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PREPARATIONS OF SELENIUM-CONTAINING HETEROCYCLES BASED ON AN INTRAMOLECULAR CYCLIZATION OF SELENOLS AND RELATIVES

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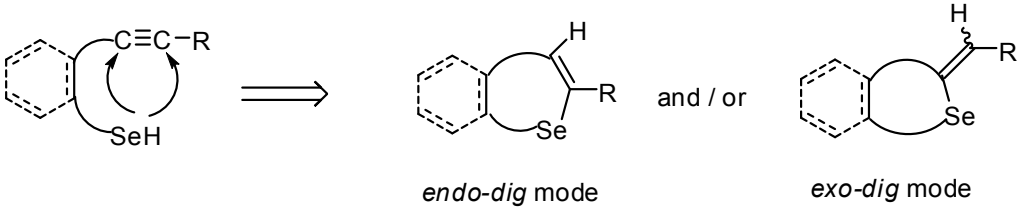
Abstract – The preparation of the five- to nine-membered selenium-containing heterocycles using the intramolecular cyclization of selenols and relative compounds is mainly described in this review based on recent advances in our findings. Some reactions and chemical properties of the obtained products are also described.

CONTENTS

1. INTRODUCTION

In addition to selenium, which is a rare element essential to the human body,[1] inorganic and organic selenium-containing molecules have been much less developed because of their high toxicity and instability. Recently, organoselenium compounds, especially selenium-containing heterocycles, are of increasing interest because of their chemical properties, biological activity[2] and medicinal applications, such as anticancer, antiviral, antibacterial, antihypertensive and fungicidal properties. Much effort has been expended not only in the preparation of new structural heterocycles containing a selenium element but also in the development for the synthetic methodologies of selenaheterocycles.

It is already known that the intermolecular *trans*-addition of selenols[3] and tellurols[4] into a carbon-carbon triple bond regio- and stereo-specifically proceed to form vinylselenides or vinyltellurides. Therefore, this



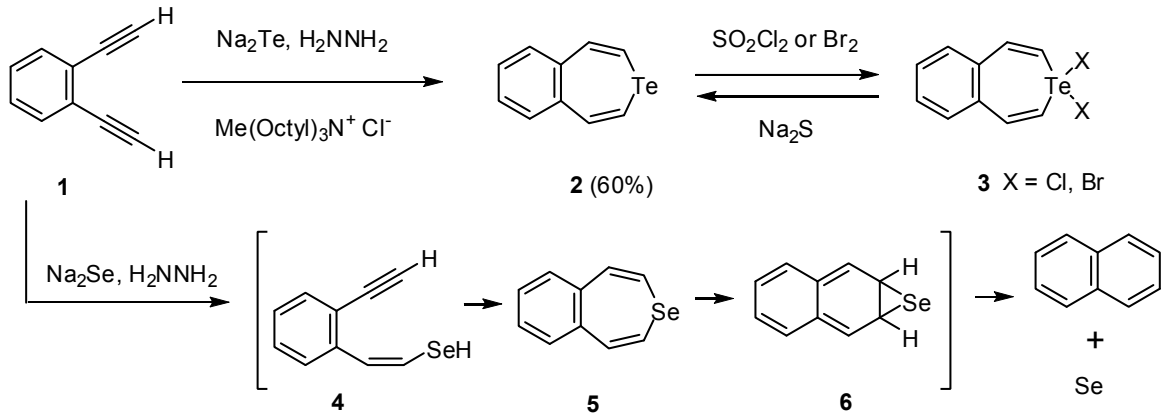
Scheme 1. Synthetic Strategy for the Preparation of Selenium-Containing Heterocycles

addition of the selenols to a triple bond using intramolecular cyclization systems for our objective,[5] which is the synthesis of various types of selenium-containing heterocyles, was extended. Scheme 1 shows our synthetic strategy for the preparation of selenium-containing heterocycles.

2. BENZOSELENEPINES

2.1. 3-Benzoselenepines and 3-benzotellurepines

In 1991, we succeeded in the synthesis and isolation of the novel 3-benzotellurepines,[6] fully unsaturated tellurium-containing seven-membered heterocycles, by the reaction of *o*-diethynylbenzene with sodium telluride (Na_2Te) as shown in Scheme 2. Diethynylbenzene (**1**) reacted with Na_2Te in the presence of hydrazine hydrate and a phase-transfer catalyst (*n*-Oct_3MeN^+ Cl^-) in benzene-water at room temperature to give the desired *C*-unsubstituted 3-benzotellurepine (**2**) in *ca*. 60% yield as a yellow oil. Tellurepine (**2**) is relatively unstable and gradually decomposes to naphthalene and tellurium. Treatment of **2** with SO_2Cl_2 gave 3,3-dichlorotellurepine (**3a**) and treatment with Br_2 afforded the 3,3-dibromo derivative **3b**. The halogeno compounds **3** are somewhat more stable than the parent **2** and reverted back to **2** upon treatment with Na_2S in hexane-water.

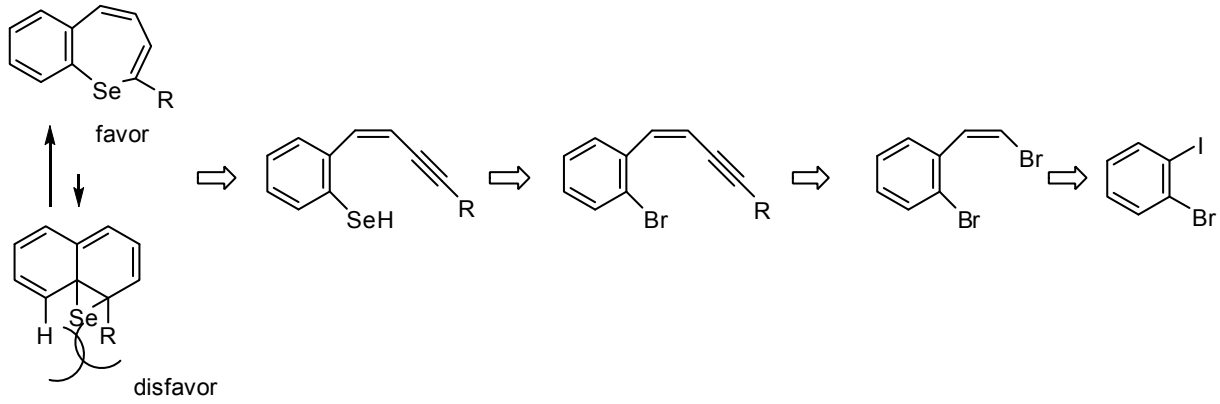


Scheme 2

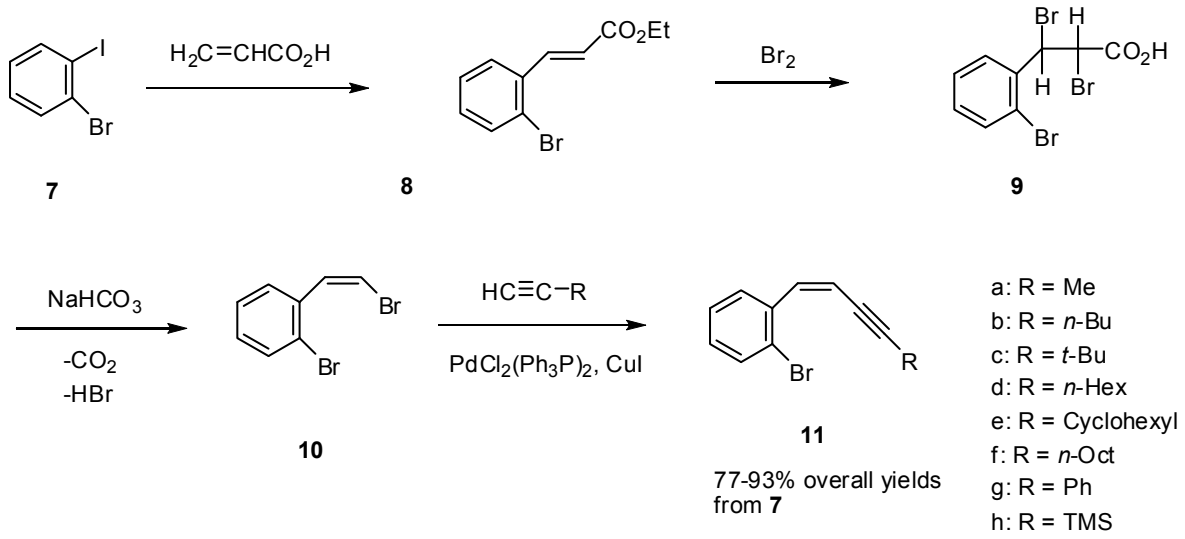
3-Benzotellurepines (**2**, **3**), which were obtained in this study, are the first synthetic examples of seven-membered tellurium-containing heterocycles. Unfortunately, under similar conditions using Na_2Se instead of Na_2Te, 3-benzoselenepine (**5**) could not be isolated in spite of many efforts; naphthalene and element selenium were obtained. The selenol (**4**) generated by the addition of Na_2Se to an ethynyl moiety of **1** cyclized into an alternative triple bond to give the desired 3-benzoselenepine (**5**). **5** undergoes ring contraction to form the selenanorcaradiene (**6**). The resulting tautomer **6** immediately extrudes a selenium element to give naphthalene. 3-Benzoselenepine having no substitutions is too unstable to be isolated.[7]

2.2. 1-Benzoselenepines

It is known[8] that simple monocyclic and benzene ring-fused thiepines are thermally unstable due to ready extrusion of the sulfur *via* the corresponding norcaradiene derivatives, but the stability of the hetereopine rings can be enhanced by introduction of bulky groups in the α–position. Therefore, the synthesis of the 1-benzoselenepines, the regioisomers of 3-benzoselenepines having a bulky group at the 2-position, was examined next. The retro-synthesis of the 1-benzoselenepine is illustrated in Scheme 3.



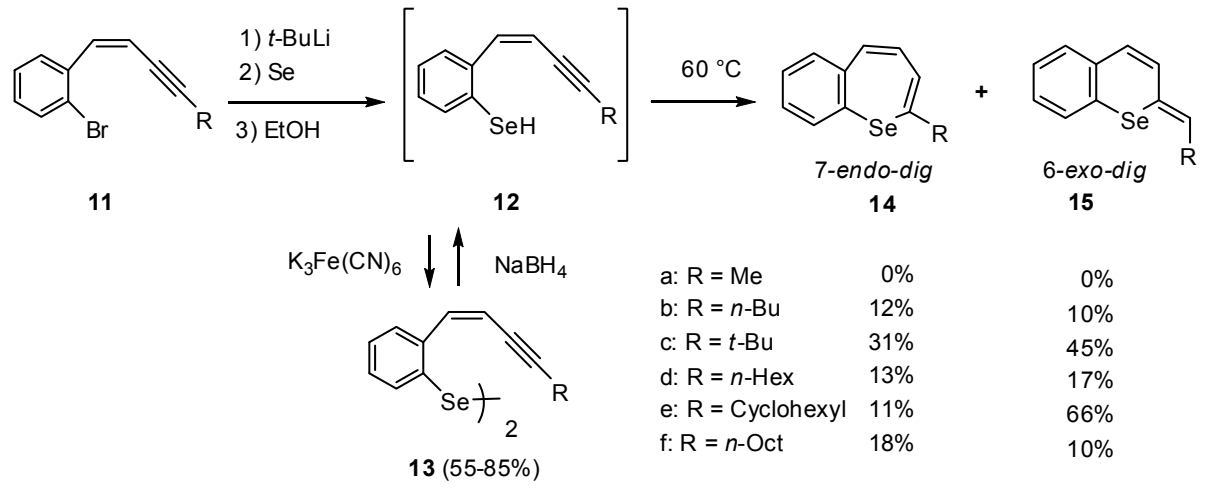
Scheme 3



Scheme 4

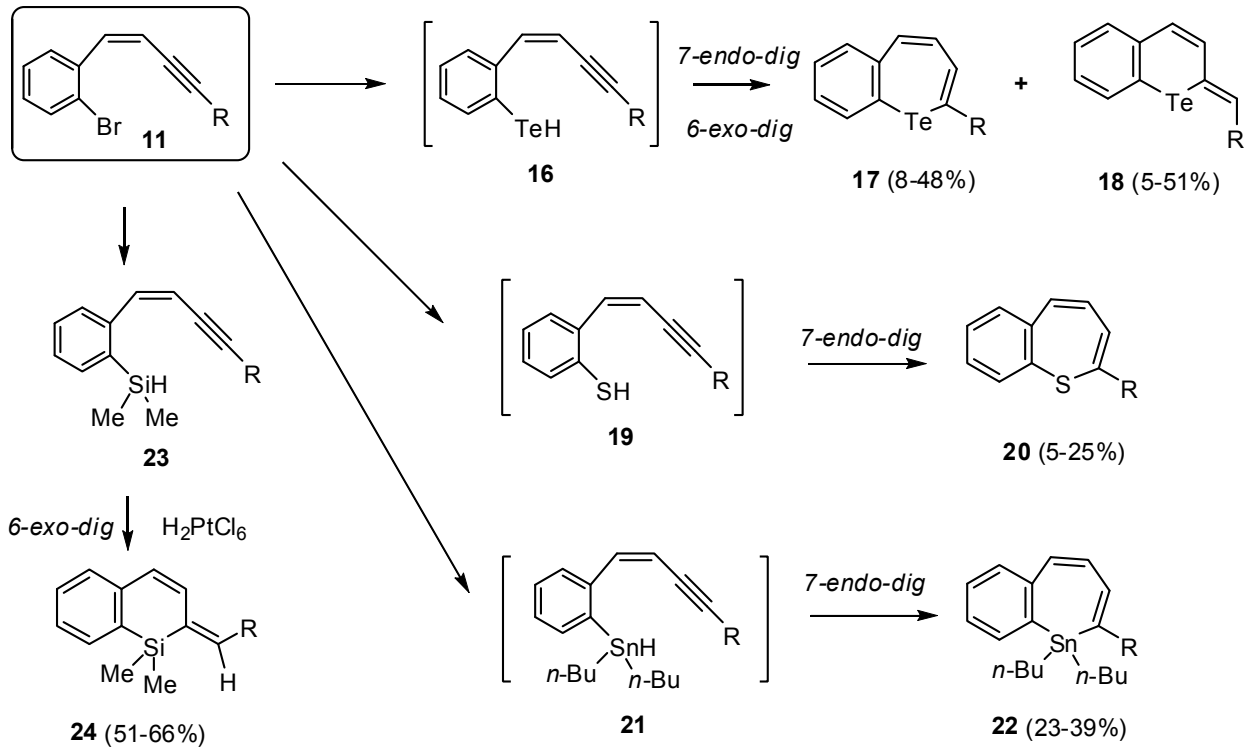
Several key starting ene-yne compounds **11a-h** were prepared as shown in Scheme 4, and obtained in 4 steps including the palladium-catalyzed Sonogashira reaction[9] of the styrylbromide (**10**) with 1-alkynes to give 77-93% yields from *o*-bromoiodobenzene (**7**). Compound **11** were lithiated with *tert*-BuLi in dry THF at -80 ˚C and then treated with elemental selenium, followed by oxidation with $K_3Fe(CN)_6$ to produce di[*o*-(buten-3-ynyl)pheny] diselenides (**13**) in one pot in 53-85% yields. $NaBH_4$ reduction of the

diselenides **13** in THF-EtOH resulted in the direct *7-endo-dig* mode ring closure to give the expected 1-benzoselenepines (**14**) with reductive cleavage of the Se-Se bond together with the *6-exo-dig* 2*H*-selenochromenes (**15**) in the yields shown in Scheme 5.[10] As expected, selenepine **14c** having the bulkiest *tert*-butyl group is stable and can be stored for several weeks at room temperature; the methyl derivative **14a** is unstable and decomposes to methylnaphthalene during the purification operations.



Scheme 5

2.3. Other 1-benzoheteroepines



Scheme 6

In a similar way, 2-alkyl-1-benzotellurepines (**17**)[10,11] and 2-methylidene-2*H*-tellurochromenes (**18**) were also obtained by the use of Na_2Te instead of Na_2Se through the intramolecular ring closure of the tellurols (**16**) in nearly similar yields with the selenium compounds. On the other hand, the thiols (**19**) and tin hydrides (**21**), which were also easily generated from the bromides **11**, gave the 2-substituted 1-benzothiepines (**20**)[11] and 1,1-dibutyl-1-benzostannepines (**22**)[12] in only the *7-endo-dig* mode reaction, respectively. The 1-benzostannepines (**22**) are hitherto unknown heterocyclic systems, and are converted into the seven-membered 1-benzostibepines[13] and 1-benzoborepines[13] involving the 1-benzotellurepines *via* a tin-metal exchange reaction.[14]

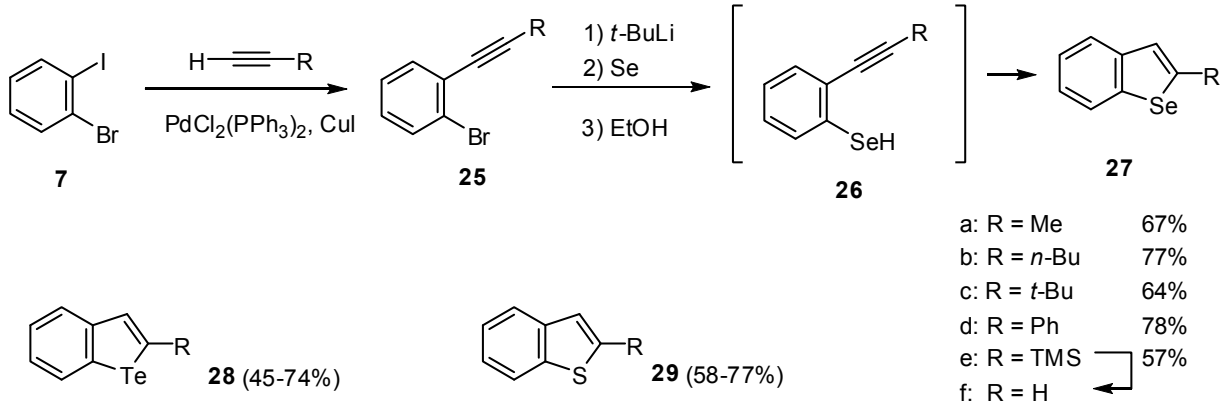
2.4. 2-Methylidenesilachromenes

The platinum-catalyzed silylation of compound **23**, which were isolated in the reaction of the bromides **11** with Me_2SiHCl, proceeded to give the (*E*)-1,1-dimethyl-2-methylidenesilachromenes (**24**)[15] as the sole products in moderate yields during the *6-exo-dig* mode cyclization as shown in Scheme 6.

3. BENZOSELENOPHENES

3.1. Benzo[*b*]selenophenes

Next, this intramolecular cyclization of phenylselenols to a triple bond for the selenium-containing heterocycles was applied for the preparation of the benzo[*b*]selenophenes which was the simplest system.[16] The key starting compounds, *o*-bromoethynylbenzenes (**25**) were readily prepared by the Sonogashira reaction[9] of *o*-bromoiodobenzene (**7**) with 1-substituted acetylenes in high yields. The treatment of **25** with *tert*-BuLi in dry Et_2O at -80 ˚C and then treatment with elemental selenium, followed by the addition of EtOH, gave the selenophenes (**27**) *via* intermediates **26** as the sole products in good yields in one pot, as shown in Scheme 7. The treatment of 2-TMS derivative **27e** with alkali in MeOH, and fluoride-anion containing H_2O or $NaBH_4$ reduction in EtOH afforded the unsubstituted selenophene. Benzotellurophenes (**28**) and thiophenes (**29**) were also conveniently obtained *via* similar

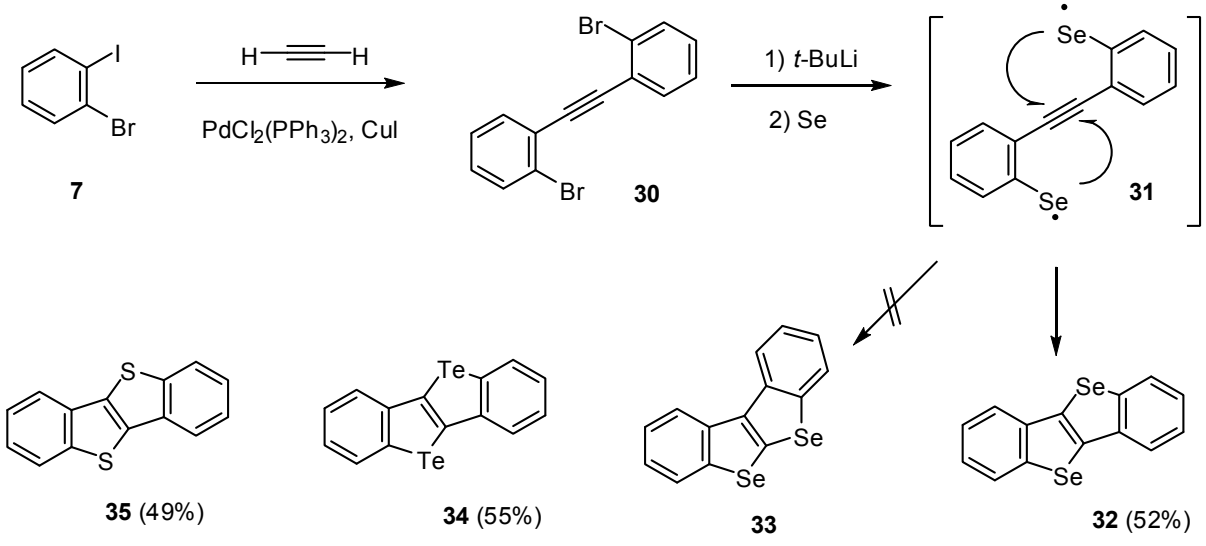


Scheme 7

reactions in moderate to good yields. Thus, this ring-closure reaction was found to be a versatile simple method for the one-pot preparation of 2-substituted and unsubstituted benzo[*b*]chalcogenophenes (**27**, **28**, **29**).

3.2. [1]Benzoseleno[3,2-*b*][1]benzoselenophene

An extension of our synthetic methodology for the preparation of this title compound to the tandem system[17] is also described. The dimeric-type compound of benzoselenophene, [1]benzoseleno[3,2-*b*][1]benzoselenophene (**32**) is similarly synthesized from **7**, as shown in Scheme 8. The starting diphenylacetylene **30** was easily prepared by the palladium-catalyzed coupling reaction of **7** with acetylene gas in 77% yield. The dibromide **30** was lithiated with *tert*-BuLi in dry Et_2O at -80 ˚C and then treated with elemental selenium, affording the desired selenophene (**32**) in 52% yield, together with diphenylacetylene in *ca*. 10% yield. In the case of the cyclization for preparing the benzoselenophenes (**27**), the addition of a proton source such as EtOH after elemental selenium insertion was essential; if not, the product were produced in quite low yields. However, this tandem cyclization did not require a proton source. Thus, this reaction for **32** may probably proceed *via* the radical intermediate **31**. The structural isomer **33** was never produced. The tellurophene (**34**) and the thiophene derivatives (**35**) were also obtained in about 50% yield.

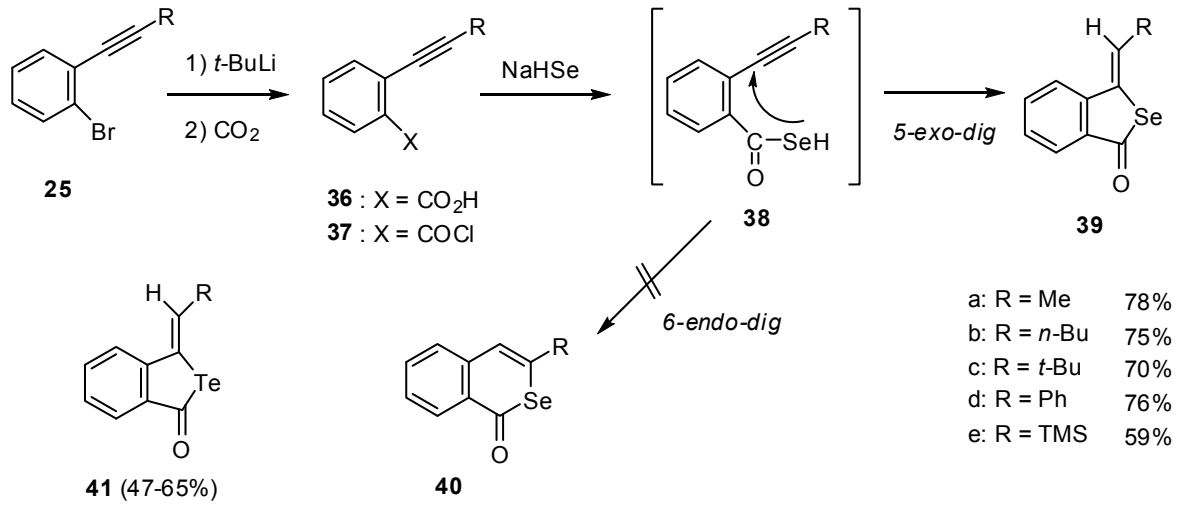


Scheme 8

These chalcogenophenes (**27**-**29**, **32**, **34**, **35**) and their synthetic methodologies were evaluated as an active semiconducting materials for organic thin film transistors.[18]

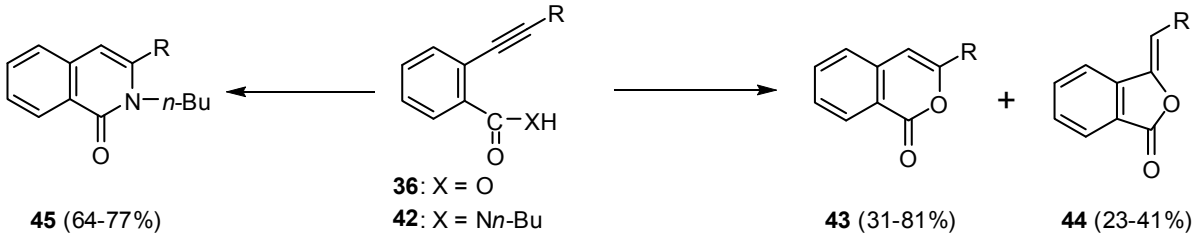
4. SELENOPHTHALIDES

This section describes the synthesis of the selenolactone-type compounds, (*Z*)-3-methylideneselenophthalides (**39**)[19] from the common starting *o*-ethynylbromobenzenes (**25**). Compounds **25** were lithiated with *tert*-BuLi in dry THF and then successively treated with excess dry ice to produce the corresponding *o*-ethynylbenzoic acids (**36**) in 70-75% yields. The acid chlorides (**37**) were generated by treatment of **36** with $SOCl_2$ in the usual manner and used for the next reaction without purification. The reaction of **37** with NaHSe in two phase solvents of H_2O-toluene in the presence of *n*-Bu_4N^+ HSO_4^- as the phase-transfer catalyst resulted in the direct *5-exo-dig* mode ring closure to regioselectively give the (*Z*)-3-methylideneselenophthalides (**39**) as the sole products *via* the probable intermediate **38**. The five derivatives of selenophthalides (**39**) were obtained in moderate to good yields; no *6-endo-dig* mode products (**40**) were produced. This cyclization is also effective for the tellurium analogues **41** by the use of NaHTe instead of NaHSe.



Scheme 9

On the other hand, the intramolecular cyclizations of the *o*-ethynylbenzoic acids (**36**) and benzamides (**42**), which are the oxygen and nitrogen analogues of **38**, proceeded to afford the corresponding *6-endo*- (**43**, **45**) and *5-exo-dig* mode products (**44**) by the palladium catalysis in moderate to good yields, respectively.[20]



Scheme 10

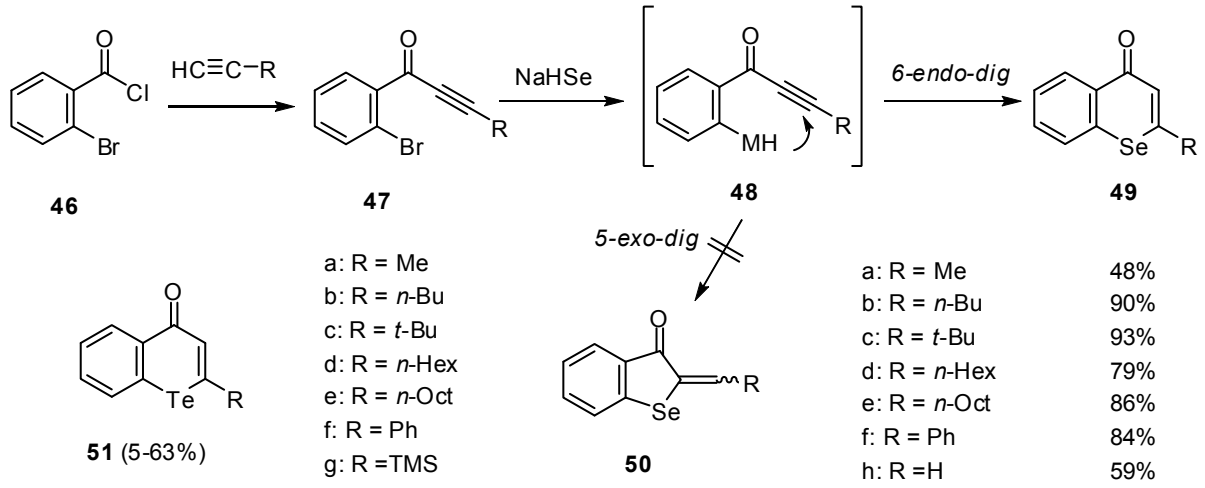
5. SELENOCHROMONES AND RELATIVES

5.1. Synthesis of selenochromenes

Scheme 11 shows the preparation of the selenochromones (**49**).[21] *o*-Bromobenzoyl chloride (**46**) was coupled with various 1-acetylenes under the Sonogashira reaction conditions or trimethylethynylstannane under the Stille coupling conditions[22] to give the corresponding ynones **47** in 70-89% yields. The treatment of the ethynyl ketones (**47**) with NaHSe in DMF gave the selenochromones (**49**) in one pot as the sole products *via* the *6-endo-dig* mode intramolecular cyclization of the presumed intermediate **48** in moderate to high yields.

The TMS derivative **47g** produced the 2-unsubstituted selenochromones (**49h**) with reductive removal of the TMS group under these conditions. No *5-exo-dig* mode products **50** were obtained. These formation results of the selenochromones (**49**) from **47** clearly indicate the following two points. (1) The essential intermediate **48** are probably generated in situ by replacement of the bromo anion with the SeH group due to the enhancement of reactivity in the presence of the carbonyl group as the electron-withdrawing group. (2) The intramolecular regioselective Michael-type addition in **48** proceeds to give the six-membered ring heterocycles **49**. This cyclization is also convenient for the synthesis of the tellurochromones (**51**).

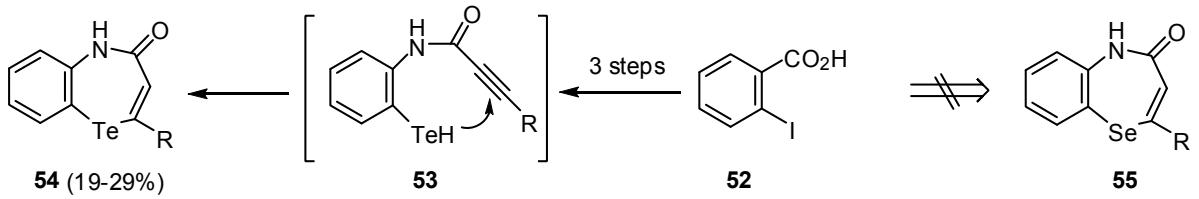
In recent years, the chemistry of the selenochromones and tellurochromones, six-membered heterocycles containing a selenium or tellurium element, and relative compounds, has attracted much attention.[23] Among the unsubstituted **49h**,[24] 2-methyl **49a**[24] and 2-phenyl derivative **49f**[24] have been synthesized; the other chromones **49b-e** are new compounds.



Scheme 11

A few applications of this successive intramolecular cyclization of the phenylselenols and telluronium analogues having an ynone moiety at the *ortho* position are examined. The propiolanilides (**53**), having a

nitrogen between the phenyl and carbonyl groups, were readily prepared from *o*-iodobenzoic acid (**52**) in 3steps and gave the tellurazepines (**54**)[25] through the *7-endo-dig* mode intramolecular ring-closure in low yields. However, the selenazepines (**55**) could unfortunately not be obtained in a similar way.

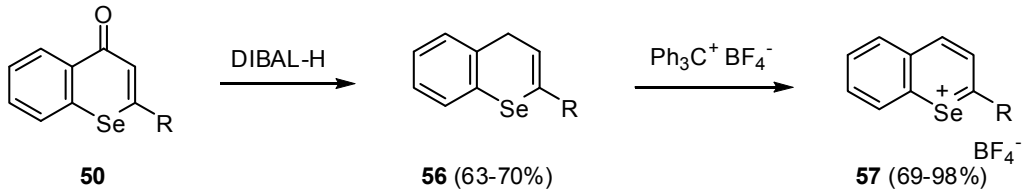


54 (19-29%) **53** **52** **55**

Scheme 12

5.2. Conversion into 1-benzoselenopyrylium salts

The general preparation of the 2-substituted 1-benzoselenopyrylium salts from the selenochromones[26] in two steps and their reactions with several nucleophiles are outlined in this section.[27] Only four examples[28] of the 1-benzoselenopyrylium salts involving the unsubstituted and phenyl derivatives as the perchlorates have been prepared; the 1-benzoselenopyrylium salts having an alkyl substituent have never been prepared until now. In addition, their stability and reactivity toward nucleophiles have received little attention. The synthesis of the 1-benzoselenopyrylium salts (**57**)[26b] from the corresponding selenochromones (**50**) is shown in Scheme 13.

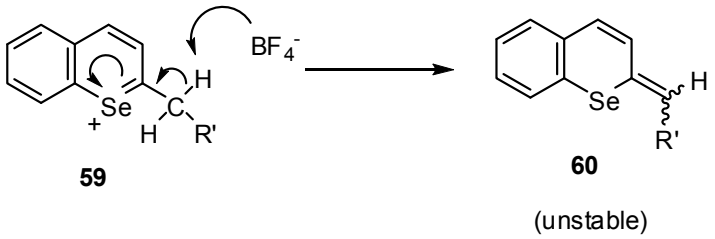


50 **56** (63-70%) **57** (69-98%)

Scheme 13

In order to obtain the 4*H*-selenochromenes (**56**), the precursors for the preparation of the salts (**57**), DIBAL-H reduction was used for the conversion of the carbonyl group to the methylene group of **50**. Treatment of the 2-*tert*-butyl- and 2-phenyl-chromenes (**56**) with Ph_3C^+ BF_4^- in $MeNO_2$, followed by the addition of dry Et_2O gave the desired 1-benzoselenopyrylium salts (**57**) in almost quantitative isolated yields as stable yellow prisms. However, a similar treatment of the chromenes (**56**) having a primary alkyl group such as methyl and *n*-butyl at the C-2 position did not produce the corresponding stable salts due to their instability. This distinction between a primary alkyl group and other carbon functionalties at the C-2 position with respect to the stability of the selenopyrylium salts (**59**) is explained as shown in Scheme 14.

BF_4^-, the counter anion of the salts,eliminated the β–hydrogen of the methylene carbon of the primary alkyl group forming the unstable *exo*-methylene compound **60**. Figure 1 shows the molecular structure of the 2-*tert*-butyl-1-benzoselenopyrylium salt (**57**).[29]



Scheme 14

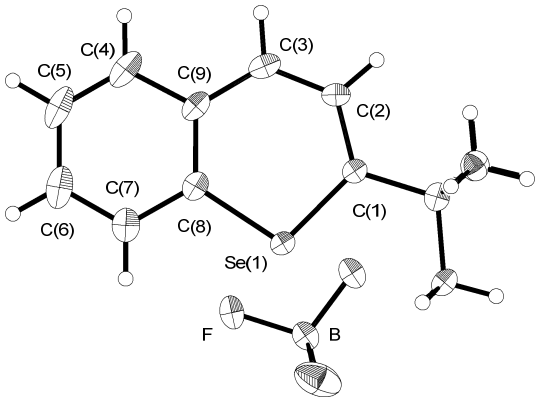
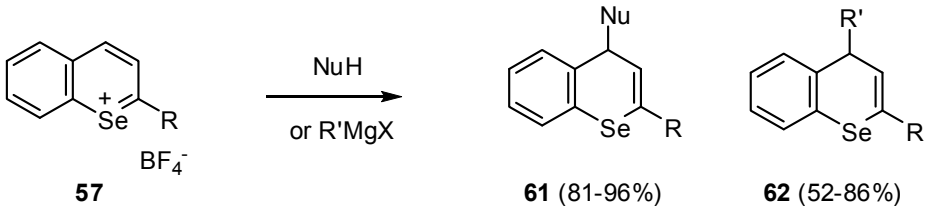


Figure 1. ORTEP drawing of **57** with 50% probability level

5.3. Reactions of 1-benzoselenopyrylium salts

Next, the reactions of the 1-benzoselenopyrylium salts (**57**) with several nucleophiles[30a] including alkoxide ions (OMe-, *i*-OPr^- and *t*-OBu^-), amines (diethylamine and *n*-butylamine), cyanide ion, Grignard reagents (MeMgI, EtMgBr, $PhCH_2MgBr$ and PhMgBr),[30b] and an active methyl compound (acetone) were examined using the stable 2-*tert*-butyl and 2-phenyl substrates. Various 4*H*-isoselenochromenes (**61**,



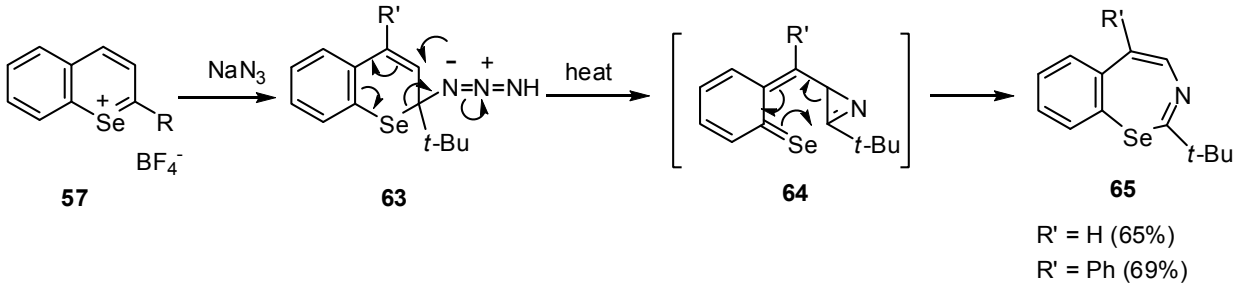
Nu = OMe, *i*-OPr, *t*-OBu, NEt_2, NH*n*-Bu,
R' = Me, Et, CH_2Ph, Ph

Scheme 15

62) having an oxygen, nitrogen and carbon functional group at the C-4 position were produced in good to excellent yields.

5.4. 1,3-Benzoselenazepines

In addition, the salts (**57**) were treated with NaN_3 in MeCN to give the 2-azido-2*H*-selenochromenes (**63**), which were heated at 100 ˚C in dioxane to expand the selenopyran ring giving the novel 1,3-benzoselenazepines (**65**)[31] with denitrogenation *via* the azirine intermediates **64** in good yields.



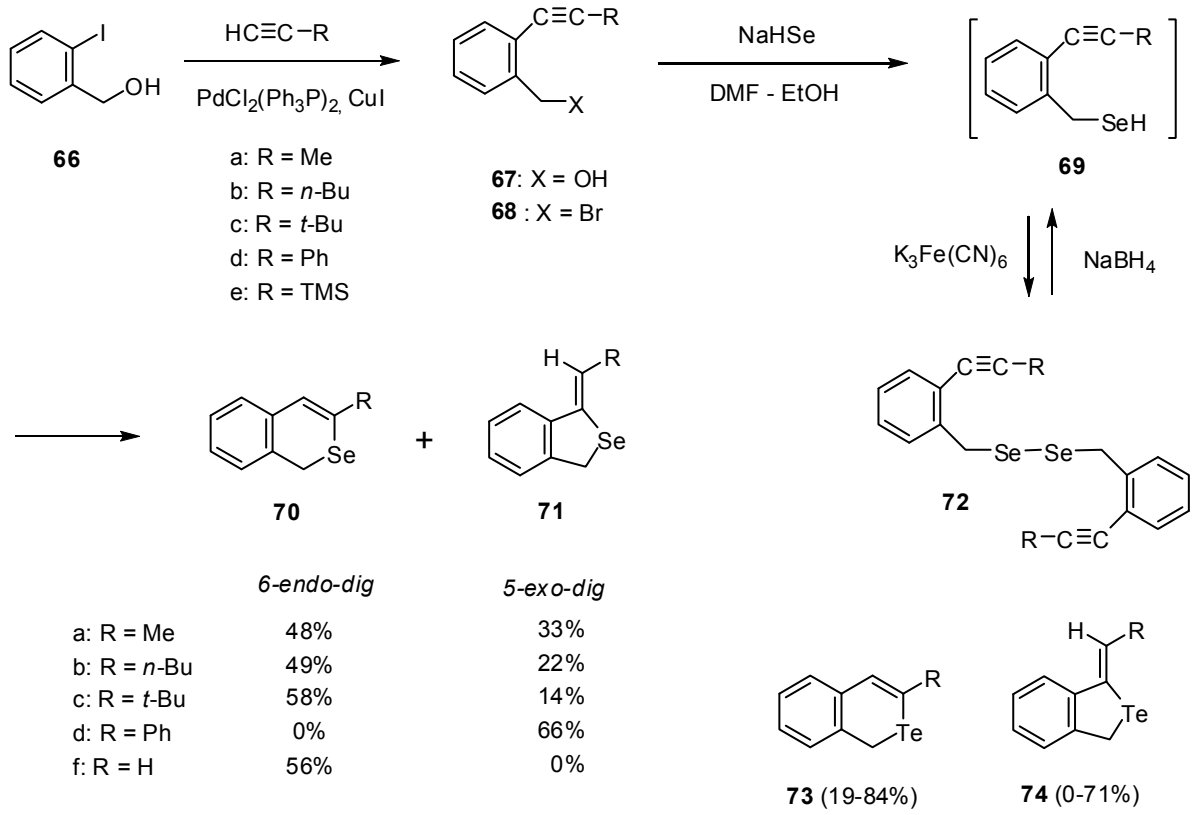
Scheme 16

6. ISOSELENOCHROMENES AND RELATIVES

This section describes the synthesis of the isoselenochromenes,[32] a theoretical possible structural isomer of **56** in the above section, and the transformation into the 2-benzoselenopyrylium salts.

6.1. Synthesis of isoselenochromenes

It is clear that the *o*-ethynylbenzyl selenols (**69**) are the precursors for the synthesis of the isoselenochromenes (**70**) and the related compounds. *o*-Ethynylbenzyl alcohols (**67**), which were prepared by the palladium catalyzed Sonogashira reaction of *o*-iodobenzyl alcohols (**66**) with 1-substituted acetylenes, were readily converted to the *o*-ethynylbenzyl bromides (**68**) by the treatment with PBr_3. Treatment of **68** with NaHSe in DMF at 0 ˚C, followed by the addition of EtOH and then heating at 90 ˚C, resulted in a direct ring closure to give the 1*H*-isoselenochromenes (**70**, *6-endo-dig* mode products) together with (*Z*)-1-methylidene-2-selenaindenes (**71**, *5-exo-dig* mode products) *via* the selenol intermediates **69** as shown in Scheme 17. The formation of **69** was characterized by the isolation of the diselenides **72**, which were obtained by the potassium ferricyanide oxidation of **69** before heating in EtOH. The diselenides **72** reverted back to the selenols **69** by treatment with sodium borohydride with reductive fission of the Se-Se bond. The isotellurochromenes (**73**) and telluraindenes (**74**) were also obtained in nearly similar manners and yields.

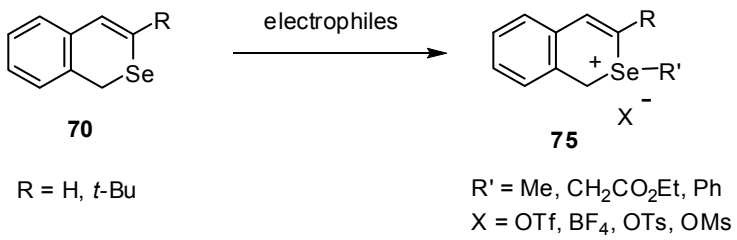


Scheme 17

6.2.Reactions with electrophiles

The isoselenochromenes (**70**) except for the 3-unsubstituted derivative **70f**[33] are hitherto unknown compounds. Only a few reports[34] are known on the preparation and alkylation or arylation of the selenium-containing heterocycles, such as isoselenochroman.

The alkylation of **70** gave the selenonium salts (**75**),[35] i.e., tetrafluoroborates, triflates, tosylates and mesylates, in good yields as well as the isotellurochromenes (**73**).[36] The phenylation reaction of **70** was conducted using the diphenyliodonium triflate and copper (II) diacetate.[37] 3-*tert*-Butylisoselenochromenium triflate (**75Fb**) was produced in 68% yield. However, the reaction of 3-unsubstitued isochromene (**70a**) under the same conditions gave a complex mixture; no 2-phenylisoselenochromenium triflate (**75Fa**) was obtained. The obtained results are listed in Table 1.



Scheme 18

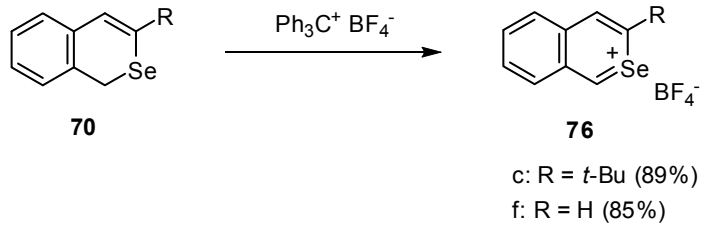
Table 1. Selenonium Salts (**75**)

Compd.	Electrophile	R'	X	Yield (%)[a]	
				a: R = H	b: R = *t*-Bu
75A	MeI, $AgBF_4$	Me	BF_4	61	94
75B	TfOMe	Me	OTf	94	90
75C	$TfOCH_2CO_2Et$	CH_2CO_2Et	OTf	95	92
75D	TsOMe	Me	OTs	98	96
75E	MsOMe	Me	OMs	87	88
75F	$TfOIPh_2$	Ph	OTf	-	68

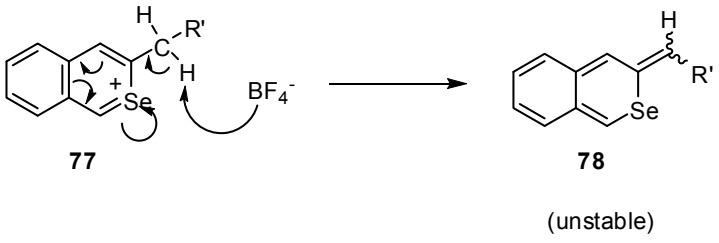
[a]Isolated yield.

6.3. Conversion into 2-benzoselenopyrylium salts

The conversion from the 1*H*-isoselenochromenes (**70**) into the 2-benzoselenopyrylium salts (**76**) and their reactivity toward several nucleophiles are disclosed in this section. With regard to the 2-benzoselenopyrylium salts, the synthesis of only the unsubstituted derivative has been reported by Renson and Pirson[33] in 1966; no 2-benzotelluropyrylium salts have been prepared until our synthesis.[32a] The isoselenochromenes (**70**) were treated with $Ph_3C^+ BF_4^-$ in $MeNO_2$ and worked up as described for the preparation of the 1-benzoselenopyrylium salts (**57**) to give the 2-benzoselenopyrylium salts (**76**) as stable yellow or green prisms in excellent yields.



Scheme 19



Scheme 20

The 3-*tert*-butyl (**76c**) and 3-unsubstituted selenopyrylium salts (**76f**) were air-stably obtained; however, the 2-benzoselenopyrylium salts having another alkyl substituted group (methyl and *n*-butyl) on the C-3

position could not be isolated.[32c] The reason why these selenopyrylium salts are not stable compared to the 3-*tert*-butyl and 3-unsubstituted derivatives might be the reaction shown in Scheme 20; this behavior is quite similar to that of the 1-benzoselenopyrylium salts (Scheme 14).

Figure 2 shows the molecular structure of the 3-*tert*-butyl-2-benzoselenopyrylium salt (**76c**).[29]

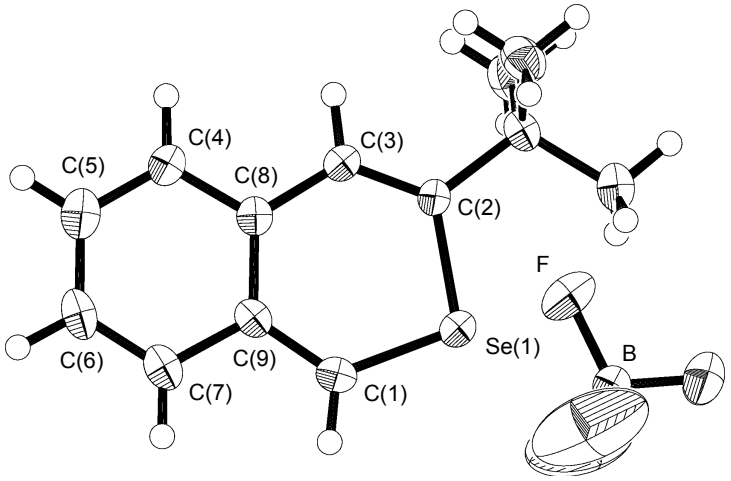
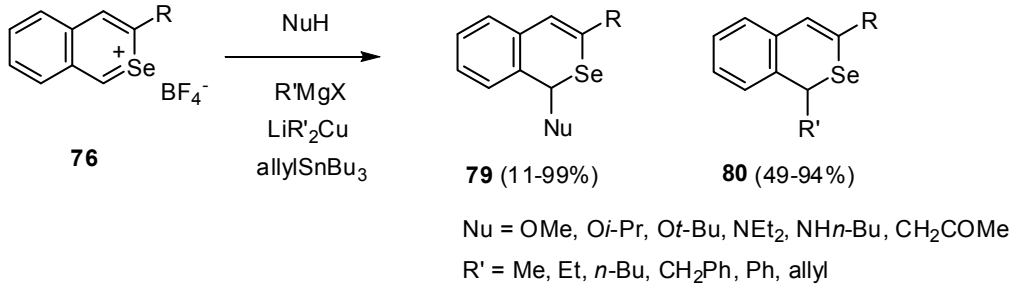


Figure 2. ORTEP drawing of **76c**

6.4. Reactions of 2-benzoselenopyrylium salts

Next, the reactions of the salts **76** with a variety of nucleophiles have been investigated. $LiAlH_4$, sodium alkoxide (NaOMe, NaO*i*-Pr and NaO*t*-Bu),[38] Et_2NH, *n*-$BuNH_2$,[38] Grignard reagents (MeMgI, EtMgBr, *n*-BuMgCl, $PhCH_2MgBr$ and PhMgBr),[39] organocopper reagents[39] and allyltin reagents[40] reacted with **76** to give the 1*H*-isoselenochromenes (**70**) and the corresponding isoselenochromenes (**79**, **80**) having a

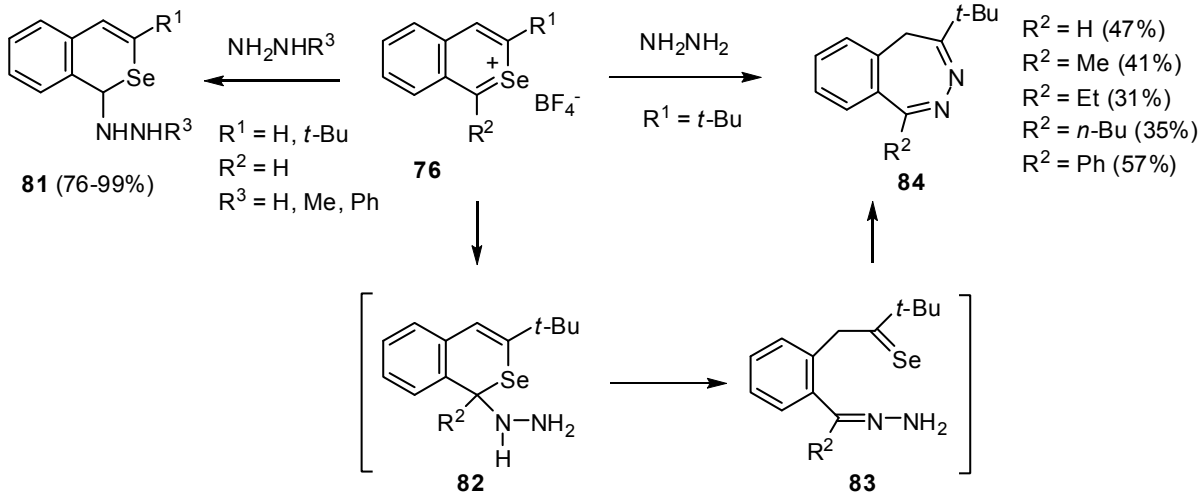


Scheme 21

oxygen, nitrogen or carbon functional group at the C-1 position under mild conditions in nearly good to high yields.

While the solvent-free reactions of the salts **76** with $MeNHNH_2$ or $PhNHNH_2$ gave the

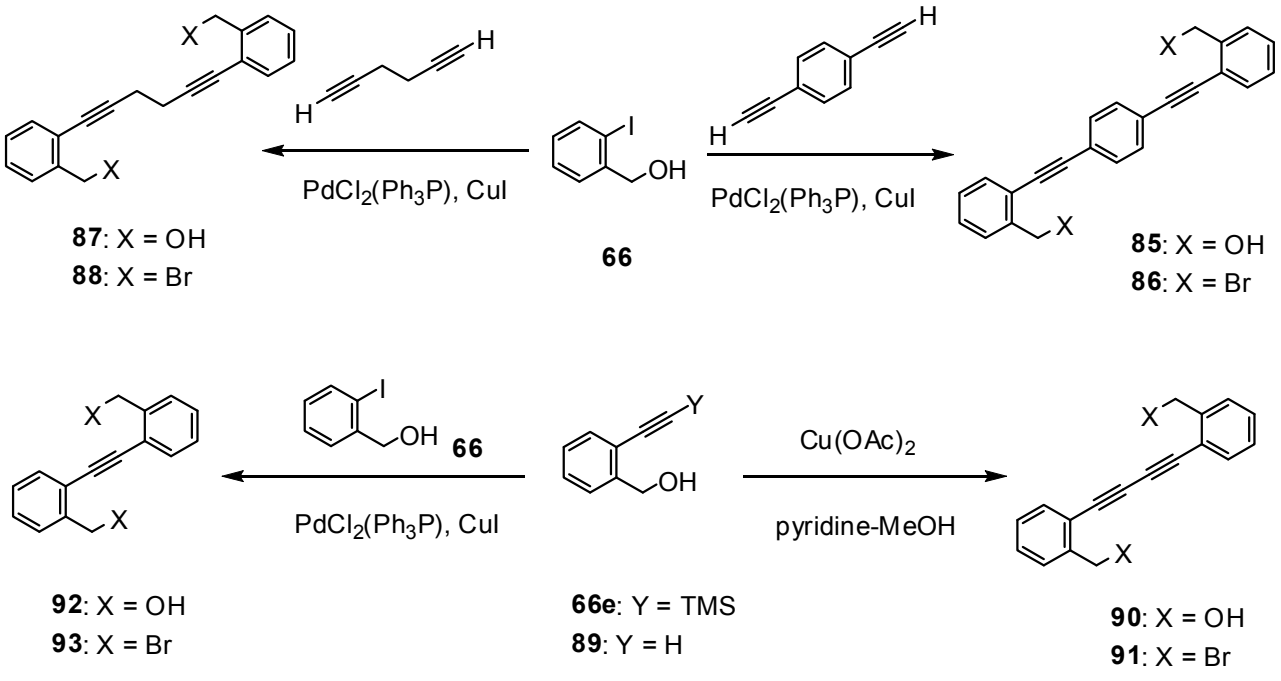
1-hydrazino-1*H*-isoselenochromenes (**81**), similar to the other nucleophiles, the treatment of **76** with anhydrous NH_2NH_2 in dry MeCN resulted in a ring transformation to produce the 5*H*-2,3-benzodiazepines (**84**)[41] in a one-pot reaction under mild conditions in moderate yields *via* the probable intermediates **82** and **83**.



Scheme 22

7. TANDEM CYCLIZATIONS OF DIBENZY DISELENOLS

As an extension of our ongoing work in which we succeeded in preparing various types of selenium-

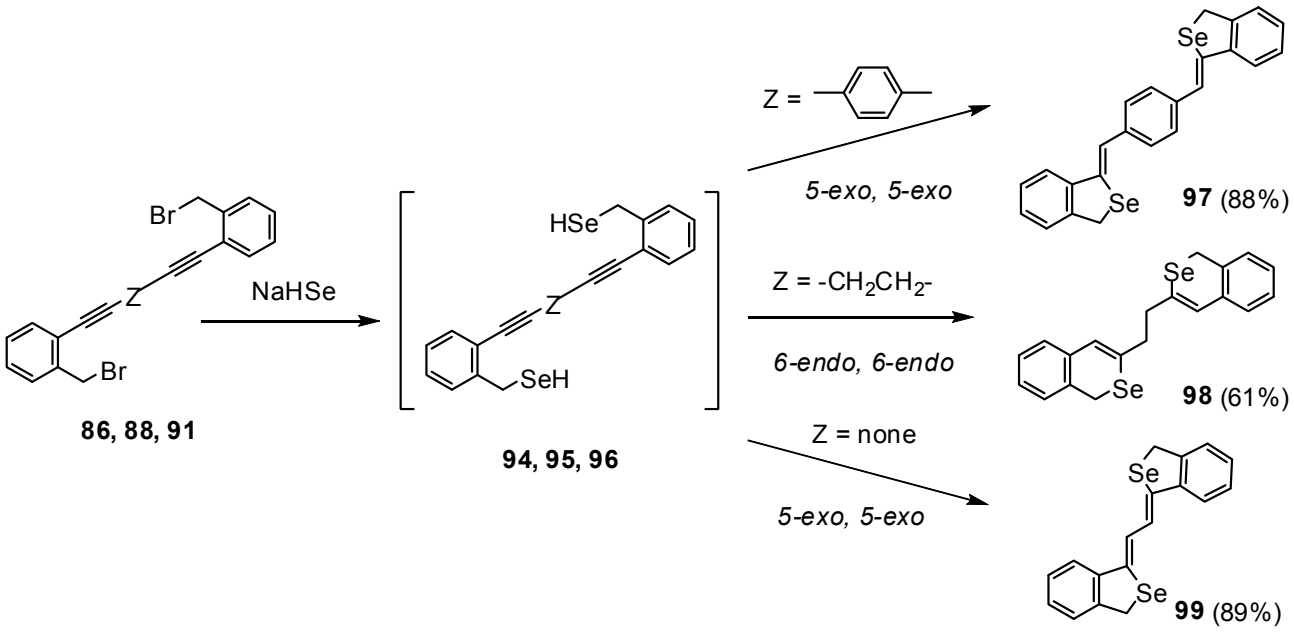


Scheme 23

containing heterocycles using the intramolecular cyclization reaction of the selenols into a triple bond, we next decided to develop a procedure for the double or tandem cyclization of dibenzyl diselenols into an ethynyl moiety.[42]

The preparation of the starting key *o*-ethynyldibenzyl bromides (**86**, **88**, **91**, **93**) is shown in Scheme 23. The Sonogashira palladium-catalyzed coupling reaction of *o*-iodobenzyl alcohol (**66**) with 1,4-diethynylbenzene, hexa-1,5-diene and *o*-ethynybenzyl alcohol (**89**), which was obtained by the desilylation of **66e**, gave the desired dibenzyl alcohols (**85**, **87**, **92**) in 72, 83 and 84% yields, respectively. Compound **66e**, when subjected to a reaction with $Cu(OAc)_2$ in pyridine-MeOH as a solvent at 100 ˚C, directly led to the diyne **90** along with removal of the TMS group in 78% yield. All benzyl alcohols **85**, **87**, **90**, **92** were readily brominated with PBr_3/pyridine to afford the key dibromides **86**, **88**, **91**, **93** in good yields.

First, in order to examine the reaction of the dibenzyl diselenol (**94**) having a benzene ring between two ethynyl moieties, its preparation was performed as shown in Scheme 24. The treatment of **86** with NaHSe in dry DMF, followed by the addition of EtOH resulted in the direct ring closure to give the benzo[*c*]selenophene derivative **97** in 88% yield without any characterized products. Compound **97** can

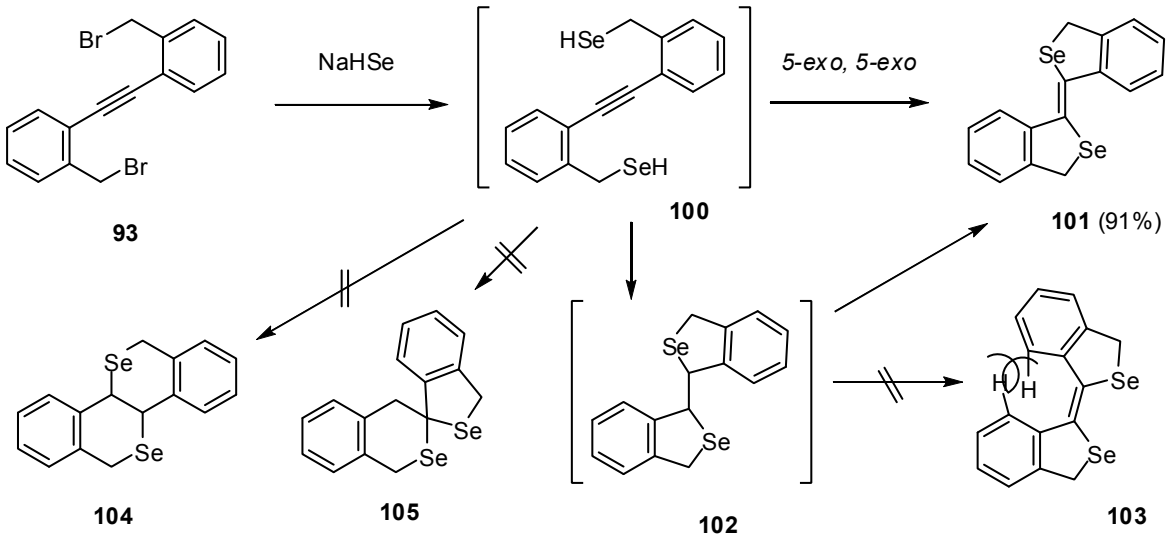


Scheme 24

be produced by the double *5-exo-dig* mode cyclization of the specific dibenzyl diselenol intermediate **94** at the sp carbon atom of the triple bond with excellent regio- and stereoselectivity.

On the contrary, the reaction of the dibromide **95**, in which two ethynyl groups are linked by the ethylene moiety, with NaHSe afforded the bis(isoselenochromenyl)ethane (**98**) which was the *6-endo-dig*,

6-endo-dig mode cyclization product, in 61% yield as the sole product. Moreover, the dibenzyl dibromide **96** having a conjugated diyne reacted with NaHSe under the same condition described above to produce the double *5-exo-dig* mode cyclization product, bi(methylidenebenzo[*c*]selenophene) (**99**) in 89% yield.



Scheme 25

The cyclization reaction of the dibenzyl diselenol (**100**) having one triple bond was finally examined. The dibromide **93** was similarly treated with NaHSe to give the *trans*-bi(benzo[*c*]selenophene) (**101**) in 91% yield without *6-endo-dig* mode ring closure product (**104**). Compound **101** will be produced by the tandem *5-exo-dig* mode cyclization of the benzyl selenol intermediate (**100**) into the triple bond with

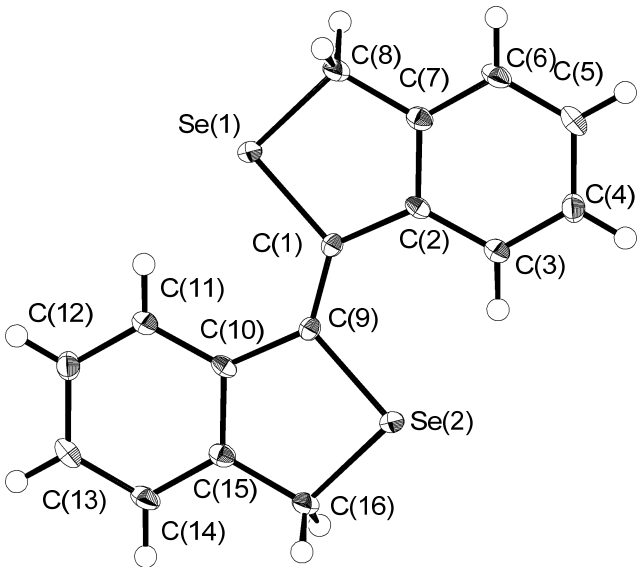


Figure 3. ORTEP drawing of **101** with 50% probability level.

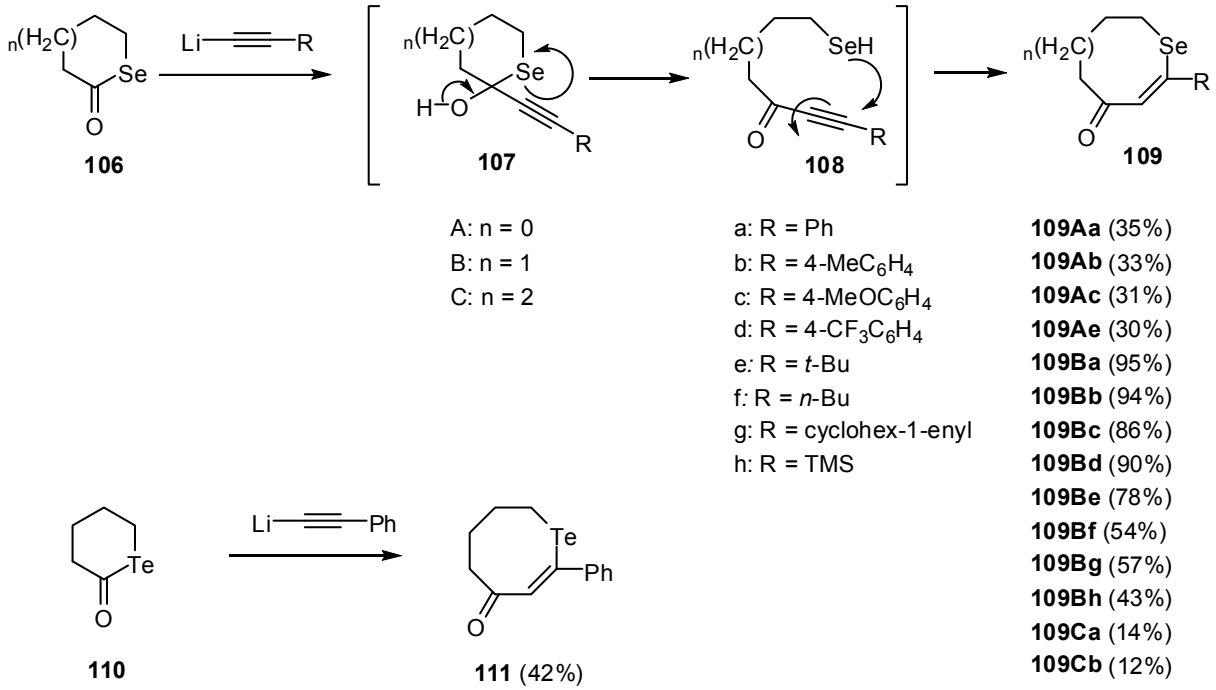
excellent regio- and stereoselectivity, followed by dehydrogenation from the essential cyclization product **102**. The formation of *trans*-**101** by the dehydrogenation of **102** is more favored than that of *cis*-**103** due to the steric hindrance between the two inner peri hydrogens of the benzene rings. The structure of *trans*-**101** including the regiochemistry of the olefin moiety was finally determined by X-ray single crystallography as shown in Figure 3.

The ORTEP drawing of **101** and crystallographic data were not given in the original paper,[42] so they are newly provided here.

In all cases of the reaction of the dibromides **86**, **88** and **91** with NaHSe, the mixed ring closure reactions of the *5-exo* and *6-endo* modes did not proceed; no spiro compound **105** was obtained from **93**.

8. TWO CARBONS RING GROWING OF SELENOLACTONES

Here, we describe the novel method involving the one-pot synthesis of selenium-containing medium-sized α,β–unsatutated cyclic ketones[43] by the intramolecular ring closure of selenols, which were generated in situ from selenolactones and ethynyllithiums in this section as shown in Scheme 26.



Scheme 26

The selenolactones (**106**) were easily prepared from the commercially available lactones *via* the bromocarboxylic chlorides, which were treated with NaHSe. Compounds **106** were lithiated with ethynyllithium, followed by the addition of aqueous 5% H_2SO_4 as a proton source to produce the two

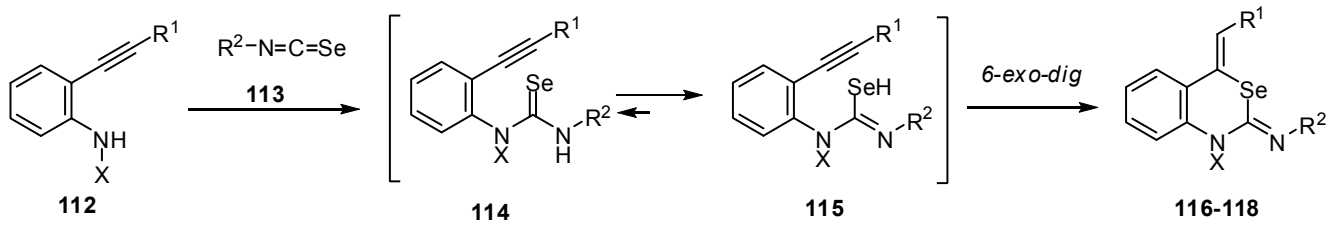
carbon ring enlargement products **109**. In general, eight-membered ring cyclic ketones **109B** were obtained from six-membered selenolactones (**106B**) in good to high yields. The ring-expansion reaction of the five- and six-membered selenolactone having a methyl group at the α– or δ– position was also carried out (12 examples); the seven- and eight-membered α,β–unsatutated cyclic ketones were similarly produced in yields ranging from 31% to 82%. The formation of the ring expanded products **109** from the selenolactones (**106**) is the following; the hydroxyselenacycloalkane (**107**) probably generated by nucleophilic attack of the ethynyllithium at the carbonyl carbon of **106**, and then hydrolyzed, undergoes ring opening with migration of the hydroxy proton to form the ethynylselenol (**108**). The regioselective intramolecular cyclization of the resulting selenol **108** to a triple bond of the ynone moiety proceeds *via* the Michael-type addition in the *endo-dig* mode to give the successful α,β-unsaturated selenacycloalkanone (**109**). The telluro analogue, tellurocin-4-one (**111**) was also obtained from the tellurolactone (**110**) in 42% yield.

9. 3-SELENA-1,2,3,4-TETRAHYDROQUINOLINES

1,3-Selenazines, which are a six-membered heterocyclic compound containing two heteroatoms, nitrogen and selenium, display significant bio-activities;[44] e.g., anti-bacterial activity against both Gram-negative and Gram-positive bacteria and potential anti-tumor effects against human cancer cells.

In this chapter, we now describe the practical solvent-free non-catalyzed one-pot preparation of the 3-selenaquinoline derivatives,[45] benzo-analogues of 1,3-selenazines by the intramolecular cyclization of the selenols, which are generated from the *o*-ethynylanilines and the isoselenocyanates as the selenium source. Isoselenocyanates are a powerful tool for the preparation of selenium-containing heterocycles because of their ease of preparation, storage, lower-toxicity and safety of handling, and recently introduced their utility in the review article.[46]

The *o*-ethynylanilines (**112**) were heated at 130 ˚C with the cyclohexyl isoselenocyanate (**113A**), a secondary aliphatic isoselenocyanate, under solvent-free conditions (method II) to afford 2-imino-3-selenaquinolines (**116**) in yields ranging from 47% to 88%; **116** were also obtained by the normal reaction conditions, in refluxing xylene (method I) in nearly similar yields (Table 2). The plausible mechanism for the formation of the selenaquinolines (**116**) from the anilines (**112**) and the isoselenocyanate **113A** is shown in Scheme 27. The initial adduct, 3-phenylselenourea (**114**), probably generated by nitrogen nucleophilic attack of the aniline **112** at the sp carbon of the isoselenocyanate **113A**, undergoes tautomerism with migration of the phenyl NH proton to form the iminoselenol **115**. The regio- and stereoselective intramolecular cyclization of the resulting selenol **115** into a triple bond proceeds *via* the *6-exo-dig* mode to give the successful 3-selenaquinoline (**116**). No *7-endo-dig* mode cyclization



Scheme 27

Table 2. 4-Methylidene-3-selena-1,4-dihydroquinolines (**116**)

Entry	X	R^1	R^2	Method[a]	Time	Product	Yield (%)[b]
1	H	*n*-Bu	*c*-Hex	I	6.5 h	**116Aa**	52
2	H	*n*-Bu	*c*-Hex	II	4 h	**116Aa**	88
3	H	*n*-Bu	*c*-Hex	III	25 min	**116Aa**	87
4	H	*n*-Bu	*n*-Bu	I	22 h	**116Ba**	44
5	H	*n*-Bu	*n*-Bu	II	7 h	**116Bb**	62
6	H	*n*-Bu	*t*-Bu	I	7 h	**116Ca**	0[c]
7	H	*n*-Bu	*t*-Bu	II	7 h	**116Cb**	0[c]
8	H	*n*-Bu	Ph	I	3.5 h	**116Da**	43
9	H	*n*-Bu	Ph	II	3.5 h	**116Db**	51
10	H	Me	*c*-Hex	II	8 h	**116Ab**	63
11	H	Me	*c*-Hex	III	26 min	**116Ab**	54
12	H	*t*-Bu	*c*-Hex	II	11 h	**116Ac**	53
13	H	*t*-Bu	*c*-Hex	III	34 min	**116Ac**	59
14	H	Ph	*c*-Hex	II	13 h	**116Ad**	68
15	H	Ph	*c*-Hex	III	48 min	**116Ad**	72
16	H	TMS	*c*-Hex	II	20 h	**116Ae**	47
17	H	TMS	*c*-Hex	III	26 min	**116Ae**	53
18	H	H	*c*-Hex	II	16 h	**116Af**	51
19	H	H	*c*-Hex	III	28 min	**116Af**	46
20	H	Ph	Ph	II	2.5 h	**116Dd**	87
21	Me	*n*-Bu	*c*-Hex	II	20 h	**117Aa**	0[d]
22	Bn	*n*-Bu	*c*-Hex	II	20 h	**118Aa**	0[d]

[a]Method I: xylene, reflux; method II: neat, 130 ˚C; method III: microwave irradiation at 115 ˚C.

[b]Isolated yield.

[c]Decomposed.

[d]No reaction.

products were obtained in this case. When the *o*-ethynylanilines (**112**) were similarly heated with the *n*-butyl (**113B**) and phenyl isoselenocyanate (**113C**) without a solvent, the corresponding 3-selenaquinolines (**106**) were obtained in moderate yields (9 examples). However, *tert*-butyl isoselenocyanate (**113D**) reacted with the anilines (**112**) to give a complex mixture without any characterized products (entries 6 and 7). Furthermore, no 1-substituted selenaquinolines (**117**, **118**) were also produced by the reaction of *N*-methyaniline and *N*-benzylaniline with isoselenocyanete **113** (entries 20 and 21).

In this reaction, the microwave-assisted (method III) synthesis of **116** was efficient and more effective, and the results indicate the following benefits; (1) a reduced reaction time from 1 h to almost within 30 minutes; (2) a solvent-free system; and (3) the products could be directly obtained by a short chromatography purification.

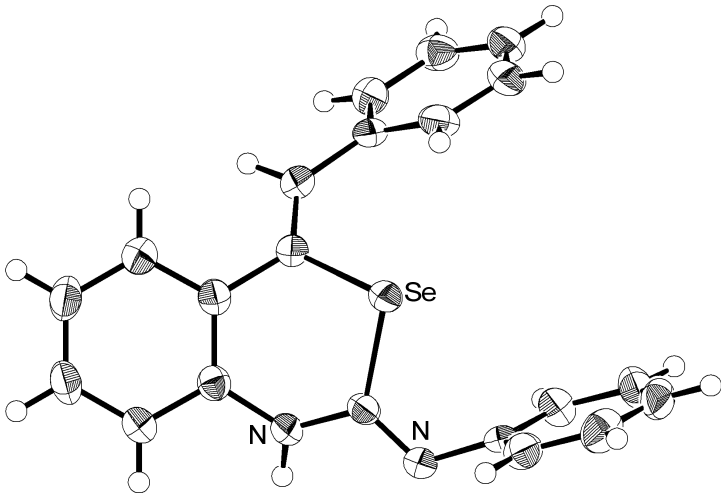


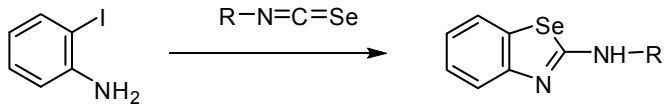
Figure 4. ORTEP drawing of **116Dd**

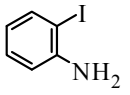
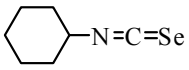
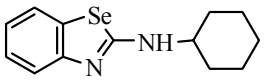
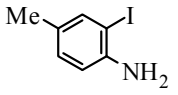
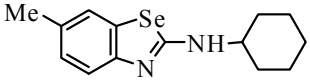
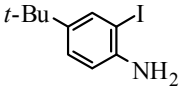
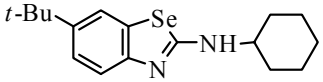
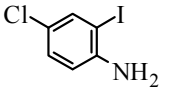
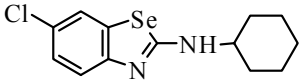
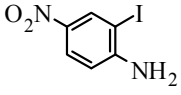
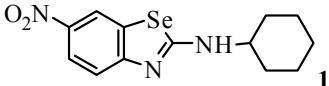
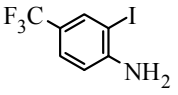
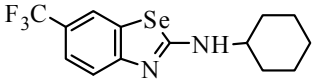
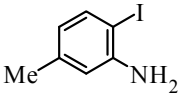
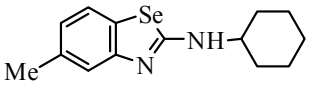
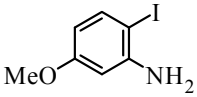
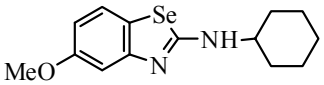
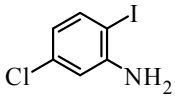
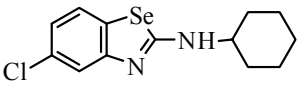
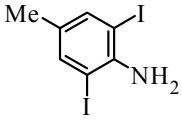
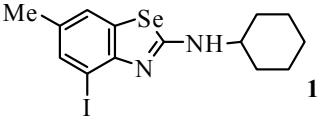
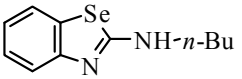
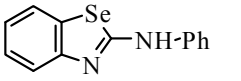
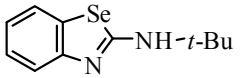
The structure of **116** including the regiochemistries of the olefin moiety and the C=N bond was finally determined by X-ray single crystallography[29] using **116Dd** as shown in Figure 4.

10. 1,3-BENZOSELENAZOLES

Next, an efficient and simple preparation of the 2-amino-1,3-benzoselenazoles[47] by the copper catalyzed one-pot reaction of 2-iodoanilines and isoselenocyanates is described in this chapter. There are only a few reports on the preparation of the 2-substituted benzoselenazoles[48] and related compounds,[49] and their chemistry still remains unknown. After a careful survey to optimize the reaction conditions, the combination of copper(II) triflate [$Cu(OTf)_2$] and Cs_2CO_3 in refluxing xylene was found to be the best conditions for this tandem addition-cyclization reaction for the synthesis of 2-aminobenzoselenazoles.

Table 3. 2-Aminobenzoselenazoles (**120**)

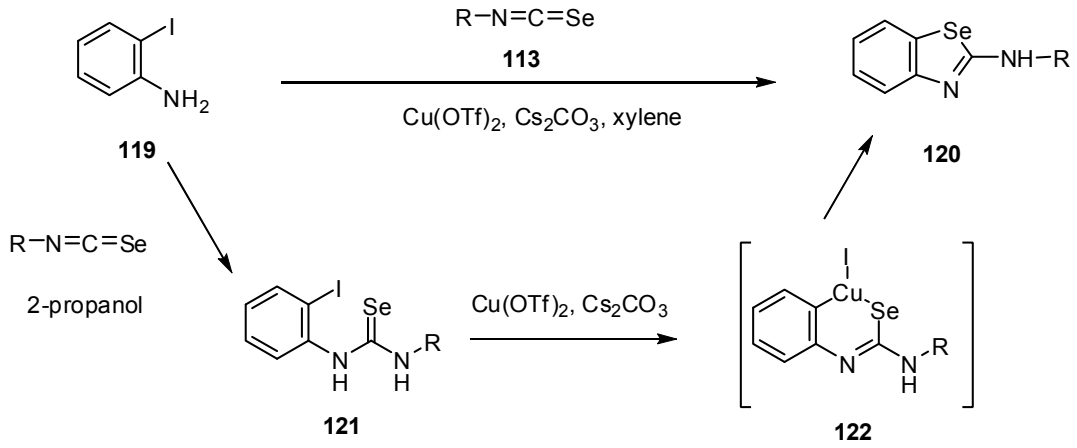


Entry	Anilines	Isoselenocyanate	Product	Yield (%)[a]
1	 **119a**	 **113A**	 **120Aa**	97
2	 **119b**	**113A**	 **120Ab**	90
3	 **119c**	**113A**	 **120Ac**	91
4	 **191d**	**113A**	 **120Ad**	87
5	 **119e**	**113A**	 **120Ae**	63
6	 **119f**	**113A**	 **120Af**	50
7	 **119g**	**113A**	 **120Ag**	83
8	 **119h**	**113A**	 **120Ah**	78
9	 **119i**	**113A**	 **120Ai**	93
10	 **119j**	**113A**	 **120Aj**	62
11	**119a**	*n*-Bu−N=C=Se **113B**	 **120Ba**	57
12	**119a**	Ph−N=C=Se **113C**	 **120Ca**	77
13	**119a**	*t*-Bu−N=C=Se **113D**	 **120Da**	3

[a]Isolated yield.

The extension of this reaction to 2-iodoanilines having various functional groups involving an electron-withdrawing and -donating group at the C-4 or C-5 position with some isoselenocyanates was carried out, and the results are summarized in Table 3.

The primary aliphatic isoselenocyanate, *n*-butyl isoselenocyanate (**113B**), and aromatic isoselenocyanate (**113C**) also reacted with 2-iodoaniline (**119a**) to afford the corresponding 2-aminobenzoselenazoles (**120Ba** and **120Ca**) in 57 and 77% yields, respectively. However, replacing the isoselenocyanate by *tert*-butyl isoselenocyanate (**113D**) gave a complex mixture involving a slight yield of 2- *tert*-butylamino-selenazole (**120Da**); the starting 2-iodoaniline (**119**) was recovered because of the gradual decomposition of the isoselenocyanate under the same conditions. The lower reactivity of *tert*-butyl isoselenocyanate (**113D**) may be due to the steric hindrance by the bulky tertiary butyl group. A possible mechanism for the 2-aminoselenazoles (**120**) from **119** and **113** is shown in Scheme 28.



Scheme 28

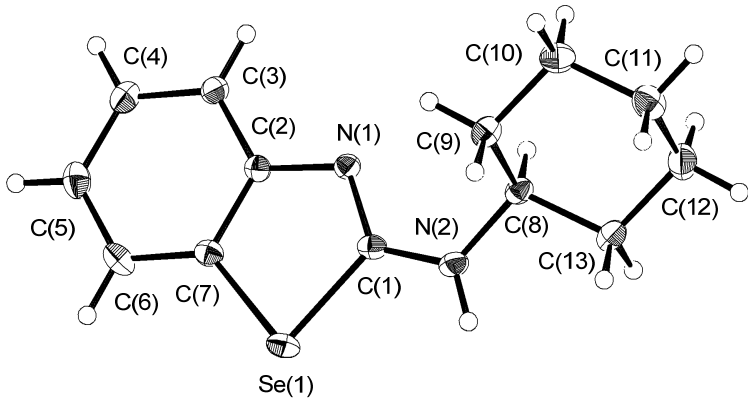


Figure 5. ORTEP drawing of **120**

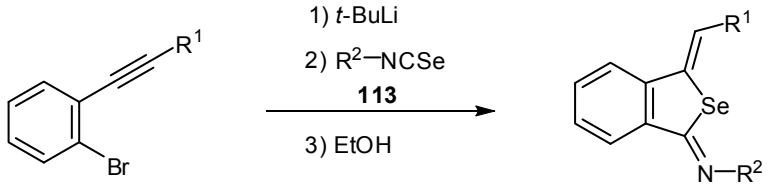
The structures of these 2-aminobenzoselenazoles (**120**) were determined by their spectra and elemental analyses and finally established by single-crystal X-ray studies using cyclohexyl derivative (**120Aa**).[28]

11. BENZO[*c*]SELENOPHENES

The synthesis of the benzo[*c*]selenophene derivatives by the tandem addition-cyclization of the *o*-ethynylphenyllithiums and the isoselenocyanates was achieved.[50] The reaction of isoselenocyanates with the active methylene compounds such as a malononitrile and cyanoacetate is well known.[51] However, there are only a few reports on the reaction with a carbanion.[52] The *o*-bromopropynylbenzene (**25a**) was lithiated with *tert*-BuLi in anhydrous Et_2O, followed by treatment with cyclohexyl isoselenocyanate (**113A**) at room temperature, and then ethanolyzed to give the desired (*Z*)-3-methylidenebenzo[*c*]selenophene (**123Aa**) in 78% yield in a one-pot reaction (Table 1, entry 1).

When **25b** was similarly treated with **113A** in anhydrous Et_2O, **123Ab** was produced in 61% yield (entry 2). On the contrary, use of anhydrous THF as a solvent gave the benzo[*c*]selenophene (**123Ab**) in only 13% yield; no starting material was recovered (entry 3). Similarly, this tandem addition-cyclization of *o*-ethynylphenyl lithiums (**25c-e**) having *tert*-butyl, phenyl and TMS groups at the triple bond with cyclohexyl isoselenocyanate (**2A**) proceeded to afford the corresponding (*Z*)-3-methylidenebenzo[*c*]-selenophenes (**123Ac-e**) in good to high yields (entries 4-6). The reaction of *o*-bromohexynylbenzene (**25b**) with *n*-butyl isoselenocyanate (**113B**), the primary aliphatic isoselenocyanate, also occurs under the same conditions to afford the selenophene **123Ba** in 54% yield (entry 7). However, the use of *tert*-butyl

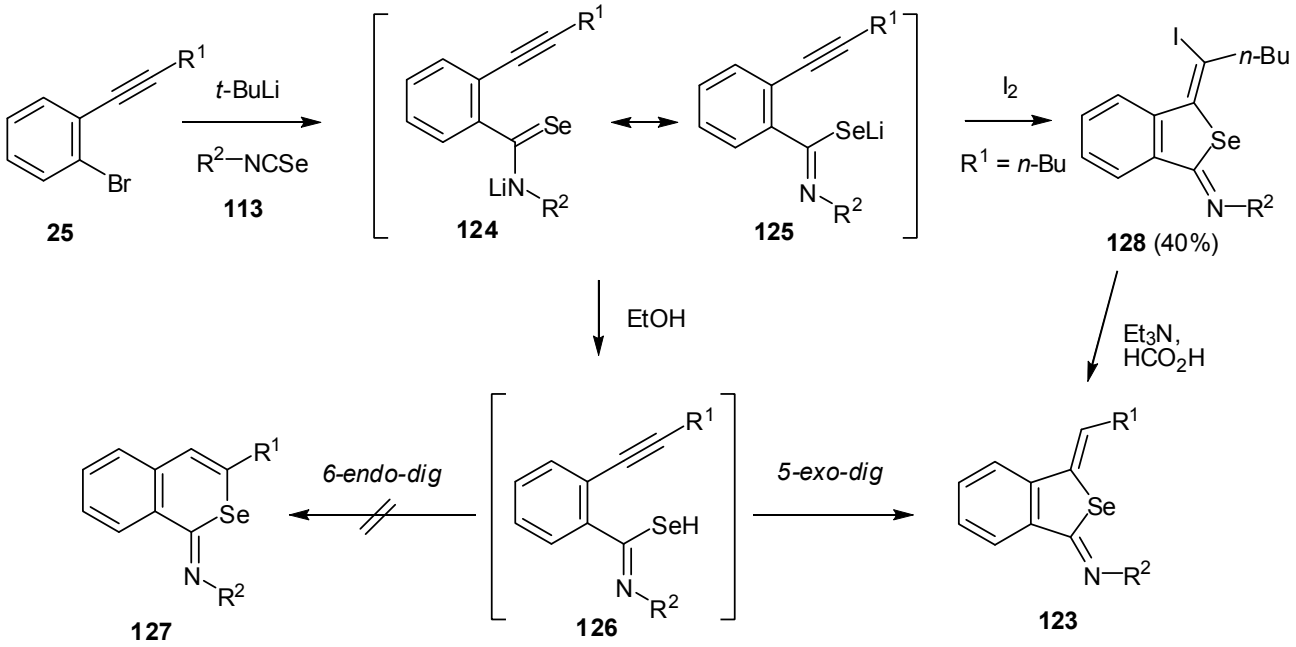
Table 4. 3-Methylidenebenzo[*c*]selenophenes (**123**)



Entry	Substrate	Isoselenocyanate	Solvent (temp.)	Product	Yield (%)[a]
1	**25a** (R^1 = Me)	**113A** (R^2 = *c*-Hex)	Et_2O (r.t.)	**123Aa**	78
2	**25b** (R^1 = *n*-Bu)	**113A**	Et_2O (r.t.)	**123Ab**	61
3	**25b**	**113A**	THF (r.t.)	**123Ab**	13
4	**25c** (R^1 = *tert*-Bu)	**113A**	Et_2O (r.t.)	**123Ac**	85
5	**25d** (R^1 = Ph)	**113A**	Et_2O (r.t.)	**123Ad**	69
6	**25e** (R^1 = TMS)	**113A**	Et_2O (r.t.)	**123Ae**	83
7	**25b**	**113B** (R^2 = *n*-Bu)	Et_2O (r.t.)	**123Bb**	54
8	**25b**	**113C** (R^2 = *tert*-Bu)	Et_2O (r.t.)	**123Cb**	---
9	**25b**	**113D** (R^2 = Ph)	Et_2O (r.t.)	**123Db**	2
10	**25b**	**113D**	Et_2O (reflux)	**123Db**	64

[a]Isolated yield.

isoselenocyanate **113C** gave a complex mixture; no corresponding selenophene **123Ca** was obtained (entry 8). The lower reactivity of *tert*-butyl isoselenocyanate (**113C**) may be due to the steric hindrance by the bulky tertiary butyl group. Although **25a** also reacted with phenyl isoselenocyanate (**113D**) to produce the phenylimino derivative **123Da** in Et_2O at room temperature in only 2% yield, **123Da** was obtained in refluxing Et_2O in 64% yield (entry 9 vs. 10).

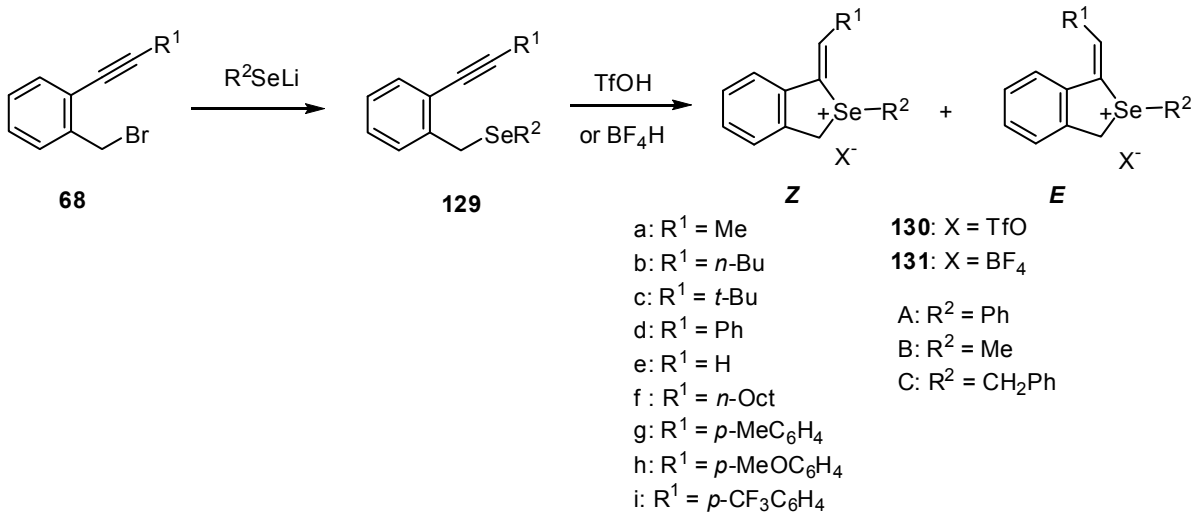


Scheme 29

Next, the iodocyclization of *o*-ethynylphenyllithiums with isoselenocyanates (**113**) was found to proceed affording the (*E*)-1'-iodo-3-methylidenebenzo[*c*]selenophenes (**128**) stereoselectively as shown in Scheme 29. *o*-Ethynylphenyllithium generated from **25b**[16] was similarly treated with cyclohexyl isoselenocyanate (**113A**) and then protonated with *t*-BuOH, followed by iodination with I_2, gave the desired (*E*)-1'-iodobenzo[*c*]selenophene (**128**) in a one-pot reaction in 40% yield. This iodobenzo[c]selenophene (**128**) can be reduced to **123** by treatment with HCOOH/Et_3N in the presence of a palladium catalyst and further functionalized by palladium-catalyzed Suzuki and Sonogashira coupling reactions.

12. BENZO[*c*]SELENOPHENIUM SALTS

As an extension of our more ongoing work, the high regioselective *5-exo-dig* mode electrophilic ring-closure reaction of the benzyl selenides, in which the hydrogen of the selenol is replaced by a phenyl group, is described in the final section of this review as shown in Scheme 30.[53]



Scheme 30

Table 5. 1-Methylidene-2-phenyl-1,3-dihydro1*H*-benzo[*c*]selenophenium Salts (**130**, **131**)

Entry	R^1	R^2	Acid	Product	Yield %[a]	Ratio *Z*:*E*[b]
1	Ph	Me	TfOH	**130Aa**	76	4:1
2	Ph	*n*-Bu	TfOH	**130Ab**	71	4:1
3	Ph	*t*-Bu	TfOH	**130Ac**	82	4:1
4	Me	*t*-Bu	TfOH	**130Bc**	0[c]	-
5	CH_2Ph	*t*-Bu	TfOH	**130Cc**	0[c]	-
6	Ph	*t*-Bu	BF_4H	**131Ac**	-	5:3
7	Ph	Ph	TfOH	**130Ad**	78	1:0
8	Ph	H	TfOH	**130Ae**	77	-
9	Ph	*n*-Oct	TfOH	**130Af**	78	4:1
10	Ph	*p*-MeC_6H_4	TfOH	**130Ag**	92	1:0
11	Ph	*p*-$MeOC_6H_4$	TfOH	**130Ah**	78	1:0
12	Ph	*p*-$CF_3C_6H_4$	TfOH	**130Ai**	73	1:0

[a]Isolated yield.

[b]Determined by ^1H NMR spectra.

[c]Decomposed.

The starting materials, *o*-ethynylbenzyl phenyl selenides (**129A**) were readily synthesized in good yields by the coupling reaction of the benzyl bromides (**68**)[32c] with lithium phenylselenolate, which was freshly generated from elemental selenium and phenyllithium in dry THF. The reaction of the *o*-ethynylbenzyl

phenyl selenides (**129A**) having an alkyl group at the ethynyl moiety with a small excess of TfOH in CH_2Cl_2 at 0 ˚C provided the *5-exo-dig* mode cyclization products, (*Z*)-1-methylidene-2-phenyl-1*H*-benzo[*c*]selenophenium triflates (***Z*-130**) as major products, together with the *E*-derivatives ***E*-130** (Table 5, entries 1-3). However, a similar treatment of methyl selenide (**129B**) and benzyl selenide (**129C**) with TfOH resulted in decomposition to give a complex mixture without any identifiable products (entries 4, 5).

The structures of these 2-phenyl-1,3-dihydro1*H*-benzo[*c*]selenophenium salts (**130**) were determined by their spectra and elemental analyses and were finally established by single-crystal X-ray studies using the *t*-butyl derivative (**130Ca**).[29]

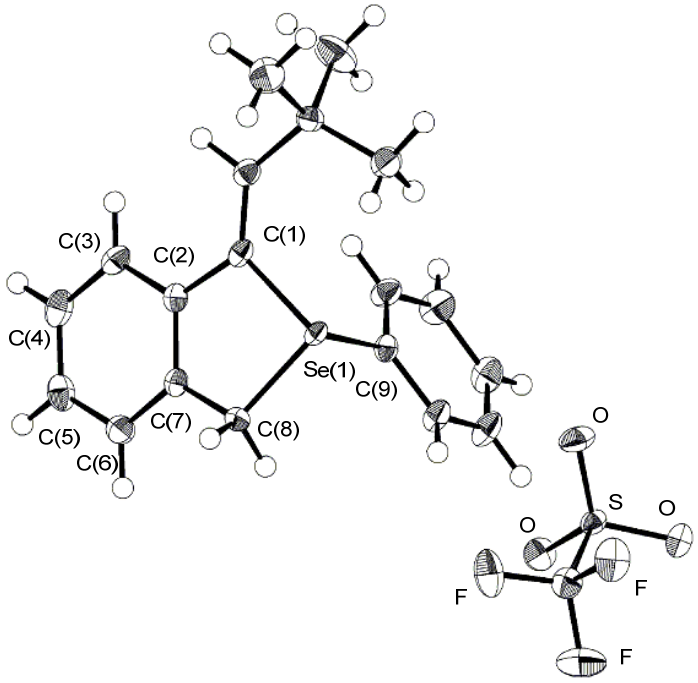


Figure 6. ORTEP drawing of **130Ca**

13. CONCLUSION

Recent advances in our laboratory concerning the preparations of the selenium-containing heterocycles, e.g., 1-benzoselenepines, benzo[*b*]selenophenes, selenophthalides, selenochromones, isoselenochromenes, γ-selena-α,β-unsaturated cyclic ketones, 3-selenaquinolines, benzoselenazoles and other related compounds were reviewed. The simple and versatile synthetic methods for the selenaheterocycles are mainly based on our original intramolecular cyclization of selenols to a triple bond and using isoselenocyanates as a selenium source. I hope that this review will be useful and helpful to synthetic, heterocyclic and also medicinal chemists.

14. ACKNOWLEDGEMENTS

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