The Metallocarbene Route to Heterocyclic Compounds

by

Soyfur Miah

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of

Doctor of Philosopy

of Loughborough University

October 1997

Abstract

The use of intramolecular aromatic substitution reactions of metallocarbenes derived from α-diazocarbonyl substrates for the preparation of benzo-fused heterocyclic compounds is reviewed.

The preparation and metal catalysed decomposition of selected diazomalonamide esters is outlined. These, and other compounds described, are designed to explore several competing carbenoid reaction pathways, each leading to a different heterocyclic product. Dramatic ligand effects are reported and other factors influencing selectivity are discussed. The use of rhodium(II) perfluorocarboxamides for highly efficient preparation of oxindoles, *via* the intramolecular aromatic substitution reaction, was established.

The methodology developed for oxindole preparation from diazoamides is exploited in the synthesis of the novel marine alkaloid convolutamydine C, in 8 or 10 steps from 3,5-dibromobenzoic acid.

Synthetic studies towards the total synthesis of the uvarindole alkaloids are reported, with the key steps being formation of an oxindole from a diazomalonamide and elaboration in 3 steps to a 1,3-dibenzylindole.

Efforts to explore the possibility of diastereoselectivity in the intramolecular Buchner reaction (IMBR) are reported. Chiral diazomalonamides proved to be poor substrates for this reaction, probably due to conformational effects. Excellent levels of diastereocontrol were observed with chiral diazomalonates, but the recovery of diastereomerically pure products was found to be modest. Attempts to improve the yield of IMBR products are described.

Full experimental details for the synthetic studies are included.

X-Ray crystallographic data for selected α-diazocarbonyl substrates and products from their metal catalysed decomposition are appended.

Acknowledgements

Thanks are due to my supervisor, Chris Moody, for his enthusiastic backing through thick and thin. Also, I appreciated his many efforts in helping to bring our work into the light of day in the form of papers and in this thesis. My industrial supervisor Dr. Ian Richards, ably supported by Dr. Darren Mansfield, contributed a great deal to my research experience. I wish to thank them and the many other staff at AgrEvo UK Ltd for their generous support over the past three years. I also take this rare opportunity to thank all my teachers, past, present and future.

I thank the EPSRC and AgrEvo UK Ltd for generous sponsorship of this research through a CASE award. The staff at Loughborough deserve special thanks. Dr. Russ Bowman and Prof. Harry Heaney have been helpful for many years. A big thank you to Alex Slawin (super X-ray crystallographer!). The technical assistance was appreciated, especially from Alistair Daley, John Kershaw (NMR/MS), and Linda Sands (MS).

Drs. Jon Roffey and Mark Bagley must be thanked for their patient endurance of my constant barrage of questions and demands for advice. Their knowledge and experience hopefully rubbed off on me.

I am grateful to my friends and colleagues in the organic section who lightened my burden on so many occasions with continuous humour and support. They include Dr. Moharem El-Gihani, Dr. Roshan Jumnah, Dr. John Rudderham, Mike Simcox, Richard Buck, Neil Morfitt, Mutasem Taha, Simon Sesay...!!!

On the social side there are a huge band of people who made life in Loughborough not just bearable but in fact pleasurable. Largely because of them I shall sorely miss this town (especially the dinner parties!). My close friends, to whom I remain indebted include Shahzad, Dr. Saeed al-Qahtani, Musaid, Tarek, Hammad, Khalid, Adnan, Uthman, Zahid to mention but a few.

My deepest gratitude is reserved for my family. For my parents who have always been there for me. Needless to say they have helped immeasurably to get me to this point in my life. And a word of thanks to my in-laws for their generosity over more recent times. And, of course, my wife and two daughters who could not possibly be thanked enough for having filled my life with every joy, helping me to get through so many gloomy days and lighting up every last corner.

S. M. (October 1997)

Contents

Chapter One:

The Synthesis of Benzo-fused Heterocycles *via* the Intramolecular Aromatic Substitution Reactions of Metallocarbenes

1.1. Introduction 1
1.2. Nitrogen-containing Heterocycles 2
1.3. Oxygen-containing Heterocycles 9
1.4. Sulfur-containing Heterocycles 13
1.5. Conclusions 14

Chapter Two:

Chemoselectivity of Competitive Intramolecular Carbenoid Reactions

2.1. Introduction 16
2.1.1. Substituents Effects 18
2.1.2. Ligand Effects 24
2.1.3. Conclusions 27
2.2. Three-Way Competition Carbenoid Reactions 29
2.2.1. Preparation of Ethyl 2-Diazomalonyl Chloride 29
2.2.2. Design and Preparation of Competition Substrates 30
2.2.3. Rhodium(II) Acetate Catalysed Reactions 32
2.2.4. Rhodium(II) Perfluorobutyramide Catalysed Reactions 35
2.3. One- and Two-Way Competition Carbenoid Reactions 38
2.3.1. *N*,*N*-Diphenyl Diazomalonamide 38
2.3.2. *Bis*-Diazomalonamide 39
2.3.3. *N*,*N*-Dibenzyl Diazomalonamide 41
2.3.4. 3-(Arylsulfanyl)-2-diazo-3-oxopropanoates 42
2.4. Four-Way Competition Carbenoid Reactions 44
2.4.1. Design and Preparation of Competition Substrates 44
2.4.2. Copper(II) Catalysed Reactions 47
2.4.3. Rhodium(II) Perfluorobutyramide Catalysed Reactions 48
2.4.4. Rhodium(II) Acetate Catalysed Reactions 49
2.4.5. Preparation and Decomposition of *N*-Pyridyl Diazomalonamide Ester 51
2.5. Conclusions

Chapter Three:

Total Synthesis of the Marine Alkaloid Convolutamydine C

3.1.	Introduction	59
3.2.	Recent Synthetic Approaches to the Oxindole Ring System	60
	3.2.1. Reduction of Nitroaromatics	60
	3.2.2. Modified Gassman Synthesis	61
	3.2.3. Lithiation of 2-Methylanilines	62
	3.2.4. Radical Methods	63
	3.2.5. Vicarious Nucleophilic Substitution	69
	3.2.6. Vinylogous Pummerer Reactions	70
	3.2.7. Intramolecular Heck Reactions	71
3.3.	Retrosynthetic Analysis of Convolutamydine C	75
3.4.	Preparation and Rhodium(II) Catalysed Reaction of *N*-Boc Diazocarbonyl	77
3.5.	Preparation and Rhodium(II) Catalysed Reaction of *N*-Benzyl Diazoamide	79
3.6.	Attempted Total Synthesis using *N*-Benzyl Protected Precursors	82
3.7.	Preparation and Rhodium(II) Catalysed Reaction of *N*-4-Methoxybenzyl Diazoamide: Total Synthesis of Convolutamydine C	90
3.8.	Conclusions	95

Chapter Four:

Towards Total Synthesis of the Uvarindole Alkaloids

4.1.	Introduction	97
4.2.	The Diazoamide-Oxindole-Indole Route to the Uvarindole Alkaloids	101
	4.2.1. Retrosynthetic Analysis of Uvarindole B	101
	4.2.2. Synthetic Studies	103
4.3.	Conclusions	115

Chapter Five:

Diastereoselectivity in the Intramolecular Buchner Reaction (IMBR)

5.1.	Introduction	117
5.2.	Chiral Diazoamides as Substrates for the IMBR	118

5.3. Chiral Diazomalonates as Substrates for the IMBR 125
5.3.1. Literature Examples of Diazomalonates as Substrates for the IMBR 125
5.3.2. Preparation and Rhodium(II) Catalysed Reactions of Diazomalonates 128
5.4. Attempts to Improve the Yield of IMBR Products 134
5.5. Conclusions 138

Chapter Six:

Experimental Details

6.1. General Experimental Points 141
6.2. Experimental Details for Chapter 2 142
6.3. Experimental Details for Chapter 3 170
6.4. Experimental Details for Chapter 4 184
6.5. Experimental Details for Chapter 5 193

References 208

Appendix A: X-Ray Crystallographic Data for Selected α-Diazocarbonyl Compounds

Appendix B: X-Ray Crystallographic Data for Selected Cyclisation Products

Appendix C: Notes on Molecular Modelling Studies Conducted on Diazomalonamides

Abbreviations

Ac	acetyl
AIBN	2,2'-azobis-(2-methylpropionitrile)
aq	aqueous
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bn	benzyl
CAN	ceric ammonium nitrate
DCC	*N,N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	diastereomeric excess
eq	equivalents
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
e.e.	enantiomeric excess
Et	ethyl
FGI	functional group interconversion
h	hours
Me	methyl
m.p.	melting point
Ms	methylsulfonyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Ph	phenyl
PMB	4-methoxybenzyl
Pr	propyl
py	pyridine
rt	room temperature
TIPS	triisopropyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

Chapter One

The Synthesis of Benzo-fused Heterocycles *via* the Intramolecular Aromatic Substitution Reactions of Metallocarbenes

1.1. Introduction

The explosion in numbers of the synthetic applications of diazocarbonyl compounds has been recognised by a recent, comprehensive review.[1] In particular, the metal salt catalysed decomposition of diazocarbonyl compounds has become one of the most useful methods for generating transient electrophilic metal-bound carbenes (metallocarbenes).[2-4] Reaction types include cyclopropanation,[2,5] ylide formation and rearrangement,[4,6] C-H insertion,[7] X-H insertion (X=N, O, S),[8] aromatic cycloaddition,[9] and aromatic substitution.[10] Of the many catalysts described for these decomposition processes the rhodium(II) carboxylates (and carboxamides) have assumed a pre-eminent role. These dimeric rhodium species all share the "lantern" structure, in which four ligands bridge the two rhodium atoms leading to octahedral D_{4h} symmetry (**Figure 1** shows rhodium(II) acetate dimer as an example).[11]

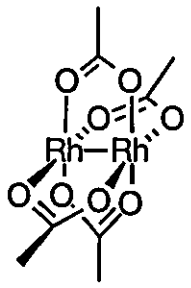
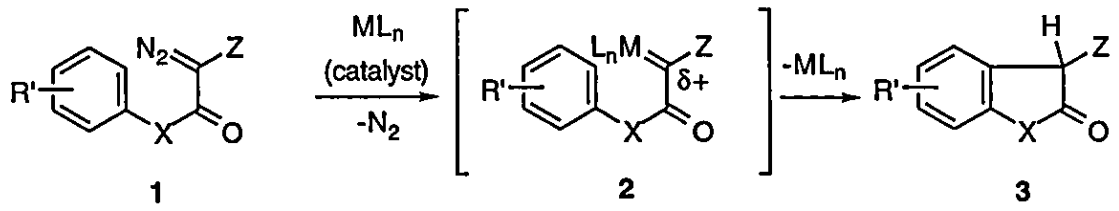


Figure 1

Heterocyclic compounds play a very substantial role in both chemistry and biology. Indeed, about half of the know organic compounds have at least one heterocyclic component. Many heterocyclic compounds occur naturally and their functions are often of fundamental importance to living systems.

This chapter will review reported syntheses of benzo-fused heterocycles *via* the intramolecular aromatic substitution reactions of metallocarbenes derived from α-diazocarbonyl compounds. A large number of studies detailing the preparation of benzo-fused carbocycles have not been included for the sake of brevity and to maintain the heterocyclic theme of the current work.[12] The basic outline of reports selected for presentation in the current review is summarised in schematic form below (**Scheme 1**). Thus, a substrate **1** which contains an α-diazocarbonyl unit tethered to an aromatic ring by a heteroatom containing link (X), is decomposed with a metal catalyst to give a transient reactive metallocarbene intermediate **2**. This electrophilic intermediate then undergoes an intramolecular attack on the aromatic ring (aromatic substitution) to furnish heterocyclic products **3** (effectively inserting into the aromatic C-H bond).



1 2 3

X= heteroatom containing link

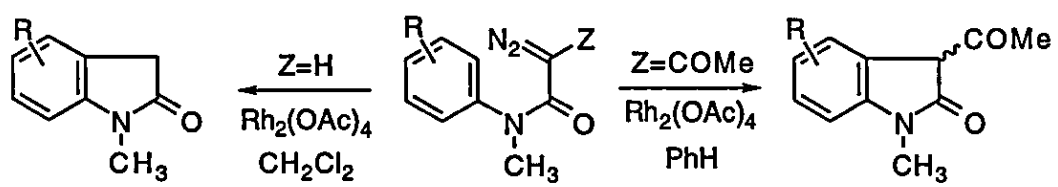
Scheme 1

Examples of acid-promoted intramolecular aromatic substitution of diazocarbonyl compounds have also been reported for the formation of heterocycles, and since these are relatively few in number they will be discussed briefly.

1.2. Nitrogen-containing Heterocycles

There are a large number of reports describing the preparation of benzo-fused nitrogen heterocycles, and in particular indolin-2-ones (also called oxoindolines or oxindoles; the latter name will be used henceforth).

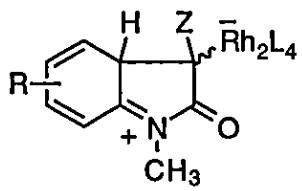
Much of the early work in this area of research was pioneered independently by the groups of Durst, Doyle and Wee. Thus, in 1988 Doyle showed that various substituted *N*-aryldiazoacetamides **4** (Z=H) and *N*-aryldiazoacetoacetamides **5** (Z=COMe) could be cyclised under rhodium(II) acetate catalysis to afford the respective oxindole products, **6** and **7**, in high to excellent yields (**Scheme 2**).[10] Examples of substitution patterns included methyl and alkoxy groups (R) on the aryl ring and the substituent on the amide nitrogen could be methyl, ethyl or benzyl; in all cases no competing carbenoid reactions were observed. These results were confirmed later by Müller who further demonstrated that the reactions could be performed in the presence of methanol without competing insertion into the O-H of this solvent.[13]



6 4, Z=H 5, Z=COMe 7

Scheme 2

Doyle proposed that the mechanism of the carbenoid reaction is an electrophilic aromatic substitution proceeding *via* the intermediate **8**. Thus, the carbenoid is regarded as a carbocation stabilised by the rhodium and its bridging ligands, which attacks the aromatic ring in a rate determining step to give intermediate **8**; the aromatic C-H bond is broken subsequently in a fast, none rate-limiting step to return the aromaticity lost in the first step, and to furnish ultimately the oxindole.

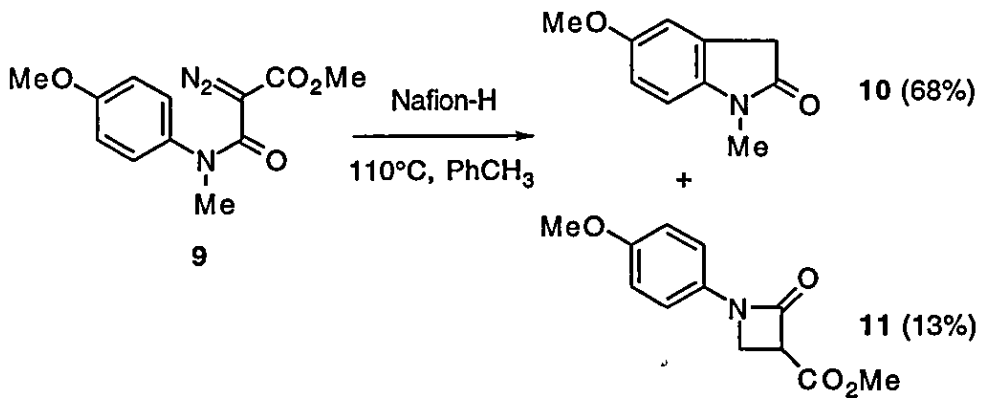


8

Figure 2

In 1988, Doyle showed, for the first time, that the perfluorinated resin sulfonic acid Nafion-H catalysed the cyclisation reactions of diazoacetamides **4** to give high yields of oxindoles **6**; however it failed to catalyse the decomposition of the diazoacetoacetamides **5**, possibly as a consequence of the steric effect of these bulkier substrates as they attempt to enter the catalytically active protonic regions in the resin.[10] This ability of strong acids to catalyse decomposition of diazoacetamides is taken as a support for the proposed electrophilic aromatic substitution mechanism of the rhodium(II) catalysed reactions.

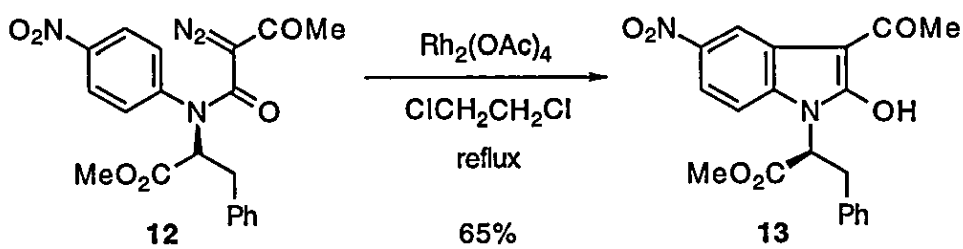
Wee expanded on this work with reports of Nafion-H catalysed decomposition of *N*-aryl-diazomalonamides (for example **9**) for the preparation of oxindoles. It was proposed that the oxindoles formed undergo immediate decarboxylation following the cyclisation. However, the ester group is similar to the acetyl group, and in light of Doyles observed failure to cyclise diazoacetoacetamides **5**, it might be speculated that the decarboxylation takes place before the aromatic substitution reaction. Moreover, Wee showed that β-lactams are also formed competitively along with the oxindoles (**Scheme 3** shows one example).[14] This pathway proceeds with retention of the ester group; presumably the decarboxylation is only partial and the reactive electrophilic intermediate which carries the retained ester group undergoes chemoselective C-H insertion into the *N*-methyl group to furnish **11**. The decarboxylated carbenoid intermediate, on the other hand, undergoes aromatic substitution to give the oxindole product **10**.



Scheme 3

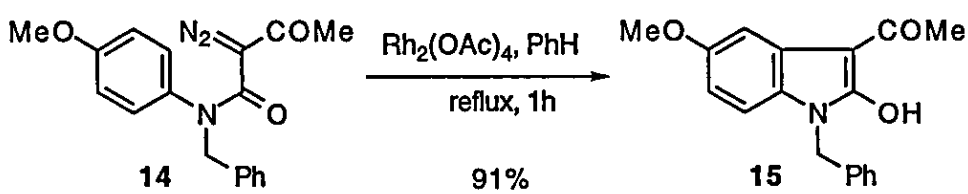
Smith and Bahzad have recently shown that the cyclisation of diazomalonamide **9** could also be effectively promoted by zeolite Kβ to afford the oxindole **10** in high yield (89% by GC); the β-lactam **11** is formed in just 7% yield.[15]

In a recent report from Zaragoza, the more complex *N*-aryldiazoacetoacetamide **12** was found to undergo rhodium(II) acetate catalysed cyclisation onto the electron deficient aryl ring to afford the 2-hydroxyindole **13** in good yield (**Scheme 4**).[16]

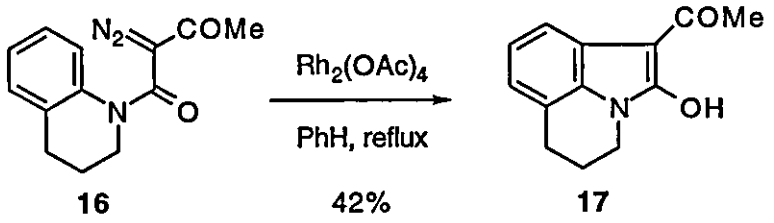


Scheme 4

Several more examples of 3-acetyloxindole preparations *via* rhodium(II) acetate catalysed cyclisation of diazoacetoacetamides have appeared in the literature and some are presented below (**Schemes 5**,**6** and **7**).[17-19]

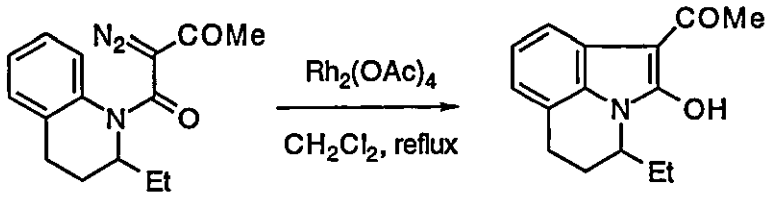


Scheme 5



16 42% 17

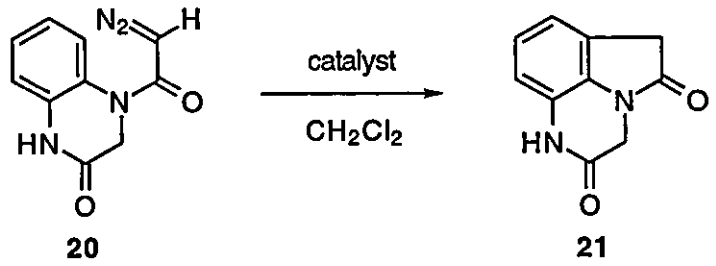
Scheme 6



18 88% 19

Scheme 7

Another oxindole forming cyclisation was undertaken by workers at the Upjohn Company as part of a medicinal chemistry research program. Decomposition of the diazo quinoxalinone **20** with rhodium(II) trifluoroacetate afforded the desired lactam **21** in 60% yield (**Scheme 8**). Rhodium(II) acetate was found to be a poor catalyst for this particular cyclisation (**Table 1**).[20]



20 21

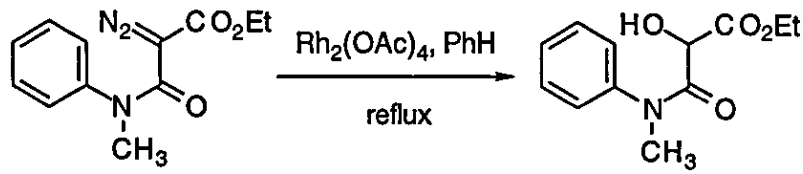
Scheme 8

Catalyst	Yield (%)
$Rh_2(O_2CCF_3)_4$	60
$Rh_2(OAc)_4$	<10

Table 1

In contrast to the good yields of 3-acyl- and 3,3-dihydrooxindoles obtained by Doyle and others from diazoamides, the presence of an α-ester group as, for example, in compound **22** results in complete inhibition of the aromatic substitution pathway.[18] Durst reports that the only product obtained was **23**, assumed to arise from interception of adventitious water by the reactive carbenoid intermediate (**Scheme 9**). The same

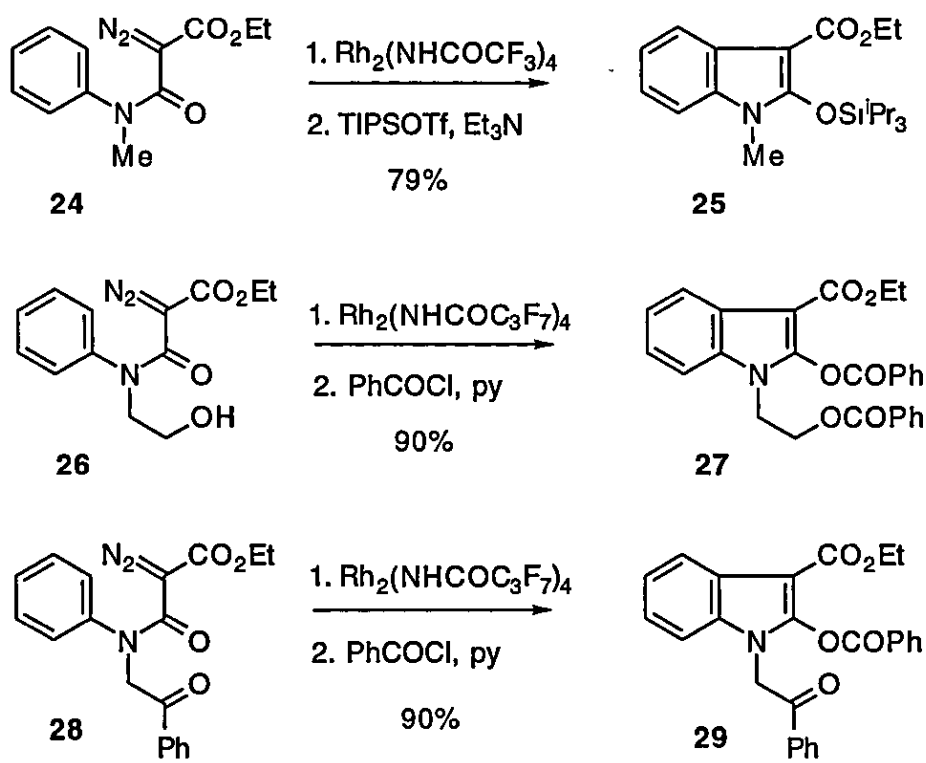
report continues to describe other competing carbenoid reactions as being favoured over the aromatic substitution reaction (Chapter 2). Wee reported that the methyl ester analogue of **22** did undergo C-H insertion into the *N*-methyl group in good yield (see Chapter 2 for details).



22 12% **23**

Scheme 9

The Moody group, in collaboration with Padwa and co-workers, presented a number of examples of oxindole synthesis which overcame the inhibitory effect of an α-ester group on the aromatic substitution pathway. This is achieved by the use of rhodium(II) perfluorocarboxamides as catalysts in place of rhodium(II) acetate. In general they demonstrated that rhodium(II) perfluorocarboxamides strongly favour the aromatic substitution reaction over competing C-H insertion, O-H insertion, and ylide formation. Examples of this dramatic ligand effect are illustrated below (**Scheme 10**).[21]



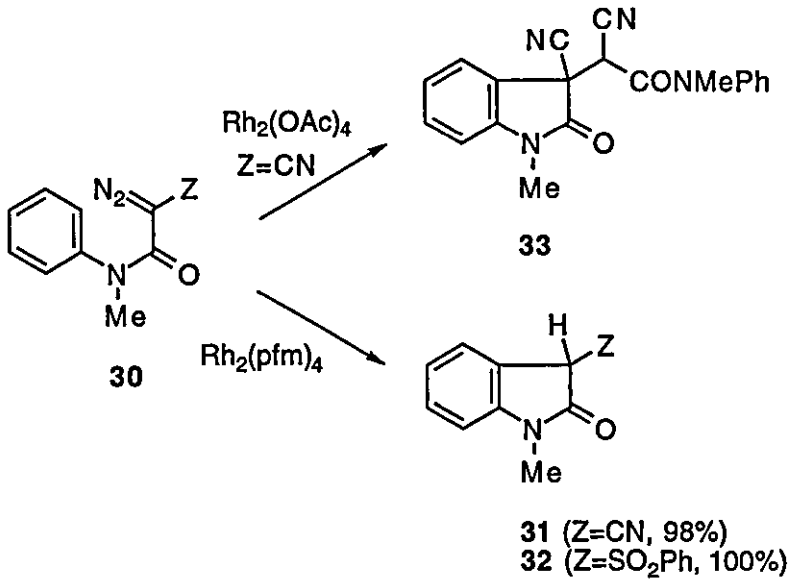
24 **25**

26 **27**

28 **29**

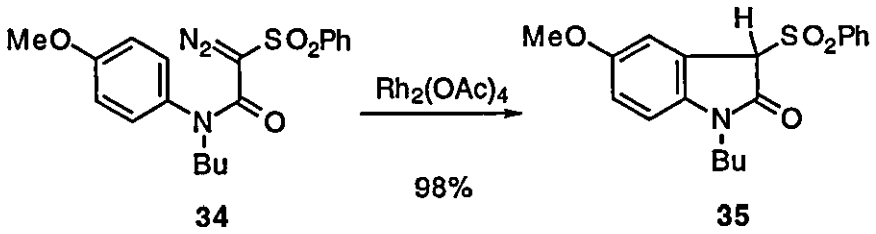
Scheme 10

In a recent follow-up report, the Padwa group have shown that the aromatic substitution reaction can be used to prepare oxindoles with C-3 functionality other than the widely reported hydrogen, acetyl, and ester groups. Thus, for example, the 3-cyanooxindole **31** and the 3-phenylsulfonyloxindole **32** can be obtained in high yield upon rhodium(II) perfluorobutyramide catalysed decomposition of the appropriate diazoamide precursor **30**. Interestingly, if the catalyst is changed to rhodium(II) acetate then the oxindole formed, **31**, immediately undergoes a C-H insertion reaction at C-3 with another molecule of the diazo starting material to give the unusual dimer **33** in high yield; it was also noteworthy that the *N*-methyl group was again not attacked (**Scheme 11**).[22]



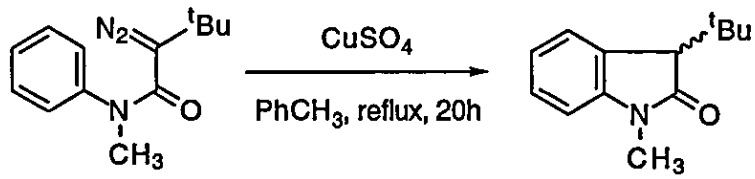
Scheme 11

It was noted, however, that the preparation of 3-phenylsulfonyloxindole **35**, which is related to **32**, had been reported several years earlier by Wee and employed the standard catalyst, rhodium(II) acetate, to equal effect.[19] This facile cyclisation is presumably due to the presence of the methoxy group which activates the aromatic ring to attack by the carbenoid.



Scheme 12

Copper(II) salts are found to be relatively poor catalysts for the aromatic substitution method of oxindole ring formation when compared to rhodium(II) compounds, and a recent example is illustrated below (**Scheme 13**). Copper(II) sulfate did not promote C-H insertion into the *N*-methyl group of diazoamide **36**.[23]

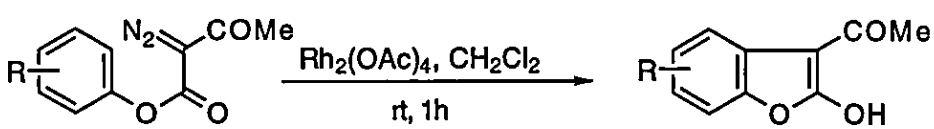


36 35% **37**

Scheme 13

1.3. Oxygen-containing Heterocycles

Durst has also presented early reports on the efficient preparation of benzofuranones *via* the intramolecular aromatic substitution reaction of rhodium carbenoids.[24] Thus, several α-diazo-β-ketoesters **38** were transformed in near quantitative yields to 3-acetyl-2-hydroxybenzofurans **39** (**Scheme 14** and **Table 2**).



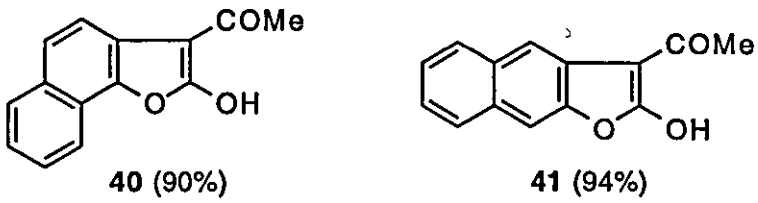
38 **39**

Scheme 14

Diazo **38** R	Product **39** R	Yield (%)
H	H	98
2-Me	7-Me	98
2-Br	7-Br	92
3,4-OCH_2O-	5,6-OCH_2O-	91

Table 2

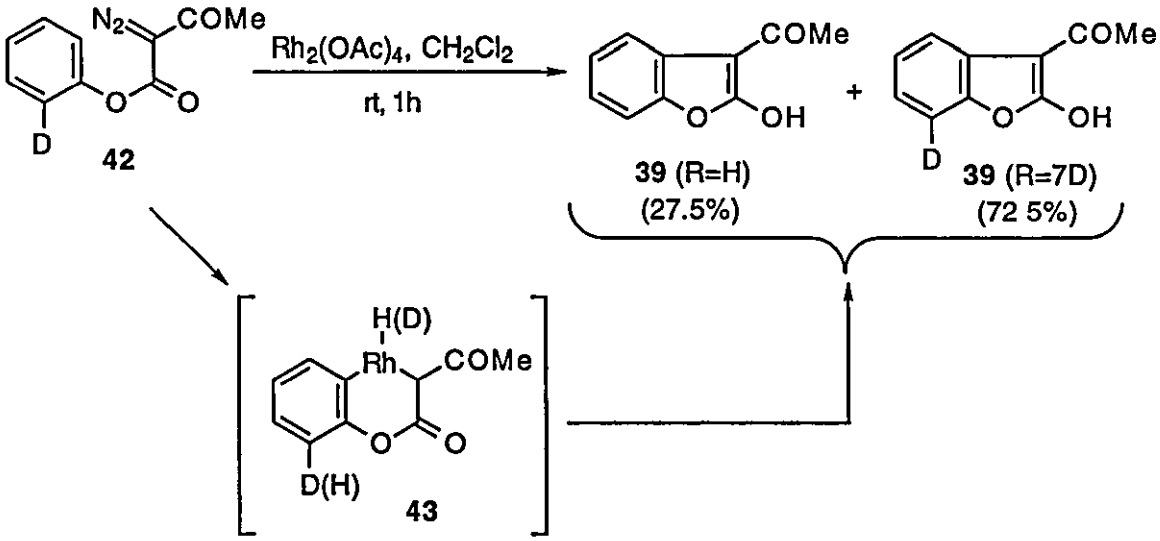
Further examples of this useful transformation included the exclusive formation of two naphthofuranones **40** and **41** from their respective α-diazo-β-ketoester precursors; alternative products were not observed (**Figure 3**).



40 (90%) **41** (94%)

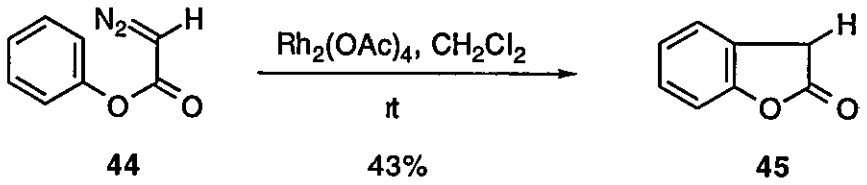
Figure 3

Durst also went on to show that a significant deuterium isotope effect was measurable for the cyclisation of (2-deuterophenyl) 2-diazoacetoacetate **42** under rhodium(II) acetate catalysis. The deuterium bearing cyclisation product **39** (R=7D) was found to be in preponderance over the none deuterated product **39** (R=H) and the ratio indicated a hydrogen-deuterium isotope effect (k_H/k_D) of about 2.65. Normal electrophilic aromatic substitution reactions, in which the breaking of the aromatic C-H bond is not the slow rate-determining step, have small hydrogen-deuterium isotope effects (<1.3). The observation of a relatively large isotope effect for **42** was taken as support for a C-H insertion mechanism for the intramolecular cyclisation of diazoacetoacetates such as **38**. The six membered metallocycle, formed *via* slow C-H/C-D insertion, **43** was proposed as an intermediate in this C-H insertion mechanism (**Scheme 15**).



Scheme 15

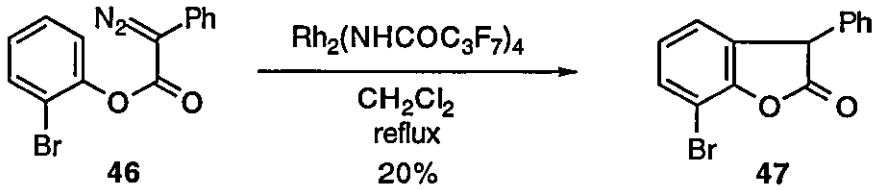
More recently, Müller has shown that the phenyldiazoacetate **44** also underwent aromatic substitution to afford benzofuranone **45** but in lower yield than the corresponding diazoacetoacetate **38** (**Scheme 16**).[13] Presumably the additional carbonyl substituent in **38** renders the intermediate carbenoid more electrophilic.



44 43% **45**

Scheme 16

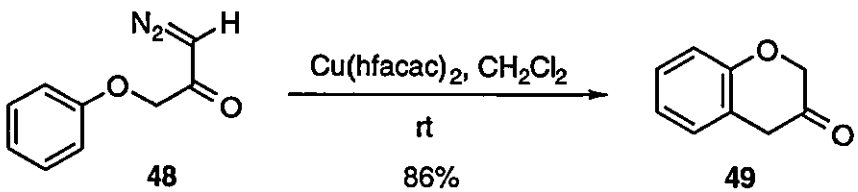
As part of a synthetic program targeted at total synthesis of the complex marine natural product diazonamide A, the Moody group have recently reported an intramolecular aromatic substitution reaction for the construction of 7-bromobenzofuranone **47** from the diazoester **46** (**Scheme 17**). Again the yield was lower than for the preparation of related 3-acetylbenzofuran-2-ones.[25]



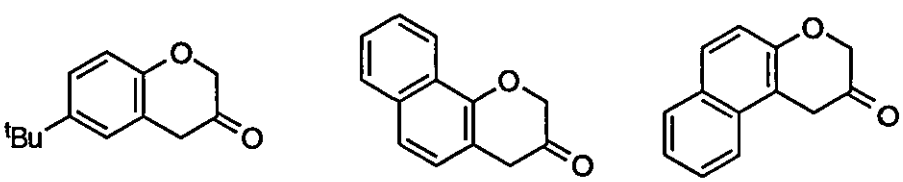
46 20% **47**

Scheme 17

Saba has demonstrated that copper(II) hexafluoroacetylacetonate is an excellent catalyst for the cyclisation of 1-diazo-3-aryloxy-2-propanones (such as **48**) to afford benzopyran-3-ones (**49**, and **50** amongst others) and naphthopyran-3- or -2-ones (**51**, and **52** are examples). Competing side reactions such as dimerisation and aromatic cycloaddition were not observed (**Scheme 18**).[26]



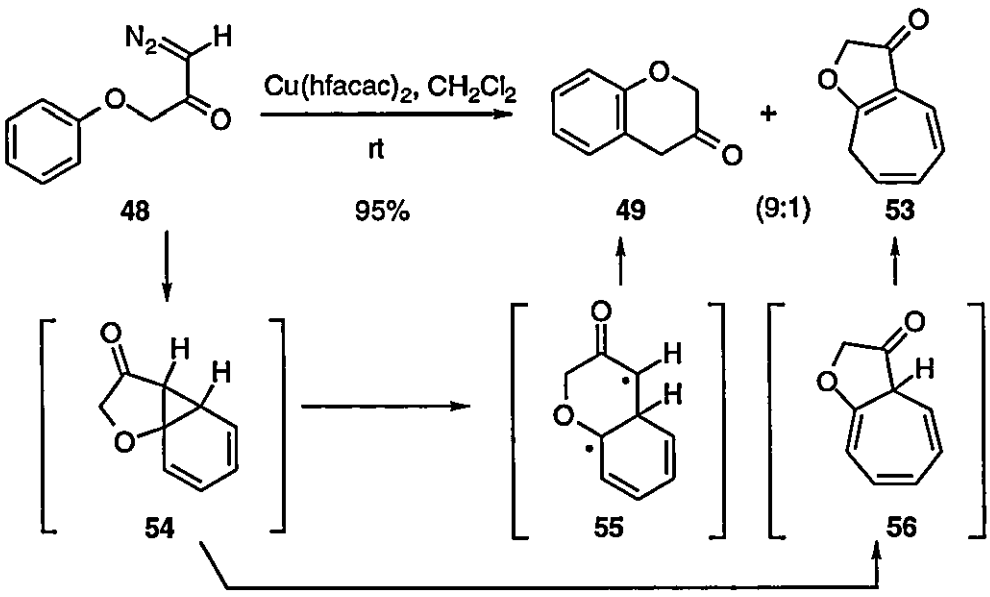
48 86% **49**



50 (80%) **51** (84%) **52** (87%)

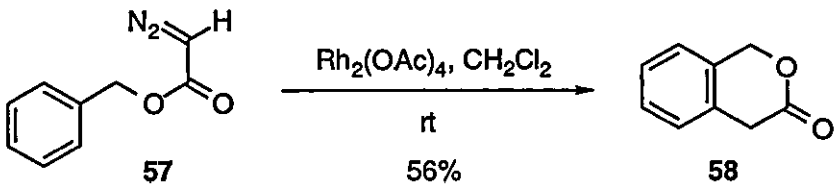
Scheme 18

However, a subsequent more thorough investigation of the reactions of the 1-diazo-3-phenoxy-2-propanones from Saba and co-workers showed that the aromatic cycloaddition pathway did indeed compete and might possibly be the actual originating reaction for all the products observed.[27] Thus, they showed that the actual products from decomposition of **48** was a 9:1 mixture of benzopyranone **49** and the cycloheptafuranone **53** (not as previously claimed to be exclusively **49**). They also found that substitution at the 3-position of the diazo precursors favoured the furanone products over the benzopyranones. Interestingly they proposed that both product types arise from the common norcaradiene intermediate **54**, with the benzopyranone **42** being produced *via* homolytic C-C bond cleavage, [1,2]-hydrogen shift and C-C bond formation. They support this proposal through observation of a depression of the favoured benzopyranone formation when the phenyl ring is pentasubstituted with deuterium atoms (the ratio of benzopyranone to furanone falls to 7:3) (**Scheme 19**). They also noted that having a methyl on the diazo carbon, instead of the hydrogen as in **48**, also strongly promoted formation of the cycloheptatriene products over chromanones and it would appear that this substituent suppresses hydrogen shift.



Scheme 19

Also, in line with these observations of Saba,[26] Müller showed that when benzyl diazoacetate **57** was decomposed with rhodium(II) acetate it afforded the product of aromatic substitution **58** in modest yield. Though the possibility of intramolecular aromatic cycloaddition to give a norcaradiene/cycloheptafuranone exists, it was not observed (**Scheme 20**).[13]

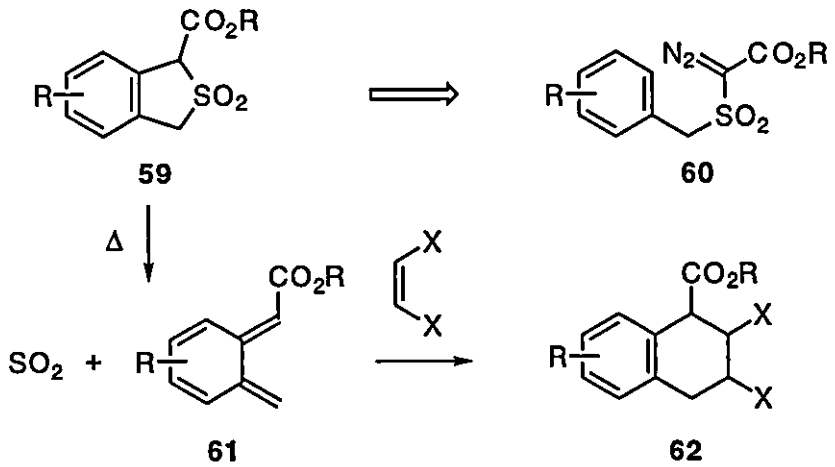


57 58

Scheme 20

1.4. Sulfur-containing Heterocycles

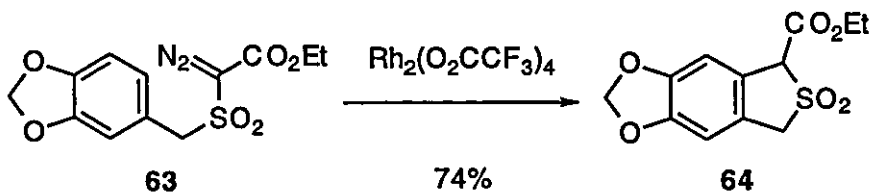
Durst has reported the preparation of 1-alkoxycarbonyl-1,3-dihydrothiophene 2,2-dioxides **59** *via* the rhodium(II) acetate catalysed decomposition of α-diazo-β-arylmethanesulfonyl esters of the type **60** (**Scheme 21**).[28] Substrates **59** are useful precursors to the *o*-quinodimethanes **61**, obtained by thermal extrusion of sulfur dioxide. These dienes can then be utilised in Diels-Alder reactions.



59 **60** **61** **62**

Scheme 21

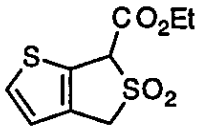
The yields of products given as examples of the above cyclisation were in the range of 14% to 56%, and the best example involved use of a different catalyst (rhodium[II] trifluoroacetate) on a favourable substrate **63** (**Scheme 22**).



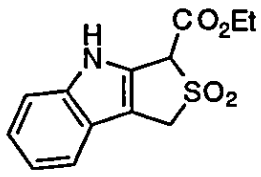
63 **64**

Scheme 22

This cyclisation strategy is also applicable to the preparation of 2,5-dihydrothiophene sulfones fused onto the 2,3-position of thiophene and indole though the yields from the respective diazoesters are only modest (**Figure 4**).[29]



65 (50%)



66 (24%)

Figure 4

As with the diazoacetoacetate **42**, the diazosulfone **60** (R=2D) also showed a significant hydrogen-deuterium isotope effect (k_H/k_D=5.45). This again was interpreted as indicating that aromatic C-H bond cleavage is a slow, rate-determining step and occurs *via* carbenoid insertion into the C-H bond.

1.5. Conclusions

The above summary of synthetic preparations of benzo-fused heterocycles *via* intramolecular cyclisation of metallocarbenes demonstrates that this method can be valuable in terms of simplicity, efficiency and versatility. Careful choice of substituents and catalyst lead to excellent yields of cyclised products, and these can contain a variety of functionality for further elaboration. In particular, rhodium(II) perfluorocarboxylates and carboxamides have emerged as the catalysts of choice for the preparation of substituted oxindoles from *N*-aryldiazoamides. The mechanism of the cyclisation reaction is as yet unclear, but the strongest arguments are for electrophilic aromatic substitution or aromatic C-H insertion, and this may differ with substrate and catalyst.

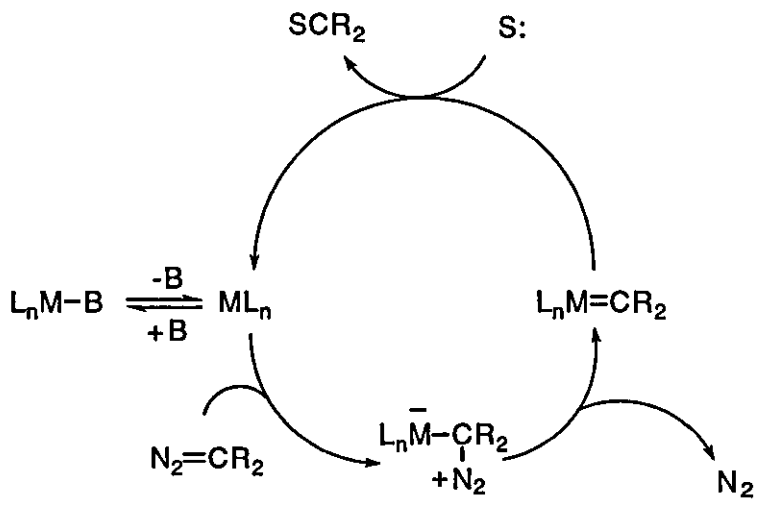
Chapter Two

Chemoselectivity of Competitive Intramolecular Carbenoid Reactions

2.1. Introduction

The catalytic generation of metallocarbenes from diazo compounds and their synthetic use has attracted a great deal of attention in recent years.[1] This is evidenced by a large and ever-growing number of publications including several useful reviews. The first example of metal-mediated reaction of an α-diazocarbonyl compound was described by Silberrand and Roy in 1906.[30] Copper dust catalysed the decomposition of ethyl diazoacetate to give triethyl 4,5-dihydropyrazole-3,4,5-tricarboxylate. Since then a large number of metals and an huge variety of their complexes have been screened as potential catalysts for the decomposition of diazo compounds, and particularly diazocarbonyl compounds.[2] Carbenoids, being metal-bound carbenes, are by their very nature highly reactive intermediates and this raises the issue of the selectivity of subsequent reactions and its practical control. Careful choice of catalyst should offer one tool for meeting this crucial aim of modern synthetic organic chemistry.

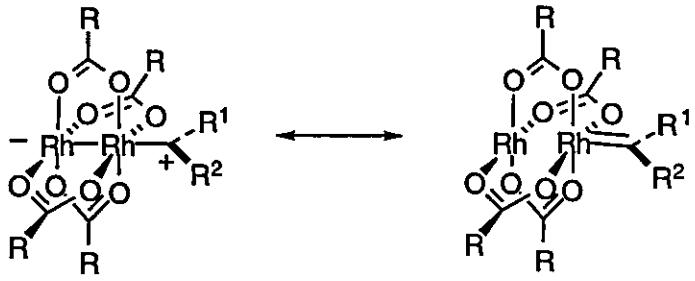
Doyle has proposed a general mechanism for the transition metal catalysed reaction of α-diazocarbonyl compounds and this cycle is detailed schematically below (**Scheme 23**). The first step of the sequence is decomplexation of the metal (M) from the Lewis base (B; that is, the solvent). This is followed by attack of the diazo group at the metal to form a zwitterionic metallo intermediate. Then nitrogen is extruded to form the metal carbenoid which can go on to react with the substrate present (S) to give the observed product (SCR_2). The catalyst is regenerated to complete the cycle.[2]



Scheme 23

Out of the large number of catalysts screened, the rhodium(II) dimers have emerged as a family of catalysts of particular merit in several respects. Dirhodium(II) complexes act as catalysts for the decomposition of α-diazocarbonyl compounds thereby generating

transient electrophilic rhodium carbenoids which can subsequently undergo a range of synthetically useful reactions.[1-10] These transformations include cyclopropanation,[2,5] ylide formation and rearrangement,[4,6] C-H insertion,[7] X-H insertion (X=N, O, S),[8] aromatic cycloaddition,[9] and aromatic substitution.[10] Thus, this catalytic methodology has assumed strategic importance in C-C bond-forming reactions in organic synthesis. Though rhodium(II) carbenoids have never actually been isolated or observed by spectroscopy the resonance forms **67a** and **67b** have been proposed by Doyle as a useful description (**Figure 5**). The diazo compound attacks the catalyst at the vacant axial coordination site to give **67** which is considered as a stabilised carbocation, with the stabilisation arising through electron donation into the dirhodium framework.[31]



67a **67b**

Figure 5

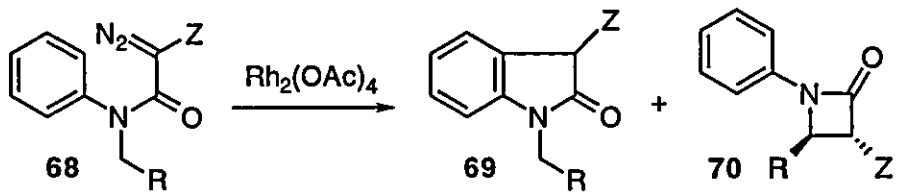
Taber has proposed a mechanism for C-H insertion reactions of rhodium carbenoids in which the Rh-O bonds are broken on attack of the diazo compound at the axial position of the rhodium dimer. He proposed that the Rh-Rh bond is broken to allow nitrogen extrusion and carbenoid formation.[32] This mechanism is, however, not consistent with the high degrees of stereoselectivity normally observed with C-H insertion reactions especially in the use of chiral dirhodium catalysts for enantioselective reactions.[33]

The dirhodium(II) framework is particularly useful among the several transition metal complexes which catalyse the decomposition of α-diazocarbonyl compounds because it is amenable to ligand modification, and it has been demonstrated that carbenoid reaction selectivities can be effectively controlled by careful choice of the ligands on the metal. Thus, a number of studies have shown that, despite their high reactivity, rhodium-bound carbenoids often display a remarkable degree of chemoselectivity when there is choice between two or more reaction pathways.[34] Site selectivity has been found to depend on the type of α-diazocarbonyl compound used as well as steric,[12,32,35-38] conformational,[39] and electronic factors.[40-44] A valuable review of the effects of ligands on the chemoselectivity of transition metal catalysed reactions of α-diazocarbonyl compounds has recently been published by Padwa and Austin.[45]

It is, never the less, worthwhile reviewing some of the work which has appeared in the literature to date, describing the effects of substituents in the diazocarbonyl substrate and ligands on the catalyst upon the chemoselectivity of metallocarbene reactions. Within the context of the current work, particular emphasis will be placed on examples which are based on intramolecular cyclisation reactions for the preparation of heterocycles. A large number of reports dealing with the chemoselectivity of carbocycle formation have been excluded.[46] Also some relevant material has already been detailed in the introductory chapter (Chapter 1).

2.1.1. Substituent Effects in Competitive Carbenoid Reactions

A number of research groups have investigated the effect of subsituents on the course of competitive carbenoid processes. Thus, the most widely used catalyst, rhodium(II) acetate, was used for the catalytic decomposition of a set of differing *N*-alkyl-2-diazo-*N*-phenylamides **68**. A competition between two reaction pathways was observed. These were aromatic substitution into the *N*-phenyl ring, leading to oxindole **69**, and aliphatic C-H insertion into the methylene α to the amide nitrogen, leading to *trans* β-lactam **70** (**Scheme 24**). The selectivity of these reactions was found to be strongly dependent on the substituents on the diazo starting material **68** (**Table 3**).



Scheme 24

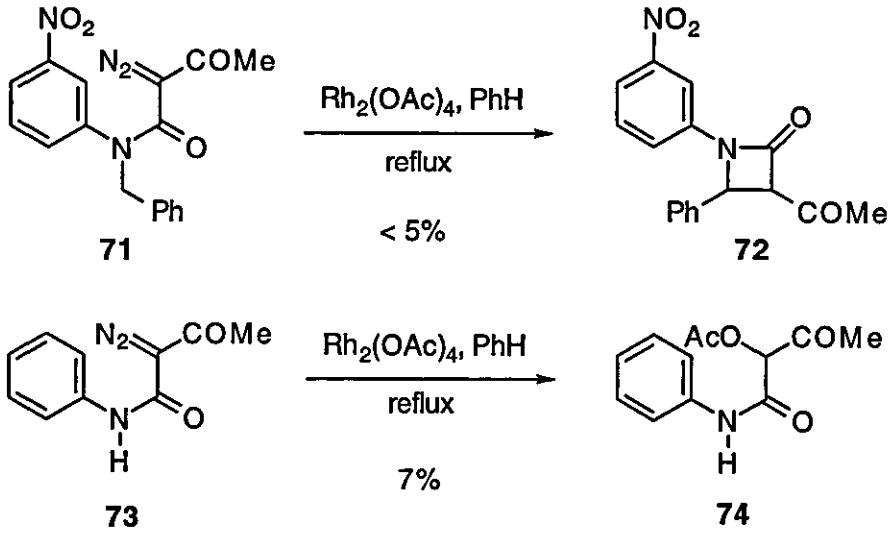
Substrate	Z	R	% 69	% 70
68a	H	H	86	0
68b	COMe	H	86[i]	0
68c	H	Ph	87	0
68d	COMe	Ph	80[i]	0
68e	CO_2Et	H	0	0
68f	CO_2Et	Ph	28[ii]	61
68g	CO_2Me	H	0	51
68h	CO_2Me	Me	0	51

(*i.* exists as 3-acyl-2-hydroxyindole tautomer; *ii.* yield quoted from NMR data)

Table 1

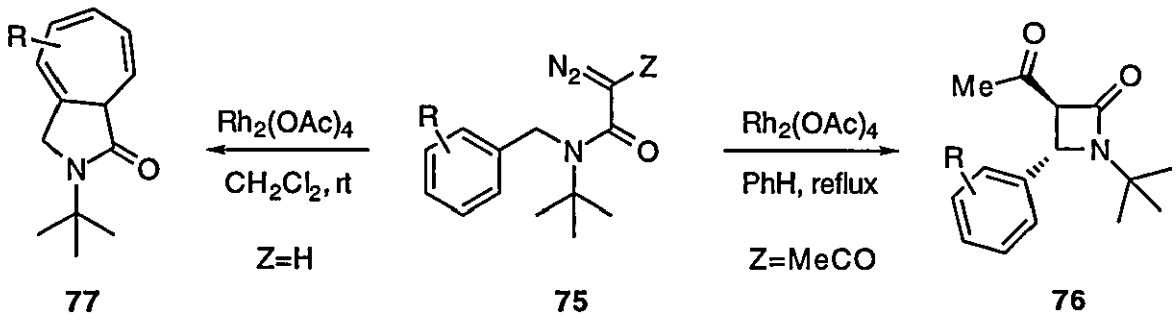
Doyle reported that diazoacetamides **68a** and **68c**, and diazoacetoacetamides **68b** and **68d** all underwent efficient intramolecular aromatic substitution with no other products detected (see **Scheme 2**).[10] This is in stark contrast to an example cited by Durst in which the acetyl group of **68b** is replaced with an ethyl ester group as in **68e**. In this case attack into the phenyl group is completely inhibited by the introduction of the ester group and the only isolated product is that of insertion of the transient carbenoid into adventitous water (12% yield of the 2-hydroxyamide). Also, no insertion into the *N*-methyl group was observed.[18] This is complemented by a report from the Moody group in which the *N*-methyl is changed for *N*-benzyl to give **68f**. In this example both the competing processes were observed. The β-lactam **70f** was actually isolated as the major product (61%) along with the oxindole **69f** in a lower yield (28%).[21] It is apparent that the benzylic methylene is far more susceptible to attack by a rhodium carbenoid than a methyl group. Wee reported that C-H insertion into an *N*-methyl group of compound **68g** did take place and gave only the β-lactam **70g** with no attack of the aromatic ring; this result stands in contrast to that observed for **68e** which only differs from **68g** in being an ethyl rather than a methyl ester and yet gives no β-lactam at all. And, similarly, the *N*-ethyl analogue **68h** also gave only the β-lactam **70h**.[19] Thus, minor changes in structure can lead to significant shifts in product distribution (compare **68b** to **68e** and **68g**), and considerable care needs to be excercised in any planned use of metallocarbenes for target synthesis.

Not all diazoacetacetamides give efficient cyclisation to oxindoles on rhodium(II) acetate catalysed decomposition. Thus, compound **68d** should be compared to the related diazocarbonyl compound **71**. When the aryl ring is substituted with an electron-withdrawing nitro group, as in **71**, its nucleophilicity is reduced sufficiently to divert attack by the electrophilic carbenoid away from the ring and onto the benzylic methylene to afford the β-lactam **72** as the only isolated product. Also, if a secondary amide, such as **73**, is decomposed it gives no oxindole and the only product isolated is the unusual acetate **74** arising from insertion into a displaced ligand of the catalyst (**Scheme 25**).[18]



Scheme 25

Another set of interesting results which show that small changes in structure can lead to shifts in selectivity was reported by Doyle. Treatment of a series of *N*-benzyl-*N*-*tert*-butyldiazoacetoacetamides **75** (Z=MeCO) with rhodium(II) acetate (1 mol%) in refluxing benzene resulted in the exclusive production of *trans*-disubstituted β-lactams **76** in high yields.[39a] In contrast, the *N*-benzyl-*N*-*tert*-butyldiazoacetamides **75** (Z=H) on treatment with the same catalyst at room temperature and in dichloromethane solution underwent exclusive aromatic cycloaddition (Buchner reaction) onto the phenyl ring to afford cycloheptapyrrolones **77** in high yield (**Scheme 26, Table 4**).[47] The acetyl group of the diazo carbon clearly inhibits carbenoid addition to the aromatic ring, and this is true even when the ring is substituted with two methoxy groups to enhance its nucleophilic reactivity. In trying to explain this selectivity, Doyle proposed that conformational influences of the acetyl group inhibits aromatic cycloaddition. On the other hand, Wee suggested that the divergence in selectivity was due to the electronic nature of the substituents rather than conformational requirements.[32] This latter argument, however, cannot fully account for the observation that metallocarbenes substituted on the reactive carbon with acetyl and ester groups sometimes give rise to different products even though these substituents are electronically similar.

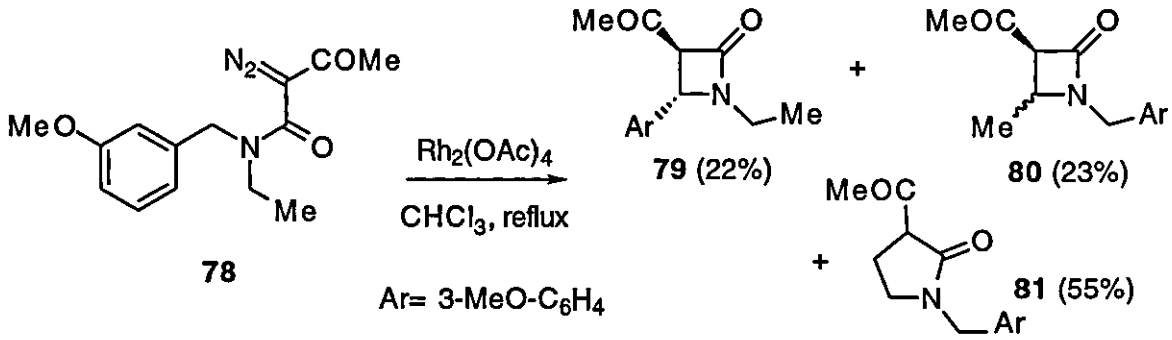


Scheme 26

yield **77** (%)	R in **75**	yield **76** (%)
94	3,4-di-MeO	95
93	3-MeO	90
99	H	98
89	3-Br	92
-	4-NO_2	92

Table 4

The bulky *tert*-butyl group was found to be an essential substituent for clean conversion to the single products. In the decomposition of diazoacetoacetamides, replacing the bulky *tert*-butyl group with a methyl group gave the expected *trans* β-lactam from C-H insertion into the benzylic methylene in just 12% yield. No products from insertion into the methyl group or attack of the aromatic ring were found. If the substrate has an ethyl group on nitrogen as in **78** the rhodium(II) acetate catalysed decomposition gives competitive formation of products of insertion into all three available aliphatic centres (**Scheme 27**). The isopropyl analogue gives insertion into the benzylic methylene (60%) and the methine C-H (40%).[40]



Scheme 27

The conclusions that are drawn by Doyle from these observations are that selectivity in these reactions appears not to be a function of electronic influences by substituents on the reacting C-H bond. Doyle argues that the selectivity is dependent on which C-H is locked in close proximity to the carbenoid centre and that this is determined by amide conformation and steric factors. Overlap of the nitrogen non-bonding electrons with then carbonyl π-system fixes the amide conformation so that the larger nitrogen substituent is oriented toward the carbonyl group. Steric effects by the carbenoid substituents on the benzylic substituents force the aryl group away from the acetyl group and coordinated metal and place the benzylic hydrogens within the reactive environment of the carbenoid centre (**Figure 6**).[39a]

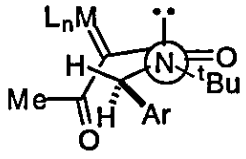
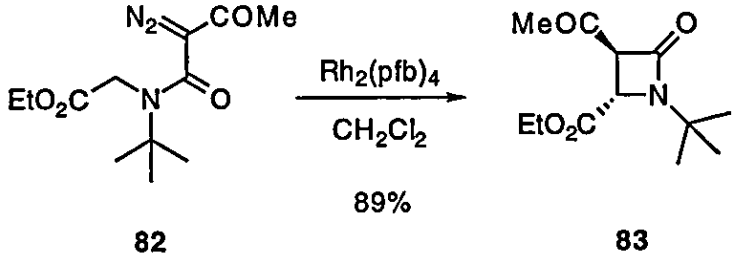


Figure 6

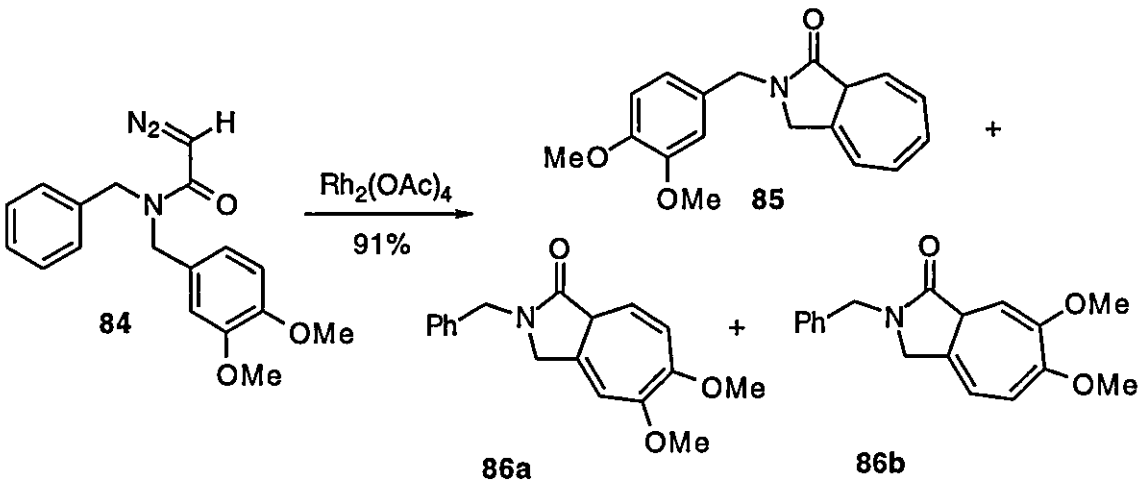
This conformational control of selectivity was then demonstrated by rhodium(II) perfluorobutyrate, $Rh_2(pfb)_4$, catalysed reaction of diazoacetoacetamide **82**. The result was conversion to the *cis* β-lactam **83** in 89% yield (**Scheme 28**).[41a] The argument is that if electronic factors were controlling selectivity, then the electron-withdrawing effect of the ester on the adjacent (α) methylene C-Hs should decrease their reactivity toward the electrophilic carbenoid, thereby promoting competing reactions. This clearly was not the case with **82**, and stands in contrast to the earlier report from Stork and Nakatani that with simple diazoketones regiocontrol is effected by the presence of electron withdrawing groups (which deactivate both α- and β-positions towards C-H insertion).[48] Indeed, Doyle goes on to contend that the explanation of electronic deactivation by the ester group is probably less valid than one of the conformation adopted as a result of repulsion of the carboxylate group by the bridging ligands on the dirhodium framework of the carbenoid intermediate.



82 **83**

Scheme 28

In a further example of this strong influence of diazo substrate conformation on the chemoselectivity of rhodium(II) catalysed reaction, the unsymmetrically substituted *N,N*-dibenzyldiazoacetamide **84** was subjected to catalytic decomposition conditions. If the relative reactivity of the two non-identical rings towards the metallocarbene intermediate was solely a function of the electron-donating ability of their respective substituents, then preferential attack should occur at the dimethoxy substituted aromatic nucleus to afford **86** as the major product. However the opposite preference is actually observed and the major product was **85** (relative ratio of **85:86** was 61:39 with rhodium(II) acetate and was found not to be strongly dependent on the ligand) (**Scheme 29**).[47] This, again, was explained using the argument that the amide adopts a conformation such that the larger substituent on the amide nitrogen is sterically required to be distant to the bulky carbenoid reactive centre, thus leaving the smaller (less subsituted benzyl) group in close proximity to that electrophilic site (refer to **Figure 6** for an analogous reaction).

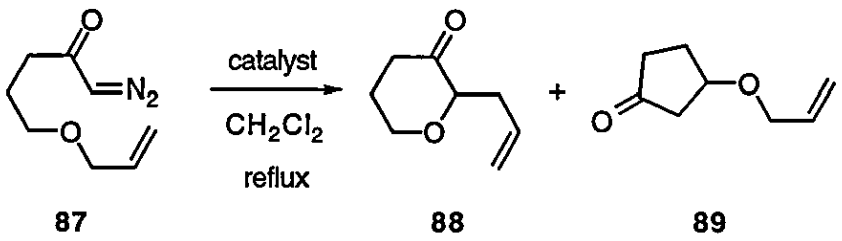


Scheme 29

2.1.2. Ligand Effects in Competitive Carbenoid Reactions

Ligand effects on the chemoselectivity of competitive carbenoid processes have also been widely explored and were recently reviewed.[45]

Examples using copper catalysis have shown that in competition reactions, these catalysts favour ylide formation and cyclopropanation over aromatic substitution and aliphatic C-H insertion. For example, the Clark group have recently demonstrated the remarkable selectivity of copper(II) hexafluoroacetylacetonate for ylide formation when in competition with aliphatic C-H insertion.[49-51] Thus, diazoketone **87** furnished oxonium ylide rearrangement product **88** as the sole product, compared to the mixture of **88** and C-H insertion product **89** obtained with rhodium(II) acetate (**Scheme 30**, **Table 5**).[50] It is also noteworthy that though copper catalysts are know to favour cyclopropanation, this is not found to compete with ylide formation in the substrate **87**. Copper(II) acetylacetonate was found to more selective for the ylide forming pathway than rhodium(II) acetate, but less so than copper(II) hexafluoroacetylacetonate (**Table 5**).



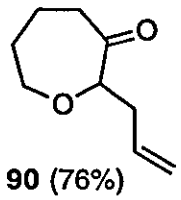
87 **88** **89**

Scheme 30

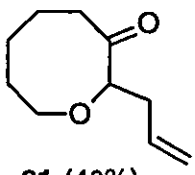
catalyst	**88** (%)	**89** (%)
$Rh_2(OAc)_4$	41	18
$Cu(acac)_2$	61	12
$Cu(hfacac)_2$	83	0

Table 5

Clark went on to demonstrate the versatility of this catalytic methodology and successfully prepared the medium-size cyclic ethers **90** and **91** in good yields from their respective *O*-allyl diazoketones using $Cu(hfacac)_2$ in refluxing dichloromethane (**Figure 7**).[50]



90 (76%)



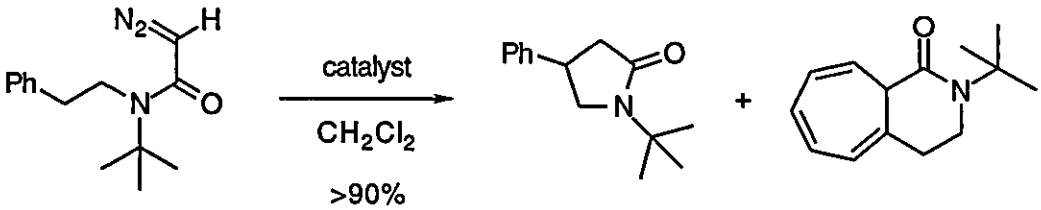
91 (40%)

Figure 7

A further example of this strong promotion of ylide formation by copper catalysts is illustrated below (**Scheme 33** and **Table 7**).

As mentioned earlier rhodium catalysts have a wider spectrum of reactivity than copper catalysts and rhodium(II) acetate has been shown to be a relatively non-selective catalyst which often gives rise to mixtures in competition reactions. Ligand modification can however effect dramatic swings in favour of a desired pathway.[45] For example, rhodium(II) perfluorocarboxamides have recently been shown to have remarkable selectivity for the aromatic substitution reaction over all other competing reaction pathways (**Scheme 10**, Chapter 1).[21]

In another example, rhodium(II) acetamide, $Rh_2(acam)_4$, has been shown to favour C-H insertion over aromatic cycloaddition (**Scheme 31**).[40] However, when rhodium(II) perfluorobutyrate is used this selectivity is reversed (**Table 6**).



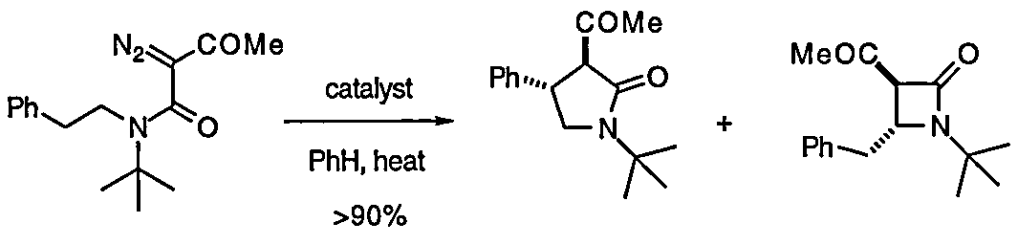
92 **93** **94**

Scheme 31

catalyst	**93** (relative %)	**94** (relative %)
$Rh_2(acam)_4$	78	22
$Rh_2(OAc)_4$	39	61
$Rh_2(pfb)_4$	8	92

Table 6

If, however, an electron-withdrawing acetyl group is placed α- to the diazo group as in diazoacetoacetamide **95** a competition between γ- and β-lactam formation is observed (giving **96** and **97** respectively) and no attack of the aromatic ring occurs. It is expected that β-lactam formation is the less favoured pathway and this is the case with the less electrophilic carbenoid derived from $Rh_2(acam)_4$ catalysis. In contrast, the reaction of the metallocarbene arising from $Rh_2(pfb)_4$ catalysed decomposition furnishes the β-lactam **97** as the major product (**Scheme 32, Table 7**). This probably arises as a result of the ability of the more reactive intermediate carbenoid arising from the latter catalyst, with its electron poor ligands, to begin bond formation at a greater distance from the C-H bond.[40]



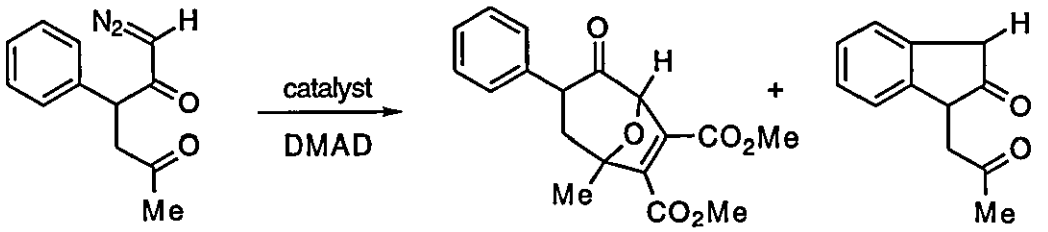
95 **96** **97**

Scheme 32

catalyst	**96** (relative %)	**97** (relative %)
$Rh_2(acam)_4$	70	30
$Rh_2(OAc)_4$	51	49
$Rh_2(pfb)_4$	22	78

Table 7

The Moody and Padwa groups showed that ligand modification can also influence ylide forming competition reactions of rhodium carbenoids. Thus, when diazoketone **98** was decomposed with rhodium(II) acetate, aromatic substitution was found to be in competition with carbonyl ylide formation. The latter reaction dominated, and the ylide formed was trapped *in-situ* by cycloaddition with dimethyl acetylenedicarboxylate, to furnish oxabicyclooctanone **99** (60%) along with the 2-indanone **100** (20%). However, on changing the catalyst to rhodium(II) caprolactamate the sole product was **99** and in contrast to this when the more electrophilic catalyst rhodium(II) perfluorobutyrate was employed the only product was **100** (**Scheme 33, Table 8**).[52] Copper(II) trifluoroacetylacetonate was found to give clean conversion to the ylide derived product **99**, mirroring the result obtained with rhodium(II) caprolactamate catalysed decomposition.



98 **99** **100**

Scheme 33

catalyst	yield **99** (%)	yield **100** (%)
$Rh_2(OAc)_4$	60	20
$Rh_2(cap)_4$	90	0
$Rh_2(pfb)_4$	0	85
$Cu(tfacac)_2$	77	0

Table 8

Changes in the bridging ligands have been shown to directly influence the Rh-Rh distances in the dimeric rhodium(II) catalysts and this has been promulgated as one factor controlling reactivities and hence selectivities of the carbenoids which arise as a result of reaction with diazo compounds.[53] What has been shown is that electron-donating ligands cause the Rh-Rh distance to be shorter than in the reference catalyst $Rh_2(OAc)_4.2H_2O$, and that electron-withdrawing ligands have the opposite effect. It is not entirely clear whether the Rh-Rh bond is actually broken and reformed in the catalytic cycle but this might be the case and would explain some of the dramatic changes in chemoselectivity of carbenoid reactions which result from ligand modification.

2.1.3. Conclusions

Though rhodium(II) acetate is relatively non-selective as a catalyst, it is often found to give the best overall yields when applied to reactions where competitive reactions are not possible. Rhodium(II) caprolactamate strongly promotes cyclopropanations and aliphatic C-H insertions over aromatic substitution and cycloaddition processes.[54] Rhodium(II) perfluorocarboxylates and carboxamides have been found to promote aromatic substitution reactions over competing alternatives. Hence, the chemoselectivity of rhodium(II) acetate catalysed reactions generally falls somewhere

between those of rhodium(II) caprolactamate and rhodium(II) perfluorocarboxylates. Copper(II) salts have been show to favour ylide formation and cyclopropanation reactions over aromatic substitution and aliphatic C-H insertion. Along with copper(II) catalysts, several rhodium(II) dimers are now commercially available. These include rhodium(II) acetate, rhodium(II) trifluoroacetate, and rhodium(II) caprolactamate.

It is difficult to draw many other general and synthetically valuable conclusions from the various studies of the effects of substituents and ligands on the selectivity of competition reactions, partly because a wide range of different diazo substrates have been scrutinised and each with different sets of catalysts. Subtle steric, electronic and conformational factors dictate the chemical outcome of these reactions, and consideration of any one factor alone can lead to misleading conclusions. It is clear that understanding of the role of substituents and ligands on chemoselectivity is still very limited and even with the large numbers of publications to date further experimental and theoretical studies are needed.

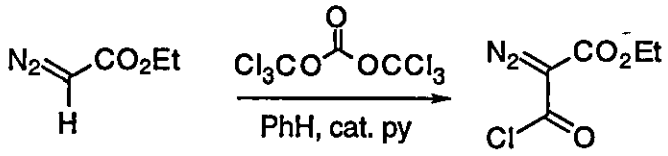
With these issues in mind , the broad aims of our work were formulated and included a more detailed study of substituent effects in the diazocarbonyl substrate, together with ligand effects in the catalysts used for their decomposition. A further aim was to apply the technology thus developed to build the core structures of relevant natural products and then to manipulate these intermediates to give the final desired targets.

2.2. Three-way Competition Carbenoid Reactions

A series of subtituted *N*-aryl-*N*-benzyldiazomalonamide ethyl esters was prepared as substrates for the investigation of the chemoselectivity of intramolecular carbenoid reactions. These were prepared from substituted anilines and ethyl 2-diazomalonyl chloride.

2.2.1. Preparation of Ethyl 2-Diazomalonyl Chloride

The preparation and utility of ethyl diazomalonyl chloride as a valuable synthetic building unit for the diazoacylation of a range of nucleophilic reagents (including amines, alcohols, thiols, and amides) was recently reported by Padwa and co-workers.[55] They described a preparative protocol wherein triphosgene in benzene was treated with a catalytic amount of pyridine followed by an excess of ethyl diazoacetate (**Scheme 34**). Isolated yields of about 44%, after distillation of the crude reaction mixture, were achieved on a large scale.



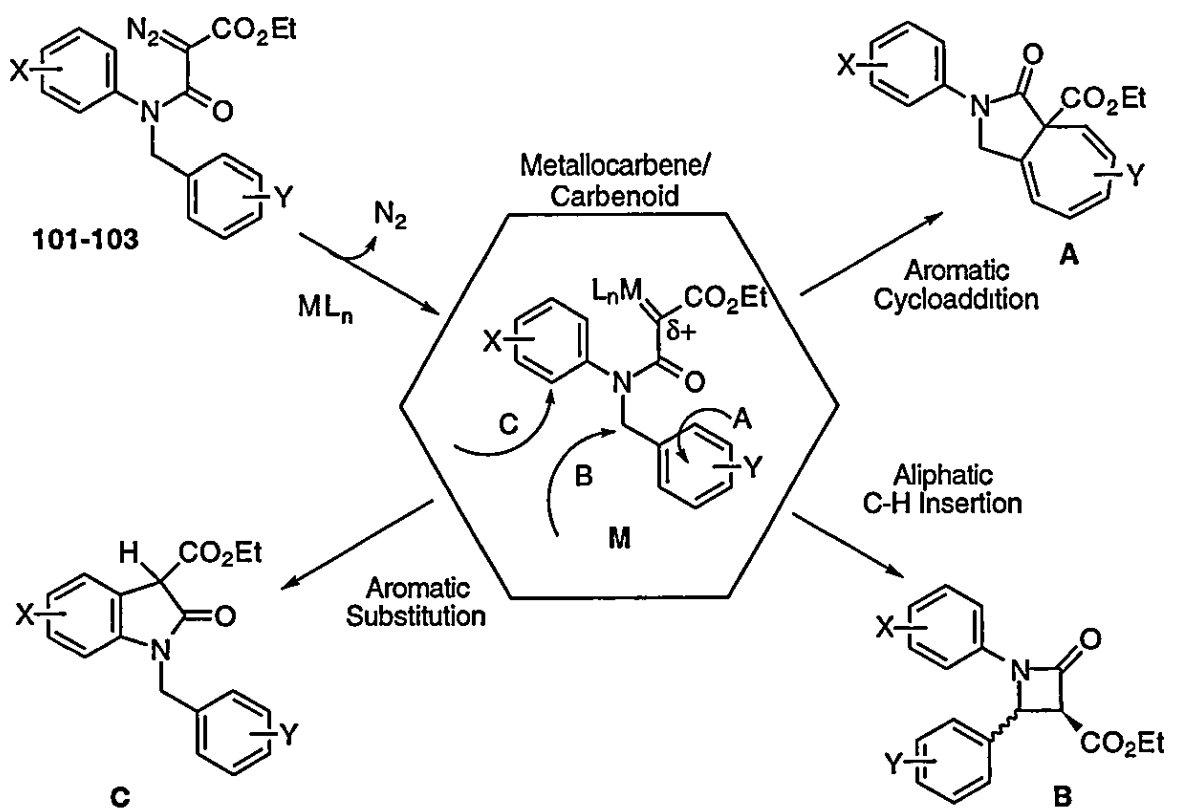
Scheme 34

Attempts to repeat the preparation of ethyl diazomalonyl chloride by this method were met with an unexpected hurdle. The product could not be distilled out of the crude mixture even under conditions of very low pressure and relatively high temperature. Eventually, this was overcome by simply subjecting the crude mixture to flash column chromatography on silica gel. This afforded the pure ethyl diazomalonyl chloride in 27% yield. In a later attempt to prepare this important reagent the benzene was successfully replaced with the less hazardous solvent toluene and without any deleterious effects (33% yield after distillation and then chromatography). During attempts to distill the crude mixture a major by-product was isolated and identified to be ethyl chloroacetate. Though the recovery is poor, the procedure is simple and the reaction can be used to prepare several grams of ethyl diazomalonyl chloride at a time. The product was stored in a fridge for period extending over years without noticeable deterioration as judged by its spectroscopic data and reactivity profile.

2.2.2. Design and Preparation of Competition Substrates

The first compounds designed for investigation of the factors controlling chemoselectivity in competing intramolecular carbenoid processes were substituted *N*-benzyl-2-diazo-*N*-phenylmalonamic acid ethyl esters **101-103** (**Scheme 35**). The reasons for this selection included ease of preparation, the potential of three competing reaction pathways, and historical experiences within the group.[21]

The substrates **101-103** were thus designed such that upon catalytic decomposition with a metal salt (ML_n) they would give rise to transient electrophilic metallocarbene (or carbenoids) **M** which would have a choice of intramolecular reaction pathways to follow, with each pathway leading to a different heterocyclic product (**Scheme 35**). The pathways envisaged to be set in competition are aromatic cycloaddition (or Buchner reaction) giving rise to cycloheptapyrrolones **A** , aliphatic C-H insertion into the benzylic methylene to give β-lactams **B**, and aromatic substitution (or C-H insertion) to afford oxindoles **C**.

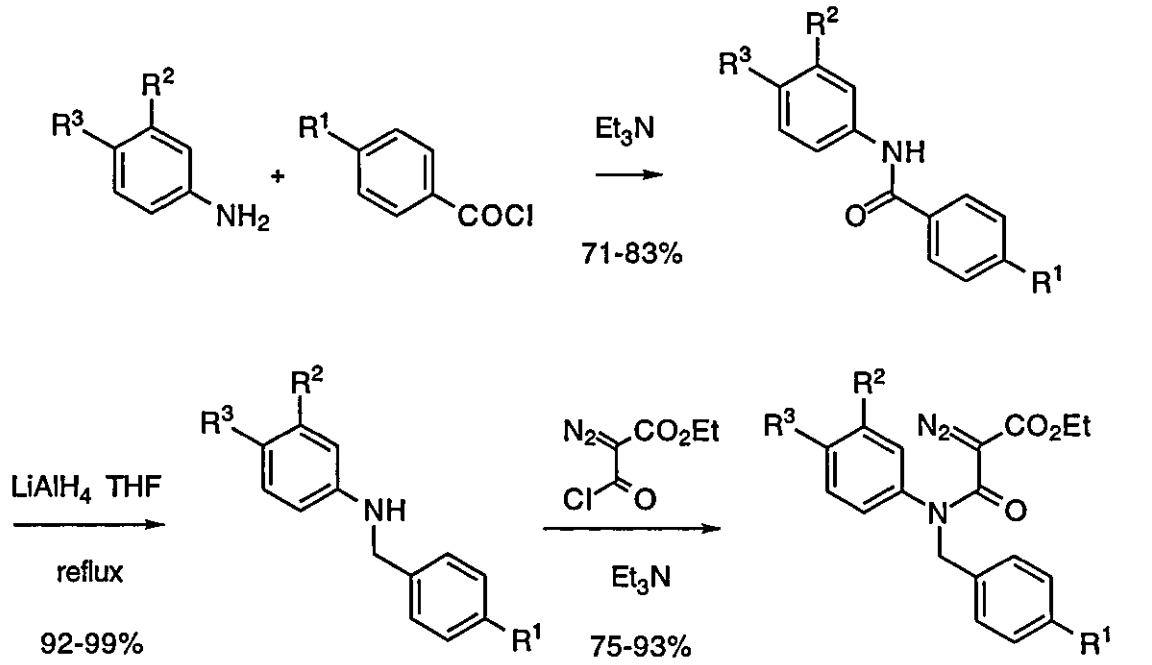


Scheme 35

It was reasoned that, since rhodium carbenoids are electrophilic in nature, the introduction of electron releasing substituents (X, Y) onto the aromatic groups of *N*-benzyl-2-diazo-*N*-phenylmalonamic acid ethyl esters should make them more

nucleophilic and thus help drive competing carbenoid processes down one of the reaction pathways (in particular, favouring attack of the activated aromatic ring) in preference to others. Also it would be valuable to investigate further the effects of different ligands in the catalysts on the direction of these competition reactions, and in particular to evaluate whether ligand effects can overcome substituent effects.

With this in mind, the series of methoxy-substituted *N*-benzyl-2-diazo-*N*-phenylmalonamic acid ethyl esters **101-103** were prepared using standard methods in high yields (**Scheme 36**).[21,55]



101 R^1 = OMe, $R^2 = R^3$ = H
102 $R^1 = R^3$ = H, R^2 = OMe
103 $R^1 = R^2$ = H, R^3 = OMe

Scheme 36

N-Benzyl-2-diazo-*N*-(3-methoxyphenyl)malonamic acid ethyl ester **102** was found to be highly crystalline and its structure was confirmed by single crystal X-ray crystallography (**Figure 8**). The structure shows that, in the solid state, the diazo group adopts a conformation in which it is *syn* to the amide carbonyl and *anti* to the ester carbonyl and is thus pointing toward the *N*-aryl group. The torsional angle between the carbonyl of the amide and the diazo group of **102** is 13°. Similar conformations have previously been noted in a related diazoamides,[21,56] and were observed in others as mentioned below. (**Appendix A**).[57]

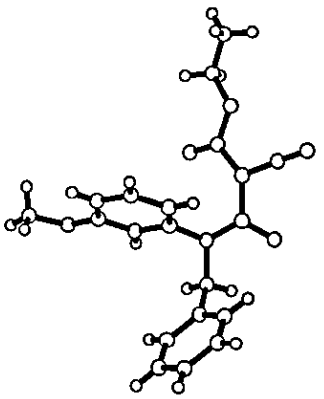
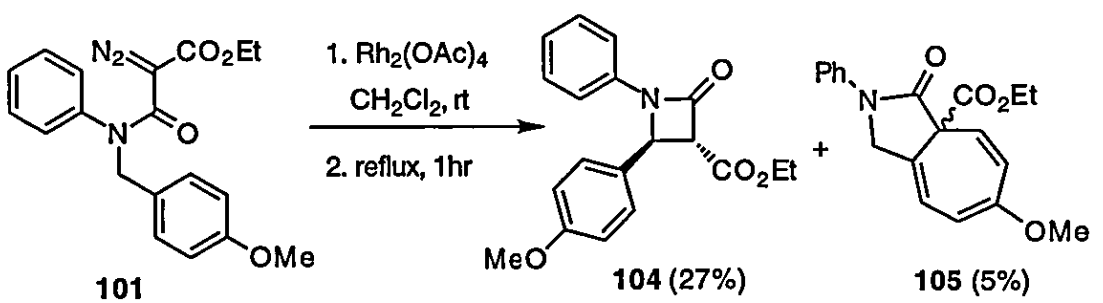


Figure 8 X-ray crystal Structure of Diazoamide **102**

2.2.3. Rhodium(II) Acetate Catalysed Reactions

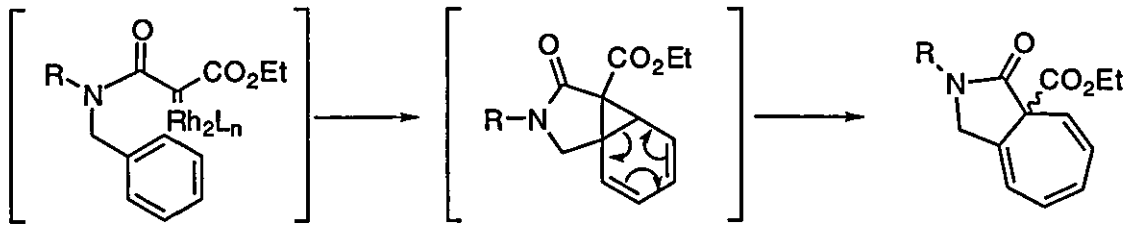
Each of the diazoamides **101-103** was subjected to rhodium(II) acetate, $Rh_2(OAc)_4$, catalysed decomposition conditions and the resulting mixtures of products analysed. Thus, 2-diazo-*N*-(4-methoxybenzyl)-*N*-phenylmalonamic acid ethyl ester **101** gave a complex mixture from which were isolated β–lactam **104** and the novel cycloheptapyrrolone **105** in a ratio of 84:16 (32% overall isolated yield) after extensive separation from decomposition by-products (**Scheme 37**).



Scheme 37

The cycloheptapyrrolone **105** was isolated in just 5% yield after trituration then recrystallisation of certain mixed fractions from the flash silica gel chromatography column. This novel product is the result of an intramolecular aromatic cycloaddition reaction (also called a Buchner reaction)[58] which involves intramolecular

cyclopropanation of the rhodium(II) carbenoid **106** to afford an intermediate norcaradiene **107** which in turn undergoes an electrocyclic rearrangement to furnish the trienic product **108** (**Scheme 38**).

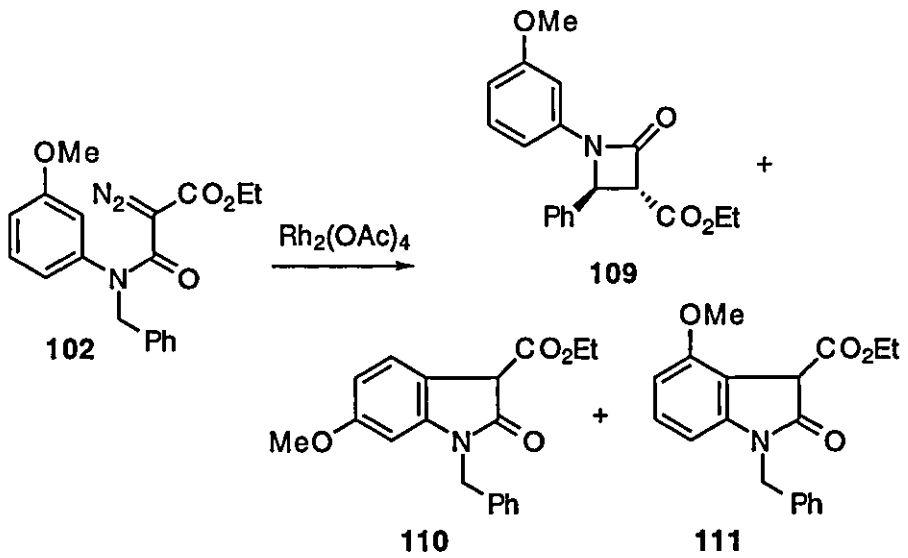


106 **107** **108**

Scheme 38 Mechanism of the Intramolecular Buchner Reaction

The structure of cycloheptapyrrolone **105** was unequivocally determined using single crystal X-ray crystallography (**Appendix B**).[57]

Rhodium(II) acetate catalysed decomposition of diazoamide **102** gave the *trans* β-lactam **109** as the only isolable product after silica gel chromatography and in low yield (27% after recrystallisation). Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy, however, revealed not only the lactam **109**, but also the isomeric oxindoles **110** and **111** with the ratio of **109:110:111** being 36:48:16 (roughly 2:3:1) (**Scheme 39**). This confirmed reported observations that oxindole-3-esters are unstable to silica.[21]



102 **109** **110** **111**

Scheme 39

The relative stereochemistry of the β-lactam **109** was confirmed as *trans* by ^{1}H NMR spectroscopy (H3-H4, J = 2.6 Hz) and by single crystal X-ray crystallograpy (**Figure 9, Appendix B**).[57]

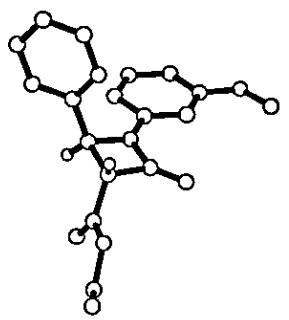
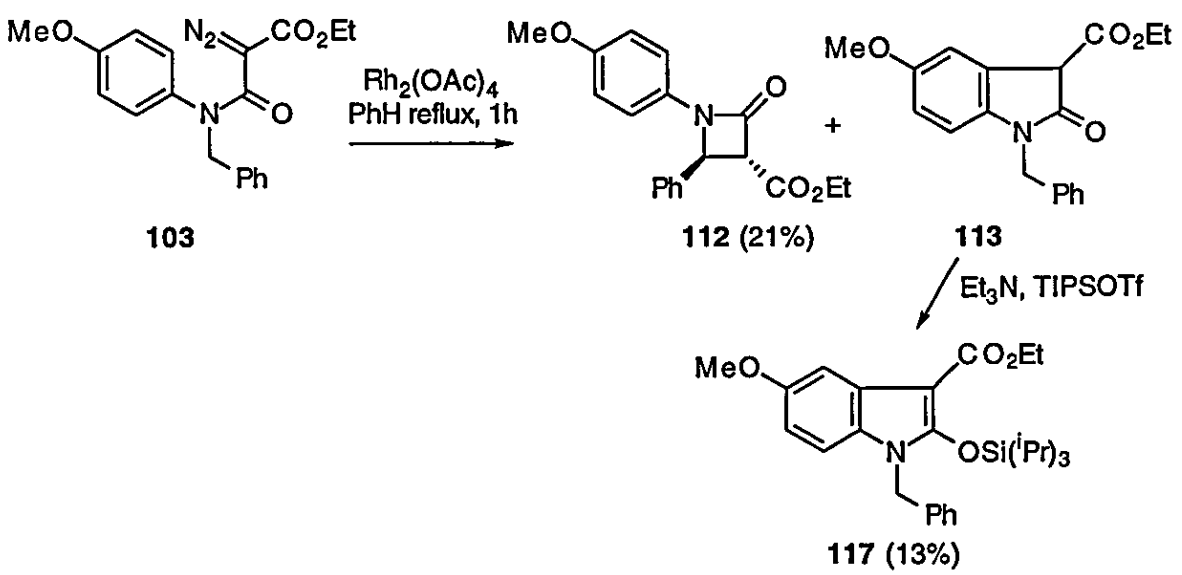


Figure 9 X-ray crystal Structure of the β-lactam **109**

N-Benzyl-2-diazo-*N*-(4-methoxyphenyl)malonamic acid ethyl ester **103** was refluxed with $Rh_2(OAc)_4$ in benzene for 1 h and the resulting mixture treated with triethylamine and tri-isopropylsilyl triflate (TIPSOTf) in order to trap any oxindole **113**, formed via aromatic substitution into the activated phenyl ring, as the silyl enol ether **117**. In the event, the β-lactam **112** was isolated along with the silylindole **117** in a ratio of approximately 3:2 (**Scheme 40**).



103 **112** (21%) **113** **117** (13%)

Scheme 40

This result is particularly interesting in light of the report from Wee and co-workers which states that the only product that they observed upon $Rh_2(OAc)_4$ catalysed decomposition of the methyl ester analogue of **103** was a *trans* β-lactam analogous to **112** in 41 % yield.[27] It is possible that the oxindole was actually formed but was lost on attempts to purify the crude reaction mixture, as was observed with **102** above.

2.2.4. Rhodium(II) Perfluorobutyramide Catalysed Reactions

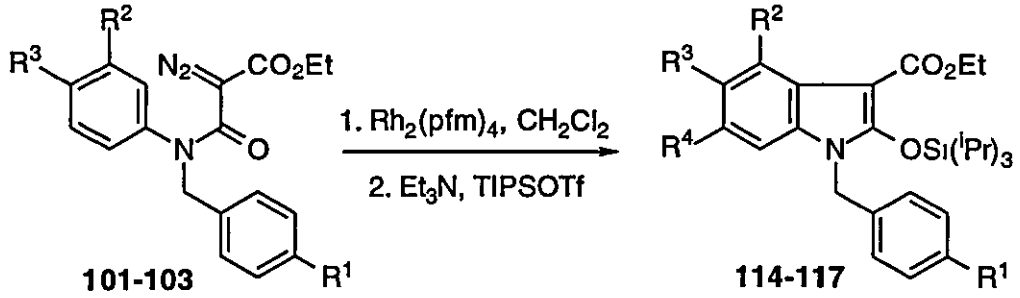
Having observed that chemoselectivity in rhodium(II) acetate catalysed reactions is generally under substrate control, the next step was to prepare and use a catalyst bearing a very different set of ligands. The catalyst chosen was rhodium(II) perfluorobutyramide, $Rh_2(NHCOC_3F_7)_4$; this dimer has recently emerged as a highly active and selective catalyst for the decomposition of diazocarbonyl compounds.[21]

Preparation of the Key Catalyst Rhodium(II) Perfluorobutyramide

The literature method for preparation of rhodium(II) perfluorobutyramide, $Rh_2(pfm)_4$, involves a combination of rhodium(II) acetate in chlorobenzene with a large excess of heptafluorobutyramide and refluxing for 60 h through a Soxhlet extractor equipped with a thimble containing a 1:1 mixture of sodium carbonate and sand (to remove acetic acid). An attempt to duplicate this proved non-trivial; the perfluorobutyramide sublimed and blocked up the Soxhlet extractor and the thimble contents quickly formed a cake which would not allow solvent to flow through. An alternate method, which avoided these practical pitfalls, was sought and the opportunity was taken to subject the reaction to high pressure in a sealed system. Thus, rhodium(II) acetate was heated with excess heptafluorobutyramide in chlorobenzene at 135-140°C under 7.5 bars of nitrogen pressure in a Berghof bomb for 17 h. Removal of excess ligand by filtration and sublimation followed by neutral alumina column chromatography gave the desired active catalyst as a blue solid. This procedure is quicker and simpler than the literature method and provides equally active and selective catalyst (no efforts were made to optimise the yield due to time constraints).

Competition Reactions

Each of the diazoamides **101-103** was subjected to $Rh_2(pfm)_4$ catalysed decomposition conditions and each produced exclusively the respective oxindole *via* aromatic substitution into the *N*-aryl ring. No competition was observed in any case. Each of the oxindole intermediates was derivatised and isolated as its respective tri-isopropylsilyl enol ether in high yields (**114-117; Scheme 41** and **Table 8**).



Scheme 41

Diazoamide	Indole	R^1	R^2	R^3	R^4	Yield (%)[a]
101	**114**	OMe	H	H	H	91
102	**115** **116**	H H	H OMe	H H	OMe H	61 (73) 23 (27)
103	**117**	H	H	OMe	H	91

[a] Yields quoted are those isolated after purification of the indoles. The numbers in parentheses refer to the relative amounts of the respective oxindoles as derived from ^{1}H-NMR data.

Table 8

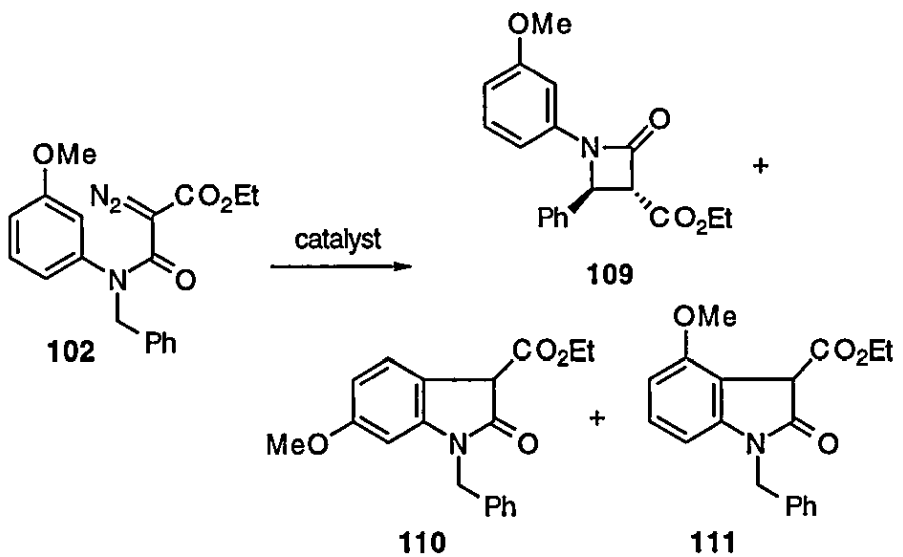
As can be seen from the table above, diazoamide **102** afforded a mixture of the two isomeric oxindoles **110** and **111** (**Scheme 39**) in a ratio of approximately 1:3. The oxindoles were pure enough and different enough to be partially characterisable from the crude NMR (see experimental section). The relative amounts of **110** to **111** is as expected for normal electrophilic aromatic substitution where cyclisation *para*- to the electron-releasing methoxy group is favoured.

It is also apparent that the electron-donating effect of the methoxy substituent in the aromatic ring of the benzyl group of substrate **101** was not sufficient to make aromatic cycloaddition a competing reaction pathway in $Rh_2(pfm)_4$ catalysed decomposition. The sole product was that arising from aromatic substitution into the *N*-phenyl ring.

To confirm the selectivity and efficiency of rhodium(II) trifluoroacetamide, $Rh_2(NHCOCF_3)_4$, as a catalyst for aromatic substitution when in competition with formal aliphatic C-H insertion[21] it was used to catalyse the decomposition of diazoamide **103** at room temperature in dichloromethane solution. Indeed, it was found that the sole

detectable product was, as with $Rh_2(pfm)_4$, an oxindole which was isolated as the derivative indole **117** in 93% yield.

In similar vein, when *N*-3-methoxyphenyldiazomalonamide **102** was decomposed under rhodium(II) trifluoroacetate, $Rh_2(O_2CCF_3)_4$, catalysis in refluxing dichloromethane, the result, as evidenced by ^1H NMR analysis of the crude reaction mixture, was a mixture of isomeric oxindoles **110** and **111** along with a small amount of the trans β-lactam **109** (ratio 72:24:4). The results of catalytic decomposition of this diazoamide with three different catalysts have been collected in the table below (**Scheme 42, Table 9**). It is clear that for a given substrate, chemoselectivity in these competition reactions is strongly influenced by the nature of the ligands on the catalyst.



Scheme 42

catalyst	NMR ratio (%)		
	109	**110**	**111**
$Rh_2(OAc)_4$	36	48	16
$Rh_2(O_2CCF_3)_4$	4	72	24
$Rh_2(pfm)_4$	0	73	27

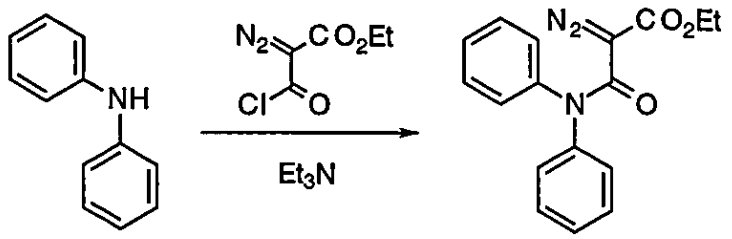
Table 9

2.3. One and Two-Way Competition Carbenoid Reactions

Three more commercially available amines and two thiophenols were condensed with ethyl 2-diazomalonyl chloride to give the respective diazocarbonyl products; these were subjects for further studies into the chemoselectivity of rhodium(II) carbenoid reactions in which fewer than three pathways were in competition.

2.3.1. *N,N*-Diphenyl Diazomalonamide

Diphenyl amine was treated with ethyl 2-diazomalonyl chloride to give the diazoamide **118** in low yield (34%; 88% based on recovered starting material; **Scheme 43**).



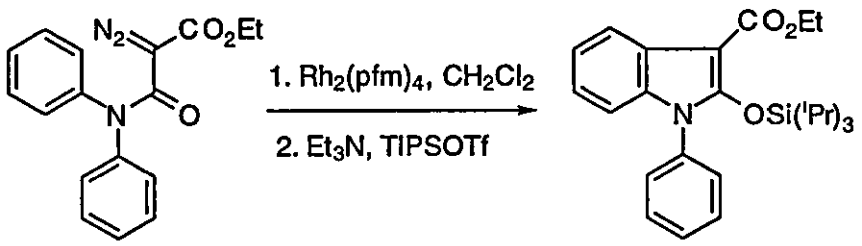
118 (88%)

Scheme 43

It is clear that this simple substrate should undergo chemoselective aromatic substitution as none of the alternative pathways described above are available. Thus, only rhodium(II) perfluorobutyramide catalysed decomposition was investigated.

Rhodium(II) Perfluorobutyramide Catalysed Reaction of **118**

$Rh_2(pfm)_4$ catalysed decomposition of the diazoamide **118** and derivatisation with TIPSOTf gave the expected *N*-phenylindole **119** in essentially quantitative crude yield, but upon attempts to purify the product by flash silica column chromatography the yield fell to just 53% (**Scheme 44**). This may have been due to decomposition on silica but, in any case, no by-products were isolated.

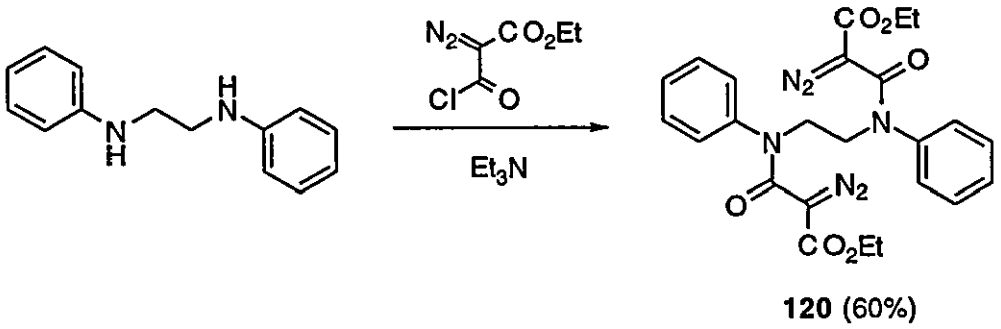


118 **119** (53%)

Scheme 44

2.3.2. *Bis*-Diazomalonamide

The *bis*-diazoamide **120** was isolated in good, recrystallised yield upon standard treatment of 1,2-dianilinoethane with ethyl 2-diazomalonyl chloride (**Scheme 45**).



120 (60%)

Scheme 45

The structure of *bis*-diazoamide **120** was confirmed by single crystal X-ray crystallography (**Figure 10, Appendix A**). The conformation adopted by the diazo group is one in which it is *syn* to the amide carbonyl and *anti* to the ester carbonyl and is thus pointing toward the *N*-aryl group. The torsional angle between the carbonyl of the amide and the diazo group is 25°.[57]

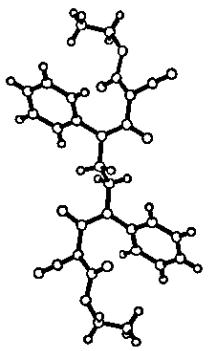
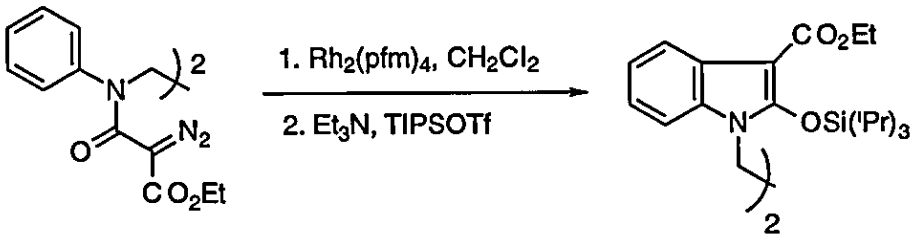


Figure 10 X-ray crystal structure of *Bis*-Diazocarbonyl Compound **120**

Rhodium(II) acetate catalysed decomposition of **120** led to an intractable mixture. However, it was interesting to investigate the possibility of two simultaneous aromatic substitution reactions upon $Rh_2(pfm)_4$ catalysed decomposition.

Rhodium(II) Perfluorobutyramide Catalysed Reaction of **120**

In the event, subjecting the *bis*-diazoamide **120** to $Rh_2(pfm)_4$ catalysed decomposition conditions followed by derivatisation gave exclusively the *bis*-indole **121** in excellent yield (91%) after recrystallisation (**Scheme 46**).

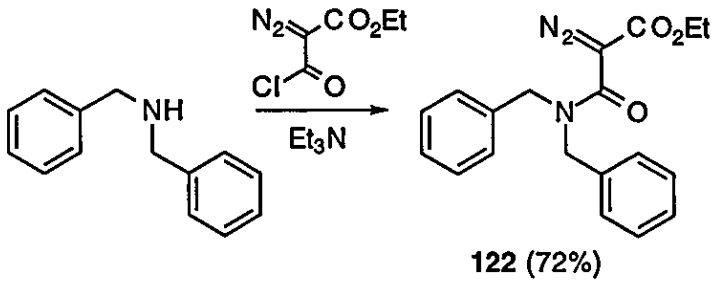


120 **121** (91%)

Scheme 46

2.3.3. *N,N*-Dibenzyl Diazomalonamide

The isolation of cycloheptapyrrolone **105** from the $Rh_2(OAc)_4$ catalysed decomposition of diazoamide **101** prompted us to investigate the decomposition of the *N,N*-dibenzyl diazoamide **122** which, by closing the oxindole formation pathway, should increase the yield of aromatic cycloaddition product.
Treatment of dibenzylamine with ethyl 2-diazomalonyl chloride afforded the diazoamide **122** in good yield (**Scheme 47**).

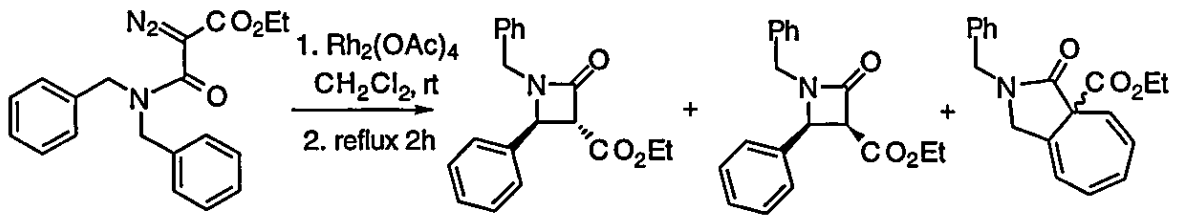


122 (72%)

Scheme 47

Rhodium(II) Acetate Catalysed Reaction of **122**

$Rh_2(OAc)_4$ catalysed decomposition of diazoamide **122** gave a mixture of the *trans* β-lactam **123**, the unexpected *cis* β-lactam **124**, and the cycloheptapyrrolone **125** in a ratio of 44:31:25 (**Scheme 48**).

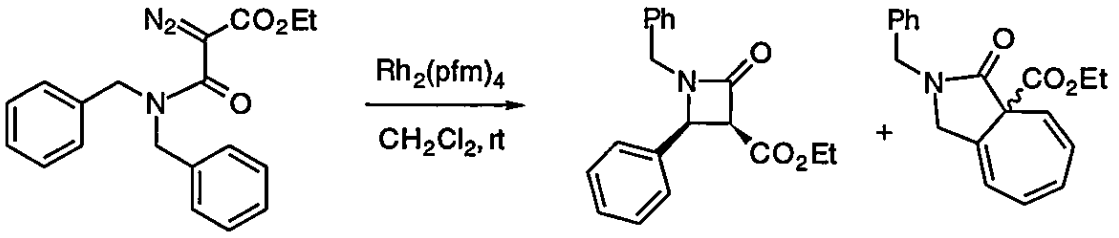


122 **123** (39%) **124** (28%) **125** (22%)

Scheme 48

Rhodium(II) Perfluorobutyramide Catalysed Reaction of **122**

$Rh_2(pfm)_4$ catalysed decomposition of **122** gave a mixture of the *cis* β-lactam **124** and the cycloheptapyrrolone **125** in a ratio of 14:86 and the two were separated in good yield (**Scheme 49**). Interestingly, no *trans* β-lactam was isolated.



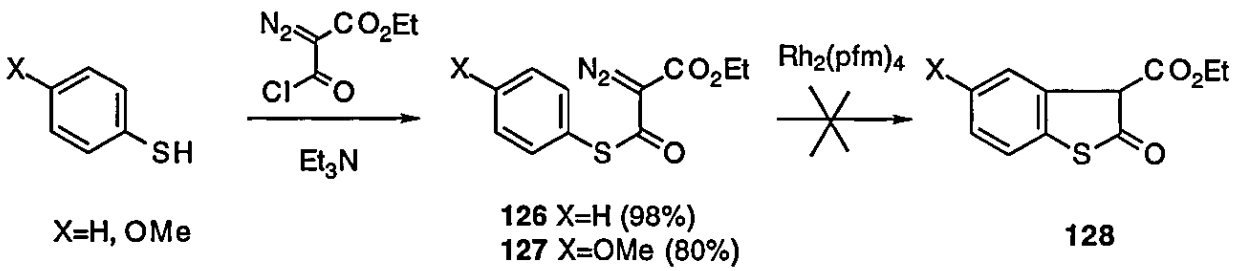
122 **124** (12%) **125** (70%)

Scheme 49

In both the above rhodium(II) catalysed reactions of diazoamide **122** some of the *cis* β-lactam was isolated; indeed no *trans* β-lactam was formed at all using rhodium(II) perfluorobutyramide, and the reasons for this remain unclear. Perhaps more significantly, $Rh_2(pfm)_4$ catalysis provided significant amounts of cycloheptapyrrolone **125** in which a new quaternary centre has been formed. There is potential for investigation into the asymmetric synthesis of this centre using metal carbenoid methodology (see Chapter 5).

2.3.4. 3-(Arylsulfanyl)-2-diazo-3-oxopropanoates

Padwa has reported the reaction of thiols with ethyl diazomalonyl chloride to give diazoacetylated products in high yield.[55] In our hands, treatment of thiophenol with ethyl diazomalonyl chloride did indeed afford the desired diazo compound **126** in 98% yield. The aim with this substrate was to attempt intramolecular aromatic substitution to prepare a benzo-fused heterocycle **128** (**Scheme 50**). However, rhodium(II) perfluorobutyramide catalysed decomposition led to an intractable mixture and no **128** could be identified. Thus, the analogous 4-methoxy substituted diazo β-keto ester **127** was prepared in the hope that the enhanced nucleophilic reactivity of the aromatic ring might promote the desired cyclisation. Unfortunately, the catalysed reaction again failed to give the desired product and nothing could be identified from the reaction mixture. The ^1H NMR spectrum did, however, show that the aromatic ring had not been attacked since the 1,4-disubstituted phenyl ring signal pattern was retained.



Scheme 50

Careful crystallisation of **127** gave crystals suitable for X-ray crystallographic analysis; it was was interesting to find that the conformation of this compound was dramatically different to the diazoamides **102** and **120**. In contrast to the amides, where the diazo group is held close to the aromatic ring, in substrate **127** the diazocarbonyl chain was extended and this placed the diazo group in a position remote to the aromatic ring (**Figure 11, Appendix A**). If these solid state conformations can be extrapolated to analogous carbenoids in the solution phase then it might be argued that attack of the aromatic ring is a conformationally and sterically disfavoured process upon metal catalysed decomposition of **127**.

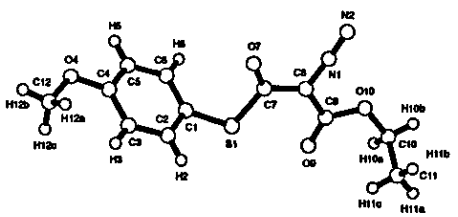
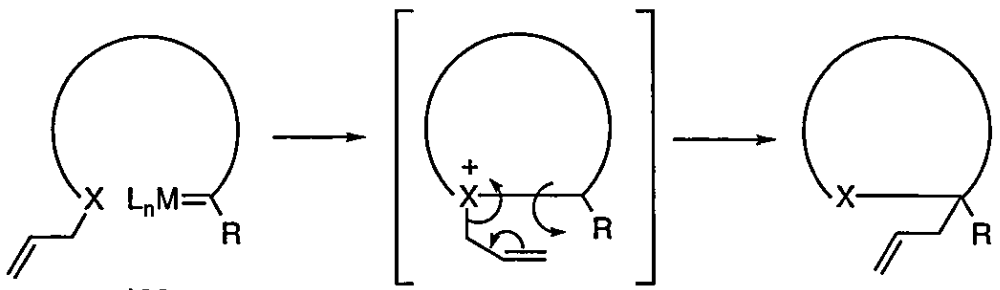


Figure 11 X-Ray Crystal Structure of (4-Methoxyphenyl)sulfanyl Diazocarbonyl **127**

2.4. Four-way Competition Carbenoid Reactions

The diazoamide substrates which are described in Sections 2.2. and 2.3. of this chapter were designed to set into competition three or fewer useful carbenoid reaction pathways. This section will be used to describe synthetic studies carried out in order to broaden the spectrum of reactions and to procure information about a further reaction pathway, that of intramolecular ylide formation followed by [2,3]-sigmatropic rearrangement to give novel heterocyclic species.[4,6] The inter- and intramolecular (illustrated) modes of this reaction of carbenoids has been reported for allylic ethers,[49-51,59] amines and halides,[60] sulfides,[61] and selenides.[62] Metal catalysed decomposition of a diazo substrate generates the metallocarbene **129** which attacks a tethered heteroatom to give intermediate ylide **130**; subsequent symmetry-allowed [2,3]-sigmatropic rearrangement furnishes the final product **131** (**Scheme 51**). Clark has suggested that the catalyst remains associated with the ylide (rather than immediately giving the free ylide **130**) and influences the course of the subsequent rearrangement.[49-50]



129 **130** **131**

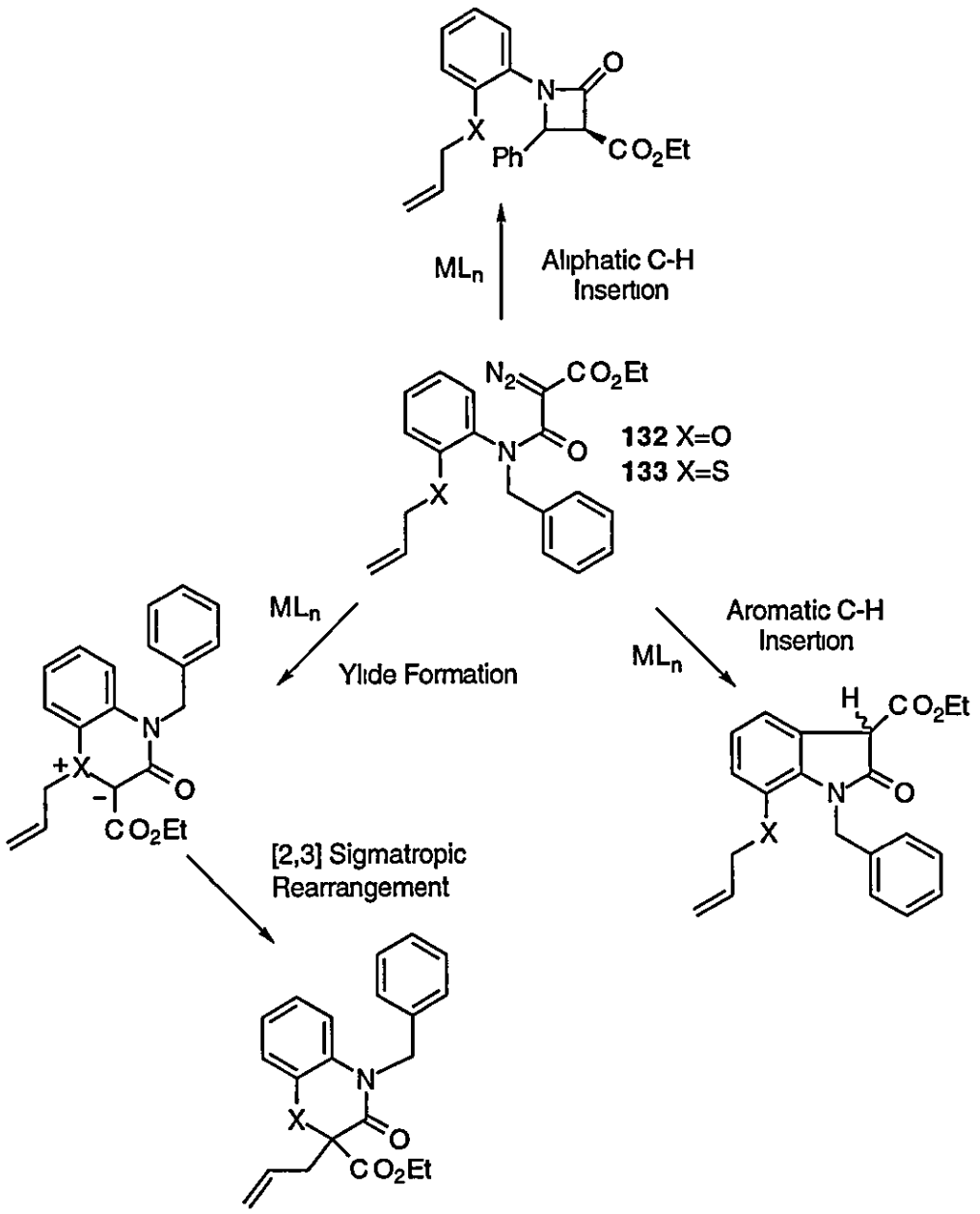
X=O, N, S, Se, Cl, Br, I

Scheme 51

Also to be reported are some other interesting heterocyclic ylide forming reactions of metallocarbenes derived from novel diazocarbonyls.

2.4.1. Design and Preparation of Competition Substrates

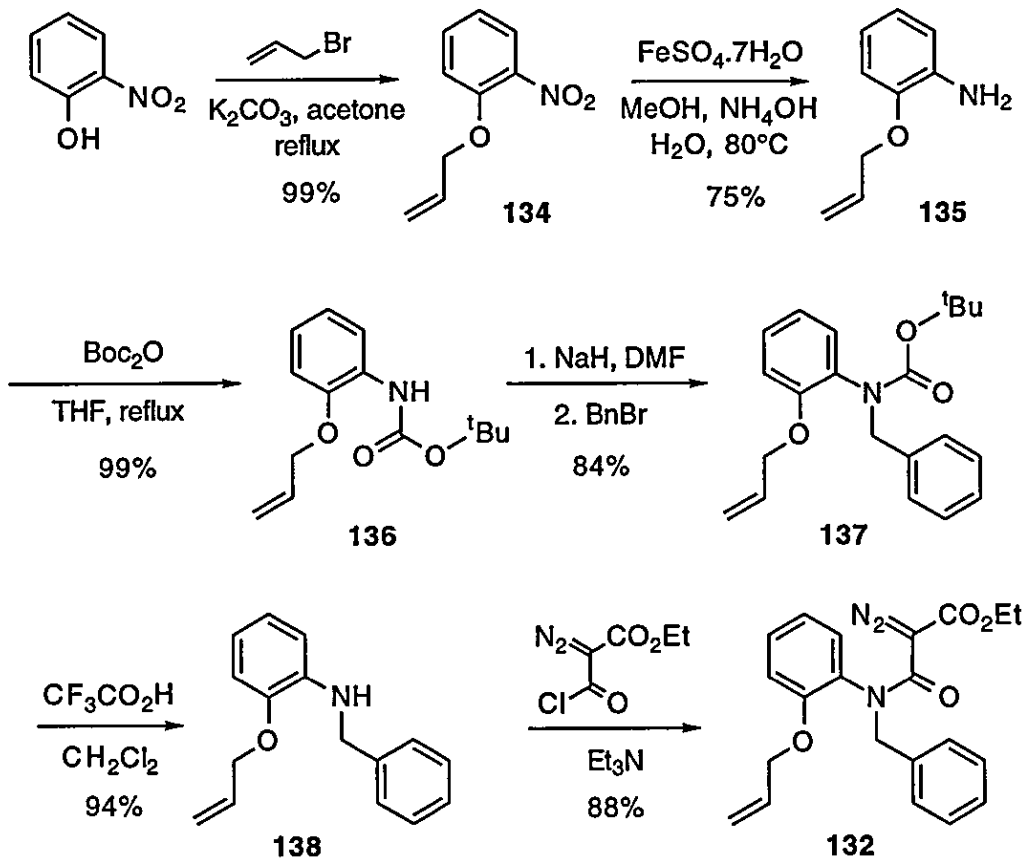
The substrates designed to open up the intramolecular ylide formation pathway were the allylic compounds **132** and **133**. Catalytic decomposition of these diazoamides should give a carbenoid which then has four possible reaction pathways it can follow (**Scheme 52**). Except for the ylide formation, which occurs *via* intramolecular attack of the carbenoid on the heteroatom lone pair, the pathways have been observed earlier as described above.



Scheme 52

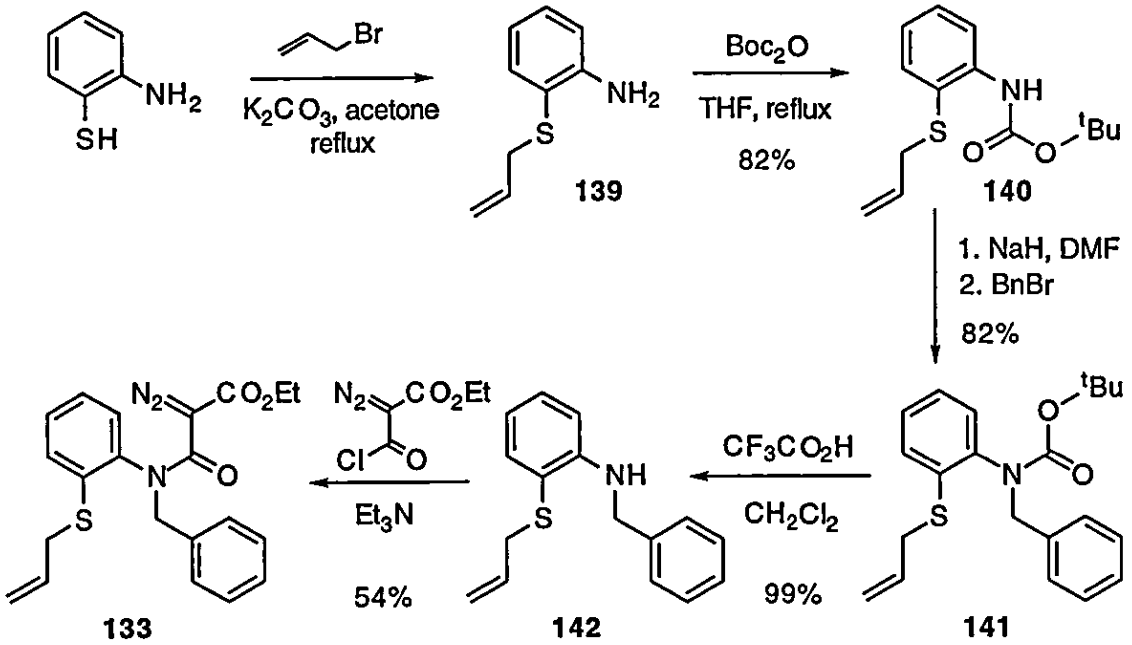
Synthetic studies in this area began with a six step synthesis of *O*-allyl diazoamide **132.** Briefly, this involved allylation of commercial 2-nitrophenol in quantitative yield followed by reduction of the nitro group to give the aniline **135.** There are an ever growing number of methods for reduction of nitrobenzenes to anilines. The method chosen for our substrate was that of Echavarren[63] and this was found, in our hands, to be a more efficient and less involved preparation than the exact literature method reported by Murphy which employed $NaBH_4$ and $Cu(acac)_2$.[64] The aniline **135** was Boc protected, and then benzylated to furnish the carbamate **137.** Removal of the Boc group, followed

by treatment of the resulting aniline **138** with ethyl 2-diazomalonyl chloride afforded the desired diazoamide **132** in excellent yield **(Scheme 53)**.



Scheme 53

Preparation of the *S*-allyl diazoamide **133** was achieved in similar vein. Thus, 2-aminothiophenol was allylated chemoselectively on sulfur using literature conditions to furnish aniline **139** (purification by distillation was not trivial, giving the desired product in low yield). Boc protection of the aniline afforded carbamate **140** which was manipulated in an analogous fashion to **136** to produce the target diazoamide **133** in 3 further steps **(Scheme 54)**.



Scheme 54

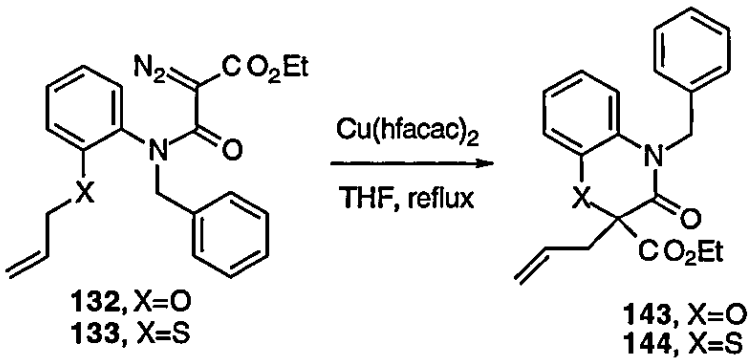
With the diazoamides **132** and **133** in hand, what remained was an investigation of the competitions in chemoselectivity of their respective metallocarbene reactions.

2.4.2. Copper(II) Catalysed Reactions

Copper(II) salts have long been used for decomposition of diazo compounds; these catalysts are widely regarded as important in the formation of ylides and for cyclopropanation reactions. It is well known that copper catalysts strongly promote ylide formation over competing reaction pathways. There are many reports in the literature of useful examples[4,6] and a some competition reactions have been illustrated in the indroduction to this chapter (**Schemes 30**, and **33** above).

With this knowledge in hand, the diazoamide **132** and **133** were subjected to copper(II) hexafluoroacetylacetonate catalysed decomposition. It was necessary to freshly sublime the catalyst prior to use, and to use conditions of refluxing THF to effect decomposition on a reasonable timescale. *O*-allyl diazoamide **132** decomposed very slowly, and after 18 h of heating at reflux only 40% of the starting material had been consumed. Heating at reflux was maintained for a further 48 h and the only identifiable product was the expected ylide rearrangement product **143**. This product was found to be unstable to silica and yields fell dramatically on efforts to purify by flash silica gel column chromatography. A much better result was obtained from the *S*-allyl analogue

133, with the reaction being complete overnight; the product **144** was stable on silica and was isolated in quantitative yield after silica gel chromatography (**Scheme 55**).



132, X=O
133, X=S

143, X=O
144, X=S

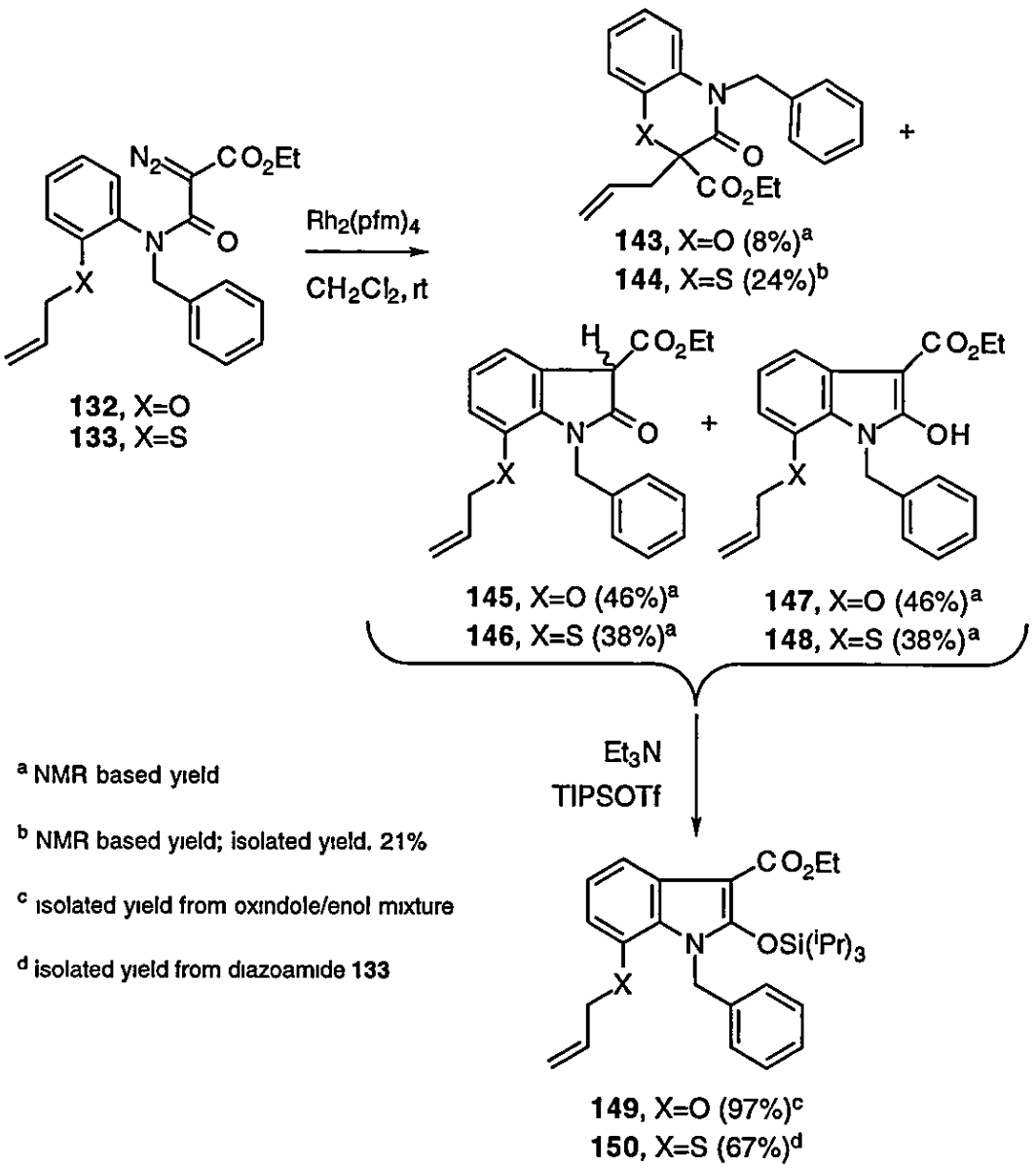
Scheme 55

2.4.3. Rhodium(II) Perfluorobutyramide Catalysed Reactions

Treatment of the *O*-allyl diazoamide **132** with a catalytic amount of $Rh_2(pfm)_4$ at room temperature in dichloromethane solution gave rapid decomposition and afforded three products. One compound was readily deduced from the ^1H NMR spectrum to be the ylide rearrangement product **143** (8%), and another larger component was the oxindole **145** (46%). The third product though constituting a major part (46%) was, however, not so easily identified and it took some investigation to deduce its structure. Thus, with the aim of derivatising the oxindole **145**, the crude reaction mixture was treated with triethylamine (0.6 eq) and TIPSOTf (0.6 eq). Analysis of the ^1H NMR spectrum after workup showed that though the desired indole **149** was formed, only some of the oxindole had been consumed. Moreover, the ratio of unreacted oxindole to the unknown compound remained the same (~1:1) whilst the ratio of ylide rearrangement product to unreacted oxindole increased. This led to the conclusion that the unknown compound was simply the enol form of the oxindole, and this was proved unambiguously by crystallising out a pure 1: 1 mixture of **145** and **147** from the derivatisation experiment crude, treating with excess triethylamine and TIPSOTf to afford a near quantitative yield of the indole **149**.

Diazoamide **133** was similarly decomposed under $Rh_2(pfm)_4$ catalysis and gave analogous products **144**, **146**, and **148** (^1H NMR of the crude reaction mixture showed a ratio of 24:38:38 respectively). As might be anticipated the relative amount of the ylide rearrangement product increased compared to **132**, this being a result of the relatively more nucleophilic sulfur atom when compared to the oxygen analogue. However, the intramolecular aromatic substitution pathway remains dominant, with the resulting

products **146** and **148** being isolated as the indole derivative **150** in 67% yield. The benzothiazine **144** was isolated in 21% yield (**Scheme 56**).

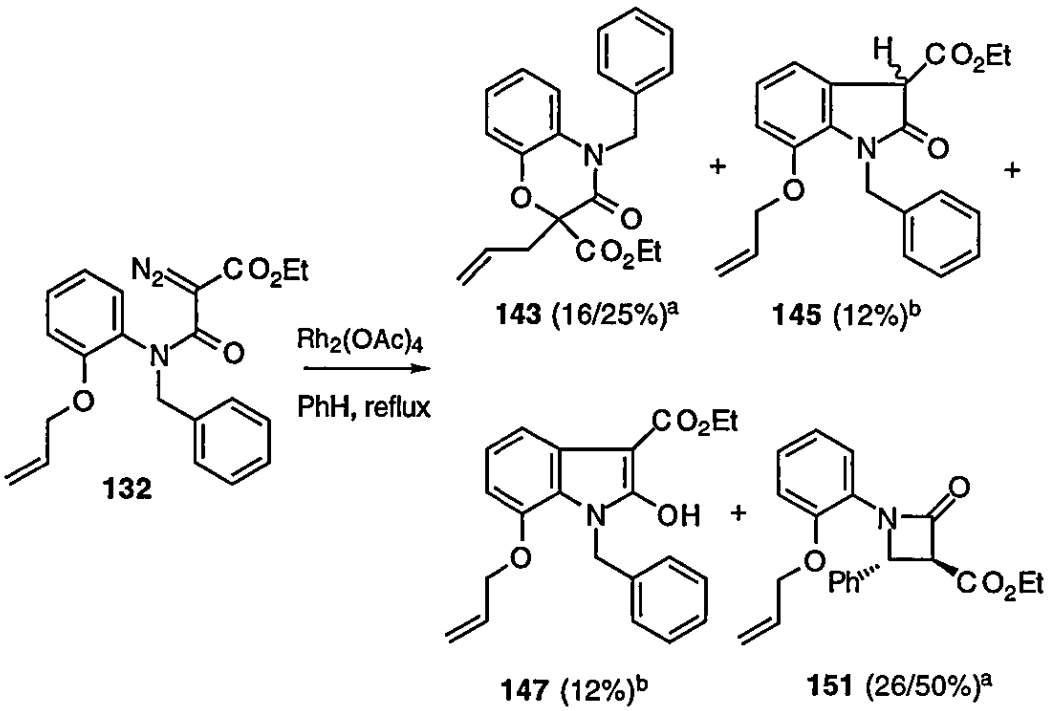


Scheme 56

2.4.4. Rhodium(II) Acetate Catalysed Reactions

Finally, to complement the above observations, the diazoamides **132** and **133** were decomposed under rhodium(II) acetate catalysis. *O*-Allyl diazoamide **132** gave a mixture of products which was analysed by ^{1}H NMR and thus deduced to consist of ylide rearrangement product **143**, oxindole **145**, enol **147**, and the *trans* β-lactam **151** in relative amounts of approximately 25:12:12:50 (**Scheme 57**). Separation of **143**, **151**

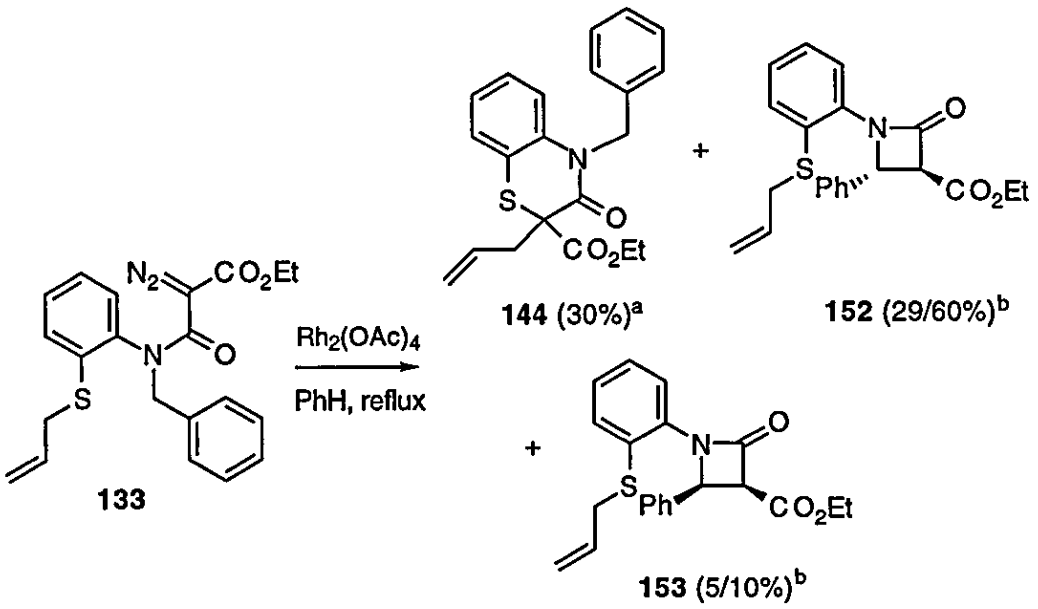
and the triisopropylsilyl enol ether derivative of **145** and **147**, **149**, was possible on silica gel, but only with significant losses (isolated yields were in the range of 11:10:26% of **143**:**149**:**151**).



[a] first number is isolated yield, second number is NMR ratio; [b] NMR ratio; **145** and **147** were isolated as indole derivative **149** in 10% yield

Scheme 57

Upon rhodium(II) acetate catalysed decomposition, allylthio diazoamide **133** gave a mixture of the products **144**, *trans* β-lactam **152**, and *cis* β-lactam **153** (30:60:10 from NMR data) (**Scheme 58**). Interestingly, the ylide forming pathway was more favourable and dominated to such an extent over the intramolecular aromatic substitution pathway that the latter was only observed as a trace from careful analysis of the crude NMR. Isolated yields were quite low and benzothiazine **144** could not be isolated clean from the silica gel column.

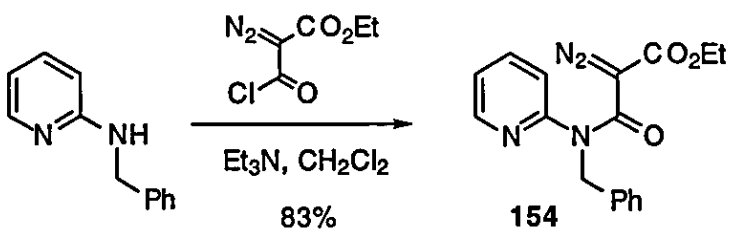


[a] NMR ratio, [b] first number is isolated yield, second number is NMR ratio

Scheme 58

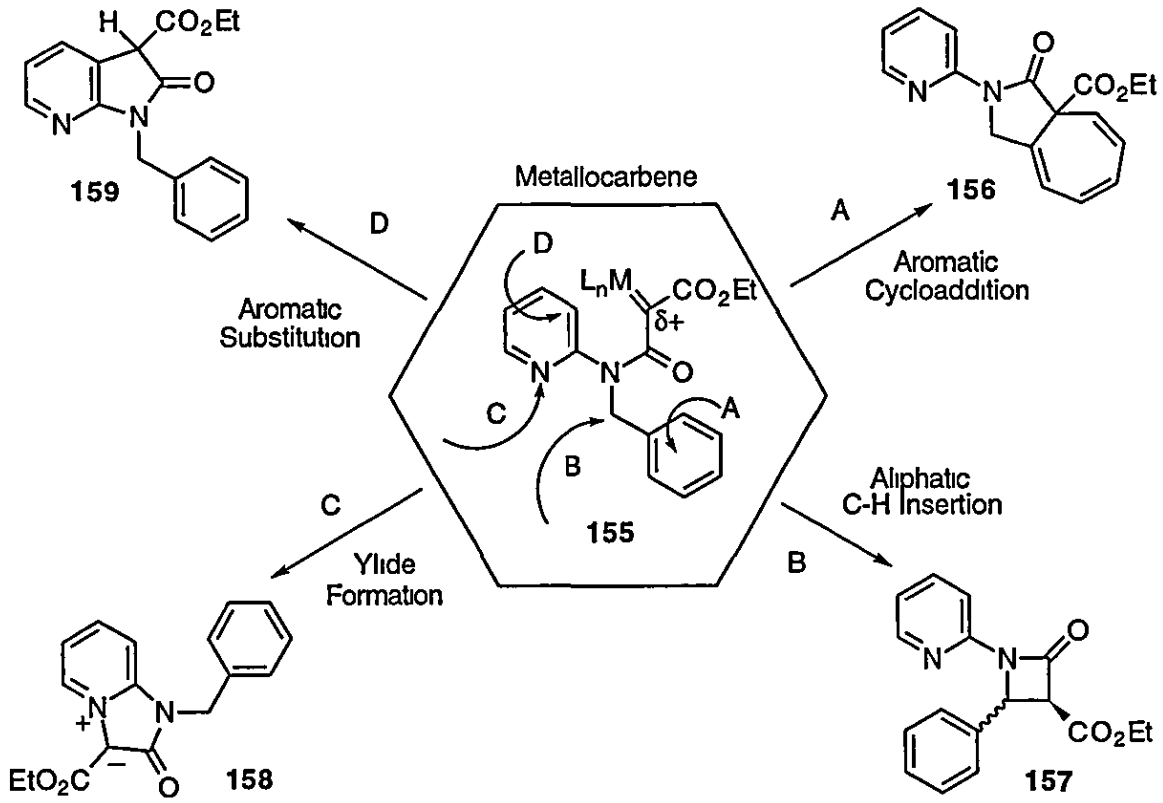
2.4.5. Preparation and Decomposition of *N*-Pyridyl Diazomalonamide Ester

Another diazoamide substrate prepared for the investigaton of its rhodium catalysed decomposition chemistry was that derived from commercially available 2-(*N*-benzyl)pyridine. Treatment with ethyl 2-diazomalonyl chloride furnished the desired diazo substrate **154** in good yield (**Scheme 59**). Unfortunately this compound was only crystalline at low temperature and was not found suitable for X-ray crystallography.



Scheme 59

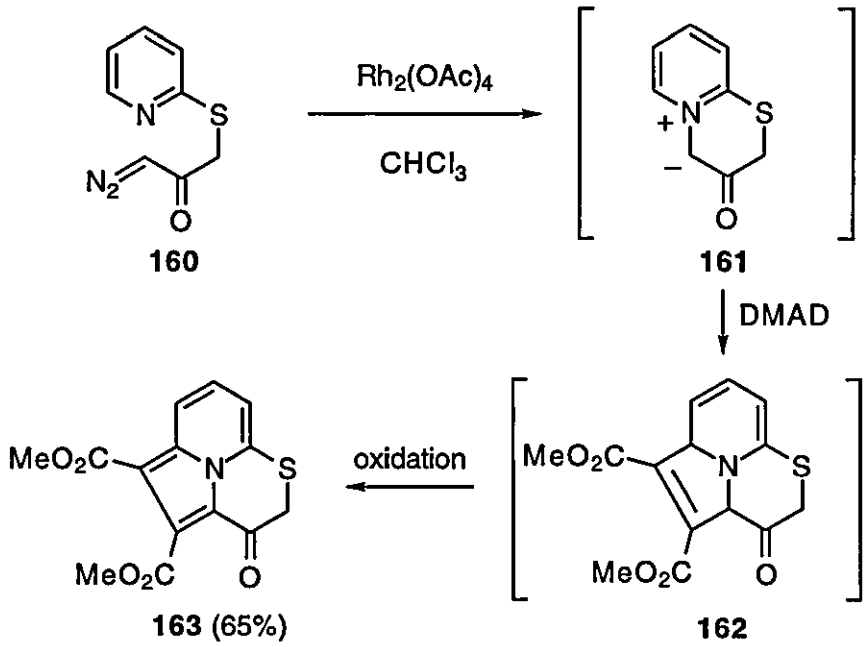
Inspection of the diazoamide **154** reveals four possible sites for intramolecular reaction of a carbenoid intermediate **155** formed by catalytic extrusion of nitrogen. These are aromatic cycloaddition (to give an *N*-pyridyl-cycloheptapyrrolone **156**), aliphatic C-H insertion (to give β-lactam **157**), attack on the pyridine nitrogen to furnish the ylide **158** , and aromatic substitution (to yield the interesting azaoxindole **159**) (**Scheme 60**).



Scheme 60

The new pathway with this *N*-pyridyl substrate **154** is the formation of ylide **158** by intramolecular attack of the electrophilic intermediate **155** upon the pyridine nitrogen non-bonding lone pair. This type of attack has wide precedent in the literature and the generation of pyridinium ylides was first introduced in 1960.[65] Early work involved intermolecular reactions of thermally or photochemically generated carbenes with pyridine to afford ylides which were sometimes quite stable,[66] and the interest was in the study of the otherwise "invisible" carbene.[67] The metal-catalysed behaviour of α-diazocarbonyl compounds with *N*-containing heteroaromatics has been less extensively studied. However, Padwa has recently disclosed several examples or inter- and intramolecular reactions of rhodium carbenoids at the nitrogen atom of pyridines to afford a number of pyridinium ylides which have then been demonstrated to undergo standard rearrangements and cycloadditions on addition of dipolarophiles.[68] Some of the intramolecular reactions have been selected for illustration below (**Schemes 61** and **62**). In particular, the Padwa group were interested in the consideration of pyridinium ylides as a special subclass of azomethine ylides, and hence the potential for a number of valuable 1,3-dipolar cycloaddition reactions leading to complex nitrogen heterocycles.[6] For example, diazoacetate **160** was decomposed with catalytic rhodium(II) acetate in the prescence of a slight excess of dimethyl acetylenedicarboxylate (DMAD), to afford the cycloadduct **163** as the major product in

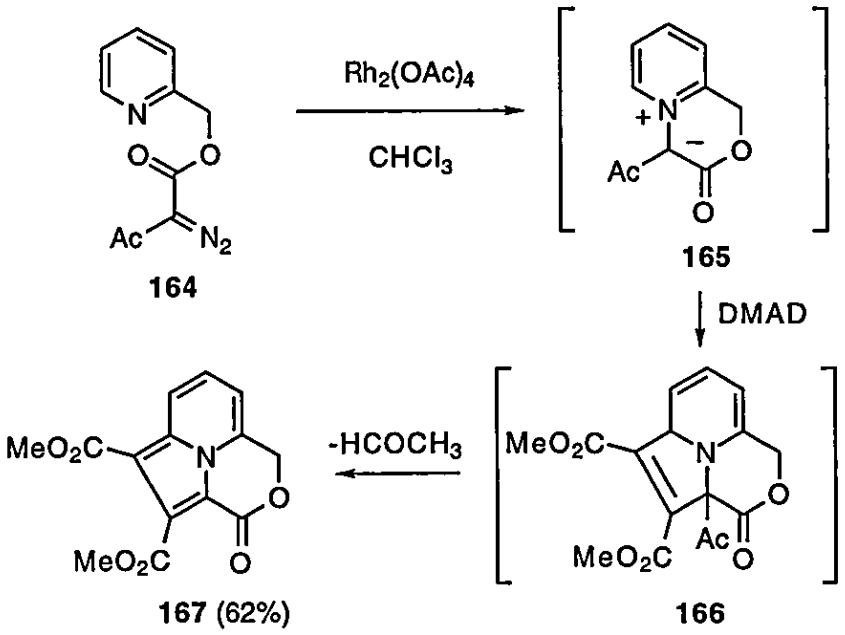
good yield. The pyridinium ylide **161** which is formed undergoes 1,3-dipolar cycloaddition with DMAD to give tricyclic intermediate **162** which spontaneously oxidises to the more stable product **163** (**Scheme 61**).



Scheme 61

An analogous cycloaddition reaction of ylide **161** can be achieved with the dipolarophile *N*-phenylmaleimide to give the corresponding tetracyclic product in 90% yield.

In similar vein, the azomethine ylide **165** was generated under the same catalytic conditions from α-diazo-β-keto ester **164**, and was found to undergo cyclisation with DMAD to give adduct **166**. Subsequent deacetylated and oxidation furnished the tricylic product **167** as the only isolable product in 62% yield (**Scheme 62**).

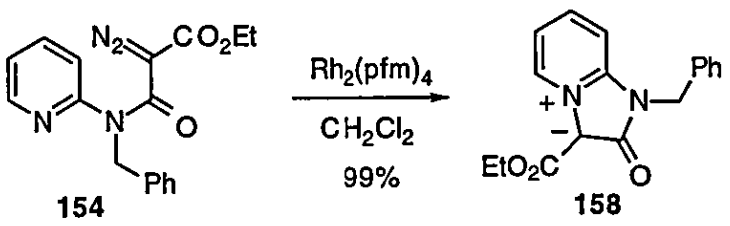


Scheme 62

It is, of course, important to note that the electronic character and hence reactivity of the pyridine ring is quite different to a benzene ring. Though pyridine has the requisite flat cycle of p-orbitals containing six π-electrons to give an aromatic electronic structure similar to that of benzene (Hückel Rule), the presence of a lone pair of electrons in the plane of the flat ring engenders the pyridine system with some characteristics of a tertiary amine. In addition, the imine-like character of pyridines makes the ring susceptible to attack by nucleophiles. In general, electrophilic attack at ring carbons of pyridines is much more difficult than with benzene analogues as cooridination to the nitrogen lone pair is generally accepted to be the first (kinetically favoured) reaction of the electrophile, and the pyridinium intermediate thus formed bears a positive charge and is far less reactive towards electrophiles. In the event of attack of an electrophile, this will usually only be accommodated at the 3- and 5-positions, with attack at other positions leading to intermediates which are destabilised by the nitrogen lone pair (through formation of unstable nitrenium ion resonance forms).

As matters transpired, rhodium(II) perfluorobutyramide catalysed decomposition of diazoamide **154** was rapid and led to a single, highly polar product (R_f= 0.19 on silica TLC with EtOAc as eluant; inspection under 254nm UV light showed a single luminous bright blue spot). Removal of the catalyst and solvent gave a foamy solid. NMR proved homogenity of the product and consideration of the chemical shifts led to tentative assignment of the structure to be that of the pyridinium ylide **158** (**Scheme 63**). However attempts to trap the ylide by normal cycloaddition reactions with dimethyl acetylenedicarboxylate and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) were

unsuccessful under a variety of conditions. Attempted hydrogenation under palladium catalysis led to no reaction. These observations lead to one of two conclusions. First, the product was not as assigned to be **158**; alternatively, that **158** was indeed formed but was particularly stable. To prove the structure unequivocally, recrystallisation was undertaken and furnished large needles which were suitable for X-ray crystallographic analysis. The result confirmed that **158** was the correct structure (**Figure 12, Appendix B**). The bicyclic ylide arrangement is remarkably flat, and the bond lengths throughout are intermediate between those expected for single and double bonds; this indicates that the electrons are distributed by resonance over the whole of the bicyclic sructure and explains, in part at least, the great stability of the compound and its lack of reactivity under standard conditions.



Scheme 63

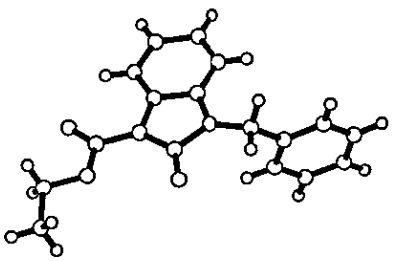


Figure 12 X-Ray Crystal Structure of Ylide **158**

Rhodium(II) acetate also effected decomposition of **154**. The reaction was slower than for $Rh_2(pfm)_4$ but the product was the same. Thus, the sole product was the ylide **158**,

isolable in quantitative yield, and this is remarkable selectivity over potential competing pathways (**Scheme 51**).

In summary, it was observed that rhodium(II) perfluorobutyramide is a highly active and chemoselective catalyst for the formation of ylide **158** from *N*-pyridyl diazoamide **154**. Rhodium(II) acetate furnishes the same product, again with complete selectivity but at a slower rate. The pyridinium ylide **158** is a crystalline solid, stable at room temperature for indefinite periods and its structure was determined unequivocally by X-ray crystallography (**Figure 12**). Bicyclic ylide **158** was found not to undergo cycloaddition with standard dipolarophiles such as DMAD and 4-phenyl-1,2,4-triazolidine-3,5-dione (PTAD). This may be a result of the particular stabilty of **158**, or possibly the excessive strain which would be present in a tricylic cycloaddition product which contains a six membered ring fused to two five membered rings.

2.5. Conclusions

The competition reactions of carbenoids derived from the rhodium(II) acetate catalysed decomposition of diazomalonamides were found to be subject to substrate control. Product distributions were significantly affected by the nucleophilicity of the reaction sites around the starting material structure. Thus, increasing the nucleophilicity of a given site by electron donation (as, for example, by the presence of a methoxy substituent on a phenyl ring) leads to a shift of selectivity in favour of attack at that site. The yields of isolated products were generally low since the mixtures produced were often complex and separation is lengthy and wasteful.

Where aromatic substitution leading to oxindole-3-esters is in competition with alternative pathways, it has been shown that the catalyst of choice for promoting that pathway is rhodium(II) perfluorobutyramide. This catalyst facilitates rapid, high yielding preparation of oxindolyl, and thereby indolyl substrates, under mild and non-hazardous conditions. The alternative pathways, such as aliphatic C-H insertions, aromatic cycloadditions and ylide formations, are suppressed. It is believed that the selectivity is due to a combination of two major factors. The electron-withdrawing perfluorobutyramide ligands increase the electrophilic reactivity of the intermediate carbenoid and thus promote formation of the kinetically favoured product. X-Ray crystallographic analysis of *N*-aryl-*N*-alkyldiazomalonamides **102**, and **120** has revealed a conformation which, if extrapolated to the rhodium carbenoid, would place the reactive metal-bound site in close proximity to the *N*-aryl ring, attack of which leads to oxindole formation.

However, when the oxindole forming pathway is precluded by substrate design, alternative pathways can be selectively promoted by rhodium(II) perfluorobutyramides. Thus, aromatic cycloaddition (Buchner reaction) is strongly favoured over competing aliphatic C-H insertion. This leads to the formation of novel cycloheptapyrrolones from *N*-alkyl-*N*-benzyldiazomalonamides in good yield. The formation of a new quaternary stereocentre in these cycloheptapyrrolones opens up the opportunity for investigations into the selective preparation of one stereoisomer of the products over the alternative using either chiral diazo substrates or chiral ligands on the catalyst (see Chapter 5).

When competition substrates bearing allylic heteroatoms were subjected to metal catalysed decomposition, the ylide formation/sigmatropic rearrangement pathway was found to compete with aromatic substitution and C-H insertion. The extent of this competition was again a function of the catalyst and the substrate. Thus, copper(II) catalysis gave exclusively ylide formation, whilst rhodium(II) perfluorobutyramide gave some ylide rearrangement product but maintained its strong preference for the aromatic substitution pathway. Rhodium(II) acetate gave mixtures of several products in low yields.

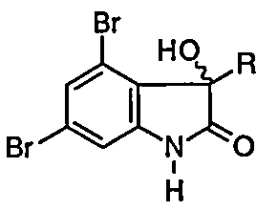
When a pyridine ring is suitably tethered to the α-diazocarbonyl unit, it was shown that the formation of a pyridinium ylide *via* intramolecular attack of the rhodium(II) generated carbenoid onto the pyridine nitrogen was exclusively favoured over competing reaction pathways.

Chapter Three

Total Synthesis of the Marine Alkaloid Convolutamydine C

3.1. Introduction

There is no doubt that the search for novel naturally occurring molecules with useful biological activity is being pursued on a huge and international scale and will continue to expand as long as there remains a need for substances of medicinal value, or even as long as synthetic organic chemistry remains the thriving science it is today. Marine organisms continue to be a rich source of interesting natural products.[69] To this end, Pettit, Kamano and co-workers have recently reported the isolation and characterisation of a novel family of alkaloids from the Floridian bryozoan *Amathia convoluta*.[70,71] The compounds, named the convolutamydines, **168-171**, share a novel 4,6-dibromo-3-hydroxyoxindole backbone and only differ from each other in the nature of the second substituent at C-3 (**Figure 13**). Interestingly, convolutamydines A and B are reported to exhibit potent activity in the differentiation of HL-60 human promyelocytic leukaemia cells.[31]



Convolutamydine A-D **168-171**

	Convolutamydine	R
168	A	CH_2COCH_3
169	B	CH_2CH_2Cl
170	C	CH_3
171	D	$CH{=}CH_2$

Figure 13

The oxindole (or oxoindoline/indolinone) ring system is common to an ever-increasing number of natural products and many of these have been the target of synthetic organic chemists. The growth in numbers of synthetic studies is also due to the strong representation that this family of compounds has amongst clinically useful molecules; examples include anaesthetic,[72] anti-rheumatic,[73] antiviral,[74] nonsteroidal cardiotonic[75] and anti-HIV agents.[76] Compounds containing the oxindole ring system have also been reported as possessing herbicidal[77] and insecticidal activity.[78] Oxindoles are also valued as immediate precursors to indoles.[79]

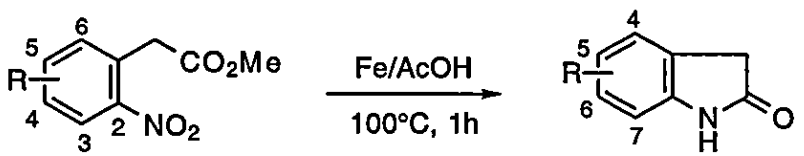
It would be interesting to review all the numerous approaches to oxindole synthesis, but this is far beyond the scope of the current work. A number of good reviews of the preparation and reactions of oxindoles have appeared in the literature,[80-82] the most recent being that of Karp.[83] In the context of the current work, what would be valuable is to group together the battery of recent reports of *de-novo* synthesis of the oxindole ring system, to discuss briefly the scope and limitations of the methods and to compare these with the diazoamide-metallocarbene route to oxindoles. The material included will cover the literature that has appeared after the review by Karp which covered the years 1970 through to mid-1992.

3.2. Recent Synthetic Approaches to the Oxindole Ring System

Chapter 1 described advances in the field of intramolecular aromatic substitution reactions of metallocarbenes for the formation of heterocycles; included in that were reports of oxindole preparations from diazoanilides, and hence this material will not be repeated here. Instead, what will be covered are other examples, reported after Karp's review of oxindoles. Also the syntheses, in continuation of the theme of this thesis, should involve construction of the heterocyclic ring of the oxindole target.

3.2.1. Reduction of Nitroaromatics

A recent report, extending a classical method for oxindole synthesis, involves reductive cyclisation of the substituted aromatic nitro esters **172** (**Scheme 64**). This method is particularly attractive as it allows for a wider range of substitution patterns in the aromatic ring compared to methods in which cyclisation is onto the aromatic ring itself.[84] Yields of oxindoles **173** were good to excellent with R=MeO, Cl, Br, F (**Table 10**).



172 60-93% **173**

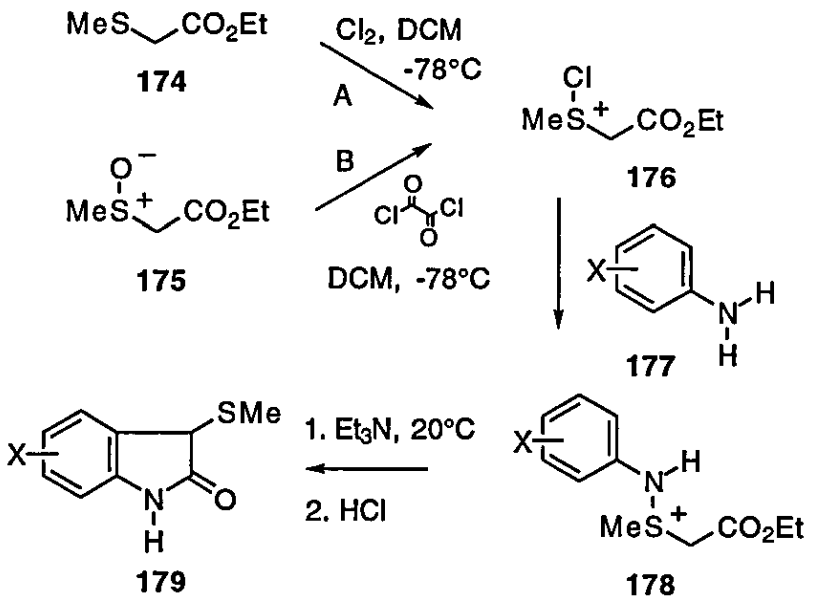
Scheme 64

Nitroaromatic **172** R	Oxindole **173** R	% Yield of Oxindole **173**
5-Cl	5-Cl	60
4-Cl	6-Cl	87
4-MeO	6-MeO	70
4-Br	6-Br	93
5-F	5-F	87
4-F	6-F	91
6-Cl	4-Cl	80

Table 10

3.2.2 Modified Gassman Synthesis

Another classical method, claimed to be one of the most useful for oxindole synthesis in terms of scope, starting material availability, brevity, and reproducibility is the Gassman protocol. The original method involves *S*-chlorination of ethyl methylthioacetate **174** with elemental chlorine to give chlorosulfonium salt **176** which is treated with an aniline **177** to give *N-S* intermediate **178** (path A, **Scheme 65**). Subsequent addition of triethylamine and then treatment with acid gives rearrangement and cyclisation to the target oxindole **179**. Wright and co-workers have highlighted a potential limitation of the Gassman synthesis in the need to use elemental chlorine which can be diffficult to dispense accurately on a small scale. The improvement they offer is the use of oxalyl chloride and sulfoxide **175** (path B) for the generation of the key chlorosulfonium salt **176** which is commonly postulated to be an intermediate of both reaction sequences (**Scheme 65**).[85] This improved method gives yields of oxindoles comparable to or better than the original, but with ease of handling on a small scale and the scope to use anilines which are sensitive to electrophilic chlorination conditions (**Table 11**). The yields are however quite variable, and the isssue of regioselectivity becomes important in some substrates where more than one position for attack of the ring is possible. Also the 3-methylthio substituent often needs to be removed in a subsequent step to allow useful chemistry to be conducted at that position, but there are a large number of methods available for this transformation.[86]



Scheme 65

Aniline **177** X	Yield of Oxindole **179** (%)	
	Gassman Cl_2 Method (A)	Modified Method (B)
H	65	63
4-MeO	53	50
2-Me	62	82
4-NO_2	12	8
3,4,5-$(MeO)_3$	-	44
3-MeS	-	50[a]
3,5-$(MeO)_2$	-	67

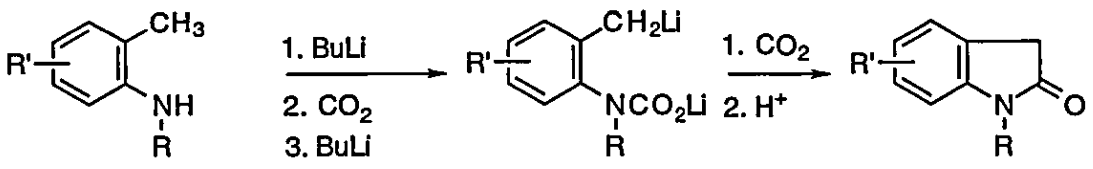
[a] 1:1 mixture of regioisomeric oxindoles

Table 11

3.2.3 Lithiation of 2-Methylanilines

A recent report from Rewcastle and co-workers describes a useful approach to the synthesis of *N*-substituted oxindoles without the risk of producing regioisomeric mixtures, a problem which is encountered with methods which involve cyclisation onto the aromatic ring. They adopt Katritzky's carbon dioxide protection procedure, whereby *N*-alkyl-2-methylanilines **180** are subjected to two sequential lithiations and carbon dioxide quenches and then treated with aqueous acid to furnish the desired oxindoles **181** (**Scheme 66**).[87] Most of the examples given were with R=Me (leading to *N*-methyloxindoles) and these are the examples selected for the table below (**Table 12**).

One other example with R=$CH_2CH_2NMe_2$ and R'=H gave 43% yield of oxindole product. Inspection of these results shows only modest yields, even without the complications of regioselectivity.



180 181 182

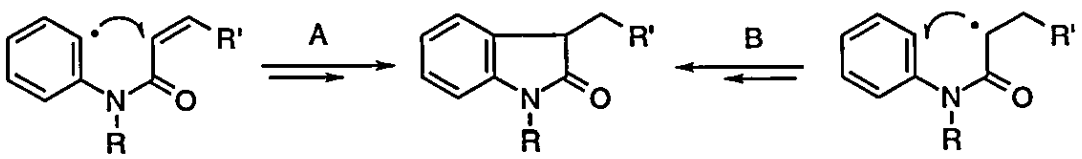
Scheme 66

Oxindole R'	% Yield of Oxindole	Oxindole R'	% Yield of Oxindole
H	55	4-OMe	45
4-Me	58	5-OMe	36
5-Me	48	6-OMe	9
6-Me	42	7-OMe	38
7-Me	42	5-Cl	41

Table 12

3.2.4. Radical Methods

There are a large number of related reports of radical cyclisations to give oxindoles, and a few examples have been selected for illustration. In particular the Jones group have been reporting for over a decade on variations to this theme and others have made valuable additions too. The basic stategy is outlined in **Scheme 67.** Two general routes are available. The first, and most widely reported, involves use of *ortho*-halo acrylamides to generate sp2-centred radicals **183** which undergo a 5-*exo* cyclisation and ultimately furnish the desired oxindoles **184** (path A). The alternative route involves radical cyclisation onto the aromatic ring (path B).

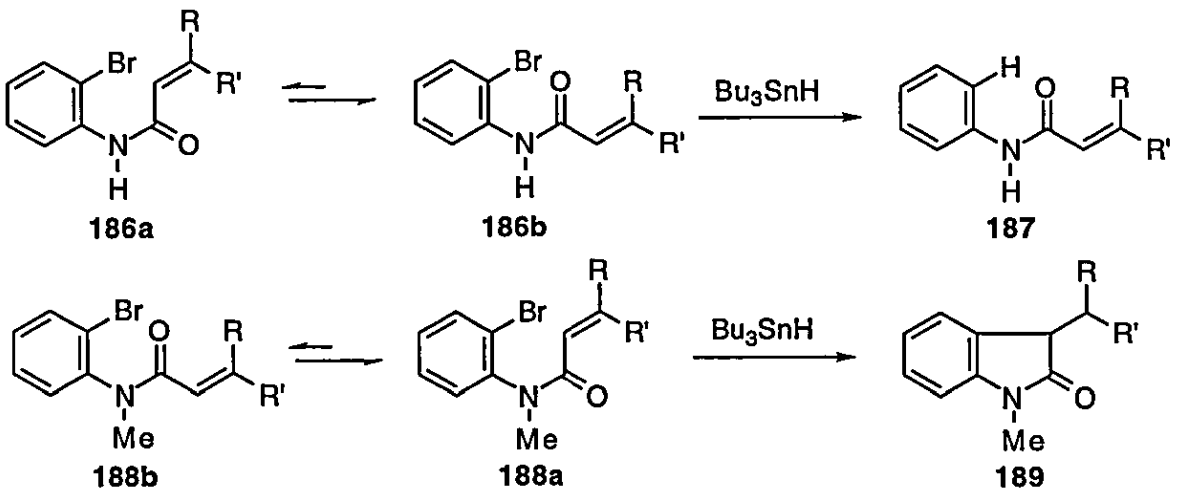


183 184 185

Scheme 67

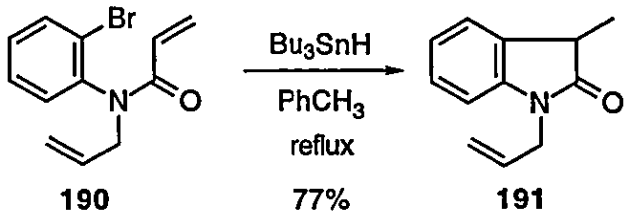
Reports from the Jones group are focused on the preparation of oxindoles *via* the intramolecular cyclisation of radicals derived from *ortho*-halo acryloylanilides (path A, **Scheme 67**).[88]

They observed that secondary amides **186** failed to cyclise under standard tributyltin hydride (TBTH) radical reaction conditions, and gave largely reduced product **187.** On the other hand, tertiary amides **188** gave clean cyclisation to the desired oxindoles **189.** This was rationalised by recalling the known propensity for secondary amides **186** to favour the *s-trans* conformation **186b** and for tertiary amides to favour the *s-cis* conformation **188a**, each respective conformation dictating the feasability of intramolecular 5-*exo* cyclisation (**Scheme 68**).[89]



Scheme 68

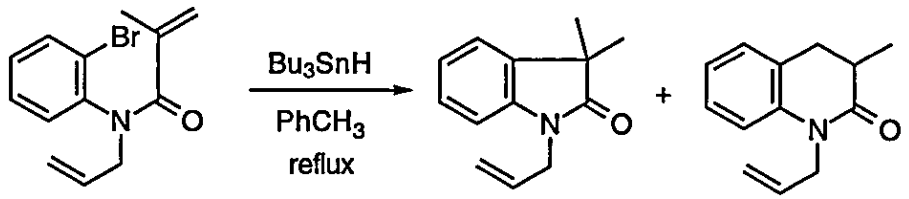
In competition reactions with substrates such as *N*-allylacryloylanilide **190** TBTH mediated reaction gave 5-*exo* cyclisation onto the relatively electron deficient double bond of the acryloyl unit selectively over the alternative allyl double bond; this afforded the *N*-allyl-2-oxindole **191** in high yield (**Scheme 69**).[90]



Scheme 69

Jones reasoned that an additional methyl substituent on the acryloyl unit double bond, as in substrate **192**, might override the selectivity arising as a result of the difference in LUMO energies of the two double bonds, thus giving competitive cyclisation onto the

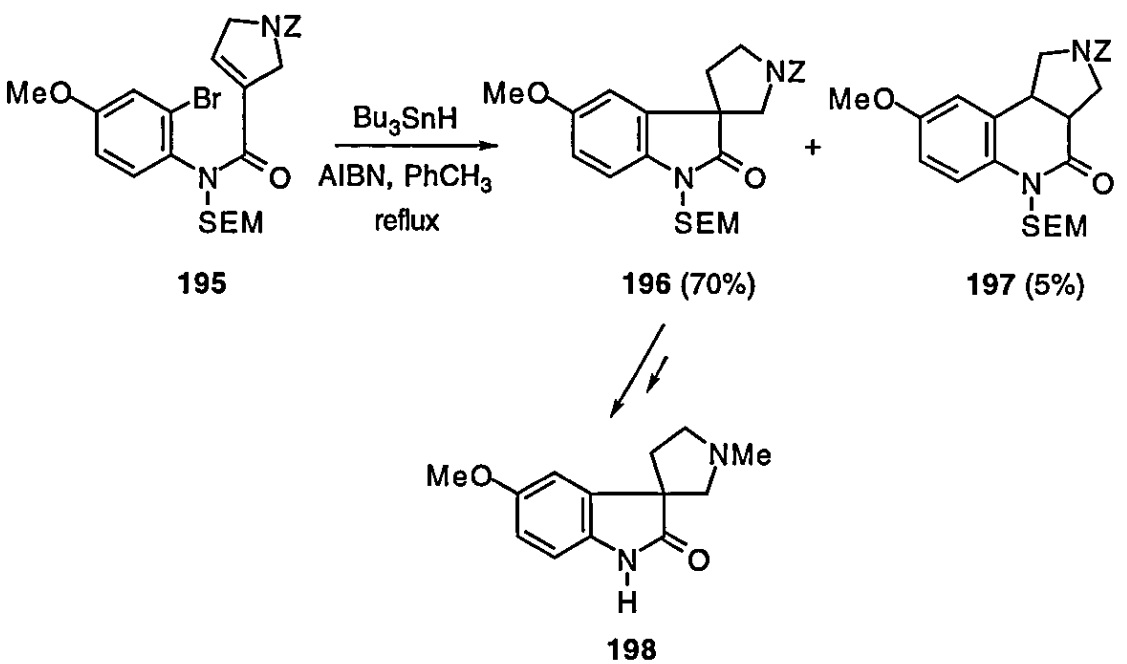
allyl double bond (**Scheme 70**). In practice attack was found, again, to be selective for the acryloyl unit double bond giving rise to 5-*exo* and 6-*endo* cylisation products (**193** and **194** respectively); the reason postulated for a failure of the allyl double bond to compete was restriction of rotation about both the amide C-N bond and the aryl C-N bond.[90]



192 **193** (74%) **194** (24%)

Scheme 70

Jones capitalised on the aryl radical cyclisation route to oxindoles for a total synthesis of horsfiline **198**, an alkaloid isolated from *Horsfieldia superba*. Preparation of the key cyclisation precursor **195** was achieved in 9 steps from ethyl glycine in about 16% overall yield. Standard radical cyclisation with TBTH gave the spirooxindole **196** in 70% yield along with 5% of the 6-endo cyclisation product **197**. Desilylation of **195**, followed by transfer hydrogenation to cleave the Z group and finally *N*-methylation under Eschweiler-Clarke conditions gave the natural product **198** in good yield (52% yield from **196; Scheme 71**).[91]

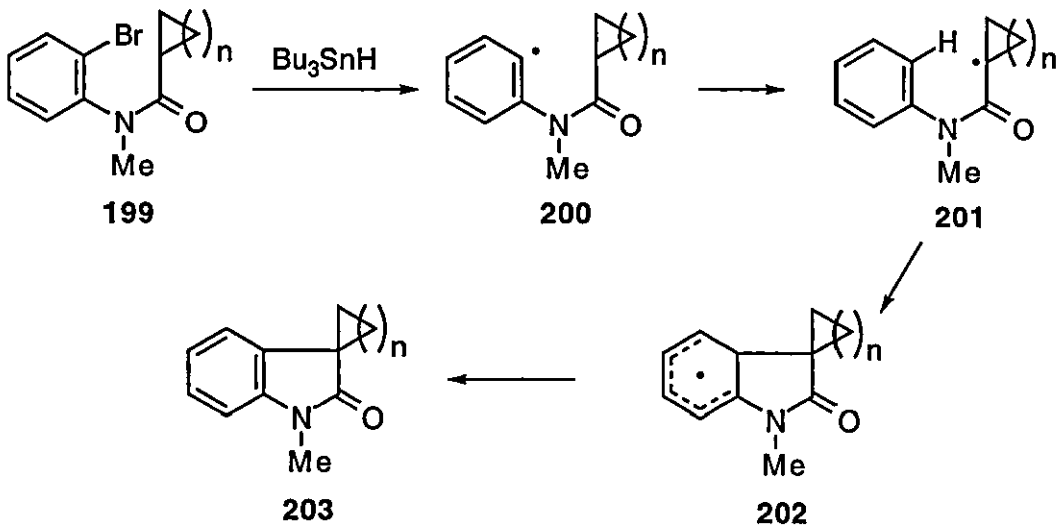


195 **196** (70%) **197** (5%)

198

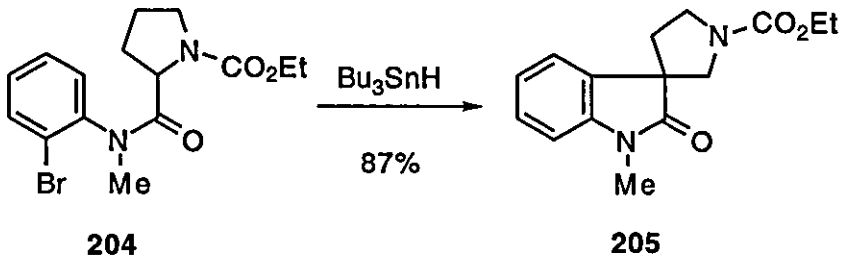
Scheme 71

Beckwith reported a convenient and efficient method for the preparation of oxindoles using tandem [1,5]-hydrogen atom transfer and homolytic aromatic substitution reactions of radical species. In this methodology the 2-bromoanilides **199** are used to produce aromatic radical intermediates **200** which, lacking the option of attack on a tethered site of unsaturation, undergo a [1,5]-hydrogen transfer to give a new carbon-centred radical **201**. This intermediate then cyclises back onto the aromatic ring, *via* what is postulated to be a pseudo $S_{RN}1$ mechanism, to afford the product oxindoles **203** (**Scheme 72**). For substrates with n=1-4, yields varied in the range of 40-87%. In a similar fashion, the simpler 1,3,3-trimethyl-2-oxindole could be prepared from its bromoanilide precursor in 70% yield.[92]



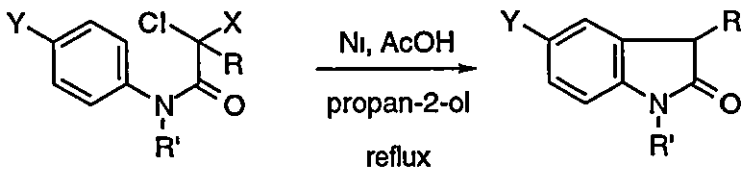
Scheme 72

As a model reaction towards total synthesis of horsfiline **198**, Beckwith demonstrated the above methodology to be highly effective for the synthesis of the spirooxindole **205** from the readily prepared precursor bromoanilide **204** (**Scheme 73**)



Scheme 73

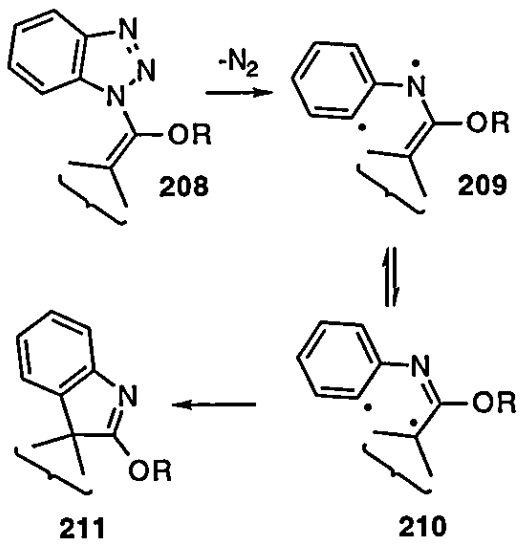
Zard has reported on the novel use of nickel powder and acetic acid to produce radical intermediates from α-haloanilides **206** which undergo a subsequent intramolecular cyclisation onto tethered aromatic rings to afford oxindoles **207** (this, of course, is an example of a reaction following path B from **Scheme 67** above).[93] The arguments offered in favour of this method over the use of *ortho*-haloacryloylanilides (path A, **Scheme 67**) include the potential for more readily available starting materials, low cost, simplicity, and tolerance of a variety of functional groups. In summary, the starting materials **206** carried substituents which include the following: R=Cl, Me, H; R'=Me, Bn, CH_2-(2,4-Cl_2-C_6H_3); X=Cl, H; Y=H, F, I, OH. The yields of oxindoles **207** varied from low to excellent, but were generally high (**Scheme 74**). The major by-products were those arising from premature reduction of the radical intermediate. It is noteworthy that any chloro-substituents left at C-3 (X or R=Cl in the starting material **206**) of the oxindole after cyclisation are reduced off under the reaction conditions (R=H in the product **207**).



206 20-78% **207**

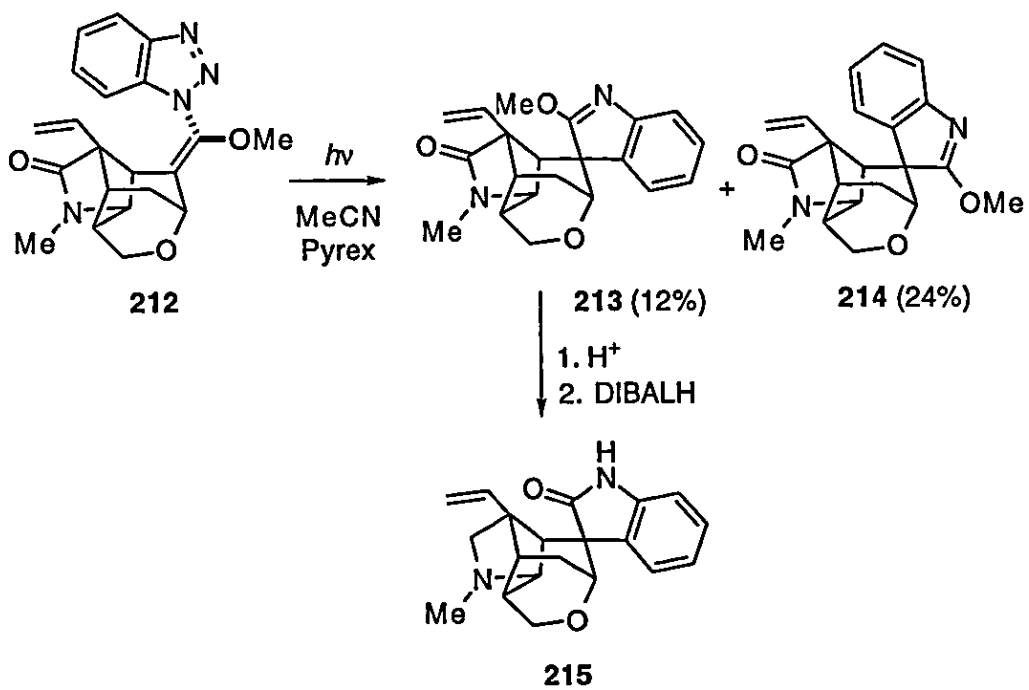
Scheme 74

A final example of the use of radical mediated cyclisation to give valuable oxindoles was demonstrated by Johnson and co-workers in their total sythesis of gelsemine **215**.[94] The challenge they met was to produce the quaternary spirocentre of the natural product and this was found to be troublesome as a result of the steric crowding around that centre. To achieve this difficult C-C bond formation they envisaged the combination of two radical centres as there was known to be very low activation energy for this type of reaction. Thus photolysis of *N*-alkenylbenzotriazole of type **208** leads to nitrogen extrusion and formation of a diradical intermediate **209** which rearranges to ultimately afford an *O*-alkyl-2-oxindole **211** (**Scheme 75**).



Scheme 75

This strategy was adopted in the key conversion of substituted benzotriazole **212** to the isomeric iminoethers **213** and **214** in rather low yield. Of the two isomeric cyclisation products, **213** was found to possess the correct stereochemistry at the spirocentre for subsequent elaboration to the natural product **215**. This was achievable by acid hydrolysis of the iminoether to reveal the bisoxindole and then selective reduction of the carbonyl group of the *N*-methyl oxindole moiety with DIBALH (**Scheme 76**).

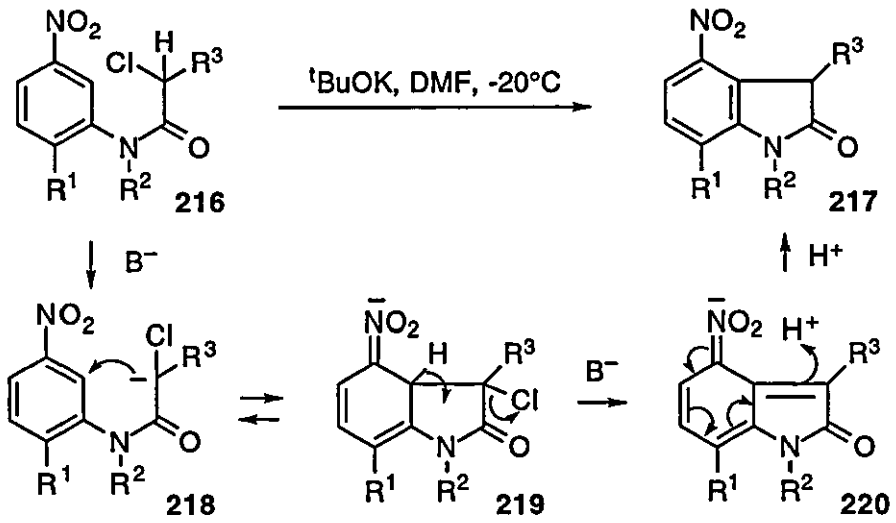


Scheme 76

Though this particular cyclisation example affords little of the desired product, the strategy has been used to better effect in simpler models.[95]

3.2.5. Vicarious Nucleophilic Substitution (VNS)

Makosza has demonstrated the use of VNS of hydrogen by treatment of 3-nitrochloroacetanilides **216** with a strong base as a viable method for preparation of oxindoles **217 (Scheme 77)**.[96] The method is limited to the preparation 4-nitro oxindoles **217**, and there is observed selectivity for substitution *ortho* to the nitro group (for example, when R^1=H, R^2=Pr and R^3=Me, the only product is a 4-nitro oxindole in 69% yield).



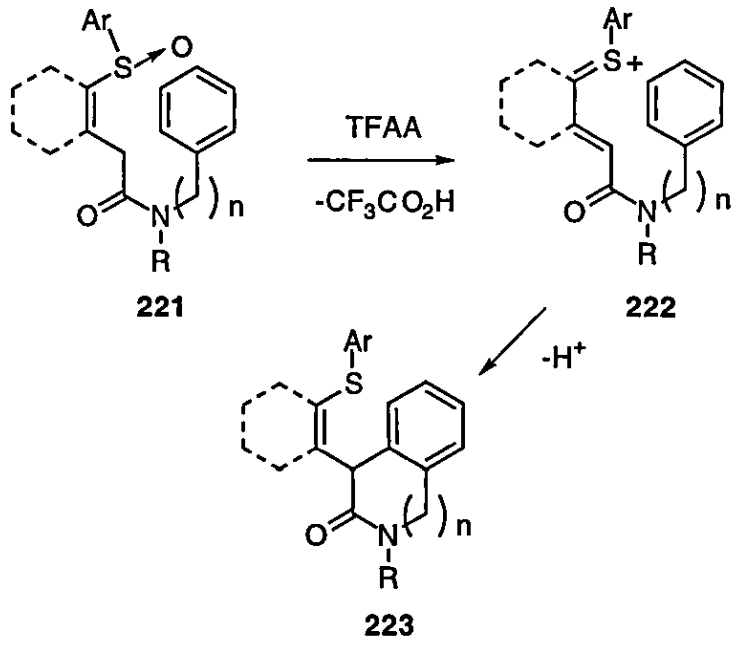
Scheme 77

R_1	R_2	R_3	% Yield of Oxindole
F	Pr	H	63
F	Pr	H	64
MeO	Me	H	29
H	Pr	Me	69
F	Pr	Me	57
MeO	Me	Me	37

Table 13

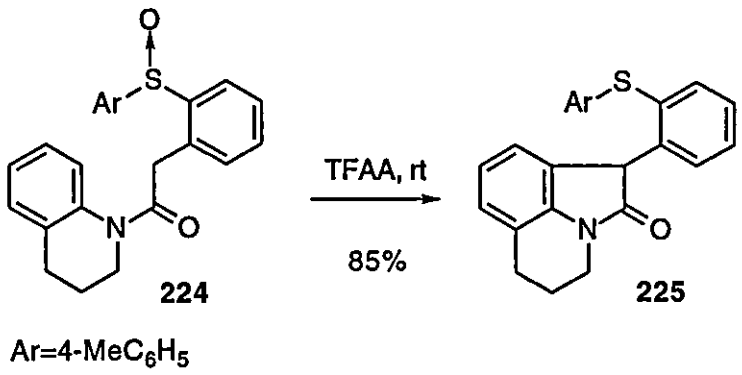
3.2.6. Vinylogous Pummerer Reaction

In a recent communication, Padwa reported that amidosubstituted sulfoxides undergo vinylogous Pummerer reaction on treatment with trifluoroacetic anhydride. Thus, when aryl amidosulfoxides of type **221** are treated with TFAA the reactive thionium intermediate **222** is generated *via* electrophilic attack of the nucleophilic oxygen and proton loss. The γ-position is activated by the positively-charged sulfur atom and intramolecular attack at this position by a tethered π-bond gives annulation to afford oxindoles (n=0) or tetrahydroisoquinolones (n=1) **223** (**Scheme 78**).[97]



Scheme 78

A good example of oxindole preparation using this new reaction is shown below (**Scheme 79**). Hence, sulfoxide **224** is used to generate an intermedate thionium ion which activates the methylene position α to the amide carbonyl for electrophilic (Friedel-Crafts like) attack onto the aromatic ring of the anilide. This ultimately furnishes oxindole **225**.



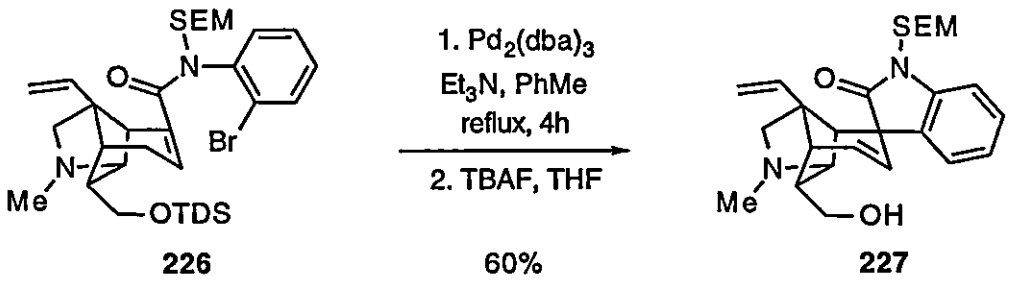
Ar=4-MeC_6H_5

Scheme 79

Padwa has also demonstrated that π-systems other than phenyl rings can be employed for cyclisation to give tetrahydroisoquinolones, and these include attack onto the 2-position of a 3-substituted furan (selectively over the alternative 4 position) and attack of a cyclohexenyl ring.

3.2.7. Intramolecular Heck Reactions

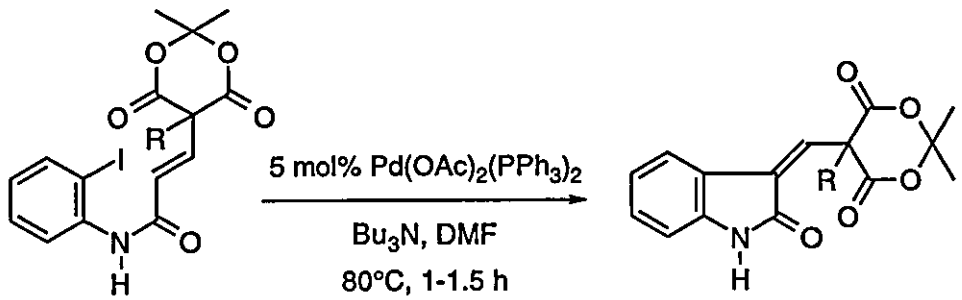
Speckamp and Hemstra have exploited a modified intramolecular Heck reaction as a key oxindole forming step in a total synthesis of gelsemine **215**.[98] The *ortho*-bromoanilide **226** was treated with catalytic palladium benzylideneacetone to furnish, after removal of a thexyldimethylsilyl protecting group, the desired oxindole **227** with correct spiro stereochemistry for elaboration to gelsemine, and in good yield (**Scheme 80**).



Scheme 80

Cacchi and coworkers have described a preparation of 3-alkylidene-2-oxindoles *via* an intramolecular Heck cyclisation reaction. The substrates discussed are a series of 5-(alken-1-yl) derivatives of Meldrum's acid which have an iodoaromatic tethered such as to facilitate intramolecular palladium(0) catalysed cyclisation reactions to give the alkylidene oxindole products. These starting anilides **228** were prepared from 5-alkyl

derivatives of Meldrum's acid by conjugate addition to α,β-ynones in good yields. Reaction under Heck conditions gives alkylidene oxindoles **229** in good to high yields. As an example of the potential synthetic utility of such Meldrums acid derivatives, one oxindole (**229**, R=Me) was shown to be readily converted in two steps to a substituted carbazole in good yield (**Scheme 81**; **Table 14**).[99]



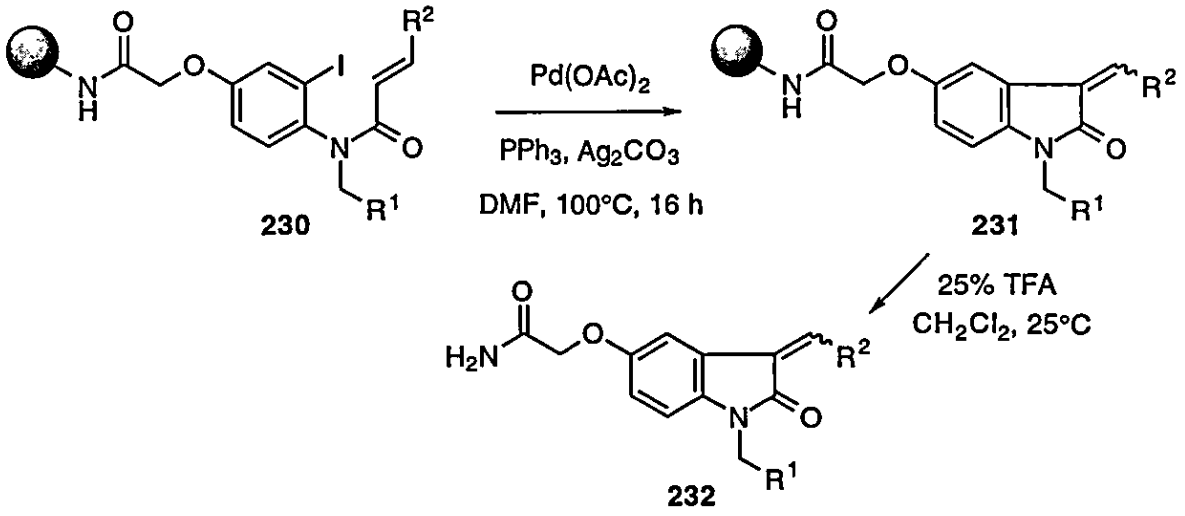
228 **229**

Scheme 81

R	% Yield of Oxindole **229**
Me	73
CH_2CH_2COMe	30
$CH_2CH_2CO_2Me$	70
CH_2-C_6H_{11}	65
^iPr	90
CH_2CH_2Ph	84
$CH(CH_3)CH_2COMe$	93
CH_2Ph	55

Table 14

Balasubramanian and co-workers have recently reported success in the solid phase intramolecular Heck cyclisation of *ortho* iodoacryloylanilides **230** to furnish Rink amide resin-bound 3-alkylidene-2-oxindoles **231** (**Scheme 82**).[100] The tertiary anilides **230** are prepared by acylation of the respective secondary anilines, which in turn are accessed by reductive alkylation of primary anilines. The cyclisation is smooth for several anilide substrates **230** where R_2=Me or Ph, giving rise to E/Z mixtures of reasonably clean alkylidene oxindoles **232** upon cleavage from the solid support using trifluoroacetic acid/dichloromethane (16h, 25°C); however, acryloyl chloride derivatives (R_2=H) afford very impure products **232**. Some examples have been selected for illustration in the table below (**Table 15**).

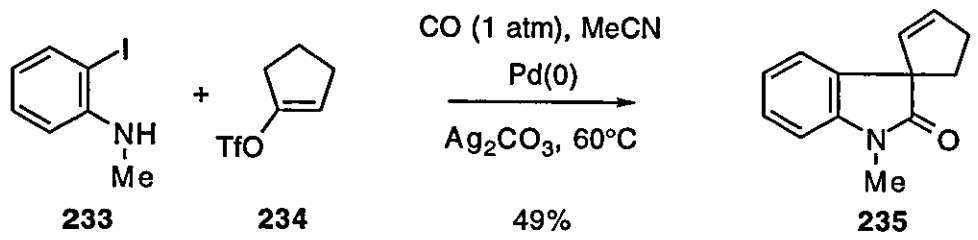


Scheme 82

R^1	R^2	Yield of **231** (%)	Purity of **232**
H	Ph	92	76
$CH_2CH(CH_3)_2$	Ph	90	70
H	H	65	10

Table 15

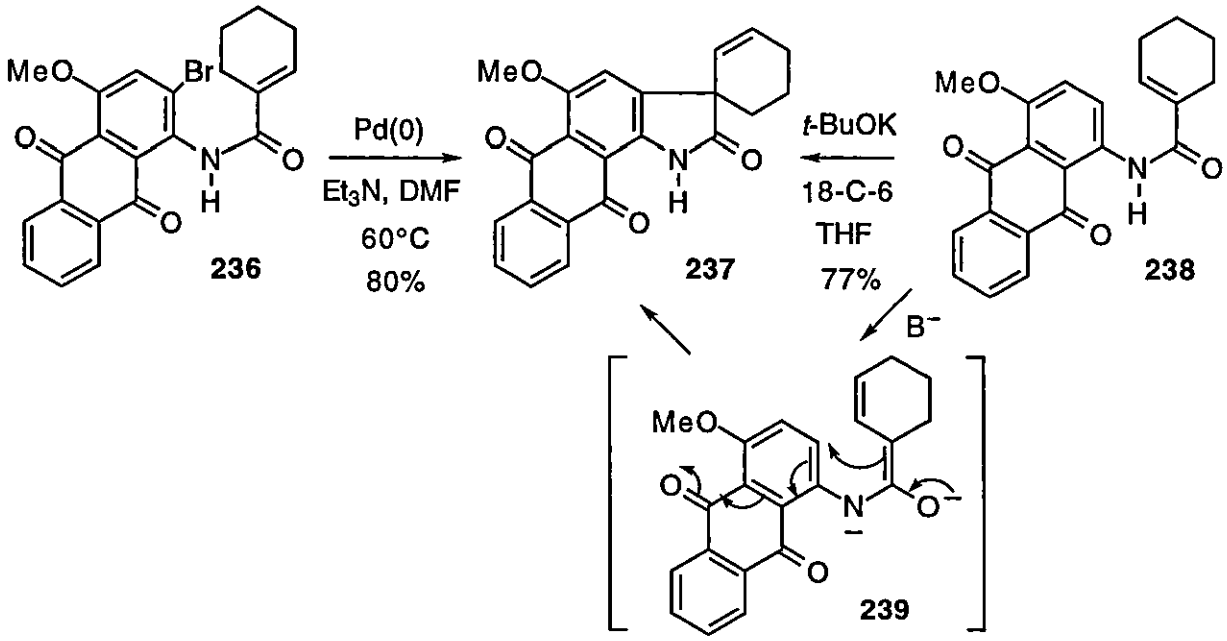
Grigg has disclosed an elegant combination of two Heck reactions as a one pot route to 3-spiro-2-oxindoles and 3-spiro-2(3*H*)-benzofuranones.[101] The 3-spiro motif is an important one and is found in many natural products. The basic strategy employed had been reported previously for two step sequences[102] and involves taking advantage of the selective insertion of Pd(0) into vinyl triflates in preference to aryl bromides or iodides. An example of Grigg's termolecular "queuing" sequence, which produces in one pot the spiro-oxindole **235**, is illustrated below (**Scheme 83**). The first step in the cascade is a termolecular carbonylative Heck reaction using the aniline **233**, triflate **234**, and carbon monoxide to generate an intermediate alkenyl *N*-methylanilide which then undergoes an intramolecular Heck cyclisation to afford the spiro-oxindole **235** in moderate yield. The catalytic Pd(0) species required for the reaction is generated *in-situ* from 10 mol% palladium(II) acetate and 20 mol% triphenylphosphine. Grigg describes the need to vary reaction conditions, in particular the base, for optimisation of any specific cyclisation, and the yields reported to date are generally modest to good.



233 **234** 49% **235**

Scheme 83

Isobe and Okita reported the preparation of spiro-oxindole **237** by two different methods.[103] The first involved an intramolecular Heck reaction on bromoanilide **236** and gave a high yield of the oxindole **237**. The alternative route involved treatment of the amide **238** with excess potassium *tert*-butoxide in the prescence of 18-crown-6. Cyclisation afforded oxindole **237** in high yield. A mechanism for this unexpected latter reaction was postulated and involved conjugate addition and elimination (**Scheme 84**). It is clear from the mechanism, therefore, that this latter base mediated cyclisation is limited to substrates containing anthroquinone backbones similar to **237**.



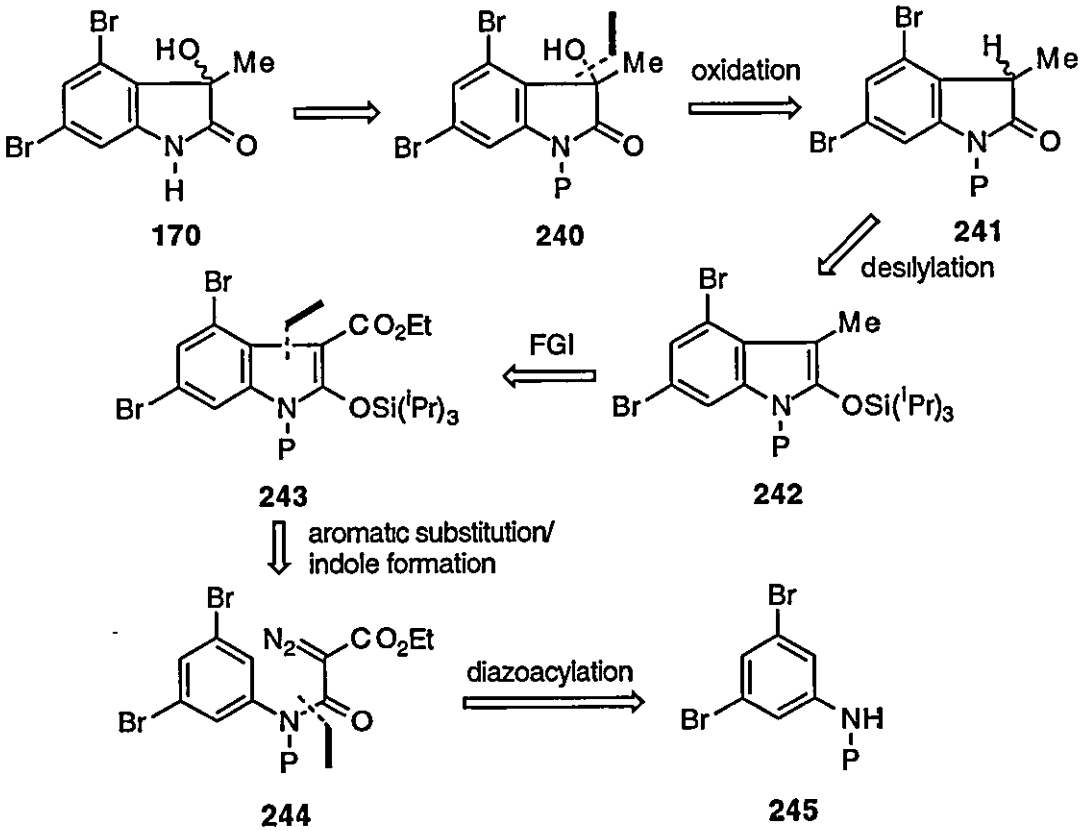
236 **237** **238** **239**

Scheme 84

3.3. Retrosynthetic Analysis of Convolutamydine C

Their novel structures, coupled with the observed bioactivity of certain members of the family, made the convolutamydines obvious targets for application of the methodology established for the preparation of substituted oxindoles in our early work (Chapter 2). This strategy should be effective for preparation of a common oxindole intermediate which could then be elaborated to all four of the natural products. On the face of things, all that was required was careful selection of protecting groups and some modification of functionality. Thus, the targets were analysed retrosynthetically.

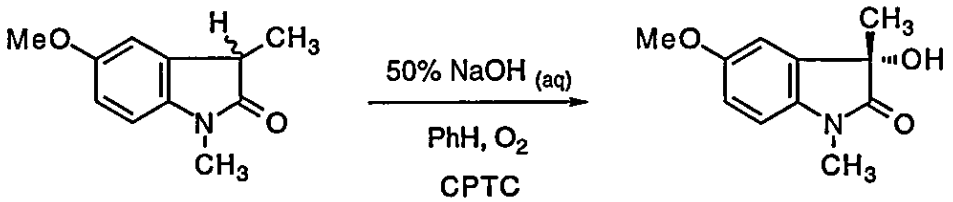
A whole array of retrosynthetic approaches to the targets in hand could be envisaged and the following scheme represents just one general outline for convolutamydine C, and incorporates the key oxindole-forming metallocarbene reaction (**Scheme 85**).



Scheme 85

The target alkaloid **170** might be obtained after deprotection of the oxindole **240** which should be available through oxidation at C-3 of the *N*-protected oxindole **241**. This functionalisation of oxindoles has fairly wide literature precedent. For example, in a report from Brossi and co-workers, hydroxylation of 3-methyloxindole **246** in benzene is

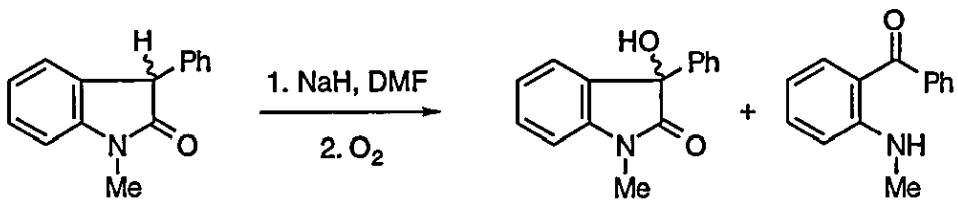
achieved by treatment with concentrated aqueous sodium hydroxide in the presence of the chiral phase transfer catalyst (CPTC) *N*-[(4-trifluoromethyl)benzyl]cinchonium bromide (**Scheme 86**).[104]



246 50% **247** (13% ee)

Scheme 86

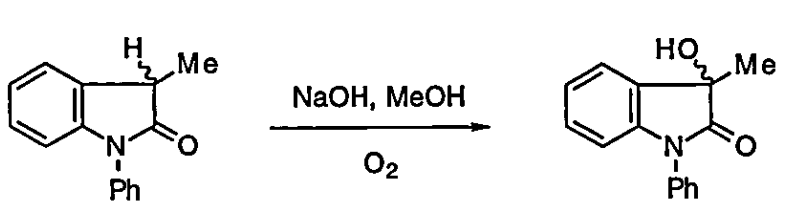
Further support for the proposed oxidation at C-3 is found in the work of Houlihan and Aeberli. In a report of 1968, they describe the oxygenation of the sodium salt of 1-methyl-3-phenyloxindole **248** to afford a mixture of the 3-hydroxyoxindole **249** (71%) along with the ring opened benzophenone **250** (7%) (**Scheme 87**).[105]



248 **249** (71%) **250** (7%)

Scheme 87

Nishio has more recently extended this work and found that oxidation of 3-methyl-1-phenyloxindole **251** can be effected by oxygenation of a methanolic solution in the presence of a catalytic amount of sodium hydroxide to furnish 3-hydroxyoxindole **252** in quantitative yield.[106] The base was found to be essential for the reaction to proceed (**Scheme 88**).



251 **252** (99%)

Scheme 88

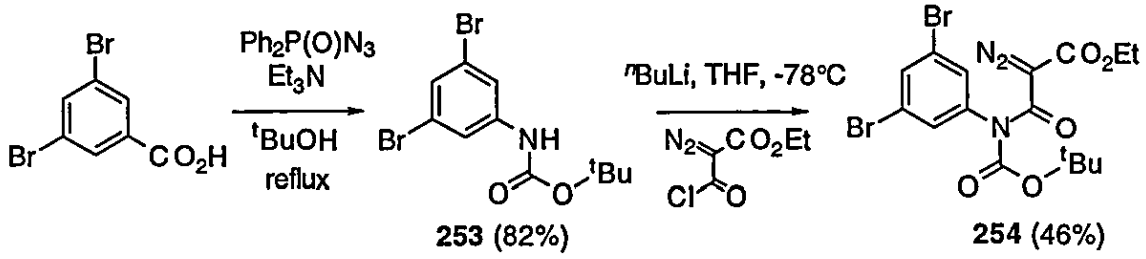
These reports auger well for the success of the proposed oxidation of an oxindole such as **241** to give 3-hydroxyoxindole **240.**

Desilylation of the the protected indole **242** should give 3-methyloxindole **241,** and this in turn should be available through functional group interconversion at C-3 of the standard indole-3-ester **243.** *N*-Protected aniline **245** should provide the diazoamide **244** required to undergo $Rh_2(pfm)_4$ catalysed decomposition to provide the indole ester **243.**

The novel dibromo-substituted diazoamide **244** should also provide additional information about the role of substituents in the chemoselectivity of carbenoid processes and, thus, this is an extension of our earlier work (Chapter 2). Previous studies in the group had, however, shown that the treatment of *N*-benzyl-2,5-dibromoaniline with ethyl 2-diazomalonyl chloride did not give the expected *N*-benzyl-2-diazo-*N*-(2,5-dibromophenyl)malonamic acid ester, and it was proposed that this was as a result of steric hinderance.[107]

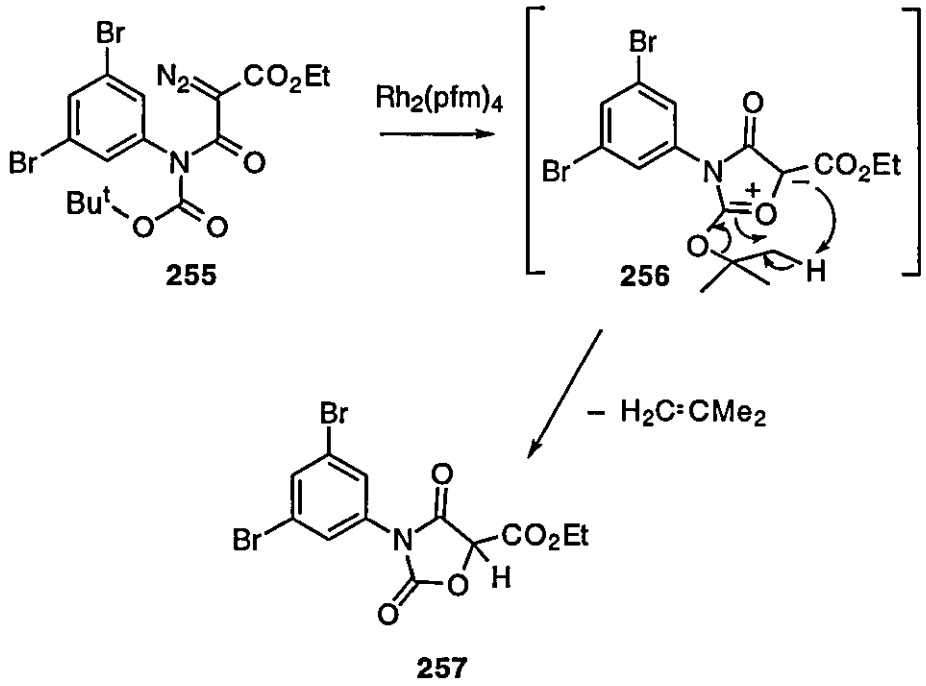
3.4. Preparation and Rhodium(II) Catalysed Reaction of *N*-Boc Diazocarbonyl

3,5-Dibromoanilines are not commercially available, so it was necessary to establish an efficient method for their preparation, which is poorly described in the literature. Shepherd described a method for the preparation of 3,5-dibromoaniline which involved diazotization and deamination of (now commercially available) 2,6-dibromo-4-nitroaniline, followed by catalytic reduction of the nitro group and this seemed somewhat cumbersome to repeat.[108] Therefore, attention was focused on Yamada's modification of the Curtius rearrangement for direct conversion of carboxylic acids to carbamates.[109] Treatment of 3,5-dibromobenzoic acid with diphenylphosphoryl azide and triethylamine in *tert*-butyl alcohol at reflux gave the carbamate **253** in 82% yield after purification. The proposed synthetic route requires some form of protection for the nitrogen of the aniline **245,** so this initial result was somewhat encouraging as the *tert*-butyoxycarbonyl group seemed to fill that role well. Adopting the method of Padwa and co-workers,[110] formation of the lithium salt of carbamate **253** with *n*-butyllithium followed by treatment with ethyl 2-diazomalonyl chloride provided the diazocarbonyl **254** as the first candidate for intramolecular aromatic substitution. The unoptimised, isolated yield was only modest but all the unreacted carbamate **253** was recovered **(Scheme 89).**



Scheme 89

Envisaging what would be a very short synthetic route to the core heterocyclic structure of the target alkaloids, an immediate attempt to cyclise the diazoamide **254** under $Rh_2(pfm)_4$ catalysed decomposition conditions was undertaken. Indeed rapid reaction did take place in dichloromethane solution at room temperature. However the result was not immediately obvious. Careful inspection of the NMR spectrum of the crude reaction mixture clearly showed no desired oxindole, but still there appeared to be a single, clean product. This product was isolated as a gummy oil, which was triturated and recrystallised to give small needles (77%; NMR spectra were the same as for the crude reaction mixture). Microanalytical data for the solid confirmed that the empirical formula was not of a product which had simply lost dinitrogen from the starting diazoamide. The most telling evidence leading to final deduction of the structure was the observation of a singlet in the ^1H NMR spectrum at 5.38 ppm integrating for one proton, and a band in the infrared spectrum at 1838 cm^{-1}. These, together with the lack of a signal for the *tert*-butyl group, indicated that the actual product was one resulting from intramolecular attack of the carbenoid on the carbonyl of the carbamate group to afford an intermediate ylide **255**. Loss of 2-methylpropene gives the oxazolidine-2,4-dione **256** and this structure fits the data exactly (**Scheme 90**).



Scheme 90

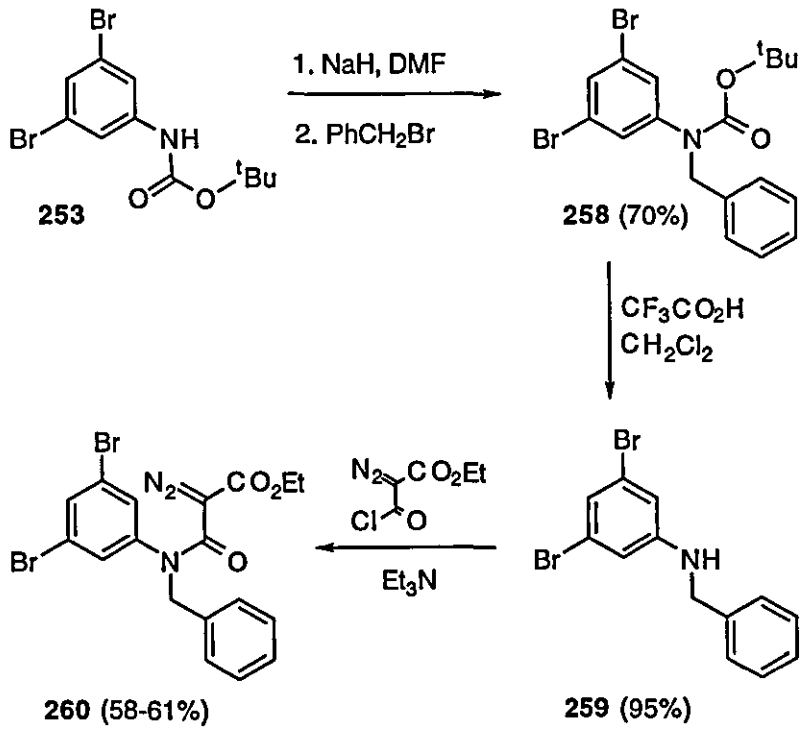
So, the introduction of several novel features to the starting diazoamide led to the discovery of some limitation to the established methodology for the preparation of oxindoles. With hindsight, one can see that the carbamate carbonyl stands susceptible to attack from the intermediate highly reactive and oxophilic carbenoid leading to the formation of an isomünchnone dipole **256**, chemistry which is well documented in the literature.[4, 6, 110] This competing pathway may be kinetically favoured over aromatic substitution given that the aromatic ring, in this case, is sterically hindered and doubly deactivated by its bromo subtituents. Wee has reported a similar process of ylide formation and elimination.[19] There is also the possibility that the carbamate functionality dramatically affects the conformation of the diazocompound **255** and hence its rhodium carbenoid to adopt one which disfavours aromatic substitution. Unfortunately, diazocarbonyl **255** could not be crystallised to produce material suitable for X-ray crystallographic analysis. Also, it was interesting to note that oxazolidine-2,4-diones closely related to **257** have interesting biological activity as clinically useful anticonvulsants,[111] and as herbicides.[112]

3.5. Preparation and Rhodium(II) Catalysed Reaction of *N*-Benzyl Diazoamide

Laying aside this interesting, if diversionary, result it was decided to return to more familiar ground; it was deemed necessary to minimise the deviation from the original substrate design (as described in Chapter 2), yet to retain features essential for a

feasible route to the target natural products. So a change of protecting group on the amide nitrogen to the more established benzyl moiety was considered. As a result of earlier experiences (Chapter 2), it was postulated, that a benzyl group was unlikely to compete with desired aromatic substitution under $Rh_2(pfm)_4$ catalysed decomposition conditions.

Thus, the anion of carbamate **253** was treated with benzyl bromide to give the protected aniline **258**. The next step was the removal of the *tert*-butoxycarbonyl group, and this was effected using either hydrogen chloride gas (bubbled through an ethereal solution of **258**) or the cleaner and more efficient method of stirring in a 1:1 mixture of dichloromethane and trifluoroacetic acid to give *N*-benzyl-3,5-dibromoaniline **259** (the overall, unoptimised, yield from 3,5-dibromobenzoic acid being 55%). These first three steps, converting 3,5-dibromobenzoic acid to aniline **259**, were repeated without full purification of intermediates **253** and **258** and the overall recrystallised yield of *N*-benzylaniline **259** was an improved 69%. This aniline was then treated with ethyl 2-diazomalonyl chloride to give the desired diazoamide **260** in moderate yields (however, most of the unreacted aniline was recovered) (**Scheme 91**). This slightly disappointing yield might be explained in terms of the steric hindrance presented by the large bromo substituents to the acylating agent as it approaches the aniline nitrogen. Similar results were found in other substrates and are described in the appropriate sections.



Scheme 91

The diazoamide **260** was found to be highly crystalline and its structure was confirmed by X-ray crystallography (**Figure 14**; **Appendix A**). In close similarity to diazoamides **102** and **120**, the conformation adopted by the diazo group is one in which it is *syn* to the amide carbonyl and *anti* to the ester carbonyl and is thus pointing toward the *N*-aryl group. The torsional angle between the carbonyl of the amide and the diazo group is 27°.[57]

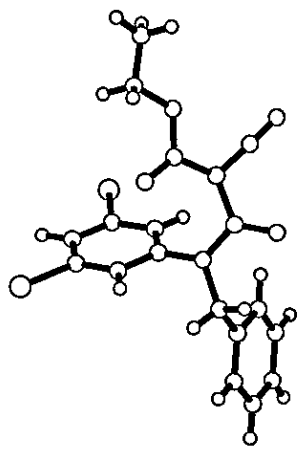
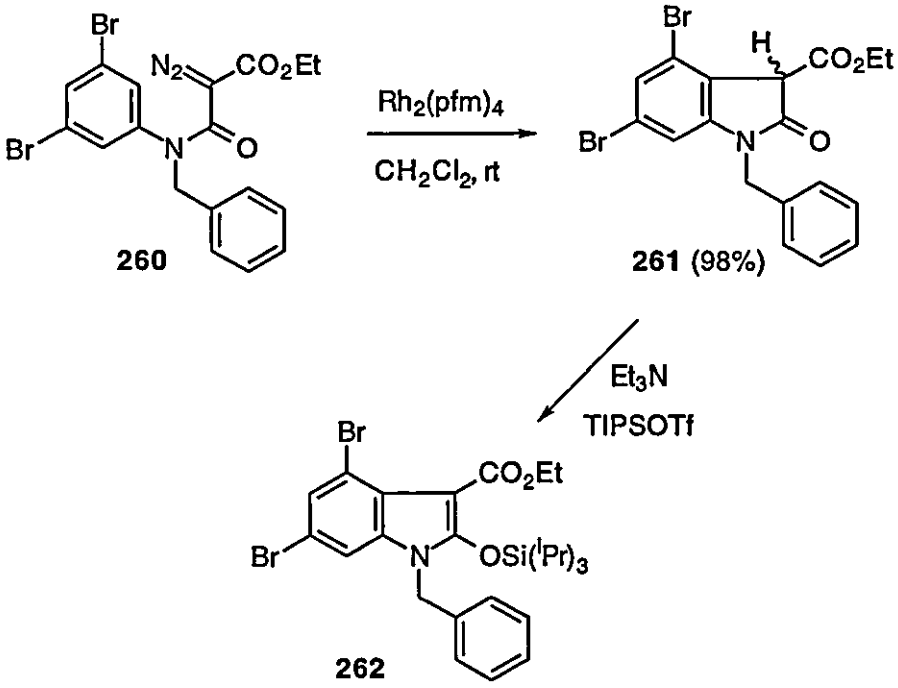


Figure 14 X-ray Crystal Structure of Diazoamide **260**

$Rh_2(pfm)_4$ catalysed decomposition of substrate **260** gave a rapid reaction and TLC showed a single, silica stable product. Filtration and removal of the solvent gave a near quantitative yield of the pure oxindole **261** which was found to be isolable, and thus fully characterisable, as a crystalline solid. NMR data gave no indication of any equilibrium of the oxindole with its enol tautomer, and this was supported by an unambiguous X-ray crystal structure (**Appendix B**). Subsequent treatment of **261** with triethylamine and TIPSOTf gave essentially pure indole **262**. However, attempts to further purify the crude indole by flash silica gel chromatography led to a dramatic fall in the yield; only 31% of material was isolated (**Scheme 92**). This phenomena was observed earlier in the preparation of indole **119**, and there is no obvious explanation for its occurrence (**Scheme 92**). However the crude indole **262** could be purified by recrystallisation without significant loss.

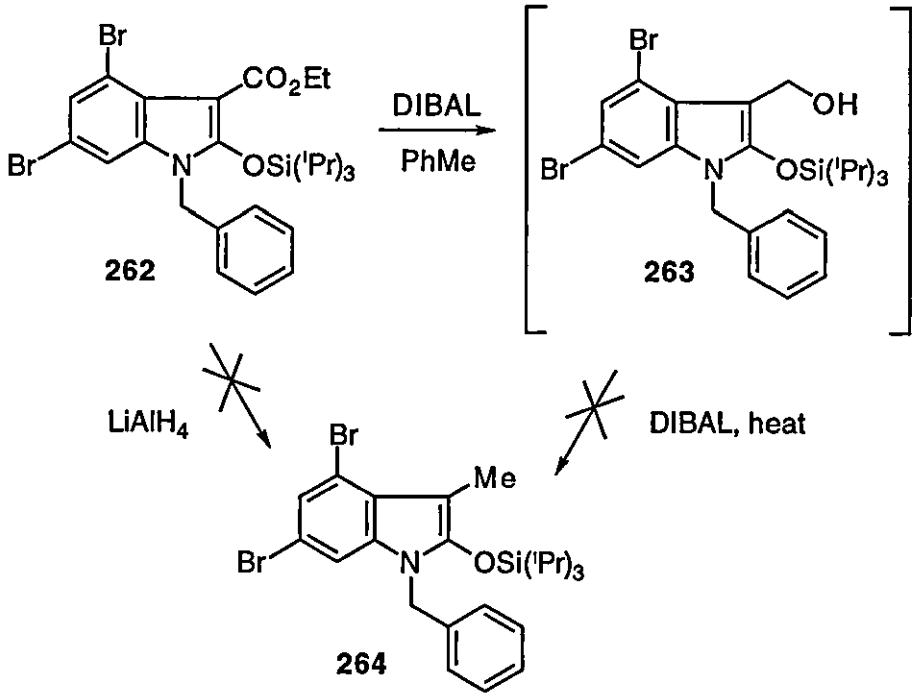


Scheme 92

3.6. Attempted Total Synthesis using *N*-Benzyl Protected Precursors

The next step towards the synthesis of convolutamydine C was the conversion of the C-3 ethyl ester of indole **262** to a methyl group. The first attempts at this were with $LiAlH_4$, but these were found either to destroy the substrate or to return it unchanged depending on the conditions employed (in THF at room temperature or at reflux; in diethyl ether at reflux).

An attempt was made to carry out this transformation on a small scale using 3 equivalents of DIBAL in toluene solution. The reaction was monitored by TLC and, at -6°C, the starting material was rapidly consumed giving rise to a single, more polar product which was tentatively concluded, from ^{1}H and ^{13}C NMR data, to be essentially pure indole-3-methanol **263**. In an attempt to further reduce this intermediate alcohol to give the desired 3-methylindole **264** the reaction mixture was allowed to warm up to room temperature and eventually heated for some time at 50-60°C. This, however, did not yield any significant amount of characterisable product (**Scheme 93**).



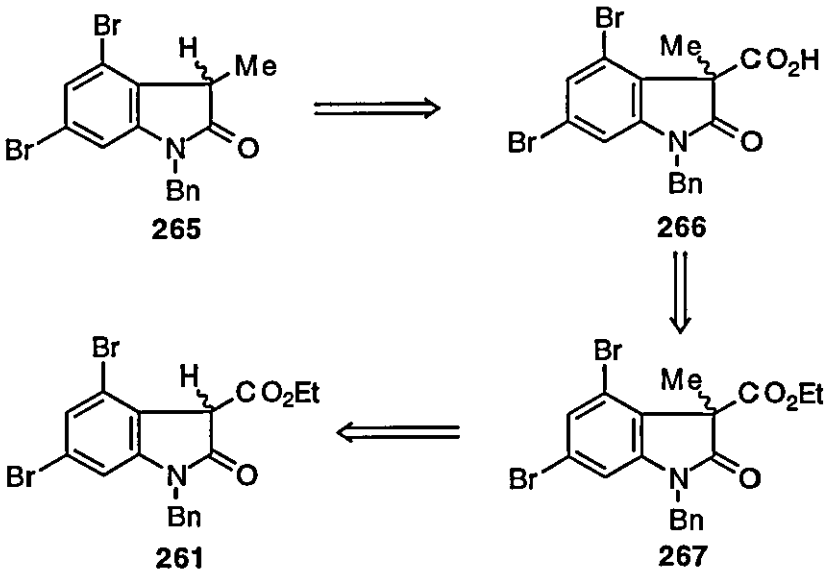
Scheme 93

Direct Manipulation of Oxindole **261**

Given the troubles encountered with the reduction of the indole-3-ester **262** directly to the desired 3-methylindole **264** a different strategy was attempted. The plan involved direct alkylation of the oxindole **261**.

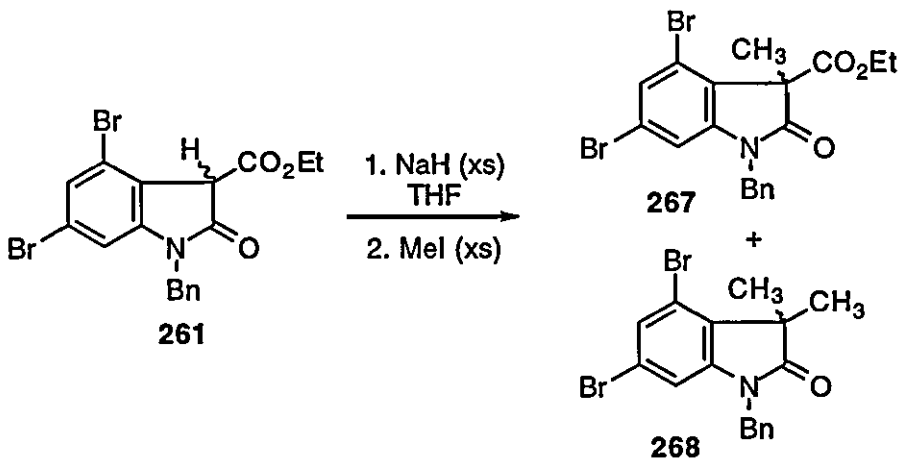
Karp and co-workers have reported investigations into the regioselective alkylations of oxindoles. They demonstrated that treatment of 1-*H*-3-(methylthio)oxindoles with sodium hydride in DMSO followed by a primary alkyl halide gives selective alkylation at C-3 without competitive *N*- or *O*-alkylation and in good yield (50-81% in 6 examples). *O*-Alkylation only competes when secondary alkyl halides are used.[113]

It was envisaged that treatment of the oxindole **261** with a suitable base should facilitate anion formation at the acidic C-3 position and subsequent quenching with an appropriate electrophile should lead to selective substitution at that position. Thus, in the case of convolutamydine C the electrophile would simply be methyl iodide. Subsequent hydrolysis of the ethyl ester **267**, followed by decarboxylation of the intermediate acid **266** should give the desired 3-methyloxindole **265** which could be further elaborated, as discussed above, to the natural product **170**. Thus, the partly revised retrosynthesis would be that outlined below (**Scheme 94**).



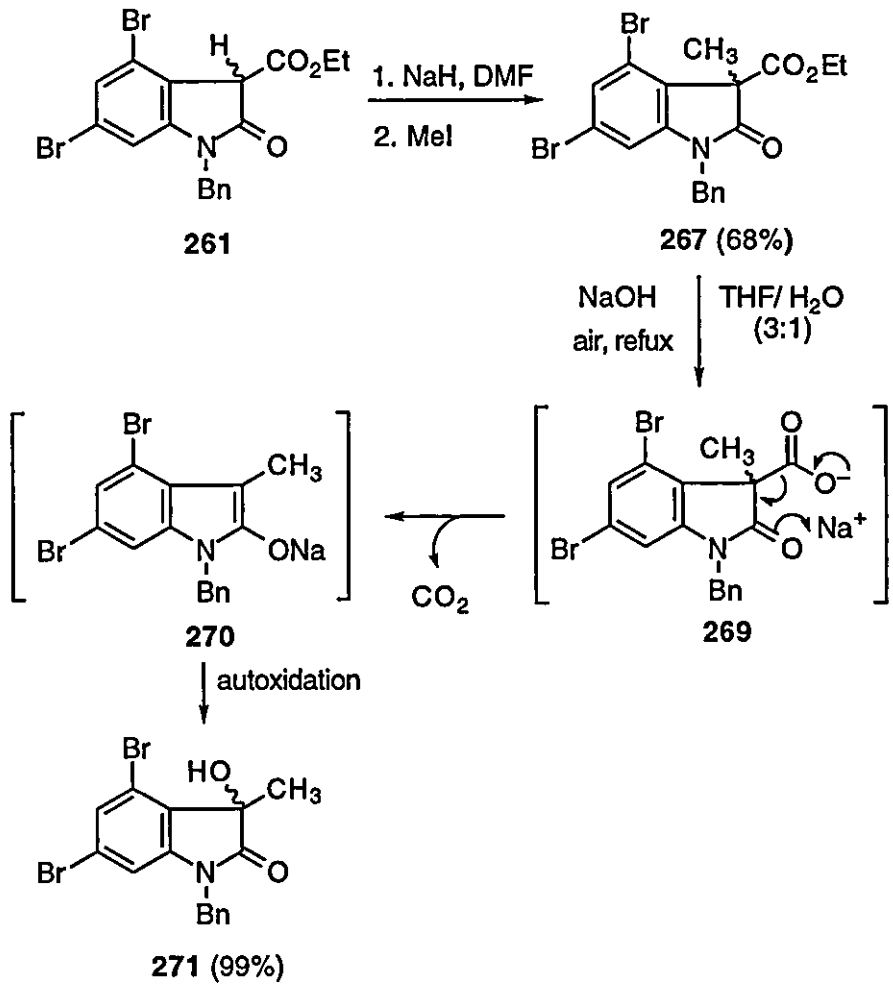
Scheme 94

Attempts to remove the proton at C-3 of oxindole **261** with sodium ethoxide were wholly unsuccessful judging by the lack of any substituted product on quenching with methyl iodide (all the starting material was recovered unchanged). In line with the above-mentioned observations of Karp,[13] treatment with sodium hydride followed by methyl iodide was found to give the desired 3-methyloxindole **267**. On a small scale (0.1 mmol), with a large excess of sodium hydride and methyl iodide in THF and stirring overnight, the desired product **267** was isolated in low yield (34%) along with the unexpected 3,3-dimethyloxindole **268** (17%) (**Scheme 95**). Apparently, the reaction conditions were enough to allow hydrolysis of the ester **267** followed by decarboxylation, an observation which led us to surmise that the desired decarboxylation of **266** to follow might well be facile.



Scheme 95

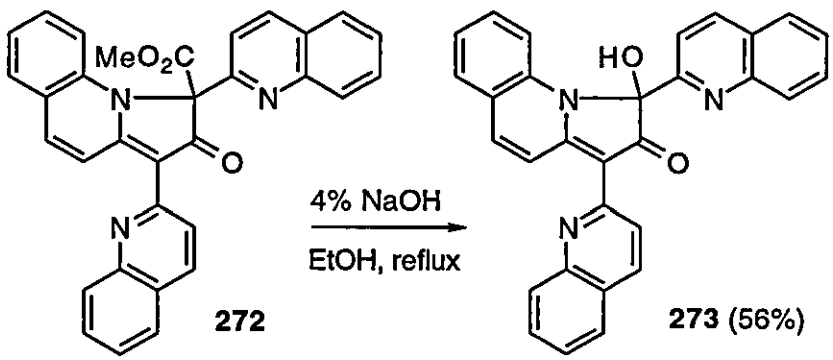
This dimethylated side-product **268** was completely avoided by treatment of the starting oxindole **261** with a single equivalent of sodium hydride in DMF and two equivalents of the electrophile. The desired product **267** was obtained in a moderate yield (54%) with some recovery of the starting material (26%). Use of only a slight excess of methyl iodide gave an acceptable 68% yield after recrystallisation. The next step was to hydrolyse the ester group of **267**, followed by decarboxylation of the resulting acid **266**. It was envisaged that the hydrolysis could be achieved by simple vigorous stirring of **267** in a two phase THF-H_2O (3:1) solvent system in the presence of excess sodium hydroxide. Indeed when this was attempted a slow conversion to a single relatively polar product was observed (the reaction was followed by TLC after acidification of the mixture). This was thought to be the acid **266**; however an attempt to decarboxylate this "acid" by heating of the acidified solution at 90°C for 4 hours did not change the TLC of the mixture. It was then speculated that the product may have immediately decarboxylated to give **270**, the sodium salt of 3-methyloxindole **265** (**Scheme 96**). Upon workup and flash silica gel chromatography the polar compound was isolated and found in actuality to be the 3-hydroxy-3-methyloxindole **271** (71%). This, of course, is *N*-benzyl-convolutamydine C. Along with this key compound 21% of unreacted starting material was recovered. Thus it seems that under the basic reaction conditions (which was not conducted under nitrogen) the intermediate acid spontaneously decarboxylated (**269—>270**)and then, with the presence of atmospheric oxygen, autoxidised at C-3 (**270—>271**). The overall transformation is slow at room temperature, taking several days, but refluxing accelerates it to completion overnight and the product **271** is isolated in quantitative yield as a crystalline solid (**Scheme 96**).



Scheme 96

The structure of the key 3-hydroxyoxindole **271** was confirmed by X-ray crystallography (**Appendix B**).

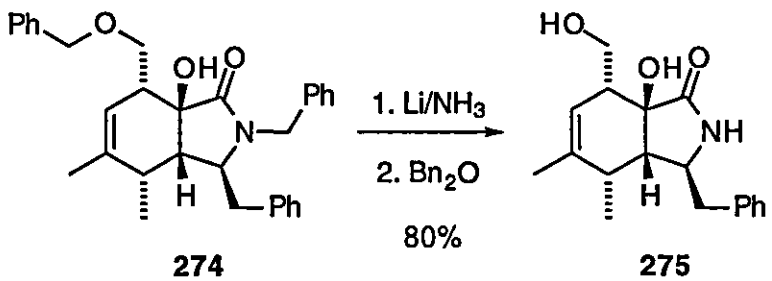
On hindsight, in view of the work of Nishio on base mediated autoxidation of simple oxindoles,[106] this serendipitous transformation of **267** to **271** can readily be rationalised. Further, an example of the full hydrolysis-decarboxylation-oxidation sequence was reported where the pyrroloquinoline **272** is converted to the tertiary alcohol **273** in modest yield (**Scheme 97**).[114] However, this does not detract from the fact that the transformation is of great value in meeting the challenge of total synthesis of the convolutamydine alkaloids.



Scheme 97

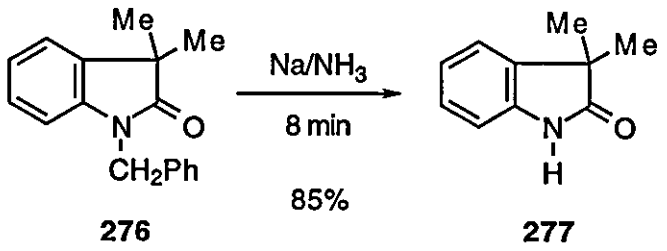
With the *N*-benzyl protected natural product **271** at hand all that remained was to find some efficient method of deprotection to furnish the target alkaloid convolutamydine C **170**. Oxindoles might be looked upon as amides and the problem for synthesis is therefore to effect debenzylation of such amides. The amide group is found in an increasing number of natural products and this raises the challenge of protecting the *N*-H from non-compatible synthetic operations. The *N*-benzyl and *N*-4-methoxybenzyl groups are among the more popular of the relatively few protecting groups now employed.[115] Their introduction is simple but their great stability to a range of conditions narrows greatly the scope for chemoselective removal of the benzyl protecting group. It is widely reported that the removal of *N*-benzyl groups from amides is often troublesome.[116] This dilemma has however been faced and met by a few specific examples in the literature and some of these are described below, along with the results of attempted debenzylation of **271** and its precursor ester **267**.

Weinreb has described the debenzylation of a tertiary amide **274** to furnish the secondary amide **275**, an important intermediate in the total synthesis of the cytochalasins, using lithium in liquid ammonia (**Scheme 98**).[117] The presence of a hydroxyl group in the starting material was tolerated and this made the approach attractive for an attempted debenzylation of **271**.



Scheme 98

Jones has reported a simpler example of debenzylation of an oxindole **276** using sodium in ammonia, in high yield but without full experimental details (**Scheme 99**).[118]

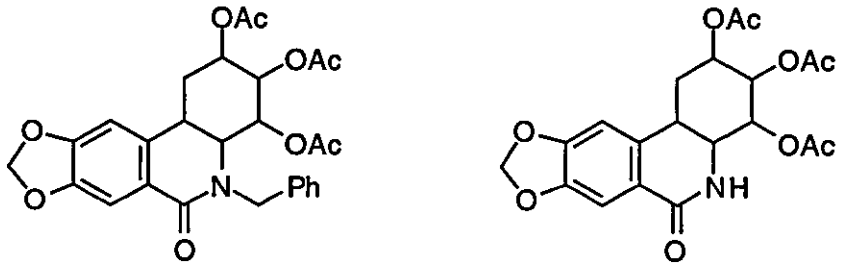


276 **277**

Scheme 99

Sadly, the result of treatment of *N*-benzylconvolutamydine C **271** with lithium in ammonia was destruction of the starting material and failure to isolate any useful products.

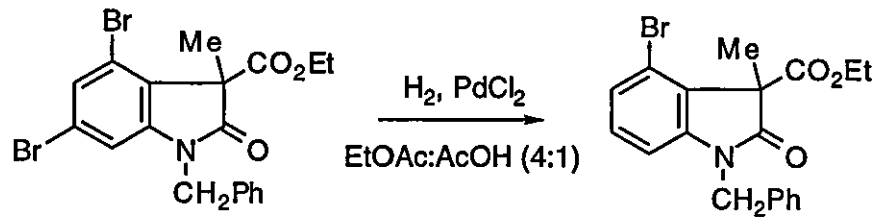
N-Benzyl amides are usually resistant to hydrogenation; however an isolated example from the Keck group was found for debenzylation of amide **278** which they described as extremely difficult. After some experimentation they succeeded in producing the secondary amide target **279** in 95% yield (**Figure 15**).[119]



278 **279**

Figure 15

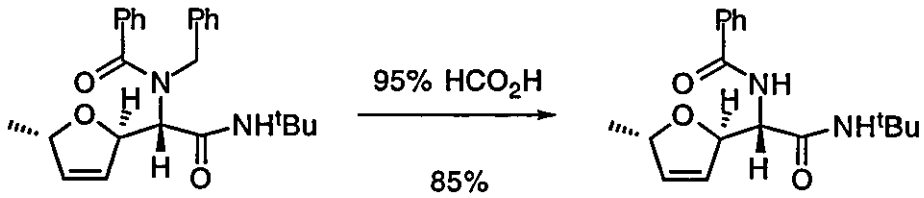
The conditions Keck described involved hydrogenolysis at atmospheric pressure using ethyl acetate:acetic acid (4:1) as solvent and with palladium(II) chloride as catalyst. Ester **267** was subjected to similar conditions but the reaction was found to be slow and after 21 h was worked up. Purification of the crude gave the unexpected product of selective mono-debromination **280** (30%) along with unreacted starting material **267** (69%) (**Scheme 100**). Thus, no further hydrogenation methods[120] were tried.



267 **280** (30%)

Scheme 100

Acidic solvolysis under forcing conditions can sometimes remove benzyl protecting groups from amides.[121, 122] An example of such a deprotection was reported by Joullié as part of a total synthesis of (+)-furanomycin. Simple treatment of amide **281** with 95% formic acid at ambient temperature for 2 h then at 50-60°C for a further 1-2 h afforded secondary amide **282** in 85% yield (**Scheme 101**).[121]



281 **282**

Scheme 101

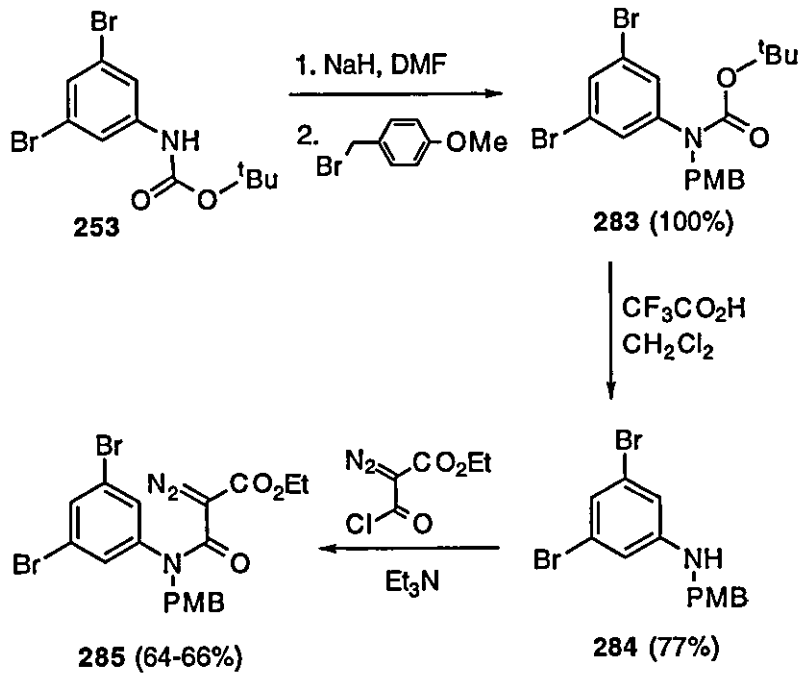
Treatment of ester **267** under similar conditions gave no useful reaction, even when heating was prolonged. Also, treatment of **271** with trifluoroacetic acid[122] at 55-60°C for extended periods led to slow destruction of the starting material.

By analogy with the facile debenzylation of *N*-benzylindoles,[123] an attempt was made to effect the desired deprotection of **271** by treatment with aluminium chloride. This method also proved fruitless.

Clearly all the possible methods for potential debenzylation of the *N*-benzyl oxindoles **267** and **271** have not been exhausted but, with limitations of time, it was decided that the use of the simple benzyl group for *N*-protection would need to be abandoned.

3.7. Preparation and Rhodium(II) Catalysed Reaction of *N*-4-Methoxybenzyl Protected Diazoamide: Total Synthesis of Convolutamydine C

Thus it was necessary to construct an oxindole with a more readily cleaved *N*-protecting group, without deviating so much from the original benzyl as to compromise the selectivity of the key Rh(II) catalysed oxindole ring-forming reaction. The alternative chosen was the 4-methoxybenzyl group, which it was envisaged would not affect the chemoselectivity of the Rh(II) catalysed reaction and should be readily removed using oxidative methods.[124] Using analogous chemistry to that described for preparation of *N*-benzylaniline **259** (**Scheme 91**), carbamate **253** was converted to *N*-*tert*-butoxycarbonyl-*N*-4-methoxybenzylaniline **283** in excellent yield. The *tert*-butoxycarbonyl group was then removed and the resulting secondary amine **284** converted to the desired diazoamide **285** in good yields (the yield of the latter step could not be improved over 66% but unreacted starting aniline was recovered and could be recycled) (**Scheme 102**).



Scheme 102

Once again, the diazoamide **285** was highly crystalline and its X-ray crystal structure displayed a very similar conformation to the diazoamides **260** (**Figure 16** and **Appendix A**).[57]

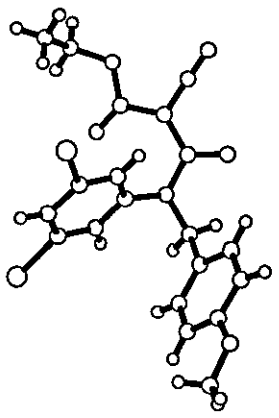
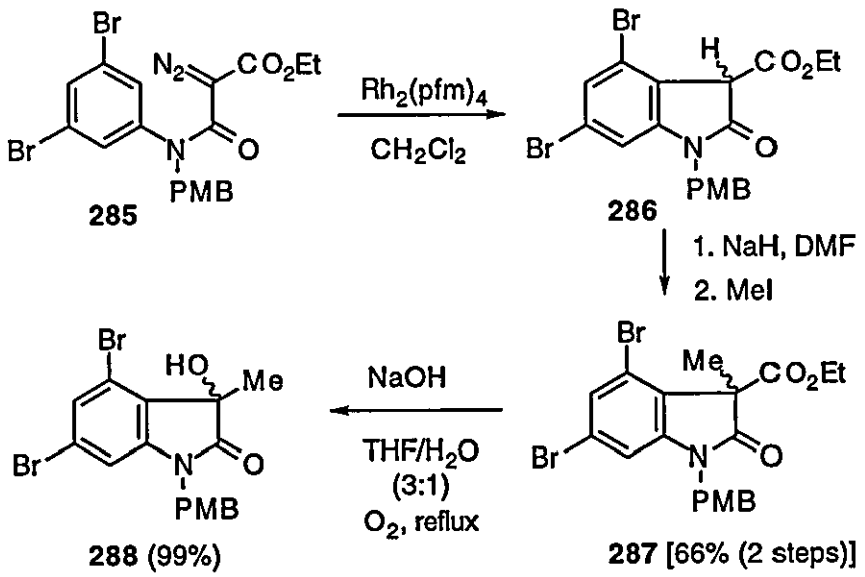


Figure 16 X-Ray Crystal Structure of Diazoamide **285**

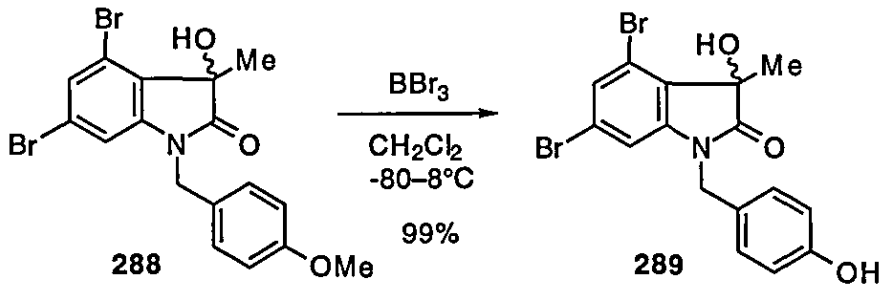
Diazoamide **285** was converted into the 3-hydroxy-oxindole **288** without incident, with both the carbenoid cyclisation and the decarboxylative oxidation steps again proceeding in quantitative yield (**Scheme 103**).



Scheme 103

Frustratingly, all attempts to remove the PMB group from **288** under oxidative conditions using ceric ammonium nitrate (CAN)[124] were unsuccessful. The excellent report of

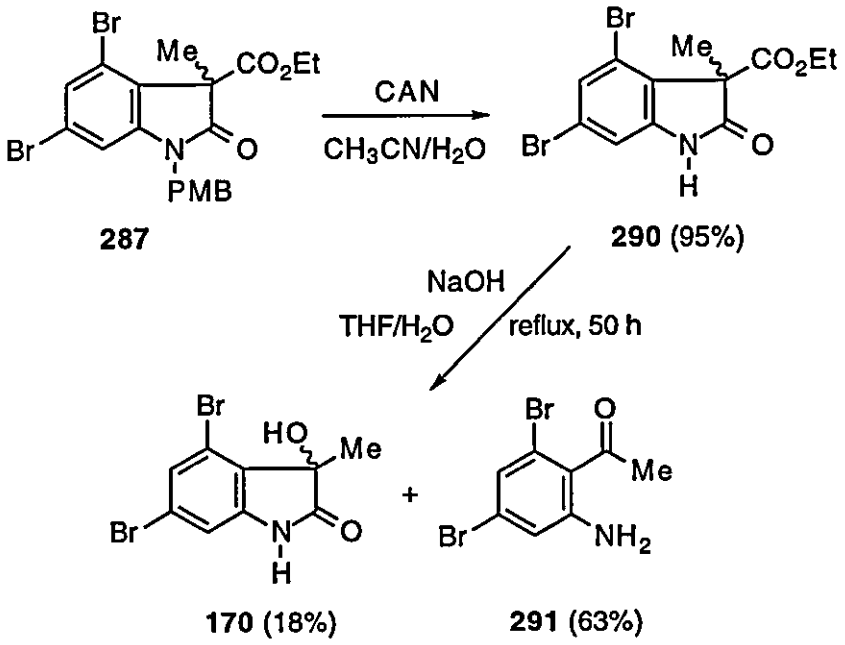
Yoshimura and co-workers did however stress the importance of concentration in the efficient cleavage of amide *N*-4-methoxybenzyl groups using CAN; the hydroxyoxindole **288** was found to be rather insoluble in the recommended solvent system (3:1 acetonitrile:water) and large volumes were needed for dissolution. This may well have contributed to the failure to effect the desired deprotection. It was also found, from analysis of the crude reaction mixtures and fractions from silica gel columns, that 4-methoxybenzaldehyde was a product of these reactions. Evidently, cleavage of the benzyl group was taking place, but the natural product was being destroyed under the strongly oxidative conditions. Likewise attempted oxidation of the corresponding *N*-(4-hydroxybenzyl) derivative **289**, readily obtained by boron tribromide demethylation of **288**, with DDQ[125] did not result in *N*-deprotection though the starting material was slowly destroyed (**Scheme 104**).



288 289

Scheme 104

It was proposed that oxidative debenzylation might be effected on the precursor ester **287**. Indeed, treatment of the oxindole ester **287** with CAN did result in clean removal of the 4-methoxybenzyl group, and gave the N-H oxindole **290** in 95% yield (**Scheme 105**). However, the decarboxylative oxidation of **290** proved much more difficult than with the *N*-protected derivatives **267** and **287**. Nevertheless, the desired oxidation did proceed to give convolutamydine C **170** in 18% yield, with the major product being the aromatic acetophenone **291** resulting from further hydrolysis and oxidation under the reaction conditions (**Scheme 105**).

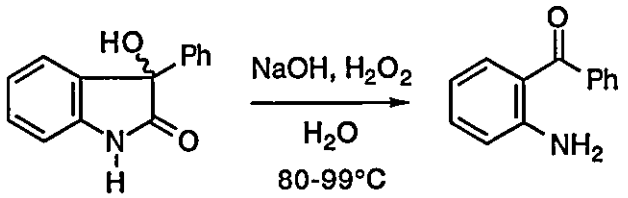


287 **290** (95%)

170 (18%) **291** (63%)

Scheme 105

This major side reaction has reasonable precedent with, for example, the report from Houlihan and Aeberli[105] describing the formation of benzophenone **250** upon oxygenation of the sodium salt of oxindole **248** (**Scheme 87** above). Also, in 1959 Bruce described the oxidation of 3-hydroxy-3-phenyl oxindole **292** with alkaline hydrogen peroxide to give 2-aminobenzophenone **293** in good yield (**Scheme 106**).[126]



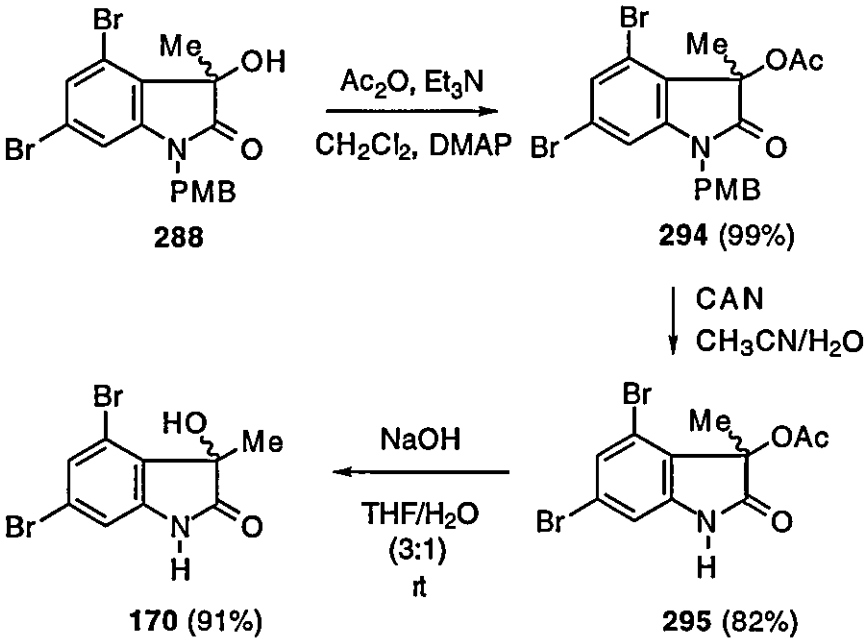
292 **293** (60%)

Scheme 106

Having completed the first total synthesis of convolutamydine C and demonstrated the synthetic utility of the diazoamide route to oxindoles, the project was placed on low priority and several months passed before a final effort was made to improve the overall yield for the preparative sequence. It was envisaged that removal of the 4-methoxybenzyl protecting group from the natural product could be effected by suitable protection of the sensitive hydroxy group of **288**. The choice of protecting group was not immediately obvious, and the standard texts[115] offered no information as to the stability of protecting groups under the oxidative conditions using CAN. However, we

have observed stability of the ester group at C-3 of the oxindole **287** to such conditions (**Scheme 105** above) and it was thus extrapolated that protection of *N*-4-methoxybenzyl convolutamydine C **288** as an acetate would allow the oxidative debenzylation and finally removal of the acetate protecting group should be straightforward.

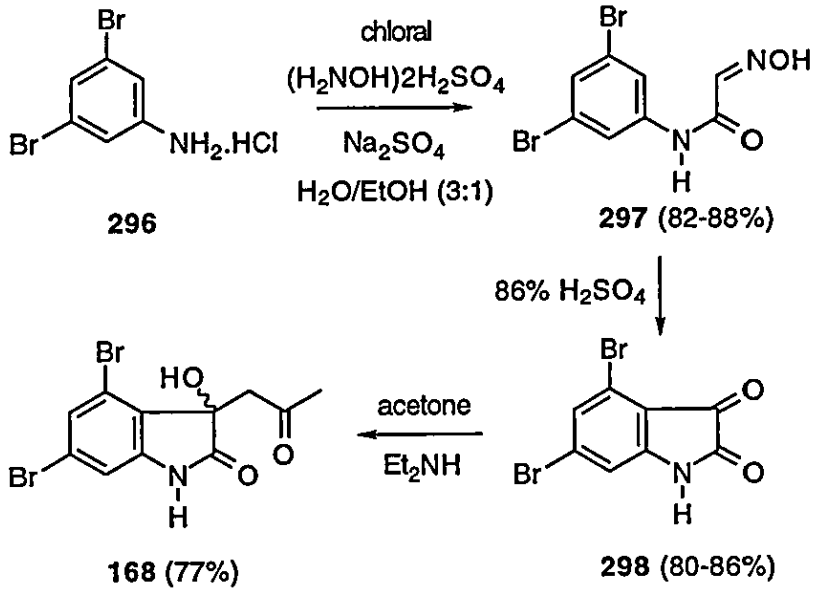
Thus, treatment of **288** with excess acetic anhydride and triethylamine with a catalytic amount of DMAP afforded the desired acetate **294** in quantitative yield. Oxidative debenzylation using CAN proceeded smoothly to give *O*-acetyl convolutamydine C **295** in an unoptimised 82% yield, and finally hydrolysis of the acetate under mild conditions gave convolutamydine C **170** in excellent yield (**Scheme 107**).



Scheme 107

After completion of this total synthesis of convolutamydine C, a communication from Garden and co-workers describing total synthesis of convolutamydine A appeared in the literature.[127] The approach used involved preparation, by literature methods, of the hydrochloride salt of 3,5-dibromoaniline **296** (82-91% overall yield in three steps from 4-nitroaniline). This aniline was then subjected to modified Sandmeyer reaction conditions to furnish the isonitrosoacetanilide **297**. After considerable experimentation, involving changes in reaction temperature, reaction time, solvents and concentrations the protocol described emerged as a high yielding, but rather involved, transformation. Subsequent cyclisation of **297** in 86% sulfuric acid (60-110°C) proceeded smoothly to afford the dibromoisatin **298**. Dissolution of this isatin in acetone with a catalytic amount of diethylamine afforded the desired alkaloid, convolutamydine A **168** in high yield (**Scheme 108**). A preparation of the isatin **298** had previously been reported in 1952,

using the same method but in considerably lower overall yield (10% from 3,5-dibromoaniline).[128]



Scheme 108

3.8. Conclusions

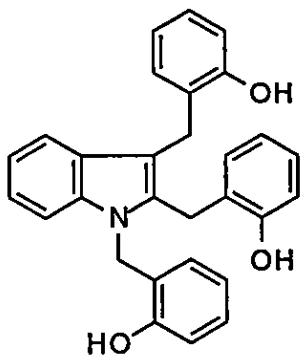
Thus, it has been demonstrated that $Rh_2(pfm)_4$ retains its ability as a chemoselective and highly active catalyst for the aromatic substitution reaction, even when steric and electronic factors disfavour this process. In particular, examination of X-ray crystal structures of *N*-phenyl-*N*-benzyldiazomalonamides **102** , **260** and **285** (see **Appendix A**) have led us to surmise that there is also a natural conformational disposition[90] favouring this cyclisation pathway over competing alternatives. This methodology can be applied to novel substituted diazoamide substrates and thus provide useful oxindolyl and indolyl intermediates. Efforts towards total synthesis of the convolutamydine alkaloids successfully incorporated this intramolecular cyclisation strategy to build the dibromooxindole backbone. Chemical manipulation of the oxindole functionality furnished convolutamydine C **170**. Overall, the total synthesis was achieved in 10 steps from commercial 3,5-dibromobenzoic acid in 31% yield (45% when recovery of unreacted aniline **284** is taken into account in the diazoacylation step; **Scheme 102**).

Chapter Four

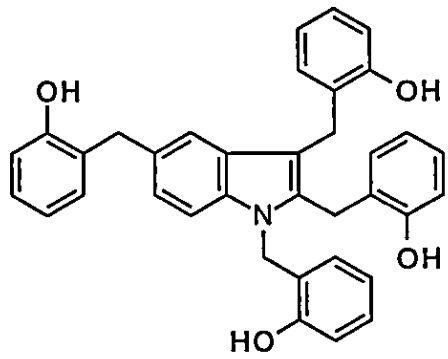
Towards Total Synthesis of the Uvarindole Alkaloids

4.1. Introduction

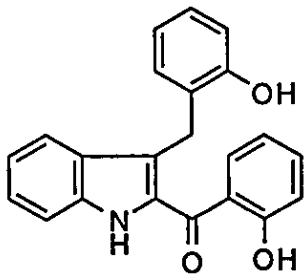
Amongst several indole-based natural products which have been considered as possible siderophores (iron chelating agents) are a family of alkaloids isolated by Waterman and Mohammad from the *Uvaria angolensis* stem bark and named the uvarindoles A-D, **299-302.**[129] The novel structures were revealed through extensive NMR and X-ray crystallographic studies and are as illustrated in **Figure 17.**



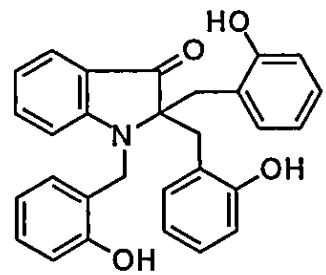
uvarindole A **299**



uvarindole B **300**



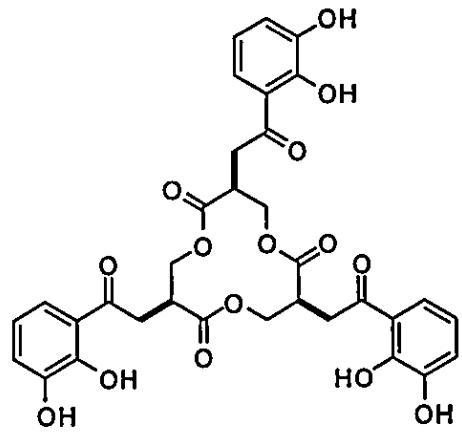
uvarindole C **301**



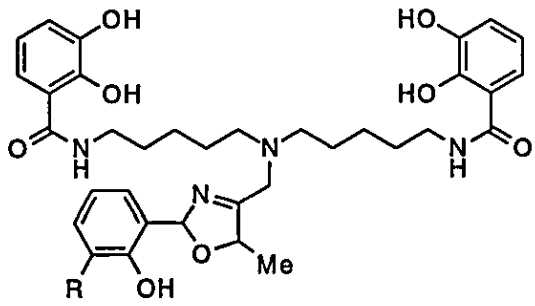
uvarindole D **302**

Figure 17 The Uvarindole Alkaloids

The polyhydroxylated nuclei of these compounds, especially in uvarindoles A and B, should present suitable sites of affinity to the iron (III) ion to give effective chelation in a plane either above or below the flat indole ring. Bearing in mind the structures of known siderophores such as enterobactin, agrobactin and parabactin (**Figure 18**),[130] it would be reasonable to assume that the catechol analogues of uvarindoles A and B would be particularly effective siderophores.



Enterobactin; log K_f = 53



Agrobactin: R = OH; log K_f = 52

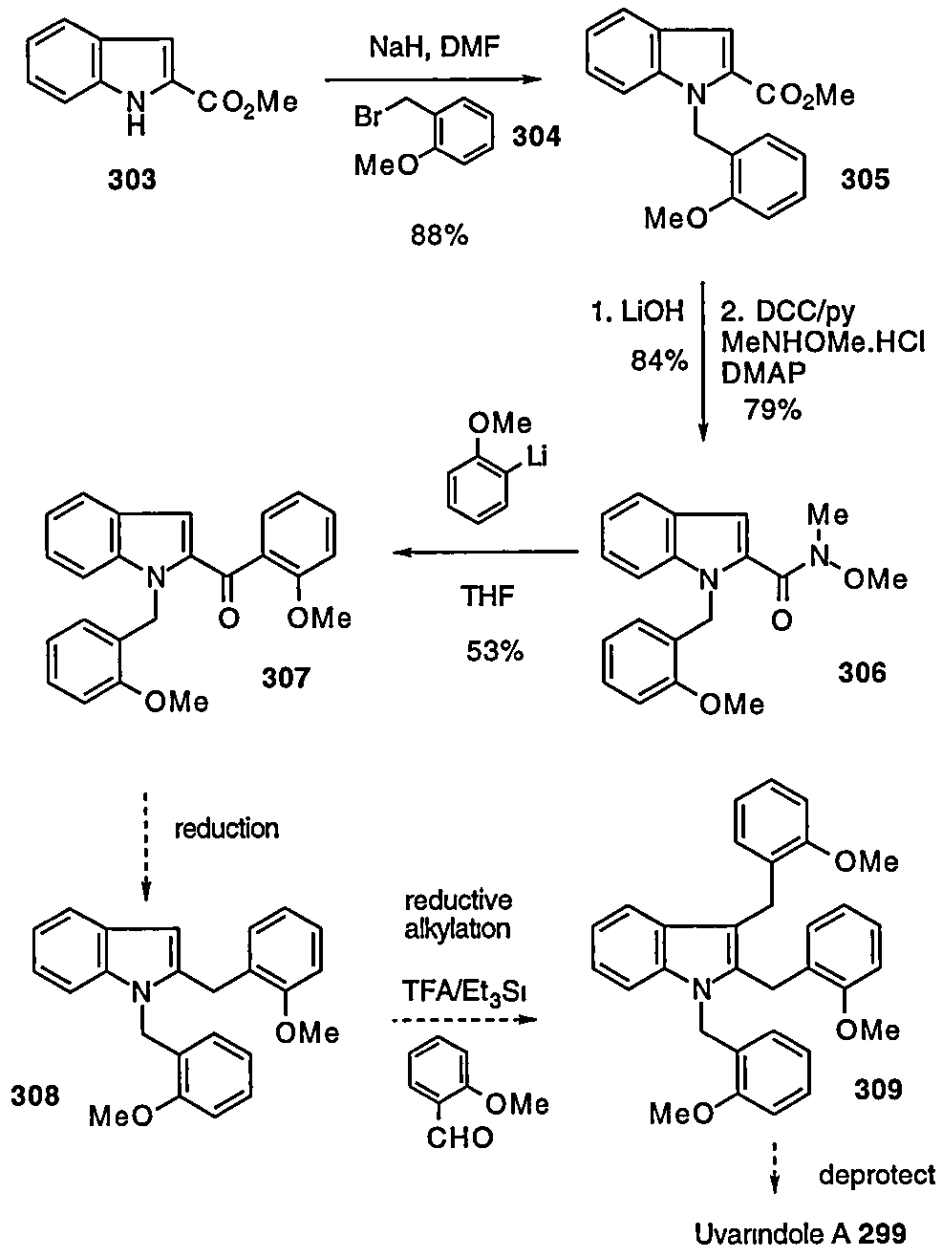
Parabactin: R =H; log K_f = 52 at pH 7

Figure 18 Literature Siderophores

Previous Synthetic Studies Towards Total Synthesis of the Uvarindole Alkaloids

More than a century of chemical investigation has resulted in a whole host of methods available for the construction of the indole nucleus and these have been reviewed extensively.[82,131] Clearly it is beyond the scope of this discussion to compare and contrast all the possible routes to the uvarindole heterocylic nucleus. An alternative is to use a commercially available indole and to functionalise at the desired positions around the ring.

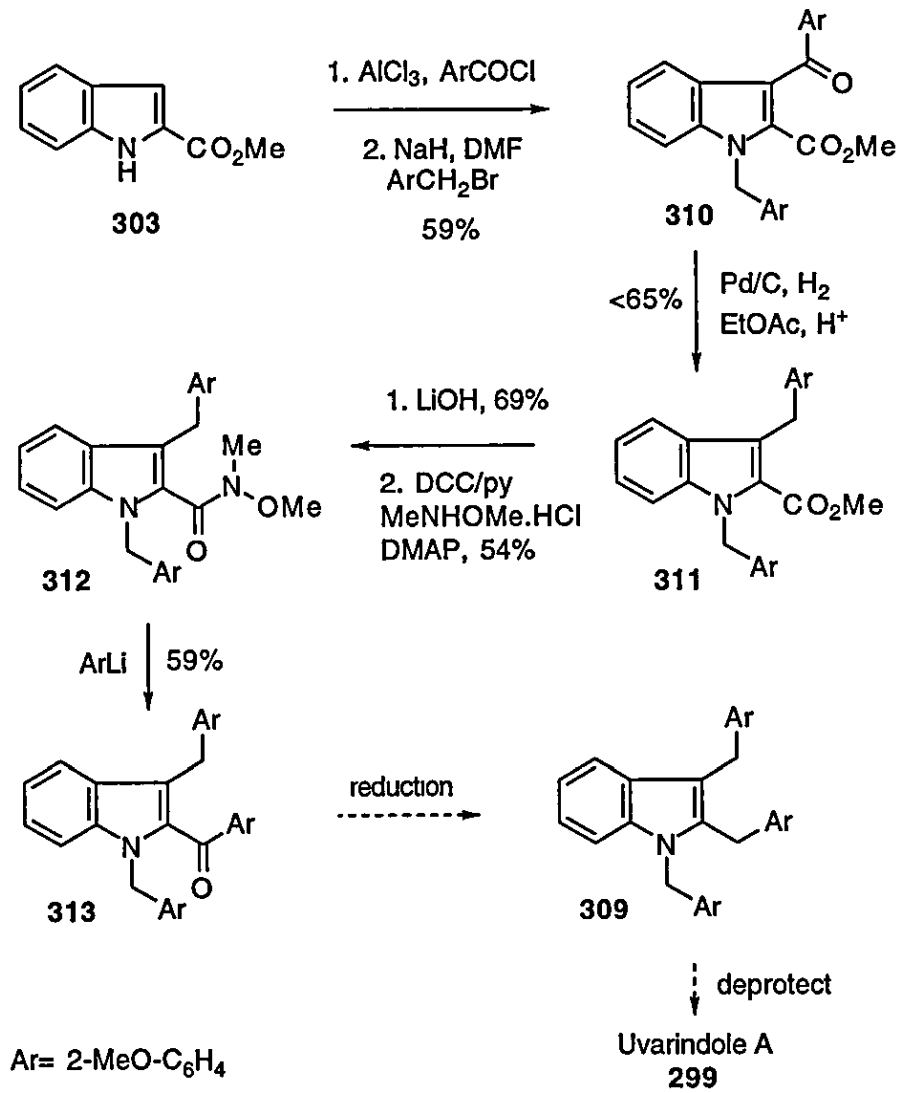
Within the Moody group, E. B. Fray conducted, as part of his doctoral research, some synthetic work towards synthesis of uvarindole A **299.**[132] The original proposal involved the following synthetic steps (**Scheme 109**).



Scheme 109

Thus the key steps are the preparation and use of a Weinreb amide **306** to give 2-acylindole **307**, followed by reduction and a reductive benzylation[133] at C-3. As illustrated, the Weinreb amide was prepared in good yield from ester **305**. Reaction with 2-anisyllithium gave the carbonyl compound **307** in 53% yield. Unfortunately the carbonyl group could not be reduced to give the desired 2-benzyl indole **308** using standard conditions.

A second synthetic proposal incorporating the Weinreb amide step was drawn up and the results are summarised below (**Scheme 110**).



Scheme 110

Once again the plan was frustrated by failure to effect reduction of the unwanted carbonyl group of the indole **313**.

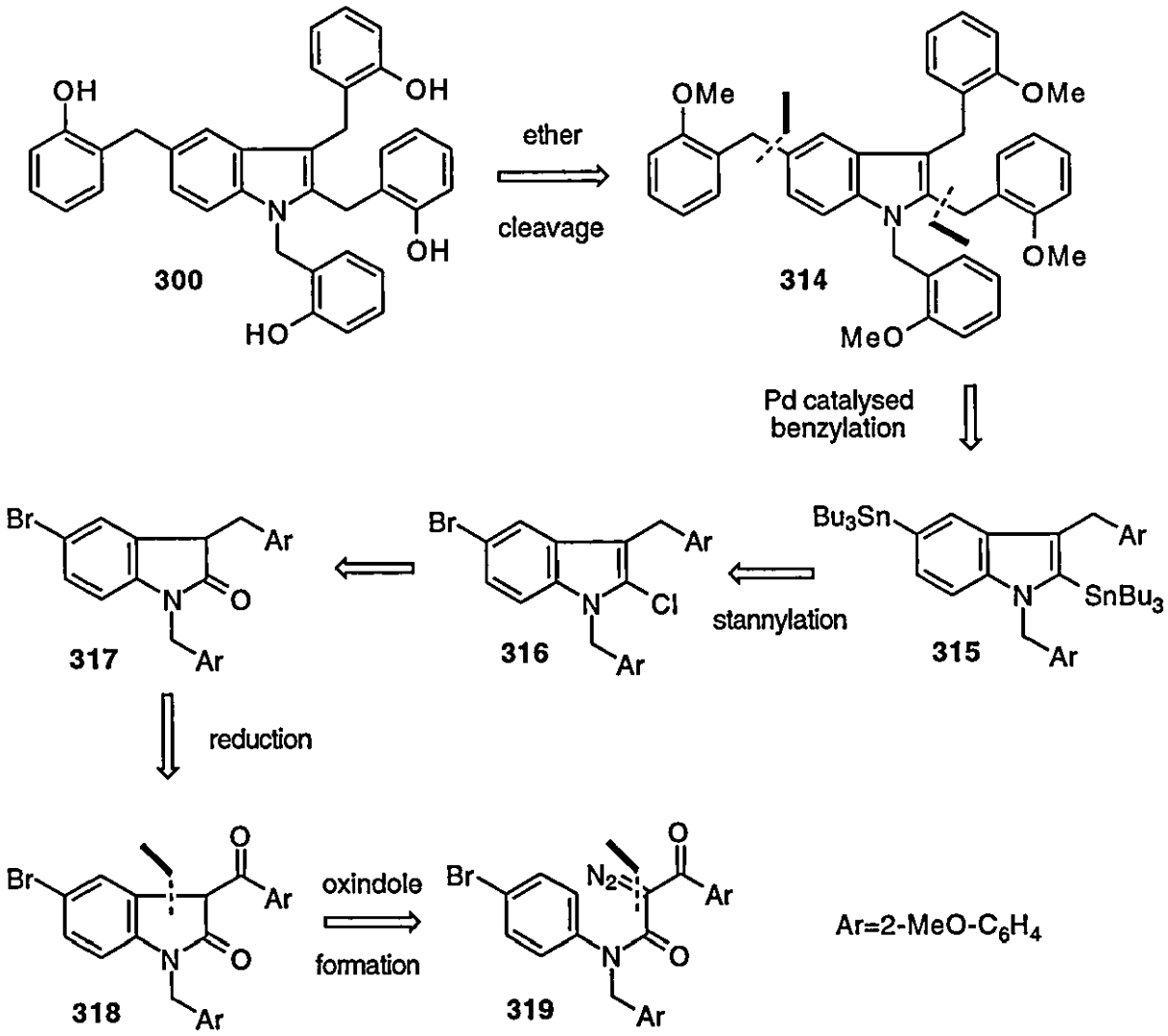
To the best of our knowledge there are no other reported studies towards the total synthesis of the uvarindole alkaloids.

4.2. The Diazoamide-Oxindole-Indole Route to Uvarindole Alkaloids

As mentioned earlier there are a large number of possible methods for *de-novo* construction of the indole ring.[82,131] Our interest in the intramolecular reactions of carbenoids to give heterocycles,[134] and in particular the aromatic substitution reaction to furnish substituted oxindoles,[135] coupled with the known conversion of oxindoles to indoles,[79] led us to draw up an alternative proposed synthetic route to the uvarindole alkaloids.

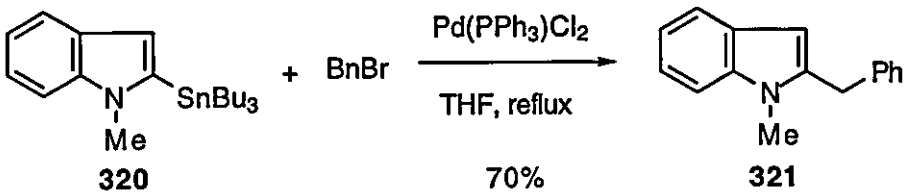
4.2.1. Retrosynthetic Analysis of Uvarindole B

Retrosythetic analysis of uvarindole B **300** was undertaken (**Schemes 111** and **113**).



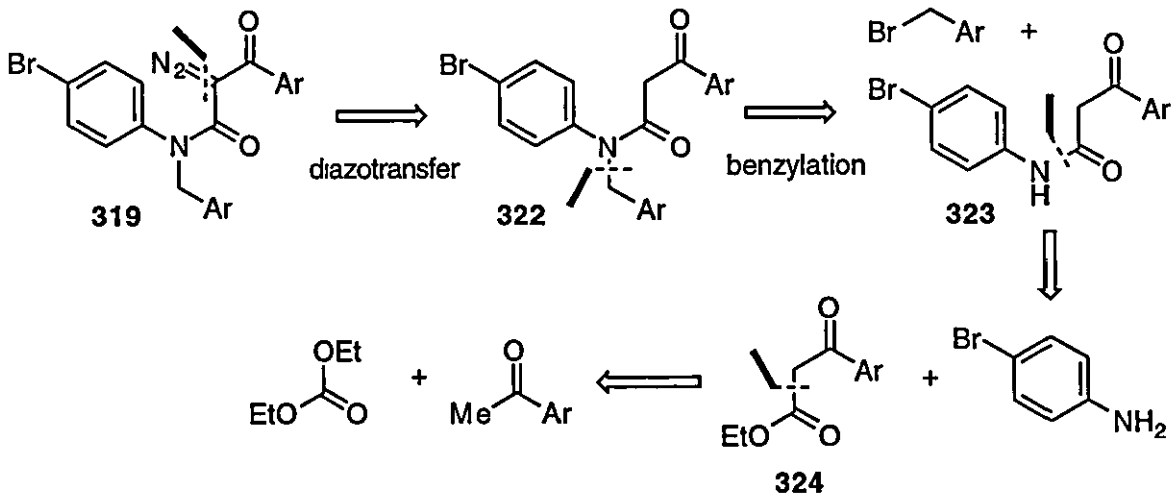
Scheme 111

The natural product **300** might best be accessed by deprotection of the polymethylated precursor **314.** This tetrabenzylated indole might be worked back to the distannylated (or more generally dimetallated) indole **315,** which in the synthetic direction could be dibenzylated using palladium catalysis. A recent useful report from Labadie showed that the 2-stannylindole **320** could be coupled with a range partners (including, as exemplified in **Scheme 112,** benzyl bromide) in the presence of catalytic bis(triphenylphosphine)palladium(II) chloride to give good yields of 2-substituted indoles.[136]



Scheme 112

Retrosynthetically, the distannylindole **315** requires a precursor dihaloindole **316** (**Scheme 111**). This 2-chloroindole **316** might be accessed from treatment of oxindole **317** with phophorus oxychloride.[137] There is good precedent for the stannylation of bromoaromatics.[138] Intermediate oxindole **317** could be derived from regioselective reduction of 3-acyloxindole **318** which itself would be a product of the key rhodium(II) catalysed cyclisation of a suitably substituted *N*-phenyl-*N*-benzyldiazoamide **319.**



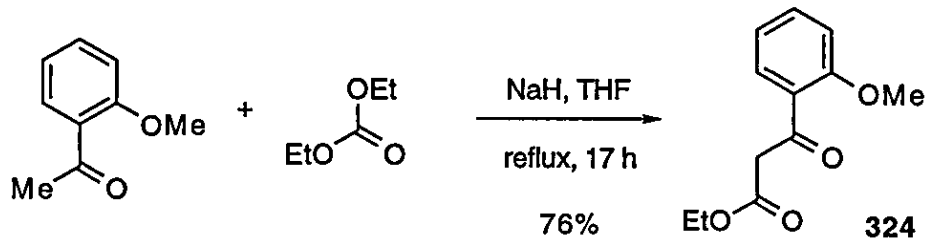
Scheme 113

The key diazoamide **319** might be prepared by diazo-transfer[139] onto the β-ketoamide **322** which might, in turn, be prepared through *N*-benzylation of the secondary amide **323.** This amide should be made available through condensation of 4-bromoaniline with

β-ketoester **324**. The ester should be available through reaction of the anion of 2-methoxyacetophenone with diethyl carbonate (**Scheme 113**).

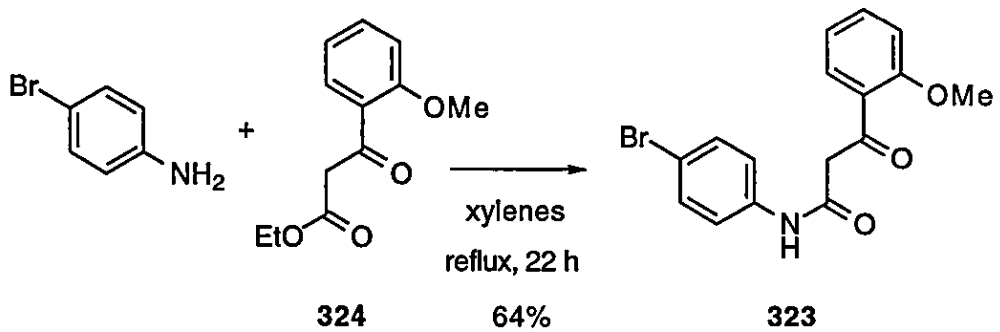
4.2.2. Synthetic Studies

The β–keto ester **324**[140] was readily prepared in good yield by analogy to the simple protocol of Mitscher and co-workers.[141] Thus, 2-methoxyacetophenone was refluxed in THF with excess sodium hydride and excess diethyl carbonate. After purification the desired ester **324** was isolated in 76% yield (**Scheme 114**).



Scheme 114

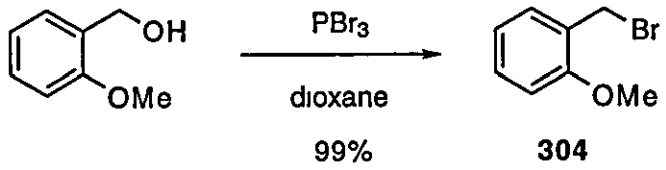
With the ester **324** in hand an attempt was made to mirror the successful preparation of *N*-phenyl-β–ketoamides described by Weissberger and co-workers.[142a] The protocol was straightforward enough, involving refluxing of an aniline with a β–ketoester in xylene solution. In our hands with 4-bromoaniline and the ester **324** the result was a good yield of the desired ketoamide **323** (**Scheme 115**).



Scheme 115

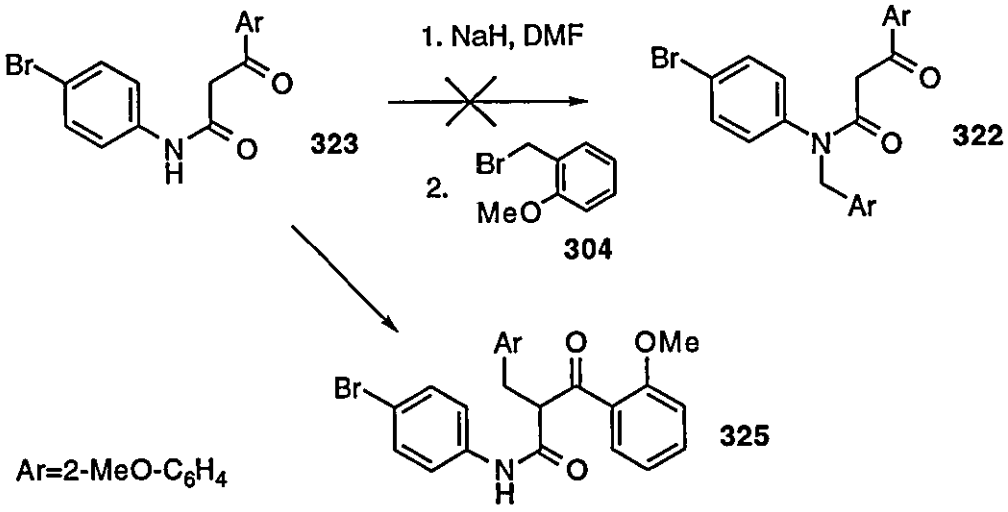
The next desired step was the selective *N*-benzylation of anilide **323**. For this it was necessary to prepare the alkylating agent, 2-methoxybenzyl bromide **304** and this was achieved using an adaptation of the method of Masci and Saccheo.[143] Simple combination of 2-methoxybenzyl alcohol in dioxane with phosphorus tribromide at room

temperature gave clean and quantitative conversion to the desired benzyl bromide **304** (**Scheme 116**). Despite the reported extreme instability of this alkylating agent,[132] no decomposition was observed for a period of months if it was stored in solution in the freezer. The solvent could be removed just prior to use and the alkylating agent gave satisfactory results.



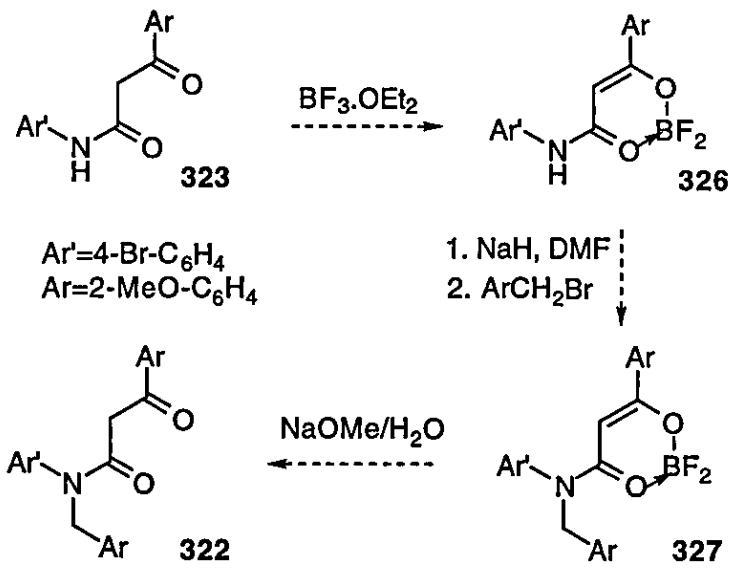
Scheme 116

It is known from the literature,[144] however, that attempts to alkylate β–ketoamides related to **323** under various conditions leads to *C*-alkylation in preference to the desired *N*-alkylation. And, indeed, this was the observed result with our specific substrate **323**, without any useful *N*-alkylation to afford **322**. The major product was, instead, the *C*-benzylated amide **325** (**Scheme 117**).



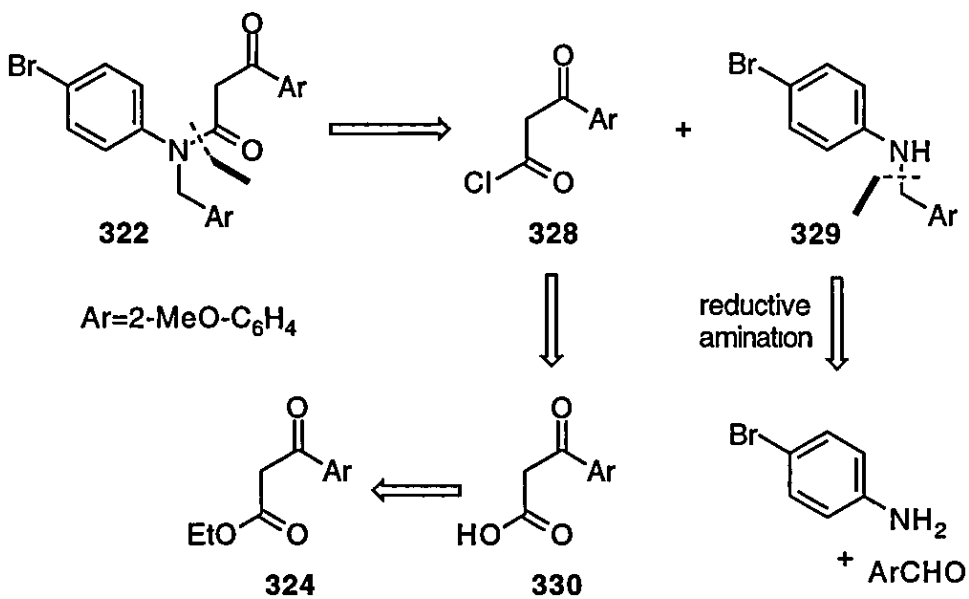
Scheme 117

Thus the proposed use of secondary amide **323** as a precursor to the diazotransfer candidate **322** was abandoned. It should however be acknowledged here that a three step sequence has been reported for the *N*-alkylation of β-ketocarboxylic acid amides related to **323**.[145] This method would involve treatment of secondary anilide **323** with boron trifluoride-etherate to give a difluorooxyborane **326** which could be *N*-benzylated and the desired tertiary anilide **322** liberated by hydrolysis (**Scheme 118**). Due to time restrictions, however, this additional method with its extra steps was not tried.



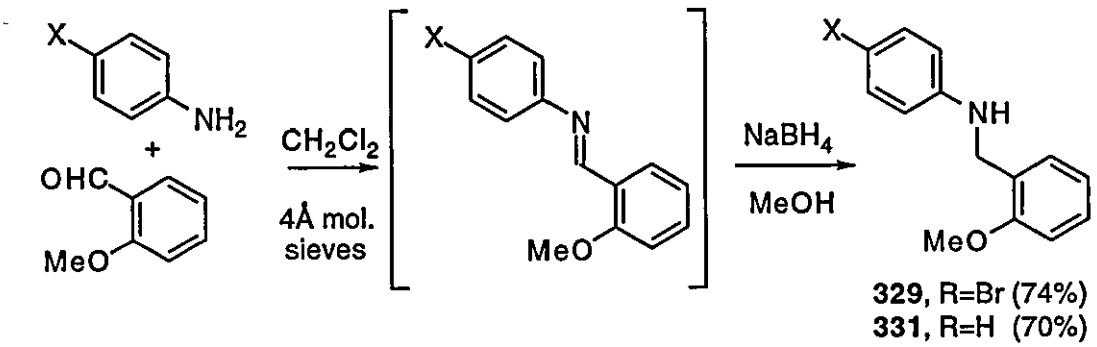
Scheme 118

A revised route to the β-ketoamide **322** was then commissioned. Disconnective scission of the amide C-N bond reveals the acid chloride **328** and the *N*-benzylaniline **329** as synthetic precursors. The acid chloride might be a derivative of β–ketoacid **330**, itself obtained by saponification of ester **324**, and the anilide **329** which should be a product of a standard reductive amination (**Scheme 119**).



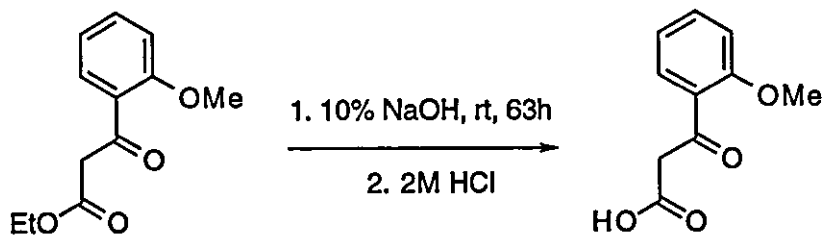
Scheme 119

Attempts to execute this plan started with the successful preparation of *N*-benzylanilines **329** and **331** in high, yet unoptimised yields. Reductive amination, on a multigram scale, was found to be facile and the reduction of the intermediate imine was achieved with sodium borohydride (**Scheme 120**).[146]



Scheme 120

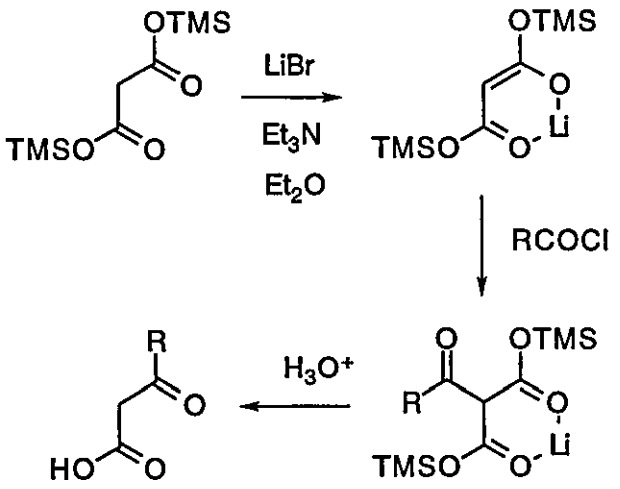
Attempts were then made to saponify the ester **324** to give carboxylic acid **330.** This proved non-trivial, and most standard methods tried led to decarboxylation of the product. The best conditions were an adaptation of the method described by Tahara[147] which involved simple stirring of the ester in dilute sodium hydroxide solution (10%) for several days to give complete and clean conversion to the desired acid after careful acidification with 2M HCl (**Scheme 121**). However, the acid thus produced was found to decarboxylate spontaneously on standing! Alternative methods were considered for the preparation of this important compound.



324 99% **330**

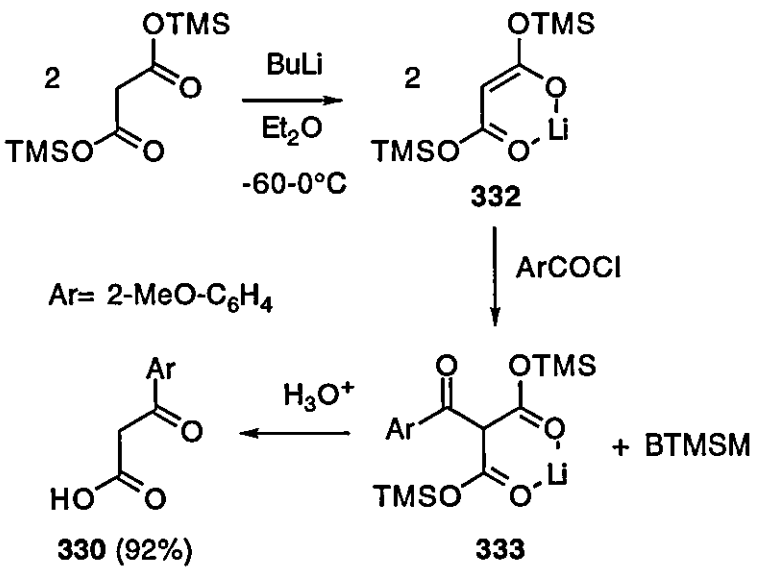
Scheme 121

An attempt to reproduce, on a large scale, the method described by Rathke (**Scheme 122**) in which lithium bromide in ether was treated with bis(trimethylsilyl)malonate (BTMSM) and then triethylamine followed by 2-methoxybenzoyl chloride gave, after acidic workup, a mixture which showed only 50% conversion to the desired product.[148]



Scheme 122

The lengthy and involved experiment described was found to be a poor substitute for an older protocol[149] which the Rathke group were trying to improve upon. Indeed, the original method which entailed treatment of two equivalents of the lithium salt of bis(trimethylsilyl)malonate (BTMSM) **332** with one equivalent of 2-methoxybenzoyl chloride followed by 2-methoxybenzoyl chloride to give the intermediate **333** was much easier experimentally. Acidic workup gave a 92% yield of the acid **330** (8:1 mixture of keto:enol tautomers) as a cream solid without the need for purification (**Scheme 123**). Interestingly, the acid produced by this method was found to be relatively stable.

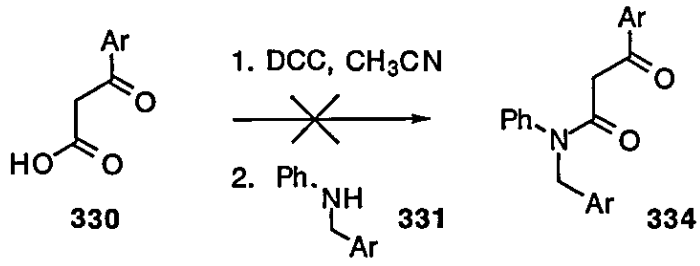


Scheme 123

Attempts to make acid chloride **328** from the acid **330** met with failure. These efforts included treatment with thionyl chloride, and with oxalyl chloride and catalytic DMF.[150] Both led to destruction of the acid and no coupling with the aniline **329** in the

presence of triethylamine. An attempt to form a mixed anhydride with ethyl chloroformate and to couple that with the aniline in dichloromethane solution[151] in the presence of triethylamine was also fruitless. Thus, it was decided that the acid chloride **128** was not readily available by routine methods from the acid **330** and again some new synthetic transformation was considered for the preparation of β-ketoamide **322.**

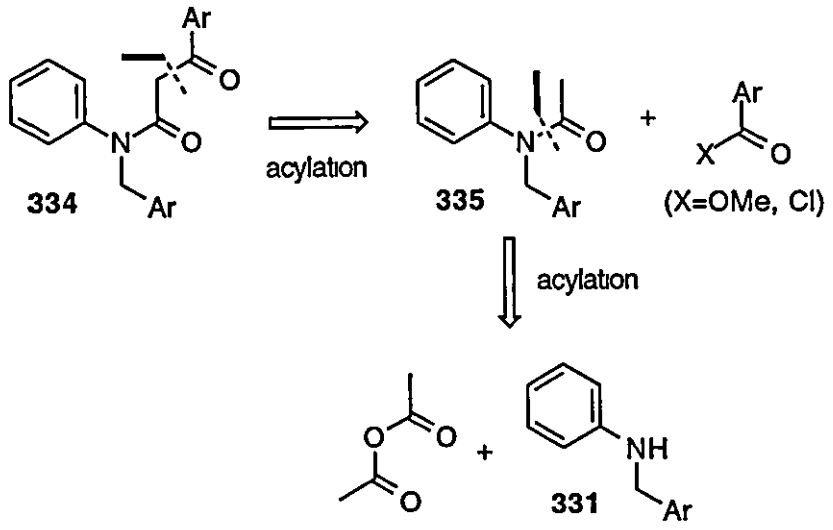
One potential alternative was to effect a DCC mediated condensation. Addition of dicyclohexylcarbodiimide (DCC) to an acetonitrile solution of the acid **330** gave an immediate reaction but after addition of the aniline **331** no desired product **334** could be detected and it appeared that the acid had been destroyed and the aniline was unreacted **(Scheme 124).**



Scheme 124

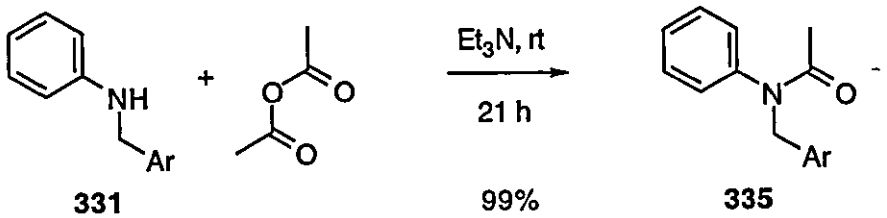
A further potential alternative, by analogy with the coupling of 4-bromoaniline with ester **324 (Scheme 115),** was that the secondary aniline **331** could similarly be made to give the desired β-ketoamide **334.** However, refluxing the ester and the aniline together in *m*-xylene led only to decomposition of the ester and no useful conversion to **334.**

As a final efffort to produce the β-ketoamide **334** it was envisaged that the anion of acetanilide **335** might be made to react with methyl 2-methoxybenzoate or 2-methoxybenzoyl chloride **(Scheme 125).**[142b] The acetanilide should be readily prepared from the aniline **331** and acetic anhydride.



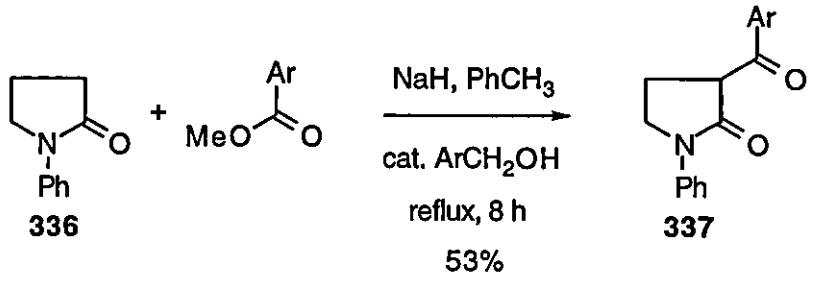
Scheme 125

In the event, acetanilde **335** was prepared by acetylation of aniline **331** in quantitative yield using standard conditions (**Scheme 126**).



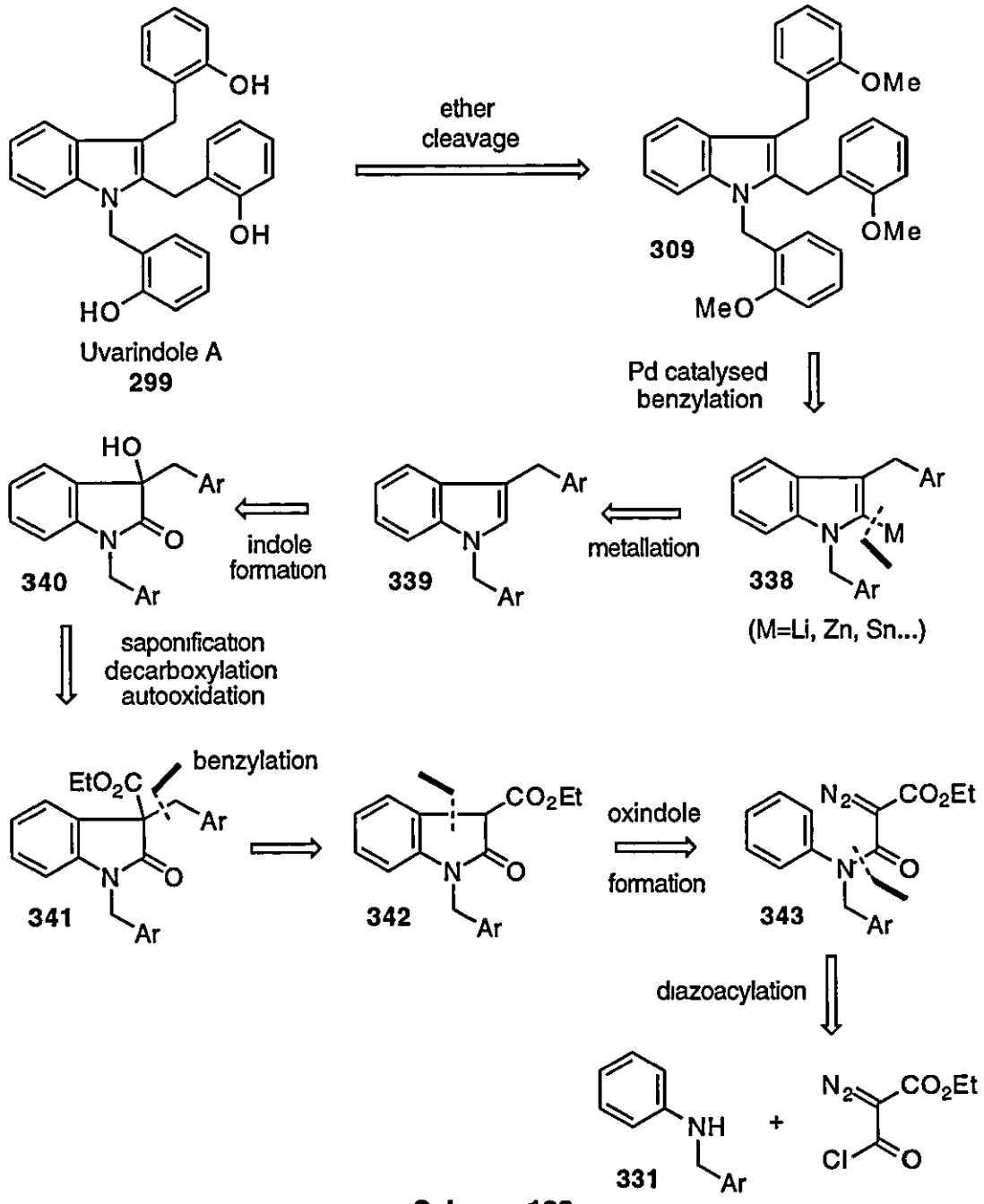
Scheme 126

Attempts to effect the desired transformation of acetanilide **335** to the tertiary amide **334**, however, met with failure. Briefly, treatment of **335** with strong bases such as sodium hydride or butyllithium and then addition of methyl 2-methoxybenzoate or 2-methoxybenzoyl chloride gave no desired product. A protocol described by Eiden for the coupling of pyrrolidinone **336** with methyl 2-methoxybenzoate by treatment of **336** with sodium hydride, followed by addition of a small amount of 2-methoxybenzylalcohol and one equivalent of methyl 2-methoxybenzoate and heating at reflux gave the β-ketoamide **337** in moderate yield (**Scheme 127**).[152] This appeared a reasonable model for preparation of **334** from **335**. Sadly, in practice, this too failed to afford the target intermediate **334**.



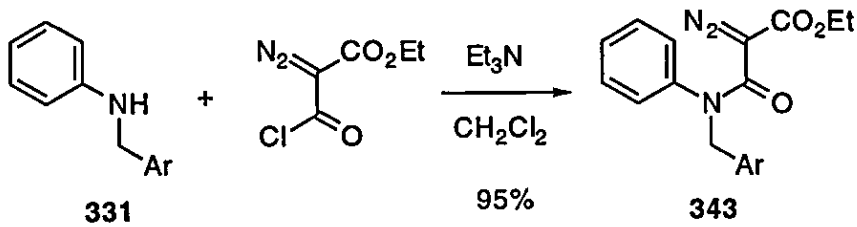
Scheme 127

With the above experiences to hand and with limitations of time, it was decided that final synthetic efforts should be made to target uvarindole A and that these should be built upon the successful chemistry of oxindole-3-esters derived from rhodium(II) perfluorobutyramide catalysed decomposition of *N*-phenyl-*N*-benzyldiazomalonamide ethyl esters (Chapters 2 and 3). The target diazo substrate thus became **343**, and this should give oxindole ester **342**. Disconnectively, one might arrive at this ester from uvarindole A as detailed in **Scheme 128**. Thus, the trimethyl protected natural product **309** might be prepared by palladium catalysed benzylation of the C-2 metallated intermediate **338** from the relatively simple dibenzylindole **339**. A key step would be the reductive elimination reaction of 3-hydroxyoxindole **340** to afford the indole **339**. The hydroxyoxindole should be available by the methods established in Chapter 3.



Scheme 128

In the synthetic direction progress was made as follows. The reductive amination product **331** was effectively diazoacylated with ethyl diazomalonyl chloride to give diazomalonamide **343** in excellent yield (**Scheme 129**).



Scheme 129

Diazoamide **343** was found to be highly crystalline and was submitted to X-ray crystallographic analysis (**Figure 19**). As expected, there was a remarkable degree of close correlation in the solid state conformation of **343** to that observed for the related diazoamides **102, 260,** and **285 (Appendix A).**

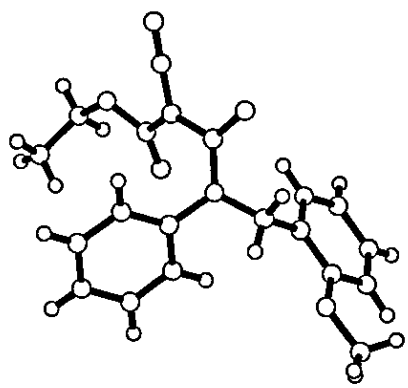
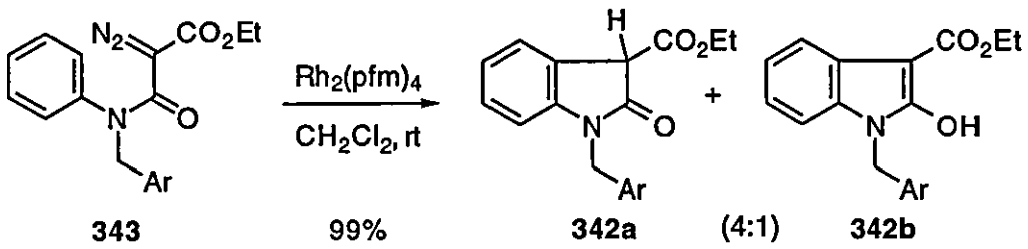


Figure 19 X-Ray Crystal Structure of Diazoamide **343**

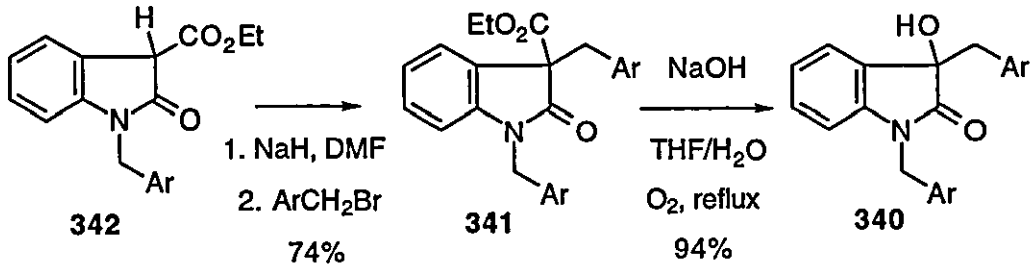
The key rhodium catalysed step proceeded smoothly to afford quantitative chemoselective aromatic substitution. The resulting oxindole product **342a** was in this case found to be in equilibrium with its enol tautomer **342b** (4:1 ratio of keto:enol tautomers) (**Scheme 130**). This mixture was not very stable to silica and was partially analysed before further elaboration.



343 99% **342a** (4:1) **342b**

Scheme 130

This tautomeric mixture of oxindole **342** was regioselectively C-3 benzylated by treatment with sodium hydride in DMF followed by substituted benzyl bromide **304** to give ester **341** in good yield. This compound was heated at reflux in aqueous THF and excess sodium hydroxide under an atmosphere of oxygen and the result was one-pot saponification of the ester, decarboxylation of the acid formed and base mediated autoxidation to give the 3-hydroxyoxindole **340** in excellent yield after chromatography (**Scheme 131**). This mirrored closely earlier results in synthetic studies leading to the total synthesis of convolutamydine C (Chapter 3).

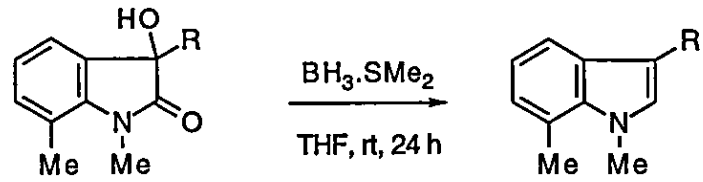


342 **341** **340**

Ar= 2-MeO-C_6H_4

Scheme 131

The next step was the crucial conversion of oxindole **340** to the dibenzylindole **339.** The conversion of 3-hydroxyoxindoles to indoles has some precedent in the literature and a several good examples are reported by Wierenga and co-workers.[153] Treatment of the relevant oxindole precursors **344** with 2.3 equivalents of borane-dimethylsulfide complex at room temperature gave, for example, good conversion to the indoles **345**, and **346** (**Scheme 132**).

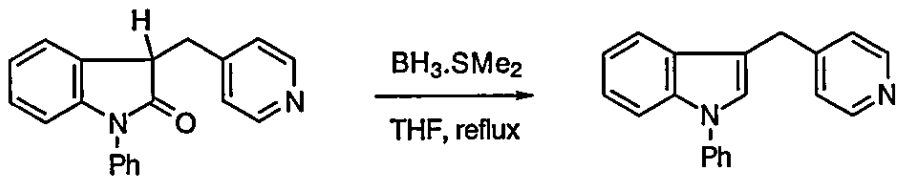


344

345, R=Me, 93%
346, R=Ph, 88%

Scheme 132

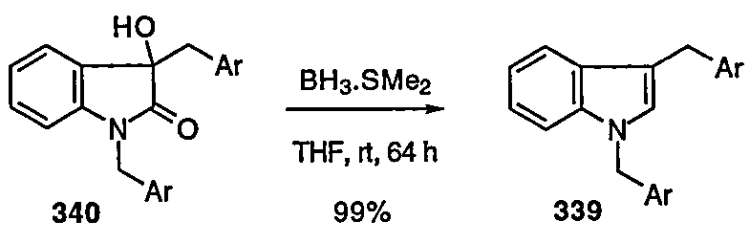
Another interesting and more recent example was the reported conversion of 98 g of oxindole **347** to the indole **348** (**Scheme 133**).[154]



347 73% crude **348**

Scheme 133

Thus, in pursuit of total synthesis of uvarindole A **299**, and following an experimental protocol incorporating details from the above two references, treatment of a solution of 3-hydroxyoxindole **340** in THF with excess borane-dimethylsulfide complex at room temperature gave a slow, clean and quantitative conversion to the desired indole **339** after acidic work-up (**Scheme 134**).



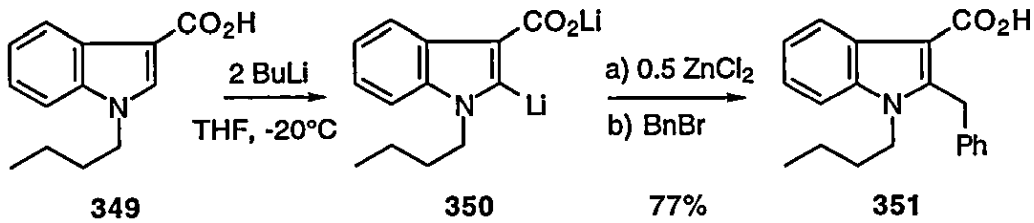
340 99% **339**

Ar= 2-MeO-C_6H_4

Scheme 134

The penultimate steps for the total synthesis required metallation of the indole **339** at C-2 and then benzylation. Simple 2-lithiation/alkylation protocols for indoles (and sp2 centred carbanions in general) are known to be problematic;[155] a single attempt at this, involving treatment of **339** with *n*-butylithium in THF at 0°C then 2-methoxybenzyl bromide **304**, gave no useful conversion. A more elaborate attempt was based on the

reported benzylation of indole **349**.[156] This involved dilithiation of **349** with *n*-butyllithium at -20°C to give **350**, followed by transmetallation by addition of 0.5 equivalents of zinc(II) chloride. Coupling was then achieved by addition of 1-2 mol% palladium tetrakis(triphenylphosphine) and benzyl bromide to give the 2-benzylindole **351** in high yield (**Scheme 135**). These workers also reported that addition of benzyl bromide to the dilithio intermediate **350** directly failed to give any benzylated product.



Scheme 135

On a superficial analysis it could be claimed that the above reaction was a reasonable model for the desired C-2 benzylation of indole **339**. Unfortunately a single attempt to achieve a similar benzylation of **339** with 2-methoxybenzyl bromide using this method proved fruitless. Due to time limitations it was not possible to pursue any other potential methods to effect this transformation.

4.3. Conclusions

In summary, the intramolecular aromatic substitution reaction of rhodium(II) carbenoids derived from *N*-phenyl-*N*-benzyl diazomalonamide esters has been demonstrated to be a very effective method for the preparation of *N*-benzyl oxindole-3-esters. Further, these oxindoles can be converted in three efficient steps to 3-alkyl indoles. This strategy was used to construct 1,3-di(2-methoxybenzyl)indole **339** which was envisaged to be a potentially valuable precursor to uvarindole A. However, attempts to benzylate this indole at C-2 were not successful.

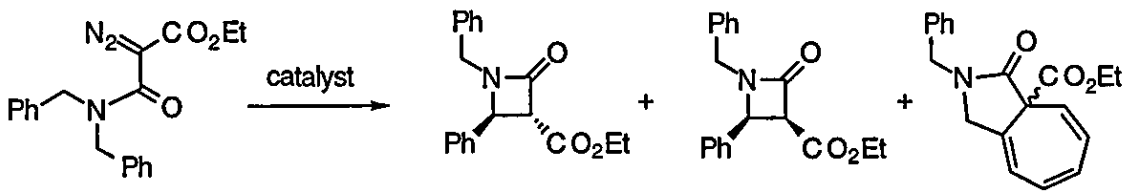
Chapter Five

Diastereoselectivity in the Intramolecular Buchner Reaction (IMBR)

5.1. Introduction

Work in this area was initiated following the advent of the somewhat taxing isolation of the cycloheptapyrrolone **105** as one of the products of rhodium(II) acetate catalysed decomposition of the diazoamide **101** (**Scheme 37**, Chapter 2).

This observation prompted investigation of the decomposition chemistry of the *N,N*-dibenzyldiazoamide **122** in the hope of obtaining higher yields of such cycloheptatrienes since one reaction pathway (oxindole formation) is precluded. In summary, rhodium(II) acetate catalysed decomposition of **122** gave the expected *trans* β-lactam **123** (39%), together with its *cis* isomer **124** (28%), and the desired cycloheptapyrrolone **125** (22%). Importantly, with rhodium(II) perfluorobutyramide catalysed decomposition of **122** attack on the aromatic rings was strongly favoured and the resulting cycloheptapyrrolone **125** was isolated after chromatography and recrystallisation in 70% yield (>80% from analysis of the crude NMR spectrum). Together with this, some *cis* β-lactam **124** was produced (**Scheme 136, Table 16**).



122 **123** **124** **125**

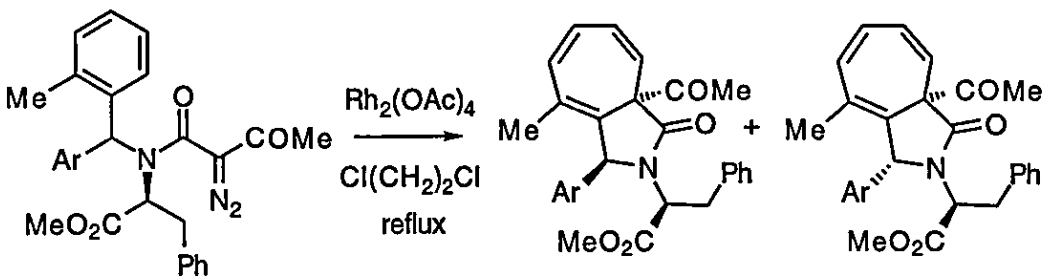
Scheme 136

catalyst	yield (%)		
	123	**124**	**125**
$Rh_2(OAc)_4$	39	28	22
$Rh_2(pfm)_4$	0	12	**70**

Table 16

Two salient points were noted. Firstly, that if substrate design precluded the aromatic substitution pathway to oxindoles but offered the alternative of an intramolecular Buchner reaction (IMBR or aromatic cycloaddition)[58,157] this would become the chemoselectively favoured pathway. And secondly, the trienes resulting from IMBR incorporated a newly formed quaternary, chiral centre (racemic in the above examples). It was thus envisaged that there were two possible modes of inducing face selectivity in the intramolecular approach of the transient rhodium(II) bound carbenoid to the aromatic ring. These were either enantioselection using chiral catalysts (ligand control), or diastereoselection using chiral diazo compounds (substrate control). Within the Moody

group a number of co-workers were actively engaged in the preparation and systematic screening of chiral transition metal catalysts for carbenoid processes.[158] So, it was appropriate for our studies to be limited to the search for diastereoselection in the intramolecular Buchner reaction of chiral diazo substrates. After the conception of this idea, an example of such a reaction involving diastereoselection in the IMBR of a diazoamide **352** was found in the literature. Zaragoza reported that the major products from rhodium acetate catalysed decomposition of **352** in refluxing 1,2-dichloroethane were the diastereomeric cycloheptapyrrolones **353** and **354** isolated in 61% yield and in a ratio of 87:13 **(Scheme 137)**.[16]



352 61% **353** (87:13) **354**

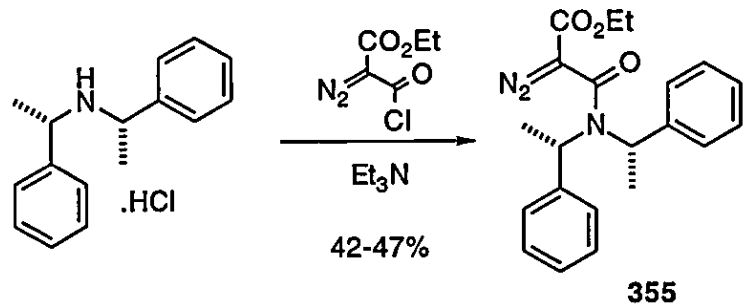
Ar= 2-Me-C_6H_4

Scheme 137

It is preferable that substrates much simpler than **352** be prepared and their potential for stereoselective IMBR investigated. These studies should ideally lead to a better understanding of the factors influencing chemoselection and stereoselection in the intramolecular competition reactions of diazocarbonyls.

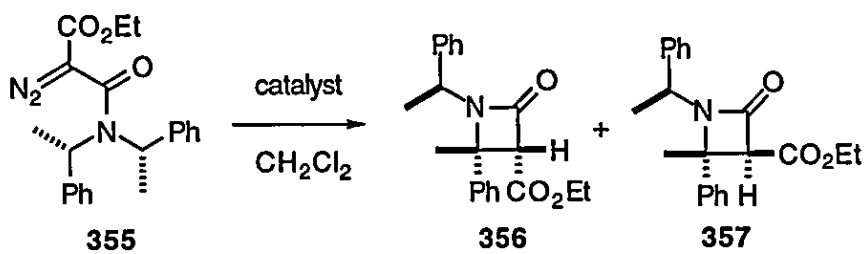
5.2. Chiral Diazoamides as Substrates for the Intramolecular Buchner Reaction

With this remit in mind a series of homochiral diazo substrates were prepared and their rhodium(II) catalysed decomposition chemistry was investigated. The first substrate, as a direct analogy to dibenzyldiazoamide **122**, was the homochiral C-2 symmetric bis-α-methylbenzyldiazomalonamide ester **355** which was readily prepared from commercially available (-)-bis[(S)-1-phenylethyl]amine and ethyl diazomalonyl chloride **(Scheme 138)**. The yield was only moderate, probably as a consequence of steric crowding around the nucleophilic amine nitrogen, but unreacted starting amine could be recovered.



Scheme 138

Substrate **355** with two identical phenyl rings appropriately tethered to the diazo moiety augured well for a good yield of IMBR products by analogy with the similar achiral diazoamide **122**. Moreover, potential for diastereoselection in the transformation was envisaged, with control being effected by the chiral centre close to the reacting aromatic ring. In the event, the catalyst of choice, rhodium(II) perfluorobutyramide led to the formation of only trace amounts (by NMR) of the desired triene(s) and the actual isolated products were a mixture of the "*cis*" β-lactam **356** along with its epimer **357** (**Scheme 139**). The overall recovery was, on the positive side, quite high. To complement this result, rhodium(II) acetate catalysed decomposition of **355** was undertaken. As expected, no cycloheptatriene formation was observed, indeed the product distribution mirrored closely that from rhodium(II) perfluorobutyramide (**Table 17**).

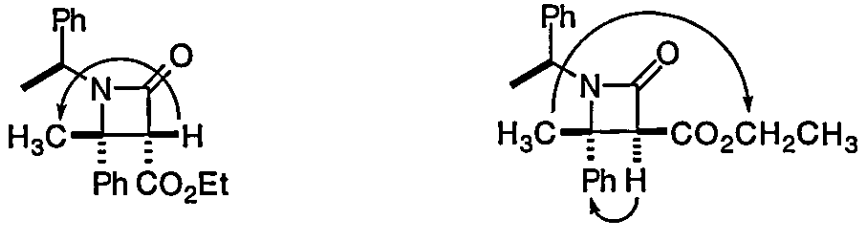


Scheme 139

catalyst	yield **356** (%)	yield **357** (%)
$Rh_2(pfm)_4$	41	27
$Rh_2(OAc)_4$	47	29

Table 17

The assignment of relative stereochemistry in the product β-lactams **356** and **357** was made from NMR studies. In particular, nOe experiments showed clearly the relative stereochemistry in the lactam ring (**Figure 20**).

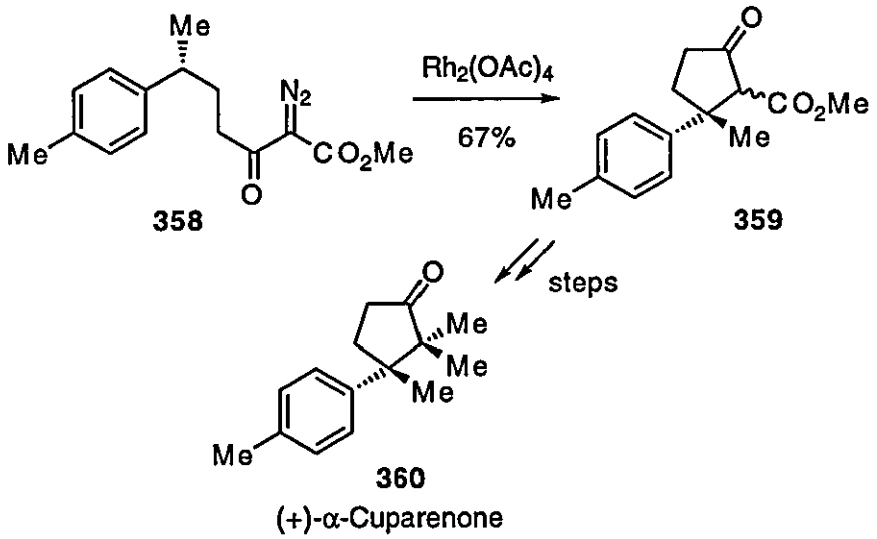


356 **357**

Figure 20: Selected Significant nOe Correlations for **356** and **357**

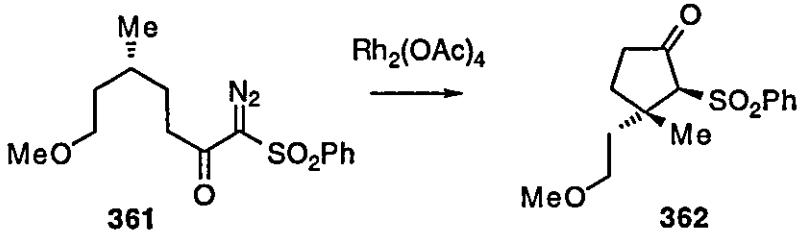
As a tool to determining more information about the stereochemistry around the β-lactam rings in **356** and **357**, a solution of the former compound in THF was treated with triethylamine at room temperature.[159] The result was partial epimerisation at the acidic C-3 position, and led to a thermodynamic equilibrium mixture of **356** and its epimer **357** in a ratio 40:60. It is interesting that the thermodynamically disfavoured isomer **356** still features as a major product in rhodium catalysed decomposition of **355**.

The absolute stereochemistry of the lactam rings was deduced through assumption that the intramolecular C-H insertion reaction, which affords the β-lactam products, proceeds with retention of stereochemistry at the reacting chiral centre. This is well precedented in the literature, for example in the observations reported by Taber during the total synthesis of (+)-α-cuparenone **360** (**Scheme 140**). Treatment of α-diazo ketoester **358** with rhodium(II) acetate in dichloromethane afforded cyclopentanone **359** in 67%. Further elaboration produced the natural product in 96% optical purity, confirming the fact that the rhodium(II) catalysed C-H insertion proceeds with near complete retention of configuration.[160]



Scheme 140

Another example of this retention of configuration in intramolecular C-H insertion reactions was found in the recently reported total synthesis of (+)-grandisol. Monteiro and co-workers showed that this was the case for rhodium(II) acetate catalysed decomposition of **361**, furnishing **362** in good yield (60% including a diazo-transfer step prior to the decomposition step; **Scheme 141**).[161]



Scheme 141

The shift of chemoselectivity when comparing the rhodium(II) catalysed decomposition of achiral *N,N*-dibenzyl diazoamide **122** with chiral diazoamide **355** away from cycloheptatriene to β-lactam formation was disappointing. In efforts to find an explanation the C-2 symmetric diazosubstrate **355** was subjected to molecular modelling studies and these gave the first possible explanation for the observed selectivity for β-lactam formation (see **Appendix C** for a summary of these studies). They indicated that the lowest energy conformations of the substrate placed the phenyl rings in a position remote to the diazo (and supposedly the carbenoid) centre. Also the two phenyl rings were found to be positioned in a favoured edge-face orientation. On the other hand, the actual favoured sites of attack (the benzylic methines) were shown to be in close proximity to the diazo carbon. Eventually, careful crystallisation afforded

crystals of diazoamide **355** which were suitable for X-crystallographic analysis. The resulting structure (**Figure 21, Appendix A**) closely matched the molecular modelling image.

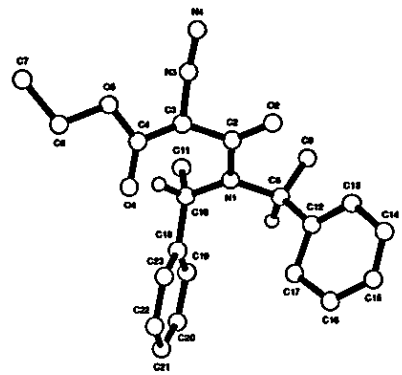
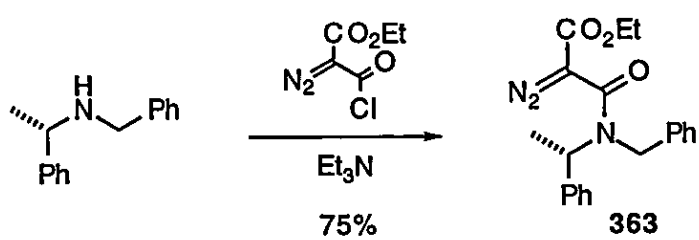


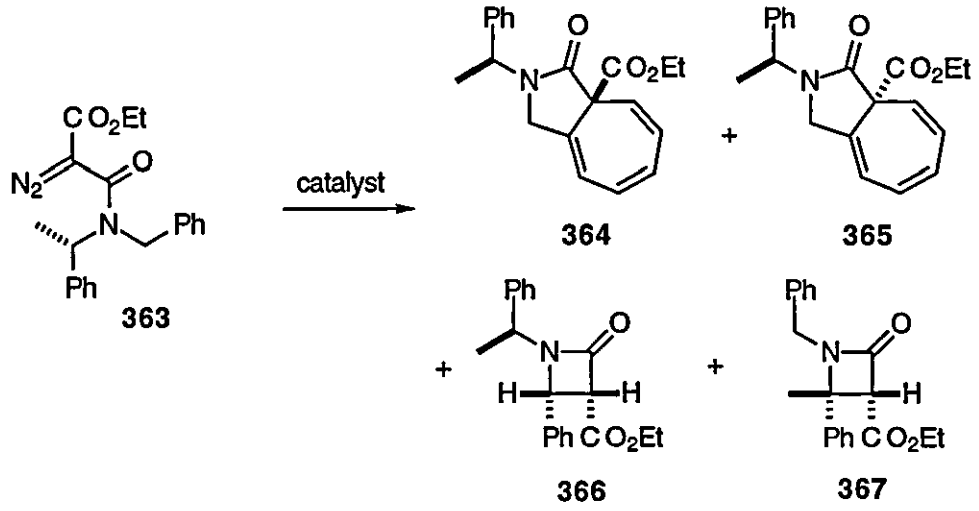
Figure 21 X-ray Crystal Structure of C-2 Symmetric Diazoamide **355**

In summary it is clear that conformational constraints within the substrate **355** control chemoselectivity and override the drive for IMBR shown earlier to be favoured by rhodium(II) perfluorobutyramide catalysed decomposition of related diazoamide **122**. The logical step, therefore, was to remove some of the introduced steric crowding. This was achieved simply by diazoacylation of commercially available S(-)-*N*-benzyl-1-phenylethylamine which proceeded in good yield to afford chiral diazoamide **363** (**Scheme 142**). It was interesting to note the improved yield of this diazoacylation compared to the preparation of the more hindered diazoamide **355**.



Scheme 142

The decomposition of diazoamide **363** was carried out using the three catalysts rhodium(II) perfluorobutyramide, rhodium(II) acetate, and rhodium(II) trifluoroacetate. The results obtained are summarised below (**Scheme 143 , Table 18**).



Scheme 143

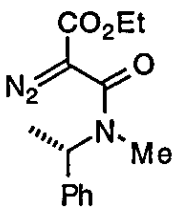
catalyst	% 364+365 (% de)	% 366	% 367
$Rh_2(OAc)_4$	20 (0)	15	65
$Rh_2(O_2CCF_3)_4$	33 (0)	33	33
$Rh_2(pfm)_4$	35 (12)	20	20

Table 18

Gratifyingly it was found that with rhodium(II) perfluorobutyramide catalysis there was a significant amount of trienic material formed. However, the isolated yield of the diastereomeric pair of cycloheptatrienes **364** and **365** amounted to only 35% after flash silica gel column chromatography, the remainder being an equal mixture of the β-lactams **366** and **367** which were isolated in 40% yield. These two pairs were further separated by preparative HPLC. NMR and analytical HPLC analysis showed that the trienes **364** and **365** were formed in a ratio of 56:44, that is, with only 12% de. The diastereocontrol afforded by the chiral "auxiliary" α-methylbenzyl group is limited due to its remoteness from the reacting centres. It was noteworthy that, again, there was no detected attack on the α-methylbenzyl moieties phenyl ring. Also it is observed that of the possible β-lactam configurations it is the "*cis*" isomers **366** and **367** which are favoured.

Rhodium(II) acetate and rhodium(II) trifluoroacetate catalysed decomposition of **363**, on the other hand, gave no trienes but gave the β-lactams **366** and **367** in varying ratios (NMR ratios are quoted in the table above; **Table 18**).

The chiral diazoamide **368**, prepared from a commercial amine and ethyl diazomalonyl chloride (93% yield) (**Figure 22**), was subjected to rhodium(II) perfluorobutyramide catalysed decomposition. However, no IMBR products could be isolated and the only product identified in the complex crude reaction mixture was the *trans* β-lactam arising from C-H insertion into the *N*-methyl group. Interestingly, X-ray crystallographic analysis of a single crystal of diazoamide **368** showed a conformation quite different to those observed for *N*-aryl diazomalonamides **101**, **120**, **260**, and **285**. Indeed the diazo carbon of **368** was found to be in close proximity to the *N*-methyl group which is attacked in its rhodium catalysed reaction (**Figure 23**).



368

Figure 22

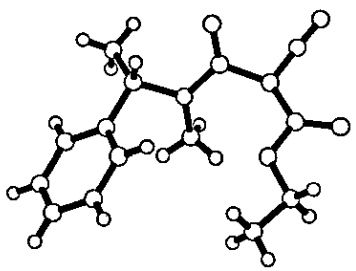


Figure 23 X-Ray Crystal Structure of *N*-Methyl-*N*-(α-Methylbenzyl) Diazoamide **368**

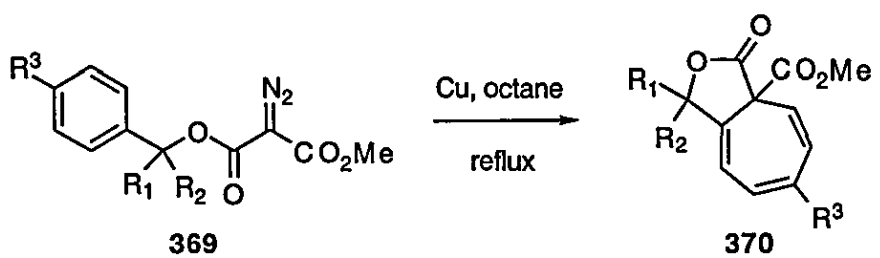
It is clear that steric and conformational effects inherent in the chosen diazoamides override the chemoselectivity drive for attack of aromatic rings normally otherwise favoured by rhodium(II) perfluorobutyramide catalysed decomposition of diazocarbonyls. In conclusion, readily prepared chiral diazoamides of type **355**, **363**, and **368** are not useful for the study of the intramolecular Buchner reaction, and hence any diastereoselectivity therein, and it was necessary to consider related alternative diazocarbonyl substrates.

5.3. Chiral Diazomalonates as Substrates for the Intramolecular Buchner Reaction

In pursuit of diastereoselection in the intramolecular Buchner reaction (IMBR) and guided by the need to extricate our study from chemoselectivity issues raised by conformational requirements of diazoamides, attention was turned to the potential use of chiral diazoesters.

5.3.1. Literature Examples of Diazoesters as Substrates for the IMBR

A search of the literature revealed some IMBR chemistry of diazoesters and diazomalonates. Of relevance was the work reported by Julia which describes the decomposition of diazomalonates **369** under copper metal catalysis in refluxing octane to furnish cycloheptafuranones **370 (Scheme 144)**.[162] The results are summarised below, and of note are the generally low yields and the complete lack of diastereoselection for the intramolecular cycloaddition products **(Table 19)**.



369 **370**

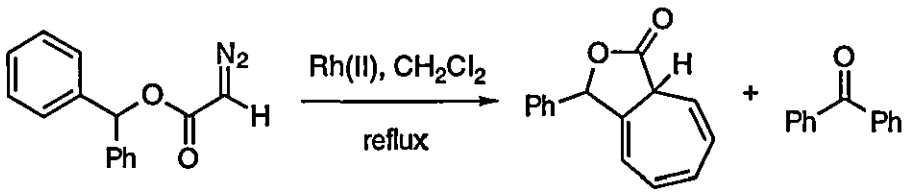
Scheme 144

R_1	R_2	R_3	reaction time (h)	yield (%)	de (%)
H	H	H	3	20	-
H	Me	H	4	19	0
Me	Me	H	3	45	-
H	H	OMe	4	~60	-

Table 19

More recently Doyle reported related work and along with this presented evidence of a new reaction pathway which gives at least a partial explanation for the observed low yields of cycloheptafuranones obtained from these metal catalysed decomposition of diazoesters.[163] Benzhydryl diazoacetate **371** was decomposed under rhodium(II) catalysis and gave cycloheptatriene **372** in amounts dependent on the specific catalyst

employed (**Scheme 145, Table 20**). Notably, though two diastereomers are possible for the product triene **371**, Doyle makes no comment in the communication about any stereoselectivity.



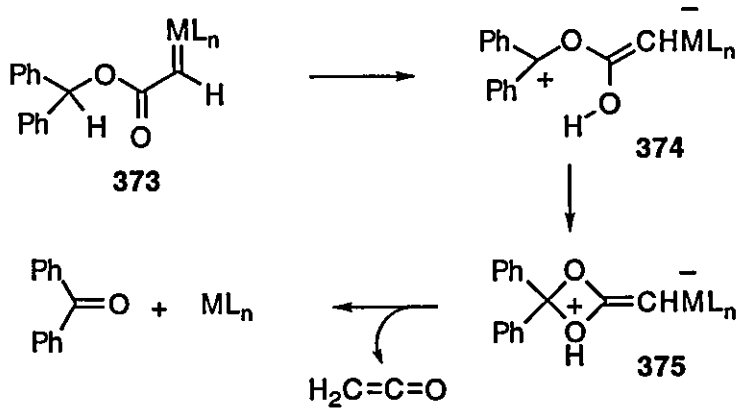
371 **372**

Scheme 145

catalyst	yield **372** (%)	yield benzophenone (%)
$Rh_2(OAc)_4$	5	5
$Rh_2(cap)_4$	39	7
$Rh_2(5S\text{-}MEPY)_4$	25	37
$Rh_2(4S\text{-}MEOX)_4$	52	24

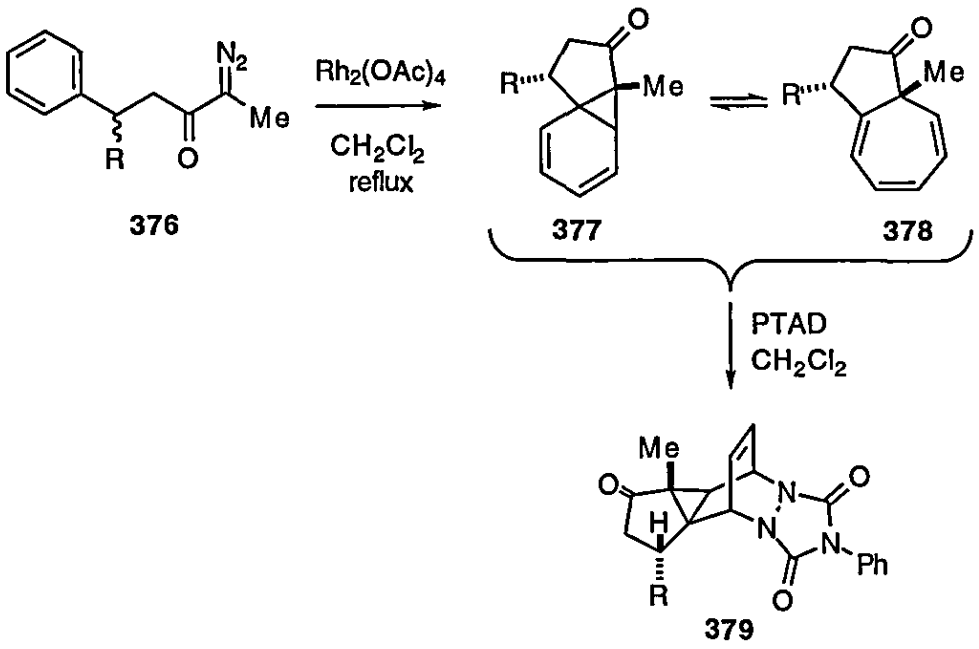
Table 20

The benzophenone side product was observed in all examples and Doyle proposes a novel intramolecular hydride abstraction mechanism as an explanation for its formation (**Scheme 146**). Briefly, this involves the ester carbonyl group of the reactive carbenoid **373** acting as the hydride acceptor to give the carbocation **374**. Intramolecular trapping of the cation by oxygen gives the intermediate **375** which quickly releases the observed benzophenone **372** along with ketene and the recycled catalyst.



Scheme 146

During the course of our studies, as described below, an important communication from the Maguire group appeared in the literature. They prepared the racemic diazoketones **376** and subjected these to rhodium(II) acetate catalysed decomposition. The products obtained were an equilibrium mixture of norcaradienes **377** and trienes **378** which were subjected to cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to give [4+2] cycloaddition products **379** (**Scheme 147**). The IMBR was in most cases completely diastereoselective (*trans*:*cis* diastereomer ratios were ≥97:3). The two steps could be carried out sequentially in one-pot and gave the yields quoted below (**Table 21**).[164]

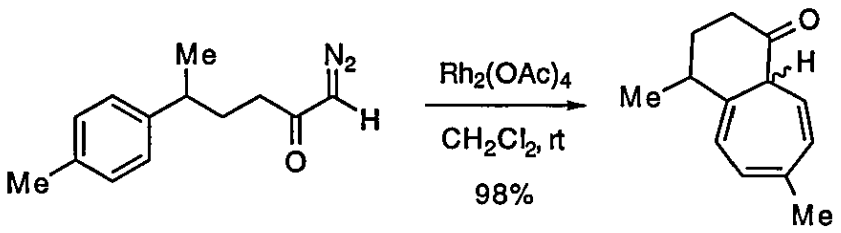


Scheme 147

R	Et	Pr	^{i}Pr	Bu	^{t}Bu	H
yield **379** (%)	66	70	74	71	75	54

Table 21

Interestingly, Sonawane and co-workers reported in 1992 that rhodium(II) acetate catalysed decomposition of diazoketone **380** leads to exclusive IMBR to furnish triene **381**, a key intermediate in the total synthesis (±)-*ar*-himachalene, in almost quantitative yield (**Scheme 148**). However, in contrast with the more recent observations of McCarthy as descibed above, the Indian workers reported that there was no diastereoselection at all in the IMBR of **380**.[165]



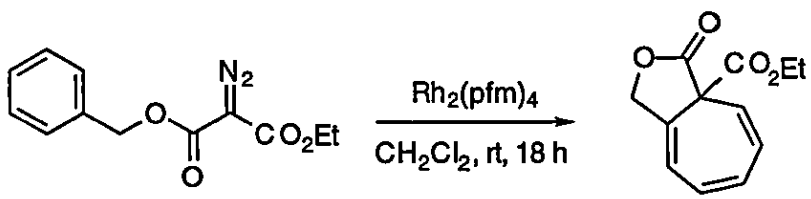
380 381

Scheme 148

5.3.2. Preparation and Rhodium(II) Catalysed Reactions of Diazomalonates

Padwa described the reaction of ethyl 2-diazomalonyl chloride with benzyl alcohol at 0°C using 2,6-lutidine as a base and dichloromethane as a solvent to afford the diazomalonate **382** in 92% yield.[55] However, an attempt to duplicate this result was met with unexpected failure; the best yield in our hands was a poor 32%. Use of sodium hydride in tetrahydrofuran gave a similarly low yield (19%). Since the primary focus was not on the chemistry of the resulting achiral malonate **382**, no further resources were expended to improve this yield. It was however interesting to hear, in a private communication, from Professor Padwa that in practice the method they adopted was different to that which they described in the literature.

Rhodium(II) perfluorobutyramide catalysed decomposition of the diazomalonate **382** at room temperature gave the cycloheptafuranone **383** in only 46% isolated yield and no other products could be isolated or characterised (**Scheme 149**).

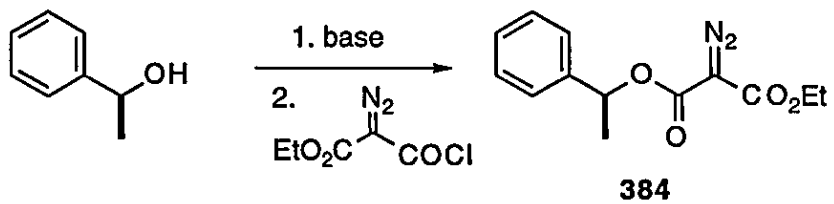


382 383

Scheme 149

Bearing in mind this synthetic potential of in-house prepared ethyl diazomalonyl chloride, it was decided that the most readily prepared substrates were chiral diazomalonates derived in one step from commercially available homochiral α-alkylbenzyl alcohols. However, initial efforts to prepare the chiral diazomalonate **384**, from commercial α-methylbenzyl alcohol and ethyl diazomalonyl chloride were painfully low yielding (**Table 22**). Gratifyingly, after some experimentation it was found that

treatment of the alcohol with *n*-butyllithium in tetrahydrofuran at about -78°C, followed by addition of a slight excess of the acid chloride gave the best results (**Scheme 150**).



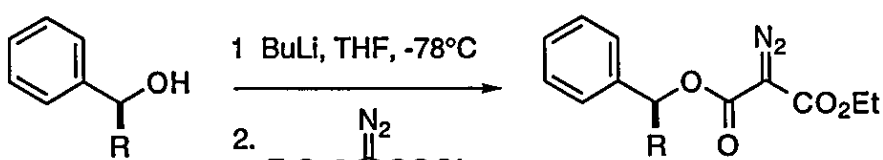
384

Scheme 150

Conditions	Result
Et_3N, CH_2Cl_2, rt	no reaction
Et_3N, CH_2Cl_2, reflux	no reaction
NaH, THF, 0°C	16%
2,6-lut, CH_2Cl_2,, reflux	40%
K_2CO_3, DMF, rt	no product
NaH, DMF, rt	no product
BuLi, THF, -78°C	**76%**

Table 22

Using the *n*-butyllithium method the homologous series of chiral diazomalonates **384-386** were prepared in high yield from their respective, commercially available chiral alcohol precursors (**Scheme 151**).



384, R=Me (76%)
385, R=Et (86%)
386, R=Pr (75%)

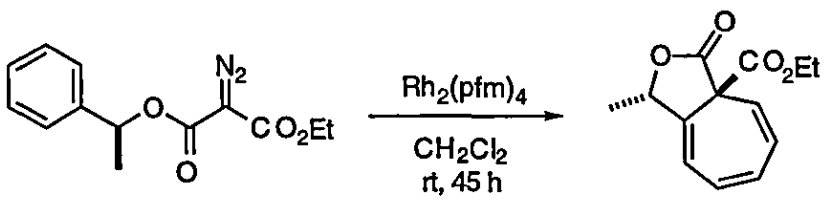
Scheme 151

In order to prove that chirality was not compromised by treatment of the homochiral alcohols with the strong base *n*-butyllithium, the racemate of **384** was prepared using the same method and the product was isolated in an excellent 94% yield. This racemic compound proved to be an excellent substrate for analysis by chiral shift NMR spectroscopy. Thus, addition of 0.2 equivalents of $Eu(hfc)_3$ admirably split the three

proton doublet at 1.60 ppm into two equal doublets at 1.65 and 1.78 ppm, proving the racemic nature of this compound. The same conditions with the product **384**, derived from homochiral (S)-phenylethyl alcohol with butyllithium at -78°C and then reaction with ethyl diazomalonyl chloride, did not give any splitting of the peak, and thus it could be concluded that the **384** had completely retained chirality within the limits of observation inherent in such an NMR experiment.

Rhodium(II) Perfluorobutyramide Catalysed Decomposition of Chiral Diazomalonates 384-386

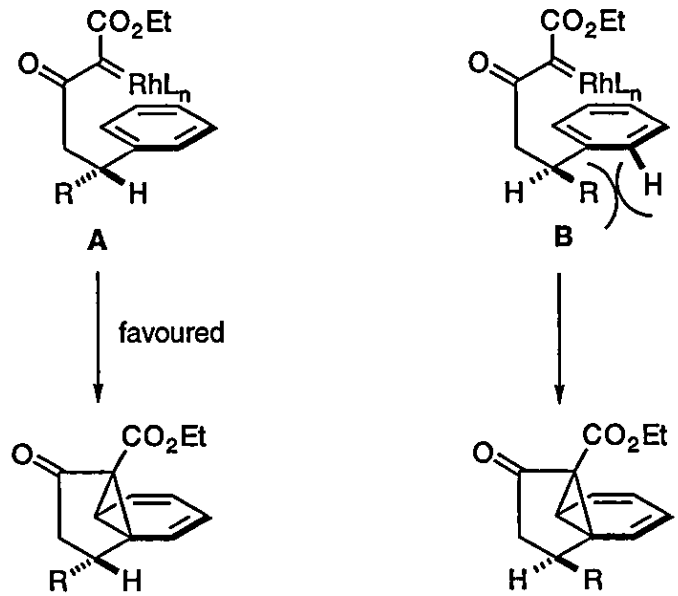
Thus the substrates **384-386** required for the key step of rhodium(II) catalysed decomposition were at hand. Homochiral diazomalonate **384** was found to decompose fairly rapidly at room temperature under rhodium(II) perfluorobutyramide catalysis in dichloromethane solution. Analysis of the ^1H NMR spectrum of the crude mixture revealed a disappointingly complex mixture but it was clear that trienic material formed a significant component. In the event, after flash silica gel column chromatography the desired cycloheptafuranone **387** was isolated in about 27% yield as an oil (**Scheme 152**). This yield could not be improved notably by changing the reaction conditions to refluxing in dichloromethane nor did the crude NMR indicate much change using refluxing benzene.



384 **387** (27%)

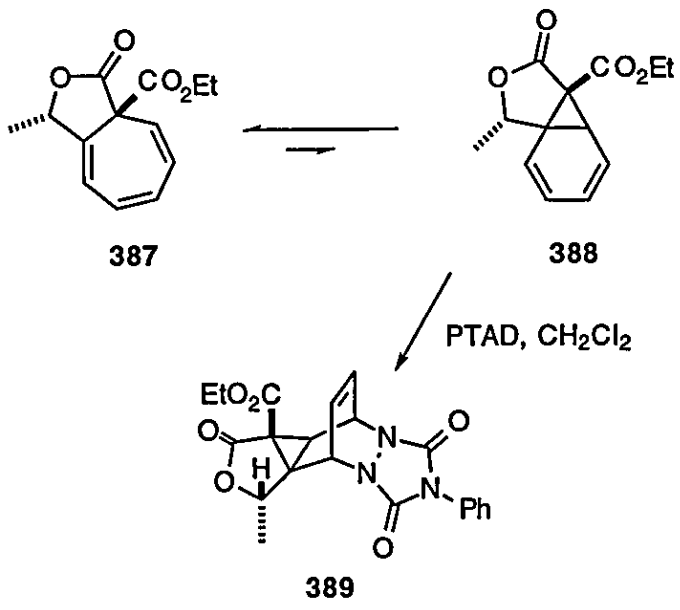
Scheme 152

Close inspection of the ^1H NMR of the crude mixture and comparison with clean **387** demonstrated that the attack of the carbenoid had indeed been completely diastereoselective, attacking the aromatic ring from one face only. Attack was assumed, intuitively, to be from the less hindered face, that opposite to the methyl group and giving rise to a triene with the methyl group "trans" or "anti" to the ethyl ester group. This mode of attack also passes the transient carbenoid through conformation **A** as opposed to conformation **B** in which the methyl group (R) experiences $A^{1,3}$ strain (**Scheme 153**).[164]



Scheme 153

Attempts to confirm this relative stereochemistry using nOe studies were unsuccessful, and some other method would clearly need to be found. The best alternative was envisaged to be X-ray crystallographic analysis. Unfortunately, the triene **387** was an oil and it would be necessary to obtain some crystalline derivative. Cycloheptatrienes have been shown to exist in dynamic equilibrium with their norcaradiene tautomeric form, and this is distinguishable on examination of NMR spectra. Moreover, the dienes are susceptible to [4+2] cycloaddition chemistry on exposure to suitable dienophiles, thus driving any equilibrium to give a single cycloaddition product. During the course of our studies in this area of probing diastereoselection in the IMBR, the Maguire group published a communication detailing related work which supported our observation of excellent levels of selectivity.[164] Their observations are summarised in **Scheme 147** above. Importantly, they took advantage of earlier reports from Saba[166] and showed the value of [4+2] cycloaddition as a means to provide a derivative of norcaradiene intermediates which could be analysed by X-ray crystallography to prove the relative stereochemistry obtained. By analogy, the triene **387** was treated with PTAD to give quantitative conversion to a single product which was fully characterised as **389**, the cycloadduct of a putative norcaradiene equilibrate **388 (Scheme 154).**



387 388

389

Scheme 154

It was gratifying to obtain, on recrystallisation of the solid **389**, material suitable for X-ray crystallographic analysis, and this confirmed unequivocally that the stereochemical outcome of the reaction was as postulated in **Scheme 153**, giving rise to a product in which the R (alkyl) group is disposed *anti* to the ester moiety (**Figure 24**; **Appendix B**).

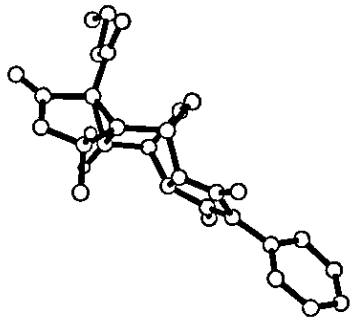


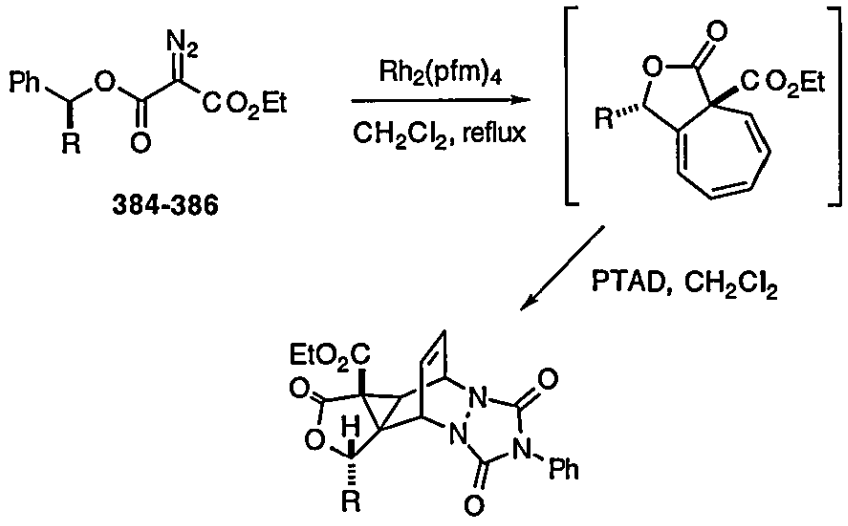
Figure 24 X-Ray Crystal Structure of Cycloadduct **389**

Since the starting diazomalonate **384** was homochiral, it would be expected that the single diastereomeric triene **387** should also be a single enantiomer (**Scheme 152**).

The first evidence of this was that the material significantly rotated the plane of polarised light ($[\alpha]_D^{25}$ -127°; c=0.09 in $CHCl_3$). To confirm this postulate, the racemic diazomalonate (±)**384** was prepared (94% yield) and decomposed under rhodium(II) perfluorobutyramide catalysis in refluxing dichloromethane; purification of the crude by flash silica gel column chromatography afforded the racemic cycloheptafuranone (±)**387** as a single diastereoisomer in about 20% yield. Chiral shift NMR using $Eu(hfc)_3$ did not give any useful splitting of peaks, and thus chiral HPLC separation of the racemate was attempted. Suitable conditions, as described in the experimental section, were readily found and this allowed comparison with the product **387** from decomposition of homochiral **384**. It was thus conclusively demonstrated that, within experimental limits, the result was a single enantiomer (>97% e.e.) arising from stereoselective intramolecular Buchner reaction.

The two steps of IMBR followed by the [4+2] cycloaddition with PTAD could be performed sequentially in one pot without isolation of the triene intermediate **387**. Thus the diazomalonate **384** was refluxed in dichloromethane under rhodium(II) perfluorobutyramide catalysis for 30 min, then the mixture was cooled to 0°C before addition of PTAD (1 equivalent) and purification by flash silica gel column chromatography to give the polycyclic cycloadduct in 39% yield of **389** (from **384**) as a crystalline solid. This yield is higher than the isolated yield of the triene **387** (28%), and since the [4+2] cycloaddition was shown to be quantitative, it would appear that the triene is partly lost during flash silica gel column chromatography.

The diazomalonates **385** and **386** were similarly converted by the one-pot protocol to their respective cycloaddition products **390** and **391** in moderate overall yields. These results are summarised below (**Scheme 155**, **Table 23**).



384-386

389-391

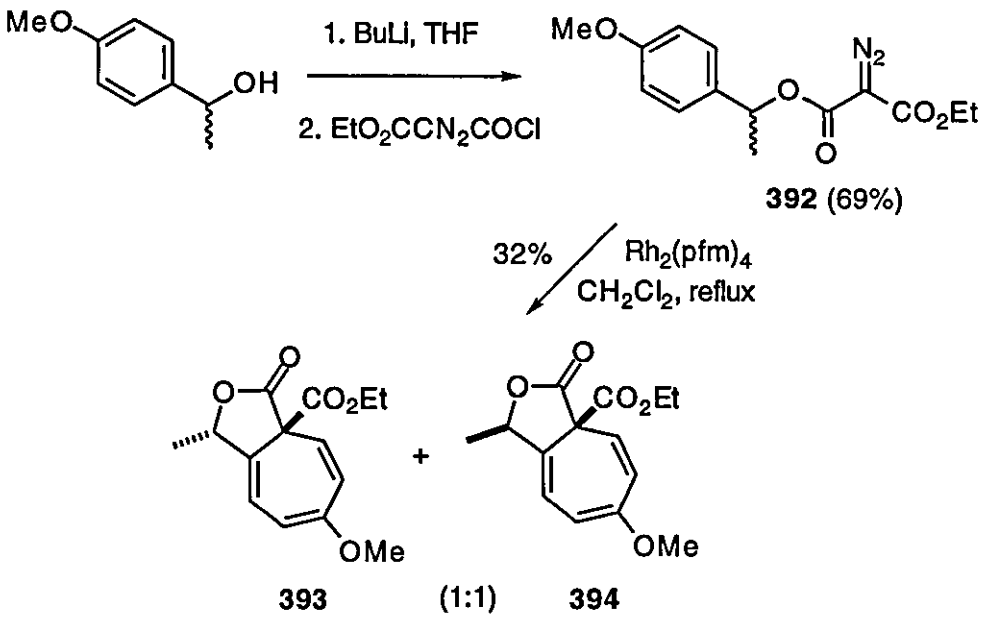
Scheme 155

R	Diazomalonate	Cycloadduct	Yield (%)	de (%)
Me	**384**	**389**	39	>95
Et	**385**	**390**	41	>95
Pr	**386**	**391**	34	>95

Table 23

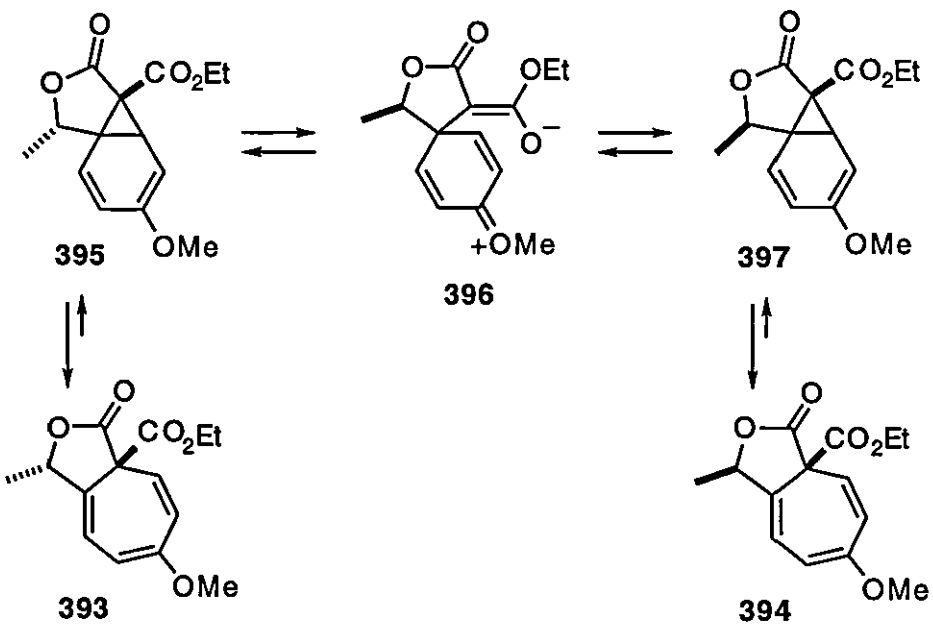
5.4. Attempts to Improve the Yield of IMBR Products

It can clearly be seen that the isolated yields of cycloheptafuranones (for example **387**) and their PTAD cycloadducts **389-391** are at best moderate (**Table 23**). In an endeavour to improve the yield, racemic diazomalonate **392**, which has a methoxy substituted aryl ring, was prepared and decomposed with rhodium(II) perfluorobutyramide in the standard fashion (**Scheme 156**). Remarkably, the result was a 1:1 mixture of diastereomers **393** and **394**, recovered in a disappointing yield of only 32% after flash silica gel column chromatography.



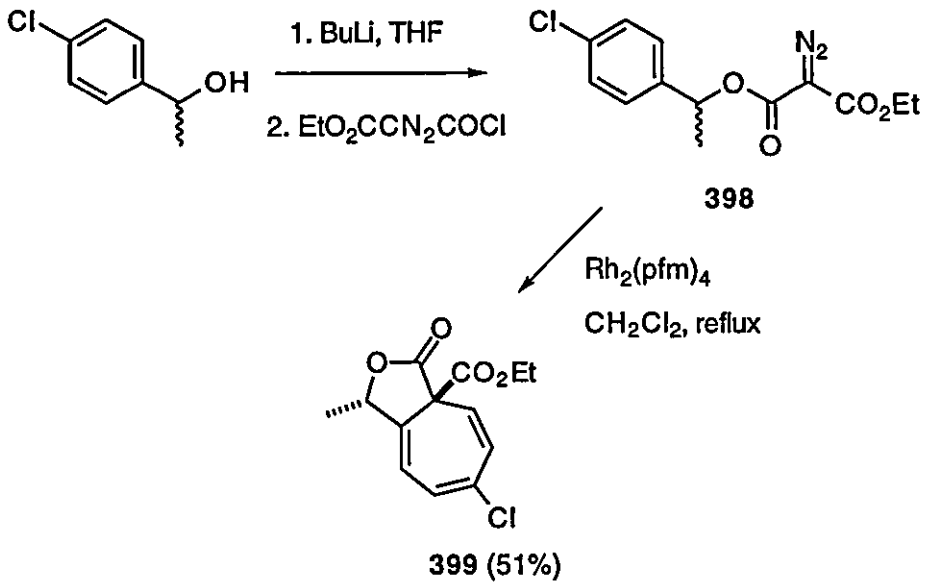
Scheme 156

After due consideration, and reflection on literature[162,167] it was concluded that the apparent complete lack of diastereoselection was actually a result of epimerisation of the newly formed chiral centre of the intermediate, single diastereomeric norcaradiene **395.** This racemisation is promoted by the methoxy substituent in the original aromatic ring donating a lone pair which moves through the norcaradiene to break one of the newly formed C-C bonds and to give the zwitterionic, spirocylic intermediate **396.** Upon equilibration either of the diastereomers **395 and 397** can be formed and these ultimately give rise to **393** and **394** respectively **(Scheme 157).**



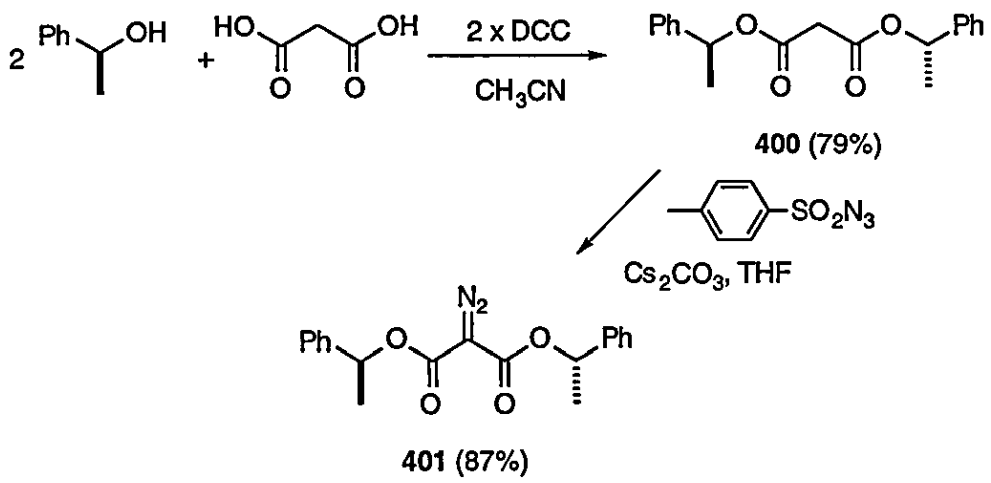
Scheme 157

With the above observation it was of interest to prepare the 4-chlorophenyl diazomalonate **398** and to see if IMBR under rhodium(II) perfluorobutyramide catalysis would be effected in higher or lower yield. The preparation of **398** was conducted without incident in good yield and rhodium catalysed decomposition afforded chloro-substituted cycloheptafuranone **399** in quite high yield (51%) as a single diastereomer (**Scheme 158**). It is possible that the chloro substituent plays some part in stabilising the norcaradiene and triene products compared to, say, the methoxy substituted analogues.



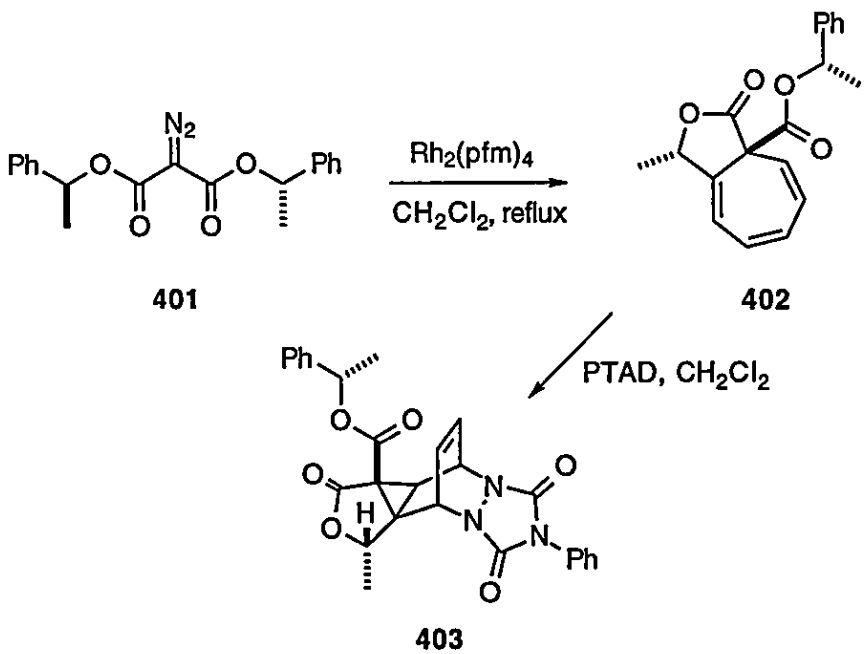
Scheme 158

A final compound of interest, in respect of attempts to improve the selectivity for IMBR products, was the C-2 symmetric diazomalonate **401**. This substrate was readily prepared by diazo transfer[139] onto the active methylene of the C-2 symmetric malonate **400**, which itself was availed of by standard dicyclohexylcarbodiimide (DCC) mediated condensation of two equivalents of (S)-(-)-1-phenylethanol with malonic acid (**Scheme 159**).



Scheme 159

Rhodium(II) perfluorobutyramide catalysed decomposition of diazo **401** gave the chiral cycloheptafuranone **402** as a single diastereomer, and this was isolated as its PTAD cycloadduct **403** in 47% yield (from **401**) (**Scheme 160**).



Scheme 160

Thus, this final endeavour proved not to increase chemoselectivity for the desired IMBR pathway, and it seems that the competing decomposition pathways leading to largely unidentified side products are always dominant in these type of substrate. In light of the observations of Maguire and co-workers[164], these limitations are probably due to controlling factors innate to the malonate substructure. One could invoke

conformational constraints as well as the reactivity of specific sites inherent in malonate structures. As, Doyle stated, it is not uncommon for reactions involving highly reactive intermediates to give results which do not fully account for the mass balance.[163]

5.5. Conclusions

- Homochiral diazomalonamide ethyl esters are readily available through reaction of commercially available chiral amines and ethyl diazomalonyl chloride.

- The chemoselectivity of rhodium catalysed decomposition of chiral diazomalonamide ethyl esters is overwhelmingly controlled by the conformational and steric factors, and largely led to formation of β-lactams as opposed to cycloheptapyrrolones *via* IMBR.

- When steric crowding around the reacting diazo group, and hence the carbenoid carbon is reduced, the IMBR product is produced in low yields and substrate controlled diastereoselection is observed albeit at very modest levels (12% de). This is probably due to the remoteness of the reacting centre to the chiral centre inducing face selection.

- Homochiral diazomalonates are readily prepared by the reaction of commercially available chiral α-alkyl benzyl alcohols and ethyl diazomalonyl chloride.

- Rhodium(II) catalysed reaction of homochiral diazomalonates gives cycloheptafuranones as the products of IMBR in good to low yields. A significant amount of the starting material is lost in the course of the reaction and purification and part of this might be explained by the intramolecular hydride abstraction pathway proposed by Doyle. It is not clear where the remainder of the starting material is consumed.

- IMBR of enantiopure diazomalonates was found to be completely diastereoselective within limits of detection, giving rise to single diastereomers and single enantiomers of cycloheptatriene products.

- Homochiral cycloheptatrienes were found to give clean [4+2] cycloaddition reaction with the dienophile PTAD. The reacting diene was actually the norcaradiene tautomer of the cycloheptatriene, and the polycyclic products were formed as single isomers (the cycloaddition was stereoselective) in modest overall yields form the

diazo precursors. The decomposition-[4+2] cycloaddition could be carried out in a one-pot procedure and led to slighty better overall yields of product.

- The sense of diastereoselection of the IMBR of chiral diazomalonates was proved by X-ray crystallographic analysis of a single crystal of cycloadduct **389** (**Figure 24**) to be such that carbenoid attack on the phenyl ring was directed from the least hindered face. This leads to the formation of a cycloheptafuranone with a *trans* relationship between the ester at the new chiral centre and the alkyl group at the chiral centre directing the selective attack.

- Due to factors which are not entirely clear the rhodium(II) perfluorobutyramide catalysed decomposition of chiral diazomalonates gives rise to only modest yields of IMBR products.

Chapter Six

Experimental Details

6.1. General Experimental Points

Commercially available reagents were generally used throughout without further purification. Unless purchased in high purity, solvents were purified before use as follows. Ether refers to diethyl ether and was distilled from calcium chloride. Dichloromethane and ethyl acetate were distilled from phosphorus pentoxide. Dichloromethane used in rhodium catalysed reactions was distilled from calcium hydride and stored over molecular sieves. Light petroleum refers to the petroleum ether fraction boiling in the range of 40-60°C, and was distilled from calcium chloride. Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately prior to use. Analytical thin layer chromatography was carried out using aluminium- or plastic-backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised under UV light (at 254 and/or 360 nm). Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Fully characterised compounds were chromatographically homogeneous.

IR spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 spectometer, or a Nicolet 510P FT-IR, with internal calibration. GGATR refers to golden-gate attenuated total internal reflection. ^{1}H and ^{13}C spectra were recorded in deuteriochloroform (unless otherwise stated) using Bruker AC-250, 300 and DPX-400 instruments; *J* values were recorded in Hz. Spectroscopic data is annoted with the following abbreviations: s, singlet; d, doublet, t, triplet, q, quartet; h, heptet; br.s, broad singlet; m, multiplet. High and low-resolution mass spectra were recorded on a Kratos MS80 instrument, and at the EPSRC Mass Specrometry Service at Swansea (VG analytical ZAB-E), or on a VG 7070E (AgrEvo Ltd.). In the mass spectra of dibromo compounds, the molecular ion is taken as the $^{79}Br^{81}Br$ peak unless otherwise stated. Elemental analyses were carried out on a Perkin-Elmer 2400 Elemental Analyser. Melting points were measured on a Riechert-Kofler hot stage apparatus and are uncorrected.

6.2. Experimental Details for Chapter 2

Ethyl 2-Diazomalonyl Chloride

Triphosgene (25.20 g) and benzene (113 ml) were stirred and cooled in an ice bath to 2°C. Pyridine (0.75 ml) was then added and a white precipitate observed, with a rise of temperature to 8°C. Ethyl diazoacetate (22.30 ml) was then added whilst maintaining the temperature below 10°C. The mixture was stirred at room temperature for 4.5 h, then filtered through a pad of Celite to give an orange-red solution. Concentration under reduced pressure gave a red solution and distillation of this under reduced pressure gave only a little recovered benzene and some ethyl diazoacetate (3.52 g, 15% recovered; b.p. 22-23°C at 2.75 mmHg). The distillation residue was subjected to flash silica gel chromatography (5:1 light petroleum:diethyl ether) to give the *ethyl 2-diazomalonyl chloride* (10.08 g, 27% yield) as a light yellow oil which characterised as described in the literature.[55]
When toluene was used as solvent in an analogous reaction the product was isolated in 33% yield.

Rhodium(II) Perfluorobutyramide

A mixture of rhodium(II) acetate (1.02 g), heptafluorobutyramide (27.68 g), and chlorobenzene (60 ml) was stirred in a small Berghof bomb and placed under 7.5 bars of nitrogen pressure. The mixture was then heated to 135-140°C and these conditions maintained for 17 h. After cooling to ambient temperature and returning to atmosperic pressure the mixture was filtered and excess heptafluorobutyramide was sublimed off to leave a purple tar. This was subjected to alumina gel column chromatography (neutral, activated form of Merck Al_2O_3 90; eluant 1:1 hexane:ethyl acetate) and the purple band was collected. Removal of the solvent furnished *rhodium(II) perfluorobutyramide* as a blue solid which displayed identical catalytic activity as a batch prepared by the literature method.

General Procedures for the Preparation of Diazoamides 101-103

Preparation of Substituted Benzanilides

A solution of the aryoyl chloride (1.0 eq) in dichloromethane was added slowly to a stirred solution of the requisite aniline (1.0 eq) and triethylamine (1.1 eq) in dichloromethane. Stirring was maintained for 18 h at room temperature. The resulting mixture was washed with aqueous HCl (2M), water and saturated brine then dried over Na_2SO_4. Concentration under reduced pressure yielded an off-white solid which could be recrystallised from ethanol to give the desired product as a crystalline white solid.

Preparation of Substituted N*-Benzylamines*

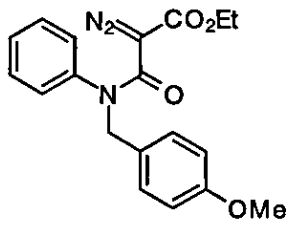
A solution of substituted benzanilide (1.0 eq) in dry THF was slowly added to a stirred suspension of $LiAlH_4$ (1.1 eq) in dry THF and the mixture refluxed for 18 h. The mixture was cooled to room temperature and then carefully quenched with water (0.07 ml per mmol of $LiAlH_4$). Whilst stirring, dilute NaOH (10%; 0.085 ml per mmol of $LiAlH_4$) and flash grade silica (0.14 g per mmol of $LiAlH_4$) were added. The resulting suspension was filtered through a pad of celite and the filtrate concentrated under reduced pressure to yield the crude product which could be further purified by distillation or by flash silica gel chromatography and recrystallisation.

Preparation of Substituted N*-Benzyl-*N*-phenyl-2-diazomalonamic Acid Ethyl Esters*

A stirred solution of the appropriate *N*- benzylamine (1.0 eq) in dichloromethane was treated with triethylamine (2.0 eq) and ethyl 2-diazomalonyl chloride (1.0 eq). The solution was stirred at room temperature for 3-18 h then washed with dilute HCl (2M), water and saturated brine. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude product which could be purified by subjecting to flash silica gel chromatography and recrystallisation.

Preparation of Diazocarbonyl Substrates for 1,2 and 3-Way Competition Carbenoid Reactions

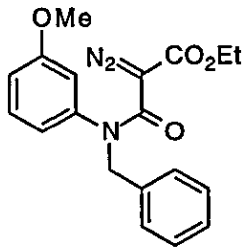
2-Diazo-*N*-(4-methoxybenzyl)-*N*-phenyl-malonamic Acid Ethyl Ester 101



Though *N*-phenyl-4-methoxybenzylamine is commercially available it was prepared by the standard methods whereby aniline was condensed with 4-methoxybenzoyl chloride (83%), and the resulting amide reduced with $LiAlH_4$ (93%).

N-Phenyl-4-methoxybenzylamine (0.285 g, 1.34 mmol) was condensed with ethyl 2-diazomalonyl chloride in the standard manner to yield the *2-diazo*-N-*(4-methoxybenzyl)*-N-*phenylmalonamic acid ethyl ester* **101** (0.44 g, 93%) as a viscous yellow oil; (Found: MH^+, 354.1454. $C_{19}H_{20}N_3O_4$ requires 354.1454); ν_{max}(neat)/cm^{-1} 2982, 2937, 2123, 1723 and 1683; δ_H (250 MHz; $CDCl_3$) 1.12 (3H, t, *J* 7.1 Hz), 3.77 (3H, s), 4.02 (2H, q, *J* 7.1 Hz), 4.93 (2H, s), 6.82-6.75 (2H, m), and 7.31-7.13 (7H, m); δ_C (100.6 MHz; $CDCl_3$) 14.18 (CH_3), 53.71 (CH_2), 55.16 (CH_3), 61.30 (CH_2), 113.71 (CH), 126.59 (CH), 126.96 (CH), 128.98 (C), 129.21 (CH), 129.80 (CH), 142.37 (C), 158.88 (C), 160.90 (C), and 161.82 (C=O); *m/z* 325 ($M-N_2^+$, 3%), 252 (11), 121 (100), and 77 (21).

N-Benzyl-2-diazo-*N*-(3-methoxyphenyl)-malonamic Acid Ethyl Ester 102

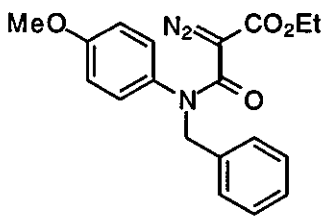


N-(3-methoxyphenyl)benzamide (6.57 g, 71%) was prepared by the condensation of benzoyl chloride (5.71 g, 40.6 mmol) and *m*-anisidine (5.00 g, 40.6 mmol) in the standard manner and was isolated, after recrystallisation from ethanol, as fine white crystals, m.p. 116°C (lit.:[168] 112°C); (Found: M^+, 227.0945. $C_{14}H_{13}NO_2$ requires 227.0946); ν_{max}(CH_2Cl_2)/cm^{-1} 3432, 1680, and 1529; δ_H (400 MHz; $CDCl_3$) 3.80 (3H, s), 6.72-6.67 (1H, m), 7.13-7.09 (1H, m), 7.25 (1H, t, *J* 8.1 Hz), 7.55-7.41 (4H, m), 7.86-7.82 (2H, m) and 8.01 (1H, br. s); δ_C (100.6 MHz; $CDCl_3$) 55.3, 205.8, 110.5, 112.35, 127.0, 128.8, 129.7, 131.8, 134.9, 139.2, 160.2, and 165.9; *m/z* 227 (M^+, 29%), 205 (100), 77 (47), 28 (28).

N-(3-Methoxyphenyl)benzamide (4.00 g, 17.61 mmol) was reduced with $LiAlH_4$ (0.668 g, 17.61 mmol) in the standard manner. Distillation of the crude product under reduced pressure yielded *N*-benzyl-3-methoxyaniline (3.447 g, 92%) as a viscous yellow oil; b.p. 150°C at 0.8 mmHg (lit.:[169] b.p. 226-227°C at 127 mmHg); ν_{max} (neat)/cm^{-1} 3029, 1497, and 1162; δ_H (250 MHz; $CDCl_3$) 3.72 (3H, s), 4.01 (1H, br.s), 4.29 (2H, s), 6.30-6.15 (3H, m), 7.06 (1H, t, *J* 8.1 Hz), and 7.38-7.20 (5H, m).

N-Benzyl-3-methoxyaniline (1.25 g, 5.87 mmol) was condensed with ethyl 2-diazomalonyl chloride (1.0359, 5.87 mmol) in the standard manner to yield *2-diazo*-N-*benzyl*-N-*(3-methoxyphenyl)malonamic acid ethyl ester* **102** (1.549 g, 75%) as pale yellow crystals after recrystallisation of the crude product from diethyl ether/ethanol, m.p. 75-76°C; (Found: C, 64.60; H, 5.27; N, 11.72. $C_{19}H_{19}N_3O_4$ requires C, 64.58; H, 5.42; N, 11.89); ν_{max} (CH_2Cl_2)/cm^{-1} 2123, 1722, and 1602; δ_H (250 MHz; $CDCl_3$) 1.15 (3H, t, *J* 7.1 Hz), 3.72 (3H, s), 4.06 (2H, q, *J* 7.1 Hz), 4.99 (2H, s), 6.79-6.60 (3H, m), and 7.29-7.15 (6H, m); δ_C (62.9 MHz; $CDCl_3$) 14.15 (CH_3), 54.18 (CH_2), 55.31 (CH_3), 61.33 (CH_2), 112.25 (CH), 112.29 (CH), 118.56 (CH), 127.38 (CH), 128.21 (CH), 128.39 (CH), 129.91 (CH), 136.93 (C), 143.62 (C), 160.11 (C), 160.87 (C), and 161.89 (C); *m/z* 325 (M-N_2^+, 20%), 279 (14), 252 (37), and 91 (100).

_N_-Benzyl-2-diazo-_N_-(4-methoxyphenyl)-malonamic Acid Ethyl Ester 103



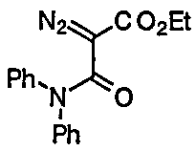
Benzoyl chloride (1.43 g, 10.2 mmol) was condensed with *p*-anisidine (1.255 g, 10.2 mmol) in the standard manner to yield *N*-(4-methoxyphenyl)benzamide (1.63 g, 71%) as colourless plates after recrystallisation from ethanol, m.p. 165-166°C (lit.:[170] 157-158°C); (Found: M^+, 227.0946. $C_{14}H_{13}NO_2$ requires 227.0946); ν_{max}(CH_2Cl_2)/cm^{-1} 3425, 1673, 1513, and 1248; δ_H (250 MHz; $CDCl_3$+DMSO-d_6) 2.68 (3H, s), 6.53 (2H, d, *J* 8.8 Hz), 7.20-7.08 (3H, m), 7.33 (2H, d, *J* 8.8 Hz), 7.61 (2H, d, *J* 7.8 Hz), and 9.35 (1H, br.s); δ_C (62.9 MHz; $CDCl_3$+DMSO-d_6) 55.10, 113.51, 122.06, 127.36, 127.97, 130.98, 131.87, 135.14, 155.77, and 165.71; *m/z* 227 ($M^{+\cdot}$, 27%), 105 (100), 77 (74), and 51 (28).

N-Benzyl-4-methoxyaniline (1.60 g, 7.1 mmol) was reduced with $LiAlH_4$ (0.27 g, 7.1 mmol) in the standard manner to give essentially pure *N*-benzyl-4-methoxyaniline which could be taken forward to the next step without further purification, m.p. 49-51°C (light petroleum/diethyl ether); (Found: M^+, 213.1154. $C_{14}H_{15}NO$ requires 213.1154); ν_{max}(CH_2Cl_2)/cm^{-1} 3436, 1514, 1235, and 822; δ_H (250 MHz; $CDCl_3$) 3.76 (3H, s), 4.30

(2H, s), 6.66-6.58 (2H, m), 6.83-6.76 (2H, m), and 7.40-7.25 (5H, m); δ_C (62.9 MHz; $CDCl_3$) 49.19, 55.75, 114.04, 114.85, 127.10, 127.48, 128.34, 128.52, 139.63, and 142.39; *m/z* 213 (M^+, 46%), 122 (67), 91 (100), and 65 (23).

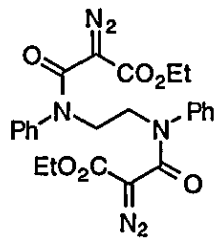
N-(4-methoxyphenyl)benzylamine (3.495 g, 6.54 mmol) was condensed with ethyl 2-diazomalonyl chloride (1.145 g, 6.54 mmol) in the standard manner to give the *2-diazo-N-benzyl-N-(4-methoxyphenyl)malonamic acid ethyl ester* **103** (2.157 g, 93% over 2 steps) as a yellow oil; (Found: M^+, 353.1376. $C_{19}H_{19}N_3O_4$ requires 353.1389); ν_{max}(neat)/cm^{-1} 2982, 2839, 2119, 1723, 1633, 1512, and 1298; δ_H (250 MHz; $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz), 3.78 (3H, s), 4.07 (2H, q, *J* 7.1 Hz), 4.94 (2H, s), 6.86-6.76 (2H, m), 7.01-6.94 (2H, m), and 7.28-7.20 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 14.24 (CH_3), 54.34 (CH_2), 55.39 (CH_3), 61.34 (CH_2), 114.39, (CH) 127.43 (CH), 128.06 (CH), 128.40 (CH), 128.56 (CH), 134.89 (C), 136.89 (C), 158.43 (C), 160.86 (C) and 162.08 (C); *m/z* 353 (M^+), 325 ($M-N_2^+$, 8%), 91 (100), and 28 (57).

2-Diazo-*N,N*-diphenylmalonamic Acid Ethyl Ester 118



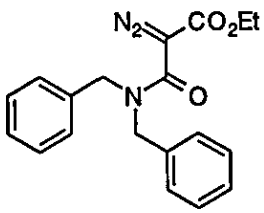
A solution of diphenylamine (0.500 g, 2.95 mmol) in dichloromethane (33 ml) was treated with triethylamine (0.82 ml, 5.90 mmol) and ethyl 2-diazomalonyl chloride (0.522 g, 2.95 mmol) and the mixture stirred at room temperature for 120 h. The resulting solution was preadsorbed on silica and subjected to flash silica gel chromatography (3:1 light petroleum:diethyl ether) to give recovered diphenylamine (0.272 g, 54%) and *2-diazo-N,N-diphenylmalonamic acid ethyl ester* **118** (0.314 g, 34%) as a yellow oil; (Found: MH^+, 310.1192. $C_{17}H_{16}N_3O_3$ requires 310.1192); ν_{max}(neat)/cm^{-1} 2125, 1722, 1644, 1492, and 1345; δ_H (250 MHz; $CDCl_3$) 1.13 (3H, t, *J* 7.2 Hz), 4.02 (2H, q, *J* 7.2 Hz), 7.27-7.14 (6H, m), and 7.39-7.28 (4H, m); δ_C (100.6 MHz; $CDCl_3$) 14.21 (CH_3), 61.50 (CH_2), 126.63 (CH), 126.75 (CH), 129.23 (CH), 143.26 (C), 161.48 (C), and 161.88 (C); *m/z* 310 (MH^+, 24%), 284 (39), 170 (100), and 52 (87).

Ethyl 2-diazo-3-({2-[(2-diazo-3-ethoxy-3-oxo-propanoyl)anilino]ethyl}anilino)-3-oxo-propanoate 120



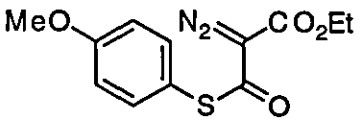
A solution of 1,2-dianilinoethane (0.50 g, 2.36 mmol) and triethylamine (1.31 ml, 9.42 mmol) was treated with ethyl 2-diazomalonyl chloride (0.83 g, 4.70 mmol) and the mixture stirred at room temperature for 5 h. The solution was then preadsorbed on silica and subjected to flash silica gel chromatography (2:1 light petroleum:diethyl ether, then diethyl ether, and then CH_2Cl_2) followed by one recrystallisation from ethyl acetate-ethanol furnished *ethyl 2-diazo-3-({2-[(2-diazo-3-ethoxy-3-oxopropanoyl)anilino]ethyl}-anilino)-3-oxopropanoate* **120** (0.692 g, 60%) as yellow crystals, m.p. >125°C (decomposes); (Found: MH^+, 493.1836. $C_{24}H_{25}N_6O_6$ requires 493.1836); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2121, 1724, 1306 and 1118; δ_H (250 MHz; $CDCl_3$) 1.11 (6H, t, *J* 7.1 Hz), 3.99 (4H, q, *J* 7.1 Hz), 4.07 (4H, s), and 7.38-7.08 (10H, m); δ_C (100.6 MHz; $CDCl_3$) 14.12 (CH_3), 48.87 (CH_2), 61.25 (CH_2), 66.42 ($C{=}N_2$), 126.01 (CH), 126.94 (CH), 129.37 (CH), 142.38 (C), 160.97 (C), and 161.64 (C); *m/z* 493 (MH^+, 1%), 441 (7), 327 (15), 208 (25), 94 (29), and 52 (100).

***N,N*-Dibenzyl-2-diazomalonamic Acid Ethyl Ester 122**



A solution of dibenzylamine (0.250 g, 1.26 mmol, 0.244 ml) in dichloromethane (15 ml) was treated with triethylamine (0.353 ml, 2.53 mmol) and ethyl 2-diazomalonyl chloride (0.224 g, 1.26 mmol) and the resulting mixture stirred at room temperature for 18 h; it was then washed with 2M HCl (20 ml), H_2O (20 ml), saturated brine (20 ml) and dried over Na_2SO_4. Preadsorption onto silica followed by flash silica gel chromatography yielded the N,N-*dibenzyl-2-diazomalonamic acid ethyl ester* **122** (0.414 g, 97%) as a light yellow oil; (Found: MH^+, 338.1505. $C_{19}H_{20}N_3O_3$ requires 338.1505); $\nu_{max}(neat)/cm^{-1}$ 2129, 1707, 1625, 1419, and 1293; δ_H (250 MHz; $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz), 4.26 (2H, q, *J* 7.1 Hz)), 4.51 (4H, s), and 7.38-7.12 (10H, m); δ_C (100.6 MHz; $CDCl_3$) 14.40 (CH_3), 50.40 (CH_2), 61.54 (CH_2), 66.89 ($C{=}N_2$), 127.62 (CH), 127.62 (CH), 127.84 (CH), 128.70 (CH), 136.32 (C), 162.41 (C=O), and 162.50 (C=O); *m/z* 338 (MH^+, 100%), 327 (56), 31 (33), and 196 (82).

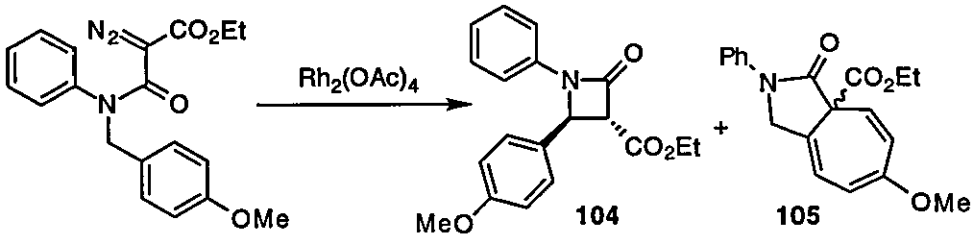
Ethyl 2-Diazo-3-[(4-methoxyphenyl)sulfanyl]-3-oxopropanaote 127



A solution of 4-methoxybenzenethiol (0.30 g, 2.14 mmol) in CH_2Cl_2 (12 ml) was treated with 2,6-lutidine (0.5 ml, 4.28 mmol) whilst cooling in an ice-water bath. Then ethyl 2-diazomalonyl chloride (0.415 g, 2.35 mmol) was added and the mixture was allowed to warm to ambient temperature over 4 h. Standard work-up afforded a cream solid which was recrystallised once from light petroleum-ether to furnish *ethyl 2-diazo-3-[(4-methoxyphenyl)sulfanyl]-3-oxopropanaote* **127** (0.480 g, 80%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3055, 2156, 2128, 1713, 1629, 1593, 1495, 1317, 1225, 1174, 1132, 926, and 830; δ_H (250 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7.1 Hz), 3.84 (3H, s), 4.38 (2H, q, *J* 7.1 Hz), 6.95 (2H, m), and 7.37 (2H, m); δ_C (62.9 MHz; $CDCl_3$) 14.29 (CH_3), 55.28 (CH_3), 61.84 (CH_2), 114.82 (CH), and 136.88 (CH) (quaternaries were not observed at 62.9 MHz).

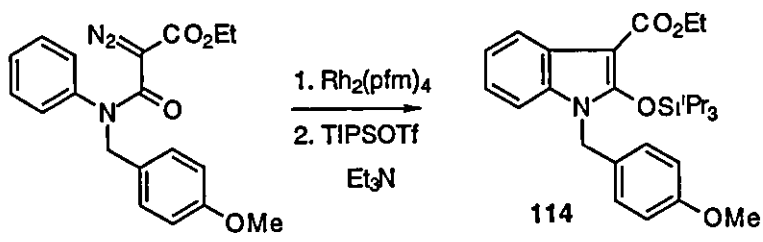
Rhodium Catalysed Competition Reactions of Diazoamides 101-103

Rhodium Catalysed Decomposition of **101**



A solution of diazoamide **101** (1.0 g, 2.83 mmol) in dry dichloromethane (20 ml) was added to a stirred suspension of $Rh_2(OAc)_4$ (0.114 g, 9 mol%) in dry dichloromethane (30 ml) and the mixture stirred at room temperature for 40 h, then refluxed until all the diazoamide had been consumed (about 1 h). The resulting multicomponent mixture was preadsorbed on silica and subjected to flash silica gel chromatography to give (i) trans *ethyl 4-(4-methoxyphenyl)-2-oxo-1-phenylazetidine-3-carboxylate* **104** (0.252 g, 27%) as a yellow oil; (Found: M^+, 325.1334. $C_{19}H_{19}NO_4$ requires 325.1314); ν_{max}(neat)/cm^{-1} 2982, 2935, 2838, 1764, 1730, 1515, and 1250; δ_H (250 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz), 3.80 (3H, s), 3.95 (1H, d, *J* 2.6 Hz), 4.28 (2H, q, *J* 7.1 Hz), 5.27 (1H, d, *J* 2.6 Hz), 6.94-6.87 (2H, m), 7.10-7.01 (1H, m), 7.35-7.20 (6H, m); δ_C (100.6

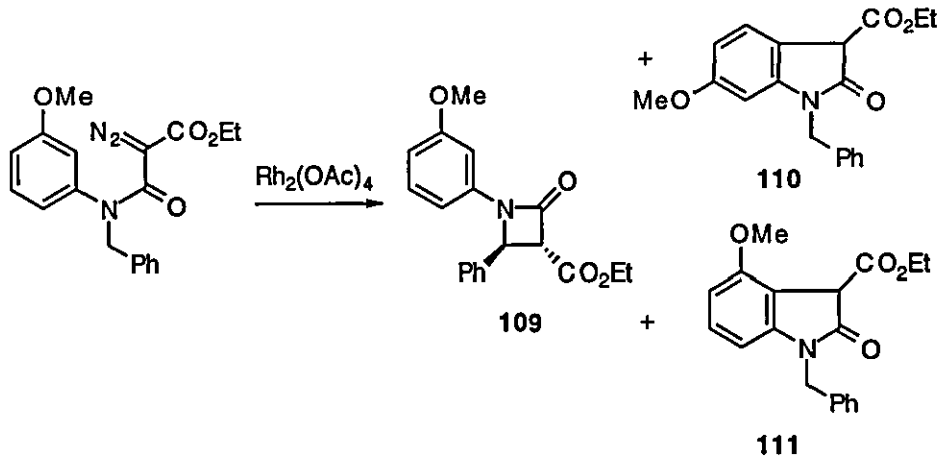
MHz; $CDCl_3$) 14.18 (CH_3), 55.35 (CH), 57.37 (CH), 62.06 (CH_2), 63.70 (CH_3), 114.69 (CH), 117.23 (CH), 124.33 (CH), 127.54 (CH), 128.13 (C), 129.07 (CH), 137.23 (C), 159.41 (C), 160.13 (C=O), and 166.41 (C=O); *m/z* 326 (MH^+), 325 (M^+), 206 (100%), 178(9), 161 (60), 134 (37), 91 (17), and 77(33); and (ii) *ethyl 6-methoxy-3-oxo-2-phenyl-1,2,3,3a-tetrahydrocyclohepta[c]pyrrole-3a-carboxylate* **105** (0.043g, 5%) as colourless crystals after trituration (light petroleum/diethyl ether) and recrystallisation (diethyl ether) of certain mixed fractions from the column, m.p. 110-112°C, (Found: M^+, 325.1314. $C_{19}H_{19}NO_4$ requires 325.1314); ν_{max} (CH_2Cl_2)/cm^{-1} 1745, 1706, 1403, 1235, and 1222; δ_H (250 MHz; $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz), 3.63 (3H, s), 4.25-4.00 (2H, m), 4.56 (1H, dd, *J* 14.1 and 1.6 Hz), 4.84 (1H, dq, *J* 14.1, 2.3, and 0.7 Hz), 5.70 (1H, dd, *J* 7.3 and 1.6 Hz), 5.84 (1H, d, *J* 10.5 Hz), 6.30 (1H, td, *J* 7.3 and 2.1 Hz), 6.35 (1H, dd, *J* 10.5 and 2.1 Hz), and 7.75-7.15 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 13.99 (CH_3), 52.00 (CH_2), 54.87 (CH_3), 60.70 (C), 61.97 (CH_2), 101.57 (CH), 119.11 (CH), 120.34 (CH), 123.36 (C), 124.39 (CH), 125.37 (CH), 126.43 (CH), 129.06 (CH), 138.56 (C), 159.19 (C), 168.98 (C=O), and 170.06 (C=O); *m/z* 326 (MH^+), 325 (M^+), 252 (100%), and 77 (19).



114

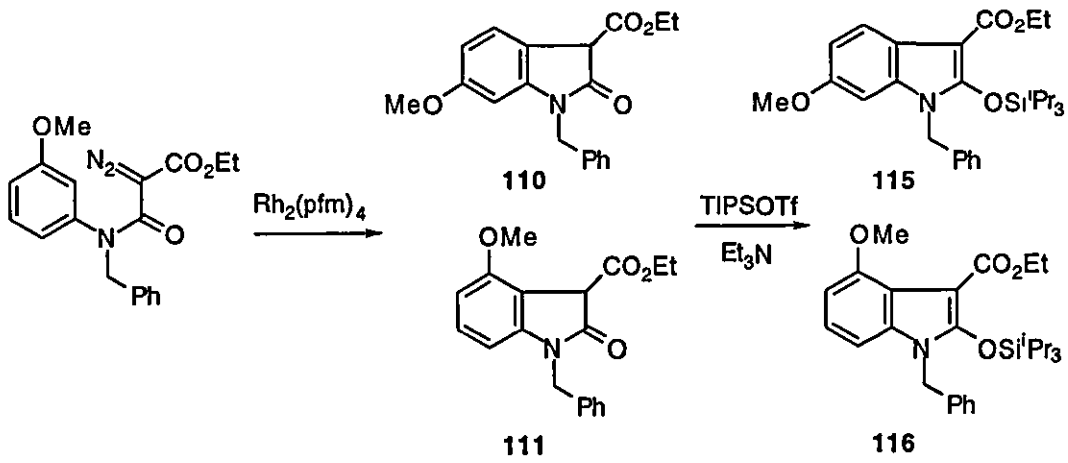
A solution of diazoamide **101** (0.230 g, 0.651 mmol) in dry dichloromethane (5 ml) was added to a stirred suspension of rhodium(II) perfluorobutyramide (0.014 g, 2 mol%) in dry dichloromethane (8 ml) and stirring was maintained for 70 minutes. The reaction mixture was then treated with triethylamine (0.11 ml, 0.78 mmol) and TIPSOTf (0.20 ml, 0.70 mmol); after 0.5 h it was washed with water (2 x 20 ml), dried over $MgSO_4$ and preadsorbed on silica before subjecting to flash silica gel chromatography to yield, after recrystallisation, *ethyl 1-(4-methoxybenzyl)-2-triisopropylsiloxyindole-3-carboxylate* **114** (0.286 g, 91%) as colourless plates, m.p. 122-124°C (light petroleum/diethyl ether); (Found: M^+, 481.2655. $C_{28}H_{39}NO_4Si$ requires 481.2653); ν_{max}(CH_2Cl_2)/cm^{-1} 2956, 2870, 1693, 1541, and 1142; δ_H (250 MHz; $CDCl_3$) 1.09 (18H, d, *J* 7.5 Hz), 1.43 (3H, t, *J* 7.1Hz), 1.50 (3H, h, 7.5 Hz), 3.74 (3H, s), 4.37 (2H, q, *J* 7.1 Hz), 5.21 (2H, s), 6.81-6.76 (2H, m), 7.20-6.95 (5H, m), and 8.01 (1H, d, *J* 7.5 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.35 (CH_3), 14.76 (CH), 17.96 (CH_3), 44.22 (CH_2), 55.22 (CH_3), 59.09 (CH_2), 89.17 (C), 109.36 (CH), 114.07 (CH), 120.82 (CH), 121.13 (CH), 121.67 (CH), 125.30 (C), 127.50, 128.37 (C), 130.90 (C), 153.20 (C), 158.87 (C), and 164.90 (C); *m/z* 482 (MH^+), 481 (M^+), 438 (25%), 121 (100), 73 (7), and 28 (27).

Rhodium Catalysed Decomposition of **102**



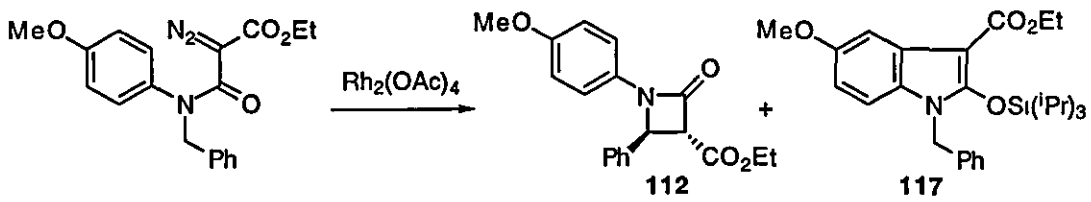
A solution of diazoamide **102** (0.432 g, 1.22 mmol) in dry dichloromethane (80 ml) was treated with $Rh_2(OAc)_4$ (0.022 g, 4 mol%) and the mixture stirred at room temperature for 23 h. Analysis of the 1H-NMR spectrum of the crude reaction mixture showed a combination of trans *ethyl 1-(3-methoxyphenyl)-2-oxo-4-phenylazetidine-3-carboxylate* **109** (36%) and the isomeric oxindoles: *ethyl 1-benzyl-6-methoxy-2-oxindole-3-carboxylate* **110** (48%); δ_H (250 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz), 3.72 (3H, s), 4.25 (2H, m), 4.45 (1H, d, J 0.9 Hz), 4.79 (1H, d, J 15.7 Hz), 5.035 (1H, d, J 15.7 Hz), 6.295 (1H, d, *J* 2.3 Hz), 6.53 (1H, dd, *J* 2.3 and 8.3 Hz), and 7.35-7.15 (6H, m); and *ethyl 1-benzyl-4-methoxy-2-oxindole-3-carboxylate* **111** (16%); δ_H (250 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz), 3.83 (3H, s), 4.25 (2H, m), 4.49 (1H, s), 4.815 (1H, d, J 15.8 Hz), 5.00 (1H, d, J 15.8 Hz), 6.37 (1H, d, *J* 7.9 Hz), 6.60 (1H, d, *J* 8.4 Hz), and 7.35-7.15 (6H, m). The mixture was then preadsorbed onto silica and subjected to flash silica gel chromatography. This yielded pure trans *ethyl 1-(3-methoxyphenyl)-2-oxo-4-phenylazetidine-3-carboxylate* **109** (0.121 g, 27%) as colourless crystals, m.p. 130-132°C (light petroleum/diethyl ether); (Found: M^+, 325.1321. $C_{19}H_{19}NO_4$ requires 325.1314); ν_{max} (CH_2Cl_2)/cm^{-1} 1767, 1732, 1603, and1496; δ_H (400 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.2 Hz), 3.72 (3H, s), 3.96 (1H, d, *J* 2.65 Hz), 4.28 (2H, q, *J* 7.2 Hz), 5.30 (1H, d, *J* 2.65 Hz), 7.20-6.55 (4H, m), and 7.50-7.30 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 14.18 (CH_3), 55.27 (OCH_3), 57.74 (CH), 62.11 (OCH_2), 63.54 (CH), 103.18 (CH), 109.38 (CH), 110.37 (CH), 126.18 (CH), 129.04 (CH), 129.32 (CH), 129.92 (CH), 136.34 (C), 138.28 (C), 159.34 (C), 160.14 (C), and 166.25 (C); *m/z* 325 (M^+, 12%), 149 (100), 131 (26), 77 (19), and 28 (62).

Rhodium(II) trifluoroacetate catalysed decomposition of **102** in refluxing dichloromethane for 1 h gave complete conversion to a mixture of **109**, **110**, and **111** in a ratio of 4:72:24 (as determined by ^1H NMR spectroscopy of the mixture).

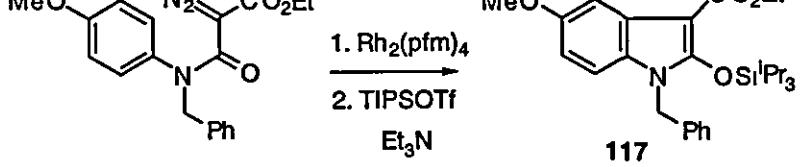


A solution of diazoamide **102** (0.200 g, 0.566 mmol) in dry dichloromethane (6 ml) was added to a suspension of rhodium(II) perfluorobutyramide (0.012 g, 2 mol%) in dry dichloromethane (7 ml) and the mixture stirred at room temperature for 2 h. Analysis of the ^{1}H-NMR spectrum of the resulting mixture revealed a clean mixture of the isomeric oxindoles: *ethyl 1-benzyl-6-methoxy-2-oxindole-3-carboxylate* **110** (73%), and *ethyl 1-benzyl-4-methoxy-2-oxindole-3-carboxylate* **111** (27%) (data as above). This oxindole mixture was treated with triethylamine (0.10 ml, 0.68 mmol) and TIPSOTf (0.191 g, 0.623 mmol), washed with water (2 x 20 ml), preadsorbed onto silica and subjected to flash silica gel chromatography to give *ethyl 1-benzyl-6-methoxy-2-triisopropylsiloxyindole-3-carboxylate* **115** (0.166 g, 63%), m.p. 93-95°C; (Found: M$^+$, 481.2625. $C_{28}H_{39}NO_4Si$ requires 481.2648); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 2945, 2867, 1696, 1547, and 1112; δ_H (250 MHz; $CDCl_3$) 1.07 (18H, d, *J* 7.5 Hz), 1.43 (3H, t, *J* 7.1 Hz), 1.46 (3H, h, *J* 7.5 Hz), 3.74 (3H, s), 4.36 (2H, q, *J* 7.1 Hz), 5.22 (2H, s), 6.535 (1H, d, *J* 2.3 Hz), 7.30-6.75 (6H, m), and 7.89 (1H, d, *J* 8.7 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.33 (CH_3), 14.75 (CH), 17.93 (CH_3), 44.76 (CH_2), 55.68 (CH_3), 59.06 (CH_2), 88.80 (C), 94.69 (CH), 109.45 (CH), 119.05 (C), 121.56 (CH), 126.23 (CH), 127.43 (CH), 128.71 (CH), 131.71 (C), 136.25 (C), 152.74 (C), 155.60 (C), and 164.83 (C); *m/z* 482 (MH$^+$), 481 (M$^+$), 438 (70), 155 (7), 91 (12), 51(14), 28 (100); and *ethyl 1-benzyl-4-methoxy-2-triisopropylsiloxyindole-3-carboxylate* **116** (0.062g, 21%), m.p. 95-96°C (*n*-pentane); (Found: M$^+$, 481.2653. $C_{28}H_{39}NO_4Si$ requires 481.2648); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 2945, 2867, 1690, 1547, and 1452; δ_H (250 MHz; $CDCl_3$) 1.06 (18H, d, *J* 7.5 Hz), 1.40 (3H, t, *J* 7.1 Hz) 1.44 (3H, h, *J* 7.5 Hz), 3.90 (3H, s), 4.35 (2H, q, *J* 7.1 Hz), 5.24 (2H, s), 6.68-6.60 (2H, m), and 7.30-6.95 (6H, m); δ_C (100.6 MHz; $CDCl_3$) 14.09 (CH_3), 14.62 (CH), 17.91 (CH_3), 44.97 (CH_2), 55.48 (CH_3), 59.82 (CH_2), 89.77 (C), 102.88 (CH), 103.27 (CH), 113.88 (C), 121.86 (CH), 126.20 (CH), 127.31 (CH), 128.63 (CH), 132.39 (C), 136.54 (C), 150.35 (C), 152.89 (C), and 165.58 (C); *m/z* 482 (MH$^+$), 481 (M$^+$), 438 (20%), 155 (23), 113 (25), 51(64), 32(100).

Rhodium Catalysed Decomposition of **103**



A solution of the diazoamide **103** (0.50 g, 1.415 mmol) in benzene (18 ml) was added to a suspension of $Rh_2(OAc)_4$ (0.013 g, 2 mol%) in benzene (13 ml). The mixture was heated under reflux for 1 h then concentrated under reduced pressure, redissolved in dichloromethane (30 ml), treated with triethylamine (0.25 ml, 1.79 mmol) and TIPSOTf (0.40 ml, 1.49 mmol) and stirred for 1.5 h. This mixture was then washed with water (2 x 30 ml), dried over $MgSO_4$ and preadsorbed onto silica. The multicomponent mixture was thus subjected to flash silica gel chromatography and this yielded (i) trans *ethyl 1-(4-methoxyphenyl)-2-oxo-4-phenylazetidine-3-carboxylate* **112** (0.096 g, 21%) as a light yellow oil; (Found: M^+, 325.1310. $C_{19}H_{19}NO_4$ requires 325.1314); ν_{max}(neat)/cm^{-1} 1927, 1761, 1732, 1514, and 1248; δ_H (250 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz), 3.74 (3H, s), 3.95 (1H, d, *J* 2.6 Hz), 4.29 (2H, q, *J* 7.1 Hz), 5.28 (1H, d, *J* 2.6 Hz), 6.81-6.75 (2H, m), 7.25-7.20 (2H, m), and 7.40-7.28 (5H, m); δ_C(62.9 MHz; $CDCl_3$) 14.10 (CH_3), 55.35 (OCH_3), 57.52 (CH), 61.98 (CH_2), 63.45 (CH), 114.26 (CH), 118.48 (CH), 126.15 (CH), 128.92 (CH), 129.20 (CH), 130.63 (C), 136.33 (C), 156.30 (C), 158.65 (C), and 166.38 (C); *m/z* 325 (M^+, 43%), 149 (100), 103 (52), and 77 (42); and (ii) *ethyl 1-benzyl-5-methoxy-2-triisopropylsiloxyindole-3-carboxylate* **117** (0.085 g, 13%) as a pale yellow, oily solid which characterised as detailed below.

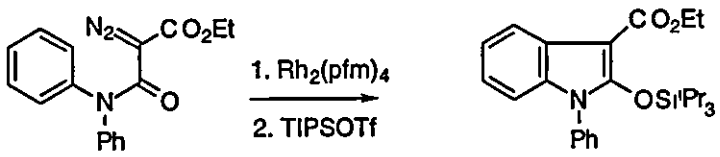


A solution of the diazoamide **103** (0.200 g, 0.566 mmol) in dichloromethane (5 ml) was added to a suspension of rhodium(II) perfluorobutyramide (0.012 g, 2 mol %) in dichloromethane (7 ml) and the mixture stirred for 0.75 h at room temperature. Treatment with triethylamine (0.10 ml, 0.718 mmol) and TIPSOTf (0.17 ml, 0.632 mmol), aqueous workup and flash silica gel chromatography in the standard manner yielded *ethyl 1-benzyl-5-methoxy-2-triisopropylsiloxyindole-3-carboxylate* **117** (0.248 g, 91%) as a colourless oil which crystallised to give a low melting solid, m.p. 59-62°C; (Found: M^+, 481.2655. $C_{28}H_{39}NO_4Si$ requires 481.2648); ν_{max} (neat)/cm^{-1} 2945, 2867, 1695, 1535;

δ_H (250 MHz; $CDCl_3$) 1.08 (18H, d, *J* 7.5 Hz), 1.44 (3H, t, *J* 7.1 Hz), 1.47 (3H, h, *J* 7.5 Hz), 3.84 (3H, s), 4.37 (2H, q, *J* 7.1 Hz), 5.25 (2H, s), 6.68 (1H, dd, *J* 2.6 and 8.7 Hz), 6.89 (1H, d, *J* 8.7 Hz), 7.10-7.02 (2H, m), 7.30-7.20 (3H, m), and 7.60 (1H, d, *J* 2.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.34 (CH_3), 14.78 (CH), 17.94 (CH_3), 44.89 (NCH_2), 55.72 (OCH_3), 59.04 (OCH_2), 89.44 (C), 104.42 (CH), 109.85 (CH), 110.02 (CH), 125.74 (C), 126.21 (CH), 127.44 (CH), 128.72 (CH), 136.41 (C), 153.33 (C), 155.69 (C), and 164.83 (C); *m/z* 481 (M^+), 438 (28%), 91 (28), 28 (100).

Similarly, treatment of diazoamide **103** (0.250 g, 0.707 mmol) with $Rh_2(NHCOCF_3)_4$ (0.096 g, 2 mol %) gave *ethyl 1-benzyl-5-methoxy-2-triisopropylsiloxyindole-3-carboxylate* **117** (0.317 g, 93%) after derivatisation of the intermediate oxindole, work up and purification.

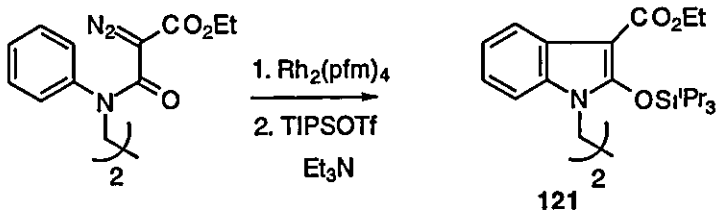
Rhodium Catalysed Decomposition of **118**



119

A solution of the diazoamide **118** (0.092 g, 0.297 mmol) in dry dichloromethane (2 ml) was added to a suspension of rhodium(II) perfluorobutyramide (0.006 g, 2 mol%) in dry dichloromethane (4 ml) and the mixture stirred at room temperature for 2 h. Then triethylamine (0.05 ml, 0.356 mmol) and TIPSOTf (0.100 g, 0.327 mmol) were added and the mixture stirred for a further 30 minutes. The reaction mixture was then washed with water (2x10 ml), dried over $MgSO_4$, preadsorbed onto silica and subjected to flash silica gel column chromatography to give the *ethyl 1-phenyl-2-triisopropylsiloxyindole-3-carboxylate* **119** (0.069 g, 53%) as a colourless solid, m.p. 92-94°C (*n*-pentane); (Found: M^+, 437.2340. $C_{26}H_{35}NO_3Si$ requires 437.2386); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2946, 2868, 1699, 1549, and 1421; δ_H (250 MHz; $CDCl_3$) 0.93 (18H, d, *J* 6.8 Hz), 1.10 (3H, h, *J* 6.8 Hz), 1.44 (3H, t, *J* 7.0 Hz), 4.40 (2H, q, *J* 7.0 Hz), 7.00-6.96 (1H, m), 7.09 (1H, m) 7.20 (1H, m), 7.55-7.37 (5H, m), and 8.07 (1H, dd, *J* 1.05 and 8.3 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.30 (CH_3), 15.17 (CH), 18.14 (CH_3), 59.50 (CH_2), 90.76 (C), 109.88 (CH), 121.22 (CH), 121.80 (CH), 122.40 (CH), 125.63 (C), 128.85 (CH), 129.78 (CH), 132.69 (C), 135.60 (C), 153.44 (C), and 165.22 (C); *m/z* 437 (1%), 394 (100), 366 (24), 119 (45), and 59 (40).

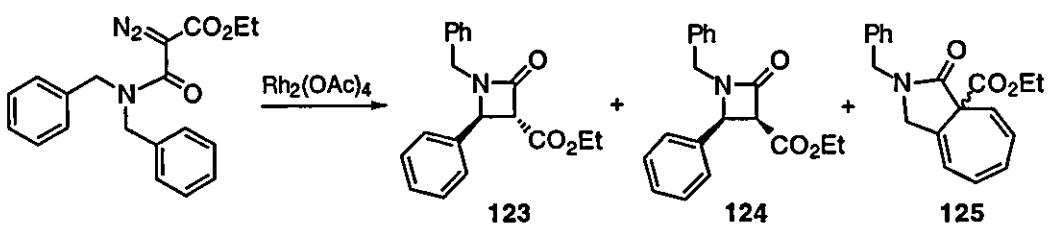
Rhodium Catalysed Decomposition of **120**



121

A solution of ethyl 2-diazo-3-({2-[(2-diazo-3-ethoxy-3-oxopropanoyl)-anilino]ethyl}-anilino)-3-oxopropanoate **120** (0.20 g, 0.406 mmol) in dry dichloromethane (4 ml) was added to a suspension of rhodium(II) perfluorobutyramide (0.009 g, 2 mol%) in dry dichloromethane (5 ml) and the mixture stirred at room temperature for 30 minutes. Then triethylamine (0.136 ml, 0.97 mmol) and TIPSOTf (0.274 g, 0.89 mmol) were added and the mixture stirred for a further 15 minutes. The reaction mixture was then washed with water (2 x 15 ml), dried over Na_2SO_4, preadsorbed onto silica and subjected to flash silica gel chromatography to give *ethyl 1-(2-{ethoxycarbonyl)-2-[(1,1,1-triisopropylsilyl)oxy]-1*H*-1-indolyl}ethyl)-2-[1,1,1-triisopropylsilyl)oxy]-1*H*-3-indolecarboxylate* **121** (0.276 g, 91%) as colourless crystals after one recrystallisation from light petroleum-diethyl ether, m.p. 142-144°C; (Found: M^+, 748.4300. $C_{42}H_{64}N_2O_6Si_2$ requires 748.4300); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2949, 2869, 1693, 1545, and 1470; δ_H (250 MHz; $CDCl_3$) 1.08 (36H, d, *J* 7.5 Hz), 1.40 (6H, t, *J* 7.2 Hz), 1.43 (6H, h, *J* 7.5 Hz), 4.32 (4H, q, *J* 7.2 Hz); 4.36 (4H, s), 6.66 (2H, d, *J* 8.0 Hz), 7.08 (2H, dt, *J* 1.6 and 7.6 Hz), and 7.91 (2H, d, *J* 7.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.24 (CH_3), 14.76 (CH), 17.92 (CH_3), 40.85 (CH_2), 58.98 (CH_2), 90.41 (C), 108.00 (CH), 121.00 (CH), 121.20 (CH), 121.72 (CH), 125.31 (C), 130.46 (C), 152.75 (C), and 164.59 (C); *m/z* 748 (M^+), 705 (100%), 186 (12), 87 (21), 73 (30), and 59 (56).

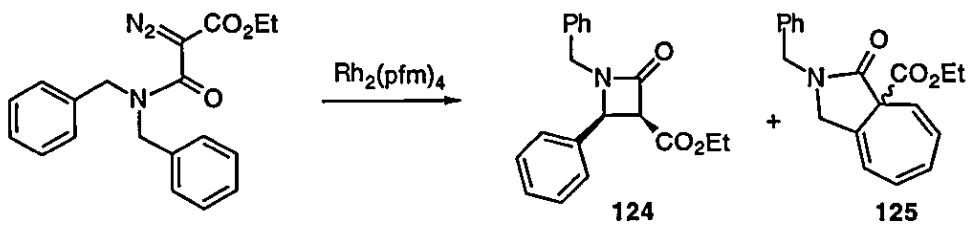
Rhodium Catalysed Decomposition of **122**



123 **124** **125**

A solution of the diazoamide **122** (0.125 g, 0.371 mmol) in dry dichloromethane (4 ml) was added to a suspension of $Rh_2(OAc)_4$ (0.003 g, 2 mol%) in dry dichloromethane (4 ml) and the mixture stirred at room temperature for 22 h. A further 4 mol% (0.007g) of

$Rh_2(OAc)_4$ was then added and the mixture refluxed for 2 h until all the starting diazoamide was consumed. Analysis of the NMR spectra of the resulting crude mixture showed 3 significant components which were separated by subjecting the mixture to flash silica gel chromatography. Thus were isolated (i) trans *ethyl 1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate* **123** (0.034 g, 39%) as a colourless oil; ν_{max} (neat)/cm^{-1} 2984, 1770, 1732, and 1194; (Found: M^+, 309.1343. $C_{19}H_{19}NO_3$ requires 309.1365); δ_H (250 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz), 3.83 (1H, AB, *J* 15.2 Hz), 3.91 (1H, d, *J* 2.2 Hz), 4.25 (2H, q, *J* 7.1 Hz), 4.70 (1H, d, *J* 2.2 Hz), 4.87 (1H, AB, *J* 15.2 Hz), and 7.40-7.15 (10H, m); δ_C (100.6 MHz; $CDCl_3$) 14.13 (CH_3), 44.88 (CH_3), 57.13 (CH), 61.79 (CH_2), 63.54 (CH), 126.80 (CH), 127.84 (CH), 128.28 (CH), 128.79 (CH), 129.03 (CH), 129.13 (CH), 134.75 (C), 136.08 (C), 162.40 (C), and 166.79 (C); *m/z* 309 (M^+, 2%), 176 (68), 103 (45), 91 (100), and 77 (39); (ii) cis *ethyl 1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate* **124** (28% from ^1H NMR) as a colourless oil, and (iii) *ethyl 2-benzyl-3-oxo-1,2,3,3a-tetrahydrocyclohepta[c]pyrrole-3a-carboxylate* **125** (0.023 g, 22%) as a crystalline solid and these latter two compounds were characterised as detailed below.

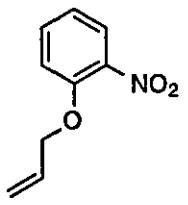


A solution of the diazoamide **122** (0.100 g, 0.296 mmol) in dry dichloromethane (2.1 ml) was added to a suspension of rhodium(II) perfluorobutyramide (0.006 g, 2 mol%) in dry dichloromethane (4.2 ml). The mixture was stirred at room temperature for 18 h, then preadsorbed onto silica and subjected to flash silica gel chromatography (1:1 light petroleum:diethyl ether) to give (i) cis *ethyl 1-benzyl-2-oxo-4-phenylazetidine-3-carboxylate* **124** (0.011g, 12%) as a colourless oil; ν_{max}(neat)/cm^{-1} 1770, 1732, and 1185; (Found: M^+, 309.1365. $C_{19}H_{19}NO_3$ requires 309.1365); δ_H (250 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7.1 Hz), 3.78 (2H, m), 3.94 (1H, d, *J* 14.9 Hz), 4.31 (1H, d, *J* 6.05 Hz), 4.72 (1H, d, *J* 6.05 Hz), 4.94 (1H, d, *J* 14.9 Hz), and 7.39-7.10 (10H, m); δ_C (100.6 MHz; $CDCl_3$) 13.65 (CH_3), 44.97 (CH_2), 56.83 (CH), 60.70 (CH), 61.11 (CH_2), 127.35 (CH), 127.99 (CH), 128.59 (CH), 128.62 (CH), 128.81 (CH), 128.89 (CH), 133.75 (C), 134.87 (C), 162.79 (C), and 165.68 (C); *m/z* 309 (M^+, 2%), 176 (96), 131 (100), and 91 (75); (ii) *ethyl 2-benzyl-3-oxo-1,2,3,3a-tetrahydrocyclohepta[c]pyrrole-3a-carboxylate* **125** (0.064 g, 70%) as colourless crystals, m.p. 92-94°C, (Found: C, 73.58; H, 6.04; N, 4.76. $C_{19}H_{19}NO_3$ requires C, 73.77; H, 6.19; N, 4.53); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1746, 1699, and 1205; δ_H (250 MHz; $CDCl_3$) 1.15 (3H, t, *J* 7.1 Hz), 4.00 (1H, dd, *J* 14.95, and 1.5

Hz), 4.07 (2H, m), 4.27 (1H, dd, *J* 14.95 and 2.2 Hz), 4.44 (1H, d, *J* 14.85 Hz), 4.79 (1H, d, *J* 14.85 Hz), 5.68-5.60 (1H, m), 6.25-6.20 (1H, m), 6.50-6.40 (3H, m), and 7.36-7.22 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 14.03 (CH_3), 46.83 (CH_2), 50.26 (CH_2), 59.99 (C), 61.77 (CH_2), 120.58 (CH), 122.51 (CH), 127.85 (CH), 128.01 (CH), 128.12 (CH), 128.40 (CH), 128.81 (CH), 129.93 (CH), 130.56 (C), 135.61 (C), 167.77 (C), and 171.10 (C); *m/z* 309 (M^+), 236 (34), and 91 (100); and .

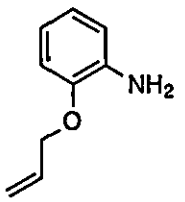
Preparation of Diazoamide Precursors 132 and 133 for 4-Way Competition Carbenoid Reactions

***O*-Allyl-2-nitrophenol 134**



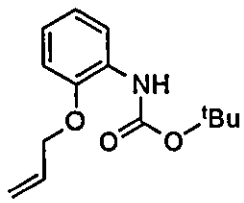
2-Aminophenol (10.0 g, 72 mmol) and potassium carbonate (10.0 g, 72 mmol) were suspended in distilled acetone (50 ml) and treated with allyl bromide (8.7 g, 72 mmol). The mixture was refluxed for 18 h and, after allowing to cool to room temperature, water (100 ml) was added before the mixture extracted with ether (100, 50, 50 ml). The ether extracts were combined and washed with 10% aqueous sodium hydroxide (2 x 50 ml) and then with saturated brine (50 ml). The resulting solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *O-allyl-2-nitrophenol* **134** (12.9 g, 99%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 3085, 2929, 2873, 1608, 1584, 1530, 1487, 1352. 1280, 994, 858, and 745; δ_H (250 MHz; $CDCl_3$) 4.69 (2H, m), 5.29-5.55 (2H, m), 5.95-6.12 (1H, m), 6.98-7.10 (2H, m), 7.51 (1H, m), and 7.83 (1H, dd, *J* 8.1 and 1.8 Hz); δ_C (62.9 MHz; $CDCl_3$) 69.90 (CH_2), 114.81 (CH), 118.23 (CH_2), 120.39 (CH), 125.56 (CH), 131.63 (CH), and 133.95 (CH); *m/z* 179 (M^+, 4%), 139 (2), 123 (32), 106 (15), and 41 (100).

O-Allyl-2-aminophenol 135



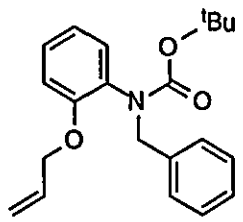
Following an adaptation of the method of Echavarren[63], *O*-allyl-2-nitrophenol **134** (2.0 g, 11.2 mmol) was reduced to, give after Kughelrohr distillation, O-*allyl-2-aminophenol* **135** (1.25 g, 75%) as a yellow oil; b.p. 130-135°C/10mmHg (lit.:[171] 129-130°C/10mmHg); (Found: M^+, 149.0842. $C_9H_{11}NO$ requires 149.0841); ν_{max} (film)/cm^{-1} 3465, 3375, 1615, 1506, 1277, 1219, 998, 929, and 741; δ_H (250 MHz; $CDCl_3$) 3.81 (2H, br.s.), 4.55 (2H, m), 5.20-5.50 (2H, m), 6.00-6.20 (1H, m), and 6.65-6.85 (4H, m); *m/z* 149 (M^+, 33%), 108 (100), 80 (80), and 53 (18).

***tert*-Butyl *N*-[2-(allyloxy)phenyl]carbamate 136**



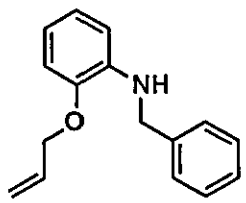
A solution of the aniline **135** (1.61 g, 10.80 mmol) and di-*tert*butyl dicarbonate (2.59 g, 11.88 mmol) in THF (11 ml) was refluxed for 2.75 h. The THF was removed under reduced pressure, and the residue taken up in EtOAc (30 ml), washed with citric acid solution (1M; 2x30 ml) and then with saturated brine (30 ml). After drying (Na_2SO_4), filtration, removal of solvent and flash silica gel column chromatography (19:1 then 9:1 light petroleum:EtOAc) tert-*butyl* N-*[2-(allyloxy)phenyl]-carbamate* **136** (2.67 g, 99%) was isolated as a colourless oil; (Found: M^+, 249.1366 $C_{14}H_{19}NO_3$ requires 249.1365); ν_{max} (film)/cm^{-1} 3441, 2979, 1730, 1603, 1520, 1480, 1450, 1368, 1235, 1156, 1048, 1024, and 745; δ_H (400 MHz; $CDCl_3$) 1.53 (9H, m), 4.56-4.62 (2H, m), 5.28-5.42 (2H, m), 6.00-6.20 (1H, m), 6.80-7.10 (4H, m), and 8.07 (1H, br.s.); δ_C (100.6 MHz; $CDCl_3$) 28.35 (CH_3), 80.30 (C), 111.29 (CH), 118.05 (CH_2), 118.16 (CH), 121.26 (CH), 122.17 (CH), 128.30 (C), 133.01 (CH), 146.40 (C), and 152.75 (C); *m/z* 249 (M^+, 11%), 193 (35), 152 (22), 108 (100), 57 (95), and 41 (49).

tert-Butyl _N_-[2-(allyloxy)phenyl]-_N_-benzyl-carbamate 137



A solution of carbamate **136** (2.60 g, 10.44 mmol) in DMF (25 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil; 0.47 g, 11.71 mmol) in DMF (25 ml) whilst cooling in an ice bath, and the resulting mixture was stirred for 0.25 h, then treated with benzyl bromide (1.82 g, 10.64 mmol). After stirring for a further 5 h, the mixture was poured into water (250 ml) and extracted with ether (250 ml). The ether layer was washed with water (3x50 ml). All the aqueous washes were combined and extracted with ether (200 ml). The ether extracts were combined and washed with saturated brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude product as a pale yellow oil. Flash silica gel column chromatography afforded tert-*butyl* N-*[2-(allyloxy)phenyl]*-N-*benzylcarbamate* **137** (2.97 g, 84%) as a viscous, colourless oil; (Found: M^+, 339.1834. $C_{21}H_{25}NO_3$ requires 339.1834); ν_{max} (film)/cm^{-1} 3067, 2979, 2932, 1791, 1748, 1694, 1503, 847, and 751; δ_H (250 MHz; 50°C; $CDCl_3$) 1.58 (9H, m), 4.47 (2H, m), 4.70 (2H, br.s.), 5.20-5.40 (2H, m), 5.85-6.05 (1H, m), 6.70-7.00 (3H, m), and 7.05-7.30 (6H, m); δ_C (62.9 MHz; $CDCl_3$) 28.76 (CH_3), 53.31 (NCH_2), 69.18 (CH_2), 80.04 (C), 112.92 (CH), 117.50 (CH_2), 120.74 (CH), 127.34 (CH), 128.25 (CH), 128.47 (CH), 128.94 (CH), 129.99 (CH), 133.44 (CH), 138.84 (C), 154.45 (C), and 156.00 (C); *m/z* 339 (M^+, 10%), 198 (94), 91 (89), 57 (100), and 41 (47).

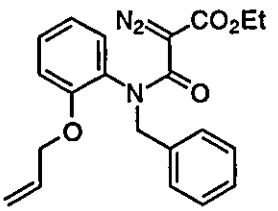
_N_-[2-(allyloxy)phenyl]-_N_-benzylamine 138



An ice bath cooled solution of the carbamate **137** (2.155 g, 2.38 mmol) in dichloromethane (15 ml) was treated with trifluoroacetic acid (15 ml). The mixture was stirred at room temperature for 42 h then concentrated under reduced pressure, diluted with dichloromethane (50 ml) and washed with sodium hydroxide solution (2M; 50 ml). The aqueous layer was extracted with dichloromethane (50 ml); the organic extracts were combined and washed with water (50 ml), and saturated brine (50 ml), then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a colourless oil

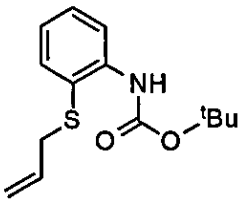
which solidified on standing and was found to be essentially pure N-*[2-(allyloxy)phenyl]*-N-*benzylamine* **138** (2.061 g, 94%); (Found: M^+, 239.1310 $C_{16}H_{17}NO$ requires 239.1310); ν_{max} (film)/cm^{-1} 3424, 3065, 3029, 2923, 2864, 1676, 1602, 1509, 1202, and 1128; δ_H (250 MHz; $CDCl_3$) 4.36 (2H, s), 4.57 (2H, d, *J* 5.4 Hz), 4.68 (1H, br.s.), 5.22-5.43 (2H, m), 5.98-6.15 (1H, m), 6.56-6.67 (2H, m), 6.76-6.87 (2H, m), and 7.20-7.40 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 49.96 (NCH_2), 69.86 (CH_2), 111.89 (CH), 113.83 (CH), 118.27 (CH_2), 119.95 (CH), 122.00 (CH), 128.02 (CH), 128.39 (CH), 129.04 (CH), 133.58 (CH), 135.71 (C), 138.08 (C), and 147.29 (C); *m/z* 239 (M^+, 16%), 198 (54), 120 (6), and 91 (100).

Ethyl 3-[2-(allyloxy)(benzyl)anilino]-2-diazo-3-oxopropanaote 132



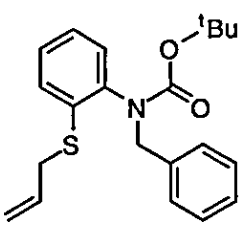
The standard method was adopted to condense ethyl diazoacetate (0.468 g, 2.65 mmol) and aniline **138** (0.629 g, 2.65 mmol) to give some recovered aniline (8%) along with the desired *ethyl 3-[2-(allyloxy)(benzyl)anilino]-2-diazo-3-oxopropanaote* **132** (0.880 g, 88%) as a yellow oil; (Found: C, 66.47; H, 5.95; N, 10.92. $C_{21}H_{21}N_3O_4$ requires C, 66.47; H, 5.57; N, 11.07); (Found: M^+, 379.1532. $C_{21}H_{21}N_3O_4$ requires 379.1532); ν_{max} (CH_2Cl_2)/cm^{-1} 3000, 2121, 1720, 1684, 1648, 1606, 1499, 1390, 1306, 1110, and 1019; δ_H (250 MHz; $CDCl_3$) 1.15 (3H, t, *J* 7.1 Hz), 4.06 (2H, q, *J* 7.1 Hz), 4.40 (2H, br. s.), 4.90 (2H, br.s.), 5.20-5.40 (2H, m), 5.81-6.00 (1H, m), 6.80-6.90 (2H, m), 6.97-7.03 (1H, m), and 7.15-7.27 (6H, m); δ_C (100.6 MHz; $CDCl_3$) 14.29 (CH_3), 53.17 (NCH_2), 61.18 (OCH_2), 69.14 (OCH_2), 113.06 (CH), 117.7 (CH_2), 120.97 (CH), 127.33 (CH), 128.11 (CH), 129.11 (CH), 129.65 (CH), 130.27 (C), 132.46 (CH), 136.90 (C), 153.58 (C), 161.84 (C=O), and 162.49 (C=O); *m/z* 379 (M^+, 2%), 351 ($M-N_2^+$, 1), 264 (11), 238 (13), and 91 (100).

tert-Butyl _N_-[2-(allylsulfanyl)phenyl]-carbamate 140



A solution of the _S_-allyl-2-aminothiopenol **139** (~1.78 g, 12.00 mmol) and di-_tert_-butyl dicarbonate (2.94 g, 13.5 mmol) in THF (12 ml) was refluxed for 4 h. After addition of more di-_tert_-butyldicarbonate (1.00 g) the mixture was heated for a further 1 h. The THF was removed under reduced pressure, and the residue subjected to flash silica gel column chromatography (19:1 then 9:1 light petroleum:EtOAc) to give tert-_butyl_ N-_[2-(allylsulfanyl)phenyl]-carbamate_ **140** (2.62 g, 82%) as a colourless oil; (Found: M^+, 265.1140 $C_{14}H_{19}NO_2S$ requires 265.1136); ν_{max}(film)/cm^{-1} 3365, 2976, 1732, 1579, 1508, 1423, 1242, 1156 and 753; δ_H (250 MHz; $CDCl_3$) 1.53 (9H, s), 3.34 (2H, d, _J_ 7.3 Hz), 4.85-5.02 (2H, m), 5.71-5.90 (1H, m), 6.91-6.99 (1H, m), 7.25-7.35 (1H, m), 7.42-7.48 (1H, m), 7.76 (1H, br.s.), and 8.08-8.15 (1H, m); δ_C (100.6 MHz; $CDCl_3$) 28.36 (CH_3), 39.41 (CH_2), 80.57 (C), 117.97 (CH_2), 118.58 (CH), 121.03 (C), 122.57 (CH), 129.88 (CH), 133.16 (CH), 135.94 (CH), 140.46 (C), and 152.69 (C); _m/z_ 265 (M^+, 23%), 209 (55), 136 (36), 124 (53), 57 (100), and 41 (74).

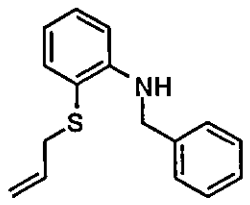
tert-Butyl _N_-[2-(allylsulfanyl)phenyl]-_N_-benzyl-carbamate 141



A solution of carbamate **140** (1.50 g, 5.65 mmol) in DMF (14 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil; 0.25 g, 6.22 mmol) in DMF (14 ml) whilst cooling in an ice bath, and the resulting mixture was stirred for 1 h, then treated with benzyl bromide (0.97 g, 5.65 mmol). After stirring for a further 2 h, water (150 ml) was added and the mixture extracted with ether (150 ml). The aqueous layer was extracted with ether (2x75 ml). The ether extracts were combined, washed with water (75 ml) and saturated brine, dried over Na_2SO_4, and subjected to flash silica gel column chromatography afford tert-_butyl_ N-_[2-(allylsulfanyl)phenyl]-_N-_benzylcarbamate_ **141** (1.64 g, 82%) as a colourless oil; (Found: M^+, 265.1140. $C_{21}H_{25}NO_2S$ requires 265.1136); ν_{max}(film)/cm^{-1} 3063, 3031, 2976, 2930, 1698, 1474, 1388, 1168, 732 and

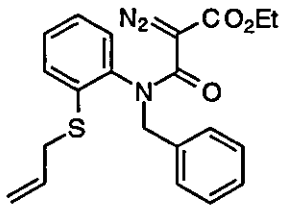
700; δ_H (250 MHz; 50°C; $CDCl_3$) 1.40 (9H, s), 3.49 (2H, d, *J* 6.7 Hz), 4.26 (2H, br.d.), 5.05-5.28 (2H, m), 5.77-5.95 (1H, m), 6.80 (1H, br.s.), 6.99 (1H, m), and 7.10-7.35 (7H, m); δ_C (100.6 MHz; $CDCl_3$) 28.61 (CH_3), 36.27 (SCH_2), 52.86 (NCH_2), 80.50 (C), 118.26 (CH_2), 126.20 (CH), 127.60 (CH), 127.77 (CH), 128.14 (CH), 128.61 (CH), 129.33 (CH), 129.99 (CH), 133.76 (CH), 135.96 (C), 138.59 (C), 141.12 (C), and 155.39 (C); *m/z* 355 (M^+, 10%), 299 (63), 255 (26), 214 (63), 164 (37), 136 (31), 91(71), and 57 (100).

_N_-[2-(allylsulfanyl)phenyl]-_N_-benzylamine 142



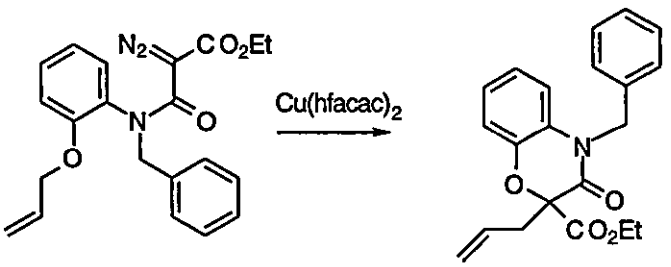
An ice bath cooled solution of the carbamate **141** (1.496 g, 5.89 mmol) in dichloromethane (14 ml) was treated with trifluoroacetic acid (14 ml). The mixture was stirred at room temperature for 1.5 h then concentrated under reduced pressure, diluted with dichloromethane (50 ml) and washed with sodium hydroxide solution (2M; 50 ml). The aqueous layer was extracted with dichloromethane (25 ml), the organic extracts were combined and washed with water (50 ml), and saturated brine (50 ml). The solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a colourless oil which solidified on standing and was found to be essentially pure N-*[2-(allylsulfanyl)phenyl]*-N-*benzylamine* **142** (1.070 g, 99%); (Found: M^+, 255.1081 $C_{16}H_{17}NS$ requires 255.1082); ν_{max} (film)/cm^{-1} 3383, 3064, 3029, 2916, 2850, 1590, 1503, 1451, 1321, 1288, 1224, 1039, 988, 918, 747, and 698; δ_H (250 MHz; $CDCl_3$) 3.34 (2H, d, *J* 7.8 Hz), 4.39 (2H, d, *J* 5.7 Hz), 4.89-5.00 (2H, m), 5.50 (1H, br.s.), 5.75-5.90 (1H, m), 6.55-6.66 (2H, m), and 7.10-7.42 (7H, m); δ_C (100.6 MHz; $CDCl_3$) 28.61 (CH_3), 38.30 (SCH_2), 48.04 (NCH_2), 110.47 (CH), 116.90 (CH), 117.26 (CH_2), 127.18 (CH), 127.23 (CH), 128.63 (CH), 130.22 (CH), 133.92 (CH), 136.62 (CH), 139.25 (C), and 149.19 (C); *m/z* 255 (M^+, 55%), 214 (100), 180 (15), 164 (16), 136 (39), 109 (18), and 91 (92).

Ethyl 3-[2[(allylsulfanyl)(benzyl)anilino]-2-diazo-3-oxopropanaote 133



The standard method was adopted to condense ethyl 2-diazomalonyl chloride (0.346 g, 1.961 mmol) and aniline **142** (0.500 g, 1.961 mmol) to give some unreacted aniline (0.224 g, 45%) and *ethyl 3-[2[(allylsulfanyl)(benzyl)anilino]-2-diazo-3-oxopropanaote* **133** (0.418 g, 54%) as a yellow oil; (Found: M^+, 395.1309 $C_{21}H_{21}N_3O_3S$ requires 395.1304); ν_{max} ($CHCl_3$)/cm^{-1} 2982, 2960, 2930, 2873, 2120, 1722, 1638, 1384, 1303, and 1110; δ_H (250 MHz; $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz); 3.46 (2H, d, *J* 6.7 Hz), 4.09 (2H, q, *J* 7.1 Hz), 4.50 (1H, d of AB, *J* 14.6 Hz), 4.90 (2H, br.s.), 5.08-5.23 (2H, m), 5.34 (1H, d of AB, *J* 14.6 Hz), 5.75-5.90 (1H, m), 6.89 (1H, d, *J* 6.9 Hz), 7.05 (1H, t, *J* 6.9 Hz), and 7.15-7.35 (7H, m); δ_C (100.6 MHz; $CDCl_3$) 14.27 (CH_3), 35.88 (SCH_2), 52.78 (NCH_2), 61.25 (OCH_2), 118.45 (CH_2), 126.06 (CH), 127.53 (CH), 128.26 (CH), 128.30 (CH), 128.72 (CH), 129.38 (CH), 129.92 (CH), 132.69 (CH), 135.92 (C), 136.54 (C), 139.46 (C), 161.17 (C=O), and 162.16 (C=O); *m/z* 379 (M^+, 2%), 351 ($M-N_2^+$, 1), 264 (11), 238 (13), and 91 (100).

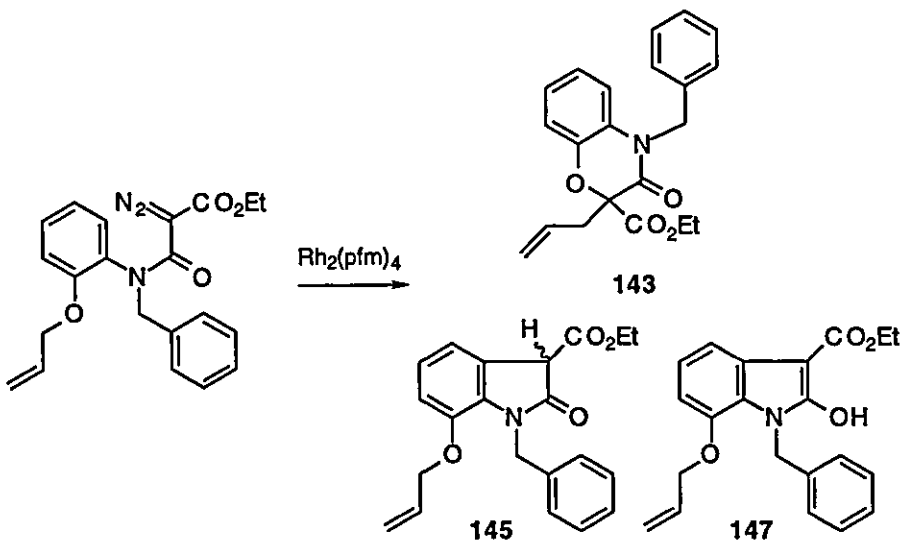
Metallocarbene Competition Reactions of Diazoamides 132 and 133



143

A solution of diazoamide **132** (0.039 g, 0.103 mmol) in dry THF was treated with a catalytic amount of copper(II) hexafluoroacetylacetonate and then refluxed for 18 h. Analysis of the ^1H NMR spectrum of the crude reaction mixture indicated clean but only partial conversion (about 40%) to *ethyl 2-allyl-4-benzyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate* **143**; thus some more catalyst was added and reflux was maintained for a further 48 h. The product was unstable to silica gel and was isolated as a yellow oil after chromatography in low yields (19% in one case); (Found: M^+, 351.1470. $C_{21}H_{21}NO_4$ requires 351.14705); ν_{max} (film)/cm^{-1} 2983, 1751, 1692, 1500,

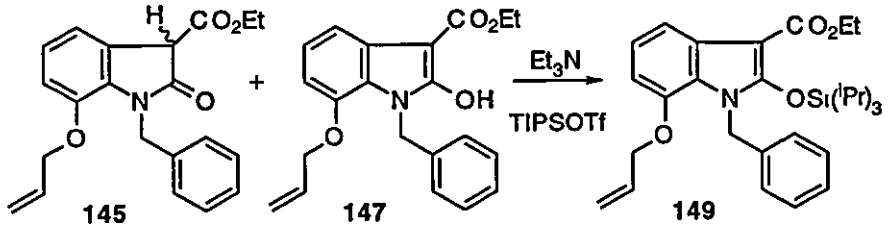
1393, 1257, 1211, 1149, 926, and 750; δ_H (250 MHz; $CDCl_3$) 1.17 (3H, t, *J* 7.1 Hz), 3.09 (2H, d, *J* 8.1 Hz), 4.17 (2H, q, *J* 7.1 Hz), 4.83 (1H, AB, *J* 16.0 Hz), 5.10-5.35 (2H, m), 5.48 (1H, AB, *J* 16.0 Hz), 5.90-6.10 (1H, m), and 6.70-7.40 (9H, m); δ_C (100.6 MHz; $CDCl_3$) 13.99 (CH_3), 38.75 (CH_2), 46.07 (CH_2), 62.29 (CH_2), 83.30 (C), 115.52 (CH), 117.67 (CH), 120.05 (CH_2), 123.03 (CH), 124.24 (CH), 126.51 (CH), 127.44 (CH), 128.38 (C), 128.79 (CH), 130.85 (CH), 136.13 (C), 144.01 (C), 163.65 (C), and 167.74 (C); *m/z* 351 (M^+, 70%), 278 (51), 210 (10), 174 (13), 120 (8), and 91 (100).



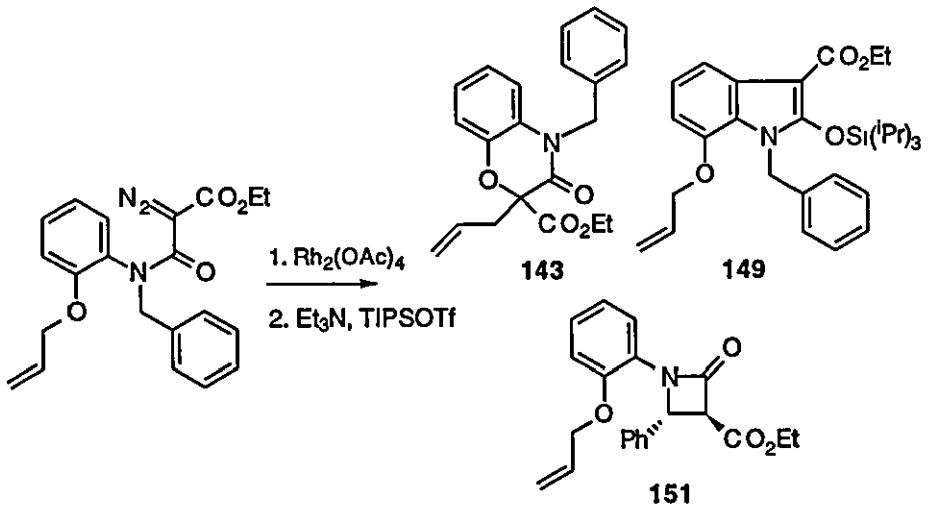
A solution of diazoamide **132** (0.103 g, 0.272 mmol) in dichloromethane (5 ml) was treated with rhodium(II) perfluorobutyramide (0.003 g, 1 mol%) and stirred for 1 h. Analysis of the ^1H NMR spectrum of the crude reaction mixture showed a mixture of *ethyl 2-allyl-4-benzyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-2-carboxylate* **143** (8%), *ethyl 7-(allyloxy)-1-benzyl-2-oxo-3-indolinecarboxylate* **145** (46%), and *ethyl 7-(allyloxy)-1-benzyl-2-hydroxy-1H-3-indolecarboxylate* **147** (46%). Benzoxazine **143** was identified by comparison with the data given above; **145** and **147** were partially characterised as below before being derivatised as silylenol ether **149**.

Ethyl 7-(allyloxy)-1-benzyl-2-oxo-3-indolinecarboxylate **145** (46%); δ_H (250 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz), 4.25 (2H, m), 4.48 (1H, s), 4.54 (2H, d, *J* 5.5 Hz), 5.16 and 5.31 (2H, AB, *J* 15.3 Hz), 5.17-5.32 (2H, m), 5.70-5.96 (1H, m), and 6.59-7.42 (8H, m).

Ethyl 7-(allyloxy)-1-benzyl-2-hydroxy-1H-3-indolecarboxylate **147** (46%); δ_H (250 MHz; $CDCl_3$) 1.45 (3H, t, *J* 7.1 Hz), 4.42 (2H, q, *J* 7.1 Hz), 4.40 (2H, m), 5.56 (2H, s), 5.17-5.32 (2H, m), 5.70-5.96 (1H, m), and 6.59-7.42 (8H, m).

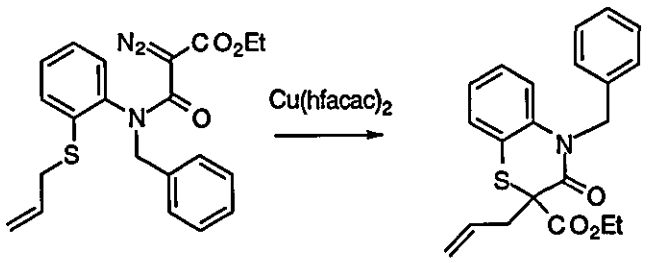


A 1:1 mixture of oxindole **145** and enol **147** (0.025 g, 0.071 mmol) was taken up in dichloromethane (5 ml) and treated with triethylamine (excess) and TIPSOTf (excess). The mixture was stirred for 15 min, before absorption onto silica and flash silica gel column chromatography to afford *ethyl 7-(allyloxy)-1-benzyl-2-[(1,1,1-triisopropylsilyl)oxy]-1*H*-3-indolecarboxylate* **149** (97%) as a colourless solid; m.p. 102.5-103.5°C; (Found: M^+, 507.2806. $C_{30}H_{41}NO_4Si$ requires 507.2805); ν_{max} (CH_2Cl_2)/cm^{-1} 2869, 1696, 1541, 1138, and 1023; δ_H (250 MHz; $CDCl_3$) 1.06 (18H, d, *J* 7.5 Hz), 1.43 (3H, t, *J* 7.1 Hz), 1.46 (3H, h, *J* 7.5 Hz), 4.36 (2H, q, *J* 7.1 Hz), 4.42 (2H, m), 5.10-5.22 (2H, m), 5.59 (2H, br.s.), 5.77 (1H, m), 6.57 (1H, d, *J* 8.0 Hz), 6.97 (2H, m), 7.04 (1H, d, *J* 8.0 Hz), 7.08-7.26 (3H, m), and 7.67(2H, dd, *J* 7.9 and 0.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.37 (CH_3), 14.75 (CH), 17.94 (CH_3), 46.77 (CH_2), 59.08 (CH_2), 69.48 (CH_2), 89.80 (C), 104.74 (CH), 113.95 (CH), 117.53 (CH_2), 120.27 (C), 121.78 (CH), 125.76 (CH), 126.72 (CH), 127.39 (C), 128.25 (CH), 133.26 (CH), 138.66 (C), 145.34 (C), 153.27 (C), and 164.88 (C=O); *m/z* 507 (M^+, 8%), 464 (100), 423 (15), 394 (14), 91 (76), 73 (15), and 59 (28).



A solution of diazoamide **132** (0.115 g, 0.303 mmol) in benzene (8 ml) was treated with rhodium(II) acetate (0.010 g, 2 mol%) and refluxed for 2 h. Treatment of the mixture with excess triethylamine and TIPSOTf and analysis of the resulting crude by ^{1}H NMR showed a mixture of: *ethyl 2-allyl-4-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-2-*

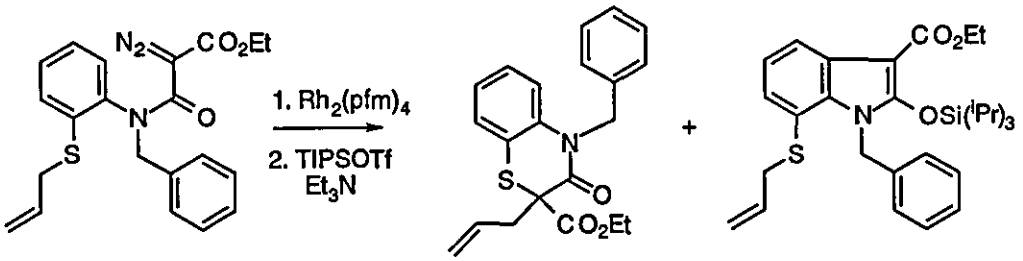
carboxylate **143** (25%), *TIPSindole* **149** (25%), and *β–lactam* **151** (50%). Flash silica gel column chromatography of the crude mixture gave essentially pure **143** (0.017 g, ~16%) as a yellow oil, which compared well with the material described above; and *ethyl 7-(allyloxy)-1-benzyl-2-[(1,1,1-triisopropylsilyl)oxy]-1*H*-3-indolecarboxylate* **149** (10%) as a colourless solid which was identical to the material described above; and trans *ethyl 1-[2-(allyloxy)phenyl]-2-oxo-4-phenylazetane-3-carboxylate* **151** (0.017 g, 26%) as a colourless solid; m.p. 96-98 °C (pentane/diethyl ether); (Found: C, 71.55; H, 5.93; N, 4.29. $C_{21}H_{21}NO_4$ requires C, 71.78; H, 6.02; N, 3.99); (Found: M^+, 351.1474. $C_{21}H_{21}NO_4$ requires 351.1471); ν_{max} (CH_2Cl_2)/cm^{-1} 1762, 1731, 1596, 1505, 1366, 1323, 1156, and 1013; δ_H (250 MHz; $CDCl_3$) 1.33 (3H, t, *J* 7.2 Hz), 3.72 (3H, s), 3.97 (1H, d, *J* 2.5 Hz), 4.28 (2H, q, *J* 7.2 Hz), 4.30-4.52 (2H, m), 5.20-5.31 (2H, m), 5.70 (1H, d, *J* 2.5 Hz), 5.93-5.76 (1H, m), 6.78 (1H, d, *J* 8.2 Hz), 7.20-7.40 (5H, m), and 7.83 (1H, dd, *J* 8.2 and 1.3 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.17 (CH_3), 60.93 (CH), 61.83 (CH_2), 64.14 (CH), 69.32 (CH_2), 113.28 (CH), 117.97 (CH_3), 121.14 (CH), 123.66 (CH), 125.23 (C), 126.08 (CH), 126.41 (CH), 128.39 (CH), 128.81 (CH), 132.73 (CH), 138.05 (C), 150.02 (C), 160.37 (C), and 166.64 (C); *m/z* 325 (M^+, 12%), 149 (100), 131 (26), 77 (19), and 28 (62).



144

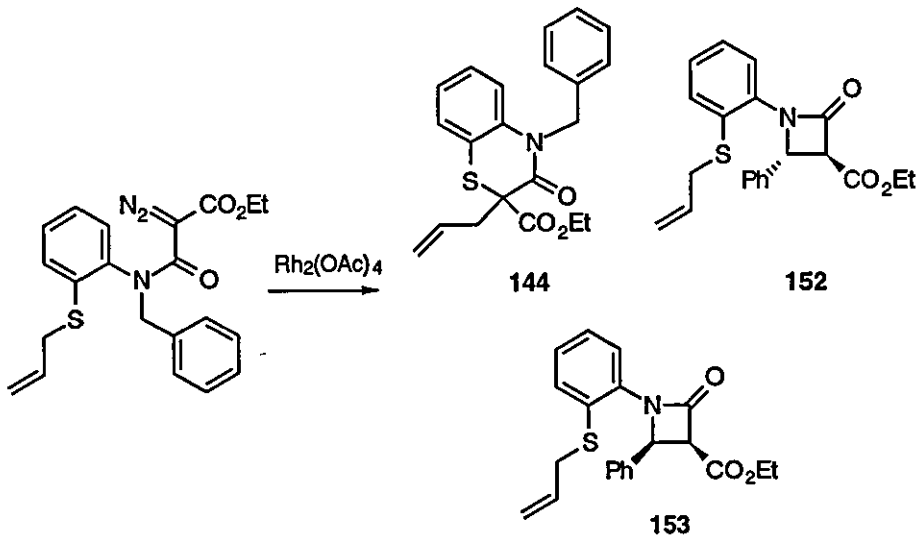
A solution of **133** (0.050 g, 0.127 mmol) in dry THF (5 ml) was treated with freshly sublimed copper(II) hexafluoroacetylacetonate (6 mg, 10 mol%) and refluxed for 19 h. NMR analysis showed clean conversion to *ethyl 2-allyl-4-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-2-carboxylate* **144** and this compound could be isolated pure, as a colourless oil, after a short pass through a silica gel column to remove the catalyst (0.047 g, 99%); (Found: M^+, 367.1242. $C_{21}H_{21}NO_3S$ requires 367.1242); ν_{max} (film)/cm^{-1} 3066, 2981, 2935, 1744, 1727, 1674, 1480, 1448, 1374, and 1227; δ_H (250 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7.1 Hz), 2.99 (2H, d, *J* 7.2 Hz), 4.06 (2H, q, *J* 7.1 Hz), 4.85 (1H, AB, *J* 16.3 Hz), 5.15-5.25 (2H, m), 5.59 (1H, AB, *J* 16.3 Hz), 5.90-6.10 (1H, m), 6.95-7.05 (2H, m), 7.06-7.15 (1H, m), and 7.20-7.42 (6H, m); δ_C (100.6 MHz; $CDCl_3$) 13.90 (CH_3), 37.69 (SCH_2), 50.22 (NCH_2), 55.95 (C), 62.45 (OCH_2), 117.82 (CH), 119.94 (=CH_2), 121.32 (C), 123.94 (CH), 126.29 (CH), 127.19 (CH), 127.87 (CH),

128.61 (CH), 128.77 (CH), 132.17 (CH), 137.07 (C), 139.58 (C), 165.00 (C), and 168.79 (C); *m/z* 367 (M^+, 100%), 326 (58), 294 (45), 213 (47), and 91 (93).



144 **150**

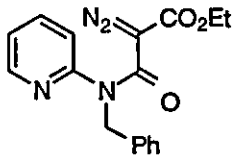
A solution of diazoamide **133** (0.080 g, 0.2025 mmol) in dichloromethane (4.1 ml) was treated with rhodium(II) perfluorobutyramide (0.0043 g, 2 mol%) and the mixture stirred for 2 h. Then an aliquot was removed (~10%) for analysis by ^1H NMR spectroscopy. This showed a mixture of the keto **146** and enol **148** forms of the oxindole product and also some ylide rearrangement product **144** (ratio 38:38:24). The remainder of the reaction mixture was then treated with excess triethylamine and TIPSOTf, and the reaction worked up in the usual way. Preadsorption, followed by flash column chromatography on silica afforded *ethyl 7-(allylthio)-1-benzyl-2-[(1,1,1-triisopropylsilyl)oxy]-1*H*-3-indolecarboxylate* **150** (0.064 g, 67%) as a pink oil; (Found: M^+, 523.2575. $C_{30}H_{41}NO_3SSi$ requires 523.2576); ν_{max} (film)/cm^{-1} 2946, 2868, 1694, 1549, 1436, 1224, 1123, 1045, and 731; δ_H (250 MHz; $CDCl_3$) 1.05 (18H, d, *J* 7.5 Hz), 1.44 (3H, t, *J* 7.1 Hz), 1.46 (3H, h, *J* 7.5 Hz), 3.09 (2H, d, *J* 7.2 Hz), 4.38 (2H, q, *J* 7.1 Hz), 4.70-4.85 (2H, m), 5.44-5.58 (1H, m), 7.08-7.25 (5H, m), and 8.06 (1H, m); δ_C (100.6 MHz; $CDCl_3$) 14.37 (CH_3), 14.72 (CH), 17.85 (CH_3), 40.93 (SCH_2), 46.07 (NCH_2), 59.21 (OCH_2), 89.47 (C), 116.06 (C), 117.56 (CH_2), 120.97 (CH), 121.84 (CH), 125.66 (CH), 126.81 (CH), 126.97 (C), 128.39 (CH), 129.18 (CH), 130.23 (C), 130.94, 133.32 (C), 138.11 (C), 154.14 (C), and 164.56 (C); *m/z* 523 (M^+, 6%), 480 (100), 440 (10), 410 (4), 103 (4), and 91 (28); and also *ethyl 2-allyl-4-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-2-carboxylate* **144** (0.014 g, 21%) which characterised as detailed above.



A solution of diazoamide **133** (0.260 g, 0.658 mmol) in benzene (15 ml) was treated with rhodium(II) acetate (catalytic amount) and the mixture refluxed for 3 h. Then an aliquot was removed for analysis by ^{1}H NMR spectroscopy. This showed a mixture of **144**, **152** and **153** (ratio 30:60:10) and trace amounts of oxindole/enol products. The reaction mixture was then preadsorbed onto silica and subjected to flash silica column chromatography to furnish: trans *ethyl 1-[2-(allylthio)phenyl]-2-oxo-4-phenylazetane-3-carboxylate* **152** (0.070 g, 29%) as a colourless oil; ν_{max} (neat)/cm^{-1} 2982, 1769, 1732, 1477, 1362, 1322, 1155, 753, and 699; (Found: M$^+$, 367.1233. $C_{21}H_{21}NO_3S$ requires 367.1242); δ_H (250 MHz; $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz), 3.47 (1H, dd, *J* 7.0 and 0.7 Hz), 4.08 (1H, d, *J* 2.6 Hz), 4.30 (2H, q, *J* 7.1 Hz), 4.96-5.06 (2H, m), 5.69-5.83 (1H, m), 5.93 (1H, d, *J* 2.6 Hz), and 7.10-7.40 (8H, m), and 7.57 (1H, dd, *J* 7.9 and 1.5 Hz) ; δ_C (100.6 MHz; $CDCl_3$) 14.57 (CH_3), 38.34 (SCH_2), 60.81 (CH), 62.35 (OCH_2), 63.87 (CH), 118.48 (CH2), 125.68 (CH), 127.30 (CH), 127.41 (CH), 128.24 (CH), 129.18 (CH), 129.31 (CH), 129.68 (C), 133.40 (CH), 134.17 (CH), 136.19 (C), 137.16 (C), 161.28 (C), and 166.99 (C); *m/z* 367 (M$^+$, 90%), 212 (37), 191 (100), and 131 (71); and essentially pure cis *ethyl 1-[2-(allylthio)phenyl]-2-oxo-4-phenylazetane-3-carboxylate* **153** (0.012 g, 5%) as a yellow oil; (Found: M-CO_2Et^+ 294.0951. $C_{18}H_{16}NOS$ requires 294.0953); ν_{max} (film)/cm^{-1} 2982, 1771, 1733, 1476, 1319, 1157, 922, and 755; δ_H (250 MHz; $CDCl_3$) 0.87 (3H, t, *J* 7.1 Hz), 3.47 (2H, d, *J* 6.9 Hz), 3.80 (2H, q, *J* 7.1 Hz), 4.55 (1H, d, *J* 6.4 Hz), 4.97-5.05 (2H, m), 5.64-5.75 (1H, m), 6.03 (1H, d, *J* 6.4 Hz), 7.10-7.45 (8H, m), and 7.72 (1H, dd, *J* 7.9 and 1.3 Hz); δ_C (100.6 MHz; $CDCl_3$) 13.62 (CH_3), 38.12 (SCH_2), 58.47 (CH), 58.53 (CH), 59.28 (OCH_2), 118.07 (CH_2), 125.42 (CH), 126.99 (CH), 127.49 (CH), 127.76 (CH), 128.34 (CH), 128.64 (CH), 128.90 (C), 132.88 (CH), 133.13 (CH), 134.39 (C), 135.65 (C), 161.52 (C), and 165.69 (C); *m/z* 367 (M$^+$, 9%), 294 (23), 212 (25), 191 (100), 155 (67), 131 (70), 103 (38), and 91 (30).

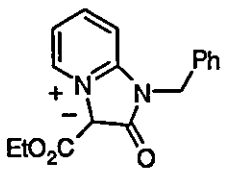
Preparation and Rhodium(II) Catalysed Competition Reactions of *N*-Pyridyl Diazoamide 154

Ethyl 3-[benzyl(2-pyridyl)amino]-2-diazo-3-oxopropanoate 154



The standard method was adopted to condense ethyl diazoacetate and *N*-(2-pyridyl)benzylamine to give *ethyl 3-[benzyl(2-pyridyl)amino]-2-diazo-3-oxopropanoate* **154** (0.219 g, 83%); (Found: M-N_2^+, 296.1165. $C_{17}H_{16}N_2O_3$ requires 296.1161); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2960, 2133, 1719, 1632, 1588, 1471, 1381, 1327, 1298, 1118, and 910; δ_H (250 MHz; $CDCl_3$) 1.08 (3H, t, *J* 7.1 Hz), 3.94 (2H, q, *J* 7.1 Hz), 5.23 (2H, s), 7.00-7.15 (2H, m), 7.20-7.40 (5H, m), 7.55-7.65 (1H, dt, *J* 7.4 and 0.9 Hz), and 8.40 (1H, m); δ_C (100.6 MHz; $CDCl_3$) 14.14 (CH_3), 52.18 (NCH_2), 61.28 (OCH_2), 70.05 ($C{=}N_2$), 118.18 (CH), 120.60 (CH), 127.22 (CH), 127.75 (CH), 128.42 (CH), 137.38 (C), 137.82 (CH), 148.45 (CH), 155.99 (C), 161.31 (C=O), and 162.15 (C=O); *m/z* 296 (M-N_2^+, 39%), 250 (10), 224 (37), 183 (18), 135 (14), and 91 (100).

Pyridinium Ylide 158



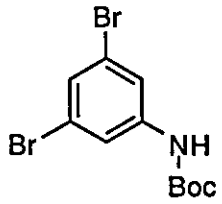
A solution of diazoamide **154** (0.075g, 0.214 mmol) in dry dichloromethane (4.6 ml) was treated with rhodium(II) perfluorobutyramide (0.003 g, 1 mol%) and the mixture stirred at room temperature for 3 h. The catalyst was filtered off through a pad of Celite and the solvent removed under reduced pressure to afford the *pyridinium ylide* **158** (0.069 g, 99%) as a near colourless foamy solid which could be made microanalytically pure after one recrystallisation; m.p. 118-120°C (light petroleum/EtOAc); (Found: C, 68.71; H, 5.40; N, 9.35. $C_{17}H_{16}N_2O_3$ requires C, 68.91; H, 5.44; N, 9.45); (Found: M^+, 296.1164 . $C_{17}H_{16}N_2O_3$ requires 296.1161); ν_{max} $(CH_2Cl_2)/cm^{-1}$ 1682, 1656, 1522, 1382, 1355, 1199, 1161, 1103, 1080, 1040, and 939; δ_H (250 MHz; $CDCl_3$) 1.44 (3H, t, *J* 7.1 Hz), 4.43 (2H, q, *J* 7.1 Hz), 5.20 (2H, s), 6.98 (1H, d, *J* 8.6 Hz), 7.08 (1H, dt, *J* 7.1 and 1.1 Hz), 7.12-7.40 (5H, m), 7.41 (1H, dt, *J* 8.1 and 1.1 Hz), and 9.63 (1H, d, *J* 6.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.70 (CH_3), 43.12 (NCH_2), 53.40 (C), 59.83 (OCH_2), 106.23 (CH), 115.55 (CH), 127.67 (CH), 128.11 (CH), 128.97 (CH), 129.11 (CH), 129.97 (CH),

135.23 (C), 135.75 (C), 157.14 (C=O), and 162.49 (C=O); *m/z* 296 (M^+, 28%), 224 (29), 105 (9), and 91 (100).

Similarly, when a solution of diazoamide **154** (0.055 g, 0.0.170 mmol) in dry dichloromethane (5 ml) was treated with rhodium(II) acetate (catalytic amount) and the mixture stirred at room temperature for 66 h; the result was clean and complete conversion to the *pyridinium ylide* **158** as evidenced by analysis of the NMR spectra of the crude reaction mixture..

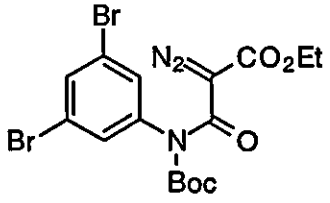
6.3. Experimental Details for Chapter 3

3,5-Dibromo-*N*-(*tert*-butoxycarbonyl)aniline 253



A mixture of 3,5-dibromobenzoic acid (4.94 g, 17.65 mmol), triethylamine (2.56 ml, 18.34 mmol), and diphenylphosphoryl azide (5.05 g, 17.65 mmol) in *tert*-butanol (30 ml) was heated under reflux for 18 h. The mixture was cooled and concentrated under reduced pressure to give a viscous yellow oil which was taken up in dichloromethane (200 ml) and washed with sodium hydroxide solution (10%; 200 ml), water (2 x 200 ml), and saturated brine (200 ml). Drying over $MgSO_4$ followed by concentration under reduced pressure afforded the crude product which could be used without further purification, or purified by flash chromatography on silica gel (9:1 then 7:1 light petroleum:ether) to give *3,5-dibromo-N-(tert-butoxycarbonyl)aniline* **253** (5.08 g, 82%) as a crystalline, colourless solid, m.p. 112°C (*n*-pentane); (Found: C, 37.5; H, 3.5; N, 3.85. $C_{11}H_{13}Br_2NO_2$ requires C, 37.6; H, 3.7; N, 4.0); (Found: M^+, 350.9296. $C_{11}H_{13}Br_2NO_2$ requires 350.9294); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3423, 3057, 1735, 1513, and 1154; δ_H (250 MHz; $CDCl_3$) 1.51 (9H, s), 6.49 (1H, br.s), 7.31 (1H, t, *J* 1.6 Hz), and 7.51 (2H, d, *J* 1.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 28.23 (CH_3), 81.55 (C), 119.90 (CH), 123.04 (C), 128.39 (CH), 140.62 (C), and 152.02 (C=O); *m/z* 351 (M^+, 2%), 295 (4), 251 (7), and 57 (100).

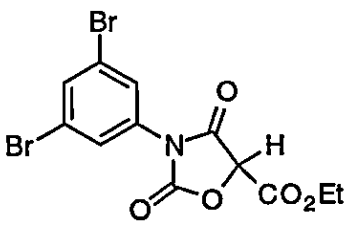
N-(3,5-Dibromophenyl)-*N*-(*tert*-butoxycarbonyl)-2-diazomalonamic Acid Ethyl Ester 254



A solution of the carbamate **253** (0.500 g, 1.42 mmol) in dry THF (12.5 ml) was cooled to -78°C and then treated with *n*-BuLi (1.6 M in hexanes; 0.99 ml, 1.58 mmol). The resulting mixture was stirred at -78°C for 20 min and then treated dropwise with ethyl 2-diazomalonyl chloride (0.280 g, 1.58 mmol) and stirring maintained for a further 2 h. The reaction was then quenched with water (10 ml) and allowed to warm up to room temperature. The organic layer was set aside and the aqueous extracted with ether (20 ml) and dichloromethane (20 ml). The organic extracts were combined, washed with

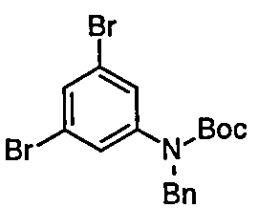
saturated brine (20 ml), and dried over $MgSO_4$ before preadsorbing on silica and subjecting to flash chromatography to give recovered starting carbamate 5 (0.269 g, 54%) and *N-(3,5-dibromophenyl)-N-(tert-butoxycarbonyl)-2-diazomalonamic acid ethyl ester* **254** (0.317 g, 46%) as a colourless solid, m.p. 63-65°C; (Found: MH^+, 491.9588. $C_{16}H_{18}Br_2N_3O_5$ requires 491.9594); $\nu_{max}(CHCl_3)/cm^{-1}$ 2985, 2142, 1731, 1663, 1373, 1152, and 1071; δ_H (250 MHz; $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz), 1.44 (9H, s), 4.31 (2H, q, *J* 7.1 Hz), 7.36 (2H, d, *J* 1.6 Hz), 7.63 (1H, t, *J* 1.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.36 (CH_3), 27.84 (CH_3), 61.95 (CH_2), 84.36(C-O), 122.48 (C), 130.43 (CH), 133.66 (CH), 140.11 (C), 151.32 (C=O), 160.63 (C=O), and 164.61 (C=O). *m/z* 492 (MH^+, <1%), 464 ($M-N_2$, <1%), 407 (18), 392 (12), 335 (10), 291 (8), 262 (16), and 57 (100).

Ethyl 3,5-dibromophenyl-2,4-dioxodihydro-oxazole-5-carboxylate 257



A solution of the diazoamide **254** (0.032 g, mmol) in dichloromethane (2 ml) was treated with rhodium(II) perfluorobutyramide (1 mg, 1 mol%) and the mixture was stirred for 2 h. When all the diazoamide had been consumed (1-H NMR) the mixture was filtered through Celite, concentrated under reduced pressure to give an oil, which was triturated with pentane-ether and recrystallised to give *ethyl 3,5-dibromophenyl-2,4-dioxodihydro-oxazole-5-carboxylate* **257** (20 mg, 77%), m.p. 109-110°C (*n*-pentane-ether); (Found: C, 35.0; H, 2.0; N, 3.3. $C_{12}H_9Br_2NO_5$ requires C, 35.4; H, 2.2; N, 3.4%); (Found: M^+, 406.8823. $C_{12}H_9Br_2NO_5$ requires 406.8829); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2987, 1838, 1755, 1566, 1447, 1338, 1191, 1168, and 1105; δ_H (250 MHz; $CDCl_3$) 1.39 (3H, t, *J* 7.1 Hz), 4.40 (2H, q, *J* 7.1 Hz), 5.38 (1H, s), 7.63 (2H, t, *J* 1.6 Hz), and 7.75 (1H, t, *J* 1.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.02 (CH_3), 64.04 (CH_2), 76.50 (CH), 123.24 (C), 127.05 (CH), 132.23 (C), 134.98 (CH), 152.03 (C=O), 161.79 (C=O), and 164.29 (C=O); *m/z* 407 (M^+, 13%), 335 (8), 278 (10), 170 (9), 57 (13), and 29 (100).

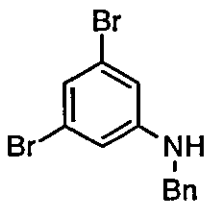
***N*-Benzyl-3,5-dibromo-*N*-(tert-butoxycarbonyl)-aniline 258**



A solution of crude carbamate **253** (3.06 g, 8.72 mmol) in DMF (18 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil; 0.384 g, 9.59 mmol) in DMF (18 ml) whilst cooling in an ice bath, and the resulting mixture was stirred for 4 h,

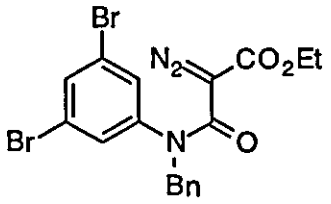
then treated with benzyl bromide (1.491 g, 8.72 mmol). After stirring for a further 0.5 h, the mixture was quenched with water (180 ml) and extracted with ether (1 x 180 ml, 2 x 90 ml). The ether extracts were combined and washed with saturated brine (2 x 90 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give crude *N-benzyl-3,5-dibromo-N-(tert-butoxycarbonyl)aniline* **258** as a pale yellow solid (~3.85 g) which was taken on to the next step without purification. A sample was recrystallised to give a colourless solid, m.p. 64-65°C (light petroleum); (Found: C, 49.0; H, 4.3; N, 3.2. $C_{18}H_{19}Br_2NO_2$ requires C, 48.9; H, 4.2; N, 3.4%); (Found: M^+, 440.9764. $C_{18}H_{19}Br_2NO_2$ requires 440.9764); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2981, 1702, 1583, and 1158; δ_H (400 MHz; $CDCl_3$) 1.43 (9H, s), 4.80 (2H, s), 7.35-7.15 (7H, m), and 7.44 (1H, t, J 1.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 28.18 (CH_3), 53.65 (CH_2), 81.59 (C-O), 122.24 (C), 127.13 (CH), 128.09 (CH), 128.62 (CH), 131.20 (CH), 137.69 (C), 144.95 (C), and 153.95 (C=O); m/z 441 (M^+, 1%), 341(25), 277(21), 91 (100), and 57 (43).

N-Benzyl-3,5-dibromoaniline 259



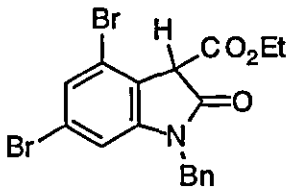
A solution of the crude carbamate **258** (~3.85 g, 8.72 mmol) in dichloromethane (30 ml), cooled in an ice bath was treated with trifluoroacetic acid (30 ml). The mixture was stirred at room temperature for 16 h then concentrated under reduced pressure, diluted with dichloromethane (50 ml) and washed with sodium hydroxide solution (2M; 50 ml). The aqueous layer was extracted with dichloromethane, the organic extracts were combined and washed with water (50 ml), and saturated brine (50 ml). The solution was dried (Na_2SO_4), preadsorbed onto silica, subjected to flash chromatography and crystallisation to afford *N-benzyl-3,5-dibromoaniline* **259** (2.061 g, 69% from 3,5-dibromo-benzoic acid) as large yellow prisms, m.p. 60-61°C (n-pentane-ether); (Found: C, 45.5; H, 3.0; N, 4.2. $C_{13}H_{11}Br_2N$ requires C, 45.5; H, 3.25; N, 4.1); (Found: M^+, 340.9246. $C_{13}H_{11}Br_2N$ requires 340.9240); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3445, 3422, 2860, 1590, 1496, 1358, 1109, 1089, 1070, 981, and 822; δ_H (250 MHz; $CDCl_3$) 4.12 (1H, br.s), 4.26 (2H, d, J 5.3 Hz), 6.67 (2H, d, J 1.6 Hz), 6.96 (1H, t, J 1.6 Hz), and 7.40-7.24 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 48.33, 114.69, 123.05, 123.88, 127.85, 128.06, 129.23, 138.41, and 150.42; m/z 341 (M^+, 11%), 91 (100), and 28 (53).

_N_-Benzyl-_N_-(3,5-dibromophenyl)-2-diazomalonamic Acid Ethyl Ester 260



A solution of _N_-benzyl-3,5-dibromoaniline **259** (0.240 g, 5.57 mmol) in dichloromethane (80 ml) was treated with triethylamine (1.24 g, 12.26 mmol, 1.71 ml) and ethyl 2-diazomalonyl chloride (0.984 g, 5.57 mmol); the mixture was stirred at room temperature for 4 h, and then heated under reflux for 40 min. The solution was allowed to cool, preadsorbed onto silica and subjected to flash chromatography (9:1 then 8:1 light petroleum: ether) to give recovered starting aniline 9 (0.649 g, 34%) and *N-benzyl-N-(3,5-dibromophenyl)-2-diazomalonamic acid ethyl ester* **260** (1.625 g, 61%) as a bright yellow crystalline solid, m.p. 119-120°C (light petroleum-ether), (Found: C, 44.7; H, 2.95; N, 8.7. $C_{18}H_{15}Br_2N_3O_3$ requires C, 44.9; H, 3.1; N, 8.7); (Found: MH+, 479.9558. $C_{18}H_{15}Br_2N_3O_3$ requires 479.9558); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2134, 1719, 1580, and1374; δ_H (250 MHz; $CDCl_3$) 1.15 (3H, t, *J* 7.1 Hz), 4.04 (2H, q, *J* 7.1 Hz), 4.97 (2H, s), 7.22 (2H, d, *J* 1.6 Hz), 7.40-7.24 (5H, m), and 7.49 (1H, t, *J* 1.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.58 (CH_3), 54.87 (NCH_2), 62.02 (OCH_2), 68.68 ($C{=}N_2$), 123.05 (C), 128.17 (CH), 128.23 (CH), 128.32 (CH), 129.09 (CH), 132.56 (CH), 136.58 (C), 145.65 (C), 161.18 (C=O), and 161.94 (C=O); *m/z* 480 (MH^+, 75%), 340 (10), and 108 (8).

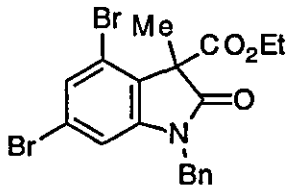
Ethyl 1-benzyl-4,6-dibromo-2-oxo-indole-3-carboxylate 261



A solution of the diazoamide **260** (0.150 g, 0.312 mmol) in dry dichloromethane (2.6 ml) was added to a suspension of rhodium(II) perfluorobutyramide (6.6 mg, 2 mol%) in dry dichloromethane (3.8 ml) and the mixture stirred at room temperature for 0.5 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give pure *ethyl 1-benzyl-4,6-dibromo-2-oxo-indole-3-carboxylate* **261** (0.138 g, 98%) as a colourless solid, m.p. 152-153°C (ethanol); (Found: C, 47.9; H, 3.2; N, 3.1. $C_{18}H_{15}Br_2NO_3$ requires C, 47.7; H, 3.3; N, 3.1); (Found: MH+, 452.9410. $C_{18}H_{15}Br_2NO_3$ requires 452.9400); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1751, 1742, and 1605; δ_H (250 MHz; $CDCl_3$) 1.13 (3H, t, *J* 7.1 Hz), 4.30 (2H, m), 4.43 (1H, s), 4.78 (1H, d, *J* 15.8 Hz), 4.97 (1H, d, *J* 15.8 Hz), 6.80 (1H, d, *J* 1.35 Hz), and 7.40-7.20 (6H, m); δ_C (100.6 MHz; $CDCl_3$) 14.09 (CH_3), 44.38 (NCH_2), 54.10 (CH), 62.59 (OCH_2), 111.84 (CH), 120.05,

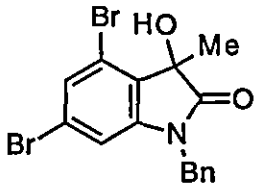
123.37, 123.74, 127.06 (CH), 127.30 (CH), 128.10 (CH), 128.43 (CH), 129.05 (CH), 134.36 (C), 146.12 (C), 164.80 (C=O), and 169.74 (C=O); *m/z* 452 (M^+, 17%), 380 (12), 110 (8), and 91 (100).

Ethyl 1-benzyl-4,6-dibromo-3-methyl-2-oxo-indole-3-carboxylate 267



A solution of the oxindole **261** (0.100 g, 0.220 mmol) in dry DMF (3 ml) was added slowly to a stirred, ice-cooled suspension of sodium hydride (60% dispersion in mineral oil; 0.0096 g, 0.240 mmol) in dry DMF (2 ml) and stirred for 1 h after which time evolution of hydrogen had ceased. Iodomethane (0.035 g, 0.240 mmol, ~15 µl) was added and stirring was continued for a further 3 h whilst allowing the reaction to reach ambient temperature. The reaction mixture was diluted with ether (20 ml) and water (20 ml). The aqueous layer was extracted with ether (20ml then 50 ml); the combined ethereal extracts were washed with saturated brine, dried ($MgSO_4$), concentrated under reduced pressure and subjected to flash silica gel column chromatography and recrystallisation to afford *ethyl 1-benzyl-4,6-dibromo-3-methyl-2-oxo-indole-3-carboxylate* **267** (0.070g, 68%) as colourless crystals, m.p. 99-101°C (*n*-pentane-ether); (Found: C, 48.7; H, 3.7; N, 3.0. $C_{19}H_{17}Br_2NO_3$ requires C, 48.85; H, 3.7; N, 3.0%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1752, 1723, 1599, 1572, 1340, and 1110; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t,*J* 7.1 Hz), 1.80 (3H, s), 4.21 (2H, dq, *J* 7.1 and 2.0 Hz), 4.77 (1H, d, *J* 15.9 Hz), 5.03 (1H, d, *J* 15.9 Hz), 6.80 (1H, d, *J* 1.4 Hz), and 7.35-7.22 (6H, m); δ_C (100.6 MHz; $CDCl_3$) 14.41 (CH_3), 18.05 (CH_3), 44.45 (NCH_2), 57.00 (C), 62.75 (OCH_2), 112.28 (CH), 119.45 (C), 123.17 (C), 127.26 (CH), 128.41 (CH), 129.24 (CH), 129.38 (CH), 130.05 (C), 134.90 (C), 145.79 (C), 167.48 (C=O), and 174.61 (C=O); *m/z* 469 (M^+, 13%), 394 (28) and 91 (100).

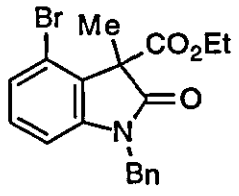
1-Benzyl-4,6-dibromo-3-hydroxy-3-methylindol-2-one 271



A stirred solution of the ester **267** (18 mg, 0. 038 mmol) in THF-water (3:1; 3.1 ml) was treated with sodium hydroxide pellets (16 mg, 0.4 mmol), and the resulting mixture heated under reflux for 18 h under an atmosphere of air. After allowing to cool to ambient temperature, the suspension was acidified with hydrochloric acid (2 M), and the

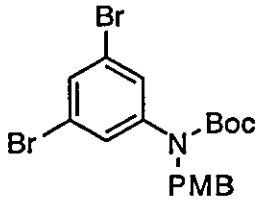
THF was removed under reduced pressure. The aqueous concentrate was extracted with ether (10 ml and 5 ml). The organic extracts were combined and washed with water (5 ml), saturated brine (5 ml), and dried over $MgSO_4$. Concentration under reduced pressure gave pure *1-benzyl-4,6-dibromo-3-hydroxy-3-methylindol-2-one* **271** (16 mg, 99%) as colourless prisms, m.p. 148-149°C; (Found: C, 46.4; H, 2.8; N, 3.2. $C_{16}H_{13}Br_2NO_2$ requires C, 46.75; H, 3.2; N, 3.4); (Found: M^+, 410.9296. $C_{16}H_{13}Br_2NO_2$ requires 410.9294); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3567, 1735, 1600, 1574, 1344, 1164, 1036, 937, and 839; δ_H (250 MHz; $CDCl_3$) 1.80 (3H, s), 2.67 (1H, br. s; removed by D_2O exchange), 4.8 (1H, d, *J* 15.8 Hz), 4.90 (1H, d, *J* 15.8 Hz), 6.80 (1H, d, *J* 1.6 Hz), and 7.38-7.20 (6H, m); δ_C (100.6 MHz; $CDCl_3$) 21.71 (CH_3), 43.05 (CH_2), 73.96 (C), 111.16 (CH), 118.81 (C), 122.68 (C), 126.21 (CH), 127.23 (CH), 127.50 (C), 128.20 (CH), 128.48 (CH), 133.64 (C), 143.93 (C), 176.46 (C=O); *m/z* 411(M^+, 14%), 302 (7), 155 (7), 113 (7), 91(100), and 57 (18).

Ethyl 1-benzyl-4-bromo-3-methyl-2-oxo-indole-3-carboxylate 280



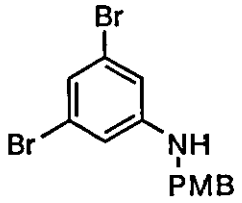
A solution of the oxindole **271** (0.036 g, 0.0077 mmol) in ethyl acetate-acetic acid (4:1; 5 ml) was treated with $PdCl_2$ (0.0087 g, 0.049 mmol) and the resulting suspension stirred under an atmosphere of hydrogen gas. The reaction was monitored by TLC; after 3 h further $PdCl_2$ (0.0168 g) was added and the mixture stirred for 18 h under hydrogen. The resulting suspension was filtered through Celite, washed with saturated $NaHCO_3$ solution, water, and saturated brine. After drying over $MgSO_4$, the mixture was preadsorbed onto silica and subjected to flash chromatography to give unreacted starting oxindole 12 (0.025 g, 69%) and *ethyl 1-benzyl-4-bromo-3-methyl-2-oxo-indole-3-carboxylate* **280** (0.009 g, 30%) as a sticky solid; (Found: M^+, 387.0469. $C_{19}H_{18}{}^{79}BrNO_3$ requires 387.04705); $\nu_{max}(CHCl_3)/cm^{-1}$ 1750, 1717, 1605, 1456, 1377, 1237, 1217 and 1169; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t,*J* 7.1 Hz), 1.83 (3H, s), 4.20 (2H, dq, *J* 7.1 and 1.8 Hz), 4.81 (1H, d, *J* 15.9 Hz), 5.07 (1H, d, *J* 15.9 Hz), 6.66 (1H, dd, *J* 7.9 and 7.6 Hz), 7.06 (1H, t, *J* 7.9 Hz), 7.15 (1H, d, *J* 7.6 Hz) and 7.40-7.18 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 14.41 (CH_3), 18.14 (CH_3), 44.35 (NCH_2), 57.29 (C), 62.56 (OCH_2), 108.88 (CH), 119.02 (C), 127.05 (CH), 127.31 (CH), 128.18 (CH), 129.23 (CH), 130.27 (C), 130.39 (CH), 135.43 (C), 144.84 (C), 168.06 (C=O), and 174.80 (C=O); *m/z* 387 (M^+, 7%), 314 (8%), 155 (4%), 119 (4%), 91 (100), and 65 (8%).

3,5-Dibromo-*N*-(*tert*-butoxycarbonyl)-*N*-4-methoxybenzylaniline 283



A solution of carbamate **253** (3.00 g, 8.55 mmol) in dry DMF (18 ml) was added to a stirred suspension of sodium hydride (60% dispersion in mineral oil; 0.376 g, 9.40 mmol) in dry DMF (18 ml) whilst cooling in an ice bath, and the resulting mixture was stirred for 20 min. 4-Methoxybenzyl chloride (1.16 ml, 1.34 g, 8.55 mmol) was then added and the mixture stirred for a further 21 h. It was quenched with water (180 ml) and extracted with ether (180 ml then 2 x 90 ml). The combined ether extracts were washed with saturated brine (2 x 90 ml), dried over $MgSO_4$, and concentrated under reduced pressure to give essentially pure *3,5-dibromo-N-(tert-butoxycarbonyl)-N-4-methoxybenzylaniline* **283** (4.03 g, 100%) as a pale yellow solid which was used without further purification. A sample was recrystallised from light petroleum-ether to give the pure **283** as colourless crystals, m.p. 82-84°C (light petroleum-ether); (Found: C, 48.4; H, 4.2; N, 2.95. $C_{19}H_{21}Br_2NO_3$ requires C, 48.4; H, 4.5; N, 3.0); (Found: M^+, 470.9871. $C_{19}H_{21}Br_2NO_3$ requires 470.9869); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3048, 2934, 2840, 1699, 1583, 1556, 1514, 1440, 1369, 1266, 1160, 1034, 909, and 858; δ_H (250 MHz; $CDCl_3$) 1.44 (9H, s), 3.80 (3H, s), 4.74 (2H, s), 6.88-6.80 (2H, m), 7.15-7.08 (2H, m), 7.26 (2H, *d*, *J* 1.7 Hz), and 7.44 (1H, t, *J* 1.7 Hz); δ_C (100.6 MHz; $CDCl_3$) 28.62 (CH_3), 53.44 (NCH_2), 55.65 (OCH_2), 81.85 (OC), 114.42(CH), 122.59 (C), 128.77 (CH), 129.04 (CH), 130.10 (C), 131.64 (CH), 145.28 (C), 154.36 (C=O), and 159.39 (C). *m/z* 471 (M^+, 2%), 415 (20), 371(13), 251(8), 121 (100), 57 (74), and 41 (42).

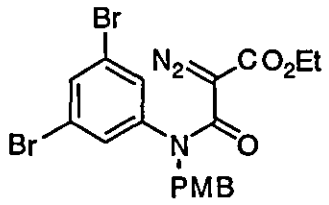
3,5-Dibromo-*N*-4-methoxybenzylaniline 284



A solution of the crude carbamate **283** (3.92 g, 8.32 mmol) in dichloromethane (30 ml) was cooled in an ice bath and treated with trifluoroacetic acid (30 ml). The mixture was stirred at room temperature for 80 min, then concentrated under reduced pressure to give an oil which was taken up in dichloromethane (50 ml) and washed with dilute sodium hydroxide solution (10%; 50 ml). The aqueous layer was extracted with dichloromethane (25 ml). The organic extracts were combined, washed with water (50 ml), saturated brine (50 ml), dried over Na_2SO_4, preadsorbed onto silica and subjected

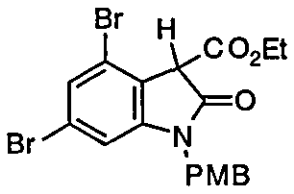
to flash chromatography to give *3,5-dibromo-N-4-methoxybenzylaniline* **284** (2.39 g, 77% for the two steps) as a colourless crystalline solid, m.p.73-74°C (*n*-pentane-ether); (Found: C, 45.1; H, 3.2; N, 3.6. $C_{14}H_{13}Br_2NO$ requires C, 45.3; H, 3.5; N, 3.8); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3423, 2840, 1590, 1560, 1514, 1264, 1176, 1034, 895, and 821; δ_H (250 MHz; $CDCl_3$) 3.81 (3H, s), 4.06 (1H, br.s), 4.19 (2H, d, *J* 4.8 Hz), 6.67(2H, d, *J* 1.6 Hz), 6.85-6.91 (2H, m), 6.96 (1H, t, *J* 1.6 Hz), and 7.27-7.20 (2H, m); δ_C (100.6 MHz; $CDCl_3$) 47.85 (CH_2), 55.71 (OCH_3), 114.65 (CH), 114.68 (CH), 122.97 (CH), 123.86 (C), 129.19 (CH), 130.39 (C), 150.45 (C), and 159.60 (C); *m/z* 371 (M^+, 30%), 251 (8), 121 (100), and 78 (19).

N-(3,5-Dibromophenyl)-2-diazo-4-methoxybenzylmalonamic Acid Ethyl Ester 285



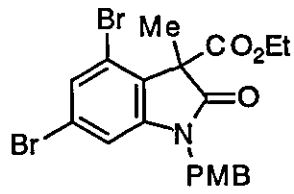
A solution of the aniline **284** (1.00 g, 2.695 mmol) in dichloromethane (39 ml) was treated with triethylamine (5.93 mmol, 0.83 ml) and ethyl 2-diazomalonyl chloride (0.476 g, 2.695 mmol); the mixture was stirred at room temperature for 70 h. The solution was washed with dilute hydrochloric acid (2 M; 50 ml), water (20 ml), and saturated brine (20 ml). Drying over Na_2SO_4 followed by preadsorption onto silica and flash chromatography (gradient elution from 8:1 to 6:1 light petroleum:ether) gave recovered starting aniline 16 (0.30 g, 30%) and *N-(3,5-dibromophenyl)-2-diazo-4-methoxybenzylmalonamic acid ethyl ester* **285** (0.907 g, 66%) as a bright yellow crystalline solid, m.p. 95°C (*n*-pentane-ether- EtOAc), (Found: C, 44.5; H, 3.05; N, 8.1. $C_{19}H_{17}Br_2N_3O_4$ requires C, 44.6; H, 3.35; N, 8.2); (Found: M^+, 510.9567. $C_{19}H_{17}Br_2N_3O_4$ requires 510.9546); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2839, 2133, 1718, 1633, 1580, 1557, 1514, 1436, 1422, 1374, 1320, and 1107; δ_H (250 MHz; $CDCl_3$) 1.14 (3H, t, *J* 7.1 Hz), 3.78 (3H, s), 4.03 (2H, q, *J* 7.1 Hz), 4.90 (2H, s), 6.84-6.80 (2H, m), 7.18-7.14 (2H, m), 7.20 (2H, d, *J* 1.6 Hz), and 7.49 (1H, t, *J* 1.6 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.21 (CH_3), 54.00 (NCH_2), 55.28 (OCH_3), 61.60 (OCH_2), 68.16 ($C{=}N_2$), 114.08 (CH), 122.64 (C), 128.18 (CH), 128.28 (C), 129.59 (CH), 132.22 (CH), 145.14 (C), 159.25 (C), 160.86 (C), and 161.46 (C); *m/z* 511 (M^+, <1%), 483 ($M-N_2$, 4%), 410 (9), 277 (5), 206 (35), 161 (13), 134 (11), and 121 (100).

Ethyl 4,6-dibromo-1-(4-methoxybenzyl)-2-oxo-indole-3-carboxylate 286



A solution of the diazoamide **285** (0.415 g, 0.812 mmol) in dry dichloromethane (18 ml) was treated with rhodium(II) perfluorobutyramide (0.0086 g, 1 mol%) and the mixture stirred at room temperature for 1.5 h. The reaction mixture was rapidly filtered through Celite and concentrated under reduced pressure to give pure *ethyl 4,6-dibromo-1-(4-methoxybenzyl)-2-oxo-indole-3-carboxylate* **286** (0.390 g, 99%) as an unstable colourless foam/solid; (Found: M^+, 482.9496. $C_{19}H_{17}Br_2NO_4$ requires 482.9506); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2987, 2939, 2840, 1750, 1723, 1605, 1515, 1250, 1178, 1157, 1034, and 836; δ_H (250 MHz; $CDCl_3$) 1.31 (3H, t, *J* 7.1 Hz), 3.79 (3H, s), 4.29 (2H, dq, *J* 7.1 & 2.5 Hz), 4.41 (1H, s), 4.72 (1H, d, *J* 15.6 Hz), 4.89 (1H, d, *J* 15.6 Hz), 6.82 (1H, d, *J* 1.3 Hz), 6.86 (2H, d, *J* 8.7 Hz), 7.20 (2H, d, *J* 8.7 Hz), and 7.34 (1H, d, J 1.3 Hz); δ_C (100.6 MHz; $CDCl_3$) 13.93 (CH_3), 43.71 (NCH_2), 53.90 (CH), 55.13 (OCH_3), 62.04 (OCH_2), 111.69 (CH), 114.24 (CH), 119.82 (C), 123.15 (C), 123.55 (C), 126.18 (C), 128.16 (CH), 128.34 (CH), 145.93 (C), 159.21 (C), 164.68 (C=O), and 169.52 (C=O); *m/z* 483 (M^+, 1%), 121 (100), 78 (6), 45 (13), and 31 (29).

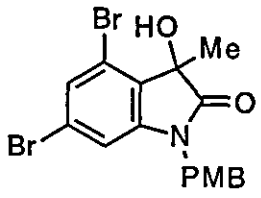
Ethyl 4,6-dibromo-1-(4-methoxybenzyl)-3-methyl-2-oxoindole-3-carboxylate 287



A solution of the oxindole **286** (0.390 g, 0.808 mmol) in dry DMF (12 ml) was added slowly to a stirred, ice-cooled suspension of sodium hydride (60% dispersion in mineral oil; 0.036 g, 0.890 mmol) in dry DMF (18 ml) and stirring was maintained for 0.5 h, when evolution of hydrogen subsided. Then iodomethane (0.126 g, 0.890 mmol, ~55.5 µl) was added and stirring was continued for a further 3 h whilst allowing the reaction to reach ambient temperature. The reaction mixture was diluted with ether (120 ml) and water (120 ml). The aqueous layer was extracted with ether (120ml then 300 ml); the combined ethereal extracts were washed with saturated brine, dried ($MgSO_4$), concentrated under reduced pressure and subjected to flash chromatography on silica gel to yield *ethyl 4,6-dibromo-1-(4-methoxybenzyl)-3-methyl-2-oxoindole-3-carboxylate* **287** (0.265 g, 66%) as a colourless oil which crystallised on cooling, m.p.120-120.5°C (*n*-pentane); (Found: C, 48.3; H, 3.7; N, 2.8. $C_{20}H_{19}Br_2NO_4$ requires C, 48.3; H, 3.7; N,

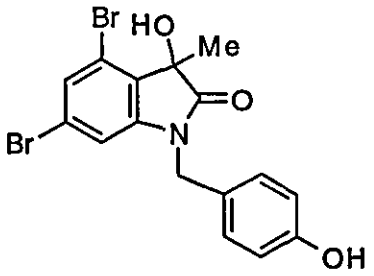
2.8); (Found: M^+, 496.9665. $C_{20}H_{19}Br_2NO_4$ requires 496.9662); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1752, 1723, 1600, 1515, 1112, and 838; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t, *J* 7.1 Hz), 1.79 (3H, s), 3.79 (3H, s), 4.20 (2H, dq, *J* 7.1 and 2.0 Hz), 4.77 (1H, d, *J* 15.9 Hz), 5.03 (1H, d, *J* 15.9 Hz), 6.82 (1H, d, *J* 1.4 Hz), 6.86 (2H, d, *J* 8.6 Hz), 7.18 (2H, d, *J* 8.6 Hz), and 7.31 (1H, d, *J* 1.4 Hz); δ_C (100.6 MHz; $CDCl_3$) 14.40 (CH_3), 18.03 (CH_3), 44.00 (NCH_2), 55.68 (OCH_3), 56.99 (C), 62.68 (OCH_2), 112.32 (CH), 114.79 (CH), 119.39 (C), 123.125 (C), 126.93 (C), 128.71 (CH), 129.13 (CH), 129.38 (C), 129.33 (C), 145.84 (C), 159.765 (C), 167.49 (C=O), and 174.56 (C=O); *m/z* 497 (M^+, 22%), 304 (4), 121 (100), 91 (10), and 78 (16).

4,6-Dibromo-3-hydroxy-1-(4-methoxybenzyl)-3-methylindol-2-one 288



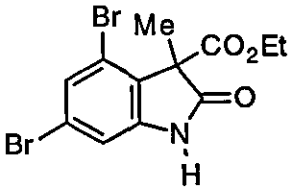
A stirred solution of the ester **287** (0.245 g, 0.493 mmol) in THF-water (3:1; 40 ml) was treated with sodium hydroxide pellets (0.203 g, 5.075 mmol), and the resulting mixture heated under reflux for 21 h under an atmosphere of air. After allowing the mixture to cool to ambient temperature, the suspension was acidified carefully with aqueous hydrochloric acid (2 M), and the THF was removed under reduced pressure. The aqueous concentrate was extracted with ether (60ml and 30 ml). The organic extracts were combined, washed with water (60 ml), saturated brine (30 ml), and dried over $MgSO_4$. Concentration under reduced pressure gave *4,6-dibromo-3-hydroxy-1-(4-methoxybenzyl)-3-methylindol-2-one* **288** (0.214 g, 99%) as an amorphous, colourless solid, m.p.168-169°C; (Found: C, 46.3; H, 3.1; N, 2.9. $C_{17}H_{15}Br_2NO_3$ requires C, 46.3; H, 3.4; N, 3.2); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3413, 2934, 2840, 1735, 1601, 1574, 1514, 1343, 1161, and 1034; δ_H (250 MHz; $CDCl_3$) 1.79 (3H, s), 2.67 (1H, br. s), 3.79 (3H, s), 4.72 (1H, d, *J* 15.5 Hz), 4.86 (1H, d, *J* 15.5 Hz), 6.83 (1H, d, *J* 1.5 Hz), 6.86 (2H, m), 7.18 (2H, m), and 7.34 (1H, d, 1*J* 1.5 Hz); δ_C (100.6 MHz; $CDCl_3$) 22.97 (CH_3), 43.82 (NCH_2), 75.26 (C), 112.48 (CH), 114.85 (CH), 120.02 (C), 123.96 (C), 126.85 (C), 128.67 (C), 128.92 (CH), 129.96 (CH), 145.17 (C), 159.77 (C), and 177.66 (C=O). *m/z* 441(M^+, 6%), 320 (1), 155 (2), and 121(100).

4,6-Dibromo-3-hydroxy-1-(4-hydroxybenzyl)-3-methylindol-2-one 289



The oxindole **288** (0.052 g, 0.118 mmol) was taken up in dry dichloromethane (1 ml) and the solution was cooled to -80°C in a dry ice/ acetone bath, then treated slowly with BBr_3 (1M solution in dichloromethane; 0.37 ml, 0.37 mmol). The mixture was stirred for 16 h whilst allowing to warm up slowly to 8°C; water and dichloromethane (5 ml) were added and the suspension stirred. The organic layer was washed twice with water, and dried ($MgSO_4$). Concentration under reduced pressure yielded *4,6-dibromo-3-hydroxy-1-(4-hydroxybenzyl)-3-methylindol-2-one* **289** (0.050 g, 99%) as a colourless solid, m p. 167°C (*n*-pentane-light petroleum-ethyl acetate); (Found: M^+, 426.9245. $C_{16}H_{13}Br_2NO_3$ requires 426.9244); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3686, 3576, 2930, 1735, 1601, 1516, 1162, and 839; δ_H (250 MHz; $CDCl_3$) 1.78 (3H, s), 2.85 (1H, br. s), 4.72 (1H, d, *J* 15.6 Hz), 4 81 (1H, d, *J* 15.6 Hz), 5.25 (1H, br. s), 6.78 (2H, m), 6.82 (1H, d, *J* 1.5 Hz), 7.11 (2H, m), and 7.34 (1H, d, *J* 1.5 Hz); δ_C (100.6 MHz; $CDCl_3$) 22.84 (CH_3), 43.86 (CH_2), 75.38 (C), 112.56 (CH), 116.38 (CH), 120.07 (C), 123.99 (C), 126.73 (C), 128.67 (C), 129.05 (CH), 129.84 (CH), 145.03 (C), 155.96 (C), and 178.00 (C=O); *m/z* 427 (M^+, <1%), 121 (100), and 78 (5).

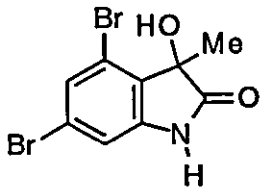
Ethyl 4,6-dibromo-3-methyl-2-oxoindole-3-carboxylate 290



The oxindole **287** (0.050 g, 0.101 mmol) was dissolved in acetonitrile (1.21 ml) and water (0.40 ml) was added. The solution was treated with ceric ammonium nitrate (0.221 g, 0.402 mmol), stirred for 2.5 h, poured into water and extracted with ethyl acetate (x2; brine was added to help clear emulsions). The organic extracts were combined, washed with water, saturated brine, and dried ($MgSO_4$). Preadsorption on silica followed by flash column chromatography gave *ethyl 4,6-dibromo-3-methyl-2-oxoindole-3-carboxylate* **290** (0.036 g, 95%) as a colourless powder, m.p. 175-176°C (pentane - ethyl acetate); (Found: C, 37.9; H, 2.8; N, 4.0. $C_{12}H_{11}Br_2NO_3$ requires C, 38.2; H, 2.9; N, 3.7); (Found: M^+, 376.9092. $C_{12}H_{11}Br_2NO_3$ requires 376.9087);

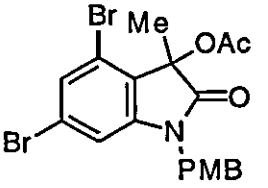
$\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3417, 2959, 1755, 1735, 1610, 1426, and 1112; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t, *J* 7.15 Hz), 1.77 (3H, s), 4.10-4.30 (2H, m), 7.06 (1H, d, *J* 1.5 Hz), 7.36 (1H, d, *J* 1.5 Hz), and 8.07 (1H, br. s); δ_C (100.6 MHz; $CDCl_3$) 14.12 (CH3), 57.46 (C), 62.84 (CH_2), 113.13 (CH), 119.62 (C), 123.21 (C), 129.28 (CH), 129.86 (C), 143.65 (C), 167.38 (C=O), and 176.29 (C=O); *m/z* 377 (M^+, 15%), 304 (100), 223 (30), 195 (13), 155 (33), 116 (24), 89 (23), and 29 (81).

4,6-Dibromo-3-hydroxy-3-methyl-2-indolinone (convolutamydine C) 170



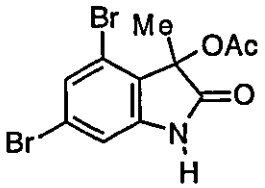
A stirred solution of the ester **290** (0.0240 g, 0.0637 mmol) in THF - water (3:1; 5 ml) was treated with sodium hydroxide pellets (0.025 g, 0.610 mmol), and the resulting mixture heated under reflux for 50 h under an atmosphere of oxygen. After allowing to cool to ambient temperature, the suspension was acidified carefully with aqueous hydrochloric acid (2 M) and the THF was removed under reduced pressure. The aqueous concentrate was extracted with ether. The organic extracts were combined and washed with water, saturated brine, and dried ($MgSO_4$). Preadsorption on silica, followed by flash column chromatography (3:1 then 2:1 light petroleum:EtOAc) gave (i) *convolutamydine C* **170** as a colourless solid (2.4 mg, 18%), m.p. decomp. >160°C (light petroleum-ethyl acetate) (lit.,[70] 175-180°C from acetone); (Found: M^+, 318.8844. Calc. for $C_9H_7{}^{79}Br{}^{79}BrNO_2$: 318.8845); (Found: M^+, 320.8829. Calc. for $C_9H_7{}^{79}Br{}^{81}BrNO_2$: 320.8825); $\nu_{max}(CHCl_3)/cm^{-1}$ 3691, 3607, 2928, 1749, 1602; δ_H (250 MHz; $CDCl_3$) 1.76 (3H,s, Me), 2.67 (1H, br, OH), 7.00 (1H, d, *J* 1.5 Hz), 7.38 (1H, d, *J* 1.5 Hz) and 7.45 (1H, NH); δ_C (100.6 MHz; acetone-d_6) 19.9 (Me), 73.0 (C3), 111.0 (C7), 118.3 (C6), 121.1 (C4), 126.5 (C5), 143.3 (C7a), and 176.9 (C2); C3a not observed; *m/z* 321 (M^+, 24%), 306 (38), 278 (33), 170 (11), 90 (19), 74 (12), 63 (29), and 43 (100); and (ii) *2-amino-4,6-dibromoacetophenone* **291** as a pale yellow solid (10.0 mg, 63%), m.p. 89-91°C; (Found: M^+, 292.8877. $C_8H_7Br_2NO$ requires 292.8876); $\nu_{max}(CHCl_3)/cm^{-1}$ 3502, 3399, 3093, 3011, 2928, 2856, 1680, 1604, 1581, 1539, 1409, 1355, and 1253; δ_H (250 MHz; $CDCl_3$) 2.63 (3H, s), 4.68 (2H, br.s, exchangeable with D_2O), 6.80 (1H, d, *J* 1.7 Hz), and 7.09 (1H, d, *J* 1.7 Hz); δ_C δ_C (100.6 MHz; $CDCl_3$) 32.41 (CH_3), 118.78 (CH), 121.56 (C), 125.23 (CH), 125.42 (C), 147.79 (C), and 203.93 (C=O); *m/z* 293 (M^+, 8%), 278 (100), 250 (5), 170 (8), 90 (5), 63 (17), and 43 (37).

4,6-Dibromo-1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-3-indolyl acetate 294



Tertiary alcohol **288** (0.025 g, 0.057 mmol) was taken up in dry dichloromethane (2 ml) and treated with triethylamine (~0.024 g, mmol), acetic anhydride (~0.015 g, mmol), along with a catalytic amount of 4-dimethylaminopyridine. After stirring at room temperature for 25 h the solvent was removed under reduced pressure. The residue was taken up in ether (10 ml), washed sequentially with dilute HCl (2N; 2 x 5 ml), water and saturated brine. The ether solution was dried ($MgSO_4$), filtered, then concentrated under reduced pressure to yield *4,6-dibromo-1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-3-indolyl acetate* **294** (0.028 g, 99%) as an oily, colourless solid which was used directly without crystallisation, (Found: M^+, 482.9519 $C_{19}H_{17}Br_2NO_4$ requires 482.9506); ν_{max}(film)/cm^{-1} 3081, 2998, 2934, 2837, 1739, 1602, 1515, 1164, 1105, 1043, and 734; δ_H (250 MHz; $CDCl_3$) 1.74 (3H, s), 2.14 (3H, s), 3.79 (3H, s), 4.75 (1H, d of AB q, *J* 15.7 Hz), 4.93 (1H, d of AB q, *J* 15.7 Hz), 6.76 (1H, d, *J* 1.5 Hz), 6.88 (2H, m), and 7.20-7.36 (3H, m); δ_C (100.6 MHz; $CDCl_3$) 20.01 (CH_3), 20.60 (CH_3), 43.64 (CH_2), 55.27 (CH_3), 77.62 (C), 112.13 (CH), 114.38 (CH), 117.83 (C), 123.46 (C), 126.28 (C), 126.50 (C), 128.48 (CH), 128.81 (CH), 144.89 (C), 159.30 (C), 169.20 (C=O), and 174.48 (C=O); *m/z* 483 (M^+; 2%), 423 (M-$CO_2CH_3^+$; 23), 394 (2), 121 (100), and 43 (28).

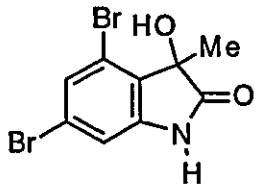
4,6-Dibromo-3-methyl-2-oxo-2,3-dihydro-1*H*-3-indolyl acetate 295



N-4-Methoxybenzyloxindole **294** (0.026 g, 0.054 mmol) was dissolved in CH_3CN (0.65 ml) and then H_2O (0.22 ml) was added. The solution was treated with $Ce(NH_4)_2(NO_3)_6$ (0.118 g, 0.215 mmol), stirred for 3.5 h, then H_2O (10 ml) was added and the mixture extracted with EtOAc (2 x 10ml). The organic extracts were combined, washed with saturated brine and dried ($MgSO_4$). Preadsorption on silica followed by flash silica gel column chromatography afforded *ethyl 4,6-dibromo-3-methyl-2-oxoindole-3-carboxylate* **295** (0.016 g; 82%) as colourless needles; m.p. 155-165°C (dec) (light petroleum-EtOAc-EtOH); (Found: M^+, 362.8929. $C_{11}H_9Br_2NO_3$ requires 362.8930; ν_{max}(CH_2Cl_2)/cm^{-1} 3420, 1756, 1743, 1612, 1578, 1372, 1172, 1104, 1022, 950, and 841; δ_H (250 MHz; $CDCl_3$) 1.73 (3H, s), 2.13 (3H, s), 7.00 (1H, d, *J* 1.5 Hz), 7.31 (1H,

d, *J* 1.5 Hz), and 8.30 (1H, br. s); δ_C (66 MHz; $CDCl_3$) 20.00 (CH_3), 20.23 (CH_3), 77.72 (C), 112.97 (CH), 118.12 (C), 123.55 (C), 126.57 (C), 128.93 (CH), 142.83 (C), 169.39(C=O), and 176.00 (C=O); *m/z* 363 (M^+, 41%), 320 (15), 304 (34), 278 (12), 225 (4), and 43 (100).

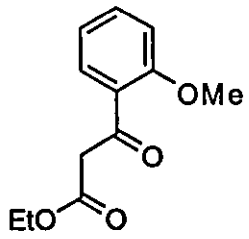
4,6-Dibromo-3-hydroxy-3-methyl-2-indolinone (convolutamydine C) 170



The acetate **295** (0.0075 g, 0.0207 mmol) was taken up in EtOH (0.5 ml) and treated with excess aqueous NaOH (1M; 5 drops) and the mixture stirred for 3 h. TLC showed clean conversion to the desired product. Thus the mixture was cooled in an ice bath and acidified with dilute hydrochloric acid (4%; 10 drops), saturated with brine and extracted with EtOAc (3 x 10 ml). The combined extracts were dried ($NaSO_4$), filtered and concentrated under reduced pressure to give essentially pure (^1H NMR spectroscopy) convolutamydine C **170**. The solid was preadsorbed on silica and subjected to flash silica column chromatography (2:1 light petroleum:EtOAc) to yield pure *convolutamydine C* **170** (0.0061 g, 91%) as a colourless solid; data as given above.

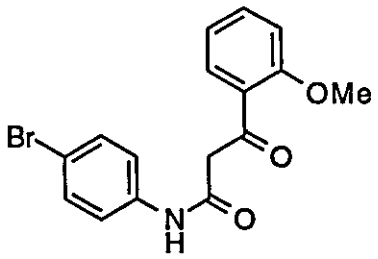
6.4. Experimental Details for Chapter 4

Ethyl 3-(2-methoxyphenyl)-3-oxo-propanoate 324[172]



A solution of 2-methoxyacetophenone (1.00 g, 6.67 mmol) in dry THF (50 ml) was treated with sodium hydride (60% dispersion in mineral oil; 0.986 g, 24.64 mmol), and diethyl carbonate (2.36 g, 19.98 mmol). The mixture was refluxed for 17 h, then allowed to cool to room temperature before quenching dropwise (CARE!) with glacial acetic acid (2.4 ml) to produce a gelatinous suspension. Rigourous concentration under reduced pressure while heating in a water bath at 50°C gave an orange/brown solid residue which was taken up in ether (100 ml) and the solution washed with saturated brine (10 ml). The aqueous layer was extracted with ether (50 ml). The ether extracts were combined and washed with saturated brine (50 ml), dried (MgSO4), filtered, and the solvent removed under reduced pressure. The crude residue was subjected to FSGCC (9:1-8:1 light light petroleumeum:EtOAc) to afford *ethyl 3-(2-methoxyphenyl)-3-oxopropanoate* **324** (1.12 g, 76%) as a yellow oil; (Found: M+, 222.0892. $C_{12}H_{14}O_3$ requires 222.0892); ν_{max}(film)/cm^{-1} 2983, 1739, 1673, 1598, 1486, 1328, 1255, and 1025; δ_H (250 MHz; $CDCl_3$) 1.23 (3H, t, J 7.1 Hz), 3.89 (3H, s), 3.96 (3H, s), 4.18 (2H, q, *J* 7.1 Hz), 6.93-7.05 (2 H), 7.45-7.54 (1H, m), and 7.85-7.90 (1H, m); δ_C (62.5 MHz; $CDCl_3$) 14.04 (CH_3), 50.59 (CH_2), 55.26 (CH_3), 60.82 (OCH_2), 111.47 (CH), 120.44 (C), 120.74 (CH), 130.96 (CH), 134.61 (C), 159.04 (C=O), 168.10 (C=O); *m/z* 222 (M+, 43%), 204 (10), 135 (100), 105 (12), 92 (17), and 77 (36).

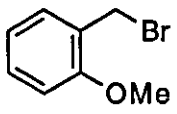
Ethyl 1-(4-bromophenyl)-3-(2-methoxy-phenyl)-3-oxopropanoate 323



A solution of 4-bromoaniline (0.183 g, 1.06 mmol), mixed xylenes (25 ml) and ethyl 3-(2-methoxyphenyl)-3-oxopropanoate (0.251 g, 1.13 mmol) was heated at reflux for 22 h. The xylenes were removed under reduced pressure at elevated temperature. The resulting residue was taken up in ethyl acetate and washed with dilute HCl (2M; 50 ml),

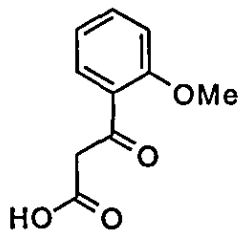
water (50 ml), and saturated brine (25 ml). The crude was preadsorbed onto silica and subjected to FSGCC (3:1 light light petroleumeum:EtOAc) to give *ethyl 1-(4-bromophenyl)-3-(2-methoxyphenyl)-3-oxopropanoate* **323** (0.236 g, 64%) as an off white solid; m.p. 119-120°C (light light petroleumeum/EtOAc); (Found: C, 54.97; H, 4.04; N, 3.96%. $C_{16}H_{14}BrNO_3$ requires C, 55.19; H, 4.05; N, 4.02%); (Found: M^+, 347.0150. $C_{16}H_{14}BrNO_3$ requires 347.0158); ν_{max}(parrafin oil)/cm^{-1} 3321, 1675, 1655, 1589, 1508, 1253, 1115, 1032, 817, and 768; δ_H (250 MHz; $CDCl_3$) 3.94 (3H, s), 4.14 (2H, s), 6.95-7.08 (2H, m), 7.40-7.58 (5H, m), 7.75 (1H, dd, *J* 7.7 & 1.8 Hz), and 9.42 (1H, br.s); δ_C (62.5 MHz; $CDCl_3$) 49.93 (CH_2), 55.68 (CH_3), 111.79 (CH), 116.82 (C), 120.94 (CH), 121.68 (CH), 127.19 (C), 130.64 (CH), 131.91 (CH), 135.07 (CH), 136.93 (C), 159.05 (C), 164.61 (C=O), and 198.55 (C=O); *m/z* 349 (M^+, 9%), 347 (M^+, 9), 173 (27), 171 (28), 135 (100), 105 (7), 92 (22), and 77 (33).

2-Methoxybenzyl bromide 304



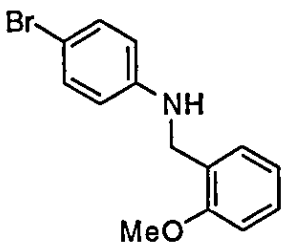
2-Methoxybenzyl alcohol (0.690 g, 5.0 mmol) in dioxane (22 ml) was treated with a solution of phosphorous tribromide (~0.755 g, 2.8 mmol) in dioxane (3 ml) and the mixture stirred under a nitrogen atmosphere for 3 h. TLC showed complete conversion and thus the reaction was carefully quenched with water (3 ml) and chloroform (45 ml) was added. After stirring for a few minutes the mixture was neutralised with saturated sodium bicarbonate solution. The organic layer was separated and dried over Na2SO4 before filtration and removal of solvent from an aliquout for analysis purposes. This gave pure *2-methoxybenzyl bromide* **304** (99%) as a colourless solid, which could be stored in solution (dioxane/CHCl3, ~1:3; ~1g/100 ml) in the freezer for several months without significant decomposition; m.p. 44-46°C (lit.,[173] 46°C); δ_H (250 MHz; $CDCl_3$) 3.90 (3H, s), 4.57 (2H, s), 7.00-6.85 (2H, m), and 7.20-7.40 (2H, m); δ_C (62.5 MHz; $CDCl_3$) 29.00 (CH_2), 55.51 (CH_3), 110.90 (CH), 120.62 (CH), 126.02 (C), 130.15 (CH), 130.84 (CH), and 157.40 (C).

3-(2-Methoxyphenyl)-3-oxopropanoic acid 330



Following the method of van der Baan et. al.,[149] two equivalents of the lithium salt of bis(trimethylsilyl)malonate at 0°C was treated with 2-anisoyl chloride (1 eq, 5 mmol). After workup essentially pure *3-(2-methoxyphenyl)-3-oxopropanoic acid* **330** (0.890 g, 92%) was isolated as a cream solid (~8:1 mixture of keto:enol tautomers by ^{1}H NMR); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3400-2500, 1749, 1718, 1673, 1599, 1487, 1446, 1438, 1245, 1164, and 1023; δ_H (250 MHz; $CDCl_3$) keto: 3.94 (3H, s), 4.09 (2H, s), 6.98-7.10 (2h, m), 7.52-7.60 (1H, m), 7.89-7.93 (1H, m); enol: 3.91 (3H, s), 6.09 (1H, s), and 12.43 (<1H, s); δ_C (100.6 MHz; $CDCl_3$) keto: 49.33 (CH_2), 55.29 (CH_3), 111.69 (CH), 120.45 (C), 120.80 (CH), 131.00 (CH), 135.19 (CH), 159.33 (C), 173.07 (C=O), and 193.62 (C=O).

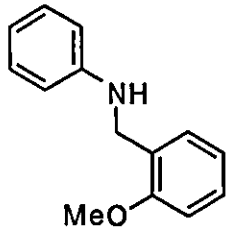
***N* 1-(2-methoxybenzyl)-4-bromoaniline 329**



4-Bromoaniline (2.82 g, 32.8 mmol) was taken up in dichloromethane (10 ml) and molecular sieves (4Å; oven dried; 11 g) were added. The mixture was cooled in an ice bath then a solution of 2-methoxybenzaldehyde (2.26 g, 16.4 mmol) in dichloromethane (2.5 ml) was added slowly with stirring, followed by more molecular sieves (4Å; oven dried; 11 g), then more aldehyde (2.26 g, 16.4 mmol) in dichloromethane (2.5 ml). After stirring for 1 h the molecular sieves were filtered off over Celite. The solvent was removed under reduced pressure to give the imine product (7.1 g) as a yellow oil; the imine was taken up in methanol (10 ml) and the solution cooled in an ice bath before slow addition of suspension of sodium borohydride (2.365 g, 62.5 mmol). The reaction was stirred for 2.5 h and then quenched with saturated sodium bicarbonate (30 ml). The resulting mixture was stirred overnight then water (50 ml) was added and the solution extracted with ether (75 ml, 2x50 ml). The combined ether extracts were washed with water (50 ml) and saturated brine, then dried (Na_2SO_4). Removal of the desiccant and solvents afforded essentially pure *N 1-(2-methoxybenzyl)-4-bromoaniline* **329** (7.08 g, 74%) as an oil which solidifies to an off-white solid on cooling, and which

could be recrystallised (light light petroleumeum/EtOAc at -25°C) to give colourless crystals of microanalytical purity; m.p. 57-58°C (light light petroleumeum/EtOAc); (Found: C, 57.47; H, 4.81; N, 4.75%. $C_{14}H_{14}BrNO$ requires C, 57.55; H, 4.83; N, 4.79%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3684, 2941, 1596, 1497, 1466, and 816; δ_H (250 MHz; $CDCl_3$) 3.85 (3H, s), 4.20 (1H, br.s), 4.29 (2H, s), 6.47-6.55 (2H, AA'BB'), 6.85-6.95 (2H, m), and 7.18-7.28 (4H, m); δ_C (62.5 MHz; $CDCl_3$) 43.47 (CH_2), 55.29 (CH_3), 108.85 (C), 110.29 (CH), 114.62 (CH), 120.51 (CH), 126.74 (C), 128.46 (CH), 128.77 (CH), 131.81 (CH), 147.31 (C), and 157.34 (C); *m/z* 291 (M^+, 100%), 213 (31), 171 (22), 121 (95), and 91 (92).

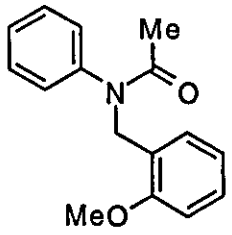
_N_ 1-(2-methoxybenzyl)aniline 331



Aniline (3.055 g, 32.8 mmol) was taken up in dichloromethane (10 ml) and molecular sieves (4A; oven dried; 11 g) were added. The mixture was cooled in an ice bath then a solution of 2-methoxybenzaldehyde (2.23 g, 16.4 mmol) in dichloromethane (2.5 ml) was added slowly with stirring, followed by more molecular sieves (4A; oven dried; 11 g), then more aldehyde (2.23 g, 16.4 mmol) in dichloromethane (2.5 ml). After stirring for 2.5 h the molecular sieves were filtered off and washed with dichloromethane. The solvent was removed under reduced pressure to give the imine product (5.80 g) as a yellow oil; the imine was taken up in methanol (30 ml) and the solution cooled in an ice bath before slow addition of sodium borohydride (1.86 g, 49.2 mmol). The reaction was stirred for 1.5 h and then quenched with saturated sodium bicarbonate (30 ml). Water (50 ml) was added and the solution extracted with ether (80 ml, 2x100 ml). The combined ether extracts were washed with water (50 ml) and saturated brine, then dried (Na_2SO_4). Removal of the dessicant and solvents afforded essentially pure *N 1-(2-methoxybenzyl)aniline* **331** (5.62 g, 80%) as an off-white solid, which could be recrystallised (light light petroleumeum/EtOAc) to give cream coloured crystals of microanalytical purity (4.90 g, 70 %); m.p. 94°C (light light petroleumeum/EtOAc; lit.,[174] 94°C from ethanol); (Found: C, 78.84; H, 7.16; N, 6.60%. $C_{14}H_{15}NO$ requires C, 78.84; H, 7.09; N, 6.57%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3443, 2910, 2840, 1602, 1590, 1330, 1179, 1121, 1091, 1066, 1049, 1030, and 872; δ_H (250 MHz; $CDCl_3$) 3.85 (3H, s), 4.20 (1H, br.s), 4.32 (2H, s), 6.60-6.72 (3H, m), 6.85-6.94 (2H, m), and 7.11-7.32 (4H, m); δ_C (62.5 MHz; $CDCl_3$) 43.41 (CH_2), 55.24 (CH_3), 110.18 (CH), 113.01 (CH), 117.27 (CH),

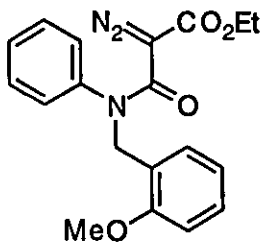
120.47 (CH), 127.26 (C), 128.24 (CH), 128.84 (CH), 129.12 (CH), 148.36 (C), and 157.33(C).

_N_ 1-(2-methoxybenzyl)-_N_-1-phenyl-acetamide 335



Aniline **331** (1.075 g, 5.05 mmol) was taken up in dichloromethane (30 ml) and treated with triethylamine (1.41 ml, 10.10 mmol) and acetic anhydride (0.566 g, 5.55 mmol). The solution was stirred vigourously for 21 h, then the solvent and excess reagents were removed under reduced pressure and the residue taken up in dichloromethane. Preadsorption on silica and FSGCC on a short column (1:1 light light petroleumeum/EtOAc) gave *N 1-(2-methoxybenzyl)-N-1-phenylacetamide* **335** (~1.3 g, 99%) as a pale yellow oil; (Found: M^+, 255.1259. $C_{16}H_{17}NO_2$ requires 255.1259); ν_{max}(film)/cm^{-1} 2937, 2837, 1654, 1596, 1496, 1395, 1244, 1120, 1029, 756, and 700; δ_H (250 MHz; $CDCl_3$) 1.91 (3H, s), 3.58 (3H, s), 4.95 (2H, s), 6.75 (1H, d, *J* 8.2 Hz), 6.89 (1H, t, *J* 7.4 Hz), 6.95-7.14 (2H, m), and 7.15-7.35 (4H, m); δ_C (100.6 MHz; $CDCl_3$) 22.69 (CH_3), 47.22 (CH_2), 55.95 (CH_3), 110.11 (CH), 120.31 (CH), 125.30 (C), 127.47 (CH), 127.94 (CH), 128.31 (CH), 129.07 (CH), 129.70 (CH), 143.15 (C), 157.24 (C), and 170.37 (C=O); *m/z* 255 (M^+, 33%), 212 (11), 155 (11), 121 (100), 91 (55), and 77 (14).

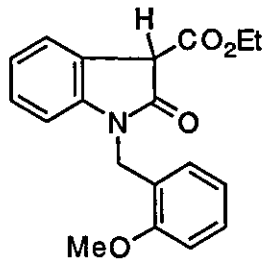
Ethyl 2-diazo-3-[(2-methoxybenzyl)-anilino]-3-oxopropanoate 343



Standard methods were used to condense ethyl diazomalonyl chloride (0.448 g, 2.54 mmol) with *N* 1-(2-methoxybenzyl)aniline **331** (0.452 g, 2.12 mmol) to afford *ethyl 2-diazo-3-[(2-methoxybenzyl)anilino]-3-oxopropanoate* **343** (0.709 g, 95%) as yellow crystals after FSGCC and recrystallisation; m.p. 95°C (light petroleum/EtOAc/EtOH); (Found: C, 64.68; H, 5.23; N, 11.71. $C_{19}H_{19}N_3O_4$ requires C, 64.58; H, 5.42; N, 11.89); (Found: MH^+, 354.1454. $C_{19}H_{20}N_3O_4$ requires 354.1454); δ_H (250 MHz; $CDCl_3$) 1.12 (3H, t, *J* 7.1 Hz), 3.66 (3H, s), 4.01 (2H, t, *J* 7.1 Hz), 5.04 (2H, s), 6.78 (1H, d, *J* 8.3 Hz), 6.91 (1H, dt, *J* 7.4 and 0.7 Hz), 7.10-7.32 (6H, m), and 7.40 (1H, dd, *J* 7.4 and 1.4 Hz);

δ_C (100.6 MHz; $CDCl_3$)14.13 (CH_3), 49.26 (NCH_2), 55.02 (CH_3), 61.24 (OCH_2), 66.71 ($C=N_2$), 110.04 (CH), 120.46 (CH), 125.05 (C), 125.94 (CH), 126.57 (CH), 128.37 (CH), 128.85 (CH), 128.92 (CH), 143.09 (C), 157.00 (C), 160.94 (C=O), and 161.89 (C=O); *m/z* (CI) 354 (MH^+, 66%), 328 (48), 254 (42), 214 (32), 212 (100), and 136 (19).

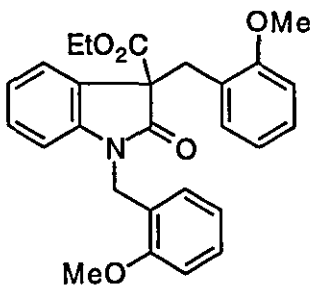
Ethyl 1-(2-methoxybenzyl)-2-oxo-3-indolinecarboxylate 342



A solution of diazoamide **343** (0.542 g, 1.535 mmol) in dichloromethane (17 ml) was treated with a catalytic amount of pfm. After 4 h analysis of the crude by infrared and NMR spectroscopy showed completion of reaction. The result was a clean mixture of oxindole **342a** and its enol tautomer **342b** (approximately 4:1). No attempt was made to purify by chromatography as streaking on TLC was an indication of instability on silica; the material was taken on to the next step.

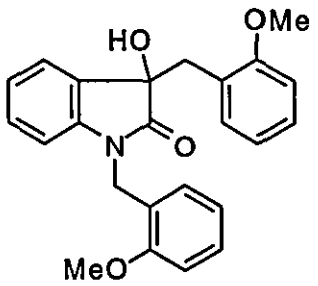
(Found: MNH_4^+, 343.1658. $C_{19}H_{23}N_2O_3$ requires 343.1658); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3684, 2962, 2841, 1743, 1714, 1614, 1493, 1467, 1365, 1300, 1243, 1162, 1149, 1117, and 1029; δ_H (250 MHz; $CDCl_3$) keto tautomer: 1.28 (3H, t, *J* 7.1 Hz), 3.88 (3H, s), 4.25 (2H, m), 4.50 (1H, s), 4.88 and 5.04 (2H, AB, *J* 16.3 Hz), 6.70-7.36 (8H, m); δ_H (250 MHz; $CDCl_3$) enol tautomer: 1.45 (3H, t, *J* 7.1 Hz), 3.88 (3H, s), 4.43 (2H, q, *J* 7.1 Hz), 4.94 (1H, br.s), 5.26 (2H, s), 6.70-7.36 (7H, m), and 7.76 (1H, d, *J* 7.7 Hz); δ_C (62.5 MHz; $CDCl_3$) keto tautomer: 13.97 (CH_3), 38.43 (CH_2), 55.27 (CH_3), 61.99 (CH_2), 109.51 (CH), 110.20 (CH), 120.61 (CH), 122.61 (CH), 123.20 (C), 123.44 (C), 124.17 (CH), 127.82 (CH), 128.57 (CH), 129.03 (CH), 143.98 (C), 156.92 (C), 166.98 (C=O), and 170.96 (C=O); δ_C (62.5 MHz; $CDCl_3$) enol tautomer: 14.55 (CH_3), 39.87 (CH_2), 55.27 (CH_3), 59.97 (CH_2), 109.68 (CH), 110.15 (CH), 119.15 (CH), 120.56 (CH), 121.06 (CH), 121.95 (CH), 122.11 (C), 123.95 (C), 127.62 (CH), 127.70 (C), 127.99 (C), 128.50 (C), and 128.71 (CH); *m/z* (CI) 343 (MNH_4^+, 23%), 326 (46), 254 (100), 138 (8), and 121 (8)

Ethyl 1,3-di(2-methoxybenzyl)-2-oxo-3-indolinecarboxylate 341



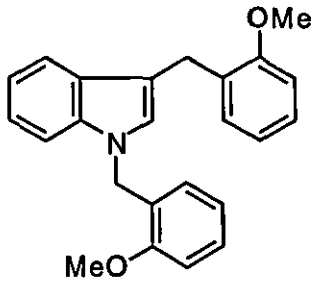
Sodium hydride (0.038 g, 1.58 mmol) was suspended in DMF (6 ml) and cooled in an ice bath before slow addition of a solution of oxindole **342** (0.428 g, 1.317 mmol) in DMF (12 ml). The resulting mixture was stirred for 40 mins and then treated with a solution of 2-methoxy benzyl bromide (0.318 g, 1.582 mmol) in DMF (6 ml). The mixture was stirred for a further 1.5 h allowing the temperature to rise to ambient, before quenching carefully with a few drops of water. The suspension was poured into water (250 ml) and extracted with ether (250, 200 and 150 ml). The extracts were combined, washed with water (250 ml) then saturated brine, and finally dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded crude product as a yellow oil which on scratching gave a cream solid. Recrystallisation from light petroleum/ethyl acetate/ethanol gave pure *ethyl 1,3-di(2-methoxybenzyl)-2-oxo-3-indolinecarboxylate* **341** (0.448 g, 77%) as colourless crystals; m.p. 138-139°C (light petroleum/EtOAc/EtOH); (Found: C, 72.70; H, 5.93; N, 2.66. $C_{27}H_{27}NO_5$ requires C, 72.79; H, 6.11; N, 3.14); (Found: M^+, 445.1889. $C_{27}H_{27}NO_5$ requires 445.1889); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1739, 1714, 1610, 1495, 1366, and 1030; δ_H (250 MHz; $CDCl_3$) 1.19 (3H, t, *J* 7.1 Hz), 3.48 (3H, s), 3.49 (1H, AB, *J* 13.5 Hz), 3.85 (3H, s), 4.01 (1H, AB, *J* 13.5 Hz), 4.12-4.22 (2H, m), 4.83 (2H, s), 6.41-6.72 (5H, m), and 6.80-7.33 (7H, m); δ_C (100.6 MHz; $CDCl_3$) 13.88 (CH_3), 31.94 (CH_2), 38.36 (NCH_2), 54.55 (OCH_3), 55.23 (OCH_3), 60.86 (OCH_2), 61.93 (OCH_2), 109.77 (CH), 109.86 (CH), 109.91 (CH), 120.07 (CH), 120.49 (CH), 121.54 (CH), 123.26 (C), 123.58 (C), 124.68 (CH), 127.16 (CH), 127.39 (C), 128.02 (CH), 128.08 (CH), 128.52 (CH), 131.53 (CH), 143.41 (C), 156.73 (C), 157.45 (C), 169.62 (C), and 174.33 (C); *m/z* 445 (M+, 2%), 399 (1), 324 (1), 121 (100), and 91 (77).

3-Hydroxy-1,3-di(2-methoxybenzyl)-2-indolinone 340



Sodium hydroxide pellets (0.370 g, 9.25 mmol) were added to a solution of ester **341** (0.410 g, 0.921 mmol) in THF/water (3:1; 75 ml). The mixture was stirred vigourously and set to reflux for 19 h under an oxygen atmosphere. After cooling to room teperature the mixture was carefully acidified with dilute HCl (2M; added until cloudiness just disappears), and then partitioned between ether (210 ml) and water (160 ml). The aqueous layer was further extractedwith ether (210 ml). The ether extracts were combined and washed with water (100 ml) and then saturated brine (50 ml), before drying ($MgSO_4$), filtration and concentration under reduced pressure to afford crude product. FSGCC (3:1 light petroleum: ethyl acetate) gave the desired *3-hydroxy-1,3-di(2-methoxybenzyl)-2-indolinone* **340** (0.335 g, 94%) as a colourless solid; m.p. 141-142°C (light petroleum/EtOAc); (Found: MH^+, 390.1705. $C_{24}H_{24}NO_4$ requires 390.1705); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3190, 2941, 2840, 1722, 1616, 1494, 1468, 1364, 1177, 1116, 1051, and 1029; δ_H (250 MHz; $CDCl_3$) 2.93 and 3.70 (2H, AB, *J* 13.5 Hz), 3.72 (3H, s), 3.88 (3H, s), 4.72 and 5.02 (2H, AB, *J* 16.4 Hz), 6.64 (1H, d, *J* 7.8 Hz), 6.78-7.00 (8H, m), 7.10-7.32 (6H, m), and 7.05-7.28 (3H, m); δ_C (100.6 MHz; $CDCl_3$) 38.34 (CH_2), 38.56 (CH_2), 55.28 (CH_3), 55.31 (CH_3), 109.22 (CH), 110.13 (CH), 110.59 (CH), 120.54 (CH), 120.66 (CH), 122.14 (CH), 122.97 (C), 123.48 (C), 124.91 (CH), 127.74 (CH), 128.45 (CH), 128.56 (CH), 129.21 (CH), 129.68 (C), 132.59 (CH), 142.54 (C), 156.93 (C), 157.78 (C), and 178.50 (C=O); *m/z* (CI) 390 (MH+, 14%), 374 (87), 268 (23), 254 (100), 238 (18), 138 (30), and 123 (28).

1,3-Di(2-methoxybenzyl)-1 *H*-indole 339



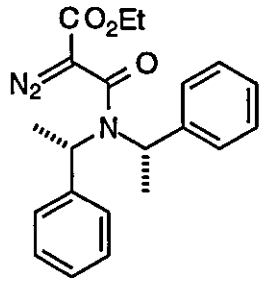
Hydroxy oxindole **340** (0.297 g, 0.763 mmol) was taken up in THF (35 ml) and then treated with borane-dimethyl sulfide complex (~10M; 0.19 ml, 1.90 mmol). The solution

was stirred gently at room temperature for 64 h and a white precipitate was observed. The reaction was quenched with dilute HCl (2M; 8 ml), diluted with water (40 ml) and extracted with ether (3 x 90 ml). The ether extracts were combined and washed with water (90 ml) and saturated brine (90 ml). Drying ($MgSO_4$), filtration and removal of solvents under reduced pressure gave pure *1,3-di(2-methoxybenzyl)-1H-indole* **339** (0.273 g, 99%) as an oily solid; m.p. 78-79°C (light petroleum/EtOAc); (Found: C, 80.41; H, 6.39; N, 3.52. $C_{24}H_{23}NO_2$ requires C, 80.64; H, 6.49; N, 3.92); (Found: M^+, 357.1729. $C_{24}H_{23}NO_2$ requires 357.1729); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3051, 2937, 2836, 1493, 1464, 1439, 1243, 1030, and 752; δ_H (250 MHz; $CDCl_3$) 3.84 (3H, s), 3.85 (3H, s), 4.10 (2H, s), 5.26 (2H, s), 6.65-6.70 (6H, m), and 7.00-7.30 (6H, m); δ_C (100.6 MHz; $CDCl_3$) 25.13 (CH_2), 44.86 (NCH_2), 55.24 (CH_3), 55.32 (CH_3), 109.65 (CH), 110.00 (CH), 110.10 (CH), 113.78 (C), 118.67 (CH), 119.33 (CH), 120.35 (CH), 120.55 (CH), 121.36 (CH), 126.18.97 (C), 126.92 (CH), 127.16 (CH), 127.76 (CH), 128.21 (C), 128.47 (CH), 129.83 (C), 129.85 (CH), 136.79 (C), 156.60 (C), and 157.24 (C);*m/z* 357 (M+, 18%), 236 (11), 220 (15), 130 (10), 121 (100), and 91 (92).

6.5. Experimental Details for Chapter 5

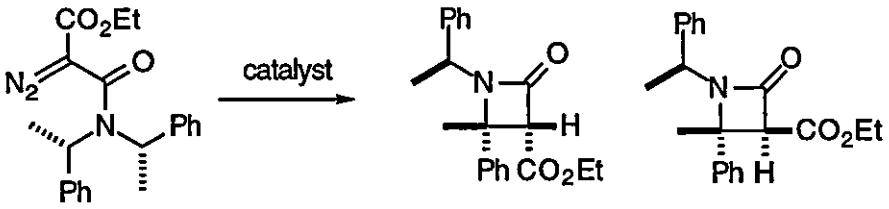
Preparation and Rh(II) Catalysed Decomposition Chemistry of Chiral Diazomalonamides

Ethyl 2-diazo-3-{di[(1S)-1-phenylethyl]amino}-3-oxopropanoate 355



Standard procedures were adopted to convert (-)-*bis*[(S)-1-phenylethyl]amine hydrochloride salt to *ethyl 2-diazo-3-{di[(1S)-1-phenylethyl]amino}-3-oxopropanoate* **355** (0.171 g, 47%); m.p. 52-53°C (light petroleum); (Found: C, 69.01; H, 6.45; N, 11.38. $C_{21}H_{19}N_3O_6$ requires C, 69.02; H, 6.34; N, 11.49); $[\alpha]_D^{21}$ -85.4 (c= 0.192, $CHCl_3$); ν_{max}(GGATR)/cm^{-1} 2983, 2127, 1715, 1615, 1417, 1323, 1283, and 1099; δ_H (300 MHz; $CDCl_3$) 1.30 (3H, t, J 7.1 Hz), 1.77 (3H, d, J 7.0 Hz), 4.26 (2H, q, *J* 7.1 Hz), 4.91 (1H, q, *J* 7.0 Hz), and 7.10-7.25 (10H, m); δ_C (75.5 MHz; $CDCl_3$) 14.44 (CH_3), 18.62 (CH_3), 55.94 (NCH), 61.45 (OCH_2), 127.24 (CH), 127.74 (CH), 128.04 (CH), 140.43 (C), 160.35 (C=O), 163.21 (C=O); *m/z* 337 ($M-N_2^+$, 2%), 264 ($M-N_2-CO_2Et^+$, 6), 222 (14), 208 (8), 190 (24), 105 (100), and 77 (31).

Rhodium Catalysed Decomposition of Diazoamide 355



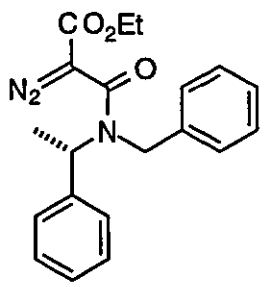
356 **357**

A solution of diazoamide **355** (0.100 g, 0.274 mmol) in dry dichloromethane (5.5 ml) was treated with rhodium(II) perfluorobutyramide (0.006 g) and the mixture stirred at room temperature until the starting material was largely consumed (TLC; about 21 h). The mixture was preadsorbed onto silica and subjected to flash silica gel column chromatography to afford a mixure of: *ethyl (2R, 3R)-2-methyl-4-oxo-2-phenyl-1-[(1S)-1-phenylethyl]azetane-3-carboxylate* **356** (41%): (Found: M^+, 37.16688. $C_{21}H_{23}NO_3$

requires 337.16779); ν_{max}(film)/cm^{-1} 3064, 2981, 2935, 1760, 1732, 1448, 1316, 1262, 1029, 913, 731, and 699; δ_H (300 MHz; $CDCl_3$) 0.76 (3H, t, J 7.1 Hz), 1.72 (3H, d, J 7.1 Hz), 1.91 (3H, s), 3.64 (2H, m), 3.96 (1H, s), 4.40 (1H, q, *J* 7.1 Hz), 7.17 (5H, m), 7.26-7.40 (3H, m), and 7.46 (2H, m); δ_C (75.5 MHz; $CDCl_3$) 13.48 (CH_3), 21.66 (CH_3), 25.05 (CH_3), 54.86 (CH), 60.90 (OCH_2), 64.92 (C), 66.88 (CH), 126.68, (CH), 127.36 (CH), 127.52 (CH), 127.93 (CH), 128.04 (CH), 128.67 (CH), 138.46 (C), 141.89 (C), 160.73 (C=O), 166.08 (C=O); *m/z* 337 (M^+, 2%), 322 (2), 264 (M-CO_2Et^+, 6), 190 (98), 160 (23), 145 (72), 132 (25), 115 (34), 105 (100), and 77 (38); and *ethyl (2R,3S)-2-methyl-4-oxo-2-phenyl-1-[(1S)-1-phenylethyl]azetane-3-carboxylate* **357** (27%): (Found: M^+, 337.16721. $C_{21}H_{23}NO_3$ requires 337.16779); ν_{max}(film)/cm^{-1} 2978, 1755, 1725, 1679, 1447, 1307, 1256, and 1179; δ_H (300 MHz; $CDCl_3$) 1.29 (3H, t, J 7.1 Hz), 1.62 (3H, d, J 7.2 Hz), 1.72 (3H, s), 3.93 (1H, s), 4.25 (2H, m), 4.51 (1H, q, *J* 7.2 Hz), and 7.20-7.40 (10H, m); δ_C (75.5 MHz; $CDCl_3$) 14.26 (CH_3), 19.64 (CH_3), 20.74 (CH_3), 54.81 (NCH), 61.40 (OCH_2), 62.90 (C), 66.46 (CH), 125.55, (CH), 127.35 (CH), 127.56 (CH), 127.96 (CH), 128.53 (CH), 128.57 (CH), 141.50 (C), 142.06 (C), 162.68 (C=O), 166.67 (C=O); *m/z* 337 (M^+, 1%), 322 (1), 264 (M-CO_2Et^+, 8), 190 (76), 145 (65), 132 (24), 115 (26), 105 (100), 91 (12), and 77 (38); along with a little starting material (0.006 g, 6%) and a trace of cyloheptapyrrolone product.

Rhodium(II) acetate catalysed decomposition of diazoamide **355** at room temperature in dichloromethane for 71 h gave a mixture of **356** and **357** (47 and 29% isolated yields respectively).

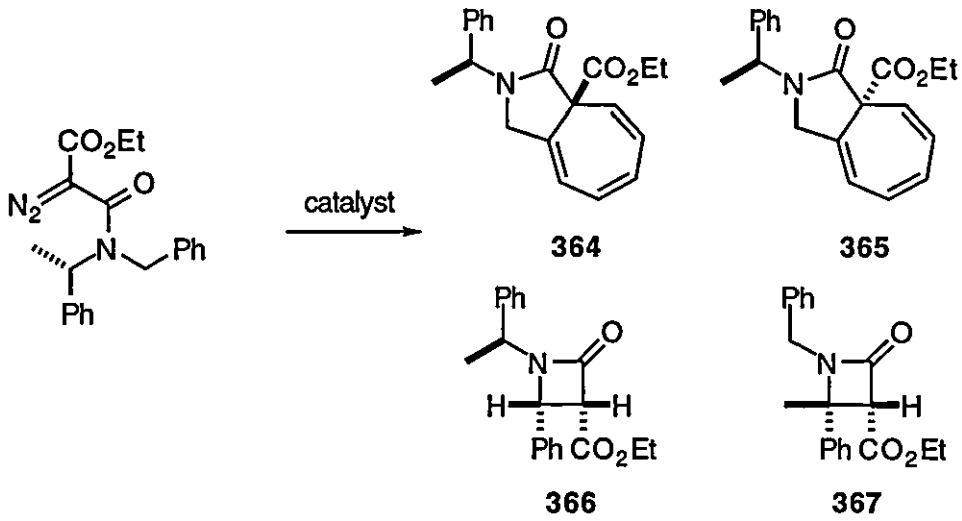
Ethyl 3-{benzyl[(1S)-1-phenylethyl]amino}-2-diazo-3-oxopropanoate 363



Standard procedures were adopted to convert (S)(-)-*N*-benzyl-1-phenylethylamine to *ethyl 3-{benzyl[(1S)-1-phenylethyl]amino}-2-diazo-3-oxopropanoate* **363** (0.262 g, 75%); (Found: MH^+, 352.1661. $C_{20}H_{22}N_3O_3$ requires 352.1661); $[\alpha]_D^{22}$ -74.0 (c= 0.164, $CHCl_3$); ν_{max}(GGATR)/cm^{-1} 3029, 2125, 1706, 1621, 1411, 1280, 1107, and 747; δ_H (300 MHz; $CDCl_3$) 1.29 (3H, t, J 7.1 Hz), 1.62 (3H, d, J 7.0 Hz), 4.03 (1H, AB, *J* 16.1 Hz), 4.26 (2H, q, *J* 7.1 Hz), 4.66 (1H, AB, *J* 16.1 Hz), 5.47 (1H, q, *J* 7.0 Hz), and 7.09-7.40 (10H, m); δ_C (75.5 MHz; $CDCl_3$) 14.44 (CH_3), 17.32 (CH_3), 47.57 (NCH_2), 56.53

(NCH), 61.43 (OCH_2), 67.24 ($C=N_2$), 126.72 (CH), 126.96 (CH), 127.20 (CH), 127.64 (CH), 128.43 (CH), 128.65 (CH), 138.18 (C), 140.40 (C), 162.51 (C=O), 162.54 (C=O); *m/z* 352 (M^+, 18%), 341 ($[MNH_4-N_2]^+$, 12), 326 (22), 210 (100), 134 (24), and 120 (14).

Rhodium Catalysed Dcomposition of Diazoamide 363



A solution of diazoamide **363** (0.140 g, 0.40 mmol) in dry dichloromethane (8 ml) was treated with rhodium(II) perfluorobutyramide (catalytic amount) and the mixture stirred at room temperature until the starting material was consumed (TLC; about 48 h). The mixture was preadsorbed onto silica and subjected to flash silica gel column chromatography to afford a mixure of diastereomers **364** and **365** (56:44 ratio by analytical HPLC; 12% d.e.; 0.045 g, 35%) along with a mixture of **366** and **367** (0.051 g, 40%). The two mixtures were separated by preparative HPLC (Dynamax column; eluant 10:90 and 2:98 ethyl acetate:hexane for the two mixtures respectively; flow rate 15 ml/min; UV detection at 260 nm) to give each component as a colourless oil:

364/365: *ethyl (3aS)-3-oxo-2-[(1S)-1-phenylethyl]-1,2,3,3a-tetraydrocyclohepta[c]-pyrrole-3a-carboxylate* and *ethyl (3aR)-3-oxo-2-[(1S)-1-phenylethyl]-1,2,3,3a-tetraydro-cyclohepta[c]pyrrole-3a-carboxylate* of which:

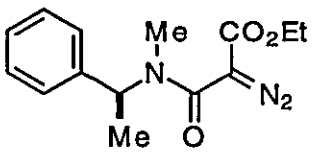
diastereomer 1: (Found: M^+ 323.15147. $C_{20}H_{21}NO_3$ requires 323.15214); ν_{max} (film)/cm^{-1} 2925, 2853, 1740, 1706, 1497, 1455, 1388, 1224, 1028, 735, and 700; δ_H (250 MHz; $CDCl_3$) 1.11 (3H, t, J 7.1 Hz), 1.59 (3H, d, J 7.1 Hz), 3.95-4.25 (4H, m), 5.60-5.65 (2H, m), 6.25 (1H, m), 6.40-6.52 (3H, m), and 7.25-7.50 (5H, m); δ_C (75.5 MHz; $CDCl_3$) 13.97 (CH_3), 16.22 (CH_3), 46.25 (NCH_2), 49.49 (NCH), 61.68 (OCH_2), 120.51 (CH), 122.45 (CH), 127.06 (CH), 127.69 (CH), 128.20 (CH), 128.30 (CH), 128.61 (CH), 129.90 (CH), 130.71 (C), 139.30 (C), 168.00 (C=O), and 171.08 (C=O); *m/z* 323 (M^+, 2%), 250 (74), 176 (8), 146 (12), 128 (14), 105 (100), 91 (38), and 77 (20); diastereomer 2: (Found: M^+ 323.15147. $C_{20}H_{21}NO_3$ requires 323.15214); ν_{max}

(film)/cm^{-1} 2981, 2928, 1734, 1702, 1654, 1457, 1363, 1223, 1028, and 700; δ_H (250 MHz; $CDCl_3$) 1.17 (3H, t, *J* 7.1 Hz), 1.63 (3H, d, *J* 7.1 Hz), 3.72 and 4.33 (2 x 1H, AB, *J* 15.0 Hz), 4.00-4.25 (2H, m), 5.60 (1H, q, *J* 7.1 Hz), 5.64 (1H, m), 6.22 (1H, m), 6.39-6.46 (3H, m), and 7.25-7.45 (5H, m); δ_C (75.5 MHz; $CDCl_3$) 14.05 (CH_3), 15.90 (CH_3), 46.31 (NCH_2), 49.78 (NCH), 61.74 (OCH_2), 120.64 (CH), 122.41 (CH), 127.02 (CH), 127.79 (CH), 128.04 (CH), 128.43 (CH), 128.71 (CH), 129.79 (CH), 130.86 (C), 139.25 (C), 167.85 (C=O), and 170.61 (C=O); *m/z* 323 (M^+, 2%), 250 (63), 176 (10), 146 (13), 128 (15), 105 (100), 91 (8), and 77 (18); along with: *ethyl (3R,4R)-2-oxo-4-phenyl-1-[(1S)-1-phenylethyl]azetane-3-carboxylate* **366** (Found: M^+ 323.15243. $C_{20}H_{21}NO_3$ requires 323.15214); ν_{max} (film)/cm^{-1} 2980, 1761, 1720, 1496, 1456, 1371, 1299, 1185, 1018, and 769; δ_H (300 MHz; $CDCl_3$) 0.81 (3H, t, *J* 7.1 Hz), 1.44 (3H, d, *J* 7.2 Hz), 3.76 (2H, q, *J* 7.1 Hz), 4.19 (1H, d, *J* 6.3 Hz), 4.59 (1H, d, *J* 6.3 Hz), 5.06 (1H, q, *J* 7.2 Hz), and 7.20-7.40 (10H, m); δ_C (75.5 MHz; $CDCl_3$) 13.65 (CH_3), 19.29 (CH_3), 52.98 (CH), 52.11 (CH), 60.02 (CH), 61.06 (CH_2), 127.33 (CH), 127.54 (CH), 127.98 (CH), 128.31 (CH), 128.76 (CH), 128.87 (CH), 135.50 (C), 139.43 (C), 163.14 (C=O), and 165.82 (C=O); *m/z* 323 (M^+, 2%), 250 (1), 194 (8), 176 (86), 148 (19), 131 (83), 105 (100), and 77 (36); and, *ethyl (2R,3R)-1-benzyl-2-methyl-4-oxo-2-phenylazetane-3-carboxylate* **367** (Found: M^+ 323.15274. $C_{20}H_{21}NO_3$ requires 323.15214); ν_{max} (film)/cm^{-1} 3023, 1768, 1723, 1217, and 749; δ_H (300 MHz; $CDCl_3$) 0.80 (3H, t, *J* 7.1 Hz), 1.66 (3H, s), 3.67 (2H, q, *J* 7.1 Hz), 3.99 (1H, s), 4.07 and 4.84 (2 x 1H, AB, *J* 15.0 Hz), and 7.25-7.40 (10H, m); δ_C (75.5 MHz; $CDCl_3$) 13.57 (CH_3), 25.22 (CH_3), 44.63 (NCH_2), 61.01 (OCH_2), 64.85 (C), 67.48 (CH), 126.54 (CH), 127.02 (CH), 128.22 (CH), 128.40 (CH), 128.71 (CH), 128.78 (CH), 136.32 (C), 137.78 (C), 162.70 (C=O), and 165.84 (C=O); *m/z* 323 (M^+, 1%), 250 (17), 208 (15), 190 (50), 161 (12), 145 (44), 115 (17), 91 (100), and 77 (14).

Diazomalonate **363** (0.052 g, 0.148 mmol) in dichloromethane (3 ml) was decomposed under $Rh_2(OAc)_4$ catalysis at room temperature. The reaction was followed by ^1H NMR and took about 5 days to go to completion. NMR analysis of the crude showed a mixture of **364, 365, 366,** and **367** in a ratio of approximately 10:10:15:65.

Diazomalonate **363** (0.051 g, 0.145 mmol) in dichloromethane (2.9 ml) was decomposed under $Rh_2(O_2CCF_3)_4$ catalysis at room temperature. The reaction was followed by ^1H NMR and took about 5 days to go to completion, including one day at reflux and addition of more catalyst. NMR analysis of the crude showed a mixture of **364, 365, 366,** and **367** in a ratio of approximately 16:16:33:33.

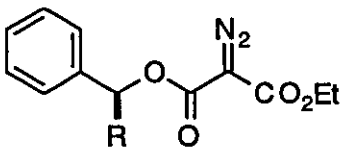
Ethyl 3-{methyl[(1S)-1-phenylethyl]amino}-2-diazo-3-oxopropanoate 368



Standard procedures were adopted to convert (S)-(-)-*N*-α-dimethylbenzylamine to *ethyl 3-{methyl[(1S)-1-phenylethyl]amino}-2-diazo-3-oxopropanoate* **368**, which was isolated as large yellow crystals (0.473 g, 93%); m.p. 30-31°C (pentane); (Found: C, 61.08; H, 6.45; N, 15.06. $C_{14}H_{17}N_3O_3$ requires C, 61.08; H, 6.22; N, 15.26); (Found: M^+, 275.1271. $C_{14}H_{17}N_3O_3$ requires 275.1270); $[\alpha]_D^{21}$ -163.0 (c= 0.378, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2948, 2940, 2133, 1710, 1618, 1400, 1288, 1267, 1076, and 896; δ_H (250 MHz; $CDCl_3$) 1.29 (3H, t, J 7.1 Hz), 1.60 (3H, d, J 7.0 Hz), 2.69 (3H, s), 4.25 (2H, q, *J* 7.1 Hz), 5.65 (1H, q, *J* 7.0 Hz), and 7.22-7.40 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 14.40 (CH_3), 15.92 (CH_3), 31.05 (NCH_3), 53.70 (NCH), 61.39 (OCH_2), 66.57 ($C=N_2$), 127.24 (CH), 127.44 (CH), 128.52 (CH), 139.87 (C), 161.96 (C=O), 162.40 (C=O); *m/z* 276 (MH^+, 78%), 275 (<1), 248 (66), 190 (52), 174 (85), 134 (83), 118 (72), and 105 (100);

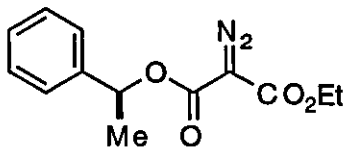
Chiral Diazomalonates and their Rh(II) Catalysed Decomposition Chemistry

General Procedure for the Preparation of Chiral Diazomalonates



A solution of the appropriate homochiral alcohol (1.0 eq) in dry THF (10 ml per mmol alcohol) was cooled to -78°C and treated with *n*-BuLi (1.6M solution in hexanes; 1.2 eq). After stirring for 1h, ethyl diazomalonyl chloride (1.3 eq) was added and the resulting mixture stirred for a further 2 h whilst allowing the temperature to rise to ambient level. The reaction was quenched with saturated NH_4Cl, diluted with water and extracted with EtOAc (x3). The combined extracts were washed with water and saturated brine, then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude product. Flash silica gel column chromatography (eluting with 9:1 light petroleum: EtOAc) afforded the desired product as a pale yellow oil.

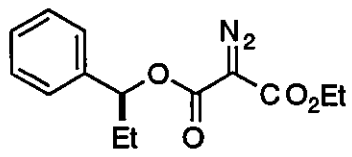
1-Ethyl 3-[(1S)-1-phenylethyl] 2-diazo-malonate 384



(R=Me; 76%)

(Found: M+NH_4^+, 280.1297. $C_{13}H_{18}N_3O_4$ requires 280.1297); $[\alpha]_D^{25}$ +29.0 (c= 0.276, $CHCl_3$); ν_{max}(GGATR)/cm^{-1} 3023, 2983, 2938, 2144, 1748, 1728, 1689, 1369, 1339, 1310, 1271, 1081, and 750; δ_H (300 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz), 1.60 (3H, d, *J* 6.6 Hz), 4.30 (2H, q, *J* 7.1 Hz), 6.04 (1H, q, *J* 6.6 Hz), and 7.39-7.26 (5H, m); Chiral Shift NMR: δ_H (250 MHz; $CDCl_3$), Eu(hfc)$_3$ (0.2 equivalents) CH_3 doublet does not split (cf. racemate); δ_C (75.5 MHz; $CDCl_3$) 14.35 (CH_3), 22.43 (CH_3), 61.66 (CH_2), 73.77 (CH), 126.05 (CH), 128.12 (CH), 128.59 (CH), 141.02 (C), 160.46 (C=O), and 161.05 (C=O); *m/z* (CI) 280 (M+NH4$^+$, 14%), 254 (20), 176 (100), 138 (75), 122 (95), and 105 (39).

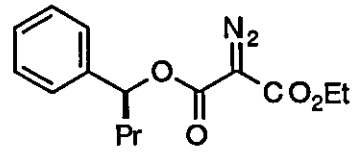
1-Ethyl 3-[(1S)-1-phenylpropyl] 2-diazo-malonate 385



(R=Et; 86%)

(Found: M+NH_4^+, 294.1454. $C_{14}H_{20}N_3O_4$ requires 294.1454); $[\alpha]_D^{23}$ +6.8 (c= 0.35, $CHCl_3$); ν_{max}(film)/cm^{-1} 2974, 2879, 2142, 1762, 1734, 1685, 1373, 1323, 1269, and 1096; δ_H (300 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7.35 Hz), 1.31 (3H, t, *J* 7.2 Hz), 1.80-2.00 (2H, m), 4.29 (2H, q, *J* 7.2 Hz), 5.81 (1H, t, *J* 6.8 Hz), and 7.39-7.25 (5H, m); δ_C (75.5 MHz; $CDCl_3$) 9.79 (CH_3), 14.36 (CH_3), 29.36 (CH_2), 61.65(CH_2), 65.42 ($C=N_2$), 78.69 (CH), 126.54 (CH), 128.09 (CH), 128.48 (CH), 139.84 (C), 160.61 (C=O), and 161.07 (C=O); *m/z* 294 (M+NH_4^+, 34%), 268 (21), 176 (100), 152 (80), 149 (35), 135(34), and 105 (42).

1-Ethyl 3-[(1S)-1-phenylbutyl] 2-diazo-malonate 386

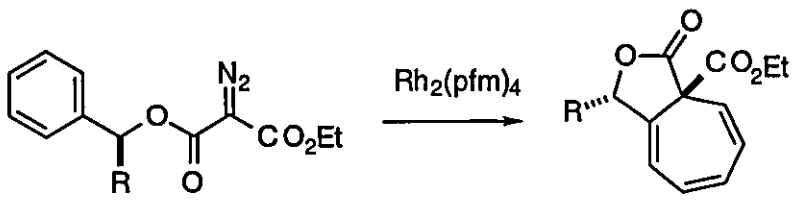


(R=Pr; 75%)

(Found M+NH_4^+ 308.1610. $C_{15}H_{22}N_3O_4$ requires 308.1610); $[\alpha]_D^{24}$= +11.8 (c=0.44; $CHCl_3$); ν_{max}(GGATR)/cm^{-1} 2967, 2150, 1761, 1735, 1692, 1371, 1309, 1273, and 1077; δ_H (300 MHz; $CDCl_3$) 0.91 (3H, t, J Hz), 1.20-1.44 (2H, m), 1.31 (3H, t, J 7.1 Hz), 1.59-1.90 (1H, m), 1.90-2.05 (1H, m), 4.29 (2H, q, J 7.1 Hz), 5.89 (1H, t, J 6.9 z), and

7.20-7.50 (5H, m); δ_C (75.5 MHz; $CDCl_3$) 13.76 (CH_3), 14.35 (CH_3), 18.67 (CH_2), 38.41 (CH_2), 61.45 (OCH_2), 77.30 (OCH), 126.51 (CH), 128.08 (CH), 128.50 (CH), 140.16 (C), 160.60 (C=O), and 161.09 (C=O); *m/z* (CI) 308 ($M+NH_4^+$, 11%), 282 (17), 176 (83), 166 (100), 150 (45), 149 (83), 132 (14), and 105 (21).

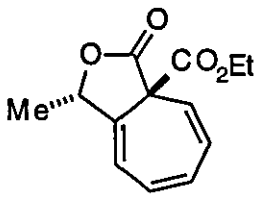
General Procedure for $Rh_2(pfm)_4$ Catalysed Decomposition of Diazomalonates



A solution of the diazomalonate in CH_2Cl_2 (ml per mmol) was set to reflux and immediately treated with a catalytic amount (1-2 mol%) of $Rh_2(pfm)_4$. reflux was maintained for 30 minutes and then the mixture was allowed to cool to ambient temperature, then filterd through Celite and the solvent removed under reduced pressure to give crude triene. Analysis of the crude NMR showed a single diastereoisomer (R= Me, Et, Pr). The trienes were in dynamic equilibrium with their norcaradiene forms but these were not detectable in NMR spectra.

Flash silica gel column chromatography (eluting with 9:1 light petroleum-EtOAc) for R=Me at this stage yielded the triene **387** as a colourless oil:

Ethyl (1S, 3aS)-1-methyl-3-oxo-3,3a-dihydro-1H-cyclohepta[c]furan-3a-carboxylate 387

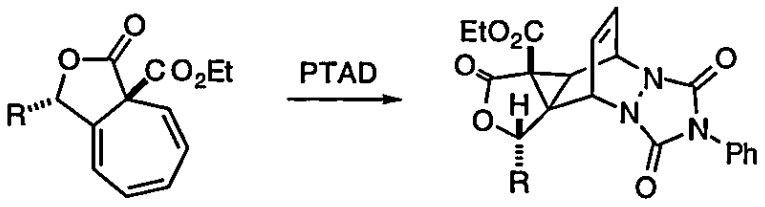


(R=Me, 28%)

(Found M-CO_2Et^+ 161.0593. $C_{10}H_9O_2$requires 161.0603); $[\alpha]_D^{27}$ -126.7 (c= 0.086, $CHCl_3$); ν_{max}(GGATR)/cm^{-1} 2924, 2846, 1778, 1735, 1454, 1215, 1928, and 757; δ_H (300 MHz; $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz), 1.50 (3H, d, *J* 6.5 Hz), 4.08 (2H, q, *J* 7.1 Hz), 5.51 (1H, dq, *J* 6.5 and 2.1 Hz), 5.57 (1H, m), 6.25 (1H, m), and 6.43-6.52 (3H, m); δ_C (75.5 MHz; $CDCl_3$) 13.93 (CH_3), 22.14 (CH_3), 58.33 (C), 62.39 (CH_2), 78.68 (CH), 119.48 (CH), 121.31 (CH), 128.42 (CH), 128.85 (CH), 130.34 (CH), 138.17 (C), 165.79 (C=O), 173.02 (C=O); *m/z* 234 (M^+, 3%), 206 (3), 161 (100), 117 (75), 105 (60), 91 (40), and 77 (45).

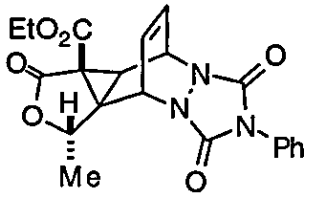
Chiral HPLC: Chiracel OD column, eluent: 99:1 hexane: isopropyl alcohol; flow rate: 0.75 ml/min; UV detection at 254 nm; retention time: 20.28 min.

General Procedure for [4+2] Cycloaddition Trapping of Norcaradienes with PTAD



Fresh CH_2Cl_2 was added to the crude triene/norcaradiene. The solution was cooled in an ice bath and treated with PTAD (1.0 eq). After stirring for 15-30 min the mixture was preadsorbed onto silica and subjected to flash silica gel column chromatography (gradient elution: 25-50% EtOAc in light petroleum) to afford the cycloadduct as a colourless solid which could be made analytically pure by recrystallisation.

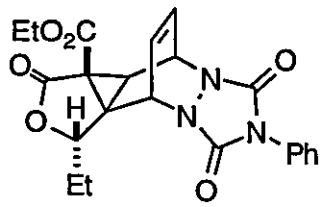
Ethyl (3S, 6R, 7R)-3-methyl-5,10,12-trioxo-11-phenyl-4-oxa-9,11,13-triazapentacyclo-[6.5.2.0^{2,6}.0.^{2,7}.0^{9,13}]pentadec-14-ene-6-carboxylate 389



(R=Me, 39%)

m.p. 166-1678°C; (Found: C, 61.51; H, 4.94; N, 10.06. $C_{21}H_{19}N_3O_6$ requires C, 61.61; H, 4.67; N, 10.26); (Found: M$^+$, 409.1283. $C_{21}H_{19}N_3O_6$ requires 409.1274); $[\alpha]_D^{25}$ -52.9 (c= 0.140, $CHCl_3$); ν_{max}(GGATR)/cm^{-1} 2981, 1778, 1718, 1502, 1408, 1251, 1073, and 766; δ_H (300 MHz; $CDCl_3$) 1.29 (3H, t, J 7.2 Hz), 1.53 (3H, d, J 6.1 Hz), 2.18 (1H, d, 4.6 Hz), 4.19 (2H, m), 5.08 (1H, q, J 6.1 Hz), 5.31 (1H, d, J 5.8 Hz), 5.525 (1H, t, J 4.6 Hz), 6.10 (1H, m), 6.29 (1H, m), and 7.30-7.50 (5H, m); δ_C (75.5 MHz; $CDCl_3$) 13.99 (CH_3), 16.64 (CH), 20.38 (CH_3), 38.28 (C), 42.68 (C), 52.21 (CH), 52.24 (CH), 62.61 (CH_2), 76.99 (CH), 125.42 (CH), 126.85 (CH), 127.43 (CH), 128.73 (CH), 129.26 (CH), 130.80 (C), 156.67 (C=O), 156.74 (C=O), 163.38 (C=O), 168.61 (C=O); *m/z* 409 (M$^+$, 1%), 336 (M-CO_2Et^+, 13), 177 (10), 161 (43), 115 (34), 105 (13), 91 (25), and 77 (17).

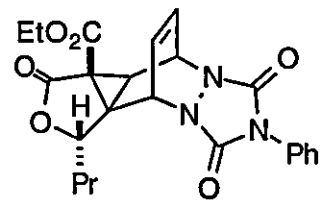
Ethyl (3S, 6R, 7R)-3-ethyl-5,10,12-trioxo-11-phenyl-4-oxa-9,11,13-triazapentacyclo-[6.5.2.0^{2,6}.0.^{2,7}.0^{9,13}]pentadec-14-ene-6-carboxylate 390



(R=Et, 41%)

m.p. 190°C (light light petroleumeum /EtOAc/EtOH); (Found: C, 62.47; H, 5.19; N, 9.79. $C_{22}H_{21}N_3O_6$ requires C, 62.40; H, 4.99; N, 9.92); (Found: M$^+$, 423.1430. $C_{22}H_{21}N_3O_6$ requires 423.1430); $[\alpha]_D^{23}$ -96.4 (c= 0.278, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1774, 1720, 1601, 1503, 1407, 1315 and 1012; δ_H (250 MHz; $CDCl_3$) 1.13 (3H, t, J 7.2 Hz) 1.28 (3H, t, J 7.2 Hz), 1.53 (3H, d, J 6.1 Hz), 2.22 (1H, d, 4.6 Hz), 4.18 (2H, m), 4.86 (1H, dd, J 9.9 and 2.6 Hz), 5.32 (1H, dd, J 5.8 and 1.5 Hz), 5.52 (1H, t, J 5.0 Hz), 6.10 (1H, m), 6.29 (1H, m), and 7.30-7.50 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 10.49 (CH_3), 13.95 (CH_3), 20.83 (CH), 24.85 (CH_2), 37.74 (C), 42.50 (C), 52.29 (CH), 52.36 (CH), 62.54 (CH_2), 82.40 (CH), 125.39 (CH), 126.79 (CH), 127.41 (CH), 128.67 (CH), 129.22 (CH), 130.89 (C), 156.67 (2xC=O), 163.38 (C=O), and 168.63 (C=O); *m/z* 423 (M$^+$, 1%), 378 (M-OEt$^+$, 2), 350 (M-CO_2Et^+, 19), 175 (PTAD$^+$, 100), 131 (38), 119 (43), 91 (85), and 77 (25).

Ethyl (3S, 6R, 7R)-3-propyl-5,10,12-trioxo-11-phenyl-4-oxa-9,11,13-triazapentacyclo-[6.5.2.0^{2,6}.0.^{2,7}.0^{9,13}]pentadec-14-ene-6-carboxylate 391



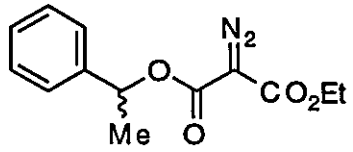
(R=Pr, 34 %)

m.p. 112-115°C (light light petroleumeum/EtOAc); (Found: C, 63.16; H, 5.67; N, 9.43. $C_{23}H_{23}N_3O_6$ requires C, 63.15; H, 5.29; N, 9.60 %); (Found: M+NH_4^+, 455.1931. $C_{23}H_{27}N_4O_6$ requires 455.1931); $[\alpha]_D^{25}$ -83.25 (c 0.386, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$1774, 1720, 1601, 1503, 1407, 1314, 1141, and 1012; δ_H (300 MHz; $CDCl_3$) 1.00 (3H, t, J 7.0 Hz) 1.29 (3H, t, J 7.0 Hz), 1.20-1.45 (2H, m), 1.46-1.84 (1H, m), 1.95-2.05 (1H, m), 2.20 (1H, d, J 4.7 Hz), 4.18 (2H, 1H, dq, J 7.0 and 2.5 Hz), 4.92 (1H, m), 5.31 (1H, dd, J 5.9 and 1.4Hz), 5.51 (1H, m), 6.09 (1H, m), 6.28 (1H, m), and 7.25-7.60 (5H, m); δ_C (100.6 MHz; $CDCl_3$) 14.17 (CH_3), 14.36 (CH_3), 21.16 (CH), 33.75 (CH_2), 38.17 (C), 42.81 (C), 52.69 (CH), 52.73 (CH), 62.96 (CH_2), 81.27 (CH), 125.80 (CH), 127.16 (CH), 127.83 (CH), 129.09 (CH), 129.63 (CH), 131.25 (C), 157.09 (C=O), 157.13 (C=O), 163.82 (C=O), and 169.09 (C=O); *m/z* (CI) 455 (M+NH_4^+, 6%), 280 (59), 219 (84), 154 (44), 137 (34), 119 (15), and 94 (100).

Preparation of Racemic Diazomalonates

Procedures described above for the preparation of chiral diazomalonates **384-386** were adopted for the preparation of the racemic diazomalonates (±)**384**, **392**, and **398** through the condensation of the appropriate commercially available racemic alcohol and ethyl diazomalonyl chloride. These diazomalonates were isolated as light yellow oils after flash silica gel column chromatography purification.

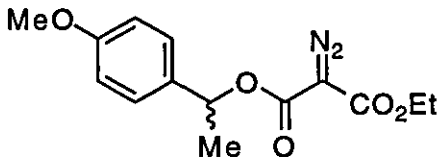
1-Ethyl 3-[(1S)-1-phenylethyl] 2-diazomalonate (±)384



(0.404 g; 94%)

(Found: MH^+, 263.1036. $C_{13}H_{15}N_2O_4$ requires 263.1032); ν_{max}(film)/cm^{-1} 2984, 2938, 2141, 1760, 1732, 1691, 1372, 1310, 1268, 1093, 760 and 700; δ_H (250 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz), 1.60 (3H, d, *J* 6.6 Hz), 4.30 (2H, q, *J* 7.1 Hz), 6.04 (1H, q, *J* 6.6 Hz), and 7.39-7.26 (5H, m); Chiral Shift NMR: δ_H (250 MHz; $CDCl_3$) Eu(hfc)$_3$ (0.2 equivalents) CH_3 doublet splits into two doublets (1.66 and 1.79 ppm) of ratio 1:1; δ_C (100.6 MHz; $CDCl_3$) 14.31 (CH_3), 22.38 (CH_3), 61.61 (CH_2), 73.74 (CH), 126.02 (CH), 128.08 (CH), 128.56 (CH), 141.02 (C), 160.42 (C=O), and 161.01 (C=O); *m/z* 263 (MH^+, 18%), 215 (24), 159 (76), 121 (26), 105 (100), and 77 (18).

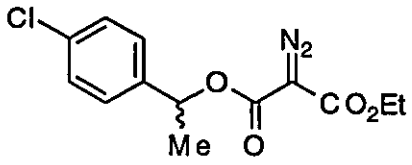
1-Ethyl 3-[(1S)-1-(4-methoxyphenyl) ethyl]-2-diazomalonate 392



(0.066 g, 69%)

(Found: M^+, 292.1059. $C_{14}H_{16}N_2O_5$ requires 292.1059); ν_{max}(film)/cm^{-1} 2938, 2839, 2141, 1756, 1732, 1694, 1516, 1372, 1311, 1246, 1077, 1034, and 833; δ_H (250 MHz; $CDCl_3$) 1.31 (3H, t, *J* 7.1 Hz), 1.58 (3H, d, *J* 6.5 Hz), 4.29 (2H, q, *J* 7.1 Hz), 6.01 (1H, q, *J* 6.5 Hz), 6.88 (2H, AA'BB') and 7.31 (2H, AA'BB'); δ_C (100.6 MHz; $CDCl_3$) 14.73 (CH_3), 22.52 (CH_3), 55.68 (OCH_3), 61.99 (CH_2), 73.91 (OCH), 114.33 (CH), 127.99 (CH), 133.49 (C), 159.87 (C), 160.86 (C=O), and 161.47 (C=O); *m/z* 292 (M^+, 2%), 191 (10), 151 (20), and 135 (100).

1-Ethyl 3-[(1S)-1-(4-chlorophenyl) ethyl]-2-diazomalonate 398



(0.226 g, 75%)

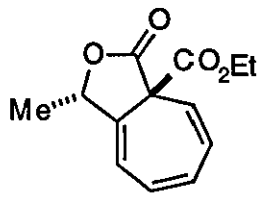
(Found: M^+, 296.0559. $C_{13}H_{13}ClN_2O_4$ requires 296.0564); ν_{max}(film)/cm^{-1} 2985, 2141, 1759, 1732, 1693, 1372, 1313, 1269, 1093, and 1015; δ_H (250 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz), 1.58 (3H, d, *J* 6.6 Hz), 4.30 (2H, q, *J* 7.1 Hz), 5.99 (1H, q, *J* 6.6 Hz), and 7.27-7.33 (4H, m); δ_C (100.6 MHz; $CDCl_3$) 14.32 (CH_3), 22.28 (CH_3), 61.67 (CH_2), 65.90 (C=N_2), 73.04 (OCH), 127.49 (CH), 128.78 (CH), 133.93 (C), 139.54 (C), 160.42 (C=O), and 161.01 (C=O); *m/z* 297 (MH^+, 2%), 296 (M+, <1%), 224 (9), 159 (41), 139 (100), 103 (53), and 77 (28).

Rhodium(II) Perfluorobutyramide Catalysed Decomposition of Racemic Diazomalonates

Decomposition of the racemic diazomalonates under standard conditions of rhodium(II) perfluorobutyramide catalysis in refluxing dichloromethane afforded the respective racemic cycloheptafuranone(s) and these were isolated after chromatography as oils.

Decomposition of **(±)384**

Ethyl 1-methyl-3-oxo-3,3a-dihydro-1H-cyclohepta[c]furan-3a-carboxylate (±)387



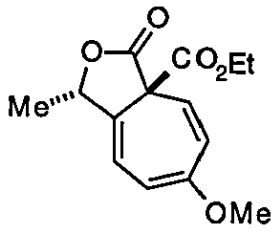
(racemate; isolated yield: 20%)

(Found: MH^+: 235.0970. $C_{13}H_{15}O_4$ requires: 235.0970); ν_{max}(film)/cm^{-1} 2984, 1780, 1744, 1449, 1322, 1197, 1167, 1054, 1028, 762, and 711; δ_H (250 MHz; $CDCl_3$) 1.17 (3H, t, *J* 7.1 Hz), 1.51 (3H, d, *J* 6.5 Hz), 4.09 (2H, q, *J* 7.1 Hz), 5.52 (1H, dq, *J* 6.5 and 2.1 Hz), 5.57 (1H, m), 6.25 (1H, m), and 6.43-6.52 (3H, m); δ_C (100.6 MHz; $CDCl_3$) 13.90 (CH_3), 22.10 (CH_3), 58.32 (C), 62.34 (CH_2), 78.62 (CH), 119.44 (CH), 121.32 (CH), 128.38 (CH), 128.81 (CH), 130.32 (CH), 138.17 (C), 165.75 (C=O), and 172.96 (C=O); *m/z* (CI) 252 (M+NH_4^+, 65%), 235 (MH^+, 17), 191 (100), 180 (28), and 122 (13).

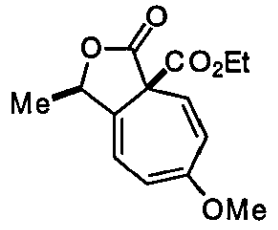
Chiral HPLC: Chiracel OD column, eluent: 99:1 hexane: isopropyl alcohol; flow rate: 0.75 ml/min; UV detection at 254 nm; retention time: 19.20 min (1S, 3aR enantiomer), 26.56 min (1R, 3aS enantiomer).

Decomposition of **392**

Ethyl 6-methoxy-1-methyl-3-oxo-3,3a-dihydro-1H-cyclohepta[c]furan-3a-carboxylate (±)393



Ethyl 6-methoxy-1-methyl-3-oxo-3,3a-dihydro-1H-cyclohepta[c]furan-3a-carboxylate (±)394

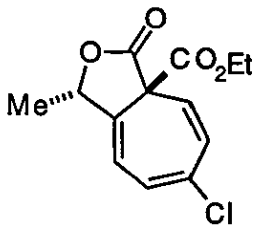


(racemic mixture of inseparable diastereomers[1:1 ratio]; combined isolated yield: 32%)

(Found: M^+: 264.0994. $C_{14}H_{16}O_5$ requires: 264.0998); ν_{max}(film)/cm^{-1} 2938, 1779, 1739, 1672, 1635, 1514, 1371, 1321, 1238, 1165, 1065, 1038, 965, and 862; δ_H (250 MHz; $CDCl_3$) 1.178 and 1.184 (2 x 3H, t, *J* 7.1 Hz), 1.49 and 1.71 (2 x 3H, d, *J* 6.4 Hz), 3.62 (2 x 3H, s), 4.00-4.20 (2 x 2H, m), 5.24 (1H, q, *J* 6.4 Hz), 5.48 (1H, q, *J* 6.4 Hz), 5.60-5.75 (2 x 2H, m), 6.14 (2 x 1H, m), and 6.25-6.40 (2 x 1H, m); δ_C (100.6 MHz; $CDCl_3$) 13.79 and 13.85 (CH_3), 21.83 and 21.95 (CH_3), 54.87 (2 x CH_3), 57.86 (2 x C), 62.32 and 62.37 (OCH_2), 78.74 and 79.01 (OCH), 101.25 and 101.65 (CH), 117.98 and 118.07 (CH), 122.65 and 122.71 (CH), 126.99 and 127.22 (CH), 159.30 and 159.42 (C), 165.98 and 166.14 (C=O), and 173.01 and 173.36 (C=O); *m/z* 264 (M^+, 9%), 221 (9), 206 (23), 191 (100), 178 (56), 135 (38), 105 (40), 91 (34), and 77 (34).

Decomposition of **398**

Ethyl 6-chloro-1-methyl-3-oxo-3,3a-dihydro-1H-cyclohepta[c]furan-3a-carboxylate (±)399



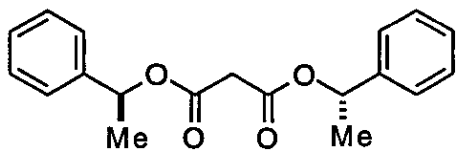
(racemate; isolated yield: 51%)

(Found: M-CO_2Et^+, 195.0213. $C_{10}H_8ClO_2$ requires 195.0213); ν_{max}(film)/cm^{-1} 2984, 2936, 1841, 1781, 1748, 1328, 1229, 1201, 1167, 1064, 836, and 771; δ_H (250 MHz; $CDCl_3$) 1.20 (3H, t, *J* 7.1 Hz), 1.51 (3H, d, *J* 6.5 Hz), 4.05-4.25 (2H, m), 5.50 (1H, dq, *J*

6.5 and 1.1 Hz), 5.62 (1H, d, *J* 10.3 Hz), 6.17 (1H, dd, *J* 6.9 and 2.3), 6.46 (1H, dd, *J* 10.3 and 1.1 Hz), and 6.67 (1H, d, *J* 6.9 Hz); δ_C (100.6 MHz; $CDCl_3$) 13.83 (CH_3), 21.98 (CH_3), 58.08 (C), 62.76 (CH_2), 78.63 (CH), 118.00 (CH), 122.56 (CH), 126.87 (CH), 130.76 (CH), 135.64 (C), 165.27 (C=O), and 172.15 (C=O); *m/z* 268 (M^+, 10%), 225 (45, 195 ($M-CO_2Et^+$, 100), 115 (45), 116 (81), 89 (41), 43 (35), and 29 (48).

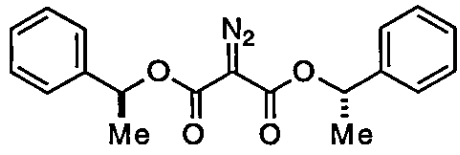
Preparation and Rhodium(II) Perfluorobutyramide Catalysed Decomposition of C-2 Symmetric Diazomalonate 401

Di[(1S)-1-phenylethyl] malonate 400



A solution of malonic acid (0.104 g, 1.0 mmol) in acetonitrile (5 ml) was treated with (S)-α-methylbenzylalcohol (0.244 g, 2.0 mmol), and then dicyclohexylcarbodiimide (0.412 g, 2.0 mmol). An exothermic reaction ensued immediately, and after stirring at room temperature for 2 hours the precipitated dicyclohexylurea was filtered off and washed with ethylacetate. Solvent was then stripped under reduced pressure and the residue taken up in ethyl acetate (20 ml), washed with water (2 x 20 ml) and then saturated brine (20 ml). The resulting solution was dried (Na_2SO_4) and then subjected to flash silica gel column chromatography (9:1 light light petroleumeum:ethyl acetate) to furnish *di[(1S)-1-phenylethyl] malonate* **400** (0.246 g, 79%) as a colourless oily solid; (Found: $M+NH_4^+$, 330.1705. $C_{19}H_{24}NO_4$ requires 330.1705); ν_{max} (film)/cm^{-1} 3036, 2984, 2935, 1732, 1496, 1456, 1268, 1152, and 1063; δ_H (250 MHz; $CDCl_3$) 1.56 (6H, d, *J* 6.5 Hz), 3.41 (2H, s), 5.93 (2H, q, *J* 6.5 Hz), and 7.25-7.36 (10H, m); δ_C (60.5 MHz; $CDCl_3$) 21.87 (CH_3), 42.07 (CH_2), 73.53 (OCH), 126.03 (CH), 127.95 (CH), 128.43 (CH), 140.81 (C), and 165.65 (C=O); *m/z* 330 ($M+NH_4^+$, 72%), 225 (100), 122 (100), and 100 (41).

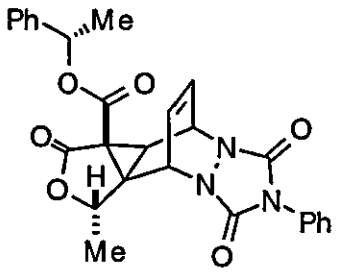
Di[(1S)-1-phenylethyl]-2-diazomalonate 401



A solution of malonate **400** (0.069 g, 0.221 mmol) in dry THF (1.9 ml) was treated with cesium carbonate (0.072 g, 0.221 mmol) and then a solution of *p*-toluenesulfonylazide (0.44 g, 0.221 mmol) in THF (0.5 ml) was added. After stirring at room temperature for about 4 hours the mixture was filtered through a pad of Celite and stripped of solvent to

give an oily residue. *p*-Toluenesulfonamide was triturated out with ether and filtered off. The filtrate was preadsorbed onto silica and subjected to flash silica gel column chromatography (14:1 light petroleum:ethyl acetate) to afford *di[(1S)-1-phenylethyl]-2-diazomalonate* **401** (0.065 g, 87%) as a pale yellow oil; (Found: M+NH_4^+, 356.1610. $C_{19}H_{22}N_3O_4$ requires 356.1610); ν_{max} (film)/cm^{-1} 3065, 3035, 2983, 2934, 2143, 1757, 1729, 1690, 1366, 1342, 1304, 1268, 1092, 1061, 1029, 759, and 699; δ_H (250 MHz; $CDCl_3$) 1.59 (6H, d, *J* 6.6 Hz), 6.05 (2H, q, *J* 6.6 Hz), and 7.26-7.40 (10H, m); δ_C (60.5 MHz; $CDCl_3$) 22.36 (CH_3), 73.67 (OCH), 125.98 (CH), 128.05 (CH), 128.52 (CH), 140.91 (C), and 160.32 (C=O); *m/z* 356 (M+NH_4^+, 10%), 330 (36), 252 (31), 226 (18), 180 (12), 138 (23), and 122 (100).

(1S)-1-phenylethyl (3S, 6R, 7R)-3-methyl-5,10,12-trioxo-11-phenyl-4-oxa-9,11,13-triaza-pentacyclo[6.5.2.$0^{2,6}$.$0^{2,7}$.$0^{9,13}$]pentadec-14-ene-6-carboxylate 403



Diazomalonate **401** (0.064 g, 0.189 mmol) was decomposed with rhodium(II) perfluorobutyramide under the standard conditions described above and the crude reaction mixture treated with PTAD to give crude cycloadduct. Flash silica gel column chromatography gave pure *cycloadduct* **403** (0.043 g, 47%) as a colourless solid; m.p. 191.5-192.5C (light petroleum/EtOAc); (Found: C, 66.64; H, 4.79; N, 8.26. $C_{27}H_{23}N_3O_6$ requires C, 66.80; H, 4.78; N, 8.66); $[\alpha]_D^{21}$ -122.0 (c= 0.282, $CHCl_3$); ν_{max} (CH_2Cl_2)/cm^{-1} 1776, 1722, 1503, 1407, 1306, 1204, 1140, 1071, 1029, and 1008; δ_H (250 MHz; $CDCl_3$) 1.52 (2H, d, *J* 6.3 Hz), 1.60 (3H, d, *J* 6.7 Hz), 2.16 (1H, d, *J* 4.6 Hz), 5.07 (1H, q, *J* 6.3 Hz), 5.18 (1H, dd, *J* 5.9 and 1.4 Hz), 5.46 (1H, t, *J* 5.0 Hz), 5.55 (1H, m), 5.81 (1H, t, *J* 6.7 Hz), 5.95 (1H, q, *J* 6.7 Hz), and 7.26-7.52 (10H, m); δ_C (60.5 MHz; $CDCl_3$) 16.54 (CH_3), 20.27 (CH_3), 20.72 (CH_3), 38.40 (C), 42.80 (C), 52.02 (=CH), 52.08 (=CH), 74.75 (OCH), 125.35 (CH), 126.85 (CH), 127.11 (CH), 128.57 (CH), 128.64 (CH), 128.74 (CH), 129.15 (CH), 130.68 (C), 139.39 (C), 156.47 (C=O), 156.62 (C=O), 162.48 (C=O), and 168.53 (C=O); *m/z* (CI) 503 (MNH_4^+, 7%), 328 ([MNH_4-PTAD]$^+$, 24), 180 (98), and 122 (100).

References

References

1. Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091.
2. (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919; (b) Doyle, M. P. *Acc. Chem. Res* **1986**, *19*, 348.
3. (a) Burke, S. D.; Grieco, P. A. *Org. React.* (N. Y.) **1979**, *26*, 361; (b) Maas, G. *Top. Curr. Chem* **1987**, *137*, 75; (c) Adams, J.; Spero, M. *Tetrahedron* **1991**, *47*, 1765; (d) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385.
4. (a) Padwa, A. *Acc. Chem. Res.* **1991**, *24*, 22; (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263..
5. Doyle, M. P.; Bagheri, V.; Wandless, T. J. ; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906.
6. For a recent review of the elegant use of metallocarbene cascade processes for assembly of complex polycycles, see: Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.
7. Taber, D. F. *Comprehensive Organic Synthesis,* Trost, B. M., Fleming, I. Eds., **1991**, *3*, 1045.
8. Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811.
9. (a) Ledon, H ; Cannic, G.; Linstrumelle, G.; Julia, S. *Tetrahedron Lett.* **1970**, 3971; (b) Scott, L T. *J. Chem. Soc., Chem. Comm.* **1973**, 882, (c) Kennedy, M ; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1047.
10. Doyle, M. P.; Shanklin, M. S.; Hoan, Q. P.; Surendra, N. M. *J. Org. Chem* **1988**, 1017.
11. Boyer, E. B.; Robinson, S. D. *Coordination Chemistry Rev.* **1983**, *50*, 109; Ed. Lever, A. B. P.; Elsevier.
12. for example see: Hashimoto, S-I.; Watanabe, N.; Ikegami, S. *J. Chem. Soc., Chem. Comm.* **1992**, 1508.
13. Motallebi, S.; Müller, P. *Helv. Chim. Acta* **1993**, *76*, 2803.
14. (a) Liu, B.; Wee, A. G. *Heterocycles* **1993**, *36*, 445; (b) Liu, B.; Wee, A. G. *Tetrahedron* **1994**, *50*, 609.
15. Smith, K.; Bahzad, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2793
16. Zaragoza, F. *Tetrahedron* **1995**, *51*, 8829.
17. Hügel, H. M.; Greenwood, R. J.; Mackay, M. F. *Aust. J. Chem.* **1992**, *45*, 1953.
18. Etkin, N.; Babu, S.D.; Fooks, C.J.; Durst, T. *J. Org. Chem.* **1990**, *55*, 1093.
19. Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404.
20. Mickleson, J. W.; Jacobsen, E. K.; Carter, D. B.; Im, H. K.; Im, W. B.; Schreur, P. J. K. D.; Sethy, V. H.; Tang, A. H ; McGee, J. E.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 4652.
21. Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P., Jr.; Padwa, A *J. Org. Chem.* **1994**, *59*, 2447.
22. Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P.; Semones, M. A ; Padwa, A.; Richards, I. C. *Tetrahedron* **1996**, *52*, 2489.
23. Villalgordo, J. M.; Enderli, A.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1995**, *78*, 1983.
24. Hrytsak, M.; Durst, T. *J. Chem. Soc., Chem. Comm.* **1987**, 1150.

25. (a) Moody, C. J.; Doyle, K. J ; Elliot, M. C.; Mowlem, T. J. *Pure Appl. Chem.* **1994**, 66, 2107; (b) Moody, C. J.; Doyle, K. J.; Elliot, M. C.; Mowlem, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2413.
26. Saba, A. *Synthesis* **1984**, 268.
27. Pusino, A.; Saba, A ; Rosnati, V. *Tetrahedron* **1986**, *42*, 4319.
28. Hrytsak, M.; Etkin, A.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 5679.
29 Babu, S. D.; Hrytsak, M.; Durst, T. *Can. J. Chem.* **1989**, *67*, 1071.
30. Silberrad, O.; Roy, C. S. *J. Chem. Soc.* **1906**, *89*, 179.
31. (a) Doyle, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305.
32. Taber, D. F.; Ruckle, R. E. Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686.
33. Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423.
34. (a) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874; (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 8669; (c) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Price, A. T. *Tetrahedron Lett.* **1992**, *33*, 6427.
35 (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808; (b) Taber, D. F.; Amedio, Jr., J. C.; Sherill, R. G *J. Org. Chem.* **1986**, *51*, 3382, (c) Taber, D. F.; Ruckle, Jr., R. E. *Tetrahedron Lett.* **1985**, *26*, 3059; (d) Taber, D. F.; Amedio, Jr., J. C.; Raman, K. *J. Org. Chem.* **1988**, *53*, 2984; (e) Taber, D. F. ; Hennessy, M J.; Hoermer, R. S.; Raman, K.; Ruckle, Jr., R. E.; Schuchardt, J. S. in *Catalysis of Organic Reactions*; Blackburn D. W., Ed.; Marcel Dekker: New York, 1988; Chap. 4, p. 43.
36. Doyle, M. P.; Westrum, L. J.; Wolthuis, N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.
37. Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 1650.
38. Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709.
39. (a) Doyle, M. P.; Shanklin, M. S.; Oon, S. M.; Pho, H. Q.; Van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384; (b) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397; (c) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J Org. Chem.* **1991**, *56*, 820.
40. Doyle, M. P. *Advances in Chemistry Series* **1992**, *No. 230*, 443.
41. (a) Doyle, M. P.; Tauton, J ; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397; (b) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.
42. Taber, D. F.; Hennessy, M. J.; Louey, J-P. *J. Org. Chem.* **1992**, *57*, 436.
43. Matsumoto, M.; Watanabe, N.; Kobayashi, H. *Heterocycles* **1987**, *26*, 1479.
44. Sundberg, R. J.; Baxter, E. W.; Pitts, W. J.; Schofield, R. A.; Nishiguchi, T. *J. Org. Chem.* **1988**, *53*, 5097.
45. Padwa, A.; Austin, D. J. *Angew. Chem. Int. Edn. Engl.* **1994**, *33*, 1797.

46. for a recent example, see: (a) Estevan, F.; Lahuerta, P.; Pérez-Prieto, J.; Sanaú, M.; Stirıba, S-E.; Ubeda, M. A. *Organometallics* **1997**, *16*, 880; (b) Estevan, F.; Lahuerta, P.; Pérez-Prieto, J ; Stirıba, S-E.; Ubeda, M. A. *Synlett* **1995**, 1121.
47. Doyle, M. P.; Shanklın, M. S.; Pho, H. Q. *Tetrahedron Lett.* **1988**, *29*, 2639. (CHT)
48 Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.
49. Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193.
50. Clark, J. S.; Krowaık, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385.
51. Clark, J. S ; Dossetter, A. G.; Whıttıngham, W. G. *Tetrahedron Lett.* **1996**, *37*, 5605.
52. Cox, G. G.; Moody, C. J.; Austın, D. J; Padwa, A. *Tetrahedron* **1993**, *49*, 5109.
53. Felthouse, T. R. *Prog. Inorg. Chem.* **1982**, *29*, 73.
54. For a brıef, but clear review of the chemoselectıvıty of rhodıum carbenoıd reactıons, see: Boger, D. L ; Johnson, D. S. *Chemtracts* **1994**, *7*, 31.
55. Marıno,J. P.; Osterhout, M. H.; Prıce, A. T.; Sheehan, S. M.; Padwa, A. *Tetrahedron Lett.* **1994**, *35*, 849.
56. Beagley, B.; Betts, M. J.; Prıtchard, R. G.; Schofıeld, A.; Stoodley, R. J.; Vohra, S. *J. Chem Soc., Perkin. Trans. 1* **1993**, 1761.
57. The authors have deposıted atomic coordınates with the Cambridge Crystallographic Data Centre The coordinates can be obtaıned, on request, from the Dırector, Cambridge Crystallographic Data Centre, 12 Union Road, Cambrıdge, CB2 1EZ, UK.
58. Burke, S. D.; Greıco, P. A. *Org. React.* **1970**, *26*, 361.
59 (a) Pırrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060; (b) Pırrung, M. C.; Brown, W. L.; Rege, S. *J. Am. Chem. Soc.* **1991**, *113*, 8561; (c) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.
60. (a) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094; (b) Doyle, M. P.; Grıffın, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917.
61. Kıdo, F.; Abıko, T.; Kato, M. *J. Chem. Soc., Perkin. Trans. 1* **1992**, 229.
62. Giddings, P. J.; John, D. I.; Thomas, E. J.; *J. Chem. Soc., Perkin. Trans. 1* **1982**, 2757.
63. Echavarren, A. M. *J. Org. Chem.* **1990**, *55*, 4255
64. Fletcher, R. J.; Lampard, C.; Murphy, J. A.; Lewıs, N. *J. Chem. Soc., Perkın. Trans. 1* **1995**, 623.
65. Danıels, R.; Salemı, O. L. *Proc. Chem. Soc.* **1960**, 286.
66. See, for example (a) Lloyd, D.; Singer, M. I. C. *J. Chem. Soc. (C)* **1971**, 2939 (b) Reıser, J ; Friedrıch, K. *Liebigs. Ann. Chem.* **1976**, 666.
67. For example: Chen, N.; Jones, M.; White, W. R.; Platz, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 4981.
68 Padwa, A.; Austın, D. J.; Precedo, L.; Zhi, L. *J. Org. Chem.* **1993**, *58*, 1144.
69. Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355; **1995**, *12*, 223; **1996**, *13*, 75.
70. Kamano, Y.; Zhang, H. P.; Ichıhara, Y.; Kızu, H.; Komıyama, K.; Pettıt, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783.
71. Zhang, H. P.; Kamano, Y.; Ichıhara, Y.; Kızu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523.

72. Kornet, M. J.; Thio, A. P. *J. Med Chem.* **1976**, *19*, 892.
73. Robinson, R. P. et. al. *J. Med. Chem* **1996**, *39*, 10.
74. Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, *31*, 7277.
75. Mertens, A.; Muller-Beckmann, B.; Kampe, W ; Holck, J.-P.; von der Saal, W. *J. Med. Chem.* **1987**, *30*, 1279.
76. Joshi, K. C.; Dandia, A.; Bhagat, S. *J. Indian Chem. Soc.* **1990**, *67*, 753.
77. Condon, M. E.; Karp, G. M.; Birk, J. H. *Chem. Abs.* **1992**, *117*, 48332w.
78. Joshi, K. C.; Jain, R.; Nishith, S. *J. Indian Chem. Soc.* **1990**, *67*, 490.
79. Baeyer, A. *Ann.* **1866**, *140*, 295.
80. Julian, P. L.; Meyer, E. W.; Printy, H. C. *Heterocyclic Compounds* Elderfield, R. C., Ed , John Wiley and Sons, NY, **1952**, *Vol. 3*, pp.126-186.
81. Sumpter, W. C.; Miller, F. M. *The Chemistry of Heteriocyclic Compounds* Weissberger, A., Ed., Interscience, NY, **1954**, *Vol. 8*, Chapter 4.
82. Sundberg, R. J. *The Chemistry of Indoles* Blomquist, A. T., Ed., Academic Press, NY, **1970**, *Monograph 18*, Chapter 7.
83. Karp, G. M. *Org. Prep. Proc. Int* **1993**, *25*, 481.
84. G. J. Quallich, G. J.; Morrissey, P. M. *Synthesis* **1993**, 51.
85. Wright, S. W.; McClure, L. D.; Hageman, D. L. *Tetrahedron Lett.* **1996**, *37*, 4631.
86. For a recent example of a very mild, non-reductive method see: Connolly, T. J.; Durst, T. *Synlett* **1996**, 663.
87. Rewcastle, G. W.; Denny, W. A *Heterocycles* **1994**, *37*, 701.
88. Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, *30*, 2657.
89. Jones, K.; Wilkinson, J.; Richard, E. *Tetrahedron Lett.* **1994**, *35*, 7673.
90. Jones, K.; Storey, J. M. D. *J. Chem. Soc., Chem. Comm.* **1992**, 1766.
91. Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Comm* **1992**, 1767.
92. Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Comm.* **1995**, 977.
93. Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 9553.
94. Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Comm.* **1994**, 765.
95. Pleynet, D. P. M.; Dutton, J. K.; Thorton-Pett, M.; Johnson, A. P. *Tetrahedron Lett.* **1995**, *36*, 6321.
96. Makosza, M.; Hoser, H. *Heterocycles* **1994**, *37*, 1701.
97. Keuthe, J. T.; Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 7082.
98. Newcombe, N. J ; Ya, F.; Vijn, R. J.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Chem. Comm.* **1994**, 767.
99. Arcadi, A.; Cacchi, S.; Marinelli, F.; Pace, P. *Synlett* **1995**, 547.
100. Arumugam, V.; Routledge, A.; Abell, C.; Balasubramanian, S. *Tetrahedron Lett.* **1997**, *38*, 6473.
101. Grigg, R.; Putnikovic, B ; Urch, C. J. *Tetrahedron Lett.* **1996**, *37*, 695.
102. Abelman, M. M.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.
103. Okita, T.; Isobe, M. *Tetrahedron* **1994**, *38*, 11143.

104. Q. Yu, Q.; Li, Y.; Luo, W.; Brossi, A. *Heterocycles* 1993, *36*, 1791.
105. Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1968**, *33*, 1640.
106. Nishio,T. *J. Chem. Soc., Perkin Trans. 1* 1991, 1717.
107. Elliot, M. C. *PhD Thesis* **1994**, Loughborough University.
108. Shepherd, R. G. *J. Org. Chem.* **1947**, *12*, 275.
109. (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203; (b) Eaton, P.E, Shankar, B. K. R.; Price, G. D.;Pluth, J. J.; Gilbert,E. E.; Alster, J; Sandus, O. *J. Org. Chem.* **1984**, *49*, 185; (a)Thomas, A. V., in *Encyclopedia of Reagents for Organic Synthesis*, ed. Paquette, L. A., Wiley, Chichester, **1995**, p. 2242
110. Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418.
111. Shapiro, S. L.; Rose, I. M.; Testa, F. C.; Roskin, E.; Freedman, L. *J Am Chem. Soc.* **1959**, *81*, 6498.
112. Casadei, M. A.; Cesa, S.; Inesa, A. *Tetrahedron* **1995**, *51*, 5891.
113. Karp, G. M. *J. Org. Chem.* **1992**, *57*, 4765.
114. Watanabe, M.; Kodera, M.; Kinoshita, T.; Furukawa,S. *Chem. Pharm. Bull.* **1975**, *23*, 2598.
115. Greeene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis* **1991**, Wiley, New York.
116. Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451.
117. Kin, M. Y.; Starett, J. E.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 5383.
118. Storey, J. M. D.; McCarthy, C.; Jones, K. *J. Chem. Soc., Chem. Comm.* **1991**, 892.
119. Keck, G. E.; Boden, E ; Sonnewald,U. *Tetrahedron Lett.* **1981**, *22*, 2615.
120. Rigby, J. H.; Gupta, V. *Synlett* **1995**, 547.
121. Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505.
122. Smith III, A B.; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008.
123. Murakami,Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738.
124. Yamaura, M.; Suzuki, T.; Hashimoto, J.; Okamoto, T.; Shin, C.-G. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1413.
125. Oikawa,Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5393.
126. Bruce, J. M. *J. Chem. Soc.* **1959**, 2366.
127. Garden, S. J.; Silva, R. B.; Pinto, A. C. *Tetrahedron Lett.* **1997**, *38*, 1501.
128. Baker, B. R.; Schaub, R. E.; Joseph, J. P.; McEvoy, F. J.; Williams, J. H *J. Org. Chem.* **1952**, *17*, 149.
129. Waterman, P. G.; Mohammad, I. *J. Chem. Soc. Chem. Commun.* **1984**, 1280.
130. Bergeron, R. J. *Chem. Rev.* **1984**, *84*, 587.
131. (a) Gribble, G. W. *Cotemp. Org. Syn.* **1994**, 145; (b)Sundberg, R. J. *The Chemistry of Indole*, Academic Press, New York, **1970**, Chapter II; (c) Brown, R. K. *Indoles, The Chemistry of Heterocyclic Compounds* ed. Houlihan, W. J., Interscience, **1972**, *25*, part1, Chapter II; (d)

Sundberg, R. J. *Comprehensive Heterocyclic Chemistry* ed. Katritzky, A. R.; Rees, C. W.; Bird, C. W.; Cheeseman, G. W. H., Pergamon, Oxford, **1984**, *4*, 313-376.

132. Fray, E. *PhD Thesis* **1994**, Loughborough University of Technology.
133. Appleton, J. E.; Dack, K. N.; Green, A. D ; Steele, J. *Tetrahedron Lett.* **1993**, *34*, 1529.
134. Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P.; Semones, M. A.; Padwa, A.; Richards, I. C. *Tetrahedron* **1996**, *52*, 2489.
135. Miah, S.; Moody, C. J.; Richards, I. C.; Slawin, A. M. Z. *J. Chem. Soc , Perkin Trans. I* **1997**, 2405.
136. Labadie, S. S.; Teng, E. *J. Org. Chem.* **1994**, *59*, 4250.
137. (a) Kubo, A.; Nakai, T. *Synthesis* **1980**, 365; (b) Brennan, M. R ; Erickson, K. L.; Szmalc, F. S.; Tansey, M. J ; Thornton, J. M. *Heterocycles* **1986**, *24*, 2879.
138. Guiles, J. W.; Diana, G. D.; Pevear, D. C. *J. Med. Chem.* **1995**, *38*, 2780.
139. Lee, J. C ; Yuk, J. Y. *Synth. Comm.* **1995**, *25*, 1511.
140. Sicker, D.; Mann, G. *Collect. Czeck. Chem. Comm.* **1988**, *53* , 839-850.
141. Högberg, T.; Khanna, I ; Drake, S. D.; Mitscher, L. A.; Shen, L. L *J Med Chem.* **1984**, *27*, 306.
142. (a) Brown, G. H.; Gledhill, R. J.; Figueras, J.; Kibler, C. J.; McCrossen, F. C.; Parmerter, S. M.; Vittum, P. W.; Weissberger, A. *J. Am. Chem. Soc.* **1957**, *79*, 2919.; (b) Koelsch, C. F.; Britain, J. W. *J. Org Chem.* **1959**, *24*, 1551.
143. Masci, B.; Saccheo,S. *Tetrahedron* **1993**, *49*, 10739.
144. Searles, A. L.; Ressler, D. *J. Am. Chem. Soc.* **1958**, *80*, 3656.
145. Staskun, B. *J. Org. Chem.* **1979**, *44*, 875.
146. Billman, J. H.; Diesing, A. C. *J. Org. Chem.* **1957**, *22*, 1068.
147. Tahara *Chem Ber.* **1892**, *25*, 1307.
148. Rathke, M. W.; Nowak, M. A. *Synth. Comm.* **1985**, *15*, 1039.
149 Barnick, J. W. F. K.; van der Baan, J. L.; Bickelhaupt, F. *Synthesis* **1979**, 787.
150. Carling, R. W.; Leeson, P. D.; Moore, K. W.; Smith, J. D.; Christopher, R. M.; Moyes, C. R.; Mawer, I. M.; Thomas, S.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A ; Marshall, G. R.; Tricklebank, M. D.; saywell, K. L. *J. Med. Chem.* **1993**, *36*, 3397.
151. Ferrer, M.; Galcean, M.; Sanchez-Baeza, F.; Casas, J.; Messeguer, A. *Liebigs Ann. Chem.* **1993**, 507.
152. Eiden, F.; Baumann, E.; Lotter, H. *Liebigs Ann. Chem.* **1983**, 165.
153. Wierenga, W.; Griffin, J.; Warpehoski, M A. *Tetrahedron Lett.* **1983**, *24*, 2437.
154. Pierce, M ; Huhn, G. F.; Jensen, J. H.; Sigvardson, K. W.; Islam, Q.; Xing, Y. *J. Heterocyclic Chem.* **1994**, *31*, 17.
155. Buttery, C. D. ; Jones, R. G.; Knight, D. W. *J. Chem. Soc., Perkin Trans. I* **1993**, 1425.
156. Fisher, L. E.; Labadie, S. S.; Reuter, D. C.; Clark, R. D. *J. Org. Chem.* **1995**, *60*, 6224.
157. (a) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q. *Tetrahedron Lett.* **1988**, *29*, 2639; (b) Kennedy, M.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2565.

158. Ferris, L.; Haigh, D.; Moody, C. J. *Tetrahedron Lett.* **1996**, *37*, 2639; (b) Buck, R. T.; Doyle, M. P.; Drysdale, M. J.; Ferris, L.; Forbes, D. C.; Haigh, D.; Moody, C. J.; Pearson, N. D.; Zhou, Q-L. *Tetrahedron Lett.* **1996**, *37*, 7631
159. Watanabe, N.; Anada, M.; Hashimoto, S-I.; Ikegami, S. *Synlett*, **1994**, 1031.
160. Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
161. Monteiro, H. J.; Zukerman-Schpector, J. *Tetrahedron* **1996**, *52*, 3879.
162. Ledon, H.; Cannic, G.; Linstrumelle, G.; Julia, S. *Tetrahedron Lett.* **1970**, 3971.
163. Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 619.
164. Maguire, A. R.; Buckley, N. R.; O'Leary, P.; Ferguson, G. *Chem. Comm* **1996**, 2595.
165. Sonawane, H. R.; Bellur, S. N.; Sudrik, S. G. *Indian J. Chem., Sect. B* **1992**, *31*, 606.
166. Saba, A. *Tetrahedron Lett.* **1990**, *31*, 4657.
167. Ledon, H.; Linstrumelle, G.; Julia, S. *Tetrahedron* **1973**, *29*, 3609.
168. Grammaticakis, P. *Bull. Soc. Chim. France* **1951**, *18*, 220.
169. Pratt, E. F.; McGovern, T. P. *J. Org. Chem.* **1964**, *29*, 540.
170. Cline, G. W.; Hanna, S. B. *J. Am. Chem. Soc.* **1987**, *109*, 3087.
171. Sommers, A. H ; Biermacher, U.; Brehm, S. B.; Short, J. H. *J. Med. Chem.* **1970**, *13*, 581.
172. Iinuma, M.; Tanaka, T.; Hamada, K.; Mizuno, M.; Asai, F. *Chem. Pharm. Bull.* **1987**, *35*, 3909.
173. Carney, R. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 2549
174 Moritz *Spectrochim. Acta* **1959**, *15*, 242.

Appendices

Appendix A: X-Ray Crystal Structures and Data for Selected α-Diazocarbonyl Compounds

All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation.

Structure Solution	Direct Methods (SIR88)
Refinement	Full-matrix least squares
Function Minimised	$\Sigma\omega([Fo] - [Fc])^2$
Least Squares Weights	$1/(\sigma^2 (Fo)) = 4\ Fo^2/ (\sigma^2 (Fo^2))$
Anomalous Dispersion	All non-hydrogen atoms

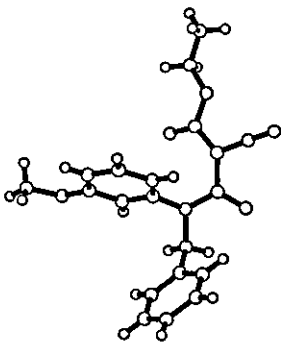


Figure 8 *X*-Ray Crystal Structure of the *N*-3-Methoxyphenyl) Diazoamide **102**

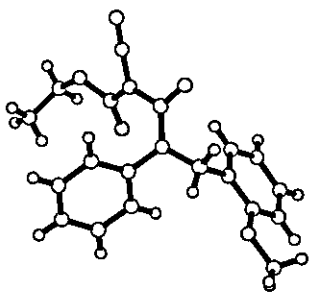


Figure 19 *X*-Ray Crystal Structure of the *N*-(2-Methoxybenzyl) Diazoamide **343**

Crystal Data	**Compound 102**	**Compound 343**
Empirical Formula	$C_{19}H_{19}N_3O_4$	$C_{19}H_{17}Br_2N_3O_4$
Formula Weight	353.38	353.38
Crystal System	monoclinic	monoclinic
Lattice Parameters	a = 8.782 (1) Å	a = 8.587 (2) Å
	b = 18.394 (2) Å	b = 21.798 (4) Å
	c = 11.650 (2) Å	c = 10.210 (2) Å

	$\beta = 104.61\ (1)^\circ$	$\beta = 108.63\ (2)^\circ$
	$V = 1821.1\ (5)\ Å^3$	$V = 1811.0\ (7)\ Å^3$
Space Group	$P2_1/n$ (#14)	$P2_1/c$ (#14)
Z value	4	4
D_{calc}	1.289 g/cm^3	1.296 g/cm^3
μ(CuKα)	7.21 cm^{-1}	7.25 cm^{-1}
Intensity Measurements		
Cu Radiation	$\lambda = 1.54178Å$	$\lambda = 1.54178\ Å$
Scan Type	ω–2θ	ω
No. Reflections Measured Total	3175	2989
Unique	2816 ($R_{int} = 0.215$)	2789 ($R_{int} = 0.109$)
Corrections	Lorentz-polarisation	Lorentz-polarisation
Structure Solution and Refinement		
p-factor	0.002	0.009
No. Observations (I>3.00σ (I))	1224	1789
No. Variables	236	236
Reflection/Parameter Ratio	5.19	7.58
Residuals: R, Rw	0.040, 0.025	0.040; 0.040
Goodness of Fit Indicator	2.12	2.25
Max Shift/Error in Final Cycle	0.13	0.06
Maximum peak in Final Diff. Map	0.11 $e^-/Å^3$	0.12 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.14 $e^-/Å^3$	-0.14 $e^-/Å^3$

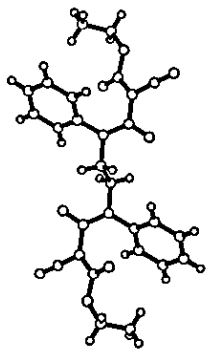


Figure 10 *X*-Ray Crystal Structure of the Bis-Diazoamide **120**

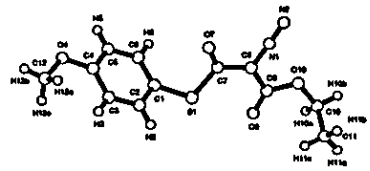


Figure 11 *X*-Ray Crystal Structure of the *S*-(4-Methoxyphenyl) Diazo **127**

Crystal Data	**Compound 120**	**Compound 127**
Empirical Formula	$C_{24}H_{24}N_6O_6$	$C_{12}H_{12}N_2O_4S$
Formula Weight	492.49	280.30
Crystal System	monoclinic	orthorhombic
Lattice Parameters	a = 9.182 (2) Å	a = 14.093 (2) Å
	b = 15.183 (1) Å	b = 16.814 (1) Å
	c = 9.526 (2) Å	c = 5.486 (1) Å
	β = 114.21 (1)°	
	V = 1211.1 (4) Å^3	V = 1299.9 (3) Å^3
Space Group	$P2_1/n$ (#14)	$P2_12_12_1$ (#19)
Z value	2	4
D_{calc}	1.350 g/cm^3	1.432 g/cm^3
μ(CuKα)	7.91 cm^{-1}	22.92 cm^{-1}
Intensity Measurements		
Cu Radiation	λ = 1.54178Å	λ = 1.54178 Å
Scan Type	ω	ω
No. Reflections Measured Total	2013	1175

	Unique	1888 (R_{int} = 0.024)	
Corrections		Lorentz-polarisation	Lorentz-polarisation
Structure Solution and Refinement			
p-factor		0.003	0.004
No. Observations (I>3.00σ (I))		1571	1093
No. Variables		164	173
Reflection/Parameter Ratio		9.58	6.32
Residuals: R, Rw		0.045, 0.042	0.026; 0.026
Goodness of Fit Indicator		5.58	3.30
Max Shift/Error in Final Cycle		0.31	0.06
Maximum peak in Final Diff. Map		0.16 e^-/Å^3	0.11 e^-/Å^3
Minimum peak in Final Diff. Map		-0.18 e^-/Å^3	-0.12 e^-/Å^3

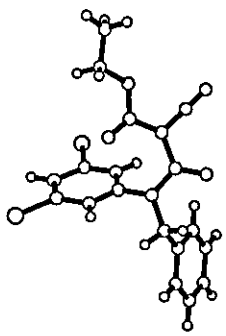


Figure 14 *X*-Ray Crystal Structure of the *N*-Benzyl Diazoamide **260**

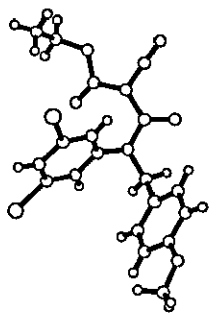


Figure 16 *X*-Ray Crystal Structure of the *N*-4-Methoxybenzyl Diazoamide **285**

Crystal Data	**Compound 260**	**Compound 285**
Empirical Formula	$C_{18}H_{15}Br_2N_3O_3$	$C_{19}H_{17}Br_2N_3O_4$
Formula Weight	481.14	511.17
Crystal System	triclinic	monoclinic

Lattice Parameters	a = 11.176 (3) Å	a = 18.54 (1) Å
	b = 10.440 (3) Å	b = 9.728 (9) Å
	c = 10.007 (3) Å	c = 23.97 (1) Å
	α = 118.18 (2)°	β = 100.30 (5)°
	β = 68.45 (2)°	
	γ = 100.20 (2)°	
	V = 957.2 (5) Å^3	V = 4254 (5) Å^3
Space Group	P1 (#2)	$C2/_c$ (#9)
Z value	2	8
D_{calc}	1.669 g/cm^3	1.596 g/cm^3
μ(CuKα)	56.12 cm^{-1}	51.22 cm^{-1}
Intensity Measurements		
Cu Radiation	λ = 1.54178Å	λ = 1.54178 Å
Scan Type	ω	ω
No. Reflections Measured Total	2939	3498
Unique	2861 (R_{int} = 0.132)	3373 (R_{int} = 0.027)
Corrections	Lorentz-polarisation	Lorentz-polarisation
Structure Solution and Refinement		
p-factor	0.0080	0.0160
No. Observations (I>2.00σ (I))	2395	1677
No. Variables	236	254
Reflection/Parameter Ratio	10.15	6.60
Residuals: R, Rw	0.038, 0.041	0.071; 0.075
Goodness of Fit Indicator	3.88	3.45
Max Shift/Error in Final Cycle	0.09	0.01
Maximum peak in Final Diff. Map	0.41 e^-/Å^3	0.79 e^-/Å^3
Minimum peak in Final Diff. Map	-0.44 e^-/Å^3	-0.74 e^-/Å^3

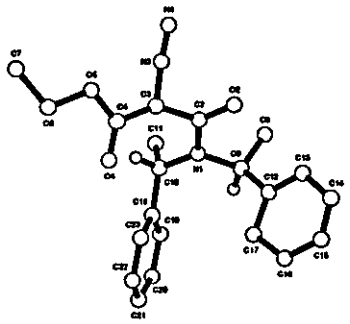


Figure 21 *X*-Ray Crystal Structure of the C-2 Symmetric Diazoamide **355**

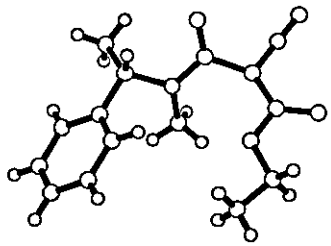


Figure 23 *X*-Ray Crystal Structure of the *N*-Methyl-*N*-(α-Methylbenzyl) Diazoamide **368**

Crystal Data	**Compound 355**	**Compound 368**
Empirical Formula	$C_{21}H_{23}N_3O_3$	$C_{14}H_{17}N_3O_3$
Formula Weight	365.43	275.31
Crystal System	orthorhombic	monoclinic
Lattice Parameters	a = 8.405 (7) Å	a = 7.296 (1) Å
	b = 35.51 (2) Å	b = 12.535 (1) Å
	c = 6.649 (2) Å	c = 8.379 (1) Å
		β = 105.01 (1)°
	V = 1984 (2) Å^3	V = 1811.0 (2) Å^3
Space Group	$P2_12_12_1$ (#19)	$P2_1$/(#4)
Z value	4	2
D_{calc}	1.223 g/cm^3	1.235 g/cm^3
μ(CuKα)	6.37 cm^{-1}	7.31 cm^{-1}
Intensity Measurements		
Cu Radiation	λ = 1.54178Å	λ = 1.54178 Å
Scan Type	ω	ω

No. Reflections Measured Total	1784	1269
		1170 (R_{int} = 0.146)
Corrections	Lorentz-polarisation	Lorentz-polarisation
Structure Solution and Refinement		
p-factor	0.0170	0.0070
No. Observations (I>3.00σ (I))	425	895
No. Variables	245	182
Reflection/Parameter Ratio	1.73	4.92
Residuals: R, Rw	0.049, 0.051	0.062; 0.061
Goodness of Fit Indicator	2.71	4.55
Max Shift/Error in Final Cycle	0.00	0.03
Maximum peak in Final Diff. Map	0.14 e^-/Å^3	0.24 e^-/Å^3
Minimum peak in Final Diff. Map	-0.16 e^-/Å^3	-0.25 e^-/Å^3

Appendix B: X-Ray Crystal Structures and Data for Selected Cyclisation Products

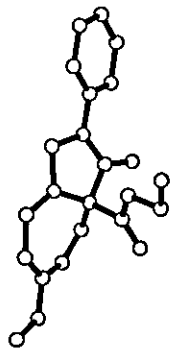


Figure 25 *X*-Ray Crystal Structure of the Cycloheptapyrrolone **105**

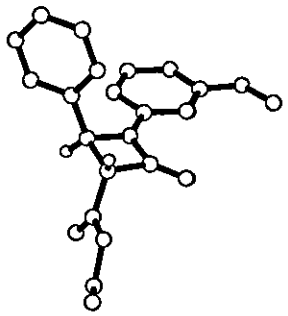


Figure 9 *X*-Ray Crystal Structure of the β-lactam **109**

Crystal Data	**Compound 105**	**Compound 109**
Empirical Formula	$C_{19}H_{19}NO_4$	$C_{19}H_{19}NO_4$
Formula Weight	325.36	325.36
Crystal System	monoclinic	monoclinic
Lattice Parameters	a = 13.213 (1) Å	a = 10.830 (1) Å
	b = 6.763 (1) Å	b = 10.230 (1) Å
	c = 19.355 (1) Å	c = 15.427 (2) Å
	β = 102.656 (5)°	β = 90.000 (9)°
	V = 1687.6 (4) Å^3	V = 1709.1 (3) Å^3
Space Group	$P2_1/n$ (#14)	$P2_1/n$ (#14)
Z value	4	4
D_{calc}	1.281 g/cm^3	1.264 g/cm^3
μ(CuKα)	6.99 cm^{-1}	6.90 cm^{-1}
Intensity Measurements		
Cu Radiation	λ = 1.54178Å	λ = 1.54178 Å

Scan Type	ω	ω
No. Reflections Measured Total	2681	2881
Unique	2555 (R_{int} = 0.043)	2721 (R_{int} = 0.011)
Corrections	Lorentz-polarisation	Lorentz-polarisation
Structure Solution and Refinement		
p-factor	0.005	0.003
No. Observations (I>2.00σ (I))	1832	2373
No. Variables	218	218
Reflection/Parameter Ratio	8.40	10.89
Residuals: R, Rw	0.050, 0.049	0.051; 0.049
Goodness of Fit Indicator	4.78	6.75
Max Shift/Error in Final Cycle	0.00	0.22
Maximum peak in Final Diff. Map	0.23 e^-/Å^3	0.30 e^-/Å^3
Minimum peak in Final Diff. Map	-0.22 e^-/Å^3	-0.28 e^-/Å^3

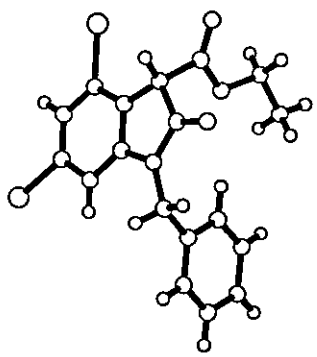


Figure 26 *X*-Ray Crystal Structure of the Oxindole-3-ester **261**

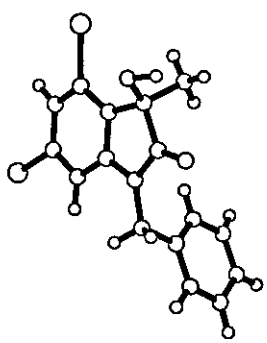


Figure 27 *X*-Ray Crystal Structure of the 3-Hydroxy-oxindole **271**

Crystal Data	**Compound 261**	**Compound 271**

Empirical Formula	$C_{18}H_{15}Br_2NO_3$	$C_{16}H_{13}Br_2NO_2$
Formula Weight	453.13	411.09
Crystal System	monoclinic	monoclinic
Lattice Parameters	a = 11.281 (1) Å	a = 11.698 (2) Å
	b = 13.438 (2) Å	b = 25.230 (4) Å
	c = 12.424 (1) Å	c = 11.023 (2) Å
	β = 109.846 (8)°	β = 104.19 (2)°
	V = 1771.5 (3) Å^3	V = 3154.4 (9) Å^3
Space Group	$P2_1/a$ (#14)	C_c (#9)
Z value	4	8
D_{calc}	1.699 g/cm^3	1.731 g/cm^3
μ(CuKα)	7.11 cm^{-1}	65.55 cm^{-1}
Intensity Measurements		
Cu Radiation	λ = 1.54178Å	λ = 1.54178 Å
Scan Type	ω	ω
No. Reflections Measured Total	2929	3410
Unique	2774 (R_{int} = 0.272)	3208 (R_{int} = 0.038)
Corrections	Lorentz-polarisation	Lorentz-polarisation
Structure Solution and Refinement		
p-factor	0.0050	0.0000
No. Observations (I>2.00σ (I))	2067	1402
No. Variables	218	380
Reflection/Parameter Ratio	9.48	3.69
Residuals: R, Rw	0.055, 0.054	0.030; 0.024
Goodness of Fit Indicator	3.78	1.53
Max Shift/Error in Final Cycle	0.01	0.19
Maximum peak in Final Diff. Map	0.58 e^-/Å^3	0.19 e^-/Å^3
Minimum peak in Final Diff. Map	-0.95 e^-/Å^3	-0.20 e^-/Å^3

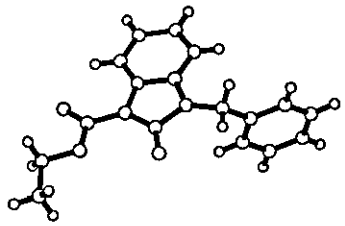


Figure 12 *X*-Ray Crystal Structure of the Pyridinium Ylide **158**

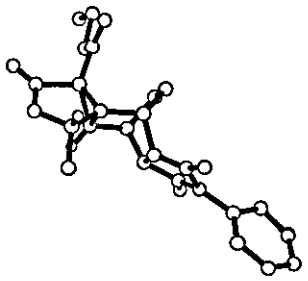


Figure 24 *X*-Ray Crystal Structure of the Cycloadduct **389**

Crystal Data	**Compound 158**	**Compound 389**
Empirical Formula	$C_{17}H_{16}N_2O_3$	$C_{21}H_{19}N_3O_6$
Formula Weight	296.33	409.40
Crystal System	monoclinic	monoclinic
Lattice Parameters	a = 16.701 (1) Å	a = 9.882 (4) Å
	b = 8.704 (2) Å	b = 8.881 (7) Å
	c = 20.563 (1) Å	c = 12.002 (4) Å
	β = 92.765 (5)°	β = 112.79 (2)°
	V = 2985.6 (6) Å^3	V = 971.0 (8) Å^3
Space Group	C2/c (#14)	$P2_1$ (#4)
Z value	8	2
D_{calc}	1.318 g/cm^3	1.400 g/cm^3
μ(CuKα)	7.51 cm^{-1}	8.31 cm^{-1}
Intensity Measurements		
Cu Radiation	λ = 1.54178Å	λ = 1.54178 Å
Scan Type	ω	ω

No. Reflections Measured Total	2497	1646
Unique	2401 (R_{int} = 0.0.025)	1549 (R_{int} = 0.011)
Corrections	Lorentz-polarisation	Lorentz-polarisation
Structure Solution and Refinement		
p-factor	0.0010	0.0020
No. Observations (I>2.00σ (I))	1565	768
No. Variables	200	122
Reflection/Parameter Ratio	7.83	6.30
Residuals: R, Rw	0.042, 0.033	0.121; 0.103
Goodness of Fit Indicator	2.97	2.55
Max Shift/Error in Final Cycle	0.05	0.07
Maximum peak in Final Diff. Map	0.16 e^-/Å^3	0.46 e^- /Å^3
Minimum peak in Final Diff. Map	-0.11 e^-/Å^3	-0.50 e^- /Å^3

Appendix C

Notes on Molecular Modelling Studies Conducted on Diazomalonamides

Four conformations of *N,N*-dimethyl malonamic acid ethyl ester (with the carbonyl oxygens *syn* and *anti* to the diazo) were built in Chem-X (Chem-X, developed and distributed by Chemical Design Ltd, Oxon, England) as models to investigate the preferred orientation of the ester and amide groups. The geometries were optimised using MOPAC version 6.00 (Quantum Chemistry Program Exchange 455) with keywords AM1 XYZ PRECISE NODIIS.

The heats of formation for the four conformations were:

1) -56.02 kcal/mol, ester oxygen *syn*, amide oxygen *syn* (to diazo group)
2) -50.24 kcal/mol, ester oxygen *syn*, amide oxygen *anti*
3) -56.84 kcal/mol, ester oxygen *anti*, amide oxygen *syn*
4) -49.90 kcal/mol, ester oxygen *anti*, amide oxygen *anti*

There is a clear preference for the amide oxygen to be *syn* to the diazo group in these models.

The MOPAC/AM1 optimised geometries for models 1, 2 and 3 were elaborated into the C-2 symmetric diazomalonamide ester **355** in Chem-X (model 2 was only considered for a degree of completeness; it is clearly energetically disfavoured). In each case the backbone of the malonate is twisted introducing another element of chirality. Two models were therefore built for each of the three structures with the 'handedness' of the twist reversed in one of each pair. Systematic conformational analysis was carried out on these six structures in Chem-X, rotating the four non-terminal bonds of the *N*-(α-methyl)-benzyl groups through 30°C increments and calculating the Chem-X molecular mechanics energy at each point. Symmetry allows the phenyl groups to be rotated through only 180°, giving 5184 conformations for each structure. An in-house routine was used to identify the local minima in each of the conformational spaces. Each of the resulting geometries was optimised in MOPAC (same keywords as above) and any duplicates discarded.

Of the resulting 17 geometries, two of the lowest energy are based on model 3 above, with the ester oxygen *anti* and the amide oxygen *syn* to the diazo group. As expected, the highest energy structures are based on model 2.

The second-lowest energy calculated structure was later found to be the most similar to the X-ray geometry (**Appendix A**). It differs primarily in the torsion angle of the *endo* C-N bond. This may be due to the difference in the geometry at the diazo carbon (X-ray angle 142°, whereas the calculated angle is 121°) which leads to the significant change in the steric interaction between the *endo* amide substituent and the ester carbonyl oxygen. **Figure 28** shows a space-filling molecular modelling image based on the calculated second-lowest energy conformation.

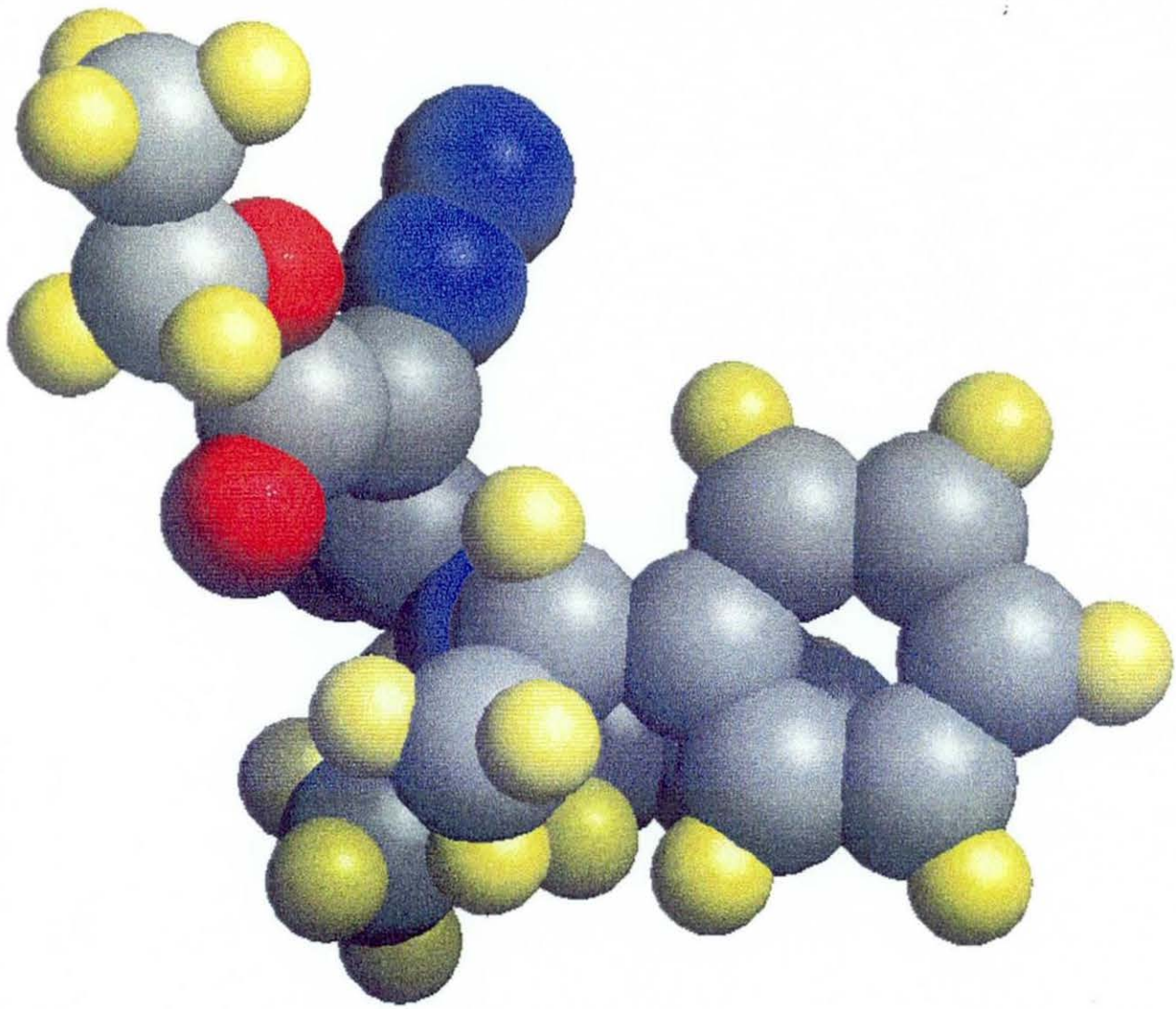


Figure 28