Evaluation of *peri*-like fluorene and carbazole diselenides as glutathione peroxidase mimics

by

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Acknowledgments

So here it is, the summation of 3 years of work and of my life. There were points where I didn't think I would make it this far, but somehow, I made it.

Firstly, I would like to offer my endless gratitude to Dr Richard Grainger, for providing me an opportunity to do a PhD when many others passed me over for consideration. Richard has been a fantastic mentor, without his guidance, optimism and boundless enthusiasm for chemistry this thesis would not have been possible.

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Lastly, I would like to thank my late uncle Saudagar Jagdev for pointing me in the direction of chemistry. I really wish he was around to see the fruits of my labours.

Abstract

This thesis reports the synthesis and evaluation of 4, 5-disubstituted fluorene and carbazole diselenides as GPx mimics.

Chapter 1 describes the role of glutathione peroxidase as an important mammalian antioxidant and investigations towards developing organoselenium molecules as glutathione peroxidase mimics. Chapter 2 describes the preparation of 4,5-disubstituted fluorene diselenides *via* a dilithiation reaction, as well as the oxidation of these diselenides using *m*CPBA to monoxides and seleninic anhydrides. A DTT oxidation assay with these compounds showed that the fluorene diselenides have similar activity to the 1,8-naphthalene diselenides developed by Back. Studies have shown that the selenic anhydrides act as precatalysts in the reaction.

Chapter 3 reports the elaboration of carbazoles into diselenides via regioselective 4,5-dilithiation. This transformation is made possible by protecting the carbazole with a TIPS protecting group. Further elaboration of the carbazole scaffold gave compounds that were water-soluble. Additionally, two fluorene diselenides were made water-soluble. A water-based NMR assay were used to determine the catalytic activity of the water-soluble species.

Abbreviations

Å	angström
Ac	acetyl
Ad	adamantyl
ap.	apparent
aq.	aqueous
ASAP	Atmospheric Solids Analysis Probe
br	broad
Bu	butyl
Boc	*tert*-butyloxycarbonyl
c.	concentrated
C	Celsius
cat.	catalytic
d	doublet
DMEDA	1,2-dimethylethylenediamine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DTT	dithiothreitol
EDG	electron-donating group
EI	electron impact
equiv.	equivalent
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
FT-IR	fourier transform infrared
g	gramme(s)
GPx	glutathione peroxidase
GSH	glutathione

GSSG	glutathione disufide
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HSAB	hard and soft acids and bases
HSQC	heteronuclear single quantum coherence
Hz	hertz
i	iso
IR	infrared
J	coupling constant (in NMR)
L	litre
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
m	*meta*
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
mol	moles
mp	melting point
m/z	mass/charge
n	normal
NADPH	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
[O]	oxidation
o	*ortho*

p	*para*
pet ether 60-80 °C	petroleum ether
Ph	phenyl
ppm	part(s) per million
Pr	propyl
q	quartet
quant.	quantitative
rt	room temperature
ROS	reactive oxygen species
r.d.s.	rate-determining step
s	singlet
SOD	superoxide dismutase
STAB	sodium triacetoxyborohydride
t	*tert*
t	triplet
*t*BuOOH	*tert*-butyl hydroperoxide
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
*p*TsOH	*p*-toluenesulfonyl
u	atomic mass unit
UV	ultraviolet
vs.	versus
v	frequency

Contents

Chapter 1 Selenium-containing compounds as a glutathione peroxidase mimic

1.1 Oxidative stress and glutathione peroxidases

Reactive oxygen species (ROS) are classically defined as oxygen containing radicals capable of independent existence with one or more unpaired electrons.[1] The definition of ROS has been expanded to include compounds without unpaired electrons; such as hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$).[1] ROS are often generated as by-products in cells during aerobic respiration.[1, 2] These by-products include superoxide radicals ($O_2^{\bullet-}$), H_2O_2 and hydroxyl radicals ($^{\bullet}OH$). ROS are known to oxidise enzymes, nucleic acids and proteins leading to cellular damage. Superoxide radicals ($O_2^{\bullet}$) are generated upon the reduction of O_2 (Scheme 1, Reaction 1).[1] Superoxide causes the inactivation of enzymes such as glutathione peroxidase (GPx), and the oxidation of intracellular components, but it cannot damage DNA directly. Superoxide dismutase (SOD) catalyses the reduction of $O_2^{\bullet-}$ to H_2O_2 and O_2 (Scheme 1, Reaction 2). Hydrogen peroxide is not a radical species and is relatively stable. Hydrogen peroxide will oxidise proteins causing cellular damage. Cellular enzymes such as glutathione peroxidase scavenge H_2O_2 by reducing it to H_2O (Scheme 1, Reaction 3). Hydrogen peroxide can also be reduced by intracellular transition metal active ions to produce hydroxyl radicals ($OH^{\bullet}$) in a Fenton reaction (Scheme 1, Reaction 4).[3,] Hydroxyl radicals ($OH^{\bullet}$) are very reactive; oxidising lipids, proteins and nucleic acids. Significant DNA damage has also been reported.[3, 4]

(1) $O_2 + e^- \rightarrow O_2^{\bullet-}$

(2) $2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2$

(3) $2H_2O_2 \rightarrow 2H_2O + {}^1O_2$

(4) $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^-$

Scheme 1 Reactive oxygen species (ROS) generation and decomposition reactions

The accumulation or imbalance of ROS is known as oxidative stress. If ROS are left to accumulate they can cause damage to cellular structures, nucleic acids, lipids and proteins; damage to these cellular components can lead to medical conditions such as cancer and neurodegenerative diseases.[1,5] Medical conditions such as cancer, cystic fibrosis and atherosclerosis have been shown to compromise the cellular radical scavenging systems exacerbating the imbalance of ROS, causing further tissue damage.[6,7]

Cells maintains ROS levels with a sophisticated antioxidant regulation system.[7] Cells employ enzymes that act as radical scavengers such as glutathione peroxidase (GPx, Figure 1). This enzyme family contains selenium in the form of selenocysteine (Sec) **1**. Glutathione peroxidase (GPx) works in conjunction with glutathione (GSH) **2**; GSH is a tripeptide (comprising cysteine, glutamic acid, and glycine) which is the most abundant thiol within a cell (Figure 1). Glutathione (GSH) is a major component in cellular antioxidant systems acting as a cofactor for GPx; acting as a scavenger for endogenous radical species.[8] Currently eight forms of GPx have been identified, five are selenoenzymes (GPx1-4 and GPx6).[9] The first selenoprotein identified was GPx1.[10] This isozyme is located in the cytosol and the mitochondrion. This isozyme is known to reduce H_2O_2 and fatty acid hydroperoxides. GPx2 is present in epithelial tissue located in the gastrointestinal tract. GPx3 is found in plasma. GPx4 is expressed ubiquitously through a number of tissues.[11] GPx4 is unique amongst the GPx isoforms as it is the only one capable of esterifying oxidised fatty acids.[11] GPx5, 7 and 8 are thiol enzymes which contain no selenium. GPx6 is only found in adult olfactory epithelium and developing human embryos.[12] GPx1-3 are homotetrameric species while GPx4 is monomeric.

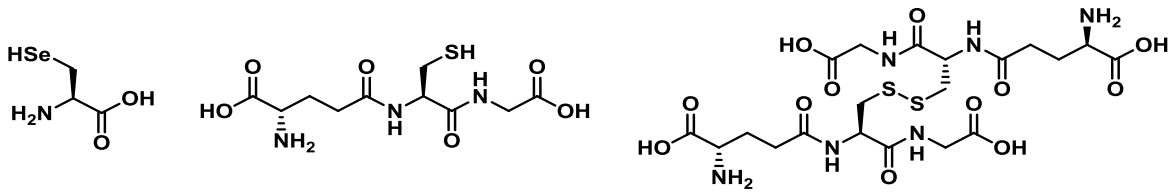
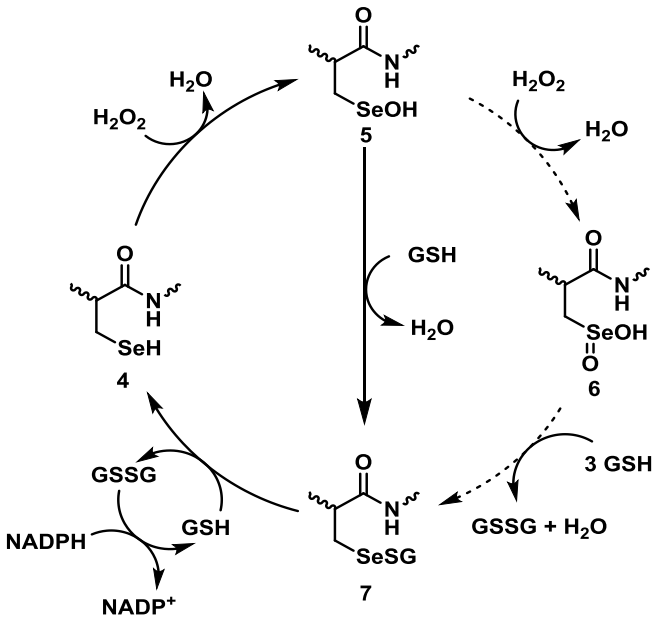


Figure 1 Structures of selenocysteine **1,** glutathione **2** and glutathione disulfide **3**

The reduction of H_2O_2 mediated by GPx has been investigated. The catalytic mechanism is shown below (Scheme 2).[13] Selenol **4** is oxidised to selenenic acid **5** by H_2O_2 generating water. Selenenic acid **5** in turn reacts with cofactor thiol (GSH) producing selenenylsulfide **7**. Selenenylsulfide **7** reacts with GSH regenerating selenol **4**, generating glutathione disulfide **3** (GSSG) in the process. Glutathione disulfide is reduced by NAPDH, regenerating cofactor GSH. In the presence of excess H_2O_2, seleninic acid **5** is oxidised to seleninic acid **6**, which is catalytically inactive. This intermediate reduces the catalytic activity of GPx. Rapid conversation of seleninic acid **6** to selenenylsulfide **7**, by sequential reductions, is therefore important to maintaining the activity of the enzyme.[14,15]



Scheme 2 Reduction of H_2O_2 mediated by GPx

Due to the integral role of GPx in mammalian antioxidant defence, significant attention has been directed towards mimicking the function of selenocysteine, towards the goal of developing therapeutic drug molecules. The applications of such molecules would be the treatment of oxidative stress induced ischemia-reperfusion injuries caused by blood supply returning to hypoxic tissue; furthermore, these molecules could also treat patients with compromised cellular radical scavenging systems.[1]

1.2 Organoselenium Compounds as GPx Mimetics

The first organoselenium compound reported for its neuroprotective properties was ebselen **8**; pharmacological investigations of this compound began in the 1980's.[10, 11, 16, 17] The catalytic cycle of ebselen-mediated H_2O_2 reduction has been extensively interrogated (Scheme 3); like GPx, the reduction of peroxides by ebselen is dependent on a thiol cofactor.[12, 18, 19] Ebselen initially reacts with a thiol to give a selenenylsulfide **9**; this species then disproportionates to diselenide **10** and generates PhSSPh. Diselenide **10** is then oxidised by two equivalents of H_2O_2 to give selenenic acid **11**, which reacts with either PhSH to give selenenylsulfide **9** or undergoes an intramolecular cyclisation to ebselen **8**. In this cycle the rate-determining step is the formation of diselenide **10**.

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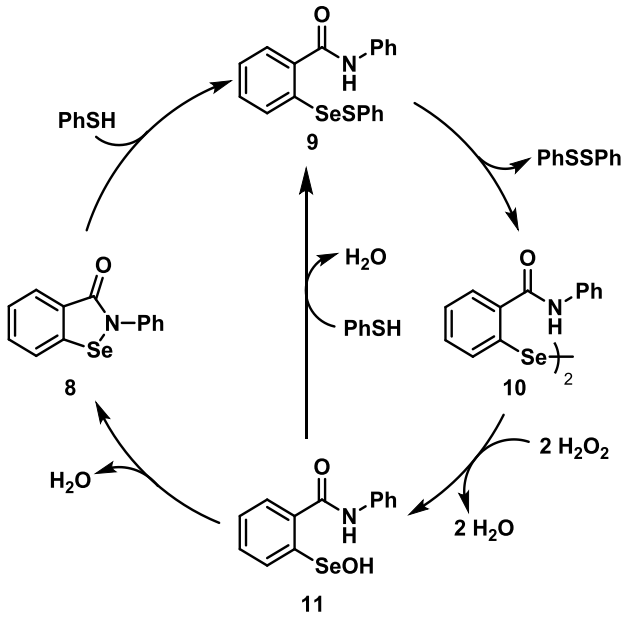
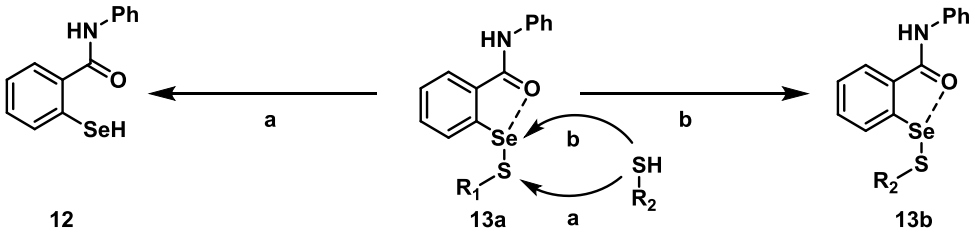


Scheme 3 Catalytic cycle of ebselen

Subsequent investigations have revealed that ebselen is a relatively inefficient catalyst (Scheme 4).[13] Studies conducted by Mugesh have shown that poor catalytic activity is due to a thiol exchange reaction that takes place at selenenylsulfide **13a** (Scheme 4). Nucleophilic attack by thiols at the selenium atom is disfavoured and will not produce any selenol **12**. This is due to the presence of strong Se–O non bonding interactions in intermediate **13a** which makes the selenium atom more electropositive, facilitating attack at the selenium atom, leading to a thiol exchange reaction. Despite trials showing ebselen as a non-toxic compound, it has shown a lack of activity and poor water solubility in trial assays.[14,20]



Scheme 4 Reduction of catalytic activity of ebselen via thiol exchange

The selenylsulfide exchange pathway shows an important feature of organoselenium chemistry relating to the design of GPx mimics. Polarisation of the selenium-sulfur bond dictates the reactivity of the selenenylsulfide intermediate; if the selenium atom is the most δ+, then the thiol exchange reaction is dominant reducing the reactivity of the catalyst. The presence of Se–O and Se–N non bonding interactions influences the dipole direction of the selenium-sulfur bond. Mugesh investigated the effects of different thiols and the influence of neighbouring group participation on the nature of the selenium-sulfur bond.[21] The calculated ^{77}Se NMR chemical shift for **13** (604 ppm) is shifted substantially downfield compared to that of PhSeSPh (437 ppm). This suggests that the amide group interaction is increasing the electropositive character of the selenium atom in **13**.

Due to the importance of ebselen there has been significant interest in synthesising analogues which have improved catalytic profiles. Mugesh evaluated the catalytic effect of different nitrogen substituents with the unaltered core structure of ebselen (Figure 2).[22, 23] The catalytic activity of these compounds was tested using H_2O_2, *tert*-butyl hydroperoxide (*t*BuOOH) or cumene hydroperoxide (Cum-OOH) as substrates. GSH or PhSH were used as thiol cofactors. These studies showed that the nature of the peroxide had little effect on the catalytic activity of the test compounds. Assays using PhSH as a cofactor showed that compounds **14-18** had similar activities to that of ebselen. This was contrasted with the GSH assay, which showed significantly variable activities for each compound. Compound **14** showed activity that was lower than ebselen indicating that substitution on nitrogen is required for high catalytic activity. Compounds **15-18** all displayed activities at least twice than that of ebselen.

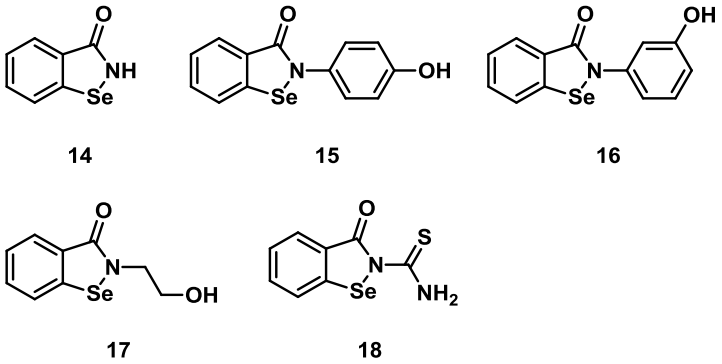
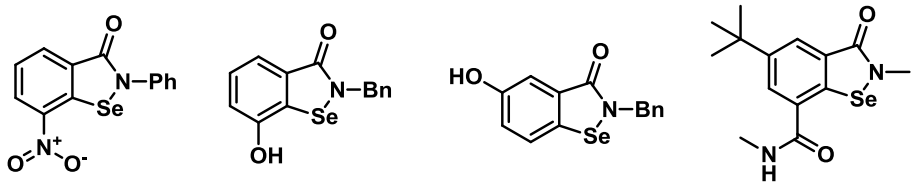


Figure 2 Nitrogen-substituted ebselen analogues

In vitro tests have shown that aryl and benzylic thiols are poorer cosubstrates than natural thiols such as GSH. Observations show that ebselen's catalytic rate of reduction of H_2O_2 in the presence of aromatic thiols was much lower than that in the presence of GSH and also notably lower than those of the control reaction. This effect has been ascribed to the presence of strong Se–O noncovalent interactions in the selenenylsulfide which makes the thiol exchange reaction more likely.[21, 22]

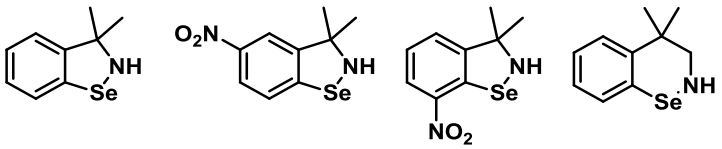
Derivatising the core structure of ebselen has given compounds with improved catalytic properties. Nitro derivative **19** was nine times more active than ebselen but was also significantly more toxic (Figure 3).[24] The enhanced activity of **19** may be due to the nitro group preventing the thiol exchange reaction at the selenium centre. Proximity effects can also be seen with compounds **20** and **21**. Both hydroxyl-substituted compounds displayed significantly higher activity than ebselen. The position of the hydroxyl group had a significant impact on catalysis, as compound **20** displayed an activity that was 1.5 times higher than **21**.[25] This was attributed to proximity effects between the OH group and the selenium centre. *Ortho* coordinating groups such as the amide in **22** could participate in Se–O non-bonding interactions, which increased the activity 3-fold over ebselen.[26]



19 20 21 22

Figure 3 Effects of different substituents on the aromatic ring of ebselen

Chaudiere *et al.* have developed analogues of ebselen where the carbonyl group has been replaced with a quaternary carbon. Compound **23** displays lower catalytic activity than ebselen.[27, 28] Interestingly **24** is catalytically inert; in contrast *ortho*-nitro derivative **25** was very active, but was found to be very toxic.[29] The increased activity was attributed to the nitro group, which prevented a thiol exchange reaction at the selenenylsulfide intermediate. There are a number of investigations reporting the antioxidant properties of compound **26** also known as ALT 2074, which displayed a catalytic activity twice that of ebselen. Compound **26** has been investigated for the prevention of ischemic-reperfusion injury.[30] This compound is the subject of trails by Synvista Inc. for the treatment of plaque psoriasis.[31, 32]



23 24 25 26

Figure 4 Ebselen analogues with quaternary carbon centers

Iwaoka *et al.* developed a range of water-soluble redox catalysts.[33] First amongst these was selenolane **27** and selenoxide **28** (Figure 5); initial tests showed that **28** and **27** function in the same catalytic cycle. Linear water-soluble selenides with different functional terminal groups **29, 30** and **31** (OH, NH_2 and COOH) were also synthesised. The GPx like catalytic activity of these compounds was first investigated using an assay that used H_2O_2 as an oxidant and GSH as a monothiol substrate in the presence of NADPH and glutathione reductase. The reaction progress

was followed by UV spectroscopy, measuring the decreasing concentration of NADPH. Compound **30** was the most active compound, compound **31** was the least effective. Cyclic selenoxide **28** displayed a higher activity than its linear counterpart, **29**. The high activity of **30** could be attributed to the ionisation of carboxylic groups to COO^-, the negative charge inductively increased the oxidisability of the selenium atom. Conversely the presence of NH_3^+ in **31** would decrease the oxidisability of the selenium atom.[34]

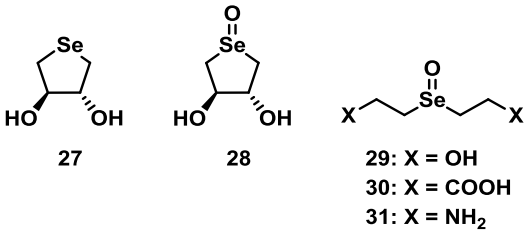
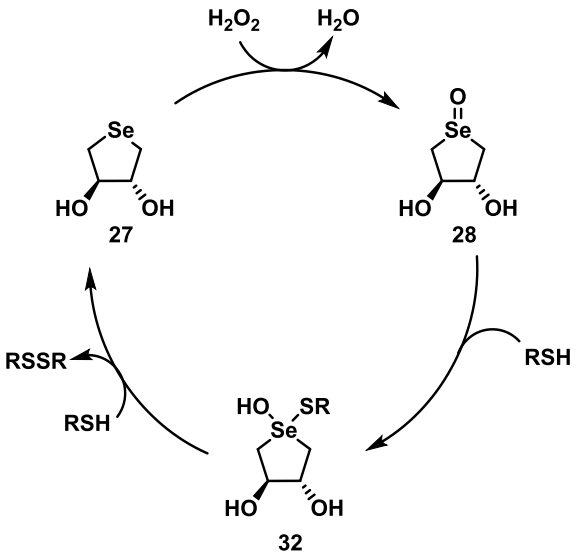


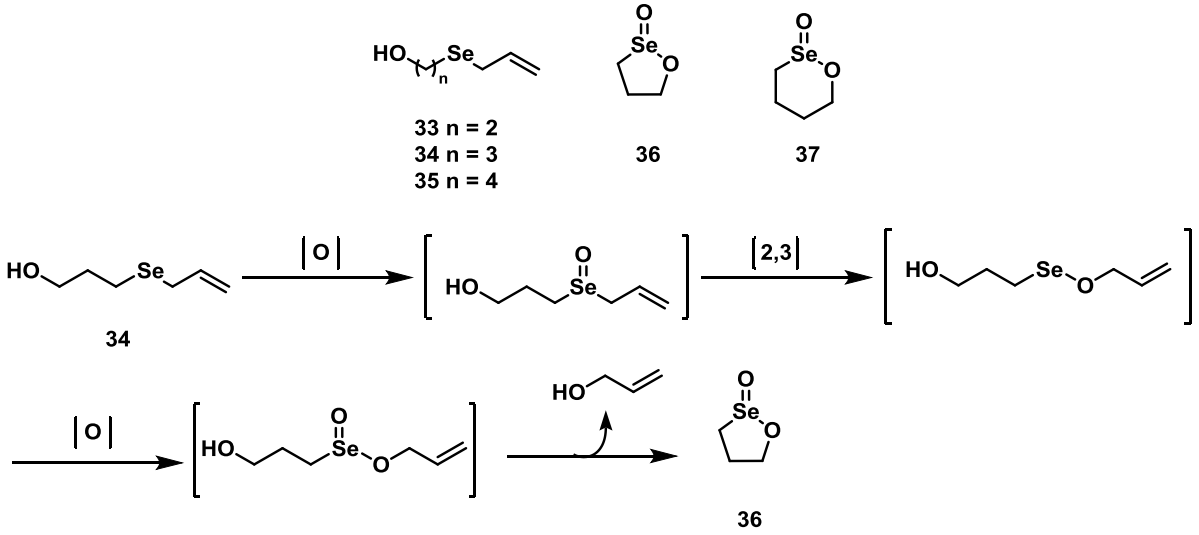
Figure 5 Linear and cyclic selenolanes and selenoxides

The catalytic mechanism of these compounds was investigated using ^{77}Se NMR (Scheme 5). Compound **27** did not react with GSH in H_2O. ^{77}Se NMR indicates that the oxidation of compound **27** to selenoxide **28** with H_2O_2 is the rate determining step of the catalytic cycle. Selenoxide **28** reacted with GSH to give the corresponding selenide **27**. Intermediate **32** could not be detected; it was therefore surmised that the unobserved intermediate must be very reactive (Scheme 5).



Scheme 5 Reduction of H_2O_2 mediated by **27**

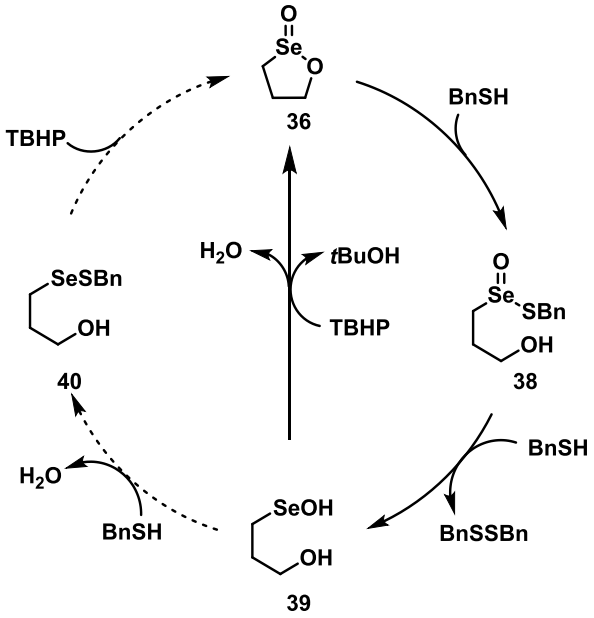
Back *et al.* synthesised hydroxyalkyl allyl selenides **33-35** that displayed catalytic activities that were ten times higher than ebselen (**Error! Reference source not found.**). [35, 36] The carbon chain length had a large effect on catalysis; compound **34** had the greatest activity with a $t_{1/2}$ of 4.8 h which was at least 1.6 times greater than **33** and **35**. Further investigations of the mechanism showed that allyl selenide **34** was functioning as a precatalyst, as a more active catalytic species was formed during catalysis via a rapid [2,3]sigmatropic rearrangement to give selenenic ester **36**.[35] Compound **36** was twice as active as its parent compound with a $t_{1/2}$ of 2.5 h. Selenenic ester **37** was also isolated from **35** with a longer chain length. However, both of these compounds displayed lower activity than **34** and **36**, indicating that the carbon chain length of three was the optimum.[37]



Scheme 6 Allyl selenides and selenenic esters as GPx mimics and proposed formation of selenenic ester **36** *via* [2,3]sigmatropic rearrangement of allyl selenide **34**

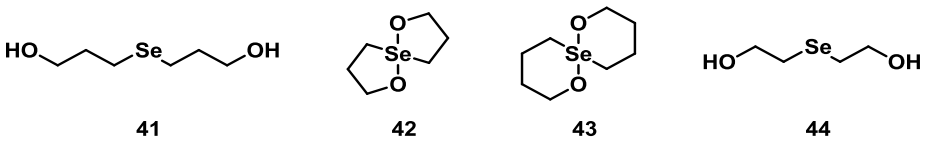
The catalytic cycle shown below was proposed for **36** (Scheme 7). It was found that **36** did not oxidise any further in the presence of the oxidant (*tert*-butyl hydroperoxide). Introduction of benzyl thiol produced thioseleninate **38**; addition of a second equivalent of thiol produced dibenzyldisulfide and selenenic acid **39**. In the presence of an oxidant, **39** was converted back to

36. In the presence of excess BnSH, selenenylsulfide **40** was produced as a byproduct. Further investigation showed that **40** has a $t_{1/2}$ of 35 hours, which is 14 times slower than cyclic seleninate **36**. Therefore, the formation of **40** can be considered a deactivation pathway.



Scheme 7 Reduction of H_2O_2 mediated by **36**

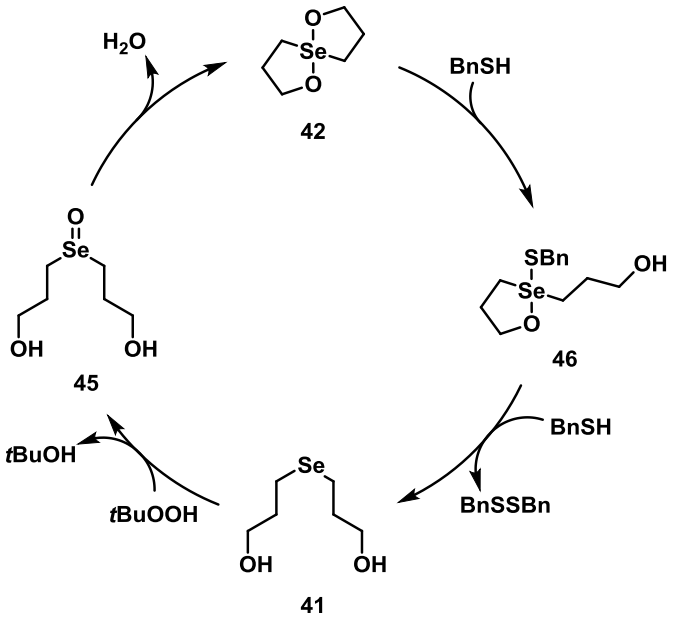
Symmetrical alkyl selenides have also been investigated by Back (Figure 6); as with the allyl selenides, terminal hydroxyl groups enhanced catalytic activity.[38] Selenide **41** was found to catalyse the reduction of H_2O_2 in the presence of BnSH with a $t_{1/2}$ of 2.9 h. Investigations into the catalytic cycle revealed that **41** was inert towards thiols but reacted rapidly in the presence of *tert*-butyl hydroperoxide; if no thiol was present spirodioxaselenanonane **42** was recovered. If this compound was subjected to the assay, it had the same activity as the parent compound; but was the sole selenium-containing compound at the end of the reaction. Spirodioxaselenanonane **43** was prepared from di(4-hydroxybutyl) selenide, which showed a $t_{1/2}$ of 5.1 h. Compound **44** was shown to be catalytically inert as it did not cyclise; this was attributed to the increased strain in forming the corresponding spiro compound.



41 42 43 44

Figure 6 Symmetrical alkyl selenides and spirodioxaselenanonane's

The proposed catalytic cycle for **41** and **42** is shown below (Scheme 8). Selenide **41** was oxidised with *t*BuOOH to give transient selenoxide **45** which rapidly cyclises to give **42**. Spirodioxaselenanonane **42** in the presence of BnSH undergoes substitution of one alkoxy group to produce intermediate **46**, which undergoes reductive elimination with a second equivalent of thiol, regenerating selenide **41**.



Scheme 8 Reduction of H_2O_2 mediated by **41**

Seleninate ester **36** and spirodioxyselenurane **42** proved to be very effective catalysts with activities surpassing that of ebselen.[39] Both moieties could be synthesised easily from inexpensive starting materials. Both compounds were also stable for extended periods at 0 °C. This prompted investigations into incorporating seleninate ester and spirodioxyselenuranes into aromatic frameworks;[40, 41] as aromatic selenium compounds tend to have lower toxicities than their aliphatic counterparts due to greater metabolic stability of the carbon selenium bond.

[40] Back *et al.* developed a number of aromatic derivatives (Figure 8).[40] All of these compounds proved to be poorer catalysts than their aliphatic counterparts, and the aromatic seleninate esters had lower activity than ebselen. There was a clear correlation between the electron-donating/withdrawing nature of the substituent and catalytic activity. The electron-withdrawing halogens suppressed catalytic activity; the effects of the strongly electron-donating methoxy group greatly enhanced catalytic activity. Spirodioxyselenuranes **47a** and **47e** were six times more active than ebselen. The catalytic activity of **47g** was close to its aliphatic counterpart.[39]

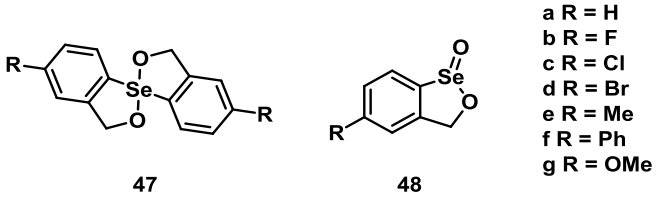


Figure 7 Aromatic spirodioxyselenuranes and seleninate esters

Reactions catalysed with aromatic seleninate esters did not proceed rapidly. Upon closer observation disulfides produced during the reaction were over oxidised during the latter parts of the reaction. Independent tests with aromatic and aliphatic disulfide species in the presence H_2O_2 and **48a** resulted in the formation of the corresponding thiolsulfinates. This could prove to be detrimental *in vivo,* as essential native proteins and peptides could undergo unwanted oxidation reactions.[42]

Further improvements to the spirodioxyselenuranes were made by Back *et al*.[43] A range of analogues were synthesised where one of the aryl groups was replaced for 3-hydroxypropyl groups (Figure 8). This was shown to increase the aqueous solubility and catalytic activity of the selenides; the arylseleno moiety was not removed in order to retain the stability and low toxicity properties of arylseleno groups. Compounds **49a-49e** were not adequately water-soluble; a parallel series with an additional hydroxyl group was created to increase water solubility. Both series of compounds were tested in an HPLC assay in the presence of H_2O_2 and benzyl thiol in a

mixture of CH_2Cl_2 and methanol. Compound series **49** and **50** showed similar activities in this assay. The presence of electron-donating groups at different positions of the ring had significant effects on the reaction rates. *p*-Methoxy derivatives **49c** and **50c** were more effective than the *ortho* and *meta* isomers **49a**-**49b** and **50a**-**50b**. The inclusion of two methoxy groups did not appreciably increase the catalytic activity of **49d** and **50d**-**50e** with the exception of **49e** which was the most potent catalyst. Compound series **50** was subjected to an NMR assay in the presence of H_2O_2 and GSH in D_2O. All of the compounds were catalytically active in this assay and displayed the same relative activities shown in the HPLC assay.[44]

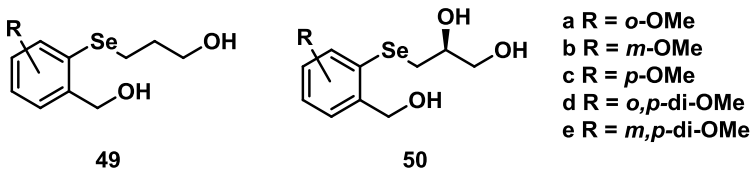


Figure 8 Pincer selenuranes as GPx mimics

The catalytic activity of spirodioxyselenuranes prompted the investigation of other catalysts based on the selenium spirocycles. Back *et al.* investigated the nitrogen-containing analogue of **47a,** spirodiazaselenuranes **51** (Figure 9).[45] However, **51** proved to be relatively unstable and could not be synthesised; the corresponding azaselenonium chloride **52** was isolated. The catalytic activity of **52** was still 12 times higher than that of ebselen.

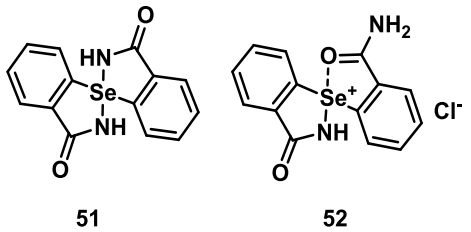


Figure 9 Spirodiazaselenuranes **51** and **52** as GPx mimics

Further investigations revealed that the substituents attached to the amide nitrogen atoms help stabilise spirodiazaselenurane. Mugesh *et al.* synthesised spirodiazaselenuranes **53** (Figure 10).[46]

Further research led to the addition of more complex substituents (Figure 10).[47] Spirodiazaselenurane of **53** was 1.2 times more active than ebselen. The nature of the substituents effected the activity of the catalysts; compounds **54a** and **54c** were shown to be the poorest, **54b** and **54d** showed activity 1.4 times higher than parent **53**.

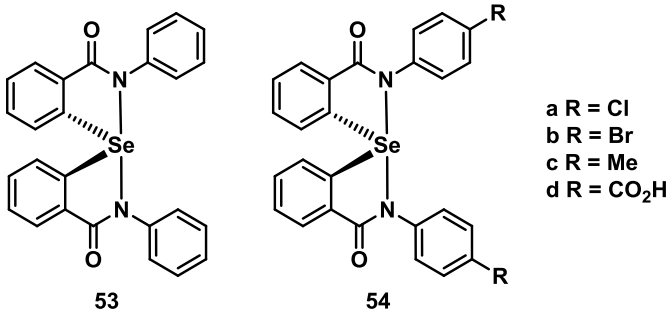
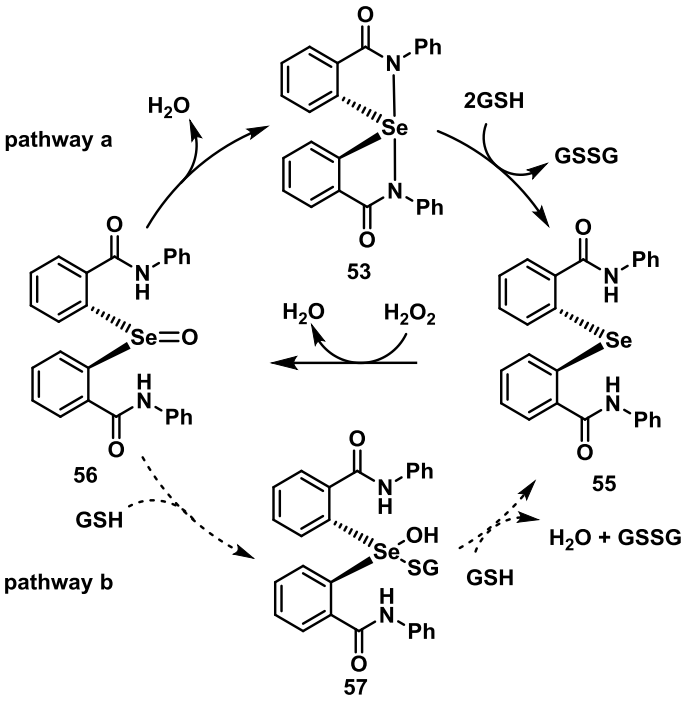


Figure 10 Symmetrical spirodiazaselenurane as GPx mimics

The mechanism of action of these compounds has been investigated (Scheme 9).[47] Compound **53** is reduced giving selenide **55**, consuming 2 equivalents GSH; **55** is oxidised to selenoxide **56** with H_2O_2. Compound **53** is regenerated by the elimination of water. This pathway is favoured at high concentrations of peroxide. Pathway b is favoured with higher thiol concentrations. In this cycle intermediate **57** is formed when selenoxide **56** reacts with GSH. Selenide **55** is regenerated after intermediate **57** reacts with GSH.



Scheme 9 Reduction of H_2O_2 mediated by **53**

Seleninic acid anhydrides have also been investigated as potential GPx mimics.[48] Kuhn *et al.* have synthesised a novel salicyloylglycine seleninic acid anhydride **58** (Figure 11). The salicyloylglycine moiety was chosen as it exhibited a low *in vivo* toxicity and improved the compounds anti-inflammatory properties. Catalytic testing of this compound showed the activity was four times greater than ebselen.

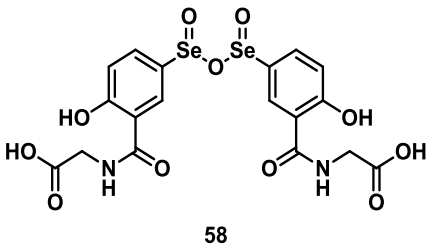
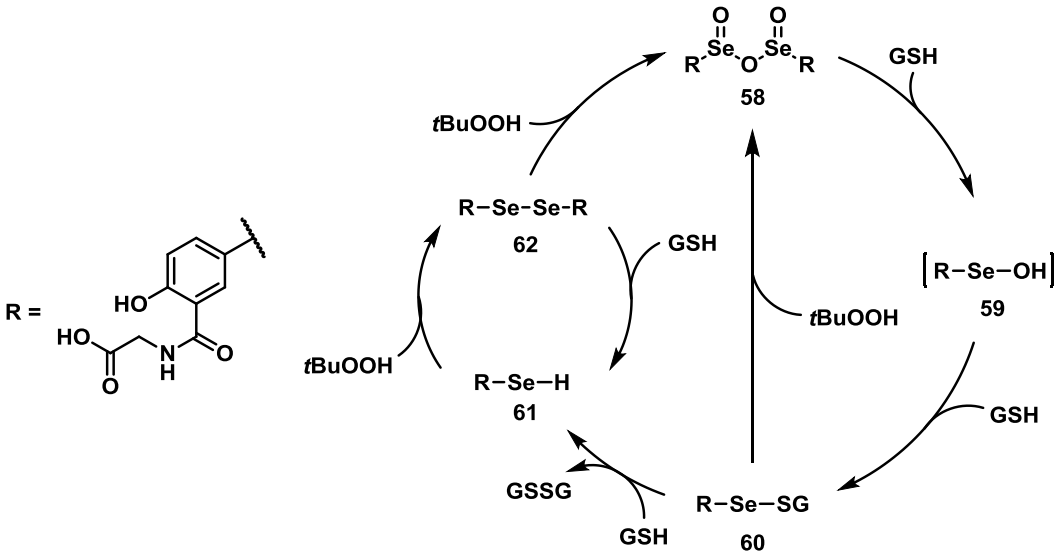


Figure 11 Salicyloylglycine seleninic acid anhydride **58**

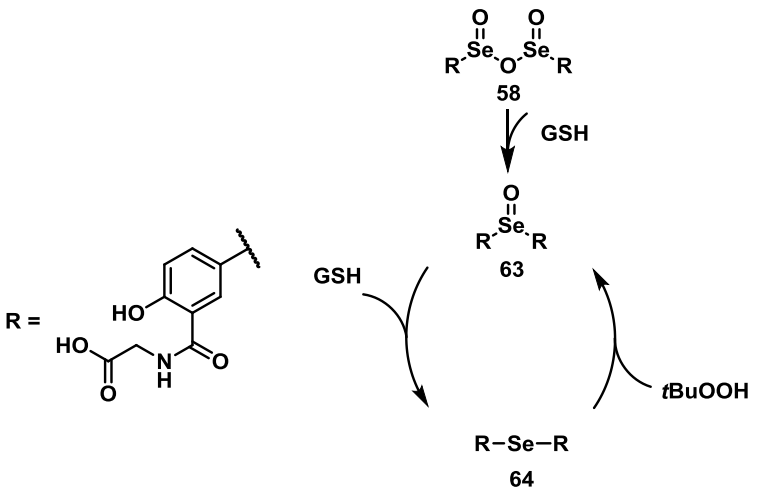
The catalytic mechanism of **58** was explored by reacting it with varying amounts of reductant (Scheme 10). When **58** was reacted with a 1:1 molar ratio of GSH, selenenylsulfide **60**, monoselenoxide **63** and dialkylselenide **64** were observed and **58** was returned in 40**%** yield. When the ratio was increased to 1:3 the observable products were **60**, **62, 64** and diselenide **61**.

Selenenylsulfide **60** decomposed to diselenide **62** over time. The reduction products were reacted with GSH and *tert*-butyl hydroperoxide to determine the catalytic cycles. Compound **58** reacts with one molecule of GSH to give transient intermediate **59**; further reactions with GSH to give **60**, which can oxidise to give the parent compound **58**, however this process is slow. Diselenide **62** also gave the parent compound after oxidation with *t*BuOOH.



Scheme 10 Catalytic cycle of seleninic acid anhydride **58**

Dialkyl selenide **64** oxidised to monoselenide **63**; in the presence of GSH this compound was reduced back to **64**. This data supports the existence of three catalytic cycles. Pathway C is an independent pathway; as soon as **64** is formed, the parent compound cannot be reformed (Scheme 11). Analysis of the composition of by-products shows that components of pathway C are present in small amounts, therefore pathway C is considered to have a minor contribution towards the catalytic activity. Independent catalytic measurements of this pathway show it possesses lower catalytic activity than pathways A and B.



Scheme 11 Pathway C, the formation and catalytic mechanism of dialkyl selenide **64**

There has been considerable interest in selenoxo derivatives such as selenoureas, selenocarbamates and selenoamides as ROS scavengers. López *et al.* synthesised a range of selenoureas, selenocarbamates and selenoamides (Figure 12).[49] The catalytic activity of compounds **65-70** were tested in a H_2O_2 reduction assay. The selenocarbamates **65** and **68** and selenoamide **66** displayed the worst activity with $t_{1/2}$ ranging from 100 to 108 min; selenoureas based on the naphthalene and monosaccharide scaffold **67** and **69** displayed the best activity with $t_{1/2}$ ranging from 2 to 13 min. Further investigations yielded a diosgenin-derived selenourea **70**, when this compound was tested in the same assay it had a $t_{1/2}$ of 5 min; this compound also displayed anticancer activity in a number of cell lines.[50, 51]

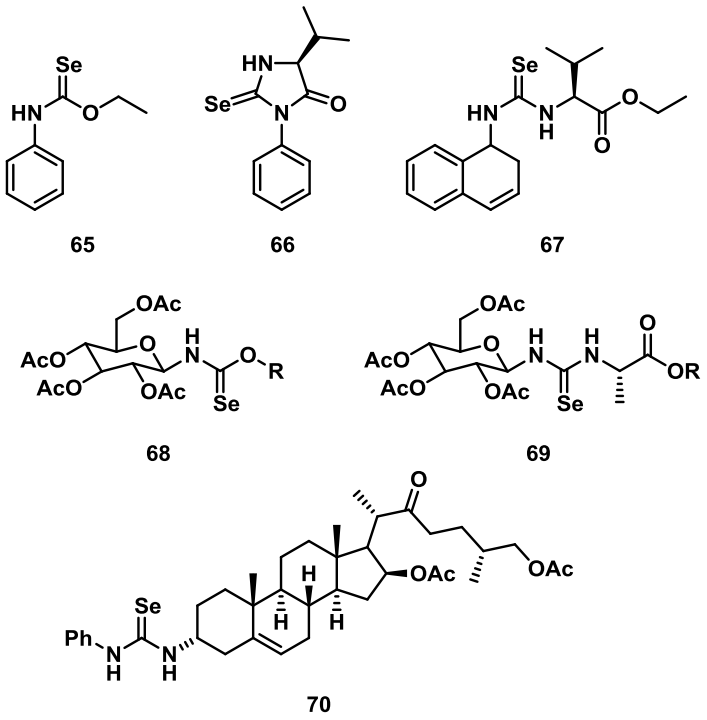
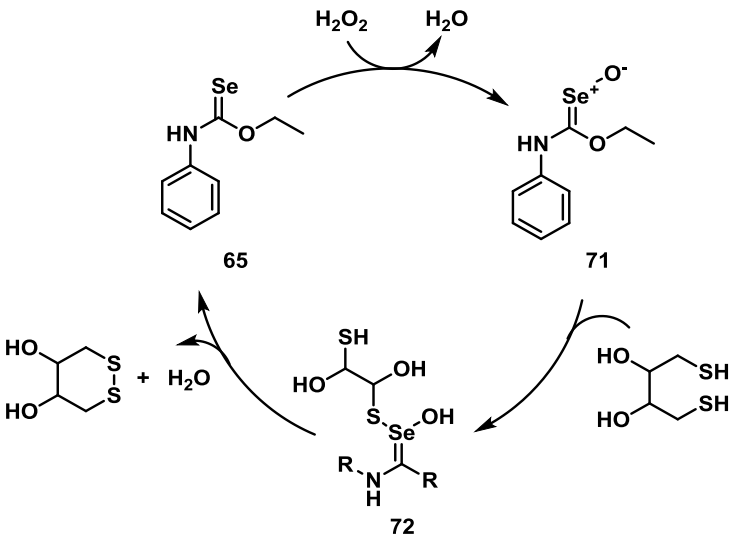


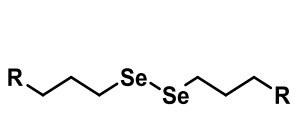
Figure 12 Selenoureas, selenocarbamates and selenoamides as ROS scavengers

The proposed catalytic cycle for selenoxo derivatives is shown below (Scheme 12). Compound **65** is oxidised by H_2O_2 to give a seleno oxide **71**, which then reacts with thiol (DTT) to give selenylsulfide **3**. Upon reaction with a second equivalent of thiol, disulfide is expelled and the catalyst is reformed. The higher stabilisation provided by selenourea may explain the higher activity of this class of compounds.



Scheme 12 Reduction of H_2O_2 mediated by **65**

Diselenides have become appealing targets as GPx mimics. Back *et al.* prepared a selection of symmetrical alkyl diselenides with carboxylic acid, methyl ester, amido, carbamate, amino or hydroxyl termini **73-77** (Figure 13).[37] These compounds displayed poorer catalytic activity than ebselen. The exception to this was acetamide **77** which had a catalytic activity that was 7 times greater than ebselen. Investigations with these compounds were halted as they are difficult to prepare in a pure state.

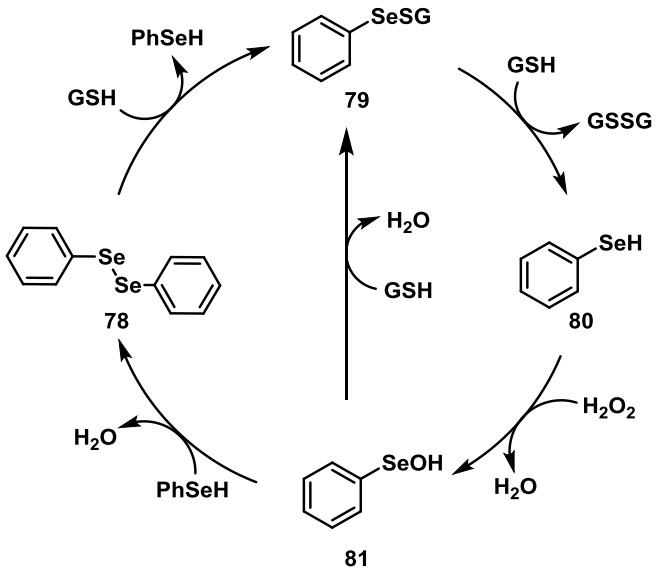


73 R = OH
74 R= NH_2
75 R= CO_2H
76 R= PhCONH
77 R= AcNH

Figure 13 Symmetrical alkyl diselenides as GPx mimics

The activity of diphenyl diselenide **78** in the presence of H_2O_2 and GSH is reported to be twice that of ebselen.[52] Iwaoka and Tomoda investigated the mechanism of action of diselenides using ^{77}Se NMR spectroscopy (Scheme 13).[53] Diphenyl diselenide **78** enters the catalytic cycle following reduction to selenylsulfide **79** and selenol **80**; selenylsulfide **79** reacts with a second equivalent of GSH, generating **80** and GSSG. Selenol **80** reduces peroxides with concomitant formation of selenenic acid **81**. In the presence of excess thiol this species regenerates selenosulfide **79**; in the

absence of additional thiol, **81** reacts with selenol **80** to regenerate **78**. Interestingly, tests on mice have shown diphenyl diselenide to be less toxic than ebselen.[54, 55]



Scheme 13 Reduction of H_2O_2 mediated by **78**

Further investigations found that the addition of heteroatoms in close proximity to the diselenide bond could influence the catalytic activity of the compound through non-bonding interactions.[56, 57] Wilson *et al.* reported that the introduction of nitrogen substituents to the 6 position would further increase the rate of diphenyl diselenides catalysis (Figure 14).[52] The catalytic activity of compounds **82** and **83** were 5 times greater than that of diphenyl diselenide. Nitrogen-selenium non-bonding interactions are thought to increase activity by assisting the activation of selenol intermediate **80** and preventing thiol exchange reactions of the selenenylsulfide intermediate **79**. It should be noted that the diselenides had a higher catalytic activity than their selenide counterparts **84** and **85**, which only showed trace activity in the assay. Diselenide **86** was shown to be catalytic inactive.[58]

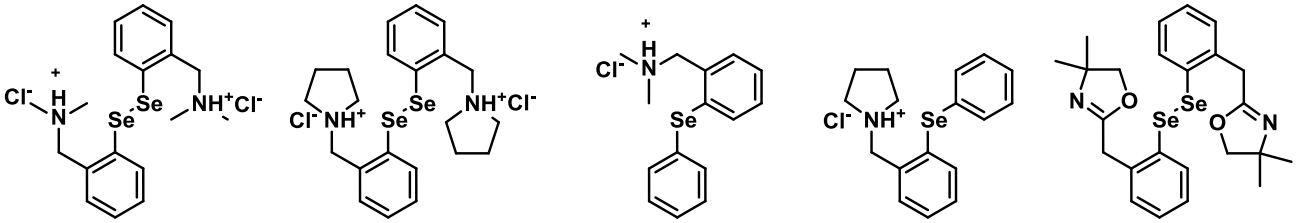


Figure 14 Proximity effects on heteroatoms on GPx catalysis

The strength of Se-N through space non-bonding interactions has a large effect on the GPx-like activity of diselenides. Diselenides that have weak Se-N interactions display activity greater than that of diselenides that have much stronger Se-N interactions. Investigations into this phenomenon were preformed using ^{77}Se NMR and computational studies to analyse the selenenylsulfide intermediates (Figure 15). Compounds **13**, **87** and **88** have calculated ^{77}Se NMR chemical shifts of 588, 562 and 574 ppm, respectively; Se positive charges were calculated at 0.377, 0.289 and 0.352 respectively, **13** has the most electropositive selenium atom and is an inactive catalyst.[59] The results show that the stronger Se-N interactions in **13** and **88** increased the electropositive character of the selenium atom in the selenenylsulfide intermediates, this favours thiol exchange reactions of the selenenylsulfide effectively retarding the catalytic activity.[21, 59] Compounds with nitrogen substituents that produce selenenylsulfide intermediates that have stronger Se-N non-bonding interactions are less effective catalysts.

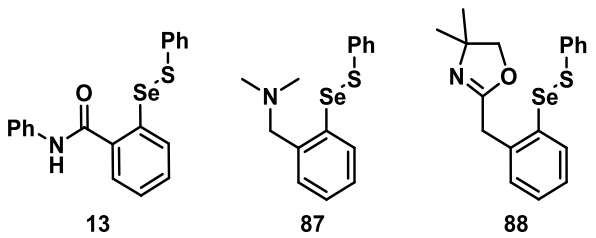


Figure 15 Selenenylsulfide intermediates

The catalytic activity of a number of diaryl diselenides have been investigated by Mugesh (Figure 16).[58-60] The activity of these compounds was tested in an assay using H_2O_2 and PhSH and

monitored *via* UV spectroscopy. Compound **89** had an activity that was the same as **90**. Compound **91** was shown to be inactive; [31] this was due to strong Se–N interactions halting catalysis. Bis-naphthalene **92** activity was ten times greater than phenyl-based diselenide **82.** Ferrocene diselenide **93** displayed activity that was lower than that of diphenyl diselenide; proximal amino groups proved to be beneficial as **94** had an activity 100 times greater than **93**. A dramatic increase in the initial reduction rate of **94** compared with **93** may be ascribed to the synergistic effect of amino substituents and the redox-active ferrocenyl groups. The observed activity of **95** with amide groups was 40 times lower than **94**.[61] This may be due to the strong electron-withdrawing nature of the amide groups, which makes the oxidation more difficult than in the unsubstituted ferrocene.

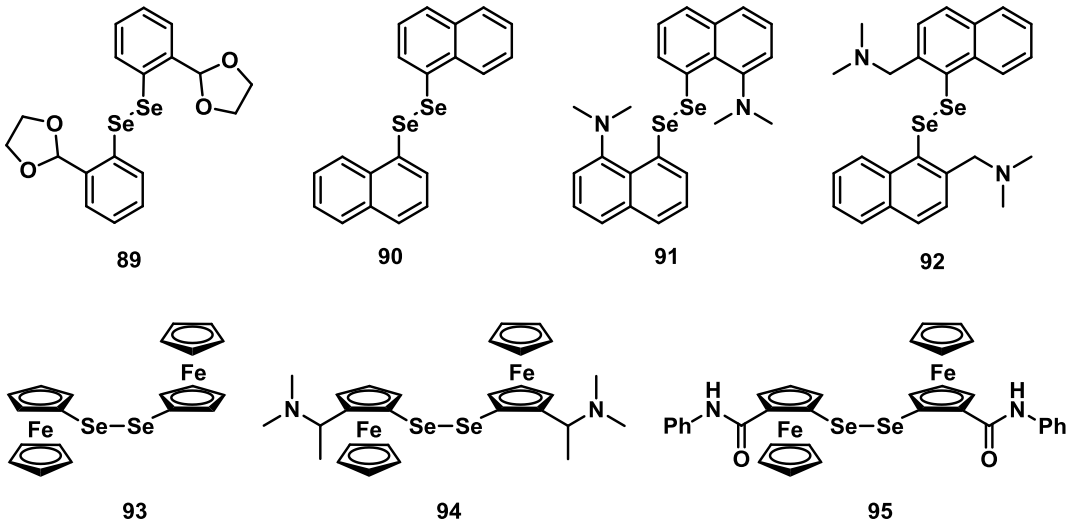
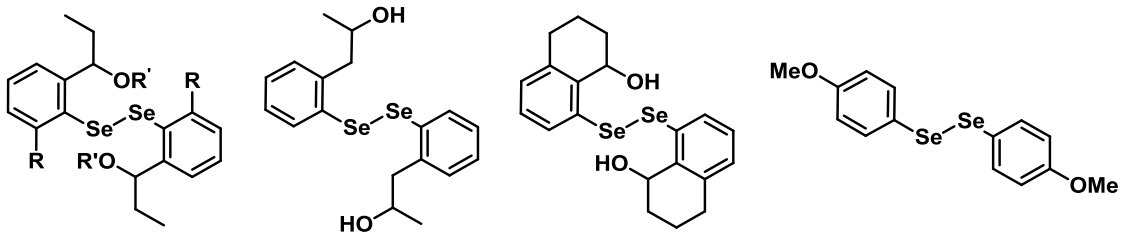


Figure 16 Diaryl diselenides and Ferrocene diselenide as GPx mimics

Wirth *et al.* investigated the role of Se–O non-bonding reactions on diselenides (Figure 17). Compounds **96-103** were evaluated in a glutathione reductase coupled assay with H_2O_2.[62] All of the compounds showed catalytic activity. The bis-*ortho*-substituted diselenides **98-100** showed the lowest activity in this assay; this was attributed to these compounds being more sterically demanding. Compound **100** had the worst activity in this assay, this observation shows that electron-withdrawing substituent seem to be detrimental for GPx-like activity. Conversely

electron-donating substituents increased the rate of catalysis; compound **103** displayed the highest activity in the assay. Interestingly the methoxy group on **97** had a detrimental effect on catalysis, as this compound only showed 50% of the activity of **96**. Compound **96** and **102** showed similar levels of activity. Compound **101** displayed an activity 1.6 times lower than **96** and **102**, which indicates that the increased oxygen-selenium interaction is detrimental.



96 R = H, R' = H
97 R = H, R' = Me
98 R = Me, R' = H
99 R = CH(OH)Et, R' = H
100 R = CF_3, R'= H

101 **102** **103**

Figure 17 Oxygen-selenium non-bonding interactions and proximity effects on diselenides

Organoselenium catalysts based on nicotinic acid and nicotinamide show significant enhancement of GPx catalytic activity. Nicotinic acid and nicotinamide are important bio molecules that have shown anti-inflammatory and antioxidant activities.[63, 64] Compound **103** was the first selenium GPx mimic based upon pyridine that displayed GPx catalytic activity (Figure 18).[65] Jain and coworkers have synthesised a range of selenium compounds **104–108** that incorporate the nicotinic acid motif.[66] The catalytic activity of these compounds was tested in the presence of GSH and H_2O_2. Compound **104** was the most active catalyst; the observed t_{50} was six times greater than ebselen and four times greater than selenocysteine.[67] Pyridoxine-like diselenides were also investigated. Compound **107** was shown to have a lower activity than **108**. The greater activity of the dibromo-derivative was attributed to the bromine groups electron-withdrawing effects increasing the δ+ nature of the diselenide; which facilitates nucleophilic attack of GSH on the diselenide.[68]

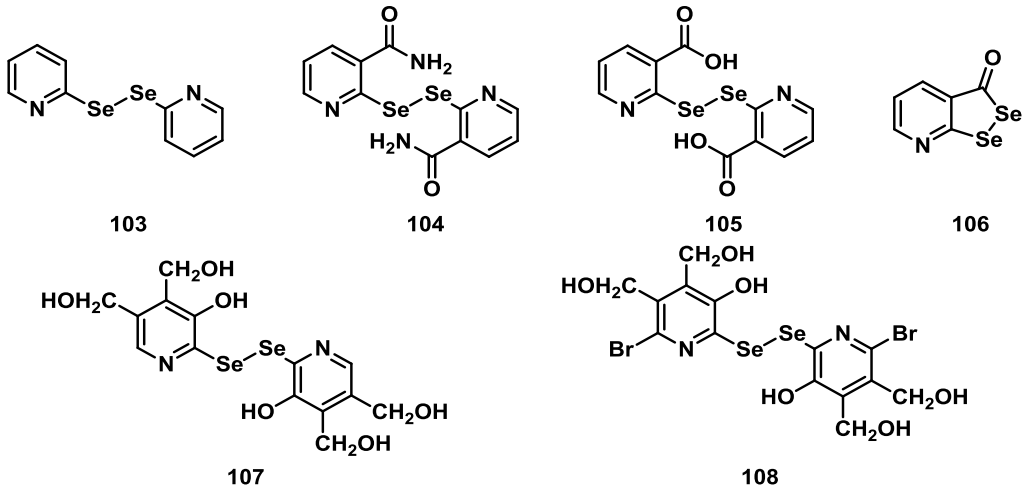


Figure 18 Nicotinoyl based organoselenium compounds

Bailly *et al.* reported 4-mercaptoimidazoles **109** derived from naturally occurring ovothiols (Figure 19).[69] These compounds were shown to be powerful peroxide scavengers. This work continued with the synthesis of a range of organoselenium compounds based on the imidazole scaffold. The catalytic activity of these compounds were evaluated; all of the compounds were better catalysts than ebselen and diphenyl diselenide. The most active compounds was **110** which was 4 times more active than ebselen.

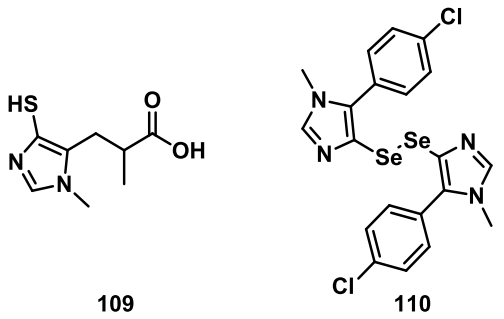


Figure 19 Ovothiol-derived diselenides

1,8-Disubstituted naphthalene diselenides have been investigated by Back *et al.* (Figure 20).[70] These compounds displayed very interesting structural properties. *Peri*-substituted diselenides have rigid and planar structures, this is in stark contrast to acyclic diaryl diselenides such as diphenyl diselenide which have dihedral angles that are nearly orthogonal at 87°. Additionally,

the Se-Se bond length is reported to be 2.36 Å which is longer than diphenyl diselenide.[24] These unique structural properties are proposed to lower the oxidation potential of the diselenide moiety which would enhance the overall catalytic activity. Diselenide **111** displayed activity that was 13 times greater than diphenyl diselenide. The addition of electron-donating methoxy groups to the naphthalene scaffold increased the catalytic activity; **112** had an activity that was 1.3 times greater than **111**. Oxidation of **112** with *m*CPBA yielded selenoseleninate **113,** this compound displayed an activity 1.2 times greater than the parent compound. However, further investigations revealed that **113** was not an independent catalytic species, but a component of the catalytic mechanism of **112**. Further oxidation of **112** gave seleninic anhydride **114**, but this compound could not be submitted for testing due to poor solubility issues.

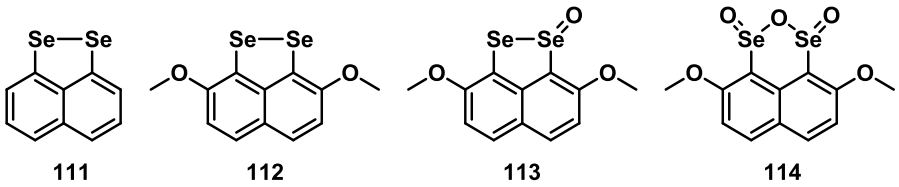
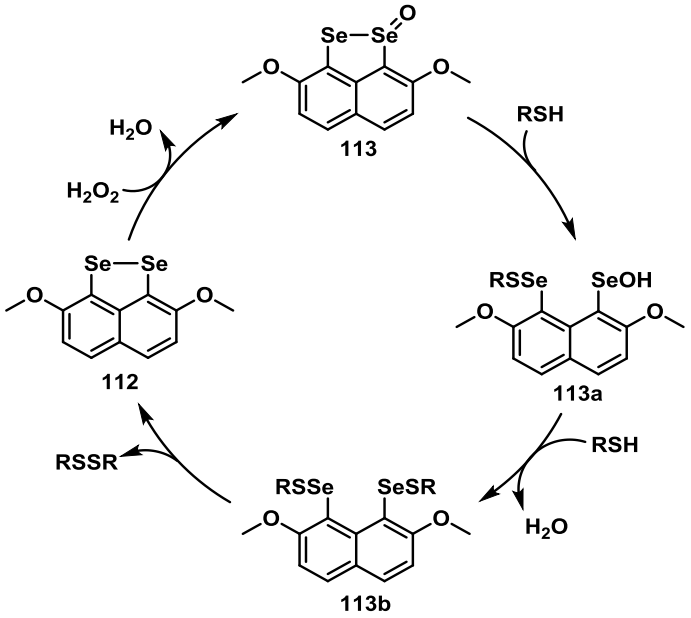


Figure 20 *Peri*-substituted naphthalene diselenides

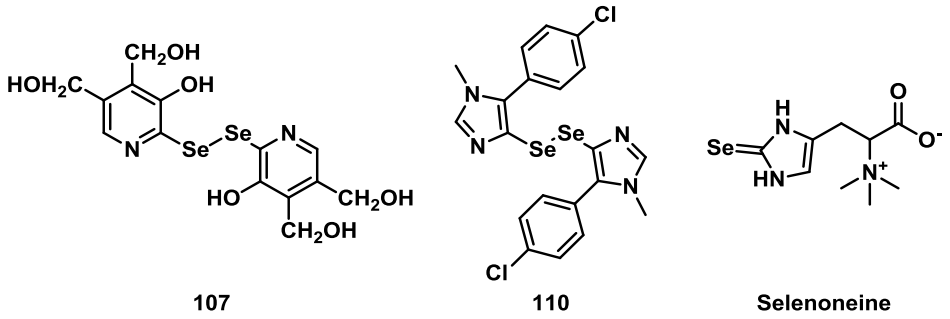
Investigation into the catalytic cycle of 1,8-naphthalene diselenides found that oxidation of diselenide **112** with 1 eq of *m*CPBA gave selenolseleninate **113** (Scheme 14). Compound **112** could be further oxidised by using 3 eq of *m*CPBA producing seleninic anhydride **114**. However, the only oxidation product observed under experimental conditions using H_2O_2 as an oxidant was selenolseleninate **113**. If selenolseleninate **113** was treated with H_2O_2 there was no observable reaction; treatment with thiol resulted in a rapid reaction which gave **112** and disulfide. When diselenide **112** was treated with excess thiol there was no reaction even after prolonged reaction times of 12 h. These experiments inform the mechanism shown below. Diselenide **112** is converted into selenolseleninate **113** in the rate determining step; **113** is rapidly reduced by

benzyl thiol to the starting diselenide *via* intermediates **113a** and **113b**. These intermediates were not isolated.



Scheme 14 Reduction of H_2O_2 mediated by **112**

To summarise there has been significant interest in developing a small molecule organoselenium GPx mimic. A wide range of selenium functionality has been incorporated into GPx mimics, with diselenides generally showing higher catalytic activities than selenides. Many of these diselenides incorporate polar groups to enhance water solubility. A recent trend in the design of organoselenium GPx mimics is to incorporate modified biological motifs such as pyridoxine and ovothiol, which may impart favourable therapeutic properties.[68, 69] The most recent literature investigates the chemical synthesis and catalytic activity of the natural product selenoneine (Figure 21).[71] This study highlights the fact that more attention needs to be paid to the absorption, distribution, metabolism and excretion characteristics of organoselenium molecules in order to produce effective therapeutic GPx mimics.



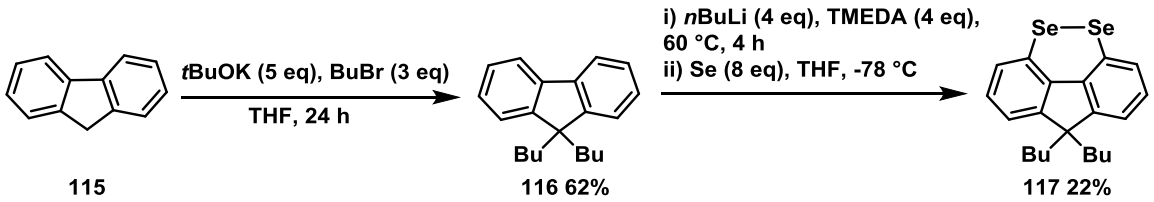
107 110 Selenoneine

Figure 21 Organoselenium compounds based on biological motifs

Chapter 2 *peri*-Like fluorene diselenides, and their oxides, as glutathione peroxidase mimics

2.1 Previous group work

The Grainger group has previously investigated *peri*-substituted naphthalene diselenides and *peri*-like fluorene diselenides in the context of [FeFe]-Hydrogenase mimics.[72-74] The synthesis of fluorene diselenide **117** begins with commercially available fluorene **115** which is dialkylated with 1-bromobutane giving **116** in 62% yield. This is followed by a double deprotonation with *n*BuLi and quenching with selenium to give diselenide **117** in 22% yield (Scheme 15).



Scheme 15 Preparation of diselenide **117**

The crystal structure of diselenide **117** was obtained by Jack Lownes.[75] Selected bond lengths and angles of **117** are shown in Table 1, and compared with naphthalene diselenide **111**.

The X-ray crystal structure of **117** shows that the Se-Se bond is similar to that of naphthalene diselenide **111** (entry 1, Table 1). The C(1)-Se(1)-Se(2)-C(11) dihedral angle in **117** is 44 °; the naphthalene compound shows a much smaller twist of 2.28 ° (entry 4, Table 1). Further evidence of torsional strain within the fluorene scaffold can be seen in the C(1)-C(13)-C(12)-C(11) bond angle which shows a 13.4° twist away from planarity, unsubstituted fluorenes are planar(entry 6, Table 1).[76]

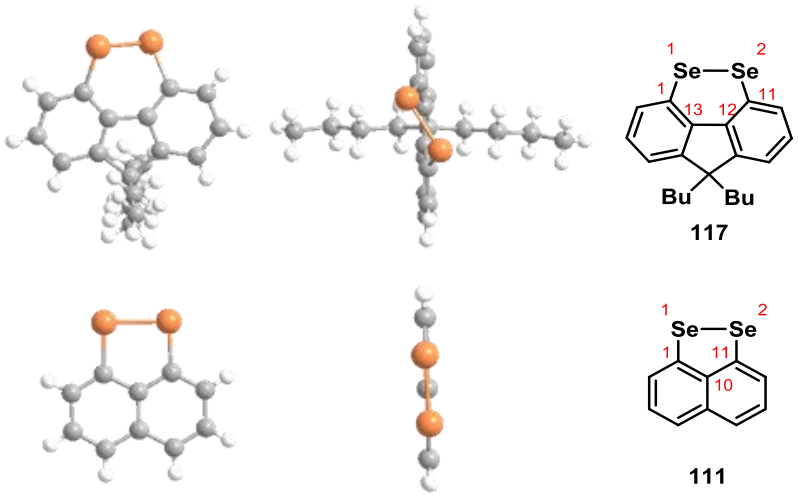


Figure 22 Crystal structure of compounds **111** and **117**

Entry	Compound	117	111
1	Se-Se	2.341	2.363
2	Se(1)-C(1)	1.930	1.914
	Se(2)-C(11)		1.907
3	C(1)-Se(1)-Se(2)	98.90	91.66
	C(11)-Se(2)-Se(1)		91.87
4	C(1)-Se(1)-Se(2)-C(11)	44.00	-2.28
5	Se(1)-C(1)-C(11)-Se(2)	32.3	-2.17
6	C(1)-C(13)-C(12)-C(11)	9.0	
7	Se(1)-C(1)-C(13) – 120°	0.98	-3.1
	Se(2)-C(11)-C(12) – 120°		-2.6(2)

Table 1 Selected bond lengths (Å) and angles (°) for compounds **111**, and **117**. Compound **117** contains four crystallography-independent molecules, average values from all four molecules are given.

2.2 Aims and objectives

In all the mechanisms thus far presented the oxidation step is universally the most important for GPx like catalysis. Therefore, any proposed catalyst must have a low oxidation potential.

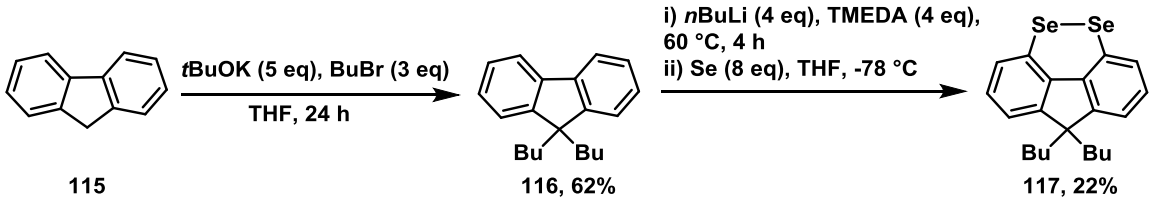
As outlined in chapter 1, there is considerable interest in diselenides. *Peri*-disubstituted naphthalene diselenides reported by Back display greater GPx-like activity than non-constrained diselenides. This has been attributed to the diselenide moiety having a low oxidation potential, caused by the physical properties of *peri*-substitution which lengthens the Se-Se bond and twists C-Se-Se-C bond into planarity.

X-ray data of fluorene diselenide **117**, obtained by the Grainger group, demonstrates that the Se-Se bond length is similarly elongated to **111**. The C-Se-Se-C dihedral angle of the diselenide moiety on the fluorene scaffold is not planar as in **111**, but has still deviated far from the 85° typical of non-constrained diselenides.

It is feasible to hypothesise that fluorene diselenides with physical properties similar to those of naphthalene diselenides, will have a similar effect reducing the oxidation potential of the Se-Se bond. To investigate this hypothesis, the GPx-like activity of fluorene diselenides will be evaluated using an NMR assay with the aim of comparing the fluorene and naphthalene scaffolds. The mechanism of action of the proposed species will also be explored, with the aim of studying the effect of *peri*-like disubstitution on GPx catalysis.

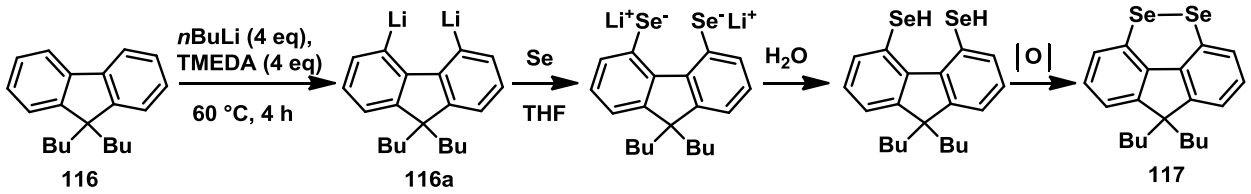
2.3 Result and discussion

The synthesis of diselenide **117** has been previously investigated by the Grainger group (Scheme 16). The synthesis began with commercially available fluorene, which was alkylated using *t*BuOK in the presence of BuBr to give dibutylfluorene **116** in a 62% yield. The lithiation of fluorene and subsequent sulfur quench has been reported in the literature by Bonifácio.[77] The Grainger group previously modified the procedure to incorporate selenium in place of sulfur.[75] Using this procedure, the synthesis of **117** was achieved in a 22% yield.



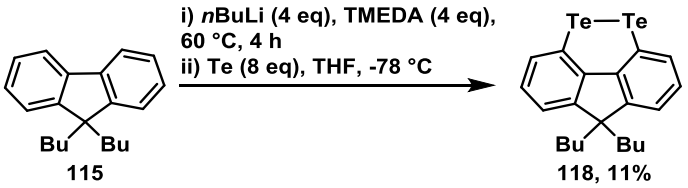
Scheme 16 Preparation of diselenide **117**

The reaction is presumed to proceed through sequential TMEDA-directed deprotonations to form **116a**. The selenium quench produces a diselenol which forms diselenide **117** upon oxidation with O_2 (Scheme 17).



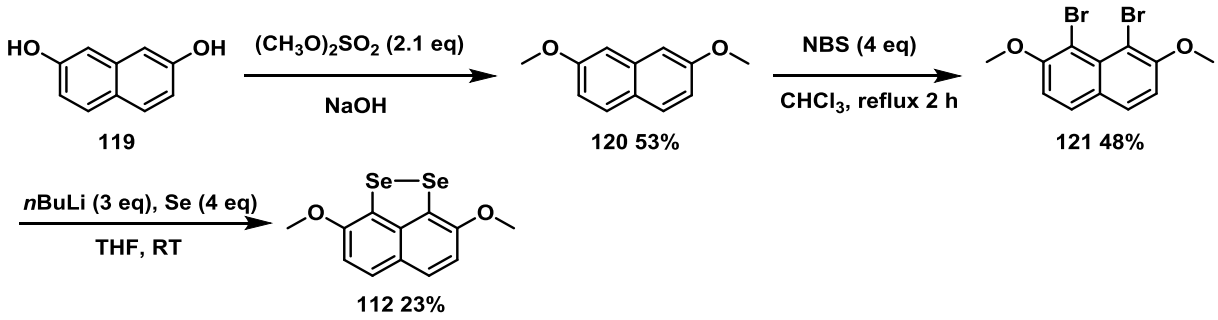
Scheme 17 Proposed intermediates in the formation of diselenide **117** from fluorene **116**

Tellurium analogues of selenium GPx mimics have also been shown to be active as GPx mimics; naphthalene ditellurides, synthesised by Back, have shown catalytic activities greater than their diselenide analogues.[70] Modifying the existing procedure, selenium was exchanged for elemental tellurium giving fluorene ditelluride **118** in 11% yield (Scheme 18).



Scheme 18 Preparation of ditelluride **118**

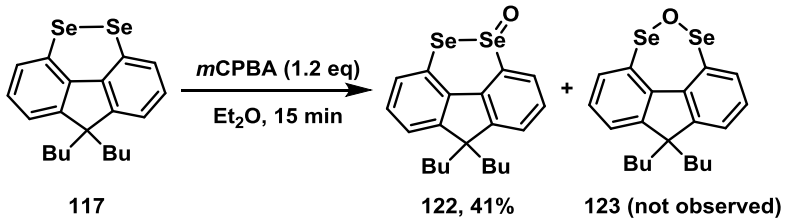
In order to assess the relative activity of the synthesised GPx mimics**,** it was decided to synthesize a naphthalene compound reported by Back, to be used as a positive control in a ^{1}H-NMR based assay.[70] Following Back's procedures, dihydroxynaphthalene **119** was dimethylated to give bis-ether **120** in 53% yield. Subsequent dibromination of **120** using NBS gave dibromide **121** in a 48% yield. After a lithium-halogen exchange reaction followed by quenching of the anion with selenium, diselenide **112** was isolated in a 23% yield (Scheme 19).



Scheme 19 Preparation of naphthalene diselenide **112**

With diselenide **117** in hand, it was decided to investigate if oxidation with *m*CPBA would give a selenolseleninate analogous to the naphthalene systems. The oxidation of naphthalene diselenides has previously been reported by Kice and Back.[70, 78] Following Back's procedure the synthesis of a selenolseleninate could be achieved (Scheme 20). Addition of 1.5 eq of *m*CPBA to diselenide **117** in CH_2Cl_2 gave selenolseleninate **122** in 25% yield. The starting material was returned in 75% yield. Increasing the amount of *m*CPBA in subsequent reactions did not increase the yield. However, conducting the reaction in Et_2O with 1.2 equivalents of *m*CPBA gave **122** in a 41% yield. It has been reported that when naphthalene diselenide was oxidised with 1 eq of

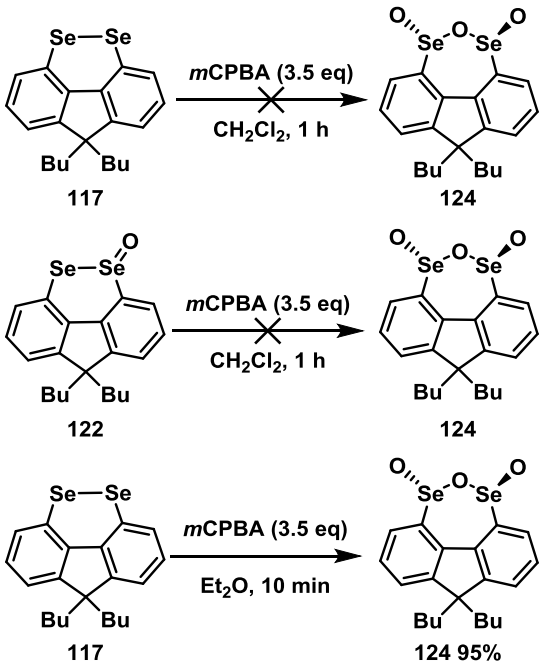
*m*CPBA in Et_2O, a 60:40 mixture of the selenolseleninate and a cyclic selenenic anhydride was present.[70, 78] ^1H and ^{13}C NMR analysis of the isolated product showed no evidence of any selenenic anhydride **123**. The spectra for the isolated material supported selenolseleninate **122** as the product, which had 6 different aromatic proton environments and 12 different aromatic carbon environments. This suggested the molecule had no symmetry. ^{77}Se–NMR showed that there were 2 different selenium environments at 710.0 and 1046.2 ppm**.** Altogether, this data is indicative of selenolseleninate **122** being the isolated product, rather than selenic anhydride **123**



Scheme 20 Preparation of selenolseleninate **122**

Back and Kice reported that the peri-substituted naphthalene diselenides could be oxidised beyond the selenolseleninate to a seleninic anhydride, by increasing the loading of *m*CPBA.[70, 78] When 3.5 eq of *m*CPBA was added to the diselenide **117** no seleninic anhydride species was observed. The reaction only gave compound **122** in a 30% yield along with unreacted starting material. Attempts to oxidise the selenolseleninate **122** with *m*CPBA were unsuccessful, no reaction was observed. The reaction procedure was modified by changing the reaction solvent from CH_2Cl_2 to Et_2O. Upon addition of 3.5 equivalents of *m*CPBA to a solution of **117** in Et_2O there was an instant disappearance the characteristic burgundy colour of the solution followed by precipitation of the seleninic anhydride **124** in a 95% yield (Scheme 21). Unlike the previous examples of seleninic anhydrides which were insoluble in a broad range of solvents, with the notable exception of compound **114** which was only soluble in DMSO, the fluorene species was soluble in a range of polar solvents including alcohol and THF. Compound **124** was assigned as a

seleninic anhydride as mass spec data indicated the molecule contained three oxygen atoms and ^{77}Se NMR showed the presence of 1 peak at 1175.9 ppm which was indicative of seleninic anhydride moiety. The selenium atoms in naphthalene seleninic anhydride **114** are stereocentres which produced two diastereomers. Seleninic anhydride **124** also has two diastereomers, the *cis* and the *trans*-form.



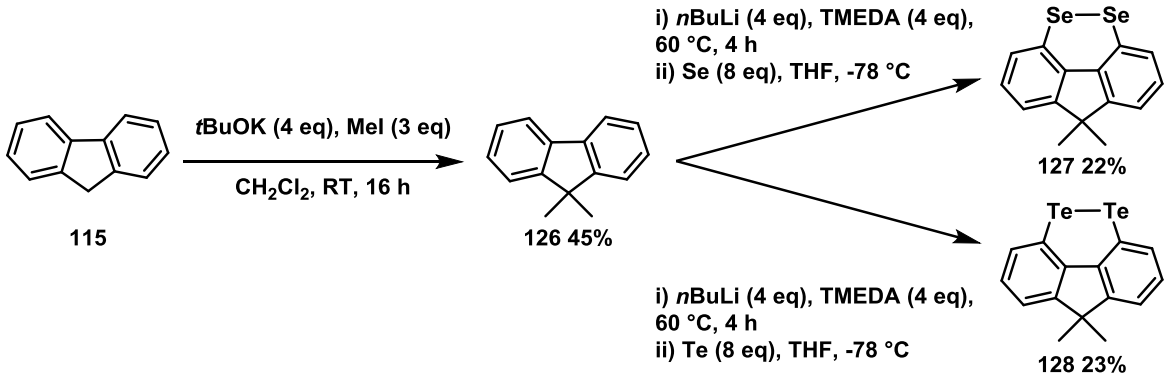
Scheme 21 Preparation of seleninic anhydride **124**

NMR analysis indicated that only one diastereomer was present but did not provide conclusive evidence of which diastereomer was present. Therefore, X-ray data was required to unambiguously assign the structure of seleninic anhydride **124**. However, due to the difficulties in growing sufficient quality crystals of seleninic anhydride **124** for single crystal X-ray analysis, structural alterations to the fluorene scaffold were made to promote crystal formation.

The primary concern was that the *n*butyl groups were preventing efficient crystal packing and thus formation of a single crystal. Based on this hypothesis, the *n*butyl chains were replaced with methyl groups to prevent crystal packing disruption.

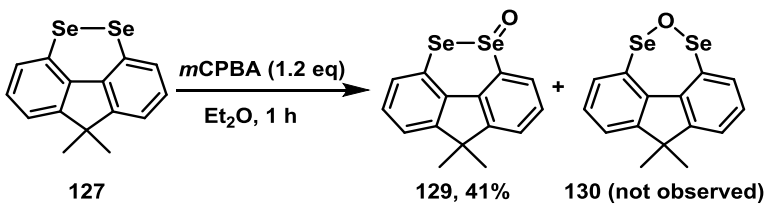
Dimethylated diselenide **127** was therefore targeted. The synthesis of **127** began with the dimethylation of **115** to give compound **126**. The alkylation was achieved using *t*BuOK in the presence of MeI giving the desired material in a 45% yield.[79] Using the existing lithiation procedure, diselenide **127** was obtained in a 22% yield (Scheme 22).

It was also envisioned that the ditelluride analogue of **127** could be accessed via a similar procedure. Dimethylfluorene **126** was therefore subjected to an analogous lithiation tellurium quench sequence to afford ditelluride **128** in a 23% yield (Scheme 22).



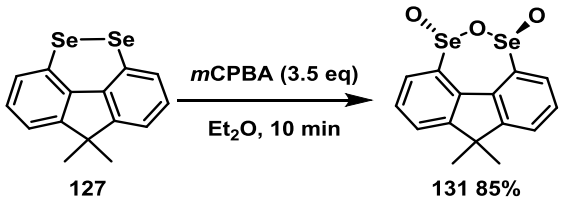
Scheme 22 Preparation of diselenide **127** and ditelluride **128**

Oxidation of diselenide **127** to the corresponding selenolseleninate **129** was achieved using the same conditions shown in Scheme 20. Treating **127** with 1.5 eq of *m*CPBA yielded selenolseleninate **129** in a 41% yield with the starting material returned in a 55% yield (Scheme 23). The use of CH_2Cl_2 as the reaction solvent reduced the yield to 30%; increasing the loading of *m*CPBA did not increase the yield in CH_2Cl_2. Analytical data for the isolated compound again suggested formation of selenolselinate **129** rather than a selenic anhydride **130**.



Scheme 23 Preparation of selenolseleninate **129**

Treating diselenide **127** with 3.5 equivalents of *m*CPBA in Et_2O yielded seleninic anhydride **131** in an 85% yield (Scheme 24). Unfortunately, this compound, like the previous seleninic anhydride **124**, did not produce crystals; therefore, no X-ray data could be collected. Only one signal was observed in the ^{77}Se NMR for **131** and no inequivalent proton environments were observed. Therefore compound **131** has been thought to exist exclusively as the *trans*-diastereomer.



Scheme 24 Preparation of *trans*-seleninic anhydride **131**

The Se atoms in naphthalene seleninic anhydride **114** and fluorene seleninic anhydride **131** are stereogenic centres.[70] NMR analysis of **114** by ^{77}Se NMR highlighted two different signals; two inequivalent proton environments were also observed in the ^{1}H NMR. Selenic anhydride **114** exists as two diastereomers, the *cis* and the *trans*-. In contrast, only one signal is observed in the ^{77}Se NMR for compounds **124** and **131** and no inequivalent proton environments where observed; these data suggested that the isolated compounds were present exclusively as the C_2-symmetric, *trans*-diastereomers **124** and **131** (Figure 23). However, it should be noted that both fluorene seleninic anhydride diastereomers may have indistinguishable ^{1}H and ^{77}Se NMR spectra and that there may be no observable difference between diastereomers.

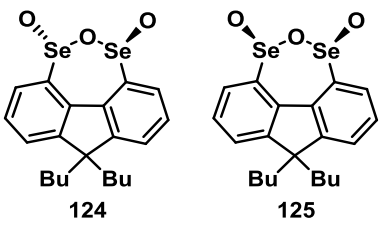
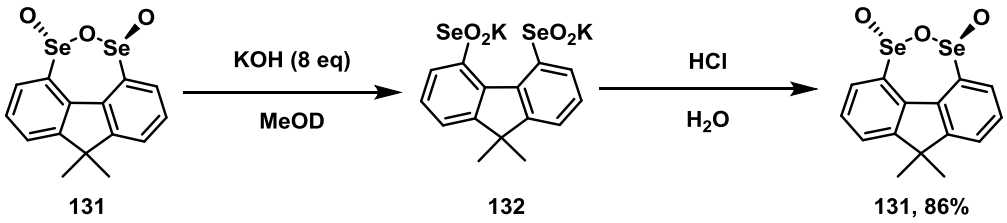


Figure 23 *Trans*-seleninic anhydride **124** and its *cis*-diastereomer **125**

Back *et al.* showed that *cis* and *trans* naphthalene seleninic anhydride **114** converged to a single dipotassium salt upon treatment with potassium hydroxide. In order to gain further insight into kinetic vs thermodynamic control in the sole formation of **124** and **131**, seleninic anhydride **131** was exposed to excess potassium hydroxide in MeOD giving dipotassium salt **132** (Scheme 25). Only one ^{77}Se NMR signal was observed for this compound. When the solution was acidified, seleninic anhydride **131** was reformed. Reformation of compound **131** suggests that the *trans*-diastereomer may be the most thermodynamically stable seleninic anhydride configuration in the case of fluorene.



131 **132** **131, 86%**

Scheme 25 Preparation of dipotassium salt **132**

2.3 X-ray analysis of fluorene diselenide 127

The crystal structure of the novel diselenide **127** was obtained. Selected bond lengths and angles for **127** are shown in Table 2. and compared with fluorene diselenide **117**.

The X-ray crystal data of **127** shows that the compound is structurally similar to **117**. The Se-Se bond is the same for both **117** and **127.** The C(1)-Se(1)-Se(2)-C(11) dihedral angle in **117** is 44 °; diselenide **127** shows a smaller twist of 42 ° (entry 4, Table 2). There is no significant difference in the torsional strain within the fluorene scaffolds shown in the C(1)-C(13)-C(12)-C(11) bond angle (entry 6, Table 2). The most notable difference is that diselenide **117** has 4 independent molecules in the unit cell.

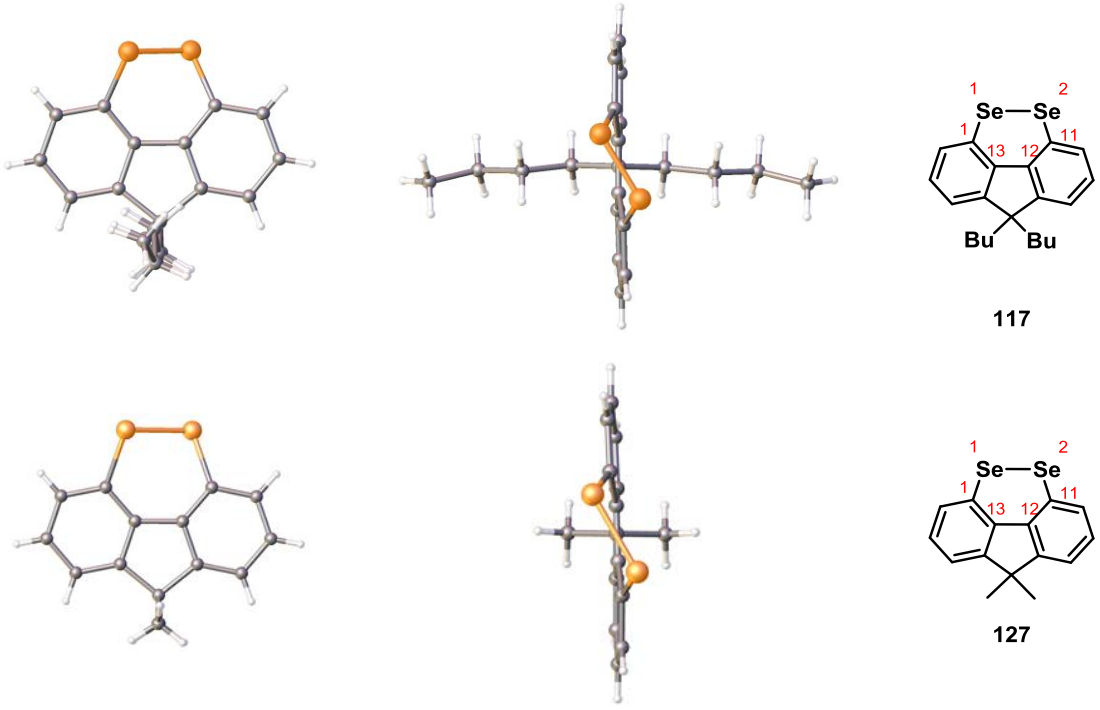


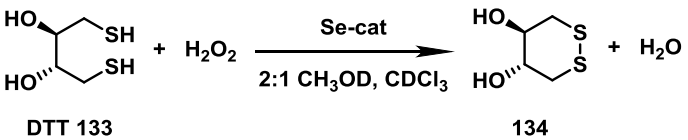
Figure 24 Crystal structure of compounds **117** and **127**

Entry	Compound	117	127
1	Se-Se	2.341	2.341
2	Se(1)-C(1) Se(2)-C(11)	1.930	1.919
3	C(1)-Se(1)-Se(2) C(11)-Se(2)-Se(1)	98.90	99.5
4	C(1)-Se(1)-Se(2)-C(11)	44.00	42.3
5	Se(1)-C(1)-C(11)-Se(2)	32.3	30.9
6	C(1)-C(13)-C(12)-C(11)	9.0	10.0
7	Se(1)-C(1)-C(13) – 120° Se(2)-C(11)-C(12) – 120°	0.98	0.63

Table 2 Selected bond lengths (Å) and angles (°) for compounds **117** and **127**

2.4 GPx-like activity of fluorene diselenides, monoxides and trioxides

The GPx-like activity of diselenides **112**, **117** and **127**, monoxides **122** and **129**, trioxides **124** and **131**, and ditellurides **118** and **128** was evaluated the ^{1}H NMR assay developed by Iwaoka *et al*.[34] This assay uses dithiothreitol (DTT) **133** as a thiol surrogate in the presence of H_2O_2 (Scheme 26). Iwaoka's kinetic assay is also adaptable as it can accommodate a number of different solvent systems.[9] Catalyst efficiency was measured as the time required for a given catalyst to decrease the thiol concentration by 50% (Figure 25). This study was carried out in collaboration with Prof Antonella Capperucci and Dr Damiano Tanini at the University of Florence.



Scheme 26 Oxidation of DTT **133** with H_2O_2 in the presence of chalcogen-containing catalysts (10 mol%).

The assay had to be modified as the standard solvent CH_3OD did not solubilise the majority of the catalysts. $CDCl_3$ was capable of solubilising catalysts **112**, **117**, **118**, **122**, **127**, **128** and **129** but not seleninic anhydrides **124** and **131,** which were only soluble in polar solvents. A 2:1 mixture

of CH_3OD and $CDCl_3$ was therefore utilised to enable the full solubilisation of compounds **124** and **131**.

Compounds **112**, **117**, **118**, **122**, **124**, **127**, **128**, **129** and **131** were tested in the assay. The results are shown in Figure 25 and Graph 1. The values are reported as an average of three experiments carried out under standard conditions. $t_{1/2}$ is the time required, in minutes, to halve the initial thiol concentration after the addition of H_2O_2.

The compounds displayed varying levels of activity. The control experiment was used to determine the rate of thiol oxidation, in the absence of any catalyst. The $t_{1/2}$ of the conversion of DTT **133** to **134** in the absence of any catalyst was measured at 2657 min. In this assay, the $t_{1/2}$ of the known naphthalene catalyst **112** (Figure 25) was 374 min. Fluorene diselenides **117** and **127** displayed similar activities to that of naphthalene diselenide **112** with a $t_{1/2}$ of 391 and 420 min respectively. Selenolseleninates **122** and **129** displayed greater activities than **112** and the parent diselenides (Figure 25), with $t_{1/2}$ of 253 and 141 min respectively. Seleninic anhydrides **124** and **131** (Figure 25) were the most active selenium catalysts, with compound **131** being the most active; the $t_{1/2}$ of **124** was 105 min and **131** was 52 min. Seleninic anhydride **131** was eight times more active than the corresponding diselenide. Interestingly the carbon substituents at C-9 of the fluorene had an effect on catalytic activity; compounds with methyl groups were generally 1.5 times greater than compounds with butyl groups. Tellurium compounds **118** and **128** were shown to be the most active catalysts with $t_{1/2}$ below three minutes.

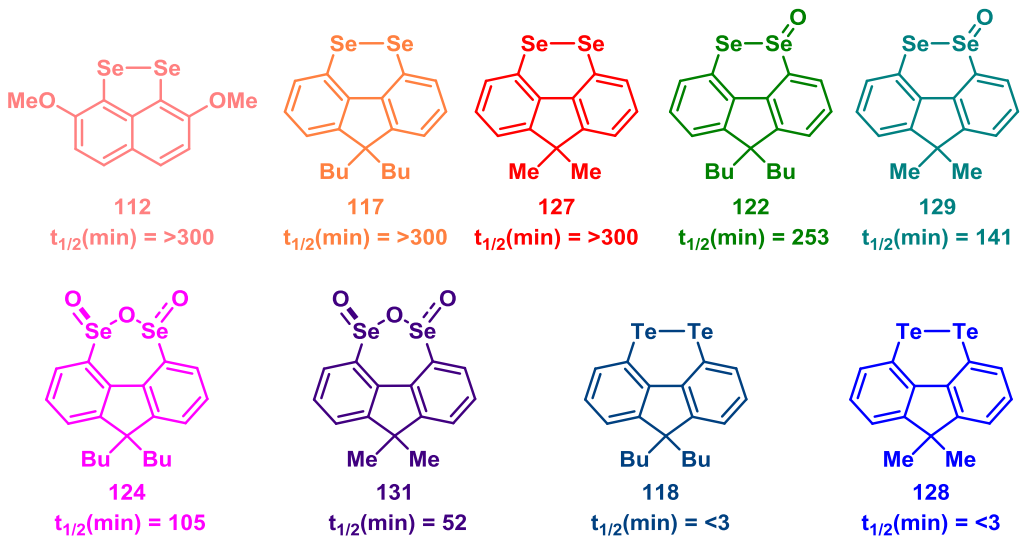
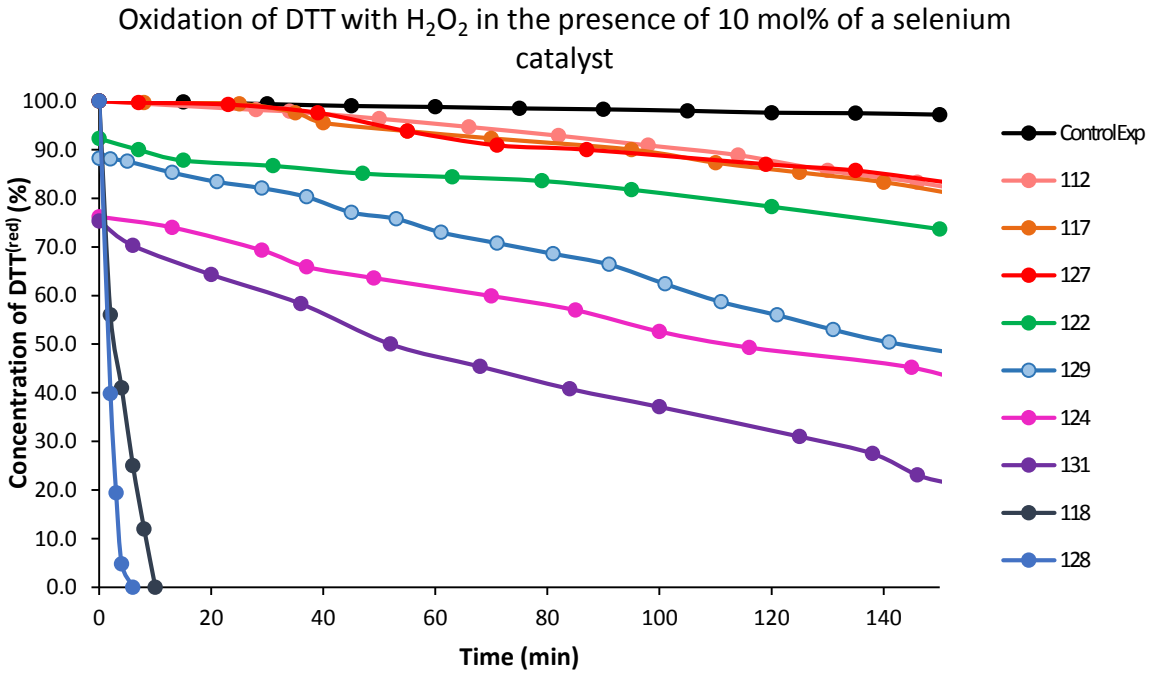


Figure 25 $t_{1/2}$ of the conversion of DTT **133** to DTT **134**



Graph 1 Oxidation of DTT with H_2O_2 in the presence of chalcogen-containing catalysts (10%). Reaction conditions: DTT=0.14 M, H_2O_2=0.14 M, catalyst=0.014 M. Reactions performed in a 2:1 $CD_3OD/CDCl_3$ (0.6 mL). Reported are the mean values of 3 separate experiments.

Catalysts **122**, **129**, **124** and **131** initially react rapidly with the thiol substrate, before the first NMR reading can be taken (entries 3-6, Table 3). Selenolseleninates **122** and **129** consume 8 and 12% of the thiol substrate respectively (entries 3 and 4, table 3). Seleninic anhydrides **124** and **131** consumed 25% thiol substrate at the start of the reaction (entries 5 and 6, table 3). These

results may indicate that catalysts **122**, **129**, **124** and **131** may act as transient intermediates or precatalysts in a catalytic cycle. These results are rationalised below in section 2.5.

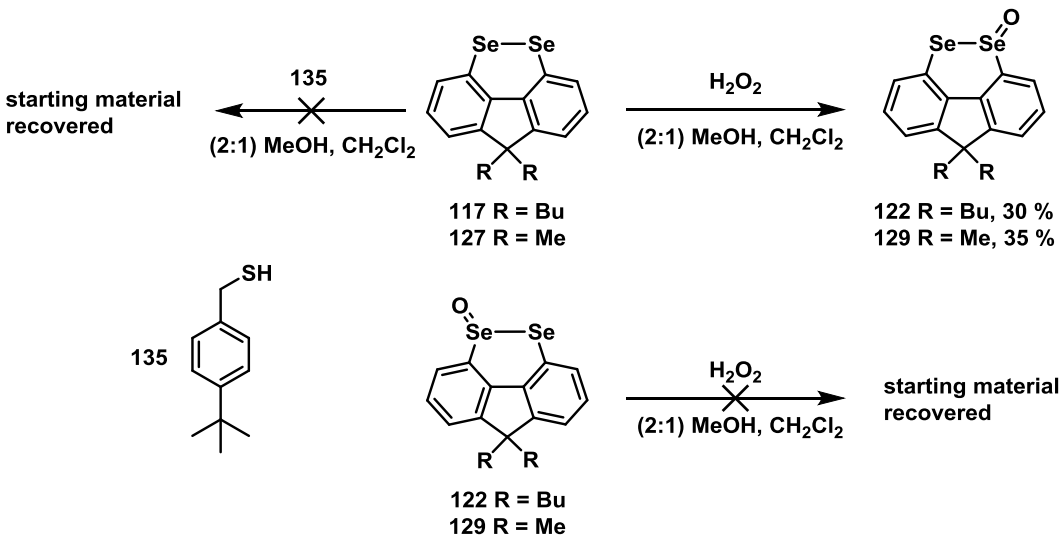
Entry	Catalyst	*DTTred (%)*
1	**117**	100
2	**127**	100
3	**122**	92
4	**129**	88
5	**124**	75
6	**131**	75

Table 3 Consumption of DTT at t_0

2.5 Investigations into the catalytic cycle of fluorene diselenides

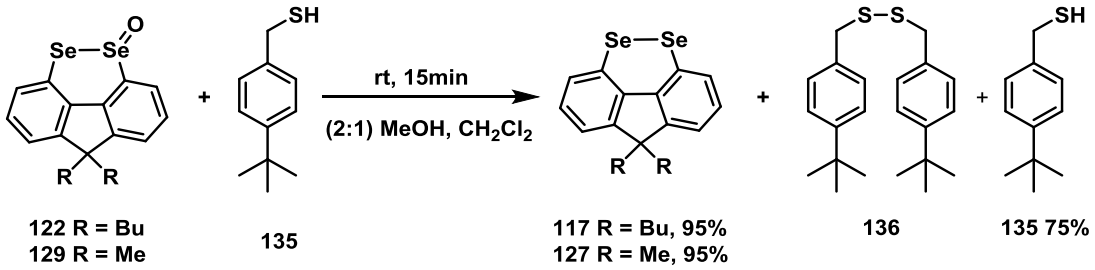
A series of experiments was carried out in order to gain insight into the mechanism of the GPx-like catalytic activities of fluorene diselenides **117** and **127**, selenolseleninates **122** and **129**, and seleninic anhydrides **124** and **131**. 4-*tert*-Butylbenzylthiol **135** was chosen for stoichiometric studies because it was easy to handle and relatively non odorous.

When diselenides **117** and **127** were treated with 10 equivalents 4-*tert*-butylbenzylthiol **135** in the absence of H_2O_2, no reaction was observed over a period of 24 hours (Scheme 27). When **117** and **127** were treated with 1 equivalent of H_2O_2 in the absence of thiol, the corresponding selenolseleninates **122** and **129** were formed over a 24-hour period in 30% and 35% yield respectively. The starting material recovery was 70% and 63% respectively. Selenolseleninates **122** and **129** were subjected to the same experiments. When **122** and **129** were exposed to excess H_2O_2 no further oxidation was observed over a 24-hour period.



Scheme 27 Reactions of H_2O_2 and 4-*tert*-butylbenzylthiol **135** with **117, 122, 127** and **129**

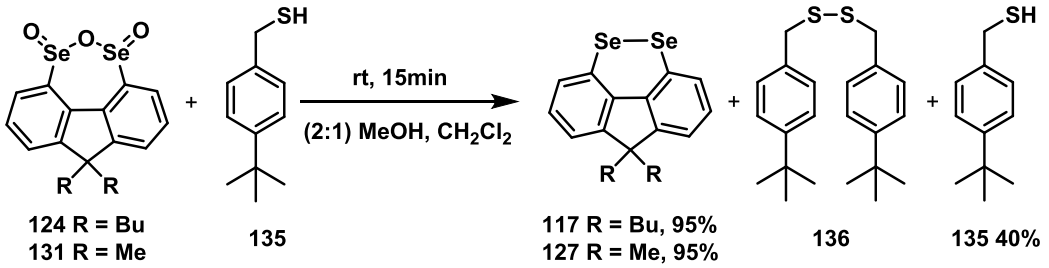
However, when **122** and **129** were treated with 4-*tert*-butylbenzylthiol **135** in the absence of H_2O_2, thiol **135** was rapidly consumed, giving the corresponding diselenide and disulfide **136** as the only products. In order to determine the stoichiometry of this reaction, selenolseleninate **122** and **129** was treated with 10 equivalents of 4-*tert*-butylbenzylthiol, diselenide **127** was obtained in 95% yield and 4-*tert*-butylbenzylthiol was recovered in 75% yield, indicating two equivalents of thiol had been consumed and one molar equivalent of disulfide **136** relative to selenoseleniate had been produced (Scheme 28).



Scheme 28 Reactions of 4-*tert*-butylbenzylthiol **135** with **122** and **129**

Seleninic anhydrides **124** and **131** were also subjected to these mechanistic investigations. No further oxidation was observed when **124** or **131** was treated with H_2O_2 in the absence of thiol **135**. However, when **124** or **131** was treated with thiol **135** there was an immediate reaction

which generated the corresponding diselenide in a 95% yield and disulfide **136**. Compounds **124** and **131** were subjected to the same stoichiometry experiments as the selenolseleninates. When compounds **124** and **131** were treated with 10 equivalents of 4-*tert*-butylbenzylthiol **135**, the corresponding diselenides were both isolated in 95% yield; 4-*tert*-butylbenzylthiol **135** was recovered in 40% yield, indicating six equivalents of thiol had been consumed. Three molar equivalents of disulfide **136** had been produced (Scheme 29).

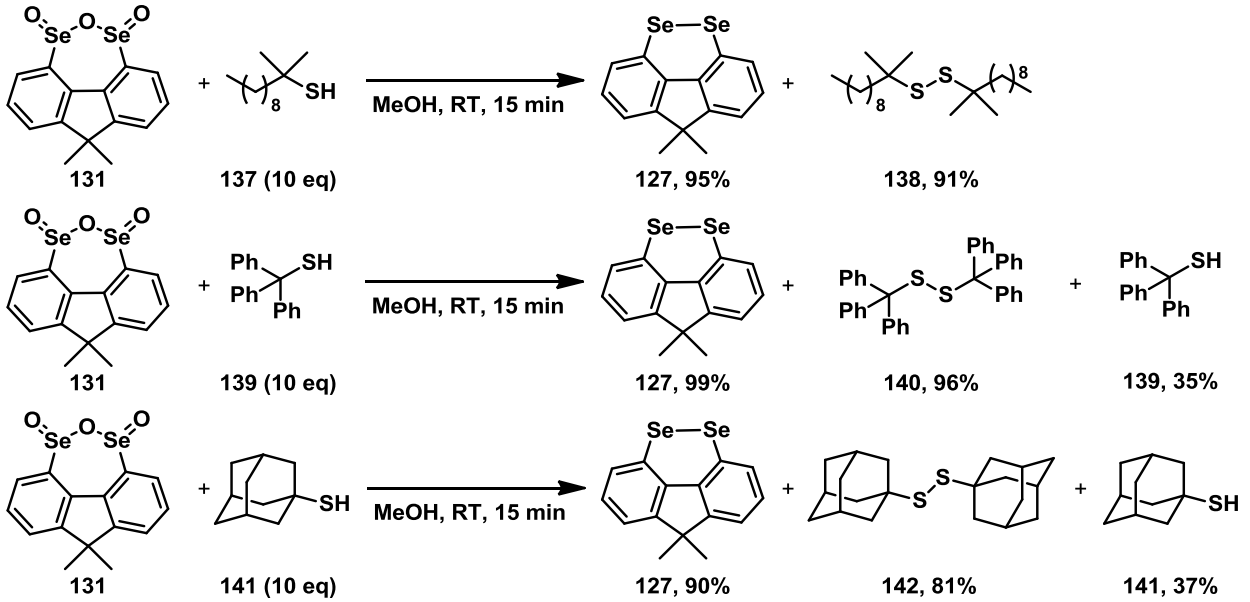


Scheme 29 Reaction of 4-*tert*-butylbenzylthiol **135** with **124** and **131**

Due to the rate of the reaction between selenolseleninates **122** and **129** and seleninic anhydrides **124** and **131** with thiol **135**, no intermediates could be observed. Previous work by Kice *et al.* reported the isolation of selenenylsulfides derived from 1,8-naphthalene diselenide and *tert*-butylthiol.[78] It was therefore proposed that treatment of **129** or **131** with a sterically bulky thiol would allow isolation of an intermediate in the reduction of selenolselinates or seleninic anhydrides to fluorene diselenides.

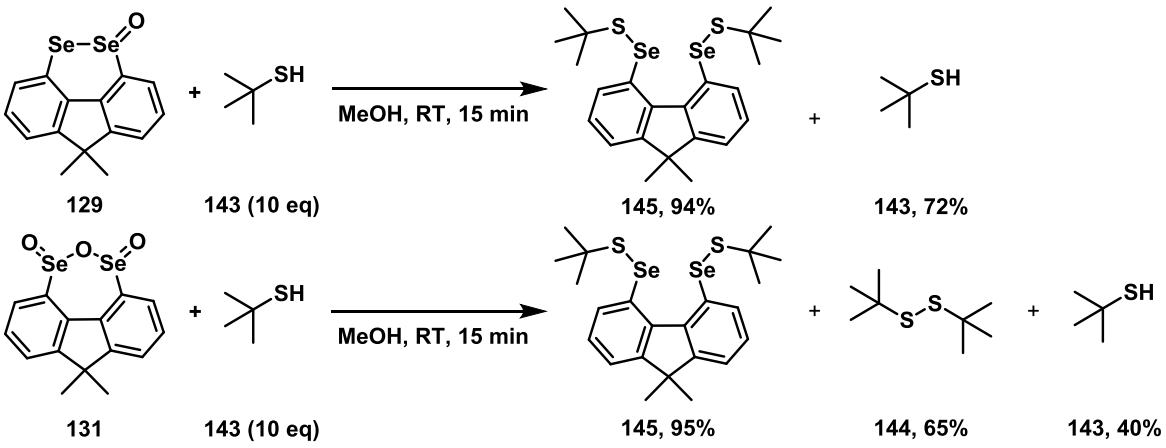
Seleninic anhydride **131** was subjected to a range of different tertiary thiols, in search of an isolable intermediate (Scheme 30). When **131** was reacted with *tert*-dodecanethiol **137** at 0 °C a new compound was formed which could be isolated by flash column chromatography. This compound however was unstable and broke down over 24 hours to give **127** and disulfide **138**. Unfortunately, this intermediate could not be characterised. Seleninic anhydride **131** was reacted with 10 equivalents of triphenylmethanethiol **139** and 1-adamantanethiol **141**. However, both of

these reactions were rapid and did not generate an isolable intermediate, but rather gave diselenide **127** and disulfides **140** and **142**, with thiol **139** and **141** also recovered.



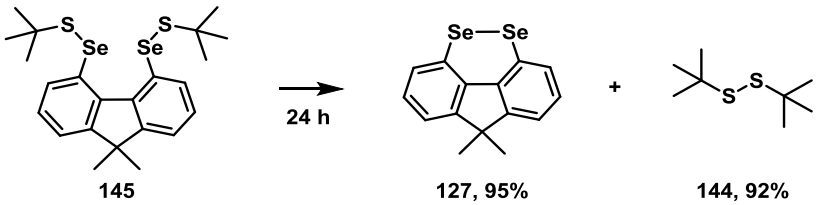
Scheme 30 Reactions of **131** with **138, 140** and **142**

Selenosulfide **145** was obtained when **129** or **131** was treated with 10 equivalents of *tert*-butylthiol **143** (Scheme 31). The reaction between **143** and **131** was complete within 5 minutes and gave a mixture of diselenide **127**, disulfide **144** and selenylsulfide intermediate **145**. The identity of this species as a bisselenylsulfide was supported by ^{1}H and ^{13}C NMR, which showed the molecule was symmetrical, and ^{77}Se NMR showed that there was only one Se environment at 398.6 ppm which was indicative of a Se-S moiety. The stoichiometry of the reactions shows that compound **131** consumed 6 equivalents of *tert*-butylthiol **143** and generated 2 equivalents of disulfide **144**. Under identical conditions, selenolseleninate **129** consumed 2 equivalents of **143**.



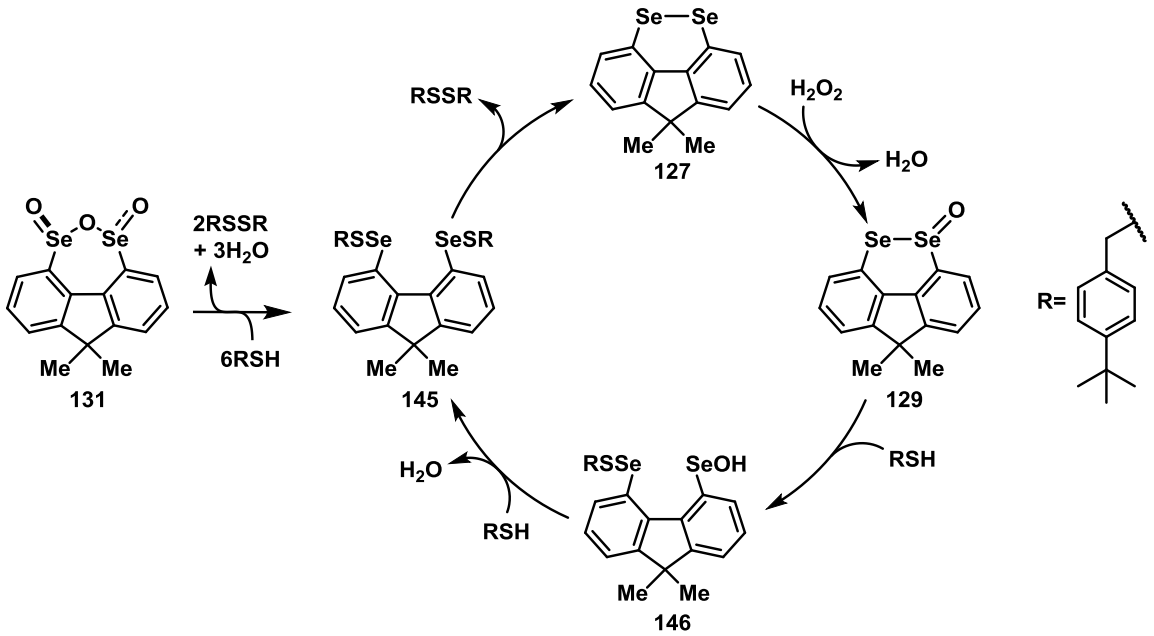
Scheme 31 Preparation of intermediate **145**

Selenosulfide **145** was unstable and decomposed at room temperature. The products of decomposition are diselenide **127** and disulfide **144** (Scheme 32). Degradation of **145** was tracked by ^{77}Se NMR. Complete decomposition of this intermediate at room temperature takes 24 h. Cooling **145** to 0 °C does not appreciably slow this degradation. The decomposition of **145** indicates that an additional thiol is not required for the expulsion of disulfide from the molecule, and that this process may be an intramolecular reaction rather than intermolecular. Additional thiol may catalyse the rate of degradation via an intermolecular reaction. In order to test this hypothesis *tert*-butylthiol was added to **145**, however this did not increase the rate of decomposition. In a separate experiment 4-*tert*-butylbenzylthiol **133** was added to **145**, but this again did not speed up degradation; in addition, **144** was the only disulfide that was isolated after this reaction. This indicates that regeneration of **127** is an intramolecular process. It should be noted that the *tert*-butyl moiety in **145** is sterically demanding and will thus disfavour intermolecular attack at sulfur, and so the preferred intramolecular decomposition of **145** may not necessarily be mirrored for other thiols.



Scheme 32 Degradation of intermediate **143**

These mechanistic studies suggest the catalytic cycle shown in Scheme 33, which is directly analogous to the catalytic cycle for naphthalene diselenide **112** proposed by Back (Scheme 14). The initial step of this reaction is the oxidation of **127** to selenolseleninate **129**, this step is the slowest and therefore the rate-determining step. This is followed by rapid capture by thiol to form transient selenenic acid **146**. Addition of a second molecule of thiol generates selenylsulfide **145**, expelling a molecule of water. Selenylsulfide **145** rapidly expels a molecule of disulfide and regenerates **127,** this process may be inter or intramolecular, and may be catalysed by addition of thiol, but is proposed to be intramolecular for R = *tert*-butyl. Seleninic anhydride **131** rapidly reacts with thiols and joins the catalytic cycle through intermediate **145**. Seleninic anhydride cannot be regenerated by H_2O_2; therefore **131** acts as a precatalyst in this cycle.



Scheme 33 Proposed mechanism of GPx-like catalysis of compounds **127, 129** and **131**

Ditellurides **118** and **128** were the most active catalysts, producing reaction rates that were almost too fast to measure under the assay conditions. This activity is similar to that observed with *peri*-substituted naphthalene ditellurides. Back *et al.* noted that after prolonged reactions, the yields of dibenzyl disulfide were reduced. This suggested that the ditellurides were catalysing the oxidation of disulfides.[70] When ditelluride **128** was reacted with **136** in the presence of excess oxidant H_2O_2, no thiolsulfinates or any overoxidation products were observed. Despite displaying the best catalytic activities, it was decided to cease investigations into producing other ditellurides. This was due to concerns over the toxicity of organotellurium compounds. Organotellurium compounds have been shown to be more toxic than organoselenium compounds; they have been shown to be highly toxic to the central nervous system of rodents.[55, 80]

In summary, fluorene diselenides **117** and **127** have shown GPx-like activity similar to that of naphthalene diselenide **112** in a dithiothreitol NMR assay, and mechanistic investigations suggest the same catalytic cycle may be operating for both systems. Just like the naphthalene systems, the fluorene scaffolds have low aqueous solubility. However, it was anticipated that the water solubility could be increased through appropriate modification of the fluorene scaffold, and that this would be easier to achieve than in the naphthalene series.

2.6 Design and synthesis of water-soluble fluorene diselenides

Derivatizations of the fluorene scaffold could be achieved by derivatization at C-9 (Figure 26). Compounds **148** and **149** are known compounds which can be synthesised from fluorene and contain functionalities that would make the synthesis of water-soluble catalysts more expedient. Further investigations will look at fluorenone **147** as a potential starting material towards water-soluble fluorene diselenides; this compound possesses a carbonyl group at carbon 9 which may

make any derivatisations to the scaffold more expedient than fluorene, and potentially increase the scope of transformations available.

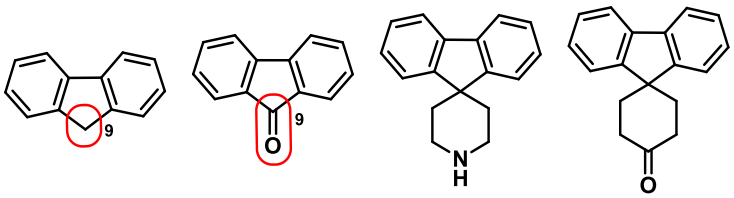
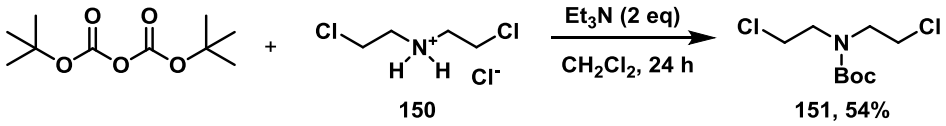


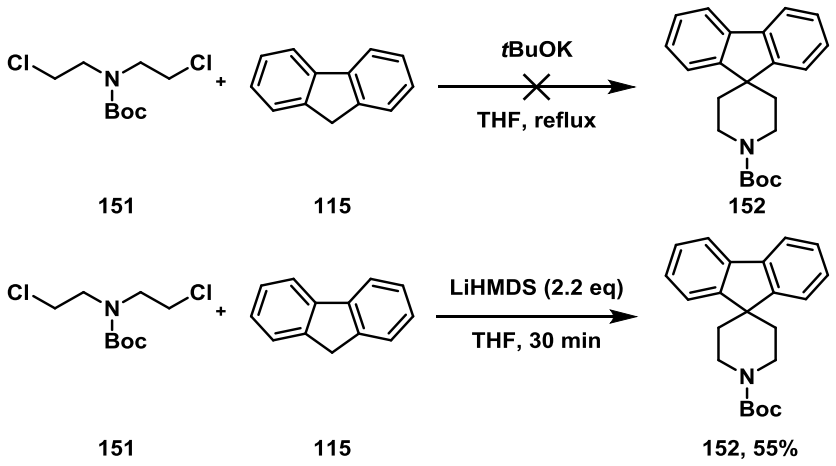
Figure 26 Potential synthetic precursors to water-soluble fluorene diselenides

The synthesis of compound **148** started with the Boc-protection of bis-(2-chloroethyl)amine hydrochloride **150** (Scheme 34). Following the procedure of Evans and coworkers, Boc-protected amine **151** was synthesised in 54% yield.[81]



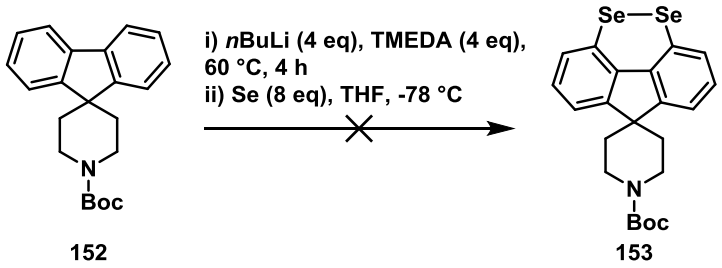
Scheme 34 Boc protection of amine **151**

The next step towards the synthesis of **148** required the dialkylation of **115** with Boc-protected bis-chloroethyl amine **151**. The synthesis of compound **152** was attempted using the alkylation procedure previously used for compounds **116** and **126** (Scheme 16 and Scheme 22). The use of *t*BuOK at 30 °C or at reflux in THF quantitatively returned the starting materials. Compound **152** had been previously prepared by Evans and coworkers.[81] Following their procedure commercially available fluorene **115** was treated with 2 equivalents of lithium hexamethyldisilazide, Boc protected amine **151** was then added to give **152** in a 55% yield after purification (Scheme 35).



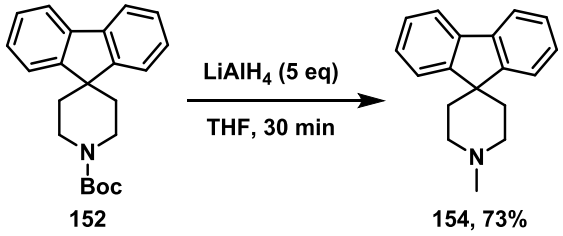
Scheme 35 Alkylation of fluorene **115** with amide **151**

With compound **152** in hand it was decided to attempt the lithiation procedure to insert selenium onto the fluorene scaffold. However, application of the previous reaction conditions failed to give the desired diselenide product, with only a complex mixture of unidentifiable products obtained (Scheme 36). The proposed reason for the reaction failure was the Boc-group acting as a directing group, facilitating the deprotonation of the proton adjacent to the nitrogen of the spirocyclic piperidine ring by *n*BuLi.



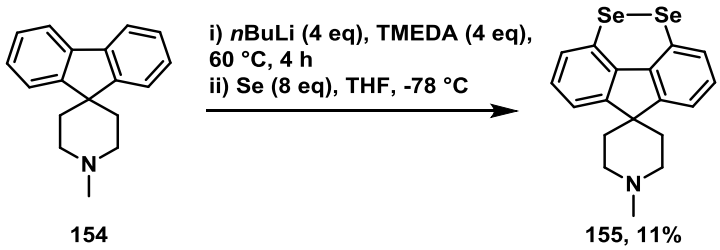
Scheme 36 Attempted lithiation of diselenide **153**

The selenium insertion reaction could not take place in the presence of the Boc protecting group. Deprotecting the molecule was not a viable option as this would give a secondary amine, which would not tolerate the reaction conditions of selenium insertion. It was decided to reduce the Boc-group to give a tertiary amine **154**. Compound **152** was treated with $LiAlH_4$ giving tertiary amine **154** in 73% yield (Scheme 37).



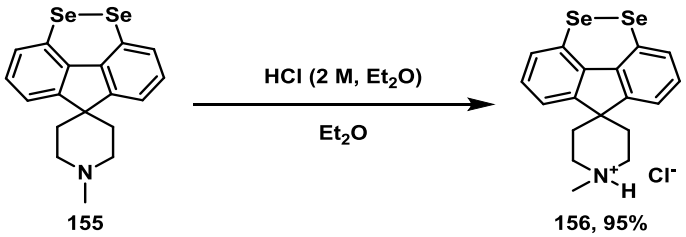
Scheme 37 $LiAlH_4$-mediated reduction of **152**

Compound **154** was subjected to the selenium insertion reaction.[77] This reaction successfully gave diselenide **155**, albeit in a low 11% yield.



Scheme 38 Preparation of diselenide **155** *via* lithiation

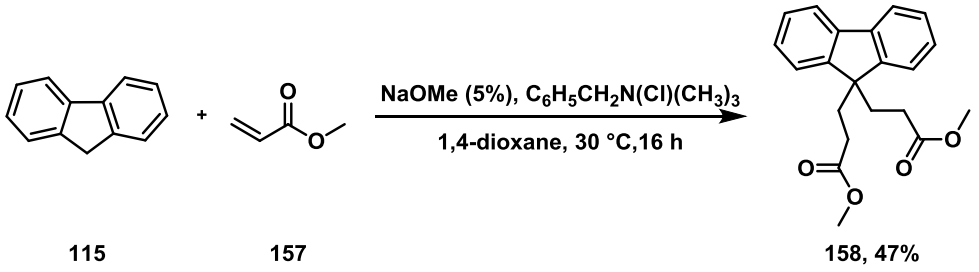
The tertiary amine group of **155** was then exploited to give a quaternary ammonium salt. Compound **155** was dissolved in THF and HCl was added, giving quaternary ammonium salt **156** in 95% yield after evaporation with no further purification required (Scheme 39). This compound proved to be water-soluble. The catalytic activity of diselenide **156** will be discussed in chapter 3.



Scheme 39 Preparation of quaternary ammonium salt **156**

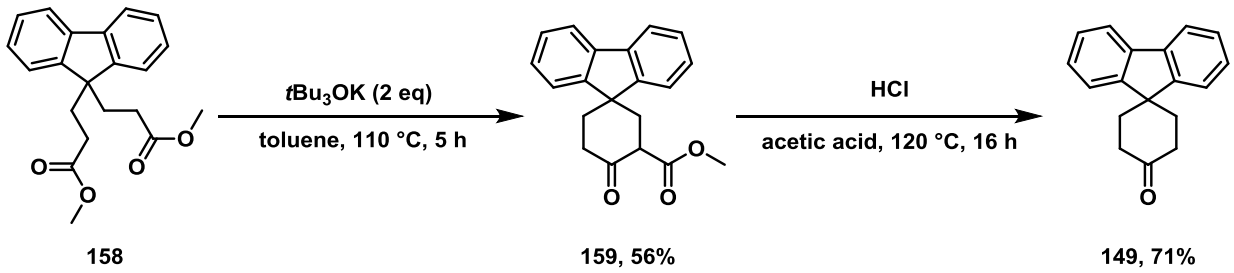
The synthesis of diselenide **149** was first attempted according to the literature procedure.[82] Fluorene and methyl acrylate were mixed with sodium hydroxide in toluene. However, this reaction failed to give any of target diester **158** and the starting material was recovered quantitively. Michael-addition reaction with fluorene and methyl acrylate in the presence of the

phase-transfer catalyst benzyltrimethylammonium chloride in 1,4-dioxane gave compound **158** in 47% yield (Scheme 40). The yield for this reaction was lower than the 92% reported by the literature. TLC analysis indicated that the reaction had not reached completion. Increasing the reaction time to 72 h and increasing the reaction temperature had no effect on the yield.



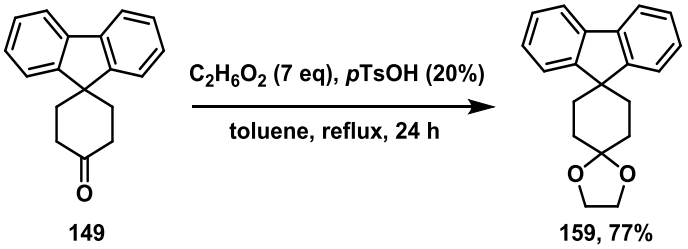
Scheme 40 Preparation of diester **158** *via a* Michael-addition reaction

Following a literature procedure, Dieckmann cyclisation of diester **158** gave keto ester **159** in 56% yield after purification.[82] Keto ester **159** was then heated in a mixture of conc $HCl_{(aq)}$ and acetic acid. These reaction conditions effectively hydrolysed ester **159** and decarboxylated the resulting carboxylic acid in one step, yielding spirocyclic ketone **149** in 71% yield (Scheme 41).



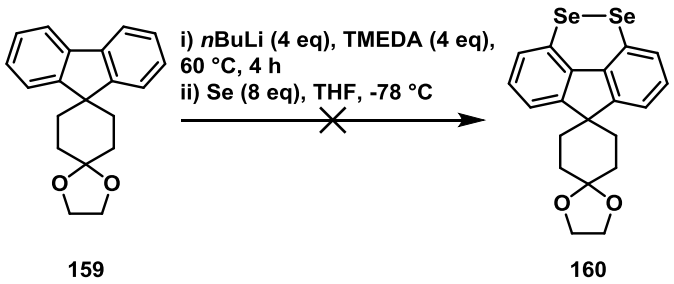
Scheme 41 Dieckmann cyclisation of diester **158** and decarboxylation of keto ester **159**

In order to insert selenium into this compound the carbonyl group had to be protected. It was decided to protect the carbonyl as a cyclic acetal, as the addition and removal of this protecting group was convenient. Spiroketone **149** was reacted with ethylene glycol to give compound **158** in 77% yield (Scheme 42).



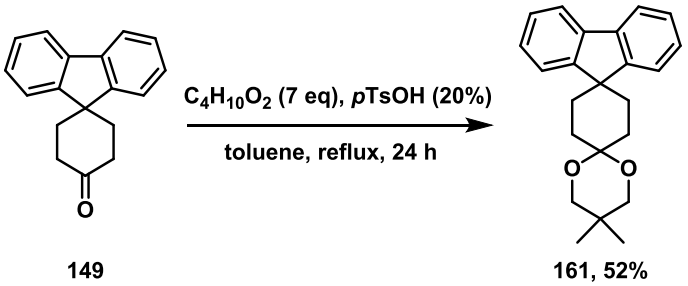
Scheme 42 Acetal protection of compound **149**

No diselenide was obtained after compound **159** was reacted in the selenium insertion reaction (Scheme 43). The only material that was observed after the reaction was an unidentifiable mixture of compounds that could not be characterised. Further analysis using ^{13}C NMR indicated that the acetal protecting group had been removed during the reaction.



Scheme 43 Attempted selenium insertion of **159**

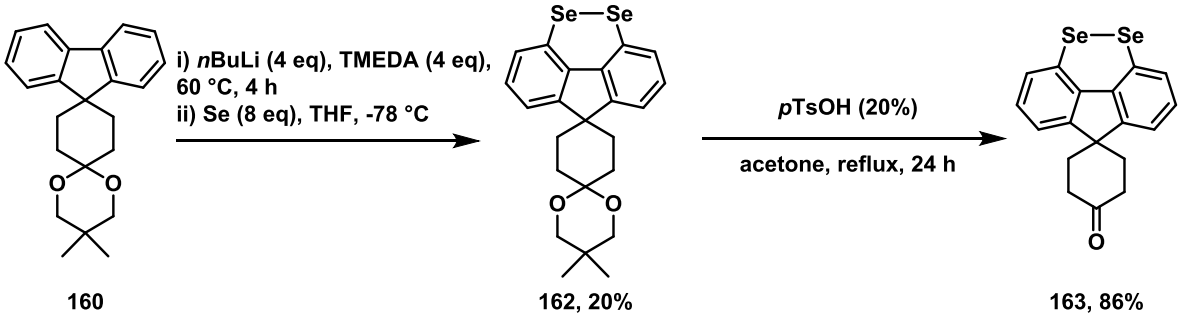
It was decided to change the type of acetal protecting group to one that may survive the harsh conditions of the selenium insertion reaction. Spirocyclic ketone **147** was reacted with neopentyl glycol to give compound **161** in 52% yield (Scheme 44).



Scheme 44 Acetal protection of compound **149** with neopentyl glycol

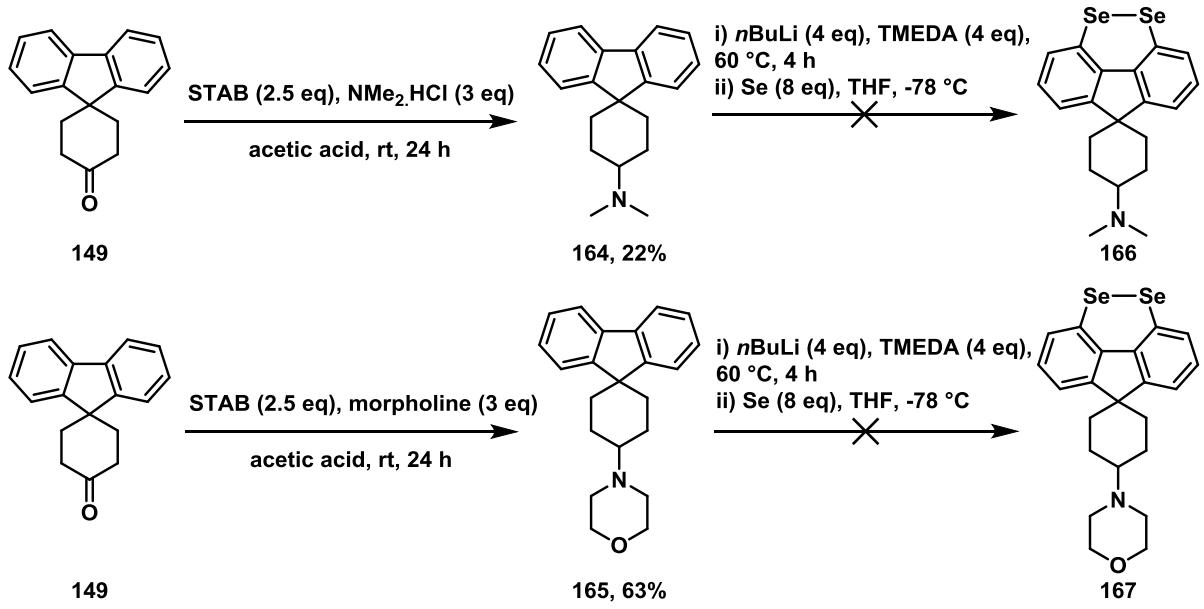
This protecting group proved to be more stable and survived the selenium insertion procedure. The reaction gave diselenide **162** in 20% yield after purification (Scheme 45). Deprotection of

compound **161** with catalytic amounts of *p*TsOH in acetone gave spirocyclic ketone **162** in 86% yield.



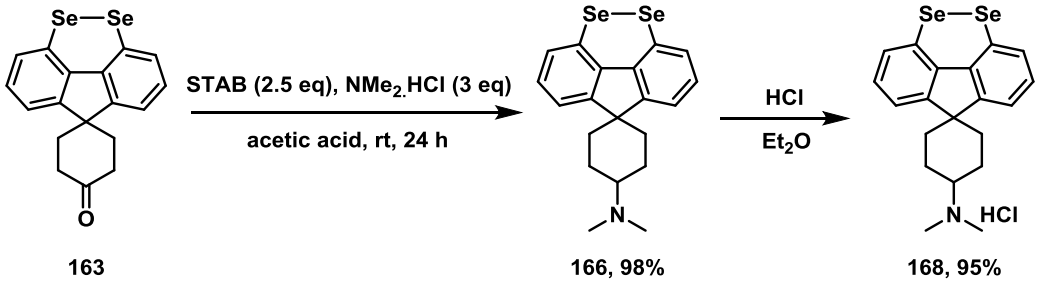
Scheme 45 Synthesis of diselenide **162** and acetal deprotection to spirocyclic ketone **163**

In an effort to reduce the number of steps in this synthetic pathway it was decided to conduct a reductive amination instead of protecting the ketone. Compound **147** was subjected to reductive amination reactions with both dimethyl-amine and morpholine giving tertiary amines **164** and **165** in 22% and 63% yields respectively. However, when **164** and **165** were subjected to the lithiation conditions they did not give the desired diselenides. Both reactions gave a mixture of unidentifiable compounds (Scheme 46).



Scheme 46 Reductive amination of spirocyclic acetal **149** with morpholine and dimethyl-amine and attempted formation of diselenides

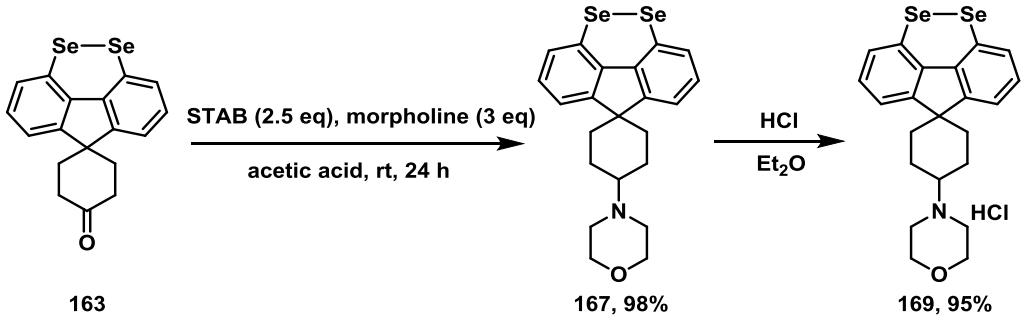
With **163** in hand, it was decided that the most expedient way to make the scaffold water-soluble was to prepare a tertiary amine group *via* a reductive amination reaction. Compound **163** was exposed to dimethylamine and sodium triacetoxyborohydride to give tertiary amine **166** in 98% yield. When amine **166** was exposed to a 2 M solution of HCl in diethylether, ammonium salt **168** was precipitated in 95% yield. Unfortunately, this salt did not prove to be sufficiently water-soluble for catalytic testing (Scheme 47).



163 166, 98% 168, 95%

Scheme 47 Reductive amination of diselenide **163** with dimethyl amine

It was decided to change the dimethylamine group for a more polar substituent. Compound **163** was exposed morpholine and sodium triacetoxyborohydride to give **167** in 98% yield. Amine **167** was then exposed to a 2 M solution of HCl in diethylether and ammonium salt **169** was precipitated in 95% yield (Scheme 48). This salt proved to be water soluble. The catalytic activity of diselenide **169** will be discussed in chapter 3.

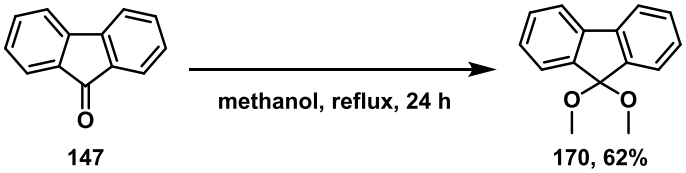


163 167, 98% 169, 95%

Scheme 48 Reductive amination of diselenide **163** with morpholine

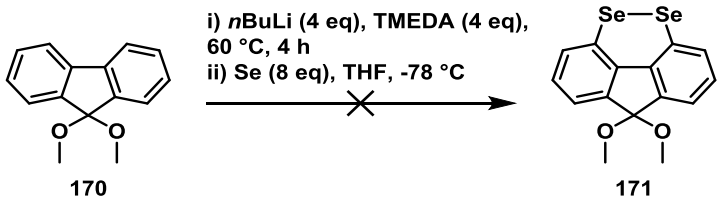
Fluorenone possess the same tricyclic ring system as fluorene and if selenium could be inserted into fluorenone, it potentially offers a route into much more complex molecules owing to the

inbuilt carbonyl component of the scaffold. However, the carbonyl group of fluorenone requires protection before the lithiation reaction. It was decided to protect the carbonyl as a dimethylacetal. Following a literature procedure, fluorenone was treated with methanol, trimethyl orthoformate and camphorsulfonic acid as an acidic catalyst.[83] The resulting reaction gave the dimethylacetal **170** in 62% yield (Scheme 49). Compound **170** could not be stored as it was especially susceptible to hydrolysis.



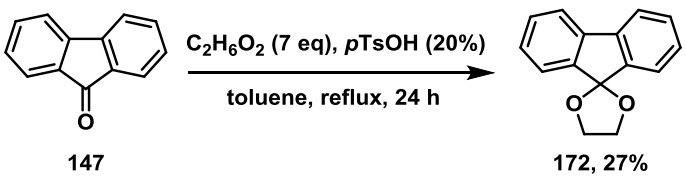
Scheme 49 Protection of fluorenone **170** as a dimethyl acetal

Attempted selenium insertion on fluorene **170** did not give product **171** but gave a complex mixture of compounds that could not be identified (Scheme 50). This suggested that the protecting group did not tolerate the reaction conditions.



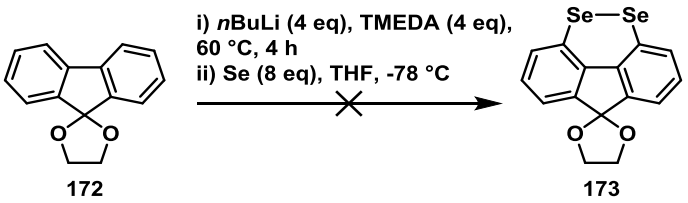
Scheme 50 Attempted lithiation and selenium insertion of fluorene dimethylacetal **170**

It was decided to protect the carbonyl of **147** as a cyclic acetal. Fluorenone was treated with ethylene glycol with *p*TsOH as an acidic catalyst. The resulting reaction gave protected compound **171** in 27% yield (Scheme 51).



Scheme 51 Protection of fluorenone **170** as cyclic acetal **172**

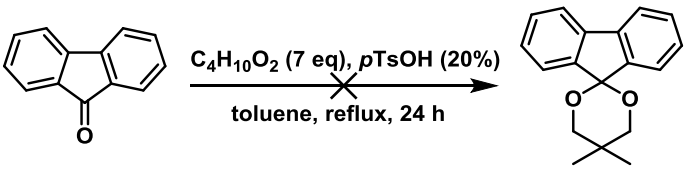
As with the previous attempt using the same cyclic acetal protecting group, the selenium insertion reaction on **172** did not give diselenide **173** but gave a complex mixture of compounds that could not be identified (Scheme 52). It appeared that the protecting group was removed during the reaction as none of the starting material was recovered.



172 173

Scheme 52 Attempted lithiation and selenium insertion of cyclic acetal **172**

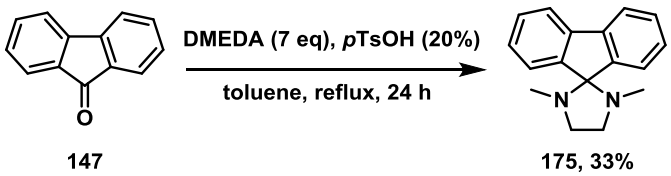
It was decided to protect fluorenone with the same cyclic acetal that successfully withstood the lithiation reaction conditions (Scheme 45). Fluorenone was submitted to the same conditions shown in Scheme 51 and reacted with neopentyl glycol in the presence of *p*TsOH. However, there was no evidence of acetal formation over a 24 or 48 h period (Scheme 53).



147 174

Scheme 53 Attempted acetal protection of fluorenone **174** with neopentyl glycol

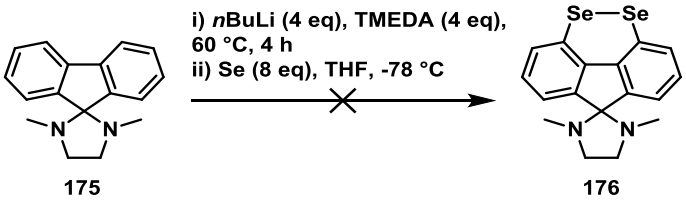
It was also decided to investigate the protection of fluorenone as an aminal, if the selenium incorporation proved to be compatible, the resulting aminal would not need to be deprotected, but could be used as a precursor to a water-soluble salt. Fluorenone was treated with 1,2-dimethylethylenediamine (DMEDA) with *p*TsOH as an acid catalyst for 72 h. The resulting reaction gave aminal **174** in 33% yield (Scheme 54). The low yield was due to incomplete reaction with starting material, which was recovered in 65% yield.



147 175, 33%

Scheme 54 Aminal protection of fluorenone **175**

Subjecting compound **174** to the selenium insertion reaction did not give the desired product, but again gave a complex mixture of compounds that could not be identified (Scheme 55). It appears the protecting group was removed during the reaction as none of the starting material was recovered.



175 176

Scheme 55 Attempted lithiation of aminal **175**

In summary, an acetal or aminal-protected fluorenone that could be subsequently lithiated and selenated has not been found. It was anticipated that acetal **174** would be the most likely to undergo the selenium insertion reaction, but **174** proved unexpected difficult to make, and hence could not be tested.

2.7 Conclusion

The synthesis of fluorene diselenides **117** and **127** has been achieved. The synthesis of fluorene selenolseleninates **122** and **127** along with seleninic anhydrides **124** and **131** from oxidation of their respective diselenides has been achieved; unfortunately, none of the seleninic anhydrides could be recrystallised, therefore no X-ray data could be gathered for this class of compounds. Novel ditellurides **118** and **128** have also been synthesised from alkylated fluorenes.

Fluorene diselenides **117** and **127** display similar GPx-like activity to that of naphthalene diselenide **112** in the ^{1}H NMR based DTT assay shown in Figure 25. Seleninic anhydrides **124** and **131** and ditellurides **118** and **128** show a significant rate enhancement over all of the catalysts.

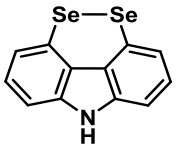
The mechanism of GPx-like catalysis mediated by fluorene diselenides has been investigated. The rate-determining step of the reaction is the oxidation of the diselenides by H_2O_2 to selenolseleninate. The enhanced catalytic activity of fluorene selenolseleninates over fluorene diselenides can be attributed to an initial rapid reaction with DTT, as the initial oxidation step is circumvented. Fluorene seleninic anhydrides **124** and **131** display significant rate enhancements over fluorene diselenides; stoichiometric studies have shown that fluorene seleninic anhydrides act as precatalysts. Once this species is consumed, it cannot be regenerated by the H_2O_2 present in the assay.

Water-soluble fluorene diselenides **167** and **168** were synthesised, however the overall yield of the route was low. Unfortunately, investigations towards the synthesis of a water-soluble diselenide from a fluorenone scaffold were unsuccessful.

Chapter 3 *Peri*-like carbazole diselenides as glutathione peroxidase mimics

3.1 Introduction

The difficulty in preparing water-soluble fluorene diselenides, as described in the previous chapter, highlighted the need for a simpler scaffold that retained the design features of the naphthalene and fluorene GPx mimics but would be easier to derivatise. 4,5-Disubstituted carbazole diselenides **177** were proposed as a potential solution to this problem (Figure 27).



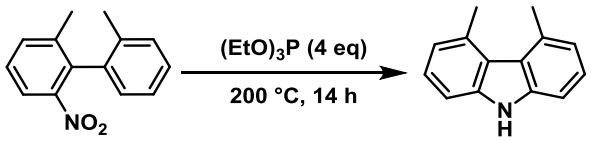
177

Figure 27 Target carbazole diselenide

3.2 Synthetic approaches to 4, 5-carbazoles

Carbazoles are fused *N*-heterocycles. Carbazole and its derivatives are an important class of molecule with applications in medicinal chemistry.[84-86] They have also been widely exploited in material chemistry, particularly as organic light emitting diodes, conducting polymers and synthetic dyes.[87-89] Due to the importance of carbazoles, there have been a large number of reports regarding strategies to synthesise carbazoles.[90, 91]

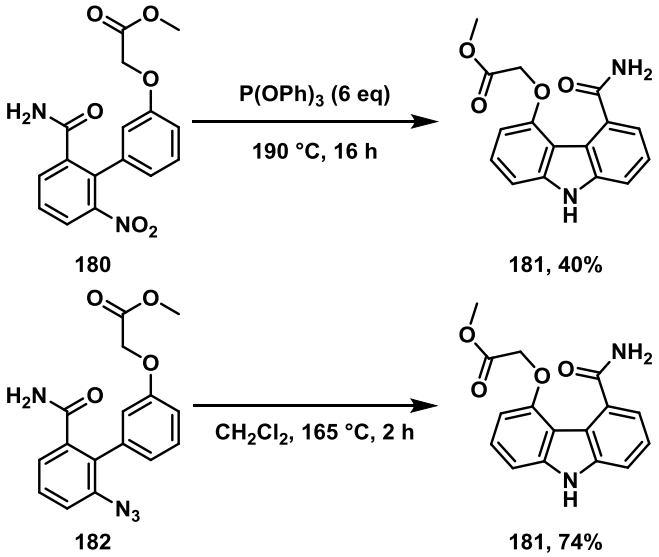
The Cadogan cyclisation is a valuable method for preparing carbazole derivatives. 4,5-Disubstituted carbazole **179** was obtained *via* Cadogan cyclisation of 2,2'-dimethyl-6-nitrobiphenyl **178** with triphenylphosphine, however this reaction was low yielding (Scheme 56).[92] The low yield was presumed to be caused by unfavourable steric interactions of the two methyl groups preventing ring closure of the nitrene intermediate.[93]



178 179, 0.2%

Scheme 56 Cadogan cyclisation of 2,2'-dimethyl-6-nitrobiphenyl **178** to give 4,5-dimethylcarbazole **179**

May *et al.* used the Cadogan cyclisation to give the more elaborate 4,5-disubstituted carbazole derivative **181** (Scheme 57). However this reaction only gave a maximum yield of 40%.[94] Formation of the target compound *via* the thermal decomposition of azide **182** was attempted, in an effort to increase the yield. This reaction did give compound **181** in a 74% yield; however, this reaction was only conducted on a small scale due to the inherent hazards in the use of an azide.

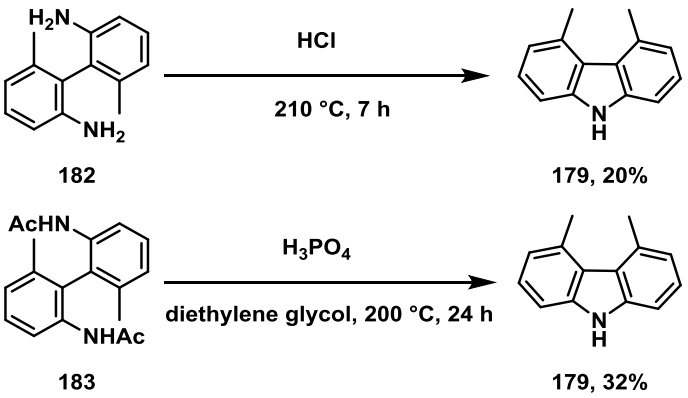


180 181, 40%

182 181, 74%

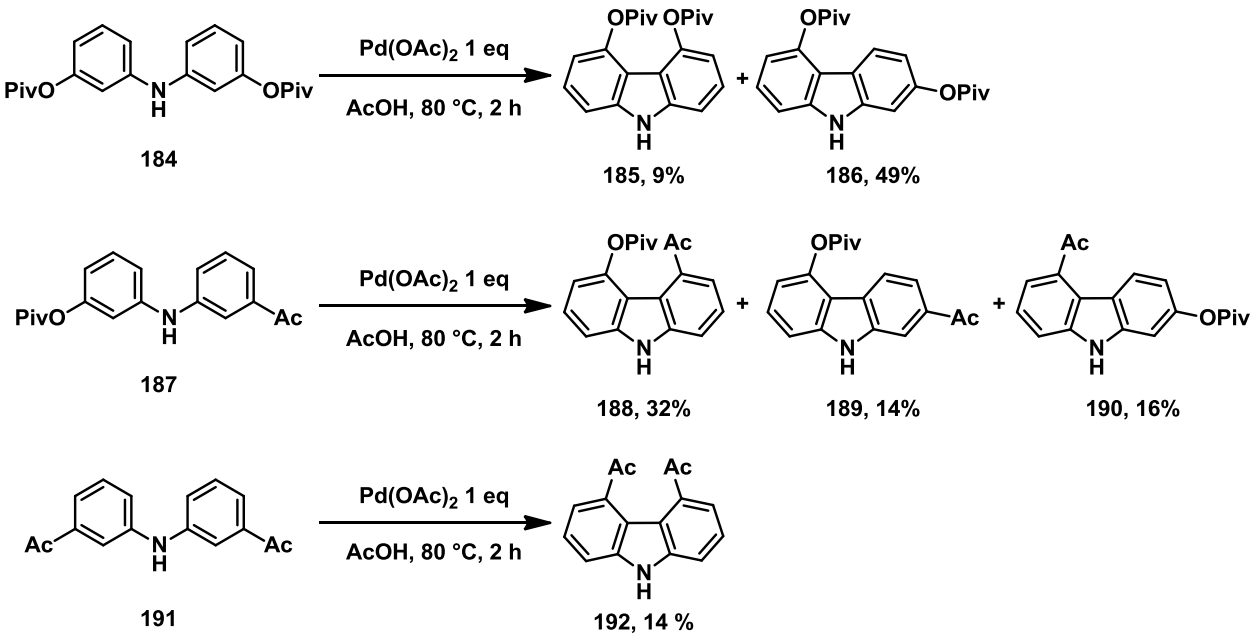
Scheme 57 Cadogan cyclisation and azide decomposition to give carbazole **181**

4, 5-Disubstituted carbazole **179** was also synthesised from 2,2'-diamino-6,6'-dimethylbiphenyl **182** *via* the Täuber carbazole ring synthesis giving **179** in a 20% yield (Scheme 58).[92] This ring closure reaction employed biaryl diamine **183** in H_3PO_4 and diethylene glycol. This procedure only increased the yield to 32%.[95] Both of these reactions require strongly acidic environments and high reaction temperatures.



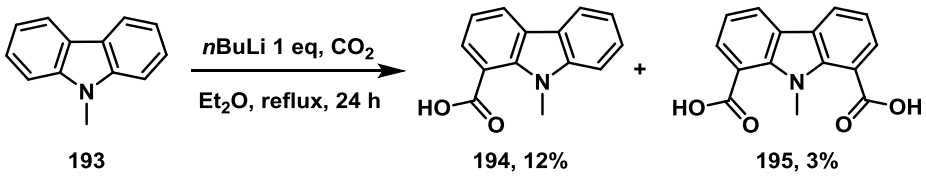
Scheme 58 Synthesis of 4,5-disubstituted carbazole **179** *via* the Täuber carbazole ring synthesis

Palladium(II)-catalysed oxidative C–C coupling reactions have been used to create carbazoles from biarylamines. This method has been used to produce 4,5-disubstituted carbazoles (Scheme 59).[96] The palladium(II)-catalysed oxidative cyclisation of biarylamine **184** gave carbazole **185** in a 9% yield, but also gave the 2,5 and 3,6-disubstituted carbazoles in 49% and 1% yield respectively. Mechanistic studies showed that the substituents had a strong regiodirecting effect. In order to promote the formation of a 4,5-disubstituted isomer one of the pivaloyl groups was replaced with an acetyl group. This gave **188** in a 32% yield, while two other regioisomers **189** and **190** were also produced.



Scheme 59 Palladium(II)-catalysed oxidative C–C coupling reactions of biarylamines for carbazole synthesis

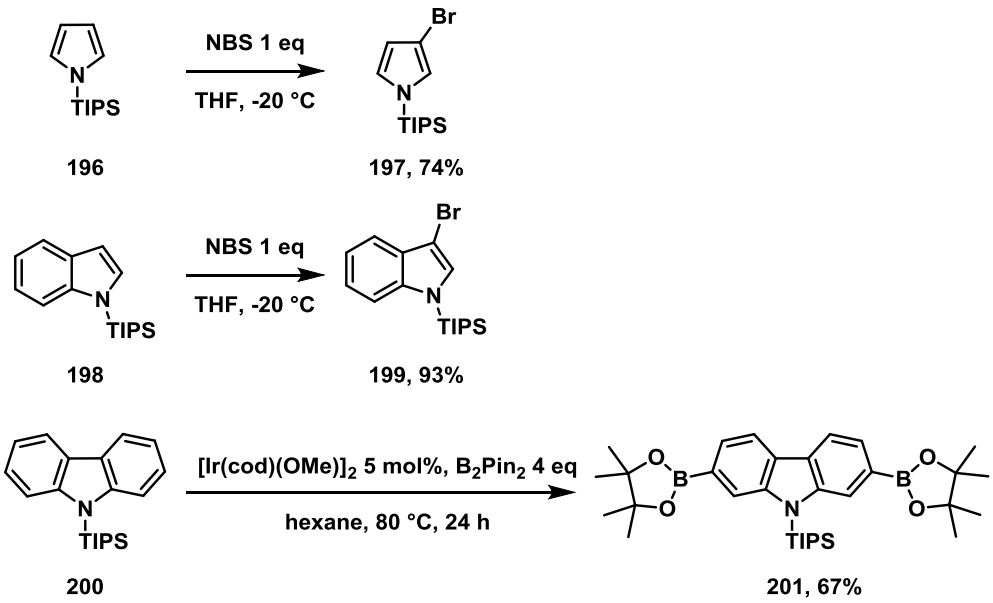
The metalation of carbazole with *n*BuLi has been documented; Gilman *et al.* reacted *N*-methylcarbazole **193** with *n*BuLi and then carbonated to give mono-carboxylic acid **194** in 12% yield and dicarboxylic acid **195** in 3% yield (Scheme 60).[97] Interestingly, when *N*-ethylcarbazole was exposed to the same reaction conditions only mono-carboxylic acid was formed. This was attributed to the larger ethyl group making dimetalation more difficult. The yield of this reaction could be increased using a directing group.[98] These lithium mediated metalations occur exclusively on the 1 or 1,8 position of the carbazole.[97, 99, 100]



Scheme 60 Lithiation of carbazoles

Substitution of nitrogen-containing heterocycles such as pyrrole and indole can be directed by the use of a sterically demanding groups such as *N*-TIPS on nitrogen (Scheme 61).[101-103] This methodology can be used on carbazole, effectively blocking the 1,8 positions to yield 2,7-bis-

borylated carbazole **201**.[103] *tert*-Butyl and trityl moieties have also been used in the same capacity as the TIPS moiety, but these groups have proven to be difficult to remove.[101]



Scheme 61 TIPS-directed substitution of pyrrole, indole and carbazole using

3.3 Aims and objectives

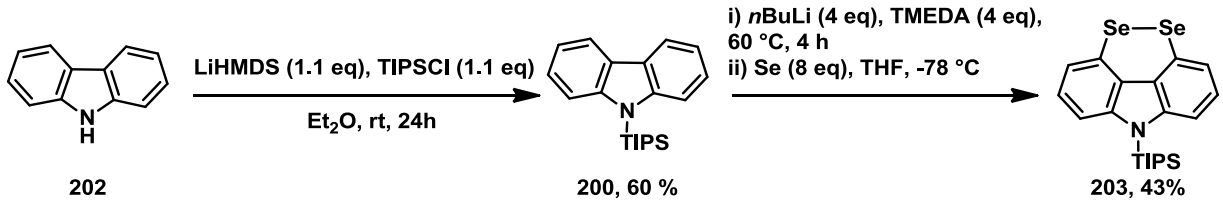
Fluorene diselenides have displayed activity that is similar to that of naphthalene-based diselenides. However, the initial fluorene compounds were not water-soluble. In order to make compounds based on the diselenide scaffold viable drug targets, water solubilising moieties must be added. The previous chapter detailed the synthesis of two water-soluble fluorene diselenides **167** and **169** (Scheme 36, 43). However, these compounds were difficult to synthesize.

The aim of the research included in this chapter is to prepare and investigate carbazole diselenides as GPx mimics. The TMEDA-mediated dilithiation of naphthalene and fluorene previously described in chapter 2 has not been used on a carbazole system. In addition, lithiation of the carbazole scaffold is directed to the 1 and the 8 position (Scheme 60). The use of a bulky nitrogen substituent such as TIPS to direct lithiation and subsequent selenium insertion in the 4 and 5 positions of the carbazole ring system will be explored.

The GPx-like activity of the water-soluble fluorene and carbazole systems will be investigated. The effects of electron-donating groups and electron-withdrawing groups on the GPx-like activity of any carbazole diselenides will also be explored.

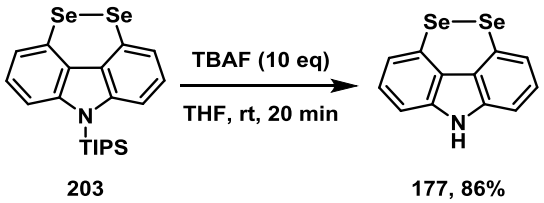
3.4 Results and discussion

Commercial carbazole **202** was protected using triisopropylsilyl chloride (TIPSCl), following a literature procedure.[103] The initial reaction using *n*BuLi as a base was successful and gave a high yield of *N*-TIPS carbazole **200**. These results could not be replicated as subsequent reactions repeatedly gave low yields of the product with much of the starting material left unreacted. LiHMDS was more reliable and consistently gave yields of 60% (Scheme 62). With **200** in hand, it was decided to conduct the lithium mediated selenium insertion reaction. Diselenide **203** was obtained in 43% yield after purification. This transformation is the first example of carbazole being 4,5-substituted in one step.



Scheme 62 TIPS protection of carbazole and preparation of diselenide **203**

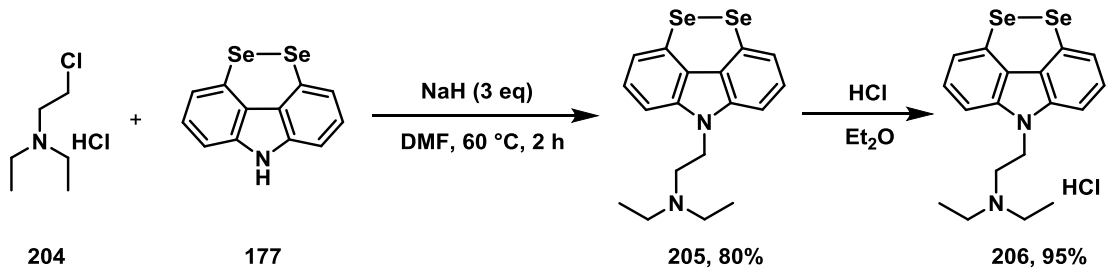
With the diselenide moiety in place the TIPS protecting group was no longer needed. The TIPS protecting group was removed using TBAF after 15 min of stirring at room temperature (Scheme 63). Compound **177** was obtained in 95% yield after purification.



Scheme 63 TIPS deprotection of compound **203**

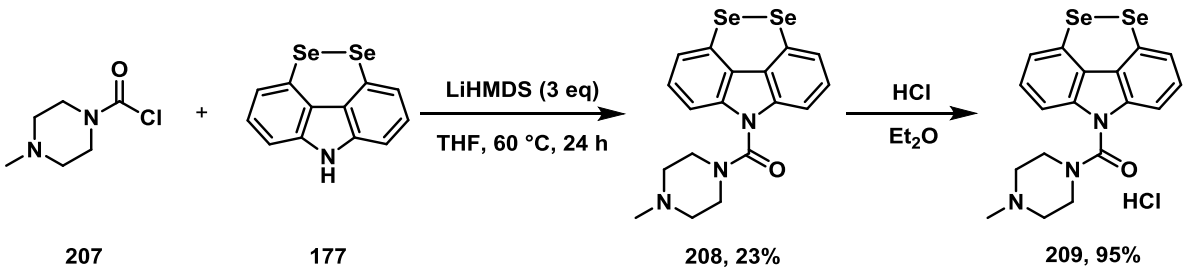
It was decided to add a polar group to the carbazole to improve the water solubility of the scaffold, adding a tertiary amine centre would be the most expedient way to achieve this. Diselenide **177** was reacted with 2-chloro-*N,N*-diethylethylamine hydrochloride **204** in the

presence of sodium hydride giving **205** in 80% yield after purification (Scheme 64). When amine **205** was exposed to a 2 M solution of HCl in diethylether, ammonium salt **206** was precipitated in 95% yield.



Scheme 64 Preparation of carbazole **205** *via N*-alkylation

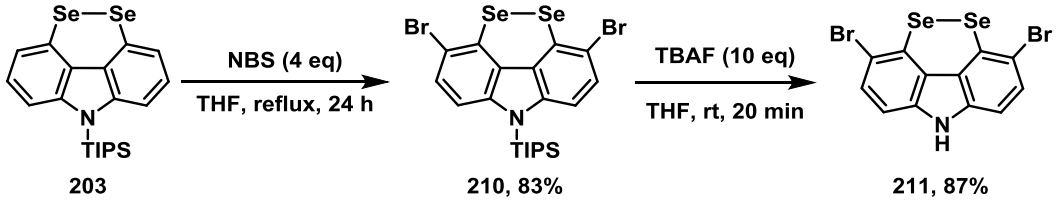
The effects of electron-withdrawing substituents on the carbazole ring on the catalytic activity of the diselenide was of interest as these groups are suspected to reduce catalytic activity. To investigate these effects, it was decided to add a group that was both electron-withdrawing and sufficiently polar to allow the molecule to become water-soluble. Carbazole **177** was reacted with 4-methyl-piperazine-1-carbonyl chloride **207** in the presence of LiHMDS giving **208** in 23% yield (Scheme 65). When amine **208** was exposed to a 2 M solution of HCl in diethylether, ammonium salt **209** was precipitated in 95% yield.



Scheme 65 Preparation of carbazole **207**

Halogen substituents are also capable of modulating GPx like activity of selenium compounds (Figure 11, p16). The 3,6-substituted dibromide **210** was prepared using a modified literature procedure.[104] Diselenide **203** was brominated using *N*-bromosuccinimide (NBS) giving **210** in 83%

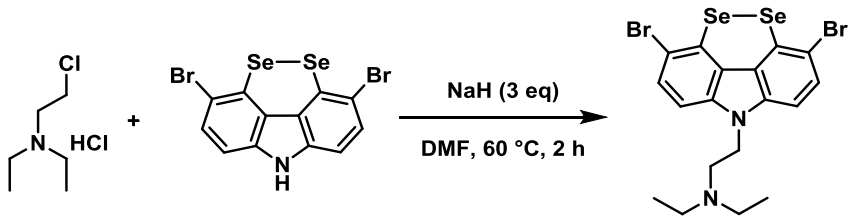
yield. Following this the TIPS protecting group was removed using TBAF after 15 min of stirring at room temperature. Diselenide **211** was obtained in 87% yields after purification.



203 **210, 83%** **211, 87%**

Scheme 66 Bromination of diselenide **203** and TIPS deprotection of dibromide **210**

In order to investigate the effects of halogens on the rate of catalytic activity, it was decided to add tertiary amine **204** to make a water-soluble dibromide (Scheme 67).[21, 56] Diselenide **211** was alkylated using 2-chloro-*N,N*-diethylethylamine hydrochloride **204** using the same conditions as shown in Scheme 64. Compound **211** was reacted with 2-chloro-*N,N*-diethylethylamine hydrochloride in the presence of sodium hydride giving **212** in 90% yield after purification. Amine **212** was then dissolved in Et_2O and acidified in an attempt to yield the corresponding HCl salt. However, the material produced at the end of the reaction was not soluble in water or any other solvent. Therefore, it could not be characterised or used.

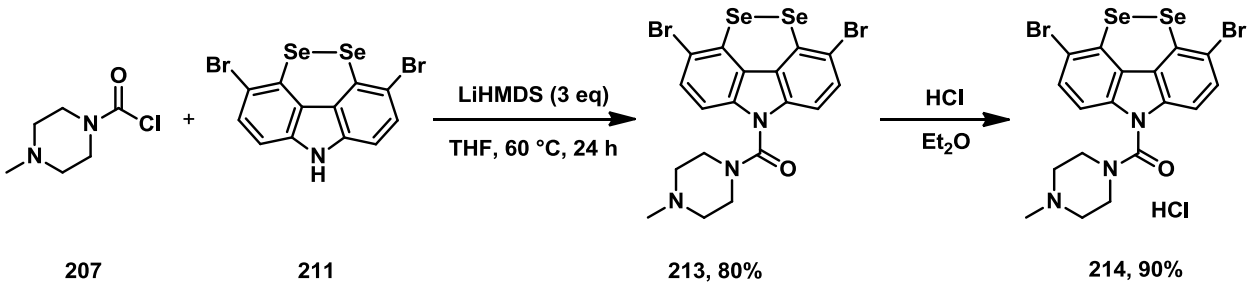


204 **211** **212, 90%**

Scheme 67 Preparation of carbazole **212** *via N*-alkylation

To make direct comparisons between the carbazole compounds easier, it was decided to add 4-methyl-piperazine-1-carbonyl chloride **207** to **211**, as this amine was used on carbazole catalyst **209**. Carbazole **211** was reacted with 4-methyl-piperazine-1-carbonyl chloride **209** in the

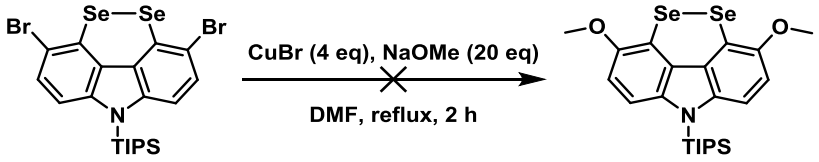
presence of LiHMDS giving **213** in 80% yield (Scheme 68). Compound **213** was then dissolved in Et_2O and acidified giving the corresponding water-soluble HCl salt in 90% yield.



207 211 213, 80% 214, 90%

Scheme 68 Preparation of carbazole **213**

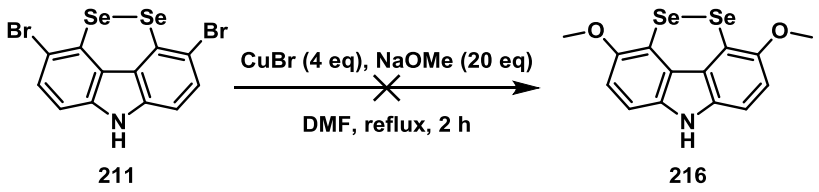
Investigations towards developing selenium based GPx mimics have shown that the presence of electron-donating groups increases the catalytic activity. Disubstitution of 3,6-dibromocarbazole **210** using an Ullman reaction is known. The first attempts to substitute both bromine groups of **210** for methoxy groups used a modified literature procedure, using CuI or CuBr catalyst in the presence of sodium methoxide. [105] This reaction failed to yield the desired product. The TIPS protecting group was removed in the first 5 minutes of the reaction, giving **211**.



210 215

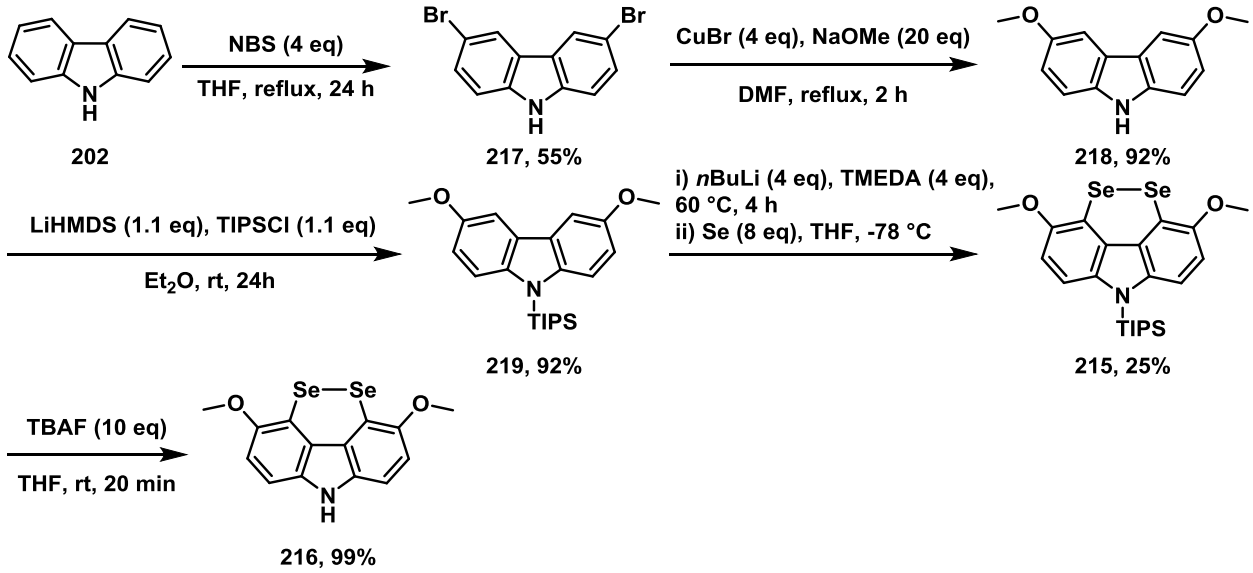
Scheme 69 Attempted preparation of 3,6-dimethoxy carbazole **215** *via* an Ullman reaction

Subsequently, the same conditions were attempted on deprotected diselenide **211**. However, no reaction was observed after 72 h at reflux in DMF, returning only starting material. CuI was replaced with CuBr, with no effect on the outcome of the reaction.



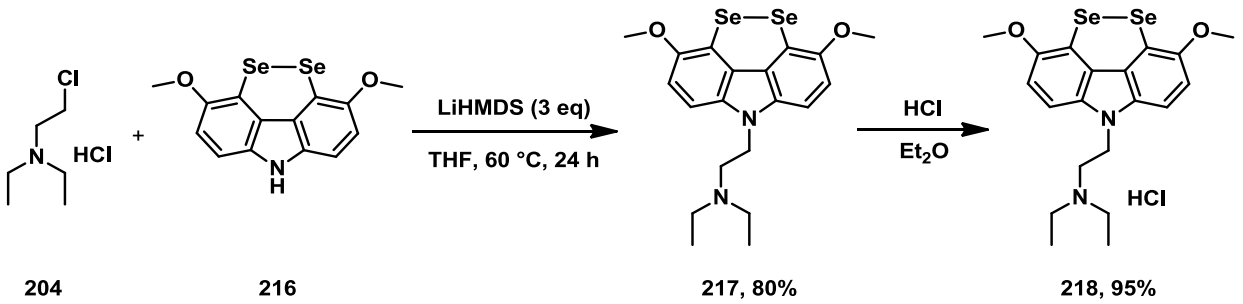
Scheme 70 Attempted preparation of 3,6-dimethoxy carbazole **216** *via* an Ullman reaction

The target compound **215** was next pursued *via* a different route (Scheme 71). Dibromocarbazole **217** was prepared following the same bromination procedure used for dibromide **210**. This reaction gave 3,6-dibromocarbazole **217** in 55% yield. Synthesis of dimethoxy carbazole using the Ullman type reaction with CuI gave 3,6-dimethoxy-carbazole **218** in 92% yield. Treating **218** with LiHMDS and TIPSCl gave the TIPS-protected bismethoxide **219** in 92% yield. Treatment of **219** with *n*BuLi and TMEDA and subsequent addition of selenium yielded diselenide **215** in 25% yield. Removal of the TIPS protecting group using TBAF gave compound **216** in 99% yield.



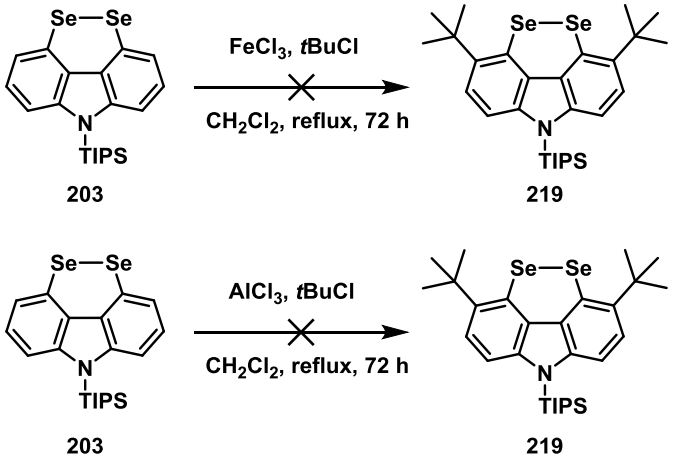
Scheme 71 Preparation of 3,6-bismethoxy-diselenide **216**

Compound **216** was reacted with 2-chloro-*N,N*-diethylethylamine hydrochloride in the presence of LiHMDS giving **217** in 80% yield after purification. Compound **217** was then dissolved in Et_2O and acidified giving the corresponding HCl salt **218** in 75% yield. This salt was readily soluble in water.



Scheme 72 Preparation of carbazole **217** *via* N-alkylation

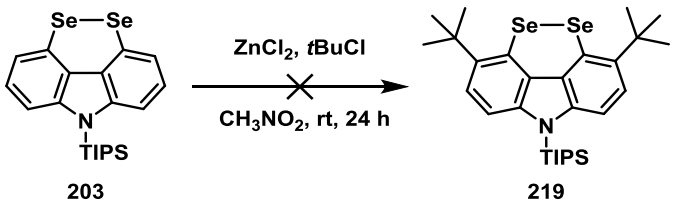
Of additional interest was the introduction of *tert*-butyl groups adjacent to the diselenide group. The steric buttressing from the *tert*-butyl groups may alter the Se-Se bond length, which could in turn modulate the catalytic activity of the carbazole scaffold. The synthesis of **219** followed a procedure that had been previously published by the Grainger group on a naphthalene scaffold (Scheme 73).[106] This Friedel-Crafts alkylation did not produce any product over a 72 h period, with starting material recovered. Changing the Lewis acid to $AlCl_3$ also resulted in no reaction. The quality and age of $AlCl_3$ was considered but repeating the reaction with a fresh bottle of $AlCl_3$ also failed to produce **219**.



Scheme 73 Attempted synthesis of 3,6-di-*tert*-butyl carbazole diselenide **219** *via* Friedel-Crafts alkylation

The Friedel-Crafts alkylation of carbazole **202** with *tert*-butyl chloride has been reported by Hou *et al*.[107] Following this procedure, carbazole **203** was treated with *tert*-butyl chloride and $ZnCl_2$ in

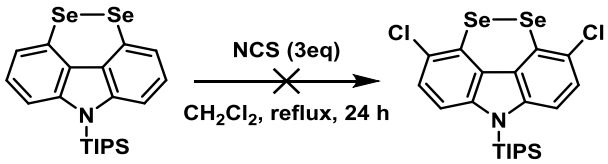
CH_3NO_2. After 24 h the reaction had given a mixture of unidentifiable compounds. Reducing the reaction temperature to 0 °C also gave a mixture of unidentifiable compounds.



203 219

Scheme 74 Attempted synthesis of 3,6-di-*tert*-butyl carbazole diselenide **219** *via* Friedel-Crafts alkylation with $ZnCl_2$

The synthesise of dichloride **220** from carbazole **203** was also unsuccessful. Following a literature procedure published by Rodríguez-Molina *et al*, diselenide **203** was reacted with NCS in CH_2Cl_2.[108] However, the reaction did not produce any product at room temperature over 24 h; heating the reaction at reflux for over 72 h also did not give any product. The starting materials were returned quantitively. No reaction was also observed when the chlorinating agent was changed to SO_2Cl_2.



203 220

Scheme 75 Attempted synthesis of 3,6-di-chloro-carbazole diselenide **220**

3.5 X-ray analyses of carbazole diselenide 216

The crystal structure of carbazole diselenide **216** was obtained. Selected bond lengths and bond angles of fluorene diselenide **127** and carbazole diselenide **216** are shown in Table 4. The X-ray crystal structure of **216** shows that the Se-Se bond length is similar to that of fluorene diselenide **127** (entry 1, Table 5). The dihedral bond angle C(1)-Se(1)-Se(2)-C(11) in **216** shows that the Se-Se bond is twisted by 47.0 ° (entry 4, Table 5), this is a larger angle than that observed for fluorene diselenide **127**. Torsional strain within the fluorene and carbazole scaffold are very similar, as shown by the C(1)-C(13)-C(12)-C(11) bond angle (entries 6, table 5).

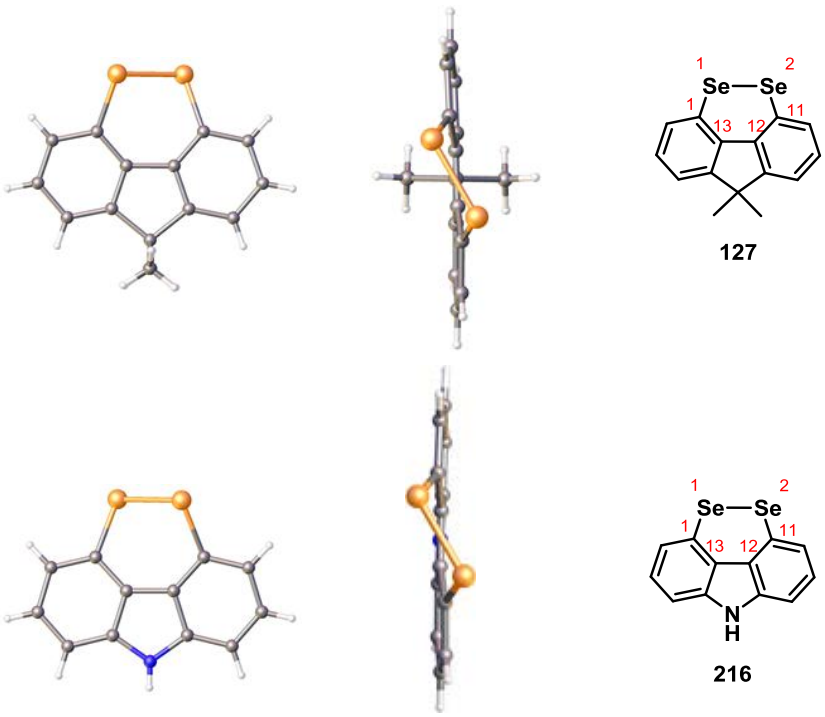


Figure 28 Crystal structure of compounds **127** and **216**

Entry	Compound	117	216
1	Se-Se	2.341	2.361
2	Se(1)-C(1)	1.919	1.918
	Se(2)-C(11)		1.917
3	C(1)-Se(1)-Se(2)	99.5	98.6
	C(11)-Se(2)-Se(1)		98.6
4	C(1)-Se(1)-Se(2)-C(11)	42.3	47.0
5	Se(1)-C(1)-C(11)-Se(2)	30.9	34.5
6	C(1)-C(13)-C(12)-C(11)	13.4	13.6
7	Se(1)-C(1)-C(13) – 120°	0.6	-2.8
	Se(2)-C(11)-C(12) – 120°		-2.1

Table 4 Selected bond lengths (Å) and angles (°) for diselenides **127,** and **216**

3.6 GPx activity of water-soluble diselenides

The GPx-like activity of the water-soluble diselenides were evaluated with an aqueous based ^{1}H-NMR assay previously reported in the literature.[36, 43] This assay allows for the direct observation of the oxidation of GSH to GSSG mediated by H_2O_2 (Figure 29). This assay cannot be conducted at a physiological pH, as this causes spontaneous oxidation of GSH to GSSG. This would cause greater reaction times and poorer reproducibility, as the background oxidation would be too rapid. The assay was conducted with a phosphate-buffered D_2O solution at a pD of 2.3, as reported by Back *et al*.[43] This phosphate buffer suppresses the background oxidation and allows for reproducible results.[109]

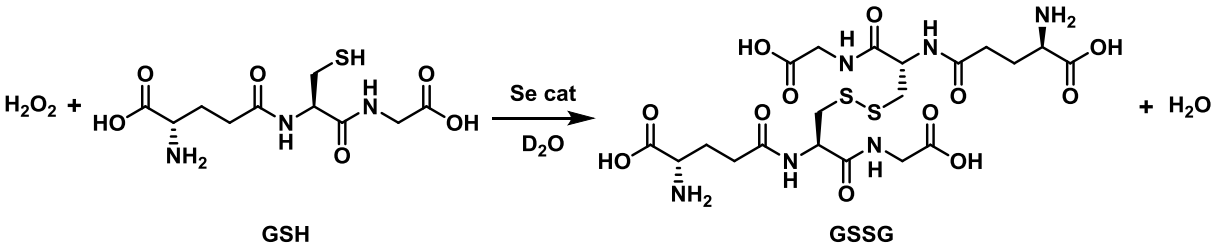


Figure 29 The oxidation of GSH to GSSG by H_2O_2 mediated by a selenium-containing catalyst

Catalyst efficiency was measured as the time required for a given catalyst to decrease the GSH concentration by 50% ($t_{1/2}$). The oxidation of GSH to GSSG can be monitored by ^{1}H-NMR spectroscopy (Figure 30). Spectrum A was recorded prior to the addition of hydrogen peroxide (t_0), spectrum B represents when the reaction had reached 50% completion ($t_{1/2}$), and spectrum C was obtained at the end of the reaction and compared against an authentic sample of GSSG. These spectra show that the signal for H-2 (GSH) and H-2’ (GSSG) remains unchanged in this process, while that for H-4 (GSH) gradually disappears and the corresponding peak H-4’ (GSSG) appears further downfield, where it overlaps with the residual water peak. The signal for H-5’a is well-separated from its diastereotopic counterpart H-5’b (GSSG) as well as from H-5 (GSH).

Hence, it is possible to integrate the disappearance of the H-4 against the constant H-2 plus H-2' signal to determine the extent of the reaction.

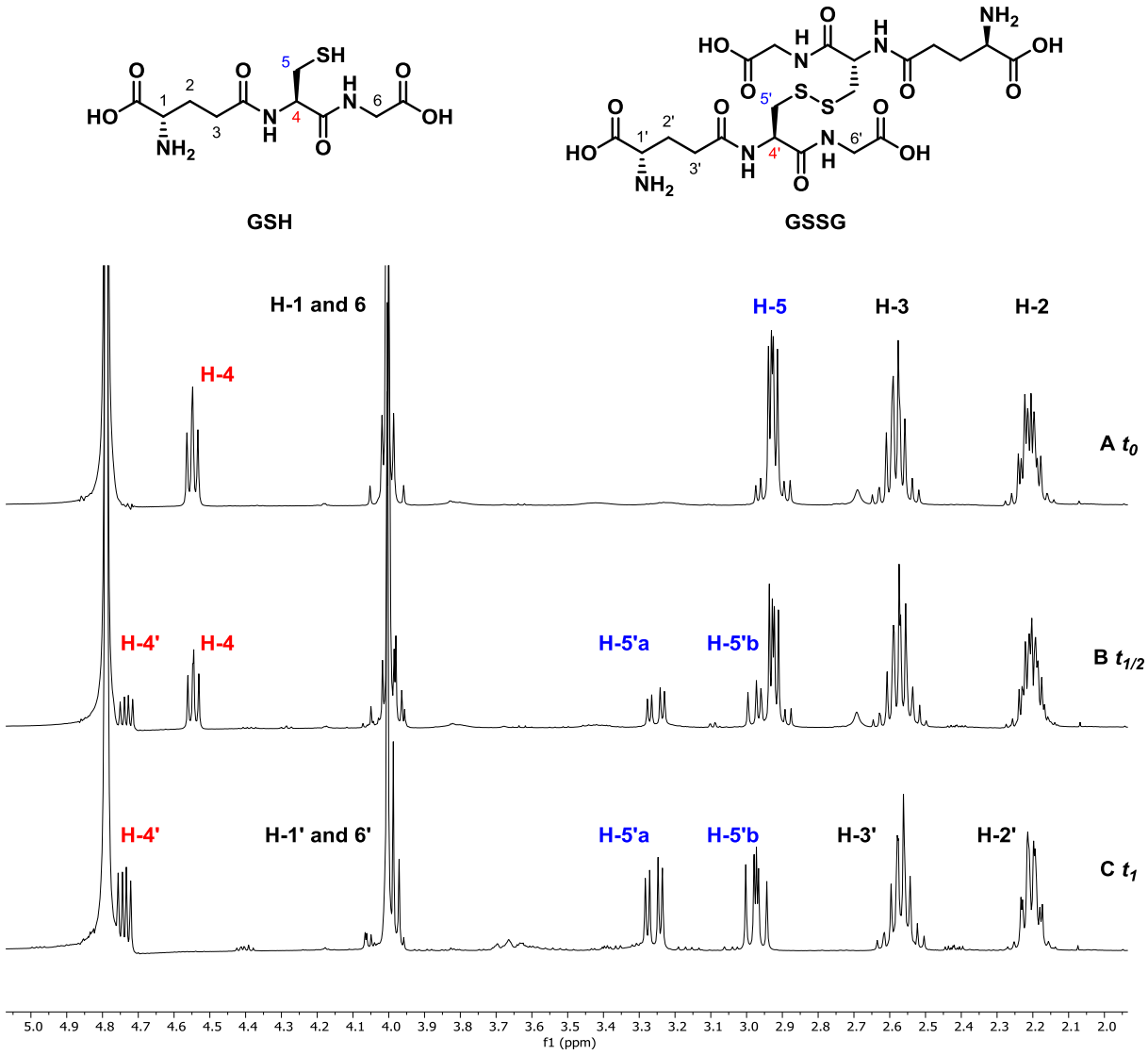


Figure 30 Conversion of GSH to GSSG with H_2O_2 in the presence of 10 mol % of diselenide **206**, as monitored by 1H-NMR (400 MHz) spectroscopy. Spectrum A: at t_0. Spectrum B: at $t_{1/2}$. Spectrum C: authentic GSSG.

Compounds **168**, **169**, **206**, **209**, **214** and **218** were evaluated in the assay. The results are shown in Figure 31 and Graph 2. The values are reported as an average of three experiments. Fluorene diselenide **168** was the most active catalyst with a $t_{1/2}$ of 40 min. Carbazole diselenide **206** had a $t_{1/2}$ of 406 min. The addition of an electron-donating OMe groups to the carbazole scaffold had a positive effect on the activity of the carbazole scaffold, with **218** displaying a $t_{1/2}$ of 297 min. This

was 1.4 times greater than carbazole diselenide **206**. The addition of an electron-withdrawing acyl group on the nitrogen had a negative effect on the activity, as compound **209** displayed a $t_{1/2}$ of 604 min making it almost 1.5 times less active than **206**. The addition of the dibromo moiety was also detrimental to the activity of carbazole scaffold as diselenide **214** displayed a $t_{1/2}$ of 1372 min, 2.2 times longer than carbazole **209**.

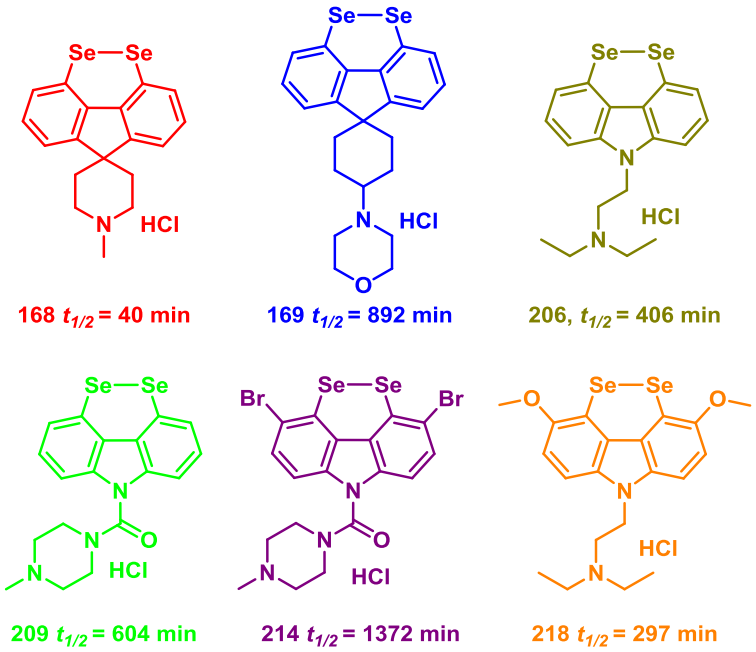
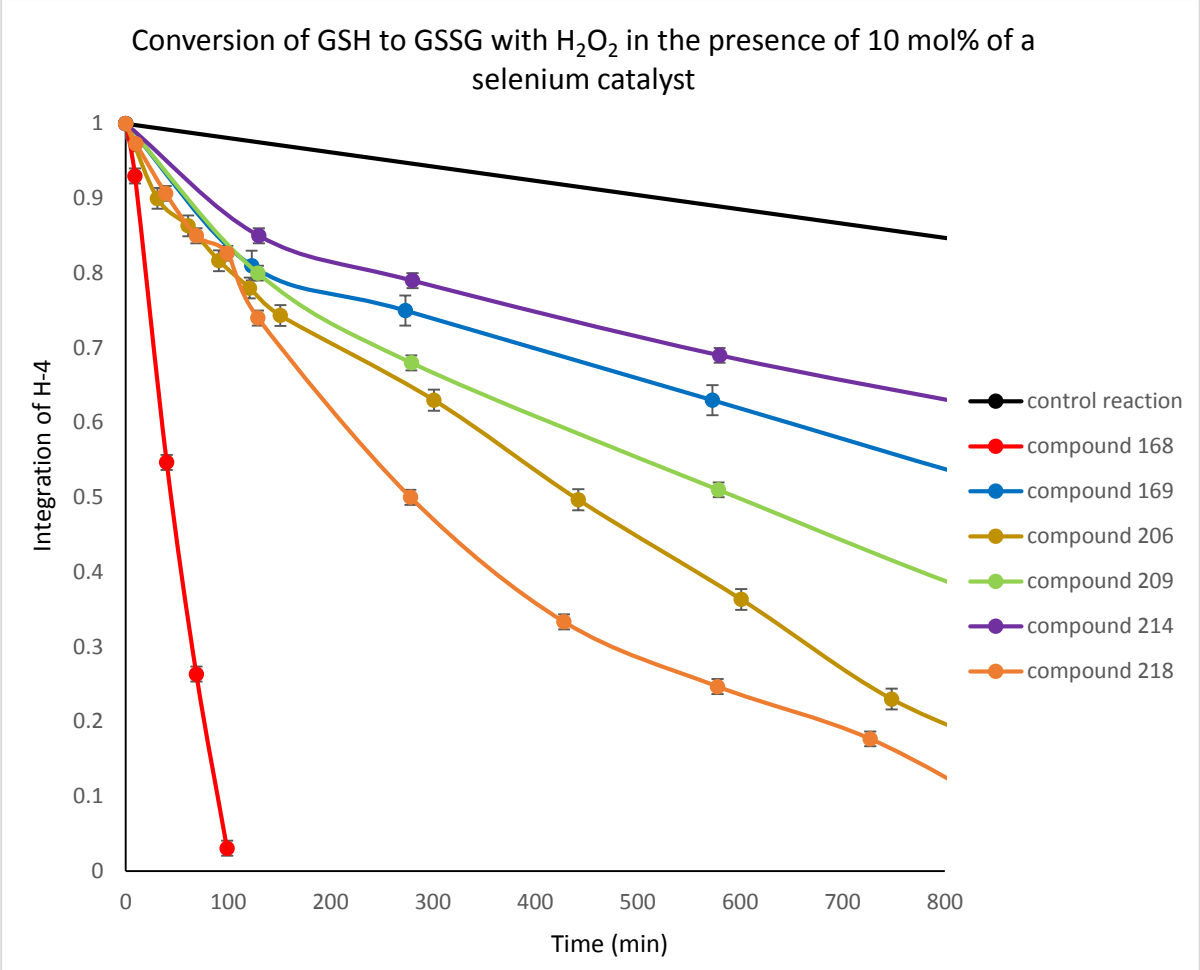


Figure 31 $t_{1/2}$ of selenium catalysts submitted to the GSH oxidation assay



Graph 2 Oxidation of GSH with H_2O_2 in the presence of chalcogen-containing catalysts (10%). Reaction conditions: GSH= 31 mM, H_2O_2= 35 mM, catalyst= 3.1 mM. Reactions were performed in D_2O (0.6 mL). Reported are the mean values of 3 separate experiments.

3.7 Conclusion

The synthesis of 4,5-disubstituted carbazole diselenides **203** and **215** has been achieved using a lithium-mediated selenium insertion reaction. This transformation is the first reported case of carbazole being 4,5-substituted in one step, and offers significant opportunities for carbazole elaboration with other electrophiles. The use of the TIPS protecting group has successfully directed the lithiation away from the 1,8-positions of the carbazole, and the TIPS protecting group could be easily removed (Scheme 63). The carbazole scaffold was easily elaborated, achieving dibromo-carbazole in high yields using NBS and *N*-alkylation was also high yielding, giving water-soluble carbazole diselenides **206**, **209**, **214** and **218**. The X-ray analysis of **177** shows that the diselenide moiety is very similar to that of fluorene diselenide **127**. Attempts to synthesise a dichlorinated carbazole were unsuccessful. Attempts to introduce dimethoxy groups with an Ullman reaction using diselenides **210** and **211** were not successful (Scheme 69, Scheme 70). Dimethoxy carbazole **215** was obtained *via* an alternative route (Scheme 71). Introduction of *t*Bu groups to carbazole **203** *via* the Friedel-Crafts alkylation did not give the desired product.

The GPx-like activity of water-soluble diselenides **168**, **169**, **206**, **209**, **214** and **218** were measured in an assay with GSH using ^{1}H-NMR spectroscopy. The results show that the fluorene scaffold was not inherently superior to the carbazole scaffold, fluorene diselenide **168** has a GPx like activity superior to that of carbazole diselenide **112** but fluorene diselenide **169** was the second slowest catalyst. The addition of electron-donating MeO groups to the carbazole scaffold significantly enhanced the activity. The presence of electron-withdrawing groups on the carbazole scaffold predictably reduced the activity, while the presence of halogen groups also reduced the activity.

3.8 Future work

Further work can be carried out to optimise the synthesis of fluorene diselenide **163**. The ketone functionality of **163** can be manipulated with the aim of improving the catalytic activity and water solubility of this scaffold. It would be desirable for additional work to be conducted on the fluorenone scaffold with the aim of synthesising fluorenone diselenide **221**, as this compound will be easier to derivatise than the fluorene scaffolds.

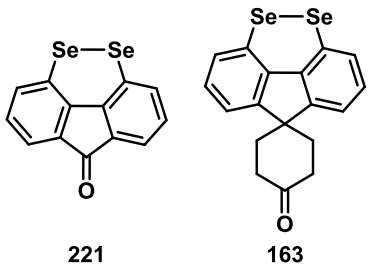


Figure 32 Target compounds for synthesis and optimisation

The ease of synthesis of water soluble carbazole diselenides using inexpensive starting materials make this an important scaffold for further improvement. The addition of a more electron donating group on the carbazole nitrogen could further improve the catalytic activity. Different electron donating groups with additional coordinating sites could be placed on the 3,6 position with the same aim. In addition to further improvement of GPx-like activity, there will be a need to investigate potential drug candidates through ex vivo and eventually in vivo studies.

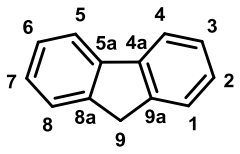
Chapter 4 Experimental procedures

Solvents and reagents were purified as follows:

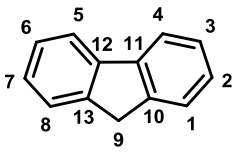
*n*BuLi was purchased as a 2.5 M solution in hexane and the solutions titrated with menthol in the presence of 1-(biphenyl-4-yl)-3-phenyl-2-azapropene ("BLUE"). 1-(biphenyl-4-yl)-3-phenyl-2-azapropene ("BLUE") was synthesised according to literature procedure.[110] TMEDA was distilled from CaH_2. LiHMDS was purchased as a 1 M solution in THF. Sulfur was recrystallized from toluene. *m*CPBA was purified by washing with a pH 7 phosphate buffer which was prepared from 0.1 M $NaOH_{(aq)}$ (154 mL) and 0.2 M $KH_2PO_{4(aq)}$ (94 mL), distilled water was added up to 376 mL. A solution of *m*CPBA (77% w/w, 10 g) in Et_2O (100 mL) was washed with the buffer solution; the combined organic layers were then dried over $MgSO_4$, evaporated under reduced pressure to yield pure *m*CPBA (7.3 g, 73%). All other reagents and solvents were purchased from Merck, Alfa Aesar, Fisher Scientific and were used as received. Dry solvents were obtained and purified using a Pure Solv-MD solvent purification system (SPS) and were transferred under argon. The following cooling baths were used: 0 °C (ice/water) and –78 °C (dry ice/acetone). All reactions in non-aqueous solvents were carried out under argon in oven dried glassware. Analytical t.l.c. was carried out on Merck 60 F245 aluminium-backed silica gel plates. Short wave UV (245 nm) and $KMnO_4$ were used to visualize components. Compounds were purified by flash column chromatography using Merck silica gel 60. Melting points were determined using open glass capillaries on a Gallenkamp or Stuart scientific SMP10 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR data were recorded on a Bruker AVIII300 (300 MHz ^1H, T = 293 K) and Bruker AVIII400 (400 MHz ^1H, 101 MHz ^{13}C, T = 293 K). ^{77}Se NMR data was recorded on a Bruker AVIII400 (76 MHz ^{77}Se, T = 293 K) with diphenyl diselenide (δ 463 ppm) as the external standard.[111] Spectra were recorded in CD_2Cl_2 referenced to residual CH_2Cl_2 (^1H, 5.33 ppm; ^{13}C, 53.84 ppm), $CDCl_3$ referenced to residual $CHCl_3$ (^1H, 7.26 ppm; ^{13}C, 77.16 ppm) and CD_3OD

referenced to residual MeOH (^{1}H, 4.78, 3.31 ppm; ^{13}C, 49.15 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hz. The following abbreviations are used to describe multiplicity: s-singlet, d-doublet, t-triplet, q-quartet, sext-sextet, m-multiplet, br-broad. All the reported coupling constants are averaged, when the coupling constants are close in values. Spectral assignments of where indicated, were based upon COSY, HMBC and HSQC analysis. Mass spectra were recorded on a LCT spectrometer utilising electrospray ionisation (recorded in the positive mode) with a methanol mobile phase, or electron impact ionisation, and are reported as (*m/z* (%). IR spectra were recorded neat on a Perkin Elmer 100-series FT-IR spectrometer.

Numbering of atoms in structures shown in this Chapter was made for convenience in indicating spectral assignments and does not necessarily reflect IUPAC nomenclature.



IUPAC



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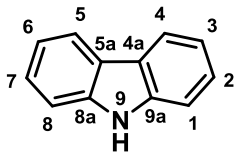
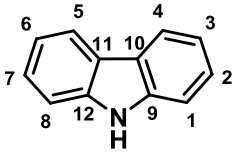


IUPAC



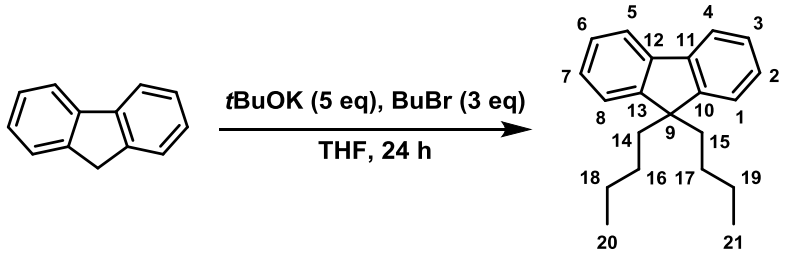
This thesis

For the DTT oxidation NMR assay. DTT^{red} (0.14 M) and selenium or tellurium catalyst (0.014 M) were dissolved in 2:1 $CD_3OD/CDCl_3$ (06 mL) solution. Then the solution was treated with 35% H_2O_2 (15 µL, 0.15 mmol) to start the reaction. ^{1}H NMR spectra were measured at a variable reaction time at 25 °C. These experiments were carried out by Prof Antonella Capperucci and Dr Damiano Tanini at the University of Florence.

For the GSH oxidation NMR assay, a D_2O buffer solution was prepared by dissolving NaH_2PO_4 (105 mg, 0.875 mmol) and phosphoric acid (111 µL, 85%, 0.162 mmol) in 25 mL of D_2O to afford a solution with pD= 2.3. A fresh solution of GSH (47 mg, 0.15 mmol) and the catalyst (0.015 mmol) in the buffered D_2O solution (25 mL) was prepared in a clean, new vial for each run. Aqueous 30% H_2O_2 (18 µL, 0.15 mmol) was added to produce a final concentration 35.4 mM, thereby initiating the reaction. The solution was pipetted into a clean, dry NMR tube and immediately placed in the spectrometer. Acquisition of data typically commenced within 7-9 min of the addition of hydrogen peroxide, and data collection continued until nearly complete conversion of GSH to GSSG had occurred.

4.1 Chapter 2 experimental

Preparation of 9,9-dibutyl-9H-fluorene (**116**)

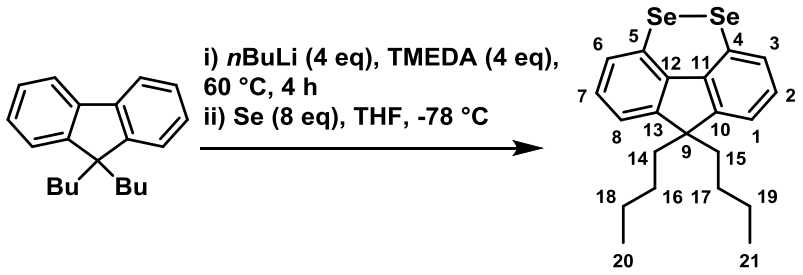


115 **116**

Known compound **116** was prepared according a modified literature procedure.[77] *t*BuOK (2.72 g, 24.2 mmol) was added in one portion at rt to a solution of fluorene (967 mg, 5.82 mmol) in THF (40 mL). 1-Bromobutane (2.0 mL, 18.0 mmol) was added dropwise to the solution over 1 min. The reaction mixture was then allowed to stir at rt for 16 h. NH_4Cl (50 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (*n*-hexane 100%). Compound **116** (990 mg, 62%) was obtained as a white crystalline solid; R_f 0.60 (*n*-hexane); mp 49–50 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2927, 2927, 2856, 1465, 1447, 1376, 1332, 1299, 1221, 1128; δ_H (400 MHz, $CDCl_3$) 7.73–7.17 (2 H, m, H-4 and H-5), 7.37–7.29 (6 H, stack, H-1, H-2, H-3, H-6, H-7 and H-8), 2.01–1.96 (4 H, m, H-14 and H-15), 1.07 (4 H, sext, *J* = 8.0, H-16 and H-17), 0.67 (6 H, t, *J* = 7.0, H-20 and H-21), 0.54–0.64 (4 H, m, H-18 and H-19); δ_C (101 MHz, $CDCl_3$) 150.8 (C, C-10 and C-13), 141.2 (C, C-11 and C-12), 127.1, 126.8, 123.0 and 119.8 (CH, C-1 and C-8 or C-2 and C-7 or C-3 and C-6 or C-4 and C-5), 55.1 (C, C-9), 40.3 (CH_2, C-14 and 15), 26.1 (CH_2, C-16 and 17), 23.2 (CH_2, C-18 and 19), 13.9 (CH_3, C-20 and 21); *m/z* (AP$^+$) 279 ([M+H]$^+$ 279.1, 11%), 221.2 (12), 179.1 (53), 167.1 (100).

Analytical data are in agreement with literature values.[112]

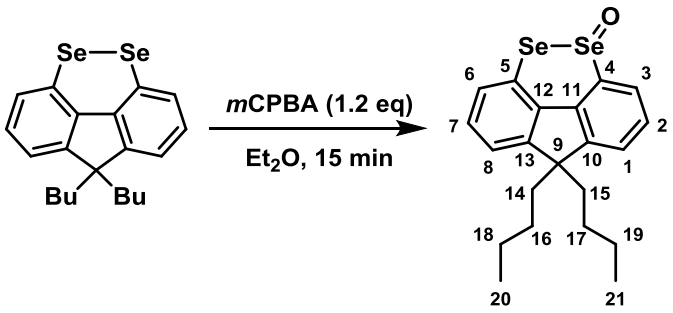
Preparation of 9,9-dibutyl-9H-fluoreno[4,5-cde][1,2]diselenine (**117**)



116 **117**

Compound **117** was prepared according a modified literature procedure.[77] *n*BuLi (2.15 M in hexanes, 19.3 mL, 41.2 mmol) was added dropwise over 10 min to a solution of compound **116** (500 mg, 1.80 mmol) in TMEDA (1.0 mL, 7.20 mmol). The reaction mixture was then stirred at 60 °C for 4 h. The reaction mixture was then cooled to –78 °C and THF (5 mL) was added followed by addition of selenium (1.40 g, 18.00 mmol) as a single portion. The cooling bath was removed and the reaction was allowed to stir for 16 h. H_2O (35 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (100% *n*-hexane), diselenide **117** was obtained as a dark burgundy crystalline solid (200 mg, 22%). R_f 0.54 (*n*-hexane); mp 129–133 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3038, 2953, 2924, 2851, 1561, 1405, 1106, 999, 789, 733; δ_H (400 MHz, $CDCl_3$) 7.27–7.23 (2 H, m, H-2 and H-7), 7.18–7.16 (4 H, stack, H-1, H-3, H-6 and H-8), 1.98–1.94 (4 H, m, H-14 and H-15), 1.00 (4 H, sext, *J* = 8.0, H-16 and H-17), 0.75 (6 H, t, *J* = 8.0, H-20 and H-21), 0.71–0.66 (4 H, m, H-18 and H-19); δ_C (101 MHz, $CDCl_3$) 151.5 (C, C-10 and C-13), 139.6 (C, C-11 and C-12), 129.3 (CH, C-3 and C-6), 126.0 (CH, C-2 and C-7), 122.0 (CH, C-3 and C-6), 121.9 (CH, C-1 and C-8)117.8 (CH, C-4 and C-5), 55.5 (C, C-9), 39.7 (CH_2, C-14 and 15), 26.1 (CH_2, C-16 and 17), 23.1 (CH_2, C-18 and 19), 13.9 (CH_3, C-20 and 21); ^{77}Se NMR (76 MHz, $CDCl_3$) 235.2; *m/z* (EI^+) found 436.0208 ($M^{+\bullet}$, $C_{21}H_{24}{}^{80}Se_2$ requires 436.0208)

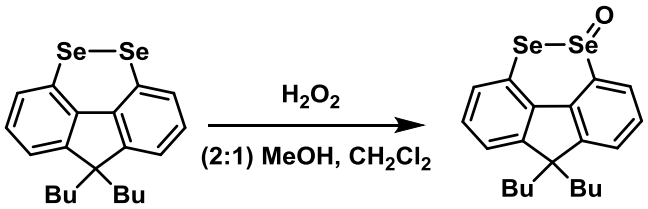
Preparation of 9,9-dibutyl-9H-fluoreno[4,5-cde][1,2]diselenine 4-oxide (**122**)



117 **122**

*m*CPBA (59 mg, 0.34 mmol) was added as a single portion to a solution of diselenide **117** (105 mg, 0.28 mmol) in Et_2O (5 mL) and allowed to stir at rt for 15 min. Compound **122** precipitated during this time. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). Compound **122** was obtained as a yellow powder (43 mg, 40%). R_f 0.15 (Et_2O); mp 147–149 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2955, 2916, 2274, 1368, 1246, 816, 732; δ_H (400 MHz, $CDCl_3$) 7.75–7.70 (1 H, m, H-3), 7.59–7.58 (2 H, stack, H-1 and H-2), 7.47–7.41 (2 H, stack, H-6 and H-7), 7.39 (1 H, *dd*, *J* = 7.8, 1.4, H-8), 2.06–2.02 (4 H, m, H-14 and H-15), 1.12–1.05 (4 H, m, H-16 and H-17), 0.68 (6 H, q, *J* = 7.8, H-20 and H-21), 0.59–0.52 (4 H, m, H-18 and H-19); δ_C (101 MHz, $CDCl_3$) 153.3 (C, C-10), 152.5 (C, C-13), 135.5 (C, C-11), 134.7 (C, C-12), 130.5 (C, C-4), 129.9 (CH, C-7), 129.2 (CH, C-2), 126.6 (CH, C-6), 126.3 (CH, C-1), 125.4 (CH, C-3), 121.6 (CH, C-8), 116.8 (C, C-5), 55.7 (C, C-9), 39.7 (CH_2, C-14 and 15), 26.0 (CH_2, C-16 and 17), 22.9 (CH_2, C-18 and 19), 13.7 (CH_3, C-20 and 21); ^{77}Se NMR (76 MHz, $CDCl_3$) 710.0, 1046.2; *m/z* (ASAP$^+$) 453.0239 ($[M+H]^+$, $C_{21}H_{25}{}^{80}Se_2O$ requires 453.0240)

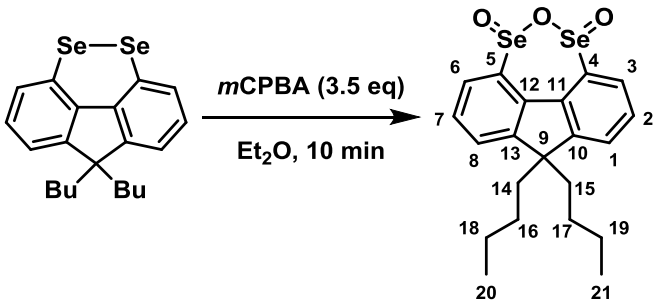
Preparation of 9,9-dibutyl-9H-fluoreno[4,5-cde][1,2]diselenine 4-oxide *via* H_2O_2 oxidation (**122**)



117 **122**

$H_2O_{2(aq)}$ (9.77 M in H_2O, 0.2 mL, 2.22 mmol) was added rapidly to a solution of diselenide **117** (100 mg, 0.22 mmol) in a 2:1 mixture of MeOH and CH_2Cl_2 (15 mL) and allowed to stir at rt for 24 h. The solvent was removed under reduced pressure. H_2O (15 mL) was added and the mixture was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: Et_2O), diselenide **117** (65 mg, 65%) was taken from the column first, followed by **122** (31 mg, 30%).

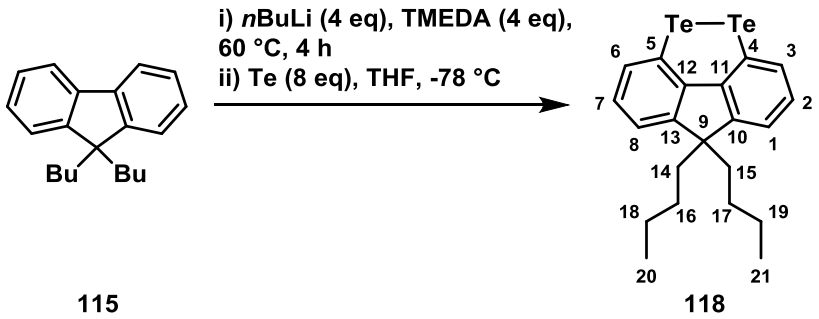
Preparation of seleninic anhydride (**124**)



117 **124**

Compound **124** is a novel compound, prepared according to a modified literature procedure.[78] *m*CPBA (395 mg, 2.38 mmol) was added as a single portion at rt to a solution of diselenide **117** (284 mg, 0.65 mmol) in Et_2O (5 mL). The reaction mixture was allowed to stir at rt for 15 min. Compound **124** precipitated during this time. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). Seleninic anhydride **124** was obtained as a white powder (300 mg, 95%) that required no further purification. mp 175–178 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2956, 2927, 2854, 2394, 1457, 1405, 818, 797, 737, 671; δ_H (400 MHz, CD_3OD) 7.69 (2 H, dd, *J* = 7.1, 1.4, H-3 and H-6 or H-1 and H-8), 7.67 (2 H, dd, *J* = 7.8, 1.4, H-3 and H-6 or H-1 and H-8), 7.58 (2 H, t, *J* = 7.8, H-2 and H-7), 2.13 – 1.95 (4 H, m, H-14 and H-15), 0.99 – 0.84 (4 H, m, H-16 and H-17), 0.59 (6 H, t, *J* = 7.4, H-20 and H-21), 0.25 – 0.14 (4 H, m, H-18 and H-19); δ_C (101 MHz, CD_3OD) 155.5 (C, C-10 and C-13), 146.6 (C, C-11 and C-12), 139.8 (C, C-4 and C-5), 129.2 (CH, C-1 and C-8), 127.7 (CH, C-3 and C-6), 127.1 (CH, C-2 and C-7), 56.4 (C, C-9), 41.3 (CH_2, C-14 and C-15), 27.0 (CH_2, C-16 and C-17), 23.8 (CH_2, C-18 and C-19), 14.0 (CH_3, C-20 and C-21); ^{77}Se NMR (76 MHz, CD_3OD) 1175.9; *m/z* (ASAP$^+$) 485.0147 found ([M+H]$^+$, $C_{21}H_{25}{}^{80}Se_2O_3$ requires 485.0138)

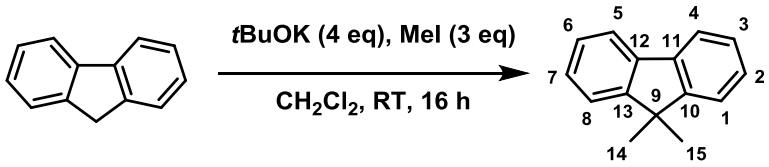
Preparation of 9,9-dibutyl-9H-fluoreno[4,5-cde][1,2]ditellurine (**118**)



115 **118**

Compound **118** is a novel compound, prepared according to a modified literature procedure.[77] *n*BuLi (2.13 M in hexanes, 3.4 mL, 7.19 mmol) was added dropwise over 10 min at rt to a solution of compound **115** (500 mg, 1.79 mmol) in TMEDA (0.8 mL, 7.2 mmol). The reaction mixture was allowed to stir at 60 °C for 4 h. The reaction mixture was cooled to –78 °C and THF (15 mL) was added followed by addition of tellurium (1.80 g, 14.38 mmol) as a single portion. The cooling bath was removed and the reaction mixture was allowed to warm to rt and left to stir for 16 h. H_2O (150 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (100% *n*-hexane) yielding ditelluride **188** as a dark purple crystalline solid (104 mg, 11%). R_f 0.10 (*n*-hexane); mp degradation above 250 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2953, 1556, 1451, 1417, 1396, 1183, 782, 727; δ_H (400 MHz, $CDCl_3$) 7.44 (2 H, dd, *J* = 7.4, 1.1, H-1 and 8), 7.14 – 7.10 (4 H, stack, H-2, 3, 6 and 7), 1.92 – 1.88 (4 H, m, H-14 and H-15), 1.06 (4 H, sext, *J* = 8.0, H-16 and H-17), 0.67 (6 H, t, *J* = 7.3, H-20 and H-21), 0.59 – 0.51 (4 H, m, H-18 and H-19); δ_C (101 MHz, $CDCl_3$) 152.2 (C, C-10 and C-13), 145.9 (C, C-11 and C-12), 132.5 (CH, C-3 and C-6), 129.2 (CH, C-2 and C-7), 122.9 (CH, C-1 and C-8), 90.0 (C, C-4 and C-5), 54.1 (C, C-9), 40.2 (CH_2, C-14 and C-15), 25.9 (CH_2, C-16 and C-17), 23.1 (CH_2, C-18 and C-19), 13.9 (CH_3, C-20 and C-21); *m/z* (ASAP$^+$) found 536.0015 (M^+, $C_{21}H_{24}{}^{130}Te_2$ requires 536.0005)

Preparation of 9,9-dimethyl-9H-fluorene (**126**)

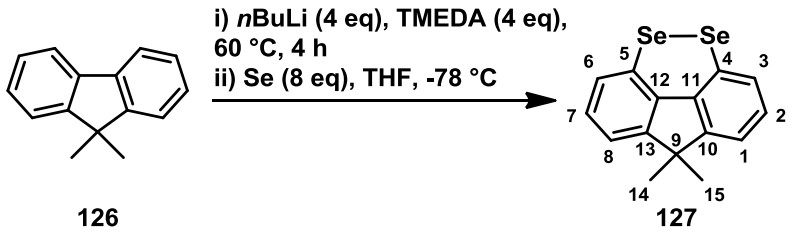


115 **126**

Known compound **126** was prepared according to the literature procedure.[79] *t*BuOK (11.80 g, 105.00 mmol) was added as a single portion at rt to a solution of fluorene (5.00 g, 30.00 mmol) in THF (50 mL). Iodomethane (10.00 g, 75.00 mmol) was added dropwise over a period of 10 min. The reaction mixture was allowed to stir at rt for 16 h. The mixture was filtered and the filtrate was treated with saturated NH_4Cl solution (250 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (*n*-hexane 100%) giving compound **126** (1.08 g, 45%) as a white crystalline solid. R_f 0.42 (*n*-hexane); mp 96–98 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2927, 2927, 2856, 1465, 1447, 1376, 1332, 1299, 1221, 1128; δ_H (400 MHz, $CDCl_3$) 7.86 – 7.83 (2 H, m, H-1 and H-8), 7.56 – 7.54 (2 H, m, H-4 and H-5), 7.48 – 7.40 (4 H, stack, H-2, H- 3, H-6 and H-7), 1.65 (6 H, s, H-14 and H-15); δ_C (101 MHz, $CDCl_3$) 153.7 (C, C-10 and C-13), 139.3 (C, C-11 and C-12), 127.4 (CH C-2 and C-7), 127.1 (CH, C-3 and C-6), 122.7 (CH, C-4 and C-5), 120.1 (CH, C-1 and C-8), 46.9 (C, C-9), 27.3 (CH_3, C-14 and C-15); *m/z* (ASAP$^+$) found 195.1178 ([M+H]$^+$, $C_{15}H_{15}$ requires 195.1174)

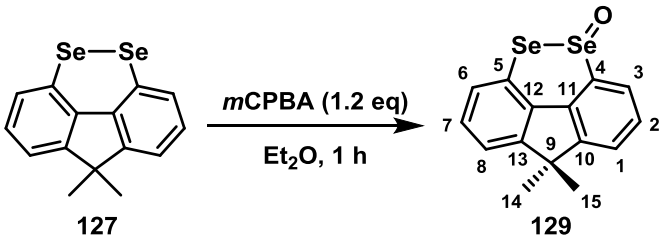
Analytical data are in agreement with literature values.[113]

Preparation of 9,9-dimethyl-9H-fluoreno[4,5-cde][1,2]diselenine (**127**)



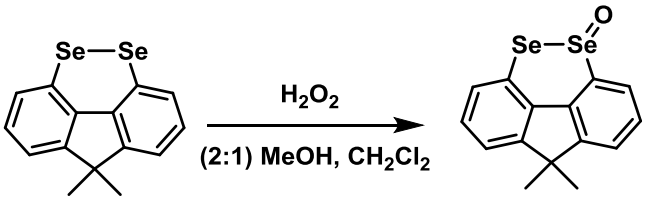
Compound **127** is a novel compound, prepared according to a modified literature procedure.[77] *n*BuLi (2.39 M in hexanes, 8.6 mL, 20.60 mmol) was added dropwise over 10 min at rt to a solution of compound **126** (1.00 g, 5.2 mmol) in TMEDA (2.7 mL, 20.6 mmol). The reaction mixture was stirred at 60 °C for 4 h. The reaction mixture was cooled to –78 °C and THF (15 mL) was added followed by the addition of selenium (3.20 g, 41.2 mmol) as a single portion. The cooling bath was removed and the reaction mixture was allowed to stir for 16 h. H_2O (150 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (100% *n*-hexane), diselenide **127** was obtained as a dark burgundy crystalline solid (200 mg, 22%). R_f 0.54 (*n*-hexane); mp 135–136 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3052, 2956, 2895, 2859, 1561, 1403, 1188, 937, 782, 727; δ_H (400 MHz, $CDCl_3$) 7.23 – 7.19 (6 H, stack, H-1, H-2, H-3, H-6, H-7 and H-8), 1.45 (6 H, s, H-14 and H-15); δ_C (101 MHz, $CDCl_3$) 154.1 (C, C-10 and C-13), 137.7 (C, C-11 and C-12), 129.5 (CH, C-1 and C-8 or C-2 and C-7 or C-3 and 6), 126.3 (CH, C-1 and C-8 or C-2 and C-7 or C-3 and C-6), 121.6 (CH, C-1 and C-8 or C-2 and C-7 or C-3 and C-6), 117.8 (C, C-4 and C-5), 47.2 (C, C-9), 26.5 (CH_3, C-14 and C-15); ^{77}Se NMR (76 MHz, $CDCl_3$) 236.2; *m/z* (ASAP$^+$) found 351.9285 ($M^{+\bullet}$, $C_{15}H_{12}{}^{80}Se_2$ requires 351.9272)

Preparation of 9,9-dimethyl-9H-fluoreno[4,5-cde][1,2]diselenine 4-oxide (**129**)



*m*CPBA (59 mg, 0.34 mmol) was added as a single portion at rt to a solution of diselenide **127** (105 mg, 0.28 mmol) in Et_2O (5 mL) and allowed to stir at rt for 15 min. Compound **129** precipitated during this time. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). Compound **129** was obtained as a yellow powder (43 mg, 41%). R_f 0.15 (Et_2O); mp 191–192 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2957, 2919, 2858, 1567, 1427, 1407, 830, 782; δ_H (400 MHz, $CDCl_3$) 7.73 (1 H, dd, *J* = 7.6, 1.0, H-3), 7.67 (1 H, dd, *J* = 7.5, 1.0, H-1), 7.60 (1 H, t, *J* = 7.6, H-2), 7.49 (1 H, dd, *J* = 7.6, 1.5, H-6), 7.45 (1 H, t, *J* = 7.6, H-7), 7.39 (1 H, dd, *J* = 7.1, 1.4, H-8), 1.57 (3 H, s, H-14 or H-15), 1.55 (3H, s, H-14 or H-15); δ_C (101 MHz, $CDCl_3$) 156.0 (C, C-10), 155.3 (C, C-13), 134.1 (C, C-11), 133.4 (C, C-12), 130.7 (C, C-4), 130.2 (CH, C-7), 129.5 (CH, C-2), 127.0 (CH, C-6), 126.2 (CH, C-1), 125.5 (CH, C-3), 121.3 (CH, C-8), 116.7 (C, C-5), 47.6 (C, C-9), 27.1 (CH_3, C-14 or C-15), 26.5 (CH_3, C-14 or C-15); ^{77}Se NMR (76 MHz, $CDCl_3$) 1047.3, 709.0; *m/z* (ASAP$^+$) found 368.9302 ($M^{+\bullet}$, $C_{15}H_{12}O^{80}Se_2$ requires 368.9300)

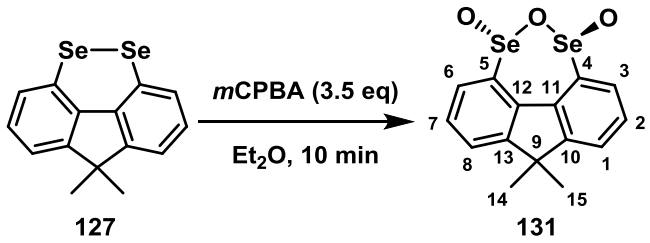
Preparation of 9,9-dimethyl-9H-fluoreno[4,5-cde][1,2]diselenine 4-oxide *via* H_2O_2 oxidation (**129**)



127 **129**

$H_2O_{2(aq)}$ (9.77 M in H_2O, 0.3 mL, 2.80 mmol) was added rapidly to a solution of diselenide **127** (100 mg, 0.28 mmol) in a 2:1 mixture of MeOH and CH_2Cl_2 (20 mL) and allowed to stir at rt for 24 h. The solvent was removed under reduced pressure. H_2O (15 mL) was added and the mixture was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: Et_2O), diselenide **127** (59 mg, 60%) was taken from the column first, followed by **129** (36 mg, 35%).

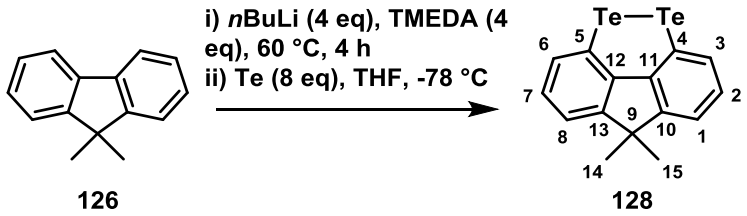
Preparation of *trans*-seleninic anhydride (**131**)



127 131

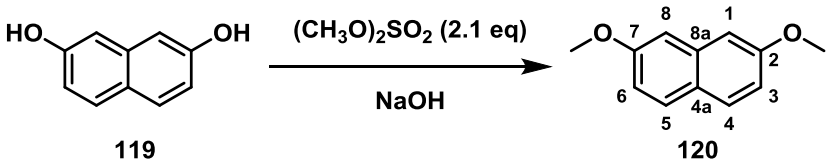
Compound **131** is a novel compound, prepared according to a modified literature procedure.[70] *m*CPBA (395 mg, 2.28 mmol) was added as a single portion at rt to a solution of diselenide **127** (350 mg, 1.15 mmol) in Et_2O (5 mL) and allowed to stir at rt for 15 min. Seleninic anhydride precipitated during this time. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). Seleninic anhydride **131** was obtained as a white powder (389 mg, 85%) that requires no further purification. mp 221–222 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2951, 2924, 2852, 2397, 1453, 1411, 813, 795, 736, 673; δ_H (400 MHz, $CDCl_3$) 7.71 – 7.68 (4 H, stack, H-1, H-3, H-6 and H-8), 7.60 (2H, t, *J* = 7.6, H-2 and H-7), 1.54 (6 H, s, H-14 and H-15); δ_C (101 MHz, $CDCl_3$) 157.3 (C, C-10 and C-13), 148.3 (C, C-11 and C-12), 135.5 (C, C-4 and C-5), 129.2 (CH, C-1 and C-8 or C-3 and C-6), 127.2 (CH, C-1 and C-8 or C-3 and C-6), 127.0 (CH, C-2 and C-7), 47.8 (C, C-9), 27.1 (CH_3, C-14 and C-15); ^{77}Se NMR (76 MHz, $CDCl_3$) 1278.3; *m/z* (ASAP$^+$) found 400.9204 ($M^{+\bullet}$, $C_{15}H_{12}{}^{80}Se_2O_3$ requires 400.9198)

Preparation of 9,9-dimethyl-9H-fluoreno[4,5-cde][1,2]ditellurine (**128**)



Compound **128** is a novel compound, prepared according to a modified literature procedure.[77] *n*BuLi (2.13 M in hexanes, 4.7 mL, 10.00 mmol) was added dropwise over 10 min to a solution of compound **126** (500 mg, 2.70 mmol) in TMEDA (1.2 mL, 10.0 mmol). The reaction mixture was stirred at 60 °C for 2 h. The reaction mixture was cooled to –78 °C and THF (15 mL) was added followed by addition of tellurium (2.54 g, 20.0 mmol) as a single portion. The cooling bath was removed and the reaction mixture was allowed to warm to rt and stirred for 16 h. H_2O (150 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (100% *n*-hexane) ditelluride **128** was obtained as a dark purple crystalline solid (284 mg, 23%). R_f 0.10 (*n*-hexane); mp degradation above 250 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2953, 1556, 1451, 1417, 1396, 1183, 782, 727; δ_H (400 MHz, $CDCl_3$) 7.44 (2 H, dd, *J* = 7.4, 1.1, H-1 and H-8), 7.20 (2 H, dd, *J* = 7.5, 1.1, H-2 and H-7), 7.13 (2 H, t, *J* = 7.5, H-3 and H-6), 1.43 (6 H, s, H-14 and H-15); δ_C (101 MHz, $CDCl_3$) 155.0 (C, C-10 and C-13), 143.9 (C, C-11 and C-12), 132.6 (CH, C-3 and C-6), 129.5 (CH, C-2 and C-7), 122.7 (CH, C-1 and C-8), 94.2 (C, C-4 and C-5), 46.0 (C, C-9), 27.0 (CH_3, C-14 and C-15); *m/z* (ASAP$^+$) found 452.9141 ($M^{+\bullet}$, $C_{15}H_{12}{}^{130}Te_2$ requires 452.9143)

Preparation of 2,7-dimethoxynaphthalene (**120**)

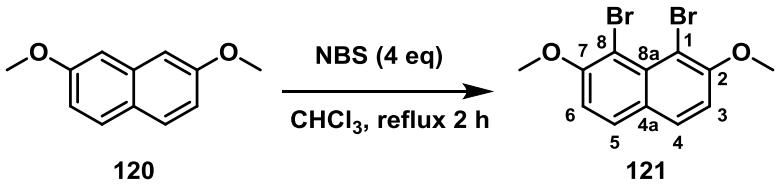


119 120

Known compound **120** was prepared according to the literature procedure.[70] Dimethyl sulfate (16.60 g, 131.8 mmol) was added dropwise over a period of 10 min to an ice-cooled solution of 2,7- dihydroxynaphthalene (10.00 g, 62.5 mmol) in a 10% $NaOH_{(aq)}$ (60.0 mL). The reaction mixture was allowed to warm to rt and stirred for 4 h. H_2O (40 mL) was added forming a precipitate. The mixture was filtered and the solid was dissolved in CH_2Cl_2 (60 mL) and then washed with a $NaOH_{(aq)}$ (1 M, 3 × 30 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated under reduced pressure, **120** was obtained as a grey powder (6.17 g, 53%) which required no further purification. R_f 0.35 (*n*-hexane); mp 138–139 °C; δ_H (400 MHz, $CDCl_3$) 7.68 (2 H, d, *J* = 8.9, H-4 and H-5), 7.11 (2 H, d, *J* = 2.4, H-1 and H-8), 7.03 (2 H, dd, *J* = 8.8, 2.4, H-3 and H-6), 3.92 (6 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 158.1 (C, C-2 and C-7), 135.9 (C, C-8a), 129.2 (CH, C-4 and C-5), 124.3 (C, C-4a), 116.0 (CH, C-3 and C-6), 105.3 (CH, C-1 and C-8), 55.3 (CH_3); *m/z* (EI^+) found 188.1 ($M^{+\bullet}$, $C_{12}H_{12}O_2$ requires 188.1), 188.1 (100%), 159.1 (21), 145.1 (83), 130.1 (61), 102.1 (56).

Analytical data are in agreement with literature values.[70]

Preparation of 1,8-dibromo-2,7-dimethoxynaphthalene (**121**)

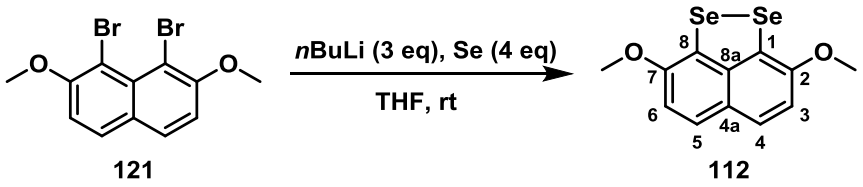


120 **121**

Known compound **121** was prepared according to the literature procedure.[70] A solution of 2,7-dimethoxynaphthalene (1.00 g, 5.31 mmol) in $CHCl_3$ (10 mL) was added dropwise over 10 min at rt to a solution on *N*-bromosuccinimide (3.77 g, 21.2 mmol) and pyridine (2.0 mL, 2.03 mmol) in $CHCl_3$ (60 mL). The reaction mixture was heated at reflux for 2 h. The mixture was then allowed to cool to rt and then treated with $HCl_{(aq)}$ (1 M, 30 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: EtOAc), dibromide **121** (886 mg, 48%) was obtained as as a pale brown solid. R_f 0.28 (4:1, *n*-hexane: EtOAc); mp 129–130 °C; δ_H (400 MHz, $CDCl_3$) 7.72 (2 H, d, *J* = 8, H-4 and H-5), 7.14 (2 H, d, *J* = 9.0, H-3 and H-6), 4.01 (6H, s, 2 × CH_3); δ_C (101 MHz, $CDCl_3$) 156.6 (C, C-2 and C-7), 131.8 (C, C-1 and C-8), 130.2 (CH, C-4 and C-5), 127.6 (C, C-4a), 111.9 (CH, C-3 and C-6), 106.2 (C, C-8a), 57.2 (CH_3); *m/z* (EI^+) 347.9 ($M^{+\bullet}$, $C_{12}H_{10}O_2{}^{81}Br_2$ requires 347.9), 347.9 (50%), 345.9 (100), 343.9 (49), 302.9 (44), 287.9 (24).

Analytical data are in agreement with literature values.[70]

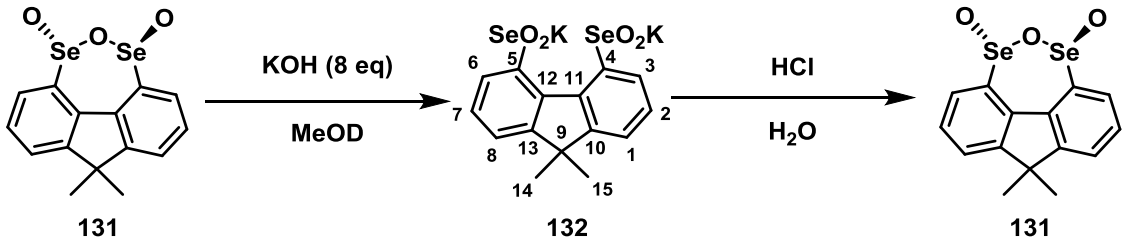
Preparation of 2,7-Dimethoxynaphtho[1,8-cd][1,2]diselenole (**112**)



Known compound **112** was prepared according to the literature procedure.[70] A solution of *n*BuLi (1.06 M in hexane, 3.5 mL, 3.6 mmol) was added dropwise over a period of 10 min, to a solution of 1,8-dibromo-2,7dimethoxynaphthalene (422 mg, 1.20 mmol) in THF (5 mL) at −78 °C. The cooling bath was removed and the mixture was allowed to stir for 1.5 h. Selenium (333 mg, 4.20 mmol) was added in one portion and the mixture was allowed to stir for 3 h. A saturated $NH_4Cl_{(aq)}$ solution (15 mL) was added. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: EtOAc) to afford diselenide **112** (95 mg, 23%) as a purple crystal. R_f 0.38 (4:1, *n*-hexane: EtOAc); mp 155–156 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2933, 2955, 2832, 1614, 1500, 1424, 1256, 1051, 805; δ_H (400 MHz, $CDCl_3$) 7.54 (2 H, d, *J* = 8.8, H-4 and H-5), 6.96(2 H, d, *J* = 8.8, H-3 and H-6), 3.97 (6 H, s, 2 × CH_3); δ_C (101 MHz, $CDCl_3$) 153.1 (C, C-2 and C-7), 139.9 (C, C-1 and C-8), 127.9 (C, C-4a), 125.7 (CH, C-4 and C-5), 122.8 (C, C-8a), 111.7 (CH, C-3 and C-6), 56.4 (CH_3, 2 × CH_3); ^{77}Se NMR (76 MHz, $CDCl_3$) 408.0; *m/z* (EI^+) found 344.1 ($M^{+\bullet}$, $C_{12}H_{10}O_2{}^{78}Se^{80}Se$ requires 344.1), 344.2 (45%), 346.1 (100), 343.9 (60), 312.1 (28), 305.1 (18)

Analytical data are in agreement with literature values.[70]

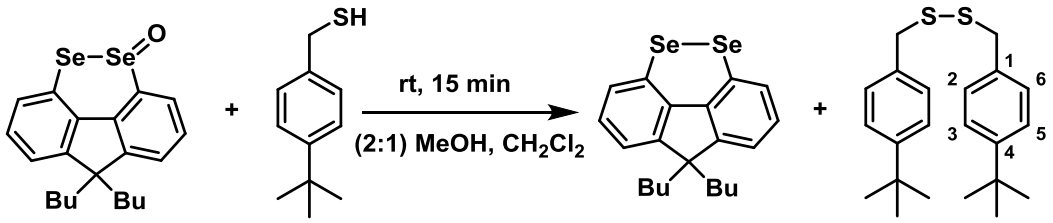
Preparation of potassium 9,9-dimethyl-5-((oxidoselanyl)oxy)-9H-fluorene-4-seleninate (**132**) and reformation of *trans*-seleninic anhydride (**131**)



Seleninic anhydride 131 (50 mg, 0.125 mmol) was added as a single portion to a solution of KOH (56 mg, 1.00 mmol) in MeOD (4.0 mL). The reaction mixture was allowed to stir at rt for 2 h. NMR spectrometry revealed the presence of **132**. $HCl_{(aq)}$ (1 M, 5 mL) was added to the reaction mixture to afford a precipitate. The solid was filtered under vacuum and washed with Et_2O (3 × 10 mL). Seleninic anhydride **131** was obtained as a white powder (43 mg, 86%) that requires no further purification.

132; δ_H (400 MHz, MeOD) 7.34 (2 H, d, *J* = 7.8, H-3 and H-6), 6.77 (2 H, t, *J* = 7.6, H-2 and H-7), 6.46 (2 H, d, *J* = 7.6, H-1 and H-8), 0.33 (6 H, s, H-14 and H-15); δ_C (101 MHz, MeOD) 154.9 (C, C-10 and C-13), 149.5 (C, C-11 and C-12), 134.9 (C, C-4 and C-5), 128.8 (CH, C-2 and C-7), 124.6 (CH, C-1 and C-8 or C-3 and C-6), 124.5 (CH, C-1 and C-8 or C-3 and C-6), 46.0 (C, C-9), 26.5 (CH_3, C-14 and C-15); ^{77}Se NMR (76 MHz, MeOD) 1136.0

Stoichiometric reaction 9,9-dibutyl-9H-fluoreno[4,5-cde][1,2]diselenine 4-oxide and 4-*tert*-butylphenylmethanethiol



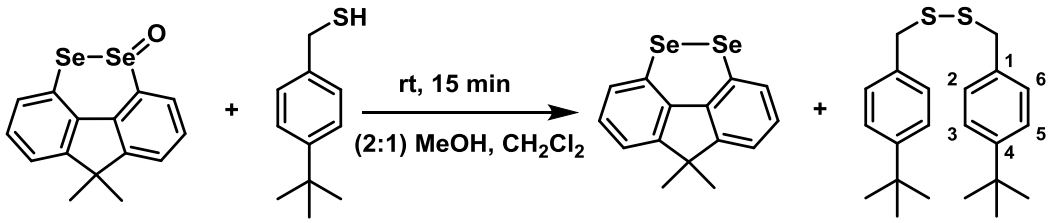
122 **135** **117** **136**

4-*tert*-Butylphenylmethanethiol (504 mg, 2.80 mmol) was added to a solution of **122** (125 mg, 0.28 mmol) in a 2:1 mixture of MeOH and CH_2Cl_2 (15 mL) and stirred at rt for 15 min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (9:1, hexane: Et_2O) to first afford diselenide **117** (115 mg, 95%), followed by disulfide **136** (92 mg, 0.25 mmol, 92%), followed by thiol **135** (393 mg, 78%).

Disulfide **136**; R_f 0.30 (*n*-hexane); mp 63–64 °C; δ_H (400 MHz, $CDCl_3$) 7.25 (4 H, d, *J* = 8.3, H-3 and H-5), 7.09 (4 H, d, *J* = 8.4, H-2 and H-6), 3.51 (4H, s, CH_2), 1.22 (18 H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 150.5 (C, C-4), 134.3 (C, C-1), 129.2 (CH, C-2 and C-6), 125.5 (CH, C-3 and C-5), 43.0 (CH_2), 34.6 (C), 31.5 (CH_3); *m/z* (ASAP$^+$) found 376.2133 ($[M + NH_4]^+$, $C_{22}H_{34}NS_2$ requires 376.2133)

Analytical data are in agreement with literature values.[114]

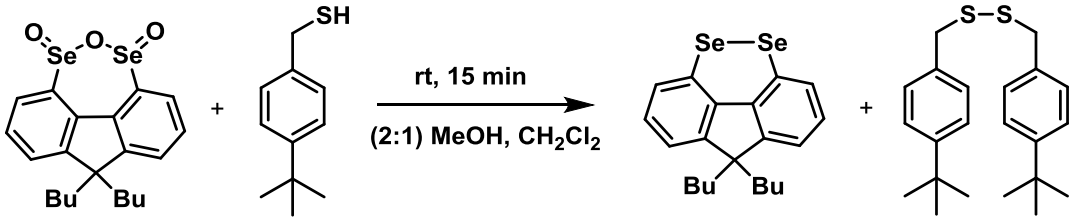
Stoichiometric reaction between 9,9-dimethyl-9H-fluoreno[4,5-cde][1,2]diselenine 4-oxide and 4-*tert*-butylphenylmethanethiol



129 **135** **127** **136**

4-*tert*-Butylphenylmethanethiol (720 mg, 4.00 mmol) was added to a solution of **129** (150 mg, 0.4 mmol) in a 2:1 mixture of MeOH and CH_2Cl_2 (28 mL) and stirred at rt for 15 min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (9:1, hexane: Et_2O) to first afford diselenide **127** (122 mg, 95%), followed by disulfide **136** (133 mg, 0.37 mmol, 94%), followed by thiol **135** (540 mg, 75%).

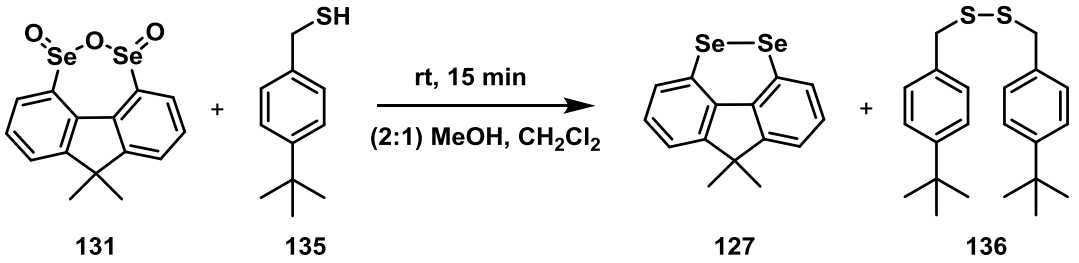
Stoichiometric reaction between seleninic anhydride **124** and 4-*tert*-butylphenylmethanethiol



124 **135** **117** **136**

4-*tert*-Butylphenylmethanethiol (540 mg, 3.00 mmol) was added to a solution of **124** (150 mg, 0.3 mmol) in a 2:1 mixture of MeOH and CH_2Cl_2 (15 mL) and stirred at rt for 15 min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (9:1, hexane: Et_2O) to first afford diselenide **117** (117 mg, 90%), followed by disulfide **136** (285 mg, 0.79 mmol, 88%), followed by thiol **135** (194 mg, 36%).

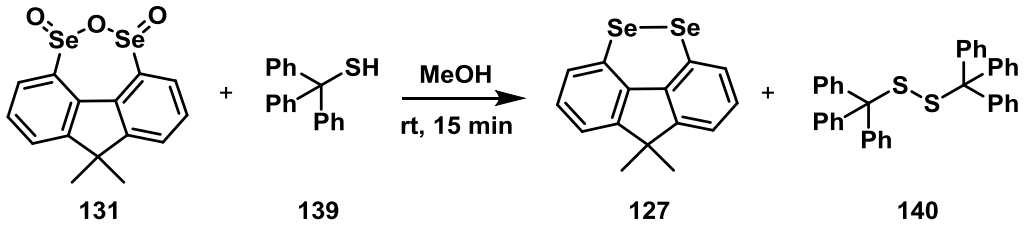
Stoichiometric reaction between seleninic anhydride **131** and 4-*tert*-butylphenylmethanethiol



131 **135** **127** **136**

4-*tert*-Butylphenylmethanethiol (676 mg, 3.80 mmol) was added to a solution of **131** (150 mg, 0.37 mmol) in a 2:1 mixture of MeOH and CH_2Cl_2 (26 mL) and stirred at rt for 15 min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (9:1, hexane: Et_2O) to first afford diselenide **127** (126 mg, 96%), followed by disulfide **136** (357 mg, 0.99 mmol, 90%), followed by thiol **135** (269 mg, 40%).

Reaction of seleninic anhydride with triphenylmethanethiol



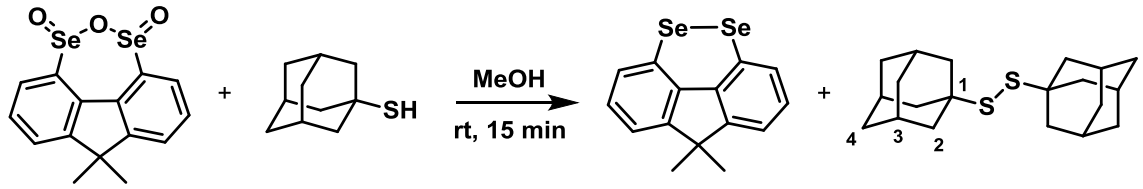
131 **139** **127** **140**

Trityl thiol (692 mg, 2.51 mmol) was added to a solution of **131** (100 mg, 0.25 mmol) in MeOH (12.0 mL) and allowed to stir at rt for 15 min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane 100%) to first afford diselenide **127** (86 mg, 99%), followed by trityl disulfide **140** (397 mg, 0.72 mmol, 96%), followed by trityl thiol **139** (242 mg, 35%)

Disulfide **140**; R_f 0.30 (*n*-hexane); mp 150–152 °C; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.32 (30 H, m); δ_C (101 MHz, $CDCl_3$) 143.8 (C), 129.4 (CH), 127.8 (CH), 126.9 (CH), 73.5 (C)

Analytical data are in agreement with literature values.[115]

Reaction of seleninic anhydride with 1-adamantanethiol



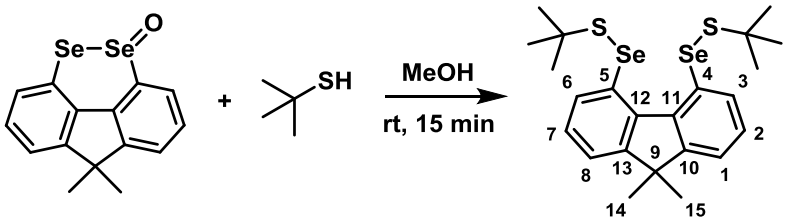
131 141 127 142

1-Adamantanethiol (210 mg, 1.2 mmol) was added to a solution of **131** (50 mg, 0.12 mmol) in MeOH (6.0 mL) and allowed to stir at rt for 15 min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane 100%) to first afford diselenide **127** (39 mg, 90%), followed by 1-adamantane disulfide **142** (97 mg, 0.29 mmol, 81%), followed by 1-adamantanethiol **141** (74 mg, 37%)

Disulfide **142**; R_f 0.36 (*n*-hexane); mp 223–224 °C; δ_H (400 MHz, $CDCl_3$) 2.06 (3 H, s, H-3), 1.82 (6 H, s, H-2), 1.70–1.63 (6 H, m, H-4); δ_C (101 MHz, $CDCl_3$) 47.4 (C, C-1), 43.2 (CH_2, C-2), 36.2 (CH_2, C-4), 30.1 (CH, C-3)

Analytical data are in agreement with literature values.[116]

Reaction of 9,9-dimethyl-9H-fluoreno[4,5-cde][1,2]diselenine 4-oxide with *tert*-butylthiol

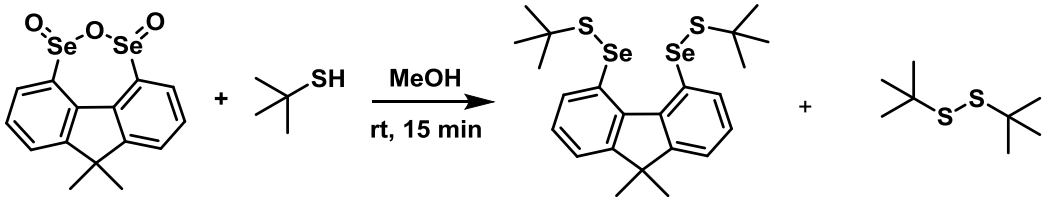


129 143 145

tert-Butylthiol (414 mg, 4.60 mmol) was added to a solution of **129** (169 mg, 0.46 mmol) in MeOH (23.0 mL) and stirred at 0 °C for 15 min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane 100%) giving **145** as a gel (230 mg, 94%), *tert*-butyl thiol **143** was recovered (300 mg, 72%). R_f 0.32 (*n*-hexane); δ_H (400 MHz, $CDCl_3$) 8.00 (2 H, dd, *J* = 6.4, 2.5, H-3 and H-6), 7.39–7.34 (4H, stack, H-1, H-2, H-7 and H-8), 1.41 (6 H, s,

H-14 and H-15), 0.97 (18 H, s, 6 × CH_3); δ_C (101 MHz, $CDCl_3$) 153.9 (C, C-10 and C-13), 147.3 (C, C-11 and C-12), 135.6 (CH, C-2 and C-7), 129.2 (CH, C-1 and C-8 or C-3 and C-6), 128.2 (C, C-4 and C-5), 121.9 (CH, C-1 and C-8 or C-3 and C-6), 47.0 (C), 46.8 (C, C-9), 30.5 (CH_3), 27.9 (2 x CH_3, C-14 and C-15); ^{77}Se NMR (76 MHz, $CDCl_3$) 398.6; *m/z* (AP^+) found 530.0121 ($M^{+\bullet}$, $C_{23}H_{30}S_2{}^{80}Se_2$ requires 530.0119)

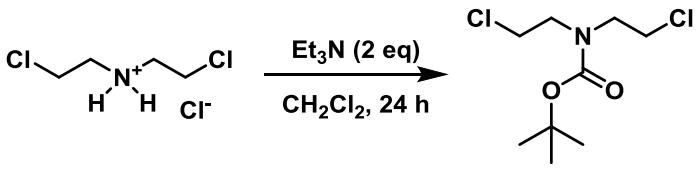
Reaction of seleninic anhydride with *tert*-butylthiol



131 **143** **145** **144**

tert-butylthiol (252 mg, 2.80 mmol) was added to a solution of **131** (112 mg, 0.28 mmol) in MeOH (14.0 mL) and stirred at 0 °C for 5 min allowed to stir at 0 °C for 15 min. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (*n*-hexane 100%) giving **145** as a gel (140 mg, 95%) and *tert*-butyl disulfide **144** (99 mg, 65%), *tert*-butyl thiol **143** was recovered (100 mg, 40%).

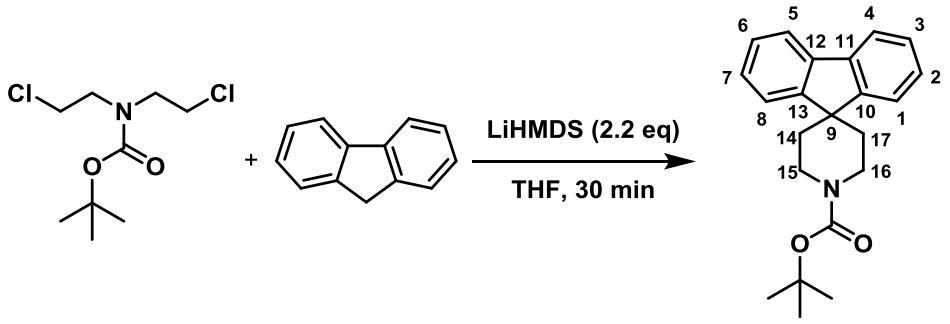
Preparation of *N*-(*tert*-butyloxycarbonyl)bis(2-chloroethyl)amine (**151**)



150 **151**

Known compound **151** was prepared according to the literature procedure.[112] Di-*tert*-butyl dicarbonate (11.55 g, 53.0 mmol) was added as a single portion at rt to a solution of bis-(2-chloroethyl)amine hydrochloride (8.00 g, 44.0mmol) in CH_2Cl_2 (70.0 mL). The reaction mixture was allowed to stir at rt of 10 min. Et_3N (12.2 mL, 88.0 mmol) was added dropwise over 10 mins. The reaction mixture was allowed to stir at rt for 24 h. A solution of $HCl_{(aq)}$ (1 M, 30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (9:1, *n*-hexane: Et_2O) affording **151** (5.80 g, 54%) as a clear oil. ν_{max}(solid neat, ATR)/cm^{-1} 2976, 1757, 1692, 1405, 1366, 1155, 655; δ_H (400 MHz, $CDCl_3$) 3.73 (8H, m, CH_2), 1.47 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 146.5 (CO, C-1), 85.2 (C), 46.0 (CH_2), 45.4 (CH_2) 27.4 (CH_3);

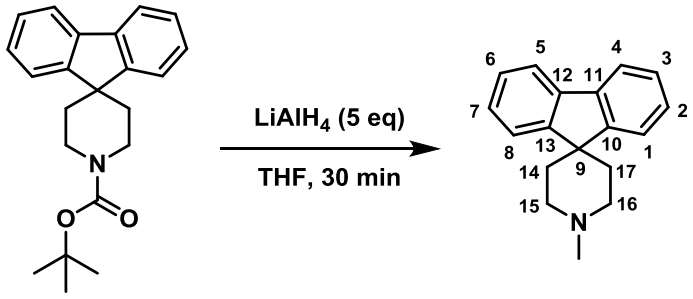
Preparation of Spiro[9H-fluorene-9,4'-piperidine]-1'-carboxylic acid, 1,1-dimethylethyl ester (**152**)



151 **115** **152**

Known compound **152** was prepared according to the literature procedure.[81] LiHMDS (1M in THF, 7.6 mL, 7.60 mmol) was added dropwise over 2 min to a solution of fluorene (630 mg, 3.80 mmol) in THF (10 mL) at 0 °C. This solution was transferred via cannula over 7 mins to a solution of **151** (836 mg, 3.45 mmol) in THF (10 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 2 h, the ice bath was removed and the reaction was allowed to stir for 24 h. H_2O (30 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (9:1, *n*-hexane: Et_2O), amide **152** (631 mg, 55%) was obtained as a pure orange solid. R_f 0.28 (9:1, *n*-hexane: Et_2O); mp 129–130 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3006, 2961, 1688, 1403, 1238, 1011, 734; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 7.4, H-4 and H-5), 7.62 (2H, d, *J* = 7.4, H-1 and H-8), 7.39 (2H, td, *J* = 7.4, 1.1, H-2 and H-7 or H-3 and H-6), 7.32 (2H, td, *J* = 7.6, 1.2, H-2 and H-7 or H-3 and H-6), 3.88 (4H, t, *J* = 6.0, H-15 and H-16), 1.87 (4H, t, *J* = 6.0, H-14 and H-17), 1.54 (9H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 154.5 (CO), 151.5 (C, C-10 and C-13), 139.8 (C, C-11 and C-12), 127.5 (CH, C-2 and C-7 or C-3 and C-6), 127.3 (CH, C-2 and C-7 or C-3 and C-6), 124.3 (CH, C-1 and C-8), 120.2 (CH, C-4 and C-5), 79.8 (CH_2, C-15 and C-16), 48.3 (C, C-9), 34.9 (CH_2, C-14 and C-17), 28.7 (CH_3); *m/z* (ES^+) 358.1785 ($[M+Na]^+$, $C_{22}H_{25}NO_2Na$ requires 358.1783)

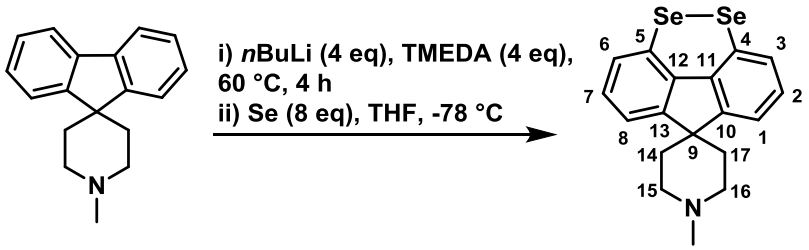
Preparation of 1'-methyl-spiro[fluorene-9,4'-piperidine] (**154**)



152 **154**

A solution of **152** (1.10 g, 3.29 mmol) in THF (15 mL) was transferred via cannula over 5 min to a suspension of $LiAlH_4$ (625 mg, 16.45 mmol) in THF (10 mL) at 0 °C. The reaction mixture was heated to reflux and stirred for 1 h. The mixture was allowed to cool to rt. H_2O (10 mL) was added dropwise over a period of 5 min. The mixture was filtered over celite and washed with Et_2O (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. No purification was required, amine **154** (606 mg, 73%) was obtained as a pale orange solid. R_f 0.28 (9:1, *n*-hexane: Et_2O); mp 129–130 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3058, 2935, 2793, 1477, 1434, 1286, 754; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* = 6.4, H-4 and H-5), 7.71 (2H, d, *J* = 7.4, H-1 and H-8), 7.37 (2H, td, *J* = 7.4, 1.2, H-2 and H-7 or H-3 and H-6), 7.31 (2H, td, *J* = 7.3, 1.3, H-2 and H-7 or H-3 and H-6), 2.87 (4H, t, *J* = 8.0, H-15 and H-16), 2.54 (3H, s, CH_3), 1.99 (4H, t, *J* = 8.0, H-14 and H-17); δ_C (101 MHz, $CDCl_3$) 152.3 (C, C-10 and C-13), 139.8 (C, C-11 and C-12), 127.3 (CH, C-3 and C-6), 127.1 (CH, C-2 and C-7), 124.6 (CH, C-1 and C-8), 119.9 (CH, C-4 and C-5), 52.4 (CH_2, C-15 and C-16), 46.8 (CH_3), 47.7 (C, C-9), 35.6 (CH_2, C-14 and C-17); *m/z* (ES^+) 250.1630 ($[M+H]^+$, $C_{18}H_{19}NNa$ requires 250.1596)

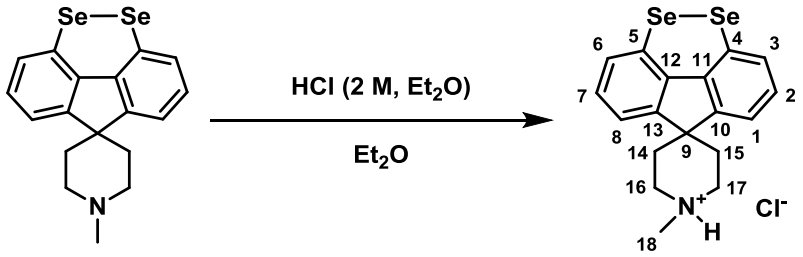
Preparation of 1'-methyl-spiro[fluoreno[4,5-cde][1,2]diselenine-9,4'-piperidine] (**155**)



154 **155**

*n*BuLi (1.96 M in hexanes, 2.0 mL, 3.50 mmol) was added dropwise over 10 min at rt to a solution of compound **154** (273 mg, 1.00 mmol) in TMEDA (464 mg, 4.00 mmol). The reaction mixture was then stirred at 60 °C for 4 h. The reaction was cooled to –78 °C and THF (5 mL) was added rapidly to the mixture followed by the addition of selenium (790 mg, 10.00 mmol) as a single portion. The cooling bath was removed and the reaction was allowed to stir for 16 h. H_2O (35 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography (2:7:1, *n*-hexane: Et_2O: Et_3N), diselenide **155** (45 mg, 11%) was obtained as a dark burgundy crystalline solid. R_f 0.27 (2:7:1, *n*-hexane: Et_2O: Et_3N); mp 138–139 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3072, 2932, 2787, 1423, 1403, 1283, 768; δ_H (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* = 8.2, H-3 and H-6), 7.26 (2H, d, *J* = 8.1, H-1 and H-8), 7.22 (2H, t, *J* = 8.2, H-2 and H-7), 2.85 (4H, t, *J* = 8.0, H-15 and H-16), 2.55 (3H, s, CH_3), 1.97 (4H, t, *J* = 8.0, H-14 and H-17); δ_C (101 MHz, $CDCl_3$) 152.9 (C, C-10 and C-13), 138.3 (C, C-11 and C-12), 129.2 (CH, C-3 and C-6), 126.8 (CH, C-2 and C-7), 123.6 (CH, C-1 and C-8), 118.1 (C, C-4 and C-5), 52.3 (CH_2, C-15 and C-16), 47.9 (C, C-9), 46.7 (CH_3), 34.9 (CH_2, C-14 and C-17); ^{77}Se NMR (76 MHz, $CDCl_3$) 231.3; m/z (ASAP$^+$) 407.9794 ($M^{+\bullet}$, $C_{18}H_{17}{}^{78}Se_2N$ requires 407.9773)

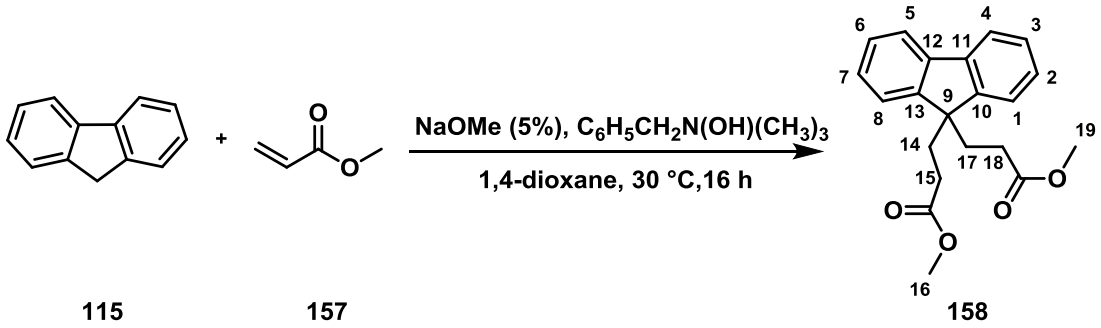
Preparation of 1'-methyl-spiro[fluoreno[4,5-cde][1,2]diselenine-9,4'-piperidine]; hydrochloride (**156**)



155 **156**

HCl (2.0 mL, 4.00 mmol, 2.0 M in Et_2O) was added rapidly at rt to a solution of compound **155** (200 mg, 0.49 mmol) in Et_2O (10 mL). The reaction mixture was then stirred at rt for 30 min. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). The salt was collected as a beige crystalline solid (200 mg, 92%). ν_{max}(solid neat, ATR)/cm^{-1} 3072, 2932, 2787, 1423, 1403, 1283, 768; δ_H (400 MHz, $(CD_3)_2SO$) 8.05 (1H, d, *J* = 7.7, H-8), 7.26 (1H, d, *J* = 7.7, H-6), 7.41 – 7.36 (3H, stack, H-1, H-2 and H-3), 7.30 (1H, t, *J* = 7.7, H-7), 4.3 (NH), 3.51 – 3.45 (4H, m, H-16 and H-17), 2.97 (3H, d, *J* = 4.8, H-18), 2.88 – 2.71 (2H, m, H-14 and H-15), 1.60 – 1.47 (2H, m, H-14 and H-15); δ_C (101 MHz, $(CD_3)_2SO$) 151.9 (C, C-10), 150.4 (C, C-13), 137.3 (C, C-15), 136.7 (C, C-11), 130.3 (CH, C-1 or C-2 or C-3), 129.5 (CH, C-7), 127.5 (CH, C-1 or C-2 or C-3), 127.4 (CH, C-8), 124.2 (C, C-5), 122.0 (CH, C-1 or C-2 or C-3), 117.8 (C, C-4), 117.8 (C, C-4), 50.1 (CH_2, C-16 and C-17), 45.7 (C, C-9), 42.0 (CH_3, C-15), 31.1 (CH_2, C-14 and C-18); ^{77}Se NMR (76 MHz, $(CD_3)_2SO$) 231.3; m/z (ASAP$^+$) 407.9792 ($M^{+\bullet}$, $C_{18}H_{17}{}^{78}Se_2N$ requires 407.9773)

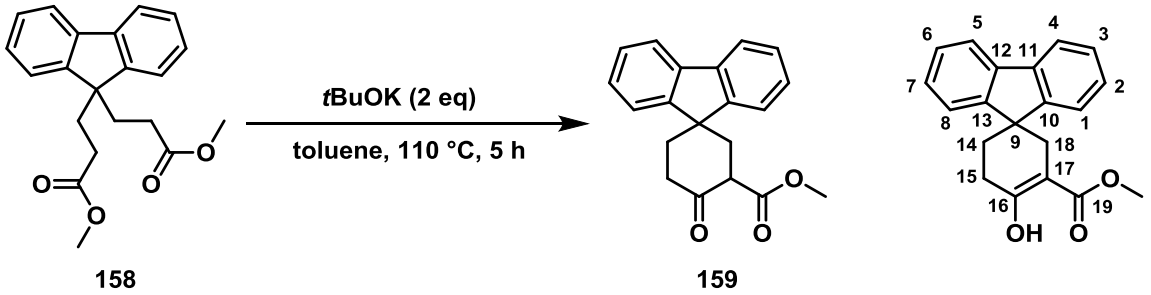
Preparation of 2,2'-(9H-fluorene-9,9-diyl)dipropionate dimethyl ester (**158**)



115 **157** **158**

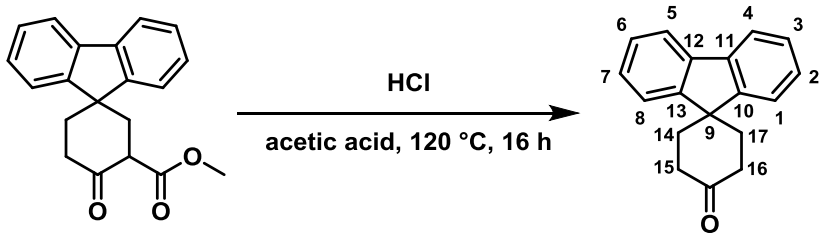
Known compound **158** was prepared according to the literature procedure.[82] Benzyltrimethylammonium hydroxide (1.3 mL, 2.45 mmol, 1.89 M in MeOH) was added rapidly to a solution of fluorene (10.0 g, 60.0 mmol) and sodium methoxide (162 mg, 3.00 mmol) in dioxane (250 mL). The reaction mixture was heated to 30 °C and then methyl acrylate (11.0 mL, 126.0 mmol) was added dropwise to the reaction mixture over 10 min. The reaction mixture was allowed to stir at 30 °C for 16 h. $HCl_{(aq)}$ (1 M, 25 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: Et_2O), diester **158** (9.63 g, 47%) was obtained as a white crystalline solid. R_f 0.15 (4:1, *n*-hexane: Et_2O); mp 82–84 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3070, 2952, 1727, 1436, 1366, 1288, 1162; δ_H (400 MHz, $CDCl_3$) 7.63 (2H, m, H-1 and H-8), 7.27 (6H, stack, H-2, H-3, H-4, H-5, H-6 and H-7), 3.38 (6H, s, H-16 and H-19), 2.34 (4H, t, *J* = 8.0, H-15 and H-18), 1.48 (4H, t, *J* = 8.0, H-14 and H-17); δ_C (101 MHz, $CDCl_3$) 173.9 (CO), 147.5 (C, C-10 and C-13), 141.3 (C, C-11 and C-12), 127.8 (CH, C-2 and C-7 or C-3 and C-6), 127.7 (CH, C-2 and C-7 or C-3 and C-6), 123.0 (CH, C-4 and C-5), 120.1 (CH, C-1 and C-8), 53.6 (C, C-9), 51.4 (CH_3, C-16 and C-19), 34.7 (CH_2, C-15 and C-18), 28.9 (2 × CH_2, C-14 and C-17); *m/z* (ASAP$^+$) 338.1513 ($M^{+\bullet}$, $C_{21}H_{22}O_4$ requires 338.1518)

Preparation of 2,2'-(9H-fluorene-9,9-diyl)dipropionate dimethyl ester (**159**)



Known compound Compound **159** was prepared according to the literature procedure.[82] *t*BuOK (366 mg, 3.27 mmol) was added as a single portion at rt to a solution of methyl 9,9-fluorenedipropionate (0.5 g, 1.5 mmol) in toluene (10 mL). The reaction mixture was then stirred at 110 °C for 5 h. H_2O was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. **159** (275 mg, 56%) was obtained as a white solid of sufficient purity to not require any further purification. R_f 0.60 (4:1, *n*-hexane: Et_2O); mp 119–120 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2943, 2847, 1651, 1613, 1436, 1282, 1211, 733; δ_H (400 MHz, $CDCl_3$) 12.42 (1H, s, OH) 7.76 (2H, d, *J* = 7.5, H-1 and H-8), 7.41 (2H, d, *J* = 7.7, H-4 and H-5), 7.37 (2H, d, *J* = 7.4, H-3 and H-6), 7.29 (2H, t, *J* = 7.5, H-2 and H-7), 3.71 (3H, s, CH_3), 2.71 (2H, t, *J* = 6.7, H-15), 2.66 (2H, s, H-18), 1.92 (2H, t, *J* = 6.7, H-14); δ_C (101 MHz, $CDCl_3$) 172.8 (CO, C-19), 171.6 (COH, C-16), 151.3 (C, C-10 and C-13), 139.7 (C, C-11 and C-12), 127.8 (CH, C-3 and C-6), 127.5 (CH, C-2 and C-7), 123.6 (CH, C-4 and C-5), 120.4 (CH, C-1 and C-8), 97.4 (C, C-17), 51.5 (CH_3), 49.1 (C, C-9), 32.1 (CH_2, C-18), 31.5 (CH_2, C-14), 27.7 (CH_2, C-15); *m/z* (AP^+) 307.1205 ($[M+H]^+$, $C_{20}H_{18}O_3$ requires 307.1250)

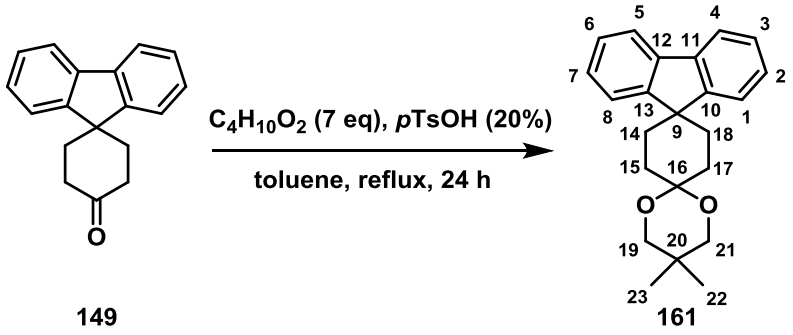
Preparation of spiro-4-one, spiro[cyclohexane-1,9'-fluoren]-4-one (**149**)



159 **149**

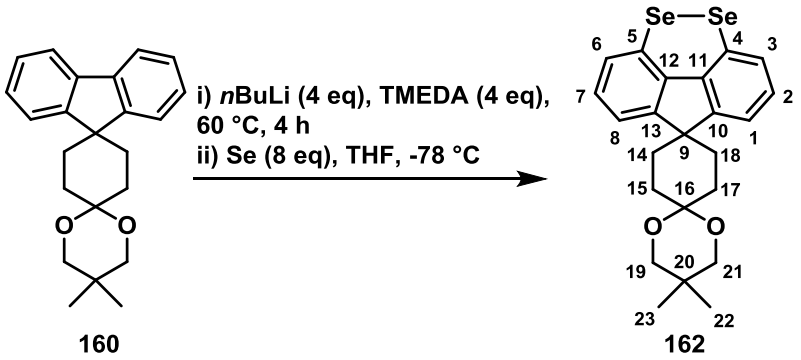
Known compound **149** was prepared according to the literature procedure.[82] $HCl_{(aq)}$ (11 M,4.0 mL) was added rapidly at rt to a solution of **159** (3.06 g, 10.0 mmol) in acetic acid (150 mL). The reaction mixture was heated at reflux and allowed to stir for 16 h. $NaOH_{(aq)}$ (1 M, 200 mL) was added and the mixture was extracted with ethyl acetate (3 × 80 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Ketone **149** (1.78 g, 71%) was obtained as a pure white solid that required no further purification. R_f 0.23 (4:1, *n*-hexane: Et_2O); mp 211–212 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3038, 2926, 1649, 1435, 1282, 1211, 733; δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* = 7.5, H-1 and H-8), 7.51 (2H, d, *J* = 7.5, H-4 and H-5), 7.34 (2H, td, *J* = 7.5, 6.0, 1.2, H-3 and H-6), 7.26 (2H, td, *J* = 7.5, 6.0, 1.2, H-2 and H-7), 2.85 (4H, t, *J* = 7.0, H-15), 2.13 (4H, t, *J* = 7.0, H-14); δ_C (101 MHz, $CDCl_3$) 211.5 (CO), 150.7 (C, C-10 and C-13), 139.8 (C, C-11 and C-12), 127.7 (CH, C-3 and C-6), 127.4 (CH, C-2 and C-7), 123.7 (CH, C-1 and C-8), 120.3 (CH, C-4 and C-5), 48.9 (C, C-9), 39.0 (CH_2, C-15 and C-16), 35.7 (2 × CH_2, C-14 and C-17); *m/z* ($ASAP^+$) found 249.1277 ($[M+H]^+$, $C_{18}H_{16}O$ requires 249.1279)

Preparation of 5'',5''-dimethyldispiro[fluorene-9,1'-cyclohexane-4',2''-[1,3]dioxane] (**161**)



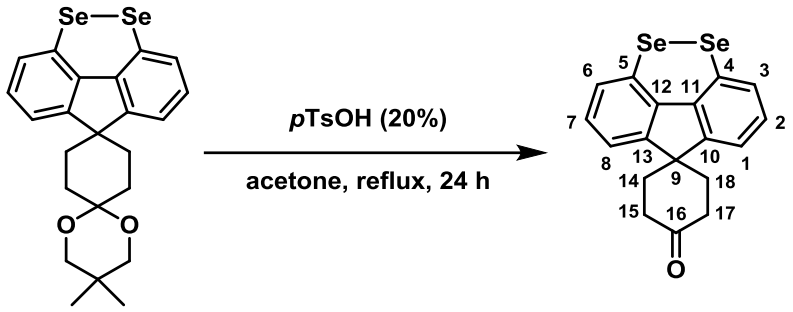
Neopentyl glycol (2.2 g. 21.1 mmol) was added as a single portion at rt to a solution of compound **149** (750 mg. 3.02 mmol) and *p*TsOH (114 mg, 0.60 mmol) in toluene (100 mL). The reaction mixture was heated at reflux for 24 h under a water separator (Dean Stark). $Na_2CO_{3(aq)}$ (1 M, 50 mL) was added and the mixture was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crude material purified by recrystallisation with *n*-hexane. Acetal **161** (534 mg, 52%) was obtained as a pure white solid. R_f 0.52 (4:1, *n*-hexane: Et_2O); mp 150–151 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2947, 2863, 1437, 1288, 1118, 1101, 757, 736; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* = 7.3, H-1 and H-8), 7.65 (2H, d, *J* = 7.5, H-4 and H-5), 7.36 (2H, td, *J* = 7.5, 6.0, 1.2, H-3 and H-6), 7.28 (2H, td, *J* = 7.5, 6.0, 1.2, H-2 and H-7), 3.64 (4H, s, H-19 and H-21), 2.27 (4H, t, *J* = 8.2, H-15 and H-17), 1.88 (4H, t, *J* = 8.2, H-14 and H-18), 1.05 (6H, s,H-22 and H-23); δ_C (101 MHz, $CDCl_3$) 152.2 (C, C-10 and C-13), 139.6 (C, C-11 and C-12), 127.1 (CH, C-3 and C-6), 127.0 (CH, C-2 and C-7), 124.1 (CH, C-1 and C-8), 119.9 (C, C-4 and C-5), 97.4 (C, C-16), 70.1 (CH_2, C-19 and C-21), 49.7 (C, C-9), 32.0 (CH_2, C-15 and C-17), 30.3 (C, C-20), 29.5 (CH_2, C-14 and C-18), 22.8 (CH_3, C-22 and C-23); *m/z* (ES^+) 335.2007 ($[M+H]^+$, $C_{23}H_{26}O_2$ requires 335.2011)

Preparation of 5'',5''-dimethyldispiro[fluoreno[4,5-cde][1,2]diselenine-9,1'-cyclohexane-4',2''-[1,3]dioxane] (**162**)



*n*BuLi (2.15 M in hexanes, 0.7 mL, 1.56 mmol) was added dropwise over 10 min at rt to a solution of **160** (131 mg, 0.39 mmol) in TMEDA (0.18 mg, 1.56 mmol). The reaction mixture was then stirred at 60 °C for 4 h. The reaction was cooled to –78 °C and THF (5 mL) was added to the mixture followed by addition of selenium (300 mg, 3.90 mmol) as a single portion. The cooling bath was removed and the reaction mixture was allowed to warm to rt and left to stir for 16 h. H_2O (15.00 mL) was added to the mixture and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: Et_2O), diselenide **162** (36 mg, 20%) was obtained as a dark burgundy crystal. R_f 0.35 (4:1, *n*-hexane: Et_2O); mp 178–180 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2951, 2864, 1562, 1403, 1111, 906, 726; δ_H (400 MHz, $CDCl_3$) 7.34 (2H, d, *J* = 7.4 , H-1 and H-8), 7.18 (2H, d, *J* = 7.7 , H-3 and H-6), 7.12 (2H, t, *J* = 7.6, H-2 and H-7), 3.62 (4H, s, H-19 and H-21), 2.22 (4H, t, *J* = 8.0, H-15 and H-17), 1.83 (4H, t, *J* = 8.0, H-14 and H-18), 1.04 (6H, s, H-22 and H-23); δ_C (101 MHz, $CDCl_3$) 153.1 (C, C-10 and C-13), 138.2 (C, C-11 and C-12), 129.3 (CH, C-3 and C-6), 126.8 (CH, C-2 and C-7), 123.3 (CH, C-1 and C-8), 118.1 (C, C-4 and C-5), 97.3 (C, C-16), 70.3 (CH_2, C-19 and C-21), 50.1 (C, C-9), 31.6 (CH_2, C-15 and C-17), 30.5 (C, C-20), 29.6 (CH_2, C-14 and 18), 22.9 (CH_3, C-22 and C-23); ^{77}Se NMR (76 MHz, $CDCl_3$) 231.5; *m/z* (ES^+) 492.0113 ($M^{+\bullet}$, $C_{23}H_{24}O_2{}^{80}Se_2$ requires 492.0111)

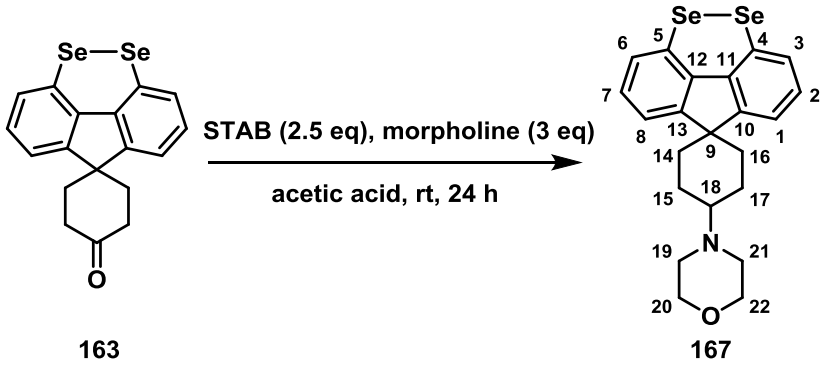
Preparation of spiro[cyclohexane-1,9'-fluoreno[4,5-cde][1,2]diselenin]-4-one (**163**)



162 **163**

*p*TsOH (19 mg, 0.09 mmol) was added rapidly at rt to a suspension of compound **162** (280 mg, 0.57 mmol) in acetone (10 mL). The reaction mixture was heated at reflux for 16 h. The reaction mixture was allowed to cool to rt. $NaHCO_3$ (1 M, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: Et_2O), diselenide **163** (200 mg, 86%) was obtained as a dark burgundy crystalline solid. R_f 0.14 (4:1, *n*-hexane: Et_2O); mp 178–180 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2951, 2864, 1562, 1403, 1111, 906, 726; δ_H (400 MHz, $CDCl_3$) 7.37 (2H, d, *J* = 7.4, H-1 and H-8), 7.32 (2H, d, *J* = 7.7, H-3 and H-6), 7.26 (2H, d, *J* = 7.5, H-2 and H-7), 2.82 (4H, t, *J* = 7.0, H-15 and H-17), 2.18 (4H, t, *J* = 7.0, H-14 and H-18); δ_C (101 MHz, $CDCl_3$) 210.8 (CO, C-16), 151.5 (C, C-10 and C-13), 138.4 (C, C-11 and C-12), 129.6 (CH, C-3 and C-6), 127.3 (CH, C-2 and C-7), 122.7 (CH, C-1 and C-8), 118.7 (C, C-4 and C-5), 49.3 (C, C-9), 39.0 (CH_2, C-15 and C-17), 35.1 (CH_2, C-14 and C-18); ^{77}Se NMR (76 MHz, $CDCl_3$) 231.5; *m/z* (ASAP$^+$) found 406.9453 ([M+H]$^+$, $C_{18}H_{15}O^{80}Se_2$ requires 406.9457)

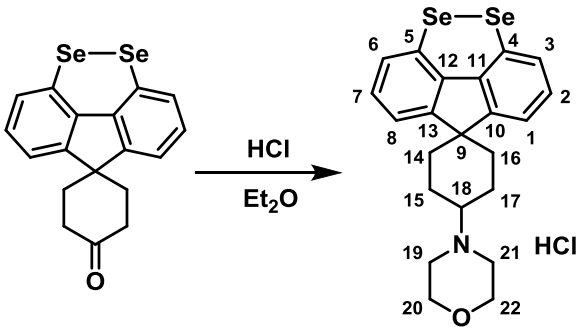
Preparation of 4-(spiro[cyclohexane-1,9'-fluoreno[4,5-cde][1,2]diselenin]-4-yl)morpholine (**167**)



163 **167**

STAB (91 mg, 0.43 mmol) was added in one portion at rt to a solution of **163** (70 mg, 0.17 mmol) in THF (10 mL). Morpholine (45 mg, 0.51 mmol) and acetic acid (24 mg, 0.43 mmol) were added rapidly to the mixture. The reaction was allowed to stir at rt for 24 h. $NaHCO_{3\ (aq)}$ (1 M, 30 mL) was added and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (19:1, EtOAc: Et_3N), diselenide **167** (75 mg, 92%) was obtained as a dark burgundy crystalline solid. R_f 0.10 (19:1, EtOAc: Et_3N); mp degradation above 250 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2944, 2843, 1575, 1438, 1118, 876, 761; δ_H (400 MHz, $CDCl_3$) 7.59 (1H, d, *J* = 7.6, H-8), 7.29 – 7.26 (1H, m, H-6), 7.25 – 7.14 (4H, stack, H-1, H-2, H-3 and H-7), 3.73 (4H, t, *J* = 4.6, H-20 and H-22), 2.57 – 2.44 (1H, m, H-18), 2.18 (4H, t, *J* = 4.6, H-19 and H-21), 2.08 – 1.89 (6H, m, H-14, H-15, H-16 and H-17), 1.59 – 1.54 (2H, m, H-14 and H-16); δ_C (101 MHz, $CDCl_3$) 153.9 (C, C-13), 152.4 (C, C-10), 138.6 (C, C-12), 137.9 (C, C-11), 129.6 (CH, C-1 or C-2 or C-3 or C-7), 128.8 (CH, C-1 or C-2 or C-3 or C-7), 126.8 (CH, C-1 or C-2 or C-3 or C-7), 126.7 (CH, C-6), 124.7 (CH, C-8), 121.9 (CH, C-1 or C-2 or C-3 or C-7), 118.1 (C, C-4 or C-5), 118.0 (C, C-4 or C-5), 67.5 (CH_2, C-20 and C-22), 63.1 (C, C-18), 50.3 (CH_2, C-19 and C-21), 50.2 (C, C-9), 34.4 (CH_2, C-14 and C-16), 25.3 (CH_2, C-15 and C-17); ^{77}Se NMR (76 MHz, $CDCl_3$) 232.2; *m/z* (ASAP$^+$) found 478.0200 ([M+H]$^+$, $C_{22}H_{24}NO^{80}Se_2$ requires 478.0193)

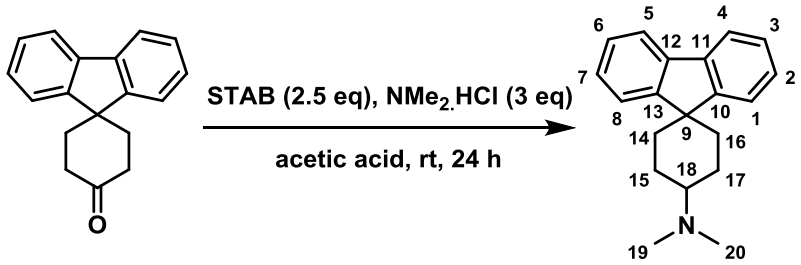
Preparation of 4-(spiro[cyclohexane-1,9'-fluoreno[4,5-cde][1,2]diselenin]-4-yl)morpholine hydrochloride (**169**)



167 **169**

HCl (1.0 mL, 2.00 mmol, 2.0 M in Et_2O) was added rapidly at rt to a solution of compound **167** (100 mg, 0.22 mmol) in Et_2O (10 mL). The reaction mixture was then stirred at rt for 30 min. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). The salt was collected as a beige crystalline solid (80 mg, 71%). mp degradation above 250 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3405, 3324, 3072, 1474, 1348, 1281, 863; δ_H (400 MHz, $(CD_3)_2SO$) 7.40 (1H, d, *J* = 7.4, H-8), 7.10 – 7.00 (1H, m, H-6), 6.85 – 7.55 (4H, stack, H-1, H-2, H-3 and H-7), 3.59 (4H, t, *J* = 4.1, H-20 and H-22), 2.51 – 2.42 (1H, m, H-18), 1.99 (4H, t, *J* = 4.6, H-19 and 21), 1.91 – 1.84 (6H, m, H-14, H-15, H-16 and H-17), 1.55 – 1.48 (2H, m, H-14 and H-16); δ_C (101 MHz, $(CD_3)_2SO$) 153.8 (C, C-13), 152.1 (C, C-10), 137.9 (C, C-12), 137.2 (C, C-11), 129.1 (CH, C-1 or C-2 or C-3 or C-7), 127.6 (CH, C-1 or C-2 or C-3 or C-7), 126.2 (CH, C-1 or C-2 or C-3 or C-7), 125.7 (CH, C-6), 124.9 (CH, C-8), 122.4 (CH, C-1 or C-2 or C-3 or C-7), 118.0 (C, C-4 or C-5), 117.2 (C, C-4 or C-5), 67.4 (CH_2, C-20 and C-22), 61.8 (C, C-18), 50.3 (CH_2, C-19 and C-21), 50.7 (C, C-9), 34.6 (CH_2, C-14 and C-16), 24.1 (CH_2, C-15 and C-17); ^{77}Se NMR (76 MHz, $(CD_3)_2SO$) 230.7; *m/z* (ASAP$^+$) found 478.0200 ($[M+H]^+$, $C_{22}H_{24}NO^{80}Se_2$ requires 478.0193)

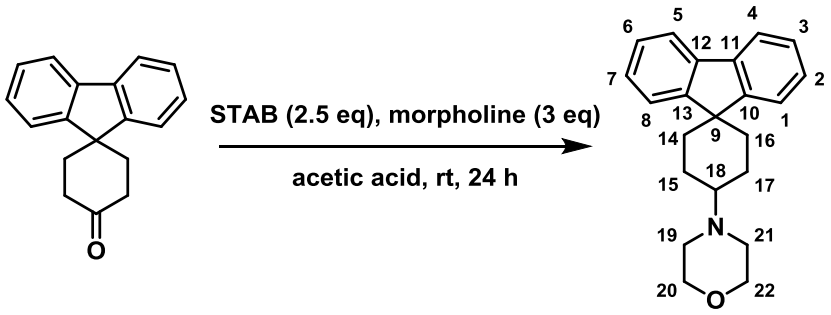
Preperation of *N,N*-dimethylspiro[cyclohexane-1,9'-fluoren]-4-amine (**164**)



149 **164**

STAB (473 mg, 2.07 mmol) was added in a single portion at rt to a solution of **149** (200 mg, 0.80 mmol) in THF (10 mL). Dimethyl amine (2 M in THF, 1.4 mL, 2.88 mmol) and acetic acid (0.1 mL, 2.07 mmol) were added rapidly to the mixture. The reaction was allowed to stir at rt for 24 h. $NaHCO_{3\,(aq)}$ (1 M, 30 mL) was added and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (8:1:1, *n*-hexane: EtOAc: Et_3N), amine **164** (50 mg, 22%) was obtained as a white crystalline solid. R_f 0.05 (4:1, *n*-hexane: EtOAc); mp degradation above 250 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2947, 2742, 1576, 1435, 1121, 871, 765; δ_H (400 MHz, $CDCD_3$) 7.85 (1H, d, *J* = 7.7, H-1), 7.80 – 7.76 (1H, m, H-3), 7.74 – 7.71 (1H, m, H-5), 7.42 – 7.39 (1H, m, H-8), 7.39 – 7.36 (1H, m, H-4), 7.35 – 7.31 (2H, stack, H-6 and H-7), 7.29 (1H, td, *J* = 7.5, 1.3, H-2), 2.51 – 2.49 (1H, m, H-18), 2.45 (6H, s, H-19 and H-20), 2.06 – 2.01 (6H, m, H-14, H-15, H-16 and H-17), 1.66 – 1.62 (2H, m, H-14 and 16); δ_C (101 MHz, $CDCl_3$) 153.2 (C, C-13), 151.2 (C, C-10), 140.1 (C, C-11), 139.3 (C, C-12), 127.3 (CH, C-4), 127.0 (CH, C-6 or C-7), 127.1 (CH, C-6 or C-7), 126.6 (CH, C-2), 125.8 (CH, C-1), 122.7 (CH, C-8), 120.1 (CH, C-3), 119.6 (CH, C-5), 63.4 (C, C-18), 49.7 (C, C-9), 42.1 (CH_2, C-19 and C-20), 34.9 (CH_2, C-14 and C-16), 25.4 (CH_2, C-15 and C-17); *m/z* (ASAP$^+$) found 278.1907 ($[M+H]^+$, $C_{20}H_{23}N$ requires 278.1909)

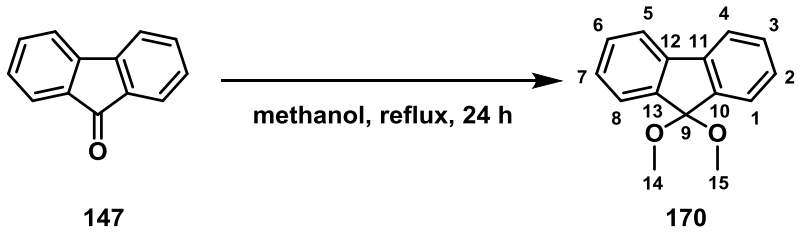
Preparation of 4-(spiro[cyclohexane-1,9'-fluoren]-4-yl)-morpholine (**165**)



149 **165**

STAB (1.15 g, 5.49 mmol) was added in a single portion at rt to a solution of **149** (545 mg, 2.10 mmol) in THF (20 mL). Morpholine (570 mg, 6.59 mmol) and acetic acid (0.3 mL, 5.49 mmol) were added rapidly to the mixture. The reaction was allowed to stir at rt for 24 h. Conc $NaHCO_{3\ (aq)}$ (30 mL) was added and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (19:1, EtOAc: Et_3N), amine **165** (428 mg, 63%) was obtained as a white crystalline solid. R_f 0.25 (19:1, EtOAc: Et_3N); mp degradation above 250 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2944, 2843, 1575, 1438, 1118, 876, 761; δ_H (400 MHz, $CDCD_3$) 7.84 (1H, d, *J* = 7.6, H-1), 7.80–7.76 (1H, m, H-3), 7.74 – 7.71 (1H, m, H-5), 7.44 – 7.40 (1H, m, H-8), 7.40 – 7.36 (1H, m, H-4), 7.35 – 7.32 (2H, stack, H-6 and H-7), 7.29 (1H, td, *J* = 7.5, 1.3, H-2), 3.75 (4H, t, *J* = 4.6, H-20 and H-22), 2.66 (4H, t, *J* = 4.6, H-19 and H-21), 2.54 – 2.48 (1H, m, H-18), 1.96 – 1.93 (6H, m, H-14, H-15, H-16 and H-17), 1.58 – 1.56 (2H, m, H-14 and H-16); δ_C (101 MHz, $CDCl_3$) 153.9 (C, C-13), 151.2 (C, C-10), 140.1 (C, C-11), 139.3 (C, C-12), 127.3 (CH, C-4), 127.1 (CH, C-6 or C-7), 127.1 (CH, C-6 or C-7), 126.6 (CH, C-2), 125.6 (CH, C-1), 122.8 (CH, C-8), 120.1 (CH, C-3), 119.7 (CH, C-5), 67.4 (CH_2, C-20 and C-22), 63.4 (CH, C-18), 50.2 (CH_2, C-19 and C-21), 49.8 (C, C-9), 34.9 (CH_2, C-14 and C-16), 25.2 (CH_2, C-15 and C-17); *m/z* (ASAP$^+$) found 320.2013 ([M+H]$^+$, $C_{22}H_{25}NO$ requires 320.2014)

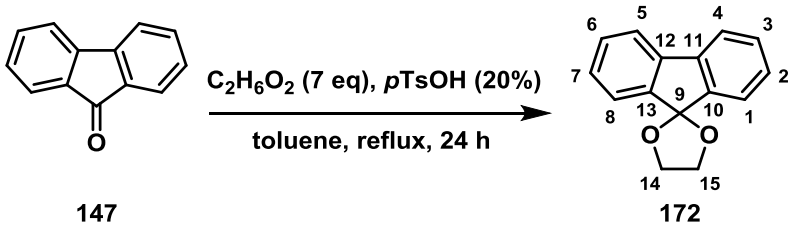
Preparation of 9,9-dimethoxy-9H-fluorene (**170**)



147 **170**

Known compound **170** was prepared according to the literature procedure.[83] Trimethyl orthoformate (12.7 g, 116.3 mmol) was added in one portion at rt to a solution of fluorenone (5.0 g. 27.7 mmol) and camphorsulfonic acid (646 mg, 2.7 mmol) in methanol (150 mL). The reaction mixture was heated at reflux for 24 h under a water separator (Dean Stark). Conc $NaHCO_{3\,(aq)}$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by recrystallisation with *n*-hexane, acetal **170** (3.76 g, 62%) was obtained as a pure white solid. R_f 0.32 (4:1, *n*-hexane: Et_2O); mp 86–87 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3059, 1608, 1447, 1293, 1209, 729; δ_H (400 MHz, $CDCl_3$) 7.62 (2H, dt, *J* = 7.5, 1.0, H-4 and H-5), 7.59 (2H, dt, *J* = 7.3, 1.1, H-1 and H-8), 7.40 (2H, td, *J* = 7.5, 1.2, H-2 and H-7), 7.32 (2H, td, *J* = 7.4, 1.2, H-3 and H-6), 3.38 (6H, s, H-14); δ_C (101 MHz, $CDCl_3$) 141.5 (C, C-11 and C-12), 139.9 (C, C-10 and C-13), 129.9 (CH, C-2 and C-7), 127.7 (CH, C-3 and C-6), 124.5 (CH, C-1 and C-8), 120.0 (CH, C-4 and C-5), 107.7 (C-9), 51.4 (CH_3, C-14 and C-15)

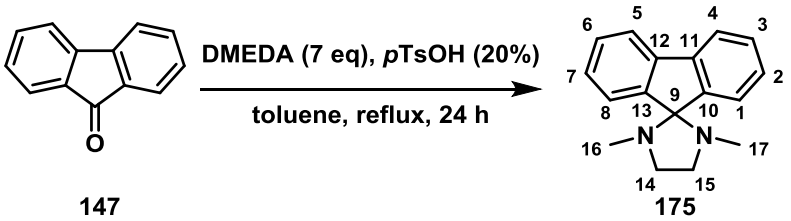
Preparation of spiro[1,3-dioxolane-2,9'-fluorene] (**172**)



147 **172**

Known compound **172** was prepared according to modified literature procedure.[83] Ethylene glycol (7.0 g, 113.4 mmol) was added as a single portion at rt to a solution of fluorenone (3.0 g. 16.2 mmol) and *p*TsOH (620 mg, 3.24 mmol) in toluene (50 mL). The reaction mixture was heated at reflux for 24 h under a water separator (Dean Stark). $NaOH_{(aq)}$ (50 mL, 1M) was added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: Et_2O), acetal **172** (985 mg, 27%) was obtained as a pure white solid. R_f 0.42 (4:1, *n*-hexane: Et_2O); mp 131–132 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3059, 1730, 1448, 1209, 1059, 983, 729; δ_H (400 MHz, $CDCl_3$) 7.55 (2H, d, *J* = 7.5, H-4 and H-5), 7.45 (2H, dt, *J* = 7.4, H-1 and H-8), 7.37 (2H, td, *J* = 7.5, 1.2, H-2 and H-7), 7.27 (2H, td, *J* = 7.4, 1.2, H-3 and H-6), 4.43 (4H, s, H-14 and H-15); δ_C (101 MHz, $CDCl_3$) 144.2 (2 × C, C-11 and C-12), 139.8 (2 × C, C-10 and C-13), 130.3 (2 × CH, C-2 and C-7), 128.4 (2 × CH, C-3 and C-6), 123.8 (2 × CH, C-1 and C-8), 120.1 (2 × CH, C-4 and C-5), 112.6 (1 × C, C-9), 66.0 (2 × CH_3, C-14 and C-15); *m/z* (ES^+) 225.0902 ($[M+H]^+$, $C_{15}H_{12}O_2$ requires 225.0916)

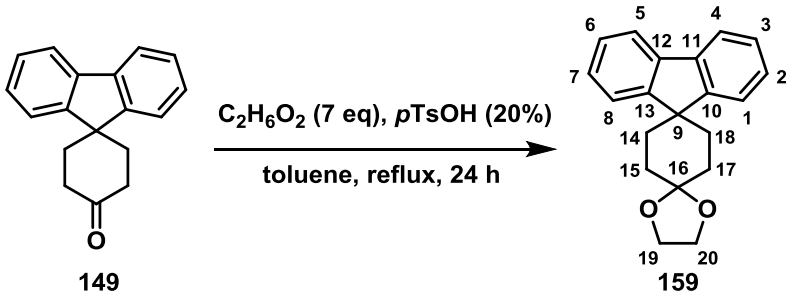
Preparation of 1',3'-dimethylspiro[fluorene-9,2'-imidazolidine] (**175**)



147 **175**

Novel compound **175** was prepared according to modified literature procedure.[83] 1,2-Dimethylethylenediamine (352 mg, 4.00 mmol) was added rapidly at rt to a solution of fluorenone (200 mg. 1.00 mmol) and *p*TsOH (42 mg, 0.20 mmol) in toluene (15 mL). The reaction mixture was heated at reflux for 24 h under a water separator (Dean Stark). H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (9:1, Et_2O: Et_3N), aminal **175** (94 mg, 33%) was obtained as a pure white solid. R_f 0.25 (9:1, Et_2O: Et_3N); mp 78–79 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2904, 2810, 2778, 1442, 1262, 1175, 905, 731; δ_H (400 MHz, $CDCl_3$) 7.51 (2H, d, *J* = 7.4, H-4 and H-5), 7.29 (2H, dt, *J* = 7.3, H-1 and H-8), 7.25 (2H, td, *J* = 7.4, 1.2, H-2 and H-7), 7.17 (2H, td, *J* = 7.4, 1.2, H-3 and H-6), 3.28 (4H, s, H-14 and H-15), 1.82 (6H, s, H-16 and H-17); δ_C (101 MHz, $CDCl_3$) 144.5 (C, C-11 and C-12), 140.8 (C, C-10 and C-13), 128.8 (CH, C-2 and C-7), 127.3 (CH, C-3 and C-6), 125.7 (CH, C-1 and C-8), 119.6 (CH, C-4 and C-5), 91.6 (C, C-9), 52.0 (CH_2, C-14 and C-15), 35.7 (CH_3, C-16 and C-17); *m/z* (AP^+) 251.1555 ($[M+H]^+$, $C_{17}H_{18}N_2$ requires 251.1548)

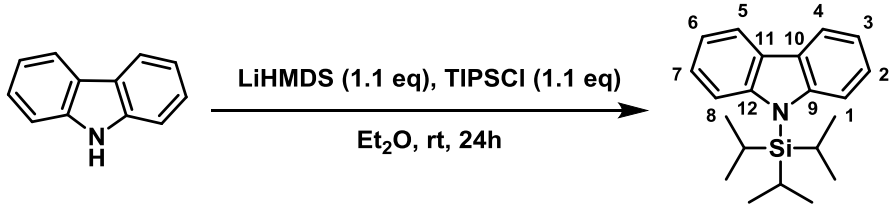
Preparation of dispiro[fluorene-9,1'-cyclohexane-4',2''-[1,3]dioxolane] (**159**)



Known compound **159** was prepared according to modified literature procedure.[83] Ethylene glycol (3.0 g, 49.0 mmol) was added in a single portion at rt to a solution of **149** (1.78 g. 7.00 mmol) and *p*TsOH (266 mg, 1.40 mmol) in toluene (55 mL). The reaction mixture was heated at reflux for 24 h under a water separator (Dean Stark). $NaOH_{(aq)}$ (50 mL, 1M) was added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (*n*-hexane), acetal **159** (94 mg, 33%) was obtained as a pure white solid. R_f 0.37 (*n*-hexane); mp 149–150 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2931, 1702, 1442, 1105, 1087, 941, 733; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* = 7.6, H-4 and H-5), 7.69 (2H, d, *J* = 7.8, H-1 and H-8), 7.39 (2H, td, *J* = 7.5, 1.3, H-2 and H-7), 7.33 (2H, td, *J* = 7.5, 1.3, H-3 and H-6), 4.09 (4H, s, CH_2), 2.15 (4H, t, *J* = 8.0, H-15 and H-17), 2.00 (4H, t, *J* = 8.0 , H-14 and H-18); δ_C (101 MHz, $CDCl_3$) 151.0 (C, C-11 and C-12), 138.6 (C, C-10 and C-13), 126.0 (CH, C-2 and C-7), 125.9 (CH, C-3 and C-6), 123.0 (CH, C-1 and C-8), 118.8 (CH, C-4 and C-5), 107.5 (C, C-16), 63.3 (CH_2, C-19 and C-20), 48.2 (C, C-9), 32.4 (CH_2, C-14 and C-18), 31.1 (CH_2, C-15 and C-17); *m/z* (ES^+) 293.4008 ($[M+H]^+$, $C_{20}H_{20}O_2$ requires 293.4014)

4.2 Chapter 3 experimental

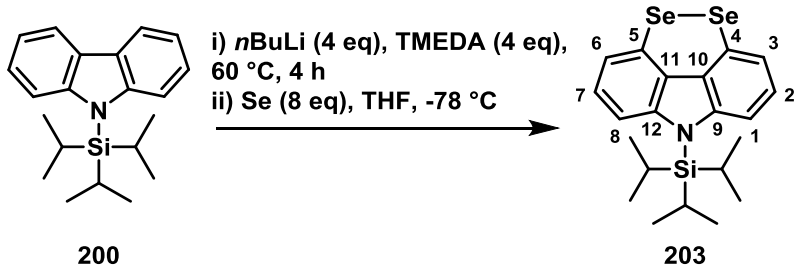
Preparation of 9-(triisopropylsilyl)-9H-carbazole (**200**)



202 **200**

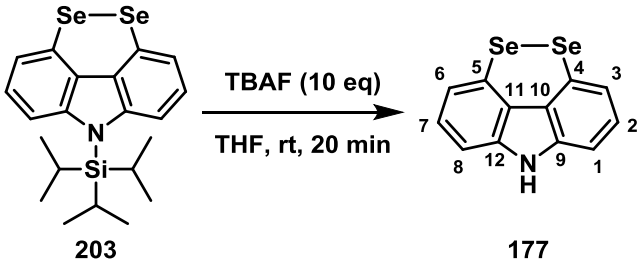
Known compound **200** was prepared according to a literature procedure.[103] LiHMDS (1 M in THF, 32.5 mL, 32.45 mmol) was added dropwise over 20 min to an ice cooled solution of carbazole (5.0 g, 29.5 mmol) and TIPSCl (6.8 mL, 31.00 mmol) in THF (30 mL). The reaction was allowed to warm to rt and then stirred overnight. Water (50 mL) was added and then the resulting mixture extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (*n*-hexane 100%), carbazole **200** (7.7 g, 80%) was obtained as a white crystalline solid. R_f 0.6 (*n*-hexane); mp 90–92 °C; δ_H (400 MHz, $CDCl_3$) 8.09 (2H, d, *J* = 8.2, H-4 and H-5), 7.72 (2H, d, *J* = 8.5, H-1 and H-8), 7.38 (2H, m, H-2 and H-7), 7.25 (2H, t, *J* = 7.4, H-3 and H-6), 2.03 (3H, p, CH), 1.23 (18H, d, CH_3); δ_C (101 MHz, $CDCl_3$) 145.2 (C, C-9 and C-12), 126.6 (CH, C-2 and C-7), 125.4 (C, C-10 and C-11), 119.8 (CH, C-1 and C-8), 119.6 (CH, C-4 and C-5), 114.2 (CH, C-3 and C-6), 18.7 (CH_3), 13.9 (CH); *m/z* (ASAP$^+$) found 324.2145 ([M+H]$^+$, $C_{21}H_{29}NSi$ requires 324.2148)

Preparation of 9-(triisopropylsilyl)-9H-carbazole (**203**)



Novel compound **203** was prepared according to a literature procedure.[77] *n*BuLi (2.0 M in hexanes, 5.0 mL, 9.93 mmol) was added dropwise over 10 min to a solution of compound **200** (800 mg, 2.48 mmol) in TMEDA (1.5 mL, 9.93 mmol) at rt. The reaction mixture was then heated to 60 °C for 4 h. The reaction mixture was cooled to -78 °C and THF (8 mL) was added to the mixture, followed by the addition of selenium (1.56 g, 19.8 mmol) as a single portion. The reaction mixture was allowed to warm to rt and left to stir for 16 h. H_2O (50 mL) was added to the reaction mixture and then the resulting mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (100% *n*-hexane), diselenide **203** (512 mg, 43%) was obtained as a dark burgundy crystalline solid. R_f 0.43 (*n*-hexane); mp 140–141 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2950, 2885, 1597, 1460, 1419, 1256, 989; δ_H (400 MHz, $CDCl_3$) 7.51 (2H, d, *J* = 8.1, H-3 and H-6), 7.27 (2H, dd, *J* = 8.5, 7.4, H-2 and H-7), 7.14 (2H, d, *J* = 7.4, H-1 and H-8), 1.96 (3H, p, *J* = 7.5, CH), 1.19 (18H, d, *J* = 7.5, CH_3); δ_C (101 MHz, $CDCl_3$) 144.8 (C, C-9 and C-12), 127.2 (CH, C-2 and C-7), 125.5 (C, C-10 and C-11), 119.3 (CH, C-1 and C-8), 116.6 (C, C-4 and C-5), 113.9 (CH, C-3 and C-6), 18.6 (CH), 13.9 (CH_3); ^{77}Se NMR (76 MHz, $CDCl_3$) 244.6; *m/z* (AP$^+$) 481.0247 (M$^+$, $C_{21}H_{27}NSi^{80}Se_2$ requires 481.0243)

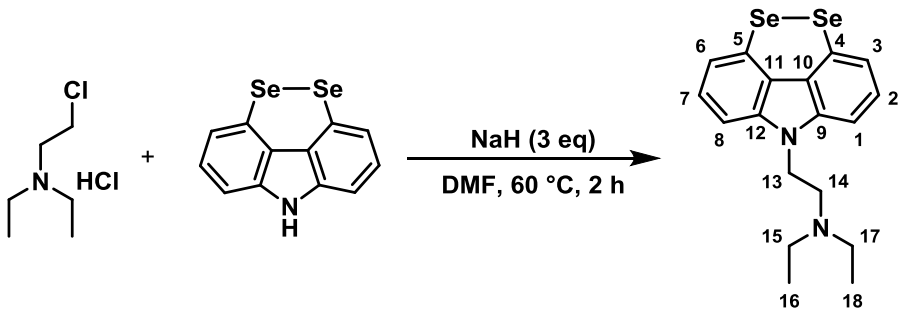
Preparation of 9-(triisopropylsilyl)-9H-[1,2]diselenino[3,4,5,6-def]carbazole (**177**)



203 **177**

Novel compound **177** was prepared according to a modified literature procedure.[103] TBAF (1M solution in THF, 7.5 mL, 7.50 mmol) was added rapidly to a solution of compound **203** (361mg, 0.75 mmol) in THF (15 mL) at rt. The reaction was allowed to stir for 20 min. H_2O (20 mL) was added to the reaction mixture and the resulting mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Diselenide **177** (210 mg, 86%) was obtained as a red crystalline solid, which required no further purification. R_f 0.43; (4:1, *n*-hexane: Et_2O); mp 143–144 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3392, 1586, 1426, 1420, 1306, 1168, 888, 710; δ_H (400 MHz, $CDCl_3$) 8.04 (1H, br, NH), 7.32 (2H, dd, *J* = 8.1, 7.4, H-2 and H-7), 7.23 (2H, dd, *J* = 8.1, 0.7, H-3 and H-6), 7.13 (2H, dd, *J* = 7.4, 0.7, H-1 and H-8); δ_C (101 MHz, $CDCl_3$) 138.6 (C, C-9 and H-12), 128.0 (CH, C-2 and H-7), 122.9 (C, C-10 and H-11), 118.7 (CH, C-1 and H-8), 116.8 (C, C-4 and H-5), 110.3 (CH, C-3 and H-6); ^{77}Se NMR (76 MHz, $CDCl_3$) 265.6; *m/z* (EI^+) 325.9004 (M^+, $C_{21}H_{27}NSi^{80}Se_2$ requires 325.8990)

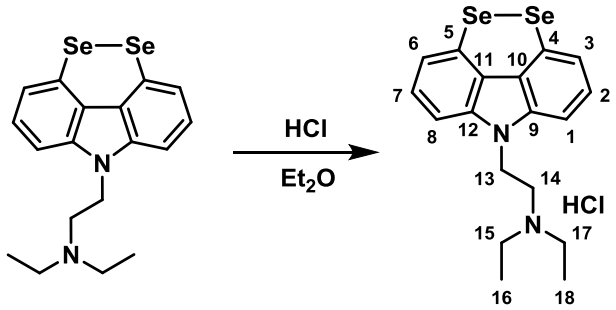
Preparation of 2-(9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)-*N,N*-diethylamine (**205**)



204 **177** **205**

NaH (190 mg, 3.96 mmol) was added rapidly to a solution of compound **177** (427 mg, 1.32 mmol) and 2-chloro-*N,N*-diethylethylamine hydrochloride (272 mg, 1.58 mmol) in DMF (15 mL) at rt. The reaction mixture was then heated at 60 °C for 2 h. The reaction mixture was then allowed to cool. H_2O (40 mL) was added to the reaction mixture and the resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (3:2, *n*-hexane: CH_2Cl_2), amine **205** (445 mg, 80%) was obtained as a dark burgundy gel. R_f 0.15 (3:2, *n*-hexane: CH_2Cl_2); ν_{max}(solid neat, ATR)/cm^{-1} 3240, 2966, 2930, 2803, 1573, 1553, 1420, 1286, 1022, 783; δ_H (400 MHz, $CDCl_3$) 7.34 (2H, dd, *J* = 8.2, 7.4, H-2 and H-7), 7.20 (2H, dd, *J* = 8.0, 0.5, H-3 and H-6), 7.10 (2H, dd, *J* = 7.4, 0.6, H-1 and H-8), 4.28 (2H, t, *J* = 7.6, H-13), 2.77 (2H, t, *J* = 7.6, H-14), 2.60 (4H, q, *J* = 7.1, H-15 and H-17), 1.02 (6H, t, *J* = 7.1, H-16 and H-18); δ_C (101 MHz, $CDCl_3$) 139.9 (C, C-9 and 12), 128.1 (CH, C-2 and C-7), 122.7 (C, C-10 and C-11), 118.6 (CH, C-1 and C-8), 117.1 (C, C-4 and C-5), 108.8 (CH, C-3 and C-6), 51.8 (CH_2, C-14), 48.1 (CH_2, C-15 and C-17), 43.0 (CH_2, C-13), 12.5 (CH_3, C-16 and C-18); ^{77}Se NMR (76 MHz, $CDCl_3$) 260.0; *m/z* (ES^+) found 325.0043 ($[M+H]^+$, $C_{18}H_{20}N_2{}^{80}Se_2$ requires 325.0038)

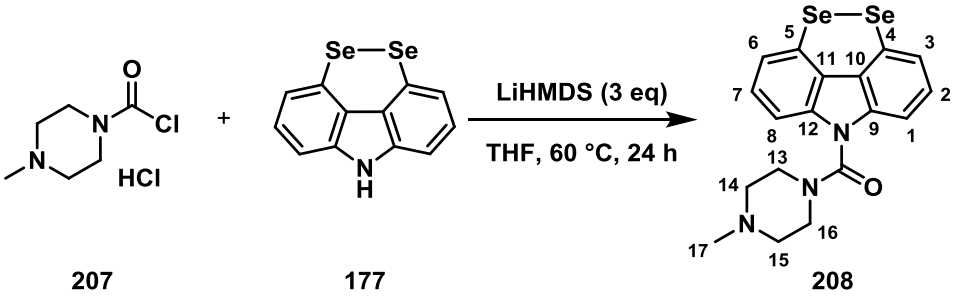
Preparation of 2-(9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)-*N,N*-diethylamine hydrochloride (**206**)



205 **206**

HCl (2.0 M in Et_2O, 2.0 mL, 4.00 mmol) was added to a solution of compound **205** (200 mg, 0.61 mmol) in Et_2O (10 mL). The reaction mixture was then stirred at rt for 30 min. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). The salt was collected as a beige crystalline solid (180 mg, 90%). ν_{max}(solid neat, ATR)/cm^{-1} 3424, 3324, 3072, 2932, 2787, 1423, 1403, 1283, 768; δ_H (400 MHz, $(CD_3)_2SO$) 7.71 (2H, d, *J* = 8.2, H-2 and H-7), 7.45 (2H, dd, *J* = 8.0, 7.4, H-3 and H-6), 7.10 (2H, dd, *J* = 7.4, H-1 and H-8), 4.95 (2H, t, *J* = 7.8, H-13), 3.42 – 3.32 (2H, m, H-14), 3.28 – 3.15 (4H, m, H-15 and H-17), 1.25 (6H, t, *J* = 7.2, H-16 and H-18); δ_C (101 MHz, $(CD_3)_2SO$) 138.9 (C, C-9 and C-12), 128.2 (CH, C-2 and C-7), 121.4 (C, C-10 and C-11), 118.7 (CH, C-1 and C-8), 115.9 (C, C-4 and C-5), 109.4 (CH, C-3 and C-6), 48.4 (CH_2, C-14), 46.0 (CH_2, C-15 and C-17), 37.8 (CH_2, C-13), 8.2 (CH_3, C-16 and C-18); ^{77}Se NMR (76 MHz, $(CD_3)_2SO$) 258.1; *m/z* (ES^+) found 325.0043 ($[M+H]^+$, $C_{18}H_{20}N_2{}^{80}Se_2$ requires 325.0038)

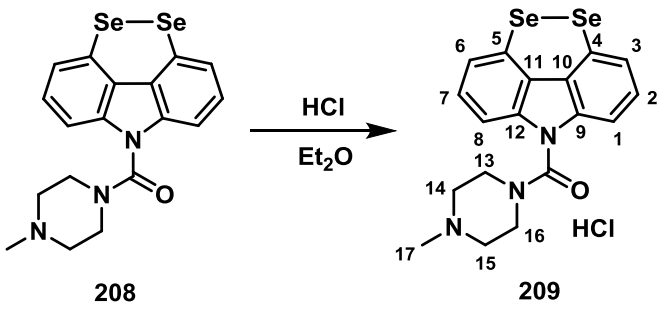
Preparation of (9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)(4-methylpiperazin-1-yl)methanone (**208**)



207 **177** **208**

4-Methylpiperazine-1-carbonyl chloride monohydrochloride (243 mg, 1.22 mmol) was added as a single portion at rt to a solution of LiHMDS (1.0 M in THF, 3.0 mL, 3.03 mmol) and compound **177** (329 mg, 1.01 mmol) in THF (10 mL). The reaction was then heated to 60 °C and stirred for 24 h. H_2O (40 mL) was added and the resulting mixture was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (99:1, Et_2O: Et_3N), urea **208** (274 mg, 27%) was obtained as a dark burgundy crystalline solid. R_f 0.14 (99:1, Et_2O: Et_3N); mp 132–133 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3362, 2939, 2443, 1674, 1408, 1299, 1258, 974, 793; δ_H (400 MHz, $CDCl_3$) δ 7.41 (2H, dd, *J* = 8.3, 0.8, H-3 and H-6), 7.33 (2H, dd, *J* = 8.3, 7.4, H-2 and H-7), 7.32 (2H, dd, *J* = 7.4, 0.8, H-1 and H-8), 3.57 (4H, t, *J* = 4.9, H-13 and H-16), 2.45 (4H, t, *J* = 5.0, H-14 and H-15), 2.31 (3H, s, H-17); δ_C (101 MHz, $CDCl_3$) 153.2 (CO), 138.2 (C, C-9 and C-12), 128.6 (CH, C-2 and C-7), 123.8 (C, C-10 and C-11), 120.9 (CH, C-1 and C-8), 117.3 (C, C-4 and C-5), 112.2 (CH, C-3 and C-6), 54.9 (CH_2, C-14 and C-15), 46.5 (CH_2, C-13 and C-16), 46.1 (C-17); ^{77}Se NMR (76 MHz, $CDCl_3$) 261.7; *m/z* (ASAP$^+$) found 451.9782 ($[M+H]^+$, $C_{18}H_{17}N_3O^{80}Se_2$ requires 451.9781)

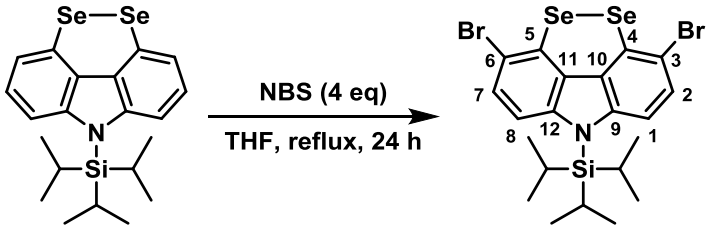
Preparation of (9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)(4-methylpiperazin-1-yl)methanone hydrochloride (**209**)



208 **209**

HCl (2.0 M in Et_2O, 2.0 mL, 4.00 mmol) was added rapidly at rt to a solution of compound **208** (150 mg, 0.33 mmol) in Et_2O (10 mL). The reaction mixture was then stirred at rt for 30 min. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). The salt was collected as a beige crystalline solid (134 mg, 90%). ν_{max}(solid neat, ATR)/cm^{-1} 3480, 3405, 2921, 2655, 1468, 1428, 937, 727; δ_H (400 MHz, D_2O) δ 7.02 – 6.91 (2H, br, 0.8, H-3 and H-6), 6.88 – 6.79 (2H, br, H-2 and H-7), 6.78 – 6.72 (2H, br, H-1 and H-8), 3.57 – 3.31 (4H, br, H-13 and H-16), 3.00 – 2.88 (4H, br, H-14 and H-15), 2.59 (3H, s, H-17); δ_C (101 MHz, D_2O) 153.5 (CO), 137.3 (C, C-9 and C-12), 128.9 (CH, C-2 and C-7), 123.8 (C, C-10 and C-11), 120.2 (CH, C-1 and C-8), 117.6 (C, C-4 and C-5), 112.2 (CH, C-3 and C-6), 52.4 (CH_2, C-14 and C-5), 46.5 (CH_2, C-13 and C-16), 46.1 (C-17); ^{77}Se NMR (76 MHz, D_2O) 274.2; *m/z* (ASAP$^+$) found 451.9782 ([M+H]$^+$, $C_{18}H_{17}N_3O^{80}Se_2$requires 451.9781)K

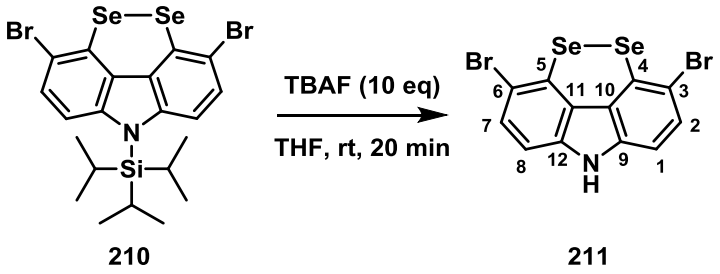
Preparation of 3,6-dibromo-9-(triisopropylsilyl)-9H-[1,2]diselenino[3,4,5,6-def]carbazole (**210**)



203 **210**

Novel compound **210** was prepared according to a modified literature procedure.[104] NBS (693 mg, 3.98 mmol) was added in one portion at rt to a solution of compound **203** (474 mg, 0.98 mmol) in THF (15 mL). The reaction mixture was heated at reflux and stirred for 24 h. The reaction was then allowed to cool. H_2O (40 mL) was added and then the resulting mixture was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (1:1, *n*-hexane: CH_2Cl_2), dibromide **210** (520 mg, 83%) was obtained as a dark burgundy powder. R_f 0.24 (1:1, *n*-hexane: CH_2Cl_2); mp 123–124 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2945, 2866, 1592, 1464, 1407, 1241, 1018, 991, 877, 792; δ_H (400 MHz, $CDCl_3$) 7.41 (2H, d, *J* = 9.0, H-2 and H-7), 7.32 (2H, d, *J* = 9.0, H-1 and H-8), 1.88 (3H, p, *J* = 7.5, CH), 1.17 (18H, d, *J* = 7.5, CH_3); δ_C (101 MHz, $CDCl_3$) 143.7 (C, C-9 and C-12), 130.5 (CH, C-2 and C-7), 127.0 (C, C-10 and C-11), 119.7 (C, C-4 and C-5), 114.8 (CH, C-1 and C-8), 112.8 (C, C-3 and C-6), 18.5 (CH), 13.8 (CH_3); ^{77}Se NMR (76 MHz, $CDCl_3$) 265.0; *m/z* (ES^+) 637.8477 (M^+, $C_{21}H_{25}NSi^{80}Se_2{}^{79}Br_2Si$ requires 637.8467)

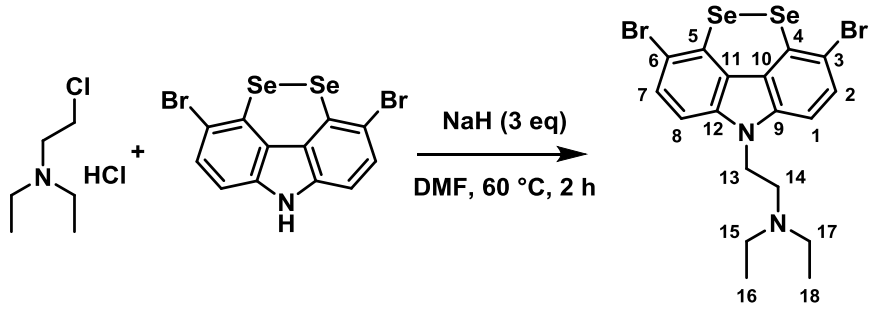
Preparation of 3,6-dibromo-9H-[1,2]diselenino[3,4,5,6-def]carbazole (**211**)



210 **211**

Novel compound **211** was prepared according to a modified literature procedure.[103] TBAF (1M in THF, 2.1 mL, 2.11 mmol) was added rapidly at rt to a solution of compound **210** (450 mg, 0.70 mmol) in THF (25 mL). The reaction mixture was allowed to stir for 20 min. H_2O (20 mL) was added and then the resulting mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (1:1, *n*-hexane: CH_2Cl_2), diselenide **211** (267 mg, 87%) was obtained as a dark burgundy powder. R_f 0.22 (1:1, *n*-hexane: CH_2Cl_2); mp 146–147 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3206, 2926, 1853, 1587, 1410, 1274, 1024, 792, 589; δ_H (400 MHz, $(CD_3)_2SO$) 7.53 (2H, d, *J* = 8.6, H-2 and H-7), 7.28 (2H, d, *J* = 8.6, H-1 and H-8); δ_C (101 MHz, $(CD_3)_2SO$) 138.0 (2 × C, C-9 and C-12), 130.8 (2 × CH, C-2 and C-7), 122.5 (2 × C, C-10 and C-11), 118.5 (2 × C, C-4 and C-5), 112.5 (2 × CH, C-1 and C-8), 109.8 (2 × C, C-3 and C-6); ^{77}Se NMR (76 MHz, $(CD_3)_2SO$) 302.0; *m/z* (EI^+) 482.7111 ($[M+H]^+$, $C_{12}H_5NSi^{79}Br_2{}^{80}Se_2$ requires 482.7100)

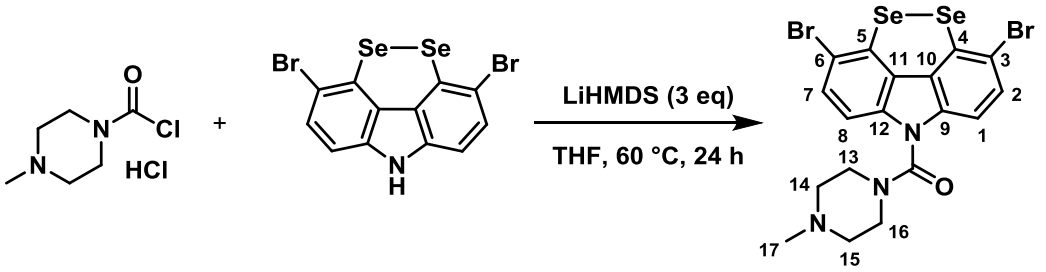
Preparation of 2-(3,6-dibromo-9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)-*N,N*-diethylethan-1-amine (**212**)



204 **211** **212**

NaH (68 mg, 1.42 mmol) was added as one portion at rt to a solution of compound **211** (229 mg, 0.47 mmol) and 2-chloro-*N,N*-diethylethylamine hydrochloride (98 mg, 0.57 mmol) in DMF (20 mL). The reaction mixture was then heated at 60 °C for 2 h. The reaction mixture was then allowed to cool to rt. H_2O (40 mL) was added and then the resulting mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were- dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: CH_2Cl_2), amine **212** (245 mg, 90%) was obtained as a dark burgundy crystalline solid. R_f 0.25; (4:1, *n*-hexane: CH_2Cl_2); mp 153–154 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2966, 2930, 2803, 1573, 1553, 1420, 1286, 1022, 783; δ_H (400 MHz, $CDCl_3$) 7.44 (2H, d, *J* = 8.7, H-1 and H-8), 7.01 (2H, d, *J* = 8.7, H-2 and H-7), 4.20 (2H, t, *J* = 7.6, H-13), 2.72 (2H, *t*, *J* = 7.6, H-14), 2.60 (4H, q, *J* = 7.1, H-15 and H-17), 1.02 (6H, t, *J* = 7.1, H-16 and H-18); δ_C (101 MHz, $CDCl_3$) 138.7 (C, C-9 and C-12), 130.9 (CH, C-2 and C-7), 123.5 (C, C-10 and C-11), 119.7 (C, C-4 and C-5), 111.4 (C, C-3 and C-6), 109.7 (CH, C-1 and C-8), 51.6 (CH_2, C-14), 47.8 (CH_2, C-15 and C-17), 43.0 (CH_2, C-13), 12.5 (CH_3, C-16 and C-18); ^{77}Se NMR (76 MHz, $CDCl_3$) 288.0; *m/z* (ASAP$^+$) found 580.8243 ([M+H]$^+$, $C_{18}H_{19}{}^{79}Br_2N_2{}^{80}Se_2$ requires 580.8228)

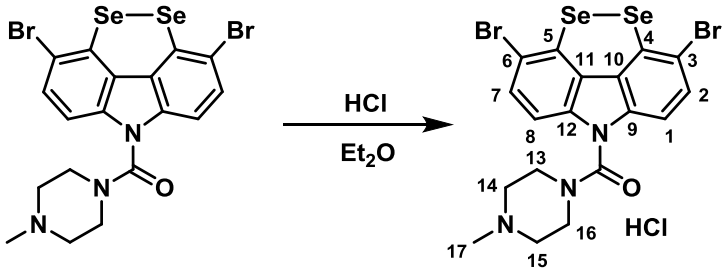
Preparation of (3,6-dibromo-9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)(4 methylpiperazin-1-yl)methanone (**213**)



207 **211** **213**

4-Methylpiperazine-1-carbonyl chloride monohydrochloride (105 mg, 0.52 mmol) was added in one portion at rt to a solution of LiHMDS (1.0 M in THF, 1.0 mL, 1.00 mmol) and carbazole **211** (169 mg, 0.35 mmol) in THF (15 mL). The reaction was heated at 60 °C and stirred for 24 h. The reaction was then allowed to cool. H_2O (20 mL) was added and then the resulting mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (99:1, Et_2O: Et_3N) urea **213** (172 mg, 80%) was obtained as a dark burgundy crystalline solid. R_f 0.17 (99:1, Et_2O: Et_3N); mp degradation above 250 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3362, 2939, 2443, 1674, 1408, 1299, 1258, 974, 793; δ_H (400 MHz, $CDCl_3$) δ 7.51 (2H, d, J = 8.7, H-1 and H-8), 7.25 (2H, d, J = 8.7, H-2 and H-7), 3.56 (4H, t, J = 5.0, H-13 and H-16), 2.48 (4H, t, J = 5.0, H-14 and H-15), 2.33 (3H, s, H-17); δ_C (101 MHz, $CDCl_3$) 153.6 (CO), 137.3 (C, C-9 and C-12), 132.1 (CH, C-2 and C-7), 125.0 (C, C-10 and C-11), 120.6 (C, C-4 and C-5), 114.3 (C, C-3 and C-6), 113.2 (CH, C-1 and C-8), 54.9 (CH_2, C-14 and C-15), 46.6 (CH_2, C-13 and C-16), 46.0 (CH_3, C-17); ^{77}Se NMR (76 MHz, $CDCl_3$) 288.0; *m/z* (ES^+) found 607.8002 ($[M+H]^+$, $C_{18}H_{15}N_3O^{79}Br_2{}^{80}Se_2$ requires 607.7985)

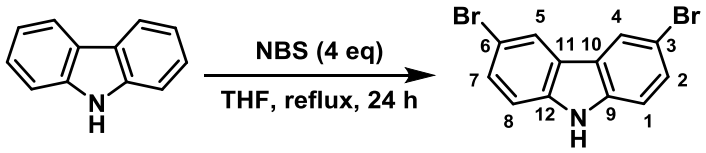
Preparation of (3,6-dibromo-9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)(4 methylpiperazin-1-yl)methanone hydrochloride (**214**)



213 **214**

HCl (2.0 M in Et_2O, 2.0 mL, 4.00 mmol) was added rapidly at rt to a solution of compound **213** (150 mg, 0.33 mmol) in Et_2O (10 mL). The reaction mixture was then stirred at rt for 30 min. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). The salt was collected as a beige crystalline solid (134 mg, 90%). mp degradation above 250 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3462, 2855, 2424, 1680, 1468, 1183, 932, 662; δ_H (400 MHz, $(CD_3)_2SO$) δ 7.59 (2H, d, J = 8.7, H-1 and H-8), 7.44 (2H, d, J = 8.7, H-2 and H-7), 3.78 (4H, t, J = 5.0, H-13 and H-16), 2.98 (4H, t, J = 5.0, H-14 and H-16), 2.57 (3H, s, H-17); δ_C (101 MHz, $(CD_3)_2SO$) 151.2 (CO), 136.2 (C, C-9 and 12), 131.9 (CH, C-1 and C-8), 124.8 (C, C-10 and C-11), 119.3 (C, C-4 and C-5), 113.5 (C, C-3 and C-6), 112.8 (CH, C-2 and C-7), 53.7 (CH_2, C-14 and C-15), 46.1 (CH_2, C-13 and C-16), 45.5 (CH_3, C-17); ^{77}Se NMR (76 MHz, $CDCl_3$) 287.2; *m/z* (ES^+) found 607.8002 ($[M+H]^+$, $C_{18}H_{15}N_3O^{79}Br_2{}^{80}Se_2$ requires 607.7985)

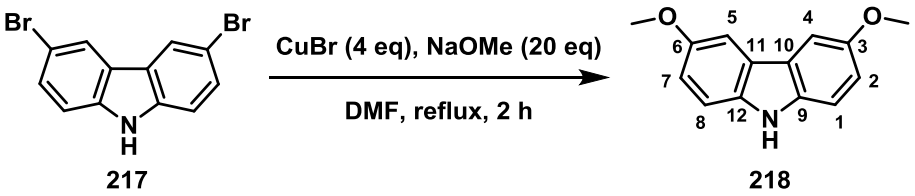
Preparation of 3,6-dibromo-9H-carbazole (**217**)



202 **217**

Known compound **217** was prepared according to a modified literature procedure.[104] NBS (13.2 g, 74.80 mmol) was added as one portion at rt to a solution of carbazole **202** (5.0 g, 29.90 mmol) in THF (150 mL). The reaction mixture was heated at reflux and stirred for 24 h. The reaction was then allowed to cool. H_2O (150 mL) was added to the reaction mixture and then the resulting mixture was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1, *n*-hexane: Et_2O,), dibromide **217** (5.44 g, 55%) was obtained as a dark beige powder. R_f 0.18 (4:1, *n*-hexane: Et_2O); mp 120–121 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3419, 1697, 1430, 1285, 1186, 866, 799; δ_H (400 MHz, $CDCl_3$) 8.13 (2H, d, *J* = 1.9, H-4 and H-5), 7.52 (2H, dd, *J* = 8.6, 1.9, H-2 and H-7), 7.31 (2H, dd, *J* = 8.5, 0.6, H-1 and H-8); δ_C (101 MHz, $CDCl_3$) 138.4 (C, C-9 and C-12), 129.4 (CH, C-2 and C-7), 124.2 (C, C-10 and C-11), 123.4 (CH, C-4 and C-5), 112.7 (C, C-3 and C-6), 112.3 (CH, C-1 and C-8); *m/z* (ASAP$^+$) 324.8935 ([M+H]$^+$, $C_{12}H_7N^{79}Br_2$ requires 324.8925)

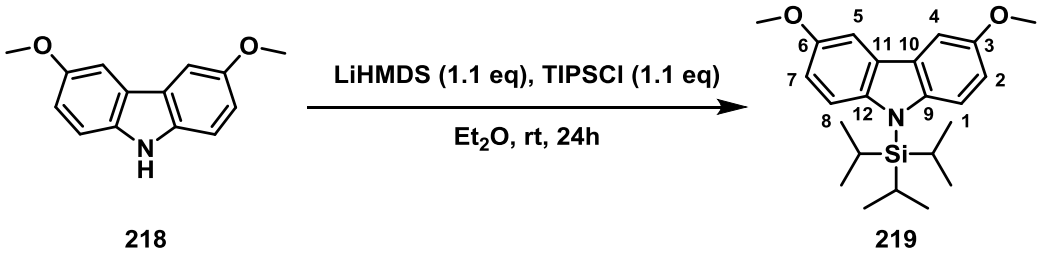
Preparation of 3,6-dimethoxy-9H-carbazole (**218**)



217 218

Known compound **218** was prepared according to a literature procedure.[105] NaOMe (4 M in MeOH, 1.5 mL, 6 mmol) was added rapidly at rt to a solution of compound **217** (100 mg, 0.30 mmol) and CuBr (171 mg, 1.20 mmol) in DMF (5 mL). The reaction mixture was heated at reflux and stirred for 2 h. The reaction mixture was then allowed to cool and then filtered on celite. H_2O (20 mL) was added to and then the resulting mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (1:1, *n*-hexane: CH_2Cl_2), dimethoxy carbazole **218** (63 mg, 92%) was obtained as a beige solid. R_f 0.14 (1:1, *n*-hexane: CH_2Cl_2); mp 90–92 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3355, 1575, 1496, 1469, 1208, 1151, 777; δ_H (400 MHz, $CDCl_3$) 7.77 (1H, s, NH), 7.51 (2H, d, *J* = 2.5, H-4 and H-5), 7.30 (2H, d, *J* = 8.8, H-1 and H-8), 7.06 (2H, dd, *J* = 8.8, 2.5, H-2 and H-7), 3.94 (6H, s, CH_3); δ_C (101 MHz, $CDCl_3$) 153.7 (C, C-3 and C-6), 135.37 (C, C-9 and C-12), 123.8 (C, C-10 and C-11), 115.3 (CH, C-1 and C-8), 111.6 (CH, C-2 and C-7), 102.9 (CH, C-4 and C-5), 56.2 (OCH_3); *m/z* (ASAP$^+$) found 228.1047 ([M+H]$^+$, $C_{14}H_{14}NO_2$ requires 228.1024)

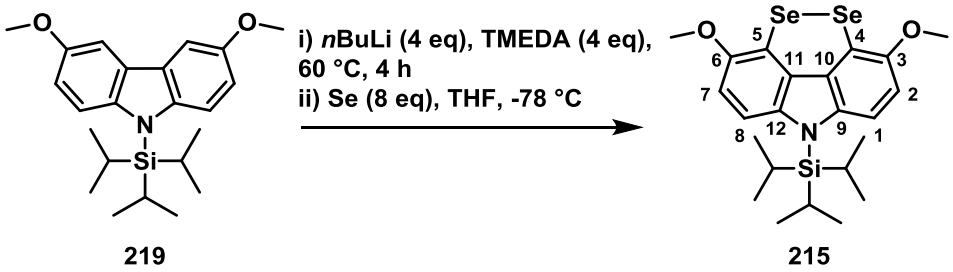
Preparation of 3,6-dimethoxy-9-(triisopropylsilyl)-9H-carbazole (**219**)



218 **219**

Novel compound **219** was prepared according to a modified literature procedure.[103] TIPSCl (1.6 mL, 7.49 mmol) was added rapidly to a solution of LiHMDS (1 M in THF, 7.49 mL, 7.49 mmol) and compound **218** (1.41 g, 6.24 mmol) in THF (30 mL) at 0 °C. The reaction mixture was allowed to warm to rt and then stirred for 16 h. H_2O (50 mL) was added and then the resulting mixture was extracted with Et_2O (2 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (3:2, *n*-hexane: CH_2Cl_2), **219** (2.2 g, 92%) was obtained as a white crystalline solid. R_f 0.30 (3:2, *n*-hexane: CH_2Cl_2); mp 91–92 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2946, 2866, 1576, 1431, 1457, 1193, 1033, 785; δ_H (400 MHz, $CDCl_3$) 7.60 (2H, d, *J* = 9.1, H-1 and H-8), 7.51 (2H, d, *J* = 2.6, H-4 and H-5), 7.02 (2H, t, *J* = 9.1, 2.7, H-2 and H-7), 3.95 (6H, s, OCH_3), 1.97 (3H, p, *J* = 7.5, CH), 1.21 (18H, d, *J* = 7.6, CH_3); δ_C (101 MHz, $CDCl_3$) 153.5 (C, C-3 and C-6), 140.5 (C, C-9 and C-12), 127.0 (C, C-10 and C-11), 115.0 (CH, C-1 and C-8), 114.4 (CH, C-2 and C-7), 102.1 (CH, C-4 and C-5), 55.9 (2 × CH_3), 18.6 (6 × CH_3), 13.9 (3 × CH); *m/z* (ASAP$^+$) found 384.2362 ($[M+H]^+$, $C_{23}H_{33}NO_2Si$ requires 384.2359)

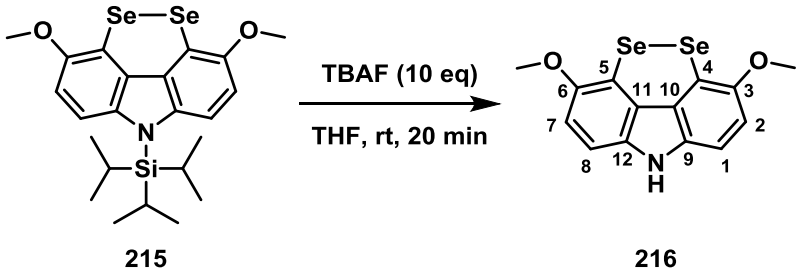
Preparation of 3,6-dimethoxy-9-(triisopropylsilyl)-9H-[1,2]diselenino[3,4,5,6-def]carbazole (**215**)



219 **215**

Novel compound **215** was prepared according to a modified literature procedure.[77] *n*BuLi (2.5 M in hexanes, 3.1 mL, 7.83 mmol) was added dropwise over 10 min to a solution of compound **219** (750 mg, 1.95 mmol) in TMEDA (1.2 mL, 7.83 mmol) at rt. The reaction was then heated to 60 °C for 4 h. The reaction was cooled to -78 °C and THF (8 mL) was added to the mixture, followed by the addition of selenium (1.23 g, 15.6 mmol) as a single portion. The reaction mixture was allowed to warm to rt and left to stir for 16 h. H_2O (50 mL) was added to the reaction mixture and then the resulting mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (100% *n*-hexane), diselenide **215** (255 mg, 25%) was obtained as a dark burgundy crystalline solid. R_f 0.25 (100% *n*-hexane); mp 193–194 °C; ν_{max}(solid neat, ATR)/cm^{-1} 2946, 2866, 1576, 1431, 1457, 1193, 1033, 785; δ_H (400 MHz, $CDCl_3$) 7.36 (2H, d, *J* = 9.1, H-2 and H-7), 6.94 (2H, d, *J* = 9.0, H-1 and H-8), 3.92 (6H, s, OCH_3), 1.90 (3H, p, *J* = 7.5, CH), 1.17 (18H, d, *J* = 7.5, CH_3); δ_C (101 MHz, $CDCl_3$) 149.5 (C, C-3 and C-6), 141.0 (C, C-9 and C-12), 125.35 (C, C-10 and C-), 113.2 (CH, C-2 and H-7), 112.2 (2 × CH, C-1 and C-8), 111.6 (C, C-4 and C-5), 57.4 (OCH_3), 18.6 (CH_3), 13.9 (CH); ^{77}Se NMR (76 MHz, $CDCl_3$) 189.0; *m/z* (ASAP$^+$) found 541.0583 (M^+, $C_{23}H_{31}NO_2Si^{80}Se_2$ requires 541.0570)

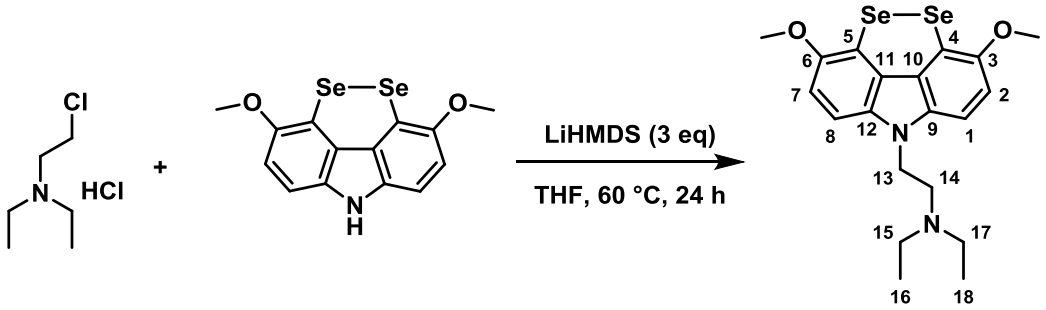
Preparation of 3,6-dimethoxy-9H-[1,2]diselenino[3,4,5,6-def]carbazole (**216**)



215 **216**

Novel compound **216** was prepared according to a modified literature procedure.[103] TBAF (1M in THF, 1.0 mL, 1.05 mmol) was added rapidly at rt to a solution of compound **215** (227 mg, 0.42 mmol) in THF (10 mL). The reaction mixture was allowed to stir for 20 min. H_2O (20 mL) was added and then the resulting mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (1:1, *n*-hexane: CH_2Cl_2), diselenide **216** (160 mg, 99%) was obtained as a dark burgundy powder. R_f 0.20 (1:1, *n*-hexane: CH_2Cl_2); mp 195–197 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3385, 2931, 2866, 1569, 1477, 1422, 1246, 1096; δ_H (400 MHz, $CDCl_3$) 7.70 (1H, br, NH), 7.08 (2H, d, *J* = 8.7, H-2 and H-7), 7.23 (2H, d, *J* = 8.7, H-1 and H-8), 3.91 (6H, s, OCH_3); δ_C (101 MHz, $CDCl_3$) 149.5 (C, C-3 and C-6), 135.4 (C, C-9 and C-12), 123.2 (C, C-10 and C-11), 113.2 (CH, C-2 and C-7), 109.8 (CH, C-1 and C-8), 104.3 (C, C-4 and C-5), 57.6 (OCH_3); ^{77}Se NMR (76 MHz, $CDCl_3$) 217.3; *m/z* (ASAP$^+$) 385.9200 ($[M+H]^+$, $C_{14}H_{11}NO_2{}^{80}Se_2$ requires 385.9201)

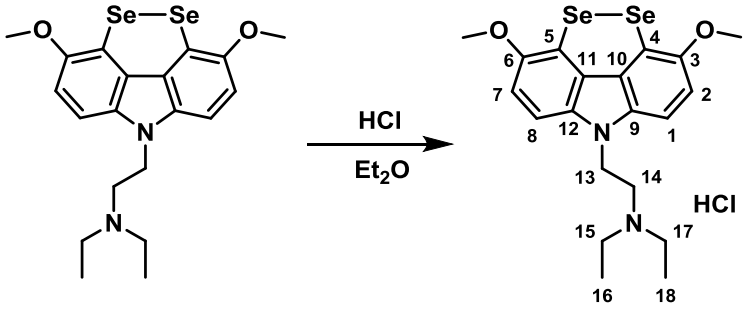
Preparation of 2-(3,6-dimethoxy-9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)-*N,N*-diethylethan-1-amine (**217**)



204 **216** **217**

LiHMDS (1 M in THF, 0.3 mL, 0.30 mmol) was added rapidly at rt to a solution of compound **216** (37 mg, 0.09 mmol) and 2-chloro-*N,N*-diethylethylamine hydrochloride (18 mg, 0.10 mmol) in THF (5 mL). The reaction mixture was then heated at 60 °C for 24 h. The reaction mixture was then allowed to cool. H_2O (20 mL) was added and then the resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (19:1, EtOAc: Et_3N), amine **217** (35 mg, 75%) was obtained as a dark burgundy crystalline solid. R_f 0.14 (19:1, EtOAc: Et_3N); mp 183–184 °C; ν_{max}(solid neat, ATR)/cm^{-1} 3385, 2931, 2866, 1569, 1477, 1422, 1246, 1096; δ_H (400 MHz, $CDCl_3$) 7.09–7.00 (4H, stack, H-1, H-2, H-7 and H-8), 4.22 (2H, t, *J* = 7.4, H-13), 3.92 (6H, s, OCH_3), 2.74 (2H, t, *J* = 7.3, H-14), 2.60 (4H, q, *J* = 7.1, H-15 and H-17), 1.02 (6H, t, *J* = 7.1, H-16 and H-18); δ_C (101 MHz, $CDCl_3$) 149.3 (C, C-3 and C-6), 136.3 (C, C-9 and C-12), 122.4 (C, C-10 and C-11), 113.8 (CH, C-2 and C-7), 107.9 (CH, C-1 and C-8), 104.5 (C, C-4 and C-5), 57.7 (OCH_3), 51.5 (CH_2, C-14), 47.8 (CH_2, C-15 and C-17), 42.7 (CH_2, C-13), 12.2 (CH_3, C-16 and C-18); ^{77}Se NMR (76 MHz, $CDCl_3$) 214.8; *m/z* (ASAP$^+$) found 485.0250 ([M+H]$^+$, $C_{20}H_{24}N_2O_2{}^{80}Se_2$ requires 485.0250)

Preparation of 2-(3,6-dimethoxy-9H-[1,2]diselenino[3,4,5,6-def]carbazol-9-yl)-*N,N*-diethylethan-1-amine hydrochloride (**218**)



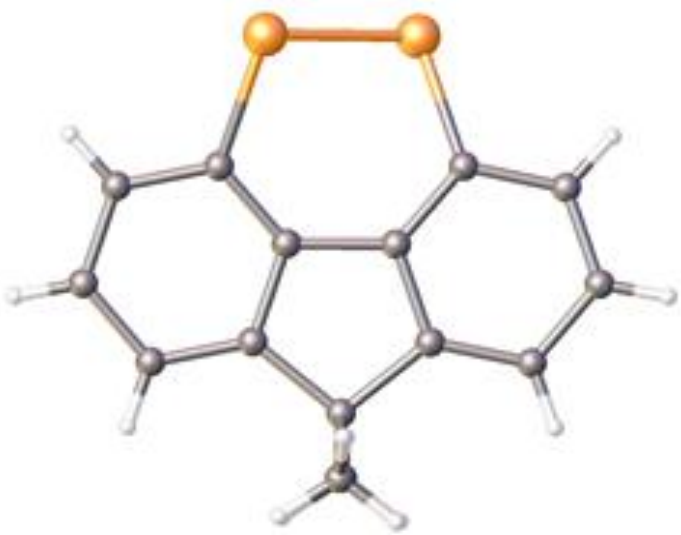
217 **218**

A solution of HCl in Et_2O (2.0 M in Et_2O, 2.0 mL, 4.00 mmol) was added rapidly at rt to a solution of compound **217** (200 mg, 0.61 mmol) in Et_2O (10 mL). The reaction mixture was then stirred at rt for 30 min. The solid was filtered under vacuum and washed with Et_2O (3 × 15 mL). The salt was collected as a beige crystalline solid (180 mg, 90%). ν_{max}(solid neat, ATR)/cm^{-1} 3385, 2931, 2866, 1569, 1477, 1422, 1246, 1096; δ_H (400 MHz, D_2O) 6.94–6.80 (4H, stack, H-1, 2, 7 and 8), 4.56 (2H, t, *J* = 7.4, H-13), 3.54 (6H, *s*, OCH_3), 2.47 (2H, t, *J* = 7.3, H-14), 2.39 (4H, q, *J* = 7.1, H-15 and H-17), 1.00 (6H, t, *J* = 7.1, H-16 and H-18); δ_C (101 MHz, D_2O) 149.1 (C, C-3 and C-6), 135.9 (C, C-9 and C-12), 120.3 (C, C-10 and C-11), 113.2 (CH, C-2 and C-7), 106.7 (CH, C-1 and C-8), 103.8 (C, C-4 and C-5), 57.5 (OCH_3), 49.6 (CH_2, C-14), 45.9 (CH_2, C-15 and C-17), 43.2 (CH_2, C-13), 10.5 (CH_3, C-16 and C-18); ^{77}Se NMR (76 MHz, D_2O) 216.2; *m/z* (ASAP$^+$) found 485.0250 ($[M+H]^+$, $C_{20}H_{24}N_2O_2{}^{80}Se_2$ requires 485.0250)

X-ray crystallography

Suitable crystals were selected and datasets for **127** and **177** were measured on an Agilent SuperNova diffractometer using an Atlas detector. The data collections were driven and processed and absorption corrections were applied using CrysAlisPro. The structures were solved using ShelXT and were refined by a full-matrix least-squares procedure on F^2 in ShelXL.[117, 118] Figures and reports were produced using OLEX2.[119] All non-hydrogen atoms were refined with anisotropic displacement parameters. In **177** the hydrogen atom bonded to N(1) was located in the electron density and freely refined. All remaining hydrogen atoms in **177** and all hydrogen atoms in **127** were fixed as riding models and the isotropic thermal parameters (U_{iso}) were based on the U_{eq} of the parent atoms. Crystals for **127** and **177** were grown by slow evaporation from CH_2Cl_2.

X-ray for data for **127**



Identification code	**127**
Empirical formula	$C_{15}H_{12}Se_2$
Formula weight	350.17
Temperature/K	100.00(10)
Crystal system	tetragonal
Space group	I-4
a/Å	17.1924(2)
b/Å	17.1924(2)
c/Å	8.8177(2)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2606.32(8)
Z	8
ρcalcg/cm^3	1.785
μ/mm^{-1}	6.862
F(000)	1360.0
Crystal size/mm^3	0.126 × 0.123 × 0.081
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.272 to 149.15
Index ranges	-21 ≤ h ≤ 21, -21 ≤ k ≤ 19, -10 ≤ l ≤ 10
Reflections collected	12547
Independent reflections	2627 [R_{int} = 0.0198, R_{sigma} = 0.0134]
Data/restraints/parameters	2627/0/156
Goodness-of-fit on F^2	1.065
Final R indexes [I>=2σ (I)]	R_1 = 0.0146, wR_2 = 0.0368
Final R indexes [all data]	R_1 = 0.0147, wR_2 = 0.0369
Largest diff. peak/hole / e Å^{-3}	0.21/-0.35

X-ray for data for **177**

Identification code	**177**
Empirical formula	$C_{12}H_7NSe_2$
Formula weight	323.11
Temperature/K	100.00(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	9.9907(4)
b/Å	6.7480(3)
c/Å	14.9843(6)
α/°	90
β/°	95.086(4)
γ/°	90
Volume/Å^3	1006.22(7)
Z	4
ρcalcg/cm^3	2.133
μ/mm^{-1}	8.847
F(000)	616.0
Crystal size/mm^3	0.173 × 0.125 × 0.053
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.238 to 148.818
Index ranges	-12 ≤ h ≤ 12, -4 ≤ k ≤ 8, -14 ≤ l ≤ 18
Reflections collected	3677
Independent reflections	1999 [R_{int} = 0.0172, R_{sigma} = 0.0207]
Data/restraints/parameters	1999/0/140
Goodness-of-fit on F^2	1.120
Final R indexes [I>=2σ (I)]	R_1 = 0.0215, wR_2 = 0.0550
Final R indexes [all data]	R_1 = 0.0236, wR_2 = 0.0561
Largest diff. peak/hole / e Å^{-3}	0.35/-0.54

Appendix 1

Averaged data for the DTT oxidation assay. The mean SD values of three separate experiments are reported. This study was carried out by Prof Antonella Capperucci and Dr Damiano Tanini at the University of Florence.

112		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	100.0	
28	98.2	2.6
34	97.9	2.5
50	96.4	3.0
66	94.7	2.7
82	92.9	3.0
98	90.9	2.5
114	88.9	2.8
130	85.7	2.8
146	83.3	3.1
162	80.0	2.7
178	76.7	2.8
194	72.2	2.9

117		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	100	
8	99.7	3.1
25	99.4	2.9
35	97.6	3.2
40	95.5	3.0
55	93.8	3.1
70	92.3	2.8
95	90.0	3.1
110	87.3	3.3
125	85.3	3.3
140	83.3	3.1
155	80.4	3.1

118		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	100	
2	39.8	4.2
3	19.4	3.6
4	4.8	4.4
6	0	3.4

122		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	92.3	2.0
7	90.0	2.4
15	87.8	2.4
31	86.7	2.6
47	85.1	2.4
63	84.4	2.7
79	83.6	2.8
95	81.8	2.8
120	78.3	2.9
150	73.7	2.6
216	63.0	3.2
250	52.4	3.0

124		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	76.2	2.1
13	74.0	1.8
29	69.3	2.6
37	65.9	2.4
49	63.6	3.0
70	59.9	2.8
85	57.0	2.9
100	52.6	2.8
116	49.3	3.2
145	45.2	2.9
160	40.0	3.4

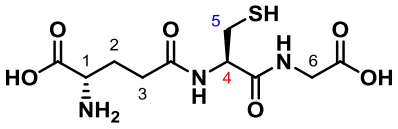
127		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	100.0	
7	99.7	3.2
23	99.3	3.1
39	97.6	3.2
55	93.8	2.8
71	90.9	3.1
87	90.0	2.6
119	87.0	3.1
135	85.7	3.2
151	83.3	3.1
151	83.3	2.8
195	80.0	2.6
225	76.7	2.7
255	71.4	3.3
285	66.7	4.2
315	63.0	3.9
345	60.0	4.4
375	54.5	4.6

128		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	100.0	
2	56.0	3.6
4	41.0	4.2
6	25.0	3.8
8	12.0	4.2
10	0.0	3.9

131		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	75.3	2.1
6	70.3	2.3
20	64.3	2.9
36	58.3	2.9
52	50.0	3.4
68	45.4	3.8
84	40.8	3.7
100	37.1	3.9
125	31.0	4.1
138	27.5	4.2
146	23.1	4.1
152	21.3	4.4

129		
Time (min)	**DTT^{red} (%)***	**Std. Dev.**
0	88.2	2.1
2	88.1	2.3
5	87.6	2.2
13	85.3	2.2
21	83.4	2.3
29	82.1	2.5
37	80.3	2.8
45	77.1	2.8
53	75.8	2.9
61	73.0	3.0
71	70.8	3.0
81	68.6	2.9
91	66.4	3.0
101	62.4	3.1
111	58.7	3.1
121	56.0	3.0
131	53.0	3.1
141	50.4	2.9
160	46.8	3.1

Data for the GSH oxidation assay. The Integration of H-4 (int H-4) relative to H-2 is shown. Selected data for three separate experiments are reported with the average result. The mean standard deviation values of three separate experiments are reported. Standard deviation calculated using $\sigma = \sqrt{\frac{\Sigma(x-\mu)^2}{N}}$



GSH

	Compound number (exp number)				
	168 (1)	168 (2)	168 (3)		
Time (min)	int H-4	int H-4	int H-4	avg	Std. Dev.
0	1	1	1	1	
9	0.94	0.91	0.94	0.93	0.01
40	0.58	0.48	0.58	0.54	0.05
69	0.30	0.18	0.31	0.26	0.07
99	0.04	0.04	0.01	0.03	0.01

	Compound number (exp number)				
	169 (1)	169 (2)	169 (3)		
Time (min)	int H-4	int H-4	int H-4	avg	Std. Dev.
0	1	1	1	1	
7	0.88	0.86	0.89	0.87	0.01
123	0.82	0.81	0.82	0.81	0.01
273	0.78	0.73	0.77	0.76	0.02
573	0.65	0.61	0.63	0.63	0.02
873	0.54	0.48	0.53	0.50	0.03
1023	0.47	0.42	0.45	0.44	0.02
1146	0.40	0.38	0.39	0.39	0.01

	Compound number (exp number)				
	206 (1)	206 (2)	206 (3)		
Time (min)	int H-4	int H-4	int H-4	avg	Std. Dev.
0	1	1	1	1	
31	0.96	0.88	0.86	0.90	0.05
61	0.92	0.84	0.83	0.86	0.04
91	0.84	0.80	0.81	0.81	0.02
121	0.81	0.78	0.75	0.78	0.03

151	0.76	0.74	0.73	0.74	0.01
301	0.73	0.58	0.58	0.63	0.08
442	0.55	0.48	0.46	0.49	0.04
601	0.43	0.33	0.33	0.36	0.05
748	0.2	0.23	0.26	0.23	0.03
901	0.11	0.14	0.17	0.14	0.03
1021	0.03	0.05	0.06	0.04	0.01

	Compound number (exp number)				
	209 (1)	**209 (2)**	**209 (3)**		
Time (min)	**int H-4**	**int H-4**	**int H-4**	**avg**	**Std. Dev.**
0	1	1	1	1	
8	0.91	0.92	0.9	0.91	0.01
129	0.81	0.78	0.81	0.80	0.01
279	0.69	0.66	0.71	0.68	0.02
579	0.53	0.46	0.54	0.51	0.04
879	0.38	0.31	0.38	0.35	0.04
1179	0.25	0.22	0.26	0.24	0.02
1479	0.14	0.11	0.14	0.13	0.01

	218 (1)	**218 (2)**		
Time (min)	**int H-4**	**int H-4**	**avg**	**Std. Dev.**
0	1	1	1	
10	0.95	0.98	0.97	0.02
39	0.91	0.92	0.90	0.01
69	0.85	0.86	0.85	0.01
99	0.79	0.80	0.82	0.01
129	0.74	0.74	0.74	0.00
278	0.50	0.48	0.51	0.04
428	0.27	0.30	0.33	0.08
578	0.23	0.24	0.23	0.02
727	0.16	0.18	0.16	0.01
877	0.06	0.07	0.06	0.01

	Compound number (exp number)				
	214 (1)	**214 (2)**	**214 (3)**		
Time (min)	**int H-4**	**int H-4**	**int H-4**	**avg**	**Std. Dev.**
0	1	1	1	1	
9	0.9	0.9	0.91	0.90	0.01
130	0.86	0.85	0.86	0.85	0.01
280	0.8	0.8	0.79	0.79	0.01
580	0.7	0.69	0.69	0.69	0.01
880	0.63	0.61	0.61	0.61	0.01
1180	0.54	0.52	0.53	0.53	0.01
1420	0.49	0.51	0.47	0.49	0.02

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