Catalyst, additive and substrate effects in intramolecular aromatic additions of α-diazoketones

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To my parents, Tom and Sheila, and my sister Emma, I want to thank you for your constant love and support throughout the course of my studies. Mum and Dad, I wish to dedicate this thesis to you both, I could not have completed it without you. Dad, I know we have had to curtail a few planned trips to Old Trafford over the last 2 years but I promise things will now return to normal!

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Abstract

This thesis is focused on transition metal catalysed reaction of α-diazoketones leading to aromatic addition to form azulenones, with particular emphasis on enantiocontrol through use of chiral copper catalysts.

The first chapter provides an overview of the influence of variation of the substituent at the diazo carbon on the outcome of subsequent reaction pathways, focusing in particular on C-H insertion, cyclopropanation, aromatic addition and ylide formation drawing together for the first time input from a range of primary reports.

Chapter two describes the synthesis of a range of novel α-diazoketones. Rhodium and copper catalysed cyclisation of these to form a range of azulenones is described. Variation of the transition metal catalyst was undertaken using both copper and rhodium based systems and ligand variation, including the design and synthesis of a novel bisoxazoline ligand. The influence of additives, especially NaBARF, on the enantiocontrol was explored in detail and displayed an interesting impact which was sensitive to substituent effects. Further exploration demonstrated that it is the sodium cation which is critical in the additive effects. For the first time, enantiocontrol in the aromatic addition of terminal diazoketones was demonstrated indicating enantiofacial control in the aromatic addition is feasible in the absence of a bridgehead substituent. Determination of the enantiopurity in these compounds was particularly challenging due to the lability of the products. A substantial portion of the work was focused on determining the stereochemical outcome of the aromatic addition processes, both the absolute stereochemistry and extent of enantiopurity. Formation of PTAD adducts was beneficial in this regard.

The third chapter contains the full experimental details and spectral characterisation of all novel compounds synthesised in this project, while details of chiral stationary phase HPLC and ^{1}H NMR analysis are included in the appendix.

To Mum and Dad

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Chapter 1

Introduction

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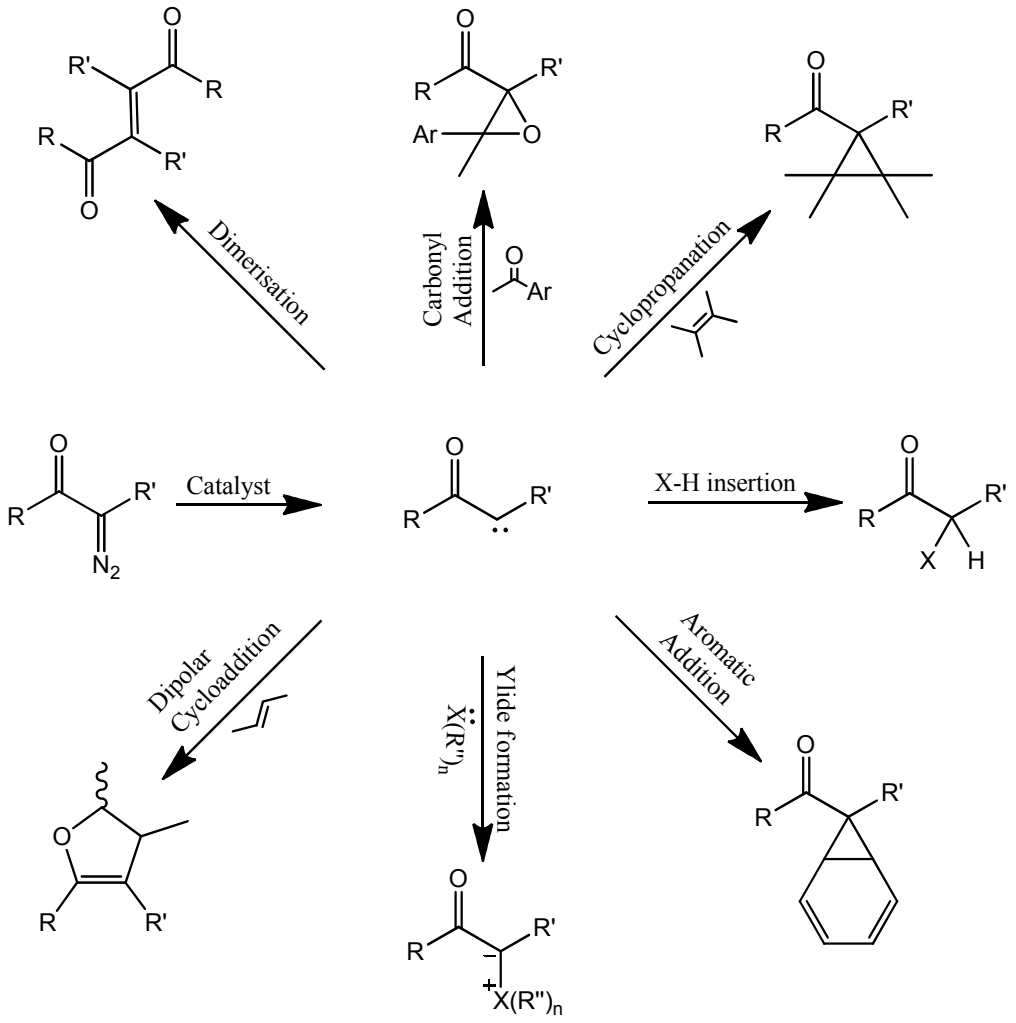
1.1 Introduction

α-Diazocarbonyl compounds have become very versatile in the construction of key organic molecules since their first generation over 100 years ago.[1,2] Most notably, the last 30 years has seen an acceleration in the progress of research into the structure, synthesis and reaction pathways of these compounds.[3-7]

The transition metal catalysed reaction of diazo compounds generates a metal-complexed intermediate, termed a carbenoid. Such carbenoids generated *in situ* can undergo a broad spectrum of chemical transformations, including cyclopropanation, X-H insertion aromatic addition, ylide formation, dipolar cycloaddition and dimerisation (Scheme 1.1).



Scheme 1.1

While the chemistry of α-diazocarbonyl compounds has been extensively reviewed,[4-36] the influence of substitution at the reacting diazo carbon has not been discussed in a systematic fashion (Figure 1.1). Therefore, this introductory chapter will discuss the effects in variation of the substituent (R') at the diazocarbon on the chemoselectivity and stereoselectivity (diastereoselectivity and enantioselectivity) of a number of diazocarbonyl transformations. Specifically, substitution effects in transformations including C-H insertion, cyclopropanation, aromatic addition and ylide formation followed by either [2,3]-sigmatropic rearrangement or dipolar cycloaddition, will form the basis of this chapter.

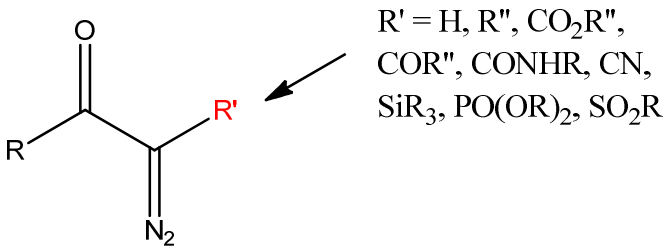


Figure 1.1

In general, the presence of a second electron withdrawing substituent on the diazo carbon modifies significantly the reactivity through both inductive and resonance effects. Where diazocarbonyl compounds are flanked by a second carbonyl group or indeed sulfone or phosphonate moieties, the stabilities of the compounds are noticeably enhanced. Significant impacts on chemo-, regio- and stereoselectivity are seen on varying the nature of the substituents.

1.2 C-H insertion

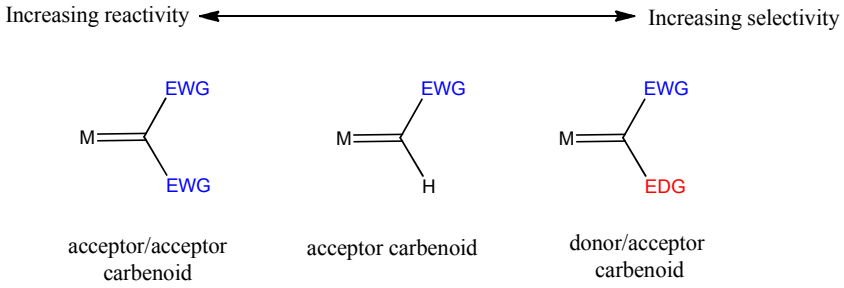
Insertion reactions of carbenes into C-H bonds have gained significant attention since the first discovery by Meerwein, Rathjen and Werner.[37] The insertion of a carbene into an unactivated C-H bond is a well-known transformation of free carbenes. While the transformation is attractive for carbon-carbon bond formation, its main challenge for synthetic development is control of the insertion selectivity. This insertion process can proceed either by an intermolecular or intramolecular pathway.[7] The intermolecular C-H insertion reaction of α-diazocarbonyl compounds has not generally been regarded as a

synthetically efficient reaction,[7,35] while in contrast, intramolecular C-H insertion reactions provide a general approach to a wide array of compounds in a highly selective manner.[18,27] The intermolecular version of the reaction was thought to have been hampered by competing intramolecular reactions and lack of selectivity of the conventional metal carbenoid intermediates.[7,35] However, a discovery by Davies highlighted that highly enantioselective intermolecular C-H reactions can be achieved with aryldiazoacetates and vinyldiazoacetates, precursors to donor/acceptor carbenoids.[38]

1.2.1 Intermolecular C-H Insertion

Davies' research team has had a long-standing interest in the chemistry of rhodium-stabilised vinylcarbenoids.[39] Classic carbenoids which contained acceptor groups like the carbenoid derived from ethyl diazoacetate have been widely applied to C-H insertion reactions. Interestingly, the tandem cyclopropanation/Cope rearrangement between vinyl carbenoids and dienes led Davies to the fact that carbenoids flanked by an acceptor group and a donor group displayed much more selectivity than the conventional carbenoids.[40]

Recent studies have shown that rhodium-stabilized carbenoids, substituted with both a donor and an acceptor group, are capable of a range of new and highly selective transformations (Figure 1.2).[24,41] The reduced reactivity of donor/acceptor carbenoids makes them capable of undergoing a range of stereoselective intermolecular transformations Furthermore, due to their enhanced stability they are less susceptible to dimer formation.[42]

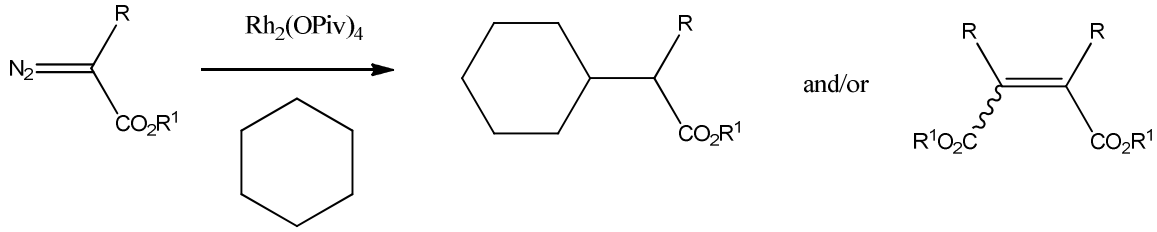


EWG = CO_2R, COR, NO_2, $PO(OR)_2$, CF_3 or SO_2R

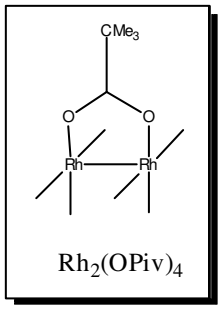
EDG = vinyl, aryl or heteroaryl

Figure 1.2

The influence of substitution at the diazo carbon on chemoselectivity in intermolecular C-H insertion reactions was first reported in 1998.[43] Davies and co-workers illustrated that the outcome of the rhodium pivalate catalysed reaction of diazoacetates **1**-**4** in the presence of cyclohexane **5** was highly dependent on the carbenoid structure (Scheme 1.2).[43] Each of the diazo compounds used resulted in the formation of significant amounts of C-H insertion products. However, in the case of ethyl diazoacetate **4**, carbene dimerisation predominated to give fumarates **6** or maleates **7**. No dimerisation products were formed for diazoacetates **1**-**3**.



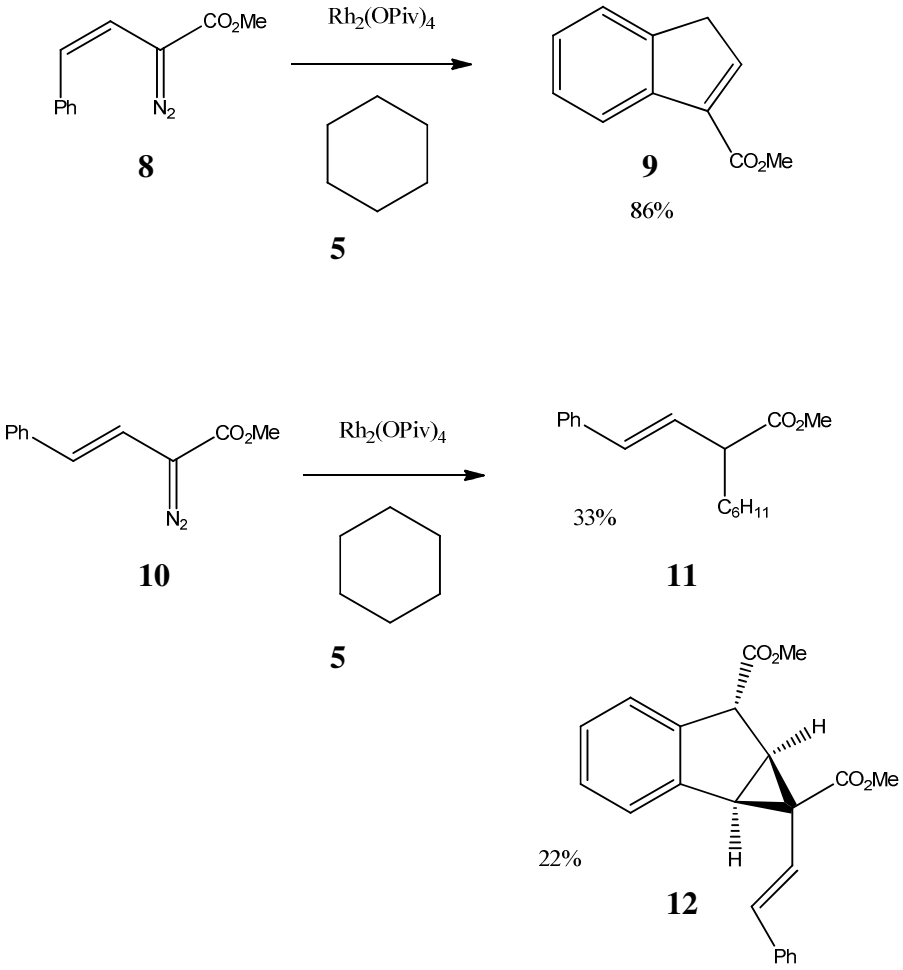
1-**4** **5** **6** **7**



Entry	Substrate	R	R^1	Yield (%) of **6**	Yield (%) of **7**
1	**1**	$CH=CHCO_2Et$	Et	67	0
2	**2**	Ph	Me	94	0
3	**3**	COMe	Me	65	0
4	**4**	H	Et	10	67

Scheme 1.2

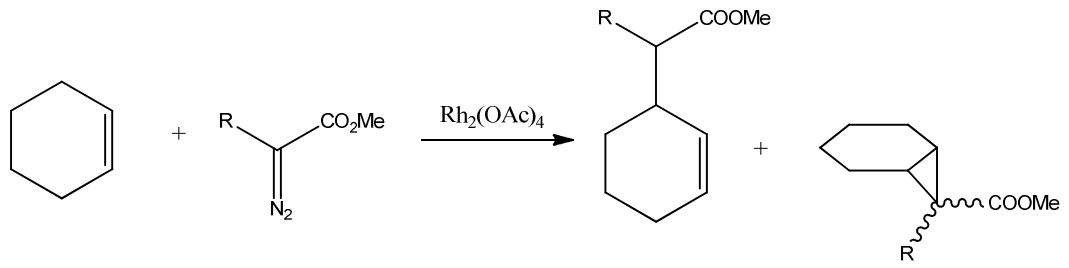
Both competing intermolecular and intramolecular C-H insertion reactions were reported as a result of variation of the substitution pattern (Scheme 1.3).[43] Thus, reaction of vinyldiazoacetates **8** and **10** led to some unprecedented carbenoid transformations. The reaction of **8** in a cyclohexane **5** solution led to intramolecular C-H insertion to form indene **9**, however, the reaction of the corresponding *trans*-isomer **10** gave a mixture of the intermolecular C-H insertion product **11** (33% yield) and the cyclopropylindene derivative **12** in a 22% yield (Scheme 1.3).



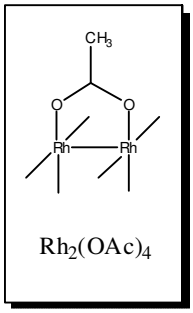
Scheme 1.3

Müller later investigated the ratio for intermolecular C-H insertion versus intermolecular cyclopropanation products, upon reaction of cyclohexene **13** with a range of diazoacetate esters **2**, **3**, **14** and **15** (Scheme 1.4).[44] Müller varied the parameters which are known to influence carbene selection, notably the metal, ligand and substituents on the diazo compound. Specifically, variation of the substituent at the diazo carbon had an interesting effect on the chemoselectivity. The reaction of **14** produced neither insertion product **16** nor cyclopropanation product **20**. Dimethyl diazomalonate **3** gave a 32:68

ratio in favour of the cyclopropanation product **21**. The highest chemoselectivity was observed with methyl-2-diazophenylacetate **2** which afforded a ratio of **18**:**22**, 75:25 with rhodium acetate. Interestingly, the introduction of a *p*-nitro substituent to the diazo compound **15** only had a minor effect on the product ratio.



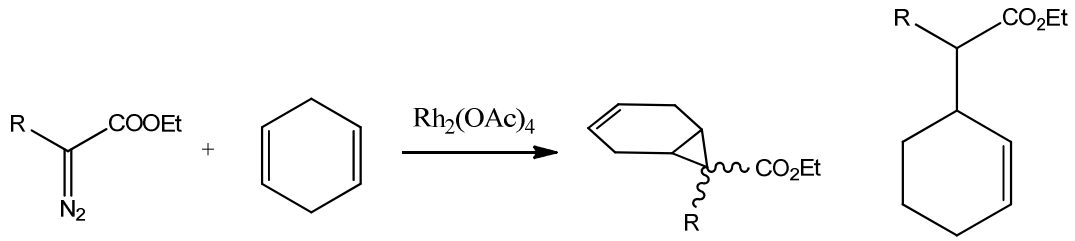
13 **2**, **3**, **14**, **15** **16**-**19** **20**-**23**



Diazoketone	R	Insertion Product	Cyclopropanation Product	Combined Yield (%)	Ratio
14	Me	**16**	**20**	0	-
3	COMe	**17**	**21**	96	**17**:**21**, 38:62
2	Ph	**18**	**22**	50	**18**:**22**, 75:25
15	4-NO_2-Ph	**19**	**23**	47	**19**:**23**, 69:31

Scheme 1.4

Similarly, the impact of the substituent at the diazo carbon on chemoselectivity was also observed in the intermolecular C-H insertion of diazoesters **4** and **24** with 1,4-cyclohexadiene **25** (Scheme 1.5).[44] The reaction of **4** in the presence of $Rh_2(OAc)_4$ resulted exclusively in the formation of cyclopropane **26**, while, ethyl 2-diazopropionate **24** in turn reacted by insertion at the allylic position to afford **29** in a 82% yield.

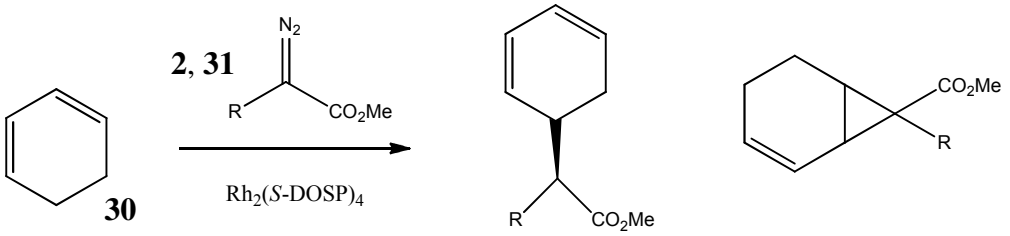


4, **24** **25** **26**, **27** **28**, **29**

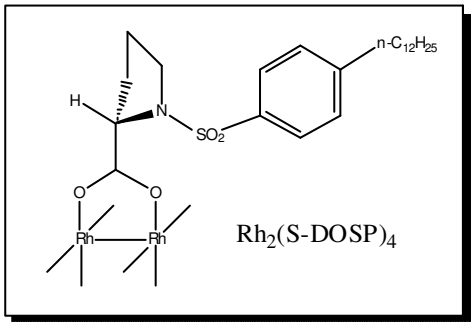
Diazoketone	R	Cyclopropanation Product	Insertion Product	Ratio	Combined Yield (%)
4	H	**26**	**28**	**26**:**28**, >98:2	90
24	Me	**27**	**29**	**27**:**29**, <2:98	82

Scheme 1.5

The reaction of methyl phenyldiazoacetate **2** with a 1,3-cyclohexadiene **30** system was found to produce a 4:1 mixture of C-H activation product **32a** and cyclopropanation product **33a** (Scheme 1.6).[45] Interestingly, a switch in chemoselectivity was observed for the reaction with methyl thiophen-3-yldiazoacetate **31** in which the formation of the cyclopropane **33b** product was favoured by a ratio of 1.3:1 over C-H activation **32b**. The enantioselectivity in the C-H insertion is influenced by the nature of the substituent R as illustrated in Scheme 1.6.



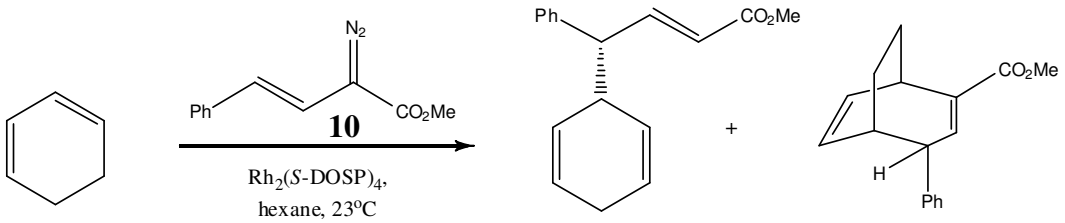
32a-b **33a-b**



Diazoester	R	Product **32a-b** Yield (%)	de (%)	ee (%)	Ratio	Product **33a-b** Yield (%)	de (%)	ee (%)
2	Ph	48	60	92	**32a**:**33a**, 4:1	12	–	–
31	Thiophen-3-yl	23	–	70	**32b**:**33b** 1:1.3	29	–	73

Scheme 1.6

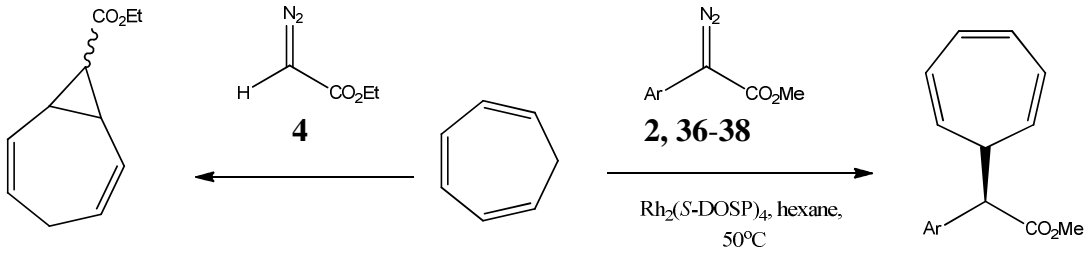
An unprecedented carbenoid reaction was reported by Davies for the reaction of 1,3-cyclohexadiene **30** with vinyldiazoacetate **7** (Scheme 1.7).[45] The reaction did not afford the expected C-H activation product, instead generating the 1,4-cyclohexadiene product **34**. A second product **35** arising from the tandem cyclopropanation/Cope rearrangement was also obtained as shown in Scheme 1.7. Thus the introduction of the vinyl group in **10** substantially altered the reaction pathway compared to the reaction of **31** in Scheme 1.6.



30 **34** 5.3:1 **35**

Scheme 1.7

3,5-Cycloheptatriene **39** underwent highly selective C-H insertion to form **41**-**44** with a wide variety of aryldiazoacetates **2** and **36**-**38** in 53-64% yield and 91-95% ee (Scheme 1.8).[46] No competing cyclopropanation reactions to form **40** were observed, although this is the dominant reaction with ethyl diazoacetate **4**.[46]

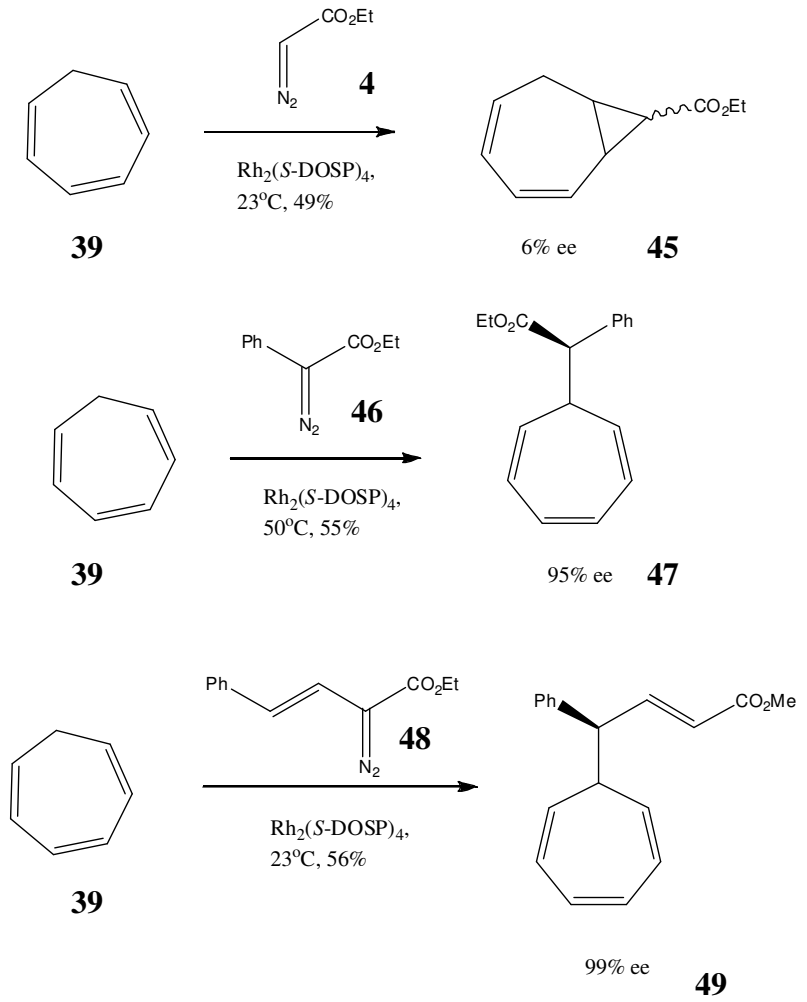


40 **39** **41**-**44**

Diazoester	Ar	Product	Yield (%)	ee (%)
2	C_6H_5	**41**	55	95
36	*p*-ClC_6H_4	**42**	64	95
37	*p*-MeC_6H_4	**43**	60	94
38	2-naphthyl	**44**	53	91

Scheme 1.8

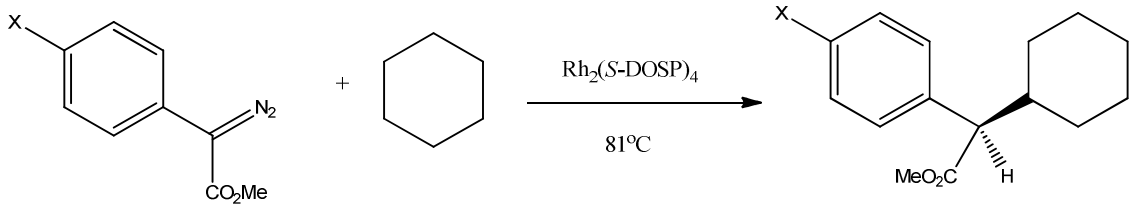
Comparison of the reaction of ethyl diazoacetate **4** with the corresponding phenyl and vinyl substituted diazoacetates **46** and **48** with 1,3-cycloheptatriene **39** reveals interesting differences as reported by Davies and co-workers.[46] Cyclopropanation is the predominant pathway with the simple ethyl diazoacetate **4**, albeit with very low enantiocontrol. In contrast, C-H insertion is the predominant pathway with the more substituted diazo derivatives **46** and **48** with excellent enantiocontrol through the use of the rhodium prolinate catalyst [Rh_2(*S*-DOSP)$_4$]. Interestingly, reaction with vinyl diazoacetate **48** proceeds *via* a combined C-H activation/Cope rearrangement.



Scheme 1.9

In 1997, Davies and co-workers reported the first asymmetric intermolecular C-H insertion reaction using metal carbenoid intermediates (Scheme 1.10).[38] Reaction of a range of aryl diazoacetates **2**, **36** and **50** by Rh_2(*S*-DOSP)$_4$ with cyclohexane **5** were shown to give products **51**-**53** with high levels of enantioselectivity and in excellent

yields. In Davies' study, asymmetric induction was noted to increase upon changing from an electron donating (OMe, 67% ee) to an electron withdrawing (Cl, 86% ee) aromatic substituent for the diazoacetate precursors **2**, **36** and **50**.

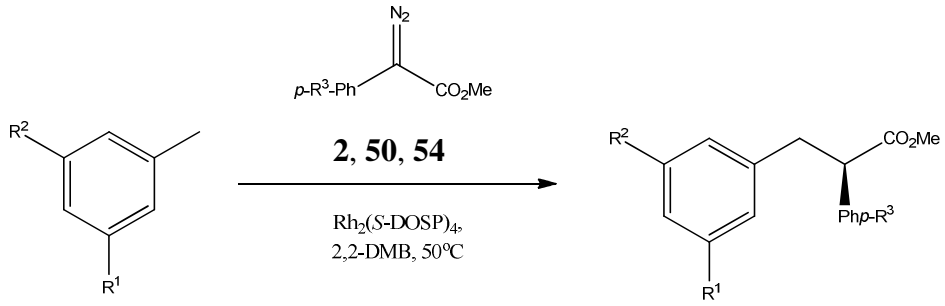


2, **36**, **50** **5** **51-53**

Entry	Diazoacetate	X	Product	Yield (%)	ee (%)
1	**2**	H	**51**	83	81
2	**36**	Cl	**52**	91	86
3	**50**	OMe	**53**	85	67

Scheme 1.10

A similar modest electronic effect on the enantioselectivities, upon varying the substituent at the reactive diazo position, has also been reported across a range of substrates.[47-49] For example, successful C-H activation of primary benzylic positions was accomplished with a range of substituted diazoacetates **2**, **50** and **54** to form 2,3-diarylpropanoates **56a**-**f** (Scheme 1.11).[50] A notable trend involving the increase of yields and enantioselectivities obtained was observed for aryldiazoacetates possessing electron withdrawing groups over those possessing electron donating groups. It appears that those carbenoids which have slightly more electrophilic character tend to undergo more effective C-H activations, coupled with enhanced enantioselection.



55a-b **56a-f**

Product	R^1	R^2	R^3	Yield (%)	ee (%)
56a	OMe	H	Br	71	74
56b	OMe	H	H	67	71
56c	OMe	H	OMe	35	67
56d	OTBS	OMe	Br	80	77
56e	OTBS	OMe	H	80	75
56f	OTBS	OMe	OMe	30	67

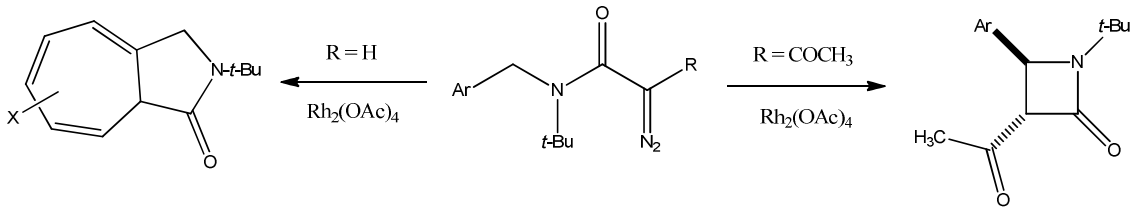
Scheme 1.11

1.2.2 Intramolecular C-H Insertion

Intramolecular C-H insertion reactions allow remote functionalisation through C-C bond formation. This reaction provides a general approach for the synthesis of a variety of carbocyclic and heterocyclic structures in a regio- and stereocontrolled manner. In most cases, the intramolecular C-H insertion favours the formation of a five-membered ring. Regio- and stereocontrolled C-H insertions have been employed for the contruction of cyclopentanones,[51-55] dihydrofuranones,[56,57] γ-lactones,[58] γ-lactams,[59-62] tetrahydrofurans,[63,64] and tetrahydrothiophenes.[65]

As seen in intermolecular C-H insertion reactions, the enhanced stability of donor/acceptor substituted carbenoids results in highly regio- and stereoselective intramolecular C-H activation reactions.

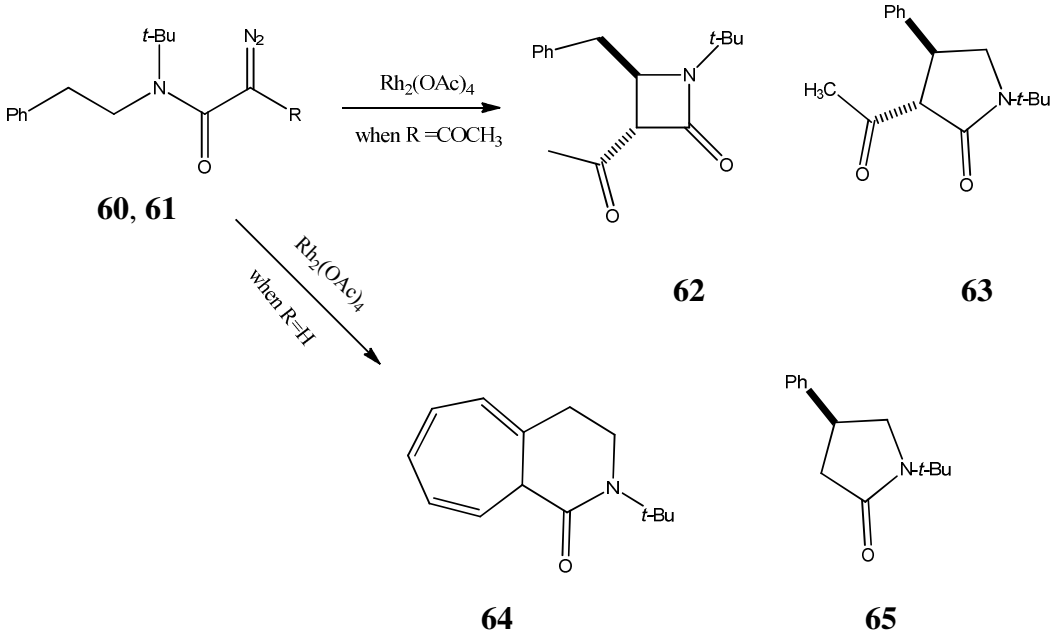
The C-H insertion reaction of α-diazoamides is highly dependent on the α-substituents of the diazo carbon as well as *N*-substituents.[66-68] Doyle demonstrated the influence of carbene substituents on chemoselectivity using the dirhodium(II) catalysed reaction of **57** (Scheme 1.12). When R = H, only aromatic cycloaddition occurs with $Rh_2(OAc)_4$ catalysis but when R = $COCH_3$, only the C-H insertion product β-lactam **37** is observed.[68]



58 **57** **59**

Scheme 1.12

A similar dramatic influence of diazo carbon substituents on chemoselectivity was observed for the rhodium acetate catalysed reaction of diazoamide **60** and **61** (Scheme 1.13).[68,69] For diazoamide **60** (where R=$COCH_3$), β-lactam formation competes with the production of γ-lactam in a ratio of 49:51, interestingly, the aromatic cycloaddition product is completely absent. However, when R=H as in **61**, the cycloaddition product **64** is formed along with the γ-lactam **65** in a ratio of 68:32. It is clear that the presence of the acetyl group completely closes the pathway to aromatic cycloaddition.

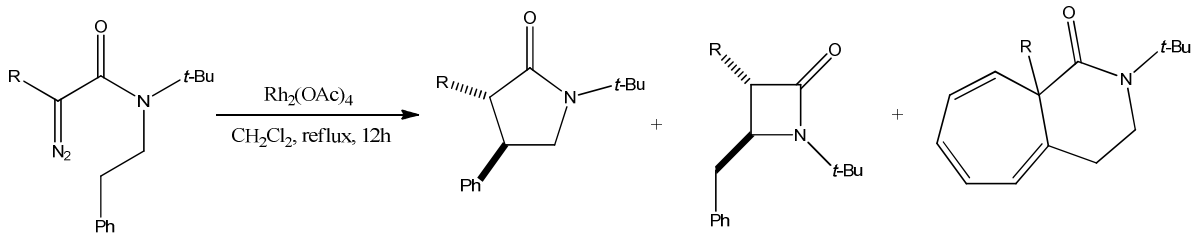


Entry	Diazoamide	R	Yield (%)	Product Ratio			
				62	**63**	**64**	**65**
1	**60**	$COCH_3$	94	49	51	–	–
2	**61**	H	85	–	–	68	32

Scheme 1.13

As discussed in Scheme 1.13, Wee reported that the C-H insertion of α-diazo-α-acetoacetamide **60** afforded a mixture of β- and γ-lactam **62/63** (Scheme 1.13).[69] Interestingly, Jung and co-workers have shown that the C-H insertion reaction of the diazo substrate **66** using $Rh_2(OAc)_4$ affords the *trans*-γ-lactam **68** exclusively in 95% yield without the formation of β-lactam **69** or aromatic cycloaddition product **70** (Scheme 1.14).[70,71] This result implies that the insertion reaction of α-diazo-α-(phenylsulfonyl)acetamide **66** proceeds *via* a later transition state as a result of the extra stabilization by the phenylsulfonyl group. Afonso expanded the scope of this intramolecular C-H insertion by applying the α-diazo-α-(dialkylphosphoryl)acetamide **67**.[71] As **67** is less electron withdrawing than its carbonyl counterpart, it stabilises the electrophilic carbenoid carbon, thereby causing the insertion reaction to proceed through

a relatively late transition state, with the resulting selectivity in line with the reported results for the phenylsulfonyl group.

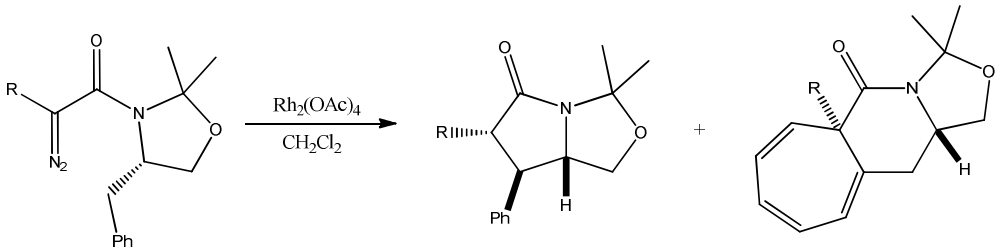


60, **61**, **66**, **67** **68** **69** **70**

Entry	Diazo Precursor	R	Yield (%)	Ratio **68**: **69**: **70**		
1[69]	**60**	$COCH_3$	94	51	49	–
2[70]	**66**	SO_2Ph	95	100	–	–
3[68]	**61**	H	85	32	–	68
4[71]	**67**	$(EtO)_2PO$	81	100	–	–

Scheme 1.14

In the chemically constrained system **71a-d**, the presence of the electron withdrawing α-substituted **71a-c** exclusively leads to C-H insertion to form **72a-c**. In contrast, with the unsubstituted diazoamide **71d**, the reaction pathway switches completely to aromatic addition with no evidence of C-H insertion in this instance (Scheme 1.15).[61]

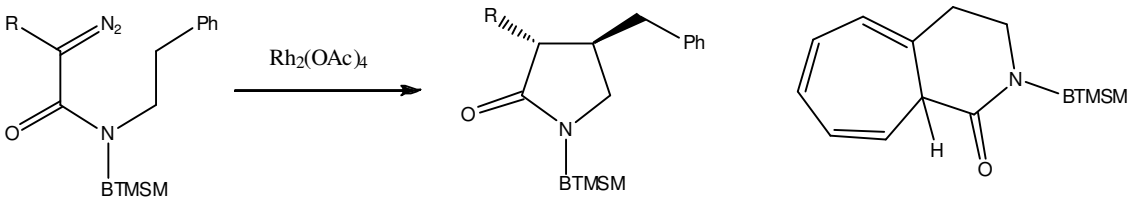


71a-d **72a-d** **73a-d**

Entry	Substrate	R	Yield (%)	Product **72**: **73**	
1	**71a**	$PhSO_2$	91	100	–
2	**71b**	EtO_2C	95	100	–
3	**71c**	MeCO	93	100	–
4	**71d**	H	84	–	100

Scheme 1.15

Similarly, in the more conformationally flexable *N*-BTMSM substituted diazoamides **74a-c** only the C-H insertion products **75a** and **75b** were observed in the diazo compounds with a diazo ester or ketone moiety, while with the unsubstituted **74c**, aromatic addition competed with C-H insertion (Scheme 1.16).[62,72]



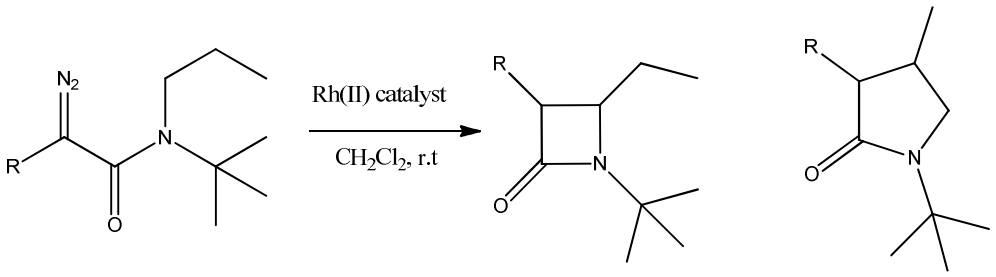
74a-c **75a-c** **76a-c**

Entry	Diazo Substrate	R	Product Ratio **75**: **76**	
1	**74a**	CO_2Me	82	–
2	**74b**	Ac	86	–

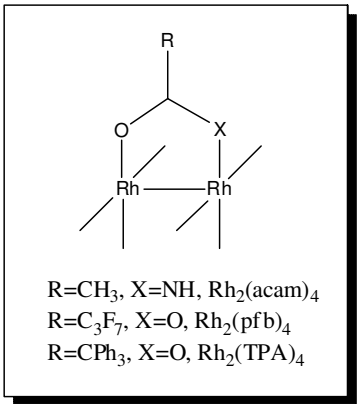
3	**74c**	H	65	34

Scheme 1.16

Ikegami investigated site control in the construction of a range 2-azetidinones *via* the C-H insertion process (Scheme 1.17).[73] The cyclisation of α-diazoacetamide **77a** with each of the rhodium catalysts produced 2-pyrrolidone **79a** exclusively. However, introduction of the additional ketone and ester substituents in diazo compounds **77b** and **77c** had a substantial impact on the regioselectivity of the C-H insertion resulting in most cases of in mixtures of β-lactams **78b-c** and **79b-c**. Significantly with $Rh_2(TPA)_4$, β-lactam **78c** was formed exclusively.



77a-c **78a-c** **79a-c**

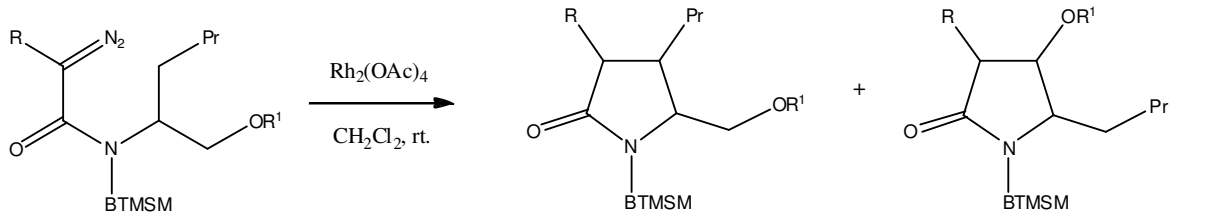


		Ratio **78**: **79**			
Substrate	R	$Rh_2(OAc)_4$	$Rh_2(acam)_4$	$Rh_2(pfb)_4$	$Rh_2(TPA)_4$
77a	H	<1:>99	<1:>99	<1:>99	<1:>99

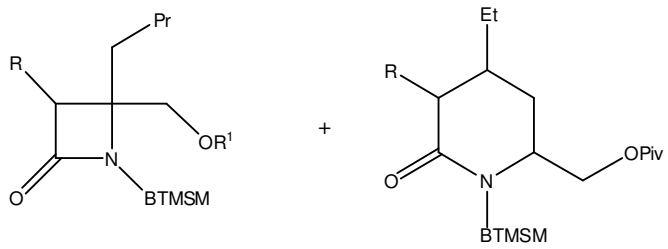
77b	$COCH_3$	50.50	25:75	50:50	45:55
77c	CO_2CH_3	69:31	33:67	84:16	>99:>1

Scheme 1.17

The $Rh_2(OAc)_4$ catalysed reaction of diazoamides **80a-d** was carried out to assess the regioselectivity of the reaction (Scheme 1.18).[74] As illustrated in Scheme 1.18, γ-lactam formation is clearly influenced by the subtle electronic effects from the α-substituent on the carbenoid carbon and also the O-substituent of the oxymethylene group. For diazoamide **80a**, preferential C-H insertion to give the γ-lactam **81a** was observed along with the minor β-lactam product **83a**. Unexpectedly, with the unsubstituted diazoamide **80b**, insertion at the ether C-H bond competes to form a mixture of lactams **81b** and **82b**. Reaction of **80c** gave the γ-lactam **81c** as the major product and **83c** as the minor product in a **81c**:**83c**, 80:20 ratio. Interstingly, for diazoamide **80d** C-H insertion at the butyl group to give **81d** was more favoured than the formation of γ-lactam **82d**. Unexpectedly, the δ-lactam **84d** was also obtained, albeit in low yield.



80a-d **81a-d** **82a-d**

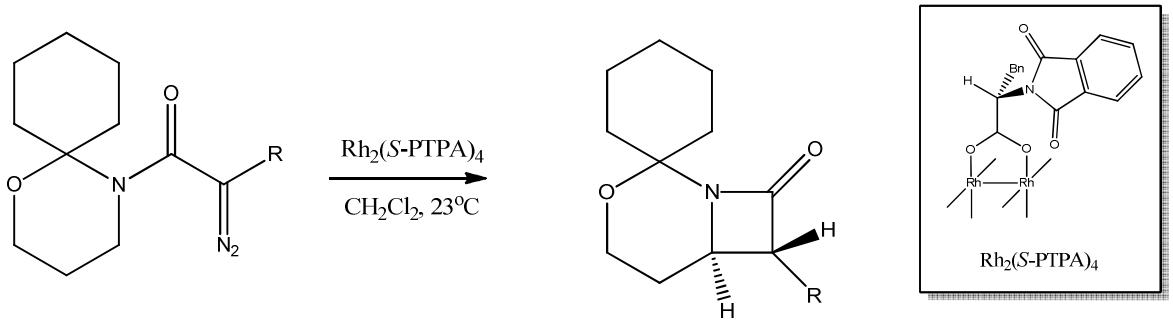


83a-d **84a-d**

Entry	Diazo	R	R^1	Relative Yields (%)			
				81	**82**	**83**	**84**
1	**80a**	Ac	MOM	89	0	11	0
2	**80b**	H	MOM	34	66	0	0
3	**80c**	Ac	Piv	80	0	20	0
4	**80d**	H	Piv	78	8	8	6

Scheme 1.18

The C-H activation reaction of α-diazoacetoacetamide **86** and α-methoxycarbonyl-α-diazoacetamide **87** resulted in a highly selective β-lactam formation (Scheme 1.19).[75] In contrast, the reaction of diazoacetamide **85** gave a complex mixture of products, while cyclisation of **87** gave the β-lactam **90** in good yield. In the case of α-diazoacetoacetamide **86** the product **89** was racemic, whereas the ester derivative gave **90** in 90% ee at 23°C and 96% ee when conducted at 0 °C. These results highlight the dramatic effect the substituent adjacent to the carbenoid can have on not only the chemoselectivity of the intramolecular C-H insertion reaction but also the stereocontrol.



85-87 **88-90**

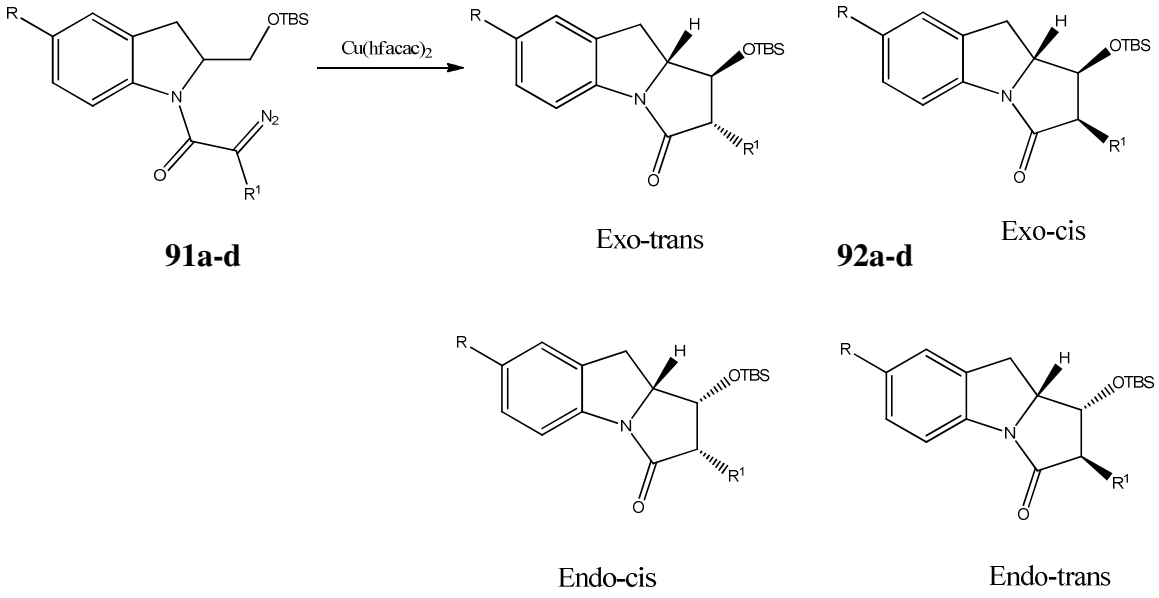
Diazo Substrate	R	Product	Yield (%)	ee (%)
85	H	**88**	–[a]	–
86	$COCH_3$	**89**	84	0
87	CO_2CH_3	**90**	89	90
87	CO_2CH_3	**90**	94	96[b]

a. Complex mixture of products obtained.

b. Reaction was carried out at 0°C

Scheme 1.19

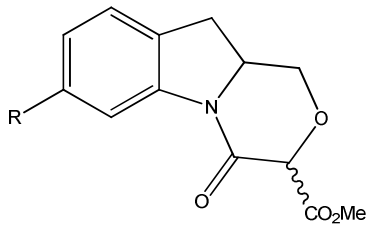
Wee and co-workers investigated the intramolecular metallocarbenoid C-H insertion reaction of indoline diazoamides **91a-d**, which possess a CH_2X substituent (X = $OSiMe_2Bu$-*t*, Me, NPh, OAc, N_3 and SCH_2CHCH_2) at the C-2 position of the indoline nucleus (Scheme 1.20).[76]



Diazoamide	R	R^1	Diastereoisomers	Side Product **93a**, **93c**
91a	H	CO_2Me,	Exo-*trans*/Exo-*cis* **92a**(48%;4.6:1), Endo-*trans* **92a** (4.1%)	39%
91b	H	SO_2Ph	Exo-*trans*/ Exo-*cis*/ Endo-*trans* **92b** (80%; 5:1.5:4)	–
91c	OMe	CO_2Me	Exo-*trans*/ Exo-*cis* **92c** (34%; 2.7:1), Endo-*trans* **92c** (16.8%)	10%
91d	OMe	SO_2Ph	Exo-*trans*/ Exo-*cis*/ Endo-*trans* **92d** (76%; 1.5:0:1)	–

Scheme 1.20

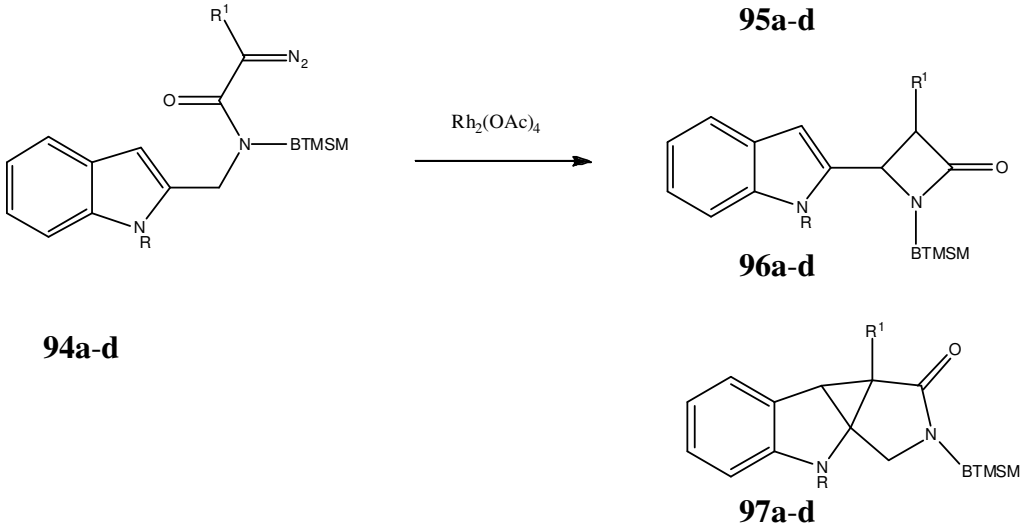
In general, three diastereomeric products of **92**, exo-*trans*, exo-*cis* and endo-*trans* were obtained from metallocarbenoid insertion into the methylene C-H of the CH_2 moiety; no aromatic substitution products were detected. The product distribution is sensitive to the substituent at the diazo carbon, with enhanced recovery of endo-*t* of sulfones **92b** and **92d** relative to the ester derivatives **92a** and **92c**. Interestingly, for diazoamides **91a** and **91c** where R^1= CO_2Me, O-interception products **93a** and **93c** were obtained in the copper catalysed reaction (Figure 1.3). The analogous product was not observed for diazoamides **91b** and **91d** where R^1=SO_2Ph.



93a, 93c

Figure 1.3

Wee and co-workers investigated the intramolecular metallocarbenoid reaction of 2-indolyl *N*-BTMSM diazoamides **94a-d** (Scheme 1.21).[77] Focusing initially on *N*-methyl derivatives **94a-b**, the outcome of the rhodium acetate catalysed reaction is strongly influenced by the nature of the substituent R^1. With the terminal diazoketone **94b**, cyclopropanation dominates leading to **97b**, while with the ester derivative **94a**, the aromatic addition product **95a** is the only product reported. With the *N*-benzenesulfonyl derivatives, once again the cyclopropanation pathway dominates the terminal diazoketone **94d**, while with the ester derivative both the cyclopropanation product **97c** and the C-H insertion product **96c** are seen.



94a-d

95a-d

96a-d

97a-d

Entry	Diazoamide	R	R^1	Isolated Yield (%)		
				95	**97**	**96**
1	**94a**	Me	CO_2Et	89	–	–
2	**94b**	Me	H	–	95	–
3	**94c**	$PhSO_2$	CO_2Et	–	59	20
4	**94d**	$PhSO_2$	H	–	87	–

Scheme 1.21

1.3 Cyclopropanation

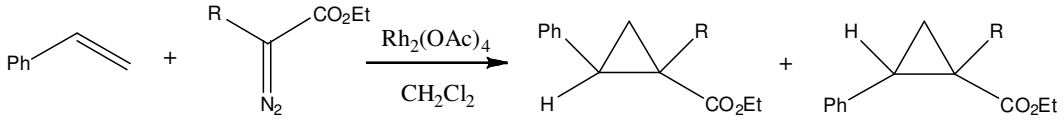
The transition metal catalysed reaction of an α-diazo carbonyl compound with an alkene is an efficient method for the preparation of cyclopropane derivatives.[7,35,78-80] These substituted cyclopropane derivatives have received considerable attention due to their prevalence in natural products, their biological significance and synthetic utility.

In general, there have only been a few examples of variation of the α-substituent at the diazo carbon in both intermolecular and intramolecular cyclopropanation reactions. Predominantly, this effect has had a limited impact on chemoselectivity while the greatest impact has been observed with stereoselectivities (both diastereoselectivity and enantioselectivity). This is in contrast to both inter- and intramolecular C-H insertion reactions where both chemoselectivity and stereoselectivity were significantly affected (see Section 1.2).

1.3.1 Intermolecular Cyclopropanation

The intermolecular cyclopropanation reactions have been limited to only simple diazocarbonyl precursors like diazoketones or diazoesters.[7] The earliest reports of substitution at the α-diazo position influencing chemoselectivity in intermolecular cyclopropanation reactions were based on a competing C-H insertion reaction as discussed in section 1.2.1 (Scheme 1.3, 1.4).[43 44]

Doyle and Davies demonstrated the variation in diastereoselectivity that can be found with different carbene substituents in the rhodium acetate catalysed intermolecular cyclopropanation reaction with styrene **98** (Scheme 1.22).[81,82]

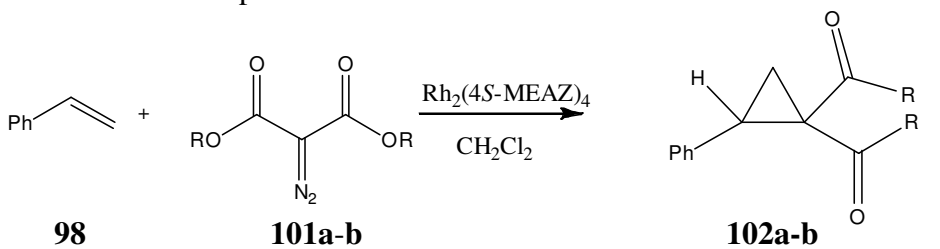


98 **1**, **4**, **99** **100a** **100b**

Entry	Diazo	R	Yield (%)	d.r **100a**: **100b**
1	**4**	H	93	62:32
2	**1**	$EtO_2CCH=CH$	96	89:11
3	**99**	PhCH=CH	94	>95:5

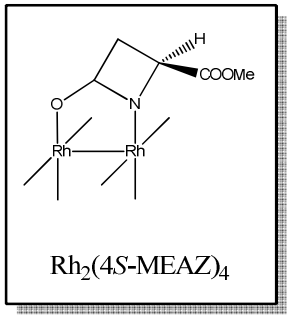
Scheme 1.22

Doyle and co-workers described the selectivities in intermolecular cyclopropanation reactions of diazomalonates **101a**-**b** with styrene **98** using a chiral rhodium azetidinone-carboxylate catalyst [Rh_2(4*S*-MEAZ)$_4$] as illustrated in Scheme 1.23.[83] Dimethyl diazomalonate **101a** produced the cyclopropanation product **102** in high yield and an enantioselectivity of 44% ee. Interestingly, in an experiment designed to investigate the possibility of steric enhancement of enantiocontrol through the use of di-*t*-butyl diazomalonate **101b**, it was observed that a competing insertion reaction into the ester primary C-H bond occurred. This resulted in a ratio of cyclopropanation to C-H insertion product of **102**:**103**, 25:75 and an enantioselectivity of 28% ee. The change in chemoselectivity with *t*-Bu substituents reflects the enhanced steric demand and associated conformational impact.

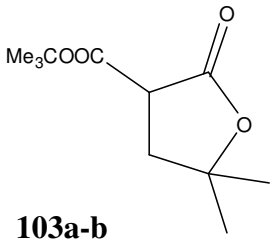


98 **101a-b** **102a-b**

+



Rh_2(4*S*-MEAZ)$_4$

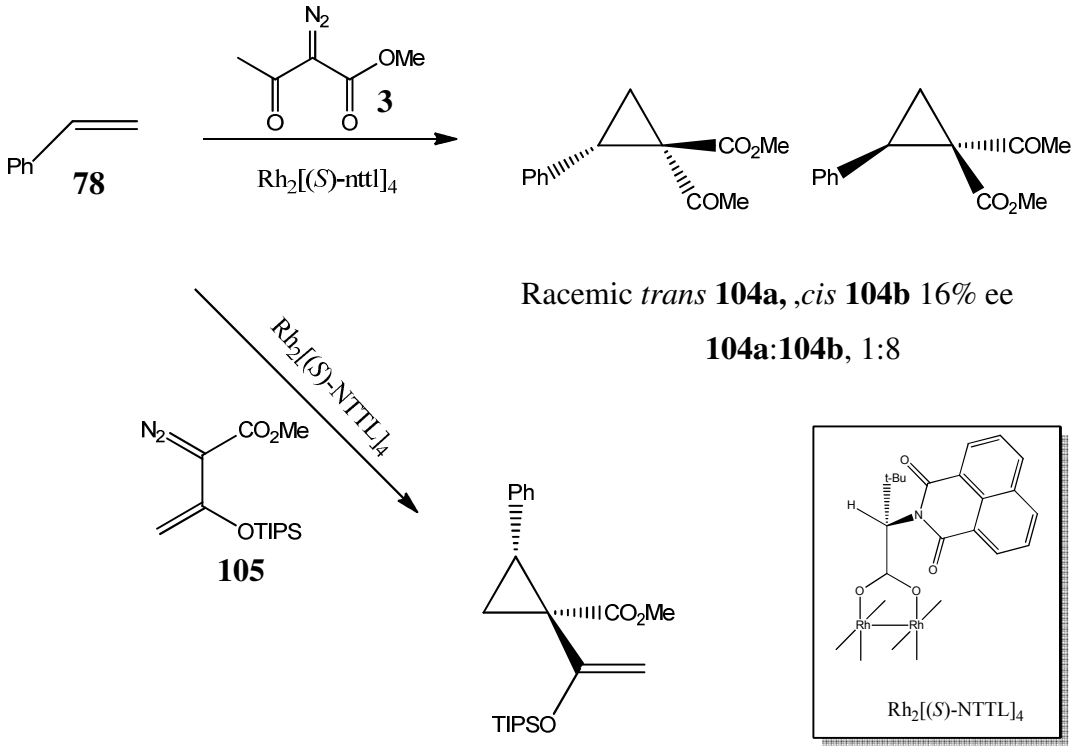


103a-b

Entry	Diazo	R	Yield (%)	Ratio **102**: **103**	ee (%) of **102**
1	**101a**	Me	97	100:0	44
2	**101b**	CMe_3	60	25:75	28

Scheme 1.23

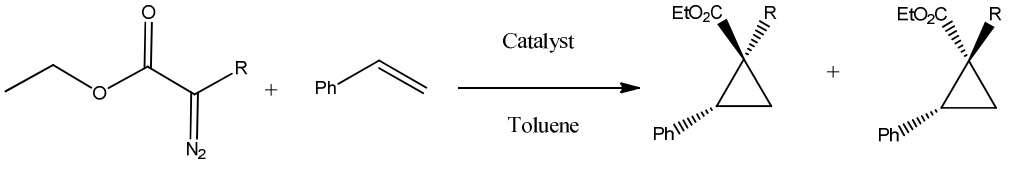
Muller reported the intermolecular cyclopropanation of styrene **74** with methyl diazoacetoacetate **3** in the presence of $Rh_2[(S)\text{-NTTL}]_4$ in a 68% yield to give a mixture of racemic *trans*-adduct **104a** and enantio-enriched *cis* **104b** of 16% ee in a 1:8 ratio (Scheme 1.24).[84] Interestingly, replacement of **3** by the silyl ether **105** resulted in a dramatic increase in selectivity. The reaction afforded the *cis* isomer of the adduct **106** with 95% diastereoselectivity and 95% enantioselectivity.



106, 95% dr, 95% ee

Scheme 1.24

In 2005, Ghanem and co-workers carried out the intermolecular cyclopropanations of styrene **98** with diazoacetates **107a** and **107b** affording the carboxylates **108a** and **108b** with a similar diastereomeric ratio (82% *trans*/*cis* isomers) (Scheme 1.25).[85] The cyclopropanation was also carried out with 3,3,3-trifluoro-2-diazopropionate **107c** and rhodium acetate to afford a mixture of *cis*/*trans* cyclopropanes in a 70% yield.



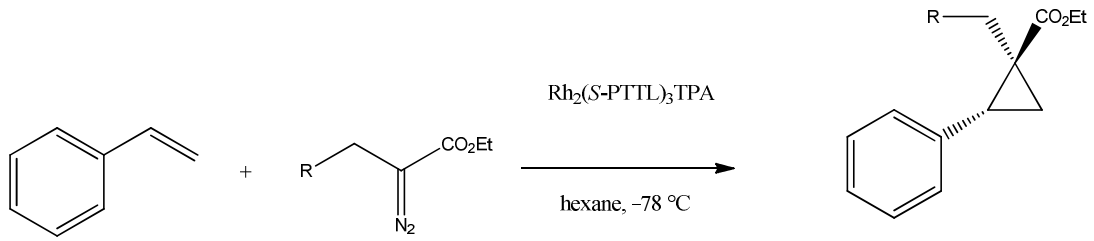
107a-c **98** ***cis*-108a-c** ***trans* 108a-c**

Entry	Diazo	R	Product	d.r.[a] *trans:cis*
1	**107a**	$SiEt_3$	**108a**	82%
2	**107b**	$SiPhMe_2$	**108b**	82%
3	**107c**	CF_3	**84c**	Mixture

a. As described in original paper.[85]

Scheme 1.25

Recently, the rhodium catalyst Rh_2(*S*-PTTL)$_3$TPA was applied to the cyclopropanation of styrene derivatives with a range of α-alkyl diazoesters **109a-c**. (Scheme 1.26).[86] The highest enantioselectivities and diastereomeric ratio were observed with the alkyl diazoesters **109b** and **109c** with a longer chain alkyl group substituted at the diazo position.

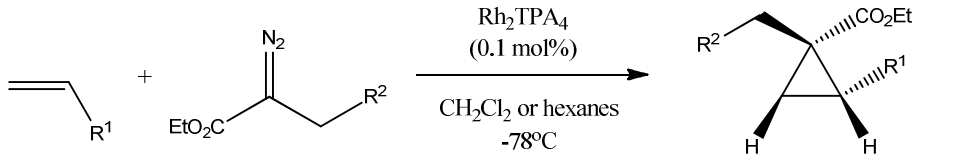


98 **109a-c** **110a-c**

Diazoacetate	R	Product	dr (ratio)	ee (%)
109a	Me	**110a**	96:4	88
109b	Et	**110b**	99:1	95
109c	*n*-Pr	**110c**	99:1	96

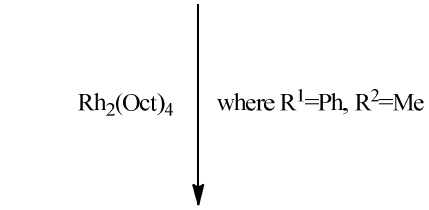
Scheme 1.26

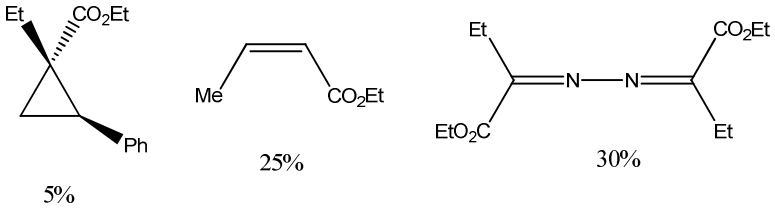
While diazoesters with extended alkyl chains (e.g. **24** and **109a**-**b**) are readily available and attractive precursors to Rh-carbenoids, such carbenoids have only limited applicability in intermolecular cyclopropanation reactions due to their propensity to undergo β-hydride elimination.[87] However, Fox has described several rhodium catalysed intermolecular transformations of diazoesters that suppress β-hydride elimination.[88,89] In 2008, Fox described a chemoselective and diastereoselective rhodium catalysed protocol for the intermolecular cyclopropanation of alkenes **98** and **111a**-**c** with α-alkyl-α-diazoesters **24** and **109a**-**b** (Scheme 1.27). Fox investigated the substrate scope by varying the substituent at the reacting diazo carbon. No significant impact on diastereoselectivity was observed upon variation of the α-substituent at the diazo carbon. However, there was a slight variation in yield as illustrated in Scheme 1.27. The catalyst $Rh_2(TPA)_4$ was found to suppress β-hydride elimination along with being effective in terms of diastereoselectivity. When $Rh_2(Oct)_4$ was applied, only small amounts of cyclopropane products **112a** were observed, *cis*-ethyl crotonate **113** and azine **114** dominated.



98, 111a-c **24,109a-b** > 95:5 dr unless noted otherwise

112a-j





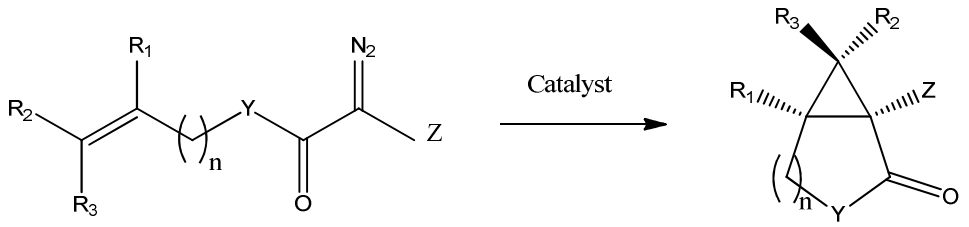
112a **113** **114**

Styrene	R^1	Diazoester	R^2	Product	Yield (%)
98	C_6H_5	**109a**	Me	**112a**	92
111a	C_6H_4F	**109a**	Me	**112b**	83
111b	$C_6H_4OCH_3$	**109a**	Me	**112c**	91
111c	2-napthyl	**109a**	Me	**112d**	80
98	C_6H_5	**24**	H	**112e**	94
111a	C_6H_4F	**24**	H	**112f**	97
111b	$C_6H_4OCH_3$	**24**	H	**112g**	95
111c	2-napthyl	**24**	H	**112h**	79
98	C_6H_5	**109b**	Pr	**112i**	99
111a	C_6H_4F	**109b**	Pr	**112j**	95

Scheme 1.27

1.3.2 Intramolecular Cyclopropanation

An extensive range of synthetic applications associated with diazo compounds has been described since the first report of catalytic intramolecular cyclopropanation by Stork and Ficini.[90] The range of applicable diazo compounds extends from vinyl substitution to carbonyl substitution, with the majority being diazocarbonyl substitution (Scheme 1.28) A significant advantage of intramolecular cyclopropanation over intermolecular is that only one diastereoisomer is formed, while control of diastereoselectivity is a major consideration in intermolecular cyclopropanation reactions.[7] In contrast to intermolecular cyclopropanation where reactions have been limited to predominantly diazoesters or diazoketones, the intramolecular version has been applied to a broader range of diazo precursors (Scheme 1.28).



Z = H, SO_2R, COOR, $COCH_3$

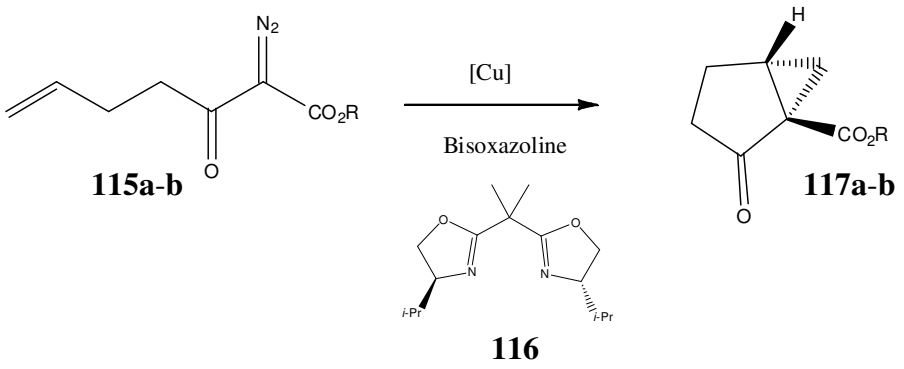
Y = O, NR, CR_2

n = 0, 1, 2…..

Scheme 1.28

Since the first example of enantioselective intramolecular cyclopropanation reported by Nozaki *et al.*,[91] some excellent enantioselectivities have been reported for asymmetric intramolecular cyclopropanation of α-diazoketones, dizaoacetates and diazoacetamides. [92-96] Interestingly, the nature of the α-substituent at the diazo carbon can have a minor influence on selectivity, as will be outlined in the following discussion.

The intramolecular cyclopropanation of α-diazo-β-ketoester **115a** with the copper bisoxazoline ligand **116** provided the 2-oxobicyclo[3.1.0]hexane **117a** in 56% ee (Scheme 1.29). When the more bulky ester **115b** was applied to the intramolecular cyclopropanation a lower enantioselectivity of 52% ee was obtained, although with a significantly higher yield than **117a**.[97-99]

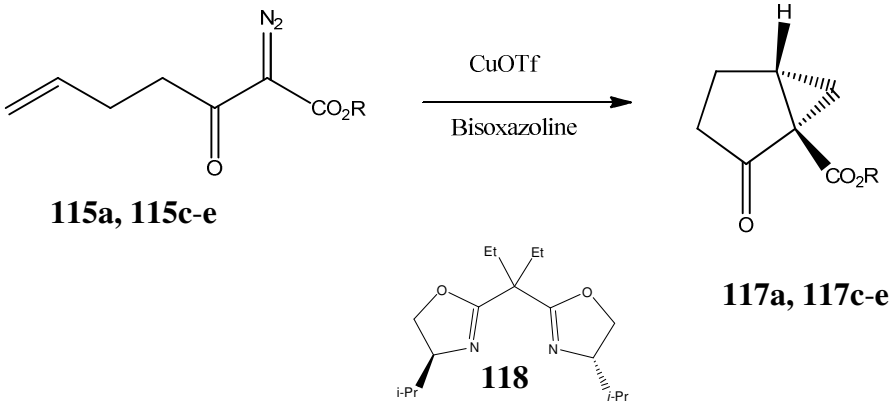


115a-b **117a-b** **116**

Entry	α-Diazo-β-Keto Ester	R	Product	Yield (%)	ee (%)
1	**115a**	Me	**117a**	68	56
2	**115b**	1-Methyl-1-Phenylethyl	**117b**	90	52

Scheme 1.29

Nakada also reported the catalytic asymmetric intramolecular cyclopropanation of a range of α-diazo-β-ketoesters **115a**, **115c-e** substituted at the diazo carbon (Scheme 1.30). The highest enantioselectivity of 78% ee was obtained with the bulky α-diazo-β-ketoester **115e**, while a poor enantioselectivity of 38% ee was reported with **115a**.

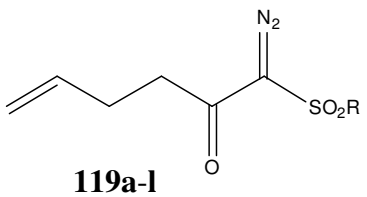


115a, 115c-e **117a, 117c-e** **118**

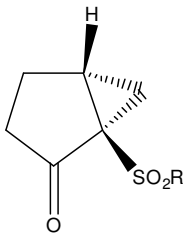
Entry	R	α-Diazo-β-Keto Ester	Product	Yield (%)	ee (%)
1	Me	**115a**	**117a**	57	38
2	CMe_2Ph	**115c**	**117c**	87	50
3	Mes	**115d**	**117d**	82	66
4	2,6-(*t*-Bu)$_2$-4-MeC_6H_2	**115e**	**117e**	56	78

Scheme 1.30

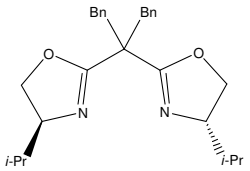
Subsequently, Nakada and co-workers developed a highly enantioselective intramolecular cyclopropanantion of α-diazo-β-ketosulfones **119a**-**l** (Scheme 1.31).[100,101] Nakada postulated that higher enantioselectivities would be obtained as the sulfonyl group is sterically different from the ester group described in Scheme 1.29. Nakada then introduced the more bulky sulfone **119b** to the intramolecular cyclopropanation reaction, resulting in higher enantioselectivity. These interesting results by Nakada highlight the impact varying the substituent at the diazo carbon position can have on enantioselectivity. Further investigation was then carried out into the catalytic asymmetric intramolecular cyclopropanation (CAIMCP) of α-diazo-β-ketosulfones and their application to the total synthesis of natural products.[101] Within this work, the synthesis of a bicyclo[3.1.0]hexane system **120c**-**l** was carried out using a range of substituted sulfones **119c**-**l** (Scheme 1.31).[100,102] The intramolecular cyclopropanation of 2,3-xylyl sulfone **119f** with ligand **118** afforded the product **120f** with the highest enantiomeric excess. Interestingly, the 1-naphthyl sulfone **120l** was obtained in a 93% yield and 83% ee, suggesting that a factor other than the bulkiness of the aryl group could influence the enantioselectivity in the asymmetric intramolecular cyclopropanation reaction.



119a-l



120a-l



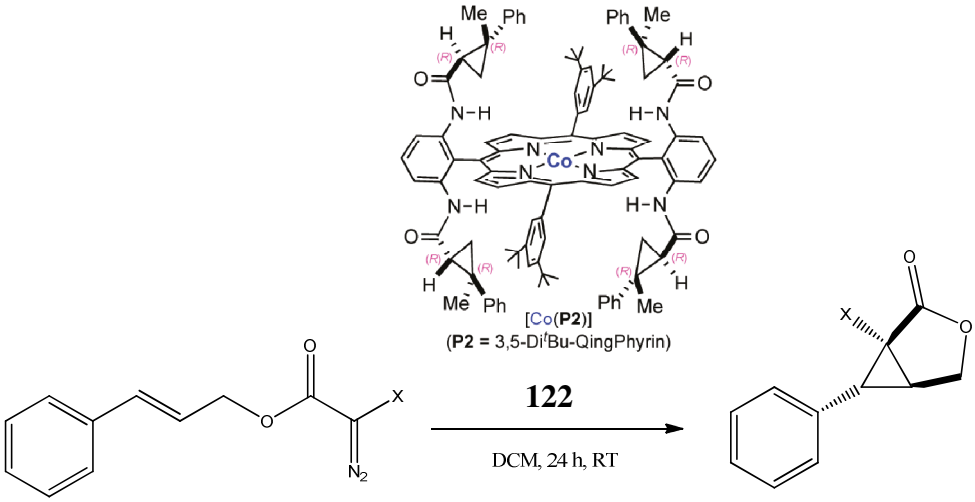
121

Entry	R	Diazosulfone	Ligand	Product	Yield (%)	ee (%)
1	Ph	**119a**	**116**	**120a**	91	65
2	Mes	**119b**	**116**	**120b**	93	83
3	Ph	**119a**	**121**	**120a**	61	74
4	Mes	**119b**	**121**	**120b**	87	93
5	2-Me-C_6H_4	**119c**	**121**	**120c**	98	86
6	3-Me-C_6H_4	**119d**	**121**	**120d**	97	77
7	4-Me-C_6H_4	**119e**	**121**	**120e**	95	69
8	2,3-$Me_2C_6H_3$	**119f**	**118**	**120f**	95	93
9	2,4-$Me_2C_6H_3$	**119g**	**121**	**120g**	97	81
10	2,5-$Me_2C_6H_3$	**119h**	**121**	**120h**	90	82
11	2,6-$Me_2C_6H_3$	**119i**	**121**	**120i**	82	91
12	3,4-$Me_2C_6H_3$	**119j**	**121**	**120j**	94	72
13	3,5-$Me_2C_6H_3$	**119k**	**121**	**120k**	91	62

14	1-naphthyl	**119l**	**118**	**120l**	93	83

Scheme 1.31

Zhang has extended asymmetric intramolecular cyclopropanation to allyl diazoacetates with acceptor substituted diazoacetates such as cyano, nitro and ketone groups as seen in Scheme 1.33. Zhang and co-workers showed that the metalloradical catalyst **122** was effective for asymmetric intramolecular cyclopropanation of allyl diazoacetates **123a-f** with different α-substituted groups (Scheme 1.33).[103] The cyano-substituted diazoacetate **123a** gave the corresponding product **124a** in high yield and enantioselectivity, while the highest enantioselectivity was achieved with the unsubstituted diazoacetate **123e**. Zhang's report is the first example of asymmetric intramolecular cyclopropanation of allyl nitrodiazoacetates.[103]



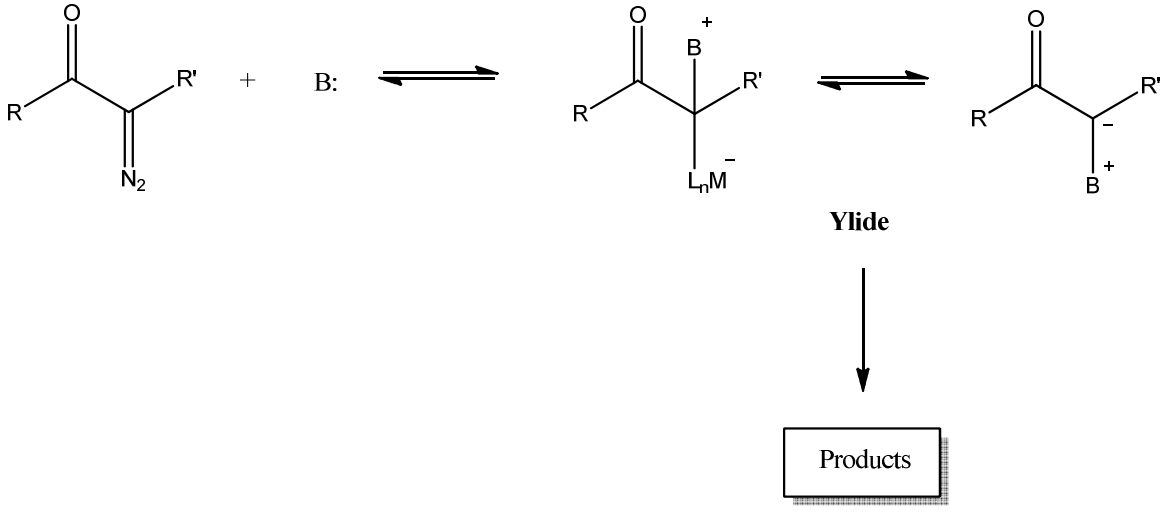
123a-f **124a-f**

Entry	Diazoacetate	X	Product	Yield (%)	ee (%)
1	**123a**	CN	**124a**	99	96
2	**123b**	NO_2	**124b**	95	89
3	**123c**	COMe	**124c**	62	99
4	**123d**	CO_2Et	**124d**	99	90
5	**123e**	H	**124e**	95	99
6	**123f**	Me	**124f**	82	73

Scheme 1.32

1.4 Ylide Formation

Catalytically generated metal carbenes are highly electrophilic and therefore react quickly with any available Lewis base such as nitrogen, oxygen and sulfur heteroatoms to form an ylide (Scheme 1.33); both intramolecular and intermolecular reactions have been widely reported.[7,35,79,104] Once generated, the ylide can undergo one of several transformations, [2,3]-sigmatropic rearrangement of allyl-substituted ylide intermediates, [1,2]-insertion, β-hydride elimination and dipolar cycloaddition of carbonyl ylides.[7,104]

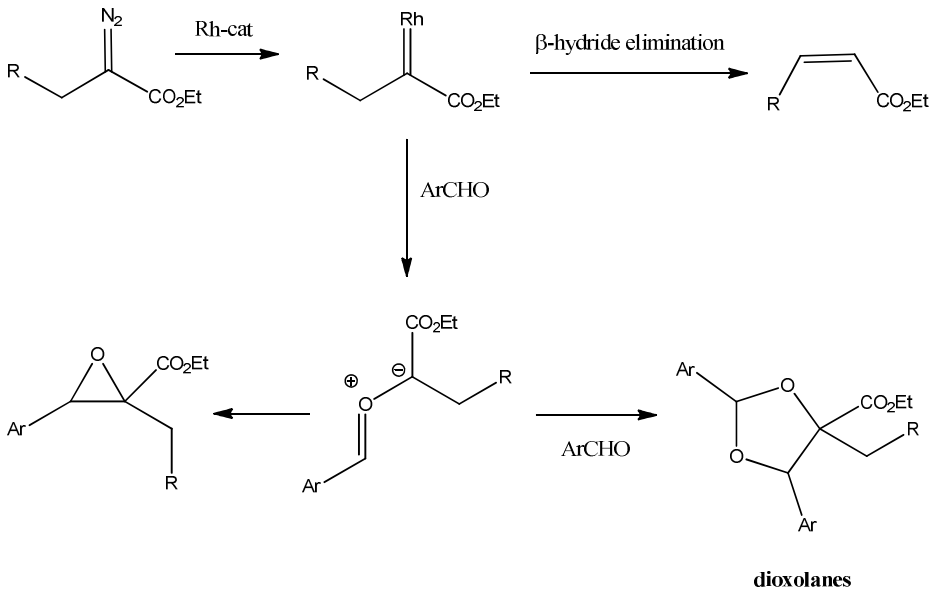


Scheme 1.33

Examples in variation of the α-substituent at the diazo carbon in intermolecular ylide formations generally do not display any significant effect on chemoselectivity or stereoselectivity. Meanwhile, variation of the α-substituent at the diazo carbon in intramolecular ylide reactions has a strong effect on chemoselectivity while only a modest impact on enantioselectivity has been reported. Equally, similar effects were observed in [2,3]-sigmatropic rearrangement reactions.

1.4.1 Intermolecular Cycloaddition Reactions

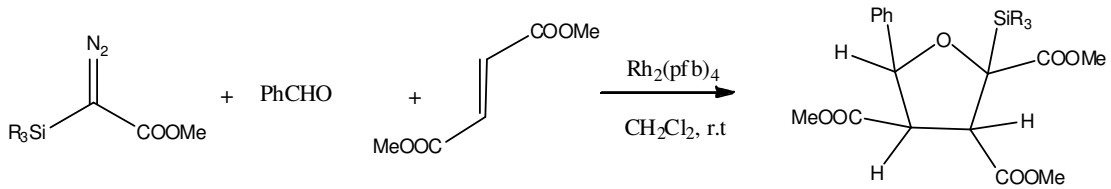
The intermolecular formation of carbonyl ylides is considered to be a synthetically ineffective process compared to the intramolecular reaction due to their low selectivity and competitive reactions such as cyclisation to give epoxides,[105,106] or [3+2] cycloaddition with a second aldehyde equivalent to yield dioxolanes (Scheme 1.34).[107-111] For α-alkyl diazoesters, the scenario is further complicated by the possibility of intramolecular β-hydride elimination to form alkenes. [112] Due to these possible reactions, realising chemo and stereoselectivity in intermolecular reactions of carbonyl ylides is a significant challenge.



Scheme 1.34

The limited reports of the intermolecular formation of carbonyl ylides mainly involve trapping by a carbonyl compound, either in an intermolecular process to produce dioxolanes or in intramolecular 1,3-dipolar cycloaddition to produce 1,3-dioxoles.[107,113,114] The earliest example of variation of substitution at the α-position of a

diazocarbonyl in the intermolecular formation and trapping of carbonyl ylides was reported by Maas (Scheme 1.35).[111] No significant difference was observed between the two diazoesters **125a** and **125b**.



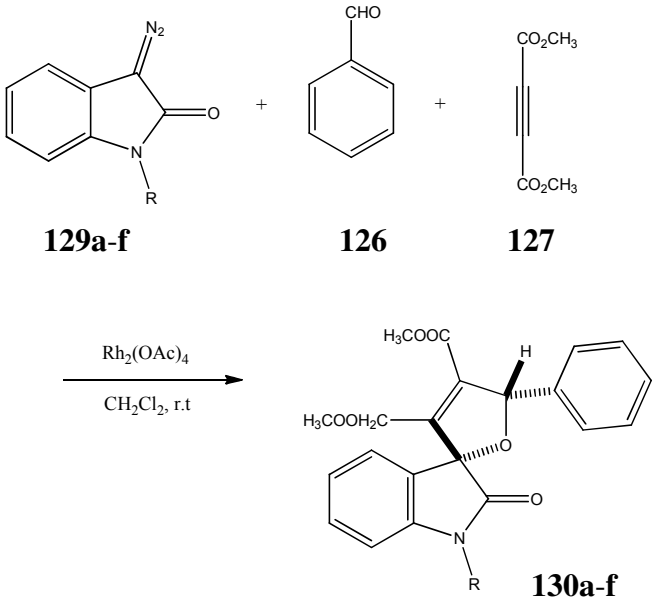
R = Me **125a** **126** **127** **128**

R = Et **125b**

Yield: 41-46%

Scheme 1.35

In 2004, Muthusamy and co-workers reported results from the first multicomponent reactions of cyclic diazoamides **129a-f** through an intermolecular generation of carbonyl ylides in the presence of aryl aldehydes and heteroaryl aldehydes (Scheme 1.36).[115] No significant difference was observed for the substituted diazoxindole **129a-e**, however, the unsubstituted diazoxindole **129f** exhibited a slow reaction resulting in a low yield. Muthusamy postulated that the reason for this may be result of poisoning of the catalyst by unsubstituted amide functionaility.[36] Subsequent work by Muthusamy demonstrated a novel three-component reaction for the synthesis of spiroindolodioxolanes from substituted cyclic diazoamides and aromatic aldehydes.[116] No significant variation was observed from substitution of the cyclic diazoamides at the diazo carbon.



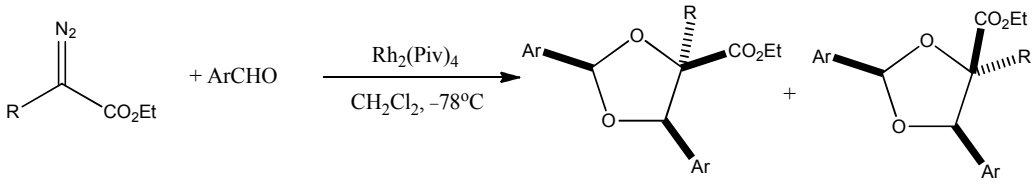
129a-f **126** **127**

130a-f

Entry	Diazoamide	R	Reaction Time	Product	Yield (%)
1	**129a**	CH_3	30 min	**130a**	62
2	**129b**	Bn	25 min	**130b**	64
3	**129c**	*p*-xylenyl	20 min	**130c**	50
4	**129d**	allyl	25 min	**130d**	55
5	**129e**	propargyl	25 min	**130e**	58
6	**129f**	H	5 h	**130f**	25

Scheme 1.36

The first general method for generating carbonyl ylides from α-diazoesters **131a-c** that possess β-hydrogens was reported by Fox and co-workers (Scheme 1.37).[117] Formation of dioxolanes **132a-h** was reported across a variety of aldehydes and with an array of ethyl diazoesters substituted at the diazo carbon. No significant difference was observed in yield or diastereomer ratio except for diazoester **131b** which had the lowest diastereoselective ratio of 84:16 when the subsequent ylide formed reacted with *p*-NO_2PhCHO.



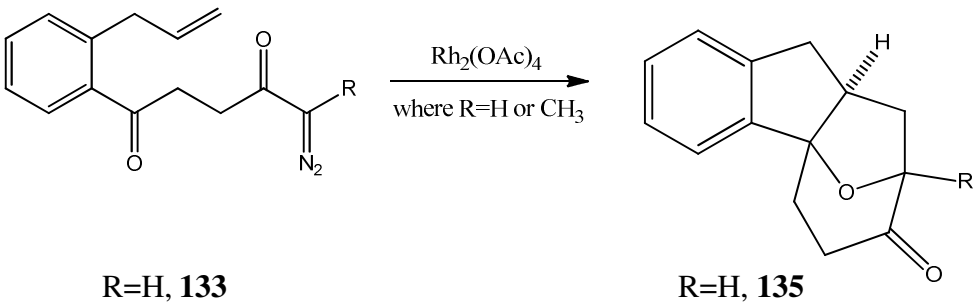
131a-c **132a-h**

Entry	R	Diazoester	Ar	Product	Yield (%)	dr ratio
1	Me	**131a**	Ph	**132a**	65	>95:5
2	CH_2Ph	**131b**	Ph	**132b**	60	95:5
3	Et	**131c**	Ph	**132c**	53	92:8
4	Me	**131a**	*p*-NO_2Ph	**132d**	64	94:6
5	CH_2Ph	**131b**	*p*-NO_2Ph	**132e**	56	84:16
6	Et	**131c**	*p*-NO_2Ph	**132f**	66	90:10
7	Me	**131a**	*p*-ClPh	**132g**	75	95:5
8	CH_2Ph	**131b**	*p*-ClPh	**132h**	57	95:5

Scheme 1.37

1.4.2 Intramolecular Cycloaddition Reactions

Intramolecular carbonyl ylide formation has proved to be a versatile methodology for the construction of a range of organic compounds. Ibata and co-workers[118,119] were the first to describe the methodology and subsequently Padwa has expanded the scope of the reaction.[120] Particularly relevant to the present discussion, Padwa prepared α-diazoketones **133**, **134** and **137** with different substituents at the diazo position to study their effect on the intramolecular trapping of the carbonyl intermediate and resulting formation of a range of cycloadducts **135**, **136** and **138** (Scheme 1.38).[121] Interestingly, the same reaction pathway was seen with the α-diazoesters **133** and **134** and the α-diazo ketoester **137** through carbonyl ylide formation and cycloaddition.

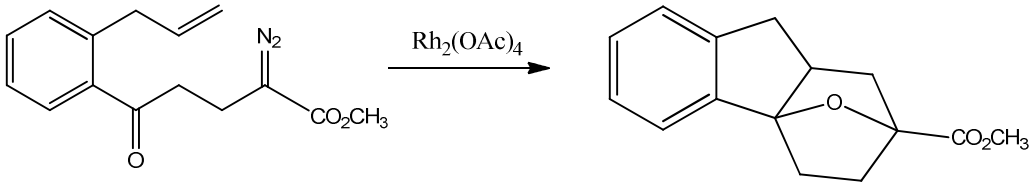


R=H, **133**

R=Me, **134**

R=H, **135**

R=Me**, 136**

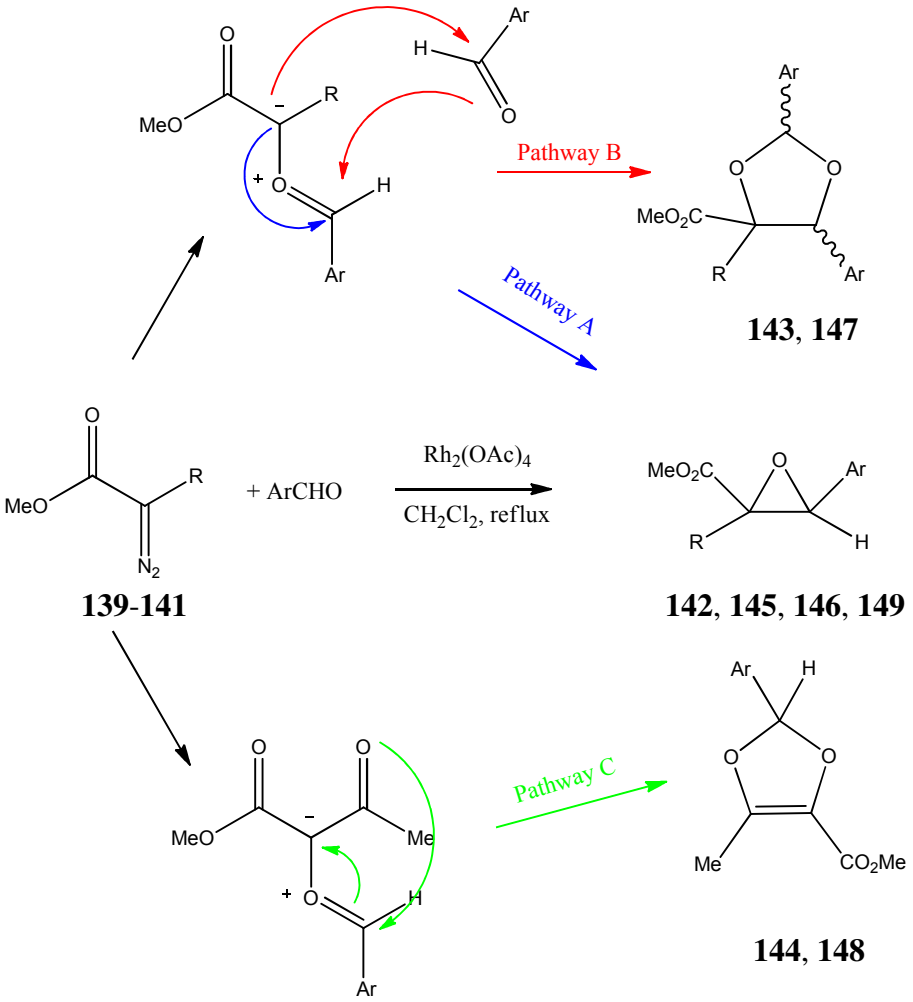


137

138

Scheme 1.38

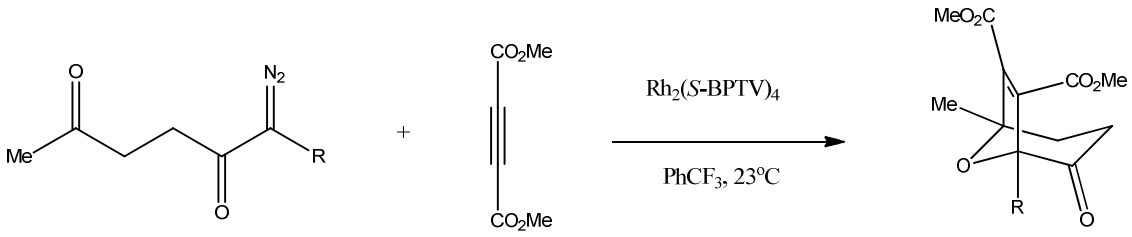
In 2004, Doyle demonstrated the extent of competiton that exists in the reaction of carbonyl ylides (Scheme 1.39).[109] With dimethyl diazomalonate **139**, competition exists between direct ring closure to form the epoxide ring **142** (Pathway A) and trapping with a second mole of the aldehyde to form the dioxolane **143** (Pathway B). When methyl diazoacetoacetate **140** is used, intramolecular trapping of the intermediate carbonyl ylide by the ketone carbonyl (Pathway C) leads to the sole production of dioxolenes **144**. Interestingly, reactions with the vinyl ether substituted diazoacetate **141** resulted solely in the formation of epoxide **145**. Addition of the *p*-methoxy substituent to the aromatic aldehyde led to similar reaction pathways except that with dimethyl diazomalonate **139**, formation of the epoxide **146** was formed exclusively without **147**.



Entry	Diazoacetate	R	Ar	Yield (%)	Product	Ratio
1	**139**	CO_2Me	C_6H_5	53	**142/143**	56:44
2	**140**	COMe	C_6H_5	50	**144**	–
3	**141**	$TBDMSOC=CH_2$	C_6H_5	50	**145**	–
4	**139**	CO_2Me	*p*-$MeOC_6H_4$	62	**146/147**	100:0
5	**140**	COMe	*p*-$MeOC_6H_4$	43	**148**	–
	141	$TBDMSOC=CH_2$	*p*-$MeOC_6H_4$	57	**149**	–

Scheme 1.39

Independent studies by Hashimoto and Hodgson illustrated that the steric and/or electronic nature of the substituent at the diazo has an important bearing upon the level of asymmetry induced in a tandem ylide formation-cycloaddition to form **151a-c** (Scheme 1.40).[122-124] The highest enantioselectivity of 80% was achieved with the terminal diazoketone **150a**.

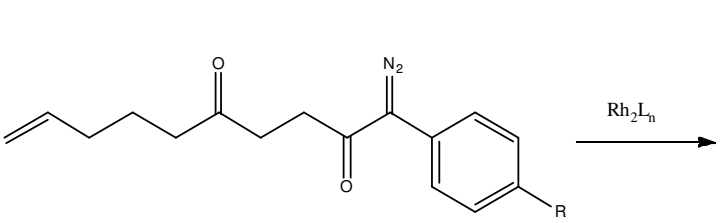


150a-c **127** **151a-c**

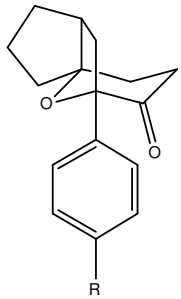
Entry	Diazoketone	R	Product	Yield (%)	ee (%)
1	**150a**	H	**151a**	50	80
2	**150b**	Me	**151b**	65	51
3	**150c**	CO_2Et	**151c**	23	33

Scheme 1.40

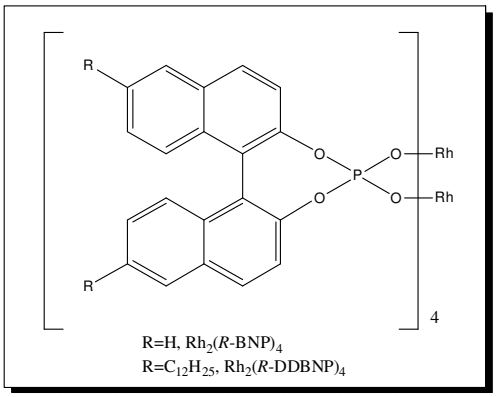
Further work by Hodgson and co-workers demonstrated for the first time the clear role that electronic effects have on determining the level of asymmetric induction in intramolecular cycloadditions (Scheme 1.41).[125] Hodgson anticipated that the presence of the electron withdrawing nitro group on the diazodione **152b** may lead to a higher enantioselectivity in the cycloaddition reaction compared to the diazodione **152a**. The enantioselectivities observed were modest, however in some cases a difference in the enantioselectivity between cycloadducts **153a-b** existed, arising from the two different carbonyl ylides formed. This is highlighted in entries 4 and 9 in Scheme 1.40.

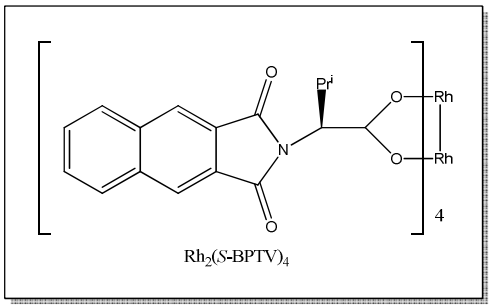


152a-b



153a-b

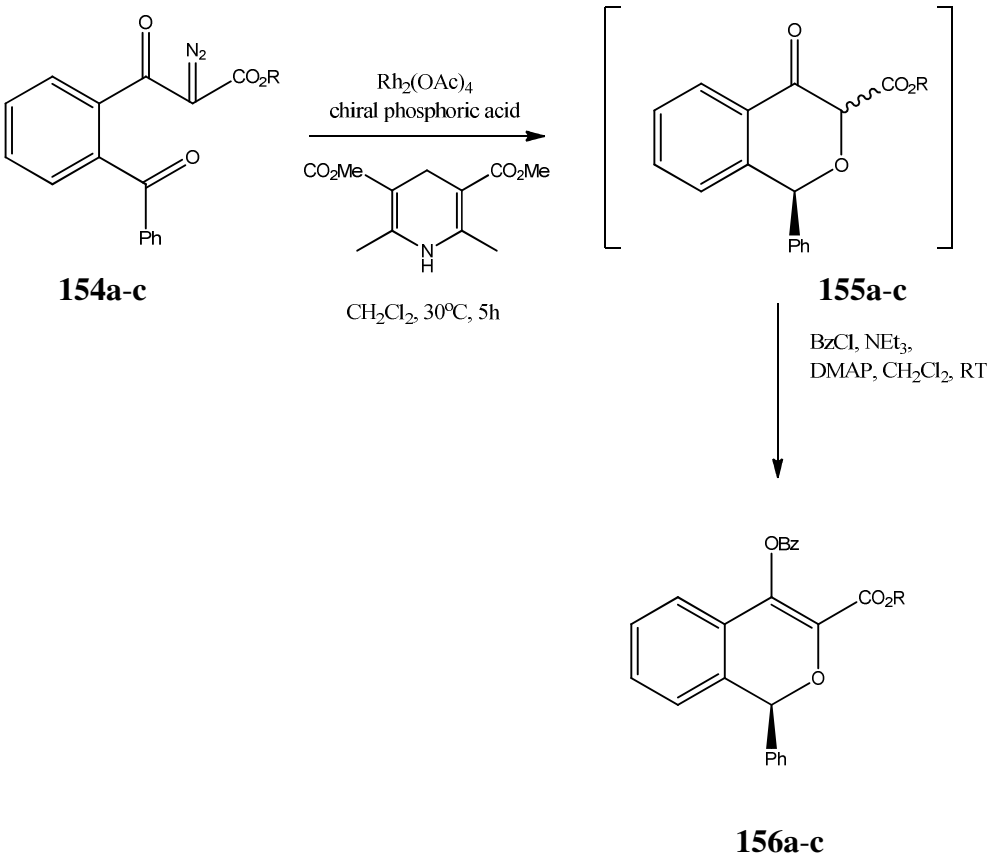




Entry	Diazoketone	R	Catalyst	Temp	Solvent	Yield (%)	ee (%)
1	**152a**	H	Rh_2(*S*-DOSP)$_4$	25	Hexane	75	12
2	**152a**	H	Rh_2(*R*-BNP)$_4$	reflux	Hexane	81	19
3	**152a**	H	Rh_2(*R*-DDBNP)$_4$	reflux	Hexane	87	19
4	**152a**	H	Rh_2(*R*-DDBNP)	25	Hexane	87	35
5	**152a**	H	Rh_2(*S*-BPTVP)4	25	$PhCF_3$	74	14
6	**152b**	NO_2	Rh_2(*S*-DOSP)$_4$	25	Hexane	8	–
7	**152b**	NO_2	Rh_2(*R*-BNP)$_4$	Reflux	Hexane	97	20
8	**152b**	NO_2	Rh_2(*R*-DDBNP)$_4$	Reflux	Hexane	Quant	28
9	**152b**	NO_2	Rh_2(*R*-DDBNP)	25	Hexane	Quant	51
10	**152b**	NO_2	Rh_2(*S*-BPTVP)$_4$	25	$PhCF_3$	98	13

Scheme 1.41

Terada and co-workers demonstrated one-pot relay catalysis employing carbonyl ylide formation using a binary catalytic system (Scheme 1.42).[126] The proposed relay catalysis consisted of four consecutive reactions: a) decomposition of the diazocarbonyl compound **154a-c** to give the rhodium carbene complex; b) intramolecular cyclisation to afford the carbonyl ylide **155a-c**; c) protonation of the transient species to afford ion pairs of the stable isobenzopyrlium ion and the conjugate base; d) termination through reduction of the cationic intermediate using the Hantzsch ester. Interestingly, variation of the size of the ester group had no impact on yield but noticeably influenced enantioselectivity. Increasing the steric effect at the diazo ester decreased enantioselectivies as can be seen with the sterically bulky *t*-butyl substituted diazoester **154b** which produced the lowest enantioselectivity of 60% ee.



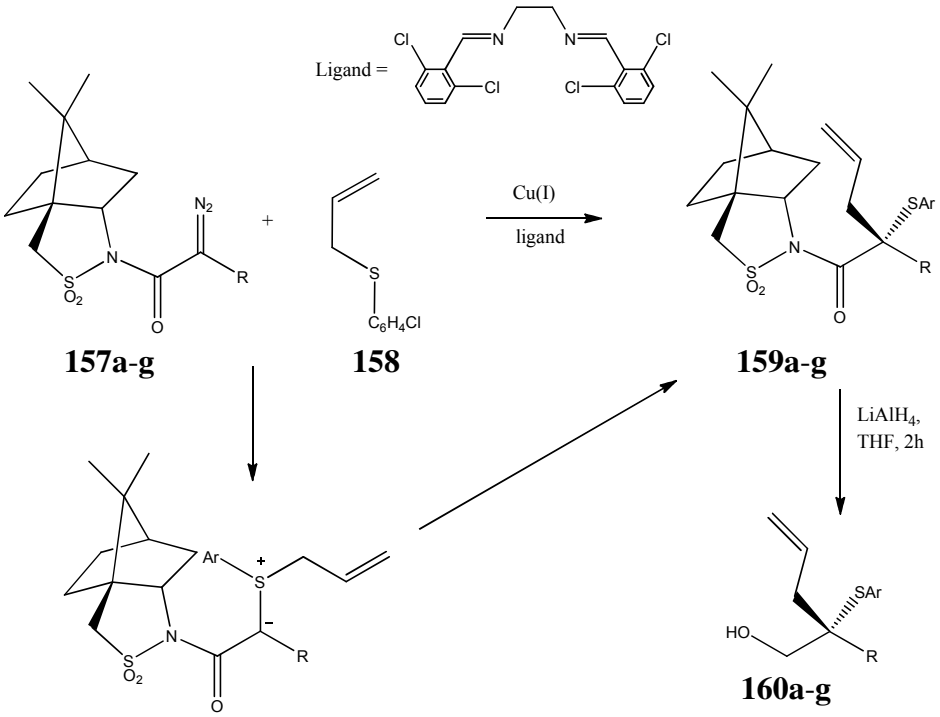
154a-c **155a-c** **156a-c**

Entry	Diazoketone	R	Product	Yield (%)	ee(%)
1	**154a**	Et	**156a**	81	84
2	**154b**	*t*Bu	**156b**	85	60
3	**154c**	Me	**156c**	83	90

Scheme 1.42

1.33 [2,3]-Sigmatropic Rearrangement

The [2,3]-sigmatropic rearrangement of allyl substituted ylides is one of the most versatile C-C/C-S bond formations in organic synthesis and sulfonium ylides have played a central role in their development.[104,127] Transition metal catalysed carbenoid reactions have proved to be a successful alternative to the traditional methods of deprotonation and desilylation in the generation of sulfonium ylides.[7,29] In 2005, Wang prepared a range of diazo compounds bearing Oppolzer's camphor sultam auxiliary (Scheme 1.43). Their reaction through [2,3]-sigmatropic rearrangement of sulfur ylides formed in the presence of allyl sulphides and a Cu(I) complex was investigated. The results show that aryldiazoacetamides as well as methyl and unsaturated diazoacetamides **157a**-**g** react with **158** in good yields and enantioselectivities. For the aryldiazoacetamides **157a**-**d** reaction was relatively slow but led to the rearrangement products with good enantioselectivity. The presence of the electron withdrawing NO_2 group in **157d** resulted in the lowest enantioselectivity. With the alkyl or unsaturated substituted substrates **157e**-**g**, the reaction proceeded much more rapidly than with the aryl series, albeit with a slight decrease in enantiocontrol.[128]

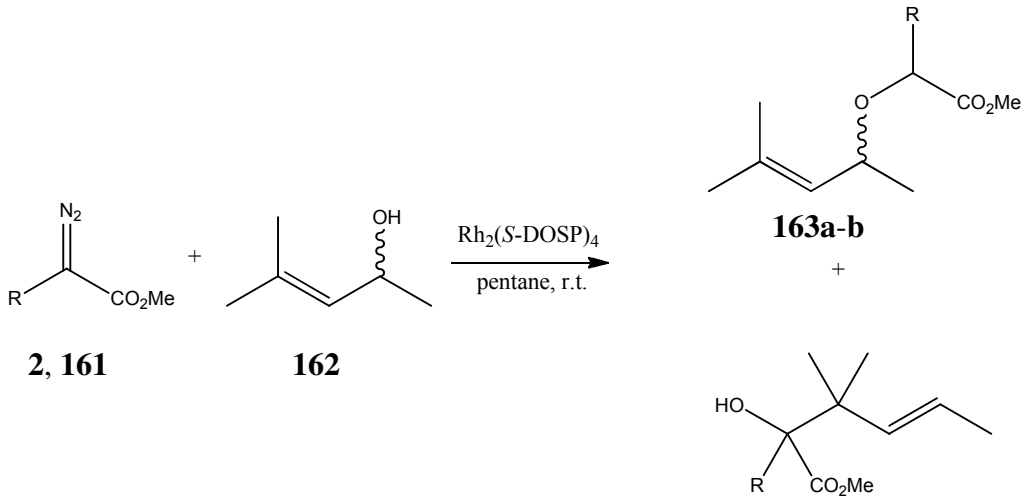


Entry	Substrate	R	Reaction Time	Yield (%)	ee (%)
1	**157a**	C_6H_5	10 h	72	92
2	**157b**	*p*-BrC_6H_4	6 h	82	94
3	**157c**	*m*, *p*-$Cl_2C_6H_3$	12 h	58	90
4	**157d**	*p*-$NO_2C_6H_4$	48 h	43	70
5	**157e**	CH_3	15 min	67	82
6	**157f**	CH_3CH=CH	15 min	76	78
7	**157g**	PhCH=CH	15 min	88	85

Scheme 1.43

In 2009, Davies reported competition between O-H insertion and [2,3]-sigmatropic rearrangement upon variation of the substituent at the diazo carbon in the rhodium catalysed reaction of racemic alcohol **162**.[129] As illustrated in Scheme 1.44 entry 2, the reaction of methyl diazomalonate **161** with allyl alcohol **162** generated the O-H insertion product **163b** and the [2,3]-sigmatropic rearrangement product **164b**. Significantly, the outcome was quite different when the reaction was conducted with a donor/acceptor

carbenoid. The reaction of ethyl phenyldiazoacetate **2** (Scheme 1.44, entry 1) gave a 86% combined yield of products, in which the [2,3] sigmatropic rearrangement product **164a** was the major product favoured over the O-H insertion product **163a** by a ratio of 6:1. In addition, **164a** was produced with good asymmetric induction (86% ee) even though the starting alcohol **162** was racemic.

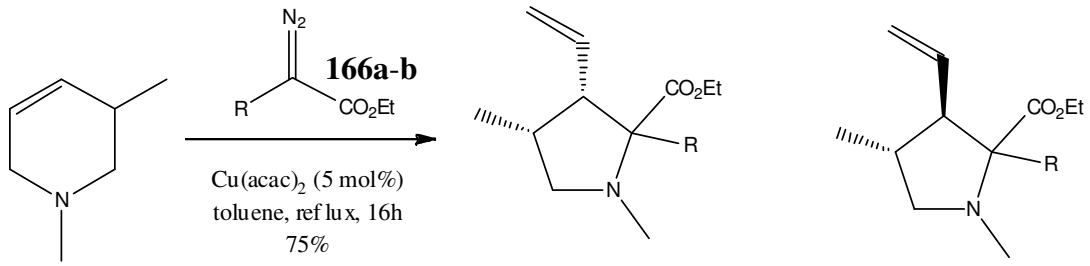


2, **161** **162** **163a-b** + **164a-b**

Entry	Diazoester	R	Product **163**:**164**	Yield (%)	ee (%)
1	**2**	Ph	1:6	86	86, **164a**
2	**161**	CO_2Me	2:1	52	Racemic

Scheme 1.44

While probing allylic substitution on cyclic ammonium ylide [2,3]-sigmatropic rearrangements, Sweeney and co-workers varied the substituent at the diazo carbon and observed a variation in diastereoselectivity and yield.[130] Tetrahydropyridine **165** reacted with diazomalonate **166a** in the presence of $Cu(acac)_2$ to give the *cis* and *trans* pyrolidine **167** and **168** in a ratio of 53:47 and in excellent yield (Scheme 1.45). However, when diazoketoester **166b** was applied to the same reaction, the *cis* isomer was favoured in a mixture of 3,4-cis and 3,4-trans-isomers (75:25).



165 *cis* **167** *trans* **168**

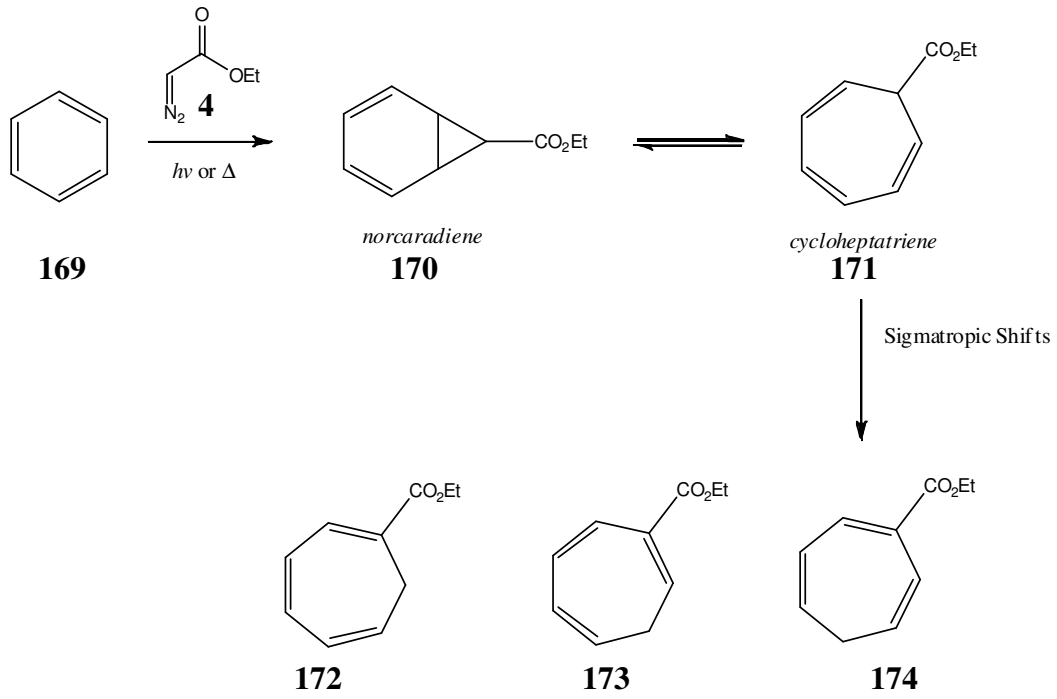
Entry	Diazoketoester	R	Ratio **167**: **168**	Yield (%)
1	**166a**	CO_2Et	53:47	75
2	**166b**	CO*i*Pr	75:25	47

Scheme 1.45

1.5 Aromatic Addition

The catalytic decomposition of diazocarbonyl compounds followed by addition to an aromatic ring with concomitant rearrangement (by 6π electrocyclisation) of the resulting norcaradiene product to a cycloheptatriene isomer, is commonly known as the Buchner reaction.[9,131,132] The formation of these seven membered carbocycles can occur both inter- and intramolecularly.[7,35,133] Buchner's work initially focused on the thermal decomposition of ethyl diazoacetate **4** with unsaturated hydrocarbons. Benzene **169** was originally investigated, which resulted in the isolation of what was thought to be a single ester. However, subsequent alkaline hydrolysis yielded a mixture of several isomeric carboxylic acids to which Buchner tentatively assigned norcaradiene structures.[132] In 1950, Doering re-examined the reaction and characterised four isomeric cycloheptatriene products,[134] speculating that they were formed from the norcaradiene structure **170**, which is in dynamic tautomeric* equilibrium with the more stable cycloheptatriene structure **171**, and that the remaining compounds **172**-**174** were generated from a series of sigmatropic shifts (Scheme 1.46).

*The phrase tautomer is commonly used for the norcaradiene/cycloheptatriene equilibrium although technically it differs from tautomers such as keto/enol interconversion.



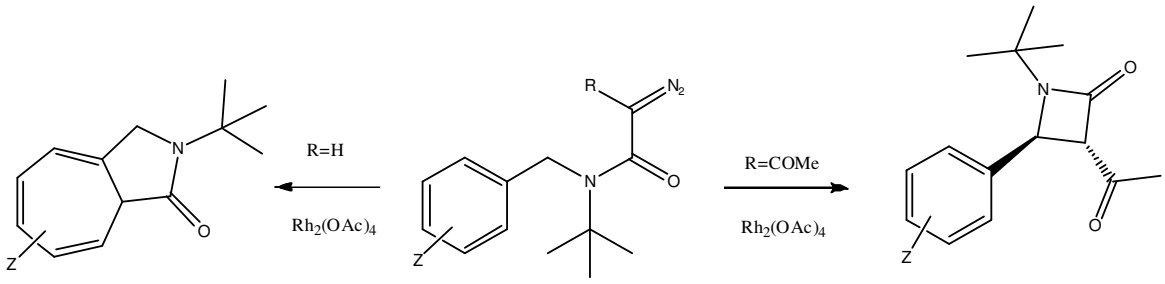
Scheme 1.46

Due to the isolation of these complex product mixtures, research into the intermolecular Buchner reaction has been limited and has largely focused on diazoesters.[135-137] Significantly, no variation of the substituent at the reacting diazo carbon has been reported in the intermolecular Buchner reaction.

In contrast, the intramolecular Buchner reaction has attracted considerable attention from both a synthetic and mechanistic point of view.[8,138-153] High levels of chemoselectivity and regiocontrol have been reported through the use of careful substrate and catalyst selection.[66,68,139,147,154-159] In particular, stereocontrol, which encompasses both diastereo- and enantioselectivity, has been restrictive in advancing the synthetic utility of the aromatic addition reaction. Studies have shown that both the structure of the diazo compound and moreover the catalyst employed can provide effective stereocontrol.[141,145,146,148,160-164] However, a highly enantioselective Buchner reaction remains elusive. In general, examples of variation of the α-substituent at the diazo carbon have been limited. Primarily, this has had an impact on the chemoselectivity and efficiency of the reaction as outlined in Section 1.5.1. Crucially, the impact on both diastereo- and enantioselectivity has not been reported.

1.5.1 Intramolecular Aromatic Addition

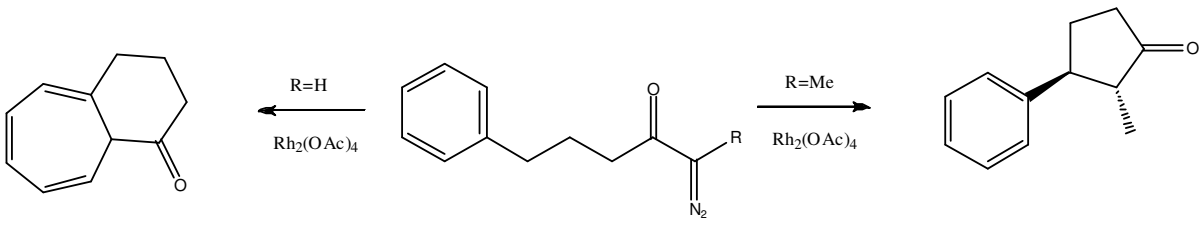
The presence of substituents on the carbene carbon has been observed to have a dramatic effect on the chemoselectivity of the intramolecular Buchner reaction independent of the catalyst employed. This has been clearly demonstrated by the two reactions shown in Scheme 1.47. Doyle reported that in the case of diazoketones of general structure **175a-c**,[66] when R=H only the product of the intramolecular Buchner cycloaddition **176a-c** was observed in all three cases, but that on exchanging the hydrogen for an acetyl group only the products of C-H insertion **177a-c** were recovered. It was postulated that the acetyl group inhibits approach of the carbene centre to the aromatic ring, thereby eliminating this reaction pathway. McKervey observed a similar effect in the aromatic addition of **178a-b**,[158] when R=H, the ring expanded products **179a-b** were obtained in quantitative yield; however, on exchanging the hydrogen for a methyl group only the products of C-H insertion **180a-b** were observed.



176a, Z=H — **175a**, Z=H — **177a,** Z=H

176b, Z=Br — **175b**, Z=Br — **177b**, Z=Br

176c, Z=OMe — **175c**, Z=OMe — **177c**, Z=OMe

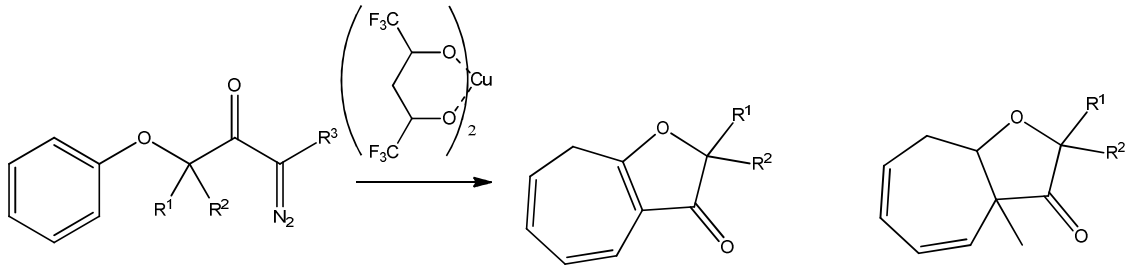


178a, R=H — **177a**, R=H — **179a**, R=H

178b, R=Me — **177b**, R=Me — **179b**, R=Me

Scheme 1.47

In 1986, Saba reported the copper(II) catalysed intramolecular aromatic addition of diazoketones **181a**-**h** bearing α-phenoxy substituents (Scheme 1.48).[161] Interestingly, Saba varied the substituent at the reacting diazo carbon and reported the formation of conjugated cycloheptafuranones **182a**-**d** when R^3=H and cycloheptafuranones **183e**-**h** when R^3=Me. The efficiency of the reaction increased significantly when the diazoketone was substituted at the α-position.



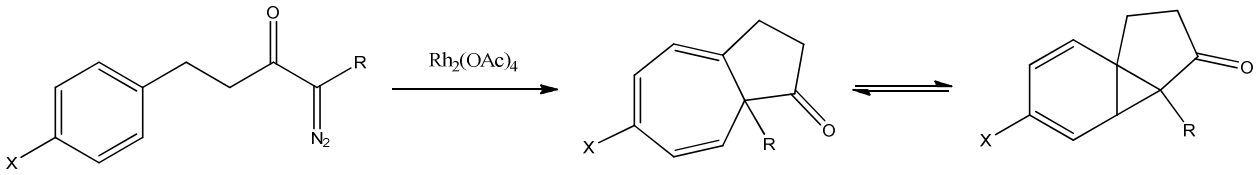
181a-**h** **182a**-**d** **183e**-**h**

Entry	α-substituent		R^3	Diazoketone	Product	Yield (%)	
	R^1	R^2				**182**	**183**
1	H	H	H	**181a**	**182a**	9.5	–
2	Me	H	H	**181b**	**182b**	32	–
3	Ph	H	H	**181c**	**182c**	38	–
4	Me	Me	H	**181d**	**182d**	43	–
5	H	H	Me	**181e**	**183e**	–	26
6	Me	H	Me	**181f**	**183f**	–	95
7	Ph	H	Me	**181g**	**183g**	–	88
8	Me	Me	Me	**181h**	**183h**	–	86

Scheme 1.48

McKervey reported that the intramolecular aromatic addition of *p*-substituted terminal diazoketones **184a**-**c** afforded the corresponding azulenones **184a**-**c** in excellent yield (≥95%) as illustrated in Scheme 1.50.[138,158] However when O'Leary exposed under similar conditions the corresponding internal diazoketones **184d**-**f**,[165] a decrease in

reaction efficiency was observed. This comparison demonstrates that under the same reaction conditions the cyclisation of a terminal diazoketone is more efficient than that of the internal analogue. McKervey reported that the use of $Rh_2(TFA)_4$ with the non-terminal diazoketones proved to be more effective.[158]

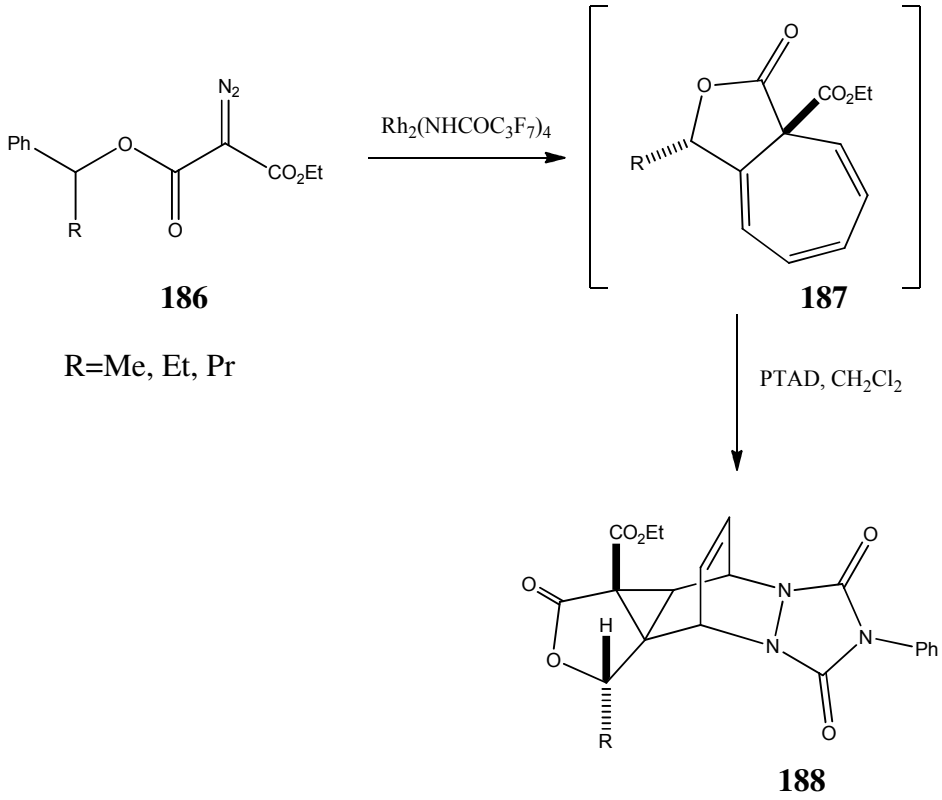


184a-f **185a-f**

Entry	R	X	Diazoketone	Azulenone	Efficiency
1	H	H	**184a**	**185a**	95[138,158]
2	H	Me	**184b**	**185b**	>95[158]
3	H	OMe	**184c**	**185c**	>95[158]
4	Me	H	**184d**	**185d**	95[158]
5	Me	Me	**184e**	**185e**	82[165]
6	Me	MeO	**184f**	**185f**	80[165]

Scheme 1.49

Moody has demonstrated aromatic addition processes are feasible with ester moieties as illustrated in Scheme 1.50.[155]



186

R=Me, Et, Pr

187

188

Scheme 1.50

1.6 Conclusion

This review summarises the influence of variation of substitution on the diazo carbon on chemo- and stereoselectivity in addition to reaction efficiency. Depending on the reaction pathway, both steric and electronic factors operate, leading to a variation in reaction outcome. Significantly, while trends can be seen with each reaction pathway there is no clear trend across different reactions.

From a synthetic perspective, judicial choice of substituent at the diazo carbon may be effective in achieving a desired reaction outcome. This review draws together outcomes from different studies highlighting for the first time the impact of variation in diazo substitution, frequently drawing on reports whose focus is in a different area.

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Chapter 2

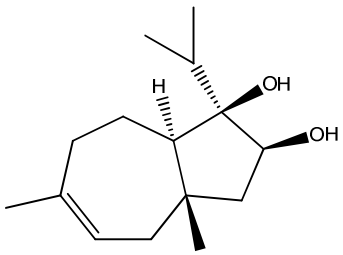
Results and Discussion

Table of Contents

2.1 Project Background

As the bioactivity of enantiomers of organic compounds may differ, appropriate strategies for asymmetric synthesis are very important, especially for pharmaceutical applications.[1-4] While use of chiral auxillaries has proven to be effective, asymmetric catalysis provides a particularly attractive approach, as a small amount of an enantiopure catalyst can potentially provide a large amount of an enantioenriched product.

A multitude of terpenoids with varying bioactivity have been and continue to be isolated from natural sources.[5-9] Research in our group in recent years has focused on synthetic approaches to sesquiterpenoids bearing the bicyclo[5.3.0]decane sesquiterpenoid skeleton, based on the intramolecular aromatic addition of α-diazoketones.[10] CAF-603 **1** is one such terpenoid, originally isolated from the culture broth of a strain of *Trichoderma virens* (*Gliocladium virens* IFO 9166), by Watanabe and co-workers in 1990 (Figure 2.1).[11] One challenge which remains in the synthesis of these natural products lies in the limited reports of asymmetric intramolecular aromatic addition of diazocarbonyl compound.[10,12]



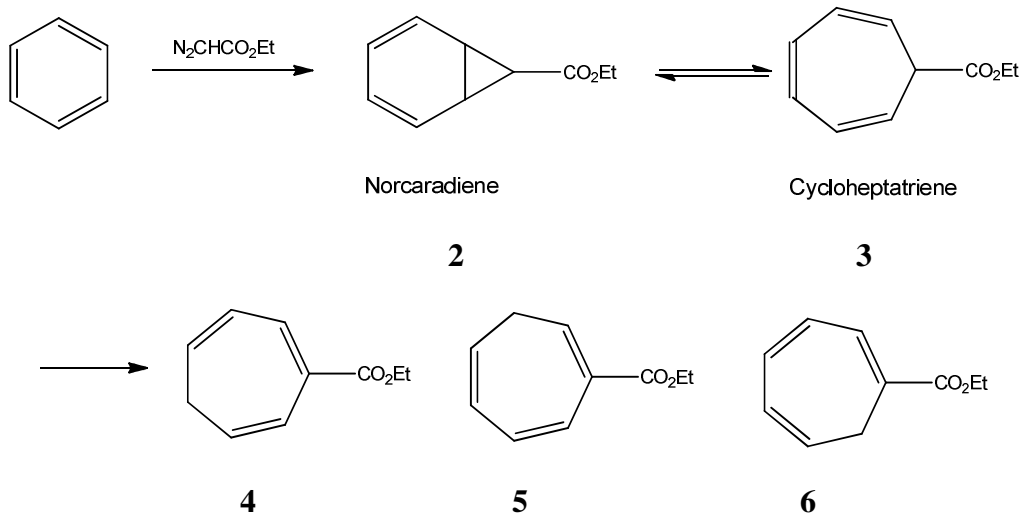
CAF-603 **1**

Figure 2.1

2.2 The Buchner Reaction

The Buchner reaction involves cyclopropanation of an aromatic ring by carbenoid addition to form a norcaradiene derivative which is in dynamic equilibrium with the cycloheptatriene tautomer (*via* a 6π electrocyclic ring opening/closure), as illustrated in Scheme 2.1. The first example of aromatic addition to diazocarbonyl compounds was the thermal decomposition of ethyl diazoacetate in benzene, which was reported by Buchner and Curtius in 1885,[13,14] resulting in the addition of the α-diazoester to the aromatic

solvent. Buchner believed that the product of the reaction was the norcaradiene structure **2**, however, Doering later showed that the norcaradiene product is transformed under the reaction conditions to give four isomeric cycloheptatriene products **3**-**6**,[15] related to each other by a series of sigmatropic shifts. The norcaradiene compound **2** reported by Buchner exists in dynamic tautomeric equilibrium with the cycloheptatriene form **3**.

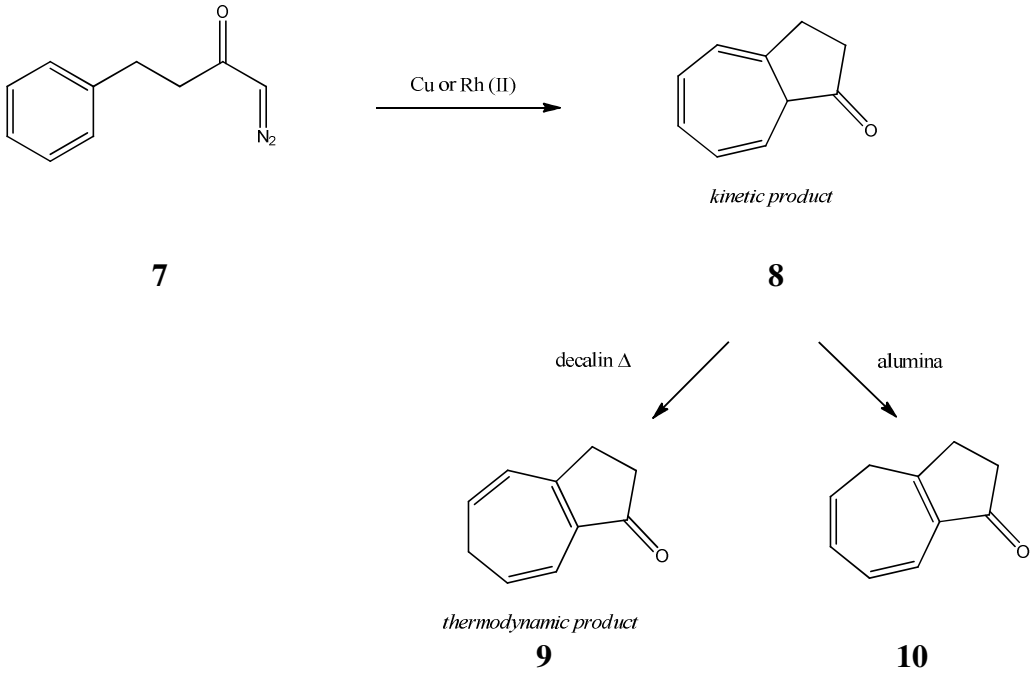


Scheme 2.1

The thermal reaction described above requires high temperatures and it was not until the discovery by Teyssié that transition metal catalysts were capable of catalyzing the aromatic addition reaction of diazocarbonyl compounds under extremely mild conditions that it became synthetically useful. Teyssié and co-workers prepared a range of substituted cycloheptatrienyl esters in high yields using rhodium(II) trifluoroacetate for the decomposition of ethyl diazoacetate. The use of the rhodium catalyst in the intermolecular Buchner reaction dramatically increased selectivity and efficiency.[16,17] Teyssié repeated the original aromatic addition reaction of ethyl diazoacetate and benzene with $Rh_2(OAc)_4$ and isolated the kinetic product in quantitative yield.[18]

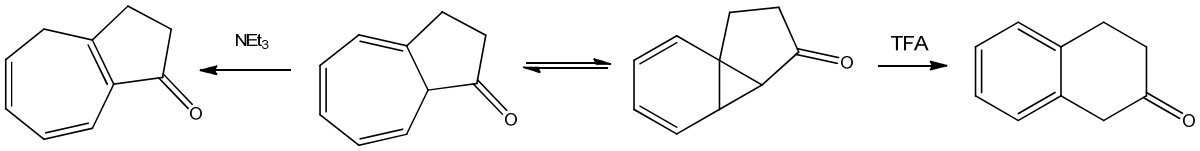
Early work on the intramolecular Buchner reaction involved the use of copper catalysts. Both Julia and Scott reported copper as a catalyst for the intramolecular aromatic addition reaction. Julia prepared the conjugated azulenone **9** in low yield (13%) *via* the copper catalysed decomposition of 1-diazo-4-phenylbutan-2-one **7** (Scheme 2.2).[19] When Scott repeated this reaction at lower temperatures he was able to detect the kinetic

product **8** of the reaction by ^{1}H NMR analysis of the crude product mixture.[20] Purification by chromatography on alumina failed to afford **8** but instead led to the isolation of the more conjugated isomer **10**. In 1984, McKervey finally reported the isolation of the kinetic product **8** in 95% yield by decomposition of diazoketone **7** in the presence of $Rh_2(OAc)_4$ at room temperature.[21]



Scheme 2.2

McKervey and co-workers discovered that the β-tetralone **11** can be efficiently formed when azulenone **8** is treated with a catalytic amount of trifluoroacetic acid, while exposure of **8** to triethylamine gave the more conjugated isomer **10** (Scheme 2.3).[22] The fact that two distinct bicyclic ring systems could be formed from the same starting material depending on the reaction conditions, confirmed that the azulenone was an equilibrating mixture of the norcaradiene (NCD-**8**) and cycloheptatriene (CHT-**8**) tautomers. This pioneering work opened up the possibility of forming a range of substituted azulenones under very mild conditions, each of which can be converted to the corresponding tetralone.



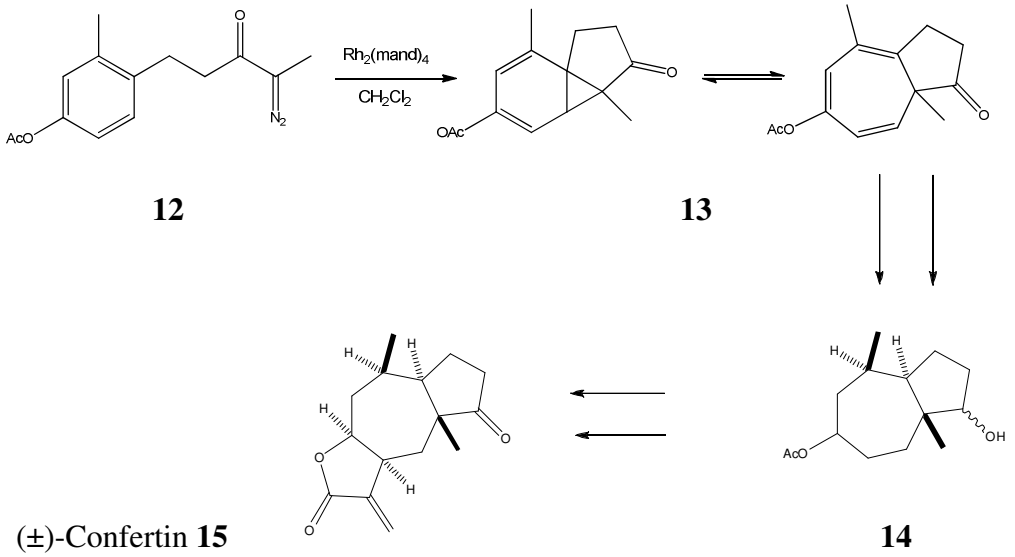
10 CHT-**8** NCD-**8** **11**

Scheme 2.3

Thus the introduction of rhodium(II) catalysts for diazocarbonyl decomposition and aromatic additions led to great advancements in highly chemo, stereo- and regioselective transformations that were largely inaccessible with conventional copper catalysts.[23-26]

2.3 Intramolecular aromatic addition in natural product synthesis

The compounds derived from the intramolecular Buchner reaction, which has been studied in detail in our group,[27-29] are structurally significant as they bear the bicyclo[5.3.0]decane skeleton which occurs in a number of naturally occuring sesquiterpenoids, which possess a wide range of biological activities. In 1991, Kennedy and McKervey used the intramolecular Buchner reaction as the key step in a formal synthesis of pseudoguaianolide (±)-confertin **15** (Scheme 2.4).[30,31]

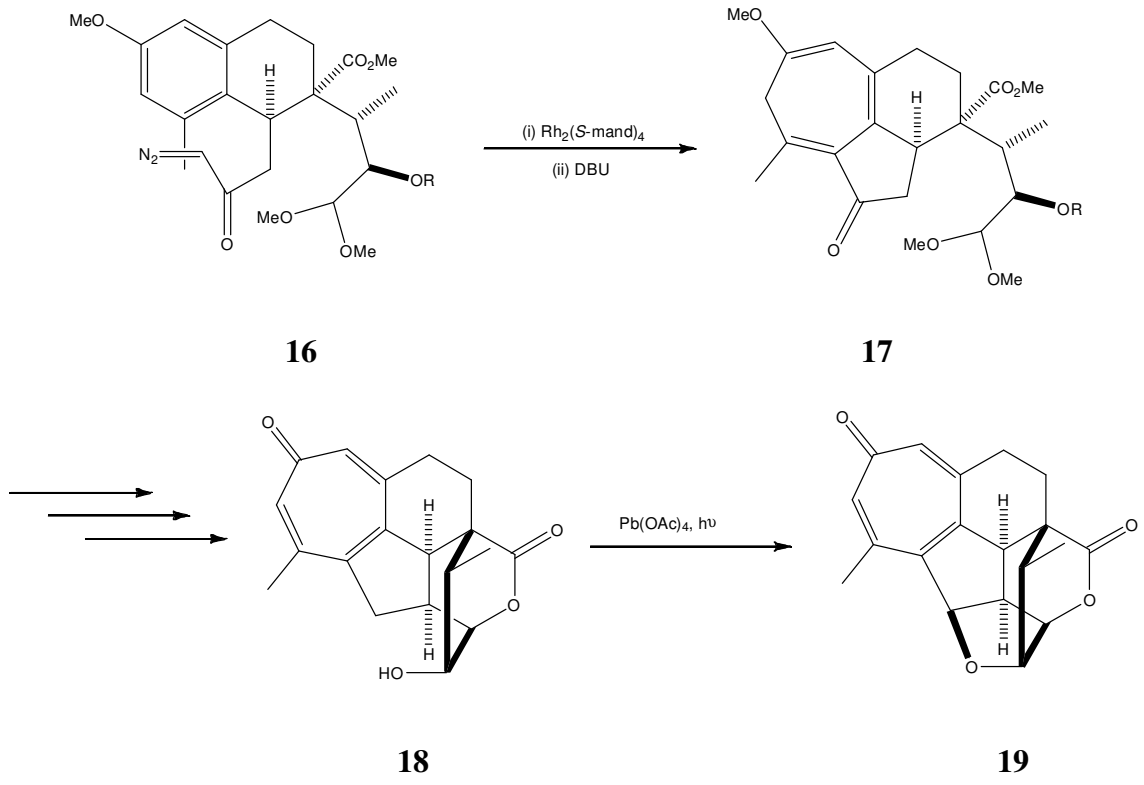


12 **13**

(±)-Confertin **15** **14**

Scheme 2.4

Subsequently in 2000, Mander and co-workers also applied the intramolecular Buchner reaction to the synthesis of the seven and five membered rings of the natural product hainanolidol **18**, which had been previously isolated from the Chinese species Cephalotaxus hainanenis (Scheme 2.5).[32,33] The natural product hainanolidol **18** is closely related to the diterpenoid tropane harringtonolide **19**, which possesses anti-neoplastic and anti-viral properties.

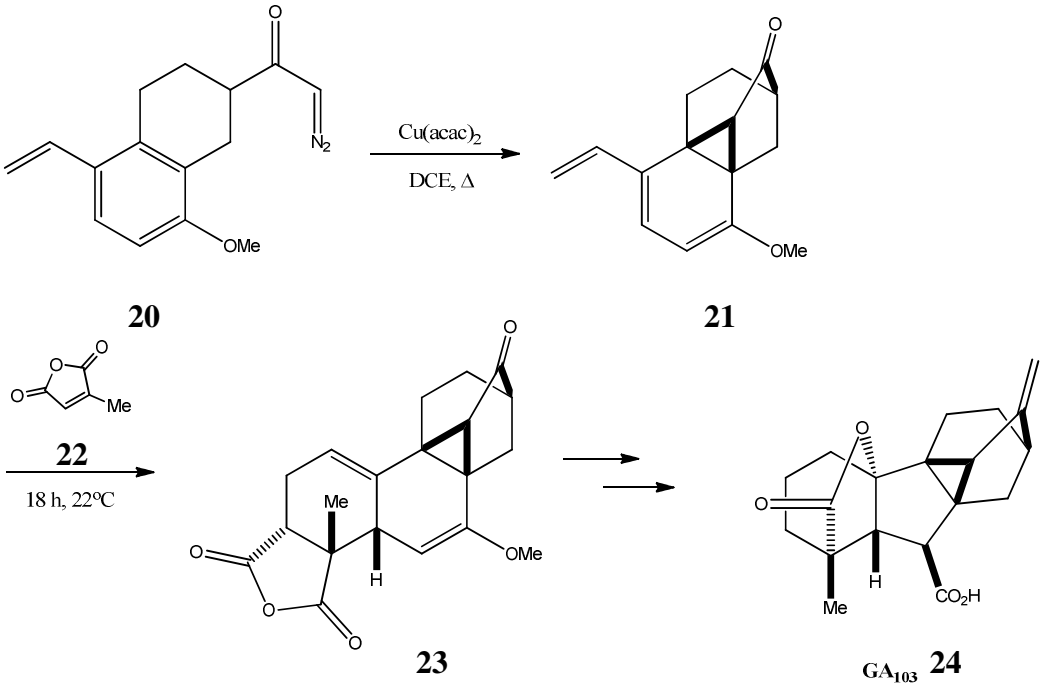


16 **17**

18 **19**

Scheme 2.5

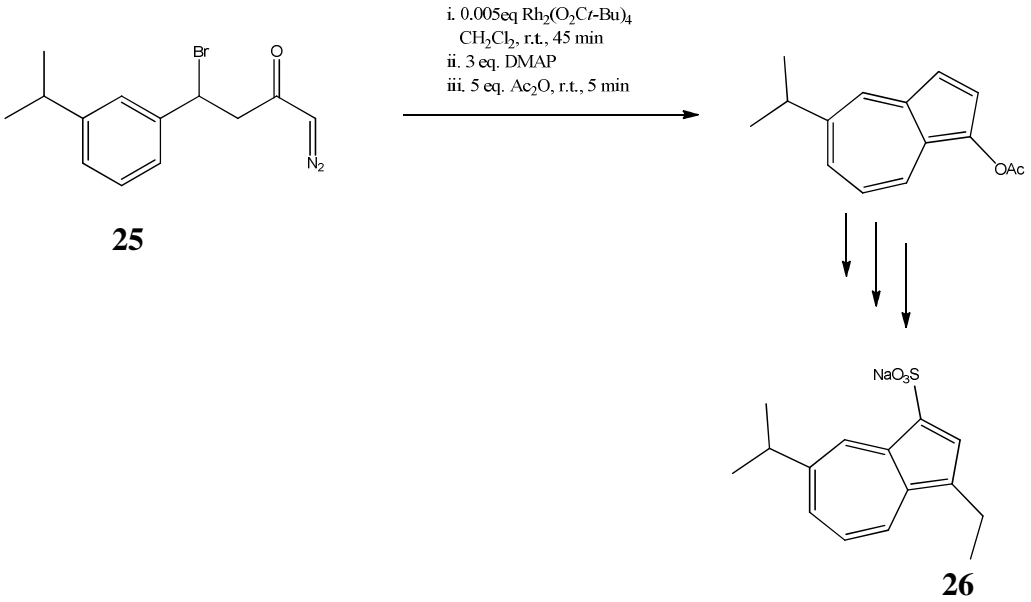
Mander also utilised the Buchner reaction as part of a cascade reaction sequence in an elegant total synthesis of gibberelin GA_{103} **24**. Treatment of α-diazoketone **20** with $Cu(acac)_2$ in refluxing dichloroethane provided the unstable norcaradiene **21** which was trapped *in situ* by addition of 3-methylfuran-2,5-dione **22** to deliver the polycyle **24** (Scheme 2.6).



Scheme 2.6

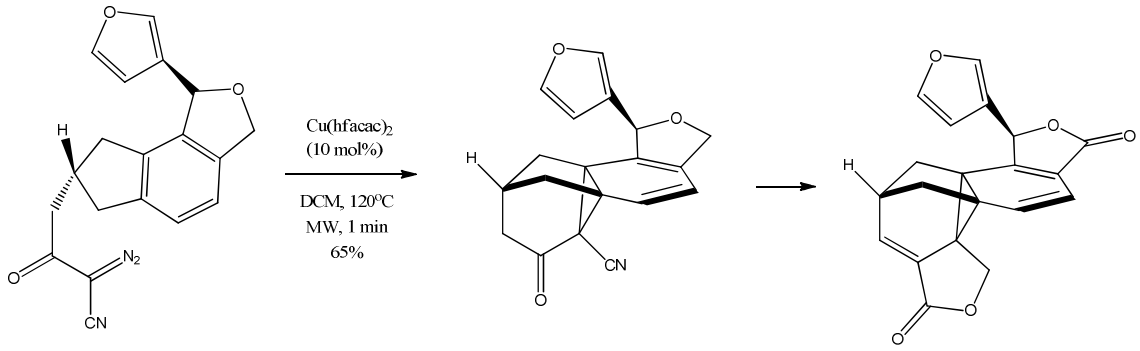
Danheiser and co-workers applied the intramolecular aromatic addition of *meta*-substituted diazoketone **25** to the synthesis of the anticancer drug egualen sodium (KT1) **26**,[34] as illustrated in Scheme 2.7.

In 2011, Reisman and co-workers reported the enantioselective total synthesis of the diterpenoid natural product (+)-salvileucalin B **28**. Their studies resulted in the development of a copper catalysed arene cyclopropanation reaction to access a norcaradiene bearing a fully substituted cyclopropane ring,[35,36] as illustrated in Scheme 2.8.



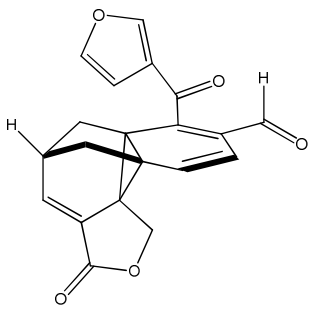
25 **26**

Scheme 2.7



27 **28a**

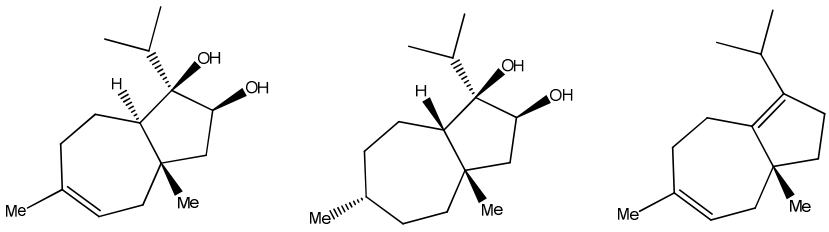
Ratio **28a**:**28b**, 2:1



28b

Scheme 2.8

For the intramolecular Buchner reaction to be an efficient mode of synthesis for a wider range of natural products, a thorough understanding of the factors which affect chemoselectivity, regioselectivity, stereoselectivity and enantioselectivity is essential. Work within the group over the years has concentrated on developing a broad body of knowledge on the synthesis of azulenones and also their further reactivity. Buckley forged the way for development in this area by investigating the effect of substituents on both the diazoketone and catalyst employed on the cyclisation, achieving yields of ~70% with high diastereoselectivities.[24,37,38] O'Leary further expanded the understanding of the norcaradiene cycloheptatriene equilibrium by studying the interesting effect of methoxy substituents.[28] Both Buckley and O'Leary carried out a preliminary investigation into the synthesis of the natural product CAF-603 **1**, a potent modulator of the calcium activated potassium (Maxi-K) channel. Foley subsequently completed the synthesis of *cis* fused dihydro analogue of CAF-603 **1**, which is used in the treatment of fever dysentery, and potentially an advanced intermediate in the synthesis of daucene, which is employed as an anti-hysteric.[29] Harrington's research examined the reactivity of the azulenone system with PTAD and singlet oxygen dienophiles to produce a range of cycloadducts and explored their reactivity.[39,40] Work by O'Keeffe led to significant advancement in the enantiocontrol of the intramolecular aromatic addition reaction of α-diazoketones, achieving 95% ee using copper catalysts based on bisoxazoline ligands,[12,41] introducing the possibility of an asymmetric catalyst with general applicability. Stack focused on investigating the reactivity of the azulenones, and in particular, the introduction of oxygen functionality through photooxygenation.[27] Both singlet oxygen ene and [4+2] cycloaddition reactions proved very effective in generating oxygenated derivatives of the bicyclo[5.3.0]decane structures. McNamara focused specifically on the investigation of the impact of halogen and acetoxy aromatic substituents on the aromatic addition and subsequent reactivity of the azulenones.[42] The halogenated azulenones were shown to undergo cycloaddition with the highly reactive dienophile PTAD, in addition to the carbon based dienophiles, maleimide, *N*-phenyl maleimide and maleic anhydride, leading to polycyclic cycloadducts with excellent diastereocontrol.



CAF-603 **1** *dihydro* CAF-603 **29** daucene **30**

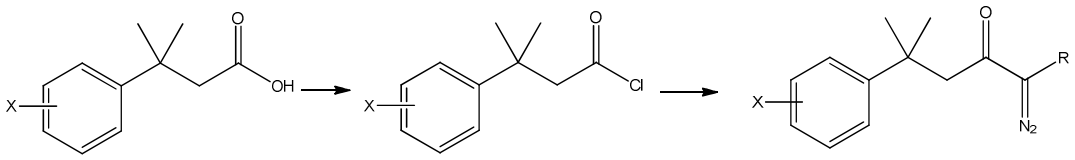
Figure 2.2

2.4 Objectives of current research

The overall objective was to further develop the synthetic methodology developed within our research group based on the intramolecular aromatic addition process, specifically extending the work to terminal diazoketones. Furthermore a detailed investigation of asymmetric catalysis, building on the preliminary results within the group was initiated, including determination of the absolute stereochemistry, an examination of the effects of ligands, counterion, metal salts and substrate structure.

The principal objectives of this project were:

- To synthesise substantial quantities of novel and known substituted internal and terminal α-diazoketones (Scheme 2.9).



R = H, CH_3

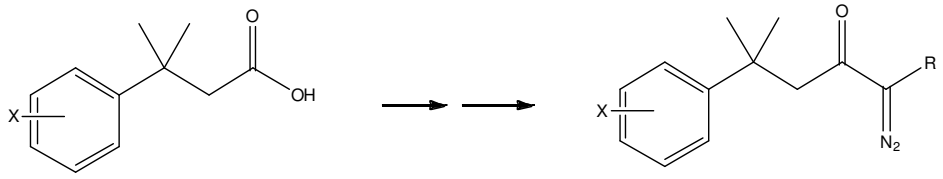
Scheme 2.9

- To explore the intramolecular aromatic addition with this series of diazoketones catalysed by a range of rhodium and copper catalysts, and specifically, to determine the effect of ligand, counterion and substrate structure.

- To evaluate the level of asymmetric induction in the copper(I) catalysed decomposition of substituted internal and terminal α-diazoketones.
- To investigate the effect on enantioselectivity of variation of the counter-ion.
- To determine the absolute stereochemistry of the major enantiomer of the product from the asymmetric intramolecular Buchner reaction.
- To design a novel ligand to optimise enantioselectivity.

2.5 Synthesis of α-diazoketones

The initial objective of this research was to synthesise a series of internal and terminal α-diazoketones with various substituents on the aromatic ring, as shown in Scheme 2.10.

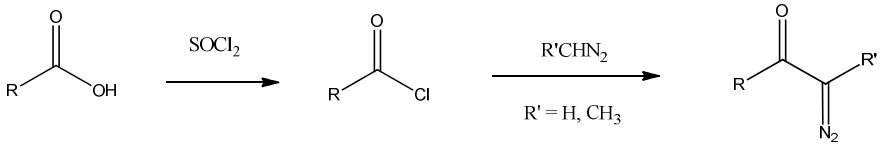


			R=Me	R=H
X =	4-H	**31**	**37**	**43**
	4-Me	**32**	**38**	**44**
	4-Cl	**33**	**39**	**45**
	4-F	**34**	**40**	**46**
	3,5-$(Me)_2$	**35**	**41**	**47**
	3,4,5-$(Me)_3$	**36**	**42**	**48**

Scheme 2.10

The design of these substrates was based on earlier research within the group.[28,37,40,41] The presence of the geminal dimethyl group in the linker chain stabilises both the precursor diazoketone and the azulenones formed by their reaction, relative to the analogous substituted products. In addition, the cyclisation is facilitated by the presence of the germinal dimethyl substituents *via* the Thorpe-Ingold effect. The choice of substituents on the aromatic ring enabled investigation of both steric and electronic effects on the aromatic addition process.

The methodology employed for the synthesis of the internal α-diazoketones from the precursor carboxylic acids is well established within our research group and it is based on the Arndt-Eistert synthesis of diazoketones.[43,44] The initial step is the formation of an acid chloride which is followed by the acylation of diazoethane/diazomethane to form the α-diazoketone as illustrated in Scheme 2.11.



Scheme 2.11

The key challenge in accessing the substrate framework was the synthesis of the precursor carboxylic acids. Routes to these carboxylic acids have been optimised over a in recent years by researchers in the group.[37,40-42] The carboxylic acids needed in this body of work were synthesised *via* Friedel Crafts alkylation of benzene derivatives for substrates **31**, **33**, **35** and **36** or following a multi-step route starting with the Knoevenagel condensation reaction for substrates **32** and **34**.

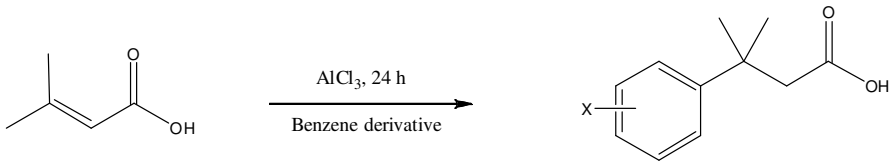
2.5.1 Synthesis of carboxylic acids

2.5.1.1 Friedel Crafts alkylation

Dippy *et al.* described the alkylation of aromatic substrates using aluminium trichloride as a catalyst in a high yielding and extremely efficient process.[45-47] The crude products are relatively clean, and no purification is required. Carboxylic acids **31**, **33**, **35** and **36** were synthesised using this method in Table 2.1.

In this work, the synthesis of the unsubstituted carboxylic acid **31**, *para*-chloro substituted acid **33** and the 3,4,5-trimethyl substituted acid **36** were repeated as previously described by earlier work in the group (Table 2.1).[37,40,41] Both were formed efficiently on multi-gram scale (~20 g) and spectroscopic characteristics were found to be in agreement with those reported earlier for these compounds.[41]

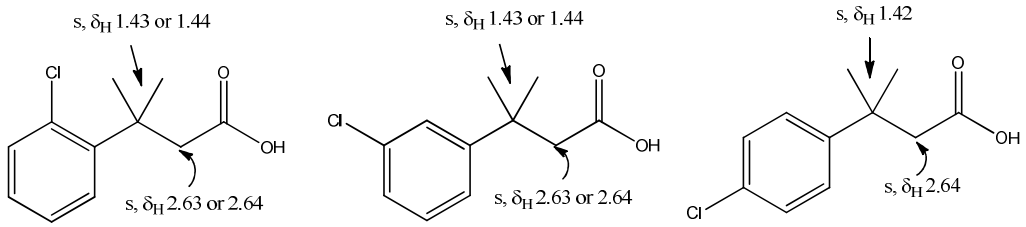
Table 2.1 *Synthesis of carboxylic acids* **31**, **33**, **35** *and* **36** *via Friedel Crafts alkylation*



X = 4-H, 4-Cl, 3,5-$(Me)_2$, 3,4,5-$(Me)_3$

Entry	Benzene Derivative	Acid	X	Crude Yield (%)
1	C_6H_6	**31**	H	94
2	ClC_6H_5	**33**	4-Cl	99
3	1,3-$(Me)_2C_6H_4$	**35**	3,5-$(Me)_2$	85
4	1,2,3-$(Me)_3C_6H_3$	**36**	3,4,5-$(Me)_3$	62

In the alkylation of chlorobenzene, formation of regioisomeric products can be envisaged. Examination of the ^{1}H NMR spectrum of both the crude and purified products were consistent with the exclusive formation of the substituted acid **33**, following a reaction time of 20 hours. This is consistent with Buckley's description where in earlier work, she described the exclusive formation of the *para*-chloro substituted regioisomer **33** while O'Keeffe reported the formation of regioisomeric acids **33**, **49** and **50**. O'Keeffe demonstrated that extending the reaction time to 120 hours led to the formation of the *para* **33** and *ortho/meta* chloro substituted regioisomers **49/50** in the ratio of *para*:*ortho/meta*, 80:20 (Figure 2.2). In the ^{1}H NMR spectrum of the crude product, O'Keeffe reported signals for each of the three compounds which could be distinguished but not easily integrated accurately due to very similar chemical shifts.



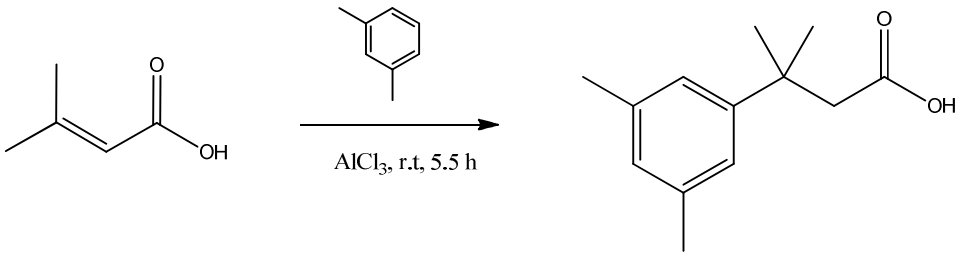
ortho **49** *meta* **50** *para* **33**

Figure 2.2

The ^{1}H NMR spectra were consistent with the exclusive formation of **33**, we subsequently discovered (see Section 2.6.2.1) that up to 9% of the *ortho* or *meta* substituted regioisomer **49/50** was present.

The Friedel-Crafts alkylation reaction was also used for the synthesis of 3-methyl-3-(3,4,5-trimethylphenyl)butanoic acid **36**, previously synthesised by O'Keeffe with excellent regiocontrol. The trimethyl substituted acid **36** was isolated in a yield of 62%. The ^{1}H NMR spectrum of the crude product contained some minor peaks (approx 7%) at δ_H 1.46 (s) and δ_H 2.66 (s). While the side product was not identified, these signals may indicate another regioisomer. In contrast, O'Keeffe reported no traces of any other regioisomers during the synthesis of 3-methyl-3-(3,4,5-trimethylphenyl)butanoic acid **36**.[41]

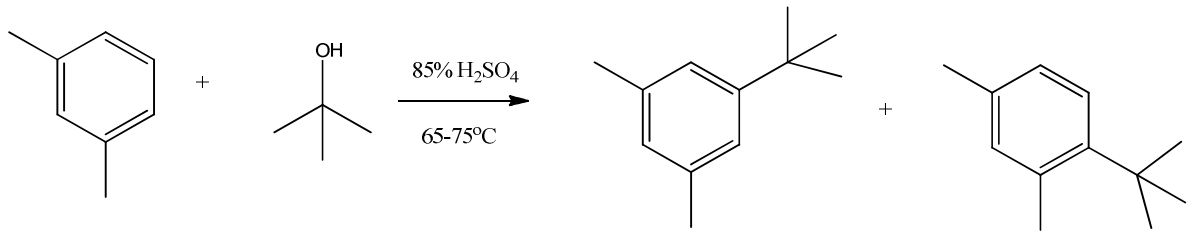
During this work the methodology was extended to the synthesis of 3-methyl-3-(3,5-dimethyl)butanoic acid **35**. The 3,5-dimethyl substituted acid **35** was isolated in analytically pure form and in excellent yield, for the first time in our group. Notably, there were no traces of any other regioisomers. Furthermore, the subsequent transformation of the acid **35** to the crystalline PTAD adduct (see Section 2.6.6.3) provided unequivocal structural evidence of the 3,5-dimethyl substituted acid. In 1943, Irvine and Spillane had previously prepared the acid **35** in a 97% yield (Scheme 2.12).[48] They stated that the alkylation of *meta*-xylene in the presence of aluminium chloride almost invariably leads to the 1,3,5-trialkylderivative.



35

Scheme 2.12

The reproducible regiochemical outcome of this reaction cannot be easily rationalised, but fortuitously leads to the desired product. Nightingale and co-workers also investigated the orientation effects in the alkylation of *meta*-xylene by various procedures and reagents.[49] Interestingly, when *meta*-xylene was alkylated by *t*-butyl alcohol and 85% sulfuric acid, Nightingale found that the trialkylbenzene formed was a mixture of 1,3-dimethyl-5-*t*-butylbenzene **51** and 1,3-dimethyl-4-*t*-butylbenzene **52** in the ratio of 2:1 as illustrated in Scheme 2.13.



2:1

51 **52**

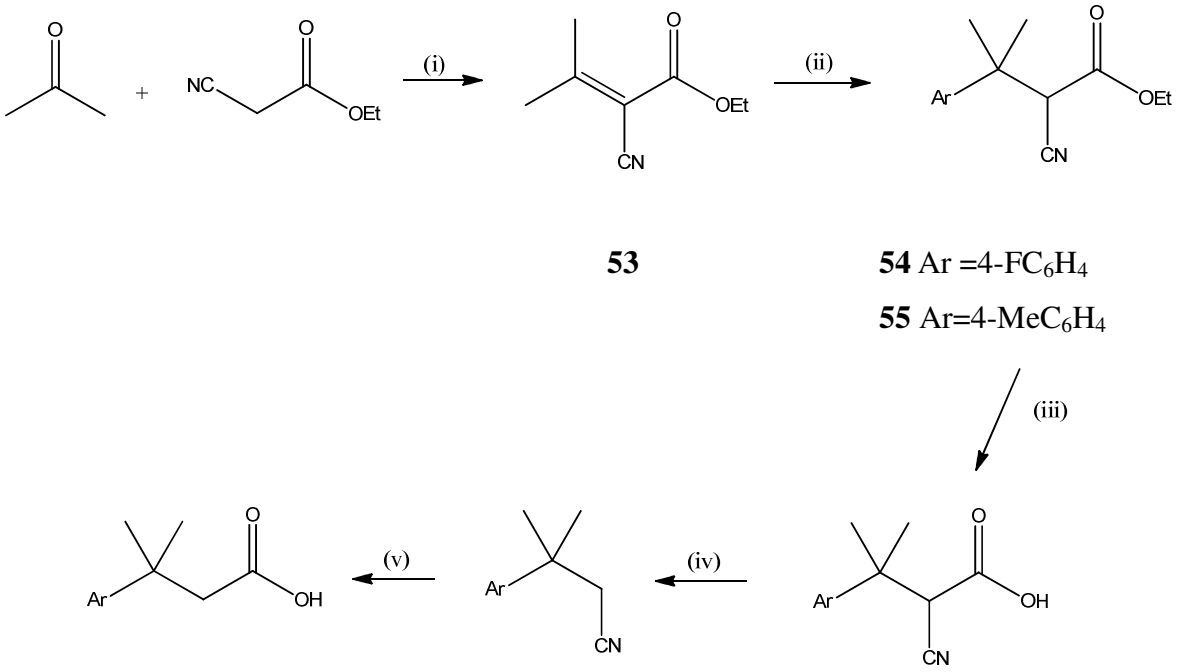
Scheme 2.13

The Friedel Crafts alkylation reaction has long been known to introduce alkyl groups into aromatics. However, it can also be used to remove alkyl groups from alkylbenzenes, thus Friedel Crafts alkylations are reversible.[50-53] The isomerisation reaction in which a group migrates from one position in a ring to another is significant as in these reactions, the meta isomer is generally the most favored product. As in the Friedel Crafts alkylation of *meta*-xylene discussed above, the 1,3,5-substituted product is generally the most favored because it is the most thermodynamically stable.[54]

2.5.1.2 Multi-step synthesis of β-dimethyl substituted acids

Upon encountering difficulties when synthesising acid **34** *via* the Friedel Crafts alkylation, O'Keeffe applied a modification of Prout's synthesis to form the substituted carboxylic acids **32** and **34**.[41,55,56] While requiring multiple steps, it produces ready access to multi gram quantities of carboxylic acid.

Table 2.2 *Multi-step synthesis of β-dimethyl substituted acids*



53

54 Ar =4-FC_6H_4

55 Ar=4-MeC_6H_4

56 Ar=4-FC_6H_4

57 Ar=4-MeC_6H_4

58 Ar=4-FC_6H_4

59 Ar=4-MeC_6H_4

34 Ar=4-FC_6H_4

32 Ar=4-MeC_6H_4

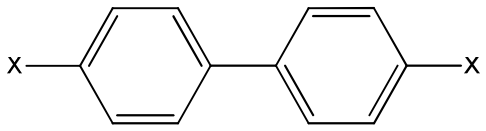
(i) β-Alanine, acetic acid, benzene, 60 h, Δ, (ii) ArMgX, Et_2O, 30 min, Δ followed by acid work-up, where X =Br when Ar = 4-Me-C_6H_4 and X = I when Ar = 4-F-C_6H_4 (iii) Ar = 4-Me-C_6H_4: NaOH/KOH (2/4 eq.), ethanol (95%), MW, ~20 min, 70 °C followed by acid work-up; Ar = 4-F-C_6H_4: NaOH (4 eq.), ethanol (95%), overnight, r.t., (iv) Neat, MW, 100 W, 30 min, 200 °C, (v) KOH (3 eq.), ethylene glycol, overnight, Δ, followed by acid work-up.

Entry	X	Cyanoester	Yield (%)	Cyanoacid	Yield (%)	Nitrile	Yield (%)	Carboxylic Acid	Yield (%)
1	Me	**55**	64[a]	**57**	81[b]	**59**	76[d]	**32**	52[e]
2	F	**54**	65	**56**	65[c]	**58**	69[d]	**34**	65[e]

a. Wurtz Coupling product was observed in the ^{1}H NMR of the crude product.
b. Synthesised in an open vessel microwave reactor.
c. Heated under reflux overnight.
d. Purified by vacuum distillation.
e. Crude product was carried through to next step without purification.

The formation of ethyl 2-cyano-3-methylbut-2-enoate **53** by a Knoevenagel condensation reaction is the first step. Ethyl cyanoacetate and acetone were heated under reflux for 60 h, in the presence of a catalytic amount of β-alanine and acetic acid.[55,56] The product ester **53** formed is needed for the synthesis of both acids **32** and **34**. The crude reaction mixture contained 8% ethyl cyanoacetate. Purification by vacuum distillation produced the ester **53** as a low melting, white solid in a 82% yield.

The transformation of the unsaturated ester **53** to the carboxylic acids **32** and **34** was undertaken as summarized in Table 2.2. The addition of the Grignard reagent prepared from 4-fluoroiodobenzene or 4-bromotoluene led effectively to the cyanoesters **54** and **55** in good yield. Interestingly the product of Wurtz coupling **60** was seen only in the reaction to form **55** with no evidence of the analogous by product **61** in the reaction of the 4-fluoro substituted Grignard (Figure 2.3).



X= Me **60**, F **61**

Figure 2.3

Subsequent hydrolysis to the cyanoacid **56** was carried out using sodium hydroxide; microwave heating was employed for the hydrolysis of the methyl substituted ester **55**, following procedures described by O'Keeffe.[41] The ensuing decarboxylations of **56** and **57** were brought about under neat conditions in an open vessel microwave reactor. Both

the crude nitriles **58** and **59** were isolated as dark brown viscous oils and both were purified by vacuum distillation, to give nitiles **58** and **59** as yellow oils.

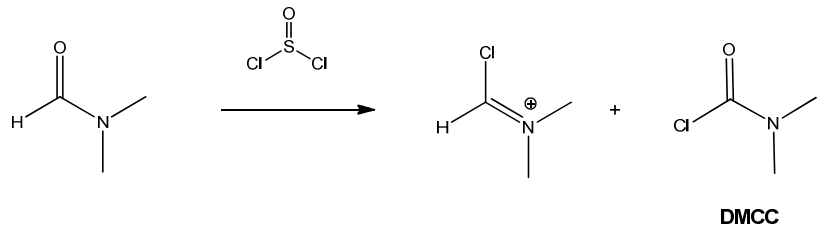
The synthesis of carboxylic acids **32** and **34** was accomplished by hydrolysis using KOH in ethylene glycol. After extractive workup, the acids **32** and **34** were obtained in 65% and 52% yields respectively.

In conclusion, the synthesis of carboxylic acids **32** and **34** was carried out successfully, leading to multi-gram quantities with relative ease. In the synthesis of carboxylic acids **32** and **34**, O'Keeffe purified the product at the end of each step of the process.[41] Due to the fact that most crude product mixtures were clean, O'Keeffe recommended that most reactions could be carried out without purification.[41] While O'Keeffe had purified each step, in this work only nitriles **58** and **59** and cyanoesters **54** and **55** were purified. Cyanoacids **56** and **57** and carboxylic acids **32** and **34** were carried through without purification.

2.5.2 Synthesis of acid chlorides

With the carboxylic acids **31**-**36** synthesised, the corresponding acid chlorides were then prepared for the formation of α-diazoketones. During this work two different methods were exploited for the synthesis of acid chlorides as summarised in Table 2.3 and Table 2.4. Use of thionyl chloride with catalytic DMF was generally employed when significant quantities of carboxylic acid precursors were available. In contrast when only limited amounts of the carboxylic acid precursors were available following the multi-step sequence, the use of oxalyl chloride was more effective for this transformation as it provided the acid chlorides in sufficiently pure form for further reaction without distillation. Acid chlorides were conventionally prepared in the laboratory by heating each of the carboxylic acids under reflux for 3h with 8 equivalents of thionyl chloride. However, in recent years O'Keeffe and Stack adopted the common method of adding a catalytic amount of *N*,*N*-dimethylformamide (DMF) to the preparations of acid chlorides.[27,41]They noted that the reaction time could be reduced to 1 h and the equivalents of thionyl chloride reduced to 5 equivalents. This method was applied in this work, however care was taken as a by-product which forms upon reaction of DMF with thionyl chloride, *N*,*N*-dimethylcarbamoyl chloride (DMCC) **62** is a potential carcinogen

in humans (Scheme 2.14).[57-59] After 3 h, the excess thionyl chloride was removed *in vacuo* and the crude acid chloride was subsequently purified by vacuum distillation.

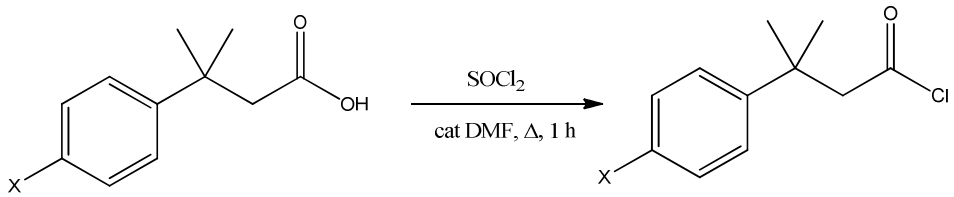


62

Scheme 2.14

IR spectroscopy was used to confirm complete transformation to the acid chloride, by the absence of the carboxylic acid stretch at 2978-2957 cm^{-1} and a shift of the carbonyl stretch from 1718-1700 cm^{-1} to 1808-1813 cm^{-1}.

Table 2.3 *Preparation of acid chlorides from crude carboxylic acids*



Entry	Acid	X	Acid Chloride	Yield (%)[a]
1	**31**	H	**63**	75
2	**33**	Cl	**64**	66
3	**34**	F	**65**	52

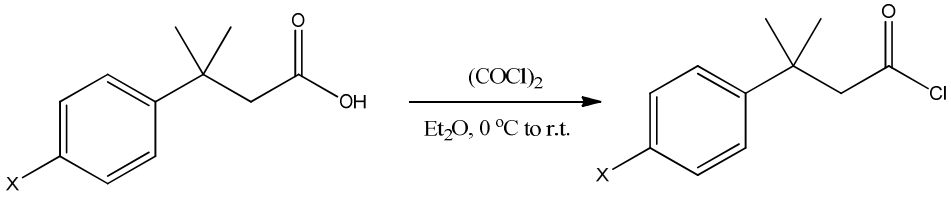
a. Yield of acid chloride recovered after purification by distillation *in vacuo*.

The acids prepared from the Friedel Crafts alkylation of benzene derivatives **31** and **33** gave higher yields of acid chlorides, compared to that from the *para*-fluoro substituted acid **34** which gave a lower yield of 52 % for the acid choride **65**. The acid chlorides **63**-**65** gave spectroscopic characteristics which agreed with the previously reported data.

Each of the distilled acid chlorides **63**-**65** were stable over long periods of time (up to 12 months) when kept under nitrogen at −20°C.

Acid chlorides **66**-**68** were prepared using oxalyl chloride in diethyl ether. The utilisation of oxalyl chloride as a chlorinating agent is favorable as the resulting acid chloride does not require purification. The excess oxalyl chloride is removed *in vacuo* and the product can be carried through directly to the next step. Storage of the acid chlorides prepared using $(COCl)_2$ leads to deterioration of product quality.

Table 2.4 *Preparation of acid chlorides from carboxylic acids using oxalyl chloride*



Entry	Acid	X	Acid Chloride	Crude Yield (%)[a]
1	**32**	Me	**66**	90
2	**35**	3,5-$(Me)_2$	**67**	96[b,c]
3	**36**	3,4,5-$(Me)_3$	**68**	96

a. Yield of crude acid chloride. It was used immediately without purification.

b. Novel acid chloride.

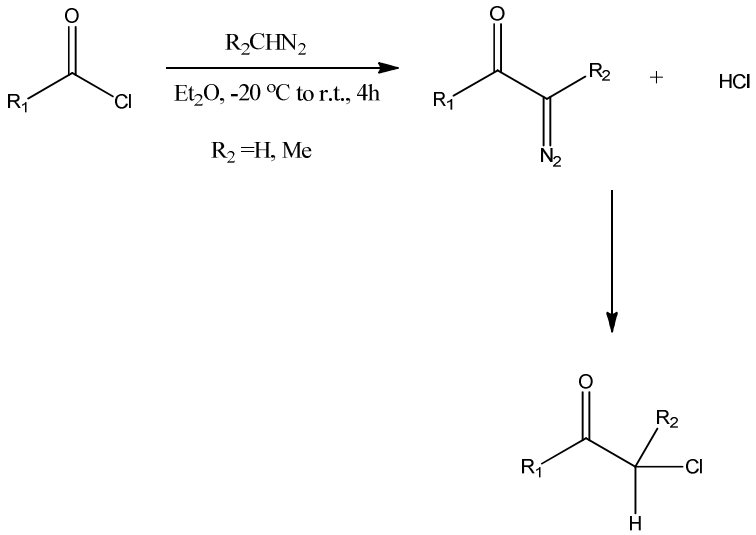
c. ^{1}H NMR of crude material contained 18% unreacted starting material.

The synthesis of **66** and **68** was repeated in this work following the same method providing the crude acid chloride in a 96% yield. Due to the lability of this compound it was used directly without purification.

Based on this, the novel acid chloride **67** was also prepared using oxalyl chloride. In the ^{1}H NMR spectrum of the crude material, signals (18%) were observed which were consistent with the presence of the unreacted acid **35**. Due to the lability of this acid chloride, the mixture was carried through without purification to the acylation of diazoalkanes where it was purified by flash chromatography.

2.5.3 Preparation of α-diazoketones

The acylation of diazoalkanes is one of the most widely used methods developed for the synthesis of α-diazoketones. Arndt and Eistert first described the acylation of diazoalkanes by acid chlorides in 1927.[43] This was to be followed by later reports by Bradley[60] and Robinson,[60,61] who illustrated that in order to generate α-diazoketones from acid chlorides an excess of diazoalkane is required in order to react with hydrogen chloride formed in the reaction. If an excess of diazoalkane is not present, then the reaction of hydrogen chloride with the α-diazoketone can lead to the formation the α-chloroketone side product (Scheme 2.15).



Scheme 2.15

In this work, a range of internal and terminal α–diazoketones (**37**-**48**) were synthesised by treating substitiuted acid chlorides (**63**-**68**) with an excess of freshly prepared diazoethane or diazomethane as summarised in Table 2.5.

N-Ethyl-*N*-nitrosourea, which was prepared by a modification of Ardnt's procedure,[44] was used to prepare diazoethane. Diazoethane was prepared from *N*-ethyl-*N*-nitrosourea without distillation.[44]

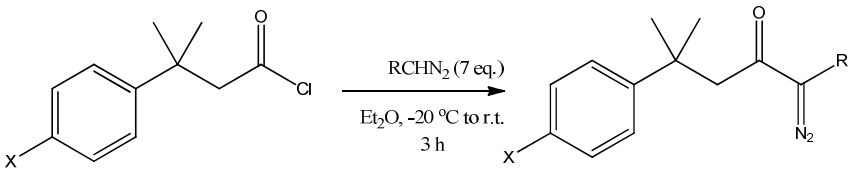
Diazomethane used to synthesise terminal α-diazoketones was prepared from Diazald®, (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide).[62] Buckley and O'Leary used

Diazald® obtained commercially, but as this is no longer available, it was prepared as described by de Boer. [28,37,63] The preparation of Diazald® was repeated on a large scale and stored in the freezer at −20 °C for up to 6 months. De Boer stated that Diazald® could be kept at room temperature for years without any significant change,[63] but there was one reported instance of spontaneous detonation after storage for several months. He recommended that for storage over long periods, the product should be recrystallised and placed in a dark bottle. Diazald was not recrystallised in this work.

To generate diazomethane, an ethereal solution of Diazald® was added dropwise over a 30 min period to a solution of potassium hydroxide, ethanol and water. An ethereal solution of diazomethane was then distilled and kept at −20 °C. [64]

A solution of the acid chloride in diethyl ether was added to the freshly prepared solution of diazoethane or diazomethane (~7 eq.) in diethyl ether while stirring at -20 °C. After the addition, the solution was allowed warm to room temperature, at which temperature it was then stirred for 3 hours. The reaction mixture was concentrated to dryness on a rotary evaporator with an acetic acid trap, and the crude α-diazoketones were isolated as dark orange oils. For both the crude internal and terminal α-diazoketones, flash chromatography of the crude α-diazoketones was carried out immediately, as storage of the crude products at room temperature or at -20°C led to decomposition. After purification, the internal α-diazoketones (**37**-**42**) were isolated as orange oils, while the terminal α-diazoketones (**43**-**48**) were isolated as yellow oils.

Table 2.5 *Preparation of internal and terminal α-diazoketones*



R = H or CH_3

Acid Chloride	X	Internal Diazoketone	Yield (%)[a]	ν C=N2 (cm^{-1})	ν CO (cm^{-1})	Terminal Diazoketone	Yield (%)[a]	ν C=N2 (cm^{-1})	ν CO (cm^{-1})
63[b]	H	**37**[40]	74	2066	1625	**43**[65]	65	2101	1637
64[b]	Cl	**39**[37]	74	2066	1633	**45**	77	2101	1636
66[c]	Me	**38**[41]	56[d]	2071	1628	**44**	50	2101	1636
65[b]	F	**40**[37]	41[e]	2074	1628	**46**	51	2103	1634
67[c]	3,5-$(Me)_2$	**41**	74	2064	1633	**47**	56	2101	1634
68[c]	3,4,5-$(Me)_3$	**42**[41]	69	2070	1634	**48**	51	2100	1636

a. Yield following purification by flash chromatography.

b. Acid chloride used was prepared using thionyl chloride followed by distillation.

c. Acid chloride used was prepared using oxalyl chloride without distillation.

d. The low yield may be associated with the use of the carboxylic acid for the multi-step synthesis carried through without purification.

e. Low yield due to difficulty in chromatographic separation.

Diazoketones (**37**-**40**, **42** and **43**) were identical in terms of yield, quality and spectroscopic characteristics to earlier reports within the group, while diazoketones (**41** and **44**-**48**) were novel and fully characterised during this work. In most cases yields were acceptable, ranging from 41-74%. The low yield observed for α-diazoketone **38** may be associated with the acid chloride **66** being prepared from the crude carboxylic acid **32** and oxalyl chloride. The crude acid chloride was then brought forward to the α-diazoketone stage without purification, due to limited material. All α-diazoketones were purified directly as they deteriorated on storage in their crude form. Yields for the terminal α-diazoketones ranged generally lower than that for the internal α-diazoketones. Purified α-diazoketones could be stored at −20 °C in the freezer under nitrogen for periods of up to a year without any decomposition. Previous workers observed that halogenated internal α-diazoketones were more labile,[27,37,41,42] particularly fluorinated diazoketones, which were seen to decompose over time. However, in this current study the *para*-chloro and fluoro substituted diazoketones **39** and **40** were stored at −20 °C in the freezer for up to a year, with no visible decomposition observed.

Each of the diazoketones showed characteristic diazo and carbonyl stretching bands which were easily identifiable in the IR spectra at ν_{max}/cm^{-1} ~ 2060 cm^{-1} and ~1630 cm^{-1} for internal α-diazoketones and at ν_{max}/cm^{-1} ~2100 and ~1630 for terminal α-diazoketones. The characteristic methyl signal in the ^{1}H NMR spectrum of the internal α-diazoketones was observed at δ_H 1.80-1.83. In general, broadening of the signals was evident for $C(4)H_2$ and $C(1)H_3$ in the ^{1}H NMR spectrum of all the internal α-diazoketones and for $C(1)H_3$ and C(2) in the ^{13}C NMR spectrum of α-diazoketone **41**. This broadening indicates restricted rotation due to extended conjugation. O'Keeffe also observed this broadening in the ^{1}H NMR spectrum of internal α-diazoketones.[41] A characteristic broad signal observed at δ_H 4.66-4.74 in the ^{1}H NMR spectrum of terminal α-diazoketones was diagnostic for the proton geminal to the diazo group. As seen with the internal α-diazoketones, the broadening of signals for $C(3)H_2$ and C(1)H was evident in the ^{1}H NMR spectrum and for $C(3)H_2$ and C(1)H signals in the ^{13}C NMR spectrum of terminal diazoketones (**43**-**48**) as illustrated in Figure 2.4

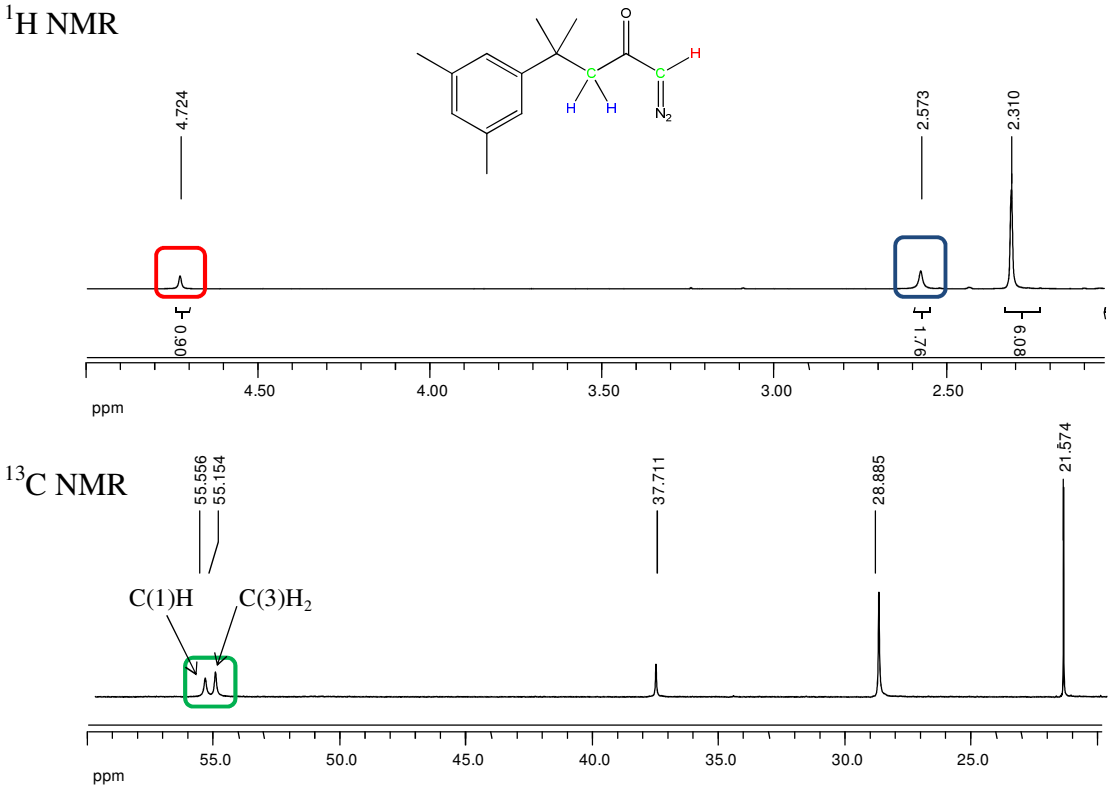


Figure 2.4 *^{1}H (300MHz, $CDCl_3$) and ^{13}C (75MHz, $CDCl_3$) NMR spectra of the novel diazoketone* **47** *illustrating broadening of the C(1)H and C(3)H_2 signals*

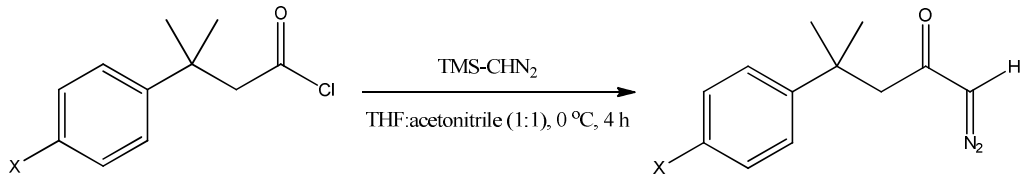
In general, for both internal and terminal α-diazoketones, the labile nature of the compounds results in the molecular ion being absent or of low intensity in the mass spectrum, when the sample was prepared in acetonitrile. However, when the sample for mass spectrometry analysis was prepared in diethyl ether, the molecular ion was observed.

In 1980, Shioiri reported for the first time the use of the non-explosive reagent trimethylsilyldiazomethane, which was used for Arndt Eistert synthesis of diazo compounds.[66] As diazomethane is highly toxic and explosive, we decided to investigate the use of trimethylsilyldiazomethane as a safer alternative. Since Shioiri's first use of trimethylsilyldiazomethane it has become a widely used reagent in organic synthesis and its uses are discussed in a review by Shioiri in 1990.[67-69]

For comparison, on one occasion the terminal α-diazoketones **43** and **45** were also synthesised using trimethylsilyldiazomethane, by Shioiri's procedure. A solution of acid

chloride **63** or **64** in THF/acetonitrile (1:1) was added dropwise to 2 equivalents of trimethylsilyldiazomethane in THF:acetonitrile (1:1) at 0°C under nitrogen. Each reaction mixture was stirred for 4 hours before being concentrated under reduced pressure to give a yellow oil which was purified directly by flash chromatography.

Table 2.6 *Preparation of terminal α-diazoketones using trimethylsilyldiazomethane*



Entry	Acid Chloride	X	Diazoketone	Yield (%)[a]
1	**63**[b]	H	**43**	39
2	**64**[b]	Cl	**45**	36

a. Yield following purification by flash chromatography, diazoketones **43** and **45** contained an unknown side product 11% and 6% respectively.

b. Acid chloride used was prepared using thionyl chloride followed by distillation.

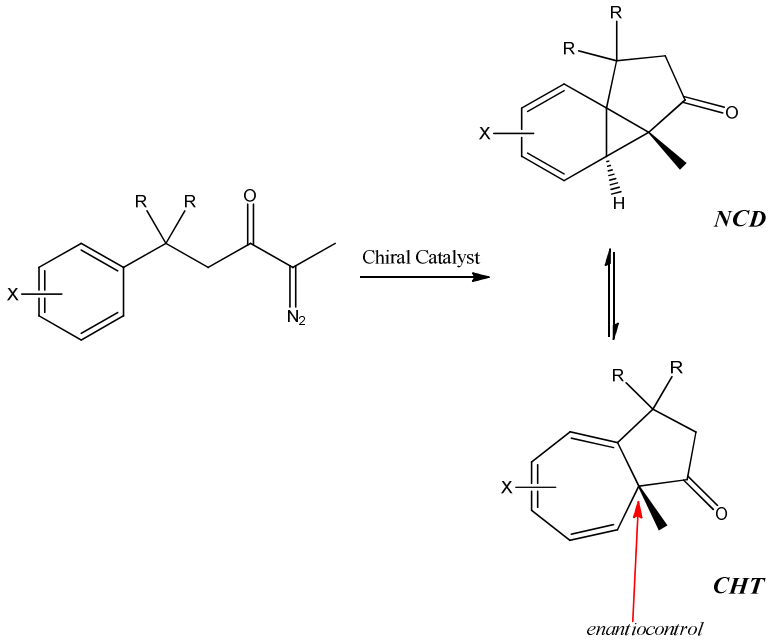
The ^{1}H NMR spectra of the crude reaction mixture of both terminal diazoketones **43** and **45** revealed the presence of an unknown side product 11% and 6% respectively. This side product could not be easily removed by flash chromatography and the same amount of side product was observed after chromatography. In comparison to the samples of the terminal α-diazoketones **43** and **45** prepared from diazomethane, the yields were very low (36% and 39% respectively). Spectral characteristics were identical to those observed for diazoketones **43** and **45** that were prepared from diazomethane.

In conclusion, the preferred reagent for the synthesis of terminal α-diazoketones is diazomethane (freshly prepared from Diazald®). However, it should be noted that the use of trimethylsilyldiazomethane was not optimised.

2.6 Asymmetric intramolecular Buchner reaction

2.6.1 Introduction

One of the principal aims of this project was to explore enantioselectivity in the intramolecular aromatic addition (Buchner reaction) of α-diazoketones. This project focuses on aromatic functionalisation through intramolecular carbenoid addition, thereby transforming the planar achiral stable aromatic ring into a chiral reactive cycloheptatriene structure with enantiocontrol as illustrated below in Scheme 2.16.

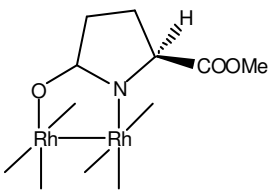


Scheme 2.16

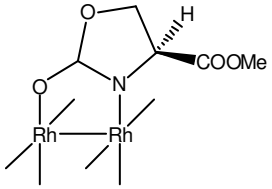
The aromatic addition reaction of diazoketones is a synthetically useful process, and can lead to the formation of both bicyclic and polycyclic compounds. A detailed discussion on the Buchner reaction and the norcaradiene/cycloheptariene equilibrium can be seen in recent reviews by Wu,[70] Maguire[71] and Reisman.[72] A detailed body of research has been carried out in our group to investigate the chemo-, regio- and diastereoselectivity of the reaction as discussed in Section 2.3 above.[24,37,37-41,73] However, the progress in advancing the area of enantioselectivity has been limited; generally Buchner reactions under substrate control have been studied in more detail. In the limited reports of asymmetric aromatic addition reactions reported by our group and by others, the majority of enantioselectivities have been poor and there remains an absence of a general chiral

catalyst. Excellent diastereocontrol has been achieved but the development of a general highly enantioselective catalyst remains elusive.[24,38,39,74] In contrast development of enantioselective catalysts for cyclopropanation and C-H insertion have been more extensively investigated. [75-79]

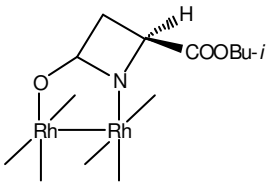
A selection of chiral catalysts which have been employed in the aromatic addition of diazcarbonyl compounds is illustrated in Figure 2.5.



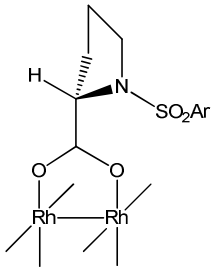
Rh_2(5*S*-MEPY)$_4$ **69**



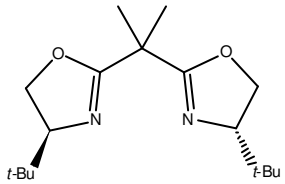
Rh_2(4*S*-MEOX)$_4$ **70**



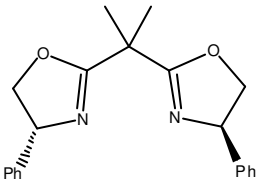
Rh_2(4*S*-IBAZ)$_4$ **71**



Ar = 1-napthyl **72**, Ph **73**,



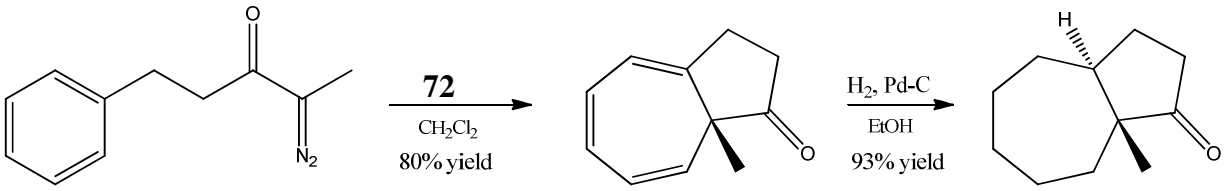
$CuPF_6$-**74**[(*S*,*S*)-*t*-Bu-BOX]



$CuPF_6$-**75**[(*R*,*R*)-Ph-BOX]

Figure 2.5 *A selection of enantioselective catalysts used in the aromatic addition of α-diazocarbonyls*

The first example of enantioselective catalysis in aromatic addition was recorded by McKervey and co-workers in 1990.[80] They reported an enantioselectivity of 33% ee, through the use of a rhodium prolinate catalyst in the cyclisation of 2-diazo-5-phenylpentan-3-one **76** to the azulenone **77** with subsequent hydrogenation to give the bicyclic ketone, *trans*-1-methylbicyclo[5.3.0]decan-2-one **78** (Scheme 2.17).

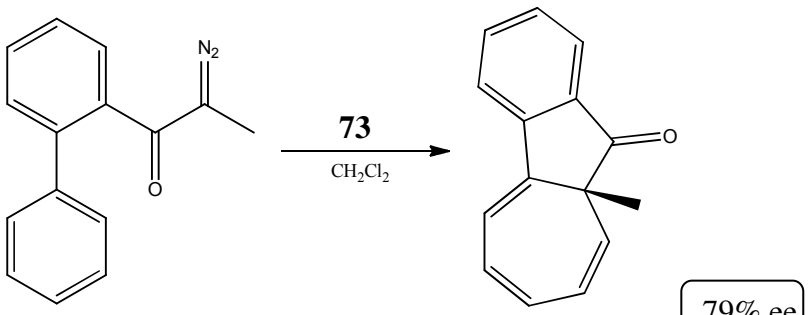


76 **77** **78**

33% ee

Scheme 2.17

The same group also detected a good enantioselectivity of 79% ee in the cyclisation of the biphenyl derived diazoketone **79**. They achieved their highest enantioselectivity using the rhodium prolinate catalyst **73** (Scheme 2.18).[81,82]



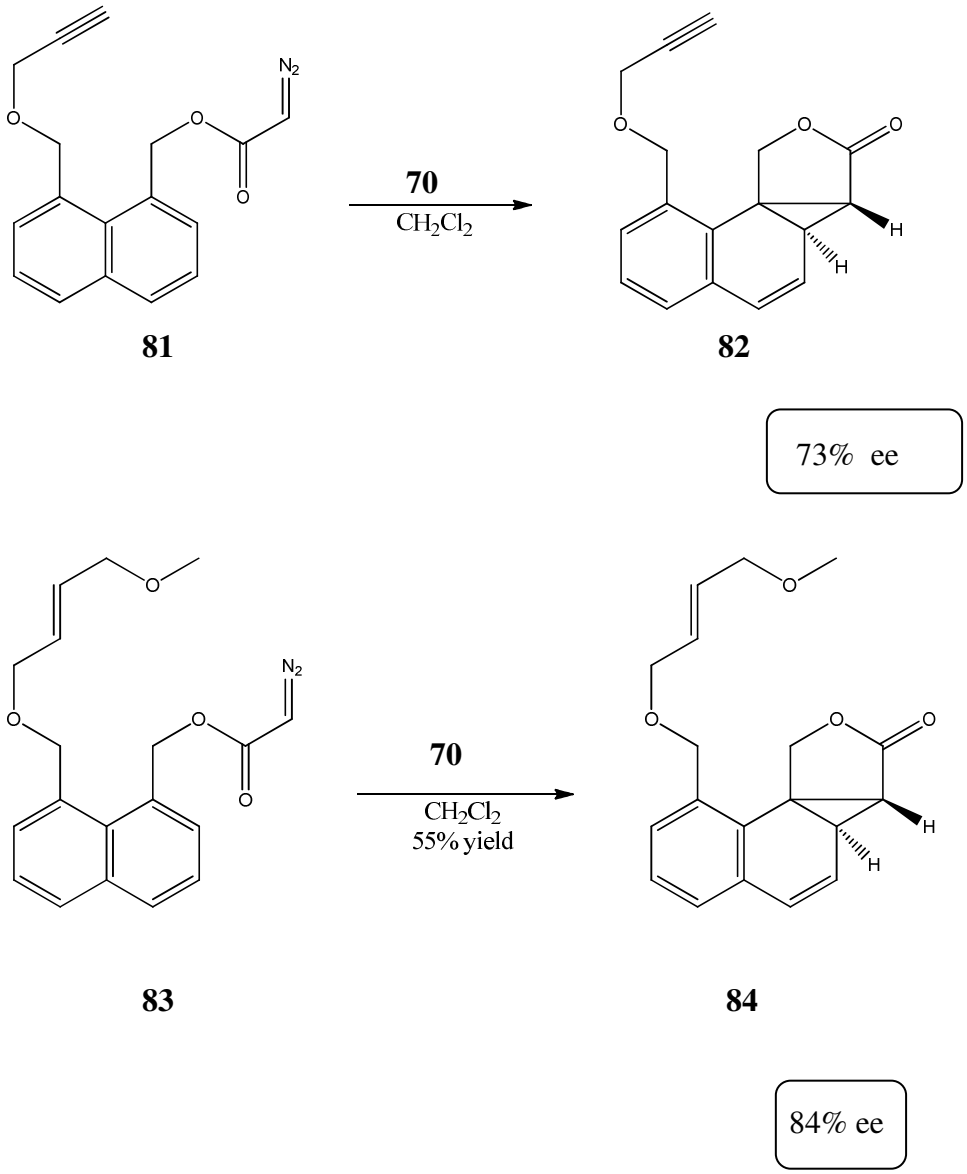
79% ee

79 **80**

Scheme 2.18

In 1999, Doyle used chiral dirhodium carboxamidate catalysts in intramolecular carbene transformations of diazoacetates.[82] Doyle reported two reacting systems that offered the opportunity to explore both chemoselectivity and enantioselectivity, and the highest levels of enantiocontrol in aromatic addition at that time were observed using

diazoester **83**. The use of diazoesters **81** and **83** with chiral rhodium carboxamidates enabled exploration of the asymmetric aromatic addition process in addition to chemoselectivity relative to cyclopropanation and ylide formation. Significantly using $Rh_2(4S\text{-MEOX})_4$, up to 84% ee was achieved in the aromatic addition process, the highest enantioselectivity achieved up to this point.

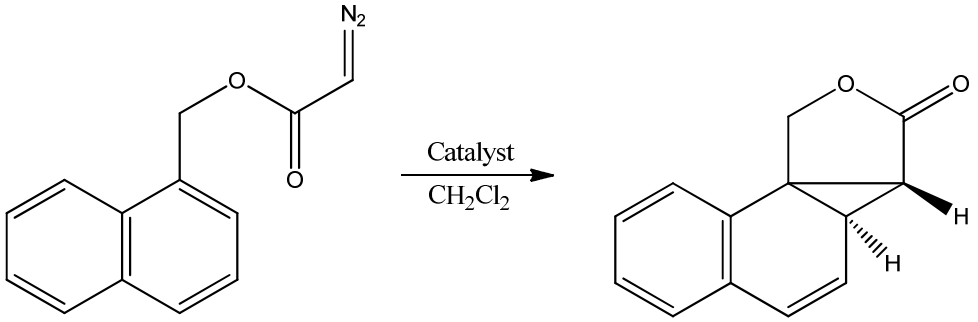


Scheme 2.19

In the same report, Doyle investigated the decomposition of diazoester **85** with a range of rhodium catalysts.[82] The product from this decomposition resulted in a enantiomeric excess of 81% ee, when the catalyst $Rh_2(4S\text{-IBAZ})_4$ **71** was used. These

results by Doyle highlight the difficulties in trying to identify one single suitable catalyst to induce asymmetry across a variety of diazocarbonyl substrates.

Table 2.7 *Effect of catalyst on the asymmetric decomposition of* **85**

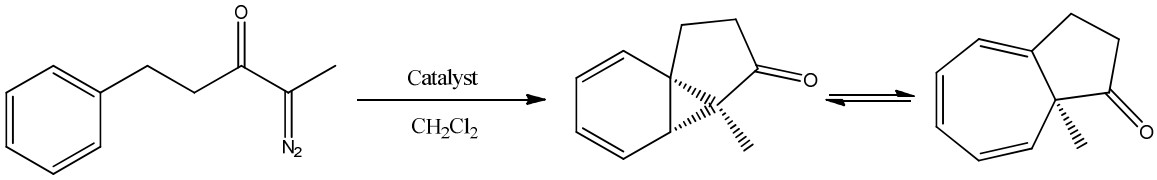


85 **86**

Entry	Catalyst	Yield (%)	ee (%)
1	Rh_2(4*S*-MEOX)$_4$ **70**	76	56
2	Rh_2(5*S*-MEPY)$_4$ **69**	72	42
3	Rh_2(4*S*-IBAZ)$_4$ **71**	87	81
4	$CuPF_6$-**74**[(*S*,*S*)-*t*-Bu-BOX]	83	42

Work within our group on a range of rhodium catalysts yielded no improvement on McKervey's result of 33% ee for the decomposition of diazoketone **76**.[80] However, Harrington re-examined the use of using copper catalysts and achieved an enantioselectivity of 67% ee for the diazoketone **76** using the Cu-(*R*,*R)*-Ph-iso-box **75** catalyst as shown in Table 2.8.[40] This was a significant result as it illustrated that copper catalysts could be effective in the intramolecular Buchner reaction. Harrington also investigated the aromatic addition of diazoketone **37** with a range of copper bisoxazoline catalysts and achieved enantioselectivities up to 80% ee (Table 2.9). These results are comparable with the best results reported by Doyle in the decomposition of α-diazoacetates **79**, **81** and **83** and by McKervey in the decomposition of diazoketone **76**.

Table 2.8 *Aromatic addition of* **76** *with chiral catalysts*[40]

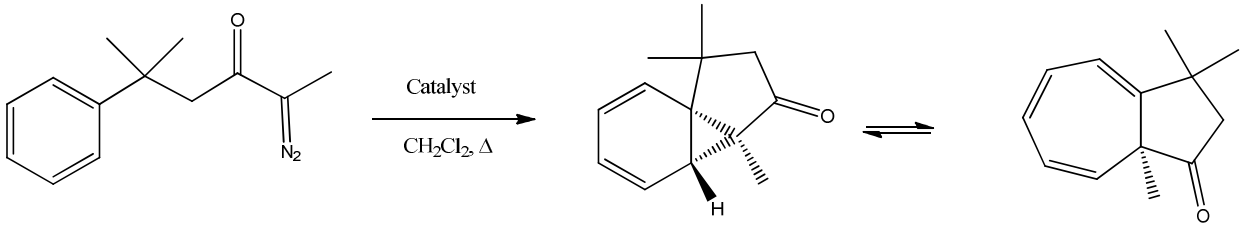


76 **77**

Entry	Catalyst	Efficiency (%)	Yield (%)	ee (%)
1[a]	Rh_2(*N*-naphthylprol)$_4$ **72**	–	70	33[c]
2[b]	$Rh_2(OAc)_4$ **87**	79	80	0[d,e]
3[b]	Cu(*R*,*R*)-Ph-*iso*-box **75**	67	54	67[d,e]

a. Results reported by McKervey.[80]
b. Results reported by Harrington.[40]
c. Determined by chiral shift ^{1}H NMR analysis.
d. Determined by chiral HPLC analysis.
e. Absolute stereochemistry not determined during Harrington's work.

Table 2.9 *Investigation of a selection of copper catalysts in the decomposition of* **37**[40]



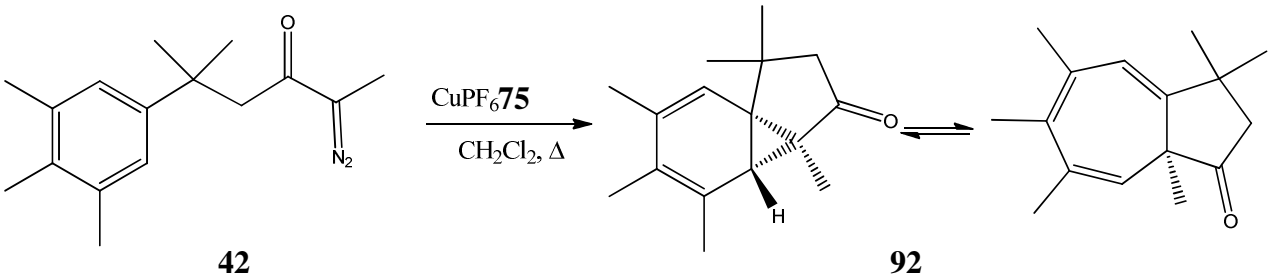
37 **88**

Entry	Catalyst[a]	Efficiency %	Yield %[b]	%ee[c,f]
1	Cu(*R*,*R*)-Ph-*iso*-box **75**	90	72	80
2	Cu(*S*,*S*)-*t*-Bu-*iso*-box **74**[d]	41	19	9
3	Cu(4*R*,5*S*)-*tetra*-Ph-*iso*-box **89**	83	53	15
5	Cu-indeno-*bis*-box **90** [e]	76	38	13

Entry	Catalyst[a]	Efficiency %	Yield %[b]	%ee[c,f]
6	Cu(*R*,*R*)-benzyl-*iso*-box **91**[e]	65	29	0

a. The catalyst was prepared with a 1.15:1:2 mixture of ligand:$CuBr_2$:$AgSbF_6$ stirred for 1 hour at ~0.1M, and 1 mol% was employed in the decomposition reaction, unless otherwise stated.
b. Yield of purified (azulenone) **88**.
c. Determined by HPLC.
d. The catalyst was prepared with a 1:1:2 mixture of ligand:$CuBr_2$:$AgSbF_6$ stirred for 6 hours at ~0.1M.
e. 5 mol% of the catalyst was employed in this reaction.
f. Absolute stereochemistry was not determined during Harrington's work.

Following on from Harrington's preliminary work, O'Keeffe explored in detail the influence of variation of substrate and ligand on the enantioselectivity in the intramolecular Buchner reaction, and through appropriate structural modification, she achieved enhancement of enantioselectivity to ≥ 95% ee with the diazoketone **42** and the copper catalyst derived from ligand **75**.[12,41] During O'Keeffe's work the absolute stereochemistry of **92** was not established; however during this study the stereochemistry was confirmed (see Section 2.6.6.3).

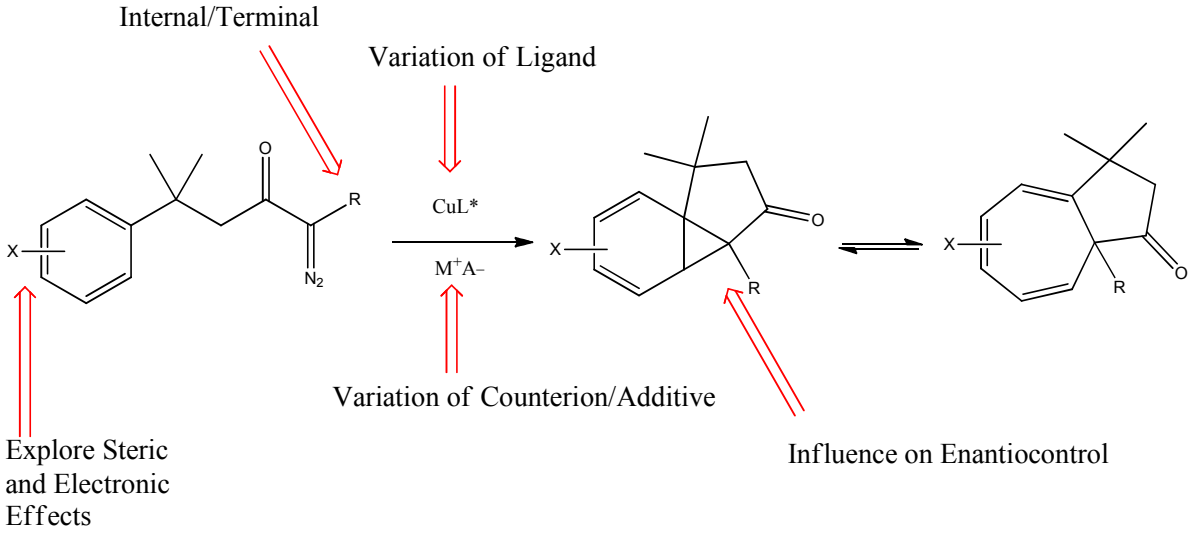


42 **92**

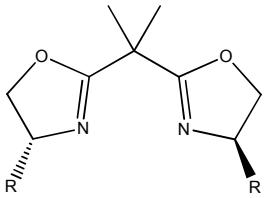
≥95% ee

Scheme 2.20

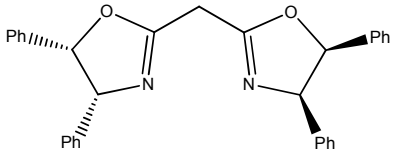
The core of this research project was the investigation of enantioselective catalysis of the aromatic addition in the series of α-diazoketones (**37**-**48**); specifically the role of ligand, counterion and substrate structure was investigated to determine the effect of the substitution at the diazo carbon (H or Me) and on the aromatic ring (Scheme 2.21).



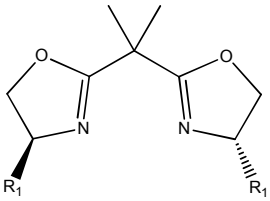
L* =



R = (*R*,*R*)-Ph-**75**, (*R*,*R*)-Bn-**91**



(4*R*, 5*S*)-*tetra*-Ph-**89**

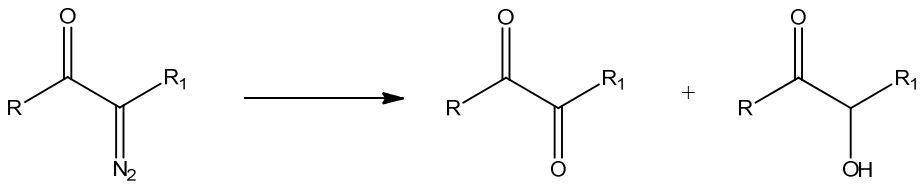


R_1= (*S*,*S*)-*t*-Bu-**74**, (*S*,*S*)-3,5-$(Me)_2$-C_6H_3-**93**

Scheme 2.21

2.6.2 Transition metal catalysed intramolecular aromatic addition of α-diazoketones

A extensive volume of work has been conducted in our group optimising the intramolecular Buchner reaction.[27,28,37,40-42] Due to the highly reactive nature of the carbene intermediate, great caution is taken to protect the reaction mixture from oxygen and water as both oxygen and water react with metal carbenes to give unwanted side-products including α-diketones and α-hydroxyketones.[24,37,38,83,84]



Scheme 2.22

To prevent these side-products forming, a number of precautions have been implmented. Firstly, the assembled apparatus was flame dried immediately before use. The dichloromethane used in the reactions was doubly distilled, first over phosphorus pentoxide, then over calcium hydride and all the reactions were carried out under an atmosphere of nitrogen. To ensure the solvent was effectively deoxygenated, a Schlenk line was employed. All reactions were conducted by dropwise addition of a solution of the α-diazoketone in dichloromethane (~80 mL) to a refluxing solution of catalyst [<1 mol% of $Rh_2(OAc)_4$ or 5 mol% of copper catalyst] in dichloromethane (~80 mL) under nitrogen (Table 2.10). Cyclisations occurred quickly and were generally complete by TLC once all of the diazoketone was added (30-40 min). Once the yellow diazoketone has been added to the catalyst solution, it turns colourless and this can serve as an indication of reaction completion.[41]

Table 2.10 *Preparation of catalyst complexes for intramolecular Buchner reaction, illustrated for ligand* **75**

Entry	Method[a]	Catalyst	Conditions
1	A	$Rh_2(OAc)_4$ (<1.0 mol%)	No pre-stirring of catalyst
2	B	$CuPF_6$-**75**	No pre-stirring of catalyst
3	C	Cu(I)Cl-NaBARF-**75**	Catalyst was pre-stirred for 2 hours at room temperature before substrate was added
4	D	Cu(I)Cl-**75**	Catalyst was pre-stirred for 2 hours at room temperature before substrate was added

5	E	Cu(I)Cl-NaBARF-**75**-(18-crown-6)	Catalyst was pre-stirred for 2 hours at room temperature before substrate was added

a. All methods involved flame drying of apparatus and deoxygenation of solvents as described above.

b. Use of methods A-E were also applied for ligands **74**, **89**, **91** and **93**.

The efficiency of the aromatic addition reactions was determined by comparison of the integration of the signals due to the azulenone with that of the signals due to the aromatic by-products in the ^{1}H NMR spectra of the crude reaction mixtures, which were obtained by concentration of the crude reaction solution (Figure 2.6)

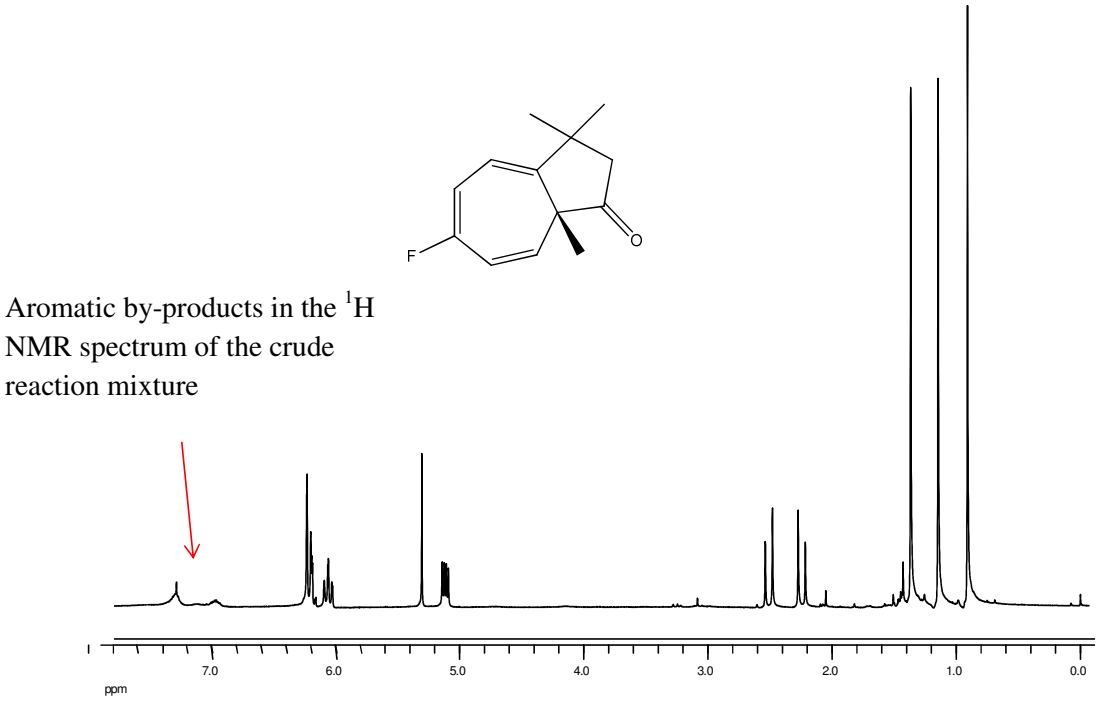


Figure 2.6 *^{1}H NMR (300MHz, $CDCl_3$) spectrum of the crude azulenone* **94** *containing 75% azulenone* **94** *and 25% aromatic by-products*

2.6.2.1 $Rh_2(OAc)_4$ catalysed intramolecular aromatic addition of internal α-diazoketones

In this study, the internal α-diazoketones examined were those bearing a geminal dimethyl substituent at carbon-5 as these were seen by O'Keeffe to promote the most efficient cyclisations.[41] O'Keeffe and Buckley reported an increase in reaction efficiency when more sterically demanding substituents were positioned at carbon-5,[37,41] this is believed to be due to the Thorpe-Ingold effect (Figure 2.7).

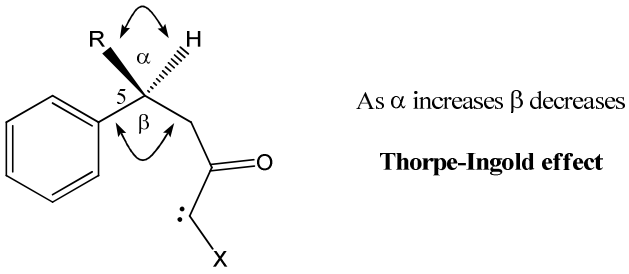


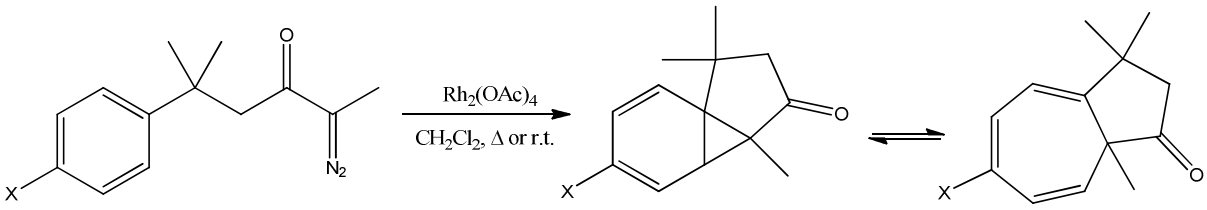
Figure 2.7 *Thorpe-Ingold effect*

The presence of the β-substituent facilitates cyclisation by encouraging the carbene to adopt a more favorable conformation for reaction with the aromatic ring. As the β-substituent increases in size, steric repulsion results in the bond angle α increasing. This in turn causes a decrease in the bond angle β (the angle between the metal carbene and the aromatic nucleus) bringing these groups closer to the conformation required for the reaction. O'Keeffe investigated substituents (H to *t*-Bu to geminal dimethyl) at carbon-5, and found efficiency to increase as the β-substituent increased in size.[41]

As summarised in Table 2.11, the rhodium catalysed cyclisation of diazoketones (**37**-**42**) was undertaken with determination of efficiency of reaction from the ^{1}H NMR spectra of the crude product. This was followed by chromatographic separation to yield the pure azulenones in good yield and purity. The results obtained for azulenones (were entirely consistent with O'Keeffe both in terms of efficiency and spectral characteristics of the products, except for azulenone **92**. O'Keeffe had previously cyclised the diazoketone **42** to give the azulenone **92** but found that it was extremely labile and therefore conducted the cyclisation at room temperature instead of reflux. In this work,

the cyclisation of **42** with rhodium acetate was again conducted at room temperature followed by filtration through basic alumina and subsequently purified directly by flash chromatography on silica gel. ^{1}H NMR spectroscopy was undertaken before and after the chromatography on silica gel and while azulenone **92** was clearly identified as the major component the spectra showed the presence of an unidentified impurity (11%) after chromatography. The purified azulenone **92** was then stored at −20°C. It should be noted O'Keeffe did not report any evidence of this impurity.[41]

Table 2.11 *Preparation of racemic azulenones*



Entry	Diazoketone[a]	X	Azulenone	Efficiency (%)[b]	Yield (%)[c]
1	**37**	H	**88**[37]	85	72
2	**39**	Cl	**95**[41]	85	75
3	**38**	Me[41]	**96**[41]	90	80
4	**40**	F	**94**[37]	81	74
5	**41**	3,5-$(Me)_2$	**97**	85	66
6	**42**	3,4,5-$(Me)_3$	**92**[41,d]	72	42

a. All diazoketones were cyclised according to the procedure for Method A.

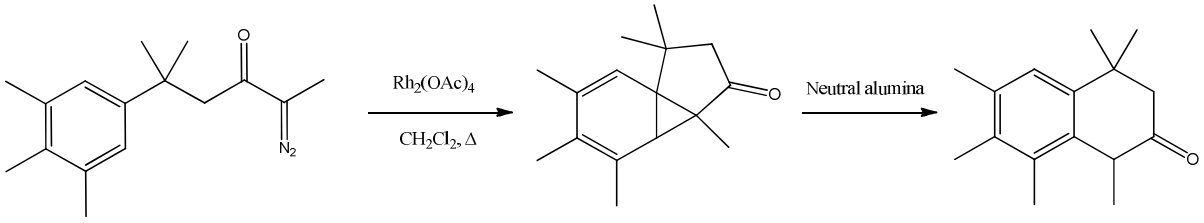
b. The efficiency of the reaction was estimated from the ^{1}H NMR spectrum of the crude product. As the yield recovered of these relatively labile compounds following chromatrography can be somewhat variable. The practice in the research team is to record the efficiency based on integration of the crude products which enables comparison of efficiencies between transformations.

c. Yield after chromatography.

d. The reaction was carried out at room temperature and the resulting solution was filtered through a plug of basic alumina; all others were conducted under reflux.

However, when the crude azulenone **92** was filtered through neutral alumina it was seen to form the dihydronapthalene **98** as a yellow oil, in a yield of 73% (Scheme 2.23).

The aromatisation of azulenone **92** to form **98** took place very rapidly on exposure to the alumina as evidenced by the appearance of a bright yellow colour. McNamara found that the dihydronapthalene **98** formed when she attempted to react azulenone **92** with maleimide.[42]



42 **92** **98**

73% yield from **42**

Scheme 2.23

It was anticipated that the novel dimethyl substituted azulenone **97** would be less labile than the trimethyl substituted azulenone **92**. Accordingly, cyclisation of **41** with rhodium acetate was undertaken under reflux in dichloromethane and it was found that azulenone **97** was formed efficiently and could be purified by flash chromatography on silica gel and then stored at −20°C, although it was seen to decompose if left at room temperature over a short period of time (~1 day). Azulenone **97** was noticeably less labile than azulenone **92** as azulenone **92** decomposed if left at room temperature over a few hours, while **97** survived for up to 24 h at room temperature.

Earlier workers in the group had clearly demonstrated the use of NMR and IR spectroscopy to characterise the azulenones and in particular to explore the position of the equilibrium of the NCD/CHT tautomers.[28,37,39-41] The ^{1}H NMR and IR spectroscopic features indicate that the azulenone **97** existed primarily as the norcaradiene tautomer. The C(8)H signal appears as a singlet and is positioned upfield at 2.52 ppm as illustrated in Figure 2.8, consistent with azulenones existing as the norcaradiene tautomer. In the IR spectra, there was only one carbonyl stretch at 1712 cm^{-1}, which confirms azulenone **97** existing essentially entirely as the norcaradiene tautomer. O'Leary previously identified

the IR stretch at 1710-1716 cm^{-1} being due to the carbonyl of the NCD tautomer and the IR band at 1740-1753 cm^{-1} being due to the carbonyl stretch of the CHT tautomer.[28]

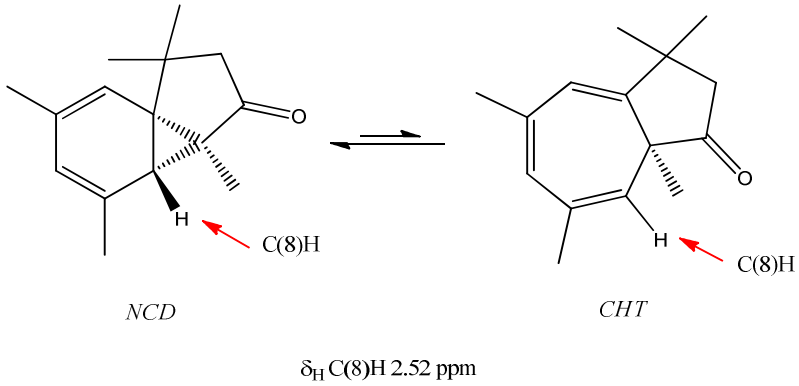
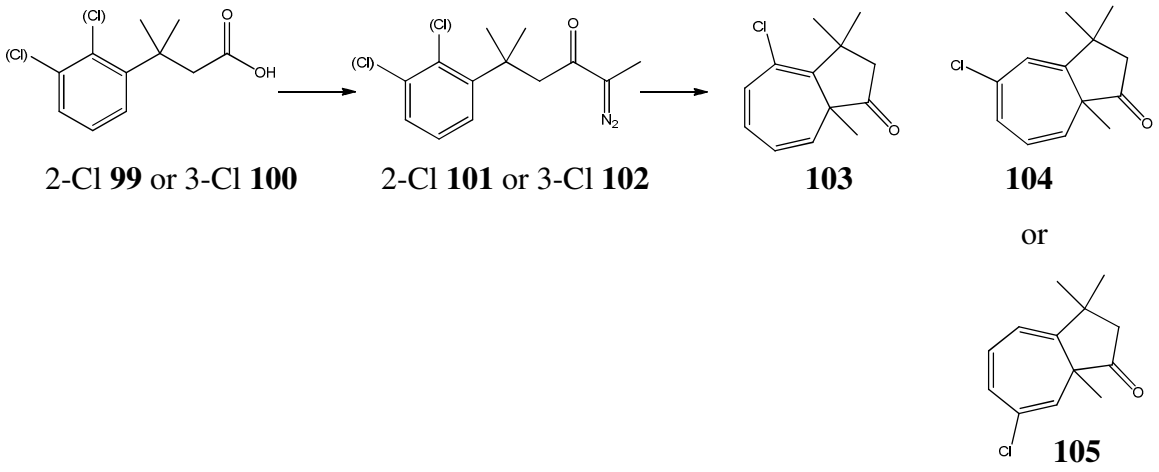


Figure 2.8

For the 6-chloro azulenone **95**, signals for another compound (9%) were observed in the ^{1}H NMR spectrum of the product after purification; these signals were also observed in the ^{1}H NMR spectrum of the crude product. They are due to the presence of the substituted regioisomers **103**, **104** or **105** derived from the regioisomeric diazoketones **101** or **102**, and ultimately the acids **99** or **100** which originated in the alkylation of chlorobenzene as discussed in Section 2.5.1.1. While the presence of regioisomeric acids **99/100** and diazoketones **101/102** were not detected by ^{1}H NMR, observation of the isomeric azulenone **103**, **104** or **105** as described by O'Keeffe provides evidence for the presence of regioisomers. The presence of this compound was also reported by O'Keeffe.[41]



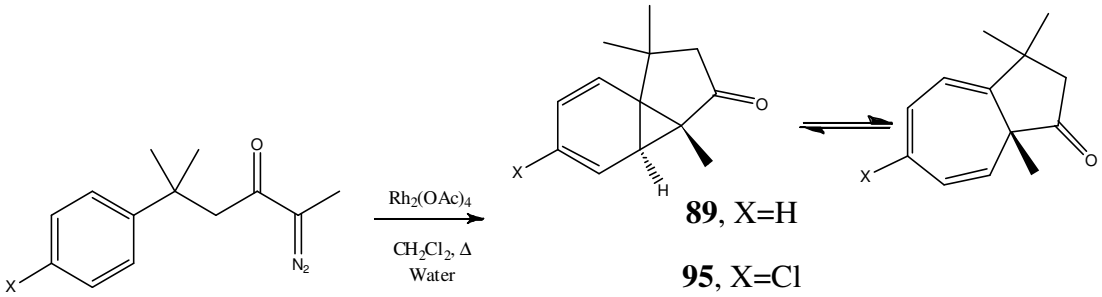
2-Cl **99** or 3-Cl **100** → 2-Cl **101** or 3-Cl **102** → **103** → **104** or **105**

Scheme 2.24 *Regioisomers of* **95**

2.6.2.2 Impact of varying the reaction conditions on the cyclisation of internal α-diazoketones

While the standard conditions were optimised to avoid side reactions, an investigation was carried out into the formation of a diketone side product generated in the cyclisation of internal α-diazoketones by introducing air or water into the reaction. In this study, the ^{1}H NMR spectrum of the crude reaction mixture from the cyclisation of diazoketone **37** in the presence of $Rh_2(OAc)_4$, dichloromethane and water showed the presence of signals from a side product which were consistent with the diketone **106** (17%). The characteristic singlet at δ_H 1.99 was present for the C(1)H_3 methyl group. This crude mixture was not purified.

Table 2.12 *The effect of the decomposition of diazoketones when water is added to the reaction*



37, X=H

39, X=Cl

89, X=H

95, X=Cl

106, X=H

107, X=Cl

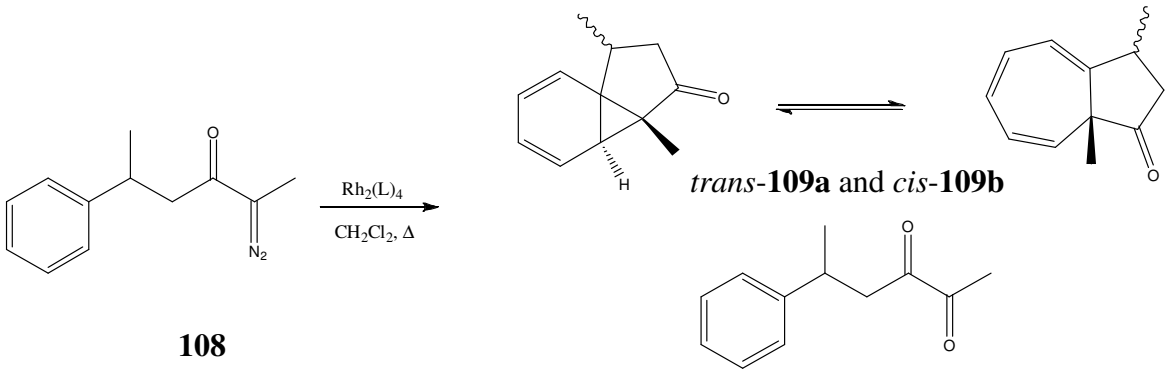
Entry	Diazoketone	Conditions	X	Azulenone	Diketone	Crude Ratio Azul:Diket	Efficiency (%)[a]
1	**37**	Δ, with DCM/Water[b]	H	**89**	**106**	83:17[c]	50
2	**39**	Δ, with DCM/Water[b]	Cl	**95**	**107**	70:30[d]	20
3	**37**	Δ, under N_2	H	**89**	**106**	100:0[a]	85
4	**37**	Δ, under air	H	**89**	**106**	95:5[a]	81

a. Calculated by integration of the aromatic (by-product) signals against the azulenone in the ^{1}H NMR spectrum of the crude product.
b. 1 mL of water was added to the DCM (160 mL) before substrate addition.
c. Not purified.
d. Purified by flash chromatography. Ratio of azulenone:diketone after chromatography was 76:24.

The aromatic addition of the *para*-chloro substituted diazoketone **39** with $Rh_2(OAc)_4$ in dichloromethane and water resulted in a larger ratio of diketone **107** to azulenone **95** (Table 2.12, entry 2). The ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of the azulenone and diketone in a ratio of **95**: **107**, 30:70. The mixture was purified by flash chromatography on silica gel and this delivered two fractions. The first fraction contained the less polar diketone **107** and an unidentifiable impurity (18%). The IR spectrum of the diketone **107** showed a strong CO stretch at 1716 cm^{-1}. The characteristic signal for the C(1)H_3 methyl group was at δ_H 2.08 in the ^{1}H NMR spectrum of the purified material. The second fraction contained a mixture of the azulenone **95** and diketone **107** in the ratio of **95**:**107**, 76:24. Clearly the presence of the electron withdrawing chloro substituent in **39** slows down the rate of the aromatic addition relative to **37** and thereby results in an increased amount of the diketone byproduct.

The decomposition of diazoketone **37** using $Rh_2(OAc)_4$ was carried out under air using the standard set-up for the reaction (Table 2.12, entry 4). The main product was the azulenone **89**, along with a small amount of an unidentified byproduct (5%), with signals consistent with diketone **106**. However, the diketone **106** was not recovered following chromatographic purification.

These results illustrate that the aromatic addition process of diazoketones **37** and **39** is significantly impacted by the presence of water leading to significant amounts of diketone **106** and **107** in azulenone products, while the impact of conducting the reaction under air is noticeably less. Buckley and McNamara have previously described the isolation and characterisation of diketones, in particular when $Rh_2(cap)_4$ is used as catalyst (Scheme 2.25).[37,42] For example, McNamara isolated the diketone **110** as a by-product in the aromatic addition process, most notably when the reaction was conducted with $Rh_2(cap)_4$.

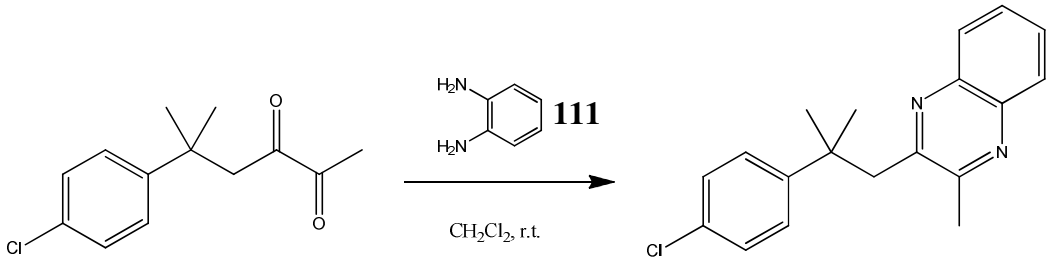


108 *trans*-**109a** and *cis*-**109b**

110

Scheme 2.25

As obtaining an analytically pure sample of diketone **107** was challenging, in line with earlier experience within the group, it was trapped as the crystalline diazanaphthalene **112** through condensation with 1,2-diaminobenzene **111** (Scheme 2.26).[37,42] Diketone **107** and diazanapthalene **112** are novel compounds and were fully characterised during the course of this work.



107 **112**

`

44% Yield

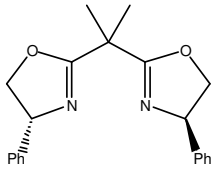
Scheme 2.26

2.6.3 Catalysts used in investigations of enantiocontrol in the intramolecular Buchner reaction

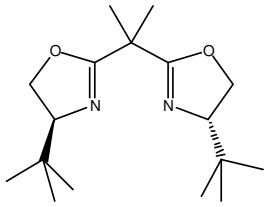
The past three decades have witnessed a major development in asymmetric catalysis. New and powerful catalysts have been designed and developed which exhibit levels of enantioselectivity previously considered beyond reach for non-enzymatic processes.[85]

Rhodium and, more specifically, dirhodium(II) complexes including carboxylates and carboxamidates (Figure 2.5) have proved to be the most effective and versatile catalysts for the aromatic addition of diazo compounds.[23,26,75,86,87] Their versatility arises from the large range of bridging ligands that can be coordinated to the dirhodium(II) skeleton, which have a marked influence on reactivity and selectivity. Nitrogen-based ligands such as bisoxazolines have emerged as an efficient class of ligands in an increasing number of asymmetric transformations including cyclopropanation, aziridination, Diels-Alder reaction, reduction, aldol reaction, ene reactions, allylic oxidation etc.[88] While coordination of these ligands to wide range of metals has been well documented, copper remains the most successful for diazocarbonyl transformations. An attractive factor is that a number of these enantiopure bis(oxazoline) ligands are commercially available.

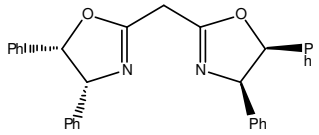
Recent studies within our research group, by Harrington and O'Keeffe,[12,40,41] have illustrated the effectiveness of copper bisoxazoline ligands in the enantioselective decomposition of internal α-diazoketones (see Table 2.8, Table 2.9, Scheme 2.20). A number of commercially available bis(oxazoline) ligands **74**, **75**, **89** and **91** were employed and in addition ligand **93** was designed and synthesised over the course of this work (Figure 2.9). The details for its synthesis are outlined below.



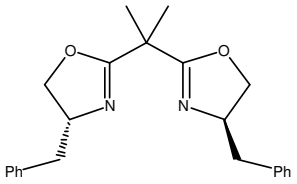
75 [(*R*,*R*)-Ph-Box]



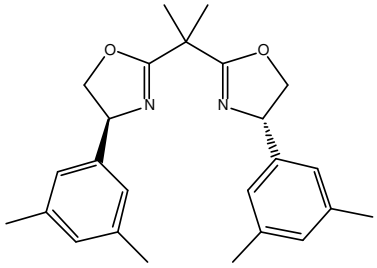
74 [(*S*,*S*)-*t*-Bu-Box]



89 [(4*R*,5*S*)-*tetra*-Ph-Box]



91 [(*R*,*R*)-Bn-Box]



93 [(*S*,*S*)-3,5-$(Me)_2C_6H_3$-Box]

Figure 2.9 *Bisoxazoline ligands employed in this study*

2.6.3.1 Synthesis of bisoxazoline ligands

Since the first report in 1989, there have been many examples of new and novel C_2-symmetric bisoxazoline ligands with different structural features synthesised.[89-96] The pioneering work on these ligands was conducted by Masamune but subsequent disclosures by Pflatz and Evans have ensured their continued growth and success. [97,98,99] A detailed account of these bisoxazoline ligands can be found in extensive reviews of the area by Desimoni in 2006,[96] and Guiry in 2009.[100]

The most successful ligand that has been applied to the intramolecular Buchner reaction in our group, in terms of enantioselectivities achieved has been the phenyl substituted bisoxazoline **75**.

O'Keeffe developed a model rationalising the enantiocontrol in the aromatic addition process based on the interaction between the phenyl ring of the ligand and the phenyl ring on the substrate undergoing aromatic addition (Figure 2.10). To explore this, a range of substituted diazoketones with electron withdrawing and electron donating

substituents on the aromatic ring were investigated, displaying increased enantioselectivity when the aryl ring was substituted with electron donating substituents, supporting O'Keeffe's model.[41]

While the preliminary results investigated by Harrington and O'Keeffe used predominantly commercially available ligands, O'Keeffe undertook a preliminary exploration of substituted bisoxazolines although limited in scope due to the challenge in obtaining substituted bisoxazolines. O'Keeffe explored the 6-methoxy and 6-fluoro substituted bisoxazolines **113** and **114**, and observed limited impact on the enantioselectivity, indicating that the electronic properties of the aryl ring of the ligand was less significant in determining the enantioselectivity than that of the aryl ring of the diazoketone, indicative of the edge-to-face rather than face-to-face interactions.[41]

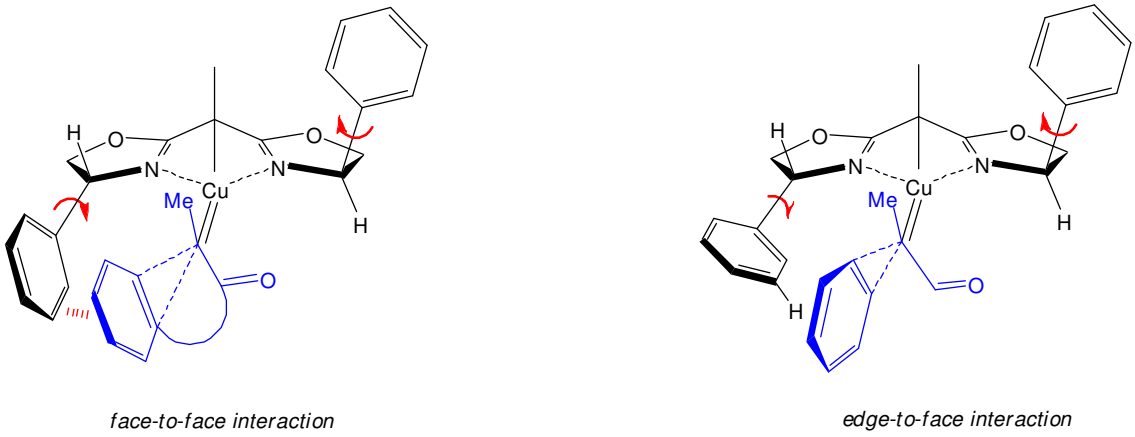
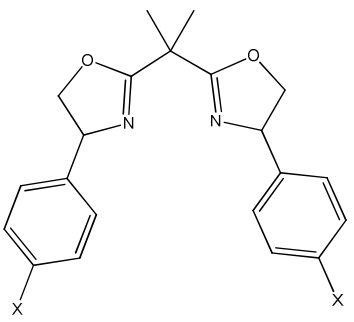
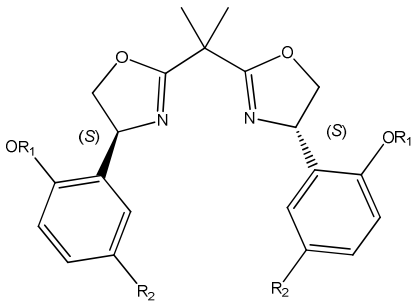


Figure 2.10

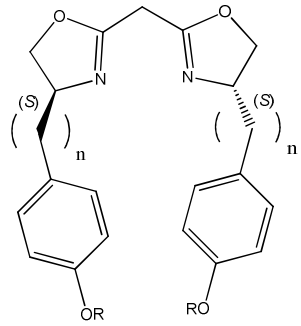
Despite the wide application of bisoxazoline ligands, particularly the bisoxazoline **75**, there are limited reports of analogues bearing substituents on the phenyl ring presumably due to the synthetic challenge in obtaining the required enantiopure phenylglycinols. To date only *p*-MeO **115** and **116**,[101,102] *p*-Cl **117**,[101] *p*-*t*-Bu **118**,[102] *p*-Br **119**,[103] 2,4,6 tri-Me **120**,[104] 3,4 di-MeO **121**,[104] *p*-Me **122**[105] and four 2-alkoxy-5-alkylphenyl substituted aryl bisoxazolines **123a-d**[106] have been reported in the literature. Also, Desimoni and Itagaki have reported naphthyl derivatives **126/127**.[107,108] Within our group, O'Keeffe synthesised the novel *para*-fluoro substituted aryl bis(oxazoline) ligand **113** from the commercially available (*R*)-4-fluorophenylglycine methyl ester hydrochloride. She also prepared the known methoxy substituted ligand **114**.[41]



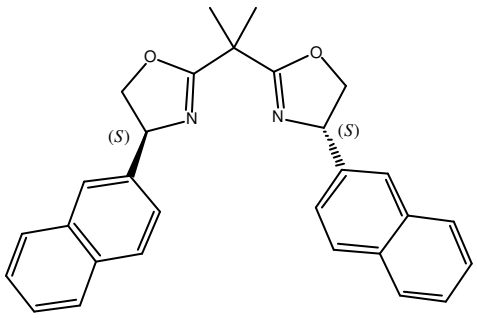
115-(*S,S*) X = MeO
117-(*S,S*) X = Cl
118-(*S,S*) X = *t*-Bu
119-(*S,S*) X = Br
120-(S,S) X = 2,4,6 trimethyl
121-(S,S) X = 3,4 diMeO
122-(*S,S*) X = Me
125-(*S,S*) X = F
75-(*R,R*) X=H
113-(*R,R*) X=F
114-(*R,R*) X=OMe



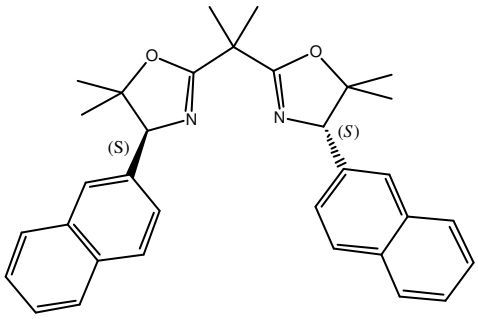
123a R^1 = Me, R^2 = H
123b R^1 = Me, R^2 = *t*-Bu
123c R^1 = Me, R^2 = Cl
123d R^1 = $(CH_2)_2Cl$, R^2 = *t*-Bu



124 *n* = 0, R = *t*-Bu
116 *n* = 1, R = Me



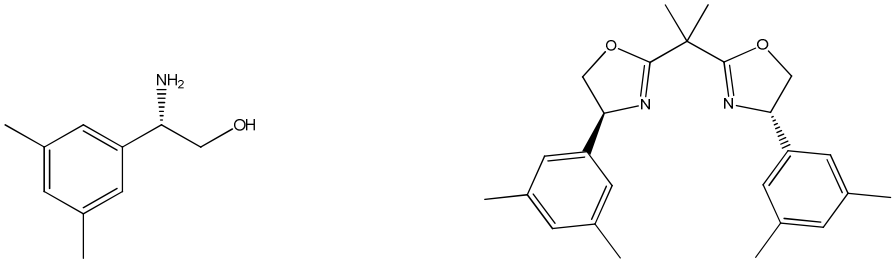
126



127

Figure 2.11

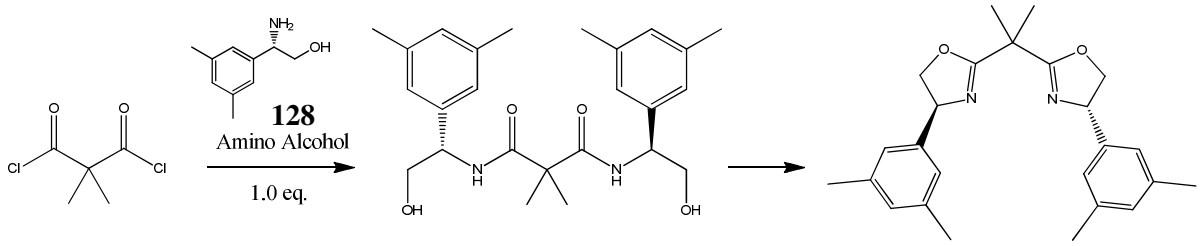
While O'Keeffe had explored the electronic effects of the substituents on the phenyl ring of **75**, in this work, the novel ligand **93** was designed to allow exploration of both steric and electronic effects due to the presence of the *meta*-methyl substituents (Figure 2.12).



128 **93**

Figure 2.12

The construction of the oxazoline rings starting from a symmetrically substituted malonic acid derivative and two equivalents of optically active amino alcohol was envisaged using the method reported by Evans and Corey (Scheme 2.26). [99;109] The principal challenge in synthesising this ligand was to access the starting amino alcohol **128** in enantiopure form.

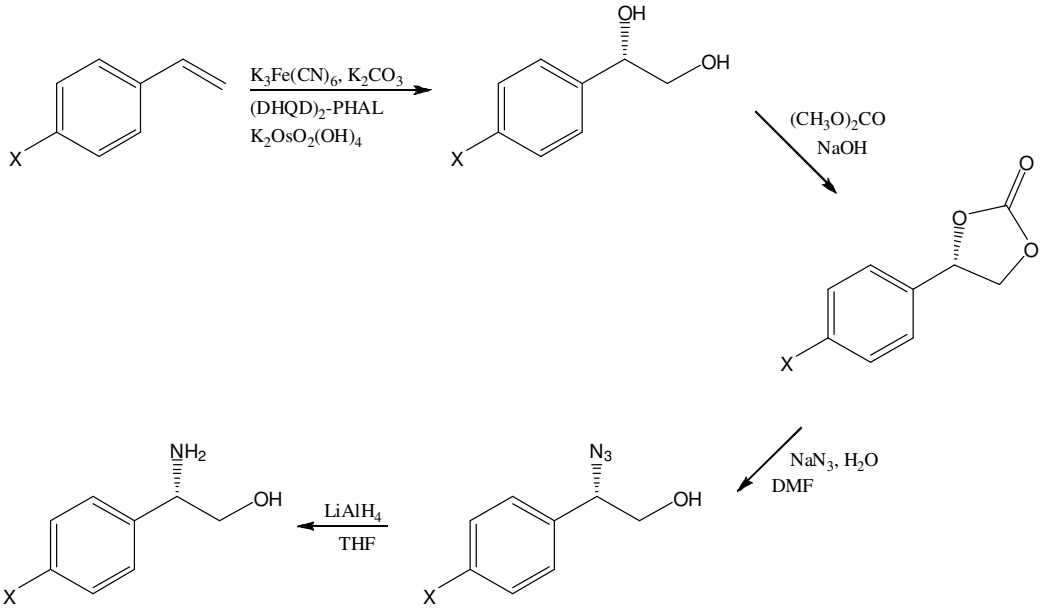


0.5 eq. *Bisamide* **129** *Bisoxazoline* **93**

Scheme 2.26

2.6.3.2 Synthesis of amino alcohols

Enantiopure amino alcohols have been prepared by several methods such as Evans' route to the amino alcohols which was derived from an amalgamation of work by Sharpless and Katsuki and involved four synthetic steps, [101;110;111] beginning with the 4-substituted styrene derivatives (Scheme 2.27). These were subjected to Sharpless asymmetric dihydroxylation followed by the treatment of the diol with dimethyl carbonate which was followed by the regioselective ring opening of the cyclic carbonate with sodium azide, and finally the reduction of the resulting azido alcohol with $LiAlH_4$.



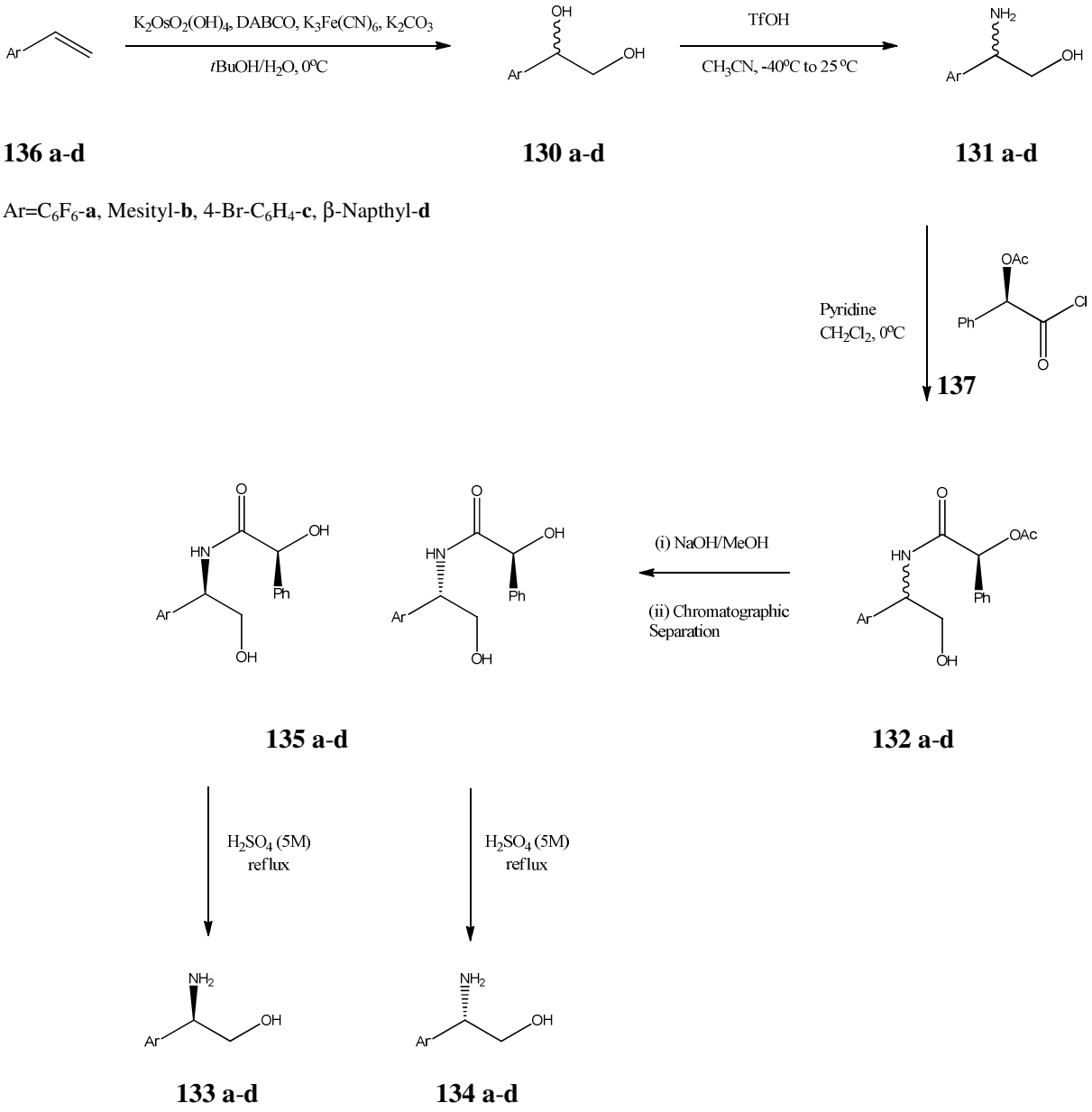
Scheme 2.27

2.6.3.2.1 Cozzi's synthesis of arylglycinols

Cozzi had reported a two-step synthesis of racemic arylglycinols together with a simple and straightforward methodology for their resolution as shown in Scheme 2.28. Cozzi reported that chiral β-amino alcohols were isolated in good yields and with up to 99% enantiomeric excesses. [112] High regioselectivities and stereoselectivities were achieved independent of the electronic characteristics of the aromatic rings of the starting styrene. Cozzi's route appeared very attractive for our studies as it appeared very straight forward to conduct and should in principle be applicable to the synthesis of a wide range of phenylglycinols.

Cozzi synthesised a series of racemic 1,2-diols **130a-d** by osmium catalysed dihydroxylation.[112] The preparation of the corresponding racemic arylglycinols **131a-d** was accomplished by an adaptation of the Ritter rearrangement reaction as described by the Merck group.[113-115] Each of the subsequent amino alcohols **131a-d** was treated with (*S*)-*O*-acetylmandeloyl chloride in dichloromethane in the presence of pyridine. Cozzi isolated the amides **132a-d** as a mixture of two diastereoisomers and the separation of these diasteroisomers was successfully accomplished by chromatography after hydrolysis of the acetyl group. Finally, the optically active amino alcohols **133a-d** and **134a-d** were

isolated after acidic hydrolysis of the corresponding enantiomerically pure amides **135a-d** (Scheme 2.28).



136 a-d **130 a-d** **131 a-d**

Ar=C_6F_6-**a**, Mesityl-**b**, 4-Br-C_6H_4-**c**, β-Napthyl-**d**

137

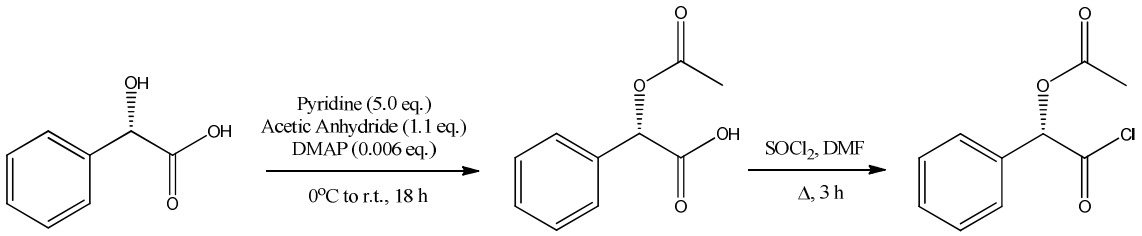
135 a-d **132 a-d**

133 a-d **134 a-d**

Scheme 2.28

To assess the practicality of Cozzi's methodology for our purposes, we first treated phenylglycinol **138** with (*S*)-*O*-acetylmandeloyl chloride **137** (Scheme 2.30). (*S*)-*O*-Acetyl-mandelic acid **139** was readily accessed from commercially available *S*-mandelic

acid following the literature procedure as summarised in Scheme 2.29, in a yield of 86%. The spectroscopic data and specific rotation was comparable to the literature data.[116]



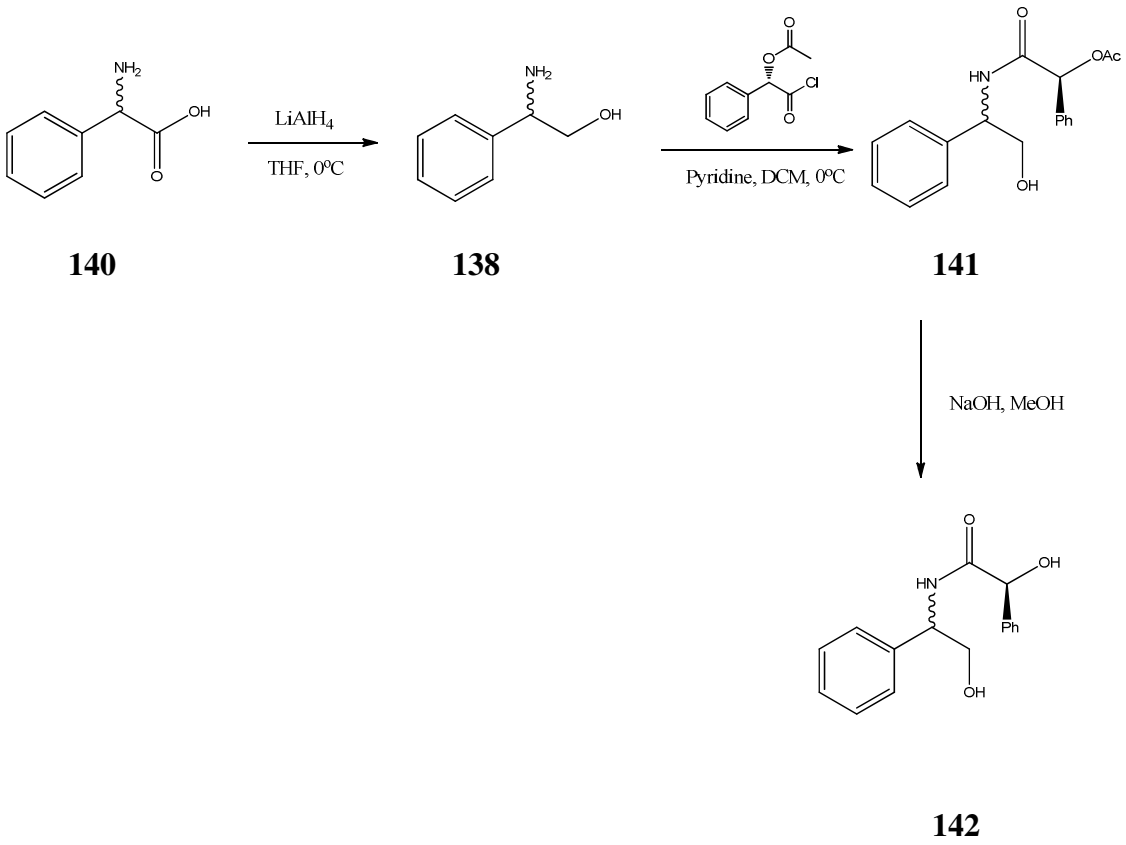
139 **137**

86% 77%

137, $[\alpha]_D^{20}$ 146.1 (*c* 1.0, $CHCl_3$)

Scheme 2.29

(*S*)-*O*-Acetylmandeloyl chloride **137** was synthesised in a yield of 77%, by treating the acid **139** with 1.1 equivalents of thionyl chloride ($SOCl_2$) and a catalytic amount of dimethylformamide (DMF) (Scheme 2.29). The brown oil formed was purified by vacuum distillation to give the acid chloride as yellow oil. An IR spectrum of the crude material showed formation of the desired acid chloride **137** due to a strong absorption at 1804 cm^{-1}. In the ^1H NMR spectrum of the pure product the broad singlet seen for the carboxylic acid was absent, indicating complete formation of the acid chloride **137**.



140 **138** **141** **142**

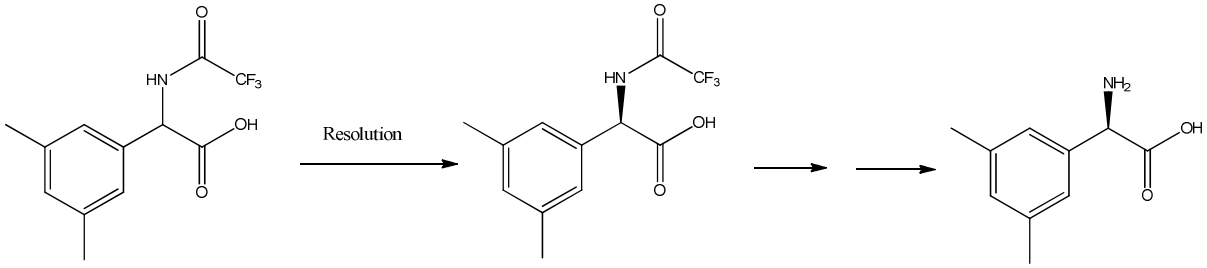
Scheme 2.30

Lithium aluminium hydride reduction of racemic phenylglycine **140** to phenylglycinol **138** in 93% yield was the next step (Scheme 2.30).[117] Reaction of phenylglycinol **138** with (*S*)-*O*-acetylmandeloyl chloride **137** and pyridine (1.1 eq.) was carried through following Cozzi's procedure.[112] In the first attempt, this was carried out through directly to the subsequent hydrolysis as described by Cozzi without isolation of the intermediate acetylated amide **141**. However, the ^{1}H NMR of the crude compound did not correspond to the expected mixture of diastereoisomers of **142**. Following purification by chromatography, the individual components were not recovered. Accordingly the experiment was repeated, but this time attempting to isolate the intermediate **141** for spectroscopic characterisation and to attempt to separate the diastereoisomers. While this first step was undertaken a number of times, the ^{1}H NMR spectra were more complex than expected. It was not possible to definitely characterise the respective amides **141** and **142** in the crude or purified products for any of the series of experiments. Interestingly, Cozzi never described the characterisation of the acetylated amides **141** but instead carried through them through directly to the diols (**133a-d, 134a-d).** Based on our results,

we envisage that their interpretation of the outcome may not be comprehensive and they may have overlooked side products due to alcohol acetylation in addition to amide formation.

2.6.3.2.2 Koga's synthesis of enantiopure 3,5-dimethylphenylglycine

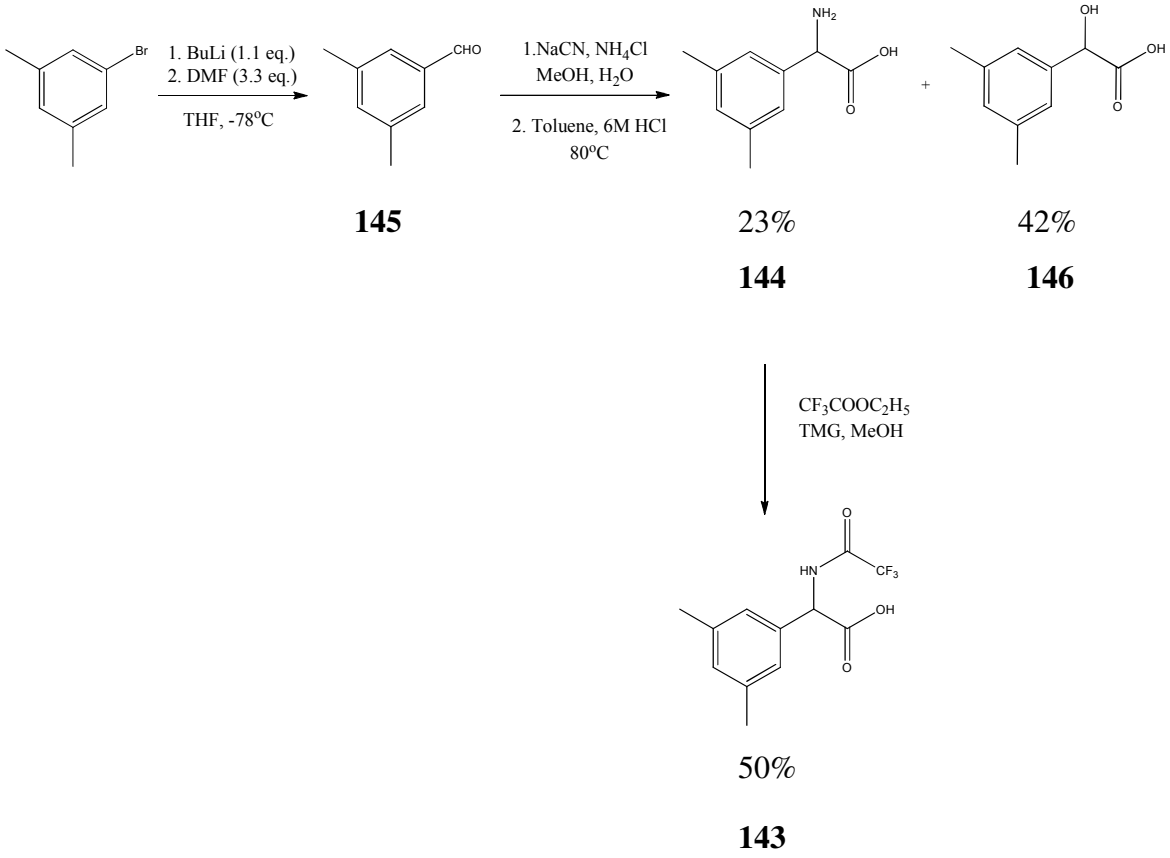
Koga described the synthesis of a range of chiral bidentate amines using a multi-step synthesis starting from optically active amino acids; his method of obtaining the optically active amino acid appeared attractive for our purposes. He prepared racemic 3,5-dimethylphenylglycine, and this was resolved *via* its *N*-trifluoroacetyl derivative by crystallisation as cinchonine salt (Scheme 2.31).[118]



143 **(*R*)-143** **(*R*)-144**

Scheme 2.31

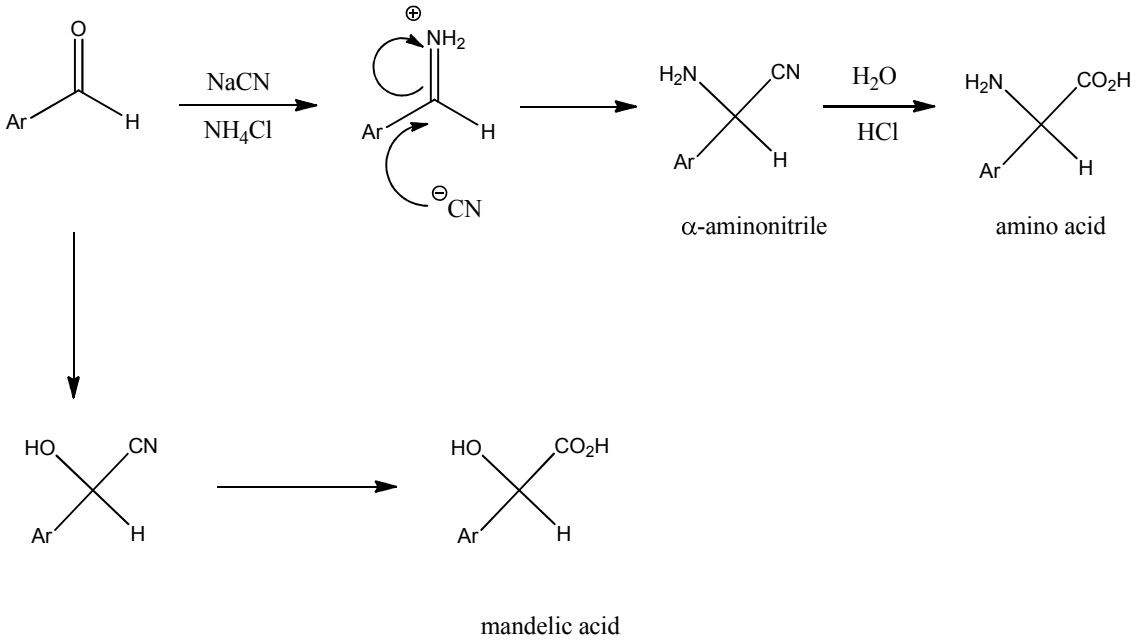
The initial task in the synthetic plan was to generate racemic 3,5-dimethylphenylglycine **144** from 3,5-dimethylbenzaldehyde **145** *via* the Strecker reaction. While 3,5-dimethylbenzaldehyde **145** is commercially available it is expensive. As relatively large quantities would be required for subsequent reactions, it was prepared from 1-bromo-3,5-dimethylbenzene *via* bromine-lithium exchange reaction followed by reaction with DMF affording the aldehyde **145** as a green oil in a yield of 58%.[119] The relative cost of purchasing 3,5-dimethylbenzaldehyde **145** commercially (5 g - €150) was much more expensive than synthesising it in the lab from 1-bromo-3,5-dimethylbenzene (100 g - €100).[120,121]



Scheme 2.32

Koga described the preparation of 3,5-dimethylphenylglcyine **144** *via* the Strecker reaction from **145** although he did not provide any experimental detail. [122-124] When this approach was followed in this current study, using the standard conditions for the Strecker reaction two products were recovered, the expected substituted phenylglycine **144** in 23% yield and the unexpected mandelic acid **287** in a 42% yield. The identity of **144** was confirmed spectroscopically with characteristic signals in the IR at 3013 cm^{-1} and 1758 cm^{-1} and in the ^1H NMR (d_6-DMSO) via a singlet at δ_H 4.97 ppm and a broad singlet at δ_H 8.76 ppm for the C(2)H and NH_2 signals respectively. The mandelic acid **146** was identified by ^1H NMR by a characteristic singlet at δ_H 5.15 ppm for the C(2)H signal in $CDCl_3$. To confirm the formation of the two acids, the ^1H NMR spectra of each of the products were recorded in D_2O showing clearly two distinct components. The C(2)H signal for amino acid **144** was observed at δ_H 4.90 ppm, which was further upfield than the C(2)H signal seen at δ_H 5.07 ppm for mandelic acid **146**.

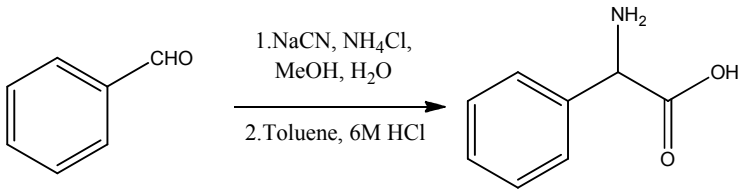
The mechanistic pathway envisaged for the Strecker synthesis involves cyanide addition to the iminium ion leading to formation of the α-aminonitrile (Scheme 2.33). While cyanide addition to the highly electrophilic iminium ion is envisaged to occur much more rapidly than addition to the aldehyde, it seems that in this instance direct addition of the cyanide to the aldehyde competed effectively resulting in a mixture of amino acid **145** and mandelic acid **146**.



Scheme 2.33

Variation of the reaction conditions was undertaken with the objective of enhancing the efficiency in the synthesis of amino acid **144**. While the relative amount of the two products varied, both were isolated in all instances. As the two products partitioned between aqueous and organic layers in the work up, in practice each of the two are readily obtained as single components.

To establish the side reaction was due to the presence of the two methyl substituents, the Strecker reaction was carried out with benzaldehyde under the same conditions and led to the α-amino acid **140** in a reasonable yield, with no evidence of mandelic acid formation (Scheme 2.34).[122]

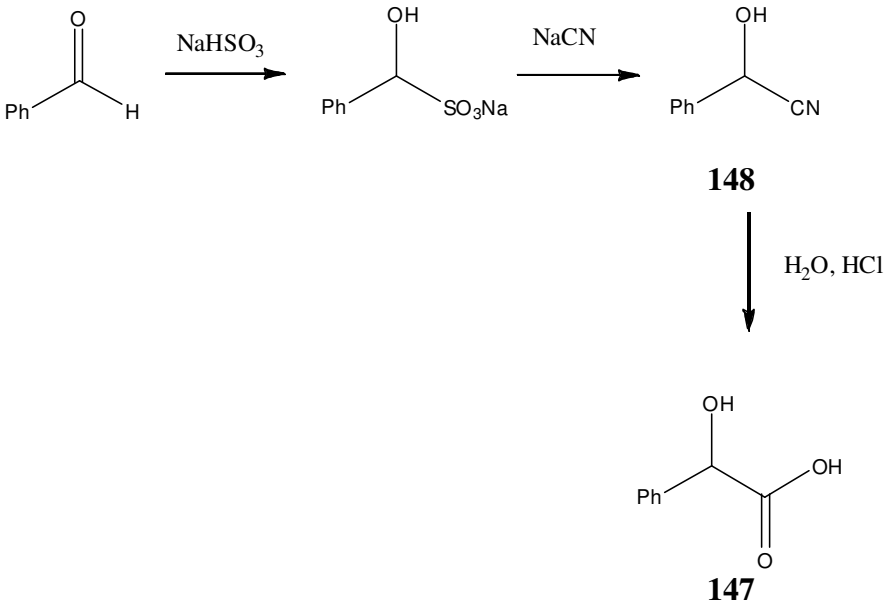


56%

140

Scheme 2.34

In 1926, Corson reported the formation of mandelic acid by treating benzaldehyde with sodium metabisulfate and sodium cyanide (Scheme 2.35). He reported that the mandelic acid **147** was formed was through hydrolysis of the mandelonitrile **148** with hydrochloric acid.[125] This supports the proposed mechanism for the formation of **146** in Scheme 2.33.



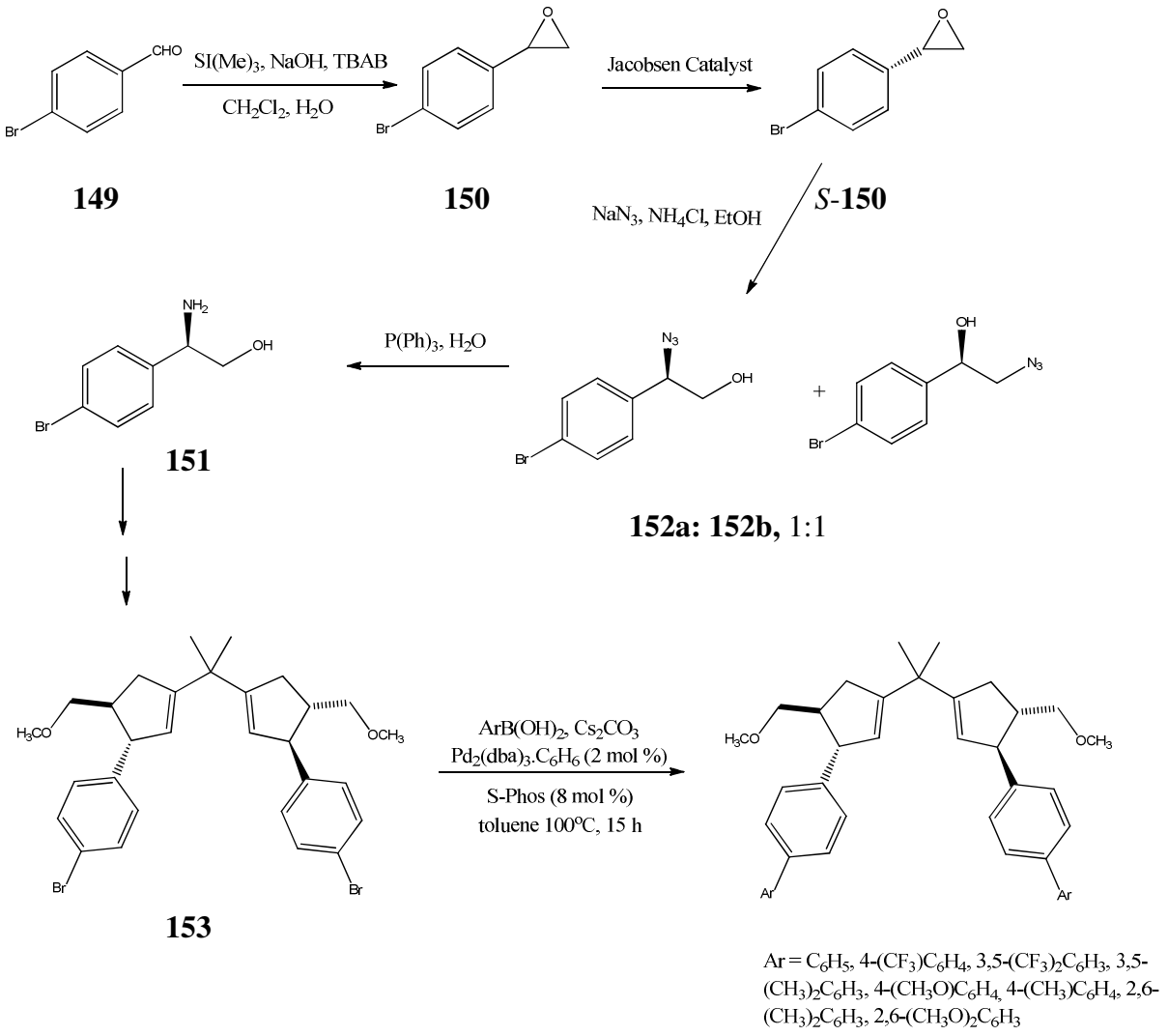
Scheme 2.35

The next step was trifluoroacetylation of the amino acid **144** which was previously reported by Koga using ethyl trifluoroacetate and tetramethylguanidine in methanol. This subsequently afforded **143** which existed as a white solid in 50% yield (Scheme 2.32). The yield and spectroscopic characteristics were comparable to those described by Koga. While Koga had described successful resolution of **143** through recrystallisation as a

cinchonine salt, he had conducted the reaction on a very large scale (~140 g). In our hands as only ~2.00 g of racemic acid **144** was available, the repeated recrystallisation for effective resolution was challenging and was not pursued, as an alternative route appeared more feasible.

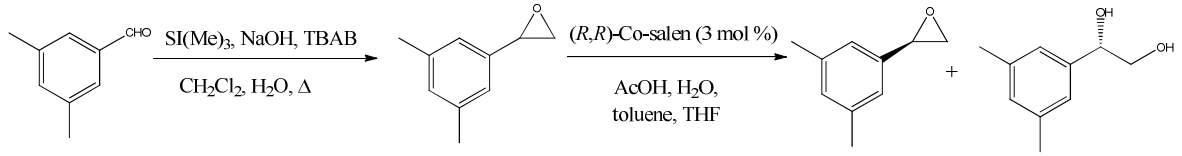
2.6.3.2.3 Synthesis of enantiopure 3,5 dimethylphenylglycine via Jacobsen's epoxidation

Pericas has shown that a wide variety of modular, enantiopure amino alcohols can be easily synthesised *via* ring-opening of enantiomerically pure synthetic epoxides with nitrogen nucleophiles including azides,[103] using Suzuki cross coupling as the main tool for structural diversity (Scheme 2.36).



Scheme 2.36

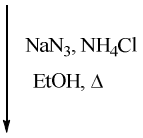
This method of synthesising enantiopure amino alcohols was attractive and we decided to attempt to synthesise enantiopure amino alcohol **128** *via* Pericas' route (Scheme 2.37). The synthesis of the precursor was initiated by a Corey-Chaykovsky reaction on aldehyde **145** to give 2-(3,5-dimethylphenyl)oxirane **154** as a green oil in a 41% yield.[103]

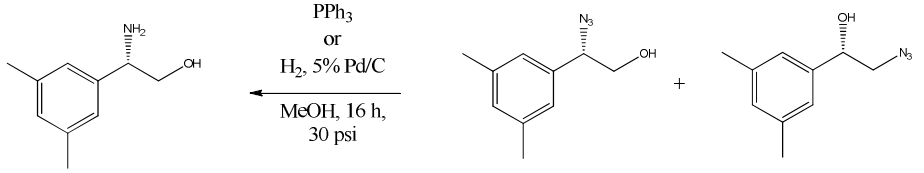


145 **154**, 41% ***R*-154** **155**

48%, 98% ee

$[\alpha]_D^{20}$ +23.0 [*c* 0.25, $CHCl_3$].





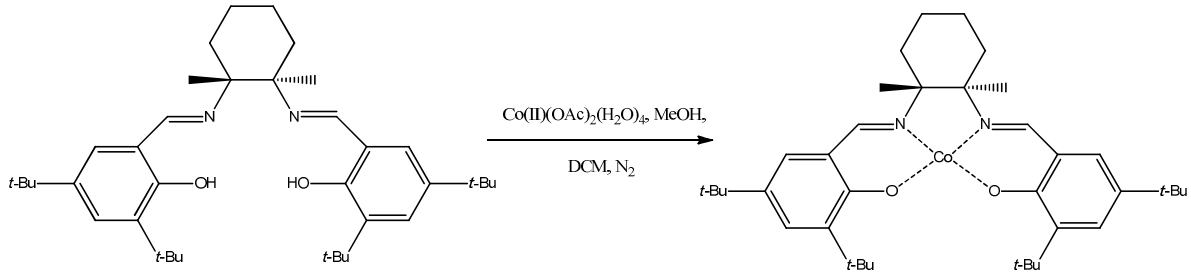
S-**128**,42% *S*-**156a** **156b**

51%, 90% ee, *S*-**156a:156b**, 90:10 in crude

$[\alpha]_D^{20}$ +15.92 [*c* 0.65, C_2H_5OH] $[\alpha]_D^{20}$ +188.6 [*c* 1.0, $CHCl_3$]

Scheme 2.37

The next step was the hydrolytic kinetic resolution of the epoxide **154** using Jacobsen's procedure.[126] The (*R*,*R*)-Co(salen) catalyst **157** was prepared by Jacobsen's method to give a bright red solid in a 83% yield (Scheme 2.38).



157, 83%

Scheme 2.38

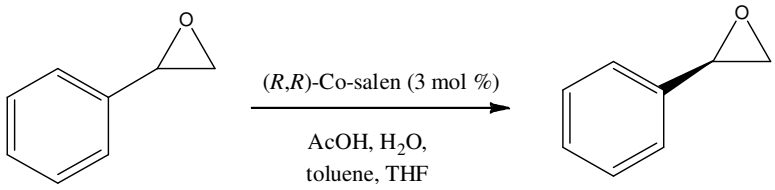
The catalyst formed was stored under nitrogen in the freezer for up to 6 months with no decrease in catalytic activity observed. Oxidation of the Co(II) complex by acetic acid followed by addition of the racemic epoxide **154** in tetrahydrofuran (THF) was carried out first. Water was added slowly and the reaction mixture was stirred at room temperature for 40 hours. Following work-up, purification by vacuum distillation gave the (*R*)-epoxide **154** as a clear, colourless oil in 48% yield (Scheme 2.37). The reaction was conducted on a number of occasions; on each occasion the epoxide (*R*)-**154** was obtained as a pure compound; however, on one occasion the epoxide (*R*)-**154** isolated following distillation contained approximately 50% of another compound. The signals in the ^{1}H NMR were consistent with the diol **155**. However, diol **155** was never isolated in pure form from this reaction.

The enantiomers of the epoxide **154** were readily resolved using a Chiracel® OD-H column resulting in an enantioselectivity of 98% (see appendix 3). In the initial experiments there were some variability in the enantiopurities of the epoxide recovered from the kinetic resolution yielding samples of **154** typically with 94-98% ee, but on one occasion dropping as low as 30% ee. The highest enantiopurity obtained was with the reaction as described above where the product was isolated as a mixture with diol **155** rather than as a pure compound. Due to the inconsistency of enantiopurities it was decided to investigate the kinetic resolution of 2-phenyloxirane **158** following the same procedures as **154** (Table 2.13).

Kinetic resolution in the ring opening of 2-phenyloxirane **158** using Jacobsen's catalyst **157** was conducted at two different concentrations as illustrated in Table 2.13.

Interestingly it was found that the increased concentration was required to lead to efficient kinetic resolution. Jacobsen describes to use of 1 mL:1 g but did not discuss the importance of concentration on the efficiency of resolution.[126] Accordingly it is believed that the variability in the resolution of **154** is most likely due to the use of reaction mixtures which were too dilute.

Table 2.13 *Investigation into concentration of epoxide* **158** *in THF during kinetic resolution*



158 *R*-**158**

Entry	THF: **299**	ee %[a]
1	6 mL: 1 g	19[b]
2	1 mL:1 g	98[b]

a. Determined by chiral HPLC.

b. Major Enantiomer = (+).

Based on this model study further experiments to explore the kinetic resolution of epoxide **154** with careful control of the concentration of the epoxide **154** enabled reproducible, efficient kinetic resolution to form *R*-**154** in a 48% yield and up to 98% ee. The kinetic resolution was conducted on up to 2 gram scale with the limitation being the cost of Jacobsen's ligand.

The absolute stereochemistry of the recovered optically active *R*-**154** was assigned by comparison of the specific rotation data to that of the related compounds described by Jacobsen, and on the basis of Jacobsen's description of the sense of enantioselectivity in the epoxide ring opening.[126]

Pericas found that transformation to the amino alcohol **128** was best effected by a two-step sequence involving ammonium chloride catalysed azidolysis of the epoxide and

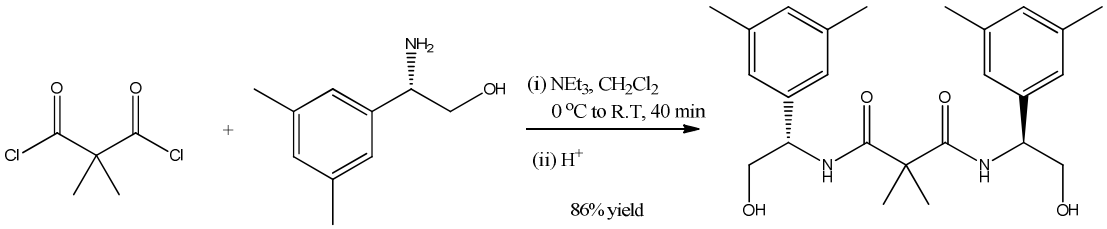
reduction of the azido group by the Staudinger protocol.[103] Following this method, epoxide *R*-**154** was heated under reflux for 12 hours with ammonium chloride and sodium azide in ethanol (Scheme 2.37). Although a 90:10 regioisomeric mixture of azido alcohols **156a:156b** was obtained, the desired azido alcohol **156a** could be easily separated by flash chromatography. The epoxide can undergo ring opening *via* two competing pathways - attack at the benzylic carbon or at the primary carbon. The optical purity of the obtained azido alcohol **156a** was 90% ee using a Chiracel® OJ-H column. Pericas obtained; a 1:1 regioisomeric mixture of azido alcohol **152a:152b** as illustrated in Scheme 2.36.[103]

Reduction of the azido alcohol **156** with triphenylphosphine was attempted using the method described by Pericas.[103] However, it was difficult to remove the triphenylphosphine oxide from the desired crude alcohol **128** by flash chromatography or trituration. Therefore it was decided that an alternative reduction *via* hydrogenation would be carried out. The azido alcohol **156** in methanol was shaken under hydrogen at 30 psi for 16 h over Pd/C at room temperature (Scheme 2.37). ^{1}H NMR analysis of the crude product indicated excellent purity; however, recrystallisation was undertaken as described by Pericas from hot toluene to give the novel amino alcohol **128** as white needle-like crystals in a yield of 42%. The enantiopurity of the amino alcohol **128** could not be obtained by chiral HPLC, therefore it was carried directly through to the next step. Interestingly, Pericas had not described the enantiopurity of the analogous bromo substituted amino alcohol. It is possible the enantiopurity of **128** was enhanced through the recrystallisation from 90% ee in **156a** as the ligand obtained ultimately had ≥99% ee, however this was not confirmed. In conclusion, while the isolation of racemic **128** has been described,[127] the isolation of amino alcohol *S*-**128** in excellent enantiopurity was achieved for the first time during this work and the compound was fully characterised.

2.6.3.3 *Synthesis of the novel bisoxazoline* 93

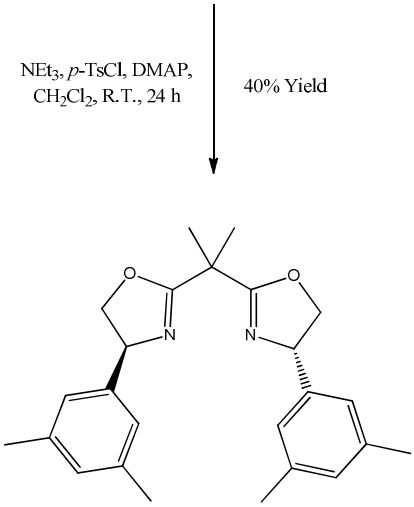
There are several possible methods for the synthesis of bisoxazolines from amino alcohols *via* bisamides. Itagaki *et al.* demonstrated the dehydration of bisamido alcohols using titanium isopropoxide as catalyst,[108] while Sakakura and co-workers used molybdenum(VI) oxide as catalysts for highly effective dehydrative cyclisations for the formation of oxazoline complexes.[128] However, Evans reported that cyclisation to the bisoxazoline *via* the bis(alkyl chloride) followed by thermal cyclisation, was the best procedure for the oxazoline ring-forming step.[129] As O'Keeffe had successfully applied the Evans method to the synthesis of the methoxy substituted ligand **114**, it was also applied in this investigation to synthesise the novel bisoxazoline **93**. Based on Jacobsen's and Pericas' work, recovery of (*R*)-154 was envisaged on exposure of **154** to the (*R*,*R*)-Co(salen) **157** catalyst. The direction of the enantioselection was confirmed later in the sequence by comparison of the specific rotation and chiral HPLC characteristics of the novel bisoxazoline ligand **93** with known compounds such as (*R*,*R)*-**113** { $[\alpha]_D^{20}$ +183.2 [*c* 0.5, $CHCl_3$]} and (*R*,*R)*-**114**{ $[\alpha]_D^{20}$ +125.7 [*c* 0.3, $CHCl_3$]}.[41]

The reaction was first conducted with the racemic amino alcohol **128** then applied to the enantioenriched amino alcohol (*R*)-**128**. The initial step was the acylation of the amino alcohol **128** with 0.5 equivalents of dimethylmalonyl chloride **159** to give the bisamide **160** (Scheme 2.39).



159 a. (±)-**128** a. **160** Diastereoisomers 78:22

b. (*S*)-**128** b. (*S,S*)-**160**, 86%, $[\alpha]_D^{20}$ 33.75 [*c* 0.2, $CHCl_3$]



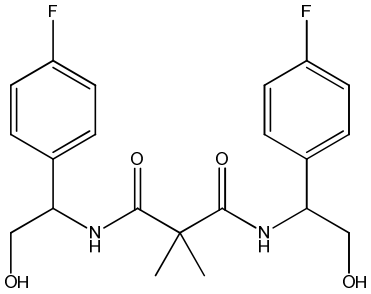
a. **93** [(*R*,*R*) and (*S*,*S*)] diastereoisomers only

b. (*S*,*S*)-**93**, 40%, >99%ee, $[\alpha]_D^{20}$ -97.0 [*c* 0.1, $CHCl_3$]

Scheme 2.39

The ^{1}H NMR spectrum of the crude bisamide **160** derived from the racemic amino alcohol **128** contained a mixture of diastereoisomers in the ratio of 78:22 with the major diastereoisomer the same by ^{1}H NMR as (*S,S*)-**160**. O'Keeffe reported that for the *para*-F substituted bisamide **161**, signals for the diastereoisomers appeared as one set in the ^{1}H NMR spectrum (Figure 2.13).[41] Recrystallisation from a mixture of dichloromethane and hexane did not alter the ratio of diastereoisomers, but a low yield of 47% was obtained. Critically for the novel bisamide (*S*,*S*)-**160** derived from (*S*)-**128** there was no evidence of the meso diastereoisomer in the crude product isolated in 86% yield. As the enantiopurity of (*R*)-**128** was never directly measured, absence of the meso diastereoisomer in (*S*,*S*)-**160**

confirms that (*R*)-**128** was enantiopure. To maximize yield, the chiral bisamide (*S,S*)-**160** was not purified and was carried through directly to the corresponding bisoxazoline.



161

Figure 2.13

The bisamide **160** was treated with *p*-toluenesulfonyl chloride (*p*-TsCl) and triethylamine (NEt_3) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) to give the novel bisoxazoline **93** (Scheme 2.39). The reaction was conducted firstly with the racemic bisamide **160** to give a racemic mixture of [(*R*,*R*) and (*S*,*S*)] of the bisoxazoline **93** in a yield of 56%. The other diastereoisomers [(*R*,*S*) and (*S*,*R*)] were identifiable in the ^{1}H NMR of the crude material and were not isolated from the reaction.

The synthesis was then applied to the enantioenriched bisamide (*S,S*)-**160**. The low yield of 40% was due to difficulties encountered during purification. The bisoxazoline *(S*,*S*)-**93** was purified by flash chromatography on silica gel using diethyl ether/hexane as solvent. TLC analysis proved to be the most challenging aspect as the bisoxazoline *(S*,*S*)-**93** was not UV active and could only be seen when the plate was stained with potassium permanganate solution. However, while the spot appeared bright white initially, it faded after a short period of time.

Chiral HPLC analysis of the racemic and enantiopure samples showed that the batch of [*S*,*S*]-bisoxazoline **93** was generated in enantiopure form (>99% ee) (Figure 2.14), while a ^{1}H NMR spectrum of (S,S)- **93** is illustrated in Figure 2.15.

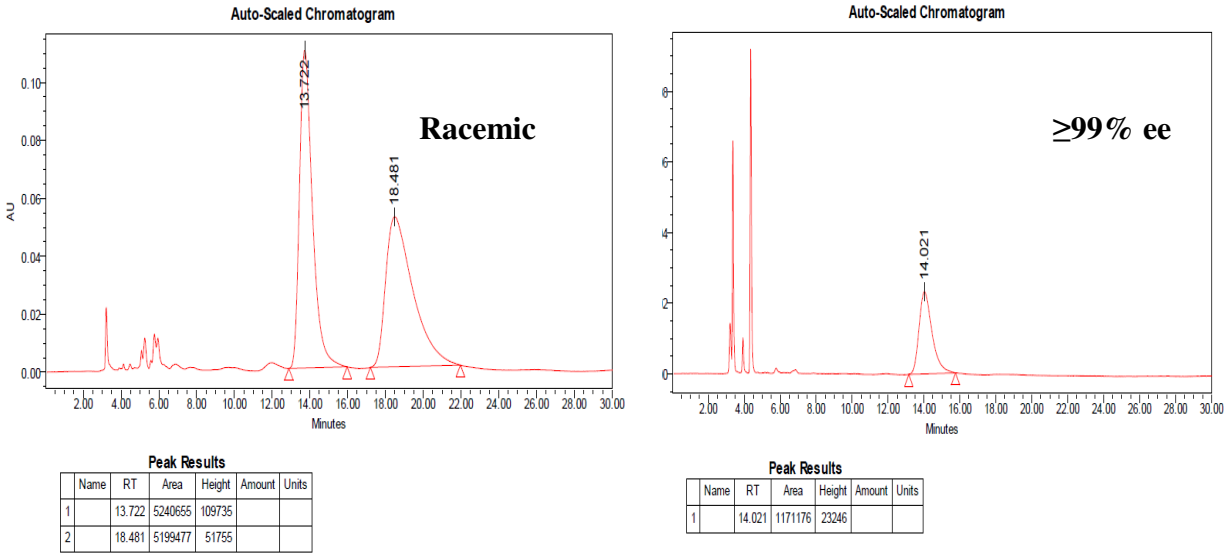


Figure 2.14 *Chiral HPLC analysis of the racemic and enantiopure samples of [S,S]-bisoxazoline* **93**

Isolation of the 3,5-disubstituted bisoxazoline ligand **93** is potentially of value in a wide range of catalytic transformations. While phenylglycinol derived bisoxazolines have been described bearing substituents on the phenyl ring, derivatives at the 3,5-positions are rare and thus **93** enables exploration of the steric and electronic effects of the methyl substituents.

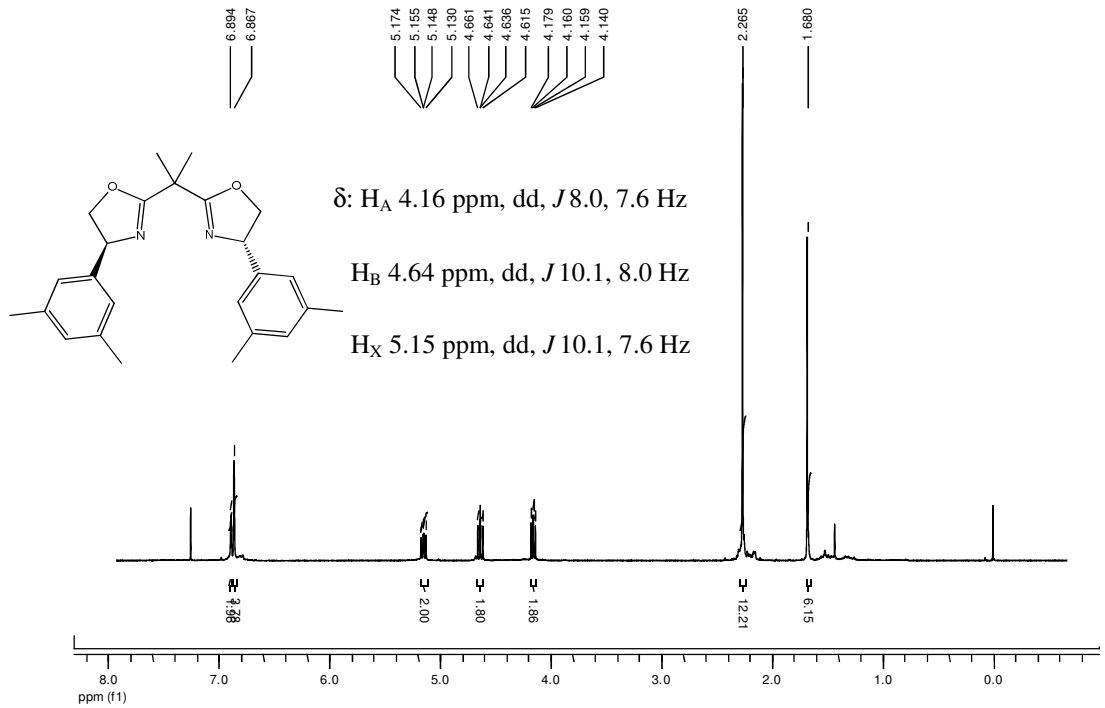
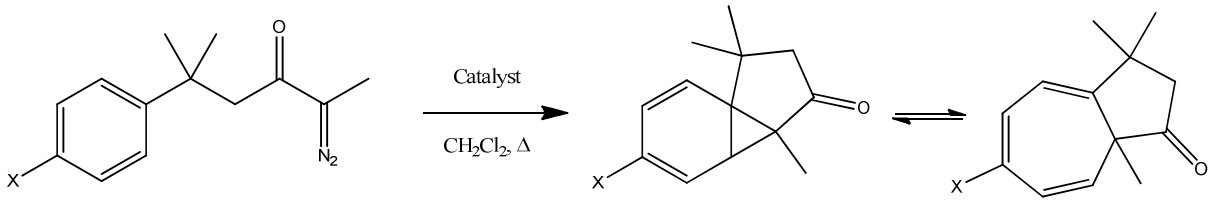


Figure 2.15 *^{1}H NMR spectrum of the pure bisoxazoline* **93**

2.6.4 Enantioselectivity in the cyclisation of internal α-diazoketones

The first task in this study was to repeat the reactions carried out by O'Keeffe[12,41] for the *geminal*-dimethyl diazoketones **37**-**42** using the bisoxazoline ligands **74**, **75** and **89** in order to evaluate the reproducibility of the reaction and enantioselectivities obtained as shown in Table 2.14. O'Keeffe[41] employed the copper salt $Cu(CH_3CN)_4PF_6$. The conditions employed were those previously described by O'Keeffe with 6 mol% of $Cu(CH_3CN)_4PF_6$ and 8 mol% of ligand and the catalyst was prepared following the procedure for Method B (Table 2.10). The reactions were found to be complete by TLC once all of the diazoketone was added over 1 h. In general, the copper(I)-bisoxazoline complexes catalysed the aromatic addition reaction of α-diazoketones in good yield and were comparable to those described by O'Keeffe.[41] Following concentration, a crude ^{1}H NMR spectrum was recorded allowing determination of the reaction efficiency as summarised in Table 2.14. The ^{1}H NMR spectrum was well resolved even in the presence of the catalyst, although storage in the crude form lead to significant degradation.

Table 2.14 *Cyclisation of diazoketones* **37**-**42** *with copper bis(oxazoline) ligands*



Entry	Diazoketone[a]	X	Catalyst	Azulenone	Method	Eff (%)[b]	Yield (%)[c]	ee (%)[d] This Study	ee(%)[d] O'Keeffe
1	**37**	H	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	**88**	A	79	74	78[e]	76
2	**37**	H	$CuPF_6$-**89**[(4*R*,5*S*)-*tetra*-Ph-Box]	**88**	A	87	58	68[e]	0
3	**39**	Cl	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	**95**	A	73	63	62[e]	62
4	**39**	Cl	$CuPF_6$-**74**[(*S*,*S*)-*t*-Bu-Box]	**95**	A	89	46	11[f]	44
5	**38**	Me	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	**96**	A	80	74	80[e]	80
6	**40**	F	$CuPF_6$-**75**[(*R*,*R*)-	**94**	A	86	81	56[e]	59

			Ph-Box]						
7	**42**	3,4,5 tri Me	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	**92**	A	87	62	-[e,g]	≥95
8[i]	**41**	3,5 di Me	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	**97**	A	88	72	-[e,h]	-

a. Diazoketone was added over 1 h and the reaction was complete at the end of the addition.
b. Calculated by integration of the aromatic (by-product) signals against the azulenone in the ^{1}H NMR spectrum of the crude product.
c. Yield after chromatography.
d. Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
e. Major Enantiomer = (−).
f. Major Enantiomer = (+).
g. Unable to calculate % ee due to decomposition. When sample was trapped with PTAD **162**, the enantioselectivity was determined as 93% ee (of adduct **163,** see Section 2.6.6.3).
h. Unable to calculate % ee due to poor separation of peaks in chiral ^{1}H NMR study. When sample was trapped with PTAD **162**, the enantioselectivity was determined as 92% ee (of the adduct **164**, see Section 2.6.6.3)
i. Novel compound
Note:$CuPF_6$ refers to $Cu(CH_3CN)_4PF_6$

The majority of enantioselectivities observed (11-80% ee) were in agreement with those recorded by O'Keeffe both in terms of direction and extent of enantiocontrol,[41] illustrating that the cyclisations proceed with excellent reproducibility (Table 2.14). In this study, the highest level of enantiocontrol was provided by the catalyst complex comprised of the phenyl substituted ligand **75** (80% ee) in the cylisation of diazoketone **38** (Table 2.14, entry 5). This result is in agreement with O'Keeffe's findings.

However, the tetraphenyl substituted ligand **89** provided the azulenone **88** in 68% ee, which is in contrast to O'Keeffe's result where she reported that the tetraphenyl substituted ligand **89** provided the azulenone **88** in racemic form (Table 2.14, entry 2). Otherwise the data reported in Table 2.14 mirrors very effectively O'Keeffe's results and it is difficult to rationalise the substantial difference in enantiocontrol in entry 2. Notably the 68% ee seen in this work is more consistent with the later results in the presence of additives and therefore is believed to be more accurate. Cyclisation of **37** using catalyst **89** was repeated and led to the same outcome within experimental error. Reactions in entries 1 and 3 were also reproduced highlighting the reliability of the enantioselectivity in the aromatic addition process. While O'Keeffe had rationalised the difference in enantiocontrol between entries 1 and 2 as being due to conformational restriction in the diphenyl ligand **89**, the results in this work indicate that the extra phenyl substituent has minimal impact on asymmetry in the cyclisation of diazoketone **37** (Table 2.14).

The enantiopurity of azulenone **92** was not readily determined directly due to the extremely labile nature of the compound as discussed in Section 2.6.2.1. O'Keeffe reported enantiopurities of ≥95% ee by chiral HPLC,[41] but in this work the azulenone **92** was observed to decompose quickly from a pale green to a yellow oil. As a result, analysis by chiral HPLC or chiral ^{1}H NMR was not possible. Resolution of one of C(3)$(CH_3)_2$ signals of the enantiomers of azulenone **97** was evident by ^{1}H NMR spectroscopy using (+)-Eu$(hfc)_3$ as chiral shift reagent but due to the relatively high enantioselectivity observed an accurate integration of these signals was not possible. Both these issues were solved by trapping each of the crude azulenones **92** and **97** *in situ* with PTAD **162** to form their stable Diels-Alder adducts and their enantioselectivities were subsequently determined by chiral HPLC (as 93% ee and 92% ee respectively, see Table

2.24). This will be discussed in more detail in Section 2.6.6.3. The excellent enantioselectivities achieved in the cyclisation of both the dimethyl and trimethyl substituted diazoketones **41** and **42** using catalyst $CuPF_6$-**75**[(*R*,*R*)-Ph-Box] confirmed O'Keeffe's earlier result with diazoketone **42**.[41,130] Essentially the same outcome is achieved with just two methyl substituents in diazoketone **41**.

The aryl ring of the diazoketone has two enantiotopic faces, and preferential addition of the carbenoid to one face is required to lead to enantioselective aromatic addition reactions (Figure 2.16). Thus the presence of the chiral copper catalyst must in some way lead to selective addition of the carbenoid to one face resulting in the preferential formation of the major enantiomer.

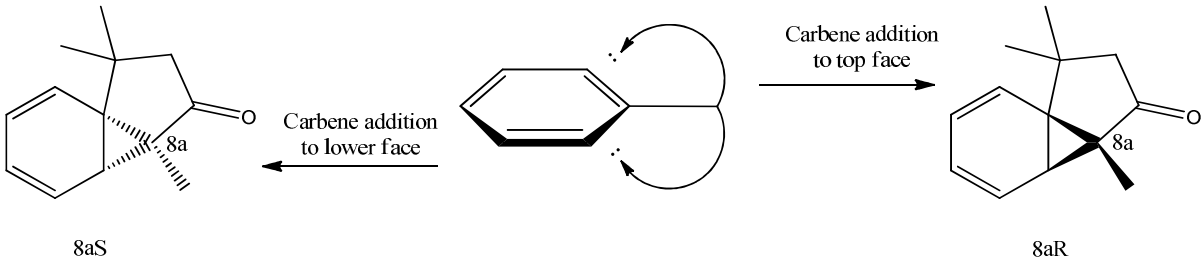


Figure 2.16

O'Keeffe postulated that the selectivity observed in the intramolecular Buchner reaction is caused by the shielding of one face of the reacting phenyl ring as a result of interactions between the bisoxazoline and the diazoketone. This interaction is believed to hold the catalyst and substrate pair in a defined conformation, controlling the trajectory of the carbene centre to the aromatic ring, and ultimately resulting in good enantioselection (Figure 2.17).

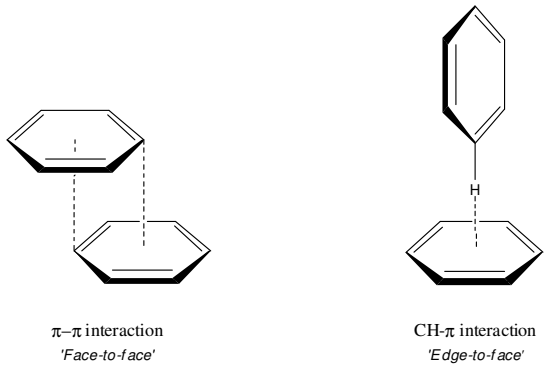
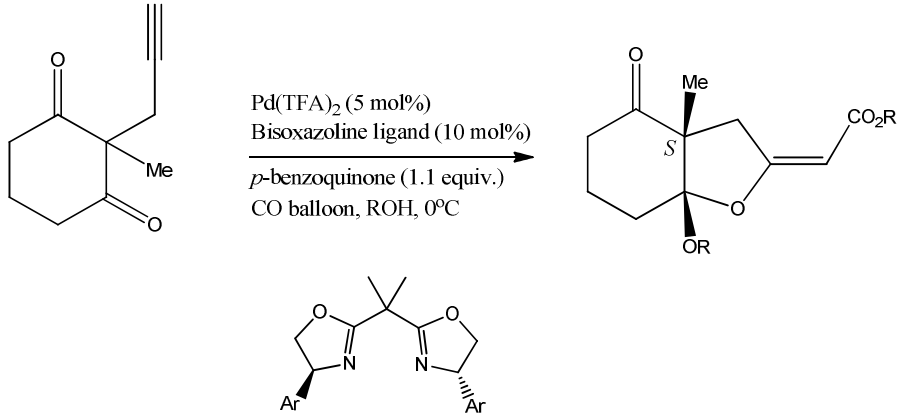


Figure 2.17

2.6.4.1 *Investigation into the enantioselectivity when using the novel bisoxazoline ligand (S,S)*-93

An exploration of the impact of variation in the electronic properties of bisoxazoline ligands on enantioselectivity is relatively uncommon, unlike the effect of steric alterations which have been well studied. Ligands derived from substituted phenylglycinols have been investigated in a number of catalytic transformations. For example, Kato and co-workers investigated various aromatic substituents at the C-4 position of the bisoxazoline ring for the asymmetric cyclisation-methoxycarbonylation of 2-methyl-2-propargylcyclohexane-1,3-dione (Scheme 2.40).[104]



where **120** Ar = 2,4,6- trimethylphenyl 52% ee

115 Ar = 4-MeOPh 51% ee

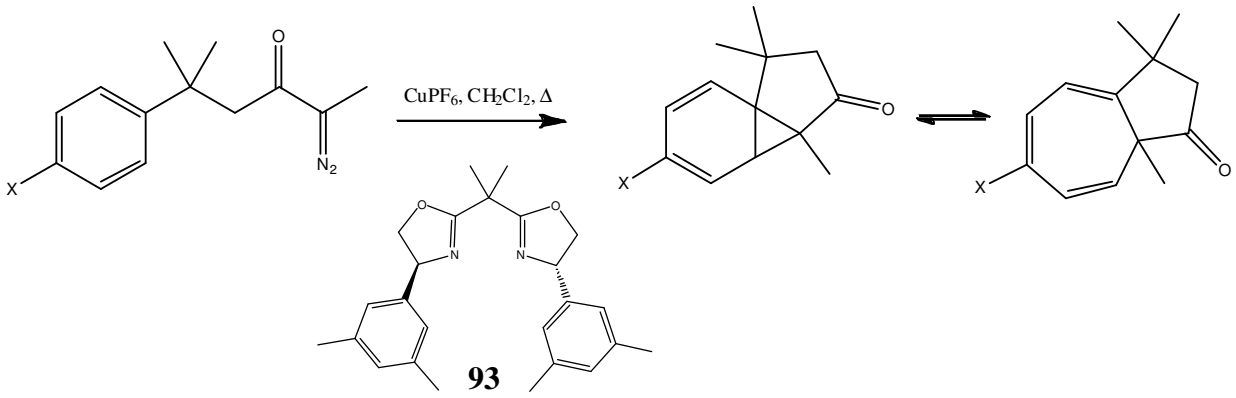
121 Ar = 3,4-dimethoxyphenyl 69% ee

Scheme 2.40

Kato reported modest enantioselectivities of 51 and 52% ee respectively when ligands **115** and **120** were applied to the asymmetric cyclisation-methoxycarbonylation reaction. Interestingly when the ligand **121** bearing the electron donating group on the aromatic ring was introduced, the enantioselectivity increased to 69% ee and when the reaction was carried out at −20°C an enantioselectivity of 76% ee was reported. This result clearly demonstrates the positive effect of having a more electron donating group on the phenyl ring of the bisoxazoline ligand.[104] There are no reports of this effect in diazocarbonyl chemistry.

Evans and co-workers also investigated the significant role of electronic effects on the enantioselectivity of a series of copper catalysed hetero Diels-Alder reactions.[101] They observed no significant differences in enantioselectivity when bisoxazoline ligands with electron poor or rich aryl moieties were applied, the contribution of electronic effects was not discounted. Evans highlighted the precedent for stereoselective processes in which dipole-dipole and Van der Waals attractions are implicated but are unaffected by perturbations in the π-donor capability of the phenyl group.[131,132]

Table 2.15 *Cyclisation of diazoketones* **37**-**40** *in the presence of the novel bisoxazoline ligand [(S,S)-3,5-di-Me-C_6H_3-Box]*-**93**



93

Entry	Diazoketone	X	Azulenone	$CuPF_6$- **93**[(*S*,*S*)-3,5-di-Me-C_6H_3-Box][a]			$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][a]		
				Eff (%)[b]	Yield (%)[c]	ee (%)[d]	Eff (%)[b]	Yield (%)[c]	ee (%)[d]
1	**37**	H	**88**	85	69	68[e]	79	74	78[f]
2	**38**	Me	**96**	80	65	73[e]	80	74	80[f]
3	**39**	Cl	**95**	80	68	71[e]	73	63	62[f]
4	**40**	F	**96**	90	71	51[e]	86	81	59[f]

a. Catalysts prepared *via* Method A.

b. Calculated by integration of the aromatic by-product signals against the azulenone in the ^{1}H NMR spectrum of the crude product.

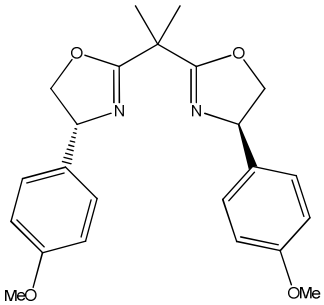
c. Yield after chromatography.

d. Calculated from chiral shift ^{1}H NMR experiments.

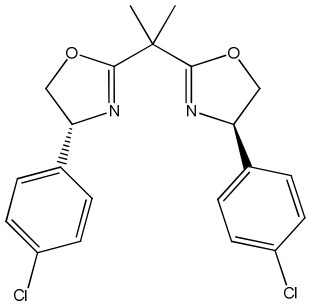
e. Major Enantiomer = (+).

f. Major Enantiomer = (−).

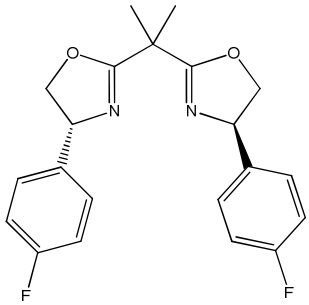
The aromatic addition of diazoketones **37**-**40** in the presence of the novel bisoxazoline ligand [(*S*,*S*)-3,5-di-Me-C_6H_3-Box]-**93** provided efficient reactions in moderate yields and generated good enantioselectivities (Table 2.15). Interestingly, the use of the 3,5-dimethyl substituted ligand **93** in the cyclisation of three of the four diazoketones **37**-**40** lead to a slight decrease in the enantioselectivity compared to those obtained with the phenyl substituted ligand **75** (Table 2.14), while a slightly increased asymmetric induction was observed with the novel ligand **93** in the cyclisation of diazoketone **39**. These results are in line with earlier results reported by O'Keeffe where ligands **165**, **166** and **167** (Figure 2.18) resulted in very similar asymmetric induction to those achieved with the unsubstituted ligand **75**. Thus O'Keeffe had demonstrated electronic effects had minimal impact on enantiocontrol; this study indicates steric effects are equally insignificant.[41]



165



166



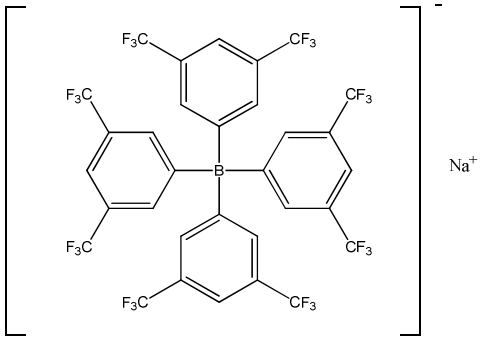
167

Figure 2.18

2.6.4.2 Enhancement of enantioselection by variation of the counterion

Since Evans' report in 1991 that the variation of counterion had a significant impact on both efficiency and enantioselectivity of asymmetric cyclopropanation catalysed by copper bisoxazoline complexes,[99] there have been many reports of the counterion influencing enantioselectivity in copper bisoxazoline catalysed asymmetric cyclopropanation reactions.[133-136] However, there has been no discussion of variation of the counterion affecting enantioselectivity in intramolecular carbenoid addition to aromatic rings.

Zhou developed the first highly enantioselective catalytic insertion of α-diazoesters into N-H bonds by using copper complexes of chiral spiro bisoxazoline ligands as catalysts.[137] Zhou reported that the nature of the counterions of the catalysts significantly influenced the enantioselectivity and the reactivity of the catalyst. CuOTf gave the insertion product in only 5% ee, which showed that the smaller and more coordinating OTf^- ion is evidently inferior to the PF_6^- ion, which gave the product in a 43% ee. Interestingly, by employing the larger non-coordinating ion tetrakis[3,5-bis(trifluromethyl)phenyl]borate ($BARF^-$) in the reaction, enantioselectivities increased up to 98% ee. NaBARF has also been employed in a wide variety of transformations such as intermolecular cyclopropanation, asymmetric hydrogenation of olefins and hydrovinylation reactions.[138-141] $BARF^-$ is a large non-coordinating anion, and shows excellent solubility in organic solvents (Figure 2.19). It is believed that the weakly coordinating nature of NaBARF **168** is due to steric effects.[142]

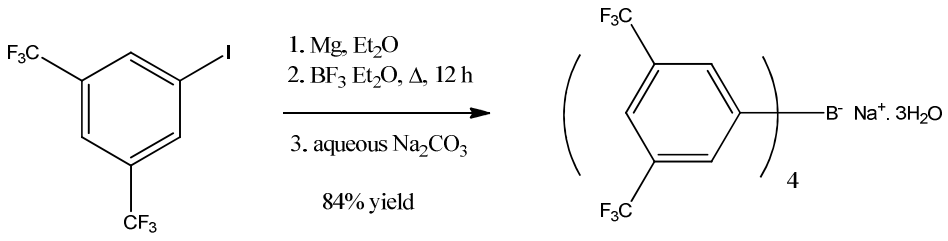


168

Figure 2.19

Zhou also reported the use of NaBARF **168** to enhance enantioselectivities in copper catalysed insertion of carbenoids into Si-H bonds and the O-H insertion into phenols and water.[143,144] In 2008, Zhou described the highly efficient copper catalysed enantioselective ring opening of oxa-bicylic alkenes with Grignard reagents using chiral spiro phosphine ligands and NaBARF **168** as an additive. He stated that the high activity of the catalyst may be rationalized by the generation of a more active cationic species through the exchange of the counterion of the catalyst to the noncoordinating anion $BARF^-$.[145] The presence of NaBARF **168** has also been reported to result in enhanced efficiency and selectivity in [3+2] cycloadditions of α-aryldiazoesters with terminal alkenes,[146] and in another instance, altered efficiency and regioselectivity in intramolecular C-H insertion processes with ethyl diazoacetate.[147] With these reports in mind, it was decided to explore the impact on the aromatic addition process by using NaBARF **168** as an additive to a catalytic mixture consisting of CuCl and a bisoxazoline ligand. Subsequently Flynn and Slattery extended the use of NaBARF in copper mediated reactions of α-diazocarbonyl compounds in our research team.[148,149]

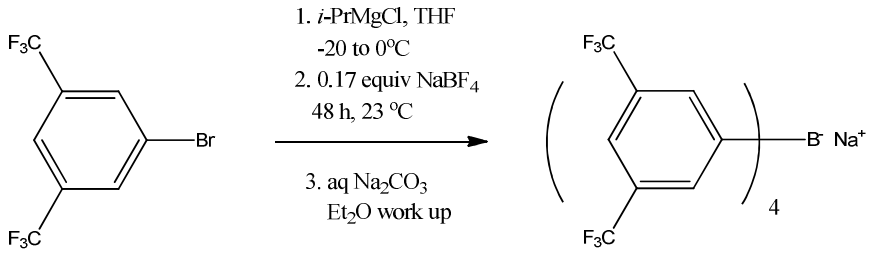
The synthesis of tetraarylborate ($BARF^-$) as its sodium salt was first reported by Kobayashi in 1984 (Scheme 2.41).[150] This counterion was of interest to them as they found that the strongly electron withdrawing effect caused by the trifluoromethyl substituents would suppress any electrophilic attack by a proton on the phenyl ring carbon adjacent to the boron, therefore increasing its stability against acids. Brookhart also prepared NaBARF **168** using a modification of Kobayashi's procedure.[151]



168

Scheme 2.41

While Zhou also prepared NaBARF **168** by using the procedure developed by Kobayashi,[150] an earlier report by Leazer highlighted the associated risk with this synthetic procedure.[152] During the course of Leazer's work he stated that trifluoromethylphenyl Grignard reagents can detonate upon moderate heating or loss of solvent contact. Pfizer scientists reported a violent explosion of 3-(trifluoromethyl)phenylmagnesium bromide resulting in extensive laboratory damage.[153] Another report mentioned the detonation of 4-(trifluoromethyl)phenylmagnesium bromide resulting in destruction of a factory and loss of life.[154] Leazer instead recommended an alternative procedure reported by Bergman.[155] Bergman used a safe, convenient preparation of NaBARF **168** utilising a magnesium bromine exchange reaction in the absence of metallic magnesium. The procedure designed by Bergman was used to prepare NaBARF **168** is this work (Scheme 2.42)



34%

168

Scheme 2.42

When the copper catalysed transformations were undertaken, NaBARF **168** was calculated as its anhydrous form (6 mol %). In retrospect it was recognised that this material was hydroscopic and therefore it was likely that the NaBARF **168** employed was either partially or fully hydrated, therefore the amount added was slightly less than that calculated. Furthermore, the degree of hydration may have changed over time with older samples likely to have been more hydrated. The yield was calculated for NaBARF **168** in its anhydrous form. NaBARF **168** was stored under nitrogen at −20 °C.

A detailed study was undertaken using four diazoketones **37**-**40** with variation of the copper salt, ligand and with and without the addition of NaBARF **168** (Table 2.16).

Table 2.16 *Copper catalysed intramolecular Buchner reaction of diazoketones in the presence of NaBARF*

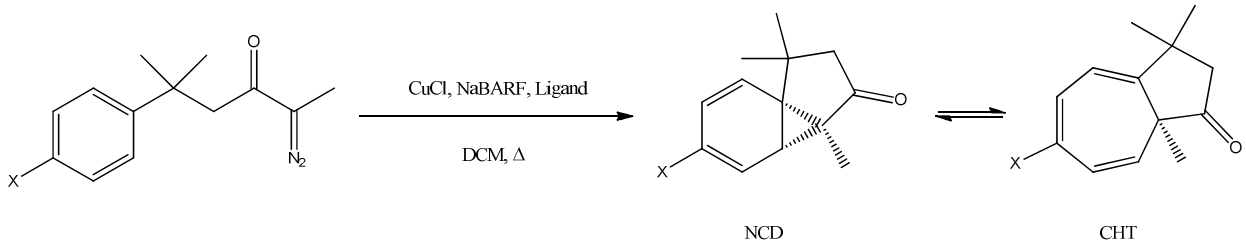
Entry	Diazoketone[a]	X	Azulenone	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box][b]			CuCl-NaBARF-**74**[(*S*,*S*)-*t*-Bu-Box][b]			CuCl-NaBARF-**89**[(4*R*,5*S*)-*tetra*-Ph-Box][b]			CuCl-NaBARF-**91**[(*R*,*R*)-Bn-Box][b]		
				Eff (%)[c]	Yield (%)[d]	ee (%)[e]	Eff (%)[c]	Yield (%)[d]	ee (%)[e]	Eff (%)[c]	Yield (%)[d]	ee (%)[e]	Eff (%)[c]	Yield (%)[d]	ee (%)[e]
1	**37**	H	**88**	72	52	78[f]	60	48	24[g]	71	52	73[f]	-	-	-
2	**38**	Me	**96**	62	46	80[f]	75i	50	27[g]	55	49	70[f]	58	42	30[f]
3	**39**	Cl	**95**	65	54	78[f]	47[h]	35	23[g]	62	44	68[f]	66	47	24[f]
4	**40**	F	**94**	54[j]	51	72[f]	34[k]	30	18[g]	65	48	72[f]	70[l]	47	32[f]

a. Diazoketones were added in an ethereal solution over 2 hours. Reaction was complete by TLC following an additional hour under reflux.
b. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20°C before substrate was added.
c. Efficiency refers to the percentage azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude product.
d. Yield of isolated product after flash chromatography.
e. Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
f. Major Enantiomer = (+).
g. Major Enantiomer = (−).
h. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **106** (6%) and starting diazoketone **39** (18%).
i. The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown impurity (18%). Signals were observed at δ_H (300 MHz) 0.86 (6H, s), 1.44 (3H, s), 1.80 (1H, s), 2.30 (2H, s), 3.87-3.93 (1H, m), 4.20-4.37 (2H, m).
j. The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown impurity (10%). Signals were observed at δ_H (400 MHz): 1.32 (6H, s), 1.99 (3H, s), 4.12 (3H, t, *J* 8,3), 4.55 (2H, t, *J* 10.1), 4.96 (3H, dd, *J* 10.1, *J* 8.0).
k. The ^{1}H NMR spectrum of the crude reaction mixture contained an impurity (15%). Signals were consistent with the diketone impurity. Signals were observed at δ_H (300 MHz): 1.45 (6H, s), 2.11 (3H, s), 3.10 (2H, s).
l. The ^{1}H NMR spectrum of the crude reaction mixture contained an impurity (3%), the signals were consistent with the diketone impurity. Signals were observed at δ_H (300 MHz): 1.43 (6H, s), 2.05 (3H ,s), 3.08 (2H, s).

Table *Continued*

Entry	Diazoketone[a]	X	Azulenone	CuCl-**75**[(*R*,*R*)-Ph-Box][b]			$CuPF_6$-NaBARF-**75**[(*R*,*R*)-Ph-Box][c]			CuOTf-NaBARF-**75**[(*R*,*R*)-Ph-Box][d]		
				Eff (%)[e]	Yield (%)[f]	ee (%)[g]	Eff (%)[e]	Yield (%)[f]	ee (%)[g]	Eff (%)[e]	Yield (%)[f]	ee (%)[g]
1	**37**	H	**88**	37[h]	31	37[i]	-	-	-	-	-	-
2	**38**	Me	**96**	79[j]	45	44[i]	-	-	-	-	-	-
3	**39**	Cl	**95**	66[k]	49	0[i]	67[l]	43	72[i]	74	56[m]	77[i]
4	**40**	F	**94**	-[n]	-[n]	-[n]	-	-	-	-	-	-

a. Diazoketones were added in an ether solution over 2 hours. Reaction was complete by TLC following an additional hour under reflux. For CuCl-**75**[(*R*,*R*)-Ph-Box] reaction was complete by TLC following an additional 16 hours under reflux.
b. The catalyst was prepared from 1.3:1 molar mixture of ligand: CuCl. Catalyst was stirred for 2 h at 20°C before substrate was added.
c. The catalyst was prepared from 5 mol% $CuPF_6$, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20°C before substrate was added. **Note:** $CuPF_6$ refers to $Cu(MeCN)_4PF_6$.
d. The catalyst was prepared from 5 mol% CuOTf, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20°C before substrate was added.
e. Efficiency refers to the percentage azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude product.
f. Yield of isolated product after flash chromatography.
g. Determined by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
h. The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown impurity (approx 18%). Signals were observed at δ_H (300 MHz) 0.86 (6H, s), 1.44 (3H, s), 1.80 (1H, s), 2.30 (2H, s), 3.87-3.93 (1H, m), 4.20-4.37 (2H, m).
i. Major Enantiomer = (−).
j. The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown impurity (approx 22%). Signals were observed at δ_H (400 MHz) 1.42-1.46 (3H, m), 2.25-2.33 (2H, m).
k. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **106** (5%).
l. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **106** (4%).
m. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **106** (3%).
n. Complex mixture of unidentifiable products.



37-**40** **88**, **94**-**96**

Scheme 2.43 *Copper catalysed intramolecular Buchner reaction of diazoketones* **37**-**40** *in the presence of NaBARF* **168**

For these reactions, the catalyst was prepared by stirring copper(I) chloride (5 mol%), bisoxazoline ligand (6 mol%) and NaBARF (6 mol%) in dichloromethane at room temperature for 2 hours prior to heating to reflux followed by dropwise addition of the diazoketone substrate based on the method reported by Zhou.[137,143,156] This is in contrast to the catalyst preparation discussed in Section 2.6.4, where a 1.3:1 molar mixture of bisoxazoline ligand and pre-prepared $[Cu(MeCN)_4]PF_6$ were heated in dichloromethane to reflux directly prior to the dropwise addition of the diazoketone without pre-stirring for 2 hours. In an earlier study, O'Keeffe noted very similar outcomes using SbF_6^-or PF_6^- as counterion, while in this work there were clear differences through use of $BARF^-$ and PF_6^- as counterions. The catalyst CuCl-ligand was prepared identically to CuCl-NaBARF-ligand catalyst.

As discussed in Section 2.6.4 for the $Cu[(MeCN)_4]PF_6$-ligand catalyst, aromatic addition reactions shown in Table 2.14 were complete by TLC once all the diazoketone was added. In contrast a decrease in reaction rate was observed for the CuCl-NaBARF-ligand catalysed processes. In these instances, reactions required additional heating beyond the end of the diazoketone addition to achieve complete transformation and were typically complete within 3 hours (1 h beyond addition) relative to reactions discussed in section 2.6.4 where reactions were complete once all the diazoketone was added over 1 hour. Use of the CuCl-**75** system required up to 18 hours (16 h beyond 2 h addition) for complete reaction of the diazoketone. A comparison of the reaction completion times for the catalyst systems $Cu(MeCN)_4]PF_6$-ligand, CuCl-NaBARF-ligand and CuCl-ligand as shown in Figure 2.21

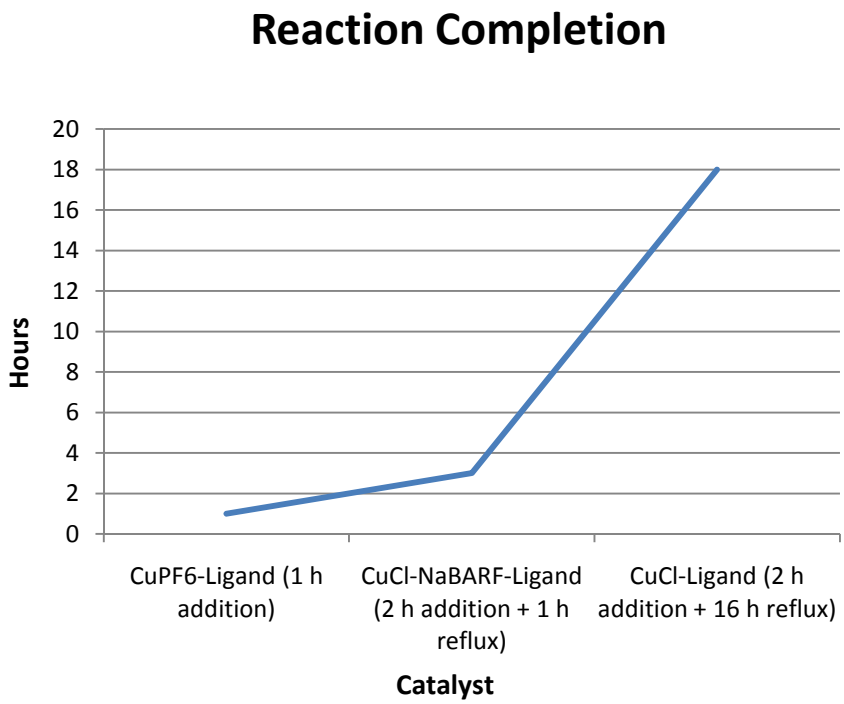


Figure 2.20 *Comparison of the reaction completion times for different catalysts with diazoketones* **37**-**40**

As shown in Table 2.16, the efficiencies and yields of the reaction were strongly influenced by the catalyst systems employed. For example, the efficiency in formation of azulenone **94** decreased from 86% for $CuPF_6$-**75**[(*R*,*R*)-Ph-Box] to 54% for the CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box] catalyst, and the yield decreased from 81% (Table 2.14, entry 6) to 51% (Table 2.16, entry 4). The differences in reaction efficiency when the catalysts $CuPF_6$-**75**[(*R*,*R*)-Ph-Box] and CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box] are employed is illustrated in Figure 2.22.

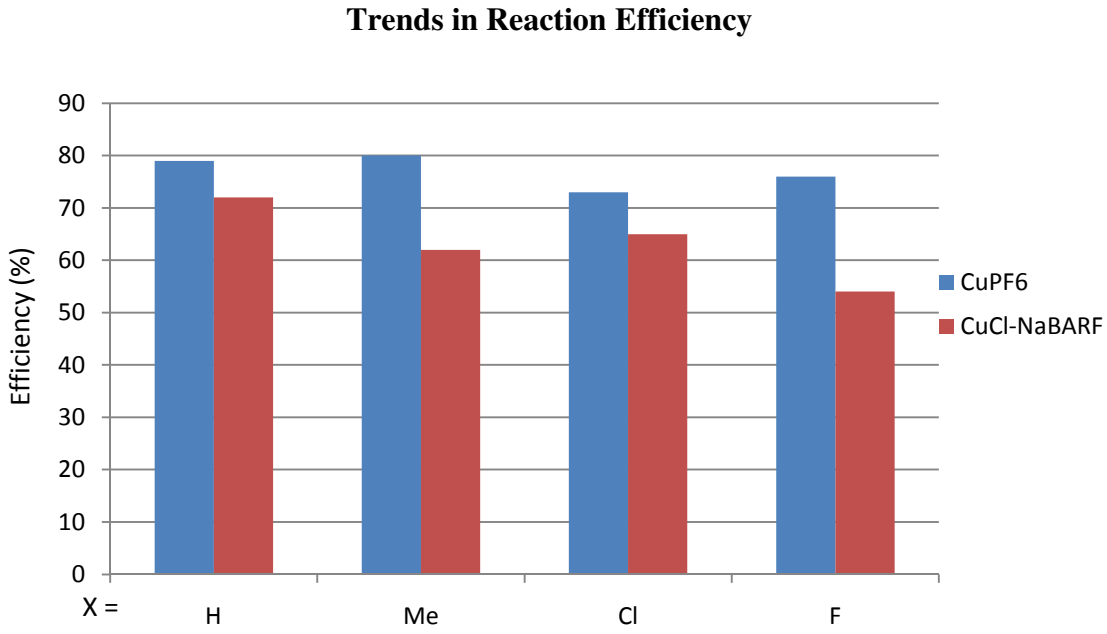


Figure 2.21 *Trends in reaction efficiency for ligand* (R,R)-*Ph-Box*-**75** *as determined from* ^{1}*H NMR spectra of the crude products*

A number of impurities were detected in the cyclisation products, including the diketone **107** (~6%). When the diazoketone **39** was cyclised with CuCl-NaBARF-**74**[(*S,S*)-*t*-Bu-Box], the ^{1}H NMR of the crude product contained small amounts of diketone **107** (6%), while signals for the unreacted diazoketone **39** were also seen (18%). For the diazoketone **39**, the ^{1}H NMR of the crude product contained the diketone **107** (~5%) when the CuCl-**75** catalyst was used. An unknown impurity (approx 18%) was observed in the ^{1}H NMR of the crude product when the diazoketone **38** was cyclised with the CuCl-NaBARF-**74**[(*S,S*)-*t*-Bu-Box]. The analogous unknown impurity was more commonly seen in the decomposition of diazoketone **40**. Separately, an impurity which had signals consistent with diketone formation was seen for the cyclisations using catalysts CuCl-NaBARF-**74**[(*S,S*)-*t*-Bu-Box] and CuCl-NaBARF-**91**[(*R,R*)-Bn-Box]. In the case of the 6-fluoro substituted diazoketone **40**, the azulenone was not detected in the reaction catalysed by CuCl-**75**[(*R,R*)-Ph-Box] and the ^{1}H NMR of the crude spectrum showed the presence of a complex mixture of unidentified products. It is important to note that the presence of the impurities described above had no impact on the

determination of enantioselectivities by chiral ^{1}H NMR. Possibly due to the longer reaction times, reaction efficiencies and yields in the CuCl-NaBARF-ligand catalysed reactions were generally modest. In the ^{1}H NMR spectrum of the crude reaction mixture of all reactions containing NaBARF, signals were present at δ_H 7.46 (s) and 7.64 (s), indicating the presence of BARF in the crude reaction. These peaks were not included in reaction efficiency calculations.

Critically, a variation in enantioselectivity was observed when the CuCl-NaBARF-ligand catalyst was employed. As shown in Table 2.14, when the cyclisations of diazoketones (**37**-**40**) were conducted using $[Cu(MeCN)_4]PF_6$-**75** catalyst, enantioselectivities of 56-80% ee were achieved with variation depending on the nature of the substituent on the aryl ring.[12] With the electron donating methyl substituent in diazoketone **38** increased enantioselectivity was seen, while with the electron withdrawing halogen substituent in diazoketones **39** and **40** there is a distinct decrease in enantioselectivity, and indeed, the effect is greater with the more electronegative fluoro substituent.

When the CuCl-NaBARF-**75** catalyst was applied the enantioselectivities observed in the cyclisations of diazoketones **39** and **40** were significantly and reproducibly increased (78% ee *vs* 62% ee for **95** and 72% ee *vs* 56% ee for **94**) while with the methyl substituted and unsubstituted derivatives **96** and **88**, there was no noticeable impact on enantioselection (Table 2.16). This increase in enantioselectivity observed for the electron withdrawing halogen substituents with the CuCl-NaBARF-**75** catalyst was also seen across a range of bisoxazoline ligands. For the CuCl-NaBARF-**89** catalyst, enantioselectivities observed in the cyclisations of diazoketones **39** were increased, in comparison to results obtained by O'Keeffe using $[Cu(MeCN)_4]PF_6$-**89** (68% ee vs 48% ee for **95**).

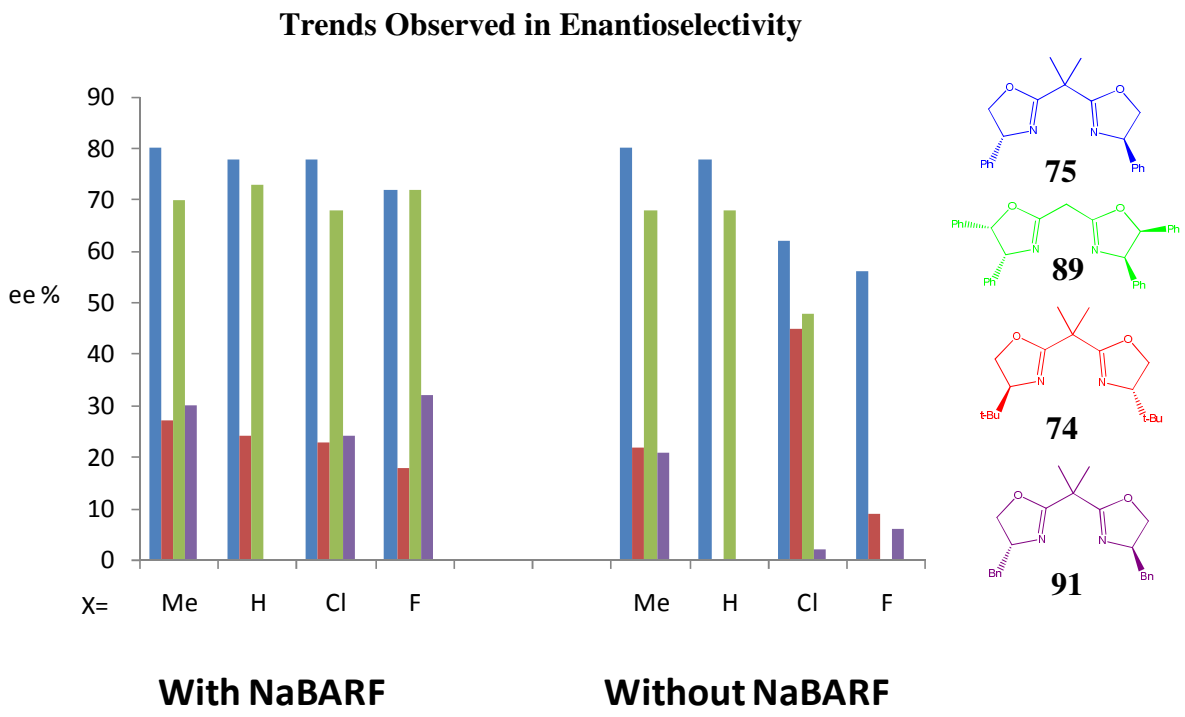


Figure 2.22 *Trends observed in enantioselectivity for the diazoketones* **37**-**40**

Importantly, to rule out the influence of the chloride anion on enantioselectivity and therefore confirm the influence of NaBARF, diazoketones (**37**-**40**) were cyclised with the catalyst CuCl-**75** in the absence of NaBARF. Interestingly, CuCl-**75** did not result in enhanced enantioselectivities as they were seen to dramatically decrease across the range of diazoketones. For example, diazoketone **39** cyclised with the CuCl-**75** catalyst resulted in a racemic sample being obtained, while when diazoketone **39** was cyclised with CuCl-NaBARF-**75** a 78% ee was observed. Other copper salts such as $Cu(OTf)_2$ and $CuPF_6$ were examined alongside NaBARF in the cyclisation of diazoketone **39**. However, no further positive impact on enantioselection was observed. Therefore, the use of CuCl as the copper source results in reduced enantioselectivities comparable to reactions employing $CuPF_6$.

Effects of Copper Salts on Enantioselectivity

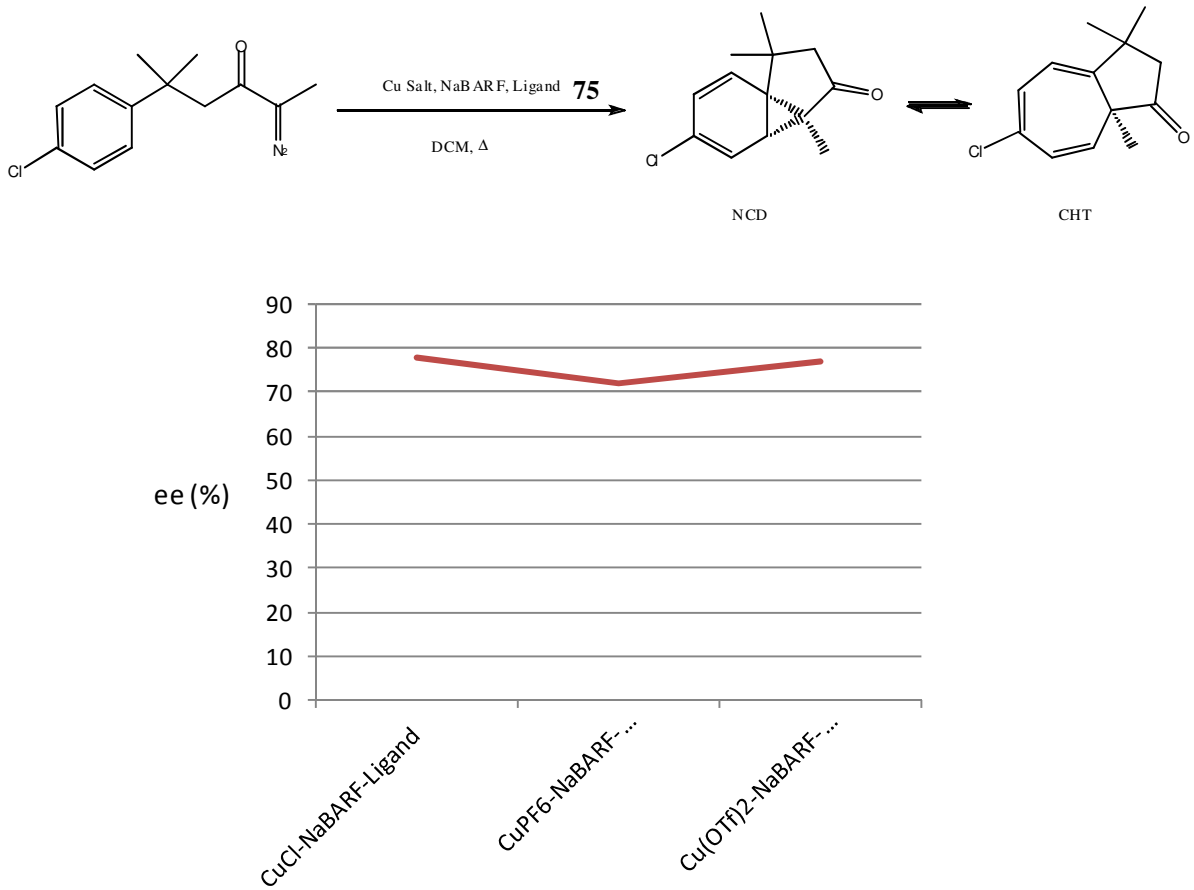


Figure 2.23 *Effect of different copper salts on the enantioselectivity of the cyclisation of diazoketone* **39** *using ligand* **75**

The use of the additive NaBARF results in dramatically increased enantioselectivities when used with CuCl and to a lesser extent with $CuPF_6$, Perhaps the most important observation is that, in the presence of NaBARF, enantioselectivities were restored for the diazoketones bearing the chloro and fluoro substituents on the ring (Figure 2.22).

Slattery also applied NaBARF to the asymmetric copper catalysed intramolecular C-H insertion reactions of α-diazo-β-keto sulfones.[149] Slattery pre-generated the catalyst species for 1.5 h prior to addition of the diazosulfone and observed an increase in enantioselectivity. Slattery conducted a number of experiments where the diazo compound and catalytic mixture were added directly to the reaction mixture prior to heating to reflux with significant detrimental effect on the enantioselectivity, but without a noticeable effect on reaction efficiency. Interestingly, this is in contrast to results obtained by Flynn where NaBARF was

used in the copper catalysed C-H insertion reactions of α-diazosulfones.[148] Flynn observed a longer reaction time and an increase in yield and enantioselectivity in comparison to results seen with the $[Cu(MeCN)_4]PF_6$-**75** catalyst. Flynn observed that preformed catalysts were not necessary to achieve the high enantiopurities associated with NaBARF. To further investigate the effect of pre-generating the catalytic species, diazoketone **39** was cyclised using the catalyst CuCl-NaBARF-**75** which was pre-formed under three different conditions (Table 2.17). In contrast to Slattery's observations, no difference in enantioselectivity was found for diazoketone **39** cyclised using CuCl-NaBARF-**75**, which was prestirred for 0, 2 and 24 hours respectively. There were slight variations in reaction efficiency and yield but it is evident that the most favorable preparation for high enantioselectivity is when the catalyst is pre-stirred for 2 hours. Interestingly, when the catalyst is not pre-stirred the reaction was found to be complete once all the diazoketone **39** was added.

Table 2.17 *Effect of catalyst complexation times on enantioselectivity of diazoketone* **39**

Entry	Catalyst	Method	Time (h)[a]	Eff (%)[b]	Yield (%)[c]	ee (%)[d]
1	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]	C	0[e]	68	44	68[f]
2	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]	C	2[g]	65	54	78[f]
3	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]	C	24[f]	69	32	74[f]

a. Number of hours catalyst was stirred before diazoketone was added.
b. Efficiency refers to the percentage azulenone formed relative to aromatic byproducts and is determined from the crude ^{1}H NMR spectrum of the product.
c. Yield of isolated product after flash chromatography.
d. Determined by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
e. Reaction was found to be complete once all the diazoketone was added.
f. Major Enantiomer = (–).
g. Diazoketone was added over 2 h and the reaction was found to be complete 1 hour after addition.

In conclusion, it is evident that the enantioselectivity of the intramolecular reaction of α-diazoketones can display sensitivity to the nature of the counterions present in the copper catalyst.

While Zhou had also described enhancement of enantioselection through the use of NaBARF, he had not commented on the mode of action of the additive.[137,143,144] To explore the mechanistic role of NaBARF, it was replaced in the Buchner reaction by a number of additives (Table 2.18).[157] As previously discussed, in the absence of the additives, little or no enantioselectivity is achieved using CuCl and the bisoxazoline ligand **75**. When $NaPF_6$ was added to the catalytic mixture in the cyclisation of diazoketones **37** and **39**, good enantioselectivities were obtained in each case and were comparable to those obtained with NaBARF. The use of $LiPF_6$ was less effective than $NaPF_6$, with the enantioselectivity decreasing to 54% ee. A decrease in enantioselection to 63% ee was observed when KBARF was used in the decomposition of diazoketone **39**, relative to when the cyclisation was carried out with NaBARF (78% ee). Interestingly, when the additives NaCl and NaI, were introduced to the reaction instead of NaBARF, enantioselectivities decreased to 0% ee. While the diazoketone was added over 2 hours to the catalytic mixture for both NaCl and NaI in line with each of the other reactions, interestingly for these reactions heating under reflux for up to 18 hours was required before completion. As previously discussed, these long reactions times were also seen when just CuCl and the bisoxazoline ligand were applied to the reaction.

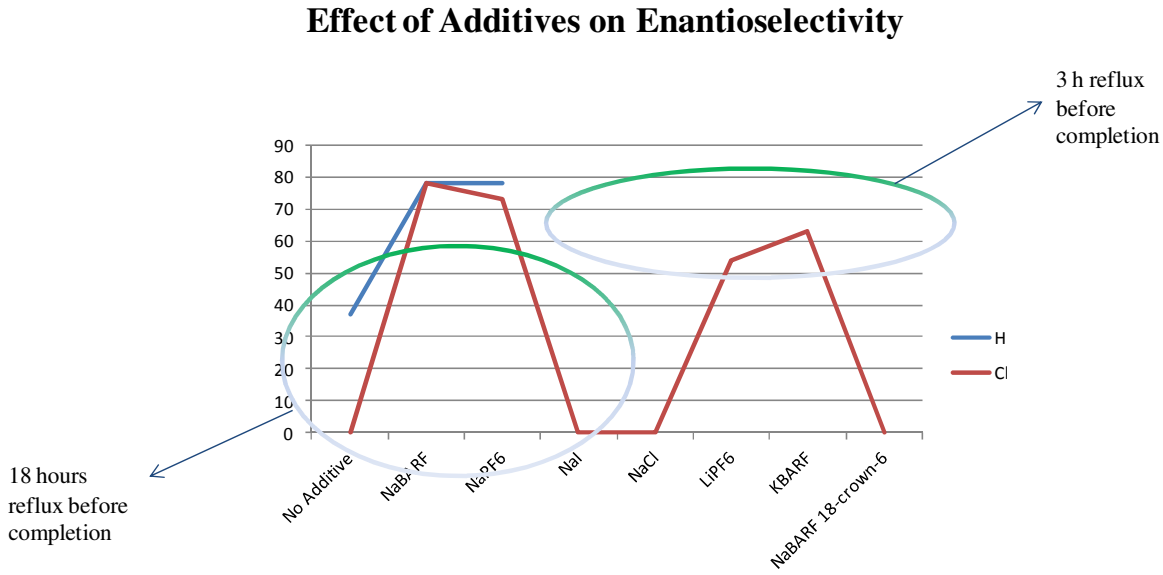
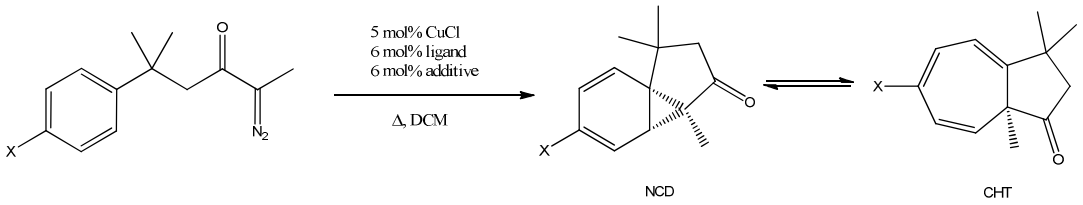


Figure 2.24 *Effect of different additives on the enantioselectivity of diazoketones* **37** *and* **39** *employing ligand* **75**

From these results it is feasible that the main role of these additives is to provide a "naked" alkali metal cation which may play a significant role in the formation of a highly efficient catalytic species. To explore this theory a reaction was conducted in the presence of NaBARF together with an equimolar amount of 18-crown-6. Significantly, the enantioselectivity reduced dramatically in the cyclisation of both diazoketones **37** and **39** in the presence of the crown ether catalyst, supporting the hypothesis for the critical role of the 'naked' alkali metal cation. In retrospect, use of 15-crown-5, which is a better complexing agent for sodium cations would probably have been more appropriate, but it is clear that even with the large 18-crown-6 the 'naked' sodium cation is effectively complexed to the crown. Further work in the research team based on these preliminary results has confirmed that the use of 15-crown-5 effectively reduces the enantioselectivity in comparable reactions.[157] It is believed that the likely role of the metal cationic species is chloride abstraction.[138,158,159]

Table 2.18 *Copper catalysed intramolecular Buchner reaction of diazoketones* **37** *and* **39** *in the presence of additives*



Entry	Catalyst	Diazoketone	X	Azulenone	Eff (%)[a]	Yield (%)[b]	ee (%)[c]
1	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]	**37**	H	**88**	72	52	78
2	CuCl-NaBARF-**75** [(*R*,*R*)-Ph-Box]	**39**	Cl	**95**	65	54	78
3	CuCl-**75** [(*R*,*R*)-Ph-Box]	**37**	H	**88**	37	31	37
4	CuCl-**75** [(*R*,*R*)-Ph-Box]	**39**	Cl	**95**	66	49	0
5	CuCl-$NaPF_6$-**75**[(*R*,*R*)-Ph-Box][d]	**37**	H	**88**	72	65	78
6	CuCl-$NaPF_6$-**75**[(*R*,*R*)-Ph-Box][d]	**39**	Cl	**95**	62	56	73

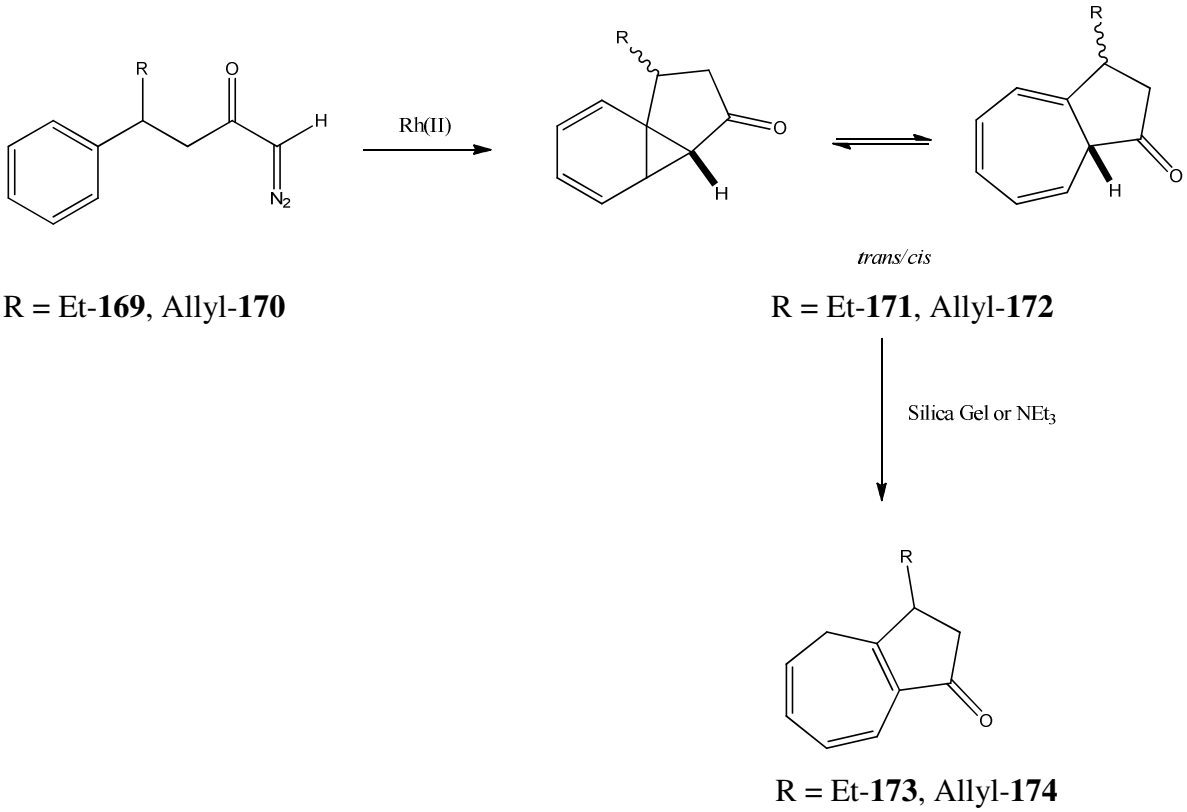
7	CuCl-NaI-**75**[(*R*,*R*)-Ph-Box][e]	**39**	Cl	**95**	58	44	0
8	CuCl-NaCl-**75**[(*R*,*R*)-Ph-Box][f]	**39**	Cl	**95**	43	38	0
9	CuCl-$LiPF_6$-**75**[(*R*,*R*)-Ph-Box][g]	**39**	Cl	**95**	73	66	54
10	CuCl-KBARF-**75**[(*R*,*R*)-Ph-Box][h]	**39**	Cl	**95**	72	65	63
11	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]-18-Crown-6[i]	**37**	H	**88**	50	46	39
12	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]-18-Crown-6[i]	**39**	Cl	**94**	51	47	0

a. Efficiency refers to the percentage azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude product.
b. Yield of isolated product after flash chromatography.
c. Determined by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
d. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% $NaPF_6$. Catalyst was stirred for 2 h at 20°C before substrate was added.
e. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaI. Catalyst was stirred for 2 h at 20°C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (12%).
f. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaCl. Catalyst was stirred for 2 h at 20°C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (15%).
g. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% $LiPF_6$. Catalyst was stirred for 2 h at 20°C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (7%).
h. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% KBARF. Catalyst was stirred for 2 h at 20°C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (4%).
i. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand, 6 mol% NaBARF and 6 mol% 18-crown-6. Catalyst was stirred for 2 h at 20°C before substrate was added.

2.6.5 Transition metal catalysed intramolecular aromatic addition of terminal α-diazoketones

The synthesis of azulenones *via* the intramolecular carbenoid addition of terminal α-diazoketones was first reported by both Julia and Scott (Scheme 2.2) and since has been reported by a number of other groups. [19,20,22,30,31,65,80,160,161] In fact the aromatic addition reaction has been more widely investigated with terminal diazoketones than with the internal diazoketones employed in this study.

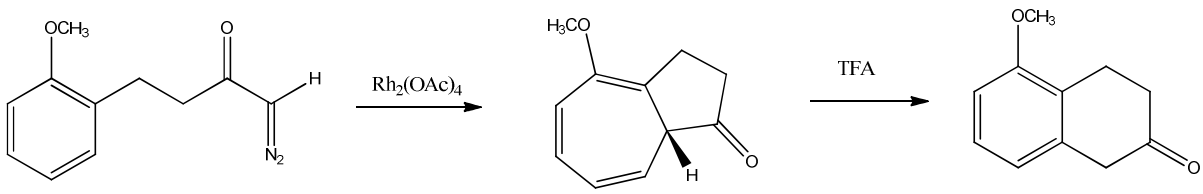
Within our group, Buckley applied a range of rhodium(II) complexes to investigate both the efficiency and diastereoselectivity of the aromatic addition reaction from β-substituted terminal α-diazoketones **169** and **170** (Scheme 2.44).[37]



Scheme 2.44

Upon attempted purification of the crude azulenones **171** and **172** *via* chromatography on silica gel, or treatment with triethylamine, the azulenones rearranged to form the conjugated cycloheptatrienes. This had previously been reported by Scott for the unsubstituted azulenone **8** (Scheme 2.2).

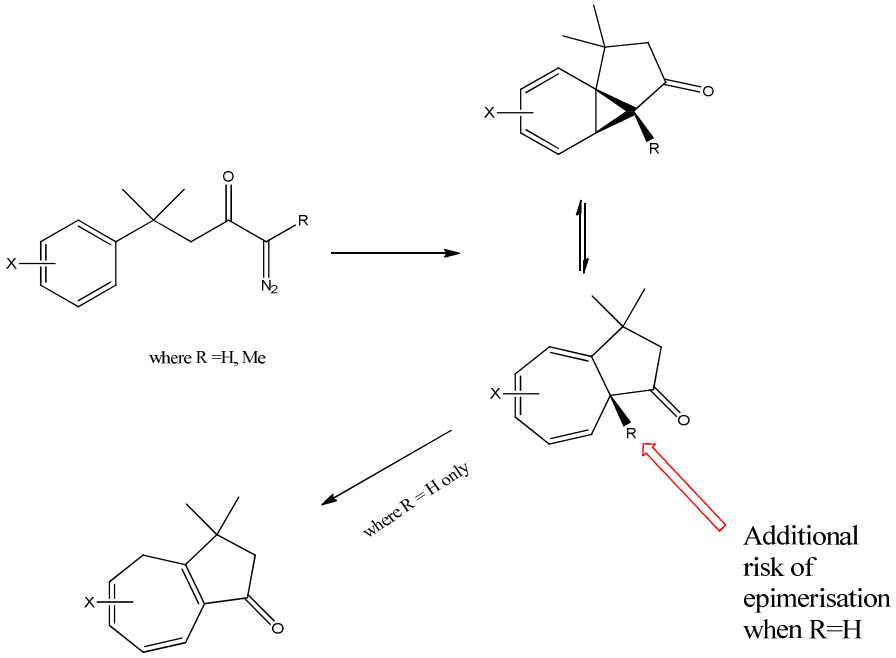
O'Leary also investigated the cyclisation of the terminal α-diazoketone **175** bearing a methoxy group at the ortho position of the aryl ring.[28] He reported that treating the crude azulenone **176** with trifluoroacetic acid resulted in the formation of the tetralone **177** (Scheme 2.45).



175 **176** **177**

Scheme 2.45

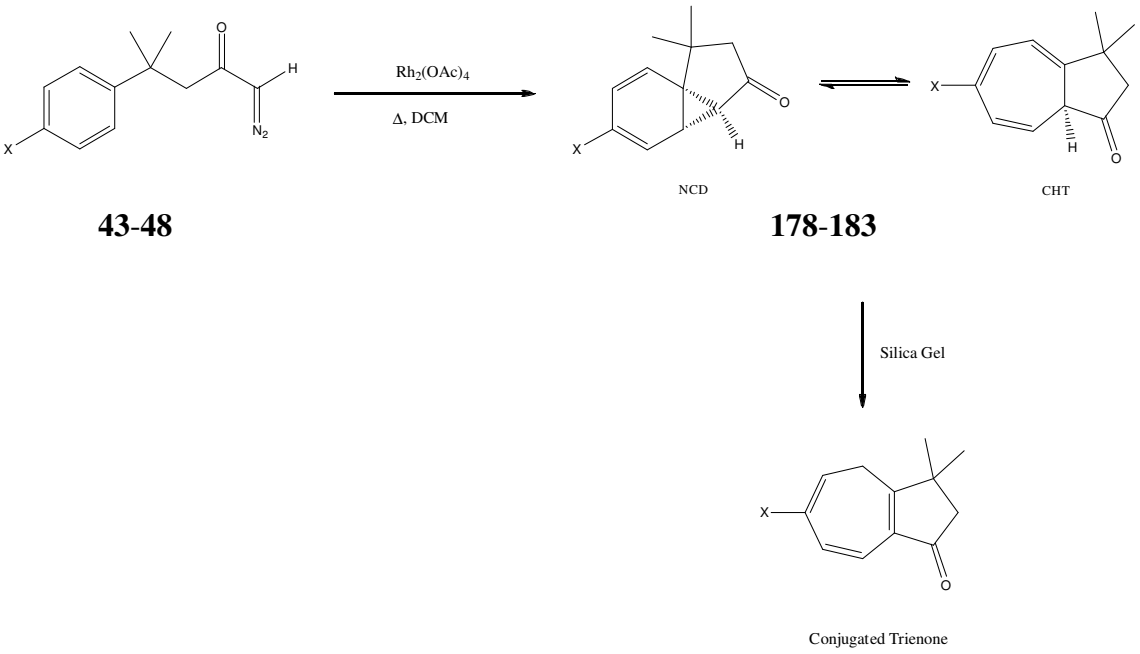
Having developed enantioselective aromatic addition processes with the internal diazoketones it was decided to explore use of these catalyst systems with a number of terminal diazoketones to establish if enantioselectivities could be demonstrated with a hydrogen at the bridgehead in place of the methyl group used to date. Due to the lability of azulenones such as **178**, **179** and **180**, determining enantiopurities in the azulenones was more challenging than with a bridgehead methyl group present. Furthermore potential for racemisation must be considered as in principle the bridgehead hydrogen can epimerise as illustrated in Scheme 2.46.



Scheme 2.46

In this work, the crude azulenone **178** along with the novel crude azulenones **179-181** were synthesised by the intramolecular aromatic addition of terminal α-diazoketones as illustrated below (Table 2.19). As discussed in Section 2.6.2, a number of precautions were undertaken to prevent the formation of unwanted side products forming during the Buchner reaction. Similar to the cyclisation of internal diazoketones, the reactions were set up as per Method A (Section 2.6.2).

Table 2.19 *$Rh_2(OAc)_4$ catalysed aromatic addition of terminal α-diazoketones* **43-48**.



43-48 **178-183**

Entry	Diazoketone	X	Catalyst[a]	Azulenone	Eff (%)[b]	Crude Yield (%)	Trienone	Purified Yield (%)[c]
1	**43**	H	$Rh_2(OAc)_4$	**178**	84	95	**184**	54
2	**44**	Me	$Rh_2(OAc)_4$	**179**	93	98	**185**	64
3	**45**	Cl	$Rh_2(OAc)_4$	**180**	66	97	**186**	60
4	**46**	F	$Rh_2(OAc)_4$	**181**	–[d]	97	**187**	54[e]
5	**47**	3,5-$(Me)_2$	$Rh_2(OAc)_4$	**182**	–	–	**188**	–[f]

6	**48**	3,4,5-$(Me)_3$	$Rh_2(OAc)_4$	**183**	–	–	–	–[f]

a. < 1 mol% of $Rh_2(OAc)_4$.
b. Efficiency refers to the percentage azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude product.
c. Purified by flash chromatography (EtOAc: Hexane, 20:80).
d. The ^{1}H NMR spectrum of the crude reaction mixture contained unidentifiable peaks (46%). Signals were observed at: δ_H (300 MHz) 2.36 (1H, s), 7.16-7.28 (2H, m). Efficiency, usually measured for azulenone signals in relation to aromatic by-products, was 81%.
e. The ^{1}H NMR spectrum of the purified trienone contained an unknown impurity (50%). Signals were observed at: δ_H (300 MHz) 1.43 (6H, s), 2.56 (1H, s), 6.98-7.52 (3H, m); δ_C (75.5 MHz) 28.4, 50.1, 130.0, 131.6, 134.6, 137.3, 140.8, 145.9, 157.4, 160.6, 172.3, 177.6, 177.7, 187.6, 204.5.
f. A ^{1}H NMR spectrum of the crude reaction mixture showed a complex mixture of unidentifiable products and did not contain any signals which could be attributed to the starting diazoketone or azulenone.

Accordingly the diazoketones **43**-**45** were explored to enable comparison with the corresponding internal diazoketones (section 2.5.3). Initially the $Rh_2(OAc)_4$ catalysed cyclisations of each of the terminal α-diazoketones was undertaken to generate reference samples of the racemic azulenones as summarized in Table 2.19.

Crude azulenones **178**-**181** were recovered as dark green oils due to the presence of residual rhodium. They were unstable and were seen to decompose to a dark brown oil if left at room temperature over a short period of time (typically one day). In general, the reactions were found to be complete once all the diazoketone was added over 1 hour. The cyclisations of terminal α-diazoketones **43**-**45** were very efficient reactions and efficiencies were comparable to those observed in the cyclisation of internal α-diazoketones. In particular, the efficient (93%) cyclisation of the electron donating *para*-methyl substituted diazoketone **44** is noteworthy, while the aromatic addition of the electron withdrawing *para*-chloro substituted diazoketone **45** proceeded with a poorer efficiency of 66% as had been seen in the analogous internal diazoketone **39** (Table 2.14, entry 3). Notably the efficiency of the aromatic addition in the presence of the fluorine substituent was substantially reduced with a significant impurity present following the rhodium catalysed reaction. Reduction in the efficiency of the aromatic addition in the presence of the electron withdrawing chlorine and fluorine substituents had been observed by Buckley and McNamara and is readily rationalised for the electrophilic carbene addition to the aromatic ring.[24,37,42]

In the IR spectra of the crude azulenones **178**-**180** there was only one carbonyl stretch at ~1750 cm^{-1}. In comparison, during the aromatic addition of internal α-diazoketones two bands were seen, O'Leary stated that the IR stretch at 1710-1716 cm^{-1} is due to the carbonyl of the NCD tautomer and the IR band at 1740-1753 cm^{-1} is due to the carbonyl stretch of the CHT tautomer.[28] This indicates that crude azulenones **178**-**180** formed exist solely or predominantly as the CHT tautomer.

The $C(2)H_2$ signals in the ^1H NMR of the crude azulenones coupled to the C(8a)H signal to form an ABX system. The C(8a)H signal was observed as a broad doublet with unresolved fine splitting in the X of the ABX system see for example azulenone **179** in Figure 2.25. In contrast, for the azulenones prepared from internal α-diazoketones, the $C(2)H_2$ signals were observed as an AB system.

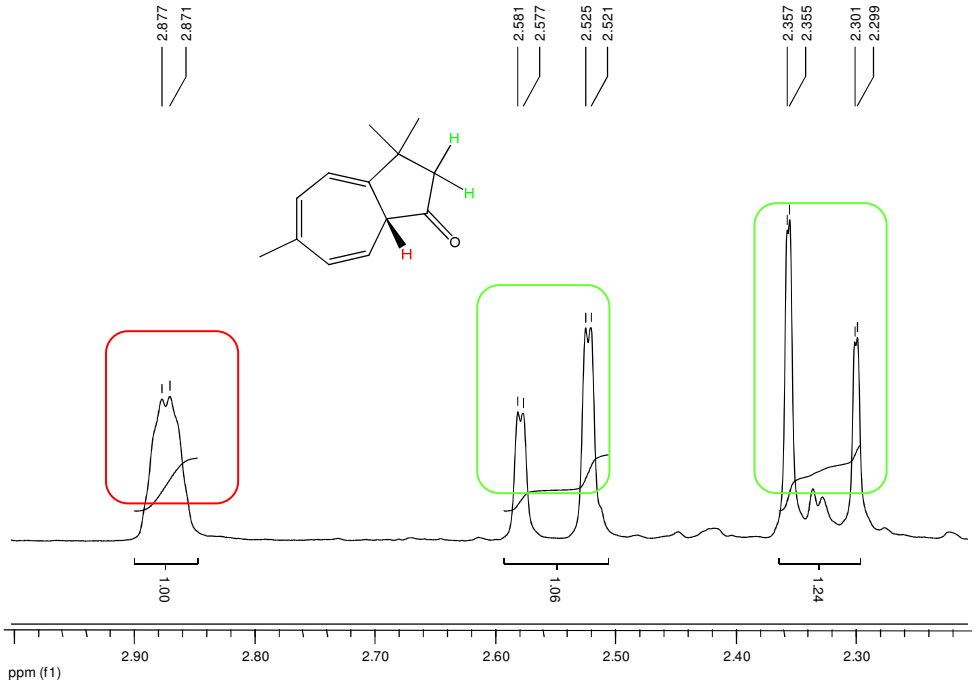
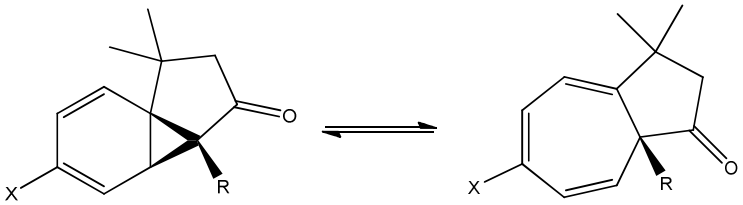


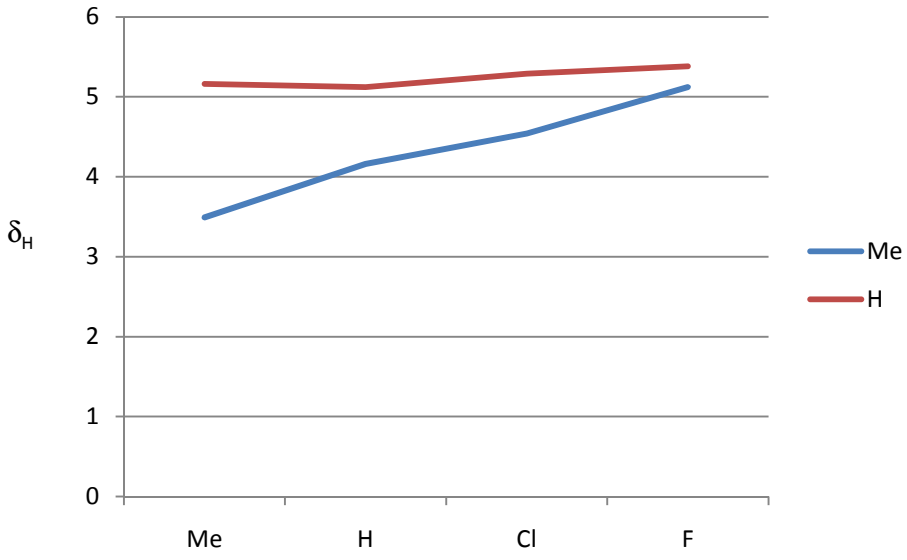
Figure 2.25 *ABX system in the ^1H NMR of azulenone* **179**

The C(8)H signal was observed as a doublet of doublets at δ_H 5.16-5.29 ppm for azulenones **178**-**180**. For the more electron withdrawing substituted azulenone **181**, the C(8)H signal existed as a multiplet due to coupling to ^{19}F and was positioned further downfield at δ_H 5.38-5.45 ppm. The position of the C(8)H signal is consistent with each of the azulenones **178**-**180** existing predominantly as the cycloheptatriene tautomers. The

key ^{1}H NMR data for the C(8)H signals in the azulenones both with and without the bridgehead methyl group are summarized in Table 2.20. With azulenones **178**-**180** it is very clear that in the absence of the bridgehead methyl group, the position of tautomeric equilibrium lies almost entirely on the side of the CHT tautomer, with little or no sensitivity to the nature of the substituent X. In contrast, in the presence of the bridgehead methyl group, there is a substantial shift towards the NCD tautomer, with a very strong influence evident when the electronic properties of the substituent are varied.

Table 2.20 *Comparison of the ^{1}H NMR C(8)H signals for the azulenones formed from both internal and terminal diazoketones*





		R=Me		R=H
X	Azulenone	$\delta_{H\text{-}8}$ ppm[a]	Azulenone	$\delta_{H\text{-}8}$ ppm[b]
H	**88**	4.16, d, *J* 8.1	**178**	5.12, dd, *J* 9.3, 4.0

Me	**96**	3.49, d, *J* 6.9	**179**	5.16, dd, *J* 9.5, 4.1
Cl	**95**	4.54, d, *J* 9.0	**180**	5.29, dd, *J* 9.7, 4.4
F	**94**	5.12, dd, *J* 10.0, 5.1	**181**	5.38-5.45, m

a. Obtained from the ^{1}H NMR spectrum of the pure azulenone.

b. Obtained from the ^{1}H NMR spectrum of the crude azulenone.

While diazoketones **47** and **48** reacted quickly on exposure to rhodium acetate, in both cases the ^{1}H NMR spectra of the crude products indicated the presence of a complex mixture of unidentifiable products. It is likely that the azulenones **182** and **183** are formed but are labile under the reaction conditions. As discussed later in section 2.6.5.2, conjugated trienone **188** was recovered from the reaction of diazoketone **47** with PTAD trapping, thereby supporting this proposal.

Though when the crude azulenones **178**-**181** were initially isolated as dark green oils, when purified by flash chromatography on silica gel an immediate colour change to yellow could be seen. The ^{1}H NMR spectra of the purified products showed complete rearrangement to the conjugated trienones **184**-**187**. The formation of the conjugated trienones was confirmed by IR spectroscopy where the characteristic carbonyl stretch had shifted from ν_{max} 1750 cm^{-1} (C=O) to ν_{max} 1704 cm^{-1} (C=O). Also the conjugated trienone **184** was characterised by the disappearance of the C(8a)H signal and the presence of the C(4)H$_2$ signal at δ_H 2.72 ppm [2H, d, *J* 6.6] and the C(5)H signal at δ_H 5.40 ppm [1H, ddd (appears as a dt), *J* 9.7, 6.5, 6.5] (see for example **184** in Figure 2.26).

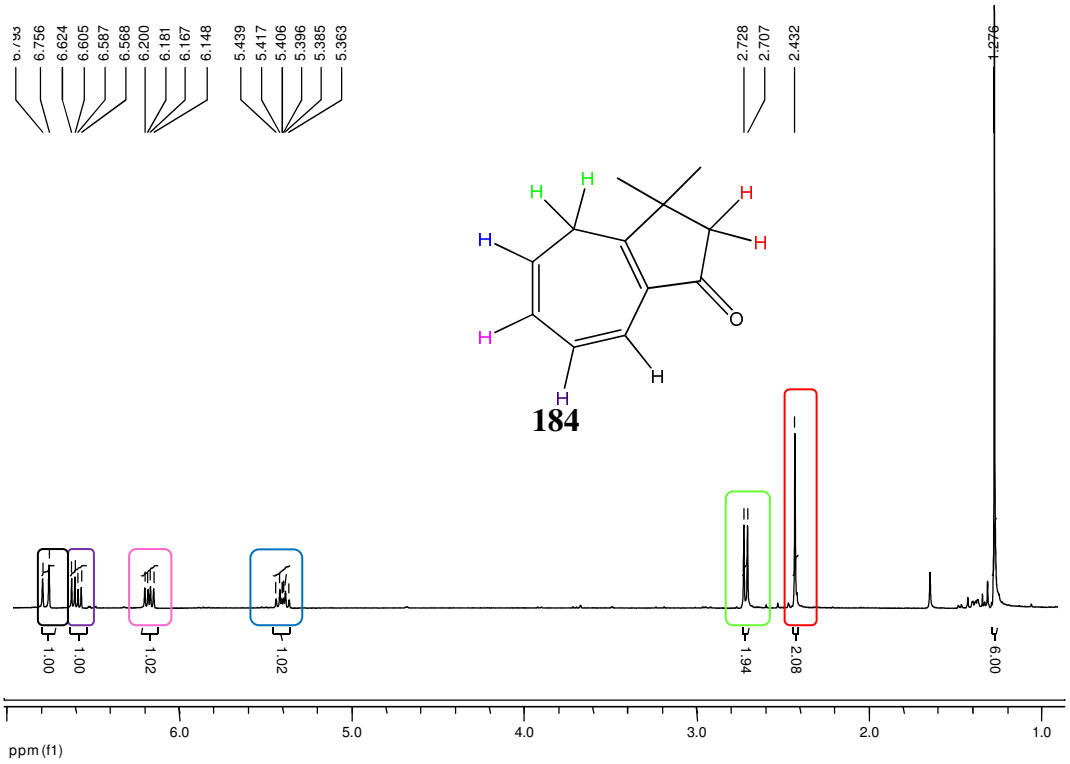


Figure 2.26 *^{1}H NMR spectrum of the pure conjugated trienone* **184**

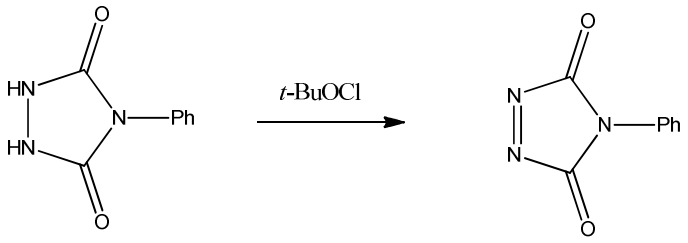
However as chromatographic purification of the azulenones was not possible, use of Eu-(hfc)$_3$ with the crude azulenones was explored to establish if the signals for the enantiomers could be resolved without chromatographic purification. However, the azulenone formed was too labile and decomposed to a complex mixture of unidentified products.

To prevent the formation of the conjugated trienones **184**-**187** during purification on silica gel, alternative methods of purification were examined. A solution of the crude azulenones were filtered on different occasions through silica gel, basic alumina, neutral alumina and Celite® but in all cases complete formation of the conjugated trienone was observed, highlighting the lability of these azulenones. As loss of the stereogenic center results occurs during the trienone rearrangement, it was essential to develop a method for determination of enantiopurity in the crude azulenones, thereby avoiding shift of the double bond into conjugation.

In conclusion, direct determination of enantiopurity in the cyclisation of diazoketones **43**-**45** was unlikely to be achieved. Accordingly, trapping of the labile azulenones **178**-**180** to form a more stable product was explored with a view to determining enantiopurity.

2.6.5.1 Preparation of PTAD cycloadducts

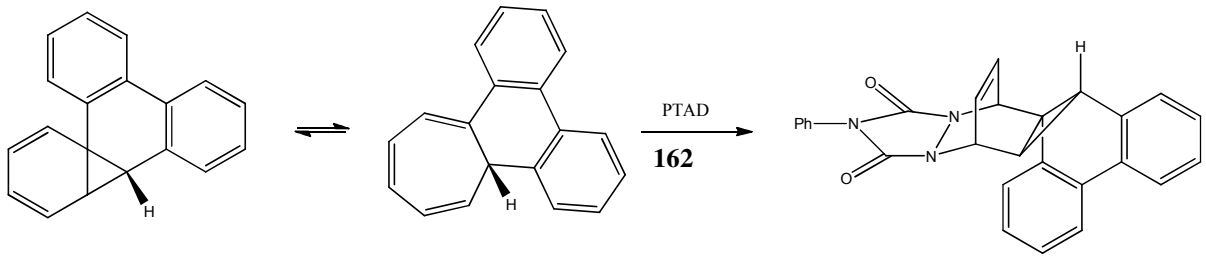
The use of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) **162** as a dienophile in Diels-Alder cycloaddition reactions has been extensively studied.[162-169] Preparation of the high yielding dienophile **162** by oxidation of 4-phenyl urazole **189** with *t*-butyl hypochlorite was first reported by Cookson (Scheme 2.47).[170]



189 **162**

Scheme 2.47

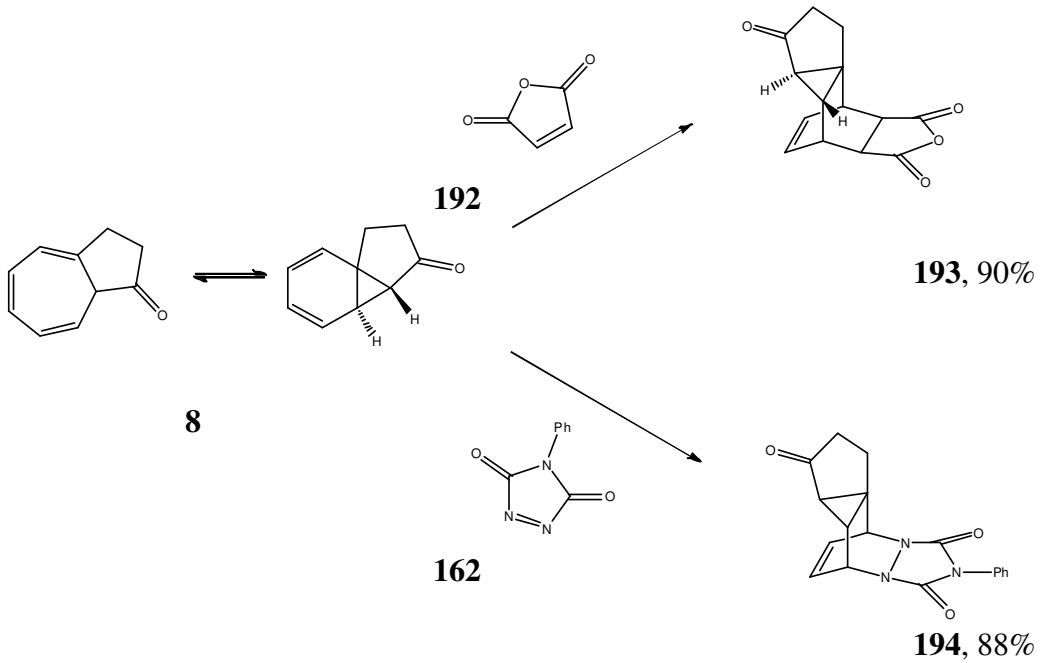
Adam was the first to report the use of PTAD to selectively trap the norcaradiene (NCD) tautomer of the intramolecular Buchner reaction.[165] Subsequently Fischer,[171] Saba[172], Moody[74] and Maguire[37,40,42] have all investigated such transformations. Fischer demonstrated that PTAD **162** reacts exclusively with the NCD tautomer of the equilibrating *bis*-norcaradiene **190** to give the cycloadduct **191** as the only product (Scheme 2.48). The structure of the cycloadduct **191** was confirmed unequivocally by X-ray crystallography.



NCD **190** CHT **191**

Scheme 2.48

In 2007, Balci described the [4+2] cycloaddition of maleic anhydride **192** and PTAD **162** with the azulenone **8** to yield the norcaradiene derived cycloadducts **193** and **194** in excellent yields (Scheme 2.49).[173] While the azulenone derived from the intramolecular Buchner reaction exists as two rapidly equilibrating tautomers (norcaradiene and cycloheptatriene), for azulenone **8** the cycloheptatriene is known to predominate; however in Balci's work only the norcaradiene derived adduct was isolated. Work within our laboratory has further confirmed that for the equilibrating norcaradiene (NCD) and cycloheptatriene (CHT) systems, PTAD effectively traps the norcaradiene tautomer only.[28,37,39,40,42]



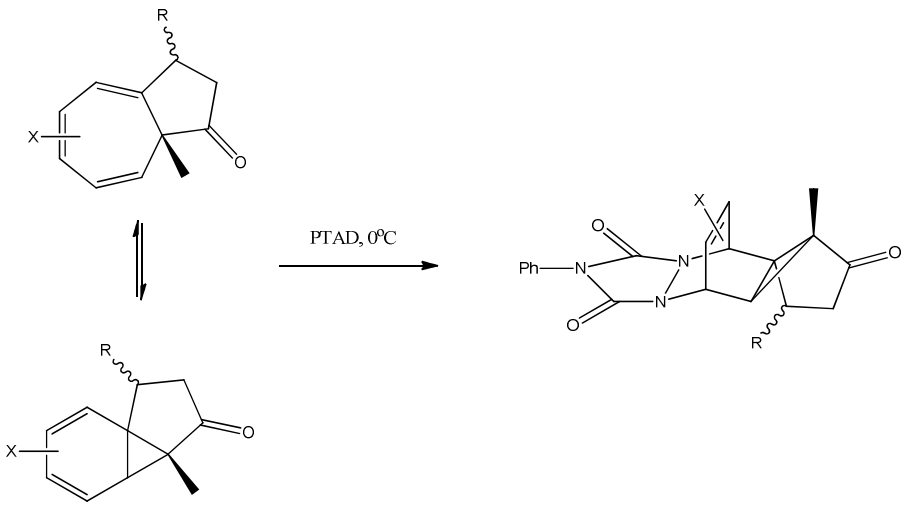
Scheme 2.49

The primary objective of using PTAD **162** is this work was to trap the crude azulenones formed by the intramolecular carbenoid addition of terminal α-diazoketones to give stable cycloadducts, thereby avoiding the rearrangement to the conjugated trienone.

2.6.5.2 Preparation of PTAD cycloadducts from azulenones derived from terminal α-diazoketones

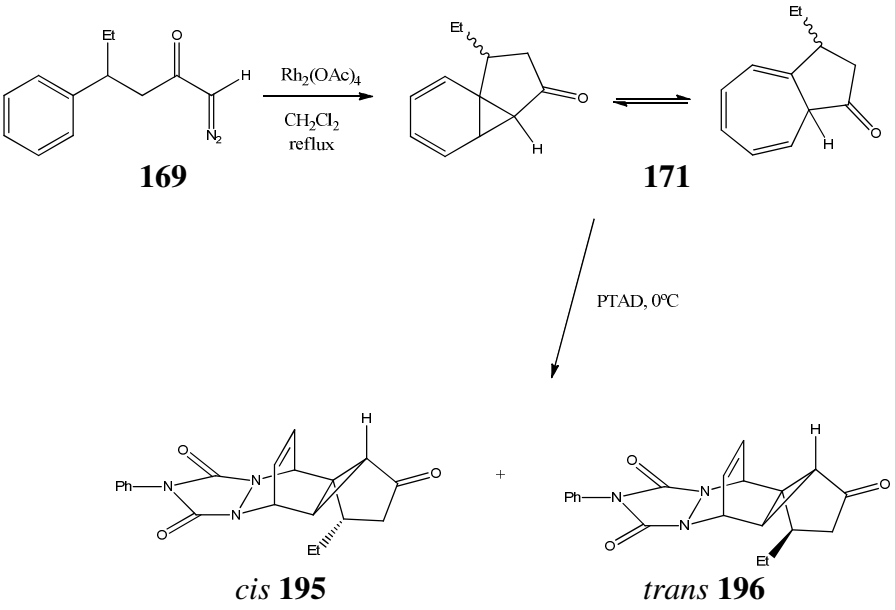
The rearrangement of crude azulenones prepared from terminal α-diazoketones to conjugated trienones when purified, would prove to be a challenge when attempting to study the enantioselectivity in the intramolecular carbenoid addition of terminal α-diazoketones. As discussed in Section 2.6.4, determining the degree of enantioselection with the analogous internal α-diazoketones by ^{1}H NMR chiral shift studies proved to be a successful method. However in this work the attempted treatment of crude azulenones formed from terminal α-diazoketones with (+)-Eu(hfc)$_3$ {europium(III)tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate}resulted in complete decomposition of the azulenone.

Work within the group had previously demonstrated the trapping of a wide range of crude azulenones formed from internal α-diazoketones using 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) **162** as a dienophile *via* a cycloaddition reaction to form the stable cycloadducts (Scheme 2.50).[28,37,40,42]



Scheme 2.50

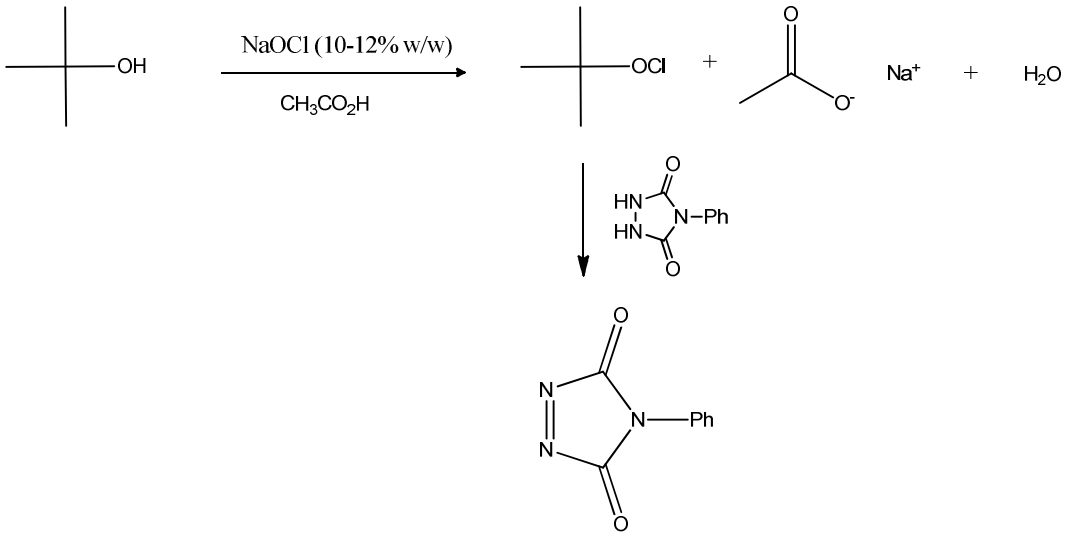
Interestingly, Buckley had prepared the stable diastereomeric cycloadducts **195** and **196** directly in a one pot synthesis from the terminal ethyl diazoketone **169**, using the same procedure described above for the internal diazoketones (Scheme 2.51). The diastereomeric mixture of the resulting adducts (*trans* **196**: *cis* **195**, 85 : 15), following chromatography on silica gel, was the same as that detected for the recrystallised mixture, (*trans* : *cis* 85 : 15).



Scheme 2.51

As a result of Buckley's report of the stable cycloadduct **195/196** formed from the terminal ethyl substituted diazoketone **169**, we investigated the application of this method to the cycloaddition of crude azulenones formed from the terminal α-diazoketones **43**-**48**. A particular advantage of this account was that the cycloaddition can be conducted in one-pot through addition of the PTAD directly to the reaction mixture without isolation of the intermediate labile azulenone. For the reactions employing chiral catalysts, the ability to trap the azulenone *in situ* to avoid any potential epimerisation of the labile stereogenic center would be particularly advantageous.

The first step was the formation of PTAD **162**. *t*-Butyl hypochlorite was used to oxidise 4-phenylurazole to PTAD **162**.[28,37,40,42,164,170] The *t*-butyl hypochlorite was prepared following the method described by Mintz and Walling from *t*-butanol, sodium hypochlorite solution (10-12% w/w) and glacial acetic acid (Scheme 2.52).[174] Following preparation, the [*t*-BuOCl] could be stored in the fridge for a prolonged period of time with no apparent degradation of the solution or reduction in its reactivity.



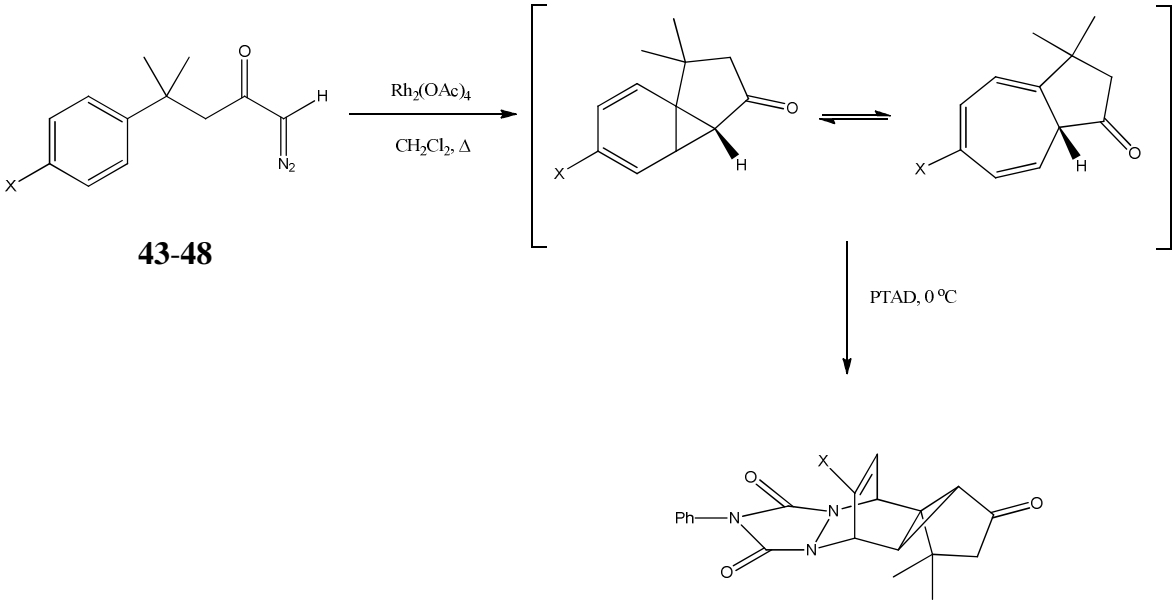
162

Scheme 2.52

Buckley and O'Leary generally used one equivalent of sublimed PTAD **162** for their cycloaddition studies, either added as a solid or a solution in dichloromethane.[28,37] However, Harrington described the use of crude PTAD **162** without sublimation.[40]

Initially in this current study, crude PTAD **162** was used to prepare the cycloadduct **199**. Subsequently, it was observed that the ^{1}H NMR spectra of the crude cycloadducts were less complex when sublimed PTAD **162** was used. All cycloadducts were prepared from a stock of sublimed PTAD **162**, this sublimed PTAD **162** was stored in the freezer at −20 ºC over approximately one year without any noticeably change or degradation. This sublimed batch of dienophile was used to synthesise adducts **200** and **201**. As illustrated in Table 2.21 each of the diazoketones were initially treated with $Rh_2(OAc)_4$ where the diazoketone was added dropwise to the catalyst in refluxing dichloromethane. Once complete disappearance of the diazoketone was confirmed by TLC, the reaction mixture was then cooled to 0 ºC. Without concentration of the reaction solution, one equivalent of PTAD **162** was added directly to the reaction mixture.

Table 2.21 *One pot reaction of terminal α-diazoketones* **43-48** *with $Rh_2(OAc)_4$ followed by cycloaddition with PTAD* **162** *to form cycloadducts* **197-199**



43-48

197-199

Entry	Diazoketone	X	Azulenone[a]	PTAD Adduct	Time (h)[b]	Yield (%)
1	**43**	H	**178**	**197**[c]	1	42[d]
2	**44**	Me	**179**	**198**[e]	1	53[f]
3	**45**	Cl	**180**	**199**[e]	4	80[f,g]
4	**46**	F	**181**	**200**[e]	-	-[h]
5	**47**	3,5-$(Me)_2$	**182**	**201**[e]	-	-[i]
6	**48**	3,4,5-$(Me)_3$	**183**	**202**[e]	-	-[j]

a. Reaction was complete once all diazoketone was added.

b. Time the reaction mixture was allowed to stir at room temperature after the addition of the dienophile at 0 °C.

c. Adduct prepared using crude PTAD.

d. Purified by recrystallisation from hot ethyl acetate.

e. Adduct prepared using sublimed PTAD.

f. Purified by flash chromatography (20% ethyl acetate:hexane).

g. ^{1}H NMR spectrum of the crude product showed the presence of the crude adduct **199** and a side product believed to be the CHT adduct **203** in the ratio of **199**:**203**, 60:40. This mixture could not be separated by flash chromatography. Treatment of the crude mixture with zinc chloride resulted in the pure adduct **199** being isolated by chromatography in 80% yield.

h. ^{1}H NMR spectrum of the crude product showed a complex mixture of unidentifiable products and no presence of the desired adduct **200** or starting azulenone **181.**

i. ^{1}H NMR spectrum of the crude product showed the presence of the conjugated trienone **188** (49%) and purification by flash chromatography gave the pure trienone in a 40% yield (Scheme 2.53)

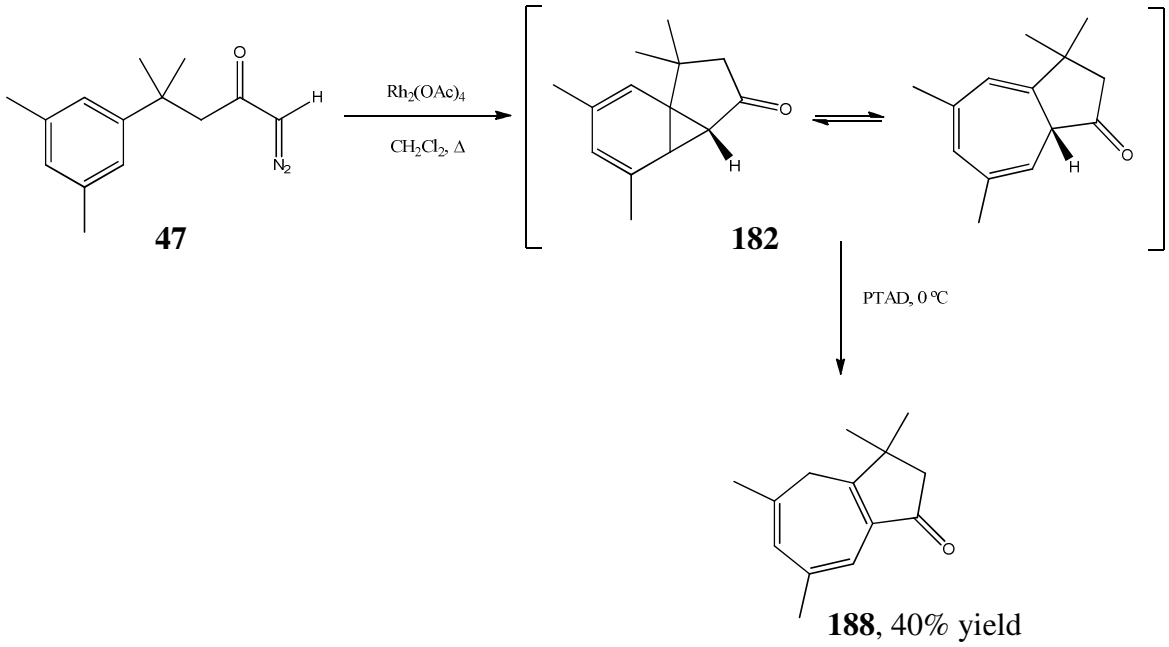
j. ^{1}H NMR spectrum of the crude product showed a complex mixture of unidentifiable products.

Progress of the cycloaddition reaction can be monitored visually with a distinct colour change from the bright red colour of the dienophile to a colourless or pale yellow solution observed upon reaction completion, often within 0.5 to 1 hour of addition of the dienophile. With azulenones **178** and **179** the colour change was observed after 0.5 to 1 hour indicating rapid cycloaddition while use of the chlorine substituted azulenone **180** led to a noticeably slower reaction requiring 4 hours for complete transformation. Any excess of the dienophile present will result in retention of the red colour even after all of the azulenone has reacted and for this reason cycloaddition reactions were also monitored by TLC analysis.

Three novel PTAD adducts **197**-**199** were prepared the one-pot method starting from the corresponding diazoketones as illustrated in Table 2.21. As all adducts prepared in this study were novel they were fully characterised using COSY spectra to aid in the assignment of all coupling relationships in the ^{1}H NMR spectrum. Recrystallisation of **197** from hot ethyl acetate gave the pure cycloadduct **197** as a white solid in 42% yield. Recrystallisation of **198** from hot ethyl acetate resulted in light brown oil forming and as a result, purification by flash chromatography on silica gel gave the pure cycloadduct **198** as a white solid in 53% yield. In the IR spectra of the pure products **197** and **198**, there was a strong absorption at ν_{max} ~1780 cm^{-1} (C=O) and a second weaker carbonyl stretch at ν_{max} ~1700 cm^{-1} (C=O). The adducts displayed a characteristic ABX system in the ^{1}H NMR spectrum. For the unsubstituted adduct **197** signals were seen for the C(3a)H at δ_H 1.60 ppm (1H, s, X of ABX, C(3a)H) and the C(2)H$_2$ signals seen at δ_H 2.02 ppm (1H, dd, A of ABX, J_{AB} 17.7, J_{AX} 1.4) and δ_H 2.23 ppm (1H, d, B of ABX, J_{AB} 17.7), while the C(3b)H signal appeared as a doublet of doublets at δ_H 2.22 ppm (1H, dd, *J* 4.8, 1.5). Similarly for cycloadduct **198**, the characteristic C(3a)H and C(2)H$_2$ signals appeared as an ABX system, while the C(3b)H signal appeared as a broad multiplet at δ_H 2.18-2.20 ppm. The ^{1}H NMR spectrum of the pure product **198** showed water present which could not be removed by drying. Elemental analysis was consistent with the cycloadduct **198** in addition to 0.5 H$_2$O.

When the electron withdrawing fluorine substituted azulenone **181** was treated with PTAD **162** the adduct **200** was not recovered. The ^{1}H NMR spectrum of the crude material showed an unidentifiable product with no evidence of the desired adduct **200** or starting azulenone **181**. Similarly, a complex mixture of unidentifiable products was obtained when the trimethyl substituted azulenone **183** was treated with PTAD **162**.

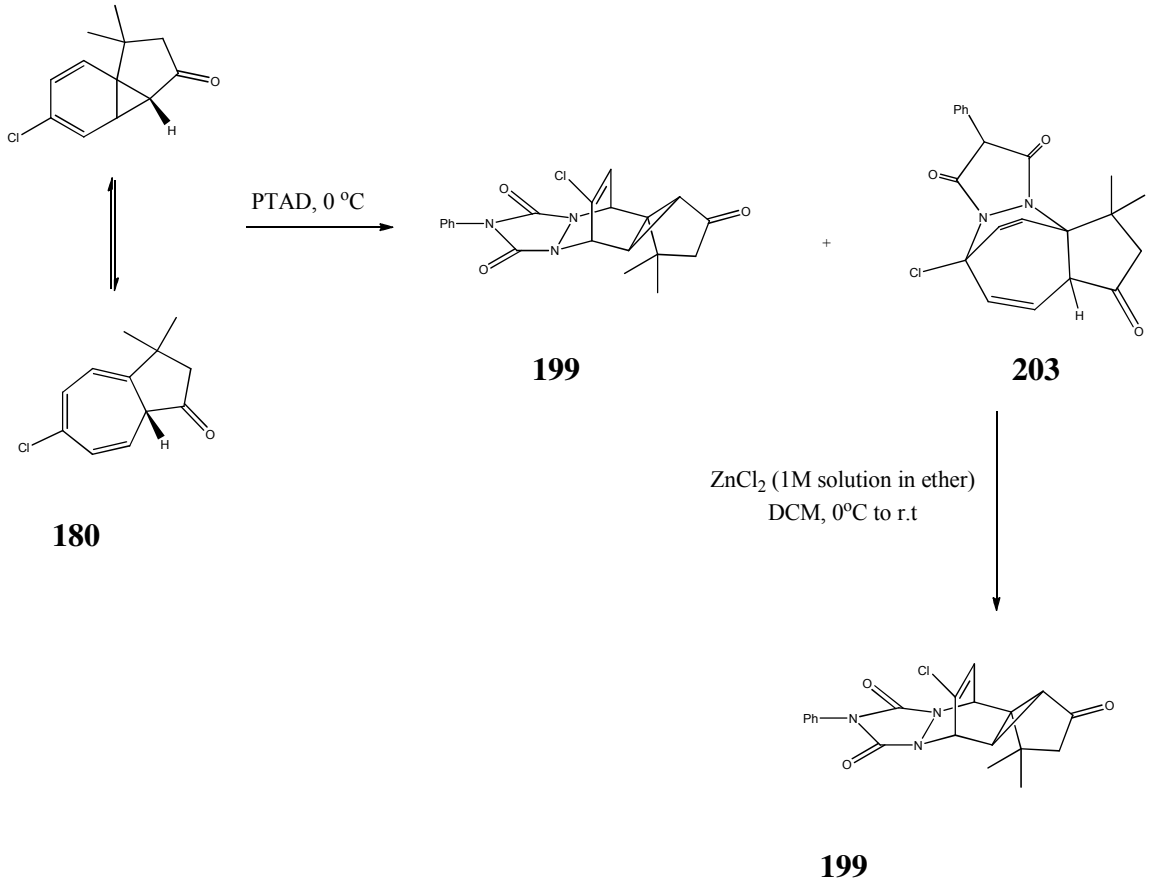
Significantly, the conjugated trienone **188** was isolated from the reaction of azulenone **182** with PTAD **162**. Isolation of the trienone **188** confirmed the cyclisation to form the azulenone does, in fact, occur, but the product is too labile to isolate. Purification by flash chromatography gave the pure trienone in a 40% yield (Scheme 2.53).



47 **182** **188**, 40% yield

Scheme 2.53

In contrast to the cycloadducts discussed above, the reaction leading to the *para*-chloro substituted PTAD adduct **199** requires 4 hours for completion. The reaction was monitored by TLC as decolourisation to give a colourless solution did not occur. The brown coloured solution was concentrated under reduced pressure to give a brown oil. The ^{1}H NMR spectrum of the crude product showed the presence of the adduct **199** and a side product believed to be the cycloheptatriene adduct **203** in the ratio of **199**:**203**, 60:40. The mixture could not be separated by flash chromatography.



Scheme 2.54

As it did not prove possible to isolate **199** in pure form, it was decided to conduct a further transformation following the precedent set by earlier research in the team, with a view to separation of the resulting products.[37,40,42] Reaction of PTAD cycloadducts with $ZnCl_2$ had been examined by Buckley, Harrington and McNamara leading to cyclopropane ring cleavage. [37,40,42] As a result, treatment of a mixture of adduct **199** and *CHT* adduct **203** with $ZnCl_2$ was undertaken as summarized in Scheme 2.54.

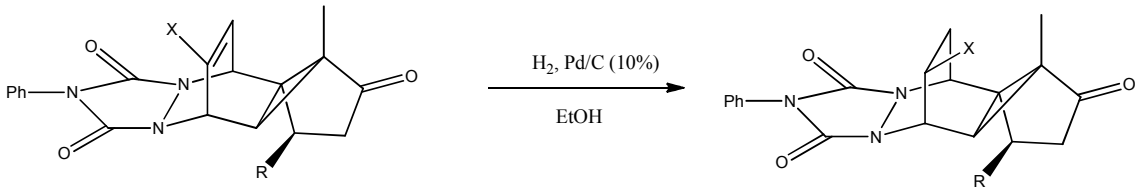
However, when zinc chloride (5 equivalents) was added to a stirring solution of the crude mixture of adduct **199** and *CHT* adduct **203** in dichloromethane (DCM) for 24 hours, the pure adduct **199** was isolated following flash chromatography on silica gel (Scheme 2.54). The ^{1}H NMR of the crude product showed the presence of the *CHT* adduct **199** and additional signals at δ_H 7.03 ppm (1H, dd, *J* 12.0, 2.7), 7.21 (1H, dd, *J* 12.5, 2.7), 7.28 (1H, d, *J* 8.4), which were presumably due to the reaction of the *CHT* adduct **203** with zinc chloride.

The pure cycloadduct **199** was isolated following flash chromatography on silica gel to give a light brown coloured solid in a 80% yield. Based on the recoveries, it is likely that **203** is interconverted to **199** on exposure to $ZnCl_2$, presumably through retro-Diels Alder followed by Diels-Alder cycloaddition. The infrared spectrum of the pure adduct **199** showed two characteristic carbonyl stretches, a strong absorption at ν_{max} 1790 cm^{-1} (C=O) and a weak absorption at ν_{max} 1724 cm^{-1} (C=O). The ^1H NMR of the pure cycloadduct showed the presence of the characteristic C(3a)H and C(2)H_2 signals appearing as an ABX system as discussed earlier for analogous cycloadducts **197** and **198**. Once again, the ^1H NMR of the pure cycloadduct **199** showed the presence of water which could not be removed by drying under molecular sieves. The elemental analysis obtained was in agreement with the cycloadduct **199** in addition to 0.4 H_2O. Clearly the cycloadduct **199** does not react with $ZnCl_2$ under the same conditions with which clean cyclopropane ring cleavage in the presence of the bridgehead methyl group occurs.[40] Evidently the degree of substitution at the bridgehead position is important in terms of the stability of the incipient carbocationic character at this centre in the $ZnCl_2$ mediated cyclopropane ring opening. However, the isolation of cycloadduct **199** in pure form was of significant value during the course of this work.

In conclusion, trapping of labile azulenones **178**-**180** as the analogous PTAD adduct **197**-**199** successfully provided stable adducts overcoming the lability of the azulenones and thereby freezing the labile stereogenic center. This approach proved important in later studies using chiral catalysts.

2.6.5.3 Hydrogenation of PTAD adducts

Hydrogenation of PTAD cycloadducts was first explored by Buckley when she took a range of adducts and reacted them under an atmosphere of hydrogen in the presence of palladium on carbon as catalyst (10%) to yield the hydrogenated adducts in good yield following purification by flash chromatography on silica gel (Scheme 2.55).[37]

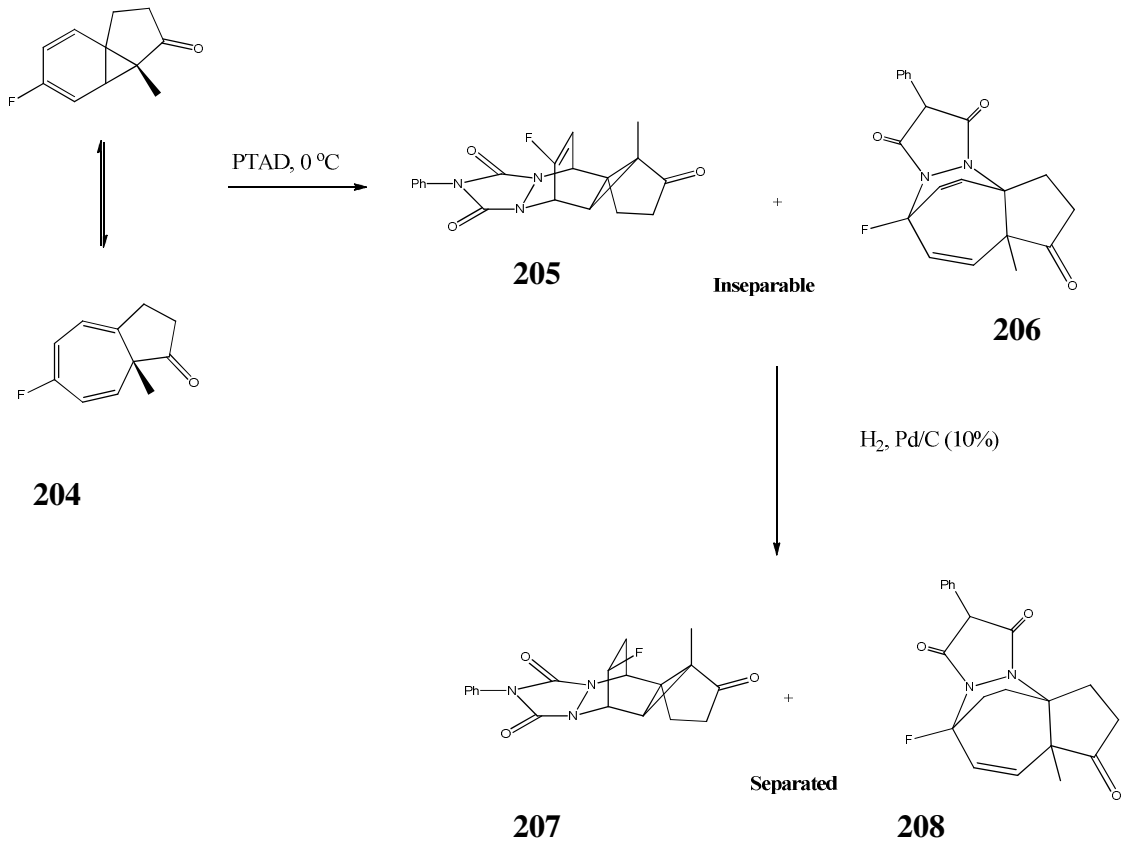


where R = *n*-Bu, *i*-Pr, diMe, 87-94%

X = H, F

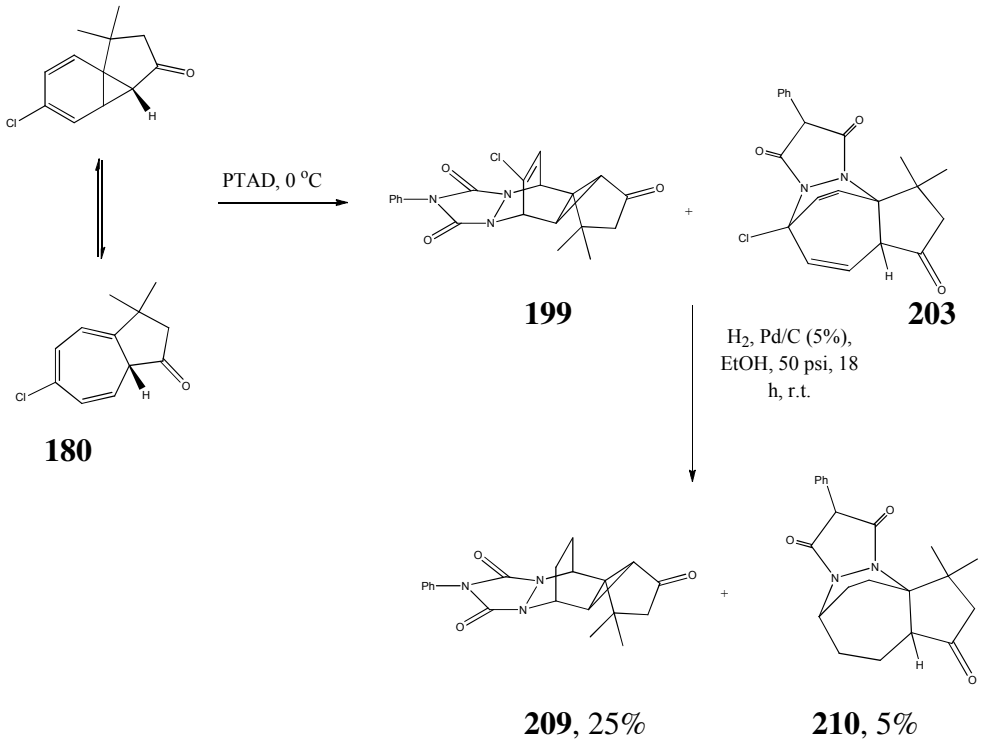
Scheme 2.55

Previously McNamara had hydrogenated a mixture of the inseparable PTAD adduct **205** and cycloheptatriene adduct **206** resulting from the cycloaddition of PTAD **162** to the 6-fluoro azulenone **204** (Scheme 2.56). The resulting hydrogenated adducts **207** and **208** were each isolated as single compounds by chromatography and/or recrystallisation and fully characterised by McNamara.[42]



Scheme 2.56

Following the precedent in McNamara's work, in this study the crude mixture of adduct **199** and CHT adduct **203** were hydrogenated in the presence of Pd/C (5%) for 18 hours at 50 psi. This was carried out in an attempt to separate the mixture of **199** and **203** and thereby confirm the structure of the CHT adduct **203**. Concentration of the solution post hydrogenation gave both the hydrogenated NCD adduct **209** and CHT adduct **210**. However the ratio of the hydrogenated NCD adduct **209** and CHT adduct **210** was unable to be determined due to the complex nature of the ^{1}H NMR spectrum of the crude reaction mixture. Following purification by flash chromatography on silica gel two fractions were isolated. The first least polar fraction was obtained as a yellow oil in a 5% yield and was tentatively assigned as the hydrogenated CHT adduct **210**, an unidentifiable impurity (~30%) was also present in the isolated product. The second fraction was a mixture of products one of which was partially assigned as the hydrogenated NCD adduct **209** as a white solid in a 25% yield. The ^{1}H NMR and ^{13}C NMR of the hydrogenated NCD adduct **209** contained a complex mixture of products. It is believed that the complexity of the product mixture may be due, in part, to partial hydrogenlysis of the carbon chlorine bond, leading to release of HCl, which may trigger a side reaction.



Scheme 2.57

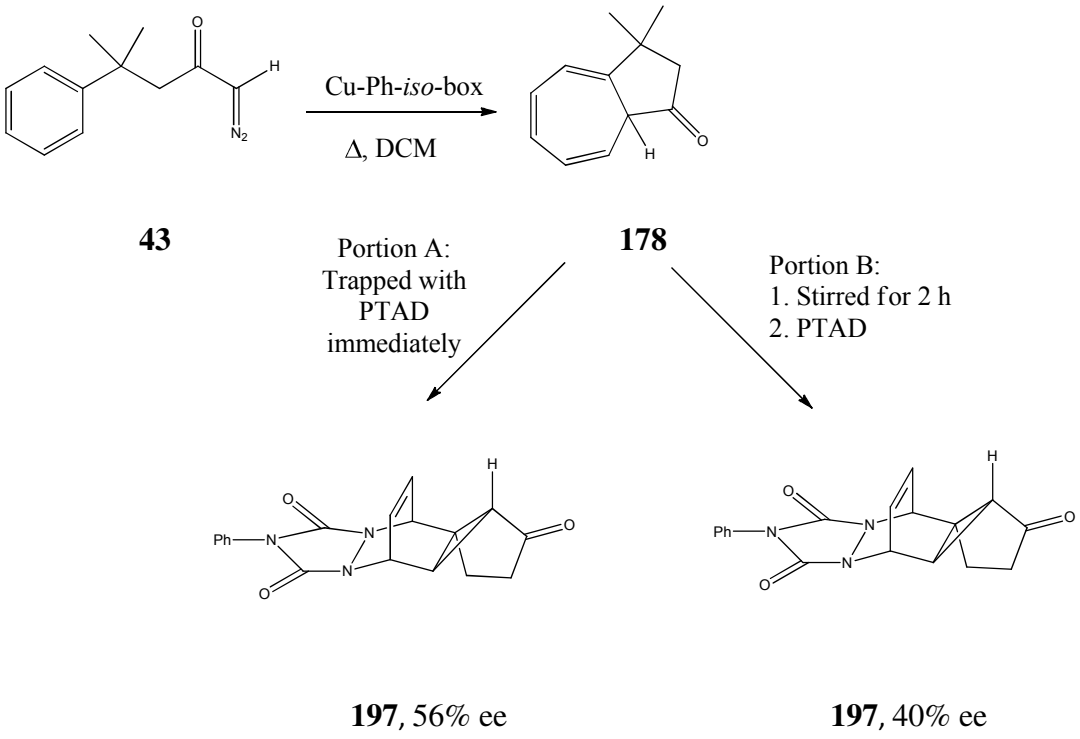
2.6.5.4 Enantioselectivity in the copper catalysed cyclisation of terminal α-diazoketones which were trapped via Diels Alder cycloaddition

In an effort to investigate for the first time the effect that the presence of a hydrogen at the bridgehead position instead of a methyl may have on the enantioselectivity in the intramolecular Buchner reaction of diazoketones, we synthesised azulenones **43**, **44** and **45** in the presence of copper bisoxazoline catalyst complexes. The resulting crude azulenones were unstable and were subsequently trapped with PTAD **162** *via* a Diels Alder cycloaddition reaction to give the novel stable adducts as discussed in section 2.6.5.2. As discussed above for the racemic sample, PTAD adduct **199** was further reacted with zinc chloride and purified by column chromatography on silica gel to result in a pure sample of each.

With racemic batches of the cycloadducts prepared, an investigation was undertaken to determine the enantiomeric purity of cycloadducts **197**-**199**. Initially, use of (+)-Eu(hfc)$_3$ enabled resolution of the signals for one of C(1)$(CH_3)_2$ in **197** and then applying this to the enantioenriched sample in entry 2 in Table 2.22, enabled determination of the enantiopurity (16% ee). In contrast, use of chiral shift ^{1}H NMR did not prove successful with adducts **197** and **199** when the spectra were recorded in the presence of (+)-Eu(hfc)$_3$ and when employing a range of solvents such as C_6D_6, $(CD_3)_2SO$, CD_3OD or $(CD_3)_2O$. Subsequently, it was found that chiral HPLC could be used for the determination of the enantiopurity of **197**-**199** and accordingly, in later studies this approach was employed. Previous attempts within the group at separating the adducts by HPLC had not been rewarding.

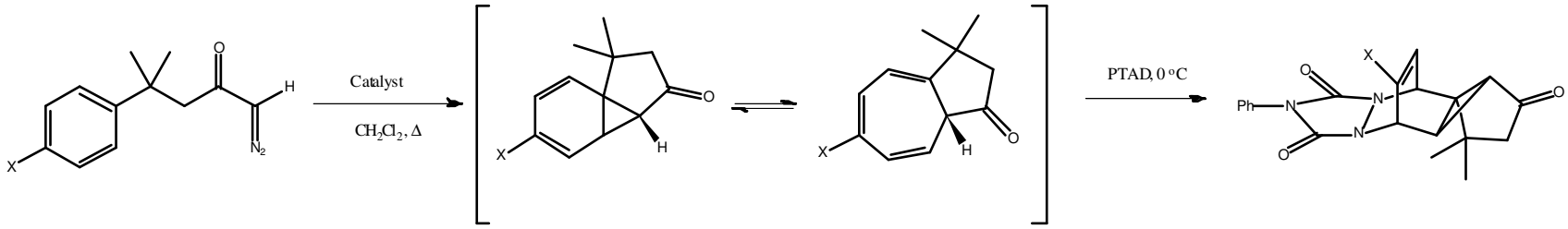
As illustrated in Table 2.22, the cycloadducts obtained from the cyclisation in the presence of the copper bisoxazoline catalysts had up to 83% enantiomeric excess, indicating considerable enantiofacial discrimination, with the terminal diazoketones as had been seen with the analogous internal diazoketones. Notably, when the cycloadduct **197** was recrystallised prior to the determination of enantiomeric purity, the enantiomeric excess determined (16% ee) was notably decreased relative to that seen in the sample analysed without recrystallisation (56% ee). This highlights the importance of avoiding any selective dissolution or recrystallisation prior to enantiomeric analysis.

Due to the presence of an enolisable hydrogen at position C(8a)H in the azulenones formed from terminal diazoketones, reactions were monitored by TLC to avoid stirring for prolonged periods and the associated risk of epimerisation and loss of stereochemical integrity. To explore this, a sample of azulenone **178** prepared from $CuPF_6$-**75** [(*R*,*R*)-Ph-Box] was split into two separate portions (A and B) once the cyclisation from terminal diazoketone **43** was complete (Scheme 2.58). First, portion A was trapped with PTAD **162** immediately, while the second portion B was stirred for a further 2 h at room temperature before being trapped with PTAD **162**. The enantiopurity of the PTAD adduct **197** obtained from portion A was 56% ee while the enantiopurity of adduct **197** obtained from portion B was reduced to 40% ee. This clearly illustrates epimerization at the C(8a)H position in azulenones formed from terminal diazoketones. Aromatic addition in the presence of *in situ* PTAD has not been explored.



Scheme 2.58

Table 2.22 *Effect of catalyst on enantioselectivity of the cyclisation of terminal diazoketones* **43**, **44** *and* **45**



Entry	Diazoketone	X	PTAD	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][a]		$CuPF_6$-**74**[(*S*,*S*)-*t*-Bu-Box][a]		$CuPF_6$-**89**[(4*R*,5*S*)-*tetra*-Ph-Box][a]		$CuPF_6$-**91**[(*R*,*R*)-Bn-Box][a]		CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box][b]		CuCl-NaBARF-**74**[(*S*,*S*)-*t*-Bu-Box][b]	
				Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]	Yield (%)[c]	ee (%)[d]
1	**43**	H	**197**[e]	63[g]	56[h,i]	62[j]	77[k,i]	49[l]	7[h,i]	61[m]	12[h,i]	66	46[h,i]	63	61[k,i]
2	**43**	H	**197**[f]	49	16[h,n,o]	–	–	–	–	–	–	–	–	–	–
2	**44**	Me	**198**[e]	47	25[h,i]	55	30[k,i]	65	23[h,p]	54	4[h,p]	–	–	–	–
3	**45**	Cl	**199**[e]	63	83[h,p,q]	48	–[r]	–	–	–	–	–	–	–	–

(a) The catalyst was prepared from 1.3:1 molar mixture of ligand: $Cu(CH_3CN)_4PF_6$.

(b) The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20°C before substrate was added.

(c) Yield of isolated product after flash chromatography (20% ethyl acetate:hexane).

(d) Determined by HPLC.

(e) Adduct prepared using sublimed PTAD.

(f) Adduct prepared using crude PTAD.

(g) The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown side-product (13%). Signals were observed at δ_H (300 MHz); 1.14 (4H, s), 1.21 (3H, s), 1.21 (3H, s), 1.40 (6H, d, *J* 1.0), 2.38-2.46 (7H, m), 4.93 (1H, d, *J* 5.1), 5.19 (1H, dd, *J* 9.3, 3.9), 5.59-5.68 (1H, m), 5.96 (1H, dd, *J* 9.1, 5.1), 6.20 (2H, d, *J* 4.8), 6.47-6.79 (7H, m), 7.02 (1H, dd, *J* 11.1, 6.0), 7.71-7.79 (5H, m).

(h) Major Enantiomer = (−).

(i) Determined by HPLC using OD-H column.

(j) The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown side-product (10%). Signals were observed at δ_H (300 MHz); 1.21 (2H, s), 1.39-1.40 (4H, m), 4.88 [1H, d, *J* 3.0], 5.08 [1H, d, *J* 6.0], 5.96 [1H, dd, J 9.0, 6.0], 6.90 [1H, d, *J* 12.0], 7.05 [1H, dd, *J* 12.0, 6.0].

(k) Major Enantiomer = (+).

(l) The ^{1}H NMR spectrum of the crude reaction mixture contained starting azulenone **178**(51%).

(m) The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown side-product (27%). Signals were observed at δ_H (300 MHz);1.14 (2H, s), 1.21 (4H, s), 1.25-1.29 (8H, m), 1.39-1.40 (4H, m), 1.46-1.47 (8H, m), 2.38-2.67 (12H, m), 4.80-4.84 (1H, m), 4.93 (1H, d, *J* 9.9), 5.04 -5.08 (1H, m), 5.19 (1H, dd, *J* 9.3, 4.2), 5.62-5.76 (1H, m), 5.96 (2H, dd, *J* 12.9, 5.1).

(n) Purified by recrystallisation from hot ethyl acetate.

(o) Determined by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$

(p) Determined by HPLC using Chiradex column.

(q) Crude PTAD adduct was subsequently treated with $ZnCl_2$ to give the pure adduct **199**.

(r) Enantiomers not fully resolved by chiral HPLC.

The highest enantioselectivity in the copper catalysed cyclisation of the unsubstituted diazoketone **43** was achieved using the *t*-butyl ligand **74** (77% ee, Table 2.22, entry 1). Interestingly the level of asymmetric induction decreased with the phenyl-ligand **75** (56% ee) while the tetraphenyl substituted ligand **89** and benzyl substituted ligand **91** provided the azulenone **178** with enantioselectivities of just 7% ee and 12% ee respectively. A comparison of enantioselectivities observed in the cyclisations of the internal and terminal unsubstituted diazoketones **37** and **43** with different ligands is illustrated in Figure 2.27.

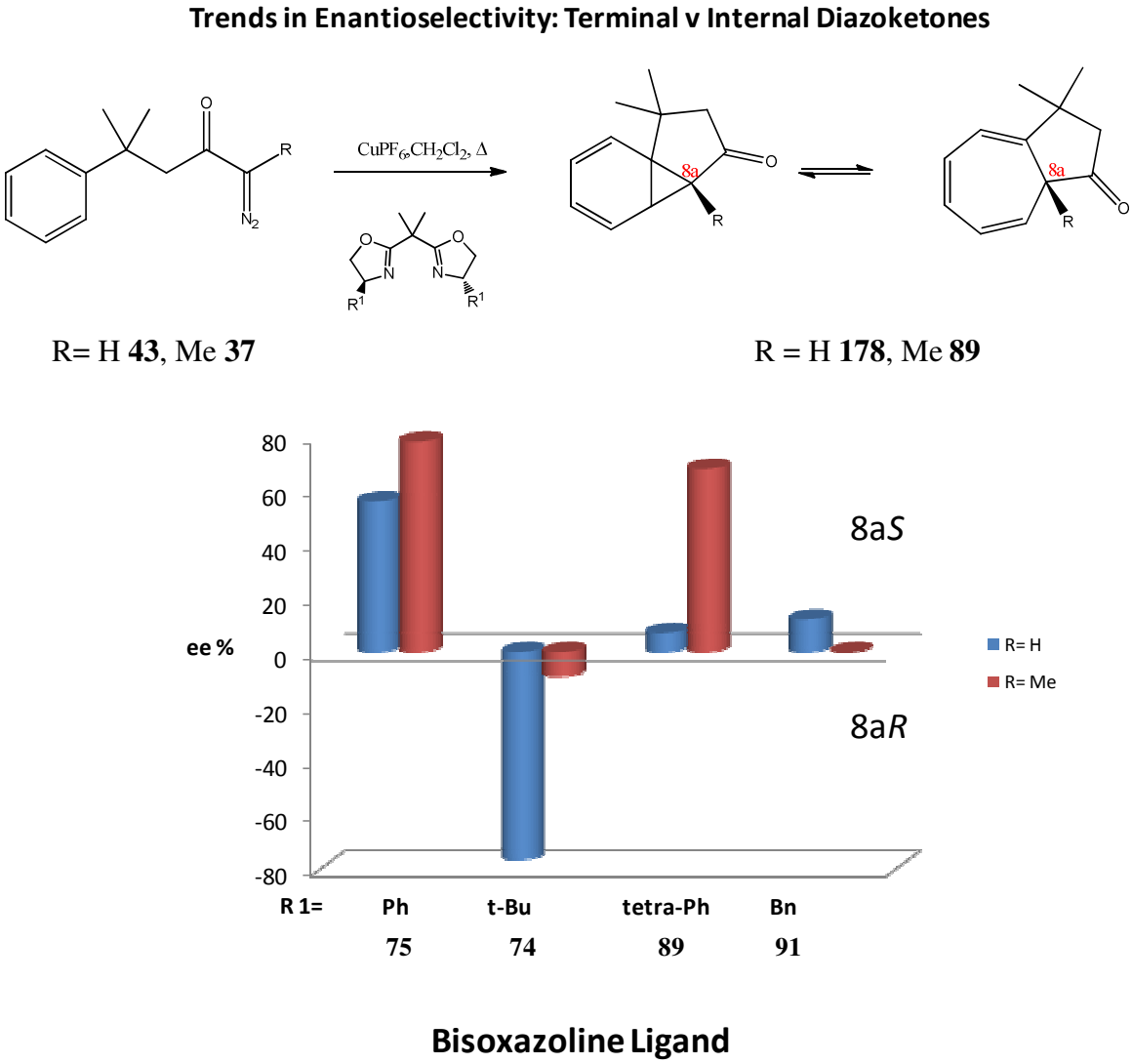
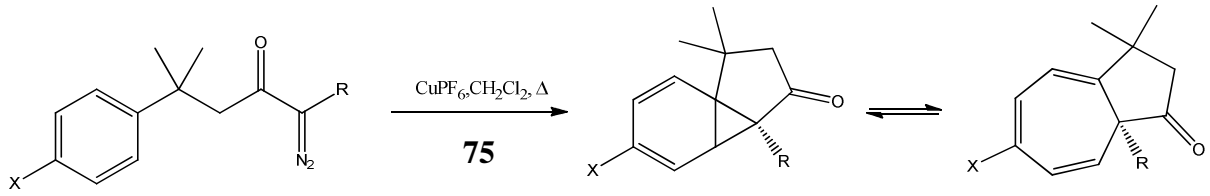


Figure 2.27 *Comparison of the enantioselectivities observed in the cyclisations of the internal and terminal unsubstituted diazoketones* **37** *and* **43** *(determined from PTAD cycloadduct* **197** *for* **178** *but directly for azulenone* **89***)*

The trends in enantioselectivities with variation of the ligand were very different in the cyclisations of the internal and terminal α-diazoketones, highlighting the significance of substitution at the carbene center influencing enantiofacial approach in the copper catalysed aromatic addition. Critically, for the unsubstituted internal diazoketone **37** the highest enantioselectivities were obtained with the phenyl **75** and tetraphenyl **89** ligands (78% ee and 68% ee, see Section 1.6.4), while the *t*-butyl ligand **74** resulted in a poor enantioselectivity of 9% ee (reported by O'Keeffe).[41] However, in the unsubstituted terminal diazoketone **43** the use of the *t*-butyl ligand **74** resulted in the higher enantioselectivity of 77% ee (Table 2.22, entry 1) while the enantioselectivity decreased significantly when the phenyl **75** and tetraphenyl **89** ligands were applied (78% ee to 56% ee for **75** and 68% ee to 7% ee for **89**) as illustrated in Figure 2.27.

As shown in section 1.6.4, where the aromatic addition of internal diazoketones was carried out using the phenyl ligand **75**, the extent of asymmetric induction was decreased by the presence of inductively electron withdrawing substituents on the aromatic ring (62% ee for Cl-**39**, 56% ee for F-**40** using ligand **75**). The highest enantioselectivity was observed with the electron donating *para*-methyl substituted diazoketone **38** (80% ee). Significantly, this trend appears to be reversed for the aromatic addition reaction of terminal diazoketones (see Figure 2.27 and Table 2.22 and 2.23). Enantioselectivities obtained from the aromatic addition of the electron donating methyl substituted diazoketone **44** were generally poor across a range of ligands (≤30% ee). The aromatic addition of the electron withdrawing substituted diazoketone **45** resulted in an enantioselectivity of 83% ee (entry 3, table 2.22) being obtained with the phenyl ligand **75**. This is the highest level of asymmetric induction reported to date for the intramolecular aromatic addition reaction of terminal diazoketones and was shown to be reproducible. The aromatic addition of diazoketone **45** was repeated using the *t*-butyl ligand **74** but although the enantioselectivity appeared high, the enantiomers were not fully resolvable by chiral HPLC.

Table 2.23 *Comparison of enantioselectivities obtained from a range of both terminal and internal diazoketones using ligand* **75**



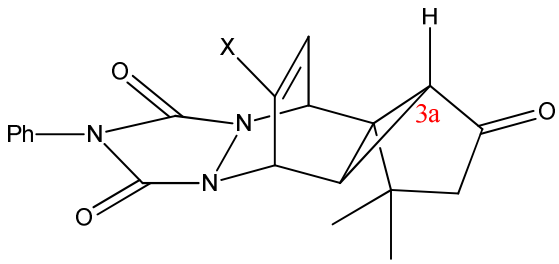
	Azulenone		ee (%)	
X	R=H	R=Me	R=H[a]	R=Me[b]
H	**178**	**89**	56	78
Me	**179**	**96**	25	80
Cl	**180**	**95**	83	62

a. Determined by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$.

b. Determined by HPLC.

Interestingly, a reduction in enantioselection was observed for the terminal diazoketone **43** when the additive NaBARF was introduced into the cyclisation. When catalysts CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box] and CuCl-NaBARF-**74**[(*S,S*)-*t*-Bu-Box] were applied to the cyclisation of diazoketone **43**, enantioselectivities of 46% ee and 61% ee were obtained respectively (entry 1, Table 2.22). This reduction is presumably due to epimerisation at the C(8a)H position as a result of longer reaction times associated with NaBARF.

While the absolute stereochemistry of the azulenones and cycloadducts in terminal diazoketone series has not been confirmed, based on the behavior in chiral ^{1}H NMR and chiral HPLC, it appears that the major enantiomer is the same as that obtained with the internal diazoketone series. Thus using the *t*-butyl ligand **74**, the 3a*R* enantiomer is believed to be formed in the cycloadduct as illustrated in Figure 2.28, although this is not confirmed. The opposite enantiomeric series was achieved for *t*-butyl ligand **74** compared to the other ligands.



3a*R*

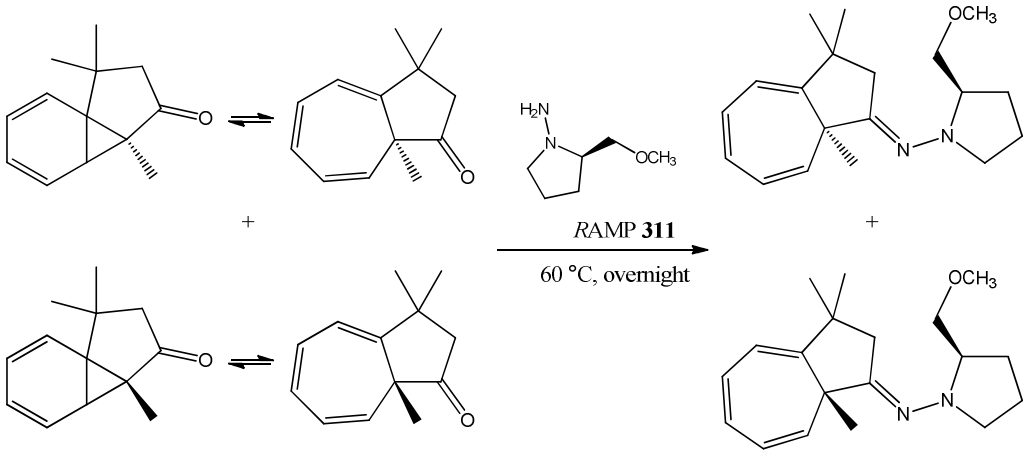
Figure 2.28

2.6.6 Determination of the absolute stereochemistry of azulenones

While this program of research spans 15 years, determination of the absolute stereochemistry of the major enantiomer from the intramolecular Buchner reaction was achieved for the first time in this work. It was envisaged that structure elucidation would provide insight into the orientation of the carbenoid in the transition state which would enhance our understanding of how the carbenoid adds to the phenyl ring, and ultimately assist in the optimisation of ligand structure.

*2.6.6.1 Reaction of cycloadduct with chiral hydrazine RAMP (***R)-311**

O'Keeffe had previously attempted to form hydrazones **312** from reaction of an enantioenriched azulenone **89** with a chiral hydrazine (Scheme 2.59).[41] In theory, separation of the diastereomeric hydrazone products **312** followed by X-ray crystallography would enable assignment of the absolute stereochemistry of the major enantiomer. Unfortunately O'Keeffe reported that while the formation of the hydrazone **312** was feasible, the efficiency of the reaction was low, and as a result it was not possible to isolate the diastereomerically pure hydrazones **312**. Moreover, the hydrazone mixture was isolated as an oil.



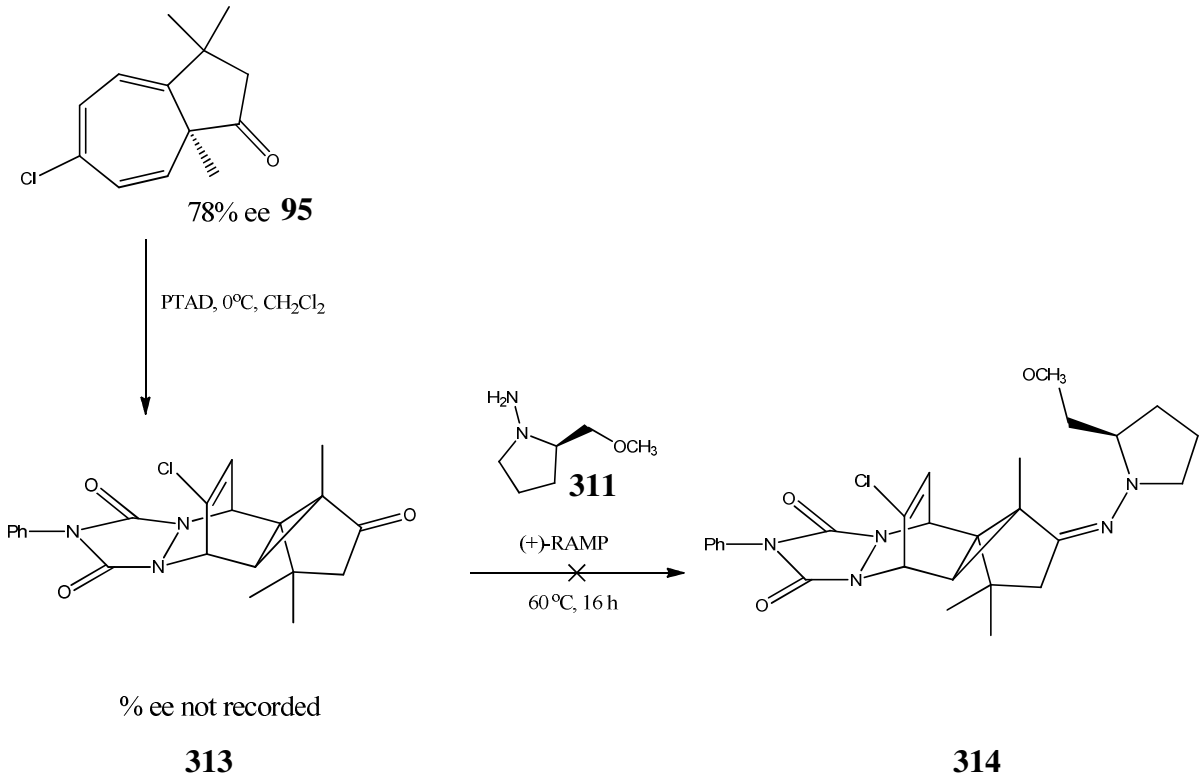
74% ee, **89** **312**

Scheme 2.59

It was decided in this study to attempt to form the diastereomeric hydrazones from an enantioriched cycloadduct rather than azulenones. This approach offers two potential advantages; firstly the cycloadducts are more stable than the labile azulenone and therefore easier to work with. Secondly, the likelihood of obtaining a crystalline derivative from the crystalline adducts is substantially higher than from the azulenones which exist as an oil. Based on O'Keeffe's work (*R*)-(+)-1-amino-2-(methoxymethyl)pyrrolidine **311**–(*R*) (RAMP) was selected as the chiral derivatising agent.[41] RAMP **311** is a chiral auxiliary and has been successfully applied to asymmetric syntheses especially natural product synthesis.[175-177]

An enantioenriched sample of cycloadduct **313** was prepared from the reaction of azulenone **95** {78% ee, catalyst CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]}with unsublimed PTAD. Subsequently, RAMP **311** and the cycloadduct **313** were stirred as a 1:1 neat mixture at 60 ºC overnight (Scheme 2.60). After work-up a ^{1}H NMR spectrum of the crude material indicated that the starting cycloadduct **313** was present in a complex mixture. Following purification by flash chromatography, two fractions were isolated. The first fraction contained the azulenone **95** although this had not been identified in the crude mixture, and a number of unidentifiable peaks. The second fraction contained a

complex mixture of adduct **313** and unidentifiable products. Due to the difficulty in synthesising the hydrazone **314**, an alternative method of assigning the absolute stereochemistry of the major enantiomer of the Buchner reaction was sought.



Scheme 2.60

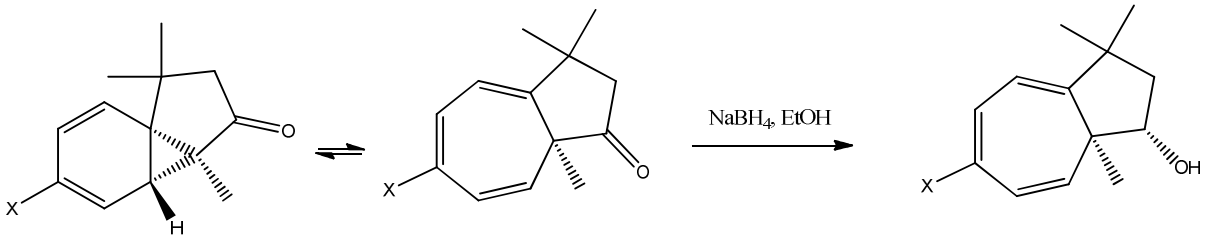
2.6.6.2 Synthesis of azulenols and their subsequent esterification

In a further effort to determine the absolute stereochemistry of azulenones, the reduction of an enantioenriched azulenone followed by esterification with a mandelic acid derivative was explored. Selective recrystallisation of the major enantiomer would potentially result in the assignment of the absolute stereochemistry by X-ray crystallography.

The first step in this work was to prepare azulenols **315** and **316** through the dropwise addition of the enantioenriched azulenones **89** and **95** to an excess of the reducing agent sodium borohydride (~5 equivalents) in ethanol, while stirring at 0 ºC under nitrogen. Each of the starting precursors **89** and **95** had an enantiopurity of 78% ee and were prepared from the catalysts $CuPF_6$-**75**[(*R*,*R*)-Ph-Box] and CuCl-NaBARF-

75[(*R*,*R*)-Ph-Box] respectively (see sections 2.6.4 and 2.6.4.2). In general, the borohydride reduction reactions were stirred overnight without any attempt to monitor their completion as reported by Buckley and O'Keeffe.[37,41] Following isolation, the diastereomeric ratio of the alcohols was estimated from the ^{1}H NMR spectra of the crude product. The azulenones were reduced to give the azulenol **315** and the novel azulenol **316** and their results are outlined below in Table 2.23.

Table 2.23 *Reduction of azulenones* **89** *and* **95**



89: X = H, 78% ee
95: X = Cl, 78% ee

315a/b: X = H

316a/b: X = Cl

Entry	X	Azulenol	Product Ratio[a] **a:b** Crude	Product Ratio[a] **a:b** Pure	Yield (%)[b]	δ_{H-8}**a/b** (ppm)	δ_{C-8}**a/b** (ppm)
1	H	**315**	77:23	–[c]	85%	**315a:** 5.30, d, *J* 10.0 **315b:** 5.56, d, *J* 9.9	–[d] –[e]
2	Cl	**316**	82:18	89:11	75%	**316a:** 5.36, d, *J* 10.5 **316b:** 5.69, d, *J* 10.3	**316a:** 134.0 **316b:** –[e]

a. Calculated from the integration of the ^{1}H NMR spectrum.
b. Isolated yield after chromatography.
c. Crude material was carried through to the next step.
d. Described by O'Keeffe.
e. ^{13}C NMR signal of the minor diastereoisomer is too weak to be assigned with any degree of certainty.

The two diastereomers of azulenol **316** co-eluted upon purification by column chromatography and could not be separated. The pure ratio of 89:11, **316a: 316b** is slightly different to the crude ratio of 82:18, **316a: 316b**. While O'Keeffe had also reported co-elution of azulenols.[41] Buckley had previously subjected azulenone **89** to reduction and succeeded in separating the diastereoisomers **315a/b** chromatographically.[37] The ^{1}H NMR spectrum of the crude azulenol **315** was clean enough to be carried through to the next step without purification.

Buckley performed reduction reactions on azulenones unsubstituted at carbon-3.[37] Like McKervey, Buckley postulated that the reaction between the substrate and the metal hydride favoured the formation of the *cis*-azulenol (Figure 2.30).[22,30,31] The rationale put forward was based on the accessibility of the carbonyl function to the attacking hydride reagent. It is argued that approach from the upper β-face is sterically disfavoured due to the presence of the bridgehead methyl group and the reduction is perceived to occur predominantly from the lower, α-face resulting in the stereoselective formation of the *cis*-azulenol (Figure 2.29).

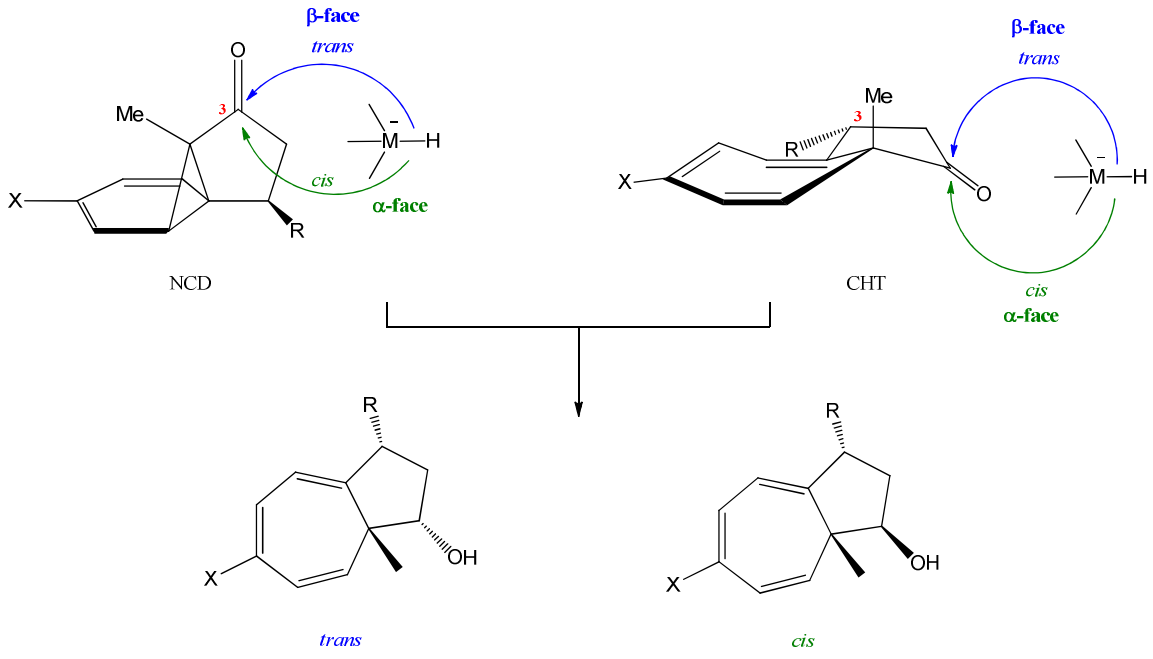
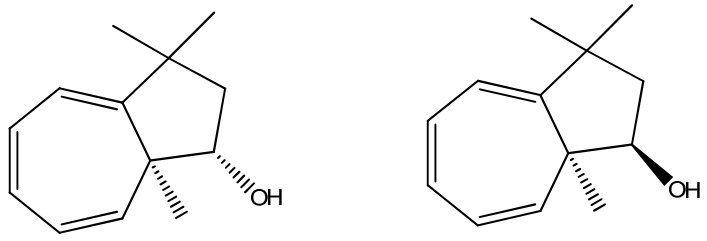


Figure 2.29

By analogy with the data reported by Buckley, O'Keeffe assigned the stereochemistry of major diastereoisomer of the azulenol **315a** as the *cis*-isomer (Figure 2.30).[41] The stereochemical assignment was made cautiously, and vigilance must be exercised until a crystal structure can be obtained.

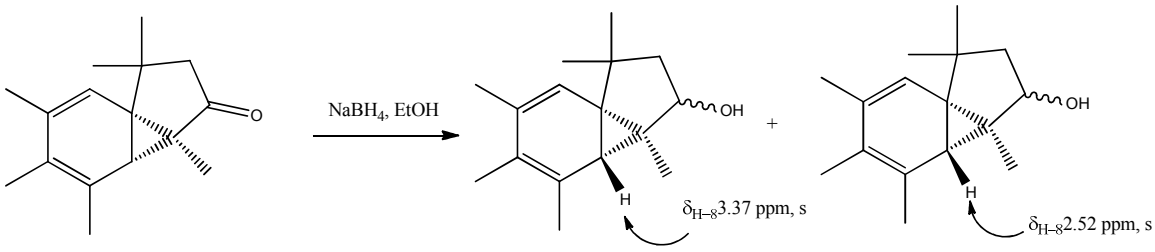


cis **315a** *trans* **315b**

Figure 2.30

In the case of the novel azulenol **316**, the position of the C(8)H signal in the ^{1}H NMR of the spectrum for the major isomer (δ_{H-8} 5.36, d, *J* 10.5) is comparable to the position of the C(8)H signal for azulenol **315a** (δ_{H-8} 5.30, d, *J* 10.0). In addition, the C(8) signal for the minor diastereoisomer of azulenols **316b** (δ_{H-8} 5.69, d, *J* 10.0) and **315b** (δ_{H-8} 5.56, d, *J* 9.9) are also comparable indicating that the stereochemistry of the major diastereoisomer of the novel azulenol **316a** is also the *cis*-isomer**.**

It should be noted that in the case of this thesis, azulenols **315** and **316** are generally shown as the CHT tautomer. However, Buckley reported that azulenols exist as an equilibrating mixture of the NCD and CHT tautomers.[37,71] O'Keeffe confirmed the existence of the NCD tautomer in the case of the trimethyl substituted azulenol **317a/b** (Scheme 2.61).[71] As was the case of the azulenone compounds, the position of equilibrium depends strongly on the substituents attached to the azulenol structure.

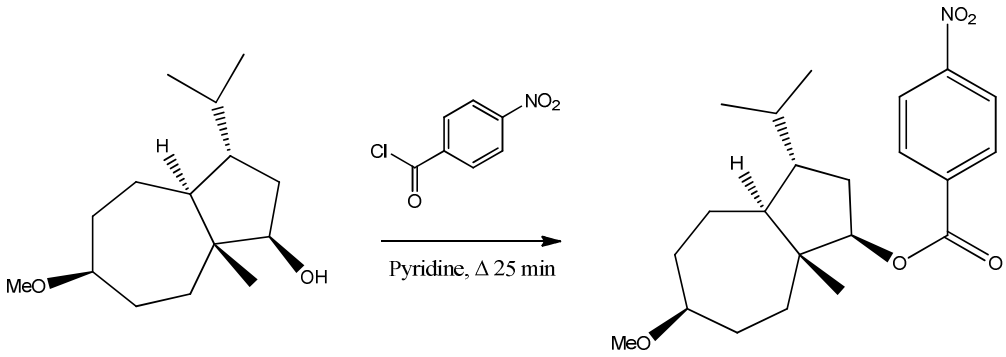


92 **317a** **317b**

Scheme 2.61

In summary, reduction of azulenones **89** and **95** proceeds efficiently in line with earlier results by Buckley, O'Leary and O'Keeffe.[28,37,41] The resulting product azulenols **315** and **316** exist as a mixture of diastereomeric azulenols which in this work were inseparable by chromatography.

Previously, work in the group had demonstrated that the conversion of the perhydroazulenol **318** to the *p*-nitrobenzoate ester **319**. However, the ester **319** did not produce crystals suitable for X-ray crystal determination to establish the stereochemical nature of the compound **319** (Scheme 2.62).[28]



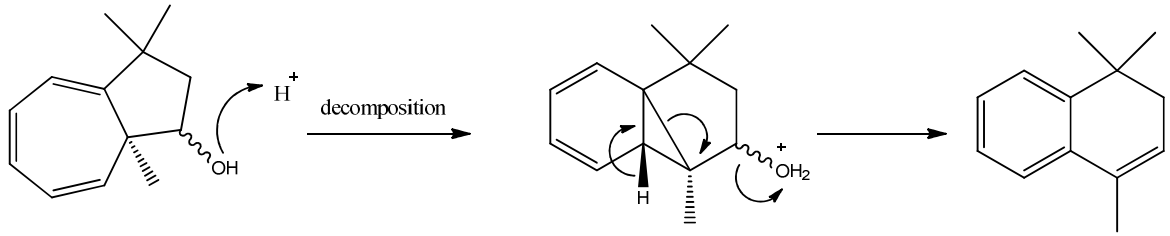
318 **319**

Scheme 2.62

In this work, O'Leary's procedure for the synthesis of **319** was repeated using the novel azulenol **316**. 4-Nitrobenzoyl chloride was added to a stirring solution of azulenol **316a: 316b**, 89:11 and a catalytic amount of DMAP in pyridine (Scheme 2.63). The crude reaction mixture was concentrated to give a brown solid, a ^{1}H NMR spectrum of the crude product showed no presence of the starting azulenol **316a/b**. The crude product was subsequently recrystallised from dichloromethane/diethyl ether to give a orange

coloured crystalline solid. A ^{1}H NMR spectrum of the recrystallised product indicated only the presence of 4-nitrobenzoic acid **321**.

Consequently a number of other esterification reactions were carried out on azulenols **315** and **316** in an attempt to produce a crystalline ester derivative (Scheme 2.63). Firstly esterification of the crude azulenol **315a: 315b,** 77:23 was attempted by heating (*S*)-mandelic acid, PTSA and benzene under reflux for 12 h under a Dean-Stark trap. There was no evidence of the desired ester **322** in the ^{1}H NMR spectrum of the crude reaction mixture. Purification by column chromatography yielded a clear oil in a 54% yield which was tentatively assigned as the dihydronaphthalene **323** presumably formed by acid catalysed dehydration (Scheme 2.63). Signals for **323** were not seen in the ^{1}H NMR spectrum of the crude material, so **323** may have formed on during chromatography on silica gel.



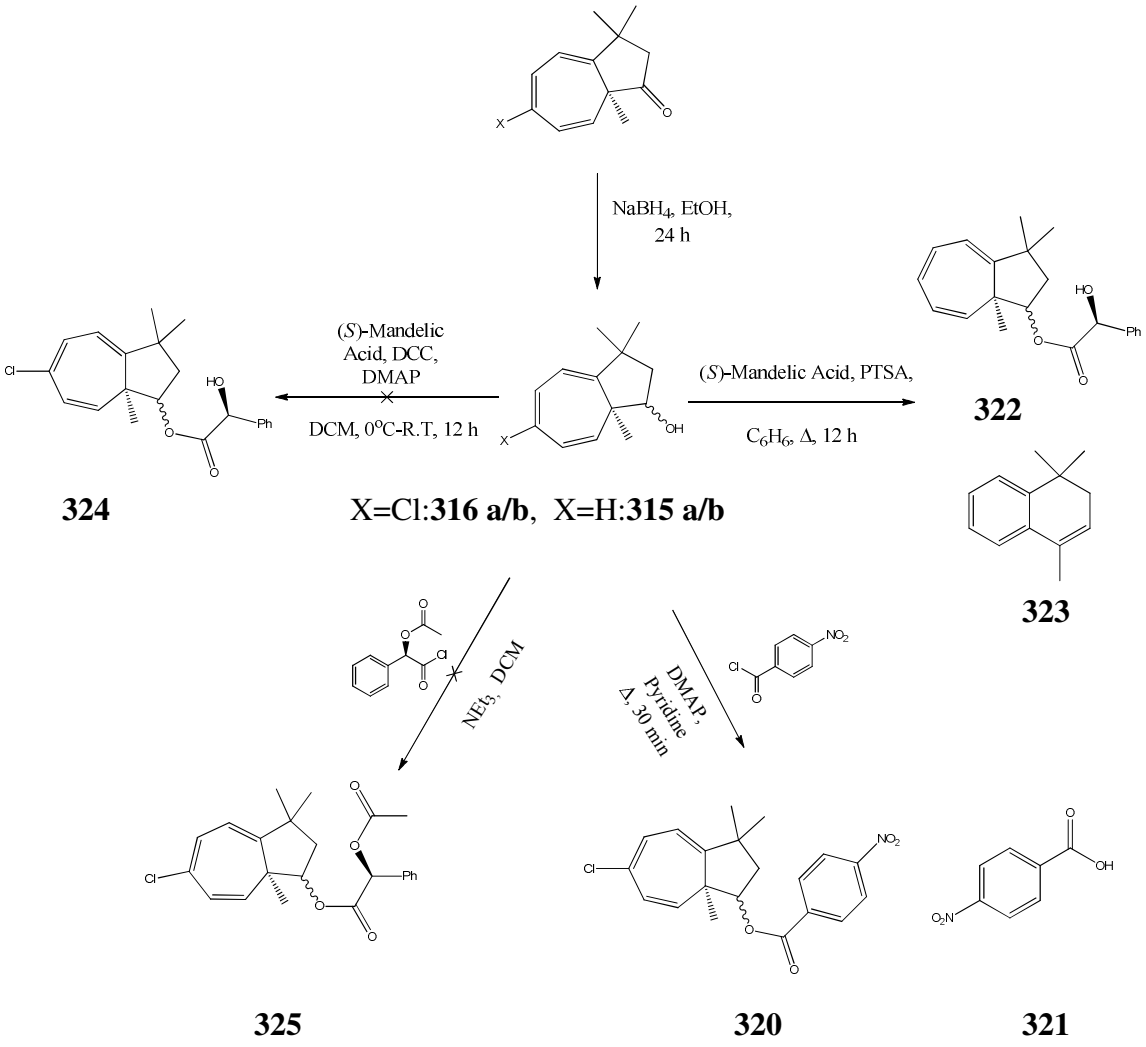
315a **323**

Scheme 2.63

Alternatively, esterification of azulenol **316a: 316b**, 89:11 was attempted by stirring (*S*)-mandelic acid, DCC and a catalytic amount of DMAP in dichloromethane at 0 ºC for 30 min and then warmed to room temperature and stirred for a further 14 h (Scheme 2.64). A ^{1}H NMR spectrum of the crude product did not indicate the presence of the desired product **324.** Attempted purification of the mixture by column chromatography yielded a clear oil which by ^{1}H NMR showed a complex mixture of unidentfiable products and no trace of the ester **324**.

Finally, an attempt to convert azulenol **316a: 316b**, 89:11 to ester **325** was carried out by treating it with triethylamine in dichloromethane which was then followed by the dropwise addition of (*S*)-*O*-acetylmandeloyl chloride **137** (Scheme 2.64). The solution

was stirred for 14 h and following work-up was concentrated to give a clear oil. A ^{1}H NMR spectrum showed no evidence of the desired ester or the starting azulenol **316**.



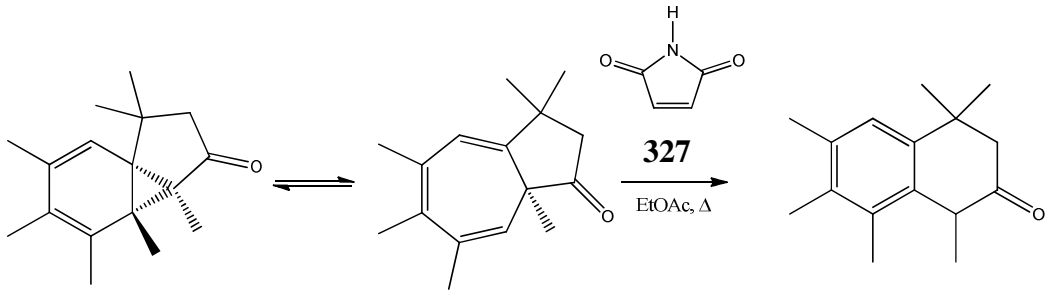
Scheme 2.64

Due to the difficulty in synthesising the esters described above, an alternative method of assigning the absolute stereochemistry of the major enantiomer of the Buchner reaction was sought.

2.6.6.3 PTAD cycloadducts derived from enantioenriched azulenones **92/97**

As discussed in section 2.6.4, the enantiopurity of the trimethyl substituted azulenone **92** was not readily determined directly due to the extremely labile nature of the compound. O'Keeffe had previously determined the enantioselectivity to be ≥95% ee by chiral HPLC but this was not reproduced during this work.[12] In addition, confirmation of the enantiopurity of the 3,5-dimethyl substituted azulenone **97** was not possible. While resolution of one of C(3)$(CH_3)_2$ signals of the enantiomers of azulenone **97** by ^{1}H NMR spectroscopy using (+)-Eu$(hfc)_3$ as chiral shift reagent was evident, due to the relatively high enantioselectivity observed an accurate integration of these signals was not possible. In an attempt to solve these issues both azulenones **92** and **97** were trapped with PTAD *in situ*.

McNamara had previously attempted the cycloaddition of azulenone **92** with maleimide **327**, but only the tetralone **326** was observed in the ^{1}H NMR spectrum of the crude product.[42]



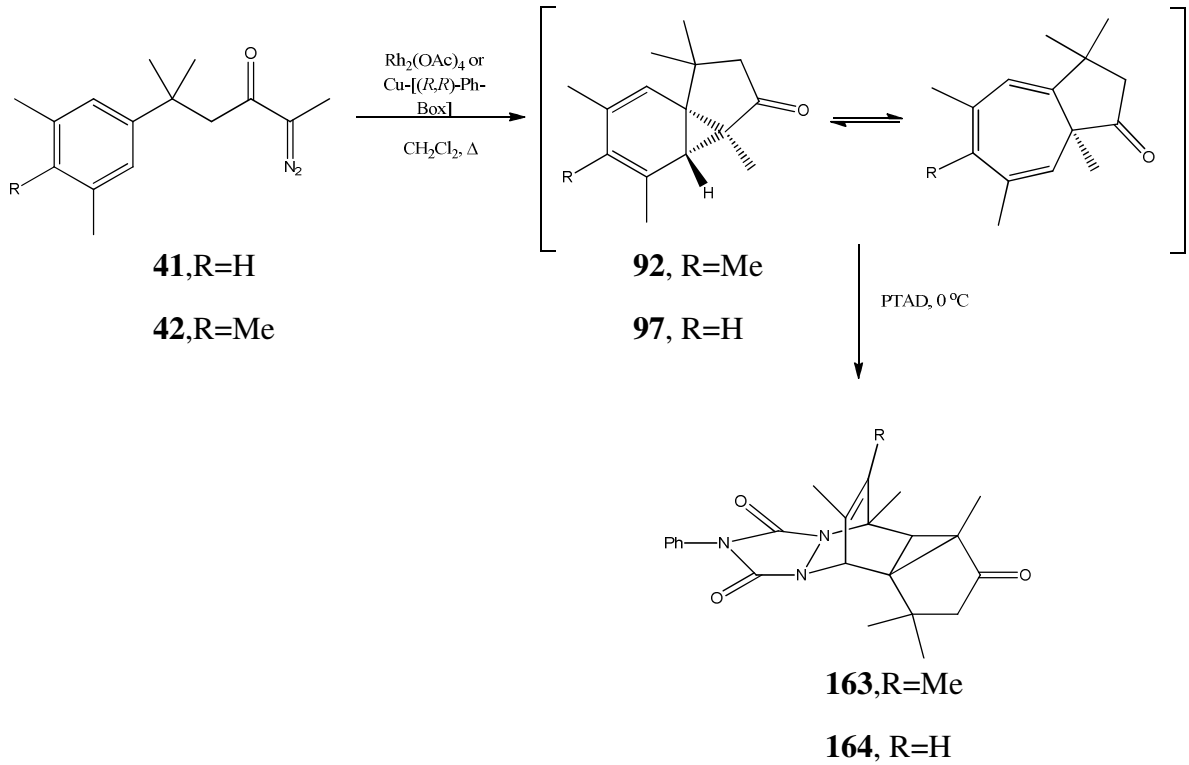
92 **326**

Scheme 2.65

As illustrated in Table 2.24 each of the diazoketones **41** and **42** were initially treated with $Rh_2(OAc)_4$ and PTAD to produce racemic stable cycloadducts **163** and **164**. Subsequently diazoketones **41** and **42** were cyclised in the presence of $CuPF_6$-**75**[(*R*,*R*)-Ph-Box] *via* the same procedure that was discussed in section 2.6.4. Once diazoketone addition was complete, disappearance of the diazoketone was confirmed by TLC and the reaction mixture was then cooled to 0ºC. Without concentration of the reaction solution, one equivalent of PTAD was added directly to the reaction mixture. Progress of the reaction could be monitored by both TLC and colour change. The cycloadditions of

azulenones **92** and **97** were very efficient and were found to be complete by TLC within 1 h. For the cycloadducts **163** and **164**, the reaction solution went from the bright red colour of the dienophile to a colourless solution after stirring for 1 hour at room temperature. The solutions were concentrated under reduced pressure to give white solids. The racemic stable cycloadducts **163** and **164** were both recrystallised from hot ethyl acetate to give the pure products as white solids in 65% and 72% yield respectively. The enantioenriched stable cycloadducts **163** and **164** were purified by column chromatography (20:80, ethyl acetate:hexane) to avoid selective recrystallisation, to give the pure cycloadducts **163** and **164** in 64% and 80% yield respectively As the cycloadducts **163** and **164** prepared in this study were novel, they were also subjected to full characterisation. As in discussed in section 2.6.5.2, correlated spectroscopy (COSY) was a key tool in deducing the cycloadduct structures, as it was used to detect all the coupling relationships.

Table 2.24 *Cycloaddition of azulenones* **92** *and* **97** *with PTAD* **162**



41,R=H

42,R=Me

92, R=Me

97, R=H

163,R=Me

164, R=H

Entry	Diazoketone	R	Azulenone	Adduct	Time (h)[a]	Yield (%)[b]		ee (%)[c]
						$Rh_2(OAc)_4$	Cu-Ph-*iso*-box	
1	**41**	H	**97**	**164**	1	72	64	92[d]
2	**42**	Me	**92**	**163**	1	65	80	93[e]

(a) Number of hours over which diazoketone was added.
(b) Yield of isolated product after flash chromatography (20% ethyl acetate:hexane as eluant) with Cu catalyst; recrystallisation with $Rh_2(OAc)_4$.
(c) Determined by HPLC.
(d) Specific Rotation: $[\alpha]_D^{20}$ 154.9 [*c* 0.5, $CHCl_3$].
(e) Specific Rotation: $[\alpha]_D^{20}$ 96.5 [*c* 1.0, $CHCl_3$].

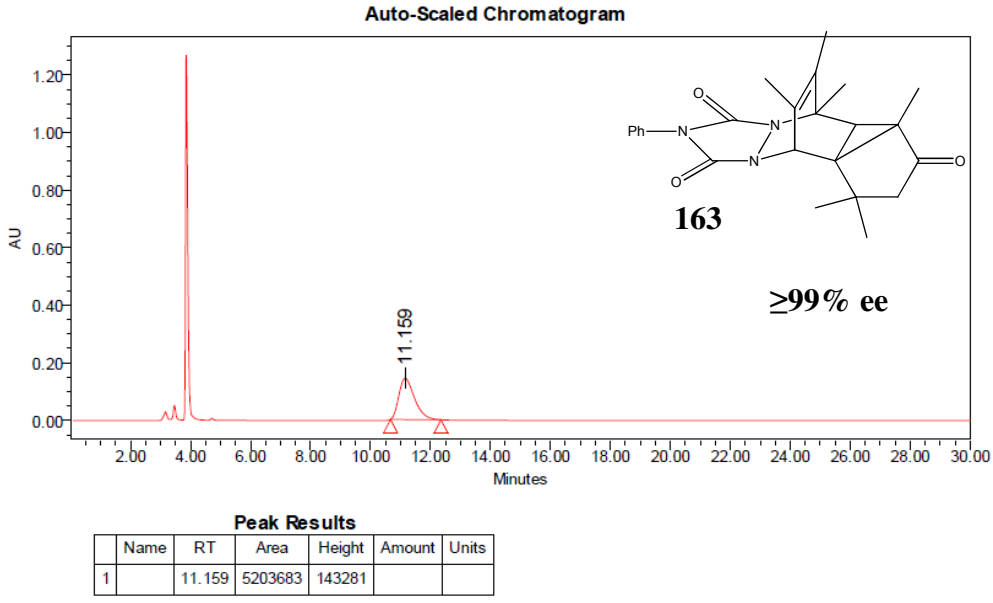
Conditions for the resolution of the enantiomers of the racemic enantiomers were developed by chiral HPLC, which were then applied to the determination of the enantioenriched samples.

The enantiopurities of adducts **163** and **164** were determined by chiral HPLC and were confirmed to be 93% ee and 92% ee respectively (Table 2.24, Figure 2.31). This verifies O'Keeffe's reported enantiopurity of ≥95% ee by HPLC for azulenone **92**.[12] Significantly, essentially the same enantioselectivity is achieved with two methyl substituents in the reaction of diazoketone **41**.

In order to determine the absolute stereochemistry of cycloadducts **163** and **164**, an enantiopure sample (≥99% ee) was required for X-ray crystallography. Both adducts **163** and **164** (93% ee and 92% ee respectively) were separately recrystallised from hot ethyl acetate to give a white crystalline solid. Analysis by chiral HPLC showed that for both adducts, the major enantiomer had selectively crystallised.

Subsequently, X-ray crystallography of a single crystal from each of the adducts **163** and **164** determined that the stereochemistry of the major enantiomer was 3a*S*. To confirm unambiguously that the crystal selected corresponded to the major enantiomer, the crystal of adduct **163** employed for X-Ray diffraction was dissolved and injected for chiral HPLC analysis, confirming that it corresponded to the major peak. While the

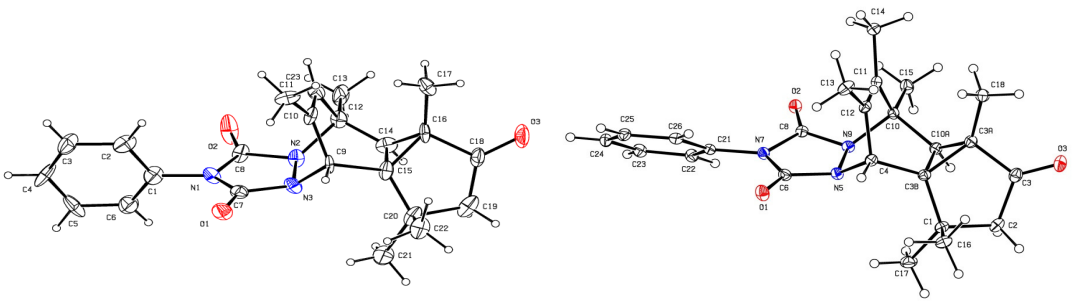
crystal of **164** was not reanalyzed by chiral HPLC, it is reasonable to assume that the crystal reflected the major enantiomer based on HPLC and specific rotation. This is the first time that determination of the absolute stereochemistry of the major enantiomer from the intramolecular Buchner reaction has been achieved.



	Name	RT	Area	Height	Amount	Units
1		11.159	5203683	143281		

Figure 2.31 *Chiral HPLC trace of the single crystal of adduct* **163** *(≥99% ee)*

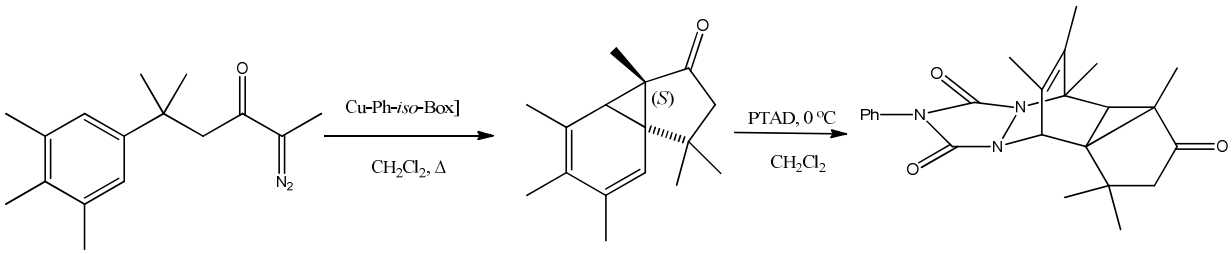
The crystal structures of the major enantiomer of adducts **163** and **164** is illustrated in Figure 2.32 below.



X= H, **164** X= Me, **163**

Figure 2.32 *View of the major enantiomer of adducts* **163** *and* **164** *showing the structure and absolute stereochemistry*

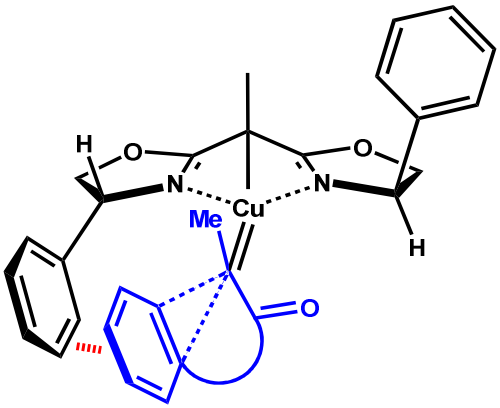
The determination of the stereochemistry (8a*S*) of the major enantiomer of adducts **163** and **164** is consistent with O'Keeffe's proposed model to explain the enantioselectivity of the intramolecular Buchner reaction. If the aromatic addition were to follow a mechanism similar to that depicted in Figure 2.33, the 8a*S* enantiomer would form preferentially (O'Keeffe incorrectly proposed *via* the mechanistic model shown below that the major enantiomer was 8a*R*).[41]



42

93% ee, **92**

163 recrystallised from hot ethyl acetate, > 99% ee



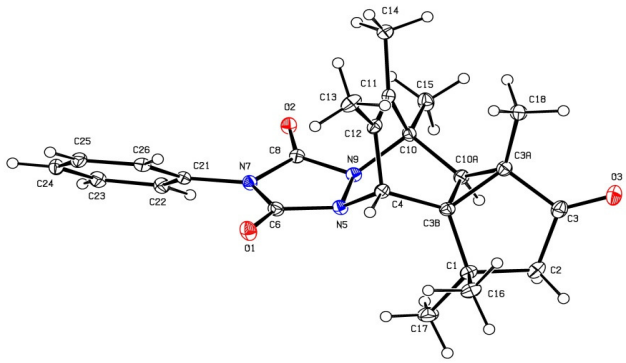


Figure 2.33

2.7 Conclusion

In the course of this work, substantive developments in our understanding of enantiocontrol in the aromatic addition reaction of α-diazoketone were uncovered;

- For the first time enantiocontrol in aromatic addition reactions of terminal diazoketones was demonstrated, despite the lability of the enolisable stereogenic center.
- Role of NaBARF as an additive in enhancing enantiocontrol was demonstrated.
- Influence of substituent effects at the carbene site and aromatic ring was determined.
- Determination of the absolute stereochemistry in the aromatic addition has been achieved for the first time.
- Design and synthesis of a novel bisoxazoline ligand was achieved.
- From a synthetic perspective, access to a number of azulenones with ≥80% ee was achieved.

2.8 Reference List

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Chapter 3
Experimental

Table of Contents:

3.1 General Procedures

All solvents were distilled prior to use as follows: acetone was distilled from potassium permanganate, dichloromethane was firstly distilled from phosphorus pentoxide and when used in diazoketone cyclisations was further distilled from calcium hydride and stored over activated 4 Å molecular sieves. Ethyl acetate was distilled from phosphorus pentoxide and hexane was distilled prior to use. Diethyl ether was obtained commercially from Riedel de Haen. HPLC grade acetone from Sigma-Aldrich was used for PTAD generation. Ethanol (abs) used in hydrogenation reactions was not distilled, as the catalyst used was usually wet. Molecular sieves were dried by heating at >100 °C overnight. Organic phases were dried using anhydrous magnesium sulphate. All reactions were carried out under an atmosphere of inert nitrogen unless otherwise stated.

The rhodium acetate dimer employed was kindly donated by Johnson Matthey. Tetrakis(acetonitrile)copper(I) hexafluorophosphate[1] was prepared by Dr. Alan Ford. Diazomethane was generated from Diazald® using clear glass joints.

^{1}H (400 MHz) spectra were recorded on a Bruker Avance 400 NMR spectrometer and ^{1}H (300MHz) and ^{13}C (75.5MHz) NMR spectra were recorded on a Bruker (300 MHz) NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were assigned with the aid of DEPT experiments. Compounds which were assigned with the aid of DEPT experiments were assigned by identifying both the carbon, (CH_3, CH_2, CH or C), and also the atom number of the carbon, for example, (CH, C-5). For compounds where DEPT spectra were not recorded, the carbon spectra were assigned by comparison to analogous compounds. In order to distinguish the characterisation of these compounds from DEPT aided assignments, compounds for which DEPT spectra were not recorded, were identified using a combination of both atom numbering and signal identification, for example, [*C*(4)H3].

Chemical shifts (δ_H and δ_C) are expressed in parts per million (ppm) relative to TMS and coupling constants in Hertz (Hz). Splitting patterns in ^{1}H and ^{13}C spectra are

designated as s (singlet), br (broad), br s (broad singlet), br d (broad doublet), br t (broad triplet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), ddt (doublet of doublet of triplets), AB (AB system), dm (doublet of multiplets) and m (multiplet), apparent doublet refers to a baseline separation not achieved. ^{13}C spectra were calibrated using the solvent signals, *i.e.* $CDCl_3$: δ_C 77.0 ppm, DMSO-d_6: δ_C 39.5 ppm. All spectroscopic details for compounds previously made were in agreement with those previously reported unless otherwise indicated.

Diastereomeric ratios (d.r) were determined by ^1H NMR spectroscopy. The main diastereoisomer is denoted as **a,** and minor diastereoisomer as **b**.

Where used, a chiral shift study by ^1H NMR spectroscopy employed *tris*-[3-heptafluoropropyl-hydroxymethylene-(+)-camphorato]europium (III) derivative, [(+)-$Eu(hfc)_3$] as chiral shift reagent.

Enantiopurity of the chiral compounds were determined by chiral HPLC performed on Chiralcel OD-H, Chiralcel OJ-H or reverse phase LiChroCART 250-4 ChiraDex® column. Details of the column conditions and mobile phases employed are included in the experimental section under the corresponding compound.

Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 589 nm in a 10 cm cell; concentrations (*c*) are expressed in g/100 mL. [α] is the specific rotation of a compound and is expressed in units 10^{-1} deg cm^2 g^{-1}.

Microwave assisted synthesis was done using the CEM Discover Labmate Synthesiser in conjunction with Chem Driver software (Version 3.5.0) and the CEM Discover S-Class Synthesiser in conjunction with Synergy software.

Infrared spectra were measured as pressed potassium bromide (KBr) discs for solids or thin films on sodium chloride plates for liquids on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Melting points were carried out on a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected. Bulb to bulb distillations were carried out on an Aldrich Kugelrohr apparatus and the oven temperature is given as the boiling point of the substrate.

Wet flash column chromatography was carried out using Kieselgel 60, 0.040-0.063 mm (Merck) and the fractions are reported in the order with which they eluted unless otherwise stated. Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation of compounds on TLC plates was achieved by UV (254nm) light detection, vanillin staining, ceric sulfate and potassium permanganate staining.

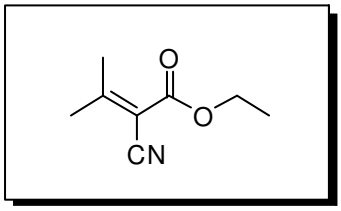
The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. It was not possible to obtain bromine elemental analysis on any compounds containing bromine and also it was not possible to obtain chlorine analysis on compounds that had both bromine and chlorine in the molecule. Fluorine and chlorine elemental analysis were carried out and those compounds with both a fluorine and chlorine can be analysed for both.

Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluant; samples were made up in acetonitrile. High resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC-MS instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluant; samples were made up in acetonitrile except for diazo compounds which were made up in dietyl ether.

Single crystal X-ray data was collected at University College Cork on a Bruker APEX II DUO diffractometer at temperature 100 – 293 K using graphite monochromatic Mo Kα (λ = 0.7107 Å) radiation. The structures were solved using direct methods and refined on F^2 using SHELXL-97. Analysis was undertaken with the SHELX suite of programs[2] and diagrams prepared with Mercury 2.3.[3] All non-hydrogen atoms were located and refined with anisotropic thermal parameters. Hydrogen atoms were included in calculated positions or they were located and refined with isotropic thermal parameters.

3.2 Synthesis of esters:

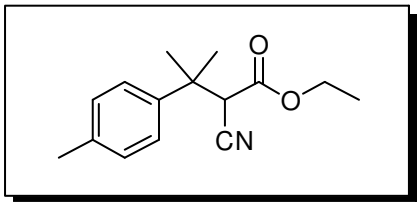
Ethyl 2-cyano-3-methylbut-2-enoate 53[4,5]



A solution of β-alanine (13.36 mg, 0.15 mmol), ethyl cyanoacetate (1.80 mL, 0.30 mmol), acetone (104 mL, 1.44 mmol) and acetic acid (6 mL) in benzene (70 mL) was refluxed for 60 h using a Dean Stark trap. The ^{1}H NMR spectrum of the crude material indicated that it consisted of 8% starting material, ethyl cyanoacetate.* Purification by vacuum distillation gave the pure ester **53** (37.82 g, 82%) as a white low melting solid, b.p 115°C at 14 mmHg (Lit.,[5] 120°C at 14 mmHg); ν_{max}/cm^{-1} (film) 2986, 2227 (CN), 1732 (CO), 1612, 1444, 1371, 1335, 1285, 1086; δ_H (300 MHz) 1.35 [3H, t, *J* 7.4, CH_2CH_3], 2.31, 2.41 [2 ×3H, 2 × s, C(3)CH_3, C(4)CH_3], 4.27 [2H, q, *J* 7.2, CH_2CH_3].

*Ethyl cyanoacetate; δ_H (300 MHz) 3.50 [2H, s, C(2)H_2]. N.B Peaks for CH_2CH_3, CH_2CH_3 were obscured by those of the product ester.

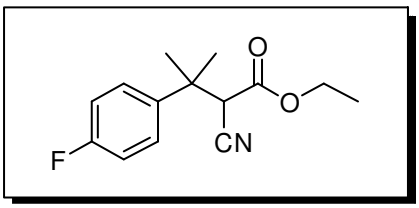
Ethyl 2-cyano-3-methyl-3-(4-methylphenyl)butanoate 55[4,5]



Ethyl 2-cyano-3-methylbut-2-enoate **53** (15.00 g, 97.90 mmol) was added dropwise to 4-tolyl magnesium bromide [freshly prepared from magnesium (5.95 g, 244.90 mmol), iodine (one crystal) in diethyl ether (60 mL), and 4-bromotoluene (41.90 g, 245.00 mmol) in diethyl ether (30 mL)] at room temperature under nitrogen and the mixture was refluxed for 30 min. The reaction mixture was cooled to room temperature and carefully poured onto aqueous hydrochloric acid (10%, 30 mL). The layers were separated and the aqueous layer was washed with diethyl ether (40 mL). The combined organic layers were washed with brine (20 mL), dried, filtered and concentrated under reduced pressure to give the crude ester (15.50 g) as an orange oil. A ^{1}H NMR spectrum of the crude material showed it to contain the Würtz coupling product (~36 %). Purification by flash chromatography using ethyl acetate/hexane (5:95) as eluent gave the *ester* **55** (15.21 g, 64%) as a clear oil; ν_{max}/cm^{-1}

(film) 2980, 2247 (CN), 1740 (CO), 1610, 1516, 1466, 1370, 1326, 1140, 1036; δ_H (300 MHz) 1.08 (3H, t, *J* 7.4, CH_2CH_3), 1.60 [6H, s, C(3)CH_3, C(4)H_3], 2.32 [3H, s, C(4′)CH_3], 3.71 [1H, s, C(2)H], 4.03 (2H, q, *J* 7.2, CH_2CH_3), 7.15 [2H, d, *J* 8.4, C(3′)H, C(5′)H], 7.27 [2H, d, *J* 8.4, C(2′)H, C(6′)H]. The Würtz coupling product **60**[6] was isolated as a yellow solid, m.p. 116-119°C (Lit.,[7] 125°C); ν_{max}/cm^{-1} (KBr) 2974, 1742, 1447, 1266, 1113; δ_H (300 MHz) 2.39 [6H, s, C(4)CH_3, C(4′)CH_3], 7.13-7.27 [4H, m, C(2)H, C(6)H, C(2′)H, C(6′)H] and 7.44-7.49 [4H, m C(3)H, C(5)H, C(3′)H, C(5′)H].

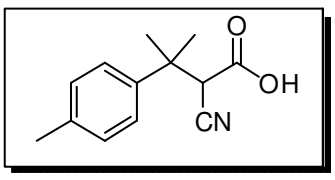
Ethyl 2-cyano-3-methyl-3-(4-fluorophenyl)butanoate 54[4,5]



Ethyl 2-cyano-3-methylbut-2-enoate **53** (7.34 g, 47.91 mmol) was added dropwise to 4-fluorophenyl magnesium bromide [freshly prepared from magnesium (3.50 g, 144.00 mmol), iodine (one crystal) in ether (60 mL), and 1-fluoro-4-iodobenzene (32.04 g, 144.00 mmol) in diethyl ether (60 mL)] at room temperature under nitrogen and the mixture was heated under reflux for 30 min. The reaction mixture was cooled to room temperature and carefully poured onto aqueous hydrochloric acid (10%, 30 mL). The layers were separated and the aqueous layer was washed with diethyl ether (40 mL). The combined organic layers were washed with brine (20 mL), dried, filtered and concentrated under reduced pressure to give the crude ester as an orange oil. Purification by flash chromatography using ethyl acetate/hexane (20.80) as eluent gave the *ester* **54** (7.80 g, 65 %) as a clear oil; ν_{max}/cm^{-1} (film) 2982, 2248 (CN), 1741 (CO), 1604, 1513, 1236; δ_H (400 MHz) 1.09 (3H, t, *J* 7.2, CH_2CH_3), 1.62 [6H, s, C(3)CH_3, C(4)H_3], 3.68 [1H, s, C(2)H], 4.01-4.09 (2H, m, CH_2CH_3), 7.01-7.07, 7.35-7.40{2 x 2H, m, [C(2′)H, C(6′)H and C(3′)H, C(5′)H]}.

3.3 Synthesis of cyanoacids:

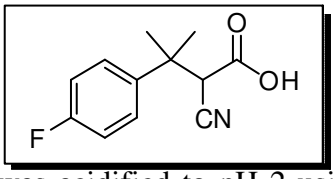
2-Cyano-3-methyl-3-(4-methylphenyl)butanoic acid 57[5]



A 100 mL round bottom flask equipped with a magnetic stirred bar was charged with ethyl-2-cyano-3-methyl-3-(4-methylphenyl)butanoate **55** (8.50 g, 34.60 mmol), sodium

hydroxide (2.78 g, 69.30 mmol) and ethanol (95%, 60 mL). The flask was attached to a gas bubbler and subsequently heated in an open vessel microwave reactor for 15 min at 200 W at 80 °C. The reaction mixture was cooled to room temperature and carefully poured onto aqueous hydrochloric acid (10%, 145 mL) in ice (150 g). The layers were separated and the aqueous layer was washed with diethyl ether (2 × 100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried, filtered and concentrated under reduced pressure to give crude acid (8.23 g), which contained some ethanol, as a yellow oil which solidified after 5 days *in vacuo* to afford the pure *acid* **57** (6.10 g, 81%), m.p 88-91 °C (Lit.,[5] 89-90°C); ν_{max}/cm^{-1} (KBr) 2981 br (OH), 2253 (CN), 1716, 1516, 1287; δ_H (300 MHz) 1.62, 1.64 [2 × 3H, 2 × s, C(3)CH_3, C(4)H_3], 2.34 [3H, s, C(4′)CH_3], 3.76 [1H, s, C(2)H], 7.15-7.19 [2H, m, C(3′)H, C(5′)H], 7.25-7.31 [2H, m, C(2′)H, C(6′)H].

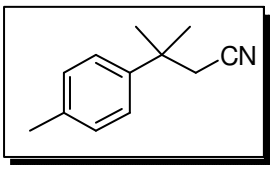
2-Cyano-3-methyl-3-(4-fluorophenyl)butanoic acid 56[5]



Ethyl-2-cyano-3-methyl-3-(4-fluorophenyl)butanoate **54** (3.65 g, 14.66 mmol) was stirred with sodium hydroxide (2.34 g, 58.66 mmol) in ethanol (95%, 25 mL) overnight. The solution was acidified to pH 2 using aqueous hydrochloric acid (10 %). The aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried, filtered and concentrated under reduced pressure to give crude acid (3.21 g) as a yellow oil which solidified after 5 days *in vacuo* to afford the pure *acid* **56** (2.10 g, 65%), m.p. 98-102 °C (Lit.,[5] 100-101°C); ν_{max}/cm^{-1} (KBr) 2980 br (OH), 1728, 1604, 1513; δ_H (400 MHz) 1.63, 1.64 [2 × 3H, 2 × s, C(3)CH_3, C(4)H_3], 3.73 [1H, s, C(2)H], 7.01-7.08 [2H, m, C(3′)H, C(5′)H], 7.34-7.40 [2H, m, C(2′)H, C(6′)H].

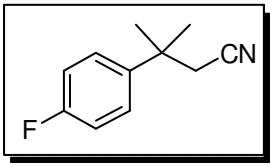
3.4 Synthesis of nitriles:

3-Methyl-3-(4-methylphenyl)butanenitrile 59[5,8]



A 100 mL round bottomed flask equipped with a magnetic stirred bar was charged with 2-cyano-3-methyl-3-(4-methylphenyl)butanoic acid **57** (2.00 g, 9.20 mmol). The flask was attached to a gas bubbler and subsequently heated in an open vessel microwave reactor for 30 min at 100 W at 200 °C. As 170 °C was reached, degassing through the bubbler was evident. The reaction mixture was cooled to room temperature to give the crude nitrile as a viscous brown oil (1.80 g). Purification by vacuum distillation gave the *nitrile* **59** (1.21 g, 76%) as pale yellow oil, b.p 120 °C at 0.04 mmHg (Lit.,[8] 138-140 °C at 10 mmHg); ν_{max}/cm^{-1} (film) 2970, 2961, 2248 (CN), 1740, 1682, 1516, 1370, 817; δ_H (300 MHz) 1.50 [6H, s, C(3)CH_3, C(4)H_3], 2.35 [3H, s, C(4′)CH_3], 2.60 [2H, s, C(2)H_2], 7.14-7.19 [2H, m, C(3′)H, C(5′)H], 7.24-7.28 [2H, m, C(2′)H, C(6′)H].

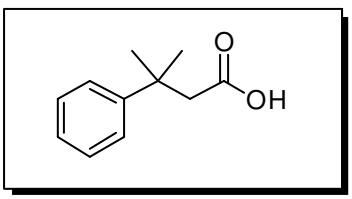
3-Methyl-3-(4-fluorophenyl)butanenitrile 58[5]



This was prepared following the procedure described for **59**, from crude 2-cyano-3-methyl-3-(4-fluorophenyl)butanoic acid **56** (5.60 g, 25.31 mmol) to give the crude nitrile as viscous brown oil (5.21 g). Purification by distillation gave the *nitrile* **58** (3.10 g, 69%) as a pale yellow oil, b.p. 110 °C at 0.10 mmHg (Lit.,[8] 138-140 °C at 10 mmHg); ν_{max}/cm^{-1} (film) 2972, 2250 (CN), 1604, 1513; δ_H (400 MHz) 1.43 [6H, s, C(3)CH_3, C(4)H_3], 2.52 [2H, s, C(2)H_2], 6.94-7.00, 7.24-7.31{2 x 2H, 2 x m, [C(3′)H, C(5′)H] and [C(2′)H, C(6′)H]}.

3.5 Synthesis of carboxylic acids:

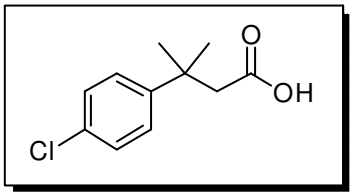
3-Methyl-3-phenylbutanoic acid 31[5,9-11]



Aluminium trichloride (25.0 g, 187.50 mmol) was added slowly to 3-methylbut-2-enoic acid (10.10 g, 100.80 mmol) in benzene (200 mL) while stirring at 0 °C under nitrogen.

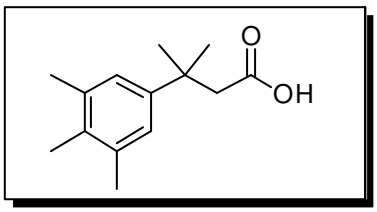
Once the addition was complete the reaction mixture was stirred for 24 h at room temperature. The reaction mixture was then carefully poured onto hydrochloric acid (10%, 200 mL) and diethyl ether (250 mL) while stirring. The layers were separated and the aqueous layer was washed with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried, filtered and concentrated under reduced pressure to yield the crude *acid* **31** (16.95 g, 94%) as a white solid, m.p 56-57 °C (Lit.,[9] 57-58 °C); ν_{max}/cm^{-1} (KBr) 2978 br (OH), 1700 (CO), 1498, 1440, 1409, 1317; δ_H (300 MHz) 1.47 [6H, s, C(3)CH_3, C(4)H_3], 2.56 [2H, s, C(2)H_2], 7.20-7.60 (5H, m, ArH).

3-Methyl-3-(4-chlorophenyl)butanoic acid 33[5,9,11]



This was prepared following the procedure for **31**, from aluminium trichloride (25.00 g, 190.00 mmol), 3-methylbut-2-enoic acid (10.00 g, 100.0 mmol) in chlorobenzene (200 mL) to yield the crude *acid* **33** (21.72 g, 99%) as a pale yellow solid, m.p. 65-68 °C (Lit.,[12] 66-67 °C); ν_{max}/cm^{-1} (KBr) 2975 br (OH), 1705 (CO), 1491, 1324, 1105; δ_H (300 MHz) 1.42 [6H, s, C(3)CH_3, C(4)H_3], 2.64 [2H, s, C(2)H_2], 7.18-7.36 (4H, m, ArH).

3-Methyl-3-(3,4,5-trimethylphenyl)butanoic acid 36[5,9]

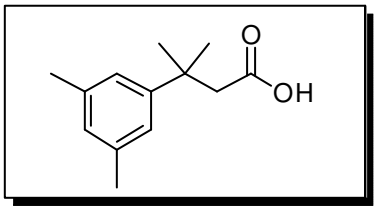


This was prepared following the procedure described for **31**, from aluminium trichloride (8.21 g, 61.56 mmol), 3-methylbut-2-enoic acid (3.08 g, 30.78 mmol) in 1,2,3-trimethylbenzene (7.40 g, 61.56 mmol), under an atmosphere of nitrogen overnight to yield the crude acid. The crude reaction mixture was subsequently extracted with aqueous sodium hydroxide (20%, 2 × 40 mL)* to remove excess starting material 1,2,3-trimethylbenzene, and then the aqueous layer was acidified to pH 1 with aqueous hydrochloric acid (10%) and extracted with diethyl ether (3 × 75 mL). The organic layer was then dried, filtered and concentrated under reduced pressure to give the crude *acid* **36** (4.20 g, 62%) as a pale brown solid, m.p 101-108°C (Lit,[13] 111-112°C); ν_{max}/cm^{-1}(KBr) 2957 br (OH), 1703 (CO), 1644 1415; δ_H (300 MHz) 1.44 [6H, s, C(3)CH_3, C(4)H_3], 2.14 [3H, s, C(4′)CH_3], 2.28 [6H, s, C(3′)CH_3, C(5′)CH_3], 2.64 [2H,

s, C(2)H_2], 7.00 [2H, s, C(2′)H, C(6′)H]. The ^{1}H NMR spectrum of the crude product contained some minor (7%) peaks at δ_H 1.46 (s) and δ_H 2.66 (s) due to an unidentifiable side product.

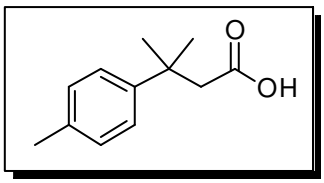
*It was difficult to remove excess trimethylbenzene *in vacuo* and the purpose of the basic workup was to try to remove the aforementioned starting material.

3-Methyl-3-(3,5-dimethyl)butanoic acid 35[9]



This was prepared following the procedure described for **31**, from aluminium trichloride (6.25 g, 47.00 mmol), 3-methylbut-2-enoic acid (2.50 g, 25.0 mmol) in *m*-xylene (45 mL) to yield the crude *acid* **35** (4.40 g, 85%) as a white solid, m.p. 100-105°C (Lit,[14] 111-112°C); (Found: C, 75.62; H, 8.83. $C_{13}H_8O_2$ requires C, 75.69, H, 8.80%); ν_{max}/cm^{-1} (KBr) 2966 br (OH), 1718, 1388, 1163; δ_H (300 MHz) 1.44 [6H, s, C(3)(CH_3), C(4)H_3], 2.30 [6H, s, C(3')H_3, C(5')CH_3], 2.63 [2H, s, C(2)H_2], 6.85 [1H, s, C(4')H], 6.97 [2H, s, C(2')H, C(6')H]; δ_C (75.5 MHz) 21.6 [CH_3, C(3)CH_3, C(5)CH_3], 28.8 [CH_3, C(3')CH_3, C(5')H_3], 36.8 [C, C(3)], 47.9 [CH_2, C(2)H_2], 123.3 [CH, C(2′)H, C(6′)H], 127.8 [CH, C(4′)H], 137.6 [C, C(3′), C(5′)], 148.1 [C, C(1′)], 177.3 [C, C(1)]; m/z (EI+) 248 [$(M+C_2H_3N)^+$, 100%], 230 [$(M+Na)^+$, 25%], 207 (20%), 105 (60%).

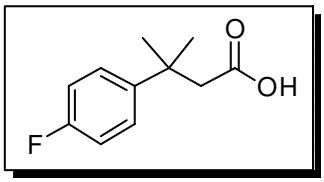
3-Methyl-3-(4-methylphenyl)butanoic acid 32[4,5]



A solution of potassium hydroxide (3.62 g, 64.65 mmol) in ethylene glycol (20 mL) was added to 3-methyl-3-(4-methylphenyl)butanenitrile **59** (3.50g, 20.21 mmol) and the resulting solution was heated under reflux overnight. The solution was then acidified to pH 2 using aqueous hydrochloric acid (10%). The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with aqueous sodium hydroxide (10%, 50 mL), and then the aqueous layer was acidified to pH 1 with aqueous hydrochloric acid and extracted with diethyl ether (3 x 50 mL). The combined organic layers were then dried, filtered and concentrated under reduced pressure to give the pure *acid* **32** (2.01 g, 52%) as a viscous, pale yellow oil which solidified as a crystalline solid after standing at room temperature for 12 h, m.p.

78-81°C (Lit.,[12] 73-74°C); ν_{max}/cm^{-1} (KBr) 2974 br (OH), 1701 (OH), 1516, 1462, 1313, 810 ; δ_H (300 MHz) 1.48 [6H, s, C(3)CH_3, C(4)H_3], 2.32 [3H, s, C(4′)CH_3], 2.63 [2H, s, C(2)H_2], 7.12 (2H, d, *J* 8.1, ArH), 7.24-7.27 (2H, m, ArH).

3-Methyl-3-(4-fluorophenyl)butanoic acid 34[4,5,11]

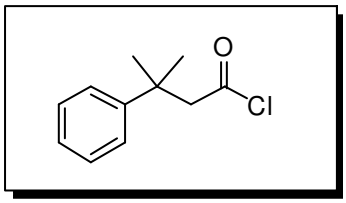


This was prepared following the procedure described for **32**, from 3-methyl-3-(4-fluorophenyl)butanenitrile **58** (4.55 g, 25.40 mmol) and a solution of potassium hydroxide (4.55 g, 81.20 mmol) in ethylene glycol (25 mL) to give the crude *acid* **34** (3.25 g, 65%) as a viscous pale yellow oil which solidified as a crystalline solid after standing at room temperature for 12 h, m.p. 63-69°C (Lit.,[15] 60-62°C); ν_{max}/cm^{-1} (KBr) 2918 br (OH), 1708, 1512, 1232, 833; δ_H (300 MHz) 1.43 [6H, s, C(3)CH_3, C(4)H_3], 2.63 [2H, s, C(2)H_2], 6.99-7.15 [2H, m, C(2′)H, C(6′)H], 7.24-7.34 [2H, m, C(3′)H, C(5′)H].

3.6 Synthesis of acid chlorides:

Caution! When DMF is exposed to thionyl chloride *N*,*N*-dimethylcarbamoyl chloride (DMCC) is formed. Extreme caution must be exercised when carrying out a reaction under such conditions as DMCC is a potent carcinogen in animals[16] and is believed to have a similar effect in humans.[17]

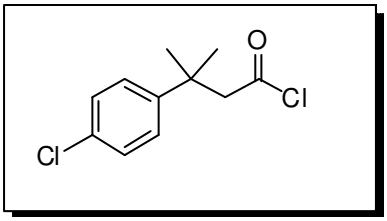
3-Methyl-3-phenylbutanoyl chloride 63[5,10,11,18]



3-Methyl-3-phenylbutanoic acid **31** (5.30 g, 29.80 mmol) and thionyl chloride (10.86 mL, 149.00 mmol) along with a catalytic amount of DMF (3 drops) was heated under reflux for 3 h while stirring under nitrogen. Excess thionyl chloride was evaporated under reduced pressure to give the crude acid chloride **63** as a brown oil. Purification by vacuum distillation gave the *acid chloride* **63** (4.41 g, 75%) as a red oil, b.p. 70 °C at 0.1 mmHg (Lit.[18] 84-86.5 °C at 3.0 mmHg; Lit.,[11] 123-125 °C at 0.9 mmHg; Lit.,[5] 72 °C at 0.1 mmHg); ν_{max}/cm^{-1} (film) 2970, 1809 (CO), 1497, 1445; δ_H (300 MHz) 1.48 [6H, s, C(3)$(CH_3)_2$], 3.28 [2H, s, C(2)H_2], 7.30-7.36 (5H, m, ArH).*

***Note:** All distilled acid chlorides were stable over long periods of time (up to 12 months) while kept under nitrogen at -20°C.

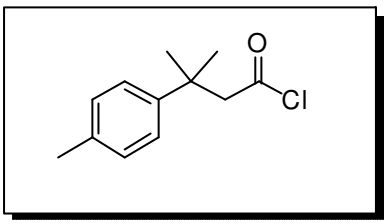
3-Methyl-3-(4-chlorophenyl)butanoyl chloride 64[5,11]



This was prepared following the procedure described for **63**, from 3-methyl-3-(4-chlorophenyl)butanoic acid **33** (29.72 g, 119.90 mmol), and thionyl chloride (43.74 mL, 599.50 mmol) along with a catalytic amount of DMF (3 drops) to give the crude acid chloride as a brown oil. Purification by vacuum distillation gave the *acid chloride* **64** (18.30 g, 66%) as a clear oil. b.p. 100 °C at 0.03 mmHg (Lit.,[11] 129-130 °C at 0.85 mmHg; Lit.,[5] 102 °C at 0.35 mmHg); ν_{max}/cm^{-1} (film) 2971, 1808 (CO), 1596, 1496, 1402; δ_H (300 MHz) 1.41 [6H, s, C(3)CH_3, C(4)H_3], 3.27 [2H, s, C(2)H_2], 7.01-7.34 (4H, m, ArH).*

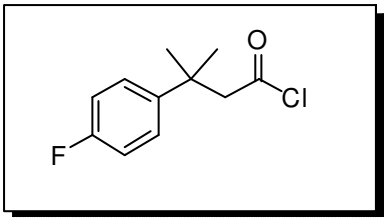
***Note:** All distilled acid chlorides were stable over long periods of time (up to 12 months) while kept under nitrogen at -20°C.

3-Methyl-3-(4-methylphenyl)butanoyl chloride 66[5]



Oxalyl chloride (2.80 mL, 33.18 mmol) in diethyl ether (10 mL) was added dropwise over 5 min to 3-methyl-3-(4-methylphenyl)butanoic acid **32** (5.80 g, 30.17 mmol) in diethyl ether (10 mL) while stirring at 0 °C under nitrogen. The solution was then slowly allowed to return to room temperature while stirring over 14 h. The solvent and residual reagent were removed under reduced pressure to give the crude *acid chloride* **66** (5.76 g, 90%) as a yellow oil which was used immediately without purification. ν_{max}/cm^{-1} (film) 2971, 1812 (CO), 1517; δ_H (300 MHz) 1.44 [6H, s, C(3)CH_3, C(4)H_3], 2.32 [3H, s, C(4′)CH_3], 3.27 [2H, s, C(2)H_2], 7.11-7.18 (2H, m, ArH), 7.22-7.39 (2H, m, ArH).

3-Methyl-3-(4-fluorophenyl)butanoyl chloride 65[5,11]

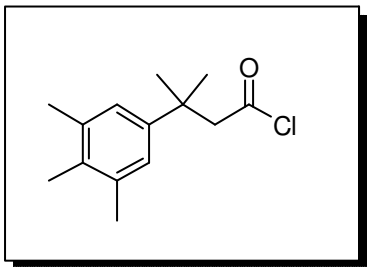


This was prepared following the procedure described for **63**, from 3-methyl-3-(4-fluorophenyl)butanoic acid **34** (2.17 g, 11.06 mmol) and thionyl chloride (4.01 mL, 55.30 mmol) along with a catalytic amount of DMF (3 drops) to give the crude acid chloride as a brown oil. Purification by vacuum distillation

gave the *acid chloride* **65** (1.23 g, 52%) as a violet oil, b.p. 90 °C at 0.3 mmHg (Lit.,[19] 132-138 °C; Lit.,[5] 70 °C at 0.25 mmHg); ν_{max}/cm^{-1} (film) 2969, 1809 (CO), 1602, 1513, 1234, 1166, 833; δ_H (300 MHz) 1.44 [6H, s, C(3)CH_3, C(4)H_3], 3.26 [2H, m, C(2)H_2], 6.97-7.08 [2H, m, C(2)H, C(6)H], 7.26-7.37 [2H, m, C(3)H, C(5)H].*

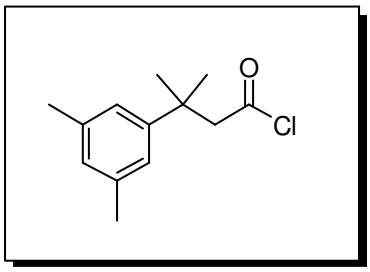
***Note:** All distilled acid chlorides were stable over long periods of time (up to 12 months) while kept under nitrogen at -20°C.

3-Methyl-3-(3,4,5-trimethyl)butanoyl chloride 68[5]



This was prepared following the procedure described for **66**, from 3-methyl-3-(3,4,5-methyl)butanoic acid **36** (3.40 g, 15.43 mmol), oxalyl chloride (1.50 mL, 16.97 mmol) to give a crude *acid chloride* as a brown oil **68** (3.80 g, 96%), which was used immediately without purification; ν_{max}/cm^{-1} (film) 2970, 1810 (CO), 1608, 1579, 1445, 1386; δ_H (300 MHz) 1.45 [6H,s, C(5)CH_3, C(6)H_3], 2.14 [3H, s, C(4′)CH_3], 2.28 [6H, s, C(3′)H_3, C(5′)H_3], 3.26[2H, s, C(2)H_2], 6.91-7.09 (2H, s, ArH).

3-Methyl-3-(3,5-dimethyl)butanoyl chloride 67

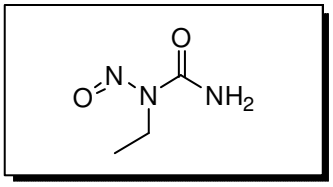


This was prepared following the procedure described for **66**, from crude 3-methyl-3-(3,5-methyl)butanoic acid **35** (1.00 g, 4.85 mmol), oxalyl chloride (0.45 mL, 5.34 mmol) in diethyl ether (10 mL) to give the crude *acid chloride* **67** (1.05 g, 96 %) as a yellow oil which was used immediately without purification. ν_{max}/cm^{-1} (film) 2970, 1813 (CO), 1604, 1473, 1325, 1178; δ_H (300 MHz) δ_H (300 MHz) 1.45 [6H, s, C(5)CH_3, C(6)H_3], 2.32 [6H, s, C(3′)H_3, C(5′)H_3], 3.27 [2H, s, C(2)H_2], 6.85-6.87 [1H, m, C(4′)H], 6.94-6.98 [2H, m, C(2′)H, C(6′)H].

The ^{1}H NMR spectrum of the crude material indicated that it consisted 18% starting material, 3-methyl-3-(3,5-methyl)butanoic acid **35**; δ_H (300 MHz) 1.44 [6H, s, C(5)CH_3, C(6)H_3], 2.64 [2H, s, C(2)H_2]. N.B Peaks for C(3′)CH_3, C(5′)CH_3 were obscured by those of the product acid chloride.

3.7 Synthesis of diazoketones:

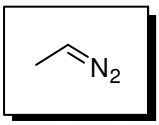
N-Ethyl-*N*-nitrosourea 328[20]



Aqueous ethylamine (70%, 192.80 g) was placed with water (115 mL) in a 1L round bottom flask. Concentrated hydrochloric acid (37%, *ca*. 310 mL) was added slowly until the solution was strongly acidic. Water (*ca*. 204 mL) was then added. This was carried out at 0 °C. Urea (>99.5%, 600 g) was added over 10 min and the solution was refluxed gently for 2.5 h and then vigorously for 30 min. The solution was then cooled to RT and then sodium nitrite (210 g) was added. Once the sodium nitrite had dissolved the solution was cooled to 0°C and added slowly over 50 min to a mechanically stirred mixture of conc. sulfuric acid (110 mL) and ice (1.2 kg) cooled at -20 °C using a ice-salt bath. *N*-Ethyl-*N*-nitrosourea formed as a foamy, crystalline precipitate, which was collected by suction filtration and washed with ice-cooled water (3 × 40 mL) to give a pale yellow powder (150 g), which was stored in freezer.

Caution: *N*-Ethyl-*N*-nitrosurea **328** is a carcinogen and should be handled with appropriate care.[21,22]

Diazoethane 329[20]



N-Ethyl-*N*-nitrosourea **328** (12.30 g, 105 mmol) was added portion wise over 30 min to a mixture of diethyl ether (78 mL) and aqueous potassium hydroxide (50% w/w, 33.5 mmol) while stirring at -20 °C. Once the addition was complete the reaction mixture was stirred for a further 30 min at -20 °C. The ethereal solution of diazoethane **329** was then decanted into a 250 mL conical flask containing potassium hydroxide pellets, cooled at -20 °C using a salt ice bath and then dried over two portions of potassium hydroxide pellets to give a solution of diazoethane **329** in diethyl ether, which was used without any further purification and freshly prepared each time before use.

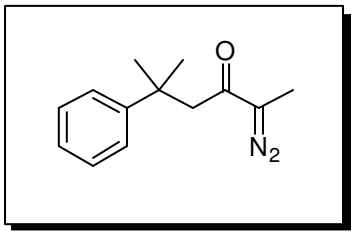
Caution! Diazoethane **329** is both toxic and explosive. All operations should be carried out in a well ventilated fume-hood with adequate shielding. The glassware used for the

generation of diazoethane **329** should have clear-glass joints to minimise the risk of explosion. Any items which come in contact with diazoethane **329** should be washed with aqueous acetic acid before being removed from fumehood.

3.7.1 Preparation of internal α-diazoketones.

Note: Broadening of the signals for $C(4)H_2$ and $C(1)CH_3$ in the ^1H NMR spectrum and for $C(1)H_3$ and C(2) in ^{13}C NMR spectrum of the α-diazoketones is evident indicating restricted rotation due to extended conjugation.

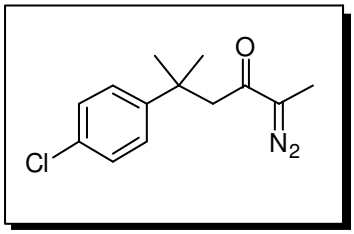
2-Diazo-5-methyl-5-phenylhexan-3-one 37[5,10,11]



Distilled 3-methyl-3-phenylbutanoyl chloride **63** (4.41 g, 22.46 mmol) in diethyl ether (100 mL) was added dropwise over ~1 h to an ethereal solution of diazoethane **329** [prepared from *N*-ethyl-*N*-nitrosourea **328** (18.40 g, 157.00 mmol) while stirring at -20 °C under nitrogen.

The solution was then allowed to slowly return to room temperature over 3 h, with the inert atmosphere removed for the last 0.5 h. The ether and residual diazoethane were evaporated under reduced pressure using a safety rotary evaporator with an acetic acid trap, resulting in the crude diazoketone as an orange oil (4.10 g), which was then purified by flash chromatography on silica gel using (20:80) ethyl acetate-hexane as eluent to give pure *diazoketone* **37** (3.60 g, 74%) as an orange oil. ν_{max}/cm^{-1} (film) 2965, 2066, 1625, 1351, 1267, 1054; δ_H (300 MHz) 1.47 [6H, s, $C(5)CH_3$, $C(6)H_3$], 1.80 [3H, s, $C(1)H_3$], 2.69 [2H, s, $C(4)H_2$], 7.18-7.37 (5H, m, ArH).

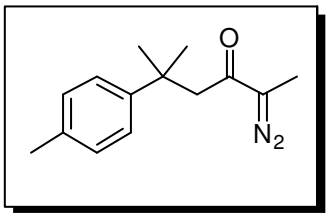
2-Diazo-5-methyl-5-(4-chlorophenyl)hexan-3-one 39[5,11]



This was prepared following the procedure outlined for **37**, from distilled 3-methyl-3-(4-chlorophenyl)butanoyl chloride **64** (7.02 g, 29.90 mmol) in diethyl ether (100 mL) and an ethereal solution of diazoethane **329** [prepared from *N*-ethyl-*N*-nitrosourea **328** (22.46 g, 209.00 mmol)].

Purification by flash chromatography on silica gel using ethyl acetate-hexane (5:95) as eluent gave the pure *diazoketone* **39** (5.23g, 74%) as an orange oil; ν_{max}/cm^{-1} (film) 2967, 2066, 1633, 1360, 1280, 1012; δ_H (300 MHz) 1.45 [6H, s, C(5)CH_3, C(6)H_3], 1.82 [3H, s, C(1)H_3], 2.69 [2H, s, C(4)H_2], 7.26-7.33 (4H, m, ArH).

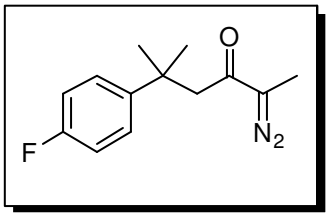
2-Diazo-5-methyl-5-(4-methylphenyl)hexan-3-one 38[5]



This was prepared following the procedure outlined for **37**, from crude 3-methyl-3-(4-methylphenyl)butanoyl chloride **66** (5.81 g, 27.53 mmol) in diethyl ether (100 mL) and an ethereal solution of diazoethane **329** [prepared from *N*-ethyl-*N*-nitrosourea **328** (22.45 g, 192.17 mmol)].

Purification by flash chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent gave the pure *diazoketone* **38** (3.45 g, 56%) as an orange oil; ν_{max}/cm^{-1} (film) 2966, 2071, 1628; δ_H (300 MHz) 1.45 [6H, s, C(5)CH_3, C(6)H_3], 1.82 [3H, s, C(1)H_3], 2.32 [3H, s, C(4)CH_3], 2.68 [2H, s, C(4)H_2], 7.12 {2H, d, *J* 8.1, one of [C(2′)H, C(6′)H] or [C(3′)H, C(5′)H]}, 7.23 {2H, d, *J* 8.3, one of [C(2′)H, C(6′)H] or [C(3′)H, C(5′)H]}.

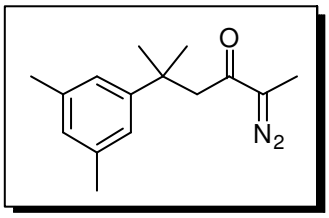
2-Diazo-5-methyl-5-(4-fluorophenyl)hexan-3-one 40[5,11]



This was prepared following the procedure outlined for **37**, from distilled 3-methyl-3-(4-fluorophenyl)butanoyl chloride **65** (1.30 g, 6.06 mmol) in diethyl ether (50 mL) and an ethereal solution of diazoethane **329** [prepared from *N*-ethyl-*N*-nitrosourea **328** (4.96 g, 42.42 mmol)].

Purification by flash chromatography on silica gel using ethyl acetate-hexane (5:95) as eluent gave the pure *diazoketone* **40** (0.62 g, 41%) as an orange oil; ν_{max}/cm^{-1} (film) 2968, 2074, 1628; δ_H (400 MHz) 1.46 [6H, s, C(5)CH_3, C(6)H_3], 1.81 [3H, s, C(1)H_3], 2.68 [2H, s, C(4)H_2], 6.96-7.05 {2H, m, one of [C(2′)H, C(6′)H] or [C(3′)H, C(5′)H]}, 7.29-7.33{2H, m, one of [C(2′)H, C(6′)H] or [C(3′)H, C(5′)H]}.

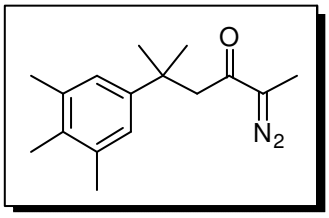
2-Diazo-5-methyl-5-(3,5-dimethylphenyl)hexan-3-one 41



This was prepared following the procedure outlined for **37**, from crude 3-methyl-3-(3,5-dimethylphenyl)butanoyl chloride **67** (3.02 g, 15.45 mmol) in diethyl ether (100 mL) and an ethereal solution of diazoethane **329** [prepared from *N*-ethyl-*N*-nitrosourea **328** (22.55 g, 192.17 mmol)].

Purification by flash chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent gave the pure *diazoketone* **41** (2.51 g, 74%) as an orange oil; ν_{max}/cm^{-1} (film) 2966, 2064, 1633, 1495, 1360, 1280, 1104; δ_H (300 MHz) 1.45 [6H, s, C(5)CH_3, C(6)H_3], 1.80 [3H, s, C(1)H_3], 2.30 [6H, s, C(3′)H_3, C(5′)H_3], 2.66 [2H, C(4)H_2], 6.84 [1H, s, C(4′)H], 6.95 [2H, s, C(2′)H, C(6′)H]; δ_C (75.5 MHz) 8.2 [CH_3, br, C(1)H_3], 21.5 [CH_3, C(3′)CH_3, C(5′)CH_3], 28.5 [CH_3, C(5)CH_3, C(6)H_3], 38.2 [C, C(5)], 50.8 [CH_2, (C(4)H_2], 63.7 [C, br, C(2)], 123.4 [CH, C(2′)H, C(6′)H], 127.7 [CH, C(4′)H], 137.5 [C, C(3′), C(5′)], 148.0 [C, C(1′)], 193.2 [C, C(3)]. Exact mass calculated for $C_{15}H_{20}N_2O$ [$(M+H)^+$], 245.1654. Found 245.1665 m/z (ES+) 245 [$(M+H)^+$], 100%], 246 (20%), 217 [$(M-N_2)^+$, 70%], 155 (80%), 75 (50%).

2-Diazo-5-methyl-5-(3,4,5-trimethylphenyl)hexan-3-one 42[5]

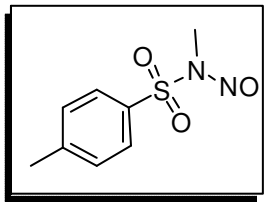


This was prepared following the procedure outlined for **37**, from crude 3-methyl-3-(3,4,5-trimethylphenyl)-butanoyl chloride **68** (4.03 g, 16.71 mmol) in diethyl ether (100 mL) and an ethereal solution of diazoethane **329** [prepared from *N*-ethyl-*N*-nitrosourea **328** (13.68 g, 116.90 mmol)].

Purification by flash chromatography on silica gel using ethyl acetate-hexane (5:95) as eluent gave the pure *diazoketone* **42** (2.59 g, 69%) as an orange oil; ν_{max}/cm^{-1} (film) 2966, 2070, 1721, 1634, 1445, 1348; δ_H (300 MHz) 1.43 [6H, s, C(5)CH_3, C(6)H_3], 1.83 [3H, s, C(1)H_3], 2.14 [3H, s, C(4′)CH_3], 2.28 [6H, s, C(3′)CH_3, C(5′)CH_3], 2.67 [2H, s, C(4)CH_2], 6.97 [2H, s, C(2′)H, C(6′)H].

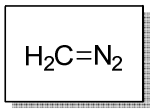
3.7.2 Preparation of terminal α-diazoketones.

Diazald® 330 [23]



A total of (32.00 g) of *p*-toluenesulfonyl chloride was divided into three portions (19.00 g, 9.00 g, and 4.00 g) and a solution of alkali was prepared by dissolving NaOH (7.00 g) in water (7.0 mL). The first portion of *p*-toluenesulfonyl chloride was added with swirling over 5 min, to aqueous methylamine (17.40 mL) contained in a 500 mL round bottom flask. The mixture was allowed to heat up to 80-90 ºC in order to maintain sulfonylmethylamine in a molten condition. As soon as the mixture became acidic, 50% NaOH solution (5.0 mL) was added carefully. This was followed by the immediate gradual addition of *p*-toluenesulfonyl chloride (9.00 g). When the mixture again becomes acidic, 50% NaOH solution (2.50 mL) was added. This was followed by the final portion of *p*-toluenesulfonyl chloride (4.00 g). After the mixture became acidic, the remainder of 50% sodium hydroxide solution was added. The mixture was then heated for 15 min, and the hot reaction mixture was poured onto glacial acetic acid (150 mL) and the smaller flask was rinsed with glacial acetic acid (15.0 mL). The solution was then cooled in an ice bath to 0 ºC, and a solution of sodium nitrite (12.40 g) in water (25.0 mL) was added dropwise over 45 min. The temperature was kept below 10 ºC upon addition of sodium nitrite solution. A yellow solid began to precipitate out of solution. Water (100 mL) was added to the mixture and the precipitate was separated and dried by vacuum filtration, to give a yellow solid (31.10 g) which was washed with cold water (2 × 10 mL) to remove excess acetic acid.

Diazomethane 331[24]



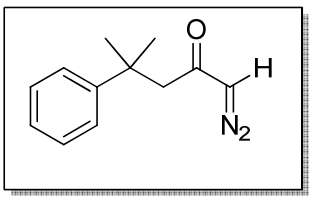
Diazald® **330** (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) (14.07 g, 65.69 mmol) in diethyl ether (80 mL) was added dropwise over 30 min to a solution of potassium hydroxide (5.31 g, 94.59 mmol) in ethanol (21 mL) and water (5.50 mL) while stirring at 65-68 ºC. The rate of addition was regulated so that the addition of one drop of the solution of Diazald® **330** coincided with the distillation of one drop of diazomethane. Once the addition was complete, diethyl ether (20 mL) was added and the distillation was continued in until most of the ether had distilled across, to give a solution

of diazomethane **331** (2.06 g, 49.00 mmol) in diethyl ether (95 mL) which was freshly prepared each time before use. **Caution!** Diazomethane **331** is highly toxic and explosive. The preparation should be carried out in a well ventilated fume-hood with adequate shielding. Explosive decomposition of diazomethane **331** can be initiated by sharp surfaces thus only glassware with clear glass joints should be used for distillation. Also the distillation apparatus should not be exposed to strong sun or artificial light.

Note: Broadening of signals for $C(3)H_2$ and C(1)H is evident in ^1H NMR spectrum and for the $C(3)H_2$ and C(1)H signals in the ^{13}C NMR spectrum of the □-diazoketones is evident indicating restricted rotation due to extended conjugation

1-Diazo-4-methyl-4-phenylpentan-2-one 43[25]

(a) Synthesis using Diazald® **330** *(*N-*methyl*-N-*nitroso-p-toluenesulfonamide):*



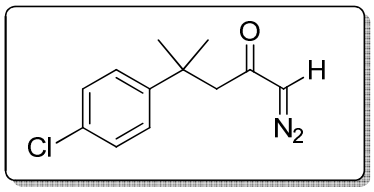
3-Methyl-3-phenylbutanoyl chloride **63** (1.50 g, 7.63 mmol) in diethyl ether (20 mL) was added dropwise over 20 min to the diazomethane **331** solution [freshly prepared from Diazald® **330** (14.07 g, 65.69 mmol) and cooled to -20 ºC using a salt ice bath] while stirring under nitrogen. The solution was then allowed to slowly return to room temperature while stirring for 4 h. The ether and residual diazomethane were evaporated under reduced pressure at room temperature, using a rotary evaporator fitted with an acetic acid trap. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (10:90) as eluent, gave the pure *diazoketone* **43** (1.01 g, 65%) as a yellow oil. ν_{max}/cm^{-1} (film) 2965 (CH), 2101 (N_2), 1637 (CO), 1361; δ_H (300 MHz) 1.45 [6H, s, $C(4)CH_3$, $C(5)H_3$], 2.60 [2H, s, $C(3)H_2$], 4.66 [1H, s, C(1)H], 7.19-7.26 [1H, m, C(4′)H], 7.31-7.40 [4H, m, C(2′)H, C(3′)H, C(5′)H, C(6′)H]; δ_C (75.5 MHz) 28.8 [CH_3, C(4)CH_3, $C(5)H_3$], 37.9 [C, C(4)], 55.2 [CH_2, br, $C(3)H_2$], 55.63 [CH, br, C(1)H], 125.6 [CH, C(2′)H, C(6′)H], 126.2 [CH, C(4′)H], 128.4 [CH, C(3′)H, C(5′)H], 148.0 [C, C(1′)], 193.5 [C, C(2)]. Exact mass calculated for $C_{12}H_{14}N_2O$ [$(M+H)^+$], 203.1184. Found 203.1193 m/z (ES+) 551 (30%), 231 (30%), 203 [$(M+H)^+$, 100%], 75 (40%).

(b) Synthesis using trimethylsilyldiazomethane:[26]

A solution of 3-methyl-3-phenylbutanoyl chloride **63** (1.00 g, 5.08 mmol) in THF:CH_3CN (10 mL, 1:1) was added dropwise to trimethylsilyldiazomethane (5.1 mL, 10.16 mmol, 2M in hexanes) in THF:CH_3CN (10 mL, 1:1) at 0 ºC under nitrogen. The reaction mixture was stirred for 4 h, and then concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography on silica gel using ethyl acetate-hexane (10:90) as eluent, gave the pure *diazoketone* **43** (0.40 g, 39%) as a yellow oil; ν_{max}/cm^{-1} (film) 2964 (CH), 2101 (N_2), 1634 (CO), 1360; δ_H (400 MHz) 1.45 [6H, s, C(4)CH_3, C(5)H_3], 2.60 [2H, s, C(3)H_2], 4.65 [1H, s, C(1)H], 7.20-7.24 [1H, m, C(4′)H], 7.30-7.40 [C(2′)H, C(3′)H, C(5′)H, C(6′)H]; The ^{1}H NMR spectrum of the pure product contained 11% of an impurity which could not be removed by flash chromatography. Signals were observed at: δ_H (400 MHz) 1.48 (6H, s), 2.66 (2H, s), 4.68 (1H, s). These signals were also present in the ^{1}H NMR spectrum of the crude product.

1-Diazo-4-methyl-(4-chlorophenyl)-pentan-2-one 45[27]

*(a) Synthesis using Diazald® **369** (*N-*methyl*-N-*nitroso-p-toluenesulfonamide):*

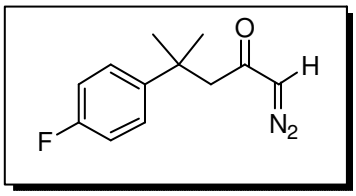


This was prepared following the procedure described for **43**, from 3-methyl-3-(4-chlorophenyl)-butanoyl chloride **64** (1.00 g, 4.36 mmol) in diethyl ether (15 mL) and an ethereal solution of diazomethane **331** [freshly prepared from Diazald® **330** (7.94 g, 37.06 mmol)]. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (5:95) as eluent, gave the pure *diazoketone* **45** (0.78 g, 77%) as a yellow oil; ν_{max}/cm^{-1} (film) 2966 (CH), 2101 (N_2), 1636 (CO), 1357; δ_H (300 MHz) 1.43 [6H, s, C(4)CH_3, C(5)H_3], 2.57 [2H, s, C(3)H_2], 4.76 [1H, s, C(1)H], 7.20-7.29 (4H, s, ArH); δ_C (75.5 MHz) 28.9 [CH_3, C(4)*C*H_3, C(5)H_3], 37.7 [C, C(4)], 54.7 [CH_2, br, C(3)H_2], 55.8 [CH, br, C(1)H], 127.2 [CH, C(2′)H, C(6′)H], 128.4 [CH, C(3′)H, C(5′)H], 131.9, 146.6 [2 × C, C(1′), C(4′)], 192.9 [C, C(2)]. Exact mass calculated for $C_{12}H_{13}{}^{35}ClN_2O$ [$(M+H)^+$], 237.0795. Found 237.0785. m/z (ES+) 489 (20%), 239 {[$(C_{12}H_{13}{}^{37}ClN_2O+H]^+$, 25%}, 237 {[$(C_{12}H_{13}{}^{35}ClN_2O+H]^+$, 30%}., 149 (30%), 116 (100%), 117 (8%).

(b) Synthesis using trimethylsilyldiazomethane:[26]

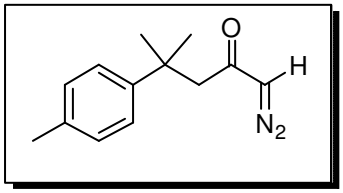
This was prepared following the procedure described for **43**, from 3-methyl-3-(4-chlorophenyl)-butanoyl chloride **64** (2.48 g, 10.59 mmol) in THF:CH_3CN (20 mL, 1:1) and trimethylsilyldiazomethane (10.59 mL, 21.18 mmol, 2M in hexanes) in THF:CH_3CN (20 mL, 1:1). Purification by flash chromatography on silica gel using ethyl acetate-hexane (10:90) as eluent, gave the pure *diazoketone* **45** (0.90 g, 36%) as a yellow oil; ν_{max}/cm^{-1} (film) 2965 (CH), 2101 (N_2), 1634 (CO), 1362; δ_H (400 MHz) 1.43 [6H, s, C(4)CH_3, C(5)H_3], 2.57 [2H, s, C(3)H_2], 4.76 [1H, s, C(1)H], 7.29 (4H, s, ArH); The ^{1}H NMR spectrum of the pure product contained 6 % of an impurity which could not be removed by flash chromatography. Signals were observed at: δ_H (400 MHz) 1.45 (6H, s), 2.64 (2H, s), 4.80 (1H, s). These signals were also present in the ^{1}H NMR spectrum of the crude product.

1-Diazo-4-methyl-(4-fluorophenyl)-pentan-2-one 46



This was prepared following the procedure described for **43**, 3-methyl-3-(4-fluorophenyl)-butanoyl chloride **65** (1.36 g, 6.35 mmol) in diethyl ether (15 mL) and a ethereal solution of diazomethane **331** [freshly prepared from Diazald® **330** (11.71 g, 54.64 mmol)]. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (5:95) as eluent, gave the pure *diazoketone* **46** (0.75 g, 51%) as a yellow oil; ν_{max}/cm^{-1} (film) 2967 (CH), 2103 (N_2), 1634 (CO), 1512, 1360; δ_H (300 MHz) 1.44 [6H, s, C(4)CH_3, C(5)H_3], 2.57 [2H, s, C(3)H_2], 4.74 [1H, s, C(1)H], 6.98-7.04 (2H, m, ArH), 7.31-7.35 (2H, m, ArH); δ_C (75.5 MHz) 29.1 [CH_3, C(4)*C*H_3, C(5)H_3], 37.6 [C, C(4)], 55.0 [CH_2, br, C(3)H_2], 55.8 [CH, br, C(1)], 115.0 [CH, $^3J_{CF}$ 21, C(3′)H, C(5′)H], 127.2 [CH, $^3J_{CF}$ 8, C(2′)H, C(6′)H], 143.7 [C, C(1′)], 161.1 [C, d, $^1J_{CF}$ 245, C(4′)], 193.2 [C, C(2)]. Exact mass calculated for $C_{12}H_{13}FN_2O$ [$(M+H)^+$], 221.1090. Found 221.1090 m/z (ES+) 221 [$(M+H)^+$], 100%], 217 (40%), 203 (35%), 175 (30%), 75 (60%).

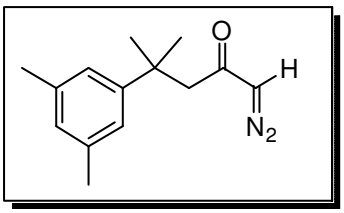
1-Diazo-4-methyl-(4-methylphenyl)-pentan-2-one 44



This was prepared following the procedure described for **43**, crude 3-methyl-3-(4-methylphenyl)-butanoyl chloride **66**

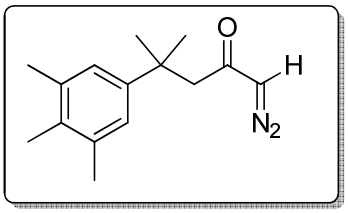
(1.15 g, 5.48 mmol) in diethyl ether (20 mL) and an ethereal solution of diazomethane **331** [freshly prepared from Diazald® **330** (9.97 g, 46.54 mmol)]. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (5:95) as eluent, gave the pure *diazoketone* **44** (0.57 g, 50%) as a yellow oil; ν_{max}/cm^{-1} (film) 2965 (CH), 2101 (N_2), 1636 (CO), 1357; δ_H (300 MHz) 1.42 [6H, s, C(4)*C*H_3, C(5)H_3], 2.32 [3H, s, C(4′)CH_3], 2.58 [2H, s, C(3)H_2], 4.68 [1H, s, C(1)H], 7.13 (2H, d, *J* 8.1, ArH), 7.23-7.27 (2H, m, ArH); δ_C (75.5 MHz) 20.9 [CH_3, C(4′)CH_3], 29.0 [CH_3, C(4)*C*H_3, C(5)H_3], 37.6 [C, C(4)], 55.3 [CH_2, br, C(3)H_2], 55.5 [CH, br, C(1)H], 125.5 [CH, C(2′)H, C(6′)H or C(3′)H, C(5′)H], 129.0 [CH, C(3′)H, C(5′)H or C(2′)H, C(6′)H], 135.6, 145.0 [2 × C, C(1′), C(4′)CH_3], 193.6 [C, C(2)]. Exact mass calculated for $C_{13}H_{16}N_2O$ [$(M+H)^+$], 217.1341. Found 217.1350. m/z (ES+) 433 (60%), 218 (35%), 217 [$(M+H)^+$, 100%], 149 (5%), 116 (20%).

1-Diazo-4-methyl-(3,5-dimethylphenyl)-pentan-2-one 47



This was prepared following the procedure described for **43**, crude 3-methyl-3-(3,5-dimethylphenyl)-butanoyl chloride **67** (1.00 g, 4.45 mmol) in diethyl ether (15 mL) and an ethereal solution of diazomethane **331** [freshly prepared from Diazald® **330** (8.46 g, 39.43 mmol)]. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (5:95) as eluent, gave the pure *diazoketone* **47** (0.58 g, 56%) as a light orange oil; ν_{max}/cm^{-1} (film) 2966 (CH), 2101 (N_2), 1634 (CO), 1358; δ_H (300 MHz) 1.41 [6H, s, C(4)CH_3, C(5)H_3], 2.31 [6H, s, C(3′)H_3, C(5′)H_3], 2.57 [2H, s, C(3)H_2], 4.72 [1H, s, C(1)H], 6.85 [1H, s, C(4′)H], 6.97 [2H, s, C(3′)(CH_3), C(5′)(CH_3)]; δ_C (75.5 MHz) 21.6 [CH_3, C(3′)H_3, C(5′)H_3], 28.9 [CH_3, C(4)*C*H_3, C(5)H_3], 37.7 [C, C(4)], 55.2 [CH_2, br, C(3)H_2], 55.6 [CH, br, C(1)H], 123.5 [CH, C(2′)H, C(6′)H], 127.8 [CH, C(4′)H], 137.6 [C, C(3′)H_3, C(5′)H_3], 148.0 [C, C(1′)], 193.7 [C, C(2)]. Exact mass calculated for $C_{14}H_{18}N_2O$ [$(M+H)^+$], 231.1497. Found 231.1492. m/z (ES+) 433 (70%), 232 (65%), 231 [$(M+H)^+$], 100%], 75 (25%).

1-Diazo-4-methyl-(3,4,5-trimethylphenyl)-pentan-2-one 48



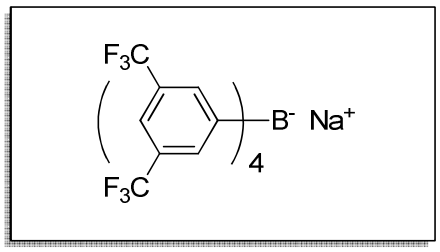
This was prepared following the procedure described for **43**, crude 3-methyl-3-(3,4,5-trimethylphenyl)-butanoyl chloride **68** (1.36 g, 6.35 mmol) in diethyl ether (15 mL) and an ethereal solution of diazomethane **331** [freshly prepared from Diazald® **330** (7.93 g, 37.06 mmol)]. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (5:95) as eluent, gave the pure *diazoketone* **48** (0.75 g, 51%) as a light orange oil; ν_{max}/cm^{-1} (film) 2966 (CH), 2100 (N_2), 1636 (CO), 1358, 1173; δ_H (600 MHz) 1.40 [6H, s, C(5)CH_3, C(6)H_3], 2.14 [3H, s, C(4′)H_3], 2.29 [6H, s, C(3′)H_3, C(5′)H_3], 2.58 [2H, s, C(3)H_2], 4.74 [1H, s, C(1)H], 7.00 (2H, s, ArH); δ_C (150 MHz) 15.1 [CH_3, C(4′)CH_3], 20.9 [CH_3, C(3′)CH_3, C(5′)CH_3], 28.9 [CH_3, C(5)CH_3, C(6)H_3], 37.4 [C, C(4)], 55.2 [CH_2, C(3)H_2], 55.6 [CH, C(1)H], 124.8 [CH, C(2′)H, C(6′)H], 132.8 [C, C(1′) or C(4′)], 136.2 [C, C(3′), C(5′)], 144.8 [C, C(1′) or C(4′)], 193.9 [C, C(2′)]. Exact mass calculated for $C_{15}H_{20}N_2O$ [$(M+H)^+$], 245.1654. Found 245.1653. m/z (ES+) 461 (20%), 245 [$(M+H)^+$, 100%], 246 (20%), 217 [$(M-N_2)^+$, 10%], 75 (25%).

3.8 Preparation of azulenones

3.8.1 General procedure for the preparation of catalysts

Sodium tetrakis[3,5-bis(trifluromethyl)phenyl]borate 168

(a) Synthesis using Brookhart's[28] modification of Kobayashi's procedure[29]



3, 5-Bis(trifluromethyl)bromobenzene (5.00 g, 17.10 mmol) in diethyl ether (25 mL) was added dropwise over 2 h to magnesium turnings (0.51 g, 21.00 mmol) in diethyl ether (15 mL) while stirring under nitrogen. The light yellow coloured solution was then heated under reflux for 30 min resulting in a dark grey solution of the aryl Grignard reagent. Upon addition of sodium tetrafluoroborate (0.41 g, 3.70 mmol) *via* a solid addition funnel, the heterogeneous reaction mixture was stirred for 48 h at room temperature under nitrogen, after which time the solution became dark brown in colour.

The reaction mixture was then added to sodium carbonate (7.50 g, 70.76 mmol) in water (100 mL) and stirred for 40 min. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were then extracted with water (100 mL), dried and treated with decolourising charcoal. The solution was then filtered and concentrated under reduced pressure to give the crude product as a brown oil. The product was dried under vacuum for 48 h at 100 ºC at 0.1 mmHg to give NaBARF* **168** as tan solid (2.43 g, 16%); ν_{max}/cm^{-1} (film) 3712, 1631, 1359, 1284, 1144; δ_H (300 MHz) 7.54 [4H, s, C(4)H], 7.69 [8H, br s (with fine splitting), *J* 2.3, C(2)H, C(6)H].

Caution! There have been reported detonations associated with the preparation of trifluoromethylphenyl Grignard reagents.[30-37] Detonations may be attributed to loss of contact with solvent, runaway exothermic side reactions and potentially the presence of a highly activated form of magnesium.

(b) Synthesis using commercially available iso-*propyl-magnesium chloride*[38] *(preferred procedure)*

A solution of *iso*-propyl-magnesium chloride (18.86 mL, 38.83 mmol, 2.0 M in THF) was added dropwise over 45 min to a stirred solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (5.88 mL, 34.13 mmol) in THF (30 mL) chilled to -20ºC while stirring under nitrogen. After the reaction mixture was warmed from -20ºC to 0 ºC over 1 h, sodium tetrafluoroborate (0.65 g, 5.88 mmol) was quickly added as a solid while stirring under nitrogen. The mixture then was stirred for 48 h at room temperature under nitrogen. The contents were then poured onto a solution of sodium carbonate (10.62 g, 100.19 mmol) and sodium bicarbonate (4.83 g, 126.41 mmol) in water (150 mL). This mixture was stirred vigorously for 1 h and then extracted with diethyl ether (4 × 75 mL). The combined organic layers were then washed with brine and dried. After filtration of the mixture and concentration under reduced pressure, the crude product was dried under vacuum for 48 h, 100 ºC at 0.1 mmHg to yield a tan yellow solid. The solid was washed with dichloromethane chilled to -30 ºC (3 × 10 mL) to yield a fine yellow powder which was recrystallised from hot fluorobenzene to give NaBARF* **168** (10.13 g, 34%) as a white powder; m.p. 297-300 ºC (Lit.,[38] 300-302 ºC) ν_{max}/cm^{-1} (film) 3716, 3647, 1631,

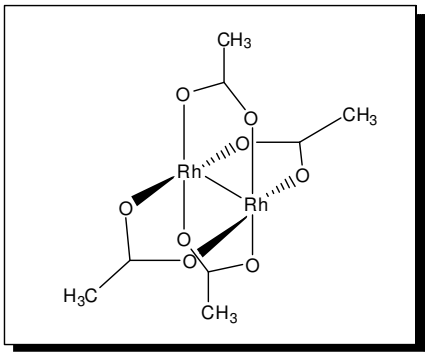
1360, 1285, 1144; δ_H [300 MHz, $(CD_3)_2CO$] 2.84 [H_2O], 7.67 [4H, s, C(4)H], 7.79 [8H, br s (with fine splitting), *J* 2.4, C(2)H, C(6)H].

*When the copper catalysed transformations were undertaken, NaBARF was calculated as its anhydrous form (6 mol %). In retrospect it is recognised that this material is hydroscopic and therefore it is likely that the NaBARF employed was either partially or fully hydrated, therefore the amount added was slightly less than that calculated. Furthermore, the degree of hydration may have changed over time with older samples likely to have been more hydrated. The yield was calculated for NaBARF in its anhydrous form.

Bergman[38] describes NaBARF as 2.6 H_2O, prepared as described above.

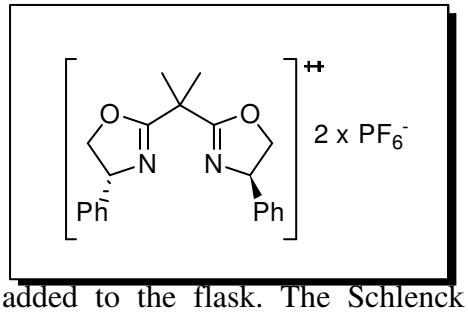
Note: All catalyst complexes were prepared using one of the four general procedures outlined below.

Method A: Aromatic addition reaction catalysed by dirhodium tetraacetate [$Rh_2(OAc)_4$] 87



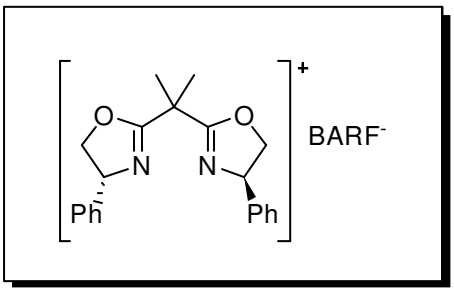
A three necked round-bottom flask with a condenser and pressure equalising addition funnel was first flame dried under nitrogen. The set-up was attached to the vacuum/inert gas manifold *via* flexible tubing. Doubly distilled dichloromethane (80 mL) was added to the flask. The Schlenck line stopcock was opened. The vacuum/inert gas manifold was opened to vacuum for 20 s. The vacuum/inert gas manifold was then opened to nitrogen and the round-bottom flask filled with nitrogen. This was repeated three times. $Rh_2(OAc)_4$ **87** (0.5 mg, <1 mol%) was then added to the solvent and once again the system was evacuated and refilled with nitrogen as before. The solution of diazoketone (1 mmol) in doubly distilled dichloromethane (80 mL) was added to the pressure equalising addition funnel and once more the system was evacuated and back filled with nitrogen (three times). Once these steps have been carried out the solvent was brought to reflux and the diazoketone was added dropwise over 1 h**.** The reaction was found to be complete by TLC once all the diazoketone was added.

Method B: Aromatic addition reaction catalysed by [Cu(II)-(*R*)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline)]$^{2+}$ (PF_6^-)$_2$ ($CuPF_6$-75)[5]



A three necked round-bottom flask with a condenser and pressure equalising addition funnel was first flame dried under nitrogen. The set-up is attached to the vacuum/inert gas manifold *via* flexible tubing. Doubly distilled dichloromethane (80 mL) was added to the flask. The Schlenck line stopcock was opened. The vacuum/inert gas manifold was opened to vacuum for 20 s. The vacuum/inert gas manifold was then opened to nitrogen and the round-bottom flask filled with nitrogen. This was repeated three times. (*R*)-(+)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline) (18.6 mg, 0.06 mmol) **75** and $[Cu(CH_3CN)_4]PF_6$[1] (20.6 mg, 0.08 mmol) were then added to the solvent and once again the system was evacuated and refilled with nitrogen (3 times) as before. The solution was stirred for 10 min at room temperature. The solution of diazoketone (1.00 mmol) in doubly distilled dichloromethane (80 mL) was added to the pressure equalising addition funnel and once more the system was evacuated and back filled with nitrogen (three times). Once these steps have been carried out the solvent was brought to reflux and the diazoketone added dropwise over 1 h**.** The reaction was found to be complete by TLC once all the diazoketone was added.

Method C: Aromatic addition reaction catalysed by [Cu(II)-(*R*)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline)]$^+$ (NaBARF) [Cu(I)Cl-NaBARF-75]

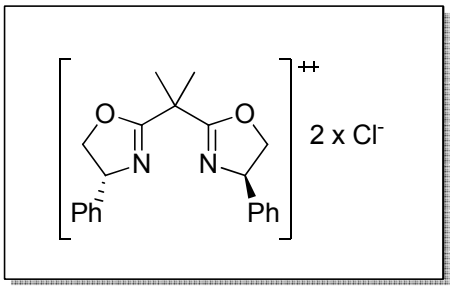


A three necked round-bottom flask with a condenser and pressure equalising addition funnel was first flame dried under nitrogen. The set-up was attached to the vacuum/inert gas manifold *via* flexible tubing. Doubly distilled dichloromethane (80 mL) was added to the flask. The Schlenck line stopcock was opened. The vacuum/inert gas manifold was opened to vacuum for 20 s. The vacuum/inert gas manifold was then opened to nitrogen and the round-bottom flask filled with nitrogen. This was repeated three times. (*R*)-(+)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline) **75** (20.0 mg, 0.06 mmol), Cu(I)Cl (5.0 mg, 0.05 mmol) and NaBARF* **168**

(53.2 mg, 0.06 mmol) were then added to the solvent and once again the system was evacuated and refilled with nitrogen (3 times) as before. The solution was stirred for 2 h at room temperature under an atmosphere of nitrogen. The solution of diazoketone (1.00 mmol) in doubly distilled dichloromethane (80 mL) was added to the pressure equalising addition funnel and once more the system was evacuated and back filled with nitrogen (three times). Once these steps have been carried out the solvent was brought to reflux and the diazoketone was added dropwise over 2 h**.** Heating was continued while stirring under reflux for an additional 1 h, at which point the reaction was found to be complete by TLC.

Note: In the ^{1}H NMR spectrum of the crude reaction mixture of all reactions containing NaBARF **168**, signals were present at δ_H 7.46 (s) and 7.64 (s) indicating the presence of BARF in the crude reaction. These peaks were not included in reaction efficiency calculations.

Method D: Aromatic addition reaction catalysed by [Cu(II)-(*R*)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline)]$^{+}$ (Cl^{-})$_2$ [Cu(I)Cl-75]

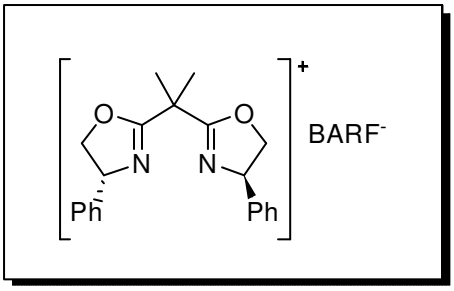


A three necked round-bottom flask with a condenser and pressure equalising addition funnel was first flame dried under nitrogen. The set-up was attached to the vacuum/inert gas manifold *via* flexible tubing. Doubly distilled dichloromethane (80 mL) was added to the flask. The Schlenck line stopcock was opened. The vacuum/inert gas manifold was opened to vacuum for 20 s. The vacuum/inert gas manifold was then opened to nitrogen and the round-bottom flask filled with nitrogen. This was repeated three times. (*R*)-(+)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline) **75** (20.0 mg, 0.06 mmol), Cu(I)Cl (5.0 mg, 0.05 mmol) were then added to the solvent and once again the system was evacuated and refilled with nitrogen (3 times) as before. The solution was stirred for 2 h at room temperature under an atmosphere of nitrogen. The solution of diazoketone (1.00 mmol) in doubly distilled dichloromethane (80 mL) was added to the pressure equalising addition funnel and once more the system was evacuated and back filled with nitrogen (three times). Once these steps have been carried out the solvent was brought to reflux and the diazoketone was added dropwise over 2 h**.** Heating was

continued while stirring under reflux. The reaction was monitored by TLC and found to be complete after 18 h.

Method D is identical to Method C but for the absence of NaBARF and a longer reaction time of 18 h.

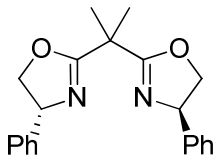
Method E: Aromatic addition reaction catalysed by [Cu(II)-(*R*)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline)]$^{+}$ (NaBARF) (18-crown-6) [Cu(I)Cl-NaBARF-75-(18-crown-6)]



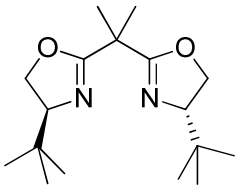
A three necked round-bottom flask with a condenser and pressure equalising addition funnel was first flame dried under nitrogen. The set-up was attached to the vacuum/inert gas manifold *via* flexible tubing. Doubly distilled dichloromethane (80 mL) was added to the flask. The Schlenck line stopcock was opened. The vacuum/inert gas manifold was opened to vacuum for 20 s. The vacuum/inert gas manifold was then opened to nitrogen and the round-bottom flask filled with nitrogen. This was repeated three times. (*R*)-(+)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline) **75** (8.0 mg, 0.06 mmol), Cu(I)Cl (2.0 mg, 0.05 mmol), NaBARF* **168** (21.2 mg, 0.06 mmol) and 18-crown-6 (6.32 mg, 0.06 mmol) were then added to the solvent and once again the system was evacuated and refilled with nitrogen (3 times) as before. The solution was stirred for 2 h at room temperature under an atmosphere of nitrogen. The solution of diazoketone (1.00 mmol) in doubly distilled dichloromethane (80 mL) was added to the pressure equalising addition funnel and once more the system was evacuated and back filled with nitrogen (three times). Once these steps have been carried out the solvent was brought to reflux and the diazoketone was added dropwise over 2 h**.** Heating was continued while stirring under reflux. The reaction was monitored by TLC and found to be complete after 18 h.

Note: In the ^{1}H NMR spectrum of the crude reaction mixture of all reactions containing NaBARF **168**, signals were present at δ_H 7.46 (s) and 7.64 (s) indicating the presence of BARF in the crude reaction. These peaks were not included in reaction efficiency calculations.

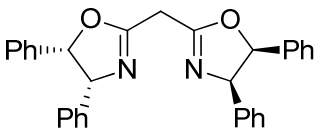
Figure 3.1 *Copper catalysts and ligand structures*



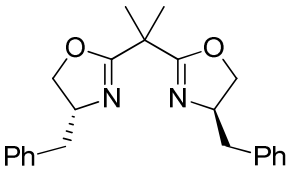
75 [(*R*,*R*)-Ph-Box]



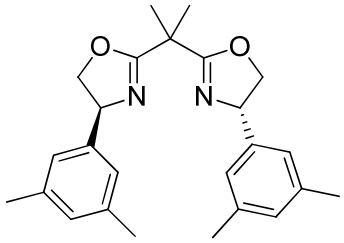
74 [(*S*,*S*)-*t*-Bu-Box]



89 [(4*R*,5*S*)-*tetra*-Ph-Box]

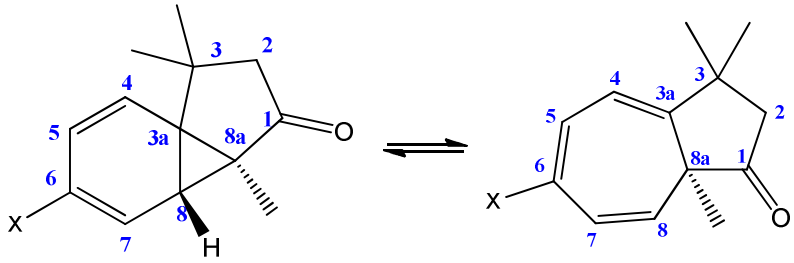


91 [(*R,R*)-Bn-Box]



93 [*S*,*S*-3,5-di-Me-Ph-Box]

3.8.2 Transition metal catalysed cyclisation of internal α-diazoketones:



Numbering scheme for azulenones

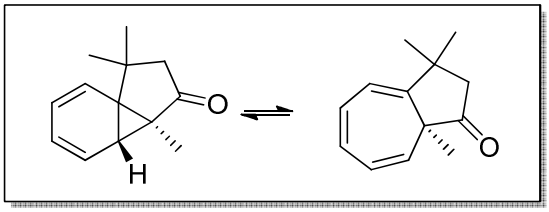
Efficiency refers to the % azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude reaction product.

Provided azulenones (except for azulenones **92** and **97**) are purified and stored in a freezer at -20 ºC, they are stable over long periods without degradation. Partial degradation was seen for azulenone **97** at room temperature over 12 h, or storage in a freezer at -20 ºC over a long period of time. Azulenone **92** was observed to decompose to a yellow oil at room temperature over 1 h, or storage in a freezer at -20 ºC over a long period of time.

The absolute stereochemistry of azulenones **92** and **97** was established through X-ray diffraction on the analogous PTAD adducts **163** and **164** demonstrating that the use of the [(*R*,*R*)-Ph-Box]-**75** ligand leads to the 3a*S* enantiomer of azulenones **92** and **97**. By analogy, it is assumed that the direction of asymmetric induction in the formation of the remaining azulenones is similar, although this has not been established. The use of the [(*S,S*)-*t*-Bu-Box]-**74** ligand leads to the opposite enantiomeric series, as evident by specific rotations.

3,8a-Dihydro-3,3,8a-trimethylazulen-1(2*H*)-one 89[5,10,11]

(a) Preparation of azulenone **89**



This was prepared following the procedure described for Method A, from 2-diazo-5-methyl-5-phenylhexan-3-one **37** (500 mg, 2.17 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). A ^1H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 85%. Purification by flash chromatography, using ethyl acetate/hexane (15:85) as eluent, gave the *azulenone* **89** (310 mg, 72%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 3042, 2923, 1747 (CO), 1716 (CO); δ_H (300 MHz) 0.75 [3H, s, C(8a)CH_3], 1.14, 1.31 [2 × 3H, 2 × s, C(3)(CH_3)$_2$], 2.20 [1H, A of AB, J_{AB} 17.4, one of C(2)H_2], 2.28 [1H, B of AB, J_{AB} 17.4, one of C(2)H_2], 4.16 [1H, d, *J* 8.1, C(8)H], 6.07-6.14 [1H, m, C(7)H], 6.24-6.41 [2H, m, C(4)H, C(5)H, C(6)H].

(b) Effect of catalyst on the decomposition of diazoketone **37**

Table 3.1 *Effect of catalyst on the cyclisation of diazoketone* **37**

Entry	Catalyst	Method	Time (h)[a]	Eff (%)[b]	Yield (%)[c]	ee (%)[d]
1	$Rh_2(OAc)_4$ **87**	A	1	85	72	-
2	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][e]	B	1	79	74	78[l]
3	$CuPF_6$-**89**[(4*R*,5*S*)-*tetra*-Ph-Box][e]	B	1	87	58	68[l]
4	CuCl-**75**[(*R*,*R*)-Ph-Box][f,g]	D	2	37	31	37[l]
5	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box][h]	C	2	72	52	78[l,n]
6	CuCl-NaBARF-**74**[(*S*,*S*)-*t*-Bu-Box][h,i]	C	2	60	48	24[m]
7	CuCl-NaBARF-**89**[(4*R*,5*S*)-*tetra*-Ph-Box][h]	C	2	71	52	73[l]

8	CuCl-NaBARF-**91**[(*R,R*)-Bn-Box][h]	C	2	70	54	27[l]
9	$CuPF_6$-**93**[(*S,S*)-3,5-di-Me-C_6H_3-Box][e]	B	1	85	69	68[m]
10	CuCl-$NaPF_6$-**75**[(*R,R*)-Ph-Box][j]	C	2	72	65	78[l]
11	CuCl-NaBARF-**75**[(*R,R*)-Ph-Box]-18- Crown-6[k]	E	2	50	46	39[l]

a. Number of hours over which diazoketone was added.

b. Efficiency refers to the percentage azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude product.

c. Yield of isolated product after flash chromatography.

d. Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.

e. The catalyst was prepared from 1.3:1 molar mixture of ligand: $Cu(CH_3CN)_4PF_6$.

f. The catalyst was prepared from 1.3:1 molar mixture of ligand: CuCl.

g. The ^{1}H NMR spectrum of the crude reaction mixture contained a mixture of impurities (20%). Signals were observed at δ_H (300 MHz): 1.34-1.36 (3H, m), 1.45-1.47 (8H, m), 1.61-1.69 (8H, m), 2.91 (1H, A of AB, J_{AB} 15.9), 3.10 (1H, B of AB, J_{AB} 15.6), 4.70 (1H, t, J 8.9), 5.24-5.27 (1H, m).

h. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20^{o}C before substrate was added.

i. The ^{1}H NMR spectrum of the crude reaction mixture contained starting material **37** (10%).

j. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% $NaPF_6$. Catalyst was stirred for 2 h at 20^{o}C before substrate was added.

k. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand, 6 mol% NaBARF and 6 mol% 18-crown-6. Catalyst was stirred for 2 h at 20^{o}C before substrate was added.

l. Major Enantiomer = (−).

m. Major Enantiomer = (+).

n. Specific Rotation: $[\alpha]_D^{20}$ −15.22 [*c* 1.85, CH_2Cl_2]

(c) Conditions for resolution of the enantiomers of azulenone **89** *{$CuPF_6$-***75***[(*R,R*)-Ph-Box]} by ^{1}H NMR analysis*

Table 3.2 *Position of signals with varying amounts of (+)-Eu(hfc)$_3$ added to ~5 mg of azulenone* **89** *in 0.5 mL of $CDCl_3$*

Entry	Quantity of Eu(hfc)$_3$ added	C(8a)CH_3	× 2 C(3)CH_3	C(2)H_2	C(8)H	C(7)H	C(4)H, C(5)H, C(6)H
1	0 mg	0.75, s	a.1.14, s b. 1.31, s	2.20,d 2.28,d	4.14, d	6.08-6.13, m	6.24-6.41, m
2	5.5mg	1.14, s	a. 1.50, s b. 1.66, s 1.68,s	3.21,d 3.34,d	4.75, d 4.78, d	6.32-6.38, m	6.47-6.61, m
3	11.5mg	1.36, s	a.1.46, s b. **1.64, s**[b] **1.67**, **s**[c]	3.17,d 3.30,d	4.72, d 4.74, d	6.31-6.37, m	6.47-6.64, m

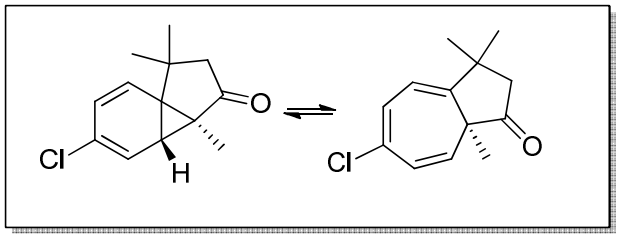
a. The relative integration of the highlighted signals was used to estimate the %ee.
b. Signal due to the dextrorotatory (+) enantiomer.
c. Signal due to the levorotatory (-) enantiomer

See Appendix 2 for stack plots of azuleone **89**.

Note: Treatment of azulenone **89** with (+)-Eu(hfc)$_3$ as a chiral shift reagent resulted in the resolution of not only the C(3)$(CH_3)_2$ signals of the enantiomers but also the resolution of the C(2)H_2 AB system. In some instances, enantioselectivities were calculated by integration of the C(2)H_2 signals.

3,8a-Dihydro-6-chloro-3,3,8a-trimethylazulen-1(2*H*)-one 95[5,39]

(a) Preparation of azulenone **95**



This was prepared following the procedure described for Method A, from 2-diazo-5-methyl-5-(4-chlorophenyl)-hexan-3-one **39** (250 mg, 0.99 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). A ^{1}H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 85%. Purification by flash chromatography, using ethyl acetate/hexane (3:97) as eluent, gave the *azulenone* **95** (180 mg, 75%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 2961, 2925, 1749 (CO), 1715 (CO); δ_H (300 MHz)* 0.86 [3H, s, C(8a)CH_3], 1.14, 1.33 [2 × 3H, 2 × s, C(3)(CH_3)$_2$], 2.22 [1H, A of AB, J_{AB} 17.4, one of C(2)H_2], 2.39 [1H, B of AB, J_{AB} 17.4, one of C(2)H_2], 4.54 [1H, d, *J* 9.0, C(8)H], 6.14 [1H, dd, *J* 8.7, 0.9, C(7)H], 6.23 [1H, d, *J* 8.1, C(4)H], 6.52 [1H, dd, *J* 8.1, 1.5, C(5)H].

*The ^{1}H NMR spectrum of the pure product contained an impurity (9%) which is possibly an isomer of *azulenone* **95**. Signals were observed at: δ_H (300 MHz) 0.88, 1.18, 1.35 (3 × 3H, 3 × s), 2.25 (1H, A of AB, J_{AB} 17.3), 2.43 (1H, B of AB, J_{AB} 17.4), 4.71 (1H, d, *J* 9.0). The signals were also present in the ^{1}H NMR spectrum of the crude product. This isomer was seen in all entries in **Table 3.4**, but did not affect estimation of the enantioselectivities.

(b) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **39**

Table 3.4 *Effect of catalyst on cyclisation of diazoketone* **39**

Entry	Catalyst	Method	Time (h)[a]	Eff (%)[b]	Yield (%)[c]	ee (%)[d]
1	$Rh_2(OAc)_4$**87**	A	1	85	75	-
2	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][e,f]	B	1	73	63	62[s]
3	$CuPF_6$-**74**[(*S*,*S*)-*t*-Bu-Box][e]	B	1	89	46	11[s,y]
4	CuCl-**75**[(*R*,*R*)-Ph-Box][g,h]	D	2	66	49	0
5	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box][i]	C	2	65	54	78[s,u]
6	CuCl-NaBARF-**74**[(*S*,*S*)-*t*-Bu-Box][i,j]	C	2	47	35	23[t]
7	CuCl-NaBARF-**89**[(4*R*,5*S*)-*tetra*-Ph-Box][i]	C	2	62	44	68[s]
8	CuCl-NaBARF-**91**[(*R*,*R*)-Bn-Box][i]	C	2	66	47	24[s]
9	$CuPF_6$-**93**[(*S*,*S*)-3,5-di-Me-C_6H_3-Box][e]	B	1	80	68	71[t]
10	CuCl-$NaPF_6$-**75**[(*R*,*R*)-Ph-Box][k]	C	2	62	56	73[s,v]
11	$CuPF_6$-NaBARF-**75**[(*R*,*R*)-Ph-Box][l]	C	2	67	43	72[s,w]
12	CuOTf-NaBARF-**75**[(*R*,*R*)-Ph-Box][m]	C	2	74	56	77[s,x]
13	CuCl-NaI-**75**[(*R*,*R*)-Ph-Box][n]	D	2	58	44	0
14	CuCl-NaCl-**75**[(*R*,*R*)-Ph-Box][o]	D	2	43	38	0
15	CuCl-$LiPF_6$-**75**[(*R*,*R*)-Ph-Box][p]	C	2	73	66	54[s]
16	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-	E	2	51	47	0

	Box]-18-Crown-6[q]					
17	CuCl-KBARF-**75**[(*R*,*R*)-Ph-Box][r]	C	2	72	65	63[s]

a. Number of hours over which diazoketone was added.
b. Efficiency refers to the percentage azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude product.
c. Yield of isolated product after flash chromatography.
d. Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
e. The catalyst was prepared from 1.3:1 molar mixture of ligand: $Cu(CH_3CN)_4PF_6$.
f. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (7%).
g. The catalyst was prepared from 1.3:1 molar mixture of ligand: CuCl.
h. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (5%).
i. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20^{o}C before substrate was added.
j. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (6%) and starting diazoketone **39** (18%).
k. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% $NaPF_6$. Catalyst was stirred for 2 h at 20^{o}C before substrate was added.
l. The catalyst was prepared from 5 mol% $CuPF_6$, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20^{o}C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (4%)
m. The catalyst was prepared from 5 mol% CuOTf, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20^{o}C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (3%).
n. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaI. Catalyst was stirred for 2 h at 20^{o}C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (12%).
o. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6mol% NaCl. Catalyst was stirred for 2 h at 20^{o}C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (15%).
p. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% $LiPF_6$. Catalyst was stirred for 2 h at 20^{o}C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (7%).
q. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand, 6 mol% NaBARF and 6 mol% 18-crown-6. Catalyst was stirred for 2 h at 20^{o}C before substrate was added.
r. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% KBARF. Catalyst was stirred for 2 h at 20^{o}C before substrate was added. The ^{1}H NMR spectrum of the crude reaction mixture contained the diketone **107** (4%).
s. Major Enantiomer = (−).
t. Major Enantiomer = (+).
u. Specific Rotation: $[\alpha]_D^{20}$ −26.19 [*c* 1.85, CH_2Cl_2].
v. Specific Rotation: $[\alpha]_D^{20}$ −23.86 [*c* 0.66, CH_2Cl_2].
w. Specific Rotation: $[\alpha]_D^{20}$ −22.29 [*c* 0.16, CH_2Cl_2].
x. Specific Rotation: $[\alpha]_D^{20}$ −21.50 [*c* 0.20, CH_2Cl_2].
y. Low yield due to another fraction containing azulenone being impure.

*(c) Conditions for resolution of the enantiomers of azulenone {$CuPF_6$-**75**[(R,R)-Ph-Box]} **95** by ^1H NMR analysis*

Table 3.5 *Position of signals with varying amounts of (+)-Eu(hfc)$_3$ added to ~5 mg of azulenone* **95** *in 0.5 mL of $CDCl_3$*

Entry	Quantity of Eu(hfc)$_3$ added	C(8a)CH_3	C(3)CH_3	C(3)CH_3	C(2)H_2	C(8)H	C(4)H, C(5)H, C(7)H
1	0 mg	0.86, s	1.14, s	1.33, s	2.21, d 2.39, d	4.54, d	6.14, dd 6.23, d 6.51, dd
2	7 mg	1.26, s	1.26, s	1.51 s 1.52, s	2.28-2.96, m	4.90, d	6.26, dd 6.38, d 6.62, dd
3	11 mg	1.26, s	1.26, s	1.51s 1.52, s	2.73-2.99, m	4.89, d 4.95, d	6.27, dd 6.38, d 6.62, dd
4	13 mg	1.32, s	1.44, s	**1.59, s**[b] **1.60, s**[c]	2.97-3.25, m	5.04-5.09, m	6.31-6.35, m 6.44-6.51, m 6.66, dd

a. The relative integration of the highlighted signals was used to estimate the %ee.
b. Signal due to the dextrorotatory (+) enantiomer.
c. Signal due to the levorotatory (−) enantiomer.

Note: Treatment of azulenone **95** with (+)-Eu(hfc)$_3$ as a chiral shift reagent resulted in the resolution of not only the C(3)$(CH_3)_2$ signals of the enantiomers but also the resolution of the C(2)H_2 AB system. In some instances, enantioselectivities were calculated by integration of the C(2)H_2 signals.

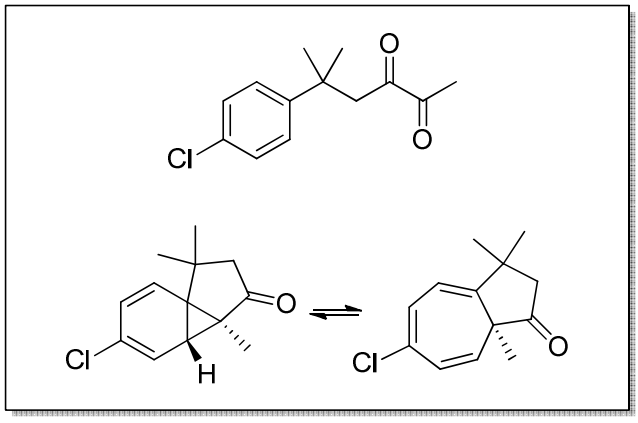
(d) Effect of catalyst complexation times on the enantioselectivity of the decomposition of diazoketone **39**

Table 3.6 *Effect of catalyst complexation times on enantioselectivity of diazoketone* **39**

Entry	Catalyst	Method	Time (h)[a]	Eff (%)[b]	Yield (%)[c]	ee (%)[d]
1	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]	C	0	68	44	68[e]
2	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]	C	2	65	54	78[e]
3	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box]	C	24	69	32	74[e]

a. Number of hours catalyst was stirred before diazoketone was added.
b. Efficiency refers to the percentage azulenone formed relative to aromatic byproducts and is determined from the crude ^{1}H NMR spectrum of the product.
c. Yield of isolated product after flash chromatography.
d. Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
e. Major Enantiomer = (−).

(e) Preparation of 5-(4-chlorophenyl)-5-methylhexane-2,3-dione **107** *by the decomposition of 2-diazo-5-methyl-5-(4-chlorophenyl)-hexan-3-one* **39** *with $Rh_2(OAc)_4$ in dichloromethane and water.*



This was prepared following the procedure described for Method A, from 2-diazo-5-methyl-5-(4-chlorophenyl)-hexan-3-one **39** (120 mg, 0.54 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL) and water (1 mL) to give the crude *diketone* **107** and *azulenone* **95** (110 mg) in the ratio of **107**:**95** 70:30 as a bright green oil. Purification by flash chromatography, using ethyl acetate/hexane (3:97) as eluent, gave the two fractions.

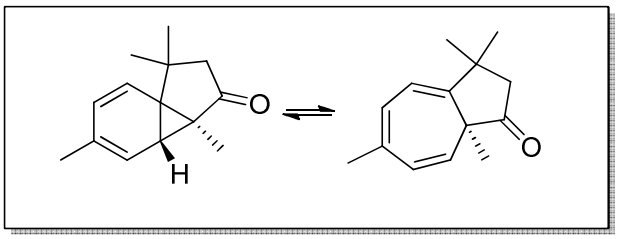
The first, least, polar fraction gave the *diketone* **107** and an unidentifiable impurity (18%) (0.021 g). ν_{max}/cm^{-1} (film) 1716, 913, 743; δ_H (300 MHz) *diketone* **107** 1.42 [6H, s,

C(5)$(CH_3)_2$], 2.08 [3H, s, C(1)H_3], 3.09 [2H, s, C(4)H_2], 7.25-7.27 [4H, m, ArH]. Unidentifiable signals were seen at; δ_H (300 MHz) 0.83-0.91 (6H, m), 0.96 (1H, d, *J* 6.5), 1.25 -1.27 (6H, m), 1.31 (2H, s), 2.17 (1H, s), 7.15 -7.34 (3H, m).

The second, most polar, fraction contained the *diketone* **107** and *azulenone* **95** (0.069 g) in the ratio of **107**:**95**, 76:24. ν_{max}/cm^{-1} (film) 2967, 1750, 1715, 1497, 1401, 1348; δ_H (300 MHz) *diketone* **107** 1.42 [6H, s, C(5)$(CH_3)_2$], 2.08 [3H, s, C(1)H_3], 3.09 [2H, s, C(4)H_2], 7.25-7.27 [4H, m, ArH]; δ_H (300 MHz) *azulenone* **95** 0.86 [3H, s, C(8a)CH_3], 1.14, 1.33 [2 × 3H, 2 × s, C(3)(CH_3)$_2$], 2.21 [1H, A of AB, J_{AB} 17.4, one of C(2)H_2], 2.39 [1H, B of AB, J_{AB} 17.4, one of C(2)H_2], 4.54 [1H, d, *J* 9.0, C(8)H], 6.14 [1H, dd, *J* 8.7, 0.9, C(7)H], 6.23 [1H, d, *J* 8.1, C(4)H], 6.52 [1H, dd, *J* 8.1, 1.5, C(5)H]; δ_C (75.5 MHz) *diketone* **107** 23.1 [CH_3, C(1)H_3], 29.1 [CH_3, C(5))$CH_3)_2$)], 37.1 [C, C(5)], 47.5 [CH_2, C(4)H_2], 127.1, 128.4 [2 × CH, ArH], 197.7, 198.3 [C, C(2), C(3)].

3,8a-Dihydro-3,3,6,8a-tetramethylazulen-1(2*H*)-one 96[5]

(a) Preparation of azulenone **96**



This was prepared following the procedure described for Method A, from 2-diazo-5-methyl-5-(4-methylphenyl)hexan-3-one **38** (100 mg, 0.44 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). A ^{1}H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 90%. Purification by flash chromatography, using ethyl acetate/hexane (3:97) as eluent, gave the *azulenone* **96** (71 mg, 80%) as a clear oil; ν_{max}/cm^{-1} (film) 2961, 2925, 1749 (CO), 1716 (CO), 1451; δ_H (300 MHz) 0.68 [3H, s, C(8a)CH_3], 1.08, 1.26 [2 × 3H, 2 × s, C(3)(CH_3)$_2$], 1.95 [3H, apparent d, *J* 1.1, C(6)CH_3], 2.08 [1H, A of AB, J_{AB} 17.3, one of C(2)H_2], 2.15 [1H, B of AB, J_{AB} 17.3, one of C(2)H_2], 3.49 [1H, d, *J* 6.9, C(8)H], 5.81 [1H, d of q, *J* 7.0, 1.1, C(7)H], 6.16-6.18 [2H, m that appears as a d at 6.17, *J* 1.1, C(4)H, C(5)H].

(b) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **38**

Table 3.7 *Effect of catalyst on the cyclisation of diazoketone* **38**

Entry	Catalyst	Method	Time (h)[a]	Eff (%)[b]	Yield (%)[c]	ee (%)[d]
1	$Rh_2(OAc)_4$**87**	A	1	90	80	-
2	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][e]	B	1	80	74	80[j]
3	CuCl-**75**[(*R*,*R*)-Ph-Box][f,g]	D	2	79	45	44[j]
4	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box][h]	C	2	62	46	80[j,l]
5	CuCl-NaBARF-**74**[(*S,S*)-*t*-Bu-Box][h,i]	C	2	75	50	27[k]
6	CuCl-NaBARF-**89**[(4*R*,5*S*)-*tetra*-Ph-Box][h]	C	2	55	49	70[j]
7	CuCl-NaBARF-**91**[(*R,R*)-Bn-Box][h]	C	2	58	42	30[j]
8	$CuPF_6$-**93**[*S*,*S*-3,5-di-Me-C_6H_3-Box][e]	B	1	80	65	73[k]

a. Number of hours over which diazoketone was added.
b. Efficiency refers to the percentage azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude product.
c. Yield of isolated product after flash chromatography.
d. Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
e. The catalyst was prepared from 1.3:1 molar mixture of ligand: $Cu(CH_3CN)_4PF_6$.
f. The catalyst was prepared from 1.3:1 molar mixture of ligand: CuCl.
g. The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown impurity (22%). Signals were observed at δ_H (400 MHz) 1.42-1.46 (3H, m), 2.25-2.33 (2H, m).
h. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20^{o}C before substrate was added.
i. The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown impurity (18%). Signals were observed at δ_H (300 MHz) 0.86 (6H, s), 1.44 (3H, s), 1.80 (1H, s), 2.30 (2H, s), 3.87-3.93 (1H, m), 4.20-4.37 (2H, m).
j. Major Enantiomer = (−).
k. Major Enantiomer = (+).
l. Specific Rotation: $[\alpha]_D^{20}$ -2.69 [*c* 0.3, $CHCl_3$].

*(c) Conditions for resolution of the enantiomers of azulenone {$CuPF_6$-**75**[(R,R)-Ph-Box]} **96** by ^1H NMR analysis*

Table 3.8 *Position of signals with varying amounts of (+)-Eu(hfc)$_3$ added to ~20 mg of azulenone* **96** *in 0.5 mL of $CDCl_3$*

Entry	Quantity of Eu(hfc)$_3$ added	C(8a)CH_3	× 2 C(3)CH_3	C(6)CH_3	C(2)H_2	C(8)H	C(4)H, C(5)H, C(7)H
1	0 mg	0.68, s	a.1.08, s b. 1.26, s	1.95, s	2.08, d 2.15, d	3.49, d	5.81, d of q, *J* 7.0, 1.1 6.17, d, *J* 1.1
2	3.5mg	1.03, s	a. 1.18 s b. 1.42, s 1.44	2.04, s	2.55-2.59, m	3.75, d	5.91, d of q, J 7.0, 6.25, br d 6.31, br d
3	8.5 mg	1.34, s	a.1.53, s b. 1.66, s 1.69, s	2.09, s	3.23-3.35, m	4.14, d	6.08, br d, *J* 7.0 6.37, d, *J* 8.8 6.49-6.53,m
4	12.5 mg	1.51, s	a.1.92, s 1.98, s b. 2.08, s	2.18, s	3.98-4.20, m	4.58, d	6.27, br d, *J* 7.0 6.53, d, *J* 8.8 6.73-6.76, m
5[a]	14.5 mg	1.33, s	a.1.51, s **b.1.64, s**[b] **1.68, s**[c]	2.08, s	3.18-3.33, m	4.12, d	6.06, br d 6.36, d 6.47-6.52, m

a. The relative integration of the highlighted signals was used to estimate the %ee.
b. Signal due to the dextrorotatory (+) enantiomer.
c. Signal due to the levorotatory (–) enantiomer.

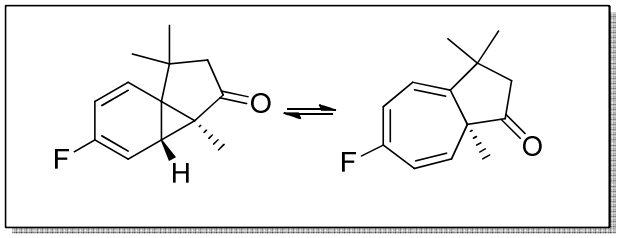
See Appendix 2 for stack plots of azulenone **96**.

Note: Treatment of azulenone **96** with (+)-Eu(hfc)$_3$ as a chiral shift reagent resulted in the resolution of not only the C(3)$(CH_3)_2$ signals of the enantiomers but also the resolution of

the $C(2)H_2$ AB system. In some instances, enantioselectivities were calculated by integration of the $C(2)H_2$ signals.

3,8a-Dihydro-6-fluoro-3,3,8a-trimethylazulen-1(2*H*)-one 94[5,11]

(a) Preparation of azulenone **94**



This was prepared following the procedure described for Method A, from 2-diazo-5-methyl-5-(4-fluorophenyl)hexan-3-one **40** (100 mg, 0.43 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). A ^1H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 75%. Purification by flash chromatography, using ethyl acetate/hexane (3:97) as eluant, gave the *azulenone* **94** (65 mg, 74%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 2964, 2872, 1753 (CO), 1652, 1532; δ_H (300 MHz) 0.91 [3H, s, C(8a)CH_3], 1.15, 1.37 [2 × 3H, 2 × s, C(3)(CH_3)$_2$], 2.24 [1H, A of AB, J_{AB} 17.4, one of $C(2)H_2$], 2.50 [1H, B of AB, J_{AB} 17.4, one of $C(2)H_2$], 5.12 [1H, dd, J_{HH} 10.0, J_{HF} 5.1, C(8)H], 6.03-6.10 [1H, m, C(7)H], 6.16-6.30 [2H, m, C(4)H, C(5)H].

(b) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **40**

Table 3.9 *Effect of catalyst on the cyclisation of diazoketone* **40**

Entry	Catalyst	Method	Time (h)[a]	Eff (%)[b]	Yield (%)[c]	ee (%)[d]
1	$Rh_2(OAc)_4$**87**	A	1	81	74	-
2	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][e]	B	1	86	81	56[k]
3	CuCl-**75**[(*R*,*R*)-Ph-Box][f]	C	-[m]	-[m]	-[m]	-[m]
4	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box][g,h]	C	2	54	51	72[k,n]
5	CuCl-NaBARF-**74**[(*S*,*S*)-*t*-Bu-Box][g,i]	C	2	34	30	18[k]
6	CuCl-NaBARF-**89**[(4*R*,5*S*)-	C	2	65	48	72[l]

	tetra-Ph-Box][g]					
7	CuCl-NaBARF-**91**[(*R,R*)-Bn-Box][g,j]	C	2	70	47	32[k]
8	$CuPF_6$-**93**[*S,S*-3,5-di-Me-C_6H_3-Box][e]	B	1	90	71	51[l]

a. Number of hours over which diazoketone was added.
b. Efficiency refers to the percentage azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude product.
c. Yield of isolated product after flash chromatography.
d. Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
e. The catalyst was prepared from 1.3:1 molar mixture of ligand: $Cu(CH_3CN)_4PF_6$.
f. The catalyst was prepared from 1.3:1 molar mixture of ligand: CuCl.
g. The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20°C before substrate was added.
h. The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown impurity (10%). Signals were observed at δ_H (400 MHz): 1.32 (6H, s), 1.99 (3H, s), 4.12 (3H, t, *J* 8,3), 4.55 (2H, t, *J* 10.1), 4.96 (3H, dd, *J* 10.1, *J* 8.0).
i. The ^{1}H NMR spectrum of the crude reaction mixture contained an impurity (15%). Signals were consistent with the diketone impurity. Signals were observed at δ_H (300 MHz): 1.45 (6H, s), 2.11 (3H, s), 3.10 (2H, s).
j. The ^{1}H NMR spectrum of the crude reaction mixture contained an impurity (3%), the signals were consistent with the diketone impurity. Signals were observed at δ_H (300 MHz): 1.43 (6H, s), 2.05 (3H ,s), 3.08 (2H, s).
k. Major Enantiomer = (–).
l. Major Enantiomer = (+).
m. No reaction.
n. Specific Rotation: $[\alpha]_D^{20}$ -6.72 [*c* 0.32, $CHCl_3$].

*c) Conditions for resolution of the enantiomers of azulenone {$CuPF_6$-**75**[(R,R)-Ph-Box]} **94** by ^{1}H NMR analysis*

Table 3.10 *Position of signals with varying amounts of (+)-Eu(hfc)$_3$ added to ~5 mg of azulenone* **94** *in 0.5 mL of $CDCl_3$*

Entry	Quantity of Eu(hfc)$_3$ added	C(8a)CH_3	C(3)CH_3	C(3)CH_3	C(2)H_2	C(8)H	C(4)H, C(5)H, C(7)H
1	0 mg	0.91, s	1.15, s	1.37, s	2.24,d *(H_A)* 2.50,d *(H_B)*	5.12, dd	6.03-6.10, m, *C(7)H* 6.16-6.30, m, *C(4)H-C(5)H*
2	6 mg	1.10, s	1.21, s	1.44, s 1.45,s	2.51,d *(H_A)* 2.74,d *(H_B)*	5.29-5.33, m	6.08-6.16, m 6.21-6.31, m

					2.80,d *(H_B)*		
3	10mg	1.19, s 1.21,s	1.25, s	1.49, s 1.50, s	2.65,d *(H_A)* 2.89,d *(H_B)* 2.94,d *(H_B)*	5.39, dd 5.42, dd	6.12-6.19, m 6.24-6.35, m
4	13.5 mg	1.29, s	1.29, s 1.31, s	1.53, s 1.64, s	2.81,d *(H_A)* 3.07-3.18, m	5.52-5.57, m	6.15-6.22, m 6.27-6.39, m
5[a]	18 mg	1.38, s	1.57, s 1.59, s	**1.65, s[b]** **1.66, s[c]**	3.15-3.17, m 3.40-3.50, m	5.80-5.87, m	6.24-6.31, m 6.34-6.49, m

a. The relative integration of the highlighted signals was used to estimate the %ee.

b. Signal due to the dextrorotatory (+) enantiomer.

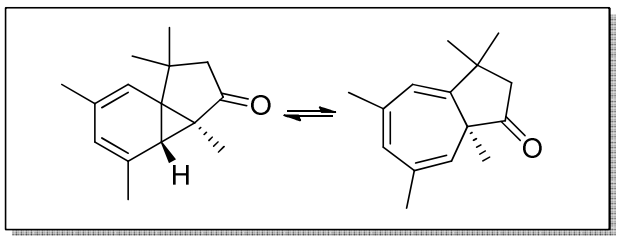
c. Signal due to the levorotatory (–) enantiomer.

See Appendix 2 for stack plots of azulenone **94**.

Note: Treatment of azulenone **94** with (+)-Eu(hfc)$_3$ as a chiral shift reagent resulted in the resolution of not only the C(3)(CH$_3$)$_2$ signals of the enantiomers but also the resolution of the C(2)H$_2$ AB system. In some instances, enantioselectivities were calculated by integration of the C(2)H$_2$ signals

3,8a-Dihydro-3,3,5,7,8a-hexamethylazulen-1(*2H*)one 97

(a) Preparation of **97** *in refluxing dichloromethane*



This was prepared following the procedure described for Method A, from 2-diazo-5-methyl-5-(3,5-dimethylphenyl)-hexan-3-one **41** (100 mg, 0.41 mmol) in dichloromethane (80 mL) and Rh$_2$(OAc)$_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). The reaction mixture was filtered through a plug of silica gel and the resulting clear solution

concentrated at reduced pressure to give the crude product **97** (96 mg) as a pale yellow oil. A ^{1}H NMR spectrum of the crude *azulenone* **97** estimated the efficiency of the reaction as 85%. Purification by flash chromatography, using ethyl acetate/hexane (5:95) as eluent, gave the *azulenone* **97** (58 mg, 66%) as a clear oil; ν_{max}/cm^{-1} (film) 2925, 2867, 1712 (CO), 1448; δ_H (300 MHz) 0.61 [3H, s, C(8a)CH_3], 1.03, 1.20 [2 × 3H, 2 × s, C(3)(C*H*$_3$)$_2$], 1.90 [1H, A of AB, J_{AB}17.4, one of C(2)H_2], 1.91 [3H, br s, C(5)CH_3 or C(7)CH_3], 1.92 [3H, d, *J* 1.2, C(5)CH_3 or C(7)CH_3], 2.11 [1H, B of AB, J_{AB} 17.4, one of C(2)H_2], 2.52 [1H, s, C(8)H], 5.75, 5.99 [2 × 1H, 2 × br s, C(4)H, C(6)H]; δ_C (75.5 MHz) 5.4 [CH_3, C(8a)*C*H_3], 21.9, 23.4, 25.3, 27.0 [4× CH_3, C(3)(*C*H_3)$_2$,C(5)*C*H_3, C(7)*C*H_3], 28.8, 37.9 {2 × C, two of [C(3), C(3a), C(8a)]}, 44.9 [CH, br, C(8)H], 47.7 [CH_2, C(2)H_2], 115.1, 125.2 [2 × CH, C(4)H, C(6)H], 134.0, 134.1 [2 × C, C(5), C(7)], 217.7 [C, C(1)]; HRMS (ES+): Exact mass calculated for $C_{15}H_{20}O$ [$(M+H)^+$] 217.1592. Found 217.1598. m/z (ES+) 305 (100%), 258 (18%), 217 [$(M+H)^+$, 30%].

*The azulenone **97** was observed to decompose to a yellow oil at room temperature over 12 h.

(b) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **41**

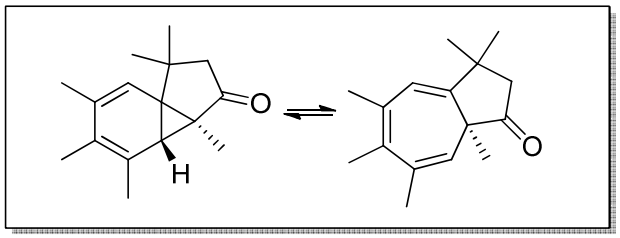
Table 3.11 *Effect of catalyst on the cyclisation of diazoketone* **41**

Entry	Catalyst	Method	Time (h)[a]	Eff (%)[b]	Yield (%)[c]	ee (%)[d]
1	$Rh_2(OAc)_4$**87**	A	1	85	66	-
2	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	B	1	88	72	-[e,f]

a. Number of hours over which diazoketone was added. Reaction was found to be complete once all diazoketone was added.
b. Efficiency refers to the percentage azulenone formed relative to aromatic byproducts and is determined from the ^{1}H NMR spectrum of the crude product.
c. Yield of isolated product after flash chromatography.
d. Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent.
e. Unable to accurately determine % ee due to poor separation of peaks by chiral ^{1}H NMR.
f. When sample was trapped with PTAD **305**, the enantioselectivity was determined as 92% ee and X-ray diffraction established that the stereochemistry of the major enantiomer of azulenone **97** was 3a*S* (see Section 3.11.2)

3,8a-Dihydro-3,3,5,6,7,8a-hexamethylazulen-1(*2H*)one 92[5]

(a) Preparation of **92** *in dichloromethane at room temperature*



2-Diazo-5-methyl-5-(3,4,5-trimethylphenyl)hexan-3-one **42** (100 mg, 0.39 mmol) in dichloromethane (80 mL) was added dropwise over 2.5 h to a solution of $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%)) in dichloromethane (80 mL). The progress of the reaction was monitored by TLC and was found to be complete once the addition of the diazoketone was complete. A ^1H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 72%. The ^1H NMR of the crude reaction mixture contained an unknown impurity (20%). Signals were observed at δ_H (300 MHz) 1.25 [6H, m], 1.42 [4H, s], 2.27 [3H, s], 2.84 [1H, A of AB, J_{AB} 15.3], 3.01 [1H, A of AB, J_{AB} 15.3], 3.85 [1H, q, *J* 6.7]. The reaction mixture was filtered through basic alumina and the resulting clear solution concentrated at reduced pressure to give the crude *azulenone** **92** as a yellow oil. The ^1H NMR spectrum showed that the sample prior to exposure to basic alumina was cleaner than after filtration.

Purification by flash chromatography, using ethyl acetate/hexane (5:95) as eluant, gave the *azulenone* **92** (55 mg, 42%) as a green oil; ν_{max}/cm^{-1}(film) 2925, 2360, 1710 (CO), 1449; δ_H (300 MHz) 0.55 [3H, s, C(8a)CH_3], 1.02, 1.19 [2 × 3H, 2 × s, C(3)(CH_3)$_2$], 1.85 [1H, A of AB, J_{AB}17.3, one of C(2)H_2], 1.86, 1.89 {2 × 3H, 2 × s, C(6)CH_3 and one of [C(5)CH_3, C(7)CH_3]}, 1.96 {3H, apparent d, *J* 1.1, one of [C(5)CH_3, C(7)CH_3]}, 2.08 [1H, B of AB, J_{AB}17.3, one of C(2)H_2], 2.47 [1H, s, C(8)H], 5.80 [1H, br s, C(4)H]; A number of peaks (11%) of an unidentifiable product were seen in the ^1H NMR spectrum of the pure product at δ_H (300 MHz) 0.96 [[1H, d, *J* 6.5], 1.25 [6H, m], 1.42 [4H, s], 2.27 [3H, s], 2.84 [1H, A of AB, J_{AB} 15.3], 3.01 [1H, A of AB, J_{AB} 15.3], 3.85 [1H, q, *J* 6.7].

*The azulenone **92** was observed to decompose to a yellow oil if left at room temperature over a short period of time.

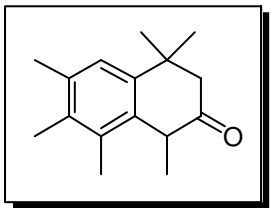
(b) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **42**

Table 3.12 *Effect of catalyst on the cyclisation of diazoketone* **42**

Entry	Catalyst	Time (h)	Eff. (%)	Yield (%)	%ee[b]
1	$Rh_2(OAc)_4$**87**[b]	2.5	72	42	-
2	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	2.5	87	62	-[c]

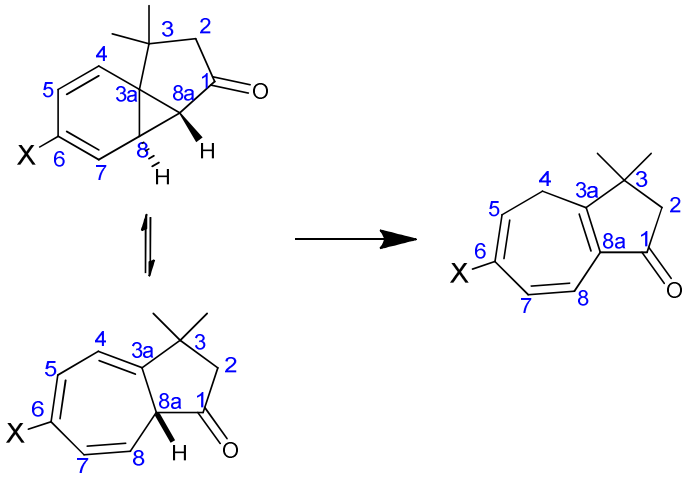
a. Yield of isolated product after flash chromatography.
b. Could not be calculated due to decomposition.
c. When sample was trapped with PTAD **162**, the enantioselectivity was determined as 93% ee and X-ray diffraction established that the stereochemistry of the major enantiomer of azulenone **92** was 3a*S* (see Section 3.11.2).

(c) Filtration of crude 3,8a-dihydro-3,3,5,6,7,8a-hexamethylazulen-1(2H)one **92** *through neutral alumina to form 1,4,4,6,7,8-hexamethyl-3,4-dihydronapthalen-2(1H)-one* **98**[39]



2-Diazo-5-methyl-5-(3,4,5-trimethylphenyl)hexan-3-one **42** (100 mg, 0.39 mmol) in dichloromethane (80 mL) was added dropwise over 2.5 h to a solution of $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). The progress of the reaction was monitored by TLC and was found to be complete once the addition of the diazoketone was complete. The reaction mixture was filtered through neutral alumina and the resulting clear solution concentrated at reduced pressure to give the crude *dihydronapthalenone* **98** as a yellow oil. Purification by flash chromatography, using ethyl acetate/hexane (5:95) as eluant, gave the *dihydronapthalenon*e **98** (65 mg, 73%) as a yellow oil. ν_{max}/cm^{-1}(film), 1716, (CO), 913, 744; δ_H (300 MHz) 1.30, 1.34 [2 × 3H, 2 × s, C(4)$(CH_3)_2$], 1.43 [3H, d, *J* 7.3, C(1)CH_3], 2.19, 2.22, 2.31 [3 × 3H, 3 × s, C(6)CH_3, C(7)CH_3, C(8)CH_3], 2.48 [1H, A of AB, J_{AB} 13.8, one of C(3)H_2], 2.65 [1H, B of AB, J_{AB} 13.8, one of C(3)H_2], 3.62 [1H, q, *J* 7.3, C(1)H], 7.10 [1H, s, C(5)H].

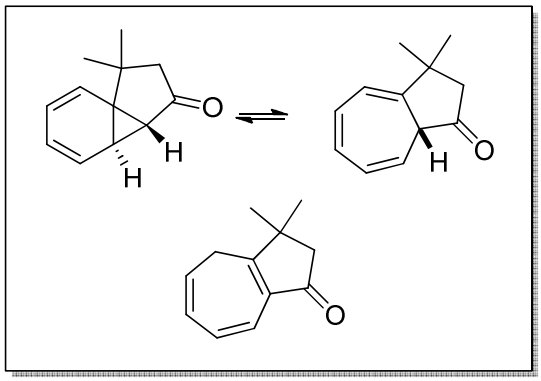
3.8.3 Transition metal catalysed decomposition of terminal α-diazoketones and formation of conjugated azulenone.



Numbering scheme for azulenone and conjugated trienone

Efficiency refers to the % azulenone formed relative to aromatic by-products and is determined from the ^{1}H NMR spectrum of the crude reaction product. Crude azulenones formed by the decomposition of terminal α-diazoketones were unstable and were seen to decompose over a short period of time (typically 1 day at room temperature). ^{1}H NMR analysis obtained for these azulenones were carried out on crude samples. Purification was not possible due to rearrangement to conjugated trienones. All attempts to remove the transition metal catalyst, by filtration through silica gel, alumina or celite failed as rearrangement to the conjugated trienone occurred.

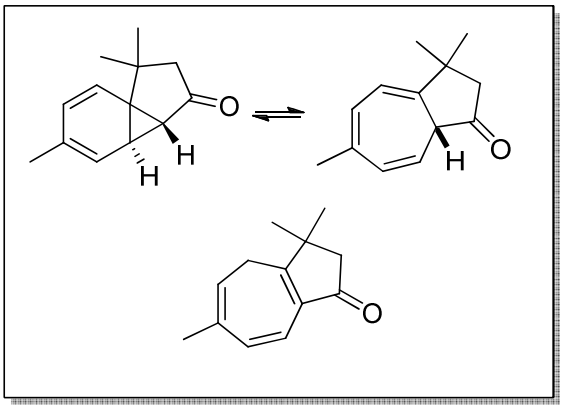
3,8aH-Dihydro-3,3-dimethylazulen-1(2*H*)-one 178[40] and 3,3-dimethyl-2,3-dihydroazulen-1(4H)-one 184[40,41]



This was prepared following the procedure described for Method B, from 1-diazo-4-methyl-4-phenylpentan-2-one **43** (0.47 g, 2.73 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in

dichloromethane (80 mL). A ^{1}H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 84%. Concentration under reduced pressure gave the crude *azulenone* **178** (0.45 g, 95%) as a dark green oil; ν_{max}/cm^{-1} (film) 2962, 1751, 1641, 1594; δ_H (300 MHz) 1.14, 1.40 [2 × 3H, 2 × s, C(3)(C*H*$_3$)$_2$], 2.36 [1H, d, A of ABX, J_{AB}16.9, J_{AX} 0.0, one of C(2)H$_2$], 2.59 [1H, dd, B of ABX, J_{AB} 16.9, J_{BX} 0.8, one of C(2)H$_2$], 2.87-2.91 [1H, br d (with unresolved fine splitting), X of ABX, *J* 3.0, C(8a)H], 5.20 [1H, dd, *J* 9.3, 4.0, C(8)H], 6.12-6.17 [1H, m, C(7)H], 6.20 [1H, dd, *J* 5.8, 1.6, C(4)H], 6.44 [1H, dd, *J* 11.2, 5.6, C(5)H or C(6)H], 6.53 [1H, dd, *J* 11.2, 5.6, C(5)H or C6)H] . Purification by flash chromatography on silica gel, using ethyl acetate/hexane (20:80) as eluent, resulted in rearrangement of the azulenone to the *conjugated trienone* **184** (0.26 g, 54%) which was isolated as a yellow oil; ν_{max}/cm^{-1} (film) 2962, 1704 (CO), 1288, 1199; δ_H (300 MHz) 1.28 [6H, s, C(3)(C*H*$_3$)$_2$], 2.43 [2H, s, C(2)H$_2$], 2.72 [2H, d, *J* 6.6, C(4)H$_2$], 5.40 [1H, ddd (appears as a dt), *J* 9.7, 6.5, 6.5, C(5)H], 6.15-6.20 [1H, dd, *J* 9.6, 5.7, C(6)H], 6.57-6.63 [1H, dd, *J* 11.1, 5.7, C(7)H], 6.78 [1H, d, *J* 11.1, C(8)H]; δ_C (75.5 MHz) 26.6 [CH$_2$, C(4)H$_2$], 27.8 [CH$_3$, C(3)(*C*H$_3$)$_2$], 40.0 [C, C(3)], 51.7 [CH$_2$, C(2)H$_2$], 121.0 [CH, C(5)H], 122.3 [CH, C(8)H], 128.7 [CH, C(6)H], 131.2 [CH, C(7)H], 134.8, 173.9 [2 × C, C(8a), C(3a)], 204.7 [C, C(1)]; HRMS (ES+): Exact mass calculated for $C_{12}H_{14}O$ [(M+H)$^+$] 175.1123. Found 175.1122. m/z (ES+) 551 (30%), 349 [($C_{24}H_{28}O_2$+H)$^+$, 80%], 189 (30%), 175 [(M+H)$^+$, 100%].

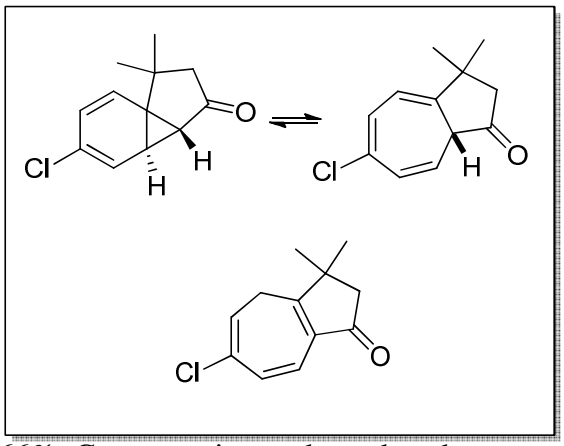
3,8aH-Dihydro-3,3,6-trimethylazulen-1(2*H*)-one 179 and 3,3,6-trimethyl-2,3-dihydroazulen-1(4H)-one 185



This was prepared following the procedure described for Method B, from 1-diazo-4-methyl(4-methylphenyl)pentan-2-one **44** (0.20 g, 0.92 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane 80 mL). A ^{1}H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 93%. Concentration under reduced pressure gave the crude *azulenone* **179** (0.17 g, 98%) as a dark green oil; ν_{max}/cm^{-1} (film) 2964, 1750 (CO), 1412, 913, 743; δ_H (300 MHz)

1.13, 1.37 [2 × 3H, 2 × s, C(3)(C*H*$_3$)$_2$], 2.01 [3H, s, C(6)CH$_3$], 2.33 [1H, dd, A of ABX, J_{AB} 16.9, J_{AX} 0.6, one of C(2)H$_2$], 2.51 [1H, dd, B of ABX, J_{AB} 16.9, J_{BX} 1.3 one of C(2)H$_2$], 2.87 [1H, br d (with unresolved fine splitting), X of ABX, *J* 3.3, C(8a)H], 5.16 [1H, dd, *J* 9.5, 4.1, C(8)H], 5.97 [1H, d, *J* 9.5, C(7)H], 6.02 [1H, d, *J* 6.1, one of C(4)H, C(5)H], 6.31 [1H, d, *J* 6.1, one of C(4)H, C(5)H]; Purification by flash chromatography on silica gel, using ethyl acetate/hexane (20:80) as eluent, resulted in rearrangement of the azulenone to the *conjugated trienone* **185** (0.13 g, 64%) which was isolated as a red oil; ν_{max}/cm^{-1} (film) 2960, 1704, 1275, 750; δ_H (500 MHz) 1.26 [6H, s, C(3)(C*H*$_3$)$_2$] 1.86 [3H, s, C(6)CH$_3$], 2.41 [2H, s, C(2)H$_2$], 2.62 [2H, d, *J* 6.5, C(4)H$_2$], 5.16 [1H, br t (with fine splitting), *J* 5.8, C(5)H], 6.50 [1H, d, *J* 11.3, C(7)H or C(8)H], 6.68 [1H, d, *J* 11.3, C(7)H or C(8)H]; δ_C (125.75 MHz) 22.2 [CH$_3$, C(6)CH$_3$], 26.1 [CH$_2$, C(4)H$_2$], 27.6 [CH$_3$, C(3)(*C*H$_3$)$_2$], 39.9 [C, C(3)], 51.7 [CH$_2$, C(2)H$_2$], 117.3 [CH, C(5)H], 121.4 [CH, C(7)H or C(8)H], 134.5 [C, C(6)], 134.5 [CH, C(7)H or C(8)H], 136.5, 176.0 [2 × C, C(8a), C(3a)], 204.7 [C, C(1)]; HRMS (ES+): Exact mass calculated for $C_{13}H_{16}O$ [$(M+H)^+$] 189.1279. Found 189.1282. m/z (ES+) 378 (40%), 377 [$(C_{26}H_{32}O_2+H)^+$, 100%], 219 (10%), 187 (8%).Unidentifiable signal at δ_H (300 MHz) 2.01 (1.50H, s) and δ_C (125.75 MHz) 1.18.

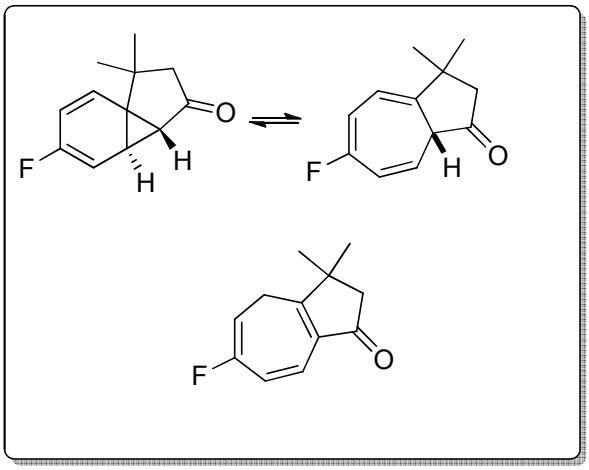
3,8aH-Dihydro-6-chloro-3,3-dimethylazulen-1(2*H*)-one 180 and 6-chloro-3,3-dimethyl-2,3-dihydroazulen-1(4H)-one 186



This was prepared following the procedure described for Method B, from 1-diazo-4-methyl(4-chlorophenyl)pentan-2-one **45** (0.05 g, 0.24 mmol) in dichloromethane (80 mL) and Rh$_2$(OAc)$_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). A ^{1}H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 66%. Concentration under reduced pressure gave the crude *azulenone* **180** (45 mg, 97%) as a dark brown oil; ν_{max}/cm^{-1} (film) 2963, 1751, 1412, 1194, 987; δ_H (300 MHz) 1.11, 1.40 [2 × 3H, 2 × s, C(3)(C*H*$_3$)$_2$], 2.34 [1H, dd, A of ABX, J_{AB} 16.9, J_{AX} 0.7, one of C(2)H$_2$], 2.57 [1H, dd, B of ABX, J_{AB} 16.9, J_{BX} 0.8, one of C(2)H$_2$], 3.02-3.06 [1H, br d

(with unresolved fine splitting), X of ABX, *J* 3.0, C(8a)H], 5.29 [1H, dd, *J* 9.7, 4.4, C(8)H], 6.09-6.17 {2H, m, C(7)H, and one of [C(4)H, C(5)H]}, 6.70 [1H, d, *J* 6.5, C(5)H or C(4)H]. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (20:80) as eluent, resulted in rearrangement of the azulenone to the *conjugated trienone* **186** (0.03 g, 60%) which was isolated as a brown oil; ν_{max}/cm^{-1} (film) 2962-2869, 1706, 1620, 1287 913, 744; δ_H (300 MHz) 1.28 [6H, s, C(3)(C*H*$_3$)$_2$], 2.44 [2H, s, C(2)H$_2$], 2.76 [2H, d, *J* 7.1, C(4)H$_2$], 5.50-5.55 [1H, t (with fine splitting), *J* 8.7 C(5)H], 6.51 [1H, dd, *J* 11.5, 1.3, C(7)H or C(8)H], 6.76 [1H, dd, *J* 11.5, 0.5, C(7)H or C(8)H]; δ_C (75.5 MHz) 25.3 [CH$_2$, C(2)H$_2$], 27.4 [CH$_3$, C(3)(*C*H$_3$)$_2$], 40.3 [C, C(3)], 51.5 [CH$_2$, C(4)H$_2$], 118.4 [CH, C(5)H], 124.0 [CH, C(7)H or C(8)H], 131.2 [CH, C(7)H or C(8)H], 131.5, 134.6, 176.1 [3 × C, C(8a), C(3a), C(6)], 203.7 [C, C(1)]; HRMS (ES+): Exact mass calculated for $C_{12}H_{14}OCl$ [$(M+H)^+$] 209.0733. Found 209.0740. m/z (ES+) 417 (20%), 211 [$(C_{12}H_{14}O^{37}Cl+H)^+$, 40%], 209 [$(C_{12}H_{14}O^{35}Cl+H)^+$, 100%], 85 (50%).

3,8aH-Dihydro-6-fluoro-3,3-dimethylazulen-1(2*H*)-one 181 and 6-fluoro-3,3-dimethyl-2,3-dihydroazulen-1(4H)-one 187



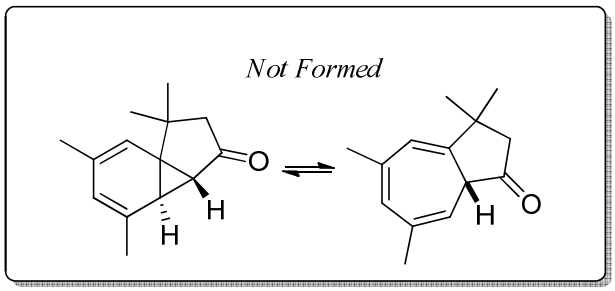
This was prepared following the procedure described for Method B, from 1-diazo-4-methyl(4-fluorophenyl)pentan-2-one **46** (0.10 g, 0.48 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). A ^{1}H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 81%. Concentration under reduced pressure gave the crude *azulenone* **181** (0.09 g, 97%) as a dark green oil; ν_{max}/cm^{-1} (film) 1751, 1411, 913; δ_H (300 MHz) 1.09, 1.42 [2 × 3H, 2 × s, C(3)(C*H*$_3$)$_2$], 2.34 [1H, d, A of ABX, J_{AB} 16.9, J_{AX} 0.0, one of C(2)H$_2$], 2.60 [1H, d, B of ABX, J_{AB} 16.5, J_{BX} 0.0, one of C(2)H$_2$], 2.98-3.03 [1H, br m (with unresolved fine splitting), X of ABX, C(8a)H], 5.38-5.45 [1H, m, C(8)H], 6.08-6.18 [2H, m, C(7)H, C(5)H], 6.26 [1H, ddd, *J* 12.8, 6.9, 1.7, C(4)H]. The ^{1}H NMR spectrum of the crude reaction mixture contained unidentifiable peaks (46%). Signals were observed at: δ_H (300 MHz) 2.36 (1H, s), 7.16-7.28 (2H, m).

Purification by flash chromatography, using ethyl acetate/hexane (20:80) as eluent, resulted in rearrangement of the azulenone to the *conjugated trienone* **187** (50 mg, 54%) which was isolated as a dark brown oil; ν_{max}/cm^{-1} (film) 2963, 1709, 1244, 913, 742; δ_H (300 MHz) 1.28 [6H, s, C(3)(CH_3)$_2$], 2.44 [2H, s, C(2)H_2], 2.73 [2H, dd, *J* 7.0, 2.1, C(4)H_2], 5.02-5.13 [1H, br m, C(5)H], 6.35-6.46 [1H, m, C(7)H], 6.80 [1H, dd, J_{HH}11.8, J_{HF} 4.0, C(8)H]; δ_C (75.5 MHz) 21.0 [CH_2, d, $^3J_{CF}$ 9.0, C(4)H_2], 27.3 [CH_3, C(3)(CH_3)$_2$], 40.5 [C, C(3)], 51.4 [CH_2, C(2)H_2], 99.6 [CH, d, $^2J_{CF}$ 27.2, C(5)H], 123.9 [CH, d, $^2J_{CF}$ 35.5, C(7)H], 125.2 [CH, d, $^3J_{CF}$ 12.8, C(8)H], 134.6* or 137.3* [C, C(8a) or C(3a)], 159.0 [C, d, $^1J_{CF}$ 239, C(6)], 172.3* or 177.6* [C, C(8a) or C(3a)], 203.8 [C, C(1)]; HRMS (ES+): Exact mass calculated for $C_{12}H_{13}FO$ [$(M+H)^+$] 193.1028 Found 193.1029. m/z (ES+) 385 (20%), 193 [(M+H)+, 40%], 189 (100%).

The ^{1}H NMR spectrum of the pure trienone **187** contained an unknown impurity (50%). Signals were observed at: δ_H (300 MHz) 1.43 (6H, s), 2.56 (1H, s), 6.98-7.52 (3H, m); δ_C (75.5 MHz) 28.4, 50.1, 130.0, 131.6, 134.6, 137.3, 140.8, 145.9, 157.4, 160.6, 172.3, 177.6, 177.7, 187.6, 204.5.

*Unable to definitively distinguish quaternary carbon signals from impurity in ^{13}C spectrum.

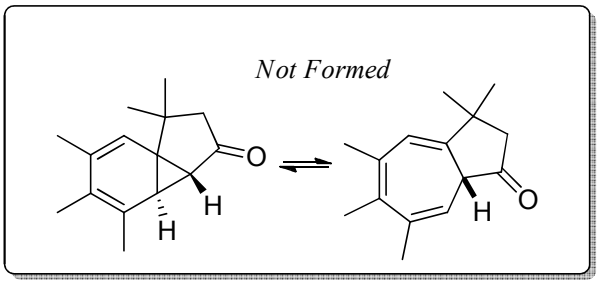
Attempted synthesis of 3,8aH-dihydro-3,3,5,6,7-tetramethylazulen-1(*2H*)one 182 from 1-diazo-4-methyl(3,5-dimethylphenyl)-pentan-2-one 47 and $Rh_2(OAc)_4$ 87



This was prepared following the procedure described for Method B, from 1-diazo-4-methyl(3,5-dimethylphenyl)-pentan-2-one **47** (200 mg, 0.87 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). The reaction was monitored by TLC and there appeared to be no starting material remaining after all the diazoketone was added. The green coloured solution was concentrated under reduced pressure to give a brown oil. ν_{max}/cm^{-1} (film) 2962, 2926, 1713, 1599, 1452; A ^{1}H NMR spectrum of the crude reaction mixture showed a complex mixture of unidentifiable products and did not contain any signals which could be attributed to the

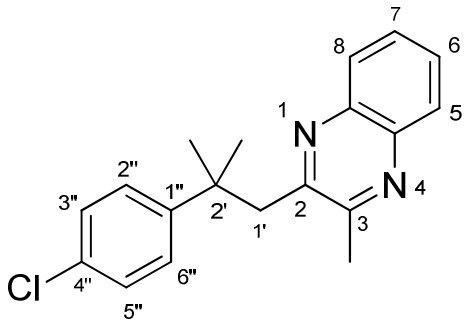
starting *diazoketone* **47** or desired *azulenone* **182**. Attempted purification by flash chromatography, using ethyl acetate/hexane (10:90) as eluent gave a yellow oil (110 mg). A ^{1}H NMR of this material showed a complex mixture of unidentifiable products.

Attempted synthesis of 3,8aH-dihydro-3,3,5,6,7-pentamethylazulen-1(*2H*)one 183 from 1-diazo-4-methyl(3,4,5-trimethylphenyl)-pentan-2-one 48 and $Rh_2(OAc)_4$ 87



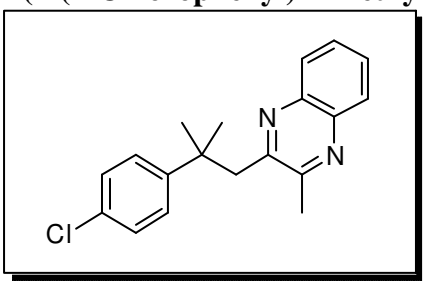
This was prepared following the procedure described for Method B, from 1-diazo-4-methyl(3,4,5-trimethylphenyl)-pentan-2-one **48** (200 mg, 0.82 mmol) in dichloromethane (80 mL) and $Rh_2(OAc)_4$ **87** (0.5 mg, < 1 mol%) in dichloromethane (80 mL). The reaction was monitored by TLC and there appeared to be no starting material remaining after all the diazoketone was added. The green coloured solution was concentrated under reduced pressure to give a brown oil. ν_{max}/cm^{-1} (film) 2966, 2927, 2252, 1789, 1752, 1713, 1639, 1608; A ^{1}H NMR spectrum of the crude reaction mixture showed a complex mixture of unidentifiable products and did not contain any signals which could be attributed to the starting *diazoketone* **48** or desired *azulenone* **183**. Attempted purification by flash chromatography, using ethyl acetate/hexane (10:90) as eluent gave a yellow oil (130 mg). A ^{1}H NMR of this material showed a complex mixture of unidentifiable products.

3.9 Synthesis of diazanaphthalene (quinoxaline)[11,39,42]



Numbering scheme for diazanaphthalenes

2-(2-(4-Chlorophenyl)-2-methylpropyl)-3-methylquinoxaline 112



1,2-Diaminobenzene **111*** (18 mg, 0.17 mmol) was added in one portion to a stirring solution of 5-(4-chlorophenyl)-5-methylhexane-2,3-dione **107** (20 mg, 0.084 mmol) in dichloromethane (5 mL) while stirring under nitrogen at room temperature for 1 h. Reaction progress was monitored by TLC. The crude reaction mixture was then concentrated under reduced pressure to give the crude *diazanaphthalene* **112** (35 mg) as a brown solid. A ^{1}H NMR spectrum of the crude product indicated the presence of unreacted *diaminobenzene* **111** along with the product *diazanaphthalene* **111** in the ratio of 111**:**112 6.7:1**. Purification by flash chromatography, using ethyl acetate/hexane (40:60) as eluent, gave the *diazanaphthalene* **112** as a clear oil (12 mg, 46%); ν_{max}/cm^{-1} (film) 2966, 1729, 1485, 1398, 1206, 1102; δ_H (300 MHz) 1.52 [6H, s, C(2′)$(CH_3)_2$], 2.31 [3H, s, C(3)CH_3], 3.24 [2H, s, C(1′)H_2], 7.11-7.21 [4H, m, AA′ BB′, C(2″)H, C(3″)H, C(5″)H, C(6″)H], 7.64-7.70 [2H, m, C(6)H, C(7)H or C(5)H, C(8)H], 7.92-7.97 [2H, m, C(6)H, C(7)H or C(5)H, C(8)H]; δ_C (75.5 MHz) 23.1 [CH_3, C(3)CH_3], 28.7 [CH_3, C(2′)$(CH_3)_2$], 39.5 [C, C(2′)], 48.4 [CH_2, C(1′)H_2], 127.4, 128.2, 128.3, 128.7, 129.1 [5 × CH signals seen for 6C, C(5)H, C(6)H. C(7)H, C(8)H, C(2″)H, C(3″)H, C(5″)H, C(6″)H], 131.8 [C, C(4″)Cl], 140.7, 140.8, 147.0, 154.0, 154.2 [5 × C, C(2), C(3), C(1″), 2 × C-N]; HRMS (ES+):

Exact mass calculated for $C_{19}H_{19}N_2Cl^{35}$ $[(M+H)^+]$ 311.1315 Found 311.1320. m/z (ES+) 352 (5%), 313 $[(C_{19}H_{19}N_2Cl^{37}+H)^+$, 30%], 311 $[(C_{19}H_{19}N_2Cl^{35}+H)^+$, 80%], 83 (20%), 42 (100%).

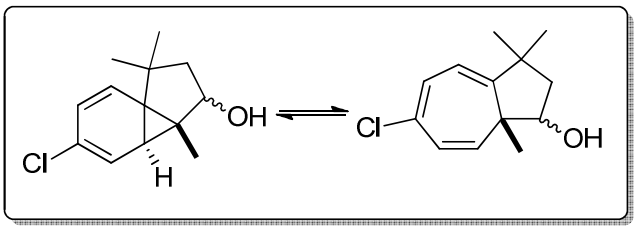
*1,2-Diaminobenzene **111** (0.50 g, 4.6 mmol) was freshly purified by recrystallisation from hot dichloromethane including treatment with activated charcoal with hot filtration to remove coloured impurities.[43] This gave the *amine* **111** (0.22 g, 44%) as an off-white crystalline solid which was immediately used for the condensation reaction with the *diketone* **107**.

**The product ratio observed in ^{1}H NMR of crude material not easily rationalised.

3.10 Synthesis of azulenols

Note 1: Two diastereomeric azulenols were expected after the reduction of the analogous azulenone. The azulenols are given one number, while each diastereomer is given the notation **a** and **b**, where isomer **a** is the major isomer. The relative stereochemistry of each diastereomer is unknown.

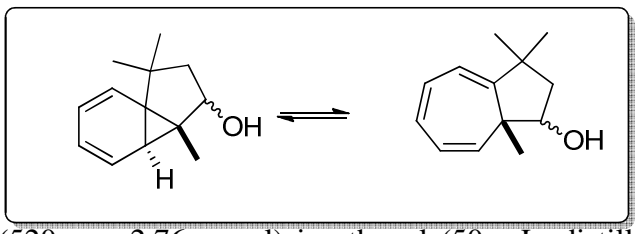
(1R, 8aS),-6-Chloro-1,2,3,8a-tetrahydro-3,3,8a-trimethylazulen-1-ol and (1R, 8aR),-6-Chloro-1,2,3,8a-tetrahydro-3,3,8a-trimethylazulen-1-ol 316



3,8a-Dihydro-6-chloro-3,3,8a-trimethylazulen-1(2H)-one **95** (500 mg, 2.25 mmol) in ethanol (40 mL, HPLC grade) was added dropwise over 30 min to sodium borohydride (423 mg, 11.18 mmol) in ethanol (40 mL, HPLC grade) while stirring at 0 ºC, under nitrogen. Stirring was continued for 24 h at room temperature. The reaction was subsequently quenched by dropwise addition of water (50 mL). The reaction solution was evaporated until just the water remained. Diethyl ether (40 mL) was added and the layers separated. The aqueous layer was washed with diethyl ether (3 x 40 mL). The combined organic extracts were washed with brine (60 mL), dried and concentrated under reduced pressure. A ^{1}H NMR spectrum of the crude material estimated the diastereomeric ratio as 82:18 and showed the reaction was very clean. Purification by flash chromatography, using ethyl acetate/hexane (3:97), gave a mixture of the two diastereomeric *azulenols* **316a: 316b**, 89:11, as a white solid (0.38 g, 75%),

m.p. 77-81 ºC; (Found: C, 69.66; H, 7.57; Cl, 15.98; $C_{13}H_{17}ClO$ requires C, 69.48, H, 7.62, Cl, 15.78%); ν_{max}/cm^{-1} (KBr) 3390-2865, 1627, 1456, 1364, 1067, 1025, 997; δ_H (300 MHz) **316a** 0.79 [3H, s, C(8a)CH_3], 1.04, 1.28 [2 × 3H, 2 × s, C(3)(C*H*$_3$)], 1.70 [1H, br s, OH], 1.77 [1H, dd, A of ABX, J_{AB} 12.3, J_{AX} 10.0, one of C(2)H_2], 1.89 [1H, dd, B of ABX, J_{AB} 12.3, J_{BX} 6.3, one of C(2)H_2], 4.24 [1H, br dd, X of ABX, J_{AX} 9.9, J_{BX} 6.3, C(1)H], 5.36 [1H, d, *J* 10.5, C(8)H], 5.93 [1H, d, *J* 7.4, C(4)H], 6.07 [1H, dd, *J* 10.5, 1.5, C(7)H], 6.52-6.56 [1H, m, C(5)H]; δ_H (300 MHz) **316b** 0.75 [3H, s, C(8a)CH_3], 1.09, 1.23 [2 × 3H, 2 × s, C(3)(C*H*$_3$)], 1.96 [1H , dd, *J* 12.3, 6.3, one of C(2)H_2], 4.32 [1H, dd, *J* 9.7, 6.0, C(1)H], 5.69 [1H, d, *J* 10.3, C(8)H], 6.02 [1H, d, *J* 6.9, C(4)H], 6.15-6.19 [1H, m, C(7)H], 6.67-6.69 [1H, m, C(5)H]; δ_C (75.5 MHz) **316a** 12.4 [CH_3, C(8a)CH_3], 29.9, 32.4 [2 × CH_3, C(3)$CH_3)_2$], 40.6 [C, C(3)], 47.0 [CH_2, C(2)H_2], 49.2 [C, C(8a)], 79.8 [CH, C(1)H], 115.3 [CH, C(4)H], 126.6 [CH, C(7)H], 127.0 [CH, C(5)H], 132.1 [C, C(3a)], 134.0 [CH, C(8)H], 156.9 [C, C(6)]; The ^{13}C NMR signals for the **316b** diastereoisomer are too weak to be assigned with any degree of certainty, so the signals are just listed, δ_C (75.5 MHz) 18.7, 29.9, 40.9, 47.9, 115.4, 119.2, 123.0, 125.9, 127.2; m/z (ES+) 236 (60%), 207 [$(M\text{-}OH)^+$, 100%], 189 (20%), 57 (15%).

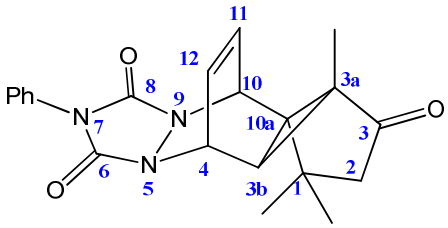
(1R, 8aS)-1,2,3,8a-Tetrahydro-3,3,8a-trimethyl-azulen-1-ol and (1R, 8aR)-1,2,3,8a-tetrahydro-3,3,8a-trimethyl-azulen-1-ol 315[5,11]



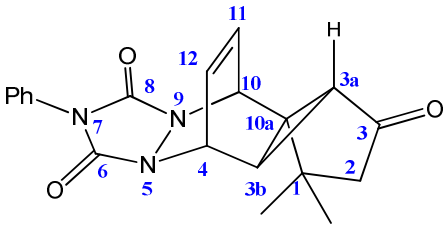
This reaction was carried out following the procedure described for **316a** and **316b**, from 3,8a-dihydro-3,3,8a-trimethylazulen-1(2*H*)-one **89** (520 mg, 2.76 mmol) in ethanol (50 mL, distilled) and sodium borohydride (520 mg, 13.76 mmol) in ethanol (50 mL, distilled). A ^1H NMR spectrum of the crude material estimated the diastereomeric ratio as **315a**:**315b**, 77:23. The crude material was clean enough to be carried through to next step as a mixture of *azulenols* **315a**:**315b**, 77:23 (without purification), which existed as a clear oil (0.45 g, 85%); ν_{max}/cm^{-1} (film) 3367-2864, 1635, 1459, 1062; δ_H (300 MHz) **315a** 0.74 [3H, s, C(8a)CH_3], 1.06, 1.30 [2 × 3H, 2 × s, C(3)$(CH_3)_2$], 1.79 [1H, dd, A of ABX, J_{AB} 12.2, J_{AX} 9.8, one of C(2)H_2], 1.89 [1H, dd, B of ABX, J_{AB} 12.2, J_{BX} 6.2, one of C(2)H_2], 4.22-4.27 [1H, sym m, C(1)H], 5.30 [1H, d, J 10.1, C(8)H], 6.02-6.11 [2H, m, C(4)H, C(7)H], 6.27-6.38 [2H, m, C(5)H,

C(6)H]; δ_H (300 MHz) **315b** 0.67 [3H , s, C(8a)CH3], 1.10, 1.25 [2 × 3H, 2 × s, C(3)$(CH_3)_2$], 1.47 [1H, dd, A of ABX, J_{AB} 12.2, J_{AX} 9.7, one of C(2)H2], 1.96 [1H, dd, B of ABX, J_{AB} 12.2, J_{BX} 6.0, one of C(2)H_2], 4.31-4.36 [1H, sym m, C(1)H], 5.56 [1H , d, *J* 9.9, C(8)H], 6.20 [1H, dd, *J* 9.9, 6.2 C(7)H], 6.43-6.54 [2H, m, C(5)H, C(6)H]. Signal for C(4)H not distinguishable in region 6.02-6.12 ppm.

3.11 Preparation of PTAD cycloadducts



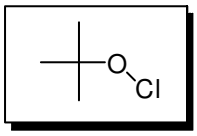
Internal



Terminal

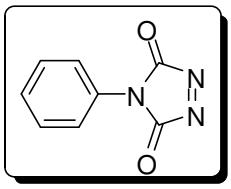
Sample numbering scheme

t-Butyl hypochlorite 332 [44]



A commercial bleach solution (10-12% w/w, 500 mL) was stirred in a 1L round bottom flask at 0 ºC (The lights in the fumehood were turned off at this point as *t*-butyl hypochlorite is light sensitive). A solution of *t*-butyl alcohol (39.3 g, 50.0 mL, 531.1 mmol) and glacial acetic acid (42.0 g, 40.0 mL, 700.0 mmol) was added in a single portion to the bleach solution and stirring was continued for 3 min. The top organic layer was a cloudy yellow layer. This was washed with aqueous Na_2CO_3 (10%, 2 × 25 mL) and water (1 × 25 mL). The organic layer was then dried over $CaCl_2$ and filtered into a brown bottle to yield *t*-butyl hypochlorite **332** (43.60 g, 68 %) as a yellow liquid with a strong hypochlorite smell. It was stored over $CaCl_2$ in the fridge.

4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) 162[5,10,11,45,46]



t-Butyl hypochlorite **332** (6.07 g, 6.82 ml, 55.9 mmol) was added dropwise to a solution of 4-phenyl urazole (10.00 g, 56.4 mmol) in dry acetone (300 mL) while stirring under nitrogen at -40 ºC. After 30 min the reaction mixture was removed from the cold bath and allowed warm to room temperature. The solvent was removed under reduced pressure keeping the temperature of the water bath below 10 ºC to give the crude *dienophile* **162**. Sublimation under reduced pressure (110 ºC at 0.10 mmHg) gave the dienophile **162** (0.38 g, 38%) as a bright red solid, m.p.175-178 ºC (Lit.,[45] 170-180 ºC).

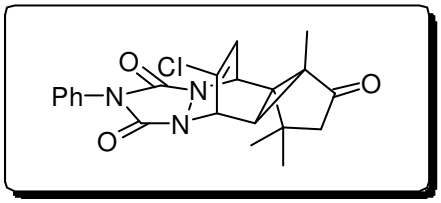
Note: The majority of the PTAD adducts prepared in the following work were prepared in a one-pot method starting from the corresponding diazoketone as this was considered the most efficient preparation.

Racemic PTAD cycloadducts synthesised from internal α-diazoketones were purified by hot recrystallisation from ethyl acetate. This method of purification has previously been used by other researchers in the group.[10,11,39] PTAD cycloadducts generated *via* enantioenriched azulenones were purified by flash chromatography on silica gel to avoid selective recrystallisation.

The ^{1}H NMR spectra of crude PTAD cycloadducts generated from terminal α-diazoketones were much cleaner when sublimed PTAD was used. When the crude dienophile was used ^{1}H NMR spectra of the crude reaction mixture were more complex. As a result, 1.00 g of PTAD was sublimed and stored in the freezer at -20 ºC over approximately one year. This sublimed batch of dienophile was used to synthesise adducts **164**, **198**, **199**.

3.11.1 Reaction of internal α-diazoketones with PTAD

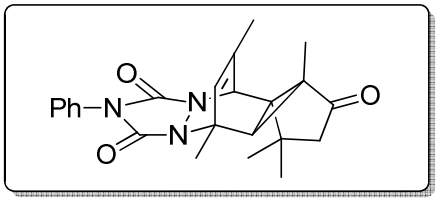
(3a*R,3b*S**)-1,2,3b,4-Tetrahydro-1,1,3a -trimethyl-7-phenyl-4,10-etheno-12-chlorocyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 313**[11,39]



2-Diazo-5-methyl-5-(4-chlorophenyl)hexan-3-one **39** (2.25 g, 9.00 mmol) in doubly distilled dichloromethane (80 mL) was added dropwise over ~ 1 h to a refluxing solution of $Rh_2(OAc)_4$ **87** (0.5 mg) in deoxygenated doubly distilled dichloromethane (80 mL). The reaction was monitored by TLC and was found to be complete once all the diazoketone was added. The reaction mixture was then cooled to 0 ºC and crude 4-phenyl-1,2,4-triazoline-3,5-dione **162** [freshly prepared from *t*-butyl hypochlorite **332** (0.98 g, 9.00 mmol), 4-phenyl urazole (1.61 g, 9.00 mmol) in dry acetone (40 mL)] was added as a solid in one portion. The reaction mixture was stirred at 0 ºC for 5 min after which the ice-bath was removed and the reaction mixture was warmed to room temperature. The reaction mixture turned from the brick-red colour of the dienophile to a clear solution within minutes of its addition, indicating completion of the reaction. It was stirred for a further 30 min before concentration of the reaction mixture under reduced pressure gave the crude adduct as an off-white solid. Recrystallisation from hot ethyl acetate gave the pure *adduct* **313** as a white solid (1.62 g, 46%), m.p. 183-187 ºC (Lit.,[11] 181-184 ºC, Lit.,[39] 185-189 ºC); ν_{max}/cm^{-1} (KBr) 2925, 1721, 1503, 1404, 1241; δ_H (400 MHz) 1.28, 1.33 [2 × 3H, 2 × s, C(1)$(CH_3)_2$], 1.36 [3H, s, C(3a)CH_3], 1.99 [1H, d, *J* 4.9, C(3b)H], 2.03 [1H, A of AB, *J* 18.0, one of C(2)H_2], 2.17 [1H, B of AB, *J* 18.0, one of C(2)H_2], 5.29-5.32 [1H, m, C(4)H], 5.51 [1H, d, *J* 6.0, C(10)H], 6.26-6.30 [1H, m, C(11)H], 7.33-7.56 (5H, m, ArH].

(3a*R,3b*S**)-1,2,3b,4-Tetrahydro-1,1,3a,4,11-pentamethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 164**

(a) Reaction of crude azulenone **97** *with PTAD* **162**



This was prepared from the procedure described for **313**, from 2-diazo-5-methyl-5-(3,5-dimethylphenyl)hexan-3-one **41** (0.20 g, 0.82 mmol) in doubly distilled dichloromethane (80 mL), $Rh_2(OAc)_4$ **87** (0.5 mg) in doubly distilled dichloromethane (80 mL) and sublimed 4-phenyl-1,2,4-triazoline-3,5-dione **162** (0.18 g, 1.00 mmol)) to give the crude product as a yellow solid. Recrystallisation from hot ethyl acetate gave the gave the pure *adduct* **164** as a white solid (0.23 g, 72%), m.p. 178-181 ºC; (Found: C, 70.43; H, 6.90; N, 10.23; $C_{23}H_{25}N_3O_3$ requires C, 70.57, H, 6.44, N, 10.73%); ν_{max}/cm^{-1} (KBr) 2927, 2956, 2972, 1763, 1705 s, 1597, 1502, 1410; δ_H (300 MHz) 1.25 (6H, s), 1.32 (3H, s) [C(1)$(CH_3)_2$, C(3a)CH_3], 1.74 [1H, s, C(3b)H], 1.92 [3H, d, *J* 1.9, C(4)CH_3], 1.96 [1H, A of AB, *J* 18.0, one of C(2)H_2], 2.00 [3H, s, C(11)CH_3] 2.13 [1H, B of AB, *J* 17.8, one of C(2)H_2], 5.11 [1H, d, *J* 1.7, C(10)H]], 5.65-5.69 [1H, m, C(12)H], 7.32-7.39 [1H, m, ArH], 7.42-7.47 [4H, m, ArH]; δ_C (75.5 MHz) 9.0 [CH_3, C(3a)CH_3], 19.8, 22.5 [2 × CH_3, C(4)CH_3, C(11)CH_3], 23.9, 27.1 [2 × CH_3, C(1)$(CH_3)_2$], 34.0 [CH, C(3b)H], 36.7, 40.7, 44.5 [3 × C, C(1), C(3a), C(10)], 48.3 [CH_2, C(2)H_2], 56.2 [CH, C(10)H], 64.7 [C, C(4)], 125.5, 126.2 [2 × CH, aromatic CH], 128.2 [CH, C(12)H], 129.0 [CH, aromatic CH], 131.3 [C, aromatic C], 137.3 [C, C(11)], 155.4, 155.9 [2 × C(6), C(9)], 211.7 [C, C(3)]; HRMS (ES+): Exact mass calculated for $C_{23}H_{25}N_3O_3$ [$(M+H)^+$] 392.1974 Found 392.1974. m/z (ES+) 393 (30%), 392 [$(M+H)^+$, 100%], 215 (20%).

(b) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **41**, *where the crude azulenone* **97** *was trapped with PTAD* **162** *to give adduct* **164**

Table 3.13 *Effect of catalyst on enantioselectivity of the decomposition of diazoketone* **41**

Entry	Catalyst	Method	Time (h)[a]	Yield (%)[b]	ee (%)[c]
1	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	B	1	64	92[d,e]

a. Number of hours over which diazoketone was added. Reaction was found to be complete once all of the diazoketone was added.
b. Yield of isolated product after flash chromatography (20% ethyl acetate:hexane as eluant).
c. Determined by chiral HPLC.
d. Major Enantiomer = (+). Crystal structure confirmed major enantiomer 3a*S*. [see Section (d) below] The 92% ee sample of adduct was recrystallised to give ≥ 99% ee, , a crystal was employed for X-ray diffraction and then redissolved and analysed by HPLC, which confirmed ≥ 99% ee.
e. Specific Rotation: $[\alpha]_D^{20}$ 154.9 [*c* 0.5, $CHCl_3$].

(c) Conditions for resolution of the enantiomers of PTAD adduct **164** *on HPLC.*

Resolution of the *PTAD adduct* **164** was achieved using a Chiracel® OD-H column at room temperature, with isopropanol:hexane (10:90) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 218 nm. Under these conditions dextrorotatory (+)-**164** elutes at 10.0 min and the levorotatory (–)-**164** elutes at 12.7 min.

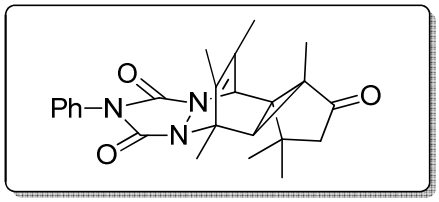
(d) Absolute stereochemistry data by single crystal X-ray diffraction on recrystallised (≥99% ee) sample of 92 % ee PTAD adduct **164**

Recrystallised from hot ethyl acetate. Crystal Data: $C_{23}H_{25}N_3O_3$, M = 391.46, tetragonal, a = 7.7426(2) Å, c = 68.433(2) Å, V = 4102.4(2) Å^3, T = 296(2) K, space group $P4_32_12$, Z = 8, 22513 reflections measured, 3383 unique (R_{int} = 0.0334). The final R_1 values were 0.0532 ($I > 2\sigma(I)$) and 0.0547 (all data). The final $wR(F^2)$ values were 0.1607 ($I > 2\sigma(I)$) and 0.1623 (all data). Flack parameter = 0.1(4), Hooft y parameter = 0.15(7).

Note: Crystal structure confirmed that the (+) enantiomer of **164** is derived from 3a*S* enantiomer in the azulenone **97**. Subsequent to X-ray diffraction, the crystal was redissolved and analysed by chiral HPLC, confirming the sample was ≥99% ee of the major enantiomer.

(3a*R,3b*S**)-1,2,3b,4-Tetrahydro-1,1,3a,4,11,12-hexamethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 163**

(a) Reaction of crude azulenone **92** *with PTAD* **162**



This was prepared from the procedure described for **313**, from 2-diazo-5-methyl-5-(3,4,5-trimethylphenyl)hexan-3-one **42** (0.50 g, 1.94 mmol) and crude 4-phenyl-1,2,4-triazoline-3,5-dione **162** ~(0.35 g) [freshly prepared from *t*-butyl hypochlorite **332** (0.24 g, 2.18 mmol), 4-phenyl urazole (0.39 g, 2.20 mmol) in acetone (10 mL)] to give the crude product as a yellow solid. Recrystallisation from hot ethyl acetate gave the pure *adduct* **163** as a white solid (0.51 g, 65%), m.p. 176-178 ºC; (Found: C, 70.63; H, 7.17; N, 9.85; $C_{24}H_{27}N_3O_3$ requires C, 71.09, H, 6.71, N, 10.36%); ν_{max}/cm^{-1} (KBr) 2970, 2920, 1767 w, 1729 s, 1707 s, 1495, 1408; δ_H (500 MHz) 1.13 [3H, s, C(3a)CH_3] 1.25, 1.31 [2 x 3H, 2 x s, C(1)$(CH_3)_2$], 1.70 [1H, s, C(3b)H], 1.74 [3H, d, *J* 1.0, C(4)CH_3], 1.84 [3H, d, *J* 1.0, C(11)CH_3], 1.93 [1H, A of AB, *J* 17.8, one of C(2)H_2], 2.02 [3H, s, C(12)CH_3], 2.13 [1H, B of AB, *J* 17.8, one of C(2)H_2], 5.12 [1H, s, C(10)H]], 7.23-7.40 [1H, m, ArH], 7.41-7.56 [4H, m, ArH]; δ_C (125MHz) 7.6 [CH_3, C(3a)CH_3], 13.3, 16.8 [2 × CH_3, C(4)CH_3, C(11)CH_3], 21.1 [CH_3, C(12)CH_3], 23.9, 27.1 [2 × CH_3, C(1)$(CH_3)_2$], 34.5 [CH, C(3b)H], 36.4, 41.0, 43.5 [3 × C, C(1), C(3a), C(10a)], 48.5 [CH_2, C(2)H_2], 57.3 [CH, C(10)H], 66.3 [C, C(4)], 125.4, 128.1, 129.0 [3 × CH, ArH], 129.6 [C, aromatic C], 130.7, 131.5 [2 × C, C(11), C(12)], 155.4, 156.1 [2 × C, C(6), C(9)], 211.7 [C, C(3)]; HRMS (ES+): Exact mass calculated for $C_{24}H_{27}N_3O_3$ [$(M+H)^+$] 406.2131 Found 406.2147. m/z (ES+) 406 [$(M+H)^+$, 100%], 229 (30%), 105 (30%).

(b) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **42***, where the crude azulenone* **92** *was trapped with PTAD* **162** *to give adduct* **163**

Table 3.14 *Effect of catalyst on enantioselectivity of the decomposition of diazoketone* **42**

Entry	Catalyst	Method	Time (h)[a]	Yield (%)[b]	ee (%)[c]
1	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box]	B	1	80	93[d,e]

a. Number of hours over which diazoketone was added. Reaction was found to be complete once all of the diazoketone was added.
b. Yield of isolated product after flash chromatography (20% ethyl acetate:hexane as eluant).
c. Determined by chiral HPLC.
d. Major Enantiomer = (+). Crystal structure confirmed major enantiomer 3a*S*. [see Section (d) below] The 93% ee sample of adduct was recrystallised to give ≥ 99% ee, , a crystal was employed for X-ray diffraction and then redissolved and analysed by HPLC, which confirmed ≥ 99% ee.
e. Specific Rotation: $[\alpha]_D^{20}$ 96.5 [*c* 1.0, $CHCl_3$].

(c) Conditions for resolution of the enantiomers of PTAD adduct **163** *on HPLC.*

Resolution of the *PTAD adduct* **163** was achieved using a Chiracel® OD-H column at room temperature, with isopropanol:hexane (10:90) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 229 nm. Under these conditions dextrorotatory (+)-**163** elutes at 11.4 min and the levorotatory (−)-**163** elutes at 14.1 min.

(d) Absolute stereochemistry data by single crystal X-ray diffraction on recrystallised (≥ 99% ee) sample of 93 % ee PTAD adduct **163**

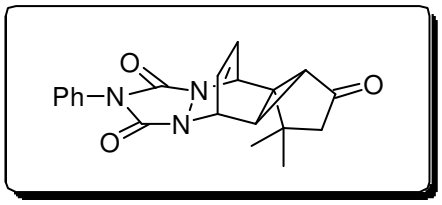
Recrystallised from hot ethyl acetate. Crystal Data: $C_{24}H_{27}N_3O_3$, M = 405.49, orthorhombic, a = 7.829(1) Å, b = 8.6480(11) Å, c = 31.752(4) Å, V = 2,149.8(5) Å^3, T = 100(2) K, space group $P2_12_12_1$, Z = 4, 19559 reflections measured, 3789 unique (R_{int} = 0.0248). The final R_1 values were 0.0274 ($I > 2\sigma(I)$) and 0.0277 (all data). The final $wR(F^2)$ values were 0.0688 ($I > 2\sigma(I)$) and 0.0691 (all data). Flack parameter = 0.04(16), Hooft y parameter = 0.01(5).

Note: Crystal structure confirmed that the (+) enantiomer of **163** is derived from 3a*S* enantiomer of the azulenone **92**. Subsequent to X-ray diffraction, the crystal was redissolved and analysed by chiral HPLC, confirming the sample was ≥99% ee of the major enantiomer.

3.11.2 Reaction of crude azulenones synthesised from terminal α-diazoketones with PTAD

(3a*S, 3b*R**)-1,2,3b,4-Tetrahydro-1,1,3a-dimethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 197**

(a) Reaction of crude azulenone **178** *with PTAD* **162**



1-Diazo-4-methyl-4-phenylpentan-2-one **43** (0.48 g, 2.73 mmol) in doubly distilled dichloromethane (80 mL) was added dropwise over ~ 1 h to a refluxing solution of $Rh_2(OAc)_4$ **87** (0.5 mg) in deoxygenated doubly distilled dichloromethane (80 mL). The progress of the reaction was monitored by TLC and was found to be complete once all of the diazoketone was added. The reaction mixture was then cooled to 0 ºC and crude 4-phenyl-1,2,4-triazoline-3,5-dione **162** [freshly prepared from *t*-butyl hypochlorite **332** (0.30 g, 0.34 mL, 2.73 mmol), 4-phenyl urazole (0.48 g, 2.73 mmol) in dry acetone (10 mL)] was added as a solid in one portion. The reaction mixture was stirred at 0 ºC for 5 min after which the ice-bath was removed and the reaction mixture was warmed to room temperature. The reaction mixture turned from the brick-red colour of the dienophile to a clear solution within minutes of its addition, indicating completion of the reaction. It was stirred for a further 30 min before concentration of the reaction mixture under reduced pressure gave the crude *adduct* **197** (0.50 g) as an off-white solid. Purification by recrystallisation from hot ethyl acetate gave the pure *adduct* **197** (0.35 g, 42%) as a white solid, m.p. 195-198 ºC; (Found: C, 69.08; H, 5.44; N, 12.25; $C_{20}H_{19}N_3O_3$ requires C, 68.75, H, 5.48, N, 12.03%); ν_{max}/cm^{-1} (KBr) 2963, 2924, 2867, 1780 w, 1700 s, 1413; δ_H (300 MHz) 1.35, 1.36 [2 x 3H, 2 x s, C(1)$(CH_3)_2$], 1.60 [1H, s, X of ABX†, C(3a)H], 2.02 [1H, dd, A of ABX, J_{AB} 17.7, J_{AX} 1.4, one of C(2)H_2], 2.22 [1H, dd, *J* 4.8, 1.5, C(3b)H], 2.23 [1H, d, B of ABX, J_{AB} 17.7,

one of C(2)H_2], 5.29-5.37 [2H, m, C(4)H, C(10)H], 6.07-6.13 [1H, m, C(11)H], 6.33-6.40 [1H, m, C(12)H], 7.34-7.45 (5H, m, ArH); δ_C (75.5 MHz) 20.2 [CH, C(3a)H], 24.6, 26.8 [2 × CH_3, C(3)(CH_3)$_2$], 36.3, 37.6 [2 × C, C(1), C(3a)], 38.2 [CH, C(3b)H], 51.0 [C(2)H_2], 51.7, 53.2 [2 × CH, C(4)H, C(10)H], 124.9, 125.5, 128.4, 128.8, 129.2 [5 × CH, C(11)H, C(12)H, aromatic CH], 131.2 [C, aromatic C], 156.4, 156.8 [2 × C, C(6), C(8)], 208.9 [C, C(3)]; m/z (ES+) 391 (40%), 351 (20%), 350 [$(M+H)^+$, 100%], 105 (35%).

† While C(3a)H appeared as a singlet, remote coupling to one of C(2)H_2 is visible (*J* 1.4).

(b) *Effect of catalyst on enantioselectivity of the decomposition of diazoketone* **43***, where the crude azulenone* **178** *was trapped with PTAD* **162** *to give adduct* **197**

Table 3.15 *Effect of catalyst on enantioselectivity of the decomposition of diazoketone* **43**

Entry	Catalyst	Method	Time (h)[a]	Yield (%)[b]	ee (%)[c]
1	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][d,g,k]	B	1[f]	63	56[m,q]
			1[f] + 2h stirring	55	40[m]
3	$CuPF_6$-**74**[(*S*,*S*)-*t*-Bu-Box][d,h,k]	B	1	62	77[n]
4	$CuPF_6$-**89**[(4*R*,5*S*)-*tetra*-Ph-Box][d,i,k]	B	1	49	7[m,r]
5	$CuPF_6$-**91**[(*R*,*R*)-Bn-Box][d,j,k]	B	1	61	12[m]
6	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box][e,,k]	C	2	66	46[m]
7	CuCl-NaBARF-**74**[(*S*,*S*)-*t*-Bu-Box][e,k]	C	2	63	61[n,s]
8	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][d,l]	B	1	49[i]	16[m,o,p]
9	CuCl-NaBARF-**75**[(*R*,*R*)-Ph-Box][e,l]	C	2	40[i]	0[m,o,p]

(a) Number of hours over which diazoketone was added.
(b) Yield of isolated product after flash chromatography (20% ethyl acetate:hexane as eluant).
(c) Determined from chiral HPLC.

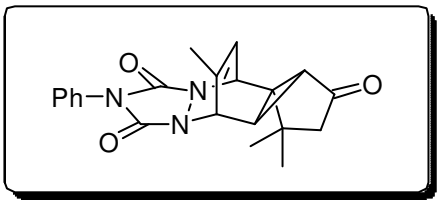
(d) The catalyst was prepared from 1.3:1 molar mixture of ligand: $Cu(CH_3CN)_4PF_6$.
(e) The catalyst was prepared from 5 mol% CuCl, 6 mol% ligand and 6 mol% NaBARF. Catalyst was stirred for 2 h at 20°C before substrate was added.
(f) Azulenone **178** was split into two separate mixtures once reaction was complete. The diazoketone was added over 1 h and was found to be complete once all substrate was added. First mixture was trapped with PTAD immediately. Second mixture was stirred for a further 2 h before being trapped with PTAD.
(g) The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown side-product (13%). Signals were observed at δ_H (300 MHz); 1.14 (4H, s), 1.21 (3H, s), 1.21 (3H, s), 1.40 (6H, d, *J* 1.0), 2.38-2.46 (7H, m), 4.93 (1H, d, *J* 5.1), 5.19 (1H, dd, *J* 9.3, 3.9), 5.59-5.68 (1H, m), 5.96 (1H, dd, *J* 9.1, 5.1), 6.20 (2H, d, *J* 4.8), 6.47-6.79 (7H, m), 7.02 (1H, dd, *J* 11.1, 6.0), 7.71-7.79 (5H, m).
(h) The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown side-product (10%). Signals were observed at δ_H (300 MHz); 1.21 (2H, s), 1.39-1.40 (4H, m), 4.88 [1H, d, *J* 3.0], 5.08 [1H, d, *J* 6.0], 5.96 [1H, dd, J 9.0, 6.0], 6.90 [1H, d, *J* 12.0], 7.05 [1H, dd, *J* 12.0, 6.0],
(i) The ^{1}H NMR spectrum of the crude reaction mixture contained starting azulenone **178** (51%).
(j) The ^{1}H NMR spectrum of the crude reaction mixture contained an unknown side-product (27%). Signals were observed at δ_H (300 MHz);1.14 (2H, s), 1.21 (4H, s), 1.25-1.29 (8H, m), 1.39-1.40 (4H, m), 1.46-1.47 (8H, m), 2.38-2.67 (12H, m), 4.80-4.84 (1H, m), 4.93 (1H, d, *J* 9.9), 5.04 -5.08 (1H, m), 5.19 (1H, dd, *J* 9.3, 4.2), 5.62-5.76 (1H, m), 5.96 (2H, dd, *J* 12.9, 5.1).
(k) Adduct prepared from sublimed PTAD.
(l) Adduct prepared from crude PTAD.
(m) Major Enantiomer = (+).
(n) Major Enantiomer = (−).
(o) Purified by recrystallisation from hot ethyl acetate.
(p) Determined by chiral ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent
(q) Specific Rotation: $[\alpha]_D^{20}$ 37.3 [*c* 0.5, $CHCl_3$].
(r) Specific Rotation: $[\alpha]_D^{20}$ 5.7 [*c* 0.35, $CHCl_3$].
(s) Specific Rotation: $[\alpha]_D^{20}$ -43.5 [*c* 0.5, $CHCl_3$].

(c) Conditions for resolution of the enantiomers of PTAD **197** *adduct on HPLC*

Resolution of the *PTAD adduct* **197** was achieved using a Chiracel® OD-H column at 40 ºC , with isopropanol:hexane (10:90) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 227 nm. Under these conditions dextrorotatory (+)-**197** elutes at 59.6 min and the levorotatory (−)-**197** elutes at 55.1 min.

(3a*S, 3b*R**)-1,2,3b,4-Tetrahydro-1,1,3a,12-trimethyl-7-phenyl-4,10-etheno-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 198**

(a) Reaction of crude azulenone **179** *with sublimed PTAD* **162**



This was prepared from the procedure described for **198**, 1-diazo-4-methyl-(4-methylphenyl)pentan-2-one **44** (0.097 g, 0.45 mmol) in doubly distilled dichloromethane (80 mL), $Rh_2(OAc)_4$ **87** in deoxygenated doubly distilled dichloromethane (80 mL) and sublimed 4-phenyl-1,2,4-triazoline-3,5-dione **162** (0.08 g, 0.45 mmol) to give the crude product as a yellow solid. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (40:60) as eluent gave the pure *adduct* **198** (0.045 g, 53%) as a yellow solid, m.p. 155-161 ºC; [Found: C, 67.74; H, 5.82 N, 11.36; $C_{21}H_{21}N_3O_3$ (adduct +0.4H_2O) requires C, 67.86, H, 5.69 N, 11.31%]*; ν_{max}/cm^{-1} (KBr) 2965, 2931, 2870, 1951, 1782 w, 1731 s, 1403; δ_H (300 MHz) 1.34, 1.35 [2 × 3H, 2 × s, C(1)$(CH_3)_2$], 1.48 [1H, s, X of ABX, C(3a)H], 1.84 [3H, d, *J* 3.0, C(12)CH_3], 2.02 [1H, dd, A of ABX, J_{AB}† 17.7, J_{AX} 1.5, one of C(2)H_2], 2.18-2.20 [1H, br m, C(3b)H], 2.20 [1H, d, B of ABX, J_{AB}† 21.6, one of C(2)H_2], 5.11 [1H, dd, *J* 4.8, 2.1, C(4)H], 5.26 [1H, d, *J* 6.0 C(10)H], 5.92-5.99 [1H, m, C(11)H], 7.34-7.49 (5H, m, ArH); δ_C (75.5 MHz) 19.5 [CH_3, C(12)CH_3], 19.9 [CH, C(3a)H], 24.5, 26.9 [2 × CH_3, C(3)$(CH_3)_2$], 36.3, 39.3 [2 × C, C(1), C(3a)], 37.8 [CH, C(3b)H], 51.00 [C(2)H_2], 52.5, 57.5 [2 × CH, C(4)H, C(10)H], 120.8 [CH, C(11)H], 125.3, 128.4, 129.1, 131.3 [4 × CH, aromatic CH], 135.7 [C, ArC], 156.7, 157.0 [2 × C, C(6), C(8)], 208.6 [C, C(3)]; HRMS (ES+): Exact mass calculated for $C_{21}H_{21}N_3O_3$ [$(M+H)^+$] 364.1661 Found 364.1677. m/z (ES+) 364 [$(M+H)^+$, 30%], 83 (50%), 42 (100%).

* ^{1}H NMR showed the presence of water. Elemental analysis is in agreement with the adduct **198**+0.5H_2O.

† Geminal coupling constants differ somewhat (J_{AB} 17.7, 21.6) and are not easily rationalised.

(b) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **44**, *where the crude azulenone* **179** *was trapped with sublimed PTAD* **162** *to give adduct* **198**

Table 3.16 *Effect of catalyst on enantioselectivity of the decomposition of diazoketone* **44**

Entry	Catalyst	Method	Time (h)[a]	Yield (%)[b]	ee (%)[c]
1	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][d]	B	1	47	25[e,g]
2	$CuPF_6$-**74**[(*S*,*S*)-*t*-Bu-Box][d]	B	1	55	30[f,g]
3	$CuPF_6$-**89**[(4*R*,5*S*)-*tetra*-Ph-Box][d]	B	1	65	23[e,h]
4	$CuPF_6$-**91**[(*R*,*R*)-Bn-Box][d]	B	1	54	4[e,h]

a. Number of hours over which diazoketone was added.
b. Yield of isolated product after flash chromatography (20% ethyl acetate:hexane as eluant).
c. Determined from chiral HPLC.
d. The catalyst was prepared from 1.3:1 molar mixture of ligand: $Cu(CH_3CN)_4PF_6$.
e. Major Enantiomer = (+).
f. Major Enantiomer = (–).
g. Chiral HPLC using OD-H column
h. Chiral HPLC using Chiradex column.
i. Specific Rotation: $[\alpha]_D^{20}$ 10.00 [*c* 0.5a, $CHCl_3$].

(c) Conditions for resolution of the enantiomers of PTAD **198** *adduct on HPLC using OD-H column*

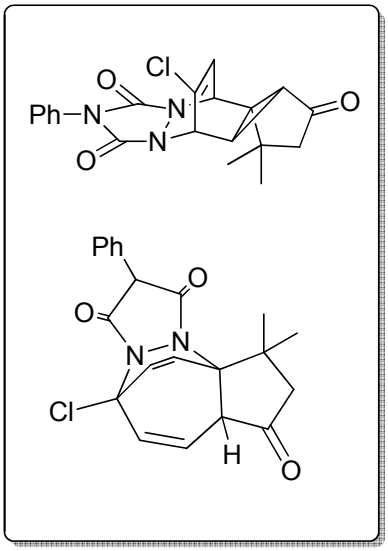
Resolution of the PTAD adduct **198** was achieved using a Chiracel® OD-H column at 40 ºC , with isopropanol:hexane (2:98) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 219 nm. Under these conditions dextrorotatory (+)-**198** elutes at 100.9 min and the levorotatory (–)-**198** elutes at 85.0 min.

(d) Conditions for resolution of the enantiomers of PTAD **198** *adduct on HPLC using reverse phase Chiradex column.*

Resolution of the *PTAD adduct* **198** was achieved using a reverse phase LiChroCART 250-4 ChiraDex® at room temperature, with water/methanol (60:40) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 230 nm. Under these conditions dextrorotatory (+)-**198** elutes at 19.9 min and the levorotatory (−)-**198** elutes at 23.0 min.

(3a*S,3b*R**)-1,2,3b,4-Tetrahydro-1,1,3a-dimethyl-7-phenyl-4,10-etheno-12-chloro-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 199 and *CHT* adduct 203**

(a) Reaction of crude chlorinated azulenone **180** *with sublimed PTAD* **162**



This was prepared from the procedure described for **197**, 1-diazo-4-methyl-(4-chlorophenyl)pentan-2-one **45** (0.20 g, 0.85 mmol) in doubly distilled dichloromethane (80 mL), $Rh_2(OAc)_4$ **87** in deoxygenated doubly distilled dichloromethane (80 mL) and sublimed 4-phenyl-1,2,4-triazoline-3,5-dione **162** (0.20 g, 0.85 mmol).The progress of the reaction was monitored by TLC and required stirring at room temperature for 4h before going to completion to give a brown coloured solution. The solution was concentrated under reduced pressure to give the crude *adduct* **199** and a side product believed to be the *CHT* adduct **203**, in the ratio **199**:**203**, 60:40 as a dark brown oil; ν_{max}/cm^{-1} (film) 1721,1503, 1405, 1255, 1199; δ_H (300 MHz) 1.35 [6H, s, C(1)$(CH_3)_2$], 1.66 [1H, s, X of ABX, C(3a)H], 2.04 [1H, dd, A of ABX, J_{AB} 17.7, J_{AX} 1.2, one of C(2)H_2], 2.22 [1H, d, B of ABX, J_{AB} 22.5, one of C(2)H_2], 2.24 [1H, d, *J* 1.8, C(3b)H], 5.34 [1H, dd, *J* 5.1, 2.7, C(4)H], 5.40 [1H, d, *J* 6.5, C(10)H], 6.28 [1H, dd, *J* 6.3, 2.4, C(11)H], 7.19-7.50 (5H, m, ArH);

Peaks for CHT adduct **203** partially assigned as δ_H (300 MHz) **203** 1.21, 1.43 [2 × 3H, 2 × s, C(3)(C*H*$_3)_2$], 2.49-2.54 [2H, m, C(2)H_2], 5.05 [1H, d, *J* 6.5, C(4)H or C(5)H or C(7)H], 6.06 [1H, finely split d, *J* 6.3, C(4)H or C(5)H or C(7)H], 6.96 [1H, dd, A of ABX, J_{AB} 11.7, J_{AX} 0.0, C(7)H or C(8)H], 6.94 [1H, dd, B of ABX, J_{AB} 11.7, J_{BX} 1.2, C(7)H or C(8)H]

The mixture could not be separated by flash chromatography.

(b) Reaction of the crude PTAD adduct **199** *and CHT adduct* **203** *mixture with zinc chloride*

Zinc chloride (1M solution in ether, 5.26 mL, 5.26 mmol) was added to a stirring solution of crude (3a*S**, 3b*R**)-1,2,3b,4-tetrahydro-1,1,3a-dimethyl-7-phenyl-4,10-etheno-12-chloro-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione **199** and the *CHT* adduct **203** (0.40 g, 1.05 mmol) (**199**:**203**, 60:40) in dichloromethane (30 mL) at 0 ºC under nitrogen. The ice-bath was then removed and the reaction mixture was allowed warm to room temperature. The reaction mixture was stirred for 24 h at room temperature under nitrogen. Saturated aqueous sodium carbonate (20 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL), the combined organic layer was then washed with water (50 mL), brine (50 mL), dried, filtered and concentrated under reduced pressure to give the crude adduct as a brown solid. ^{1}H NMR of the crude material showed major product was *adduct* **199** (50%) and additional signals at δ_H 7.03 (1H, dd, *J* 12.0, 2.7), 7.21 (1H, dd, *J* 12.5, 2.7), 7.28 (1H, d, *J* 8.4), presumably due to the reaction of CHT adduct **203**. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (40:60) as eluent gave the pure starting *adduct* **199** (0.32 g, 80%) as a yellow solid, m.p. 145-149 ºC; [Found: C, 61.33; H, 5.06; N, 10.48; Cl, 9.35; $C_{20}H_{18}ClN_3O_3$ (adduct +0.4H_2O) requires C, 61.58, H, 4.65, N, 10.77; Cl, 9.09%]*; ν_{max}/cm^{-1} (KBr) 2969, 2928, 1790 w, 1724 s, 1413; δ_H (300 MHz) 1.35 [6H, s, C(1)$(CH_3)_2$], 1.66 [1H, s, X of ABX, C(3a)H], 2.04 [1H, dd, A of ABX, J_{AB} 17.7, J_{AX} 1.2 one of C(2)H_2], 2.22 [1H, d, B of ABX, J_{AB} 22.5, one of C(2)H_2], 2.24 [1H, d, *J* 1.8, C(3b)H], 5.34 [1H, dd, *J* 5.1, 2.7, C(4)H], 5.40 [1H, d, *J* 6.5, C(10)H], 6.28 [1H, dd, *J* 6.3, 2.4, C(11)H], 7.32-7.50 (5H, m, ArH);

δ_C (75.5 MHz) 19.6 [CH, C(3a)H], 24.5, 26.9 [2 × CH_3, C(1)$(CH_3)_2$], 36.3 [C, C(1) or C(3a)], 37.4 [CH, C(3b)H], 38.8 [C, C(1) or C(3a)], 50.8 [C(2)H_2], 53.0, 60.0 [2 × CH, C(4)H, C(10)H], 123.4 [CH, C(11)H], 125.4, [CH, aromatic CH], 127.9 [C, aromatic C], 128.7, 129.3 [2 × CH, aromatic CH], 130.9 [C, C-Cl], 156.3, 156.4 [2 × C, C(6), C(8)], 207.5 [C, C(3)]; HRMS (ES+): Exact mass calculated for $C_{20}H_{18}Cl^{35}N_3O_3$ [(M+H)$^+$]

384.1115 Found 384.1101. m/z (ES+) 384 [$(C_{20}H_{18}Cl^{35}N_3O_3+H)^+$, 20%], 101 (30%), 60 (100%). In HRMS (ES+), $(C_{20}H_{18}Cl^{37}N_3O_3+H)^+$ detected at 386.1083.

* ^{1}H NMR showed the presence of water. Elemental analysis is in agreement with the adduct **199**+0.4H_2O.

(c) Effect of catalyst on enantioselectivity of the decomposition of diazoketone **45***, where the crude azulenone* **180** *was trapped with sublimed PTAD* **162** *to give the pure adduct* **199**

A sample of diazoketone **45** was cyclised with the catalyst shown in Table 3.27, followed by reaction with $ZnCl_2$ as described in section (b) to remove *CHT adduct* **203**. Enantiopurity of remaining *adduct* **199** could be determined by HPLC.

Table 3.17 *Effect of catalyst on enantioselectivity of the decomposition of diazoketone* **45**

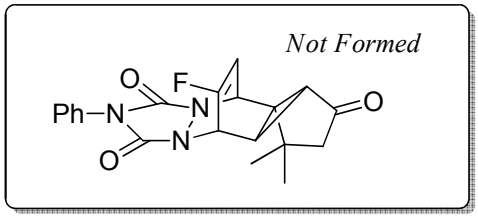
Entry	Catalyst	Method	Time (h)[a]	Yield (%)[b]	ee (%)[c]
1	$CuPF_6$-**75**[(*R*,*R*)-Ph-Box][d]	B	1	63	83[e,f]

a. Number of hours over which diazoketone was added.
b. Yield of isolated product **199** after flash chromatography (20% ethyl acetate:hexane as eluant).
c. Determined from chiral HPLC.
d. The catalyst was prepared from 1.3:1 molar mixture of ligand: $Cu(CH_3CN)_4PF_6$.
e. Major Enantiomer = (+).
f. Specific Rotation: $[\alpha]_D^{20}$ 23.2 [*c* 0.55, $CHCl_3$].

(d) Conditions for resolution of the enantiomers of PTAD **199** *adduct on HPLC using reverse phase Chiradex column.*

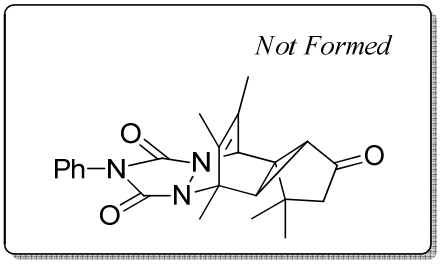
Resolution of the *PTAD adduct* **199** was achieved using a reverse phase LiChroCART 250-4 ChiraDex® at room temperature, with water/methanol (60:40) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 230 nm. Under these conditions dextrorotatory (+)-**199** elutes at 18.9 min and the levorotatory (−)-**199** elutes at 27.0 min.

Attempted synthesis of (3a*S,3b*R**)-1,2,3b,4-Tetrahydro-1,1,3a-dimethyl-7-phenyl-4,10-etheno-12-fluoro-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 200**



Synthesis was attempted following the procedure described for **197**, from 1-diazo-4-methyl-(4-fluorophenyl)pentan-2-one **46** (0.10 g, 0.45 mmol) in doubly distilled dichloromethane (80 mL), $Rh_2(OAc)_4$ **87** in deoxygenated doubly distilled dichloromethane (80 mL) and sublimed 4-phenyl-1,2,4-triazoline-3,5-dione **162** (0.084 g, 0.48 mmol) to give the crude reaction mixture as a brown oil. A ^{1}H NMR spectrum of the crude reaction mixture showed no presence of the desired *adduct* **200** or starting *azulenone* **181**. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (10:90) as eluent gave an unidentifiable product as a brown oil (30 mg). ν_{max}/cm^{-1} (film) 2934, 1714, 1503, 1412, 1199; δ_H (300 MHz) 1.43 [6H, s,], 2.56 [2H, s], 7.03 [1H, dd, *J* 12.0, 2.4], 7.21 [1H, dd, *J* 12.3, 2.7], 7.28 [1H, d, *J* 8.1], 7.44 [1H, d, *J* 12.0].

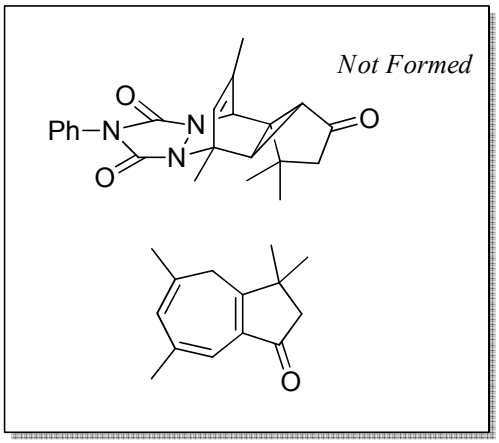
Attempted synthesis of (3a*S,3b*R**)-1,2,3b,4-Tetrahydro-1,1,4,11,12-pentamethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 202**



Synthesis was attempted following the procedure described for **197**, from 1-diazo-4-methyl-(3,4,5-trimethylphenyl)-pentan-2-one **48** (0.11 g, 0.45 mmol) in doubly distilled dichloromethane (80 mL), $Rh_2(OAc)_4$ **87** in deoxygenated doubly distilled dichloromethane (80 mL) and crude 4-phenyl-1,2,4-triazoline-3,5-dione **162** [freshly prepared from *t*-butyl hypochlorite **332** (0.05 g, 0.51 mmol), 4-phenyl urazole (0.09 g, 0.52 mmol) in dry acetone (10 mL)] was added as a solid in one portion to give the crude reaction mixture as a brown oil. A ^{1}H NMR spectrum of the crude reaction showed a complex mixture of unidentifiable products. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (5:95) as eluent gave an unidentifiable product (60 mg); ν_{max}/cm^{-1} (film) 2965, 1775 (w), 1713 (s), 1599, 1503, 1427; δ_H (300 MHz) 1.03 (2H, s), 1.28 (3H, s), 1.31 (3H, s), 1.46

(6H, s), 1.80 (2H, s), 2.12 (2H, s), 2.16 (1H, s), 2.21 (1H, s), 2.26 (3H, s), 2.29 (3H, s), 2.32 (1H, s), 2.40 (3H, s), 3.52 (1H, s), 4.15 (1H, s), 6.05 (1H, s), 6.77 (1H, s), 7.00 (1H, s), 7.24 (1H, s).

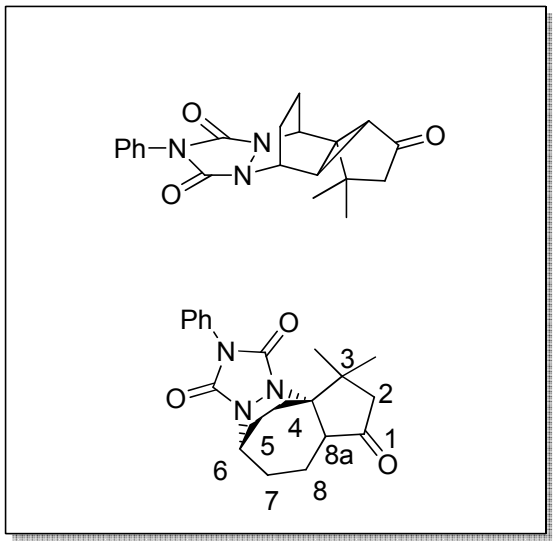
(3a*S,3b*R**)-1,2,3b,4-Tetrahydro-1,1,4,12-tetramethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 201 and 3,3,5,7-tetramethyl-2,3-dihydroazulen-1(4H)-one 188**



This was prepared from the procedure described for **197**, 1-diazo-4-methyl-(3,5-dimethylphenyl)pentan-2-one **47** (0.050 g, 0.22 mmol) in doubly distilled dichloromethane (80 mL), $Rh_2(OAc)_4$ **87** in deoxygenated doubly distilled dichloromethane (80 mL) and sublimed 4-phenyl-1,2,4-triazoline-3,5-dione **162** (0.047 g, 0.27 mmol) to give the crude reaction mixture as a yellow oil. ^{1}H NMR of the crude reaction mixture showed the presence of *trienone* **188** (49%). Purification by flash chromatography on silica gel, using ethyl acetate/hexane (40:60) as eluent gave the pure conjugated *trienone* **188** as a yellow oil (19 mg, 40%); ν_{max}/cm^{-1} (film) 2961, 2355, 1727, 1554, 1199, 913, 743; δ_H (300 MHz) 1.32 [6H, s, C(3)(C*H*$_3$)$_2$], 2.20 [3H, s, C(5)CH_3 or C(7)CH_3], 2.33 [3H, s, C(5)CH_3 or C(7)CH_3], 2.54 [2H, s, C(2)H_2], 3.47 [2H, s, C(4)H_2], 6.93 [1H, s, C(6)H or C(8)H], 7.10 [1H, s, C(6)H or C(8)H]; δ_C (75.5 MHz) 19.8, 21.2 [2 × CH_3, C(5)CH_3, C(7)CH_3], 29.7 [CH_3, C(3)(*C*H$_3$)$_2$], 37.4 [C, C(3)], 41.4, 54.0 [2 × CH_2, C(2)H_2, C(4)H_2], 122.8 [CH, C(6)H or C(8)H], 128.0 [C, one of C(5), C(7), C(3a), C(8)], 129.2 [CH, C(6)H or C(8)H], 136.2, 144.3 [2 × C, two of C(5), C(7), C(3a), C(8)], 210.1 [C, C(1)]. 3 × C signals seen at 128.0, 136.2, 144.3 for 4 quaternary C [C(5), C(7), C(3a), C(8a)] in vinylic region of ^{13}C NMR spectrum; HRMS (ES+): Exact mass calculated for $C_{14}H_{18}O$ [$(M+H)^+$] 203.1436 Found 203.1442. m/z (ES+) 244 (30%), 203 [$(M+H)^+$, 100%], 201 (60%), 83 (65%).

3.11.3 Synthesis of hydrogenated cycloadduct

(3a*S, 3b*R**)-1,2,3b,4-Tetrahydro-1,1,3a-dimethyl-7-phenyl-4,10-ethano-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 209 and hydrogenated CHT adduct 210**

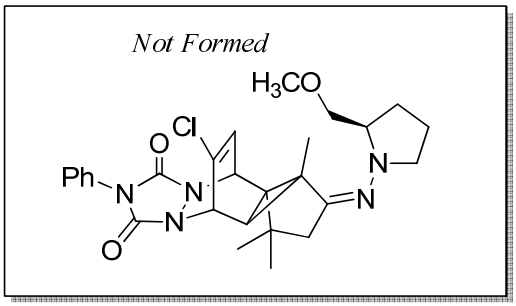


A mixture of crude *PTAD adduct* **199** and *CHT adduct* **203** (0.15 g, 0.39 mmol) in the ratio of **199**:**203**, 70:30, and palladium on carbon (5%, 30 mg) in absolute ethanol (20 mL) was shaken under hydrogen at 50 psi, for 18 h at room temperature. The crude reaction mixture was passed through a pad of Celite® to remove the hydrogenation catalyst. The product was rinsed through the Celite® with ethanol (3 × 50 mL) to fully elute it, while keeping the catalyst wet. Concentration of the solution under reduced pressure gave the *hydrogenated NCD adduct* **209** and *hydrogenated CHT adduct* **210** (100 mg). The ratio of the *hydrogenated NCD adduct* **209** to *hydrogenated CHT adduct* **210** was unable to be determined due to the complex nature of the ^{1}H NMR spectrum of the crude reaction mixture. Purification by flash chromatography, using ethyl acetate/hexane (30:70) as eluent gave a two fractions. The first less polar fraction gave a yellow oil, which was tentatively assigned as the *hydrogenated CHT adduct* **210** (6 mg, 5%) which also contained an unidentifiable impurity (~30% of the sample); δ_H (300 MHz) 1.22 [6H, s, C(3)$(CH_3)_2$], 2.34 [2H, s, C(2)H_2], 2.51-2.56 [2H, m, one of C(4)H_2, C(5)H_2, C(7)H_2, C(8)H_2], 2.60-2.68 [4H, m, two of C(4)H_2, C(5)H_2, C(7)H_2, C(8)H_2], 2.75-2.79 [2H, m, one of C(4)H_2, C(5)H_2, C(7)H_2, C(8)H_2], 3.43-3.57 [1H, m, C(6)H], 7.45-7.53 [5H, ArH]; δ_C (75.5 MHz) 18.8 [CH_2, one of C(4)H_2, C(5)H_2, C(7)H_2, C(8)H_2], 23.1 [CH_2, one of C(4)H_2, C(5)H_2, C(7)H_2, C(8)H_2], 26.8 [CH_3, C(3)$(CH_3)_2$], 40.5, 41.6, 50.4 [CH_2, C(2)H_2, C(4)H_2, C(5)H_2, C(7)H_2, C(8)H_2], 129.3 [CH, aromatic CH]; m/z (ES+) 355 (60%), 298 (30%), 278 (100%), 251 (30%), 207 (40%); The second fraction was a white solid which was partially assigned as the *hydrogenated NCD adduct* **209** (35 mg, 25%). The ^{1}H and ^{13}C NMR spectra of the second fraction illustrated a complex

mixture of products, the signals of the partially assigned *hydrogenated NCD adduct* **209**, which could be clearly identified are listed below; m.p. 176-181 ºC; ν_{max}/cm^{-1} (film) 2960, 1704, 1503, 1412, 1199; δ_H (300 MHz) 1.23, 1.29 [2 × 3H, 2 × s, C(1)$(CH_3)_2$], 2.03-2.10 [4H, m, C(2)H_2, C(11)H_2, C(12)H_2], 2.27-2.29 [2H, m, C(2)H_2, C(11)H_2, C(12)H_2], 2.55-2.66 [1H, m, C(3a)H], 4.83-4.86 [1H, m, C(4)H or C(10)H], 4.92 [1H, finely split s, *J* 1.2, C(4)H or C(10)H], 7.45-7.54 [5H, m, ArH]; δ_C (75.5 MHz) 23.9, 26.6 [2 × CH_3, C(1)$(CH_3)_2$], 27.9 [CH_2, C(2)H_2, C(11)H_2, C(12)H_2], 36.9 [CH_2, C(2)H_2, C(11)H_2, C(12)H_2], 48.2, 48.9, 49.0 [2 × CH, C(4)H, C(10)H], 125.5, 129.2 [2 × CH, aromatic CH], 151.8, 152.0 [2 × C, C(6), C(8)], 209.0 [C, C(3)]; HRMS (ES+): Exact mass calculated for $C_{20}H_{21}N_3O_3$ [$(M+H)^+$] 352.1661 Found 352.1657. m/z (ES+) 352 [$(M+H)^+$, 20%], 346 (10%), 236 (40%), 195 (100%).

3.11.4 Synthesis of hydrazone

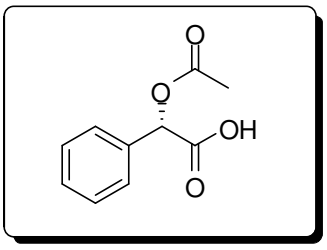
Attempted synthesis of hydrazone 314 with (*R*)-RAMP 352 from cycloadduct 313



(R)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine –(R) (RAMP) (83 mg, 0.65 mmol) was added neat to *cycloadduct* **313** (0.25 g, 0.65 mmol) and the mixture was heated at 60 ºC overnight, while stirring under nitrogen. Diethyl ether (20 mL) was subsequently added to the brown oil and the resulting solution was washed with water (10 mL). The layers were separated, and the organic layer was washed with brine (10 mL), dried and concentrated under reduced pressure to give a brown oil. The ^1H NMR spectrum of crude material showed the presence of *adduct* **313**. Purification by flash chromatography, using ethyl acetate/hexane (30:70) as eluent, gave two fractions. The first least polar fraction contained the *azulenone* **95** (10 mg, 7%) and a number of unidentifiable peaks. The second fraction contained a complex mixture of starting *adduct* **314** (120 mg) and unidentifiable products.

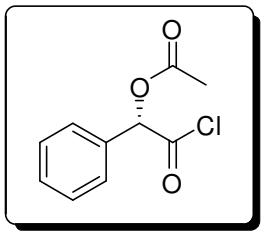
3.12 Synthesis of Bisoxazoline Ligands:

(*S*)-2-Acetoxy-2-phenylacetic acid 139[47]



(*S*)-Mandelic acid (5.00g, 32.86 mmol) was added to a mixture, while stirring at 0°C, of pyridine (12.5 mL, 155.0 mmol), acetic anhydride (3.34 mL, 35.48 mmol), dimethylaminopyridine (0.025 g, 0.2 mmol) and diethyl ether (50 mL). The mixture was allowed warm slowly to room temperature while stirring overnight. The mixture was acidified with aqueous hydrochloric acid (2M, 50 mL) and washed with diethyl ether (4 × 20 mL). The combined organic layers were extracted with water (50 mL), brine (50 mL), dried and concentrated under reduced pressure to give the *acid* **139** (5.50 g, 86%) as a white solid, m.p. 80-83 °C (Lit.,[47] 79-81 °C) ; ν_{max}/cm^{-1} (film) (KBr) 3448 br (OH), 1726 (CO), 1700; δ_H (300 MHz) 2.19 [3H, s, CH_3], 3.87 [3H, s (br), OH]*, 5.95 [1H, s, CH], 7.38-7.41 [3H, m, ArH], 7.47-7.50 [2H, m, ArH]. $[\alpha]_D^{20}$ 146.1 (*c* 1.0, $CHCl_3$), {Lit.,[47] $[\alpha]_D^{25}$ 107.8 (*c* 1.25, $CHCl_3$}.* Broad signal seen at 3.87 ppm believed to be H_2O/CO_2H.

(S)-2-Acetoxy-2-phenylacetyl chloride 137[48]

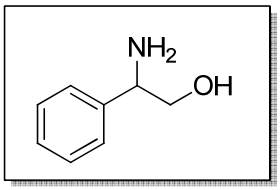


This was prepared following the procedure described for **63**, from crude (*S*)-2-acetoxy-2-phenylacetic acid **139** (10.00 g, 51.95 mmol), thionyl chloride (6.74 g, 4.31 mL, 56.64 mmol) and a catalytic amount of DMF (3 drops), to give a crude acid chloride as a brown oil. The brown oil formed was then purified by vacuum distillation (110°C, 0.60 mmHg, Lit.,[49] 125-130°C, 10 mmHg) to give the pure acid chloride **137** (8.54 g, 77%) as a yellow oil; ν_{max}/cm^{-1} (film) 2917, 1804 (CO), 1751 (CO), 1372, 1221; δ_H (300 MHz) 2.21 [3H, s, CH_3], 6.08 [1H, s, CH], 7.43-7.51 [5H, m, ArH]; $[\alpha]_D^{20}$ 107.3 (*c* 1.0, $CHCl_3$), {Lit.,[50] $[\alpha]_D^{27}$ 186 (*c* 3.5, $CHCl_3$)}.

Caution! When DMF is exposed to thionyl chloride *N*,*N*-dimethylcarbamoyl chloride (DMCC) is formed. Extreme caution must be exercised when carrying out a reaction

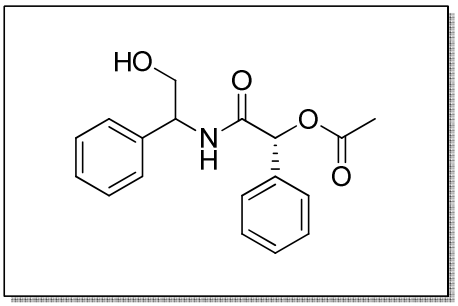
under such conditions as DMCC is a potent carcinogen in animals[16] and is believed to have a similar effect in humans.[51,52]

2-Amino-2-phenylethanol 138 [53,54]



Lithium aluminium hydride (2.75 g, 72.3 mmol) was suspended in tetrahydrofuran (100 mL) at 0 °C. Phenylglycine (5.00 g, 33 mmol) was added slowly in small portions. The reaction mixture was heated under reflux overnight and then cooled to room temperature. Saturated potassium carbonate (50 mL) was added slowly. The mixture was filtered and the filter cake washed with tetrahydrofuran (3 × 50 mL), The resulting solution was concentrated under reduced pressure to give the *amino alcohol* **138** (4.21 g, 93%) as a yellow oil; ν_{max}/cm^{-1} (film) 3349-2400 (OH), 1954, 1882, 1813, 1602, 1494, 1453; δ_H (300 MHz) 2.05 [3H, br s, NH_2, OH], 3.55 [1H, dd, A of ABX, J_{AB} 10.8, J_{AX} 8.1, one of C(1)H_2], 3.74 [1H, dd, B of ABX, J_{AB} 10.8, J_{BX} 4.4, one of C(1)H_2], 4.04 [1H, dd, X of ABX, J_{AX} 8,1, J_{BX} 4.4, C(2)H], 7.26-7.36 (5H, m, ArH).

***O*-Acetyl-(2-hydroxy-1-phenylethyl)mandelamide 141**[55]

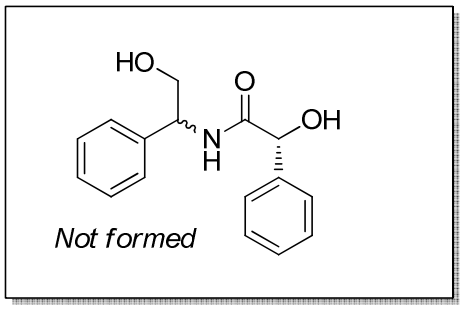


Pyridine (0.69 g, 0.71 mL, 8.75 mmol) was added dropwise to a solution of 2-amino-2-phenylethanol **138** (1.00 g, 7.29 mmol) in dichloromethane (20 mL) and the mixture was cooled to 0 °C. Once at 0 °C, (*S*)-2-acetoxy-2-phenylacetyl chloride **137** (1.86 g, 8.75 mmol) in dichloromethane (10 mL) was added dropwise over 30 min to form a light green coloured solution. The reaction solution was stirred for 18 h at 0 °C. The reaction was then quenched with hydrochloric acid (10 %, 10 mL). The layers were separated and the aqueous layer was washed with dichloromethane (3 × 20 mL). The combined organic layers were then washed with water (10 mL), brine (10 mL), dried and concentrated under reduced pressure to give a green oil (0.86 g), as a mixture of diastereoisomers **141a**:**141b**, 90:10. Purification by flash chromatography on silica gel, using ethyl acetate/hexane (5:95) as eluent gave two complex fractions. The main fraction was a clear oil (0.45 g), which was tentatively assigned as the *amino alcohol* **141** existed as a mixture of diasteroisomers in the ratio of

141a: **141b,** 65:35; ν_{max}/cm^{-1} (film) 3314, 3067, 1746, 1683, 1605, 1512, 1455, 1374, 1231; **141a** δ_H (300 MHz) 2.17-2.18 [3H, m. CH_3], 4.33-4.49 [2H, m, C(1)H_2], 5.14-5.28 [1H, m, C(2)H], 6.01-6.09 [1H, m, C(4)H], 7.27-7.50 [16H, m ArH], 7.83-7.87 [1H, m, NH]; **141b** δ_H (300 MHz) 2.09-2.11 [3H, m, C(6)H_3], 4.52-4.74 [2H, m, C(1)H_2], 4.52-4.74 [2H, m, C(2)H], 5.80-5.88 [2H, m, C(4)H], 6.80-7.13 [8H, m, ArH]; δ_C (75.5MHz) 20.6, 20.9, 20.9 [CH_3, *C*(6)H_3], 51.9, 52.0, 52.2 [CH, C(2)H], 66.5 [C], 66.6 [CH], 67.1 [C], 74.6, 74.7, 75.3, 75.4, 75.5 [5 × CH], 115.5, 115.5,115.8, 115.8, 116.1 [6 × CH], 125.5, 127.2, 127.3, 127.3, 127.4, 127.5, 127.6, 128.1, 128.2, 128.4, 128.5, 128.7, 128.8, 128.9, 129.0, 129.1, 129.5, 129.5, 130.0, 135.2, 135.3 [22 × CH, aromatic CH], 160.6-170.7 [12 × C]; m/z (ES+) 530 (100%), 464 (80%), 332 (40%), 270 (60%), 83 (100%).

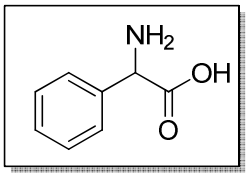
This experiment was repeated on a number of occasions. The ^{1}H NMR spectrum obtained varied somewhat between different experiments, but in all cases were more complex than would be expected for a single diastereoisomer of **141**.

(2*R*)-2-hydroxy-*N*-(2-hydroxy-1-phenylethyl)-2-phenylacetamide 142



A solution of amide **141** (1.70 g, 5.42 mmol) was dissolved in methanol (20 mL) and was treated with sodium hydroxide (5 N, 5 mmol). The resulting mixture was stirred at room temperature for 24 h, and TLC was then applied to monitor the disappearance of the starting material. The reaction was diluted with ethyl acetate (20 mL) and quenched with an aqueous solution of hydrochloric acid (1N, 10 mL). The two phases were separated and the aqueous layer was extract with ethyl acetate (3 ×10 mL). Finally, the combined organic phases were collected, washed with brine (50 mL), dried and concentrated under reduced pressure to give a green oil. Purification by flash chromatography on silica gel, using ethyl methanol/dichloromethane (5:95) as eluent gave two complex fractions. The main fraction was an unidentifiable white solid (0.80 g, 54%); ν_{max}/cm^{-1} (film) 3409, 2254, 2128, 1655, 1026; δ_H (300 MHz) 3.63 [2H, d, *J* 4.8], 4.82 [1H, q, *J* 6.0], 4.98 [1H, d, *J* 2.4], 5.03 [1H, s], 6.27 [1H, d, *J* 4.0], 7.20-7.27 [1H, m], 7.27-7.31 [6H, m], 7.33-7.37 [4H, m], 7.42-7.49 [3H, m], 8.28 [1H, d, *J* 8.0, NH].

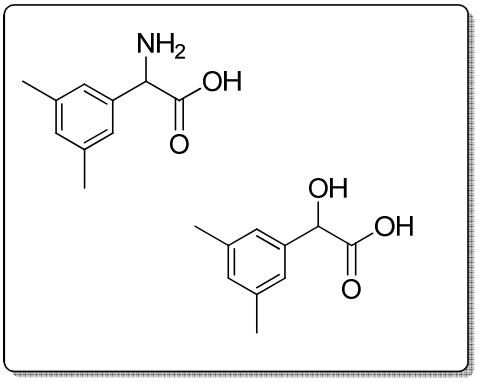
2-Amino-2-phenylacetic acid 140[56-58]



Ammonium chloride (0.51 g, 9.42 mmol) dissolved in water (20 mL) was added while stirring to benzaldehyde (1.00 g, 9.42 mmol) in methanol (10 mL). Sodium cyanide (0.46 g, 9.42 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. Then benzene (30 mL) was added to the light yellow coloured solution. The layers were separated and 6M hydrochloric acid (20 mL) was added to the organic layer, and the mixture was heated at 80 ºC for 4 h. Then the mixture was cooled to room temperature and concentrated under reduced pressure to give the *amino acid* **140** as a yellow solid (0.80 g, 56%), m.p. 215-220 ºC, (Lit.,[59] 252 ºC); ν_{max}/cm^{-1} (KBr) 2923 (br OH), 1731, 1481, 1379, 1064; δ_H (300 MHz) 5.02 [1H, s, C(2)H], 7.17-7.50 [15H, m, ArH]; {Lit.,[57] δ_H (D_2O) 5.10 [CH, C(2)H], 7.35 [5H, s, ArH]}

*Integration higher in aromatic region in ^{1}H NMR spectrum. While analytically pure phenylglycine **140** was not recovered from this experiment the critical observation was that there was only one α-CH signal with no evidence of the formation of mandelic acid.

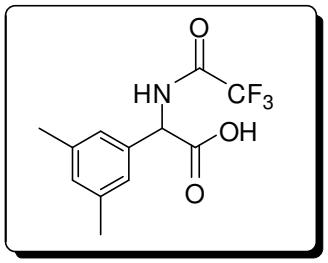
(*R*/*S*)-(3,5-Dimethyl)-phenylglycine 144[60] **and (*R*/*S*)-(3,5-Dimethyl)-mandelic acid 146**[61]



This was prepared following the procedure described for **140**, from ammonium chloride (4.88 g, 91.40 mmol), water (6 mL), commercially available 3,5-dimethylbenzaldehyde **145** (6.13 g, 45.70 mmol), methanol (10 mL) and sodium cyanide (4.48 g, 91.40 mmol). After stirring for at room temperature for 2 h, toluene (20 mL) was added to the light green coloured solution. The layers were separated and hydrochloric acid (6M, 20 mL) was added to the organic layer, and the mixture was heated at 80 ºC for 4 h. Then the mixture was allowed to cool and the layers were separated. Both aqueous and organic layers were allowed to stand at room temperature for 18 h. After 18 h, a white solid had precipitated from the aqueous layer. This was collected by filtration and dried to give the *amino acid* **144** (1.82 g, 23%), m.p. 220-223 ºC [Lit.,[60] m.p. > 220 ºC for

(*R*)-**144**]; ν_{max}/cm^{-1} (KBr) 3013 (br OH), 2986, 1738, 1611, 1496, 1408, 1216; δ_H (400 MHz, D_2O) 2.20 [6H, s, C(3′)CH_3, C(5′)CH_3], 4.90 [1H, C(2)H], 6.98-7.03 [2H, m, C(2′)H, C(6′)H], 7.07 [1H, s, C(4′)H]; δ_H [600 MHz, $(CD_3)_2SO$] 2.30 [6H, s, C(3′)CH_3, C(5′)CH_3], 4.97 [1H, s, C(2)H], 7.09 [1H, s, C(4′)H], 7.12 [2H, s, C(2′)H, C(6′)H], 8.76 [2H, br s, NH_2]; δ_C (150 MHz, $(CD_3)_2SO$) 20.8 [CH_3, C(3′)CH_3, C(5′)CH_3], 55.5 [CH, C(2)H], 126.7 [CH, C(2′)H, C(6′)H], 130.6 [CH, C(4′)H], 133.0 [C, C(1′)], 138.0 [C, C(3′), C(5′)], 169.7 [C, C(1)]; Exact mass calculated for $C_{10}H_{13}NO_2$ [$(M+H)^+$] 180.1025 Found 180.1019. m/z (ES+) 221 (30%), 180 [(M+H)+, 100%], 179 (60%), 144 (15%). After 18 h, a white solid had precipitated from the organic layer. This solid was collected by filtration and dried to give *DL-(3,5-dimethyl)-mandelic acid* **146** as a white crystalline solid (3.50 g, 42%), m.p. 88-90 ºC; (Found: C, 66.34; H, 6.62. $C_{10}H_{12}O_3$ requires C, 66.65, H, 6.71 %); ν_{max}/cm^{-1} (KBr) 3419-3100 (OH), 1722, 1611, 1411, 1255, 1198; δ_H (400 MHz, D_2O) 2.17 [6H, s, C(3′)CH_3, C(5′)CH_3], 5.07 [1H, s, C(2)H], 6.91-7.16 [3H, ArH]; δ_H (300 MHz) 2.31 [6H, s, C(3′)CH_3, C(5′)CH_3], 5.15 [1H, s, C(2)H], 5.23-6.31 [1H, br s, OH], 6.98 [1H, s, C(4′)H], 7.03 [2H, s, C(2′)H, C(6′)H]; δ_C (75.5 MHz) 21.3 [CH_3, C(3′)CH_3, C(5′)CH_3], 72.8 [CH, C(2)H], 124.4 [CH, C(2′)H, C(6′)H], 130.6 [CH, C(4′)H], 137.3 [C, C(1′)], 138.5 [C, C(3′), C(5′)], 178.0 [C, C(1)]. m/z (ES-) 180 (20%), 179 [(M−H)+, 100%], 135 (10%).

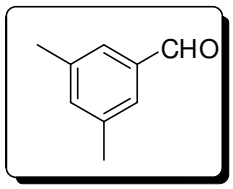
(*R,S*)-*N*-(Trifluoroacetyl)-2-(3,5-dimethylphenyl)glycine 143[60,62]



A solution of (3,5-dimethyl)phenylglycine **144** (0.26 g, 1.46 mmol), tetramethylguanidine (0.50 g, 4.40 mmol) and ethyl trifluoroacetate (0.25 g, 1.76 mmol) in methanol (5 mL) were stirred at room temperature for 24 h. Evaporation of the solvent gave a light brown residue, which was dissolved in aqueous hydrochloric acid (5%, 5 mL), and the solution was then extracted with diethyl ether (3 × 15 mL). The organic extracts were combined, washed with aqueous HCl (5%, 10 mL), water (10 mL) and brine (10 mL). The organic phase was dried, filtered and concentrated under reduced pressure to give the crude protected *amino acid* **143** which was recrystallised from benzene/diethyl ether to give *amino acid* **143** (0.20 g, 50%) as a white solid, m.p. 158-161 ºC, (Lit.,[60,63] 173-174 ºC); (Found: C, 52.7; H, 4.77; N, 4.77; $C_{12}H_{12}F_3O_3$ requires C, 52.37, H, 4.39, N, 5.09 %); ν_{max}/cm^{-1} (film) (KBr) 3398 (OH),

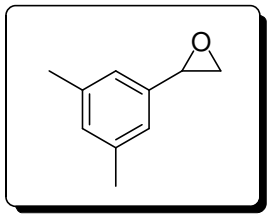
2923, 1723 (CO), 1611, 1465, 1211; δ_H [$(CD_3)_2SO$, 300 MHz] 2.27 [6H, s, C(3′)CH_3, C(5′)CH_3], 5.34 [1H, d, *J* 6.0, C(2)H], 7.00 [1H, s, C(4)H], 7.04 [2H, s, C(2′)H, C(6′)H], 10.12 [1H, d, *J* 6.0, NH]; δ_H (300 MHz) 2.30 [6H, s, C(3′)CH_3, C(5′)CH_3], 5.15 [1H, s, C(2)H], 6.97 [1H, s, C(4)H], 7.02 [2H, s, C(2′)H, C(6′)H], 7.14-7.45 [1H, m (br), NH]; Exact mass calculated for $C_{12}H_{12}F_3NO_3$ [$(M+H)^+$] 276.0848. Found 276.0850. m/z (ES-) 550 (30%), 549 (100%), 275 (10%), 274 [(M-H)+, 50%].

3,5-Dimethylbenzaldehyde 145[64]



n-Butyllithium (2.14M solution in hexanes, 40.2 mL, 59.62 mmol) was added dropwise over 1 h to a stirring solution of 1-bromo-3,5-dimethylbenzene (10.03 g, 54.20 mmol) in freshly distilled tetrahydrofuran (100 mL) at -78 ºC under an atmosphere of nitrogen, to give a thick white slurry. The addition of *n*-butyllithium was monitored to ensure the temperature did not rise above -70 ºC. Once the addition was complete, anhydrous dimethylformamide (13.19 g, 13.92 mL, 180.48 mmol) was subsequently added dropwise to the reaction mixture over 30 min. Once the addition was complete, the reaction mixture was allowed to warm slowly to room temperature and stirred overnight to form a light green coloured solution. The reaction mixture was then quenched by pouring onto concentrated hydrochloric acid (10%, 50 mL). The layers were separated and the aqueous layer washed with diethyl ether (2 × 50 mL). The combined organic layers were then washed with brine, dried, filtered and concentrated under reduced pressure to give the *crude aldehyde* **145** as a green oil. Purification by flash chromatography, using ethyl acetate/hexane (10:90) as eluant, gave the *aldehyde* **145** (4.21 g, 58%) as a light green oil. ν_{max}/cm^{-1} (film) 2958, 1698, 1609, 1599; δ_H (300 MHz) 2.38 [6H, s, C(3′)CH_3, C(5′)CH_3], 7.25 [1H, s, C(4′)H], 7.47 [2H, s, C(2′)H, C(6′)H], 9.93 [1H, s, CHO].

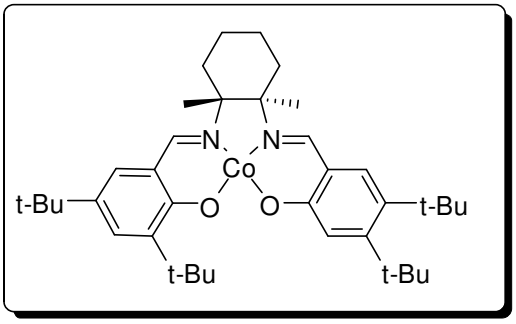
2-(3,5-Dimethylphenyl)oxirane 154[65,66]



To a solution of 3,5-dimethylbenzaldehyde **145** (3.99 g, 29.73 mmol), trimethylsulfonium iodide (6.06 g, 29.73 mmol), and tetrabutylammonium bromide (0.14 g, 0.45 mmol) in dichloromethane (40 mL), was added an aqueous sodium hydroxide solution (50%, 40 mL). The mixture was heated and after 60 h heating under

reflux while stirring, the mixture was cooled, poured onto ice (100 g), and extracted with dichloromethane (2 × 40 mL). The combined organic extracts were sequentially washed with water (30 mL), saturated aqueous sodium metabisulfite (30 mL), water (30 mL), brine, dried, filtered and concentrated under reduced pressure to give the crude *epoxide* **154** as a yellow oil. Purification by flash chromatography, using ethyl acetate/hexane (10:90) as eluant, gave the *epoxide* **154** (1.78 g, 41%) as a yellow oil. ν_{max}/cm^{-1} (film) 2958, 2920, 1725, 1684, 1608, 1477, 839; δ_H (300 MHz) 2.29 [6H, s, C(3′)CH_3, C(5′)CH_3], 2.74 [1H, dd, *J* 5.5, 2.5, one of C(1)H_2], 3.07 [1H, dd, *J* 5.5, 4.0, one of C(1)H_2], 3.75 [1H, dd, *J* 4.0, 2.6, C(2)H], 6.88 [2H, s, C(2′)H, C(6′)H], 6.97 [1H, s, C(4′)H]; δ_C (75.5 MHz) 21.2 [CH_3, C(3′)CH_3, C(5′)CH_3], 51.0 [CH_2, C(1)CH_2], 52.4 [CH, C(2)H], 123.3 [CH, C(2′)H, C(6′)H], 129.9 [CH, C(4′)H], 137.6 [C, C(1′)], 138.1 [C, C(3′)CH_3, C(5′)CH_3]; Exact mass calculated for $C_{10}H_{12}O$ [$(M+H)^+$] 149.0966 Found 149.0960. m/z (ES+) 261 (40%), 191 (20%), 190 (100%), 149 [$(M+H)^+$, 20%]

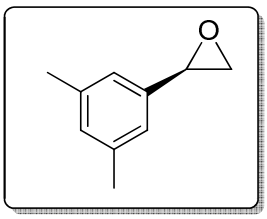
[(*R*,*R*)-*N*,*N*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) 157[67]



A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in methanol (80 mL) was added to a solution of ligand[(*R,R*)-*N,N*-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine] (10.90 g, 20.0 mmol) in dichloromethane (80 mL) *via* cannula under an atmosphere of nitrogen with careful extrusion of air. A brick-red solid began to precipitate before addition was complete. The sides of reaction flask were rinsed with methanol (20 mL), and the mixture was stirred for 15 min at room temperature and 30 min at 0 ºC. Precipitated solids were isolated by vacuum filtration and rinsed with cold (0 ºC) methanol (2 × 75 mL). The red solid was collected and dried under vacuum to yield [(*R*,*R*)-*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) **157** (10.00 g, 83%) as a red brick coloured solid.

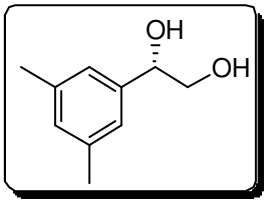
(*R*)-2-(3,5-Dimethylphenyl)oxirane 154[66,68]

*(a) Preparation of (*R*)-2-(3,5-Dimethylphenyl)oxirane* **154**



Acetic acid (1.19 g, 19.97 mmol) was added to a solution of the (*R*,*R*)-Co(salen) catalyst **157** (0.43 g, 0.69 mmol) in toluene (4 mL). The mixture was stirred for 30 min under a gentle stream of air, and then concentrated in *vacuo* to give a dark brown residue. A solution of racemic 2-(3,5-dimethylphenyl)oxirane **154** (3.42 g, 23.50 mmol) in tetrahydrofuran (4 mL) was then added, and the mixture was cooled to 0 ºC, and water (0.22 g, 11.75 mmol) was added slowly. The reaction mixture was stirred for 40 h at room temperature and filtered through a plug of silica gel. The silica was then washed with ethyl acetate/hexane (20:80) (2 × 100 mL). The dark red coloured solution was concentrated under reduced pressure to give a dark red residue, which was then distilled under reduced pressure (60ºC, 0.06 mmHg) to yield the optically pure *(*R*)-2-(3,5-dimethylphenyl)oxirane* **154** as a clear oil (1.64 g, 48%) containing 50 mol% of an impurity tentatively assigned as the diol **155**. Analysis of *(*R*)-epoxide* **154** by HPLC showed the enantioselectivity was 98% ee. $[\alpha]_D^{20}$ +23.0 [*c* 0.25, $CHCl_3$].

Spectral characteristics were identical to those described for racemic sample except for an



impurity (~50%) which is tentatively assigned as the diol **155**;

δ_H (300 MHz) 3.62 [1H, dd, *J* 8.7, 6.3, C(1)H_2], 3.70 [1H, dd, *J* 8.7, 2.7, C(1)H_2], 4.71 [1H, dd, *J* 6.0, 2.7, C(1)H].

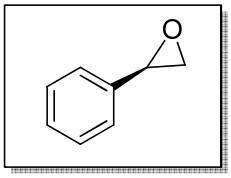
Note: This kinetic resolution was conducted on a number of occasions and while the product isolated from the experiment described above was eventually a 50:50 mixture of epoxide **154** and diol **155**, on other occasions the epoxide **154** was isolated in pure form δ_H (300 MHz) δ_H (300 MHz) 2.29 [6H, s, C(3′)CH_3, C(5′)CH_3], 2.74 [1H, dd, *J* 5.5, 2.5, one of C(1)H_2], 3.07 [1H, dd, *J* 5.5, 4.0, one of C(1)H_2], 3.75 [1H, dd, *J* 4.0, 2.6, C(2)H], 6.88 [2H, s, C(2′)H, C(6′)H], 6.97 [1H, s, C(4′)H];. The enantiopurity of samples isolated from a series of experiments varied between 94-98% ee.

(b) Conditions for resolution of the enantiomers of epoxide **154** *on HPLC*

Resolution of the *epoxide* **154** was achieved using a Chiracel® OD-H column at 0 ºC, with isopropanol:hexane (5:95) as eluant, a flow rate of 1.0 mL/min, and the detector set at λ 254 nm. Under these conditions the dextrorotatory (+)-**154** elutes at 18.0 minutes and the levorotatory (−)-**154** elutes at 24.3 minutes. The column temperature was maintained using an Igloo-Cil® column heater/cooler.

(*R*)-2-Phenyloxirane 158[69,70]

(a) Preparation of ((R)-2-phenyloxirane **158**



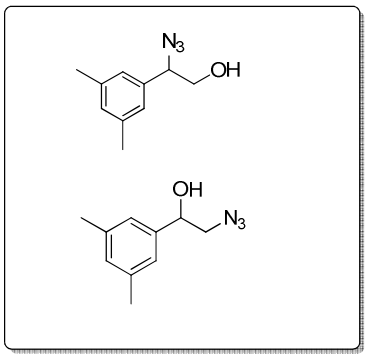
This was prepared following the procedure described for **154**, from commercially available 2-phenyloxirane (1.00 g, 8.32 mmol), (*R*,*R*)-Co(salen) catalyst **157** (0.15 g, 0.25 mmol), acetic acid (0.42 g, 7.07 mmol), water (74 mg, 4.16 mmol), dichloromethane (1 mL) and tetrahydrofuran (1 mL) to give (*R*)-2-phenyloxirane **158** as a dark red oil which was then distilled under reduced pressure (27ºC, 0.15 mmHg) to yield the optically pure *epoxide* **158** (0.45 g, 45%) as a clear oil; ν_{max}/cm^{-1} (film) 2988, 2356, 1608, 1497, 1477, 1454, 1201; δ_H (300 MHz) 2.80 [1H, dd, *J* 5.4 2.7, CH_2], 3.15 [1H, dd, *J* 5.4, 3.9, CH_2], 3.86 [1H, dd, *J* 3.9, 2.4, CH], 7.25-7.37 [5H, ArH]. Analysis of *epoxide* **158** by HPLC showed the enantioselectivity was 99% ee. $[\alpha]_D^{20}$ +11.50 [*c* 0.4, $CHCl_3$], {Lit.,[71] $[\alpha]_D^{20}$ +33.0 [neat]}.

(b) Conditions for resolution of the enantiomers of epoxide **158** *on HPLC.*

Resolution of the *epoxide* **158** was achieved using a Chiracel® OD-H column at 0 ºC, with isopropanol:hexane (5:95) as eluant, a flow rate of 1.0 mL/min, and the detector set at λ 223 nm. Under these conditions the dextrorotatory (+)-**158** elutes at 9.8 minutes and the levorotatory (−)-**158** elutes at 9.0 minutes. The column temperature was maintained using an Igloo-Cil® column heater/cooler.

2-Azido-2-(3,5-dimethylphenyl)ethanol 156[66]

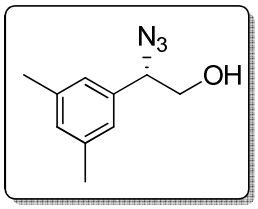
(a) Preparation of racemic sample of azide **156a**



A mixture of ammonium chloride (0.98 g, 18.53 mmol), sodium azide (5.96 g, 91.76 mmol) and racemic 2-(3,5-dimethylphenyl)oxirane **154** (1.36 g, 9.17 mmol) in ethanol (15 mL) was heated while stirring under reflux for 12 h. After cooling, it was partitioned between diethyl ether (20 mL) and water (20 mL). The aqueous phase was extracted with diethyl ether (2 × 10 mL), the combined organic phases were washed with water (2 × 10 mL), brine, dried and concentrated under reduced pressure to give an orange oil, which was a mixture of three compounds, the two regioisomers in the ratio **156a**:**156b:**, 90:10, and the starting epoxide **154** (10%). Separation of regioisomers was achieved by flash chromatography, using ethyl acetate/hexane (10:90) as eluant, to give only *azide* **156a** as a single compound (0.85 g, 49%). ν_{max}/cm^{-1} (film) 3368 (OH), 2921, 2103 (N_3), 1608, 1463; δ_H (400 MHz) 2.13 [1H, t, *J* 5.5, OH], 2.32 [6H, s, C(3′)CH_3, C(5′)CH_3], 3.71 [2H, dd appears as a t, *J* 5.8, 5.8 C(1)H_2], 4.59 [1H, t, *J* 6.4, C(2)H], 6.92 [2H, s, C(2′)H, C(6′)H], 6.93 [1H, s, C(4′)H]; δ_C (75.5 MHz) 21.3 [CH_3, C(3′)CH_3, C(5′)CH_3], 66.5 [CH_2, C(1)CH_2], 68.0 [CH, C(2)CH], 124.9 [CH, C(2′)H, C(6′)H], 130.4 [CH, C(4′)H], 136.1 [C, C(1′)], 138.6 [C, C(3′)CH_3, C(5′)CH_3]; HRMS (ES+): Exact mass calculated for $C_{10}H_{13}N_3O$ [$(M-N_2+H)^+$] 164.1075 Found 164.1073. m/z (ES+) 305 (30%), 164 [$(M-N_2+H)^+$, 70%], 83 (100%).

Signals for minor regioisomer **156b** from ^{1}H NMR spectrum of the crude material are as follows; δ_H (400 MHz) 3.43 [2H, ddd, *J* 12.4, 8.0, 4.0, C(1)H_2], 4.80 [1H, dd, *J* 8.4, 4.0, C(2)H].

(b) Preparation of enantiopure sample of (S)*-2-azido-2-(3,5-dimethylphenyl)ethanol* **156**



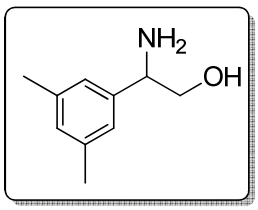
This was prepared following the procedure described for **156**, from ammonium chloride (0.36 g, 6.75 mmol), sodium azide (2.19 g, 33.73 mmol) and (*R*)-2-(3,5-dimethylphenyl)oxirane **154** (0.50 g, 3.37 mmol, 98% ee) in absolute ethanol (15 mL) to give the crude *(*S*)-azide* **156** (0.46 g) as a orange oil. The ^{1}H NMR of the crude product showed 20% of minor regioisomer **156b** present. Purification by flash chromatography, using ethyl acetate/hexane (10:90) as eluant gave the *(*S*)-azide* **156a** (0.30 g, 51%,) as a yellow oil with spectral characteristics identical to those reported for racemic sample above. Analysis of *(*S*)-azide* **156a** by HPLC showed an enantioselectivity of 96% ee. $[\alpha]_D^{20}$ +188.6 [*c* 1.0, $CHCl_3$].

(c) Conditions for resolution of the enantiomers of azide **156a** *on HPLC*

Resolution of the *azide* **156a** was achieved using a Chiracel® OJ-H column at 23 ºC, with isopropanol:hexane (5:95) as eluant, a flow rate of 0.5 mL/min, and the detector set at λ 226 nm. Under these conditions the dextrorotatory (+)-**156a** elutes at 11.5 minutes and the levorotatory (−)-**156a** elutes at 12.0 minutes.

2-Amino-2-(3,5-dimethylphenyl)ethanol 128[66,72]

(a) Preparation of amino alcohol **128** *of using triphenylphosphine.*



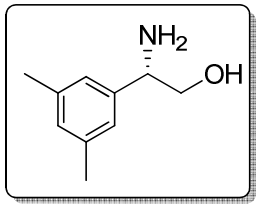
A mixture of 2-azido-2-(3,5-dimethylphenyl)ethanol **156** (0.29 g, 1.51 mmol), triphenylphosphine (0.59 g, 2.27 mmol) and water (0.16 g, 9.11 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature for 15 h. Diethyl ether (5 mL) and concentrated hydrochloric acid (10%, 10 mL) were added and the phases were separated. The aqueous phase was washed with diethyl ether (2 × 5 mL), then basified by the addition concentrated sodium hydroxide solution (10%, 10 mL). The mixture was then extracted with dichloromethane (3 x 5 mL) and the combined organic phases were washed with brine, dried and concentrated under reduced pressure to yield the *amino alcohol* **128** as a white solid, δ_H (300 MHz) 3.51 [1H, dd, *J* 10.6, 8.3, C(1)H], 3.69 [1H, dd, *J* 10.6, 4.3, C(1)H], 3.94 [1H, dd, *J* 8.1, 4.4 C(2)H]. Removal of triphenylphosphine oxide from the

amino alcohol **128** by trituration with cold diethyl ether or flash chromatography was not possible. Therefore an alternative method was sought.

(b) Preparation of a racemic sample of amino alcohol **128** *by hydrogenation.*

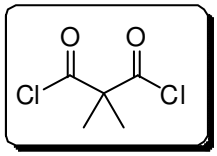
A mixture of 2-azido-2-(3,5-dimethylphenyl)ethanol **156** (0.54 g, 3.24 mmol) and palladium on carbon (10%, 50 mg) in methanol (30 mL), was shaken under hydrogen at 30 psi, for 16 h at room temperature. The crude reaction mixture was filtered through a short column of silica gel using ethyl acetate as eluant to remove the hydrogenation catalyst. Concentration of the solution gave the crude *amino alcohol* **128** (0.45 g, 85%) as a white solid, m.p. 84-85 ºC; ν_{max}/cm^{-1} (KBr) 3600-2300 (OH and NH), 1603, 1449, 1359, 1066; δ_H (400 MHz) 2.30 [6H, s, C(3′)CH_3, C(5′)CH_3], 2.49 [3H, s, NH_2,OH], 3.51-3.57 [1H, br m, C(1)H], 3.70-3.73 [1H, br m, C(1)H], 3.94-3.99 [1H, br m, C(2)H], 6.91 [3H, s, ArH]; δ_C (75.5 MHz) 21.33 [CH_3, C(3′)CH_3, C(5′)CH_3], 57.29 [CH, C(2)CH], 68.03 [CH_2, C(1)CH_2], 124.24 [CH, C(2′)H, C(6′)H]; HRMS (ES+): Exact mass calculated for $C_{10}H_{15}NO$ [$(M+H)^+$] 166.1232 Found 166.1236. m/z (ES+) 207 (10%), 167 (15%), 166 [$(M+H)^+$, 100%], 149 (25%).

(c) Preparation of an enantiopure sample of (S)-2-amino-2-(3,5-dimethylphenyl)ethanol **128** *by hydrogenation.*



This was prepared following the procedure described for **128**, from (*S*)-2-azido-2-(3,5-dimethylphenyl)ethanol **156a** (0.90 g, 4.70 mmol, 96% ee), palladium on carbon (5%, 100 mg) and methanol (80 mL) to give the crude *amino alcohol* **128** (0.82 g) as a white solid. Recrystallisation from hot toluene gave the pure *(*S*)-amino alcohol* **128** (0.32 g, 42%) as white crystals, with spectral characteristics identical to those reported for the racemic sample above. δ_H (400 MHz) 2.30 [6H, s, C(3′)CH_3, C(5′)CH_3], 2.49 [3H, s, NH_2,OH], 3.51 [1H, dd, *J* 10.6, 8.3, C(1)H], 3.69 [1H, dd, *J* 10.6, 4.3, C(1)H], 3.94 [1H, dd, *J* 8.1, 4.4 C(2)H], 6.91 [3H, s, ArH]; $[\alpha]_D^{20}$ 15.92 [*c* 0.65, C_2H_5OH].

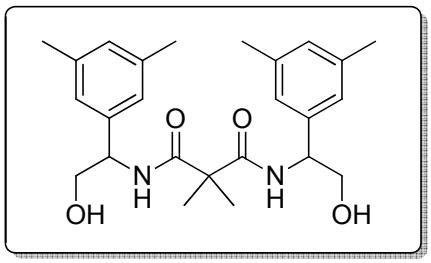
Dimethylmalonyl chloride 159[5,73]



This was prepared following the procedure described for **63**, from dimethylmalonic acid (15.16 g, 78.1 mmol) and thionyl chloride (92.89 g, 56.70 mL, 780.8 mmol). Purification by vacuum distillation gave the *acid chloride* **159** (10.16 g, 78%) as a clear, colourless oil; b.p. 80 ºC at 12 mmHg (Lit.,[74] 60 ºC at 10 mmHg); ν_{max}/cm^{-1} (film) 2999, 2947, 1792 br, 1467, 1393, 1372; δ_H (400 MHz) 1.69 [6H, s, $C(CH_3)_2$].

***N,N*-Bis(1-(3,5-dimethylphenyl)-2-hydroxyethyl)-2,2-dimethylmalonamide 160**

(a) Preparation of a racemic sample of N,N-*bis(1-(3,5-dimethylphenyl)-2-hydroxyethyl)-2,2-dimethylmalonamide* **160**

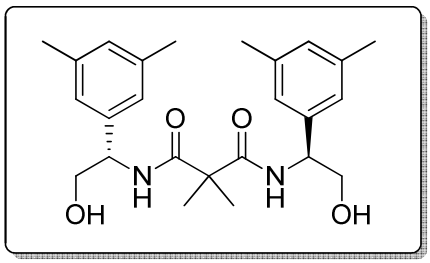


Dimethylmalonyl chloride **159** (0.19 g, 1.13 mmol) in doubly distilled dichloromethane (1 mL) was added dropwise to a heterogeneous solution of 2-amino-2-(3,5-dimethylphenyl)ethanol **128** (0.37 g, 2.26 mmol) and triethylamine (0.78 ml, 5.66 mmol) in doubly distilled dichloromethane (8 mL) at 0 ºC under an atmosphere of nitrogen. The homogeneous reaction mixture was removed from the bath and stirred for 40 min. Aqueous hydrochloric acid (10%, 10 mL) was added to the reaction mixture and the biphasic mixture was stirred for 15 min. The layers were separated and the aqueous layer was washed with dichloromethane (2 x 10 mL). The combined organic layer was washed with saturated aqueous sodium bicarbonate (10 mL). The aqueous layer was back extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure to give the crude *bisamide* **160** as a mixture of diastereoisomers **160a:160b**, in the ratio of 78:22. Purification by recrystallisation from a mixture of dichloromethane and hexane gave the pure *bisamide* **160** (230 mg, 47%) as two diastereoisomers **160a**:**160b**, in the ratio of 78:22, which existed as a white solid, m.p. 243-246 ºC; [Found: C, 69.39; H, 8.00; N, 6.39; $C_{25}H_{34}N_2O_4$ (Bisamide **160** +0.3H_2O) requires C, 69.46, H, 7.93, N, 6.48%]*; ν_{max}/cm^{-1} (KBr) 3329 (OH), 2919, 1641, 1608, 1530, 1468; **160a** δ_H (400 MHz) 1.50 [6H, s, $C(CH_3)_2$], 2.27 [12H, s, C(3′)CH_3, C(5′)CH_3], 2.29 [2H, s, OH], 3.74 [2H, dd, A of ABX, J_{AB} 11.5, J_{AX}

7.4, one of C(2)H_2], 3.86 [2H, dd, B of ABX, J_{AB} 11.5, J_{BX} 3.5, one of C(2)H_2], 5.03 [2H, t of d, X of ABX, J_{AX} 7.6, J_{BX} 3.9, C(1)H], 6.85 [4H, s, ArH], 6.92 [2H, s, ArH], 7.03 [2H, d, *J* 8.0, NH] ; **160b** δ_H (400 MHz) 4.94-4.98 [2H, m, C(1)H], 7.17-7.20 [2H, m, NH]; **160a** δ_C (75.5 MHz) 21.3 [CH_3, C(3′)CH_3, C(5′)CH_3], 23.7 [CH_3, C(*C*H_3)$_2$], 49.9 [C, *C*(CH_3)$_2$], 55.9 [CH, C(1)H], 66.6 [CH_2, C(2)H_2], 124.3 [CH, C(2′)H, C(6′)H], 129.6 [CH, C(4′)H], 138.3 [C, C(1′)], 138.5 [C, C(3′), C(5′)], 174.0 [C, CO]; **160b** δ_C (75.5 MHz) 56.1 [CH, C(1)H]; HRMS (ES+): Exact mass calculated for $C_{25}H_{34}N_2O_4$ [$(M+H)^+$] 427.2597 Found 427.2593. m/z (ES+) 428 (30%), 427 [(M+H)+, 100%], 333 (20%), 102 (20%).:

* ^{1}H NMR showed the presence of water. Elemental analysis is in agreement with the bisamide **160** +0.36H_2O.

(b) Preparation of an enantiopure sample of N,N-*Bis[(*S*)-2-hydroxy-1-(3,5-dimethylphenyl)ethyl)-2,2-dimethylmalonamide* **160**

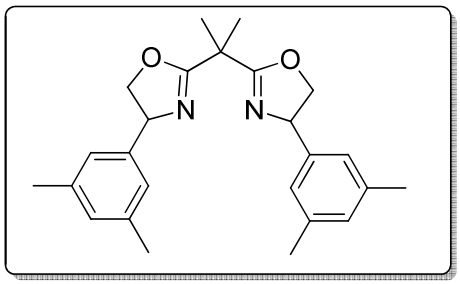


This was prepared following the procedure described for **160**, from (*S*)-2-amino-2-(3,5-dimethylphenyl)ethanol **128** (0.25 g, 1.51 mmol, 96% ee from (*S*)-azide **156a**), dimethylmalonyl chloride (0.13 g, 0.76 mmol), triethylamine (0.38 g, 3.78 mmol) and doubly distilled dichloromethane (1 mL) to give the crude *bisamide* **160** (0.28 g, 86%) as a white solid. It was carried through to the next step without purification. Spectral characteristics were similar to those reported for the racemic sample above. $[\alpha]_D^{20}$ 33.75 [*c* 0.2, $CHCl_3$].

Note: ^{1}H NMR indicated the presence of **160** (70-80%) although not analytically pure. There was no evidence for the diastereoisomer **160b**.

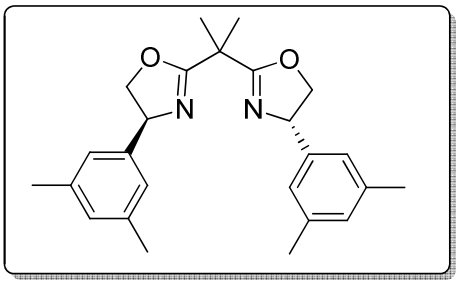
2,2-Bis{2-[4-(3,5-dimethylphenyl)-1,3-oxazolinyl]}propane 93[75]

(a) Preparation of racemic sample of 2,2-Bis{2-[4-(3,5-dimethylphenyl)-1,3-oxazolinyl]}propane **93**



Triethylamine (0.18 g, 1.79 mmol) was added dropwise to a solution of *N,N*-bis(1-(3,5-dimethylphenyl)-2-hydroxyethyl)-2,2-dimethylmalonamide **160** (0.17 g, 0.41 mmol) and 4-(dimethylamino)pyridine (5 mg, 0.04 mmol) in doubly distilled dichloromethane (5 mL) over 2 min under an atmosphere of nitrogen. The flask was placed in a room temperature water bath, and a solution of *p*-toluenesulfonyl chloride (0.16 g, 0.81 mmol) in doubly distilled dichloromethane (2 mL) was added dropwise over 3 min. The yellow solution was stirred at room temperature for 24 h. Saturated aqueous ammonium chloride (3 mL) was added to the solution and the biphasic mixture was stirred for 15 min. The layers were then separated and the aqueous layer was washed with dichloromethane (3 x 10 mL). The combined organic extracts were then washed with saturated aqueous sodium bicarbonate (10 mL). Once again the aqueous layer was washed with dichloromethane (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried, filtered and concentrated under reduced pressure to give the crude *bis(oxazoline)* **93** as a yellow/green oil. Purification by flash chromatography, using diethyl ether/hexane (80:20) as eluant (using $KMnO_4$ stain to give a white spot which faded over time) gave the *bis(oxazoline)* **93** (90 mg, 56%) as a clear oil. There was no evidence for the second diastereisomer; ν_{max}/cm^{-1} (film) 2919, 1656, 1607, 1519, 1467, 1255, 1199; δ_H (400 MHz) 1.68 [6H, s, $C(CH_3)_2$], 2.27 [12H, s, C(3′)CH_3, C(5′)CH_3], 4.16 [2H, dd, A of ABX, J_{AB} 8.0, J_{AX} 7.6, one of C(5)H_2], 4.64 [2H, dd, B of ABX, J_{BX} 10.1, J_{AX} 8.0, one of C(5)H_2], 5.15 [2H, dd, X of ABX, J_{BX} 10.1, J_{AX} 7.5, C(4)H], 6.87 [4H, s, C(2′)H, C(6′)H], 6.89 [2H, s, C(4′)H]; δ_C (75.5 MHz) 21.3 [CH_3, C(3′)CH_3, C(5′)CH_3], 24.5 [CH_3, $C(CH_3)_2$], 38.9 [C, $C(CH_3)_2$], 69.5 [CH, C(4)H], 75.5 [CH_2, C(5)H_2], 124.4 [CH, C(2′)H, C(6′)H], 129.2 [CH, C(4)H], 138.2 [C, C(3′)CH_3, C(5′)CH_3], 142.3 [C, C(1′)], 170.2 [C, C(1)] HRMS (ES+): Exact mass calculated for $C_{25}H_{30}N_2O_2$ [$(M+H)^+$] 391.2386 Found 391.2392. m/z (ES+) 727 (15%), 427 (100%), 409 (45%), 391 [$(M+H)^+$, 100%].

*(b) Preparation of enantiopure sample of (4*S*,4'*S*)-2,2-Bis{2-[4-(3,5-dimethylphenyl)-1,3-oxazolinyl]}propane* **93**



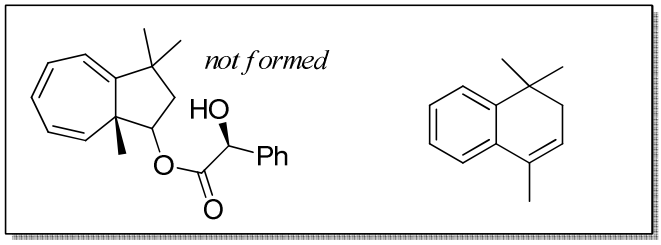
This was prepared following the procedure described for **93**, from *N,N*-bis[(*S*)-2-hydroxy-1-(3,5-dimethylphenyl)ethyl)-2,2-dimethylmalonamide **160** (0.22 g, 0.52 mmol), triethylamine (0.23 g, 2.27 mmol), *p*-toluenesulfonyl chloride (0.19 g, 1.03 mmol) and 4-(dimethylamino)pyridine (6 mg, 0.05 mmol) in doubly distilled dichloromethane (10 mL) to give the crude enantiopure *bisoxazoline* **93** (0.19 g) as a clear oil. Purification by flash chromatography, using diethyl ether/hexane (80:20) as eluant (using $KMnO_4$ stain to give a white spot which faded over time) gave two fractions. The first least polar fraction contained a mixture of the *(4*S*,4'*S*)-bis(oxazoline)* **93** and *bisamide* **160** in the ratio **93**,**160** 70:30. The second fraction gave the pure *(4*S*,4'*S*)-bis(oxazoline)* **93** (80 mg, 40%) as a clear oil. Spectral characteristics were consistent to those reported for the racemic sample above. Analysis of *(4*S*,4'*S*)-bis(oxazoline)* **93** by HPLC showed an enantioselectivity ≥99% ee. $[\alpha]_D^{20}$ -97.0 [*c* 0.1, $CHCl_3$].

(c) Conditions for resolution of the enantiomers of bisoxazoline **93** *on HPLC*

Resolution of the *bisoxazoline* **93** was achieved using a Chiracel® OD-H column at 23 ºC, with isopropanol:hexane (3:97) as eluant, a flow rate of 0.5 mL/min, and the detector set at λ 218 nm. Under these conditions the levororotatory (–)-**93** elutes at 13.7 minutes and the dextrotatory (+)-**93** elutes at 18.4 minutes.

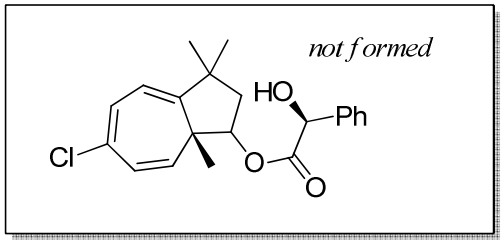
3.13 Esterification Reactions

Attempted preparation of ester 322 derived from the reaction of (1*R*, 8aS)-1,2,3,8a-tetrahydro-3,3,8a-trimethyl-azulen-1-ol 315 with (*S*)-mandelic acid



Azulenols **315a:315b**, in a ratio of 77:23 (0.41 g, 2.15 mmol), (S)-mandelic acid (0.33 g, 2.15 mmol) and *p*-toluenesulfonic acid (41 mg, 0.215 mmol) in benzene (20 mL) were heated while stirring under reflux for 12 h, using a Dean Stark trap. The resulting mixture was cooled to room temperature and washed with aqueous saturated sodium bicarbonate (20 mL). Ethyl acetate (20 mL) was added and the layers were separated. The aqueous layer was washed with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried and concentrated under reduced pressure to give a clear oil. Purification by flash chromatography, using ethyl acetate/hexane (5:95) gave a clear oil that is tentatively assigned as the *dihydronapthalene* **323**[76] (0.20 g, 54%); ν_{max}/cm^{-1} (film) 3028, 2963, 2823, 1484, 1446, 1382, 1359; δ_H (400 MHz) 1.25 [6H, s, C(4)$(CH_3)_2$], 2.05-2.06 [3H, finely split s, C(1)CH_3], 2.11-2.20 [2H, m, C(3)H_2], 5.72-5.78 [1H, m, C(2)H], 7.12-7.50 [4H, m, ArH]; δ_C (75.5 MHz) 19.5 [CH_3, C(1)CH_3], 28.6 [CH_3, C(4)$(CH_3)_2$], 33.7 [C, C(4)], 38.9 [CH_2, C(3)H_2], 123.3, 123.7, 124.2, 126.0, 127.3 [5 × CH, C(2)H, C(6)H, C(7)H, C(8)H, C(9)H], 131.5 [C, C(1)], 134.5 [C, C(10)], 144.1 [C, C(5)].

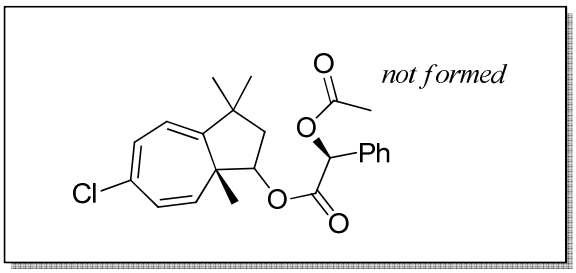
Attempted preparation of ester 324 derived from the reaction of (1R, 8aS),-6-chloro-1,2,3,8a-tetrahydro-3,3,8a-trimethylazulen-1-ol 316 with (S)-mandelic acid



A mixture of DMAP (3.5 mg, 0.029 mmol) and (S)-mandelic acid (45 mg, 0.29 mmol) in doubly distilled dichloromethane (5 mL) was added at 0 ºC to a stirred solution of azulenol **316** (75 mg, 0.34 mmol) and *N,N'*-dicyclohexylcarbodiimide (65 mg, 0.32 mmol) in doubly distilled dichloromethane (5 mL). The mixture was stirred

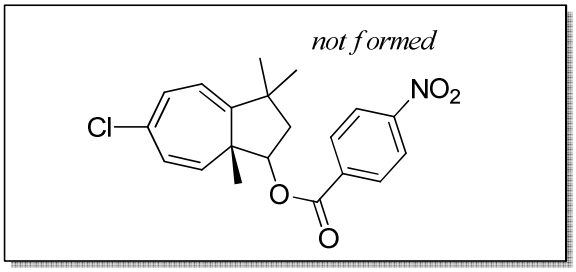
at 0 ºC for 30 min and at room temperature for 14 h. The insoluble material was removed by filtration through a sintered glass funnel and washed with dichloromethane (3 ×20 mL). The combined organic solutions were concentrated under reduced pressure to give a clear oil. A ^{1}H NMR spectrum of the crude product did not indicate the presence of the desired product **324**. Attempted purification of the mixture by flash chromatography, using ethyl acetate/hexane (5:95) as eluent, yielded a clear oil which by ^{1}H NMR showed no trace of the desired ester **324**.

Attempted preparation of ester 325 derived from the reaction of (1R, 8aS),-6-chloro-1,2,3,8a-tetrahydro-3,3,8a-trimethylazulen-1-ol 316 with (S)-2-acetoxy-2-phenylacetyl chloride 137



Triethylamine (21 mg, 0.21 mmol) was added dropwise to a solution of azulenol **316** (43 mg, 0.19 mmol) in doubly distilled dichloromethane (5 mL). The mixture was stirred for 30 min followed by the dropwise addition of a solution of (*S*)-2-acetoxy-2-phenylacetyl chloride **137** (45 mg, 0.21 mmol) in doubly distilled dichloromethane (5 mL). The solution was stirred for 14 h and carefully poured onto hydrochloric acid (10%, 10 mL). The layers were separated and the aqueous layer was washed with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried and concentrated under reduced pressure to give the crude product (30mg) as a clear oil. A ^{1}H NMR spectrum showed no presence of the desired ester **325** and indicated the presence of the starting azulenol **316**.

Attempted preparation of ester 320 derived from the reaction of (1R, 8aS),-6-chloro-1,2,3,8a-tetrahydro-3,3,8a-trimethylazulen-1-ol 316 with 4-nitrobenzoyl chloride



4-Nitrobenzoyl chloride (32 mg, 0.17 mmol) was added to a solution of the azulenols **316a**: **316b**, in a ratio of 89:11 (26 mg, 0.16 mmol) and DMAP (4 mg, 0.016 mmol) in pyridine (1 mL). The reaction mixture was heated under reflux for 30 min and was then cooled to room

temperature. It was then poured onto hydrochloric acid (1M, 5 mL). Aqueous sodium carbonate (1M, 10 mL) was added and the solution stirred for 5 min. The solution was extracted with diethyl ether (3 × 20 mL). The combined organic layers were combined and washed with water (20 mL), brine (20 mL), dried and concentrated under reduced pressure to give a brown solid. A ^{1}H NMR spectrum of the crude product showed the presence of the *azulenol* **316**. The crude product was recrystallised from dichloromethane/diethyl ether to give an orange crystalline solid. A ^{1}H NMR spectrum of the recrystallised product indicated the presence of 4-nitrobenzoic acid (25 mg), m.p. 236-239 ºC, (Lit.,[77] 240 ºC); ν_{max}/cm^{-1} (KBr) 3429, 2253, 2127, 1661, 1261, 1027; δ_H (400 MHz) 8.16-8.19 [2H, m, C(2)H, C(6)H or C(3)H, C(5)H], 8.32-8.34 [2H, m, C(2)H, C(6)H or C(3)H, C(5)H].

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Appendix 1 Abbreviations

AB AB system

Ar aryl

Bu butyl

BuLi butyllithium

Bn benzyl

bp boiling point

br Broad

BTMSM bis(trimethysilyl)methyl

CHT cycloheptatriene

COSY correlation spectroscopy

DBU 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC *N*,*N*'-Dicyclohexylcarbodiimide

DCE 1,2-dichloroethane

DCM dichloromethane

DEPT distortionless enhancement of polarisation transfer

DMAP (dimethylamino)pyridine

DMB dimethylbutane

DMCC *N*,*N*-dimethylcarbamoyl chloride

DMF dimethylformamide

DMSO dimethylsulfoxide

d Doublet

dd doublet of doublets

ddd doublet of doublet of doublets

dt doublet of triplets

ddt doublet of doublet of triplets

ee enantiomeric excess

EN endo

Et ethyl

EDG electron donating group

ESI electrospray ionization

EWG electron-withdrawing group

equiv equivalents

EX exo

g gram

h hour(s)

HETCOR heteronuclear correlation

HPLC high performance liquid chromatography

HRMS high resolution mass spectrometry

Hz Hertz

i iso

IR infrared

L ligand

lit literature

M molar

Me methyl

Mes mesityl

mg milligram

MHz megahertz

min minute(s)

mp melting point

m Multiplet

NaBARF sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate

NCD norcaradiene

NMR nuclear magnetic resonance

OAc acetate

OMe methoxy

OPiv pivalate

PCC pyridinium chlorochromate

Ph phenyl

Pr propyl

PTAD 4-Phenyl-1,2,4-triazoline-3,5-dione

PTSA *p*-Toluenesulfonic acid

q Quartet

RAMP (*R*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine

rt room temperature

s Singlet

t tert

t Triplet

THF tetrahydrofuran

TLC thin layer chromatography

TMS tetramethylsilane

UV ultraviolet

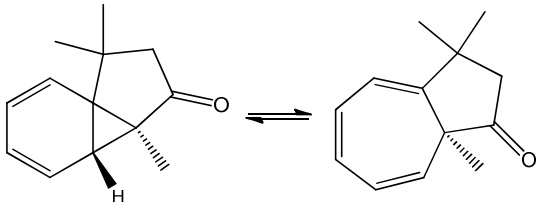
Appendix 2 Stack Plots

3,8a-Dihydro-3,3,8a-trimethylazulen-1(2*H*)-one 89

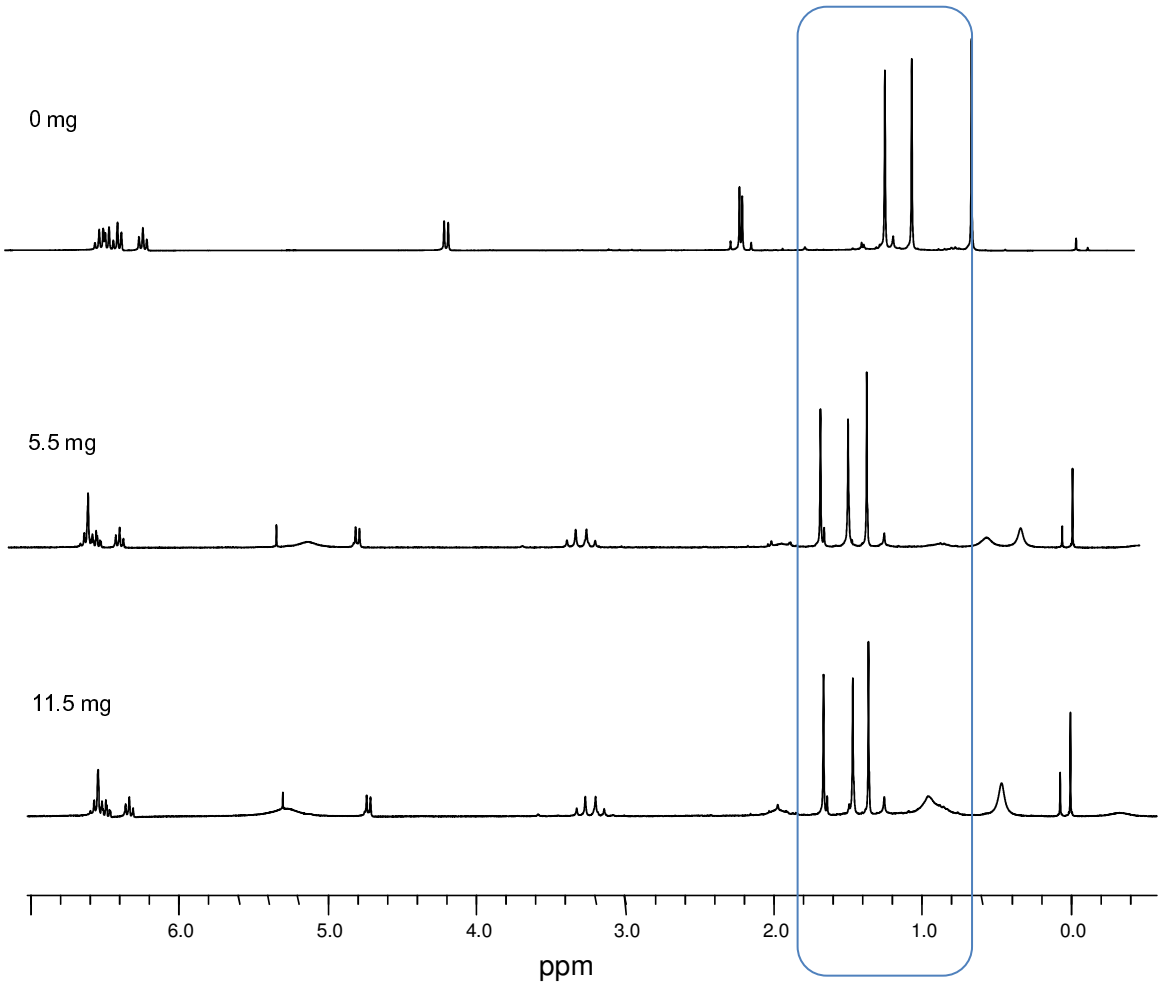
Catalyst: $CuPF_6$-**75**-[(*R,R*)-Ph-BOX].

^1H NMR spectra run at 20°C.

20 mg of azulenone in 0.5mL $CDCl_3$.

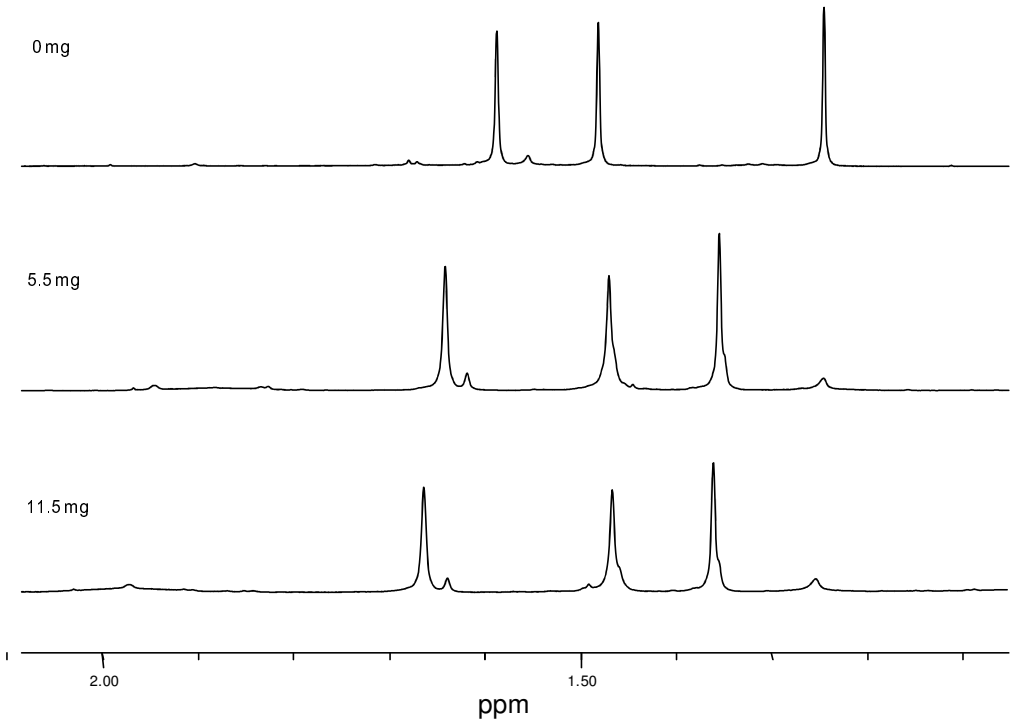


See **Table 3.2** for numerical values.



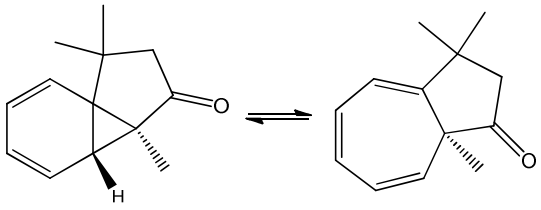
3,8a-Dihydro-3,3,8a-trimethylazulen-1(2*H*)-one 89

Expanded Region δ_H 1.1-2.00 *ppm*



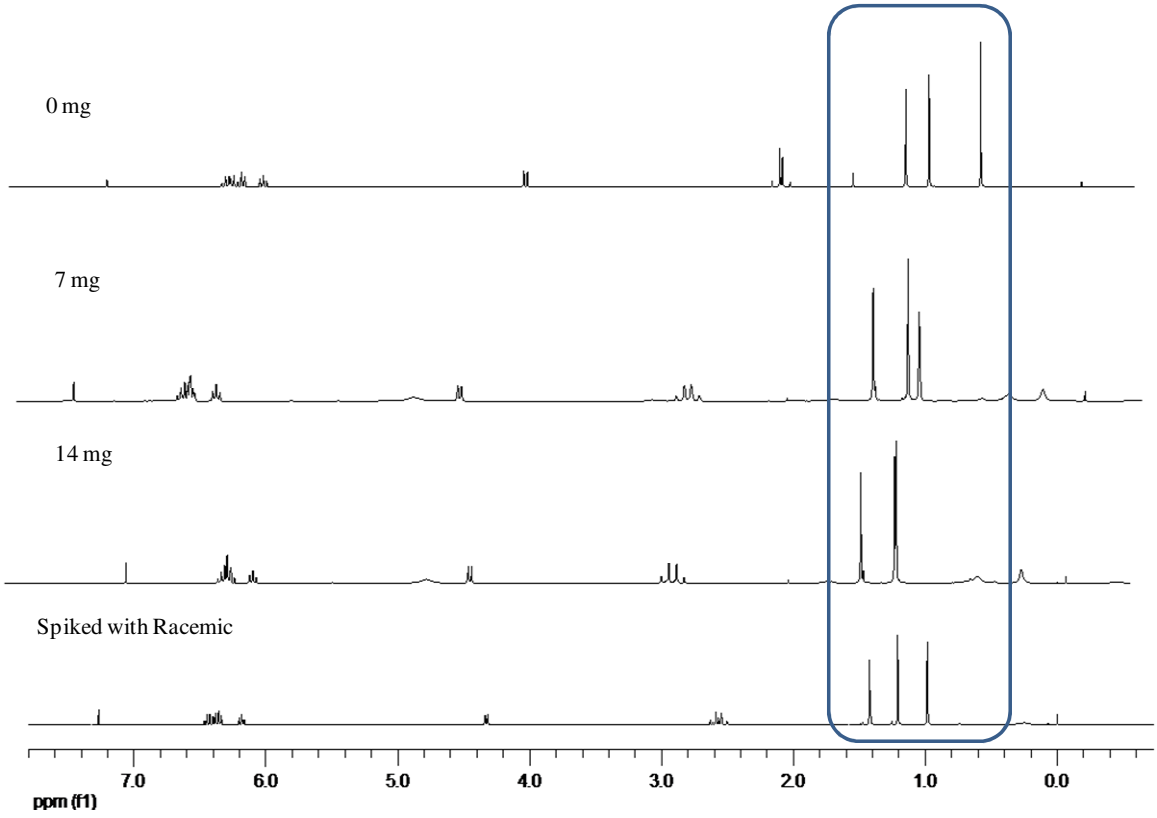
3,8a-Dihydro-3,3,8a-trimethylazulen-1(2*H*)-one 89

Catalyst: CuCl-NaBARF-**219**-[(*R,R*)-Ph-BOX].



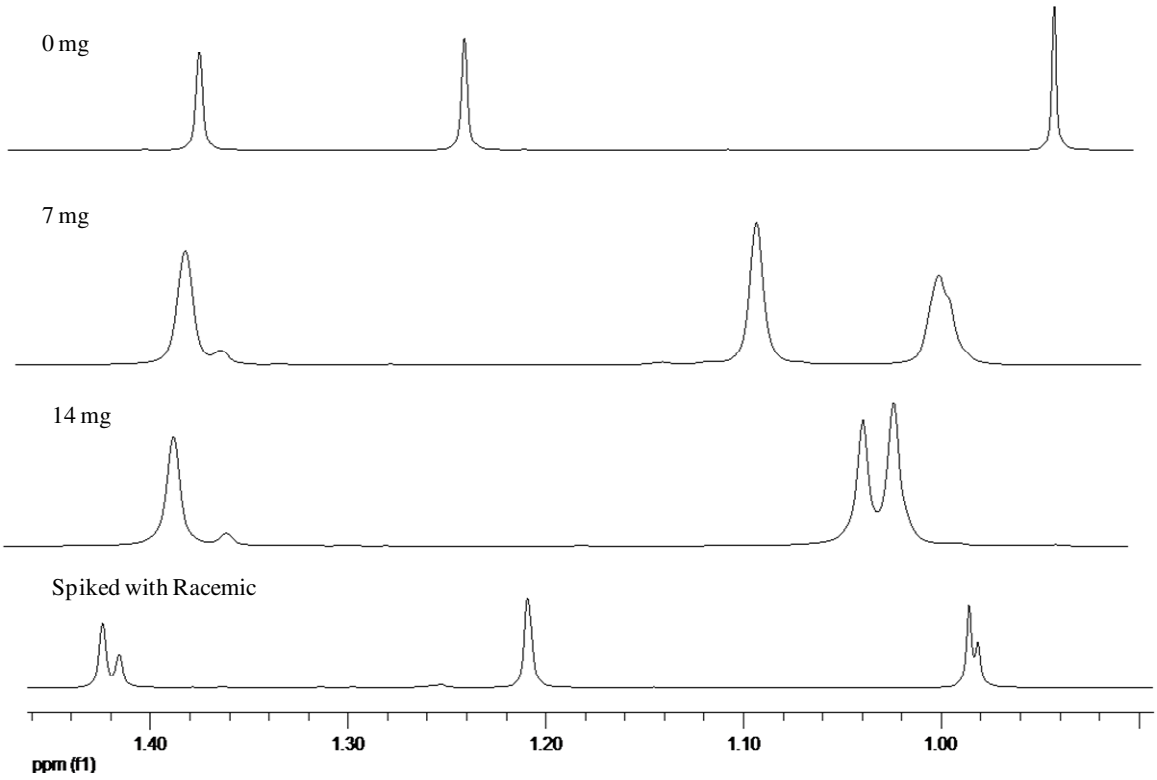
^{1}H NMR spectra run at 20°C.

20 mg of azulenone in 0.5mL $CDCl_3$.



3,8a-Dihydro-3,3,8a-trimethylazulen-1(2*H*)-one 89

Expanded Region δ_H 0.5-1.50 *ppm*



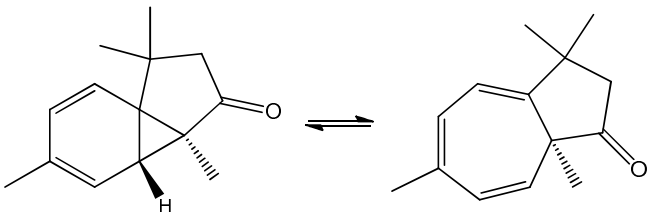
3,8a-Dihydro-3,3,6,8a-tetramethylazulen-1(2*H*)-one 96

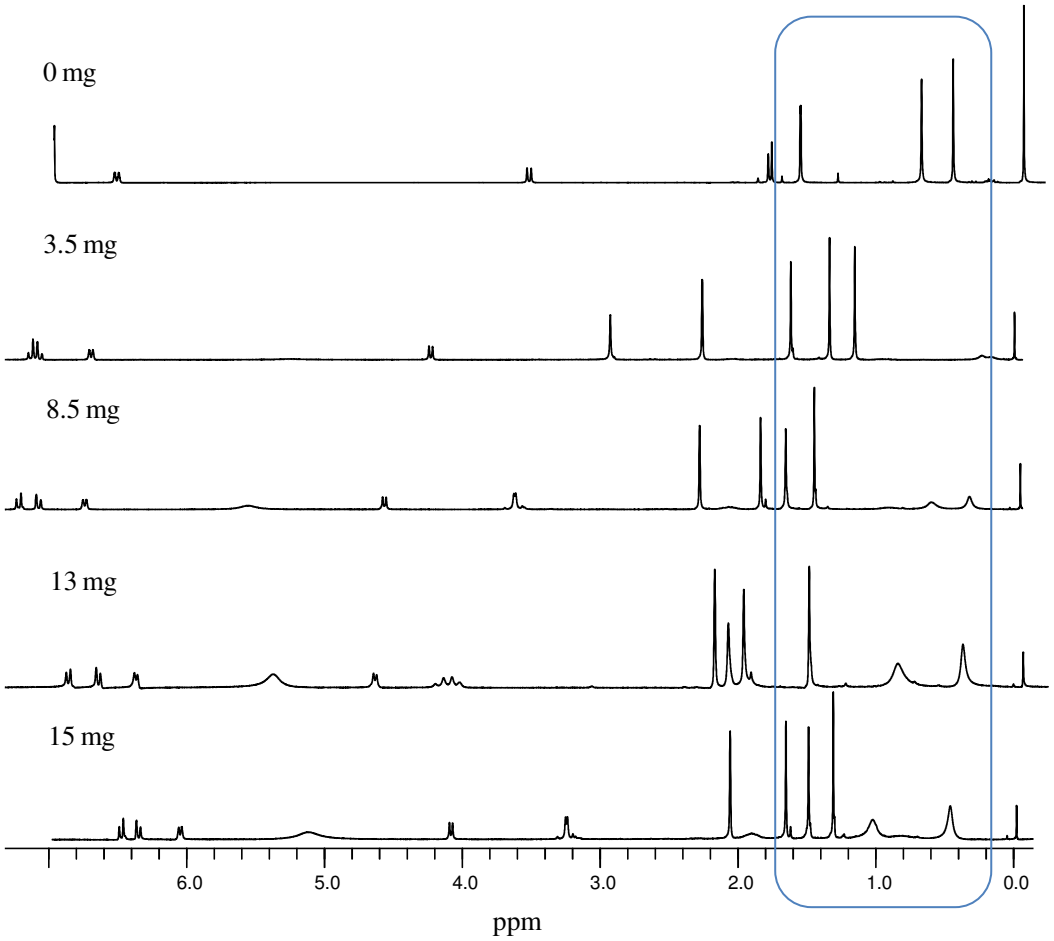
Catalyst: $CuPF_6$-**75**-[(*R*,*R*)-Ph-BOX].

^1H NMR spectra run at 20 °C.

20 mg of azulenone in 0.5 mL $CDCl_3$.

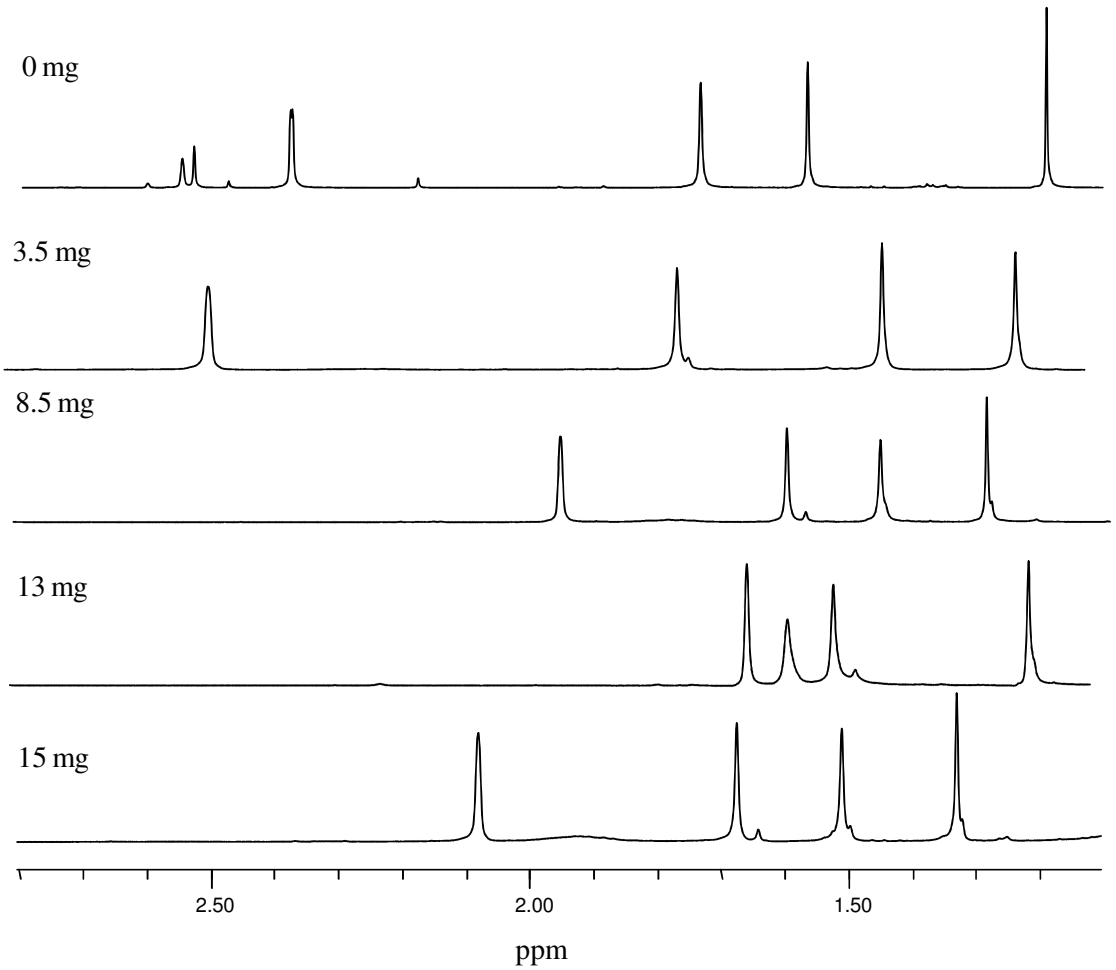
See **Table 3.8** for numerical values.





3,8a-Dihydro-3,3,6,8a-tetramethylazulen-1(2*H*)-one 96

Expanded Region δ_H 1.20-2.52 *ppm*



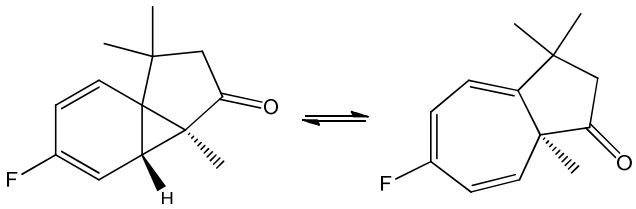
3,8a-Dihydro-6-fluoro-3,3,8a-trimethylazulen-1(2*H*)-one 94

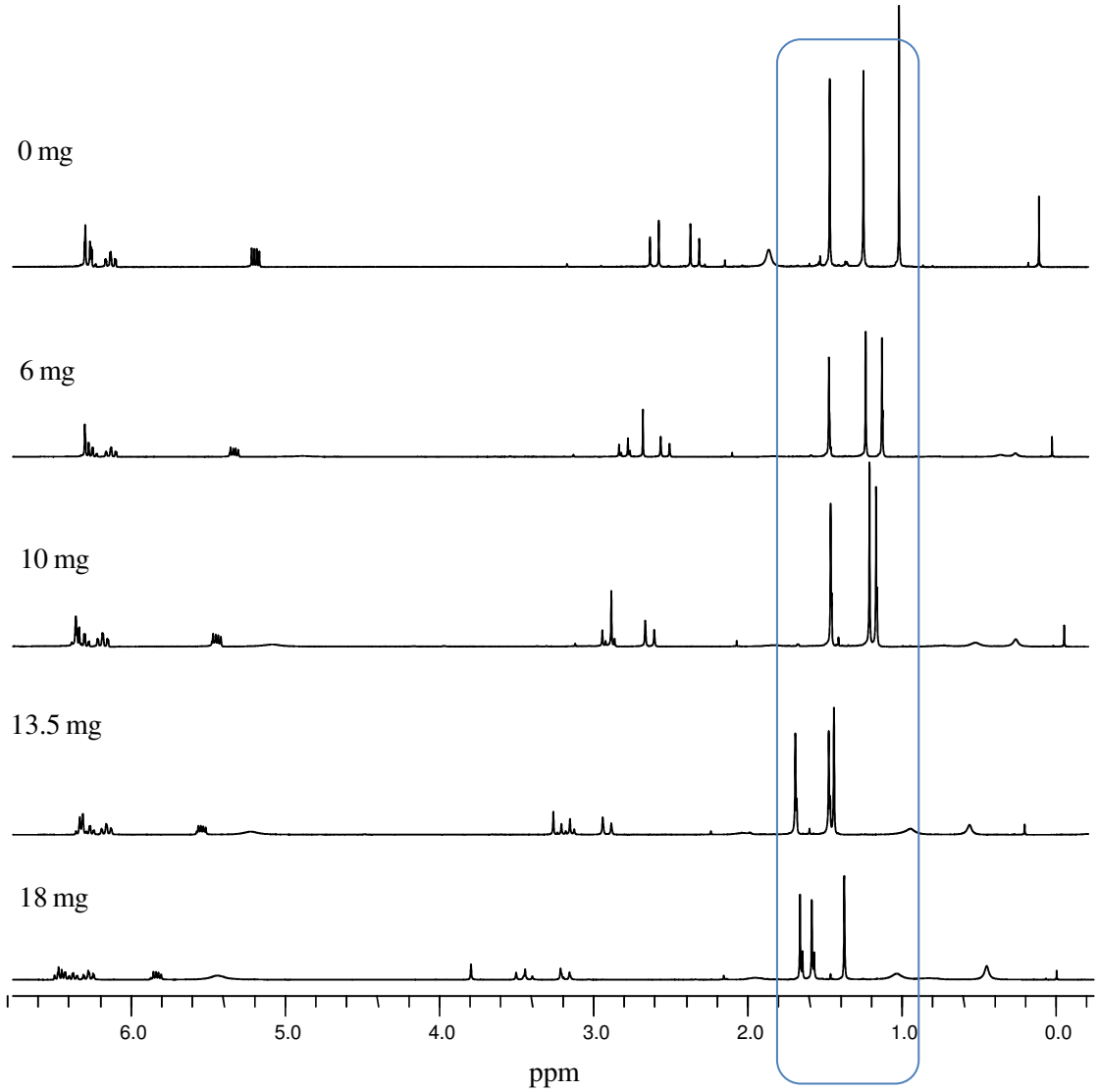
Catalyst: $CuPF_6$-**75**-[(*R*,*R*)-Ph-BOX].

^1H NMR spectra run at 20°C.

20 mg of azulenone in 0.5mL $CDCl_3$.

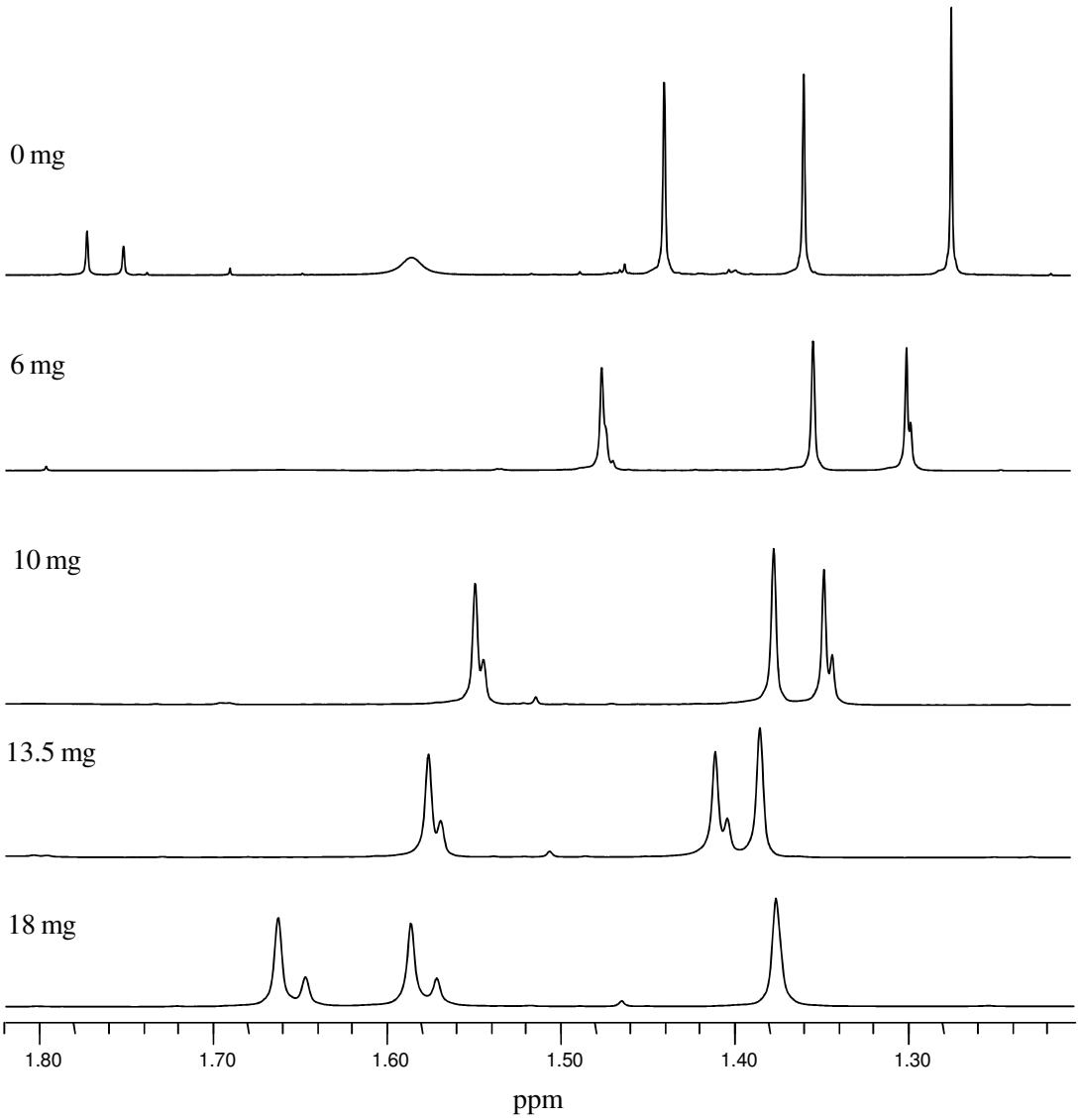
See Table **3.10** for numerical values.





3,8a-Dihydro-6-fluoro-3,3,8a-trimethylazulen-1(2*H*)-one 94

Expanded Region δ_H 1.30- 1.80 *ppm*



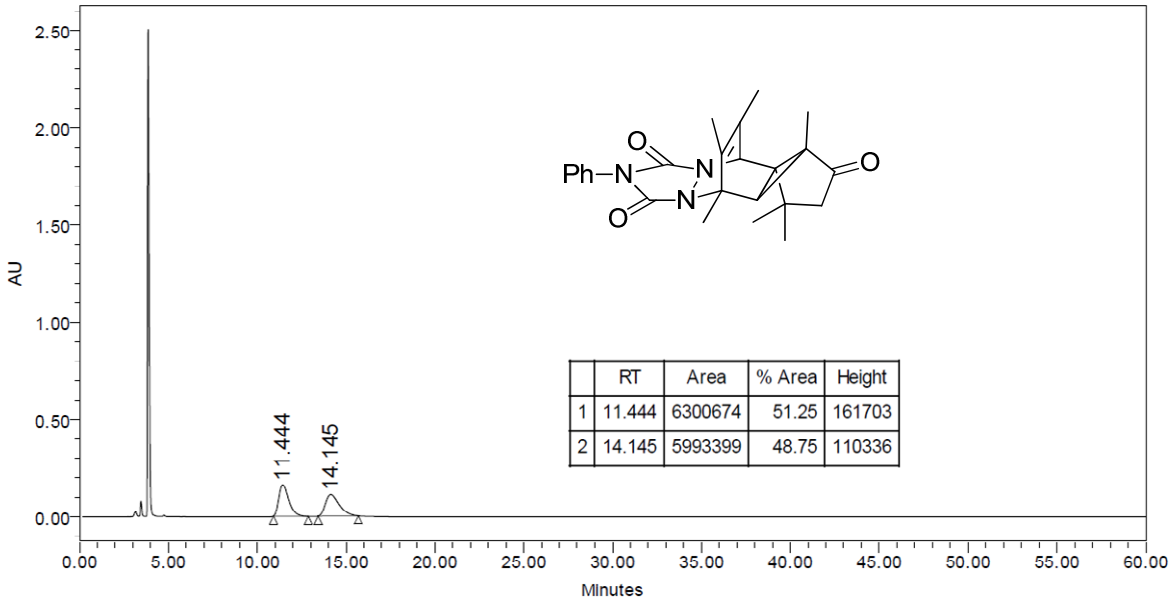
Appendix 3 Chiral Stationary Phase HPLC

All chiral stationary phase HPLC analysis was conducted at room temperature unless otherwise stated.

Injection volume was 10 µl for all compounds unless otherwise stated.

Notably, the retention times can change per injection (particularly for long run times), however, the elution sequence of enantiomers remains the same.

(3a*R,3b*S**)-1,2,3b,4-Tetrahydro-1,1,3a,4,11,12-hexamethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 163**



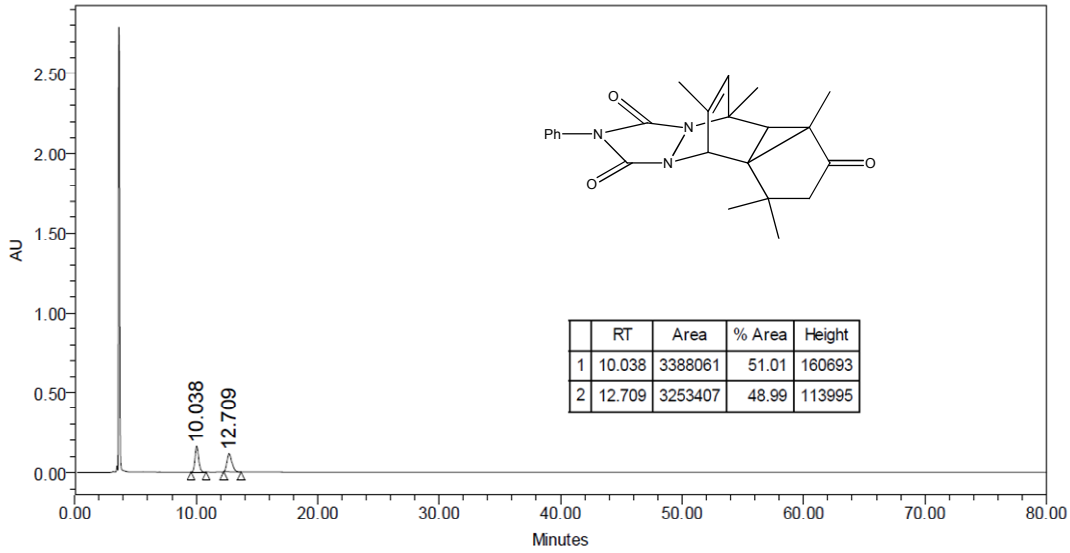
	RT	Area	% Area	Height
1	11.444	6300674	51.25	161703
2	14.145	5993399	48.75	110336

Resolution of the *PTAD adduct* **163** was achieved using a Chiracel® OD-H column at room temperature, with isopropanol:hexane (10:90) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 229 nm. Under these conditions dextrorotatory (+)-**163** elutes at 11.4 min and the levorotatory (–)-**163** elutes at 14.1 min.

(+) enantiomer of PTAD cycloadduct **163**: $[\alpha]_D^{20}$ 96.5 [*c* 1.0, $CHCl_3$, 93% ee].

Note: Please see **Table 3.14** for more information.

(3a*R,3b*S**)-1,2,3b,4-Tetrahydro-1,1,3a,4,11-pentamethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 164**



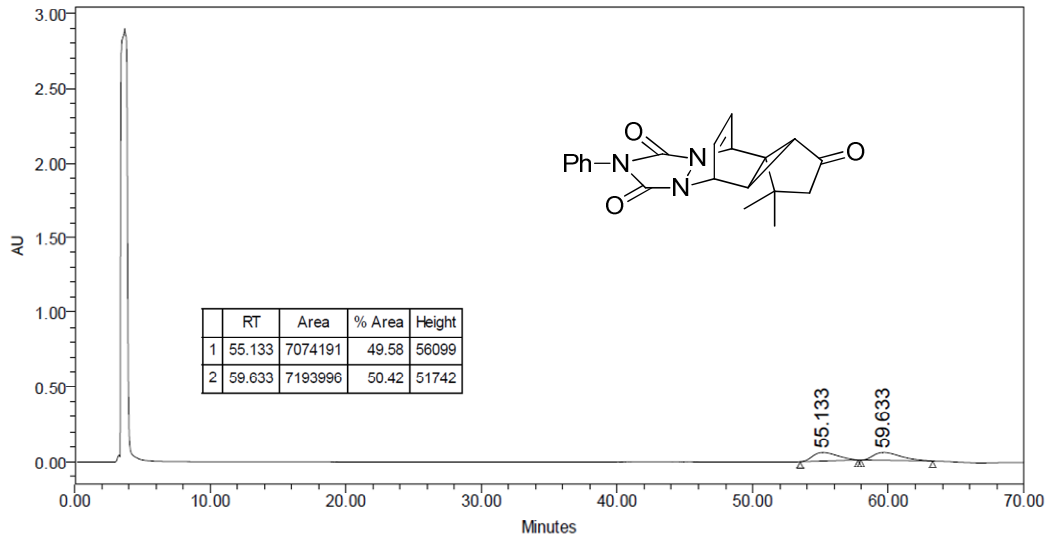
	RT	Area	% Area	Height
1	10.038	3388061	51.01	160693
2	12.709	3253407	48.99	113995

Resolution of the *PTAD adduct* **164** was achieved using a Chiracel® OD-H column at room temperature, with isopropanol:hexane (10:90) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 218 nm. Under these conditions dextrorotatory (+)-**164** elutes at 10.0 min and the levorotatory (−)-**164** elutes at 12.7 min.

(+) enantiomer of PTAD cycloadduct **164**: $[\alpha]_D^{20}$ 154.9 [*c* 0.5, $CHCl_3$, 92% ee].

Note: Please see **Table 3.13** for more information.

(3a*S, 3b*R**)-1,2,3b,4-Tetrahydro-1,1,3a-dimethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 197**



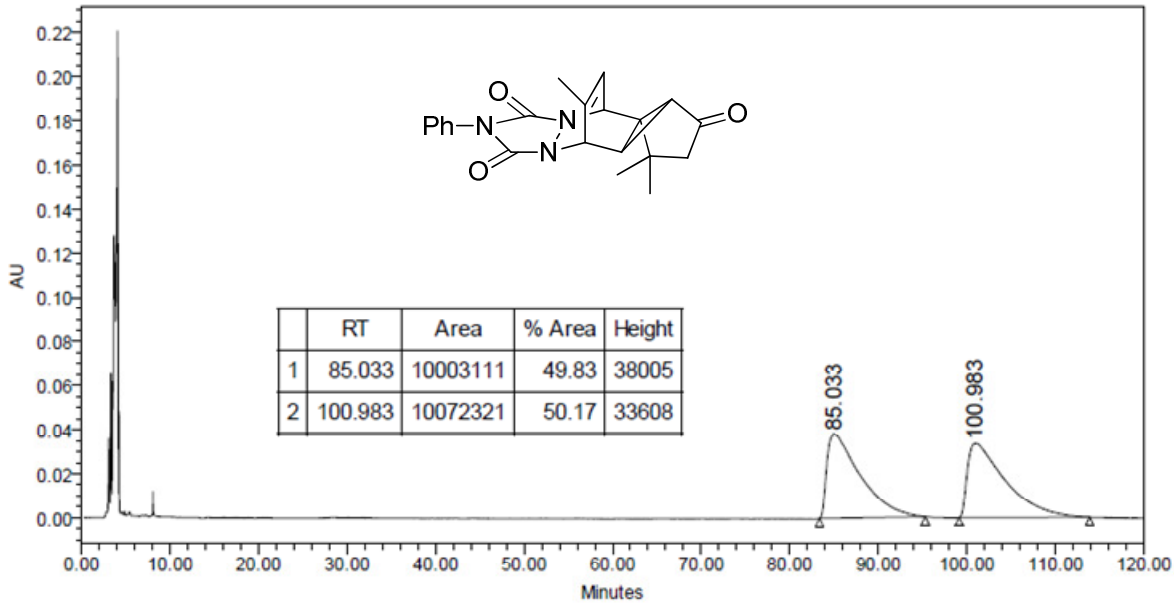
	RT	Area	% Area	Height
1	55.133	7074191	49.58	56099
2	59.633	7193996	50.42	51742

Resolution of the *PTAD adduct* **197** was achieved using a Chiracel® OD-H column at 40 ºC, with isopropanol:hexane (10:90) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 227 nm. Under these conditions dextrorotatory (+)-**197** elutes at 59.6 min and the levorotatory (−)-**197** elutes at 55.1 min.

Note: For details on specific rotations and enantioselectivities of adduct **197** please see **Table 3.15**.

(3a*S, 3b*R**)-1,2,3b,4-Tetrahydro-1,1,3a,12-trimethyl-7-phenyl-4,10-etheno-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 198**

(e) Conditions for resolution of the enantiomers of PTAD **198** *adduct on HPLC using OD-H column*

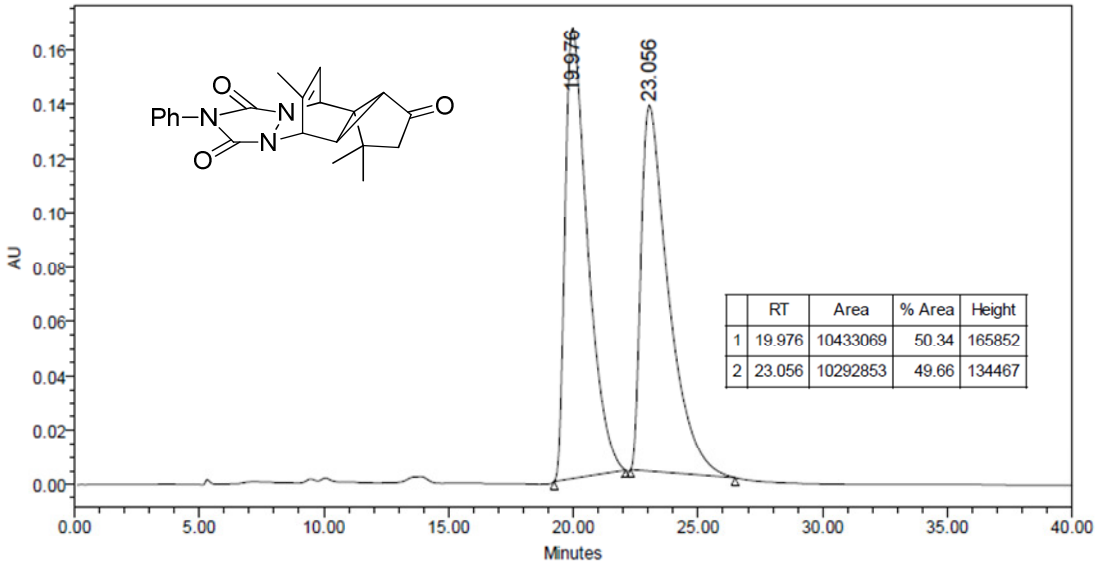


	RT	Area	% Area	Height
1	85.033	10003111	49.83	38005
2	100.983	10072321	50.17	33608

Resolution of the PTAD adduct **198** was achieved using a Chiracel® OD-H column at 40 ºC, with isopropanol:hexane (2:98) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 219 nm. Under these conditions dextrorotatory (+)-**198** elutes at 100.9 min and the levorotatory (–)-**198** elutes at 85.0 min.

Note: For details on specific rotations and enantioselectivities of adduct **198** please see **Table 3.16**.

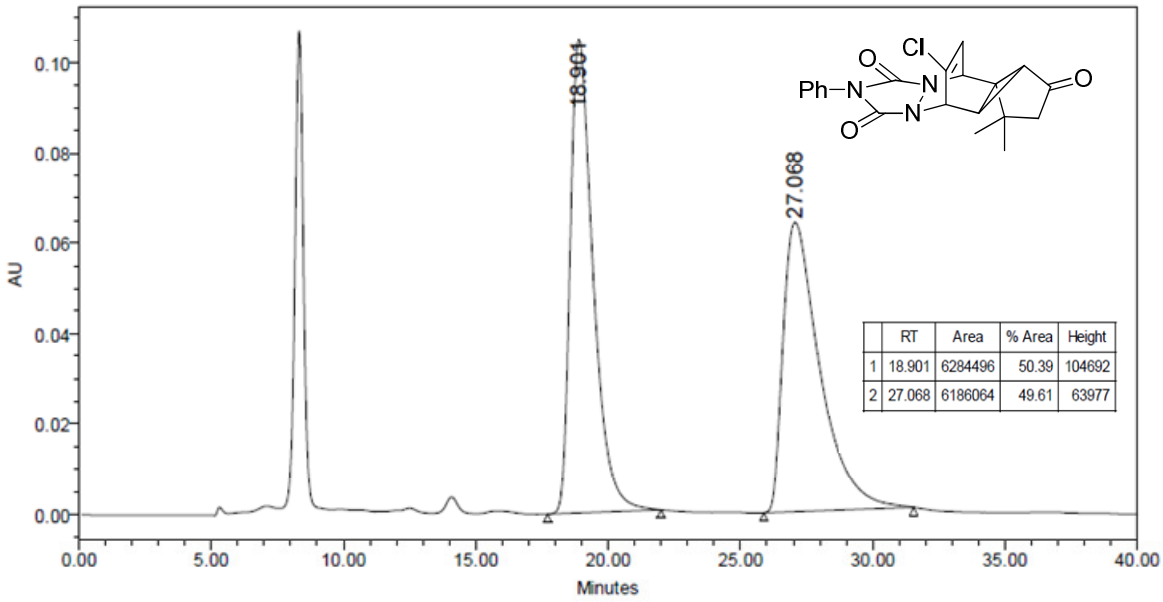
(f) Conditions for resolution of the enantiomers of PTAD **198** *adduct on HPLC using reverse phase Chiradex column.*



Resolution of the *PTAD adduct* **198** was achieved using a reverse phase LiChroCART 250-4 ChiraDex® at room temperature, with water/methanol (60:40) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 230 nm. Under these conditions dextrorotatory (+)-**198** elutes at 19.9 min and the levorotatory (–)-**198** elutes at 23.0 min.

Note: For details on specific rotations and enantioselectivities of adduct **198** please see **Table 3.16**.

(3a*S,3b*R**)-1,2,3b,4-Tetrahydro-1,1,3a-dimethyl-7-phenyl-4,10-etheno-12-chloro-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3a*H*,7*H*)-trione 199**

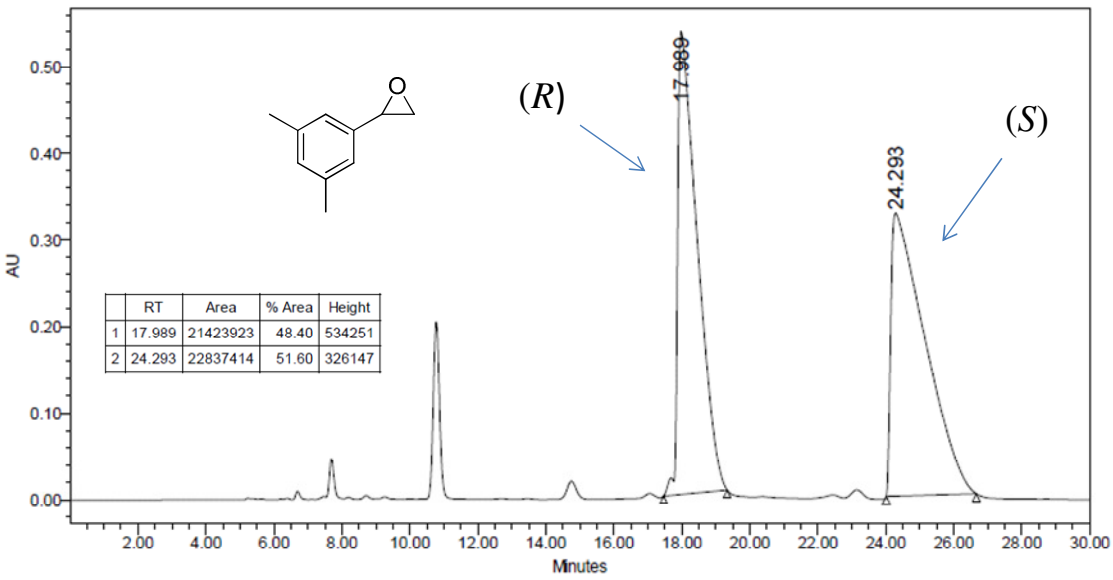


Resolution of the *PTAD adduct* **199** was achieved using a reverse phase LiChroCART 250-4 ChiraDex® at room temperature, with water/methanol (60:40) as eluant, a flow rate of 0.5 ml/min, and the detector set at λ 230 nm. Under these conditions dextrorotatory (+)-**199** elutes at 18.9 min and the levorotatory (−)-**199** elutes at 27.0 min.

A sample of diazoketone **45** was cyclised with the catalyst shown in **Table 3.17**, followed by reaction with $ZnCl_2$ to remove *CHT adduct* **203**. Enantiopurity of remaining *adduct* **199** could be determined by HPLC.

(+) enantiomer of PTAD adduct **199**: $[\alpha]_D^{20}$ 23.2 [*c* 0.55, $CHCl_3$, 83% ee].

2-(3,5-Dimethylphenyl)oxirane 154



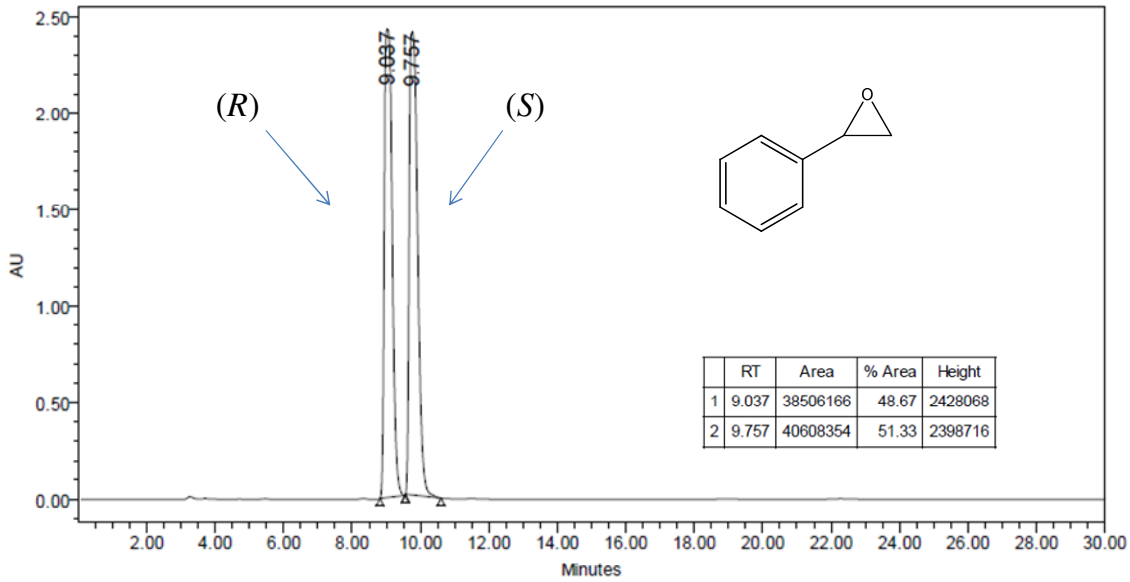
	RT	Area	% Area	Height
1	17.989	21423923	48.40	534251
2	24.293	22837414	51.60	326147

Resolution of the *epoxide* **154** was achieved using a Chiracel® OD-H column at 0 ºC, with isopropanol:hexane (5:95) as eluant, a flow rate of 1.0 mL/min, and the detector set at l 254 nm. Under these conditions the dextrorotatory (+)-**154** elutes at 18.0 minutes and the levorotatory (−)-**154** elutes at 24.3 minutes. The column temperature was maintained using an Igloo-Cil® column heater/cooler.

(*R*)-2-(3,5-Dimethylphenyl)oxirane **154***:* $[\alpha]_D^{20}$ +23.0 [*c* 0.25, $CHCl_3$, 98% ee].

i

2-Phenyloxirane 158

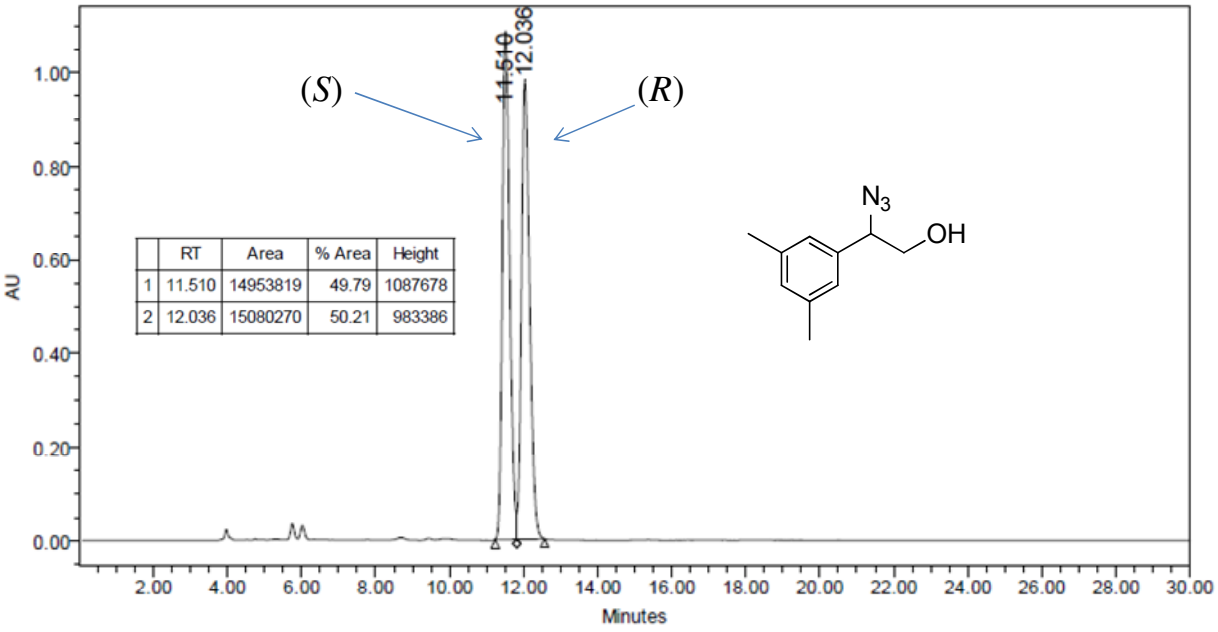


	RT	Area	% Area	Height
1	9.037	38506166	48.67	2428068
2	9.757	40608354	51.33	2398716

Resolution of the *epoxide* **158** was achieved using a Chiracel® OD-H column at 0 ºC, with isopropanol:hexane (5:95) as eluant, a flow rate of 1.0 mL/min, and the detector set at λ 223 nm. Under these conditions the dextrorotatory (+)-**158** elutes at 9.8 minutes and the levorotatory (−)-**158** elutes at 9.0 minutes. The column temperature was maintained using an Igloo-Cil® column heater/cooler.

(*R*)-2-Phenyloxirane **158**: $[\alpha]_D^{20}$ +11.50 [*c* 0.4, $CHCl_3$, 99% ee],

2-Azido-2-(3,5-dimethylphenyl)ethanol 156



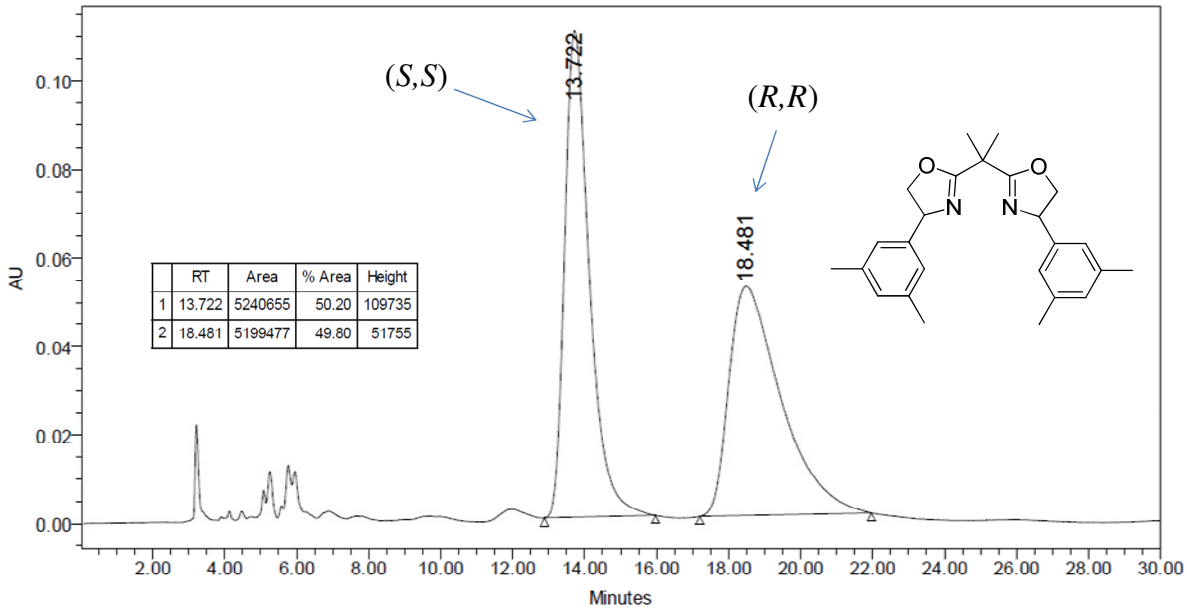
	RT	Area	% Area	Height
1	11.510	14953819	49.79	1087678
2	12.036	15080270	50.21	983386

Conditions for resolution of the enantiomers of azide **156** *on HPLC*

Resolution of the *azide* **156** was achieved using a Chiracel® OJ-H column at 23 ºC, with isopropanol:hexane (5:95) as eluant, a flow rate of 0.5 mL/min, and the detector set at λ 226 nm. Under these conditions the dextrorotatory (+)-**156** elutes at 11.5 minutes and the levorotatory (−)-**156** elutes at 12.0 minutes.

(*S*)-2-azido-2-(3,5-dimethylphenyl)ethanol **156**: $[\alpha]_D^{20}$ +188.6 [*c* 1.0, $CHCl_3$, 96% ee].

2,2-Bis{2-[4-(3,5-dimethylphenyl)-1,3-oxazolinyl]}propane 93



Resolution of the *bisoxazoline* **93** was achieved using a Chiracel® OD-H column at 23 ºC, with isopropanol:hexane (3:97) as eluant, a flow rate of 0.5 mL/min, and the detector set at λ 218 nm. Under these conditions the levororotatory (–)-**93** elutes at 13.7 minutes and the dextrotatory (+)-**93** elutes at 18.4 minutes.

(4*S*,4'*S*)-2,2-Bis{2-[4-(3,5-dimethylphenyl)-1,3-oxazolinyl]}propane **93**: $[\alpha]_D^{20}$ -97.0 [*c* 0.1, $CHCl_3$, ≥ 99% ee]

Appendix 4: *Publications*

Investigation of additive effects in enantioselective copper-catalysed C–H insertion and aromatic addition reactions of α-diazocarbonyl compounds

Catherine N. Slattery, Leslie-Ann Clarke, Shane O'Neill, Aoife Ring, Alan Ford, Anita R. Maguire

Synlett, **2012**, *23*, 765–767.

Enhancement of enantioselection in the copper-catalysed intramolecular Buchner reaction by variation of the counterion

Shane O'Neill, Sarah O'Keeffe, Francis Harrington, Anita, R. Maguire

Synlett, **2009**, *14*, 2312–2314.