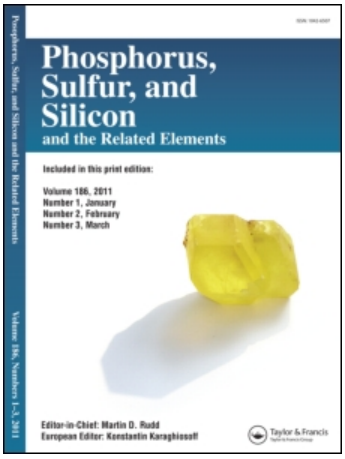

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Inter and Intramolecular Nucleophilic Substitutions of Activated Phenylselanyl Groups

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Inter and Intramolecular Nucleophilic Substitutions of Activated Phenylselanyl Groups

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This review assembles the results of studies out in my laboratory and related to nucleophilic substitutions and cyclization reactions involving unsaturated and functionalized phenylselenides. Three modes of activation of the phenylselanyl group were used. The halogen treatment has produced dihalo adducts whose decomposition has led to various halogenated unsaturated and functionalized structures, sometimes with rearrangement. The $PhSe^+$ activation was involved during the selenium-induced cyclization of homoallylic amines, allowing the formation of β-halopyrrolidines. The synthesis of aziridines was achieved, for the first time, through the intermediate formation of β -amino methylselenonium salts. Br^+ and $PhSe^+$ activations have also allowed the preparation of these azahetorocycles.

Keywords: Selenonium salt; nucleophilic substitution; dihaloselenurane; azaheterocycle; carbonyl compound; ester; allylic compound

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INTRODUCTION

The important place of the selenium methodology in organic synthesis results from large differences of reactivity between sulfur and selenium functionalities involved in structural modifications. The selenium atom is larger, more polarisable, more nucleophilic than the sulfur one and the C-Se bond weaker and less polar than the C-S bond. Selenium reagents are now usually used[1-4] and extensions to asymmetric synthesis[5] and radical chemistry[6] were the subject of recent works.

Selenoxides play a pivotal role since the facile oxidation of alkyl phenylselenides allows the preparation of olefinic compounds and allylic alcohols under very mild conditions. The unstability of most selenoxides, connected with this behaviour, prevents their oxidation into selenones which were only studied in few occasions[7]. The greater leaving group ability of the phenylselenonyl group, compared to that of the phenylsulfonyl one, was illustrated by works involving nucleophilic substitution[2,8], ring enlargement[9], reduction[2], epoxide formation[2], cyclopropanation[10] and 1,2-phenyl migration[11]. The difficulties encountered for an efficient access to selenones limit the use of the phenylselenonyl substituent as leaving group.

Phenylselenonium salts are stable and very accessible compounds. As their sulfur analogs, α-deprotonation leads to ylides[2], from which a molecule of alkyl phenylselenide can be displaced in the course of nucleophilic substitution or elimination reactions[2].

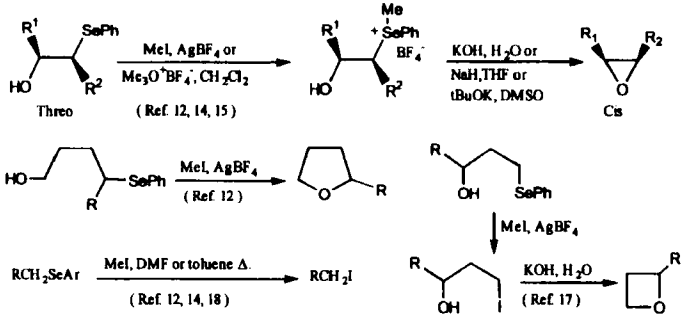
The objective of this lecture is to present recent works on nucleophilic substitutions carried out on phenylselenides after activation of the PhSe group by alkylation, halo-adduct formation or selenenylation. The first part will be devoted to studies published by other groups. The two last sections will describe results from my laboratory concerned with nucleophilic displacements on various selenenylated structures.It will be presented successively the halogenation of unsaturated and functional compounds, the synthesis of azetidines and pyrrolidines from homoallylic amines and the preparation of aziridines from β-aminoalkyl phenylselenides.

I. NUCLEOPHILIC SUBSTITUTION OF AN ACTIVATED PHENYLSELANYL GROUP

I-1. Me^+ activation

Alkyl arylselenides are easily alkylated into methylselenonium salts using MeI and $AgBF_4$ or $(Me)_3O^+BF_4^-$ in methylene chloride[2,12]. The conjugated dienic moiety of 5S-thiolactomicin was formed by an aqueous KOH elimination reaction achieved of an allylic methylselenonium intermediate[13]. The same sequence is now a classical procedure for the anti-stereospecific synthesis of epoxides[2,12,14,15] starting from β-hydroxy phenylselenides and the preparation of tetrahydrofurans[12] from hydroxyalkyl phenylselenides

(scheme 1). ω-Hydroxyalkyl methylselenides have been used as substrates for the preparation of tetrahydropyrans[16]. It was observed that if the tetrahydrofuran ring can be formed by a direct nucleophilic attack of the hydroxy group, the cyclization giving an oxetane needs the intermediate formation of an hydroxyalkyl iodide[17]. Primary alkyl iodides were prepared by reaction of alkyl arylselenides with MeI followed by thermal decomposition of the methylselenonium salt in DMF[12,14] or toluene[18] (scheme 1). Dimethylselenide was also displaced during the reaction of an alcoolate with benzylic dimethylselenonium tetrafluoroborates[19]. The intermediate formation of a methyl phenylselenonium ion was proposed to explain the O-glycosylation of thioglycosides in the presence of benzeneselenenyl triflate[20].



SCHEME 1

I-2. X^+ activation

Selenoxides can been formed by alkaline hydrolysis of dichloro-adducts derived from alkyl phenylselenides[21,22]. The fast syn-

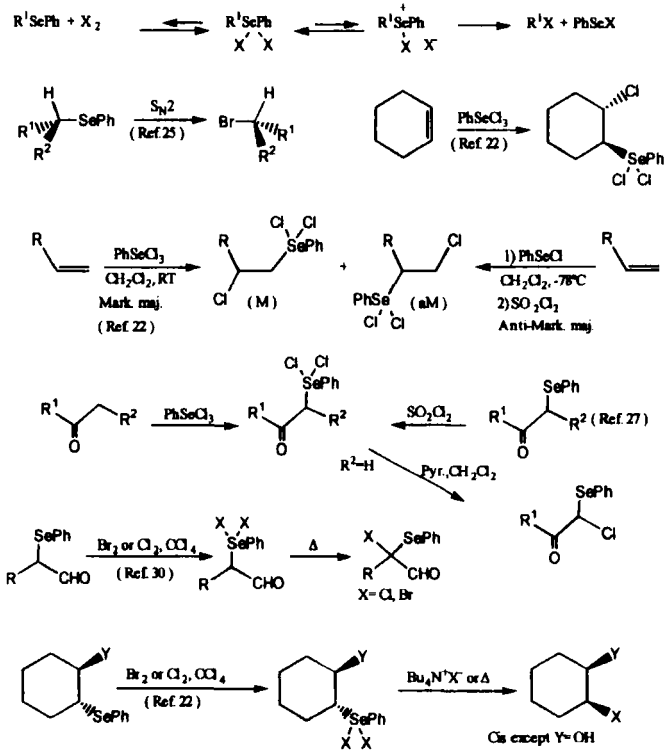
elimination reaction has led to conjugated enones[23]. Dihalo-adducts are formed instantaneously by treatment of selenides with bromine, chlorine or sulfuryl chloride[2], in various solvents. These compounds are described as neutral selenuranes with a trigonal bipyramid structure for X = Cl, Br, and as molecular complexes for X = I. The haloselenonium halide form (X = Cl, Br) must explain their reactivity which occurs very quickly for bromo-adducts[12,17,25]. The unstable dibromo derivatives decompose in solution, at room temperature, with formation of alkyl bromide and benzeneselenenyl bromide[25]. The dichloro compounds have provided the corresponding alkyl chlorides only on heating[26]. An inversion of configuration was observed for the preparation of secondary alkyl bromides[25] (scheme 2).

Dichloro-adducts have been prepared, in very good yields, by addition of phenylselenium trichloride ($PhSeCl_3$) to alkenes[21] or reaction with enolisable ketones especially with methylketones[27-29]. They are also conveniently prepared by SO_2Cl_2 treatment of the corresponding selenides[21,27]. Reaction of chlorine with linear α-phenylselanyl aldehydes has provided isolable dichloro-adducts[30]. These selenuranes and those derived from methylketones[28] were transformed into α-chloro α-phenylselanyl aldehydes and ketones respectively. A "Seleno Pummerer" reaction must explain the α-chlorination (scheme 2). In absence of neighbouring group participation[31], the decomposition of dichloro-adducts, on heating in a neutral solvent such as CCl_4, has led to alkyl chlorides according to a S_N2 mechanism.

N-Bromo or N-iodo succinimide treatment of alkyl phenyl selenides generates also haloselenonium ions. The presence of a non-

nucleophilic counter-ion allows the attack of various nucleophilic reagents. An illustration was given with the synthesis of oligosaccharides[32] and glycosyl fluorides[33].

This family of haloselenonium compounds has no equivalent in the sulfur series. Alkyl phenyltelluride dihalo-adducts are stable compounds prepared as their selenium analogs (X = Cl, Br, I)[34,35]. They can be hydrolysed into telluroxide[36] and decomposed into alkyl halide and benzenetellurenyl halide only on heating in DMF[34].



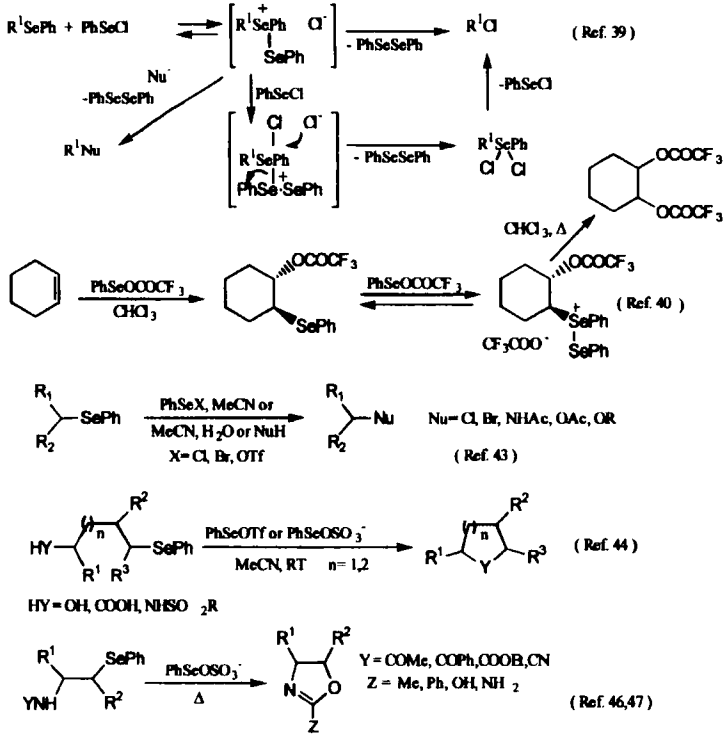
SCHEME 2

I-3. $PhSe^+$ activation

β-Halo phenylselenides are easily prepared by trans-addition of PhSeX (X = Cl, Br) on olefins in neutral solvents with intermediate formation of a seleniranium cation[2]. The anti-Markownikov product, trapped as dichloro-adduct by SO_2Cl_2 addition[22], predominates under kinetic conditions (CCl_4 or CH_2Cl_2, low temperature). The 2-halo-1-alkyl phenylselenide was the major product when the reaction is carried out on terminal olefins under thermodynamic control[37]. In the presence of a nucleophilic reagent, the corresponding addition product was synthetized in such experimental conditions[38].

With two molar equivalents of PhSeX (X = Cl, Br), halo-deselenenylation of the product often occurs. A kinetic study of the PhSeCl addition, carried out on some olefins, has revealed an affinity of the PhSe group towards the soft electrophilic reagent[39] (scheme 3). The intermediate formation of a selanylselenonium ion allows a later nucleophilic attack. This sequence has led to the stereospecific synthesis of vic-dichlorides[31]. A large excess of PhSeCl allows then the appearance of the corresponding dichloro-adduct which finally decomposes to give an allylic chloride[39].

Benzeneselenenyl trifluoroacetate ($PhSeOCOCF_3$) was reacted with cyclohexene to give a trans-addition product. In dry chloroform an excess of reagent has led to a stable phenylselanylselenonium salt On heating, this salt provided a bis (trifluoroacetate) derivative whose stereochemistry was not precised[40] (scheme 3).



SCHEME 3

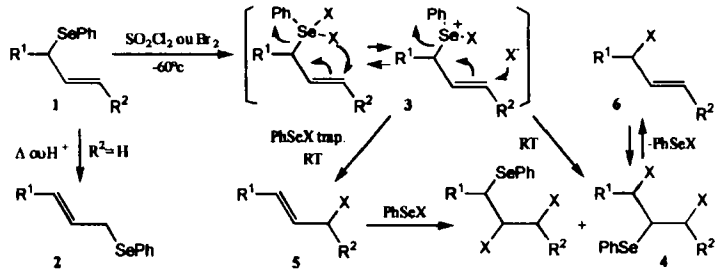
$PhSe^+$ activation has allowed the preparation of α-bromoketones[41], 2-chlorocyclohexanols[42] and chloro-acetoxylated styrene derivatives[29]. The use of PhSeOTf, reagent having a non-nucleophilic counter-ion, or the in "situ" generation of $PhSe^+$ by oxidation of diphenyldiselenide with $PhI(OAc)_2$ or ammonium persulfate, have allowed the introduction of various nucleophiles in the place of the PhSe group[43,44] and the synthesis of 5- and 6-membered O, N-heterocycles[45-47]. Glycosylation reactions were also achieved[43].

With the persulfate oxidation method, nucleophilic substitutions can be achieved with a catalytic amount of PhSeSePh[43,46]. Phenylselanyl glycosides were used as glycosyl donors by simple activation with silver triflate[48].

II. SYNTHESIS OF HALOGENATED UNSATURATED AND FUNCTIONALIZED COMPOUNDS

II-1. Allylic chlorides and bromides

γ-Substituted or γ-functionalized allylic phenylselenides were prepared by Wittig, Emmons-Horner olefination[49] or Knoevenagel condensation[50] from α-phenylselanyl aldehydes and ketones. Allylic selenides such as **1** (scheme 4) isomerize on heating under acid catalysis into primary allylic selenides **2**[50, 51]. Allylic selenides **1** and **2** were treated with Br_2 or SO_2Cl_2. Decomposition of the corresponding unstable adducts **3** occured with allylic substitution, leading to allylic halides **4** and PhSeX which adds regioselectivity on the shifted double bond. PhSeX elimination between the β and γ carbon atoms give rise to allylic halides **6** apparently formed by direct substitution. The introduction of an olefinic compound, such as ethyl vinylether, which reacts faster with PhSeX, has allowed the isolation of the allylic halides **4**. Without capture of PhSeX , a mixture of products **4**, **5**, **6** was obtained [50] (scheme 4).

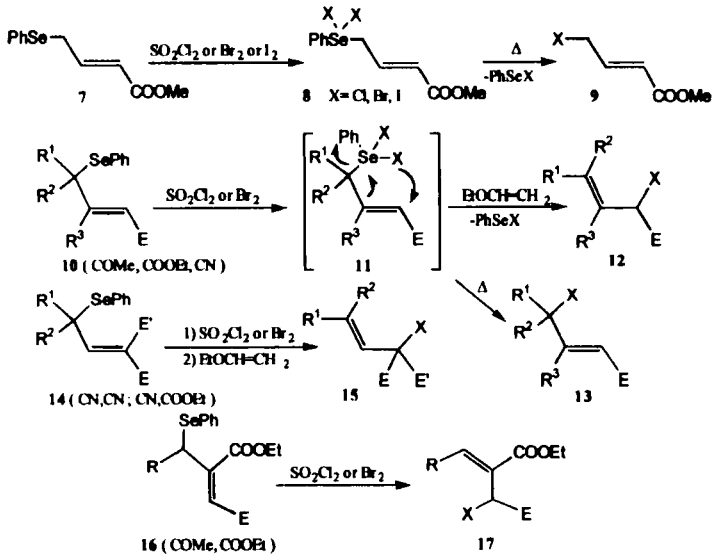


SCHEME 4

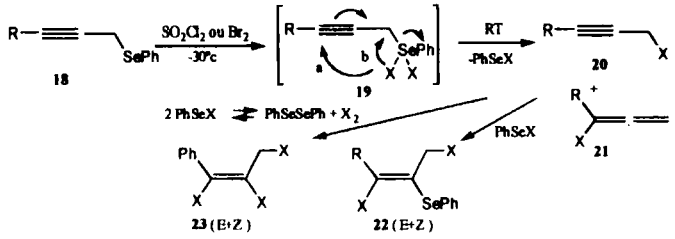
Methyl (4-phenylselanyl) but-2-enoate **7** was subjected to the reaction with X_2 (SO_2Cl_2, Br_2, I_2). The dihalo-adducts **8** were very stable compounds. The thermal decomposition has led to the isolation of γ-halo α,β-unsaturated esters **9** (scheme 5). The decomposition-allylic substitution process was then carried out on γ-functionalized[50,52], γ,γ-difunctionalized[50] and β,γ-difunctionalized[53] allylic selenide dihalo-adducts formed from allylic selenides **10**, **14** and **16** respectively. These selenuranes were found very unstable. Adducts **11** were decomposed in solution into γ-haloesters **13**. In the presence of ethyl vinylether, α-haloesters **12** and **15** were synthetized with good yields. Decomposition of the adducts derived from **16** was achieved without ethyl vinylether. The presence of a PhSeX trap was not needed in these cases since the shifted double bond is always conjugated.

The unstable dihalo-adducts **19**, formed at −30°C from the propargylic selenides **18** (R = H, Me, Ph) were decomposed at room temperature. We have observed the formation of E,Z-1,3-dihalo 2-phenylselanylpropene derivatives **22** contaminated with the corresponding trihalostyrene derivative **23** (E+Z) for R = Ph[54]. The

intermediate formation of the propargylic halide **20** and the haloallene **21** was demonstrated. An equilibrium between PhSeX and PhSeSePh must explain the presence of Cl_2 or Br_2 which adds to **20** or **21**, leading to the trihalo compounds **23** (scheme 6).



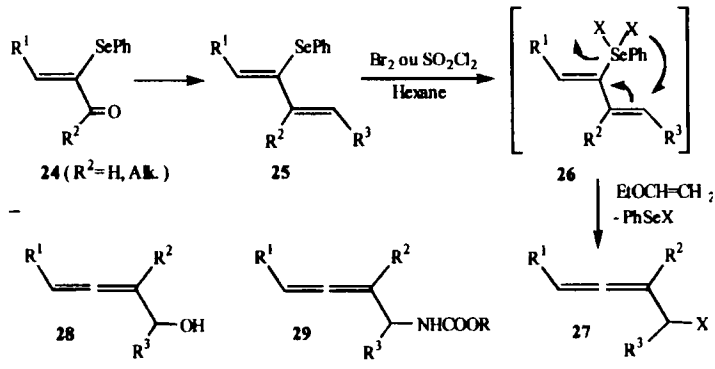
SCHEME 5



SCHEME 6

II-2. 1-Haloalkyl allenes

2-Phenylselanyl 1,3-dienes **25**[50] were prepared by Wittig-Horner olefination of α-phenylselanyl α,β-unsaturated aldehydes and ketones **14**[55]. The corresponding unstable dihalo-adducts **26** were decomposed in the presence of ethyl vinylether. Addition of PhSeX was avoided and 1-haloalkyl allenes **27** were isolated as diastereoisomeric mixtures[50]. In the same time, allenyl alcohols **28** and allenyl carbamates **29** were synthetized by [2,3]-sigmatropic rearrangement of selenoxides and selenilimines, respectively, formed from the same phenylselanyldienes **25**[50] (scheme 7). In these transformations, the hydridization change of the selenenylated carbon, from sp^2 to sp, does not prevent the decomposition-allylic substitution process and the sigmatropic rearrangement.

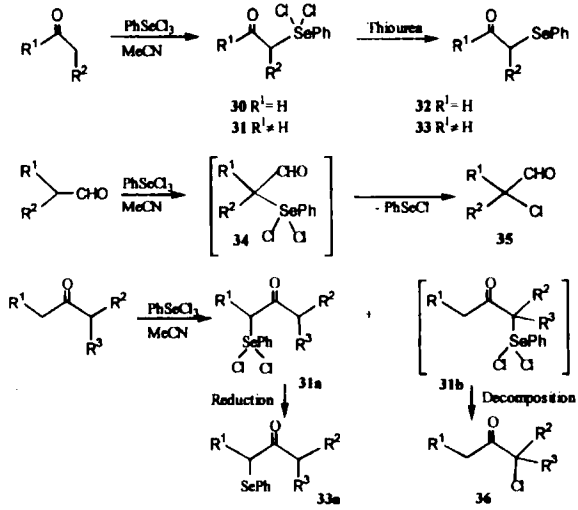


24 (R^2=H, Alk.) 25 26 27 28 29

SCHEME 7

II-3. α-Halocarbonyl compounds

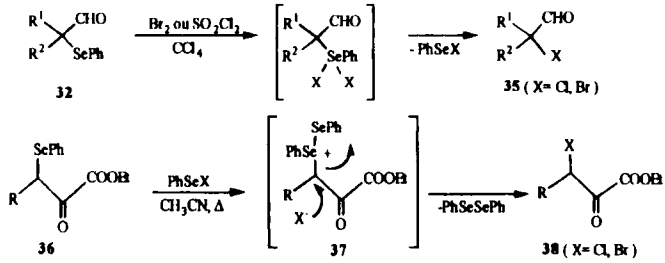
α-Phenylselanyl aldehydes and ketones **32** and **33** are pivotal substrates for numerous studies carried out in my laboratory. An mentioned in section I-2 (scheme 2), $PhSeCl_3$ is an efficient reagent for the preparation of α-phenylselanyl ketone dichloro-adducts **31**[27-29]. We have observed that adducts **30** were easily and quantitatively formed from linear aldehydes. Compounds **30** and **31** were reduced instantaneously by addition of thiourea[56] (scheme 8). We were able to prepare, in a multigramme scale, α-phenylselanyl aldehydes **32** previously synthetized by selenenylaton of aldehydes using N-phenylselanyl morpholine[57] or other selenenamides[58] as electrophilic selenium reagents.



SCHEME 8

Aldehydes with two α-alkyl groups have gave very unstable adducts **34** which were immediatly decomposed into α-chloro aldehydes **35**. α-Branched ketones have shown a similar behaviour. This observation allowed us to propose an efficient and regiocontrolled synthesis of α-phenylselanyl ketones **33a**[56]. $PhSeCl_3$ treatment of an unsymmetrical aliphatic ketone has given the two adducts **31a** and **31b** with different stabilities. The adduct **31b** decomposed rapidly with formation of the α-chloroketone **36** easily separated from the selenenylated ketone **33a** (scheme 8).

As indicated in section I-2, dibromo-adducts cannot be isolated. The decomposition of dichloro-adducts **34** and of the corresponding dibromo derivatives formed by halogenation of α-branched α-phenylselanyl aldehydes have led, respectively to α-chloro aldehydes **35** and α-bromo aldehydes of same structure[30]. In the course of this study, we have observed that an enantiomerically enriched sample of 2-phenyl-2-phenylselanyl propanal afforded the corresponding α-chloro aldehyde with retention of configuration[30,58]. More recently, we have prepared β-halo α-oxoesters **38** from β-phenylselanyl α-oxoesters **36** ,in good yields, through halide ion displacement of PhSeSePh from phenylselanylselenonium halides **37**[50] (scheme 9).



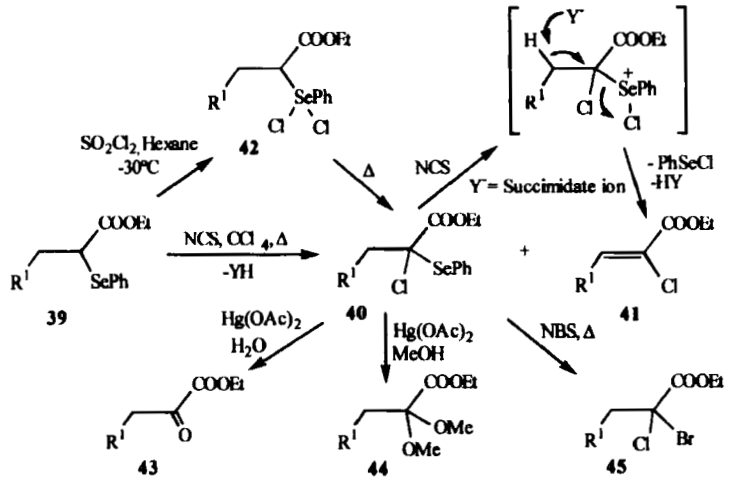
SCHEME 9

II-4. α-Chloro, β-chloro and α,β-dichloroesters

Besides our studies based on the reactivity of α-phenylselanyl carbonyl compounds[53], we were interested by reactions carried out on esters **39**. These substrates were conveniently prepared by selenenylation of ester enolates or alkylation of α-phenylselanyl ester enolates without important deselenenylation[59]. N-Chlorosuccinimide treatment of esters **39**, in hot CCl_4, afforded α-chloro α-phenylselanyl esters **40** in mixture with the unsaturated α-chloroesters **41**. Formation of **40** must involve an electrophilic chlorination of the selenium atom, followed by α-deprotonation by the succinimidate ion and 1,2-shift of chlorine. A second molar equivalent of NCS provided, in very good yields, the Z-unsaturated chloroesters **41**. A second selenium chlorination, followed by β-deprotonation and loss of PhSeCl, must occur (scheme 10).

SO_2Cl_2 treatment of esters **39** afforded very stable dichloro-adducts **42** leading to mixtures of compounds **39**, **40** and **41** on heating in various solvents. Mercuric acetate treatment of α-chloro α-

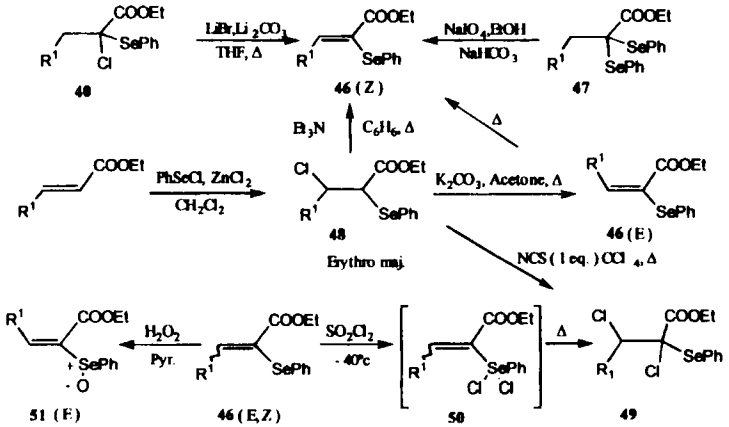
phenylselanyl esters **40** in acetone and water has produced α-oxoesters **43** and the corresponding dimethyl acetals **44** when the reaction was achieved in methanol. Reaction of N-bromosuccinimide with esters **40** has provided α-bromo α-chloroesters **45**, albeit isolated in poor yields[59] (scheme 10).



SCHEME 10

Thermal HCl-elimination on α-chloro α-phenylesters **40**, in the presence of LiBr and Li_2CO_3, has provided a new method for the preparation of α-phenylselanyl α,β-unsaturated esters **46**. The same Z-isomers of **46** were also obtained by sodium periodate oxidation of α,α-bis(phenylselanyl) esters **47**, prepared by selenenylation of α-phenylselanyl enolates[59]. A third route to the Z-esters **46** was obtained by dehydrochlorination of erythro β-chloro α-phenylselanyl esters **48**, synthetized from E-α,β-unsaturated esters[60]. The kinetic E-isomer of

46 was first formed on heating in acetone in the presence of K_2CO_3 (scheme 11). α,β-Dichloro α-phenylselanyl esters **49** were synthetized by NCS treatment of esters **48** and resulted also from decomposition of the unstable dichloro-adducts **50** formed at low temperature from unsaturated esters **46**. During this study, it was observed that esters **46** afforded stable vinylic selenoxides **51** with E-configuration whatever the stereochemistry of the substrate[59] (scheme 11).



SCHEME 11

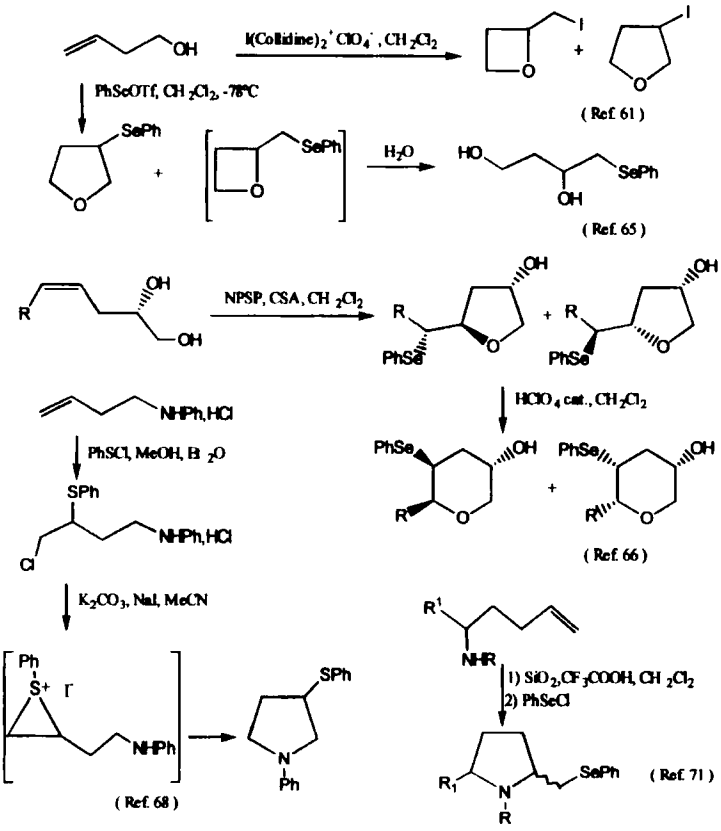
III. SYNTHESIS OF AZETIDINES AND PYRROLIDINES

III-1. Selenium-induced cyclization reactions

The selenium-induced cyclization allowing access to various saturated heterocyclic compounds is well known[2]. This methodology

was applied in numerous synthesic works and compares well with the iodo-cyclization method for the synthesis of tetrahydrofuranes, tetrahydropyranes and lactones from unsaturated alcohols and carboxylic acids. According to Baldwin's rules, the exo-mode is favoured for cyclizations leading to 5- and 6-membered heterocycles. Using $I(collidine)_2^+$ perchlorate[61] or iodide[62-64], 2-iodomethyloxetane derivatives were synthetized. Iodo-cycloetherification of but-3-enol has produced a mixture of two compounds corresponding to the exo and endo modes[61] (scheme 12). Geminal and vicinal disubstituent effects were found to favour formation of oxetane through a 4-exo process[62,63]. Using the selenium route, 2-(phenylselanylmethyl)oxetane was not isolated. Hydrolysis has led to 4-phenylselanylbutane-1,3-diol[65]. In a recent work[66], it was found that acid catalyzed cyclization of pent-4-ene-1,3-diols with N-phenylselanyl phthalimide afforded mixtures of 3-hydroxy tetrahydrofuranes slowly isomerized into 3-hydroxy tetrahydropyranes. Formation of oxetane derivatives were not observed (scheme 12).

Under acid catalysis, the carbamate group is a good nucleophilic group allowing access to pyrrolidines[2] and piperidines[67]. Ethyl hex-5-enylcarbamate was easily cyclized into ethyl-2-(phenylselanylmethyl) piperidine-1-carboxylate as shown in scheme 12[67]. Reaction of the HCl salt of N-phenyl but-3-enylamine with benzenesulfenyl chloride afforded the kinetic adduct then cyclized into 1-phenyl-3-phenylsulfanyl pyrrolidine according to a 5-endo mode[68]. Using the selenium methodology, scarce results were obtained with the cyclisation of N-alkyl pent-5-enylamines[69-71] and pyrrolidine derivatives were only isolated (scheme 12).



SCHEME 12

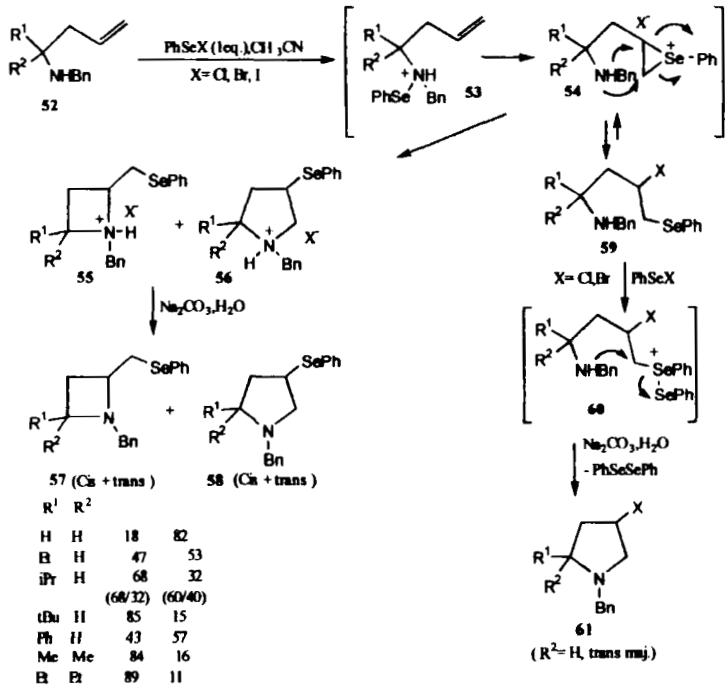
III-2. 2-(phenylselanylmethyl)azetidines and 3-phenylselanyl pyrrolidines

As recalled in section II-3, PhSeX (X = Cl, Br) reacts with secondary amines (2 eq.) to form unstable selenenamides[57, 58] and also

with olefinic compounds leading to addition products whose regiochemistry depends on the experimental conditions (paragraph I-3).

In a preliminary communication, we have disclosed that PhSeCl or PhSeBr (1.5 eq.) reacted in CH_2Cl_2 or CH_3CN at room temperature, in presence of sodium carbonate, with homoallylic benzylamines easily prepared from imines by a Barbier type reaction (allylchloride, Mg, THF)[72]. Silica gel chromatography has allowed the separation of cis-azetidine **57** from cis and trans-pyrrolidines **58** (R = H). A ^{77}Se NMR study of the crude products has revealed the presence of the four isomers. The unstable trans-azetidine **57** was isomerized during the purification. Trans-azetidines **57** (R^1 = iPr, R^2 = H and R^1 = tBu, R^2 = H) were however stable enough to be isolated. The ratio of azetidines was found to increase with the size of R^1 (R^2 = H) and when two α-substituents are present, according to previous observations in relation with the steric hindrance on the α- position[62,63]. In these cases, cis-azetidines **57** were isolated with more than 50% yield. A more detailed kinetic study has shown that the overall process is very complex. In the presence of sodium carbonate, we have first observed the formation of diphenyldiselenide, the two addition products and the corresponding dihalo-adducts, before a slow cyclisation ileading to **57** and **58**. The azetidinium and pyrrolidinium salts **55** and **56** were more rapidly formed in the absence of sodium carbonate. This observation seems to indicate that salts **55** and **56** result from the two diastereoisomeric selenonium intermediates **54**. We think that the selenoammonium salt **53** was first formed since a small ^{77}Se NMR signal, attributed to the corresponding selenenamide[73], was observed (scheme 13). The more important fact of this study was the first synthesis of azetidines by

electrophilic induced cyclization of homoallyl amines. The mechanism of this new reaction is not completely elucidated but it seems that the selenenamide group is not the nucleophile in the formation of the heterocycle.



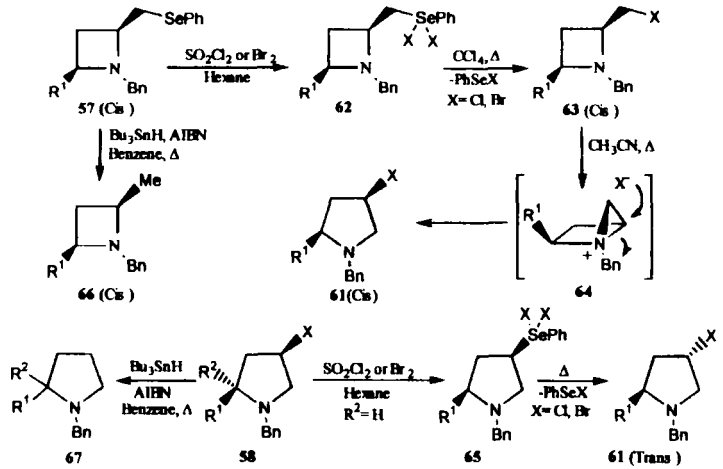
SCHEME 13

Another surprising result was the isolation of 3-halopyrrolidines **61** (R^2 = H, trans major), after basic treatment, when more than 2.5 molar equivalents of PhSeX were used.. A prolonged heating in CH_3CN was needed for amines **52** (R^1, $R^2 \neq H$)[50]. The mechanism of the overall process is under investigation but we think that formation of the

halopyrrolidines **61** results from $PhSe^+$ activation of the thermodynamic addition product **59**. The intermediate selanylselenonium salt **60** must undergo a nucleophilic attack of the amine group with loss of diphenyldiselenide. The trans-isomer was the major product (trans/cis = 90/10) for R^2= H.

III-3. Stereocontrolled synthesis of 1,2-disubstituted-3-halopyrrolidines

In continuation of our study on selenide dihalo-adducts, the cis-(phenylselanylmethyl)azetidines **57** were converted into dihalo derivatives **62** which were found especially stable for X = Cl. The decomposition was carried out in boiling CCl_4 and the cis-halomethyl azetidines **63** were isolated. On prolonged heating in CH_3CN, a ring-expansion occured with formation of cis-2-alkyl-4-chloro or 4-bromo pyrrolidines **61** (cis) via the aziridinium intermediate **64**. Such stereospecific rearrangements are known on azetidines[74] and pyrrolidines[75] having a 2-methyl substituent bearing a good leaving group. The decomposition of dihalo-adducts, derived from 3-phenylselanyl pyrrolidines **58** (cis), was an interesting entry to trans 2-alkyl 4-halopyrrolidines **61**[65]. The reductive deselenelylation of azetidines **57** (cis) and pyrrolidines **58**, using the classical radical method, has allowed the synthesis of 1,2,4-trialkylazetidines **66** (cis) and 1,2,2-trialkylpyrrolidines **67**[50] (scheme 14).



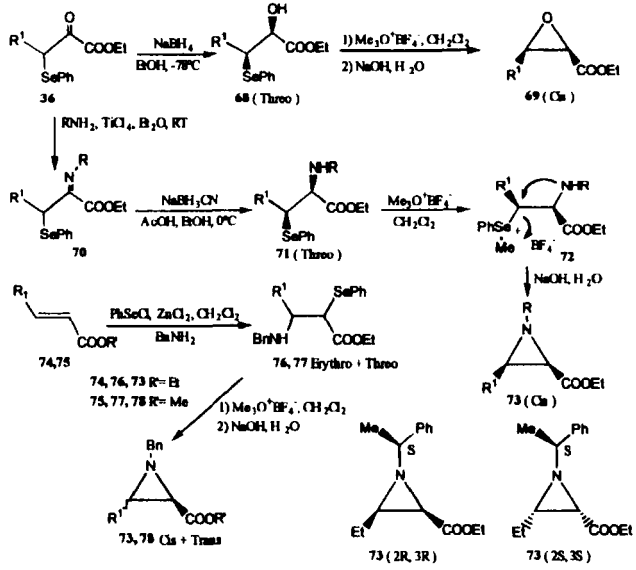
SCHEME 14

IV. REACTIVITY OF β-AMINOALKYL PHENYLSELENIDES

IV-1. Aziridination of α-alkylamino β-selanylesters and β-amino α-selanylesters

β-Phenylselanyl α-oxoesters **36** were reduced into threo hydroxyesters **68**, at low temperature with an excellent stereoselectivity. These hydroxyesters were cyclized into cis epoxy-esters **69** using the experimental conditions given in I-1[76]. The corresponding imines **70** (R = Bn, (S)-CH(Ph)Me) were reduced by $NaBH_3CN$ into α-aminoesters **71** with the same threo selectivity induced by the ester group (scheme 15). It must be observed that reduction of ketones **36** and imines **70** was achieved with a very low hydride deselenenylation.

The corresponding methylselenonium tetrafluoroborates 72 were formed and treated with an alkaline solution. They were stereospecificially cyclized into cis-ethyl aziridinecarboxylates 73 with correct yields[77]. The two diastereoisomers 73 (2S,3S) and 73 (2R,3R) were formed in equal amounts when the (S)-2-phenylethyl aminoester 71 (R^1 = Et) was used as substrate. No isomerisation has occured during the alkaline treatment of the selenonium salt 72. This new aziridination process was achieved on β-benzylamino α-phenylselanyl esters 76 and 77 (erythro, threo mixtures) prepared by activated amino-selenenylation of α,β-unsaturated esters 74 and 75[60]. The aziridination process, applied to the aminoesters 76 and 77, has led to cis/trans mixtures of alkyl aziridinecarboxylates 73 and 78[77] (scheme 15).

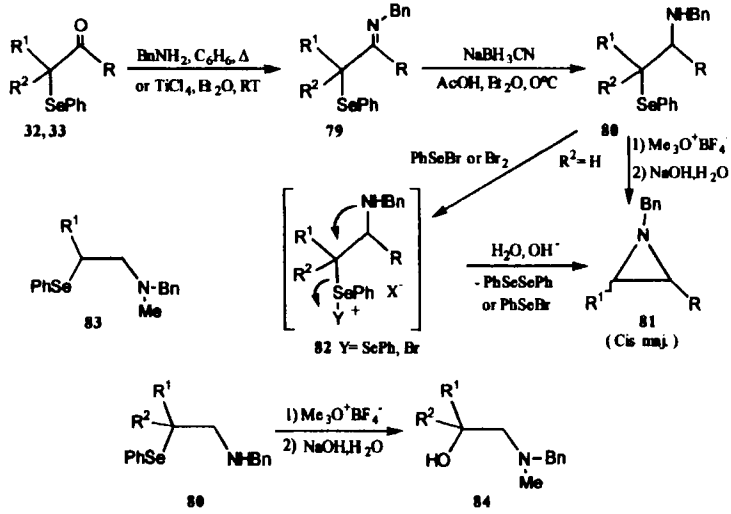


SCHEME 15

IV-2. Aziridination of β-aminoalkyl phenylselenides

The aziridination process above described was then applied to non-functionalized β-alkylamino phenylselenides **80**. These substrates were prepared by $NaBH_3CN$ reduction of imines **79** prepared by reaction of aldehydes **32** and ketones **33** with benzylamine on heating in benzene[78] or in the presence of $TiCl_4$ at room temperature[77]. A total threo selectivity was observed during the reduction of **80** (R = Ph) as for imino-esters **70**. The threo isomer was the major product in the other cases and the competitive deselenenylation was found very low.

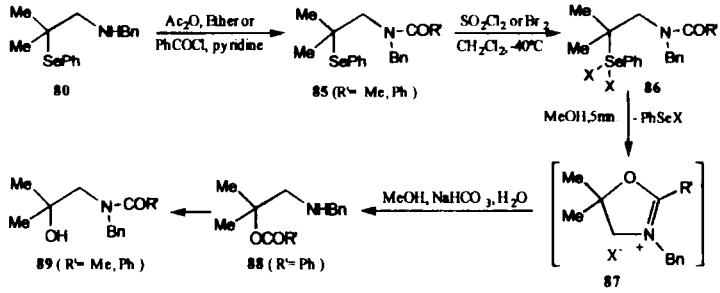
The aziridination was observed only when R^2 = H as for epoxidation reactions[12,14,15]. Cis/trans mixtures of aziridines **81** and trans-aziridine **81** (R = Ph, R^1 = Me) were formed. The stereochemistry reflects the erythro/threo ratio of the substrates[77]. Methylation of the nitrogen atom did not occured before that of the selenium atom except for **80** (R = H, R^1 = iPr). In this case, the tertiary amine **83** (R^1 = iPr) was also formed. The amino selenide **80** (R^1 = R^2 = Me) has led to the amino alcohol **84** after alkylation of the amino group and hydrolysis of the selenonium salt. More recently, we have found that aziridines **81** can be also prepared, in good yields, by Br_2 or PhSeBr activation and formation of the intermediate **82** (Y = Br or SePh)[50] (scheme 16).



SCHEME 16

IV-3. β-Aminoalkyl phenylselenide dihalo-adducts

Acetamide and benzamide **85** (R = H), derived from aminoselenide **80** (R = H, R^1 = R^2 = Me), afforded stable dihalo-adducts **86** (X = Cl, Br). NaOMe treatment of **86** in methanol has led quite instantaneously to the oxazolinium salts **87** isolated for R^1 = Ph. A prolonged treatment has provided the hydroxy amides **89** via the amino esters **88** characterized for R = Ph. The whole sequence was equivalent to an activated hydrolysis of the N-(phenylselanylmethyl) amides **85**[78] (scheme 17).



SCHEME 17

CONCLUSION

In this lecture, I have assembled recent results related to various nucleophilic substitutions and cyclizations achieved on phenylselenenylated structures activated as selenonium species. Alkyl selenonium salts are not only good substrates for the generation of stabilized ylides and carbenium ions, but are also efficient leaving groups in S_N2-type reactions. After the well-known synthese of epoxydes from β-hydroxy selenides, we can now add the stereospecific preparation of aziridines from β-alkylamino selenides. Dichloro and dibromo-adducts are useful intermediates for the synthesis of various functionalized halo-compounds through direct S_N2 displacement or S_N2' halogenation of allylic structures. The ability of some phenylselanyl substituents to form unstable selanylselenonium salts by capture of $PhSe^+$ from PhSeX (X = Cl, Br, I, OTf, $OCOCF_3$, OSO_3^-...) allows numerous nucleophilic substitutions especially useful for the synthesis of N- and O-heterocyclic compounds. All these reactions,

carried out on easily accessible functionalized structures bearing a PhSe group, increase the interest of the selenium methodology in organic synthesis.

References

[1] T. Wirth, *Organoselenium Chemistry: Modern developments* in *Organic Synthesis. Topics* in *Current Chemistry*, Vol. 208, Springer Berlin (2000).

[2] C. Paulmier, *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press, Oxford (1986).

[3] D. Liotta, *Organoselenium Chemistry*,Wiley, New-York (1987).

[4] S. Patai, *The Chemistry of Organic Selenium and Tellurium Compounds*, Wiley, New-York, Vol 1 and 2 (1987).

[5] T. Wirth, *Tetrahedron*, **55**, 1 (1999).

[6] W.R. Bowman, C.F. Bridge, P. Brookes, *J. Chem. Soc., Perkin Trans. 1*, 1 (2000). P. Reanud, L. Andrau, L. Schenk, *Synlett.*, 1462 (1999). J. Zhang, D.L.J. Clive, *J. Org. Chem.*, **64**, 770 (1999). A. Ogawa, I. Ogawa, R. Obayashi, K. Umezu, M. Doi, T. Hirao, *J. Org. Chem.*, **64**, 86 (1999). D. Crich, X-S. Mo, *J. Am. Chem. Soc.*, **120**, 8298 (1998). J.H. Byers, E.H. Shaughnessy, T.N. Mackie, *Heterocycles*, **48**, 2071 (1998) and references cited therein.

[7] A. Krief, N. Dumont, J-N. Denis, G. Evrard, B. Norberg, *Chem. Commun.*, 569 (1985).

[8] A. Krief, W. Dumont, J-N. Denis, *Chem. Commun.*, 571 (1985).

[9] A. Krief, W. Dumont, J-L. Laboureur, *Tetrahedron Lett.*, **29**, 3265 (1988). A. Kaye, S. Neidle, C.B. Breese, *Tetrahedron Lett.*, **29**, 2711 (1988).

[10] A. Krief, W. Dumont, A.F. De Mahieu, *Tetrahedron Lett.*, **29**, 3269 (1988).

[11] M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, D. Bartoli, *Gazz. Chim. Ital.*, **117**, 423 (1987).

[12] A. Krief, *Tetrahedron*, **36**, 2531 (1980).

[13] M.S. Chambers, E.J. Thomas, *Chem. Commun.*, 23 (1989).

[14] M. Clarembeau, A. Cravador, W. Dumont, L. Hevesi, A. Krief, J. Lucchetti, D. Van Ende, *Tetrahedron*, **41**, 4793 (1985).

[15] D. Labar, A. Krief, B. Norberg, G. Evrard, F. Durant, *Bull. Soc. Chim. Belg.*, **94**, 1083 (1985).

[16] A. Krief, J. Bousbaa, M. Hobe, *Synlett*, 320 (1992).

[17] M. Sevrin, A. Krief, *Tetrahedron Lett.*, **21**, 5856 (1980).

[18] D.H.R. Barton, D. Crich, Y. Herve, P. Potier, J. Thierry, *Tetrahedron*, **41**, 4347 (1985).

[19] M. Hori, T. Kataoka, M. Shimizu, K. Tsutsumi, *J. Org. Chem.*, **52**, 1397 (1987).

[20] Y. Ito, T. Ogawa, *Tetrahedron Lett.*, **29**, 1061 (1988).

[21] L. Engman, *Tetrahedron Lett.*, **28**, 1463 (1987).

[22] L. Engman., *Chem. Scripta*, **27**, 515 (1987). L. Engman, *J. Org. Chem.*, **52**, 4086 (1987).

[23] L. Engman, *J. Org. Chem.*, **54**, 884 (1989).

[24] L. Engman, *Tetrahedron Lett.*, **26**, 6385 (1985).

[25] M. Sevrin, W. Dumont, L. Hevesi, A. Krief, *Tetrahedron Lett.*, 2647 (1976). M. Sevrin, A. Krief, *J. Chem. Soc., Commun.*, 656 (1980).

[26] O.K. Edwards, W.R. Gaythwaite, J. Kenyon, H. Phillips, *J. Chem. Soc.*, 2293 (1928). D.G. Foster, *J. Am. Chem. Soc.*, **55**, 822 (1933). D.G. Foster, *Rec. Trav. Chim. P.B.*, **53**, 405 (1934). O. Behagel, K. Hofmann, *Ber.*, **72**, 697 (1939).

[27] L. Engman, *J. Org. Chem.*, **53**, 4031 (1988).

[28] L. Engman, J. PERSON, U. TILSTAM, *Tetrahedron Lett.*, **30**, 2665 (1989).

[29] M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, D. Bartoli, *Tetrahedron*, **44**, 2261 (1988).
[30] C. Paulmier, F. Outurquin, J-C. Plaquevent, *Tetrahedron Lett.*, **29**, 5893 (1988).
[31] (a) A.M. Morella, A.D. Ward, *Tetrahedron Lett.*, **25**, 1197 (1984). (b) A.M. Morella, A.D. Ward, *Tetrahedron Lett.*, **26**, 2899 (1985).
[32] P. Grice, S.V. Ley, J. Pietruszka, H.W.M. Priepke, E.P.E. Walther, *Synlett*, 781 (1995).
[33] G. Horne, W. Mackie, *Tetrahedron Lett.*, **40**, 8697 (1999).
[34] K. Chikamatsu, T. Otsubo, F. Ogura, H. Yamaguchi, *Chem. Lett.*, 1081 (1982).
[35] S. Uemura, S-I. Fukuzawa, T. Yamauchi, K. Hattori, S. Mizukati, K. Tamaki, *J. Chem. Soc., Perkin Tr. I*, 1983 (1986).
[36] S. Uemura, K. Ohe, S-I. Fukuzawa, *Tetrahedron Lett.*, **26**, 8958 (1985).
[37] S. Raucher, *Tetrahedron Lett.*, 3909 (1977). S. Raucjer, *J. Org. Chem.*, **42**, 2950 (1977).
[38] L. Engman, *J. Org. Chem.*, **54**, 884 (1989).
[39] G.H. Schmidt, D.G. Garratt, *Tetrahedron*, **41**, 4787 (1985).
[40] J. Kutateladze, J.L. Kice, T.G. Kutateladze, N.S. Zefiron, N.V. Zyk, *Tetrahedron Lett.*, **33**, 1949 (1992).
[41] Y.J. Abul-Hajj, *J. Org. Chem.*, **51**, 3380 (1986).
[42] P. Ceccherelli, M. Curini, M.C. Marcotullio, O. Rosati, *Tetrahedron Lett.*, **30**, 3175 (1989).
[43] M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, D. Bartoli, *Tetrahedron*, **44**, 2273 (1988).
[44] M. Tingoli, M. Tiecco, L. Testaferri, A. Temperini, *J. Chem. Soc., Chem. Commun.*, 1883 (1994).
[45] M. Tingoli, L. Testaferri, A. Temperini, M. Tiecco, *J. Org. Chem.*, **61**, 7085 (1996).
[46] M. Tiecco, L. Testaferri, A. Temperini, F. Marini, L. Bagnoli, C. Santi, *Synth. Commun.*, **27**, 4131 (1997).
[47] M. Tiecco, L. Testaferri, F. Marini, A. Temperini, L. Bagnoli, C. Santi, *Synth. Commun.*, **29**, 1773 (1999).
[48] S. Metha, B.M. Pinto, *J. Org. Chem.*, **58**, 3269 (1993).
[49] P. Lerouge, C. Paulmier, *Tetrahedron Lett.*, **25**, 1983 (1984). P. Lerouge, C. Paulmier, *Tetrahedron Lett.*, **25**, 1987 (1984).
[50] Unpublished results.
[51] K.B. Sharpless, R.F. Lauer, *J. Org. Chem.*, **37**, 3973 (1972). T. Di Giamberardino, S. Halazy, N. Dumont, A. Krief, *Tetrahedron Lett.*, **24**, 3413 (1983). A. Spaltenstein, P.A. Carpino, F. Miyake, P.B. Hopkins, *J. Org. Chem.*, **52**, 3759 (1987).
[52] J-F. Duclos, F. Outurquin, C. Paulmier, *Tetrahedron Lett.*, **34**, 7417 (1993).
[53] S. Boivin, F. Outurquin, C. Paulmier, *Tetrahedron*, **53**, 16767 (1997).
[54] J-F. Duclos, F. Outurquin, C. Paulmier, *Tetrahedron Lett.*, **36**, 2627 (1995).
[55] P. Lerouge, C. Paulmier, *Bull. Soc. Chim. Fr. II*, 1219 (1985). J-F. Huot, Thesis, Rouen (1991).
[56] D. Houllemare, S. Ponthieux, F. Outurquin, C. Paulmier, *Synthesis*, 101 (1997).
[57] C. Paulmier, P. Lerouge, *Tetrahedron Lett.*, **23**, 1557 (1982). P. Lerouge, C. Paulmier, *Bull. Soc. Chim. Fr. II*, 1219 (1985).
[58] C. Paulmier, F. Outurquin, J-C. Plaquevent, *Tetrahedron Lett.*, **29**, 5889 (1988). C. Paulmier, *Encyclopedia of Reagents for Organic Synthesis*. Wiley ed. (1995).
[59] L. Lebarillier, Thesis, Rouen (1999).
[60] G.C. Torchiarolo, F. D'Onofrio, R. Margarita, L. Parlanti, G. Piancatelli, M. Bella, *Tetrahedron*, **54**, 15657 (1998).
[61] R.D. Evans, J.W. Magee, J.H. Schauble, *Synthesis*, 862 (1988).
[62] M.E. Jung, C.J. Nichols, *Tetrahedron Lett.*, **37**, 7667 (1996).
[63] M.E. Jung, *Synlett*, **51**, 843 (1999).
[64] P. Galatsis, S.D. Millan, P. Nechala, G. Fergusson, *J. Org. Chem.*, **59**, 6643 (1994).
[65] S. Murata, T. Suzuki, *Tetrahedron Lett.*, **28**, 4297 (1987).

[66] M. Gruttadauria, R. Noto, *Tetrahedron Lett.*, **40**, 8477 (1999).
[67] A.M. Morella, A.D. Ward, *Aust. J. Chem.*, **48**, 445 (1995).
[68] T. Ohsawa, M. Ihara, K. Fukumoto, T. Kametani, *J. Org. Chem.*, **48**, 3644 (1983).
[69] S.R. Wilson, R.A. Sawicki, *J. Org. Chem.*, **44**, 287 (1979).
[70] S. Danishefsky, E.M. Berman, M. Ciufolini, S.J. Etheredge, B.E. Segmuller, *J. Am., Chem. Soc.* **107**, 3891 (1985).
[71] M. Wawa, H Aiura, K. Akiba, *Heterocycles*, **26**, 929 (1987).
[72] B. Berthe, F. Outurquin, C. Paulmier, *Tetrahedron Lett.*, **38**, 1393 (1997).
[73] C. Paulmier, P. Lerouge, F. Outurquin, S. Chapelli, P. Granger, *Magn. Res. Chem.*, **25**, 955 (1987).
[74] T. Masuda, A. Chinone, M. Ohta, *Bull. Chem. Soc. Jpn.*, **43**, 3787 (1970).
[75] E.G. Brain, F.P. Doyle, M.D. Mehta, *J. Chem.Soc.*, 633 (1961). J-M. Surzur, L. Stella, P. Tordo, *Bull. Soc. Chim. Fr.*, 115 (1970). J.A. Deyrup, S.C. Clough, *J. Org. Chem.*, **39**, 902 (1974). K.E. Harding, S.R. Burks, *J. Org. Chem.*, **49**, 40 (1984). J. Cossy, C. Duma, D.G. Pardo, *Eur. J. Org. Chem.*, 1693 (1999).
[76] S. Boivin, Thesis, Rouen (2000).
[77] S. Boivin, F. Outurquin, C. Paulmier, *Tetrahedron Lett.*, **41**, 663 (2000).
[78] S. Boscher, Thesis, Rouen (1994).