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THE ASYMMETRIC MICHAEL ADDITION REACTIONS USING CHIRAL IMINES

Dedicated to Professor Gilbert Stork on the occasion of his 70th birthday

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1 - INTRODUCTION

Owing to its wide occurrence and its amphiphilic properties (electrophilic at the carbon center and nucleophilic at the α–position), the carbonyl group plays a commanding role in organic synthesis.

In this respect, the use of *enamines*, revealed by the pioneering work of Stork in 1954[1], proved to be a fundamental contribution. Indeed, the easily accessible enamine derivatives constitute synthetic equivalents of the parent carbonyl compounds, *with enhanced nucleophilic properties.*

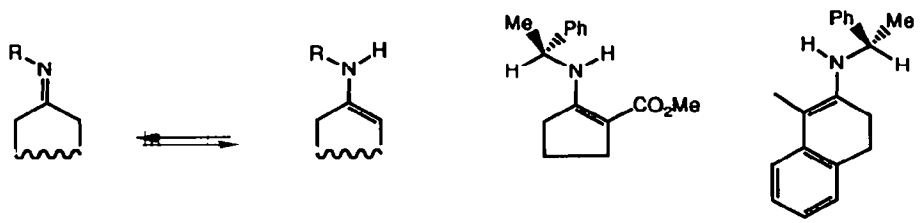
One of the main applications of enamines is their conjugate (Michael-type) addition to electrophilic alkenes. Although efficient, this C-C bond forming reaction suffered undeniably for a long time from two major drawbacks : the lack of methods to control the regioselectivity, especially at *the more* substituted α–position, when non-symmetrical enamines are used, and the absence of general, simple solutions to solve the crucial problem of the control of the absolute configuration(s) at the newly created stereogenic center(s).

The present review is devoted to a new asymmetric Michael addition reaction which we first published in 1985[2], using chiral imines *under neutral conditions* (a process which involves in fact their secondary enamine tautomers as nucleophilic partners). *We show that this reaction is highly regio- and stereoselective*, thus solving simultaneously the two aforementioned old, vexing problems.

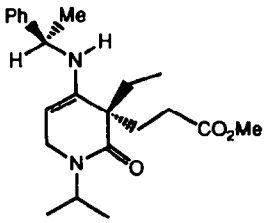
2 - GENERAL CONSIDERATIONS

2.1 - The imine – secondary enamine tautomerism

It has long been postulated that imines **1** are in tautomeric equilibrium with their secondary enamine forms **2**[3]. In general, except where the enamine form is stabilized by further conjugation, either with an electron-withdrawing group (*eg* **3**)[4] or an aromatic nucleus (*eg* **4**)[5], or by other less definite stabilizing factors (*eg* **5**[6],**6**[7]), this equilibrium is almost completely in favor of imine form **1**. This has been established by spectroscopic studies of **1**, including IR[8] and ^{1}H NMR[9], H/D exchange of the α, α'-protons in MeOD[10], and more generally by the nucleophilic reactivity of imines at the α, α'-carbon center(s). It has also been proposed that E / Z isomerization of chiral imine **7** proceeds through the tautomeric secondary enamine **8**[11]. Another convincing demonstration is given by the converse isomerization of the thermodynamically unstable secondary enamines **2**, generated by protonolysis of the N-metallo derivatives **9**, into imines **1**[12].



1 **2** **3** **4**



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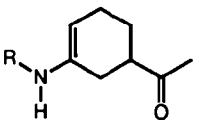

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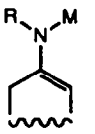
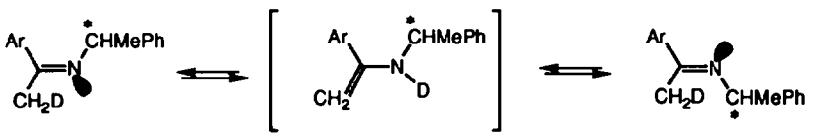


9

(M= Li, MgX, SnR_3, SiR_3)

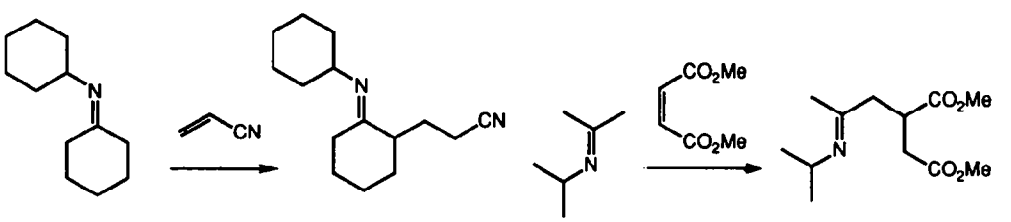


(Z)-7 8 (E)-7

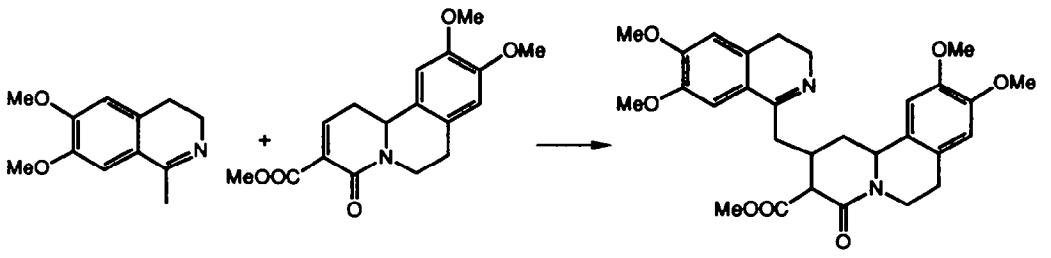
2.2 - Imines in Michael additions

As mentioned in the previous section, imines exhibit nucleophilic properties (*via* their secondary enamine tautomers).

The conjugate addition of imines to electrophilic alkenes leads thus to the expected Michael-type adducts. This was first demontrated in 1956 by Krimm in two patents[13]; for example N-cyclohexyliminocyclohexane **10** was added to acrylonitrile at 150°C, giving adduct **11.** This reaction was reinvestigated in 1970 by Pfau[10] who reported that N-isopropylideneisopropylamine **12** adds to dimethyl maleate to produce **13** in high yield. Similarly Kametani [14] described the addition of *cyclic* imine **14** to electrophile **15,** thus exploiting the enamine character of the former compound. Very interestingly, De Jeso and Pommier [12a] have shown that secondary enamine **17** reacts much more faster than its imine tautomer **18** with acrylonitrile, giving the same Michael adduct **19.**



10 11 12 13



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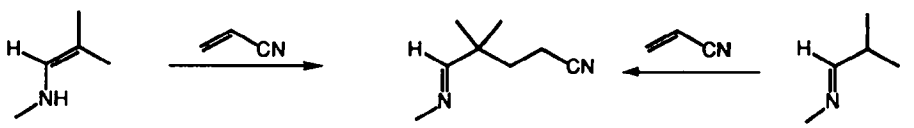
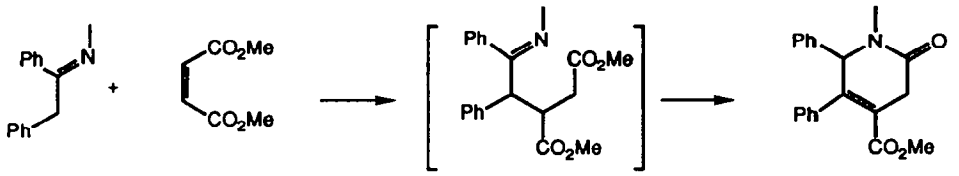
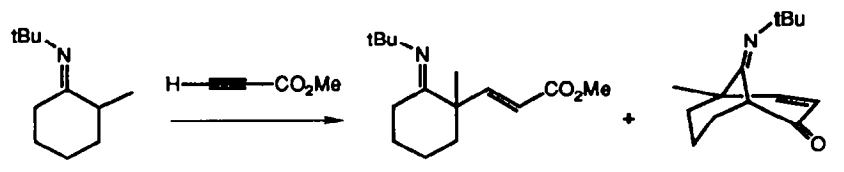


17 19 18

Many additional examples of Michael-type alkylation of imines are found in the literature. For instance, Barluenga described the reaction of ketimine **20** with dimethyl maleate, in the presence of aluminum chloride, leading to piperidone **21**[15]. Ito and coworkers reported that the addition of imine **22** to methyl propiolate gave a mixture of adducts **23** and **24**[16]. The addition of enaminoester **25** to 2-chloroacrylonitrile can be also compared with the preceding alkylations[17]; this reaction led to pyrrole derivative **27**, probably *via* the intermediary primary Michael adduct **26**.



20 21



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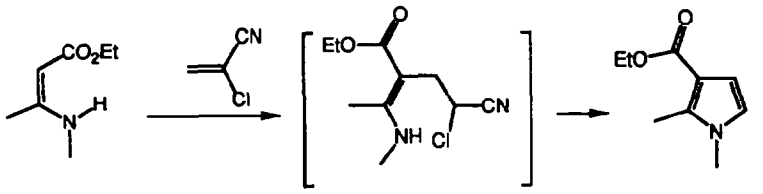
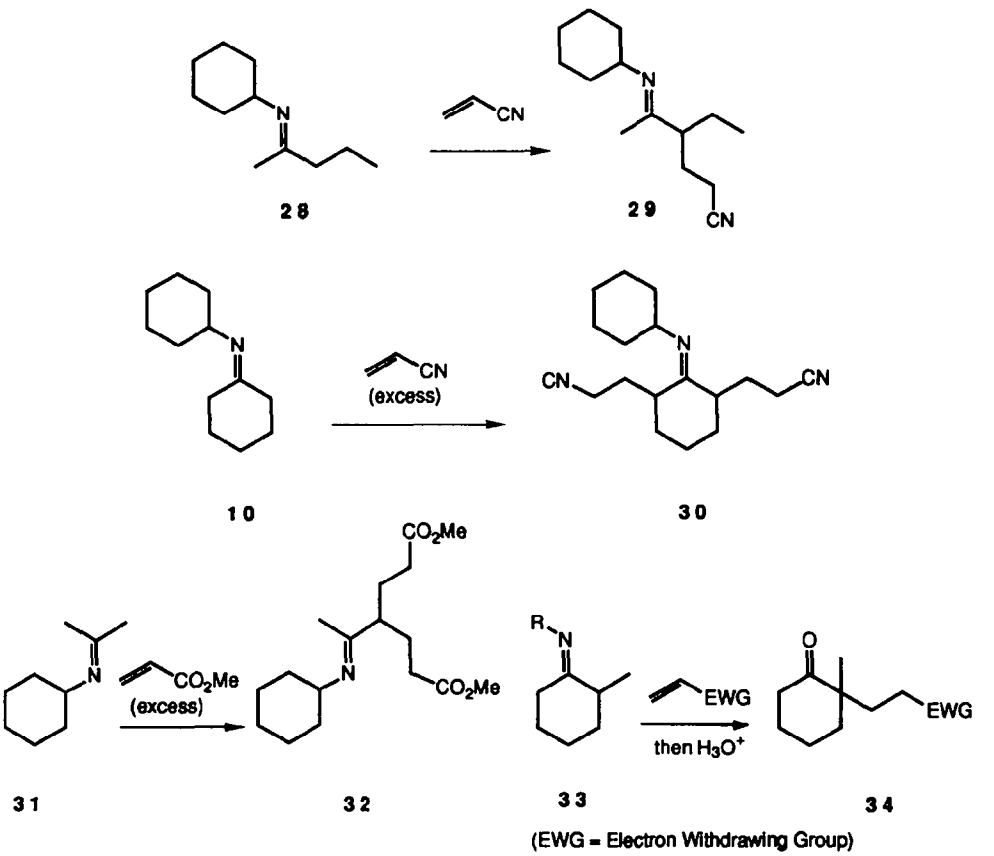


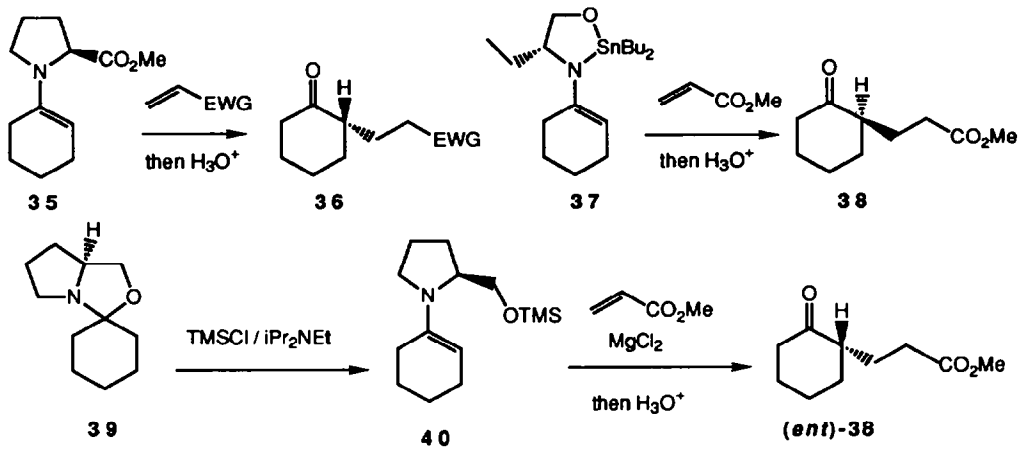
25 26 27

In sharp contrast to *tertiary* enamines[1], the conjugate addition of non-symmetrical ketimines to electrophilic alkenes gives rise generally to *the more* substituted adducts. Thus Krimm[13] noted that addition of imine **28** to acrylonitrile takes place at *the more* substituted α-side. In contrast, when an excess of acrylonitrile was added to imine **10**, the dialkylated derivated **30** was obtained, in which the second alkylation has occurred at *the less* substituted position. Later on, several authors reported that such Michael additions take place at *the more* substituted α-side of imines : Pfau[18] (**31** → **32**), Hickmott[19] (**33** → **34**) and Ito (**22** → **23** + **24**, *vide supra*)[16]. It should be noted that a *quaternary carbon center* is created in the conversion (**33** → **34**).



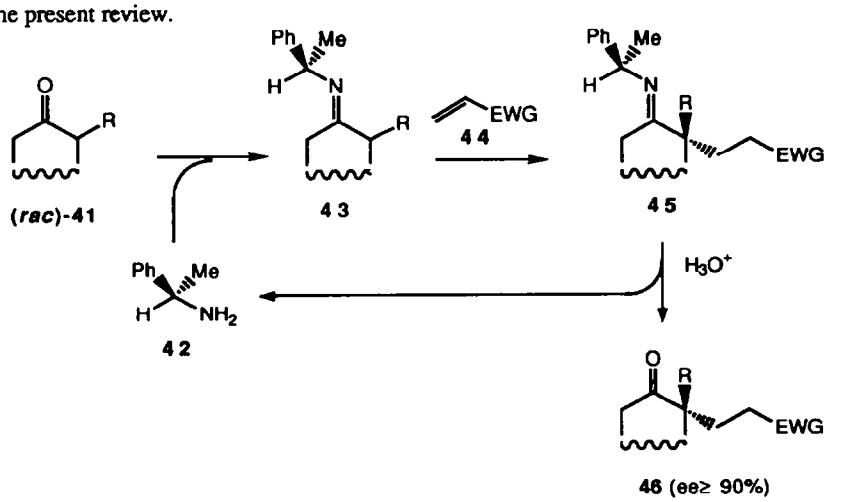
28 29 10 30 31 32 33 34

The *stereochemistry* of the Michael additions involving *tertiary* enamines was first investigated by Yamada[20], using various proline esters as chiral inducers (**35** → **36**); the best optical yields obtained were in the range of 40-60 %. More recently a better selectivity (86 % ee) was observed by De Jeso and Pommier [21] in the Michael addition of organotin enamine **37** to methyl acrylate. Ito reported that chiral enamine **40**, generated by cleavage of N,O-acetal **39**, adds to methyl acrylate in the presence of magnesium chloride, leading to adduct (*ent*)-**38** with an excellent selectivity (95 % ee)[22].



In 1985 we reported that chiral imines **43**, derived from *racemic* 2-alkylcyclanones **41** and optically active 1-phenylethylamine **42**, add to electrophilic alkenes **44**, giving adducts **45**[2].Acidic hydrolysis of **45** led to 2,2-dialkylcyclanones **46**, obtained with an excellent overall yield and with a high degree of regio- and steroselectivity, along with the recovered, unchanged chiral auxiliary amine.

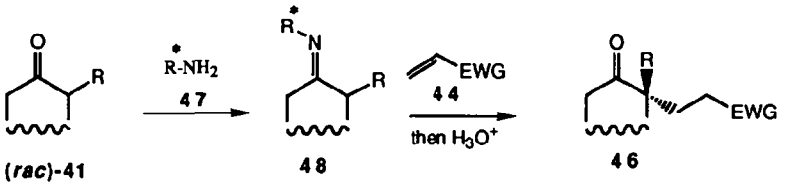
The scope of this "*deracemizing alkylation reaction*" and its application to synthesis constitute the purpose of the present review.



3 - SCOPE AND LIMITATIONS

Apart from the intramolecular versions presented in section 3.4, all the asymmetric Michael addition reactions discussed in this chapter can be typified by the conversion (**41** → **46**).

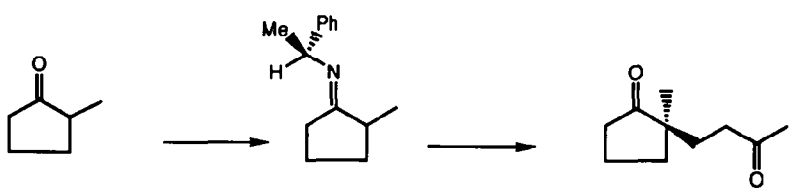
As described below, the reactivity, the regio- and stereoselectivity in this reaction depend greatly on the nature of the starting cyclanone **41**, the auxiliary chiral amine **47**, the electrophilic alkene **44**, and the reaction conditions.

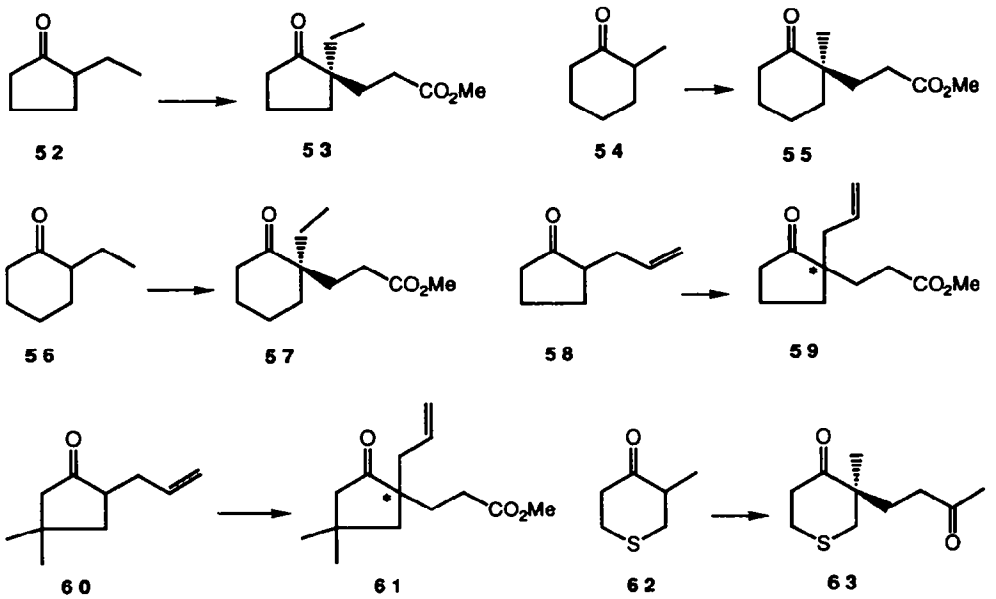


3.1 - Nature of the starting cyclanone

Forty cyclanones have been tested. The given chemical yields are calculated for the conversion **41**→**46** (including therefore the formation of imine **48**, the Michael addition to electrophile **44** and the hydrolysis of the primary imine adduct). In all cases, 1-phenylethylamine was used as chiral inducer, and the stated enantiomeric excesses (ee) were corrected for the enantiomeric purity of this amine.

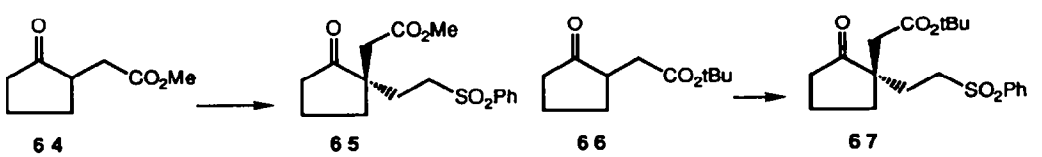
Chiral imine **50**, prepared from 2-methylcyclopentanone **49** and (*S*)-(-)-1-phenylethylamine was added to MVK, leading to diketone (*R*)-**51** (83 % yield 89 % ee)[2]. Similarly, but using methyl acrylate as electrophile, 2-ethylcyclopentanone **52** was converted into (*R*)-**53** (83 % yield, 91 % ee)[23], 2-methylcyclohexanone **54** into (*R*)-**55** (81 % yield, 90 % ee)[2], 2-ethylcyclohexanone **56** into (*R*)-**57** (80 % yield, 88 % ee)[24], 2-allylcyclopentanone **58** into **59** (93 % ee, configuration not determined)[25] and 2-allyl-4,4-dimethylcyclopentanone **60** into **61** (ee not determined)[25]. Thianone **62** was converted similarly into diketone (*R*)-**63** [(*S*)-1-phenylethylamine, MVK, 38 % yield, 65 % ee][26].

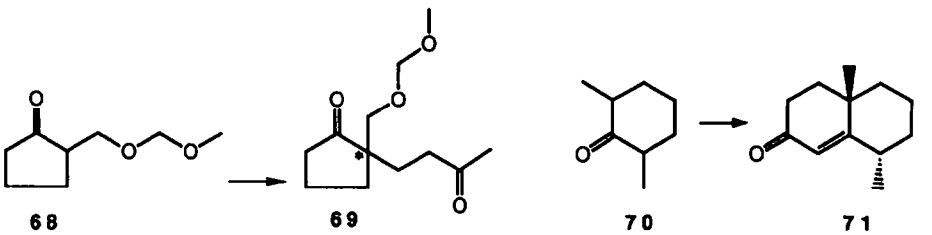


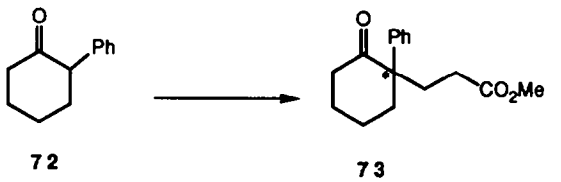


The presence of an acetate side-chain at C-2 in the starting cyclanones does not alter the features of the reaction; thus, using (*R*)-1-phenylethylamine and phenyl vinyl sulfone, **64** was converted into (*S*)-**65** (74 % yield, 91 % ee)[23] and **66** into (*S*)-**67** (55 % yield, 90 % ee)[23]. The chiral imine derived from ketone **68** and (*R*)-1-phenylethylamine proved to be thermally unstable, the corresponding MVK adduct **69** being obtained in only 15 % yield (90 % ee, configuration not determined)[27]. A significant decrease in the stereoselectivity was observed with the imine derived from 2,6-dimethylcyclohexanone **70** and (*R*)-1-phenylethylamine : the ee oberved in the corresponding MVK adduct, (*S,S*)-**71** (after Robinson annulation of the intermediary diketone) being 73 % (61 % yield)[28].

An important decrease in the nucleophilic reactivity was observed with the chiral imine derived from 2-phenylcyclohexanone **72** : attempts at Michael addition of this imine to methyl acrylate under thermal conditions were unsuccessful; however, by using the high pressure activation technique (12 Kbar, 20°C, see section 3.5), the optically active adduct **73** was obtained (ee not determined)[27]

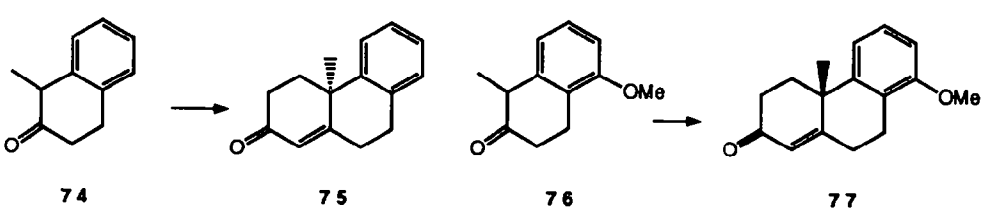


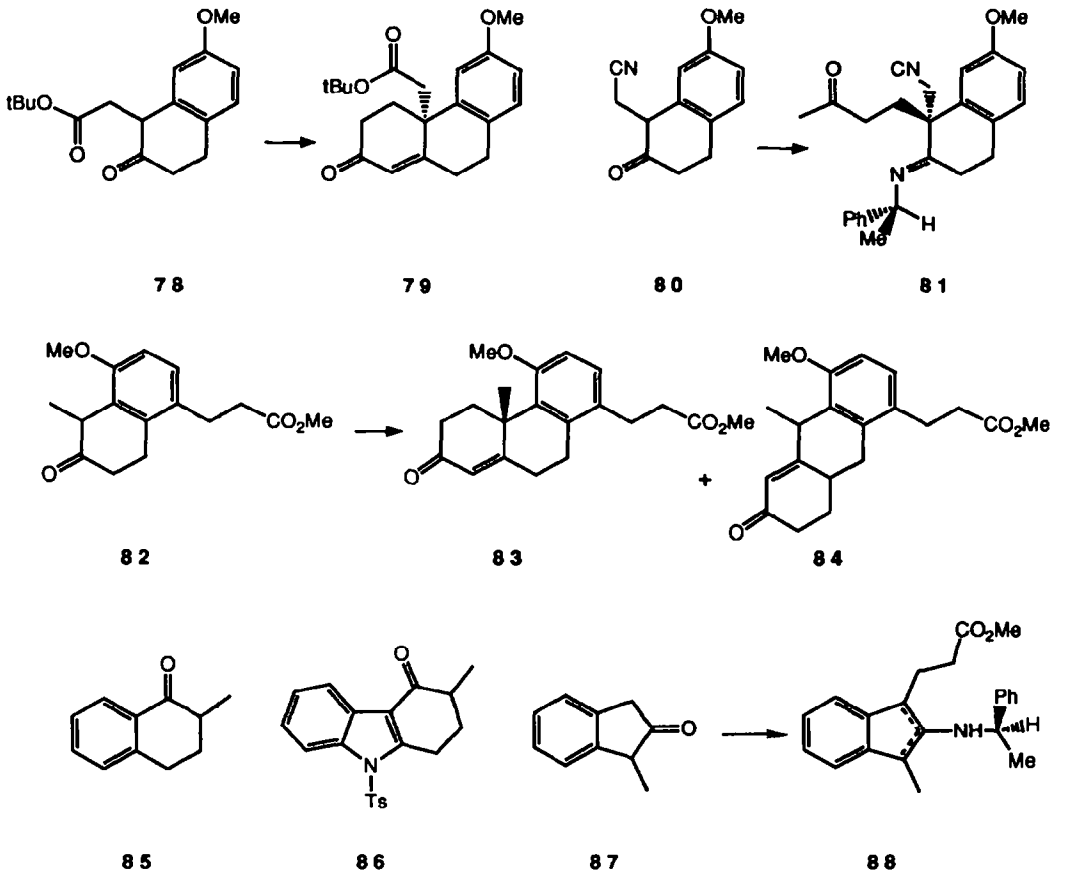




Secondary enamine **4** (section 2.1), prepared from 1-methyl-2-tetralone **74** and (*S*)-1-phenylethylamine, was added to MVK leading, after Robinson annulation, to phenanthrone (*R*)-**75** (50 % overall yield, 92 % ee)[5]. Similarly, enamine derived from **76** and (*R*)-1-phenylethylamine, led to adduct (*S*)-**77** (71 % yield, 92 % ee)[29]. Phenanthrone (*S*)-**79** (70 % yield, 95 % ee) was prepared in a similar fashion, by using tetralone **78** and (*S*)-1-phenylethylamine[30]. It is noteworthy that all attempts at conversion into the corresponding diketone (and hence the transformation into phenanthrone) of imine adduct **81** derived from the nitrile analogue **80** were unsuccessful, due to participation reactions of the nitrile function [31].

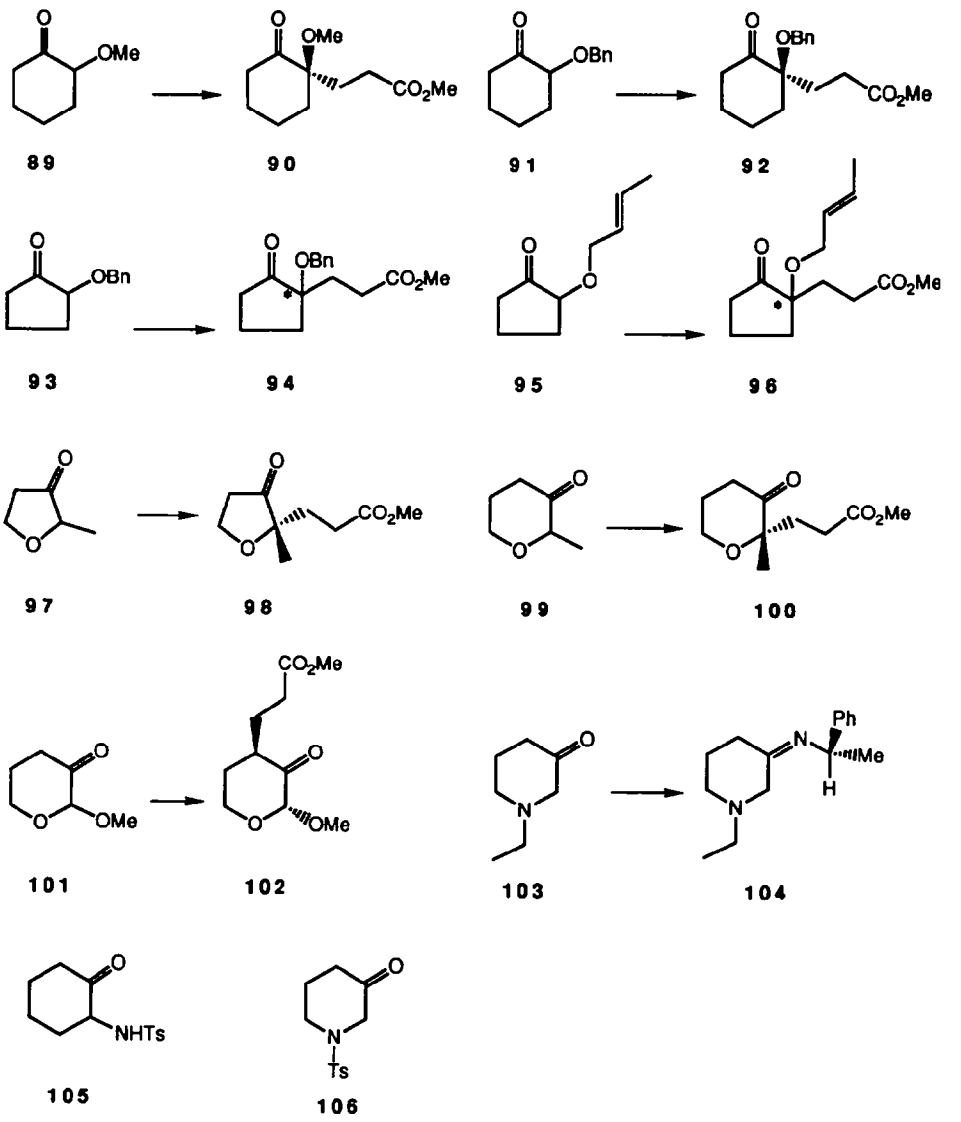
A dramatic loss of regiocontrol was observed with the imine derived from tetralone **82** and (*R*)-1-phenylethylamine : the addition to MVK led to a nearly equimolar mixture of phenanthrones (*S*)-**83** (88 % ee) and **84** with an overall yield of 50 % (see section 4.3)[5]. We have established that chiral imines derived from 2-methyl-1-tetralone **85**[24], or from carbazolone **86**[32], exhibit a complete lack of reactivity toward electrophilic alkenes (see section 4.1). Addition of the secondary enamine, derived from 1-methyl-2-indanone **87** and (*R*)-1-phenylethylamine, to methyl acrylate, took place at *the less* substituted position, leading to **88**. Attempts to hydrolyze this imine adduct were unsuccessful[33].





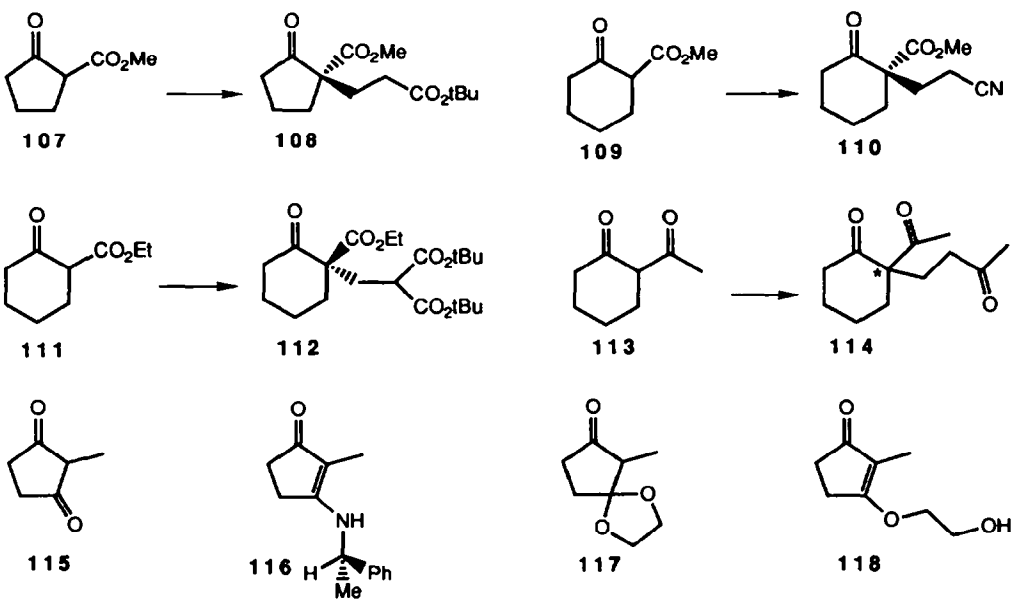
Very interestingly, the presence of an oxygen atom in the position α-to the carbonyl group in the starting cyclanones does not modify the remarkable features of these Michael addition reactions. Thus the imine derived from 2-methoxycyclohexanone **89** and (*R*)-1-phenylethylamine adds to methyl acrylate, leading to adduct (*R*)-**90** (80 % yield, 97 % ee)[34]. Similarly the benzyloxy derivative **91** led to compound (*R*)-**92** (75 % yield, 98 % ee)[34] and **93** to **94** (ee not determined)[24]. The imine derived from cyclanone **95** and (*R*)-1-phenylethylamine proved to be relatively unstable at room temperature : its addition to methyl acrylate led to the expected adduct **96** in only 30 % yield (ee not determined), along with 20 % of a compound resulting from the Claisen-type rearrangement of the starting imine (see section 5.1)[35]. By using (*R*)-1-phenylethylamine and methyl acrylate, furanone **97** led to adduct (*S*)-**98** (80 % yield, 96 % ee)[36] and pyranone **99** to (*S*)-**100** (75 % yield, 98 % ee)[37]. The chiral imine, derived from methoxy-pyranone **101** and (*R*)-1-phenylethylamine, was added to methyl acrylate, leading to *the less* substituted alkylated derivative **102**, isolated as single, optically active, diastereoisomer (20 % ee, absolute configuration not determined)[35].

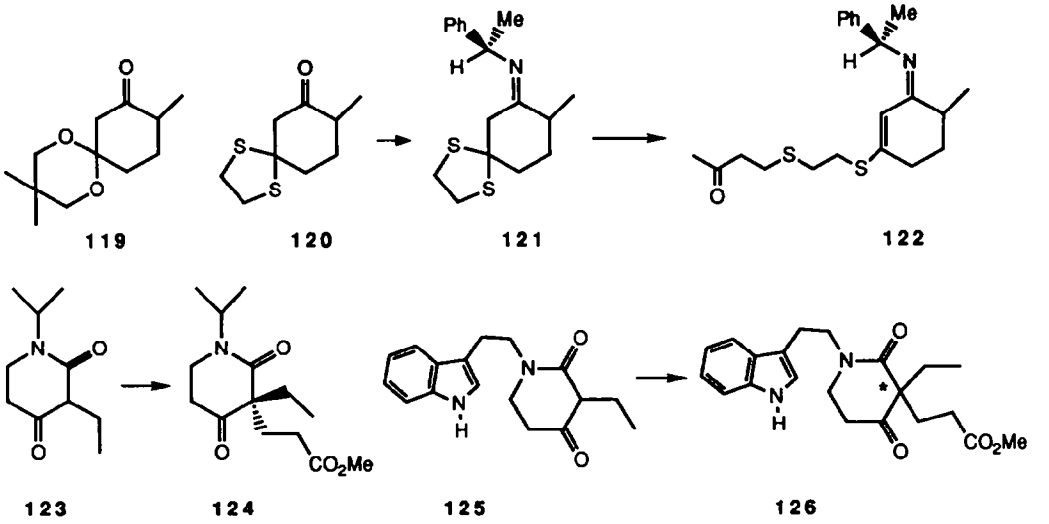
The present Michael reaction does not tolerate the presence of a nitrogen atom at the position α-to the keto group in the starting cyclanones, the corresponding imines exhibiting a poor thermal stability. Thus imine **104**, prepared from piperidone **103**, was characterized spectroscopically but was found to be very unstable in solution at room temperature[38]. Likewise, all attempts to prepare chiral imines from ketones **105** and **106** were fruitless[38].



When an electron-withdrawing group is present at the α-position of the carbonyl group of the starting cyclanones, the corresponding chiral *secondary enamines* (see section 2.1), stabilized by further conjugation, are formed by reaction with 1-phenylethylamine. In general such species are noticeably less reactive than the aforementioned imines, the Michael addition to electrophilic alkenes requiring in general activation by high pressures or by a Lewis acid as catalyst (see section 3.5). Thus, the enaminoester derived from keto-ester **107** and (*S*)-1-phenylethylamine, when added to *tert*-butyl acrylate (14 Kbar, 20°C), gave adduct (*S*)-**108** (45 % yield, 86 % ee)[4]. Similarly, using acrylonitrile, **109** led to (*S*)-**110** ($ZnCl_2$, Et_2O, -20°C, 85 % yield, 90 % ee)[39]. The enaminoester, prepared from keto-ester **111** and (*R*)-1-phenylethylamine, was added to the very reactive di-*tert*-butyl methylenemalonate, in the absence of a Lewis acid, giving adduct (*R*)-**112** (65 % yield, 95 % ee)[40].

Enaminone, derived from diketone **113** and (*S*)-1-phenylethylamine was added to MVK, leading to triketone **114** (58 % yield, 65 % ee, configuration not determined)[40]. In contrast, enaminone **116**, derived from dione **115** proved to be completely unreactive[41]. Reaction of 1-phenylethylamine with monoacetal **117** led to compound **118**, resulting from the cleavage of the acetal ring[42]. Although all attempts to prepare chiral imines derived from monoketal **119** were unsuccessful[24], the corresponding thioketal **120** led to the expected imine **121**[24]. However, reaction of this imine with MVK gave compound **122**, instead of the expected Michael adduct[24]. Enaminolactam, prepared from piperidione **123** and (*S*)-1-phenylethylamine, was added to methyl acrylate, leading to adduct (*R*)-**124** (70 % yield, 94 % ee)[6]. Compound **126** was prepared similarly, starting from **125** (63 % yield, 90 % ee, configuration not determined)[43].





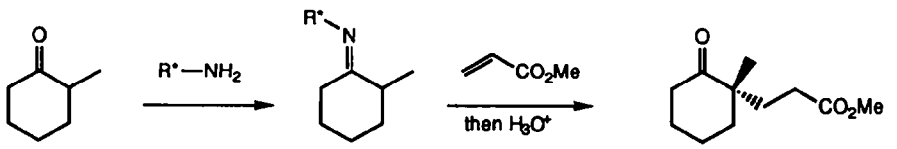
119 120 121 122

123 124 125 126

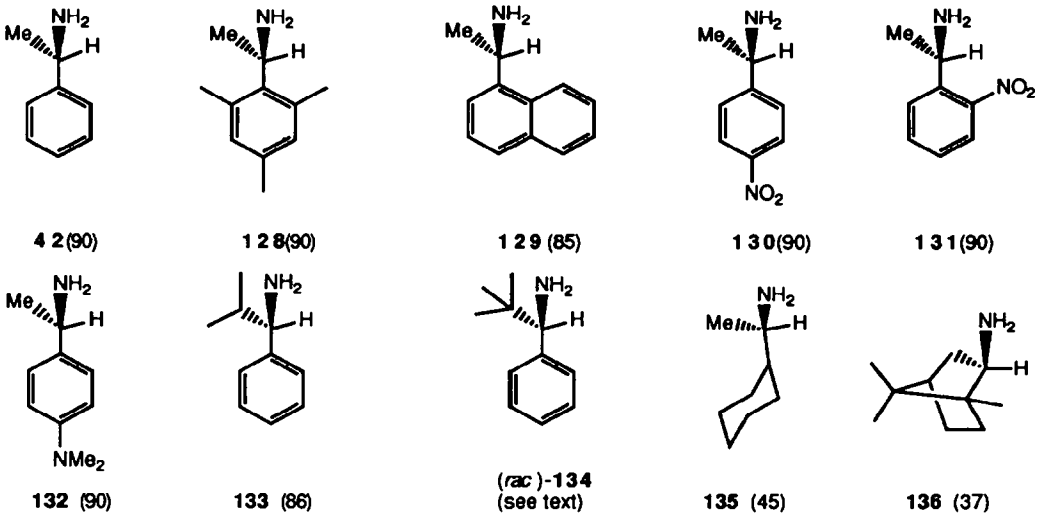
3.2 - Nature of the auxiliary chiral amine

Ten *(R)*- chiral amines (**42**, **128** -**136**) have been examined in the model reaction [**54** →**127** →(*ent*)-**55**]. The ee (in brackets) in the corresponding adduct (*ent*)-**55** were corrected for the enantiomeric purity of these amines, the *S* isomer in all cases predominating[44]. These auxiliaries can be classified into two categories : those bearing an aromatic nucleus in the position α-to the amine group (**42**, **128**-**134**) and two others (**135** and **136**) containing no aromatic moiety.

Within the amines of the first category, no significant change of the ee was observed. Thus when the phenyl group of 1-phenylethylamine **42** was replaced by more bulky aromatic nuclei (amines **128** and **129**) or when this phenyl was substituted, either by an electron-withdrawing group (amines **130** and **131**) or an electron-donating group (amine **132**), no notable variation of the ee was detected. Likewise the replacement of the methyl group by an isopropyl substituent (amine **133**) resulted in no substantial change of the ee, while the imine derived from amine **134** (*tert*-butyl analog of **42** and **133**) was found to be completely unreactive towards methyl acrylate. In sharp contrast with "benzylic" amines **42**, **128**-**133**, a striking decrease of the ee was observed with the amines of the second category (**135** and **136**); thus, *the presence of an aromatic nucleus in the position α-to the amine group of the auxiliary chiral amine appears essential to ensure a good enantioselectivity in the present Michael process.*



54 127 (*ent*)-55



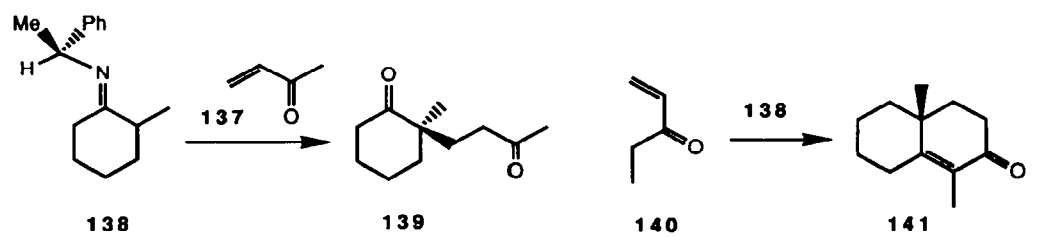
42 (90) **128** (90) **129** (85) **130** (90) **131** (90)

132 (90) **133** (86) (*rac*)-**134** (see text) **135** (45) **136** (37)

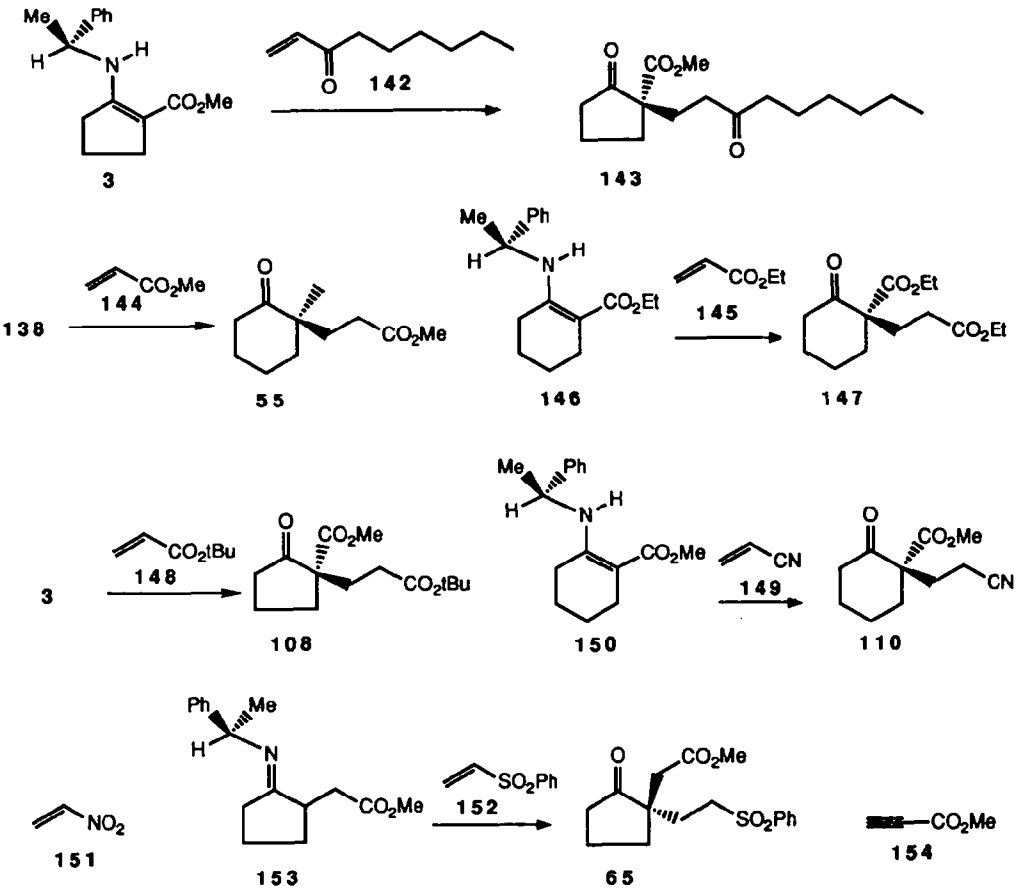
3.3 - Nature of the electrophilic alkene

Twenty-six electrophilic alkenes have been tested. Methyl vinyl ketone (MVK) **137** was added to imine **138**, prepared from 2-methylcyclohexanone and (*S*)-1-phenylethylamine, leading to diketone (*R*)-**139** (88 % yield, 91 % ee)[2]; similarly ethyl vinyl ketone **140** and **138** gave, after Robinson annulation, octalone (*R*)-**141** (67 % yield, 85 % ee)[28]. A significant decrease in the enantioselectivity was observed in the reaction of *n*-hexyl vinyl ketone **142** with enaminoester (*S*)-**3**, the adduct (*S*)-**143** being obtained in 82 % yield and 70 % ee[45].

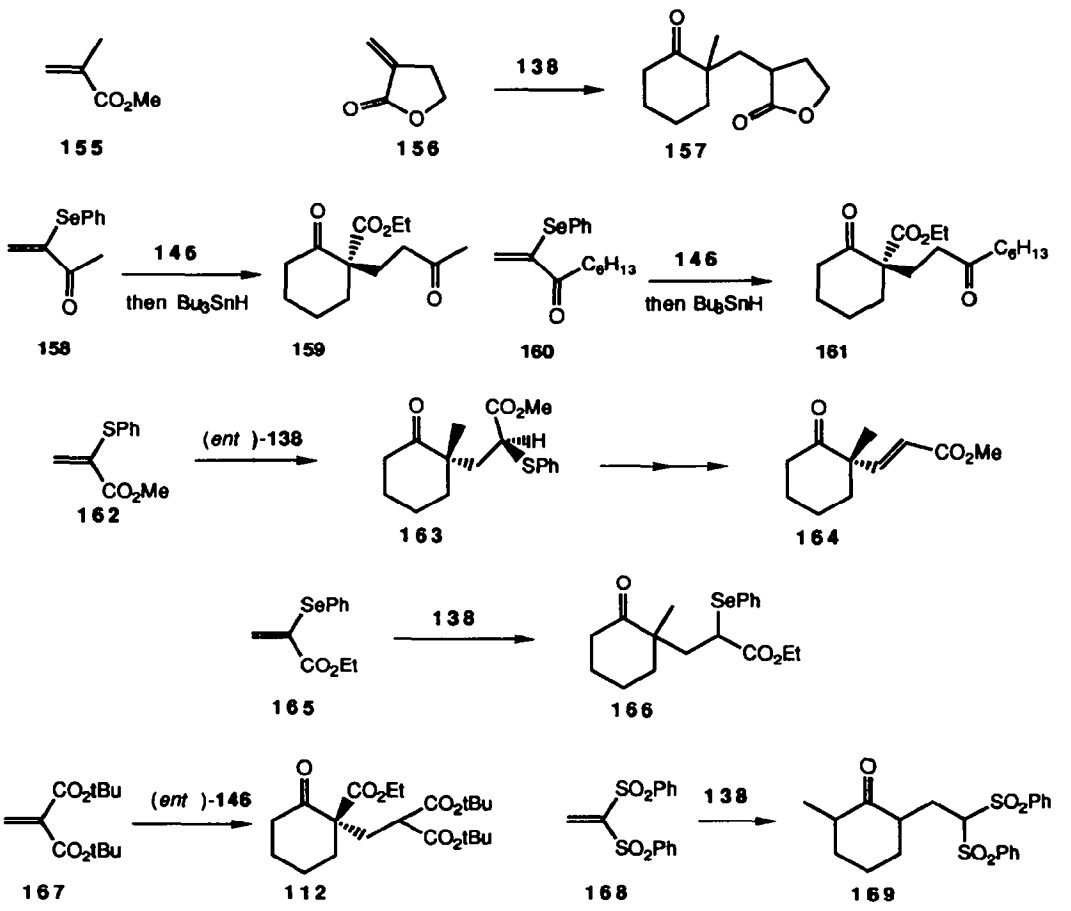
Methyl acrylate **144** and imine **138** led to adduct (*R*)-**55** (81 % yield, 90 % ee)[2], ethyl acrylate **145** and enaminoester (*S*)-**146**, to compound (*S*)-**147** (80 % yield, 79 % ee)[4], *tert*-butyl acrylate **148** and **3**, to adduct (*S*)-**108** (45 % yield, 89 % ee)[4]. Reaction of acrylonitrile **149** with enaminoester (*S*)-**150** gave derivative (*S*)-**110** (89 % ee)[39], while attempts at addition with imine **138** led to a complex mixture of compounds[27]. The reaction of imine **138** with nitroethylene **151** leads exclusively to polymeric materials, even at -40°C[46]. Phenyl vinyl sulfone **152** added to imine **153** at 80°C, to give adduct (*S*)-**65** (74 % yield, 91 % ee)[23]. In contrast, no definite compounds were obtained in the addition of methyl propiolate **154** to imine **138**[27] (however, see section 2.2).



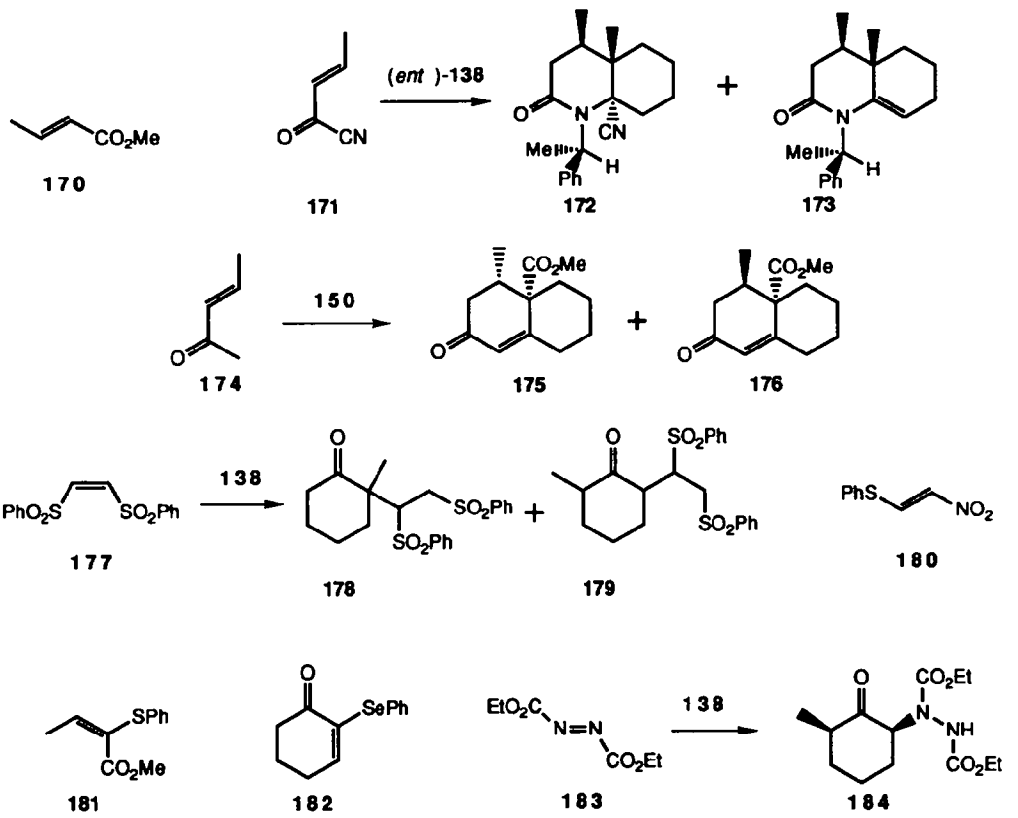
138 **139** **140** **141**



Methyl methacrylate **155** polymerized in the presence of imine **138**[24], while α-(methylene) butyrolactone **156** led to adduct **157** (single diastereoisomer, ee not determined)[24]. The addition of α-(phenylseleno) methyl vinyl ketone **158** to enaminoester **146** led, after cleavage of the phenylseleno group with Bu_3SnH, to adduct (*S*)-**159** (65 % ee)[27]; similarly, enone **160** and **146** furnished (*S*)-**161** (55 % yield, 70 % ee)[45]. Methyl α–(phenylthio)acrylate **162** and (*ent*)-**138** led to adduct **163** (80 % yield, single diastereoisomer) which was converted into (*S*)-**164** (90 % ee)[47]. Similarly, addition of ethyl α-(phenylseleno) acrylate **165** to imine **138** gave adduct **166** (de and ee not determined)[27]. The very reactive di-*tert*-butyl methylenemalonate **167** and (*ent*)-**146** led to compound (*R*)-**112** (65 % yield, 95 % ee)[40]. An almost complete inversion of the regioselectivity was observed with 1,1-bis-phenylsulfonyl-ethylene **168** : its addition to imine **138** has given essentially *the less* substituted adduct **169** (de and ee not determined)[48].



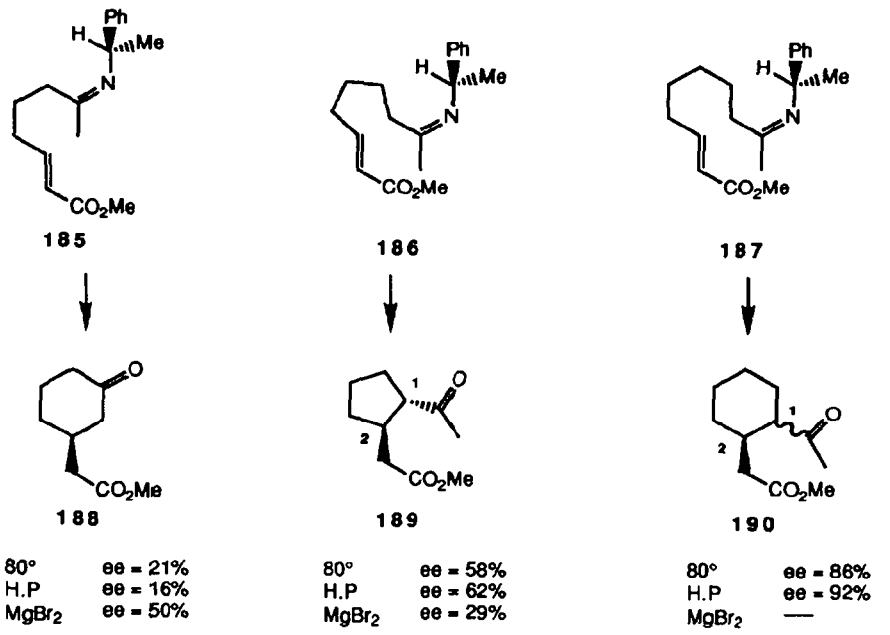
A dramatic decrease of the reactivity was generally noted when the electrophilic alkenes bear a substituent in the β-position with respect to the electron-withdrawing group. Thus methyl crotonate **170** did not react with imine **138**, even at 100°C[46]. In contrast, crotonyl cyanide **171** added smoothly to (*ent*)-**138**, at 0°C in cyclohexane, leading to a mixture of bicyclic lactams **172** and **173**[47]. The configurations at the three newly created stereogenic centers in **172** were established by X-ray analysis. Addition of 3-penten-2-one **174** to enaminoester **150**, in the presence of $ZnCl_2$, led with a modest yield (35 %), after Robinson annulation, to a 9:1 mixture of diastereoisomeric octalones **175** and **176** (ee not determined)[39]. Bis-sulfone **177** reacted with imine **138**, at 0°C, giving a mixture of regioisomeric adducts **178** and **179**[27]. Electrophilic alkenes **180**, **181** and **182** exhibited a complete lack of reactivity towards imine **138**[27]. In contrast, diethyl azodicarboxylate **183** added to imine **138** at 0°C, giving adduct **184**, resulting from the alkylation at *the less* substituted α-side of imine (single *cis* diastereoisomer, ee not determined)[24].



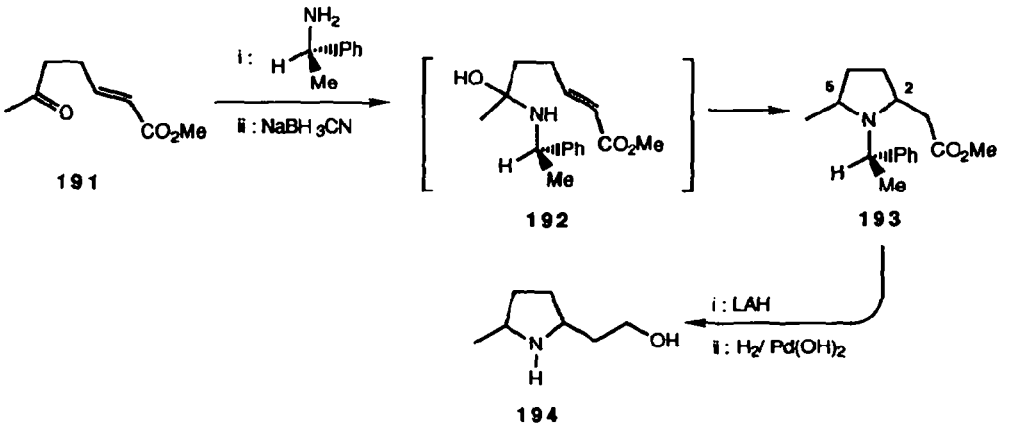
3.4 - Intramolecular variants

It is worthy of note that, although methyl crotonate is completely unreactive towards chiral imines (see section 3.3), the intramolecular versions of this reaction led to the expected adducts (see below). A notable increase in the rate of the addition, due to entropic factors, is therefore observed.

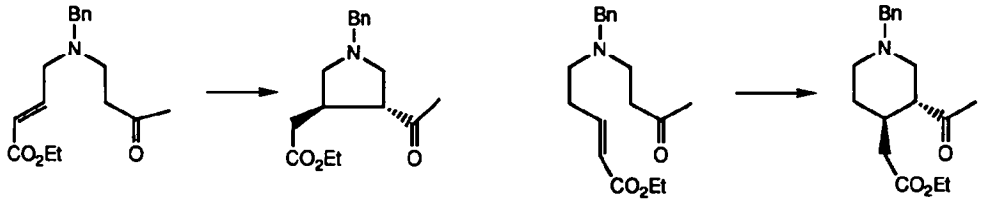
We have established that chiral imines **185**, **186**, and **187**, derived from (*R*)-1-phenylethylamine, in which the imine function is separated from the enoate moiety by a 3,4 or 5-carbon-atom chain, undergo a facile *intramolecular carbocyclization*, leading to adducts (*S*)-**188**, (1*S*, 2*R*)-**189** and (2*R*)-**190**, respectively[49]. Although similar ee are obtained by using thermal or high pressure-induced (12 Kbar, 20°C) conditions of cyclization, the use of $MgBr_2$ as Lewis acid catalyst strongly modifies the selectivity.



A completely different behavior was observed with ketoenoate **191**, in which the keto group is separated from the enoate moiety by a two-carbon-atom chain. Reaction of this compound with (*R*)-1-phenylethylamine led, instead of the expected imine, to pyrrolidine **193**, after reduction ($NaBH_3CN$) of the primary adduct[25]. This implies that the intermediary carbinolamine **192** undergoes a facile *intramolecular N-heterocyclization*. A rather good diastereocontrol between the two side chains at C_2 and C_5 in adduct **193** was observed (*trans/cis* = 9:1). However, *both* diastereoisomers of **194**, derived from **193**, proved to be *racemic*, thereby revealing the absence of "chirality tranfer" in the present process.

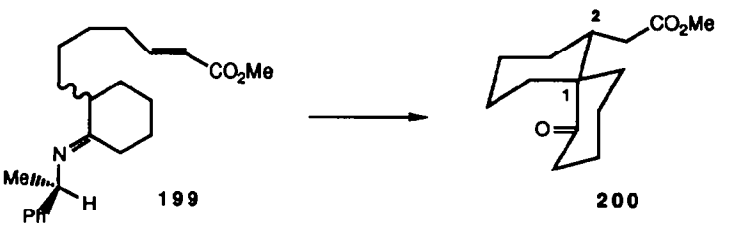


Hirai has reported that ketoenoates **195** and **197** are cyclized in the presence of (*R*)-1-phenylethylamine (THF, 5°C, molecular sieves), leading to heterocyclic adducts (*R,R*)-**196** (62 % ee) and (*R,R*)-**198** (80 % yield, 90 % ee), respectively[50].



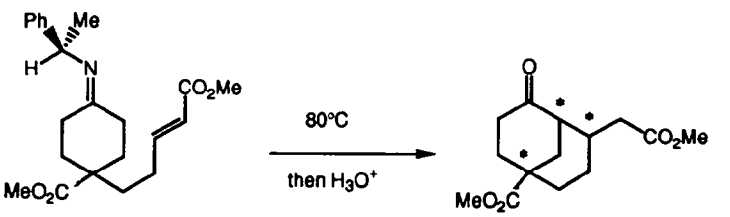
195 **196** **197** **198**

Iminoester **199**, prepared from (*R*)-1-phenylethylamine, undergoes a *spiroannulation* (refluxing toluene) furnishing adduct (1*S*, 2*R*)-**200** with a high control (≥ 90 %) of the relative and absolute configurations of the two newly created stereogenic centers[51].



199 **200**

We have recently established that the *bridging annulation* of imine **201**, derived from (*R*)-1-phenylethylamine, gave adduct **202** (≥ 95 % de and 90 % ee, configurations not determined)[52].

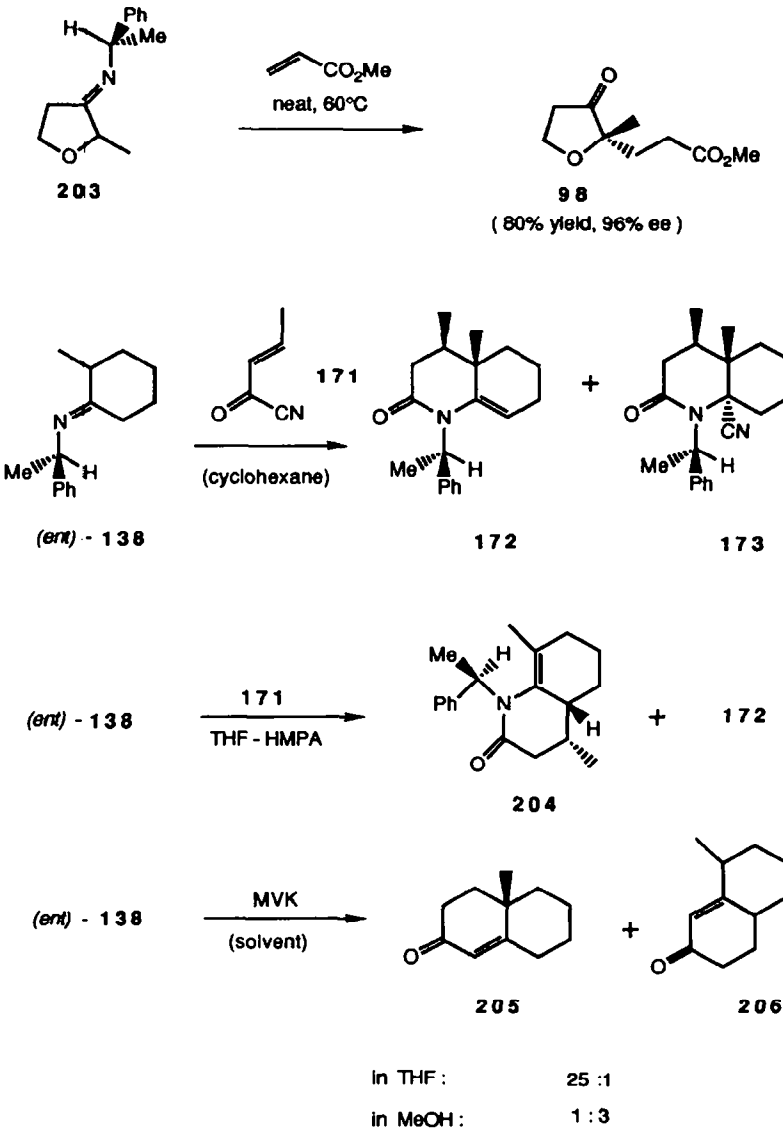


201 **202**

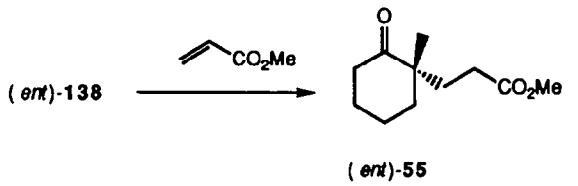
3.5-Influence of the reaction conditions

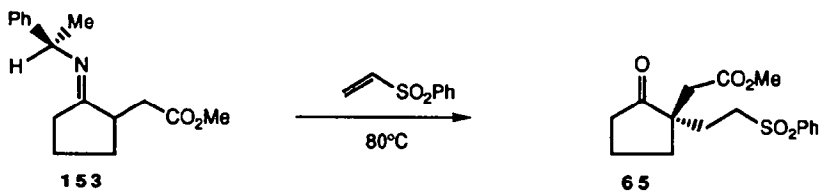
In many cases these Michael additions can be performed without any solvent, for example [**203** →**98**][36]. Practically, any *aprotic solvent* (cyclohexane, ether, toluene, THF, etc..) can be used. However, very polar media should be avoided, since in general they strongly alter the regioselectivity. Thus, addition of

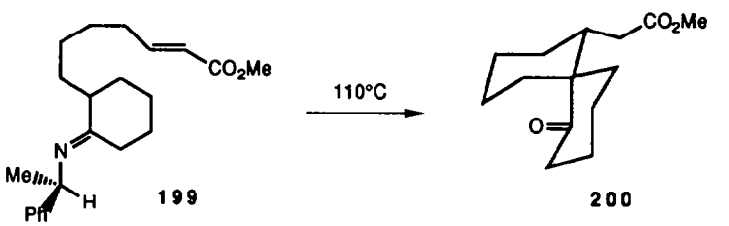
crotonyl cyanide **171** to imine (*ent*)-**138** takes place exclusively at *the more* substituted α-side of the imine in cyclohexane, leading to bicyclic lactam **172** and **173**[47]. When the same reaction was performed in a mixture of THF-HMPA (4:1), the alkylation occurred essentially at *the less* substituted side of (*ent*)-**138**, giving a (13:1) mixture of adducts **204** and **172**[46]. As mentioned in section 4.3, the regioselectivity of these additions can be ruined by the presence of a proton-donating solvent. For example, addition of imine (*ent*)-**138** to MVK leads almost exclusively to **205** in THF, while important amounts of regioisomer **206** are formed in methanol[27].



Somewhat surprisingly, the stereoselectivity of these Michael additions is not appreciably affected by substantial variations of reaction temperature. Thus addition of imine (*ent*)-**138** to methyl acrylate, leading to (*ent*)-**55**, requires 7 days at 20°C and only 12 h at 60°C, but the same ee (90 %) was observed in both cases[46]. Several other additions have been performed at relatively high temperatures without significant decrease of the selectivity, for example **153** → (*S*)-**65** (91 % ee)[23] and **199** → **200** (≥ 90 % ee)[51].

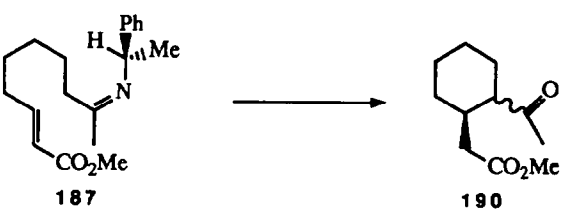


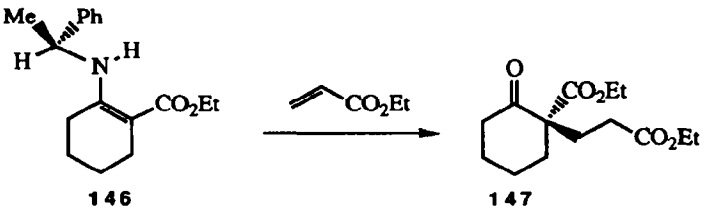




As was observed for an increase of temperature, *high pressures* accelerate the rate of these additions, without appreciable modification of the selectivity. Thus addition of imine (*ent*)-**138** to methyl acrylate gave (*ent*)-**55** in a few hours at 20°C under 10 Kbar with 90 % ee, while the thermal reaction requires 7 days at 20°C, giving the same ee (*vide supra*)[27]. Likewise, high pressure-promoted cyclization (12 Kbar, 20°C) of **187** led to **190** with 92 % ee, and the thermal reaction (80°C) gave **190** with 86 % ee[49].

High pressures proved also to be efficient in the addition of poorly nucleophilic species, like enaminoesters, to electrophilic alkenes. Thus, enaminoester **146** added to ethyl acrylate (11 Kbar, 40°C), leading to adduct **147** (63 % yield, 88 % ee)[4].



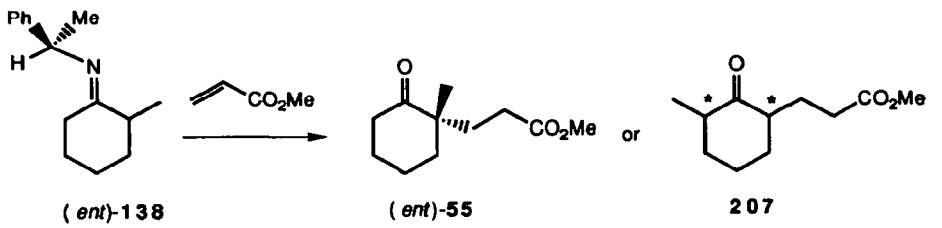


146 **147**

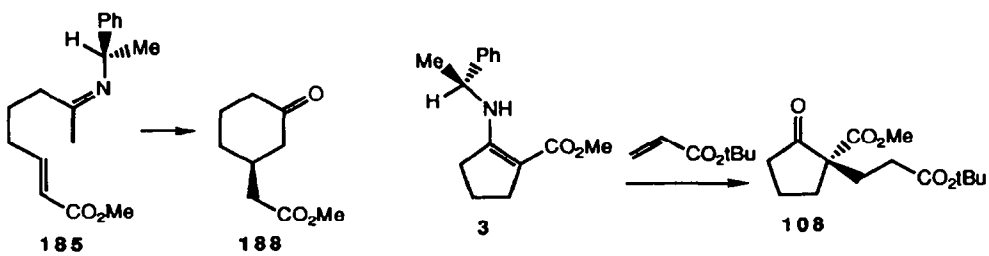
The use of a Lewis acid as catalyst has a striking effect in these additions: the rate of the reaction is usually greatly accelerated, while the regio- and/or enantioselectivity are frequently strongly modified.

This is exemplified by the addition of imine (*ent*)-**138** to methyl acrylate. Although thermal (7 days at 20°C) or high pressure-induced (10 Kbar, 20°C, 10h) reaction led exclusively to *the more* substituted adduct (*ent*)-**55** (90 % ee), *the less* substituted regioisomer **207** (equimolar mixture of optically active diastereoisomers, ee not determined) was obtained nearly quantitatively in the presence of 2 eq of $MgBr_2$ (Et_2O, 5 min at 0°C !)[25]. Likewise, cyclization of imine **185** into **188** under thermal conditions was achieved in 40h at 80°C (21 % ee) and in only 5 min at 0°C, in the presence of 2 eq of $MgBr_2$ (50 % ee)[49].

Enaminoesters proved to be much less reactive than imines, their Michael-type additions to electrophilic alkenes requiring in general high pressure-activation (*vide supra*) or the presence of a Lewis acid. Thus **3** was added to *tert*-butyl acrylate in the presence of 1 eq of $MgBr_2$ (3h at 20°C), leading to adduct **108** (60 % yield, 90 % ee)[4]. By using MVK as the electrophilic alkene, enaminoester **146** was similarly converted into adduct **159** (1 eq of $ZnCl_2$, 1.5 h at -78°C, 80 % yield, 79 % ee)[4].



(*ent*)-**138** (*ent*)-**55** **207**



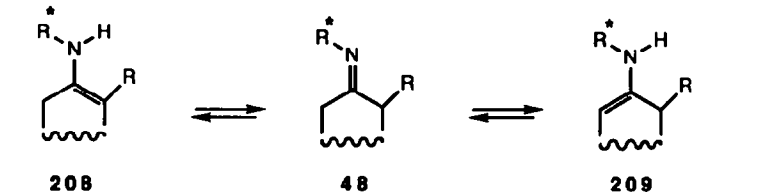
185 **188** **3** **108**

146 159

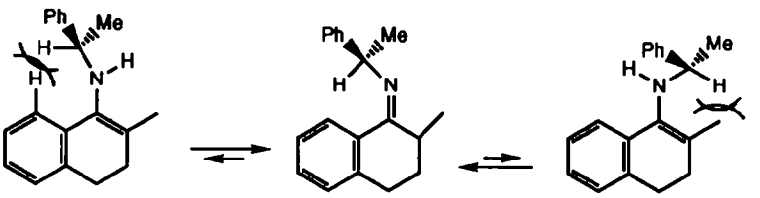
4 - MECHANISTIC ASPECTS

4.1 - Generalities

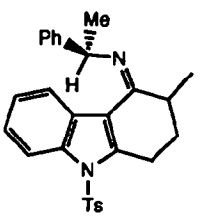
It is manifest that the nucleophilic partners implicated in the Michael additions of imines **48** to electrophilic alkenes are the secondary enamine tautomers **208** and **209** (see section 2.1). Indeed, imines **211**[24] and **213**[32], in which the tautomeric equilibria with the corresponding enamines (for example **210** ⇆ **211** ⇆ **212**) are sterically hindered, are completely unreactive. The absence of such an equilibrium was established in the case of **213** : there was no incorporation of deuterium in this imine, after prolonged standing in the presence of MeOD[24].



208 48 209



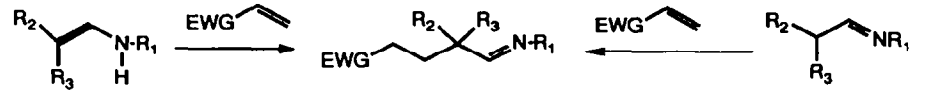
210 211 212



213

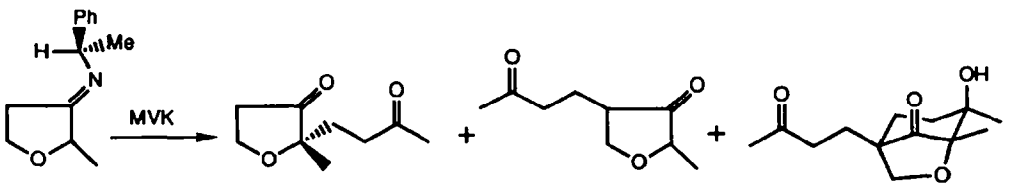
The tautomeric equilibrium imine-secondary enamine constitutes also the rate limiting step in the Michael-type addition of imines to electrophilic alkenes. This has been brillantly demonstrated by De Jeso and

Pommier who reported that the addition of secondary enamines **214** to electrophilic alkenes is fast and exothermic, while in the case of the corresponding tautomeric imines **216**, the reaction is either very slow (24h at 80°C) or does not take place [12a].



214 **215** **216**

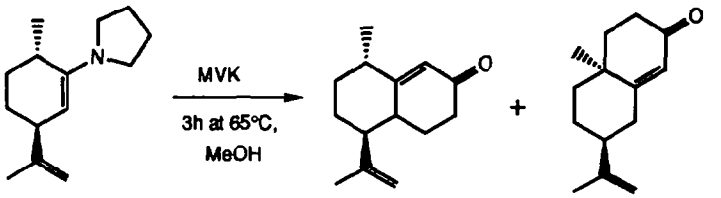
Assuming that the associated internal proton transfer should render these additions *irreversible* (section 4.2), we may consider that most of the aforementioned Michael reactions are *kinetically controlled.* Nevertheless, we have postulated that a competitive reversibility is involved in the unprecedented lack of regioselectivity observed in the addition of imine **217** to MVK[36].



217 **218** **219** **220**

Operating conditions				Chemical yields(%)		
MVK/217 Ratio of eq	solvent	temperature °C	duration h	**218**	**219**	**220**
1.5	Et_2O	20	24	19	19	traces
1.6	Et_2O	20	115	15	15	25
2	Et_2O	5	140	7	28	7
1.6	cyclohexane	20	94	13	18	15
4	cyclohexane	20	24	8	18	15
3	neat	40	12	traces	traces	80

A close observation was reported by Huffman who noted a dramatic effect of stoichiometry on the regioselectivity of the addition of tertiary enamine **221** to MVK[53]. Thus when 1 eq of MVK was used, *the less* substituted octalone **222** was obtained, while *the more* substituted regioisomer **223** was formed exclusively with 5 eq of MVK. This has also been interpreted in terms of reversibility of the Michael process.

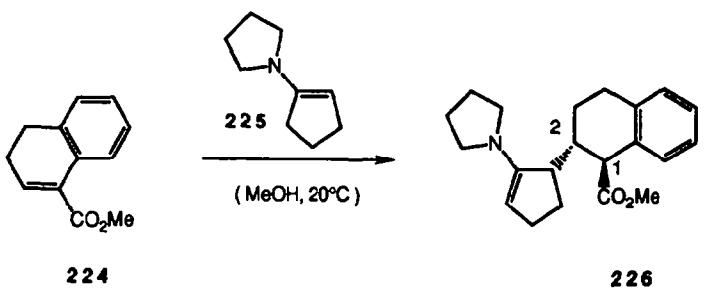


221 222 223

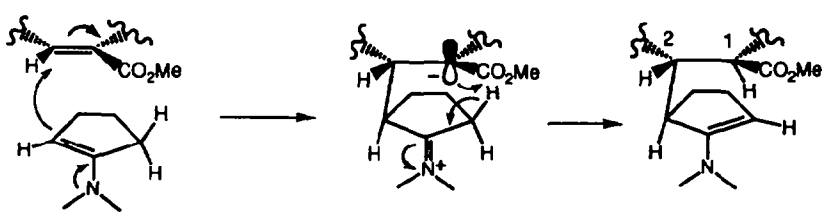
MVK / 221 (ratio of eq)	222 / 223
1	100 / 0
2	56 / 44
5	0 / 100

4.2 - *Nature of the transition state*

Several observations suggest that a *cyclic transition state* (and therefore a *syn* approach of the reactants) is implicated in such additions .Thus Pandit proposed, on the basis of the stereochemical results, that the addition of ethylenic ester **224** to tertiary enamine **225** involves the *syn* approach of reactants **227**, followed by an internal proton transfer (**228**)[54]. That the reaction follows an intramolecular course was revealed by experiments carried out in MeOD : there was essentially no incorporation of deuterium at C_1-center of adduct **226**.

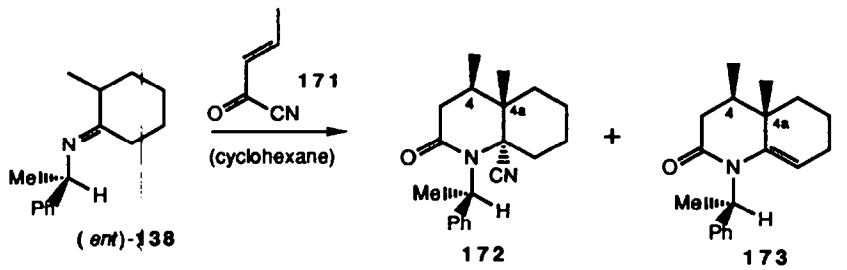


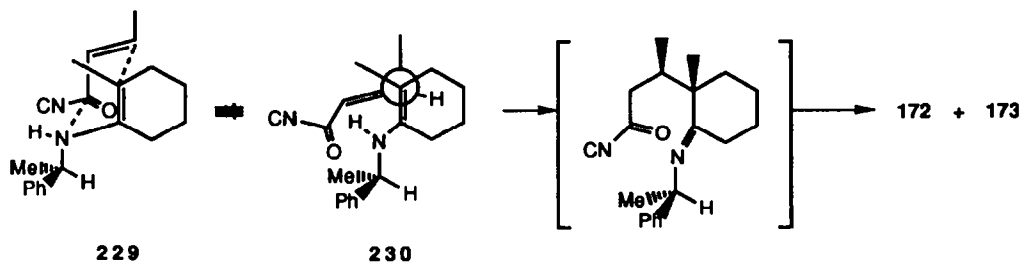
224 226



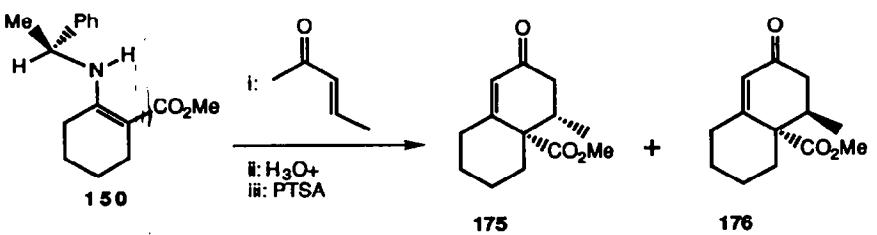
227 228 226

We have shown that imine (*ent*)-**138** adds smoothly to very reactive crotonyl cyanide **171**, giving a mixture of bicyclic lactams **172** and **173** (section 3.3)[47]. The *cis* relationship observed between the methyl groups at C-4 and C-4a in these adducts suggests that the reaction proceeds through the cyclic, chair-like transition state **229**. This involves a *gauche* (synclinal) arrangement of the reactant partners, as depicted in the Newman projection **230**.



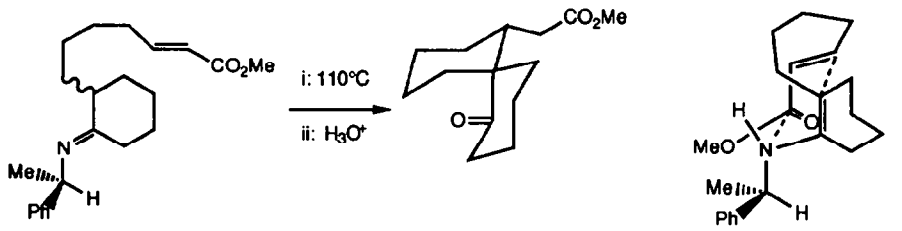


Addition of enaminoester **150** to 3-penten-2-one led with a 35 % yield to a 9:1 mixture of octalones **175** and **176**[39]. The *cis* relationship observed between the Me and COOMe groups in major isomer **175** may be interpreted, by evoking the participation of a cyclic, chair-like transition state.



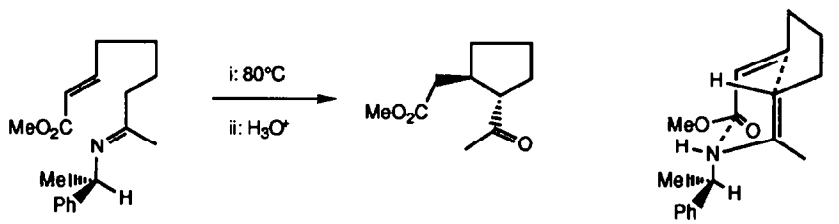
Considering their stereochemical courses, it is manifest that most of the intramolecular versions of these Michael additions (section 3.4) also involve cyclic transition states.

Thus imine **199** undergoes a facile intramolecular cyclization, leading to the spiro derivative **200** with a high degree of stereoselectivity[51]. This may be rationalized by assuming that the reaction proceeds through the compact approach **231**.



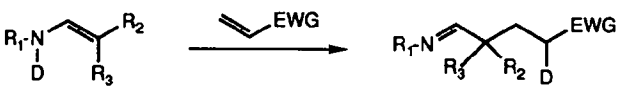
199 **200** **231**

Similarly, the intramolecular carbocyclization [**186** →**189**] may be interpreted, by making the assumption that this reaction proceeds through the cyclic, chair-like transition state **232**[49].



186 **189** **232**

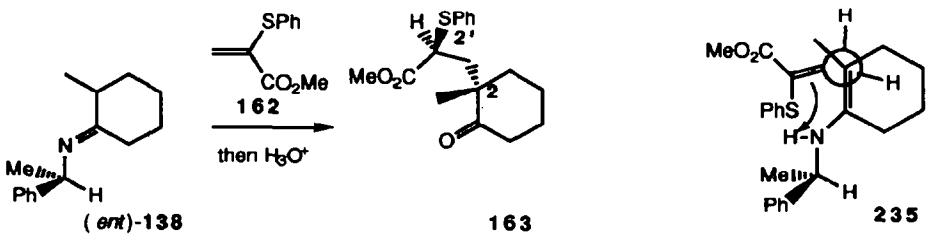
The *internal proton transfer* accompanying these Michael additions was first unambiguously established by De Jeso and Pommier . Indeed these authors have found that additions of N-deuteriated enamines **233** to electrophilic alkenes furnish adducts **234**, having a deuterium atom in the α-position with respect to the electron-withdrawing group[12a].



233 **234**

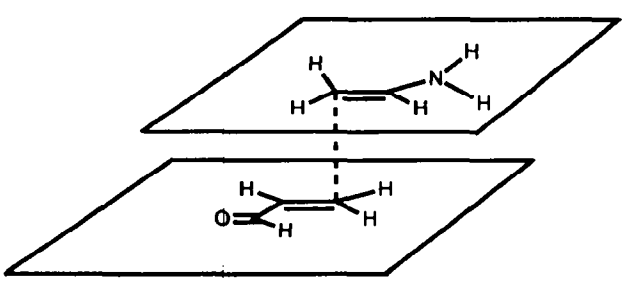
In addition, we have shown that imine (*ent*)-**138** adds to methyl α-(phenylthio)acrylate **162**, leading, after hydrolytic work-up, to adduct (*S,S*-)-**163**[47]. It is clear that the high stereocontrol level observed at C-2' in this adduct implies that the proton borne by the nitrogen atom of the enamine partner [tautomer to (*ent*)-**138**] should be transferred to the α-carbon center of acceptor **162**, *concertedly* with the creation of the C-C bond (arrow in Newman projection **235**).The *(S)*-stereochemistry observed at C-2' in adduct **163** also involves that

the electrophilic alkene **162** should be arranged such as depicted in approach **235**, namely the ester group eclipsing the vinylic methyl of the enamine partner.

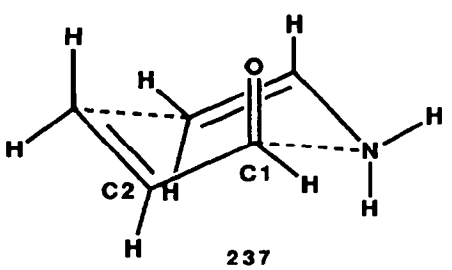


The process implicated in the addition of secondary enamines to electron-deficient alkenes has been theoretically simulated by ab initio SCF calculations, using ethyleneamine and propenal as prototype structures[55].

The *all-trans, anti* geometry **236** exhibits an energy of 7.81 Kcal mole^{-1}, the chair-like structure **237**, 8.79 Kcal mole^{-1} and the zwitterion **238**, 89.50 Kcal mole^{-1} (energies relative to the reactant partners at infinite distance). Thus the compact structure **237** is not appreciably disfavored with respect to approach **236**, which still minimizes all steric factors. It is therefore clear that extra stabilization comes from MO interactions. The most important interaction (Fig. **239**) arises between the HOMO of the donor (enamine) and the LUMO of the acceptor (propenal). In such a structure *the orbitals at the N center and at the carbonyl group interact in a bonding fashion.* A secondary attractive effect also arises between the oxygen atom of propenal (when the C=O is cisoid) and the C-1 center of the enamine (broken lines in **239**). In a compact geometry such as **237**, *the hydrogen transfer from NH_2 to C_2 of propenal is easy since these centers are close to each other.* This proton transfer might be more or less concerted with the addition step in order to avoid, as far as possible, the creation of an energetically disfavored charged transient species. In contrast, no concomitant H-transfer is expected in the *anti* approach **236** ; consequently the formation of an intermediate zwitterion would necessarily result from this attack. However, the high energy potential of such a zwitterionic species renders this reaction path very unlikely.



236



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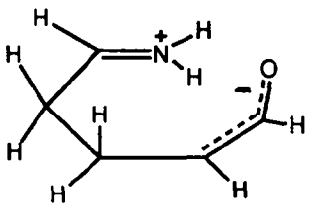
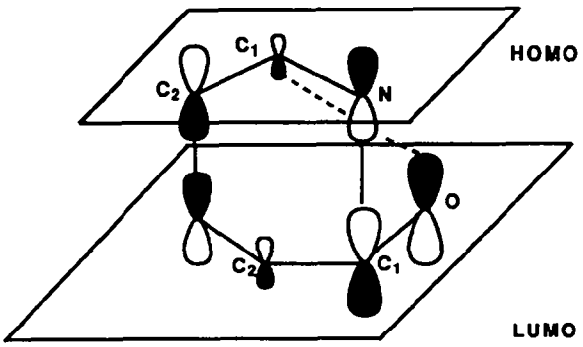
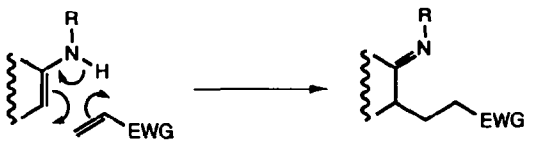


238



239

In conclusion, it is apparent that the mechanism of the addition of secondary enamines to electrophilic alkenes involves a *syn* approach of the reactant partners, and consequently a *cyclic* (chair-like) transition state. Moreover the proton borne by the nitrogen atom of the enamine should be transferred to the α-center of the electrophile, *more or less concertedly* with the creation of the C-C bond ("*aza-ene-synthesis-like*" transition state **240**).

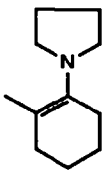


240 241

4.3 - Factors determining the regioselectivity

We have shown that the Michael-type additions of imines to electrophilic alkenes are generally highly regioselective, the alkylation taking place at the *more* substituted α–side of the imine function. The factors determining this remarkable regioselectivity are discussed in the present section.

The isomer ratio, at equilibrium, of *tertiary* enamines derived from 2-methylcyclohexanone has been examined[56]. This ratio is strongly dependent on the nature of substituents on the nitrogen atom. Interestingly, the lower the overlap between the nitrogen lone pair and the double bond, the greater the proportion of *the more* substituted double-bond isomer. Thus in compound **244** the lone pair on nitrogen should conjugate predominantly, if not entirely, with the phenyl nucleus and not with the enamine double bond. If so, there would be no requirements for coplanarity between the olefinic substituents and the groups attached to nitrogen. This has been confirmed lately. Indeed enamine **246** adopts a non-planar conformation with the lone-pair near to the π-plane, with the steric barrier to rotation of the diethylamino group through the plane being 8.1 Kcal $mole^{-1}$ [57].



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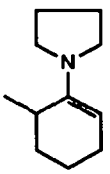

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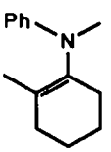

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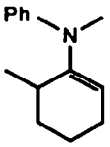
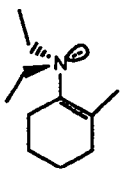


245

Isomer ratio at equilibrium : 10 : 90 100 : 0

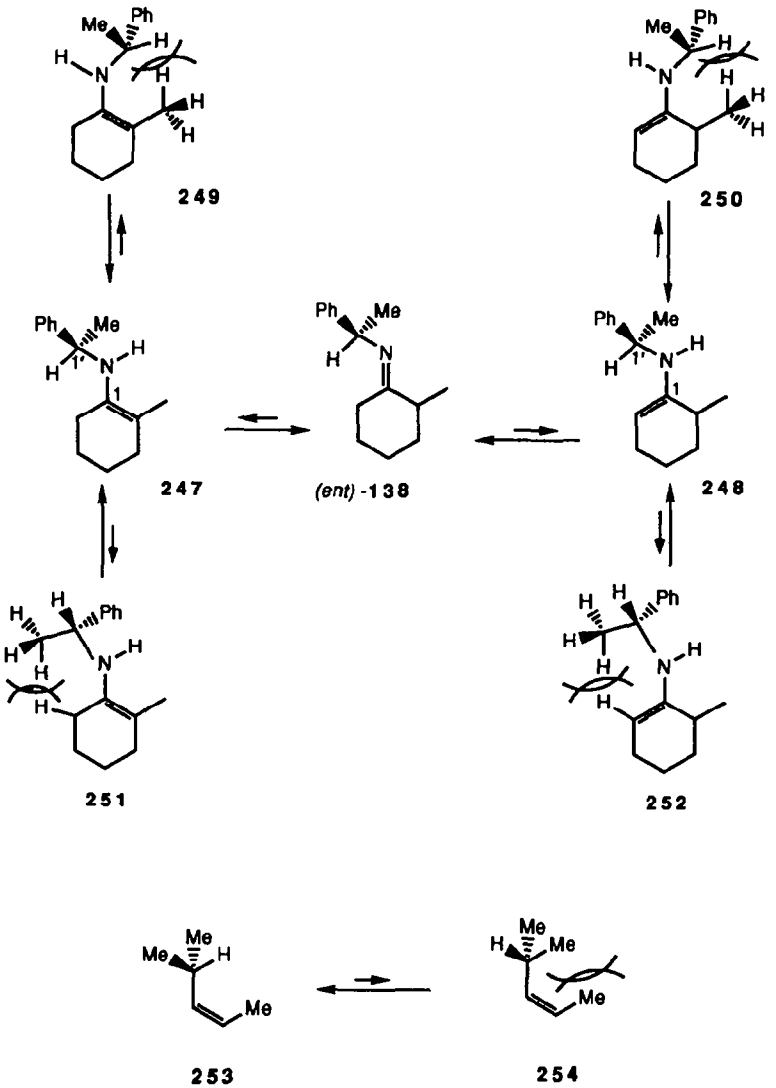


246

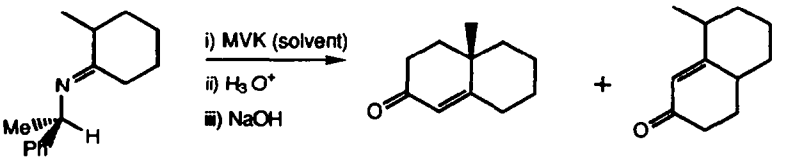
We will now examine the relative stabilities of the regioisomeric secondary enamines in tautomeric equilibrium with the starting chiral imines, *bearing in mind that the regioselectivities observed in the Michael additions of these imines do not reflect necessarily the populations of these regioisomers in the ground state* (Curtin-Hammett principle).

Consider the tautomeric equilibrium of chiral imine (*ent*)-**138** with the two corresponding regioisomeric secondary enamines. It is clear that the energetically preferred (*coplanar*) conformations of these enamines are those depicted in formulas **247** and **248**, in which the main steric interactions are minimized. Indeed, these structures exhibit two main degrees of freedom (rotations around C_1-N and $C_{1'}$-N bonds). By rotation of 180° around the C_1-N axis, **247** leads to **249** and **248** to **250**. By rotation of 120° around $C_{1'}$-N bond, **247** and **248** give **251** and **252**, respectively. All the conformers **249**, **250**, **251** and **252** suffer from a strong destabilizing steric interaction which is not encountered in the parent structures **247** and **248**. These conformational equilibria can be compared to the closely related system [**253** ⇆ **254**], in which a difference in energy of 3.44 Kcal mole^{-1} between the two rotamers has been calculated[58].

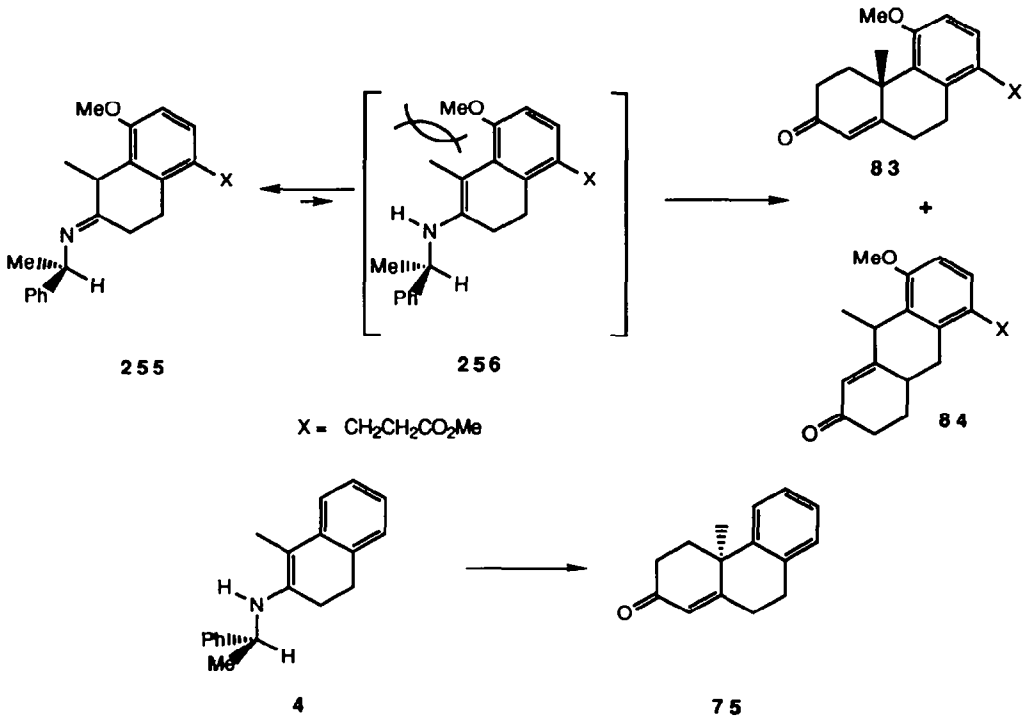
Recall that the Michael addition of imines to electrophilic alkenes involves the transfer of the proton on the nitrogen atom of the tautomeric secondary enamine to the α-center of the electrophile, *concertedly* with the creation of the C-C bond (section 4.2). In *the more* substituted enamine **247**, the NH bond is *syn* to the double bond and consequently the internal, concerted proton transfer is allowed. In contrast, in the case of *the less* substituted regioisomer **248**, the concerted proton transfer is prevented for obvious geometrical reasons (the NH and C=C bonds being *anti*). *It is manifest that the remarkable regiocontrol observed originates from this crucial internal proton transfer*, allowed only in the case of *the more* substituted enamine **247**.



The following set of experiments provides strong support for our proposal. The Michael addition of imine (*ent*)-**138** to MVK, *in an aprotic solvent* (THF), led almost exclusively, after Robinson annulation, to octalone **205**. The latter derivative resulted from the alkylation of *the more* substituted secondary enamine tautomer **247**. When an *external proton source* was used (MeOH as solvent), important amounts of regioisomeric octalone **206** were formed, implicating *the less* substituted enamine **248**[27].



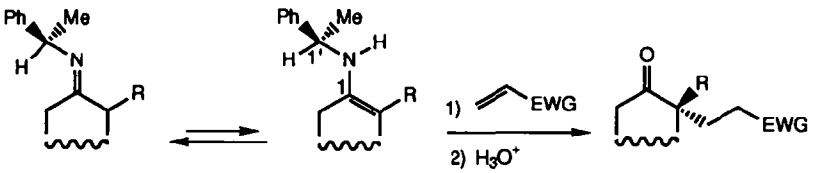
It should be noted that an important loss of regiocontrol was observed with *imine* **255**, in which the tautomeric equilibrium towards the more substituted, conjugated secondary enamine form **256** is thwarted for steric reasons : a nearly equimolar mixture of adducts **83** and **84** was actually observed by reaction with MVK[5]. That the loss of regiocontrol originates from steric interactions was demonstrated by using the demethoxy analog **4**. Indeed, addition of this *secondary enamine* to MVK led exclusively to phenanthrone 75[5].



4.4 - Factors determining the stereoselectivity

As a general rule, we have observed that the previous Michael-type alkylations took place predominantly on the π-face opposite to the phenyl ring of the chiral amine moiety of the reactive secondary

enamine, depicted in its energetically preferred conformation **257** (section 4.3). The origin of this π-face discrimination phenomenon is discussed in the present section.

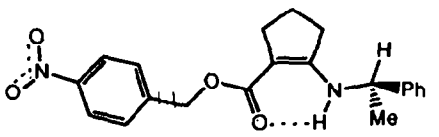


43 **257** **46**

The ee usually observed in these reactions are in the range of 90-98 % (which correspond to energy differences ΔΔG, at 25°C, between 1.75 Kcal mole^{-1} and 2.7 Kcal mole^{-1}). When the phenyl nucleus in imine **43** was replaced by a cyclohexyl ring, a dramatic decrease of the enantioselectivity was observed (section 3.2), the ee being of 45 % (ΔΔG 0.55 Kcal mole^{-1}).

We consider that enaminoesters (R = COOR' in **257**) constitute particularly pertinent models in the present investigation, for the following reasons. (*a*) The ee and the sense of induction observed with these enaminoesters are the same as those obtained with imines **43** (R = alkyl). (*b*) The tautomeric equilibrium imine-enamine is completely displaced towards the reactive secondary enamine form, by further conjugation with the ester function. (*c*) Due to the high degree of orbital overlap, *the nitrogen atom of enaminoesters is perfectly planar* (see, for example, the X-ray structure **259**); in contrast, enamines generally exhibit a pyramidal nitrogen atom [59], the facile inversion of which introducing a supplementary conformational degree of freedom. (*d*) The intramolecular hydrogen bonding NH···OC prevents the rotation around C_1-N bond, thereby simplifying greatly the analysis of the system : *the only degree of freedom which we have to take into account is the residual rotation around N-C_1' axis*. Incidentally, one should also note that the hydrogen bonding "blocks" the N-H linkage in the *syn* position relatively to the enamine double bond, which is precisely the geometry required for the concerted proton transfer implicated in the present Michael process (section 4.3). (*e*) The X-ray crystal analysis of (*R*)-enaminoester **258** has been made, providing essential geometrical data (structure **259**)[44]. In this respect, it is worth noting that the conformation of **258**, "frozen" in the crystal matrix, and of **247**, the proposed reactive enamine conformer in these Michael additions (section 4.3), are practically identical.

Let us examine now the diastereotopic approaches of an electrophilic alkene to the two π-faces of **258** (Fig **260** : in this perspective view, molecule **259** has been rotated of 90° to visualize the π-faces, and the *p*-nitrobenzyl ester part has been omitted for clarity). At first sight, it appears that the approach to the *si*-π-face should be significantly encumbered by the presence of the bulky phenyl nucleus, while the *re*-π-face is apparently free of steric hindrance.



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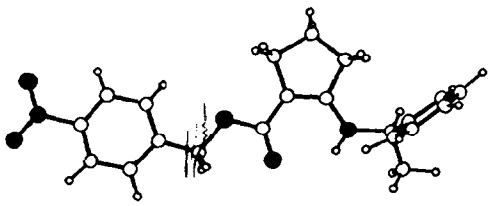
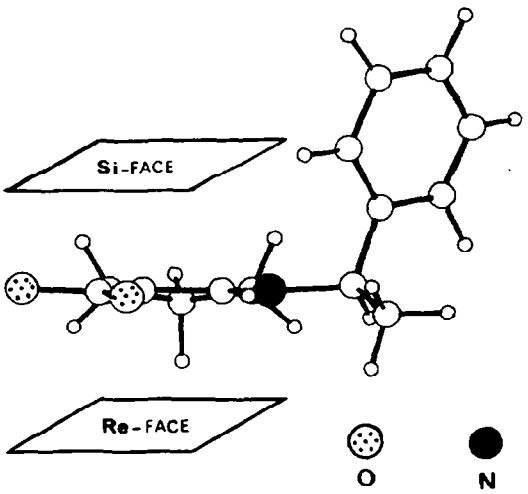


259

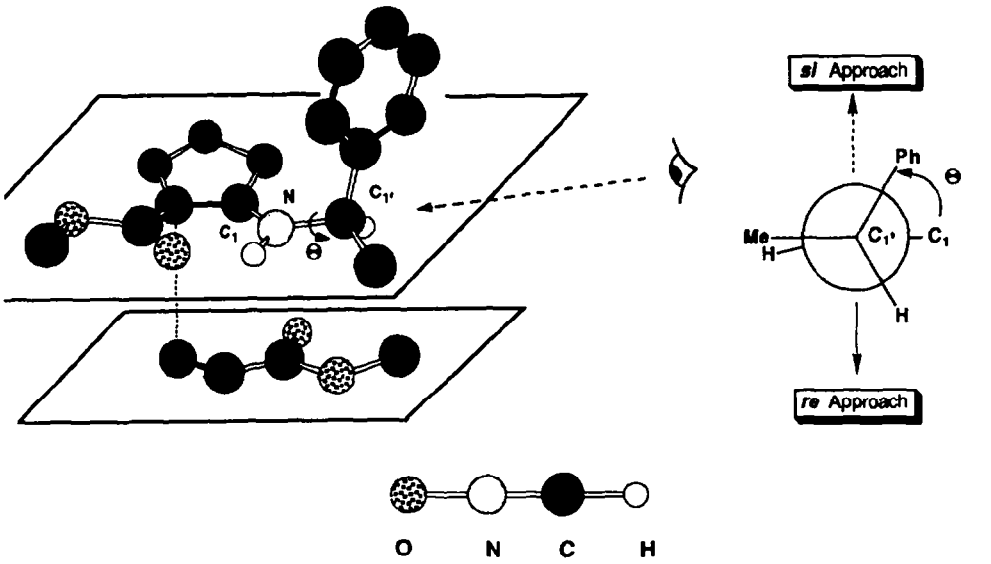


260

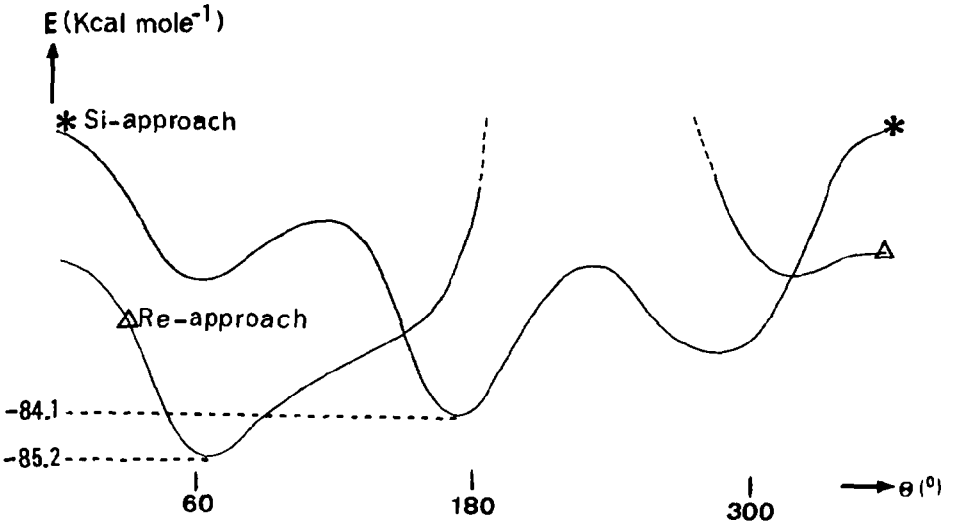
Approaches involving the methyl analog of enaminoester **258**, derived from (*R*)-1-phenylethylamine, and methyl acrylate have been theoretically simulated, by using the MOPAC Program[60]. In these calculations the two reactants, kept at 3 Å in two parallel planes, were linked in a perpendicular attack to form a chair-like arrangement (see section 4.2), (Fig **261** : in this picture, only the *re*-approach has been represented for clarity). The only significant degree of freedom in compact structure **261** remaining is rotation around the $N\text{-}C_{1'}$ bond of the enaminoester partner, the conformational energy curves corresponding to the two diastereotopic approaches have been determined, by rotating through 360° around this axis, the dihedral angle $C_1\text{-}N\text{-}C_{1'}\text{-}Ph$ being defined as θ (Fig. **262**).

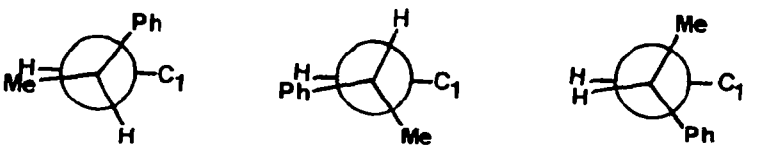
Energy minima of -85.2 Kcal $mole^{-1}$ and -84.1 Kcal $mole^{-1}$ have been calculated for the *re*- and *si*-approaches, respectively [which correspond to the conformations θ = 60° (close to the corresponding dihedral angle found in **258** in the crystalline state, 75°) and θ = 180°, respectively].

A difference in energy of 1.1 Kcal $mole^{-1}$, in favor of the *re*-approach, is therefore observed. This value, as well as the sense of the induction, are in good agreement with the experimental findings (*vide supra*), thereby providing support for the reliability of the present analysis.


si Approach
re Approach
Ph
Θ
Me
H
H
N
C1'
C1
O
N
C
H

261


E (Kcal mole-1)
* Si-approach
Δ Re-approach
-84.1
-85.2
60
180
300
θ (0)


Ph
H
Me
C1
H
H
Ph
C1
Me
Me
H
C1
Ph

262

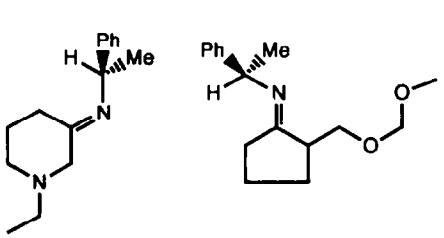
5 - SYNTHETIC APPLICATIONS

Experimental protocols for the elaboration of chiral synthons, prepared by means of the present asymmetric Michael addition reactions, and their use in the synthesis of natural products are reported in this chapter.

5.1 - Experimental protocols

The chiral inducer used in these Michael additions, *1-phenylethylamine*, has been prepared in its optically active forms, either by asymmetric synthesis[61], or by resolution of the racemic mixture. (*rac*)-1-Phenylethylamine (prepared from acetophenone by Leuckart's reaction)[62] has been thus efficiently resolved, by using *l*-malic acid and *l* or *d*-tartaric acid[62,63]. The two enantioforms of the chiral amine were thus obtained in 90-98 % enantiomeric purity. "Enantiomerically pure" 1-phenylethylamines ($[\alpha]_D^{22}$ 40.7, neat; ee ≥ 99.5 %) have been prepared by upgrading the partially enriched amines, *via* their sulfate salts[63]. It is worthy of note that both enantiomers of this amine are commercially available at moderate price (60 US $ per mole, for 100 g, and 10 US $ per mole, for 50 Kg, for the 94-96 % ee grade)[64].

Various methods have been used to prepare the requisite *chiral imines*, depending on the reactivity of the starting carbonyl compound, and on the stability of the imines. (*a*) By stirring a cyclohexane or THF solution of the two reagents in the presence of anhydrous K_2CO_3, molecular sieves, or a mixture of molecular sieves and a silica-alumina catalyst[65]. (*b*) By the azeotropic method, in refluxing cyclohexane, toluene, etc. (*c*) By using the $TiCl_4$[66] or Bu_2SnCl_2[67] procedures. In most cases, these chiral imines were used without any further purification in the subsequent Michael additions. However, when necessary, they can be purified by distillation under reduced pressure. Although most of these imines are reasonably stable, some of them, like **104**, **263** and **264**, exhibit an exceptionally low thermal stability. Thus imine **264** undergoes a facile [3,3] sigmatropic rearrangement (implicating in fact the more substituted enamine tautomer), detectable at room temperature, leading to compound **265**[35].

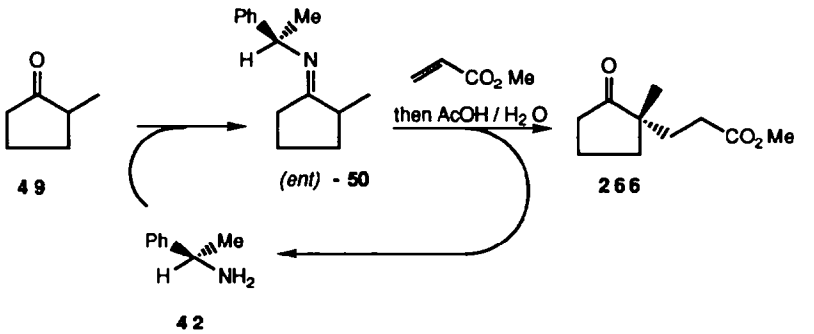


104 **263** **264** **265**

Procedures for addition of chiral imines to electrophilic alkenes depend greatly on the nature of the two partners (see chapter 3). The "one pot", *one mole-scale conversion* [**49** → **266**], using standard laboratory equipement, is given as an example.

Imine (*ent*)-**50** was prepared azeotropically from 98 g (1 mole) of 2-methylcyclopentanone **49** and 121 g (1 mole) of (*R*)-1-phenylethylamine **42** (98 % ee) in 400 mL of toluene (Dean-Stark trap, 12 h of reflux

under dry nitrogen). Most of the toluene was removed by distillation at atmospheric pressure and, after cooling at room temperature, 103g (1.2 mole) of dry methyl acrylate were added. The resulting mixture was kept at room temperature for 7 days (in an alternative, less time-consuming procedure, the mixture was heated for 12h at 60°C). The excess of methyl acrylate was removed by distillation under reduced pressure (20 Torr). Acetic acid (72 g, 1.2 mole), water (400 mL) and MeOH (200 mL) were then added and the mixture was vigorously stirred for 2h. The solution was saturated with NaCl and thoroughly extracted with hexane. The combined organic layers were washed with 1N HCl, brine, and dried over magnesium sulfate. Solvents were removed under reduced pressure and the residue was distilled (0.1 Torr), leading to 167 g (91 % yield) of ketoester (*S*)-**266** (90 % ee). In addition 112 g (93 %) of unchanged chiral amine **42** were recovered from the combined aqueous layers, after neutralization with NaOH.

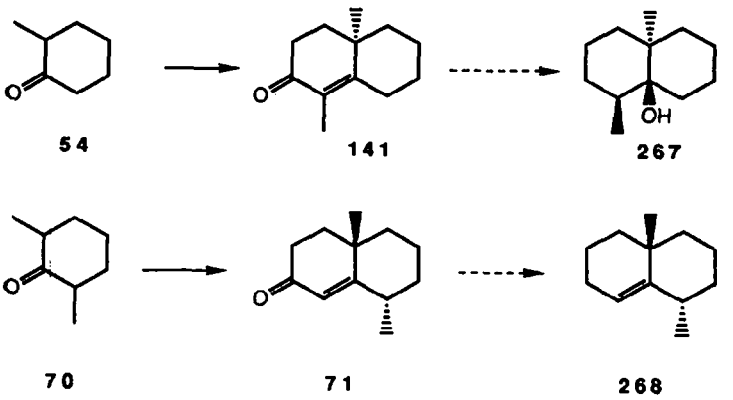


The enantiomeric purity of the chiral synthons obtained by using the present asymmetric Michael addition reactions is in general ≥ 90 %. This optical purity is suitable for most synthetic purposes. However, when necessary, "enantiomerically pure" synthons (ee ≥ 99 %) can be prepared through the recrystallization of an adequate derivative (for example the semicarbazone derivative in the case of **266**).

5.2 - Approaches to natural compounds

This section deals with the use of the aforementioned chiral synthons in approaches to natural products (and related compounds).

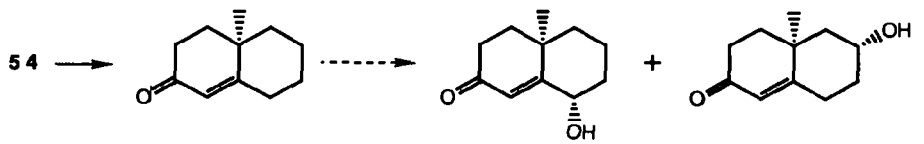
Octalone (*R*)-**141**, synthesized from 2-methylcyclohexanone **54**, (*S*)-1-phenylethylamine and MVK (65 % yield, 85 % ee) has been converted in 4 steps (40 % overall yield into the terpene (-)-geosmin **267**[28]; (*ent*)-(+)-geosmin has been prepared in a similar fashion[28]. (+)-Octalone **71**, derived from 2,6-dimethylcyclohexanone **70**, (*R*)-1-phenylethylamine and MVK (61 % yield, 73 % ee) was transformed, according to a know route, into naturally occurring (+)-octalin **268**[28].



54 **141** **267**

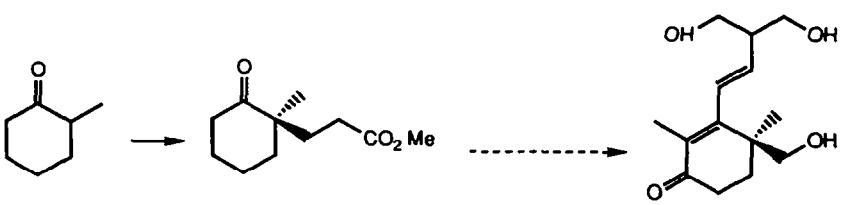
70 **71** **268**

Oxidative microbial conversions, induced by various fungal strains, of octalones (*S*,*S*)-**71**, (*S*)-**205** and (*ent*)-**205** have been studied[68]; by way of illustration octalone (*ent*)-**205** [prepared from **54**, (*R*)-1-phenylethylamine and MVK (74 % yield, 91 % ee)][2] furnished a mixture of hydroxylated metabolites **269** and **270**.



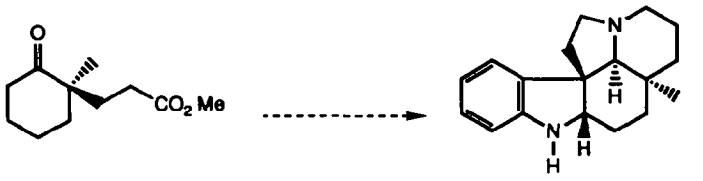
(ent) - **205** **269** **270**

Ketoester (*R*)-**55**, prepared from 2-methylcyclohexanone **54**, (*S*)-1-phenylethylamine and methyl acrylate (81 %, yield, 90 % ee) has been converted into (+)-cassiol **271**, a potent antiulcerogenic agent (15 steps, 8.5 % overall yield)[69].

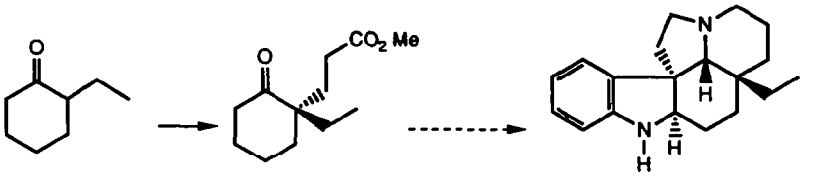


54 **55** **271**

Also ketoester **55** has been converted into (-)-19-nor-aspidospermidine **272**[32,70] (19 steps, 5 % overall yield). By using the same methodology, naturally occurring (+)-aspidospermidine **273** has been prepared from ketoester (*ent*)-**57**, itself derived from 2-ethylcyclohexanone **56**, (*R*)-1-phenylethylamine and methyl acrylate (80 % yield, 88 % ee)[24].

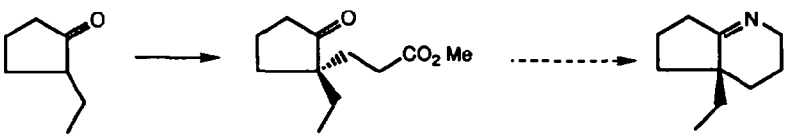


55 272



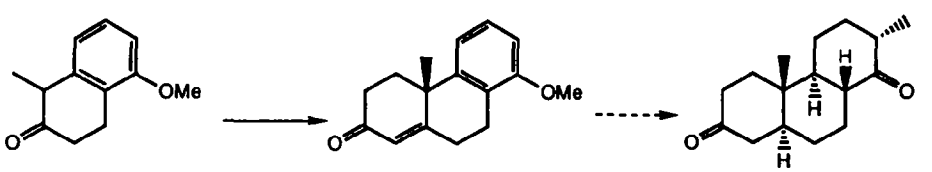
56 (ent) - 57 273

Ketoester (*ent*)-53, prepared from 2-ethylcyclopentanone **52**, (*R*)-1-phenylethylamine and methyl acrylate (80 % yield, 90 % ee), has been recently transformed in 4 steps into compound (*R*)-**274**[71], a pivotal subunit in the synthesis of the indole alkaloid vallesamidine[72].

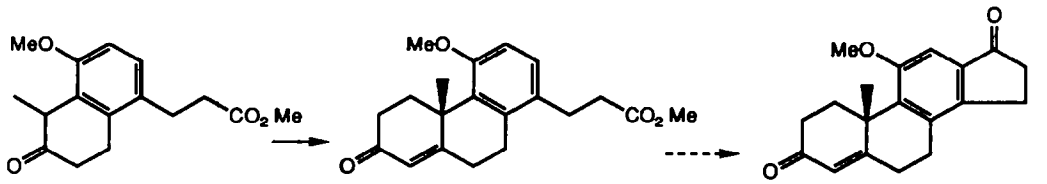


52 (ent) -53 274

Phenanthrone (*S*)-**77**, derived from tetralone **76**, (*R*)-1-phenylethylamine and MVK (73 % yield, 92 % ee) has been transformed in 9 steps (19 % overall yield) into tricyclic compound **275**, a potential [ABC]-type intermediary in the synthesis of steroids [29]. Likewise, the C-aromatic steroid (*S*)-**276** has been prepared in two steps (55 % yield), from (*S*)-**83**, derived from tetralone **82**, (*R*)-1-phenylethylamine and MVK (88 % ee, but only 25 % yield due to the formation of a regioisomer, see sections 3.1 and 4.3)[5].

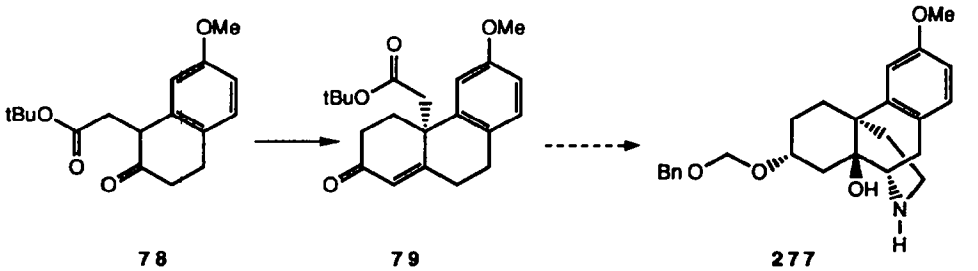


76 77 275



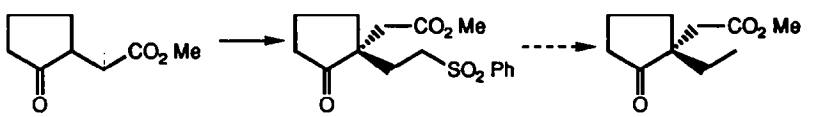
82 **83** **276**

Phenanthrone (*S*)-**79**, prepared from tetralone **78**, (*S*)-1-phenylethylamine and MVK (76 % yield, 95 % ee) has been converted into 14-hydroxyisomorphinan **277** (8 steps, 25 % overall yield)[30].



78 **79** **277**

Adduct (*S*)-**65**, derived from ketoester **64**, (*R*)-1-phenylethylamine and phenyl vinyl sulfone (74 % yield, 91 % ee), has been transformed in two steps into compound (*R*)-**278** (65 % yield)[23]. Conversion of the latter derivative into *Aspidosperma* and *Hunteria* alkaloids, according to the Fuji's methodology, is currently under investigation[23].

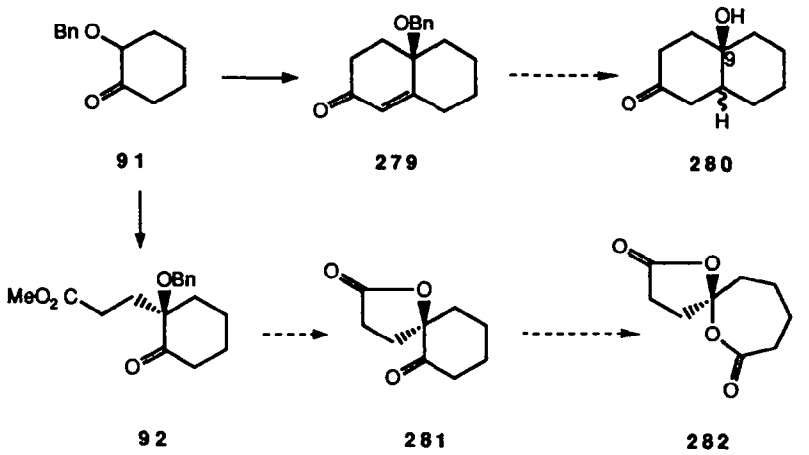


64 **65** **278**

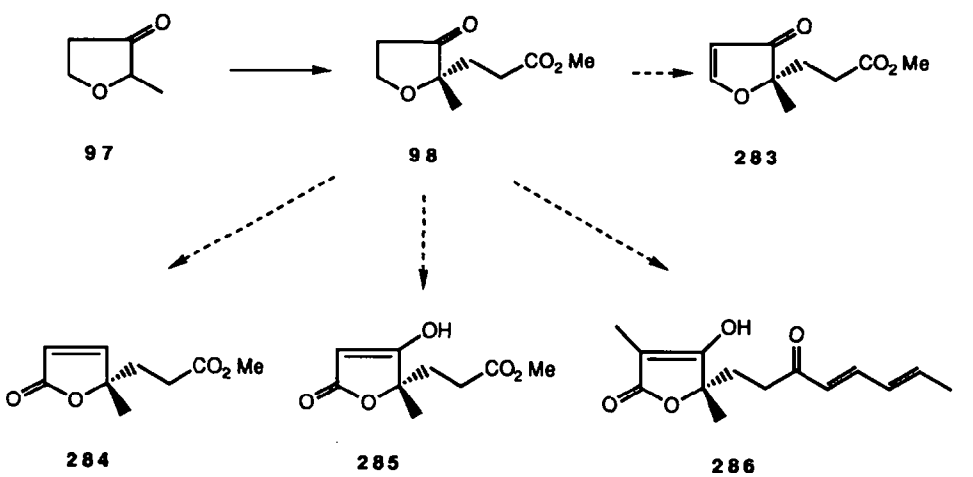
Octalone (*R*)-**279**, prepared from 2-benzyloxycyclohexanone **91**, (*R*)-1-phenylethylamine and MVK (75 % yield, 97 % ee), has been converted quantitatively into a *cis/trans* mixture of decalones (9*R*)-**280**[34].

Ketoester (*R*)-**92**, prepared in a similar fashion (80 % yield, 97 % ee), was transformed into spirolactone (*R*)-**281** (2 steps, 75 % yield) and spiro-bislactone (*R*)-**282** (85 % yield from **281**)[34].

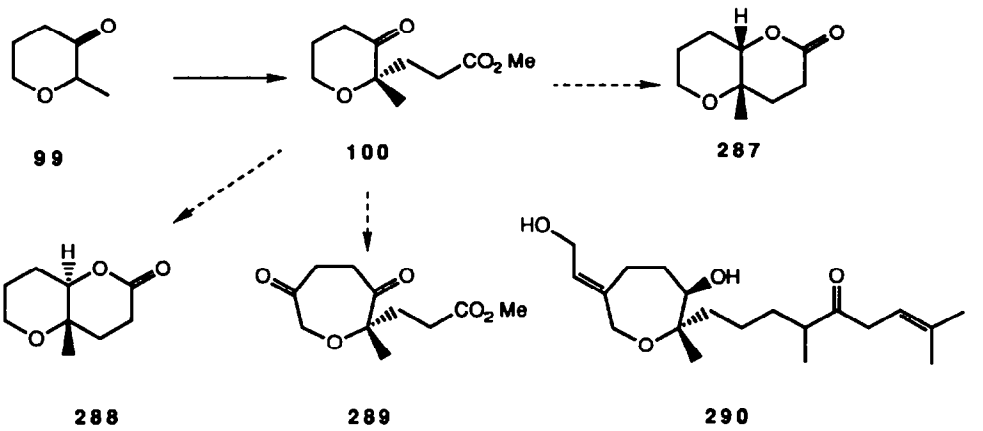
These compounds would constitute useful chiral synthons, since the spirolactone moiety and related spiroketal unit are key structural features of many natural products.



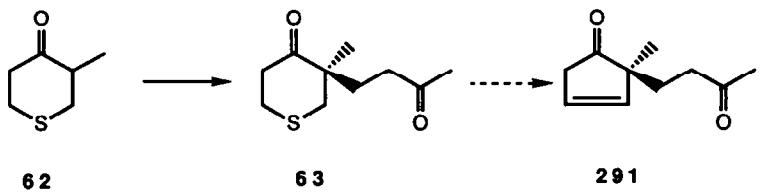
Adduct (*S*)-**98**, obtained from dihydrofuranone **97**, (*R*)-1-phenylethylamine and methyl acrylate (80 % yield, 95 % ee) has been converted into (*S*)-**283** (2 steps, 75 % yield) and (*S*)-**284** (4 steps, 50 % yield)[36]. Tetronic acid derivative (*S*)-**285** has been prepared from **98** in 5 steps (40 % overall yield)[24]. Adduct **98** has also been converted into the mycotoxin (-)-vertinolide **286** in 12 steps (11 % overall yield)[24].



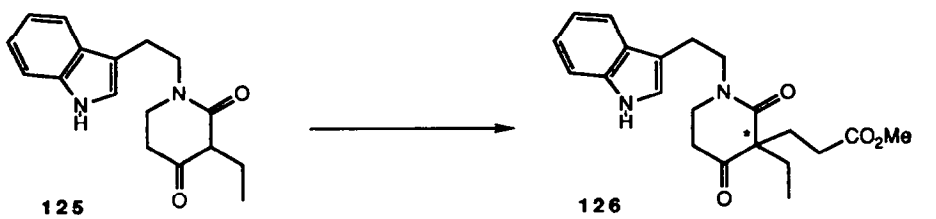
Adduct (*S*)-**100**, prepared from pyranone **99**, (*R*)-1-phenylethylamine and methyl acrylate (72 % yield, 98 % ee) has been transformed stereoselectively into pyrano-pyrans *cis*-**287** and *trans* -**288**[37]. The same adduct has also been converted in 7 steps into seven-membered compound (*S*)-**289**, a potential intermediary for the synthesis of the antifertility agent zoapatanol **290**[37].



Diketone (*R*)-**63**, derived from thianone **62**, (*S*)-1-phenylethylamine and MVK (38 % yield, 65 % ee) has been converted, *via* Ramberg-Bäcklund reaction, into cyclopentenone (*S*)-**291** (3 steps, 47 % overall yield)[26].

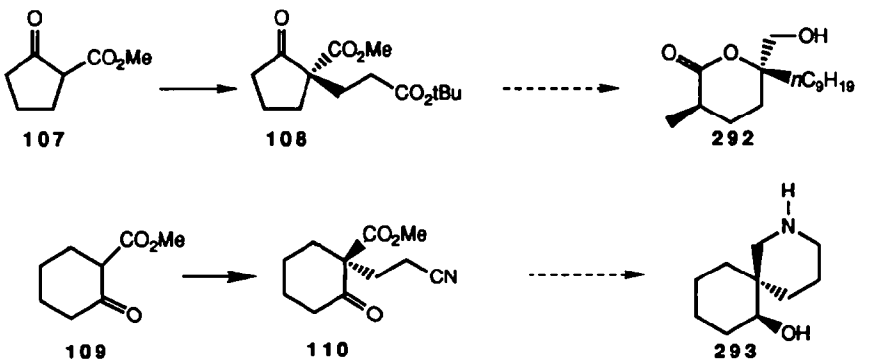


Optically active adduct **126** has been prepared from ketolactam **125**, (*S*)-1-phenylethylamine and methyl acrylate (63 % yield, 90 % ee, configuration not determined)[43]. Several approaches to *Vinca* alkaloids, starting from **126**, are currently under investigation.

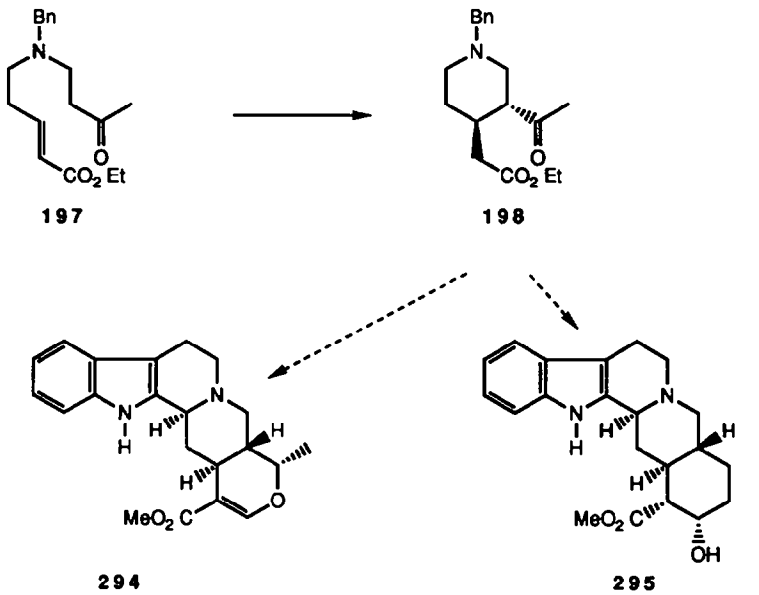


Adduct (*S*)-**108**, prepared from ketoester **107**, (*S*)-1-phenylethylamine and *tert*-butyl acrylate (60 % yield, 90 % ee) has been converted in 10 steps into (-)-malyngolide **292**[45].

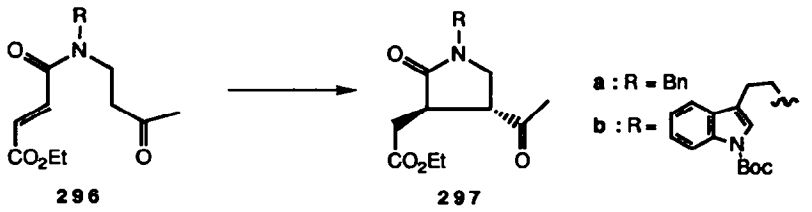
Adduct (*S*)-**110**, derived from ketoester **109**, (*S*)-1-phenylethylamine and acrylonitrile (85 % yield, 90 % ee) has been transformed in 4 steps into (-)-nitramine **293**[39].



Piperidine (*R*,*R*)-**198** has been synthesized by intramolecular Michael-type cyclization of ketoenoate **197**, in the presence of (*R*)-1-phenylethylamine (80 % yield, 90 % ee)[50].This compound has been converted further into the known, key intermediates for the syntheses of (-)-ajmalicine **294**[50] and (+)-yohimbine **295**[73].



By treatment with (*S*)-1-phenylethylamine, the acyclic precursors **296** led to pyrrolidones (*S*,*S*)-**297** (84-95 % yield, 63-65 % ee)[74]. Compounds **297a** and **297b** would constitute useful chiral building blocks for the syntheses of α-allo-kainic acid and *Strychnos* alkaloids, respectively.



6 - CONCLUDING REMARKS

It is well established that the two antipodal forms of a given chemical mediator interact often very differently with biological receptors[75]. This observation, of fundamental importance for drug development (the enantiomers of chiral molecules used in therapeutics frequently exhibit undesirable effects), has precipitated worldwide research activity in the field of the *control of enantioselectivity*.

In the recent past, numerous elegant enantioselective syntheses have been achieved, integrating the elements of the "chiral pool". Nevertheless such a methodology suffers greatly from the limited selection of the natural chiral starting materials. Much more powerful is *asymmetric synthesis*, because of its versatility and general application.

An impressive number of enantioselective reactions have thus been developed the last decade or so, which can be broadly classified into two main groups. The former category is related to the reductive or oxidative processes which implicate a sp^2-type prochiral site on the substrate.These include some of the most useful asymmetric reactions known to date, for example the asymmetric catalytical hydrogenation or the Brown asymmetric hydroboration of alkenes, and the Sharpless asymmetric epoxidation of allylic alcohols[76]. In the second group are found the enantioselective processes that contribute to the elaboration of the framework of the target molecules (essentially C-C bond forming reactions). Though highly promising, the latter strategy remains with a few exceptions a challenging problem. Indeed, *practical methods* (efficient, simple and economical)[77] for the enantioselective creation of C-C bonds are scarce.

In this regard, the asymmetric Michael addition reactions using chiral imines which we have presented in this review offer the following major advantages :

- the chemical yields are good to excellent,
- the process is highly regioselective (the alkylation taking place at the more substituted α-side of the imine),
- the enantiomeric excesses are high (up to 98 % , generally ≥ 90 %),
- the experimental protocols are simple and the reaction conditions are exceptionally mild (in most cases, the additions were performed at room temperature under neutral conditions),
- the chiral auxiliary, 1-phenylethylamine, is a common chemical (both isomers of this amine are commercially available in high enantiomeric purity and at moderate price),
- this chiral inducer can be very easily and nearly quantitatively recovered without any loss of optical activity.

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