*Tetrahedron* Vol 46, No 5, pp 1385-1489, 1990
Printed in Great Britain

0040-4020/90 $3 00+ 00


# TETRAHEDRON REPORT NUMBER 270

## Developments in Cyclisation Reactions

C Thebtaranonth and Y Thebtaranonth

Department of Chemistry,
Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

(*Received* 9 *May* 1989)

## CONTENTS

**Introduction**

**I. Cationic cyclisations**

I 1 Cyclisation of Iminium ions 1387

I.2 Cyclisation of Thionium ions 1399

I 3 Cyclisation of vinyl, allyl, propargyl and allenyl silanes 1401

I.4 Cyclisation-rearrangement Reactions 1408

**II Radical cyclisations**

II 1 Alkyl radicals 1412

II.2 Vinyl and aryl radicals 1424

II 3 Allylic radicals 1428

II.4 Acyl, thioacyl and imidoyl radicals 1430

II.5 Alkoxy radicals and radical anions 1436

**III. Anionic cyclisations**

III.1 Anionic cyclisations at $sp^3$ carbon 1439

III.2 Anionic cyclisations at $sp^2$ and sp carbons 1441

**IV. Metal-promoted cyclisations**

**IV.1** Carbon - carbon bond formation 1460

**IV.2** Carbon - heteroatom bond formation 1472

**IV.3** Multiple bond formation 1479

**Conclusion**

## INTRODUCTION

The desire to imitate nature and living organisms in their extraordinary ability to build complex ring systems with complete regio- and stereocontrol makes ring construction a fundamental interest in synthetic organic chemistry Contemporary methods of ring construction encompass basic reactions which may be categorized as those involving cationic, radical and anionic intermediates, as well as metal-catalysed and pericyclic reactions (cycloadditions, electrocyclic reactions and sigmatropic rearrangements) Rather than a comprehensive review, which would require a book of its own, the objective of this report is to provide an overview of the most recent developments in cyclisation reactions that involve cationic, radical, anionic, and metal-complexed intermediates Pericyclic ring-forming reactions will not be included

# I. CATIONIC CYCLISATIONS

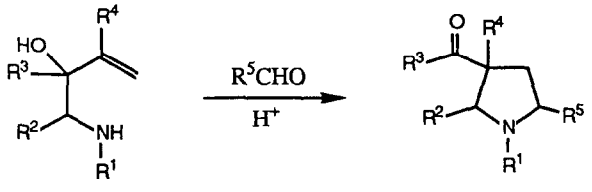
Cyclisations involving cationic intermediates can be grouped into four main types, *viz*

1 Cyclisation of iminium ions
2 Cyclisation of thionium ions
3 Cyclisation of vinyl, allyl, propargyl and allenyl silanes
4 Cyclisation-rearrangement reactions

## I.1 Cyclisation of iminium ions

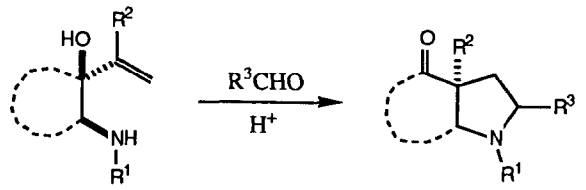
### Carbon Nucleophiles

Revived interest in the synthesis of alkaloids and nitrogen heterocycles coupled with the results from Overman's extensive studies have re-directed attention to iminium ion cyclisations Although a review of this subject has already been written,[1] many interesting post-review reports have appeared Ten years ago Overman[2] reported an acid-catalysed reaction between aldehydes and homoallylic amines carrying a hydroxy group at the allylic position **1**, to give rearrangement product 3-acylpyrrolidines **2** (eq 1) Recently, by employing cyclic amino alcohols, fused-pyrrolidines in which the initial ring is enlarged by one atom have been prepared (eq 2) [3]




**1** **2** eq 1

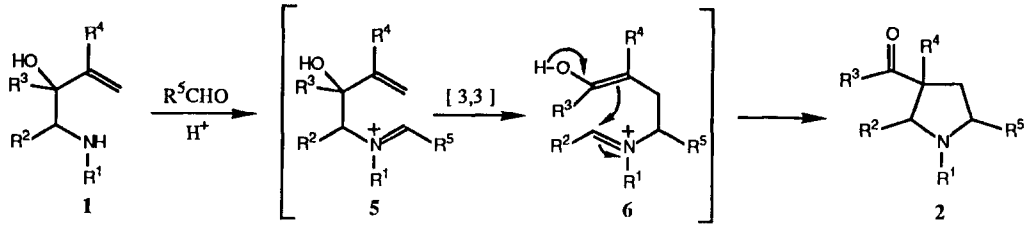
This reaction constitutes the key step in the syntheses of amaryllidaceae and aspidosperma alkaloids [4-6] The mechanism of this highly stereoselective process, after long study,[7,8] is now




3 4 eq 2

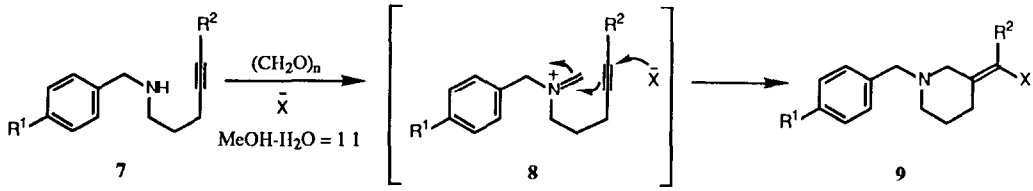
known[9] to involve the formation of an iminium ion intermediate **5**, which undergoes a [3,3]-sigmatropic rearrangement followed by intramolecular cyclisation to give product **2** (Scheme 1)

**Scheme 1**




Besides the iminium cyclisation shown in the above Scheme several related cyclisations have been reported recently, for example, the cyclisation of acetylenic iminium ion **8** (generated *in situ*), induced by an external nucleophile (here a halide ion), to give methylene piperidine **9** (Scheme 2) [10]

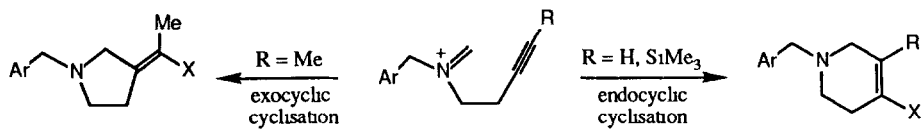
**Scheme 2** .




| $R^1$ | $R^2$ | X | % yield |
|---|---|---|---|
| OMe | Me | I | 80 |
| H | Me | $N_3$ | 72 |
| H | Me | SCN | 82 |
| OMe | H | I | 56 |

With a shorter acetylenic chain, either a 5- or 6- membered ring can be formed, depending upon the mode of cyclisation, which, in turn, is found to be influenced by the substituent " R " Thus, when R = Me, the iminium ion **10** cyclises in an exocyclic fashion to give alkylidine pyrrolidines **11**, but with terminal alkynes (R = H) or silyl alkynes, endocyclic cyclisation prevails to give tetrahydropyridines **12** (Scheme 3)

**Scheme 3**



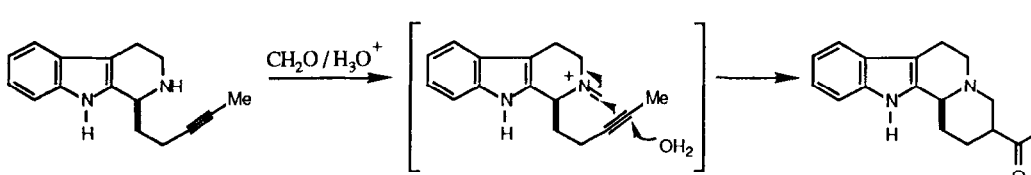

**11** **10** **12**

X = I ( 90 % )
= Br (75 % )
= $N_3$ ( 45 % )

R = H , X = I ( 87 % )
R = $SiMe_3$ , X = I ( 60 % )
R = $SiMe_3$ , X = Br ( 44 % )

However, it should be pointed out that reactions of the type shown in Schemes 2 and 3 have been used a long time ago in alkaloid synthesis,[11,12] for example, the cyclisation of iminium ion intermediate **14** (generated from **13**) to yield **15** as a mixture of stereoisomers (49%), or the rearrangement-cyclisation of **17** to **20**, whose mechanism *via* [3,3]-sigmatropic rearrangement of **17** to **18** (making the latter, not the former, the cyclising entity) has been thoroughly studied [12,13]

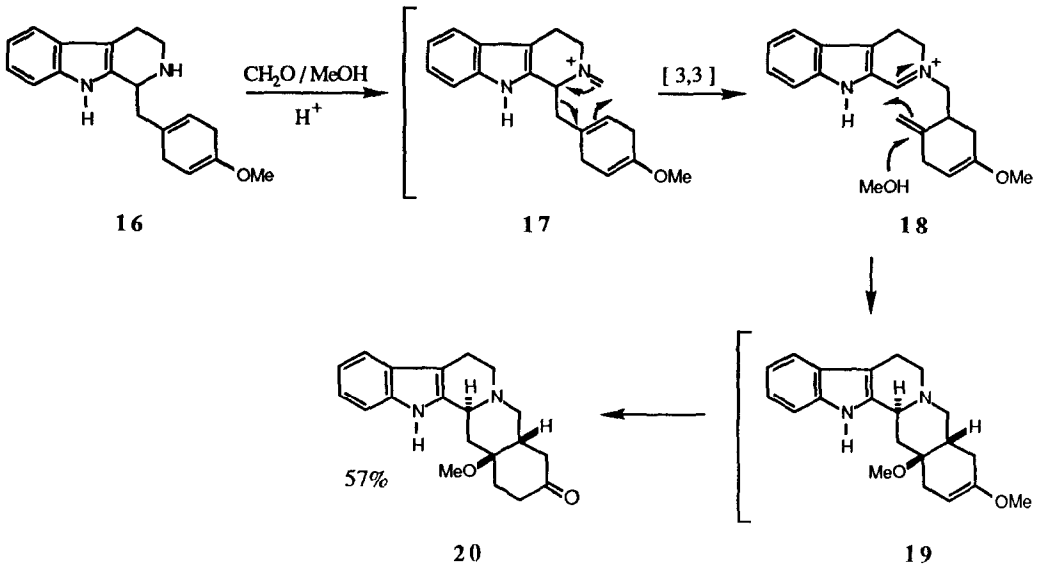
**Scheme 4**




**13** **14** **15**

Another related cyclisation, recently reported by Grieco,[14] is the heterogeneous reaction between allylsilane, trifluoroacetate salt of a primary amine, and aqueous formaldehyde The mixture directly yields product **26** from iminium ion cyclisation with water acting as nucleophile (Scheme 6)

**Scheme 5**




**Scheme 6**

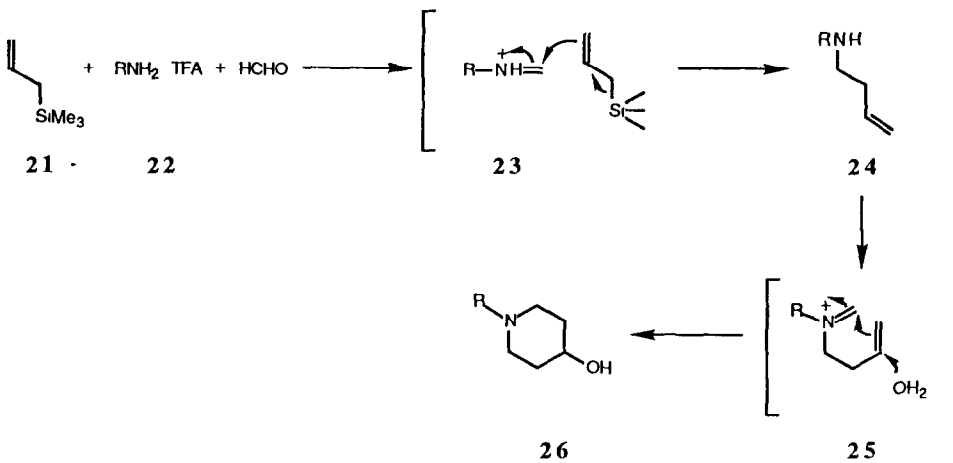
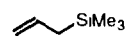
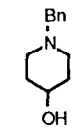
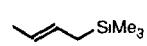
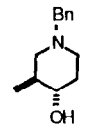
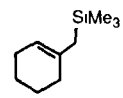
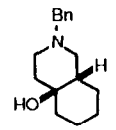
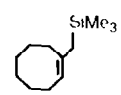
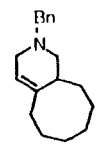
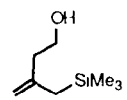
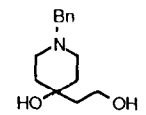
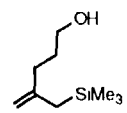
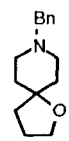
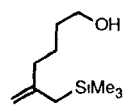
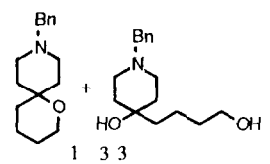



Table 1 shows further examples of this reaction, including the use of hydroxy silanes whose hydroxy groups can act as internal nucleophiles, providing that the size of the ring being formed is appropriate (entries f and g)

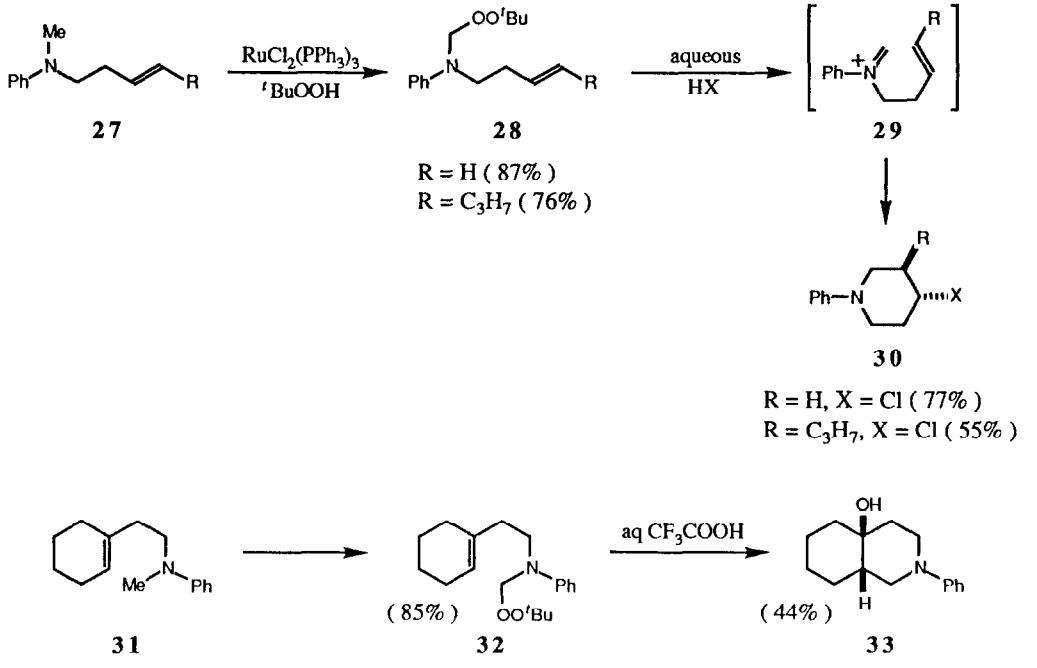
**Table 1** Cyclisation of allylsilane and $BnNH_2$ TFA in the presence of aqueous formaldehyde

| Entry | Allylsilane | Product | % yield |
|---|---|---|---|
| a |  |  | 81 |
| b |  |  | 54 |
| c |  |  | 94 |
| d |  |  | 62 |
| e |  |  | 100 |
| f |  |  | 58 |
| g |  |  1 3 3 | 83 |

A similar reaction is the cyclisation of **29**,[15] the intermediate formed from the reaction of **28** with acid The preparation of **28** can be accomplished by ruthenium-catalysed oxidation of tertiary amine **27** with alkyl hydroperoxide (Scheme 7)

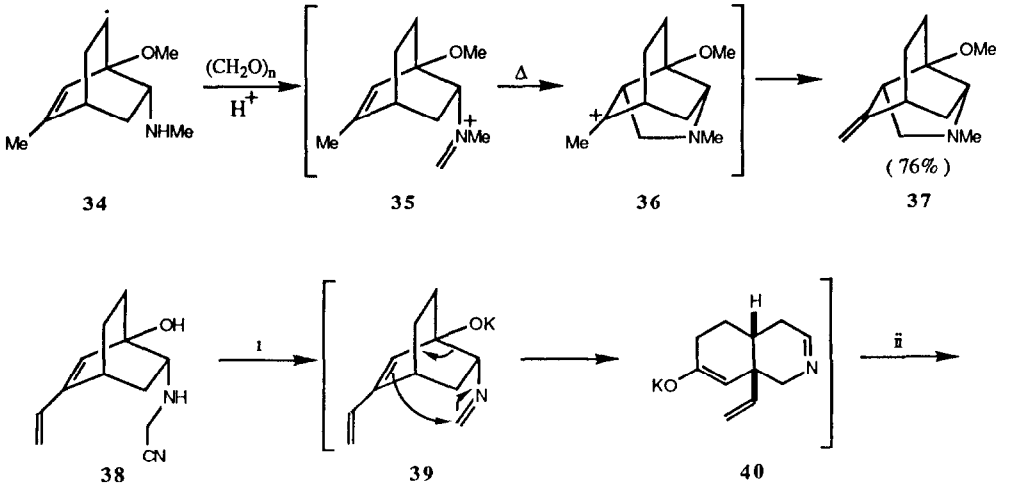
In another study, the iminium salt **35**, generated from the corresponding bicyclic amine **34**, is found to undergo simple Mannich cyclisation to **37**[16] and not the expected aza-Cope rearrangement However, activating the transition state through the use of potassium salt **39** results in

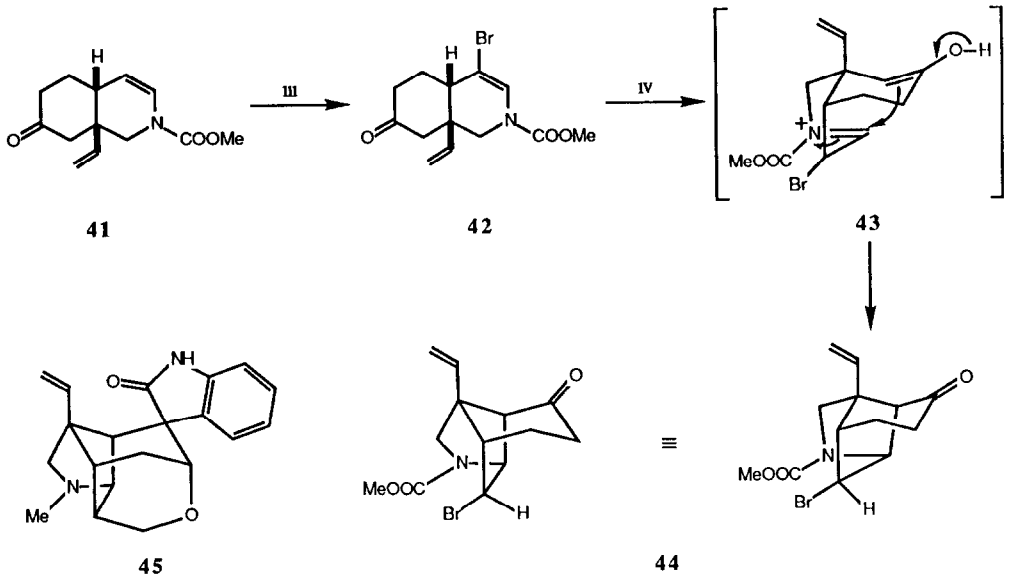
**Scheme 7**




rearrangement similar to that observed earlier in the carbon analogue,[17] to give **40.** After conversion to **42** and heating in trifluoroacetic acid, cyclisation *via* a boat-shape transition state **43**

**Scheme 8**



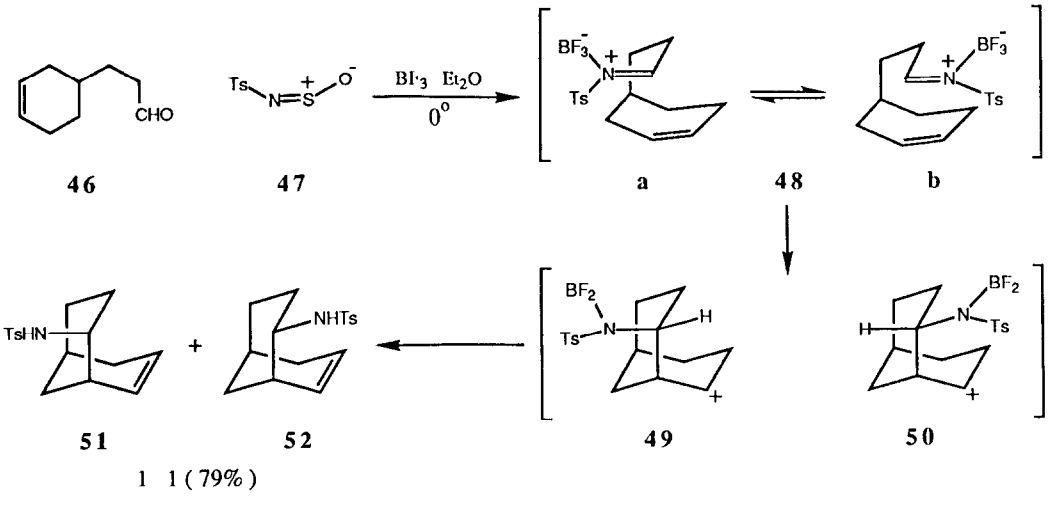



Reagents i) KH, THF, 23° ii) ClCOOMe, pyridine , KOH, MeOH-$H_2O$ (70-90% from **31**) iii) $Br_2$, 1,2,2, 6,6-pentamethylpiperidine (88%) iv) $CF_3COOH$, reflux (85%)

yields tricyclic product **44**,[18] an advanced intermediate in the synthetic route to gelsemine **45** (Scheme 8)

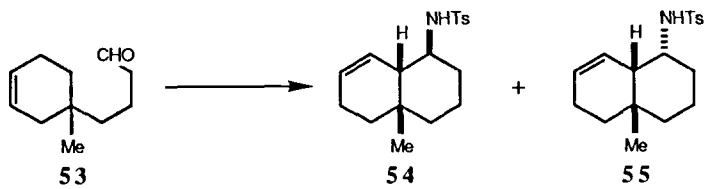
There are several other recent examples of these electrophilic cyclisations, employing various electrophiles, with potential application in organic synthesis In the reaction of olefinic enolisable

**Scheme 9**



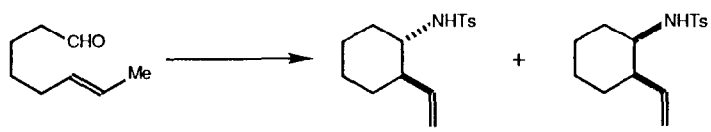
aldehyde **46** with *N*-sulphinyltoluenesulphonamide **47**, boron trifluoride-etherate has the dual function of promoting first the *in situ* formation of *N*-tosyliminium complex, then the cyclisation to a 1 1 mixture of **51** and **52** [19] Strictly speaking the formation of **52** could result from an ene reaction of iminium ion **48b**, but the fact that a mixture of **51** and **52** was obtained favours the carbonium ion mechanism as shown in Scheme 9

High stereoselectivity of the reaction is observed in the examples shown in equations 3 and



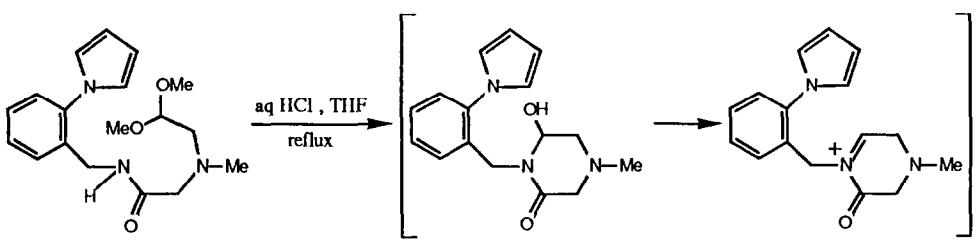

**53** **54** **55** eq 3

3 1 (52%)

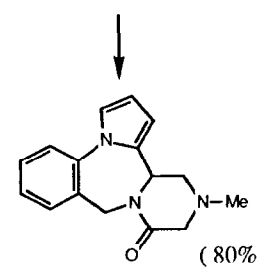



**56** **57** **58** eq 4

3 1 (50%)

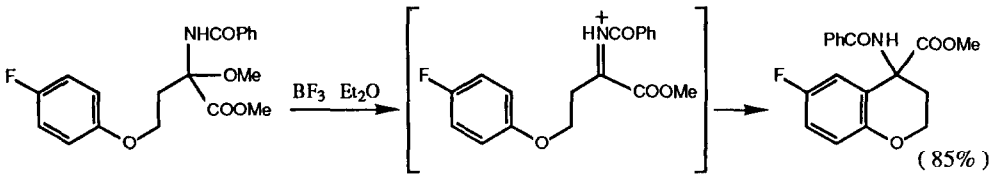



**59** **60** **61**




(80%)

**62** eq 5

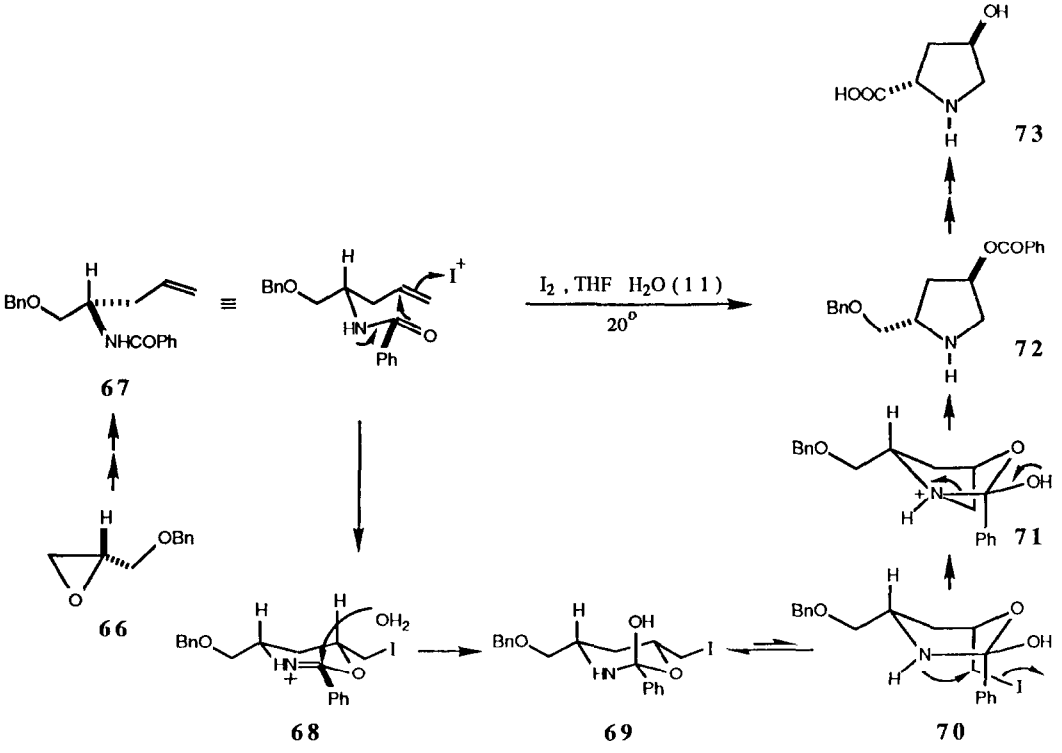



63 64 65 eq 6

4, while equations 5 [20] and 6 [21] demonstrate a different method of generating the iminium ion and application of the reaction in the syntheses of tetracyclic amides Compound **65** is an intermediate in the synthesis of sorbinol, an aldose reductase inhibitor

Although iodine-mediated cyclisations have long been in use, the recently reported stereoselective route to (2*S*, 4*R*)-4-hydroxyproline **73** from (*S*)-*O*-benzylglycidol **66** as shown in Scheme 10 is nonetheless a clever innovation [22] The key step of the synthesis is the iodine-mediated cyclisation of $\gamma,\delta$-unsaturated amide **67** to cyclic iminium salt **68**, followed by stereoelectronically-controlled[23] axial attack of water to give **69** A conformational change from **69**

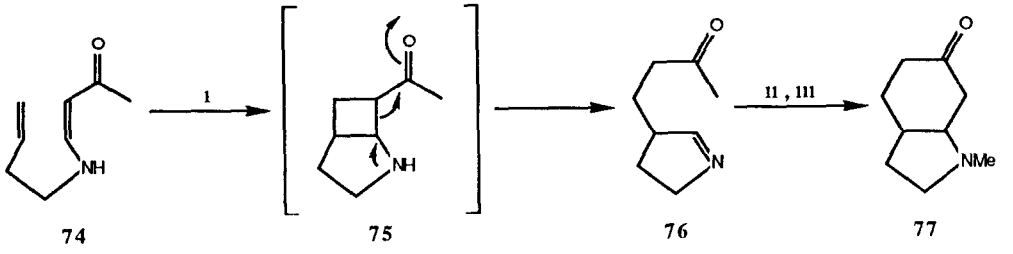
**Scheme 10**



to **70** allows a second cyclisation to form **71**, and thereafter, **72**

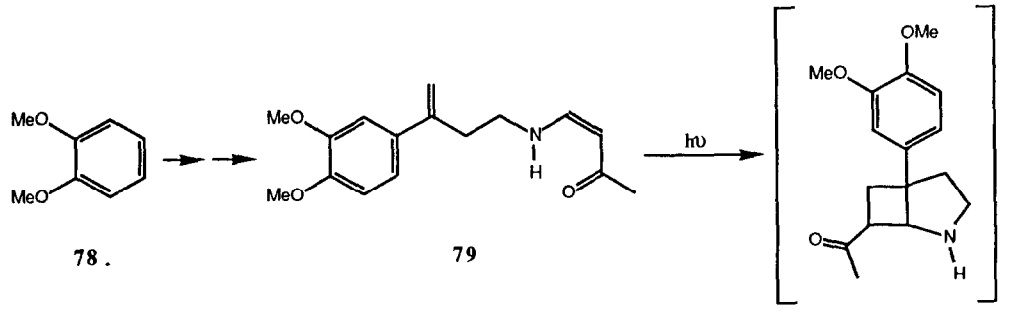
A synthetically useful process is the tandem photocycloaddition-retro Mannich reaction of unsaturated enaminone **74** to yield imine **76** which can be further cyclised in a Mannich fashion to bicyclic **77** An example of application of this process is the synthesis of mesembrine **82** from veratrole **78**, accomplished in seven steps and in 33% overall yield [24]

**Scheme 11**

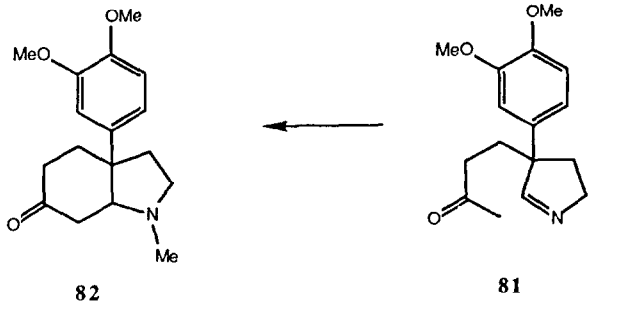



74 75 76 77

Reagents i) hυ, $CH_3CN$ ii) $Me_3\overset{+}{O}\,\overset{-}{B}F_4$ iii) aq HCl



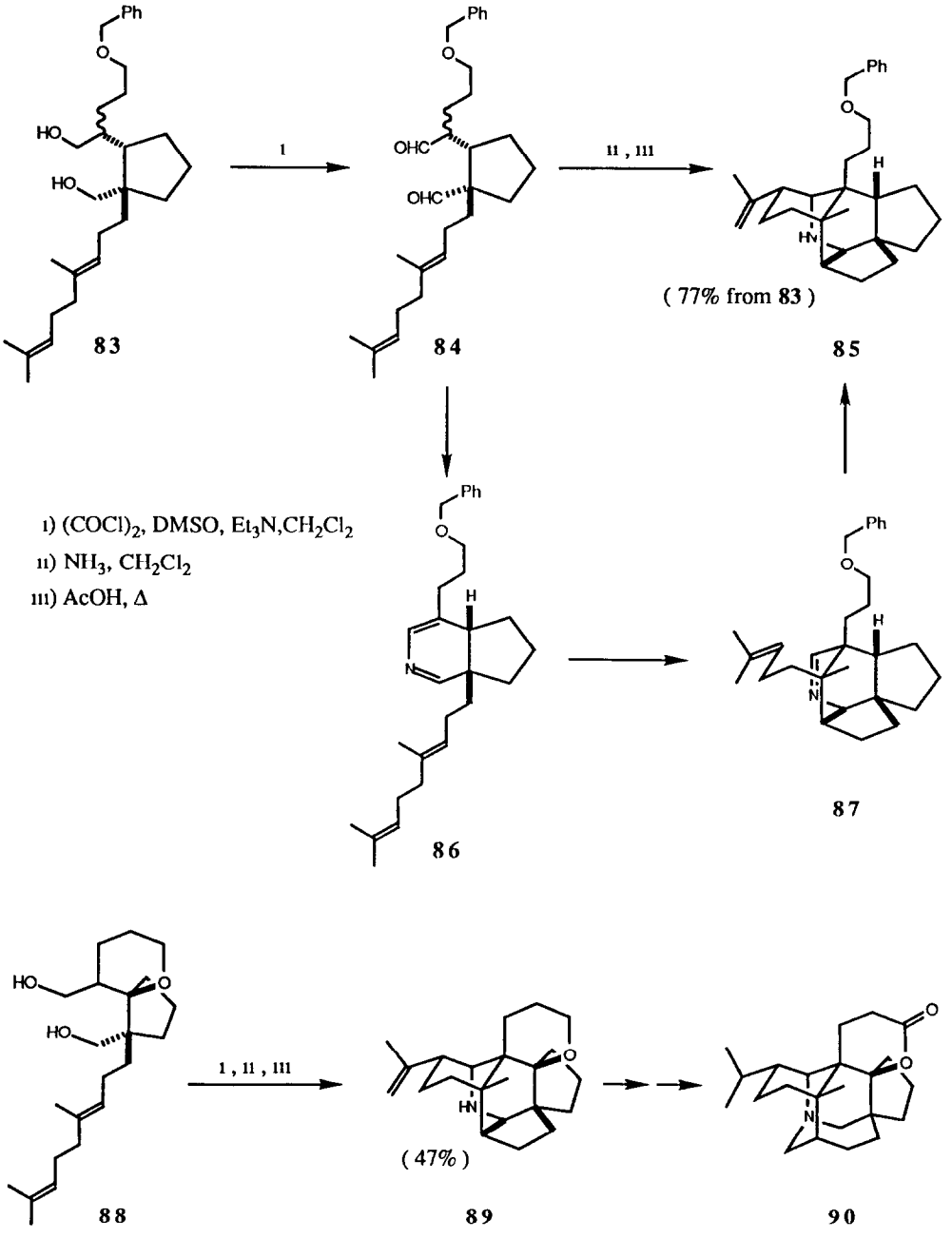

78. 79 80




82 81

The most spectacular cyclisation involving the iminium ion intermediate reported recently is probably the tetracyclisation process shown in Scheme 12[25] Both intermediates **86** and **87** were

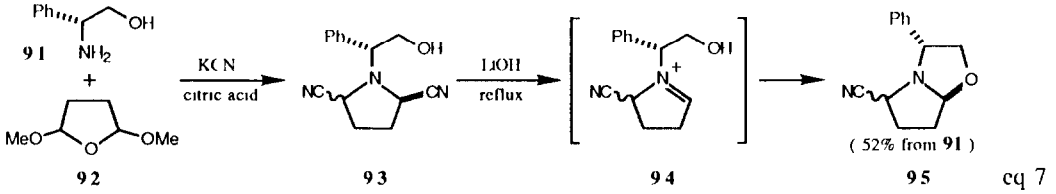
**Scheme 12**



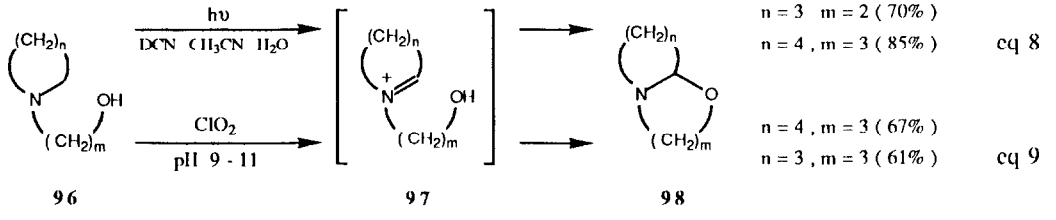
isolated The reaction has led Heathcock[26] to the successful synthesis of daphnilactone A **90** from key intermediates **88** and **89**

## Oxygen Nucleophiles

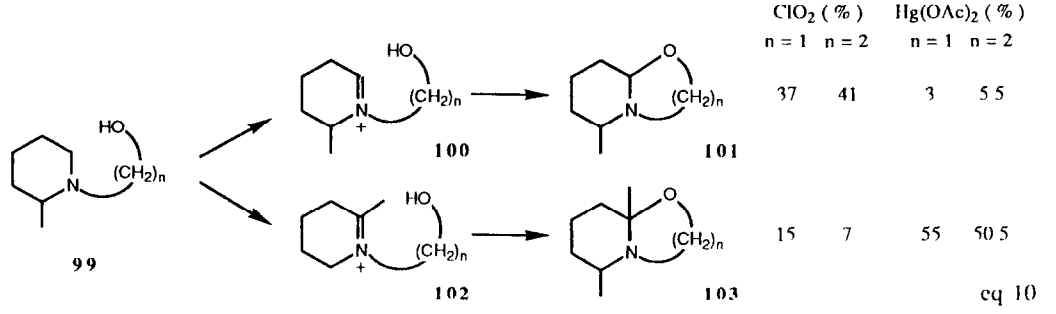
Some interesting recent examples of cyclisations by oxygen nucleophiles are shown below, all of which involve intramolecular attack of alcohol on the iminium ion intermediate, but differ in the manner of generation of iminium ion, which are elimination of cyanide ion (eq 7),[27] irradiation in the presence of 1,4-dicyanonaphthalene (DCN) *via* single electron transfer process (eq 8),[28,29] and oxidation with chlorine dioxide ($ClO_2$) in a mild basic medium (eq 9)[30] The latter beautifully complements earlier observations[31] where mercuric acetate was found to oxidize tertiary amines to iminium salts which were internally trapped by oxygen Oxidation by $ClO_2$ takes place preferentially




eq 7




eq 8 eq 9



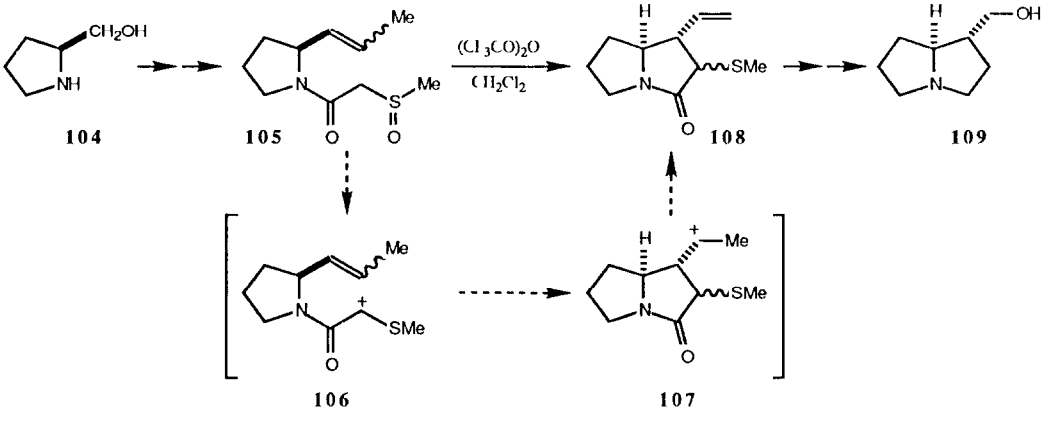

eq 10

at the less hindered carbon, in contrast to that by mercuric acetate The results from comparative studies are shown in equation 10

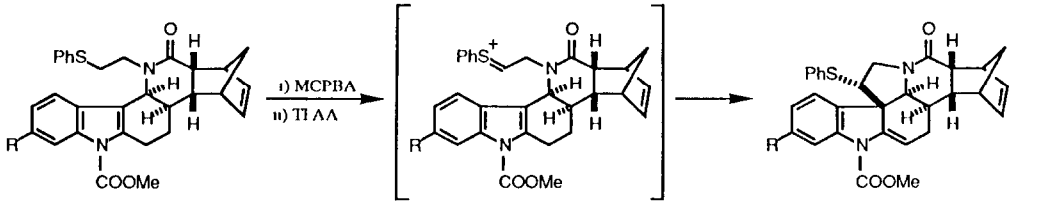
## 12 Cyclisation of Thionium Ions

Thionium ion intermediates in the Pummerer reaction find important use in cyclisation reactions For example, treatment of **105** with a stoichiometric amount of trifluoroacetic anhydride in dichloromethane at room temperature affords **108** in 87% yield *via* intermediate **106** This reaction forms the key step in the synthesis of optically active trachelanthamidine **109** from *L*-prolinol **104** (Scheme 13) [32]

**Scheme 13**




Utilization of intramolecular Pummerer reaction is also reported in the synthesis of chemical



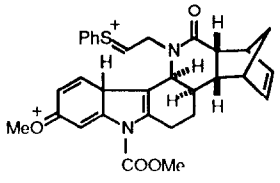

**110** R = H **111** R = H **112** R = H

**113** R = OMe **114** R = OMe **115** R = OMe

eq 11

models of aspidosperma alkaloids [33] More recently the same group, working on the Pummerer reaction of the sulphoxide derived from **110**, finds it to yield, *via* intermediate **111**, stereospecifically **112** (80%) [34]

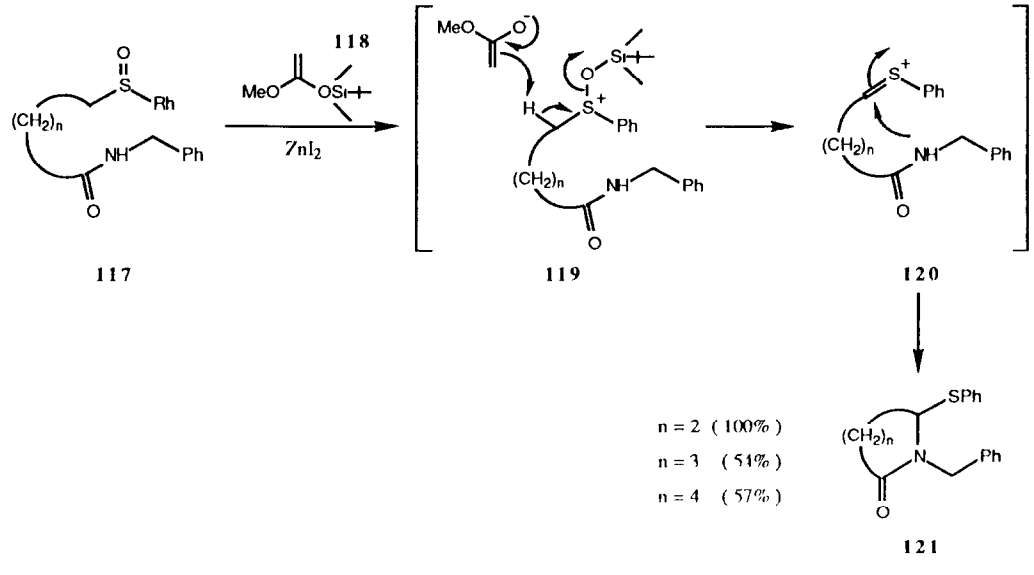
An interesting observation in connection with this reaction is that **113**, the methoxy derivative of **110**, fails to cyclise to **115**, even though its aromatic system is expected to be more nucleophilic A possible explanation is the formation of protonated species **116**, from protonation of **114** by trifluoroacetic acid generated in the Pummerer reaction This is borne out by successfully carrying out the cyclisation with the addition of 2,6-di-*tert*-butyl-4-methylpyridine, and obtaining **115** in 65% yield [34]

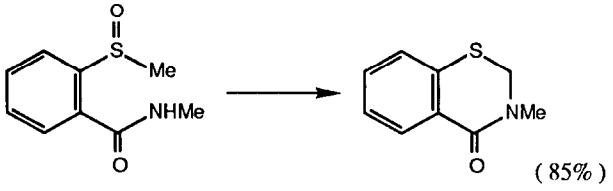



116

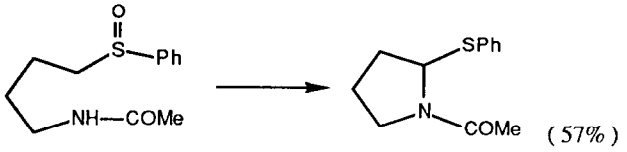
Another mode of thionium ion cyclisation is shown in Scheme 14 Thionium salt **120**, generated from the reaction of sulphoxide **117** with silylketene acetal **118** in the presence of zinc

**Scheme 14**






**122** **123** eq 12



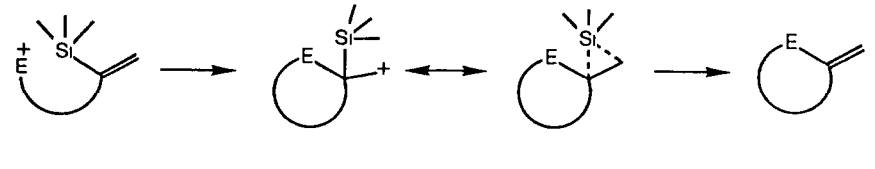

**124** **125** eq 13

iodide, undergoes intramolecular cyclisation to give lactam **121** in reasonable-to-good yields [35,36] This reaction has been applied to the synthesis of **123** and **125** (eq 12, 13)

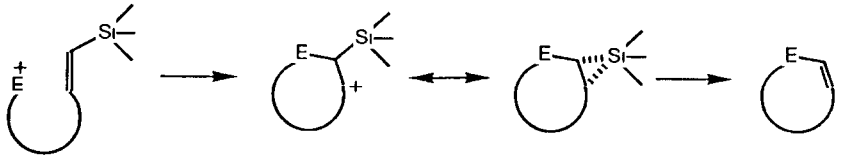
## 13 Cyclisation of vinyl, allyl, propargyl and allenyl silanes

### Vinylsilanes

The extensively studied[1] cyclisation of vinylsilanes, which is finding increasing application, follows the general pathways shown in equations 14 and 15 The regiospecificity associated with the reaction is a result of the well known " $\beta$-effect" of silicon [37] As for the nature of the electrophile ($E^+$), most studies report using the iminium ion with only a few examples of other alternatives

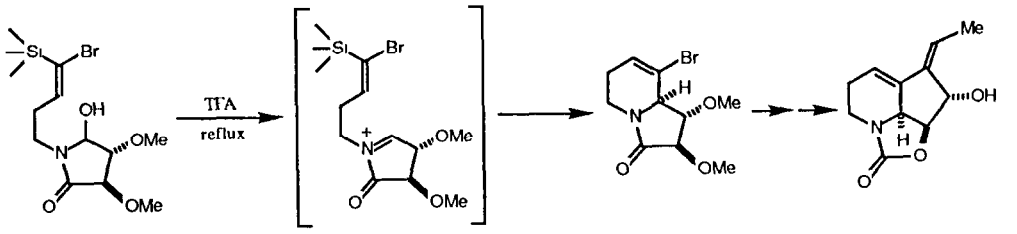



eq 14

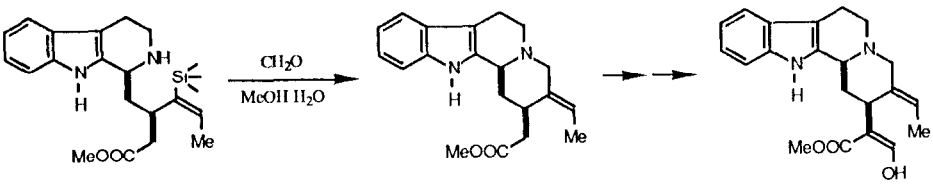



eq 15

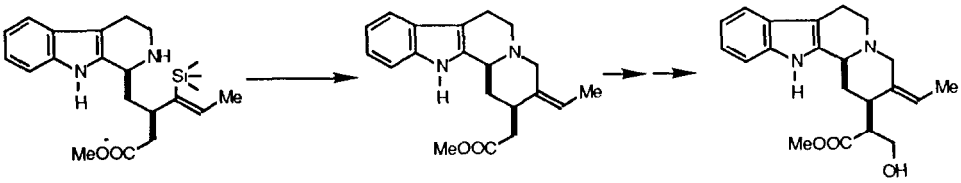
The cyclisation may proceed in a stereospecific manner as in the synthesis of antibiotic streptazolin **129** from tartrate-derived iminium ion **127** (eq 16),[38] or of geissoschizine **132** (eq 17) and (*Z*)-isositsirikine **135** (eq 18)[39] There are, however, cases e g acyclic **136**, where the cyclisation renders no asymmetric induction at all (eq 19),[38] perhaps due to the geometry of the iminium ion involved (here **137**)



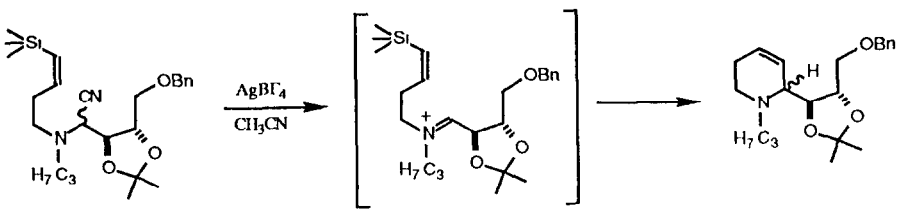

**126** **127** **128** **129** eq 16




**130** **131** **132** eq 17



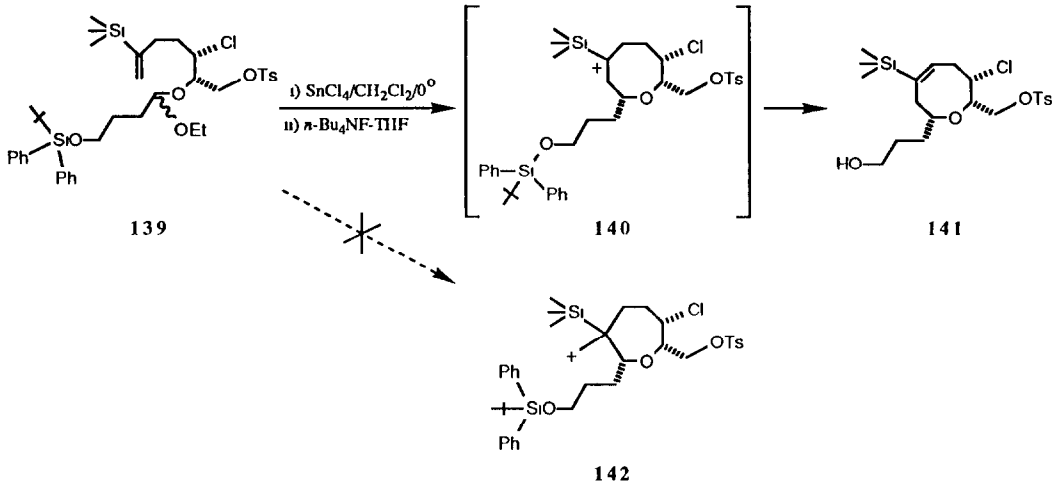
**133** **134** **135** eq 18




**136** **137** **138** eq 19

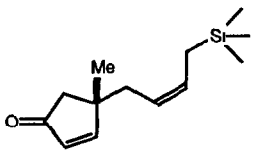
A special mention must also be made of an unusual cyclisation of vinylsilane in which the $\alpha$-silyl cation appears to triumph over its $\beta$- counterpart The reaction of **139** with $SnCl_4$ in dichloromethane followed by *O*-desilylation with fluoride ion produces **141** in 37% purified yield [40,41] Instead of proceeding *via* $\beta$-silyl cationic intermediate **142** to a 7-membered ring product, the reaction seems to prefer the $\alpha$-silyl cation (**140**) pathway to give exclusively the 8-membered ring product (Scheme 15) Details of the apparent mechanism remain to be confirmed

**Scheme 15**

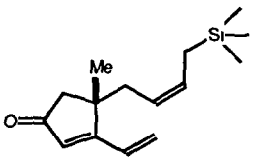



## Allyl, propargyl and allenyl silanes

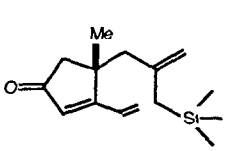
Allyl, propargyl and allenyl silanes are treated here for appropriate continuity, despite the debatable (cationic) character of their cyclisation The Sakurai reaction[42] continues to enjoy popularity in organic synthesis, in particular the intramolecular cyclisation of allylsilanes to conjugated enones which is a very effective method for constructing bicyclic systems such as [5,5], [5,6], [6,6], [6,7] and [6,8] fused ring systems The reaction entails addition of the allylsilane moiety in a 1,2-, 1,4- or 1,6- fashion to the enone Direction and stereochemistry of cyclisation are dependent on the substrate and catalyst employed Commonly used catalysts include Lewis acids such as $TiCl_4$, $EtAlCl_2$, $BF_3$-$Et_2O$ and the fluoride ion Equations 20-23 are examples of earlier work while equations 24-27 cover the more recent reports



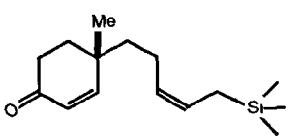

| 143 | | 144 | 145 | |
|---|---|---|---|---|
| | $F^-$ | 85% | – | |
| | $TiCl_4$ | – | 45% | eq 20[43] |



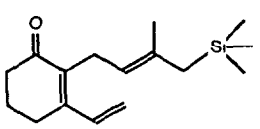

| 146 | | 147 | 148 | 149 | |
|---|---|---|---|---|---|
| | $F^-$ | 33% | 23% | – | |
| | $EtAlCl_2$ | – | – | 60% | eq 21[44] |



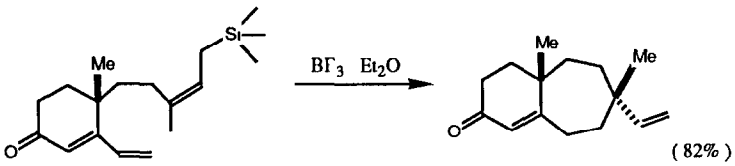

| 150 | | 151 | 152 | 153 | |
|---|---|---|---|---|---|
| | $F^-$ | – | 28% | 33% | |
| | $EtAlCl_2$ | 70% | – | – | eq 22[44] |



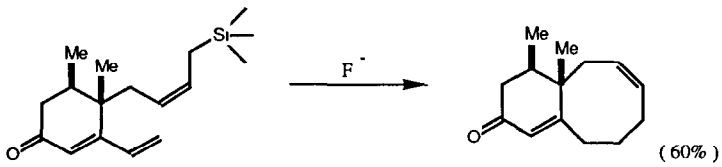

| 154 | | 155 | 156 | |
|---|---|---|---|---|
| | $I^-$ | 39% | 39% | |
| | $EtAlCl_2$ | 16% | 47% | eq 23[45] |



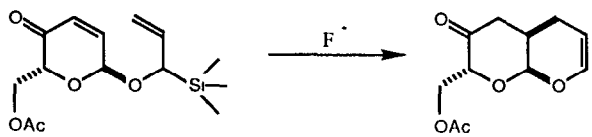

157 158 (90%) eq 24[46]




159 160 (82%) eq 25[46]

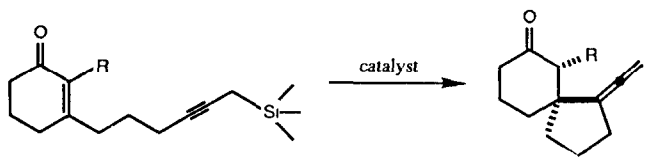



161 162 (60%) eq 26[46]




163 164 (20 25%) eq 27[47]

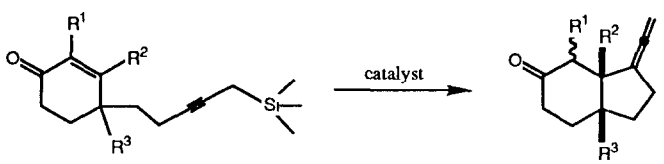
The above type of intramolecular conjugate addition to enones can also be accomplished with propargylsilanes to furnish spiro compounds (eq 28) or fused ring allenes (eq 29, 30)




165 166

R = H , $EtAlCl_2$ 62%
R = Me , $TiCl_4$ 46%
} single isomer

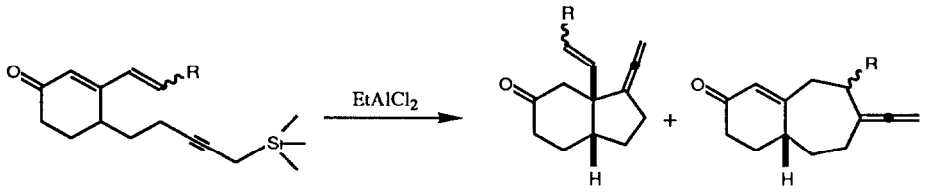
eq 28[48,49]




167 168

| | | | |
|---|---|---|---|
| $R^1 = R^2 = R^3 = H$ | $EtAlCl_2$ | 50% | single isomer |
| $R^1 = R^3 = H$ , $R^2 = Me$ | $EtAlCl_2$ | 87% | single isomer |
| $R^1 = R^2 = R^3 = Me$ | $TiCl_4$ | 84% | [2 1 mixture of isomers at $R^1$] |

eq 29[48,49]

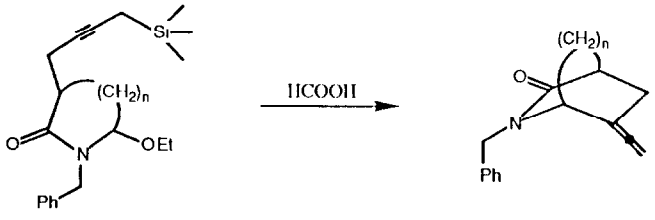



**169** **170** **171**

| | | |
|---|---|---|
| R = H | 80% | 8% |
| R = Me | 67% | 7% |

eq 30[48]

In a similar manner bridged azabicyclic allene compounds can be constructed *via* intramolecular cyclisation of acetylenic silanes onto *N*-acyliminium ions generated *in situ* (eq 31) [50,51]




**172** **173**

n = 1 , 82%

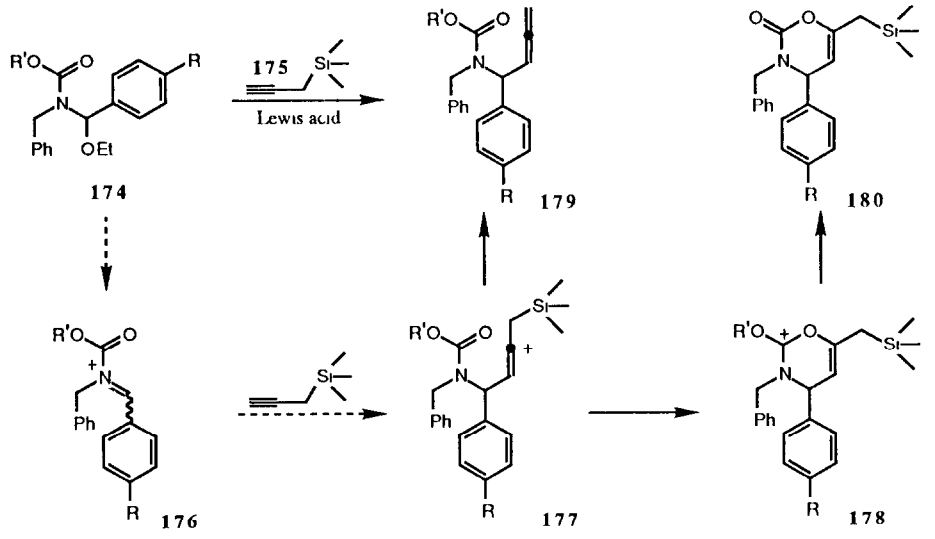
n = 2 , 98%

eq 31

An interesting study of the reaction of **174** with propargyltrimethylsilane in the presence of Lewis acid shows that, contingent upon the substrate and catalyst employed, either oxazinone **180** or a mixture of **180** and allene **179** can be formed [52] The results are explained as shown in Scheme 16 The formation of iminium ion **176** is proposed, whose addition to the silane generates intermediate **177** that can either cyclise to **178** which subsequently gives **180**, or undergo silyl elimination to yield allene **179**

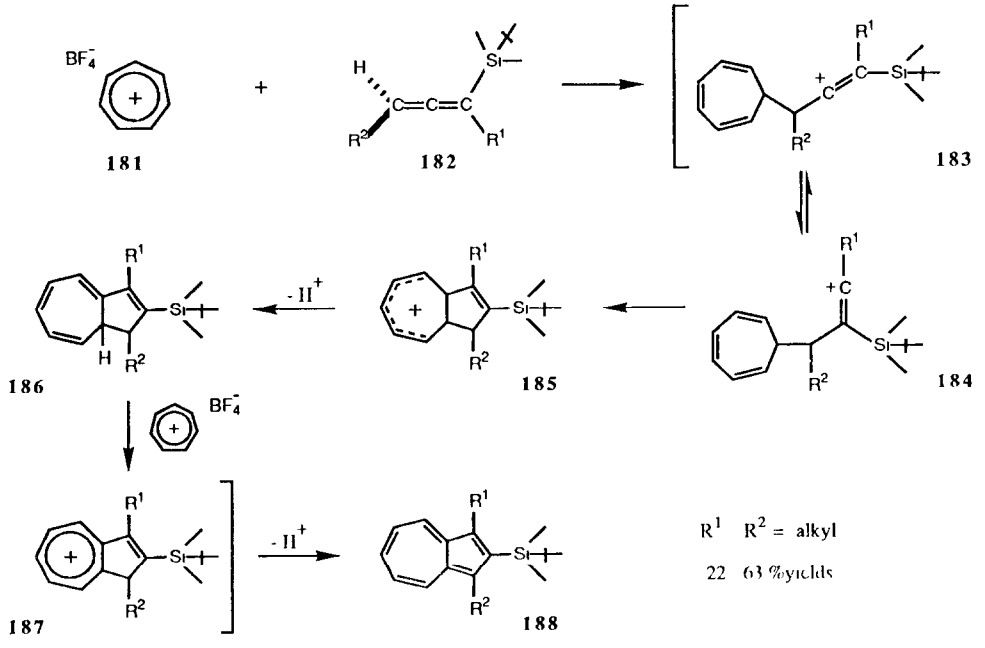
A few years ago there was a report on the synthesis of hydroazulenes utilizing the reaction of iron tricarbonyltropylium salts with allenylmetal reagents [53] A recent publication reports the use of allenylsilane **182** with tropylium tetrafluoroborate **181** in a related reaction to yield substituted azulenes (Scheme 17) [54]

## Scheme 16



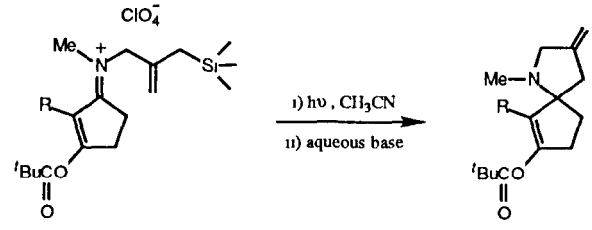

| | Lewis acid | ratio of 180 | 179 | % overall yield |
|---|---|---|---|---|
| R = H , R' = Et | $SnCl_4$ | 100 | 0 | 48 |
| | $EtAlCl_2$ | 34 | 66 | 45 |
| R = OMe , R' = $^t$Bu | $EtAlCl_2$ | 100 | 0 | 67 |

## Scheme 17

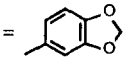
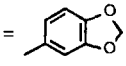


### Photocyclisation of allylsilyl iminium salts

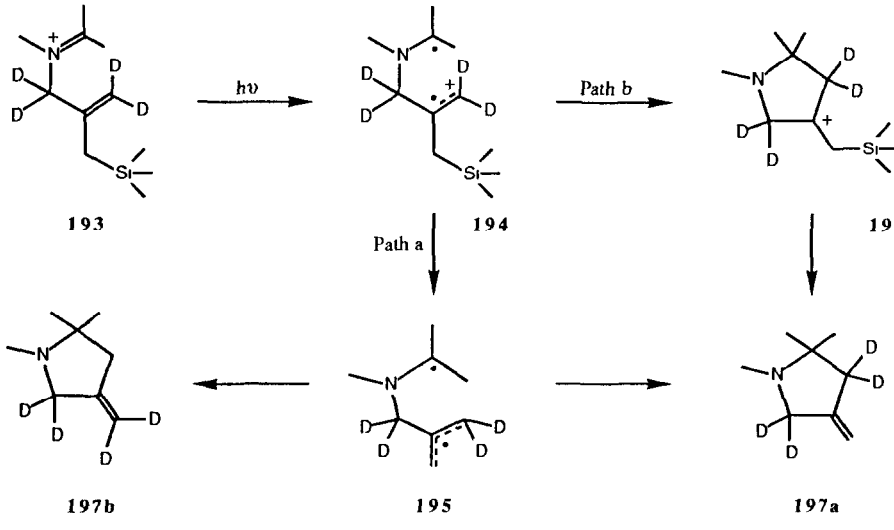
In connection with allylsilyl iminium salts a mention should also be made of the photocyclisation of **189** and **191** to the corresponding spiro products (eq 32) [55,56] The mechanism[57,58] of the reaction is now proved[59] to be dual radical and radical cation according to path a and path b, respectively, in Scheme 18




**189** (R = H) **190** (R = H)

**191** (R =  ) **192** (R =  ) eq 32

### Scheme 18




**193** **194** **196**

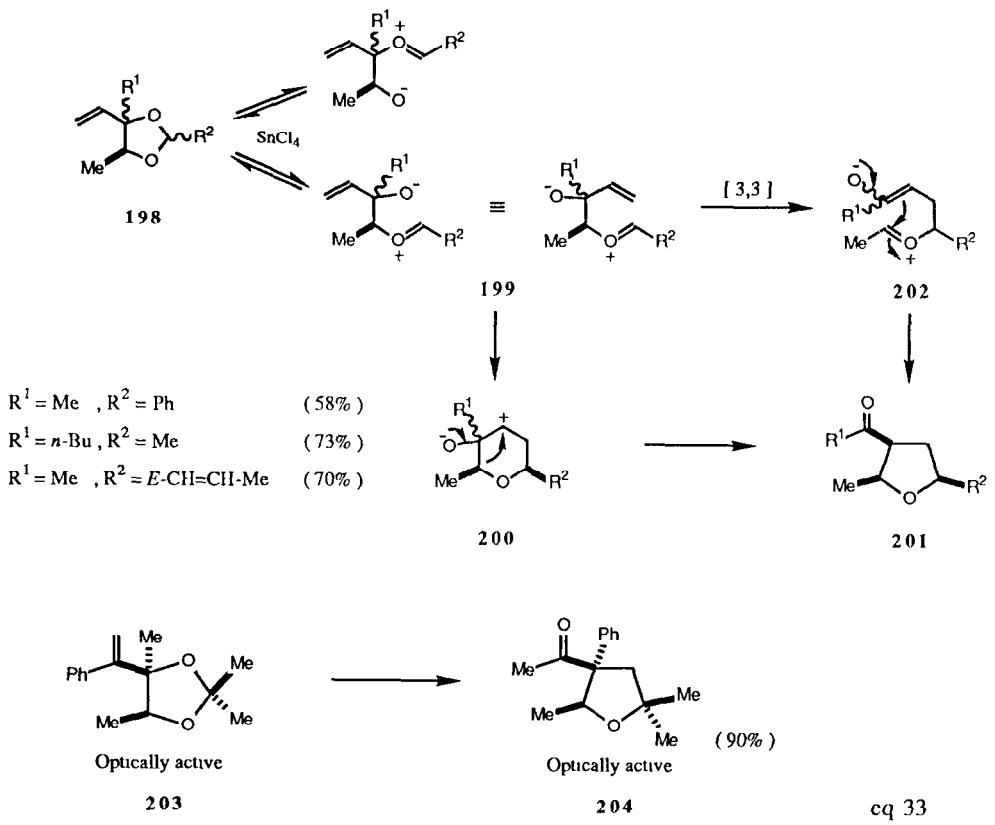
**197b** **195** **197a**

## I.4 Cyclisation-Rearrangement Reactions

Cationic-initiated cyclisation followed by rearrangement is observed upon treatment of acetal **198** with $SnCl_4$ in dichloromethane Evidently the initially formed oxonium ion **199** is trapped by the

internal alkene to give the carbonium ion **200** which undergoes a pinacolic rearrangement to yield tetrahydrofuran **201** as the final product (Scheme 19) [60] Evidence against the alternative mechanism of [3,3]-sigmatropic rearrangement of **199** to **202** lies in the high stereoselectivity of the reaction, product **204** being obtained with high enantiomeric purity from optically active acetal **203** (eq 33)

**Scheme 19**

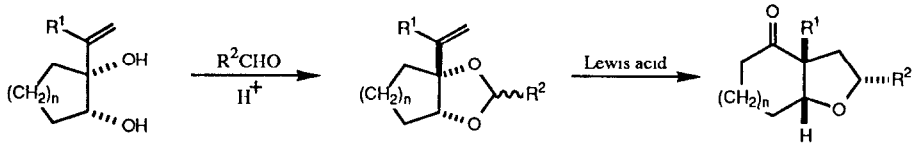



eq 33

Besides $SnCl_4$, other Lewis acids can also be used to catalyse the reaction, for example $BF_3$-$Et_2O$, $TiCl_4$, $EtAlCl_2$ and $MgBr_2$ Equation 34 illustrates the utilization of this sequence in ring-enlarging furan annulation reactions [61]

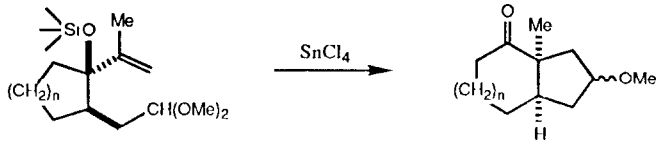
In the case of carbon analogues just recently investigated (eq 35-37), the reaction offers a convenient method for the preparation of fused cyclopentane skeletons, the tricyclic structure **212**

can be assembled in a completely stereospecific manner in 56% yield from **210**



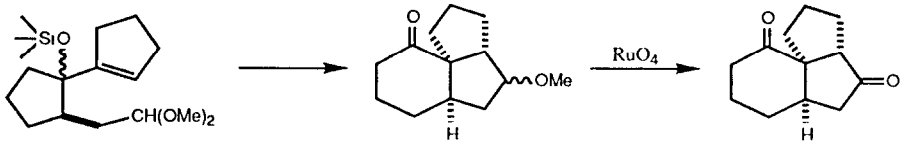
**205** **206** **207**

$n = 2, R^1 = H, R^2 = Me$ (74%)
$n = 2, R^1 = H, R^2 = Ph$ (63%)
$n = 2, R^1 = H, R^2 = E\text{-}CH{=}CHPh$ (53%)
$n = 1, R^1 = Ph, R^2 = Me$ (80%) eq 34

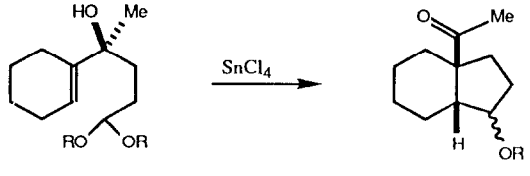


**208** **209**

n = 1 (82%)
n = 2 (90%)
n = 3 (75%) eq 35[62]



**210** **211** **212** eq 36[62]

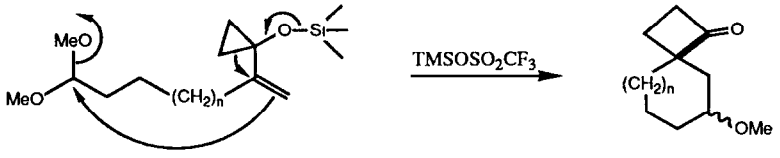


**213** **214**

R = Me, Et, $CH_2Ph$ (60 - 90 %) eq 37[63]

Trost[64] has also extended this type of reaction[65] to the synthesis of 6-, 7- and 8-membered

ring spiro compounds **216** from silylacetal **215** in the presence of trimethylsilyltrifluoromethane sulphonate




**215** **216**

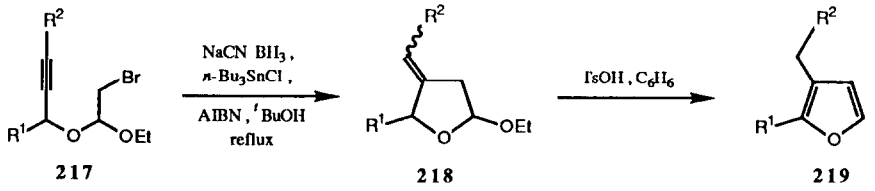
n = 1 (93%)
n = 2 (93%)
n = 3 (64%) eq 38

# II. RADICAL CYCLISATIONS

Renewed interest in the chemistry of free radicals has precipitated a host of applications, especially in the area of radical cyclisation However, since reviews of the topic have already been written,[66-68] only the latest developments will be included here

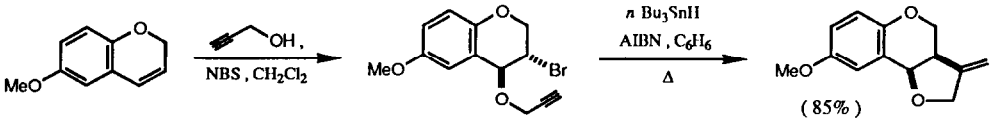
## II.1 Alkyl radicals

It is established that olefinic and acetylenic alkyl radicals generated by standard methods cyclise predominantly in the 5-*exo*-trig mode to provide 5-membered rings Much use is already made of the reaction, *viz* synthesis of substituted furans **219** (eq 39),[69,70] methylene-furobenzopyran **222** (eq 40),[71] the natural product andirolactone **226** (eq 41),[72] Corey lactone **230** (eq 42),[73] bis-lactone **234**[74] (a precursor of the antifungal mold metabolite isoavenaciolide **235**) (eq 43),[75] and the carbohydrate pyranosides **237** and **239** (eq 44 and 45) [76]




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

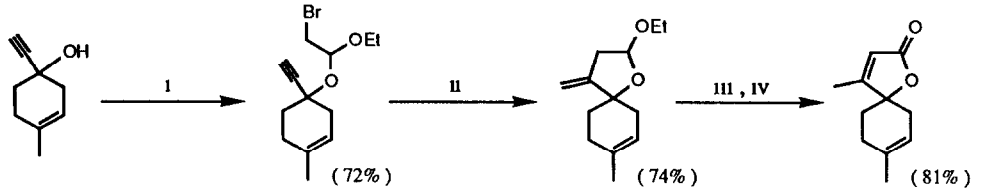
$R^1$ = alkyl
$R^2$ = alkyl, aryl
Overall yields 57 - 74 % eq 39




**220** **221** **222**

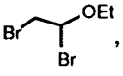
eq 40

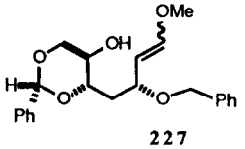
Intermolecular reaction between cyclooctadiene **240** and radical R to yield substituted bicyclo [3 3 0]octane **241**, which achieves concomitant production of three stereo centres in one operation,



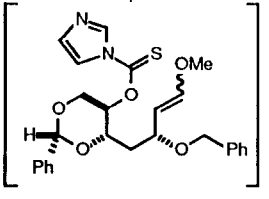

223 224 225 226

eq 41

Reagents i)  , $PhNMe_2$, $CH_2Cl_2$ ii) *n*-$Bu_3SnH$, AIBN, $C_6H_6$ iii) Jones [O] iv) Silica gel

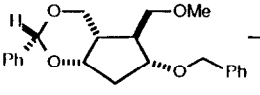



227



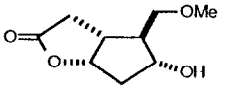

228

*n* $Bu_3SnH$ ,
AIBN $PhCH_3$
Δ



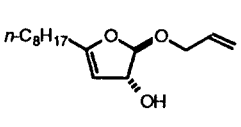

( 58% from 227 )

229

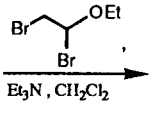


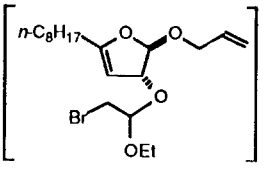

230

eq 42



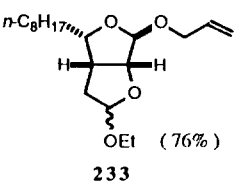

231



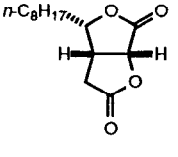

232

*n*-$Bu_3SnH$ ,
AIBN , $C_6H_6$
Δ

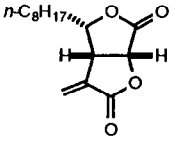



(76%)

233

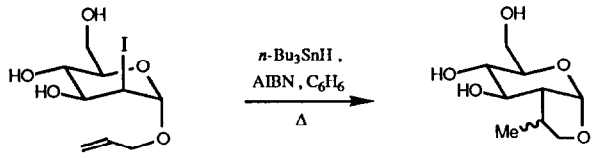



234



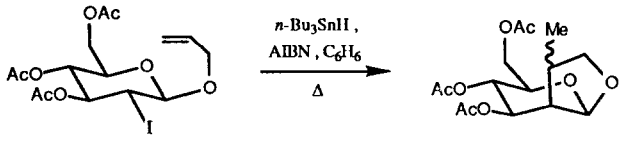

235

eq 43




( 94% , isomer ratio = 3 1 )

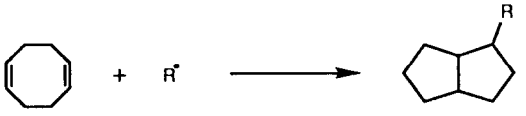
236 237 eq 44



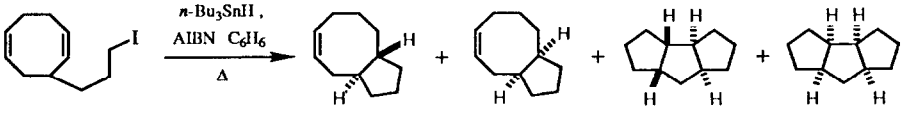

( ~100% , isomer ratio = 4 1 )

238 239 eq 45

was reported over twenty years ago (eq 46) [77,78] Intramolecular radical cyclisation of **242**, on the other hand, was only recently reported, and is found to give a mixture of *trans*-bicyclo[6 3 0]undecane **243** (major product), the *cis*-isomer **244**, and tricyclic products **245** and **246** [79] The influence of appropriately placed substituents on the stereochemical course of cyclisation is manifested in the ratio of products (eq 47, Table 2) [80] Thus with suitable modifications the *trans*- isomer can be obtained almost exclusively



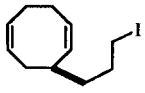
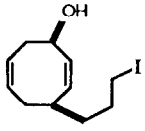
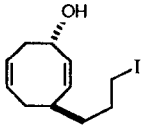
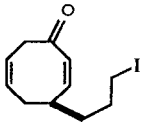

240 241 eq 46



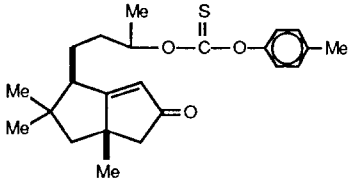

242 243 244 245 246 eq 47

Apart from undergoing intramolecular additions to unactivated double and triple bonds, free radicals are quite amenable to 1,4-additions equivalent to the Michael addition in anionic reactions Equations 48 [81] and 49 [82] illustrate such cyclisations of radical intermediates generated from the corresponding thiocarbonate **247** and bromide **249** respectively The high stereoselectivity of the

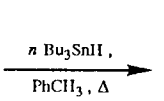
**Table 2**

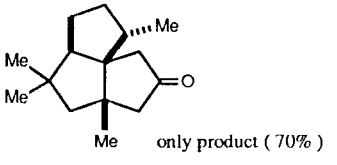
| Starting material | Product ratio | | | | % yield |
|---|---|---|---|---|---|
|  | 73 (X=H,H) | 11 | 11 | 5 | 61 |
|  | >99 (X=OH,H) | <1 | – | – | 65 |
|  | 50 (X=H OH) | 10 | 20 | 20 | 70 |
|  | 95 (X=O) | 5 | – | – | 65 |

reaction is noteworthy



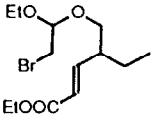

247



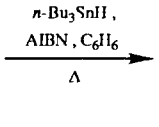



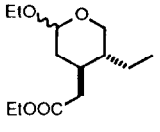

248

eq 48



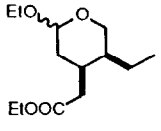

249




250

+




251

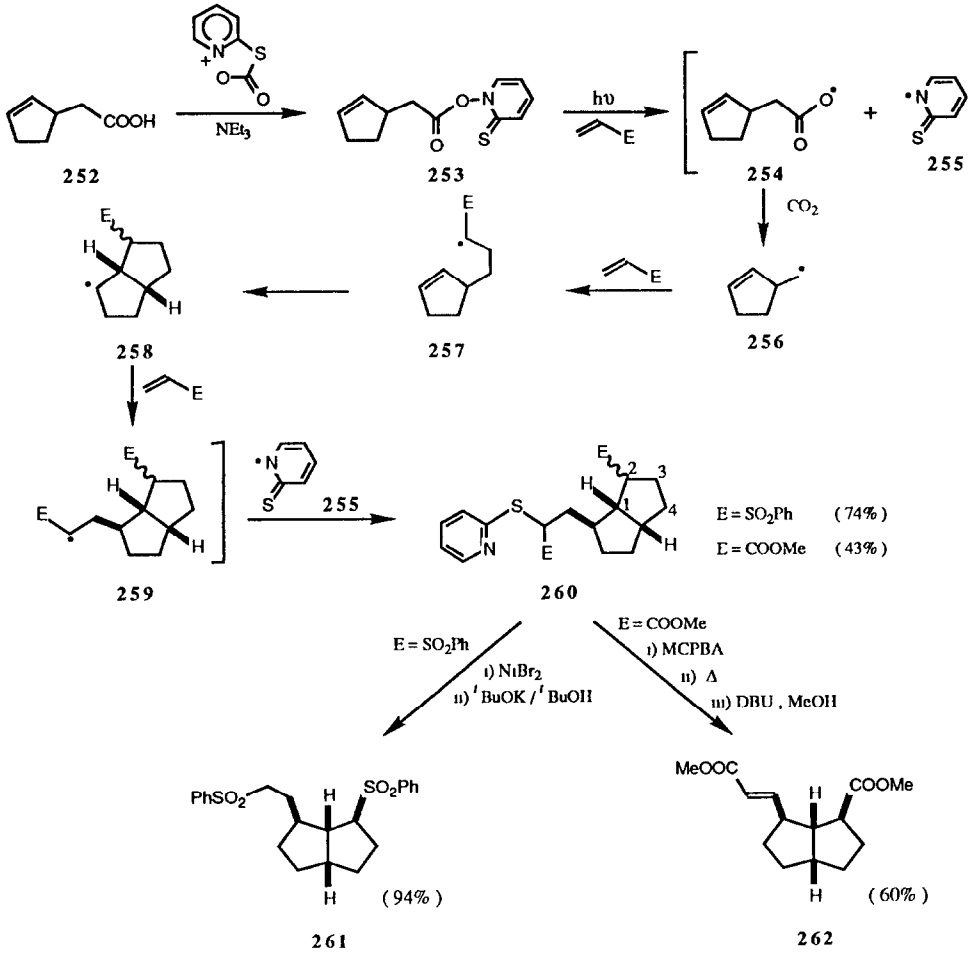
4 1 (96%)

eq 49

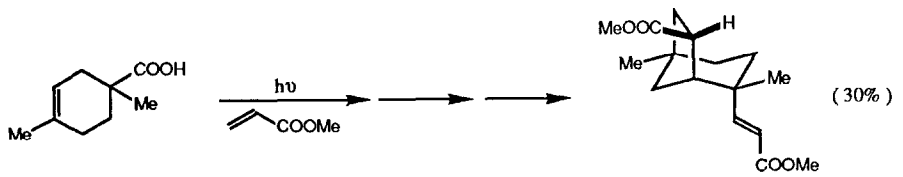
Barton[83] has reported a very interesting process involving the reaction of radical **256** (generated by irradiation of thiohydroxamate ester **253** prepared *in situ* from the corresponding acid)

with an $\alpha,\beta$-unsaturated ester or sulphone Tandem addition-cyclisation results first in the intermediate bicyclic radical **258**, which then adds to a second molecule of olefin, the addition this time terminating in the coupling of intermediate radical **259** with **255** (present in the reaction) to give **260** Salient features of the conversion of **260** to the final products are the ease with which the thiopyridinyl group can be removed and the epimerisation of C-2 to give, stereospecifically, **261** or **262** from epimeric mixture **260** (Scheme 20)

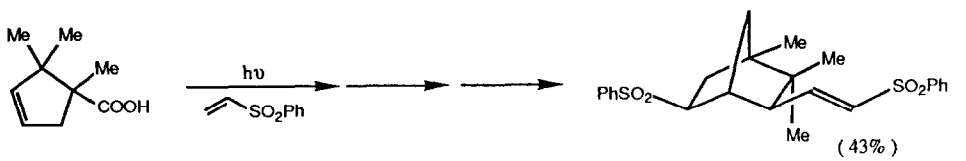
**Scheme 20**




Examples of synthetic applications of the reaction are shown in equations 50 and 51 Remarkably high stereoselectivity is observed

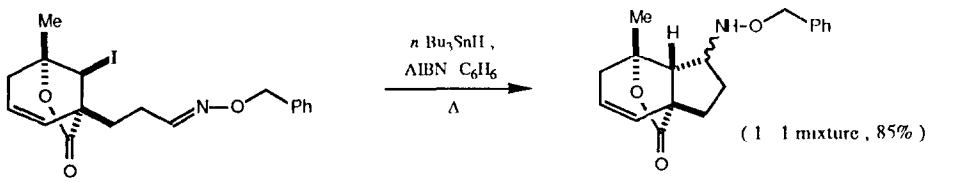



263 264 eq 50

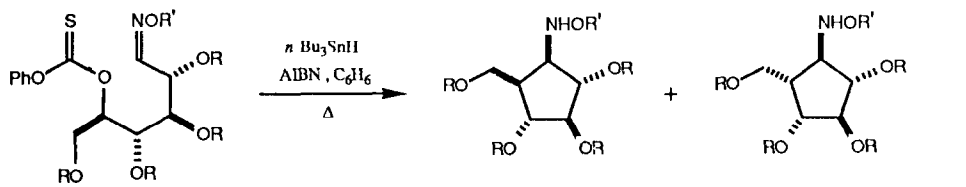



265 266 eq 51

Besides addition to $\alpha,\beta$-unsaturated carbonyls and sulphones, radical addition to oxime ethers have also been reported as demonstrated in equations 52 [84] and 53 [85]




267 268 eq 52

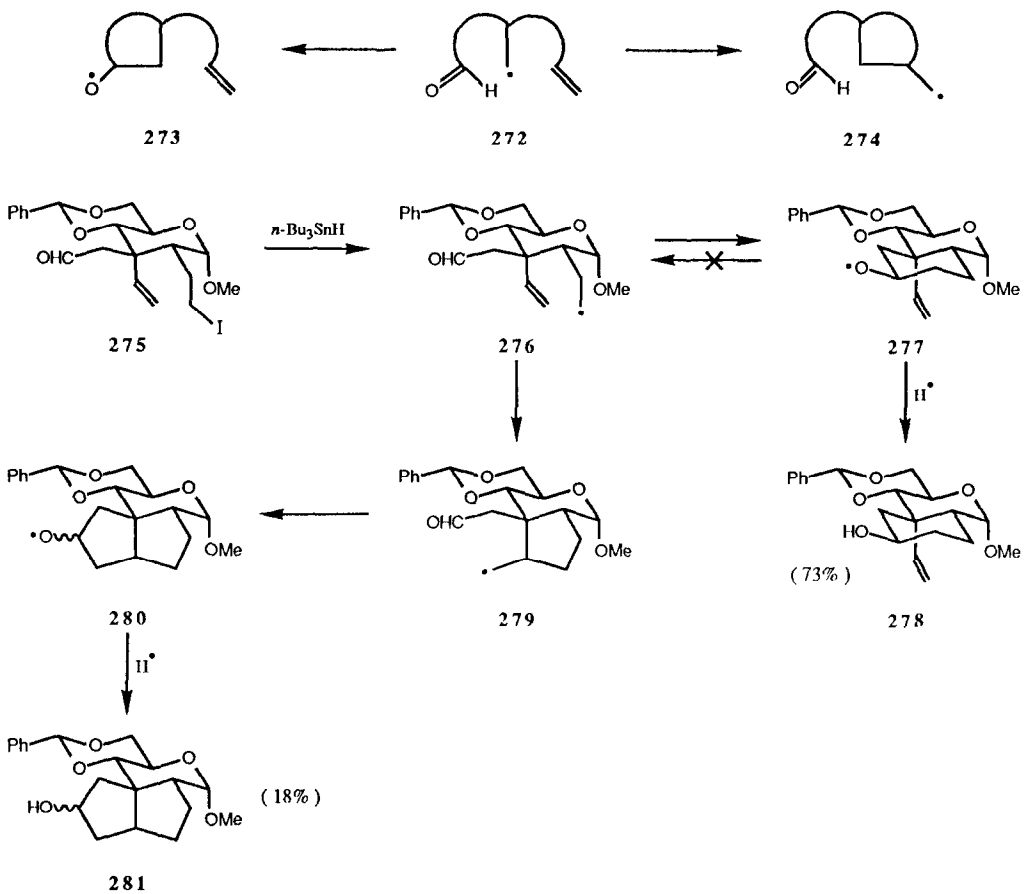



269 270 271

R, R' = Me or $CH_2Ph$ ~6 ~4 (~90%) eq 53

Competition between the olefinic and the aldehyde groups as internal traps for the alkyl radical has been studied in detail (Scheme 21) and the latter (**272** → **273**) is found to be much preferred over the former (**272** → **274**) [86-88] It is also shown that this intramolecular radical addition to aldehyde carbonyl is not reversible,[89] the cyclisation of radical **276** giving **278** and **281** in a ratio of 4 1 respectively (91% yield)

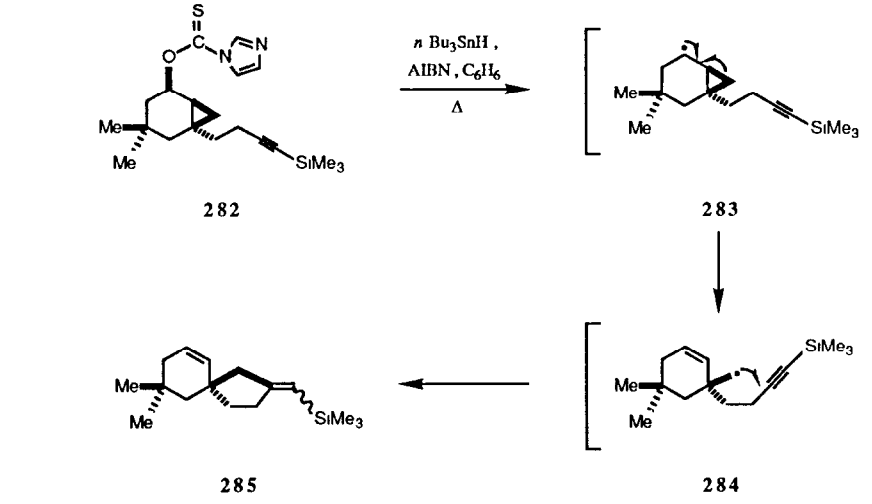
**Scheme 21**



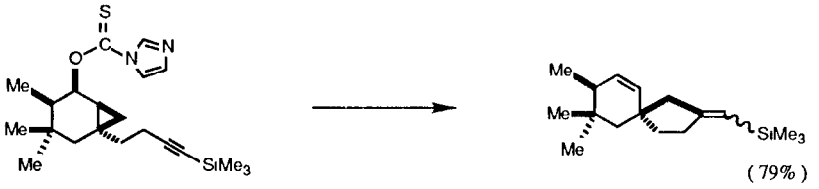

Tandem rearrangement-cyclisation of alkyl radical is observed with α-cyclopropyl radical **283** Radical-induced cyclopropane ring opening leads to **284** which is trapped by the alkynyl group in a 5-*exo*-dig reaction to produce spiro compound **285** (Scheme 22) [90] The reaction is stereospecific and can be employed as shown in equations 54 and 55

The presence of hetero atoms on the α-carbon is not deterrent to the cyclisation of alkyl radicals For example, α-alkoxy or alkylthio (eq 56)[91] and α-amino radicals (eq 57,[92] 58[93] and 59[94]) have all been employed The methods used to provide the α-aminoalkyl radical are variously different, e q photolytic cleavage of the α-aminocarbon-silyl bond of **296** in equation 58 and reduction of iminium salt **299** with samarium diiodide in the presence of camphorsulphonic acid (CSA) in equation 59 The requirement of CSA for higher yields of product in the latter reaction

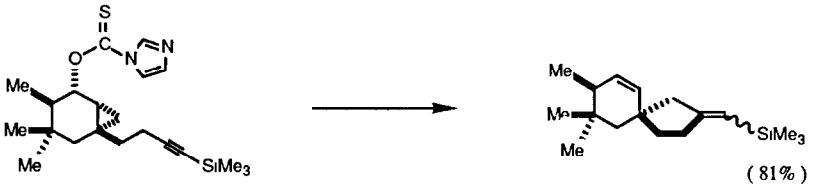
**Scheme 22**




282 283 284 285

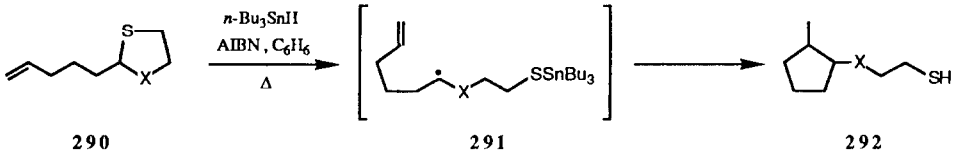


286 287 eq 54



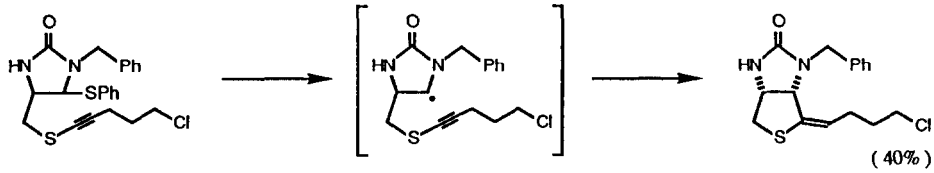
288 289 eq 55

indicates that here the protonated $\alpha$-amino radical cyclises more readily than the non-protonated species



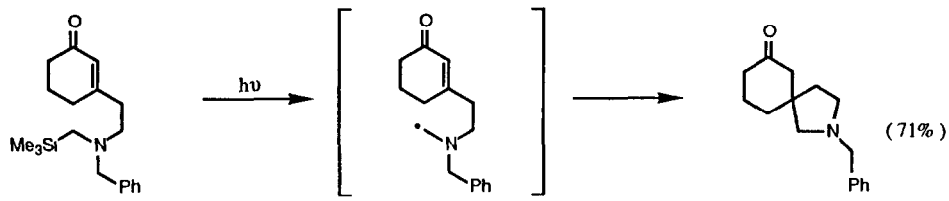

| 290 | 291 | 292 |
|---|---|---|
| X = O | X = O | 60% ( one isomer ) |
| X = S | X = S | 60% ( *cis* *trans* = 2 1 ) |

eq 56



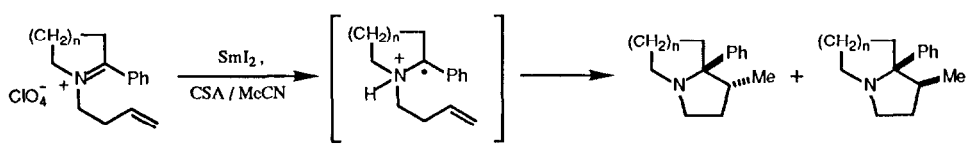

293 294 295

eq 57




296 297 298

eq 58




299 300 301 302

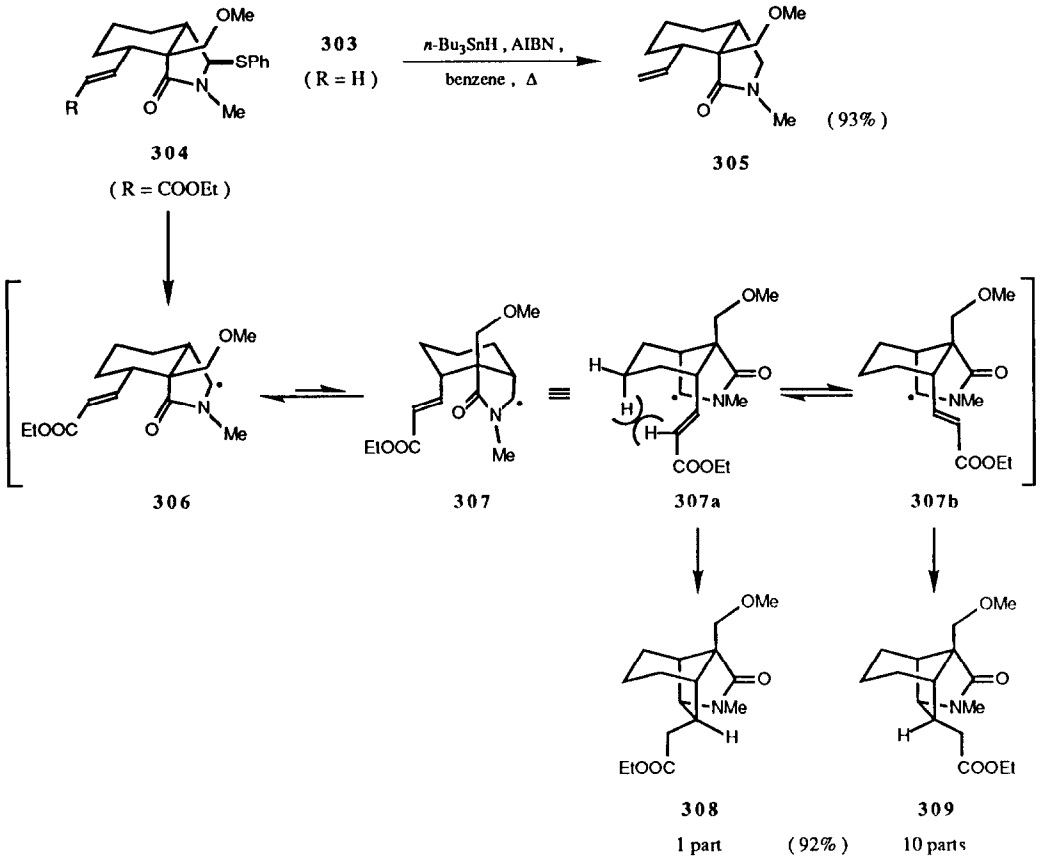
| | | | |
|---|---|---|---|
| n = 1 | (82%) | 10 | 1 |
| n = 2 | (60%) | 1 | 1 |

eq 59

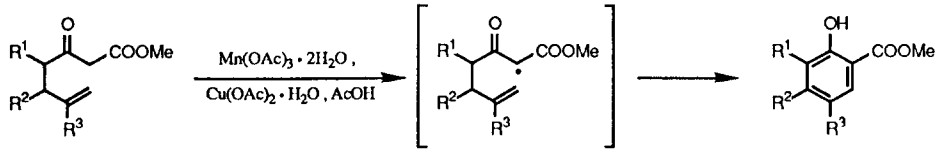
One of the most interesting $\alpha$-heteroalkyl radical cyclisations is that of radical **306** (prepared from the corresponding sulphide **304**) to give tricyclic products **308** and **309**, which structures form part of the gelsemine skeleton (*cf* Scheme 8) An interesting feature of Scheme 23 is that cyclisation of radical **306** is possible only with the less favourable conformers **307a** and/or **307b** However, interaction between hydrogen atoms as shown in **307a** further inhibits this conformation with the result that product **309** is predominantly formed over **308** in a ratio of 10 1 [95] Meanwhile, in remarkable contrast to **306**, the radical intermediate from **303** does not cyclise, but gives only the reduction product **305**, a significant indication that radical addition to an isolated olefinic bond is less preferable than conjugate addition to an $\alpha,\beta$-unsaturated carbonyl group

$\alpha$-Oxoalkyl radicals, generated by manganese acetate oxidation of $\beta$-ketoesters, can undergo intramolecular cyclisation with appropriately placed olefinic substituents to give salicylate esters

## Scheme 23

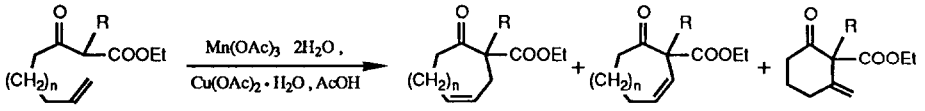



(eq 60)[96,97] or other 7- and 8-membered ring products (eq 61) [98]




| | |
|---|---|
| $R^1 = R^2 = R^3 = H$ | 78% |
| $R^1 = Me$, $R^2 = R^3 = H$ | 78% |
| $R^1 = R^3 = H$, $R^2 = Me$ | 38% |
| $R^1 = R^2 = H$, $R^3 = Me$ | 17% |

eq 60

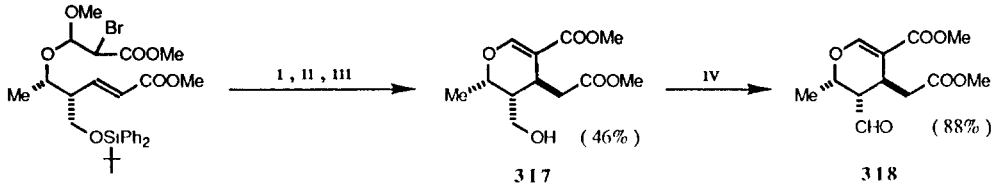



313 314a 314b 315

| | | | |
|---|---|---|---|
| n = 1 , R = Me ( 46% ) | 3 | 1 | 1 |
| n = 1 , R = Cl ( 68% ) | 3 | – | 1 |
| n = 2 , R = Me ( 38% ) | only | – | – |
| n = 2 , R = Cl ( 47% ) | only | – | – |

eq 61

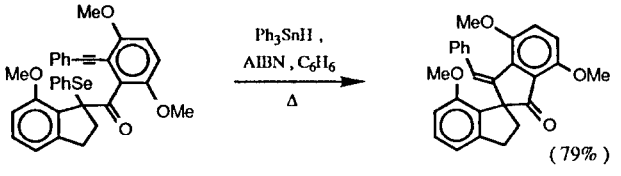
Synthetic applications of $\alpha$-oxoalkyl radicals include the synthesis of (-)-methyl elenolate **318** (eq 62)[99] and spiro compound **320** which is a synthetic model for fredericamycin A (eq 63) [100]




316 317 318

eq 62

Reagents i) *n*-$Bu_3SnH$, AIBN, $C_6H_6$, Δ ii) TsOH, Δ iii) aq HF, MeOH (1 3) iv) Swern [O]

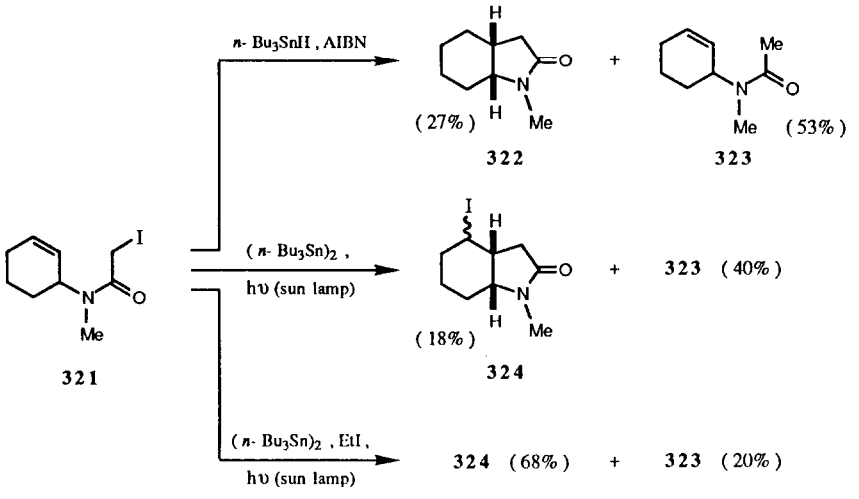



319 320

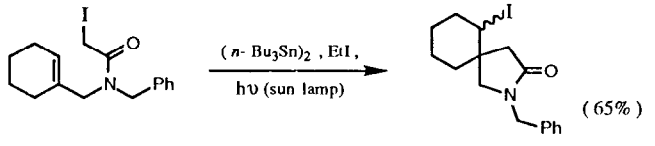
eq 63

The behaviour of the $\alpha$-amidoalkyl radical has also been studied Treatment of iodoacetamide **321** with *n*-BuSnH / AIBN under normal homolytic cleavage conditions gives mainly the reduction product **323** with a small amount of cyclisation product **322** Irradiation of the reaction mixture, in contrast, results in formation of the iodine-transferred cyclised product **324** together with **323** in a ratio of 1 2 Addition of ethyl iodide not only improves the overall reaction yield (88%), but dramatically alters the product ratio in favour of cyclised product **324** (Scheme 24) [101] Ethyl iodide is attributed a dual role, that of an S-*trans*-acetamide radical sink as well as an iodine atom source

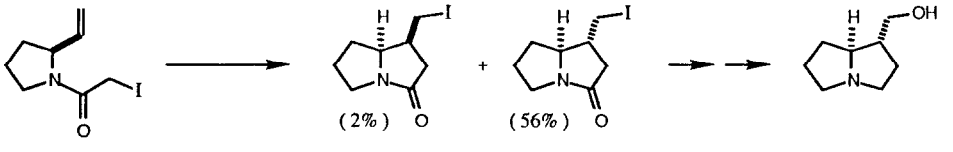
**Scheme 24**




The reaction has been applied to the synthesis of spirolactam **326** (eq. 64) and natural product trachelanthamidine **330** (eq. 65).[101]




.... eq 64

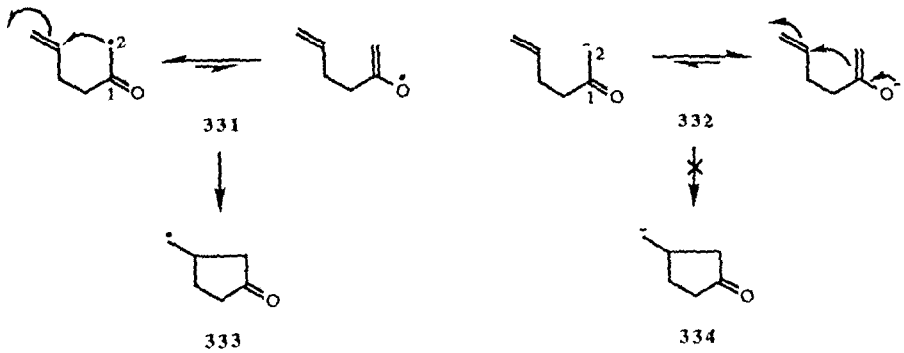


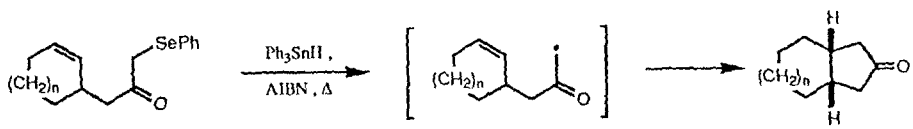

.... eq 65

An interesting rationalization of the difference between α-oxoalkyl radicals such as **331** and their anionic counterpart, for example **332** is as follows. The C(1)-C(2) bond in **331** has single bond character with a rotational barrier of approximately 9 kcal/mole[102] whilst the corresponding bond in anion **332** has much higher double bond character with a rotational barrier of more than 27 kcal/

mole [103] Consequently cyclisation reaction **331** → **333** proceeds readily as, for example, in Scheme 24 and equations 63-66,[104] whilst cyclisation **332** → **334** is unfavourable due to torsional strain in the transition state of the 5-(enol-*endo*)-*exo*-trig reaction (Scheme 25) [105]

**Scheme 25**

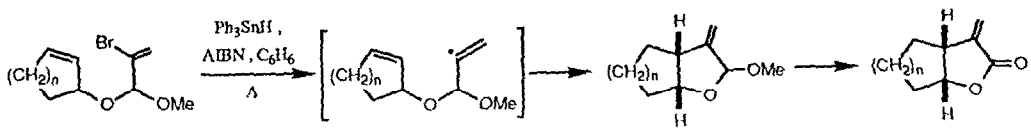


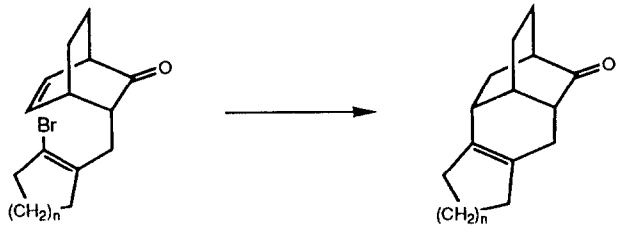

n = 0, 1, 2 eq 66

## II 2 Vinyl and aryl radicals

Recent examples of vinyl and aryl radical cyclisations mostly concern their utilization in synthesis These include the syntheses of α-methylene-γ-butyrolactone (eq 67),[106] functionalized polycyclic carbocycles (eq 68),[107] fused benzofuran and chroman (eq 69 and 70),[108,109] the formal synthesis of aflatoxin $B_1$ **350** (eq 71)[110] and the construction of the indole nucleus (eq 72) [111]

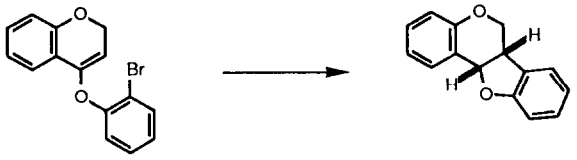



n = 1-3 (92-96%) eq 67



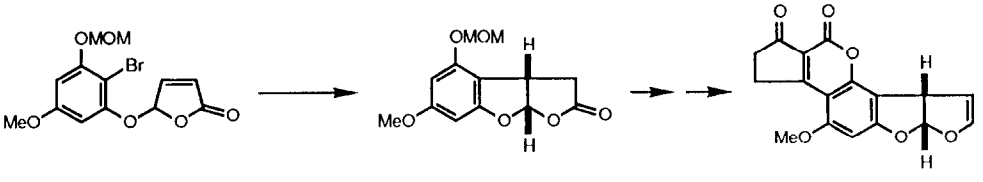
342 343

n = 1 (85%), n = 2 (86%) eq 68



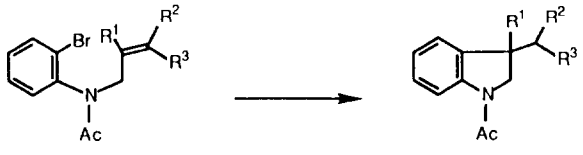
344 345 (82%) eq 69

346 347 (71%) eq 70



348 349 350

eq 71

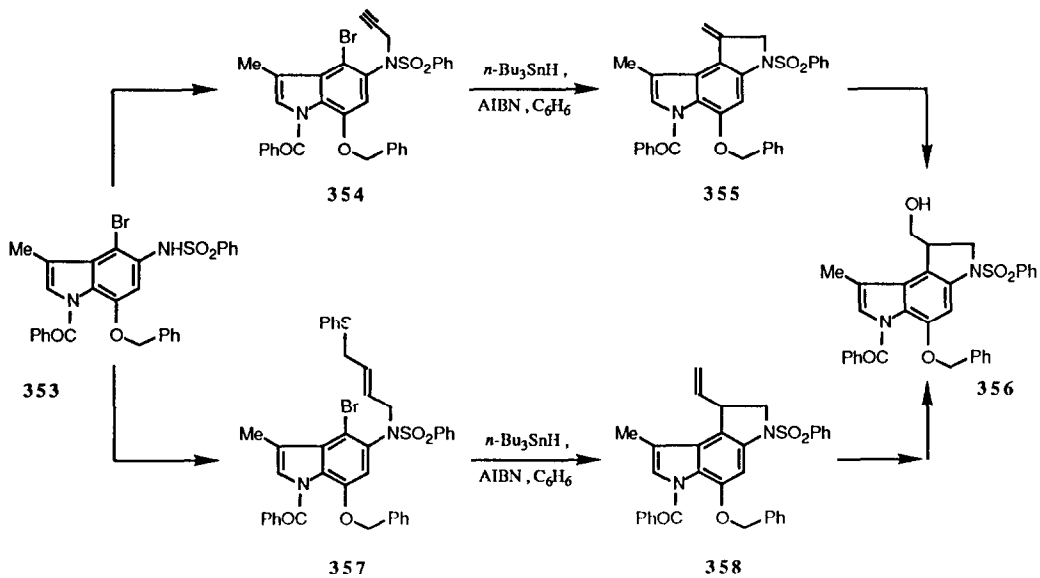


351 352

$R^1, R^2, R^3$ = H, Me (>90%) eq 72

The total synthesis of antibiotic CC-1065 (isolated from *Streptomyces zelensis* [112]) and its derivatives involves the construction of precursor **356** which can be formed from **353** by two complementary cyclisation modes [113]

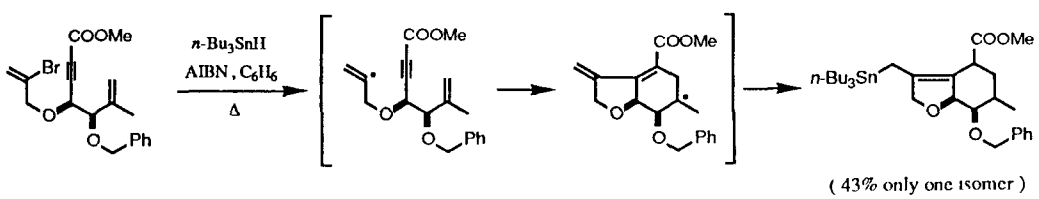
**Scheme 26**




Tandem radical cyclisations have been employed to assemble the morphine tetracyclic skeleton in *cis,cis*-hexahydrophenanthrofurans **361** and **362** Aryl radical **360**, generated from **359**, undergoes successive additions to the olefin then to the oxime ether functional groups as shown in equation 73 [114] A similar use of tandem vinyl radical cyclisations for the simultaneous construction


359 360 361 362

eq 73



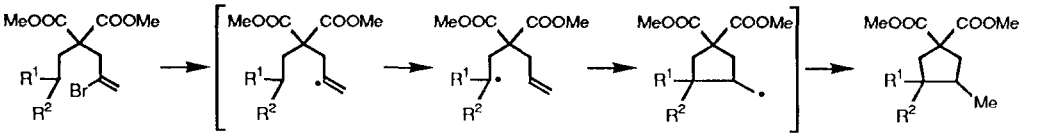

363 364 365 366

eq 74

of fused rings is demonstrated in the preparation of hexahydrobenzofuran **366** (eq 74) [115]

Two beautiful radical cyclisation reactions have been reported recently [116] The first is illustrated in equation 75 Initial generation of vinyl radical **368** is followed by 1,5-hydrogen atom transfer to afford stabilised radical **369** which subsequently cyclises back onto the reinstated olefinic function Substituents $R^1$ and $R^2$ can be any of various radical stabilising groups such as alkoxyls, esters and aryls

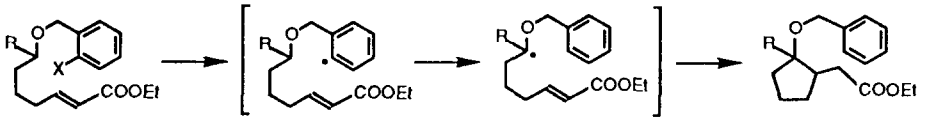
The second reaction makes use of the benzylic protecting group as the initial site of radical formation The aryl radical (**373**) then proceeds through a similar sequence of hydrogen transfer and subsequent conjugate addition cyclisation as depicted in equation 76




**367** **368** **369** **370** **371**

| | % yield | isomeric ratio |
|---|---|---|
| $R^1$ = H , $R^2$ = OTBS | 66 | 2 3 |
| $R^1$ = OMe , $R^2$ = Me | 78 | 1 4 5 |
| $R^1$–$R^2$ = O-$CH_2$-$CH_2$-O | 38 | |
| $R^1$ = H , $R^2$ = COOMe | 60 | 4 5 1 |
| $R^1$ = H , $R^2$ = Ph | 45 | 1 1 |

eq 75




**372** **373** **374** **375**

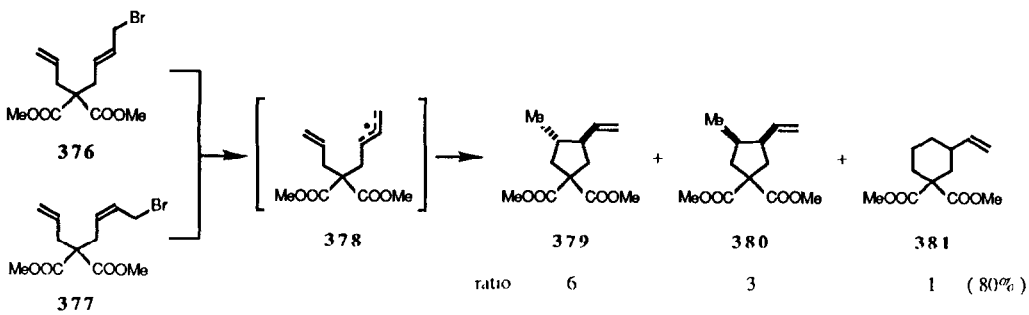
| | % yield | isomeric ratio |
|---|---|---|
| R = H , X = I | 56 | 1 2 5 |
| R = H , X = Br | 46 | 1 2 5 |
| R = Me , X = I | 54 | 1 4 |

eq 76

## II.3 Allylic radicals

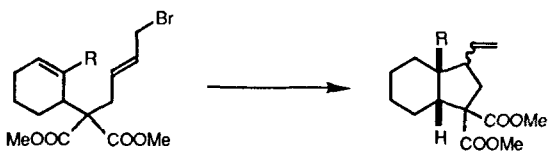
Although reports on allylic radicals are few, they are nevertheless of interest and of high potential in organic synthesis Allylic radicals in cyclisation reactions are currently generated by either one of two methods reductive cleavage of an allylic halide or allylic hydrogen transfer to a preformed radical

Allylic radicals formed by the reaction of an allylic bromide with tributyltin hydride are shown to readily undergo intramolecular cyclisations with olefinic (eq 77-78), acetylenic (eq 79) and

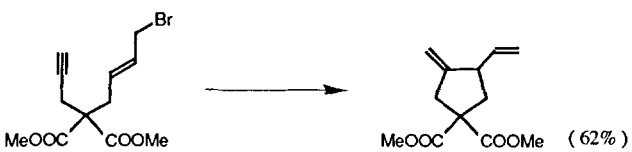



ratio 6 3 1 (80%)

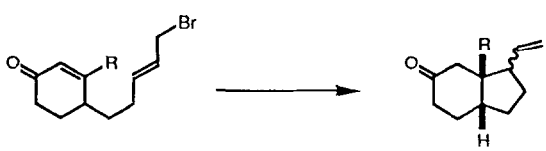
eq 77




R = H (86%) β-vinyl α-vinyl = 2 4 1
R = Me (92%) β-vinyl α vinyl = 3 1 eq 78




eq 79

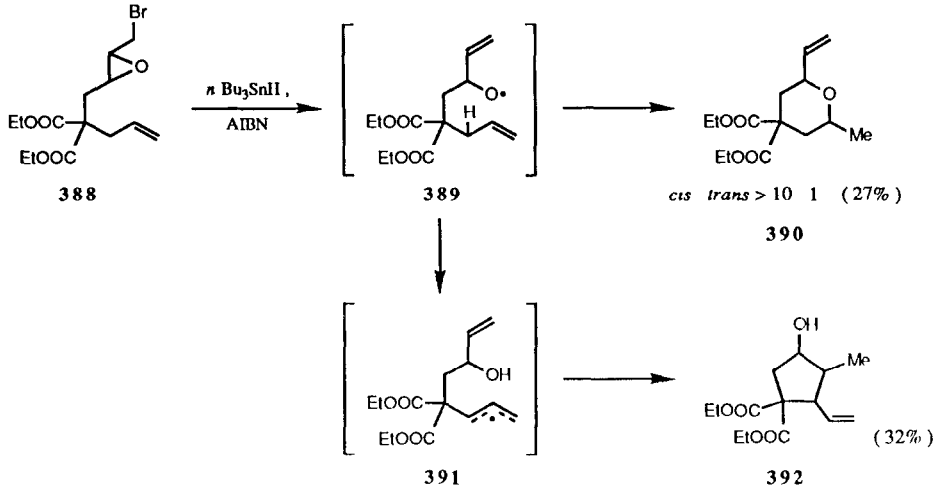



R = H (93%) β-vinyl α vinyl = 4 1
R = Me (59%) β vinyl α-vinyl = 5 1 eq 80

$\alpha,\beta$-unsaturated ketone moieties (eq 80) [117]

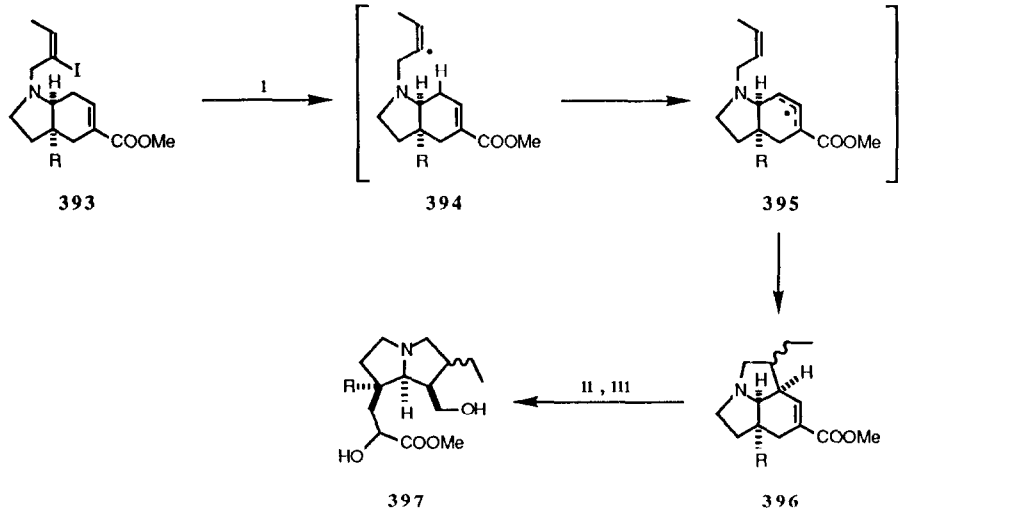
Treatment of bromoepoxide **388** with tributyltin hydride produces alkoxide radical **389** which may directly cyclise to vinylpyran **390** or follow the hydrogen transfer pathway to afford intermediate allylic radical **391**, which then cyclises to vinylpentanol **392** as illustrated in Scheme 27 [118]

**Scheme 27**




An elegant route to the pyrrolizidine ring system also utilizes allylic radical cyclisation

**Scheme 28**

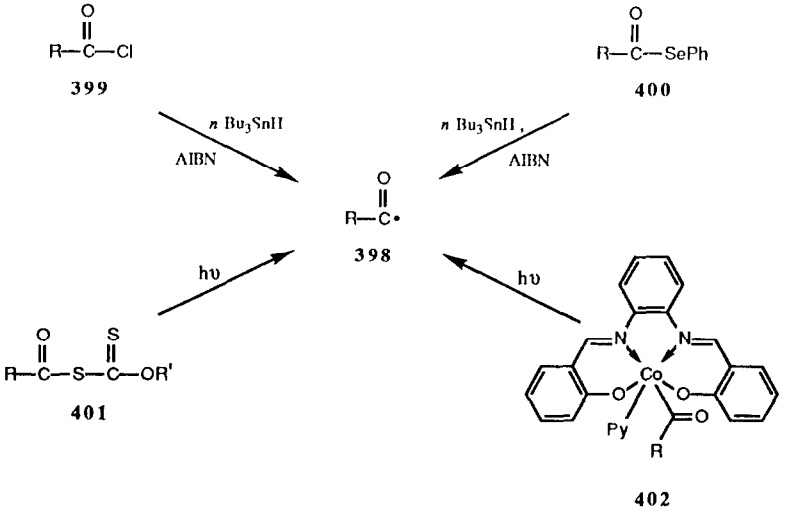


Generated *via* the hydrogen transfer mechanism, allylic radical **395** undergoes cyclisation to **396** which can eventually be converted to **397** (Scheme 28) [119]

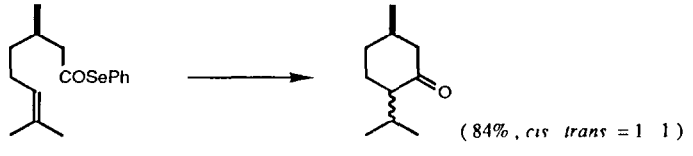
## II.4 Acyl, thioacyl and imidoyl radicals

The first preparation of acyl radical **398** was from the reaction of acid chlorides with tributyltin hydride [120] In the last two years several interesting methods have been reported for the generation of acyl radicals, for example the use of phenyl selenoesters **400**[121] in place of acid chlorides and irradiation of *S*-acylxanthates **401**[122] and acylcobalt salophenpyridine complexes **402**,[123,124] as summarized in Scheme **29**

**Scheme 29**



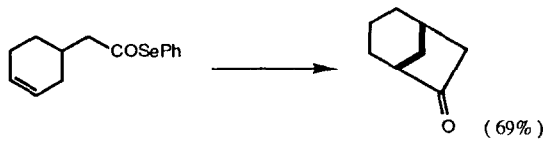

Once generated, acyl radicals can be trapped inter- or intramolecularly, provided that an appropriate group with affinity for radicals is present The reaction is exemplified in equations 81-87 [121,125]




403 404 eq 81

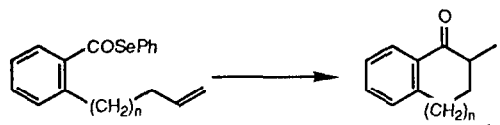

( 86% )

**405** **406** eq 82



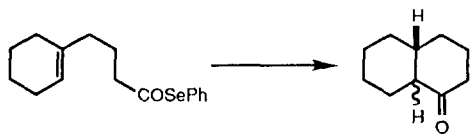

( 69% )

**407** **408** eq 83




( n = 0 - 2 74 - 81% )

**409** **410** eq 84

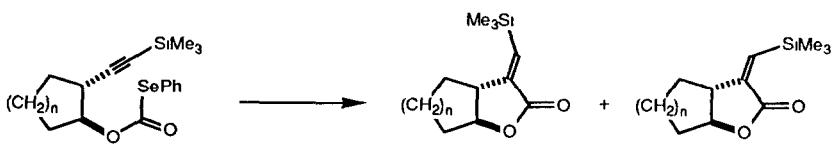



( 82% , *cis trans* = 2 3 )

**411** **412** eq 85


**413** **414**

n = 0 , m = 1 - 3 ( 84 - 92% )
n = 2 , m = 0 , 1 ( 71 - 83% ) eq 86

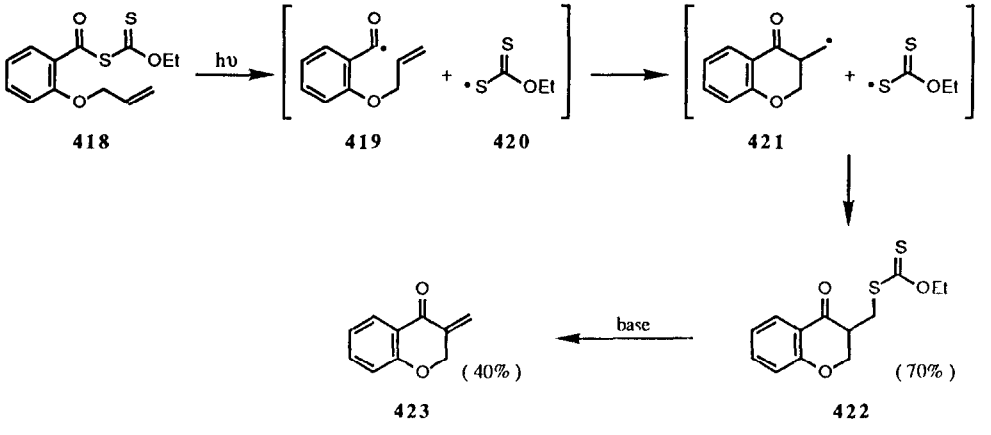



**415** **416** **417**

| | | |
|---|---|---|
| n = 2 | 6% | 74% |
| n = 3 | 8% | 84% |

eq 87

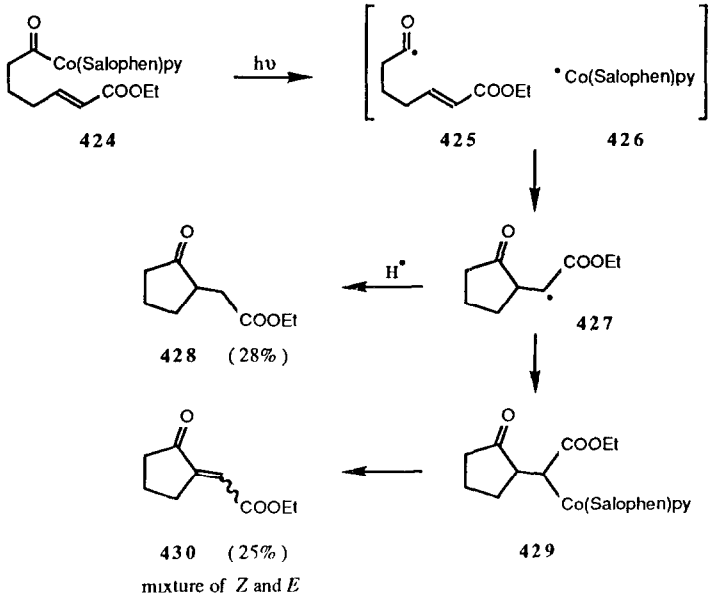
In the irradiation of *S*-acylxanthate and acylcobalt salophenpyridine complexes **418** and **424**, acyl radicals are produced, add to $\pi$-bonds, and the process is eventually terminated by coupling with xanthate or cobalt salophenpyridine radicals Xanthate coupling product **422** (eq 88) has been isolated and treated with base to yield 3-methylene-4-chromanone **423**,[122] whereas cobalt salophenpyridine coupling product **429** apparently suffers spontaneous elimination to yield $\alpha,\beta$-unsaturated ketone **430** isolated along with **428** from alternative process termination with hydrogen




418 419 420 421 423 422

eq 88

**Scheme 30**



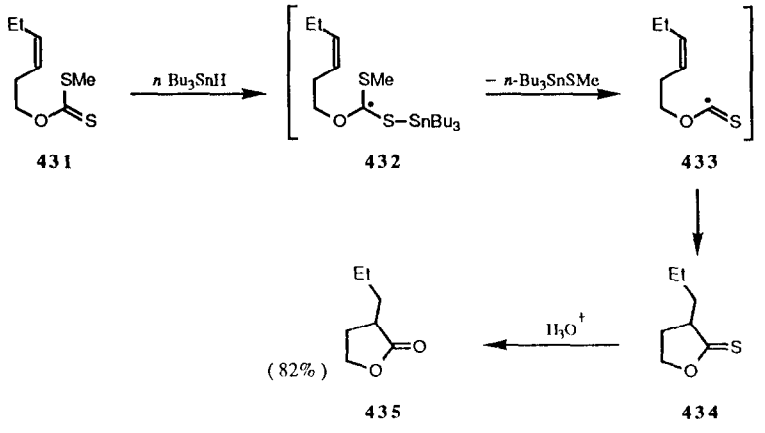

424 425 426 427 428 (28%) 429 430 (25%)

mixture of *Z* and *E*

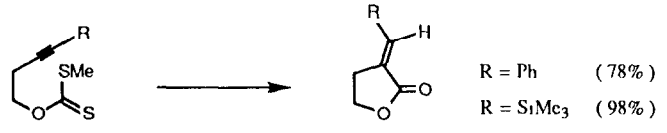
radical (Scheme 30) [123,124]

Treatment of the dithiocarbonate of homoallylic alcohol **431** with tributyltin hydride produces thioacyl radical **433**, which upon cyclisation and subsequent hydrolysis, yields γ-butyrolactone **435** (Scheme 31) [125]

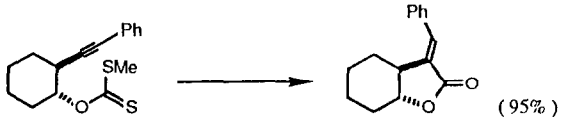
**Scheme 31**




The process can equally well be applied to homopropargylic alcohols **436** and **438** to efficiently provide α-methylene-γ-butyrolactones **437** and **439** respectively (eq 89 and 90) [125,126]




eq 89

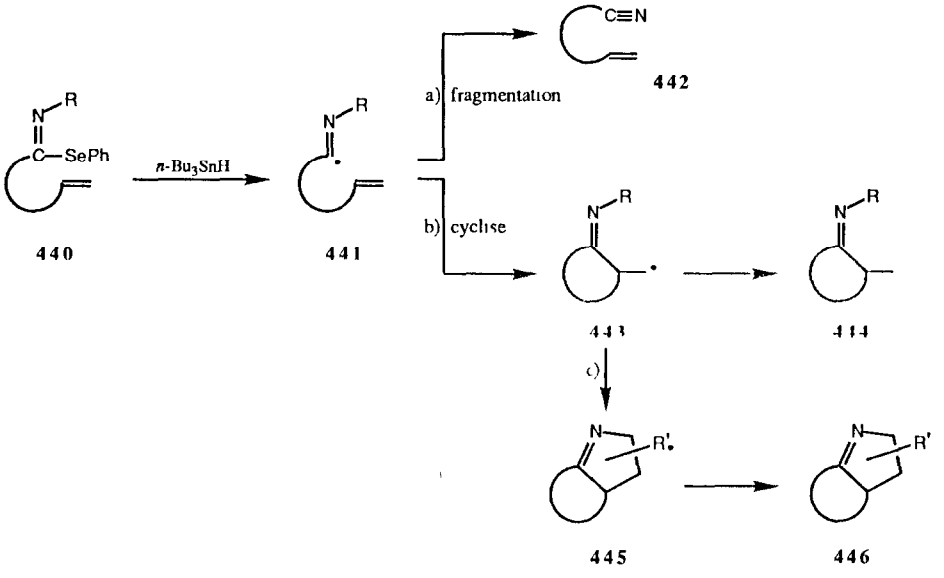



eq 90

The generation and use of the imidoyl radical, a species isoelectronic with the vinyl, acyl and thioacyl radicals, has only recently been investigated Reduction of selenoimidate **440** with tributyltin

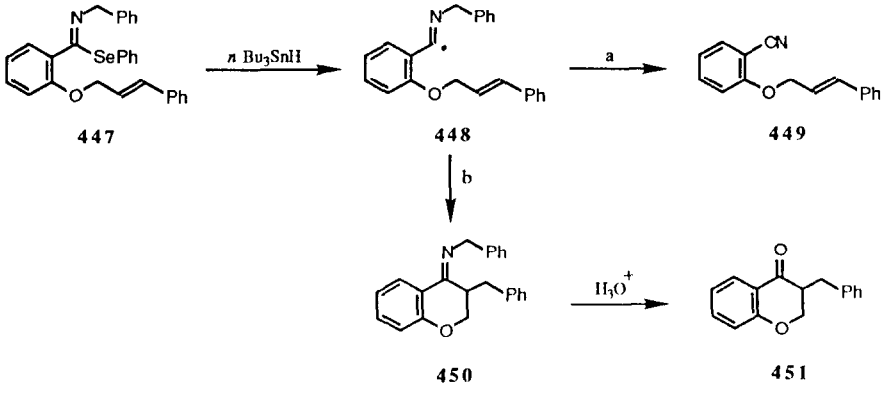
hydride under standard conditions is used to generate the imidoyl radical **441** which, contingent upon substituent R, can react in any of two ways fragmentation to give nitrile **442** (pathway "a"), or cyclisation *via* intermediate **443** (pathway "b") to **444** In the case that R is a radical acceptor, however, tandem cyclisations (pathway "b" followed by "c") resulting in product **446** is observed as illustrated in Scheme 32 [127]

**Scheme 32**



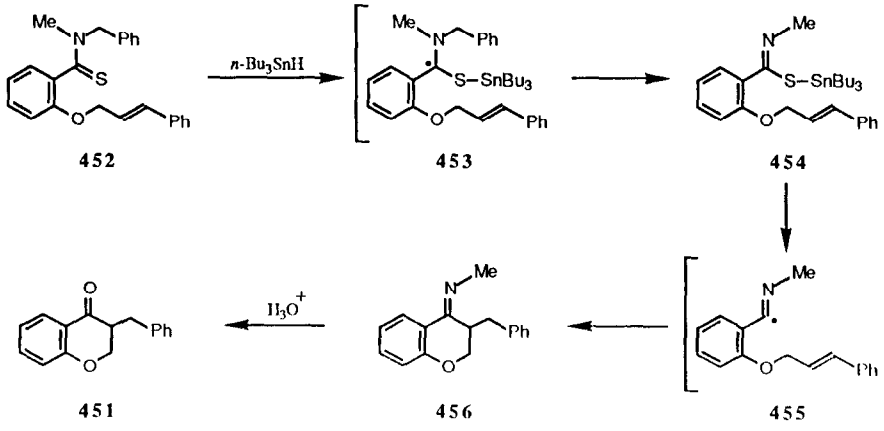

The influence of substituent R on the fate of the imidoyl radical is clearly demonstrated in the

**Scheme 33**



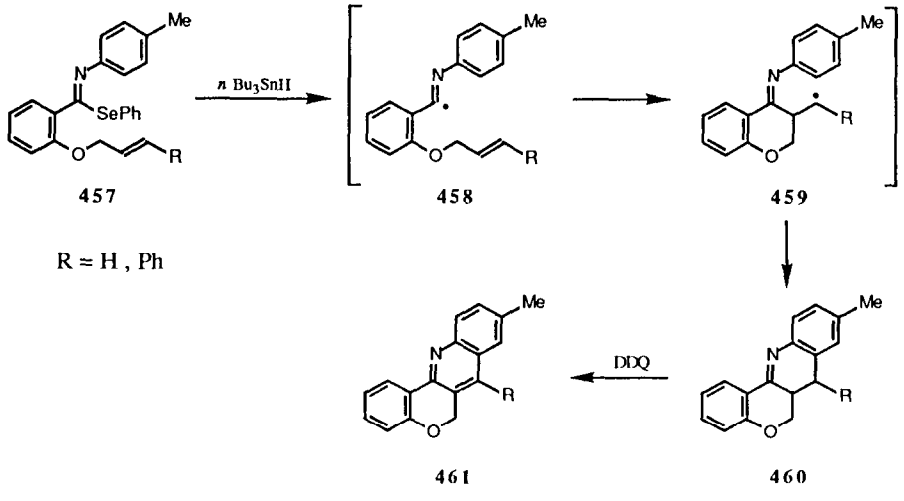
examples shown in Schemes 33 and 34 *N*-Benzylimidoyl radical **448** gives a quantitative yield of a 1 1 mixture of nitrile **449** and chromanone **451**, whereas the *N*-methyl analogue **455** (generated in a different manner as shown in Scheme 34) does not undergo fragmentation but gives solely, after hydrolysis, chromanone **451** in 60% yield

**Scheme 34**



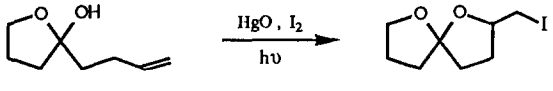

An example of tandem cyclisations (pathway "c" in Scheme 32) is given in Scheme 35 The resulting product **460** is further dehydrogenated with DDQ to provide a high yield of chromanoquinoline **461** (R=H, 86% form **457** , R=Ph, 84%) [127]

**Scheme 35**



## II.5 Alkoxy radicals and radical anions

The combination of iodocyclisation, a well known process, with alkoxy and peroxy radicals is gaining acceptance as an organic synthetic tool Irradiation of hydroxy homoallylic tetrahydrofuran **462** with mercuric oxide in the presence of iodine, a condition congenial to the generation of alkoxy radicals,[128] results in the formation of one isomer of spiroketal **463** in 68% yield (eq 91) [129] Other examples are shown in equations 92 and 93

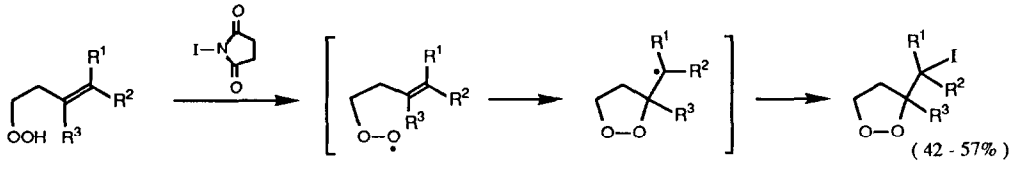



**462** **463** eq 91


**464** **465** eq 92


**466** **467** eq 93

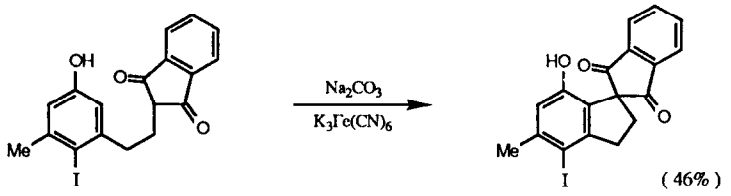
The reaction of unsaturated hydroperoxide **468** with an equimolar quantity of *N*-iodosuccinimide in dichloromethane at room temperature affords the dioxolane **471** (eq 94) [130] The mechanism of the reaction is believed to involve peroxy radical **469** rather than the conventional iodonium ion intermediate, the reason being that a 1 1 mixture of diastereoisomeric **471** is always obtained regardless of the starting geometry of the alkene




**468** **469** **470** **471**

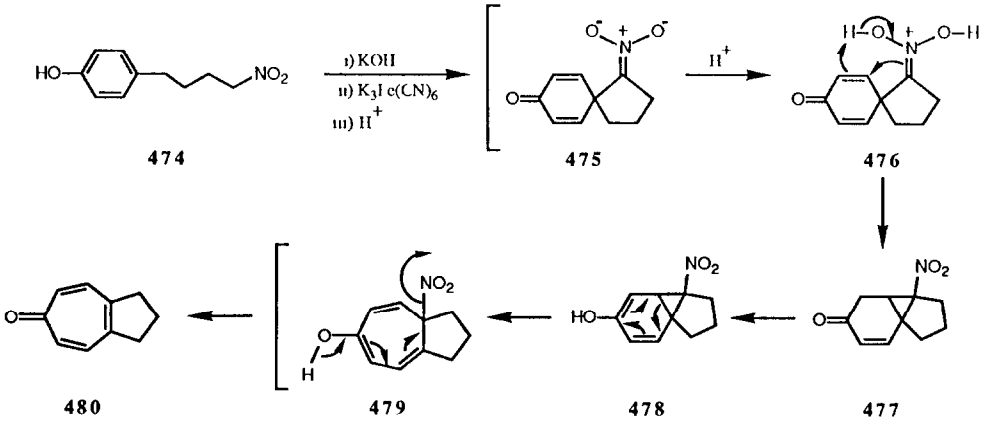
a) $R^1 = R^2 = R^3 = H$
b) $R^1 = R^2 = H$ , $R^3 = Me$
c) $R^1 = Et$ , $R^2 = R^3 = Me$
d) $R^1 = R^3 = H$ , $R^2 = Et$ eq 94

Kende[131] has studied intramolecular phenolic cyclisations such as phenolic β-diketone **472** to spirodiketone **473** (eq 95), and *p*-(nitrobutyl)phenol **474** to tropone **480** which constitutes a fantastically short and efficient synthesis (80% overall yield) of such tropone systems The mechanism of the reaction is proposed as shown in Scheme 36 [132]




**472** **473** eq 95

**Scheme 36**




**474** **475** **476** **477** **478** **479** **480**

Awareness of its enormous synthetic potential has led to a detailed mechanistic study of the reaction [133,134] In particular, the different results obtained with $K_3Fe(CN)_6$ and $K_2IrCl_4$ have been studied and rationalized in terms of the difference in oxidizing potentials (0 48 V and 0 89 V respectively) Consideration of the new findings in conjunction with former evidences and observations on related oxidative couplings has allowed the building of a complete mechanistic picture as illustrated in Scheme 37 [134] This can be summarized as follows

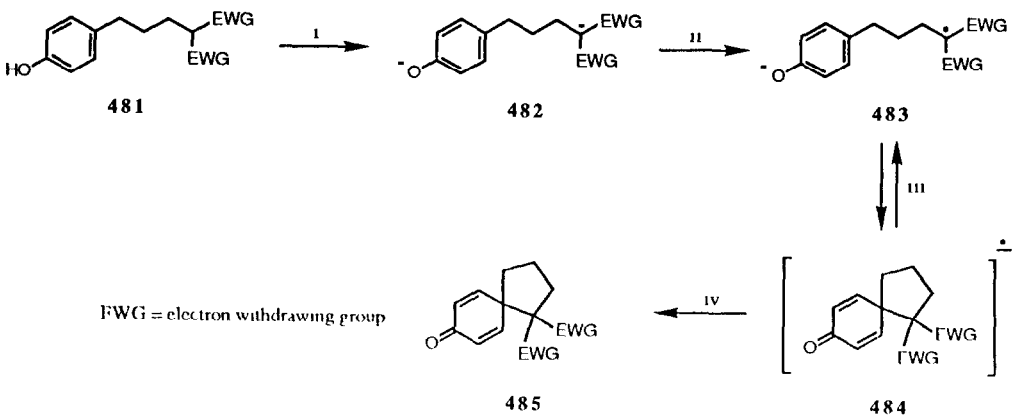
i) formation of dianion **482** by base,

ii) a one-electron oxidation of the enolate anion to form enol radical **483**,

iii) addition of the enol radical to the phenoxide ring to give radical anion intermediate **484**, followed by

iv) rapid electron transfer from the cyclised intermediate to yield product **485**

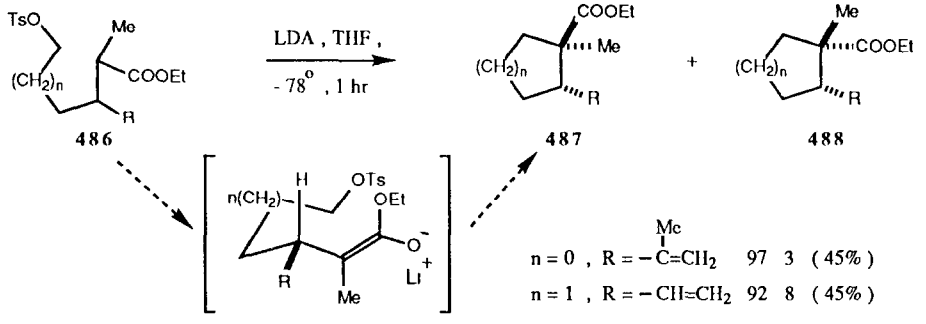
**Scheme 37**



# III. ANIONIC CYCLISATIONS

## III.1 Anionic cyclisations at $sp^3$ carbon

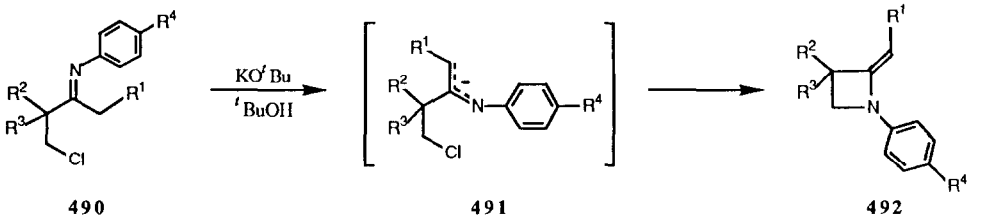
The simple-looking intramolecular nucleophilic displacement of tosylate group by ester enolate as depicted in equation 96 has been found to be highly stereoselective,[136,137] thus potentially useful in organic synthesis The stereoselectivity of the cyclisation is attributed to stringent conformational requirements of the transition state **489** as shown [138]




**486** **487** **488** **489**

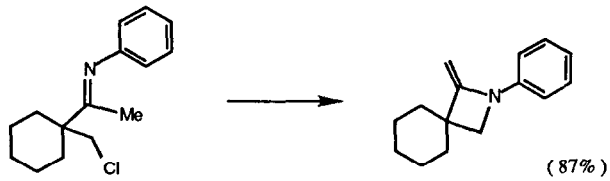
eq 96

A convenient general method is recently reported for the synthesis of methyleneazetidines 1-Azaallyl anion **491**, readily generated from **490**, undergoes intramolecular displacement of chloride to give, exclusively, 2-methyleneazetidines **492** in high yields The method is demonstrated in the synthesis of spiro- **494** (eq 98) and bicyclic compounds **496** (eq 99) [139] It is also found that the methyleneazetidines are stable only when aromatic substituents are present on nitrogen and water is excluded from the reaction procedures

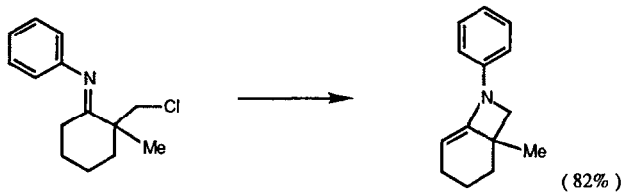



**490** **491** **492**

$R^1, R^2, R^3, R^4$ = H , Me ( 87 - 95% ) eq 97

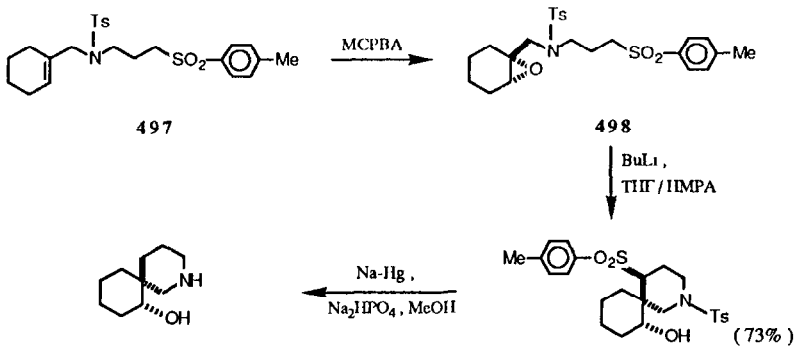



493 494 eq 98



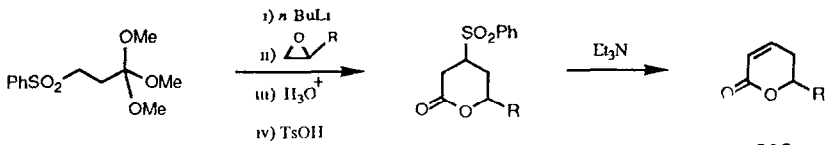

495 496 eq 99

A short and completely stereocontrolled synthesis of the alkaloid (±)nitramine **500** has been reported, the key step of which involves spirocyclisation of epoxy sulphone **498** (eq 100) [140]




497 498 499 500 eq 100

In another application, the carbanion derived from 3-phenylsulphonylorthopropionate **501** reacts with an epoxide to give, after acidic work up, the lactone **502** which subsequently yields **503** (eq 101) [141]




501 502 503

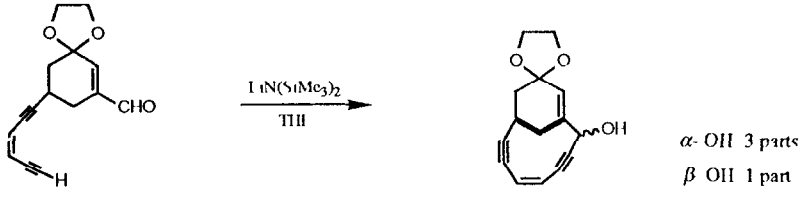
R = alkly, aryl (55 - 82%) eq 101

## III.2 Anionic cyclisations at $sp^2$ and sp carbons

Nucleophilic addition to $sp^2$ and sp centres constitutes a common approach to organic synthesis in general, consequently a multitude of examples are encountered

### Ring closure *via* addition to the carbonyl group

A reported synthesis of the strained bicyclo[7 3 1] trideca-4,9-diene-2,6-diyne system **505** (a common aglycone framework of novel antibiotics, the esperamicins[142] and calicheamicins,[143]) employs cycloaddition reaction in its key step [144] However, Kende[145] finds that such complex bicyclic systems can be directly synthesised by anion chemistry methodology Thus, inverse addition of **504** to a solution of $LiN(SiMe_3)_2$ in THF gives 42% yield of **505** (eq 102)



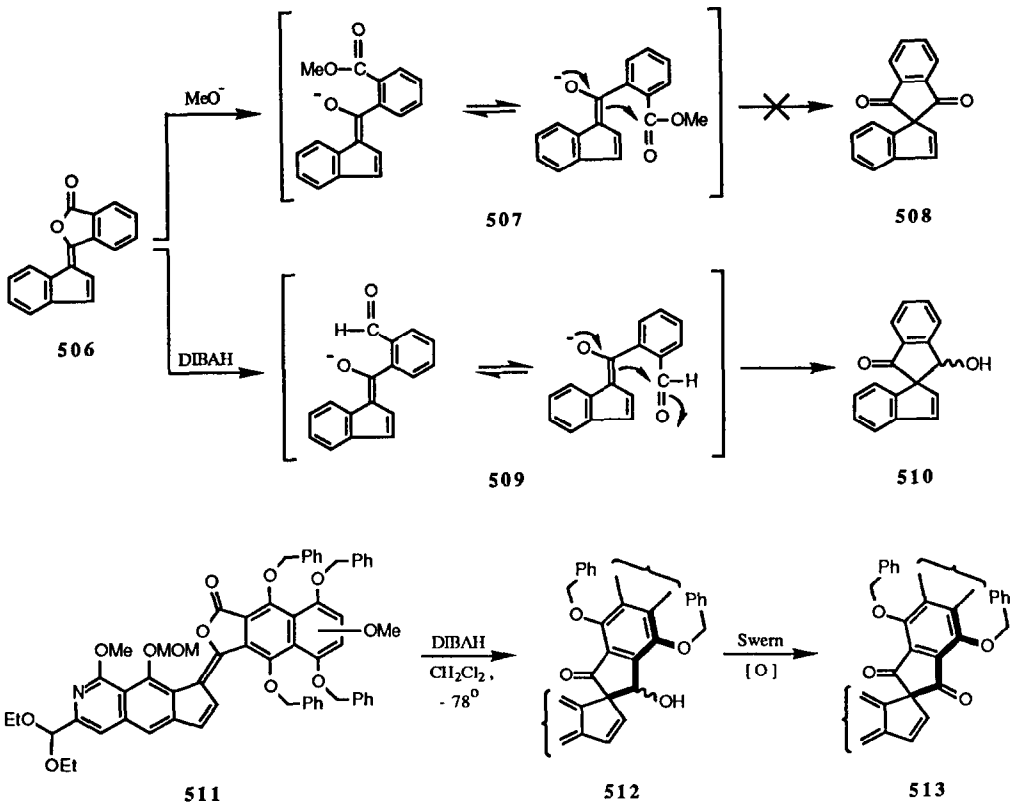

**504** **505**

eq 102

In a model study of the synthesis of spiro compound **513**, an important intermediate in the synthesis of fredericamycin A (*cf* eq 63), unsaturated lactone **506** is treated with sodium methoxide in anticipation of ring opening to give keto-enolate **507** which should then cyclise onto the ester carbonyl to give **508** Apparent failure is ascribed to the reaction being a disfavoured 5-(enol-*endo*)-*exo*-trig cyclisation[105] (*cf* Scheme 25) Surprisingly, however, the same type of cyclisation is found to proceed smoothly with aldehyde **509** (obtained from the treatment of **506** with DIBAH) to yield keto alcohol **510** Thus **513** is prepared in 50% overall yield from **511** as shown in Scheme 38 [146]

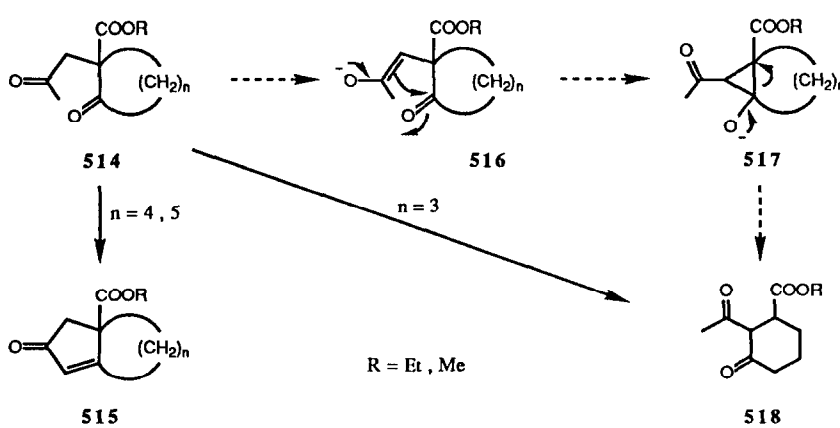
The perplexing 5-(enol-*endo*)-cyclisation will probably continue to baffle the chemist for a long while to come How far can Baldwin's rules be applied ? Take, for example, the greatly successful and widely used condensation of 1,4-diketones to cyclopentenones which involves a 5-(enol-*endo*)-cyclisation step [147] The reaction is assumed to be favourable under thermodynamically controlled conditions However, recent examples have been reported which prove that other factors also

**Scheme 38**



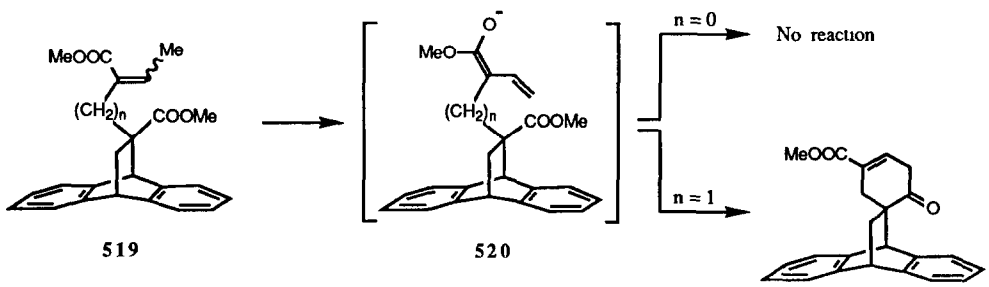

influence the cyclisation of these ketones As shown in Scheme 39, base-catalysed condensation of

**Scheme 39**



cycloalkanones **514** proceed as expected, when n = 4, 5, to give fused cyclopentenones **515**, but yields **518** when n = 3 [148]

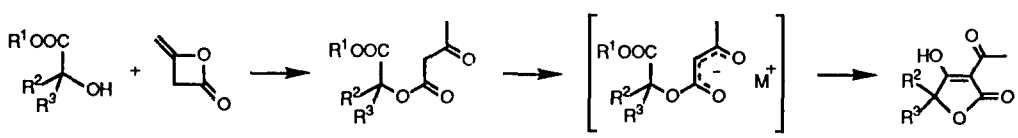
In fact a close encounter with Baldwin's rules was experienced in the author's synthesis of sarkomycin a few years ago [149] All attempts to cyclise anthracene adduct **519** (n = 0) failed but cyclisation took place when n = 1,[150] in keeping with the ruling of 5- and 6-(enol-*endo*)-cyclisations as favoured and disfavoured reactions respectively (eq 103)




519 520 521

eq 103

In principle the synthesis of 3-acetyltetronic acid derivative **526** should be easily achievable *via* cyclisation of **524**, as shown in equation 104 However, the reaction turned out to be neither straightforward nor general in application, being sensitive to i) substituent R, ii) solvent and iii) enolate counterion ($M^+$) [151]

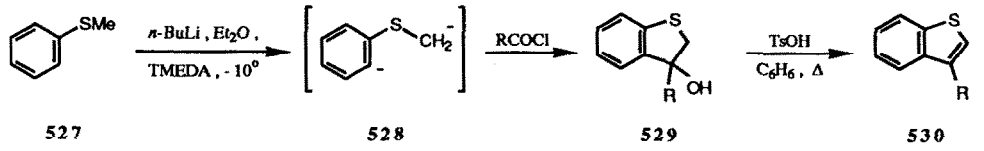



522 523 524 525 526

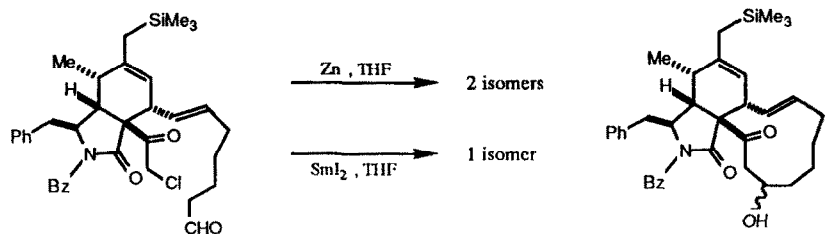
eq 104

Other interesting examples of anionic cyclisations involving addition of anion to the carbonyl group include the synthesis of benzothiophene **530** (eq 105)[152] and modified Reformatsky cyclisations as shown in equations 106 and 107 Particularly noteworthy is the novel use of $SmI_2$[153] in the construction of the macrocyclic ring (eq 106) to yield a single isomer,[154] in contrast to the formation of two diastereomers from the usual Reformatsky conditions reported earlier [155] Also

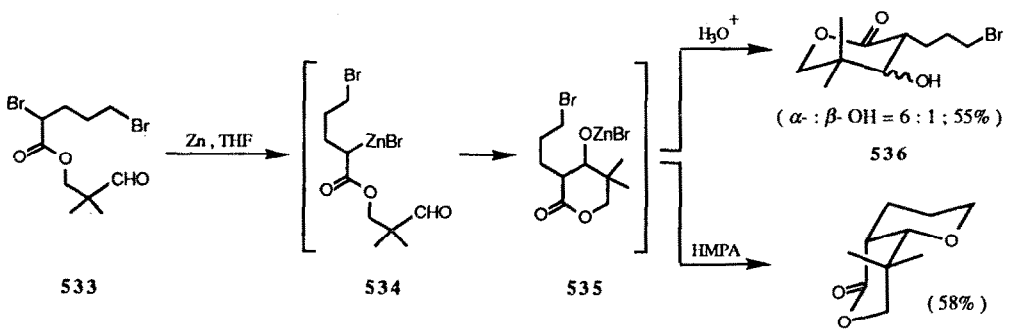
noteworthy is the incorporation of HMPA to promote bis-annulation in an otherwise normal Reformatsky reaction (eq. 107).[156] This model study paved the way for the synthesis of tricyclic lactam **539** in a study of daphniphyllum alkaloid synthesis as shown in equation 108 (*cf.* Scheme 12).



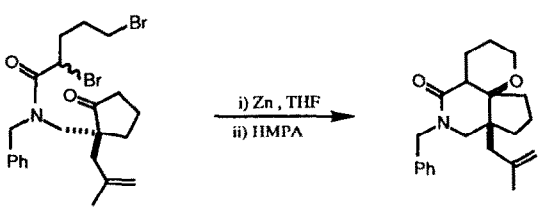

R = alkly , aryl ( 47 - 63% overall yields ) .... eq 105




.... eq 106



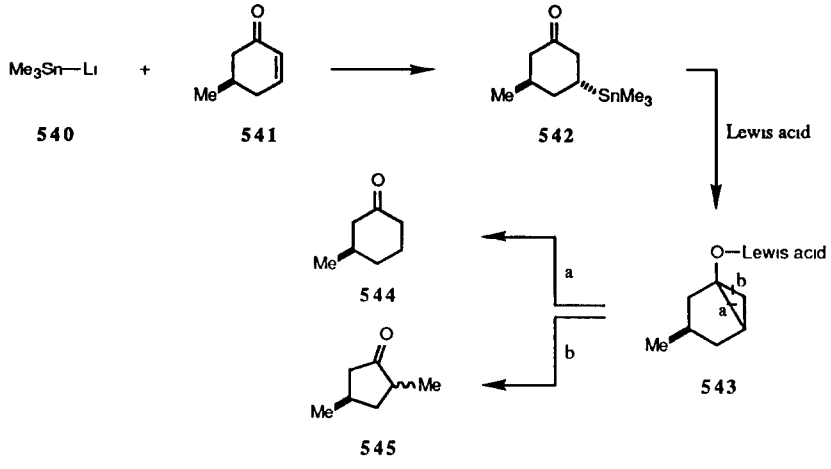

.... eq 107




.... eq 108

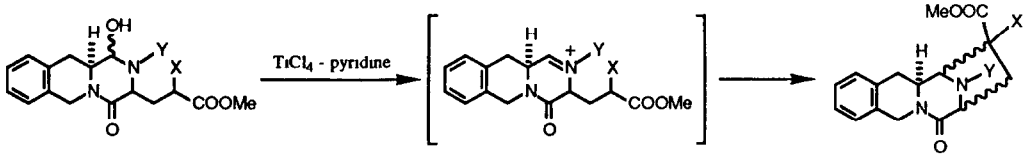
Taking advantage of an earlier discovery[157] that conjugate addition of trimethylstannyllithium **540** to methylcyclohexenone **541** gives mainly the *trans*-product **542**, Sato[158] treated **542** with Lewis acids and obtained two products derived from intermediate **543** The reaction can be manipulated to yield solely cyclopentenone **545** (52% *cis* *trans* = 1 28) by using trimethylsilyl trifluoromethanesulphonate (TMSOTf) as the Lewis acid (Scheme 40)

**Scheme 40**




**Ring closure *via* addition to iminium and thionium groups**

An interesting example of anionic cyclisation involving an iminium electrophilic centre is that shown in equation 109 Attempts to cyclise **546a** under various reaction conditions failed, until increasing the nucleophilic character of the starting material to **546b** successfully effected cyclisation to **548b** upon treatment with $TiCl_4$-pyridine in THF [159]

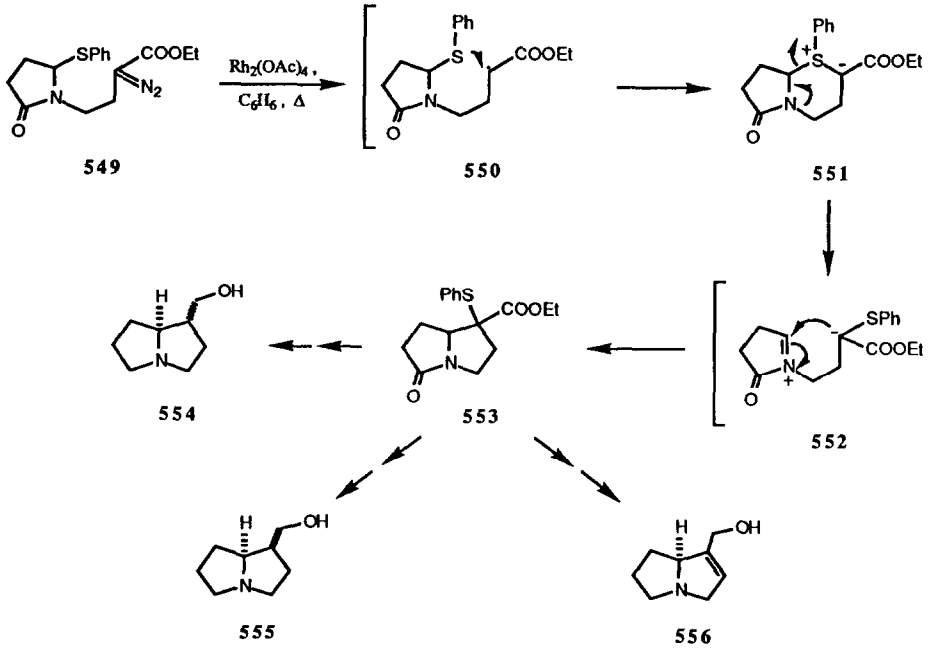



**546** a X = H , Y = $COOCH_2Ph$ **547** **548**

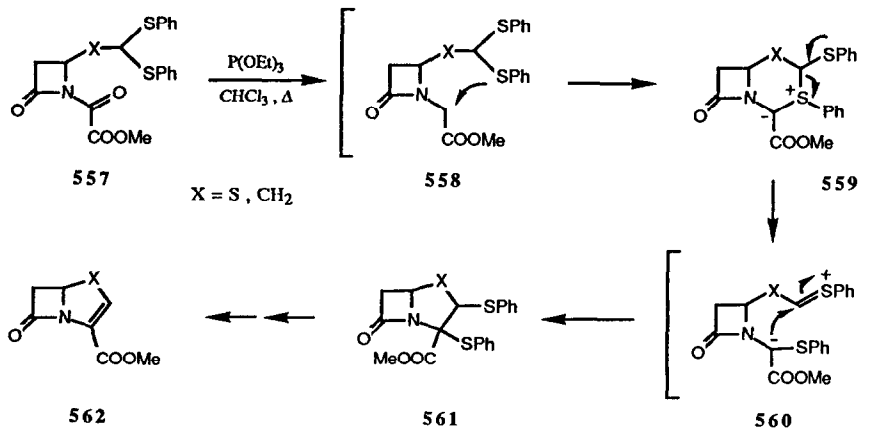
b X = COOMe , Y = $COOCH_2Ph$ eq 109

The synthetic strategy involving *in situ* formation of sulphonium ylides *via* sulphide-carbene interaction has received continuous attention [160-162] Very recently several pyrrolizidine alkaloids, i e trachelanthamidine **554**, isoretronecanol **555** and supinidine **556** have been synthesised *via* the sequence of carbene **550** → ylide **551** → cyclisation of zwitterion **552** as outlined in

**Scheme 41**

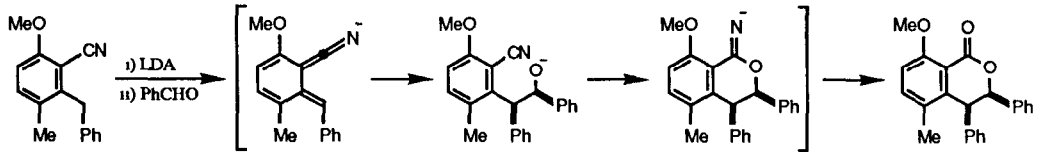



**Scheme 42**



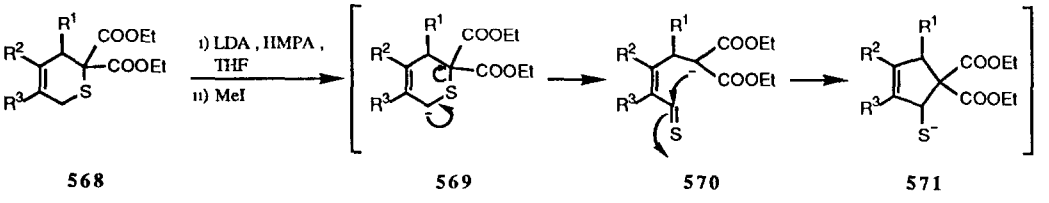
Scheme 41 [163] A similar approach, shown in Scheme 42, paved the way for the synthesis of penems and carbapenems [164] Both processes (Schemes 41 and 42) exploit anion addition, to an iminium ion in the former and to a thionium ion in the latter

Cyclisations involving nucleophilic addition to other electrophilic centres, i e -C≡N and >C=S, have been applied to the syntheses of functionalized isochromanone **567**[165] and cyclopentenes **572**[166] respectively (eq 110, 111)

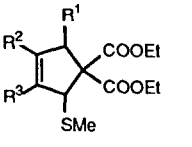



**563** **564** **565** **566** **567** (70%)

eq 110




**568** **569** **570** **571**




$R^1 = R^2 = R^3 = H$, alkyl (70 - 90%)

**572**

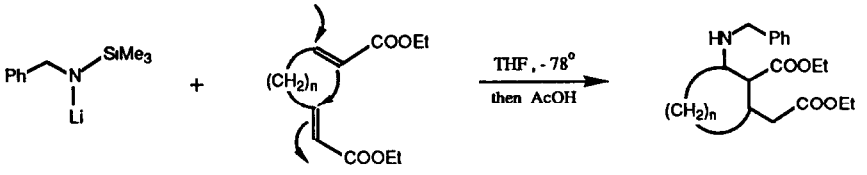
eq 111

## Ring closure involving Michael additions

Cyclisations initiated or triggered by Michael addition reactions have long been in popular use in the synthesis of simple and complex molecules The reaction allows the assembly of several structural components in one single operation Many of these cyclisations also exhibit high stereoselectivity and high asymmetric induction, e g equation 112 [167,168]

573 574 eq 112

Lithium *N*-benzyltrimethylsilylamide **575** is an excellent nucleophile which adds to crotonate

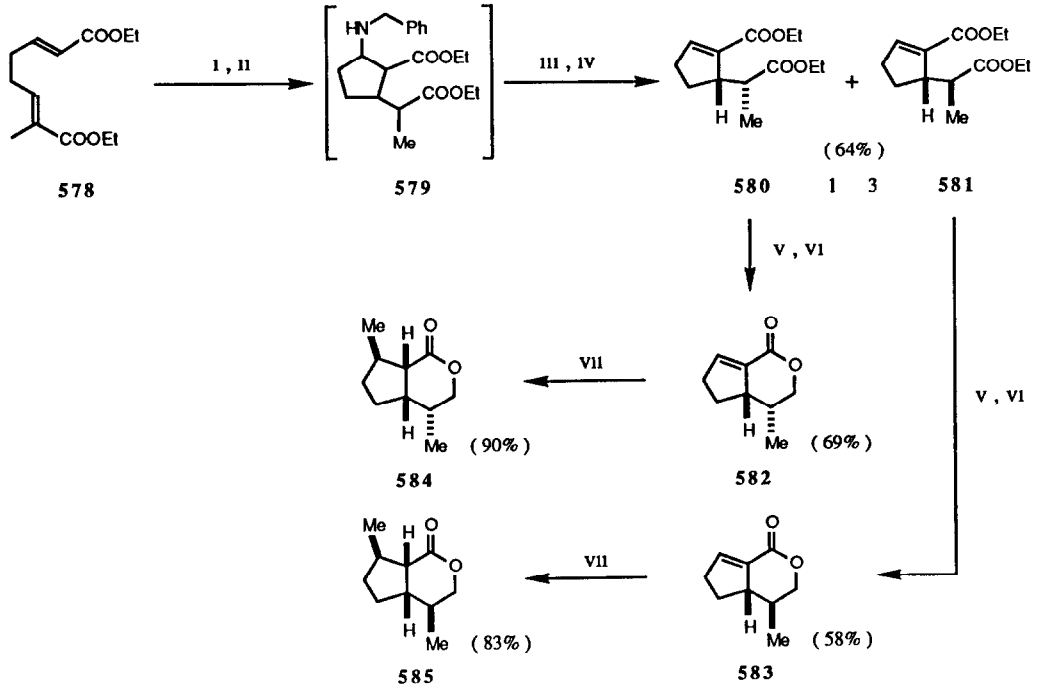


575 576 577

n = 2 (78%)

n = 3 (93%) eq 113

**Scheme 43**

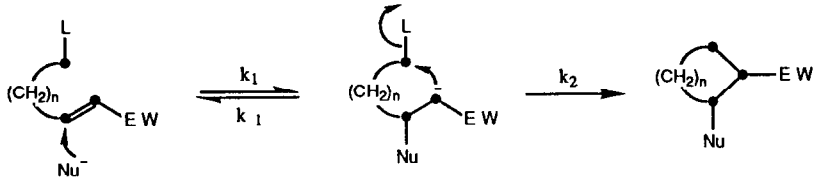


Reagents · i)  ii) $H^+$ iii) MeI, $K_2CO_3$ iv) $SiO_2$, xylene v) $LiAlH_4$ vi) $MnO_2$ vii) $Me_2CuLi$

derivatives only in Michael fashion [169] Thus it is ideal for initiating double Michael addition reactions as shown in equation 113 [170] Application of the reaction is demonstrated in the synthesis of bioactive lactones **584** and **585** as illustrated in Scheme 43

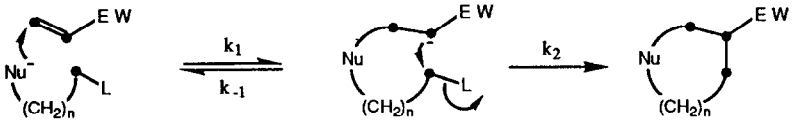
The term MIRC (**M**ichael **I**nitiated **R**ing **C**losure) was coined by Little in 1980[171] for the reaction between two reactants which involves i) nucleophilic conjugate addition to an $\alpha,\beta$-unsaturated carbonyl compound followed by ii) ring closure by the resulting enolate As a matter of fact these are not novel reactions but earlier reports are rather scattered The course of reaction is categorized as Type I or Type II as outlined in equations 114 and 115

**Type I**




**586** **587** **588** eq 114

**Type II**

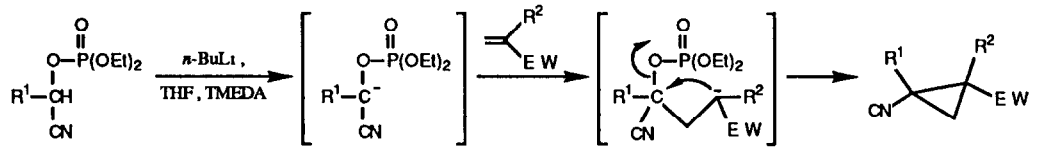



**589** **590** **591** eq 115

E W = Electron Withdrawing group , L = Leaving group

The success of the MIRC reaction in general depends on two factors first, stability of the Michael addition intermediate (**587** or **590**) relative to the nucleophile (as in **586** or **589** respectively) and second, rate of cyclisation ($k_2$) [172,173] The reactions shown in equation 113 and Scheme 43 are in fact examples of Type I MIRC cyclisations which are very useful for the preparation of cyclic compounds of various ring sizes [171-175]

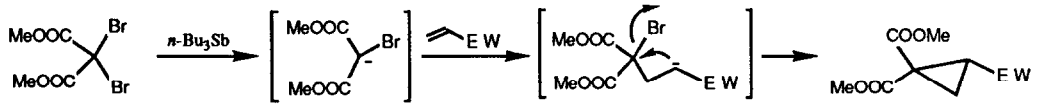
Type II MIRC cyclisations have lately enjoyed increasing use with innovative substrates Carbocycles, particularly cyclopropane derivatives, can be easily prepared Equations 116-121 demonstrate the versatility of the reaction




592 593 594 595

E W = COOEt , CN , $R^1$ = Aryl , -CH=CH-R , $R^2$= H , Me (40 - 85%)

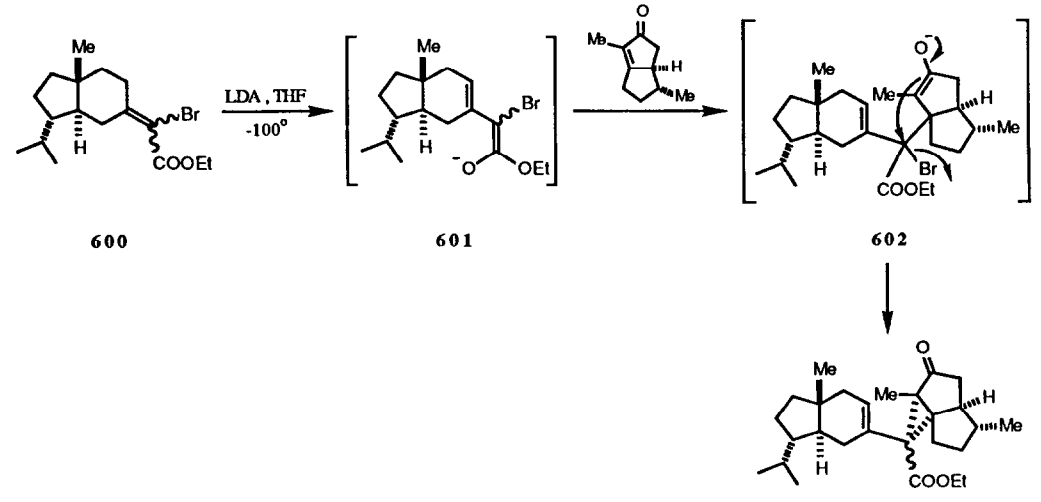
eq 116[176]




596 597 598 599

E W = CHO (86%)
= COMe (84%)
= CN (59%)
= COOEt (43%)

eq 117[177]

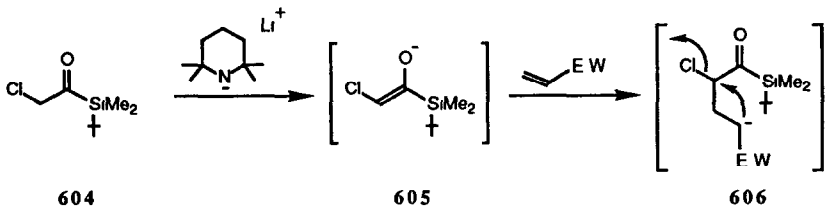



600 601 602

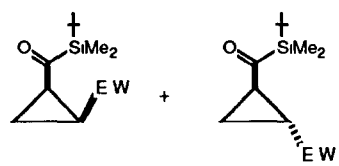
50% ( 1 1 mixture )

603

eq 118[178]



604 605 606

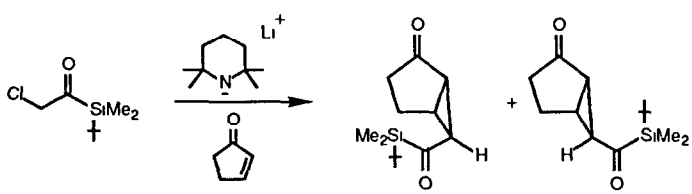


EW = COMe (75% , 19 1)
= COOEt (83% , 35 1)

major minor

607 608

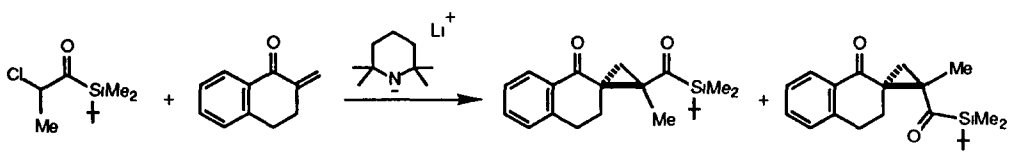
eq 119[179]



604 609 610

25 1 (41%)

eq 120[179]



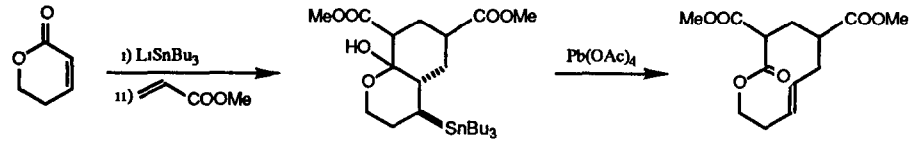
611 612 613 614

7 1 (83%)

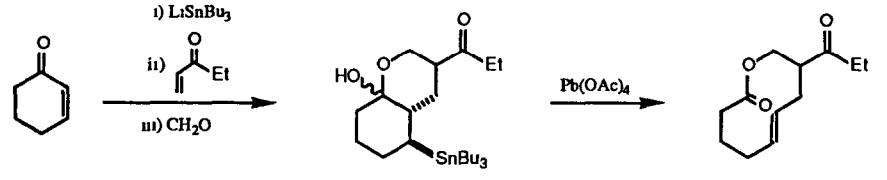
eq 121[179]

Numerous types of cyclisation initiated by Michael addition are known and have been superbly documented [180] These include the double Michael addition (Michael-Michael-ring closure, MIMIRC) and triple Michael addition (Michael-Michael-Michael-ring closure, MIMI-MIRC) of two or more reacting components Two of the most recent examples are shown below Equation 122 illustrates triple Michael addition of four reacting components while equation 123 presents the Michael-Michael-

aldol-ring closure process (MIMI-ARC) Tri-*n*-butylstannyl anion serves a dual purpose in both reactions, first as Michael addition initiator and then as leaving group in the final step [181]

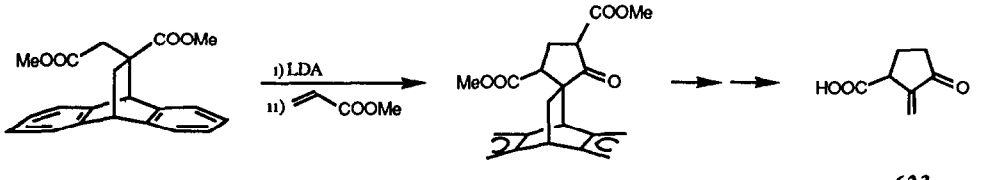



615 616 617 eq 122



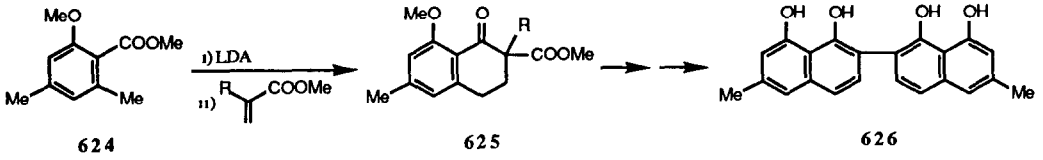

618 619 620 eq 123

Of special interest is the use of tandem Michael addition-Dieckmann cyclisation as key steps in the short and efficient syntheses of antibiotic sarkomycin **623**[149] and anthelmintic diospyrol **626**.[182,183] The acrylate unit conveniently serves as the Michael acceptor in both processes, reacting with itaconate anion (derived from **621**) in the former and with toluate anion (from **624**) in the latter (eq 124, 125 respectively)




621 622 623

eq 124



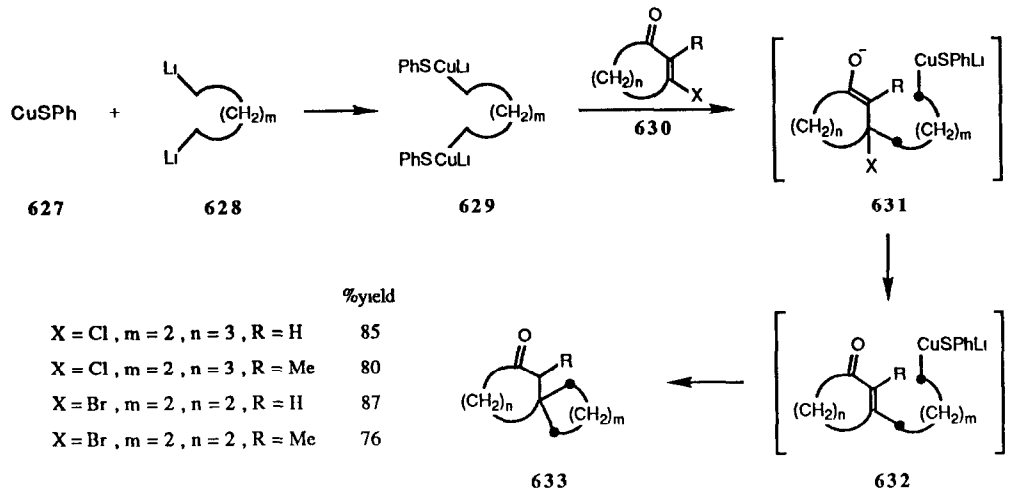

624 625 626

eq 125

A new class of reagents, the organobis(thiocuprates) **629**, readily prepared as shown in Scheme 44, are extremely efficient nucleophiles in a one-pot synthesis of spiro compounds[184] (e g

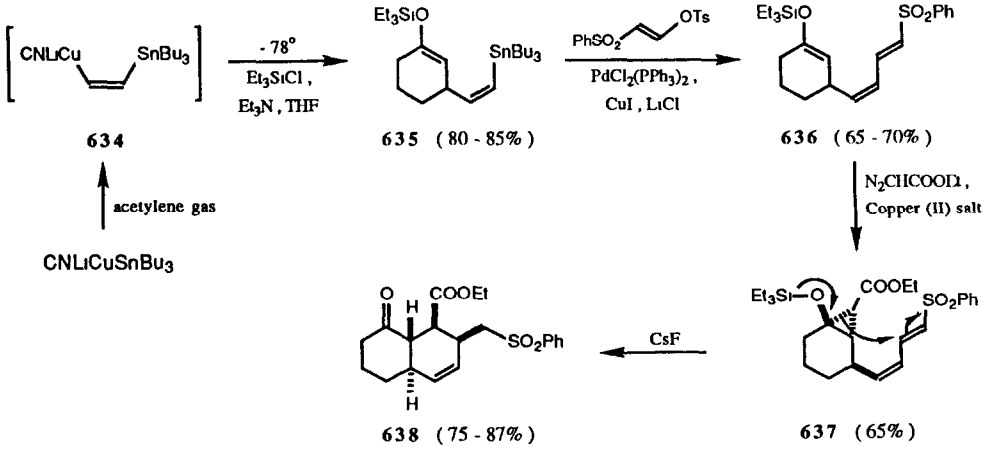
[4 4]nonanes, [4 5]decanes and [5 5]undecanes) The reaction mechanism involves sequential Michael addition-elimination-Michael addition

**Scheme 44**




Another organocuprate reagent, *cis*-2-tri-*n*-butylstannylvinyl cuprate **634**, also plays an important role in the process shown in Scheme 45 [185] The cuprate **634** first adds to cyclohexenone, then undergoes the Stille reaction[186] to give **636**, which is cyclopropanated to give **637**, before eventually cyclising *via* a cyclopropane ring opening-Michael addition sequence to yield **638**

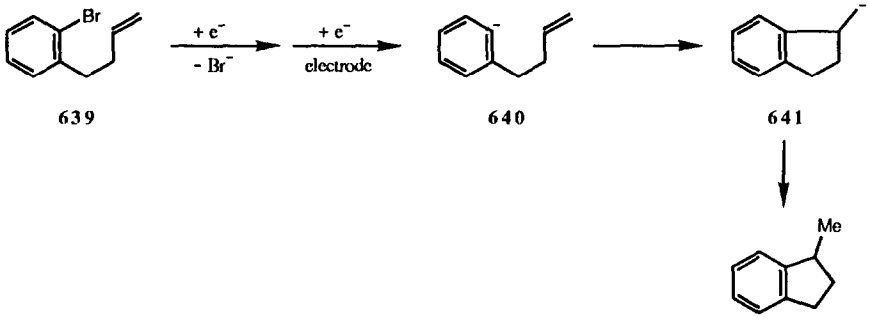
**Scheme 45**



**Ring closure *via* addition to the unactivated olefinic bond**

Unlike the cationic- and radical-initiated polyolefinic cyclisations which are now well established methods for the construction of complex polycyclic systems, the anionic counterpart remained, until very recently, unprecedented (The foregoing examples have all involved activated olefinic bonds) However, research in the last few years have shown promising results and chemists are optimistic that the reactions may yet turn to be useful tools in organic synthesis

Electrochemical reduction of *o*-(3-butenyl)bromobenzene **639** in DMF in the presence of tetrabutylammonium perchlorate (TBAP) evidently generates **640** which cyclises and is finally isolated as indane **642** in moderate yield after work up (eq 126) [187]




639 640 641 642 eq 126

A report on the generation of alkenyllithiums and their cyclisation products appeared in 1987 [188] It was shown that treatment of 6-iodo-1-hexene with *t*-BuLi in pentane/ether with or without TMEDA at -78$^0$ effects metal-halogen exchange to give the organometal **644** which can be trapped by various electrophiles On warming to room temperature, however, the anion cyclises in a 5-*exo*-trig fashion similar to that observed with radicals, giving **645** which is isolated as **647** (Scheme 46) Detailed experimental results shown in Table 3 indicate that the yields of cyclised products are variable

An earlier reported treatment of allylstannylmethyl ether **648** with butyllithium results in a tin-lithium exchange to give **649** which smoothly undergoes anionic [3,2]-sigmatropic rearrangement to **651** [189] In contrast, substitution of the allylic with a homoallylic group entirely alters the course of reaction Here (**653**), sigmatropic rearrangement is not possible, and intramolecular cyclisation occurs instead to give **655** (predominantly the *cis*-isomer) in 54% yield (Scheme 47) [190]

**Scheme 46**

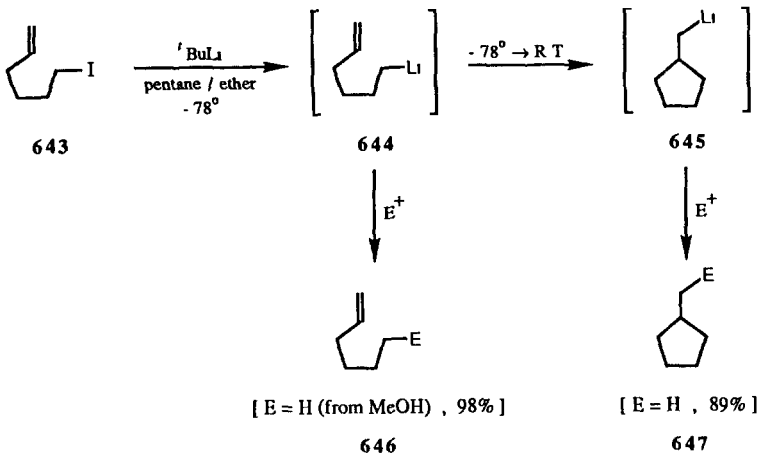
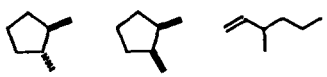
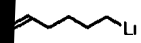
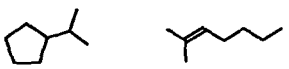
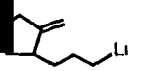
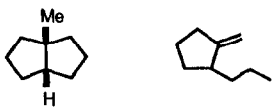
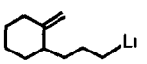
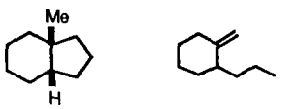
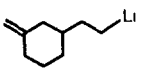
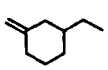
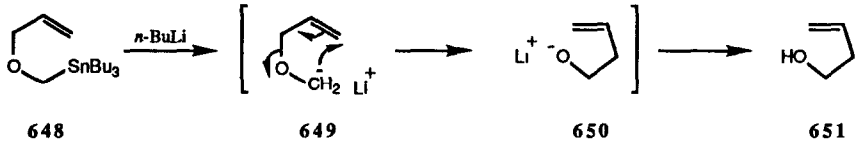


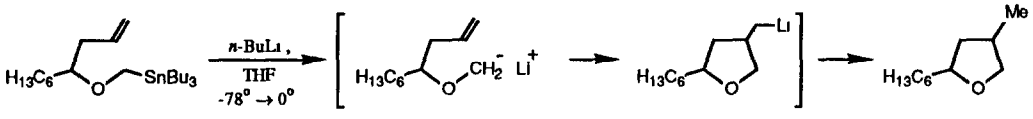

**Table 3** Cyclisation of alkenyllithiums [ degassed MeOH used as eletrophile ]

| Entry | Alkenyllithium | TMEDA (eq.) | Time at R T (hr) | Products ( %yield , GLC analysis ) |
|---|---|---|---|---|
| 1 | [redacted] | [redacted] | 1 |  (76) (56) (142) |
| 2 |  | 0 | 3 |  (56) (863) |
| 3 |  | [redacted] | 3 |  (15) (84) |
| | | 2 | 4 | (62) (15) |
| 4 |  | 0 | 5 |  (65) (35) |
| | | 2 | 4 | (94) (51) |
| 5 |  | 2 | 3 | -  (>98) |

**Scheme 47**

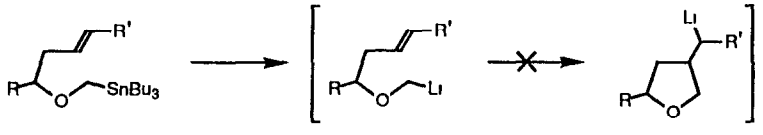



**648** **649** **650** **651**



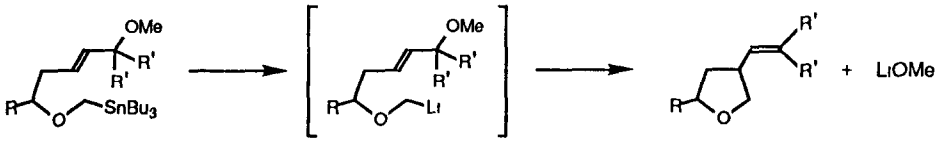

**652** **653** **654** **655**

An interesting observation of the reaction is that no cyclised product can be obtained with **656** The explanation put forward is that the secondary carbanion **658** is electronically less favourable than its primary counterpart **657** This reasoning also accounts for the poor yield of cyclised product



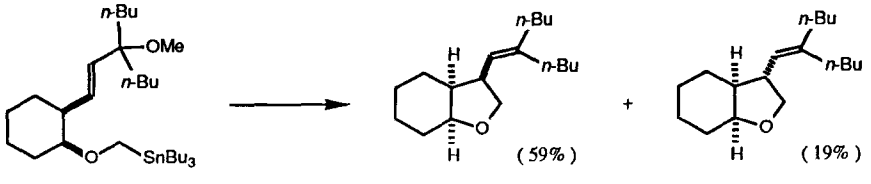

**656** **657** **658**

a) R = H , R' = *n*-decyl
b) R = *n*-octyl , R' = *n*-propyl eq 127




**659** **660** **661**

R = *n*-hexyl , R' = H ( 85% , *cis* *trans* = 13 1 )
R = *n*-hexyl , R' = Me ( 80% , *cis* *trans* = 10 1 ) eq 128

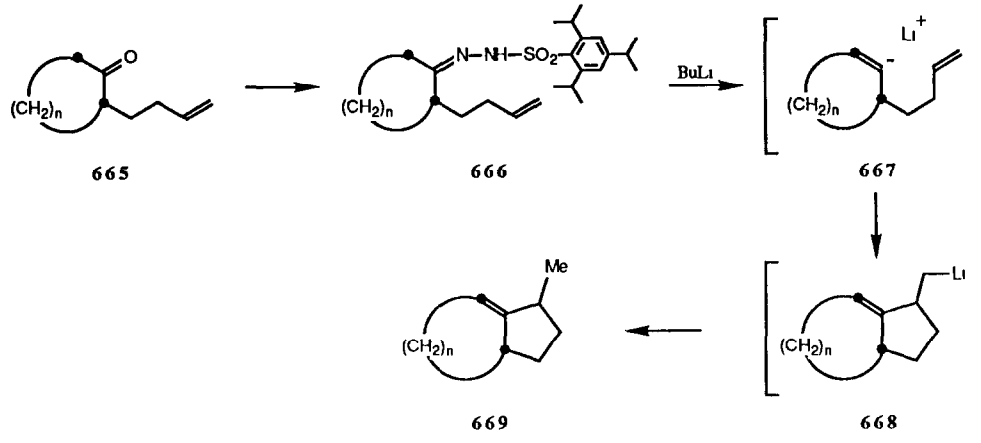



**662** **663** **664** eq 129

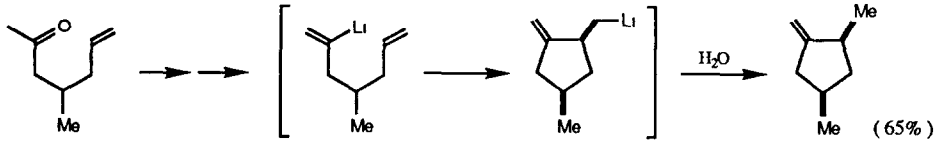
in entry 2 of Table 3 Replacing the allylic substituent with good leaving groups (e g **659**, **662**), on the other hand, leads to smooth cyclisation as might be expected (equations 128, 129) [190]

Similar cyclisation is also observed with the vinyllithium reagent **667**, generated from the corresponding hydrazones (Scheme 48) [191]

**Scheme 48**




However, the reaction seems favourable only when n = 2 , when yields of product **669** are 49-87% Yields are extremely poor when n = 3 Nevertheless, the reaction appears to operate quite well with open chain substrates (equation 130)



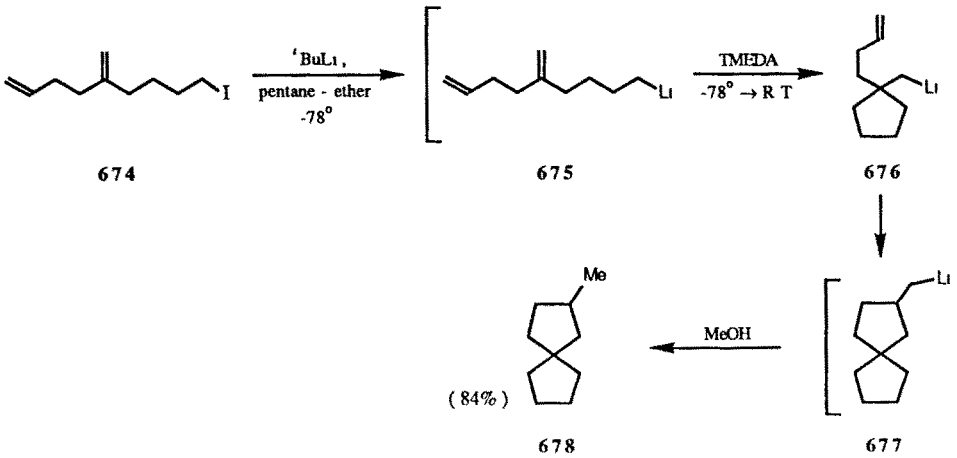

eq 130

Apart from the anionic reactions so far discussed there are also other recent examples whose mechanism, though not yet certain, could well involve the same type of anion-initiated cyclisation [192]

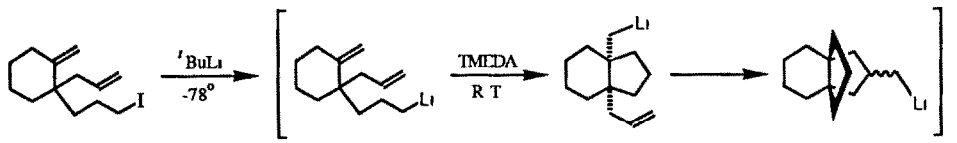
Soon after basic research had conclusively established the viability of intramolecular cyclisation of organolithium reagents onto unactivated olefinic bonds, dramatic tandem anionic

cyclisations were announced [193] As outlined in Schemes 49 and 50, spiro[4 4]nonane **678** and functionalized [4 3 3]propellanes **683** can indeed be obtained in quite respectable yields *via* tandem anionic cyclisations

**Scheme 49**




**Scheme 50**




| $E^+$ | E | %yield of 683 |
|---|---|---|
| MeOH | H | 81 |
| MeOD | D | 75 |
| $CO_2$ | COOH | 60 |
| PhCHO | CH(OH)Ph | 80 |
| MeCOMe | $C(OH)Me_2$ | 80 |
| $Br\text{-}CH_2\text{-}CH{=}CH_2$ | $CH_2\text{-}CH{=}CH_2$ | 82 |
| $Cl\text{-}SiMe_3$ | $SiMe_3$ | 73 |

Important features of the above reactions appear to the following i) a fast metal-halogen exchange at low temperature is essential for a successful, efficient cyclisation (lithium-iodine

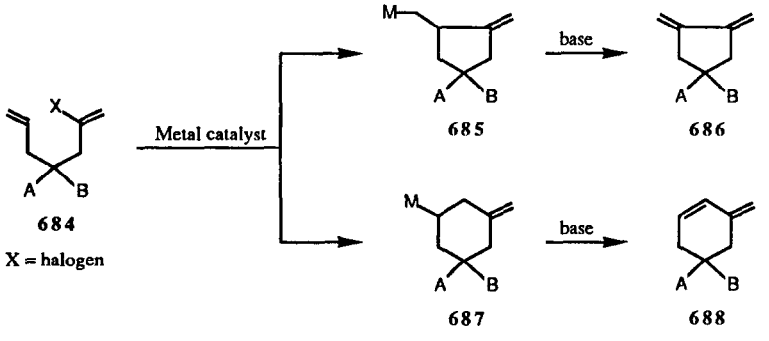
exchange is much more effective than lithium-bromine or lithium-chlorine),[194] ii) the presence of TMEDA is also necessary, iii) the reaction favours the 5-*exo*-trig pathway in the same manner as radical cyclisation and iv) functionalization of the final anion (cyclisation product, e g **682**) is easily accomplished This last feature of the reaction is good indication that further cyclisation(s) are feasible provided the presence of appropriately placed olefinic substituents in the molecule It is indeed exciting to watch for the outcome of future development of the reaction and the direction that it will take towards complex organic synthesis

# IV. METAL-PROMOTED CYCLISATIONS

The explosive growth of current research in the area of metal-catalysed reactions merits a comprehensive review of its own, this has recently appeared [195-197] Nevertheless, the latest developments, especially regarding cyclisation reactions, deserve further documentation

## IV.1 Carbon-carbon bond formation

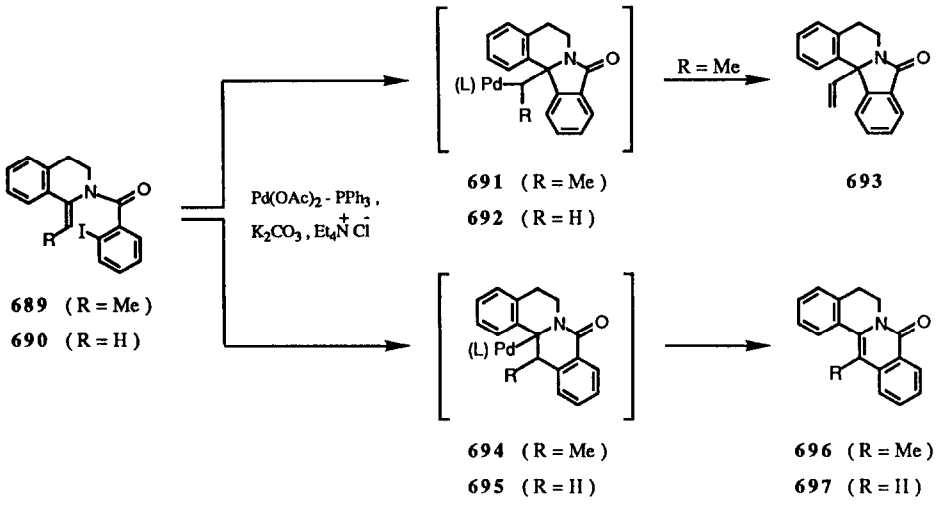
The most widely used metal-catalysed reaction for C-C bond formation, the Heck reaction,[198] is used to construct 5- and 6-membered rings with the aid of a Palladium catalyst The dependence of reaction pathway on the choice of metal catalyst, base and reaction conditions permits manipulations, e g of substrate **684**, to yield cyclopentane **686** and/or cyclohexene **688**, *via* 5-*exo*-trig or 6-*endo*-trig cyclisations respectively (eq 131)



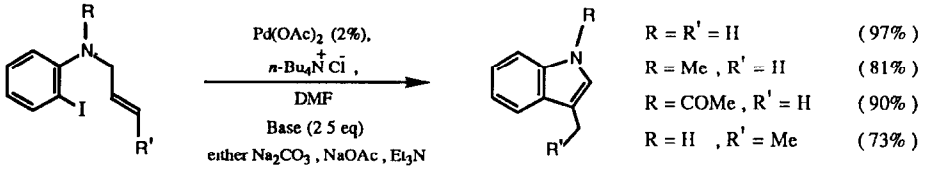

eq 131

Similar to that observed with radical and anionic cyclisations, the 5-*exo*-trig mode seems, in general, to be the preferred pathway unless otherwise manoeuvred A good example is shown in Scheme 51 where palladium acetate-catalysed cyclisation of **689** yields a mixture of **693** and **696** in a 4 1 ratio, while the reaction of modified substrate **690** gives only **697** [199] The rationale for the latter behaviour is that organopalladium intermediate **692** from a 5-*exo*-trig cyclisation of **690** lacks the necessary $\beta$-hydrogen to eliminate to the product Therefore, the reaction is forced to take the 6-*endo*-trig path *via* **695** to the observed **697**

**Scheme 51**




A variety of weak bases may be employed for the elimination of the Pd-H fragment in the last step of the Heck reaction Tertiary amines, carbonates, bicarbonates or acetates of sodium or potassium are all comparable Characteristically, the Heck reaction is superior to other metal-catalysed cyclisations, as testified by the impressive yields obtained in the preparation of indole derivatives shown in equation 132 Cobalt and Nickel complexes can also serve as catalysts, albeit with much lower efficiency than Palladium [200]

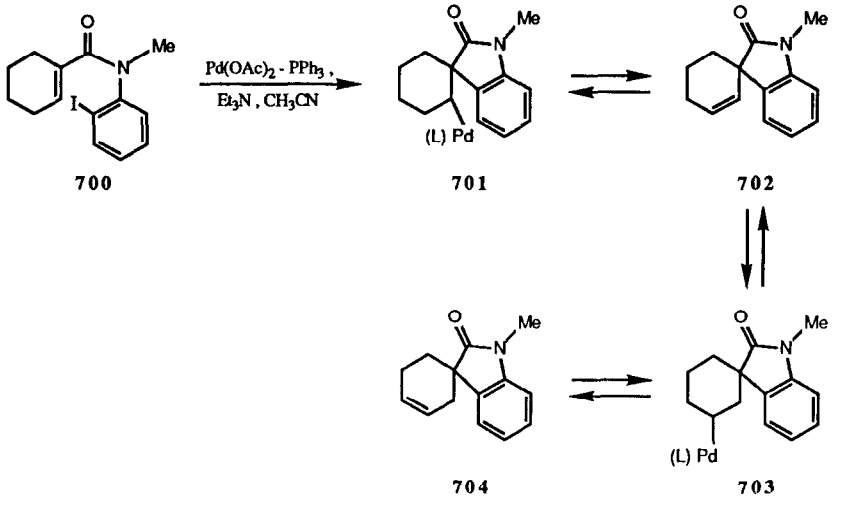



**698** **699** eq 132

The frustrating isomerisation of double bond observed in the products in certain cases is only recently understood For instance, the cyclisation of iodo-compound **700** with palladium acetate-triphenylphosphine catalyst produces lactam **702** and its double bond isomer **704** in a 1 1 ratio The latter product is now believed to arise from re-addition-elimination of the Pd-H species to **702** *via* the intermediacy of **703** (Scheme 52) This mechanism is consistent with the finding that addition of silver nitrate to the reaction suppresses double bond isomerisation, resulting in a 26 1 mixture (70%

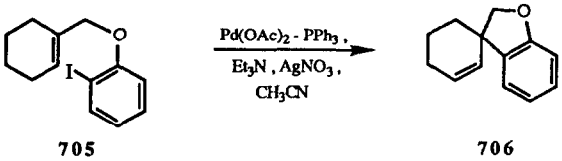
yield) of products **702** and **704** The silver salt probably traps the hydriodic acid generated in the reaction and thus stops re-addition of the Pd-H species to **702** [201] Further examples are presented in equations 133-135

**Scheme 52**

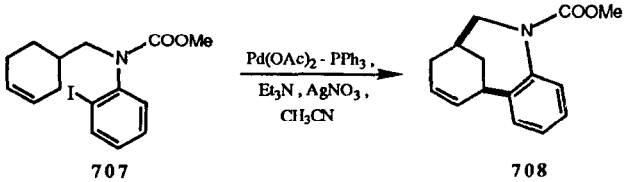



**700** $\xrightarrow[Et_3N,\ AgNO_3,\ CH_3CN]{Pd(OAc)_2 - PPh_3,}$ **702** + **704**

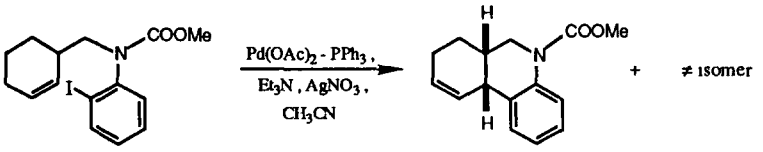
26 1 (70%)




34 1 (71%) eq 133



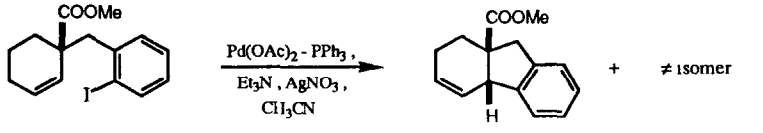

4 1 (83%) eq 134




709 710

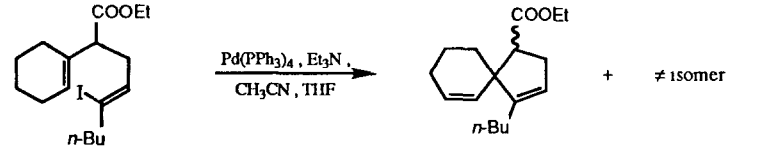
19 1 (74%) eq 135

Apart from the synthesis of heterocyclic compounds, the Heck reaction also offers great versatility in the construction of various fused, bridged and spirofused carbobicyclic and carbopolycyclic compounds, with the use of a variety of palladium catalysts e g $Pd(PPh_3)_3$, $Pd(OAc)_2$ or $Pd(OAc)_2$-$PPh_3$ (eq 136-140)



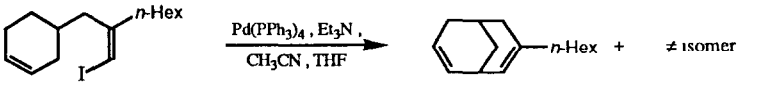

711 712

30 1 (86%) eq 136[201]



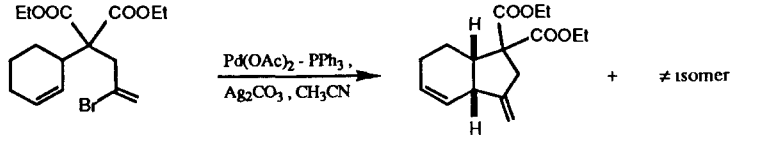

713 714

4 1 (86%) eq 137[202]



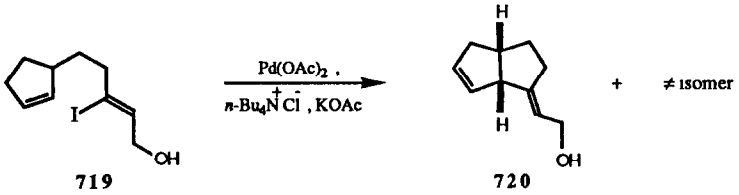

715 716

9 1 (70%) eq 138[202]




717 718

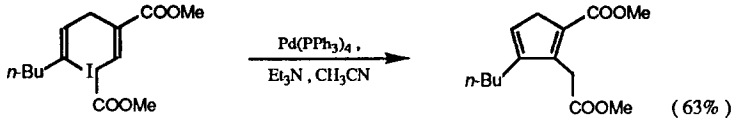
10 1 (91%) eq 139[203]



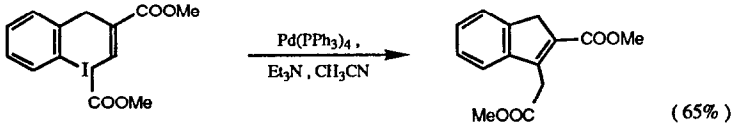

719 720

28 1 (61%) eq 140[203]

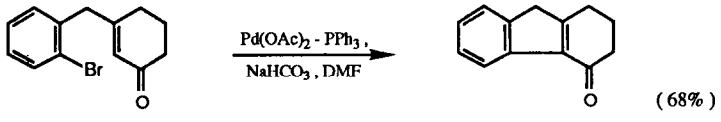
The problems of reduced regioselectivity and double bond isomerisation in the Heck reaction can be controlled by the incorporation of an $\alpha,\beta$-unsaturated carbonyl group Palladium-catalysed cyclisations of alkenyl and aryl halides containing appropriately placed $\alpha,\beta$-unsaturated carbonyl groups are highly regioselective (eq 141-145) and formation of exocyclic double bonds in the products are also stereoselective (eq 144, 145) [204]



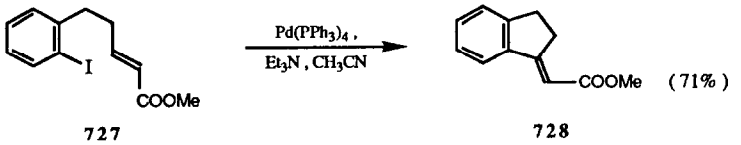

721 722 (63%) eq 141



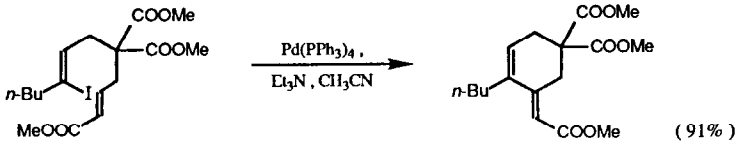

723 724 (65%) eq 142




725 726 (68%) eq 143



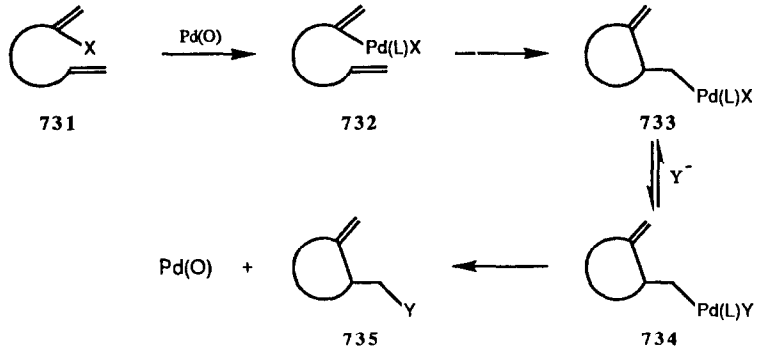

727 728 (71%) eq 144



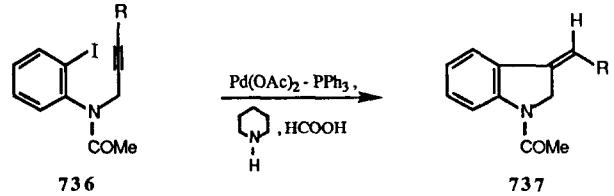

729 730 (91%) eq 145

Prior to elimination to product, the advanced intermediate **733** in the Heck reaction may be captured by hydride or other anions according to a recently proposed mechanism shown in Scheme 53 [205]

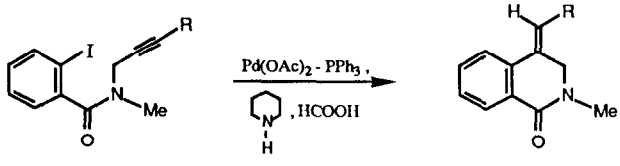
**Scheme 53**



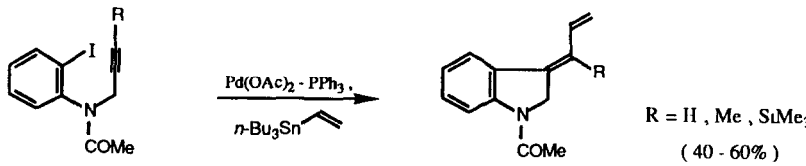

The tandem cyclisation-anion capture process shown above will predictably become a valuable methodology in future organic synthesis The reaction is conducted with a catalyst composed of 10 mol % palladium acetate and 20 mol % triphenylphosphine in acetonitrile, and with the addition of piperidine (4 mol) and formic acid (3 mol) which provide the base and hydride ion source (eq 146, 147) [205] Besides piperidine-formic acid, organotin compounds can also be used to capture the intermediate palladium complex (eq 148, 149) [206] With $\pi$-allylpalladium intermediates such as **743** or **745**, organotin adds in conjugate addition fashion to yield products **744** or **746** respectively (eq 150, 151) [206]



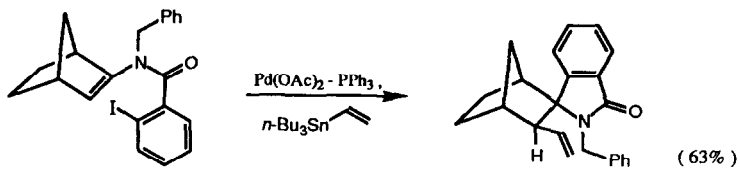

736 737 eq 146



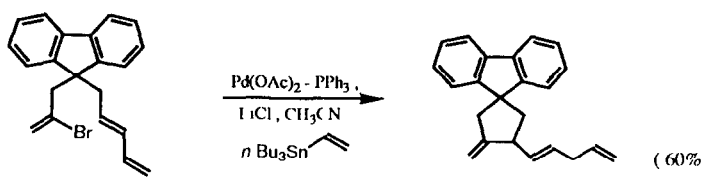

738 739 eq 147



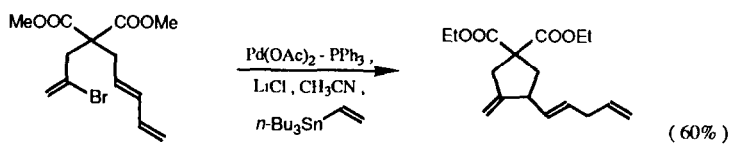

736 740 eq 148




741 742 eq 149




743 744 eq 150

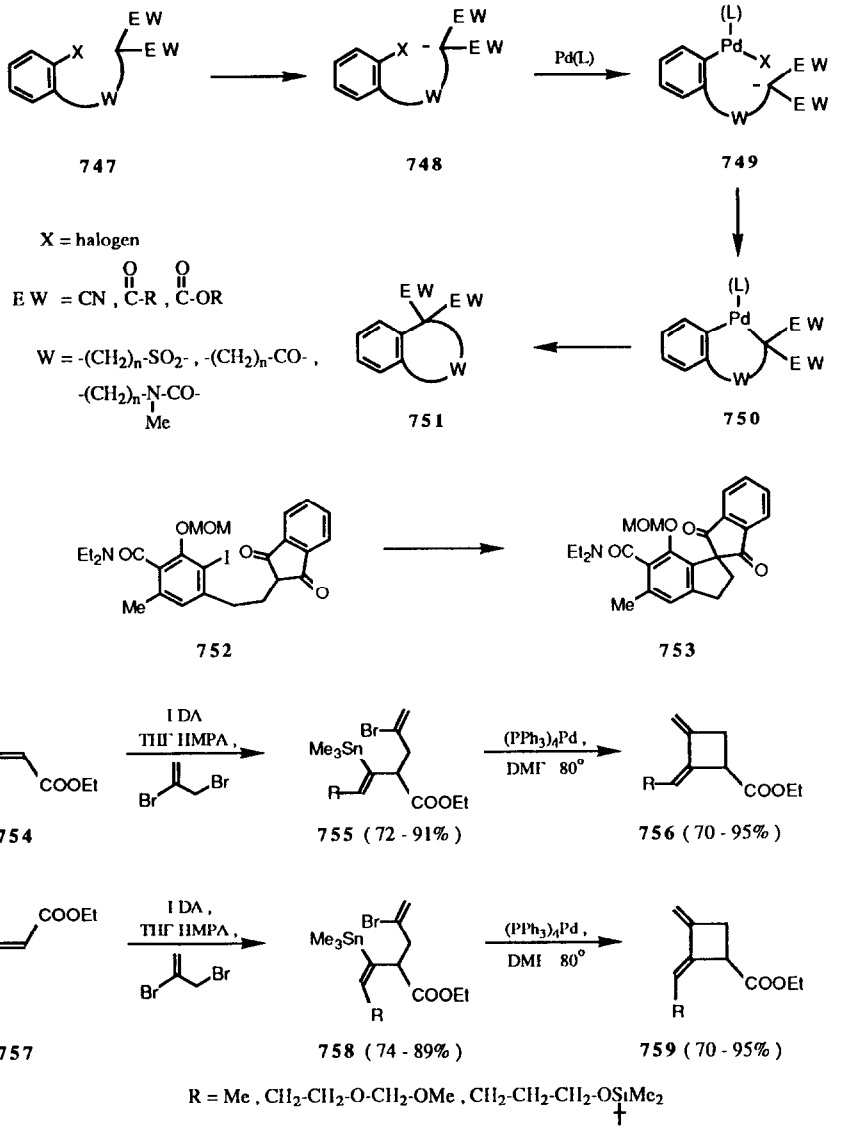



745 746 eq 151

Ring formation *via* palladium-catalysed displacement of halide from aromatic substrates as shown in Scheme 54 [207] is essentially the same type of reaction as discussed above Here the intermediate palladium complex is intramolecularly captured by stabilised enolate **749** to give **750**, and subsequently **751** Although yields are moderate, the reaction provides a beautiful access to spirostructures such as **753**

A *related reaction is the* palladium-catalysed 4-*exo*-trig cyclisation of geometrically isomeric bromostannanes **755** and **758** [208] to products **756** and **759** respectively (eq 152, 153) [209] The *starting bromostannanes can be regio- and stereospecifically prepared by deprotonation and* alkylation of the corresponding vinylstannanes **754** and **757** [208] The reaction provides a very good *general method for the preparation of 1,2-dialkylidenecyclobutanes*

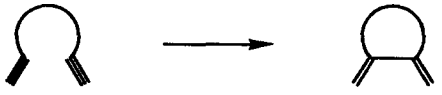
**Scheme 54**



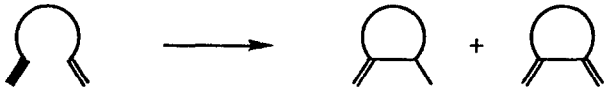

Metal-catalysed cyclisations of dienes, diynes, enynes and enallenes (as represented in equations 154-157) have been widely studied Numerous examples employing an assortment of metal complexes have been reported and form the subject of recent reviews [195,196] Nevertheless, due to its immense synthetic potential, the reaction continues to stimulate research and new

discoveries are constantly being reported These deserve mention even though some reaction mechanisms are still unclear

760 761 eq 154



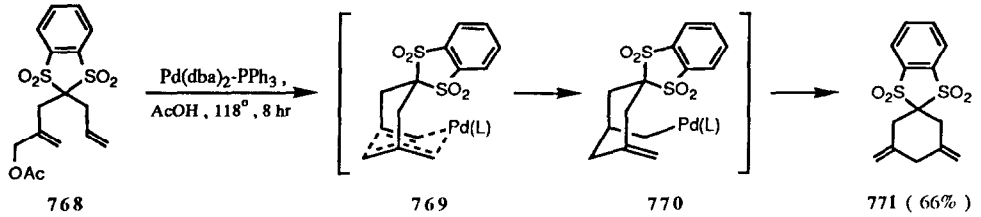
762 763 eq 155



764 765 763 eq 156

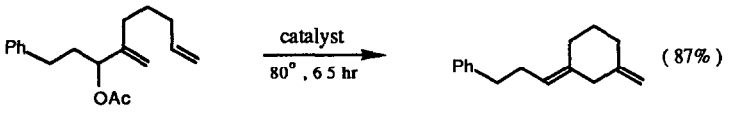
766 767 eq 157

Heating allyl acetate **768** at 118°C in acetic acid with Pd(dba)2-PPh3 yields the " palladium-ene " β-elimination product **771**, probably *via* intermediates **769** and **770** Removing the steric interaction between sulphone and palladium moieties inherent in transition state **769** enables the reaction to proceed more efficiently under less severe conditions Thus substrate **772** undergoes a regio- and stereocontrolled cyclisation at 80°C to give product **773** in very high yield [210] It should be noted that these reactions are, in fact, analogous to the " magnesium-ene cyclisation " reported




768 769 770 771 ( 66% )

eq 158

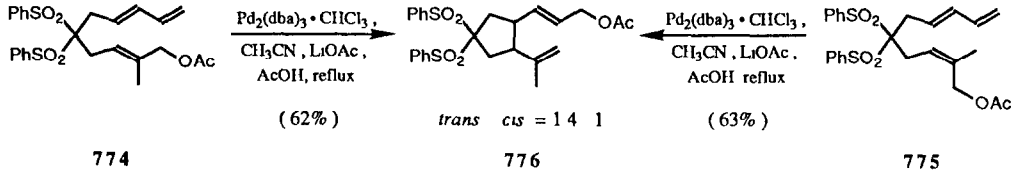



772 773 eq 159

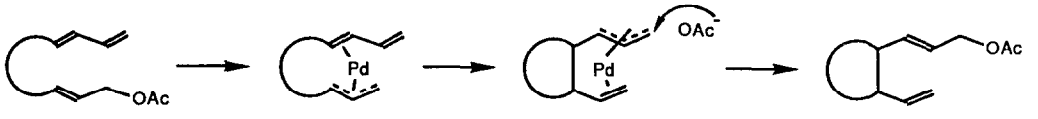
several years ago [211]

A similar reaction involving the $\pi$-allylpalladium intermediate is the cyclisation of isomeric **774** and **775** to give **776** The overall transformation is ring formation with migration of the acetate group as depicted in Scheme 55 The geometry of the double bond in the starting material apparently has no influence on either the yield (62-63%) or the stereochemistry of product (*trans cis* = 1 4 1) High diasteroselectivity is observed in certain cases, e g equation 160

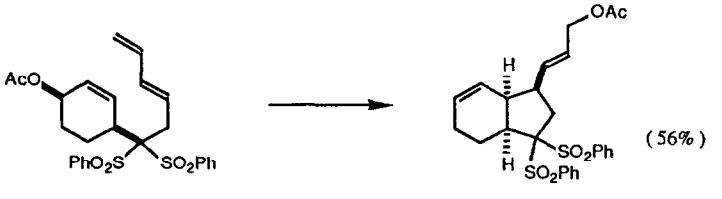
**Scheme 55**




774 776 775

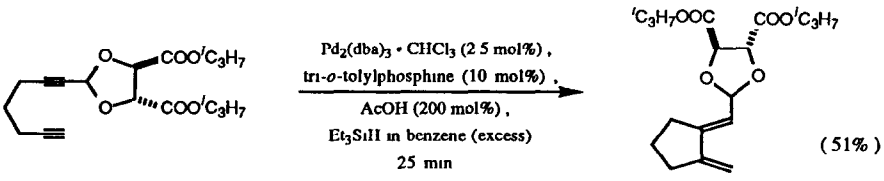



777 778 779 780

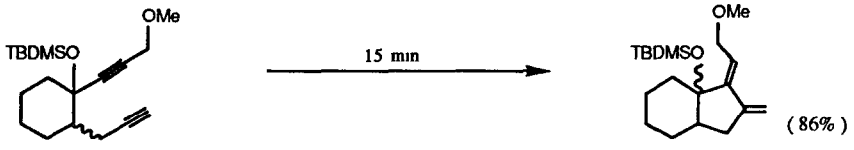



781 782 eq 160

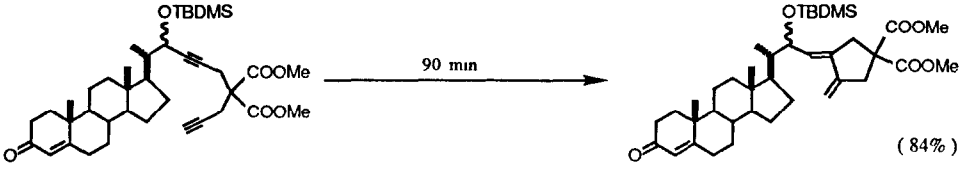
Reductive catalytic cyclisation of diynes to dialkylidenecycloalkanes using metal catalysts such as low valent titanium and/or zirconium complexes are known [195] Recently Trost has developed an alternative catalytic system to accomplish the reductive transformation The newly introduced method is effective with a variety of substrates, giving moderate to excellent yields as exemplified in equations 161-163




783 784 eq 161

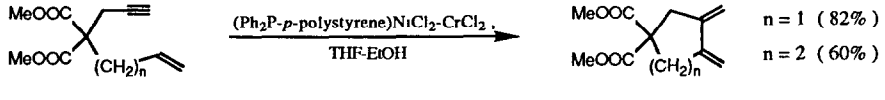



785 786 eq 162

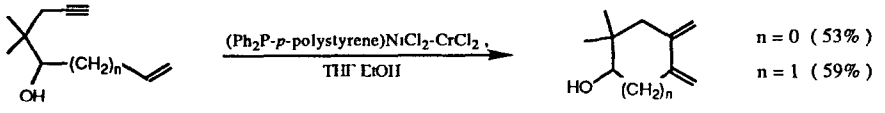



787 788 eq 163

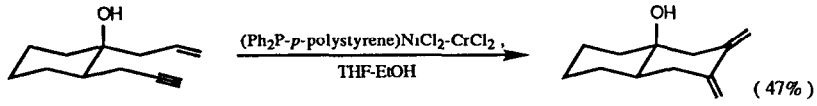
The problematic cyclisation of the enyne system (cf equation 156), catalysed by nickel-chromium complex $(PPh_3)_2NiCl_2$-$CrCl_2$, generally affords low yields of product consistently accompanied by polymerised material The difficulty is now overcome by using catalyst on a polymer support [(*p*-diphenylphosphinopolystyrene)$NiCl_2$-$CrCl_2$] with enhanced catalytic activity The yields of the reaction shown in equations 164-166 are much improved by this method, now considered useful in the realm of cyclisations [214]




789 790 eq 164

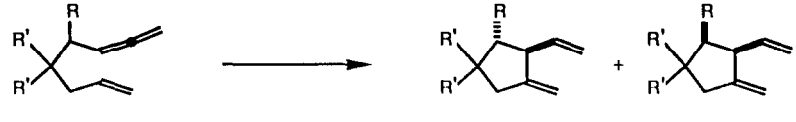



791 792 eq 165



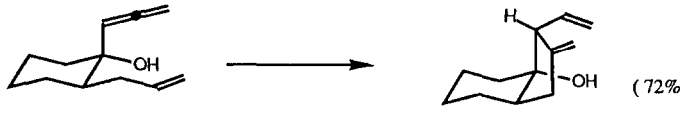

793 794 eq 166

The polymer support catalyst system functions well also with enallene substrates (see equation 157) As demonstrated in equations 167-171, product yields are respectable and several advantages are apparent first, good to excellent diastereoselectivity is obtained, second, it is allowable for the allene and/or alkene functions to occupy tertiary or quarternary carbon sites, and third, a free hydroxy group $\alpha$- to the allene or alkene poses no problem to cyclisation [215]

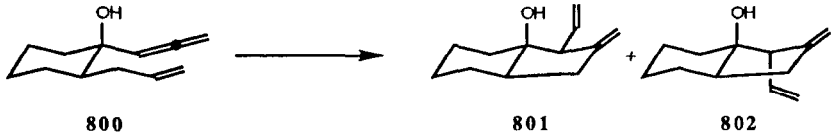



795 796 797

| | | | | |
|---|---|---|---|---|
| R = H , R' = COOMe | | | (80%) | |
| R = OH , R' = Me | 3 | 1 | (55%) | |
| R = OSiMe$_2$ † , R' = Me | >99 | 1 | (78%) | eq 167 |

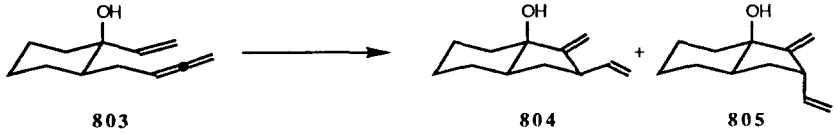



798 799 (72%) eq 168



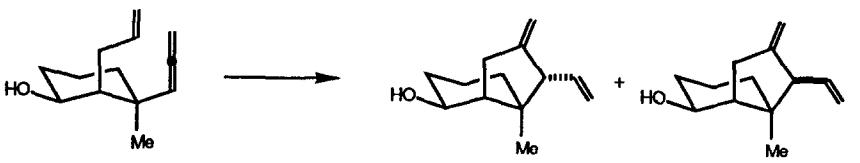

800 801 802

| | | | |
|---|---|---|---|
| 10 | 1 | (78%) | eq 169 |




803 804 805

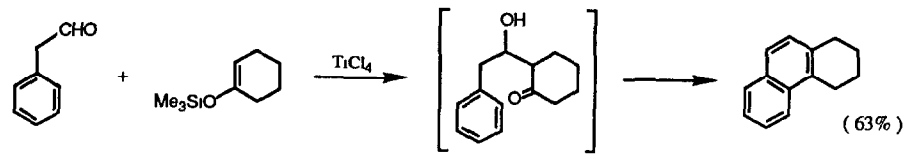
| | | | |
|---|---|---|---|
| 10 | 1 | (73%) | eq 170 |



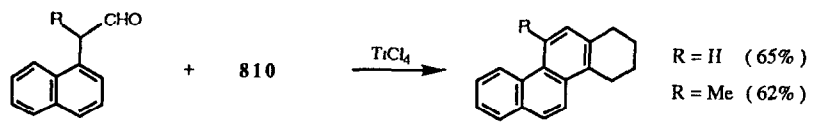

806 807 808

15 1 (86%) eq 171

Besides palladium, several other metals are used to catalyse cyclisation reactions A new example reports using titanium chloride as a catalyst for effecting tandem cross aldol condensation-cyclisation The reaction constitutes a novel synthesis of polycyclic aromatic hydrocarbons (eq 172, 173) [216]




809 810 811 812 eq 172



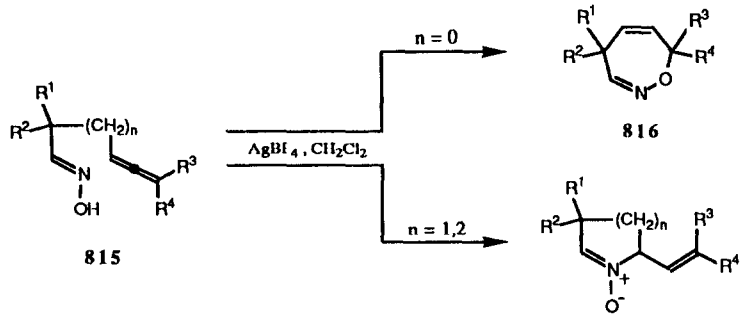

813 814 eq 173

## IV.2 Carbon-heteroatom bond formation

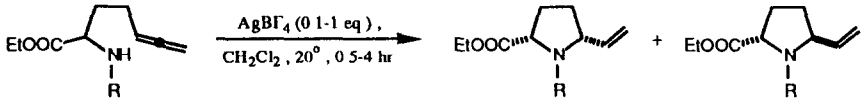
### Synthesis of heterocyclic compounds

Silver, mercury and palladium salts enjoy popular use as metal catalysts for cyclisations involving carbon-heteroatom bond formation The silver tetrafluoroborate-catalysed ring closure between nitrogen and the allenic function in oxime **815** may, depending upon chain length, yield either dihydrooxazepine **816**, [217,218] or vinyl nitrone **817**, [219] from respective *endo-* or *exo-* modes of reaction

Application of this same catalyst system to allenic amine **818** results in pyrrolidines **819** and **820** Interestingly, if R ≠ H, the *cis*-product **819** predominates overwhelmingly and in high yield [220,221]




815 816 817 eq 174

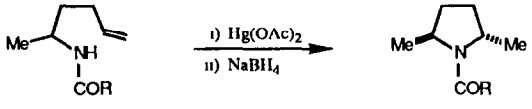



818 819 820

| | | | |
|---|---|---|---|
| R = $SO_2$–C$_6$H$_4$–Me | >50 | 1 | (100%) |
| = $CH_2Ph$ | >50 | 1 | (93%) |
| = $COO^tBu$ | >50 | 1 | (70%) |
| = H | 1 | 1 | (60%) |

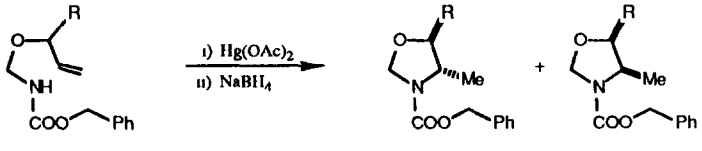
eq 175

The difficult-to-predict regio- and stereochemistry of the reaction shown in equation 175 are influenced by several factors such as catalyst, substrate nature and reaction conditions (kinetically or thermodynamically controlled) For instance, the amidomercuration of **821** or Harding cyclisation




821 822

R = Me , OMe , OEt , $OCH_2Ph$ >70% eq 176



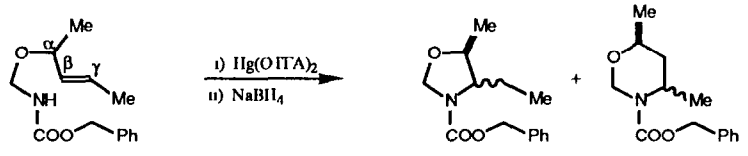

823 824 825

| | | |
|---|---|---|
| R = Me | 3 | 1 |
| = $CHMe_2$ | >19 | 1 |
| = Ph | >19 | 1 |

eq 177

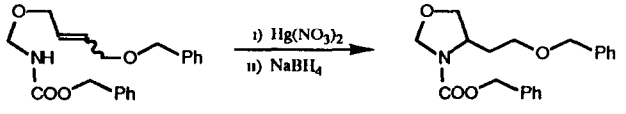
reported in 1981 [222] is both regiospecific and stereospecific, giving **822** as the sole product in high yield (eq 176) The reaction has even led to the synthesis of the valuable optically active 2,5-dimethylpyrrolidine [223] Analogous amidomercuration of substrate **823**, although not stereospecific, still yields predominantly the *trans*-product (eq 177) [224]

On the other hand, substrate **826**, in complete contrast to the almost identical **823**, undergoes the amidomercuration reaction in both *endo*- and *exo*- fashion to give, respectively, products **828** and **827** in a 1 4 ratio (60%) The explanation put forward is that the oxygen atom presence in the cyclising chain destabilises the carbocation character at the position $\beta$ to itself, forcing ring closure to occur at the alternative $\gamma$-position in an *endo*- fashion to yield **828** (eq 178) Support for this rationale is provided by the observations shown in equation 179 When substrate **829** or **830**, which has balanced oxygen presence at both termini of the double bond, is subjected to cyclisation followed by reduction with borohydride, only oxazolidine **831** from *exo*-cyclisation is obtained [225]




**826** **827** **828**

1 4 (60%) eq 178




**829** *Z*

**830** *E*

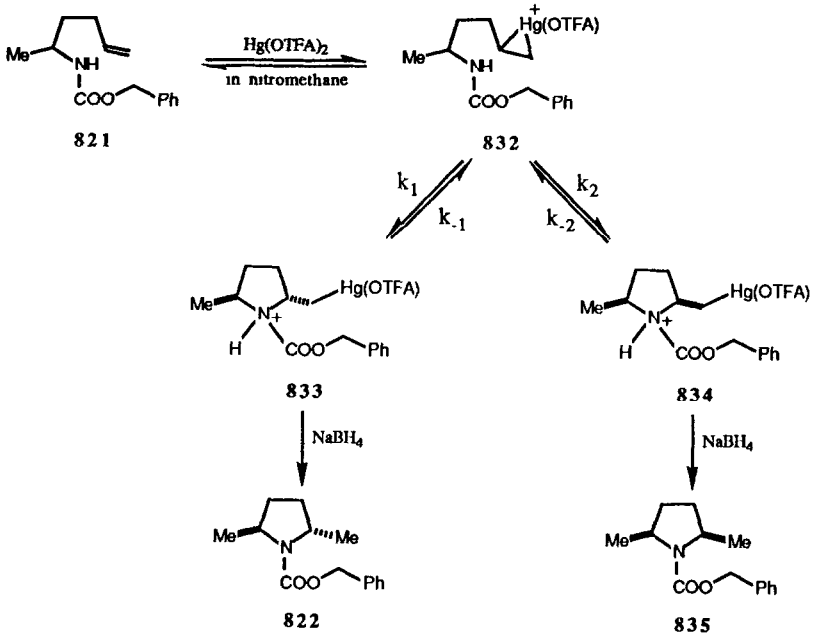
**831** (65% from **829**)

(81% from **830**) eq 179

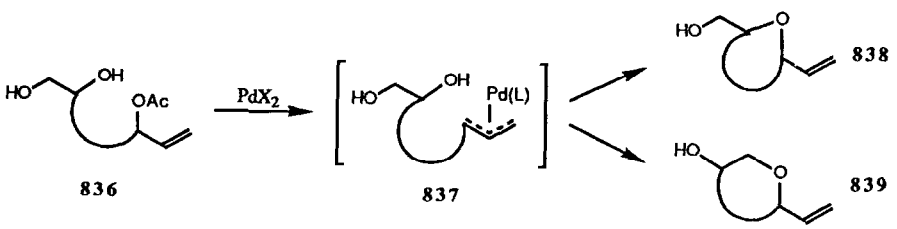
Although more information is obviously needed for a full understanding of the amidomercuration reaction, the above examples nevertheless help shed light on the regioselective nature of the reaction Meanwhile, regarding stereoselectivity, Harding has re-examined the reaction shown in equation 176 and discovered that it can be controlled to yield mainly the reverse stereoisomer by simple manipulations of reaction conditions Thus treatment of **821** with mercuric trifluoroacetate in nitromethane for 9 days followed by reduction with borohydride leads predominantly to the *cis*-isomer **835** [226] This stereochemical puzzle has been disentangled through

detailed mechanistic studies In short, stereoselective amidomercuration of δ-alkenylcarbamate (e g **821**, R = $OCH_2Ph$) requires conditions which do not lead to equilibration (e g $Hg(OAc)_2$ in THF), otherwise the thermodynamically more favourable (*cis*) product will predominate (e g $Hg(OTFA)_2$ in nitromethane) As shown in Scheme 56, $k_1 > k_2$ and the initial reaction results principally in the formation of *trans*-mercuration intermediate **833** which yields *trans*-product **822** upon reduction However, when **833** is left to equilibrate, a mixture consisting of 7 3 of *cis trans* isomers (**834** **833**) is eventually obtained In a similar study, the homologous ε-alkenylcarbamates also exhibit similar behaviour [226,227]

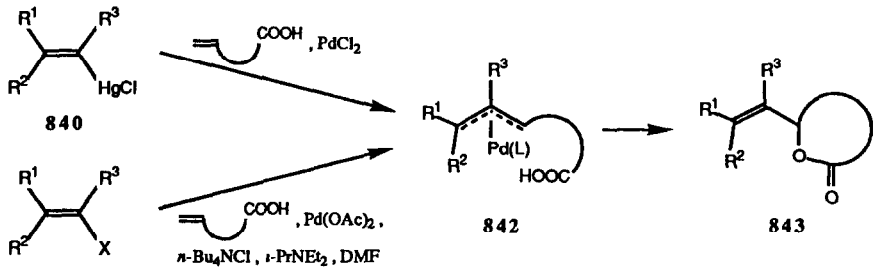
**Scheme 56**




As regards ring-closure with heteroatom nucleophiles that involve π-allylpalladium complexes,




eq 180

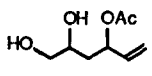
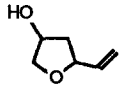
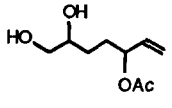
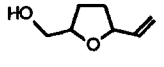
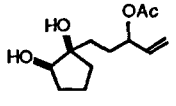
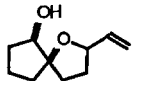
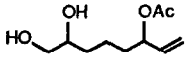
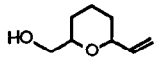



eq 181

there are reports of recent applications in the syntheses of cyclic vinyl ethers[228] and vinyl lactones[229,330] as outlined in equations 180 and 181 respectively

Examples of reactions of the type depicted in equation 180 are shown in Table 4 The smaller ring ether is preferentially formed in all cases except in entry 1, where strained oxetane ring formation is unfavourable The high stereoselectivity observed with five-membered ring products (entries 1-3) is noteworthy

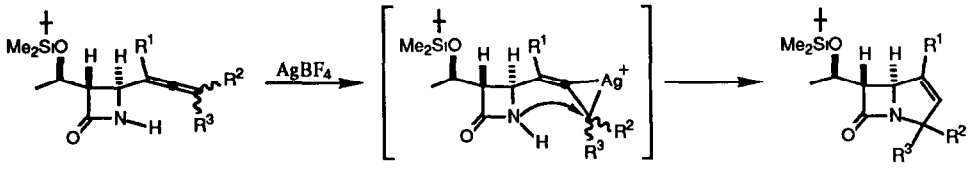
**Table 4** Cyclisation of diolacetates using $Pd_2(dba)_3 \cdot CHCl_3$-$PPh_3$ as catalyst system

| Entry | Starting material | Product | %yield | Diastereomeric ratio |
|---|---|---|---|---|
| 1 |  |  | 95 | 91 9 |
| 2 |  |  | 86 | 100 0 |
| 3 |  |  | 93 | 100 0 |
| 4 |  |  | 95 | 1 1 |

Due to technical limitations in their preparations, vinyl mercurials **840** [229] have been superseded by vinyl halides **841** [230] as substrates in the synthesis of vinyl lactones according to equation 181 The reaction works well in the preparation of $\gamma$-vinyl-$\gamma$-butyrolactones

## Synthesis of mono- and bicyclic β-lactams

The synthesis of β-lactams continues to be a favourite excercise in synthetic organic chemistry New syntheses are constantly being reported and reviewed [231] A current synthesis of carbapenems utilizes silver-mediated cyclisation of 4-allenylazetidinones **844** (eq 182) The reaction proceeds very smoothly with terminal allenes **844a** and **844b**, requiring as little as 0 1 equivalent of the silver catalyst However, formation of nitrogen-carbon bond in allenes **844c** - **844e** is slower, and a minimum of 0 5 - 1 equivalent of silver tetrafluoroborate is necessary [232]

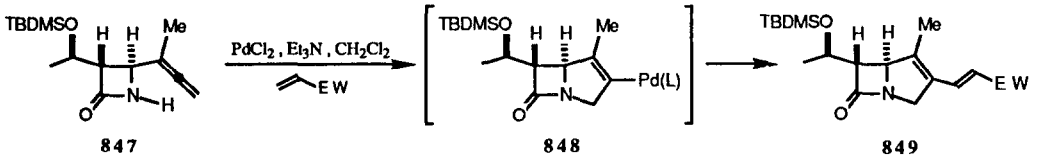



**844** **845** **846**

| | Diastereomeric ratio | %yield |
|---|---|---|
| a) $R^1 = R^2 = R^3 = H$ | | 75 |
| b) $R^1$ = Me , $R^2 = R^3 = H$ | - | 70 |
| c) $R^1 = H$ , $R^2$, $R^3$ = H , Me | 1 2 | 65 |
| d) $R^1$ = Me , $R^2$, $R^3$ = H , Me | 1 2 8 | 62 |
| e) $R^1$ = H , $R^2$, $R^3$ = Me , *n*-Bu | 1 2 2 | 58 |

eq 182

The above reaction is also catalysed by palladium This catalyst offers the added advantage of further functionalization capture of the palladium intermediate with electrophiles, e g an activated alkene, yields functionalized carbapenems **849** (eq 183) [233] This method is a useful variation of the former synthesis of carbapenems reported in 1986 [234]



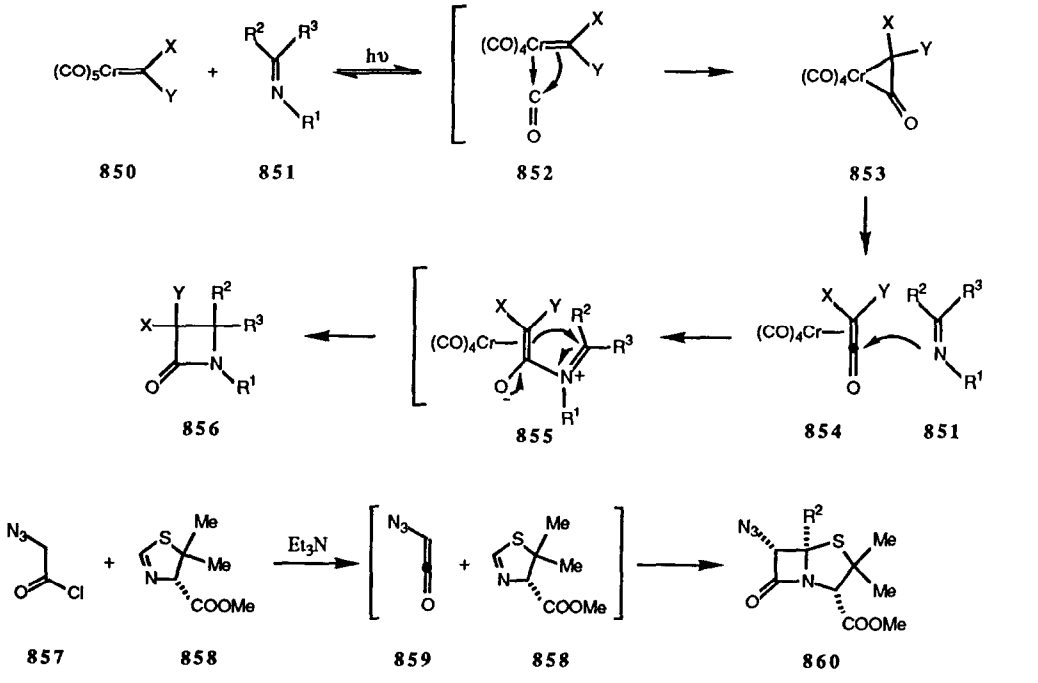

**847** **848** **849**

| EW | %yield | |
|---|---|---|
| COOEt | 46 | |
| COMe | 46 | |
| CHO | 40 | |
| CN | 53 | (3 1 *E*/*Z*) |

eq 183

The discovery of monocyclic β-lactam nocardicin A and B in 1976 [235] sparked off interest in their synthesis A general method widely used to construct the β-lactam nucleus is the [2 + 2]-cycloaddition reaction between ketene (generated *in situ* from acid chloride) and imine [236] A recent synthesis,[237,238] involving metal catalysed cyclisation, reports the photolysis of imine with chromium-carbene complex **850** as illustrated in Scheme 57 The reaction mechanism[237] is believed to involve the intermediate chromium-coordinated ketene **854** which is attacked by the imine to result in β-lactam **856** The reaction is applicable to the synthesis of both mono- and bicyclic β-lactams and is far superior to the conventional method of using free ketene The intermediate

**Scheme 57**




850 851 852 853 854 855 856 857 858 859 858 860

(6-13%, >98% ee) eq 184

861 862

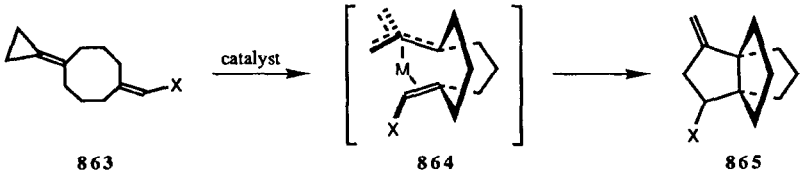
(93%, >98% ee) eq 185

chromium-coordinated ketenes **853** and **854** advantageously eliminate problems normally associated with free ketenes, e g dimerisation, hence overall yields are much improved The same stereochemistry prevails in the photolytic reaction (eq 185)[237] as in the reaction of free ketene with imine (eq 184) [239]

## IV.3 Multiple bond formation

Similar to cationic, radical and anionic cyclisation reactions, metal-catalysed tandem cyclisations can be effected to create multiple bonds in one single operation Suitable catalysts are the palladium complexes which have been reviewed up to early 1986 [240]

The latest advances in metal-promoted tandem cyclisations include the synthesis of [3 3 3] propellanes **865** as illustrated in equation 186 [241] Comparative studies show palladium to be distinctly superior to nickel complexes as a catalyst system for the reaction, furnishing an exceedingly high yield of propellane



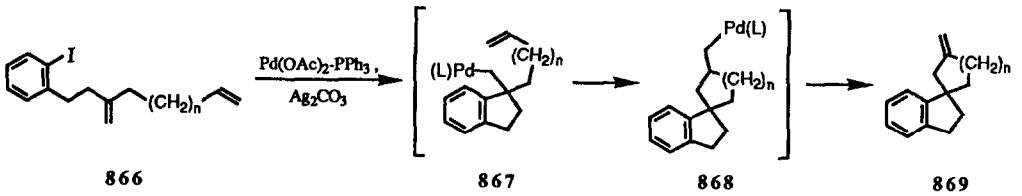

**863** **864** **865**

| X | Catalyst | %yield |
|---|---|---|
| H | $PdCl_2$-$PPh_3$, DIBAH | 74 |
| COOEt | $PdCl_2$-$PPh_3$, DIBAH | 98 |
| COOEt | $Ni(cod)_2$-$PPh_3$ | 74 |

eq 186

Another example is the tandem Heck reaction of **866**, in which spiro product **869** is formed *via* double cyclisation (eq 187) [242] Again the use of silver salt as trapping agent for hydriodic acid is practised (cf Scheme 52)

Substrate **870** provides a good example of a more complex situation Several reaction paths were anticipated, with **874**, **876** and **877** as possible products The actual results are shown in Scheme 58



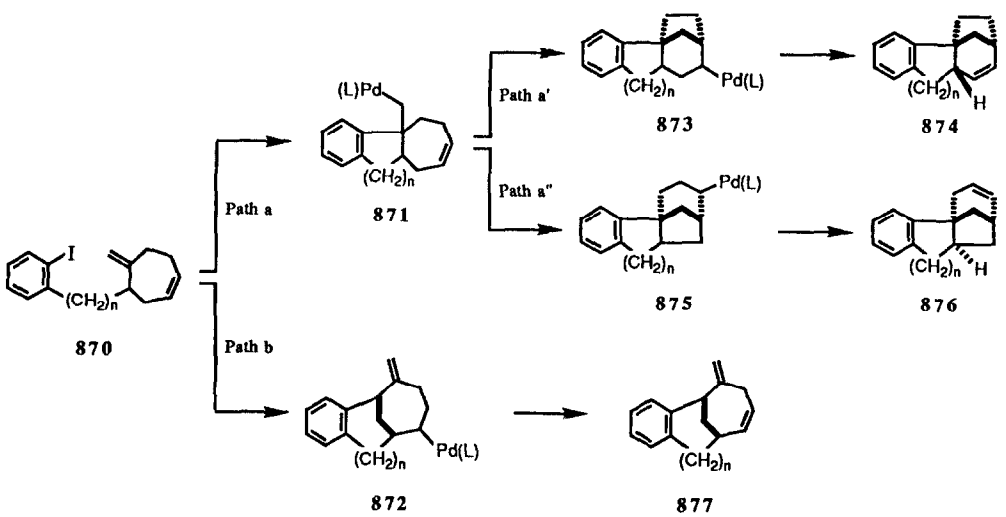

866 867 868 869

n = 1 86%

n = 2 85%

eq 187

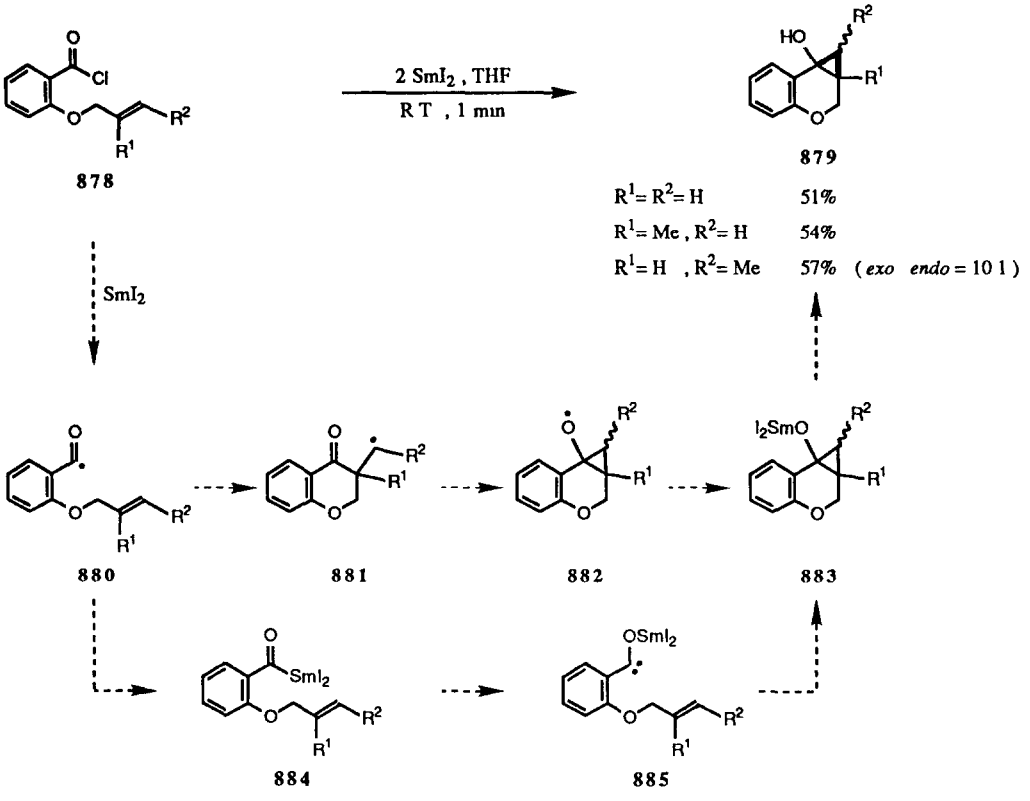
**Scheme 58**




n = 1 , yielded **874** + **877** ( 1 7 1 , 68% )

n = 2 , yielded **874** + **876** ( 1 3 1 , 90% )

The double cyclisation of allyloxybenzoyl chloride **878**, catalysed by samarium diiodide as shown in the last Scheme (Scheme 59), is extremely fast, going to completion within one minute, giving a moderate yield of **879** It is still unclear whether the reaction operates *via* acyl radical **880** (cf Scheme 29) or carbene complex **885** Whatever the mechanism, this reaction is exceedingly attractive and looks promisingly useful for the construction of other molecular structures apart from **879**


2 SmI2 , THF
R T , 1 min
878
879
R1= R2= H 51%
R1= Me , R2= H 54%
R1= H , R2= Me 57% (exo endo = 10 1)
SmI2
880
881
882
883
884
885

## CONCLUSION

Recent developments in cyclisation reactions that involve cationic, radical and anionic intermediates, as well as those catalysed by metal complexes are compiled in the report In each area we find significant advances ranging from modifications of known reactions to discoveries of new reagents and methodologies Under this active atmosphere, therefore, we can probably expect to witness new and exciting cyclisations for years to come

## Acknowledgement

Financial support from Chulabhorn Research Institute (CRI) is gratefully acknowledged The authors also thank Miss Bongkoch Tarnchompoo, Mr Sirichai Kittivarapong and Mr Veerapat Rujiravanish for their tremendous efforts in the total preparation of the manuscript

## REFERENCES :


1 T A Blumenkopf, L E Overman, *Chem Rev*, 1986, **86**, 857
2 L E Overman, M Kakimoto, *J Am Chem Soc*, 1979, **101**, 1310
3 L E Overman, E J Jacobsen, R J Doedens, *J Org Chem*, 1983, **48**, 3393
4 L E Overman, L T Mendelson, E J Jacobsen, *J. Am Chem Soc*, 1983, **105**, 6629
5 L E Overman, S Sugai, *Helv Chem Acta*, 1985, **68**, 745
6 L E Overman, M Sworin, R M Burk, *J Org Chem*, 1983, **48**, 2685
7 L E Overman, M Kakimoto, M E Okazaki, G P Meier, *J Am Chem Soc*, 1983, **105**, 6622
8 S F McCann, L E Overman, *J Am Chem Soc*, 1987, **109**, 6107
9 E J Jacobsen, J Levin, L E Overman, *J Am Chem Soc*, 1988, **110**, 4329
10 L E Overman, M J Sharp, *J Am Chem Soc*, 1988, **110**, 612
11 F Bohlmann, E Winterfeldt, *Chem Ber*, 1960, **93**, 1956
12 V U Ahmad, K -H Feuerherd, E Winterfeldt, *Chem Ber*, 1977, **110**, 3624
13 A I Meyers, D B Miller, F H White, *J Am Chem Soc*, 1988, **110**, 4778
14 S D Larsen, P A Grieco, W F Fobare, *J Am Chem Soc*, 1986, **108**, 3512
15 S -I Murahashi, T Naota, K Yonemura, *J Am Chem Soc*, 1988, **110**, 8256
16 W G Earley, E J Jacobsen, G P Meier, T Oh, L E Overman, *Tetrahedron Lett*, 1988, **29**, 3781
17 M L Steigerwald, W A Goddard III, D A Evans, *J Am Chem Soc*, 1979, **101**, 1994
18 W G Earley, T Oh, L E Overman, *Tetrahedron Lett*, 1988, **29**, 3785
19 M J Melnick, A J Freyer, S M Weinreb, *Tetrahedron Lett*, 1988, **29**, 3891
20 S Massa, A Mai, F Corelli, *Tetrahedron Lett*, 1988, **29**, 6471
21 F J Urban, *Tetrahedron Lett*, 1988, **29**, 5493
22 S Takano, Y Iwabuchi, K Ogasawara, *J Chem Soc, Chem Commun*, 1988, 1527
23 P Deslongchamps, "Stereoelectronic Effects in Organic Chemistry", Pergamon Press, Oxford, 1983
24 J D Winkler, C L Muller, R D Scott, *J Am Chem Soc*, 1988, **110**, 4831
25 R B Ruggeri, M M Hansen, C H Heathcock, *J Am Chem Soc*, 1988, **110**, 8734
26 R B Ruggeri, K F McClure, C H Heathcock, *J Am Chem Soc*, 1989, **111**, 1530
27 J Royer, H -P Husson, *Tetrahedron Lett*, 1987, **28**, 6175
28 G Pandey, G Kumaraswamy, *Tetrahedron Lett*, 1988, **29**, 4153
29 G Pandey, G Kumaraswamy, A Krishna, *Tetrahedron Lett*, 1987, **28**, 2649
30 C -K Chen, A G Hortmann, M R Marzabadi, *J Am Chem Soc*, 1988, **110**, 4829
31 N J Leonard, W K Musker, *J Am Chem Soc*, 1960, **82**, 5148
32 H Ishibashi, H Ozeki, M Ikeda, *J Chem Soc, Chem Commun*, 1986, 654
33 P Magnus, P M Cairns, *J Am Chem Soc*, 1986, **108**, 217
34 K Cardwell, B Hewitt, M Ladlow, P Magnus, *J Am Chem Soc*, 1988, **110**, 2242
35 Y Kita, O Tamura, F Itoh, H Yasuda, T Miki, Y Tamura, *Chem Pharm Bull*, 1987, **35**, 562

36 Y Kita, O Tamura, T Miki, Y Tamura, *Tetrahedron Lett*, 1987, **28**, 6479
37 M A Cook, C Eaborn, D R M Walton, *J Organometal Chem*, 1970, **24**, 301
38 C J Flann, L E Overman, *J Am Chem Soc*, 1987, **109**, 6115
39 L E Overman, A J Robichaud, *J. Am. Chem Soc*, 1989, **111**, 300
40 L E Overman, A S Thompson, *J Am Chem Soc*, 1988, **110**, 2248
41 L E Overman, T A Blumenkopf, A Castaneda, A S Thompson, *J Am Chem Soc*, 1986, **108**, 3516
42 H Sakurai, *Pure Appl Chem*, 1982, **54**, 1
43 G Majetich, K Hull, J Defauw, T Shawe, *Tetrahedron Lett*, 1985, **26**, 2755
44 G Majetich, K Hull, J Defauw, R Desmond, *Tetrahedron Lett*, 1985, **26**, 2747
45 G Majetich, J Defauw, K Hull, T Shawe, *Tetrahedron Lett*, 1985, **26**, 4711
46 G Majetich, J Defauw, C Ringold, *J Org Chem*, 1988, **53**, 50
47 J S Panek, M A Sparks, *Tetrahedron Lett*, 1988, **29**, 4517
48 D Schinzer, G Dettmer, M Ruppelt, S Solyom, J Steffen, *J Org Chem*, 1988, **53**, 3823
49 D Schinzer, J Steffen, S Sólyom, *J Chem Soc, Chem Commun*, 1986, 829
50 W J Klaver, M J Moolenaar, H Hiemstra, W N Speckamp, *Tetrahedron*, 1988, **44**, 3805
51 W J Klaver, H Hiemstra, W N Speckamp, *Tetrahedron*, 1988, **44**, 6729
52 P M Esch, H Hiemstra, W N Speckamp, *Tetrahedron Lett*, 1988, **29**, 367
53 J C Watkins, M Rosenblum, *Tetrahedron Lett*, 1985, **26**, 3531
54 D A Becker, R L Danheiser, *J Am Chem Soc*, 1989, **111**, 389
55 J W Ullrich, F -T Chiu, T Tiner-Harding, P S Mariano, *J Org Chem*, 1984, **49**, 220
56 F -T Chiu, J W Ullrich, P S Mariano, *J Org Chem*, 1984, **49**, 228
57 K Ohga, P S Mariano, *J Am Chem Soc*, 1982, **104**, 617
58 K Ohga, U C Yoon, P S Mariano, *J Org Chem*, 1984, **49**, 213
59 C -L Tu, P S Mariano, *J Am Chem Soc*, 1987, **109**, 5287
60 M H Hopkins, L E Overman, *J Am Chem Soc*, 1987, **109**, 4748
61 P M Herrinton, M H Hopkins, P Mishra, M J Brown, L E Overman, *J Org Chem*, 1987, **52**, 3711
62 G C, Hirst, P N Howard, L E Overman, *J Am Chem Soc*, 1989, **111**, 1514
63 M Sworin, W L Neumann, *J Org Chem*, 1988, **53**, 4894
64 B M Trost, D C Lee, *J Am Chem Soc*, 1988, **110**, 6556
65 B M Trost, A Brandi, *J Am Chem Soc*, 1984, **106**, 5041
66 W P Neumann, *Synthesis*, 1987, 665
67 M Ramaiah, *Tetrahedron*, 1987, **43**, 3541
68 D P Curran, *Synthesis*, 1988, 417 and 489
69 A Srikrishna, G Sunderbabu, *Tetrahedron Lett*, 1987, **28**, 6393
70 A Srikrishna, G Sunderbabu, *Chem Lett*, 1988, 371
71 G Ramamala, K K Balasubramanian, *Tetrahedron Lett*, 1988, **29**, 3335
72 A Srikrishna, G V R Sharma, *Tetrahedron Lett*, 1988, **29**, 6487
73 T V RajanBabu, *J Org Chem*, 1988, **53**, 4522
74 C E McDonald, R W Dugger, *Tetrahedron Lett*, 1988, **29**, 2413
75 R C Anderson, B Fraser-Reid, *J Org Chem*, 1985, **50**, 4781
76 C Audin, J -M Lancelin, J -M Beau, *Tetrahedron Lett*, 1988, **29**, 3691

77 L Friedman, *J Am Chem Soc*, 1964, **86**, 1885
78 R Dowbenko, *Tetrahedron*, 1964, **20**, 1843
79 J D Winkler, V Sridar, *J Am Chem Soc*, 1986, **108**, 1708
80 J D Winkler, V Sridar, *Tetrahedron Lett*, 1988, **29**, 6219
81 Y K Rao, M Nagarajan, *Tetrahedron Lett*, 1988, **29**, 107
82 M Ihara, N Taniguchi, K Fukumoto, T Kametani, *J Chem Soc, Chem Commun*, 1987, 1438
83 D H R Barton, E da Silva, S Z Zard, *J Chem Soc, Chem Commun*, 1988, 285
84 D J Hart, F L Seely, *J Am Chem Soc*, 1988, **110**, 1631
85 P A Bartlett, K L McLaren, P C Ting, *J Am Chem Soc*, 1988, **110**, 1633
86 R Tsang, B Fraser-Reid, *J Am Chem Soc*, 1986, **108**, 2116
87 R Tsang, B Fraser-Reid, *J Am Chem Soc*, 1986, **108**, 8102
88 R Tsang, J K Dickson, Jr, H Pak, R Walton, B Fraser-Reid, *J Am Chem Soc*, 1987, **109**, 3484
89 B Fraser-Reid, G D Vite, B -W A Yeung, R Tsang, *Tetrahedron Lett*, 1988, **29**, 1645
90 J D Harling, W B Motherwell, *J Chem Soc, Chem Commun*, 1988, 1380
91 V K Yadav, A G Fallis, *Tetrahedron Lett*, 1988, **29**, 897
92 E J Corey, M M Mehrotra, *Tetrahedron Lett*, 1988, **29**, 57
93 W Xu, Y T Jeon, E Hasegawa, U C Yoon, P S Mariano, *J Am Chem Soc*, 1989, **111**, 406
94 S F Martin, C -P Yang, W L Laswell, H Rueger, *Tetrahedron Lett*, 1988, **29**, 6685
95 J -K Choi, D -C Ha, D J Hart, C -S Lee, S Ramesh, S Wu, *J Org Chem*, 1989, **54**, 279
96 B B Snider, J J Patricia, S A Kates, *J Org Chem*, 1988, **53**, 2137
97 B B Snider, J J Patricia, *J Org Chem*, 1989, **54**, 38
98 J E Merritt, M Sasson, S A Kates, B B Snider, *Tetrahedron Lett*, 1988, **29**, 5209
99 S Hatakeyama, N Ochi, H Numata, S Takano, *J Chem Soc, Chem Commun*, 1988, 1202
100 D L J Clive, *Pure Appl Chem*, 1988, **60**, 1645
101 R S Jolly, T Livinghouse, *J Am Chem Soc*, 1988, **110**, 7536
102 D M Camaioni, H F Walter, J E Jordan, D W Pratt, *J Am Chem Soc*, 1973, **95**, 7978
103 L M Jackman, R C Haddon, *J Am Chem Soc*, 1973, **95**, 3687
104 D L J Clive, D R Cheshire, *J Chem Soc, Chem Commun*, 1987, 1520
105 a) J E Baldwin, *J Chem Soc, Chem Commun*, 1976, 734, b) J E Baldwin, L I Kruse, *J Chem Soc, Chem Commun*, 1977, 233, c) J E Baldwin, M J Lusch, *Tetrahedron*, 1982, **38**, 2939
106 J P Dulcere, M N Mihoubi, J Rodriguez, *J Chem Soc, Chem Commun*, 1988, 237
107 T Rajamannar, K K Balasubramanian, *Tetrahedron Lett*, 1988, **29**, 5789
108 A Gopalsamy, K K Balasubramanian, *J Chem Soc, Chem Commun*, 1988, 28
109 S A Ahmad-Junan, D A Whiting, *J Chem Soc, Chem Commun*, 1988, 1160
110 C P Sloan, J C Cuevas, C Quesnelle, V Snieckus, *Tetrahedron Lett*, 1988, **29**, 4685
111 J P Dittami, H Ramanathan, *Tetrahedron Lett*, 1988, **29**, 45
112 L J Hanka, A Dietz, S A Gerpheide, S L Kuentzel, D G Martin, *J Antibiot*, 1978, **31**, 1211
113 D L Boger, R S Coleman, *J Am Chem Soc*, 1988, **110**, 4796

114 K A Parker, D M Spero, J Van Epp, *J Org Chem*, 1988, **53**, 4628
115 P J Parsons, P A Willis, S C Eyley, *J Chem Soc, Chem Commun*, 1988, 283
116 D P Curran, D Kim, H T Liu, W Shen, *J Am Chem Soc*, 1988, **110**, 5900
117 G Stork, M E Reynolds, *J Am Chem Soc*, 1988, **110**, 6911
118 A Johns, J A Murphy, *Tetrahedron Lett*, 1988, **29**, 837
119 D C Lathbury, P J Parsons, I Pinto, *J Chem Soc, Chem Commun*, 1988, 81
120 Z Čeković, *Tetrahedron Lett*, 1972, 749
121 D L Boger, R J Mathvink, *J Org. Chem*, 1988, **53**, 3377
122 P Delduc, C Tailhan, S Z Zard, *J Chem Soc, Chem Commun*, 1988, 308
123 D J Coveney, V F Patel, G Pattenden, *Tetrahedron Lett*, 1987, **28**, 5949
124 V F Patel, G Pattenden, *Tetrahedron Lett*, 1988, **29**, 707
125 K Nozaki, K Oshima, K Utimoto, *Tetrahedron Lett*, 1988, **29**, 6127
126 M D Bachi, E Bosch, *Tetrahedron Lett*, 1986, **27**, 641
127 M D Bachi, D Denenmark, *J Am Chem Soc*, 1989, **111**, 1886
128 M Akhtar, D H R Barton, *J Am Chem Soc*, 1964, **86**, 1528
129 G A Kraus, J Thurston, *Tetrahedron Lett*, 1987, **28**, 4011
130 A J Bloodworth, R J Curtis, *J Chem Soc, Chem Commun*, 1989, 173
131 A S Kende, F H Ebetino, T Ohta, *Tetrahedron Lett*, 1985, **26**, 3063
132 A S Kende, K Koch, *Tetrahedron Lett*, 1986, **27**, 6051
133 A Leboff, A -C Carbonnelle, J -P Alazard, C Thal, A S Kende, *Tetrahedron Lett*, 1987, **28**, 4163
134 A S Kende, K Koch, C A Smith, *J Am Chem Soc*, 1988, **110**, 2210
135 P D McDonald, G A Hamilton, *J Am Chem Soc*, 1973, **95**, 7752
136 S H Ahn, D Kim, M W Chun, W -K Chung, *Tetrahedron Lett*, 1986, **27**, 943
137 D Kim, H S Kim, *J Org Chem*, 1987, **52**, 4633
138 D Kim, Y M Jang, I O Kim, S W Park, *J Chem Soc, Chem Commun*, 1988, 760
139 P Sulmon, N De Kimpe, N Schamp, *J Org Chem*, 1988, **53**, 4462
140 D Tanner, H H Ming, M Bergdahl, *Tetrahedron Lett*, 1988, **29**, 6493
141 J C Carretero, L Ghosez, *Tetrahedron Lett*, 1988, **29**, 2059
142 J Golik, G Dubay, G Groenewold, H Kawaguchi, M Konishi, B Krishnan, H Ohkuma, K Saitoh, T W Doyle, *J Am Chem Soc*, 1987, **109**, 3462
143 M D Lee, T S Dunne, C C Chang, G A Ellestad, M M Siegel, G O Morton, W J McGahren, D B Borders, *J Am Chem Soc*, 1987, **109**, 3466
144 S L Schreiber, L L Kiessling, *J Am Chem Soc*, 1988, **110**, 631
145 A S Kende, C A Smith, *Tetrahedron Lett*, 1988, **29**, 4217
146 T Ross Kelly, S H Bell, N Ohashi, R J Armstrong-Chong, *J Am Chem Soc*, 1988, **110**, 6471
147 R A Ellison, *Synthesis*, 1973, 397
148 Z -F Xie, H Suemune, K Sakai, *J Chem Soc, Chem Commun*, 1988, 612
149 M Kodpinid, T Siwapinyoyos, Y Thebtaranonth, *J Am Chem Soc*, 1984, **106**, 4862
150 M Kodpinid, Y Thebtaranonth, *Tetrahedron Lett*, 1984, **25**, 2509
151 D J Ager, S J Mole, *Tetrahedron Lett*, 1988, **29**, 4807

152 S Cabiddu, D Cancellu, C Floris, G Gelli, S Melis, *Synthesis*, 1988, 888
153 T Tabuchi, K Kawamura, J Inanaga, M Yamaguchi, *Tetrahedron Lett*, 1986, **27**, 3889
154 E Vedejs, S Ahmad, *Tetrahedron lett*, 1988, **29**, 2291
155 R T Arnold, S T Kulenovic, *Synth Commun*, 1977, **7**, 223
156 R B Ruggeri, C H Heathcock, *J Org Chem*, 1987, **52**, 5745
157 G Wickham, H A Olszowy, W Kitching, *J Org Chem*, 1982, **47**, 3788
158 T Sato, T Watanabe, T Hayata, T Tsukui, *J Chem Soc, Chem Commun*, 1989, 153
159 H Saito, T Hirata, *Tetrahedron Lett*, 1987, **28**, 4065
160 T Kametani, N Kanaya, T Mochizuki, T Honda, *Heterocycles*, 1982, **19**, 1023
161 T Kametani, A Nakayama, A Itoh, T Honda, *Heterocycles*, 1983, **20**, 2355
162 T Kametani, H Yukawa, T Honda, *J Chem Soc, Chem Commun*, 1986, 651
163 T Kametani, H Yukawa, T Honda, *J Chem Soc, Chem Commun*, 1988, 685
164 T Kametani, S -D Chu, A Itoh, T -C Wang, A Nakayama, T Honda, *J Chem Soc, Chem Commun*, 1988, 544
165 L Crenshaw, S P Khanapure, U Siriwardane, E R Biehl, *Tetrahedron Lett*, 1988, **29**, 3777
166 S D Larsen, *J Am Chem Soc*, 1988, **110**, 5932
167 G Stork, N A Saccomano, *Tetrahedron Lett*, 1987, **28**, 2087
168 G Stork, N A Saccomano, *Nouv J Chim*, 1986, **10**, 677 [through *Chemical Abstract*, 1987, **107**, 217115d]
169 T Uyehara, N Asao, Y Yamamoto, *Tetrahedron*, 1988, **44**, 4173
170 T Uyehara, N Shida, Y Yamamoto, *J Chem Soc, Chem Commun*, 1989, 113
171 R D Little, J R Dawson, *Tetrahedron Lett*, 1980, **21**, 2609
172 P Prempree, S Radviroongit, Y Thebtaranonth, *J Org Chem*, 1983, **48**, 3553
173 M Joucla, M El Goumzili, B Fouchet, *Tetrahedron Lett*, 1986, **27**, 1677
174 M P Cooke, Jr, *Tetrahedron Lett*, 1979, 2199
175 M P Cooke, Jr, J Y Jaw, *J Org Chem*, 1986, **51**, 758
176 T Kurihara, K Santo, S Harusawa, R Yoneda, *Chem Pharm Bull*, 1987, **35**, 4777
177 C Chen, Y -Z Huang, Y Shen, *Tetrahedron Lett*, 1988, **29**, 1033
178 T Hudlicky, L Radesca-Kwart, L Li, T Bryant, *Tetrahedron Lett*, 1988, **29**, 3283
179 J S Nowick, R L Danheiser, *Tetrahedron*, 1988, **44**, 4113
180 G H Posner, *Chem Rev*, 1986, **86**, 831
181 G H Posner, K S Webb, E Asirvatham, S Jew, A D'Innocenti, *J Am Chem Soc*, 1988, **110**, 4754
182 B Tarnchompoo, C Thebtaranonth, Y Thebtaranonth, *Synthesis*, 1986, 785
183 B Tarnchompoo, C Thebtaranonth, Y Thebtaranonth, *Tetrahedron Lett*, 1987, **28**, 6671
184 P A Wender, A W White, *J Am Chem Soc*, 1988, **110**, 2218
185 J P Marino, J K Long, *J Am Chem Soc*, 1988, **110**, 7916
186 W J Scott, G T Crisp, J K Stille, *J Am Chem Soc*, 1984, **106**, 4630
187 M D Koppang, G A Ross, N F Woolsey, D E Bartak, *J Am Chem Soc*, 1986, **108**, 1441
188 W F Bailey, T T Nurmi, J J Patricia, W Wang, *J Am Chem Soc*, 1987, **109**, 2442
189 W C Still, A Mitra, *J Am Chem Soc*, 1978, **100**, 1927
190 C A Broka, W J Lee, T Shen, *J Org Chem*, 1988, **53**, 1336
191 A R Chamberlin, S H Bloom, L A Cervini, C H Fotsch, *J Am Chem Soc*, 1988, **110**, 4788

192 P G Gassman, C Lee, *J Am Chem Soc*, 1989, **111**, 739
193 W F Bailey, K Rossi, *J Am. Chem Soc*, 1989, **111**, 765
194 W F Bailey, J J Patricia, T T Nurmi, *Tetrahedron Lett*, 1986, **27**, 1865
195 E Negishi, *Acc Chem Res*, 1987, **20**, 65.
196 H Yasuda, A Nakamura, *Angew Chem Int Ed Engl*, 1987, **26**, 723
197 R A Abramovitch, D H R Barton, J -P Finet, *Tetrahedron*, 1988, **44**, 3039
198 R F Heck, *Org React*, 1982, **27**, 345
199 R Grigg, V Sridharan, P Stevenson, T Worakun, *J Chem Soc, Chem Commun*, 1986, 1697
200 R C Larock, S Babu, *Tetrahedron Lett*, 1987, **28**, 5291
201 M M Abelman, T Oh, L E Overman, *J Org Chem*, 1987, **52**, 4130
202 E Negishi, Y Zhang, B O'Connor, *Tetrahedron Lett*, 1988, **29**, 2915
203 R C Larock, H Song, B E Baker, W H Gong, *Tetrahedron Lett*, 1988, **29**, 2919
204 B O'Connor, Y Zhang, E Negishi, *Tetrahedron Lett*, 1988, **29**, 3903
205 B Burns, R Grigg, V Sridharan, T Worakun, *Tetrahedron Lett*, 1988, **29**, 4325
206 B Burns, R Grigg, P Ratananukul, V Sridharan, *Tetrahedron Lett*, 1988, **29**, 5565
207 M A Ciufolini, H -B Qi, M E Browne, *J Org Chem*, 1988, **53**, 4149
208 E Piers, A V Gavai, *J Chem Soc, Chem Commun*, 1985, 1241
209 E Piers, Y -F Lu, *J Org Chem*, 1988, **53**, 926
210 W Oppolzer, R E Swenson, J -M Gaudin, *Tetrahedron Lett*, 1988, **29**, 5529
211 W Oppolzer, R Pitteloud, H F Strauss, *J Am Chem Soc*, 1982, **104**, 6476
212 B M Trost, J I Luengo, *J Am Chem Soc*, 1988, **110**, 8239
213 B M Trost, D C Lee, *J Am Chem Soc*, 1988, **110**, 7255
214 B M Trost, J M Tour, *J Am Chem Soc*, 1987, **109**, 5268
215 B M Trost, J M Tour, *J Am Chem Soc*, 1988, **110**, 5231
216 P D Raddo, R G Harvey, *Tetrahedron Lett*, 1988, **29**, 3885
217 J Grimaldi, A Cormons, *Tetrahedron Lett*, 1985, **26**, 825
218 J Grimaldi, A Cormons, *Tetrahedron Lett*, 1986, **27**, 5089
219 D Lathbury, T Gallagher, *Tetrahedron Lett*, 1985, **26**, 6249
220 R Kinsman, D Lathbury, P Vernon, T Gallagher, *J Chem Soc, Chem Commun*, 1987, 243
221 P Vernon, T Gallagher, *J Chem Soc, Chem Commun*, 1987, 245
222 K E Harding, S R Burks, *J Org Chem*, 1981, **46**, 3920
223 R H Schlessinger, E J Iwanowicz, *Tetrahedron Lett*, 1987, **28**, 2083
224 K E Harding, R Stephens, D R Hollingsworth, *Tetrahedron Lett*, 1984, **25**, 4631
225 K E Harding, D R Hollingsworth, *Tetrahedron Lett*, 1988, **29**, 3789
226 K E Harding, T H Marman, *J Org Chem*, 1984, **49**, 2838
227 K E Harding, T H Marman, D Nam, *Tetrahedron Lett*, 1988, **29**, 1627
228 B M Trost, A Tenaglia, *Tetrahedron Lett*, 1988, **29**, 2927
229 R C Larock, D J Leuck, L W Harrison, *Tetrahedron Lett*, 1987, **28**, 4977
230 R C Larock, D J Leuck, *Tetrahedron Lett*, 1988, **29**, 6399
231 W Durckheimer, J Blumbach, R Lattrell, K H Scheunemann, *Angew Chem Int Ed Engl*, 1985, **24**, 180

232 J S Prasad, L S Liebeskind, *Tetrahedron Lett*, 1988, **29**, 4253
233 J S Prasad, L S Liebeskind, *Tetrahedron Lett*, 1988, **29**, 4257
234 B M Trost, S -F Chen, *J Am Chem Soc*, 1986, **108**, 6053
235 M Hashimoto, T Komori, T Kamiya, *J Am Chem Soc*, 1976, **98**, 3023
236 D R Wagle, C Garai, M G Monteleone, A K Bose, *Tetrahedron Lett*, 1988, **29**, 1649
237 L S Hegedus, G de Weck, S D'Andrea, *J Am Chem Soc*, 1988, **110**, 2122
238 L S Hegedus, S D'Andrea, *J Org Chem*, 1988, **53**, 3113
239 R A Firestone, N S Maciejewicz, B G Christensen, *J Org Chem*, 1974, **39**, 3384
240 B M Trost, *Angew Chem Int Ed Engl*, 1986, **25**, 1
241 S Yamago, E Nakamura, *J Chem Soc, Chem Commun*, 1988, 1112
242 M M Abelman, L E Overman, *J Am Chem Soc*, 1988, **110**, 2328
243 M Sasaki, J Collin, H B Kagan, *Tetrahedron Lett*, 1988, **29**, 6105