# Enantioselective synthesis of heterocyclic compounds mediated by organoselenium reagents

**Marcello Tiecco,* Lorenzo Testaferri, Luana Bagnoli, Francesca Marini, Claudio Santi, Andrea Temperini, Catalina Scarponi, Silvia Sternativo, Raffaella Terlizzi, and Cristina Tomassini**

*Dipartimento di Chimica e Tecnologia del Farmaco, Sezione di Chimica Organica, Università di Perugia, Italy*
*E-mail: tiecco@unipg.it*

**Abstract**
The syntheses of several types of enantiopure or enantiomerically enriched heterocyclic compounds by electrophilic additions, nucleophilic substitutions and radical additions ring closure reactions, promoted by chiral non racemic as well as by achiral organoselenium reagents, are presented and discussed.

**Keywords:** Diselenides, organoselenium reagents, selenonium ions, selenones, cyclization reactions, intramolecular radical additions

## Table of Contents



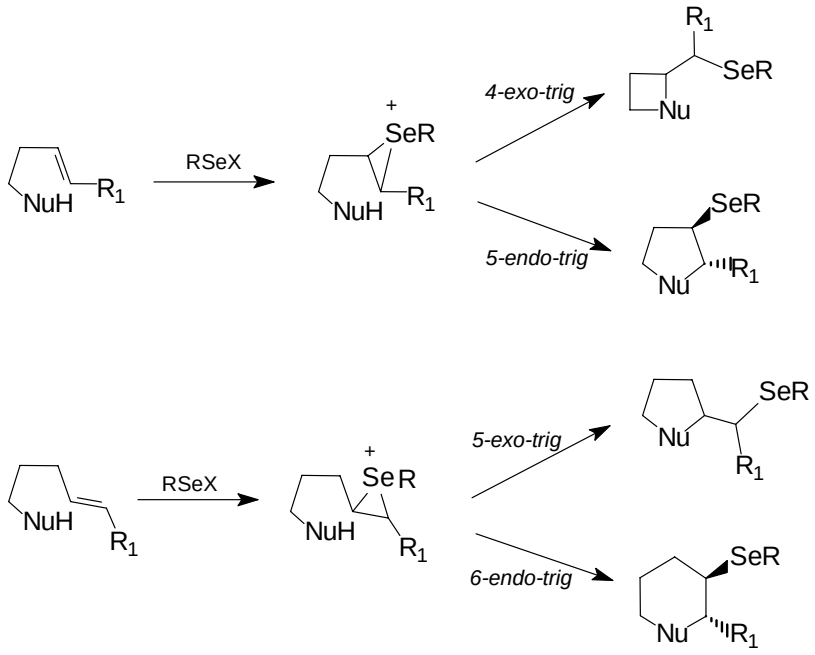
## Introduction

Owing to the great importance of heterocyclic compounds as final products or as reaction intermediates, several different methods are currently used for their construction. Among the various kinds of ring forming reactions, those based on the reaction of an electrophilic reagent

with an alkene holding a suitably positioned nucleophilic group are certainly very useful. The term of cyclofunctionalization is generally employed to describe this kind of process which can be promoted by several electrophilic reagents. The increasing popularity gained in recent years by selenium reagents to effect ring closure reactions, not only by electrophilic additions but also by nucleophilic substitutions and by radical addition reactions, is due to the easy availability of the reagents, to the numerous chemical manipulations which can be effected on the selenium moiety before or during its removal, and to the mild reaction conditions required in the various steps.

## 1. Syntheses and Reactions of Organoselenium Reagents

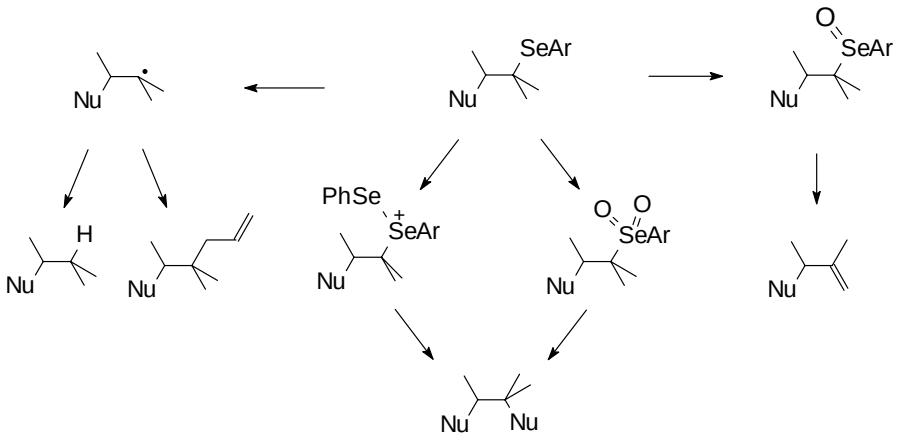
Selenium promoted cyclization reactions thus provide an easy access to a wide variety of heterocyclic compounds in general and to those containing oxygen and/or nitrogen heteroatoms in particular.[1] Scheme 1 illustrates the possible modes of cyclization depending on the relative position of the nucleophile and of the double bond in the starting alkene.




**Scheme 1**. Cyclofunctionalization reactions

The deselenenylation of the final products is an important process since in most cases the removal of the selenium group can be used to effect other cyclization reactions. As indicated in Scheme 2, the reaction with tri-*n*-butyl tin hydride affords a carbon radical which can directly abstract a hydrogen atom or it can add to a multiple bond and then abstract a hydrogen atom. If

the tri-*n*-butyl allyl tin is employed the carbon radical add to the double bond and the allyl derivative is obtained. By oxidation a selenoxide is obtained which easily gives rise to the classical *syn* elimination to produce an alkene. Much less known are the deselenenylation reactions which occur by substitution after conversion of the ArSe group into a good leaving group such as a selenonium ion or a selenone. In most of these processes the organoselenium reagent can be recovered as a diselenide.



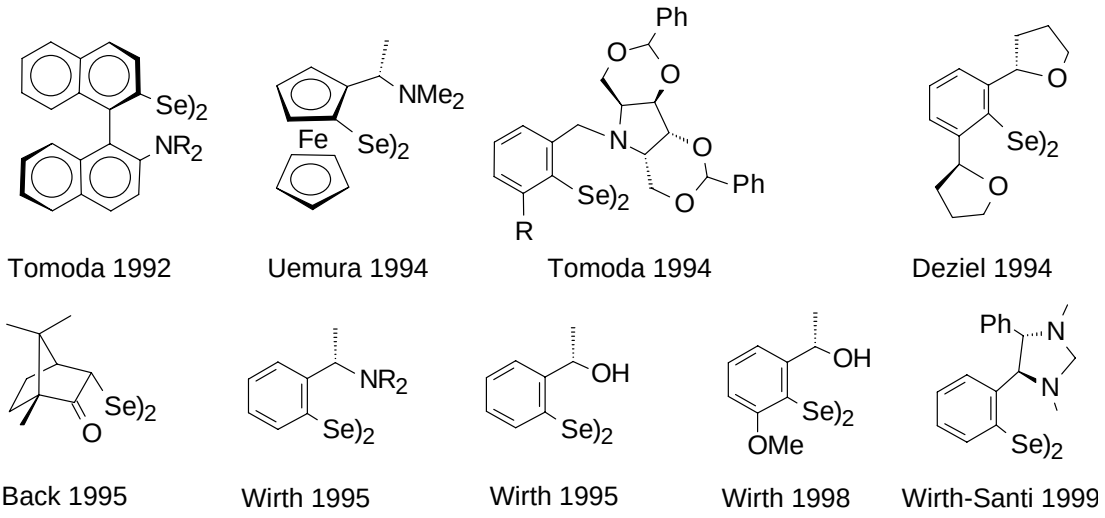

**Scheme 2**. Deselenenylation reactions.

Perhaps the most important aspect of organoselenium chemistry is due to the fact that several chiral non racemic diselenides have been introduced in recent years.[2-9] Starting from these diselenides a large number of heterocyclic compounds have been obtained in an enantiomerically pure form. Examples of the diselenides which have been described in the literature since 1992 are indicated in Scheme 3.

The possibility of disposing of optically pure reagents is a peculiar and unique property of organoselenium reagents. Enantioselective cyclofunctionalization reactions promoted by other commonly used electrophilic reagents have not been discovered so far.

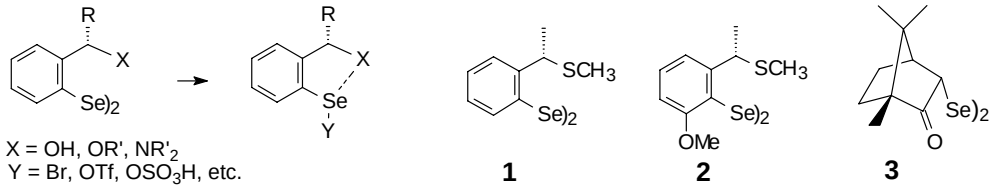
The chiral non racemic electrophilic organoselenium reagents can be prepared *in situ* from the corresponding diselenides by treatment with bromine, thionyl chloride, bromine and silver triflate or with ammonium persulfate. In the cases of the selenenyl triflates[10] and sulfates,[11] the anions are scarcely nucleophilic and this is a considerable advantage for the regio and stereoselectivity of the reactions.

A common characteristic of all these diselenides is the close proximity of an heteroatom (oxygen, nitrogen) to the selenium atom. On the basis of crystal structure determinations, NMR investigations and theoretical calculations it has been suggested that an orbital interaction occurs between the heteroatom lone pair and the low-lying Se-Y antibonding orbital.[5e,f] This interaction will force the chiral center to come closer to the reaction center and this will produce a better transfer of chiral information in the selenenylation reaction (Scheme 4).




**Scheme 3.** Chiral non racemic diselenides.

With the expectation that this interaction could be more important, and hence the transfer of chirality more efficient, if the heteroatom close to the selenium atom were a sulfur atom[12] instead of an oxygen or a nitrogen atom we have synthesized the sulfur containing diselenide **1** indicated in Scheme 4. In the present case the conversions into the selenenyl bromide and chloride afforded crystalline products which could be analysed by X-Ray. As expected the distances between the selenium and the sulfur atom (2,470 and 2,344 A in the bromide and chloride respectively) were much shorter than the sum of the Van der Waals radii of selenium (2,0 Å) and sulfur (1,85 Å).




**Scheme 4.** Sulfur containing diselenides.

As a matter of fact these electrophilic reagents, as well as those deriving from the methoxy derivative **2** gave rise to extremely enantioselective reactions.[13] These two diselenides were extensively used in our laboratory. We have also employed the easily available camphor diselenide **3** which was introduced by Back.[6] In our hands the reactions effected starting from **3** were not greatly stereoselective but they presented the important advantage which consists in the easy separation by column chromatography of the two diastereomeric reaction products.

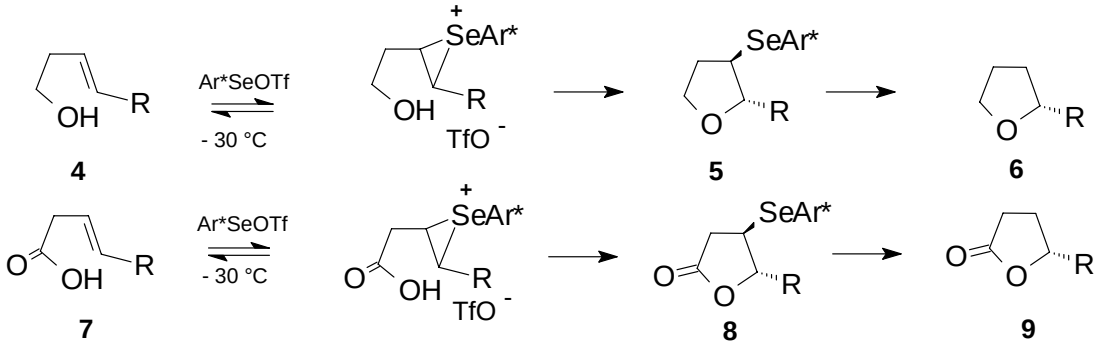
The ring closure reactions which are described below take place by formation of carbon-oxygen, carbon-nitrogen or carbon-carbon bonds. With some nucleophilic groups a competition

between the formation of C-O or C-N bonds is observed. The asymmetric syntheses of heterocyclic compounds were effected either starting from enantiopure organoselenium reagents and achiral substrates or starting from achiral organoselenium reagents and enantiopure substrates.

## 2. Cyclization Reactions by Formation of Carbon Oxygen Bonds

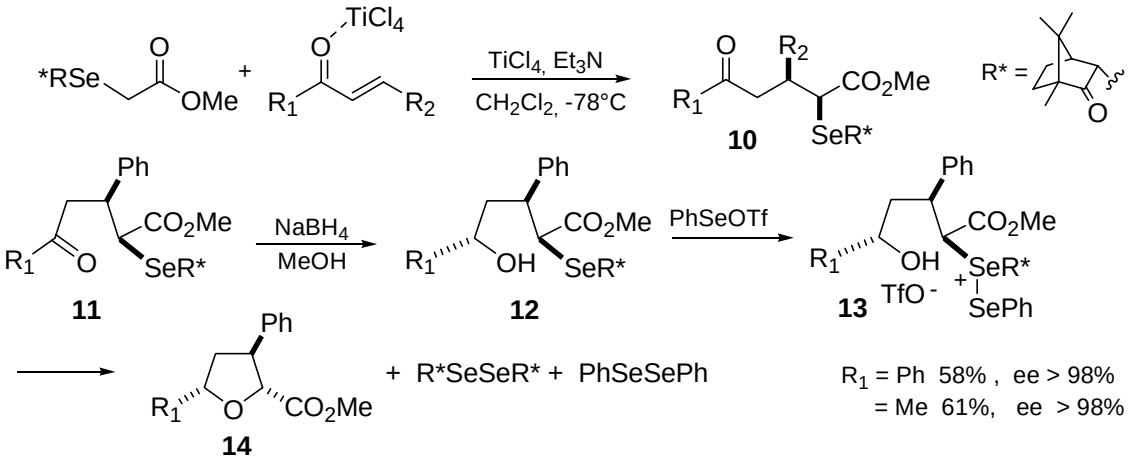
The first examples refer to the cyclofunctionalizations of alkenols **4** (Selenoetherification), promoted by the sulfur containing diselenide **1**, to afford tetrahydrofuran derivatives **5** (Scheme 5). The diastereoselectivity is very good in every case (from 91:9 to 96:4). Only in the case of the formation of a quaternary stereogenic centre the diastereomeric ratio (D.r.) is slightly lower.[12,13,14] The two diastereoisomeric selenium containing reaction products could not be separated and the reductive deselenenylation afforded tetrahydrofurans **6** with an ee equal to the D.r.

Under the same conditions the cyclofunctionalizations of alkenoic acids **7** (Selenolactonization) afforded seleno γ-lactones **8** and then the γ-lactones **9** with similarly good diastereoselectivities (Scheme 5).[12,13,14]



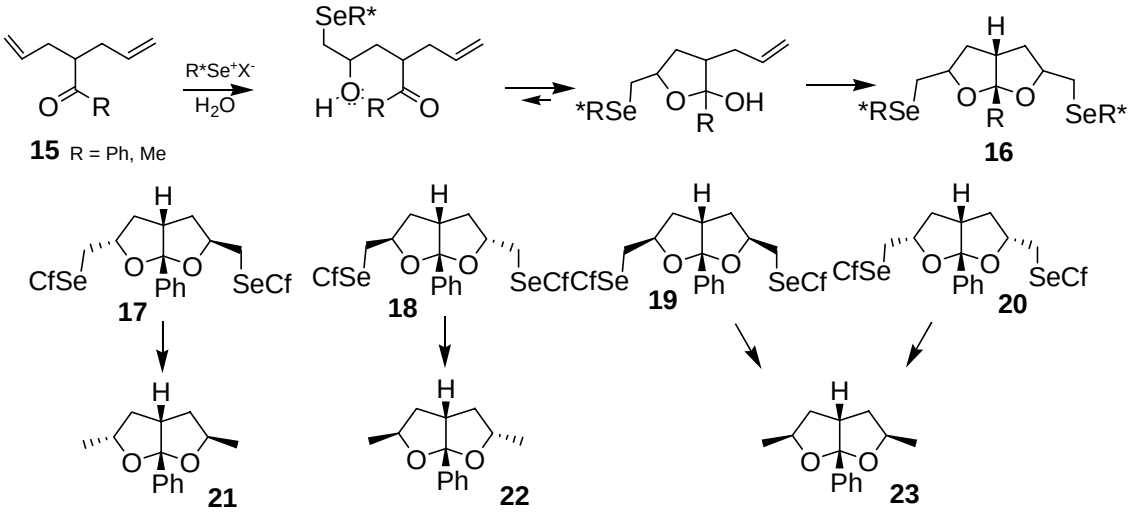

**Scheme 5**. Selenoetherification and selenolactonization reactions

Tetrahydrofuran derivatives were also obtained in a completely different way. In a recent work we have described the conjugate additions of selenium containing enolates to enones.[15] In this case we used the camphor diselenide **3**. These reactions were highly diastereoselective and only the *syn* adducts **10** were obtained. As indicated in Scheme 6, in the case of the phenyl derivative **11** the reduction of the carbonyl group afforded the camphor seleno alcohol **12**. Treatment with phenylselenenyl triflate gave the selenonium ion **13**. The diselenide is an extremely good leaving group and therefore the OH group gave rise to an intramolecular stereospecific $S_N2$ substitution to afford the enantiopure tetrahydrofuran derivative **14**. The displaced mixed diselenide disproportionates and the camphor diselenide can thus be recovered.




**Scheme 6**. Enantioselective synthesis of trisubstituted tetrahydrofurans

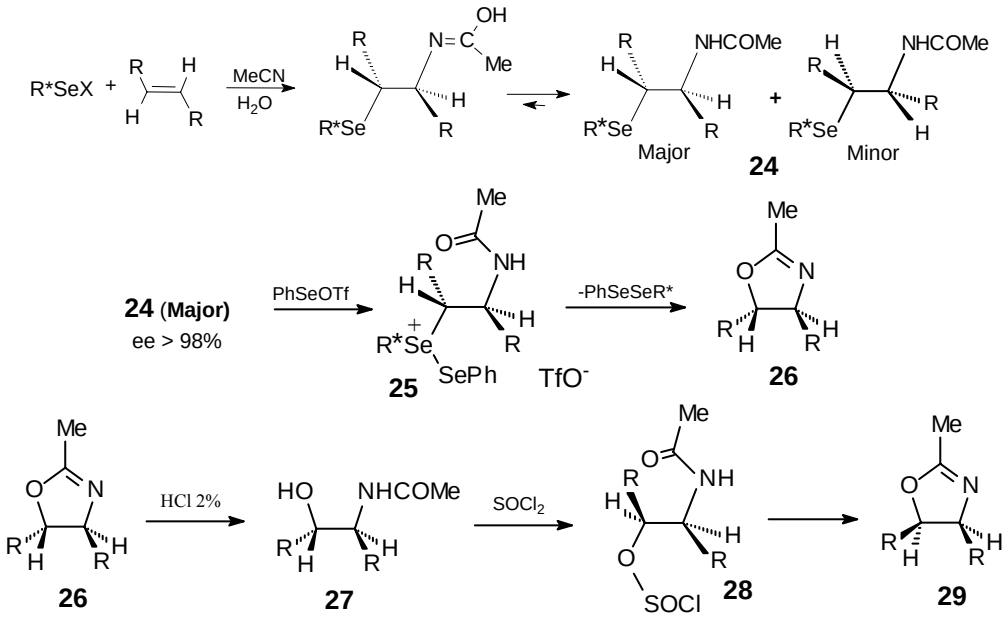
An interesting example of the *in situ* formation of the OH group is represented by the one-pot double cyclization of bis-allyl ketones **15** promoted by camphor selenenyl sulfate and water (Scheme 7).[16] The first intermediate is the product of the seleno hydroxylation of one of the two double bonds and the formed hydroxy group acts as the internal nucleophile in the double cyclization. The final products are therefore the seleno substituted perhydro[2,3-b]furans **16**. The four possible enantiopure diastereoisomers **17-20** were all formed and were separated by column chromatography. The deselenenylation of the first two compounds afforded the two enantiomeric methyl derivatives **21** and **22** in an optically pure form and the third isomer gave the meso compound **23**. Strangely enough the forth diastereoisomer **20**, which was present in minute amounts, afforded the same meso derivative **23**.




**Scheme 7.** Enantioselective synthesis of perhydrofuro[2,3-b]furans

The starting products for the synthesis of enantiopure oxazolines were prepared from the asymmetric acetamido selenenylation of alkenes promoted by camphor selenenyl sulfate in acetonitrile and water.[17] The reaction steps are indicated in Scheme 8. The acetamido selenenylation of alkenes occurs with moderate to poor facial selectivity (D.r. from 65:35 to 80:20). However, the two diastereomeric addition products **24** can be easily separated by column chromatography and can be converted into enantiomerically pure oxazolines by PhSeOTf promoted deselenenylation. Once again selenonium ions **25** are produced as intermediates and the stereospecific intramolecular substitution by the oxygen atom affords the enantiopure *trans* oxazolines **26**. The same procedure applied to the minor isomers affords the enantiomeric oxazolines. The same procedure applied to thioacetamido selenides afforded enantiopure thiazolines.

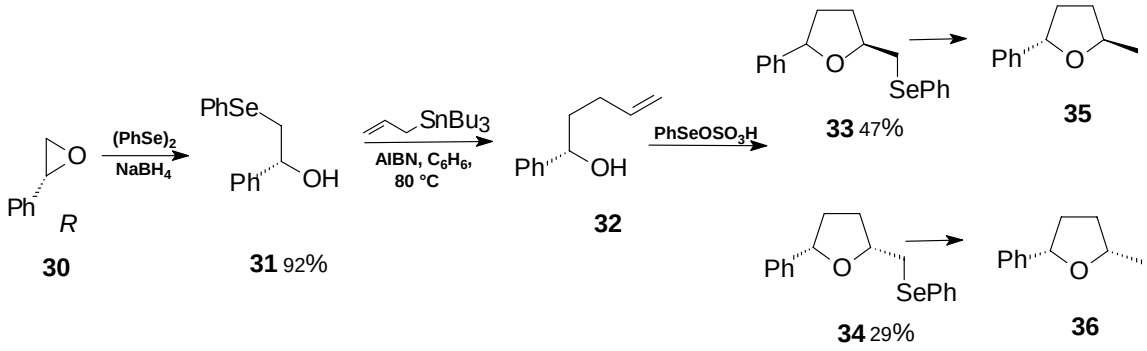
Using a method described in the literature[18] the *trans* oxazolines **26** can be converted into *cis* oxazolines **29** by ring opening with dilute hydrochloric acid to give **27** and transformation of the OH group into the chlorosulfite **28** which can suffer intramolecular substitution with inversion of configuration at the carbon atom. Thus, all the possible four stereoisomers of 4,5-bis-substituted oxazolines could be obtained in an enantiomerically pure form.




**Scheme 8**. Synthesis of enantiopure oxazolines

All the examples reported so far refer to cyclization reactions by formation of carbon-oxygen bond using enantiopure organoselenium reagents. Some examples will now be presented in which enantiopure heterocyclic compounds are produced from the reactions of achiral organoselenium reagents (PhSeX) with enantiopure substrates. The first example refers again to the synthesis of tetrahydrofurans.

The opening of the commercially available (*R*)-styrene oxide **30** with phenylselenium anions affords the hydroxy selenide **31**. The reaction with tributyl allyl tin gives rise to the alkenol **32** (Scheme 9). Cyclization of **32** promoted by phenyl selenenyl sulfate gave a mixture of two diastereomeric tetrahydrofurans **33** and **34** which could be easily separated by column chromatography. Deselenenylation with tributyl tin hydride gave the 2-methyl-5-phenyl tetrahydrofurans **35** and **36**. Starting from the (*S*)-styrene oxide ***ent*-30** the enantiomeric compounds ***ent*-35** and ***ent*-36** were obtained.[19]




**Scheme 9**. Synthesis of enantiopure 2-methyl-5-phenyl tetrahydrofurans

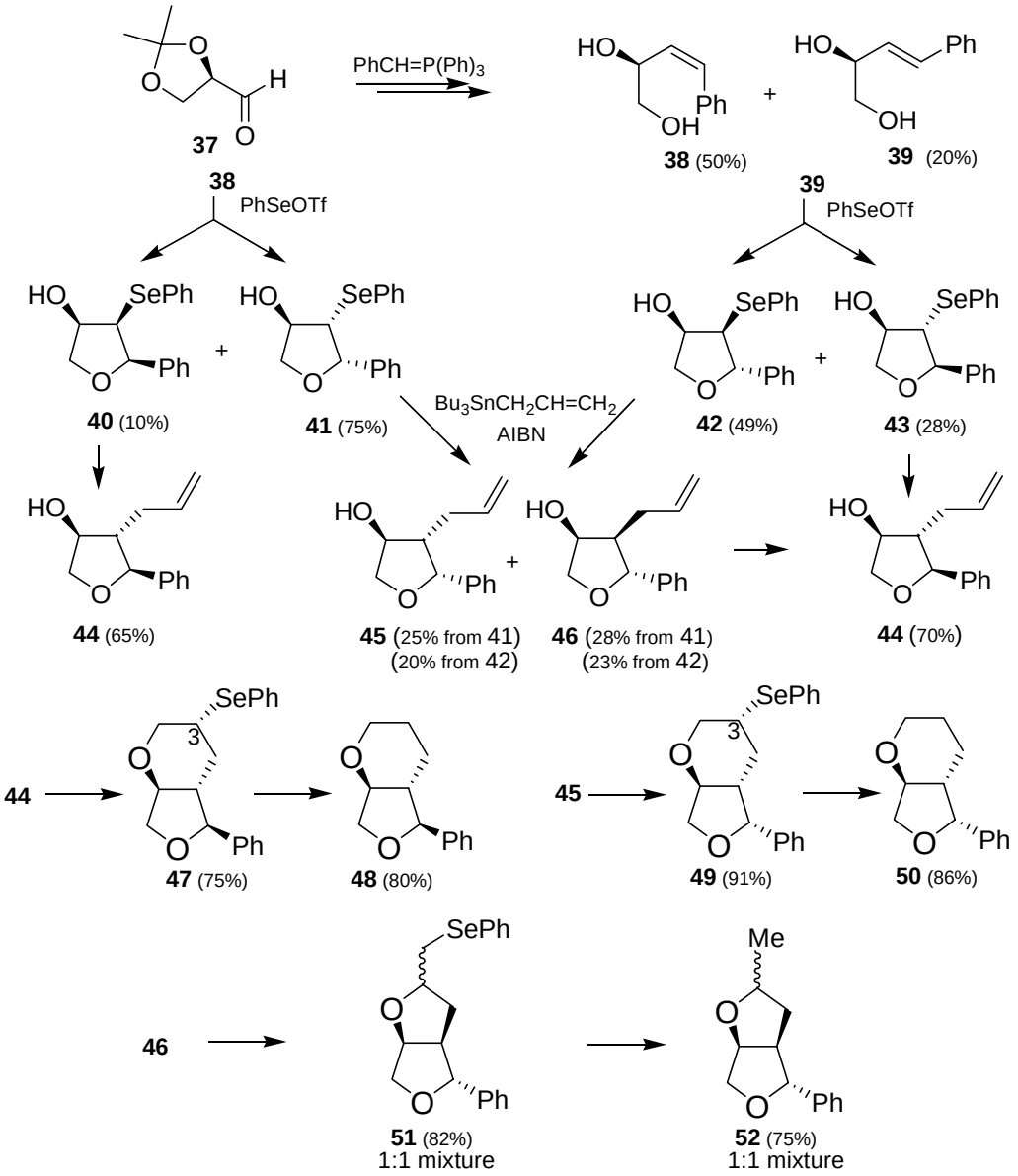
Using a similar procedure and starting from the (1*R*,2*R*)-1-phenylpropylene oxide (the opening of the epoxide was regiospecific) four diastereomeric 2,5-dimethyl-3-phenyl tetrahydrofurans were isolated. Starting from the *SS* epoxide the four enantiomeric compounds were prepared. Thus all the possible eight isomers of 2,5-dimethyl-3-phenyl tetrahydrofurans were prepared in an enantiomerically pure form.[19]

An example of the combined use of the reactivity of organoselenium reagents to promote cyclization reactions is reported in Scheme 10 which refers to the synthesis of perhydrofuro[3,4-b]pyrans and of perhydrofuro[3,4-b]furans.[20]

The ylide deriving from benzyl bromide was made to react with the D-glyceraldehyde acetonide **37**. A mixture of the *cis* and *trans* alkenols, **38** and **39**, was obtained. These were easily separated by column chromatography. The *cis* isomer could also be easily isomerized to the *trans* compound. The PhSeOTf promoted selenoetherification of **38** afforded the phenylseleno tetrahydrofurans **40** and **41**, whereas the cyclization of **39** gave the products **42** and **43**. The four compound were obtained in pure form after column chromatography. In each of these four compounds the PhSe group was replaced by the allyl group by treatment of tributyl allyl tin. Compounds **40** and **43** gave the same radical intermediate and hence the same reaction product **44**. The introduction of the allyl group was stereoselective and the less crowded compound was obtained as the sole reaction product. Compounds **41** and **42** gave the same radical intermediate and hence the same mixture of compounds **45** and **46** which were separated by column chromatography.

The PhSeOTf promoted selenoetherification of **44** and **45** gave **47** and **49** and after reductive deselenenylation, afforded the perhydrofuro[3,4-b]pyrans **48** and **50**, respectively.

Compound **46** instead gave a mixture of two phenylseleno perhydrofuro[2,3-b]furans **51** which could not be separated. Reductive deselenenylation gave **52**.

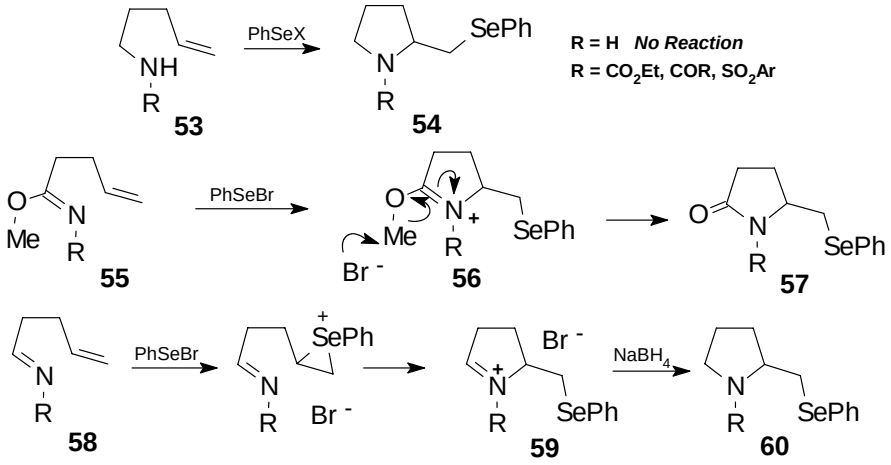



**Scheme 10.** Stereospecific synthesis of perhydro[3,4-b]pyrans and perhydro[3,4-b]furans

## 3. Cyclization Reactions by Formation of Carbon Nitrogen Bonds

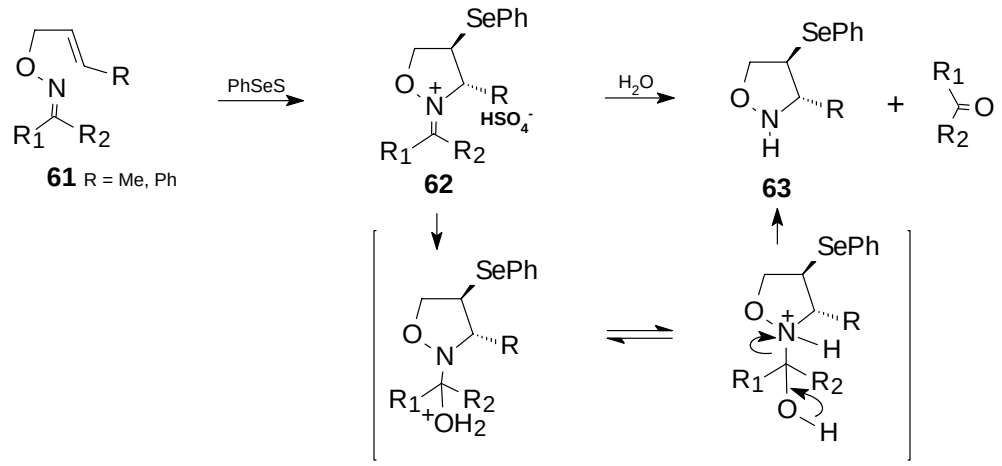
The first examples of the selenium promoted cyclization of alkenes containing internal nitrogen nucleophiles **53** were reported by Danishetsky[21] who demonstrated that with the primary amino group the cyclization reaction does not take place. As indicated in Scheme 11, the reaction occurs easily to give **54** only if an electron-withdrawing group is linked to the nitrogen atom.

Uemura[22] showed that if the nitrogen atom is that of an imidate **55** the cyclization occurs easily provided the PhSeBr is employed. This is because the bromine anion effects an $S_N2$ reaction attacking the methyl group of **56** and allowing the lactam **57** to act as the leaving group. Finally, in a series of papers De Kimpe[23] demonstrated that the nitrogen of imines **58** is sufficiently nucleophilic to trap the intermediate seleniranium ion and give the cyclic iminium ion **59** which was reduced to **60** with sodium borohydride.



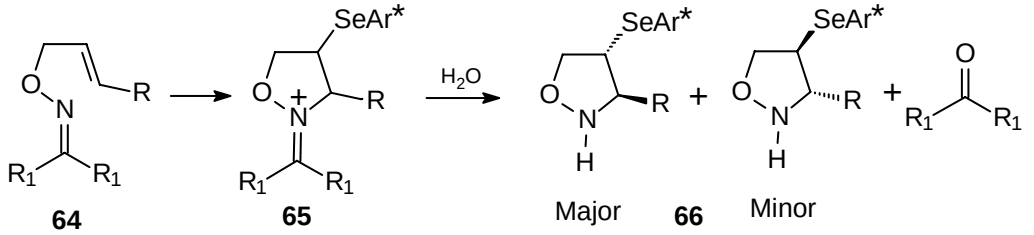

**Scheme 11.** Selenocyclization by formation of C-N bonds

We have found that successful cyclization reactions can be effected starting from O-allyl oximes **61** (Scheme 12). The reaction with phenylselenenyl sulfate gave the iminium ions **62** which can be reduced with sodium borohydride or they can be hydrolyzed to give the isoxazolidine **63** and the starting ketones.[24]



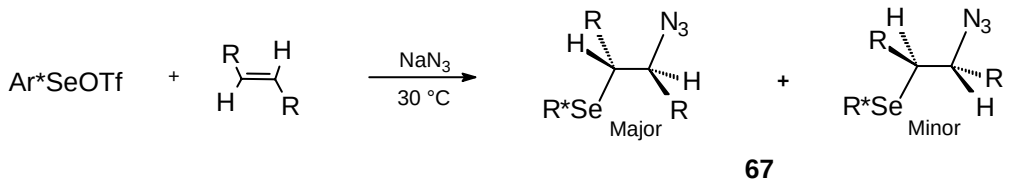

**Scheme 12.** Synthesis of isoxazolidines by cyclization of O-allyl oximes.

The asymmetric version of these reactions was effected starting from our sulfur containing diselenide **1**. From the oximes **64** a mixture of the two iminium salts **65** and then of the isoxazolidines **66** was obtained with the diastereomeric ratios reported in Scheme 13. The best results were obtained in the case in which R was a phenyl.[25]




**Scheme 13.** Asymmetric synthesis of isoxazolidines from O-allyl oximes

Very recently we have described[26] the interesting asymmetric synthesis of the azidoselenides **67.** As illustrated in Scheme 14 these compounds were obtained starting from alkenes and using the methoxy substituted sulfur containing diselenide **2**.

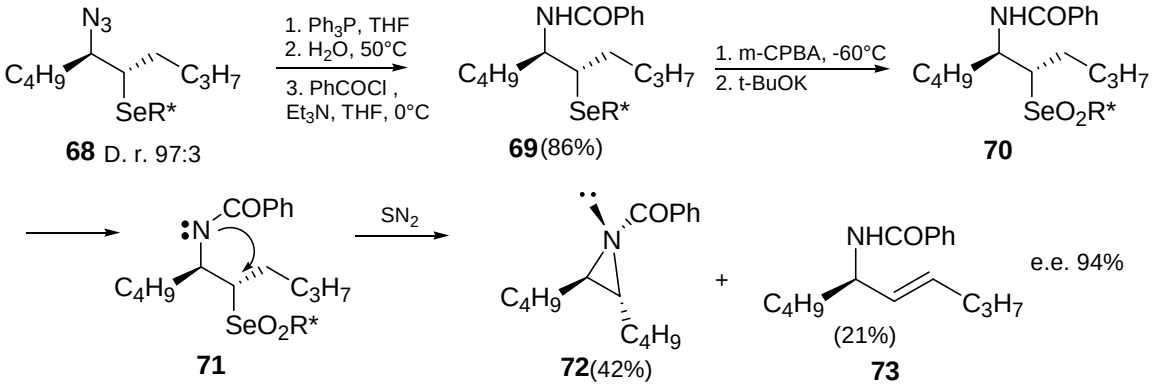



**Scheme 14.** Asymmetric azidoselenenylation of alkenes

With the exception of the reaction of cyclohexene (D.r = 61:39) in all the other cases the diastereomeric ratios were extremely good being equal or greater than 95:5.

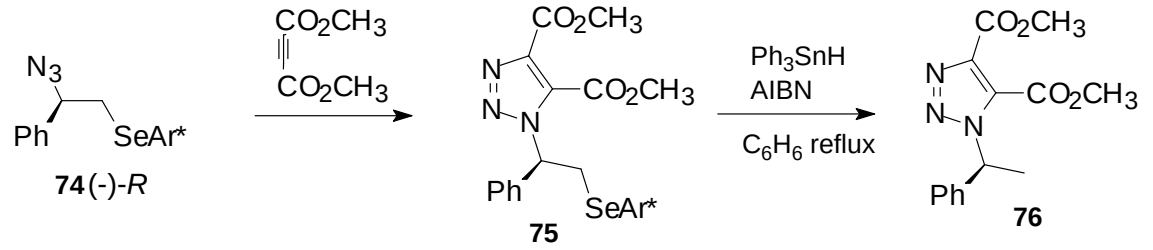
The azido selenides thus obtained are very useful and versatile intermediates because they have two groups, the azido and the arylseleno, which can be easily transformed into several different functional groups.

The first example reported here refers to the asymmetric synthesis of aziridines indicated in Scheme 15.[26] The azido group of compounds **68** was first reduced and the resulting amine was protected by benzoylation. The so formed benzoyl amido selenide **69** was oxidized with an excess of *m*-chloroperbenzoic acid to afford the corresponding selenone **70**. The nitrogen anion **71** was generated by treatment with a strong base and the aziridine **72** was then formed by intramolecular $S_N2$ substitution of the selenone group. The product **73**, deriving from the elimination of the intermediate selenoxide, was also isolated. In both reaction products the ee (94%) corresponded to the diastereomeric ratio (97:3) of the starting products.




**Scheme 15.** Asymmetric synthesis of aziridines.

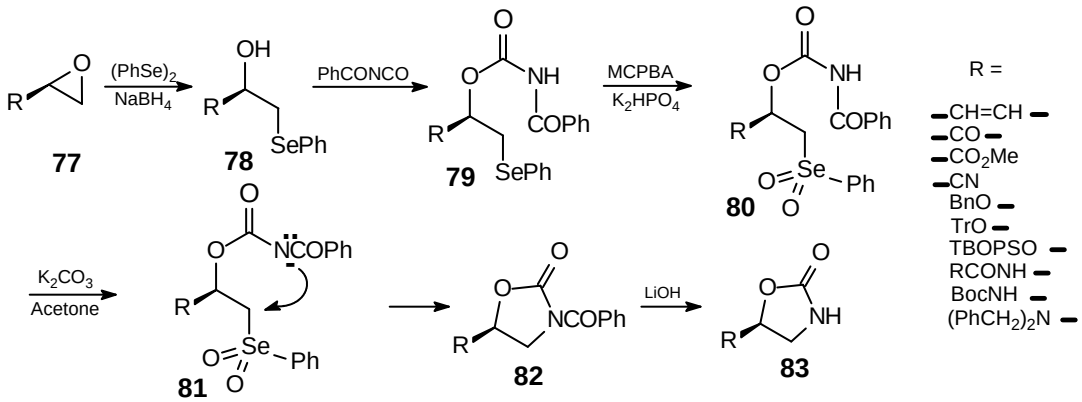
The azido selenide derived from styrene **74** was also treated with methyl acetylene dicarboxylate to afford **75** and after deselenenylation the selenium free triazole **76** in excellent yield and with an ee of 94% (Scheme 16).[26]




**Scheme 16.** Asymmetric synthesis of triazoles.

Nitrogen containing heterocyclic compounds were also prepared starting from enantiopure substrates and achiral selenium reagents.

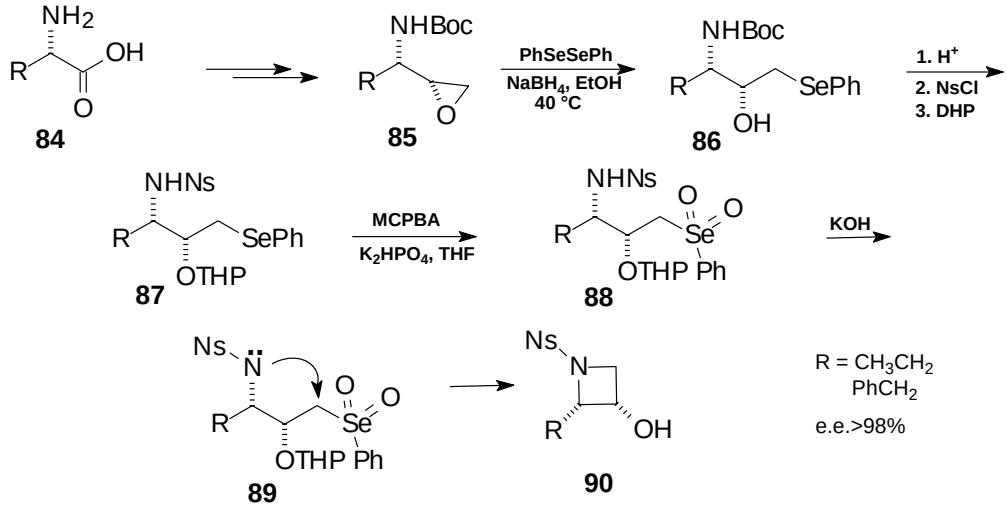
The examples reported in Schemes 17 and Scheme 18 concern again cyclization reactions by intramolecular substitution of the selenone group. In the first Scheme the various intermediates **78**, **79**, **80** and **81** for the conversion of epoxides **77** into 1,3-oxazolidin-2-ones **82** and **83** are indicated.[27]




**Scheme 17.** Synthesis of enantiopure substituted 1,3-oxazolidin-2-ones.

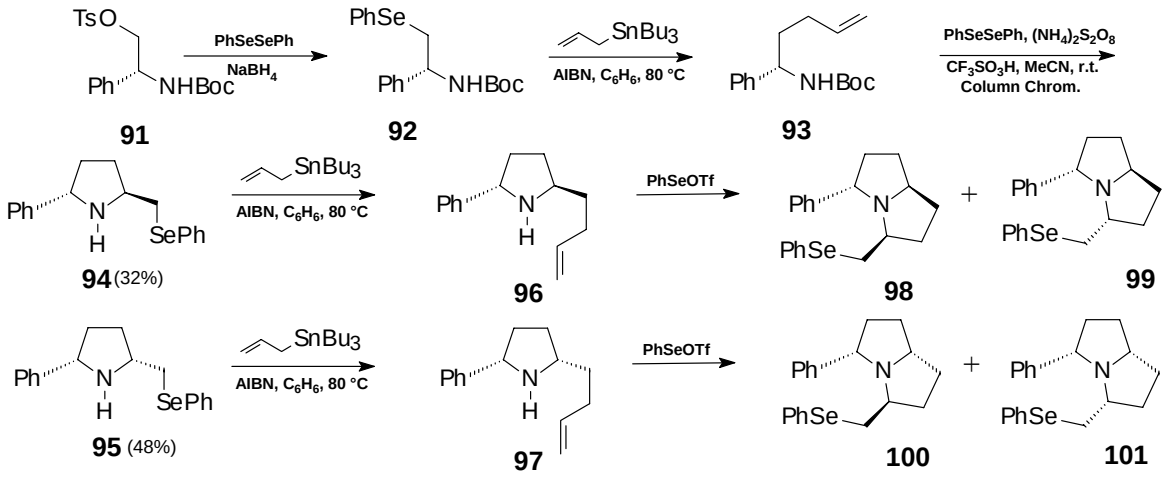
These reactions were carried out with a variety of substituents R. Starting from the 1-phenylpropylene oxide 4,5-substituted 1,3-oxazolidin-2-ones were obtained in good yields.

The same displacement reaction was also employed to form the four membered azetidines **90**.[28] The starting products were two commercially available aminoacids **84** which were converted into the epoxide **85**. The various intermediates **86**, **87**, **88** and **89** are indicated in Scheme 18.




**Scheme 18. S**ynthesis of enantiopure azetidines.

The syntheses of enantiopure pyrrolidines and perhydropirrolizines were effected starting from Boc protected β-amino tosylate **91** (Scheme 19).[28]




**Scheme 19. S**ynthesis of enantiopure perhydropyrrolizidines.

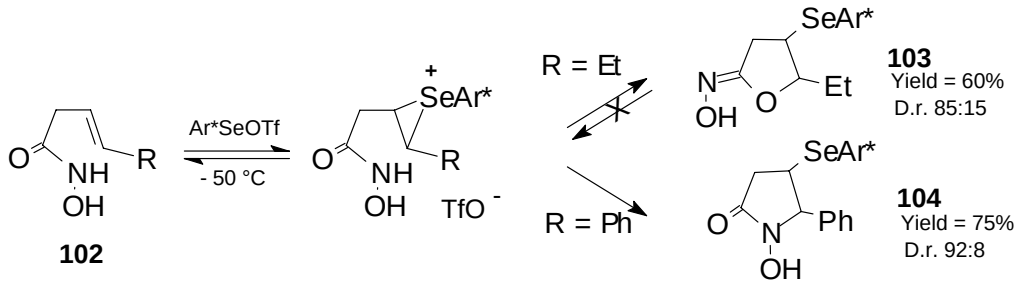
The tosyl group was substituted by phenylselenium anions to give **92** and the seleno group was replaced by the allyl group in the usual way. The cyclization of the resulting alkenyl amine **93** was promoted by phenylselenenyl sulfate and the two diastereomeric reaction products **94** and **95** were separated by column chromatography. During chromatography the protecting group was removed. Finally the reductive deselenenylation afforded the 2-methyl-5-phenyl pyrrolidines. Alternatively, the phenylseleno group can be replaced by the allyl and the resulting compound **96** and **97** can be treated with PhSeOTf to afford the bicyclic perhydropyrrolizidines. In the first case the cyclization afforded the two diastereoisomers **98** and **99** which were separated by column chromatography. In the second case compound **100** was obtained as a single product. The forth diastereoisomer **101** was not formed probably for steric reasons.

## 4. Competition between Oxygen and Nitrogen

Sometimes the internal nucleophile is an ambident group and the trapping of the seleniranium ion can occur either with the oxygen or with the nitrogen atom. In some cases the course of the reaction depends on the experimental conditions employed. Thus a competition between oxygen and nitrogen can be observed.

Some years ago we observed that the phenylselenenyl sulfate promoted cyclization of alkenyl hydroxamic acid: when the reaction was carried out at low temperature (20 °C for R=Me and -20°C for R=Ph), N-hydroxy imidates were isolated.[29] If the reaction mixture was warmed up, or the reactions was directly carried out at higher temperature (50 °C for R=Me and 20°C for R=Ph) the reaction products were the N-hydroxy γ-lactams. Clearly the imidates are the products

deriving from the kinetic control and are formed reversibly, whereas the lactams are the products deriving from the thermodynamic control of the reaction.

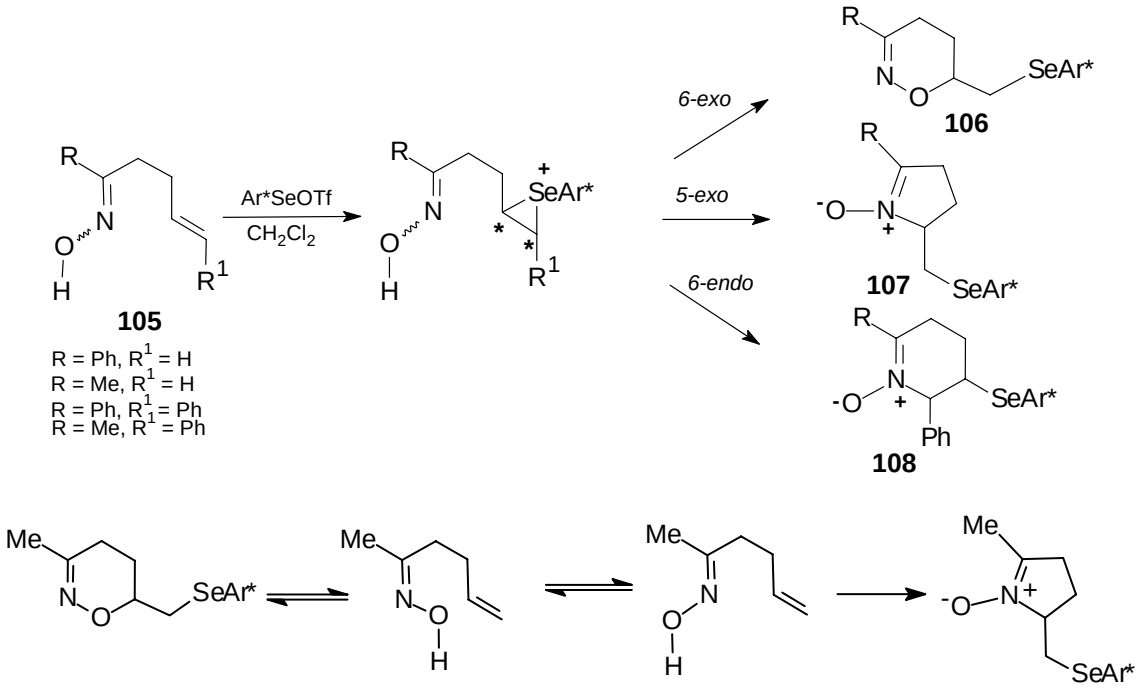



**Scheme 20.** Enantioselective synthesis of N-hydroxy imidates and γ-lactam.

The asymmetric version of this reaction, carried out with **102** and the selenenyl triflate deriving from the sulfur containing diselenide **1**, gave different results (Scheme 20).[30] The reactions were carried out at -50°C and afforded the N-hydroxy imidate **103** in the case of R=Et and the N-hydroxy γ-lactam **104** in the case of R=Ph. The increase of the reaction temperature did not produce any change in the composition of the reaction mixtures. With this selenenylating agent therefore the formation of the N-hydroxy imidate **103** is not reversible.

An interesting case is observed in the case of cyclization of the oximes. The first examples were reported by Gallagher[31] in the cyclization of allenic oximes promoted by silver tetrafluoborate. It was observed that the nature of the reaction products depended on the geometry of the starting oximes. The Z isomers gave 1,2-oxazines and the more stable E isomers gave cyclic nitrones. Under these conditions alkenyl oximes did not react. It was later observed by Grigg[32] and by ourselves[33] that the cyclization of alkenyl oximes can be effected using electrophilic phenyselenium reagents. It was observed that starting from a mixture of the two isomeric oximes the 1,2-oxazines were only present in traces.

The asymmetric version of these cyclizations was carried out using the triflate of the methoxy substituted sulfur containing diselenide **2** (Scheme 21).[34] The cyclization reaction of the alkenyl oximes **105** can take place in different ways depending on the heteroatom which acts as the nucleophile and on the carbon atom of the seleniranium ion which is attacked. A *6-exo* cyclization by the oxygen atom would afford the 1,2-oxazines **106**, whereas a *5-exo* cyclization by the nitrogen atom would afford the five membered cyclic nitrones **107**. A *6-endo* cyclization by the nitrogen atom would afford the six membered cyclic nitrones **108**. These product are observed only in the case in which $R^1$ = Ph. In every case the reactions occur with a Markovnikov regioselectivity.




**Scheme 21.** Asymmetric Synthesis of 1,2-oxazines and cyclic nitrones.

In the case of the phenyl derivative (R=Ph, $R^1$=H) the cyclization reactions afforded reaction products which reflected the geometry of the oximes. The Z isomer gave the 1,2-oxazine and the E isomer gave the cyclic nitrone. On the contrary, in the case of the methyl derivative (R=Me, $R^1$=H) the ratio of the two reaction products did not reflect the ratio of the starting oximes. Using a 2:1 mixture of the Z:E isomers after 7 hours the 1,2-oxazine was formed in 18% yields and the cyclic nitrone in 72% yield. After 17 hours the reaction mixture is constituted only by the nitrone. Thus, the formation of the nitrone is largely preferred. From the results of some parallel experiments we concluded that this behavior is due to the fact that, under the conditions employed, the two isomeric starting oximes interconvert and that the formation of the 1,2-oxazine is a reversible process (Scheme 21). Thus, the entire process is shifted towards the formation of the thermodynamically more stable nitrone.

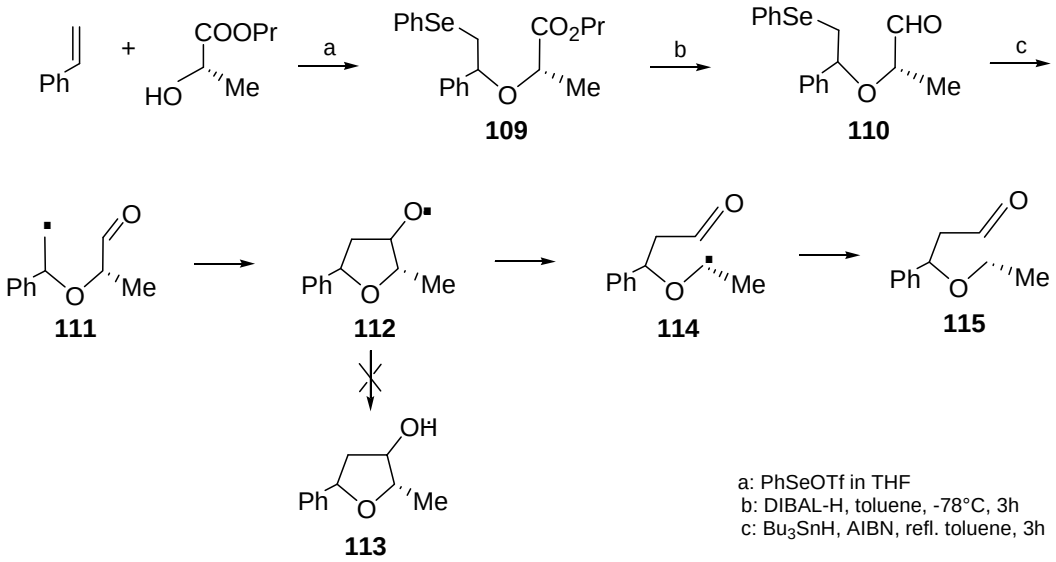
## 5. Cyclization Reactions by Formation of Carbon Carbon Bonds

Cyclization reactions of alkenes containing internal carbon nucleophiles are not very common and have been mainly employed for the formation of homocyclic compounds. The results which are presented here refer to cyclization reactions in which the ring forming process is the addition of a carbon radical to a carbon oxygen double bond. These reactions were effected starting from enantiopure substrates and achiral organoselenium reagents.

Additions of carbon radicals generated from selenides to carbon-carbon double bonds have been largely investigated. These reactions occur easily and have been employed by Engman[35] to produce a large number of oxygen and nitrogen containing heterocyclic compounds. Similar cyclizations by addition to carbon-oxygen double bond are more difficult. The alkoxy radicals can in fact suffer rapid β-scission reactions. Thus these radical cyclizations can be reversible and the trapping of the cyclic alkoxy radical is not always easy. However, substituents along the forming ring facilitate the trapping of cyclic products. As a matter of fact a successful cyclization has been recently reported by Uchiyama[36] for the synthesis of the hydroxy perhydrofuro[2,3-b]furans.

Our first experiments on the radical cyclization reaction were effected in order to synthesize some enantiopure 3-hydroxy tetrahydrofuran derivatives.[28]

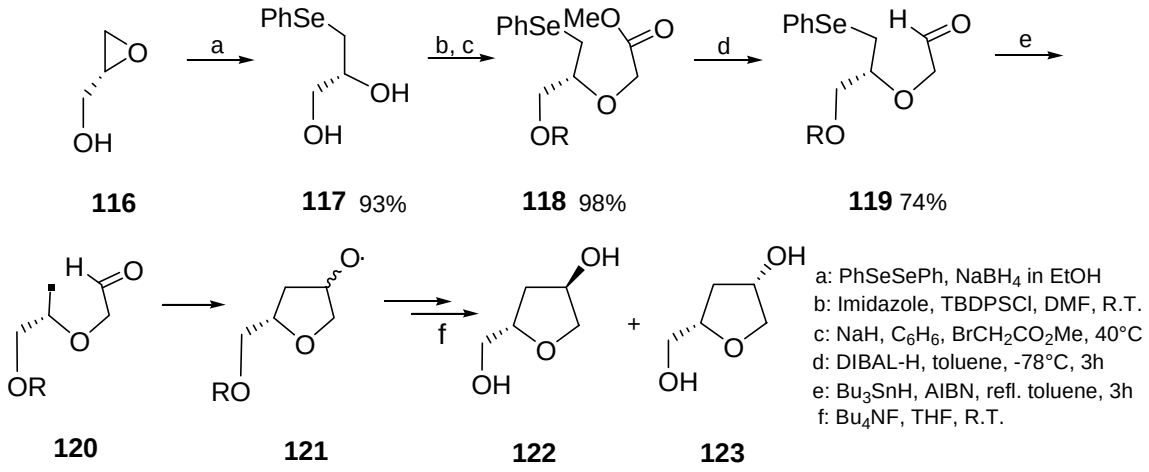
As indicated in Scheme 22, the starting product was compound **109** which was prepared in satisfactory yields from the intermolecular alkoxy selenenylation of styrene with phenylselenenyl triflate and propyl (*S*)-lactate. This ester was reduced with DIBAL to afford the corresponding aldehyde **110**. The phenyl selenium group was then removed by treatment with tributyl tin hydride and AIBN in refluxing toluene. The carbon radical thus produced **111** gave rise to the addition reaction to the carbon oxygen double bond and produced the cyclic alkoxy radical **112**. However, the rate of hydrogen abstraction to afford the desired product **113** was lower than that of the β-scission and the secondary carbon radical **114** was obtained. Hydrogen abstraction gave the observed reaction product **115**.




**Scheme 22.** Attempted synthesis of 2-methyl-3-hudroxy-5-phenyl tetrahydrofurans

In order to decrease the rate of the β-scission process we used a starting product in which the β-scission would afford a primary carbon radical. Thus, as indicated in Scheme 23, we

started from the commercially available R-(+)-glycidol (e.e. = 98%) **116**. The ring opening of the epoxide with phenyl selenium anions was regiospecific and gave the β-hydroxy selenide **117**.[28]

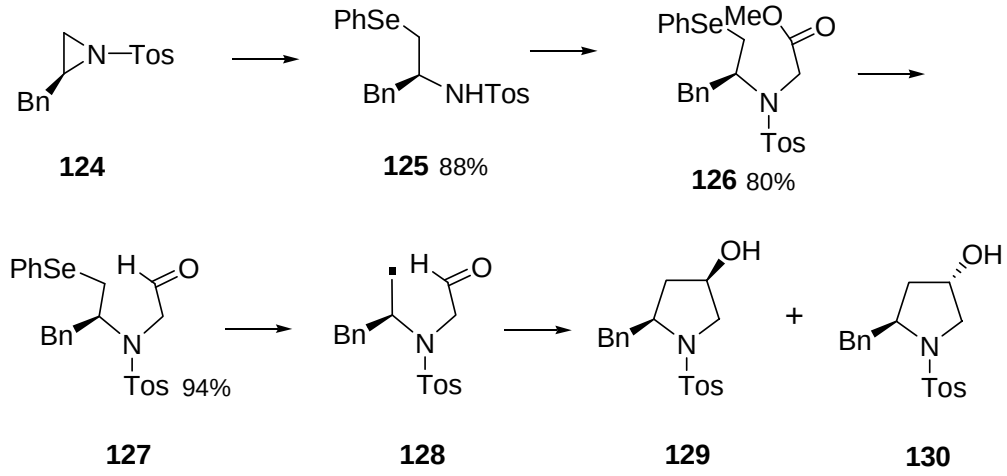



**116** **117** 93% **118** 98% **119** 74%

**120** **121** **122** **123**

**Scheme 23.** Synthesis of enantiopure β-hydroxy tetrahydrofurans

The primary OH group was then selectively protected and the resulting product was treated with methyl bromoacetate. The ester thus obtained **118** was then reduced with DIBAL to afford the corresponding seleno aldehyde **119**. Treatment with tributyl tin hydride and AIBN afforded the carbon radical **120** which added to the carbonyl group. As anticipated, in this case the trapping of the alkoxy radical **121** by the tributyl tin hydride was faster than the β-scission and the desired hydroxy tetrahydrofurans **122** and **123** were obtained as an almost equimolecular mixture of the two enantiopure diastereoisomers which were easily separated by column chromatography.




**124** **125** 88% **126** 80%

**127** 94% **128** **129** **130**

**Scheme 24.** Synthesis of enantiopure β-hydroxy pyrrolidines

On the basis of the experience gained from these experiments we have then applied a similar reaction sequence to the commercially available N-tosyl benzyl aziridine **124** (e.e. = 98%) in order to produce enantiopure hydroxy pyrrolidines **129** and **130** passing through the reaction intermediates **125**, **126**, **127** and **128** (Scheme 24).[28]
The reaction proceeded as expected and the final products were an almost equimolecular mixture (46% yield, D.r. 53:47) of the two enantiopure diastereoisomers which were separated by column chromatography.

In conclusion the results described above demonstrate that organoselenium reagents, both chiral non racemic and achiral, can be successfully employed to effect the synthesis of different types of enantiomerically enriched or in most cases enantiopure heterocyclic compounds. The examples which have been described concern the preparation of very simple compounds. However the methodologies employed are of general application and can also be used to the synthesis of much more complex molecules using properly substituted starting products. Organoselenium reagents, in fact, require very mild experimental conditions which are compatible with most of the organic functional groups.

## Acknowledgements

Financial support from Ministero dell'Istruzione, dell'Università e della Ricerca, MIUR, National Projects PRIN2003, FIRB2001, Consorzio CINMPIS, Bari and University of Perugia is gratefully acknowledged.

## References

1. (a) Tiecco, M. *Electrophilic Selenium; Selenocyclizations In Topics in Current Chemistry*: *Organoselenium Chemistry: Modern Developments in Organic Synthesis*; Wirth, T. Ed.; Springer-Verlag: Heidelberg; 2000, pp 7-54. (b) *Organoselenium Chemistry- A Practical Approach*; Back, T. G. Ed.; Oxford: New York 2000. (c) Wirth, T. *Angew Chem. Int. Ed.* **2000**, *39*, 3742.
2. (a) Tomoda; S.; Iwaoka; M. *Chem. Lett*. **1988**, 1895. (b) Tomoda, S.; Iwaoka, M.; Yakushi, K.; Kawamoto, A.; Tanaka, J. *J. Phys. Org. Chem.* **1988**, *1*,179. (c) Tomoda, S.; Iwaoka, M. *J. Chem. Soc., Chem. Commun*. **1988**, 1283. (d) Tomoda, S.; Fujita, K.; Iwaoka, M. *J. Chem. Soc., Chem. Commun.* **1990**, 129. (e) Tomoda, S.; Fujita, K.; Iwaoka, M. *Chem Lett* **1992**, 1123. (f) Tomoda, S; Fujita, K; Iwaoka, M. *Phosphorus Sulfur* **1997**, *67*, 247.
3. (a) Déziel, R.; Goulet, S.; Grenier, L.; Bordeleau, J.; Bernier, J. *J. Org. Chem.* **1993**, *58*, 3619. (b) Déziel, R.; Malenfant, E. *J. Org. Chem.* **1995**, *60*, 4660. (c) Déziel, R.; Malenfant, E.; Bélanger, G. *J. Org. Chem.* **1996**, *61*, 1875. (d) Déziel, R.; Malenfant, E.; Thibault, C.; Fréchette, S.; Gravel, M. *Tetrahedron Lett.* **1997**, *38*, 4753.

4. (a) Nishibayashi, Y.; Singh, J. D.; Uemura, S.; Fukuzawa, S. *Tetrahedron Lett.* **1994**, *35*, 3115. (b) Nishibayashi, Y.; Srivastava, S. K.; Takada, H.; Fukuzawa, S.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1995**, 2321. (c) Nishibayashi, Y.; Singh, J. D.; Fukuzawa, S..; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4114. (d) Fukuzawa, S.; Takahashi, K.; Kato, H.; Yamazaki, H. *J. Org. Chem.* **1997**, *62*, 7711.
5. (a) Fujita, K.; Iwaoka, M.; Tomoda, S. *Chem. Lett.* **1994**, 923. (b) Fujita, K.; Murata, K.; Iwaoka, M.; Tomoda, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1641. (c) Fujita, K.; Murata, K.; Iwaoka, M.; Tomoda, S. *Tetrahedron Lett.* **1995**, *36*, 5219. (d) Fujita, K.; Murata, K.; Iwaoka, M.; Tomoda, S. *Tetrahedron* **1997**, *53*, 2029. (e) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1996**, *118*, 8077. (f) Komatsu, H.; Iwaoka, M.; Tomoda, S. *J. Chem. Soc., Chem. Commun.* **1999**, 205.
6. (a) Back, T. G.; Dyck, B. P.; Parvez, M. *J. Chem. Soc., Chem. Commun.* **1994,** 515. (b) Back, T. G.; Dyck, B. P.; Parvez, M. *J. Org. Chem.* **1995**, *60*, 703. (c) Back, T. G.; Dyck, B. P. *J. Chem. Soc., Chem. Commun.* **1996**, 2567. (d) Back, T. G.; Nan, S. *J. Chem. Soc., Chem. Commun.* **1998**, 3123. (e) Back, T. G.; Dyck, B. P.; Nan, S. *Tetrahedron* **1999**, *55*, 3191.
7. (a) Wirth, T. *Angew. Chem., Int. Ed.* **1995**, *34*, 1726. (b) Wirth, T.; Fragale, G. *Chem. Eur. J.* **1997**, *3*, 1894.
8. Fragale, G.; Neuburger, M.; Wirth, T. *J. Chem. Soc., Chem. Commun.* **1998**, 1867.
9. Santi, C.; Fragale, G.; Wirth, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3625.
10. (a) Murata. S.; Suzuki, T. *Chem. Lett.* **1987**, 849. (b) Murata, S.; Suzuki, T. *Tetrahedron Lett.* **1987**, *28*, 4297. (c) Murata, S.; Suzuki, T. *Tetrahedron Lett.* **1987**, *28*, 4415.
11. (a) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *Tetrahedron Lett.* **1989**, *30*, 1417. (b) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1989.
12. Tiecco, M.; Testaferri; L.; Bagnoli, L.; Marini, F.; Temperini, A.; Tomassini, C.; Santi, C. *Tetrahedron Lett.* **2000**, *41*, 3241.
13. Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Chem. Eur. J.* **2002**, *8*, 1118.
14. Tiecco M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Santi, C.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1493.
15. Tiecco M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. *Eur. J. Org. Chem.* **2005**, 543.
16. Tiecco, M.; Testaferri, L.; Bagnoli, L.; Scarponi, C.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2005**, *16*, 2429.
17. Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Eur. J. Org. Chem*. **2000**, 3451.
18. Bannard, R. A. B.; Gibson, N. C. C.; Parkkari, J. H. *Can. J. Chem*. 1971, *49*, 2064.
19. Tiecco, M.; Testaferri, L.; Bagnoli, L.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2004**, *15*, 405.

20. Tiecco, M.; Testaferri, L.; Bagnoli, L.; Terlizzi, R.; Temperini, A.; Marini, F.; Santi, C.; Scarponi, C. *Tetrahedron: Asymmetry* **2004**, *15*, 1949.
21. Danishefsky; S.; Webb II; R.R. *Tetrahedron Lett.* **1983**, *24*, 1357.
22. (a) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1986**, 530. (b) Terao, K.; Toshimitsu, A.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1837. (c) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem*. **1987**, *52*, 2018.
23. (a) De Kimpe, N.; Boelens, M. *J. Chem. Soc., Chem. Commun.* **1993**, 916. (b) De Smaele, D.; De Kimpe, N. *J. Chem. Soc., Chem. Commun.* **1995**, 2029.
24. (a) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L. *J. Chem. Soc., Chem. Commun.* **1995**, 235. (b) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Santi, C. *Tetrahedron* **1995**, *51*, 1277.
25. Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Santi, C.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 3053.
26. Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Angew. Chem., Int. Ed*. **2003**, *42*, 3131.
27. Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Chem. Eur. J.* **2004**, *10*; 1752.
28. Unpublished results from this laboratory.
29. Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *J. Chem. Soc., Chem. Commun.* **1994**, 221.
30. Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Santi, C.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1493.
31. (a) Lathbury, D.; Gallagher, T. *J. Chem., Soc. Chem. Commun*. **1986**, 1017. (b) Lathbury, D.; Shaw, R. W.; Bates, P. A.; Hursthouse, M. B.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2415.
32. Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J. *J. Chem. Soc., Chem. Commun*. **1992**, 1537.
33. Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Marini, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1989.
34. Tiecco, M.; Testaferri, L.; Bagnoli, L.; Purgatorio, V.; Temperini, A.; Marini, F.; Santi, C. *Tetrahedron: Asymmetry* **2001**, 12, 3297.
35. (a) Ericsson, C.; Engman, L. *Org. Lett.* **2001**, *3*, 3459. (b) Berlin, S.; Ericsson, C.; Engman, L. *Org. Lett.* **2002**, *4*, 3. (c) Gupta, V.; Besev, M.; Engman, L. *Tetrahedron Lett.* **1998**, *39*, 2429. (d) Berlin, S.; Engman, L. *Tetrahedron Lett.* **2000**, *41*, 3701.
36. Uchiyama, M.; Hirai, M.; Nagata, M.; Katoh, R.; Ogawa, R.; Ohta, A. *Tetrahedron Lett.* **2001**, *42*, 4653.