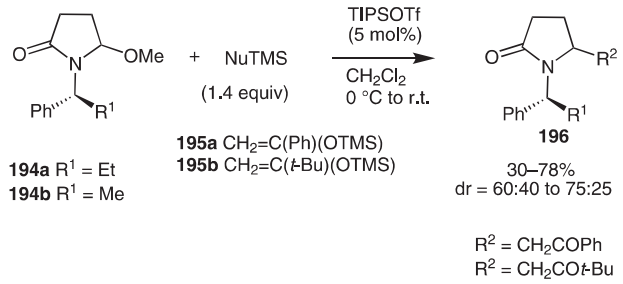
Scheme 74

Pyrrolidinones **192**, having a chiral C–N axis, reacted with allyltrimethylsilane or propargyltrimethylsilane in the presence of trimethylsilyl triflate to give products **193** in ≥99% ee (Scheme 75).[53]



Scheme 75

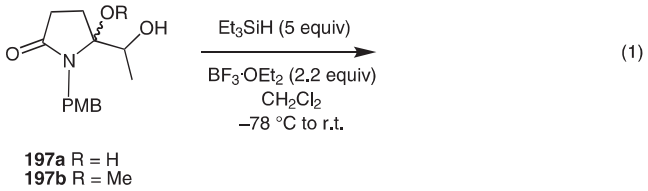
The reaction of **194a** with silyl enol ether **195a** in the presence of triisopropylsilyl triflate (5 mol%) afforded the corresponding ketone **196** in 42% yield and as a 75:25 mixture of diastereomers. The use of toluene as a solvent increased the yield (78%) but lowered the diastereoselectivity (60:40). Treatment of **194b** with **195a** under the same reaction conditions provided the desired ketone product as a mixture of isomers (dr = 60:40) in 55% yield. In that case, using toluene as a solvent did not change the diastereoselectivity but increased the yield to 74%. The reaction of **194b** with **195b** in dichloromethane or toluene afforded the desired ketone **196** with the same diastereomeric ratio of 63:37 and in 30% and 32% yields, respectively (Scheme 76).[54] The reaction of the pyrrolidinone **194b** with **195a** under catalysis by bis(trifluoromethane)sulfonimide (5 mol%) or scandium(III) triflate (5 mol%) afforded the expected ketone as a mixture of isomers (60:40 and 58:42) and in yields of 78% and 81%, respectively.[55]



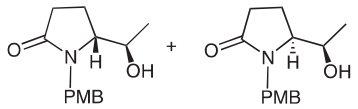
Scheme 76

The reaction of the 5-alkoxypyrrolidinone **197** with triethylsilane in the presence of boron trifluoride–diethyl ether complex yielded products **198** in yields of ranging from 86% to 97% favouring the *threo* isomer (Scheme 77, equation 1). Pyrrolidinones **199** with triethylsilane yield-

ed exclusively the *threo* isomer of product **200** under the same experimental conditions (Scheme 77, equation 2).[45]



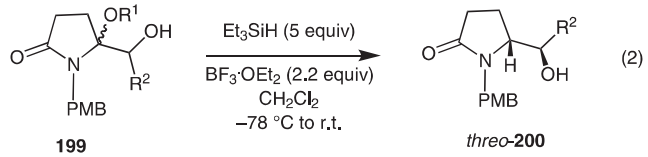
197a R = H
197b R = Me



threo-**198** *erythro*-**198**

R	Yield (%) (*threo*/*erythro*)
197a	89 (97:3)
197b	97 (97:3)
197b	86[a] (67:33)

[a] $TiCl_4$ (1.2 equiv) was used.



199

R^1 = H, Me
R^2 = Cl(CH$_2$)$_3$, *n*-C$_{12}$H$_{25}$

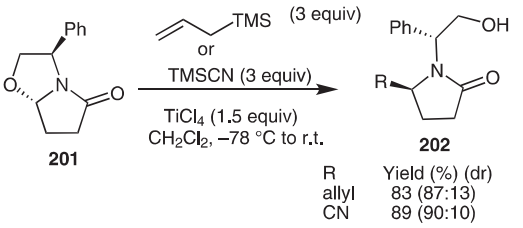
threo-**200**

71–77%
threo/*erythro* = 99:1 to 100:0

Scheme 77

Allyltrimethylsilane and trimethylsilyl cyanide reacted with the pyrrolidinone **201** under titanium(IV) chloride catalysis to give the corresponding 5-allylpyrrolidinone and 5-cyanopyrrolidinones **202** in 83% (dr = 87:13) and 89% (dr = 90:10) yields, respectively (Scheme 78).[56] Treatment of pyrrolidinone **201** with CH_2=C(Ph)(OTMS) in the presence of bis(trifluoromethane)sulfonimide (5 mol%) or scandium(III) triflate (5 mol%) gave the corresponding ketone as a 1:1 mixture of isomers and in 81% and 40% yields, respectively. The reaction of **201** with CH_2=C(Ph)(TMS), CH_2=C(OTMS)(*t*-Bu), and Me_2C=C(OMe)(OTMS) under catalysis by triisopropylsilyl triflate afforded the corresponding ketones in 93%, 50%, and 89% yields, respectively.[54,55]

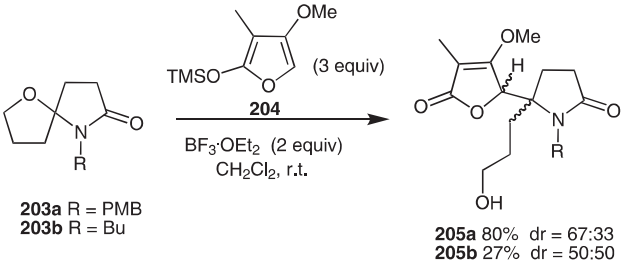
The boron trifluoride–diethyl ether complex catalysed reaction of 2-silyloxyfuran **204** and pyrrolidinone **203a** afforded adduct **205a** as a mixture of diastereomers (dr = 67:33) in 80% yield. The reaction of pyrrolidinone **203b** under the same reaction conditions gave **205b** in 27% yield and as a 1:1 mixture of diastereomers (Scheme 79).[57,58]



201 **202**

R	Yield (%) (dr)
allyl	83 (87:13)
CN	89 (90:10)

Scheme 78

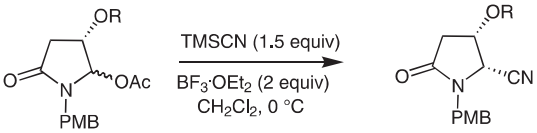


203a R = PMB
203b R = Bu

205a 80% dr = 67:33
205b 27% dr = 50:50

Scheme 79

Pyrrolidinones **206a**,**b** reacted with trimethylsilyl cyanide in the presence of boron trifluoride–diethyl ether complex to give the 5-cyanolactams **207a**,**b** (Scheme 80). Pyrrolidinone **206a** gave rise to **207a** in 98% yield as a 57:43 mixture of *cis* and *trans* isomers. Using toluene as a solvent increased the *cis* selectivity (*cis*/*trans* = 73:27) but lowered the chemical yield (70%). Under the same reaction conditions, **206b** gave **207b** in 98% yield with moderate *trans* selectivity (*trans*/*cis* = 61:39).[59]



206a R = TBS
206b R = Ac

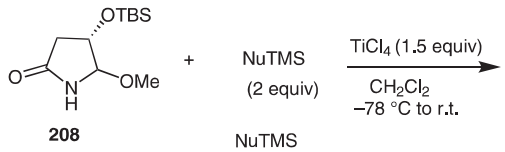
207

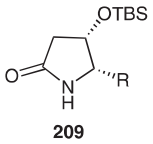
R	Yield (%) (*cis*/*trans*)
TBS	98 (57:43)
TBS	70 (73:27)[a]
Ac	98 (39:61)

[a] Toluene was used as a solvent.

Scheme 80

The 5-methoxypyrrolidinone **208** underwent addition reactions with silyl enol ethers and allylsilanes in the presence of titanium(IV) chloride to give 5-alkylpyrrolidinones **209** with good *cis* selectivity (Scheme 81).[60]



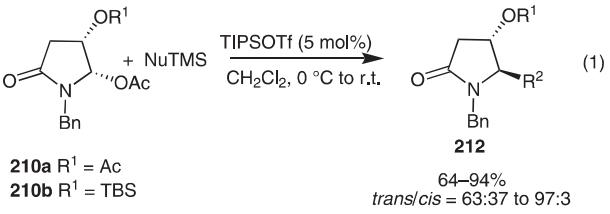


R	Yield (%) (*cis*/*trans*)
-CH(CO$_2$Et)CO$_2$Et	26 (79:21)
-CH(CO$_2$Me)COMe	52 (90:10)
-CH$_2$CH=CH$_2$	89 (91:9)
-CH$_2$C(Br)=CH$_2$	72 (87:13)

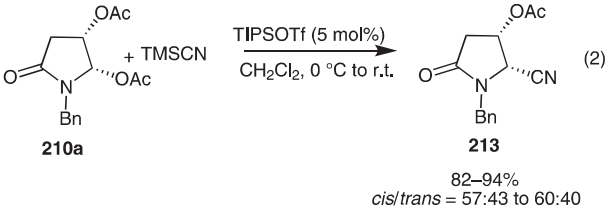
Scheme 81

The reaction of the 5-acetoxypyrrolidinones **210a** with **195b** (1.4 equiv) in the presence of triisopropylsilyl triflate in dichloromethane or toluene gave the products **212** in 74% and 64% yields, and with a diastereomeric ratio of >97:<3 and 90:10, respectively, in favour of the *trans* isomer (Scheme 82, equation 1). Treatment of **210a** with **211a** (2.0 equiv) in dichloromethane or toluene afforded the corresponding products **212** in 94% and 72% yields, respectively, and with moderate *trans* selectivity (74:26, 63:37, respectively). The reaction of **210a** with **211b** (1.4 equiv) provided product **212** in 74% yield and with a *trans*/*cis* ratio of >97:<3. The reaction of **210b** with **195a** and **211a** under the same reaction conditions provided the desired products in 80% and 67% yields and with diastereomeric *trans*/*cis* ratios of 87:13 and 30:70, respectively (Scheme 82, equation 1). Although the reactions of **210a** with **195a**,**b** and **211a** afforded the desired products with high *trans* selectivity, the reaction of **210a** with trimethylsilyl cyanide in the presence of triisopropylsilyl triflate in dichloromethane or toluene gave 5-cyanopyrrolidinone **213** with *cis*/*trans* ratios of 57:43 and 60:40, in yields of 82% and 94%, respectively (Scheme 82, equation 2).[54]

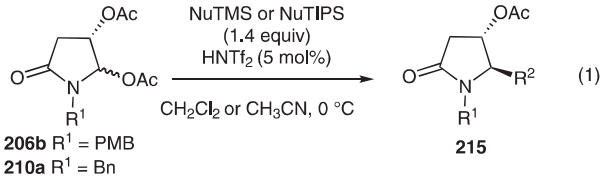
In a very similar study, treatment of the 4,5-diacetoxypyrrolidinones **210a**, **206b**, **214** with silyl nucleophiles in the presence of bis(trifluoromethane)sulfonimide (5 mol%) in dichloromethane or acetonitrile provided the desired products **215** with moderate to excellent *trans* diastereoselectivity (Scheme 83, equation 1). The reaction of pyrrolidinone **210a** with trimethylsilyl cyanide under the same reaction conditions yielded the 4,5-*cis*-pyrrolidinone **213** in 87% yield and with a diastereomeric ratio of 66:34 (Scheme 83, equation 2).[55]



NuTMS	R^2
195a CH$_2$=C(Ph)(OTMS)	-CH$_2$COPh
195b CH$_2$=C(*t*-Bu)(OTMS)	-CH$_2$CO*t*-Bu
211a CH$_2$=CHCH$_2$TMS	-CH$_2$CH=CH$_2$
211b (Me)$_2$C=C(OMe)(OTMS)	-C(Me)$_2$CO$_2$Me

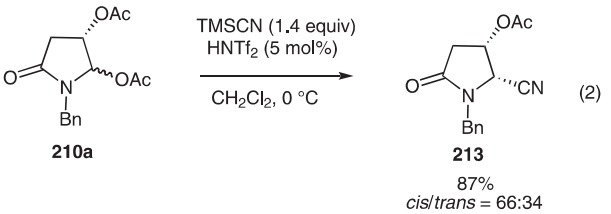


Scheme 82



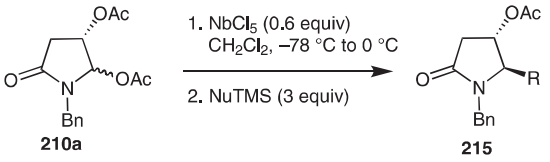
NuTMS	R^2
(Me)$_2$C=C(OMe)(OTMS)	-C(Me)$_2$CO$_2$Me
CH$_2$=C(*t*-Bu)(OTMS)	-CH$_2$CO*t*-Bu
CH$_2$=CHCH$_2$TMS	-CH$_2$CH=CH$_2$
CH$_2$=C(Ph)(OTMS)	-CH$_2$COPh
c-C$_6$H$_9$OTMS	-2-cyclohexanonyl
CH$_2$=C(OTMS)*t*-Bu	-CH$_2$CO*t*-Bu
HC≡CC(OTIPS)=CH$_2$	-CH$_2$COC≡CH

55–90%
dr = 99:1–60:40



Scheme 83

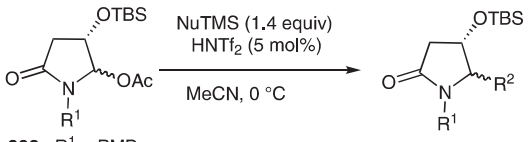
The pyrrolidinone **210a** reacted with allyltrimethylsilane and the silyl enol ether of acetophenone in the presence of niobium(V) chloride to afford adducts **215** in 86% and 81% yields and with moderate *trans* selectivity (Scheme 84).[61] The bismuth(III) triflate catalysed reaction of the pyrrolidinone **210a** with allyltrimethylsilane provided the 5-allylated pyrrolidinone in 82% yield (*trans*/*cis* = 70:30).[62]



NuTMS	R	Yield (%) (*trans*/*cis*)
$CH_2CH=CH_2$	$-CH_2CH=CH_2$	86 (67:33)
$CH_2=C(OTMS)(Ph)$	$-CH_2COPh$	81 (67:33)

Scheme 84

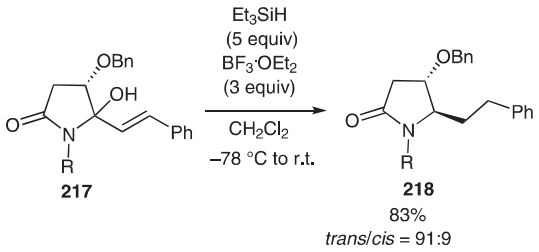
The reactions of pyrrolidinones **206a**, **210b** with silicon nucleophiles in the presence of bis(trifluoromethane)sulfonimide (5 mol%) in acetonitrile gave products **216** in yields ranging from 55% to 95% (Scheme 85).[55,63]



NuTMS	R^2
$CH_2=C(OTMS)t\text{-Bu}$	$-CH_2COt\text{-Bu}$
$c\text{-}C_6H_9OTMS$	-2-cyclohexanonyl
$CH_2CH=CH_2$	$-CH_2CH=CH_2$
TMSCN	-CN
$(Me)_2C=C(OTMS)(OMe)$	$-C(Me)_2CO_2Me$

Scheme 85

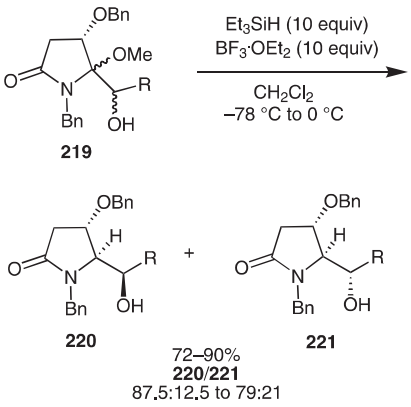
Pyrrolidinone **217** reacted with triethylsilane in the presence of boron trifluoride–diethyl ether complex to give the product **218** in a yield of 83% and with high 4,5-*trans* diastereoselectivity (Scheme 86).[64a]



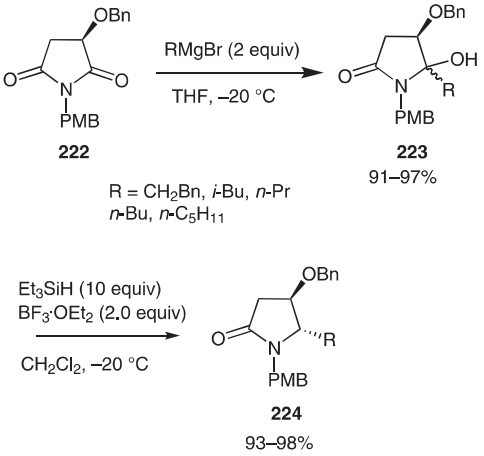
Scheme 86

The reaction of pyrrolidinone **219** with triethylsilane in the presence of boron trifluoride–diethyl ether complex provided products **220** and **221** in 72–90% yields, in favour of the *erythro* isomer (*erythro*/*threo* = 87.5:12.5 to 79:21) (Scheme 87).[65]

Treatment of imides **222** with Grignard reagents afforded 5-hydroxy-5-alkylpyrrolidinones **223** which were treated with triethylsilane in the presence of boron trifluoride–diethyl ether complex to give the 4,5-*trans* adducts **224** exclusively in yields of 93–98% (Scheme 88).[66]



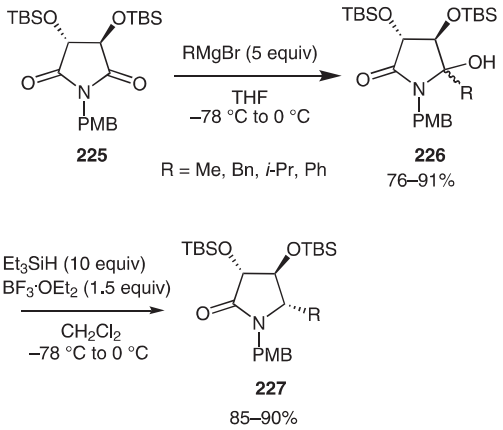
Scheme 87



Scheme 88

The reaction of imide **225** with Grignard reagents led to the formation of 5,5-disubstituted pyrrolidinones **226** in yields of 76–91%. Treatment of pyrrolidinones **226** with triethylsilane and boron trifluoride–diethyl ether complex provided the 4,5-*trans* isomer **227**, exclusively, in 85–90% yields (Scheme 89).[67]

While the addition of Grignard reagents and hydrides to imides **222** was regioselective and gave adducts of the

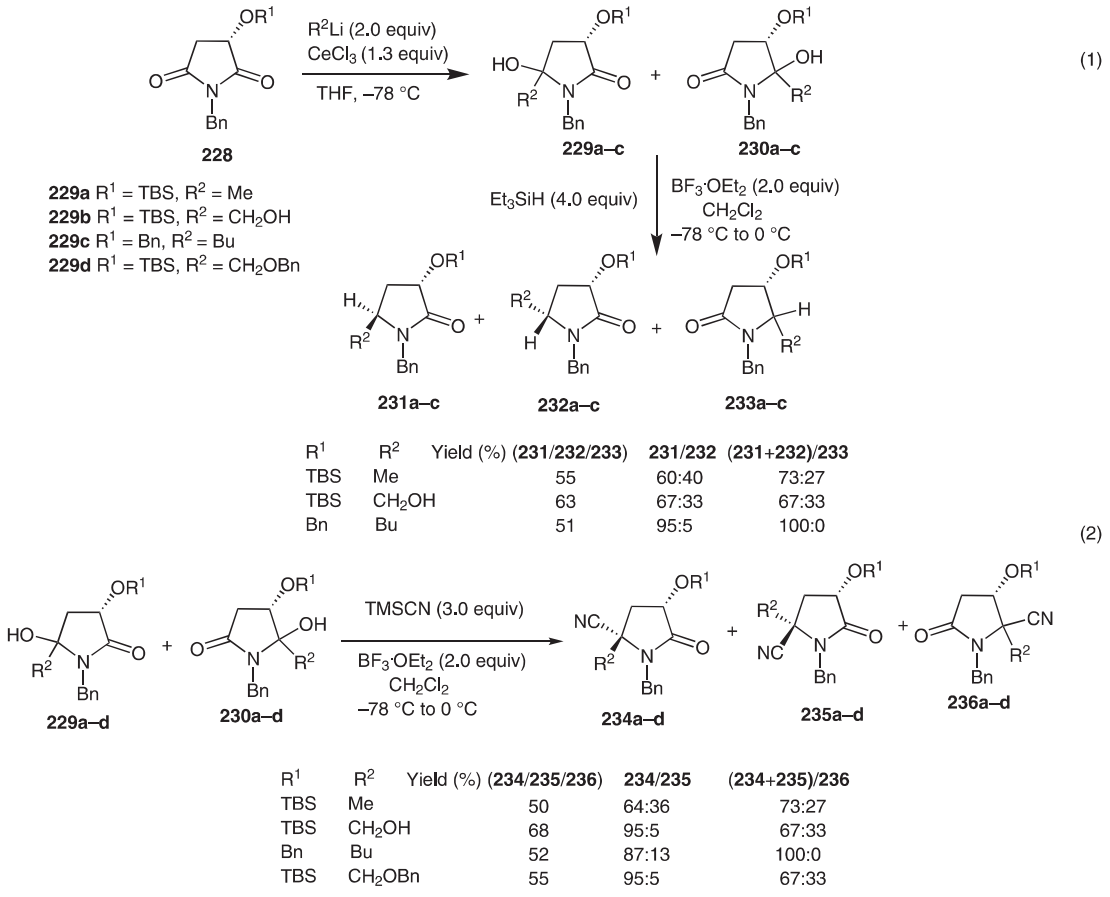


Scheme 89

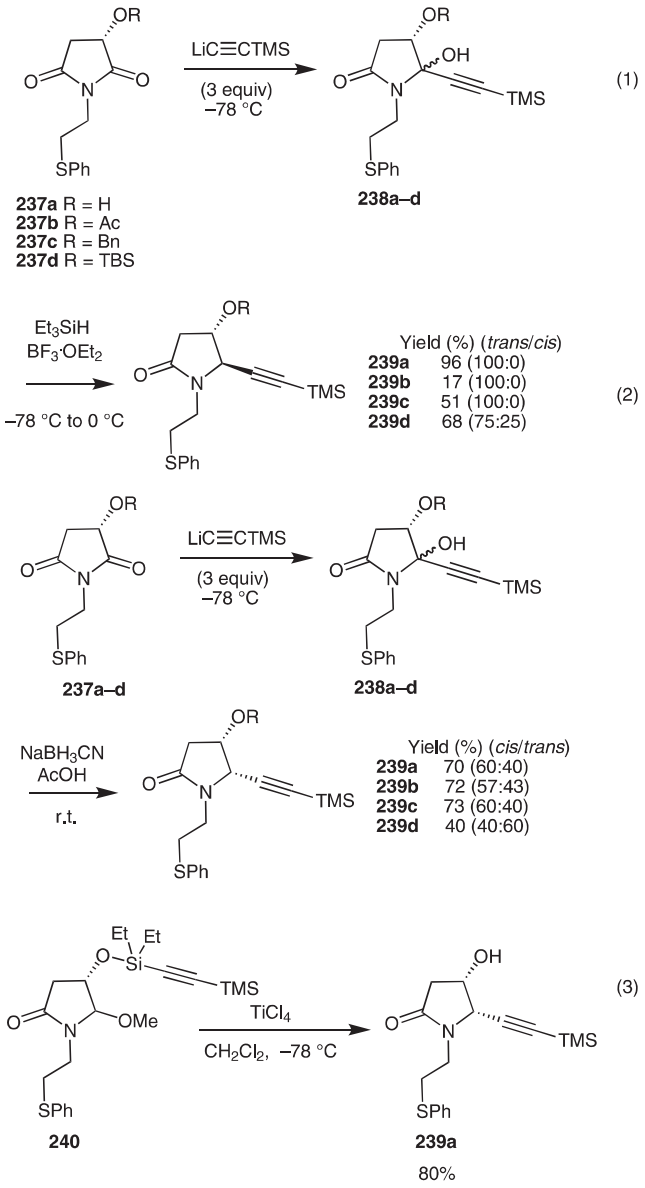
type **223** (Scheme 88), the reactions of organolithium reagents in the presence of cerium(III) chloride with imides **228** afforded regioisomeric mixtures of adducts **229** and **230**. The major adducts are **229**. These mixtures were treated with triethylsilane (Scheme 90, equation 1) in the presence of boron trifluoride–diethyl ether complex to give 3,5-*trans* alkyl-substituted pyrrolidinones. Reaction of triethylsilane with pyrrolidinones **229a**,**230a** and **229b**,**230b** gave products in 55% and 63% yields, respectively, in ratios of (**231+232**)/**233** = 73:27 and 75:25, respectively, while products **231c**,**232c** were isolated exclusively in 51% yield from the reaction of pyrrolidinone **229c** with triethylsilane. Similarly the reaction of trimethylsilyl cyanide with pyrrolidinones **229a**,**230a**, **229b**,**230b**, and **229d**,**230d** gave products in 50%, 68%, and 55% yields, respectively, with ratios of (**234+235**)/**236** = 73:27, 75:25 and 75:25. Products **234c**,**235c** were obtained exclusively, in 52% yield, from the reaction of imide **229c** with trimethylsilyl cyanide (Scheme 90, equation 2).[68]

Whereas the C-2 and C-5 carbonyl groups of imides **228a–d** reacted with organolithium reagents to give mixtures of the adducts **229** and **230** (Scheme 90), imides **237a–d** reacted only at C-2 and gave products of type **238a–d** with lithium trimethylsilylacetylide. Reduction of these 5-hydroxypyrrolidinones **238a–d** with triethylsilane and boron trifluoride–diethyl ether complex afforded products **239a–d** with very high 4,5-*trans* selectivity (Scheme 91, equation 1). In contrast, the reduction of pyrrolidinones **238a–c** with sodium cyanoborohydride and acetic acid afforded products **239a–c** with moderate 4,5-*cis* selectivity (Scheme 91, equation 2); **238d** gave the *trans* product as major isomer (*trans*/*cis* = 60:40).[65] The 4,5-*cis* isomer **239a** was prepared as a single diastereomer from the titanium chloride catalysed reaction of **240** (Scheme 91, equation 3).[69]

The addition reactions of allyltrimethylsilane to the 5-acetoxy-*N*-allylpyrrolidinones **214a** and **241** afforded products **215** and **242** with 4,5-*trans* selectivity (Scheme 92, equation 1). The highest *trans* selectivity (88:12) was observed from the reaction of pyrrolidinone **214a** with allyltrimethylsilane in the presence of titanium(IV) chloride. The use of indium(III) chloride, tin(IV) chloride or trimethylsilyl triflate as the Lewis acid in this reaction resulted in *trans*/*cis* product ratios of 80:20, 76:24 and 78:22, respectively. Treatment of pyrrolidinone **241** with allyltrimethylsilane under catalysis by boron trifluoride–diethyl ether complex or titanium(IV) chloride gave **242** in 64:36 and 69:31 diastereomeric ratios, respectively. In the same study, the reaction of the pyrrolidinone **243a**



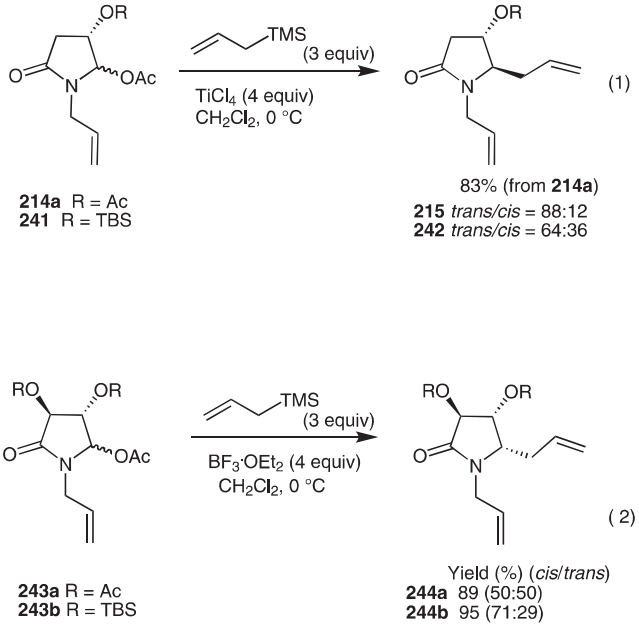
Scheme 90



Scheme 91

with allyltrimethylsilane afforded the C-5 allylated product **244a** with no selectivity (1:1) under catalysis by boron trifluoride–diethyl ether complex or titanium(IV) chloride, while pyrrolidinone **243b** gave the product **244b** with a *cis*/*trans* ratio of 71:29 under boron trifluoride–diethyl ether complex catalysis (Scheme 92, equation 2).[70]

The pyrrolidinones **245a** and **245b** were subjected to cyanation reaction conditions to afford the corresponding 5-cyanopyrrolidinones **246a**,**247a** and **246b**,**247b** in 96% and 82% yields, respectively (Scheme 93, equation 1). A 4,5-*cis* selectivity (**246a**/**247a** = 84:16) was observed in the reaction of **245a** in toluene. The use of dichloromethane as a solvent decreased the diastereomeric ratio of **246a**/**247a** to 80:20. Pyrrolidinone **245b** gave products with *trans* selectivity with a diastereomeric ratio of 82:18 and 77:23 in dichloromethane and toluene, respectively.



Scheme 92

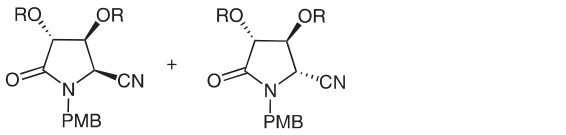
Treatment of pyrrolidinone **248**, the enantiomer of **245b**, with trimethylsilyl cyanide provided products **249** and **250** in 93% yield and as a mixture of isomers (**249**/**250** = 80:20) (Scheme 93, equation 2).[71]

The addition of the Grignard reagent benzyloxymethylmagnesium chloride to imide **251** in the presence of mercury(II) chloride afforded the 5-hydroxypyrrolidinone **252** as a diastereomeric mixture. Treatment of this mixture with triethylsilane gave exclusively the 4,5-*trans* pyrrolidinone **253** in 61% yield (Scheme 94).[72]

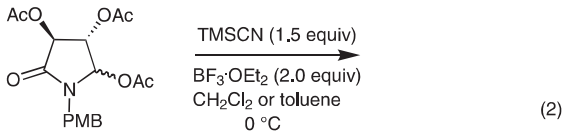
Organolithium reagents were treated with imide **254** to afford 5-hydroxy-5-alkylpyrrolidinones **255**. The 4,5-*trans* pyrrolidinones **256** were obtained from the reaction of these 5-hydroxypyrrolidinones **255** with triethylsilane in the presence of boron trifluoride–diethyl ether complex (Scheme 95). Similarly, the reaction of pyrrolidinone **257** with lithium reagents and then triethylsilane under the same reaction conditions provided 4,5-*trans* products **259** in yields of 50–66%.[73]

Treatment of **214a** with **260** (1.5 equiv) under triisopropylsilyl triflate catalysis in dichloromethane or diethyl ether gave the desired product **261a** in 50% yield and as a mixture of isomers (*trans*/*cis* = 85:15). The reaction of **243** with **195a** (1.4 equiv) provided the product **261b** with *cis* selectivity (*cis*/*trans* = 73:27) in 73% yield, while the reaction of **243** with **260** afforded product **261c** with no selectivity (dr = 50:50) and in a yield of 55% (Scheme 96).[54]

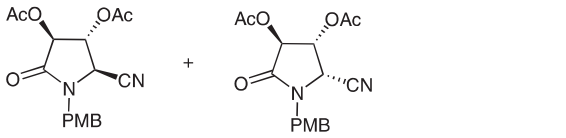
(1)



246a/247a[a] = 84:16
246a/247a[b] = 80:20
246b/247b[a] = 23:77
246b/247b[b] = 18:82
[a] Toluene was used as a solvent.
[b] CH_2Cl_2 was used as a solvent.

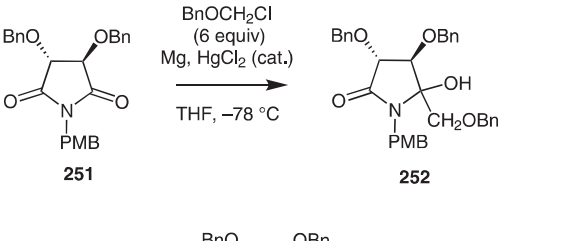


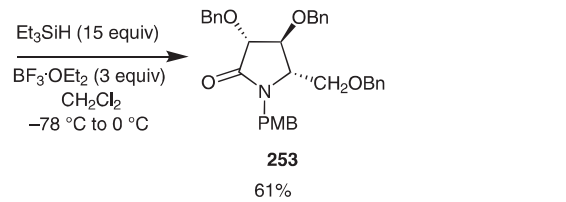
(2)



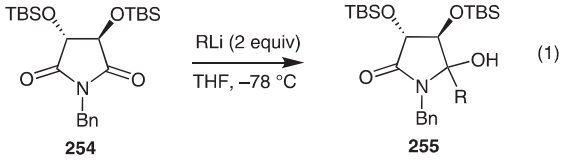
249/250 = 80:20

Scheme 93

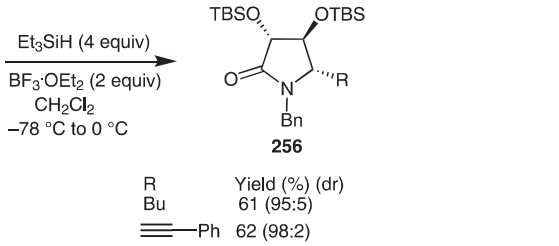




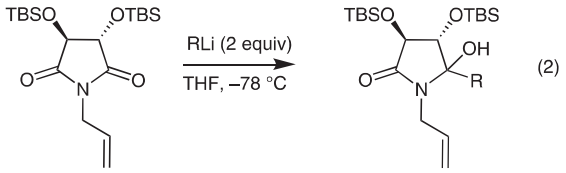
Scheme 94



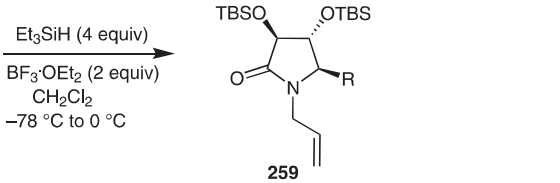
(1)



R	Yield (%) (dr)
Bu	61 (95:5)
≡—Ph	62 (98:2)

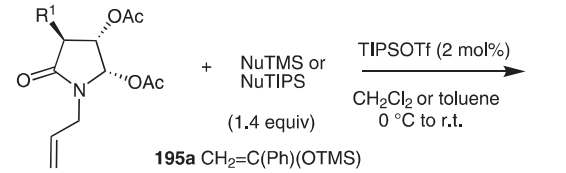


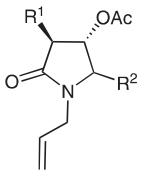
(2)



R	Yield (%) (dr)
Bu	60 (90:10)
≡—Ph	66 (98:2)
≡—TMS	50 (98:2)
≡—CH_2OTBS	52 (98:2)

Scheme 95

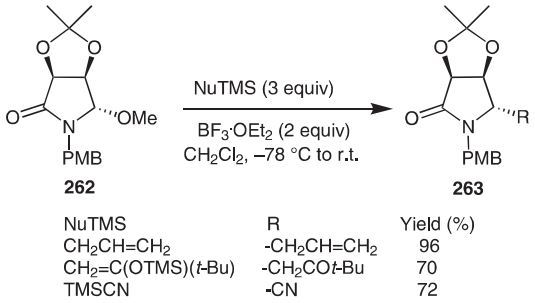




	R^1	R^2	Yield (%) (*trans*/*cis*)
261a	H	-H_2COC(C≡CH)	50 (85:15)
261b	OAc	-H_2C=COPh	73 (27:73)
261c	OAc	-H_2COC(C≡CH)	55 (50:50)

Scheme 96

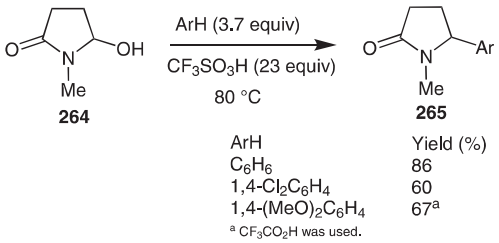
The boron trifluoride–diethyl ether complex promoted reaction of acetonide **262** with allyltrimethylsilane or the trimethylsilyl enol ether of pinacolone provided the corresponding products **263** in 96% and 70% yields, as the single isomers, whereas the reaction of **262** with trimethylsilyl cyanide gave product **263** as a mixture of diastereomers [(2*S*,3*S*,4*S*)/(2*R*,3*S*,4*S*) = 80:20] in 72% yield (Scheme 97).[74]



Scheme 97

3.2.1.2 Aromatic Nucleophiles

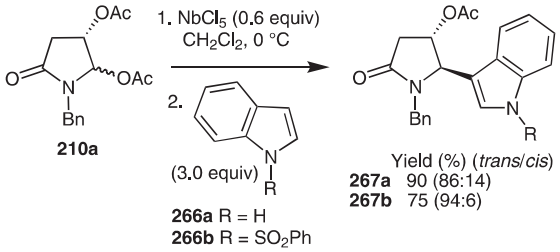
The reaction of benzene and its derivatives with the 5-hydroxypyrrolidinone **264** in the presence of trifluoromethanesulfonic acid or trifluoroacetic acid provided 5-arylpyrrolidinones **265** (Scheme 98). The reaction of benzene with **264** in the presence of trifluoromethanesulfonic acid gave **265** in 86% yield, while the less nucleophilic 1,4-dichlorobenzene gave **265** in 60% yield. 1,4-Dichlorobenzene did not react under trifluoroacetic acid catalysis; however, the more nucleophilic 1,4-dimethoxybenzene gave **265** in 67% yield.[36]



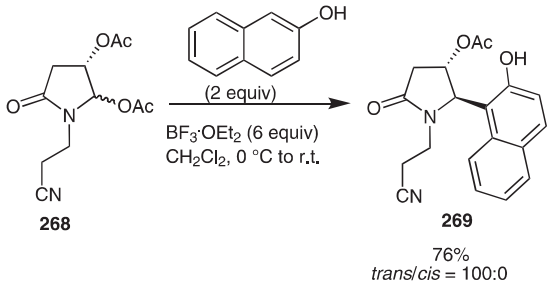
Scheme 98

Indole compounds **266a**,**b** reacted with 4,5-diacetoxypyrrolidinone **210a** in the presence of niobium(V) chloride to give *trans* adducts **267a**,**b** (Scheme 99). From **266a**, a 90% yield of **267a** (*trans*/*cis* = 86:14) was obtained, while **266b** afforded **267b** in 75% yield with a higher selectivity, *trans*/*cis* = 94:6.[61]

A boron trifluoride–diethyl ether complex mediated addition of 2-naphthol to 4,5-diacetoxypyrrolidinone **268** gave exclusively the *trans* arylated product **269** in 76% yield (Scheme 100).[75]



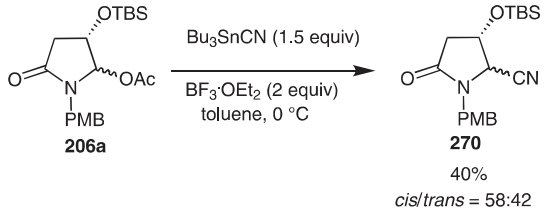
Scheme 99



Scheme 100

3.2.1.3 Organostannanes

5-Acetoxypyrrolidinone **206a** was subjected to cyanation reaction conditions with tributyltin cyanide under boron trifluoride–diethyl ether complex catalysis, and afforded the 5-cyanopyrrolidinone **270** in 40% yield and with low 4,5-*cis* diastereoselectivity (*cis*/*trans* = 58:42) (Scheme 101).[59]

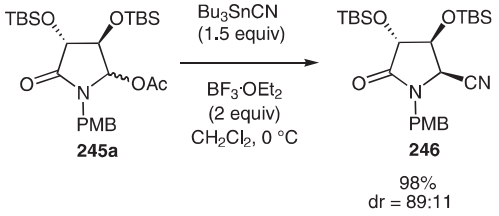


Scheme 101

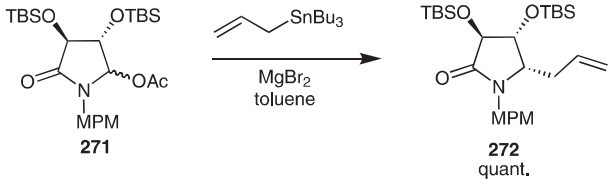
High 4,5-*cis* diastereoselectivity was obtained from the cyanation reaction of the 5-acetoxypyrrolidinone **245a** with tributyltin cyanide in the presence of boron trifluoride–diethyl ether complex. The use of dichloromethane or toluene as a solvent gave product **246** in 98% and 94% yields and with a *cis*/*trans* ratio of 89:11 and 90:10, respectively (Scheme 102).[71]

Treatment of the 5-acetoxypyrrolidinone **271** with allyltributylstannane in the presence of magnesium bromide yielded exclusively the 4,5-*cis* product **272**, and in quantitative yield (Scheme 103).[76]

Pyrrolidinones **214a**,**b** reacted with allylstannanes in the presence of Lewis acids to give the 5-allylated products **273a**,**b** (Scheme 104, equation 1). In the reaction of **214a**, titanium(IV) chloride gave the product **273a** with a *cis*/*trans* ratio of 67:33, boron trifluoride–diethyl ether com-

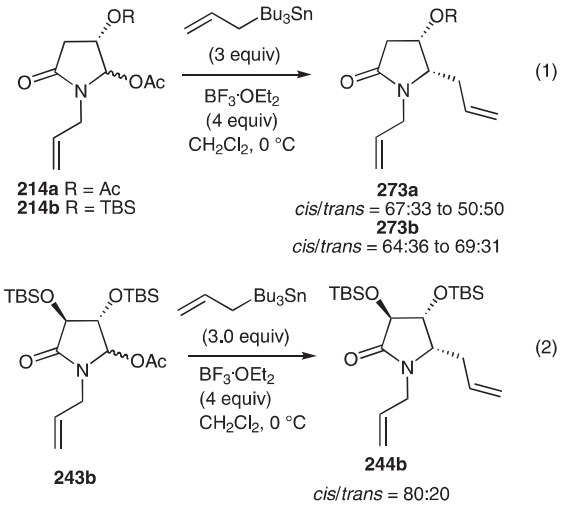


Scheme 102



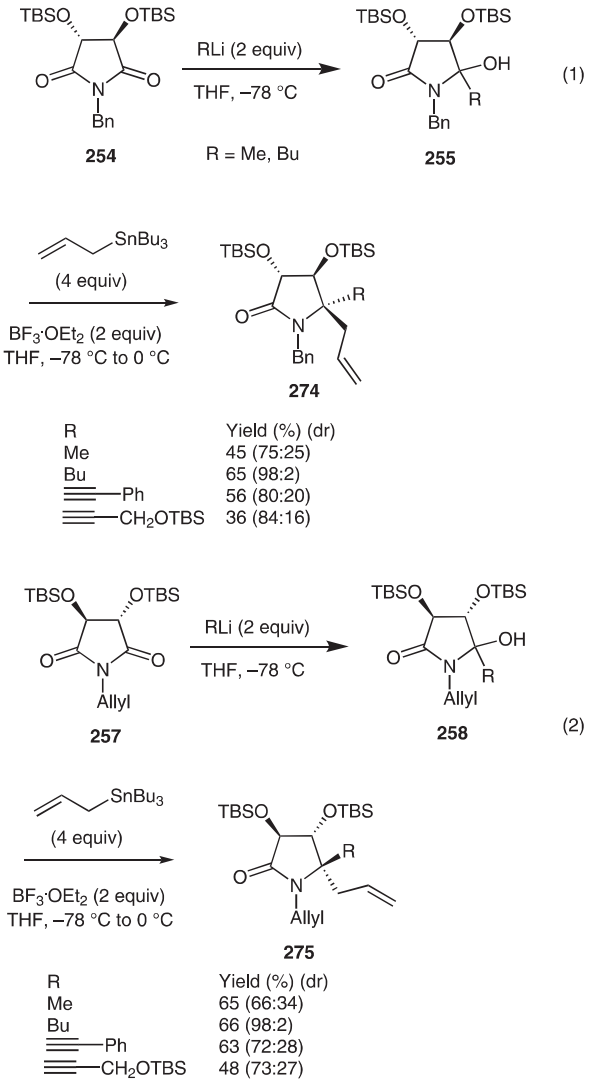
Scheme 103

plex gave a *cis*/*trans* ratio of 64:36 and titanium(IV) fluoride gave no selectivity (*cis*/*trans* = 50:50). In the reaction of pyrrolidinone **214b**, boron trifluoride–diethyl ether complex and magnesium bromide each gave a 69:31 mixture of isomers, favouring the *cis* isomer, while titanium(IV) chloride gave a 64:36 mixture of *cis*/*trans* isomers. The reaction of pyrrolidinone **243b** with allyltributyltin in the presence of boron trifluoride–diethyl ether complex provided the 5-allylated product **244b** as a mixture of isomers (*cis*/*trans* = 80:20) (Scheme 104, equation 2).[70]



Scheme 104

5-Hydroxypyrrolidinones **255**, obtained from the reaction of organolithium reagents with imides **254**, reacted with allyltributyltin in the presence of boron trifluoride–diethyl ether complex to afford 5-allyl-5-alkylpyrrolidinones **274**. The reaction of the 5-butyl-substituted pyrrolidinone with allyltributylstannane provided **274** in the highest yield (65%, dr = 98:2) (Scheme 105, equation 1). The *N*-allyl analogue, pyrrolidinone **257**, underwent addition reactions under the same conditions to afford products **275** in yields of 48–66% (Scheme 105, equation 2).[73]

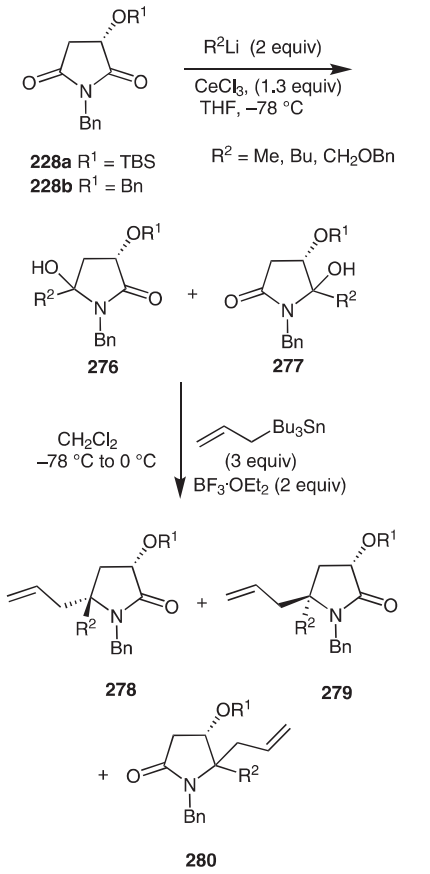


Scheme 105

The addition of organolithium compounds to imides **228a**,**b** gave a mixture of the regioisomers **276** and **277**. These isomers were subjected to allylation reactions with allyltributyltin in the presence of boron trifluoride–diethyl ether complex to give 5-alkyl-5-allylpyrrolidinones **278**, **279** and **280**, respectively. The reaction of pyrrolidinone **228a** with methyllithium and then allyltributyltin gave a mixture of **278**, **279** and **280** [(**278**+**279**)/**280** = 73:27] in 53% yield. Treatment of **228b** with butyllithium and then allyltributyltin gave only products **278** and **279** (**278**/**279** = 88:12) in 55% yield (Scheme 106).[68]

3.2.1.4 Organometallic Reagents

Zinc alkynylides, generated in situ, reacted with 5-methoxypyrrolidinone **281** in the presence of zinc triflate to afford the corresponding propargylic adducts **282** (Scheme 107).[52]

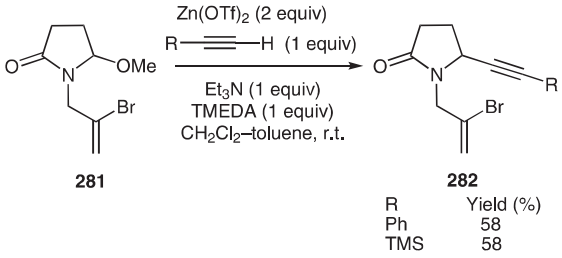


228a R^1 = TBS
228b R^1 = Bn

276 **277** **278** **279** **280**

R^1	R^2	Yield (%)	**278**/**279**	(**278**+**279**)/**280**
TBS	Me	53	70:30	60:40
Bn	Bu	55	88:12	100:0
Bn	CH_2OBn	64	98:2	67:33

Scheme 106



281 **282**

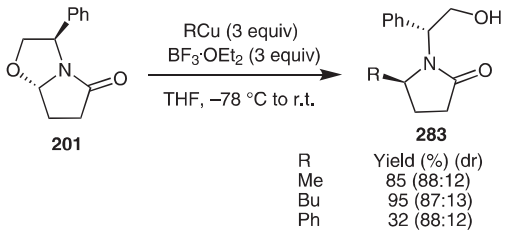
R	Yield (%)
Ph	58
TMS	58

Scheme 107

The reactions of organocopper reagents with pyrrolidinone **201** gave products **283** with good diastereoselectivities (dr = 87:13 to 88:12). Methyl and butyl cuprates gave **283** in 85% and 95% yields, respectively, while phenyl cuprate gave **283** in only 32% yield but also good diastereoselectivity (dr = 88:12) (Scheme 108).[56]

Treatment of the pyrrolidinone **284** with vinylmagnesium bromide in the presence of zinc chloride yielded the product **285** in 65% yield and with a *trans*/*cis* ratio of 80:20 (Scheme 109).[77]

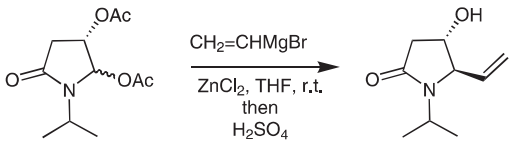
The zinc chloride–diethyl ether complex promoted reaction of pyrrolidinone **286** with Grignard reagents led to



201 **283**

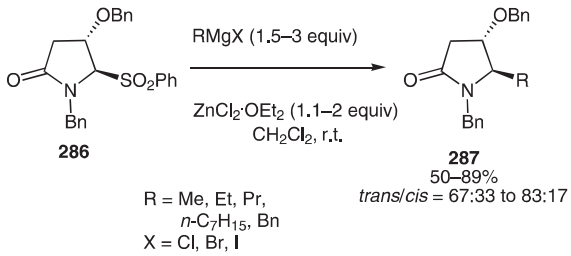
R	Yield (%) (dr)
Me	85 (88:12)
Bu	95 (87:13)
Ph	32 (88:12)

Scheme 108



284 **285**
65%
trans/*cis* = 80:20

Scheme 109



286 **287**
50–89%
trans/*cis* = 67:33 to 83:17

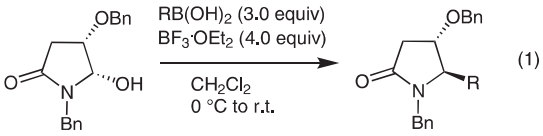
R = Me, Et, Pr, *n*-C_7H_{15}, Bn
X = Cl, Br, I

Scheme 110

the formation of products **287** in yields of 50–89%, with 4,5-*trans* selectivity (Scheme 110).[78]

Treatment of 4-benzyloxy-5-hydroxypyrrolidinone **288** with boronic acids in the presence of boron trifluoride–diethyl ether complex afforded the corresponding *trans*-4,5-disubstituted pyrrolidinones **289**. The use of 2-furanboronic acid, 2-benzofuranboronic acid, styrylboronic acid, and potassium *trans*-styryltrifluoroborate all resulted in good to high *trans* selectivity. Phenylboronic acid did not react with the pyrrolidinone, but its electron-rich derivatives 4-methoxyphenylboronic acid and 3,4-dimethoxyphenylboronic acid provided 5-arylated pyrrolidinones in 48% and 74% yields (Scheme 111, equation 1). Reaction of **290**, the 4-hydroxy analogue of pyrrolidinone **288**, with 2-furanboronic acid and 3,4-dimethoxyphenylboronic acid gave 4,5-*trans* pyrrolidinones **291** in 65% (dr = 77:23) and 72% (dr = 72:28) yields, respectively. The use of 2-benzofuranboronic acid gave the 4,5-*cis* product in 56% yield and with a diastereomeric ratio of 92:8 (Scheme 111, equation 2).[64a]

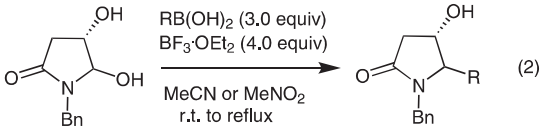
The reaction of pyrrolidinones **210a**,**b** and **292** with phenylacetylenetrifluoroborate in the presence of boron trifluoride–diethyl ether complex afforded the corresponding products **293** in 69–89% yield, with very high 4,5-*trans* selectivity (*trans*/*cis* = 90:10) (Scheme 112).[64b]



288 **289**

R =	Yield (%) (*trans*/*cis*)
(*E*)-PhCH=CH	47 (91:9)
(*E*)-PhCH=CH[a]	59 (92:8)
2-furyl	79 (71:29)
2-benzofuranyl	55 (89:11)
2-thienyl	72 (38:62)
4-$MeOC_6H_4$	48 (72:28)
3,4-$(MeO)_2C_6H_3$	74 (74:26)

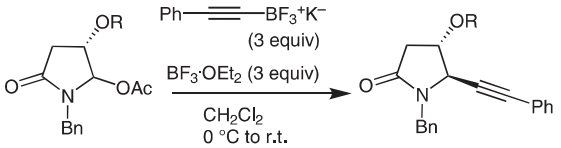
[a] The corresponding RBF_3K was used.



290 **291**

R =	Yield (%) (*trans*/*cis*)
(*E*)-PhCH=CH	20 (9:91)
2-furyl	65 (77:23)
2-benzofuranyl	56 (8:92)
3,4-$(MeO)_2C_6H_3$	44 (72:28)

Scheme 111

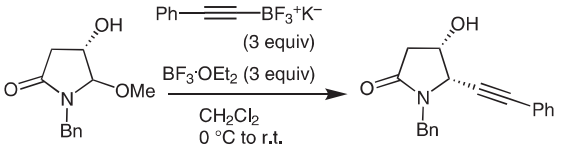


210a R = Ac
210b R = TBS
292 R = Bn

293

R	Yield (%) (*trans*/*cis*)
Ac	69 (90:10)
TBS	70 (100:0)
Bn	89 (100:0)

Scheme 112



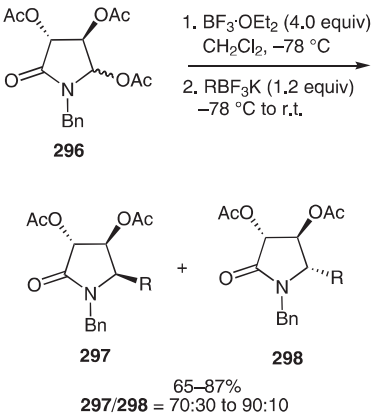
294 **295**

70%

Scheme 113

The reaction of **294** with phenylacetylenetrifluoroborate under boron trifluoride–diethyl ether complex catalysis yielded the 4,5-*cis* adduct **295** exclusively in 70% yield (Scheme 113).[64b]

In a similar study, 5-acetoxy-2-pyrrolidinone **296** reacted with potassium organotrifluoroborates under boron trifluoride–diethyl ether complex catalysis to afford the corresponding products **297** and **298** with good 4,5-*syn* diastereoselectivity and in yields of 65–87% (Scheme 114).[79]



296

297 **298**

65–87%
297/**298** = 70:30 to 90:10

R = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 3,5-$(CF_3)_2C_6H_3$, 2-MeC_6H_4, 3-thienyl, PhC≡C, *n*-BuC≡C, $MeOCH_2C{\equiv}C$

Scheme 114

3.2.1.5 Active Methylene Compounds

The reaction of 4-*tert*-butyldimethylsilyloxy-5-methoxypyrrolidinone **208** with titanium enolates derived from the active methylene compounds **299a–d** gave 4,5-disubstituted pyrrolidinones **300a–d**. Except for the reaction of the enolate derived from **299b** with **208**, high 4,5-*trans* selectivity was observed in these reactions (Scheme 115).[60]

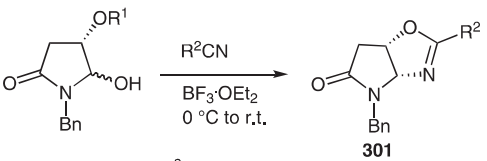
208 **300a–d**

	Yield (%) (*trans*/*cis*)
a $R^1 = R^2 = CO_2Et$	74 (90:10)
b R^1 = COMe, $R^2 = CO_2Me$	59 (9:91)
c R^1 = CN, $R^2 = CO_2Me$	43 (92:8)
d $R^1 = SO_2Ph$, $R^2 = CO_2Me$	50 (95:5)

Scheme 115

3.2.1.6 Nitrile Nucleophiles (Ritter Reaction)

Treatment of pyrrolidinones **288** and **290** with nitriles in the presence of boron trifluoride–diethyl ether complex afforded the pyrrolo[2,3-*d*]oxazoles **301** in yields of 80–93% (Scheme 116).[80]



288 R^1 = Bn
290 R^1 = H

301

R^2 = Me, *i*-Pr, Ph, 3,4-$(MeO)_2C_6H_3$ 80–93%

Scheme 116

This review continues with the chemistry of *N*-acyliminium ions derived from other five-membered heterocyclic and higher systems in the next issue of *Synthesis*.[1]

Acknowledgment

We thank the Australian Research Council for supporting our research in this area.

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APPENDIX 2: INTERMOLECULAR ADDITION REACTIONS OF *N*-ACYLIMINIUM IONS (PART 2)

Intermolecular Addition Reactions of *N*-Acyliminium Ions (Part II)[1]

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Abstract: This review highlights the advances in the literature up to July 2008 on the intermolecular reactions of acyclic and cyclic *N*-acyliminium ions. This is an update of an earlier review in 2000 on this topic and does not include intramolecular addition reactions to *N*-acyliminium ions which was recently reviewed. This review is presented in two parts, with the first part having dealt with acyclic and pyrrolidinone-based *N*-acyliminium ions. Part II continues with other five-membered heterocyclic derivatives and higher systems.

Key words: *N*-acyliminium ion, nucleophilic addition, cycloaddition, aromatic electrophilic substitution, radical addition, peptides, pyrrolidines, piperidines

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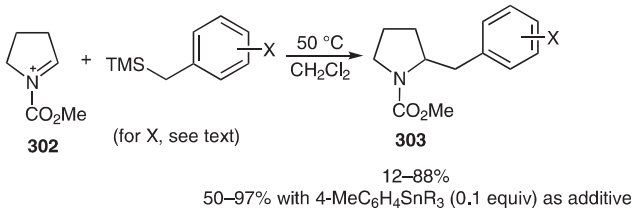
3.2.2 Reactions of *N*-Acylpyrrolidine-Based *N*-Acyliminium Ions with Nucleophiles

3.2.2.1 Silicon-Based Nucleophiles

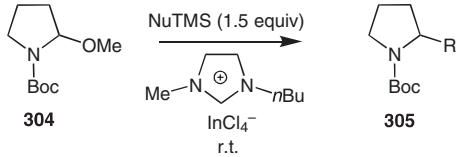
Treatment of the *N*-acyliminium ion **302** with benzyltrimethylsilanes afforded 2-benzylated pyrrolidines **303**. 4-Fluorobenzyl-, benzyl-, and 2-methylbenzyltrimethylsilane did not react with the *N*-acyliminium ion. Reactions of 3,5-dimethylbenzyl-, 4-methylbenzyl-, 2,4,6-trimethylbenzyl-, 4-methoxybenzyl-, and 2,3,4,5,6-pentamethylbenzyltrimethylsilanes gave the corresponding products in 12–88% yields. Use of 4-methylbenzylstannanes (0.1 equiv), as an additive in the reactions of 4-fluorobenzyltrimethylsilane and 4-methylbenzyltrimethylsilane, resulted in 50% and 97% yields of **303**, respectively (Scheme 117).[50]

The reaction of *N*-Boc-2-methoxypyrrolidine (**304**) with silicon nucleophiles in an ionic liquid, BMI·$InCl_4$, led to the formation of 2-substituted pyrrolidines **305** in yields of 76–80% (Scheme 118).[81]

Treatment of pyrrolidinone **304** with similar silicon nucleophiles in the presence of indium(III) chloride under solvent-free conditions afforded the corresponding prod-

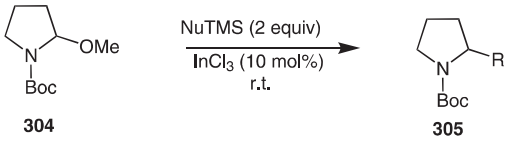


Scheme 117



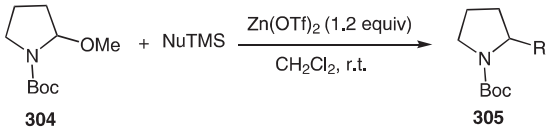
NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	80
CH_2=C(OTMS)(Ph)	-CH_2COPh	77
MeCH=C(OTMS)(Ph)	-CH(Me)COPh	76
Me_2C=C(OTMS)(OMe)	-$C(Me)_2CO_2Me$	77

Scheme 118



NuTMS	R	Yield (%)
MeC=C(OTMS)(Ph)	-CH(Me)COPh	97
$(Me)_2C$=C(OTMS)(OMe)	-$C(Me)_2CO_2Me$	100
BuCH=C(OTMS)(Bu)	-C(Bu)COBu	93
CH_2=C(OTMS)(Ph)	-CH_2COPh	92

Scheme 119



NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$,	-CH_2CH=CH_2	68
CH_2=C(OTMS)(Ph),	-CH_2COPh	71
MeCH=C(OTMS)(Ph)	-CH(Me)COPh	80 dr = 80:20

Scheme 120

ucts **305** in 92–100% yields (Scheme 119).[82a] The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.[82b]

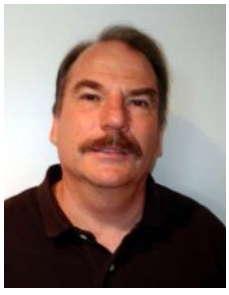
In a similar study, pyrrolidine **304** reacted with silicon nucleophiles under catalysis by zinc triflate to afford the desired adducts **305** in 68–80% yields (Scheme 120).[52]

The reactions of silicon nucleophiles with pyrrolidine **304** in the presence of bis(trifluoromethane)sulfonimide or triisopropylsilyl triflate under solvent-free conditions afforded the corresponding adducts **305** in good to excellent yields (Scheme 121). It was found that 0.3 mol% of bis(trifluoromethane)sulfonimide catalysed the reaction of allyltrimethylsilane, while the silyl enol ether of acetophenone required 1.0 mol% of catalyst. The trimethylsilyl enol ether of cyclohexanone and the triisopropylsilyl ether of methyl isobutyrate and trimethylsiloxyfuran required 5 mol% of bis(trifluoromethane)sulfonimide. The use of 1 mol% of triisopropylsilyl triflate as a Lewis acid in these reactions gave the desired adducts in the same or similar yields.[63]

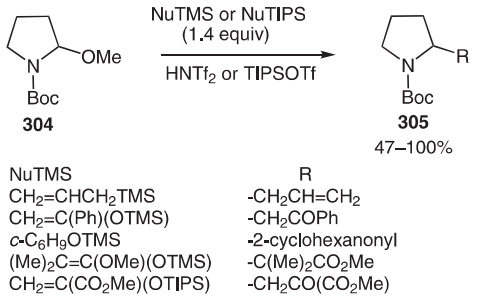
Chiral 2-methoxypyrrolidines **306a**,**b** underwent addition reactions with 2-*tert*-butyldimethylsilyloxyfuran in the presence of a catalytic amount of titanium(IV) chloride or trimethylsilyl triflate in dichloromethane at –78 °C to form only two out of four possible diastereomeric prod-

Biographical Sketches

Arife Yazici obtained her MSc degree in chemistry at Hacettepe University-Ankara (Turkey) in 2005. She is currently doing her PhD studies with Professor Stephen Pyne at the University of Wollongong. Her area of study is the total synthesis of Stemona alkaloids.

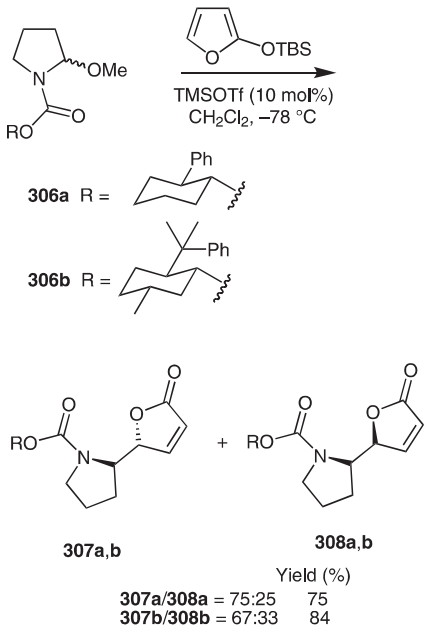


Stephen G. Pyne is a Professor of Chemistry at the University of Wollongong (UOW) and Chair of the Division of Organic Chemistry of the Royal Australian Chemical Institute. He obtained his BSc (Hons) degree at the University of Adelaide with Dr. Ralf Massey-Westrop and his PhD degree with Professor Lew Mander (Australian National University) in 1979. After post-doctoral positions with Professor Phil Fuchs (Purdue) and Professor E. J. Corey (Harvard), he was appointed a lecturer at UOW in 1985. His research interests include the total synthesis of bioactive alkaloids, natural products chemistry, drug design and synthesis, and fullerene chemistry.



Scheme 121

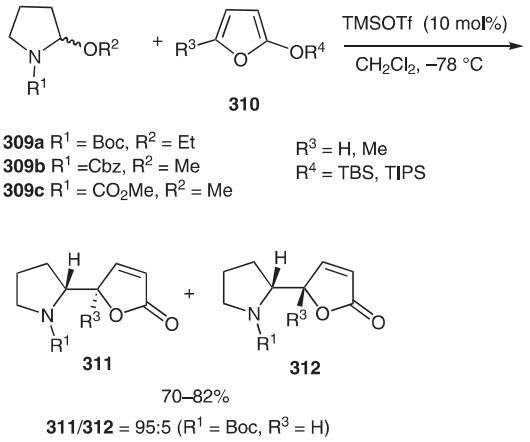
ucts, **307a**,**b** and **308a**,**b** (Scheme 122). The reactions of **306a** and **306b** with the silyloxyfuran in the presence of titanium(IV) chloride gave products in 60% and 55% yields, respectively. The use of trimethylsilyl triflate as a catalyst increased the yields to 84% and 75%, respectively. The diastereomeric ratios for **307a**/**308a** and **307b**/**308b** were found to be 75:25 and 67:33 after hydrogenation, and the stereochemistry of the major products **307** was determined as 2′*R*,5*R* by X-ray diffraction analysis.[83]



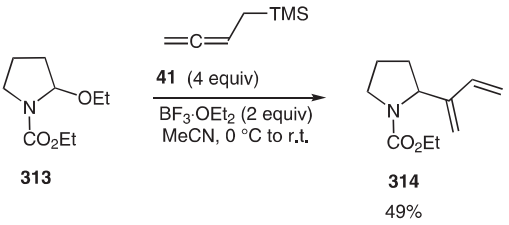
Scheme 122

Silyloxyfurans **310** reacted with 2-alkoxypyrrolidines **309** upon exposure to trimethylsilyl triflate. The *N*-Boc-protected pyrrolidine derivative **309a** gave the best yield of 82% and the highest diastereomeric ratio of 95:5 when R^3 = H (Scheme 123).[84]

The reaction of allenyltrimethylsilane with the 2-ethoxypyrrolidine **313** in the presence of boron trifluoride–diethyl ether complex provided the 2-substituted pyrrolidine **314** in 49% yield (Scheme 124). Treatment of *N*-tosyl-2-hydroxypyrrolidine under the same reaction conditions afforded the *N*-tosyl analogue of piperidine **314** in 74% yield.[30a]

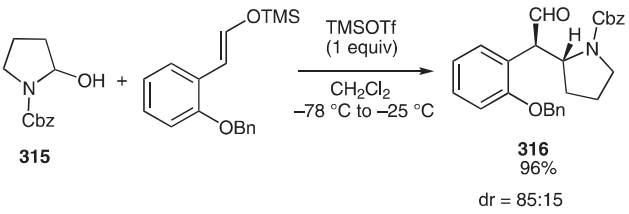


Scheme 123



Scheme 124

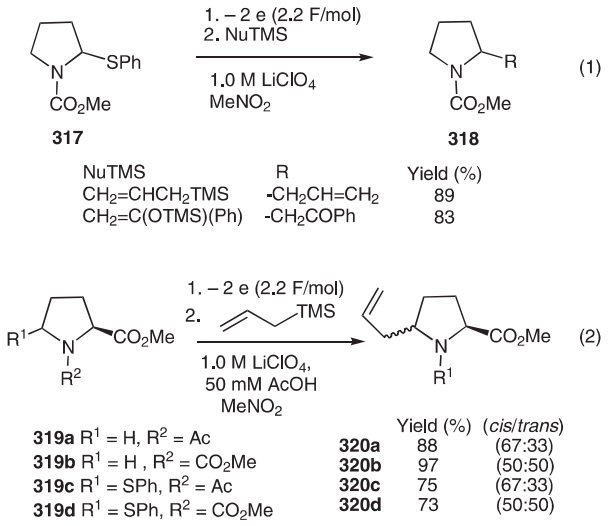
N-Carbobenzyloxy-2-hydroxypyrrolidine (**315**) reacted with a silyl enol ether in the presence of trimethylsilyl triflate (1.0 equiv) in dichloromethane to afford the 2-substituted pyrrolidine **316** in 96% yield (Scheme 125).[85]



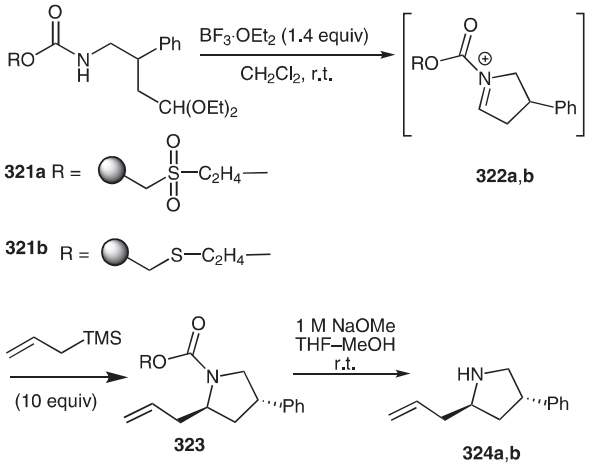
Scheme 125

The *N*-acyliminium ion which was generated by anodic oxidation of **317** was treated with silicon nucleophiles and afforded the corresponding alkylated products **318** (Scheme 126, equation 1). Similarly, the reactions of allyltrimethylsilane with the in situ generated *N*-acyliminium ion of amides and carbamates **319** under the same reaction conditions gave products **320** in 73–97% yields (Scheme 126, equation 2).[49]

Treatment of the immobilised amines **321a**,**b** with boron trifluoride–diethyl ether complex led to the formation of *N*-acyliminium ions **322a**,**b** which were trapped with allyltrimethylsilane to give the desired adducts **323** (Scheme 127). Cleavage of the adduct from the resin with 1 M sodium methoxide in tetrahydrofuran–methanol gave the *trans*-2,4-disubstituted pyrrolidines **324a**,**b** in 81% and 52% yields, respectively.[5]



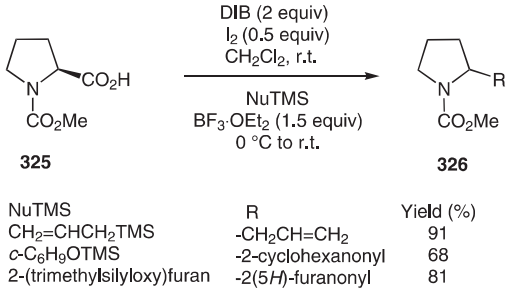
Scheme 126



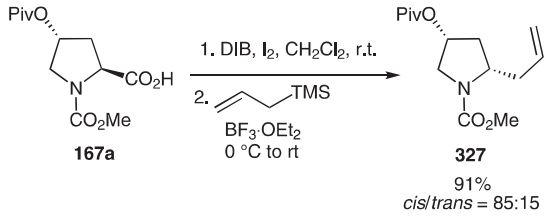
Scheme 127

Decarboxylation and oxidation of the proline derivative **325** with (diacetoxyiodo)benzene and iodine gave the corresponding *N*-acyliminium ion. The reaction of allyltrimethylsilane with the the latter under boron trifluoride–diethyl ether complex catalysis gave the 2-allylated product **326** in 91% yield (Scheme 128). The reaction did not take place in the absence of the Lewis acid: only the corresponding 2-hydroxypyrrolidine was isolated. Treatment of **325** with (trimethylsilyloxy)cyclohexene and trimethylsilyloxyfuran under the same reaction conditions gave addition products in 68% and 81% yields, respectively.[46] In a similar study, treatment of **325** with isopropenyl acetate (5.0 equiv) in the presence of boron trifluoride–diethyl ether complex afforded the expected product in 58% yield.[47]

When the one-pot decarboxylation–oxidation–alkylation methodology was applied to the 4-trimethylacetyloxy-L-proline derivative **167a**, the desired allylated product **327** was isolated in 91% yield with a *cis*/*trans* ratio of 85:15 (Scheme 129).[46,47]

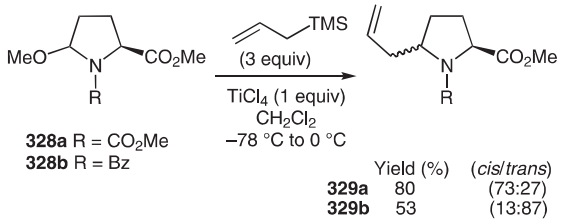


Scheme 128



Scheme 129

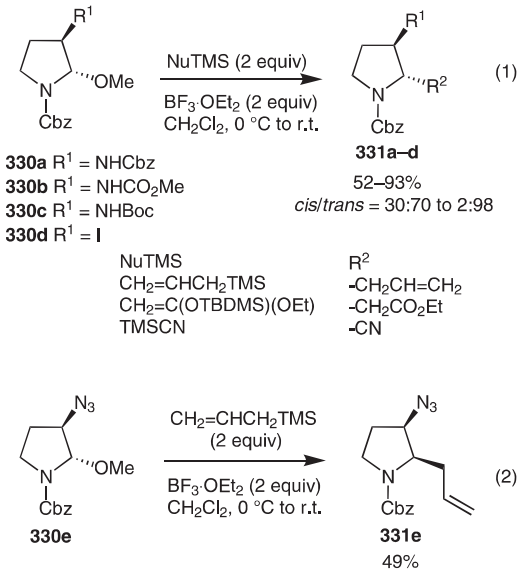
The reaction of the *N*-acylprolines **328a** and **328b** with allyltrimethylsilane in the presence of titanium(IV) chloride yielded the allylated products **329a** and **329b** in 80% and 53% yields, respectively (Scheme 130).[86]



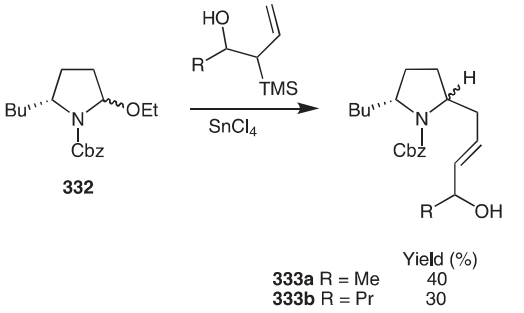
Scheme 130

The 3-substituted *N*-Cbz pyrrolidines **330a–e** reacted with allyltrimethylsilane, cyanotrimethylsilane, and *tert*-butyl[(1-ethoxyvinyl)oxy]dimethylsilane in the presence of boron trifluoride–diethyl ether complex to give products **331a–e**. 3-Carbamoyl-2-methoxypyrrolidines **330a–c** and 3-iodo-2-methoxypyrrolidine **330d** gave the adducts in moderate to excellent yields and with 2,3-*trans* selectivity (Scheme 131, equation 1), while 3-azido-2-methoxypyrrolidine **330e** gave the adduct **331e** in 49% yield and with high 2,3-*cis* selectivity (88:12) (Scheme 131, equation 2). The 2,3-*trans* selectivity in the reactions of **330a–d** was suggested to arise from neighbouring-group participation of the R^1 group (R^1 = $NHCO_2R$ or I).[87,88]

The reaction of 2-ethoxy-4-butylpyrrolidine **332** with allylsilanes afforded the corresponding adducts **333** in 30–40% yields as isomeric mixtures (Scheme 132). The diastereomeric ratios were not determined. However, when R = Me, the mixture was converted into a 80:20 mixture of indolizidines, with the major isomer having arisen from the initial 2,5-*trans* adduct.[89]

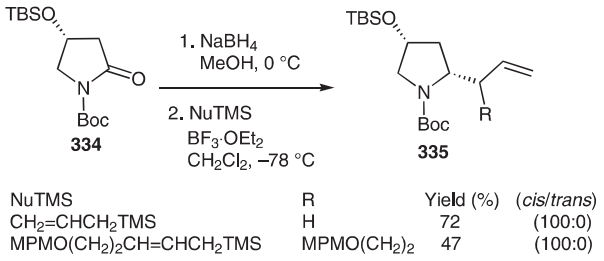


Scheme 131



Scheme 132

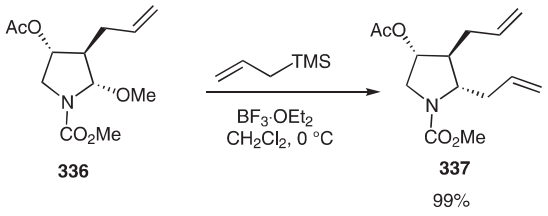
The reaction of pyrrolidine **334** with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex provided the desired adduct **335** with complete 2,4-*cis* selectivity (Scheme 133).[76]



Scheme 133

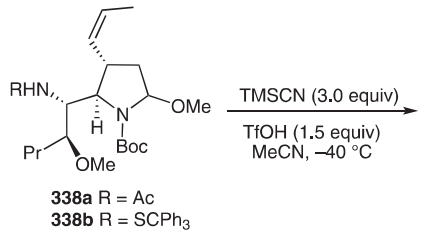
Treatment of pyrrolidine **336** with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the 2,3-*trans* product **337** in 99% yield (Scheme 134).[90]

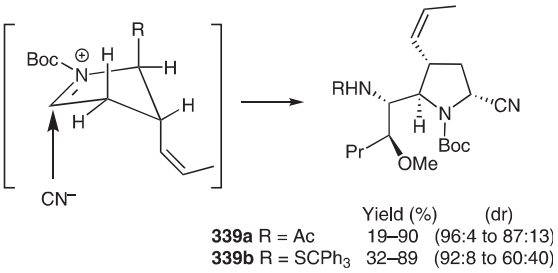
The cyano group was introduced into the *N*-Boc pyrrolidines **338a**,**b** stereoselectively (Scheme 135). The reaction of **338a** with trimethylsilyl cyanide (3.0 equiv) in the



Scheme 134

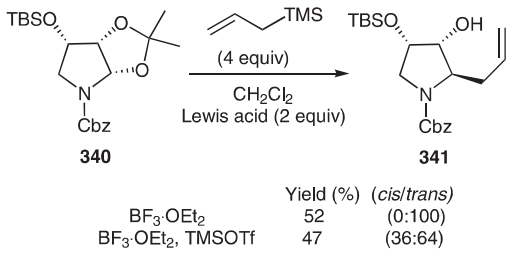
presence of trifluoromethanesulfonic acid (1.5 equiv) in acetonitrile at –40 °C resulted in the best yield (90%) and diastereomeric ratio (96:4). The use of tetrahydrofuran, toluene and dichloromethane as solvents in this reaction gave the product **339a** in poor to good yields (19–60%) with reduced diastereoselectivities (dr = 87:13 to 90:10). Using trimethylsilyl triflate as catalyst gave product **339a** in 67% yield with a diastereomeric ratio of 93:7. The reaction of **338b** with trimethylsilyl cyanide in the presence of boron trifluoride–diethyl ether complex (1.5 equiv) in dichloromethane afforded product **339b** in the highest yield (89%) and diastereomeric ratio of 92:8. The use of tin(IV) chloride and trimethylsilyl triflate as Lewis acids in toluene provided product **339b** in 32% and 68% yields and with diastereomeric ratios of 66:33 and 75:25, respectively. The high diastereoselectivity was suggested to be the result of attack of the nucleophile from the face *anti* to the C-5 substituent. This substituent was proposed to adopt a pseudo-axial orientation to minimise $A^{1,2}$ strain with the *N*-Boc group.[91]





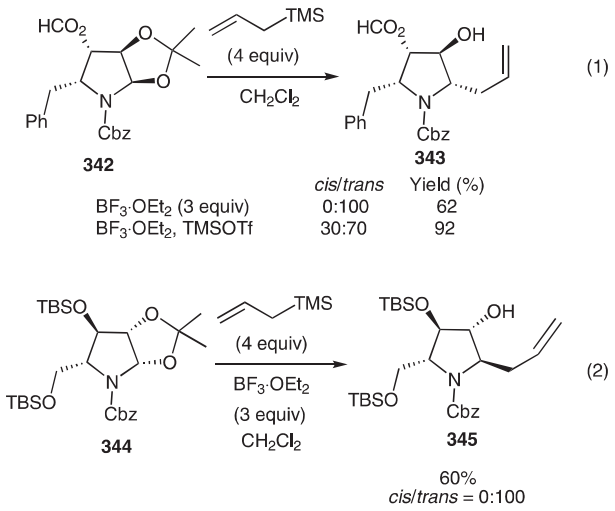
Scheme 135

The 2,3-*O*-isopropylidene-protected pyrrolidine **340** reacted with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give the 2-allylated pyrrolidine **341** in 52% yield and with complete 2,3-*trans* selectivity (*trans*/*cis* = 100:0) (Scheme 136). Magnesium bromide, tin(IV) chloride, dichlorodiisopropoxytitanium(IV), and ytterbium(III) triflate were found to be ineffective in this reaction.[92]



Scheme 136

The 5-substituted 2,3-*O*-isopropylidene-protected pyrrolidines **342** and **344** gave allylated products **343** and **345**, respectively, with exclusive 2,3-*trans* selectivity and good yields, when they were treated with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex (Scheme 137). The allyltrimethylsilane attacked from the *exo* face of the bicyclic aminal, independent of the C-4 and C-5 substituents and their configurations. The lower diastereoselectivities observed when the stronger Lewis acid mixture of boron trifluoride–diethyl ether complex and trimethylsilyl triflate was employed was thought to be due to initial cleavage of the bicyclic aminal prior to nucleophilic attack.[92]

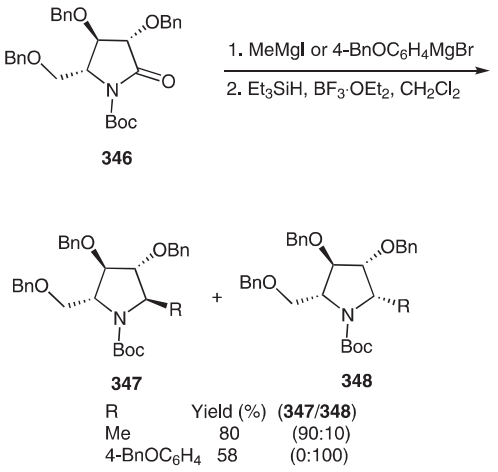


Scheme 137

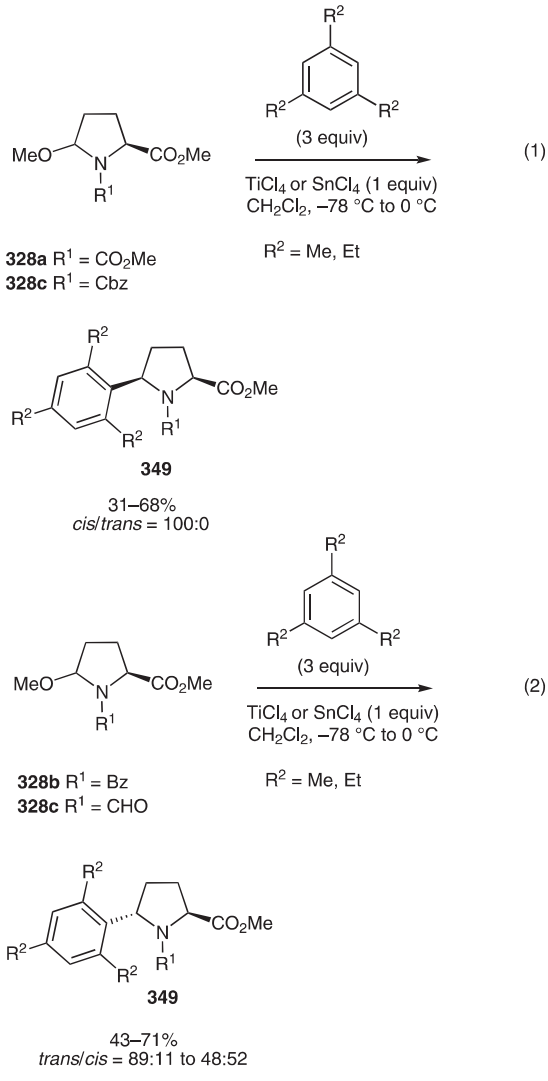
Treatment of pyrrolidinone **346** with Grignard reagents and then triethylsilane in the presence of boron trifluoride–diethyl ether complex afforded adducts **347** and **348**. This reaction sequence using methylmagnesium iodide gave adduct **347** in 80% yield and with high 3,5-*cis* selectivity, while that using of 4-benzyloxyphenylmagnesium bromide provided only the 3,5-*trans* adduct **348** in 58% yield (Scheme 138).[72]

3.2.2.2 Aromatic Nucleophiles

Treatment of benzene derivatives with the proline derivatives **328a–d** in the presence of titanium(IV) chloride or tin(IV) chloride gave the arylated adducts **349** in 31–71% yields. The prolines **328a**,**c** ($R^1 = CO_2Me$ or Cbz) gave exclusively the 2,5-*cis* products (Scheme 139, equation 1), whereas the prolines **328b**,**d** (R^1 = CHO or Bz) yielded the arylated adducts **349** as a mixture of isomers favouring the *trans* isomer (Scheme 139, equation 2).[86]



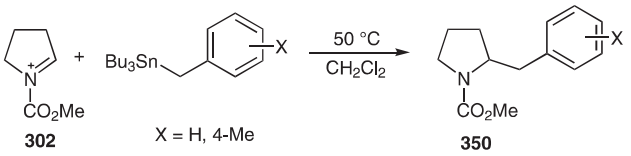
Scheme 138



Scheme 139

3.2.2.3 Organostannanes

Treatment of benzyltributylstannane and 4-methylbenzyltributylstannane with the *N*-acyliminium ion **302** provided the 2-benzylated pyrrolidines **350** in 51% and 71% yields, respectively (Scheme 140).[50]



Scheme 140

A cinnamylstannane reacted with pyrrolidines **351a–c** in the presence of boron trifluoride–diethyl ether complex to give adducts **352a–c**. While pyrrolidine **351a** gave the product **352a** in 75% yield and as a single diastereomer, **351b** and **351c** gave the products **352b** and **352c** in yields of 73% and 54%, and with a diastereomeric ratio of 70:30 and 75:25, respectively (Scheme 141, equation 1). When pyrrolidine **353** was treated under the same reaction conditions, the addition product **354** was obtained in 56% yield as a 50:50 mixture of diastereomers (Scheme 141, equation 2). In contrast to the reactions reported in Schemes 136 and 137, a ring-opened monocyclic iminium ion intermediate was proposed for the reactions of **351a–c**.[93]

3.2.2.4 Organometallic Reagents

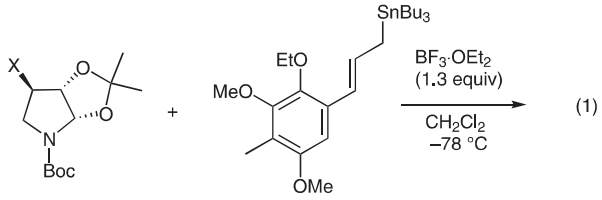
The *N*-acyliminium ion **302** underwent reactions with Grignard reagents to afford 2-substituted pyrrolidines **355** in moderate to good yields. The reaction took place with alkyl-, alkenyl-, alkynyl- and arylmagnesium halides (Scheme 142).[38]

Treatment of organozinc and organoaluminium reagents with the *N*-acyliminium ion **302** provided 2-ethylpyrrolidine **356** in 55–74% yields (Scheme 143). The use of diethylzinc, ethylzinc iodide, triethylaluminium and diethylaluminium chloride gave the ethylated product in 74%, 65%, 72%, and 55% yields, respectively.[38]

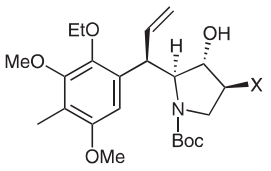
The reactions of zinc alkynylides, prepared in situ, with 2-methoxypyrrolidine **304** in the presence of zinc triflate afforded the corresponding 2-substituted products **357** (Scheme 144).[52]

Alkynes reacted with 2-methoxypyrrolidines **309b**,**c** in the presence of copper(I) bromide in water at 40–50 °C under sonication conditions to afford 2-substituted pyrrolidines **358** (Scheme 145).[94]

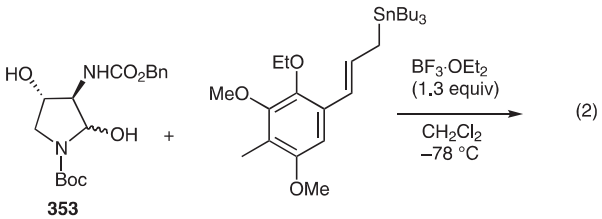
As an extension of an earlier study,[95a] the reaction of the racemic 2,3-dihydroxypyrrolidine **359** with an alkenylboronate led to the 2,3-*cis* product **360** in 99% yield and with high 2,3-*cis* selectivity (*cis*/*trans* = 98:2) (Scheme 146).[95b]

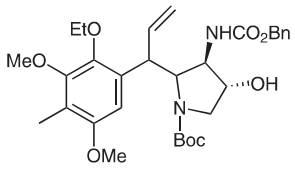


351a X = OBn
351b X = N_3
351c X = $NHCO_2Bn$

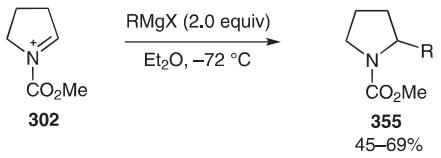


	Yield (%)	(dr)
352a	75	(100:0)
352b	73	(70:30)
352c	54	(75:25)





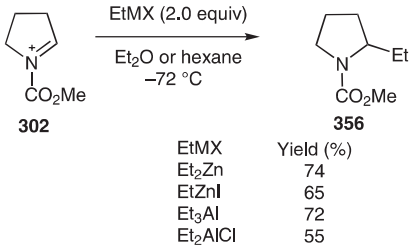
Scheme 141



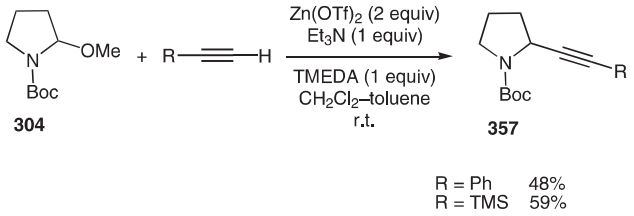
R = Et, *n*-Bu, *i*-Pr, CH_2=CH, allyl, CH_2=$CHCH_2CH_2$, 4-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$
X = Cl, Br

Scheme 142

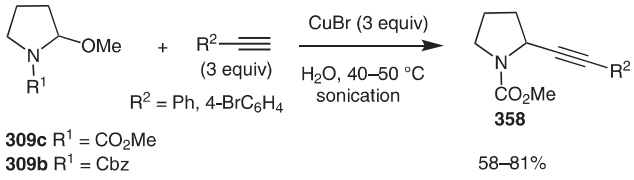
Organocopper reagents were treated with 3-substituted 2-methoxypyrrolidines **361** in the presence of boron trifluoride–diethyl ether complex to afford adducts **362** in 50–97% yields after Boc deprotection. These reactions showed 2,3-*trans* selectivity (*trans*/*cis* = 60:40 to 91:9) (Scheme 147). The *trans* selectivity increased with the use of bulky organocopper reagents.[96]



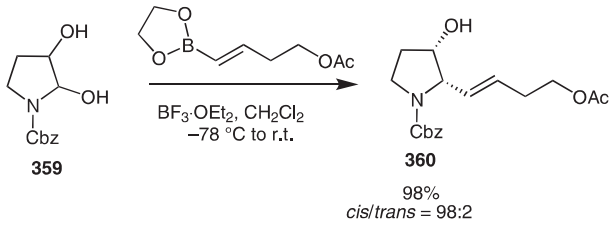
Scheme 143



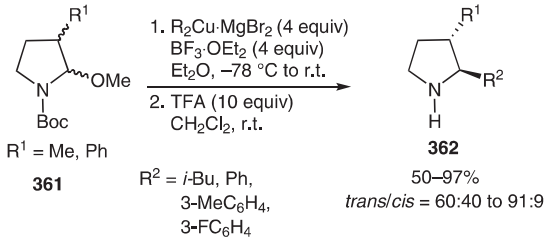
Scheme 144



Scheme 145

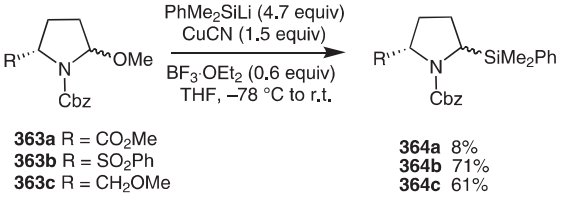


Scheme 146



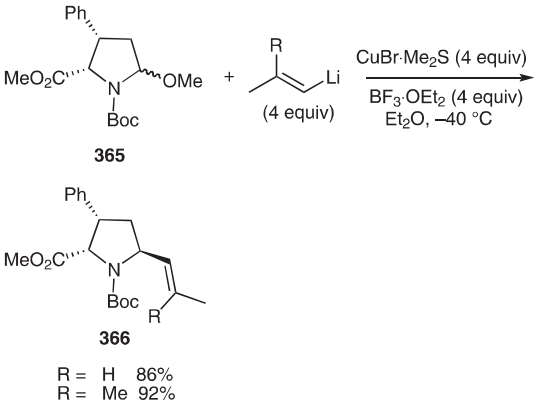
Scheme 147

The silylcuprate reagent $PhMe_2SiLi$/CuCN underwent reaction with the 5-substituted 2-methoxypyrrolidine **363a** and 2-phenylsulfonylpyrrolidine **363b** in the presence of boron trifluoride–diethyl ether complex. 2-Methoxypyrrolidine **363a** gave the desired 2,5-disubstituted adduct **364a** in 8% yield, while the 2-phenylsulfonylpyrrolidine **363b** gave adduct **364b** in 71% yield (Scheme 148). The reaction took place between 2-phenylsulfonylpyrrolidine and the silylcuprate reagent even in the absence of the Lewis acid. It was postulated that either the copper behaves as a Lewis acid to generate the *N*-acyliminium ion, or the reaction follows an S_N2 mechanism.[24]



Scheme 148

The 3,5-disubstituted *N*-Boc proline **365** reacted with 2-methylpropenyllithium and *trans*-1-lithiopropene in the presence of copper bromide–dimethylsulfide complex and boron trifluoride–diethyl ether complex to give the 2,5-*trans* products **366** (Scheme 149).[97]



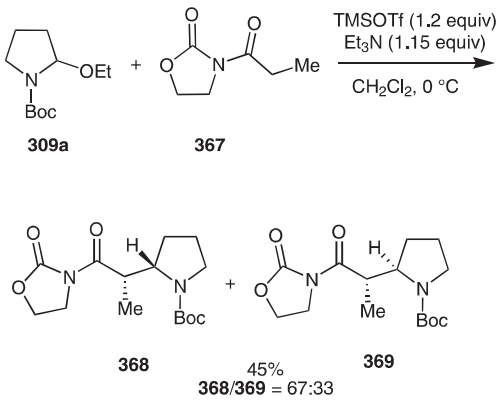
Scheme 149

3.2.2.5 Carbonyl Compounds

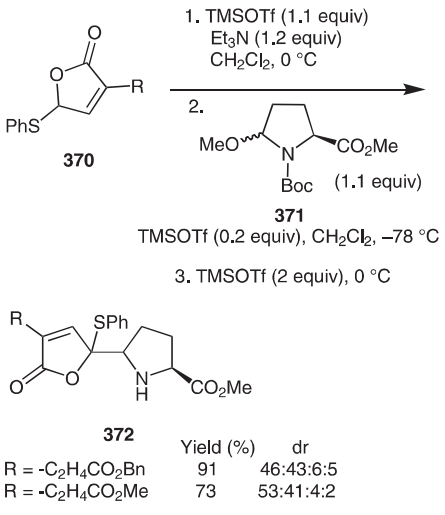
The reaction of *N*-Boc-2-ethoxypyrrolidine **309a** with the *N*,*O*-silylketene acetal, itself prepared in situ by treatment of *N*-propionyloxazolidin-2-one **367** with trimethylsilyl triflate and triethylamine, provided a 67:33 mixture of the 2-substituted pyrrolidines **368** and **369** in 45% yield (Scheme 150).[98]

The 5-methoxyproline derivative **371** reacted with trimethylsilyloxyfuran compounds, themselves generated in situ by treatment of butenolides **370** with trimethylsilyl triflate under basic conditions, in the presence of trimethylsilyl triflate at –78 °C to give a mixture of diastereomeric adducts. Addition of an excess amount of trimethylsilyl triflate to these adducts afforded deprotected pyrrolidines **372** as a mixture of four diastereomers (Scheme 151).[99]

The titanium enolates of *N*-acyloxazolidinones **373a–d** reacted with *N*-*tert*-butyloxycarbonyl-2-ethoxypyrrolidine (**309a**) to afford the corresponding 2-substituted pyrrolidines **374a–d** and **375a–d**. Treatment of pyrrolidine **309a** with **373a** and **373b** in the presence of titanium(IV)

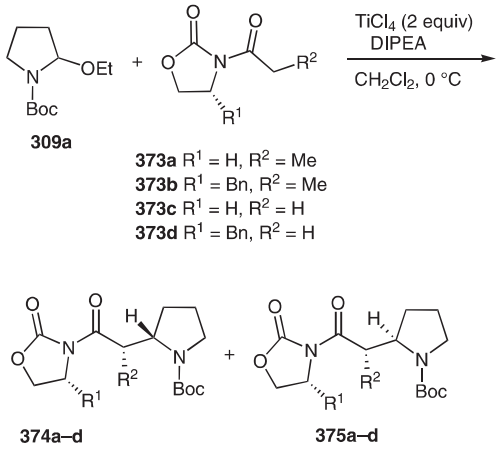


Scheme 150



	Yield (%)	dr
R = -$C_2H_4CO_2Bn$	91	46:43:6:5
R = -$C_2H_4CO_2Me$	73	53:41:4:2

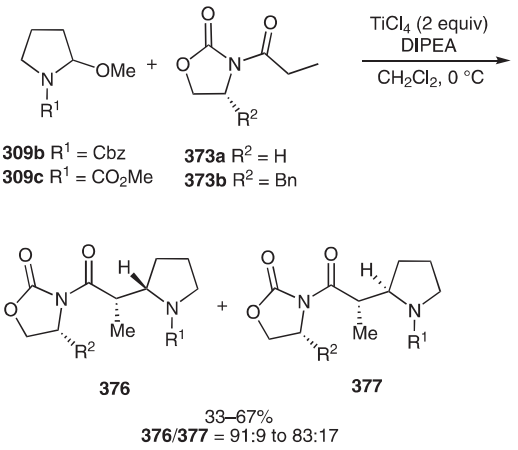
Scheme 151



Scheme 152

chloride gave the desired products with **374**/**375** ratios of 93:7 and 90:10 and in 72% and 85% yields, respectively; while treatment of **309a** with **373c** afforded only product **374c** in 46% yield. The reaction of pyrrolidine **309a** with **373d** gave the desired product in 70% yield with no selectivity (**374d**/**375d** = 50:50) (Scheme 152).[98]

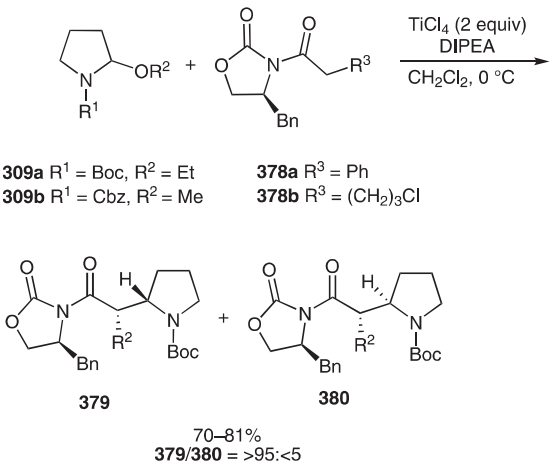
The reaction of 2-alkoxypyrrolidine **309b** with *N*-acyloxazolidinones **373a** and **373b** in the presence of titanium(IV) chloride provided the corresponding products in 67% and 57% yields, and with product ratios (**376**/**377**) of 91:9 and 83:17, respectively. Treatment of **309c** with **373a** and **373b** under the same reaction conditions resulted in 33% and 50% yields, respectively and with product ratios (**376**/**377**) of 91:9 and 86:14, respectively (Scheme 153).[98]



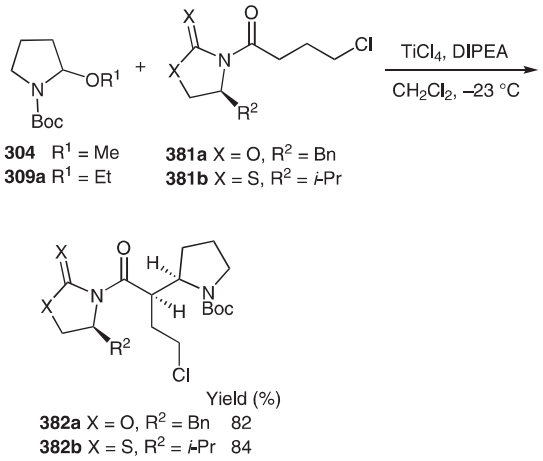
Scheme 153

The titanium enolates of **378a** and **378b** reacted with 2-alkoxypyrrolidines **309a** and **309b** to afford the *N*-Boc- and *N*-Cbz-2-substituted pyrrolidines **379** and **380**. The reactions of **309a** with **378a** and **378b** in the presence of titanium(IV) chloride and diisopropylethylamine gave products **379** and **380** with high selectivity >95:<5 in yields of 70% and 81%, respectively. Treatment of **309b** with **378b** under the same experimental conditions afforded **379** and **380** in 73% yield, with the same selectivity (Scheme 154).[98]

The 2-alkoxypyrrolidines **304** and **309a**, when treated with the titanium enolate of *N*-acyloxazolidinone **381a** (X = O) or its thio analogue **381b** (X = S), respectively,



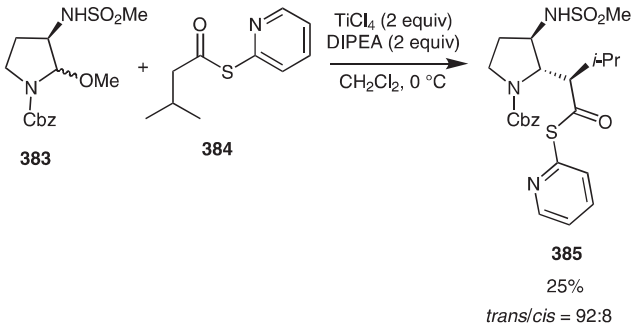
Scheme 154



Scheme 155

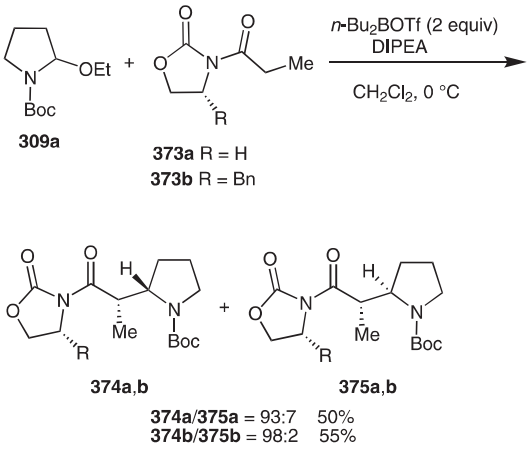
gave the addition products **382a**,**b** as single isomers in 82–84% yields (Scheme 155).[100]

The titanium enolate of 2-pyridylthio ester **384** was treated with 2-methoxypyrrolidine **383** in the presence of titanium(IV) chloride to give the 2,3-*trans* product **385** in 25% yield and with a diastereomeric ratio of 92:8 (Scheme 156).[101]



Scheme 156

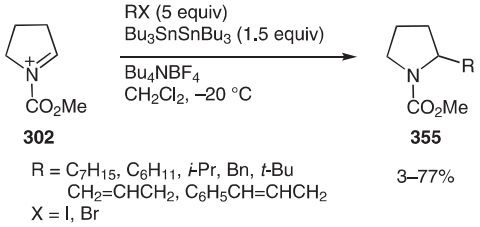
The boron enolates of the oxazolidin-2-ones **373a**,**b** were treated with *N*-*tert*-butyloxycarbonyl-2-ethoxypyrrolidine (**309a**) in the presence of dibutylboryl triflate (2.0 equiv) to afford the corresponding *N*-Boc-2-substituted pyrrolidines **374a**,**b** and **375a**,**b**. The reaction using **373a** gave a mixture of **374a** and **375a** (dr = 93:7) in 50% yield, while the reaction with **373b** under the same reaction conditions provided products **374b/375b** in 55% yield (dr = 98:2) (Scheme 157).[98]



Scheme 157

3.2.2.6 Alkyl Radicals

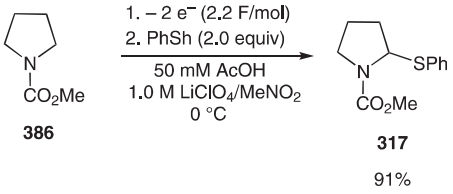
The *N*-acyliminium ion **302** reacted with alkyl halides in the presence of hexabutyldistannane to give the 2-substituted pyrrolidine adducts **355** (Scheme 158).[41,42]



Scheme 158

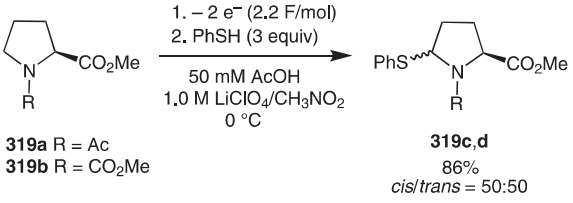
3.2.2.7 Thiols

Anodic oxidation of pyrrolidine **386** in a 1 M lithium perchlorate/nitromethane electrolytic solution in the presence of 50 mM acetic acid gave an intermediate *N*-acyliminium ion, which was trapped with thiophenol to afford the 2-phenylsulfanyl pyrrolidine **317** in 91% yield (Scheme 159).[49]



Scheme 159

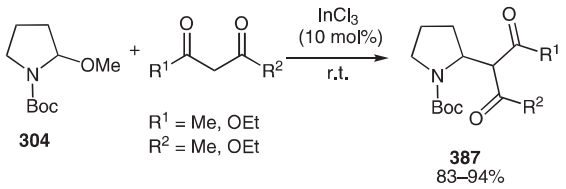
Treatment of amide or carbamate proline derivatives **319a** and **319b** with thiophenol under the same electrolytic oxidative conditions gave adducts **319c**,**d** in 86% yield as a 50:50 mixture of diastereomers (Scheme 160).[49]



Scheme 160

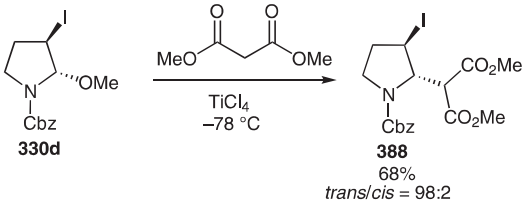
3.2.2.8 Active Methylene Compounds

1,3-Dicarbonyl compounds were treated with α-methoxypyrrolidine **304** in the presence of indium(III) chloride under solvent-free conditions to afford the 2-substituted pyrrolidines **387** (Scheme 161). Use of ethyl acetylacetonate (R^1 = Me, R^2 = OEt), acetylacetonate (R^1 = R^2 = Me) and diethyl malonate (R^1 = R^2 = OEt) gave products in 92%, 94%, and 83% yields, respectively.[82a] The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.[82b]



Scheme 161

The reaction of 3-iodo-2-methoxypyrrolidine **330d** with dimethyl malonate in the presence of titanium(IV) chloride afforded product **388** in 68% yield and high selectivity (*trans*/*cis* = 98:2) (Scheme 162).[87]

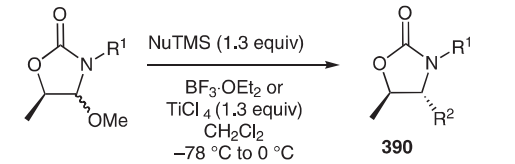


Scheme 162

3.2.3 Reactions of Oxazolidinone-Based *N*-Acyliminium Ions with Nucleophiles

3.2.3.1 Silicon-Based Nucleophiles

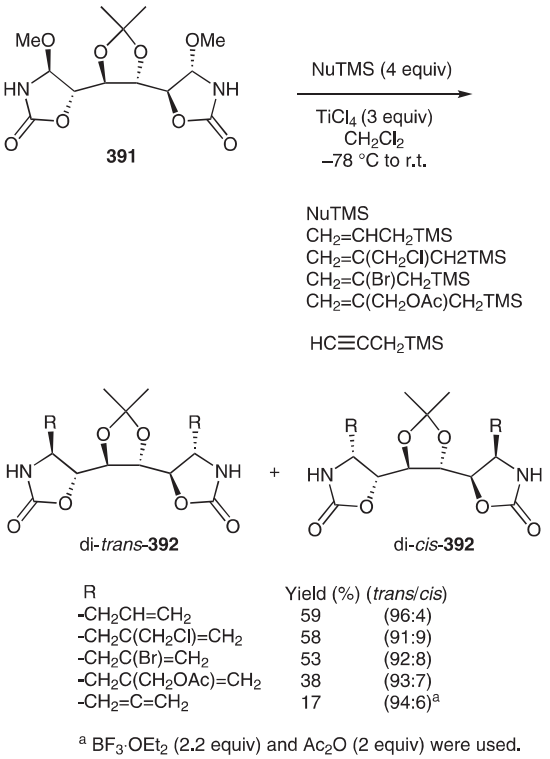
Treatment of the chiral oxazolidinones **389** with allyltrimethylsilane and 2-bromoallyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex or titanium(IV) chloride afforded 4,5-*trans* products **390** with very high selectivity (*trans*/*cis* = 87:13 to 98:2) in 85–92% yields (Scheme 163).[102]



NuTMS	R^2
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2
CH_2=$CBrCH_2TMS$	-CH_2CBr=CH_2

Scheme 163

The reaction of bisoxazolidinone **391** with silicon nucleophiles in the presence of titanium(IV) chloride gave disubstituted products **392** in yields of 17–59%, in favour of the di-*trans* products (Scheme 164).[103]



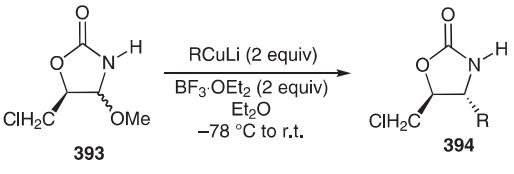
R	Yield (%)	(*trans*/*cis*)
-CH_2CH=CH_2	59	(96:4)
-$CH_2C(CH_2Cl)$=CH_2	58	(91:9)
-$CH_2C(Br)$=CH_2	53	(92:8)
-$CH_2C(CH_2OAc)$=CH_2	38	(93:7)
-CH_2=C=CH_2	17	(94:6)[a]

[a] BF_3·OEt_2 (2.2 equiv) and Ac_2O (2 equiv) were used.

Scheme 164

3.2.3.2 Organometallic Reagents

Treatment of oxazolidinone **393** with organocopper reagents in the presence of boron trifluoride–diethyl ether complex led to the formation of products **394** in 52–62% yields and good 4,5-*trans* diastereoselectivities (Scheme 165).[102]



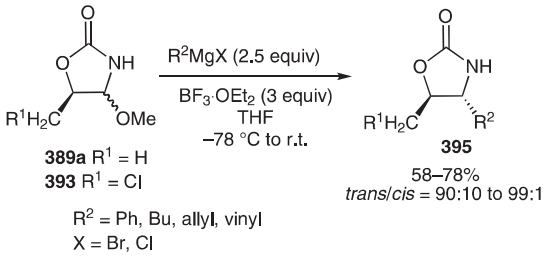
R	Yield (%)	(*trans*/*cis*)
Ph	62	(96:4)
Bu	59	(98:2)
Bu	52	(94:6)[a]

[a] *n*-BuCu/BF_3 was used.

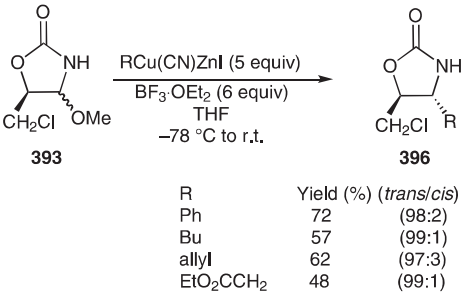
Scheme 165

The boron trifluoride–diethyl ether complex catalysed reaction of oxazolidinones **389a** and **393** with Grignard reagents provided products **395** in 58–78% yields with very high 4,5-*trans* selectivity (Scheme 166).[102]

Oxazolidinone **393** was treated with organocopper–zinc reagents in the presence of boron trifluoride–diethyl ether



Scheme 166



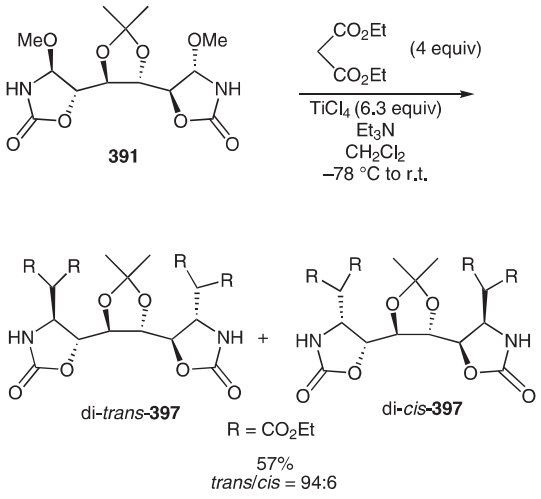
R	Yield (%)	(*trans*/*cis*)
Ph	72	(98:2)
Bu	57	(99:1)
allyl	62	(97:3)
EtO_2CCH_2	48	(99:1)

Scheme 167

complex to give the 4,5-*trans* products **396** in 48–72% yields (Scheme 167).[102]

3.2.3.3 Active Methylene Compounds

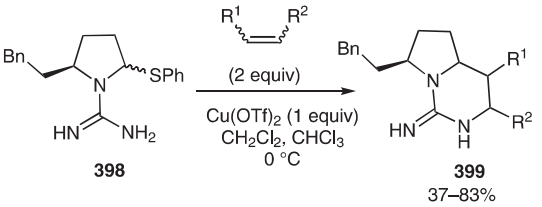
Bisoxazolidinone **391** reacted with a titanium enolate, prepared in situ from the treatment of diethyl malonate with titanium(IV) chloride in the presence of triethylamine, to afford predominantly the di-*trans* product **397** (*trans*/*cis* = 94:6) in 57% yield (Scheme 168).[103]



Scheme 168

3.2.4 Cyclocondensation Reaction of *N*-Aminidinyl Iminium Ions

The cyclocondensation reaction of **398** with alkenes and dienes provided the desired cycloadducts **399** in 37–83% yields (Scheme 169).[104]



alkene/diene
styrene, (*E*)-propenylbenzene, (*Z*)-propenylbenzene, 1*H*-indene, 1,2-dihydronaphthalene, (*E*)-1,3-hexadiene, (*E*)-ethyl-3,5-hexadionate, (*E*)-ethyl-5,7-octadionate, (*Z*)-1,3-pentadiene

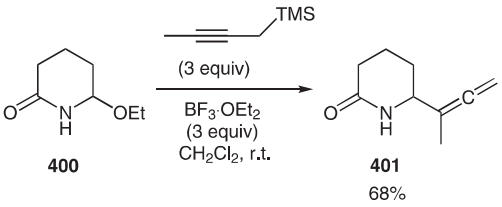
Scheme 169

3.3 Six-Membered-Ring *N*-Acyliminium Ions

3.3.1 Reactions of Piperidinone-Based *N*-Acyliminium Ions with Nucleophiles

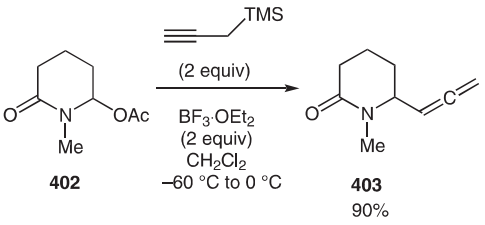
3.3.1.1 Silicon-Based Nucleophiles

The reaction of 6-ethoxypiperidinone (**400**) with but-2-ynyltrimethylsilane under catalysis by boron trifluoride–diethyl ether complex yielded 6-methylallenepiperidinone **401** in 68% yield (Scheme 170).[51]



Scheme 170

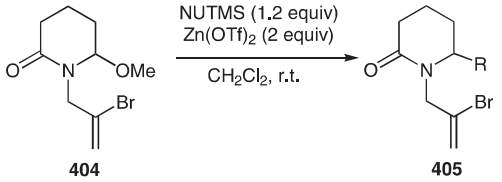
6-Acetoxypiperidinone **402** underwent reaction with propargyltrimethylsilane to provide the allene product **403** in 90% yield (Scheme 171).[105]



Scheme 171

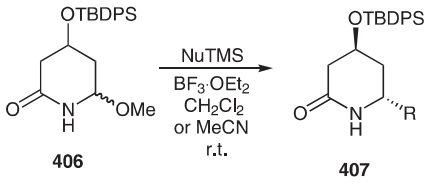
The addition reaction of silicon nucleophiles with 6-methoxypiperidinone **404** in the presence of zinc triflate provided the desired 6-substituted piperidinones **405** in 50–52% yields (Scheme 172).[52]

The reaction of racemic 6-methoxypiperidinone **406** with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex in dichloromethane or acetonitrile afforded the corresponding racemic products **407** in 42–100% yields, in favour of the 4,6-*trans* isomer (*trans*/*cis* = 57:43 to 89:11) (Scheme 173). In the same study, piperidinone **406** reacted with CH_2=C(OTMS)(Ph) in the



NuTMS	R	Yield (%)
$CH_2=CHCH_2TMS$	$-CH_2CH=CH_2$	52
$CH_2=C(OTMS)(Ph)$	$-CH_2COPh$	50

Scheme 172



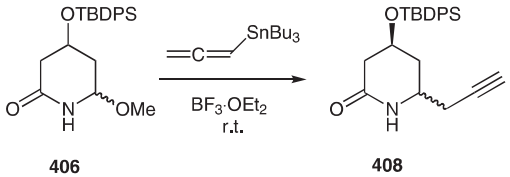
NuTMS	R
$CH_2=CHCH_2TMS$	$-CH_2CH=CH_2$
TMSCN	-CN
$CH_2=C(OTMS)(Ph)$	$-CH_2COPh$

Scheme 173

presence of scandium(III) triflate in acetonitrile to give product **407** in 88% yield and with a *trans*/*cis* ratio of 78:22.[106]

3.3.1.2 Organostannanes

Treatment of racemic piperidinone **406** with allenyltributylstannane in the presence of boron trifluoride–diethyl ether complex in acetonitrile afforded the racemic product **408** as a mixture of isomers (*trans*/*cis* = 51:49) in quantitative yield. The use of dichloromethane as a solvent decreased the yield to 85%, but increased the diastereoselectivity slightly (*trans*/*cis* = 59:41) (Scheme 174).[106]

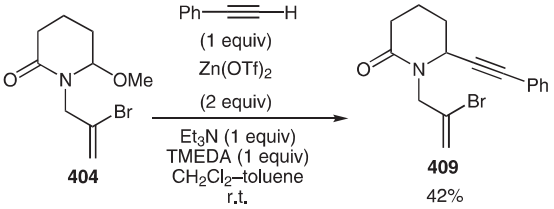


Solvent	Yield (%)	(*trans*/*cis*)
MeCN	100	(51:49)
CH_2Cl_2	85	(59:41)

Scheme 174

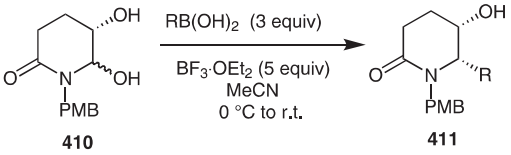
3.3.1.3 Organometallic Reagents

Treatment of piperidinone **404** with an in situ generated zinc alkynylide in the presence of zinc triflate yielded the propargylic adduct **409** in 42% yield (Scheme 175).[52]



Scheme 175

Treatment of the chiral 5,6-dihydroxypiperidinone **410** with boronic acids in the presence of boron trifluoride–diethyl ether complex afforded the products **411** in 49–77% yields, with very good 5,6-*cis* selectivity (80:20 to >98:<2) (Scheme 176). In the same study the 5-methoxy analogue of piperidinone **410** reacted with potassium (*E*)-2-styryltrifluoroborate in the presence of boron trifluoride–diethyl ether complex to give the corresponding methoxy analogue of adduct **411** in 96% yield with a *cis*/*trans* ratio of 65:35.[64]



R	Yield (%)	(*cis*/*trans*)
-CH=CHPh	77	(98:2)
-CH=CHPh[a]	72	(92:8)
-2-furyl	49	(80:20)
-2-benzofuranyl	70	(98:2)
$-C\equiv C-TMS$[a]	41	(95:5)
$-C\equiv C-TMS$[a]	37	(100:0)

[a] The corresponding RBF_3K was used.

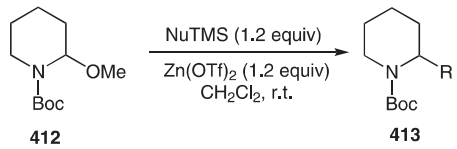
Scheme 176

3.3.2 Reactions of *N*-Acylpiperidine-Based *N*-Acyliminium Ions

3.3.2.1 Reactions with Nucleophiles

3.3.2.1.1 Silicon-Based Nucleophiles

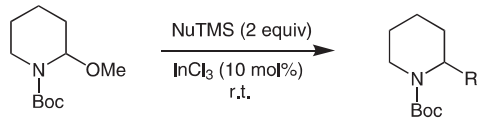
The zinc triflate mediated reaction of *N*-*tert*-butyloxycarbonyl-2-methoxypiperidine (**412**) with silicon nucleophiles afforded the expected 2-substituted piperidines **413** in 52–68% yields (Scheme 177).[52]



NuTMS	R	Yield (%)
$CH_2=CHCH_2TMS$	$-CH_2CH=CH_2$	52
$CH_2=C(OTMS)(Ph)$	$-CH_2COPh$	68
$MeCH=C(OTMS)(Ph)$	-C(Me)COPh	63 (*threo*/*erythro* = 91:9)

Scheme 177

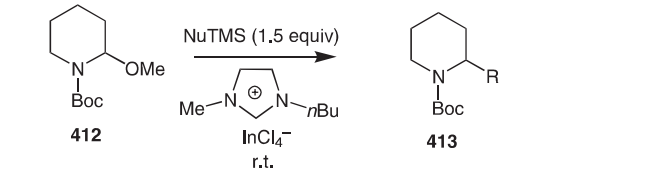
Treatment of piperidine **412** with similar silicon nucleophiles in the presence of indium(III) chloride under solvent-free conditions gave the desired 2-alkylated piperidines **413** in 79–92% yields (Scheme 178).[82a] The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.[82b]



NuTMS	R	Yield (%)
MeC=C(OTMS)(Ph)	-CH(Me)COPh	92
$(Me)_2C$=C(OTMS)(OMe)	$-C(Me)_2CO_2Me$	87
BuCH=C(OTMS)(Bu)	-C(Bu)COBu	87
CH_2=C(OTMS)(Ph)	$-CH_2COPh$	79

Scheme 178

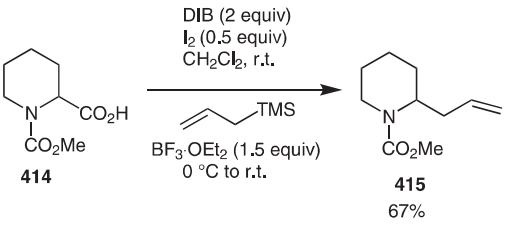
Piperidine **412** also reacted with silicon nucleophiles in an ionic liquid ($BMI{\cdot}InCl_4$) to yield the corresponding 2-substituted piperidines **413** in 65–76% yields (Scheme 179).[81]



NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	$-CH_2CH$=CH_2	69
CH_2=C(OTMS)(Ph)	$-CH_2COPh$	65
MeCH=C(OTMS)(Ph)	-CH(Me)COPh	76 (*erythro*/*threo* = 83:17)
$(Me)_2C$=C(OTMS)(OMe)	$-(Me)_2CCO(OMe)$	67

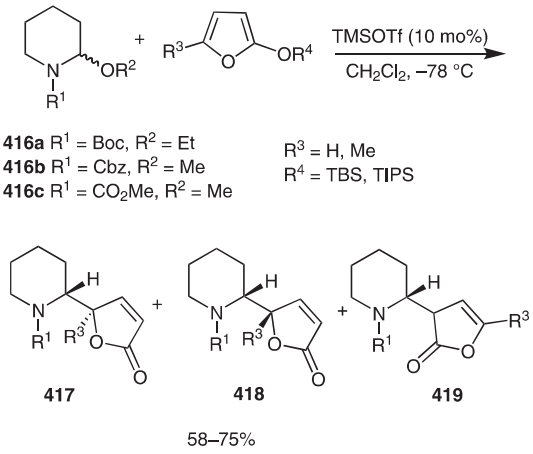
Scheme 179

The one-pot decarboxylation–oxidation–allylation reaction of *N*-methyloxycarbonyl piperidine **414** afforded 2-allylpiperidine **415** in 67% yield (Scheme 180).[47]



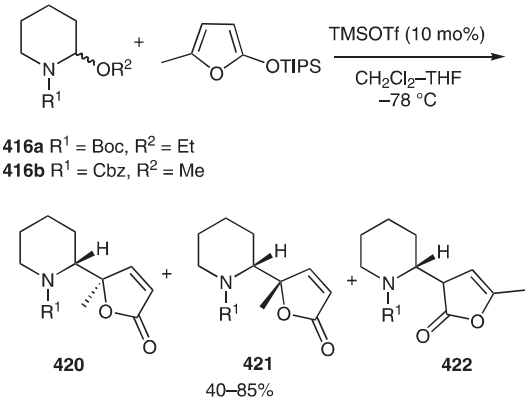
Scheme 180

Treatment of *N*-acylpiperidines **416a–c** with 2-silyloxyfurans under trimethylsilyl triflate catalysis afforded products **417**, **418** and **419** in 58–75% yields (Scheme 181). The reactions of **416a–c** with 2-silyloxyfuran (R^3 = H, R^4 = TBS) gave products **417** and **418** in 58%, 63%, and 74% yields, and with product ratios (**417**/**418**) of 88:12, 67:33, and 75:25, respectively. The reaction of piperidines **416a–c** with another silyloxyfuran (R^3 = Me, R^4 = TIPS) afforded products **417**, **418**, and **419** in 67%, 75%, and 70% yields, with **417**/**418**/**419** product ratios of 3:60:36, 33:67:0, and 16:84:0, respectively. The relative stereochemistry of **419** was not determined.[84]



Scheme 181

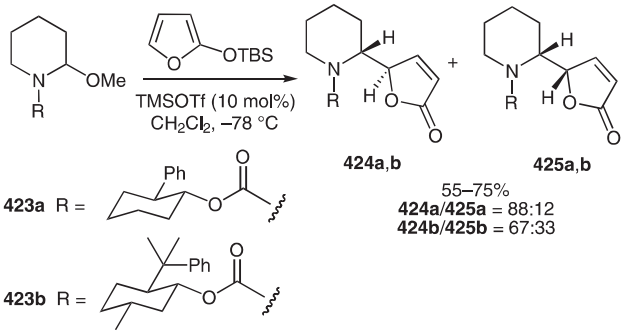
In a very similar study, piperidine **416a** reacted with 2-[(triisopropyl)siloxy]-5-methylfuran in a tetrahydrofuran and dichloromethane solvent mixture in the presence of trimethylsilyl triflate or boron trifluoride–diethyl ether complex to afford products **420**, **421** and **422** in 67% and 40% yields, respectively with product ratios (**420**/**421**/**422**) of 60:4:36 and 58:4:38, respectively. The reaction of piperidine **416b** with silyloxyfuran in the presence of trimethylsilyl triflate, titanium(IV) chloride, and boron trifluoride–diethyl ether complex in dichloromethane, diethyl ether, tetrahydrofuran, and tetrahydrofuran–dichloromethane gave products **420** and **421** in 42–85% yields and with **420**/**421** product ratios of 52:48 to 67:33. The regioisomer **422** was not obtained from the reaction of piperidine **416b** (Scheme 182).[107]



Scheme 182

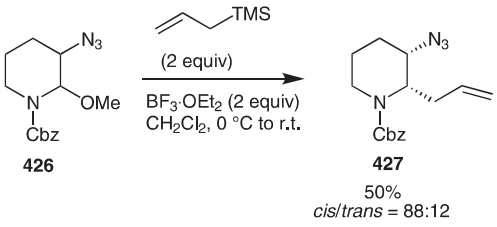
The reaction of chiral 2-methoxypiperidines **423a**,**b** with 2-*tert*-butyldimethylsilyloxyfuran under titanium(IV) chloride or trimethylsilyl triflate catalysis provided the

adducts **424a**,**b** and **425a**,**b** (Scheme 183). Treatment of **423a** with the silyloxyfuran in the presence of titanium(IV) chloride or trimethylsilyl triflate gave products **424a** and **425a** in 55% and 75% yields (**424a**/**425a** = 88:12). Reaction of **423b** with the silyloxyfuran under trimethylsilyl triflate catalysis gave the adducts **424b** and **425b** in 73% yield, with a diastereomeric ratio of 67:33.[83]



Scheme 183

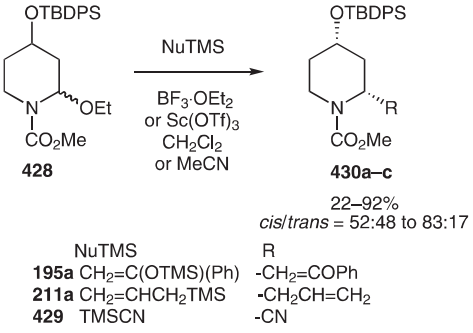
The reaction of racemic 3-azido-2-methoxypiperidine **426** with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the racemic 2-allylated piperidine **427** as a mixture of isomers with a *cis*/*trans* ratio of 88:12 in 50% yield (Scheme 184).[87,88]



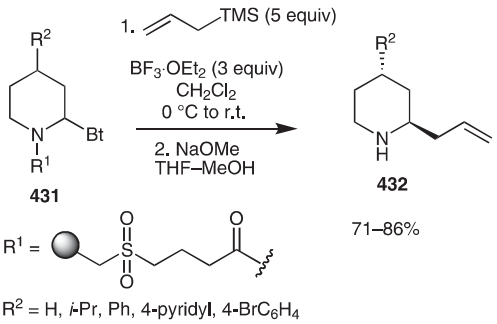
Scheme 184

Treatment of racemic piperidine **428** with silicon nucleophiles **195a**, **211a** and **429** in the presence of scandium(III) triflate in acetonitrile yielded products **430** in 89%, 92%, and 86% yields, respectively, and with *cis*/*trans* ratios of 52:48, 54:46 and 74:26, respectively. When the reaction of piperidine **428** with **211a** and **429** was performed under boron trifluoride–diethyl ether complex catalysis in acetonitrile, products **430** were obtained in yields of 92% and 79%, respectively, in favour of the *cis* isomer (*cis*/*trans* = 72:28 and 61:39, respectively). The use of dichloromethane as a solvent in the reaction of **428** with **195a** and **211a** resulted in 22% (*cis*/*trans* = 75:25) and 65% (*cis*/*trans* = 83:17) yields, respectively (Scheme 185).[106]

The boron trifluoride–diethyl ether complex mediated reaction of allyltrimethylsilane with resin-bound racemic piperidine **431** gave racemic 2,4-*trans* isomers **432** in 71–86% yields after they were cleaved from the resin (Scheme 186). Piperidine **431**, where R^2 = Ph, was treated



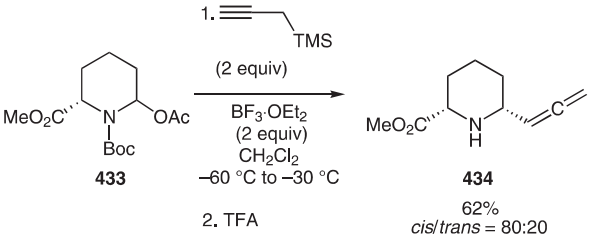
Scheme 185



Scheme 186

with CH_2=C(Me)(CH_2TMS) to afford the corresponding racemic 2,4-*trans* adduct exclusively in 76% yield.[108]

N-*tert*-Butyloxycarbonyl-6-acetoxypiperidine **433** reacted with propargyltrimethylsilane under boron trifluoride–diethyl ether complex catalysis to afford the allene **434** in 62% yield, in favour of the *cis* isomer (*cis*/*trans* = 80:20) (Scheme 187).[105]

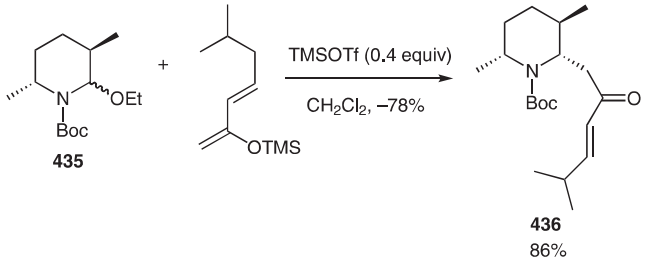


Scheme 187

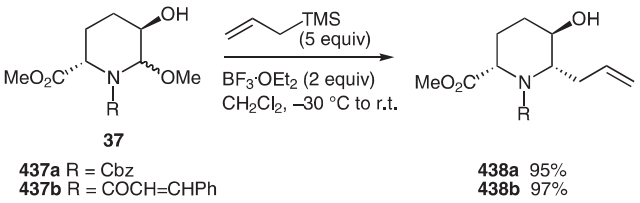
The reaction of b*N*-Boc piperidine **435** with a silyl dienol ether in the presence of trimethylsilyl triflate yielded exclusively the 2,3-*trans* isomer of adduct **436** in 86% yield (Scheme 188).[109]

The *N*-acyl piperidines **437a**,**b** were treated with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give exclusively the corresponding 2,3-*trans* adducts **438a** and **438b** in 95% and 97% yields, respectively (Scheme 189).[110]

Treatment of the *N*-Fmoc piperidine **439** with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex provided the products **440** and **441** in a

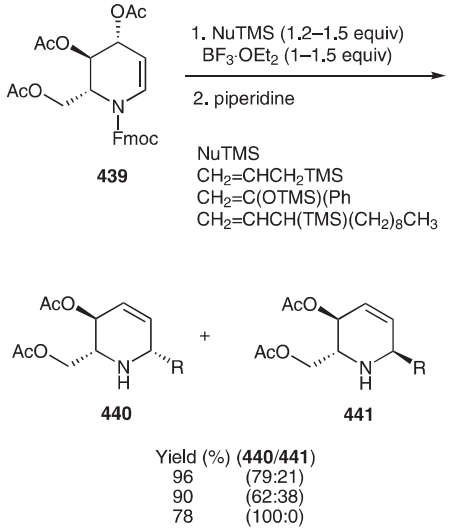


Scheme 188



Scheme 189

range of yields (78–96%), with good 2,6-*cis* selectivity. The reaction of **439** with CH_2=CHCH(TMS)$(CH_2)_8$Me afforded the corresponding 2,6-*cis* adduct exclusively (Scheme 190).[111]



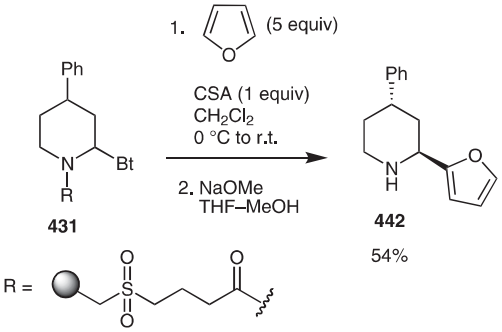
Scheme 190

3.3.2.1.2 Aromatic Nucleophiles

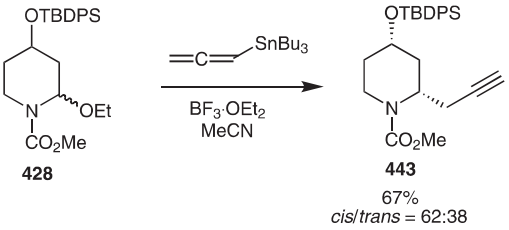
The treatment of polymer-bound racemic piperidine **431** with furan in the presence of camphorsulfonic acid provided the racemic 2-furylpiperidine adduct **442** exclusively in 54% yield (Scheme 191).[108]

3.3.2.1.3 Organostannanes

Treatment of racemic piperidine **428** with allenyltributylstannane in the presence of boron trifluoride–diethyl ether complex afforded product **443** in 67% yield, in favour of the 2,4-*cis* isomer (Scheme 192).[106]

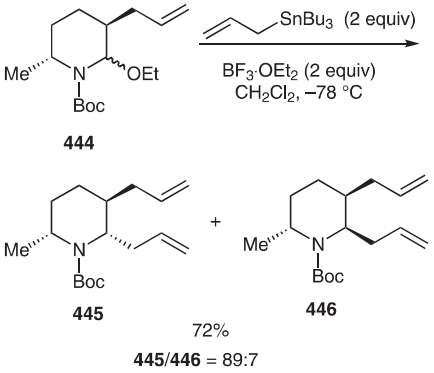


Scheme 191



Scheme 192

The reaction of the *N*-Boc piperidine **444** with allyltributylstannane in the presence of boron trifluoride–diethyl ether complex gave products **445** and **446** and one other isomer in a ratio of 89:7:4, respectively, and in combined yield of 72% (Scheme 193). The third isomer was suggested to be the result of partial epimerisation of the stereocentre in the *N*-acyliminium ion intermediate.[112]



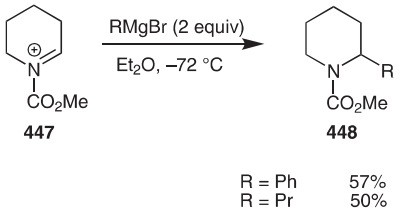
Scheme 193

3.3.2.1.4 Organometallic Reagents

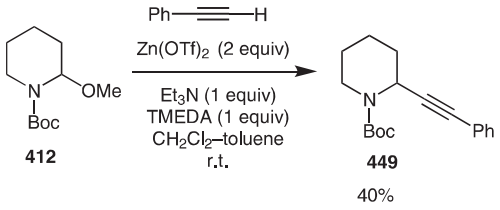
The *N*-acyliminium ion **447**, generated in situ from the corresponding carbamate by electrochemical oxidation, reacted with Grignard reagents in diethyl ether to afford the 2-substituted piperidine products **448** in 50–57% yields (Scheme 194).[38]

Piperidine **412** reacted with an in situ generated zinc alkynylide to give the corresponding propargylic adduct **449** in 40% yield (Scheme 195).[52]

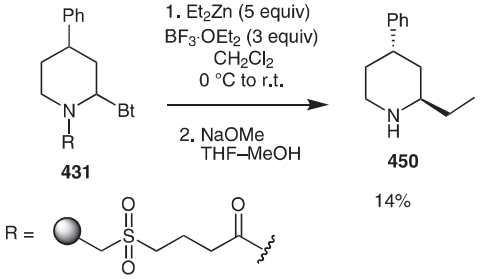
The polymer-bound racemic piperidine **431** was treated with diethylzinc in the presence of boron trifluoride–



Scheme 194



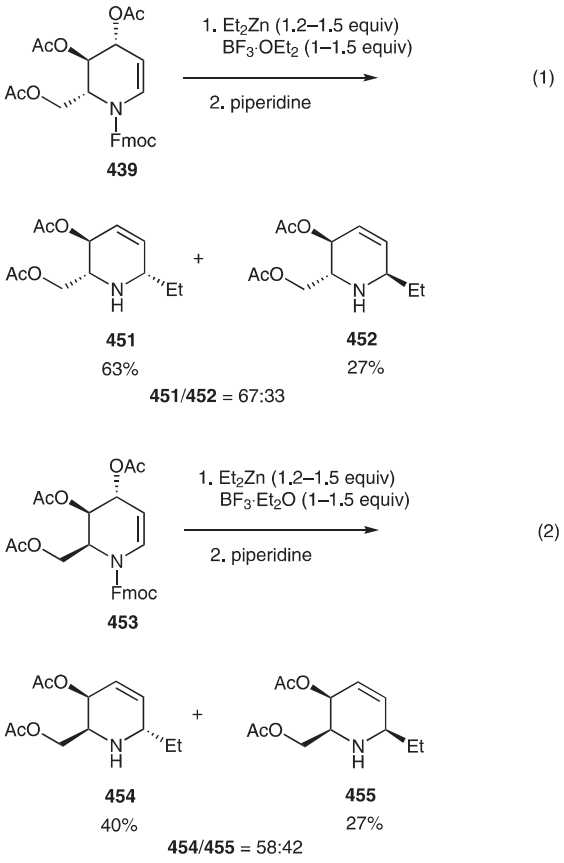
Scheme 195



Scheme 196

diethyl ether complex to give the racemic 2,4-*trans* isomer **450** exclusively in 14% yield (Scheme 196).[108]

The reaction of piperidines **439** with diethylzinc in the presence of boron trifluoride–diethyl ether complex yielded products **451** and **452** in 63% and 27% yields, respectively (Scheme 197, equation 1). Treatment of **453**, a diastereomer of piperidine **439**, with diethylzinc under the same reaction conditions afforded products **454** and **455** in yields of 40% and 27%, respectively (Scheme 197, equation 2).[111]

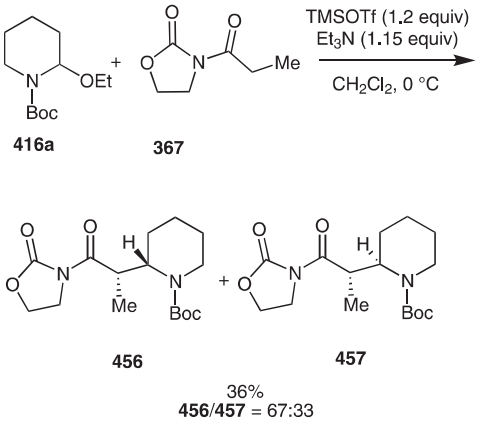


Scheme 197

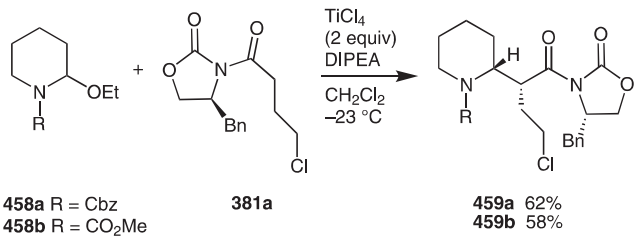
3.3.2.1.5 Carbonyl Compounds

The reaction of *N*-*tert*-butyloxycarbonyl-2-ethoxypiperidine (**416a**) with an *N*,*O*-silylketene acetal, itself prepared in situ by treatment of *N*-propionyloxazolidine-2-one **367** with trimethylsilyl triflate and triethylamine, led to the formation of 2-substituted piperidines **456** and **457** in 36% combined yield (**456**/**457** = 67:33) (Scheme 198).[98]

Treatment of the 2-methoxypiperidines **458a**,**b** with the titanium enolate of **381a** led to the formation of **459a** and **459b** in 62% and 58% yields, respectively (Scheme 199), whereas treatment of the *N*-Boc analogue of piperidine **458** with titanium enolate of **381a** under the same reaction conditions did not give the desired product.[113]

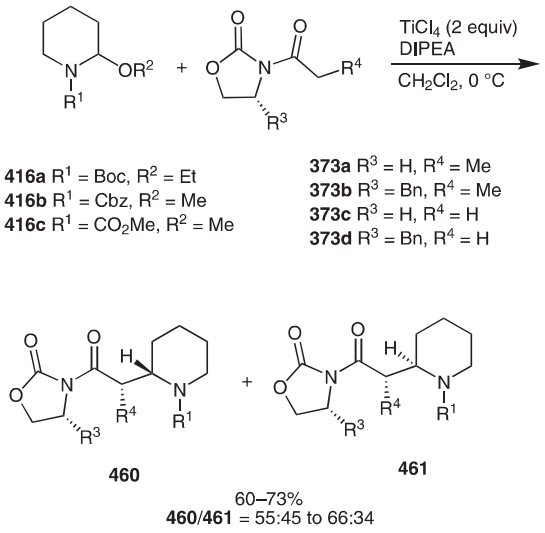


Scheme 198



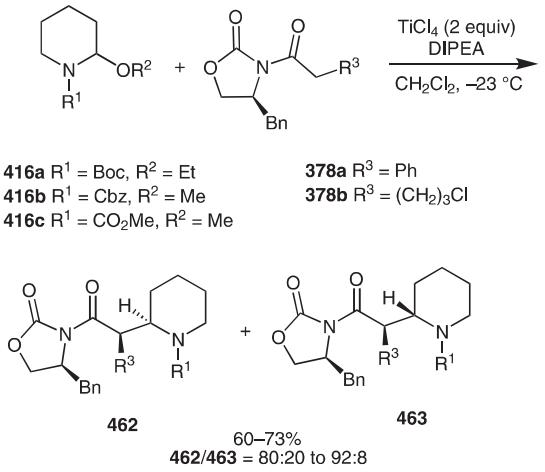
Scheme 199

The titanium enolates of **373a–d** reacted with the *N*-acyl piperidines **416a–c** to afford the diastereomeric products **460** and **461** in 60–73% yields (Scheme 200).[98]



Scheme 200

In the same study the piperidines **416a–c** reacted with the titanium enolates of **378a**,**b** to give the corresponding products **462** and **463** in 60–73% yields (Scheme 201).[98]



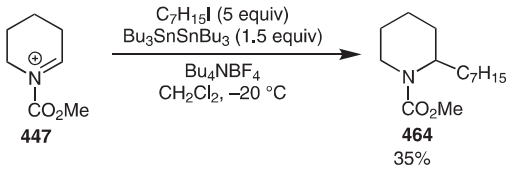
Scheme 201

3.3.2.1.6 Alkyl Radicals

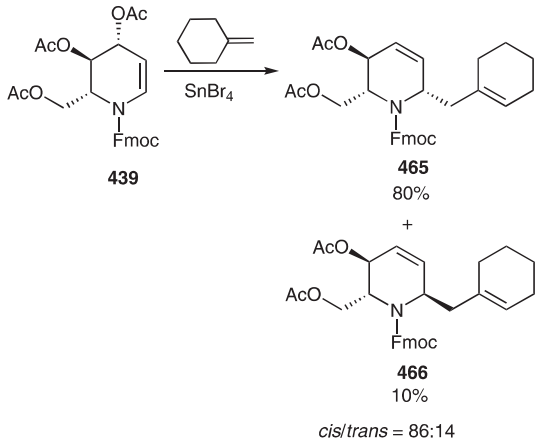
The *N*-acyliminium ion **447** was treated with heptyl iodide in the presence of hexabutyldistannane to give the 2-heptyl-*N*-acylpiperidine derivative **464** in 35% yield (Scheme 202).[41,42]

3.3.2.1.7 Alkenes

Treatment of piperidine **439** with methylenecyclohexane under catalysis by tin(IV) bromide yielded the 2,6-*cis* adduct **465** and the 2,6-*trans* adduct **466** in 80% and 10% yields, respectively (Scheme 203).[111]

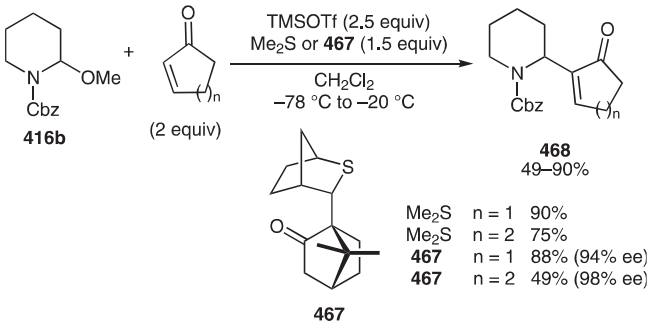


Scheme 202



Scheme 203

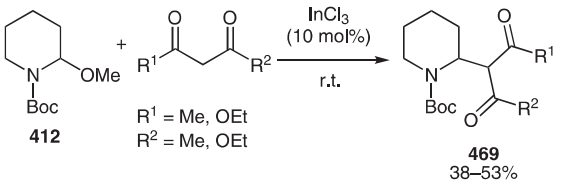
Treatment of *N*-Cbz-protected 2-methoxypiperidine **416b** with cyclopentenone or cyclohexenone and dimethyl sulfide in the presence of trimethylsilyl triflate led to the formation of products **468** in 75–90% yields. The use of a chiral sulfide **467** resulted in 49–88% yields and enantioselectivities of 94–98% ee (Scheme 204).[114]



Scheme 204

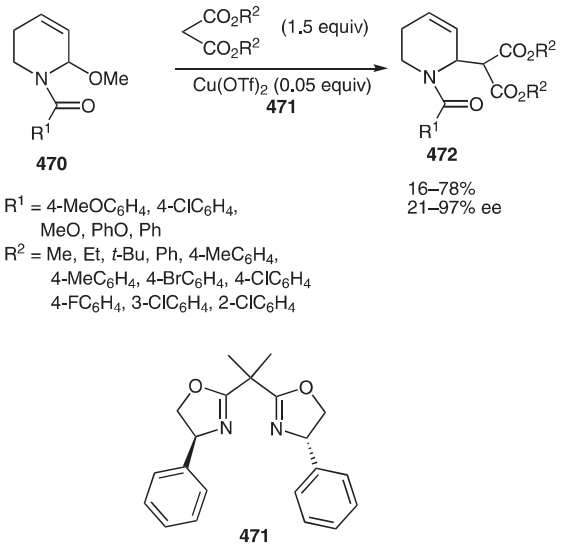
3.3.2.1.8 Active Methylene Compounds

The indium(III) chloride catalysed reaction of piperidine **412** with acetylacetonate (R^1 = Me, R^2 = OEt), acetylacetone (R^1 = R^2 = Me), and diethyl malonate (R^1 = R^2 = OEt) provided the products **469** in 53%, 38%, and 53% yields, respectively (Scheme 205).[82a] The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.[82b]



Scheme 205

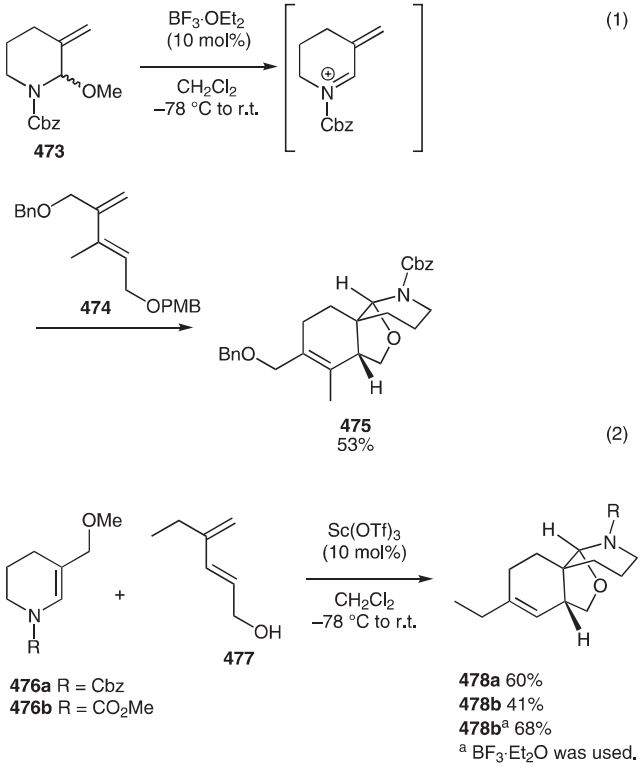
The *N*-acylpiperidines **470** reacted with 1,3-dicarbonyl compounds in the presence of copper(II) triflate and bisoxazoline ligand **471** to give products **472** in yields ranging from 16% to 78%. The highest enantioselectivity (97% ee) was obtained from the reaction of piperidine **470** (R^1 = 4-$MeOC_6H_4$) and di(4-chlorophenyl)malonate (Scheme 206).[115]



Scheme 206

3.3.2.2 Cycloaddition Reactions

The reaction of piperidine **473** with diene **474** in the presence of boron trifluoride–diethyl ether complex afforded cycloadduct **475** in 53% yield (Scheme 207, equation 1). Treatment of piperidines **476a** and **476b** with diene **477** in the presence of scandium(III) triflate afforded the corresponding cycloadducts **478a** and **478b** in 60% and 41% yields, respectively. Cycloadduct **478b** was obtained in 68% yield from the reaction of **476a** with **477** under catalysis by boron trifluoride–diethyl ether complex (Scheme 207, equation 2).[116]

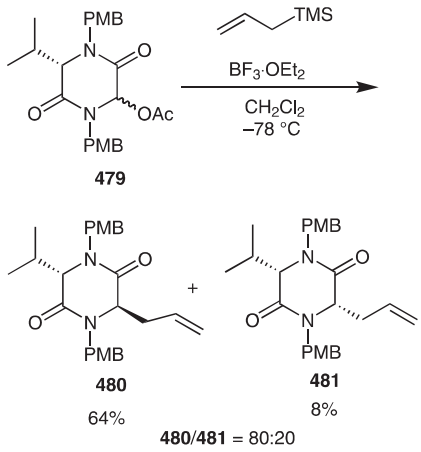


Scheme 207

3.3.3 Reactions of Piperazine-Based *N*-Acyliminium Ions with Nucleophiles

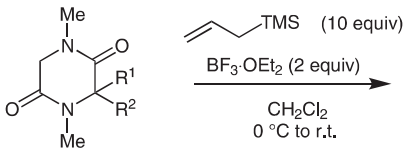
3.3.3.1 Silicon-Based Nucleophiles

Diketopiperazine **479** reacted with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to afford products **480** and **481** in 64% and 8% yields, respectively. The same product ratio was obtained from the reactions of diastereomerically pure 3,6-*trans* and 3,6-*cis* piperazines **479** with allyltrimethylsilane (Scheme 208).[117]

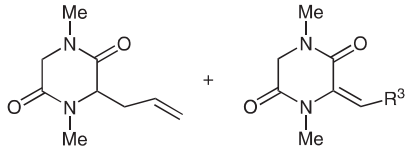


Scheme 208

The boron trifluoride–diethyl ether complex catalysed reaction of 3-methoxy-1,4-dimethylpiperazine-2,5-dione (**482a**) with allyltrimethylsilane provided allylated product **483** in 68% yield, whereas **482b** with allyltrimethylsilane under the same reaction conditions provided allylated product **483** and product **484** in 66% and 33% yields, respectively. Treatment of **482c** with allyltrimethylsilane under the same reaction conditions gave exclusively product **484** in 76% yield (Scheme 209).[48,118]



482a R^1 = H, R^2 = OMe
482b R^1 = Me, R^2 = OAc
482c R^1 = Bn, R^2 = OAc



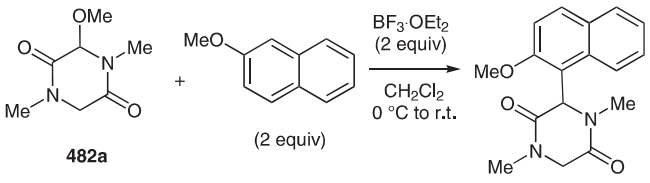
483 **484**

	Yield (%) (**483**)	Yield (%) (**484**)
a	68	0
b	66	33 (R^3 = H)
c	0	76 (R^3 = Pr)

Scheme 209

3.3.3.2 Aromatic Nucleophiles

Treatment of **482a** with 2-methoxynaphthalene in the presence of boron trifluoride–diethyl ether complex gave the corresponding arylated product **485** in 81% yield (Scheme 210).[48]



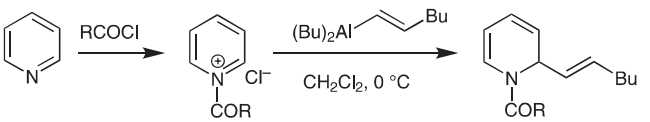
482a (2 equiv) **485**
81%

Scheme 210

3.3.4 Reactions of Pyridine-Based *N*-Acyliminium Ions with Nucleophiles

3.3.4.1 Organometallic Reagents

The reaction of pyridine with acyl chlorides generated the *N*-acyliminium ion salt **486** which was then treated with an organoaluminium reagent to yield the corresponding adducts **487** in 90–94% yields (Scheme 211).[119]



486 **487**
90–94%

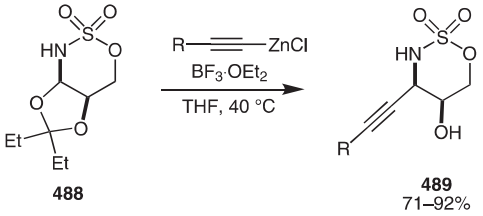
R = Bu, Ph, *c*-$C_{12}H_{14}$

Scheme 211

3.3.5 Reactions of *N*,*O*-Acetal Oxathiazinane *N*-Sulfonyliminium Ions with Nucleophiles

3.3.5.1 Organometallic Reagents

The reactions of *N*,*O*-acetal oxathiazinane **488** and related heterocycles with alkynylzinc reagents gave adducts **489** in high yields and high diastreoselectivities (Scheme 212).[120]



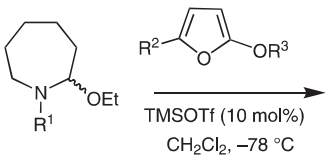
488 **489**
71–92%

Scheme 212

3.4 Seven-Membered-Ring *N*-Acyliminium Ions

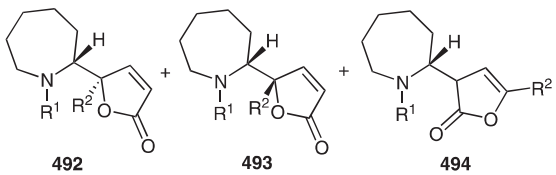
3.4.1 Reactions with Silicon-Based Nucleophiles

Treatment of the *N*-acyl-2-ethoxyazepines **490a–c** with 2-silyloxyfurans **491a**,**b** in the presence of trimethylsilyl triflate afforded products **492**, **493**, and **494** in 46–83% yields (Scheme 213). The reactions of azepines **490a–c** with **491a** in the presence of trimethylsilyl triflate afforded products **492** and **493** in ratios of 93:7, 85:15 and 80:20, respectively, while the reactions with **491b** yielded products **492**, **493**, and **494** in ratios of 13:45:42, 6:52:42, and 30:70:0, respectively. The regioisomer **494** was not obtained from the reaction of **490a–c** with **491a**.[84]



490a R^1 = Boc
490b R^1 = Cbz
490c R^1 = CO_2Me

491a R^2 = H, R^3 = TBS
491b R^2 = Me, R^3 = TIPS

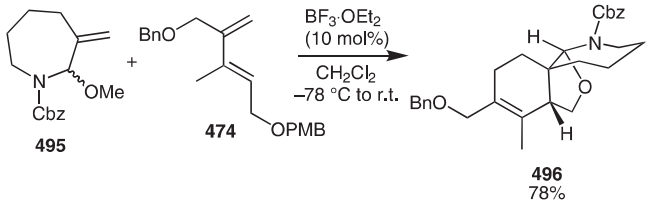


492 **493** **494**
46–83%

Scheme 213

3.4.2 Cycloaddition Reactions

Azepine **495** reacted with diene **474** in the presence of boron trifluoride–diethyl ether complex to give cycloadduct **496** in 78% yield (Scheme 214).[116]



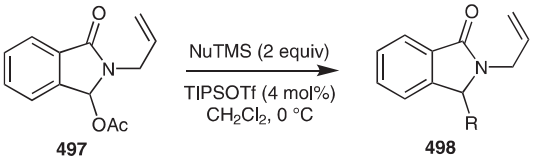
Scheme 214

3.5 Bicyclic *N*-Acyliminium Ions

3.5.1 Reactions with Nucleophiles

3.5.1.1 Silicon-Based Nucleophiles

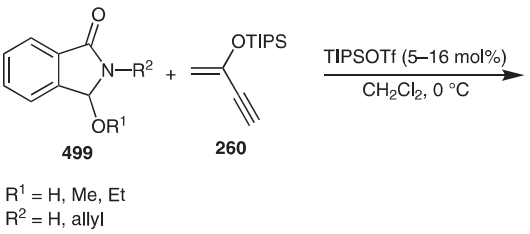
Treatment of phthalimide **497** with silicon nucleophiles under triisopropylsilyl triflate catalysis afforded the desired products **498** in 45–89% yields (Scheme 215).[54] In a similar study the phthalimide **497** reacted with CH_2=C(OTIPS)C≡CH (2 equiv) in the presence of bis(trifluoromethane)sulfonimide (0.3 mol%) at room temperature under solvent-free conditions to give the corresponding α-substituted product in 82% yield.[63]



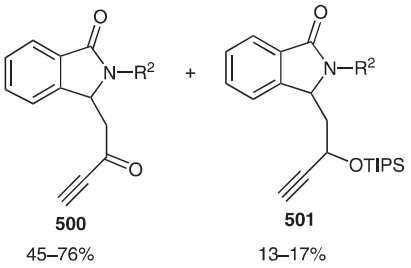
NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	88
CH_2=C(Ph)(OTMS)	-CH_2COPh	89
CH_2=C(*t*-Bu)(OTMS)	-CH_2CO*t*-Bu	87
TMSCN	-CN	82
Et_3SiH	-H	87
CH_2=C(OMe)(OTBS)	-CH_2CO_2Me	45

Scheme 215

In the same study, the triisopropylsilyl triflate catalysed reactions of phthalimides **499** with **260** gave the products **500** and **501** in 45–76% yields and 13–17% yields, respectively (Scheme 216).[54]

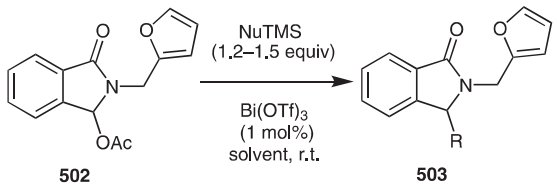


R^1 = H, Me, Et
R^2 = H, allyl



Scheme 216

Silicon nucleophiles reacted with phthalimide **502** in the presence of bismuth(III) triflate in acetonitrile to provide product **503** in yields of 64–84%. Lower yields were obtained when dichloromethane was used as a solvent (56–66%) (Scheme 217).[62]

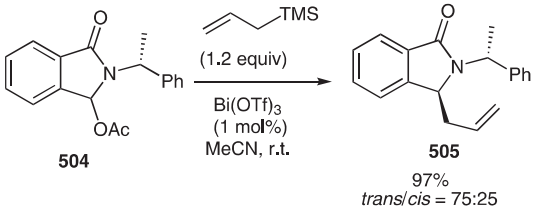


NuTMS	R	Yield (%)
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2	64 (56)[a]
CH_2=C(Ph)(OTMS)	-CH_2COPh	71 (58)[a]
CH_2=C(Me)(OTMS)	-CH_2COMe	84 (66)[a]

[a] CH_2Cl_2 was used.

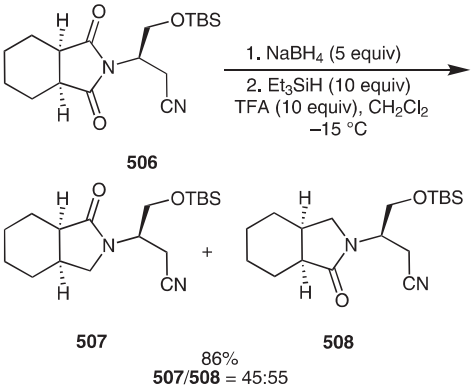
Scheme 217

In the same study, chiral phthalimide **504** reacted with allyltrimethylsilane under bismuth(III) triflate catalysis to give product **505** in a *trans*/*cis* ratio of 75:25, and in 97% yield (Scheme 218).[62]



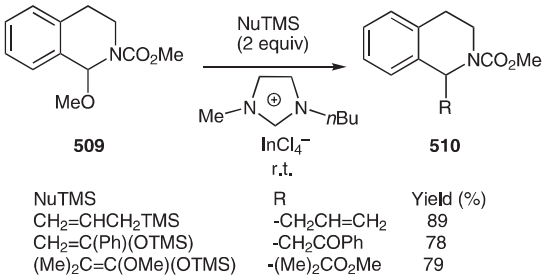
Scheme 218

Treatment of bicyclic imide **506** with sodium borohydride and then triethylsilane in the presence of trifluoroacetic acid afforded products **507** and **508** in 86% yield, in a **507**/**508** product ratio of 45:55 (Scheme 219).[75]



Scheme 219

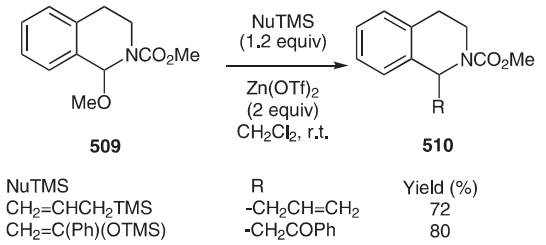
Isoquinoline derivative **509** reacted with silicon nucleophiles in an ionic liquid, BMI·$InCl_4$, to give the corre-



Scheme 220

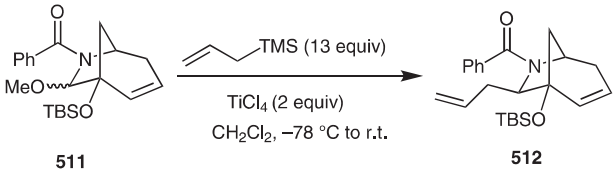
sponding α-substituted isoquinolines **510** in 78–89% yields (Scheme 220).[81]

The zinc triflate mediated addition reactions of allyltrimethylsilane and 1-phenylvinyloxytrimethylsilane to the isoquinoline **509** led to the formation of the desired α-substituted adducts **510** in 72% and 80% yields, respectively (Scheme 221).[52]



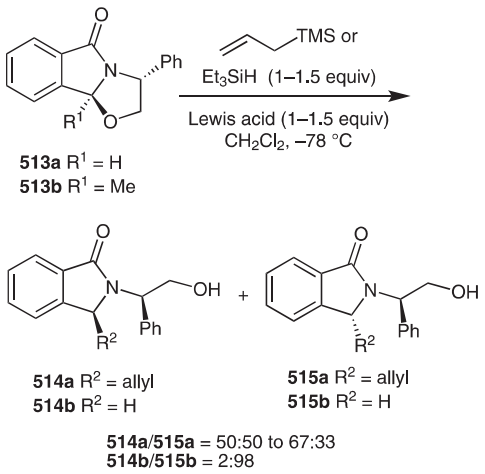
Scheme 221

The reaction of **511** with allyltrimethylsilane in the presence of titanium(IV) chloride afforded the desired α-allyl product **512** in 91% yield, as a single isomer. The stereochemistry of the product was suggested to be the result of *exo*-face attack on the intermediate *N*-acyliminium ion (Scheme 222).[121]



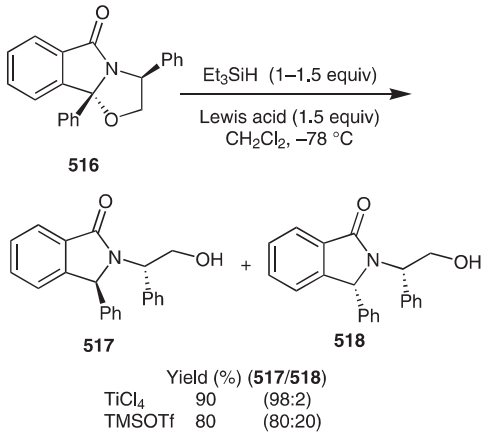
Scheme 222

The ring-opening reaction of tricyclic lactam **513a** with allyltrimethylsilane in the presence of titanium(IV) chloride, boron trifluoride–diethyl ether complex, tin(IV) chloride and trimethylsilyl triflate yielded the allylated products **514** and **515** in 86% (**514/515** = 50:50), 95% (**514/515** = 61:39), 90% (**514/515** = 60:40) and 90% (**514/515** = 67:33) yields, respectively, in favour of product **514** (Scheme 223). Lactam **513b**, however, afforded products **514b** and **515b** in a ratio of 2:98 and in 99% yield from the reaction with triethylsilane.[122]



Scheme 223

In the same study, lactam **516** reacted with triethylsilane under catalysis by titanium(IV) chloride or trimethylsilyl triflate to provide **517** and **518** in a ratio of 98:2 and 80:20 and in 90% and 80% yields, respectively (Scheme 224).[122]



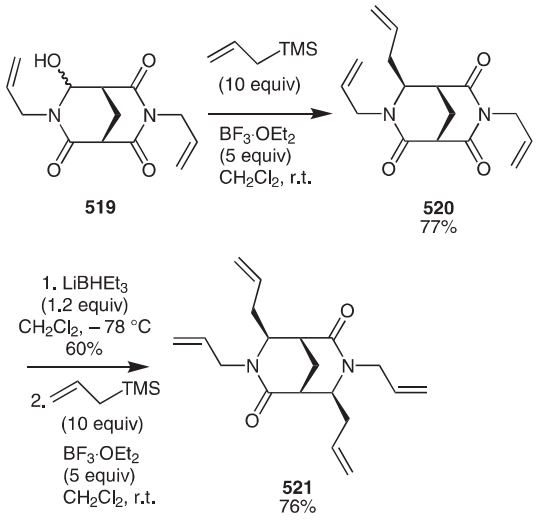
Scheme 224

The reaction of tetraoxobispidine **519** with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex afforded product **520** as a single isomer in 77% yield. Treatment of **520** with lithium triethylborohydride and then allyltrimethylsilane under the same reaction conditions yielded the diallylated product **521** as a single isomer in 76% yield (Scheme 225).[123]

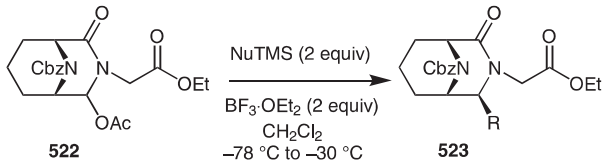
In a similar study, the boron trifluoride–diethyl ether complex catalysed reactions of bispidine **522** with silicon nucleophiles yielded products **523** in yields of 70–90% (Scheme 226).[105]

3.5.1.2 Organometallic Reagents

The addition reactions of in situ generated zinc alkynylides to isoquinoline derivative **509** gave the corre-



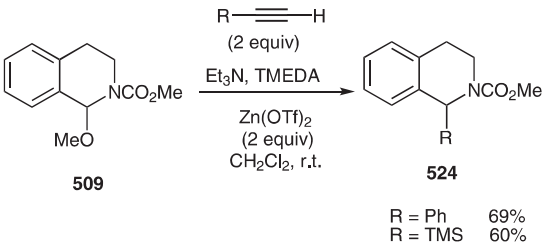
Scheme 225



NuTMS	R	Yield (%)
TMSCN	-CN	90[a]
$CH_2C(Ph)(OTMS)$	$-CH_2COPh$	70
$HC{\equiv}CCH_2TMS$	$-CH_2{=}C{=}CH_2$	90

[a] $TiCl_4$ was used.

Scheme 226

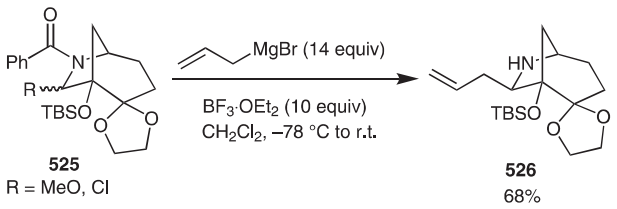


Scheme 227

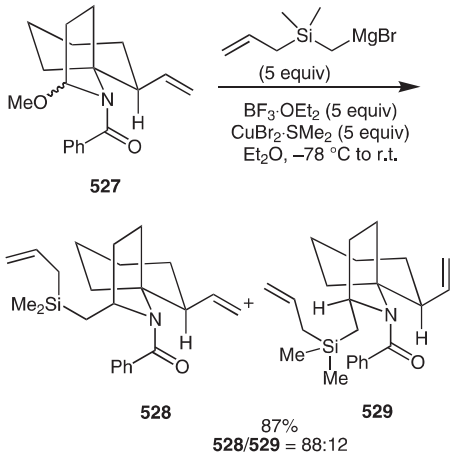
sponding products **524** in yields of 60–69% (Scheme 227).[52]

The reaction of allylmagnesium bromide with a mixture of the α-methoxy and α-chloro benzamides **525** under boron trifluoride–diethyl ether complex catalysis afforded the *exo*-allylated product **526** in 68% yield and also led to the removal of the *N*-benzoyl group (Scheme 228).[121]

Treatment of the α-methoxy lactam **527** with an organocopper reagent, generated in situ from the corresponding Grignard reagent and copper(II) bromide–dimethyl sulfide complex, led to the formation of an 88:12 mixture of products **528** and **529** in 87% yield (Scheme 229).[124]

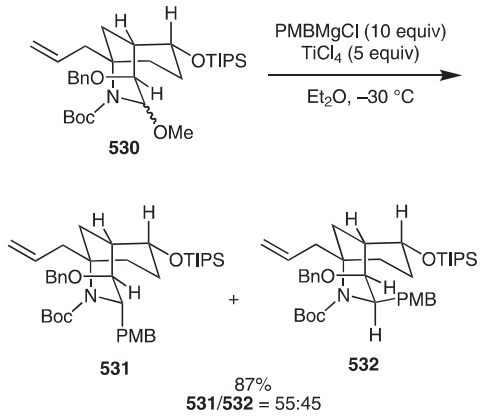


Scheme 228



Scheme 229

Treatment of **530** with 4-methoxybenzylmagnesium chloride under titanium(IV) chloride catalysis provided products **531** and **532** in a ratio of 55:45 and in 87% yield (Scheme 230).[125]

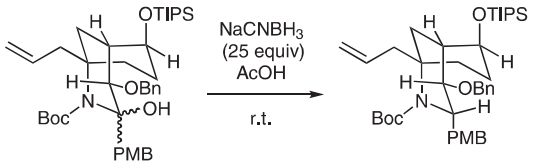


Scheme 230

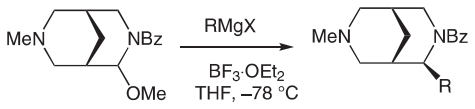
In the same study, compound **533** was treated with sodium cyanoborohydride in acetic acid to give the desired product **534** as a single isomer in 69% yield (Scheme 231).[124]

The α-methoxy bispidine **535** underwent reaction with Grignard reagents to afford the corresponding α-substituted bispidines **536** in 61–89% yields (Scheme 232).[126]

Treatment of Grignard and zinc reagents with the chiral isoquinoline derivative **537** in the presence of $Ph_3C^+BF_4^-$ led to the formation of diastereomeric products **538** and **539** in 65–98% yields (Scheme 233).[127]

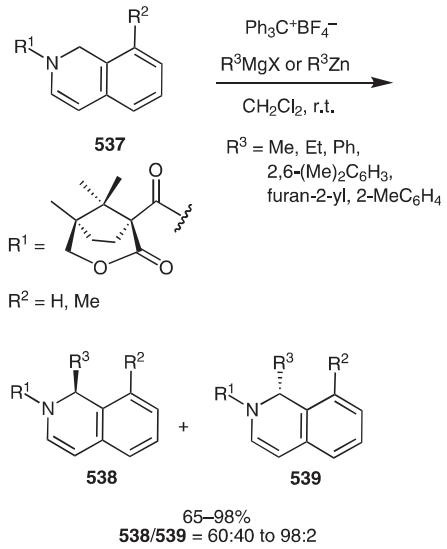


Scheme 231



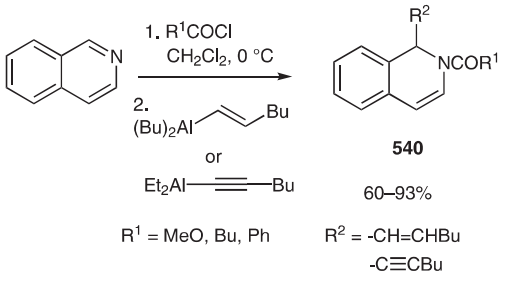
R = Me, Bn, CH_2=$CHCH_2$, CH_2=$CHCH_2CH_2$
X = Cl, Br

Scheme 232



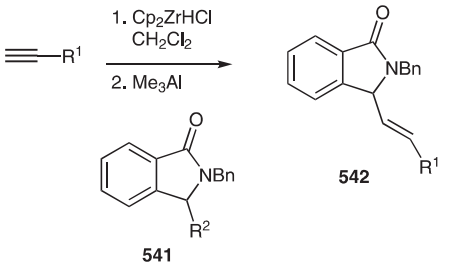
Scheme 233

Treatment of quinolidine with acyl chlorides and then organoaluminium reagents gave products **540** in yields of 60–93% (Scheme 234).[119]



Scheme 234

Phthalimide **541** was treated with alkenylalanes, themselves generated by the hydrozirconation of alkynes and transmetallation to trimethylaluminium, to give products **542** in yields of 43–81% (Scheme 235).[128]

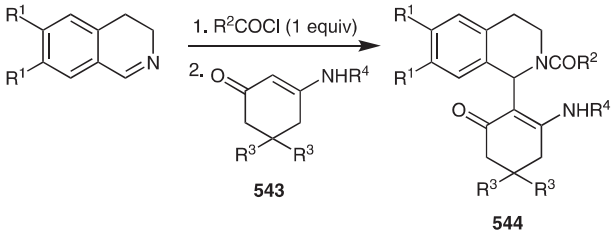


R1 = Bu, *c*-C_6H_{11}, $CH_2CH_2OTBDPS$, $CH_2CH_2N(CO_2Me)Ts$
R2 = OMe, OPiv

Scheme 235

3.5.1.3 Enamines

Cyclic enamino ketones **543** reacted with *N*-acyliminium ion salts of 3,4-dihydroquinoline to provide the adducts **544** in 31–78% yields (Scheme 236).[129]

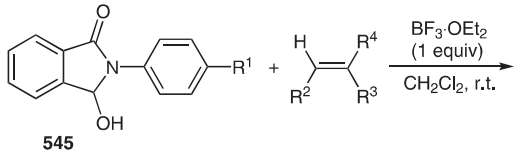


R1 = H, MeO
R2 = Me, OEt, Ph
R3 = H, Me
R4 = Ph, Bn, $PhCH_2CH_2$, 3,4-$(MeO)_2C_6H_3CH_2CH_2$

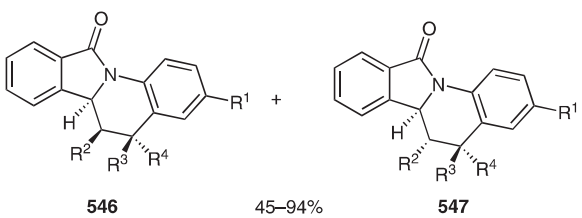
Scheme 236

3.5.2 Cycloaddition Reactions

The [4+2]-cycloaddition reaction of phthalimide **545** with alkenes in the presence of boron trifluoride–diethyl ether complex led to the formation of cycloadducts **546** and **547** in yields of 45–94% as mixtures of *cis* and *trans* products in different ratios (Scheme 237).[130]



R1 = H, Me, MeO
R2 = H, Me, $C_6H_4CH_2$-, -$(CH_2)_2O$-, -$(CH_2)_3O$-
R3 = H, Ph, Bn
R4 = H, Me, EtO

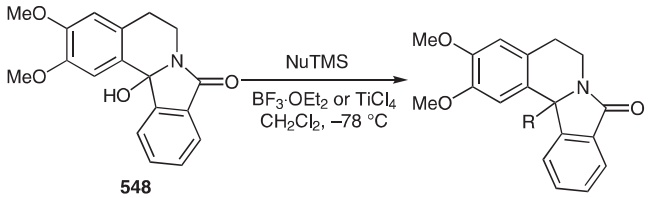


Scheme 237

3.6 Other Systems

3.6.1 Silicon-Based Nucleophiles

The addition reaction of silicon nucleophiles to α-hydroxylactam **548** in the presence of boron trifluoride–diethyl ether complex or titanium(IV) chloride yielded the α-substituted products **549** in yields of 69–95% (Scheme 238).[131]

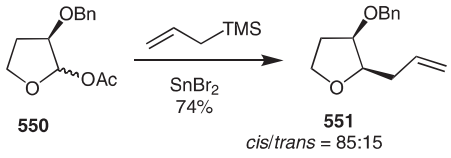


NuTMS	R
CH_2=$CHCH_2TMS$	-CH_2CH=CH_2
CH_2=$C(CH_2CH(SPh)_2)(CH_2TMS)$	-CH_2C(Me)=$CH(SPh)_2$
CH_2=C(Ph)(OTMS)	-CH_2COPh
CH_2=C(Me)(OTMS)	-CH_2COMe
CH_2=CHCH=CHOTMS	-CH_2CH=CHCHO

Scheme 238

4 Stereochemical Outcomes

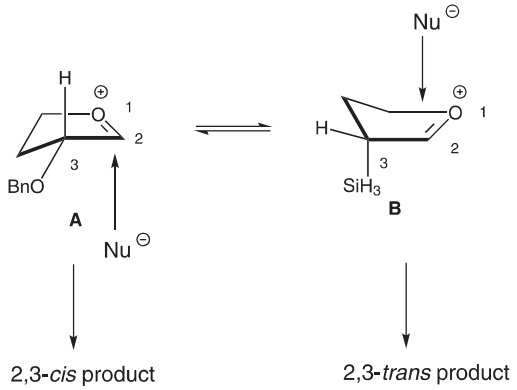
A recent paper by Woerpel[132] on the stereochemical outcomes of the additions of nucleophiles to five-membered oxocarbenium ion intermediates are of relevance to our discussion here on the reactions of related five-membered-ring iminium ion intermediates. Woerpel has shown that the allylation reaction of dihydrofuran derivative **550** was *cis* selective (Scheme 239).



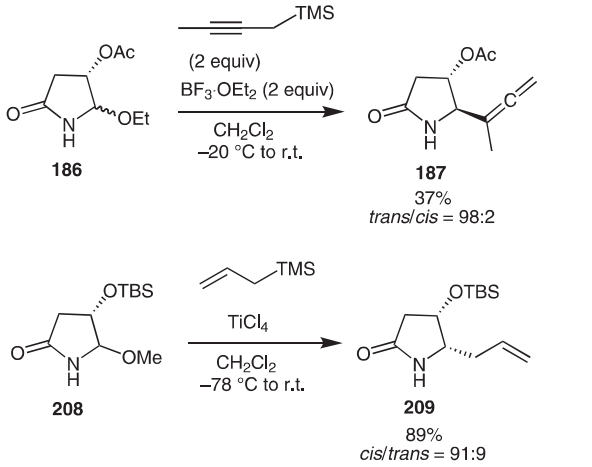
Scheme 239

This stereochemical outcome was consistent with nucleophilic attack on the oxocarbenium ion envelope conformation **A** from the 'inside' rather than on conformation **B**. Attack from the 'inside' gives rise to a more stable staggered product rather than an eclipsed product. Addition to the pseudo-equatorial conformation **A** is favoured over **B** due to stabilisation of the developing σ* orbital at C-2 by the pseudo-axial σ_{C-H} orbital at C-3 (Cieplak effect).[133] The σ_{C-H} bond is a better electron donor (more electron-rich) than the σ_{C-OBu} bond (Scheme 240).

A similar analysis on related five-membered-ring cyclic iminium ion intermediates is further complicated by the extra exocyclic or endocyclic carbonyl group, which further flattens the envelope conformation in the latter system. The N-substituent and its conformational preferences must also be considered in the latter. From a survey of the reactions in Section 3.2.1, it is clear that the nature of the O-substituent (OAc, OBn, OTBS), the N-substituent (NH, NBn, NPMB, N-allyl), the nucleophile and the Lewis acid can affect the diastereoselectivity and 4,5-*cis* to 4,5-*trans* selectivity. The examples that highlight the difference between a 4-OAc and 4-OTBS substituent in the N-unsubstituted case are shown in Scheme 241.

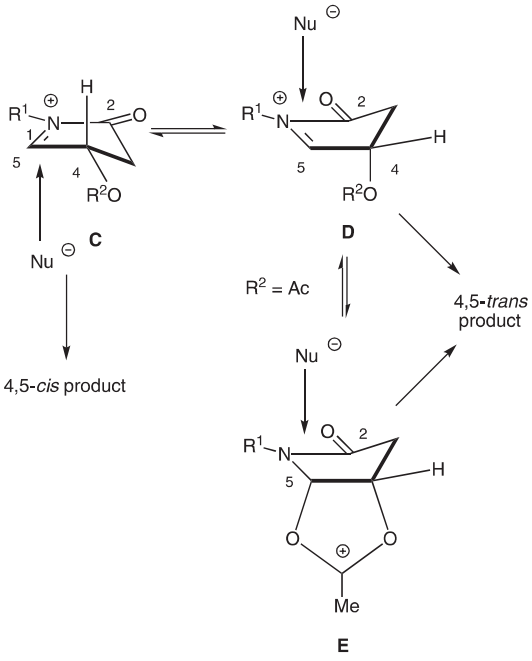


Scheme 240



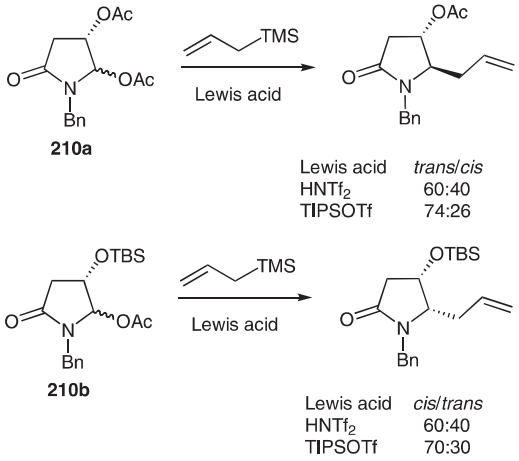
Scheme 241

Both reactions are highly diastereoselective; however, they show opposite *trans*/*cis* selectivity. The OAc derivative favours the 4,5-*trans* adduct while the OTBS derivative favours the 4,5-*cis* adduct. Thus, the OTBS derivative behaves similarly to the dihydrofuran **548** (Scheme 239) in its *cis* selectivity (Scheme 241). Indeed, the reactive envelope conformation **C** with the OTBS group (R^2 = TBS) in the favourable pseudo-equatorial orientation (Cieplak effect), can be invoked to explain this *cis* selectivity. The *trans* selectivity in the case of the OAc derivative can be rationalised by the neighbouring-group participation of the OAc group to give the bridged bicyclic cationic intermediate **E**. S_N2-like attack on this intermediate would provide the *trans* adduct (Scheme 242).



Scheme 242

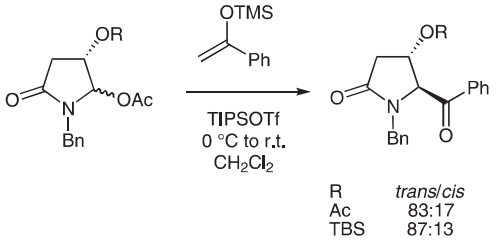
In the case of the allylation reaction of the related N-substituted pyrrolidinones,[54] the same reverse-sense *trans*/*cis* selectivity is observed between 4-OAc and 4-OTBS derivatives; however, the diastereoselectivity is considerably reduced (Scheme 243). Clearly the N-substituent is responsible for this erosion of diastereoselectivity. The influence of the N-substituent in the reactions of N-heterocyclic compounds has been well documented.[134,135]



Scheme 243

This *trans*/*cis* selectivity is also dependent upon the nucleophile, as illustrated in Scheme 244, in which the 4-OAc and 4-OTBS derivatives both favour formation of the *trans* adduct. It is possible that these reactions are under thermodynamic control.

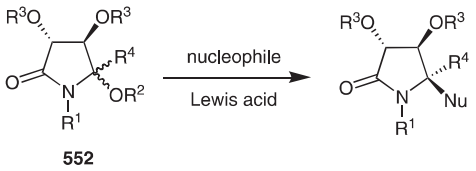
Titanium enolates are highly *trans* selective on 4-OTBS pyrrolidinone derivatives (Scheme 115). The addition of



Scheme 244

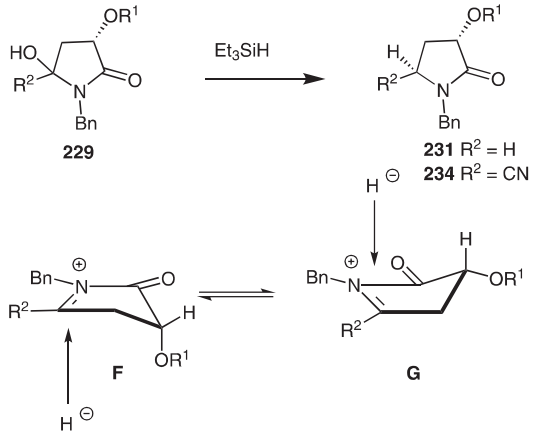
boronic acids to 4-OBn substituted pyrrolidinones are also *trans* selective (Schemes 111 and 112).

The reaction of 3,4-disubstituted pyrrolidinones **552** ($R^3 \neq$ Ac) often gave 4,5-*cis* adducts (R^4 = H) with high diastereoselectivities (Schemes 92, 93, 101, 102, and 103). 5,5-Disubstituted derivatives ($R^3 \neq$ Ac, $R^4 \neq$ H) gave products from nucleophilic addition *cis* to the C-4 OR^3 group (Schemes 89, 94, and 105). This can be attributed to the effect of the C-4 OR^3 group (Cieplak effect). In the cases where the C-3 and C-4 groups are acetate, a neighbouring-group effect by the C-3 acetate has been suggested to explain the 4,5-*cis* selectivity (Scheme 245).[79]



Scheme 245

In the case of the aminals **229**, reduction with triethylsilane and boron trifluoride–diethyl ether complex gave the 3,5-*cis* adducts (Scheme 246).

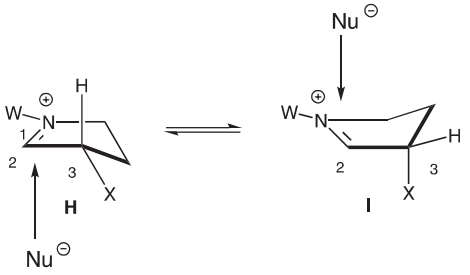


Scheme 246

In related oxocarbenium ions, the OR^1 substituent favoured the pseudo-axial orientation to help stabilise the cationic carbon of the oxocarbenium ion. A similar effect may be possible in conformation **F**; however, the OR^1 group may sterically impede the hydride nucleophile from

attacking. In conformation **F**, 1,3-allylic strain may project the *N*-benzyl group to the β-face of the iminium ion thus more effectively blocking the face to nucleophilic attack.[65]

From a survey of the reactions in Section 3.2 on *N*-acylpyrrolidines, it is clear that 2,3-*trans* products are normally favoured in the case where the 3-substituent is I (Schemes 131 and 162), $NHCO_2R$ (Scheme 131), alkyl (Scheme 147), aryl (Scheme 147) or allyl (Scheme 134). The exceptions are when the 3-substituent is OH or N_3, wherein *cis* products are formed almost exclusively (Schemes 146 and 131, respectively). When the 3-substituent is I or $NHCO_2R$, neighbouring-group participation can be used to explain the *trans* selectivity (compare with Scheme 241). When the C-3 substituent is OH, formation of a boronate intermediate can be invoked to explain the high *cis* selectivity as reported in Scheme 146. When the C-3 substituent is alkyl or N_3, steric and stereoelectronic arguments can be used to account for the stereoselectivities (Scheme 247).



Scheme 247

Because the hyperconjugative donating ability of a σ_{C-H} bond is similar to that of a σ_{C-C} bond, there would be little difference in electronic stabilisation of the transition states involving attack from the 'inside' on the pseudo-equatorial or pseudo-axial conformations **H** (X = alkyl) or **I** (Y = alkyl). Attack on conformation **H**, however, would result in unfavourable *gauche* butane interactions between the Nu and the X group, and thus attack would be expected to occur on compound **I** to give the *trans* product. When the C-3 substituent is N_3 then attack on conformation **H** would be favoured stereoelectronically since the C-3 σ_{C-H} bond is a much stronger electron donor than the σ_{C-N3} bond. Steric considerations are not important with the relatively smaller N_3 group.

Iminium ions generated from 4-substituted *N*-acylpyrrolidines give 2,4-*cis* products (Schemes 129 and 133). A reactive conformation analogous to **F** (Scheme 246) can explain the stereochemical outcome.

In general, reactions on the corresponding six-membered-ring *N*-acyliminium ion analogues have been less studied and often proceed with poorer diastereoselectivity. The stereochemical outcomes of the major products can often be rationalised as arising from axial attacks on a half-chair conformation.[134a,135]

5 Conclusions

The intermolecular addition reactions of *N*-acyliminium ions have been a major area of investigation by synthetic chemists over the past eight years. New methods to generate these cationic intermediates have been developed, including the use of new Lewis acid catalysts, polymer-supported precursors and electrochemical methods. The latter method has been successfully extended to peptide systems and can be used to prepare *N*-acyliminium ions in the absence of a nucleophile.

The reactions of *N*-acyliminium ions include the addition of nucleophiles, especially silicon-based ones, cycloaddition reactions, free-radical additions and nucleophilic aromatic substitution reactions. These latter reactions can be more selectively and efficiently performed using a micromixer. The applications of these methods to the synthesis of peptides, natural products and new pharmaceutical drugs will continue to grow over the next decade.

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