Recent Advancements in the Homoallylamine Chemistry

Cristian Ochoa Puentes and Vladimir Kouznetsov*

Laboratory of Fine Organic Synthesis, School of Chemistry, Industrial University of Santander, A.A. 678, Bucaramanga, Colombia

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New advances in preparation of homoallylamines are discussed. Novel syntheses of saturated nitrogen-containing heterocycles from *N*-substituted homoallylic amines are reviewed.

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1. Introduction.

2. Homoallylamine Synthesis.

2.1. Nucleophilic Addition to Imines and Iminium Ions.

2.1.1. Diastereoselective Addition of Allyl Organometallic Reagents.

2.1.2. Asymmetric Addition of Allylmetal Reagents.

2.1.3. Homoallylamine Synthesis by a Three-component Reaction.

2.2. [3,3]-Sigmatropic Rearrangement of *N*-Protected Amino Acid Allylic Esters.

2.3. [2,3]-Sigmatropic Rearrangements of *N*-Allyl α-Amino Esters or Allylic Ammonium Salts.

2.4. Miscellaneous Synthesis.

3. Synthesis of Saturated Nitrogen Heterocycles from Homoallylamines.

3.1. Synthesis of Azetidine, Pyrrolidine and Piperidine Derivatives.

3.2. Synthesis of Tetrahydro-quinoline and -benzazepine Derivatives.

4. Final Remarks.

5. Abbreviations.

6. Acknowledgments.

7. References.

1. Introduction.

N-Substituted but-3-enylamines, namely, homoallylamines are emerging as powerful and useful precursors for the construction of diverse saturated nitrogen heterocycles. These precursors have several important biochemical aspects. The homoallylamines are stable, available and cheap initial materials. Diverse homoallylamines possess a particular skeleton in which chemical units (C=C double bond, NH and/or N-Ar and N-Bn substituted groups as well as aryl or hetaryl substituents at the position C-1 of unsaturated chain) might be involved in the construction of heterocyclic rings of different size. Moreover, making asymmetric synthesis of homoallylic amines, they could offer real facilities to assemble chiral heterocycles in a straight way. Finally, being biogenic amines, the homoallylamines represent very attractive biological targets.

Thus, it is not surprising that these relatively simple compounds have attracted the attention of a wide range of organic, heterocyclic and medicinal chemists, which address often to prepare bioactive *N*-heterocycles.

N-Substituted but-3-enylamines (homoallylamines) are considered as CH_2-analogs of allylamines, which chemistry has been well studied. Moreover, allylic and propargylic amines play a prominent role in organic synthesis, and their importance continues to grow with time [1,2]. However, to the best our knowledge, there has not been any attempts to revise the state of chemistry of homoallylamines in the literature. This review will describe the results of new developments in the preparation of homoallylamines and their synthetic routes for straightforward synthesis of nitrogen-containing heterocycles.

2. Homoallylamine Synthesis.

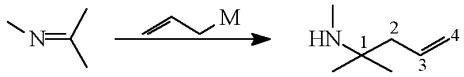
A plethora of synthetic methods have been devised for the preparation of homoallylic amines. All methods for their synthesis can be divided into four groups: a) nucleophilic addition to imines and iminium ions; b) [3,3]-sigmatropic

rearrangement of *N*-protected amino acid allylic esters; c) [2,3]-sigmatropic rearrangements of *N*-allyl α-amino esters or allylic ammonium salts; d) miscellaneous synthesis.

2.1. Nucleophilic Addition to Imines and Iminium Ions.

The addition of nucleophiles to imines is an important route to amines and has been investigated in depth. Perhaps among the synthetic arsenal of organometallic compounds, allylic derivatives are the most popular, because of their well-defined stereo- and regio-chemistry. Addition of allylic organometallics to ald- and ketimines leads to the formation of diverse *N*-substituted *N*-(but-3-enyl)amines. Among the reasons for the interest in these derivatives, the three more important are the following: i) allyl organometallic reagents are in general more reactive than nonstabilized organometallic compounds for imine addition reactions [3]; ii) reaction of these reagents with ald- and ketimines provides a potentially valuable route to enantiomerically pure homoallylic amines; iii) obtained homoallylamines represent useful precursors for nitrogen-containing compounds such as natural product and pharmaceutically important compounds. Consequently, the imines are appropriated substances for the preparation of secondary and primary homoallylic amines (Scheme 1).

Scheme 1



It should not be surprising that reactions of allylic organometallic reagents with imines have attracted constant considerable interest of a wide range of organic chemists. Enormous material [4-10] accumulated during last 10-30 years on the diastereoselective addition of organometallic compounds (*e.g.* allylic organometallic reagents) to the double bond C=N of chiral imines (derived from chiral aldehydes as well as from chiral amines) and the enantioselective addition to non-chiral imines in the presence of a chiral catalyst testimony that allylmetal compounds are really "champions" in the organometallic domain.

During these past years many efforts have been made in order to improve the selective addition of allyl organometallic reagents to imines and their analogues (oximes, hydrazones and nitrones). Continuing researches in this domain include the use of new promoters, new reagents, new substances containing the C=N bond and new methods. These aspects have been discussed in several excellent reviews [4,9]. However, to provide a good understanding of the scope of the homoallylamine preparation, recent and older allylation reactions of imines will be included.

2.1.1. Diastereoselective Addition of Allyl Organometallic Reagents.

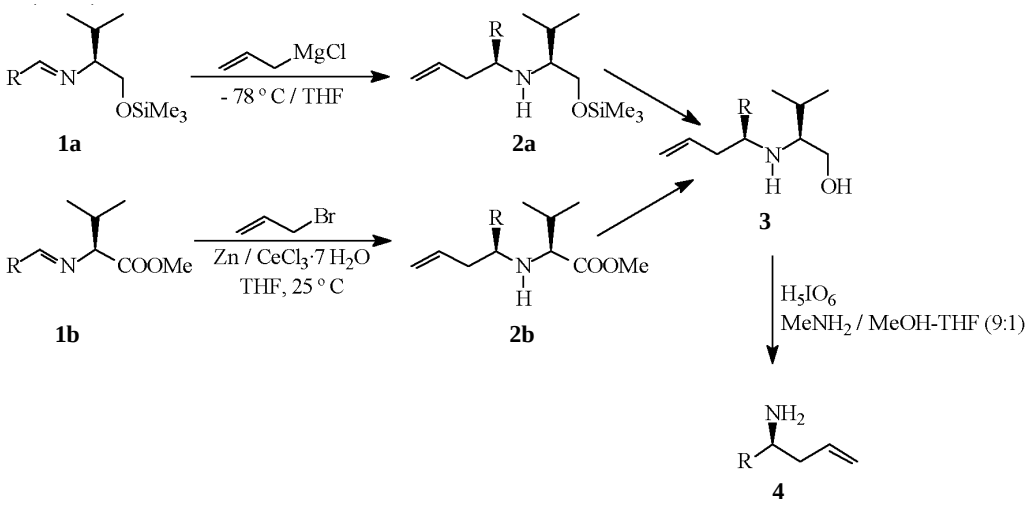
The need for the preparation of chiral compounds in enantiomerically pure form has increased lately as a result of several factors, mainly connected with a stereodiscrimination of chiral compounds by most biological systems and therefore the pressure on the pharmaceutical industry to develop nonracemic drugs. Moreover, the α-branched amine moiety is incorporated into many compounds such as amino acids or alkaloids encountered in medicinal chemistry. Since homoallylamines could be appropriate building blocks for the synthesis of chiral, enantiomerically pure *N*-heterocycles, special attention has been devoted to their preparations.

The Barbier and Grignard procedures [11,12] for imine allylation still remains one of the most reliable and efficient methods for preparing homoallylamines. When imines contain a chiral auxiliary on nitrogen (imines derived from α-arylethylamines, β-hydroxy amines, β-alkoxy amines and α-amino esters), is possible to get a high diastereoselectivity *via* the classical Grignard procedure. Since these groups allow a highly effective stereocontrol in the nucleophilic addition to the imine derivatives, due to the presence of a bulky substituent in the resident stereocentre. Moreover, the different auxiliaries allow a wide range of organometallic reagents to be applied, and sometimes provide variable levels of stereocontrol [4,5]. Various of these groups act not only as an effective chiral auxiliary, but also as *N*-protected group that could be removed to give the primary homoallylic amine, suitable for subsequent transformations. Cleavage of these groups in *N*-substituted homoallylic amines to obtain the primary amines depends generally on the nature of the *N*-protected group.

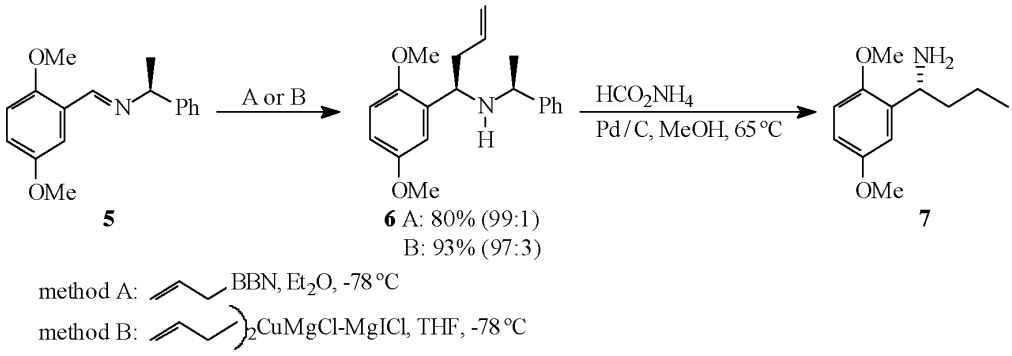
Valine methyl ester or valinol are a choice auxiliary for the synthesis of homoallylamines *via* the addition of a variety of allylmetals to either aliphatic or aromatic aldimines. For example, Savoia and co-workers reported that the (*S*,*S*)-homoallylamines **2a,b** was obtained with excellent diastereoselectivity using aldimines **1a,b** and classical allyl reagents [13,14]. Then, after acidic workup or reduction, (*S*,*S*)-homoallylamino alcohols **3** was converted to (*S*)-*N*-(1-R-but-3-enyl)amines **4** (Scheme 2).

In this case the auxiliary was easily removed from the secondary amine by oxidative cleavage with periodic acid in the presence of methylamine. Sometimes, the conditions of removal of the protecting group affect on the olefinic double bond, for example, when (*S*)-2,5-dimethoxybenzaldimine **5** are subjected to allylation reaction, corresponding secondary (*S*,*R*)-homoallylamine **6** is obtained in good yield. Usual hydrogenolysis conditions ($HCOONH_4$, Pd/C, MeOH) do not allow one to obtain to a primary amine with a suitable elaborated carbon skeleton and to produce the chiral primary (*R*)-amine **7** with a saturated chain [15] (Scheme 3).

Scheme 2



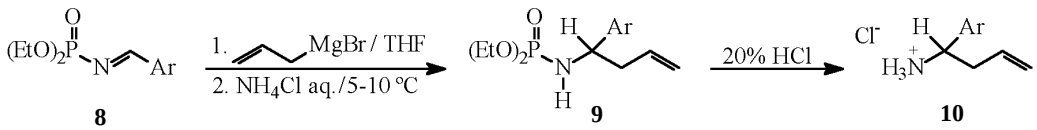
Scheme 3



The highly diastereoselective addition of allylzinc bromide to aldimines derived from (R)-phenylglycine amide is reported [16]. Final (*R*)-homoallylamines with high enantiomeric purity are obtained from the (*R,R*)-adducts in three steps on removal of the chiral auxiliary by means of a non-reductive protocol.

Alternative preparation of a primary amine molecule from different building blocks may involve the use of suitable "masked" imine derivatives such as sulfenimines, sulfonimines, *N*-diphenylphosphinylimines and *N*-(diethoxyphosphoryl)aldimines. The *N*-protected imines such as aldimines **8** reacted easily and smoothly with allylmagnesium bromide in THF at 20-25 °C to give the respective diethyl-*N*-homoallylphosphoramidates **9** in high yields. The standard deprotection of this latent group in molecule **9** resulted in the formation of *N*-(1-arylbut-3-enyl)amine hydrochlorides **10** [17] (Scheme 4). Although this method lacks stereochemical control of allyl addition, this simple procedure allows possessing primary homoallylic amines.

Scheme 4



Ar	Ph	4-MeC$_6$H$_4$	2-Thienyl	PhCH=CH	1-Naphthyl
%	65	63	57	47	59

The Barbier procedure involves the formation of the allylmetal reagent *in situ* using allyl bromide or chloride and metals such as cadmium, barium, bismuth, tantalium, indium, samarium, lead, ytterbium as well as magnesium and zinc with some additives and gives desired secondary homoallylic amines in good to excellent yields in mild conditions. Aldimines are transformed into homoallylamines by treatment with prenylbarium reagent, generated from prenyl chloride and barium in THF, in which both the α- and γ-adducts are selectively obtained by simply changing the reaction temperature [18].

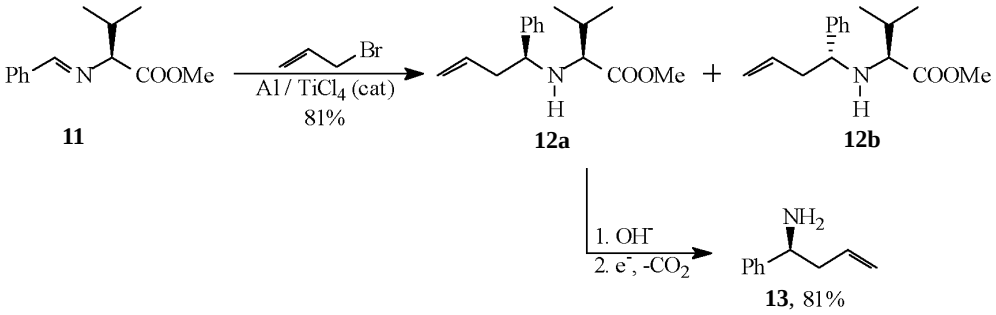
In the presence of chlorotrimethylsilane ytterbium metal can promote the allylation of aromatic aldimines with allylic bromide to give the corresponding homoallylamines in satisfactory yields in THF under mild conditions [19]. Sometimes this process lacks a high degree of diastereoselectivity [4]. However, some progress has been made in this domaine.

Barbier type allylation of ald- and ketimines has been performed successfully by the action of aluminum and titanium chloride in THF. When chiral imine **11** derived from (*S*)-valine was used, the diastereoselectivity was good (20:1) affording allylated (*S*,*S*)-*N*-benzal-valine ester **12a** and (*R*,*S*)-isomer **12b**. The major diastereoisomer was converted into the primary (S)-homoallylamine **13** by alkaline hydrolysis and electrolytic decarboxylation [20] (Scheme 5).

Among various allylmetal reagents, allylsilanes and allylstannanes are used very frequently in homoallylamine preparation. The former reagents are in general more stable, less reactive, and less toxic, whereas the latter reagents are less stable, more reactive, and significantly toxic. However, both are utilizing successfully in organic chemistry.

The allylation reaction of imines with allylsilanes in the presence of fluoride ions yields homoallylamines efficiently. To cleave the C-Si bond of these reagents, several fluoride compounds, CsF [25], NH_4F and TBAF are using as catalyst for these additions. Various homoallylamines can be prepared by the reaction of allyltrimethylsilane with aldimines in the presence of 1 mol% of TBAF. Since the commercially available TBAF contains a certain amount of water, the addition of 4Å Molecular Sieves (MS) is needed [26]. DeShong and Pilcher reported the condensation of imines and allyltrimethylsilane that is promoted by TBAT [27]. This salt is an easily handled crystalline solid that has several advantages over TBAF as a fluoride source: it is anhydrous, nohygroscopic, and soluble in most commonly used organic solvents (THF, toluene, acetonitrile), and solutions of TBAT in these solvents are significantly less basic than the corresponding

Scheme 5



11 **12a** **12b**

13, 81%

The chiral homoallylamine **12a** is obtained in quantitative yield with excellent to perfect diastereoselectivity with the help of a good additive (for example, $CeCl_3 \cdot 7H_2O$) [21].

Recently, Yanada and co-workers reported the diastereoselective Barbier type allylation of the methyl *N*-benzylidene-(*S*)-valinol with allyl halides and samarium (0) [22]. This team also reported palladium-mediated allylation of the same iminoether with allylindium reagents [23]. Both of these methods gives (*S*,*S*)-allylation product in high yields and in high diastereoselectivities.

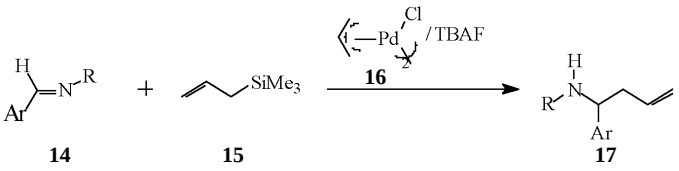
The reaction of enantiopure methyl *N*-benzyliden-(*S*)-valinate **11** with methallyl or prenylzinc reagents affords homoallylic amines having (*S*,*S*) configuration with up to 100% diastereomeric excess, but another diastereomer, (*R*,*S*)-homoallylamines, is prepared from the same iminoether by using triallylborone [24].

TBAF solutions. However, the reaction is not catalytic in the silicate salt.

Yamamoto and co-workers reported a novel allylation reaction of aldimines with allyltrimethylsilanes using a palladium-TBAF cocatalyst system [28]. The reaction of aldimines **14** with allylsilane **15** proceeded very smoothly at room temperature in the presence of a catalytic amount of π-allylpalladium chloride dimmer **16** (5 mol %) and TBAF in hexane-THF (4:1) co-solvent, giving the corresponding homoallylamines **17** (Scheme 6).

The stereoselective allylation of chiral benzaldimine chromium tricarbonyl complexes to give homoallyl amine complexes was studied [29]. The degree of this stereoselection depends on the catalyst and the reaction conditions. A

Scheme 6

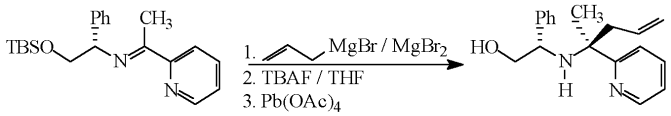


Ar	Ph	Ph	Ph	Ph	4-MeOC$_6$H$_4$	PhCH=CH (E)
R	Bn	Ph	4-MeOC$_6$H$_4$	*n*-Pr	Bn	Bn
%	69	96	89	50	57	62

good stereoselectivity in the crotylation of sulfonimines mediated by indium in aqueous media was also reported [30]. Aryl sulfonyl imines condense with chiral silane reagents in the presence of $BF_3{\cdot}OEt_2$ to form homoallylic arylsulfonyl amines with useful levels of syn selectivity [31].

Spero and Kapadia reported the synthesis of secondary (*S*,*S*)-homoallylic amine **19** using a novel method for the asymmetric synthesis of α,α-disubstituted alkylamines *via* Grignard additions to ketimine **18**, which contains (*S*)-phenylglycol moiety as the auxiliary [32]. The ee's of these reactions can be improved by the use of the TBS protected (*S*)-phenylglycol. Running this reaction in the absence of $MgBr_2$ gave a lower range of diastereoselectivities (Scheme 7). The key element in controlling the diastereoselectivity of this asymmetric Grignard reaction is chelating of the pyridine and imine nitrogens with this salt.

Scheme 7



18 **19**, 74%, 89% de

Facile oxidative cleavage (lead tetraacetate in CH_2Cl_2/MeOH) of this auxiliary resulted in the formation of the target amine with an α-branched carbon skeleton. The presence of a pyridine ring in homoallylamine **19** makes this molecule a very attractive precursor to the synthesis of biologically active pharmaceuticals.

2.1.2. Asymmetric Addition of Allylmetal Reagents.

The asymmetric addition of carbon nucleophiles to prochiral imines leading to optically active amines is a field which is still in its infancy, so the enantioselective addition of allylmetallic reagents to the C=N double bond is quite underdeveloped. However, some advances have been made in this domain [9,10].

N-Silylimines are principal precursors for the preparation of chiral primary homoallylamines. Recently, it was reported that the asymmetric allylboration of *N*-substituted imines **20**, with a variety of allylborating agents [33,34], including D-Ipc$_2$Ball **21** [35], give the (*S*) primary homoallylic amines **22** in excellent yields (Scheme 8).

Optically active *N*-sulfonylamino alcohols derived from D-camphor and norephedrine were found also to be efficient chiral ligands for the allylboration reagents. These reagents smoothly reacted with *N*-silylimines to give the corresponding homoallylic amines in high level of enantioselectivity up to 96% ee [34].

Authors [35] noted specially the importance of water in these interactions and observed that the reaction takes place during the aqueous workup. They concluded that it might have proceeded by rapid liberation of the aldimine intermediate from the *N*-trimethyl-silylaldimine derivative following the addition of water, with a fast reaction of these aldimines with allyl reagent **21**.

Enantioselective synthesis of optically active primary homoallylamines by allylboration of *N*-diisobutylaluminum imines from nitriles and DIBALH was described [36].

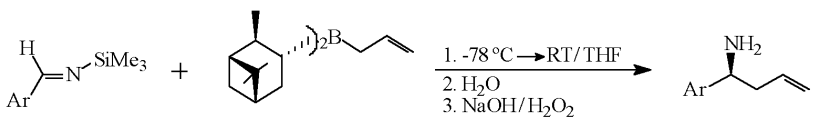
Recently, it was reported that a new catalytic enantioselective method for the formation of (*S*)-allyl α-amino acid derivatives **25** by reaction of *N*-tosyl α-imino ester **23** with tributyl allylstannane **24** in THF in the presence of chiral (*R*)-BINAP and copper (I) complexes [37] (Scheme 9).

This valuable γ,δ-unsaturated α-amino acid derivative was obtained in up to 94% and with up to 80% ee and could be used as building block for organic synthesis.

Searching an "ideal" aza-precursor containing the C=N double bond for the preparation of homoallylamines, organic chemists have used diverse chiral imine derivatives such as chiral oxime ethers, nitrones and hydrazones. There is a problem of the functional group tolerance in their use in order to obtain primary homoallylic amines. Oxime ethers appear to be privileged in this regard.

It was shown that the addition of allylmagnesium bromide to the C=N bond of oxime ethers **26** derived from (*R*)- and (*S*)-*O*-(1-phenylbutyl)hydroxylamine proceeds in

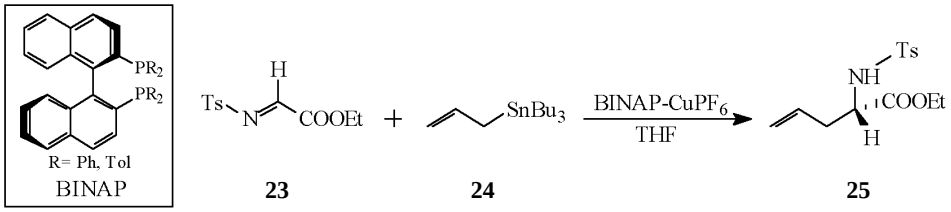
Scheme 8



20 **21** **22**, 81-92% ee

Ar = Ph, 2-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-Furyl, 2-Thienyl

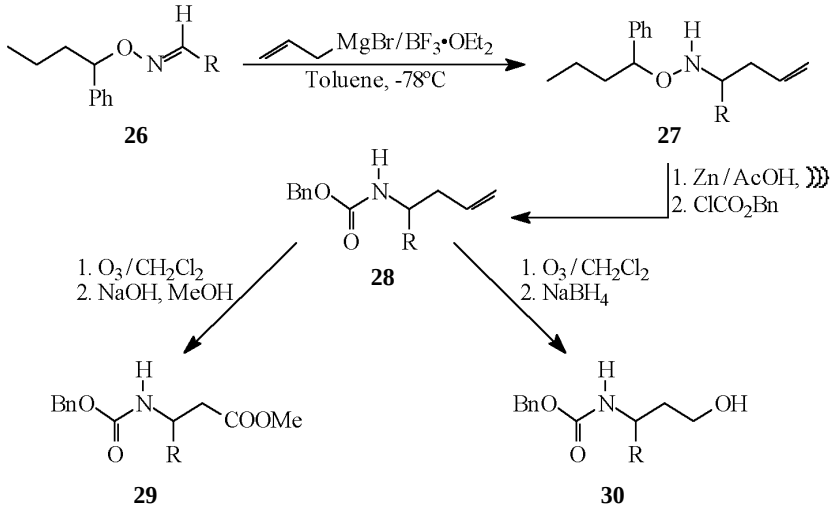
Scheme 9



23 **24** **25**

a highly diastereoselective manner [38]. The resulting allylated *O*-protected oximes **27** were subjected to cleavage of N-O bond (Zn/AcOH/ultrasound) and acylation (BnO_2CCl) to give *N*-acylated homoallylamines **28**. The latter were converted into β-amino acid derivatives **29** and γ-amino alcohols **30** (Scheme 10).

Scheme 10



26 **27** **28** **29** **30**

Acyl-or tosylhydrazones are useful imine surrogates and can be allylated. For example, allylindium adds to a variety of tosyl hydrazones from aromatic aldehydes at ambient temperature in a DMF-H_2O solvent system to afford homoallylic tosyl hydrazides [39]. Also, it was reported a high stereoselective synthesis of homoallylic amines based on addition of allyltrichlorosilanes to benzoylhydrazones [40].

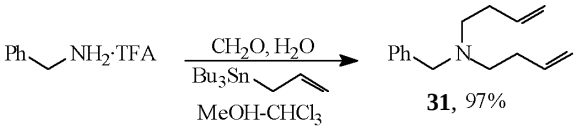
The invention and development of new efficient methods for the diastereo- and enantioselective synthesis of homoallylamines remains a major objective for synthetic organic chemists. One way to develop these methods is to apply a polymer-supported chiral π-allylpalladium catalyst [41] or a polymer-supported chiral allylmetal reagent [42] for the allylation of imines.

2.1.3. Homoallylamine Synthesis by a Three-component Reaction.

Diverse homoallylamines needed for the construction of bioactive substances are rapidly accessible by a direct three-component reaction. This methodology, which requires an aldehyde, an amine (or an amide) and a presynthesized allylic organometallic (Si, Sn or Ge), has proved to be very successful.

Grieco and co-workers reported that the water-promoted reaction of allyltributylstannane with iminium salts derived from benzylamine produces bis(homoallylamines) **31** [43] (Scheme 11).

Scheme 11



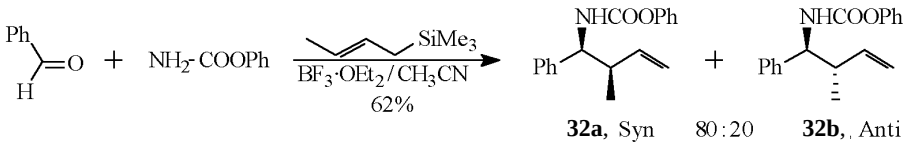
31, 97%

N-Benzyl, *N*-methylamine in this reaction with allyltributylstannane or allylsilane afforded the *N*-benzyl, *N*-(but-3-enyl)methylamine [43,44]. Similar three-component reactions of aldehydes, amines and allyltributylstanne in water in the presence of a small amount of scandium trifluromethanesulfonate and sodium dodecylsulfate were proven to be effective [45]. Three-component reaction of aldehydes, benzoylhydrazine and tetrallyltin proceeded smoothly in the presence of a catalytic amount of scandium triflate (1-5 mol %) to afford the corresponding homoallylic

hydrazines, which were readily converted to homoallylamines [46,47].

In another version of this methodology an acyliminium ion, formed *in situ* by the mixture of an aldehyde and a primary carbamate or sulfonate, is submitted to a nucleophilic of allylmetallic reagents such as allyl- and crotylsilanes [48,49]. Mann and co-workers reported a good syn diastereoselectivity in the synthesis of homoallylamines **32** using the crotylsilane [49]. The reaction between benzaldehyde, benzylcarbamate and crotylsilane in acetonitrile in the presence of $BF_3{\cdot}Et_2O$ gave a mixture (5/1) of syn- and anti- diastereomers **32a,b** (Scheme 12).

Scheme 12



32a, Syn 80 : 20 **32b**, Anti

N-Tosyliminium species, prepared *in situ* from carbonyl compounds and $TsNH_2$ with $SnCl_2$ and *N*-chlorosuccinimide, undergo nucleophilic addition of allylic silanes to the corresponding homoallylic amines [50].

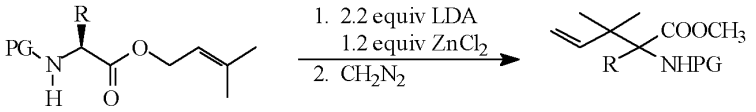
This promising methodology, which allows a direct access to homoallylamines from carbonyl compounds, is an active field of research [51-53]. Greeves and co-workers reported that the unactivated lanthanum triflate - benzoic acid catalyses the *in situ* formation and allylation of various aldimines with allyltributyltin [52]. Solid-supported three-component reaction is an efficient tool in the synthesis of a library of homoallylic amines. Such reaction, starting from the both immobilized carbamate and *N*-acyliminium species, was reported by chemists in Holland [53].

2.2. [3,3]-Sigmatropic Rearrangement of *N*-Protected Amino Acid Allylic Esters.

γ,β-Unsaturated amino acids (homoallylamines containing a carboxyl group) have become the subject of intense investigation due to their biological activity. The sigmatropic rearrangement processes (ester enolate Ireland-Claisen rearrangement) of glycine allylic esters have emerged as a new efficient method for α-substituted glycines. Ireland and co-workers introduced this methodology into amino acid chemistry in 1972-76 [54,55]. Then, Barlett and co-workers investigated the diastereoselectivity of this process [56]. Nowadays, this methodology has been applied successfully for diastereoselective synthesis of other amino acids with β-quaternary carbon centers (Kazmaier's method) [57-59]. The rearrangement of amino acid allylic esters occurs in a high diastereoselective fashion due to enolate fixation by chelation.

Deprotonation of *N*-protected amino acid allylic esters **33a** with LDA at –78 °C and subsequent addition of a metal salt ($ZnCl_2$, $AlMeCl_2$, $MgCl_2$, $Al(Oi\text{-}Pr)_3$) presumably results in the formation of chelated metal enolate, which undergoes rearrangement affording unsaturated amino acids **34** with two vicinal quaternary carbon centers [59] (Scheme 13). In general best results are obtained with zinc chloride and methylaluminum dichloride. The same rearrangement of unsymmetrically substituted allylic

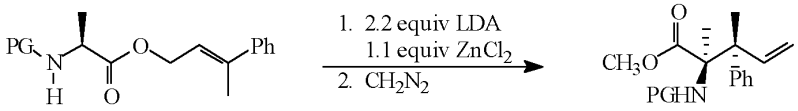
Scheme 13



33a **34**, 36-81%

PG - protecting group (Boc, Cbz, Ts or TFA)
R= H, CH_3, Bn

Scheme 14



33b **35**, 62%

PG = Boc, Cbz, Ts, TFA

esters **33b** proceeds with a high degree of diastereoselectivity, giving the syn (*S*,*S*)-product **35** (Scheme 14).

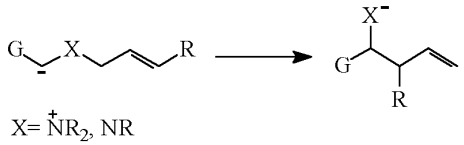
The observed diastereoselectivity (>95% ds) for the *E*-configured esters **33b** results from a preferential rearrangement *via* a chairlike transition state [59]. The similar rearrangement of *E*-silylpropene-glycinate esters under the standard Ireland-Claisen rearrangement conditions (sequential addition of the ester to LHMDS and quenching with chlorotrialkyl(aryl)silane and Et_3N) to syn α-allylsilane-amino acids gave good diastereoselectivity (19:1) favoring the formation of the syn product isomer [60].

Kazmaier's method is suitable for acyclic as well cyclic allylic esters [61,62] and can be applied to peptides [63].

2.3. [2,3]-Sigmatropic Rearrangements of *N*-Allyl α-Amino Esters or Allylic Ammonium Salts.

The [2,3]-sigmatropic rearrangement has also played an important role in providing allyl-transposed products. This rearrangement often occurs in high yields and with good degrees of stereocontrol, proceeding through a five-membered cyclic transition state. Most popular are the [2,3]-Stevens rearrangement of allylic ammonium salts and the [2,3]-aza-Wittig rearrangement of activated tertiary amines, containing a *N*-allyl moiety (Scheme 15).

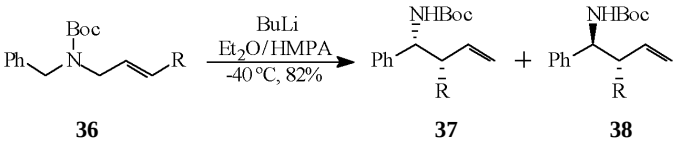
Scheme 15



Both approaches have potential for the formation of novel nonproteinogenic substituted allyl glycine derivatives, which play an important role in natural products and for biological investigations.

The one-pot *N*-alkylation and [2,3]-Stevens rearrangement of *N*-allyl-α-amino esters gives *N*,*N*-dialallylglycines in 42-65% yield [64]. Successful [2,3]-aza-Wittig rearrangements have been reported using *N*-Boc activating group in allylamine structure to afford homoallylic amides [65-68]. The rearrangement of *N*-Boc-*N*-[but-2(*E*)-enyl]benzylamine (**36**) under standard conditions for this type of sigmatropic rearrangements gave a 3:2 ratio of syn and anti diastereoisomers - (1*R*,2*S*)- **37** and (1*S*,2*S*)-**38** [65] (Scheme 16).

Scheme 16



36 **37** **38**

R	CH_3	C_2H_5	$(CH_3)_2CH$	$(CH_3)_3C$
%	82	69	54	--
37:38	3:2	1:1	4:3	--

In contrast, the reaction of similar *N*-protected tertiary benzylamines **39** led to the syn and anti homoallylic amines (1*R*,2*S*)- **40** and (1*S*,2*R*)-**41** with the high diastereoselectivities that indicate a concerted [2,3] sigmatropic mechanism [66] (Scheme 17).

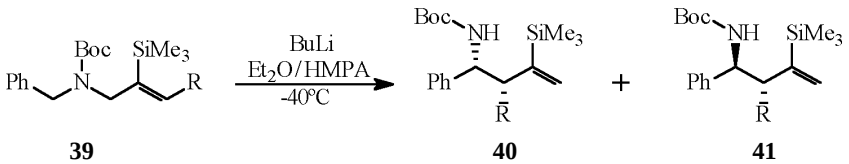
From obtained results it is clear that the trimethylsilyl group is not only acting as a steric control element in a direction consistent with the transition state model, but also increasing the rate of this reaction.

Another *N*-activated substrate suitable to use in this rearrangement is a *N*-phosphoramide tertiary amine, which furnished the related homoallylic amides [69].

Attempts to promote [2,3]-aza-Wittig rearrangement with tertiary amines leads to unreacted starting material or the [1,2] rearranged products. However, there are several reports of successful this rearrangement, using the tertiary amines in the presence of a Lewis acid [70-72]. Coldham and co-workers [70] found that the reaction of *N*-allyl α-amino esters **42a,b** to give rise to *N*-alkyl *C*-allyl glycine esters **43** in the presence of various Lewis acids in poor yield and the addition of iodomethane promotes quaternary ammonium salt formation of the tertiary amines **42a,b**, which spontaneously rearranges (DMF/K_2CO_3 DBU/40 °C) to *N*,*N*-dialkyl *C*-allyl glycine esters **44a,b** in good yields (Scheme 18).

These results suggest the aza-Wittig rearrangement of tertiary amines with Lewis acids is less effective than the [2,3]-Stevens rearrangement of quaternary ammonium salts.

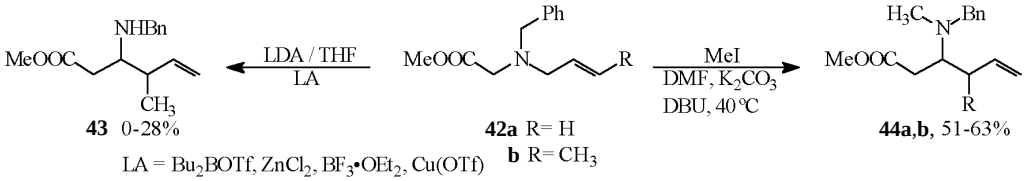
Scheme 17



39 **40** **41**

R	CH_3	C_2H_5	$(CH_3)_2CH$
%	88	92	94
40:41	1:20	1:18	1:11

Scheme 18



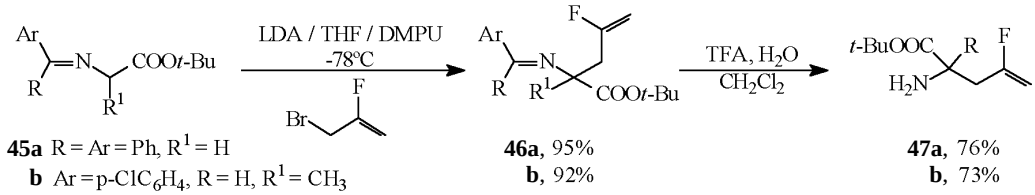
2.4. Miscellaneous Synthesis.

Because the homoallylamines are an attractive precursors for bioactive *N*-heterocycles and β-amino acids as well as β-lactams, several original reports on their synthesis were described.

C-Alkylation of *N*-tosylhexaflouroacetone imine with 4-allyl anisole *via* an ene reaction provided the *N*-tosyl-*N*-[2,2-di(triflourmethyl)-4-*p*-anisol-but-3-enyl]amine [73]. A simple method to prepare homoallylic amines from secondary homoallylic mesylates was reported [74].

Deprotonation of the Schiff's bases of glycine or alanine esters **45** by LDA in THF in the presence of DMPU at –78 °C and subsequent alkylation with 3-bromo-2-fluoropropene give α-*C*-allylated imines **46**, which afforded after hydrolysis α-amino esters **47** containing unsaturated chain [75] (Scheme 19).

Scheme 19



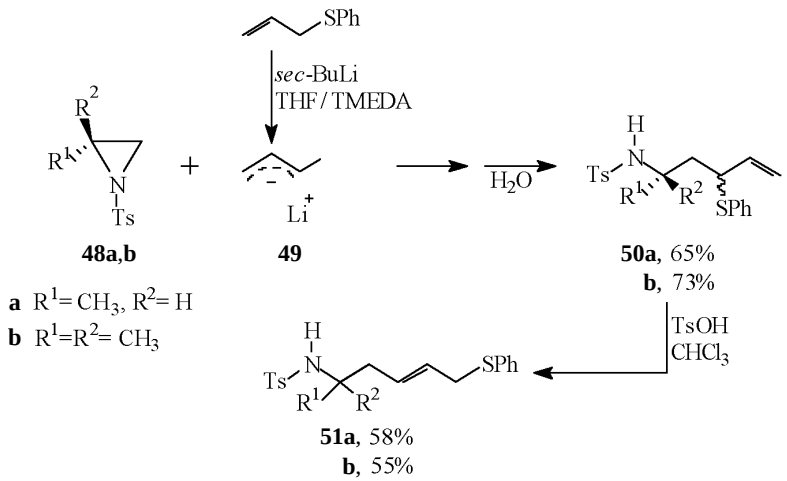
Related *C*-allylated Schiff bases were prepared by catalytic enantioselective alkylation of initial imines with allyl bromide in the presence of *O*-allyl-*N*-(9-anthracenyl methyl)cinchonidinium bromide and triton X-100 in water [76].

Following the same methodology, homochiral (*R*)-α-allyl-2-furfurylamine was prepared in 48% (96% ee) yields from the pinanone ketimine, derived from 2-furfurylamine [77].

Schaumann and co-workers reported ring opening of *N*-tosyl aziridines by hetero substituted allyl anions that proved to offer convenient access to synthetically useful homoallylic amines [78]. Reaction of aziridines **48** with phenylthio substituted allyl anion **49** afforded the adducts **50** that can rearrange with a 1,3 phenylthio shift to form the substituted homoallylamides **51** (Scheme 20).

N-Protected *N*-(2-hydroxybut-3-enyl)amines can be considered as chiral highly functionalized homoallylamines. Their synthesis involves the sequential *N*-protected (mainly, Boc group) α-amino ester reduction – diastereoselective

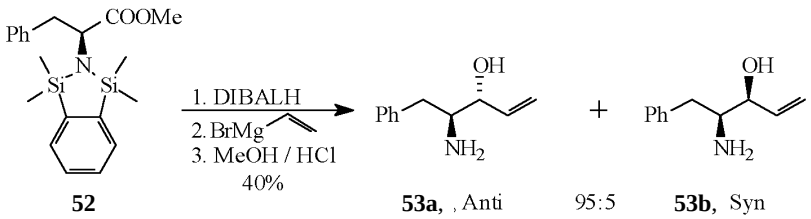
Scheme 20



addition of vinyl organometallics to the resulting aldehyde or its equivalent [79-81]. Thus, the protecting BSB group method was applied to the diastereoselective synthesis of anti and syn hydroxy homoallylamines **53a,b**, which were obtained from chiral (*S*)-ester **52** in a one-pot procedure (reduction with DIBALH followed by Grignard-type addition and deprotection) [79] (Scheme 21).

Homoallylic amines **57** were obtained in a new one-pot procedure *via* a two-step synthesis [85]. In the first step various aldehydes were condensed with dibenzylamine or diallylamine in the presence of titanium (IV) isopropoxide to afford an aminoalkoxy titanium complex **56**, which was subjected to vacuum application in order to liberate isopropanol. In the second step, THF

Scheme 21



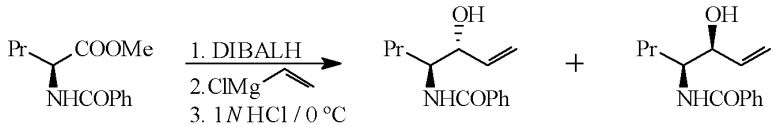
52 **53a**, , Anti 95:5 **53b**, Syn

A benzoyl group in lieu of a BOC group was used in this procedure. *N*-Benzoyl ethyl ester of D-norvaline **54** was treated with DIBALH followed by vinylmagnesium chloride to afford the 3-hydroxy-4-[(*N*-phenylcarbonyl)amino]-1-heptene in 53% yield as an 8:1 mixture of anti-(3*R*,4*R*) and syn-(3*S*,4*R*) diastereomers **55a,b** [82] (Scheme 22).

was added followed by a metal (In or Zn), and allyl bromide (Scheme 23).

Indium and zinc powder proved to be equally efficient in this method that relies on the generation in situ of iminium ions and of organometallylic species, which allows adding allyl group.

Scheme 22



54 **55a**, Anti 89:11 **55b**, Syn

Also, synthetically available (*S*)-*N*-*t*-Boc-arylglycinols can serve as a materia prima for these compounds. Its preparation consists of a two-step synthesis: Swern oxidation and vynilation of resulting aldehydes [83].

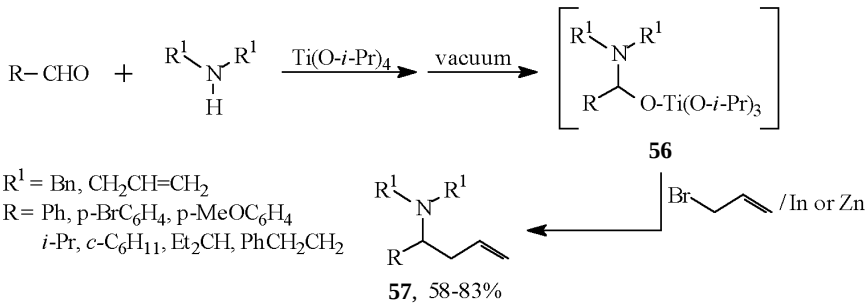
A new method for the synthesis of *N*-protected homoallylglicine was developed from glutamic acid derivatives. Its carboxylic side-chain was first transformed into the Weinreb amide by coupling with N,O-dimethylhydroxyamine and then reduced into the corresponding aldehyde that reacts with methyl-triphenylphosphonium bromide to give L- *N*-Boc-homoallylglycine [84].

The treatment of (*R*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydroinden-1-yl)zirconium dichloride **58** with ethylmagnesium chloride leads to the formation of the derived zirconocene alkene complex **59**, which react with *N*-nonylpyrrololidin-3-ene to afford chiral substituted (*R*)-homoallylamine **60** [86,87] (Scheme 24).

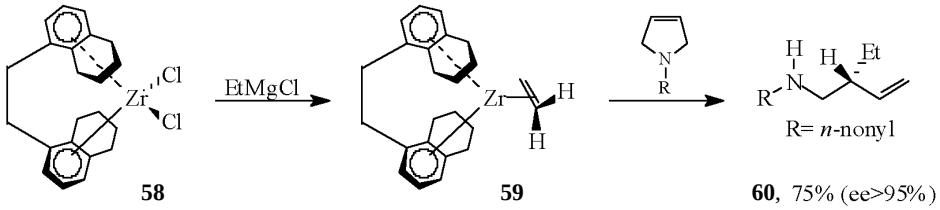
3. Synthesis of Saturated Nitrogen Heterocycles from Homoallylamines.

Because of their large diversity, it is not an easy task to devise a detailed classification of synthetic use of

Scheme 23



Scheme 24



58 **59** **60**, 75% (ee>95%)

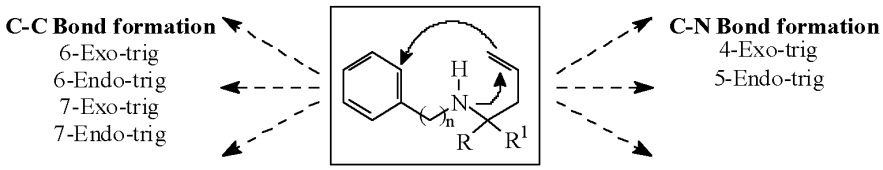
homoallylamines. This section of present review is intended to describe only intramolecular cyclization that produce saturated *N*-heterocycles based on Baldwin's rules for ring closure [88-90].

As shown in Scheme 25, Baldwin's theory allows speculating all types of cyclization for *N*-aryl(benzyl)-*N*-(but-3-enyl)amines. Their realizations could consist of two possible closures: the route *via* a C-N bond formation could lead to four- and five-membered rings with one heteroatom, while a C-C bond formation would permit one to construct six- or seven-membered ring systems.

Cyclization of homoallylic amide **61** in the presence of toluene-*p*-sulfonic acid gave the pyrrolidine **62** [73] (Scheme 27). The reaction appears to be limited to α-aryl substituted pyrrolidines, which are able to form a benzylic cation of initial homoallylamine.

Spiro[pyrrolidine-2,1'-cycloalkanes] **64** were obtained from homoallylamines **63** spiroannulated at the carbon C-1 through an aminomercuration reaction [91,92]. Treatment of the same homoallylamine with 92% sulfuric acid in chloroform at reflux and subsequent basic hydrolysis afforded azetidine derivative **65** [92] (Scheme 28).

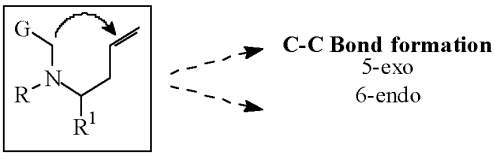
Scheme 25



n = 0, 1; R and R^1 = H, aryl, hetaryl
$R+R^1$ = cycloalkane or heterocycle

However, in practice there are a great many of diverse *N*-substituted homoallylamines, which gives the same type of *N*-heterocycles in an efficient fashion both radical and ionic cyclizations, forming a C-C bond *via* 5-exo or 6-endo process (Scheme 26). All these routes following both Schemes 25 and 26 involve the use the inactivated C=C double bond.

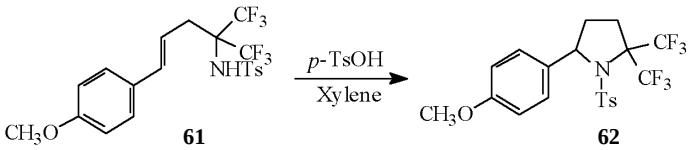
Scheme 26



3.1. Synthesis of Azetidine, Pyrrolidine and Piperidine Derivatives.

There are few works that describe direct synthesis of azetidines and pyrrolidines from secondary homoallylic amines or amides, because this route requires the disfavored C-N bond formation.

Scheme 27



61 **62**

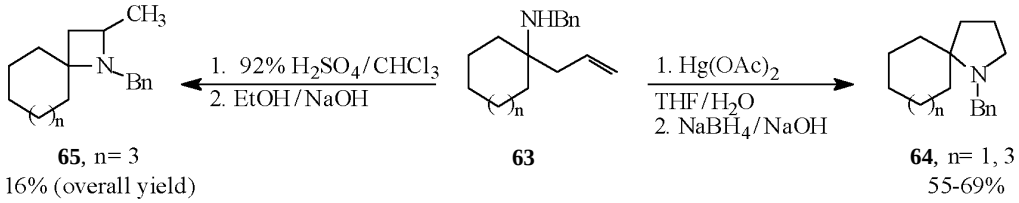
Epoxidation of homoallylamine **66** and subsequent cyclization with sodium hydroxide gave the azetidine **67** [78] (Scheme 29).

Also, formation of azetidines by electrophilic cyclizations was reported starting with homoallylic amines (4-exo mode cyclization) using bis(collidine)bromonium (I) hexaflurophosphate as an electrophile [93].

Homoallylic amines **68** can be converted to pyrrolidines **69** through a five step (epoxidation, intramolecular epoxide opening, and zinc mediated reductive cleavage-reductive amination) sequence, which is formally equivalent to 5-endo-trig ring closure [94] (Scheme 30).

Construction of C-C bonds adjacent to nitrogen is a powerful approach for synthesis of saturated nitrogen-containing compounds (Scheme 26). Such carbon-carbon bond formation usually occurs *via* one of three different

Scheme 28

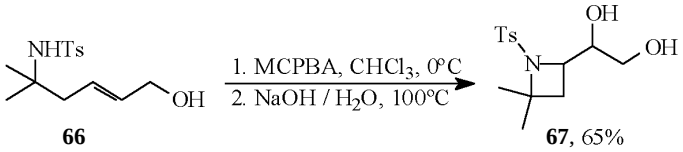


65, n= 3
16% (overall yield)

63

64, n= 1, 3
55-69%

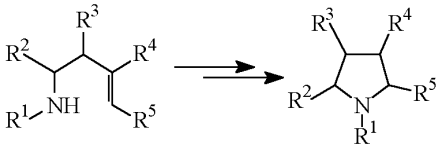
Scheme 29



66

67, 65%

Scheme 30



68

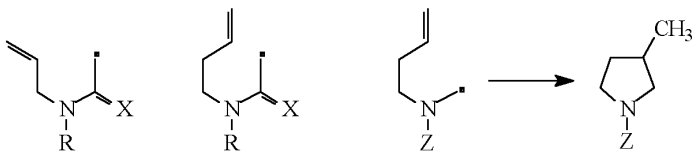
69

types of intermediates: i) α-amino-substituted carbaniones, ii) iminium ions, iii) α-amino-substituted radicals.

The last decade has witnessed an impressive growth in the development and use of radical process in organic, heterocyclic and natural product synthesis [95-97]. Much of the effort in the heterocyclic area has centered on the creation of C-C bonds using carbon centered radicals.

The 5-exo-trig cyclization of 3-aza-5-hexenyl radicals **70** have been extensively investigated and successfully applied to the synthesis of complex natural products containing a pyrrolidine ring system. In comparison, the 2-aza-5-hexenyl **71** radicals have so far not attracted the attention, but their analogs, stabilized α-amino radicals **72** were employed successfully in intramolecular cyclization to inactivated C=C bonds providing 3-methylpyrrolidine derivatives **73** [98,99] (Scheme 31).

Scheme 31



70 **71** **72** **73**

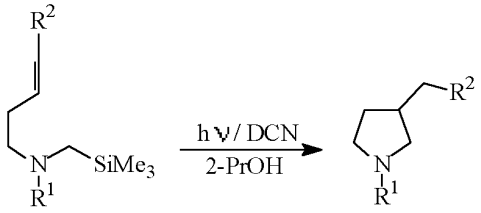
X = H, H or O

Z = COR, SO_2Ph

The cyclizations with a participation of these α-amino radicals derived from tertiary homoallylic amines occur with a great regioselectivity (5-exo>>6-endo) [97].

Selective desilylation of compounds **74** by photolysing and DCN yielded pyrrolidines **75** *via* unstabilized α-amino radical [100] (Scheme 32).

Scheme 32



74 R^1 = Bn, *n*-Bu; R^2 = H, CH_3

75, 70-78%

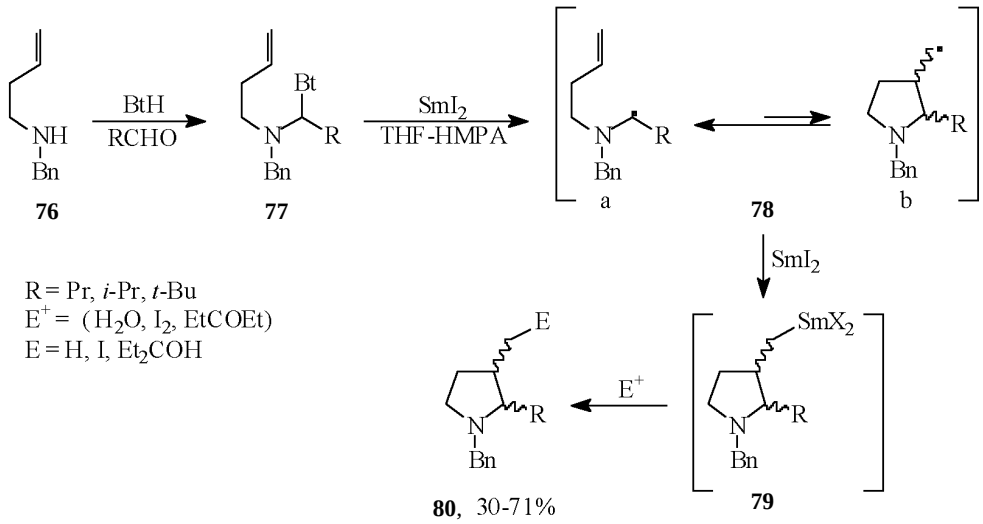
This result contrasts to those reported by Pawda and associates [101]. They found that the corresponding 2-aza-2-benzylhexenyl radical failed to cyclized, and only the product of reduction, *N*-benzyl *N*-(but-3-enyl)methylamine, was isolated. However, recently, desilylation of compounds like as **74** by photolysing in the presence of 9,10-anthracenedicarbonitrile and biphenyl, giving a pyrrolidine ring, is reported [102].

Despite some synthetic problems, radical-based methodologies for the synthesis of pyrrolidines continue to prove fruitful. Prof. Katritzky and co-workers reported the tandem cyclization of aminoalkyl radicals, which provides a new strategy for the synthesis of pyrrolidines with a functional group at C-3 [103]. *N*-(α-Aminoalkenyl)benzotriazoles **77** was prepared from the condensation of a secondary homoallylamine **76**, aliphatic aldehydes and benzotriazole. Obtained crude product was treated directly with samarium diiodide in THF-HMPA to form *via* radical intermediates **78a,b** and carbanion **79**, a mixture isomeric pyrrolidines **80** (Scheme 33).

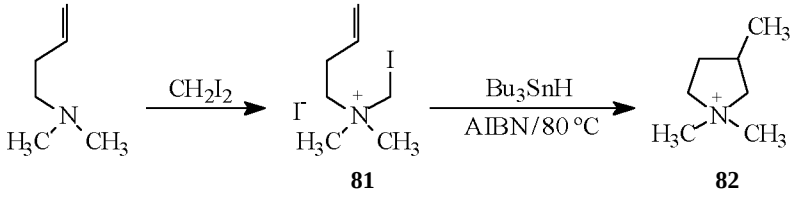
Generation of radicals adjacent to a positive nitrogen atom has been applied to preparation of the pyrrolidinium salt. Ring-closure of the 1-iodo-2,2-dimethyl-2-azonia-5-hexenyl iodide **81** proceeds smoothly and efficiently to afford pyrrolidine derivative **82** in 96% yield [104] (Scheme 34).

Anionic intermolecular cyclization has been used for the construction of heterocyclic rings for many years. Several groups reported efficient variants of Michael-Michael ring procedures for the preparation of functionalized cyclic rings.

Scheme 33

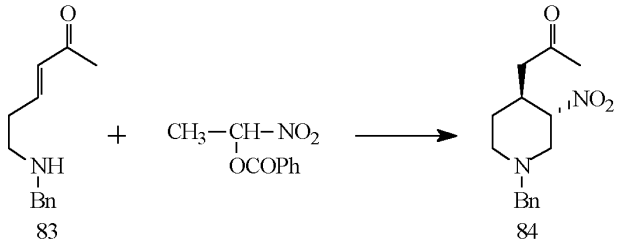


Scheme 34



Such approach to five and six-membered nitrogen heterocycles involves intermolecular conjugate addition of a nitrogen nucleophile to an acceptor molecule to generate an enolate intermediate, which is subsequently captured intramolecularly by the built in α,β-unsaturated acceptor leading to cyclization. For example, treatment of equimolecular amounts of 1-benzoyloxy-2-nitroethane and homoallylic amine **83** at room temperature led to the direct formation of *N*-benzylpiperidine derivative **84** in good yield [105] (Scheme 35).

Scheme 35



However, this example is limited by the availability of initial homoallylamine, which is obtained from benzylamine through a sequential four step procedure.

Other *N*-substituted homoallylamines, easily accessible, undergo in anionic cyclization promoted by lithium, magnesium and zinc reagents. Carbometallation of inactivated olefins is an efficient approach to enantioselective synthesis of pyrrolidines.

MeLi-promoted anionic cyclization of the corresponding homoallylamine **85** allowed for obtaining the 3-(trimethyltin)methylpyrrolidine derivative **86**, which gave the acetal derivative **87** after the cleavage of the trimethyltin group with CAN in MeOH [106] (Scheme 36).

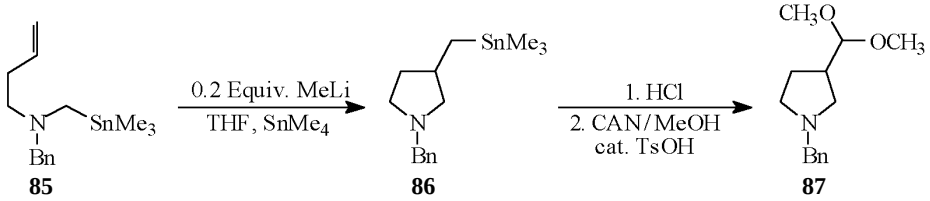
In the case of this cyclization of similar homoallylamine, the use of an α-methylbenzyl chiral auxiliary on the nitrogen atom afforded 1-α-methylbenzyl-3-methylpyrrolidine in the presence of (-)-sparteine with up to 58% de [107].

Zinc enoles addition to inactivated olefins from homoallylamines gives remarkable possibilities for enantioselective synthesis substituted pyrrolidines [108,109]. Chiral homoallylamine **88** was subjected to process of metallation-transmetallation-cyclization ($LDA/ZnBr_2/Et_2O$) following by hydrolysis to afford the chiral 3-methylproline ester **89** as a single *cis* diastereomer with a 98:2 diastereomeric ratio in 93% yield [108] (Scheme 37).

Using this powerful methodology, synthesis of homochiral tetrasubstituted pyrrolidine **91** from chiral substrate **90** was accomplished in a high diastereoselective fashion [110] (Scheme 38).

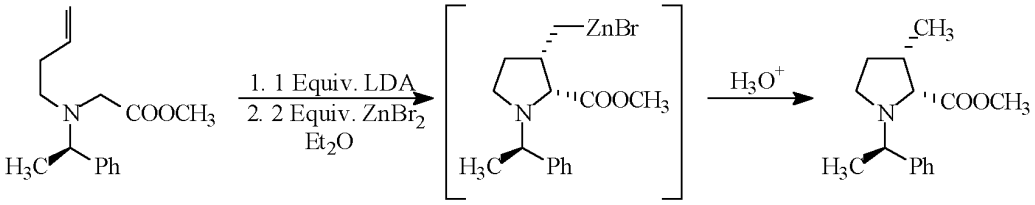
Iminium ions also participate as intermediates in the heterocyclization for substituted piperidines. Synthesis of *N*-benzyl 4-hydroxypiperidine **94** was achieved in excellent yields starting from an allylsilane, benzylamine and

Scheme 36



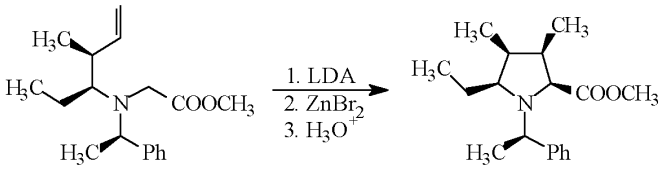
85 **86** **87**

Scheme 37



88 **89**

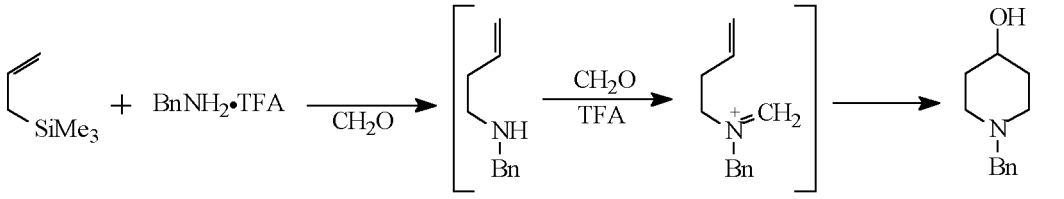
Scheme 38



90 **91**, 65% (dr>95:5)

formaldehyde in the presence of TFA [43]. In the first step of this elegant synthesis, homoallylamine **92** are formed, yielding iminium ion intermediate **93** (Scheme 39).

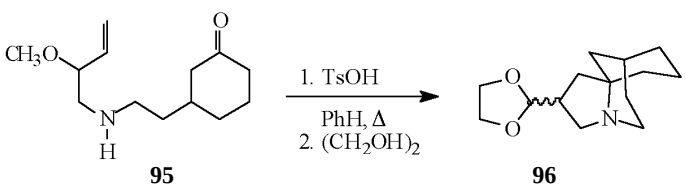
Scheme 39



92 **93** **94**, 81%

Recently, Brummond and Lu demonstrated an unprecedented tandem cationic aza-Cope rearrangement and Mannich cyclization passing through an anti-Bredt iminium ion intermediate (Scheme 40).

Scheme 40

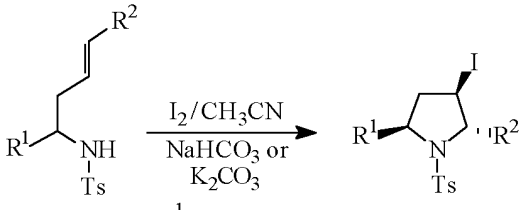


95 **96**

Their synthesis starts with the monosubstituted cyclohexanone **95** containing a homoallylamine moiety to give azatricycle **96**, an important precursor to the potent immunosuppressant FR901483 [111].

Some useful pyrrolidines containing an iodine atom can be prepared from homoallyl tosyl or benzyl amides through an iodocyclization procedure [112-115]. For instance, exposure of the homoallyl tosylamides **97** to iodine in the presence of potassium carbonate in CH_3CN led to the 2,5-*trans*-4-iodopyrrolidines **98** [112] (Scheme 41).

Scheme 41

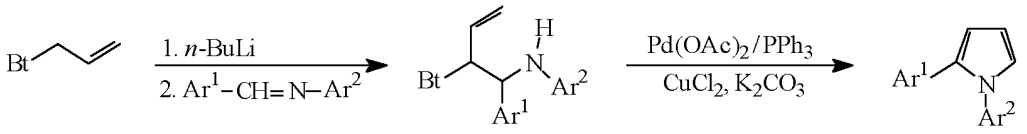


97 R^1 = alkyl or Ph, R^2 = H, alkyl **98**, 83-95%

Similar electrophile-induced 5-endo-trig cyclization of (*S*) or (*R*) configured N-glycosylhomoallylamines gave the 2-substituted pyrrolidines of high diastereomeric purity [116].

A facile synthesis of 1,2-diaryl(heteroaryl)pyrroles in a two-step procedure, using homoallylamine intermediates was reported by Katritzky [117]. Reaction of *N*-allyl-benzotriazol **99** and various aldimines affords the (2-benzotriazolyl-1-arylbut-3-enyl)- anilines **100**, which, in the presence of the system $Pd(OAc)_2$-PPh_3-$CuCl_2$-K_2CO_3, suffer an intramolecular oxidative cyclization to give the pyrroles **101** (Scheme 42).

Scheme 42



99 **100** **101**

The intramolecular cyclohydrocarbonylation of allyl and homoallyl glycinates is a direct route to pipecolic acid derivatives [118,119]. Indeed, the cyclohydro carbonylation of derivative **102** in the presence of Rh(acac)(CO_2) (1.0 mol %) and BIPHEPHOS (2.0 mol %) and 4 atm of CO_2/H_2 (1/1) in THF afforded the (*S*)-1-(methoxycarbonyl)-5,6-didehydropipecolate **103** in excellent yield [119] (Scheme 43).

With the invention of Grubbs's ruthenium catalyst [120] procedure of ring-closing olefin metathesis (RCM) has become a very powerful tool in heterocyclic synthesis [121,122]. This catalyst is especially suitable for the cyclization of functional groups containing substrates based on homoallylamine structure. Thus, diverse *N*-allylated substituted homoallylamines were used in a metathesis strategy.

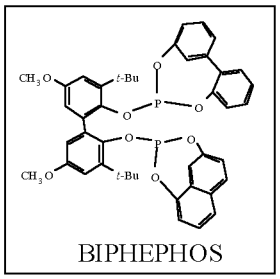
N-Allylated homoallylamines **104a,b** obtained by a three-component reaction were subjected to Grubbs's catalyst affording the corresponding 1,2,3,6-tetrahydropyridines *cis*-**105a,b** and *trans*-**106a,b** in excellent yields [49] (Scheme 44).

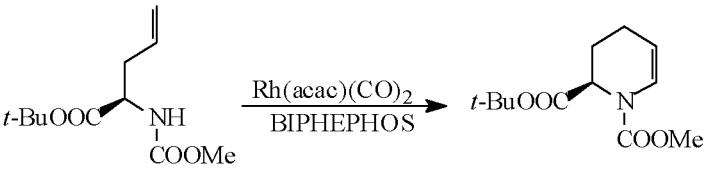
Procedure of RCM under assistance of Grubbs's catalyst offers the synthesis of 1,2,3,6-tetrahydropyridine and pipecolinic acid derivatives **109** and **110** from corresponding precursors **107** and **108** that were prepared from *N*-protected glycine derivatives [123,124] (Scheme 45).

The RCM approach was applied successfully in a solid-phase synthesis of the functionalized 6-, 7- and 8-azacycles [123].

Pearson and Aponick reported treatment of (2-azaallyl)stannanes **111** with 2.2 equivalents of allylmagnesium bromide afforded good yields of 5-aza-1,8-nonadienes

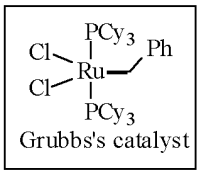
Scheme 43

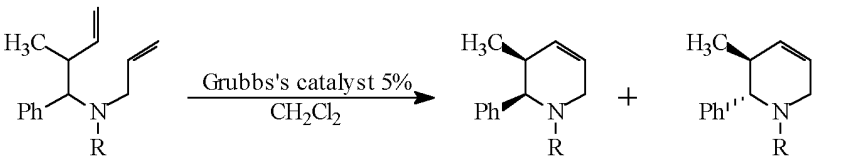




102 **103**, 99%

Scheme 44

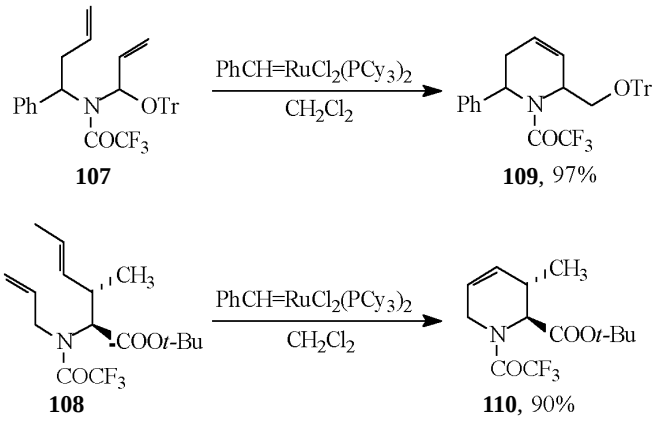




104a,b **105a,b** **106a,b**

a R= Cbz, 99% (105 / 106, 84:16)
b R= Ts, 95% (105 / 106, 88:12)

Scheme 45

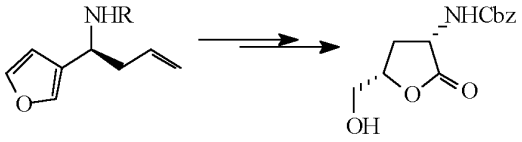


112, which possess homoallylamine fragment. Using RCM, these compounds produced 2,3,6,7-tetrahydroazepines **113** in an efficient manner [125] (Scheme 46).

RCM of diallylglycine **116**, prepared from (*S*)-allylglycine, provided azocine derivative **117** with *Z* configuration of double bonds in 80 % [127] (Scheme 48).

Finally, chiral homoallylic tosyl or benzoyl amides **118** containing a furan ring at the C-1 position can be used in the synthesis of γ-lactones [128]. For example, a facile transformation of the (2*S*,4*S*)-2-(benzyloxycarbonylamino)-4-(hydroxymethyl)butanoic acid γ-lactone **119**, a precursor of the β-lactam antibiotic clavalanine was realized from these homoallylamines [129,130] (Scheme 49).

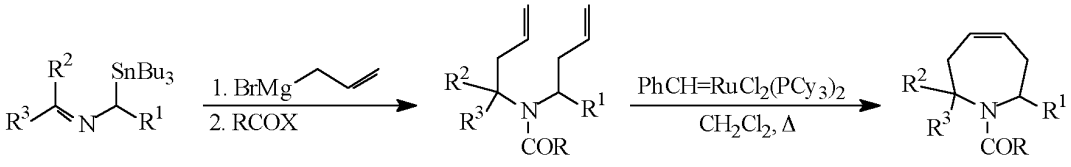
Scheme 49



118 R= Ts, PhCO

119

Scheme 46

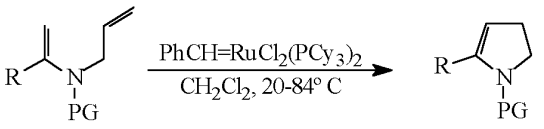


111 **112** **113**, 65-98%

R= OBn, OCH_3; R^1=R^2= H, CH_3; R^3= *i*-Pr, CH_3; R^2+R^3= $(CH_2)_5$

Recently, it was demonstrated that several enamide precursors **114** readily undergo ring closure at 20-40 °C using Grubbs catalyst to give pyrroline derivatives **115** [126] (Scheme 47).

Scheme 47



114 R= H, CH_3; PG= Ts, Bz, COOEt **115**, 59-84%

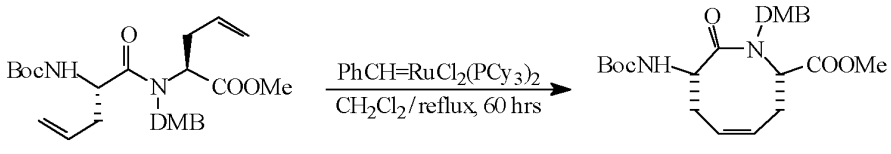
3.2. Synthesis of Tetrahydro-quinoline and -benzazepine Derivatives.

In contrast with *N*-allylanilines (allylamine derivatives), *N*-(but-3-enyl)anilines (homoallylamine derivatives) have not practically been explored in synthesis of this type of heterocycles.

Construction of quinoline and benzazepine ring from homoallylamine derivatives using aryl radical cyclization has been described by Jones and associates [131]. So, the cyclization of compound **120** using the catalytic tin hydride method of Stork gave tetrahydroquinoline **121** in 70% yield. The 7-endo product, tetrahydro-5*H*-1-benzazepine **122** was formed as a trace (<5%) (Scheme 50).

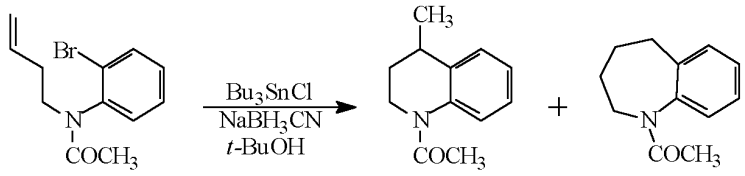
Changing the chemical nature of homoallylamine derivatives and cyclization conditions, it was possible to obtain

Scheme 48



116 **117**

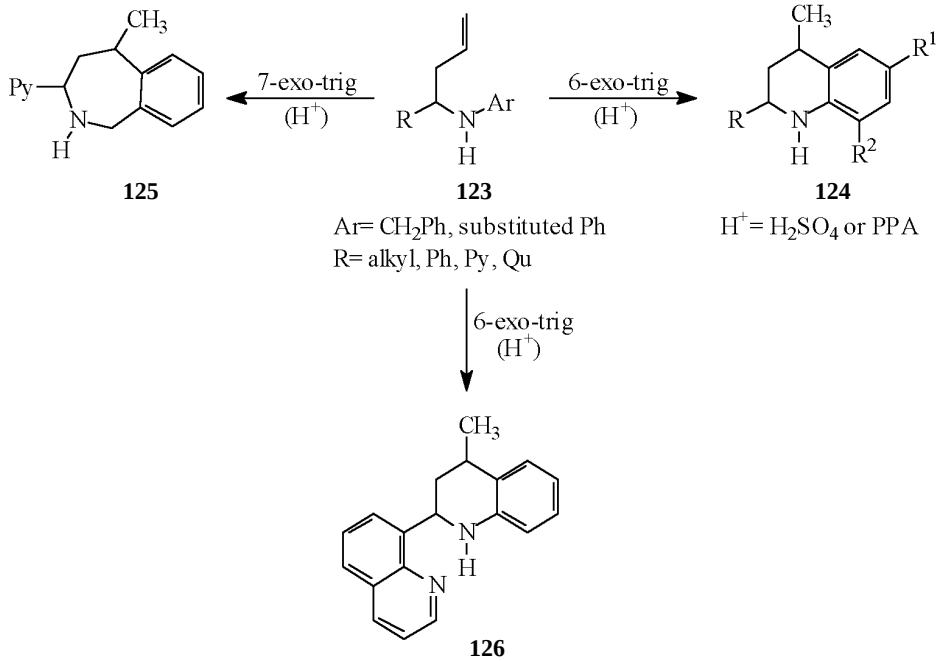
Scheme 50



120 **121** **122**

both type of heterocycles. N-(1-Alkyl, aryl or hetarylbut-3-enyl)anilines(benzylamines) **123**, obtained easily from aldimines and allylmagnesium bromide, turned out to be not only suitable synthetic precursors but also bioactive molecules against a panel of phytopathogenic fungi acting as inhibitors on β(1-3) glucan and chitin synthases [131-133]. These homoallylic amines **123**, possessing a π-electron rich aromatic ring and an allyl (electrophilic C_3 synthon) fragment, represent versatile starting materials that afford the 2-substituted 4-methyl-1,2,3,4-tetrahydroquinolines **124** [134-137] and 3-substituted 5-methyl-1,2,3,4-tetrahydro-3*H*-2-benzazepines **125** [138], respectively. The former are obtained in good yields. This simple approach, which is considered as a 6-exo-trig or 7-exo-trig process, allowed to obtain the 4-methyl-2-(8-quinolinyl)-1,2,3,4-tetrahydroquinolines **126** in 35-76% yields [139,140] (Scheme 51).

Scheme 51



125 **123** **124** **126**

The Brönsted acidic-mediated cyclizations of similar homoallylamines spiro annulated at the carbon C-1 afforded a great many of 3,4-dihydrospiro[1*H*-quinoline-2,1'-cyclanes] and 1,2,4,5-tetrahydrospiro[3*H*-2-benzazepine-3,1'-cyclanes], which are interesting biological targets [141-143].

4. Final Remarks.

Nucleophilic addition of allyl organometallic reagents to imines and iminium ions and sigmatropic rearrangements of *N*-protected amino acid allylic esters as well as of *N*-allyl α-amino esters or allylic ammonium salts covered in this review represent useful reactions for the preparation of homoallylamines. However, imine allylation still remain one of the most reliable and efficient methods for preparing homoallylamines, which are useful precursors for the construction of diverse saturated nitrogen heterocycles. One important future aspect for heterocyclic chemistry is the preparation of optically active compounds and the authors hope that it will be long before the efficient and common utilization of homoallylamines to optically pure nitrogen-containing compounds is realized.

5. Abbreviations.

BINAP	(R)-(+)-2,2'-bis(dipehylphosphino)-1,1'-binaphthyl
BOC, Boc	*tert*-butoxycarbonyl
BSB	1,2-bis(dimethylsilyl)benzene
Bt	benzotriazole
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
D-Ipc2Ball	B-allyldiisopinocampholbornane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCN	dicyano naphthalene
DIBALH	diisobutylaluminium hydride
DMB	2,4-dimethoxybenzyl
DMPU	3,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
ee	enantiomeric excess
HMPA	hexamethylphosphoric triamide
LDA	lithium diisopropylamide
LHMDS	lithium 2,2,6,6-tetramethyl piperidide
MCPBA	m-chloroperoxybenzoic acid
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldiflourosilicate
TBS	*tert*-butylsilyl
TFA	trifluoroacetic acid
Ts	p-toluenesulfonyl (tosyl)
Tr	triphenylmethyl (trityl)

6. Acknowledgments.

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