THE SYNTHESIS AND REACTIONS OF HETEROCYCLES UNDER HIGH PRESSURES: Part II

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Abstract - Recent advances in synthesis and reactions of
heterocycles under high pressures are described.

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1. INTRODUCTION

High pressure technology has already become a routine technique for synthetic chemists.[1] This technique (0.1 - 2 GPa) is applied mainly in liquid systems and to those reactions which show large and negative volumes of activation. It is a valuable tool which can be employed to stimulate organic reactions that take place too slowly, require too high temperatures or are hindered by steric or electronic factors. It may also be used in order to increase selectivity among alternative products since both regio- and stereo-selectivities change with pressure if there is a difference in activation volumes. Generally, formation of a bond, concentration of charge, and an ionized transition state leading to a negative volume of activation, whereas bond cleavage, dispersal of charge, neutralization of the transition state and diffusion control lead to a positive volume of activation. Thus, the application of high pressure accelerates (a) reactions in which the number of molecules decreases on product formation (*e.g.* cycloadditions and condensations), (b) reactions which take place through dipolar transition states (*e.g.* Menschutkin reaction, aromatic electrophilic and nucleophilic substitutions), and (c) sterically hindered reactions.

2. CYCLOADDITIONS TO HETEROCYCLES

High pressure is of special value in improving or even promoting the cycloaddition reactions that take place in spite of steric hindrance or unfavourable electronic factors. Therefore, many successful synthesis of compounds otherwise unavailable have been reported.

2.1 HETEROCYCLES AS DIENES

The high-pressure Diels-Alder addition of the 2,5-disubstituted furan (1) to 1-cyanovinyl acetate (2) gave almost quantitatively the single diastereomeric adduct (3).[2] This reaction is one of the key-steps in the synthesis of sesquiterpenes containing a 6,9-epoxycyclodeca[b]furan structural element.
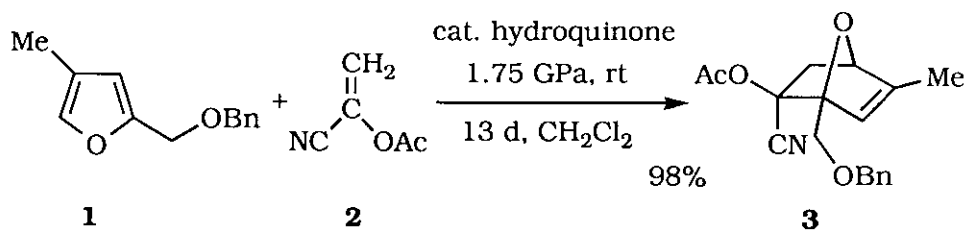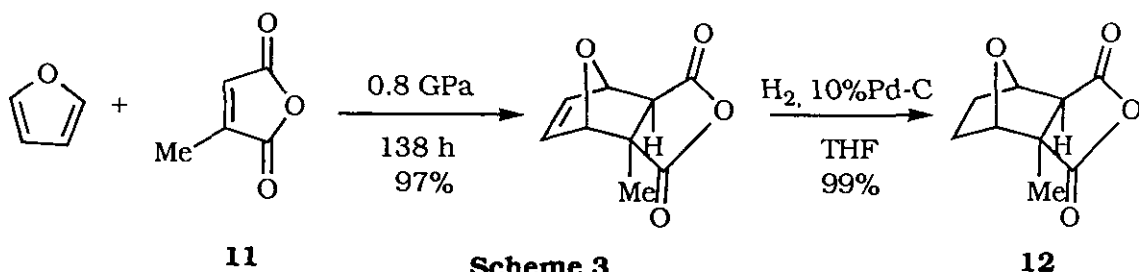

Scheme 1

The high-pressure Diels-Alder cycloaddition of 2,5-dimethylfuran (5) with DMAD (4) gave the adduct (6) which with the tropone (7) gave the adduct (8).[3] Thermolysis of 8 gives the homo-barrelone (9) and the furan (10), the 3,4-atoms of the original furan being transfered to 7; 6 acted as an acetylene synthon. In contrast, both of the double bonds of 6 reacted with cycloheptatriene at 1.0 GPa and 100 °C to give four products.[3]
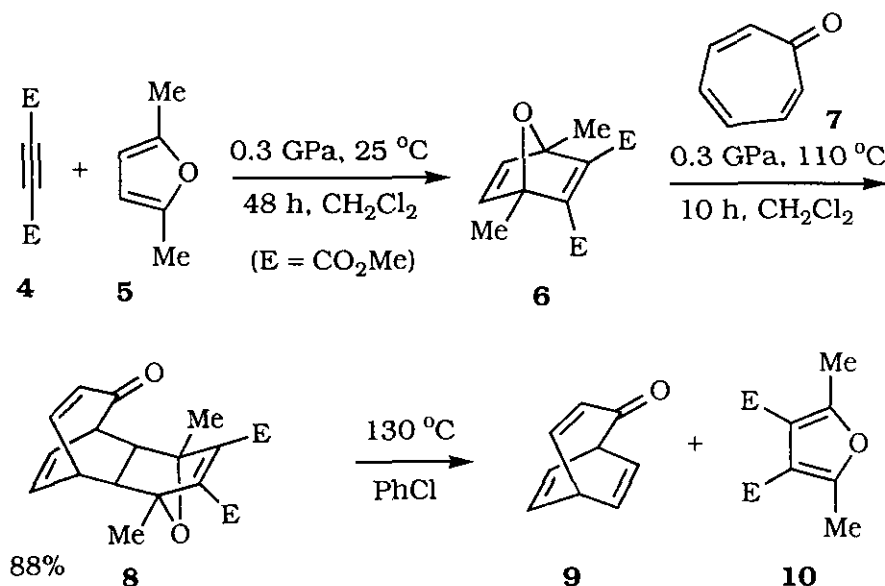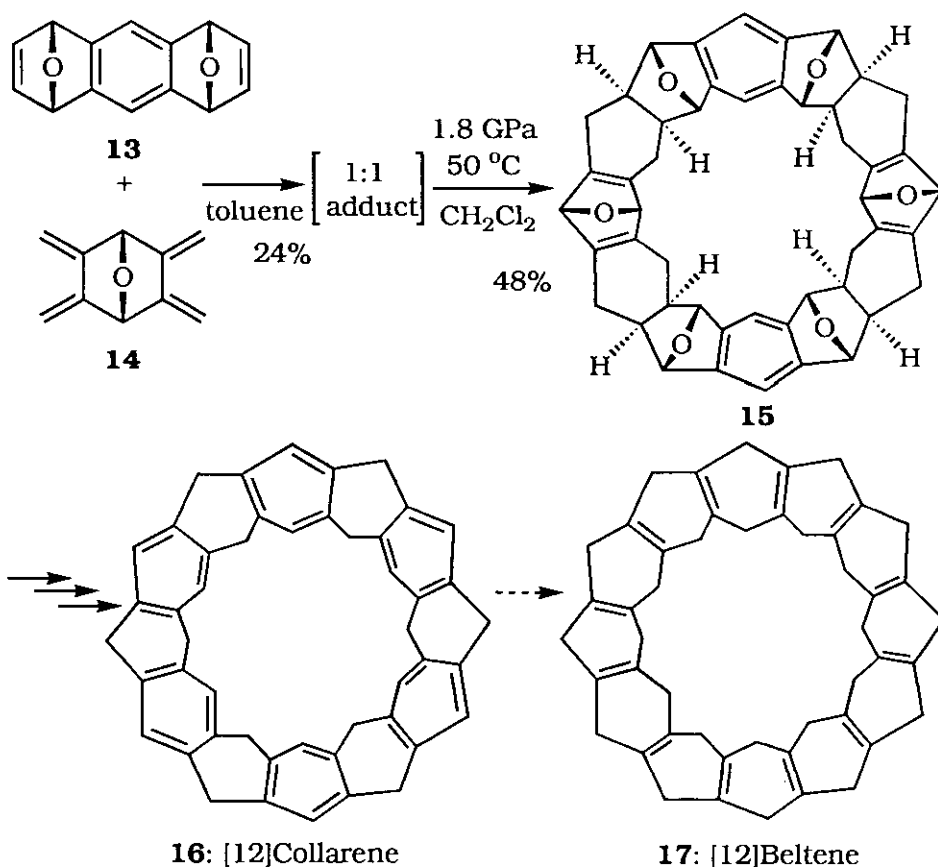

Scheme 2

(±)-Palasonin (12) was synthesised from citraconic anhydride (11) and furan at 0.8 GPa for 138 h, followed by hydrogenation over Pd-C.[4] Neither high temperatures nor Grieco reagent conditions (LiClO$_4$/Et$_2$O/H$_2$O) caused combination at atmospheric pressure.


Scheme 3

Reaction of **13** with the oxygen-bridged "bis(diene)" (**14**) afforded the corresponding 1:1 adduct which, under high pressure, gave the macrocyclic compound (**15**). This was a precursor for the synthesis of [12]collarene (**16**) and possibly of [12]beltene (**17**).[5a] Starting with **14**, the bicyclic molecular belt (**18**) has also been synthesised under high pressure.[5b]

Similar macrocycles containing norbornane and benzene or naphthalene spacer-units were also be prepared by repetitive high pressure Diels-Alder cycloadditions.[6]
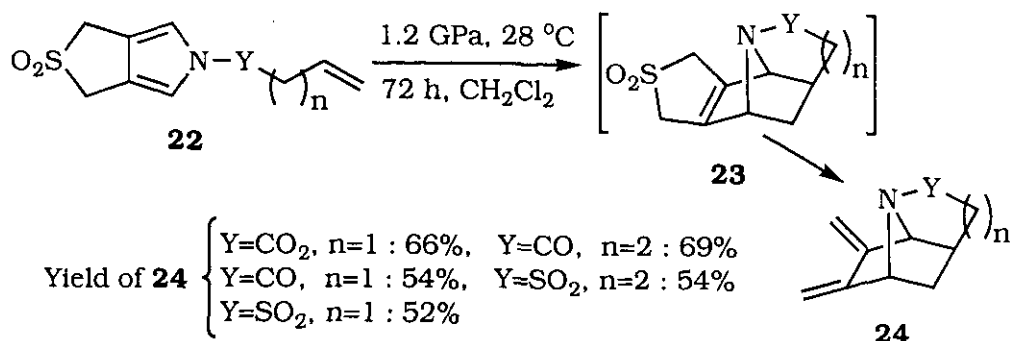

Scheme 4

Scheme 5   **18**
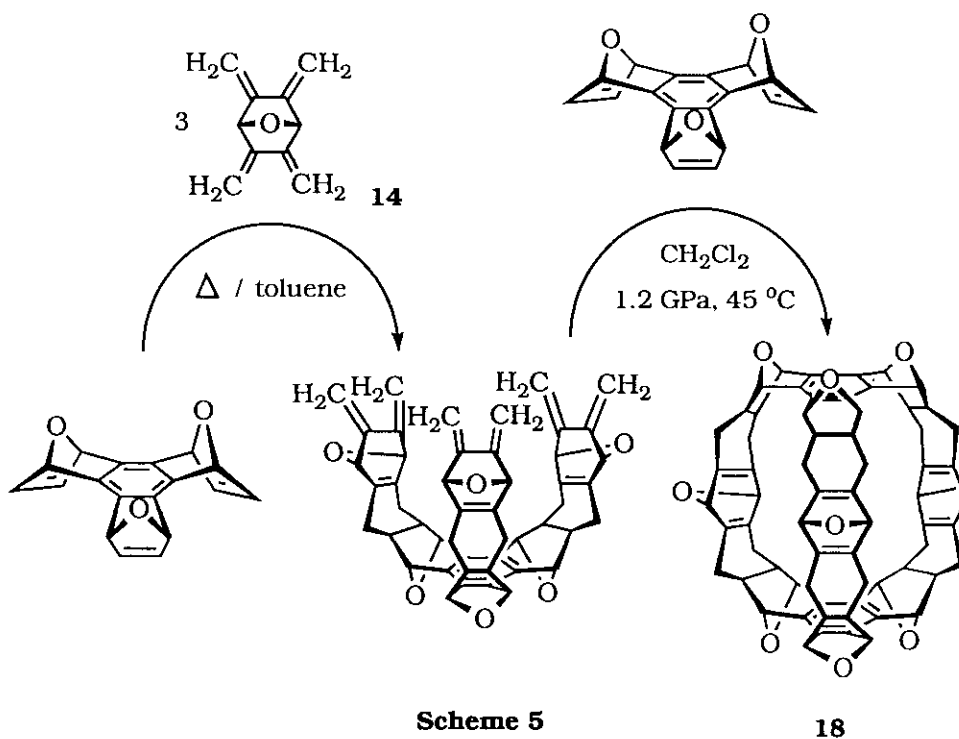
$4H$, $6H$-thieno[3,4-c]pyrrole 5,5-dioxide (**19**)[7a] with DMAD (**4**), *via* a similar reaction to that of 1-methylpyrrole at ambient pressure,[7b] gave either **20** or **21** depending on the reaction conditions. Both loss of sulfur dioxide and pyrrole elimination can occur. They differ from the mono- and bis-adducts obtained at ordinary pressure.
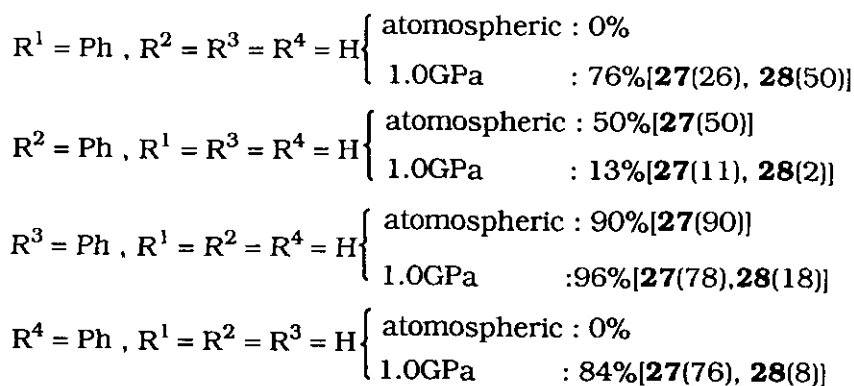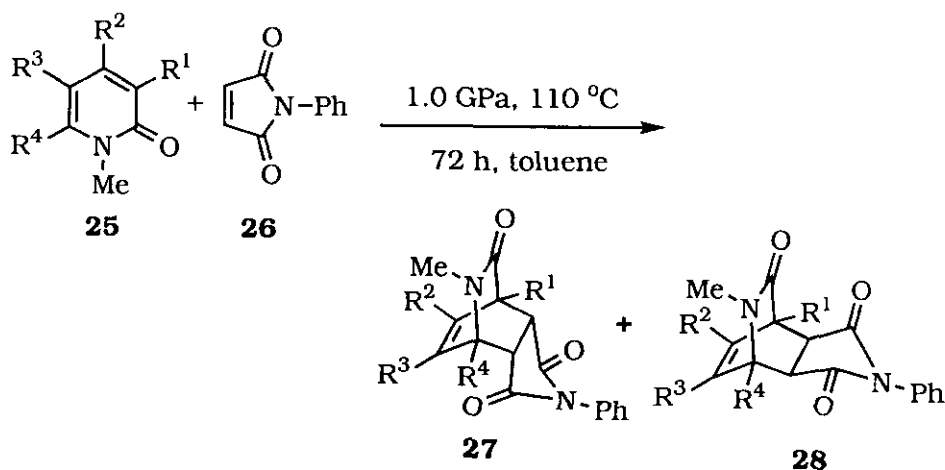

($E = CO_2Me$, $R = Bn$)

Scheme 6   **21**
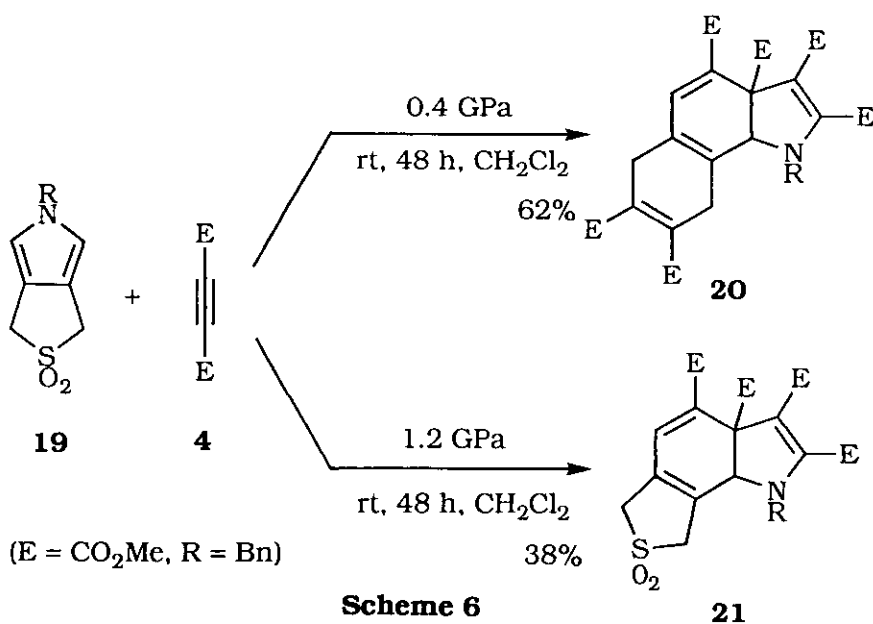
The pyrrolesulfolenes (**22**) gave, under high pressure, the intramolecular Diels-Alder cycloadducts (**23**) which lost sulfur dioxide to give the s-cis-diene (**24**).[7c]
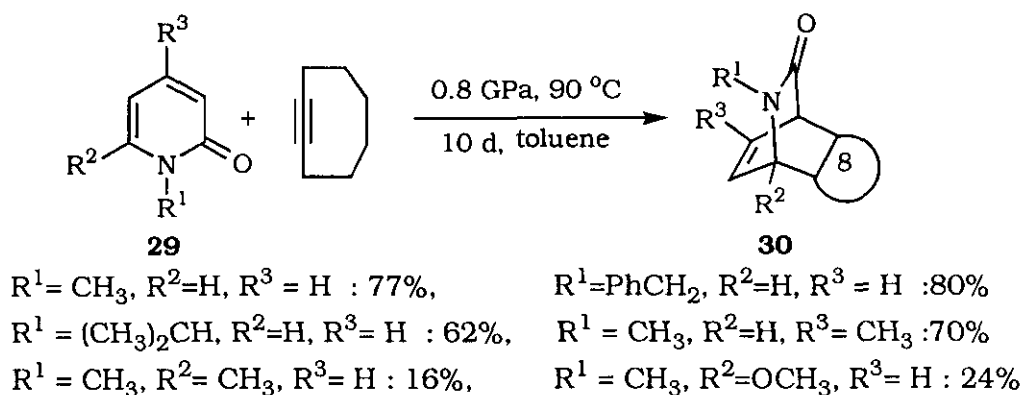

$$\text{Yield of 24} \begin{cases} Y=CO_2, \ n=1 : 66\%, \quad Y=CO, \ n=2 : 69\% \\ Y=CO, \ n=1 : 54\%, \quad Y=SO_2, \ n=2 : 54\% \\ Y=SO_2, \ n=1 : 52\% \end{cases}$$

Scheme 7

The high pressure Diels-Alder reactions of the 2(1H)-pyridones (**25**)   with N-phenylmaleimide (**26**) gave mixtures of the *endo* and *exo* cycloadducts (**27**) and (**28**). They are possible intermediates for iboga alkaloid synthesis.[8]
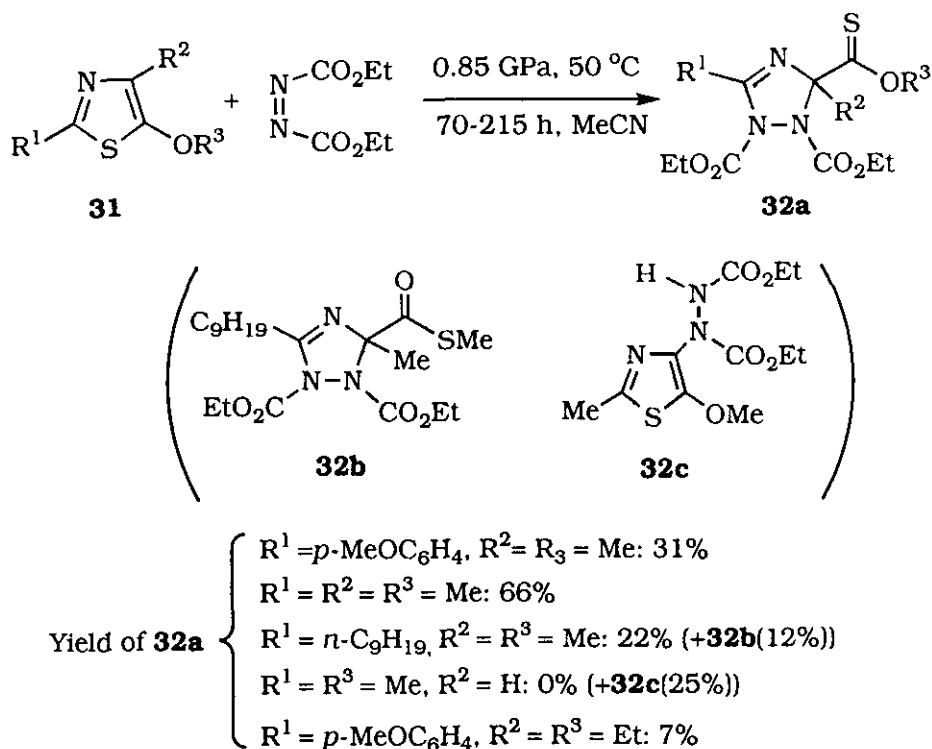

$R^1 = Ph$, $R^2 = R^3 = R^4 = H \begin{cases} \text{atomospheric : 0\%} \\ \text{1.0GPa} \qquad : 76\%[\mathbf{27}(26), \mathbf{28}(50)] \end{cases}$

$R^2 = Ph$, $R^1 = R^3 = R^4 = H \begin{cases} \text{atomospheric : 50\%}[\mathbf{27}(50)] \\ \text{1.0GPa} \qquad : 13\%[\mathbf{27}(11), \mathbf{28}(2)] \end{cases}$

$R^3 = Ph$, $R^1 = R^2 = R^4 = H \begin{cases} \text{atomospheric : 90\%}[\mathbf{27}(90)] \\ \text{1.0GPa} \qquad :96\%[\mathbf{27}(78), \mathbf{28}(18)] \end{cases}$

$R^4 = Ph$, $R^1 = R^2 = R^3 = H \begin{cases} \text{atomospheric : 0\%} \\ \text{1.0GPa} \qquad : 84\%[\mathbf{27}(76), \mathbf{28}(8)] \end{cases}$

Scheme 8

Some 2(1*H*)-pyridones (**29**) reacted, at 0.8 GPa and 90 °C, with cyclooctyne to give the stable bridged cycloadducts (**30**).[9]

29

R¹= CH₃, R²=H, R³ = H : 77%,

R¹ = (CH₃)₂CH, R²=H, R³= H : 62%,

R¹ = CH₃, R²= CH₃, R³= H : 16%,

30

R¹=PhCH₂, R²=H, R³ = H :80%

R¹ = CH₃, R²=H, R³= CH₃ :70%

R¹ = CH₃, R²=OCH₃, R³= H : 24%

Scheme 9

An unusual reaction is that of the 5-alkoxythiazoles (**31**) which with diethyl azodicarboxylate at high pressure, gave the triazoles (**32**) in low to moderate yields.[10]

31

32a

32b   **32c**

Yield of **32a**

R¹ =*p*-MeOC₆H₄, R²= R₃ = Me: 31%

R¹ = R² = R³ = Me: 66%

R¹ = *n*-C₉H₁₉, R² = R³ = Me: 22% (+**32b**(12%))

R¹ = R³ = Me, R² = H: 0% (+**32c**(25%))

R¹ = *p*-MeOC₆H₄, R² = R³ = Et: 7%

Scheme 10

2,5-Bis(trifluoromethyl)-1,3,4-thiadiazole (**33**) underwent high pressure addition to norbornene to give the product (**34**).[11a] Analogous high pressure Diels-Alder reactions of tetramethyl-4*H*-pyrazole, leading to the interesting compounds presenting nonbonding interactions between two isolated double bonds, have been described.[11b]
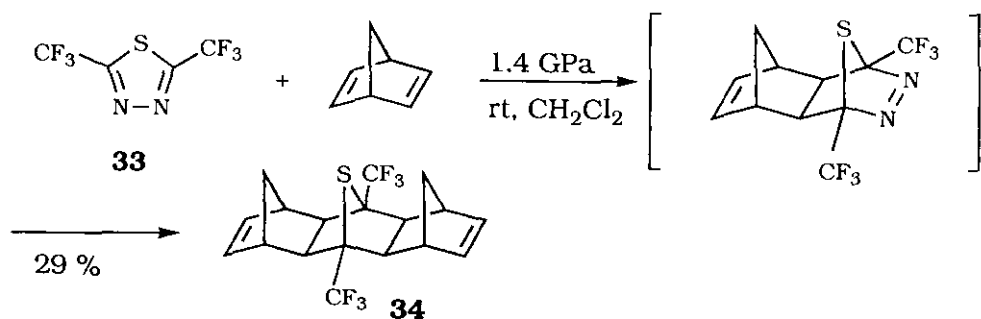
Scheme 11

## 2.2 HETEROCYCLES AS DIENOPHILES

The high-pressure Diels-Alder reactions have been used for the synthesis of some supramolecules. For example, the "bis(diene)" (**35**) reacted with the "bis(dienophile)" (**36**) and afforded, by repetitive Diels-Alder reactions, the ladder-type oligomers (**37**).[12]

37(n = 1): 41%

37(n = 5): 18%
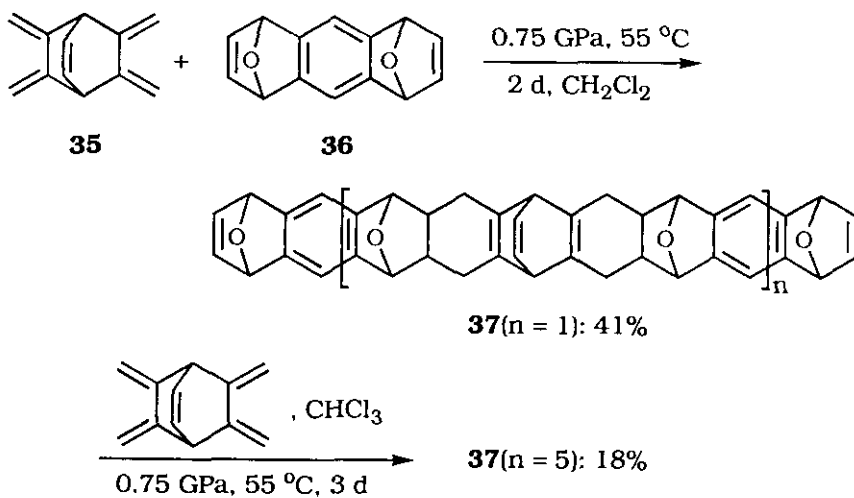
Scheme 12

Trifluoromethyldioxinone (**38**) with Danishefsky's diene at 1.1 GPa and room temperature gave a single adduct, the precursor of the enone (**39**).[13a] Similarly, good diastereoselectivity was also observed in the high pressure Diels-Alder reactions of some chiral dioxinones with *N*-phenylmaleimide.[13b]
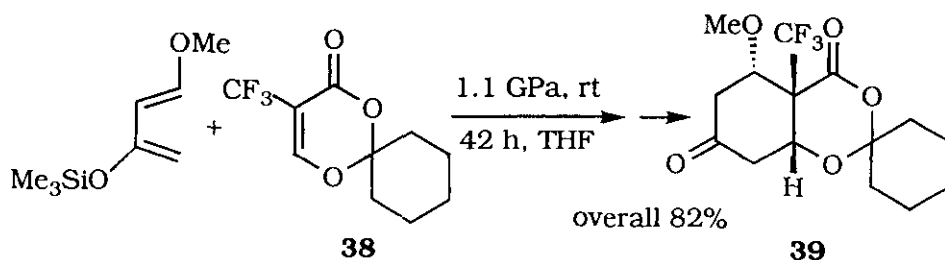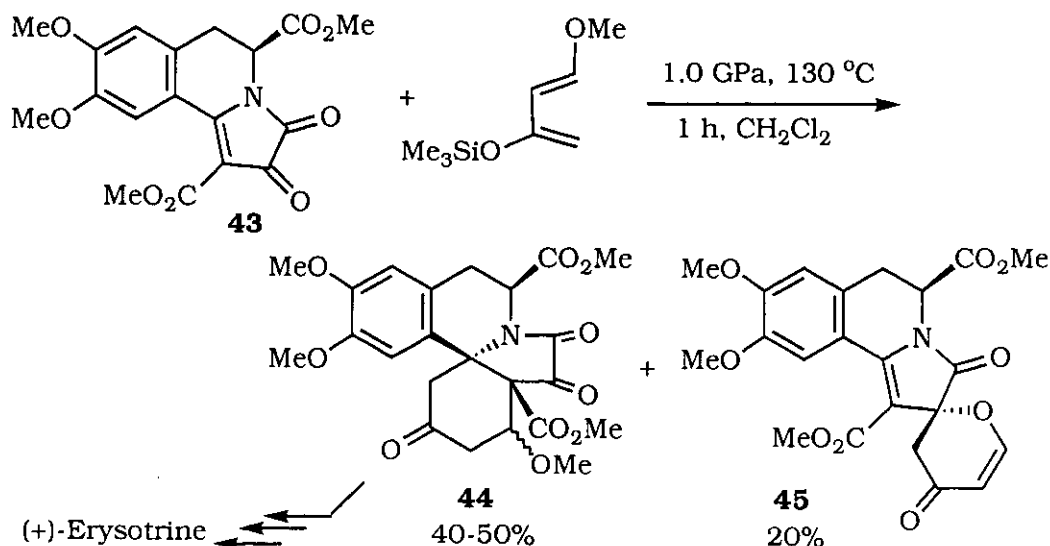

Scheme 13

Enantiomerically pure compounds can be obtained by high-pressure cycloadditions. For example, the high-pressure Diels-Alder reaction of the chiral dioxinone (**40**) with cyclopentadiene gave the *exo* adduct (**41**) along with a small amount of the *endo* adduct (**42**).[14]
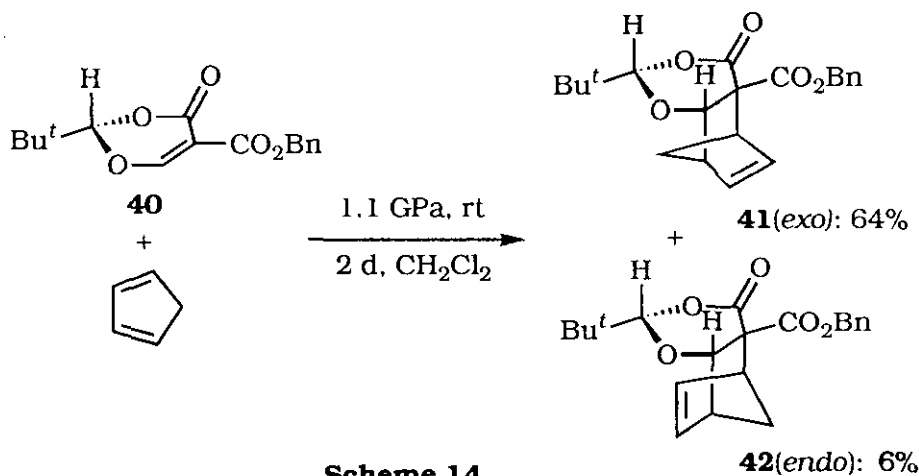
Scheme 14

The asymmetric Diels-Alder reaction of the chiral dienophile (**43**) with Danishefsky's diene gave the adduct (**44**), a key intermediate in the total synthesis of the alkaloid (+)-erysotrine, and some **45**.[15]
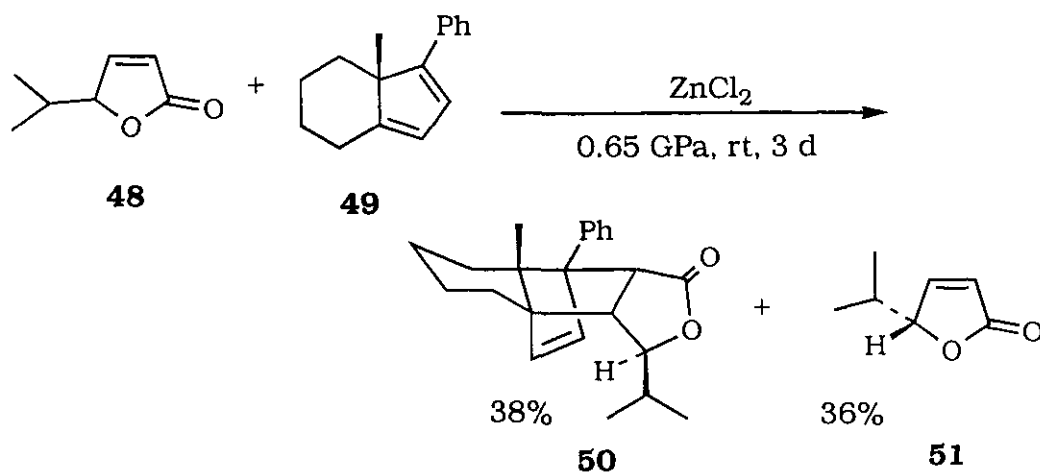
Scheme 15

In spite of significant steric hindrance, methyl palustrate (**46**) reacted, at 1.0 GPa and 80 °C, with *N*-phenylmaleimide to give the adduct (**47**).[16]
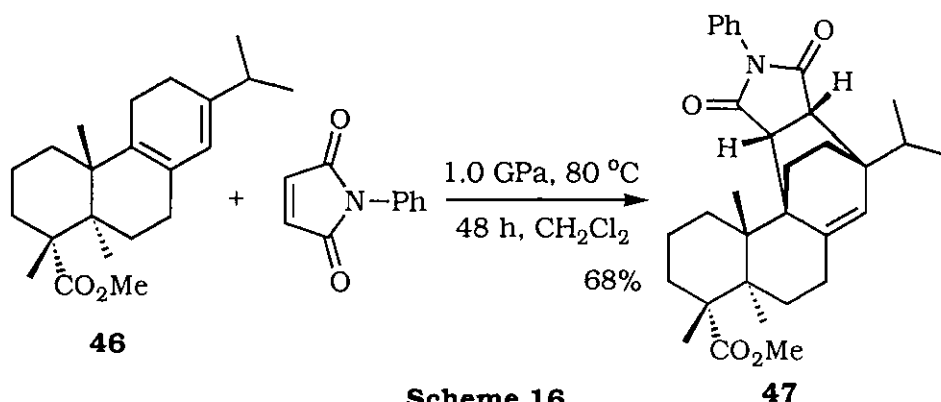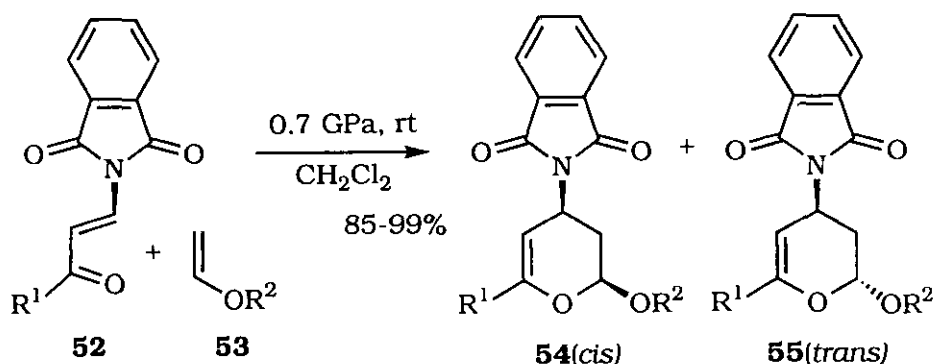

Scheme 16

High pressure has been used for kinetic resolution of chiral dienophiles; this technique did not only lead to very high ees but also provided very pure products in high yields. For example, the racemic butenolide (**48**) with the diene (**49**) yielded the adduct (**50**) and the enantiomerically pure (*R*)-butenolide (**51**), respectively. Only the enantiomer with the smaller hydrogen atom in the interior of the bicyclic cave of the molecule and the larger substituent pointing outside combined with **49**.[17] The adduct (**50**) underwent thermal retro-Diels-Alder reaction to give the corresponding (S)-butenolide.

Scheme 17

2.3 SYNTHESIS OF HETEROCYCLES

The hetero Diels-Alder reactions of the enamino ketones (**52**) with the vinyl ethers (**53**) gave, with very good yields, the cycloadducts (**54**) and (**55**) at ambient pressure.[18a] However, these cycloadditions showed a remarkable increase in diastereoselectivity in favour of the *cis* adducts (**54**) when performed at higher pressure and lower temperature.
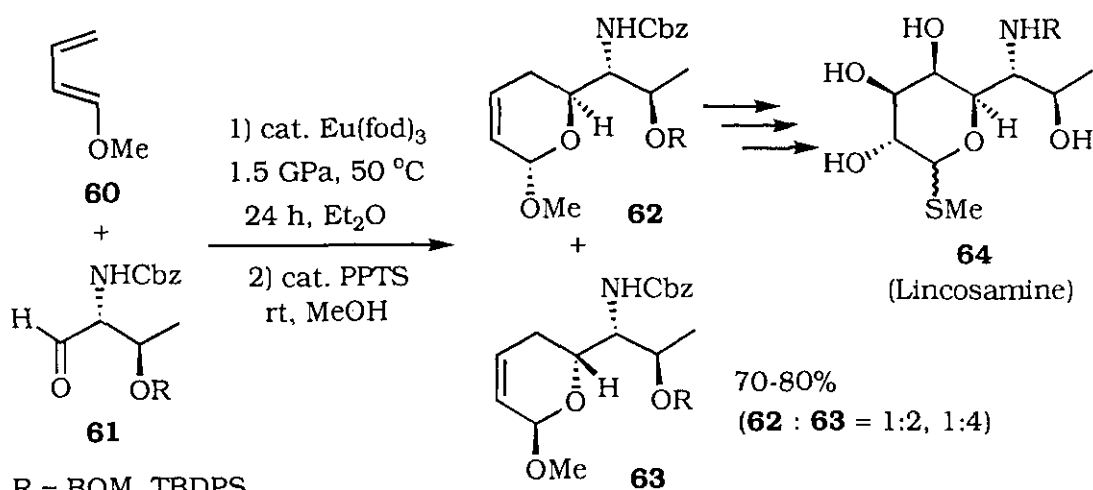

Scheme 18

High pressure can increase the enantioselectivity in Diels-Alder reactions catalysed by chiral Lewis acids. Thus, in the presence of the chiral titanium Lewis acid (**57**), the intramolecular hetero-Diels-Alder reaction of benzylidene compound (**56**) gave the two enantiomeric bridged cycloadducts (**58**) and (**59**). The compound (**59**) was formed preferentially and both yield and enantioselectivity were increased under high pressure.[18b]

0.1 MPa; **59**: 50% (4.5% ee)
0.5 GPa; **59**: 89% (20.4% ee)

Scheme 19
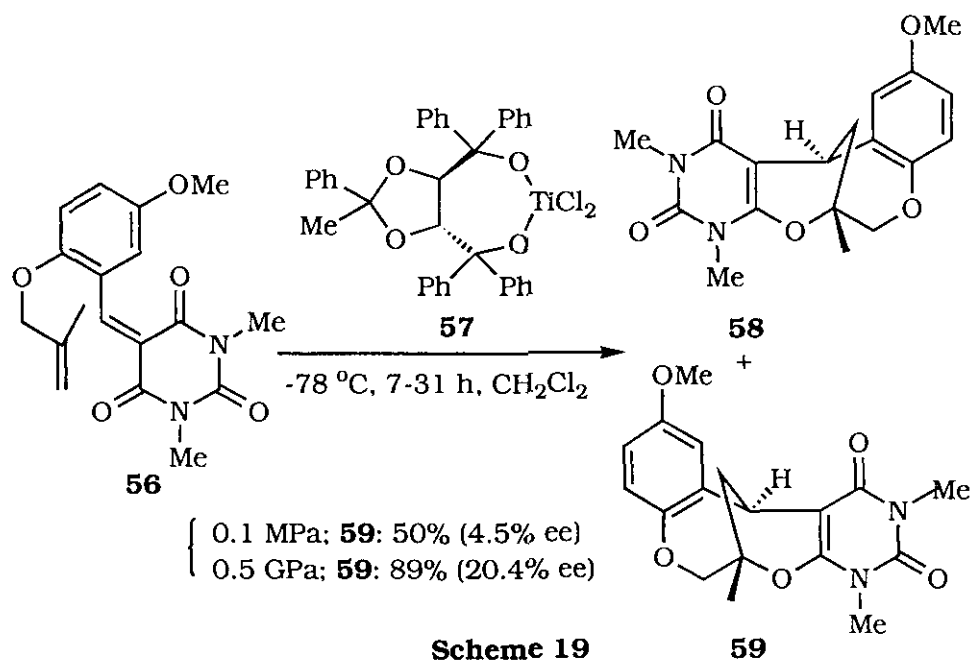
The Eu(fod)$_3$-mediated high pressure addition of *trans*-1-methoxy-1,3-butadiene (**60**) to
N,O-protected *D*-allo-threoninals (**61**) afforded mixtures of the possible diastereoisomers
(**62**) and (**63**).[19] The cycloadduct (**62**) can be converted to lincosamine (**64**).


1) cat. Eu(fod)$_3$
1.5 GPa, 50 °C
24 h, Et$_2$O

2) cat. PPTS
rt, MeOH

70-80%
(**62** : **63** = 1:2, 1:4)

R = BOM, TBDPS
PPTS : pyridinium *p*-toluenesulphonate

Scheme 20

2.4 1,3-DIPOLAR CYCLOADDITIONS

The functionalized methacrylate derivative (**66**) underwent regioselective 1,3-dipolar addition with benzyl azide (**65**) to give the triazoline (**68**), whereas a 1:1 mixture of regioisomeric triazolines (**67**) and (**68**) was obtained in refluxing benzene.[20]

	(yield)	67		68
1.2 GPa / 18 h / rt:	(83%)	<5	:	>95
0.1 MPa / 24 h / 80 °C :	(30%)	50	:	50
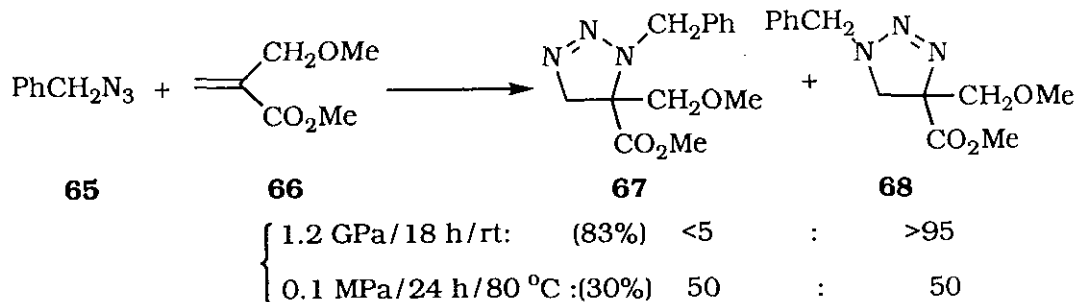
Scheme 21

The high pressure dipolar cycloadditions of di-*l*-menthyl benzylidenemalonate (**70**) to (Z)-*N*, α-diphenylnitrone (**69**) gave a mixture of four diastereoisomers (**71**).[21] The selectivity and the yield of one isomer from this reaction were considerably increased by high pressure.

|		[3S,5S]-5-*trans*	[3R,5R]-5-*trans*	[3R,5S]-5-*cis*	[3R,5R]-5-*cis*
1.0 GPa:	52%	76	15	6	3
reflux: (toluene)	<10%	54	26	10	10
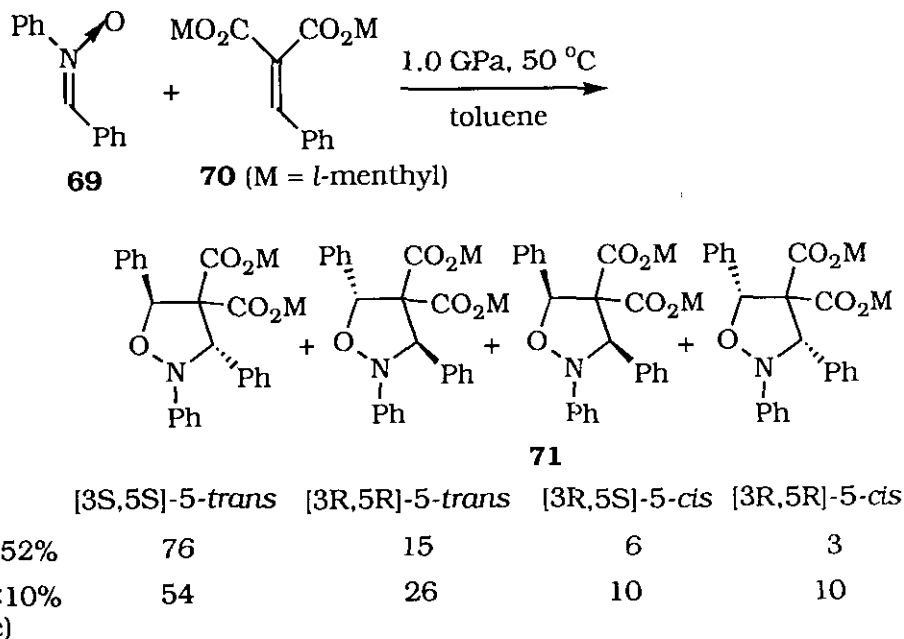
Scheme 22

The dipolar cycloadditions of various nitrones to trimethylsilylacetylene (**73**) took place smoothly under high pressure in excellent yields and high regioselectivity to give the Δ^4-isoxazolines which are intermediates in one synthesis of β-lactam antibiotics.[22] For example, the nitrone (**72**) with **73** gave the 5-silylisoxazoline (**74**).
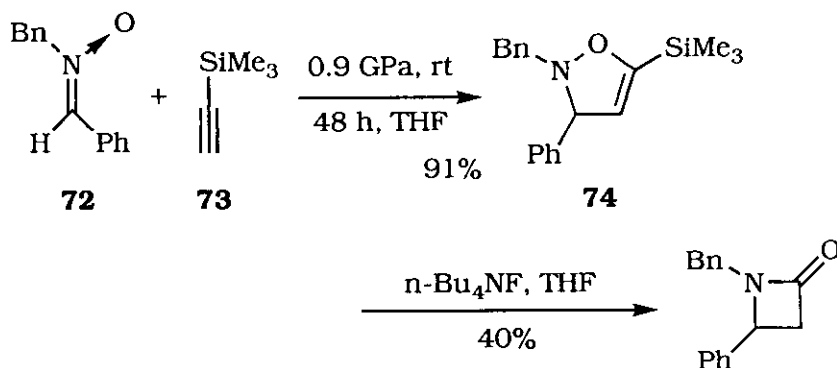
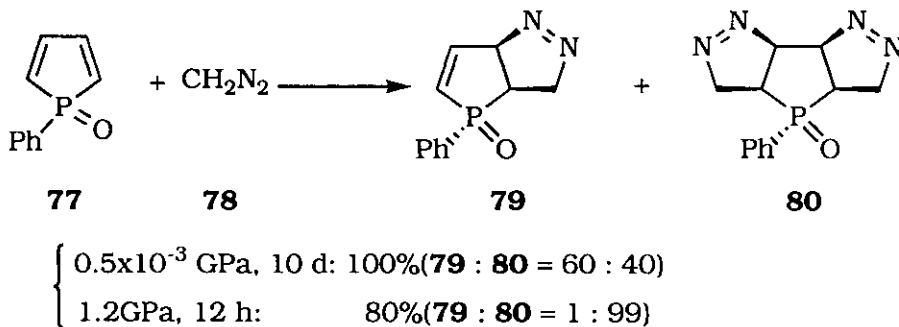**Scheme 23**

The above reaction also works with nitriles. For example, the nitrone (**69**) and benzonitrile (**75**) gave the corresponding 2,3-dihydro-1,2,4-oxadiazole (**76**).[23]
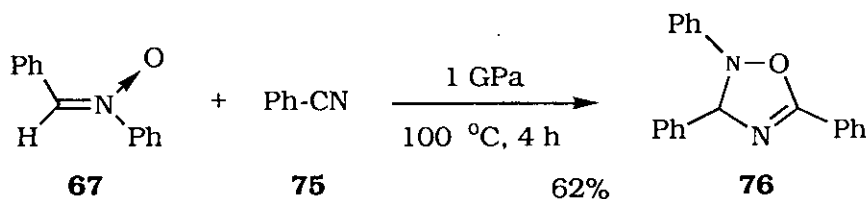
Scheme 24

The reaction of the phosphole 1-oxide (**77**) with diazomethane (**78**) at 1.2 GPa gave mainly the bis-adduct (**80**), whereas at ambient pressure the same reaction gave a mixture of the monoadduct (*anti*-**79**) and the same bis-adduct (**80**) in comparative ratio.[24]

$$\begin{cases} 0.5\times10^{-3} \text{ GPa, 10 d: } 100\%(\mathbf{79} : \mathbf{80} = 60 : 40) \\ 1.2\text{GPa, 12 h: } \quad\quad 80\%(\mathbf{79} : \mathbf{80} = 1 : 99) \end{cases}$$
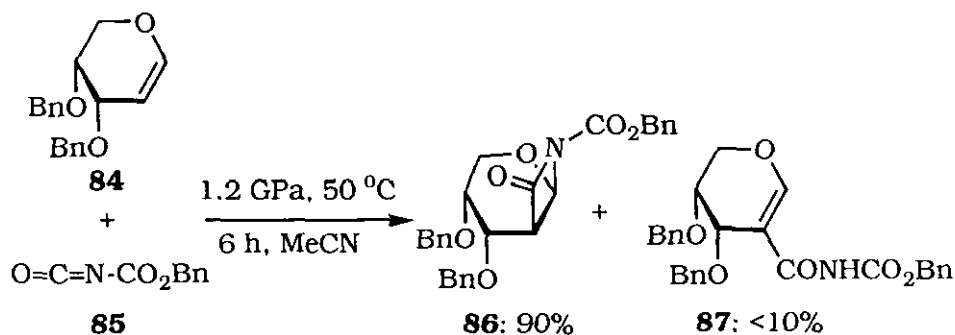
Scheme 25

2.5 [2 + 2] CYCLOADDITIONS

A simple synthesis of 4-alkoxy-β-lactams (**83**) consists of the [2 + 2] cycloaddition of 1-alkoxycyclohexenes (**81**) with phenyl isocyanate (**82**); the yields were improved by using zinc chloride as catalyst.[25]
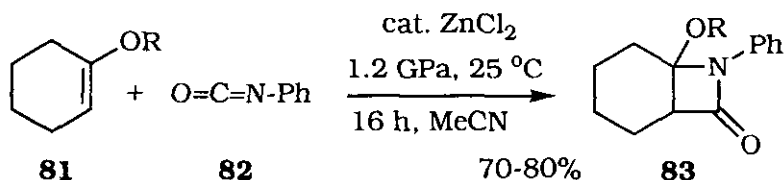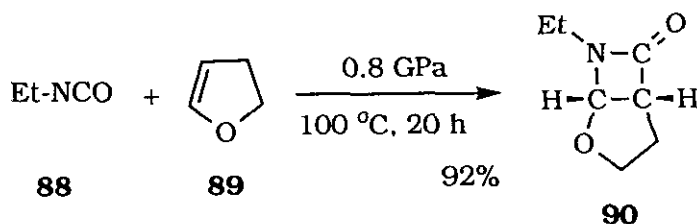

Scheme 26

The analogous reaction of di-O-benzyl-D-arabinol (**84**) with the isocyanate (**85**) proceeded with high stereoselectivity to afford the *cis*-fused bicyclic system (**86**); a by-product was α,β-unsaturated amide (**87**).[26]

Scheme 27

The similar reaction of vinyl ethers with alkyl and aryl isocyanates has been reported. For example, the cyclic vinyl ether (**89**) with ethyl isocyanate (**88**) produced the β-lactam (**90**) in high yield.[27]
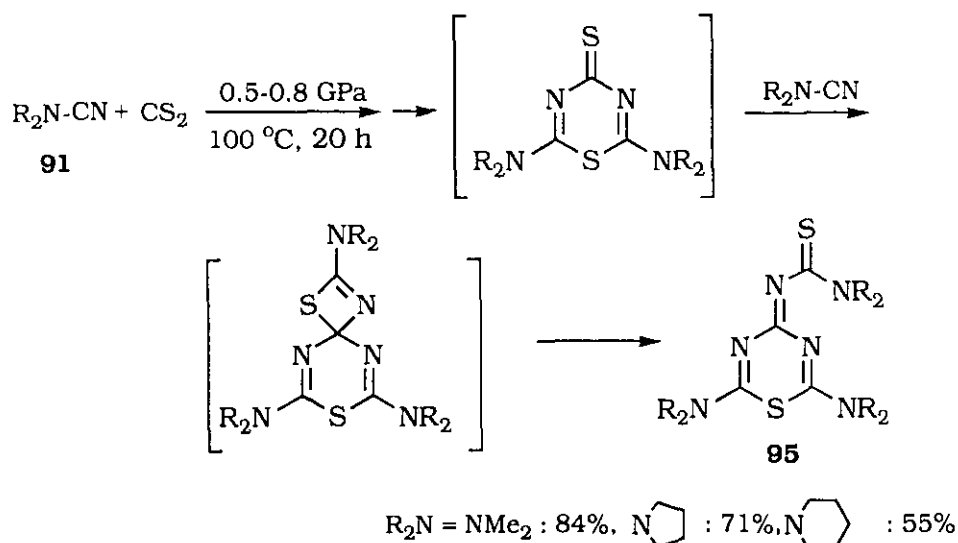

Scheme 28

N,N-Disubstituted cyanamides (**91**), carbon disufide (**92**), and benzylideneaniline (**93**) under high pressure are reported to give the thietizines (**94**), presumably *via* consecutive [2+2] reactions.[28]
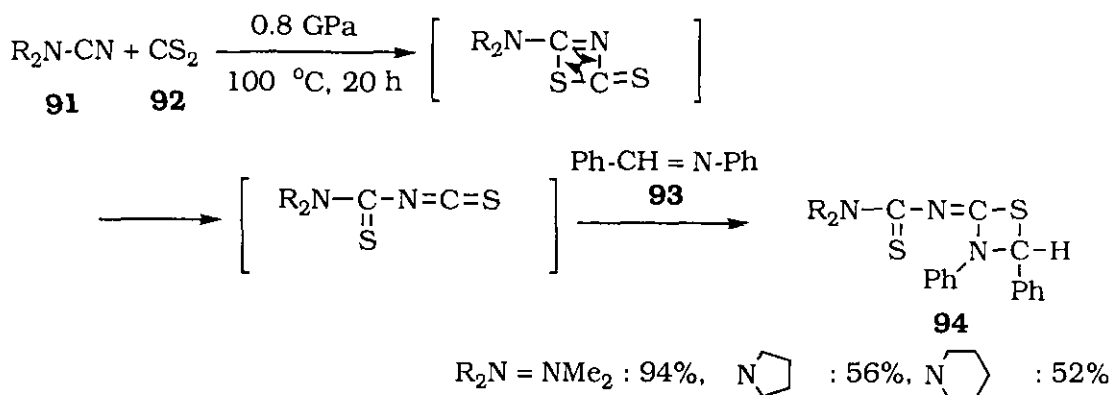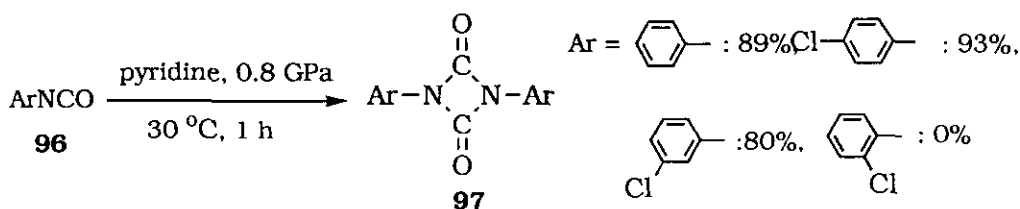

Scheme 29

A similar reaction of carbon disulfide (**92**) with the dialkylcyanamides (**91**) gave the 1,3,5-thiadiazines (**95**).[29]

Scheme 30

The aryl isocyanates (**96**) underwent dimerization in the presence of pyridine and at 0.8 GPa to give **97** but the sterically hindered 2-chlorophenylisocyanate did not react.[30]

Scheme 31

## 3. RING OPENING REACTIONS OF OXIRANES AND LACTAMS

Reactions which involve ionization are usually accelerated by the use of high pressure since both bond formation and charge separation occur during the transitions states. Thus, high pressure can promote, under mild conditions, reluctant bimolecular substitution reactions.

For example, a number of oxiranes were converted nearly quantitatively into the corresponding diols under essentially neutral conditions offered by aquous acetone at 1.0 GPa.[31] A high chemoselectivity was observed (Table 1).

In a similar way, a variety of oxiranes combined with glycine esters to form N-(β-hydroxyalkyl)glycine esters in high yields.[32] Silica gel appeared to catalyse this reaction (Table 2).
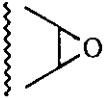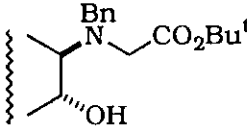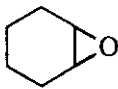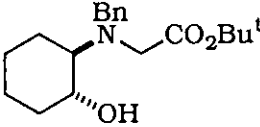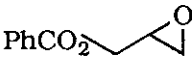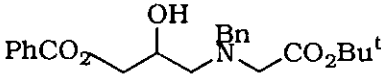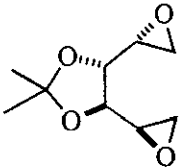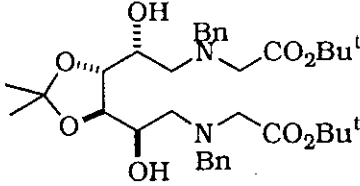
The similar reactions of oxiranes with amines have also been reported and the combined use of high pressure and Yb(OTf)$_3$ in dichloromethane has proved more effective. [33]

Indole reacted at position 3 attacking the more hindered positions of two asymmetric oxiranes yielding the corresponding alcohols (Table 3).[34a,b] This suggests that reaction proceeds through the incipient formation of the more stable of the two carbonium ions *theoretically formed by protonation and ring opening of the oxirane*. Pyrrole behaved similarly, but reacted at both 2 and 3 positions. In complete contrast in the presence of both water and a ytterbium complex, indole (**98**) reacted at the 3 position with the least hindered site of an hydroxyoxirane (**99**) (Scheme 32), a key stage in the synthesis of diolmycin A2 (**100**).[34c]

Table 1. High Pressure Hydrolysis of Epoxides
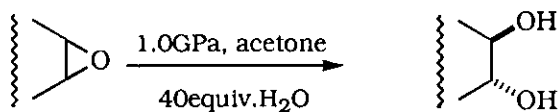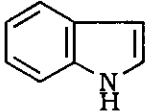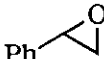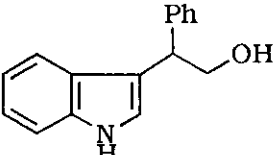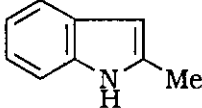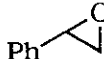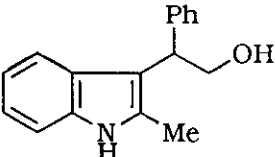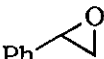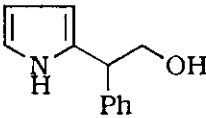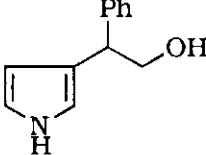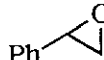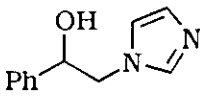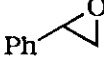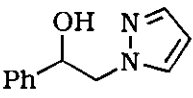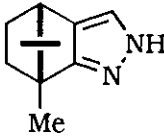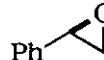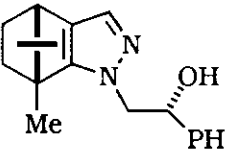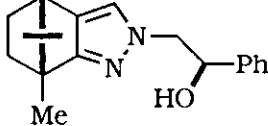

Epoxide	Reaction Conditions	Product	Yield (%)
	60 °C, 24 h		92
	80°C, 24 h		67
			25
	60 °C, 24 h		98
	80°C, 48 h		89(54%ee)
	80°C, 40 h		76

Table 2. Aminolysis of Oxiranes by Glycine Esters

Epoxide	Reaction Conditions[A]	Product	Yield(%)[b]
	A, 65 °C, 24 h		11(88)
	B, rt, 6 d		50(50)
	A, 65 °C, 24 h		82
	B, rt, 6 d		87
	A, rt, 24 h		82
	B, rt, 24 h		91

[a]**A**: in acetonitrile at 1.0GPa. **B**: silica gel catalized reaction.

[b] Brackets show recovered oxiranes.

Table 3. Ring Opening of Oxiranes with Indoles and Related Heterocycles

Heterocycle	Oxirane	Reaction Conditions[a]	Product	Yield(%)
indole	Ph-oxirane	42 °C, 24 h	3-(1-phenyl-2-hydroxyethyl)indole	56
2-methylindole	Ph-oxirane	42 °C, 24 h	2-methyl-3-(1-phenyl-2-hydroxyethyl)indole	44
pyrrole	Ph-oxirane	42 °C, 24 h	2-substituted pyrrole	22
			3-substituted pyrrole	8
imidazole	Ph-oxirane	65 °C, 3 d	1-(2-hydroxy-2-phenylethyl)imidazole	59
pyrazole	Ph-oxirane	65 °C, 3 d	1-(2-hydroxy-2-phenylethyl)pyrazole	61
Me-tetrahydroindazole	Ph-oxirane	65 °C, 3 d	N1 product	41
			N2 product	50

Scheme 32

Similarly, a variety of chiral pyrazoles and imidazoles were prepared by the *N*-alkylation of the corresponding pyrazoles and imidazoles with optically active oxiranes, which were attacked at the least hindered carbon atoms, under high pressure conditions[35] (Table 3).

In the presence of excess carbon disulfide and triethyl amine, oxiranes undergo ring opening; the 2,2-disubstituted oxirane (**101**) gave mainly the 1,3-oxathiolane-2-thione (**102**), whereas the 1-substututed oxirane (**103**) produced the 1,3-dithiolane-2-thione (**104**).[36]

The similar reactions with thiranes yielded the corresponding 1,3-dithiolane-2-thiones, e.g. (**105**).[37]
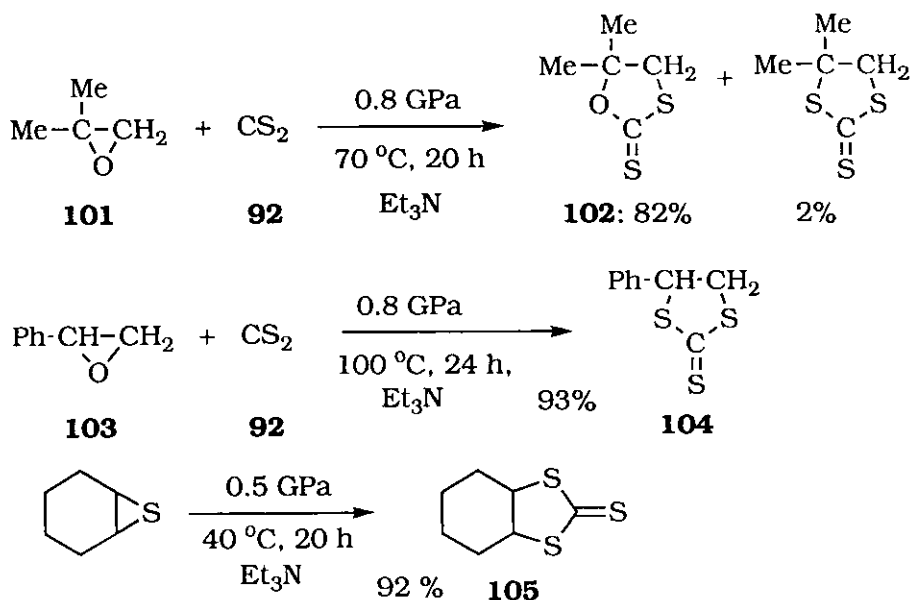
Scheme 33

Like lactones,[38] the condensation of N-Boc-lactams (**106**) with the amines (**107**) gave the amino-carboxamides (**108**) in good yields, while under ordinary pressure these reactions did not take place.[39,40]

106 (n = 1, 2)   **107**

(R = H, CO_2Me, CO_2Bu^t)
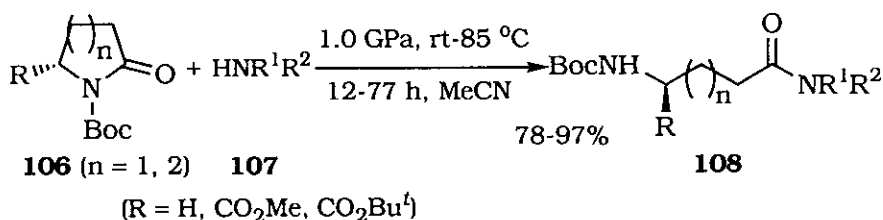
Scheme 34

4. S_NAr REACTIONS OF AMINES

4.1 S_NAr REACTIONS OF CYCLIC AMINES WITH AROMATIC HALIDES

High pressure techniques have proved useful in accelerating S_NAr reactions of aromatic halides, possessing electron-withdrawing groups, with amines, and can give N-substituted anilines in high yields.[41-43] Sterically hindered amines react relatively slowly giving poor results, while morpholine, piperidine and pyrrolidine were specially reactive.

The tetrachloronitrobenzene (**109**) with cis-1,2-diaminocyclohexane (**110**) gave a mixture of **111**, **112**, and **113**.[44] Displacement of the very hindered nitro group was the main reaction, and **113** is probably formed by the cyclization of **112**.

109

+

110

0.6 GPa, 50 °C
20 h, THF

111: 79%

+

112: 7.3%

+

113: 13%
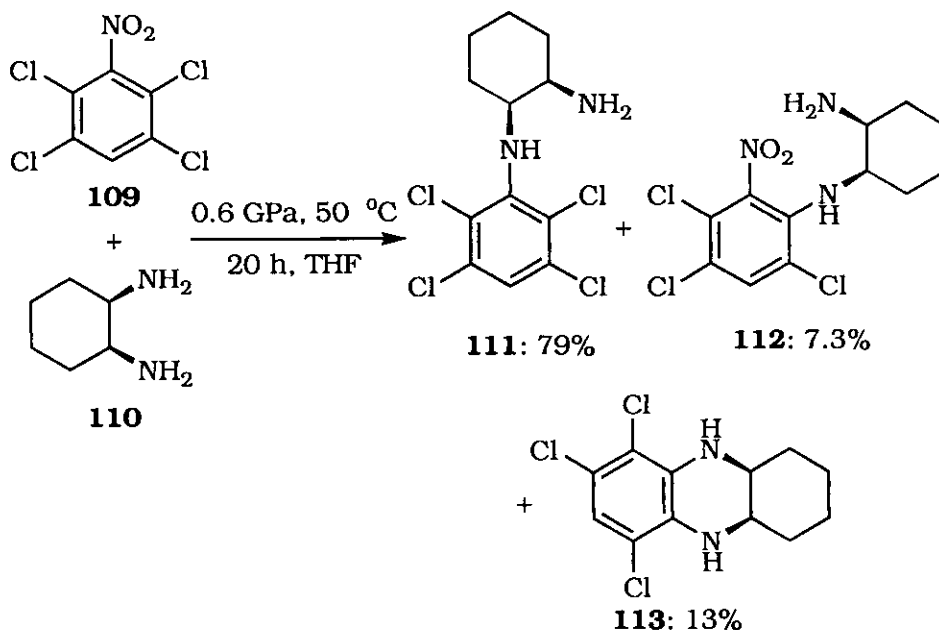
Scheme 35

High pressure induced S_NAr reactions of mono-, di-, and tri-chloronitrobenzenes with
N-substituted cyclic amines gave demethylated products (in the cases of N-
methylpiperidine and of N-methylmorpholine),[45] ring opened products (in the cases of
N-ethylaziridine and of N-ethylazetidine),[46] or mixtures of both demethylated and ring
opened products formed *via* hypothetical quaternary ammonium chloride intermediates.
For example, N-methylpyrrolidine with p-chloronitrobenzene (**114**) gave a mixture of
the demethylated product (**118**) and ring opened product (**119**).[46,47]
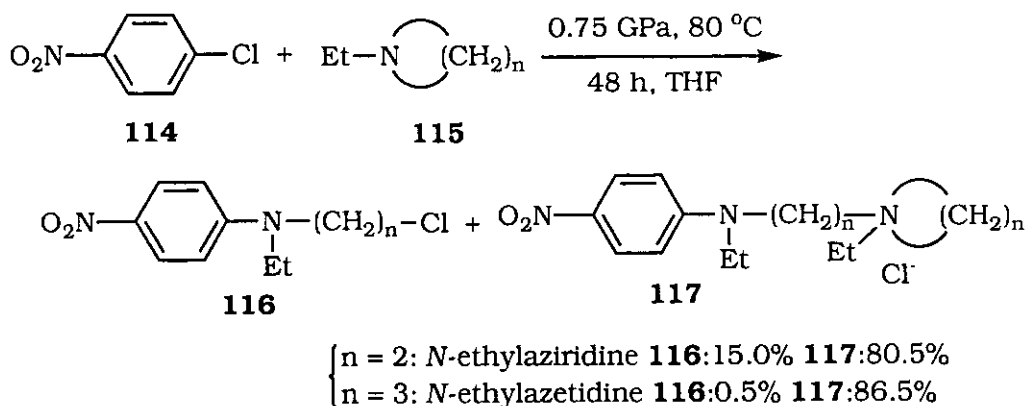
Scheme 36
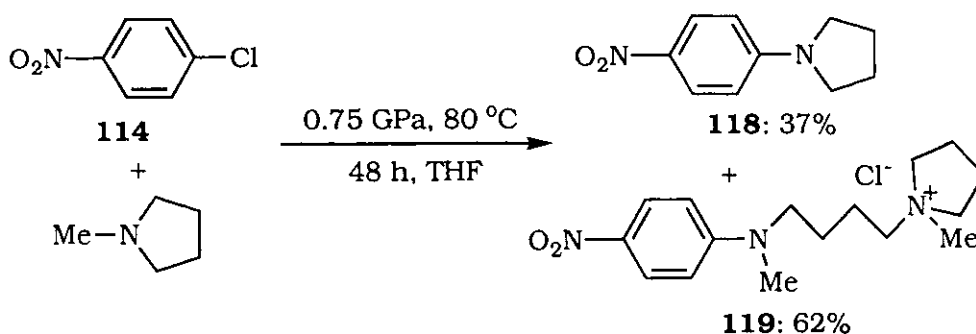
Scheme 37

The reaction of o-chloronitrobenzene (**120**) with Me-TBD (**121**) afforded both the ring
opened and ring expanded products (**122**), (**123**) through initial attack at the unsaturated
nitrogen atom.[48]

Scheme 38

122   10%   **123**   89%
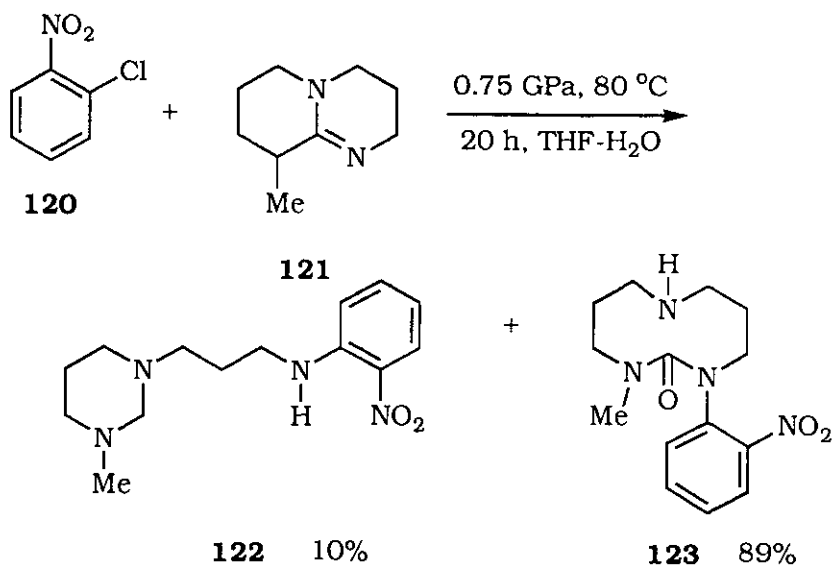
4.2 S$_N$Ar REACTIONS OF AMINES WITH HETEROAROMATIC HALIDES

The high pressure technique has proved to be very useful in promoting S$_N$Ar reactions of heteroaromatic halides with tertiary amines and has provided a new method for the preparation of heteroaromatic tertiary amines, which are only available with great difficulty from the corresponding quaternary ammonium iodides. Many examples are known but the reaction is very sensitive to steric hindrance. The heteroaromatic halides (**124**) with triethylamine (**125**) gave the amines (**126**).[49]

HetX + NEt$_3$ $\xrightarrow[\text{4 d, THF}]{\text{0.8 GPa, 100 °C}}$ ArNEt$_2$ + Et$_4$N$^+$X$^-$

124   **125**   **126**

Het =   :10%,   :31%,   :51%,   :18%
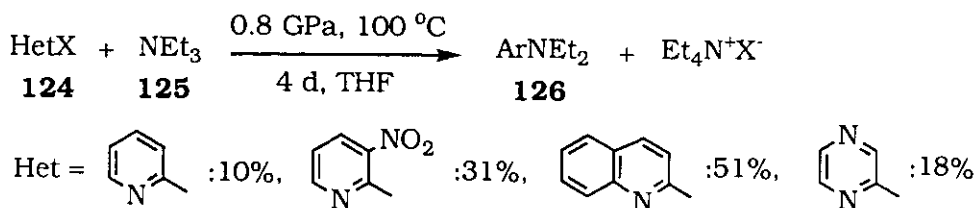
Scheme 39

2-Chlorobenzothiazole (**127**) with tri-n-propylamine, tri-n-butylamine and monocyclic tertiary amines (**128**) gave the corresponding tertiary amines (**129**) in excellent yields.[49]
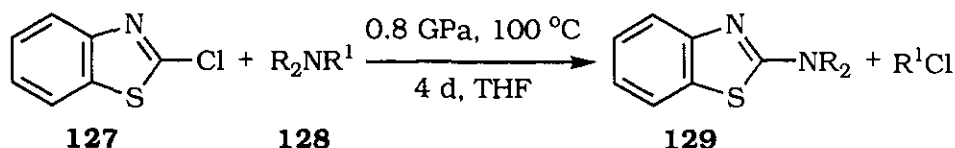
$$R^1 = R = \text{n-Pr} : 95\%, \quad R^1 = R = \text{n-Bu} : 90\%$$
$$R^1 = \text{Me, } RR = -(CH_2)_4- : 96\%, \quad R^1 = \text{Me, } RR = -(CH_2)_5- : 92\%$$

Scheme 40

When *N,N*-dimethylalkylamines (**131,** R≠Bz) were employed, the demethylation was generally favored as illustrated by the reaction of 2-chloro-5-trifluoromethylpyridine (**130**) with the tertiary amine (**131**) which gave mainly **132**, whereas *N,N*-alkylmethylbenzylamines underwent a facile debenzylation to afford mainly the corresponding alkylmethylamino derivatives (**133**).[50] Thus, dialkylbenzylamines serve as dialkylamino equivalents.

130

\+

Me$_2$NR

131   **Scheme 41**

Me Elimination

R	c-Hexyl	CH$_3$(CH$_2$)$_{17}$	*i*-Pr	Et	Benzyl	n-Oct	n-Hexyl
Me Elimination Yield (%)	97 83	74 76	69 73	73 93	2 0	82	83
R Elimination Yield (%)	3 <1	2 <1	13 13	3 7	96 90	<1	<1

R Elimination
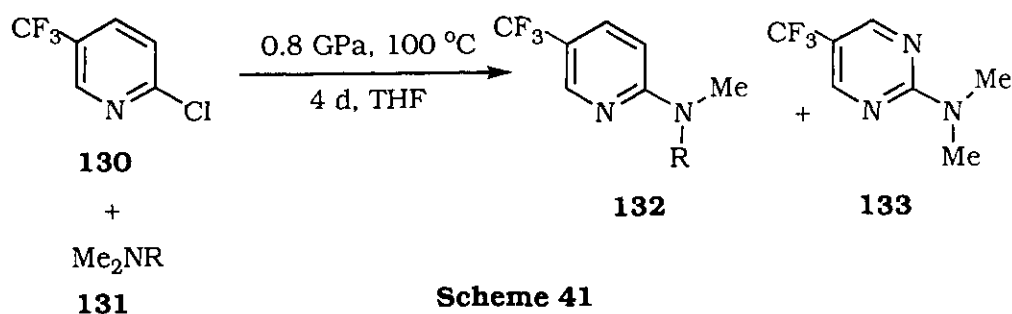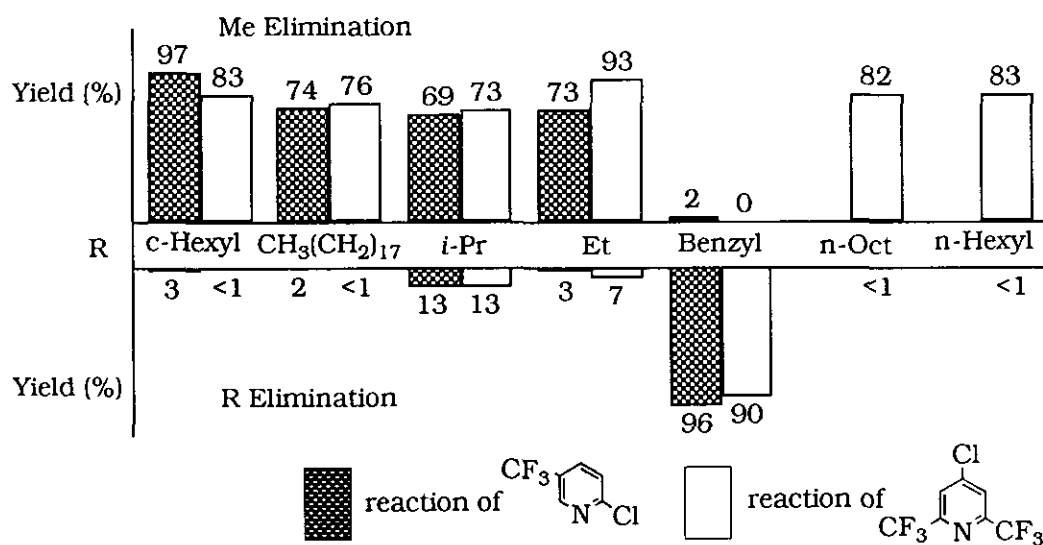
Figure 1

2,6-Dichloropyridine (**134**) with 2-aminomethylpyridine (**136**) in the presence of triethylamine gave the monosubstitution product (**137**), while the more activated 2,6-dichloro-3,5-bis(trifluoromethyl)pyridine (**135**) formed the bisamine (**138**).[51]

134: $R^1 = R^2 = R^3 = H$
135: $R^1 = R^3 = CF_3$, $R^2 = H$

137: 98%   **138**: 96%
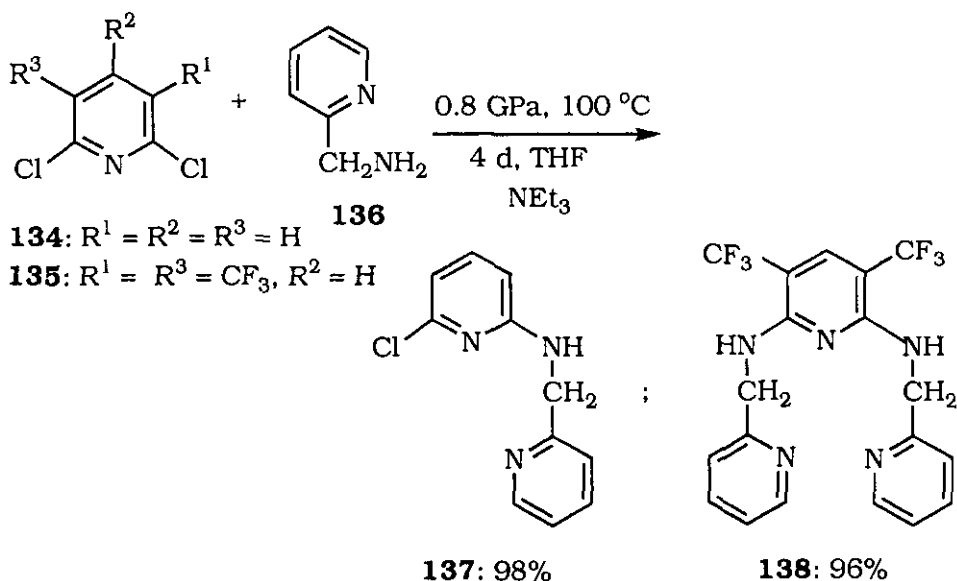
Scheme 42

The piperazines (**139**) in a similar way gave the corresponding pharmacologically interesting tertiary amines (**141**).[52]

139   **140**

141

Z = CH, Het =   : 100%,   90%,   : 92%,   : 64%

Z = N , Het =   : 96%,   : 76%,   : 31%,   : 33%
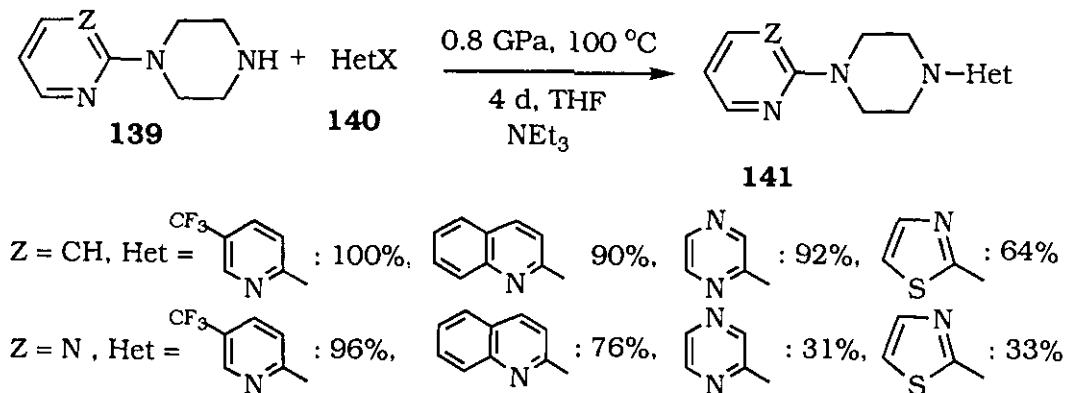
Scheme 43

Similarly, the use of high pressure was essential for the satisfactory conversion of the cyclopropylamine (**142**) to compound (**144**) by the dichloropyrimidine (**143**).[53] This substance (**144**) was cyclised under high pressure to the adenine (**145**) and subsequently converted to the cyclopropyladenine (**146**) which exhibited interesting biological activity.

142

144

145

146
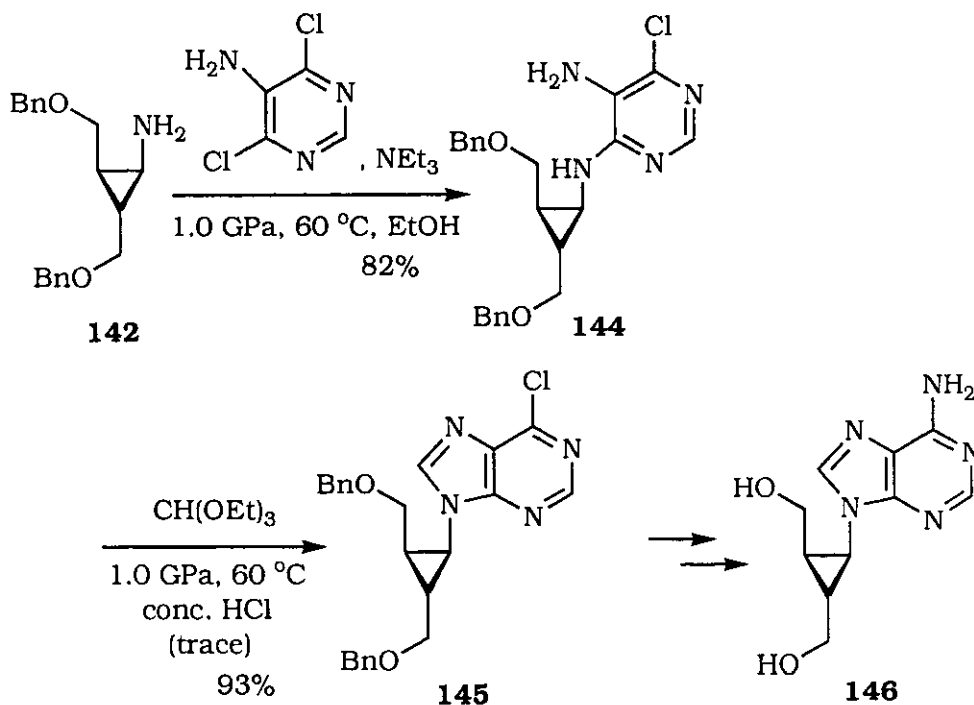
Scheme 44

5. SYNTHESIS AND FUNCTIONALIZATIONS OF MACROCYCLES
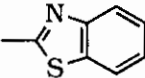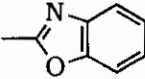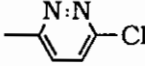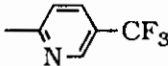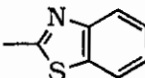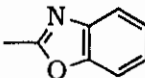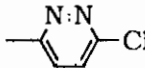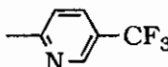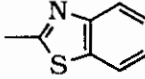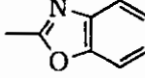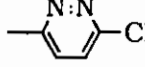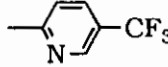
The aminolysis of esters is assisted by high pressure.[54] Dimethyl butanedioate (**147**) with the diamine (**148**) gave the 14-membered diamide (**149**) without contamination with the oligomeric and polymeric by-products which are formed at the high temperatures necessary to effect reaction at ambient pressure.[55]

147   **148**

149

Scheme 45

Scheme 46

Table 4. Synthetic Yields of N-Functionalized Diaza-crown Ethers (151; Y=NAr)

X	m	n	Ar	151; Y= NAr Yield(%)[a]
NH	1	2	thiazol-2-yl	89
			benzothiazol-2-yl	100
			benzoxazol-2-yl	95
			6-chloropyridazin-3-yl	80
			5-(trifluoromethyl)pyridin-2-yl	83
NH	2	2	thiazol-2-yl	82
			benzothiazol-2-yl	74
			benzoxazol-2-yl	64
			6-chloropyridazin-3-yl	81
			5-(trifluoromethyl)pyridin-2-yl	85

[a] 0.8 GPa, 100 °C, 4 d.
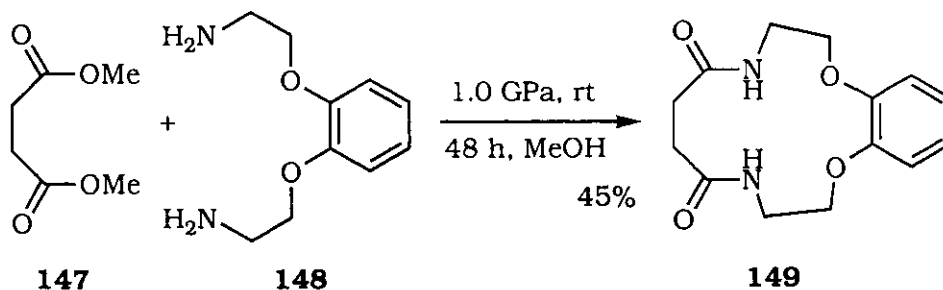
Table 5. Synthetic Yields of *N*-Functionalized Monoaza-crown Ethers (151; Y=O)
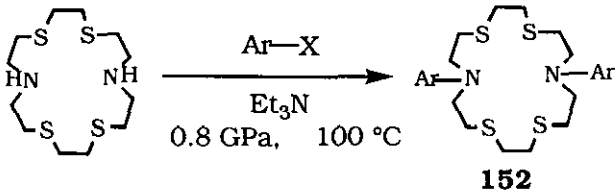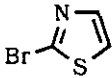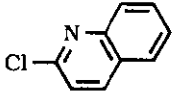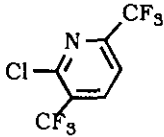
X	m	n	Ar	151; Y=O Yield(%)[a]
O	1	1	thiazol-2-yl	64
			benzothiazol-2-yl	44
			benzoxazol-2-yl	57
			3-chloropyridazin-6-yl	62
			5-(CF$_3$)pyridin-2-yl	58
O	1	2	thiazol-2-yl	99
			benzothiazol-2-yl	99
			benzoxazol-2-yl	99
			3-chloropyridazin-6-yl	96
			5-(CF$_3$)pyridin-2-yl	88
O	2	2	thiazol-2-yl	92
			benzothiazol-2-yl	99
			benzoxazol-2-yl	96
			3-chloropyridazin-6-yl	89
			5-(CF$_3$)pyridin-2-yl	92

[a] 0.8 GPa, 100 °C, 4 d.

High-pressure S$_N$Ar reactions of activated heteroaromatic halides provide a useful route to new types of crown ethers. These compounds are of potential interest in connection with molecular recognitions, analytical applications and environmental problems. A variety of double-armed diaza-crown ethers (**151**; X=NH) directly connected to aromatic heterocycles have now been obtained from the corresponding commercially available unsubstituted crown ethers (**150**; X=NH) and several heteroaromatic halides (Table 4).[56] The 2'-thiazoyl crown ethers showed an excellent selectivity for Ag$^+$ ion in binding, extraction, and transport processes.

High-pressure S$_N$Ar reactions of **150** (X=O) gave a new series of 12-, 15-, and 18-membered monoaza-crown ethers (**151**) (X=O) with various heteroaromatic substituents (Table 5) .[57]   Again, some crown ethers possessing thiazole, oxazole, pyrazine and pyridazine rings exhibited excellent Ag$^+$ ion selectivity; the mode of binding differed from that of the double armed crown ethers.

Table 6. Synthesis of Diaza-18-thiocrown Ethers (152)

Ar-X	Reaction time (d)	Yield (%)
	4	61
	5	29
	6	71
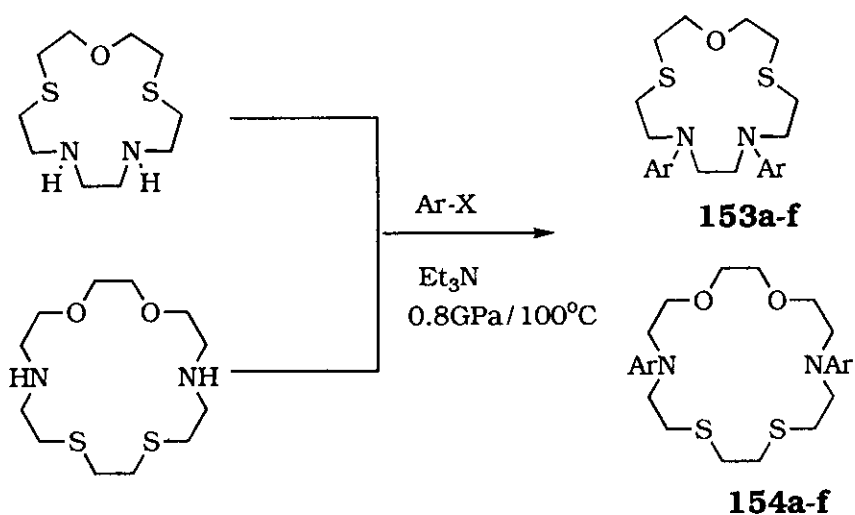
Table 7. High Pressure Synthesis of 153-f and 154a-f

Ar	X	Yield of **153** (%)		Yield of **154** (%)	
(2-ethylpyridine)	Cl	**153a**	74[a]	**154a**	86[b]
(2-methylbenzothiazole)	Cl	**153b**	56	**154b**	73
(2-methylbenzoxazole)	Cl	**153c**	49	**154c**	71
(chloropyridazine)	Cl	**153d**	34	**154d**	69
(2-methylthiazoline)	Br	**153e**	<3	**154e**	64
(2-methylpyridine)	F	**153f**	<3	**154f**	30

[a] 27% at normal pressure. [b] 22% at normal pressure.

Similar diaza-thia-18-crown ethers (**152**) without oxygen atom in macro ring and the diazathia 15- and 18-crown ethers (**153**) (**154**) with oxygenatoms in macro ring have also been prepared (Tables 6 and 7).[58] Liquid membrane transport studies demonstrated that the latter 18-crown ethers (**154b, c,** and **f**) having benzothiazole, benzoxazole, and pyridine rings exhibited Hg^{2+} and Ag^{+} ion selectivity.[58b]

By the same method various bis(single-armed crown ethers) (**155**) (**156**) [59] and tris(azacrownethers) (**157**) [60] have been prepared as shown in Schemes 47 and 48. Different spacers have also been used.

A series of armed tetraazacyclotetra-(**159**, n=1) and tetrazacyclopentadecanes (**159**,n=2) were prepared from the corresponding unsubstituted tetraazamacrocycles (**158**) by high pressure one pot S_NAr reactions with five- and six-membered heteroaromatic halides.[61]

Scheme 47

Scheme 48

157

Scheme 49

n = 1, Het = [pyridyl] : 7%, [pyrimidyl] : 88%, [pyrimidyl] : 78%, [thiazolyl] : 50%

n = 2, Het = [pyridyl] : 61%, [pyrimidyl] : 65%, [pyrimidyl] : 74%, [thiazolyl] : 23%
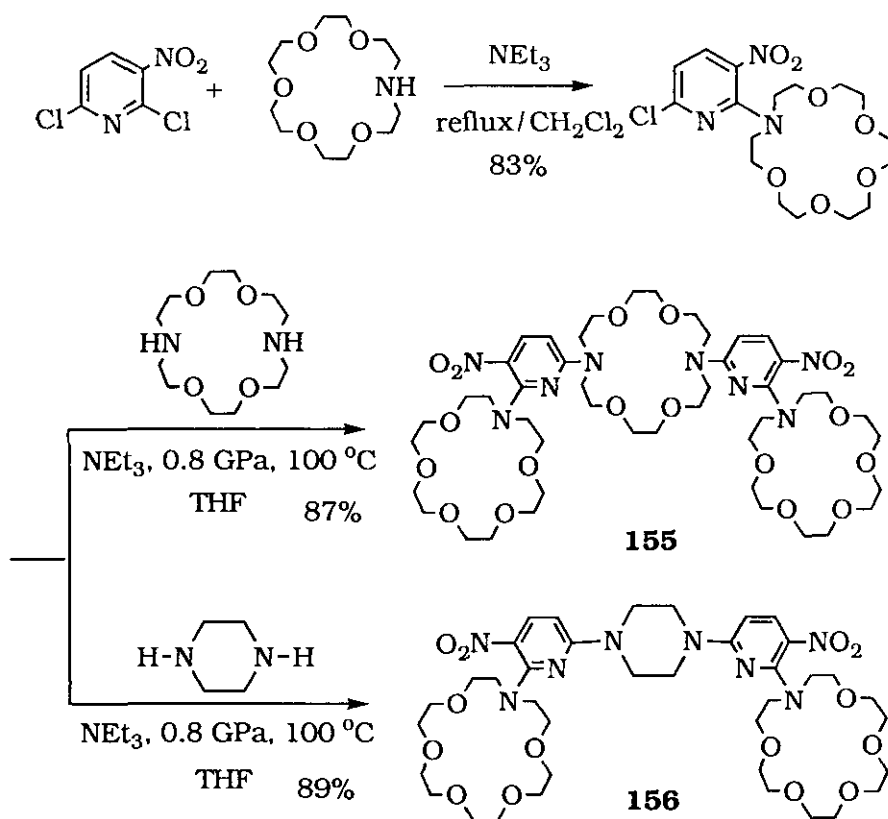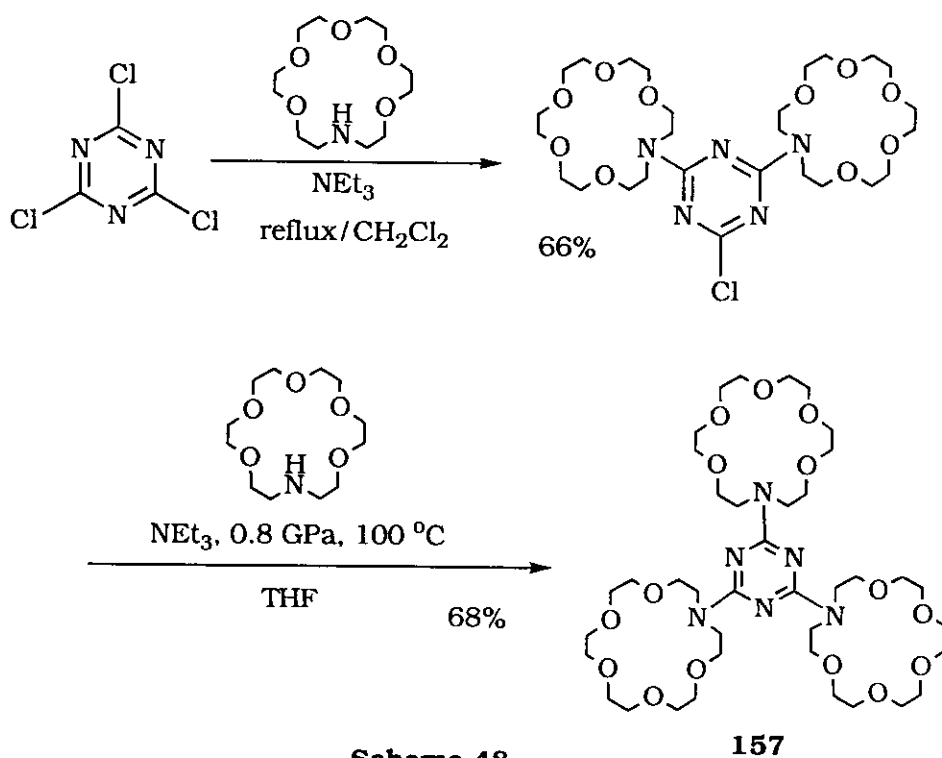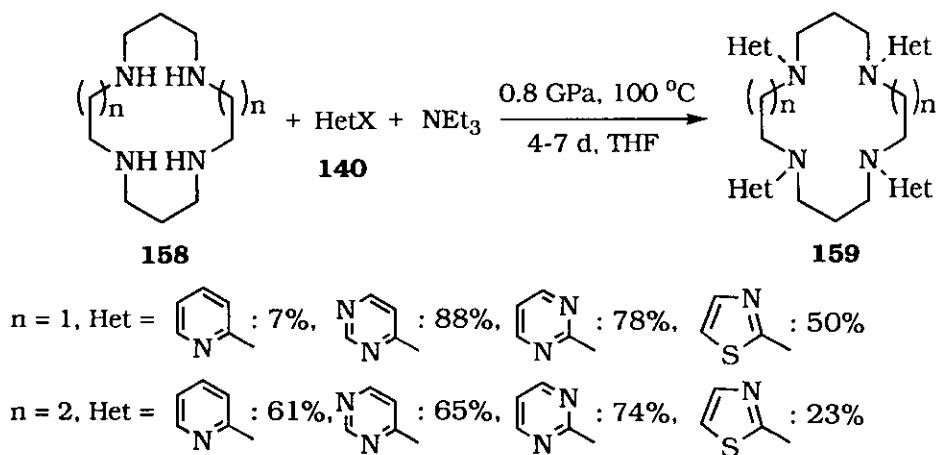
Better conversions were obtained with piperadine and homopiperadine which gave the bis(heteroaryl)piperadines and homopiperadines (**160**) in good to quantitative yields.[62]
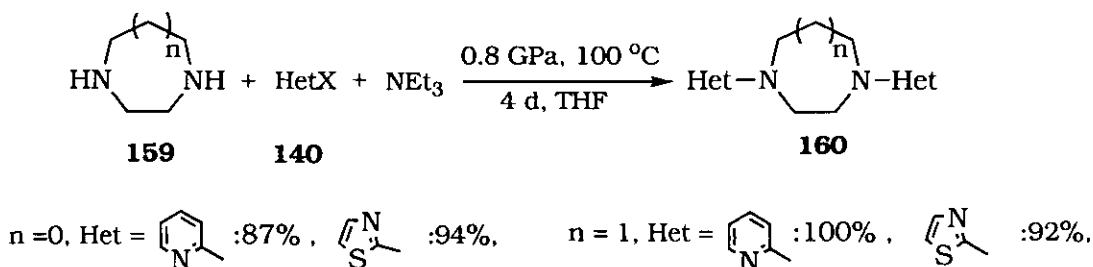
Scheme 50

A template synthesis of metal coordinated phthalocyanines has been achieved under high pressure as exemplified for **161** in Scheme 51. In the presence of hydroquinone, metal free phthalocyanines were obtained in moderate yields.[63]
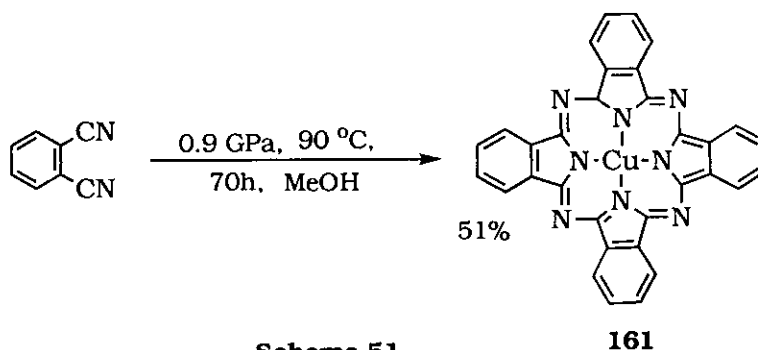
Scheme 51　　　　　**161**

6. DEAMINATION OF CARBOCYCLIC NUCLEOSIDES BY ADENOSINE DEAMINASE (ADA)

Recently it has been shown that deamination reactions of nucleosides effected by ADA take place *via* an addition-elimination mechanism.[64] Therefore, the effect of pressure on this reaction was examined. The catalytic conversion of 9-[4,5-bis(hydroxy-methyl)cyclopent-2-en-1-yl]-9*H*-adenine (**162**) (**BCA**) to 9-[4,5-bis(hydroxymethyl)cyclopent-2-en-1-yl]-9*H*-hypoxanthine (**163**) (**BCH**) was accelerated by pressure up to 0.4 GPa but above this pressure the enzyme was deactivated leading to lower conversions.[65] (+)-**BCA** was much less reactive than (-)-**BCA** and this observation was employed to effect the optical resolution of (±)-**BCA**.[65]

Similar high pressure ADA deaminations of diaminocarbovir,[66] adenine,[66] adenosine,[66] and carbocyclic adenine nucleosides[67] catalysed have been investigated.

(-)-BCA
162

Scheme 52

(-)-BCH
163
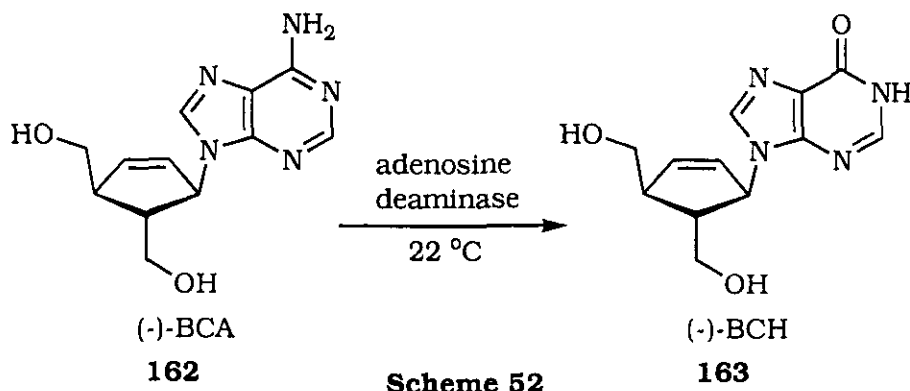
7. MISCELLANEOUS EXAMPLES

Under high pressure the reaction of 2-methylfuran (**164**) with diethyl mesoxalate (**165**) was not only strongly accelerated but also a change in product composition was observed.[68] An increase in pressure led to a gradual increase in the formation of **167** at the expense of **166** enabling the reaction course to be controlled.

atmospheric pressure ;   **166** : **167** = 75 : 25
1.2GPa   ;   **166** : **167** = 23 : 77

Scheme 53
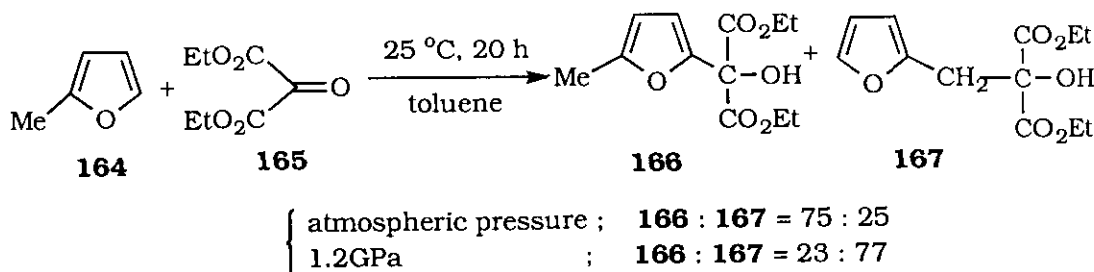
The successful synthesis of some molecular shuttles was also achieved by use of high pressures. Thus, the [2]rotaxane 4PF$_6^-$ (**171**) was obtained by the Menshutkin reaction of **169** and **170** with the dumbbell component (**168**).[69]

The 3-aminomethylindoles (**174**) were prepared from the indoles (**172**), CH$_2$Cl$_2$ and the secondary amines (**173**).[70]

Scheme 54

R = H, R^1 = R^2 = Et : 68%,   R = H, R^1-R^2 = -(CH$_2$)$_4$- : 62%,

R = H, R^1-R^2 = -(CH$_2$)$_5$- : 50%,   R = H, R^1-R^2 = -(CH$_2$)$_2$-S-(CH$_2$)$_2$- : 80%

R = H, R^1 = Me, R^2 =⟨ ⟩- : 98%, R = Me, R^1 = R^2 = Et : 18%
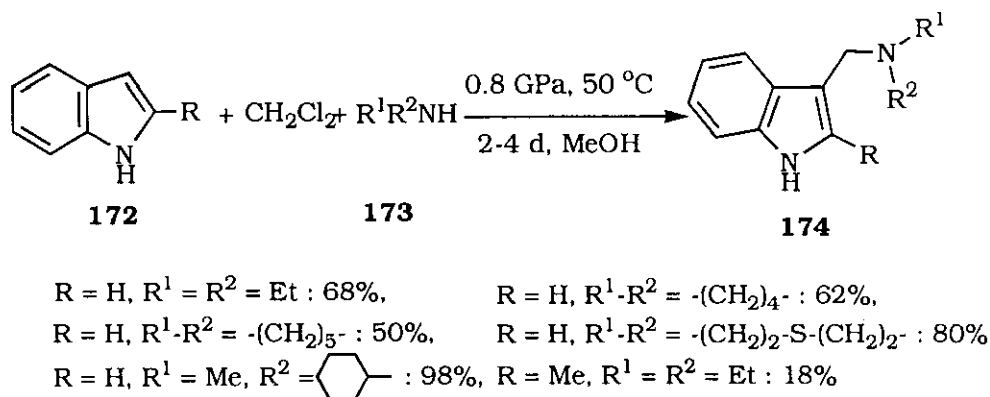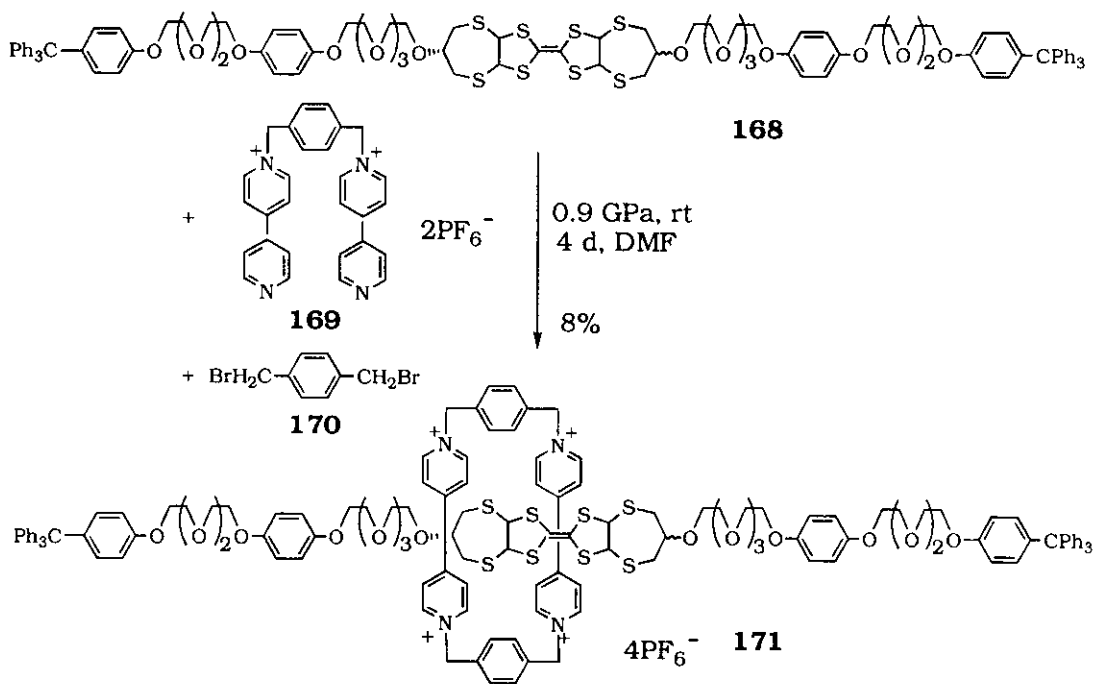
Scheme 55

The combined use of high pressure with palladium catalyst allowed the enantioselective synthesis of the phenyl substituted 2,3-dihydrofuran (**176a**) (89% ee at 1.0 GPa) from 2,3-dihydrofuran (**175a**).[71a] The regioselectivity (**176:177**), which was strongly dependent on the amount of the phosphine ligand present, could be achieved only at high pressures.

Further studies of this reaction showed that the decisive effect of high pressure was to increase the life of the palladium catalyst.[71b] At 0.8 GPa the reaction was significantly accelerated without using an excess of the specially designed ligands. Under the same conditions, 2,3-dihydropyrrole (**175b**) gave mainly **176b** .

$$
\begin{array}{c}
\text{(175)} + \text{Ph-Y} \xrightarrow[\substack{\text{0.8 GPa, 60 °C} \\ \text{36-120 h} \\ \text{THF/MeCN(1:1)}}]{\text{Pd(OAc)}_2,\ \text{PPh}_3,\ \text{NEt}_3} \text{(176)} + \text{(177)}
\end{array}
$$

a: X = O, Y = I   a: 64-100 % (**176:177** = 9:1)
b: X = NCO$_2$Et, Y = I   b: 87 %   (**176:177** = 15:1)
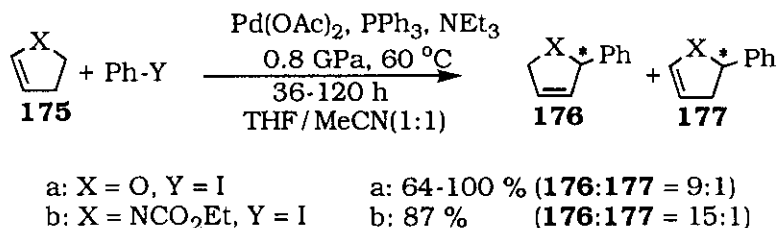
<div align="center">Scheme 56</div>

Subjecting carbonyl sulfide with cyanamides (**91**) to high pressure gave the 1,3,5-thiadiazines (**178**).[72]

R$_2$N = NMe2 ; 92%,   (N⟨⟩); 74%, (N⟨⟩) ; 94%

<div align="center">178</div>
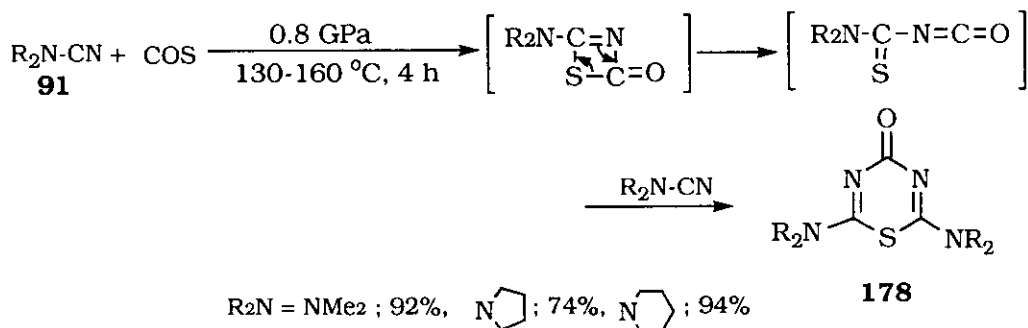
<div align="center">Scheme 57</div>

The cyanamides (**91**) with aryl isocyanates (**179**) also gave the quinazolines (**180**).[73]

R$_2$N = NMe$_2$: 86%,   (N⟨⟩): 78%, (N⟨⟩) : 62% , (N⟨⟩O) : 51%

<div align="center">180</div>
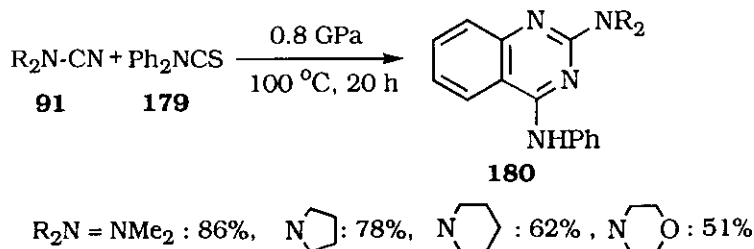
<div align="center">Scheme 58</div>

The high pressure trimerization of isocyanates (**181**) and isothiocyanates (**183**) yielded 1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)triones (**182**) and 1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trithiones (**184**), respectively.[74] Aryl isothiocyanates did not trimerize even at 0.8 GPa.
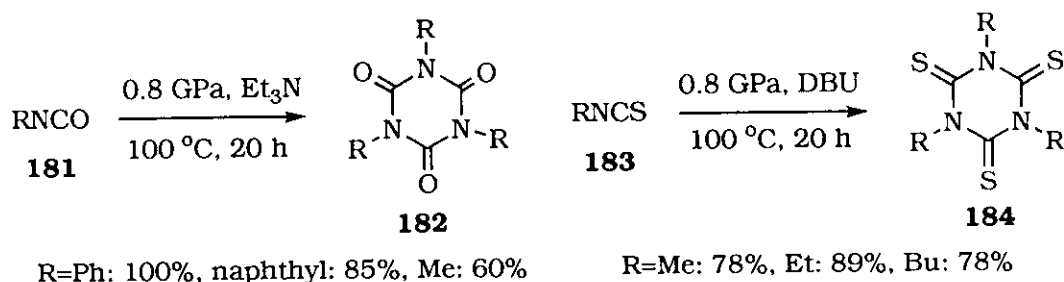
R=Ph: 100%, naphthyl: 85%, Me: 60%   R=Me: 78%, Et: 89%, Bu: 78%

Scheme 59

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