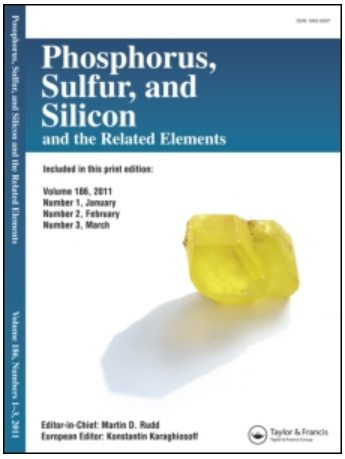

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Asymmetric Syntheses Promoted by Organoselenium Reagents

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Asymmetric Syntheses Promoted by Organoselenium Reagents

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Using chiral nonracemic electrophilic-organoselenium-reagents-asymmetric alkoxy-, hydroxy-, azido- and amido-selenenylation of alkenes were effected with high diastereoselectivity. These reagents have also been employed in catalytic amounts to promote one-pot selenenylation-deselenenylation processes. The asymmetric cyclization of properly substituted alkenes diastereoselectively afforded lactons, tetrahydrofurans oxazolines, thiazolines, pyrrolidines, isoxazolidines, 1,2-oxazines, and cyclic nitrones. Enantiopure dioxane, morpholine, tetrahydrofuran, oxazolidin-2-one and aziridine derivatives were prepared from alkenes, PhSeX, and optically active nucleophiles or substrates.

Keywords Asymmetric syntheses; catalysis; enantiopure organoselenium reagents

INTRODUCTION

Electrophilic organoselenium reagents are largely used in organic synthesis to introduce new functional groups into olefins under mild experimental conditions. These reactions are stereospecific *anti* additions which involve seleniranium ions as reactive intermediates (Scheme 1).[1]

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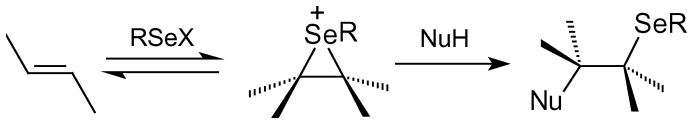
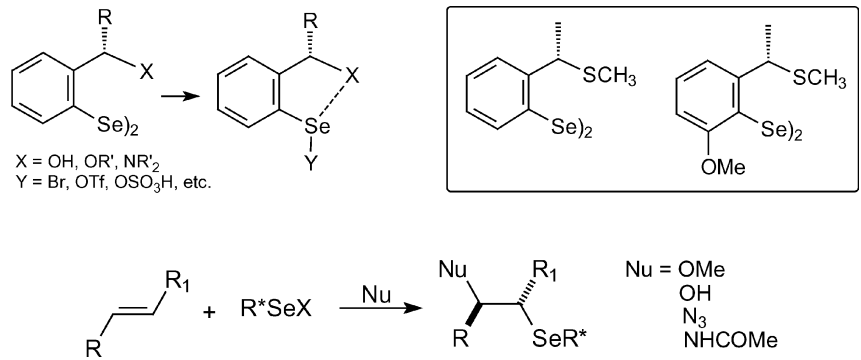


SCHEME 1

Several research groups have described the synthesis of a number of chiral nonracemic diselenides which can be transformed *in situ* into electrophilic selenenylating reagents. Addition of these reagents to alkenes affords two diastereoisomeric seleniranium intermediates which are trapped by external or internal nucleophiles to give two enantiomerically pure diastereoisomeric addition or cyclization products. These reactions proceed with good to excellent diastereoselectivities.[1–3]

On the basis of several experimental evidences it has been proposed[3–5] that the great stereoselectivity observed with these reagents is due to an orbital interaction between the lone pair of a closely positioned oxygen or nitrogen heteroatom and the low-lying antibonding orbital of the SeY ($n_x - \sigma^*$ SeY). Such an interaction will force the chiral center to come close to the reaction center during the addition reaction thus improving the transfer of chirality. In the attempt of making this interaction more efficient and to increase the diastereoselectivity of the asymmetric addition reactions, we have recently introduced the two novel diselenides[6,7] indicated in Scheme 2, which contain a sulfur instead of an oxygen or a nitrogen heteroatom.



SCHEME 2

Starting from these two diselenides several asymmetric addition reactions were effected. The products of alkoxy-selenenylation,[6,7] hydroxy-selenenylation[7] and azido-selenenylation[8] of alkenes were

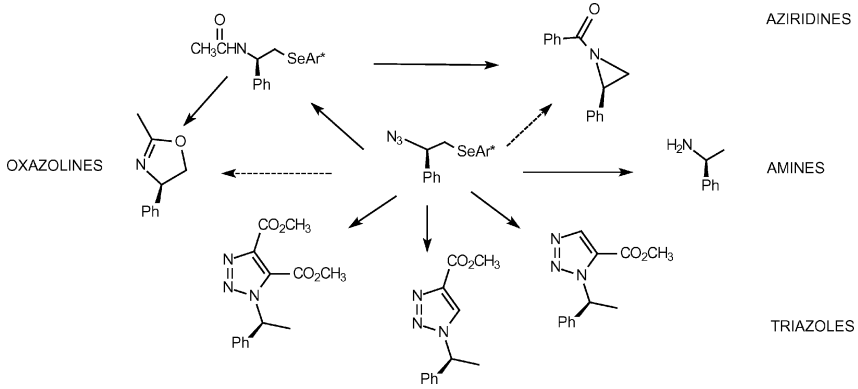
TABLE I Alkoxy, Hydroxy—, and Azido—Nelenyleton of Some Alkenes

	Selenomethoxylation		Selenohydroxylation		Selenoazidation	
Alkenes	Yield (%)	*d.r.*	Yield (%)	*d.r.*	Yield (%)	*d.r.*
Styrene	72	98:2	65	98:2	90	97:3
β−Methylstyrene	75	98:2	70	98:2	70	98:2
α−Methylstyrene	58	95:5	73	98:2	60	99:1
Trimethylstyrene	60	99:1	75	99:1		
E-5-Decene	70	96:4	79	96:4	95	95:5
Methylcyclohexene	60	98:2			70	95:5

all obtained with high diastereoselectivity. Reactions of amido-selenenylation were also carried out. In this case, however, the selenenylating agent was produced from the camphor diselenide introduced by Back.[9] All these additional products can be converted into other enantiomerically enriched derivatives.

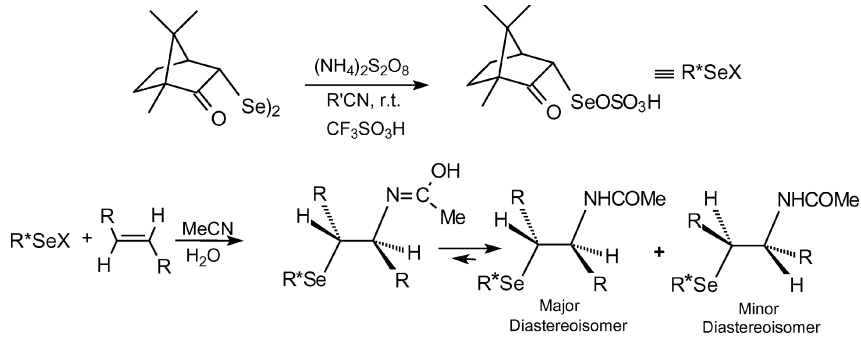
Some selected results of the alkoxy-selenenylation, hydroxy-selenenylation, and azido-selenenylation of alkenes, using the reagents derived from the diselenides reported above, are collected in Table I.

It can be seen that the reactions proceed with good yields and with excellent diastereoselectivities. The Scheme 3 illustrates some of the possible synthetic uses of the enantiomerically enriched azido selenides. Using simple conversions oxazolines, aziridines, amines, and triazoles were obtained in good chemical yields.



SCHEME 3

The amido-selenenylation of alkenes carried out with the two above reported diselenides did not give satisfactory results and therefore the reaction was effected, as anticipated, using the camphor diselenide.[10]

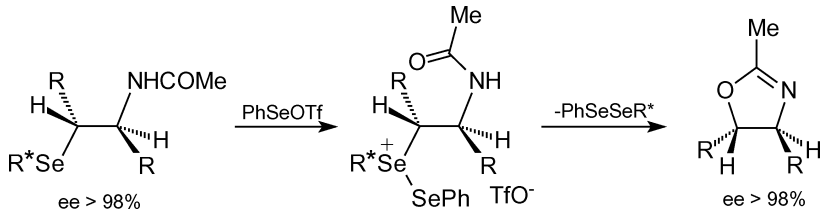


SCHEME 4

This was converted into the corresponding selenenyl sulfate by treatment with ammonium persulfate (Scheme 4). The addition occurred with poor facial selectivity and afforded a mixture of two diastereomeric reaction products. The results obtained were as follows (yields and *d.r.* are reported in parentheses): *E*-3-hexene (82%, 73:27), *E*-4-octene (78%, 75:25), *E*-5-decene (80%, 80:20), styrene (50%, 53:47), cyclohexene (61%, 65:45), and ciclooctene (86%, 60:40). However, the two enantiopure diastereomeric addition products could be easily separated by column chromatography and could be converted into allyl amides, alkyl amides, or β-substituted alkyl amides by removing the selenium containing group by oxidation, reduction or substitution, respectively.

Moreover, all the acetamido selenides thus obtained were converted into enantiopure *trans* 4,5-disubstituted oxazolines (Scheme 5). The selenium group was transformed into a good leaving group by treatment with PhSeOTf. The resulting selenonium salt gave rise to a stereospecific intramolecular substitution by the oxygen atom affording the oxazoline derivatives.

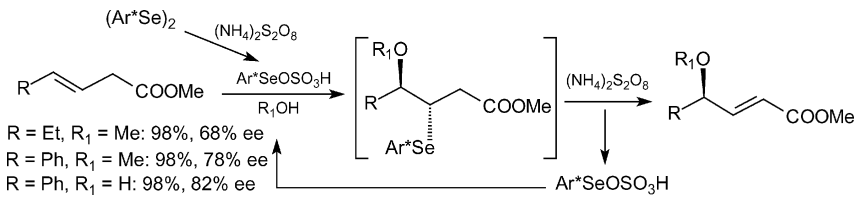
The *trans* 4,5-disubstituted oxazolines were also converted into the corresponding *cis* isomers by treatment with dilute HCl and then with thionyl chloride.[11] All these oxazolines, by hydrolysis, gave the enantiopure β-aminoalcohols.



SCHEME 5

Optically pure thiazolines were prepared in a similar way by converting the acetamido selenides into the corresponding thioacetamides by reaction with the Lawesson's reagent.[12]

Of particular importance are the one-pot selenenylation-deselenenylation processes promoted by organoselenium reagents. Our investigations in this field demonstrated that ammonium persufate not only reacts with a diselenide to produce the electrophilic reagent, but it is also capable of effecting the deselenenylation of the selenides produced in the initial addition step. In this way the electrophilic selenium reagent is regenerated and it can restart the process. Thus, multi-step conversions can be transformed into one-pot procedures that, moreover, require only catalytic amounts of the selenenylating agent or of its precursor.[13] Examples of this catalytic process are the conversions of β,γ-unsaturated esters, amides and nitriles into γ-alkoxy or γ-hydroxy α,β-unsaturated derivatives,[14] of 3-alkenols into 2,5-dihydrofurans,[15] and of β,γ-unsaturated acids into butenolides.[16] The chiral methoxy substituted diselenide was recently employed in catalytic amounts to promote the asymmetric version of this kind of one-pot selenenylation-deselenenylation processes. The investigated reaction and the results obtained are reported in Scheme 6.[7]

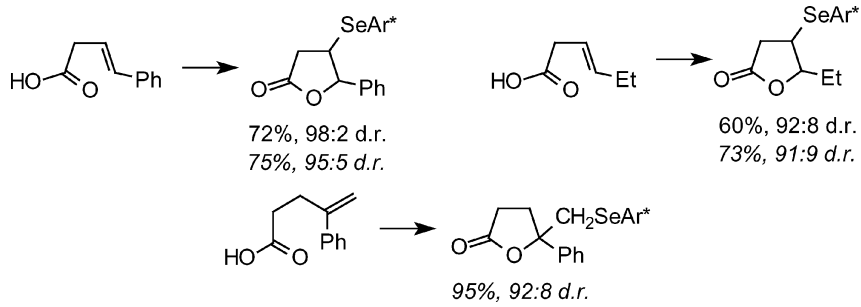


SCHEME 6

The two sulfur-containing optically active diselenides also were employed to effect asymmetric cyclization reactions starting from alkenes containing internal nucleophiles. Scheme 7 refers to the selenolactonization reactions with the methoxy substituted diselenide.[7] In italics (in Scheme 7) the results obtained with the unsubstituted sulfur containing diselenide are also reported.[17]

The second type of cyclization reactions investigated were the selenoetherifications of alkenols.[7,17] Some selected examples are reported in Table II where the results obtained by Wirth,[18,19] using an oxygen containing diselenide, are also included for comparison. These data indicate that our diselenides are very efficient.

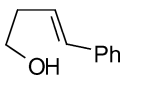
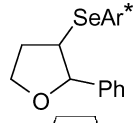
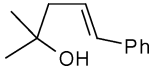
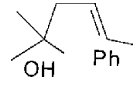
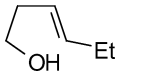
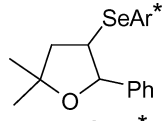
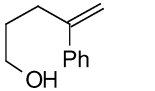
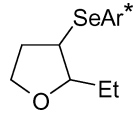
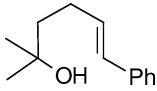
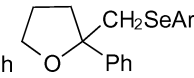
Of greater synthetic importance are those cyclization reactions in which the ring closure occurs through the formation of a new carbon-nitrogen bond. Several nitrogen-containing heterocycles can be

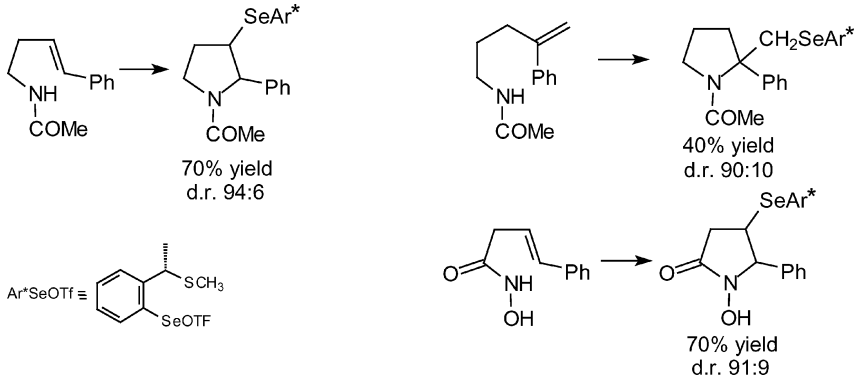


SCHEME 7

prepared in this way with high diastereoselectivity. Selected examples are reported in Scheme 8 which refers to the conversions of alkenyl amides into N-acetyl pyrrolidines and of alkenyl hydroxamic acids into N-hydroxy γ-lactams.[17]

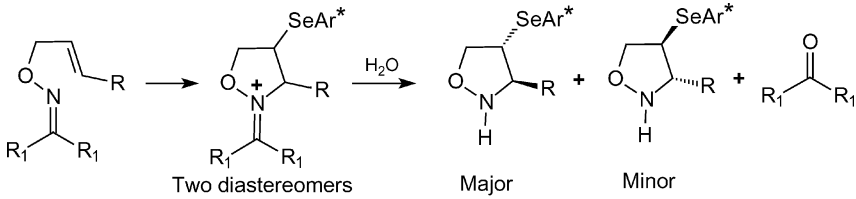
TABLE II Selenoetherification of Alkenols

Starting alkenols	Seleno etherification products	Triflate At-100°C	Triflate At-78°C	Sulfate At-30°C
		84:16 (87%)	93:7 (88%)	
			93:7 (88%)	96:4 (69%)
		50:50 (60%)	80:20 (56%)	
		80:20 (45%)	91:9 (73%)	
			94:6 (79%)	



SCHEME 8

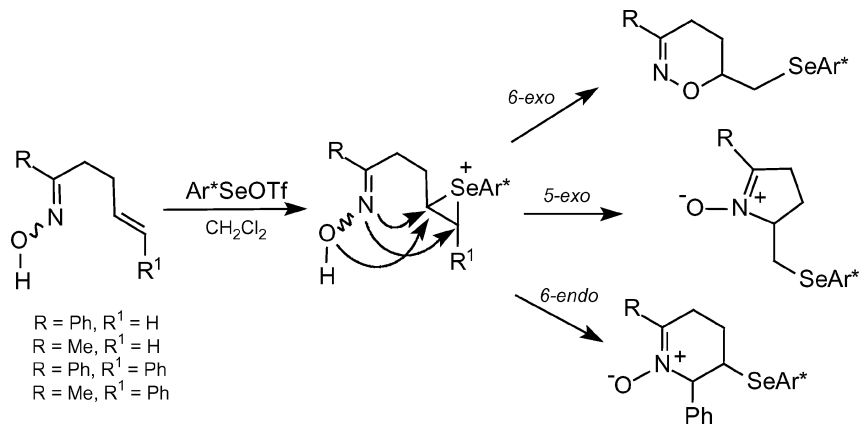
Another interesting case is the conversion of allyl oximes into isoxazolidines. The unsubstituted sulfur containing diselenide was employed. The reaction passes through the intermediate formation of cyclic iminium salts which by hydrolysis afford a mixture of two diastereomeric isoxazolidines and a ketone. Only in one case the cyclization also was effected with the methoxy substituted diselenide; the results of this experiment are reported in italics in Scheme 9.[20]



R = Me, R_1 = *n*-Pr : Yield 58%, 90:10 d.r.
R = Et, R_1 = *n*-Pr : Yield 93%, 88:12 d.r.
R = Ph, R_1 = *n*-Pr : Yield 77%, 93:7 d.r.
R = Ph, R_1 = n-Pr : Yield 70%, 96:4 d.r.

SCHEME 9

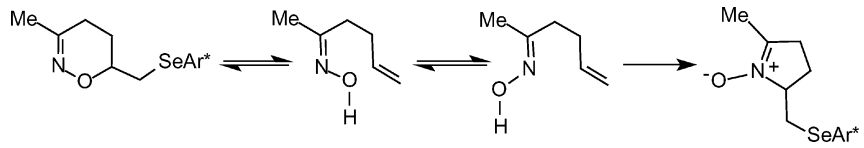
A further example is represented by the asymmetric synthesis of 1,2-oxazine and cyclic nitrones starting from alkenyl oximes.[21] In some of these reactions an interesting competition between the oxygen and the nitrogen atom in the cyclization process is observed. When R=Ph and R^1=H the structure of the reaction products reflects the geometry of the starting oximes; the *E* isomer affords the 1,2-oxazine and the *Z* isomer gives the cyclic nitrone. When R^1=Ph the nature of the group R and the geometry of the starting oximes have no influence and the six-member



SCHEME 10

nitrones are the sole reaction products (Scheme 10). Only in the case in which R=Me and R^1=H a mixture of 1,2-oxazine and cyclic nitrone is obtained. The ratio of the two products does not reflect the ratio of the two isomeric starting oximes and the formation of the nitrone largely is preferred.

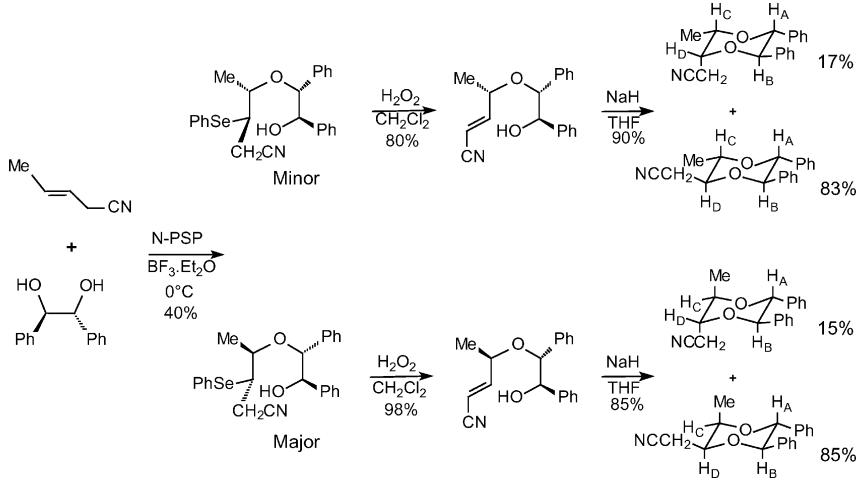
Some parallel experiments demonstrated that this is due to the fact that the two isomeric starting oximes interconvert and the formation of the 1,2-oxazine is a reversible process (Scheme 11). All these reactions were effected using both the sulfur containing diselenides. Excellent diastereoselectivities, up to 96:4, were observed in every case.



SCHEME 11

The synthesis of optically active heterocyclic compounds was also effected using a different approach consisting in the reaction of an achiral organoselenium reagent and an appropriate nucleophile or substrate in the enantiomerically pure form. In Scheme 12 the alkoxyselenenylation of alkenes in the presence of optically pure diols is indicated.

This reaction, mediated by N-(phenylseleno)phthalimide (N-PSP), can be employed as the first step to prepare enantiomerically pure tetrasubstituted 1,4-dioxanes. The two initially formed diastereoisomers were separated and deselenenylated by oxidation to form allylic ethers.

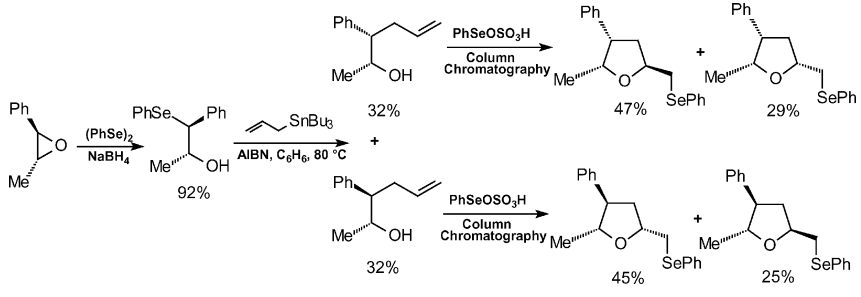


SCHEME 12

Couples of 1,4-dioxanes, easily separated by column chromatography, were finally obtained by intramolecular conjugate additions promoted by NaH.[22]

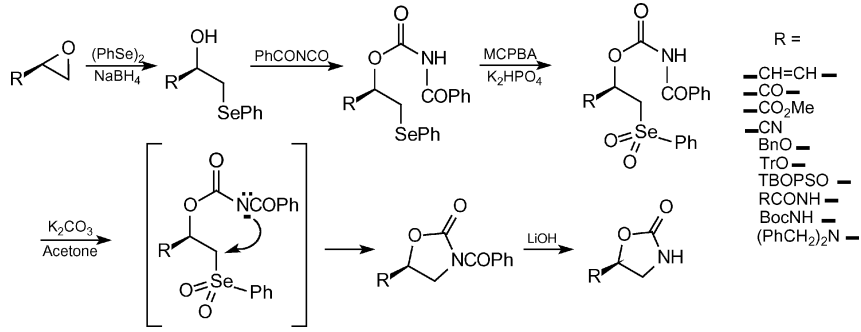
Similar sequences of reactions have been employed for the preparation of enantiomerically pure substituted morpholines using a N-protected aminoalcohol as the nucleophile.[23]

Starting from commercially available optically pure epoxides substituted enantiopure tetrahydrofurans were prepared (Scheme 13).[24] The first step of the procedure consisted in the regio- and stereoselective opening of the epoxides with phenylselenolate anions to afford hydroxyalkyl phenyl selenides. The PhSe group was then substituted by an allyl group by treatment with allyltributyltin and AIBN. The reaction of these allylic derivatives with electrophilic phenylselenyl sulfate



SCHEME 13

afforded selenium containing tetrahydrofurans as the result of a stereospecific 5-*exo-trig* cyclization. The tetrahydrofurans were finally deselenenylated with triphenyltin hydride and AIBN. This last step is not indicated in Scheme 14.

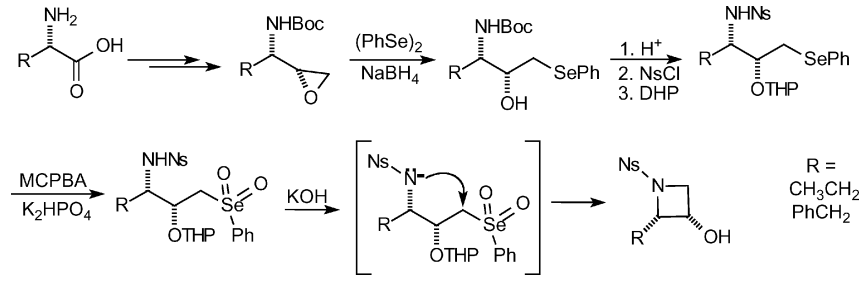


SCHEME 14

The β-hydroxyalkyl phenyl selenides can also be employed for a new and convenient stereospecific synthesis of variously substituted 1,3-oxazolidin-2-ones.[25]

After transformation into the N-tosyl or N-benzoyl carbamates, the selenides were oxidized to selenones. The crucial step of the process is the ring closure reaction which occurs by stereospecific intramolecular nucleophilic substitution of the selenone group by the nitrogen atom of the carbamate. Enantiopure 1,3-oxazolidin-2-one derivatives easily have been prepared using enantiomerically pure β-hydroxyalkyl phenyl selenides as starting products.

The stereospecific intramolecular nucleophilic substitution of the selenone group by a nitrogen was also used as the key step of a new and efficient synthesis of enantiomerically pure azetidines starting from aminoacids.[26]



SCHEME 15

As indicated in Scheme 15 the aminoacid was converted into an amino-substituted hydroxy selenide. The hydroxy group was protected and the selenide was oxidized to selenone. The treatment with KOH produced the nitrogen anion which, by displacement of the selenone group, afforded the cyclization product.

CONCLUSIONS

We have demonstrated that organoselenium chemistry is very useful to affect efficient asymmetric syntheses. We have reported that the electrophilic reagents derived from the di 2-[(1S)-1-(methylthio)ethyl]phenyl diselenide, or better from its methoxy derivative, react with alkenes to afford alkoxy-, hydroxy-, and azido-selenides, or cyclization products, with diastereoselectivities greater than 95%. In some cases these reagents can also be employed in catalytic amounts. We have also shown that the reactions of electrophilic phenylselenium reagents with optically active nucleophiles or substrates can be used to prepare enantiopure dioxane, morpholine, tetrahydrofuran, oxazolidin-2-one and aziridine derivatives.

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