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Chiral Selenium Compounds in Organic Synthesis

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To the memory of Sir Derek Barton†

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Contents

1. Introduction

Selenium was discovered in 1817 by J. J. Berzelius[1] and although the first organoselenium compound, ethyl selenol, was reported in 1847 by F. Wöhler and C. Siemens,[2] it was much too early for an efficient use of selenium in organic chemistry. In 1929 the first patent for the use of selenium dioxide as oxidant in synthetic organic chemistry appeared.[3] But it was not until 1970, when the formation of alkenes by decomposition of selenoxides was found to be a versatile process proceeding under very mild conditions, that explosive growth in the use of organoselenium chemistry occured.[4] Since that time the use and the development of selenium

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reagents beside elemental selenium and selenium dioxide have become popular in organic chemistry. First reviews[5] of the early work as well as first conference reports[6] dealing with the chemistry of selenium were published. Already in 1957 it was shown that selenium is an essential trace element for animals.[7] Biologists began to investigate its properties and it was discovered that *Glutathione Peroxidase*, a mammalian enzyme, contains a selenocystein residue in its active site.[8] Since then there has been also a growing interest of the enzymology and of the bioorganic chemistry of selenium.[9]

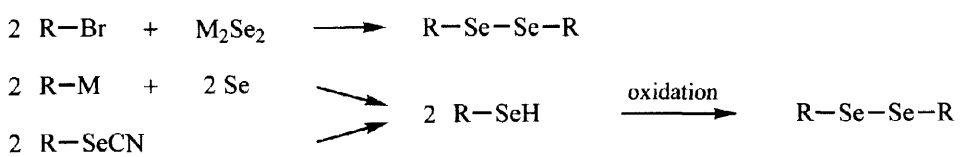
From the viewpoint of the organic chemist, the chemistry of molecules containing oxygen or sulfur is much better known and investigated. A variety of selenium compounds have been prepared and were found to be similar to the sulfur analogues. Selenium and sulfur have similar radii and similar electronegativities of 2.44 and 2.48, respectively, giving them similar reactivities. But selenium containing molecules are sometimes sensitive towards oxidation or light and are therefore less stable. Furthermore, they are sometimes evil-smelling and toxic. This is due to the fact that the carbon – selenium bond (243 kJ•mol^{-1}) is weaker than the carbon – sulfur bond (272 kJ•mol^{-1}) and the carbon – oxygen bond (356 kJ•mol^{-1}). The chalcogen – hydrogen bond energies also decrease in the same order.[10b]

Despite the similarities between sulfur containing molecules and their selenium congeners, there are several unique features of organoselenium compounds. They can be used in nucleophilic, in electrophilic, as well as in radical reactions. Therefore, many methods based on selenium have been developed into standard procedures in organic chemistry.[10]

In this report important recent advances using chiral selenium compounds as stoichiometric reagents and as catalysts in organic synthesis are reviewed. Various aspects of chiral selenium compounds in organic chemistry have been summarized in a different context.[11] Reactions with selenium containing compounds are not included in this report if the selenium does not play a crucial role in stereoselectivity.[12]

2. Synthesis of Chiral Selenium Compounds

Diselenides are the central reagents of organoselenium chemistry. Various routes for their preparation have been worked out and a manifold of different precursors can be transformed to the corresponding diselenides with high efficiency. The most important routes involve either the reaction of metal diselenides with halides or the preparation of selenols *via* metalated precursors which can be easily oxidized to the corresponding diselenides as shown in Scheme 1.[13]



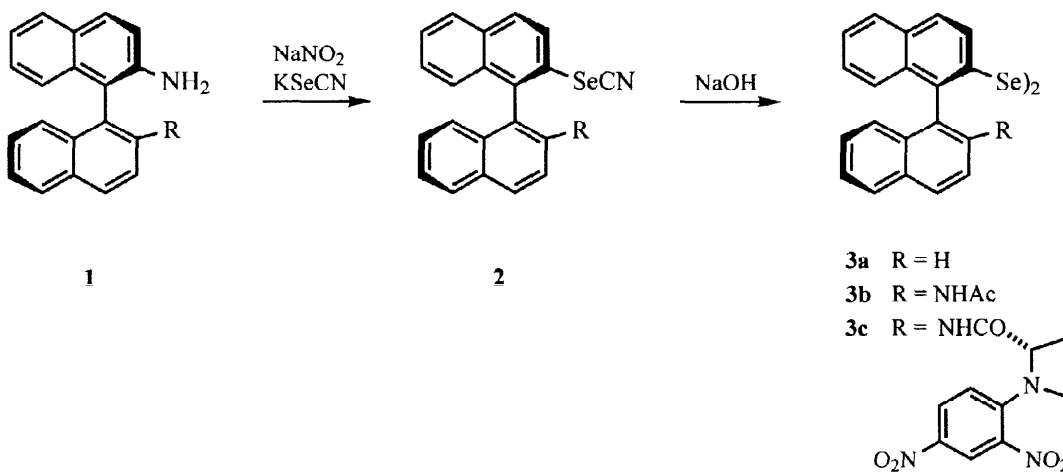
Scheme 1. Synthesis of Diselenides

For the synthesis of chiral diselenides, precursors with chiral substituents R have to be used in the synthesis. In a second class of chiral selenium compounds the chiral center is located on the selenium atom itself.

Optically active selenoxides have low configurational stability when compared with the corresponding sulfoxides. But beside selenonium salts, selenonium ylides, and selenonium imides they seem to have a larger potential with respect to stereoselective synthesis. Several methods for their preparation have been developed and in subsequent reactions a transfer of chirality is possible.[14]

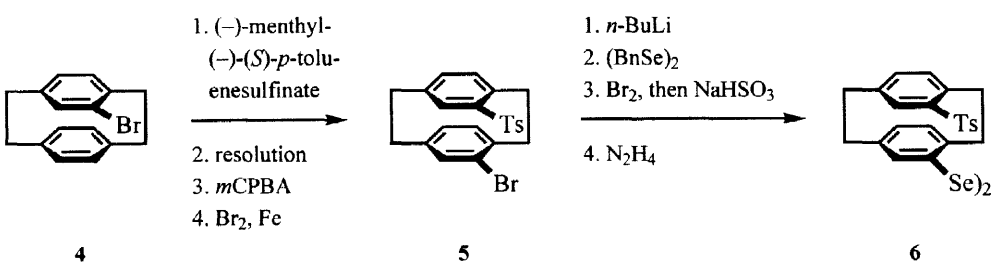
2.1. Synthesis of Chiral Diselenides of Type $(Ar^*Se)_2$

Chiral binaphthyl diselenides of type **3** were the first optically active selenium reagents which were employed by Tomoda and co-workers already in 1988 in stereoselective electrophilic selenenylations.[15] Diazotisation of various monoprotected chiral binaphthylamines **1** and addition of potassium selenocyanate gave compounds **2** and treatment with aqueous sodium hydroxide yielded the desired chiral binaphthyl diselenides **3** in about 30 % overall yield (Scheme 2).



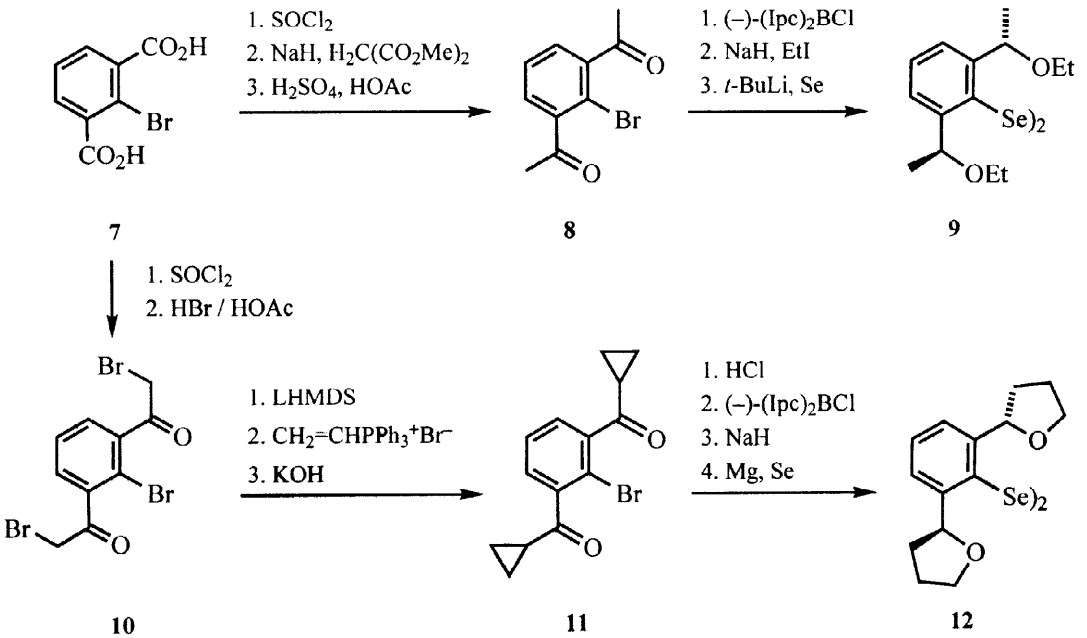
Scheme 2. Tomoda's Chiral Binaphthyl-derived Diselenides

After this finding other optically active diselenides were reported. The [2.2]paracyclophane diselenide **6** was described by Reich *et al.* in 1991.[16] The racemic 2-bromoparacyclophane **4** was transferred into the diastereomeric sulfoxides, which could be separated. Oxidation and introduction of bromine yielded **5**, and the selenium was subsequently introduced by reaction with dibenzyl diselenide. After cleavage with bromine and reduction with hydrazine the diselenide **6** was obtained in 21 % overall yield.



Scheme 3. Reich's Chiral Paracyclophane Diselenide

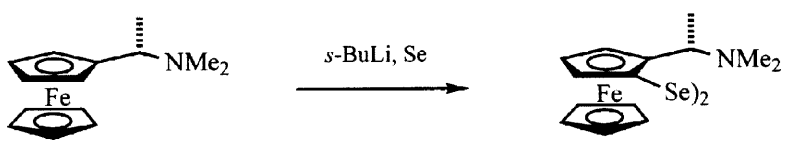
C_2-symmetrical diselenides **9** and **12** were reported by Déziel in 1993 and 1997.[17] The synthesis of **9** starts with 2-bromoisophthalic acid **7**, which is prepared by malonate addition to the acyl chloride and subsequent hydrolysis with decarboxylation. Compound **8** is reduced with (–)-*B*-chlorodiisopinocampheylborane [(–)-(Ipc)$_2$BCl], ethylated and the diselenide **9** is obtained in 20 % overall yield *via* bromine – lithium exchange and addition of elemental selenium followed by oxidative work-up. Starting from **7**, a synthetic route to the sterically more rigid diselenide **12** was reported recently. The synthesis to this diselenide is long, although **12** is obtained in about 30 % overall yield.



7 **8** **9** **10** **11** **12**

Scheme 4. C_2-symmetrical Chiral Diselenides from Déziel

Diselenides with a ferrocenyl skeleton such as **14** were synthesized by Uemura *et al.* in 1994.[18] They are readily accessible from the chiral ferrocenyl derivative **13** in 80 % yield. A drawback of this synthesis is the availability of **13**, because it is quite expensive or has to be prepared *via* a multistep synthesis.[19]

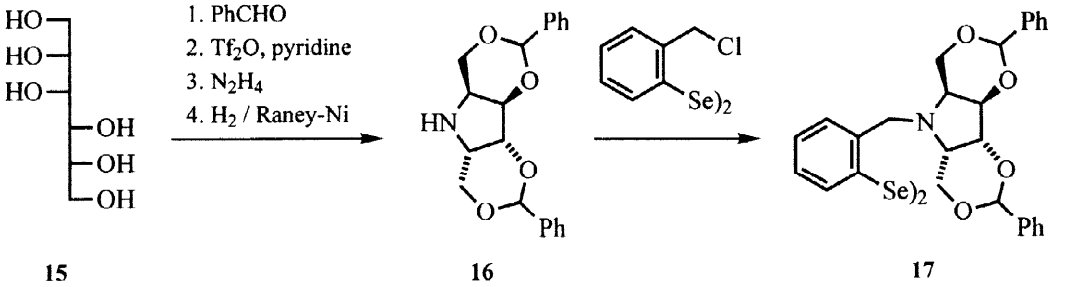


13 **14**

Scheme 5. Uemura's Chiral Ferrocenyl-Based Diselenides

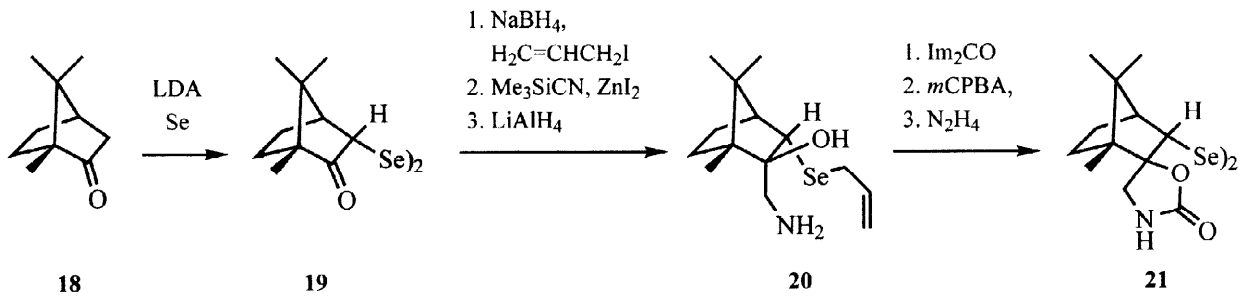
Diselenides with various chiral pyrrolidine moieties like **17** (1994) have been characterized and used in stereoselective synthesis by Tomoda *et al.*[20] The chiral moiety **16** was readily derived from D-mannitol[21] by acetalization with benzaldehyde and treatment with triflic anhydride. Cyclization was accomplished with

hydrazine and subsequent reduction yielded the C_2-symmetrical moiety **16** which was used for the synthesis of the chiral diselenide **17** in about 50 % overall yield.



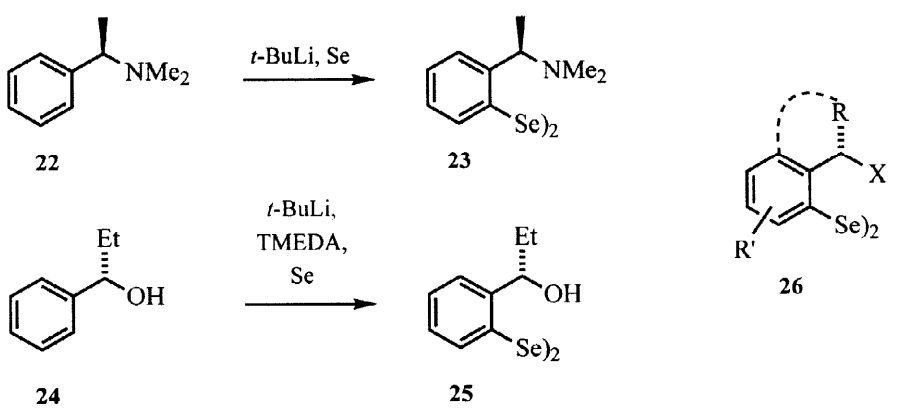
Scheme 6. Chiral Diselenides with Pyrrolidinyl-Moieties by Tomoda

Chiral diselenides derived from camphor of type **21** have been synthesized by Back *et al.* (1994).[22] The synthesis of **19** is a one-step preparation from camphor **18**. After protection of the selenium as an allyl selenide, the diselenide **21** with the cyclic carbamate moiety was prepared by formation and reduction of the cyanohydrin to compound **20** and subsequent cyclization in 53 % overall yield.



Scheme 7. Camphor-Derived Diselenides from Back

The success of the above mentioned diselenides led to the design and synthesis of more simple diselenides. Diselenides like **23** and **25** are easily accessible by a one-step synthesis from commercially available



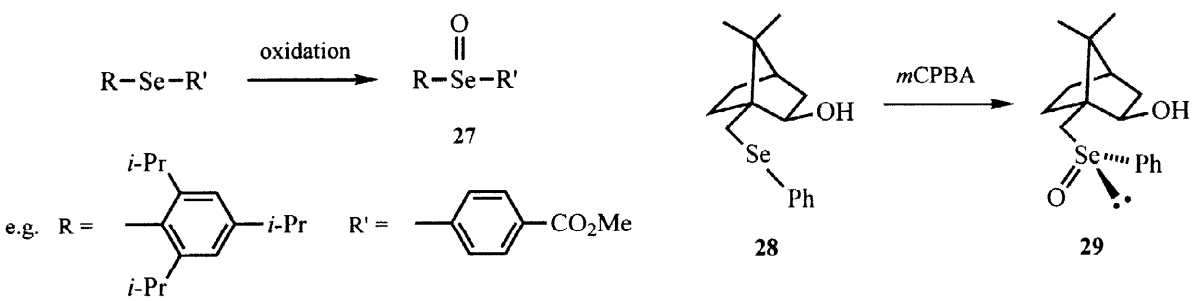
Scheme 8. Chiral Diselenides by Wirth

chiral precursors **22** and **24**. *Ortho*-lithiation and addition of elemental selenium yields after oxidative work-up the corresponding diselenides in yields of 60 – 80 %. Because of this rapid and facile method, a large number of diselenides of type **26** (X = NR"$_2$, OR") have been synthesized.[11g,23]

2.2. Synthesis of Chiral Tricoordinate Selenium Compounds

Although chiral sulfoxides can be prepared easily by chemical or enzymatic oxidations, the synthesis of the corresponding chiral selenoxides which are the most important chiral tricoordinate organoselenium species was achieved only recently. Because of facile racemization, probably *via* hydrate formation, only selenoxides of type **27** bearing bulky substituents R and R' are sufficiently stable to be isolated.

Optically active selenoxides were prepared for the first time by resolution of diastereomeric selenoxides.[4] This methodology was subsequently applied to synthesize the first configurationally stable selenoxides.[24] Alkyl aryl selenides can be oxidized either under Sharpless oxidation conditions[25] or with optically active oxaziridines.[26] If one substituent of the selenide is chiral, the oxidation can lead preferentially to one diastereomer as shown in the oxidation of selenide **28** to the selenoxide **29**.[27]



Scheme 9. Chiral Selenoxides

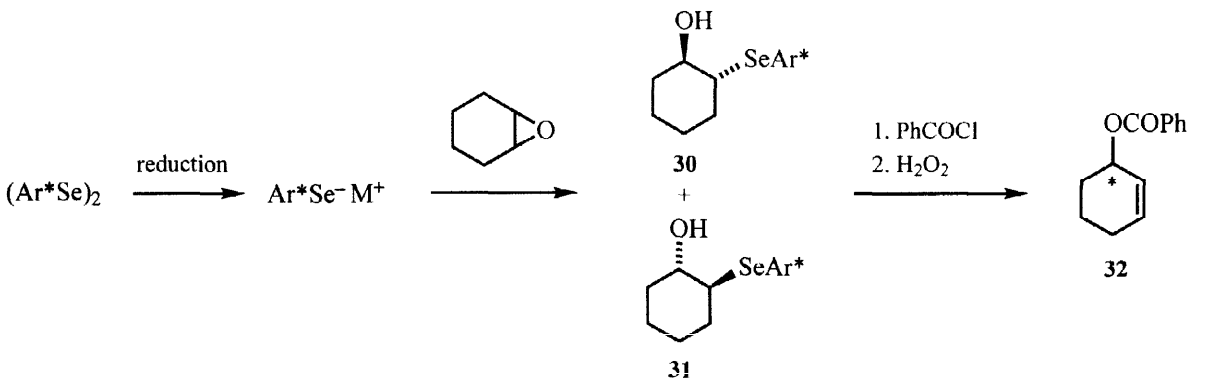
3. Chiral Selenium Compounds: Stoichiometric Applications

Although many of the chiral selenium compounds have to be prepared by multistep synthesis, they have, unril recently, been used mostly in stoichiometric reactions. Some derivatives, however, have been employed in catalytic versions of the stoichiometric reactions or as ligands in other catalyzed processes. Diselenides are versatile precursors for generating either nucleophilic species by reduction or electrophilic species by oxidation. They can even be employed to generate radical precursors, but usually selenides, rather than diselenides, are used for this purpose.

3.1. Nucleophilic Reagents

There are several methods known for the generation of aryl selenolate anions. They can be obtained directly from aryl metal compounds and elemental selenium. The reduction of aryl diselenides[28] or aryl selenocyanates[29] leads, however, to cleaner aryl selenolates which can be used for various reactions. These reagents are

soft nucleophiles and can be easily introduced into organic compounds. Aryl selenolate reagents derived from chiral diselenides have been used by different research groups in the stereoselective nucleophilic ring opening reaction of *meso*-epoxides. In these nucleophilic selenium species, since a heteroatom will not interact directly with the selenium, the chelation of the metal counterion of the reducing agent is most probably important. This might also explain the very strong dependency of the reduction conditions on the outcome of the reaction. Cyclohexene oxide was investigated by most of the research groups. It turned out that organoselenium nucleophiles with stereogenic axes are efficient in stereoselective epoxide opening reactions. In Table 1 the results from different research groups are summarized. Uemura and coworkers investigated not only the ferrocenyl diselenide **14** in this reaction, but also the corresponding sulfur and tellurium analogues. In general, they found the diastereoselectivity of the reaction increasing in the order S > Se > Te.[18d]



Scheme 10. Epoxide Ring Opening with Chiral Nucleophilic Selenium Reagents

Table 1
Stereoselective Nucleophilic Ring Opening of Cyclohexene Oxide

Diselenide	reducing agent, conditions	*de* (Configuration of **32**)	Yield (**30**+**31**)	reference
3a	$NaBH_4$, EtOH, 25 °C	50 % (*S*)	[a]	15c
14	$NaBH_4$, EtOH, 25 °C	2 % (*S*)	78	30
14	$LiAlH_4$, THF, 40 °C	69 % (*S*)	75	30
23	$NaBH_4$, EtOH, reflux	11 % [b]	87	31

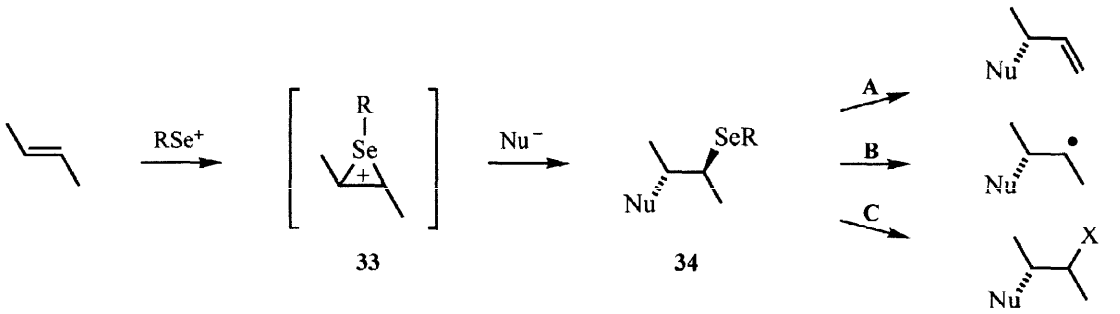
[a] not reported. [b] configuration not determined.

3.2. Electrophilic Reagents

The precursor molecules for the generation of electrophilic selenium species of the type R–SeX are again the corresponding diselenides. Reaction of C = C bonds with selenium electrophiles leads *via* the seleniranium ion intermediates **33** and subsequent *anti*-attack of nucleophiles to yield addition products **34**. This reaction has found widespread application in organic synthesis, because the addition products **34** are valuable building blocks as shown in Scheme 11.

After oxidation of the selenide to the selenoxide a β-elimination can take place. The removal of the selenium moiety makes it possible to introduce new C = C bonds into the products under very mild conditions

(path A). These double bonds are then functionalized in the allylic position. Radicals can be generated by a homolytic cleavage of the carbon – selenium bond in **34**. This opens the door for subsequent radical reactions (path B). The selenium moiety can also be replaced by other functional groups depending on the nature of the substituents (path C).

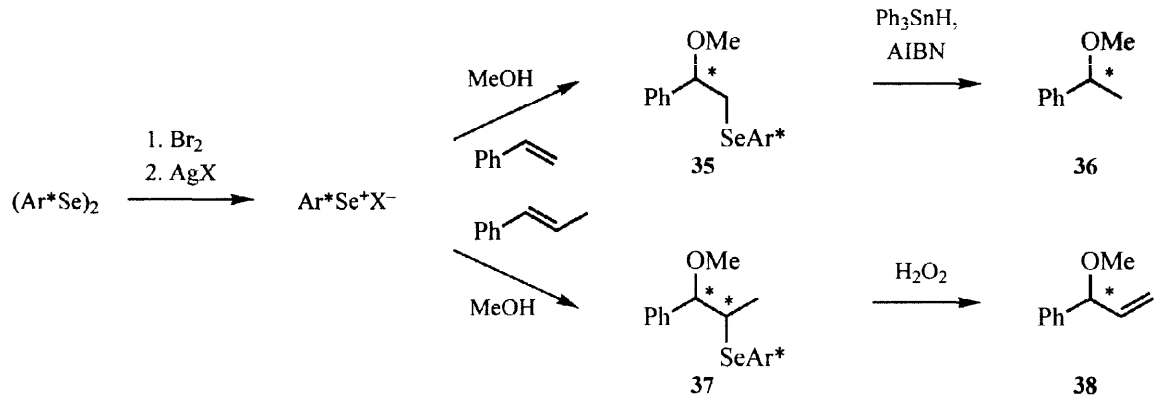


33 **34**

Scheme 11. Addition of Selenium Electrophiles to Double Bonds and Subsequent Reactions

Many efforts have been made to apply the selenenylation reaction in stereoselective synthesis. The compounds of type **34**, and the products of the subsequent reactions (path **A** – **C**) possess sp^3 carbon atoms which are generated in the selenenylation reaction from the alkene. For selective generation of these stereocenters, stereoselective selenenylation reactions have been developed. The use of chiral selenium electrophiles on the one hand or the reaction with optically active nucleophiles on the other hand provide two possibilities for such a stereoselective selenenylation reaction. The stereochemistry of the product **34** is determined by the initial face-selective addition of the selenium electrophile to the C = C double bond. The subsequent regioselective quenching of the highly reactive seleniranium ion **33** by a nucleophile is much less efficient in generating new stereogenic centers.[15e]

Chiral selenenamides were one of the first chiral selenium reagents and were used already in 1985 for stereoselective selenenylations of ketones.[32] The first stereoselective electrophilic selenenylations were carried out by the group of Tomoda who investigated several alkenes in the stereoselective methoxyselenenylation with selenium electrophiles generated from the corresponding diselenides.[15a] Thus, selenenyl bromides were formed by reaction with bromine and the nucleophilic bromide anion was then replaced by a less nucleophilic counterion (SbF_6^-, PF_6^-, BF_4^-, OTf^-) by reaction with the appropriate silver salt. This method then allows the addition of various nucleophiles like alcohols, carboxylic acids, nitrogen or carbon nucleophiles as described later. The stereoselective methoxyselenenylation using aromatic alkenes is shown in Scheme 12. Nearly all chiral diselenides have been employed in this reaction. Therefore, the results obtained by the different research groups can be compared and are summarized in Table 2. Many different alkenes can be used for this reaction. Because the selectivities obtained with styrene are not necessarily representative for the various diselenides, the addition reactions to (*E*)-1-phenylpropene are compared in Table 3. The absolute configuration of the newly generated stereocenters in **35** and **37** was determined in some cases either by analysis of the cleavage product **36** and/or of the elimination product **38**. As can be seen from Tables 2 and 3, some diselenides were found to be highly efficient with respect to selectivity and yield in the methoxyselenenylation of alkenes.



Scheme 12. Stereoselective Methoxyselenenylation of Styrene and (*E*)-1-Phenylpropene

Table 2
Stereoselective Methoxyselenenylation of Styrene

Diselenide	counterion	conditions	**35** *de*	**35** Yield	Configuration of **36**	Reference
3a	Br^-	MeOH, 25 °C	49 %	49 %	[a]	15a
9	TfO^-	Et_2O, –78 °C	77 %	88 %	(*S*)	17a
12	TfO^-	Et_2O, –78 °C	94 %	73 %	(*S*)	17d
14	TfO^-	CH_2Cl_2, –78 °C	35 %	97 %	[a]	18d
14	Br^-	CH_2Cl_2, 25 °C	97 %	21 %	(*S*)	33
17	PF_6^-	CH_2Cl_2, –78 °C	42 %	79 %	[a]	20d
19	SO_4^{2-}	CH_2Cl_2, MeOH, 25 °C	30 %[b]	91 %	(*R*)	34
19	TfO^-	CH_2Cl_2, –78 °C	47 %	77 %	(*R*)	35
23	TfO^-	Et_2O, 0 °C	10 %	64 %	[a]	23b
25	TfO^-	Et_2O, –100 °C	89 %	81 %	(*R*)	23b

[a] Configuration not determined. [b] With aliphatic alkenes usually higher selectivities are obtained.

Table 3
Stereoselective Methoxyselenenylation of (*E*)-1-Phenylpropene

Diselenide	counterion	conditions	**37** *de*	**37** Yield	Configuration of **38**	Reference
3a	Br^-	MeOH, 25 °C	24 %	49 %	[a]	15d
3c	Br^-	MeOH, 25 °C	79 %	87 %	(*R*)	15f
9	TfO^-	Et_2O, –78 °C	86 %	82 %	(*S*)	17a
12	TfO^-	Et_2O, –78 °C	98 %	81 %	(*S*)	17d
14	TfO^-	CH_2Cl_2, –78 °C	96 %	99 %	(*S*)	18d
17	Br^-	CH_2Cl_2, –78 °C	52 %	85 %	(*R*)	20d
17	PF_6^-	CH_2Cl_2, –78 °C	95 %	58 %	(*R*)	20d
25	TfO^-	Et_2O, –100 °C	80 %	45 %	(*R*)	11g

[a] configuration not determined.

3.2.1. Mechanistic Investigations

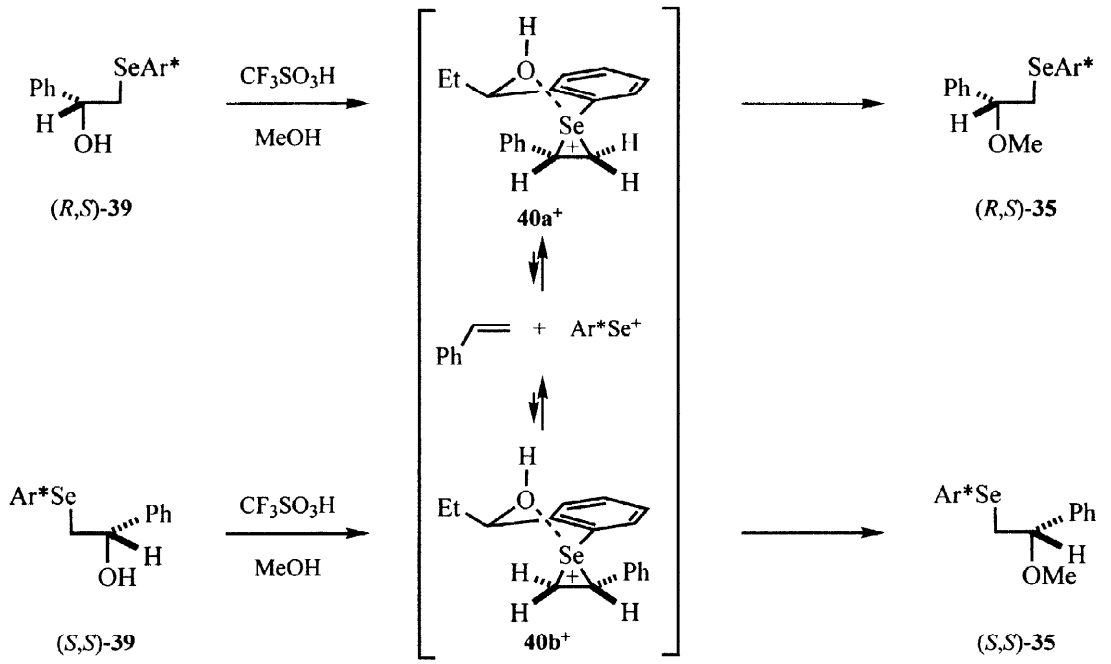
The face-selective formation of seleniranium ions is the crucial step in stereoselective selenenylation reactions. The exceptions are symmetrical *cis*-disubstituted alkenes like cyclohexene in which the attack of the nucleophile determines the stereochemistry in the product.

Most of the chiral selenium electrophiles investigated by different research groups as described above possess a heteroatom close to selenium, which is connected to a stereogenic center. This heteroatom is able to coordinate to the divalent selenium and it has been shown that this coordination leads to the formation of pseudo-high-valent selenium species in solution as well as in the solid state.[36] From these studies it is also known that the non-bonding selenium – heteroatom interaction is predominantly of the n–σ^*-type orbital interaction between the heteroatom and the selenium. It has also been shown that this interaction can clearly be recognized by the chemical shifts in the ^{77}Se NMR spectra of either the diselenides or the corresponding selenenyl electrophiles.[20d,23] The chemical shifts are dependent both on the heteroatom and on the substitution pattern.[37]

Because of the selenium – heteroatom interaction the environment around the selenium is chiral, with the result that face-selective addition reactions to alkenes becomes possible. Irrespective of the substituent pattern of the chiral side chain in the diselenides of type **26**, it was recognized that selenium electrophiles generated from these diselenides with (*S*)-configuration lead to a favored *re*-attack of styrene. In analyzing the process of chirality transfer, the formation of the seleniranium ions from the alkene and the selenium electrophile was found to be reversible under the reaction conditions.[38] This means that there is an equilibrium between the diastereomeric seleniranium ions and the position of equilibrium is dependent on the chiral moiety of the selenium electrophile and on the alkene. Because of the stereoselectivity observed in these reactions the diastereomeric seleniranium ions resulting from a *re*-attack and from a *si*-attack to the alkene must be formed in non equivalent amounts and must therefore have different stabilities.

For an examination of their relative stability, the seleniranium ions resulting from a *re*-attack and from a *si*-attack to styrene were synthesized independently using a reaction developed by Toshimitsu *et al.*[39] which involves protonation of β-hydroxy selenides and subsequent intramolecular S_N2 displacement by selenium. The use of enantiomerically pure β-hydroxy selenides **39** in this reaction should allow the independent generation of the desired seleniranium ions **40**. Subsequent reaction with methanol yields the β-methoxyselenides **35** which are identical to the methoxyselenenylated products of styrene (Scheme 12). The chiral β-hydroxyselenides **39** were available by reaction of the corresponding selenolate with styrene oxide having either the (*R*)- or (*S*)-configuration.

The seleniranium ions were generated by treatment of the β-hydroxy selenides **39** with trifluoromethanesulfonic acid at – 25 °C and subsequent reaction with methanol yielded the β-methoxyselenides **35**. Employing compound (*R*,*S*)-**39** in this reaction, the seleniranium ion **40a**$^+$ is formed selectively. Seleniranium ion **40a**$^+$ corresponds to the *re*-attack of the selenium electrophile to styrene which was assumed to be the most stable seleniranium ion and therefore formed in excess during the methoxyselenenylation reaction. Indeed, the reaction of **40a**$^+$ with methanol leads to optically pure β-methoxyselenide (*R*,*S*)-**35** without any loss of chiral information at the benzylic position.



Scheme 13. Independent Generation of the Diastereomeric Seleniranium Ions **40a**$^+$ and **40b**$^+$

The same reaction was then performed using (*S*,*S*)-**39**. The seleniranium ion **40b**$^+$ is generated first and can be regarded as the product of a *si*-attack to styrene with the selenium electrophile. This seleniranium ion is less stable than **40a**$^+$ which is confirmed by the results. Subsequent reaction with methanol lead to a 3:1 mixture of (*S*,*S*)-**35**:(*R*,*S*)-**35**. The addition product (*S*,*S*)-**35** with (*S*)-configuration at the benzylic position is obtained as the major diastereomer, but decreased optical purity at the benzylic position is observed.

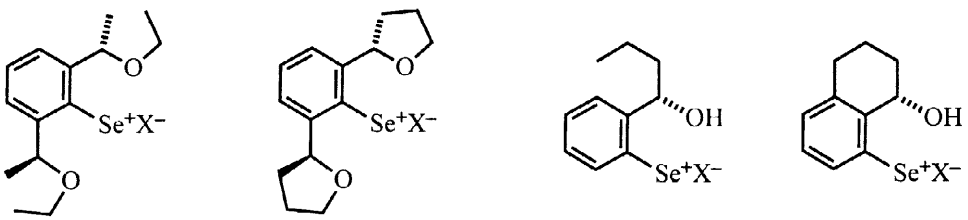
This result is rationalized by partial conversion of the less stable seleniranium ion **40b**$^+$ into the more stable seleniranium ion **40a**$^+$ before reaction with methanol by a decomplexation – complexation mechanism as outlined in Scheme 13. Because this reaction is performed in methanol, the addition reaction is competing and the major product is still the diastereomer (*S*,*S*)-**35**. The intermediate formation of styrene implied to this mechanism could not however be demonstrated. Performing the reaction starting with (*S*,*S*)-**39** in the presence of (*E*)-1-phenylpropene led to the formation of substantial amounts of **37** besides the product **35** which is an indirect proof of the decomplexation – complexation mechanism described above.[38] The structures of the diastereomeric seleniranium ions **40a**$^+$ and **40b**$^+$ have been calculated and support the stereochemical outcome of the asymmetric methoxyselenenylation reaction.

3.2.2. Optimization of Chiral Selenium Electrophiles

In all research groups investigating chiral selenium electrophiles considerable efforts have been made to optimize stereoselective selenenylation reactions. Because of the structurally different diselenides employed in these reactions the optimization of the reaction conditions cannot be generalized and even the structural variations of the chiral selenium reagents have been carried out more or less on a random basis. Hopefully, the

above mentioned recent investigations on the mechanism of the selenenylation reaction of alkenes and on the intermediate seleniranium ions can now lead to a rational design of more efficient reagents.

It has already been recognized that selenium electrophiles with reduced conformational flexibility in the chiral moiety are more efficient for stereoselective selenenylation. Comparison of the selenium electrophiles **41** with **42** and **43** with **44** in selenenylation reaction shows that with the electrophiles **42** and **44** higher selectivities can be obtained.[17,23b] The diastereoselectivities with the electrophiles **41** – **44** in the methoxyselenenylation of styrene are reported in Scheme 14.



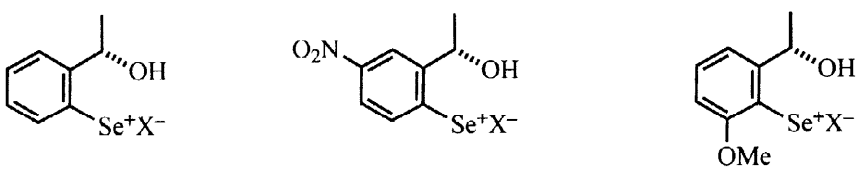
41 **42** **43** **44**

Selectivities in the methoxyselenenylation of styrene (X = OTf):

1:8 1:30 1:14 1:28

Scheme 14. Selenium Electrophiles **42** and **44** with Reduced Conformational Flexibility

Variation of the electronic properties of selenium cations **45** was also successful. Thus, the electrophiles **46**[40] and **47**,[41] synthesized from the corresponding diselenides and with a nitro-group in position 4 or a methoxy-group in position 6, respectively are again more efficient than the unsubstituted selenium electrophile **45** in the methoxyselenenylation of styrene as shown in Scheme 15.



45 **46** **47**

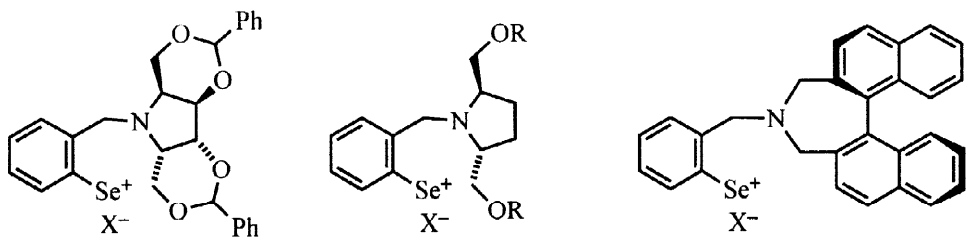
Selectivities in the methoxyselenenylation of styrene (X = OTf):

1:11 1:13 1:50

Scheme 15. Substituted Selenium Electrophiles

In particular, the methoxy-substituted electrophile **47** also showed high selectivities in various cyclization reactions. The oxygen of the methoxy-group now seems to interact with the selenium, while the oxygen of the chiral side chain is not interacting with the selenium. This had been shown by X-ray analysis of the corresponding diselenide as well as by NOE of the diselenide in solution.[41]

The chiral selenium electrophile **48**, generated from diselenide **17**, was simplified by attaching other chiral nitrogen-containing moieties. However, the electrophilic reagents of types **49** and **50** are less efficient in stereoselective selenenylation reactions as shown in Scheme 16.[20d]



48 **49** **50**

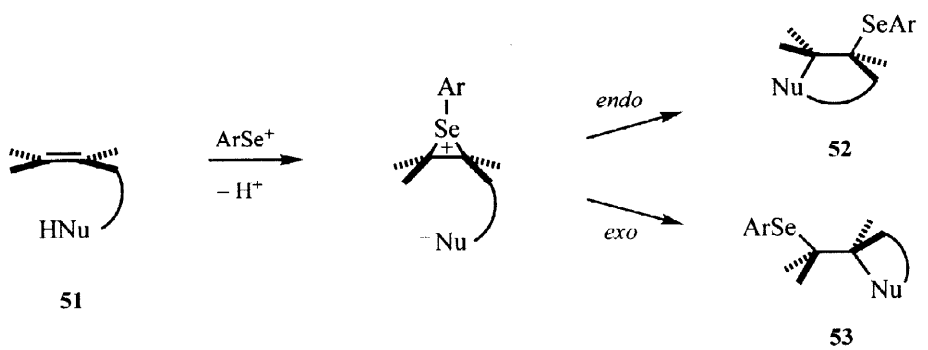
Selectivities in the methoxyselenenylation of (*E*)-1-phenylpropene (X = PF_6):

1:64 1:1.3 (R = Bn, Me) 1:2

Scheme 16. Diselenides having Various Tertiary Amino Groups

3.2.3. Stereoselective Cyclization Reactions

The term "cyclofunctionalization" was introduced for reactions where the addition of an electrophile to an alkene containing an internal nucleophile leads to a cyclization reaction.[42] Halolactonizations are well known reactions of this type. The use of organoselenium reagents for cyclization reactions was already described 20 years ago.[43] Subsequently, selenocyclizations have been widely used for the synthesis of various heterocyclic compounds.[10d,44] Only recently it was found that stereoselective ring closure reactions of alkenes **51** bearing various nucleophiles can be performed efficiently with chiral selenium electrophiles. Nearly every research group investigating chiral selenium electrophiles reported the use of these reagents in asymmetric ring closure reactions. Stereoselective selenocyclization reactions can be used to synthesize chiral heterocycles such as cyclic ethers, cyclic amines, lactones and lactams. Depending on the ring size and on the substitution pattern, the addition can occur either by an *endo* or an *exo* pathway leading to the products **52** or **53**, respectively (Scheme 17). Comparison of the various results seems to show that the nature of the nucleophile as well as the ring size has only little influence on the facial selectivity observed.

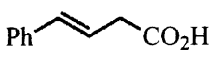
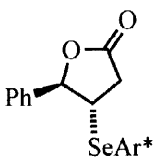
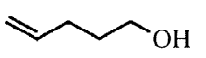
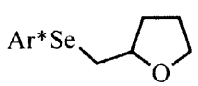


Scheme 17. Intramolecular Selenenylation Reactions

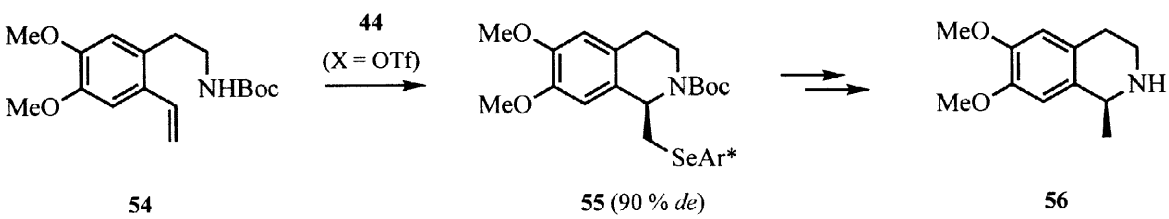
It was found by several research groups, that at least a small amount of an alcohol or an amine must be present to achieve high yields and selectivities in the selenocyclization reactions.[17b,18b,23a,45] The reason for this is not clear and currently under investigation. One hypothesis is that the additional alcohol or amine is necessary to stabilize the selenium electrophile and/or the seleniranium ion. It has been recognized earlier that alcohols as external nucleophiles cannot compete with the internal nucleophiles of the functionalized alkenes.[46]

Many cyclizations have been performed. Depending on the alkene 5-*endo*, 5-*exo*, 6-*endo* as well as 6-*exo* cyclizations can be achieved. In some cyclization products the absolute stereochemistry was assigned which then allows the distinction between a *re*-attack and a *si*-attack of the chiral selenium electrophile to the double bond. A 5-*endo* and a 5-*exo* cyclization are shown in Table 4. The diselenides, which have been the precursors for the chiral selenium electrophiles in these reactions, are additionally shown in Table 4.

Table 4
Stereoselective Selenocyclization Reactions

Alkene	Product	Diselenide $(Ar^*Se)_2$	*de* (Product)	Yield (Product)	Reference
		**9**	86 %	72 %	17b
		12	>98 %	62 %	17d
		17	92 %	87 %	20b
		25	72 %	41 %	45
		**9**	33 %	96 %	17b
		12	82 %	84 %	17d
		14	76 %	29 %	18b
		14	>95 %	97 %	47
		17	22 %	100 %	20b
		21	68 %	87 %	22c

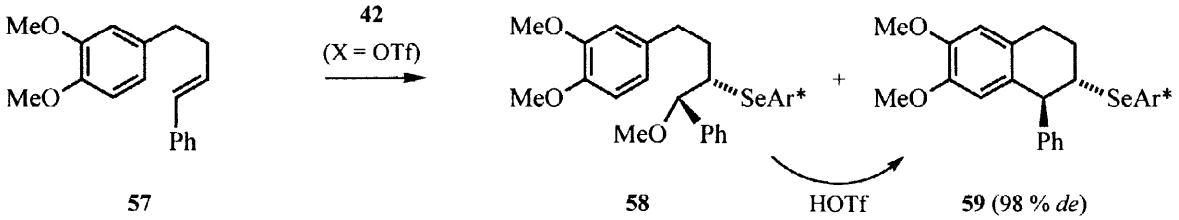
Nitrogen nucleophiles can be employed as well in these cyclization reactions. Because the products of intramolecular aminoselenenylation are nitrogen containing heterocycles, they are interesting building blocks for alkaloid synthesis. The selenium functionality is still present in the addition products and can be used for further transformations. Wirth *et al.* applied this reaction to the synthesis of tetrahydroisoquinoline alkaloids as shown in Scheme 18. Cyclization of the Boc-protected amine **54** yielded the tetrahydroisoquinoline derivative **55** with 90 % *de*, which was transformed into (–)-salsolidine **56** by radical cleavage of the selenium moiety and deprotection of the nitrogen.[48]



54 **55** (90 % *de*) **56**

Scheme 18. Aminoselenenylation in Natural Product Synthesis

Carbon-based nucleophiles can be used for selenium-mediated electrophilic additions to alkenes.[10a,49] Very recently Déziel *et al.* have shown that asymmetric variants of these reactions lead to stereoselective C – C bond formation. Also for the cyclization of the alkene **57** the addition of methanol is necessary leading to a 1:1 mixture of methoxyselenenylated product **58** beside the cyclization product **59**. The methoxyselenenylated product **58** can then be transformed into the cyclization product **59** *via* the intermediate seleniranium ion by treatment with trifluoromethanesulfonic acid. The tetrahydronaphthalene derivative **59** is then obtained in 70 % yield with 98 % diastereomeric excess.[50]



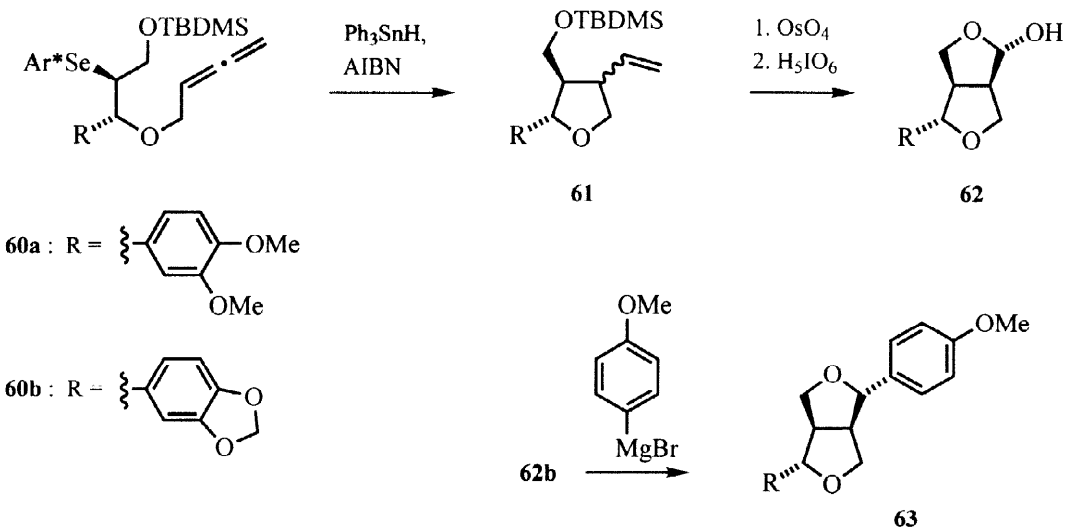
57 **58** **59** (98 % *de*)

Scheme 19. Stereoselective Arene-Alkene Cyclizations

3.2.4. Natural Product Synthesis

In stereoselective selenenylation reactions the wide range of different alkenes and nucleophiles such as alcohols or carboxylic acids which can be used confers great flexibility on this methodology. This is further enhanced through the use of nucleophiles bearing other functionalities which can be employed in the addition reactions. Thus, even alcohols bearing double or triple bonds can be added using slightly modified reaction conditions. These addition products can then be cyclized by an intramolecular radical cyclization to afford substituted cyclic ethers. This strategy of oxyselenenylation and subsequent radical cyclization was applied by Wirth *et al.* to the synthesis of furofuran lignans.

Selenenylations of TBDMS-protected allylic alcohols using 2,3-butadien-1-ol as nucleophile yield addition products **60** in about 55 % yield with diastereomeric ratios of about 15:1. The radical cyclization of the major diastereomers *via* the favored 5-*exo*-pathway then leads to the tetrahydrofuran derivatives **61**. The stereochemistry of the carbon atom bearing the aromatic substituent (C-2) is controlling the stereochemistry at the neighboring carbon atom C-3. This is explained by a transition state in which the aromatic and the bulky silyloxymethyl substituents are arranged in pseudo-equatorial positions. At C-4 a 1:1 mixture of stereoisomers was observed, because the reaction proceeds *via* a boatlike and a chairlike transition state which are similar in energy.[51] After transformation of the vinylic double bond to the aldehyde by diol formation and oxidative cleavage epimerization occurred under the conditions of deprotection and the hemiacetals **45** were formed spontaneously. Compound **62a** already represents a natural product, (+)-samin, a component of sesame oil.[52] The furofuran moiety of **62** is a precursor for several other lignans. By treatment of **62b** with 4-methoxyphenylmagnesium bromide addition and dehydration occurred completing the first total synthesis of (+)-membrin **63**.[53]



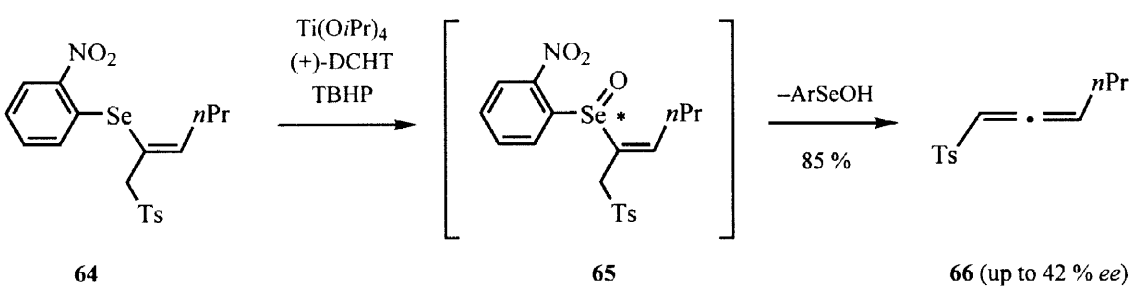
Scheme 20. Total Synthesis of Samin and Membrin

3.3. Selenides in Stereoselective Reactions

As outlined in Scheme 11, the addition products **34** can be oxidized to selenoxides and the subsequent *syn*-elimination then introduces a double bond again (path **A**). There are different possibilities to synthesize optically active selenoxides as pointed out in section 2.2. These compounds are accessible by either using chiral oxidizing agents or by employing selenides with chiral substituents in the oxidation reactions. Both routes have been investigated and, depending on the selenides, different subsequent reactions are possible. Optically active selenonium salts[54] and selenonium ylides[55] have been prepared, but thus far, have not proved to be efficient reagents in stereoselective synthesis.

3.3.1. Stereoselective Selenoxide Eliminations

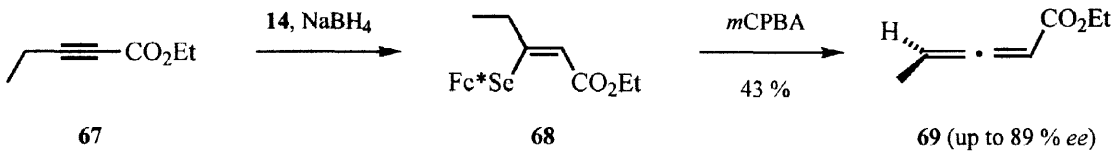
If substituted vinylic selenides are used for the preparation of selenoxides, it is possible to generate allenes by the β-elimination reaction. This reaction can also be performed in a stereoselective way to generate optically active allenes. There are various strategies to access vinylic selenides.[56] Compounds like **64** can be oxidized stereoselectively either by the method of Sharpless[25] or by the Davis chiral oxidant.[26] The subsequent elimination *via* **65** generates the chiral allenic sulfone **66** in moderate enantiomeric excess (Scheme 21).[57]



64 **65** **66** (up to 42 % *ee*)

Scheme 21. Stereoselective Selenoxide Eliminations with Sharpless Oxidation

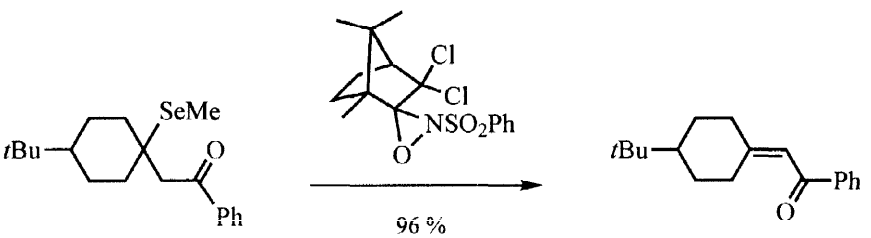
Chiral ferrocenyl substituted vinylic selenides **68** can be synthesized easily from the corresponding selenolates and the alkyne **67**. If these compounds are used in the oxidation-elimination sequence, the axially chiral allenes **69** are obtained in enantioselectivities up to 89 % as shown in Scheme 22.[18a,c]



67 **68** **69** (up to 89 % *ee*)

Scheme 22. Stereoselective Selenoxide Eliminations with Chiral Selenides

High selectivities are also obtained in the synthesis of cyclohexylidenemethyl ketones of type **70** which can be synthesized by selenoxide elimination from the appropriate precursors in up to 83 % *ee* as shown in Scheme 23.[58]



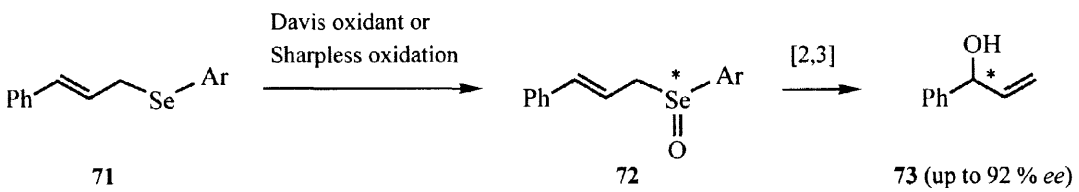
70 (up to 83 % *ee*)

Scheme 23. Stereoselective Selenoxide Eliminations with Davis Oxidant

3.3.2. Stereoselective [2,3] Sigmatropic Rearrangements

In contrast to sulfoxides,[59] the [2,3] sigmatropic rearrangement of selenoxides proceeds under very mild conditions[16,60] and is a very versatile route to allylic alcohols. Either enantiomeric or diastereomeric selenoxides can be employed in the stereoselective synthesis of allylic alcohols.

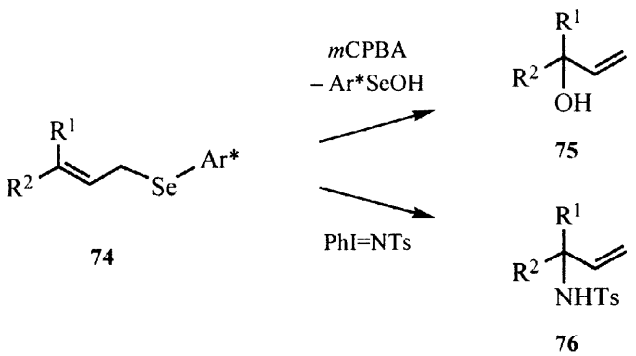
One of the first applications of this reaction was the stereoselective oxidation of the allylic selenide **71** by the Davis oxidant. The selenoxide **72** is formed and after the subsequent [2,3] sigmatropic rearrangement and hydrolysis the allylic alcohol **73** can be obtained in up to 60 % *ee*.[61] Alternatively, the Sharpless oxidation can be used for the stereoselective oxidation of compounds of type **71** and the allylic alcohol **73** can be obtained in up to 92 % *ee* (Scheme 24).[62]



71 **72** **73** (up to 92 % *ee*)

Scheme 24. Stereoselective Oxidation and Rearrangement of Allylic Selenides

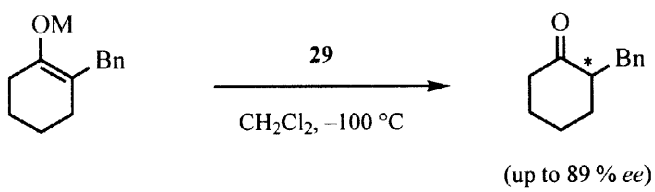
Allylic selenides with a chiral substituent Ar* on the selenium atom have also been employed in the synthesis of diastereomeric selenoxides and used for [2,3] sigmatropic rearrangements. Selenides of type **74** derived from the chiral diselenides **6**[16] and **14**[18c] have been investigated. The rearranged products **75** can be obtained in up to 89 % *ee* (R^1 = H, R^2 = Ph, Ar* = Fc*). Recently Uemura *et al.* found that the diastereoselective imination of chiral allylic selenides is possible too. The [2,3] sigmatropic rearrangement occurs without loss of optical purity and the chiral allylic amines **76** can be obtained in up to 87 % *ee* (Scheme 25).[63] Very recently, a catalytic version of the stereoselective imidation was reported.[64] The same strategy was used by Koizumi *et al.* using camphor-based allylic selenium compounds. The allylic amines **76** were obtained in up to 93 % *ee*.[65]



Scheme 25. Oxidation and Imination of Chiral Allylic Selenides

3.3.3. Enantioselective Protonation of Enolates

For the enantioselective protonation of enolates Koizumi *et al.* used the chiral γ-hydroxyselenoxide **29**. The lithium or zinc enolates are generated and subsequent reaction with **29** yielded optically active 2-benzylcyclohexanone with enantioselectivities up to 89 % (Scheme 26).[66]



Scheme 26. Enantioselective Protonation with Chiral Selenoxides.

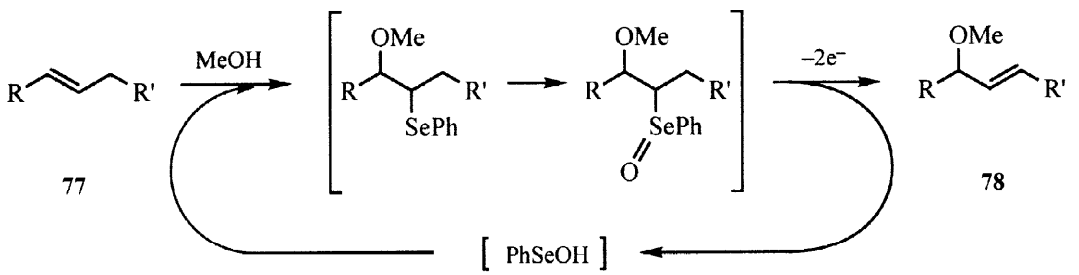
4. Chiral Selenium Compounds: Catalytic Applications

Two different fields can be recognized in terms of the catalytic applications of chiral selenium reagents. As shown in Scheme 11, selenenylations can be followed by other transformations cleaving the selenium moiety from the addition product. If the liberated selenium compound can be used again for an addition reaction, an overall reaction with only catalytic amounts of the selenium species is possible. The second field can be

characterized as metal-catalyzed transformations, in which the selenium derivatives act as chiral ligands. Different stereoselective reactions have been described recently.

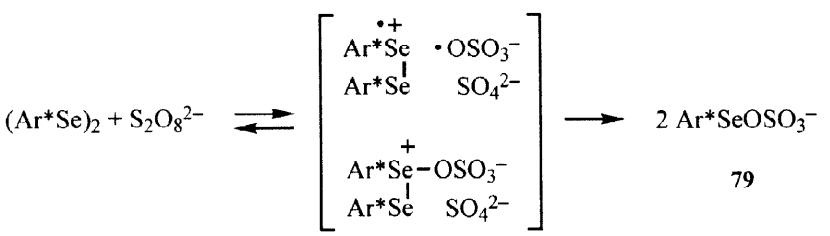
4.1. Catalytic Selenenylation - Deselenenylation Reactions

The oxidative elimination of selenoxides derived from selenenylation products proceeds under milder conditions and with higher selectivity than the reactions of the corresponding sulfoxides. The prerequisite for the development of such catalytic selenenylation - deselenenylation processes is the generation of the reactive selenenylating agent under reaction condition which also allows for the subsequent oxidation to the selenoxide and its elimination reaction. For the first time Torii *et al.* have achieved a catalytic oxyselenenylation - deselenenylation process by electrochemical methods.[67] The electrophilic selenium species is generated from diphenyl diselenide by electrochemical oxidation in the presence of an alkene **77** in methanol. The subsequent oxidation and elimination is again driven by electrochemical oxidation yielding the allylic ether **78** as shown in Scheme 27. Recently Torii *et al.* reported also the electrochemical generation of a nucleophilic selenenyl species which was used in the epoxide opening reaction.[68]



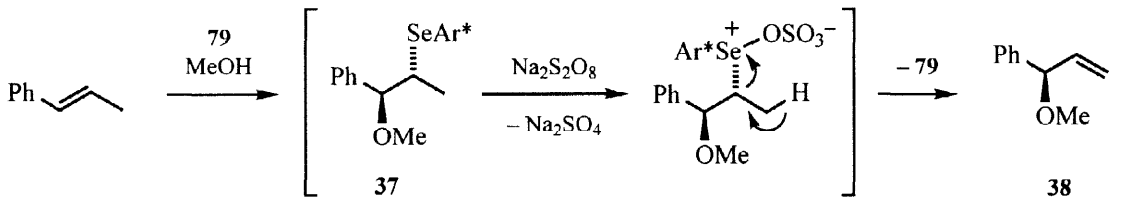
Scheme 27. Electrochemical Oxyselenenylation - Deselenenylation Reactions

Tiecco *et al.* demonstrated the possibility of generating electrophilic selenenyl sulfates by reaction of diselenides with peroxodisulfates as shown in Scheme 28.[69] Additionally, they showed the possibility of performing a one-pot process of selenenylation and elimination using a catalytic amount of diphenyl diselenide.[70] Furthermore, it is possible to use diselenides with nitrogen containing substituents in the catalytic conversion of alkenes to allylic ethers.[11e,g,71] Very recently chiral diselenides have been investigated in catalytic oxyselenenylation – elimination sequences leading to optically active allylic ethers.[18d,20a,72] These reactions are shown in Scheme 29. The electrophilic selenenyl sulfates **79** are formed by reaction of the corresponding



Scheme 28. Synthesis of Selenenyl Sulfates

diselenides with peroxodisulfates. Subsequent oxyselenenylation of (*E*)-1-phenylpropene yields the methoxyselenenylated product **37** which is oxidized by excess peroxodisulfate and then gives the elimination product **38**.

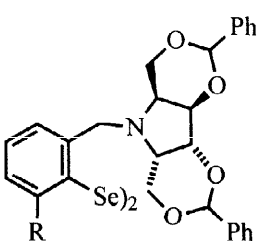


Scheme 29. Stereoselective Oxyselenenylation - Elimination Reactions

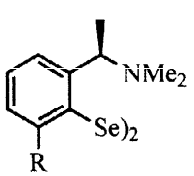
Different chiral diselenides have been employed in this reaction and stereoselectivities up to 75 % *ee* have been obtained as shown in Table 5. It was recognized by Tomoda *et al.* that a second substituent at the other *ortho*-position to selenium blocks this side and the attack of the alkene is less selective.[20a] However, Wirth *et al.* have found that a substituent at this position enhances the selectivities of oxyselenenylation reactions. The diselenides investigated in this reaction are shown in Scheme 30. Metal ions[73] as well as nitrates[74] are known to accelerate the decomposition of peroxodisulfates and the reaction conditions for performing the catalytic oxyselenenylation - elimination reactions have been investigated carefully.

Table 5
Stereoselective Oxyselenenylation - Elimination Reactions of (*E*)-1-Phenylpropene

Diselenide $(Ar^*Se)_2$	*ee*	**38** Yield	Reference
17	52 %	85 %	20a
17a	22 %	59 %	20a
23	56 %	35 %	72
23a	75 %	23 %	72



17: R = H
17a: R = OMe

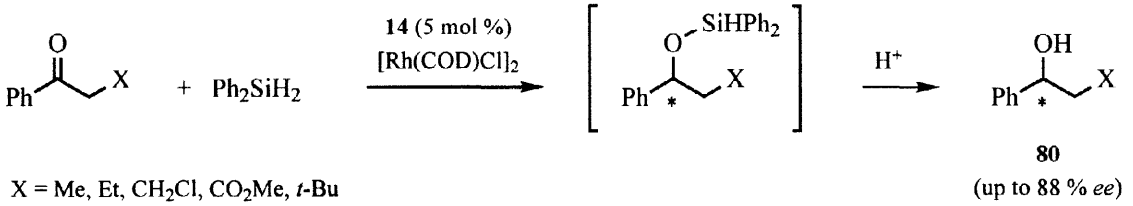


23: R = H
23a: R = OMe

Scheme 30. Chiral Diselenides with Substituents in the Second *ortho*-Position

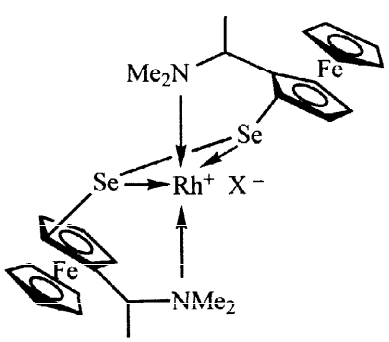
4.2. Chiral Selenium-Containing Ligands in Catalysis

The first application of chiral diselenides as ligands for transition metal-catalyzed stereoselective reactions was described by Uemura *et al.* The ferrocenyl diselenide **14** was used in the rhodium(I)-catalyzed asymmetric hydrosilylation of various ketones.[75] The reaction conditions as well as the rhodium source and the hydrosilylating reagent were all screened carefully leading to enantioselectivities of up to 88 % in the chiral alcohol products **80** (Scheme 31).



Scheme 31. Stereoselective Hydrosilylation using **14** as a Chiral Ligand

It is assumed and supported by various data, that a 1:1 complex between rhodium and **14** is formed with the ferrocenyl diselenide **14** acting as a tetradentate ligand which occupies four of the six octahedral positions as shown in **81** (Scheme 32). It was found that the corresponding ferrocenyl disulfides and the ferrocenyl ditellurides are much less efficient ligands in this catalytic hydrosilylation reaction.[76]



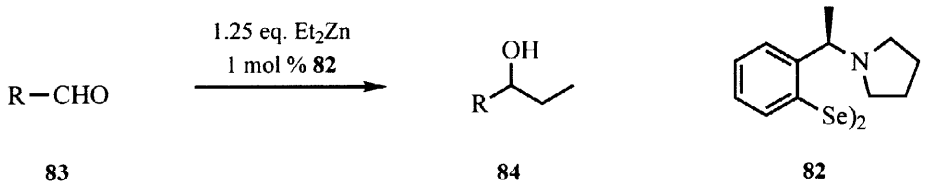
81

Scheme 32. 1:1 Complex between Rhodium and Ferrocenyl Diselenide **14**

The same ferrocenyl diselenide **14** has been investigated in rhodium(I)- as well as in iridium(I)- and ruthenium(II)-catalyzed asymmetric transfer hydrogenation reactions of ketones.[77] However, the stereoselectivities are generally lower (up to 48 % *ee*), only one example with a sterically hindered ketone being described (95 % *ee*).

The nitrogen-containing diselenides of type **23** can be used as very efficient procatalysts for the addition of organozinc reagents to aldehydes.[78] Diselenide **82** was the most efficient diselenide in the diethylzinc

addition to a variety of aldehydes **83**. Only 1 mol % of **82** is necessary in the catalytic additions yielding the secondary alcohols **84** in high enantiomeric purities as shown in Scheme 33 and in Table 6.



83 **84** **82**

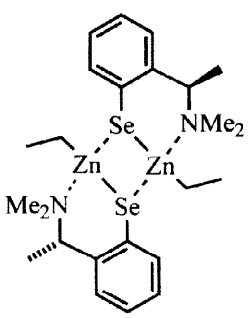
Scheme 33. Diethylzinc Addition to Aldehydes Catalyzed by the Chiral Diselenide **82**

Table 6
Addition of Diethylzinc to Aldehydes **83** Catalyzed by the Chiral Diselenide **82**

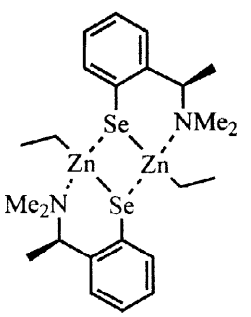
Entry	Aldehyde **83**	*ee* (Configuration)	**84** Yield
1	benzaldehyde	98 % (*S*)	97 %
2	3-(trifluoromethyl)benzaldehyde	97 %[a]	98 %
3	4-(*tert*-butyl)benzaldehyde	98 %[a]	67 %
4	2,3,4,5-tetrafluorobenzaldehyde	97 %[a]	95 %
5	2-bromocyclopent-1-ene-1-carbaldehyde	98 %[a]	97 %
6[b]	pentanal	76 % (*R*)	91 %

[a] Absolute configuration not determined. [b] 1 mol % (*S*, *S*)-**23** used as catalyst.

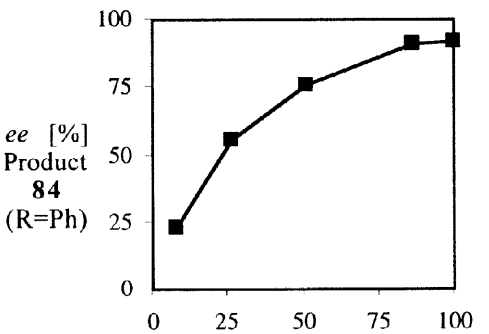
A more detailed investigation of this reaction revealed that the diselenides act as procatalysts in the addition reactions. After addition of diethylzinc, the selenium – selenium bond is cleaved rapidly and catalytically active zinc selenolates are formed. NMR analysis revealed an aggregation of the selenolates which are in dynamic exchange with other species. By analogy with the work of Noyori *et al.*[79] these compounds were assigned as the catalytically inactive *meso* dimeric species **85** and the chiral dimeric species **86** which are in equilibrium with the catalytically active monomers.



85



86



A positive nonlinear relationship (asymmetric amplification) between the optical purities of the catalyst and the product was observed, which support the findings mentioned above. With respect to the diethylzinc

addition to aldehydes, it was found that spectroscopic, chemical, and stereochemical properties are in accordance with the well investigated properties of amino alcohols.[80]

5. Conclusions

Starting in the early seventies, organoselenium reagents have been used for various selective reactions under mild conditions. It is only recently however that the application of chiral selenium-containing reagents in synthesis has been developed. The synthesis of suitable chiral diselenide precursors as summarized in this report has led to several applications. Besides detailed investigations of the mechanism of the stereoselective oxyselenenylation reaction the total syntheses of several natural products has also been achieved. Even catalytic reactions have been developed using the chiral diselenides as ligands in metal-catalyzed transformations. Improved and new chiral selenium based reagents will surely be developed in the future and may lead to enhanced stereoselectivities in known reactions as well as in new stereoselective transformations.

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Biographical sketch

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Thomas Wirth, born 1964 in Leverkusen (Germany), studied chemistry at the University of Bonn (Germany) and stayed there to carry out his diploma work under the guidance of Prof. Siegfried Blechert. Then he moved along with his supervisor to the Technical University of Berlin (Germany), where he received his Ph. D. degree in 1992. For postdoctoral studies he then joined the group of Prof. Kaoru Fuji at Kyoto University (Japan) as a JSPS fellow. At the beginning of 1994 he started his independent research at the University of Basel (Switzerland). His research interests are the development of methods and reagents for stereoselective oxidative functionalizations as well as their use in synthesis.