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ENAMINES: RECENT ADVANCES IN SYNTHETIC, SPECTROSCOPIC, MECHANISTIC, AND STEREOCHEMICAL ASPECTS—II

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CONTENTS

1. INTRODUCTION

Part I[1] of this two-part review of enamine chemistry covering the period 1969 through 1980 was concerned with developments in the methods of preparation of enamines, with factors affecting their structure and reactivity, with their spectroscopic properties, and with the reactions of enamines with electrophiles which did not lead to the construction of a new ring. In this second part, the intention is to cover principally the recent developments which have occurred in reactions leading to cyclic compounds (carbocyclic and heterocyclic). This is followed by a brief treatment of the reactions of imines which occur via their enamine tautomer, and we conclude with a survey of the chemistry of metalloenamines.

As in Part I, heterocyclic enamines[2] such as tetrahydropyridines, Δ^1-pyrrolines, indoles etc, and their exo-enamine tautomers, are considered outside the scope of this review. Since excellent reviews have also recently appeared on enaminones,[3] enaminonitriles,[4] enamides,[5] and iminium salts,[6] these topics

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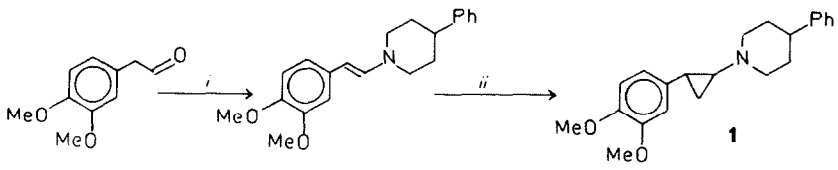
have also been omitted. Additionally we have also not attempted a detailed treatment of the chemistry of dienamines, or of such systems in which the enamine double bond is further conjugated, either with an electron-donor substituent carrying a lone pair of electrons (e.g. enediamines, enetriamines, dienediamines, halogeno-enamines, keten aminals, keten O,N- and S,N-acetals etc) or an electron acceptor unsaturated system (e.g. nitroenamines, α-cyanoenamines, enamino esters or amides, enamidines, etc) or radicophilic olefins, since these topics would probably require another complete review in order to deal with them adequately.

2. CARBOCYCLIC SYNTHESIS

In this section we are concerned with methods for ring formation (or ring expansion or contraction) which involve the introduction (or elimination) of one or more carbon atoms into an enamine system, which itself may be part of an acyclic, carbocyclic, or heterocyclic molecule. The products may therefore be carbocyclic or heterocyclic provided that in the latter case the heteroatom is already present in the enamine and is not apparently involved in the reaction taking place.

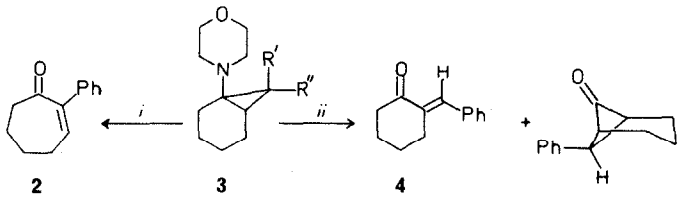
A. *Three-membered rings*

Cycloaddition of carbenes gives aminocyclopropanes from aldehyde enamines, a reaction recently utilised to prepare cyclopropyldopamine analogues[7] (1)



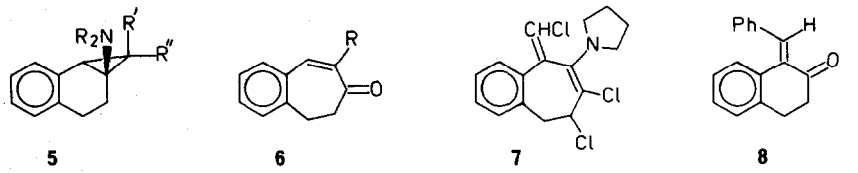
Scheme 1. Reagents: (i) 4-phenylpiperidine; (ii) $CH_2N_2/PdAc_2$.

Aminobicyclo [n.1.0] alkanes are obtained from cyclic ketone enamines.[8] When the carbene carries a good leaving group, such as a chlorine substituent, the cycloadduct may ring open to give an αβ-unsaturated carbonyl compound. In the case of a bicyclic [n.1.0] adduct, depending on which bond of the three-membered ring is broken, this may lead to the introduction of an endocyclic double bond with ring expansion or an exocyclic double bond with retention of ring size. This in turn has been shown to depend on the stereochemistry of the chloro-substituent in the cycloadduct.[9] For example reaction of phenylchlorocarbene with morpholinocyclohexene gives the bicyclic adduct as a mixture of isomers **3a** and **3b**. The former on boiling in pyridine gives the ring expanded product **2** whereas the latter gives a mixture consisting mainly of **4**. Formation of **2** is attributed to disrotatory ring opening of the



Scheme 2. Reagents: (i) pyridine, Δ, 2 h; (ii) pyridine, Δ, 45 h; (a) R′ = Ph, R″ = Cl; (b) R′ = Cl, R″ = Ph.

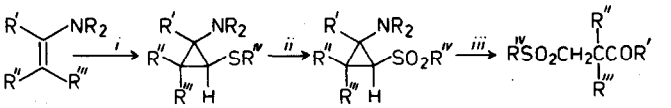
endo-chloro-isomer **3a**, without involvement of the nitrogen electron-pair, whereas electrocyclic ring opening is sterically prohibited in **3b** which therefore reacts via a dipolar intermediate involving the nitrogen electron-pair and preferential fission of the 1–7 rather than the 1–2 bond. However the course of the reaction often depends on the nature of the base-component and the ketone from which the enamine was derived, in addition to the substituents present in the carbene. For example the morpholine enamine of β-tetralone gives cycloadduct **5a** or **5b** with dichlorocarbene or phenylchlorocarbene.[10] The dimethylamine enamine gives both cycloaddition **5c** and ring expansion products **6**, and the pyrrolidine enamine gives a mixture of ring expansion products **6a** and **7** with dichlorocarbene and the α,β-unsaturated ketone **8** with phenylchlorocarbene. Similar variations in product distribution occur with α-tetralone enamines.[11]



5 6 7 8

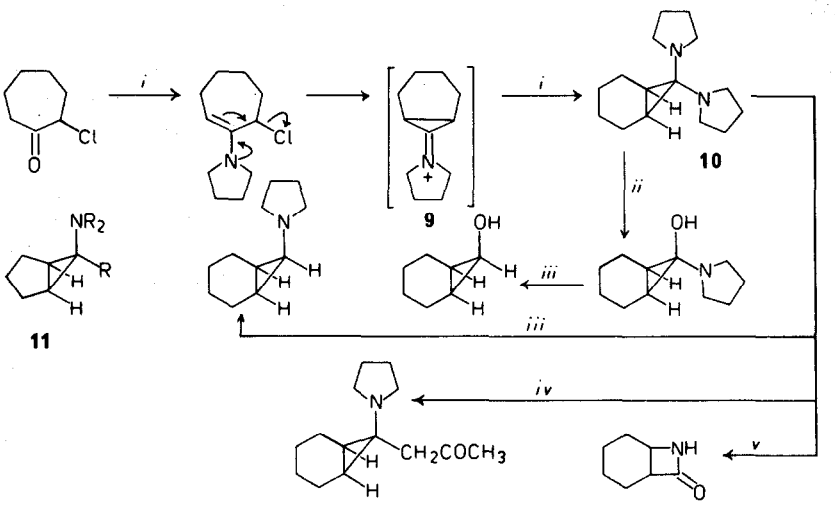
Scheme 3. Substituents: **5a**, R_2N = morpholino, R′ = R″ = Cl; **5b**, R_2N = morpholino, R′ = Cl, R″ = Ph; **5c**, R_2N = dimethylamino, R′ = Cl, R″ = Ph; **6a**, R = Cl; **6b**, R = Ph.

Cycloaddition of thiocarbenes to enamines gives aminocyclopropyl sulphides which undergo oxidative ring opening to give sulphone aldehyde or ketones in good yields.[12]



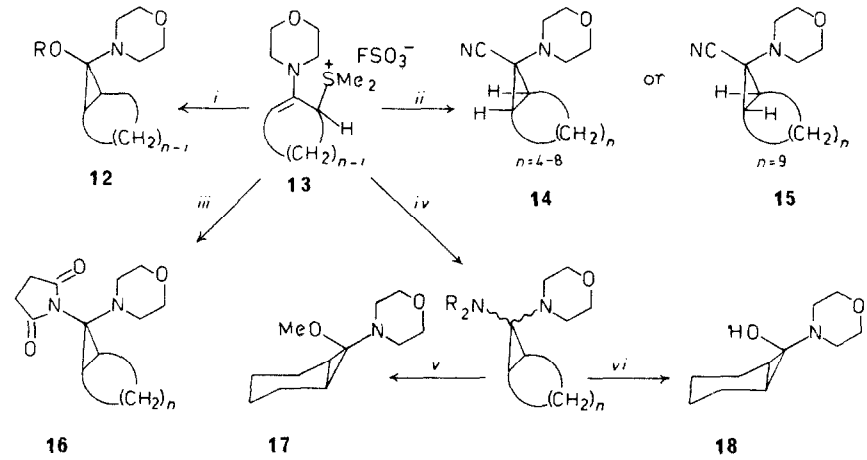
Scheme 4. Reagents: (i) $R^{IV}SCH_2Cl$, t-BuOK; (ii) $KMnO_4$; (iii) aq.HOAc.

Substituted bicyclo [n.1.0] alkanes are also obtained by condensation of 2-haloketones with secondary amines.[13] Nucleophilic replacement of an amine moiety in the resulting 1,1-diamine **10** can be effected (via the cyclopropaniminium salt **9**) to give a variety of derivatives[13,14] (Scheme 5).



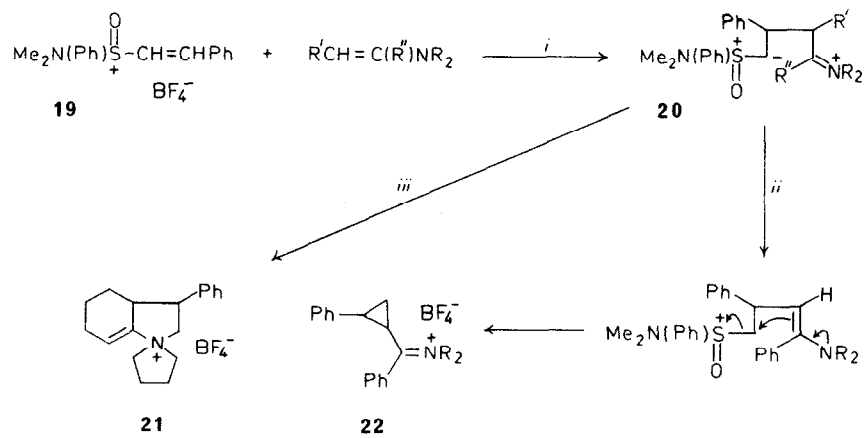
Scheme 5. Reagents: (i) pyrrolidine; (ii) aq. HCl; (iii) $NaBH_4$; (iv) acetone, pH 5.5; (v) NaN_3, pH 5.5.

Better yields of the bicyclo [3.1.0] hexane and bicyclo [4.1.0] heptane ring systems were obtained when the bromo-enamines, prepared from the 2-bromoketones by the $TiCl_4$ route [Part I, Section 4A(1)], were treated with $AgBF_4$.[15] The corresponding cyclopropaniminium salt was also isolated by treatment of the 1,1-diamine with methyl fluorosulphonate.[15] Condensation of organometallic reagents (Mg, Li, Cu) with halogeno-enamines gives α-substituted ketones, by direct replacement of the halogen, or the bicyclic product **11**, depending upon the experimental conditions employed.[16] A related and versatile synthetic procedure leading to substituted bicyclo[n.1.0]alkanes has been developed by Vilsmaier. The method involves treatment of an enamine with S,S-dimethyl-N-succinimidosulphonium fluorosulphonate to give the enaminosulphonium salt **13**.[17] The latter gives the bicyclic product with expulsion of dimethyl sulphide under the influence of a nucleophile and base. The exo-morpholine configuration is assigned to isomers **17** and **18** since both exhibit an AA′XX′ pattern for the morpholine protons in the 220 MHz NMR spectra. Isomers **12**, **14**, **15** and **16** exhibit an ABXY pattern indicative of hindered rotation or inversion in the endo-morpholine configuration.



Scheme 6. Reagents: (i) RO^-, ROH(n = 3)[18]; (ii) CN^-[19]; (iii) succinimide, R_3N[20]; (iv) R_2NH[18]; (v) H^+, MeOH (R_2N = morpholino)[18]; (vi) aq. HCl (R_2N = morpholino)[18].

The reaction with vinylsulphoximine salts **19** is interesting in that the sulphoximine group plays the dual role of activating and leaving group. Thus the zwitterion **20** produced by reaction with an enamine, instead of cyclising to the cyclobutane, undergoes a 1,3- or 1,5-proton shift to regenerate an enamine which then cyclises to a cyclopropyl derivative **22** or pyrrolidinium derivative **21**.[21]

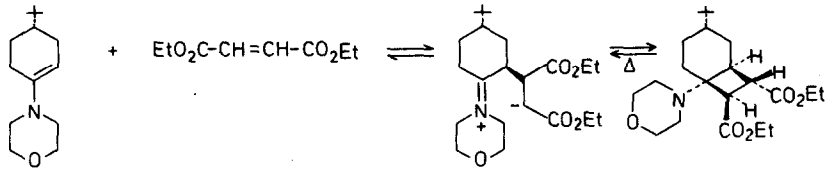


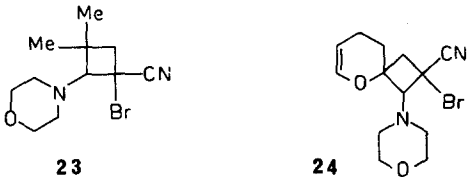
Scheme 7. Reagents: (i) THF, 0–20°, 15–20 h; (ii) R′ = H, R″ = Ph; (iii) R′R″ = $(CH_2)_4$.

Cyclopropane derivatives have also been isolated from the cycloaddition of cyclopropenones to enamines, but the reaction is complex (see Section 2C).

B. *Four-membered rings*

Cyclobutanones are obtained by 1,2-cycloaddition of ketenes to enamines, the ketene usually being generated *in situ* from the corresponding acid chloride and triethylamine.[22] Cycloaddition of electrophilic olefins to enamines, at low temperatures and in aprotic conditions, is also a well documented method for the formation of cyclobutanes from aldehyde enamines, and bicyclo[4.2.0]alkanes from enamines of cyclic ketones.[8] The reaction has been clearly demonstrated to be a two-step process and the intermediate zwitterion shown to be formed under reversible conditions, carbon-carbon bond fission readily occurring to regenerate the enamine and the (trans) electrophilic olefin.[23a] The same cycloadduct is obtained from diethyl maleate and diethyl fumarate, with the cyclohexane and cyclobutane rings cis-fused and the two adjacent ethoxycarbonyl groups mutually trans.[23b]



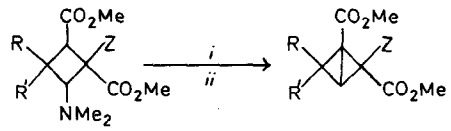


23 24

Scheme 8.

The corresponding reaction between α-bromoacrylonitrile and aldehyde enamines gives bromocyanocyclobutanes such as **23** and **24** whereas ketone enamines give primarily heterocyclic derivatives formed by alkylation at the enamine nitrogen (see next section).[24]

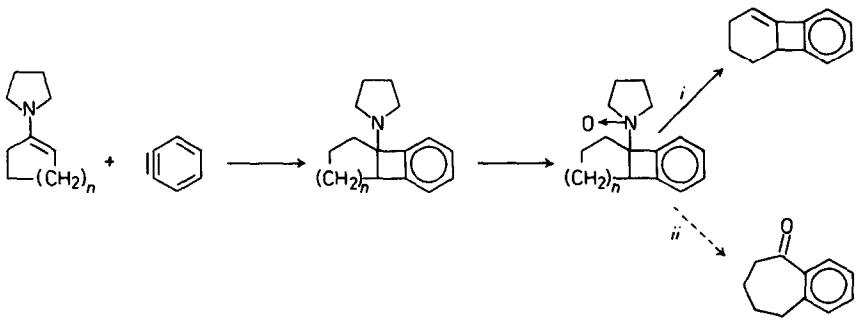
Electrophilic olefins such as trimethyl ethylenetricarboxylate or dimethyl cyanoethylene-1,2-dicarboxylate give cyclobutane adducts **25** which can be converted to bicyclo[1.1.0]butanes **26**.[25]



25 **26**

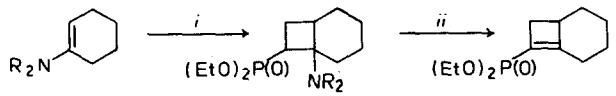
Scheme 9. Reagents: (i) CH_3SO_3Me, −70°; (ii) NaH, THF; Z = CO_2Me or CN.

Cycloaddition of arynes to enamines gives the corresponding aminobenzocyclobutene which undergo amine elimination or ring expansion on thermolysis of the amine oxide.[26]



Scheme 10. Reagents: (i) Δ (n = 2); (ii) Δ (n = 1).

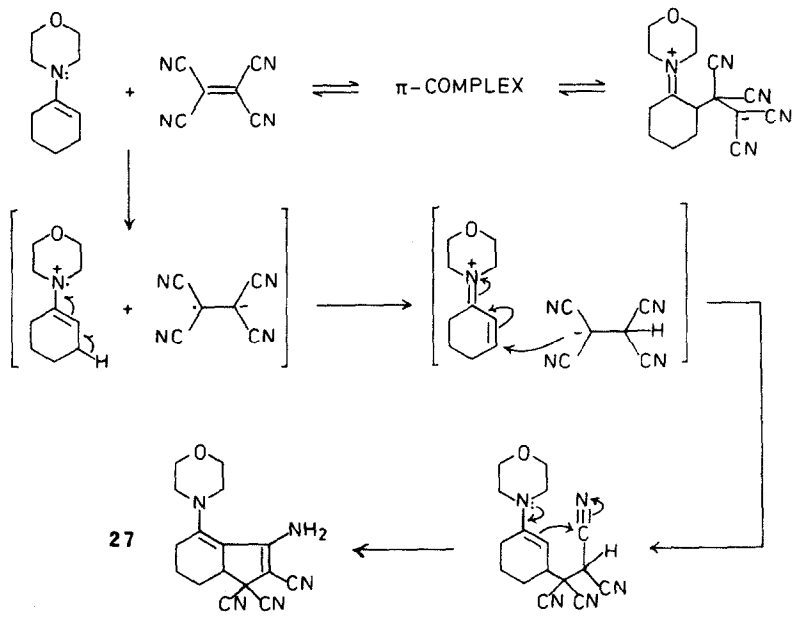
Although enamines do not react with unactivated double bonds as in 4-vinylpyridine, conversion to the pyridinium salt increases the polarization of the double bond sufficiently to allow reaction with aldehyde enamines (without a β-hydrogen) to give pyridylcyclobutanes.[27] Cycloaddition to vinylphosphonates gives cyclobutanephosphonates from aldehyde enamines and bicyclo[4.2.0]octanephosphonates from cyclohexanone enamines.[28]



Scheme 11. Reagents: (i) CH_2=CHP(O)$(OEt)_2$, 100°; (ii) NaH; R_2N = pyrrolidino.

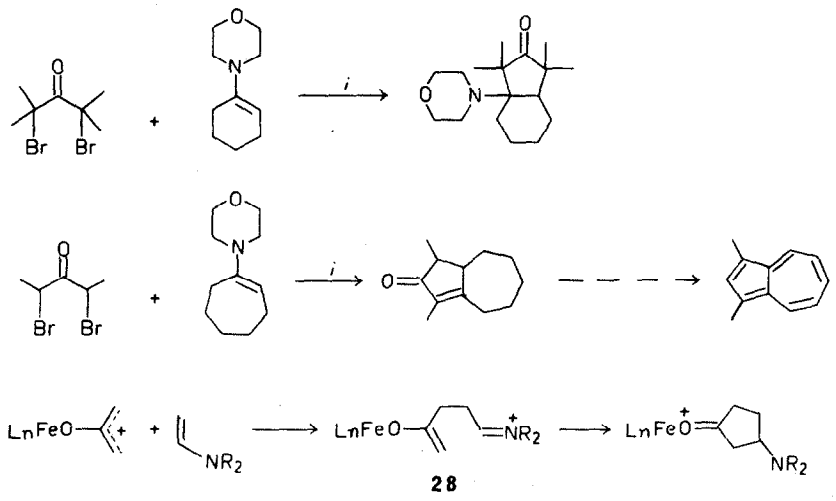
C. *Five-membered rings*

A surprising reaction occurs between cyclohexanone enamines and tetracyanoethylenes to give tetrahydroindenes **27**. The reaction occurs at the γ-position of the enamine and an initial one-electron transfer between the two reagents is proposed (Scheme 12).[29]



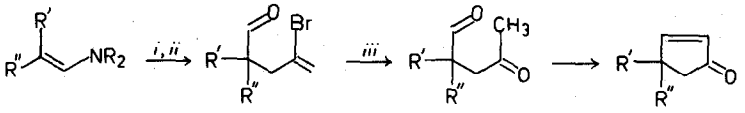
Scheme 12.

A variety of five-membered ring containing systems can be obtained in high yield from the iron carbonyl promoted reaction of α,α'-dibromo ketones and enamines.[30] If secondary dibromides are employed the initially formed β-morpholinocyclopentanone suffers ready elimination of morpholine to give a cyclopentenone. Spiro-annulation can be carried out using enamines of cycloalkanecarboxaldehydes to give spiro [n.4] alkenones. The mechanism is believed to involve the formation of an oxyallyl-Fe(II) intermediate **28**.[30]



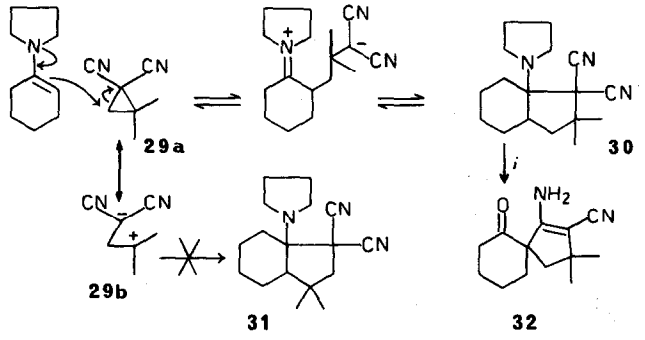
Scheme 13. Reagents: (i) $Fe_2(CO)_9$.

Cyclopentene formation, or spiro-annulation, can also be effected by reaction of aldehyde enamines with 2,3-dibromopropene or 2-chloro-3-idopropene which act as 2-oxopropyl synthons.[31,32]



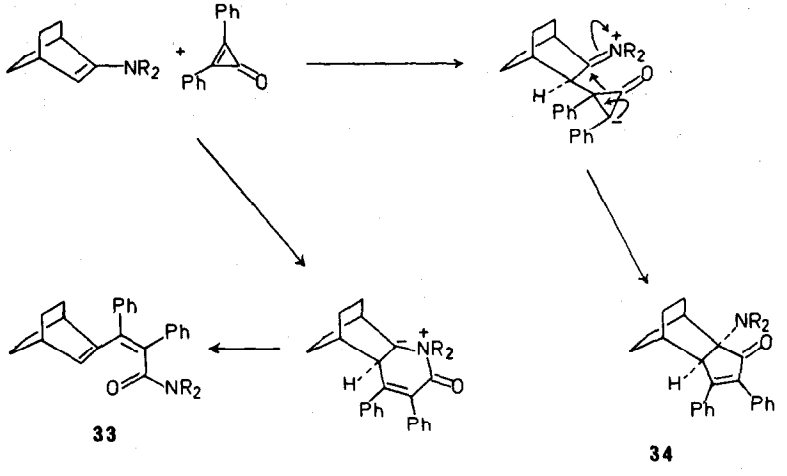
Scheme 14. Reagents: (i) $CH_2=C(Br)CH_2Br$, Δ, THF; (ii) H_2O, 20°; (iii) conc. H_2SO_4, O°[31], or mercuric acetate/boron trifluoride etherate.[32]

While activated cyclopropanes **29** suffer nucleophilic ring opening almost exclusively at the more substituted position (i.e. via zwitterion **29b**), enamines attack the less substituted position **29a** via an S_N2 mechanism to give **30** rather than **31**. The perhydroindene **30** undergoes ring opening on heating in aqueous ethanol and recyclisation to the spiro[4.5]decenone **32**.[33]



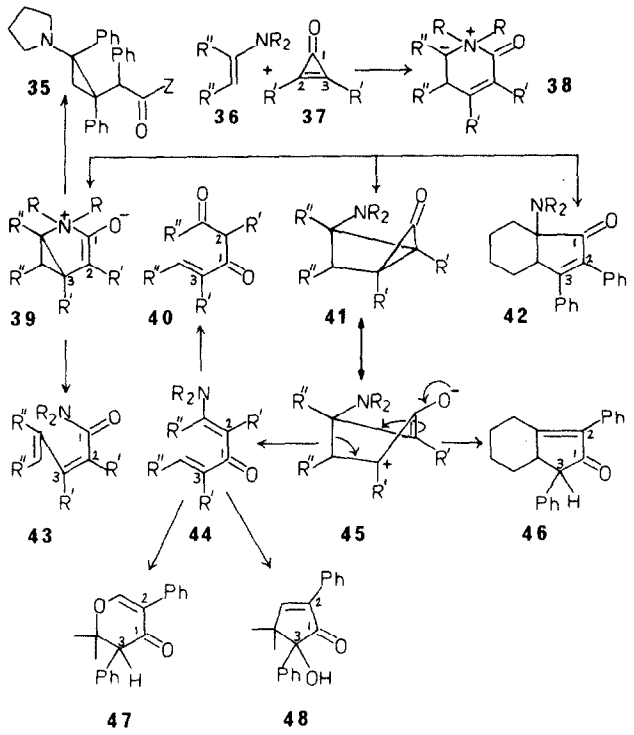
Scheme 15. Reagents: (i) 95% EtOH, Δ 19 h.

Further work on the reaction of enamines with diphenylcyclopropenone has shown that a variety of products can be formed, arising from C,N- or C,C-insertions, condensation, and addition. Bicyclic enamines give the exo fused enone 34 and, in some cases, the amide 33.[34]



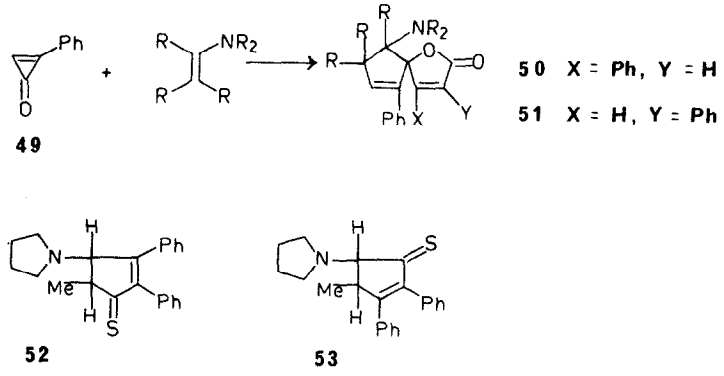
Scheme 16.

The early work of Ciabattoni and Berchtold[35] on the cycloaddition of enamines to diphenylcyclopropenone **37** (R′ = Ph), which was reported to give enamino ketones **44**, has been reinvestigated and shown to be incorrect.[36] Instead of obtaining the product of C,C-insertion **44** these workers had apparently obtained the product derived from C,N-insertion which attaches a C_3 side chain to the α-carbon of the enamine to give an amide **43** as the main product. In fact the reaction is complex and several products can be isolated (**35**, **39**, **40**, **42**, **43**, **44**, **46**, **47**, **48**), derived as indicated in Scheme 17. The primary adduct **39** has been isolated and converted into cyclopropane derivatives **35** (Z = OMe, OEt, NR_2) by acidification and ring opening with alcohols or amines.[37] Alternatively on heating in benzene the adduct **39** ring opens to give the amide **43** [R′ = Ph; R″ = H, Me, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_{10}-$] derived



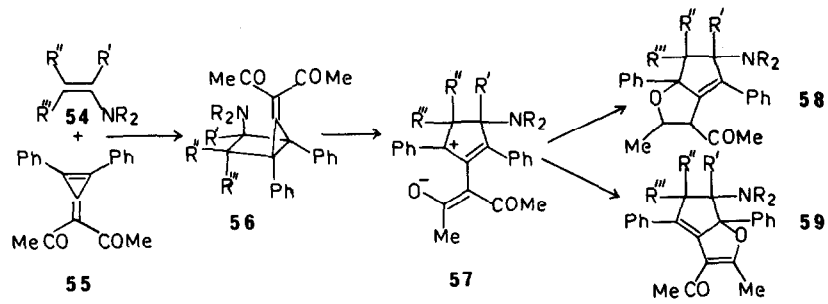
Scheme 17. R_2N = pyrrolidino.

by overall C,N-insertion. Also isolated from the reaction were the cyclopentenones **42** and **46**.[38] Products of C,C-insertion **44** have also been isolated as minor components of the reaction mixture and converted by acid into the dihydropyrone **47** and cyclopentenone **48**[38] or the dione **40** (R″, R″ = $-(CH_2)_{10}-$, R′ = Me, n-Pr, Ph).[39] Phenylcyclopropenone **49** additionally gave 2 : 1 adducts which have been assigned[40] spiro-lactone structures **50** and **51**. Reaction of 1-(pyrrolidin-1-yl)propene with diphenylcyclopropenethione has been reported[41] to give the cyclopentenethione **52**. However the spectroscopic evidence would also fit the isomeric structure **53**, derivable in the same way as **42** but from the thione analogue of **38** (Scheme 17).



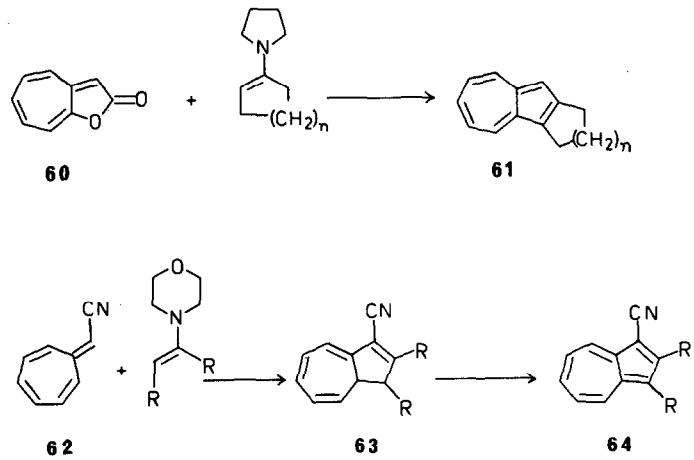
Scheme 18.

The analogous reaction with the diacylmethylenecyclopropene **55** gave the dihydrocyclopenta(b)furans **58** and **59**.[42] Although the mechanism was not given these presumably arise from ring opening of **56** (the analogue of structure **41** in Scheme 17) to give **57** which can collapse to **58** and **59**.



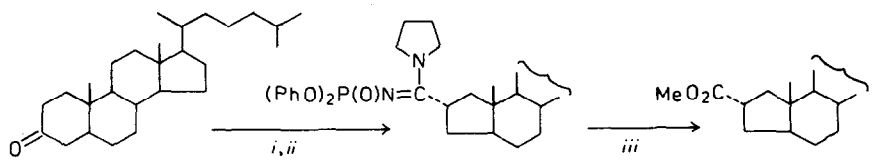
Scheme 19. Substituents: R′,R″ = Ph, H; H, Me; Ph, Me; $(CH_2)_n$(n = 3, 4, 6, 10); R‴ = H, Me; R_2N = morpholino, pyrrolidino.

Condensation of pyrrolidine enamines with the cyclohepta[b]furanone **60** give 1,2-polymethyleneazulenes **61**, with elimination of carbon dioxide and pyrrolidine.[43] Similarly cycloaddition of enamines to 8-cyanoheptafulvene **62** gives adducts **63** which can be oxidised (with tetrachloro-p-benzoquinone) to the corresponding azulene **64**.[44]



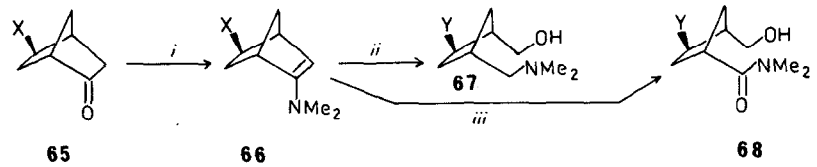
Scheme 20. Substituents: R = alkyl or ring residues; n = 1–3.

1,3-Dipolar addition of diphenylphosphorazidate (DPPA) to cholestanone and other cyclic ketone enamines results in ring contraction via a labile triazoline (see Part I, Section 5G).[45,46]



Scheme 21. Reagents: (i) pyrrolidine; (ii) $(PhO)_2P(O)N_3$, THF, 40°; (iii) 20% aq. HCl, MeOH/HCl.

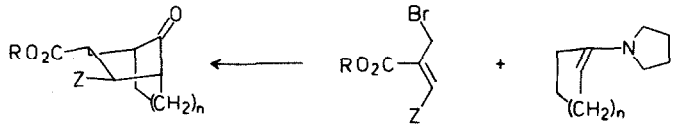
Bicyclic enamines have been prepared[47] by the method of Nelson and Pelter.[48] Oxidative cleavage of the enamine double bond gives access to cis-1,3-substituted cyclopentanes **67** and **68**.



Scheme 22. Reagents: (i) $(Me_2N)_3B$, Me_2NH, K_2CO_3, 100°, (ii) O_3, $LiAlH_4$; (iii) O_3, aq. $NaHB_4$; X = H, OAc, OTHP, OCH(Me)OEt; Y = H, OCH(Me)OEt.

D. *Six-membered rings*

(i) *Alicyclic.* Several useful reagents are available for the α,α'-annulation† of ketone enamines. Ethyl α-bromomethylacrylate (**71**; R = Et, Z = H), or a mixture of its precursor ethyl β,β'-dibromoisobutyrate and triethylamine, or dimethyl γ-bromomesaconate (**71**; R = Me, Z = CO_2Me) give the corresponding bicyclo[3.2.1]octanone **69**[53] or bicyclo[3.3.1]nonanone **70**.[54]



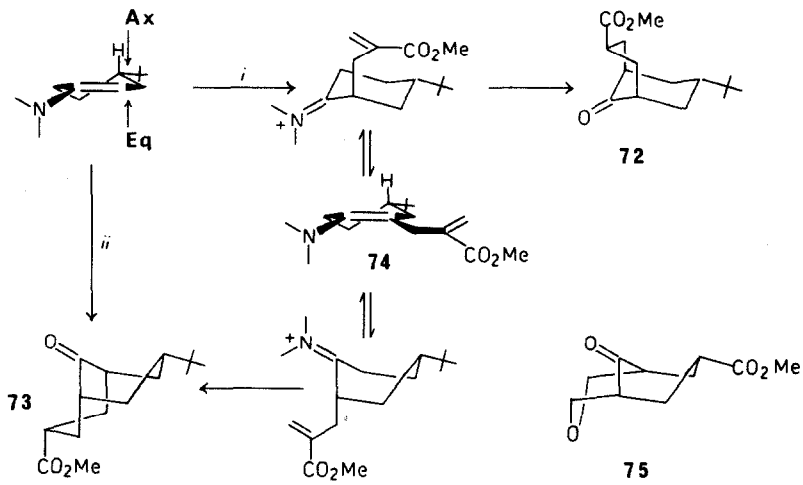
69 n = 1

70 n = 2

71

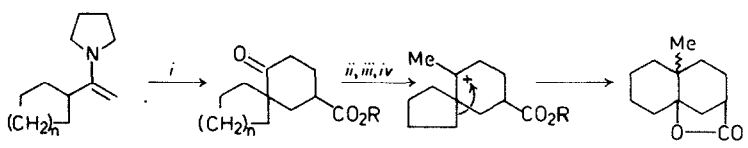
Scheme 23.

When the reaction was applied to 4-t-butylcyclohexanone enamine a mixture of two products (**72** and **73**) formally derived by axial and "equatorial" attack was obtained, although it was assumed that these were generated through epimerisation of the initially formed monoalkylation product, via the more substituted enamine **74**, prior to cyclisation.[55]



Scheme 24. Stereochemistry: (i) axial attack; (ii) equatorial attack.

The pyrrolidine enamine of 4-oxacyclohexanone and methyl β, β'-dibromoisobutyrate gives methyl 3-oxa-9-oxobicyclo[3.3.1]nonane-7-endo-carboxylate **75**.[56] A similar reaction with the pyrrolidine enamine of 2-acetylcyclopentane (or cyclohexane) gives the spiroketone **76**[57] which can be ring expanded

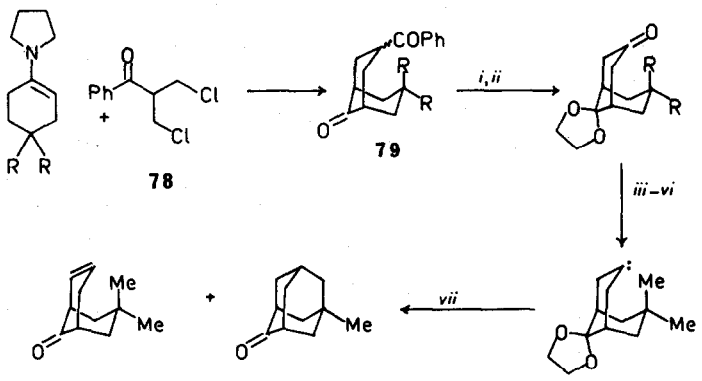


76 **77**

Scheme 25. Reagents: (i) CH_2=C(CH_2Br)CO_2Me; (ii) CH_2=PPh_3; (iii) BF_3/HOAc; (iv) n = 1.

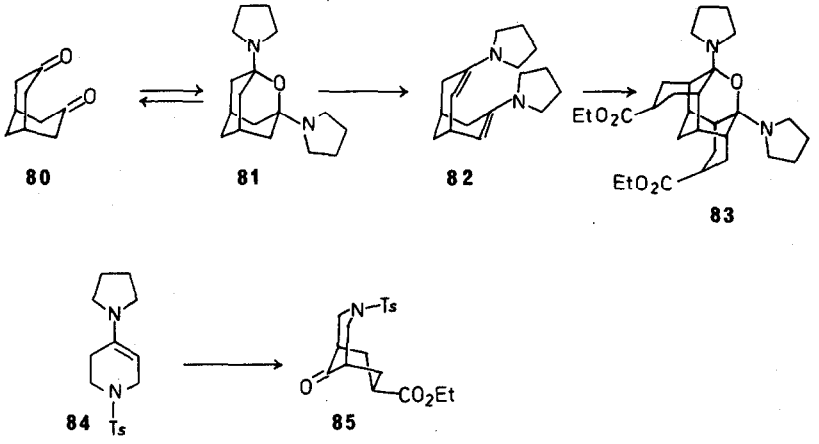
to the decalin γ-lactone **77**.[58] α,α'-Annulation of cyclohexanone enamines with 2,2-bis(chloromethyl)acetophenone **78** gives the corresponding 3-benzoylbicyclo[3.3.1]nonan-9-one **79**. This has been utilised in an adamantane synthesis by carbene insertion into an adjacent methyl group.[59]

†For recent reviews on general methods of annulation see Refs. 49–52.



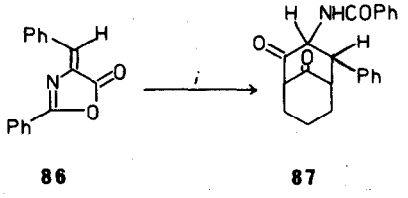
Scheme 26. Reagents: (i) $HOCH_2CH_2OH$, p-TSA; (ii) t-BuOK, O_2, DMSO; (iii) p-$CH_3C_6H_4SO_2NHNH_2$; (iv) R = Me; (v) BuLi, THF; (vi) 180°; (vii) 3% HCl, dioxane.

Bicyclo[3.3.1]nonane-3,7-dione **80** can be condensed with pyrrolidine to form 1,3-dipyrrolidino-2-oxaadamantane **81** which can be converted to the mono or bis-pyrrolidinoenamine of **80**. Bis-annulation of the bis-enamine **82** with ethyl α-bromomethylacrylate leads to the polycycle **83**.[60] The corresponding reaction with the N-tosyl piperidone enamine **84** gives the substituted 3-azabicyclo[3.3.1]nonane **85**.[61]



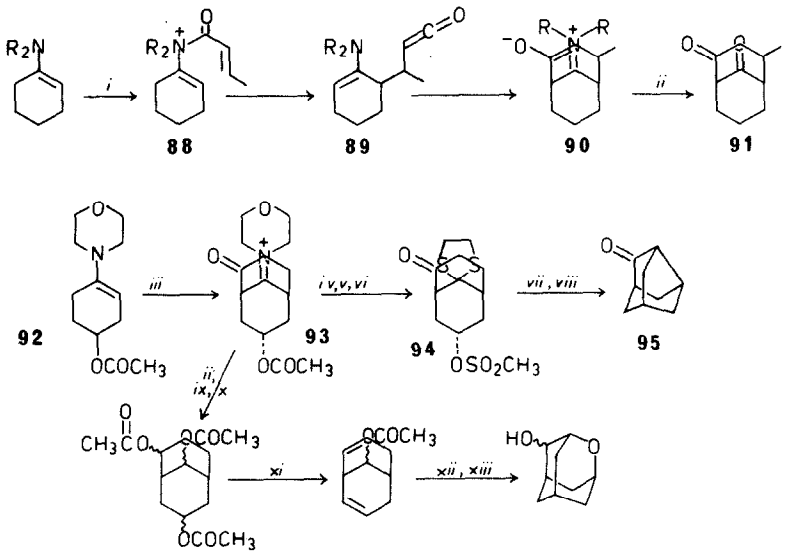
Scheme 27.

4-Benzylidene-5-oxazolone **86** has also been reported to yield bicyclo[3.3.1]nonane-2,9-dione **87** in low yield.[62]



Scheme 28. Reagents: (i) 1(pyrrolidin-1-yl)cyclohexene.

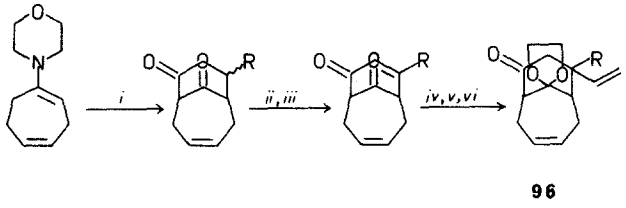
Similar α,α'-annulations can be carried out with $\alpha\beta$-unsaturated acid chlorides. This has been shown to occur via a [3,3] sigmatropic rearrangement of the N-acylated enamine **88** to give a keten intermediate **89** which cyclises on to the regenerated enamine to give an enolate anion **90**. Protonation and hydrolysis then gives the corresponding bicyclo[3.3.1]nonane-2,9-dione **91**.[63]



Scheme 29. Reagents: (i) $CH_3CH{=}CHCOCl$; (ii) H_2O, 0°; (iii) $CH_2{=}CHCOCl$; (iv) $HSCH_2CH_2SH$; (v) aq. Na_2CO_3, MeOH; (vi) $MeSO_2Cl$; (vii) NaH, dioxane; (viii) Ni, EtOH, 35°; (ix) $LiAlH_4$; (x) Ac_2O, pyridine; (xi) 530°; (xii) $Hg(OAc)_2$; (xiii) $NaBH_4$.

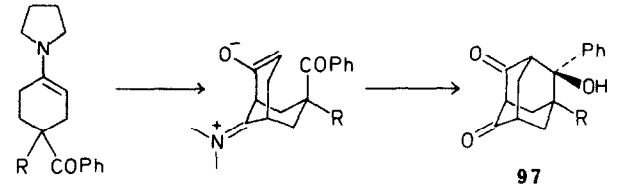
The use of a conformationally stable enamine from 2-methyl-4-t-butylcyclohexanone has shown that initial carbon–carbon bond formation (88→89) occurs predominantly from an axial direction despite developing 1,3-diaxial interactions with the 6-methyl substituent. X-ray analysis shows the molecular conformation of the bicyclic dione produced to be boat-chair.[64]

This reaction has also been used[65] to prepare heteroadamantane and noradamantane derivatives from the morpholine enamine of 4-acetoxycyclohexanone **92**. The high stereoselectivity of the annulation is again demonstrated by the formation of the required equatorial epimers **93** and **94** thus allowing subsequent cyclisation to the noradamantane system **95**.



Scheme 30. Reagents: (i) RCH=CHCOCl [slow addition (2–6 h) at 80° or rapid addition at 20°]; (ii) $PhN^+Me_3Br^-$, THF, 0°; (iii) Li_2CO_3, LiBr, DMF, 100°; (iv) ethylene glycol/H^+, 80°; (v) aq. $MgSO_4$; (vi) $CH_2{=}CHMgBr$, MeCu.

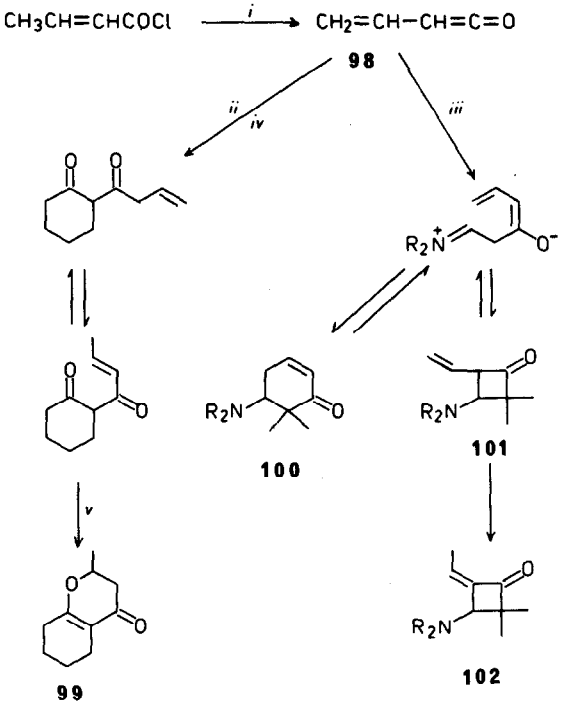
The reaction has also recently been applied to the successful synthesis of the functionalised bicyclo[4.3.1]decanone system **96** in high yield.[66] If there is an axially orientated electrophilic substituent at C-4 of the enamine then the enolate anion intermediate may cyclise to an adamantane derivative **97** as a mixture of epimers. In this reaction three carbon–carbon bonds are formed sequentially between the acid chloride and the enamine in a one-pot synthesis.[67]



Scheme 31.

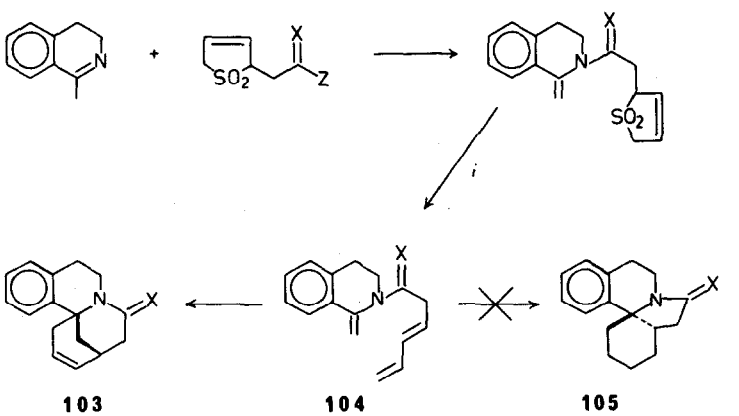
In the presence of triethylamine the course of the reaction changes dramatically owing to dehydrochlorination of the $\alpha\beta$-unsaturated acid chloride to give a vinylketen **98**. The reaction is then directed

through a C-acylation pathway, rather than N-acylation which is reversible, and leads to dihydro-γ-pyrones **99** in the case of cyclic ketone enamines and to cyclohexenones **100** and cyclobutanones **101** or **102** in the case of aldehyde enamines.[63]



Scheme 32. Reagents: (i) Et_3N; (ii) 1-N-morpholinocyclohexene; (iii) $R_2NCH{=}CMe_2$; (iv) 2NHCl, Δ, 5 h; (v) conc. HCl, 18 h, 20°.

An interesting synthesis of a bicyclo[3.3.1]azanonane system has recently appeared involving a [4+2]cycloaddition of an enamine (or an enamide†), functioning as an electron-rich dienophile, with an unactivated diene.[68] The enamine and diene were generated *in situ* by N-alkylation (or acylation) of 1-methyl-3,4-dihydroisoquinoline and sulphur dioxide extrusion respectively, the resulting intermediate **104** cyclising to the bridged system **103** rather than the expected fused bicyclic system **105**.

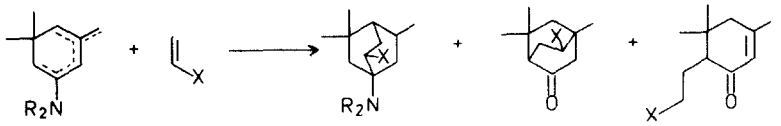


Scheme 33. Reagents: (i) 138°; X = H_2, O.

Reactions in which there is a net volume contraction in approaching the transition state are accelerated by high pressure (8–20,000 atm). Thus the thermal cycloaddition of enamines to electrophilic dienes[69] generally goes in higher yield at room temperature under high pressure.[70] Interestingly, in the

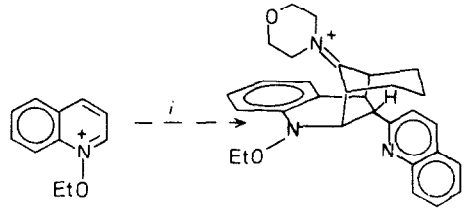
†Outside the scope of this report; but see also S. F. Martin, S. R. Desai, G. W. Phillips and A. C. Miller, *J. Am. Chem. Soc.* **102**, 3294 (1980).

cycloaddition of dienamines[71] to electrophilic olefins,[72] high pressure causes a change in the regiochemistry of the reaction[70] (Scheme 34), only the Diels–Alder adduct being obtained.

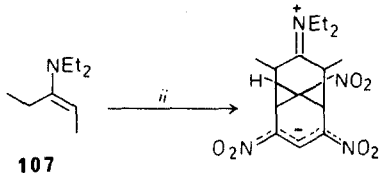


Scheme 34.					
R_2N = morpholino, X=CO_2Me	Pressure	53%	0%	0%
	Thermal	0	29	23
R_2N = piperidino, X=CN	Pressure	90	0	0
	Thermal	0	10	20.

Enamines are also reported to undergo two-step cycloaddition to a phosphonate activated butadiene and the product deaminated to a cyclohexadiene phosphonate.[73] α,α'-Annulation of enamines can also be effected with quinolinium salts[74] (106 → 109) and s-trinitrobenzene[75] (107 → 108).



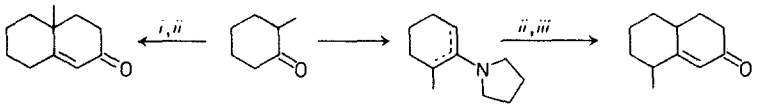
106 109



107 108

Scheme 35. Reagents: (i) 1-N-morpholinocyclohexene; (ii) 1,3,5-trinitrobenzene, 35°, 24 h.

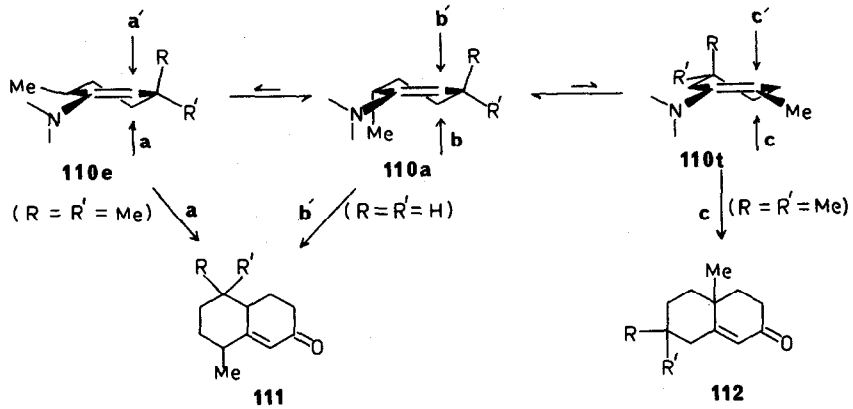
The Stork reaction[76] of methyl vinyl ketone (MVK) and enamines provides a complementary annulation procedure to the Robinson method:



Scheme 36. Reagents: (i) acid or base; (ii) CH_2=CH.COMe; (iii) H_3O^+.

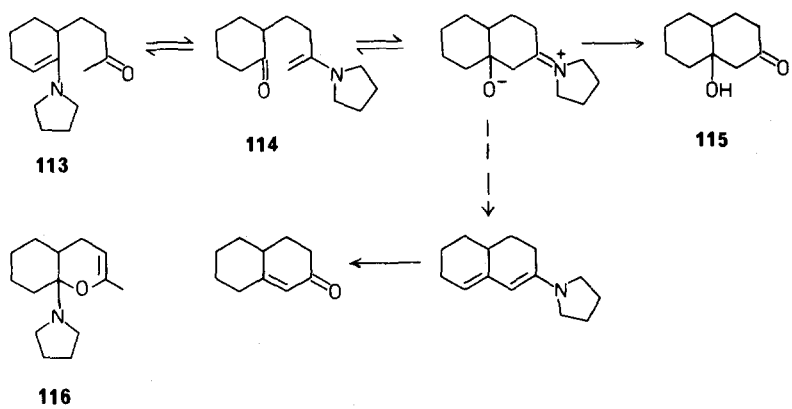
The change in the regioselectivity of the reaction is attributed to the greater *reactivity* of the less substituted form of the enamine rather than the preference for the *formation* of the less substituted form of the enamine as often stated in books and reviews (see Part I). The recently reported[77] change in the regioselectivity of the Stork reaction when substituents are present at both C-2 and C-5 of cyclohexanone has been explained in terms of the changes in the factors affecting the reversibility and energetics of the competing reaction pathways.[78] In the three conformations of the derived enamine equilibrium mixture (**110e**, **a** and **t**) reactions by paths a, a', c and c' are high energy processes owing to the developing allylic strain[79] between the Me group and the pyrrolidine ring when these groups approach coplanarity in the transition state of the reaction. Since there is ample evidence that electrophilic olefins can attack a cyclohexanone enamine from both the axial and so-called "equatorial" direction (i.e. in the plane of the p-orbitals but from the opposite face), then in aprotic solvents attack by path b' is favoured when R = R' = H, leading to octalone (**111**). When R = R' = Me path b' is sterically prevented and the

other low energy route (path b) is reversible [i.e. gives a zwitterion which cannot be stabilised by intramolecular proton transfer or undergo charge neutralisation by collapse to a cyclic intermediate (i.e. dihydropyran or cyclobutane) because of the C-3 Me group]. This leaves paths a and c available for product formation and since the former is additionally destabilised by developing gauche butane interactions with the C-6 equatorial substituent, path c is the most favoured energetically and thus leads to a majority of the cyclised product (**112**) derived from initial attack at the more substituted enamine position [see also Part I, Section 5B(i)].[78] See Note added in proof for an alternative explanation.



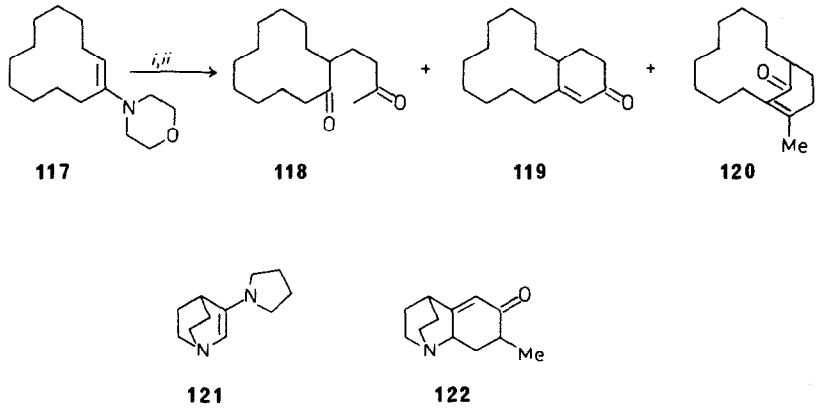
Scheme 37.

The isolation in a number of cases[80,81] of the intermediate ketol (i.e. **115**) suggests that the final cyclisation step occurs via nucleophilic attack by a side-chain enamine on the regenerated cyclohexanone carbonyl function. This implies a trans-enamination process (**113**→**114**) catalysed by a trace of water (or free enamine). The dihydropyran **116** is undoubtedly the first formed adduct, but this ring opens even at room temperature.[83]



Scheme 38.

However as Stork has pointed out, this annulation mechanism applies only to the more reactive pyrrolidine enamine.[82] With the less reactive morpholine enamine cyclisation of the initial alkylation product must occur via an enolate mechanism, the final product being the octalone itself rather than the dienamine.[76] When a large flexible cycloalkanone enamine **117** is used, a bridged enone **120** is formed in addition to the monoalkylation production **118** and the fused enone **119**.[84] The relatively inert 3-quinuclidinone enamine (**121**) was converted into the quinolone (**122**) with isoprenyl methyl ketone.[85]

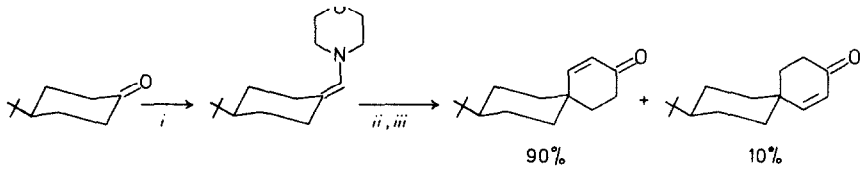


117 118 119 120

121 122

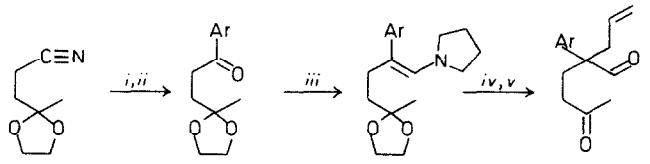
Scheme 39. Reagents: (i) CH_2=CHCOMe; (ii) H_2O, Δ.

Application of this reaction to aldehyde enamines gives cyclohexenones[76] and combination of this method with the previously described carbonyl homologation (Part I, Section 4C) provides a valuable stereoselective method for spiroannulation[86] of cyclic ketones:

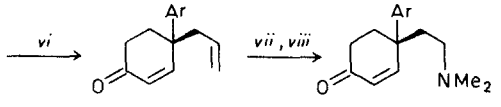


Scheme 40. Reagents: (i) diethyl pyrrolidinomethylphosphonate; (ii) CH_2=CHCOMe; (iii) H_3O^+.

The key step in several elegant syntheses[88] of Sceletium alkaloids involves the direct carbonyl homologation of the monoprotected 1,4-dione (**123**). Subsequent alkylation of enamine (**124**) generated a fully substituted carbon centre that was suitably functionalised for transformation into (±)-O-methyljoubertiamine **125**. Carbonyl homologation provides a means for the construction of a quaternary carbon



123 124

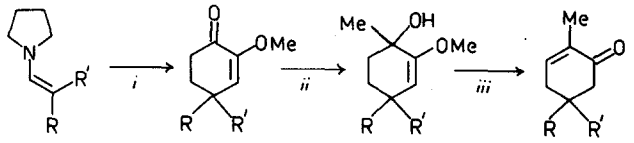


125

Scheme 41. Reagents: (i) p-$MeOC_6H_4MgBr$; (ii) NH_4Cl, H_2O; (iii) $(CH_2)_4NCHLiP(O)(OEt)_2$, THF, −78→25°; (iv) CH_2=$CHCH_2Br$, dioxane, Δ; (v) H_3O^+; (vi) aq. KOH.; (vii) O_3, CH_2Cl_2, −78°; (viii) $Me_2\overset{+}{N}H_2Cl^-$, $NaBH_3CN$, t-BuOH.

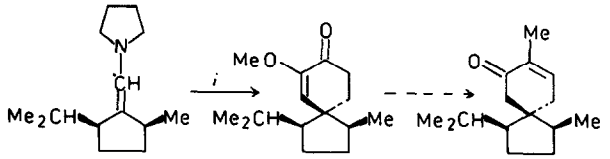
centre bearing the same or different substituents, by geminal alkylation of a carbonyl carbon (viz. $R_1COR_2 \rightarrow R_1R_2C{=}CH{-}NR_2 \rightarrow R_1R_2C(R_3){-}CH{=}\overset{+}{N}R_2 \rightarrow R_1R_2C(R_3){-}CH{=}O \rightarrow R_1R_2CR_3R_4$).

The use of 1-methoxybut-3-en-2-one instead of MVK, in the absence of solvent, provides a means for subsequent 1,2-carbonyl transposition.[87]



Scheme 42. Reagents: (i) CH_2=$CHCOCH_2OMe$, HOAc; (ii) MeMgI; (iii) p-TSA/C_6H_6, Δ, or $POCl_3/C_5H_5N$; R.R′ = alkyl or ring residues.

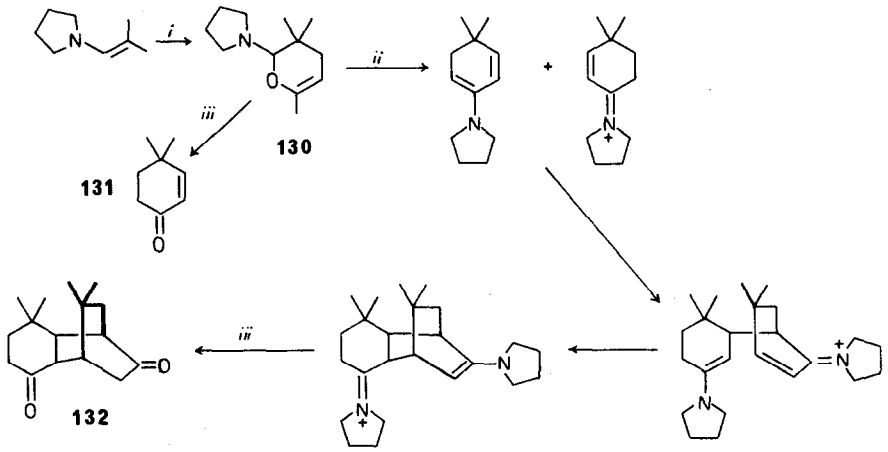
A critical step in the synthesis of the spirosesquiterpene (−)acorenone **129** involved the spiroannulation of the enamine **126** with 1-methoxybut-3-en-2-one **127** and an equivalent of acetic acid in the absence of solvent.[89] The intermediate **128** was that expected from initial Michael reaction at the least



126 **128** **129**

Scheme 43. Reagents: (i) 1-methoxybut-3-en-2-one (**127**), HOAc (1 equiv), no solvent.

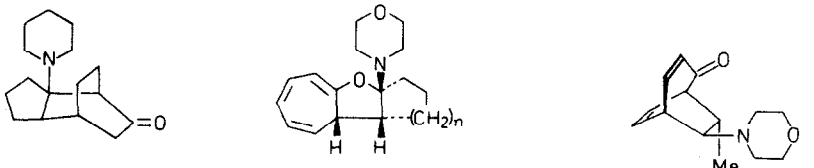
hindered α-face of the enamine followed by cycloaldolization. Interestingly when acetic acid was not present in the initial stages of the reaction an unidentified C_{15} product was formed. Presumably the acetic acid prevents the formation of this unidentified compound by promoting the acid catalysed cycloaldolization step without destroying the reactivity of the enamine by protonation. Also when solvents were used none of the desired **128** was obtained.[89] For an alternative approach to acorane sesquiterpenes involving spironannulation of the five-membered ring see Ref. 32. An interesting illustration of the complications that can arise in enamine reactions is provided by the reaction of methyl vinyl ketone with 1-(pyrrolidin-1-yl)isobutene. At ambient temperature this reaction gives the dihydropyran[90] **130** which undergoes acid catalysed hydrolysis and cyclisation to 4,4-dimethylcyclohex-2-en-1-one **131**. However if the reaction is conducted in boiling benzene the tricyclic diketone **132** is produced[91] as follows:



Scheme 44. Reagents: (i) CH_2=$CHCOMe$, 20°; (ii) 80°; (iii) H_3O^+.

A somewhat analogous reaction has been reported involving the cycloaddition of 1-piperidinocyclopentene and cyclohexenone to give **133**.[92]

The course of an enamine reaction also often critically depends upon whether a ketone or aldehyde enamine is used. For example 1-morpholinocyclohexene and 1-morpholinocyclopentene undergo cycloaddition to tropone to give the cycloheptatriene **134** whereas 1-morpholinopropene gives the bicyclo[3.2.2]nona-3,6-dien-2-one **135**.[94]

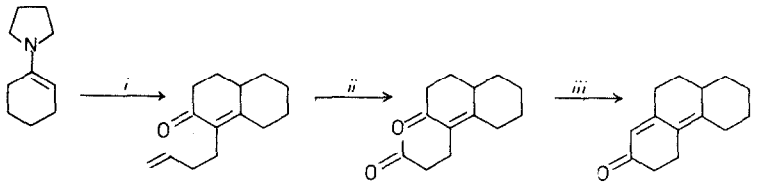


133 134 135

Scheme 45. Ring size: n = 1, 2.

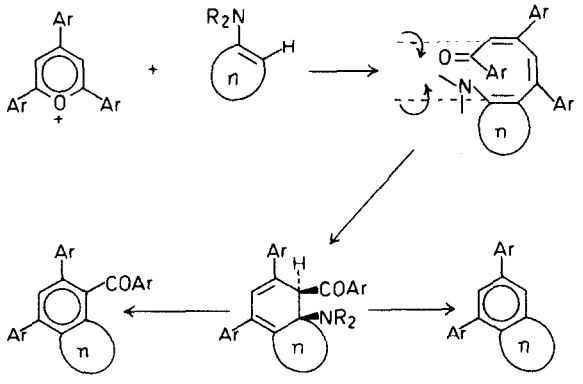
6-Fluorocyclohexenones and 3-fluoro-$\Delta^{1,9}$-octalones have been obtained by annulation of the appropriate enamine with 3-fluorobut-3-en-2-one.[93]

Bis-annulations have been effected using 1,7-octadien-3-one. After the initial annulation an acetyl function is generated by mild oxidation of the terminal olefin followed by further annulation:[95]

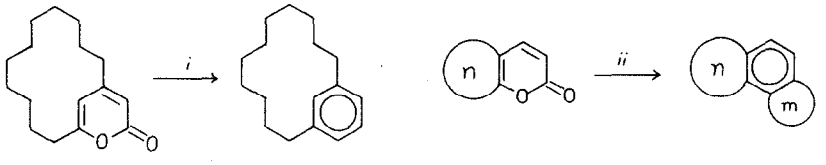


Scheme 46. Reagents: (i) CH_2=$CH(CH_2)_3COCH$=CH_2; (ii) O_2, $PdCl_2$, CuCl, aq. DMF; (iii) $KOC(Me)_2Et$.

(ii) *Aromatic.* Fused ring systems in which the one ring is aromatic can be obtained by cycloaddition

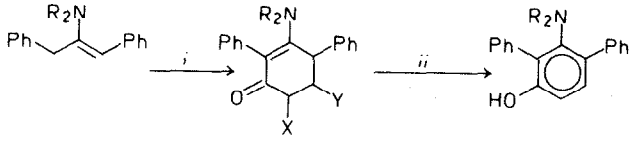


Scheme 47.



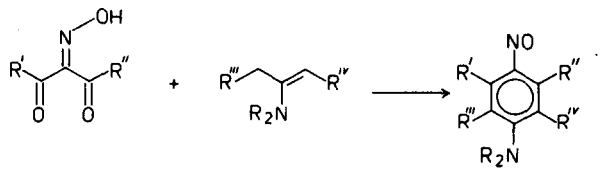
Scheme 48. Reagents: (i) N-vinylpyrrolidone; (ii) enamine of an m-membered ketone.

of pyrylium salts and α-pyrones to enamines.[96-98] The α,α'-annulation of ketone enamines with halogeno α,β-unsaturated acid chlorides is followed by elimination of halogen or hydrogenhalide to give a m-aminophenol.[99]



Scheme 49. Reagents: (i) XCH=CHYCOCl; (ii) − XY(or HX or HY).

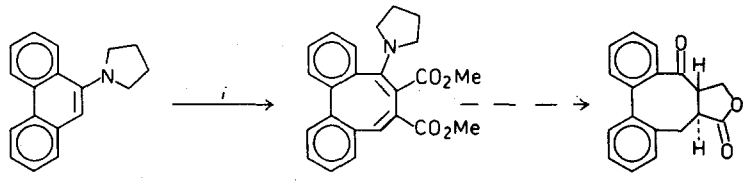
Although enamines do not normally undergo intermolecular reaction with ketone or ester carbonyl groups, condensation with isonitroso-β-dicarbonyl compounds has been reported.[100]



Scheme 50. Substituents: R′,R″ = Me, Ph, Ar, α-furyl, α-thienyl; R‴,R^{IV} = H, CO_2Et; R,R = C_6H_{11}, CH_2CH_2OH, $CHMe_2$, $(CH_2)_n$.

E. *Seven-membered and larger rings*†

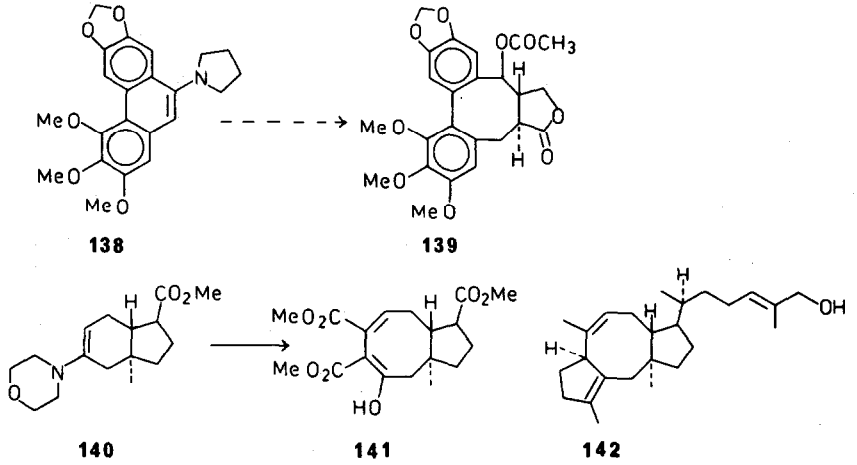
The reaction between enamines and acetylenecarboxylates produce cyclobutene intermediates which on heating lead to cyclic compounds resulting from a two-carbon ring expansion. This useful synthetic transformation has been employed[101] in a route to the analogue **137** of the naturally occurring steganone, starting from enamine **136**.



136 **137**

Scheme 51. Reagents: (i) $MeO_2CC{\equiv}CCO_2Me$.

Application of the same procedure to **138** provided a synthetic route to the antileukaemic lignan (±)-steganacin **139**;[102] in the same way **140** was converted to **141** as part of a programme directed towards the synthesis of sesterpenes such as ceroplastol II **142**.[103]



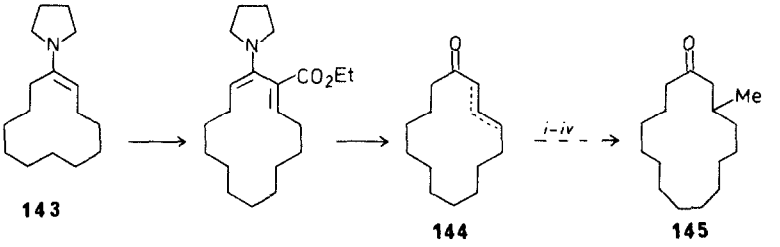
138 **139**

140 **141** **142**

Scheme 52.

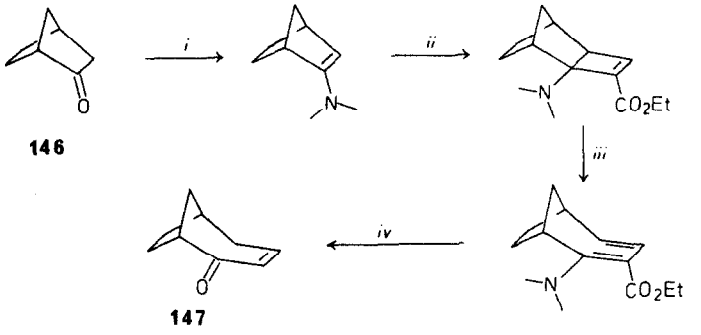
Synthesis of dl-Muscone **145** has been effected from cyclodecanone by ring enlargement of the derived enamine **143** with ethyl propiolate to give the intermediate cyclotetradecenone **144** on acid hydrolysis.[104]

†For reviews of ring expansion of ketene cycloadducts see Ref. 22.



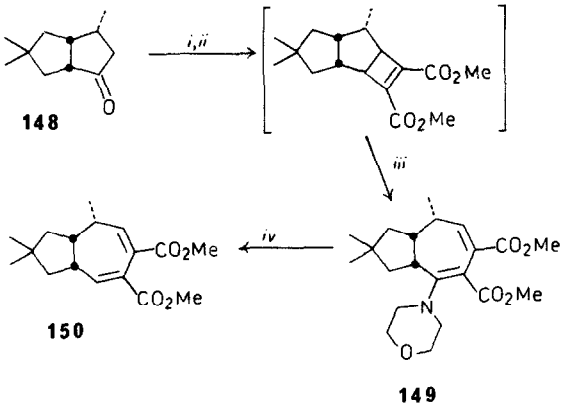
Scheme 53. Reagents: (i) Me_3Si, chloroplatinic acid, Δ; (ii) CCl_2; (iii) Me_2CuLi; (iv) $Cr(ClO_4)_2$.

Bicyclo[4.2.1]non-3-en-2-one **147** has been similarly synthesized in 41% overall yield from norbornanone **146** (Scheme 54).[105]



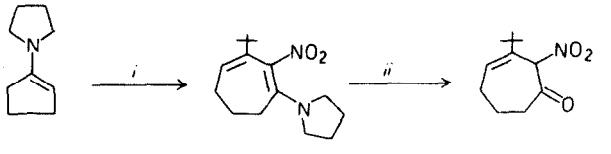
Scheme 54. Reagents: (i) Me_2NH, $SnCl_4$ or $(Me_2N)_3B$; (ii) $HC{\equiv}CCO_2Et$, Et_2O, Δ; (iii) toluene, Δ; (iv) H_3O^+, Δ.

A further example of dimethyl acetylenedicarboxylate[107] cycloaddition and ring expansion is the conversion of the bicyclic ketone **148** to the ring expanded adduct **149** and hence the azulene derivative



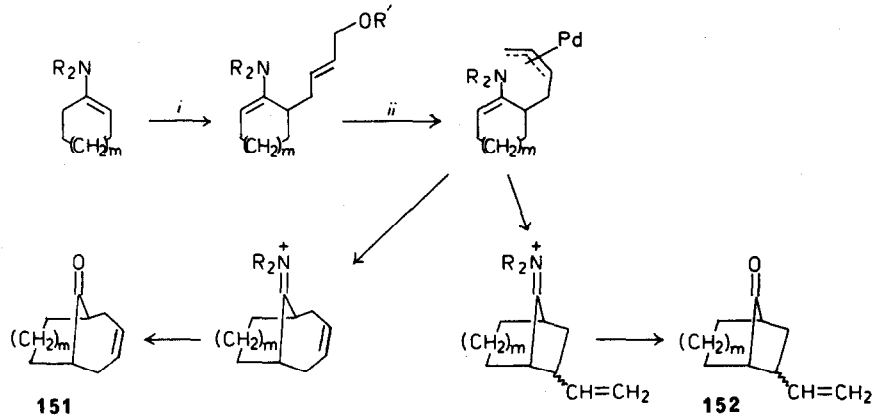
Scheme 55. Reagents: (i) morpholine, H^+, toluene; (ii) $MeO_2CC{\equiv}CCO_2Me$; (iii) Δ; (iv) B_2H_6, 0°.

150 on diborane deamination.[108]. Similar reactions occur with nitroacetylenes.[106]



Scheme 56. Reagents: (i) $Me_3CC{\equiv}CNO_2$, Et_2O, 0°; (ii) 20% H_2SO_4, 30–55°.

Palladium catalysed annulation of enamines with 1,4-diacetoxy- or 1,4-diphenoxybut-2-ene provides a means of introducing a four-carbon bridge to give bicyclo[n.4.1]alkanones **151** in moderate yield. However 1,2-addition (path b) also occurs to give the corresponding bicyclo[n.2.1]alkanone **152**.[109]

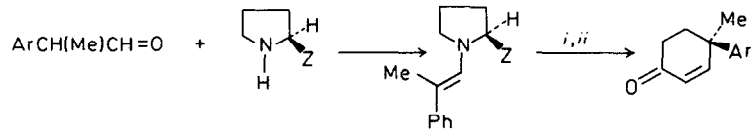


Scheme 57. Reagents: (i) $R'OCH_2CH{=}CHCH_2OR'$; (ii) $Pd(OAc)_2$, PPh_3; $R'{=}CH_3CO$, Ph; m = 0–3.

Somewhat better yields and higher purity seem to be obtained by using 1,4-dichlorobut-2-ene with ethyldiisopropylamine and potassium iodide in dimethylformamide.[110]

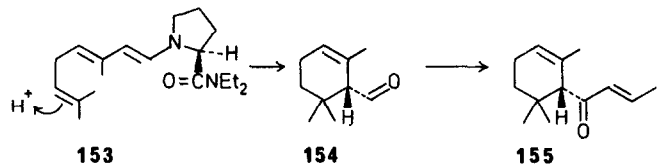
F. *Asymmetric induction*†

The Stork reaction between methyl vinyl ketone and enamines derived from chiral amines is of particular interest since chiral cyclohexenones[111–114] and $\Delta^{1,8a}$-2-octalones[115] can be obtained which are useful in many natural product syntheses. Optical yields of 20–50% have been reported.



Scheme 58. Reagents: (i) $CH_2{=}CHCOMe$; (ii) aq. HOAc; $Z{=}CO_2R$, $CONR_2$, CH_2NR_2, Me, $CHMe_2$.

Acid-catalyzed cyclization of the chiral enamine **153** gives (R)-α-cyclocitral **154** and hence trans-α-damascone **155** in 33% enantiomeric excess.[116]

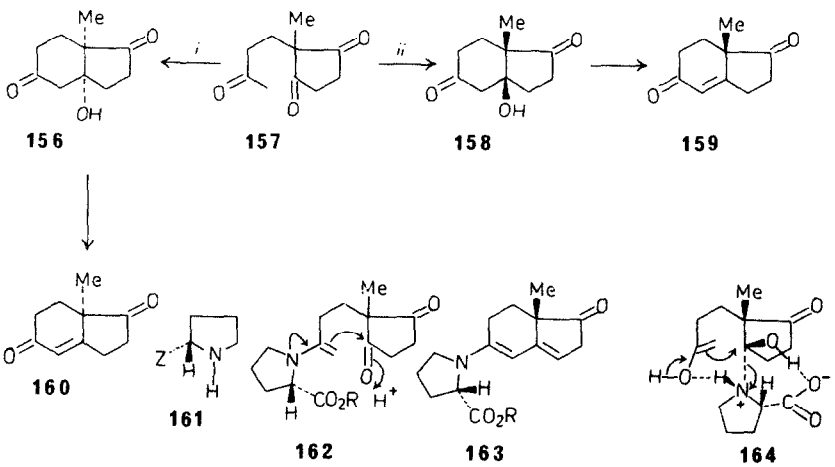


Scheme 59.

Several reports[117–120] of enantioselective intramolecular aldol condensations of type **157**→**158**, catalysed by optically active secondary but not tertiary amines, have appeared recently. The underlying principle is that an optically active asymmetric reagent can differentiate between the two identical (enantiotopic) groups attached to the quaternary carbon in triketone **157** and thus convert this prochiral centre into a chiral one. Thus Hajos and Parrish have claimed[118] incredible chemical and optical yields of over 90% for the transformation **157**→**158** using catalytic amounts of (S)-proline (**161**; $Z = CO_2H$). (S)-Homoproline (**161**; $Z = CH_2CO_2H$) was found to induce opposite chirality (i.e. **157**→**156**) (optical

†For a review of the catalytic asymmetric hydrogenation of prochiral enamides (outside the scope of this report) to chiral amides and amines, using rhodium complexes of chiral phosphines and diphosphines, see D. Valentine and J. W. Scott, *Synthesis* 329 (1978), and Refs therein.

yield 58%, chemical yield 99%).[119] To complicate the issue still further, Eschenmoser *et al.*[120] have found that the (S)-proline anilide (**161**; Z = CONMePh) produces the enantiomer of the product produced by (S)-proline (i.e. **156**) whereas the (S)-homoproline anilide (**161**; Z = $CH_2CONMePh$) produces the same product as (S)-proline (i.e. **158**). No explanation was offered for these apparent anomalies. Although enamines **162** are likely intermediates when proline derivatives are used, since enamine **162** and dienamine **163** intermediates have sometimes been isolated,[121] this has not been established unequivocally in all cases and there seems little point in speculating further about the mechanism at this stage. At least in the case of proline itself it is likely that a non-enamine intermediate **164** is involved[118–121] in the chiral cyclization step.

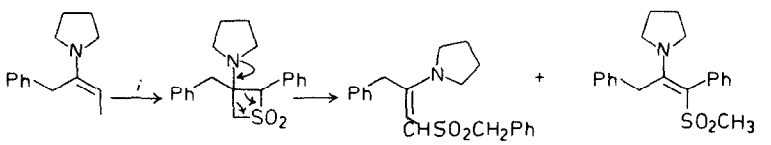


Scheme 60. Reagents: (i) (S)-homoproline or (S)-proline-N-methylanilide or (S)-$PhCH_2CH(NH_2)CH_2CO_2H$; (ii) (S)-proline or (S)-homoproline-N-methylanilide or (S)-$PhCH_2CH(NH_2)CO_2H$.

3. HETEROCYCLIC SYNTHESIS†

A. *Four-membered rings*

The Stork reaction (see Part I, Section 1)[1] with aliphatic sulphonyl chlorides leads to four-membered cyclic aminosulphones (thietane 1,1-dioxides)[122] through the intermediacy of a sulphene (RCH = SO_2).‡ In some cases open-chain sulphones are also obtained. This appears to be favoured by increasing α-substitution of the sulphonyl chloride and of the enamine.[123] For example, open-chain sulphones may be formed in the reaction of sulphone and mono-substituted sulphenes with ketone enamines,§ and in the reaction of disubstituted sulphenes with aldehyde and ketone enamines.[123] Except where there has been an obvious skeletal rearrangement (see **165**, Scheme 61) it is not known whether the open-chain sulphones are formed by direct C-acylation of the enamine or ring-opening of the thietane cycloadduct.[123]



165

Scheme 61. Reagents: (i) CH_3SO_2Cl, Et_3N.

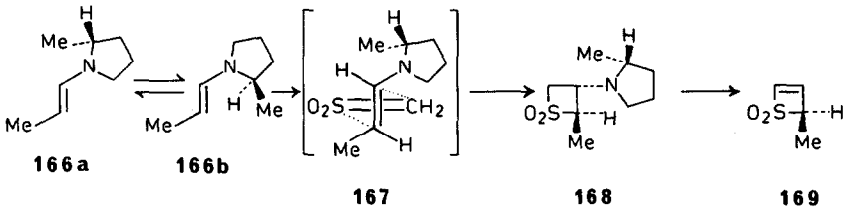
Although cycloaddition of the sulphene seems generally to have been regarded[8] as a two-step process involving a zwitterionic intermediate, evidence for a concerted process also exists in that the cycload-

†If a reaction leads to a mixture of two ring systems differing in size, for example by 1,2- and 1,4-addition of a reagent or subsequent ring expansion of the smaller ring system, the reaction is discussed in the section dealing with the smaller ring system.

‡For a summary of the extensive early literature on this subject see Ref. 8, 123 and 125.

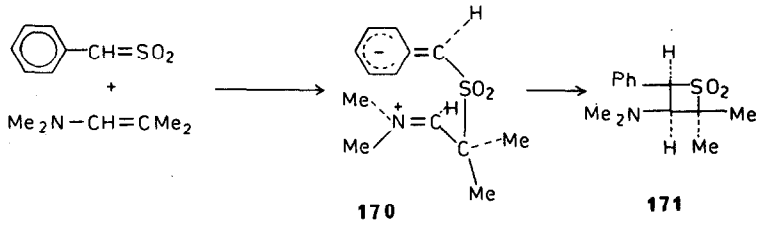
§In the case of α-cyanosulphene only the open-chain sulphone is isolated from the reaction with 1-morpholinocyclohexene.[124]

dition to E or Z N-arylenamines has been claimed to be stereospecific.[126] Also Paquette *et al.*[127] have



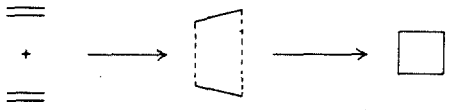
Scheme 62.

demonstrated that (R)-(−)-4-methylthiete 1,1-dioxide (**169**) is formed in 25% enantiomeric excess after cycloaddition of sulphene to the optically active enamine (**166**) followed by Hofmann elimination. These workers assume a product-like transition state for thietane ring formation and, from a product development control argument, conclude that the lowest energy process involves a $\pi^2s + \pi^2a$ orthogonal approach of sulphene from the underside of conformer **166a**, to give a transition state such as **167**, and conclude that the reaction is therefore a concerted process. However this argument falls apart if the transition state is reactant-like, in which case conformer **166a** would be expected to react equally well from either side so the observed asymmetric induction would then result from preferential attack on **166b** from the under-side. This therefore constitutes no proof of the concertedness of the reaction, and neither does the reported formation of the exo adduct from the stereoselective cycloaddition of sulphene to bicyclic enamines.[128] The stereoselectivity which results when an aryl or halogenosulphene, formed by dehydrochlorination of the sulphonyl chloride[129] or from the aryldiazomethane and sulphur dioxide,[130,131] reacts with an enamine to give the thermodynamically less stable cis cycloadduct **171** (Scheme 63) can be explained in terms of concerted cycloaddition or electrostatic attraction between the developing positive and negative centres of the 1,4-dipolar zwitterionic intermediate **170**. The fact that more trans cycloadduct is formed when a substituent is present which cannot assume appreciable negative character (as in an alkyl sulphene) argues for the intermediacy of a zwitterionic intermediate and a step-wise process.



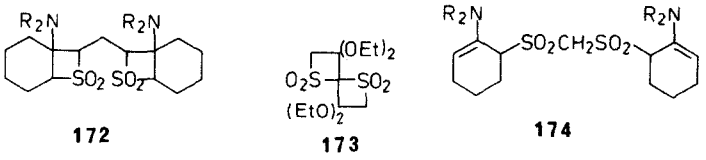
Scheme 63.

However to complicate the issue still further it has been shown[132] that the "allowed" $\pi^2s + \pi^2a$ orthogonal approach (see **167**, Scheme 62) is a higher energy process than the orbital symmetry forbidden $\pi^2s + \pi^2s$ process! It is suggested that severe steric repulsions destabilise the former, whereas the greatly increased orbital overlap resulting from proper alignment of the orbitals in a $\pi^2s + \pi^2s$ process may be reinforced by electrostatic interactions in a polar cycloaddition, and thus overshadow the effects of orbital symmetry conservation[133,134] (Scheme 64). From a consideration of LCFC-CI calculated qualitative energy surfaces, Epiotis *et al.* have concluded that whereas non-polar $\pi^2s + \pi^2s$ cycloadditions involve a high energy barrier at short intermolecular distances characteristic of a product-like transition state, polar $\pi^2s + \pi^2s$ reactions involve a lower barrier at long intermolecular distances characteristic of an early reactant-like transition state. In any event Epiotis has provided a persuasive argument for the concerted nature of a *polar* 2s + 2s cycloaddition, involving synchronous overlap of the p-orbitals at both sites of union, occurring via a cisoid rather than orthogonal transition state, as depicted in Scheme 64. However whether this appertains to sulphene cycloaddition is an open question at present.



Scheme 64.

The reaction of 1,3-propanedisulphonyl chloride with 1-N-morpholinocyclohexene in the presence of triethylamine has been shown to yield the bithietane tetroxide **172** presumably via the intermediacy of the disulphene (SO_2=CH·CH_2CH=SO_2).[135] However although methanedisulphonyl chloride reacts with ketene diethylacetal to give the spiro bithietane tetroxide **173** presumably via the disulphene (SO_2=C=SO_2), reaction with 1-N-morpholinocyclohexene gave only the bis-acylation product **174**.[136]

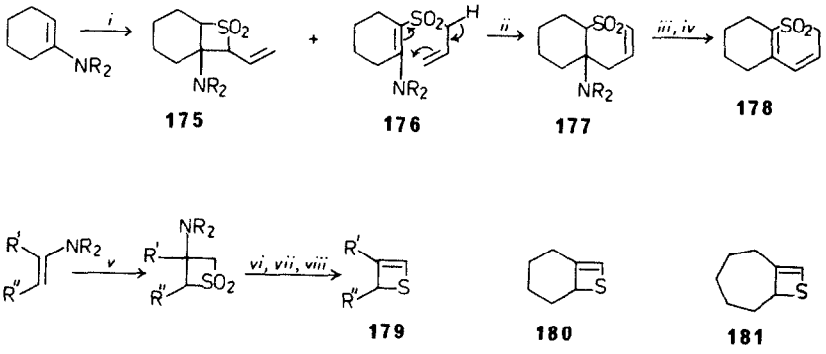


172 **173** **174**

Scheme 65.

Vinylsulphene (CH_2=CH·CH=SO_2), produced *in situ* from prop-2-ene-1-sulphonyl chloride and triethylamine, undergoes 1,2-cycloaddition to enamines to give vinylthietane 1,1-dioxides **175** together with the allylsulphones **176**. No 1,4-cycloadducts **177** were detected, but were readily obtained by treatment of the allylsulphones with base; pyrrolysis of the resulting dihydrothiopyran 1,1-dioxides **177** gave the thiopyran 1,1-dioxide **178**.[137]

Thiacyclobutenes (thietes) **179–181** have been prepared by reduction and Hofmann elimination of dialkylaminothietane-1,1-dioxides.[138] Gompper and Wetzel[139] have described stable dipoles formed from

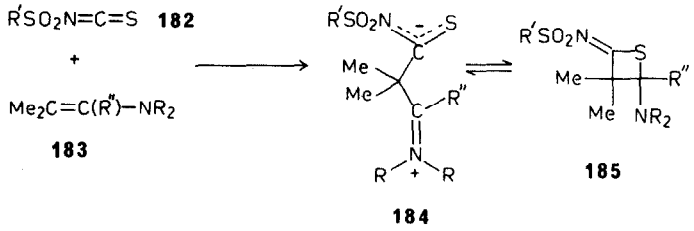


175 **176** **177** **178**

179 **180** **181**

Scheme 66. Reagents: (i) CH_2=$CHCH_2SO_2Cl$, Et_3N; (ii) Et_3N, dioxane, Δ; (iii) anhydr. HCl; (iv) 190–195°; (v) CH_3SO_2Cl, Et_3N; (vi) $LiAlH_4$; (vii) MeI; (viii) RO^- or Ag_2O, H_2O, −10°.

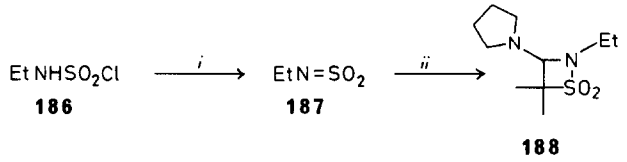
benzenesulphonylisothiocyanate with cyclic keto-enamines and ketene-S,N-acetals (outside the scope of this review). Similar dipoles **184** have been isolated from the reaction of sulphonylisothiocyanates **182** with simple aldehyde and ketone enamines **183** and shown to be in equilibrium with the thietane **185** in



182 **183** **184** **185**

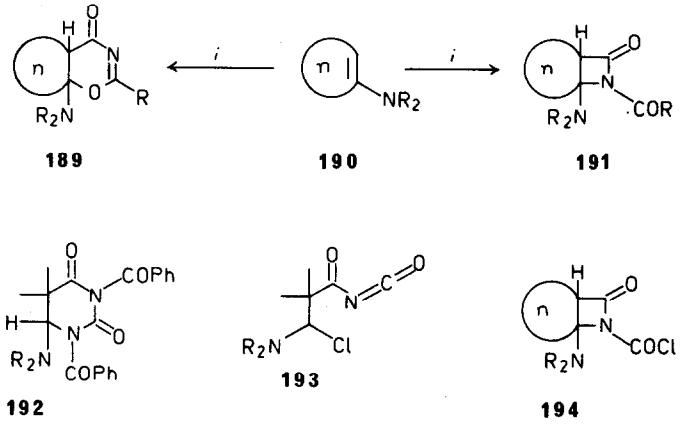
Scheme 67.

non-polar solvents.[140] The heterocumulene **187** has been generated from ethyl sulphamoyl chloride **186** and shown to react with enamines to give the [2 + 2]cycloadduct **188**.[141]



Scheme 68. Reagents: (i) Et_3N, 20°, 30 min; (ii) pyrrolidin-1-ylisobutene.

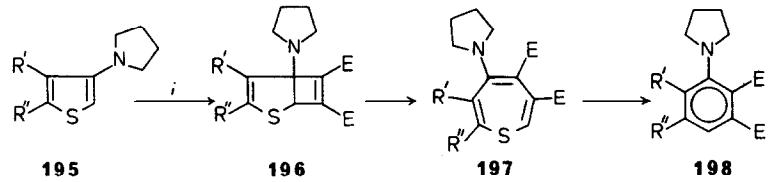
Trichloroacetyl and benzoyl isocyanates undergo [2 + 2] and [4 + 2]cycloaddition to ketone enamines to give the azetidinone **191** or oxazine **189** respectively, whereas with aldehyde enamines the dioxohexahydropyrimidine **192** is reported to be formed.[142] A similar dichotomy of behaviour is apparent with chloroformyl isocyanate which is claimed to give the acyl isocyanate **193** with aldehyde enamines and the chlorocarbonyl azetidinone **194** with cyclic ketone enamines.[143]



Scheme 69. Reagents: (i) PhCONCO or $Cl_3CCONCO$; n = 3, 4.

B. *Five-membered rings*

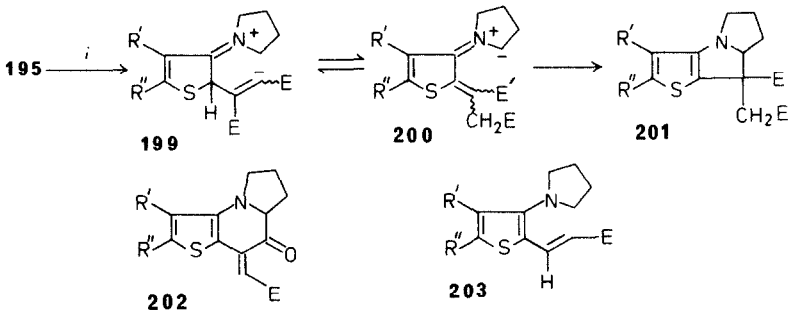
(i) *One Hetero atom.* An intriguing and versatile series of solvent-dependent reactions between thiophene enamines **195** and acetylene dicarboxylates has been reported,[144] and serves to illustrate again how the course of an enamine reaction may depend upon the experimental conditions employed.[1] In apolar solvents the benzene derivative **198** is obtained, by $[\pi^2s + \pi^2s]$-cycloaddition† followed by ring expansion and desulphurisation of the resulting thiepin[144,145] (**196** → **197** → **198**) (Scheme 70). The intermediate 2-thiabicyclo[3.2.0]hepta-3,6-diene **196** and the monocyclic thiepine **197** can also be isolated.



Scheme 70. Reagents: (i) $MeO_2CC{\equiv}CCO_2Me$, benzene; R'=H, R''=Me; E=CO_2Me.

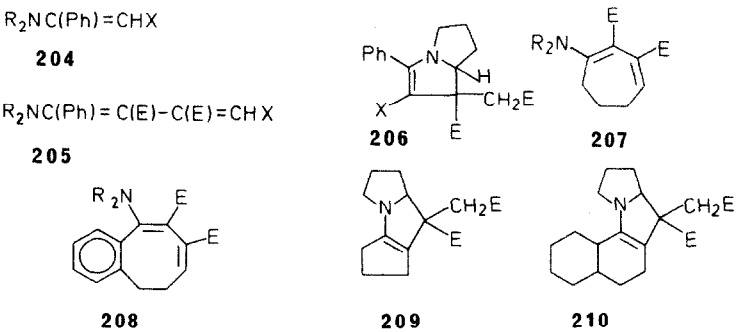
However, in methanol the tricyclic tetrahydro-5H-thieno[3,2-b]pyrrolizines **201** were formed, in 45–64% yields. This was attributed to a non-concerted cycloaddition in polar solvents to give a zwitterionic intermediate **199**, rearrangement to ylid **200**, followed by cyclisation to **201** (Scheme 71).[144] However if this is the case it is strange that **202** is apparently not formed.

†Symmetry "forbidden" but energetically favoured for reaction between electron-rich and electron-deficient addends.[133–134]



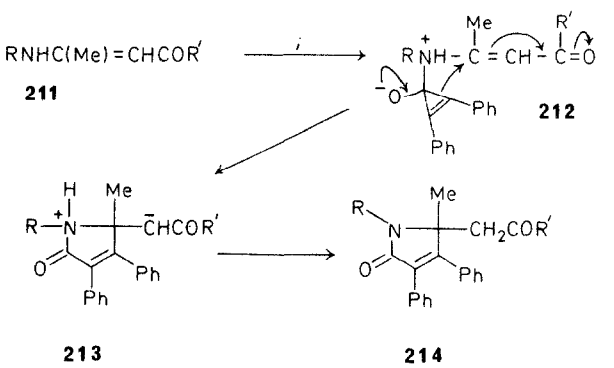
Scheme 71. Reagents: (i) $MeO_2CC{\equiv}CCO_2Me$, MeOH or $CHCl_3$; R',R'' = H, Me; Me, H; H, Ph; H, o-$MeOC_6H_4$; Ph, Ph; E = CO_2Me.

The corresponding reaction with methyl propiolate gave only the Michael adduct **203**. This is attributed to reduced electrophilicity of the exo carbon–carbon double bond in **200** (E' = H), thus inhibiting the ylid cyclisation step (**200**→**201**).† Application of the reaction to acyclic enamines **204** gave the dienamines **205** in apolar solvents (i.e. toluene or diethyl ether) and a mixture of mainly the pyrrolizine **206** together with some **205** in methanol. Similarly the pyrrolidine enamines of cyclopentanone and α-tetralone gave the ring expanded products **207** and **208** in toluene and the pyrrolizines **209** and **210**, respectively, in methanol.‡[146]



Scheme 72. Substituents: R_2N = pyrroldin-1-yl; X = SPh, OPh, Ph; E = CO_2Me.

Further synthetic applications of diphenylcyclopropenone (see Section 2) include the conversion of primary and secondary acyclic enaminones **211** into the 1,5-dihydro-2-pyrrolone **214**. The mechanism appears to differ from that proposed for the corresponding reaction with tertiary enamines (see Scheme 17, Section 2) since enaminones are also ambident electrophiles as well as nucleophiles. Thus N-acylation can be rendered *irreversible* by ring opening and nucleophilic attack on the α-position of the enaminone (**212**→**213**); rapid proton transfer then gives the observed product **214**.[147]

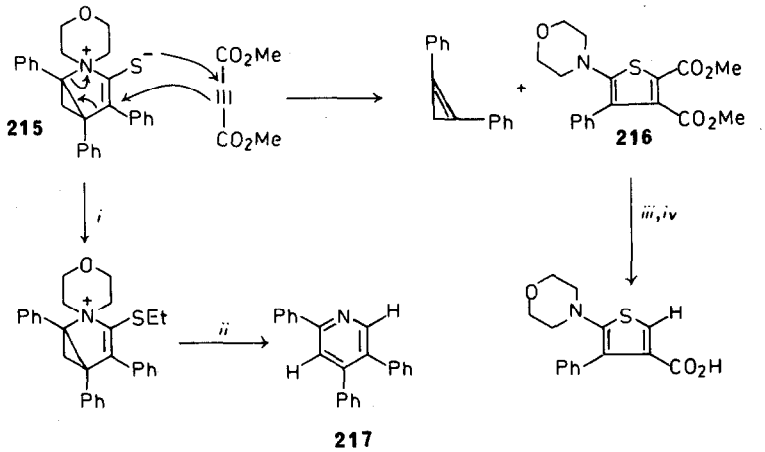


Scheme 73. Reagents: (i) diphenylcyclopropenone, 110°, 3 days.

†Certainly the extra electron-withdrawing group could lower the HOMO–LUMO energy gap [see Section 3B(iii)], thus facilitating ring closure.

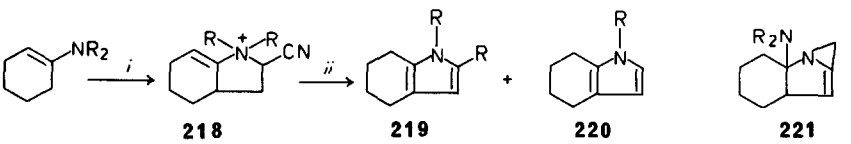
‡For applications of this reaction to heterocyclic enamines (outside the scope of this review) leading to ring expanded heterocycles, see Ref. 107.

The reaction of diphenylcyclopropenethione with the morpholine enamine of acetophenone gives the bicyclic zwitterion **215** as a primary adduct (see Section 2); the three-membered ring can be eliminated or opened to give five- and six-membered heterocycles **216** and **217** respectively.[148]



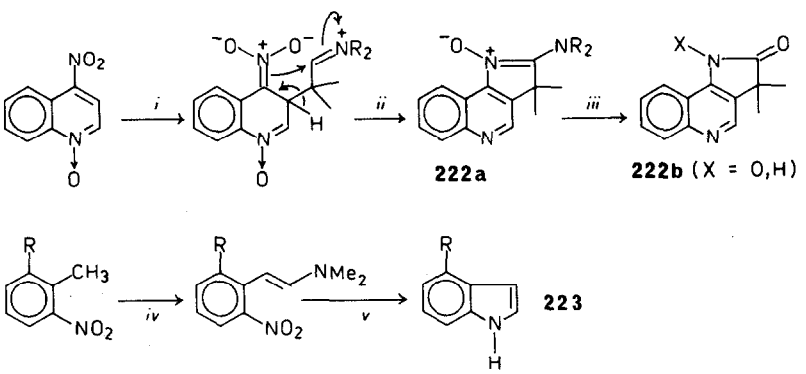
Scheme 74. Reagents: (i) $[Et_3\overset{+}{O}]BF_4^-$ or EtI; (ii) KOH, MeOH; (iii) NaOH, EtOH; (iv) H_3O^+.

Quaternary hexahydroindolium salts **218** have been obtained from the reaction of cyclohexanone enamines with α-chloro- or bromoacrylonitrile. Treatment with base leads to tetrahydroindoles **219** and **220** by competing Stevens rearrangement and Hofmann elimination respectively.[149] Similar reactions occur with methyl α-chloroacrylate.[150] In some cases cyclobutane adducts have been isolated which undergo thermal rearrangement into the hexahydroindolium salts **218**. Reductive cyclisation of the 2-cyanohexahydroindolium salt **218** with lithium aluminium hydride gave the fused aziridine derivative **221**.[151]



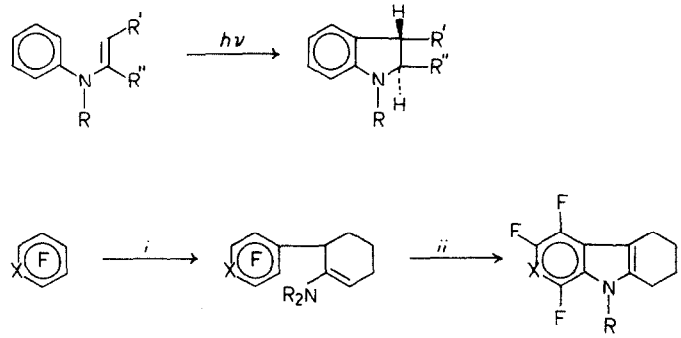
Scheme 75. Reagents: (i) CH_2=C(Br)CN, Et_3N, CH_3CN; (ii) t-BuOK, Et_2O, 20°, 20 h; R_2N = morpholino, piperidino, pyrrolidin-1-yl, Me_2N, Et_2N.

The nucleophilic attack of an enamine on 4-nitroquinoline 1-oxide is followed by cyclisation onto the nitro group, as formally represented in Scheme 76, to give pyrrolidoquinoline systems **222a** and **222b**.[152] A reductive cyclisation onto a nitro group, leading to 4-substituted indoles **223**, has also been described.[153]



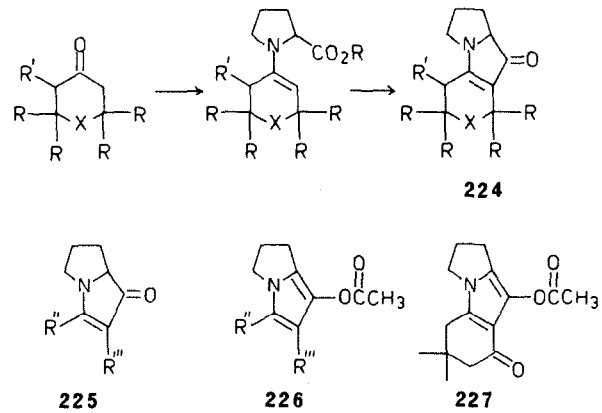
Scheme 76. Reagents: (i) 1-N-morpholinoisobutene, $CHCl_3$, 20°, 4 days; (ii) $-H_2O$; (iii) $+H_2O$; (iv) $Me_2NCH(OMe)_2$, DMF, 110°, 2 days; (v) Fe, HOAc, EtOH; R = CO_2R, CN, CH_2CO_2H.

The photocyclization of enamines is a useful method for the synthesis of 1,2-di and 1,2,3-trisubstituted 2,3-dihydroindoles and hexahydrocarbazoles, and has been the subject for further recent methanistic investigations.[154] 2,3,3-Trisubstituted-2,3-dihydroindoles have been observed in the reaction of aryl azides with α-substituted phenylacetaldehyde enamines, presumably derived from an unstable triazoline.[155] Fluorinated tetrahydrocarbazoles are obtained by condensation of perfluoroarenes with enamines[156] (see Part 1, Section 5G).



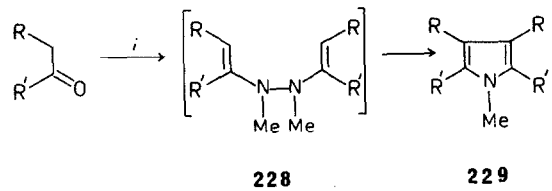
Scheme 77. Reagents: (i) 1-N-dialkylaminocyclohexene; (ii) Δ; X = CF, CCF_3, CBr, N; R′ = Me, Et, $(CH_2)_4F$.

Polyhydropyrrolo[1,2a]indoles **224**, **227** and pyrrolizines **225–6** may be obtained by condensation of some ketones with L-sodium or L-ethyl prolinate.[157,158] The bis-enehydrazines **228**, postulated as inter-



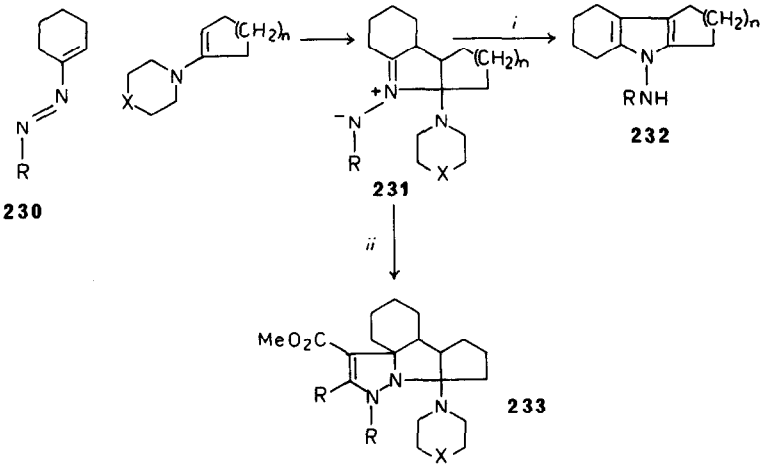
Scheme 78. Substituents: R = H, Me; R′ = H, Me, i-Pr, CH_2Ph, Ph; X = CH_2, $CHCMe_3$, $C(CO_2Et)_2$, NMe; R″ = Me, i-Pr; R‴ = Me, COMe, CO_2Et.

mediates in the Fischer-type cyclisation of carbonyl compounds with N,N′-dimethylhydrazine to give N-methylpyrroles **229**, have been isolated in some cases.[159]



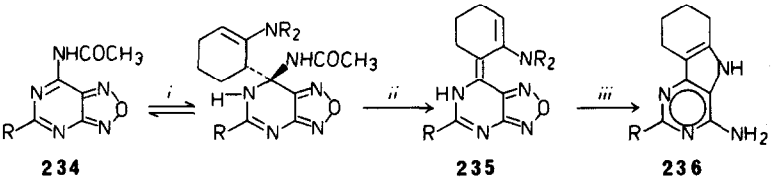
Scheme 79. Reagents: (i) MeNHNHMe; R = Ph; R′ = H; R,R′ = $(CH_2)_4$, $(CH_2)_5$, o-$C_6H_4CH_2CH_2$.

A remarkable [3 + 2]cycloaddition of enamines to 1,2-diaza-1,3-butadienes **230** (i.e. azoalkenes) has recently been observed. The intermediate azomethineimine **231** may be trapped by 1,3-dipolar cycloaddition of acetylenecarboxylates (**231** → **233**) or converted to the substituted N-aminopyrrole **232** by heating above the melting point.[160]



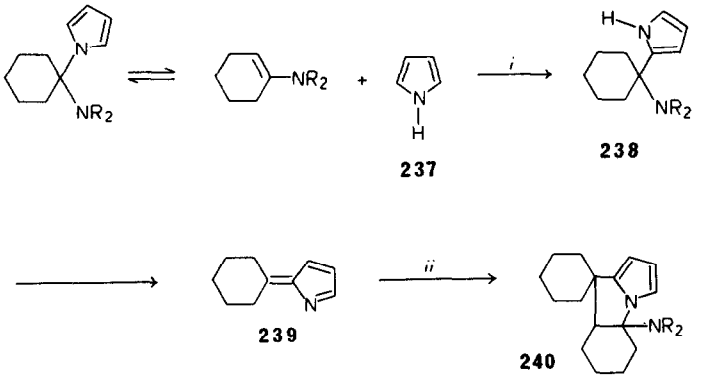
Scheme 80. Reagents: (i) Δ; (ii) R'C≡CCO$_2$Me (n = 1); R = Tos, C(O)OC(Me)$_2$CCl$_3$; R' = H, CO$_2$Me.

Enamines undergo a reversible C-alkylation by the furazano[3,4-d]pyrimidine **234**. Base catalysed elimination of acetamide gives **235** which undergoes reductive cyclisation to pyrrolo[3,2-d]pyrimidine **236** in good yield.[161]



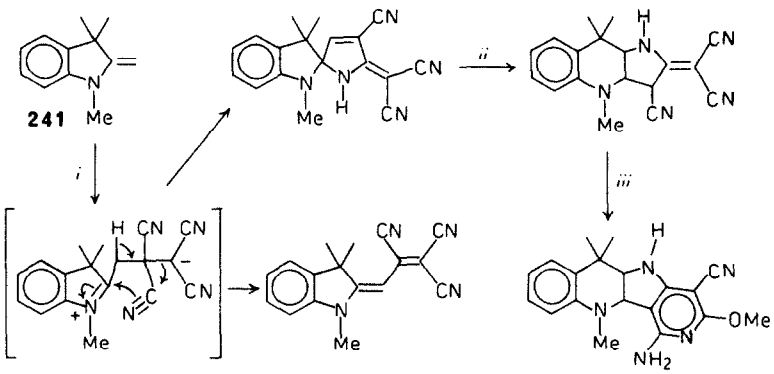
Scheme 81. Reagents: (i) 1-N-morpholinocyclohexene, 20°; (ii) Na, MeOH; (iii) Zn, HOAc.

Pyrrole has been found to react with enamines by initial C-protonation of the enamine and N-alkylation of the pyrrole by the resulting iminium salt, under mild conditions; under more forcing conditions C-alkylation occurs (**237** → **238**), followed by elimination to give an azafulvene **239** which then reacts with a second equivalent of enamine to give pyrrolizine **240**.[162]



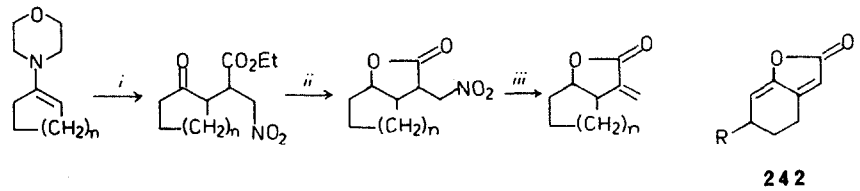
Scheme 82. Reagents: (i) 110°, 12 h; (ii) 1-(pyrrolidin-1-yl)cyclohexene.

Pyrrolines have been obtained by rearrangement of aziridinylvinylphosphonium salts;[163] a variety of other heterocycles (i.e. benzimidazoles, benzoxazoles, benzthiazoles, quinazolinones) can be obtained by ylid extrusion of o-substituted anilinovinylphosphonium salts.[164] A series of spiro and fused pyrroline derivatives have been formed from tetracyanoethylene and Fischer's base **241**.[165]



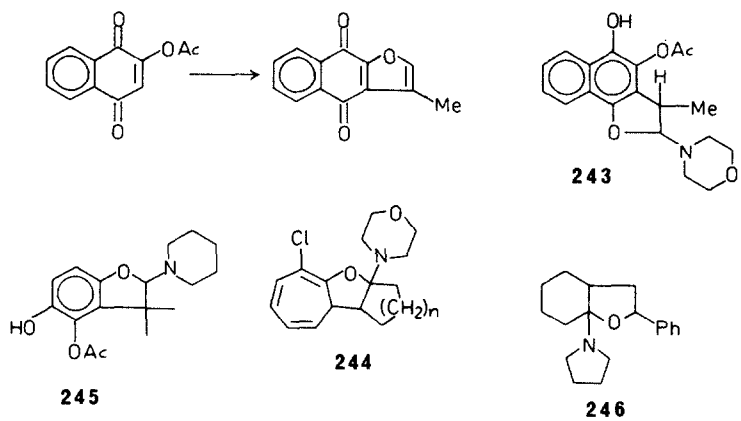
Scheme 83. Reagents: (i) $(NC)_2C{=}C(CN)_2$; (ii) MeOH, Δ, (iii) NaOMe, MeOH, Δ.

α-Methylenebutyrolactones are important in view of their potential anti-tumour activity. An efficient three-step synthesis[166] based on the alkylation of a cycloalkanone enamine is outlined in Scheme 84. Alkylation of cyclohexanone enamines with methyl 2-chloro-2-methoxyethylacetate gives a product which is readily cyclised to lactone **242**[167] (R = H, Me). Condensation of 2-acetoxy-1,4-naphthoquinone



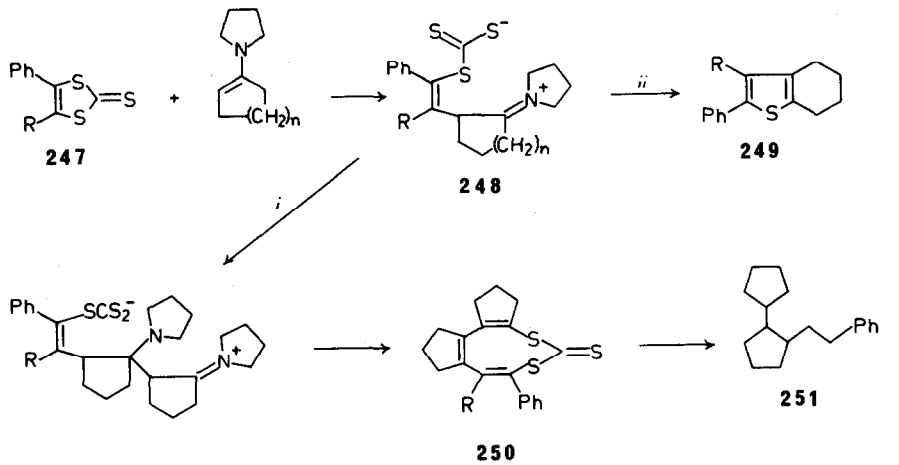
Scheme 84. Reagents: (i) $NO_2CH{=}CHCO_2Et$; (ii) $NaBH_4$, MeOH; (iii) $NH(i\text{-}Pr)_2$, $(-HNO_2)$.

and 1-morpholinoprop-1-ene gives 3-methylnaphtho[2,3-b]furan-4,9-quinone; in the absence of oxidising agent (air) the aminodihydronaphthofuran **243** is obtained.[168] Furan derivatives **244–246** have also been obtained from reaction of enamines with 2-chlorotropone,[169] 2-acetyl-1,4-benzoquinone,[170] and styrene oxide.[171]



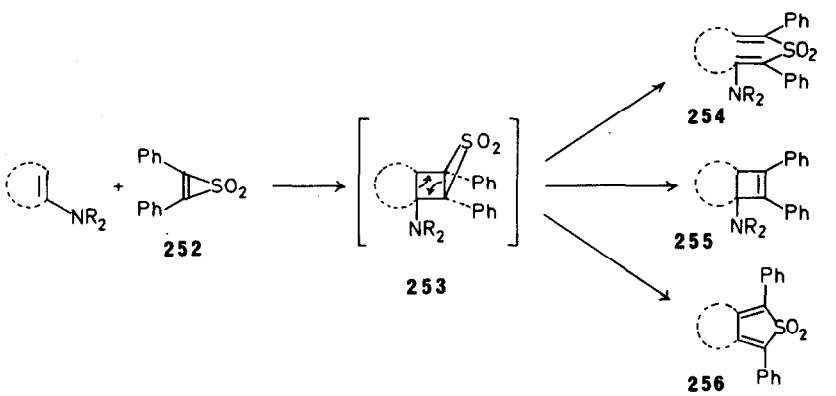
Scheme 85.

The reaction of 1,3-dithiole-2-thiones **247** with enamines provides yet another demonstration of how the course of an enamine reaction depends on the enamine used. The initially formed zwitterionic intermediate **248** apparently loses carbon disulphide when cyclohexanone enamines are used, to give the thiophene **249**, but undergoes further attack when the more reactive cyclopentanone enamine is used and thus leads to the 1,3-dithionin-2-thione **250**.[172] Reductive desulphurisation gives **251**.



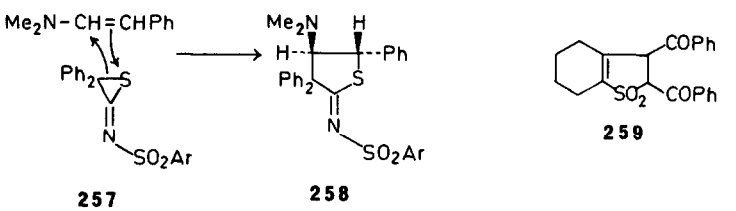
Scheme 86. Ring size; (i) n = 1; (ii) n = 2, R = H, Ph.

Like diphenylcyclopropenone the reactions of 2,3-diphenylthiirene 1,1-dioxide **252** with enamines are complex. However most of the products are of type **254–6** and appear to be derived from the bicyclic adduct **253**.[173]



Scheme 87.

Sulphonyliminothiiranes **257**, obtainable from sulphonyl isothiocyanates and diphenyldiazomethane, react with enamines to give cycloadduct **258**, the structure being confirmed by X-ray analysis.[174]

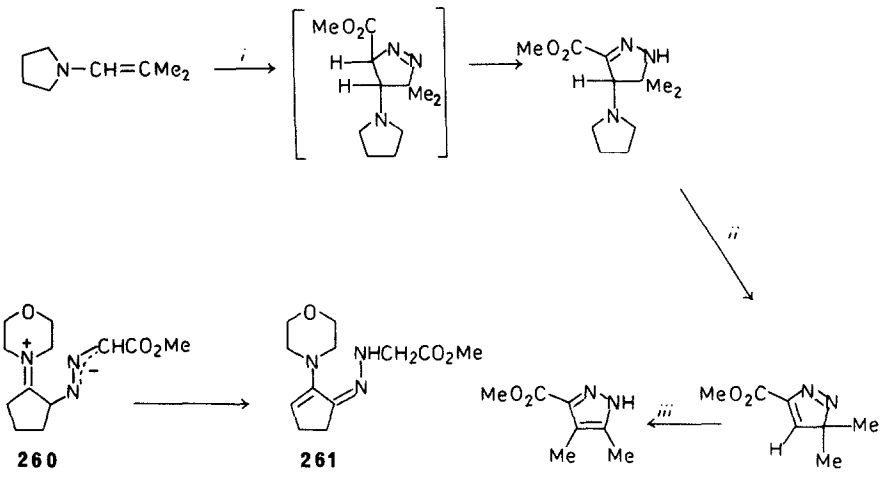


Scheme 88.

Benzoylsulphene reacts with cyclohexanone enamines to give the acyclic sulphone derivative or the five-membered cyclic sulphone **259**, presumably formed by elimination of sulphur dioxide and the amine moiety of the enamine from a 2 : 1 cycloadduct, rather than the expected thietane 1,1-dioxide.[175]

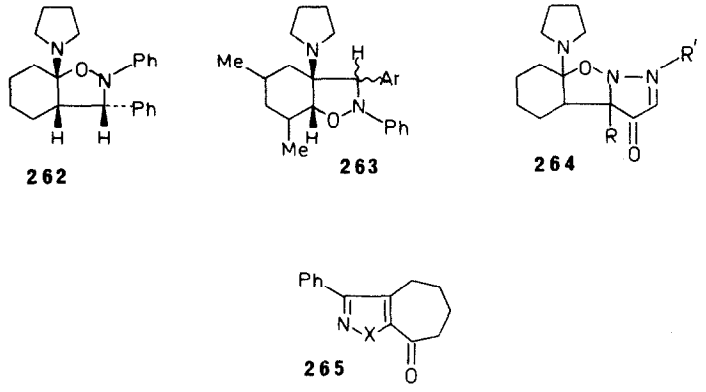
(ii) *Two hetero atoms.* Although diazomethane is inert towards enamines, α-diazo carbonyl compounds readily undergo 1,3-dipolar cycloaddition at room temperature to give pyrazoles.[176] Intermediate pyrazolines have been isolated in some cases (Scheme 89), and a frontier orbital explanation offered to account for the regioselectivity of the reaction[177] [see also Section 3B(iii)]. Interestingly although

cyclohexanone enamines give cycloadducts, cyclopentanone enamines undergo azo coupling rather than cycloaddition via a zwitterion **260**, which has also been isolated in some cases, to give the acyclic hydrazone derivative **261**.[178] The implication is that the reaction is an irreversible concerted cycloaddition in the former case, and a stepwise and reversible reaction in the latter case. Confirmatory evidence has been provided from the solvent dependence of the rate constants.[179]



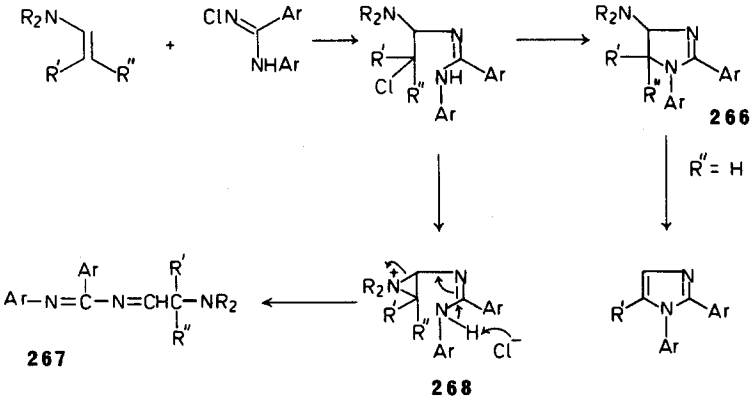
Scheme 89. Reagents: (i) N_2CHCO_2Me, $CHCl_3$, Δ, 8 h; (ii) SiO_2; (iii) Δ or cold conc. H_2SO_4.

4,5,5-Trisubstituted isoxazolidines **262** are formed by 1,3-dipolar cycloaddition of nitrones (i.e. benzylidenaniline N-oxide) to enamines; in one reaction of a more hindered enamine the "reverse" addition was observed to give the 4,4,5-trisubstituted isoxazolidine **263**.[180] Similarly diazacyclopentadienone N-oxides give **264** (R = Me, Et, Ph; R′ = O, Ph).[181] 1,3-Dipolar cycloaddition of diphenylnitrilimine (i.e. benzonitrile N-phenylimide) and benzonitrile oxide to 2-pyrrolidin-1′-ylcyclohept-2-enone gives the pyrazole **265** (X = NPh) and isoxazole **265** (X = O), respectively.[182] The 1,3-dipolar cycloaddition reactions of azides are discussed in Section 3B(iii).



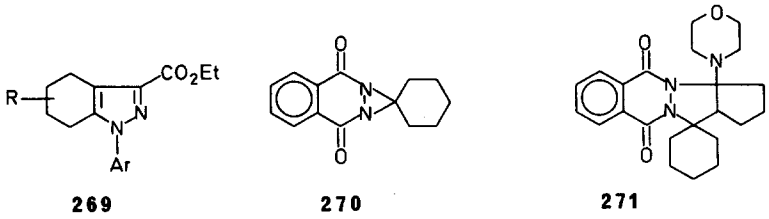
Scheme 90.

Amino-imidazolines and imidazoles may be obtained from enamines and N-chloro-N′-arylamidines. The reaction occurs by nucleophilic attack of the amidine anion on the initially formed chloro-iminium ion. The intermediate thus formed cyclises to imidazoline **266** or aziridinium chloride **268** which rearranges to amidine **267**.[183]



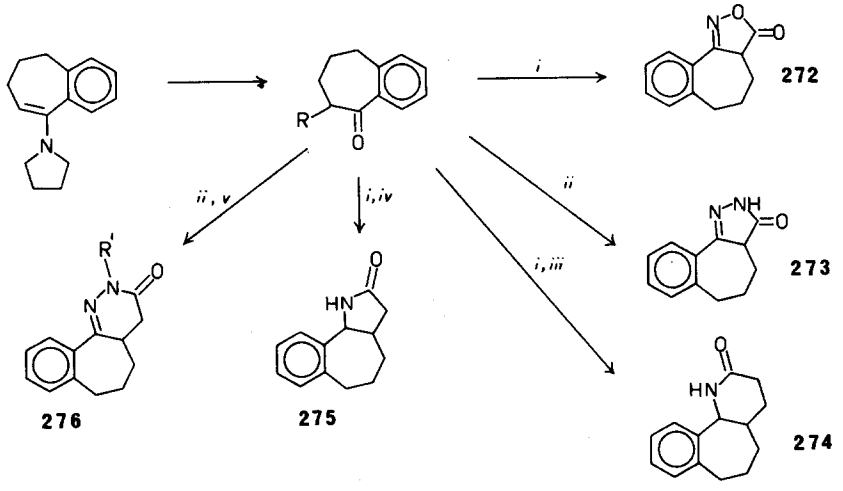
Scheme 91.

Tetrahydro-1-phenylindazoles **269** are obtained from the corresponding cyclohexanone enamine and ethyl α-bromoglyoxylate arylhydrazone [Ar NHN = C(Br)CO_2Et].[184] The diaziridine ring in **270** opens in boiling toluene to give an azomethine imine which can be trapped by 1-morpholinocyclopentene to give cycloadduct **271**.[185]



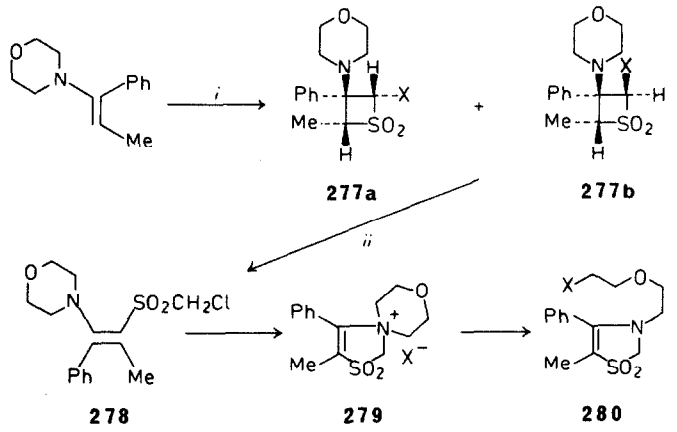
Scheme 92.

The carboxylation or carboxyalkylation of enamines provides ready access to precursors of a variety of five and six-membered heterocyles, as exemplified in the conversion of tetrahydrobenzo cyclohepten-5-one into the heterocyclic derivatives **272–276** containing a seven membered carbocyclic ring system.[186]



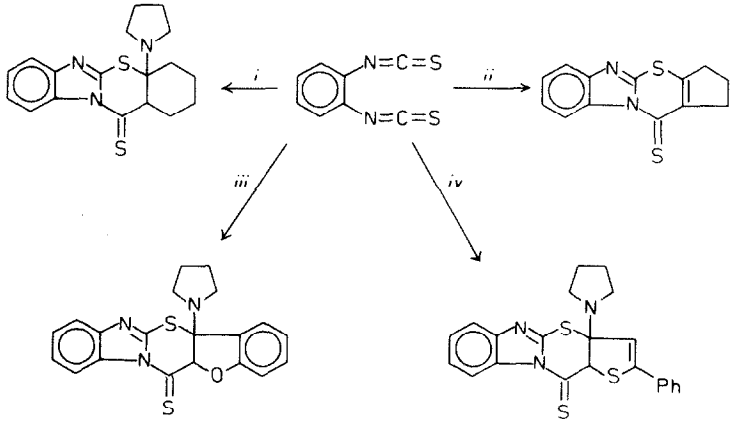
Scheme 93. Reagents: (i) NH_2OH (R = CO_2Et); (ii) NH_2NH_2 (R = CO_2Et); (iii) H_2/Pd (R = $CH_2CH_2CO_2$Et); (iv) H_2/Pd (R = CH_2CO_2Et); (v) R = CH_2CO_2Et; R′ = H, $CH_2CH_2NMe_2$, $CH_2CH_2CH_2NMe_2$.

Thiazoline 1,1-dioxides can be prepared by cycloaddition of halogenosulphenes to enamines. The initially formed 2-halogenothietane 1,1-dioxide **277** undergoes thermal rearrangement to the thiazoline **280** via the ring opened β-sulphonylenamine **278** and the quaternary salt **279**.[187]



Scheme 94. Reagents: (i) XCH_2SO_2Cl, Et_3N, 0–2° (X = Cl, Br); (ii) 80°, EtOH, 24 h.

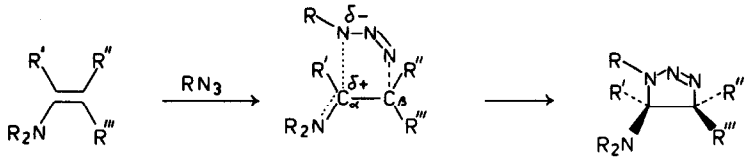
2-Aminothiazoles result from the reaction of sulphur and cyanamide with ketone enamines.[188] A variety of fused imidazothiazine systems result from the action of o-phenylene diisothiocyanates on enamines (Scheme 95).[189]



Scheme 95. Reagents: (i) 1-(pyrrolidin-1-yl)cyclohexene; (ii) 1-N-morpholinocyclohexene; (iii) 3-(pyrrolidin-1-yl)benzo[b]furan; (iv) 2-phenyl-4-(pyrrolidin-1-yl)thiophen.

(iii) *Three hetero atoms. Theoretical aspects.* The synthesis and chemical properties of Δ^2-1,2,3-triazolines and 1,2,3-triazoles have been the subject of extensive recent reviews.[190,191] Consequently in this section we are only concerned with the recent advances which have occurred in understanding the mechanism of the 1,3-dipolar cycloaddition of azides (RN_3) to enamines. This cycloaddition leads to triazolines and is stereospecific and regiospecific with respect to the enamine. The rate of reaction is increased by an electron attracting substituent in the azide, the order of reactivity being R = Ts > p-$NO_2C_6H_4$ > Ph > p-$MeOC_6H_4$. Without exception the nitrogen of the azide bearing the R substituent bonds with the carbon atom of the dipolarophile (i.e. enamine) bearing the amine moiety. These facts, together with the large negative entropy of activation[192] and relative insensitivity of rate to solvent polarity[192,193] are indicative of a concerted rather than stepwise cycloaddition process. However this does not mean that the transition state need be totally devoid of charge separation. In fact the sign and magnitude of the Hammett parameters for a series of meta and para- substituted acetophenone enamines, phenylacetaldehyde enamines, and substituted phenyl azides, are consistent with the development of positive charge at C-α of the enamine in the transition state, negative charge at the nitrogen of the azide bearing the R substituent in the transition state, and no negative charge at C-β of the enamine. These results can be accommodated by a concerted cycloaddition with the simultaneous, but uneven, formation of two new bonds.[192] The bond formation at the β-position of the enamine is considerably further advanced than that at the α-position and the resultant charge separation at the α-position accounts for the observed regiospecificity of reaction, even in sterically encumbered

transition states, whereas the concerted nature of the reaction accounts for the observed stereospecificity (Scheme 96).



281

Scheme 96.

However, the most satisfying explanations of the regioselectivity and reactivity in 1,3-dipolar cycloaddition reactions of azides, and other 1,3-dipoles, is provided by the MO perturbation treatments of Sustmann[194] and Houk.[195] Perturbation theory gives a reliable guide to the most stable geometry of approach of two addends in the early stages of a cycloaddition reaction, when the interaction between two addends is small. The resulting interaction between an occupied orbital on the one addend with an unoccupied orbital on the other has been shown to result in a stabilization which is inversely proportional to the difference in energy between the interacting orbitals, and directly proportional to the square of the sum of the products of the coefficients of the interacting centres. This means that frontier orbital interactions should provide the main electronic stabilization of a transition state (minimum energy separation between interacting orbitals) and for two regioisomeric transition states, that one will be favoured in which the largest coefficients on the HOMO and LUMO of the two addends are united, provided that steric repulsions do not overwhelm the electronic preference for one regioisomer.

Based on these considerations Sustmann[194] has shown that the reactivity of a dipolarophile towards an azide is determined by (i) the difference between azide HOMO and dipolarophile LUMO energies for electron-deficient alkenes (i.e. acetylene dicarboxylates), (ii) the difference between azide LUMO and dipolarophile HOMO energies for electron-rich alkenes (i.e . enamines), and (iii) the difference between both sets of HOMO-LUMO energy differences for conjugated alkenes (i.e. butadiene, styrene, etc.). Houk *et al.*[195b] have calculated the orbital energies and coefficients for a number of 1,3-dipoles and thus accounted for the regioselectivity of 1,3-dipolar cycloadditions. The situation is illustrated schematically in Fig. 1. For cycloaddition of azides to enamines the smallest energy gap is that between the HOMO of the enamine and the LUMO of the azide (↔) rather than the HOMO of the azide and LUMO of the enamine (←---→). It follows that bonding will be more developed at the unsubstituted terminal positions of the addends, as shown in **281**, Scheme 96. The large orbital coefficient of the central nitrogen of the azide LUMO, opposite in sign to those of the terminal atoms, introduces a destabilizing interaction in the transition state which is relieved by bending of the dipole. This bending will simultaneously increase the mutual overlap of the terminal orbitals of the two addends.

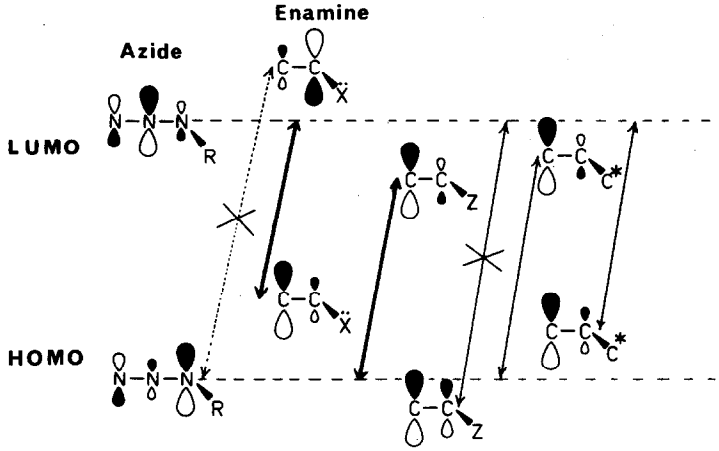


Fig. 1. Orbital energies and coefficients for 1,3-dipolar cycloaddition of azides; X = NR_2(OR, R); Z = CO_2R, CN, CH = O etc.; C* = CH=CH_2, Ph etc.

Figure 1 also provides an explanation for the observation that the rate of cycloaddition to azides, and other 1,3-dipoles, is increased by electron-attracting as well as electron donating substituents. The latter increases the HOMO energy and thus decreases the LUMO azide-HOMO enamine energy gap, whereas the former decreases the LUMO energy of the dipolarophile (C=C–Z) and thus decreases the HOMO azide-LUMO dipolarophile energy gap. A second electron-withdrawing substituent often causes a drastic increase in rate for the same reason, as observed when methyl acrylate is replaced by dimethyl fumarate for example. Conversely in reactions accelerated by electron-releasing and electron-withdrawing substituents, the reactivity is decreased if both kinds of substituents are incorporated into the one molecule. The reduced regioselectivity of cycloaddition of azides to conjugated olefins (C=C–C=C, C=C–Ph) compared to enamines is also explained since in the former case the LUMO azide-HOMO dipolarophile and HOMO azide-LUMO dipolarophile energy gaps are comparable in magnitude.

Similar considerations apply to cycloaddition reactions of other 1,3-dipoles with enamines, and other addends, leading to five-membered heterocyclic systems containing one or two hetero atoms. Calculated molecular orbital energies and atomic orbital coefficients are summarized in Table 1.

C. *Six-membered rings*

(i) *One hetero atom.* (a) *Nitrogen.* Numerous applications of the Stork reaction to the synthesis of six-membered heterocycles have appeared over the years. Stork's aza-annulation method with acryl-

Table 1. Energies* and coefficients+ of 1,3-dipoles[195b, 196≠]

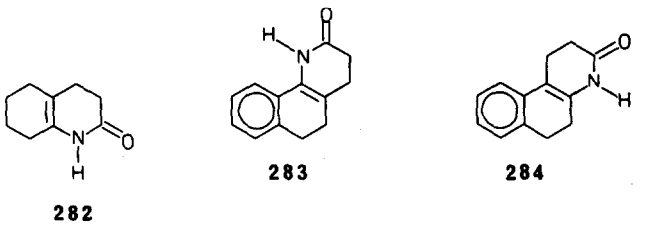
Dipole	HOMO		LUMO	
	Energy	Coefficient	Energy	Coefficient
Azides	-11.5	$HN=\overset{+}{N}=\bar{N}$ 1.55 0.72	0.1	$HN=\overset{+}{N}=\bar{N}$ 0.37 0.76
$PhN=\overset{+}{N}=\bar{N}$	-9.5		-0.2	
Azomethine imines	-8.6	$CH_2=\overset{+}{N}H-\bar{N}H$ 1.15 1.24	-0.3	$CH_2=\overset{+}{N}H-\bar{N}H$ 0.87 0.49
$PhCH=\overset{+}{N}(R)-\bar{N}Ph$	-5.6		-1.4	
Azomethine ylids	-6.9	$CH_2=\overset{+}{N}H-\bar{C}H_2$ 1.28 1.28	1.4	$CH_2=\overset{+}{N}H-\bar{C}H_2$ 0.73 0.73
$RO_2CCH=\overset{+}{N}(Ar)-\bar{C}HCO_2R$	-7.7		-0.6	
Diazoalkanes	-9.0	$CH_2=\overset{+}{N}=\bar{N}$ 1.57 0.85	1.8	$CH_2=\overset{+}{N}=\bar{N}$ 0.66 0.56
Nitrile imines	-9.2	$CH\equiv\overset{+}{N}-\bar{N}H$ 0.90 1.45	0.1	$CH\equiv\overset{+}{N}-\bar{N}H$ 0.92 0.36
$PhC\equiv\overset{+}{N}-\bar{N}Ph$	-7.5		-0.5	
Nitrile oxides	-11.0	$CH\equiv\overset{+}{N}-\bar{O}$ 0.81 1.24	-0.5	$CH\equiv\overset{+}{N}-\bar{O}$ 1.18 0.17
$PhC\equiv\overset{+}{N}-\bar{O}$	-10.0		-1.0	
Nitrile ylids	-7.7	$CH\equiv\overset{+}{N}-\bar{C}H_2$ 1.07 1.50	0.9	$CH\equiv\overset{+}{N}-\bar{C}H_2$ 0.69 0.64
$PhC\equiv\overset{+}{N}-\bar{C}H_2$	-6.4		0.6	
Nitrones	-9.7	$CH_2=\overset{+}{N}H-\bar{O}$ 1.11 1.06	-0.5	$CH_2=\overset{+}{N}H-\bar{O}$ 0.98 0.32
$CH_2=\overset{+}{N}(R)-\bar{O}$	-8.7		0.3	

* These frontier orbital energies have to be compared with those of ethylene (HOMO -10.5, LUMO 1.5), conjugated olefins (C=C–C; HOMO -9.1, LUMO 1.0), electron-deficient olefins (C=C–Z, HOMO -10.9, LUMO 0), and electron-rich olefins (C=C–X; HOMO -9.0, LUMO 3.0) and the relative magnitude of the coefficients depicted in Fig. 2, Part I[1].

+ $(C\beta)^2/15$ where C = atomic orbital coefficient and β = the resonance integral

≠ A phenyl group, being a C-substituent (see Part I, Section 2[1]), raises the energy level of the 1,3-dipole HOMO and lowers (slightly) the dipole LUMO energy level.

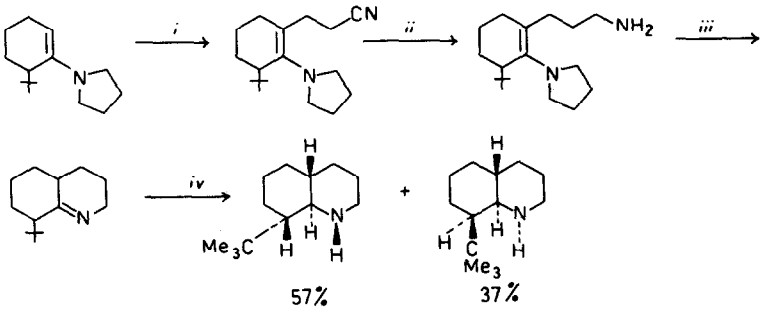
amide[197] has been extended to imines (enamine tautomers) to give tetrahydroquinoline derivatives **282–284** in good yield.[198]



282 **283** **284**

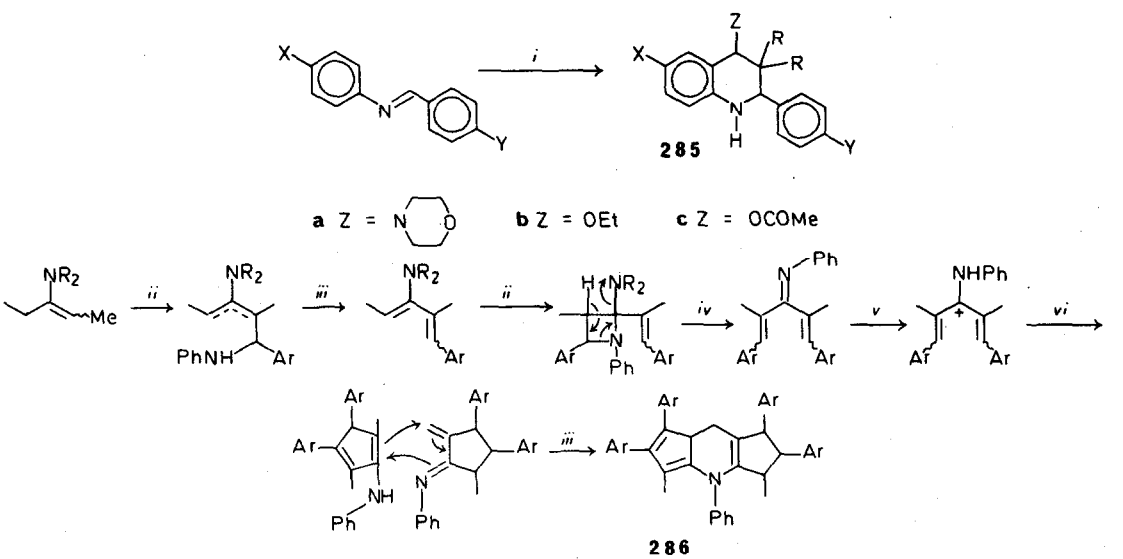
Scheme 97.

An analogous reaction is the synthesis of octahydro-$\Delta^{1,9}$-quinolines and trans-decahydroquinolines in good yield by alkylation of an enamine with acrylonitrile, reduction of the cyanoethylated product with lithium aluminium hydride and thermal cyclisation. Further reduction of the octahydroquinolines thus obtained gives the trans-decahydroquinolines with only a trace of the cis-isomer (Scheme 98).[199,200]



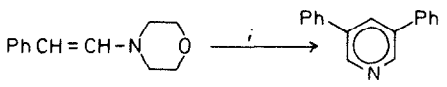
Scheme 98. Reagents: (i) CH_2=CHCN, EtOH, Δ, 36 h; (ii) $LiAlH_4$, Et_2O, 20°, 20 h; (iii) 180–200°; (iv) Na, anhydr. EtOH.

Amazingly, after all this time, simple and synthetically useful extensions to the Stork reaction are still being discovered. For example Schiff bases react with enamines in methanol to give the corresponding β-anilinoketone on hydrolysis of the enamine function (Part 1, Section 5G[1]). However now it has been found that, in the presence of acid, aldehyde enamines undergo a [4 + 2]cycloaddition to give 1,2,3,4-tetrahydroquinolines. The initially formed aminoquinoline derivative **285a** apparently undergoes ready solvolysis to **285b** and **285c**.[201] The reaction with ketone enamines takes a different course to give the 4-aza-s-indacene **286**[202] in low yield.



Scheme 99. Reagents: (i) R_2NCH=CRR′; (ii) PhN=CHAr, HOAc, 20°, 12 h; (iii) -$PhNH_2$; (iv) -morpholine; (v) H^+; (vi) conrotatory cyclisation.

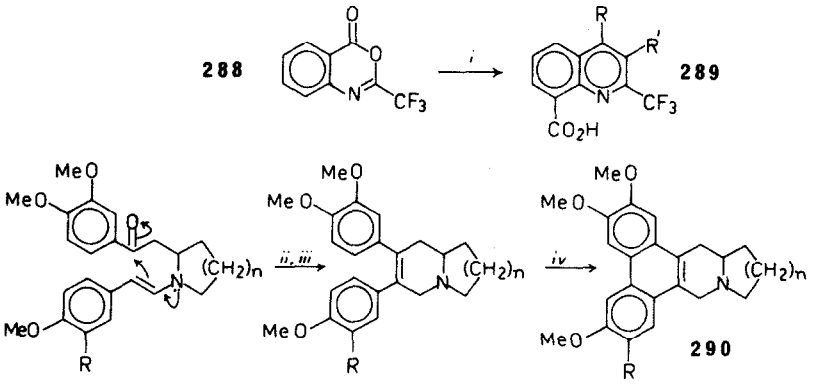
Aliphatic Schiff bases react with aldehyde enamines (two equivalents) to give the pyridine **287**. 2-t-Butyloxaziridine gives the same product.[203]



287

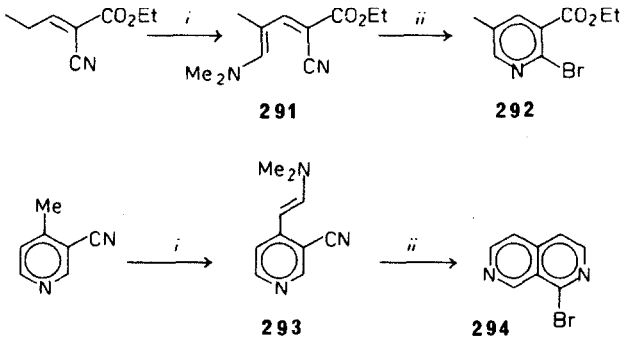
Scheme 100. Reagents: (i) CH_2=$NCMe_3$ or 2-t-butyloxaziridine.

3,1-Benzoxazin-4-ones **288** and enamines give quinoline derivatives **289**.[204] An intra-molecular enamine-ketone condensation has been effected with Lewis acids and provides access to the anti-tumour agents tylophorine **290** (R = OMe, n = 1) and cryptopleurine **290** (R = H, n = 2).[205]



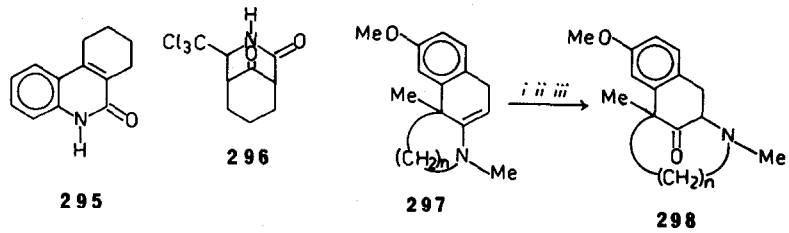
Scheme 101. Reagents: (i) $R_2NC(R)$=CHR'; (ii) $TiCl_4$, benzene; (iii) $NaBH_4$, i-PrOH; (iv) $Tl(OCOCF_3)_3$; R,R' = H, Et; $(CH_2)_4$.

Dimethylformamide dimethyl acetal condenses with activated methyl and methylene groups to give the dimethylaminomethine derivatives (i.e. **291** or **293**) which undergo acid catalysed cyclisation to the bromonicotinic acid **292**[206] or 2,7-naphthyridine **294**.[207] The 1,6- and 1,7-naphthyridines were obtained in a similar manner.



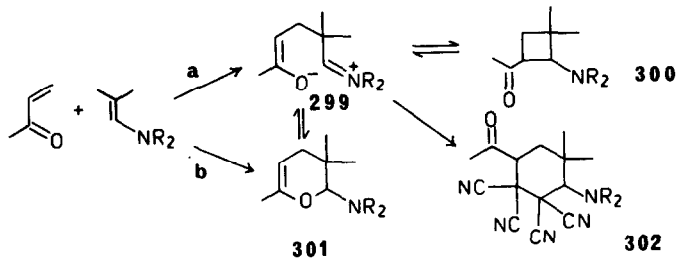
Scheme 102. Reagents: (i) $Me_2NCH(OMe)_2$, DMF, Δ, 16 h; (ii) HBr, HOAC, 40–55°.

Tetrahydrophenanthridones **295** are obtained from the reaction of enamines with aryl isocyanates followed by cyclisation of the resulting enamide with sulphuric acid.[208] 1,2,2,2-Tetrachloroethylisocyanate and cyclohexanone enamines is claimed to give azabicyclononane derivative **296**.[209] A novel ring expansion of **297** to the benzomorphan **298a** and homologue **298b** occurs on bromination.[210]



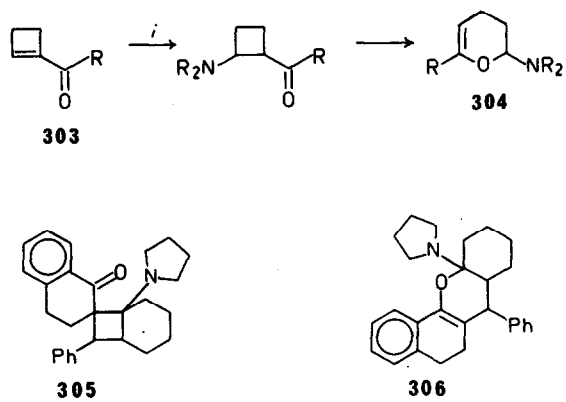
Scheme 103. Reagents: (i) Br_2; (ii) H_2O; (iii) NH_4OH; (a) n = 2; (b) n = 3.

(b) *Oxygen.* Dihydropyrans **301** have been found to be the first formed products in the reaction of methyl vinyl ketone with enamines, but appear in some cases to form an equilibrium with the corresponding cyclobutyl methyl ketone **300** via the open-chain iminium enolate anion **299**; the latter may be trapped with tetracyanoethylene to give **302**.[211]



Scheme 104.

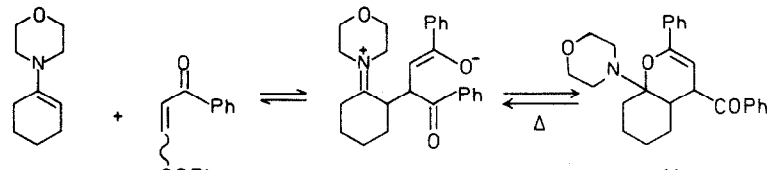
It is not surprising that the cyclobutyl ketones **300** were not isolated since their independent synthesis from **303** has shown that they readily rearrange to the thermodynamically more stable dihydropyrans **304**.[212] A report[213] that the product from 2-benzylidene-1-tetralone and 1-pyrrolidin-1'-ylcyclohexene was the spirocyclobutane **305** has been shown to be incorrect, the product being the dihydropyran **306**.[214,215]



Scheme 105. Reagents: (i) pyrrolidine, spontaneous conversion; piperidine, 20°, 1 h; morpholine, 60–80°.

The formation of dihydropyrans could occur by a concerted [4 + 2]cycloaddition (Scheme 104, path b) of the $\alpha\beta$-unsaturated ketone to the amine, or by a two step process involving cyclisation of the initially formed zwitterionic intermediate (path a). Once again convincing evidence for the two-step nature of the reaction has come from the work of Risaliti *et al.*[216] Comparison of the stereochemical behaviour of cis- and trans-isomeric electrophilic olefins has been used as a probe for determining the mechanism of their cycloaddition to enamines.[217] Following an analogous procedure it was shown that both cis- and trans-dibenzoylethylene gave one and the same dihydropyran **311**. Moreover, reaction of enamine **307** with an excess of cis- **308** gave unchanged olefin as the more stable trans- **309** under conditions (i.e. absence of free secondary amine at room temperature) which precluded interconversion

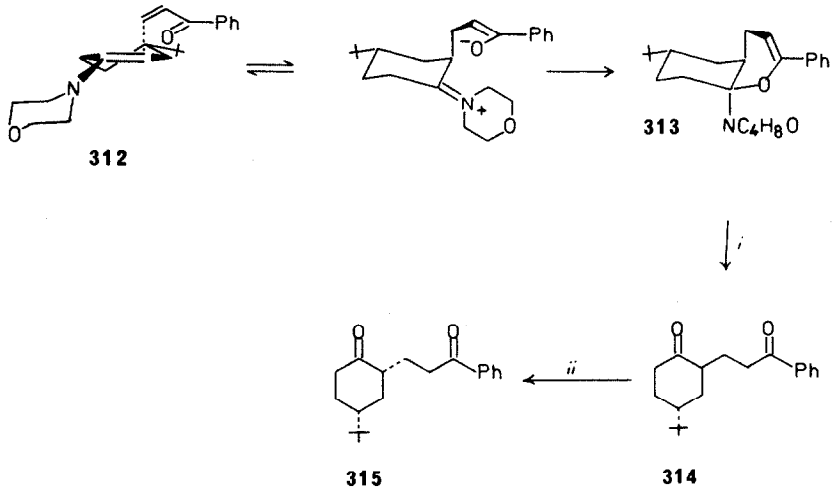
of **308** and **309**. If so then this clearly constitutes unequivocal evidence for a two-step mechanism involving the reversible formation of the zwitterionic intermediate **310**. Unfortunately the stereochemis-



307 **308 cis** **309 trans** **310** **311**

Scheme 106.

try of dihydropyran **311** could not be ascertained. The analogous reaction using 4-t-butylcyclohexanone enamine and phenylvinyl ketone gave the cis-fused product **313**, as shown by its conversion to a ketone **314** which could be epimerised to a more stable isomer **315**.[216]

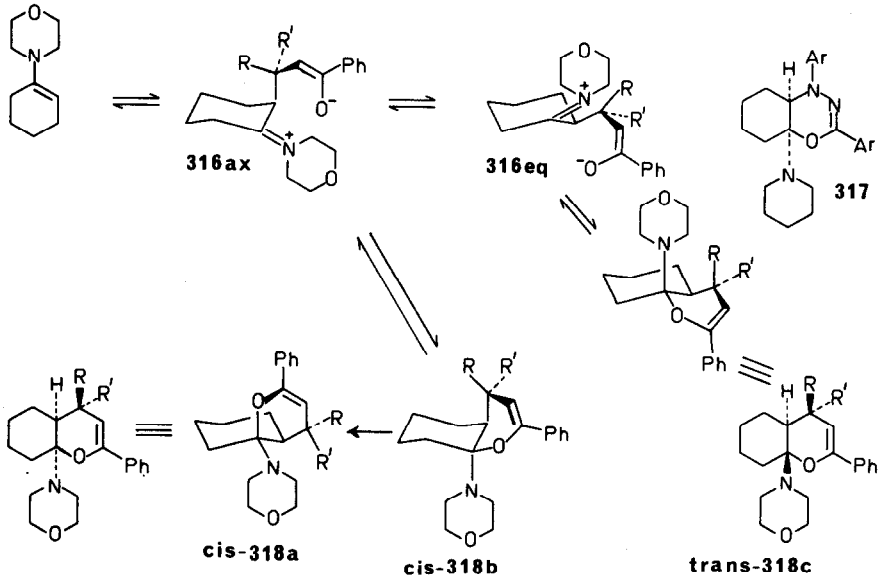


312 **313** **314** **315**

Scheme 107. Reagents: (i) cold H_3O^+; (ii) hot H_3O^+.

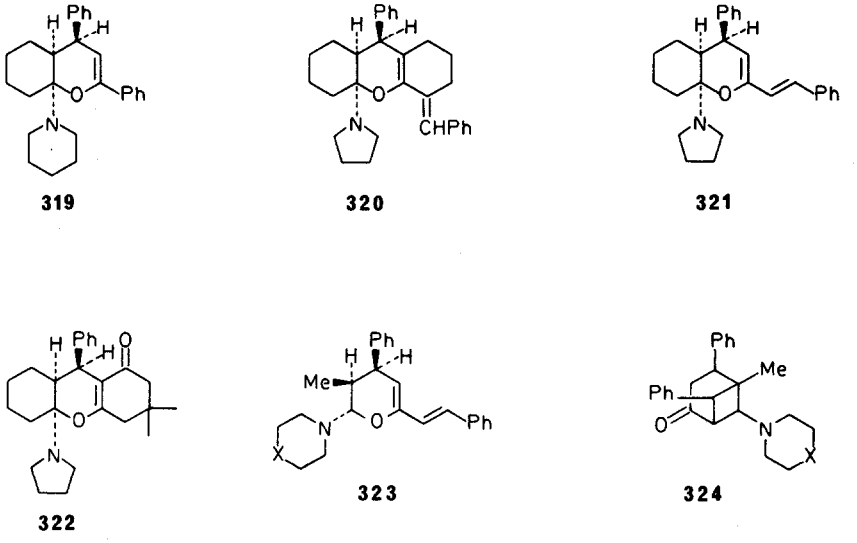
The yield of **313** (20%) was much lower than that of **318** (75%) obtained from the same reaction with cyclohexanone enamine (Scheme 108). This was taken as an indication that cis-ring closure is less favourable than trans-closure since in the latter case a conformational change of **316** ax into **316** eq could precede the cyclisation step. However, as Lewis *et al.*[218] have pointed out, since the dihydropyrans arise via a reversible two-step process, the thermodynamically more stable cis-fused adduct would be expected to be obtained, with the bulky amine substituent equatorial with respect to the cyclohexane ring (i.e. cis-**318a**).† The corresponding cis-**318a** conformation could not of course be obtained with the dihydropyran from 4-t-butylcyclohexanone. The cis-ring junction is also supported by an X-ray determination of the analogous structure **317**.[219]

†Axial with respect to the dihydropyran ring, but now there is only one 1,3-diaxial interaction and this is less than normal since the other substituent (R') is quasi-axial.



Scheme 108.

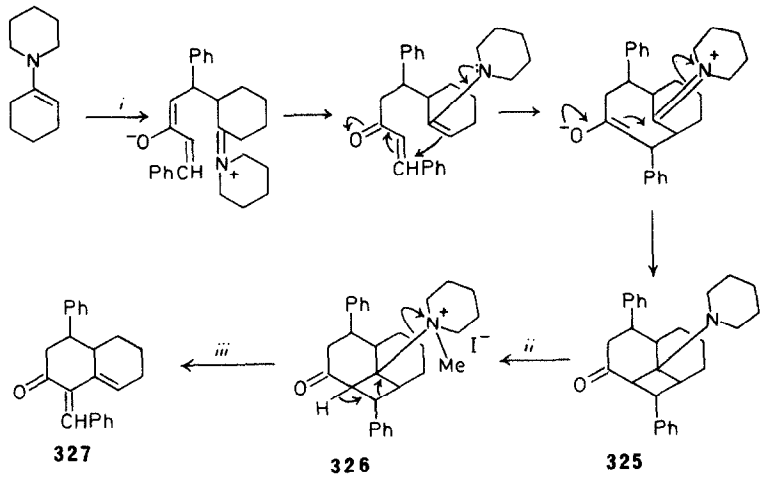
The stereochemistry of the 4 and 4a chiral centres is also in dispute. From consideration of the steric interactions between the R-substituents and the cyclohexane ring in cis-**318b**, and with the morpholine ring in trans-**318c**, it was logically concluded that the erythro configuration (**318c**; R = H, R′ = COPh) was the most probable structure for the dihydropyran **311** (Scheme 106), rather than the threo configuration (**318c**; R = COPh, R′ = H).[216] That is a [4,4a-trans] configuration would be favoured. However if cis-**318a** is the most stable conformer then these steric arguments must be reversed; as shown in cis-**318a**, R′ is then in the more crowded environment and therefore a [4,4a-cis] configuration should result (i.e. R′ = H, R = COPh), as concluded by Lewis *et al.*† from consideration of the coupling constants ($J_{4,4a}$ 8.5; $J_{3,4}$ 2 Hz)[218] in the products **319–322** derived from 1-piperidinocyclohexene and chalcone, 1-pyrrolidin-1′-ylcyclohexene and dibenzylidenecyclohexanone, 1-pyrrolidin-1′-ylcyclohexene and dibenzylideneacetone, and between 1-pyrrolidin-1′-ylcyclohexane and the monobenzylidene derivative of



Scheme 109.

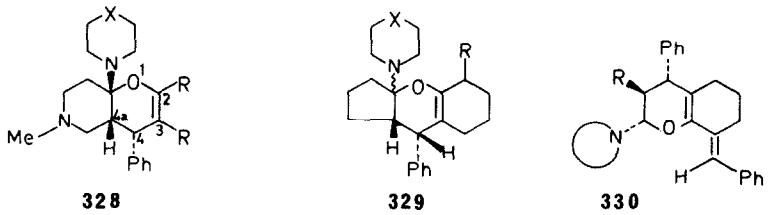
†Note however that Desimoni and Tacconi[220] appear to favour conformation cis-**318b** with a trans-4-4a configuration! However there is then no obvious explanation for the drastic reduction in yield caused by the introduction of an equatorial t-butyl group. Nevertheless the safest conclusion is probably that the question remains unanswered at present.

dimedone, respectively.[218,221] Interestingly, instead of an analogous structure to **321**, the reaction between 1-piperidinocyclohexene and dibenzylideneacetone gave the cyclobutane adduct **325** in boiling ethanol (Scheme 110),[218] and hence **326** and **327** on quaternisation and amine elimination. Application of this



Scheme 110. Reagents: (i) PhCH=CHCOCH=CHPh, EtOH, Δ; (ii) MeI; (iii) HO^-.

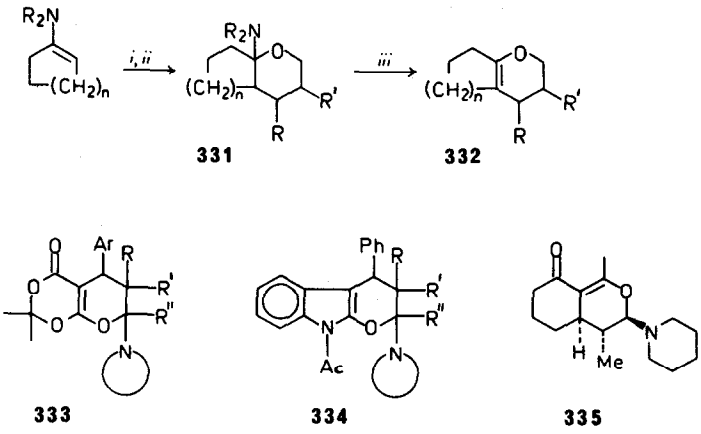
reaction to proponaldehyde enamines gave only the dihydropyrans (**323**; X = –, CH_2, –O–), none of the cyclobutane **324** being observed.[218] The reaction of 4-N-methylpiperidone enamines with various $\alpha\beta$-unsaturated ketones has also been shown to give dihydropyrans **328**; again a cis-ring fusion and a [4,4a-cis] configuration was assigned.[222]† Cyclopentanone enamines also undergo cycloaddition with 2-benzylidene- and 2,6-dibenzylidenecyclohexanone to give dihydropyrans **329**, but with benzylideneacetophenone (chalcone) only the C-alkylated enamine was isolated.[223]



Scheme 111.

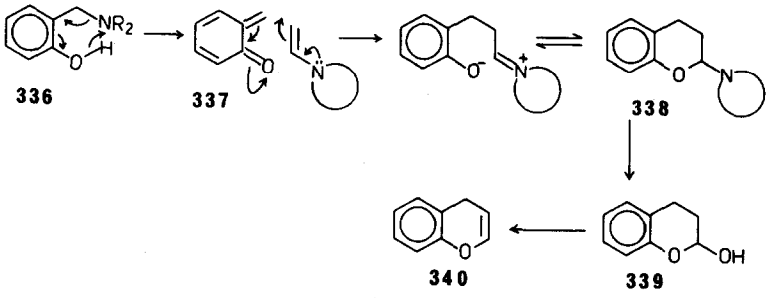
Alkylation of enamines with $\alpha\beta$-unsaturated esters give the C-alkylated enamine which undergo reductive cyclisation to tetrahydropyrans **331** and can be deaminated to **332**.[225] 5-Arylidene-1,3-dioxane-4,6-diones[226] and 3-benzaloxindole[202] derivatives react with enamines to give the condensed dihydropyrans **333** and **334** respectively [See also Part I[1], Section 5B(i)(f)]. Cycloaddition of 2-acetylcyclohex-2-enone with trans-1-piperidinopropene gives **335**.[227]

†Note however that Prasad[224] has assigned a trans, trans configuration for the substituents attached to the dihydropyran ring in cycloadduct **330** derived from acyclic enamines.



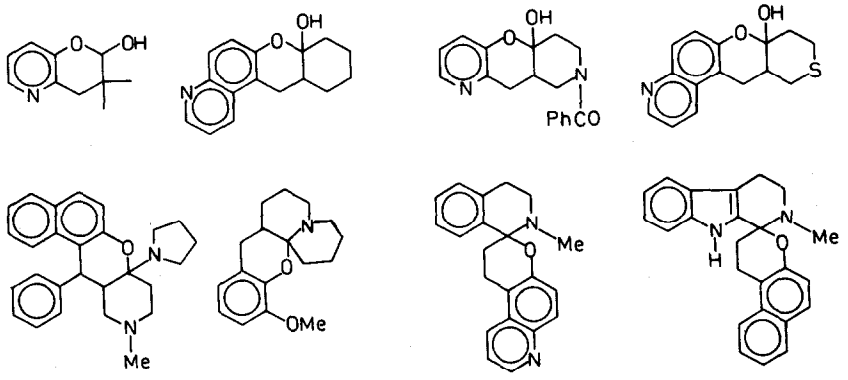
Scheme 112. Reagents: (i) $RCH{=}C(R')CO_2Et$; (ii) $LiAlH_4$; (iii) oxalic acid.

A variety of methods exist for the preparation of dihydropyrans in which the double bond is part of an aromatic system (chromans). One of the most versatile involves the reaction of enamines with quinone methides **337** generated by heating o-phenolic Mannich bases **336** in boiling dioxane or dimethylformamide for 2–12 hr. in the presence of the enamine.[228]



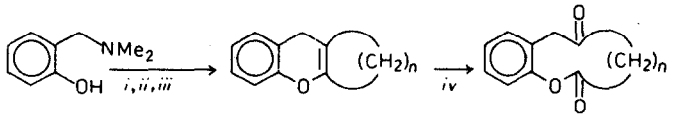
Scheme 113.

The 2-aminodihydropyrans **338** may be hydrolysed to **339** and dehydrated to the pyran **340**. The synthesis is applicable to enamines from both aldehydes and ketones. The use of heterocyclic ketones permits the synthesis of pyrans fused to heterocyclic rings. The Mannich bases vary from those with aromatic and quinoid nuclei to heteroaromatic ones derived from pyridine, courmarin, indole, quinoline, carbazole, etc. Partially reduced heterocyclic systems (outside the scope of this review) which embody an endocyclic enamine function undergo an analogous reaction but in this case the product is a spiro-heterocycle. Some examples of structures obtainable are given in Scheme 114.[228] Oxidative fission



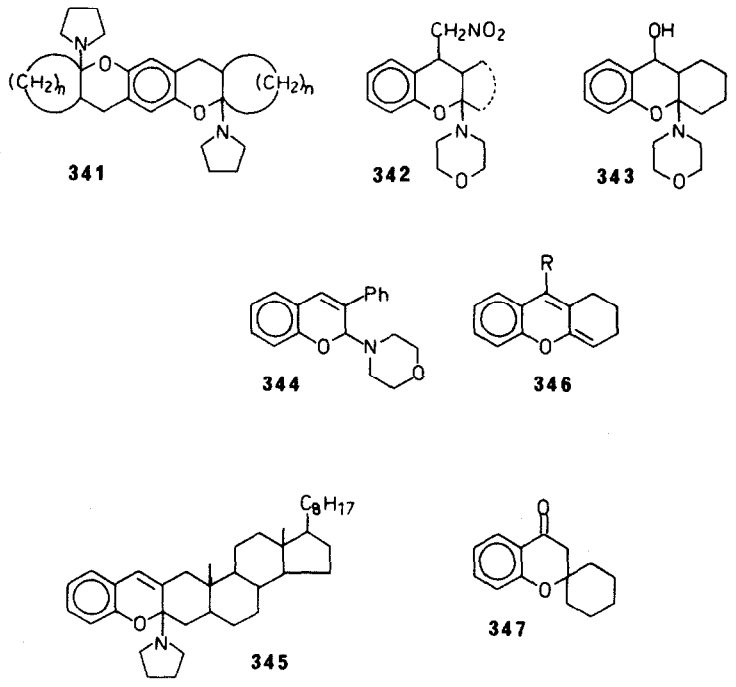
Scheme 114.

of the pyrans obtained in this way has been used for the synthesis of medium and macrocyclic ketolactones[229,230] (see also Section 3D).



Scheme 115. Reagents: (i) 1-N-dialkylaminocycloalkene, DMF or dioxan, Δ, 6–12 h; (ii) H_2O, Δ, 1 h; (iii) P_2O_5, C_6H_6, Δ, 4–6 h; (iv) m-$ClC_6H_4CO_3H$, CH_2Cl_2, 20°, n = 4, 5, 6, 10.

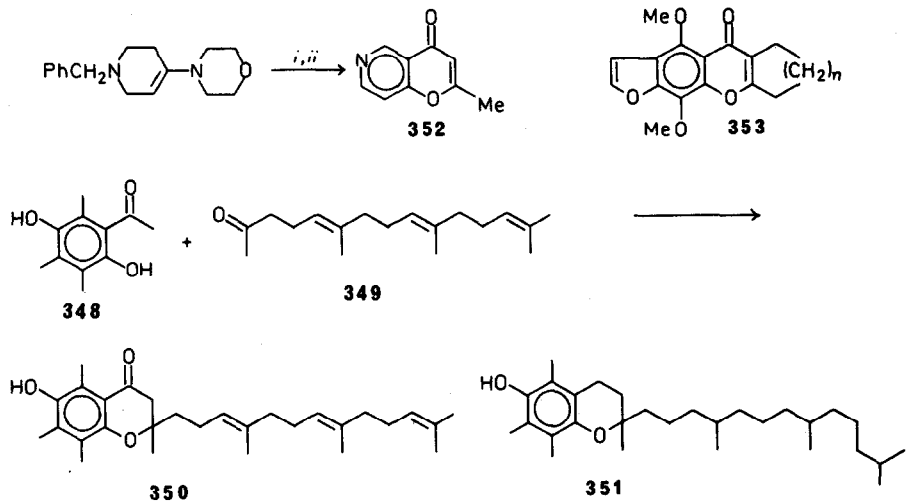
Alternatively the Mannich bases may be replaced by o-hydroxybenzyl halides[231] or o-hydroxybenzaldehydes, the latter method giving the 4-nitromethyldihydropyran **342**.[232] Bis-benzodipyrans **341** have been prepared from 2,5-bis(dimethylaminomethyl)hydroquinone. Although cyclohexanone enamines are reported to undergo cycloaddition to salicylaldehyde to give the aminohydroxydihydropyran **343**,[233] only dehydration products **344–346** were isolated from the same reaction with phenylacetaldehyde enamines,[234] certain steroidal enamines,[235] and pyrrolidin-1′-ylcyclohexene,[236] respectively. Interestingly,



Scheme 116.

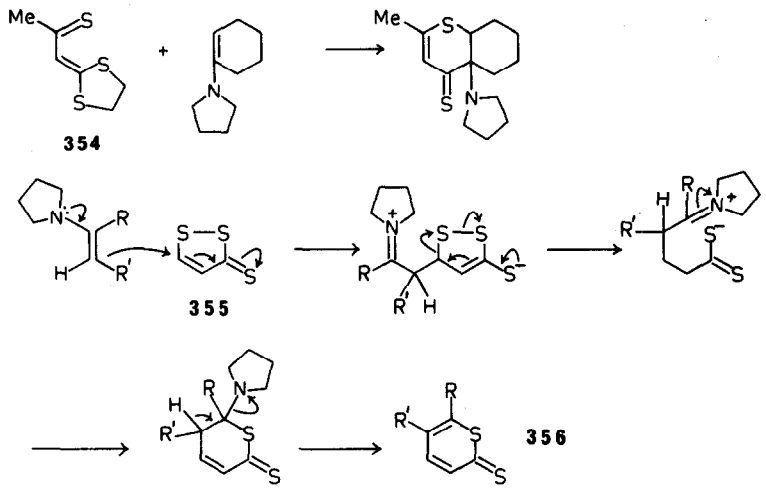
when salicylaldehyde was replaced by 2-hydroxyacetophenone the product obtained was not **346** (R = CH_3), but the spiro-4-chromanone **347**.[237] The same product can be obtained when a mixture of the two ketones is heated with pyrrolidine. In this way a mixture of **348** and **349** was induced to cyclise to **350** and converted into Vitamin E **351**.[238]

Condensation of enamines with mixed anhydrides from ethyl chloroformate and acetylsalicylic acids and their thio analogues gives 2,3-cycloalkene-chromones and thiochromones.[239] Similarly 6-acetoxy-4,7-dimethoxybenzofuran-5-carbonyl chloride gave γ-pyrones **353**.[240] γ-Pyrones, or 1,3-diketones, are formed from the reaction of diketene and enamines.[8] Application of the reaction to enamines of N-benzyl-4-piperidones gives azachromones **352**.[241]



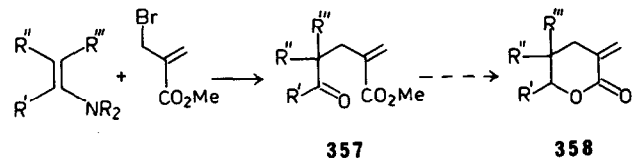
Scheme 117. Reagents: (i) diketene; (ii) Pd/C, xylene; n = 1–3.

(c) *Sulphur.* Six-membered sulphur heterocycles have been obtained by 1,4-cycloaddition of enamines to thioacylketene thioacetals **354** and related structures.[242] 1,4-Cycloaddition to 1,2-dithiole-3-thiones **355** gives the corresponding thiopyran-2-thione **356**.[243]



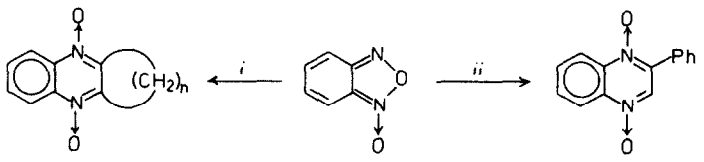
Scheme 118.

The α,α'-annulation of enamines with α-bromomethylacrylates [Section 2D(i)] can be prevented by using low temperatures. Acid hydrolysis of the monoalkylated enamine then yields unsaturated keto esters **357** and provides a route[244,245] to α-methylene-δ-lactones **358** by saponification, reduction, and lactonization.



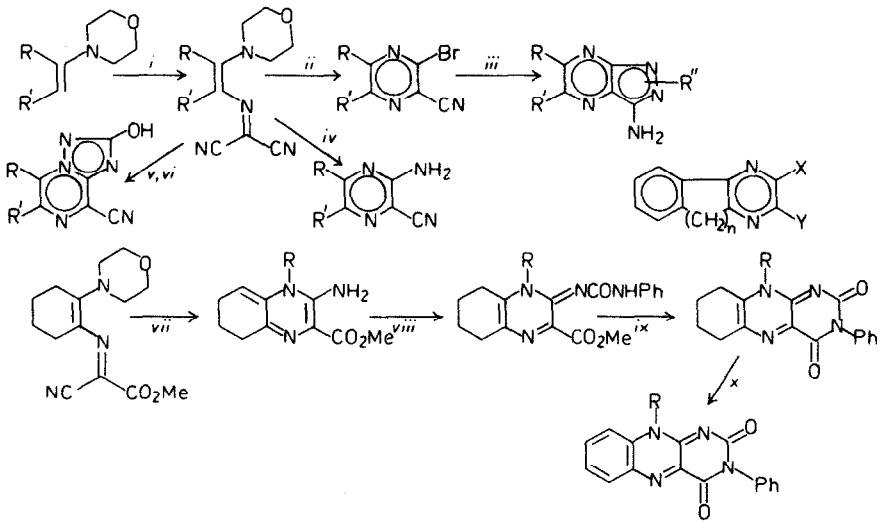
Scheme 119.

(ii) *Two or more hetero atoms.* A one-step preparation of quinoxaline 1,4-dioxides from benzofurazan 1-oxide and enamines was reported in 1965.[246] Since then the reaction has been further examplified[247] and the intermediate 2,3-dihydroquinoxaline 1,4-dioxides isolated in some cases.[248]



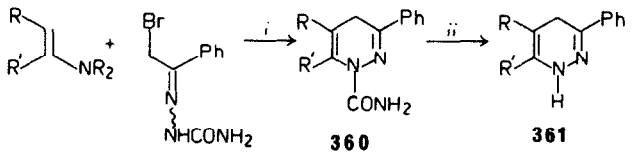
Scheme 120. Reagents: (i) 1-N-morpholinocycloalkene (n = 3–6); (ii) 1-N-morpholino-1-phenylethylene.

(O-p-Tosylisonitroso)malononitrile **359** is a useful reagent for the synthesis of aminopyrazines and other heterocycles.[249–251] 2,5-Dihydropyridazines **360** and **361** have been obtained from the reaction of



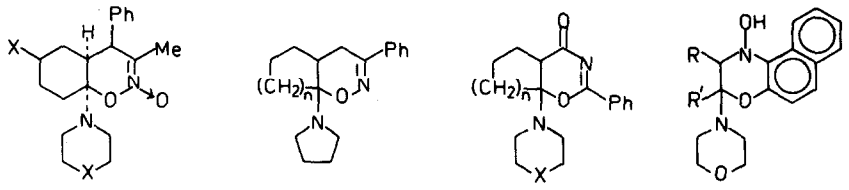
Scheme 121. Reagents: (i) T_sO–N=C(CN)$_2$ (**359**); (ii) HBr, HOAc; (iii) $RNHNH_2$; (iv) NH_3; (v) NH_2NHCO_2Me; (vi) HCl; (vii) RNH_2; (viii) PhNCO; (ix) Et_3N; (x) Pd/C; n = 1, 2; X,Y = NH_2, CN, CO_2Me.

enamines with ω-bromoacetophenone semicarbazone.[252]



Scheme 122. Reagents: (i) Et_3N, $CHCl_3$; (ii) H_2O^+.

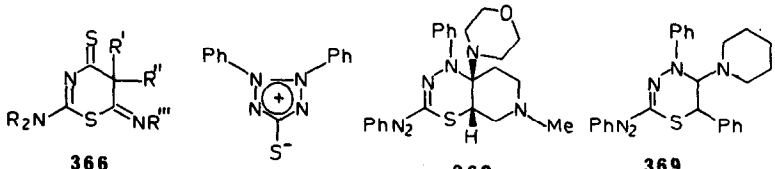
It has been established that there is a solvent equilibrium between cyclic nitronic esters **362** and their open-chain nitroethylated enamine tautomers.[253] Alkylation of enamines with phenacyl bromide oxime affords the dihydro-1,2-oxazine **363** (n = 1–3) after base catalysed cyclisation of the intermediate iminium salt.[254] Dihydro-1,3-oxazines **364** (n = 1, 2) can be obtained by [4 + 2]cycloaddition of benzoylisocyanates to enamines. Trichloroacetyl isocyanates appear to undergo preferential [2 + 2]cycloaddition to give the corresponding 2-oxoazetidine.[255] Unstable dihydro-1,3-oxazines are also reported from the cycloaddition of enamines to acylimines (i.e. R CON = CH·CCl_3), the latter being obtained by dehydrochlorination of the corresponding α-chloroalkylamide with base (triethylamine or excess enamine).[256] Dihydro-1,4-oxazines **365** have been obtained from 1-nitroso-2-naphthols and enamines,[257] but attempts to extend the reaction to o-nitrosophenols were unsuccessful.



362 363 364 365

Scheme 123.

Aliphatic thiocarbamoyl isothiocyanates [$R_2NC(S)N{=}C{=}S$] undergo [4 + 2]cycloaddition to enamines to give 1,3-thiazines **366**,[258] and the mesionic compound dehydrodithizone **367** reacts with enamines by opening of the tetrazole ring to give 1,3,4-thiadiazines such as **368** and **369**.[259] Spiro-1,3,4-thiadiazoles were isolated from the corresponding reaction with enamines derived from indan-2-one.

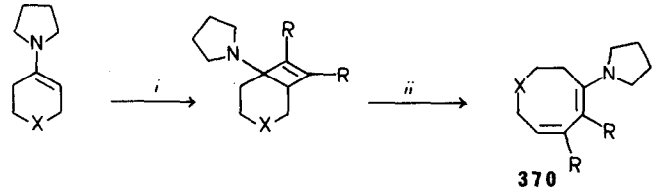


366 367 368 369

Scheme 124.

D. *Seven-membered and larger ring heterocycles*

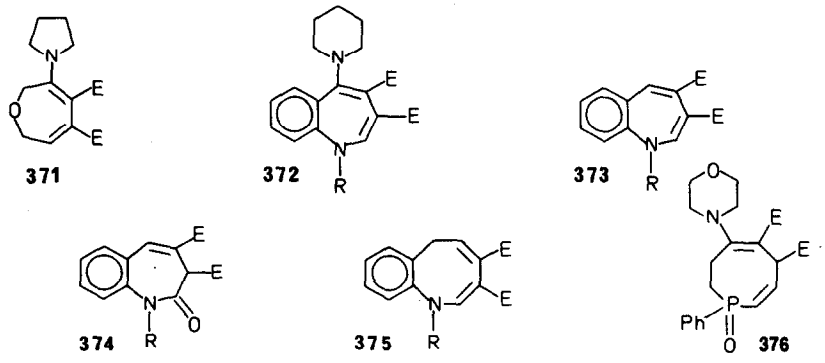
The [2 + 2]cycloaddition of acetylenic ester to enamines of cyclic ketones is a well documented method for two-carbon ring expansion leading to medium ring carboxylic systems.[8] Application of this method to enamines of heterocyclic ketones provides access to medium ring heterocycles such as tetrahydroazocines **370** (X = NMe) and dihydrothiocins **370** (X = S).[260] In a similar way structures **371**,[261]



370

Scheme 125. Reagents: (i) RC≡CR, 20°; (ii) 100°, dioxan, 2 h.

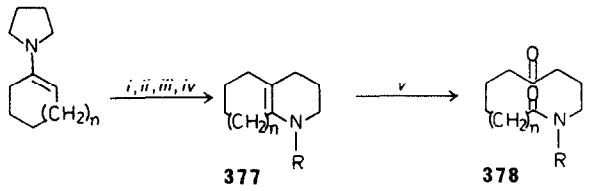
372,[262] **373**,[263] **374**,[264] **375**[265] and **376**[266] were obtained.



371 372 373 374 375 376

Scheme 126. Substituents: E = CO_2Me.

Several medium and large-ring keto-lactams **378** have been prepared by oxidation of bicyclic enamines **377** which were obtained by aza-annulation of cyclic ketone enamines[267] [see also Section 3C(i)(b)].



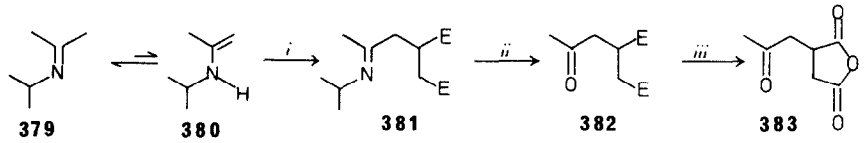
Scheme 127. Reagents: (i) CH_2=$CHCO_2Et$; (ii) H_3O^+; (iii) RNH_2, H^+, Δ; (iv) $LiAlH_4$; (v) $NaIO_4$, H_2O, MeOH, THF.

Finally we note that the crucial cyclization in Woodward's Vitamin B_{12} synthesis involved an intramolecular imino-ester-enamine condensation.[268]

4. IMINES

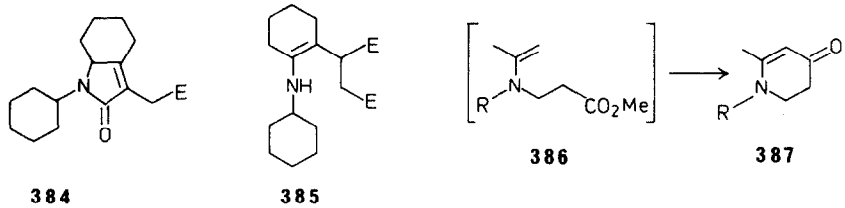
In this section we consider briefly the chemical and spectroscopic evidence for imine-enamine tautomerism, and its application to chemical synthesis. Except where the enamine form is stabilised by further conjugation,† spectroscopic studies[269,270] have shown that the equilibrium is usually almost completely in favour of the imine form for simple aldehydes and ketones. Nevertheless this imine–enamine tautomerism has been clearly demonstrated in reactions which involve the enamine form reacting with a variety of electrophilic reagents at the α-position to the original carbonyl function (C-β of the enamine).[270,275,276]

A convincing demonstration of imine–enamine tautomerism has been reported by Pfau and Ribiere[277] who showed that N-isopropylideneisopropylamine **379** reacted with dimethyl maleate to give the C-alkylated products **381–383** in high yield.



Scheme 128. Reagents: (i) cis-MeO_2CCH=$CHCO_2Me$, C_6H_6, Δ; (ii) H_2O, dioxan, 20°; (iii) Δ, E = CO_2Me.

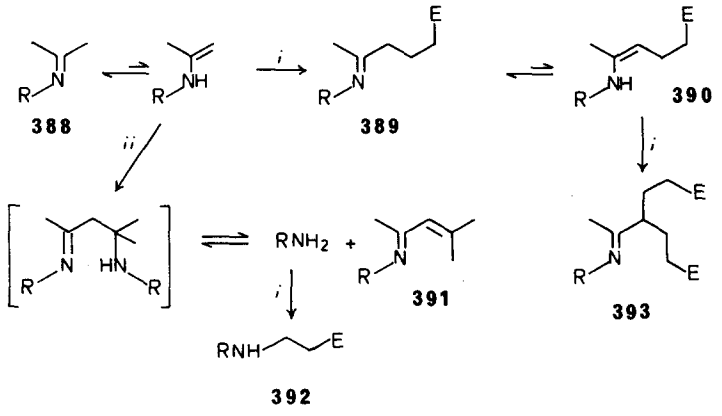
Although no olefinic signals could be observed in the NMR spectrum of **379** in methanol, the signals corresponding to the two methyls (magnetically nonequivalent) attached to the imine double bond (τ 8.06 and 7.99) rapidly disappeared in deuteriomethanol. So although at equilibrium the imine is virtually the exclusive form, these six hydrogens are rapidly exchanged via the enamine form **380**. This is a useful result since, in effect, it gives a means of preparing the enamine of acetone‡ *in situ*. Application of the dimethyl maleate reaction to the imine of cyclohexanone gave lactam **384** via the C-alkylated enamine **385**.[277,278]



Scheme 129.

†As with a carbonyl[269,271] (outside the scope of this review) or imine group,[272] or an aromatic system.[273,274]
‡Until recently thought to be too reactive to be isolated (see Part I[1]).

A recent claim[279] that only N-alkylation of N-isopropylidenecyclohexylamine occurred with methyl acrylate, in contradiction of the above work, has been shown to be incorrect.[280] In fact Pfau *et al.* have demonstrated unequivocally that with these reagents absolutely no N-alkylation occurs, not even reversibly, since the N-alkylated compound **386** cyclized spontaneously to enaminoketone **387**, none of which was present in the product mixture from the reaction of methyl acrylate with N-isopropylidene-cyclohexylamine (Scheme 130).[280] The only products isolated were **389**, **391**, **392** and **393**. The formation

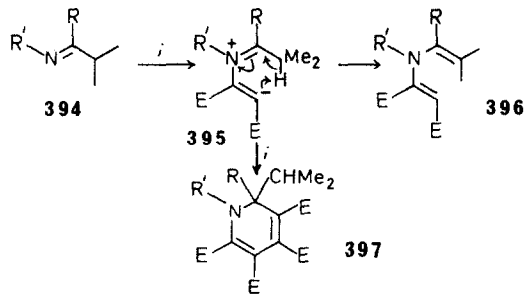


Scheme 130. Reagents: (i) CH_2=$CHCO_2Me$; (ii) **388**; E = CO_2Me, R = cyclohexyl.

of the α,α-bis-alkylated product **393** is interesting. This was produced in 86% yield when two equivalents of methyl acrylate were employed, a result which is in sharp contrast to the reaction of tertiary enamines derived from unsymmetrical ketones which react preferentially at the least substituted position (Part I;[1] Sections 2, 5A, 5B, 5C, 5F). Clearly this can be attributed to the enamine taking up a conformation (i.e. **390**) in which $A^{1,3}$-interactions[79] are minimal both in the ground state and the transition state. The steric interactions which have been used[1] to predict the course of tertiary enamine reactions are therefore no longer applicable to primary or secondary enamines.† Even so attempted bis-alkylation with the more bulky dimethyl maleate failed for steric reasons.[280] Similarly aldimines undergo mono- and bis-C-alkylation with methyl acrylate.[282] Reaction of the iso-propylamine imine of acetone with methylvinyl-ketone provides a good method for the preparation of 3-methylcyclohex-3-enone.[283] The intermediate stages may be hydrolysed or further alkylated (α,α'-dialkylation in this case!) to yield heptane-2,6-dione or undecane-2,6-10-trione respectively. The acetophenone imine was also α,α-dialkylated and isobutyraldehyde imine mono-alkylated.

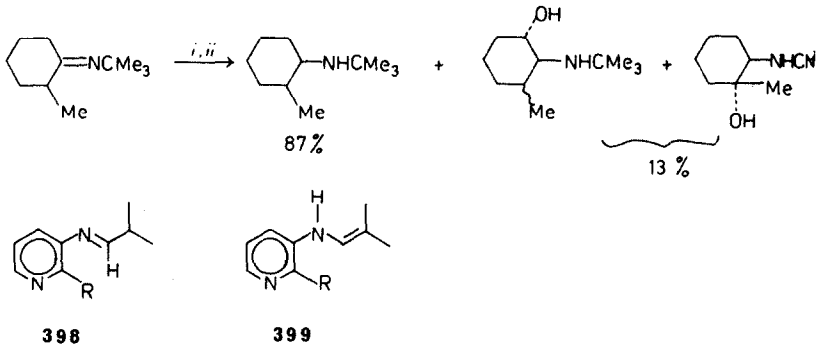
In contrast to the work of Pfau *et al.* with electrophilic olefins, reaction of imines with $\alpha\beta$-acetylenic esters has been shown to result only in compounds derived from N-alkylation of the imine **394**![274,281] Depending upon the substituents present in the imine the products obtained were either the dihydropyridine **397** or the enamino ester **396**. Savignac and Lattes[274] showed from an examination of their ^{1}H NMR spectra, that the amount of enamine tautomer present at equilibrium with the imine [Me_2CH C(R) = NR'] was as follows: R = H, R' = Me, 0%; R = Ph, R' = Me, 10%; R = H, R' = p-$CH_3C_6H_4$, 15%; R = H, R' = p-BrC_6H_4, 18%; R = Ph, R' = p-$CH_3C_6H_4$, 19%; R = Ph, R' = p-ClC_6H_4, 27%. From this it was inferred that the enamino ester **396** was derived by N-alkylation of the enamine tautomer. However the correlation between the amount of **396** formed and the amount of enamine present at equilibrium was not convincing; and if this were the case, why should there be such a drastic change in the regiochemistry of the reaction, from 100% C-alkylation with dimethyl maleate to 100% N-alkylation with dimethyl acetylene dicarboxylate? It therefore seems to the reviewer that an alternative explanation has to be considered, namely that the combined effects of the two ester groups and the triple bond lower the LUMO energy of the electrophile sufficiently to enable direct interaction with the *imine* HOMO. Whether the resulting zwitterion **395** then undergoes reversion to starting material, 1,5-proton shift to **396** or further reaction with electrophile to give **397**, could then depend on a subtle interplay of conformational, steric, and electronic factors.

†In fact preliminary investigations have shown that 2-methylcyclohexanone imines, in contrast to the corresponding tertiary enamines, react preferentially with electrophilic olefins *via* the more substituted enamine tautomer to give the 2,2-disubstituted cyclohexanone exclusively, in both protic and aprotic solvents (G. J. Davison and P. W. Hickmott, unpublished results).



Scheme 131. Reagents: (i) $MeO_2CC{\equiv}CCO_2Me$, 20°; R′ = Me, Ar; R = H, Ph; E = CO_2Me.

The equilibrium constants and the values of the thermodynamic parameters (ΔH, ΔG, and ΔS) have been determined for imine–enamine tautomerism by a variable temperature NMR study of 1,3-diphenylisopropylidenecyclohexylamine. Polar solvents were found to favour enaminization but surprisingly had little effect on the cis-trans isomerization of the enamine tautomers.[284] Although cyclohexanone imines of n-propylamine, cyclohexylamine, and 2-bornylamine do not give signals due to the enamine tautomer in their ^1H NMR spectra, the t-butylamine imine does (τ 5.4).[285] The equilibrium position is strongly solvent-dependent, the amount of enamine being 4.7% (CD_3OD), 9% ($CDCl_3$), 14.6% (CH_2Cl_2), 22.5% (C_6D_6), 30% (CCl_4 and C_6D_{12}), 33% (dioxane) and 37.8% (D_6-DMSO). The percentage concentrations of the 3,3,5,5-tetramethylcyclohexanone enamine are even higher, rising to a maximum of 53% in deuteriocyclohexane![286] A wide variation in the equilibrium position is also evident in the imines **398** derived from 3-aminopyridines,[287] and those from anilines.[288] When R = H or Me the imine **398** forms 92–100% of the product, whereas when R = Cl, OEt, or NO_2 the enamine **399** forms 83–100% of the product. The condensation product from isobutyraldehyde and 3-aminopyridine N-oxide also exists 100% in the enamine form.[287] The enamine tautomer can also be detected by diborane reduction, the imine being reduced to the saturated secondary amine whereas the enamine is converted to the corresponding β-aminoalcohol.[285]

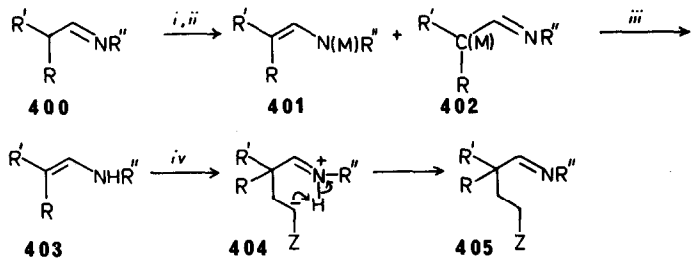


Scheme 132. Reagents: (i) B_2H_6; (ii) HO^-, H_2O_2, EtOH.

An extensive investigation into factors affecting the imine-enamine equilibrium has been conducted by Ahlbrecht *et al.*[289]

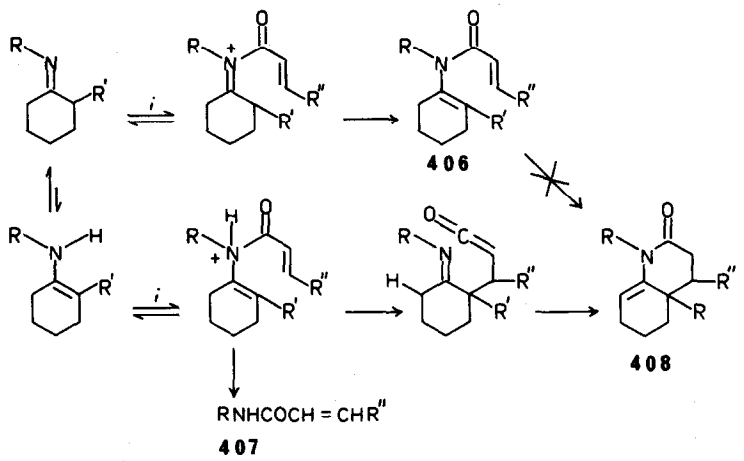
Despite the fact that secondary enamines are usually thermodynamically unstable and often undetectable, De Jeso and Pommier[291] have developed a method for the isolation and characterisation of the pure enamine tautomer. The imine **400** is first converted to the organotin (or organomagnesium) derivatives[291] **401** and **402**. These are very sensitive to protolysis (i.e. methanolysis) giving the imine **400**. However if insufficient methanol is used for complete protonolysis (i.e. 75% of theory) the secondary enamine **403** is obtained as the kinetic product of the reaction (see also Section 5E). These enamines are stable in the organotin media and can be extracted from the mixture under reduced pressure and trapped at −80°. Methanolysis using MeOD gives N-deuteriated enamines. The enamines are quite stable at −80° (imine content 25% after 18 h) and can be characterised at room temperature, when total isomerisation to the imine takes about 1 h. Treatment of the separated enamines with electrophilic olefins resulted in a fast exothermic reaction at 0° leading to the C-alkylated product **405**. The same reaction with the

corresponding imines was either very slow (24 h, 80°) or did not take place. The use of N-deuteriated enamines gave adducts **405** having a deuterium atom in the α-position with respect to the Z group, thus providing confirmation for the intramolecular proton shift depicted in **404**.[290]



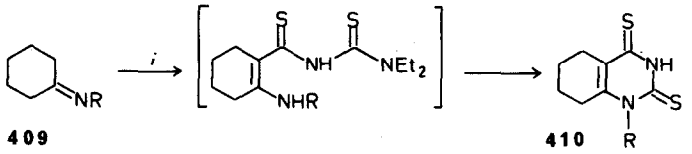
Scheme 133. Reagents: (i) i-Pr_2NLi (or i-Pr_2MgCl); (ii) Bu_3SnCl; (iii) MeOH; (iv) CH_2=CHZ; Z = CN, COMe, CO_2Me; R,R' = Me, Et, H; R'' = Me, Et, i-Pr, i-Bu; M = $SnBu_3$ (or MgCl).

The reaction of imines with aliphatic and aromatic acylating agents has previously been reported to result in the formation of N-acylated[292] and C-acylated[293] products. In their reaction with $\alpha\beta$-unsaturated acid chlorides we have found no evidence for the C-acylation of imines, the products isolated being the enamide **406** and, in some cases the amide **407**, formed by N-acylation of the imine or enamine tautomer, and heterocyclic compounds **408** formed from the enamine tautomer.[294] That the quinolone **408** was not derived by N-acylation of the imine followed from the failure of enamide **406** to undergo cyclisation to



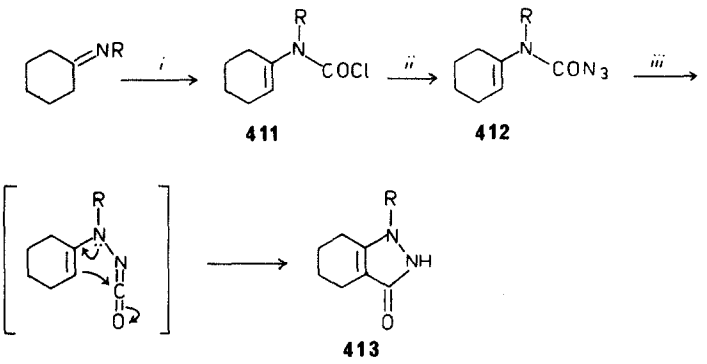
Scheme 134. Reagents: (i) R''CH=CHCOCl, C_6H_6, Δ; R = Ph, $PhCH_2$, C_6H_{11}, n-Bu; R' = H, Me; R'' = H, Me, Ph.

408 in the absence of photochemical stimulation.[295] Pyrimidinedithiones **410** have been obtained by cyclocondensation of aliphatic thiocarbamoyl isothiocyanates with imines such as **409**.[296]



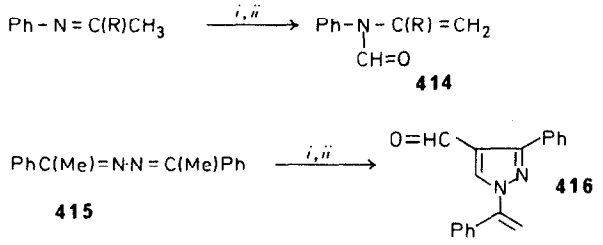
Scheme 135. Reagents: (i) $Et_2NC(S)N$=C=S; R = C_6H_{11}.

N-Acylation of imines (or the enamine tautomers) occurs with phosgene to give the enecarbamoyl chloride **411**. Conversion to the azide **412** resulted in ring closure to the tetrahydroindazolin-3-one **413**.[297]



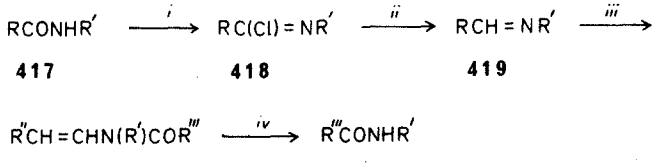
Scheme 136. Reagents: (i) $COCl_2$; (ii) NaN_3; (iii) Δ.

The Vilsmeier–Haack reaction of imines (or the enamine tautomers) gives N-formylenamines **414**. Azines **415** react twice to give the pyrazole **416**.[298]



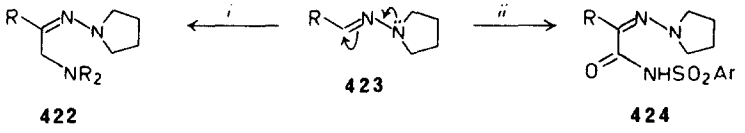
Scheme 137. Reagents: (i) $POCl_3$, DMF; (ii) HO^-.

Imines **419** can be obtained by partial reduction of imidoyl chlorides **418** which in turn are available[299] from amides **417**. N-Acylation of the imine (or the enamine tautomer) followed by hydrolysis of the resulting enamide **420** provides a mild method for the conversion of one amide **417** into another amide **421** (i.e. acyl exchange).[300]



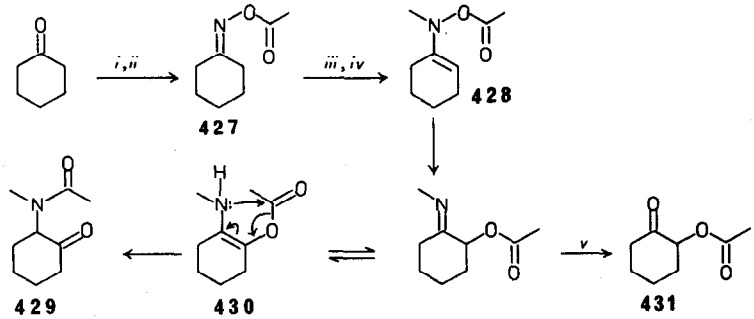
Scheme 138. Reagents: (i) $COCl_2$, C_5H_5N; (ii) $LiAl(t\text{-}BuO)_3H$; (iii) R″COCl; (iv) 0.1 N alc. HCl, 20°, or aq. NH_2OH, HCl, 40°, 30 min.

Brehme and Nikolajewski[301] have shown that aldehydehydrazones **423** may function as an aza-enamine in which the azomethin-carbon is activated to electrophilic attack. Thus reaction of **423** with the Mannich reagent **425** or the sulphonylisocyanate **426** gives **422** and **424** respectively.



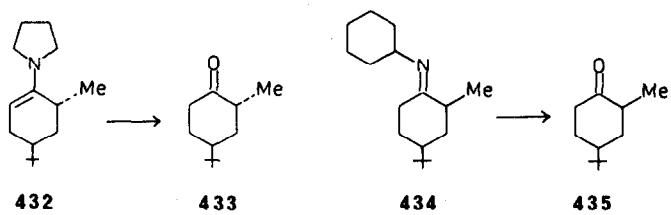
Scheme 139. Reagents: (i) $CH_2{=}\overset{+}{N}R_2Cl^-$ (**425**); (ii) $ArSO_2N{=}C{=}O$ (**426**).

O-Acetyl ketoximes **427** rearrange on successive treatment with trimethyloxonium fluoroborate and triethylamine to give α-acetoxy ketones **431** on hydrolysis. Evidence available indicates the involvement of a Claisen-type rearrangement of an intermediate N-acetoxyenamine **428**. If the reaction time is prolonged prior to hydrolysis a further rearrangement occurs via enamine **430** to the amide **429**.[302]



Scheme 140. Reagents: (i) NH_2OH; (ii) Ac_2O; (iii) $Me_3\overset{+}{O}BF_4^-$; (iv) Et_3N; (v) H_3O^+.

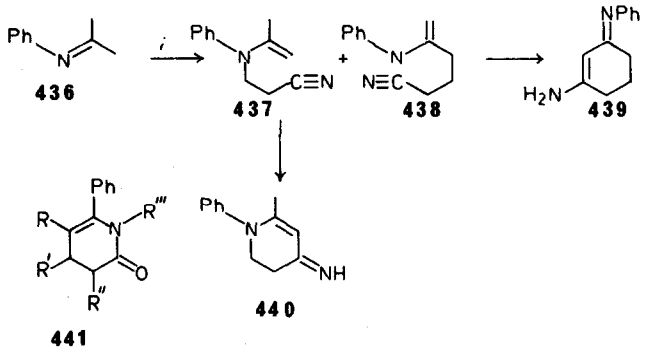
Heterocyclic imines such as Δ^1-piperideine will react as their heterocyclic enamine tautomers, for example with heterocumulenes,[303] but this is outside the scope of this review. The aza-annulation of imines with acrylamide occurs smoothly, as in the case of enamines (see Section 3C(i)(a)) illustrating the versatility of imines as effective substitutes for enamines.[304] The hydrolysis of secondary enamines or imines may have different stereochemical consequences to the hydrolysis of the corresponding tertiary enamine. For example the pyrrolidine enamine **432** gives largely the trans-ketone **433** on hydrolysis (Part I[1], Section 2) whereas the corresponding imine **434** gives the cis-ketone **435**.[79]



Scheme 141

As with tertiary enamines, the oxidation of imines with lead tetraacetate gives a complex mixture of products. Reaction occurs preferentially via the enamine tautomer giving mainly the α-acetoxyaldehyde or α-acetoxyimine.[305]

Although, as we have seen, imines react with electrophilic olefins via their enamine tautomer to give products of C-alkylation, the rate of reaction is greatly increased by the addition of a Lewis acid. The reaction can then be carried out at lower temperature for shorter times and the C-alkylated product isolated in higher yield.[306] Ketimines **436** derived from aliphatic ketones and aniline react with acrylonitrile in the presence of aluminium chloride to give products **440** and **439** derived from N- and

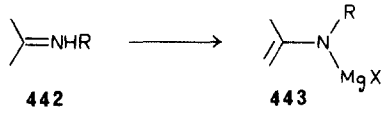


Scheme 142. Reagents: (i) CH_2=CHCN, $AlCl_3$.

C-alkylation (**437** and **438** respectively).[307] Dihydropyridones **441** are produced by reaction of acetophenone and propiophenone imines with acrylic esters and nitriles in the presence of aluminium chloride.[308]

5. METALLOENAMINES

Introduction. The nucleophilic properties of enamines[76] have long played a commanding role in processes involving the formation of new carbon–carbon and carbon–hetero-atom bonds by alkylation, acylation, annulation, and cycloaddition reactions.[1,309] These processes, exemplified by Stork and developed by numerous other investigators, have become known as the Stork reaction.[1,310] In 1963 Stork and Dowd[311] introduced a modification to this reaction which was designed to overcome some of the difficulties encountered in the C-alkylation of enamines and dienamines. This involved reaction of an imine with a Grignard reagent to give the metal derivative which was referred to as a metalloenamine (**442** → **443**). These are secondary enamine derivatives which undergo many of the reactions of a normal



442 **443**

Scheme 143.

tertiary enamine, but without some of their complications, and they are therefore to be included in the definition of the Stork reaction. Almost simultaneously and independently Wittig *et al.* reported[313] that metallated Schiff's bases condensed with aldehydes and ketones to give α,β-unsaturated aldehydes and ketones. This application of enamine chemistry is usually referred to as the Wittig directed aldol condensation. Like the early work of Stork in this field,[1,312] these modifications have also led to an enormous amount of work in other laboratories. The process now includes not only metallo derivatives of secondary enamines (imines), but also those of hydrazones and oximes (outside the scope of this review), tertiary enamines (outside the scope of this review), and labile heterocyclic systems (i.e. oxazolines, outside the scope of this review) brilliantly developed by Meyers[314] into a method for the asymmetric synthesis of α- and β-substituted carboxylic acids. Various α-, β-, β'-, or γ-metallated tertiary enamines have also been prepared recently.[315–322] However these have the properties of vinyl or allyl anions rather than enamines (although their alkylation products, for example, can be further alkylated as enamines) and are not considered further in this report.

Alternative nomenclature for metalloenamines found in the literature include imine anion, aza-allyl anion, lithio anion, lithiated ketimine or aldimine, lithioenamine, lithiochelated enamine, etc. A variety of structural formulations are also used, ranging from fully ionic to fully covalent. However there appears to be no experimental evidence available as yet on which an objective choice of structure could be made. In the absence of a carbanionic stabilising substituent elsewhere in the molecule, the electron density in a metalloenamine would normally be expected to be greatest at the more electronegative nitrogen atom, as in the case of a tertiary enamine (see Part I[1]). Several observations appear to support this contention. In particular the configurational stability about the C_1–C_2 bond and the ease of anti-syn conversion about the C_1-N bond, as evidenced by examples quoted in Section E, argue for mainly double bond character of the C_1–C_2 bond and single bond character for the C_1-N bond since the barrier to inversion about the C=N bond in ketimines, whether this occurs by rotation, lateral inversion (in which the C=N double bond is retained) or imine-enamine tautomerism,[323] has been placed[324] as high as 70–90 kJ mol^{-1}. Furthermore protonation of stannic and lithioenamines occurs almost exclusively at nitrogen, to give the unstable secondary enamine (see Section 4 and 5E), and is indicative of metallation and increased electron density at the nitrogen rather than the β-carbon. The degree of ionic character will of course depend on the electropositivity of the metal, and would therefore be expected to increase in the order tin, magnesium < lithium < sodium < potassium (< caesium). However the nature of the substituents, reagents, solvent and temperature can also influence the situation. Powerful electron donor

solvents such as hexamethylphosphoramide (HMPA) increase the ease of metalloenamine formation and, by analogy with their effect on Grignard reagents, presumably increase their degree of ionic character. Additional complications include the possibility of aggregation and the formation of contact and solvent separated ion pairs.

In view of all this uncertainty we have tended to use the nomenclature and structural formulations, whether ionic or covalent, favoured by the author of the work under review, but only as a convenient representation which may not bear too much resemblance to the true situation in some cases. However this structural uncertainty is also reflected in the diversity of mechanistic interpretation provided for the impressive regioselectivity and stereoselectivity of metalloenamine reactions. In view of the paucity of evidence available at this point in time, an unequivocal choice between the conflicting mechanistic explanations is not possible and we have therefore tended to merely recount the mechanistic explanation already given in the literature with little further comment.

A. *Spectroscopic data*

Direct observation of lithiated ketimines[325] (and the secondary enamines derived from them), lithiated hydrazones,[326] and stannic enamines[291] have recently been made by ^{1}H NMR spectroscopy (Table 2–4) and ^{13}C NMR spectroscopy (Table 5 and 6).[327–329]

B. *Metal derivatives of imines*

Stork and Dowd showed that imines derived from aliphatic primary amines and enolizable aldehydes and ketones were readily converted to the magnesium derivative **448**, by refluxing with ethyl magnesium bromide in tetrahydrofuran. These magnesium derivatives reacted with primary and secondary alkyl halides in boiling tetrahydrofuran giving, after aqueous acid hydrolysis, high yields of monoalkylated carbonyl compounds **450**. The more acidic Schiff bases derived from aromatic amines could be enaminized with sodium hydride. Apart from working well with simple primary and secondary alkyl halides, this modification of the Stork reaction has the following advantages: (i) the formation of the magnesium complex can be carried out in the presence of the alkylating agent. Unstable metalloenamines can therefore be formed and alkylated *in situ*; (ii) direct C-alkylation occurs, even with aldehyde metalloenamines. There is no aza-Claisen rearrangement, for example, with allylic halides as occurs with tertiary aldehyde enamines; (iii) alkylation may be effected with alkyl halides, such as isopropyl iodide or β-phenethyl bromide, which are easily dehydrohalogenated; (iv) alkylation of

Table 2. ^{1}H NMR chemical shifts (τ) of olefinic β protons of lithiated ketimines and their derived secondary enamines[a]

			R'CH=C(R")NRLi 444		R'CH=C(R")NHR 445			
R	R'	R"	444Z		444E	445Z		445E
Ph	Me	Me		5.35			4.97	
Ph	Ph	Me	4.87		4.73	-		-
c-C_6H_{11}	H	H		7.02			6.50	
c-C_6H_{11}	Et	H	-		6.40	-		5.78
Ph	H	Et		6.00			5.62	
Ph	H	t-Bu		5.99			5.60	
Ph	H	Ph		5.77			5.27	
Ph	Me	Et	5.38		5.50	5.10		5.02
Ph	Me	Ph	4.64		4.97	4.48		4.60
Ph	Et	n-Pr	5.50		5.57	5.20		5.00
Ph	-$(CH_2)_4$-		-		5.25	-		4.78
Ph	-$(CH_2)_5$-		-		5.08	-		4.68
Ph	-$(CH_2)_6$-		-		5.30	-		-
Ph	Ph	CH_2Ph	4.84		4.55	4.18		3.63

a THF or [D_8] THF

Table 3. ^{1}H NMR chemical shifts (τ) and coupling constants (Hz) of olefinic α protons of lithiated hydrazones

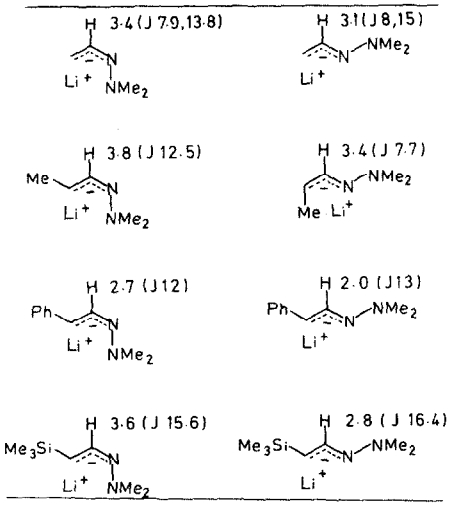


Table 4. ^{1}H NMR chemical shifts (τ) of olefinic protons of stannic enamines[a]

		$RCH_\beta=CR'_\alpha N(Et)SnBu_3$		$RCH(SnBu_3)CR'=NEt$
		446		447
R	R'	Ratio 446:447	H_β	H_α
Et	H	78:22	6.0	4.8
n-Pr	H	83:17	5.8	4.2
n-Bu	H	86:14	5.9	4.15
n-C_5H_{11}	H	85:15	6.0	4.15
n-C_7H_{15}	H	80:20	5.9	4.3
H	Me	79:21	6.8	-

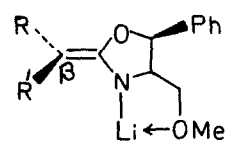
[a] Solvent not stated

Table 5. ^{13}C NMR chemical shifts of olefinic carbons in lithiated imines and hydrazones

		$R\underline{C}H=\underline{C}(R')N(X)Li$		
X	R	R'	C_1	C_2
Me	Me	H	152.9	75.2[a]
Me	i-Pr	H	149.8	92.4[a]
Me	Me	Et	160.8	74.0[a]
NMe_2	Me	H	150.2	74.7[b]
NMe_2	Me	Et	156.7	65.8[c]
NMe_2	$-CH_2CH(t\text{-}Bu)CH_2CH_2-$		150.4	70.9[c]

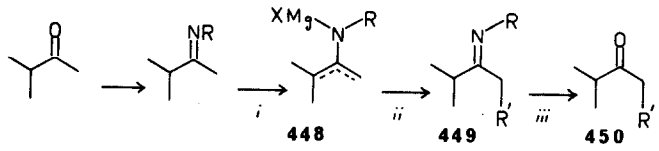
[a] THF [b] THF+HMPA [c] Metallation solution (see lit.)

Table 6. ^{13}C NMR chemical shifts of lithio oxazolines in THF

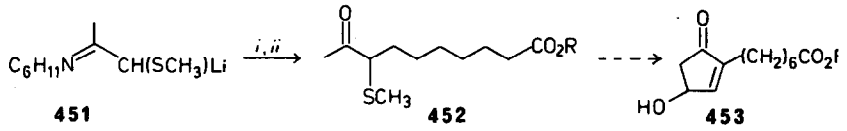


R	R'	R	R'	C_β
Me	H	12.1	-	51.5
H	Me	-	12.9	51.5
Me	Me	17.6	19.4	-

unsymmetrical ketones occurs at the least substituted α-position to give **449** (Scheme 144), as with tertiary enamines and presumably for the same reason[1] (vide infra). An exception to this has been observed in the alkylation of the lithiated imine **451** of thiomethylacetone which gives **452**, utilised in the synthesis of the PGE_1 precursor **453**.[330]

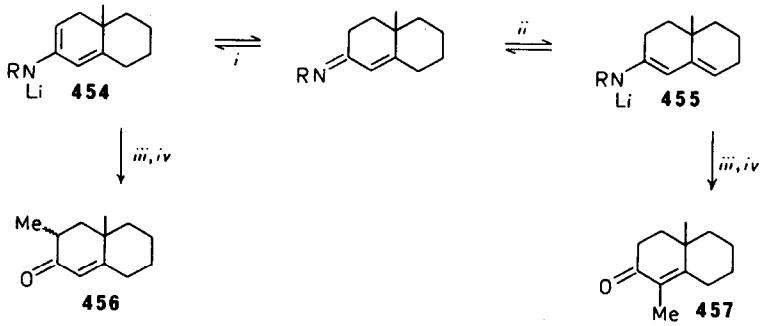


Scheme 144. Reagents: (i) EtMgBr; (ii) R'X; (iii) H_2O.

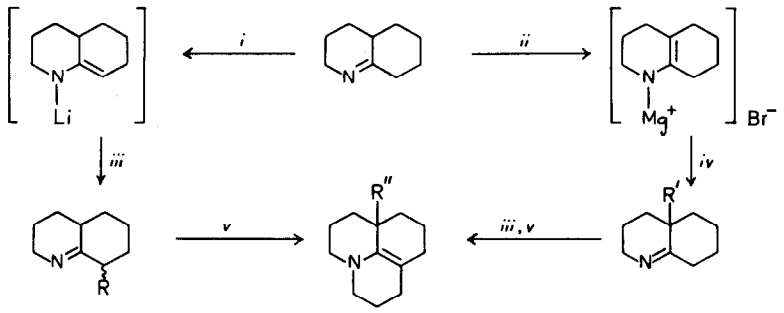


Scheme 145. Reagents: (i) $I(CH_2)_6CO_2R$, THF, −78°, 10 h; (ii) NaOAc, HOAc, H_2O, 25°.

However one of the main advantages of this modification of the Stork reaction is in its application to the mono-α-alkylation of α,β-unsaturated ketones. Although the latter are readily convertible to tertiary dienamines or dienolate anions, subsequent alkylation is frequently troublesome due to low yields or dialkylation. Conversion to the metallo derivative not only provides access to high yields of mono-alkylated product, but the regioselectivity of the reaction can apparently sometimes be controlled by conversion to the kinetically favoured cross-conjugated metallo-dienamine (**454**), by using excess of the base (butyllithium, lithium diisopropylamide, sodium hydride, etc.), or the thermodynamically favoured linear metallodienamine (**455**), by using a slight deficiency of base to enable equilibration of the metallo derivatives to take place[331] (Scheme 146). In this way either **456** or **457** can be made the main product. Metallo derivatives of the corresponding N,N-dimethylhydrazone can also be employed (see later). The same principle has been applied to the regioselective alkylation of bicyclic imines (Scheme 147).[332,333]

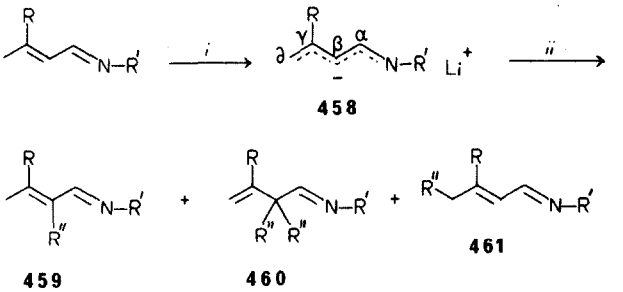


Scheme 146. Reagents: (i) LiBu (excess); (ii) $LiN(i\text{-}Pr)_2$ (< 1 equiv.), THF, Δ, 8 h; (iii) MeI, THF, Δ, 15–20 h; (iv) aq. NaOAc–HOAc–H_2O (1 : 2 : 2), Δ 4 h.



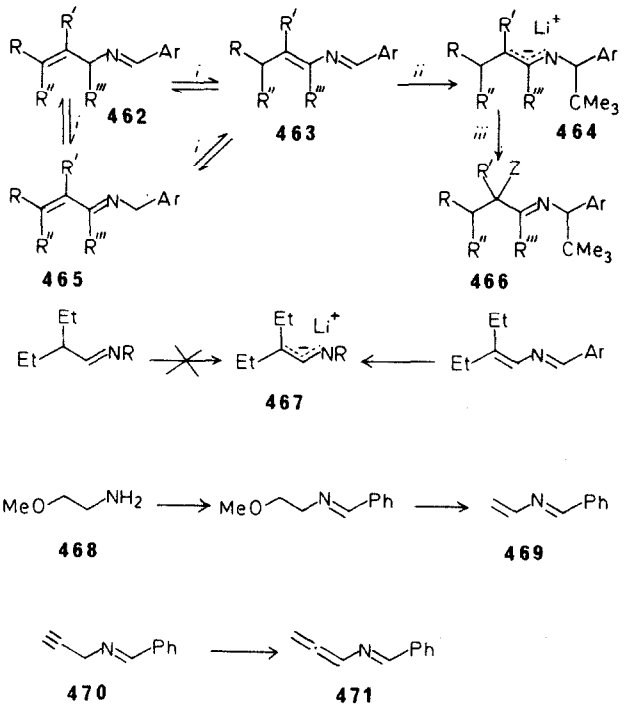
Scheme 147. Reagents: (i) $LiN(i\text{-}Pr)_2$, THF–C_6H_{12}, −50° (kinetic control); (ii) i-PrMgBr, THF, Δ (thermodynamic control); (iii) $ICH_2CH_2CH_2Cl$, −50°; (iv) MeI; (v) Δ; R = $(CH_2)_3Cl$; R' = Me; R'' = H, Me.

Lithiated α,β-unsaturated aldimines **458** have been shown to undergo β- and δ-alkylation (to give **459** and **461**, respectively) and β,β-dialkylation (**460**) depending on the experimental conditions and substituents present in these reactants.[334,335] Trimethylsilylation occurred only at the δ-position.[334]



Scheme 148. Reagents: (i) $LiN(i\text{-}Pr)_2$, Et_2O; (ii) R″X.

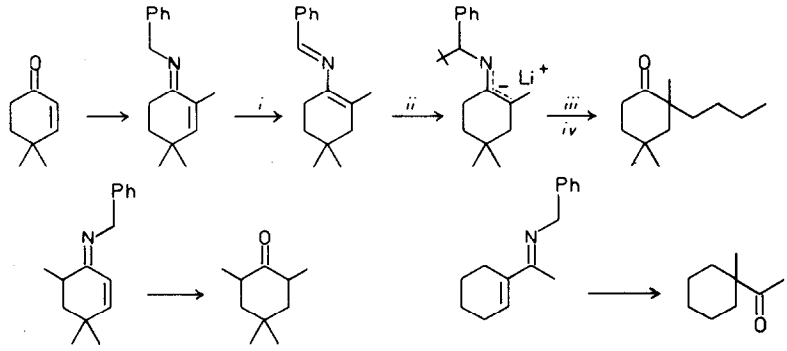
Several alternative methods for the generation of metalloenamines have been developed recently. For example nucleophilic addition of t-butyllithium to the imine group of 2-azadiene **463**, readily prepared by base catalysed isomerisation of N-allylimine **462** or α,β-unsaturated imine **465**, gives metalloenamine **464**. The method works even for metalloenamines which cannot be prepared by deprotonation of sterically hindered imines (i.e. **467**). Alkylation or acylation then gives **466**. Alternatively the anionic intermediate involved in the imine rearrangement (i.e. **462** ⇌ **465** ⇌ **463**) can be deuteriated and thus used to prepare β-deuteriocarbonyl derivatives. Furthermore the imine function can be used to facilitate eliminations (**468**→**469**) or propargylimine-allenylamine rearrangement (**470**→**471**).[336] The conversion



Scheme 149. Reagents: (i) t-BuOK, THF, 20°; (ii) t-BuLi, THF, −78°; (iii) electrophile ZX (i.e. MeI, BzBr, PhCOCl, Me_3SiCl).

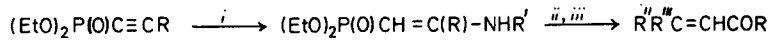
465→**466** constitutes effectively a reductive-α-alkylation of an α,β-unsaturated imine or, on hydrolysis, of an α,β-unsaturated ketone. In this context reduction is, of course, a consequence of a double bond isomerisation. An important consequence of this method for products derived from unsymmetrical ketones, is that whereas alkylation of metalloenamines derived from such ketones would occur preferentially or exclusively at the less substituted α-carbon (as with tertiary enamines[1]), by this method

alkylation occurs at what was the α-double bond position, irrespective of the substitution pattern. Some examples illustrating this point are shown in Scheme 150.[337] The same regioselectivity has been observed on lithium-ammonia reduction of α,β-unsaturated imines, followed by alkylation and hydrolysis.[337]



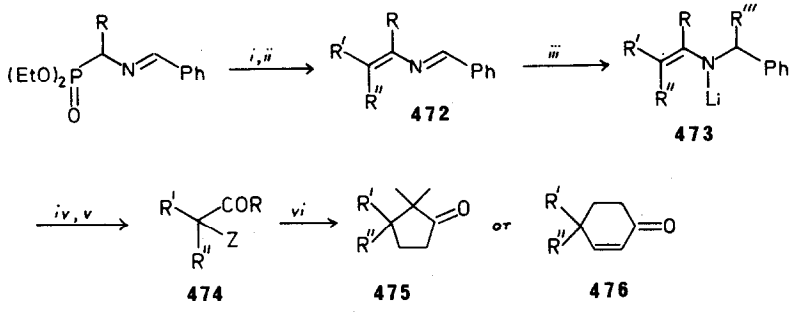
Scheme 150. Reagents: (i) t-BuOK; (ii) t-BuLi; (iii) n-BuI; (iv) H_3O^+.

Combination of metalloenamine and phosphorus chemistry provides a means of formylolefination of carbonyl compounds giving access to a variety of α,β-unsaturated aldehydes and ketones (Scheme 151).[338,339]



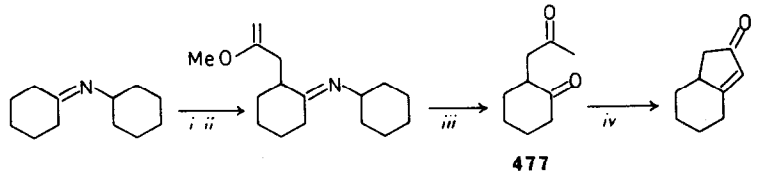
Scheme 151. Reagents: (i) $R'NH_2$; (ii) NaH, R″COR‴; (ii) aq. oxalic acid.

The previously described carbonyl homologation (Part I[1], Section 4C) has been employed by Martin *et al.*[340,341] (see also Sections 2C and 2D of this report) for the construction of quaternary carbon centres as in **474**, **475**, **476** via metalloenamines **473** derived from 2-azadienes **472**.



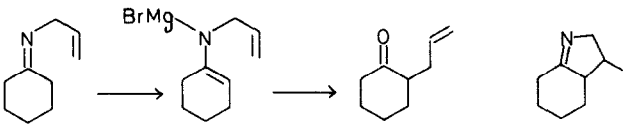
Scheme 152. Reagents: (i) BuLi; (ii) R′R″C=O; (iii) R‴Li; (iv) Z^+ (i.e. electrophiles such as RI, CH_2=C(Cl)CH_2Cl, $BrCH_2CH_2C(OCH_2CH_2O)CH_3$, PhCH=O, n-PrCH=O); (v) H_3O^+; (vi) reagents to convert Z into CH_2COCH_3 or $CH_2CH_2COCH_3$ (Z = $CH_2C(Cl)=CH_2$ or $CH_2CH_2C(OCH_2CH_2O)CH_3$).

Various acetonyl synthons, such as 3-bromo-2-methoxyprop-1-ene, give access to 1,4-diketones **477** (Scheme 153);[342–344] 1,4- and 1,5-ketoaldehydes have been obtained by alkylation of metalloenamines with α-bromoacetaldehyde and β-chloropropionaldehyde diethyl acetals respectively.[345]



Scheme 153. Reagents: (i) $LiN(i\text{-}Pr)_2$; (ii) $BrCH_2C(OMe)=CH_2$; (iii) aq. oxalic acid, THF; (iv) alc. KOH.

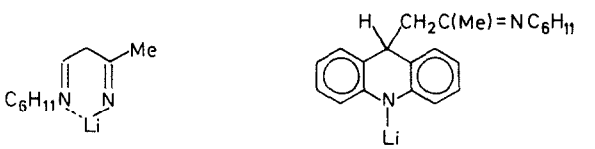
Allylimine **478** rearranges via metalloenamine **479** to give allyl ketone **480** (on hydrolysis), oxidation of which gives the 1,4-dicarbonyl derivative. Cyclisation to indole derivative **481** occurs on heating **479** in boiling benzene.[346] Oxidation of lithioenamines with air gives α-ketals.[347]



478 **479** **480** **481**

Scheme 154.

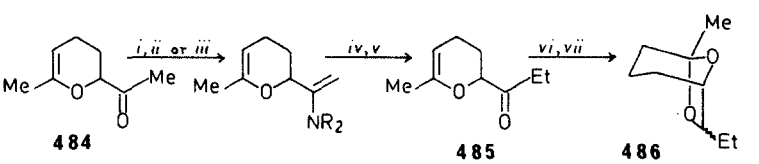
The increased reactivity of metalloenamines compared to tertiary enamines is illustrated by the alkylation of the magnesium salt of N-cyclohexylcyclohexylimine with ethylene oxide (at 0°) to give 2-β-hydroxyethylcyclohexanone,[348,350] whereas the pyrrolidine enamine of cyclohexanone failed to react with ethylene oxide, and other epoxides, to any appreciable extent unless elevated temperatures were used[171,349] (140–230°). Oxidation of the γ-hydroxy ketones thus obtained gives 1,4-diketones.[351] Oxetane failed to react with enolate anions but nucleophilic ring-opening readily took place with bromomagnesium and lithiated derivatives of N-cyclohexylcyclohexylimine.[350] Possibly the metal facilitates ring opening by acting as a Lewis acid. In a comparative study House *et al.* have shown that α-alkylation of isobutyraldehyde was best accomplished via the lithiated imine rather than the lithium enolate. Hydrolysis of the imine function was also reported to be best accomplished with aqueous acetic acid at 25° (pH ~ 4) rather than boiling hydrochloric acid.[350] Metallated imines ($C_6H_{11}N{=}CRCH_2Li$) are also sufficiently nucleophilic to react with nitriles (MeCN) and acridine to give adducts such as **482** and **483**.[352]



482 **483**

Scheme 155.

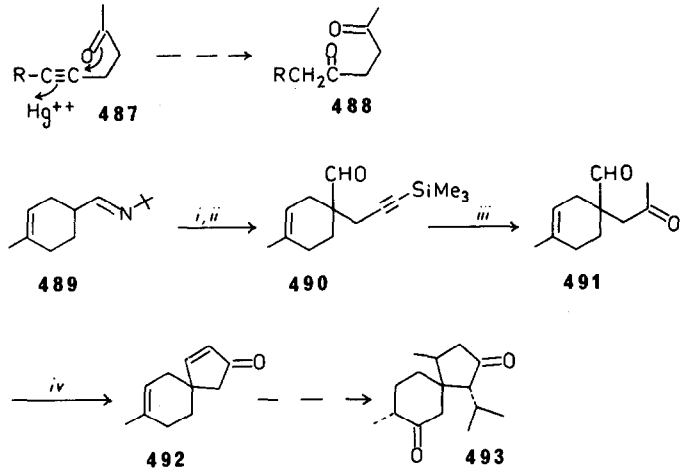
The Stork reaction, utilizing either the metalloenamine[353] or the pyrrolidine enamine[354] of **484**, has been applied to the synthesis of **485** and hence the bicyclic ketal brevicomin **486**, the aggregating sex pherome of the pine bark beetle.[354]



484 **485** **486**

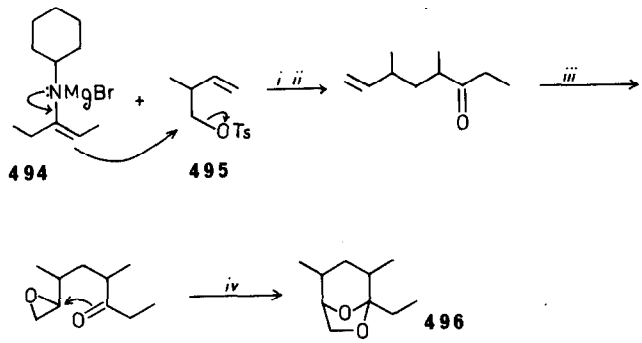
Scheme 156. Reagents: (i) $C_6H_{11}NH_2$; (ii) EtMgBr; (iii) pyrrolidine; (iv) MeI; (v) aq. HOAc; (vi) $NaBH_4$; (vii) p-TSA, C_6H_6; $R_2N = C_6H_{11}NMgBr$ or pyrrolidino.

The regiospecific hydration of acetylenic carbonyl compounds developed by Stork and Borch,[355] in which the carbonyl group participates in lowering the transition state energy for the hydration (i.e. **487** → **488**) has been applied to the synthesis of (±) acorone **493**.[356] The synthesis involved alkylation of the lithiated imine **489** to give acetylene **490** which was deprotected and hydrated in a single step to give the 1,4-dicarbonyl compound **491**, which was cyclised to the spirocyclopentenone **492**.

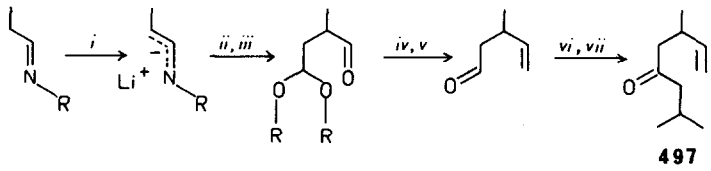


Scheme 157. Reagents: (i) $BrCH_2C{\equiv}CSiMe_3$, BuLi, dimethoxyethane; (ii) aq. HCl; (iii) $HgSO_4$, H_2SO_4, aq. THF; (iv) NaOEt.

The key step in the synthesis of the natural product multistriatin **496** involved the alkylation of 3-pentanone metalloenamine **494** with tosylate **495** of 2-methylbut-3-en-1-ol[357] (Scheme 158). A selective hydrolysis of the aldimine group in preference to the acetal function has been utilised in a synthesis of dihydrotagetone **497** (Scheme 159).[358]



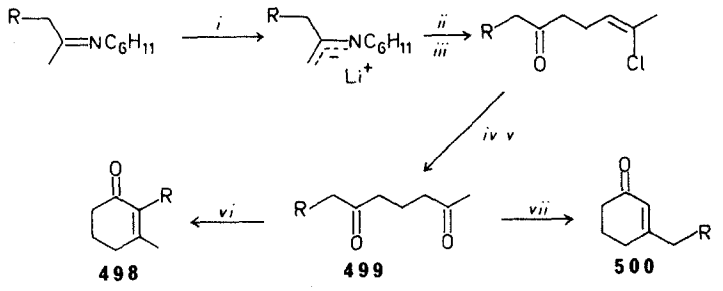
Scheme 158. Reagents: (i) 20°, THF, 45 h; (ii) 10% HCl, Δ 2.5 h; (iii) m-chloroperbenzoic acid; (iv) $SnCl_4$ or H^+.



Scheme 159. Reagents: (i) Et_2NH, Li, C_6H_6–HMPA; (ii) $BrCH_2CH(OR)_2$; (iii) tartaric acid, H_2O, 0°; (iv) $Ph_3P=CH_2$; (v) H_3O^+; (vi) Me_2CHCH_2MgBr; (vii) CrO_3–C_5H_5N, HCl.

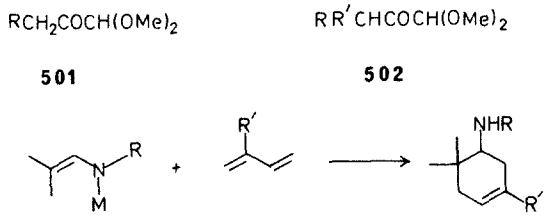
Although the metallation of α,α-dialkyl aldimines may be conveniently achieved using strong bases such as ethyl magnesium bromide[311] or n-butyl-lithium,[356] the use of lithium diisopropylamide in dimethoxyethane[359] or lithium dialkylamides generated *in situ* from lithium and a secondary amine in benzene in the presence of hexamethylphosphoramide, may sometimes be preferable. The latter, sometimes referred to as "activated lithium dialkylamides",[360,361] will effect lithiation in situations where the "usual amides", generated from butyllithium and secondary amine, failed to react. Metallated aldimines have been reacted with a variety of alkylating agents[362] including ω,ω'-dihalogenoalkanes, 1,3-

1,4- and 2,3-dihalogenoalkenes, all of which give products which can be hydrolysed to the corresponding halogenoalkyl or halogenoallyl aldehyde.[361,363] 1,5-Diketones **499** are obtained in high yield (80–95%) by reaction of 1,3-dichloro-2-alkenes with lithio-enamines followed by hydrolysis. Thermodynamically or kinetically controlled cyclisation then leads to cyclohexenones **498** or **500** respectively.[364]



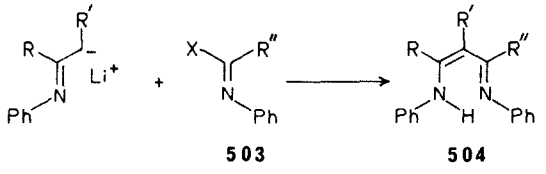
Scheme 160. Reagents: (i) Et_2NH, Li, C_6H_6–HMPA; (ii) $ClCH_2CH{=}C(Cl)CH_3$; (iii) 3 N HCl; (iv) conc. H_2SO_4; 0°; (v) H_2O; (vi) protic medium (3 N H_2SO_4, Δ); (vii) aprotic medium ($LiN(i\text{-}Pr)_2$, Et_2O, −30°).

The lithiated imine (or N,N-dimethylhydrazone) of pyruvic aldehyde dimethyl acetal can be alkylated at the least substituted position to give substituted pyruvic aldehyde derivatives **501**. Further alkylation gives **502**.[365] Epoxides undergo 1,3-cycloaddition across the α,β-positions of metallated aldimines to give 2-aminotetrahydrofurans (neutral hydrolysis) or 2-hydroxytetrahydrofurans (acid hydrolysis).[366] Metallated aldimines undergo 1,4-cycloadditions to dienes, under mild conditions[367] (Scheme 161).



Scheme 161. Substituents: M = Li, Na; R = t-Bu; R′ = H, Me, $Me_2C{=}CH(CH_2)_2$.

The difficultly accessible 1,3-dianils **504** may readily be obtained by reaction of the imidic acid derivative **503** with lithiated imines.[368]



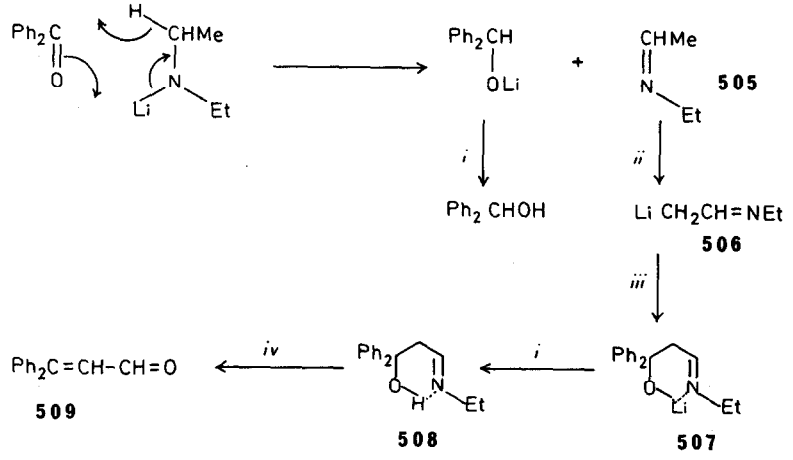
Scheme 162. (X = Cl, OEt).

Copper(I) salts of enamines have been prepared from the corresponding lithioenamine and cuprous bromide; although they may be C-allylated with 2-allyloxybenzimidazoles,[369] no reaction apparently occurs with allyl halides[370] or butyl bromide. The preparation and protolysis of organotin derivatives has been referred to previously (Section 4) since this provides a means for the isolation of unstable secondary enamines (**403**, Scheme 133).[290,291] Recently lithiated imines have been used for the same purpose (see section 5E).

Finally, although this discussion has been confined to C-alkylation or acylation metalloenamines, Heiszwolf and Kloosterziel have shown that N-alkylation can also occur, particularly with highly reactive alkylating agents such as triethyloxonium fluoroborate. For example for the metallated acetophenone anil the N : C-alkylation ratio using various alkylating agents is as follows: EtI, 5 : 90; Et_2SO_4, 49 : 42; Et_3OBF_4, 88 : 4.[371] Lithioenamines have also been reported to react with trimethylsilyl chloride to give mainly the N-trimethylsilyl enamine.[372]

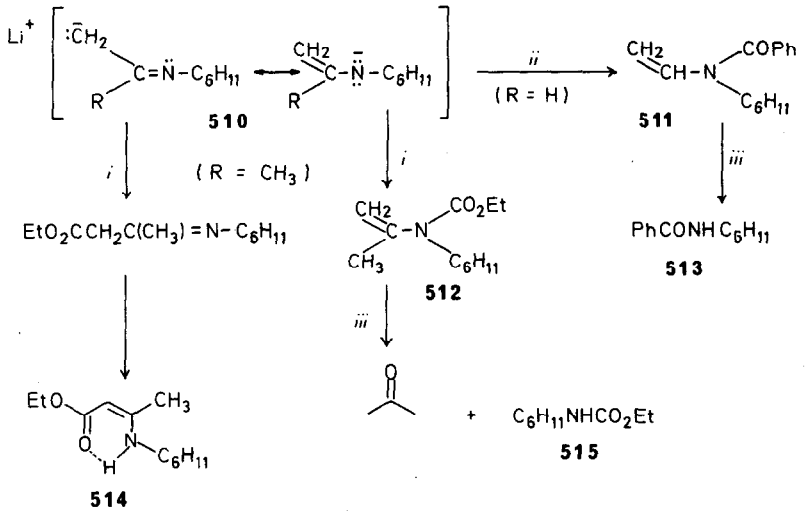
C. *Wittig directed aldol condensation*

The great contribution of Wittig in this field was to realise that metallated imines were sufficiently nucleophilic to attack even relatively inert carbonyl groups, as in a ketone. Tertiary enamines are incapable of this unless the process results in favourable ring closure (see Section 2). This realisation followed accidently from the observation[373] that lithium diethylamide could act as a hydride donor towards benzophenone, generating benzhydrol and acetaldehyde imine **505** in the process. Since imine **508** was also isolated from the reaction mixture it was deduced that this must have arisen from the metallated imine **506** (Scheme 163). Wittig further realised[313] that self-condensation of an aldehyde,



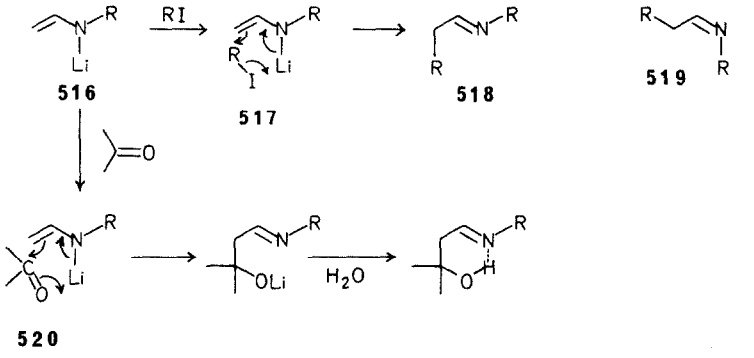
Scheme 163. Reagents: (i) H_2O; (ii) $LiNEt_2$; (iii) $Ph_2C{=}O$; (iv) H_3O^+.

which normally occurs in the mixed aldol condensation, could be circumvented by prior conversion of the aldehyde to its metallated imine. Since the addition product **507** could be hydrolysed and dehydrated to the α,β-unsaturated aldehyde **509** this constituted a directed aldol condensation (nucleophilic attack on the least reactive of two carbonyl components). The success of the method depends on the fact that self-condensation of imines is very slow compared to that of carbonyl compounds, owing to electronegativity differences (i.e. lower electrophilicity of imine carbon compared to carbonyl carbon). Wittig *et al.* also demonstrated that metallated Schiff's bases could be acylated, but that in this case they behaved as ambident nucleophiles. For example reaction of the lithiated cyclohexylamine imine of acetone **510** (R=CH_3) with ethyl chloroformate, gave 90% of ethyl β-cyclohexylaminocrotonate **514** and 5% of N-cyclohexylurethane **515** formed from the N-acylated enamine **512**. The action of benzoyl chloride on the lithiated imine of acetaldehyde gave 35% of N-cyclohexylbenzamide **513**, derived from the N-acylated enamine **511**.[374]



Scheme 164. Reagents: (i) $ClCO_2Et$; (ii) PhCOCl; (iii) H_2O.

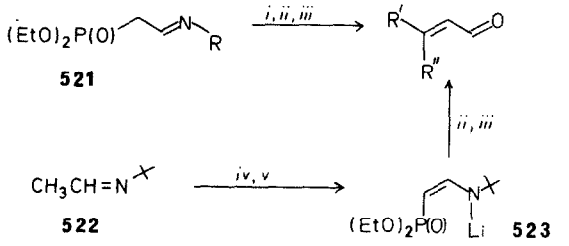
Despite representing the lithiated Schiff's bases as **506** (Scheme 163) and **510** (Scheme 164), Wittig suggested that the lithium preferentially resides on the most electronegative part of the molecule (i.e. the nitrogen). Unionized reagents such as alkyl halides and ketones were then suggested to react with the metalloenamine tautomer **516** by way of cyclic six-membered transition states, **517** and **520** respectively, from which the product can be formed by elimination of lithium halide.[374] On the other hand, with



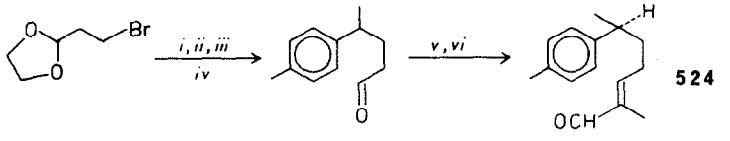
Scheme 165.

compounds which ionize readily, Wittig and Reiff suggested that the first step is rapid formation of lithium halide. The cation remaining then seeks out the centre of highest electron density, namely the nitrogen atom again.

A modification of the Wittig directed aldol condensation involves use of the phosphonate imine **521**[375] or its metallated derivative **523** formed *in situ* from the imine **522** and diethyl chlorophosphate.[376] A neat synthesis of the sesquiterpene aldehyde (±)nuciferal **524** utilising the directed aldol condensation has been reported (Scheme 167).[377]

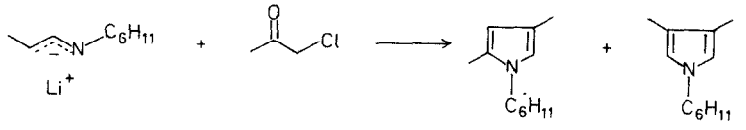


Scheme 166. Reagents: (i) NaH; (ii) R'R"C=O; (iii) H_3O^+; (iv) LiN(i-Pr)$_2$ (2 equiv.), −78°; (v) $(EtO)_2P(O)Cl$.

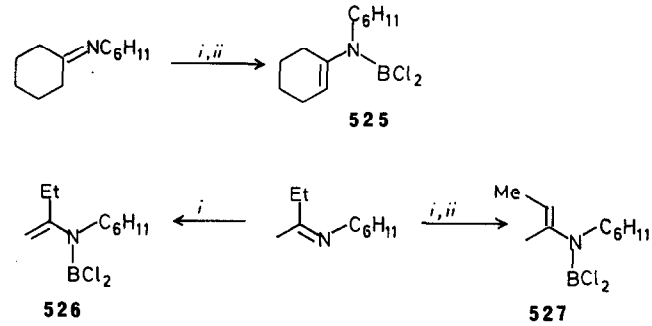


Scheme 167. Reagents: (i) Mg; (ii) p-$MeC_6H_4COCH_3$; (iii) H_2/Pd; (iv) aq. HCl, Δ; (v) LiCH(Me)CH=$NCMe_3$; (vi) aq. oxalic acid.

Lithioenamines react at both electrophilic positions of α-halogenoketones to give substituted pyrroles[378] (Scheme 168). Although not exactly metalloenamines, organodichloroboranes **525–527** have



Scheme 168.

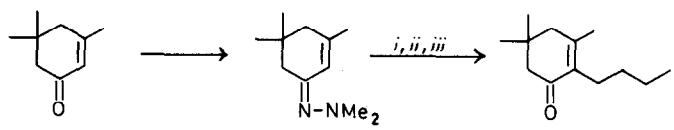


Scheme 169. Reagents: (i) BCl_3, Et_3N, CH_2Cl_2, Δ; (ii) distil.

been employed in analogous directed aldol condensations.[379]

D. *Metal derivatives of hydrazones*

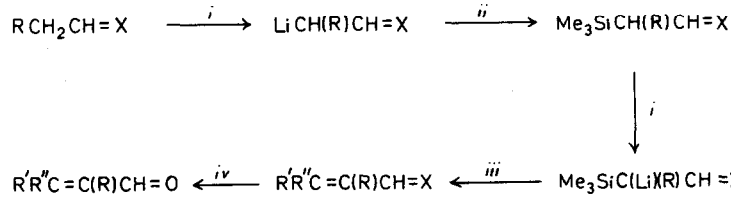
A further modification of the Stork reaction introduced in 1971[331] involved conversion of a ketone into the N,N-dimethylhydrazone (DMH), followed by metallation and alkylation (Scheme 170). The



Scheme 170. Reagents: (i) NaH, THF, HMPA, Δ 15–20 h; (ii) BuLi, 25° 3 h; (iii) 6 N HCl, Δ.

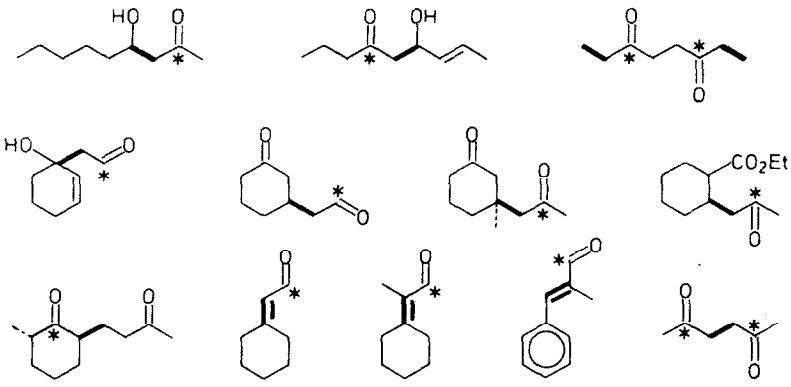
method has been greatly extended by Corey and Enders who have shown that the hydrazone can subsequently be cleaved to carbonyl under very mild conditions (i.e. aqueous sodium periodate, pH 7, 20–25°). Generally, metallation of unsymmetrical ketone N,N-dimethylhydrazones occurs very selectively at the less alkylated carbon, the only apparent exceptions being benzyl methyl ketone, whose DMH undergoes lithiation and alkylation at the benzyl carbon,[380,381] and the lithiated E-2-methylthiocyclohexanone DMH which reacts further with dimethyldisulphide to give 2,2-bis-methylthiocyclohexanone on cupric chloride assisted hydrolysis.[382] Alternatively, mercuric ion assisted solvolysis gave 2-methoxy or 2,2-dimethoxycyclohexanone derivatives.[382]

Lithiation of aldehyde dimethylhydrazones (and imines) followed by trimethylsilylation, re-lithiation and condensation with an aldehyde or ketone provides a high yield route to a variety of α,β-unsaturated aldehydes. α,β-Unsaturated aldehydes themselves undergo 1,2-addition of α-lithiated dimethylhydrazones to give unsaturated β-hydroxycarbonyl compounds.[384,385] However if the lithiated hydrazone is



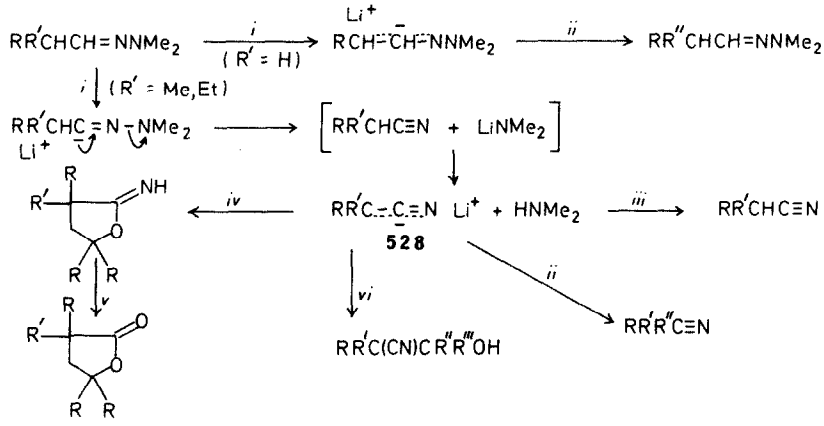
Scheme 171. Reagents: (i) LDA, THF, 0°; (ii) Me_3SiCl; (iii) R'R''C=O; (iv) H_2O, oxalic acid, pH 4.5; X = N-t-Bu or N-NMe_2.

converted to the organo-copper derivative (cuprous iodide-isopropylsulphide complex at −30°) conjugate addition to α,β-unsaturated carbonyl compounds occurs.[384,385] Bis-dimethyl hydrazones derived from diketones can be bis-metallated and bis-alkylated. Examples of products which have been prepared in high yield by these methods (i.e. alkylation, silylation-re-lithiation-carbonyl condensation, or 1,2- or 1,4-addition to α,β-unsaturated carbonyl compounds) are summarised in Scheme 172.[380,383–385] Symmetrical 1,4-dicarbonyl compounds are readily obtained from α-lithio dimethylhydrazones by treatment with iodine (one equivalent at −78°); for example the α-lithiated dimethylhydrazone of acetone gave hexane-2,5-dione in 90% yield.[384]



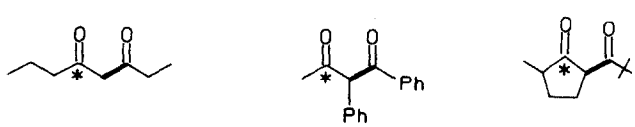
Scheme 172. The thick line represents the new bond formed and the asterisk shows the site of the dimethylhydrazone group in the starting material.

The generation and use of "activated lithiated amides" for the lithiation of hindered aliphatic aldimines has been mentioned previously (see Section 5B). Straight chain aldehyde dimethylhydrazones may be lithiated in the same way, and subsequently alkylated (Scheme 173).[386] However with α- or β-branched chain N,N-dimethylhydrazones the reaction takes a different course. With these hindered hydrazones it appears that the imine carbon is metallated and eliminates dimethylamide anion to give a nitrile anion **528** under mild conditions ($-40°$ to $-10°$, 1.5 h). Very strong bases are required, the "usual metalloamides" being insufficiently basic to break the C_1-H bond and, after hydrolysis, the unchanged hydrazone is recovered. Reaction of **528** with various electrophiles then provides a route to α-, di- or tri-substituted nitriles, β-hydroxy nitriles, or γ-butyrolactones (Scheme 173).[386,387]



Scheme 173. Reagents: (i) Et_2NH, Li, C_6H_6, HMPA; (ii) R″X; (iii) H_2O; (iv) 2,2-dialkyloxirane; (v) H_3O^+; (vi) R‴R⁗C=O.

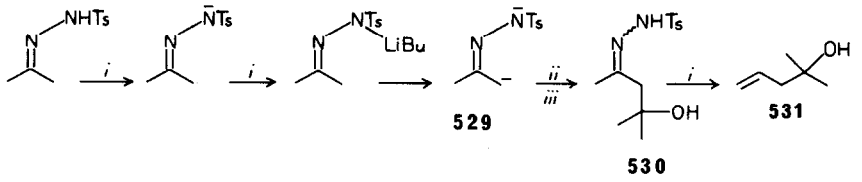
Acylation of α-lithiated ketone dimethylhydrazones with acid chlorides gives 1,3-diketones on hydrolysis (Scheme 174).[388]



Scheme 174. The thick line represents the new bond formed and the asterisk shows the site of the dimethylhydrazone group in the starting material.

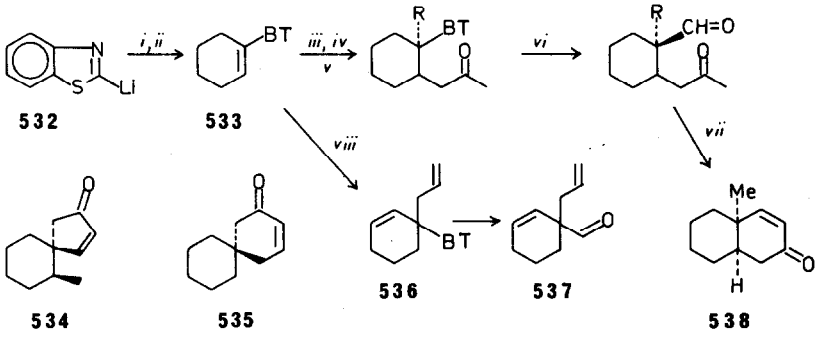
Treatment of tosylhydrazones with alkyllithium reagents is a well known method of alkene formation.[389] This reaction is known[390] to proceed via a syn dianion **529**, formed in a regiospecific manner as indicated in Scheme 175. This dianion may be trapped by aldehydes and ketones yielding β-hydroxytosyl-

hydrazones **530** which on treatment with alkyllithium are converted into homoallylic alcohols **531** in good yield.[391]



Scheme 175. Reagents: (i) BuLi; (ii) acetone (or propionaldehyde); (iii) H_2O.

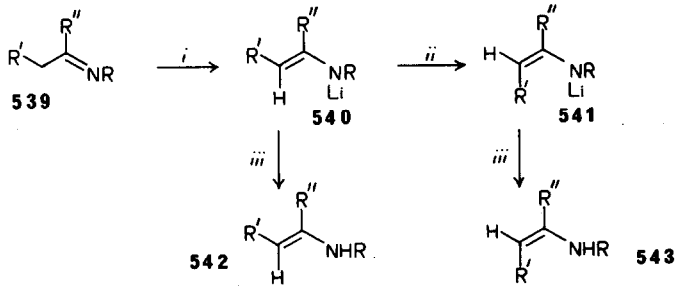
α-Lithio acetone dimethylhydrazone has been shown to undergo clean conjugate addition to the vinyl benzothiazole **533**. On quenching the resulting α-lithio derivative with methanol (R = H) or methyl iodide (R = Me) the corresponding Δ^1-3-octalone **538** could be obtained in good yield by the sequence outlined in Scheme 176.[392] Spiro compounds **534** and **535** were obtained by a modification of this technique. Alternatively vinyl benzthiazoles such as **533** can be metallated and alkylated to give **536** and hence **537**, and analogous compounds.[393]



Scheme 176. Reagents: (i) cyclohexanone; (ii) P_2O_5, CH_3SO_3H; (iii) $LiCH_2C(Me)=NNMe_2$, THF, HMPA; (iv) MeOH(R = H) or MeI (R = Me); (v) $CuCl_2$, aq. THF, pH 7; (vi) methylation ($MeOSO_2F$), reduction ($NaBH_4$), hydrolysis ($AgNO_3$, aq. CH_3CN, pH 7); (vii) p-TSA, C_6H_6, Δ ($-H_2O$); (viii) LDA, THF, $-78°$; $CH_2=CHCH_2Br$, $-78 \rightarrow 0°$; BT = 2-benzthiazolyl.

E. *Regio and stereochemistry*

Deprotonation of imine **539** gives a mixture of the E and Z aza-allyl anion reagents (**540** and **541** respectively), the former (**540**) being the kinetically controlled product.[394] These anions were shown to have considerable configurational stability about the C_1–C_2 bond since prolonged standing (in THF) at ambient temperature produced no change in the isomer distribution. Treatment of the mixture with methanol at $-70°$ resulted in stereospecific N-protonation to give the metastable sec-enamines **542** and **543** with retention of the E/Z ratio. Heating the mixture of **540** and **541** with the imine **539**, acting as an acid catalyst, resulted in slow but virtually quantitative rearrangement of **540** to the thermodynamically more stable **541**, methanolysis of which gave only Z-enamine **543**. The kinetically and thermodynamically controlled ratios of aza-allyl anions **540** : **541** and the corresponding secondary enamines **542** : **543**



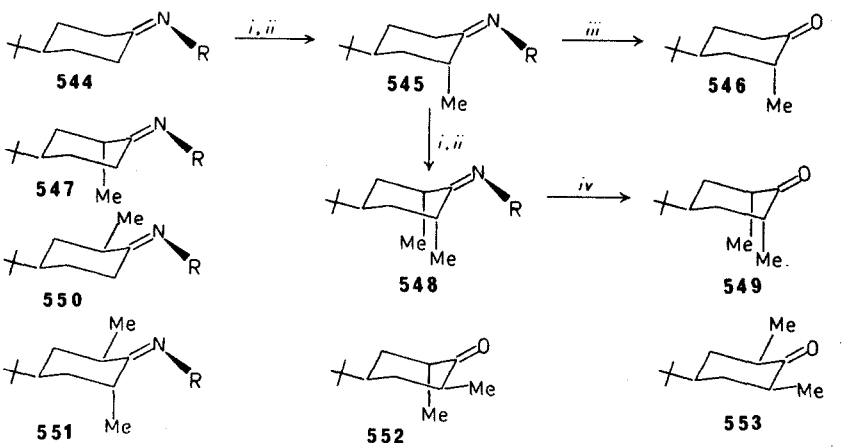
Scheme 177. Reagents: (i) $LiN(i\text{-}Pr)_2$, THF, $-70°$; (ii) imine **539**, THF, 60°; (iii) MeOH, $-70°$.

Table 7. E/Z ratios of R'CH=C(R")NRLi and R'CH=C(R")NHR

	Structure			Kinetic control		Thermodynamic control	
	R	R'	R"	540:541	542:543	540:541	542:543
a	Ph	Me	Ph	75:25	75:25	< 5:95	< 5:95
b	Ph	Ph	CH_2Ph	-	-	15:85	<23:77
c	c-C_6H_{11}	Et	H	-	-	>95:5	>95:5
d	Ph	Me	Et	80:20	70:30	< 5:95	<15:85
e	Ph	Et	n-Pr	80:20	60:40	< 3:97	< 5:95

are summarised in Table 7. In the case of **540b/541b** and **540c/541c** the thermodynamically controlled ratios were obtained directly on deprotonation. In the former case the E→Z transformation is presumably facilitated by the charge stabilization by the two phenyl groups in a mesomeric aza-allyl anionic system, which will decrease the double bond character of the C_1-C_2 bond. In the latter case the E isomer is thermodynamically more stable. In the remaining cases the kinetically favoured formation of the E isomer **540** lends support to the proposed deprotonation mechanism (vide infra: Scheme 184 for deprotonation of hydrazones is also applicable to imines); the thermodynamic preference for the Z isomer **541**, on the other hand, suggests that the NR(Li) group is "smaller" than the phenyl (R") group.[394]

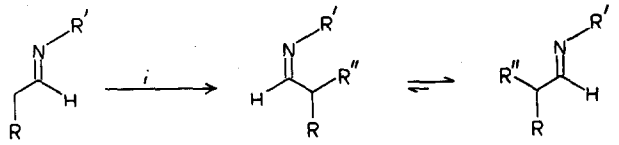
Work in many laboratories on the lithiation and alkylation of cyclohexanone derivatives, including dimethylhydrazones,[395] oximes and substituted oximes,[395] and the structurally related nitrosamines[395] and N,N-dimethylbenzamides[395] has, in every case, revealed surprising stereoselectivity in that the syn product is formed almost exclusively. This has been attributed to preferential formation of a syn anion and some controversy has centered on whether this preference stems from orbital symmetry[395] or chelation effects.[395] However doubt has been cast on both these explanations by the finding that alkylation of lithiated ketimines of 4-t-butylcyclohexanone also gives only syn-axial alkylation product **545**.[396] Although some anti-axial **547** and anti-equatorial **550** alkylation products were also isolated (7% and 3% respectively) this was attributed to isomerization of the syn-axial product. Further alkylation gave the 2,6-axial-axial dialkylated product **548** and only 6% of the axial-equatorial



Scheme 178. Reagents: (i) $LiN(i\text{-}Pr)_2$, THF, 0° 1 h; (ii) MeI, −78° 1 h; (iii) saturated NH_4Cl, $NaHCO_3$, THF, 1 h; (iv) see text.

product **551**, again attributed to isomerisation of an axial substituent since this was the thermodynamically more stable isomer. Hydrolysis of this mixture gave a mixture of isomeric products whose composition depended on the conditions used {Conditions: product (% in product mixture) [% at equilibrium]: (a) saturated NH_4Cl–$NaHCO_3$, THF, 25°, 1 h: **549** (16) [0]; **552** (76) [5]; **553** (8) [95]; (b) KH_2PO_4–NaOH buffer, 25°, 16 h, pH 7: **549** (60) [0]; **552** (40) [5]; **553** (0) [95]}. Furthermore it was shown that the relative rates of *base*-catalysed H-D exchange in acetone-N-benzylketimine was at least 50 : 1 in favour of the syn-methyl group at 20°. Similar results were obtained on alkylation of lithiated aliphatic aldimines which have been shown to give syn and anti products in a ratio of 96 : 4 respectively;[399] this

represents a difference in free energy of 5.2 kJ mol^{-1} favouring the formation of the syn form, despite the introduction of a destabilising steric effect estimated to be at least 12.8 kJ mol^{-1} which would render the anti form thermodynamically more stable. The electronic factor responsible for the preferential stabilization of the syn, or destabilisation of the anti, lithiated aldimine was therefore estimated to have a magnitude of at least 18 kJ mol^{-1}.



Scheme 179. Reagents: (i) $LiN(i\text{-}Pr)_2$, R″X.

In view of the magnitude of the energy difference between the syn and anti anions, arguments previously used to account for the syn-stereoselectivity of lithiated oximes, hydrazones, nitrosamines etc, including chelation, orbital symmetry, homoaromaticity and torsional interactions, were therefore ruled out and it was concluded that the complete syn-axial stereoselectivity of lithiated imine alkylation may be due to differential solvation effects on the syn-anti equilibrium of the anionic intermediate involved in these reactions.[396] This conclusion was based on the contrasting results of McIver *et al.*,[397] on gas phase acidities of but-2-enes compared with their solution values reported by Schlosser and Hartman.[398] This appears to demonstrate an over-riding importance of solvent in determining the position of the cis ⇌ trans butenyl anion equilibrium. It appears that the cis isomer of the 1-methylalkyl anion is *less* stable than the trans, by about 0.8 kJ mol^{-1}, in the gas phase.[397] The increasing preference[398] for the cis configuration for $CH_3{=}CHCH_2M$ in solution, as the metal becomes more electropositive (i.e. M=MgBr < Li < Na < K < Cs), cannot therefore be attributed to inherent stability of the cis anion but rather to "differences in interaction energies among the allylic skeleton, the metal, and the solvent".[397]

However this conclusion is also open to question since ion cyclotron resonance spectroscopy, on which estimation of the gas phase anion stabilities was based, provides no information regarding the structure of the ions under investigation. It has to be assumed that the deprotonation of cis and trans 2-butene gives 1-methylallyl anions rather than vinylic anions, that the cis and trans 1-methylallyl anions do not interconvert under the conditions of the measurement, and that reprotonation gives the corresponding 2-butene rather than the less stable 1-butene; breakdown of any of these assumptions would invalidate the measurements.[397] In contrast, Schleyer *et al.*[400a] have calculated that the syn anion is 6.3 kJ mol^{-1} *more* stable than the trans crotyl anion! Furthermore Houk *et al.*[400b] have concluded that the syn preference for imine anions can be attributed to electrostatic destabilisation of the anti anion. The fully optimized geometry and charges (in parentheses) calculated for the syn-acetaldehyde imine anion are shown in Fig. 2.

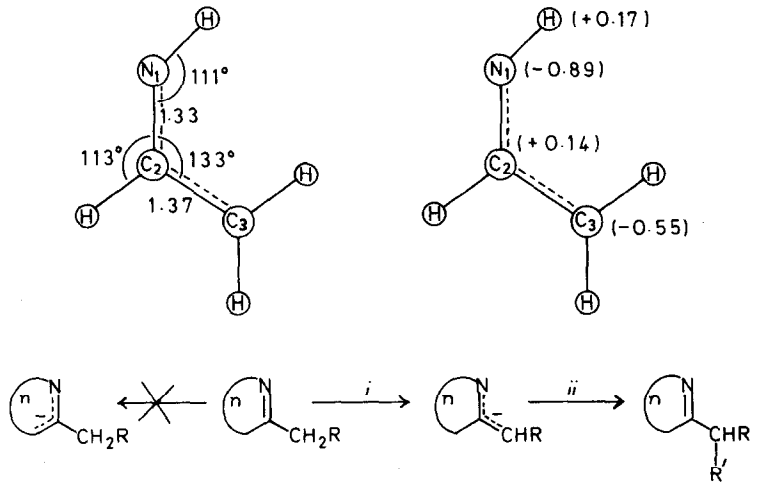
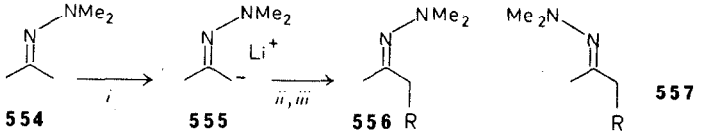


Fig. 2. Reagents: (i) LDA; (ii) R′I; n = 5–7.

It is suggested that in order to minimise electrostatic repulsion between the partial negative charge at C-3 and that in the vicinity of the N-1σ lone pair, and simultaneously to maximise attraction for the hydrogen on N-1, the syn conformation is adopted. This conclusion was supported by calculations on the effect of a negative charge placed 2Å above C-3. The preference for the syn anion was calculated to increase further, to approximately 34 kJ mol^{-1}, thus showing that electrostatic repulsions between electrons at C-3 and N-1 are of the right order of magnitude to account for the energy difference between syn and anti anions. Also, in complete contrast to acyclic or exocyclic ketimines, it was shown[400b] that endocyclic ketimines give exclusive *anti* alkylation (Fig. 2). This complete reversal of stereochemical preference was attributed to the very large CCN bond angle (133°) calculated for the syn anion. Constraint of this angle to 120° was calculated to result in a 28 kJ mol^{-1} increase in energy. In anions derived from an endocyclic imine the ring would constrain the CCN angle to 120° or less, thus resulting in appreciable angle strain in the syn anion and destabilisation relative to the unfettered anti anion, which thus becomes thermodynamically favoured.

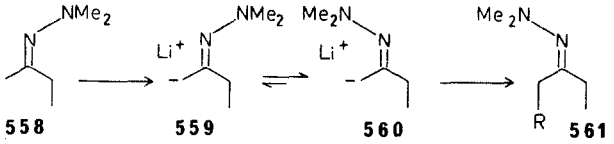
As in the case of metallated ketone imines, metallated ketone DMH's invariably give the less stable syn product on alkylation, derived from the syn anion. For example acetone DMH **554** is converted *exclusively* to the syn anion **555** and hence **556** on alkylation.[401]



554 555 556 557

Scheme 180. (i) $LiNEt_2$, Et_2O, 0° 1.5 h; (ii) RX; (iii) H_2O; R = Me, Et, $PhCH_2$, $Ph_2C(OH)$.

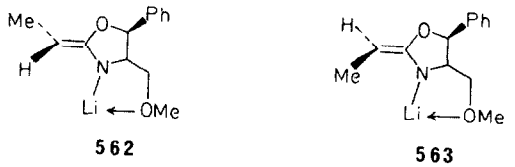
The assignment of the syn geometry is based on the chemical shift of the allylic methylene proton signal in the ^1H NMR spectrum which occurs about 0.2–0.4 ppm downfield from the corresponding signal in the thermodynamically more stable anti isomer **557**. Alkylation of other symmetrical ketone hydrazones showed the same syn-stereospecificity of alkylation.[401] However, in apparent contrast to the deprotonation of ketimines,[396] evidence exists to show that formation of the anti hydrazone anion is kinetically favoured. For example metallation and alkylation of the unsymmetrical DMH **558** from 2-butanone gave **561**. This implied initial formation of the anti anion **559**, by deprotonation of the least substituted carbon, and fast rearrangement to syn **560**. None of the product resulting from alkylation of anti **559** could be observed, suggesting a fairly large energy difference between **559** and **560** ($\geq$ 12 kJ mol^{-1}) and a low barrier to isomerization.[401] The alternative explanation that alkylation of syn



558 559 560 561

Scheme 181.

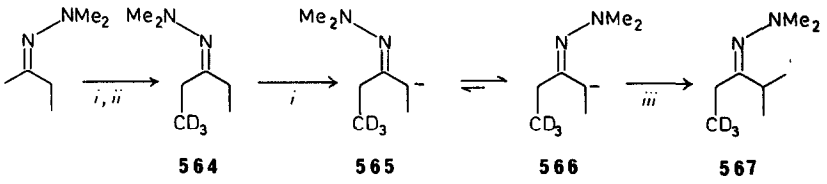
anion **560** was much faster than that for anti anion **559** was considered unlikely and is supported by more recent work in analogous systems. For example the lithiated chiral oxazolines **562** and **563** have been shown to undergo alkylation at comparable rates[328,329] despite the sterically more encumbered situation in **563**.



562 563

Scheme 182.

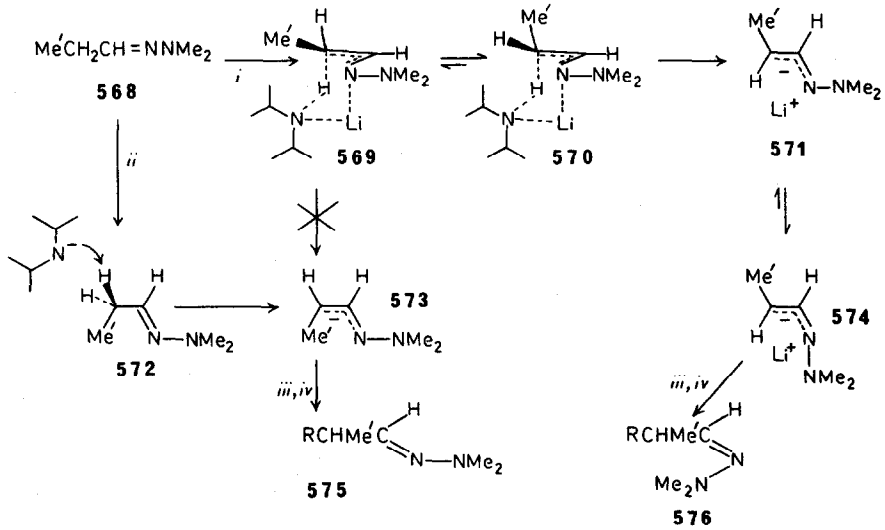
Evidence for the operation of kinetic control in the deprotonation of DMH's of symmetrical ketones was obtained by metallation and alkylation of the syn trideuteriomethyl derivative **564**. The product obtained was **567**, thus implying initial anti deprotonation to give **565** followed by fast rearrangement to syn anion **566**.[401]



564 **565** **566** **567**

Scheme 183. Reagents: (i) $LiNEt_2$, Et_2O, 0°, 1.5 h; (ii) CD_3I; (iii) MeI.

Aliphatic aldehyde dimethylhydrazones behave in the same way. The only apparent exception appears to be in the formation and alkylation of the lithio anion of propionaldehyde DMH, which is solvent dependent.[326] Deprotonation by lithium diisopropylamide in tetrahydrofuran gave mainly the anionic species **574** (>95%) having E stereochemistry about the C_1–C_2 bond and predominantly the syn configuration about the C–N bond. Alkylation gave the syn-alkylated product **576**. However deprotonation in the presence of hexamethylphosphoramide (HMPA) gave mainly the Z-anti lithio anion **573** (85%), alkylation of which gave mainly the anti-alkylated product **575** (87%). This change in the regisoselectivity has been attributed to solvation of the lithium ion in HMPA, with consequent change from a cyclic to an acyclic transition state for deprotonation. In the absence of HMPA cyclic transition states may be envisaged, such as those depicted in **569** and **570**. The former will be destabilised by developing 1,3-diaxial interactions between the methyl and isopropyl groups, thus favouring **570** which presumably leads initially to E-anti anion **571** which rearranges to the more stable E-syn anion **574**. In the presence of HMPA an acyclic transition state such as **572** is envisaged, assuming the preferred eclipsed conformation for the Me′ and C=N groups as occurs in esters, vinyl ethers and tertiary enamines.[402]



568 **569** **570** **571** **572** **573** **574** **575** **576**

Scheme 184. Reagents: (i) $LiN(i\text{-}Pr)_2$, THF, 25°; (ii) $LiN(i\text{-}Pr)_2$, THF, HMPA; (iii) $I(CH_2)_3CH_3$, −78°; (iv) H_2O, and isolation at 0°.

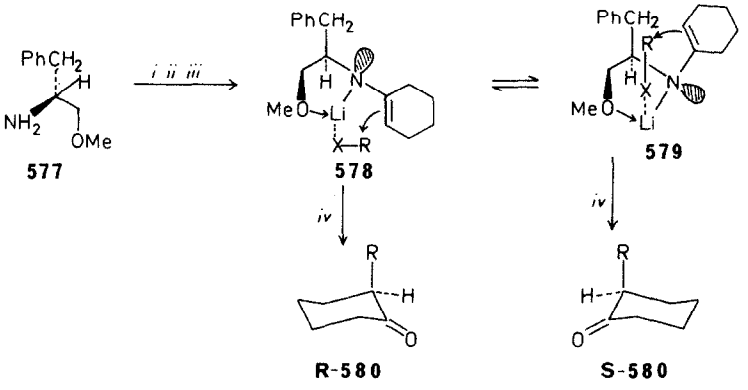
Other aldehyde hydrazones containing more bulky α-substituents (i.e. Ph or Me_3Si in place of Me′ in above scheme) were converted by LDA, in the presence or absence of HMPA, only to lithio derivatives with E configuration about the C_1–C_2 bond (i.e. as **571** and **574**, of which the latter predominated) as shown by the ^1H NMR spectrum. Presumably eclipsed conformations such as **572** are ruled out, so the Z-anti anion **573** is not formed. Methylation of the mixture of **571** and **574** thus obtained (but Me′ instead = Ph), gave a mixture of the syn hydrazone (as **576**) and the thermodynamically more stable anti

hydrazone (as **575**) [derived from the E-anti anion (as **571**) not the Z-anti anion (as **573**)] in roughly the same proportion as that of the two anionic precursors. This indicates that preferential formation of syn alkylated products is not due to more rapid alkylation of the syn anion; both syn and anti anions are alkylated when present. Similarly when acetaldehyde hydrazone was submitted to the same treatment, the ratio of isomeric alkylated syn and antihydrazones [i.e. **576** : **575** (Me′ = H, R = n-Bu or Me_3Si)] was the same as the ratio of isomeric syn and anti anions [i.e. **574** : **571** (Me′ = H)] formed in the deprotonation process, namely 9 : 1.[326]

F. *Asymmetric induction*

The methodology of asymmetric synthesis has undergone tremendous advances in the last few years. Although there is still much to be done in this area of synthetic organic chemistry, it is now possible to construct chiral centres at the α- and β-positions of carboxylic acids, and the α-position of cyclic and acyclic ketones, and aldehydes, in optical yields which are often as great as 80–100%.[314,403]

The use of chiral metalloenamines in this context was first investigated by Horeau in 1968, who was able to prepare optically active 2-methylcyclohexanone (72% e.e.) by enantioselective alkylation of the metallated (−) isobornylamine imine of cyclohexanone.[404] However use of the other alkyl halides gave 2-alkylcyclohexanones in much lower enantiomeric purity. The method was further investigated by Yamada *et al.* using various chiral amines, of which S(−)α-phenethylamine gave the best results, but even so the optical yields were only in the range 26–37% e.e.[405] This problem was solved by Meyers *et al.*[406] and Whitesell *et al.*[407] who introduced an alkoxy substituent into the chiral amine component which could complex with the metal atom. This induces rigidity into the metalloenamine system and, by inhibiting rotation about the C–N bond of the amine moiety, will reduce the number of conformations available for the alkylation process. The configurations of the 2-substituted cyclohexanones obtained were all R, except for those examples (allyl, benzyl) whose priority changes relative to the cyclohexyl group. Using the enantiomer of amine **577** the corresponding S-ketones could be produced, in 90–100% enantiomeric excess. The explanation suggested for this enantioselectivity by Meyers was as follows (Scheme 185). The lithium ion of the metalloenamine becomes coordinated to the methoxy ligand and

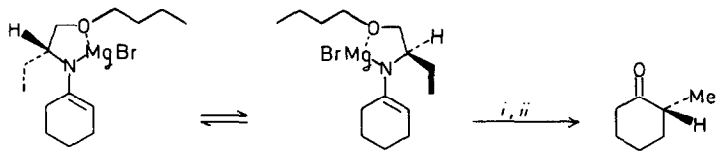


Scheme 185. Reagents: (i) cyclohexanone; (ii) $LiN(i\text{-}Pr)_2$, THF, −20°; (iii) RX, −78°; (iv) pentane-saturated oxalic acid, 20°.

results in essentially two conformers **578** and **579** which are interconvertible by nitrogen inversion. Since **578** is a trans-1,2-disubstituted chelated ring, whereas **579** is cis-1,2-disubstituted, equilibrium should favour **578**. Assuming the entering halide aligns itself as shown in **578** and **579**, so that the halogen is also coordinated to the lithium, the transition state **579** leading to **S-580** is more sterically encumbered than that (**578**) leading to **R-580**, which is therefore the main or only product.[406]

Whitesell *et al.*,[407] who prepared the magnesium bromide derivative, have offered an alternative explanation for the observed enantioselectivity. Assuming normal pπ-conjugation[1] in the enamine, then there are two conformations of the metalloenamine available for alkylation (**581** and **582**). Since the metal atom can be expected to be highly solvated and/or aggregated, attack at the β-position of the enamine system in conformation **581** may well be sterically hindered, whether the electrophile approaches from above or below the double bond. The chiral centre in conformation **582** would however

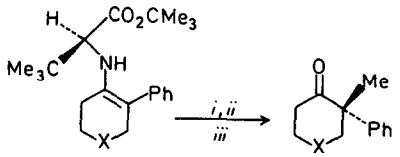
direct electrophilic attack from below the double bond, thus leading to the R-2-substituted cyclohexanone, as observed.[407] This is a similar explanation to that which we have described for the enantioselective alkylation of proline enamines (see Part I[1], Section 5B).



581 582

Scheme 186. Reagents: (i) MeI; (ii) H_2O.

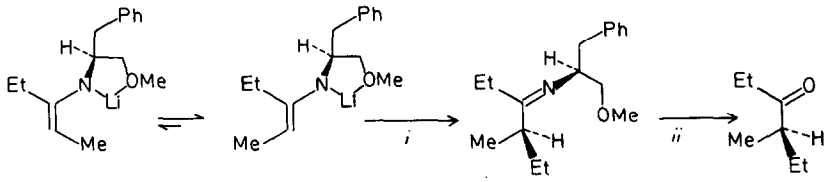
The same principle has also been employed by Hashimoto and Koga,[408] who used a tert-butyl ester instead of the ether function as the co-ordinating ligand. When the reaction was applied to 2-phenylcyclohexanone or 2-phenylcyclopentanone the more substituted form of the enamine **583** was formed, metallation and alkylation of which gave the S-2,2-disubstituted ketones **584**. This therefore constitutes an enantioselective construction of a quaternary carbon centre aided, of course, by the double bond stabilising effect of the phenyl substituent. Extension of this enantioselective alkylation of



583 584

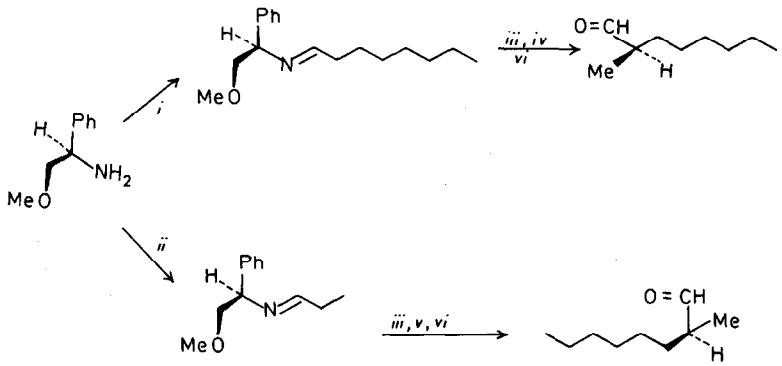
Scheme 187. Reagents: (i) LDA; (ii) MeI; (iii) H_3O^+; X = –, CH_2.

carbonyl derivatives to acyclic ketones introduces an additional complication since the metalloenamines formed can exist as E- and Z-isomers. Consequently when the imine of pentane-3-one was metallated and alkylated with ethyl iodide, the product 3-methylhexan-4-one was obtained in only 3% enantiomeric excess. However if the lithio enamine was first heated to 60°, to allow equilibration to the thermodynamically stable E-metalloenamine, and then alkylated the optical yield was increased to 76% e.e.[409] Application of the reaction to the synthesis of chiral α-alkyl aldehydes has been carried out



Scheme 188. Reagents: (i) EtI; (ii) H_3O^+.

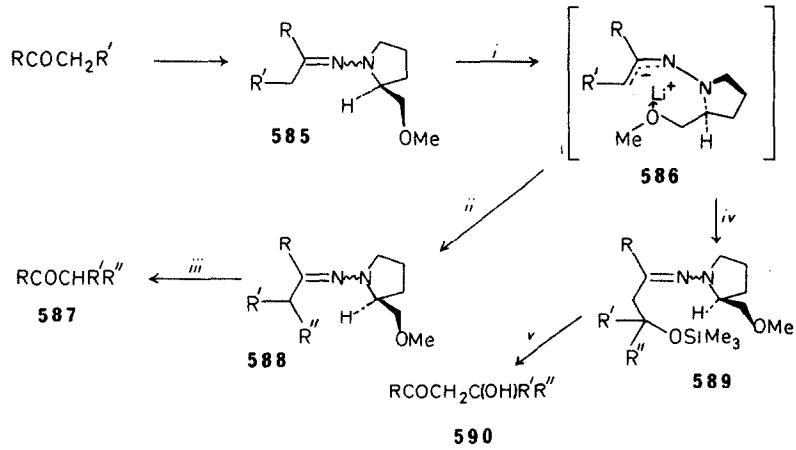
(Scheme 189) but the optical yields were lower (21–47% e.e.).[410] This was again attributed to the



Scheme 189. Reagents: (i) $CH_3(CH_2)_6CH{=}O$; (ii) $CH_3CH_2CH{=}O$; (iii) LDA; (iv) MeI; (v) $CH_3(CH_2)_5I$; (vi) H_3O^+.

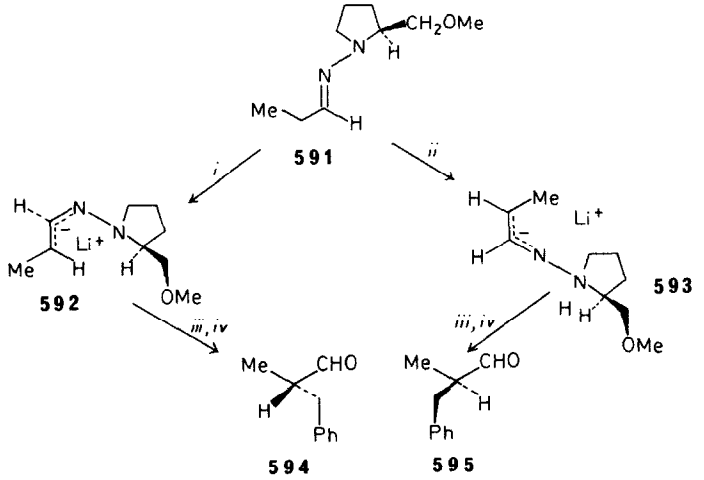
formation of both E- and Z-isomers but in this case pre-heating the metalloenamine mixture failed to improve the optical yield.

Aldehydes and cyclic and acyclic ketones have been converted into chiral hydrazones **585** with (S)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP). Metallation and alkylation gives hydrazones **588** which are readily cleaved to optically active α-chiral carbonyl compounds **587**, by ozonlysis or hydrolysis of the methiodide, in high chemical and optical yields.[411] If instead of alkylation, the lithio derivative **586** is treated with ketone and the adduct silylated, the doubly protected ketol **589** is obtained. Oxidative hydrolysis then affords the chiral ketols **590**.[412]



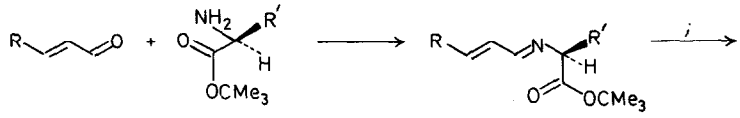
Scheme 190. Reagents: (i) LDA, THF; (ii) R″X, −95°; (iii) O_3, CH_2Cl_2, −78° or MeI, 60°/aq. HCl; (iv) R′ = H; (v) H_2O_2, MeOH, pH 7, 20–80°, 2–24 h *or* $^1O_2$ (followed by PPh_3 or Me_2S and hydrolysis).[412]

Deprotonation of the SAMP hydrazone **591** of propionaldehyde with lithium diisopropylamide in the presence, and in the absence, of hexamethylphosphoramide (HMPA) gave mainly the Z-anti lithio anion **593** (95%) or the E-syn lithio anion **592** (>98%) respectively (see Section 5E for a discussion of this stereoselective deprotonation). Benzylation and hydrolysis of **592** and **593** gave (S)-2-methyl-3-phenylpropanal **594** (82% e.e.) and (R)-2-methyl-3-phenylpropanal **595** (10% e.e.) respectively. Possibly the iow stereoselectivity for the alkylation of **593** is due to the chiral centre of the hydrazone residue being so far from the carbon undergoing alkylation.[326]

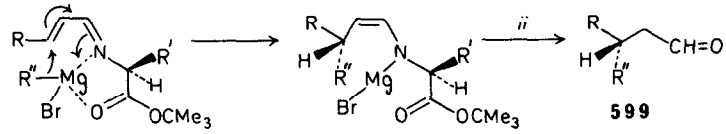


Scheme 191. Reagents: (i) LDA, THF, −78°→0°; (ii) LDA, THF, HMPA, −78°→20°; (iii) $PhCH_2Br$, −95→0°; (iv) MeI, 3NHCl, 25°.

Further developments in asymmetric synthesis include the 1,4-addition of Grignard reagents[413] and potassium diethyl malonate[414] to chiral $\alpha\beta$-unsaturated aldimines **596**. Instead of acting as a base, to give a metallodienamine, the Grignard reagent is suggested to give a chelated complex **597** which transfers an alkyl group to the adjacent electrophilic position of the aldimine (**597** → **598**). Although these are of course reactions of the imine, rather than the enamine tautomer, they illustrate the wide synthetic utility of these reagents. Hydrolysis gives the R or S aldehyde in high optical yield (63–98%) depending upon the chirality of the amine component. Alternatively the enantiomer of **599** can be obtained by simply exchanging the R group in **596** for the R″ group in the Grignard reagent while retaining the same chiral reagent.[413]



596



597 **598** **599**

Scheme 192. Reagents: (i) R″MgBr; (ii) H_2O.

Note added in proof. Some important papers which were unintentionally omitted, or which have been published since completing this review, are included below:

Part 1.[1]

Section 5B(ii)

The greater propensity of pyrrolidine enamines to undergo C-alkylation compared to morpholine and piperidine enamines has been elegantly demonstrated by reaction with crotyl and cinnamyl bromides. The pyrrolidine enamine gives predominantly the unrearranged α-crotyl or α-cinnamyl ketone on hydrolysis (71–87%), whereas the other two enamines give the rearranged α-(1-methyl or 1-phenyl allyl) ketone (85–90%) derived by initial N-alkylation and [3,3]sigmatropic rearrangement [P. Houdewind, U. K. Pandit, A. K. Bose, R. J. Brambilla and G. L. Trainor, *Heterocycles* **I**, 53 (1973)].

Part 2

Section 2D(i)

An ingenious alternative explanation for 2,2-disubstitution of 5-alkyl-2-methyl cyclohexanone enamines with methyl vinyl ketone (MVK) leading to the "abnormal" octalone (Scheme 37, **110t** → **112**) has been suggested [J. W. Huffman, C. D. Rowe and F. J. Matthews, *J. Org. Chem.* **47**, 1438 (1982)]. Surprisingly, formation of the "abnormal" octalone is favoured by the use of methanol as solvent, and excess of MVK, and it appears that the alkylation is reversible even after protonation of the initially formed zwitterionic intermediate. It is suggested that the 2,2-disubstituted product results from further alkylation of the 2,6-disubstituted enamine (before cyclisation to **111** occurs) with *simultaneous* dealkylation at C–6, an S_E2' reaction in effect.

The suggestion that this mechanism also explains the 2,2-disubstitution of 2-methylcyclohexanone enamines by methyl acrylate or acrylonitrile [*cf.* Part 1, Section 5B(i)] seems unlikely, but nevertheless requires investigation. An alternative to Huffman's S_E2' mechanism for the MVK reaction is, of course, that the "abnormal" octalone is formed by further alkylation of the 2,6-disubstituted enamine *followed* by C–6 dealkylation.

Section 5

Several significant developments have occured in metalloenamine chemistry since this report was completed:

(i) Concerning the conflicting evidence (Section 5E) with regard to the relative stabilities of the *cis* and *trans* crotyl anion (i.e. 2-butenyl anion), Bartmess and Hehre have concluded that the results of the ion cyclotron resonance measurements[397] are incorrect since equilibrium was not obtained in experiments on deprotonation of *cis* and *trans* 2-butene. It is therefore probable that the theoretical predictions of Schleyer *et al.*,[400a] that the free *cis* anion is more stable than the free trans anion, are correct (Professor K. N. Houk, personal communication).

(ii) Calculations indicate that although heteroallyl anions show an intrinsic preference of 16–25 kJ mol^{-1} for the syn conformer, lithiation turns this syn preference into a comparable (14.5 kJ mol^{-1}) anti preference due to the enhanced stability of the anti-π-lithio imine anion. This anti preference suggests that formation of heteroallyl anions in non-coordinating solvents should show anti selectivity. Completion of the first solvation sphere of the lithium cation reinstates the syn preference, but a lesser degree than for the free anion. This suggests that anion formation the presence of good lithium coordinating solvents should show syn selectivity (Robert W. Strozier, Dissertation, Louisiana State University, 1982).†

†We thank Prof. K. N. Houk for details of this work prior to publication.

(iii) Whereas lithium diisopropylamide and ethyl magnesium bromide convert an unsymmetrical imine to the syn anion, which undergoes subsequent alkylation *syn* to the substituent on nitrogen and at the *less* substituted α-position of the imine, the use of stronger bases such as n-butyl, sec-butyl, and tert-butyllithium has been shown to cause a dramatic change in the regioselectivity of deprotonation and alkylation [A. Hosomi, Y. Araki and H. Sakurai, *J. Am. Chem. Soc.* **104**, 2081 (1982)]. The stronger base favours formation of the anti imine anion! This was shown to undergo alkylation largely *anti* to the substituent on nitrogen and at the *more* substituted α-position of the imine! This appears to be a further example of kinetic versus thermodynamic control (see also Schemes 146, 147, 177 and the relevant text for further examples). However, in view of the above mentioned theoretical predictions of Houk and Strozier, an alternative possibility is that the π-litho derivative of the anion has been formed in the relatively weakly solvating medium employed. Certainly in the case of acyclic ketone imines, alkylation in the presence of hexamethylphosphoramide occurred *only* at the *less* substituted α-carbon. Unfortunately the regioselectivity of alkylation of cyclic ketimines was not changed by addition of HMPA.

The following recent publications refer to the sections indicated:

I-2 A theoretical and photoelectron spectroscopic study of the molecular and electronic structures of aliphatic enamines, K. Müller, F. Previdoli and H. Desilvestor, *Helv. Chim. Acta* **64**, 2497 (1981).

I-2: Electronic structure of vinylamine. Proton affinity and conformational analysis. R. A. Eades, D. A. Weil, M. R. Ellenberger, W. E. Farneth, D. A. Dixon and C. H. Douglass, *J. Am. Chem. Soc.* **103**, 5372 (1981).

I-2-5: Enamines of 3,3-dimethylazetidine. H. W. Thompson and J. Swistok, *J. Org. Chem.* **46**, 4907 (1981).

I-4: Isomerisation and hydrogenation of nitrogen-containing organic compounds catalyzed by heterogeneous catalysts. H. Hattori and K. Tanabe, *Heterocycles* **16**, 1863 (1981).

I-4: Formation specific enolates and enamines from 3-heteracyclohexanones. J. A. Hirsch and X. L. Wang, *Synth. Commun.* **12**, 333 (1982).

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