ORGANOSELENIUM REDOX-CATALYZED, ENANTIOSELECTIVE *SYN*-DIFUNCTIONALIZATION OF ALKENES

BY

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DISSERTATION

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Abstract.

The first part of this dissertation serves as an introduction to the current state of electrophilic organoselenium-mediated and -catalyzed reactions of alkenes, as distinguished from other modes of organoselenium reactivity (e.g. Lewis base and peroxoselenenic acid reagents). Special attention is paid to the wealth of diastereoselective selenofunctionalization reactions with chiral, enantioenriched organoselenium electrophiles, as well as the growing field of selenofunctionalization-deselenenylation reactions catalyzed by achiral organoselenium reagents. Finally the intersection of these two approaches, enantioselective selenofunctionalization-deselenenylation reactions catalyzed by chiral, enantioenriched organoselenium electrophiles are discussed.

The second part of this dissertation describes the development of a catalytic, enantioselective *syn*-dichlorination of alkenes using chiral, enantioenriched arylselenium catalysts. Enantioenriched, polyhalogenated terpenoids and lipids comprise a class of natural products of increasing academic and pharmaceutical interest; however, enantioselective methods to obtain the vicinal dihalides present in many of these molecules are lacking. The *syn*-dichlorination of alkenes catalyzed by diphenyl diselenide was first developed as a preamble to an enantioselective method, as it avoids many of the issues associated with enantioselective *anti*-dichlorination reactions involving electrophilic chlorine reagents by consequence of its mechanism. Accordingly, a wide variety of chiral diselenide precatalysts were synthesized and evaluated for enantioselectivity in the *syn*-dichlorination of alkenes. Catalysts were selected at first for evaluation based on their performance as reagents for diastereoselective methoxyselenenylations and related, non-catalytic reactions. Enantiomeric ratios were initially low, however high enough to serve as proof of concept for an asymmetric transformation. Further evaluation of a variety of catalyst scaffolds led to the development of rigid tetralin-derived diselenides. The best performing diselenide in this class afforded the *syn*-dichloride product in an enantiomeric ratio of 75:25.

Further experiments were performed to determine whether a mechanistic leak could lead to the low enantioselectivities observed. The potential for competitive pathways wherein the electrophilic arylselenium species reacts with the alkene either at oxidation state Se(II) or Se(IV) was first examined. Slow addition of oxidant was performed in one reaction and slow addition of alkene substrate in the other to increase the probability of selenium being completely oxidized before encountering olefin or encountering olefin before it had the opportunity to be oxidized,

respectively. The enantiomeric ratio of the dichloride product in both circumstances was identical to the product of the reaction where all components were combined in the usual manner. A similar result was observed when the dichloride e.r. was measured from an aliquot at one catalytic turnover and at complete conversion. It was concluded that either the organoselenium catalyst always reaches Se(IV) before reacting with the alkene or that the oxidation state of selenium at seleniranium ion formation is irrelevant to the enantiomeric ratio of the dichloride product.

^{1}H NMR experiments demonstrated that the hypothetical resting state intermediate, the β-chloroalkyl arylselenium(IV) dichloride, can revert to the olefin, theoretically through re-formation of the seleniranium ion and subsequent de-complexation. It was hypothesized that the turnover-limiting step, intermolecular displacement of ArylSe(IV)$^+$Cl by Cl$^-$, is slow enough to allow for racemization of the resting state intermediate. The dichlorination method was adapted to chlorolactonzation in an effort to make seleniranium ion ring-opening irreversible through the formation of an ester C–O bond. Unfortunately, the turnover-limiting step was not accelerated to a significant degree and lactone formation / seleniranium ion ring-opening appeared to remain reversible. It was concluded that the enantiomeric ratios of the products obtained in both dichlorination and chlorolactonization might have been the consequence of Dynamic Kinetic Asymmetric Transformations (DyKAT), wherein the relative rates of displacement of selenium from diastereomeric resting state intermediates by chloride determined the final enantiomeric makeup of the products.

The third part of this dissertation describes the adaptation of the enantioselective dichlorination method to diamination through the utilization of a bifunctional nucleophile. The tethering of the two nucleophilic atoms accelerates the second nucleophilic displacement step by virtue of intramolecularity such that it may no longer serve as the rate determining step. This change in mechanism allowed for significantly improved enantiomeric ratios for a large variety of oxazolidinone products obtained after a brief optimization of chiral catalyst to better suit the reaction conditions. Styrenyl olefins were diaminated in particularly good yields and enantioselectivities. Diaryl alkenes were difunctionalized in even higher yields and similarly good enantioselectivities; however, the products were obtained as mixtures resulting from *N,N* and *N,O*-difunctionalization in varying ratios, depending on the substrate. Dialkyl olefins were significantly less reactive and gave reduced yields with high enantiomeric ratios maintained. Attempts to extend the method to oxyamination with a carbamate reagent were met with moderate success.

For Leah, Mom, and Dad

"Research is a magical mystery tour
and everything fundamentally new
falls into your lap"
–Rudolf Criegee[*]

[*] Wang, L., 2019 Cope and Cope Scholar Award Winners. *Chem. Eng. News* January 27, 2019.

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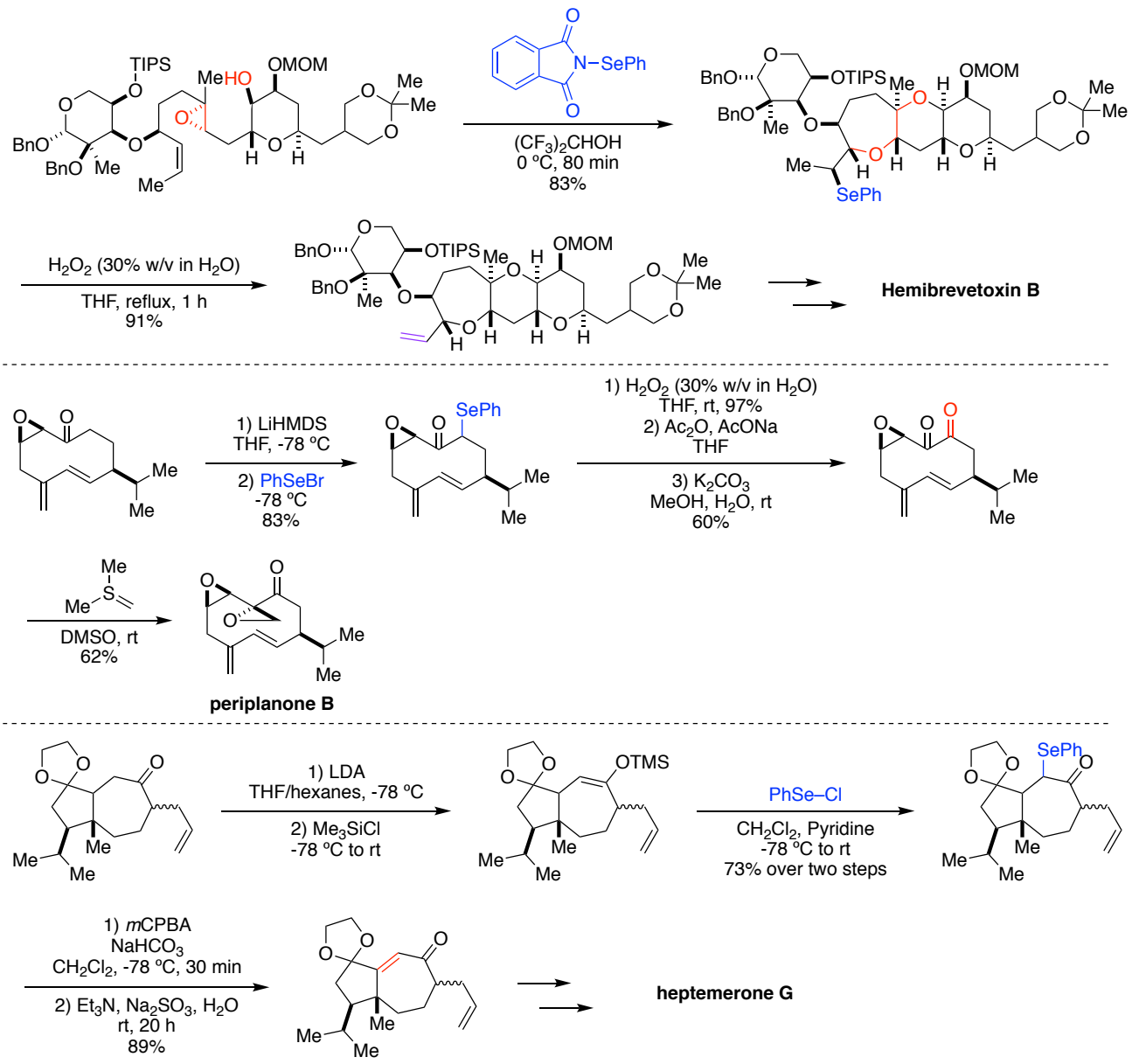
Chapter 1: Introduction to Electrophilic Organoselenium Reagents and Catalysts.

Electrophilic organoselenium reagents are frequently employed by synthetic organic chemists owing to their ready availability from shelf-stable precursors and the wide variety of transformations they can mediate (Scheme 1.1).[1] Of particular note are the α-oxidation of carbonyl compounds containing acidic α-hydrogens and the oxidative vicinal selenofunctionalization of alkenes. The resulting alkyl selenoether products serve as useful intermediates for further synthetic transformation through reductive cleavage of the selenium–carbon bond or through oxidation to the selenoxide and Pummerer-type rearrangement or fragmentation. These methods have been employed many times in a variety of target-oriented syntheses in the last several decades, cementing a position of broad recognition in the synthetic organic chemist's toolkit.

1.1. Preparation of Electrophilic Organoselenium Reagents.

Organic diselenides are among the most common precursors for electrophilic organoselenium reagents, owing to their commercial availability and stability at room temperature. Although some diselenides are labile to atmospheric oxygen or exposure to light, diphenyl diselenide is generally regarded as bench-stable, at least for short periods of time. Some oxidized, electrophilic reagents are commercially available; however, they are far less stable and are typically prepared *in-situ* or isolated, purified, and measured in inert atmosphere. Fortunately, the preparation of these useful electrophiles is operationally simple. Diselenides are treated with an oxidant, typically a halogen or halogen equivalent, in hydrocarbon, ethereal, or halogenated solvents to afford the corresponding selenenyl halide (Scheme 1.2).[1a, 2]

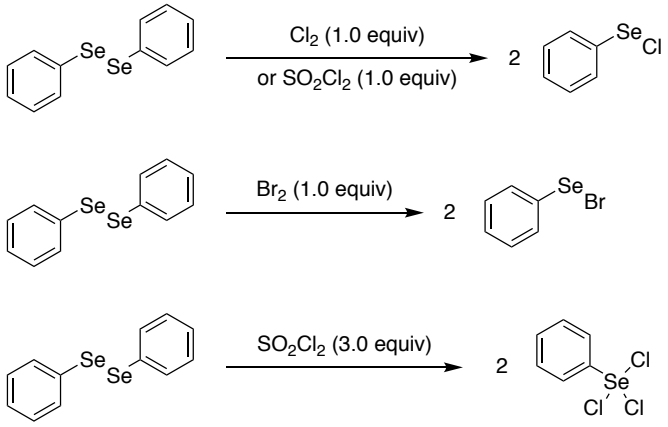
Chlorine, sulfuryl chloride, and bromine all afford the corresponding selenenyl halides in nearly quantitative yield. Iodine also reacts with diphenyl diselenide, but the actual solution structure of the product is disputed, i.e. it is not likely a monomeric, covalent complex.[3] In certain circumstances, use of an additional two equivalents of halogen (or halogen equivalent) results in further, rapid oxidation to the selenium(IV) trihalide.[4]



Scheme 1.1. Applications of electrophilic selenium reagents in organic synthesis.

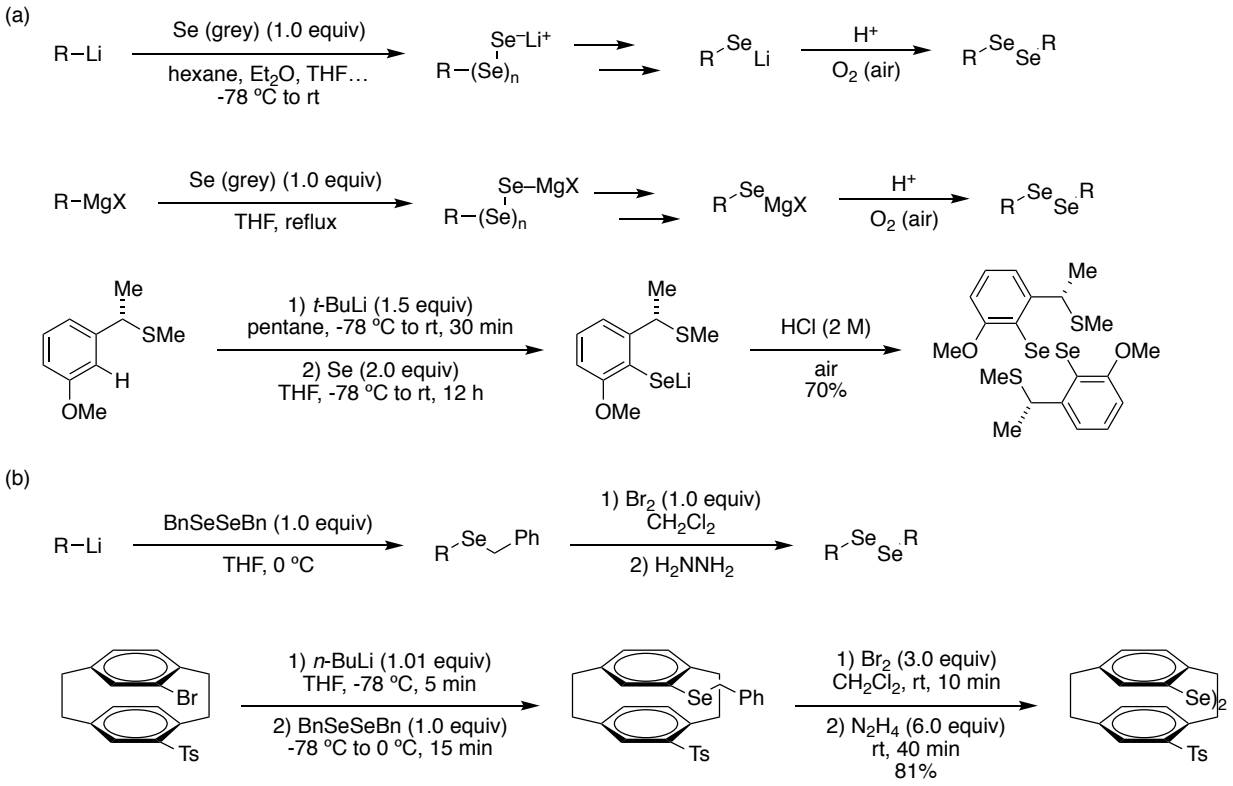
The diselenides themselves are likewise synthetically accessible from readily available precursors. Treatment of organolithium or Grignard reagents with elemental selenium at room temperature or above results in formation of a carbon-selenium bond to afford lithium or magnesium selenolate products that are rapidly oxidized to the diselenide after acidic workup in air (Scheme 1.3a).[2, 5] Although the setup of these reactions is operationally simple, attack by more structurally complex organometallic reagents on the polymeric elemental selenium can become

problematic, affording mixtures of polyselenides that often require laborious purification and afford low yield of the diselenide product.



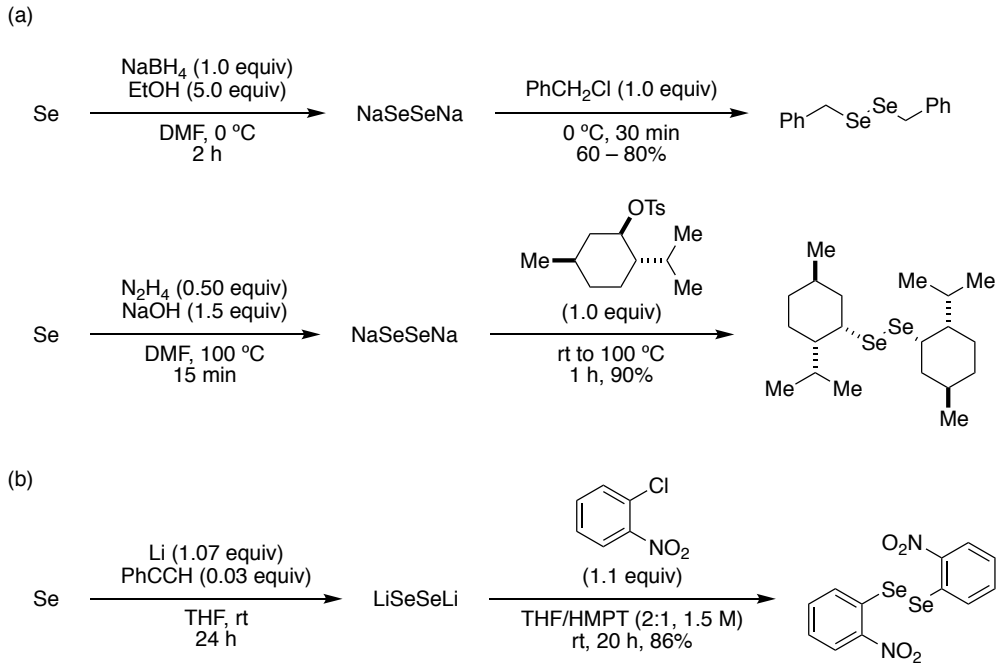
Scheme 1.2. Generation of electrophilic organoselenium reagents with halogens or halogen equivalents.

Furthermore, diselenides containing functional groups that would be sensitive to organometallic reagents at or near room temperature are inaccessible by this protocol. These more structurally complex diselenides are instead prepared by reaction of the organolithium derivative with dibenzyl or dimethyl diselenide at low temperature (–78 ºC to 0 ºC) (Scheme 1.3b).[6] The resulting methyl or benzyl selenide can be isolated, and more importantly, undergo further synthetic transformations before dealkylation by treatment of the selenoether with bromine in dichloromethane or chloroform.[6a, 6c] The immediate product upon treatment with bromine is the selenenyl bromide,[6a, 6c] which is reduced *in situ* with hydrazine,[6a] sodium ascorbate,[7] hypophosphorous acid,[6c] dithiothreitol,[8] or thiourea dioxide.[9] Selenenyl halides can also be transformed to diselenides by treatment with water to afford the selenenic acid, which undergoes spontaneous disproportionation to the seleninic acid and the diselenide.[10] The necessary loss of one-third of the organoselenium material makes the hydrolytic method less attractive than reduction by discrete reducing agents. Diselenides have also been protected by reduction to the sodium selenide anion with sodium borohydride and allylation with allyl bromide or iodide.[11] Deprotection of allyl selenides can be achieved in two steps with *m*-CPBA, then hydrazine, directly affording the diselenide.



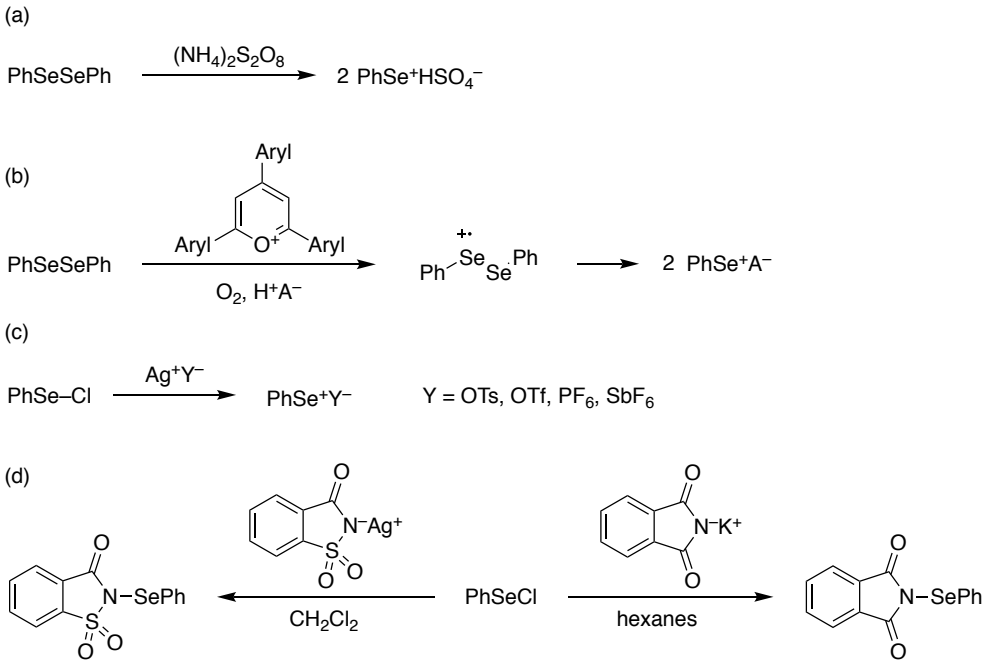
Scheme 1.3. Preparation of diselenides from organometallic reagents.

Diselenides are also frequently prepared by nucleophilic displacement of alkyl halides or sulfonates with sodium diselenide, however this protocol is of more limited utility for the preparation of aryl selenides (Scheme 1.4a).[9b, 12] Alkali metal diselenides as well as aryl and alkyl selenides are nevertheless excellent nucleophiles and engage in S_NAr reactions with electron-deficient arenes with relative ease. An alternative route to electron-deficient diaryl diselenides could therefore involve reaction of an electron-poor aryl fluoride or chloride with a selenide anion (Scheme 1.4b).[5a, 8, 9b, 12a, 13]



Scheme 1.4. Formation of C–Se bonds with selenium nucleophiles.

Recent developments in the application of electrophilic organoselenium reagents have broadened the scope of available oxidants and counterions. Peroxydisulfate oxidants such as sodium or ammonium persulfate directly afford selenenyl bisulfates (Scheme 1.5a). Oxygen, with light in the presence of a pyrylium photosensitizer, also oxidizes diphenyl diselenide through sequential one-electron oxidations (Scheme 1.5b). Treatment of organoselenenyl halides with silver salts of weakly coordinating anions (Scheme 1.5c),[1a, 2, 14] or with more strongly coordinating anions (Scheme 1.5d)[15] affords the products of salt metathesis. Electrophilic selenium reagents with noncoordinating counterions generally show enhanced reactivity, owing to the greater positive charge localized at selenium, while the reagents with more covalent ligands are generally milder and tolerate a broader range of functional groups.[15a] Furthermore, the exclusion of nucleophilic halide counterions prevents the selenohalogenation reaction frequently observed as an unproductive side reaction in selenofunctionalization reactions with phenylselenenyl chloride or bromide.

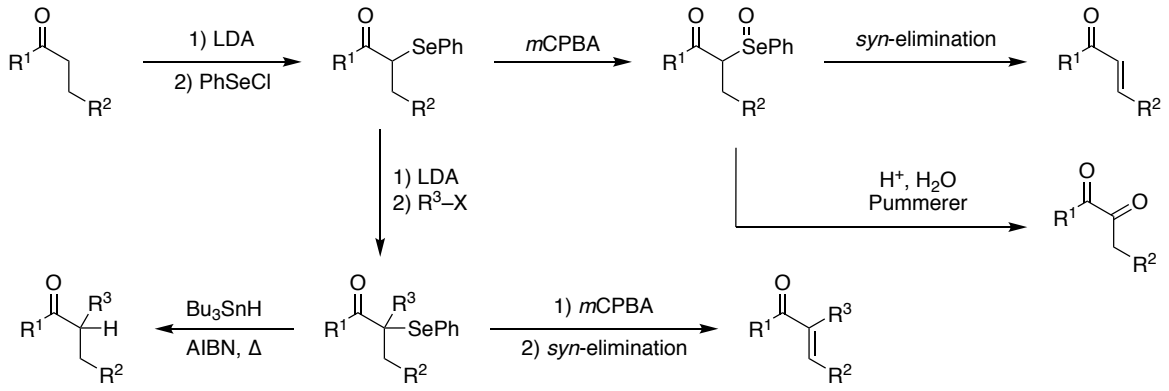


Scheme 1.5. Preparation of selenium electrophiles with alternative counterions.

1.2. Reactions of Electrophilic Organoselenium Reagents.

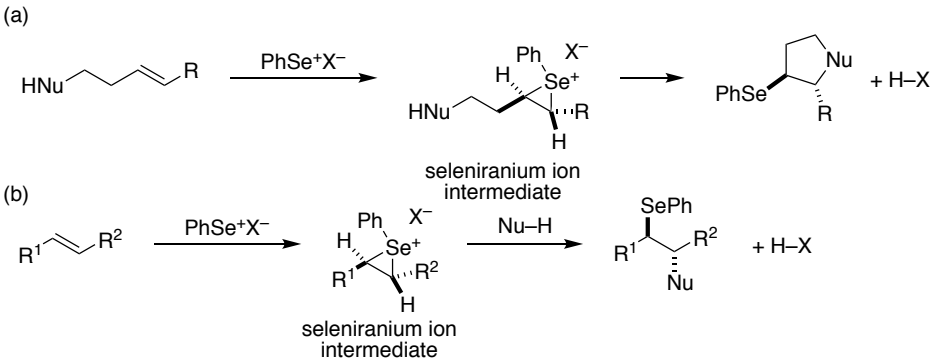
Organoselenium electrophiles are reactive towards most anionic or neutral nucleophilic reagents, but stable products are typically only generated by reaction with carbon nucleophiles. Nitrogen,[16] oxygen,[10, 16d] halogen,[17] and other heteroatom nucleophiles[16d, 18] will add to electrophilic selenium, but in general the products obtained are of limited synthetic utility and are typically sensitive to water and/or susceptible to disproportionation.

Reactions of organoselenium electrophiles with enolates and alkenes, on the other hand, reliably afford products in good yield that can be purified and handled in air. In general, the organoselenium fragment installed in these reactions is removed soon after its installation, particularly in the reaction of enolates, where selenenylation typically serves as an avenue to α-oxidation, either by selena-Pummerer rearrangement and hydrolysis to the 1,2-diketone or selenoxide elimination to the α,β-unsaturated ketone; or as an anion-stabilizing group to aid in the α-alkylation of a carbonyl compound (Scheme 1.6).



Scheme 1.6. Reactions of enolates with organoselenium electrophiles in organic synthesis.

The reaction of electrophilic organoselenium reagents with alkenes is somewhat broader in scope, as a large variety of nucleophiles can be employed to capture the intermediate seleniranium ion to form vicinal *anti*-selenofunctionalized products (Scheme 1.7). Intramolecular selenofunctionalizations (Scheme 1.7a) are frequently employed in target-oriented synthesis, as they afford cyclized products, often with very high substrate-controlled diastereoselectivities, from alkenes with tethered oxygen, nitrogen, and carbon-centered nucleophiles.

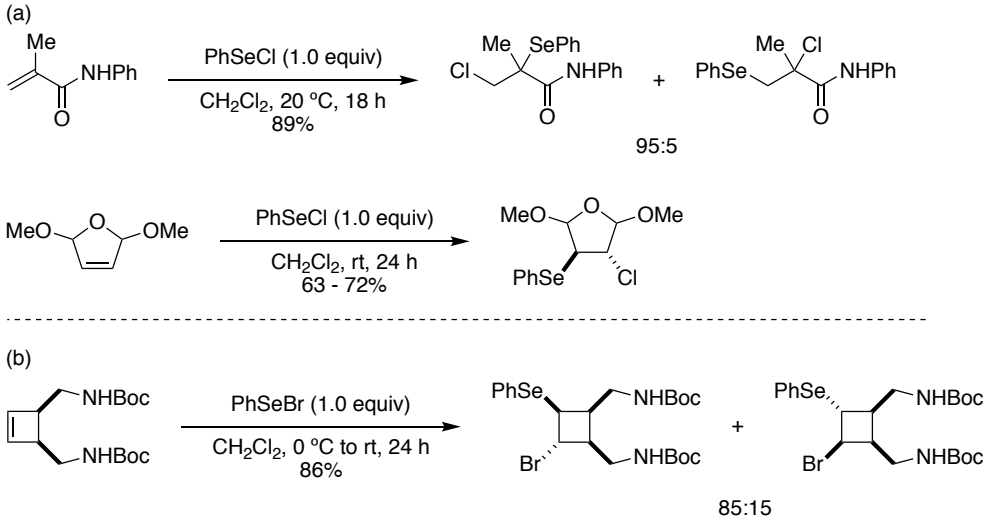


Scheme 1.7. Selenofunctionalization of alkenes.

Intermolecular capture of the seleniranium ion intermediate is also relatively facile (Scheme 1.7b). In general, the Markovnikov product, formed by seleniranium ion ring-opening at the carbon better able to support partial positive charge, is afforded in good selectivity.[1a, 1e] The nucleophilic component is typically employed in larger excess to achieve reasonable reaction rates, although there are some exceptions for stronger nucleophiles. The intermolecular transformation is therefore limited to sterically unhindered, nucleophilic reaction partners that can be conscionably used in excess, e.g. alcohols, acetonitrile, halide, azide, and simple electron-rich

aromatic compounds (*N,N*-dimethylaniline, trimethylphloroglucinol, etc.). These inter- and intramolecular selenofunctionalization reactions have been extensively reviewed.[1a, 1e, 2, 19]

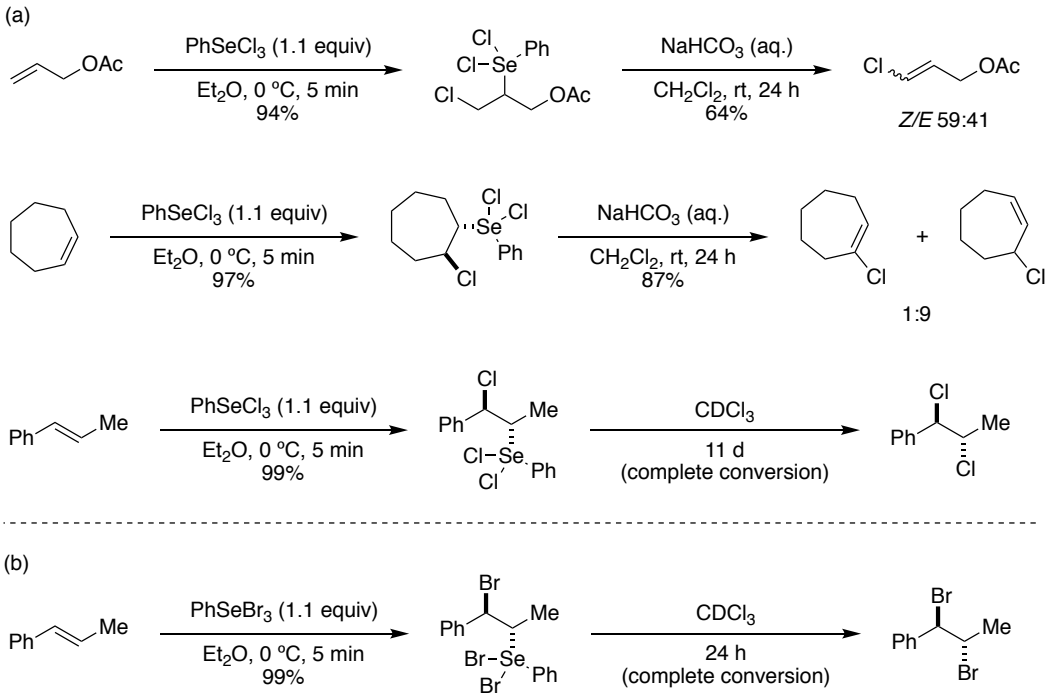
The reaction of alkenes with phenylselenenyl chloride in the absence of other nucleophiles typically results in the selective formation of the vicinal *anti*-chloroselenenylated product (Scheme 1.8a).[20] The isomeric ratios of the products are suggested to be at thermodynamic equilibrium, as the isomers are able to interconvert by way of the seleniranium ion at ambient temperature.[1a, 1e, 21] Use of phenylselenenyl bromide likewise affords the bromoselenenylated product (Scheme 1.8b).[22]



Scheme 1.8. Chloroselenenylation and bromoselenenylation of alkenes.

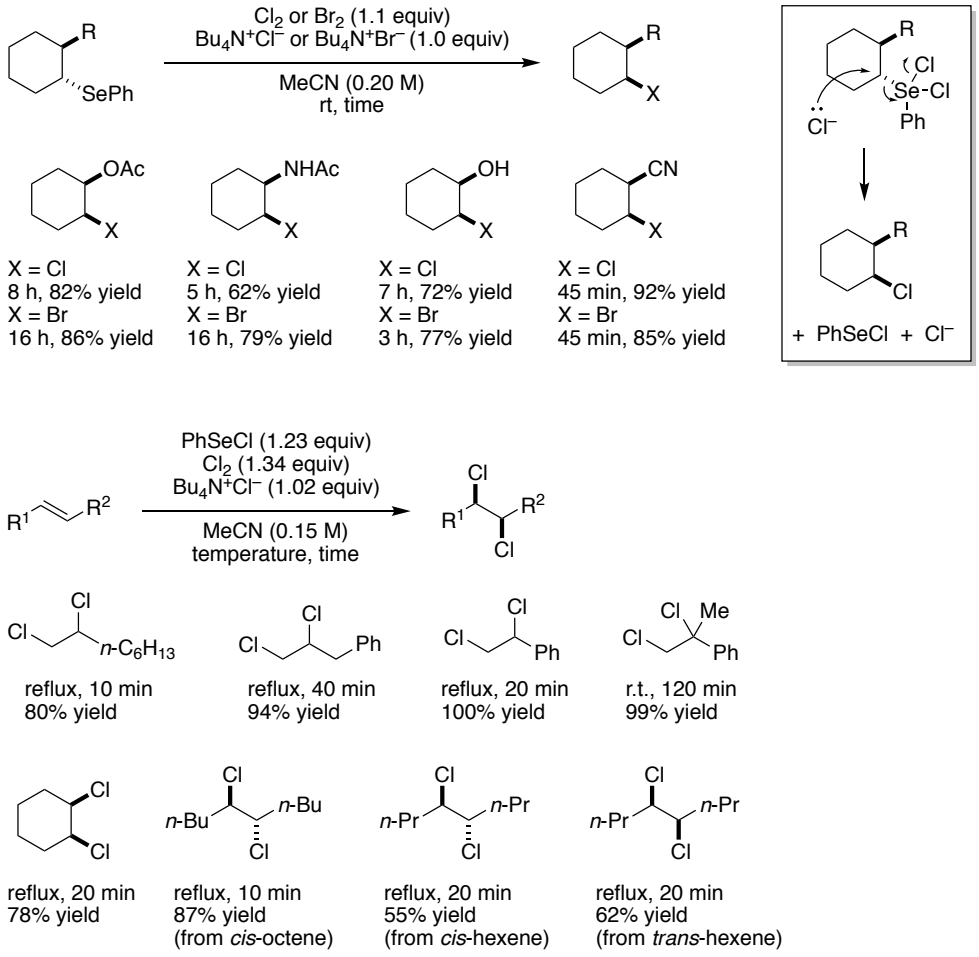
Phenylselenium(IV) trichloride ($PhSeCl_3$) analogously forms selenenylated products by addition to alkenes and enolates, but these products are uniquely susceptible to facile nucleophilic displacement or elimination of selenium without further oxidation (Scheme 1.9a).[4, 17a, 23] In most cases, hydrolysis of the β-chloroalkyl arylselenium(IV) dichloride to the selenoxide with aqueous bicarbonate can be employed to favor elimination.[23a] Phenylselenium(IV) tribromide mediates similar transformations and the bromoselenenylated adducts decompose to the dibromide much more readily (Scheme 1.9b).[4a] Notably, the dichlorides and dibromides obtained from decomposition of these Se(IV) species are of the diastereomeric composition that would theoretically result from a retentive displacement of selenium by the halide, potentially through a suprafacial 1,2-shift. Alternatively, the alkyl-aryl selenium(IV) dihalide may dissociate to reform the alkene and the phenylselenium(IV) trihalide, which could disproportionate to the

phenylselenium(II) halide and the dihalogen. Reaction of the alkene with free dihalogen would afford the same product. There are a limited few examples wherein these activated alkylselenium(IV) complexes are displaced, intramolecularly, by nitrogen nucleophiles.[24]



Scheme 1.9. Reactions of phenylselenium(IV) trichloride and tribromide with alkenes.

These alkyl phenylselenium(IV) dichlorides also undergo nucleophilic displacement by exogeneous halide to form *syn*-dichlorides and β-halo esters, amides, alcohols, and nitriles in good yields (Scheme 1.10).[25] The suprafacial selectivity of the dichlorination with PhSeCl and Cl_2 and the stereospecificity of the cyclohexane halogenations support a mechanistic hypothesis that involves an invertive displacement of the arylselenium(IV) intermediate, in contrast with the stereochemistry of the vicinal *anti*-dihalides obtained after aging these Se(IV) compounds in the absence of any exogeneous halide as seen in Scheme 1.9. In the case of alkene dichlorination, chloroselenenylation is likely occurring spontaneously upon combination of PhSeCl and the alkene, followed by rapid oxidation with Cl_2. The elevated temperatures are most likely required for the final step, the relatively slow displacement of "$PhSeCl_2^-$" immediately adjacent to a C–Cl dipole.[26]



Scheme 1.10. Nucleophilic displacement of Se(IV) by halide nucleophiles.

1.3. Chiral, Enantioenriched, Electrophilic Organoselenium Reagents.

Chiral, enantioenriched organoselenium reagents have been employed in various diastereoselective transformations since the 1980s and the electrophilic functionalization of alkenes has enjoyed the greatest focus. The reagents employed are typically prepared by oxidation of the corresponding diselenides (*vide supra*), which are in turn prepared by treatment of organolithium or –magnesium reagents with elemental selenium.

Critical to the structure and function of many of these electrophilic reagents is the involvement of *chalcogen bonding*, i.e. donation of nonbonding electrons on a Lewis-basic donor **Y** into the σ* orbital of the electrophilic selenium–halogen (or pseudohalogen) bond (Figure 1.1).[27] Crystal structures of arylselenenyl halides bearing Lewis basic donor groups show short distances (2.00 – 2.30 Å) between the Lewis basic atom **Y** and the electrophilic (Lewis acidic) selenium,

indicative of a bonding interaction, while the **Se–X** bond length is significantly longer than the sum of the covalent radii.[27b, 27e-h, 28] This donation of electrons serves to further ionize the selenium and enhance its electrophilicity while also limiting flexibility. Further evidence of n–σ* interaction is apparent in the downfield shift of ^{77}Se NMR chemical shifts when Se is adjacent to Lewis base donors. An increased downfield shift is loosely correlated with a stronger chalcogen bond (based on X-ray structure bond distances), but the relationship is not absolute.[1a, 27a]

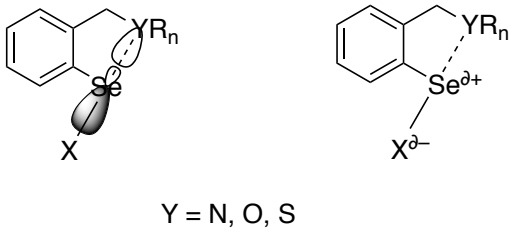
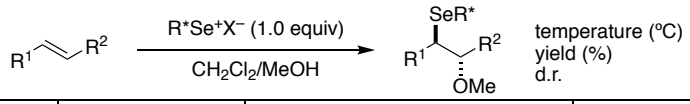
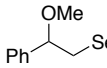
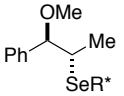
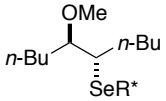
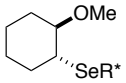
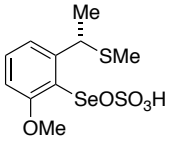
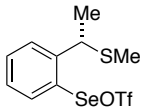
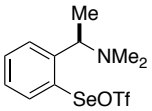
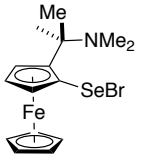
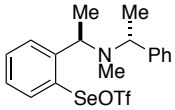
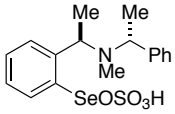
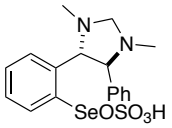
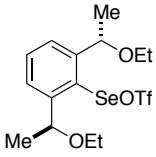


Figure 1.1. Generalized structure demonstrating chalcogen bonding in electrophilic organoselenium catalysts.

The increased conformational rigidity is suggested to be essential to achieve good diastereoselectivities in selenofunctionalization reactions, as it anchors the regions of high and low steric bulk around the reactive selenium center. In fact, in circumstances in which various chiral, enantioenriched organoselenium reagents are employed in the same transformation, diastereoselectivities are generally improved for reagents with (theoretically) stronger chalcogen bonding interactions or otherwise rigidifying structural features. Table 1.1 showcases a brief summary of the diastereoselective methoxyselenenylations performed with a range of chiral, enantioenriched organoselenium electrophiles and styrene, (*E*)-β-methylstyrene, (*E*)-5-decene, or cyclohexene. These reactions are typically run at low temperatures, –78 ºC or below in many cases, however more recently developed reagents afford good diastereoselectivities at or near room temperature (entries 1, 4, 6, and 7). The coordinating heteroatom involved in chalcogen bonding in these reagents is generally O, N, or S, while some reagents do not contain a group that would participate in chalcogen bonding (entries 16 and 17). The strength of the chalcogen bond is not necessarily dependent on the Lewis basicity of the donor atom and seems to show greater dependence on the magnitude of the orbital overlap available, limited mostly by geometric constraints. More weakly coordinating counterions on selenium result in stronger chalcogen bonds ($I^- < Br^- < Cl^- \ll TfO^- < HSO_4^-$), and this is reflected in improved diastereoselectivities upon exchanging e.g. a halide counterion for triflate, or triflate for bisulfate (entries 5 and 6). It is worth

Table 1.1. Methoxyselenenylations of Alkenes with Chiral, Enantioenriched Organoselenium Electrophiles.[a]



entry	alkene	styrene	(*E*)-β-methylstyrene	(*E*)-5-decene	cyclohexene
	product				
1[5b]		–30 72 98:2	–30 75 98:2	–78 [b] 70 96:4	–78 [b] 77 91:9
2[29]		–30 90 90:10	–78 78 96:4	–78 76 90:10	–78 75 82:18
3[30]		0 64 55:45	--	--	--
4[31]		25 [e] 43 97:3	25 [e] 20 99:1	--	25 [e] 48 60:40
5[32]		–78 40 97:3	--	--	--
6[32]		25 70 95:5	25 80 95:5	--	--
7[33]		25 95 88:12	--	--	--
8[34]		–78 [f] 88 88:12	–78 [f] 82 93:7	--	--

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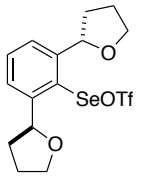
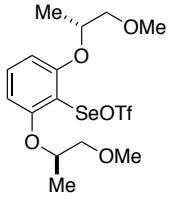
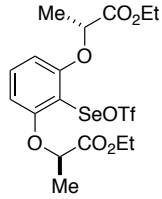
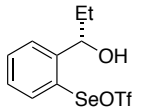
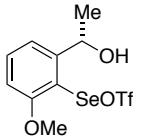
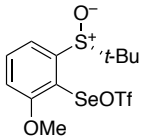
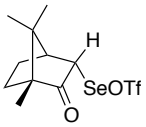
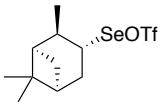
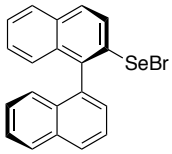
9[35]		–78 73 97:3	–78 81 >99:1	--	--
10[36]		–78 68 95:5	–78 0 --	--	--
11[37]		–78 62 93:7	–78 56 92:8	--	--
12[38]		–78 [c] 81 95:5	–78 [d] 61 86:14	--	–100 31 90:10
13[39]		–78 55 98:2	–78 50 93:7	--	--
14[40]		–78 52 86:14	–78 30 92:8	--	--
15[11b]		–78 77 74:26	--	–78 88 94:6	–78 71 75:25
16[12d]		–78 57 82:18	–78 48 65:35	--	--
17[41]		25 [g] 79 75:25	25 [g] 49 62:38	--	25 [g] 80 52:48

[a] Results are reported in the format: reaction temperature (ºC); isolated yield (%); diastereomeric ratio (measured by ^{1}H NMR). [b] With the selenenyl trifluoromethanesulfonate. [c] At –100 ºC, yield and d.r. were 81% and 95:5, respectively. [d] At –100 ºC, yield and d.r. were 45% and 90:10, respectively. [e] with 0.10 equiv ZnI_2. [f] Reaction was run in Et_2O. [g] Reaction was run in MeOH.

noting that chalcogen bonding is not necessarily *required* for a given selenofunctionalization reaction to afford products with good diastereoselectivities, it is merely a convenient strategic design feature (among potentially many) available to obtain conformational rigidity and enhanced selenium electrophilicity (entries 16 and 17).

Mechanistic investigations into these highly diastereoselective transformations suggest that the selectivity arises from a dynamic kinetic resolution of equilibrating, diastereomeric seleniranium ions (Figure 1.2).[21, 42] The diastereomeric seleniranium ions could either interconvert through dissociation to reform the organoselenium electrophile, or through a direct olefin-olefin transfer.[42d] The major product arises from rate-determining nucleophilic trapping of the lower energy seleniranium ion, rather than trapping of the kinetic seleniranium ion intermediate (that is, the seleniranium ion intermediate that is formed through the lower barrier; in fact, seleniranium ion formation from alkene and a "cationic" selenium electrophile is suggested to be barrierless).[42b] The observed decrease in selectivity as temperature increases could be attributed to an increased rate of (bimolecular) seleniranium ion capture while the rate of (unimolecular) seleniranium ion diastereomeric interconversion remains somewhat constant.

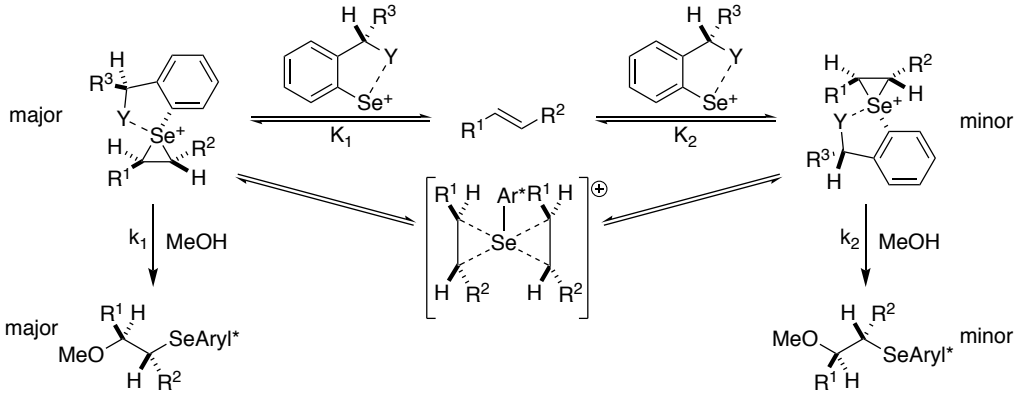
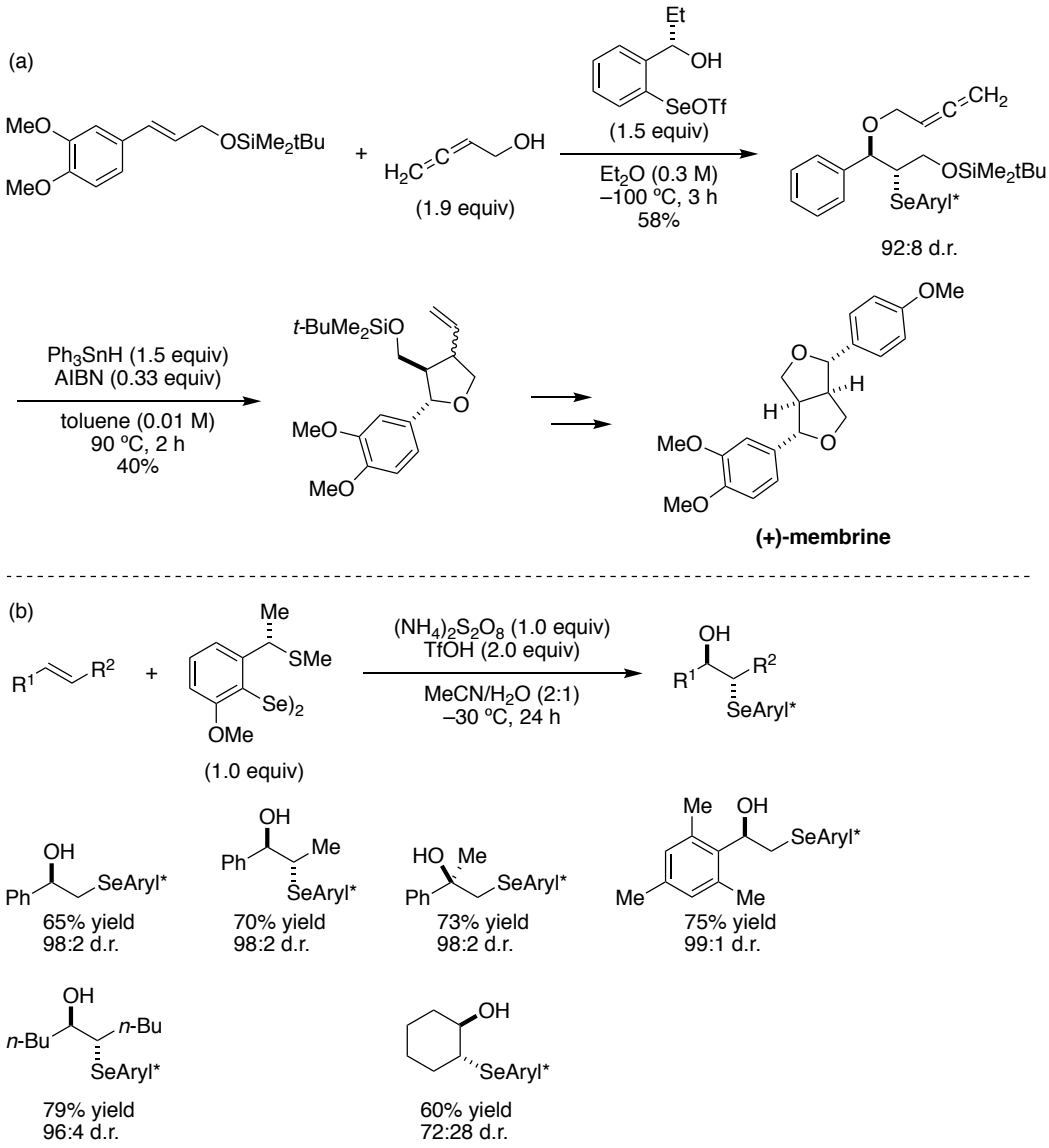


Figure 1.2. Mechanistic rationale for the diastereoselective methoxyselenenylation of alkenes.

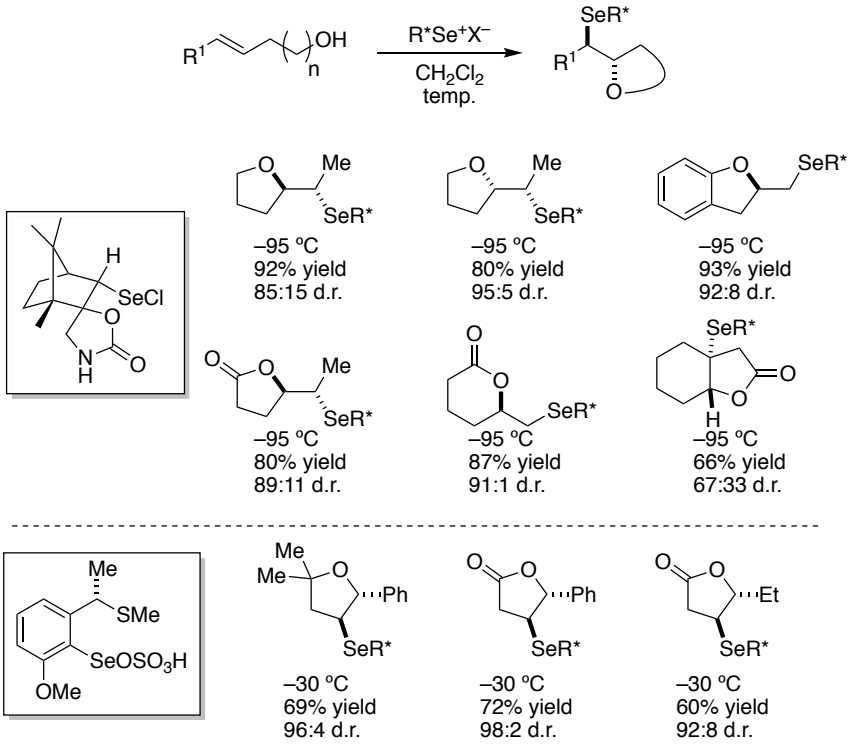
Intermolecular oxyselenenylation is the prototypical diastereoselective transformation mediated by electrophilic selenium reagents, requiring the oxygen nucleophile as either solvent or reagent, to be employed in excess, to afford *anti*-oxyselenenylated products with good to excellent diastereoselectivities. The scope of the transformation has been well elaborated with the most selective electrophilic selenium reagents for a variety of alcohols, as well as water (Scheme 1.11).[5b, 43] Interestingly, if the conditions for hydroxyselenenylation with water are modified

slightly (20 ºC, 3.0 equiv TfOH), amide products are obtained instead, in moderate to good yield and selectivity, through a Ritter-type capture of the seleniranium ion by the nitrile solvent and hydrolysis of the nitrilium to the amide.[44]



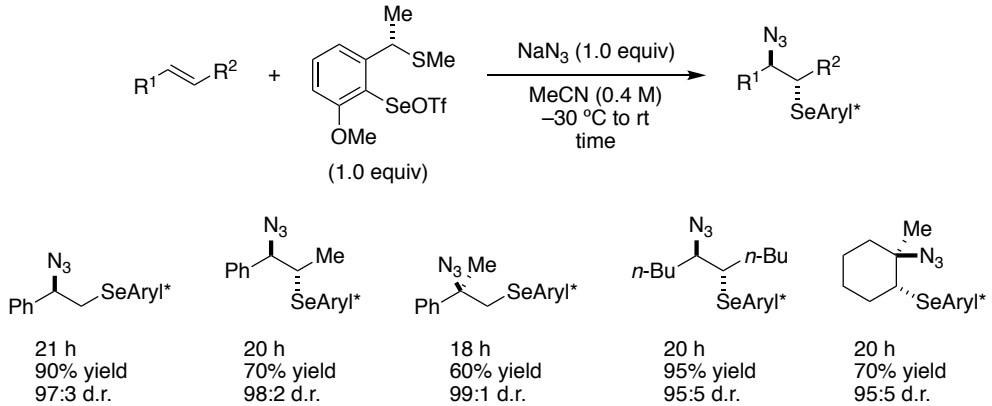
Scheme 1.11. (a) Intermolecular selenoetherification in the total synthesis of (+)-membrine. (b) Hydroxyselenenylation of alkenes with water in acetonitrile.

The scope of diastereoselective, intramolecular oxyselenenylations has also been thoroughly explored. Structurally varied electrophilic selenium reagents can afford complementary selectivities across a variety of (*E*)- and (*Z*)-aryl-alkyl, dialkyl, and trisubstituted alkenes, with alcohols, phenols, and carboxylic acids acting as nucleophiles (Scheme 1.12).[5b, 11a]



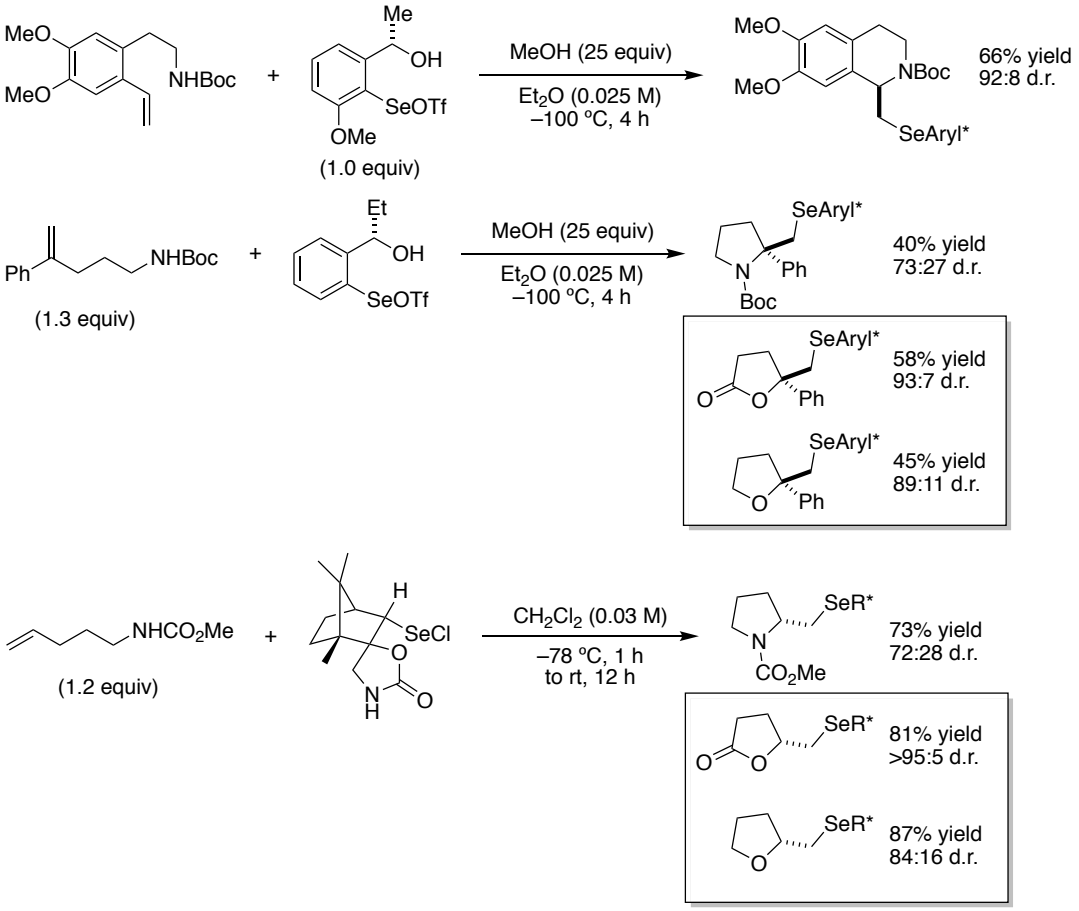
Scheme 1.12. Diastereoselective, intramolecular oxyselenenylation of alkenes with tethered oxygen nucleophiles.

Significant breakthroughs have also been made in the diastereoselective selenoazidation of alkenes (Scheme 1.13).[22c, 45] The reaction is similarly broad in scope, with styrenes, (*E*)-1,2-disubstituted (aryl-alkyl and dialkyl) alkenes and trisubstituted alkenes all affording good yields and diastereomeric ratios.[45]



Scheme 1.13. Diastereoselective selenoazidation of alkenes.

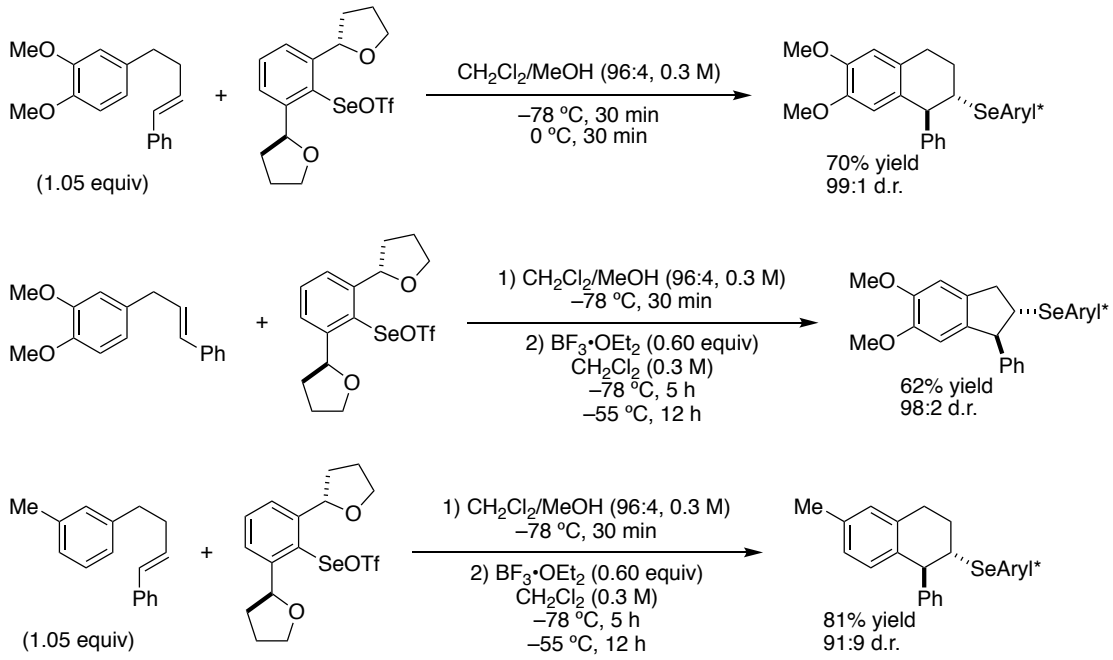
The intramolecular, diastereoselective selenoamidation of alkenes is comparatively underexplored, despite the potential synthetic utility of the cyclic amide products afforded by the reaction (Scheme 1.14).[11b, 39, 46] Acidic N–H nucleophiles, e.g. carbamates, appear to be necessary for reactivity. The yields and diastereomeric ratios of the cycloamidation products are generally worse than those of the cycloetherification and lactonization products of structurally related alcohols and carboxylic acids.



Scheme 1.14. Diastereoselective, intramolecular selenoamidation of alkenes with tethered nitrogen nucleophiles and their analogous lactonizations and cycloetherifications.

Diastereoselective reactions involving carbon nucleophiles are more limited in scope, only successful with electron rich aromatic compounds (Scheme 1.15).[47] In fact, the methoxyselenenylation product was found to be the major product for all but the most electron rich arylalkenes reacted in dichloromethane/methanol. These products were treated with boron trifluoride diethyl etherate (BF_3•OEt_2) to reform the seleniranium ion and induce cyclization.

There are only a limited few examples of inter- or intramolecular carboselenenylation of alkenes, stereoselective or otherwise, despite the comparatively broad scope of enantioselective carbo*sulfenylation* reactions that rely on thiiranium ion opening.



Scheme 1.15. Diastereoselective, intramolecular carbonselenenylation of electron-rich arylalkenes.

1.4. Catalytic Applications of Electrophilic Organoselenium Reagents.

Interest in the development of catalytic processes involving organoselenium reagents has seen rapid growth in recent decades.[48] Several reviews covering recent advances in organoselenium-mediated catalysis have recently appeared.[49] Organoselenium catalysts can operate through several mechanisms, broadly separated into three categories: (1) Lewis base catalysis, in which the oganoselenium reagent serves as a Lewis base activator and delivery agent for Lewis acidic, electrophilic reagents (Figure 1.3a);[50] (2) seleninic acid catalysis, in which the organoselenium reagent is oxidized to the seleninic acid (R–Se(=O)OH) and serves as a delivery agent for an electrophilic oxygen atom as the peroxy acid (R–Se(=O)OOH) (Figure 1.3b);[51] and (3) redox catalysis, in which the organoselenium reagent serves as an electrophile to generate an intermediate seleniranium ion, followed by ring-opening, and then cleavage of the C–Se bond (typically) by elimination (Figure 1.3c).[52] Redox catalysis has enjoyed some recent development,

although it has been somewhat overshadowed by significant developments in the other two categories, and in enantioselective methods in particular.

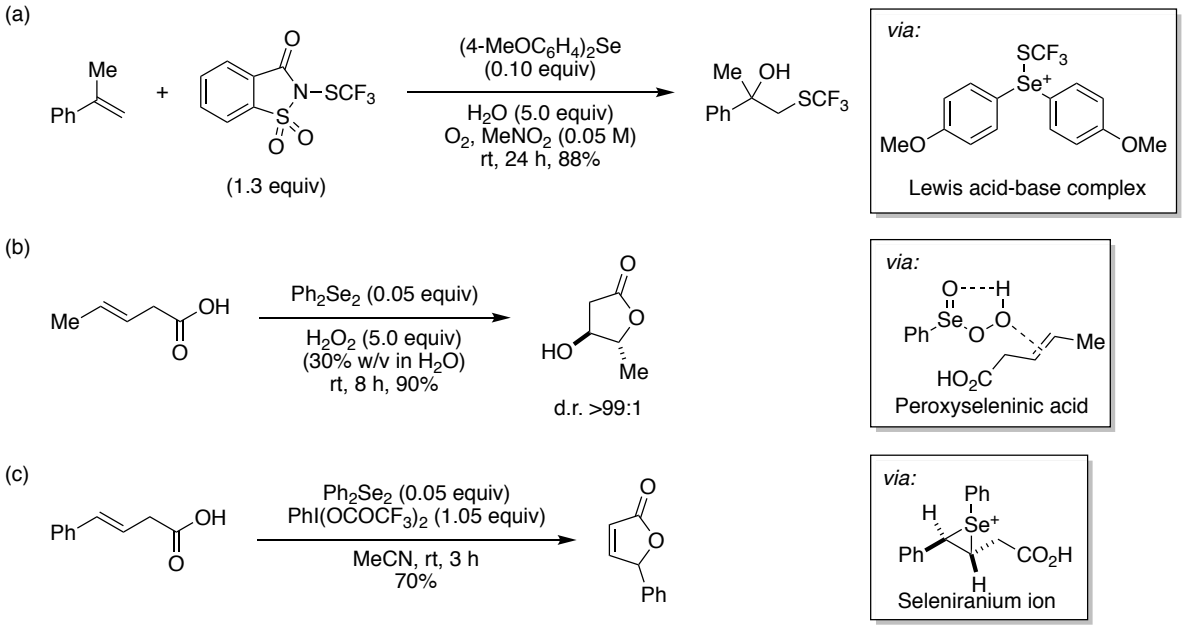


Figure 1.3. Organoselenium-catalyzed transformations.

Only processes that fit within the third category will be discussed here, as the other two categories involve reaction intermediates and mechanisms that are distinct from the stoichiometric reactions discussed above, i.e. they do not generally involve direct nucleophilic attack at an electrophilic selenium atom or a seleniranium ion intermediate. Conveniently, these organoselenium redox-catalyzed processes can be understood and explained in terms of the elementary steps of selenium oxidation, seleniranium ion formation, seleniranium ion opening, and cleavage of the C–Se bond (Figure 1.4). In general, a diselenide pre-catalyst is oxidized to the Se(II) oxidation state to form the actual catalytic species. Addition to the alkene to form the seleniranium ion then occurs. Next, nucleophilic ring-opening of the seleniranium ion affords the selenofunctionalized intermediate. The selenium atom undergoes a further oxidation to Se(IV), whereupon (unimolecular or base-promoted) elimination, or nucleophilic displacement of selenium occurs, resulting in scission of the C–Se bond and regeneration of the reduced, Se(II) catalyst. In certain circumstances, the selenium atom could be oxidized to Se(IV) prior to seleniranium ion formation, amounting to a reordering of the elementary steps but without consequence to the overall transformation. Certain reaction systems are incapable of cleaving the

Se–Se bond and the active catalyst is instead proposed to be the (counteranion-associated) diphenyl diselenonium ion, which, like the other catalytic species, carries the formal oxidation state of Se(II) and adds to alkenes to form seleniranium ions.[53]

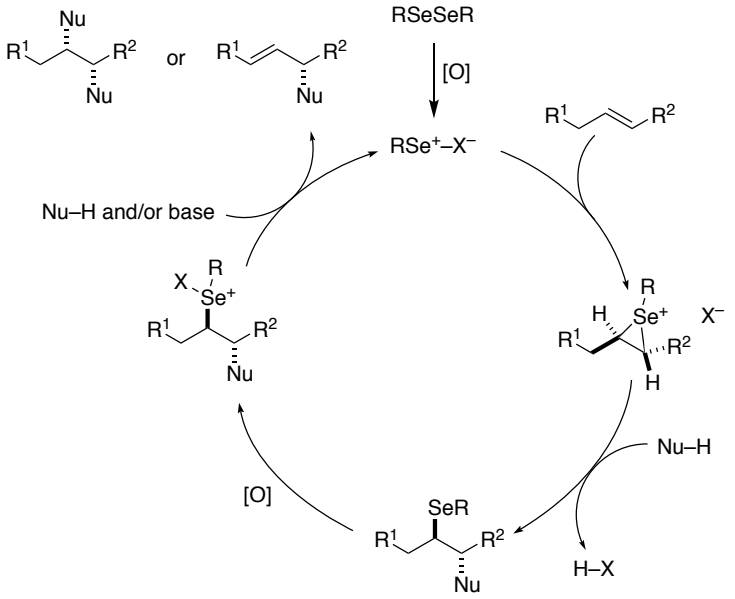


Figure 1.4. General catalytic cycle for organoselenium redox-catalyzed reactions.

Four classes of oxidant are typically employed to oxidize the pre-catalyst to Se(II) and to oxidize to Se(IV) before catalyst turnover (Figure 1.5). Peroxo reagents, and persulfate reagents in particular, were the first chemical oxidants employed in catalytic oxylselenenylation-deselenenylations (n.b., the first example of this transformation was electrochemical, without a discrete reagent as the stoichiometric oxidant, *vide infra*). These reagents have the potential to overoxidize the organoselenium catalyst to the inactive seleninic acid,[54] and have largely been replaced by other oxidants in recent years. The most commonly employed oxidants today are the *N*-F reagents, comprised of Selectfluor, *N*-fluoropyridinium reagents (PyF^+TfO^-, 2,4,6-$Me_3PyF^+BF_4^-$), and *N*-fluorobenzenesulfonimide (NFSI). Oxygen or air, in the presence of a pyrylium catalyst, also enjoys frequent use, in particular in the work of Breder and coworkers. *N*-chlorosuccinimide (NCS) and aryliodine(III) reagents have been employed in more limited circumstances.

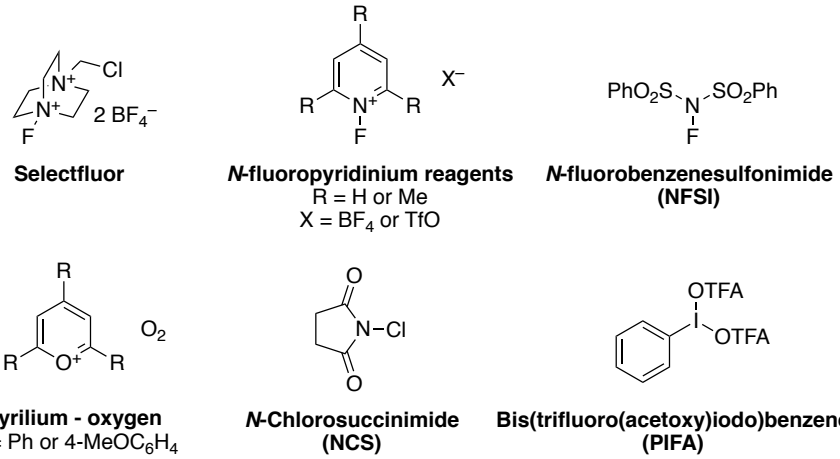
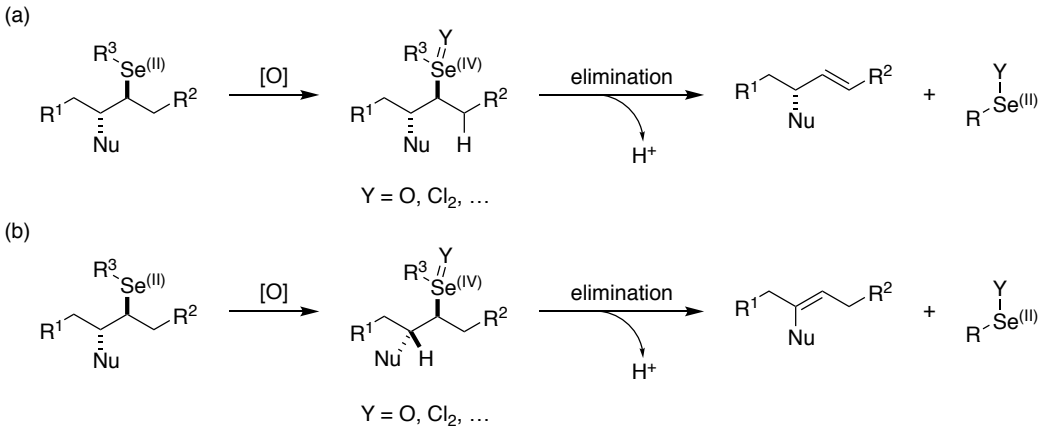


Figure 1.5. Oxidizing agents employed in electrophilic organoselenium redox catalysis.

Most of the variation between organoselenium redox-catalyzed transformations can be found in the nucleophiles that engage the seleniranium ion, and whether the step that regenerates the Se(II) catalyst occurs by elimination or nucleophilic displacement. There are a few, more unique, transformations that can be classified within this category, whose elementary steps are closely related to those described and still rely on a Se(II)-Se(IV) cycle.

Regeneration of the organoselenium catalyst almost always occurs through an elimination reaction, and thus the majority of redox-catalyzed reactions are fundamentally nucleophilic allylic functionalizations, usually involving a migration of the double bond (Scheme 1.16a). Seleniranium ion formation and ring-opening affords a vicinal *anti*-selenofunctionalized intermediate, which undergoes oxidation and elimination to form the product. In certain circumstances, elimination is favored in the direction of the nucleophilic partner to afford products with the nucleophilic atom attached to the alkene (Scheme 1.16b).

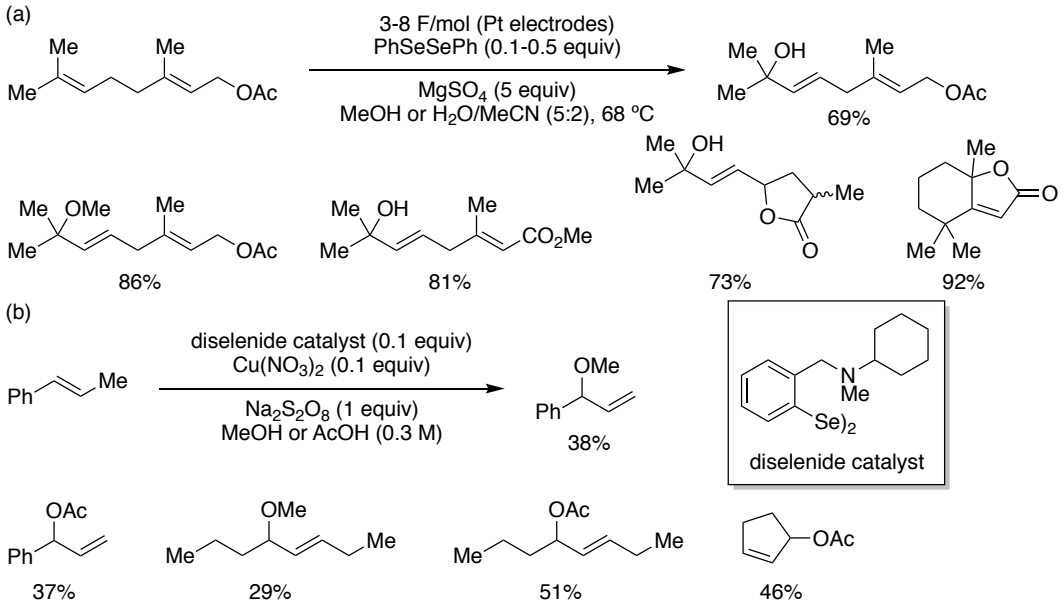


Scheme 1.16. Potential pathways for Se–C bond cleavage by elimination.

1.4.1. Allylic Functionalizations with Oxygen Nucleophiles.

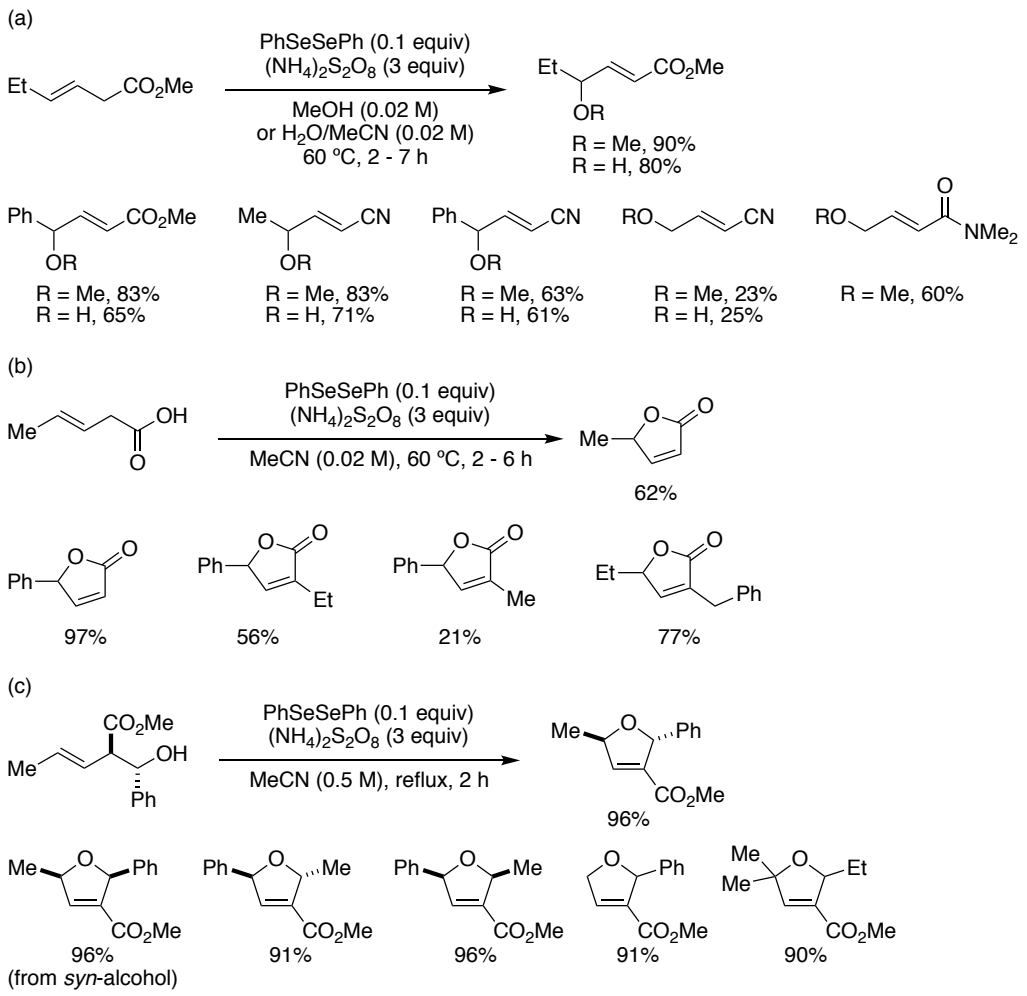
The earliest catalytic application of electrophilic organoselenium reagents was developed by Torii and coworkers in the electrochemical oxyselenenylation-deselenenylation of alkenes (Scheme 1.17a).[54] Several structurally complex alkenes can be oxidized to the corresponding allylic ethers or alcohols in good to excellent yields. The proposed mechanism involves addition of the alkene to the intermediate, electrochemically generated phenylselenenic acid (PhSeOH) or ester (PhSeOR), seleniranium ion opening by nucleophile, electrochemical oxidation of the aryl alkyl selenoether, and β-elimination. Stoichiometric amounts of an alkali or alkaline earth sulfate electrolyte are required for good conversion and yield; the authors speculate this dependence may be attributed to their inhibition of selenium overoxidation to the catalytically inactive phenylseleninic acid (PhSe(O)OH).

More than a decade later, Tomoda and coworkers demonstrated the utility of persulfate reagents as stoichiometric oxidants in the same transformation (Scheme 1.17b).[55] Substoichiometric amounts of a structurally-modified diselenide and copper(II) nitrate with stoichiometric amounts of sodium persulfate, at room temperature for seven days, affords allylic methyl ethers and acetates in moderate yields. Hydrogen peroxide was originally evaluated as a stoichiometric oxidant, but gave poor yields, likely due to the formation of seleninic and peroxyseleninic acids. The authors speculate that the $Cu(NO_3)_2$, required for good yields, is involved in the initial oxidation of the diselenide precatalyst to the active PhSe(II)OR (R = Me, Ac) catalyst.



Scheme 1.17. (a) Electrochemical inter- and intramolecular oxyselenenylation-deselenenylation of terpenes. (b) Intermolecular oxyselenenylation-deselenenylation of simple alkenes with acetic acid or methanol and sodium persulfate.

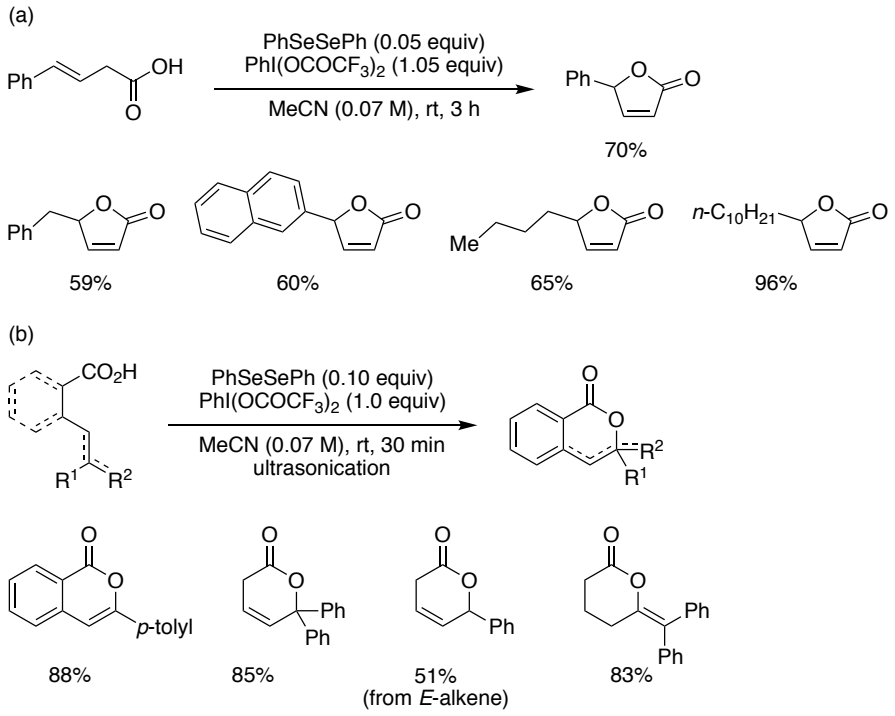
Shortly thereafter, Tiecco, Testaferri, and coworkers disclosed the catalytic oxyselenenylation-deselenenylation of alkenes bearing β-electron-withdrawing groups (Scheme 1.18a).[56] In this case, with the use of ammonium persulfate at 60 ºC, no co-catalyst is required to obtain good yields with several alkene substrates in methanol or water/acetonitrile. The same authors later disclosed the organoselenium-catalyzed selenolactonization-deselenenylation with similar reaction conditions, which affords butenolide products in good to excellent yields (Scheme 1.18b).[57] The authors note that better conversions can be obtained in methanol, but competitive intermolecular methoxyselenenylation leads to diminished yield of the lactone product. The method was further extended to selenocycloetherification-deselenenylation reactions, affording dihydrofuran products (Scheme 1.18c).[58] An electron withdrawing group at the β-position to the alkene is apparently required to aid in the deselenenylation in view of the scope of the olefin substrates evaluated.



Scheme 1.18. Oxyselenenylation-deselenenylation reactions with ammonium persulfate as the stoichiometric oxidant. (a) Intermolecular reactions with water and methanol. (b) Lactonizations to form butenolides. (c) Stereoselective cycloetherification reactions of alkenols.

More recently, Wirth and coworkers demonstrated the utility of [bis(trifluoroacetoxy)iodo]benzene (PIFA) as a stoichiometric reagent for catalytic selenolactonization-deselenenylations (Scheme 1.19a).[59] Although less atom economical, substitution of ammonium persulfate for the hypervalent iodine oxidant allows for reduction of diselenide catalyst loading from 10 to 5 mol % and reduction of reaction temperature from 60–80 ºC to 25 ºC while maintaining or improving yields of the butenolide products. Of particular note is the increase in isolated yield of the butenolide product from oct-3-enoic acid to tetradec-3-enoic acid. The authors do not speculate on the origin of this effect but, in acetonitrile, micelle formation is a possibility for long-chain fatty acids and could have a dramatic effect on local concentrations

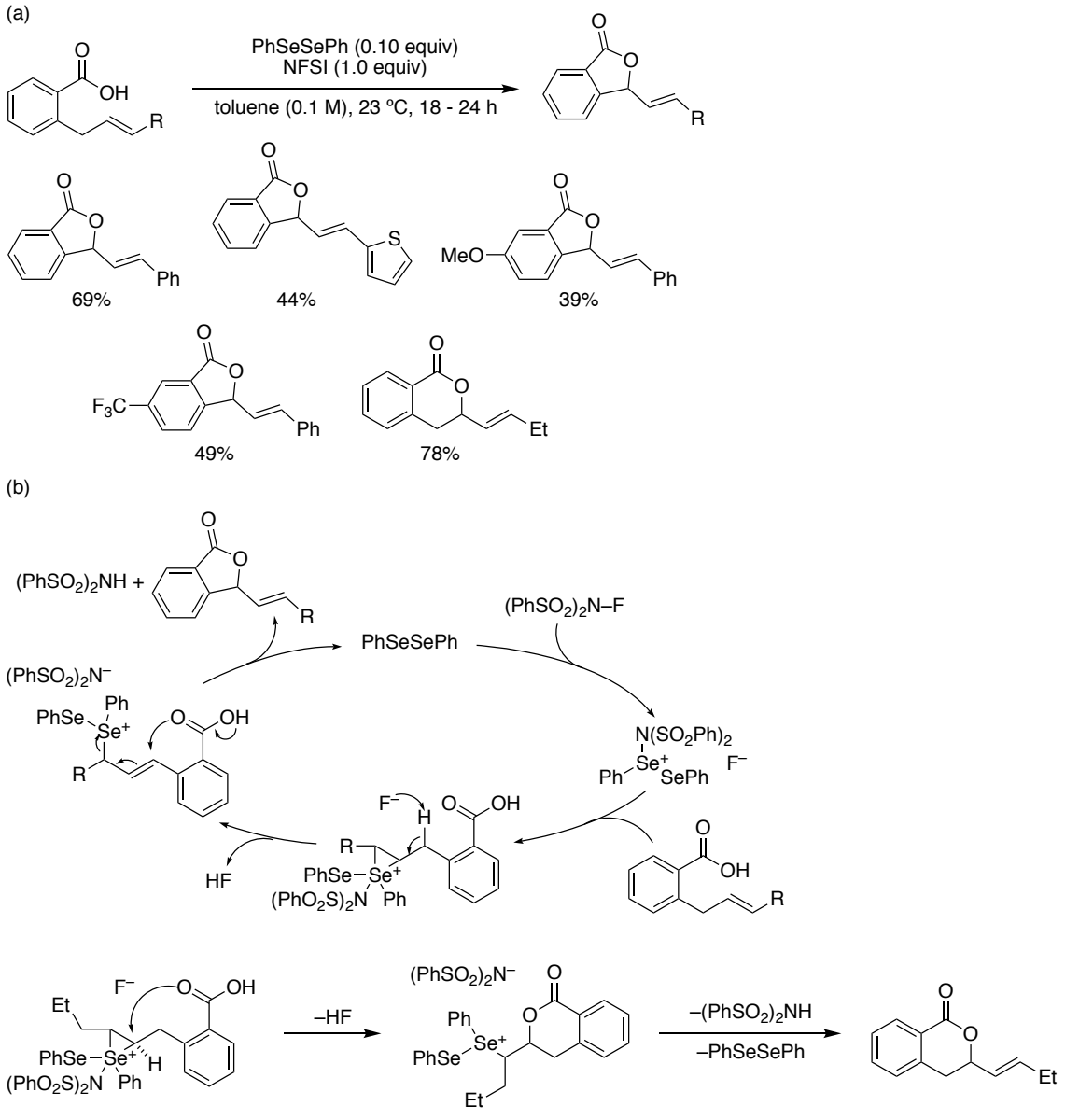
of reactive species. The identification of PIFA as an effective stoichiometric oxidant also allows for the preparation of a much wider variety of lactones (Scheme 1.19b).[60] Strongly electron-withdrawing groups at the β-position to the alkene are no longer required, significantly broadening the scope of the transformation. It is not immediately apparent what role the hypervalent iodine oxidant has in accelerating deselenenylation relative to the proposed selenoxide or selenonium bisulfate intermediates of earlier methods. It is possible that the trifluoroacetate counterion also assists in deseleneylation by deprotonation at the β-position.



Scheme 1.19. Use of PIFA as stoichiometric oxidant for oxyselenenylation-deselenenylation reactions. (a) Lactonizations to form butenolides. (b) Lactonizations to form isocoumarins and valerolactones.

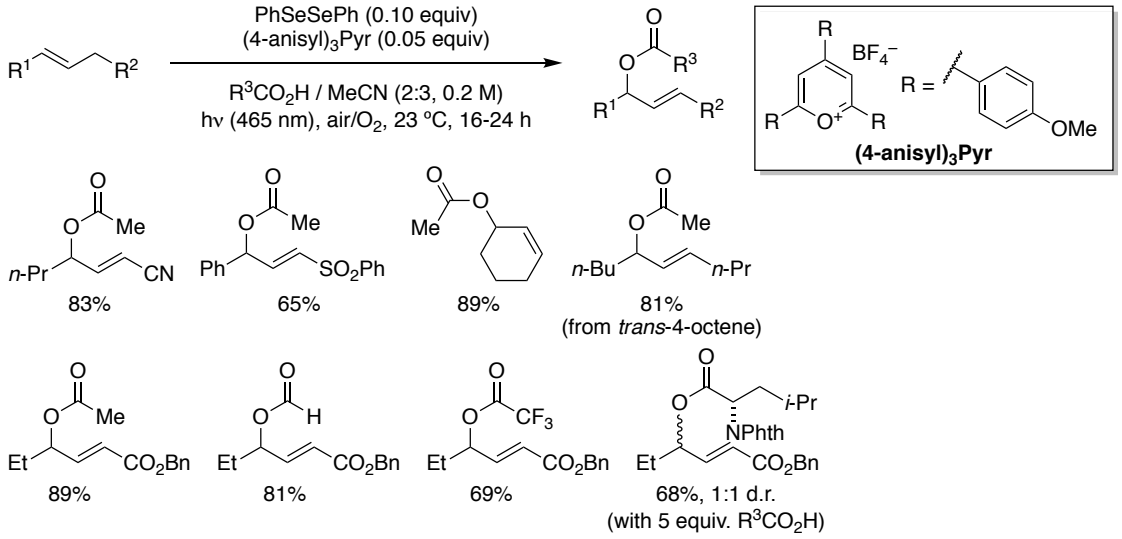
N-Fluorobenzenesulfonimide has recently been employed in similar lactonizations by Breder and coworkers (Scheme 1.20a). However, this transformation is somewhat unique relative to those discussed above, as the C–O bond is formed not with allylic transposition, but instead at the allylic (methylene) position of the alkene substrate. The authors suggest that NFSI is incapable of fragmenting the Se–Se bond of diphenyl diselenide, and that the catalytically active species is instead the diphenyl diselenonium ion – a weaker electrophile, but still capable of undergoing the same transformations as the more electropositive phenylselenenyl reagents (Scheme 1.20b).

Formation of a seleniranium ion intermediate is followed by E2-type ring-opening (mediated by fluoride), and the allylic diselenonium intermediate is displaced in an S_N2' fashion to afford the isobenzofuranone product and regenerate diphenyl diselenide. When R is not aromatic, nucleophilic opening of the seleniranium ion outcompetes elimination to form a dihydroisocoumarin product. While the mechanism of the transformation may appear distinct from what is outlined in Figure 1.4, the differences amount to a rearrangement of the elimination/deselenenylation and nucleophilic addition/seleniranium ion opening steps.



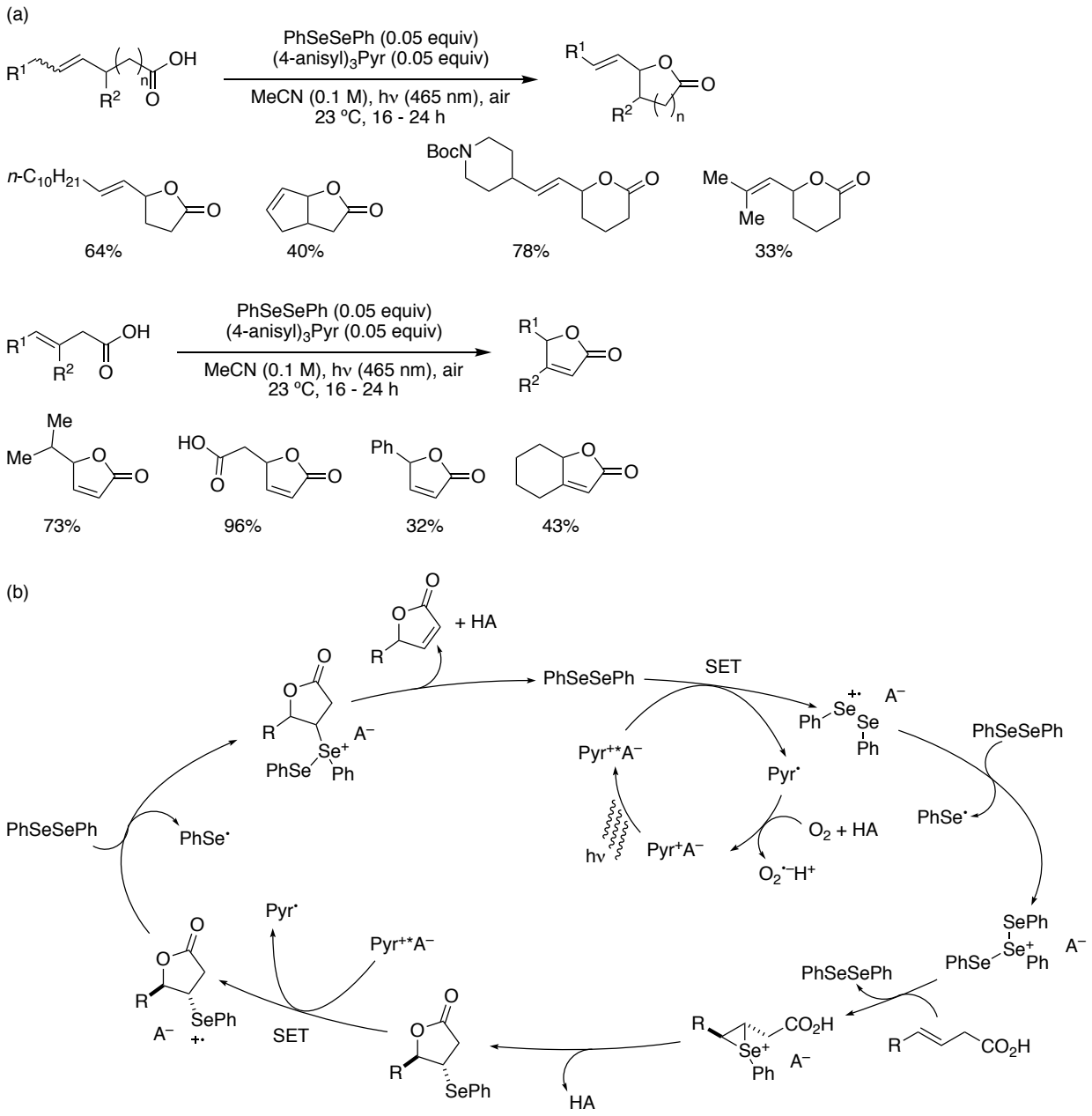
Scheme 1.20. (a) Oxyselenenylation-deselenenylation to form lactones with NFSI as the stoichiometric oxidant and (b) the mechanism proposed for the transformation.

Soon thereafter, Breder and coworkers further expanded the utility of organoselenium redox-catalyzed transformations with the use of a pyrylium photocatalyst and oxygen as the stoichiometric oxidant (Scheme 1.21).[61] Most importantly, intermolecular transformations were brought back into focus, with allylic esterification reactions affording good yields for a variety of alkenes, with or without β-electron-withdrawing groups.



Scheme 1.21. Organoselenium- and aerobic photoredox-catalyzed intermolecular allylic esterification of alkenes. Phth = phthalimide.

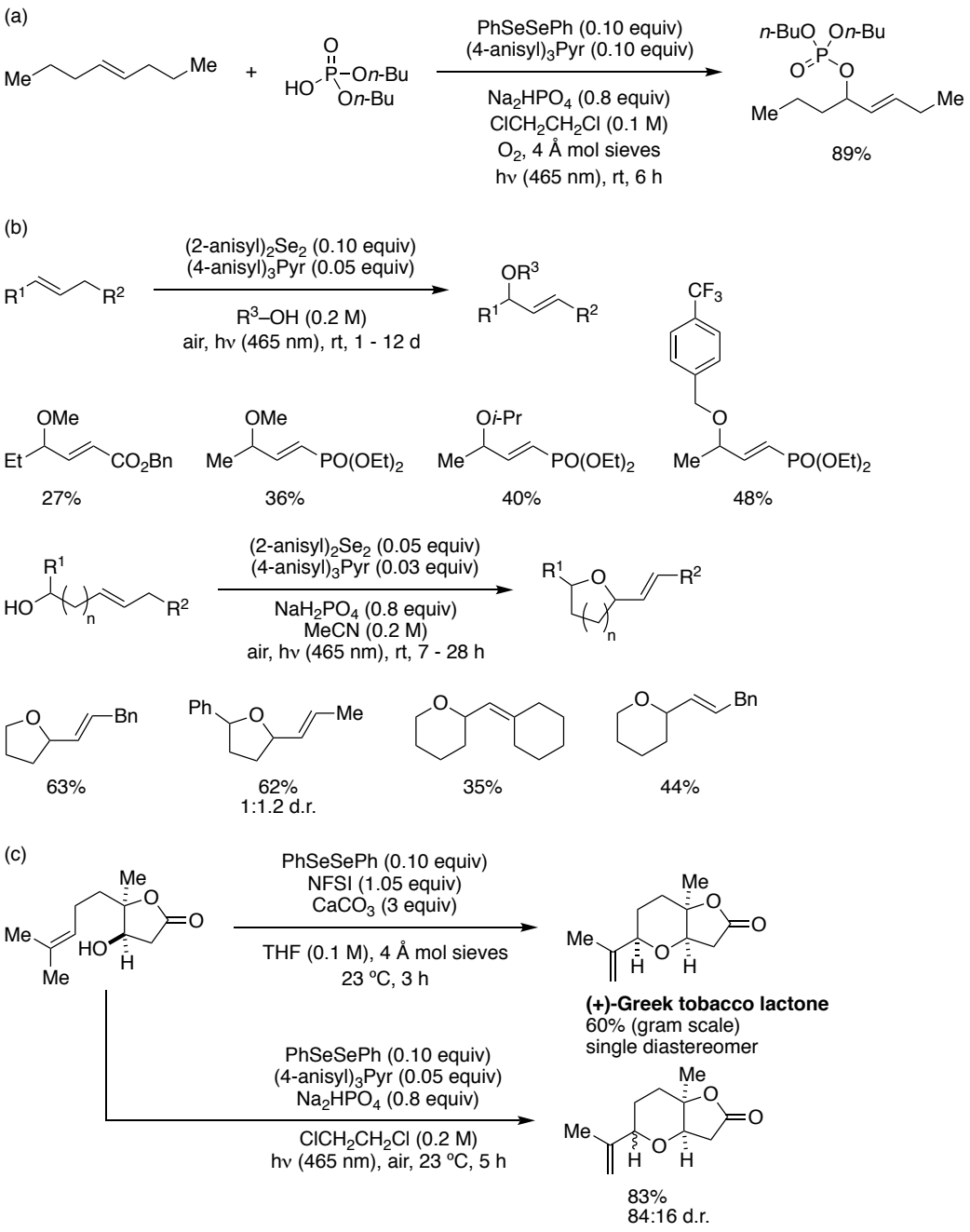
Lactonizations are equally efficacious in the aerobic photoredox system (Scheme 1.22a).[62] In-depth mechanistic investigations suggest a single-electron transfer and subsequent disproportionation are responsible for the oxidation of diphenyl diselenide to the triphenyl triselenonium ion ($Ph_3Se_3^+$), which serves to deliver a selenenium ($PhSe^+$) equivalent to the alkene to form the seleniranium ion and re-form diphenyl diselenide (Scheme 1.22b). Nucleophilic opening as usual affords the oxyselenenylated intermediate, which is oxidized to the radical cation through a second single-electron transfer. The authors suggest dimerization of the radical cation intermediate to a dicationic dimer occurs next, but interception by diphenyl diselenide to form the diphenyl diselenonium cation and phenylselenyl radical may be more likely. Regardless, the final step involves deselenenylation to form the unsaturated lactone product and diphenyl diselenide, and the catalytic cycle turns over.



Scheme 1.22. (a) Aerobic oxidative lactonization of alkenoic acids and (b) the mechanism proposed for the transformation.

This aerobic, organoselenium-catalyzed method has been further extended to the phosphorylation of alkenes (Scheme 1.23a),[63] as well as the inter- and intramolecular etherification of alkenes (Scheme 1.23b).[64] Improved yields are obtained in the etherification reactions by replacement of diphenyl diselenide with the more electron-releasing di-(2-anisyl) diselenide. The aerobic cycloetherification method is also effective in the stereoselective synthesis of (+)-Greek

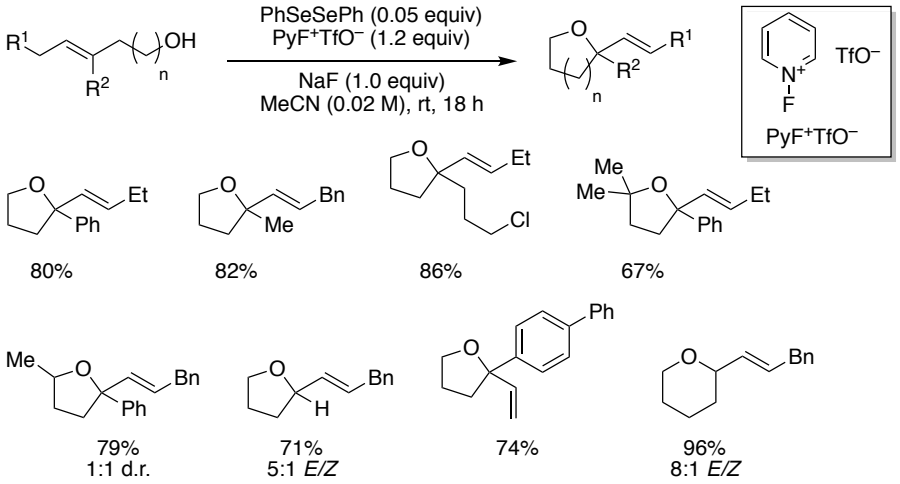
tobacco lactone, but the cyclization with NFSI as the stoichiometric oxidant results in an improved d.r. (Scheme 1.23c).



Scheme 1.23. (a) Aerobic, organoselenium- and photoredox-catalyzed phosphatation of alkenes. (b) Aerobic, organoselenium- and photoredox-catalyzed etherification of alkenes. (c) Catalytic oxyselenenylation-deselenenylation applied to the total synthesis of (+)-Greek tobacco lactone.

Zhao and coworkers simultaneously developed a closely related cycloetherification method with *N*-fluoropyridinium triflate as the stoichiometric oxidant (Scheme 1.24).[65] A variety

of alkyl and aryl, di- and trisubstituted alkenols are cyclized in good to excellent yields. Again, β-electron-withdrawing groups are no longer required for deselenenylation to proceed. Furthermore, terminal alkenes can be formed in the deselenenylation step – a transformation that is otherwise unprecedented. The stoichiometric amount of pyridine formed as a byproduct of oxidation could be acting as a base, driving the elimination of the arylselenium(IV) intermediate through an E2-like mechanism in circumstances in which deselenenylation was previously unfavorable.

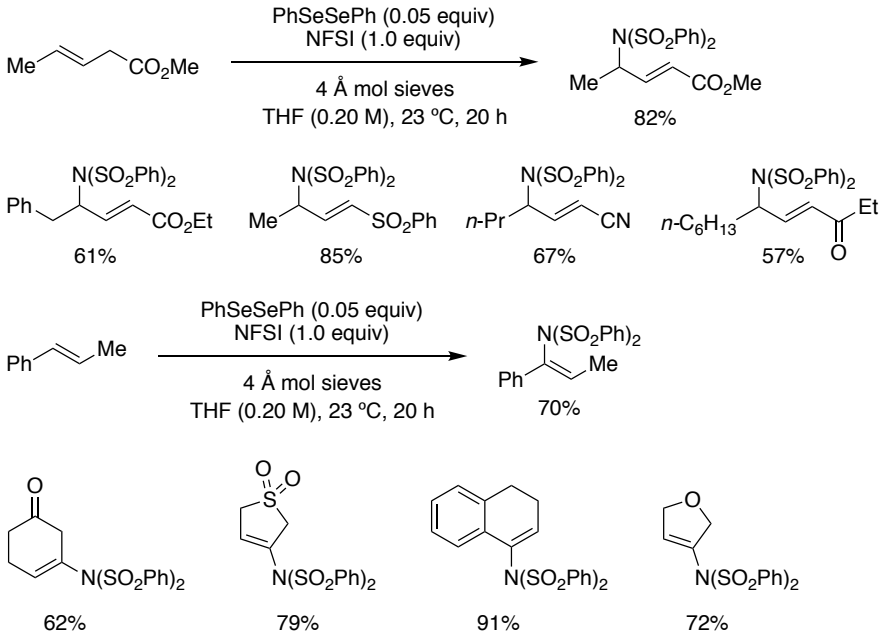


Scheme 1.24. Organoselenium redox-catalyzed cycloetherification of alkenols with *N*-fluoropyridinium triflate (PyF^+TfO^-) as the stoichiometric oxidant.

1.4.2. Allylic Functionalizations with Nitrogen Nucleophiles.

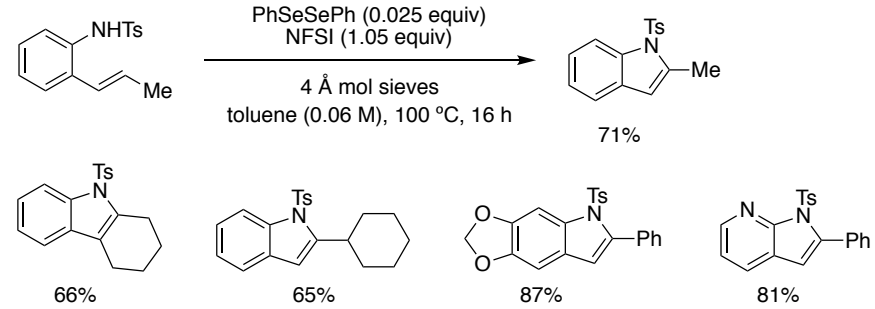
These modern methods for organoselenium-catalyzed allylic C–O bond formation are also effective with nitrogen nucleophiles, affording allylic and vinylic amine products. The Breder and Zhao laboratories have developed amination reactions, with NFSI or *N*-fluoropyridinium triflate as the terminal oxidant, to afford allylic sulfonimides, bis-sulfonylenamines, indoles, pyrrolidines, tetrahydroazepines, and vinylpyridinium salts.

Breder and coworkers discovered that the use of NFSI as the stoichiometric oxidant in the absence of an exogenous nucleophile leads to seleniranium ion capture by the $(PhSO_2)_2N^-$ anion, affording sulfonimide products (Scheme 1.25).[66] Without a β-electron-withdrawing group to direct deselenenylation, deprotonation occurs adjacent to the electron-poor nitrogen, affording enamide products.



Scheme 1.25. Oxidative amination of alkenes with NFSI.

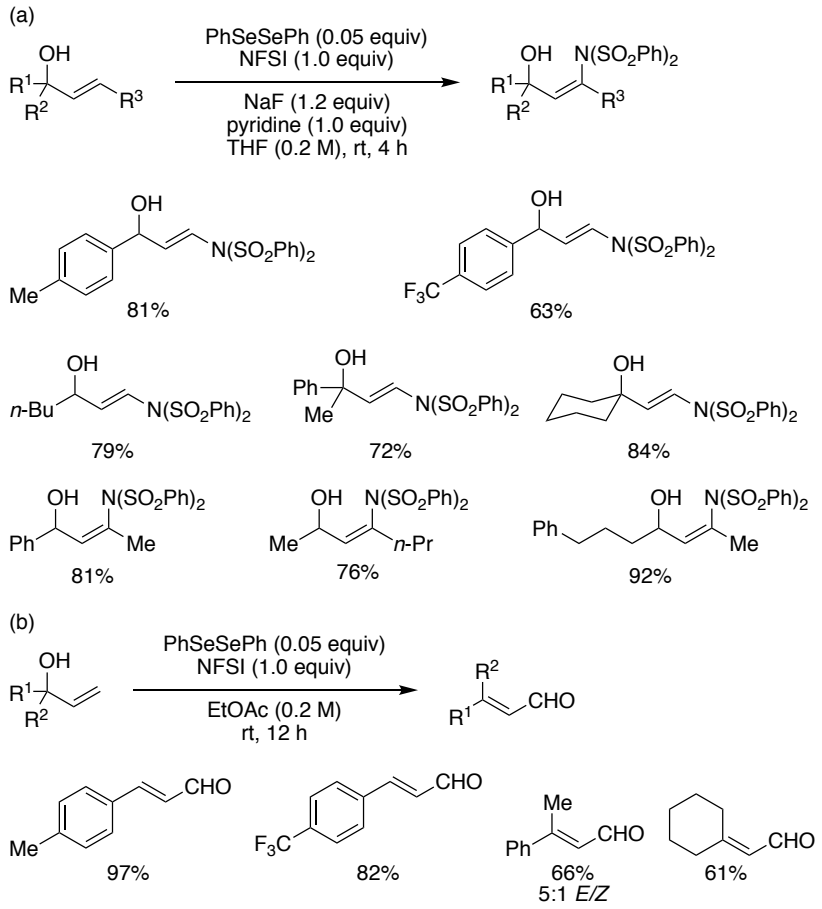
At elevated temperature in toluene, 2-vinyl-*N*-tosylanilines undergo a similar intramolecular aminoselenenylation-deselenenylation to afford a variety of functionalized indole products (Scheme 1.26).[67] The 4-toluenesulfonyl group on nitrogen is essential for good yields. The 4-nitrobenzenesulfonylaniline and methanesulfonylaniline analogues are competent but less efficacious than the 4-toluenesulfonyl; and the *N*-acetyl and *N*-trichloroacetyl afford no indole product whatsoever. Furthermore, only 1,2-disubstituted alkenes and a single 1,1,2-trisubstituted alkene give good yields in these conditions, largely limiting the scope to 2-alkyl- and arylindoles.



Scheme 1.26. Organoselenium redox-catalyzed preparation of indoles from 2-vinylanilines.

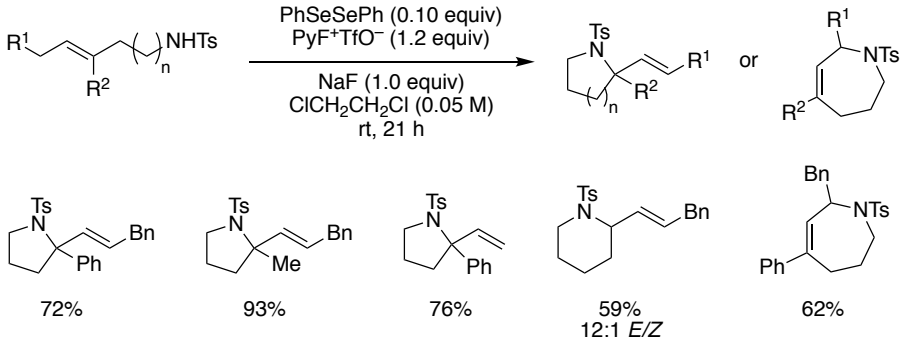
Zhao and coworkers simultaneously developed the oxidative amination of allylic alcohols to form *N,N*-di(benzenesulfonyl)enamines with NFSI as the stoichiometric oxidant (Scheme

1.27a).[53b] Good to excellent yields are obtained from a variety of vinyl-aryl, vinyl-alkyl, and trisubstituted carbinols. Without stoichiometric amounts of pyridine and sodium fluoride to neutralize the hydrofluoric acid byproduct, the desired enamines undergo spontaneous hydrolysis to α,β-unsaturated aldehydes (Scheme 1.27b). The authors propose an analogous catalytic cycle to Breder and coworkers' proposal for their NFSI system, with the diphenyl diselenonium cation serving as the active catalyst.



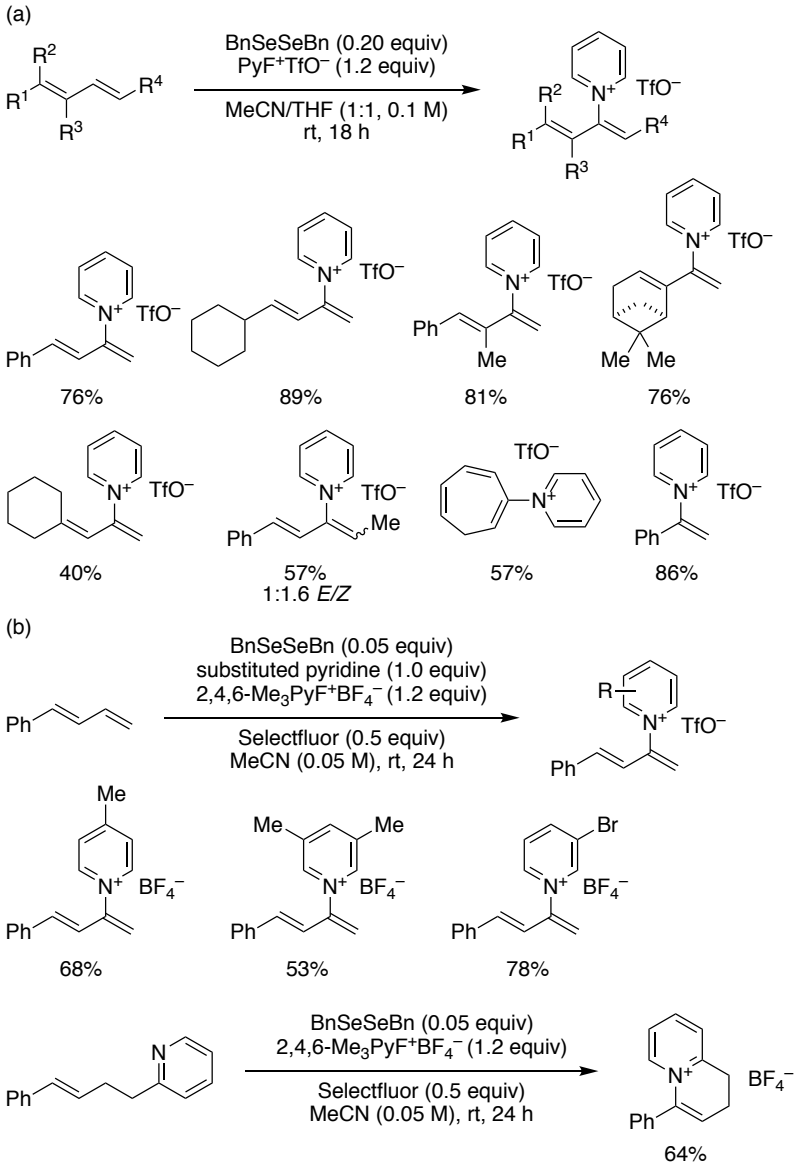
Scheme 1.27. (a) Organoselenium redox-catalyzed amination of allylic alcohols and (b) oxidation of allylic alcohols to α,β-unsaturated aldehydes.

Soon after, Zhao and coworkers disclosed an intramolecular aminoselenenylation-deselenenylation reaction with *N*-fluoropyridinium triflate as the stoichiometric oxidant (Scheme 1.28).[65] Like Breder and coworkers' synthesis of indoles, *N*-4-toluenesulfonylamines are required for the reaction to proceed. These cyclizations, however, proceed to afford a broader variety of pyrrolidines and tetrahydroazepines in good to excellent yield at room temperature.



Scheme 1.28. Organoselenium redox-catalyzed synthesis of pyrrolidines and tetrahydroazepines.

Interestingly, in the absence of other nucleophiles, the pyridine byproduct generated from the stoichiometric oxidant can capture the seleniranium ion to form pyridinium adducts. Zhao and coworkers optimized this process for the preparation of a range of vinylpyridinium products obtained from dienes and styrenes (Scheme 1.29a).[68] Optimization of catalyst, oxidant, and solvent led to the discovery of dibenzyl diselenide as the most effective catalyst. *N*-Fluoropyridinium triflate and tetrafluoroborate are similarly efficacious, while *N*-Fluoro-2,6-dichloropyridinium and -2,4,6-trimethylpyridinium triflate afford no product. It is somewhat surprising that dibenzyl diselenide acts as a catalyst in a Se(II)-Se(IV) cycle considering the relative ease with which oxidized benzyl selenides undergo Bn–Se bond cleavage (cf. Section 1.1.). *N*-Fluoro-2,4,6-trimethylpyridinium triflate is, however, a competent stoichiometric oxidant when coupled with Selectfluor as a co-oxidant and exogeneous pyridine nucleophiles (Scheme 1.29b). The authors claim that Selectfluor aids in accelerating the deselenenylation process either through more rapid oxidation of the aryl-alkyl selenoether intermediate or through deprotonation by the strongly basic amine byproduct.

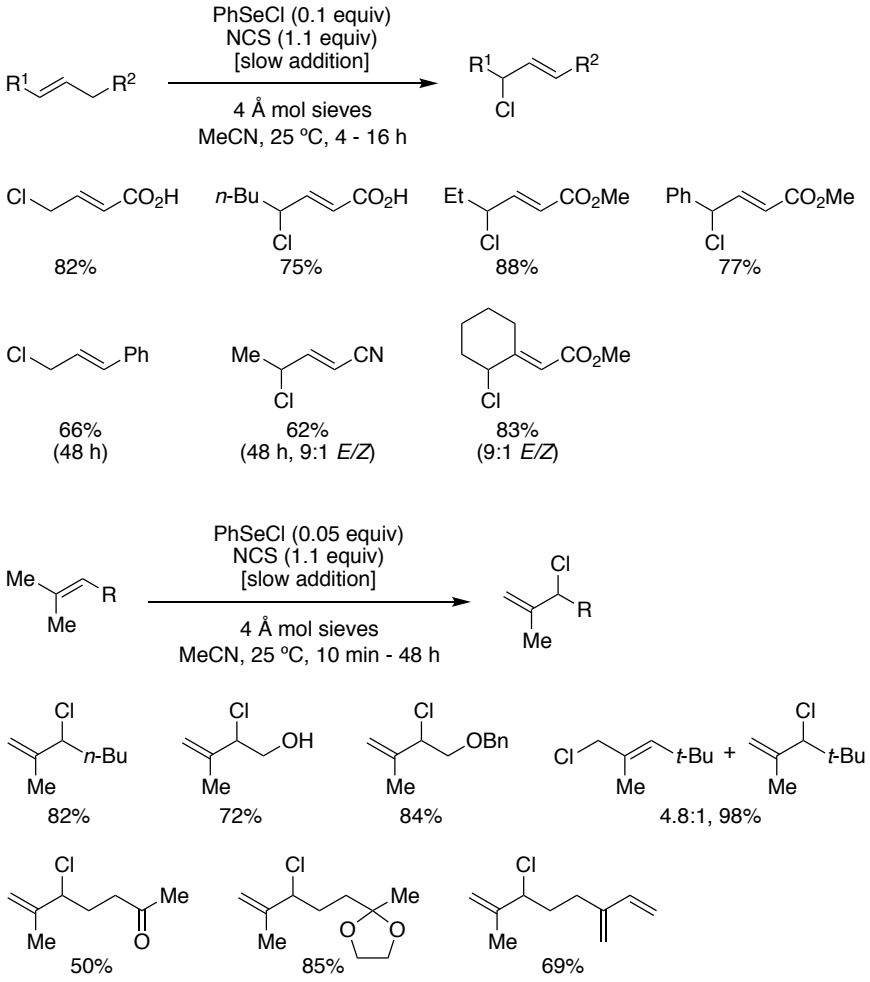


Scheme 1.29. (a) Organoselenium redox-catalyzed pyridination of alkenes and dienes. (b) Installation of substituted pyridines with dual stoichiometric oxidant system.

1.4.3. Allylic Functionalizations with Halogen Nucleophiles.

In 2004, Tunge and coworkers disclosed the phenylselenenyl chloride-catalyzed allylic chlorination of alkenes with *N*-chlorosuccinimide (NCS) as the stoichiometric oxidant (Scheme 1.30)[69] Prenyl olefins and alkenes bearing β-electron-withdrawing groups afford allylic chlorides in good yields. The authors note an inhibitory effect of NCS at higher concentrations and settle on slow addition of the oxidant as a remedy. Notably, catalytic amounts of PhSeCl with β,γ-unsaturated carboxylic acids afford the allylic chloride, whereas stoichiometric amounts of PhSeCl

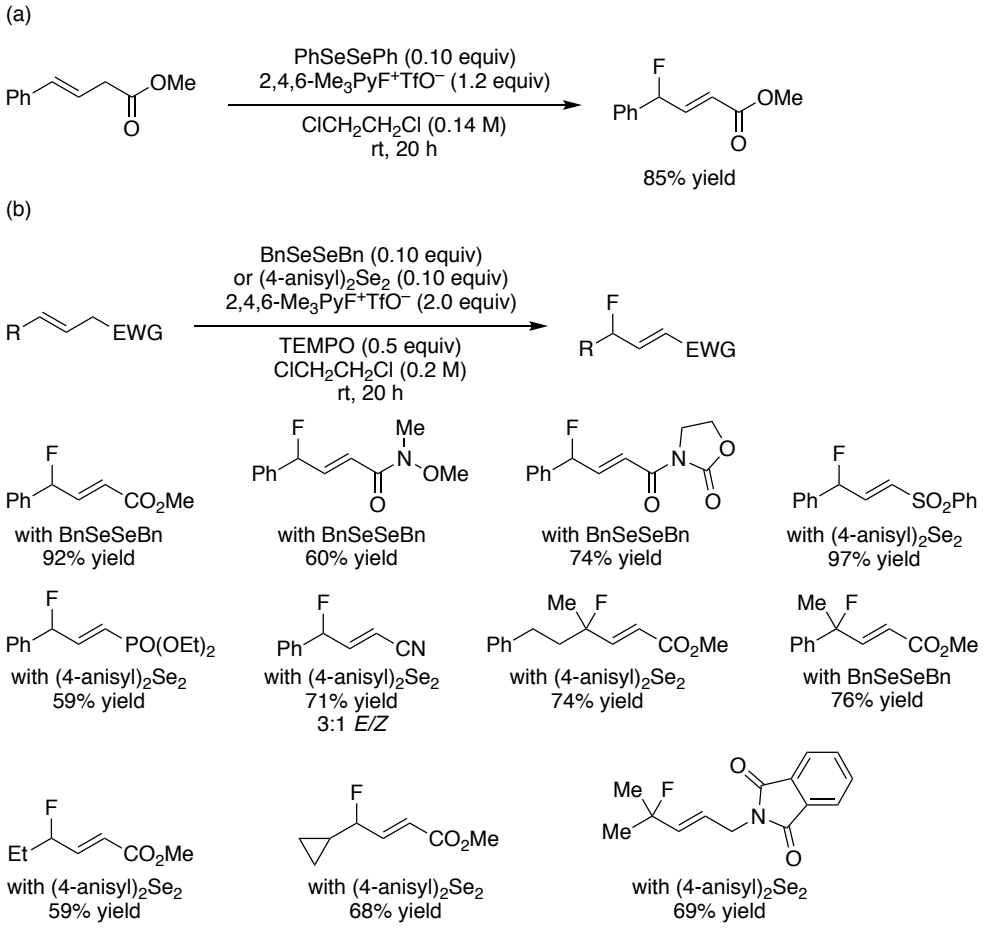
afford the lactone.[70] This arylselenenyl halide-catalyzed chlorination method has been extended to the α-chlorination of carbonyl compounds[71] and to the use of a resin-bound, recyclable selenenyl halide catalyst for the selective chlorination of complex terpenoids.[72]



Scheme 1.30. Organoselenium redox-catalyzed allylic chlorination of alkenes.

Zhao and coworkers recently modified their organoselenium-catalyzed pyridination method (*vide supra*) to instead afford allylic fluoride products from the fluoride generated as a byproduct of selenium oxidation.[73] The stoichiometric combination of alkenes and *in-situ* generated organoselenenyl fluorides (RSe–F) affords fluoroselenenylated products,[74] but this transformation could not be extended to a catalytic process. Substitution of *N*-fluoropyridinium triflate for the collidinium analogue (*N*-fluoro-2,4,6-trimethylpyridinium triflate, 2,4,6-$Me_3PyF^+TfO^-$) prevents seleniranium ion capture by the pyridine byproduct and instead affords the allylic fluoride from (*E*)-methyl 4-phenylbut-3-enoate in 85% yield (Scheme 1.31a). Extension

of the method to other substrates initially proved problematic owing to slow deselenenylation of the β-fluoroalkyl arylselenium(IV) intermediate. Replacement of diphenyl diselenide with the more nucleophilic dibenzyl diselenide or di-4-anisyl diselenide and addition of a substoichiometric amount of TEMPO enables access to a variety of allylic fluorides in good yields (Scheme 1.31b). TEMPO was initially screened as an additive for its potential role in accelerating the catalytic process by coordinating Se(IV) and accelerating deselenenylation, but was later found to serve primarily to protect the dibenzyl diselenide catalyst (BnSeSeBn) from de-benzylation (cf. Section 1.1.). The oxoammonium triflate obtained from oxidation of TEMPO is ineffectual at improving the yield of the allylic fluoride, leading the authors to conclude that *in-situ* oxidation of TEMPO by 2,4,6-$Me_3PyF^+TfO^-$ is not occurring or responsible for its activity.



Scheme 1.31. (a) Allylic fluorination catalyzed by diphenyl diselenide. (b) Optimized conditions and scope of the transformation.

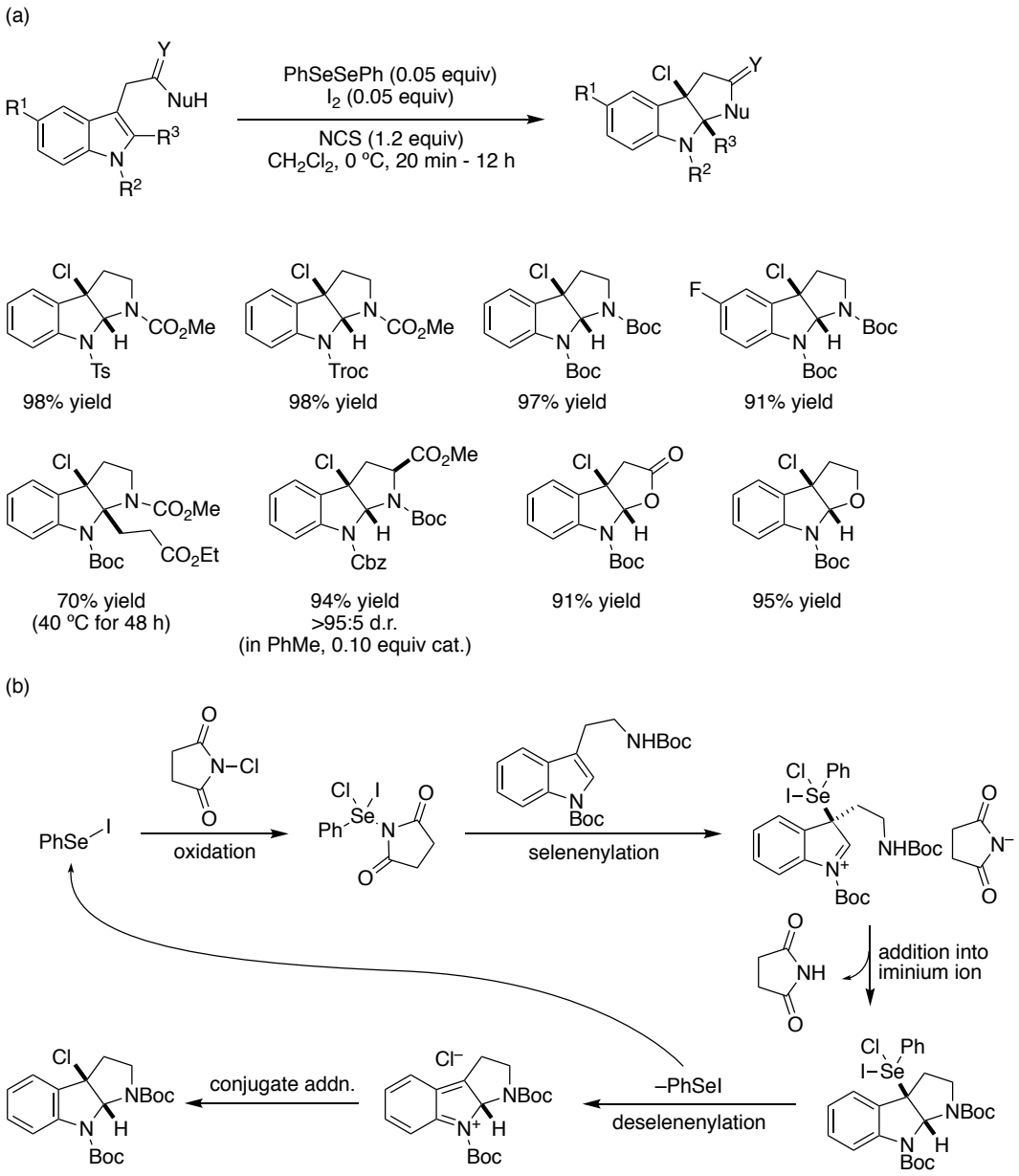
1.4.4. Alkene Difunctionalizations.

In some catalytic processes, the Se(IV) intermediate is displaced by a second nucleophile instead of undergoing elimination. These *syn*-difunctionalizations can be seen in the *syn*-dichlorination (c.f. Chapter 2) and *syn*-diamination (c.f. Chapter 3) of alkenes. Additionally, the organoselenium redox-catalyzed *syn*-oxy- and aminochlorination of indoles has recently been described by Ishihara and coworkers (Scheme 1.32a).[17b] The authors propose the iodine co-catalyst oxidizes diphenyl diselenide to phenylselenenyl iodide, which serves as the active catalyst. While the overall transformation does appear to be an organoselenium redox-catalyzed alkene *syn*-difunctionalization, the nature of the reaction may be slightly different. The mechanism proposed by the authors instead involves typical eliminative deselenenylation with assistance from the indole nitrogen, followed by stereoselective, conjugate addition of chloride into the cationic iminoquinone methide intermediate to afford the *syn*-difunctionalized products (Scheme 1.32b).

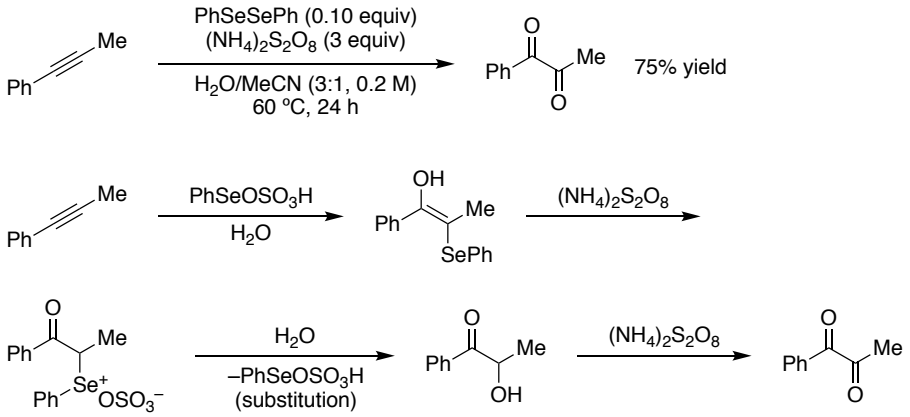
Alkynes also undergo organoselenium redox-catalyzed transformations that could be categorized within the manifold of difunctionalizations.[75] There are, in fact, a few mechanisms in which S_N2 displacement of an arylselenium(IV) is proposed – a relatively unique elementary step among what is typical for electrophilic organoselenium catalysis (Scheme 1.33). Notably, the Se(IV) intermediates that undergo displacement in these transformations are always stabilized by a carbonyl group (or equivalent) at the α-position.

1.5. Catalytic, Enantioselective Applications of Electrophilic Organoselenium Reagents.

Enantioselective reactions catalyzed by electrophilic organoselenium redox-catalysts are somewhat limited in scope especially when compared to the breadth of examples of enantioselective, organoselenium Lewis base-catalyzed transformations.[50c-e, 50i, 76] The earliest developments were borne from attempts to make the catalytic oxyselenenylation-deselenenylation process enantioselective through the application of chiral, enantioenriched diselenides. Reactions with these chiral catalysts in general suffer low turnover numbers (TON), long reaction times, and relatively low enantioselectivities. Significant advances have been made in the intramolecular selenolactonization-deselenenylation of alkenoic acids, but the problem of intermolecular selenoetherification remains largely unsolved.



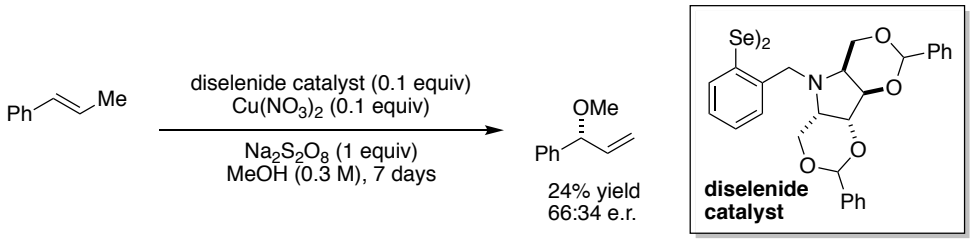
Scheme 1.32. (a) Organoselenium redox-catalyzed chlorofunctionalization of indoles and (b) the mechanism proposed for the transformation.



Scheme 1.33. Displacement of Se(IV) in the dihydroxylation/oxidation of 1-phenylpropyne.

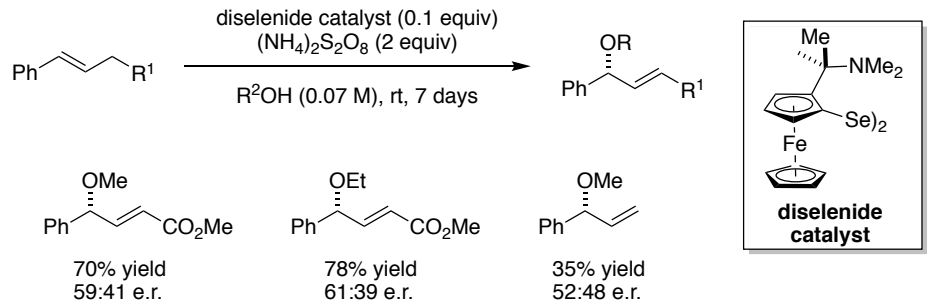
1.5.1. Intermolecular Oxyselenenylation-Deselenenylations.

The first example of a catalytic, asymmetric oxyselenenylation-deselenenylation was disclosed by Tomoda and coworkers in 1994, as an extension of the catalytic method that had been developed previously in those laboratories (Scheme 1.34).[55, 77]



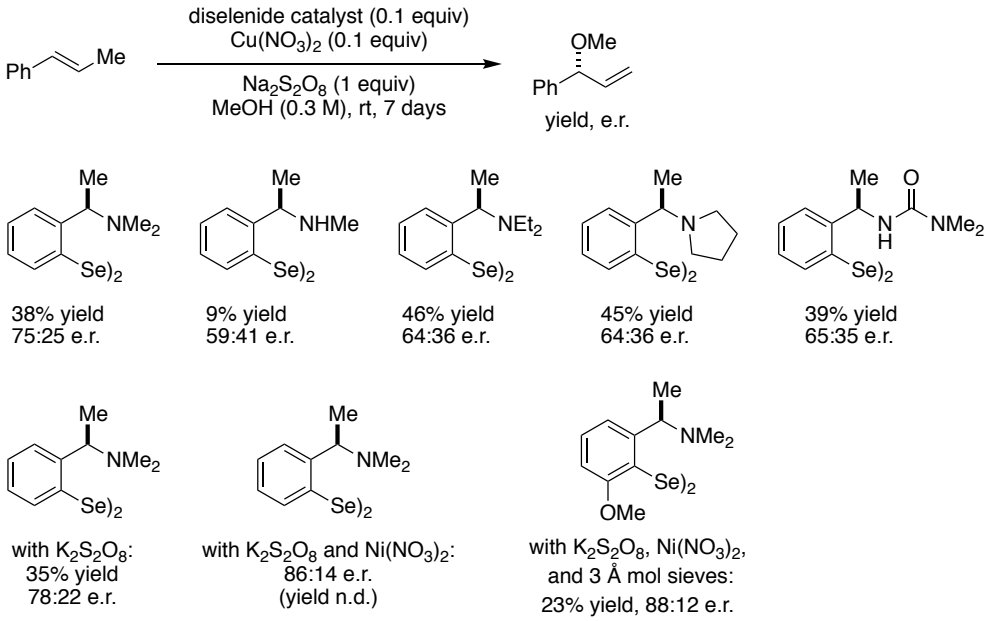
Scheme 1.34. Catalytic, enantioselective methoxyselenenylation-deselenenylation of β-methylstyrene by Tomoda and coworkers.

Fukuzawa and coworkers also sought to employ their chiral, enantioenriched ferrocene-derived diselenide as a catalyst for allylic etherification, and had the insight to evaluate substrates with β-electron-withdrawing groups to improve the rate of deselenenylation, TON, and yield of the allylic ether (Scheme 1.35).[78] Enantiomeric ratios are surprisingly low compared to the room-temperature diastereoselectivities obtained with the same ferrocenylselenium reagent as the pre-formed selenenyl bromide (Table 1.1, entry 4).



Scheme 1.35. Application of Fukuzawa's chiral ferrocenylselenium reagent to catalytic, asymmetric allylic etherification.

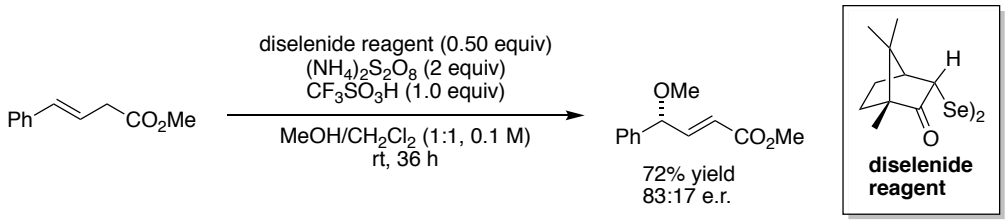
Wirth and coworkers used the conditions developed by Tomoda and coworkers with a range of chiral, enantioenriched nitrogen-containing diselenides with some success (Scheme 1.36).[79] Better enantioselectivities are obtained with a structurally simpler diselenide precatalyst than those employed previously. Exchange of sodium persulfate for the potassium salt and the use of metal additives other than copper(II) nitrate further improve the enantioselectivities.



Scheme 1.36. Evaluation of amine-containing diselenide precatalysts using catalytic allylic etherification conditions of Tomoda *et al.*

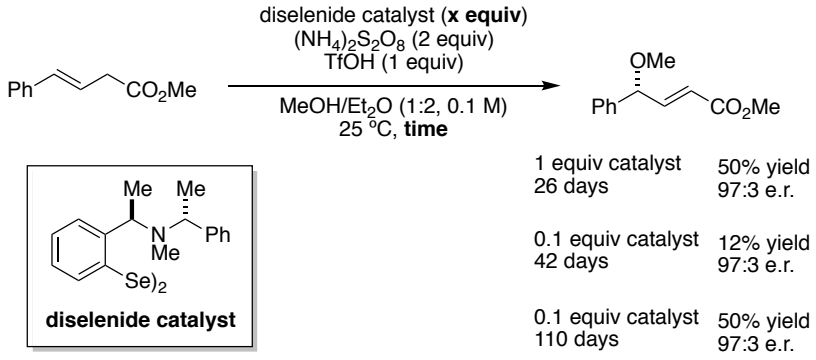
Tiecco and coworkers likewise sought to employ their camphor-derived diselenide in catalytic allylic etherification but found that conversion with substoichiometric amounts of the diselenide reagent was exceedingly slow. Instead, with 1 equivalent of the active electrophilic

selenium reagent, a tandem methoxyselenenylation-deselenenylation reaction could be achieved in moderate yield and enantioselectivity (Scheme 1.37).[80] The authors also claim that the majority of the diselenide reagent can be recovered from the reaction mixture after chromatography. The enantiomeric ratio of the product obtained from the tandem reaction closely reflects the room-temperature diastereoselectivity obtained with the same reagent and alkene.



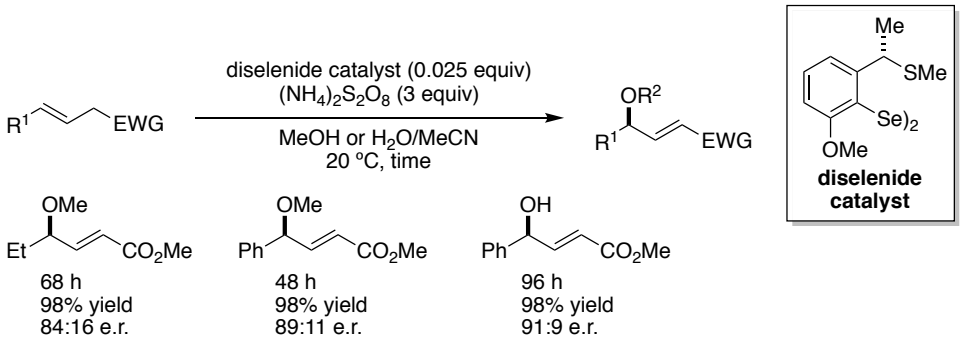
Scheme 1.37. Tandem methoxyselenenylation-deselenenylation with a camphor-derived diselenide.

Application of the phenethylamine-derived diselenide developed by Tiecco *et al.* (still in stoichiometric amounts) affords reduced reaction rate and yield but substantially improves the enantiomeric ratio of the allylic ether product (Scheme 1.38).[32] A full equivalent of diselenide affords only 50% yield after 26 days at 25 ºC, but with an excellent enantiomeric ratio of 97:3. Reduction of diselenide loading to 0.10 equiv affords 12% yield after 42 days, and 50% yield after 110 days at 25 ºC but without any change to the enantiomeric ratio. The enantioselectivity is in accordance with the room temperature diastereoselectivity obtained with the same, pre-formed arylselenenyl bisulfate.



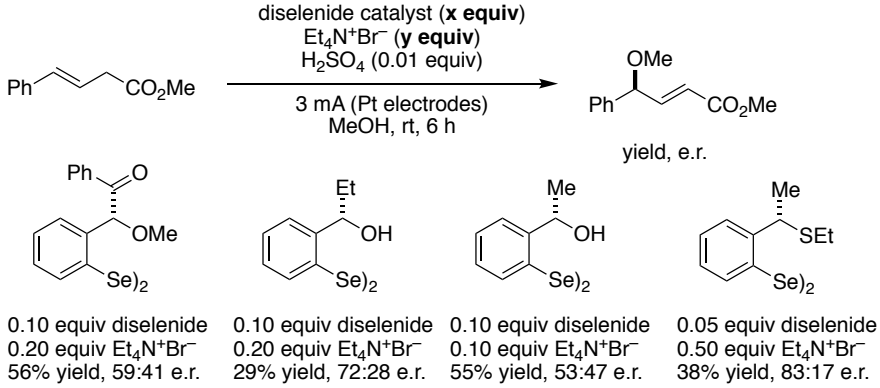
Scheme 1.38. Use of a phenethylamine-derived diselenide as a catalyst for asymmetric allylic etherification.

Further structural refinement of chiral, enantioenriched organoselenium compounds by Tiecco and coworkers led to the discovery of thioethers as exceptional coordinating groups, and the development of electrophilic selenium reagents that afford selenofunctionalized products with excellent diastereomeric ratios at higher temperatures (Table 1.1, entries 1 and 2). Application of these diselenides to the catalytic oxyselenenylation-deselenenylation reaction affords products in very good enantiomeric ratios and yields at room temperature, now within less than a week (Scheme 1.39).[5b]



Scheme 1.39. Use of a sulfur-containing diselenide as a catalyst for asymmetric allylic etherification.

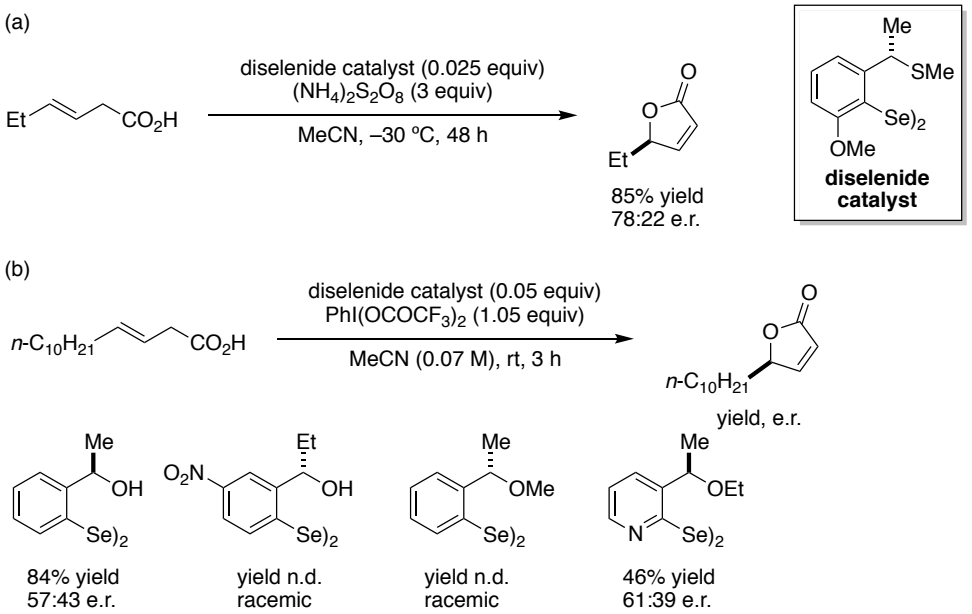
More recent endeavors in the asymmetric, intermolecular oxyselenenylation-deselenenylation reaction have involved the use of alternative oxidizing agents. Wirth and coworkers have adapted the electrochemical oxidation method, originally disclosed by Torii and coworkers,[54] for etherification reactions using a variety of chiral, enantioenriched diselenides (Scheme 1.40).[81] Enantiomeric ratios are lower than what is obtained with the thioether-containing catalyst of Tiecco *et al.*, but this may not be the result of the oxidation conditions employed.



Scheme 1.40. Asymmetric, electrochemical, organoselenium redox-catalyzed allylic etherification.

1.5.2. Intramolecular Oxyselenenylation-Deselenenylations.

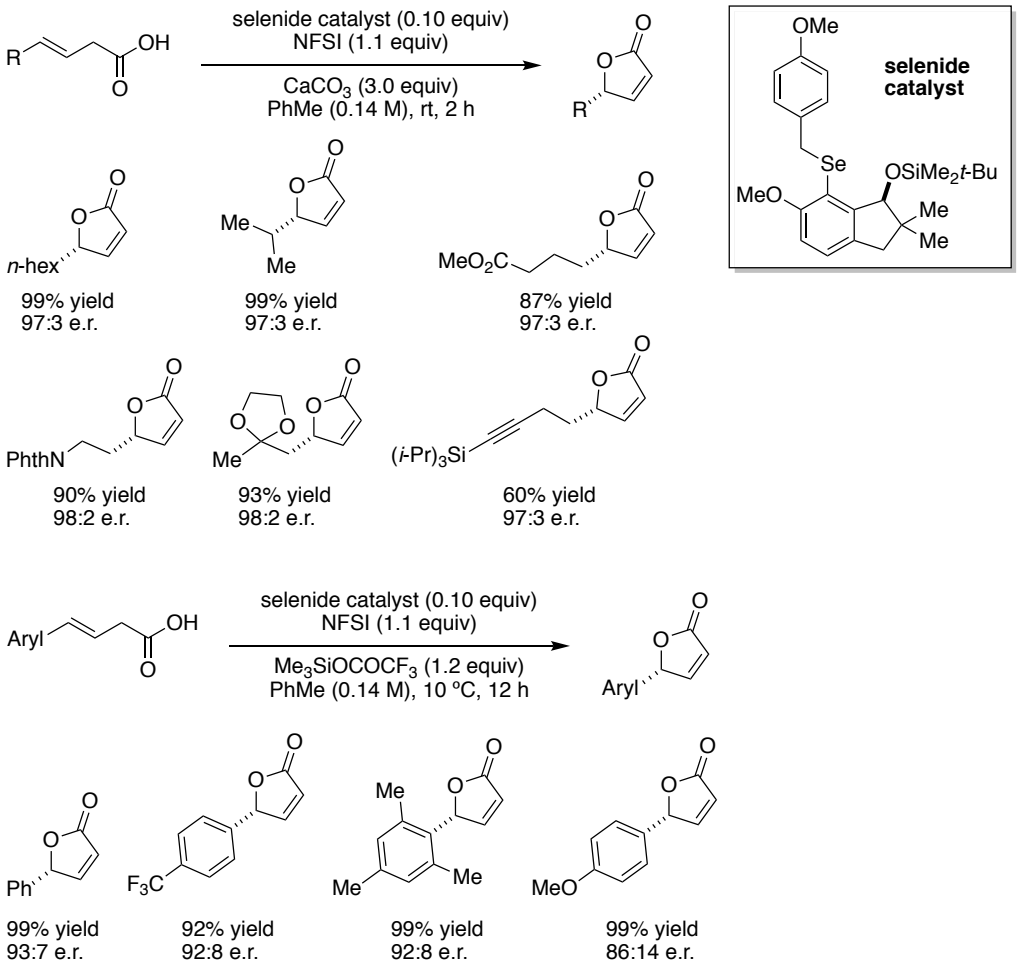
The catalytic, intramolecular oxyselenenylation-deselenenylation reaction is more limited in unique approaches but is also the method with the highest enantioselectivities within the class. Tiecco and coworkers, in conjunction with their development of the catalytic etherification process, disclosed a single selenolactonization-deselenenylation reaction (Scheme 1.41a).[5b] Wirth and coworkers likewise evaluated several chiral, enantioenriched diselenide catalysts in their PIFA-mediated system (Scheme 1.41b).[59a]



Scheme 1.41. (a) Asymmetric lactonization with a sulfur-containing diselenide. (b) Asymmetric lactonizations with PIFA as the stoichiometric oxidant.

More recently, Maruoka and coworkers have also disclosed an enantioselective selenolactonization-deselenenylation of 3-alkenoic acids (Scheme 1.42).[82] This reaction qualifies as the first general and highly enantioselective transformation within the class of organoselenium redox-catalysis. The catalyst design centers on the assumption that intermolecular chalcogen-bonding interactions fail to rigidify the typical electrophilic arylselenium structures at room temperature. A range of rigidified bicyclic catalysts were prepared and evaluated based on this premise, with the greatest selectivities obtained with a *tert*-butyldimethylsilyl ether on the stereocenter adjacent to selenium. The 4-methoxybenzyl group on selenium is likely displaced after initial oxidation. The selection of stoichiometric oxidant, base, and solvent are similar to those previously employed by the Zhao and Breder groups.[53, 65-68, 73, 83] Yields and enantiomeric

ratios are excellent for the *trans*-1,2-dialkyl olefins evaluated, while *trans*-1,2-aryl-alkyl olefins require modification of the stoichiometric base and reaction temperature for improved yield and enantioselectivity The authors speculate the trimethylsilyl trifluoroacetate serves to exchange the catalyst counterion, initially fluoride, for trifluoroacetate. The trifluoroacetate anion could be serving as a mild base, aiding in deselenenylation, recruited to close proximity by ion pairing to the cationic Se(IV) intermediate.



Scheme 1.42. The catalytic, enantioselective selenolactonization-elimination of alkenoic acids.

1.6. Conclusions and Outlook.

The use of chiral, enantioenriched selenium electrophiles for alkene selenofunctionalization could be considered a mature field at present, as most classes of alkenes can be functionalized in very good diastereoselectivity with proper choice of organoselenium reagent. Some limitations still remain in terms of the synthetic accessibility of the more selective

reagents, particularly in the chemical transformations required to install the selenium atom. The synthetic overhead associated with the preparation of these reagents and the poor atom economy associated with their stoichiometric use account for their limited utility. Structurally simple, readily available, and, potentially, recyclable reagents that are general for a wide variety of applications could rejuvenate interest in this area.

Electrophilic organoselenium catalysis has enjoyed increased interest in the last several years but continues to lag behind applications of organoselenium reagents in Lewis base and peroxide-mediated catalysis. Major limitations currently lie in the extension of the method to alkene difunctionalizations, as distinguished from the allylic functionalizations that continue to enjoy steady development. The primary challenge associated with this limitation lies in the acceleration of the rate of nucleophilic displacement of Se(IV) relative to eliminative deselenenylation.

The development of a catalytic, enantioselective method is subject to additional hurdles, owing primarily to the inverse relationship between reactivity and selectivity in reactions mediated by many chiral, enantioenriched organoselenium reagents. The conditions that afford high diastereoselectivities in transformations that employ stoichiometric amounts of organoselenium electrophile often afford catalytic reaction rates that are exceedingly slow. Novel organoselenium electrophiles must be developed with the objective of obtaining good enantioselectivities at the higher temperatures necessary for reasonable reaction rates or accelerating the rate of reaction at lower temperatures.

1.7. References.

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Chapter 2: Organoselenium Catalyzed, Enantioselective *syn*-Dichlorination of Alkenes*

2.1. Introduction and Prior Art.

The dihalogenation of alkenes has been a well-known synthetic organic transformation for more than a century. The treatment of carbon–carbon double bonds with halogens to afford vicinal, *anti*-dihalides is taught in the first weeks of every introductory organic chemistry course and is undoubtedly familiar to every organic chemist. The broad recognition of the reaction is attributable to its generality for most electron-neutral to -rich alkenes and its predictable diastereoselectivity for the *anti*-dihalide. The relative configuration of these vicinally dihalogenated products and the mechanistic explanation for the excellent diastereoselectivities obtained were hotly debated in the early 1900s.[1] The initial formation and intermediacy of haliranium ions and the stereochemical course of ring opening through an invertive displacement eventually became widely accepted. The existence of haliranium ions was supported with NMR spectroscopic evidence by the independent generation of chloriranium and bromiranium hexafluoroantimonates by Olah and coworkers, and later, with crystallographic evidence by X-ray diffraction of sterically hindered, isolable bromiranium tribromides and iodiranium trifluoromethanesulfonates by Brown and coworkers.[2]

Despite the modern wealth of mechanistic understanding in the dihalogenation of olefins, and the consistent diastereoselectivities therein obtained, there are only a limited few methods available for the enantioselective, vicinal dihalogenation of alkenes. This fundamental absence in the synthetic organic chemist's toolkit is surprising considering the many methods available for the enantioselective difunctionalization of alkenes that have been developed within the last 50 years, including but not limited to epoxidation,[3] dihydroxylation,[4] hydrogenation,[5] and intramolecular halofunctionalization.[6] In fact, the current state-of-the-art methods for enantioselective dihalogenation can be regarded as extensions of these epoxidation and dihydroxylation methods, perhaps reflecting the *a priori* assumption in development of these

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methods that the enantioselective installation of halogens should obey similar rules of reactivity and selectivity to the installation of oxygen.

The increased interest in stereoselective halogenation in recent years has largely been driven by the isolation and structural identification of a variety of polyhalogenated marine natural products, comprised in part by the chlorosulfolipids (Figure 2.1.).[7] These compounds are isolated in minute quantities from freshwater algae and saltwater mussels and are otherwise difficult to access in large quantities through traditional approaches in organic synthesis. Thus, comparatively little is known about their biological activity relative to many other marine or lipid natural products. An enantioselective approach to the dihalogenation of alkenes would enable rapid access to these natural products and their derivatives and would better enable study of the structure-activity relationships presented in their biological activity.

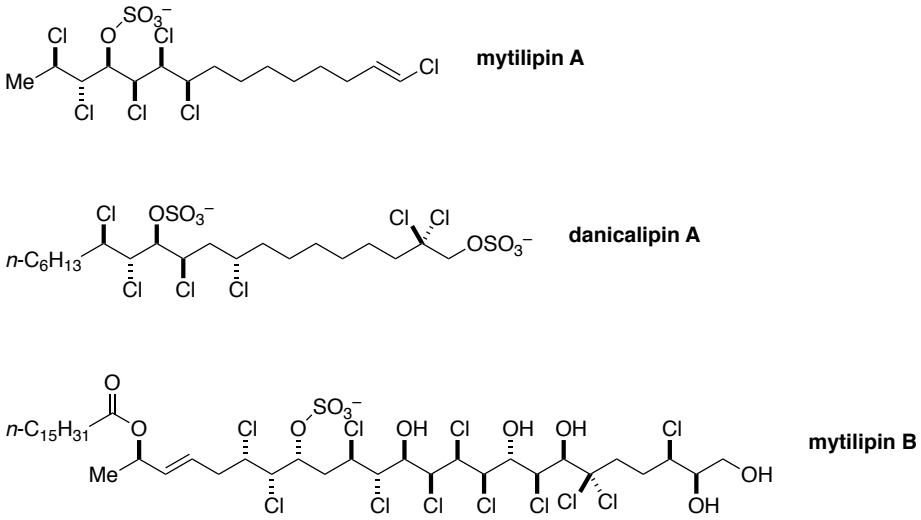
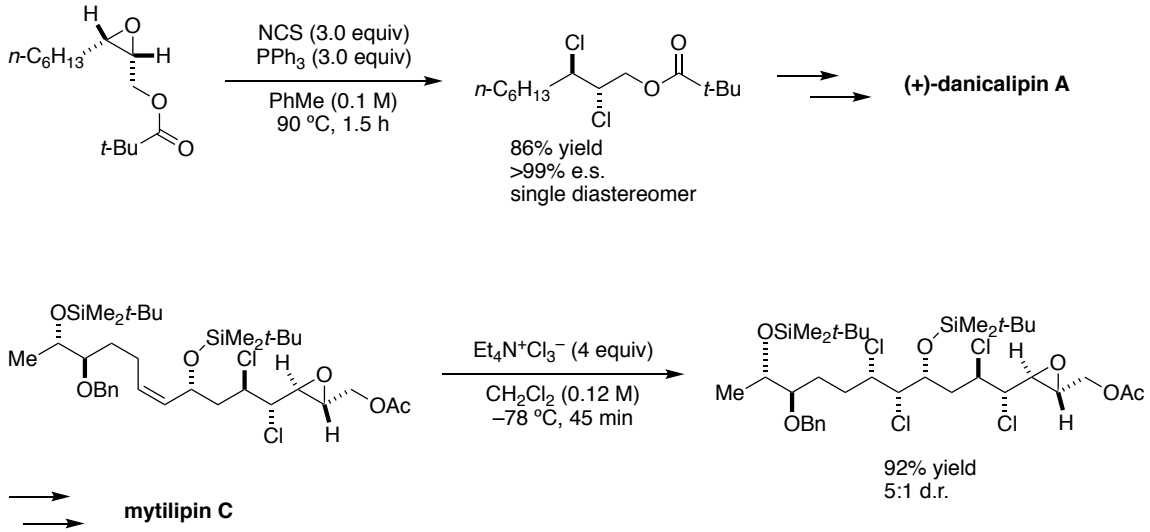


Figure 2.1. The chlorosulfolipids, a class of polyhalogenated natural products.

Current synthetic approaches to the chlorosulfolipids involve the diastereo- and enantioselective generation of oxygenated stereocenters through conventional means of enantioselective oxidation (e.g. dihydroxylation and epoxidation) and reduction (e.g. hydrogenation of ketones). These stereodefined epoxides and alcohols are then either activated and displaced stereospecifically to afford chlorohydrins or dichlorides, or are employed as directing groups for the diastereoselective dichlorination of adjacent alkenes (Scheme 2.1.).[7c, 8] These synthetic methods have enabled the successful total syntheses of several natural products within the class, however the multiple synthetic steps required for the stereoselective

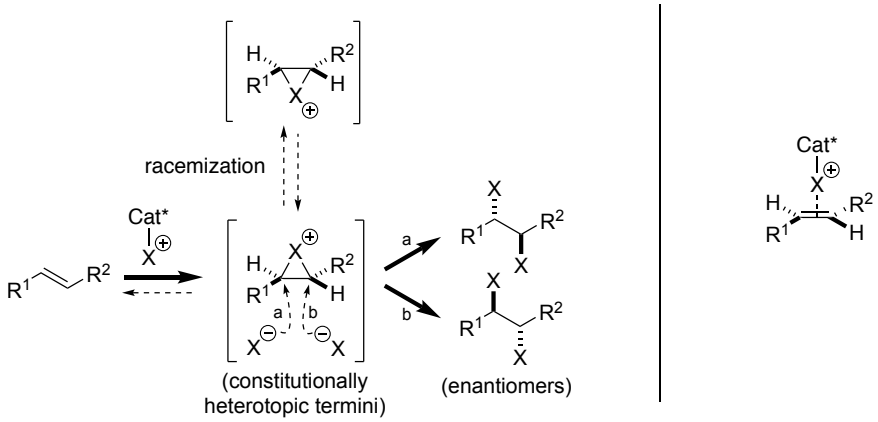
transformation of an alkene into a vicinal dichloride illustrate the potential of a direct and general enantioselective dichlorination of alkenes.



Scheme 2.1. Selected diastereospecific and -selective approaches to the total synthesis of chlorosulfolipids.

Multiple methods have been designed to follow this potential synthetic shortcut, all of which have relied on halenium ion delivery to the alkene to form a haliranium ion. The haliranium ion is then opened by nucleophilic attack of a halide ion to afford the dihalide in an overall antarafacial manner. Several hurdles are present in the design of an alkene dihalogenation following this approach (Scheme 2.2.).[9] The general schematic for these transformations features a chiral catalyst (**Cat***), associated to the electrophilic halogen source ($\mathbf{X}^+$) by hydrogen bonding, Lewis base donation of a nonbonding electron pair, and/or ion pairing interactions. The enantiofacial selectivity of halenium ion delivery results from preorganization of the alkene relative to the steric and electronic features of the **Cat***–$\mathbf{X}^+$ complex in the transition state. The magnitude of this interaction may be attenuated by the stereoelectronic requirement of overlap between the alkene π-orbital and the **Cat***–**X** σ* orbital, orienting the most significant steric effects far away from the alkene, axially opposite the halenium ion being delivered (Scheme 2.2., right). The newly formed haliranium ion undergoes nucleophilic attack by halide ($\mathbf{X}^-$), selectively at one of the two carbons, to afford the enantioenriched vicinal *anti*-dihalide product. For high enantioselectivity to be achieved in this manifold, assuming that haliranium ion formation is enantiodetermining, halenium ion transfer to the alkene must be irreversible and the haliranium

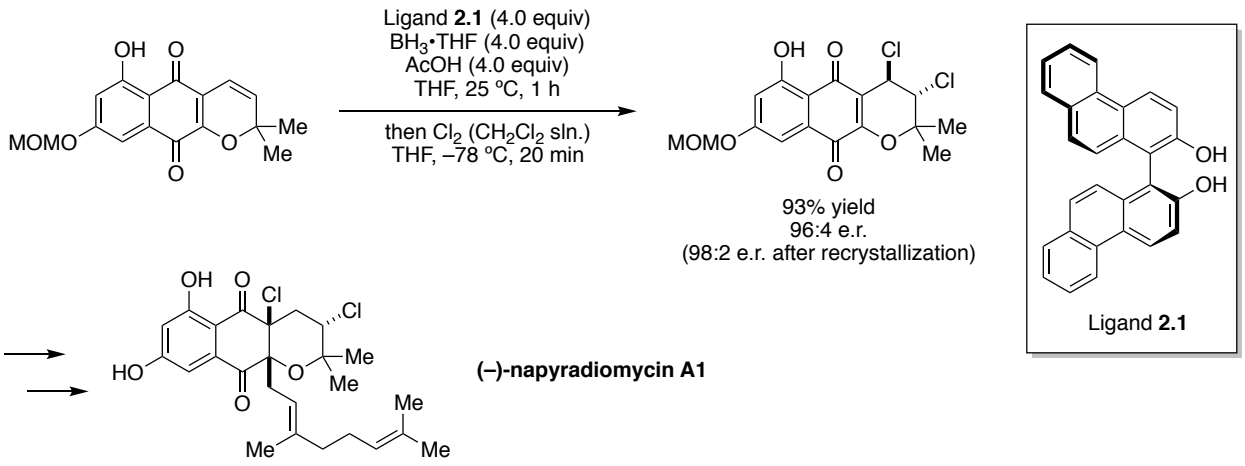
ion must be configurationally stable. Furthermore, the nucleophilic ring-opening of the haliranium ion must be biased toward one of the two carbons, as unselective ring opening affords a mixture of enantiomers. *Consequently, both haliranium ion formation and capture must be highly selective to afford highly enantioenriched vicinal dihalide products*.



Scheme 2.2. Symmetry analysis of the stereochemical transformations in a hypothetical enantioselective, vicinal, *antarafacial* dihalogenation. The theoretical enantiodetermining steps are highlighted with bold arrows. **Cat*** = chiral catalyst, **X** = halogen.

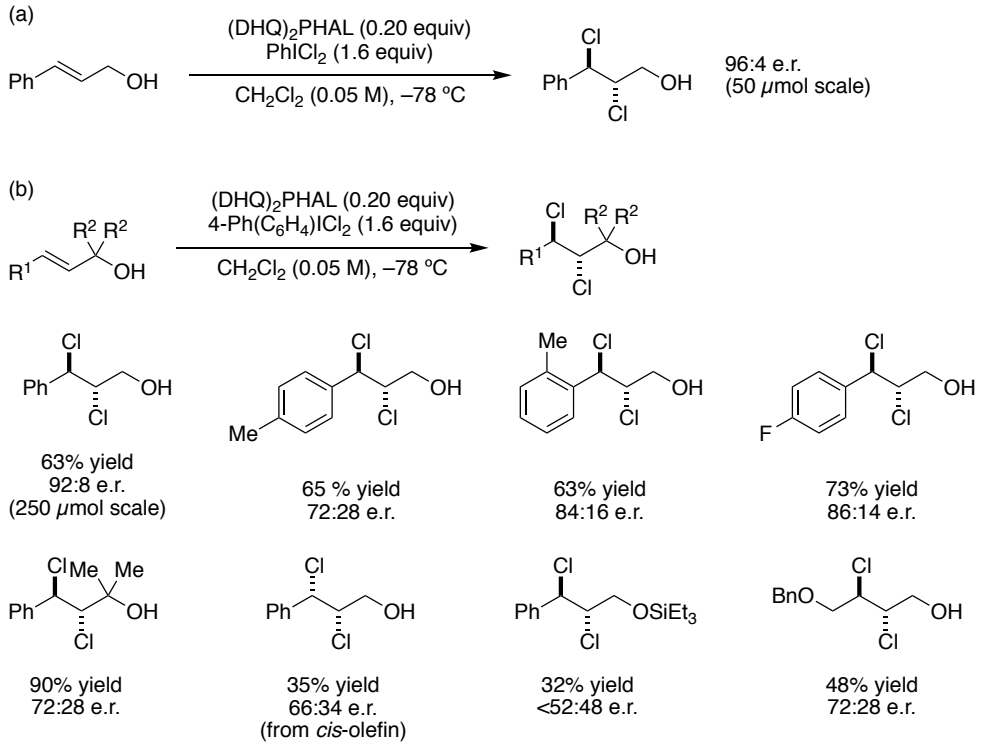
Despite these potential pitfalls to the development of enantioselective *anti*-dihalogenation methods, several approaches to the catalytic, enantioselective dichlorination of alkenes involving intermediate chloriranium ion formation have been developed.[10]

The first reagent-controlled, enantioselective dichlorination of a prochiral alkene, developed by Snyder and coworkers, is in fact not catalytic but merits inclusion. The method instead involves the pre-complexation of a superstoichiometric, chiral, enantioenriched BINOL-borate (generated *in-situ* by treatment of diol **2.1** with BH_3•THF and acetic acid) to a prenylated derivative of flaviolin, followed by low-temperature treatment of the complex with Cl_2 (Scheme 2.3.).[11] The dichloride product is obtained in good yield and enantiomeric ratio, which is further improved after recrystallization, and could be carried forward to complete the total synthesis of (–)-napyradiomycin A1. The authors propose a stereochemical model wherein the BINOL ligand blocks one face of the prochiral alkene, restricting the approach of Cl_2 to the less hindered face. This reaction is, however, only effective for the sole substrate and there has not since been any expansion in scope.



Scheme 2.3. Enantioselective dichlorination in the total synthesis of (–)-napyradiomycin A1.

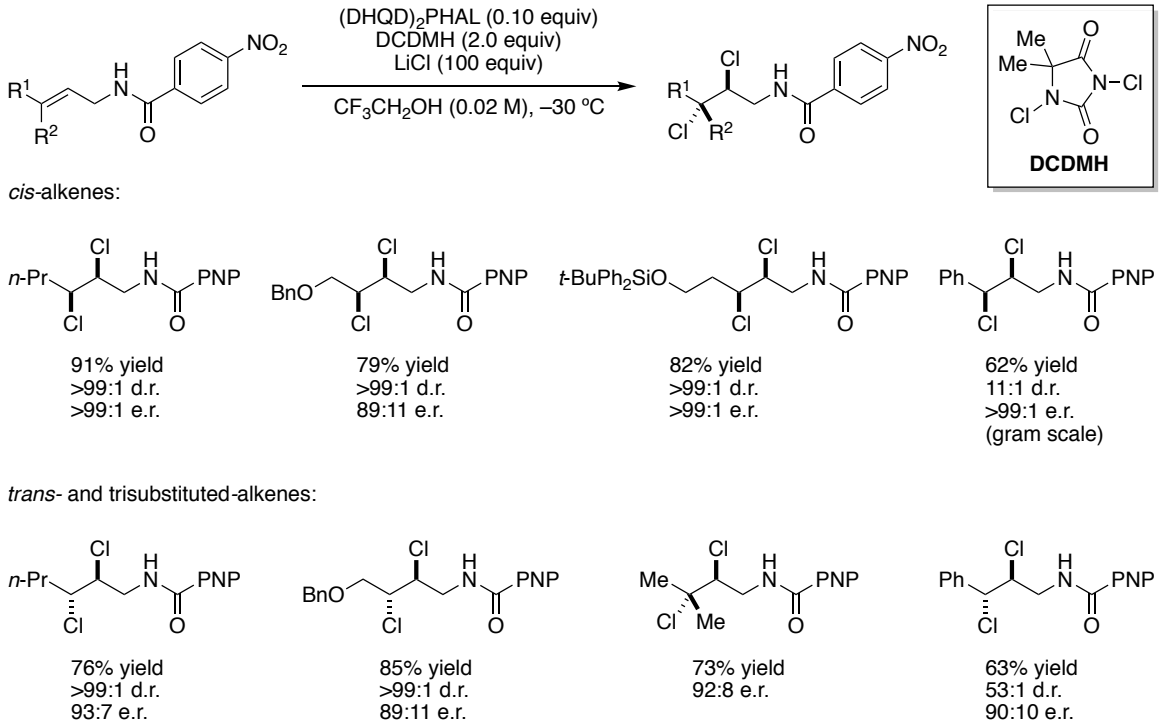
Nicolaou and coworkers are credited with the first *catalytic*, enantioselective dichlorination of alkenes. The authors screened Lewis base catalysts based on the observation that they accelerate the electrophilic halogenation of alkenes.[12] Iodobenzene dichloride ($PhICl_2$), paired with the phthalazine-dihydroquinine ligand $(DHQ)_2PHAL$ (originally employed in the catalytic, enantioselective dihydroxylation of alkenes)[4] are used based on the optimal enantiomeric ratios they afford with cinnamyl alcohol (Scheme 2.4a).[10a] The authors note that commercially available $PhICl_2$ solutions, or $PhICl_2$ generated from iodobenzene in sodium hypochlorite (NaOCl) solution, give dichloride products in reduced yield and selectivity. Only the reagent prepared from iodobenzene and Cl_2 is of the necessary quality to achieve good enantioselectivities. Furthermore, exchanging $PhICl_2$ for the biphenyl analogue (4-Ph-$(C_6H_4)ICl_2$), likewise prepared with Cl_2, results in a slight increase in the enantiomeric ratios of the dichloride products (Scheme 2.4b.). The method is limited to 3-arylprop-2-en-1-ols (cinnamyl alcohols) and affords good enantioselectivities only for a select few within the class. The reaction of a cinnamyl alcohol derivative protected with a triethylsilyl group (Et_3Si–) results in a reduced yield of nearly racemic product, while substituting the phenyl ring on the olefin for an alkyl group results in significantly reduced enantioselectivity. The authors propose that the alcohol is involved in a hydrogen bonding interaction with the catalyst that helps organize the transition state of chloriranium ion formation. The benzene ring, on the other hand, is necessary to bias nucleophilic chloriranium ion opening to the benzylic carbon through the increased stabilization of positive charge at that position.



Scheme 2.4. (a) The cinchona alkaloid catalyzed enantioselective dichlorination of cinnamyl alcohol with $PhICl_2$. (b) The scope of the enantioselective dichlorination of cinnamyl alcohols.

Borhan and coworkers have adapted this method to the dichlorination of electron-deficient allylic amides (Scheme 2.5.).[10b] Several modifications to the reaction conditions afford significantly improved yields and enantioselectivities – dichlorodimethylhydantoin (DCDMH) and lithium chloride now serve as electrophilic and nucleophilic chlorine sources, respectively, in the reaction solvent 2,2,2-trifluoroethanol (TFE). Furthermore, substitution of the cinnamyl alcohol substrate class for allylic amides allows for a broader and more versatile substrate scope. One functional group now serves both roles of: (1) hydrogen bonding to the Lewis base catalyst to control the enantiofacial selectivity of chloriranium ion formation and (2) biasing chloriranium opening by inductively stabilizing positive charge on the carbon proximal to the amide nitrogen. This effect is apparent in the lower enantiomeric and diastereomeric ratios obtained with 3-aryl, 4-benzlyoxy, and 3,3-dialkyl (trisubstituted) alkene substrates that result in stabilization of positive charge at both termini of the chloriranium ion intermediate. Notably, *Z*-olefins afford dichloride products with higher enantioselectivites than *E*-olefins, contrary to the method of Nicolaou *et al*. An electron poor amide and a large excess of LiCl are essential for good yields, as otherwise

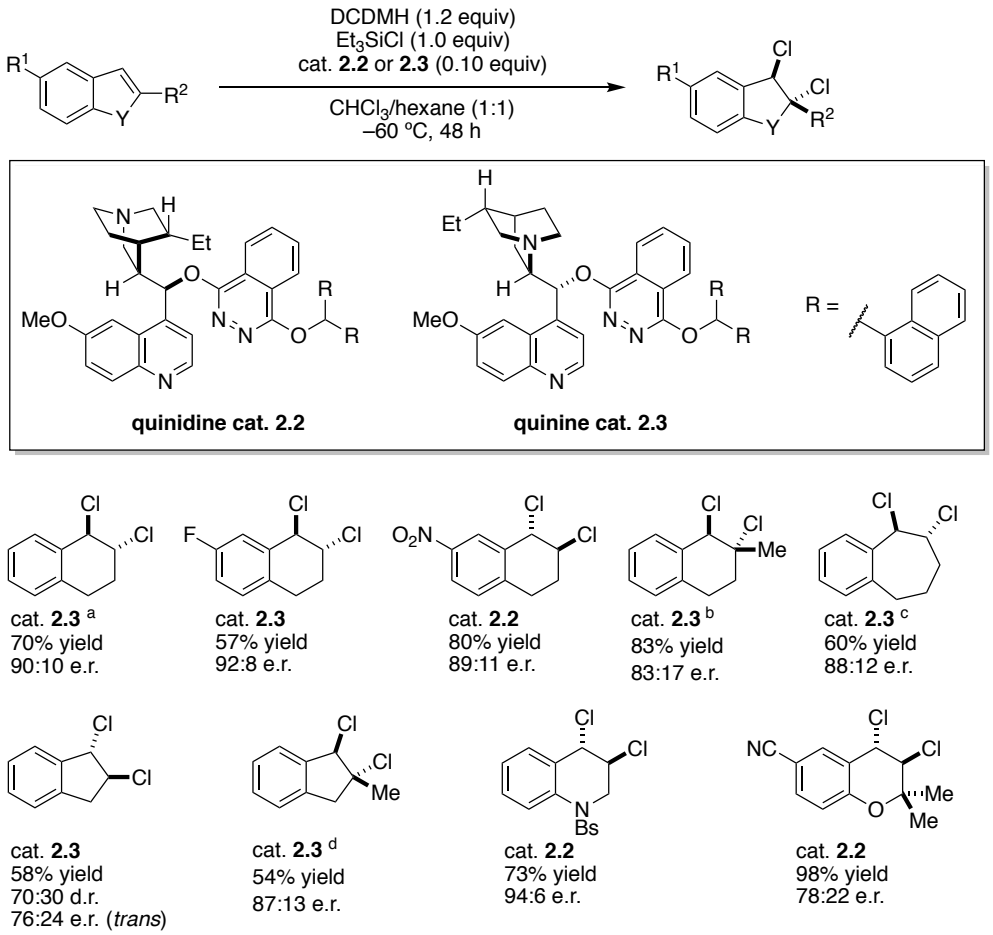
intermolecular capture by solvent to form the *O*-1-(2,2,2-trifluoroethyl) chlorohydrin or intramolecular capture by the amide to form oxazoline become competitive. The authors suggest the reaction occurs at the solid LiCl – liquid interface, based on studies on the influences of stir rate, LiCl solubility, and LiCl particle size.



Scheme 2.5. The cinchona alkaloid catalyzed enantioselective dichlorination of allylic amides.

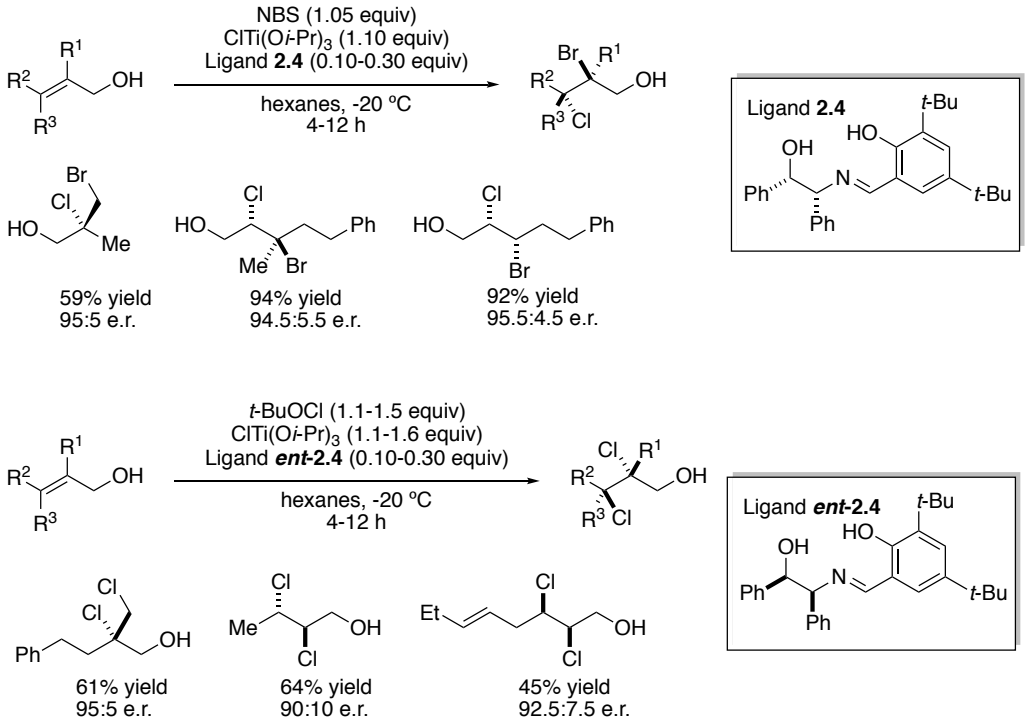
Most recently, Hennecke and coworkers further refined these dichlorination conditions for the dichlorination of dihydronaphthalenes and indenes without hydrogen-bond-donor directing groups (Scheme 2.6.).[13] Unsymmetrical phthalazine-dihydroquinine and -dihydroquinidine catalysts **2.2** and **2.3**, previously employed by Hennecke *et al*. in highly selective chlorocyclization reactions,[14] were selected for evaluation in the dichlorination reaction. The reactions are run in hexanes/chloroform, with chlorotriethylsilane (TES–Cl) as a soluble source of nucleophilic chloride. Yields and enantiomeric ratios are moderate to good for electron-neutral and -deficient dihydronaphthalenes, but generally poor for indenes, benzocycloheptenes, and trisubstituted alkenes. Acyclic *Z*-alkenes afford dichloride products in low yields, diastereomeric ratios, and enantiomeric ratios, whereas *E*-β-methylstyrene affords the racemic dichloride in high yield and a nearly 1:1 diastereomeric ratio. Interestingly, the diastereomeric catalysts **2** and **3** afford products

of similar enantiomeric ratio (with opposite absolute configuration, of course) but with substantially different yields.



Scheme 2.6. Cinchona alkaloid catalyzed enantioselective dichlorination of alkenes without directing groups. [a] Yield and e.r. with cat. **2.2** are 87% and 89:11, respectively. [b] Yield and e.r. with cat. **2.2** are 53% and 80:20, respectively. [c] Yield and e.r. with cat. **2.2** are 50% and 89:11, respectively. [d] Yield and e.r. with cat. **2.2** are 85% and 79:21, respectively.

The most general method for enantioselective dihalogenation, developed by Burns and coworkers, requires allylic alcohol substrates but is much more general for *E*-, *Z*-, di-, and trisubstituted alkenes. This method differs from the others, no longer requiring cinchona alkaloid catalysts, but instead involving stoichiometric quantities of a trialkoxytitanium(IV) halide and a halenium source (*t*-BuOCl or NBS), and a catalytic amount of a Salen-type ligand **2.4**. The method similarly affords *anti*-dihalide products through a haliranium ion intermediate, however the yields and selectivities are very good across a wide variety of alkene substitution. The scope and selectivity of the method rival the Sharpless asymmetric epoxidation (Scheme 2.7.).[10d, 10e]

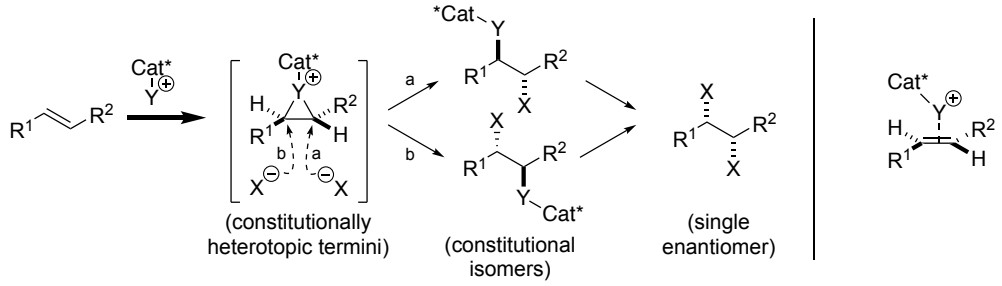


Scheme 2.7. Titanium Lewis acid-Lewis base catalyzed dihalogenation of alkenes.

Like the methods discussed above, this transformation is suggested to operate within a similar manifold of Lewis base (or ligand accelerated) catalysis. Judicious selection of halenium ion source, solvent, and temperature gives conditions that require the allylic alcohol be coordinated to a titanium center ligated by **2.4** before the haliranium ion can form (little to no background reaction is observed when **2.4** is omitted). The scope of this dihalogenation is limited by the requirement for an allylic alcohol to direct halenium and halide addition to the double bond. While this structural requirement can be leveraged to selectively dihalogenate allylic alcohols in the presence of isolated alkenes, or to selectively deliver disparate halogens to either end of the alkene, it highlights the need to overcome unselective haliranium ion opening by tethering the halide, relatively tightly bound to titanium, to the alcohol.

In contrast to these antarafacial vicinal dihalogenations, suprafacial dihalogenations converge to a single diastereomer. There are a variety of approaches to suprafacial vicinal dihalogenation, the earliest of which involved the use of high-oxidation state, pentavalent metal halides.[15] A milder, alternative approach could instead proceed through an intermediate non-halo *–iranium* ion (Scheme 2.8.). In this hypothetical transformation, an electrophilic catalyst **Cat*–Y**$^+$ reacts with an alkene with high enantiofacial selectivity to form an enantioenriched *–iranium* ion

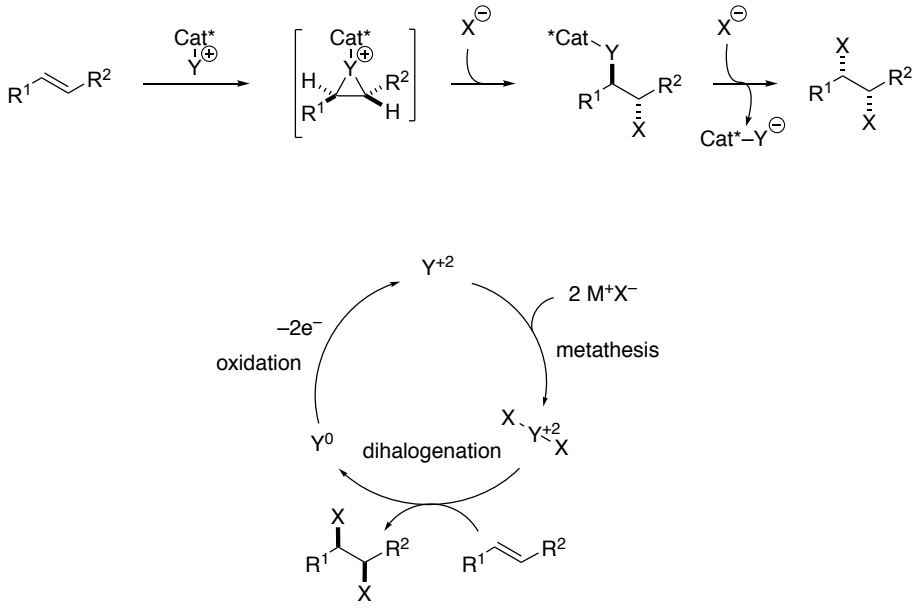
intermediate, which is opened by the halide nucleophile $\mathbf{X}^-$ at either constitutionally heterotopic carbon. The mixture of constitutional isomers afforded by this (potentially) unselective ring-opening then converges to a single product after nucleophilic displacement of $\mathbf{Cat^*–Y}^-$ (now in reduced form) by a second equivalent of $\mathbf{X}^-$. Thus, the only requirements for a selective process are now the irreversible formation of the *–iranium* ion.



Scheme 2.8. Symmetry analysis of the stereochemical transformations in a hypothetical enantioselective, vicinal, *suprafacial* dihalogenation. The theoretical enantiodetermining step is highlighted with a bold arrow. **Cat*** = chiral catalyst (or ligand), **X** = halogen.

Additionally, this hypothetical approach is distinguished by the presence of the chiral, enantioenriched catalyst backbone **Cat*** in the covalently-bound *–iranium* ion and ring-opened intermediates, as **Y** is, unlike **X** in Scheme 2.2., an atom with valence greater than 1. This higher valence also allows for greater variety in the transition state geometry of *–iranium* ion formation (Scheme 2.8, right) and the portion of the catalyst bearing features that convey stereochemical information can be brought into closer proximity to the olefin than in the necessarily linear **Cat*–X–alkene** complex (Scheme 2.2., right).

The avenue by which the two halogen atoms are incorporated into the product is also unique compared to antarafacial dihalogenation, as both are introduced as halide anions. The second equivalent of halide displaces **Cat–Y*** from the product and results in its net reduction to the formally anionic $\mathbf{Cat^*–Y}^-$ (Scheme 2.9). The reduced form of the catalyst must be independently re-oxidized for the catalytic cycle to turn over, which contrasts with the requirement of separate halide and halenium ion sources for vicinal, antarafacial dihalogenation. This type of transformation could be categorized in the larger group of "group-transfer catalysis,"[16] but can be more precisely referred to as "redox-catalysis."



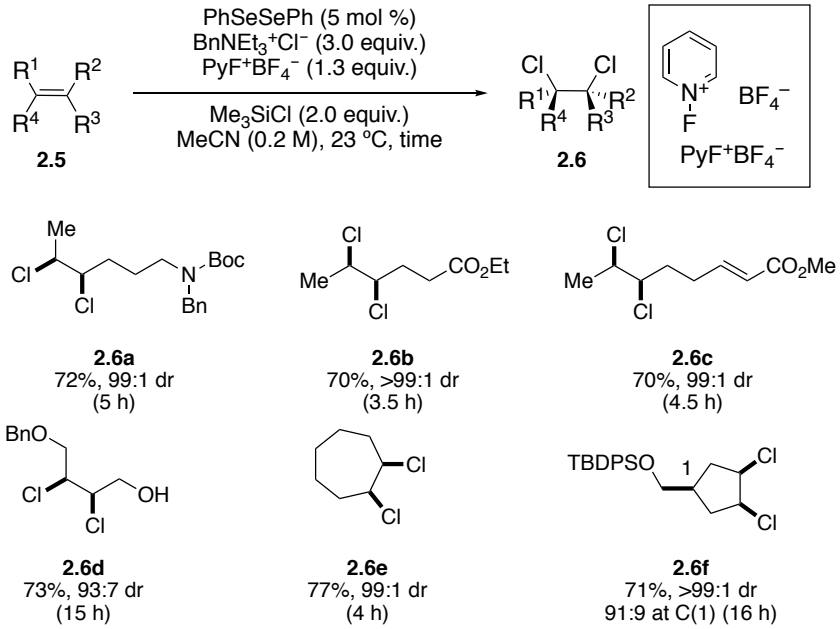
Scheme 2.9. The net transformation for suprafacial dihalogenation and the redox catalytic cycle. **Y** = transition metal or main group element; oxidation states are relative, not absolute.

The structural limitations to the scope of enantioselective, vicinal, *antarafacial* dichlorination reactions could be overcome through the use of a suprafacial dichlorination wherein the alkene need not be electronically or sterically biased toward one terminus. In the specific case of a catalytic, enantioselective *syn*-dichlorination proceeding through an alternative *–iranium* ion, and provided that the *–iranium* ion formation is irreversible, then formation of that intermediate alone would be stereodetermining. The ring-opening by nucleophilic halide would be inconsequential to the final enantiomeric ratio, thereby simplifying the challenge of the simultaneous installation of adjacent, halogenated stereocenters.

2.2. Background.

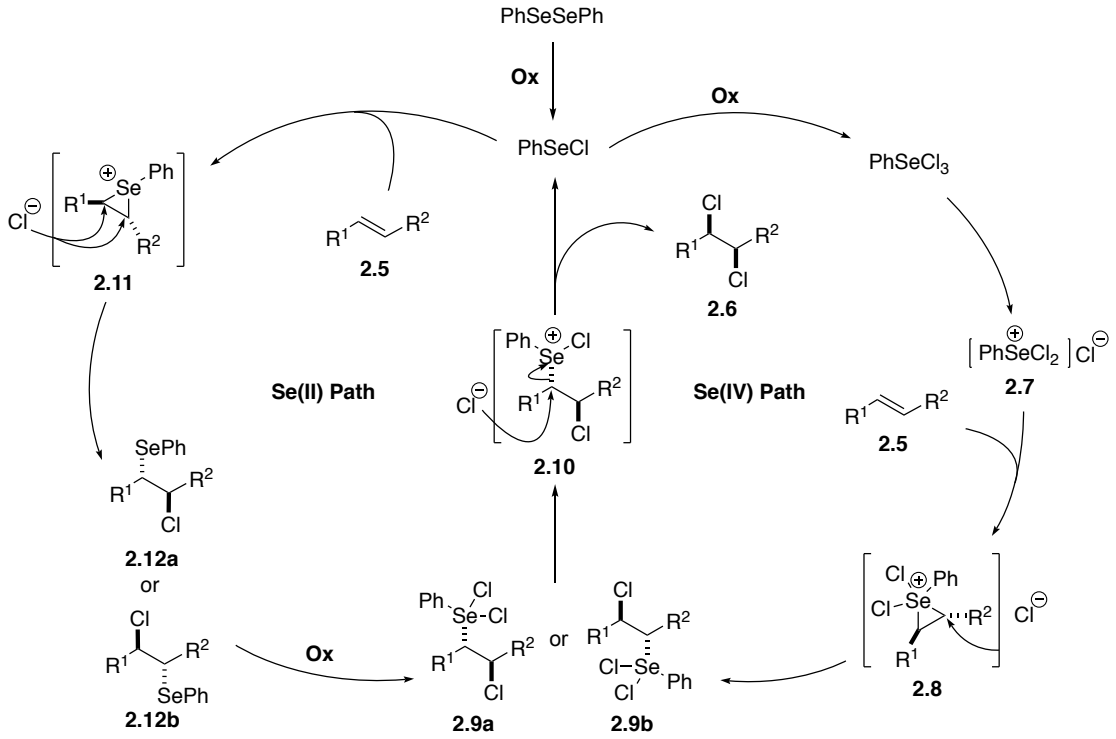
Toward that end, as a prelude to the development of an enantioselective, vicinal, *suprafracial* dihalogenation, previous studies in these laboratories established the stereospecific *syn*-dichlorination of alkenes using electrophilic organoselenium redox-catalysis (Scheme 2.10.). With diphenyl diselenide (PhSeSePh) as the precatalyst, benzyltriethylammonium chloride ($BnNEt_3^+Cl^-$) as the source of chloride anion, *N*-fluoropyridinium tetrafluoroborate ($PyF^+BF_4^-$) as the oxidant, and chlorotrimethylsilane (Me_3SiCl) as a fluoride scavenger, vicinal, *syn*-dichlorides were obtained in good yields and diastereomeric ratios from a range of mono- and (*E*- and *Z*-)

disubstituted alkenes. The reaction shows good tolerance for a variety of functional groups, affording good yields even in the presence of adjacent nucleophilic groups that might be expected to participate in anchimeric assistance (**2.6b** and **2.6d**). Electron deficient alkenes are left untouched (**2.6c**), and excellent diastereomeric ratios are obtained in reactions with chiral alkenes (**2.6f**). A variety of alternative diselenide catalysts were evaluated, in addition to Lewis basic additives, intended to accelerate the rate of deselenenylation. Electron-poor and sterically encumbered diselenides result in the formation of *anti*-dichloride as a result of background oxidation of chloride by the oxidant, while electron-rich diselenides afford slight improvements to reaction rate and yield. The major byproducts of the transformation are allylic and vinylic chlorides, produced by eliminative deselenenylation outcompeting nucleophilic displacement.



Scheme 2.10. The stereospecific *syn*-dichlorination of alkenes and representative scope. Diastereomeric ratios refer to the ratio of *syn*/*anti*-dichloride.

The mechanism and catalytic cycle proposed for the transformation are based on the understanding of the individual elementary steps, all of which are established, stoichiometric transformations (Scheme 2.11.).[17] In particular, that diphenyl diselenide is oxidized with three equivalents of chlorine (or sulfuryl chloride) to phenylselenium(IV) trichloride, phenylselenium(IV) trichloride reacts with alkenes to give β-chloroalkyl phenylselenium(IV) dichlorides, and phenylselenium(IV) dichloride can be displaced by exogeneous chloride to afford *syn*-dichlorides (cf. Chapter 1, Schemes 1.2., 1.9., and 1.10.).



Scheme 2.11. The mechanistic hypothesis for the stereospecific *syn*-dichlorination of alkenes. **Ox** = $BnNEt_3^+Cl^-$ + $PyF^+BF_4^-$ + Me_3SiCl.

At reaction onset, diphenyl diselenide is oxidized by one equivalent each of $PyF^+BF_4^-$, $BnNEt_3^+Cl^-$, and Me_3SiCl to afford two equivalents of PhSeCl (as well as the byproducts pyridine, $BnNEt_3^+BF_4^-$, and Me_3SiF). In a typical reaction, alkene is not added until all other reaction components have been stirred for 10 min at room temperature, so the same oxidation process likely occurs once more to convert the PhSeCl to $PhSeCl_3$ (Scheme 2.11., Se(IV) path). Ionization of phenylselenium(IV) trichloride to the cationic dichloride **2.7** is likely necessary to provide an open valence for alkene association,[17b] which then allows for formation of the Se(IV) seleniranium ion **2.8**. This intermediate is subsequently opened antarafacially by chloride at either of the constitutionally heterotopic carbons to afford a mixture of constitutional isomers **2.9a** and **2.9b**. Ionization to the cationic β-chloroalkyl phenylselenium(IV) chloride **2.10** followed by stereospecific, nucleophilic displacement of selenium by chloride results in a convergence of the two constitutional isomers to a single vicinal *syn*-dichloride product **2.6** and regenerates phenylselenium(II) chloride.

The isomeric mixture of β-chloroalkyl phenylselenium(IV) dichlorides **2.9a** and **2.9b** is postulated to be the catalytic resting state on the basis of their presence in the ^1H NMR spectra of

incomplete reactions. The turnover-limiting step is therefore likely the ionization of this Se(IV) intermediate to the monochloride **2.10** and/or nucleophilic displacement of selenium by chloride to afford the *syn*-dichloride product **2.6** and PhSeCl.

The catalytic process beyond the first turnover need not proceed through oxidation of PhSeCl to $PhSeCl_3$, but could instead result from the direct reaction of PhSeCl with the alkene to form a Se(II) seleniranium ion **2.11** (Scheme 2.11., Se(II) path). Antarafacial ring-opening by chloride at the constitutionally heterotopic termini affords β-chloroalkyl phenyl selenides **2.12a** and **2.12b**. The isomeric mixture is then oxidized to the β-chloroalkyl phenylselenium(IV) dichlorides **2.9a** and **2.9b** and the two catalytic cycles converge. These two paths are indistinguishable by NMR analysis of incomplete reaction mixtures, as the apparent catalytic resting state lies at the convergence of the two. Indeed, the relative rates of selenium oxidation versus seleniranium ion formation may vary with the concentration of alkene and oxidant, both of which decrease as the reaction progresses.

Whereas PhSeCl is known to add reversibly to alkenes in the presence of other nucleophiles,[18] and $PhSeBr_3$ has been suggested to undergo reversible addition,[17b, 17d, 17e] the reversibility of the addition of $PhSeCl_3$ to alkenes is not well-established. The reversibility of electrophilic selenium(IV) addition to the alkene **2.5** to afford the resting state intermediate **2.9** would have important implications for the nature of the enantiodetermining step and would need to be taken into consideration when designing chiral catalysts and reaction conditions for the enantioselective transformation. Therefore, several mechanistic studies were performed to determine whether the transformation is, in fact, reversible (Figure 2.2.).

In separate experiments, the β-chloroalkyl phenylselenium(IV) dichloride obtained from *trans*-4-octene was either prepared *in-situ* by treatment of a trifluoroacetate precursor with HCl/TFA (as shown in Figure 2.2), or in a separate reaction and isolated. The chloroselenenylated adducts (generated *in-* or *ex-situ*) were then exposed to 2 equivalents of a second, structurally similar alkene, at room temperature in deuterochloroform, and followed by ^1H NMR spectroscopic analysis.

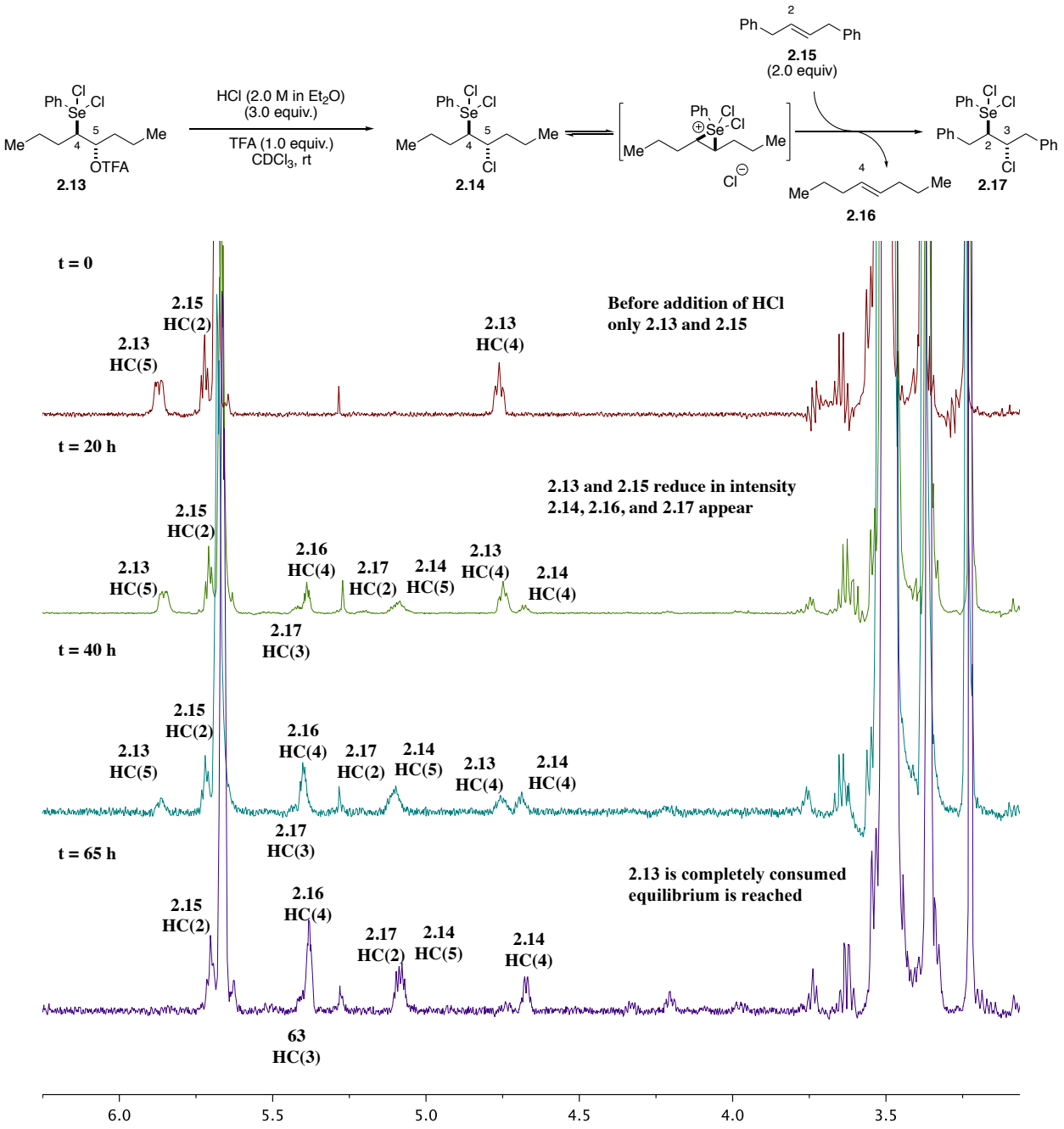
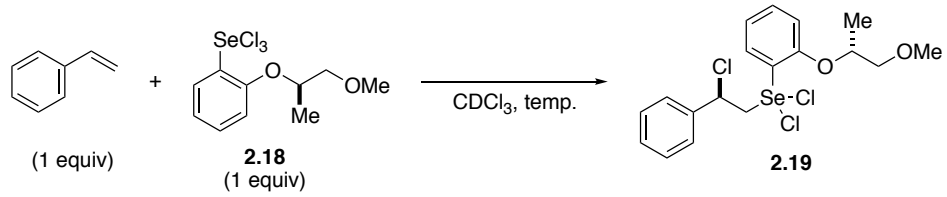


Figure 2.2. Scrambling of *in-situ* generated β-chloroalkyl phenylselenium(IV) dichloride with an exogeneous alkene, evidencing the reversibility of $PhSeCl_3$ addition to the alkene.

At t = 0 before the addition of hydrochloric and trifluoroacetic acid, only the trifluoroacetate **2.13** and 1,4-diphenyl-2-butene **2.15** are visible in the mixture. However, 20 h after the addition of acid, there is a clear increase in spectral complexity as multiple selenium adducts begin to appear. The intensities of these various signals change over the following 45 h until

equilibrium is reached. Comparison of the ^{1}H NMR spectrum of an independently prepared sample of **2.17** confirms its identity within the reaction mixture. The reverse reactions were also performed after generation of the β-chloroalkyl phenylselenium(IV) dichloride generated from 1,4-diphenyl-2-butene and subsequent exposure to *trans*-4-octene to ensure against any thermodynamic bias.

The effects of this reversibility were further explored in experiments with diastereomerically enriched products, obtained from the low-temperature addition of a chiral, enantioenriched Aryl*$SeCl_3$ to styrene (*vide infra*, structurally related selenium electrophiles afforded poor enantioselectivity in the catalytic reaction at room temperature) (Figure 2.3.).[19]



(1 equiv) **2.18** (1 equiv) **2.19**

temperature	**-65 ºC**	**0 ºC**
d.r.	86:14	72:28

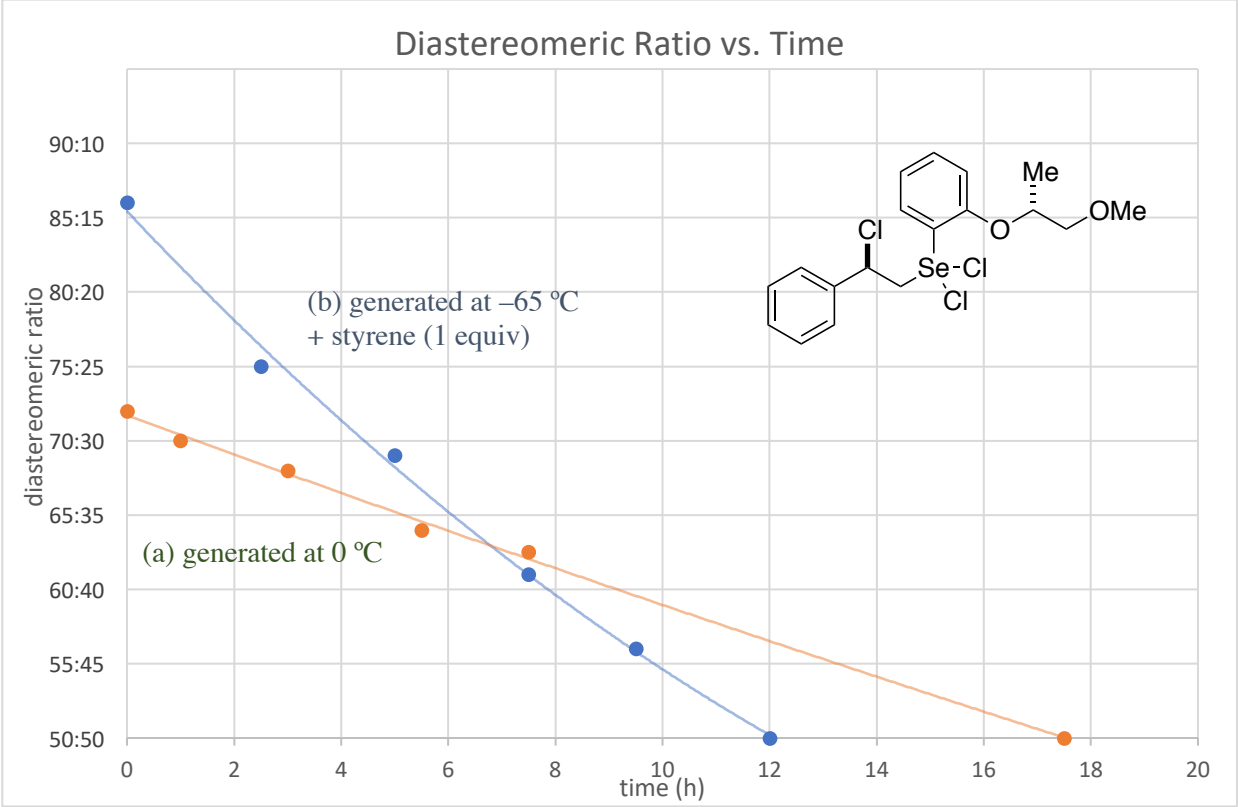


Figure 2.3. Room temperature diastereomeric erosion of Se(IV) adducts obtained at (a) 0 ºC and (b) –65 ºC with 1 equiv styrene.

Addition of styrene to the arylselenium(IV) trichloride **2.18** at –65 ºC and 0 ºC afforded adducts **2.19** in diastereomeric ratios of 86:14 and 72:28 (measured by ^{1}H NMR spectroscopy), respectively. The mixture generated at 0 ºC was warmed to room temperature and the diastereomeric ratio of the product was monitored over the following 18 h. In the absence of additional alkene, the d.r. of **2.19** decays in a nearly linear fashion to 50:50 within 17.5 h. The mixture generated at –65 ºC was exposed to an additional 1 equivalent of styrene and likewise warmed to room temperature. In the presence of this additional styrene, the rate of decay is significantly higher, reaching 50:50 within 12 h from a higher initial value. In the absence of additional styrene, it is possible that epimerization occurs through seleniranium reformation and unselective nucleophilic opening through a benzylic carbocation capable of free rotation. However, the accelerated rate of epimerization catalyzed by styrene corroborates the hypothesis that Aryl*$SeCl_3$ can reform from **2.19**, reversibly.

2.3. Research Objectives.

The research objectives for this project are the design and synthesis of chiral, enantioenriched diselenide precatalysts for the catalytic, enantioselective *syn*-dichlorination of alkenes, to afford dichloride products in good yields and enantiomeric ratios. Initial catalyst designs are founded in the wealth of diastereoselective transformations performed with these enantioenriched reagents in stoichiometric amounts (Table 1.1.) and informed by understanding of the mechanistic features of the catalytic dichlorination reaction that may lead to reduced yield or enantiomeric ratio. In particular: (1) the rate of the catalyzed reaction must be sufficiently fast to outcompete background oxidation of chloride (resulting in *anti*-dichloride product) and (2) the rate of the nucleophilic displacement of Se(IV) by chloride (the rate determining step) must be sufficiently fast to suppress epimerization of the resting state intermediate, if the enantioselectivity need be a consequence of enantiodetermining seleniranium ion formation.

2.4. Synthesis and Evaluation of Chiral, Enantioenriched Diselenides.

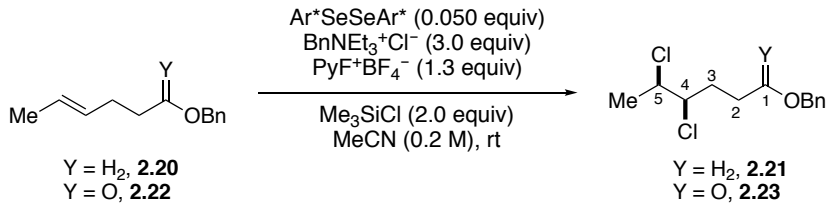
Orienting experiments for enantioselective dichlorination therefore began with the preparation of readily accessible chiral diselenides that also display high diastereoselectivities in selenofunctionalization reactions. Diselenide **2.24** (Table 1.1., entry 1) was selected first, as it could be prepared by well-described synthetic transformations in six steps from 2-

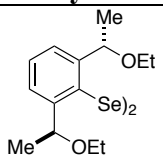
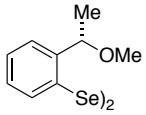
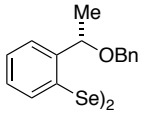
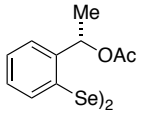
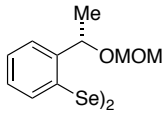
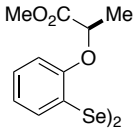
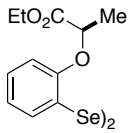
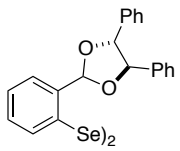
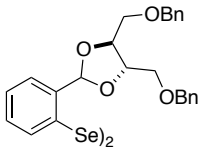
bromoisophthalic acid.[20] Preliminary *syn*-dichlorination reactions were performed with identical conditions to those used in the original, diphenyl diselenide-catalyzed transformation (Scheme 2.10.), with benzyl (*E*)-hex-4-enyl ether **2.20** as the alkene substrate. Benzyl (*E*)-4-hexenoate **2.22** eventually replaced the ether, as it could be accessed in fewer synthetic steps, its dichloride product **2.23** was simpler to purify chromatographically, and its enantiomers separated more cleanly on chiral stationary phase HPLC. Although diselenide **2.24** effected dichlorination much more slowly than diphenyl diselenide, and consequently a significant amount of *anti*-dichloride was obtained owing to background oxidation of chloride, the enantiomeric ratio of 61:39 for the *syn*-dichloride was an encouraging first result suggesting enantioselection was possible with chiral, enantioenriched diselenides (Table 2.1., entry 1).

Recognition that steric crowding around the selenium atom was likely contributing to the significant attenuation of the reaction rate motivated the investigation of diselenides with single substituents at the 2-position of the benzene ring. Thus, methyl ether **2.25**[21] (entry 2) gave substantially improved reactivity (and therefore diastereoselectivity), but with a decrease in enantioselectivity. Exchanging the methyl ether for the benzyl ether in **2.26** (entry 3) resulted in similar selectivity, while the acetate **2.27**[22] (entry 4) improved enantioselectivity with concomitant decrease in diastereoselectivity. Exchange for a methoxymethyl acetal in **2.28**[23] (entry 5) afforded nearly racemic product. Lactate ethers **2.29** and **2.30**[24] (entries 6 and 7) likewise afforded nearly racemic product, as did the acetals **2.31**[21b] and **2.32** (entries 8 and 9).[19]

It was readily apparent that the oxygen substituent in these particular catalyst geometries imparted relatively little influence on the enantioselectivity of the transformation. Finding a more selective catalyst would require examining more varied coordinating groups and catalyst geometries. Urea **2.33** was therefore selected for its alternative binding mode in which the carbonyl oxygen serves as the coordinating group to form a 7-membered ring. The dichloride products obtained with urea **2.33** and the structurally related pivalamide **2.34** (Table 2.2., entries 1 and 2) had enantiomeric ratios exceeding any of those obtained previously, with absolute configuration matching what was obtained with acetate **2.27**, suggesting a similar (carbonyl-coordinated) binding mode.

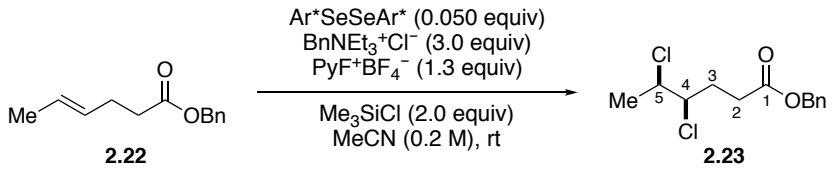
Table 2.1. *syn*-Dichlorination Selectivities with Catalysts Bearing Oxygen Coordinating Groups.



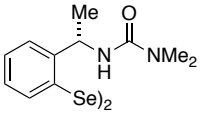
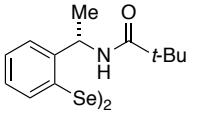
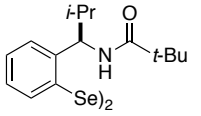
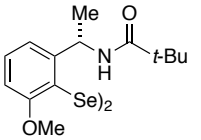
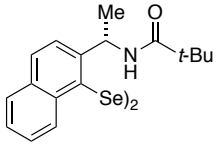
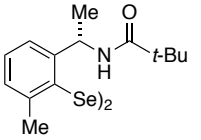
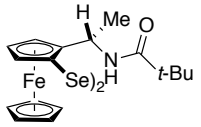
entry	catalyst		product; d.r. (*syn/anti*)[a]	e.r.[c]	configuration[b]
1		**2.24**	**2.21**; 30:70	61:39	*R,R*
2		**2.25**	**2.21**; >95:5 **2.23**; >95:5	54:46 54:46	*S,S* *S,S*
3		**2.26**	**2.21**; 90:10	55:45	*S,S*
4		**2.27**	**2.21**; 70:30	58:42	*R,R*
5		**2.28**	**2.21**; 90:10	50:50	--
6[d]		**2.29**	**2.21**; >95:5	<55:45	--
7[d]		**2.30**	**2.21**; 95:5	50:50	--
8[d]		**2.31**	**2.21**; >95:5	<55:45	--
9[d]		**2.32**	**2.21**; >95:5	<55:45	--

[a] The d.r. was determined by ^{1}H NMR integration of diagnostic signals at HC(4) and HC(5). [b] The absolute configuration of the major enantiomer was determined by elution order compared to dichloride of known configuration (for Y = O) or by analogy to the ester (for Y = H_2) [c] The e.r. was determined by chiral stationary phase HPLC. [d] Prepared and evaluated by S. T.-C. Eey.[19]

Table 2.2. *syn*-Dichlorination Selectivities with Catalysts Bearing Carbonyl Coordinating Groups.



2.22 **2.23**

entry	catalyst		2.23 d.r. (*syn/anti*)[a]	e.r.[c]	e.s.	configuration[b]
1		**2.33**	70:30	65:35	65:35	*R,R*
2		**2.34**	90:10	65:35	65:35	*R,R*
3		**2.35**	83:17	62:38	62:38	*S,S*
4		**2.36**[d]	95:5	58:42	59:41	*R,R*
5		**2.37**[e]	80:20	61:39	64:36	*R,R*
6		**2.38**[f, g]	80:20	73:27	74:26	*R,R*
7		**2.39**	>95:5	50:50	50:50	--

[a] The d.r. was determined by ^{1}H NMR integration of diagnostic signals at HC(4) and HC(5) (see Experimental). [b] The absolute configuration of the major enantiomer was determined by elution order compared to dichloride of known configuration. [c] The e.r. was determined by chiral stationary phase HPLC. [d] Prepared by O. Garry. The e.r. of the catalyst was 95:5. [e] Prepared by P. Ryabchuk. The e.r. of the catalyst was 90:10. [f] Prepared by P. Ryabchuk. The e.r. of the catalyst was 97:3. [g] Reaction with **(*Z*)-2.22** afforded predominately the *anti*-dichloride with a d.r. of 70:30 and an e.r. of 55:45.

Further examination involved structural modification to the pivalamide diselenide **2.34**. Exchange of the methyl group adjacent to the stereocenter for an isopropyl group (**2.35**) resulted in a decrease in both enantioselectivity and diastereoselectivity (entry 3). Substitution of the aromatic ring at the 6-position with a methoxy group or a benzene ring fusion (**2.36** and **2.37**) also resulted in a decrease in enantioselectivity (entries 4 and 5). Only placement of a methyl group at

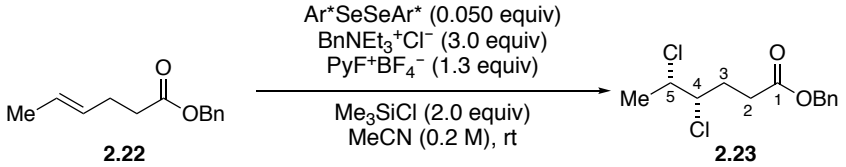
the 6-position in **2.38** resulted in an increase in enantioselectivity, with an attendant decrease in diastereoselectivity (entry 6), likely owing to increased steric crowding about the reactive center, thus attenuating the rate of reaction. Interestingly, replacement of the benzene ring of **2.33** with a ferrocene ring in **2.39**[25] (thereby also introducing stereogenic plane – the diselenide was prepared as a single diastereomer)[26] led to completely racemic product but with a significant increase in reaction rate, presumably due to the electron-releasing nature of the cyclopentadienyl ring.

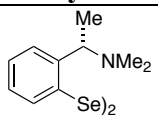
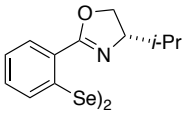
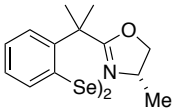
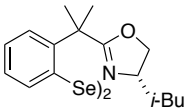
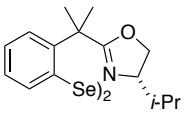
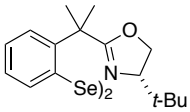
A reasonable hypothesis posited that the relatively weak binding of the ether and carbonyl coordinating groups were contributing to the low selectivities that had been obtained so far. Under this premise stronger Lewis basic donors were examined. The *N,N*-dimethyl-1-phenethylamine-diselenide **2.40** and oxazoline-diselenide **2.41** were evaluated first as they were available through short synthetic routes from chiral pool materials and their preparations had already been described in the literature (Table 2.3., entries 1 and 2).[27] Diselenide **2.40** afforded dichloride product with good enantiomeric ratio but with a poor diastereomeric ratio, potentially due to a reduction in the reaction rate with a more tightly-coordinated (and therefore sterically crowded albeit electronically activated) electrophilic selenium center. Diselenide **2.41** did not afford any enantioenrichment in the dichloride product; this result could be rationalized by the poor orbital overlap between the nonbonding electron pair on nitrogen (roughly 120º from the C=N bond) and the Se–Cl σ^*, thereby resulting in undesired rotational freedom. Oxazolines **2.42–2.45**, with six-membered ring coordination geometries, were therefore prepared and evaluated based on the premise that they would feature a more favorable n–σ^* orbital overlap. Unfortunately, regardless of the group on the stereogenic center adjacent to nitrogen, enantioselectivities were low (entries 3-6). Furthermore, diastereoselectivities decreased as the size of the group adjacent to nitrogen increased with no accompanying improvement in enantiomeric ratio. Apparently, the most significant effect of a more strongly coordinating Lewis basic heteroatom is a decrease in the catalytic reaction rate, observable by the decreased diastereomeric ratios obtained for all amine and oxazoline catalysts, resulting from increased predomination of background *anti*-dichlorination.

At this stage, greater variation in catalyst backbone was sought with a return to more weakly coordinating Lewis basic heteroatoms to potentially improve diastereoselectivity. Rigid tetralin-derived organoselenium reagents had previously been described and appeared to be suitable candidates.[21b, 23] Furthermore, related electrophilic selenium reagents had recently been

employed in redox-catalyzed lactonizations to afforded products with excellent enantiomeric ratios *at room temperature* (Scheme 1.42.).[28]

Table 2.3. *syn*-Dichlorination Selectivities with Catalysts Bearing Nitrogen Coordinating Groups.

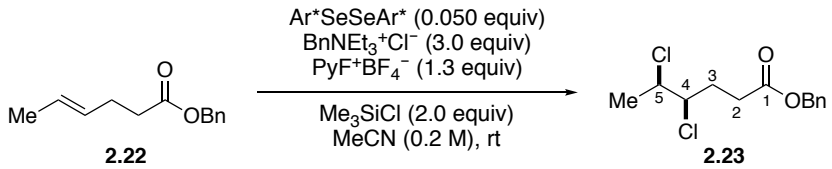


entry	catalyst		2.23 d.r. (*syn/anti*)[a]	e.r.[c]	configuration[b]
1		**2.40**	52:48	70:30	*S,S*
2		**2.41**[d]	60:40	50:50	--
3		**2.42**	90:10	54:46	*R,R*
4		**2.43**	90:10	53:47	*S,S*
5		**2.44**	83:17	52:48	*S,S*
6		**2.45**	70:30	50:50	--

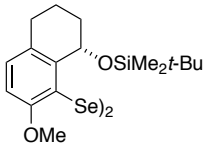
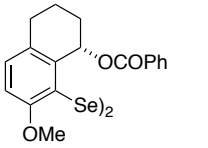
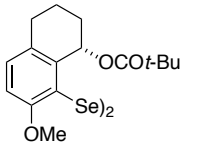
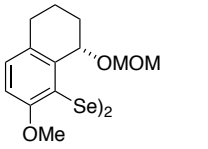
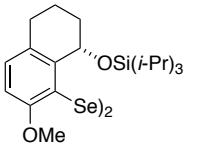
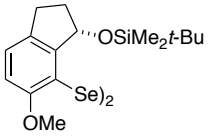
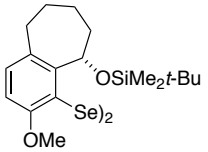
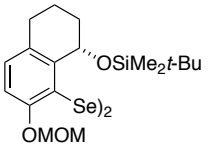
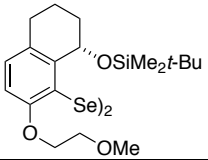
[a] The d.r. was determined by ^{1}H NMR integration of diagnostic signals at HC(4) and HC(5). [b] The absolute configuration of the major enantiomer was determined by elution order compared to dichloride of known configuration. [c] The e.r. was determined by chiral stationary phase HPLC. [d] Prepared and evaluated by S. T.-C. Eey.[19]

Silyl ether **2.46**, despite its *a priori* appearance of steric crowding around selenium, provided the dichloride in a d.r. of >95:5 and an e.r. of 74:26 (Table 2.4., entry 1). Exchanging the silyl ether for a benzoate, pivalate, or methoxymethyl acetal (**2.47–2.49**) resulted in a decrease in enantioselectivity (entries 2–4), whereas replacing the *tert*-butyldimethylsilyl ether with a triisopropylsilyl ether in **2.50** resulted in only a slight improvement in enantioselectivity (entry 5). The ring-contracted indane diselenide **2.51** gave worse selectivity, as did the ring-expanded benzosuberan diselenide **2.52** (entries 6 and 7). Exchange of the methoxy group at the 7-position

Table 2.4. *syn*-Dichlorination Selectivities with Rigid Bicyclic Diselenides.



2.22 **2.23**

entry	catalyst		2.23 d.r. (*syn/anti*)[a]	e.r.[c]	configuration[b]
1		**2.46**	>95:5	74:26	*R,R*
2		**2.47**	>95:5	65:35	*R,R*
3		**2.48**	>95:5	66:34	*R,R*
4		**2.49**	>95:5	70:30	*R,R*
5		**2.50**	>95:5	76:24	*R,R*
6		**2.51**	>95:5	63:37	*R,R*
7		**2.52**	>95:5	55:45	*R,R*
8		**2.53**	>95:5	68:32	*R,R*
9		**2.54**	>95:5	70:30	*R,R*

[a] The d.r. was determined by ^{1}H NMR integration of diagnostic signals at HC(4) and HC(5). [b] The absolute configuration of the major enantiomer was determined by elution order compared to dichloride of known configuration. [c] The e.r. was determined by chiral stationary phase HPLC.

for a methoxymethyl acetal in **2.53** or 2-methoxylethyl ether in **2.54** resulted in a decrease in enantiomeric ratio (entries 8 and 9). Notably, all of the diselenides derived from **2.46** led to significantly faster dichlorination reactions than any of the diselenides **2.24–2.45**. For example, the dichlorination of alkene **2.22** catalyzed by diselenide **2.46** was complete in 5 h – faster even than diphenyl diselenide.

2.5. Mechanistic Investigations.

Despite the wide variety of diselenide structures surveyed, many of which afforded fast reaction rates with excellent diastereoselectivities, and which afforded excellent enantioselectivities in other transformations, the enantioselectivity of the dichlorination reaction plateaued at 75:25. To better understand the mechanistic features that could be leading to reduced enantioselectivity, three potential sources were identified for consideration: (1) low intrinsic selectivity in seleniranium ion formation; (2) competing pathways of Se(II) and Se(IV) addition to the olefin, each pathway imparting a different selectivity, and (3) epimerization of catalytic intermediates owing to reversible addition of electrophilic selenium prior to catalyst turnover (*vide supra*).

2.5.1. Determination of Selenium Oxidation State at Seleniranium Ion Formation.

Before intrinsic selectivity could be considered, it was necessary to establish whether the transformation was proceeding through Se(II) or Se(IV) addition to the alkene (or some combination of the two). On the basis of X-ray crystal structure data (cf. Section 1.3.) for intramolecularly coordinated arylselenium(II) and (IV) chlorides, the two have very different geometries (Figure 2.4.).

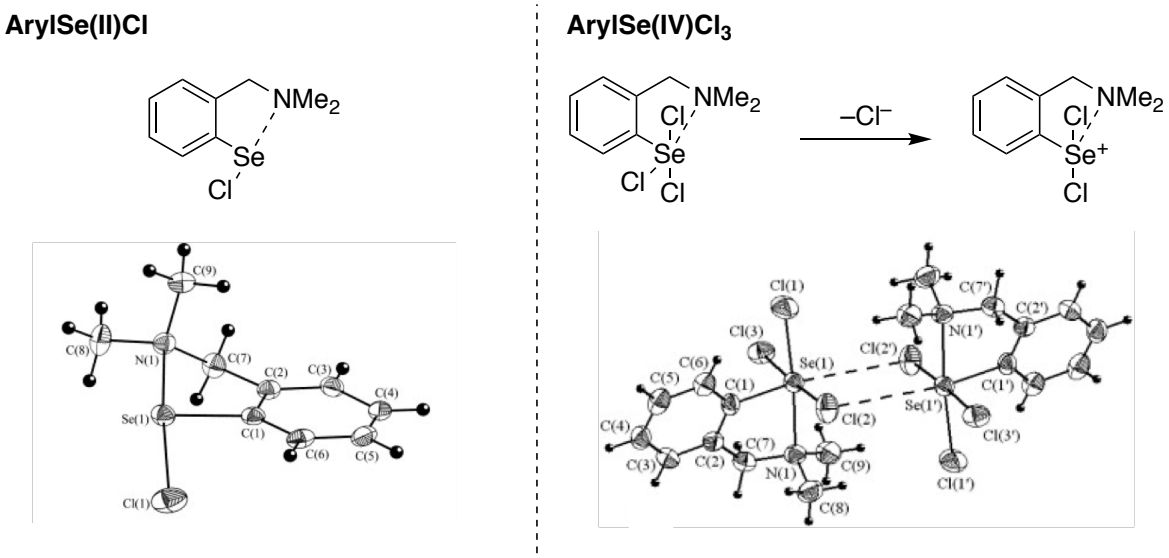
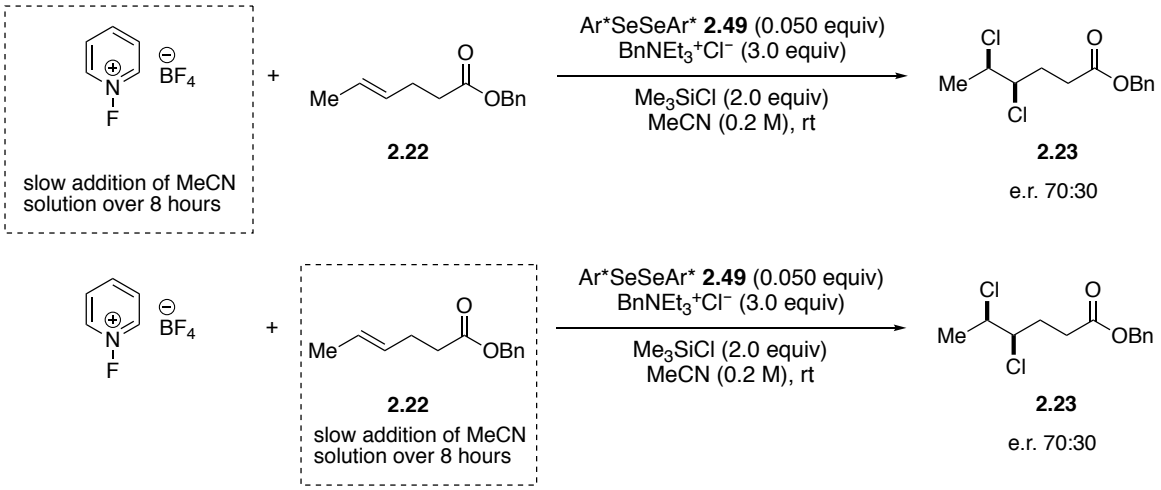


Figure 2.4. ORTEP diagrams for intramolecularly-coordinated arylselenium(II) and arylselenium(IV) chlorides. Reprinted with permission.[29] Copyright 2005 Elsevier.

The T-shape geometry of arylselenium(II) chlorides allows for side-on (relative to the aromatic ring) as well as top- and bottom-face approaches for the alkene, while the see-saw geometry of arylselenium(IV) trichlorides (after ionization of the most easily ionized chloride, *trans*- to the coordinating heteroatom, to afford $ArylSeCl_2^+$) allows only for a side-on approach of the alkene, as the top and bottom faces are blocked by apical chloride ligands. It follows that alkene approach to the electrophilic selenium atom at either oxidation state could be operative over the course of the reaction, as relative rates of oxidation and seleniranium ion formation could be differentially dependent on oxidant and olefin concentrations, respectively.

It was hypothesized that with maintained low concentration of oxidant relative to the alkene, seleniranium ion formation would proceed (at least predominately) at the Se(II) oxidation state. To maintain a low oxidant concentration for the duration of the dichlorination reaction, a solution of $PyF^+BF_4^-$ was added by syringe pump over 8 h (the typical time to full conversion) to a solution of diselenide **2.49**, $BnNEt_3^+Cl^-$, Me_3SiCl, and alkene **2.22** (Scheme 2.12.). The dichloride product had the same e.r. (70:30) as when all reagents were combined at reaction onset. Likewise, it was hypothesized that with maintained low concentration of the alkene relative to the oxidant, seleniranium ion formation would proceed at the Se(IV) oxidation state. Thus, slow addition of a solution of alkene **2.22** to oxidant **2.49**, diselenide **2.49**, $BnNEt_3^+Cl^-$, and Me_3SiCl also afforded the same e.r. (70:30). Therefore, either the same pathway is operative in all three

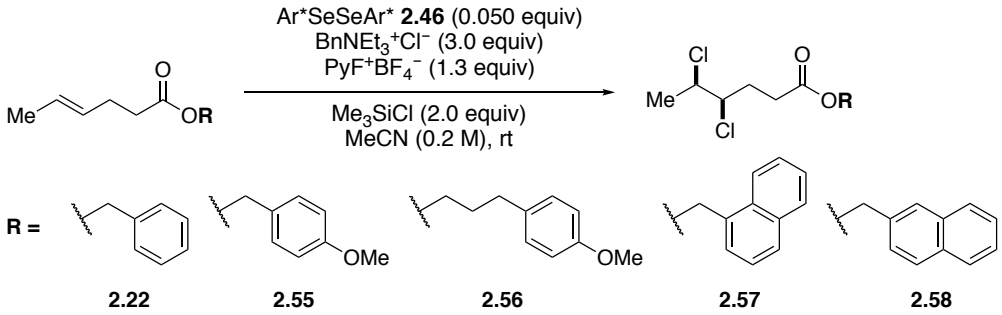
circumstances, the Se(II) and Se(IV) seleniranium ion formation pathways impart nearly identical selectivities on the overall transformation, or the selectivity of the transformation is not dependent on which pathway leads to the formation of the resting state intermediates **2.9a** and **2.9b**.



Scheme 2.12. Syringe pump addition experiments limiting the oxidation state of selenium.

A more informative experiment was then performed by measurement of the enantiomeric ratio of reaction mixture aliquots at 10% and 100% conversion. In a typical dichlorination reaction, all of the reagents save for the alkene are combined for 10 min to allow for oxidation of the diselenide precatalyst to the arylselenium(IV) trichloride catalyst.[9b] Therefore, at 10% conversion (i.e. one catalytic turnover), the vast majority of dichloride product should have arisen through Se(IV) seleniranium ion formation. At a 1 mmol sale, the amount of *syn*-dichloride product **2.23** obtained at 10% conversion was insufficient to achieve UV detection on HPLC. Thus, new olefin substrates were prepared to allow for detection at lower concentrations, while the reaction of alkene **2.22** was run on 5 mmol scale. For three of the five ester substrates evaluated, there appeared to be no significant conversion-dependent change in the enantiomeric ratio of the dichloride product (Table 2.5., entries 1–3). However, for alkenoate esters with larger aromatic π-surface areas, the enantiomeric ratio was comparable to the other substrates at 10% conversion but dropped far below the average at full conversion (entries 4 and 5). This effect is difficult to explain at present, it is possible that the larger aromatic systems bear some influence on the equilibration of the resting state intermediates, or that the Se(II) and Se(IV) pathways afford similar selectivities *unless* π-stacking or other unique intramolecular interactions become involved.

Table 2.5. Measurement of Dichloride e.r. at 10% and 100% Conversion.



entry	alkene	e.r. at 10% conversion[a]	e.r. at 100% conversion
1	**2.22**	76:24	75:25
2	**2.55**	79:21	76:24
3	**2.56**	77:23	75:25
4	**2.57**	74:26	66:34
5	**2.58**	79:21	61:39

[a] e.r. was determined by chiral stationary phase HPLC.

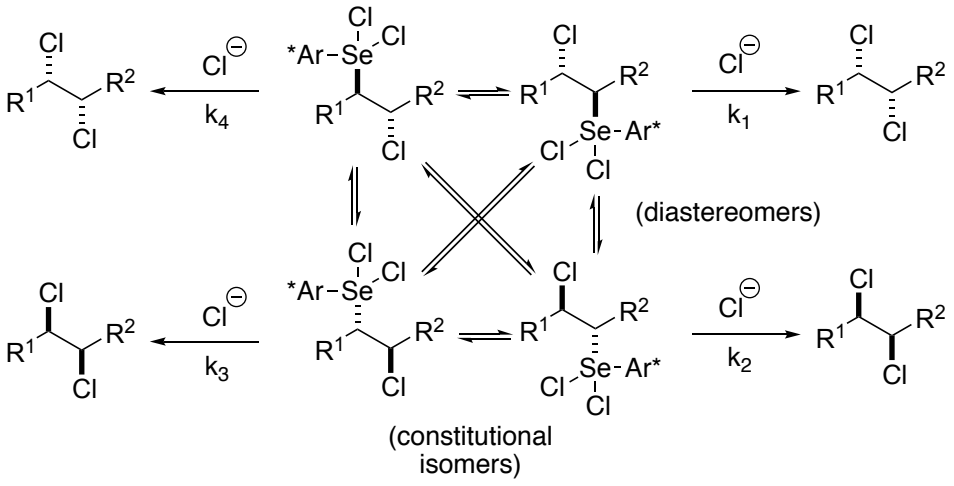
Nevertheless, it was clear for alkenes resembling **2.22** that the dichlorination reaction most likely proceeds through the Se(IV) seleniranium ion **2.8** from initiation through to full conversion, or that both the Se(II) and Se(IV) pathways afford similar enantioselectivities.

Unfortunately little is known about the enantiotopic face selectivity of Aryl*Se(IV) addition to alkenes, as the vast majority of diastereoselective selenofunctionalization reactions have been performed using reagents at the Se(II) oxidation state (cf. Section 1.3.). Attempts to measure the diastereomeric ratio of the β-chloroalkyl arylselenium(IV) dichloride product by combination of a stoichiometric amount of the arylselenium(IV) trichloride generated from diselenide **2.46** with either sulfuryl chloride or $PyF^+BF_4^-$ and $BnNEt_3^+Cl^-$ and alkene **2.22** produced ^{1}H NMR spectra too complex to make any meaningful conclusions (N.B. similar experiments were successfully performed with the $ArylSeCl_3$ reagent generated from diselenide **2.30** and *trans*-4-octene, however the results are less informative on the basis of its poor selectivity in the catalytic reaction (Table 2.1., entry 7)).[19] It was therefore difficult to rule out low facial selectivity as a contributor to the low overall selectivity based on the available evidence. There was, however, one especially compelling piece of evidence that pointed to a mechanistic origin for low enantioselectivity.

2.5.2. Reversibility of $ArSe(IV)Cl_2^+$ Addition to the Alkene.

As introduced in Section 2.2. (Figure 2.2.), early ^1H NMR studies demonstrated the reversibility of $ArylSe(IV)Cl_2^+$ addition to alkenes at room temperature. These observations indicated that, although initial seleniranium ion formation may be selective, its formation is not likely to be the enantiodetermining step *unless nucleophilic displacement is significantly accelerated*. Although the time scale for arylselenium(IV) exchange between alkenes is significantly longer than a typical catalytic dichlorination reaction (65 h vs. 8 h at 25 ºC), it was assumed that it could still be operative so long as nucleophilic displacement of $ArylSe(IV)Cl_2$ by chloride is rate-determining. None of the catalysts surveyed are likely to have had a strong enough influence on the rate of nucleophilic displacement such that it would no longer be the rate determining step.

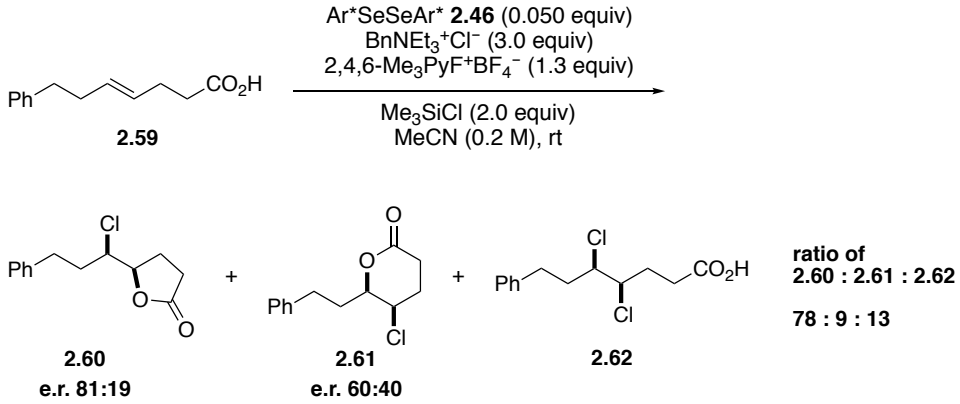
The actual mechanism of the transformation may be far more complicated than what was laid out in the initial proposal. Diastereomeric ring-opened β-chloroalkyl arylselenium(IV) dichloride intermediates could now equilibrate prior to irreversible chloride displacement. Furthermore, the diastereomeric and constitutionally isomeric alkylselenium(IV) compounds comprising this mixture have the potential to undergo S_N2 displacement by chloride at different rates, funneling the equilibrium to the intermediate that undergoes the fastest displacement by chloride, leading to a dynamic kinetic asymmetric transformation (DyKAT) (Scheme 2.13.).



Scheme 2.13. Dynamic kinetic asymmetric transformation of equilibrating β-chloroalkyl arylselenium(IV) dichlorides.

2.6. Chlorolactonization.

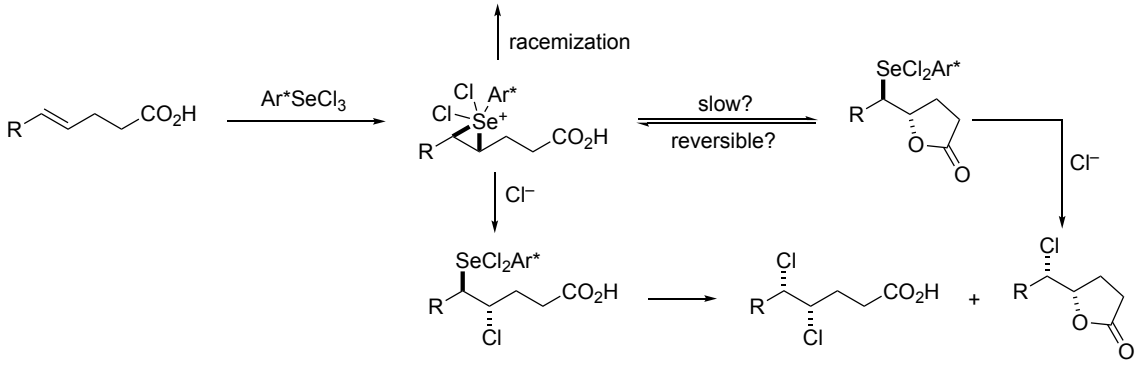
To provide support for this new mechanistic hypothesis and to make seleniranium ion formation the enantiodetermining step, a tethered nucleophile was used to preclude reversibility by rapid intramolecular capture prior to rate determining nucleophilic displacement. Adapting the method to chlorolactonization indeed proved simple. Exchanging benzyl *E*-hexenoate for (*E*)-7-phenyl-4-heptenoic acid **2.59** under identical reaction conditions afforded a mixture of *syn*-γ-lactone **2.60**, *syn*-δ-lactone **2.61**, *syn*-dichlorinated carboxylic acid **2.62**, and various elimination byproducts (Scheme 2.14.). When diselenide **2.46** was employed with similar conditions, substituting 2,4,6-$Me_3PyF^+BF_4^-$ for $PyF^+BF_4^-$ to improve reaction homogeneity, *syn*-γ-lactone **2.60** was formed in a 78:9:13 ratio with **2.61** and **2.62**, respectively, and with an e.r. of 81:19, marginally higher than the e.r. of *syn*-dichloride obtained from benzyl hexenoate with the same catalyst (Table 2.4., entry 1). The constitutional isomer **2.61** was isolated in a lower e.r. of 60:40.



Scheme 2.14. Chlorolactonization of (*E*)-7-phenylhept-4-enoic acid **2.59**.

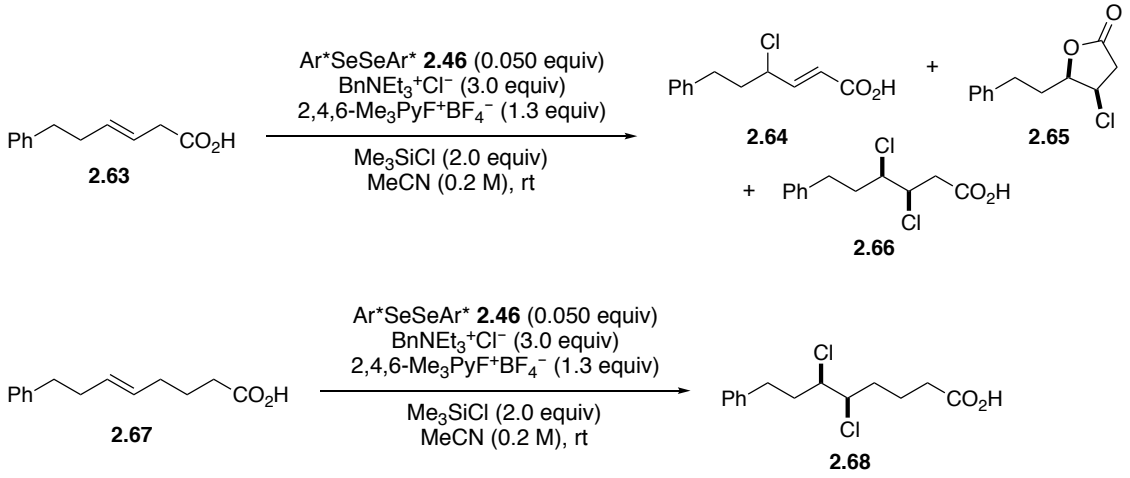
Modifying oxidant stoichiometry, chloride stoichiometry, and solvent all resulted in small changes to both the product ratio and, to a lesser degree, enantioselectivity. Unfortunately, the presence of the *syn*-dichloride regardless of the modified conditions indicated that reversibility was still operative owing to the unexpected intermolecular chloride capture of the seleniranium ion intermediate outcompeting an intramolecular capture by carboxylate. It is possible that the equivalent of acid produced as a reaction byproduct is capable of activating the lactone toward displacement by the adjacent selenium to reform the seleniranium ion (Scheme 2.15.). However, the chlorolactonization reaction in the presence of an additional equivalent of collidine did not result in improved selectivity for the lactone or improved enantiomeric ratio, and instead resulted

in the increasing predominance of byproducts produced by eliminative deselenenylation and thereby a reduction in the yield of the lactone products.



Scheme 2.15. Mechanistic hypothesis for reversibility in the chlorolactonization of (*E*)-7-phenylhept-4-enoic acid.

Examination of alkenes with alternative tether lengths generally afforded uncyclized products (Scheme 2.16.). (*E*)-6-phenylhex-3-enoic acid (**2.63**) predominately afforded elimination to the α,β-unsaturated carboxylic acid **2.64**, with some lactone **2.65** and dichloride **2.66** detected in a ratio of 7:3:1 (**2.64/2.65/2.66**) by ^{1}H NMR spectroscopic analysis, while (*E*)-8-phenyloct-5-enoic acid (**2.67**) afforded only the dichloride **2.68** and various elimination byproducts.



Scheme 2.16. Attempted chlorolactonizations with carboxylic acids of varying tether lengths.

2.7. Conclusions and Outlook.

In summary, the suprafacial dichlorination of alkenes with chiral, enantioenriched arylselenium(IV) chlorides to provide vicinal, *syn*-dichloride products was achieved with

moderate enantioselectivity. More than 30 diaryl diselenides across four general classes were evaluated for their selectivity in the dichlorination, with a maximum e.r. of 75:25 obtained with diselenide **2.50**.

The achievement of a higher product enantiomeric ratio appears to be difficult within the current catalyst design strategy, as selectivity is not likely dependent on the improvement of enantiofacial selectivity but the acceleration of the rate determining nucleophilic displacement before seleniranium ion exchange results in significant racemization. A few potential avenues are available to accelerate nucleophilic displacement (Figure 2.5.): (1) electronic or other structural modification of the organoselenium catalyst to destabilize the catalytic resting state intermediate **2.9**, stabilize the cationic pre-displacement complex **2.10**, and/or stabilize the Aryl*SeCl product, thereby improving its leaving group ability, (2) modification of the organoselenium catalyst to recruit chloride anion into closer proximity, either by tethering a cationic functional group for ion pairing or introducing a group capable of hydrogen-bonding, and (3) introduction of a co-catalyst to participate through either of these approaches by coordinating selenium in the catalytic resting state to increase its leaving group ability and/or by bringing chloride into closer proximity through similar intramolecular interactions.

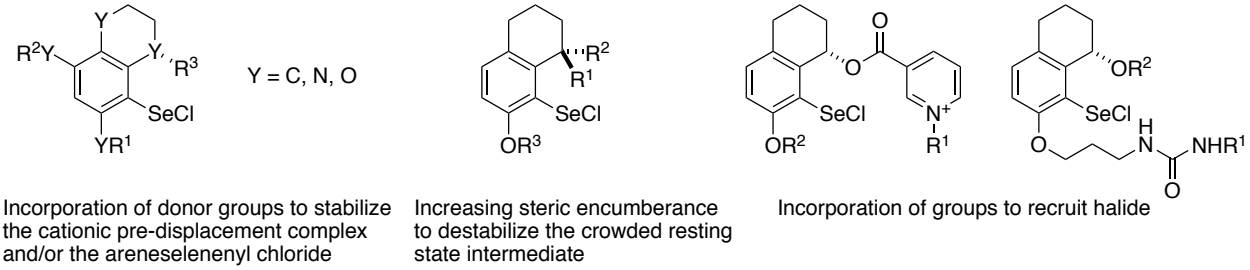


Figure 2.5. Potential structural modifications for dichlorination catalysts.

It may also be possible to slow or inhibit seleniranium ion reformation from the catalytic resting state. This particular strategy would be informed by mechanistic understanding of the olefin-olefin exchange at the Se(IV) oxidation state. While olefin-olefin transfer has been experimentally observed and rationalized computationally at the Se(II) oxidation state,[30] the mechanism for the transfer of Se(IV) between alkenes need not (and likely cannot, considering the number of ligands on selenium) follow a similar mechanism. Two alternative proposals for the mechanism of exchange are shown in Figure 2.6.: (1) selenium could potentially displace the adjacent chloride to reform the seleniranium ion and dissociate to reform $PhSeCl_3$, or (2) the β-

chloroalkyl arylselenium(IV) dichloride could chloroselenenylate the second alkene directly *prior* to seleniranium reformation and dissociation. Further studies on the mechanism of Se(IV) olefin-olefin transfer would need to be performed before any hypothesis can be made about a means of limiting its rate.

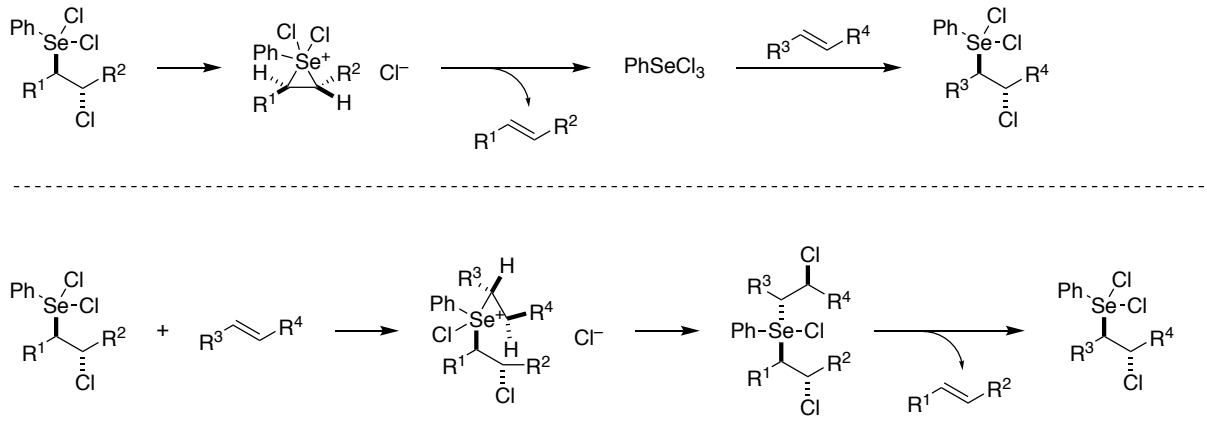


Figure 2.6. Potential routes for the olefin-olefin transfer of arylselenium(IV) chloride.

Alternative approaches to the improvement of enantiomeric ratio could instead leverage the equilibrating intermediates for a highly selective DyKAT process, potentially involving a chiral, enantioenriched ion-pairing or hydrogen-bonding co-catalyst to selectively deliver chloride to one isomer of the resting state intermediate. The design of diselenide precatalysts for this approach could contrariwise aim to achieve rapid equilibration with a strong thermodynamic bias toward one isomer, or a strong kinetic bias toward the nucleophilic displacement of one isomer. For example, the electronic destabilization of S_N2 displacement adjacent to the C–Cl dipole could be leveraged by conformational biasing of a particular most reactive isomer such that the unfavorable dipole interaction is minimized.

Indeed, the avenue selected for the attainment of high enantiomeric ratios with organoselenium redox catalysis follows the first proposal through the acceleration of nucleophilic displacement. The manner in which this is achieved does not involve tactics to accelerate nucleophilic displacement by chloride, however, rather it involves the use of an entirely different class of nucleophile that requires that the second displacement be intramolecular.

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Chapter 3: Organoselenium Catalyzed, Enantioselective *syn*-Diamination of Alkenes.*

3.1. Introduction and Prior Art.

Enantioenriched, vicinal diamines are common throughout the many disciplines of chemistry. They are prevalent in a wide variety of natural products, drugs, and other biologically active molecules and are frequently employed as ligands or in the preparation of ligands for asymmetric synthesis and catalysis (Figure 3.1.).[1] Vicinal diamines are found in the most ubiquitous natural products, e.g. vitamins such as biotin, and 2,3-diamino acids[2] present in peptide antibiotics,[3] antitumor agents,[4] and other biologically active molecules.[5] The presence of a vicinal diamine moiety is also required for the activity of certain neurokinin 1 (NK_1) antagonists,[6] e.g. rolapitant,[7] an antiemetic agent for chemotherapy patients;[6b] and antiproliferative agents such as nutlin-3.[8] Furthermore, many different chiral, enantioenriched auxiliaries, ligands, and catalysts for organic synthesis are derived from vicinal diamines;[9] including Noyori enantioselective hydrogenation catalysts,[10] *N*-heterocyclic carbenes,[11] and various ligands for asymmetric additions of organometallic reagents.[9b, 12]

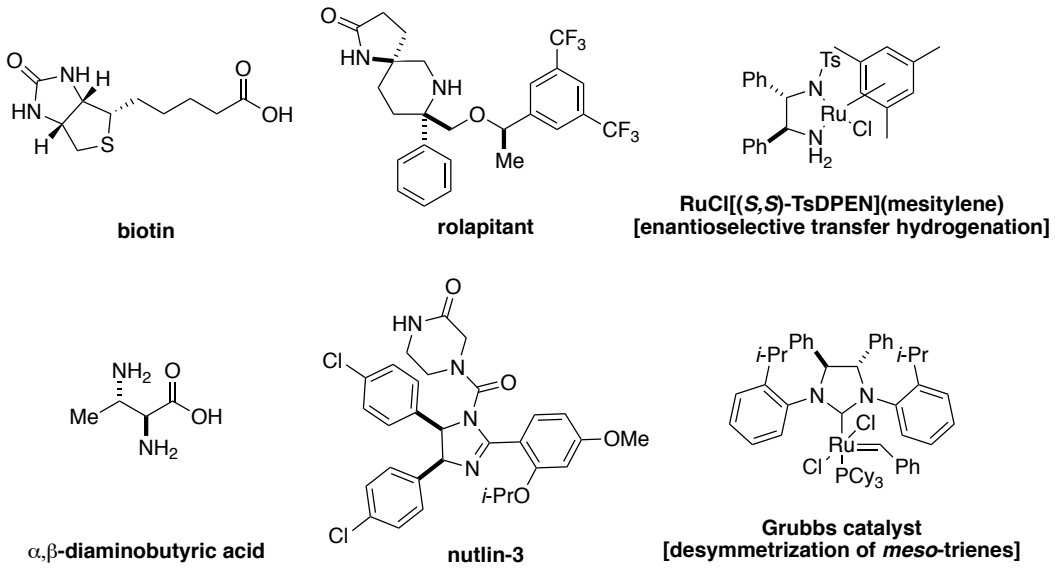
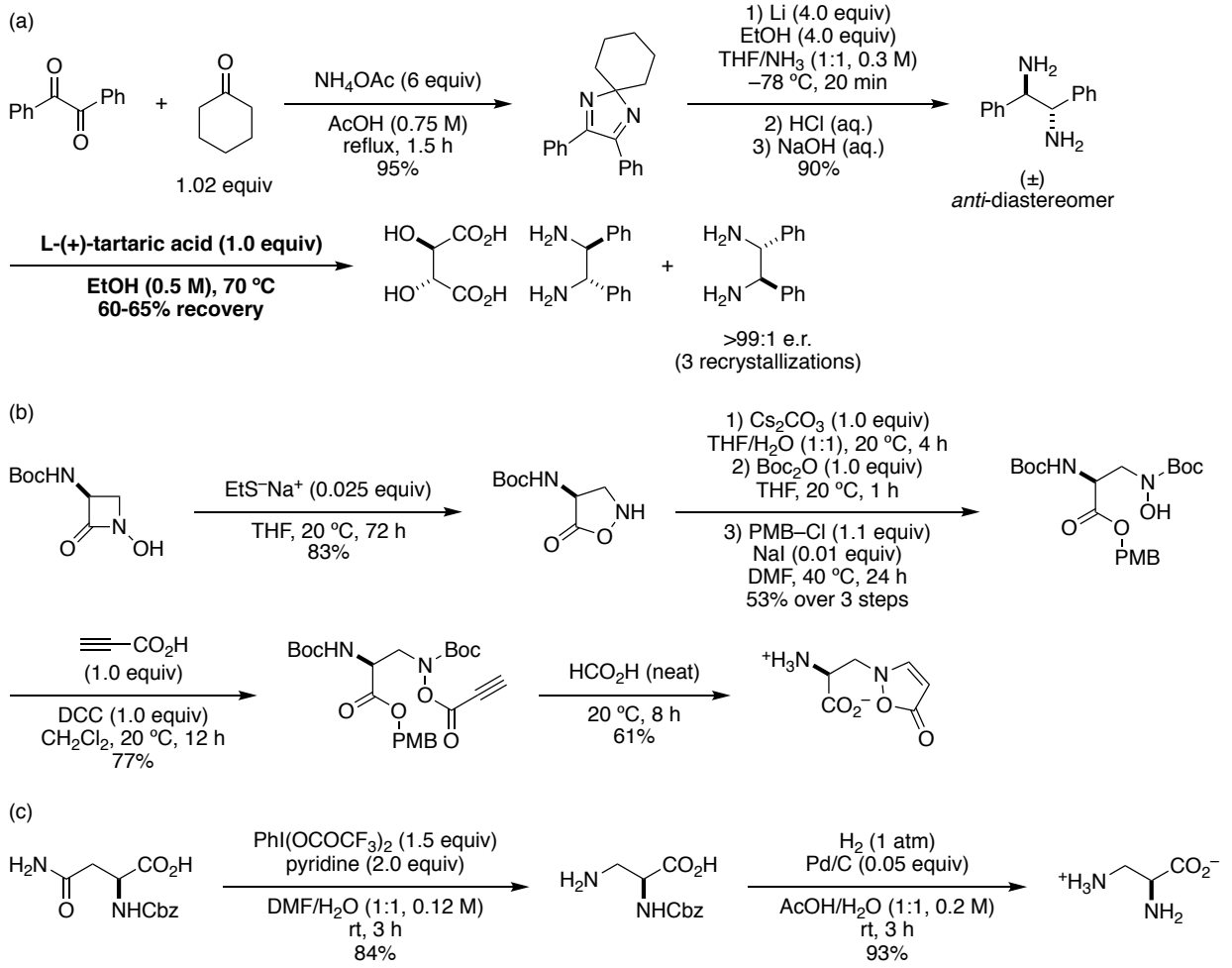


Figure 3.1. Diamines in natural products, drugs, and catalysts for organic synthesis.

* The contents of Chapter 3 are partially reproduced (adapted) from Tao, Z.; Gilbert, B. B.; Denmark, S. E. Catalytic, Enantioselective *syn*-Diamination of Alkenes. *J. Am. Chem. Soc.* **2019**, 10.1021/jacs.9b11261. This is an unofficial adaptation of an article that appeared in an ACS publication. ACS has not endorsed the content of this adaptation or the context of its use.

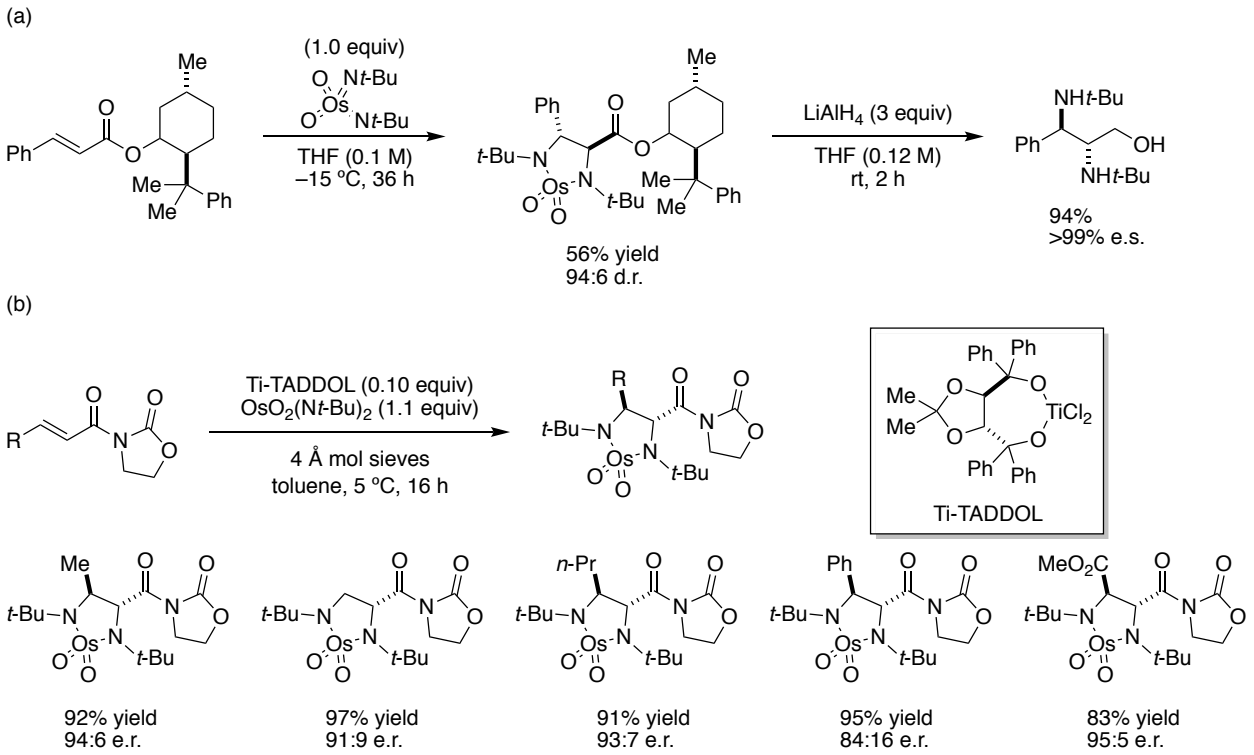
Many of these chiral diamines are still most frequently obtained in enantioenriched form by classical resolution,[13] stereocontrolled transformations of enantioenriched starting materials,[5, 14] or functional group interconversion of amino acids and other chiral pool materials (Scheme 3.1.).[1, 2b, 15]



Scheme 3.1. Synthetic approaches to enantioenriched, vicinal diamines through (a) classical resolution, (b) stereocontrolled transformation of an enantioenriched starting material, and (c) functional group interconversion (decarbonylation) of asparagine.

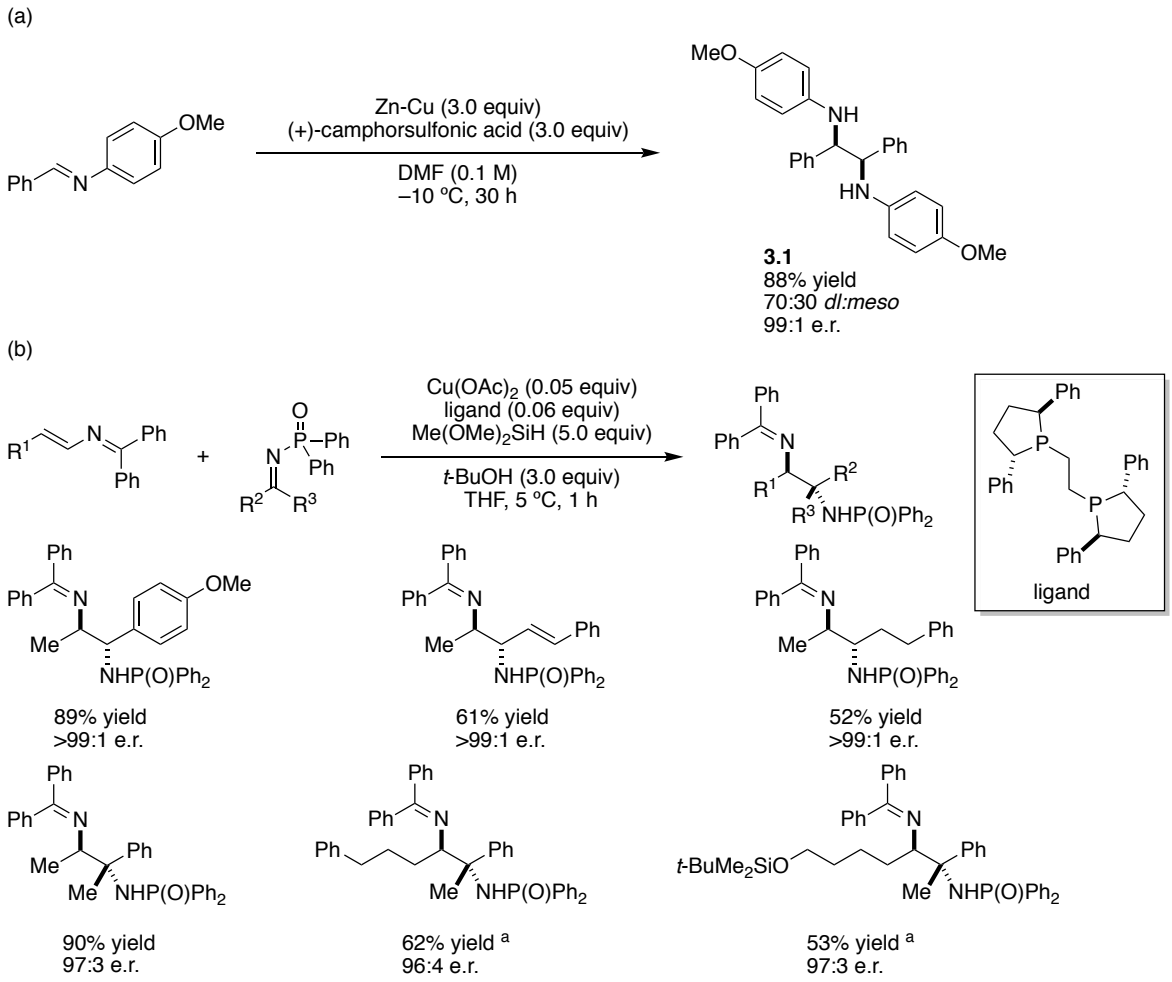
Only recently have methods for the enantioselective preparation of chiral, enantioenriched vicinal diamines from achiral starting materials become available. Early attempts to extend the Sharpless asymmetric dihydroxylation[16] to catalytic diamination were largely unsuccessful despite the success of oxyamination. Catalytic turnover cannot be achieved, owing to slow decomplexation of osmium from the bidentate diamine product (Scheme 3.2.). Thus, osmium-

mediated diaminations instead require prior preparation of the diimidoosmium reagent, which must be employed in stoichiometric amounts.[17]



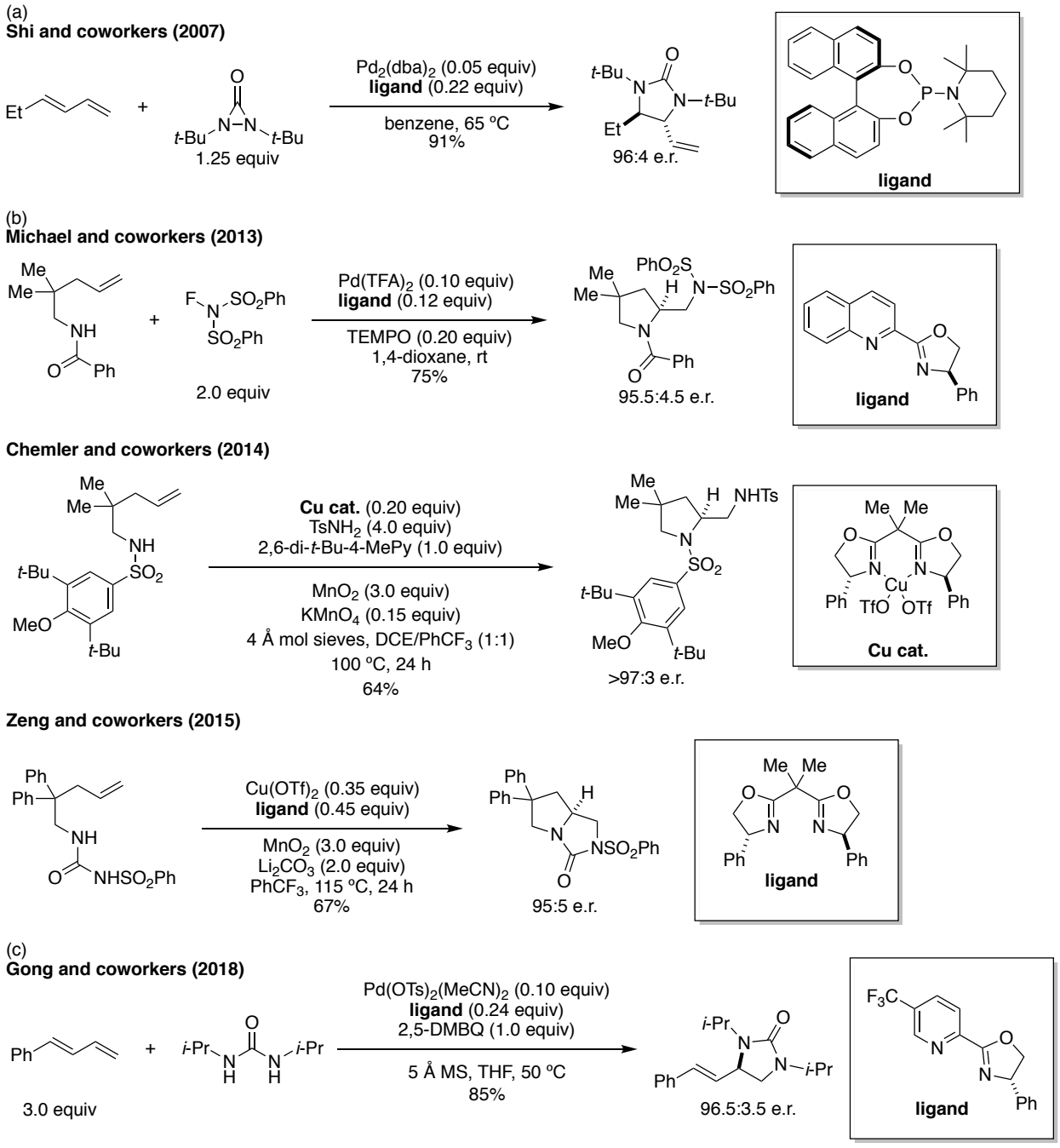
Scheme 3.2. (a) Diastereoselective diamination of alkenes with an imidoosmium reagent and a chiral auxiliary. (b) Enantioselective diamination of alkenes with an imidoosmium reagent and a Ti-TADDOL catalyst.

The catalytic, enantioselective, oxidative diamination of alkenes is perhaps the most conceptually straightforward approach to the preparation of enantioenriched vicinal diamines, however alternative methods involving reductive carbon-carbon bond formation have also been described. Early efforts in imino-pinacol couplings by Fujisawa and coworkers afforded the *N,N'*-diaryl diamine **3.1** in good yield, moderate diastereomeric ratio, and good enantiomeric ratio (Scheme 3.3a.).[18] The method was, however, not general for other imines. Recent elaboration of this method by Malcolmson and coworkers has greatly expanded the scope of this transformation, now with *N*-benzophenylidene enamines and *N*-phosphinoyl imines affording diamines in very good yields and enantioselectivities (Scheme 3.3b.).[19]



Scheme 3.3. (a) Imino-pinacol coupling with Zn-Cu couple and (+)-camphorsulfonic acid. (b) Reductive coupling of *N*-benzophenylidene enamines with phosphinoylimines. [a] Disubstituted enamines required 0.10 equiv $Cu(OAc)_2$ and 0.12 equiv ligand for 6 h.

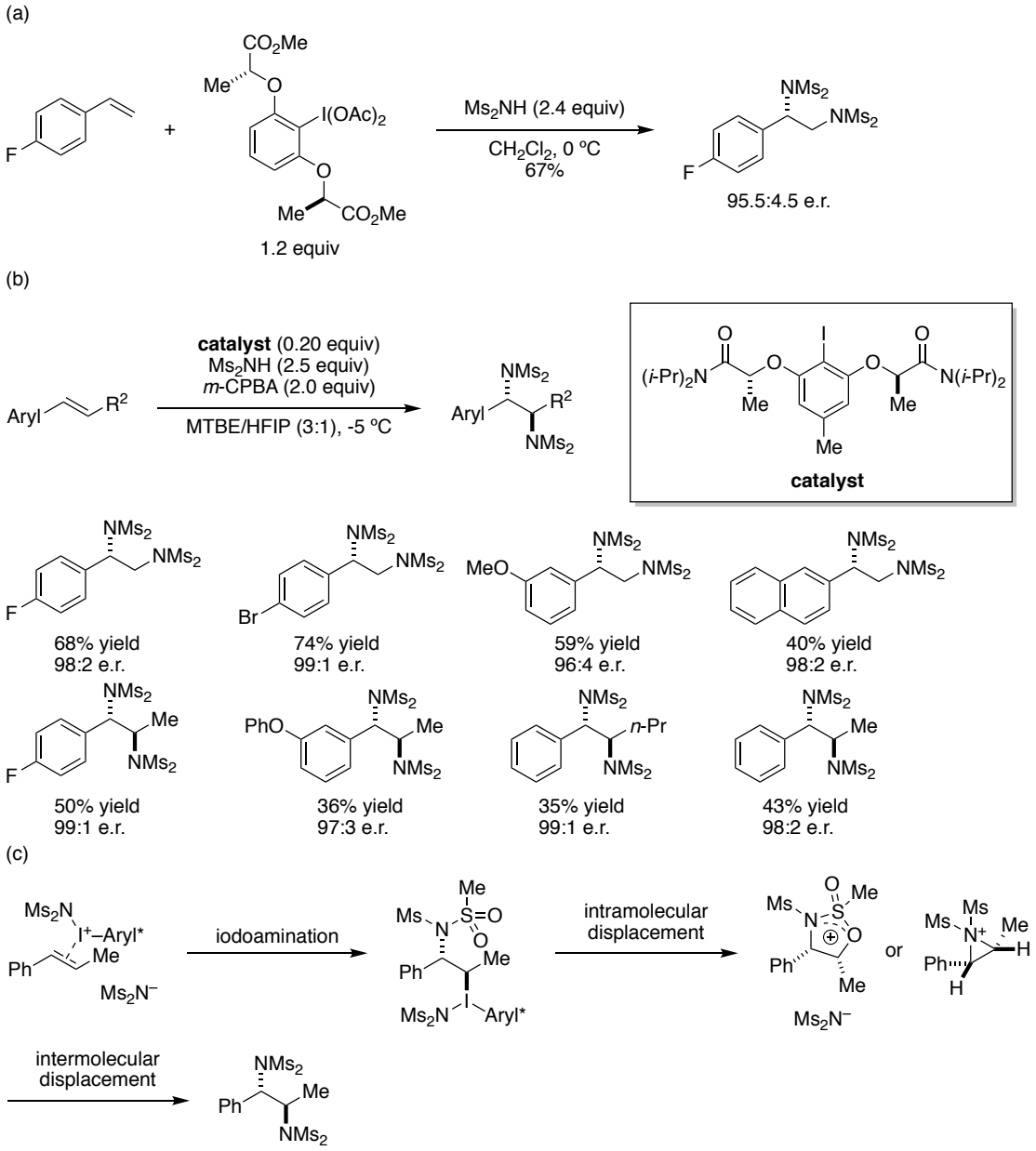
Alkene diamination has more recently been achieved in large part with palladium and copper catalysts, by N–N bond activation of hydrazine derivatives to oxidize the catalytic metal species and to generate the nucleophile (Scheme 3.4a.).[20] These methods, limited by the need for high-energy reagents, have been expanded to engage more common N–H nucleophiles (Scheme 3.4b.).[21] This approach requires an oxidant (e.g. *N*-fluorinated amines, hypervalent iodine reagents, or inorganic oxidants) to return the palladium or copper species into the catalytic cycle. However, methods employing an exogeneous oxidizing agent are largely limited to alkenes with at least one of the nitrogen nucleophiles tethered to the alkene, except in the case of aromatic dienes (Scheme 3.4c.).[22]



Scheme 3.4. (a) Diamination of alkenes with diaziridinone reagents. (b) Intramolecular diamination of alkenes with N–H nucleophiles. (c) Intermolecular diamination of aromatic dienes with N–H nucleophiles.

In 2011, Muñiz and coworkers disclosed the most general method for the intermolecular diamination of alkenes, mediated by stoichiometric amounts of a chiral, enantioenriched, hypervalent iodine complex (Scheme 3.5a.).[23] 1,2-Bis(dimethanesulfonyl)amines are obtained in

good to excellent yields and enantioselectivities from a variety of unsubstituted styrenes. Structural refinement of the iodoarene reagent in the laboratories of Muñiz and Wirth, and introduction of *m*-CPBA as the stoichiometric oxidant enabled the development of a catalytic, enantioselective method (Scheme 3.5b.).[24] Furthermore, *trans*-1,2-disubstituted alkenylbenzenes undergo diamination to afford *anti*-1,2-diaminated products, however with catalytic turnover numbers (TON) limited to ca. 2 for all disubstituted alkenes evaluated.



Scheme 3.5. (a) Enantioselective diamination with stoichiometric amounts of a chiral, enantioenriched, electrophilic iodine reagent. (b) Catalytic, enantioselective diamination with an electrophilic iodine reagent. (c) Mechanistic explanation for the observed antarafacial selectivity.

Although the diaminated products are obtained in excellent diastereomeric ratios (where relevant), the observed preference for a net antarafacial diamination to afford the *anti*-product is unexpected for a theoretical iodoamination-displacement sequence. To explain this outcome, Muñiz and coworkers propose that the initially formed, cationic iodoamination product undergoes an intramolecular displacement of the iodine to form a bis-(methanesulfonyl)aziridinium ion, followed by nucleophilic opening with a second molecule of bismethanesulfonimide to afford the product (Scheme 3.5c.). Alternatively, and perhaps more likely, is an intramolecular displacement by one of the sulfonyl oxygens to form a 5-membered, cationic, cyclosulfamate intermediate. Regardless, it appears that the intramolecular process is outcompeting intermolecular displacement of the iodoarene – a detour that could potentially be remedied by the use of a bifunctional nucleophile and a redox catalyst of higher valence to afford *syn*-diaminated products.

The modest selectivities obtained from dichlorination (cf. Chapter 2) likely resulting from the reversibility of seleniranium ion formation and slow intermolecular displacement of the β-chloroalkyl arylselenium(IV) dichloride could in theory be addressed by tethering the second nucleophile to the first. Although this solution is not possible with chloride, extension of the general concept of organoselenium redox-catalysis to diamination could potentially meet the requirements of both (a) an enantioselective, organoselenium redox-catalyzed alkene difunctionalization and (b) a general, enantioselective *syn*-diamination of alkenes. The use of a stronger nucleophile (e.g. nitrogen) delivered as a bifunctional reagent could accelerate the displacement of the arylselenium(IV) leaving group by virtue of intramolecularity, thereby inhibiting the reversibility of seleniranium ion formation. Inhibition of this reversibility would allow for the seleniranium ion formed under kinetic control to be captured, leading to a potential improvement in enantioselectivity (Figure 3.2.). The hypothetical reaction sequence in Figure 3.2 also illustrates a critical component of *syn* vs. *anti* vicinal functionalizations, namely that regioselectivity is irrelevant in the sequence affording the *syn* product because the two constitutionally isomeric intermediates converge to a single enantiomer.

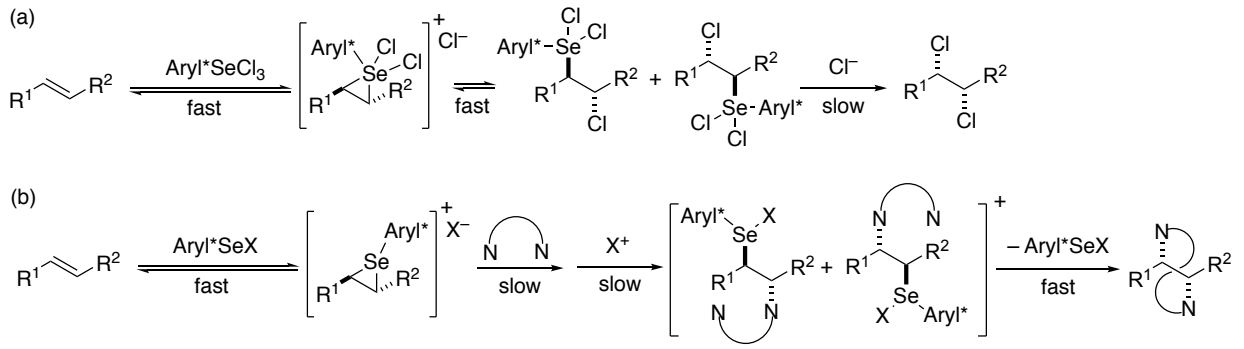


Figure 3.2. (a) Electrophilic organoselenium catalyzed *syn*-dichlorination. (b) Hypothetical electrophilic organoselenium catalyzed *syn*-diamination with a bifunctional nucleophile.

3.2. Research Objectives.

Mechanistic studies into the failure to achieve high enantioselectivity in *syn*-dichlorination provided the impetus for the development of an organoselenium redox-catalyzed, enantioselective *syn*-diamination reaction using bifunctional nucleophiles. Three primary objectives were identified for the development of this method:

(1) Identification of an efficacious combination of nitrogen nucleophile, oxidant, base, and solvent for (racemic) diphenyl diselenide-catalyzed alkene diamination. Several features of this combination of reagents need to be carefully controlled, in particular: the pK_a of the N–H nucleophile; the pK_a and solubility of the base; and the redox potential of the stoichiometric oxidant. Relatively non-acidic nitrogen nucleophiles would not likely have a large enough equilibrium concentration of the conjugate base to engage the seleniranium ion, and stronger and more soluble bases could favor eliminative deselenenylation to afford olefinic byproducts. Stoichiometric oxidants with higher oxidation potentials have the potential to react with the nucleophile directly, resulting in unproductive consumption of both. Furthermore, the selection of the oxidant needs to be informed by the compatibility of its reduced byproduct with the remainder of the reaction mixture.

(2) Evaluation and structural refinement of diselenide precatalysts to optimize the enantioselectivity of the diamination. The library of chiral, enantioenriched diselenides prepared over the course of the investigations into the enantioselective dichlorination of alkenes will be evaluated with the conditions found from the first objective. The diselenide(s) from this library affording high enantioselectivity will then undergo further structural refinement for optimal

enantiomeric ratio. The reaction conditions may need to be modified as well, either to improve enantiomeric ratio or reactivity.

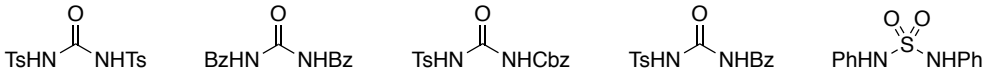
(3) Evaluation of the scope of the reaction and the synthetic utility of the products. 1,2-Dialkyl, aryl-alkyl, and dialkyl olefins bearing a variety of functional groups will be subjected to the enantioselective diamination conditions for the determination of the scope and limitations of the transformation. The method will likely be limited to mono- and disubstituted alkenes in view of the propensity for trisubstituted seleniranium ion intermediates to form open carbocationic intermediates, and basic functional groups will likely need to be excluded owing to their ability to engage in eliminative deselenenylation.

The ultimate objectives are the achievement of good yields and enantioselectivities in the diamination of alkenes with good tolerance for varied alkene substitution and a wide range of non-participating functional groups; and demonstration of the synthetic utility of the diaminated products through functional group interconversions.

3.3. Reaction Development and Scope of the Transformation.

3.3.1. Reaction Development.

Initial evaluation of reactivity began with 4-phenyl-1-butene as a test substrate. *N,N'*-bis(toluenesulfonyl)urea **3.2** was identified early on as a uniquely reactive dinucleophile, which had the distinct advantage of forming 1,2-ditosylimidazolidin-2-ones that could undergo selective functional group interconversions. *N,N'*-bis(benzoyl)urea **3.3**, *N*-toluenesulfonyl-*N'*-benzyloxycarbonylurea **3.4**, *N*-toluenesulfonyl-*N*'-benzoylurea **3.5**, and *N,N'*-diphenylsulfamide **3.6**, among others, were also evaluated but did not afford any measurable amount of product (Figure 3.3.). Organic and inorganic bases such as pyridine, DABCO, potassium carbonate, and cesium carbonate afforded trace or no yield, whereas sodium fluoride appeared to be uniquely suited to the transformation (Table 3.1.).

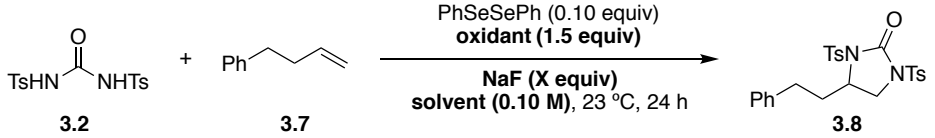


3.2 **3.3** **3.4** **3.5** **3.6**

Figure 3.3. Bifunctional nucleophiles evaluated in the diamination of alkenes.

1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (2,4,6-$Me_3PyF^+BF_4^-$) afforded good yields in the diamination reaction, whereas the unsubstituted 1-fluoropyridinium tetrafluoroborate

Table 3.1. Optimization of Diamination Reaction Conditions.[a]



3.2 **3.7** **3.8**

entry	ratio 3.2:3.7	oxidant	NaF equiv	solvent	yield (%)[b]
1	2:1	2,4,6-$Me_3PyF^+BF_4^-$	2.5	MeCN	62
2	2:1	$PyF^+BF_4^-$	2.5	MeCN	20
3	2:1	2,6-$Cl_2PyF^+BF_4^-$	2.5	MeCN	18
4	2:1	2,4,6-$Me_3PyF^+BF_4^-$	0	MeCN	43
5	2:1	2,4,6-$Me_3PyF^+BF_4^-$	5	MeCN	58
6	1.2:1	2,4,6-$Me_3PyF^+BF_4^-$	2.5	MeCN	60
7	1:2	2,4,6-$Me_3PyF^+BF_4^-$	2.5	MeCN	58
8	1:1.2	2,4,6-$Me_3PyF^+BF_4^-$	2.5	MeCN	59
9	1:1.2	2,4,6-$Me_3PyF^+BF_4^-$	2.5	CH_2Cl_2	21
10	1:1.2	2,4,6-$Me_3PyF^+BF_4^-$	2.5	PhMe	16
11	1:1.2	2,4,6-$Me_3PyF^+BF_4^-$	2.5	1,2-DCE	20
12	1:1.2	2,4,6-$Me_3PyF^+BF_4^-$	2.5	THF	5
13	**1:1.2**	**2,4,6-$Me_3PyF^+BF_4^-$ [c]**	**2.5**	**MeCN**	**59**

[a] All reactions were performed on 0.10 mmol scale. [b] Yield determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. [c] 1.3 equiv of 2,4,6-$Me_3PyF^+BF_4^-$.

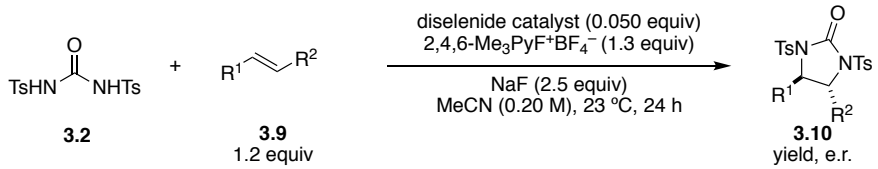
($PyF^+BF_4^-$) and 1-fluoro-2,6-dichloropyridinium tetrafluoroborate (2,6-$Cl_2PyF^+BF_4^-$) gave very low yields (entries 1-3). Sodium fluoride was important to obtain yields in excess of 50% (i.e. TON > 5) but did not appear to be necessary for the reaction to proceed (entry 4). Increasing equivalents of sodium fluoride did not, however, improve the yield any further (entry 5). The ratio of alkene and urea appeared to have relatively little effect on the yield (entries 6-8). Acetonitrile afforded good yields compared to the other solvents surveyed (entries 9-12). Reactions in other solvents were heterogeneous and the reduced yields may be a consequence of the insolubility of certain reaction components. Alkene **3.7** was employed in excess to allow for full consumption of the urea reagent **3.2** and thereby simplify purification of the product mixture. Finally, the amount of oxidant could be reduced to 1.3 equivalents without any impact on the reaction rate or yield (entry 13).

Chiral, enantioenriched diselenide catalysts were then surveyed using these conditions (Table 3.2.). Catalysts were initially selected on the basis of their selectivity and rate of reaction in the enantioselective *syn*-dichlorination of alkenes (cf. Chapter 2). Cinnamyl benzyl ether **3.9a** was initially selected for optimization of enantiomeric ratio because it afforded better enantioselectivity compared to the terminal alkene **3.7**. However, the reproducibility of the enantiomeric ratios obtained with alkene **3.9a** became irregular unless the substrate was freshly prepared (i.e. within several days), and so later catalyst surveys were performed with β-methylstyrene **3.9b** or *trans*-4-octene **3.9x**. Diselenide **3.12** afforded very good yield of **3.10a** in moderate enantiomeric ratio (entry 1). *A priori* assessment of the reaction conditions suggests the silyl ether may be cleaved by the sodium fluoride, guiding structural refinement toward more compatible functional groups. Benzoate **3.13** afforded a similar yield but with greatly improved enantioselectivity (entry 2). A benzoate derivative of an indane-derived organoselenium catalyst previously employed by Maruoka and coworkers (**3.14**)[25] was also surveyed and afforded poor yield and selectivity (entry 3). Exchanging the benzoate ester for a pivalate ester in **3.15** resulted in no change in the enantiomeric ratio or the yield (for *trans*-4-octene, at least) (entry 4). On the other hand, extending the benzoate ester **3.13** to the 2-naphthoate ester **3.16** resulted in further improvement to the enantiomeric ratio with no change in yield (entry 5). The 1-naphthoate **3.17** and 9-anthracenecarboxylate **3.18** afforded lower enantiomeric ratios (entries 6 and 7), while adamantanecarboxylate **3.19** afforded somewhat irreproducible results (entry 8), but with an average enantiomeric ratio below what was obtained with **3.16**.

3.3.2. Scope of the Transformation.

With optimized reaction conditions and chiral catalyst in hand, the generality of the transformation could now be surveyed. It was found early on in the development of the substrate scope that the use of one equivalent of sodium fluoride was sufficient to obtain complete conversion and led to improved reaction homogeneity. The reaction appears general for a variety 1,2-*trans*-disubstituted alkenes (Table 3.3.). β-Methylstyrene reacts smoothly to afford the oxazolidinone product **3.10b** in 88% yield with an e.r. of 95:5. Removing substitution or increasing steric bulk at the β-position to the alkene results in a decrease in yield and e.r. (**3.10c** and **3.10d**). However, introduction of 2-substitution on the aromatic ring does not result in any change to the enantiomeric ratio (**3.10t**) Introduction of an electron withdrawing group at the β-position does

Table 3.2. Evaluation of Chiral, Enantioenriched Diselenide Catalysts.



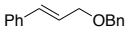
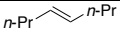
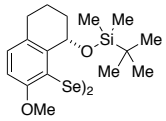
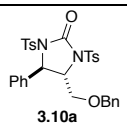
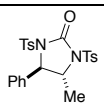
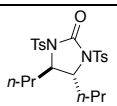
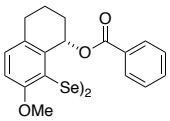
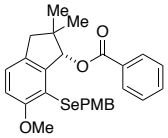
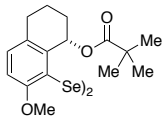
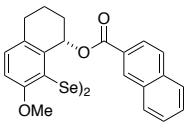
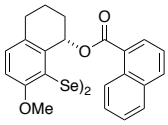
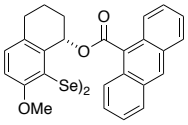
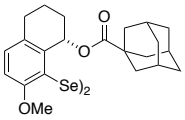
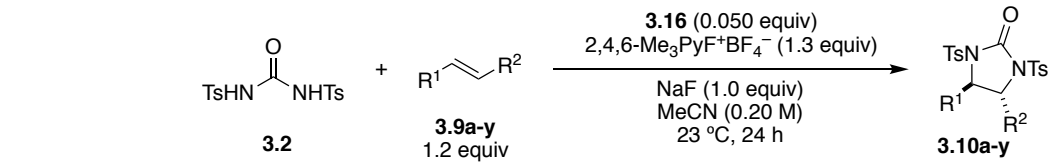
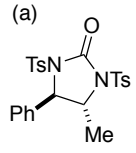
entry	catalyst	 3.9a	 3.9b	 3.9x
1	 3.12	 3.10a 89%, 82:18	 3.10b 76%, 82:18	 3.10x 23%, 90:10
2	 3.13	87%, 90:10	--	40%, 95:5
3	 3.14	69%, 73:27	--	--
4	 3.15	--	--	37%, 95:5
5	 3.16	**89%, 93:7**	**85%, 95:5**	**35%, 94:6**
6	 3.17	93%, 92:8	--	--
7	 3.18	80%, 87:13	--	--
8	 3.19	88%, 85:15	87%, 89:11	--

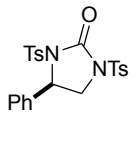
Table 3.3. Scope of the *syn*-Diamination Reaction.[a]



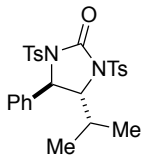
(a)



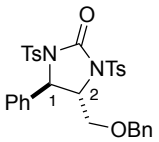
3.10b
88%, 95:5 e.r.



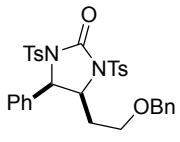
3.10c
48%[b], 81:19 e.r.



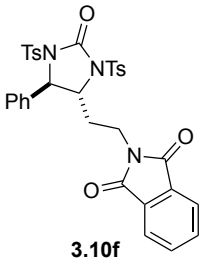
3.10d
47%, 90:10 e.r.



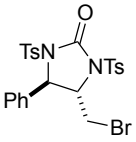
3.10a
75%, 94:6 e.r.



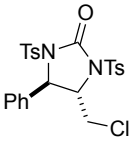
3.10e
31%, 59:41 e.r.



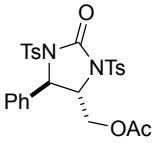
3.10f
68%, 96:4 e.r.



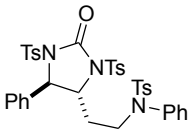
3.10g
47%, 98:2 e.r.



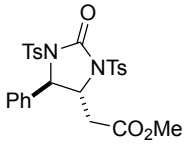
3.10h
75%, 97:3 e.r.



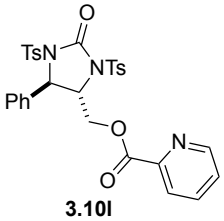
3.10i
20:1 d.r.
70%, 95:5 e.r.



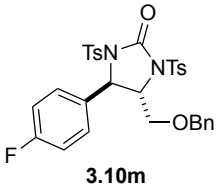
3.10j
61%, 93:7 e.r.



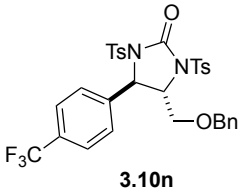
3.10k
74%, 96:4 e.r.



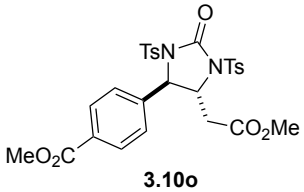
3.10l
83%, 96:4 e.r.



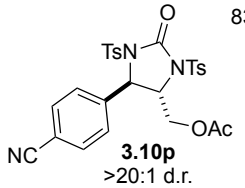
3.10m
65%, 89:11 e.r.



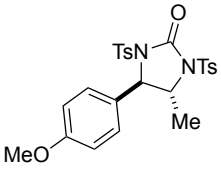
3.10n
80%, 92:8 e.r.



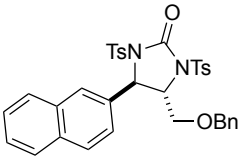
3.10o
71%, 96:4 e.r.



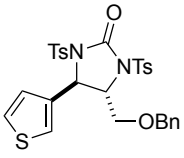
3.10p
>20:1 d.r.
72%, 94:6 e.r.



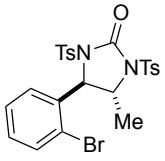
3.10q
69%, 80:20 e.r.



3.10r
71%, 90:10 e.r.

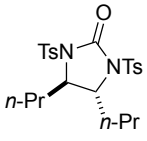


3.10s
66%, 87:13 e.r.



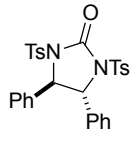
3.10t
59%, 95:5 e.r.

(c)

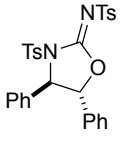


3.10x
35%, 94:6 e.r.

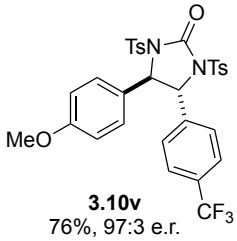
(b)



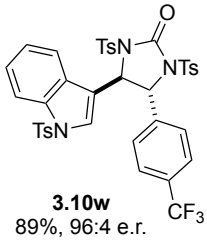
3.10u
49%, 98:2 e.r.



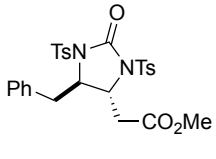
3.10u'
44%, 97:3 e.r.



3.10v
76%, 97:3 e.r.



3.10w
89%, 96:4 e.r.



3.10y
18%, 93:7 e.r.

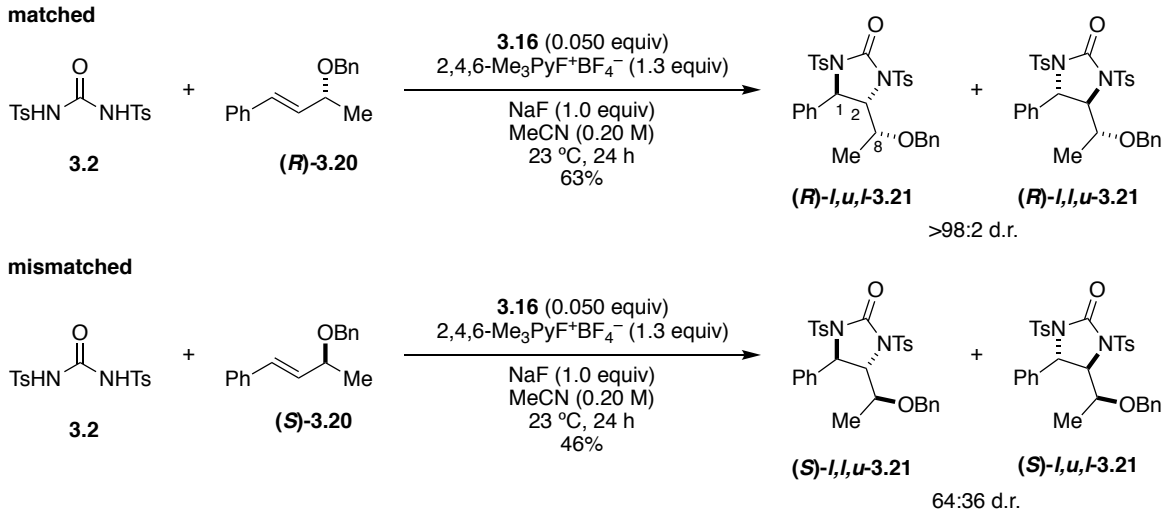
[a] All reactions were performed on 1.00 mmol scale. Enantiomeric ratios were determined after chromatographic purification by chiral stationary phase HPLC. Yields are of isolated, analytically pure material. Refer to Supporting Information for more details. [b] With 2.5 equiv of NaF.

not appear to have a significant effect on enantiomeric ratio, but in some cases leads to a decrease in yield (**3.10a, g-i, k**). Electron-withdrawing and -donating groups on the aromatic ring both lead to reduced enantiomeric ratios in some cases (entries **3.10m-t**), with the effect being more pronounced for the electron rich substrates (**3.10q-s**). The presence of an acetate group on the alkene β-substituent results in the formation of a small amount of the *anti*-diastereomer, perhaps as a result of anchimeric assistance by the carbonyl oxygen (**3.10i** and **3.10p**). Notably, this effect is not observed for the nicotinate **3.10l** or the methyl esters **3.10k** and **3.10o**. Reaction with a *cis*-1,2-disubstituted alkene affords product in low yield and enantiomeric ratio, however with maintained *syn*-diastereoselectivity (**3.10e**). Nitrogen-containing functional groups are well-tolerated so long as their basicity is attenuated (**3.10f, 3.10l,** and **3.10w**).

The stereochemical course of the reaction was established by single-crystal X-ray diffraction of the oxazolidinone product **3.10a**. The absolution configuration (1*R*,2*S*)-**3.10a** is consistent with the absolute configuration found for the *syn*-dichlorination product formed with structurally related diselenides (cf. Chapter 2).

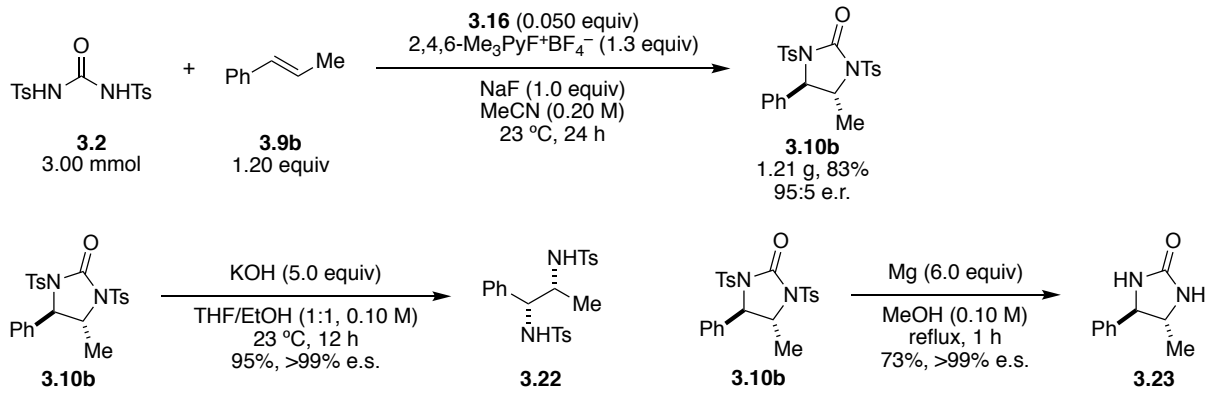
Diaryl alkenes are also competent reaction partners, affording mixtures of imidazolidin-2-one and oxazolidin-2-imine products (Table 3.3b.). Reaction with stilbene affords a ~1:1 mixture of products **3.10u** and **3.10u'** with very good enantioselectivities. However, unsymmetrical diaryl alkenes afford products with significantly higher selectivity for the imidazolidinone (i.e. diaminated) products (**3.10v** and **3.10w**) in good yields and enantiomeric ratios. Product **3.10u** was likewise found by single-crystal X-ray diffraction analysis to have absolute configuration (*R,R*)-**3.10u**, resulting from the same enantiofacial selectivity as in **3.10a**. Dialkyl alkenes undergo diamination in the standard reaction conditions with very good enantioselectivities, however in significantly reduced yield (**3.10x** and **3.10y**) (Table 3.3c.). Modification of the reaction conditions to improve the yield by increasing catalyst loading or concentration, or modifying the solvent, base, or oxidant have been unsuccessful. This class of alkenes represents an important focus of further investigation (*vide infra*). For example, diphenyl diselenide catalyzes the formation of racemic **3.10y** in 43% yield. The enantioselective formation of **3.10y** from unsymmetrical alkene **3.9y** represents a crucial advantage of this method. Because the process is *syn* stereospecific, the site selectivity of the addition is irrelevant. Were this an *anti* stereospecific process, the enantioselectivity would likely be much poorer.

Although enantioselective reactions are important for synthesis, reagent controlled diastereoselective reactions are perhaps more important for late-stage transformations in target-oriented synthesis. To evaluate the relative effects of substrate *versus* catalyst control, both enantiomers of chiral alkene **3.20** were subjected to the standard diamination reaction conditions (Scheme 3.6.). Alkene substrate (*R*)-**3.20** undergoes "matched" substrate- and catalyst-controlled diamination with diselenide precatalyst (*S*)-**3.16** to form diastereomer (*R*)-*l,u,l*-**3.21**,[26] with absolute configuration assigned by analogy to **3.10a**, and a d.r. of >98:2. Contrariwise, (*S*)-**3.20** undergoes "mismatched" diamination with (*S*)-**3.16** to afford a mixture of (*S*)-*l,l,u*-**3.21** and (*S*)-*l,u,l*-**3.21** in a 64:36 ratio. Substrate controlled selectivity apparently favors the *l,u,l*-diastereomer, but this selectivity is partially overturned by catalyst controlled selectivity for the (*Re*,*Si*) face of the alkene to prefer the *l,l,u*-diastereomer in the mismatched case.



Scheme 3.6. Diastereoselective reactions to evaluate substrate vs. catalyst control.

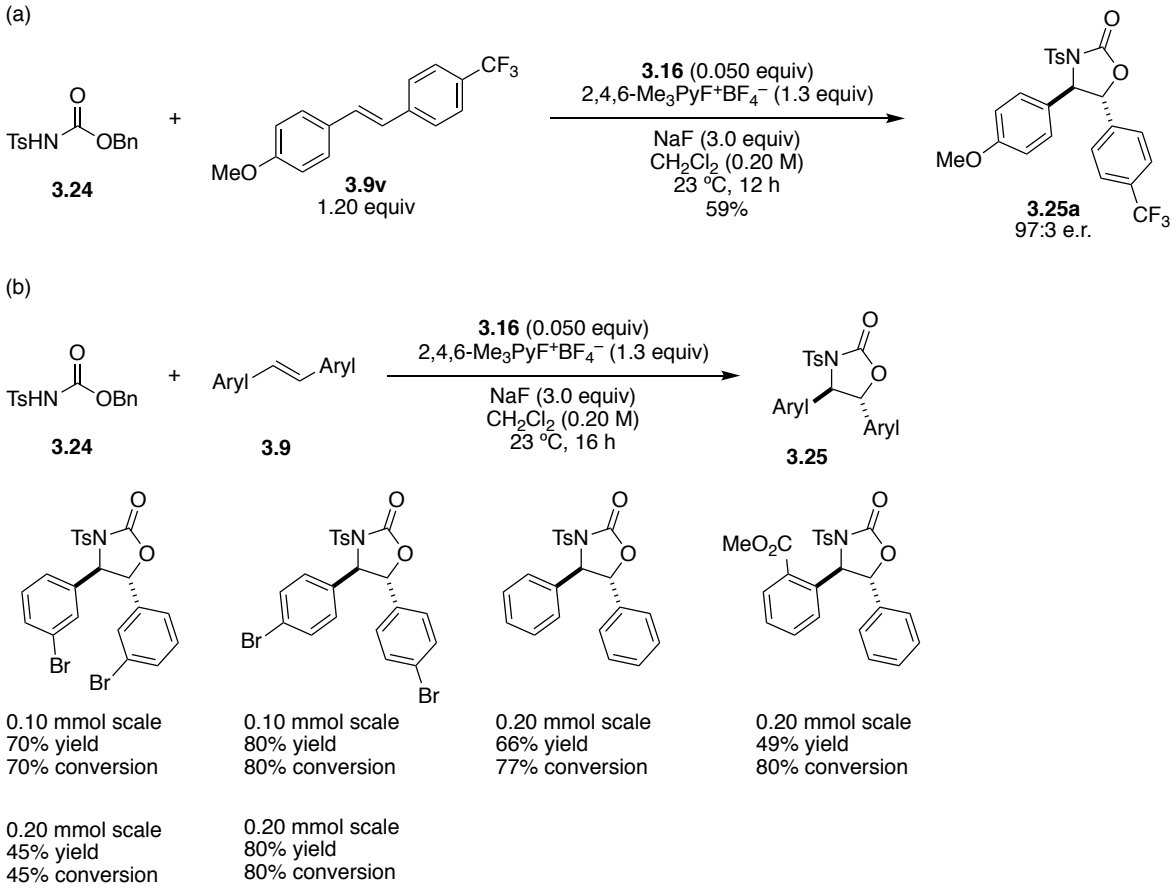
The enantioenriched imidazolidin-2-one products generated by this reaction can be prepared on gram scale and readily transformed into useful synthetic intermediates by operationally simple techniques (Scheme 3.7.). Reaction of β-methylstyrene proceeds smoothly at 3.00 mmol scale to afford 1.21 g (83% yield) of **3.10b** with an e.r. of 95:5. Treatment of **3.10b** with potassium hydroxide in THF/EtOH at room temperature affords the *syn*-ditosylamide **3.22** in 95% yield. Alternatively, treatment of **3.10b** with magnesium in refluxing methanol affords the imidazolidinone **3.23** in 73% yield.



Scheme 3.7. Synthetic transformations of the imidazolidin-2-one product.

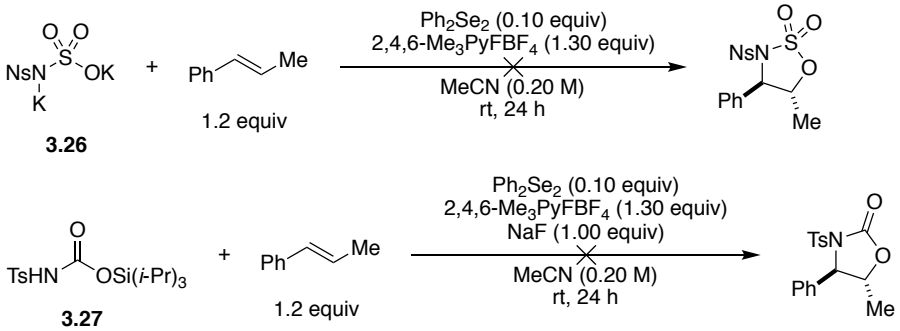
Oxyamination of stilbenes with carbamate reagent **3.24** is also possible with varying degrees of success (Scheme 3.8a.). Replacement of MeCN for CH_2Cl_2 is required for the reaction to proceed, perhaps owing to the different solubility of the deprotonated carbamate reagent. More equivalents of NaF also result in improved yield. Alkene **3.9v** can be transformed to the oxazolidin-2-one **3.25a** in 59% yield with an e.r. of 97:3, as a single constitutional isomer. However, the reaction stalls at 8 h with incomplete consumption of **3.24** on the basis of ^{1}H NMR analysis of the crude reaction mixture.

Reactions with other stilbene substrates are less successful, reaching good conversion at small scale (0.10 mmol) but stalling at significantly reduced conversion upon scale-up (Scheme 3.8b.), while reaction with aryl-alkyl substrates affords no desired product. The reaction stalling could be attributable to catalyst inactivation, but the route by which the *N*-toluenesulfonyl carbamate reagent is mediating this off-cycle pathway while the *N*-toluenesulfonyl urea reagent does not is at present unclear.



Scheme 3.8. (a) *syn*-Oxyamination of alkene **3.9v**. (b) Attempted oxyaminations of other stilbene substrates. Yields and conversion are measured by ^{1}H NMR spectroscopy with an internal standard.

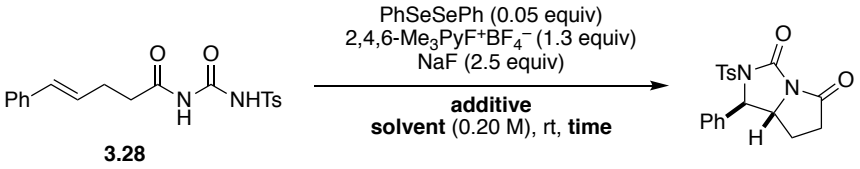
Typical reaction conditions with alternative bifunctional nucleophiles such as dipotassium *N*-toluenesulfonylsulfamate or *O*-triisopropylsilyl-*N*-toluenesulfonylcarbamate did not afford the desired cyclic sulfamate or carbamate with β-methylstyrene (Scheme 3.9.).



Scheme 3.9. Attempted oxyaminations of β-methylstyrene with alternative bifunctional nucleophiles.

Intramolecular reaction of a tethered *N*-toluenesulfonyl-*N'*-acylurea did not afford any desired product (Table 3.4.). This result is not especially surprising in view of the very specific nucleophilicity and pK_a regimes required of the bifunctional nucleophile for a successful diamination, apparent in the failure of a wide variety of alternative nucleophiles to afford any product.[*] The addition of one equivalent of 2,6-lutidine-*N*-oxide, which accelerates some organoselenium catalyzed dichlorinations,[27] did not have any effect on catalytic turnover but did result in partial hydrolysis of the acylurea reagent in dichloromethane and to a greater degree in acetonitrile. Likewise, a catalytic equivalent of urea reagent **3.2**, which may have a role in coordinating the arylselenium(II) catalyst and thereby have an influence on its solubility and reactivity, had no effect on the success of the intramolecular reaction.

Table 3.4. Attempted Intramolecular Diamination of an Alkene with a Tethered Urea Nucleophile.[a]



3.28

entry	solvent	additive, equiv	time (h)	yield (%)
1	CH_2Cl_2	--	48	0
2	MeCN	--	20	0
3	CH_2Cl_2	2,6-lutidine-*N*-oxide, 1.0	22	0 [b]
4	MeCN	2,6-lutidine-*N*-oxide, 1.0	22	0 [b]
5	CH_2Cl_2	$(TsNH)_2CO$ **3.2**, 0.10	22	0
6	MeCN	$(TsNH)_2CO$ **3.2**, 0.10	22	0

[a] All reactions were run on 0.10 mmol scale. [b] Conversion was observed to the products of urea hydrolysis.

3.4. Discussion.

A proposed catalytic cycle, founded primarily in elementary steps already described in the literature, is presented in Figure 3.4. Initial oxidation of the diselenide precatalyst **3.16** likely affords the arylselenium(II) intermediate **3.29** and *sym*-collidine as the byproduct. Unsubstituted

[*] Tao, Z. Postdoctoral Report. Manuscript in Preparation.

N-fluoropyridinium tetrafluoroborate ($PyF^+BF_4^-$) generates an equivalent of pyridine as its byproduct that could potentially mediate eliminative deselenenylation or nucleophilic displacement of selenium-containing reaction intermediates.[28] In general, oxidants that produce unhindered, strongly basic byproducts (e.g. Selectfluor), and oxidants that produce nucleophilic byproducts that could competitively capture the seleniranium intermediate (e.g. NFSI)[21a, 29] are likely similarly ill-suited for this transformation. On the other hand, the basic nitrogen of the collidine byproduct produced by 2,4,6-$Me_3PyF^+BF_4^-$ is more sterically encumbered and less likely to engage in nucleophilic displacement or eliminative deselenenylation (cf. Sections 1.4.1. and 1.4.2.). N-F reagents with higher oxidation potentials, e.g. 2,6-$Cl_2PyF^+BF_4^-$ and Selectfluor,[30] could lead to unproductive, direct oxidation of the nucleophile or olefin and consequently reduce the yield of the desired product.

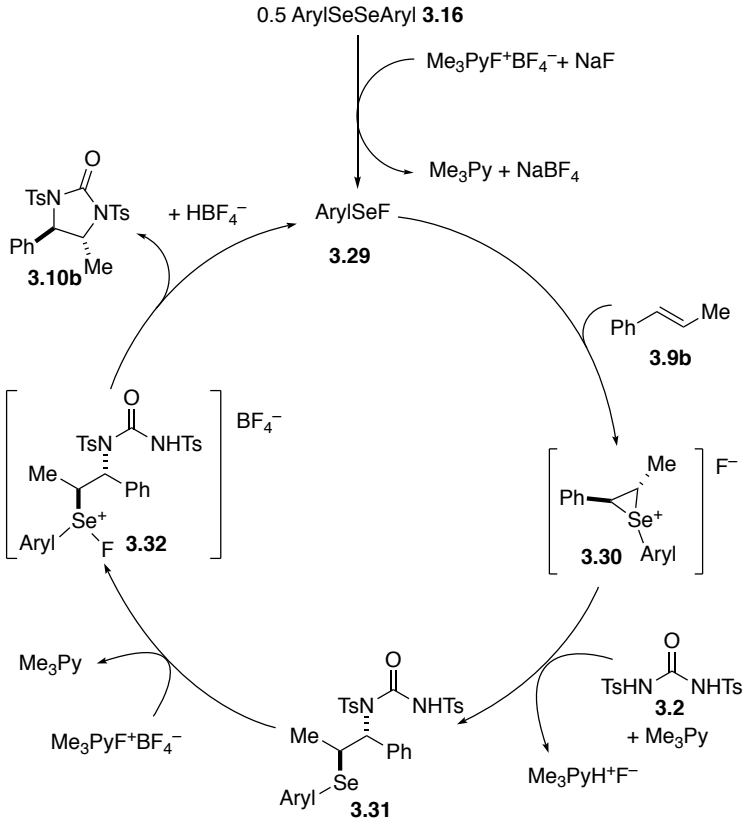


Figure 3.4. Proposed catalytic cycle for the *syn*-diamination of alkenes.

The electrophilic arylselenium(II) species **3.29** could then react with alkene **3.9b** to form the seleniranium ion intermediate **3.30** in a concerted fashion. This step is likely enantiodetermining, with the enantioselectivity resulting from kinetic enantiofacial selectivity.

The rate of this reaction step and the associated enantiofacial selectivity are significantly lower for *cis*-alkenes (e.g. **3.9e**) for different but related reasons. *cis*-Alkenes, unlike *trans*-alkenes, allow orientation of both groups on the alkene away from any significant steric interactions with the catalyst. Thus, approaches to the *Re* or *Si* face of a *cis*-olefin have comparatively little energetic difference.[31] On the other hand, the formation of a seleniranium ion from a *cis*-alkene comes at a greater energetic cost, owing to increasing eclipsing interactions between the groups on the alkene as the olefinic carbons rehybridize in a concerted fashion, leading to slower reaction rates.[32]

It is possible that seleniranium ion formation is reversible, and that enantioselectivity results from thermodynamic equilibration of diastereomeric seleniranium ions, however this mechanistic regime was found to afford poor selectivities in the dichlorination reaction (cf. Section 2.5.2.). Seleniranium ion formation may instead be occurring at the Se(IV) oxidation state, however PhSeF does not appear to undergo oxidation to $PhSeF_3$ with 2,4,6-$Me_3PyF^+BF_4^-$ alone,* instead requiring donor ligands such as chloride or an alkyl group on Se to proceed[33] (N.B. $PhSeF_3$ is typically prepared by reaction of Ph_2Se_2 with XeF_2, a much stronger oxidizing agent).[34] The deprotonated nitrogen nucleophile could potentially serve as such a donor ligand to enable this oxidation prior to seleniranium ion formation, however further mechanistic investigations into the existence of an RCO(Ts)N–SeAr* intermediate are required before any conclusions can be made.

Regardless of the oxidation state of selenium, opening of the seleniranium ion by **3.2**, likely after deprotonation by collidine, could then afford intermediate **3.31**. The pK_a of **3.2** is calculated to be 1.38 ± 2.00,[35] well within the necessary range to protonate collidine (the pK_b-H of 2,4-dimethylpyridinium is ca. 4.5).[36] This intermolecular, nucleophilic ring opening is likely to be the turnover-limiting step, and becomes especially slow with alkene substrates that are not accelerated by aromatic stabilization of a benzylic carbocation (e.g. dialkyl olefins **3.9x** and **3.9y**).

Oxidation to the arylselenium(IV) intermediate **3.31** (if oxidation has not occurred prior to seleniranium ion formation) then allows for intramolecular displacement of selenium by the second urea nitrogen to afford **3.10b** and regenerate the electrophilic selenium species **3.29**. Because only one equivalent of collidine is formed for each catalytic turnover, a catalytic equivalent of base is required to neutralize the acid that is formed in the second displacement. Sodium fluoride could be serving as the base to sequester the HF formed as sodium bifluoride. In

* E. M. Mumford has found that the much more forcing conditions of Selectfluor and CsF in MeCN can oxidize Ph_2Se_2 to $PhSeF_3$, albeit slowly at room temperature in Teflon reaction vessels.

circumstances in which the second displacement is accelerated, e.g. with diaryl alkenes such as **3.9u**, the rate of displacement by the carbonyl oxygen could become competitive with the rate of deprotonation and displacement by the second nitrogen, resulting in a mixture of products **3.10u** and **3.10u'**.

3.5. Conclusions and Outlook.

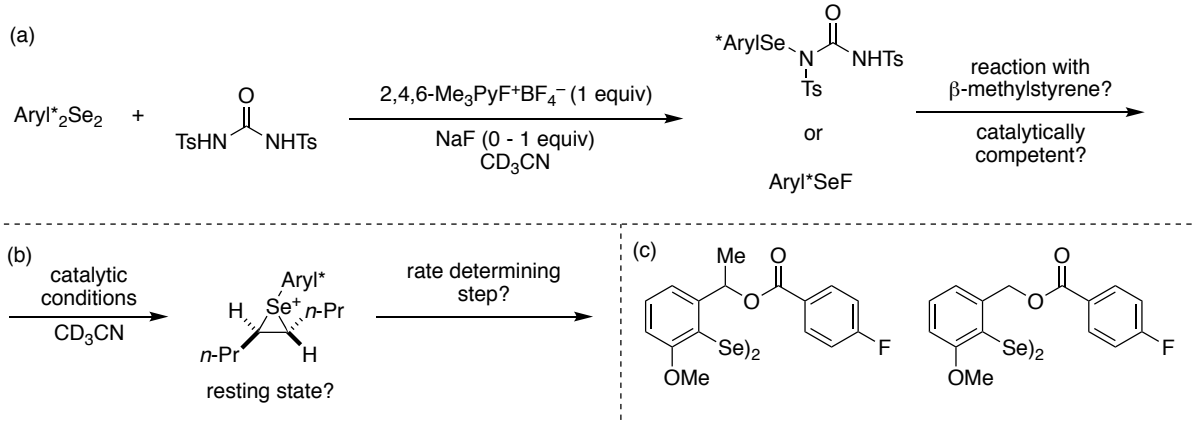
In summary, the first *syn*-stereospecific, intermolecular, enantioselective diamination of alkenes was developed. The method employs a chiral, enantioenriched arylselenium reagent as a redox catalyst for alkene oxidation and C–N bond formation. A wide variety of *trans*-1,2-disubstituted alkenes are diaminated in good yields and enantioselectivities. Aryl-alkyl olefins afford the best yields and selectivities, and preliminary examination of diaryl- and dialkyl-olefins shows promise for further method development. The product of *syn*-addition to the alkene is obtained exclusively in almost all cases, affording the potential to circumvent the issue of site-selectivity inherent in *anti*-stereospecific diaminations of sterically or electronically unbiased alkenes.

The current major limitations of this method are primarily consequences of a lack of reactivity rather than selectivity: (1) low yields are obtained with dialkyl olefins owing to slow reaction rates with attendant decomposition of the bifunctional nucleophile through an unknown mechanism and (2) low yields are obtained in oxyamination reactions with carbamate reagents owing to incomplete conversion, perhaps due to catalyst inactivation through an unknown mechanism.

Alternative bifunctional nucleophiles could be prepared to address the first limitation, as a slow reaction rate would be inconsequential should the reagent be indefinitely stable in the reaction conditions. Otherwise, catalyst design aimed at increasing the rate of seleniranium ion opening could be pursued. Structural modifications to the organoselenium catalyst that decrease the stabilization of positive charge and thus increase the buildup of positive charge on the seleniranium ion have the potential to increase the rate of nucleophilic ring opening, however with potential attendant decrease in the rate of seleniranium ion formation (as the electronic features that favor one typically disfavor the other). Following a similar approach, the reaction conditions and/or bifunctional nucleophile could be modified to increase the equilibrium concentration of the active, deprotonated nucleophile. Better understanding of: (1) the catalytic resting state intermediate, (2)

the mechanism of the decomposition of the bifunctional nucleophile, and (3) the specific ligands present on selenium prior to seleniranium ion formation would help to inform which of these approaches should take priority.

Answers to many of these questions could be gained through (^{1}H, ^{13}C, ^{19}F, ^{77}Se) NMR spectroscopic investigations. Stoichiometric combination of organoselenium reagent, N-F oxidant, and bifunctional nucleophile in CD_3CN would provide insight into the structure of the electrophilic organoselenium species prior to seleniranium ion formation (Scheme 3.10a.). Sodium fluoride may also be included in smaller quantities, as its low solubility could complicate analysis, but its role in the speciation of the reaction mixture may be important. If these conditions afford a specific intermediate that can be isolated (or at least effectively characterized *in situ*), its stability in ambient conditions, reactivity with alkenes, and ability to mediate the catalytic transformation should then be determined. Additionally, should nucleophilic opening of the seleniranium ion be the rate determining step (at least for dialkyl olefins), the seleniranium ion should be observable in reaction mixtures employing catalytic amounts of the organoselenium electrophile (Scheme 3.10b.). Simplified "model" organoselenium electrophiles may better serve these studies where enantioselectivity is not relevant, as the catalyst **3.16** adds a great deal to the overall spectral complexity (Scheme 3.10c.).



Scheme 3.10. Important preliminary spectroscopic experiments. (a) Structural determination of the Aryl*Se(II) complex prior to seleniranium formation. (b) Determination of the catalytic resting state. (c) Simplified "model" organoselenium electrophiles for spectroscopic investigations.

Efforts to address the second limitation are already underway from a practical standpoint, owing to the serendipitous discovery of an alternative class of bifunctional nucleophiles that smoothly afford oxyamination products with both aryl-alkyl and diaryl alkenes. Nevertheless,

spectroscopic studies of the unsuccessful oxyamination reactions with carbamate reagent **3.24** and other bifunctional nucleophiles may aid in understanding potential modes of catalyst inactivation and help improve the foundational knowledge for broader expansion of the scope in enantioselective, electrophilic organoselenium catalyzed alkene difunctionalizations.

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Chapter 4: Experimental.

4.1. General Experimental.

Reaction Setup: All reactions were performed in oven (160 °C) and/or flamed-dried glassware under an atmosphere of dry nitrogen, unless otherwise indicated. Room temperature (rt) was approximately 23 °C. "Brine" refers to a saturated solution of sodium chloride in H_2O.

NMR Spectroscopy: ^{1}H and $^{13}C[^{1}H]$ NMR spectra were recorded Bruker 500 (500 MHz, ^{1}H; 126 MHz, ^{13}C) MHz spectrometers. Acquisition times were 4.096 s for ^{1}H NMR, and 1.024 s for ^{13}C NMR. Spectra are referenced to residual chloroform (δ = 7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), and m (multiplet). Coupling constants, *J*, are reported in Hertz. Integration is provided and assignments are indicated. ^{1}H and ^{13}C assignments are corroborated through 2-D NMR experiments (COSY, HSQC, HMBC).

Infrared Spectroscopy: Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR-ATR system as thin films. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad).

Mass Spectrometry: Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact (EI+) spectra were performed at 70 eV using methane as the carrier gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyzer. Chemical Ionization (CI+) spectra were performed with methane reagent gas, with either a double focusing sector field (DFSF) or time-of-flight (TOF) mass analyzer. Electrospray Ionization (ESI+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100).

Melting Points: Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus in vacuum-sealed capillary tubes and are corrected.

Elemental Analysis: Elemental analysis was performed by the University of Illinois Microanalysis Laboratory. Reported data is the average of at least 2 runs.

Distillation: Bulb-to-bulb distillation was performed on a Kugelrohr, with boiling points (bp) corresponding to uncorrected air-bath temperatures (ABT). A vacuum of 10^{-5} mm Hg was achieved using a BOC Edwards SI100 diffusion pump.

Chromatography: Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 plates. Visualization was accomplished with UV light and/or potassium permanganate

(KMnO4) solution or ceric ammonium molybdate (CAM) solution. Retention factor (Rf) values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system (10 mL) described. Flash column chromatography was performed using Silicycle SiliaFlash®P60 (40-63 μm particle size, 230-400 mesh) (SiO_2). Unless otherwise specified, "silica" refers to P60 grade silica gel.

Solvents: Reaction solvents tetrahydrofuran (THF) (Fisher, HPLC grade), ether (Et_2O) (Fisher, BHT stabilized ACS grade), and dichloromethane (CH_2Cl_2) (Fisher, unstabilized HPLC grade) were dried by percolation through two columns packed with neutral alumina under a positive pressure of argon. Reaction solvent toluene (ACS grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant (supported copper catalyst for scavenging oxygen) under a positive pressure of argon. Reaction solvent dimethylformamide (DMF) (Fischer, ACS grade) was dried by percolation through two columns of activated molecular sieves. Reaction solvent acetonitrile (CH_3CN) (Fisher, amylene stabilized, ACS grade) was distilled from CaH_2 and dried over 3 Å molecular sieves for 1 day prior to use. Reaction solvent 1,2-dichloroethane ($ClCH_2CH_2Cl$) (Aldrich, ACS grade) was dried over 3 Å molecular sieves for 1 day prior to use. Reaction solvent ethanol (absolute, Decon Laboratories) was used as received. Solvents for filtration, transfers, chromatography, and recrystallization were benzene (ACS grade), dichloromethane (CH_2Cl_2) (amylene stabilized, ACS grade), ether (Et_2O) (BHT stabilized, ACS grade), ethyl acetate (EtOAc) (ACS grade), hexane (HPLC grade), ethanol (EtOH) (ACS grade), methanol (MeOH) (ACS grade), pentane (ACS grade), and petroleum ether (35–60°C, ACS grade). Analytical high pressure liquid chromatography (HPLC) was performed with a UV detector (220 nm) using Supelco Astec Cellulose, Regis *R,R*-Whelk-O1, and Daicel Chiralcel OJ-H columns.

Chemicals: Trimethylsilyl chloride (Me_3SiCl) (Aldrich, 97+%) was distilled from CaH_2 at atmospheric pressure and stored in a Schlenk bottle under nitrogen atmosphere in a –30 ºC freezer. 7-methoxy-1-tetralone (Oakwood) was recrystallized from boiling hexanes. Triethylamine (Et_3N) (Fisher) and pyridine (Fisher) were distilled from CaH_2 prior to use. Formic acid (Aldrich, 95%), RuCl[(*S,S*)-TsDPEN](mesitylene) (Strem, 99%), *n*-butyllithium (1.6 M in hexanes, Aldrich), 4-dimethylaminopyridine (DMAP) (Aldrich, 99%), 4-phenylbut-1-ene (TCI, 98%), styrene (Aldrich, *p-tert*-butylcatechol stabilized, 99%), *trans*-β-methylstyrene (TCI, 98%), (*E*)-cinnamyl chloride (Alfa-Aesar, 95%), (*E*)-cinnamyl acetate (Aldrich, 99%), *trans*-anethole

(Aldrich, 99%), *trans*-stilbene (Aldrich, 96%), *trans*-4-octene (GFS, 98%), *p*-toluenesulfonamide (TCI, 98%), and *p*-toluenesulfonyl isocyanate (Aldrich, 96%) were used as received. Benzyltriethylammonium chloride ($BnNEt_3^+Cl^-$) (Oakwood), sodium fluoride (Aldrich, 99%), 1-fluoropyridinium tetrafluoroborate (TCI, 95%), 1-fluoro-2,6-dichloropyridinium tetrafluoroborate (TCI, 96%), 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate ($2,4,6\text{-}Me_3PyF^+BF_4^-$) (TCI, 95%), and diphenyl diselenide (Ph_2Se_2) (Aldrich, 98%) were stored in the glove box and used as received.

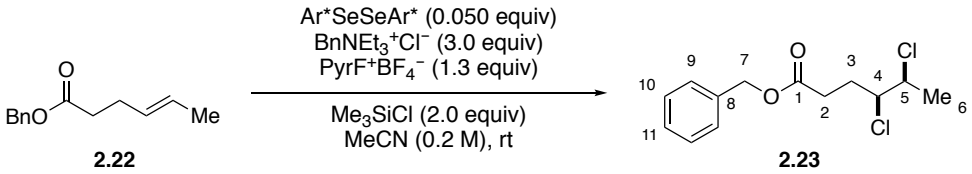
4.2. Experimental for Chapter 2.

4.2.1. Literature Preparations.

The following compounds were prepared by literature methods: (*E*)-hex-4-enoic acid,[1] (*E*)-((hex-4-en-1-yloxy)methyl)benzene **2.20**,[1] 1,2-bis(2,6-bis((*S*)-1-ethoxyethyl)phenyl)diselane **2.24**,[2] 1,2-bis(2-((*S*)-1-methoxyethyl)phenyl)diselane **2.25**,[3] (*S*)-1-(2-bromophenyl)ethan-1-ol,[4] (1*S*,1'*S*)-(diselanediylbis(2,1-phenylene))bis(ethane-1,1-diyl) diacetate **2.27**,[5] 1,2-bis(2-((*S*)-1-(methoxymethoxy)ethyl)phenyl)diselane **2.28**,[6] 1,1'-((1*S*,1'*S*)-(diselanediylbis(2,1-phenylene))bis(ethane-1,1-diyl))bis(3,3-dimethylurea) **2.33**,[7] (*S*)-*N*-(1-phenylethyl)pivalamide,[8] (*R*)-1-(2-bromophenyl)-2-methylpropan-1-amine,[9] *N*-Pivaloyl-1-ferrocenylethylamine,[10] dibenzyl diselenide,[11] (1*S*,1'*S*)-1,1'-(diselanediylbis(2,1-phenylene))bis(*N*,*N*-dimethylethan-1-amine) **2.40**,[12] 1,2-bis(2-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)diselane **2.41**,[13] 2-(2-bromophenyl)-2-methylpropanoic acid,[14] (*S*)-2-(2-(2-bromophenyl)propan-2-yl)-4-isopropyl-4,5-dihydrooxazole,[14] (*S*)-2-(2-(2-bromophenyl)propan-2-yl)-4-(*tert*-butyl)-4,5-dihydrooxazole,[14] (*S*)-2-aminopropan-1-ol,[15] (*S*)-2-amino-4-methylpentan-1-ol,[16] dimethyl diselenide,[11a, 17] 1,2-bis((*S*)-2-methoxy-8-(methoxymethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl)diselane **2.49**,[6] 6-methoxy-2,3-dihydro-1*H*-inden-1-one,[18] 1-methoxy-4-(selenocyanatomethyl)benzene,[19] 3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one,[20] [(–)-sparteine]$PdCl_2$,[21] 8-bromo-7-methoxy-3,4-dihydronaphthalen-1(2H)-one,[22] (*E*)-7-phenylhept-4-enoic acid **2.59**,[23] and (*E*)-6-phenylhex-3-enoic acid **2.63**.[24]

4.2.2. Experimental Procedures.

4.2.2.1. Representative Procedure for Catalytic *syn*-Dichlorination of Alkenes [BBG-7-018].



2.22 **2.23**

To a 15 x 45 mm dram vial was added the diselenide catalyst **2.46** (7.42 mg, 0.010 mmol, 0.050 equiv) The vial was then transferred into the glove box and $BnNEt_3^+Cl^-$ (131 mg, 0.6 mmol, 3.0 equiv) and $PyF^+BF_4^-$ (48 mg, 0.26 mmol, 1.3 equiv) were added. The vial was capped with a rubber septum and removed from the glove box. Acetonitrile (1 mL) and Me_3SiCl (51 µL, 0.4 mmol, 2.0 equiv) were added and the reaction was stirred for 10 min at room temperature. Benzyl hex-4-enoate (41 mg, 0.2 mmol) was added dropwise and the mixture was stirred at room temperature. The reaction was allowed to proceed until the olefin was completely consumed, with periodic monitoring by TLC (pentane/Et_2O, 19:1; **2.22** R_f = 0.42, **2.23** R_f = 0.25). Once complete, the reaction was quenched by the slow addition of saturated sodium bicarbonate solution (1 mL). After dilution with deionized water (2 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3x 5 mL). The combined organic layers were dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). The crude mixture was re-dissolved in Et_2O (3 mL) and filtered through a short silica plug. The crude product was characterized qualitatively by ^{1}H NMR spectroscopy to determine the diastereomeric ratio of 95:5. Diagnostic peaks were: ***syn*-2.23**: 4.25 (qd; *J* 6.7, 2.9 Hz, HC(10)); 4.10 (dt; *J* = 10.8, 3.0 Hz, HC(9)); ***anti*-2.23**: 4.10 (quint; *J* = 6.6 Hz, HC(10)); 4.01 (ddd; *J* = 10.2, 6.5, 2.6 Hz, HC(9)). Purification by silica gel column chromatography (1.5 cm ø x 20 cm column) eluting with hexanes/TBME, 95:5 gave ***syn*-2.23** (39 mg, 71%) as a clear, colorless oil.

Data for ***syn*-2.23**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.41 – 7.31 (m, 5 H, HC(aryl)), 5.14 (d, *J* = 3.1 Hz, 2 H, HC(7)), 4.25 (qd, *J* = 6.7, 2.9 Hz, 1 H, HC(5)), 4.10 (dt, *J* = 10.8, 3.0 Hz, 1 H, HC(4)), 2.67 (ddd, *J* = 16.9, 7.8, 5.6 Hz, 1 H, HC(2)), 2.57 (dt, *J* = 16.8, 7.7 Hz, 1 H, HC(2)), 2.30 (dtd, *J* = 14.4, 7.8, 2.9 Hz, 1 H, HC(3)), 2.06 (dddd, *J* = 14.4, 10.8, 7.7, 5.5 Hz, 1 H, HC(3)), 1.59 (d, *J* = 6.6 Hz, 3 H, HC(6)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.6 (C(1)), 135.9 (C(8)), 128.8 (C(10)), 128.5 (C(11)), 128.4 (C(9)), 66.7 (C(7)), 65.2 (C(4)), 59.9 (C(5)), 31.3 (C(2)), 29.4 (C(3)), 21.0 (C(6)).

HRMS: (ES+)

Found: 297.0427; Calc. for $C_{13}H_{16}O_2NaCl_2$: 297.0425

HPLC: **(*S,S*)-2.23**, t_R 14.9 min (26.2%), **(*R,R*)-2.23**, t_R 18.6 min (73.7%) (Daicel Chiralpak OJ-H; hexanes/*i*-PrOH, 9:1; 0.5 mL/min, 210 nm).

Data for ***anti*-2.23**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.45 – 7.30 (m, 5 H, HC(aryl)), 5.14 (d, J = 2.6 Hz, 2 H, HC(7)), 4.10 (p, J = 6.6 Hz, 1 H, HC(5)), 4.01 (ddd, J = 10.2, 6.5, 2.6 Hz, 1 H, HC(4)), 2.68 (ddd, J = 16.8, 8.4, 5.3 Hz, 1 H, HC(2)), 2.58 (ddd, J = 16.8, 8.1, 7.4 Hz, 1 H, HC(2)), 2.43 (dddd, J = 14.5, 8.4, 7.4, 2.6 Hz, 1 H, HC(3)), 2.01 (dddd, J = 14.6, 10.2, 8.1, 5.3 Hz, 1 H, HC(3)), 1.63 (d, J = 6.5 Hz, 3 H, HC(6)).

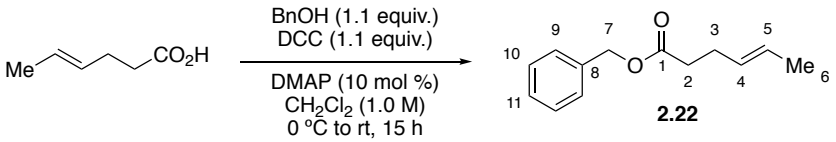
HRMS: (ES+)

Found: 297.0427; Calc. for $C_{13}H_{16}O_2NaCl_2$: 297.0425

HPLC: t_R1 34.5 min (50%), t_R2 37.0 min (50%) (Daicel Chiralpak OJ-H; hexanes/*i*-PrOH, 19:1; 0.5 mL/min; 210 nm)

4.2.2.2. Preparation of Alkenes.

Preparation of Benzyl (*E*)-Hex-4-enoate (2.22) [BBG-2-187].



2.22

To a 25-mL Schlenk flask was added *E*-4-hexenoic acid (1.01 g, 8.8 mmol), followed by CH_2Cl_2 (9.0 mL, 1 M), 4-dimethyalminopyridine (107 mg, 0.88 mmol, 10 mol %) and benzyl alcohol (1.00 mL, 9.7 mmol, 1.1 equiv). The resulting mixture was stirred and cooled to 0 ºC. Dicyclohexylcarbodiimide (2.00 g, 9.7 mmol, 1.1 equiv) was added in one portion against argon backflow. The reaction mixture was allowed to warm to room temperature. After 15 h the reaction mixture formed a white slurry. This slurry was filtered through Celite (10 g) and the filter cake

was rinsed with CH_2Cl_2 (2 x 25 mL). The filtrate was washed with 1 M HCl (2 x 10 mL) and sat. aq. $NaHCO_3$ (1 x 10 mL), dried over $MgSO_4$ (6 g), filtered and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (6 cm ø x 20 cm) eluting with pentane/Et_2O, 98:2 followed by Kugelrohr distillation (150 ºC, 7 mm Hg) provided **31** (1.23 g, 69%) as a colorless oil. Spectroscopic data is consistent with the literature.[25]

Data for **2.22**:

^{1}H NMR: (500 MHz, $CDCl_3$)

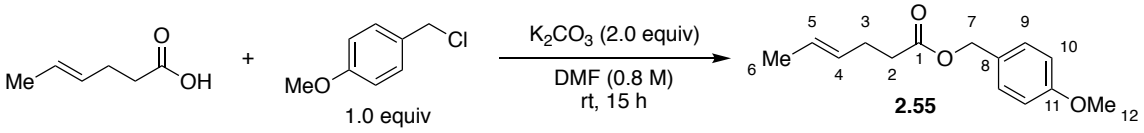
δ 7.40 – 7.30 (m, 5 H, HC(9,10,11)), 5.53 – 5.37 (m, 2 H, HC(4,5)), 5.12 (s, 2 H, HC(7)), 2.42 (ddd, J = 7.8, 7.0, 1.1 Hz, 2 H, HC(2)), 2.36 – 2.30 (m, 2 H, HC(3)), 1.63 (dd, J = 5.9, 1.2 Hz, 3 H, HC(6)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 173.3, 136.3, 129.3, 128.8, 128.43, 128.40, 126.5, 77.5, 77.3, 77.0, 66.4, 34.5, 28.1, 18.1.

TLC: R_f = 0.61 (pentane/Et_2O, 9:1) [UV, CAM]

Preparation of 4-Methoxybenzyl (*E*)-Hex-4-enoate (2.55) [BBG-9-048].



To a 25-mL round bottom flask was added *E*-4-hexenoic acid (228 mg, 2.00 mmol), followed by DMF (3 mL, 0.8 M). K_2CO_3 (553 mg, 4.00 mmol, 2.00 equiv) was added, and the mixture was stirred at room temperature for 10 min. 4-methoxybenzyl chloride (271 µL, 2.00 mmol, 1.00 equiv) was added dropwise via syringe and the reaction mixture was then stirred at room temperature. After 15 h, the resulting suspension was transferred into a 250-mL separatory funnel with a water (2 × 10 mL) and EtOAc (3 × 10 mL) rinse. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with water (2 × 25 mL), 10% aq. NaOH (10 mL), sat. aq. $NaHSO_3$ (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (40 g,

ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 9:1 over 20 min afforded **2.55** (297 mg, 63%) as a clear, colorless oil.

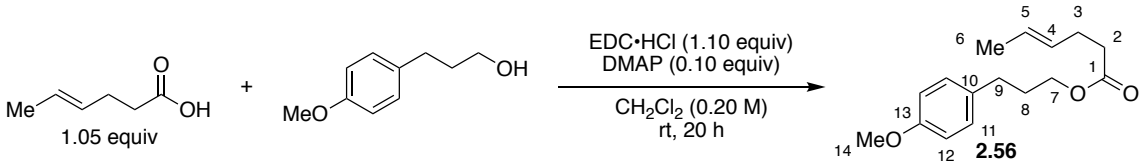
Data for **2.55**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.29 (d, J = 8.6 Hz, 2 H, HC(9)), 6.89 (d, J = 8.7 Hz, 2 H, HC(10)), 5.55 – 5.32 (m, 2 H, HC(4,5)), 5.05 (s, 2 H, HC(7)), 3.81 (s, 3 H, HC(12)), 2.38 (ddd, J = 7.7, 6.7, 1.6 Hz, 2 H, HC(2)), 2.30 (ddt, J = 8.8, 6.8, 3.6 Hz, 2 H, HC(3)), 1.62 (dd, J = 6.0, 1.1 Hz, 3 H, HC(6)).

TLC: R_f 0.36 (hexanes/EtOAc, 9:1) [UV, $KMnO_4$]

Preparation of 3-(4-Methoxyphenyl)propyl (*E*)-Hex-4-enoate (2.56) [BBG-9-071].



To a 50-mL Schlenk flask were added *E*-4-hexenoic acid (599 mg, 5.25 mmol, 1.05 equiv) and CH_2Cl_2 (20 mL). EDC•HCl (1.05 g, 5.50 mmol, 1.10 equiv) and DMAP (61.1 mg, 0.500 mmol, 0.100 equiv) were then each added in one portion at room temperature. After 5 min, 3-(4-methoxyphenyl)propanol (831 mg, 5.00 mmol) in CH_2Cl_2 (5 mL) was added dropwise via syringe. The syringe was then rinsed into the reaction mixture with CH_2Cl_2 (1 mL) and the reaction mixture was stirred at room temperature. After 20 h, the reaction mixture was transferred to a 250-mL separatory funnel with a CH_2Cl_2 rinse (2 × 10 mL). The organic layer was washed with water (20 mL), 1 M HCl (2 × 20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (120 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 9:1 over 15 min afforded **2.56** (811 mg, 62%) as a clear, colorless oil.

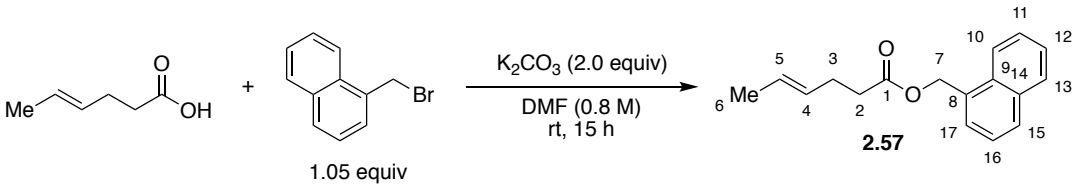
Data for **2.56**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.09 (d, *J* = 8.6 Hz, 2 H, HC(11)), 6.83 (d, *J* = 8.6 Hz, 2 H, HC(12)), 5.46 (ddddd, *J* = 21.2, 15.2, 13.4, 6.6, 1.3 Hz, 2 H, HC(4,5)), 4.08 (t, *J* = 6.5 Hz, 2 H, HC(7)), 3.79 (s, 3 H, HC(14)), 2.63 (dd, *J* = 8.5, 6.8 Hz, 2 H, HC(2)), 2.40 – 2.26 (m, 4 H, HC(3,9)), 1.99 – 1.87 (m, 2 H, HC(8)), 1.64 (dd, *J* = 6.0, 1.3 Hz, 3 H, HC(6)).

TLC: R_f 0.31 (hexane/EtOAc, 9:1) [UV, CAM]

Preparation of Naphthalen-1-ylmethyl (*E*)-Hex-4-enoate (2.57) [BBG-9-049].



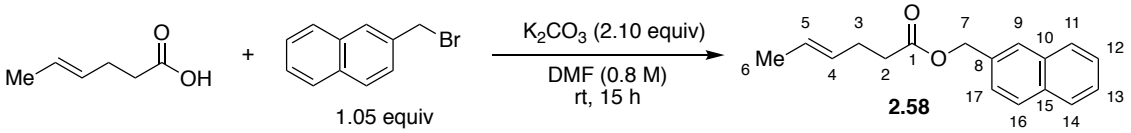
To a 25-mL round bottom flask was added *E*-4-hexenoic acid (228 mg, 2.00 mmol), followed by DMF (3 mL, 0.8 M). K_2CO_3 (553 mg, 4.00 mmol, 2.00 equiv) was added, and the mixture was stirred at room temperature for 10 min. 1-(bromomethyl)naphthalene (461 mg, 2.10 mmol, 1.05 equiv) was added dropwise via syringe and the reaction mixture was then stirred at room temperature. After 15 h, the resulting suspension was transferred into a 250-mL separatory funnel with a water (2 × 10 mL) and EtOAc (3 × 10 mL) rinse. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with water (2 × 25 mL), 10% aq. NaOH (10 mL), sat. aq. $NaHSO_3$ (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (40 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 9:1 over 20 min afforded **2.57** (436 mg, 86%) as a clear, colorless oil.

Data for **2.57**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.05 – 7.97 (m, 1 H, HC(aryl)), 7.92 – 7.83 (m, 2 H, HC(aryl)), 7.61 – 7.50 (m, 4 H, HC(aryl)), 7.46 (dd, *J* = 8.2, 7.0 Hz, 1 H, HC(aryl)), 5.58 (s, 2 H, HC(7)), 5.51 – 5.33 (m, 2 H, HC(4,5)), 2.42 (ddd, *J* = 7.7, 6.9, 1.2 Hz, 2 H, HC(2)), 2.37 – 2.27 (m, 2 H, HC(3)), 1.63 – 1.57 (m, 3 H, HC(6)).

Preparation of Naphthalen-2-ylmethyl (*E*)-Hex-4-enoate (2.58) [BBG-9-084].



To a 25-mL round bottom flask was added *E*-4-hexenoic acid (571 mg, 5.00 mmol), followed by DMF (6.3 mL, 0.8 M). K_2CO_3 (1.45 g, 10.5 mmol, 2.10 equiv) was added, and the mixture was stirred at room temperature for 10 min. 2-(bromomethyl)naphthalene (1.16 g, 5.25 mmol, 1.05 equiv) was added dropwise via syringe and the reaction mixture was then stirred at room temperature. After 15 h, the resulting suspension was transferred into a 250-mL separatory funnel with a water (2 × 10 mL) and EtOAc (3 × 10 mL) rinse. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with water (2 × 25 mL), 10% aq. NaOH (10 mL), sat. aq. $NaHSO_3$ (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (40 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 9:1 over 18 min afforded **2.58** (1.11 g, 87%) as a clear, colorless oil.

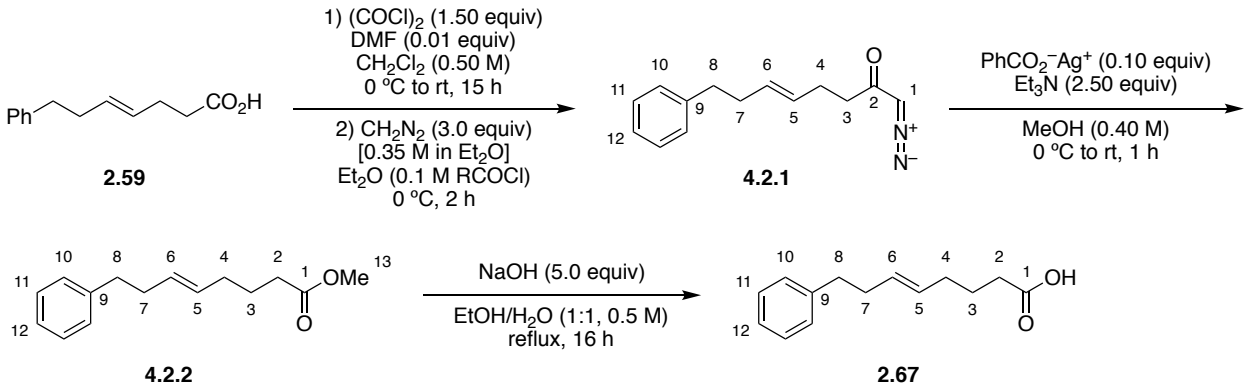
Data for **2.58**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.95 – 7.72 (m, 4 H, HC(aryl)), 7.58 – 7.40 (m, 3 H, HC(aryl)), 5.56 – 5.35 (m, 2 H, HC(4,5)), 5.28 (s, 2 H, HC(7)), 2.52 – 2.40 (m, 2 H, HC(2)), 2.39 – 2.29 (m, 2 H, HC(3)), 1.62 (d, J = 4.7 Hz, 3 H, HC(6)).

Preparation of (*E*)-8-Phenyloct-5-enoic Acid (2.67).

Preparation of (*E*)-1-Diazo-8-phenyloct-5-en-2-one (4.2.1) [BBG-10-057, BBG-10-061].



2.59 **4.2.1** **4.2.2** **2.67**

To a 50-mL Schlenk flask equipped with a magnetic stir bar and a rubber septum was added (*E*)-7-phenylhept-4-enoic acid **2.59** (2.04 g, 10.0 mmol) and CH_2Cl_2 (20 mL, 0.50 M). The solution was immersed in an ice-water bath and DMF (8 μL, 0.1 mmol, 0.01 equiv) was added. After 5 min, oxalyl chloride (1.29 mL, 15.0 mmol, 1.50 equiv) was added dropwise. The reaction mixture was removed from the ice bath and stirred for 15 h at room temperature. Solvent and excess oxalyl chloride were then removed under reduced pressure (25 ºC, 0.05 mm Hg) to afford (*E*)-7-phenylhept-4-enoyl chloride as a yellow-orange oil (2.20 g, 99%), which was carried on to the next step without purification.

Diazomethane solution in Et_2O (85 mL, 0.35 M, 3.0 equiv), generated from Diazald and titrated following a literature procedure,[26] was added to a Clear-Seal 500-mL 3-neck round bottom flask equipped with a magnetic stir bar and a Clear-Seal addition funnel. The diazomethane solution was then immersed in an ice-water bath. The addition funnel was charged with (*E*)-7-phenylhept-4-enoyl chloride (2.20 g, 10 mmol) in Et_2O (100 mL). After 5 min, the acid chloride solution was added dropwise to the vigorously stirred diazomethane solution over 20 min at 0 ºC. After the addition was complete, the reaction mixture was stirred for 2 h at 0 ºC. The reaction was then quenched by the cautious addition of acetic acid (75 mL, 0.50 M in water, 3.7 equiv). The resulting biphasic mixture was poured into a 500-mL separatory funnel containing sat. aq. $NaHCO_3$ (200 mL), shaken cautiously, and separated. The aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (100 mL), water (100 mL), and brine (100 mL), dried over $MgSO_4$ (5 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (120 g silica, ISCO MPLC) eluting with hexanes/EtOAc, continuous gradient 1:0

to 7:3 over 20 min provided **4.2.1** as a clear, yellow oil (2.09 g, 93%), contaminated with ca. 5% α-chloroketone.

Data for **4.2.1**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.37 – 7.23 (m, 2 H, HC(aryl)), 7.23 – 7.12 (m, 3 H, HC(aryl)), 5.46 (tdd, J = 21.2, 15.2, 6.0 Hz, 2 H, HC(5,6)), 5.17 (bs, 1 H, HC(1)), 2.66 (dd, J = 8.7, 6.7 Hz, 2 H, HC(3)), 2.43 – 2.22 (m, 6 H, HC(4,7,8)).

Preparation of Methyl (*E*)-8-Phenyloct-5-enoate (4.2.2) [BBG-10-062].

To a 50-mL Schlenk flask equipped with a magnetic stir bar and a rubber septum, in the dark, was added diazoketone **4.2.1** (2.09 g, 9.15 mmol) and MeOH (23 mL, 0.40 M). The resulting solution was stirred and immersed in an ice-water bath. After 5 min, a solution of silver benzoate (210 mg, 0.915 mmol, 0.100 equiv) in triethylamine (3.19 mL, 22.9 mmol, 2.50 equiv) was added dropwise over 2 min. Nitrogen bubbles immediately began to form, and the solution turned from a pale yellow to a deep red. The reaction was stirred for 15 min at 0 ºC, then warmed to room temperature and stirred for an additional 30 min. The reaction mixture was then transferred to a 100-mL round bottom flask with a methanol rinse (2 × 10 mL) and concentrated under reduced pressure by rotary evaporation (30 ºC, 4 mm Hg). IR spectroscopy of the crude reaction mixture indicated complete conversion of the diazoketone (no absorbance at 2100 cm^{-1}). Purification by silica gel column chromatography (120 g silica, ISCO MPLC) eluting with hexanes/EtOAc, continuous gradient 1:0 to 4:1 over 20 min afforded **4.2.2** (1.19 g, 56%) as a clear, colorless oil.

Data for **4.2.2**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.32 – 7.25 (m, 2 H, HC(aryl)), 7.21 – 7.14 (m, 3 H, HC(aryl)), 5.88 – 5.08 (m, 2 H, HC(5,6)), 3.67 (s, 3 H, HC(13)), 2.66 (dd, J = 8.9, 6.7 Hz, 2 H, HC(2)), 2.39 – 2.21 (m, 4 H, HC(7,8)), 2.01 (q, J = 7.3 Hz, 2 H, HC(4)), 1.67 (p, J = 7.5 Hz, 2 H, HC(3)).

Preparation of (*E*)-8-Phenyloct-5-enoic Acid (2.67) [BBG-10-069].

To a 50-mL round bottom flask equipped with a magnetic stir bar and a reflux condenser were added the methyl ester **4.2.2** (1.07 g, 5.04 mmol), ethanol (5.0 mL), and water (5.0 mL).

Sodium hydroxide (1.01 g, 25.2 mmol, 5.00 equiv) was then added in one portion at room temperature. The reaction mixture was stirred vigorously and heated to reflux. After 16 h the reaction was cooled to room temperature and concentrated under reduced pressure by rotary evaporation (40 ºC, 4 mm Hg). The resulting white paste was taken up in diethyl ether (100 mL) and water (100 mL) in a 250-mL separatory funnel. The layers were shaken and separated, and the aqueous layer was washed with diethyl ether (2 × 50 mL). The aqueous layer was collected and cooled in an ice-water bath, then acidified to pH < 2 with 35% aq. HCl. The cloudy aqueous suspension was transferred to a 250-mL separatory funnel and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation. Purification by filtration through a short silica plug (5 cm ø × 5 cm), eluting with 1:1 hexanes/EtOAc afforded **2.67** (1.08 g, 98%) as a clear, pale-yellow oil.

Data for **2.67**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 10.95 (bs, 1 H, CO_2**H**), 7.40 – 7.27 (m, 2 H, HC(11)), 7.27 – 7.16 (m, 3 H, HC(10,12)), 5.60 – 5.48 (m, 1 H, HC(6)), 5.48 – 5.34 (m, 1 H, HC(5)), 2.71 (dd, *J* = 8.8, 6.8 Hz, 2 H, HC(2)), 2.36 (q, *J* = 7.1 Hz, 4 H), 2.08 (q, *J* = 6.9 Hz, 2 H), 1.73 (p, *J* = 7.4 Hz, 2 H).

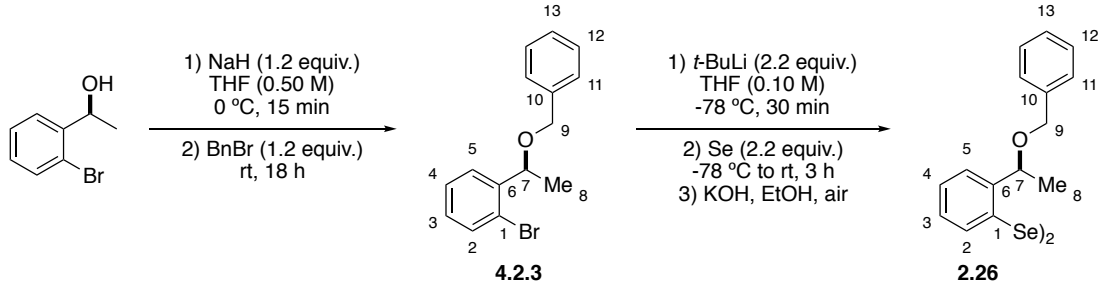
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 178.7 (C(1)), 142.1 (C(9)), 130.9 (C(11)), 129.7 (C(10)), 128.6 (C(5)), 128.4 (C(6)), 125.9 (C(12)), 36.1 (C(2)), 34.5 (C(8)), 33.1 (C(7)), 31.9 (C(4)), 24.5 (C(3)).

4.2.2.3. Preparation of Diselenides.

Preparation of 1,2-Bis(2-((*S*)-1-(benzyloxy)ethyl)phenyl)diselane (2.26).

Preparation of (*S*)-1-(1-(benzyloxy)ethyl)-2-bromobenzene (4.2.3) [BBG-2-049].



4.2.3 **2.26**

To a 10-mL Schlenk flask was added NaH (washed, 57.6 mg, 2.4 mmol, 1.2 equiv) in a glovebox. The flask was capped with a rubber septum and removed from the glovebox. THF (2 mL) was added *via* syringe. The mixture was stirred to suspension and cooled to 0 ºC in an ice bath. (*S*)-1-(2-bromophenyl)ethan-1-ol (e.r. >99:1)[6] (402 mg, 2.0 mmol), dissolved in THF (2 mL), was added dropwise to the NaH suspension. The resulting mixture was stirred for 15 min at 0 ºC. After warming to room temperature, benzyl bromide (0.59 mL, 2.4 mmol, 1.2 equiv) was added dropwise. The mixture was then stirred for 18 h at room temperature. The reaction was quenched by slow addition of sat. aq. NH_4Cl solution (3 mL) and diluted with Et_2O (3 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ (1 g), filtered and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (3.0x15.0 cm column) eluting with pentane/Et_2O, 95:5 provided **4.2.3** (568 mg, 97%) as a colorless oil.

Data for **4.2.3**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.62 (dd, *J* = 7.73, 1.76 Hz, 1 H, HC(2)), 7.56 (dd, *J* = 8.02, 1.22 Hz, 1 H, HC(5)), 7.47-7.22 (m, 6 H, HC(aryl)), 7.17 (td, *J* = 7.64, 1.75 Hz, 1 H, HC(4)), 4.96 (q, *J* = 6.40 Hz, 1 H, HC(7)), 4.48 (d, *J* = 11.60 Hz, 1 H, HC(9)), 4.36 (d, *J* = 11.60 Hz, 1 H, HC(9)), 1.48 (d, *J* = 6.40 Hz, 3 H, HC(8))

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.1, 138.6, 132.9, 129.3, 129.0, 128.9, 128.6, 128.2, 128.0, 127.8, 127.5, 122.9, 76.4, 71.0, 23.1

HRMS: (EI+)

Found: 290.0310; Calc. for $C_{15}H_{15}OBr$: 290.0306

TLC: R_f 0.85 (hexane/EtOAc, 95:5) [UV, CAM]

Preparation of 1,2-Bis(2-((*S*)-1-(benzyloxy)ethyl)phenyl)diselane (2.26) [BBG-2-117].

To a 25-mL Schlenk flask was added aryl bromide **4.2.3** (291 mg, 1.0 mmol) and THF (10 mL). The resulting solution was stirred and cooled to -78 ºC in a dry ice/*i*-PrOH bath. *tert*-Butyllithium (1.47 mL, 2.2 mmol, 2.2 equiv) was added dropwise via syringe. After stirring 30 min at -78 ºC, Se powder (174 mg, 2.2 mmol, 2.2 equiv) was added in one portion against argon backflow. The reaction mixture was then allowed to warm to room temperature and stirred for 3 h. Sat. aq. NH_4Cl (5 mL) was added dropwise to quench the reaction, followed by Et_2O dilution (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3x10 mL). Combined organic layers were dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg) to give a yellow oil. The crude product was re-dissolved in EtOH (10 mL) and transferred to a 25-mL single-neck round bottom flask. KOH (100 mg, crushed pellet) was added and the mixture was stirred under air at ambient temperature for 4 h. The reaction mixture was concentrated under reduced pressure and filtered through a short silica plug (Et_2O rinse, 3 x 5 mL) to give the crude product as a brown oil. Purification by silica gel column chromatography (3.0 x 20.0 cm column) eluting with pentane/Et_2O (95:5) provided **2.26** (143 mg, 49%, 90% pure with inseparable isomeric purity) as an orange semisolid.

Data for **2.26**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.75 (dd, J = 7.89, 1.28 Hz, 2 H, HC(2)), 7.44 (dd, J = 7.44, 1.52 Hz, 2 H, HC(5)), 7.37-7.26 (m, 12 H, HC(aryl)), 7.19 (td, J = 7.56, 1.55 Hz, 2 H, HC(4)), 4.95 (q, J = 6.52 Hz, 2 H, HC(7)), 4.40 (d, J = 11.60 Hz, 2 H, HC(9)), 4.22 (d, J = 11.60 Hz, 2 H, HC(9)), 1.49 (d, J = 6.52, 6 H, HC(8)).

^{13}C NMR: (126 MHz, $CDCl_3$)

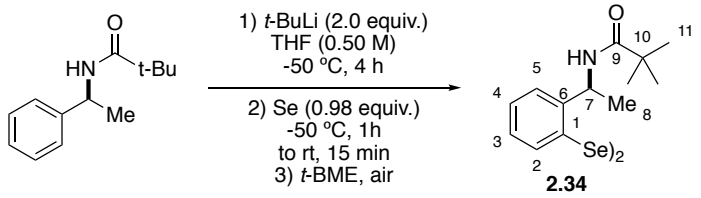
δ 144.2, 138.5, 133.7, 129.8, 128.62, 128.60, 128.5, 128.1, 127.8, 126.8, 77.1 (under solvent signal), 70.9, 23.1

HRMS: (ES+)

Found: 582.0582; Calc. for $C_{30}H_{30}O_2Se_2$: 582.0576

TLC: R_f = 0.48 (pentane/Et_2O 9:1) [Visible yellow, UV, CAM]

Preparation of *N,N′*-((1*S*,1′*S*)-(Diselanediylbis(2,1-phenylene))bis(ethane-1,1-diyl))bis(2,2-dimethylpropanamide) (2.34) [BBG-2-173].



To a 5-mL Schlenk flask was added (*S*)-*N*-(1-phenylethyl)pivalamide (e.r. >99:1)[8] (154 mg, 0.75 mmol) and THF (1.5 mL). The mixture was stirred and cooled to -50 ºC. *t*-BuLi (0.937 mL, 1.6 M in pentane, 1.5 mmol, 2.0 equiv) was added to the solution, dropwise. After 4 h at -50 ºC, Se powder (58.4 mg, 0.98 equiv) was added in one portion against argon backflow. The reaction mixture was stirred 1 h at -50 ºC, then allowed to warm to rt. After stirring 15 min at rt, the reaction was quenched with sat. aq. NH_4Cl (3 mL). The resulting solution was extracted with CH_2Cl_2 (3 x 8 mL) and the combined extracts were washed with 1 M HCl (5 mL) and brine (5 mL), dried over $MgSO_4$ (3 g), filtered and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). The resulting crude solid was recrystallized from hot *t*-BME to provide **2.34** (108 mg, 51%) as an orange solid.

Data for **2.34**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.72 (dd, *J* = 7.5, 1.1 Hz, 2 H, HC(2)), 7.26 – 7.16 (m, 4 H, HC(3,5)), 7.13 (ddd, *J* = 7.8, 5.8, 3.0 Hz, 2 H, HC(4)), 5.93 (d, *J* = 7.0 Hz, 2 H, NH), 5.26 (p, *J* = 6.9 Hz, 2 H, HC(7)), 1.40 (d, *J* = 6.8 Hz, 6 H, HC(8)), 1.14 (s, 18 H, HC(11)).

^{13}C NMR: (101 MHz, $CDCl_3$)

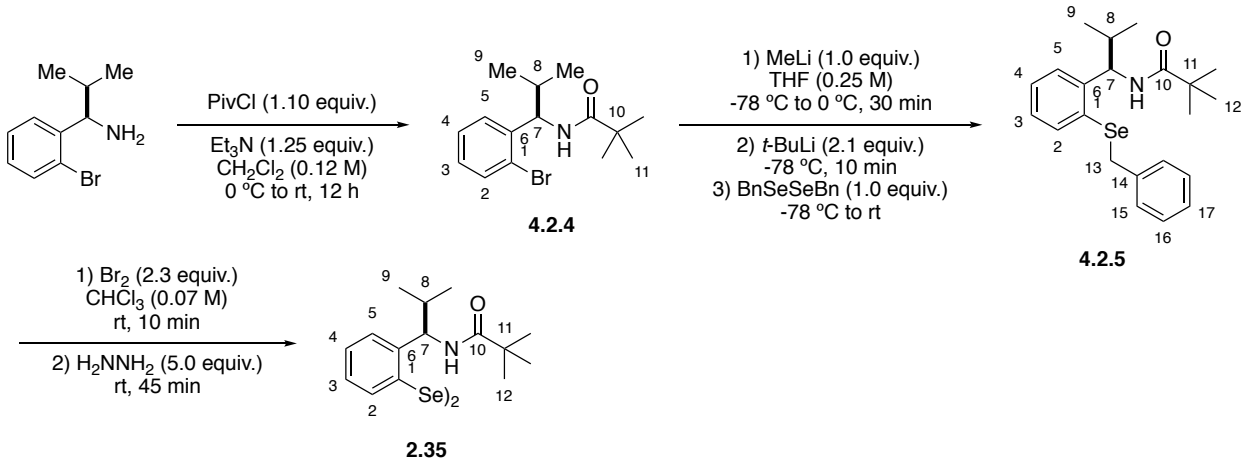
δ 177.37, 143.62, 134.19, 130.85, 128.50, 128.28, 125.81, 77.48, 77.16, 76.84, 49.26, 49.20, 38.71, 27.72, 27.66.

HRMS: (ES+)

Found: 567.1205; Calc. for $C_{26}H_{37}N_2O_2Se_2$: 567.1193

Preparation of *N*,*N*'-((1*R*,1'*R*)-(Diselanediylbis(2,1-phenylene))bis(2-methylpropane-1,1-diyl))bis(2,2-dimethylpropanamide) (2.35).

Preparation of (*R*)-*N*-(1-(2-Bromophenyl)-2-methylpropyl)pivalamide (4.2.4) [BBG-4-012].



To a 25-mL Schlenk flask was added (*R*)-1-(2-bromophenyl)-2-methylpropan-1-amine (e.r. >99:1)[9] (278 mg, 1.2 mmol) followed by CH_2Cl_2 (10 mL). The solution was cooled to 0 ºC and triethylamine (208 µL, 1.5 mmol, 1.25 equiv) was added, followed by pivaloyl chloride (162 µL, 1.32 mmol, 1.1 equiv). The reaction mixture was then allowed to warm to room temperature. After 12 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL) and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x 10 mL) and the combined organic layers were washed with 1 M HCl (10 mL), 10% NaOH (10 mL), dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by filtration through a silica plug (3 cm ø x 10 cm) eluting with hexanes/ethyl acetate 1:1 provided **4.2.4** (364 mg, 97%) as a white solid.

Data for **4.2.4**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.55 (dd, *J* = 7.9, 1.3 Hz, 1 H, HC(2)), 7.30 – 7.24 (m, 1 H, HC(4)), 7.18 (dd, *J* = 7.7, 1.8 Hz, 1 H, HC(5), 7.11 (ddd, *J* = 7.8, 7.2, 1.8 Hz, 1 H, HC(3)), 6.34 (d, *J* = 8.6 Hz, 1 H, NH), 5.00 (t, *J* = 8.3 Hz, 1 H, HC(7)), 2.38 – 2.17 (m, 1 H, HC(8)), 1.23 (s, 9 H, HC(11)), 0.99 (d, *J* = 6.7 Hz, 3 H, HC(9)), 0.88 (d, *J* = 6.7 Hz, 3 H, HC(9)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 177.75, 141.11, 133.78, 129.54, 128.69, 127.54, 123.07, 77.51, 77.46, 77.26, 77.01, 59.30, 39.11, 32.21, 27.84, 20.41, 18.69.

Preparation of (*R*)-*N*-(1-(2-(Benzylselanyl)phenyl)-2-methylpropyl)pivalamide (4.2.5) [BBG-4-013].

To a 10-mL Schlenk flask was added **4.2.4** (156 mg, 0.5 mmol) followed by THF (2 mL). The solution was cooled to -78 ºC and methyllithium (313 µL, 1.6 M in diethyl ether, 0.5 mmol, 1.0 equiv) was added dropwise. Once the addition was complete, the reaction mixture was warmed to 0 ºC and was stirred. After 30 minutes, the mixture was cooled to -78 ºC once more and *t*-BuLi (656 µL, 1.6 M in pentane, 1.05 mmol, 2.1 equiv) was added dropwise. The reaction mixture was stirred at -78 ºC for ten minutes and then dibenzyl diselenide (170 mg, 0.5 mmol, 1.0 equiv) in THF (2 mL) was added dropwise to the solution. The reaction was then allowed to warm to room temperature and subsequently quenched with chloroacetic acid (71 mg, 0.75 mmol, 1.5 equiv) in 10% NaOH (2 mL). After stirring at room temperature for 10 minutes, the solution was poured into 10% NaOH (10 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic layers were washed with 10% NaOH (10 mL) , water (10 mL), dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel chromatography (2 cm ø x 20 cm) eluting with hexanes/EtOAc 9:1 provided **4.2.5** (147 mg, 73%) as a white solid.

Data for **4.2.5**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.45 (dd, *J* = 7.7, 1.3 Hz, 1H , HC(2)), 7.33 – 7.20 (m, 10 H, HC(aryl)), 7.16 (dd, *J* = 7.7, 1.6 Hz, 1 H, HC(aryl)), 7.11 (td, *J* = 7.5, 1.6 Hz, 1 H, HC(aryl)), 6.44 (d, *J* = 8.8 Hz, 1 H, NH), 5.14 (t, *J* = 8.4 Hz, 1 H, HC(7)), 4.19 (d, *J* = 1.7 Hz, 2 H, HC(13)), 2.05 (dq, *J* = 13.9, 7.0 Hz, 1 H, HC(8)), 1.22 (s, 9 H, HC(12)), 0.94 (d, *J* = 6.7 Hz, 3 H, HC(9)), 0.80 (d, *J* = 6.7 Hz, 3 H, HC(9)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 135.93, 129.28, 128.66, 128.23, 127.92, 127.61, 127.12, 77.51, 77.47, 77.26, 77.22, 77.00, 76.96, 59.53, 33.74, 33.31, 27.91, 20.57, 18.62.

HRMS: (ES+)

Found: 402.1499; Calc for $C_{22}H_{30}NOSe$: 402.1500

Preparation of *N*,*N*'-((1*R*,1'*R*)-(Diselanediylbis(2,1-phenylene))bis(2-methylpropane-1,1-diyl))bis(2,2-dimethylpropanamide) (2.35) [BBG-4-014].

To a 10-mL Schlenk flask was added **4.2.5** (147 mg, 0.36 mmol) and $CHCl_3$ (5 mL). Bromine (43 µL, 0.83 mmol, 2.3 equiv) was added dropwise and the reaction was stirred for 10 min at room temperature. The solution was then poured into a separatory funnel and washed with 10% aq. $NaHSO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x 10 mL). Combined organic layers were transferred to a 50-mL round bottom flask and hydrazine (56 µL, 1.8 mmol, 5.0 equiv) was added. The solution was stirred for 45 min at room temperature. The solution was then washed with 1 M HCl (10 mL) and brine (10 mL), dried over $MgSO_4$ (5 g), filtered and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 20 cm) eluting with hexanes/EtOAc 4:1 provided **2.35** (70 mg, 61%) as a yellow solid.

Data for **2.35**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.72 (dd, *J* = 8.3, 1.4 Hz, 2 H, HC(2)), 7.20 (td, *J* = 7.2, 1.3 Hz, 2 H, HC(3)), 7.15 – 7.10 (m, 4 H, HC(4,5)), 6.22 (d, *J* = 8.1 Hz, 2 H, NH), 5.02 (t, *J* = 8.3 Hz, 2 H, HC(7)), 2.22 – 2.06 (m, 2 H, HC(8)), 1.18 (s, 18 H, HC(12)), 0.96 (d, *J* = 6.6 Hz, 6 H, HC(9)), 0.78 (d, *J* = 6.6 Hz, 6 H, HC(9)).

^{13}C NMR: (126 MHz, $CDCl_3$)

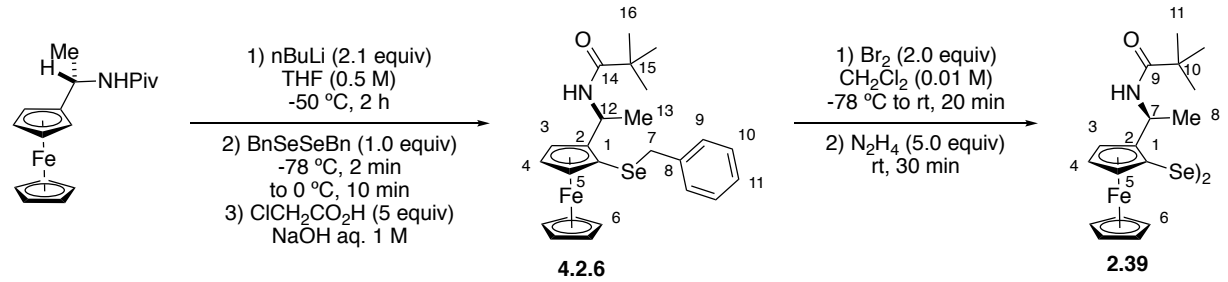
δ 177.61, 142.84, 134.88, 130.65, 128.33, 128.24, 127.79, 59.65, 39.04, 33.47, 27.88, 20.53, 18.97.

HRMS: (ES+)

Found: 623.1837; Calc for $C_{30}H_{45}N_2O_2Se_2$: 623.1819

Preparation of *N,N′*-((1*S*,1′*S*)-(Diselanediylbis(2,1-ferrocenylene))bis(ethane-1,1-diyl))bis(2,2-dimethylpropanamide) (2.39).

Preparation of (*R*)-*N*-(1-(2-(Benzylselanyl)ferrocenyl)-2-methylpropyl)pivalamide (4.2.6) [BBG-3-054].



To a 10-mL Schlenk flask was added **4.2.6** (157 mg, 0.50 mmol) followed by THF (1 mL). The solution was cooled to –50 ºC and *n*-butyllithium (656 µL, 1.6 M in hexane, 1.05 mmol, 2.1 equiv) was added dropwise. Once the addition was complete, the reaction mixture was stirred at –50 ºC. After 2 h, the mixture was cooled to –78 ºC and dibenzyl diselenide (170 mg, 0.50 mmol, 1.0 equiv) in THF (2 mL) was added dropwise to the solution. The reaction was then allowed to warm to 0 ºC and subsequently quenched with chloroacetic acid (240 mg, 2.5 mmol, 5.0 equiv) in 10% NaOH (2 mL). After stirring at room temperature for 10 minutes, the solution was poured into 10% NaOH (10 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic layers were washed with 10% NaOH (10 mL) , water (10 mL), dried over $MgSO_4$ (1 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel chromatography (2 cm ø x 20 cm) eluting with hexanes/EtOAc 9:1 provided **4.2.6** (76 mg, 32%) as an orange solid.

Data for **4.2.6**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.27 – 7.21 (m, 2 H, HC(10)), 7.21 – 7.15 (m, 1 H, HC(11)), 7.15 – 7.09 (m, 2 H, HC(9)), 6.98 (d, *J* = 8.4 Hz, 1 H, NH), 5.01 (bs, 1 H, HC(12)), 4.32 – 4.06 (m, 8 H, HC(3,4,5,6)), 3.88 (d, *J* = 11.1 Hz, 1 H, HC(7)), 3.79 (d, *J* = 11.2 Hz, 1 H, H'C(7)), 1.32 (d, *J* = 6.6 Hz, 3 H, HC(13)), 1.25 (s, 9 H, HC(16)).

Preparation of *N,N′*-((1*S*,1′*S*)-(Diselanediylbis(2,1-ferrocenylene))bis(ethane-1,1-diyl))bis(2,2-dimethylpropanamide) (2.39) [BBG-3-056].

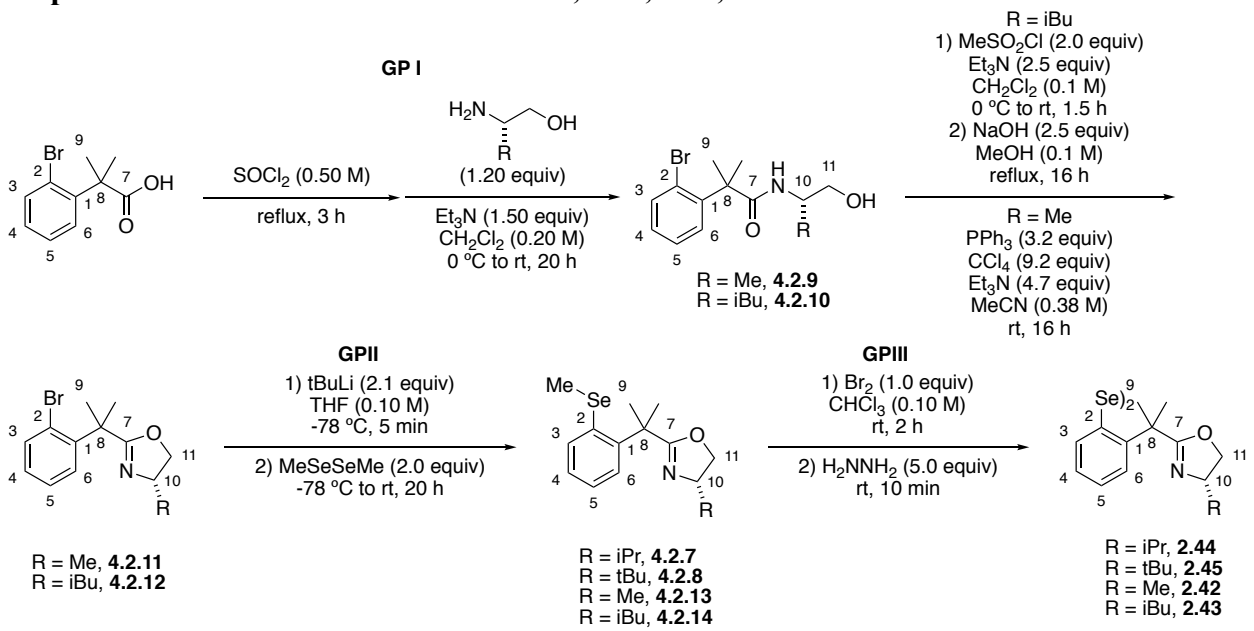
To a 10-mL Schlenk flask was added **4.2.6** (75 mg, 0.16 mmol) and CH_2Cl_2 (16 mL). The solution was cooled to –78 ºC and bromine (8.2 µL, 0.08 mmol, 2.0 equiv) was added dropwise. The reaction mixture was then warmed to room temperature over 20 min. Hydrazine (25 µL, 0.80 mmol, 5.0 equiv) was added in one portion, and the reaction mixture was stirred for at room temperature. After 30 min, the solution was poured into a 60-mL separatory funnel. The organic phase was washed with 1 M HCl (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$ (0.5 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (1 cm ø x 20 cm) eluting with hexanes/EtOAc 4:1 provided **2.39** (19 mg, 28%) as an orange solid.

Data for **2.39**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 6.53 (d, *J* = 7.9 Hz, 1 H, NH), 5.01 (p, *J* = 6.9 Hz, 1 H, HC(7)), 4.38 (d, *J* = 2.4 Hz, 1 H, HC(5)), 4.31 (d, *J* = 2.5 Hz, 1 H, HC(3)), 4.22 (d, *J* = 2.4 Hz, 1 H, HC(4)), 4.11 (s, 5 H, HC(6)), 1.48 (d, *J* = 6.7 Hz, 3 H, HC(8)), 1.27 (s, 9 H, HC(11)).

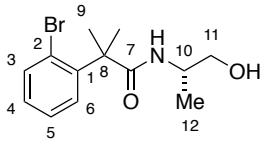
Preparation of Oxazoline Diselenides 2.42, 2.43, 2.44, and 2.45.



General Procedure I: Preparation of Amides 4.2.9 and 4.2.10

Following a literature procedure,[14] to a 25-mL 2-neck round-bottom flask equipped with a reflux condenser was added 2-(2-bromophenyl)-2-methylpropanoic acid (500 mg, 2.0 mmol) and $SOCl_2$ (4.0 mL, 0.50 M). The resulting solution was heated to reflux in an oil bath. After 3 h the reaction mixture was cooled to room temperature and $SOCl_2$ was removed under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). CH_2Cl_2 (5 mL) was added and removed under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). This process was repeated once more to remove any residual $SOCl_2$. The resulting crude acid chloride was then dissolved in CH_2Cl_2 (10 mL, 0.20 M) and the solution was cooled to 0 ºC in an ice-water bath. Et_3N (430 µL, 1.5 equiv) was added, followed by the corresponding amino alcohol (1.2 equiv), dropwise. Once the addition was complete, the reaction mixture was warmed to room temperature. After 20 h the reaction was quenched by the addition of 1 M HCl (10 mL) and the resulting biphase was stirred strongly for 30 min. The contents of the reaction vessel were transferred to a 125-mL separatory funnel, rinsing with water (10 mL) and CH_2Cl_2 (2x 10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x 20 mL). Combined organic layers were washed with 1 M HCl (20 mL), water (20 mL), 10% w/v aq. NaOH (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (5 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). The resulting crude amides were isolated in >95% purity after workup and carried forward without further purification.

Preparation of (*S*)-2-(2-Bromophenyl)-*N*-(1-hydroxypropan-2-yl)-2-methylpropanamide (4.2.9) [BBG-2019-049].



4.2.9

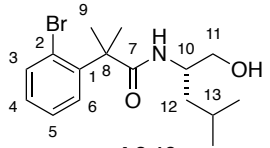
Following General Procedure I, 2-(2-bromophenyl)-2-methylpropanoic acid (500 mg, 2.0 mmol) and $SOCl_2$ (4.0 mL, 0.50 M) were reacted to give the acid chloride, then Et_3N (430 µL, 1.5 equiv), (*S*)-2-aminopropan-1-ol (185 mg, 1.2 equiv), and CH_2Cl_2 (10 mL, 0.20 M) were reacted to give **4.2.9** (551 mg, 89%) as a clear, colorless oil that slowly solidified over 24 h standing at room temperature.

Data for **4.2.9**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.63 (dd, *J* = 7.7, 1.5 Hz, 1 H, HC(3)), 7.52 (dd, *J* = 7.7, 1.5 Hz, 1 H, HC(6)), 7.37 (td, *J* = 7.7, 1.5 Hz, 1 H, HC(4)), 7.17 (td, *J* = 7.7, 1.5 Hz, 1 H, HC(5)), 5.20 (d, *J* = 6.7 Hz, 1 H, NH), 4.03 (qdd, *J* = 6.9, 6.0, 3.4 Hz, 1 H, HC(10)), 3.66 (dd, *J* = 11.0, 3.4 Hz, 1 H, HC(11)), 3.50 (dd, *J* = 11.0, 6.0 Hz, 1 H, HC(11)), 2.51 (bs, 1 H, OH), 1.65 (s, 3 H, HC(9)), 1.64 (s, 3 H, HC(9)), 1.07 (d, *J* = 6.9 Hz, 3 H, HC(12)).

Preparation of (*S*)-2-(2-Bromophenyl)-*N*-(1-hydroxy-4-methylpentan-2-yl)-2-methylpropanamide (4.2.10) [BBG-6-025].



4.2.10

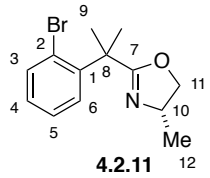
Following General Procedure I, 2-(2-bromophenyl)-2-methylpropanoic acid (500 mg, 2.0 mmol) and $SOCl_2$ (4.0 mL, 0.50 M) were reacted to give the acid chloride, then Et_3N (430 μL, 1.5 equiv), (*S*)-2-amino-4-methylpentan-1-ol (281 mg, 1.2 equiv), and CH_2Cl_2 (10 mL, 0.20 M) were reacted to give **4.2.10** (579 mg, 85%) as a clear, colorless oil.

Data for **4.2.10**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.62 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC(3)), 7.51 (dd, *J* = 7.7, 1.3 Hz, 1 H, HC(6)), 7.38 (td, *J* = 7.7, 1.3 Hz, 1 H, HC(4)), 7.18 (td, *J* = 7.7, 1.3 Hz, 1 H, HC(5)), 5.14 (d, *J* = 5.6 Hz, 1 H, NH), 3.98 (qdd, *J* = 6.9, 6.0, 3.4 Hz, 1 H, HC(10)), 3.72 (dd, *J* = 11.0, 3.4 Hz, 1 H, HC(11)), 3.51 (dd, *J* = 11.0, 6.0 Hz, 1 H, HC(11)), 2.72 (bs, 1 H, OH), 1.66 (s, 6 H, HC(9)), 1.48 (sept, *J* = 6.8 Hz, 1 H, HC(13)), 1.24 (dd, *J* = 8.9, 6.9 Hz, 2 H, HC(12)), 0.87 (dd, *J* = 10.1, 6.8 Hz, 6 H, HC(14)).

Preparation of (*S*)-2-(2-(2-Bromophenyl)propan-2-yl)-4-methyl-4,5-dihydrooxazole (4.2.11) [BBG-2019-051].



4.2.11

Following a literature procedure,[16] to a 25-mL Schlenk flask were added **4.2.9** (550 mg, 1.83 mmol) and MeCN (4.8 mL, 0.38 M) at room temperature. PPh_3 (1.52 g, 3.16 equiv) was added, followed by Et_3N (1.21 mL, 4.74 equiv), and finally CCl_4 (1.64 mL, 9.21 equiv) in one portion. The resulting mixture was stirred at room temperature and monitored by TLC. After 16 h the reaction appeared complete and was quenched by the addition of water (10 mL). The resulting biphasic mixture was poured into a 125-mL separatory funnel and the reaction vessel was rinsed with CH_2Cl_2 (2x 10 mL) and water (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x 20 mL). Combined organic phases were washed with water/brine, 1:1 (2x 20 mL), dried over $MgSO_4$ (5 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by silica gel column chromatography (4 cm ø x 18 cm column), eluting with hexanes/EtOAc, 3:1 gave **4.2.11** (427 mg, 83%) as a clear, colorless oil.

Data for **4.2.11**:

^{1}H NMR: (500 MHz, $CDCl_3$)

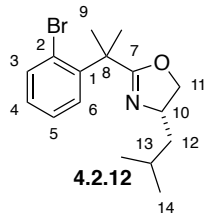
δ 7.57 (dd, *J* = 7.8, 1.4 Hz, 1 H, HC(3)), 7.44 (dd, *J* = 7.8, 1.7 Hz, 1 H, HC(6)), 7.31 (td, *J* = 7.8, 1.4 Hz, 1 H, HC(5)), 7.10 (td, *J* = 7.8, 1.7 Hz, 1 H, HC(4)), 4.34 (dd, *J* = 9.4, 7.8 Hz, 1 H, HC(11)), 4.23 (dq, *J* = 9.4, 6.6 Hz, 1 H, HC(10)), 3.78 (t, *J* = 7.8 Hz, 1 H, HC(11)), 1.72 (s, 3 H, HC(9)), 1.71 (s, 3 H, HC(9)), 1.30 (d, *J* = 6.6 Hz, 3 H, HC(12)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 171.8, 143.6, 134.7, 128.3, 127.6, 127.4, 123.9, 74.5, 61.7, 42.3, 27.4(2), 27.3(9), 20.9.

TLC: R_f = 0.17 (hexanes/EtOAc, 3:1) [UV, $KMnO_4$]

Preparation of (*S*)-2-(2-(2-Bromophenyl)propan-2-yl)-4-isobutyl-4,5-dihydrooxazole (4.2.12) [BBG-6-028].



To a 50-mL Schlenk flask was added **4.2.10** (579 mg, 1.70 mmol) and CH_2Cl_2 (17 mL, 0.10 M). The resulting solution was cooled to 0 ºC in an ice-water bath and Et_3N (3.1 mL, 2.5 equiv) was added slowly. $MeSO_2Cl$ (2.3 mL, 2.0 equiv) was added dropwise, then the reaction mixture was warmed to room temperature. After 1.5 h, the reaction mixture was poured into a 60-mL separatory funnel and diluted with CH_2Cl_2 (10 mL). The organic phase was washed with 1 M HCl (20 mL), water (20 mL), sat. aq. $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (5 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg) to afford the crude mesylate as a white foam. This foam was taken up in MeOH (5 mL) and transferred to a 50-mL round bottom flask equipped with a reflux condenser. The solution was diluted with MeOH (12 mL) and NaOH (170 mg, 2.5 equiv) was added in one portion. The reaction mixture was then heated to reflux in an oil bath. After 16 h the reaction mixture was cooled to room temperature and poured into a 125-mL separatory funnel. The methanol solution was diluted with water (50 mL) and Et_2O (50 mL) to form a biphase, and the phases were separated. The aqueous phase was extracted with Et_2O (2x 25 mL). Combined organic phases were washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$ (5 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by silica gel column chromatography (4 cm ø x 20 cm column), eluting with hexanes/EtOAc, 4:1 gave **4.2.12** (508 mg, 92%) as a clear, colorless oil.

Data for **4.2.12**:

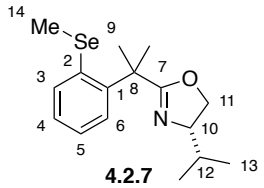
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.56 (dd, *J* = 7.8, 1.4 Hz, 1 H, HC(3)), 7.44 (dd, *J* = 7.8, 1.6 Hz, 1 H, HC(6)), 7.31 (td, *J* = 7.8, 1.4 Hz, 1 H, HC(5)), 7.10 (td, *J* = 7.8, 1.6 Hz, 1 H, HC(4)), 4.32 (t, *J* = 8.7 Hz, 1 H, HC(11)), 4.22 – 4.13 (m, 1 H, HC(10)), 3.84 (t, *J* = 7.8 Hz, 1 H, HC(11)), 1.75 – 1.62 (m, 8 H, HC(9,12)), 1.39 – 1.31 (m, 1 H, HC(13)), 0.94 (d, *J* = 6.5 Hz, HC(14)), 0.92 (d, *J* = 6.5 Hz, HC(14)).

General Procedure II: Preparation of Methyl Selenides 4.2.7, 4.2.8, 4.2.13, and 4.2.14.

To a Schlenk flask were added aryl bromide (1.0 equiv) and THF (0.10 M). The solution was cooled to -78 ºC in a dry-ice/*i*PrOH bath and *t*-BuLi (2.1 equiv., 1.6 M in pentane) was then added, dropwise, maintaining internal temperature below -65 ºC. The color of the solution immediately became yellow-orange. After 5 min, MeSeSeMe (2.0 equiv) was added and the reaction mixture was allowed to slowly warm to room temperature as the dry ice sublimed away. After 20 h, the reaction mixture was quenched with water (equivalent to THF volume) and poured into a separatory funnel (caution: stench!). The aqueous phase was extracted with Et_2O (3x) and combined organic phases were washed with water (1x) and brine (1x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification was achieved by silica gel column chromatography.

Preparation of (*S*)-4-Isopropyl-2-(2-(2-(methylselanyl)phenyl)propan-2-yl)-4,5-dihydrooxazole (4.2.7) [BBG-6-029].



4.2.7

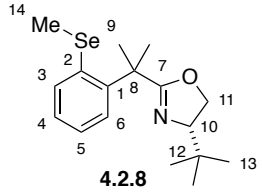
Following General Procedure II, (*S*)-2-(2-(2-bromophenyl)propan-2-yl)-4-isopropyl-4,5-dihydrooxazole[14] (465 mg, 1.50 mmol), THF (15 mL, 0.10 M), *t*-BuLi (1.97 mL, 2.1 equiv), and MeSeSeMe (284 µL, 2.0 equiv) were reacted. The reaction was quenched with water (15 mL) and extracted with Et_2O (3x 15 mL). Combined organic phases were dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (fume hood! 30 ºC, 20 mm Hg). Purification by silica gel column chromatography (3 cm ø x 20 cm column), eluting with hexanes/EtOAc, 9:1 gave **4.2.7** (267 mg, 55%) as a clear, yellow oil.

Data for **4.2.7**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.50 (d, J = 7.6 Hz, 1 H, HC(3)), 7.40 (d, J = 7.6 Hz, 1 H, HC(6)), 7.24 (t, J = 7.6 Hz, 1 H, HC(5)), 7.18 (t, J = 7.6 Hz, 1 H, HC(4)), 4.25 (m, 1 H, HC(11)), 3.99 (m, 2 H, HC(10,11)), 2.30 (t, $^2J_{Se-H}$ = 6.3 Hz, 3 H, HC(14)), 1.92 (sept, J = 6.7 Hz, 1 H, HC(12)), 1.74 (s, 3 H, HC(9)), 1.72 (s, 3 H, HC(9)), 1.30 (d, J = 6.6 Hz, 3 H, HC(12)), 0.99 (d, J = 6.7 Hz, 3 H, HC(13)), 0.88 (d, J = 6.7 Hz, 3 H, HC(13)).

Preparation of (*S*)-4-(*tert*-Butyl)-2-(2-(2-(methylselanyl)phenyl)propan-2-yl)-4,5-dihydrooxazole (4.2.8) [BBG-5-019].



4.2.8

Following General Procedure II, (*S*)-2-(2-(2-bromophenyl)propan-2-yl)-4-(*tert*-butyl)-4,5-dihydrooxazole[14] (182 mg, 0.50 mmol), THF (5 mL, 0.10 M), *t*-BuLi (656 µL, 2.1 equiv), and MeSeSeMe (95 µL, 2.0 equiv) were reacted. The reaction was quenched with water (10 mL) and extracted with Et_2O (3x 10 mL). Combined organic phases were dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (fume hood! 30 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 18 cm column), eluting with hexanes/EtOAc, 9:1 gave **4.2.8** (147 mg, 87%) as a clear, yellow oil.

Data for **4.2.8**:

^{1}H NMR: (500 MHz, $CDCl_3$)

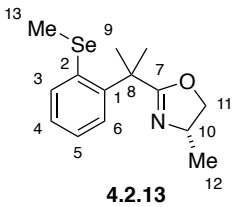
δ 7.47 (dd, *J* = 7.6, 1.6 Hz, 1 H, HC(3)), 7.37 (dd, *J* = 7.6, 1.6 Hz, 1 H, HC(6)), 7.22 (td, *J* = 7.6, 1.6 Hz, 1 H, HC(5)), 7.17 (td, *J* = 7.6, 1.6 Hz, 1 H, HC(4)), 4.18 (dd, *J* = 10.0, 8.5 Hz, 1 H, HC(11)), 4.03 (dd, *J* = 8.5, 7.5 Hz, 1 H, HC(10)), 3.93 (dd, *J* = 10.0, 7.5 Hz 1 H, HC(11)), 2.29 (t, $^2J_{Se-H}$ = 6.2 Hz, 3 H, HC(14)), 1.92 (sept, *J* = 6.7 Hz, 1 H, HC(12)), 1.73 (s, 3 H, HC(9)), 1.70 (s, 3 H, HC(9)), 0.91 (s, 9 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.5, 145.8, 133.0, 132.9, 127.5, 126.6, 125.9, 75.8, 69.2, 42.8, 34.1, 28.7, 28.0, 26.2, 9.3.

TLC: R_f = 0.37 (hexanes/EtOAc, 4:1) [UV, CAM]

Preparation of (*S*)-4-Methyl-2-(2-(2-(methylselanyl)phenyl)propan-2-yl)-4,5-dihydrooxazole (4.2.13) [BBG-2019-053].



4.2.13

Following General Procedure II, **4.2.11** (425 mg, 1.50 mmol), THF (15 mL, 0.10 M), *t*-BuLi (1.96 mL, 2.1 equiv), and MeSeSeMe (285 µL, 2.0 equiv) were reacted. The reaction was quenched with water (15 mL) and extracted with Et_2O (3x 15 mL). Combined organic phases were dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (fume hood! 30 ºC, 20 mm Hg). Purification by silica gel column chromatography (3 cm ø x 18 cm column), eluting with hexanes/EtOAc, 4:1 gave **4.2.13** (338 mg, 76%) as a clear, yellow oil.

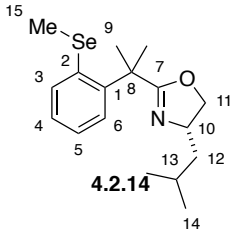
Data for **4.2.13**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.49 (dd, *J* = 7.7, 1.5 Hz, 1 H, HC(3)), 7.38 (dd, *J* = 7.7, 1.5 Hz, 1 H, HC(6)), 7.22 (td, *J* = 7.7, 1.5 Hz, 1 H, HC(5)), 7.16 (td, *J* = 7.7, 1.5 Hz, 1 H, HC(4)), 4.36 (dd, *J* = 9.4, 8.0 Hz, 1 H, HC(11)), 4.22 (ddq, *J* = 9.4, 8.0, 6.6 Hz, 1 H, HC(10)), 3.78 (t, *J* = 8.0 Hz, 1 H, HC(11)), 2.29 (t, $^2J_{Se-H}$ = 6.2 Hz, 3 H, HC(13)), 1.70 (s, 6 H, HC(9)), 1.30 (d, *J* = 6.6 Hz, 3 H, HC(12)).

TLC: R_f = 0.18 (hexanes/EtOAc, 3:1) [UV, CAM]

Preparation of (*S*)-4-Isobutyl-2-(2-(2-(methylselanyl)phenyl)propan-2-yl)-4,5-dihydrooxazole (4.2.14) [BBG-6-037].



4.2.14

Following General Procedure II, **4.2.12** (324 mg, 1.00 mmol), THF (10 mL, 0.10 M), *t*-BuLi (1.31 mL, 2.1 equiv), and MeSeSeMe (190 µL, 2.0 equiv) were reacted. The reaction was quenched with water (10 mL) and extracted with Et_2O (3x 10 mL). Combined organic phases were

dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (fume hood! 30 ºC, 20 mm Hg). Purification by silica gel column chromatography (3 cm ø x 18 cm column), eluting with hexanes/EtOAc, 9:1 gave **4.2.14** (212 mg, 63%) as a clear, yellow oil.

Data for **4.2.14**:

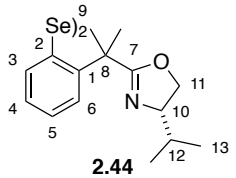
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.48 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC(3)), 7.38 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC(6)), 7.21 (td, *J* = 7.7, 1.4 Hz, 1 H, HC(5)), 7.16 (td, *J* = 7.7, 1.4 Hz, 1 H, HC(4)), 4.33 (dd, *J* = 9.0, 8.0 Hz, 1 H, HC(11)), 4.17 (qd, *J* = 9.0, 4.9 Hz, 1 H, HC(10)), 3.84 (t, *J* = 8.0 Hz, 1 H, HC(11)), 2.29 (t, $^2J_{Se-H}$ = 6.2 Hz, 3 H, HC(15)), 1.75 – 1.63 (m, 8 H, HC(9,12)), 1.36 (ddd, *J* = 13.0, 9.0, 5.4 Hz, 1 H, HC(13)), 0.93 (dd, *J* = 7.41, 6.45 Hz, 6 H, HC(14)).

General Procedure III: Preparation of Diselenides 2.42, 2.43, 2.44, 2.45, 2.46, 2.47, 2.48, and 2.50.

To a Schlenk flask was added methyl selenide (1.0 equiv) and $CHCl_3$ (0.10 M). Br_2 (1.0 equiv) in $CHCl_3$ (0.50 M Br_2) was added in one portion at room temperature. After 2 h, anhydrous H_2NNH_2 (5.0 equiv) was added in one portion at room temperature. The color of the solution changed immediately from dark brown to yellow-orange. After 5 min, the mixture was poured into a separatory funnel, rinsing with CH_2Cl_2 (2x) and water (1x). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x). Combined organic phases were washed with 1 M HCl (2x), water (1x), and brine (1x), dried over $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporation. Purification was achieved by silica gel column chromatography.

Preparation of 1,2-Bis(2-(2-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)propan-2-yl)phenyl)diselane (2.44) [BBG-6-036].



2.44

Following General Procedure III, **4.2.7** (200 mg, 0.617 mmol), $CHCl_3$ (6.0 mL, 0.10 M), Br_2 (1.23 mL, 0.500 M in $CHCl_3$, 1.0 equiv), and H_2NNH_2 (99 mg, 5.0 equiv) were reacted. The reaction mixture was diluted with CH_2Cl_2 (12 mL) and water (6 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 10 mL), and combined organic phases were washed with 1 M HCl (2x

10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 20 cm column), eluting with hexanes/EtOAc, 9:1 gave **2.44** (135 mg, 71%) as a viscous, clear, orange oil.

Data for **2.44**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.75 (dd, *J* = 7.8, 1.4 Hz, 1 H, HC(3)), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1 H, HC(6)), 7.21 (td, *J* = 7.8, 1.4 Hz, 1 H, HC(5)), 7.09 (td, *J* = 7.8, 1.4 Hz, 1 H, HC(4)), 4.25 – 4.09 (m, 1 H, HC(11)), 3.99 – 3.88 (m, 2 H, HC(10,11)), 1.86 (dq, *J* = 13.3, 6.6 Hz, 1 H, HC(12)), 1.69 (s, 3 H, HC(9)), 1.64 (s, 3 H, HC(9)), 0.96 (d, *J* = 6.8 Hz, 3 H, HC(13)), 0.83 (d, *J* = 6.8 Hz, 3 H, HC(13)).

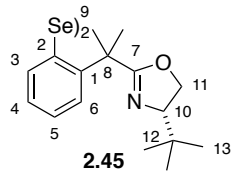
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.5, 145.2, 134.7, 132.2, 127.8, 127.7, 125.7, 72.4, 70.5, 42.7, 32.4, 28.1, 28.0, 19.5, 18.0.

HRMS: (ES+)

Found: 621.1481; Calc for $C_{30}H_{41}N_2O_2Se_2$: 621.1498

Preparation of 1,2-Bis(2-(2-((*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)propan-2-yl)phenyl)diselane (2.45) [BBG-2019-043].



2.45

Following General Procedure III, **4.2.8** (15 mg, 0.047 mmol), $CHCl_3$ (0.50 mL, 0.10 M), Br_2 (94.5 µL, 0.500 M in $CHCl_3$, 1.0 equiv), and H_2NNH_2 (7.6 mg, 5.0 equiv) were reacted. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 10 mL), and combined organic phases were washed with 1 M HCl (2x 10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$ (1 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 15 cm column), eluting with hexanes/EtOAc, 9:1 gave **2.45** (10 mg, 65%) as a viscous, clear, orange oil in ca. 95% purity.

Data for **2.45**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.73 (dd, *J* = 7.8, 1.4 Hz, 1 H, HC(3)), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1 H, HC(6)), 7.20 (td, *J* = 7.8, 1.4 Hz, 1 H, HC(5)), 7.08 (td, *J* = 7.8, 1.4 Hz, 1 H, HC(4)), 4.09 (dd, *J* = 10.0, 8.4 Hz, 1 H, HC(11)), 4.00 (t, *J* = 8.4 Hz, 1 H, HC(10)), 3.90 (dd, *J* = 10.0, 8.4 Hz 1 H, HC(11)), 1.73 (s, 3 H, HC(9)), 1.65 (s, 3 H, HC(9)), 0.88 (s, 9 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

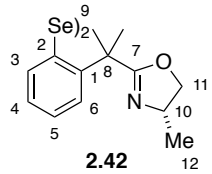
δ 172.6, 145.3, 134.4, 132.2, 128.1, 127.8, 126.1, 76.2, 69.6, 43.0, 34.3, 28.7, 28.4, 26.5.

HRMS: (ES+)

Found: 649.1816; Calc for $C_{32}H_{45}N_2O_2Se_2$: 649.1811

TLC: R_f = 0.07 (hexanes/EtOAc, 9:1) [UV, CAM]

Preparation of 1,2-Bis(2-(2-((*S*)-4-methyl-4,5-dihydrooxazol-2-yl)propan-2-yl)phenyl)diselane (2.42) [BBG-2019-057].



2.42

Following General Procedure III, **4.2.13** (150 mg, 0.506 mmol), $CHCl_3$ (5.0 mL, 0.10 M), Br_2 (1.01 mL, 0.500 M in $CHCl_3$, 1.0 equiv), and H_2NNH_2 (81 mg, 5.0 equiv) were reacted. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 10 mL), and combined organic phases were washed with 1 M HCl (2x 10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 20 cm column), eluting with hexanes/EtOAc, 1:1 gave **2.42** (157 mg, 56%) as a viscous, clear, orange oil.

Data for **2.42**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.76 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC(3)), 7.33 (dd, *J* = 7.7, 1.4 Hz, 1 H, HC(6)), 7.21 (td, *J* = 7.7, 1.4 Hz, 1 H, HC(5)), 7.09 (td, *J* = 7.7, 1.4 Hz, 1 H, HC(4)), 4.30 (dd, *J* = 9.5, 8.0 Hz, 1 H, HC(11)), 4.19 (ddq, *J* = 9.5, 8.0, 6.7 Hz, 1 H, HC(10)), 3.74 (t, *J* = 8.0 Hz 1 H, HC(11)), 1.66 (s, 3 H, HC(9)), 1.65 (s, 3 H, HC(9)), 1.28 (d, *J* = 6.7 Hz, 3 H, HC(12)).

^{13}C NMR: (126 MHz, $CDCl_3$)

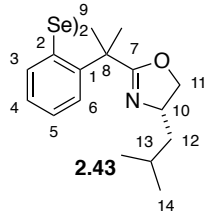
δ 173.0, 145.4, 135.2, 132.5, 128.2, 128.1, 125.9, 75.0, 62.2, 42.8, 28.2, 28.1, 21.2.

HRMS (ES+):

Found: 565.0849; Calc for $C_{26}H_{33}N_2O_2Se_2$: 565.0872

TLC: R_f = 0.07 (hexanes/EtOAc, 1:1) [UV, CAM]

Preparation of 1,2-Bis(2-(2-((*S*)-4-Isobutyl-4,5-dihydrooxazol-2-yl)propan-2-yl)phenyl)diselane (2.43) [BBG-6-039].



Following General Procedure III, **4.2.14** (212 mg, 0.600 mmol), $CHCl_3$ (6.0 mL, 0.10 M), Br_2 (1.20 mL, 0.500 M in $CHCl_3$, 1.0 equiv), and H_2NNH_2 (96 mg, 5.0 equiv) were reacted. The reaction mixture was diluted with CH_2Cl_2 (12 mL) and water (6 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 10 mL), and combined organic phases were washed with 1 M HCl (2x 10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 20 cm column), eluting with hexanes/EtOAc, 9:1 gave **2.43** (165 mg, 81%) as a viscous, clear, orange oil.

Data for **2.43**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.77 (dd, *J* = 7.8, 1.4 Hz, 1 H, HC(3)), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1 H, HC(6)), 7.20 (td, *J* = 7.8, 1.4 Hz, 1 H, HC(5)), 7.08 (td, *J* = 7.8, 1.4 Hz, 1 H, HC(4)), 4.27 (dd, *J* = 9.5, 8.0 Hz, 1 H, HC(11)), 4.13 (tdd, *J* = 9.5, 8.5, 8.0 Hz, 1 H, HC(10)), 3.80 (t, *J* = 8.0 Hz, 1 H, HC(11)), 1.79 – 1.54 (m, 8 H, HC(9,12)), 1.33 (ddd, *J* = 8.8, 6.6, 5.7 Hz, 1 H, HC(13)), 0.91 (dd, *J* = 6.6, 3.2 Hz, 6 H, HC(14)).

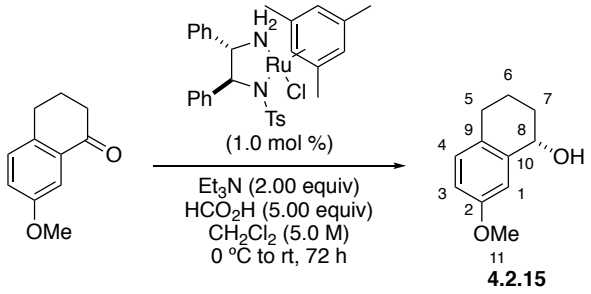
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.4, 145.2, 134.9, 132.2, 127.8, 127.7, 125.6, 73.7, 65.1, 45.0, 42.6, 28.0, 27.8, 25.6, 23.3, 22.5.

HRMS (ES+)

Found: 649.1801; Calc for $C_{32}H_{45}N_2O_2Se_2$: 649.1811.

Preparation of (*S*)-7-Methoxy-1,2,3,4-Tetrahydronaphthalen-1-ol (4.2.15) by Enantioselective Transfer Hydrogenation [BBG-2019-062].



4.2.15

Following a modification of a literature procedure,[27] triethylamine (2.79 mL, 2.00 equiv) was added to a 25-mL Schlenk flask and cooled to 0 ºC in an ice-water bath. Formic acid (1.89 mL, 5.00 equiv) was added, dropwise over 15 min, to reduce fuming and premature decomposition of the formate. The mixture was removed from the ice bath and RuCl[(*S,S*)-TsDPEN](mesitylene) (62.2 mg, 1.0 mol %) was added, in one portion, against nitrogen flow. 7-methoxy-3,4-dihydronaphthalen-1(2H)-one (1.76 g, 10.0 mmol) was then added in the same manner. CH_2Cl_2 (2.0 mL, 5.0 M ketone) was added with a syringe, rinsing down any solid stuck to the walls of the flask. The reaction was deemed complete by TLC after 72 h and quenched by the addition of water (5 mL). The biphasic mixture was then poured into a 125-mL separatory funnel and diluted with 1 M HCl (20 mL) and EtOAc (20 mL). The layers were shaken and separated, and the organic

phase was washed with 1 M HCl (20 mL) and water (20 mL). Combined aqueous phases were extracted with EtOAc (2x 20 mL), and combined organic phases were washed with water (20 mL), 10% w/v aq NaOH (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (8 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (5 cm ø x 15 cm column), eluting with a gradient of hexanes/EtOAc, 9:1 to hexanes/EtOAc, 3:1 gave **4.2.15** (1.75 g, 98%) as a clear, colorless oil. Spectroscopic data were consistent with the literature.[28]

Data for **4.2.15**:

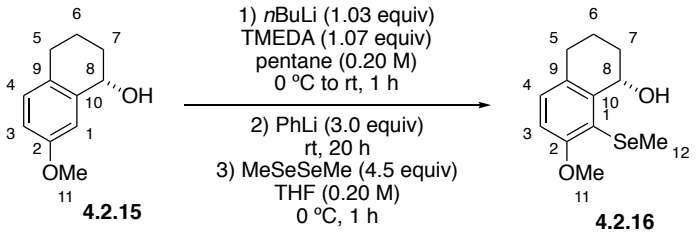
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.02 (d, J = 8.4 Hz, 1 H, HC(4)), 6.99 (d, J = 2.8 Hz, 1 H, HC(1)), 6.78 (dd, J = 8.4, 2.8 Hz, 1 H, HC(3)), 4.74 (q, J = 5.7 Hz, 1 H, HC(8)), 3.80 (s, 3 H, HC(11)), 2.76 (dt, J = 16.3, 5.8 Hz, 1 H, HC(5)), 2.66 (ddd, J = 16.3, 7.7, 5.5 Hz, 1 H, HC(5)), 2.05 – 1.83 (m, 3 H, HC(6,7)), 1.80 – 1.69 (m, 2 H, HC(7), OH).

SFC: **(*R*)-4.2.15** t_R 9.1 min (0.8%), **(*S*)-4.2.15** t_R 10.1 min (99.2%) (Daicel Chiralpak AD; CO_2/MeOH, 19:1 gradient to 4:1 over 10 min, hold 4:1 for 10 min; 2.5 mL/min; 220 nm).

TLC: R_f = 0.21 (hexanes/EtOAc, 4:1) [UV/CAM]

Preparation of (*S*)-7-Methoxy-8-(methylselanyl)-1,2,3,4-tetrahydronaphthalen-1-ol (4.2.16) [BBG-7-007].



To a 100-mL Schlenk flask were added **4.2.15** (500 mg, 2.81 mmol), pentane (15 mL, 0.20 M), and *N,N′*-tetramethylethylenediamine (450 µL, 1.07 equiv). The resulting solution was cooled in an ice-water bath to 0 ºC and *n*-BuLi (1.86 mL, 1.55 M in hexanes, 1.03 equiv) was added, dropwise. The solution became turbid and a white precipitate began to form. The ice bath was removed and the reaction mixture was warmed to room temperature. Most solids had gone back into solution after 1 h. PhLi (5.0 mL, 1.7 M in Bu_2O, 3.0 equiv) was then added, dropwise, at room temperature. After 20 h, the reaction mixture was cooled to 0 ºC in an ice-water bath and THF (15

mL, 1:1 w.r.t. pentane) was added, followed by MeSeSeMe (1.2 mL, 4.5 equiv), dropwise. After 1 h, chloroacetic acid (1.3 g, 5.0 equiv) in 10% w/v aq NaOH (40 mL) was added to the reaction mixture and the ice bath was removed. Once the internal temperature had reached ambient, the biphasic mixture was poured into a 250-mL separatory funnel (fume hood!). The mixture was diluted with diethyl ether (20 mL) and the layers were separated. The aqueous phase was extracted with diethyl ether (2x 20 mL). Combined organic phases were washed with 10% w/v aq NaOH (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (5 g), filtered, and concentrated under reduced pressure by rotary evaporation (fume hood! 40 ºC, 20 mm Hg). Purification by silica gel column chromatography (3 cm ø x 25 cm column), eluting with hexanes/EtOAc, 7:1 gave **4.2.16** (608 mg, 80%) as a clear, yellow oil.

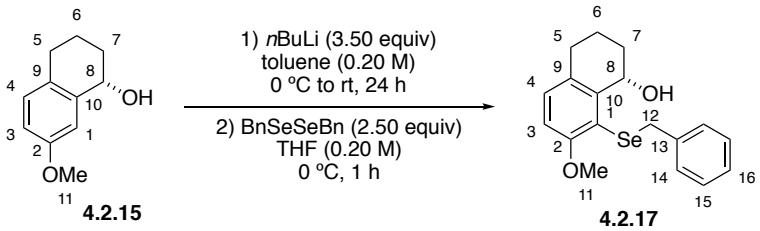
Data for **4.2.16**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.08 (d, J = 8.5 Hz, 1 H, HC(4)), 6.80 (d, J = 8.6 Hz, 1 H, HC(3)), 5.17 (q, J = 3.9 Hz, 1 H, HC(8)), 3.89 (s, 3 H, HC(11)), 3.05 (dd, J = 4.3, 1.1 Hz, 1 H, HC(5)), 2.87 – 2.73 (m, 1 H, HC(5)), 2.72 – 2.57 (m, 1 H, HC(6)), 2.27 (t, $^2J_{Se–H}$ = 6.2 Hz, 3 H, HC(12)), 2.17 (dddd, J = 13.7, 6.9, 3.0, 1.6 Hz, 1 H, HC(7)), 2.04 – 1.85 (m, 1 H, HC(6)), 1.85 – 1.70 (m, 1 H, HC(7)).

TLC: R_f = 0.35 (hexanes/EtOAc, 3:1) [UV/CAM].

Preparation of (*S*)-8-(Benzylselanyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (4.2.17) [BBG-10-083].



To a 250-mL Schlenk flask were added **4.2.15** (2.00 g, 11.2 mmol) and toluene (56 mL, 0.20 M). The solution was cooled in an ice-water bath to 0 ºC and *n*-BuLi (14.9 mL, 2.33 M in hexanes, 3.10 equiv) was added, dropwise over 10 min. The ice bath was removed and the reaction mixture was warmed to room temperature. After 20 h, the reaction was cooled in an ice-water bath to 0 ºC and THF (56 mL, 1:1 w.r.t toluene) was added in one portion, followed by BnSeSeBn (3.82 g, 2.50 equiv) in one portion, as the solid, against nitrogen back-flow. After 1 h, chloroacetic acid

(5.3 g, 5.0 equiv) in 10% w/v aq NaOH (50 mL) was added and the mixture was removed from the ice bath. After 30 min at room temperature the biphasic mixture was transferred to a 500-mL separatory funnel and diluted with Et_2O (50 mL) and water (50 mL). The layers were shaken and separated, and the organic phase was washed with 10% w/v aq NaOH (100 mL) and water (100 mL). Combined aqueous phases were extracted with Et_2O (2x 100 mL), then combined organic phases were washed with water (100 mL), and brine (50 mL), dried over $MgSO_4$ (7 g), filtered, and concentrated under reduced pressure by rotary evaporation (50 ºC, 20 mm Hg). Purification by silica gel column chromatography (5 cm ø x 15 cm column), eluting with a gradient of hexanes/EtOAc, 19:1 to hexanes/EtOAc, 7:3 gave **S25** (3.16 g, 79%, 98% pure) as a clear, yellow oil that slowly solidified at ambient temperature and pressure to a pale yellow solid.

Data for **S25**:

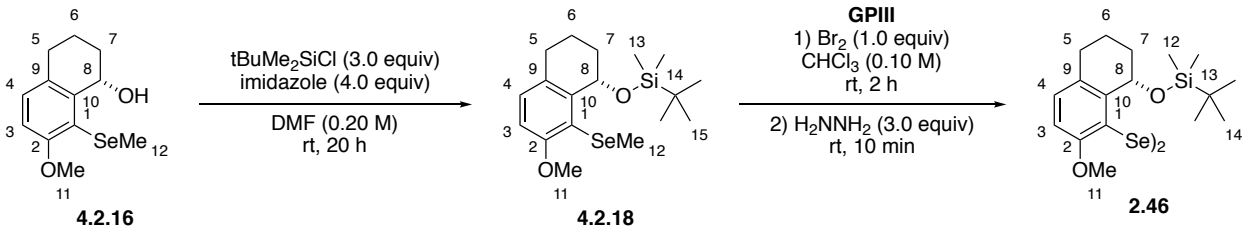
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.24 – 7.12 (m, 3 H, HC(15,16)), 7.11 – 7.03 (m, 3 H, HC(14,4)), 6.83 (d, *J* = 8.4 Hz, 1 H, HC(3)), 4.86 (q, *J* = 3.6 Hz, 1 H, HC(8)), 4.12 (d, *J* = 11.3 Hz, 1 H, HC(12)), 4.04 (d, *J* = 11.3 Hz, 1 H, HC(12)), 3.92 (s, 3 H, HC(11)), 2.74 (dddt, *J* = 16.4, 5.2, 2.6, 1.2 Hz, 1 H, HC(5)), 2.58 (dddd, *J* = 16.4, 12.0, 5.6, 1.2 Hz, 1 H, HC(5)), 2.27 (dd, *J* = 3.7, 1.4 Hz, 1 H, OH), 2.02 (ddtd, *J* = 13.7, 4.3, 2.9, 1.5 Hz, 1 H, HC(7)), 1.85 (qdd, *J* = 13.1, 5.2, 2.8 Hz, 1 H, HC(6)), 1.65 (dtt, *J* = 13.1, 5.5, 3.0 Hz, 1 H, HC(6)), 1.56 (tddd, *J* = 13.7, 4.3, 3.1, 1.3 Hz, 1 H, HC(7)).

TLC: R_f = 0.21 (hexanes/EtOAc, 4:1) [UV/CAM].

Preparation of 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.46), Route 1.

Preparation of (*S*)-*tert*-Butyl((7-methoxy-8-(methylselanyl)-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)dimethylsilane (4.2.18) [BBG-7-010].



4.2.16 **4.2.18** **2.46**

To a 10-mL Schlenk flask were added **4.2.16** (210 mg, 0.774 mmol) and DMF (4.0 mL, 0.20 M). Imidazole (211 mg, 4.0 equiv) was added at room temperature, followed by $tBuMe_2SiCl$

(350 mg, 3.0 equiv). After 20 h the reaction was quenched by the addition of 1 M HCl (5 mL). The resulting solution was poured into a 125-mL separatory funnel and diluted with water (20 mL) and Et_2O (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2x 20 mL). Combined organic phases were washed with 1 M HCl (10 mL), water (20 mL), and brine (20 mL), dried over Na_2SO_4 (4 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 25 cm column), eluting with hexanes/Et_2O, 39:1 gave **4.2.18** (275 mg, 92%) as a clear, colorless oil.

Data for **4.2.18**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.04 (d, J = 8.4 Hz, 1 H, HC(4)), 6.78 (d, J = 8.4 Hz, 1 H, HC(3)), 5.36 (t, J = 3.0 Hz, 1 H, HC(8)), 3.88 (s, 3 H, HC(11)), 2.88 – 2.78 (m, 1 H, HC(5)), 2.74 – 2.59 (m, 1 H, HC(5)), 2.20 (s, 3 H, HC(12)), 2.14 – 2.01 (m, 2 H, HC(6,7)), 1.70-1.63 (m, 2 H, HC(6,7)), 0.86 (s, 9 H, HC(15)), 0.22 (s, 3 H, HC(12)), 0.19 (s, 3 H, HC(12)).

^{13}C NMR: δ 157.9, 142.3, 130.3, 130.0, 121.7, 110.6, 68.3, 56.1, 32.4, 29.1, 26.3, 18.6, 16.9, 8.3, -3.4, -4.0.

^{77}Se NMR: (95 MHz, $CDCl_3$)

δ 77.6

TLC: R_f = 0.40 (hexanes/Et_2O, 19:1) [UV/CAM].

Preparation of 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.46) [BBG-7-014].

Following General Procedure III, **4.2.18** (275 mg, 0.713 mmol), $CHCl_3$ (7 mL, 0.1 M), Br_2 (2.78 mL, 0.256 M in $CHCl_3$, 1.0 equiv), and H_2NNH_2 (69 mg, 3.0 equiv) were reacted. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 10 mL), and combined organic phases were washed with 1 M HCl (2x 10 mL), water (10 mL), and brine (10 mL), dried over Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 20 cm column), eluting with hexanes/EtOAc, 19:1 gave **2.46** (202 mg, 77%) as an orange solid.

Data for **2.46**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.03 (d, *J* = 8.4 Hz, 1 H, HC(4)), 6.82 (d, *J* = 8.4 Hz, 1 H, HC(3)), 4.15 (t, *J* = 2.9 Hz, 1 H, HC(8)), 3.92 (s, 3 H, HC(11)), 2.73 (dd, *J* = 16.5, 5.5 Hz, 1 H, HC(5)), 2.50 (ddd, *J* = 16.4, 12.3, 6.1 Hz, 1 H, HC(5)), 1.86 (qdd, *J* = 12.9, 5.8, 2.6 Hz, 1 H, HC(6)), 1.58 (dd, *J* = 13.9, 3.4 Hz, 1H, HC(7)), 1.53 – 1.45 (m, 1 H, HC(6)), 0.85 (ddt, *J* = 13.8, 9.8, 3.2 Hz, 1 H, HC(7)), 0.76 (s, 9 H, HC(14)), 0.02 (s, 3H, HC(12)), 0.00 (s, 3 H, HC(12)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.39, 143.36, 131.43, 129.21, 121.57, 110.30, 67.32, 56.11, 31.82, 29.17, 26.25, 18.34, 16.66, -3.61, -4.53.

^{77}Se NMR: (95 MHz, $CDCl_3$)

δ 351.8

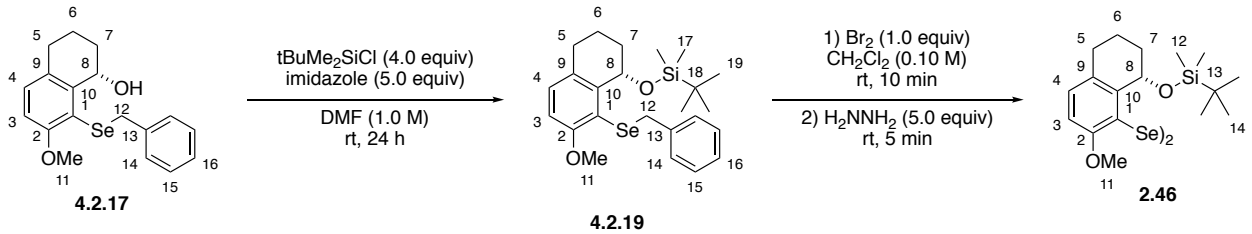
HRMS: (ES+)

Found: 765.1800; Calc for $C_{34}H_{54}O_4NaSi_2Se_2$: 765.1789.

TLC: R_f = 0.59 (hexanes/EtOAc, 4:1) [visible yellow/UV/CAM].

Preparation of 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.46), Route 2.

Preparation of (*S*)-((8-(Benzylselanyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)(*tert*-butyl)dimethylsilane (4.2.19) [BBG-10-086].



4.2.17 **4.2.19** **2.46**

To a 25-mL Schlenk flask was added **4.2.17** (3.16 g, 8.88 mmol) and DMF (9.0 mL, 1 M) at room temperature. Imidazole (3.0 g, 5.0 equiv) was added, followed by $tBuMe_2SiCl$ (5.3 g, 4.0 equiv) against nitrogen back-flow. After 15 h at room temperature, the reaction mixture was poured into water (200 mL), rinsing with water (10 mL) and Et_2O (2x 10 mL). The aqueous suspension was extracted with diethyl ether (3x 100 mL). Combined organic phases were washed with sat aq.

$NaHCO_3$ (100 mL), water (100 mL), 10% w/v aq citric acid (100 mL), water (100 mL), and brine (50 mL), dried over Na_2SO_4 (5 g), filtered, and concentrated under reduced pressure by rotary evaporation (50 ºC, 20 mm Hg). Purification was achieved by silica gel column chromatography (5 cm ø x 15 cm column), eluting with a gradient of hexanes/EtOAc, 1:0 to hexanes/EtOAc, 9:1 to give **4.2.19** (3.69 g, 90%) as a clear, pale-yellow oil.

Data for **4.2.19**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.18 – 7.08 (m, 3 H, HC(15,16)), 7.08 – 6.99 (m, 3 H, HC(14,4)), 6.81 (d, J = 8.4 Hz, 1 H, HC(3)), 4.88 (t, J = 3.0 Hz, 1 H, HC(8)), 3.97 (d, J = 11.3 Hz, 1 H, HC(12)), 3.94 (d, J = 11.3 Hz, 1 H, HC(12)), 3.91 (s, 3 H, HC(11)), 2.88 – 2.70 (m, 1 H, HC(5)), 2.57 (dddd, J = 16.4, 11.6, 6.4, 1.1 Hz, 1 H, HC(5)), 2.06 – 1.91 (m, 1 H, HC(6)), 1.87 (dtd, J = 13.8, 4.3, 3.7, 2.5 Hz, 1 H, HC(7)), 1.56 (ddd, J = 13.0, 6.6, 3.2 Hz, 1 H, HC(6)), 1.26 (tt, J = 13.4, 3.3 Hz, 1 H, HC(7)), 0.82 (s, 9 H, HC(19)), 0.14 (s, 3 H, HC(17)), 0.11 (s, 3 H, HC(17)).

TLC: R_f = 0.36 (hexanes/Et_2O, 19:1) [UV/CAM].

Preparation of 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.46) [BBG-10-088].

To a 250-mL Schlenk flask was added **4.2.19** (3.69 g, 8.00 mmol) and CH_2Cl_2 (80 mL, 0.10 M). Br_2 (8.00 mL, 1.00 M in CH_2Cl_2, 1.00 equiv) was added at room temperature and the solution immediately became dark brown. After 5 min, H_2NNH_2 (1.28 g, 5.0 equiv) was added in one portion with vigorous stirring (gas evolution). The solution went immediately from dark brown to yellow-orange. After 5 min, the consequent mixture was transferred to a separatory funnel, rinsing with CH_2Cl_2 (20 mL) and water (20 mL). The organic phase was washed with 10% w/v aq citric acid (2x 100 mL). Combined aqueous phases were extracted with CH_2Cl_2 (3x 100 mL). Combined organic phases were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 (5 g), and filtered into a 500-mL round-bottom flask. Et_3N (10 mL) was added, and the mixture was stirred at room temperature. After 16 h, the mixture was concentrated under reduced pressure by rotary evaporation (50 ºC, 20 mm Hg). Purification by recrystallization from boiling hexanes gave **2.46** (2.07 g, 70%) as orange crystals.

Data for **2.46**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.03 (d, *J* = 8.4 Hz, 1 H, HC(4)), 6.82 (d, *J* = 8.4 Hz, 1 H, HC(3)), 4.15 (t, *J* = 2.9 Hz, 1 H, HC(8)), 3.92 (s, 3 H, HC(11)), 2.73 (dd, *J* = 16.5, 5.5 Hz, 1 H, HC(5)), 2.50 (ddd, *J* = 16.4, 12.3, 6.1 Hz, 1 H, HC(5)), 1.86 (qdd, *J* = 12.9, 5.8, 2.6 Hz, 1 H, HC(6)), 1.58 (dd, *J* = 13.9, 3.4 Hz, 1H, HC(7)), 1.53 – 1.45 (m, 1 H, HC(6)), 0.85 (ddt, *J* = 13.8, 9.8, 3.2 Hz, 1 H, HC(7)), 0.76 (s, 9 H, HC(14)), 0.02 (s, 3H, HC(12)), 0.00 (s, 3 H, HC(12)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.39, 143.36, 131.43, 129.21, 121.57, 110.30, 67.32, 56.11, 31.82, 29.17, 26.25, 18.34, 16.66, -3.61, -4.53.

^{77}Se NMR: (95 MHz, $CDCl_3$)

δ 351.8

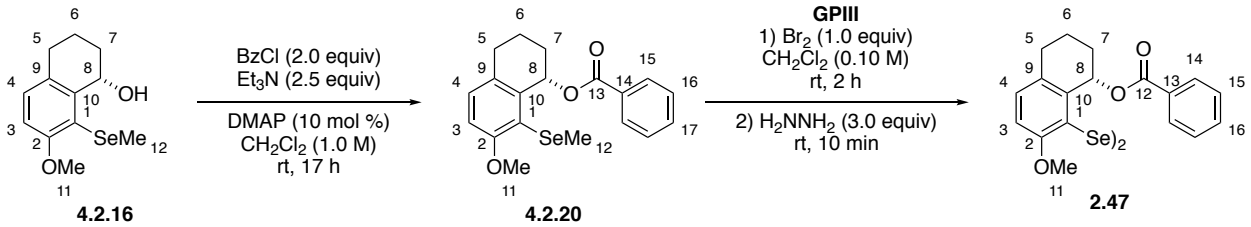
HRMS: (ES+)

Found: 765.1800; Calc for $C_{34}H_{54}O_4NaSi_2Se_2$: 765.1789.

TLC: R_f = 0.59 (hexanes/EtOAc, 4:1) [visible yellow/UV/CAM].

Preparation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Dibenzoate (2.47).

Preparation of (*S*)-7-Methoxy-8-(methylselanyl)-1,2,3,4-tetrahydronaphthalen-1-yl Benzoate (4.2.20) [BBG-6-073].



4.2.16 **4.2.20** **2.47**

To a 5-mL Schlenk flask was added **4.2.16** (100 mg, 0.369 mmol) and CH_2Cl_2 (0.4 mL, 1 M). Et_3N (129 µL, 2.5 equiv) was added at room temperature, followed by DMAP (4.5 mg, 10 mol %). Benzoyl chloride (85.7 µL, 2.0 equiv) was then added, dropwise, at room temperature. The reaction was worked up after 17 h by the addition of 1 M HCl (2 mL). The biphasic mixture was poured into a 60-mL separatory funnel and diluted with water (10 mL) and CH_2Cl_2 (10 mL). The layers were shaken and separated, and the aqueous phase was extracted with CH_2Cl_2 (2x 10

mL). Combined organic phases were washed with 1 M HCl (10 mL), water (10 mL), sat aq $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$ (1 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by column chromatography (1.5 cm ø x 15 cm column), eluting with hexanes/EtOAc, 9:1 gave **4.2.20** (96 mg, 69%) as a pale yellow solid.

Data for **4.2.20**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.00 (dd, *J* = 7.8, 1.4 Hz, 2 H, HC(15)), 7.51 (tt, *J* = 7.8, 1.4 Hz, 1 H, HC(17)), 7.37 (t, *J* = 7.8 Hz, 2 H, HC(16)), 7.15 (d, *J* = 8.4 Hz, 1 H, HC(4)), 6.89 (d, *J* = 8.4 Hz, 1 H, HC(3)), 6.47 (t, *J* = 3.2 Hz, 1 H, HC(8)), 3.91 (s, 3 H, HC(11)), 2.93 – 2.83 (m, 1 H, HC(5)), 2.81 – 2.68 (m, 1 H, HC(5)), 2.49 – 2.39 (m, 1 H, HC(7)), 2.13 (t, $^2J_{Se–H}$ = 6.0 Hz, 2 H, HC(12)), 2.02 – 1.75 (m, 3 H, HC(6,6,7)).

Preparation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Dibenzoate (2.47) [BBG-6-078].

Following General Procedure III, **4.2.20** (85 mg, 0.23 mmol), CH_2Cl_2 (2 mL, 0.1 M), Br_2 (920 µL, 0.250 M in CH_2Cl_2, 1.0 equiv), and H_2NNH_2 (22 mg, 3.0 equiv) were reacted. The reaction mixture was diluted with CH_2Cl_2 (2 mL) and water (2 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 5 mL), and combined organic phases were washed with 1 M HCl (2x 5 mL), water (5 mL), and brine (5 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (1.5 cm ø x 15 cm column), eluting with hexanes/EtOAc, 7:1 gave **2.47** (63 mg, 76%) as an orange solid.

Data for **2.47**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.85 (dd, *J* = 8.0, 1.5 Hz, 2 H, HC(14)), 7.48 – 7.41 (t, 1 H, *J* = 8.0, 1.5 Hz, HC(16)), 7.29 (t, *J* = 8.0 Hz, 2 H, HC(15)), 7.18 (d, *J* = 8.5 Hz, 1 H, HC(4)), 7.06 (d, *J* = 8.5 Hz, 1 H, HC(3)), 5.19 (t, *J* = 3.4 Hz, 1 H, HC(8)), 4.00 (s, 3 H, HC(11)), 2.81 (dt, *J* = 16.5, 3.8 Hz, 1 H, HC(5)), 2.57 (ddd, *J* = 16.5, 11.8, 5.5 Hz, 1 H, HC(5)), 2.04 (ddd, *J* = 14.0, 4.8, 2.0 Hz, 1 H, HC(7)), 1.87 – 1.53 (m, 2 H, HC(6,6)), 1.41 – 1.10 (m, 1 H, HC(7)).

^{13}C NMR: (126 MHz, $CDCl_3$)

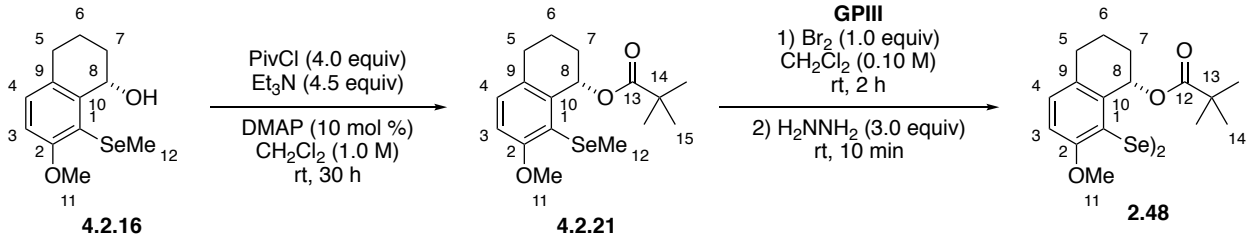
δ 165.25, 159.04, 138.28, 132.70, 131.54, 130.91, 130.45, 129.64, 128.30, 122.29, 112.00, 70.54, 56.40, 29.53, 29.01, 18.16.

HRMS: (ES+)

Found: 722.0696; Calc for $C_{36}H_{34}O_6Se_2$: 722.0686.

Preparation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis(2,2-dimethylpropanoate) (2.48).

Preparation of (*S*)-7-Methoxy-8-(methylselanyl)-1,2,3,4-tetrahydronaphthalen-1-yl Pivalate (4.2.21) [BBG-6-072].



4.2.16 **4.2.21** **2.48**

To a 5-mL Schlenk flask was added **4.2.16** (100 mg, 0.369 mmol) and CH_2Cl_2 (0.4 mL, 1 M). Et_3N (232 µL, 4.5 equiv) was added at room temperature, followed by DMAP (4.5 mg, 10 mol %). Pivaloyl chloride (181 µL, 4.0 equiv) was then added, dropwise, at room temperature. The reaction was worked up after 30 h by the addition of 1 M HCl (2 mL). The biphasic mixture was poured into a 60-mL separatory funnel and diluted with water (10 mL) and CH_2Cl_2 (10 mL). The layers were shaken and separated, and the aqueous phase was extracted with CH_2Cl_2 (2x 10 mL). Combined organic phases were washed with 1 M HCl (10 mL), water (10 mL), sat aq $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$ (1 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by column chromatography (1.5 cm ø x 20 cm column), eluting with hexanes/EtOAc, 9:1 gave **4.2.21** (78 mg, 60%) as a pale yellow solid.

Data for **4.2.21**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.10 (d, *J* = 8.4 Hz, 1 H, HC(4)), 6.85 (d, *J* = 8.5 Hz, 1 H, HC(3)), 6.19 (t, *J* = 3.2 Hz, 1 H, HC(8)), 3.90 (s, 3 H, HC(11)), 2.82 (dt, *J* = 15.6, 3.1 Hz, 1 H, HC(5)), 2.77 – 2.59 (m, 1 H, HC(5)), 2.53 – 2.15 (m, 4 H, HC(7,12)), 1.88 – 1.68 (m, 3 H, HC(6,6,7)), 1.17 (s, 9 H, HC(15)).

Preparation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis(2,2-dimethylpropanoate) (2.48) [BBG-6-079].

Following General Procedure III, **4.2.21** (60 mg, 0.17 mmol), CH_2Cl_2 (2 mL, 0.1 M), Br_2 (680 µL, 0.250 M in CH_2Cl_2, 1.0 equiv), and H_2NNH_2 (16 mg, 3.0 equiv) were reacted. The reaction mixture was diluted with CH_2Cl_2 (2 mL) and water (2 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 5 mL), and combined organic phases were washed with 1 M HCl (2x 5 mL), water (5 mL), and brine (5 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (1.5 cm ø x 20 cm column), eluting with hexanes/EtOAc, 7:1 gave **2.48** (45 mg, 78%) as an orange solid.

Data for **2.48**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.10 (d, *J* = 8.5 Hz, 1 H, HC(4)), 7.01 (d, *J* = 8.5 Hz, 1 H, HC(3)), 4.78 (t, *J* = 3.3 Hz, 1 H, HC(8)), 4.02 (s, 3 H, HC(11)), 2.73 (d, *J* = 16.3 Hz, 1 H, HC(5)), 2.48 (dt, *J* = 16.3, 9.2 Hz, 1 H, HC(5)), 1.85 – 1.74 (m, 1 H, HC(7)), 1.58 – 1.50 (m, 3 H, HC(6,6,7)), 1.08 (s, 9 H, HC(14)).

^{13}C NMR: (126 MHz, $CDCl_3$)

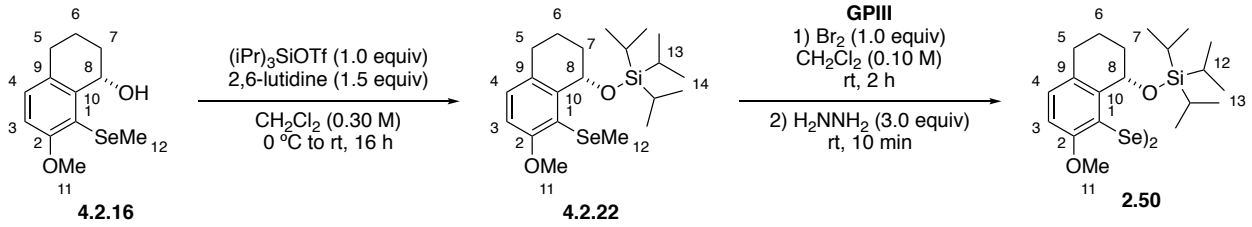
δ 176.52, 158.70, 138.12, 131.23, 129.94, 121.69, 111.65, 69.02, 56.15, 38.42, 29.22, 28.44, 27.04, 17.65.

HRMS: (ES+)

Found: 705.1223; Calc for $C_{32}H_{42}O_6NaSe_2$: 705.1210.

Preparation of 1,2-Bis((*S*)-2-methoxy-8-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.50).

Preparation of (*S*)-Triisopropyl((7-methoxy-8-(methylselanyl)-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)silane (4.2.22) [BBG-7-012].



4.2.16 **4.2.22** **2.50**

To a 5-mL Schlenk flask was added **4.2.16** (200 mg, 0.737 mmol) and CH_2Cl_2 (2 mL, 0.3 M). The solution was cooled to 0 ºC in an ice-water bath and 2,6-lutidine (128 µL, 1.5 equiv) was added. Triisopropylsilyl trifluoromethanesulfonate (198 µL, 1.0 equiv) was then added, dropwise. The reaction was removed from the ice bath and warmed to room temperature. After 16 h, the reaction was quenched by the addition of 1 M HCl (2 mL). The biphasic mixture was poured into a 60-mL separatory funnel, rinsing with water (10 mL) and CH_2Cl_2 (10 mL). The layers were shaken and separated, and the aqueous phase was extracted with CH_2Cl_2 (2x 10 mL). Combined organic phases were washed with 1 M HCl (10 mL), water (10 mL), brine (10 mL), dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 20 cm column), eluting with hexanes/Et_2O, 39:1 gave **4.2.22** (155 mg, 49%) in 95% purity (contaminated by TIPS-OH) as a pale yellow oil.

Data for **4.2.22**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.04 (d, *J* = 8.2 Hz, 1 H, HC(4)), 6.77 (d, *J* = 8.2 Hz, 1 H), HC(3), 5.56 (t, *J* = 3.0 Hz, 1 H, HC(8)), 3.88 (s, 3 H, HC(11)), 2.93 (ddd, *J* = 15.7, 6.5, 4.9 Hz, 1 H, HC(5)), 2.62 (ddd, *J* = 15.7, 9.1, 6.2 Hz, 1 H, HC(5)), 2.25 – 2.01 (m, 5 H, HC(6,7,12)), 1.72 – 1.61 (m, 2 H, HC(6,7)), 1.29 – 1.14 (m, 3 H, HC(13)), 1.08 (d, *J* = 7.4 Hz, 9 H, HC(14)), 1.02 (d, *J* = 7.4 Hz, 9 H, HC(14)).

TLC: R_f = 0.39 (hexanes/Et_2O, 19:1) [UV/CAM].

Preparation of 1,2-Bis((*S*)-2-methoxy-8-((triisopropylsilyl)Oxy)-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.50) [BBG-7-017].

Following General Procedure III, **4.2.22** (158 mg, 0.370 mmol), CH_2Cl_2 (5 mL, 0.07 M), Br_2 (1.73 mL, 0.213 M in CH_2Cl_2, 1.0 equiv), and H_2NNH_2 (36 mg, 3.0 equiv) were reacted. The reaction mixture was diluted with CH_2Cl_2 (1 mL) and water (2 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 10 mL), and combined organic phases were washed with 1 M HCl (2x 10 mL), water (10 mL), and brine (10 mL), dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 25 cm column), eluting with hexanes/Et_2O, 39:1 gave **2.50** (105 mg, 69%) as an orange solid.

Data for **2.50**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.02 (d, *J* = 8.4 Hz, 1 H, HC(4)), 6.78 (d, *J* = 8.4 Hz, 1 H, HC(3)), 4.71 (t, *J* = 3.0 Hz, 1 H, HC(8)), 3.88 (s, 3 H, HC(11)), 2.80 (ddd, *J* = 15.9, 6.4, 4.1 Hz, 1 H, HC(5)), 2.63 – 2.42 (m, 1 H, HC(5)), 2.06 – 1.83 (m, 1 H, HC(6)), 1.74 (dq, *J* = 14.3, 3.9 Hz, 1 H, HC(7)), 1.57 – 1.45 (m, 1 H, HC(6)), 1.11 – 0.98 (m, 3 H, HC(12)), 0.94 (d, *J* = 7.2 Hz, 9 H, HC(13)), 0.89 (m, 10 H, HC(7,13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.24, 143.51, 130.96, 130.06, 121.81, 110.19, 68.23, 56.22, 31.82, 28.62, 18.63, 18.61, 17.28, 13.36.

^{77}Se NMR: δ 359.4

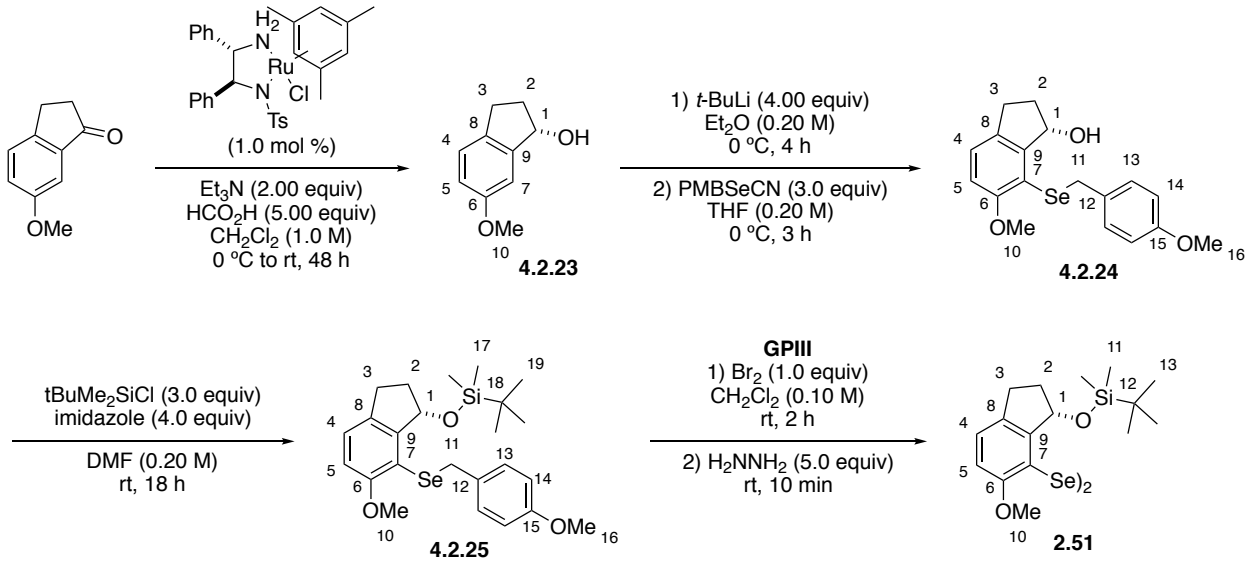
HRMS: (ES+)

Found: 849.2751; Calc for $C_{40}H_{66}O_4NaSi_2Se_2$: 849.2728.

TLC: R_f = 0.39 (hexanes/Et_2O, 19:1) [visible yellow, UV, CAM]

Preparation of 1,2-Bis((*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2,3-dihydro-1*H*-inden-4-yl)diselane (2.51).

Preparation of (*S*)-6-Methoxy-2,3-dihydro-1*H*-inden-1-ol (4.2.23) [BBG-7-050].



Following a modification of a literature procedure,[27] triethylamine (2.22 mL, 2.00 equiv) was added to a 25-mL Schlenk flask and cooled to 0 ºC in an ice-water bath. Formic acid (1.50 mL, 5.00 equiv) was added, dropwise over 15 min, to reduce fuming and premature decomposition of the formate. The mixture was removed from the ice bath and RuCl[(*S,S*)-TsDPEN](mesitylene) (50 mg, 1.0 mol %) was added, in one portion, against nitrogen flow. 6-methoxy-2,3-dihydro-1*H*-inden-1-one[20] (1.29 g, 7.95 mmol) was then added in the same manner. CH_2Cl_2 (8.0 mL, 1.0 M ketone) was added with a syringe, rinsing down any solid stuck to the walls of the flask. The reaction was deemed complete by TLC after 72 h and quenched by the addition of water (10 mL). The biphasic mixture was then poured into a 125-mL separatory funnel and diluted with 1 M HCl (20 mL) and EtOAc (20 mL). The layers were shaken and separated, and the organic phase was washed with 1 M HCl (20 mL) and water (20 mL). Combined aqueous phases were extracted with EtOAc (2x 20 mL), and combined organic phases were washed with water (20 mL), 10% w/v aq NaOH (20 mL), water (20 mL), and brine (20 mL), dried over $MgSO_4$ (8 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (5 cm ø x 25 cm column), eluting with hexanes/EtOAc, 3:1 gave **4.2.23** (1.20 g, 92%) as a clear, colorless oil. Spectroscopic data were consistent with the literature.[20]

Data for **4.2.23**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.15 (d, *J* = 8.2 Hz, 1 H, HC(4)), 6.96 (d, *J* = 2.5 Hz, 1 H, HC(7)), 6.83 (dd, *J* = 8.3, 2.5 Hz, 1 H, HC(5)), 5.21 (bs, 1 H, HC(1)), 3.81 (s, 3 H, HC(10)), 2.98 (ddd, *J* = 15.4, 8.5, 4.5 Hz, 1 H, HC(3)), 2.75 (ddd, *J* = 15.4, 8.1, 6.9 Hz, 1 H, HC(3)), 2.52 (dddd, *J* = 13.0, 8.2, 6.8, 4.5 Hz, 1 H, HC(2)), 1.95 (dddd, *J* = 13.0, 8.5, 6.8, 5.5 Hz, 1 H, HC(2)), 1.68 (bs, 1 H, OH).

HPLC: **(*S*)-S31** t_R 14.5 min (99.2%), **(*R*)-S31** t_R 16.2 min (0.8%) (Supelco Astec Cellulose DMP; hexanes/*i*-PrOH, 19:1; 1 mL/min; 220 nm).

Preparation of (*S*)-6-Methoxy-7-((4-methoxybenzyl)selanyl)-2,3-dihydro-1*H*-inden-1-ol (4.2.24) [BBG-7-085].

Following a modification of a literature procedure,[29] **4.2.23** (164 mg, 1.00 mmol) was added to a 25-mL Schlenk flask. Et_2O (5 mL, 0.2 M) was added and the solution was cooled in an ice-water bath to 0 ºC. *t*-BuLi (2.4 mL, 1.7 M in pentane, 4.0 equiv) was added, dropwise over 5 min. After 4 h at 0 ºC, THF (5 mL, 1:1 v/v Et_2O) was added, followed by PMBSeCN (678 mg, 3.0 equiv) solid, against nitrogen back-flow. The mixture was stirred at 0 ºC for 3 h, then quenched by the addition of sat aq NH_4Cl (10 mL). The biphasic mixture was transferred to a 125-mL separatory funnel (fume hood!) rinsing with EtOAc (10 mL) and water (10 mL). The layers were shaken and separated, and the aqueous phase was extracted with EtOAc (2x 10 mL). Combined organic phases were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 25 cm column), eluting with hexanes/EtOAc, 4:1 gave **4.2.24** (122 mg, 34%) as a pale yellow oil.

Data for **4.2.24**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.17 (d, *J* = 8.2 Hz, 1 H, HC(4)), 7.01 (d, *J* = 8.6 Hz, 2 H, HC(14)), 6.81 (d, *J* = 8.2 Hz, 1 H, HC(5)), 6.73 (d, *J* = 8.6 Hz, 2 H, HC(13)), 5.06 (ddd, *J* = 6.8, 4.1, 2.3 Hz, 1 H, HC(1)), 4.06 (d, *J* = 11.4 Hz, 1 H, HC(11)), 4.03 (d, *J* = 11.3 Hz, 1 H, HC(11)), 3.90 (s, 3 H, HC(10)), 3.75 (s, 3 H, HC(16)), 3.01 (dddd, *J* = 15.4, 8.6, 6.0, 1.1 Hz, 1 H, HC(3)), 2.79 (d, *J* = 2.3 Hz, 1 H, OH), 2.71 (dddd, *J* = 15.4, 8.7, 5.2, 1.0 Hz, 1 H, HC(3)), 2.28 (ddt, *J* = 13.6, 8.6, 6.6 Hz, 1 H, HC(2)), 1.98 (dddd, *J* = 13.6, 8.6, 5.3, 4.1 Hz, 1 H, HC(2)).

Preparation of (*S*)-*tert*-Butyl((6-methoxy-7-((4-methoxybenzyl)selanyl)-2,3-dihydro-1*H*-inden-1-yl)oxy)dimethylsilane (4.2.25) [BBG-7-090].

Following a modification of a literature procedure,[29] **4.2.24** (120 mg, 0.33 mmol) and DMF (2 mL, 0.2 M) were added to a 5-mL Schlenk flask. Imidazole (90 mg, 4.0 equiv) and Me2tBuSiCl (149 mg, 3.0 equiv) were added in sequence against nitrogen back-flow at room temperature. After 18 h, the reaction mixture was poured into a 125-mL separatory funnel, rinsing with water (10 mL) and Et_2O (10 mL). The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (3x 10 mL). Combined organic phases were washed with 5% w/v aq citric acid (10 mL), water (10 mL), and brine (10 mL), dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 20 cm column), eluting with hexanes/Et_2O, 39:1 gave **4.2.25** (138 mg, 88%) as a clear, colorless oil.

Data for **4.2.25**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.13 (d, *J* = 8.1 Hz, 1 H, HC(4)), 7.03 (d, *J* = 8.6 Hz, 2 H, HC(13)), 6.78 (d, *J* = 8.1 Hz, 1 H, HC(5)), 6.72 (d, *J* = 8.6 Hz, 2 H, HC(14)), 5.01 (dd, *J* = 5.9, 1.8 Hz, 1 H, HC(1)), 4.01 (s, 2 H, HC(11)), 3.89 (s, 3 H, HC(10)), 3.76 (s, 3 H, HC(16)), 3.24 – 2.98 (m, 1 H, HC(3)), 2.79 – 2.61 (m, 1 H, HC(3)), 2.12 – 1.97 (m, 1 H, HC(2)), 1.98 – 1.90 (m, 1 H, HC(2)), 0.85 (s, 9 H, HC(19)), 0.14 (s, 3 H, HC(17)), 0.11 (s, 3 H, HC(17)).

Preparation of 1,2-Bis((*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2,3-dihydro-1*H*-inden-4-yl)diselane (2.51) [BBG-7-095].

To a 10-mL Schlenk flask was added **4.2.25** (115 mg, 0.241 mmol) and CH_2Cl_2 (5 mL, 0.05 M). Br_2 (2.16 mL, 0.112 M in CH_2Cl_2, 1.00 equiv) was added at room temperature in one portion. The solution quickly turned deep brown. After 10 min, H_2NNH_2 (39 mg, 5.0 equiv) was added with vigorous stirring (gas evolution) and the brown color immediately faded to yellow-orange. The solution was transferred to a 60-mL separatory funnel, rinsing with CH_2Cl_2 (5 mL) and water (5 mL). The layers were shaken and separated, and the aqueous phase was extracted with CH_2Cl_2 (2x 10 mL). Combined organic phases were washed with 5% w/v aq citric acid (10 mL), water (10 mL), and brine (10 mL), dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (20 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 20 cm column), eluting with hexanes/EtOAc, 39:1 gave **2.51** (23 mg, 27%) as an orange solid.

Data for **2.51**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.15 (d, *J* = 8.1 Hz, 1 H, HC(4)), 6.82 (d, *J* = 8.2 Hz, 1 H, HC(5)), 4.16 (dd, *J* = 6.0, 1.3 Hz, 1 H, HC(1)), 3.89 (s, 3 H, HC(10)), 3.12 – 2.93 (m, 1 H, HC(3)), 2.61 (ddd, *J* = 15.0, 8.4, 1.8 Hz, 1 H, HC(3)), 1.71 (ddt, *J* = 13.5, 7.6, 1.8 Hz, 1 H, HC(2)), 1.57 – 1.48 (m, 1 H, HC(2)), 0.77 (s, 9 H, HC(13)), 0.00 (s, 3 H, HC(11)), -0.04 (s, 3 H, HC(11)).

^{13}C NMR: (126 MHz, $CDCl_3$)

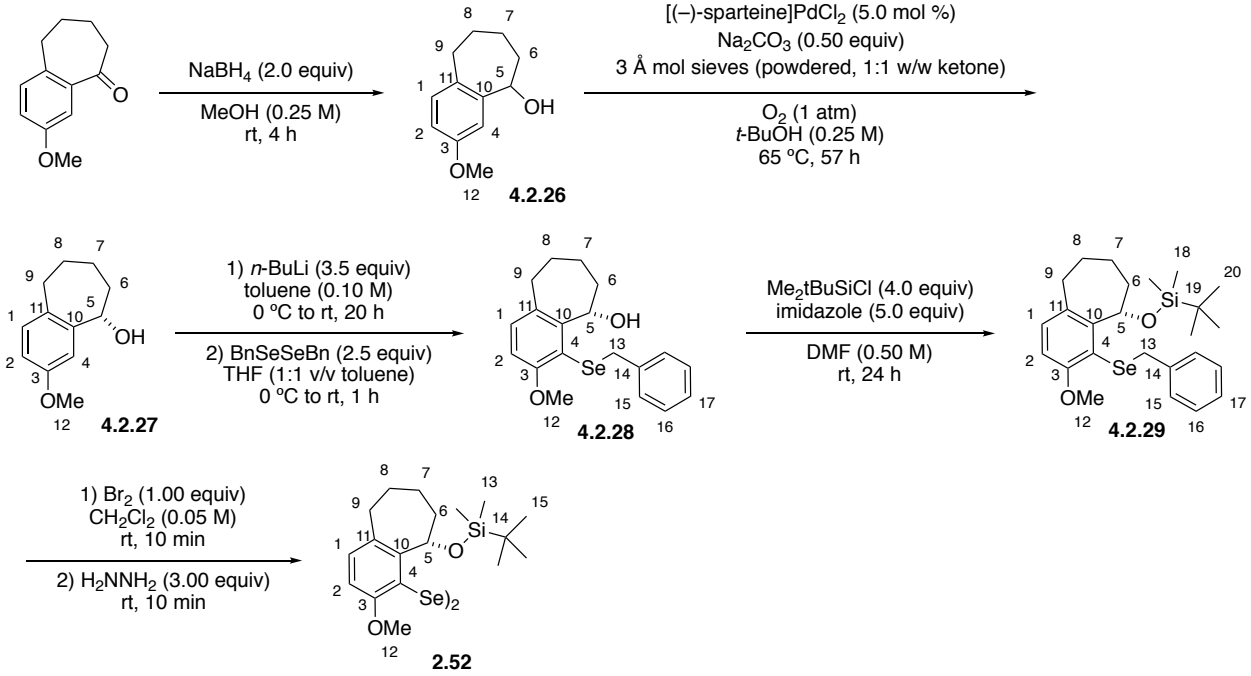
δ 159.02, 151.63, 135.60, 126.32, 116.85, 110.98, 56.34, 35.49, 30.46, 26.09, 18.12, -4.09, -4.22.

HRMS: (ES+)

Found: 737.1487; Calc for $C_{32}H_{50}O_4NaSi_2Se_2$: 737.1476.

Preparation of 1,2-Bis((*S*)-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-1-yl)diselane (2.52).

Preparation of 3-Methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol (S34) [BBG-7-098].



To a 50-mL Schlenk flask was added 3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one[22] (1.00 g, 5.26 mmol) and MeOH (20 mL, 0.25 M). The mixture was cooled to 0 ºC in an ice-water bath and $NaBH_4$ (398 mg, 2.00 equiv) was added in four portions over 10 min. Once the addition was complete, the mixture was removed from the ice bath and warmed to room temperature. After 4 h, the reaction was quenched by the cautious addition of 1 M HCl (10 mL). The biphasic mixture was poured into a 250-mL separatory funnel, rinsing with EtOAc (20 mL) and water (20 mL). The layers were shaken and separated, and the aqueous phase was extracted with EtOAc (3x 30 mL). Combined organic phases were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ (4 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). Purification by silica gel column chromatography (4 cm ø x 20 cm column) eluting with hexanes/EtOAc, 9:1 gave **4.2.26** (1.0 g, 99%) as a white solid.

Data for **4.2.26**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.06 (d, *J* = 2.7 Hz, 1 H, HC(4)), 7.01 (d, *J* = 8.1 Hz, 1 H, HC(1)), 6.67 (dd, *J* = 8.1, 2.8 Hz, 1 H, HC(2)), 4.89 (d, *J* = 8.4 Hz, 1 H, HC(5)), 3.81 (s, 3 H, HC(12)), 2.83 (dd, *J* = 14.4, 7.7 Hz, 1 H, HC(9)), 2.65 (ddd, *J* = 14.3, 10.7, 1.6 Hz, 1 H, HC(9)), 2.08 – 1.92 (m, 2 H, HC(6-8)), 1.85 (s, 1 H, OH), 1.83 – 1.71 (m, 3 H, HC(6-8)), 1.39 (q, *J* = 11.8 Hz, 1 H, HC(6-8)).

Preparation of (*S*)-3-Methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol (4.2.27) [BBG-8-005].

Following a modification of a literature procedure,[21] **4.2.26** (550 mg, 2.86 mmol) and Ph_2O (internal standard, 248 mg, 1.46 mmol) were added to a 25-mL 2-neck round-bottom flask equipped with a reflux condenser. *t*-BuOH (11 mL, 0.25 M) was added and the mixture was kept at 40 ºC in an oil bath to maintain fluidity. Powdered 3 Å molecular sieves (550 mg, 1:1 w/w substrate) were added, followed by Na_2CO_3 (53 mg, 0.50 equiv) and [(–)-sparteine]$PdCl_2$ (21 mg, 5.0 mol %). An oxygen-filled balloon was connected to the top of the reflux condenser and house vacuum was pulled through the other neck of the flask. This process was repeated three more times before closing the second neck of the flask and capping the reflux condenser with an oxygen-filled balloon to maintain static pressure. The mixture was heated to 65 ºC, and reaction progress was monitored by chiral GC analysis of periodic aliquots. After 57 h the reaction had reached 58% conversion and the alcohol e.r. was 93:7. The reaction mixture was cooled to room temperature and vacuum filtered through a pad of silica in a fritted funnel (5 cm ø x 3 cm height), rinsing with Et_2O (3x 20 mL). The filtrate was then concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (3 cm ø x 20 cm column), eluting with hexanes/EtOAc, 9:1 gave **4.2.27** (210 mg, 38%, e.r. 93:7) as a white solid. Spectral data matched that of the racemic.

Data for **4.2.27**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.06 (d, *J* = 2.7 Hz, 1 H, HC(4)), 7.01 (d, *J* = 8.1 Hz, 1 H, HC(1)), 6.67 (dd, *J* = 8.1, 2.8 Hz, 1 H, HC(2)), 4.89 (d, *J* = 8.4 Hz, 1 H, HC(5)), 3.81 (s, 3 H, HC(12)), 2.83 (dd, *J* = 14.4, 7.7 Hz, 1 H, HC(9)), 2.65 (ddd, *J* = 14.3, 10.7, 1.6 Hz, 1 H, HC(9)), 2.08 – 1.92 (m, 2 H, HC(6-8)), 1.85 (s, 1 H, OH), 1.83 – 1.71 (m, 3 H, HC(6-8)), 1.39 (q, *J* = 11.8 Hz, 1 H, HC(6-8)).

GC: **Ph_2O** t_R 3.5 min (31%), **8-methoxybenzosuberone** t_R 13.3 min (37%), **(*R*)-4.2.27** t_R 15.3 min (2%), **(*S*)-4.2.27** t_R 15.7 min (30%) (FID; Durabond Cyclosil-B; 30 m l, 0.25 mm bore, 0.25 μm film; 150 ºC for 8 min, ramp to 220 ºC over 14 min).

Preparation of (*S*)-4-(Benzylselanyl)-3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol (4.2.28) [BBG-8-018].

To a 25-mL Schlenk flask was added **4.2.27** (76.5 mg, 0.398 mmol) and toluene (4.0 mL, 0.10 M). The solution was cooled to 0 ºC and *n*-BuLi (0.87 mL, 1.6 M in hexanes, 3.5 equiv) was added, dropwise. The ice bath was then removed and the reaction mixture was warmed to room temperature. After 20 h, the reaction mixture was cooled on an ice-water bath to 0 ºC and THF (4.0 mL, 1:1 v/v toluene) was added in one portion, followed by BnSeSeBn (338 mg, 2.5 equiv) in one portion, against nitrogen back-flow. The ice bath was removed and the reaction mixture was warmed to room temperature. After 1 h the reaction was quenched by the addition of chloroacetic acid (190 mg, 5.0 equiv) in 10% w/v aq NaOH (5 mL). The biphasic mixture was stirred vigorously for 30 min and then poured into a 125-mL separatory funnel, rinsing with Et_2O (2x 5 mL) and water (2x 5 mL). The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (3x 10 mL). Combined organic phases were washed with 10% w/v aq NaOH (10 mL), water (20 mL), brine (10 mL), dried over Na_2SO_4 (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (3 cm ø x 15 cm column), eluting with hexanes/EtOAc, 1:0 gradient to 4:1 gave **4.2.28** (102 mg, 67%) as a clear, yellow oil.

Data for **4.2.28**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.20 – 7.09 (m, 3 H, HC(16,17)), 7.04 (d, *J* = 8.2 Hz, 1 H, HC(1)), 6.92 (d, *J* = 6.4 Hz, 1 H, HC(15)), 6.72 (d, *J* = 8.3 Hz, 1 H, HC(2)), 5.68 (dt, *J* = 6.9, 2.2 Hz, 1 H, HC(5)), 3.98 (d, *J* = 11.5 Hz, 1 H, HC(13)), 3.92 (s, 3 H, HC(12)), 3.88 (d, *J* = 11.5 Hz, 1 H, HC(13)), 3.22 (ddd, *J* = 14.1, 12.2, 1.9 Hz, 1 H, HC(9)), 2.49 (ddt, *J* = 14.2, 6.7, 1.4 Hz, 1 H, HC(9)), 2.07 – 1.91 (m, 2 H, HC(6-8)), 1.86 (dddd, *J* = 12.3, 5.7, 2.9, 1.4 Hz, 1 H, HC(6-8)), 1.62 – 1.53 (m, 1 H, HC(6-8)), 1.38 – 1.19 (m, 2 H, HC(6-8)), 0.72 (dd, *J* = 3.0, 1.3 Hz, 1 H, OH).

TLC: R_f = 0.16 (hexanes/EtOAc, 9:1) [UV/CAM]

Preparation of (*S*)-((4-(Benzylselanyl)-3-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)oxy)(*tert*-butyl)dimethylsilane (4.2.29) [BBG-8-020].

To a 5-mL Schlenk flask was added **4.2.28** (102 mg, 0.270 mmol) and DMF (0.5 mL, 0.5 M). Imidazole (91 mg, 5.0 equiv) was added at room temperature against nitrogen back-flow, followed by Me_2tBuSiCl (160 mg, 4.0 equiv) in the same manner. After 24 h, the reaction mixture was poured into a 60-mL separatory funnel, rinsing with water (5 mL) and Et_2O (5 mL). The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (3x 10 mL). Combined organic phases were washed with 10% w/v aq citric acid (10 mL), water (10 mL), and brine (10 mL), dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (40 ºC, 20 mm Hg). Purification by silica gel column chromatography (2 cm ø x 15 cm column), eluting with hexanes/EtOAc, 1:0 gradient to 19:1 gave **4.2.29** (112 mg, 88%) as a white solid.

Data for **4.2.29**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.22 – 7.09 (m, 5 H, HC(15,16,17)), 6.98 (d, *J* = 8.2 Hz, 1 H, HC(1)), 6.64 (d, *J* = 8.2 Hz, 1 H, HC(2)), 5.94 (d, *J* = 7.0 Hz, 1 H, HC(5)), 4.12 (d, *J* = 11.0 Hz, 1 H, HC(13)), 3.91 (d, *J* = 11.0 Hz, 1 H, HC(13)), 3.86 (s, 3 H, HC(12)), 3.49 – 3.40 (m, 1 H, HC(9)), 2.46 – 2.39 (m, 1 H, HC(9)), 2.20 – 2.05 (m, 1 H, HC(6-8)), 1.88 (dd, *J* = 13.3, 6.1 Hz, 1 H, HC(6-8)), 1.81 (ddq, *J* = 14.4, 7.2, 3.6, 3.1 Hz, 1 H, HC(6-8)), 1.58 – 1.48 (m, 1 H, HC(6-8)), 1.18 (tdd, *J* = 13.7, 11.6, 3.2 Hz, 1 H, HC(6-8)), 1.06 – 0.94 (m, 1H, HC(6-8)), 0.86 (s, 9 H, HC(20)), 0.07 (s, 3 H, HC(18)), -0.20 (s, 3 H, HC(18)).

TLC: R_f = 0.47 (hexanes/EtOAc, 9:1) [UV/CAM]

Preparation of 1,2-Bis((*S*)-9-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-1-yl)diselane (2.52) [BBG-8-022].

To a 10-mL Schlenk flask was added **4.2.29** (112 mg, 0.235 mmol) and CH_2Cl_2 (5 mL, 0.05 M). Br_2 (950 µL, 0.248 M in CH_2Cl_2, 1.00 equiv) was added in one portion at room temperature. The reaction mixture quickly became a deep brown color. After 10 min, H_2NNH_2 (23 mg, 3.0 equiv) was added with vigorous stirring. The mixture immediately became yellow-orange. After 10 min, 5% w/v aq citric acid (5 mL) and the mixture was poured into a 60-mL separatory funnel, rinsing with CH_2Cl_2 (2x 5 mL) and water (5 mL). The layers were shaken and separated, and the aqueous phase was extracted with CH_2Cl_2 (2x 10 mL). Combined organic phases were washed with 5% w/v aq citiric acid (10 mL), water (20 mL), and brine (10 mL), dried over Na_2SO_4 (2 g), filtered, and concentrated directly onto silica (2 g) under reduced pressure by rotary evaporation (30 ºC, 20 mm Hg). The product on silica was dry loaded onto a silica column (2 cm ø x 20 cm) and eluted with hexanes/EtOAc, 19:1 to give **2.52** (55.6 mg, 62%) as an orange solid.

Data for **2.52**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 6.94 (d, *J* = 8.2 Hz, 1 H, HC(1)), 6.58 (d, *J* = 8.2 Hz, 1 H, HC(2)), 5.82 (d, *J* = 7.0 Hz, 1 H, HC(5)), 3.68 (s, 3 H, HC(12)), 3.48 – 3.35 (m, 1 H, HC(9)), 2.40 (dd, *J* = 13.6, 6.4 Hz, 1 H, HC(9)), 2.22 – 1.99 (m, 1 H, HC(6-8)), 1.87 (dd, *J* = 13.9, 5.8 Hz, 1 H, HC(6-8)), 1.61 (ddd, *J* = 14.3, 7.2, 3.6 Hz, 1 H, HC(6-8)), 1.57 – 1.47 (m, 1 H, HC(6-8)), 1.28 – 1.12 (m, 1 H, HC(6-8)), 0.93 (td, *J* = 13.9, 3.2 Hz, 1 H, HC(6-8)), 0.84 (s, 9 H, HC(15)), 0.04 (s, 3 H, HC(13)), -0.22 (s, 3 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.34, 148.26, 136.78, 132.27, 120.57, 109.13, 74.28, 56.26, 35.08, 33.46, 29.19, 26.05, 24.78, 18.28, -4.31, -4.51.

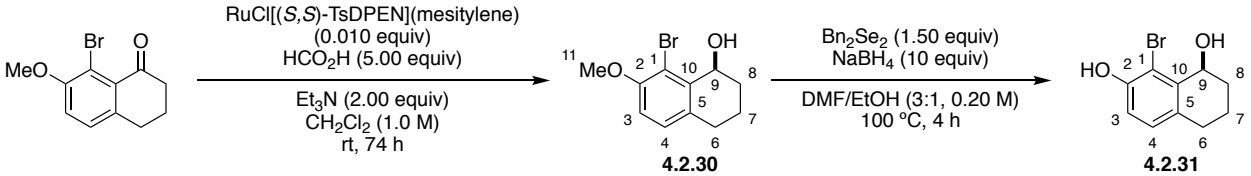
HRMS: (ES+)

Found: 770.2214; Calc for $C_{36}H_{58}O_4Si_2Se_2$: 770.2204.

TLC: R_f = 0.45 (hexanes/EtOAc, 9:1) [UV/CAM]

Preparation of (*S*)-8-Bromo-1,2,3,4-tetrahydronaphthalene-1,7-diol (4.2.31).

Preparation of (*S*)-8-Bromo-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (4.2.30) [BBG-2018-083, BBG-2018-084].



To a 25-mL Schlenk flask equipped with a magnetic stir bar was added Et_3N (2.09 mL, 15.0 mmol, 2.00 equiv). The flask was immersed in an ice-water bath and formic acid (1.41 mL, 37.5 mmol, 5.00 equiv) was added dropwise. 8-bromo-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one[22] (1.91 g, 7.50 mmol) was added, followed by RuCl[(*S,S*-TsDPEN)](mesitylene) (46.7 mg, 0.075 mmol, 0.010 equiv), and CH_2Cl_2 (7.5 mL, 1.0 M). The ice bath was removed and the reaction mixture was stirred at room temperature. After 74 h the reaction was quenched with water (5 mL) and transferred to a 250-mL separatory funnel with Et_2O (3 × 10 mL) and water (3 × 10 mL). The biphasic mixture was shaken and separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ (5 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC,

4 mm Hg). Purification by silica gel column chromatography (120 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 7:3 over 20 min afforded **4.2.30** (1.59 g, 82%) as a clear, pale-yellow oil.

For determination of the enantiomeric ratio, a small portion of the material (26 mg, 0.10 mmol) was transferred to a 5-mL condenser flask equipped with a magnetic stir bar and dissolved in toluene (1.0 mL, 0.10 M). Bu_3SnH (32 μL, 0.12 mmol, 1.20 equiv) was added and the reaction mixture was stirred and heated to reflux. AIBN (1.6 mg, 0.010 mmol, 0.10 equiv) was then added against nitrogen flow at reflux. After 12 h, the reaction mixture was cooled to room temperature and transferred to a 25-mL round bottom flask with Et_2O (2 × 5 mL). The solution was concentrated under reduced pressure by rotary evaporation (40 ºC, 4 mm Hg). The resulting concentrate was transferred to a 60-mL separatory funnel with Et_2O (10 mL) and washed with sat. aq. NH_3 (2 × 10 mL). The combined aqueous layers were extracted with Et_2O (2 × 10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ (1 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (12 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 1:1 over 15 min afforded **4.2.15** (8.4 mg, 47%).

Data for **4.2.30**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.07 (d, J = 8.4 Hz, 1 H, HC(4)), 6.82 (d, J = 8.4 Hz, 1 H, HC(3)), 5.06 (q, J = 3.5 Hz, 1 H, HC(9)), 3.88 (s, 3 H, HC(11)), 2.81 (ddd, J = 17.4, 4.8, 2.6 Hz, 1 H, HC(6)), 2.66 (ddd, J = 17.1, 12.4, 5.5 Hz, 1 H, H'C(6)), 2.52 (dd, J = 3.7, 1.4 Hz, 1 H, OH), 2.20 (ddq, J = 10.9, 4.0, 1.8 Hz, 1 H, HC(8)), 2.06 – 1.89 (m, 1 H, HC(7)), 1.83 – 1.68 (m, 2 H, H'C(7,8)).

SFC: **(*R*)-4.2.15** t_R 9.24 min (0.6%), **(*S*)-4.2.15** t_R 10.16 min (99.4%) (Daicel Chiralpak AD; CO_2/MeOH, 19:1 gradient to 4:1 over 10 min, hold 4:1 for 10 min; 2.5 mL/min; 220 nm).

TLC: R_f = 0.33 (hexanes/EtOAc, 4:1) [UV, CAM]

Preparation of (*S*)-8-Bromo-1,2,3,4-tetrahydronaphthalene-1,7-diol (4.2.31) [BBG-2018-092].

CAUTION: STENCH

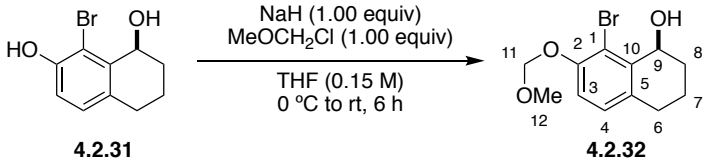
To a 50-mL Schlenk flask equipped with a magnetic stir bar was added Bn_2Se_2 (1.89 g, 5.56 mmol, 1.50 equiv). DMF (15 mL, 0.25 M) was added, and the solution was immersed in an ice-water bath. $NaBH_4$ (1.40 g, 37.1 mmol, 10.0 equiv) was added in one portion, and the ice bath was removed. Ethanol was added until the yellow color of the diselenide was no longer visible (ca. 5.4 mL, 93 mmol, 25 equiv was required). The resulting suspension was stirred at room temperature. After 5 min, **4.2.30** was added in one portion against nitrogen back-flow, and the mixture was transferred to an oil bath, pre-heated to 100 ºC. After 4 h, the reaction mixture was poured into 1 M HCl (200 mL) cooled in an ice-water bath. The resulting suspension was transferred to a 500-mL separatory funnel and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water/brine, 1:1 (3 × 100 mL), dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure by rotary evaporation (30 ºC, 4 mm Hg). Purification by silica gel column chromatography (120 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 1:1 over 28 min afforded **4.2.31** (792 mg, 88%) as a white solid.

Data for **4.2.31**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.01 (d, *J* = 8.3 Hz, 1 H, HC(4)), 6.93 (d, *J* = 8.3 Hz, 1 H, HC(3)), 5.52 (s, 1 H, ArO**H**), 4.97 (q, *J* = 3.7 Hz, 1 H, HC(9)), 2.87 – 2.74 (m, 1 H, HC(6)), 2.65 (ddd, *J* = 17.0, 12.3, 5.6 Hz, 1 H, HC(7)), 2.23 – 2.15 (m, 2 H, H'C(6)+CHO**H**), 2.02 – 1.85 (m, 1 H, HC(8)), 1.85 – 1.66 (m, 2 H, H'C(7,8)).

Preparation of (*S*)-8-Bromo-7-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (4.2.32) [BBG-2018-093].



4.2.31 **4.2.32**

To a 25-mL Schlenk flask equipped with a magnetic stir bar was added NaH (48.0 mg, 2.00 mmol, 1.00 equiv) in a glove box. The flask was sealed with a rubber septum and connected to a nitrogen purged Schlenk line. THF (8 mL) was added and the resulting suspension was stirred

and immersed in an ice-water bath. **4.2.31** (486 mg, 2.00 mmol) in THF (4 mL) was added to the NaH suspension dropwise via syringe over 30 min. The syringe was rinsed into the reaction mixture with THF (1 mL). After 30 min, chloromethyl methyl ether (1.0 mL, 2.0 M in toluene, 2.0 mmol, 1.0 equiv) was added dropwise via syringe. Once the addition was complete, the ice bath was allowed to melt, and the reaction mixture was warmed to room temperature. After 6 h, the reaction mixture was quenched by the cautious addition of water (5 mL). The biphasic mixture was transferred to a separatory funnel with Et_2O (10 mL) and water (10 mL). The layers were shaken and separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (120 g silica, 5 cm ø column) eluting with hexanes/EtOAc, 17:3 afforded **4.2.32** (446 mg, 78%) as a clear, colorless, viscous oil.

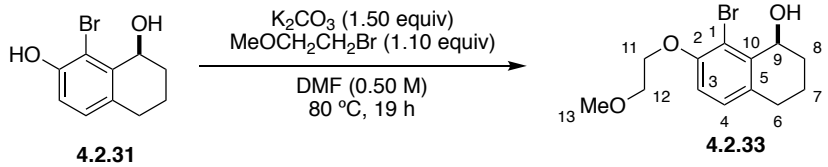
Data for **4.2.32**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.04 (s, 2 H, HC(3,4)), 5.22 (s, 2 H, HC(11)), 5.05 (q, *J* = 3.5 Hz, 1 H, HC(9)), 3.52 (s, 3 H, HC(12)), 2.81 (dddd, *J* = 16.6, 5.5, 2.4, 1.3 Hz, 1 H, HC(6)), 2.66 (ddd, *J* = 17.0, 12.3, 5.6 Hz, 1 H, H'C(6)), 2.52 (dt, *J* = 3.8, 1.0 Hz, 1 H, OH), 2.26 – 2.16 (m, 1 H, HC(8)), 2.06 – 1.89 (m, 1 H, HC(7)), 1.84 – 1.68 (m, 1 H, H'C(7,8)).

TLC: R_f = 0.30 (hexanes/EtOAc, 4:1) [UV, CAM]

Preparation of (*S*)-8-Bromo-7-(2-methoxyethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (4.2.33) [BBG-2018-091].



4.2.31 **4.2.33**

To a 10-mL Schlenk flask equipped with a magnetic stir bar was added **4.2.31** (486 mg, 2.00 mmol) and DMF (4.0 mL, 0.50 M). Once homogeneous, K_2CO_3 (415 mg, 3.00 mmol, 1.50 equiv) was added in one portion against nitrogen backflow at room temperature. 2-bromoethyl methyl ether (207 µL, 2.20 mmol, 1.10 equiv) was then added in one portion via syringe and the reaction mixture was transferred to an oil bath, pre-heated to 80 ºC. After 19 h, the reaction mixture was cooled to room temperature and poured into water (25 mL). The aqueous suspension was

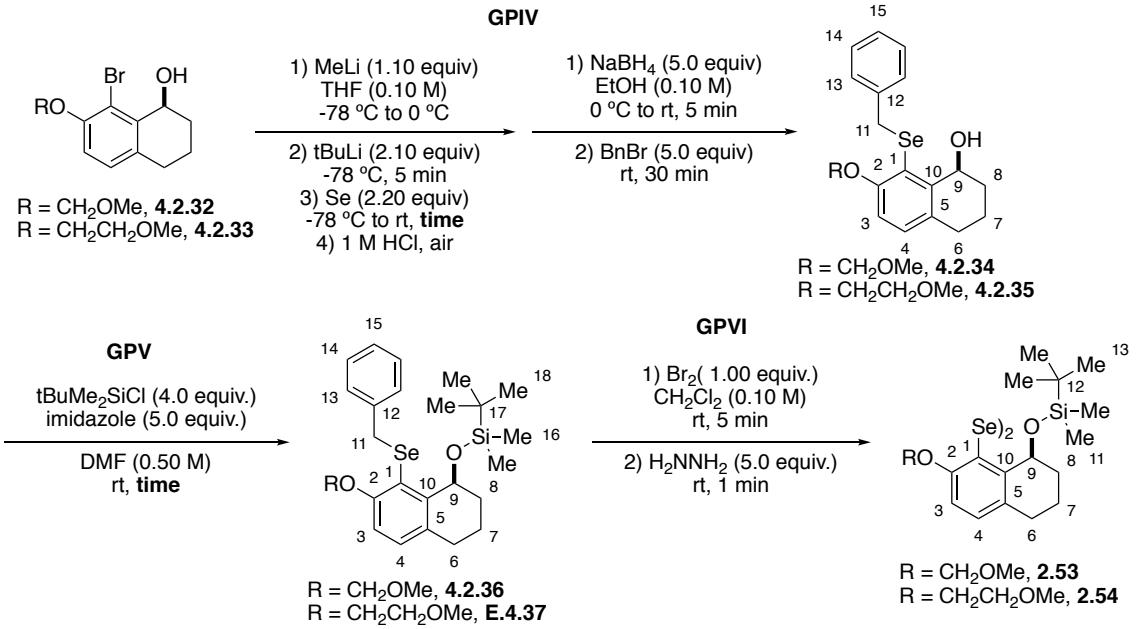
transferred to a 100-mL separatory funnel with water (10 mL) and Et_2O (10 mL). The layers were shaken and separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with water/brine, 1:1 (3 × 20 mL), 10% aq. NaOH (2 × 20 mL), water (2 × 10 mL), and brine (20 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (120 g, ISCO MPLC), eluting with hexanes/EtOAc, 1:0 gradient to 3:2 over 23 min afforded **4.2.33** (537 mg, 89%) as a clear, colorless oil.

Data for **4.2.33**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.04 (d, *J* = 8.6 Hz, 1 H, HC(4)), 6.85 (d, *J* = 8.4 Hz, 1 H, HC(3)), 5.05 (q, *J* = 3.5 Hz, 1 H, HC(9)), 4.31 – 4.03 (m, 2 H, HC(11)), 3.93 – 3.69 (m, 2 H, HC(12)), 3.49 (s, 3 H, HC(13)), 2.89 – 2.73 (m, 1 H, HC(6)), 2.66 (ddd, *J* = 17.0, 12.3, 5.5 Hz, 1 H, H'C(6)), 2.53 (dd, *J* = 3.6, 1.3 Hz, 1 H, OH), 2.28 – 2.10 (m, 1 H, HC(8)), 2.08 – 1.85 (m, 1 H, HC(7)), 1.87 – 1.66 (m, 2 H, H'C(7,8)).

Preparation of 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-(methoxymethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.53) and 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.54).

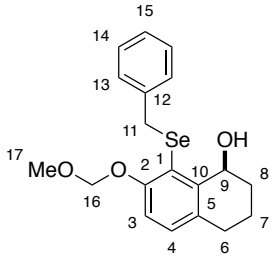


General Procedure IV: Preparation of Benzyl Selenides 4.2.34 and 4.2.35.

To a 50-mL Schlenk flask equipped with a magnetic stir bar and a thermocouple probe were added **4.2.32** or **4.2.33** (1.00 equiv) and THF (0.10 M). The resulting solution was cooled to –76 ºC (internal temperature). MeLi (1.50 M in Et_2O, 1.10 equiv) was added dropwise via syringe, maintaining internal temperature below –65 ºC. The reaction mixture was removed from the cooling bath and the internal temperature was allowed to reach 0 ºC before the being cooled once more. Once the internal temperature had returned to –76 ºC, *t*-BuLi (1.60 M in pentane, 2.10 equiv) was added dropwise via syringe, maintaining internal temperature below –65 ºC. Once the addition was complete, the reaction mixture was stirred at –76 ºC. After 5 min, Se (2.20 equiv) was added in one portion against nitrogen backflow. The flask was removed from the cooling bath and the reaction mixture was allowed to warm to room temperature. After 3 – 5 h, the resulting deep red mixture was transferred to a 500-mL Erlenmeyer flask containing 1 M HCl (100 mL) with water (2 × 10 mL) and Et_2O (2 × 10 mL). Air was bubbled through the suspension for 1 h at room temperature. The resulting aqueous suspension was transferred to a 500-mL separatory funnel and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (120 g silica, 5 cm ø column) eluting with hexanes/EtOAc, 3:1 gradient to 1:1 afforded a mixture of symmetric and unsymmetric di- and polyselenides, which was carried forward crude.

The di- and polyselenide mixture was transferred to a 25-mL Schlenk flask equipped with a magnetic stir bar and dissolved in EtOH (0.10 M). The solution was immersed in an ice-water bath and $NaBH_4$ (5.00 equiv) was added in one portion against nitrogen backflow. The reaction mixture was stirred until the yellow color disappeared and then removed from the ice bath. Once the reaction mixture reached room temperature, BnBr (5.00 equiv) was added dropwise via syringe. After 30 min, the reaction mixture was transferred to a 250-mL separatory funnel with water (2 × 20 mL) and Et_2O (2 × 20 mL). The layers were shaken and separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography (120 g silica, 5 cm ø column) eluting with hexanes/EtOAc, 5:1 (**4.2.34**) or 4:1 (**4.2.35**) afforded the benzyl selenide.

Preparation of (*S*)-8-(Benzylselanyl)-7-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (4.2.34) [BBG-2018-095, BBG-2018-097].



4.2.34

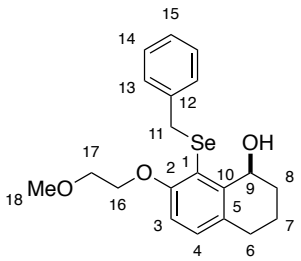
Following General Procedure IV, **4.2.32** (440 mg, 1.53 mol), MeLi (1.12 mL, 1.50 M in Et_2O, 1.69 mmol, 1.10 equiv), *t*-BuLi (2.01 mL, 1.60 M in pentane, 3.22 mmol, 2.10 equiv), and Se (266 mg, 2.20 equiv) in THF (15 mL, 0.10 M) were reacted for 5 h to afford the polyselenide mixture after acidic workup in air and partial chromatographic purification (523 mg, 119% mass balance). The mixture was reacted with $NaBH_4$ (173 mg, 4.57 mmol, 5.00 equiv) and BnBr (543 µL, 4.57 mmol, 5.00 equiv) in EtOH (9.1 mL, 0.10 M) to afford **4.2.34** (490 mg, 80%, 95% pure) as a clear, colorless oil.

Data for **4.2.34**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.23 – 7.13 (m, 3 H, HC(aryl)), 7.07 (d, *J* = 6.1 Hz, 4 H, HC(aryl)), 5.29 – 5.24 (m, 2 H, HC(16)), 4.84 (q, *J* = 3.7 Hz, 1 H, HC(9)), 4.15 (d, *J* = 11.2 Hz, 1 H, HC(11)), 4.07 (d, *J* = 11.3 Hz, 1 H, H'C(11)), 3.56 (s, 3 H, HC(17)), 2.74 (dddd, *J* = 16.5, 4.7, 2.9, 1.3 Hz, 1 H, HC(6)), 2.58 (ddd, *J* = 16.8, 11.9, 5.6 Hz, 1 H, H'C(6)), 2.28 (dd, *J* = 3.8, 1.3 Hz, 1 H, OH), 2.12 – 1.94 (m, 1 H, HC(8)), 1.94 – 1.77 (m, 1 H, HC(7)), 1.75 – 1.60 (m, 1 H, H'C(7)), 1.60 – 1.48 (m, 1 H, H'C(8)).

Preparation of (*S*)-8-(Benzylselanyl)-7-(2-methoxyethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (4.2.35) [BBG-2018-094, BBG-2018-096].



4.2.35

Following General Procedure IV, **4.2.33** (400 mg, 1.33 mol), MeLi (974 µL, 1.50 M in Et_2O, 1.46 mmol, 1.10 equiv), *t*-BuLi (1.74 mL, 1.60 M in pentane, 2.79 mmol, 2.10 equiv), and Se (231 mg, 2.20 equiv) in THF (13 mL, 0.10 M) were reacted for 3 h to afford the polyselenide mixture after acidic workup in air and partial chromatographic purification (440 mg, 110% mass balance). The mixture was reacted with $NaBH_4$ (139 mg, 3.66 mmol, 5.00 equiv) and BnBr (435 µL, 3.66 mmol, 5.00 equiv) in EtOH (9.1 mL, 0.10 M) to afford **4.2.35** (436 mg, 80%, 95% pure) as a clear, colorless oil.

Data for **4.2.35**:

^{1}H NMR: (500 MHz, $CDCl_3$)

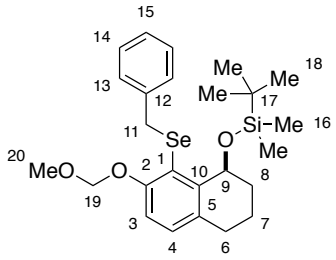
δ 7.22 – 7.08 (m, 5 H, HC(13,14,15)), 7.05 (d, *J* = 8.4 Hz, 1 H, HC(4)), 6.83 (d, *J* = 8.3 Hz, 1 H, HC(5)), 4.88 (q, *J* = 3.6 Hz, 1 H, HC(9)), 4.29 – 4.17 (m, 3 H, HC(16,11)), 4.11 (d, *J* = 11.1 Hz, 1 H, H'C(11)), 3.93 – 3.79 (m, 2 H, HC(17)), 3.49 (s, 3 H, HC(18)), 2.81 – 2.66 (m, 1 H, HC(6)), 2.58 (ddd, *J* = 16.9, 12.0, 5.6 Hz, 1 H, H'C(6)), 2.37 – 2.24 (m, 1 H, OH), 2.10 – 1.97 (m, 1 H, HC(8)), 1.93 – 1.79 (m, 1 H, HC(7)), 1.72 – 1.55 (m, 2 H, H'C(7,8)).

General Procedure V: Preparation of Silyl Ethers 4.2.36 and 4.2.37.

To a 5-mL Schlenk flask equipped with a magnetic stir bar was added **4.2.34** or **4.2.35** (1.00 equiv) and DMF (0.50 M). Imidazole (5.00 equiv) was added against nitrogen backflow at room temperature, followed by *t*-BuMe_2SiCl (4.00 equiv). After 8 – 14 h, the reaction mixture was transferred to a separatory funnel with Et_2O (2 × 10 mL) and water (3 × 10 mL). The layers were shaken and separated, and the organic phase was washed with water/brine, 1:1 (2 × 10 mL). The combined aqueous layers were back-extracted with Et_2O (10 mL). The combined organic layers were then washed with 5% w/v aq. citric acid (20 mL), water (20 mL), and water/brine, 1:1 (20

mL), dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). The resulting clear, colorless oil was placed on high vacuum (23 ºC, 0.1 mm Hg) for 8 h to remove excess chlorosilane and disiloxane. Purification was achieved by silica gel column chromatography (120 g silica, 5 cm ø column) eluting with hexanes/EtOAc, 19:1 gradient to 9:1.

Preparation of (*S*)-((8-(Benzylselanyl)-7-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)(*tert*-butyl)dimethylsilane (4.2.36) [BBG-2018-099].



4.2.36

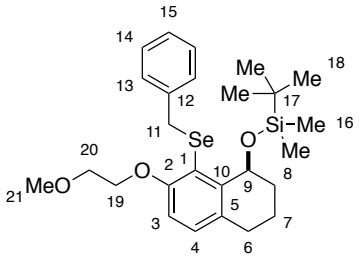
Following General Procedure V, **4.2.34** (480 mg, 1.21 mmol), imidazole (411 mg, 6.04 mmol, 5.00 equiv), and *t*-$BuMe_2SiCl$ (729 mg, 4.83 mmol, 4.00 equiv) in DMF (2.4 mL, 0.50 M) were reacted for 8 h to afford **4.2.36** (277 mg, 47%) as a clear, colorless oil.

Data for **4.2.36**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.21 – 7.09 (m, 3 H, HC(aryl)), 7.08 – 6.98 (m, 4 H, HC(aryl)), 5.27 (s, 2 H, HC(19)), 4.85 (t, *J* = 3.0 Hz, 1 H, HC(9)), 4.00 (d, *J* = 11.2 Hz, 1 H, HC(11)), 3.97 (d, *J* = 11.3 Hz, 1 H, H'C(11)), 3.56 (s, 3 H, HC(20)), 2.78 (ddd, *J* = 16.7, 6.2, 2.4 Hz, 1 H, HC(6)), 2.57 (ddd, *J* = 16.3, 11.6, 6.4 Hz, 1 H, H'C(6)), 2.07 – 1.80 (m, 2 H, HC(7,8)), 1.64 – 1.48 (m, 1 H, H'C(7)), 1.24 (ddt, *J* = 16.8, 13.5, 3.2 Hz, 1 H, H'C(8)), 0.82 (s, 9 H, HC(18)), 0.14 (s, 3 H, HC(16)), 0.10 (s, 3 H, HC(16)').

Preparation of (*S*)-((8-(Benzylselanyl)-7-(2-methoxyethoxy)-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)(*tert*-butyl)dimethylsilane (4.2.37) [BBG-2018-098].



4.2.37

Following General Procedure V, **4.2.35** (436 mg, 1.06 mmol), imidazole (360 mg, 5.29 mmol, 5.00 equiv), and *t*-BuMe_2SiCl (638 mg, 4.23 mmol, 4.00 equiv) in DMF (2.1 mL, 0.50 M) were reacted for 14 h to afford **4.2.37** (466 mg, 80%, 92% pure) contaminated with ca. 8% disiloxane.

Data for **4.2.37**:

^{1}H NMR: (500 MHz, $CDCl_3$)

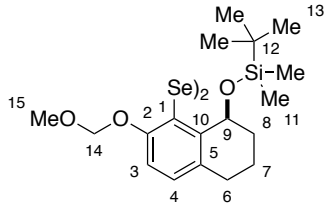
δ 7.19 – 7.05 (m, 5 H, HC(13,14,15)), 7.01 (d, *J* = 8.3 Hz, 1 H, HC(4)), 6.81 (d, *J* = 8.3 Hz, 1 H, HC(3)), 4.92 (t, *J* = 3.0 Hz, 1 H, HC(9)), 4.28 – 4.14 (m, 2 H, HC(19)), 4.05 (s, 2 H, HC(11)), 3.97 – 3.86 (m, 1 H, HC(20)), 3.86 – 3.77 (m, 1 H, H'C(20)), 3.48 (s, 3 H, HC(21)), 2.78 (ddd, *J* = 16.6, 6.5, 2.4 Hz, 1 H, HC(6)), 2.56 (ddd, *J* = 17.0, 11.5, 6.3 Hz, 1 H, H'C(6)), 2.11 – 1.80 (m, 2 H, HC(7,8)), 1.65 – 1.50 (m, 1 H, H'C(7)), 1.27 (tt, *J* = 13.5, 3.3 Hz, 1 H, H'C(8)), 0.82 (s, 9 H, HC(18)), 0.15 (s, 3 H, HC(16)), 0.11 (s, 3 H, HC(16)').

General Procedure VI: Preparation of Diselenides 2.53 and 2.54.

To a 20-mL scintillation vial equipped with a septum cap was added **4.2.36** or **4.2.37** (1.00 equiv) and CH_2Cl_2 (0.10 M). Bromine (0.50 M in CH_2Cl_2, 1.00 equiv) was added in one portion at room temperature to afford a deep red-brown solution. After 5 min, hydrazine (5.00 equiv) was added in one portion and the mixture was shaken vigorously with frequent venting (gas evolution), resulting in an immediate color change to orange. After 1 min, the contents of the vial were transferred to a 60-mL separatory funnel with CH_2Cl_2 (3 × 5 mL) and water (3 × 5 mL). The layers were shaken and separated, and the organic phase was washed with water (10 mL portions) until the aqueous layer reached pH = 7. The combined aqueous layers were back extracted with

CH_2Cl_2 (10 mL). The combined organic layers were then washed with water (10 mL) and brine (10 mL), then transferred to a 125-mL Erlenmeyer flask equipped with a magnetic stir bar. Na_2SO_4 (1 g) was added, followed by Et_3N (1 mL), and the mixture was stirred at room temperature for 20 h. The mixture was filtered and concentrated under reduced pressure by rotary evaporation (10 – 20 ºC, 4 mm Hg) to a total volume of 20 mL and transferred to a 60-mL separatory funnel. The organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried over Na_2SO_4 (1 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification was achieved by silica gel column chromatography (60 g silica, 3 cm ø column) eluting with hexanes/EtOAc, 19:1 (**2.53**) or 9:1 (**2.54**).

Preparation of 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-(methoxymethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.53) [BBG-2018-103].



2.53

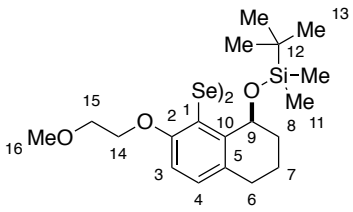
Following General Procedure VI, **4.2.36** (172 mg, 0.322 mmol), bromine (642 µL, 0.501 M, 0.322 mmol, 1.00 equiv), and hydrazine (52 mg, 1.6 mmol, 5.0 equiv) in CH_2Cl_2 (3.2 mL, 0.10 M) were reacted to afford **2.53** (74.2 mg, 58%) as an orange solid.

Data for **2.53**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.04 (d, *J* = 8.3 Hz, 1 H, HC(4)), 7.01 (d, *J* = 8.5 Hz, 1 H, HC(3)), 5.32 (d, *J* = 6.6 Hz, 1 H, HC(14)), 5.18 (d, *J* = 6.6 Hz, 1 H, H'C(14)), 4.40 – 4.28 (m, 1 H, HC(9)), 3.54 (s, 3 H, HC(15)), 2.84 – 2.66 (m, 1 H, HC(6)), 2.54 (ddd, *J* = 17.1, 12.0, 6.2 Hz, 1 H, H'C(6)), 1.89 (qdd, *J* = 12.8, 5.7, 2.8 Hz, 1 H, HC(8)), 1.66 (dd, *J* = 13.9, 3.5 Hz, 1 H, HC(7)), 1.57 – 1.48 (m, 1 H, H'C(7)), 1.02 (tt, *J* = 13.7, 3.2 Hz, 1 H, H'C(8)), 0.77 (s, 9 H, HC(13)), -0.01 (s, 3 H, HC(11)), -0.04 (s, 3 H, HC(11)').

Preparation of 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-(2-methoxyethoxy)-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (2.54) [BBG-2018-102].



2.54

Following General Procedure VI, **4.2.37** (167 mg, 0.304 mmol), bromine (606 μL, 0.501 M, 0.304 mmol, 1.00 equiv), and hydrazine (49 mg, 1.5 mmol, 5.0 equiv) in CH_2Cl_2 (3.0 mL, 0.10 M) were reacted to afford **2.53** (31 mg, 25%) as an orange solid.

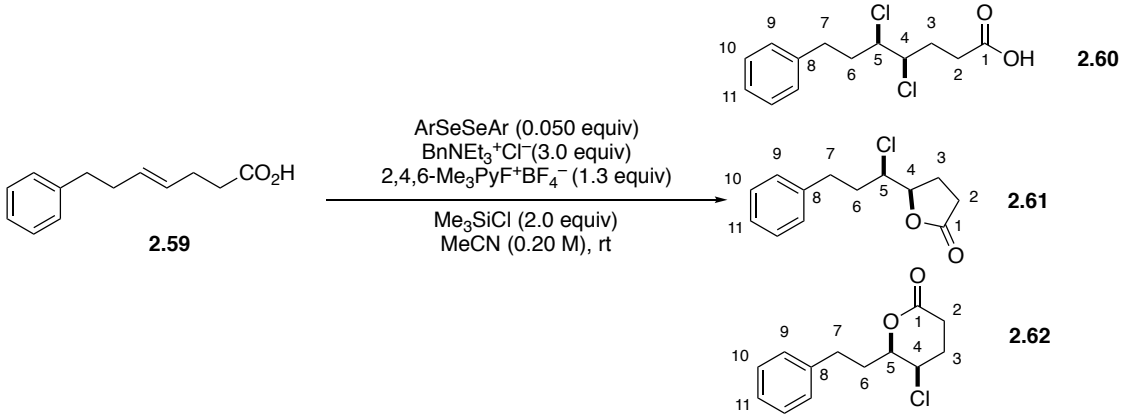
Data for **2.54**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.02 (d, *J* = 8.4 Hz, 1 H, HC(4)), 6.82 (d, *J* = 8.4 Hz, 1 H, HC(3)), 4.25 – 4.11 (m, 3 H, HC(9,14)), 3.87 (ddt, *J* = 14.7, 11.2, 5.5 Hz, 2 H, HC(15)), 3.55 (s, 3 H, HC(16)), 2.74 (dd, *J* = 16.6, 5.6 Hz, 1 H, HC(6)), 2.52 (ddd, *J* = 17.0, 12.1, 6.1 Hz, 1 H, H'C(6)), 1.98 – 1.78 (m, 1 H, HC(8)), 1.60 (dd, *J* = 14.0, 3.2 Hz, 1 H, HC(7)), 1.53 – 1.46 (m, 1 H, H'C(7)), 0.98 – 0.86 (m, 1 H, H'C(8)), 0.76 (s, 9 H, HC(13)), -0.01 (s, 3 H, HC(11)), -0.04 (s, 3 H, HC(11)').

4.2.2.4. Chlorolactonization.

Representative Procedure for Chlorolactonization of (*E*)-7-Phenylhept-4-enoic Acid (2.59) [BBG-10-017].



2.59 **2.60** **2.61** **2.62**

To a 5-mL Schlenk flask was added the diselenide catalyst **2.46** (9.3 mg, 0.050 equiv). The flask was then transferred into the glovebox and $BnNEt_3^+Cl^-$ (342 mg, 3.0 equiv) and 2,4,6-

$Me_3PyF^+BF_4^-$ (148 mg, 1.3 equiv) were added. The Schlenk flask was capped with a rubber septum, removed from the glovebox, and connected to a Schlenk line. Acetonitrile (2.5 mL, 0.20 M) and TMSCl (127 µL, 2.0 equiv) were added and the reaction was stirred for 10 min at room temperature. (*E*)-7-phenylhept-4-enoic acid (**2.59**) (102 mg, 0.50 mmol) was added against nitrogen back-flow and the mixture was stirred at room temperature. After 16 h, the reaction was quenched by the slow addition of water (2 mL). After dilution with more water (2 mL), the organic layer was separated, and the aqueous layer was extracted with Et_2O (3x 10 mL). The combined organic layers were dried over Na_2SO_4 (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). The crude product was characterized qualitatively by ^{1}H NMR spectroscopy to determine the isomeric ratio. Diagnostic peaks were: **2.60**: 4.66 (ddd, *J* = 8.1, 5.9, 3.0 Hz, 1 H, HC(4)), 3.88 (dt, *J* = 10.4, 3.0 Hz, 1 H, HC(5)); **2.61**: 4.35 (ddd, *J* = 8.6, 4.7, 1.9 Hz, 1 H, HC(5)), 4.27 (td, *J* = 3.5, 1.9 Hz, 1 H, HC(4)); **2.62**: 4.14 (dt, *J* = 10.6, 2.8 Hz, 1 H, HC(4)), 4.01 (ddd, *J* = 9.4, 4.2, 2.8 Hz, 1 H, HC(5)). Partial purification by silica gel column chromatography (2 cm ø x 20 cm column) eluting with hexanes/EtOAc, 3:1 gave mixtures of **2.60**, separately with **2.61** and **2.62** (due to streaking of the carboxylic acid). The lactones were isolated by methylation of the mixtures with diazomethane solution in diethyl ether to afford **2.60-OMe**, which could be separated by silica gel column chromatography (identical conditions), or by washing an Et_2O solution of the mixture with 10% w/v aq NaOH. Treatment with diazomethane gave **2.61** (82 mg, 69%) as a clear, colorless oil and **2.62** (10 mg, 8%) as a colorless residue.

Data for **2.61**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.37 – 7.28 (m, 2 H, HC(10)), 7.25 – 7.19 (m, 3 H, HC(9,11)), 4.66 (ddd, *J* = 8.1, 5.9, 3.0 Hz, 1 H, HC(4)), 3.88 (dt, *J* = 10.4, 3.0 Hz, 1 H, HC(5)), 2.95 (ddd, *J* = 13.4, 8.1, 4.9 Hz, 1 H, HC(2)), 2.83 – 2.74 (m, 1 H, HC(2)), 2.68 (ddd, *J* = 18.0, 10.5, 6.1 Hz, 1 H, HC(7)), 2.52 (ddd, *J* = 18.0, 10.5, 7.2 Hz, 1 H, HC(7)), 2.41 – 2.27 (m, 1 H, HC(3)), 2.27 – 2.16 (m, 2 H, HC(3,6)), 2.16 – 2.04 (m, 1 H, HC(6)).

IR: (neat)

3062 (w), 3027 (w), 2953 (w), 2862 (w), 1772 (s), 1603 (w), 1497 (w), 1454 (m), 1433 (w), 1418 (w), 1359 (w), 1275 (w), 1261 (w), 1167 (s), 1076 (m), 1060 (m), 1023 (m), 980 (m), 947 (w), 912 (m), 844 (w), 788 (w), 750 (s), 700 (s), 642 (m), 565 (w), 553 (w), 527 (w), 501 (m).

HRMS: (ES+)

Found: 239.0833; Calc for $C_{13}H_{16}O_2Cl$: 239.0839.

SFC: **(*S,S*)-66** t_R 5.41 min (18.2%), **(*R,R*)-66** t_R 6.96 min (81.8%) (Daicel Chiralpak AD; CO_2/MeOH, 9:1; 2.5 mL/min; 220 nm).

Data for **2.62**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.37 – 7.28 (m, *J* = 8.8, 6.4, 0.8 Hz, 2 H, HC(10)), 7.25 – 7.18 (m, 3 H, HC(9,11)), 4.35 (ddd, *J* = 8.6, 4.7, 1.9 Hz, 1 H, HC(5)), 4.27 (td, *J* = 3.5, 1.9 Hz, 1 H, HC(4)), 2.96 – 2.71 (m, 3 H, HC(2,2,7)), 2.61 (dt, *J* = 18.5, 4.7 Hz, 1 H, HC(7)), 2.36 – 2.21 (m, 3 H, HC(3,3,6)), 1.95 (dddd, *J* = 13.9, 8.7, 7.6, 4.7 Hz, 1 H, HC(6)).

IR: (neat)

3062 (w), 3027 (w), 2958 (w), 2927 (w), 2867 (w), 1735 (s), 1603 (w), 1496 (w), 1452 (m), 1414 (w), 1354 (m), 1305 (w), 1227 (m), 1195 (m), 1089 (m), 1053 (s), 1030 (m), 955 (w), 924 (m), 897 (w), 771 (m), 750 (m), 699 (s), 632 (w), 593 (w), 575 (w), 533 (m), 496 (m).

SFC: **(*S,S*)-67** t_R 6.77 min (38%), **(*R,R*)-67** t_R 7.27 min (62%) (Daicel Chiralpak AD; CO_2/MeOH, 9:1; 2.5 mL/min; 220 nm).

Data for **2.60-OMe**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.35 – 7.27 (m, 2 H, HC(10)), 7.25 – 7.19 (m, 3 H, HC(9,11)), 4.14 (dt, *J* = 10.6, 2.8 Hz, 1 H, HC(4)), 4.01 (ddd, *J* = 9.4, 4.2, 2.8 Hz, 1 H, HC(5)), 3.68 (s, 3 H, CO_2CH_3), 2.93 (ddd, *J* = 13.8, 8.3, 5.4 Hz, 1 H, HC(2)), 2.73 (dt, *J* = 13.8, 8.2 Hz, 1H, HC(2)), 2.65 – 2.43 (m, 2 H, HC(7)), 2.33 – 2.01 (m, 4 H, HC(3,6)).

IR: (neat)

3027 (w), 2952 (w), 2925 (w), 1735 (s), 1603 (w), 1496 (w), 1454 (m), 1436 (m), 1367 (w), 1274 (m), 1260 (m), 1198 (m), 1170 (m), 1080 (w), 1029 (w), 984 (w), 909 (w), 877 (w), 844 (w), 804 (w), 786 (w), 786 (w), 750 (s), 700 (s), 648 (w), 619 (w), 477 (w).

4.3. Experimental for Chapter 3.

4.3.1. Literature Preparations.

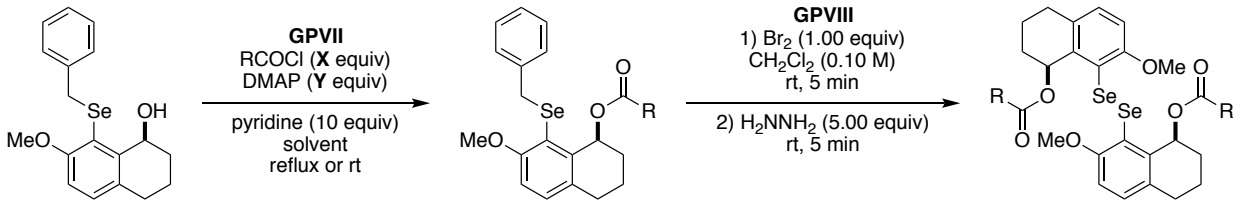
Preparation of Reagents: Dibenzyl diselenide (Bn_2Se_2),[11a] 1,2-bis((*S*)-8-((tert-butyldimethylsilyl)oxy)-2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (**3.12**),[30] (1*S*,1'*S*)-diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) dibenzoate (**3.13**),[30] (*S*)-6-methoxy-7-((4-methoxybenzyl)selanyl)-2,2-dimethyl-2,3-dihydro-1*H*-inden-1-ol,[29] and benzyl tosylcarbamate (**3.24**)[31] were prepared according to literature procedures.

Preparation of Alkenes: (*E*)-(3-(Benzyloxy)prop-1-en-1-yl)benzene (**3.9a**),[32] (*E*)-(3-methylbut-1-en-1-yl)benzene (**3.9d**),[33] (*Z*)-(4-(benzyloxy)but-1-en-1-yl)benzene (**3.9e**), (*E*)-2-(4-phenylbut-3-en-1-yl)isoindoline-1,3-dione (**3.9f**),[34] (*E*)-cinnamyl bromide (**3.9g**),[35] (*E*)-4-methyl-*N*-(*E*)-4-phenylbut-3-en-1-ol,[36] methyl (*E*)-4-phenylbut-3-enoate (**3.9k**),[37] (*E*)-cinnamyl picolinate (**3.9l**),[38] (*E*)-1-(3-(benzyloxy)prop-1-en-1-yl)-4-fluorobenzene (**3.9m**),[39] (*E*)-1-(3-(benzyloxy)prop-1-en-1-yl)-4-(trifluoromethyl)benzene (**3.9n**),[39] methyl (*E*)-4-(4-methoxy-4-oxobut-1-en-1-yl)benzoate (**3.9o**),[40] (*E*)-3-(4-cyanophenyl)allyl acetate (**3.9p**),[41] (*E*)-3-(naphthalen-2-yl)prop-2-en-1-ol,[42] (*E*)-3-(3-(benzyloxy)prop-1-en-1-yl)thiophene (**3.9s**),[43] (*E*)-1-bromo-2-(prop-1-en-1-yl)benzene (**3.9t**),[44] methyl (*E*)-5-phenylpent-3-enoate (**3.9y**),[45] 1-tosyl-1*H*-indole-3-carbaldehyde,[46] 2-((4-(trifluoromethyl)benzyl)sulfonyl)benzo[*d*]thiazole,[47] (*R*,*E*)-4-phenylbut-3-en-2-ol,[48] (*S*,*E*)-4-phenylbut-3-en-2-ol,[48] dipotassium ((4-nitrophenyl)sulfonyl)(sulfonato)amide (**3.26**),[49] triisopropylsilanol,[50] and (*E*)-5-phenylpent-4-enamide[51] were prepared according to literature procedures.

4.3.2. Experimental Procedures.

4.3.2.1. Preparation of Diselenides.

Preparation of Diselenides 3.16, 3.17, 3.18, and 3.19.



4.2.17

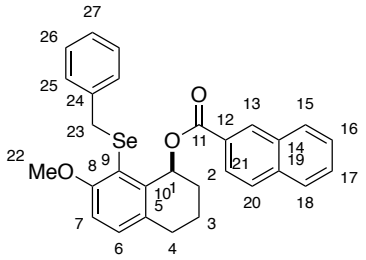
R = 2-naphthyl, **4.3.3**
R = 1-naphthyl, **4.3.4**
R = 9-anthryl, **4.3.5**
R = 1-adamantyl, **4.3.6**

R = 2-naphthyl, **3.16**
R = 1-naphthyl, **3.17**
R = 9-anthryl, **3.18**
R = 1-adamantyl, **3.19**

General Procedure VII: Preparation of Esters 4.3.3, 4.3.4, 4.3.5, and 4.3.6.

To a round-bottom flask was added DMAP (1.0 – 5.0 equiv) and the solvent (CH_2Cl_2 or toluene, 0.1 – 0.2 M). The corresponding acid chloride (2.0 – 5.0 equiv) was added in one portion as a solid against nitrogen back-flow and pyridine (10.0 equiv) was added in one portionvia syringe at room temperature. Finally, **4.2.17** (0.50 – 2.88 mmol) was added as a solution in a minimal amount of the reaction solvent. The resulting mixture was either stirred at room temperature or heated to reflux. After 12 – 24 h, the mixture was cooled to 0 ºC and sat. aq. NH_3 (2 mL/mmol) was added slowly, then warmed to room temperature. After 4 h, the reaction mixture was poured into water (10 mL/mmol) and transferred to a separatory funnel with Et_2O (4 × 5 mL/mmol). The layers were shaken and separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL/mmol). The combined organic layers were washed with water (2 × 10 mL/mmol), 1 M HCl (2 × 10 mL/mmol), water (10 mL/mmol), and brine (10 mL/mmol), dried over $MgSO_4$ (2 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by column chromatography afforded the esters **4.3.3 – 4.3.6.**

Preparation of (*S*)-8-(Benzylselanyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl 2-Naphthoate (4.3.3) [BBG-2019-084; see also: TZL-2019-212].



4.3.3

Following General Procedure VII, DMAP (1.20 g, 9.79 mmol, 3.40 equiv), toluene (14 mL), 2-naphthoyl chloride (1.87 g, 9.79 mmol, 3.40 equiv), pyridine (2.32 mL, 28.8 mmol, 10.0 equiv), and **4.2.17** (1.00 g, 2.88 mmol) were reacted at reflux (oil bath temperature 85 ºC) for 24 h. Purification by silica gel column chromatography (120 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 9:1 over 20 min afforded **4.3.3** (910 mg, 63%).

Data for **4.3.3**:

m.p. 109-110 ºC (EtOH)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.52 (s, 1 H, HC(13)), 8.01 (dd, *J* = 8.6, 1.7 Hz, 1 H, HC(21)), 7.89 (dd, *J* = 8.2, 1.2 Hz, 1 H, HC(15)), 7.83 (d, *J* = 8.59 Hz, 1 H, HC(20)), 7.81 (d, *J* = 8.72 Hz, 1 H, HC(18)) 7.54 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H, HC(17)), 7.49 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1 H, HC(16)), 7.18 (d, *J* = 8.5 Hz, 1 H, HC(6)), 7.12 – 7.03 (m, 3 H, HC(26,27)), 7.00 (dd, *J* = 7.8, 1.8 Hz, 2 H, HC(25)), 6.93 (d, *J* = 8.5 Hz, 1 H, HC(7)), 6.20 (t, *J* = 3.3 Hz, 1 H, HC(1)), 4.03 (d, *J* = 11.0 Hz, 1 H, HC(23)), 3.92 (s, 3 H, HC(22)), 3.90 (d, *J* = 11.0 Hz, 1 H, H'C(23)), 2.95 – 2.81 (m, 1 H, HC(4)), 2.69 (ddd, *J* = 17.5, 11.4, 6.1 Hz, 1 H, H'C(4)), 2.44 – 2.30 (m, 1 H, HC(2)), 1.98 – 1.81 (m, 1 H, HC(3)), 1.81 – 1.66 (m, 2 H, H'C(2,3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 165.7 (C(11)), 158.4 (C(8)), 139.2 (C(24)), 138.5 (C(10)), 135.6 (C(19)), 132.6 (C(14)), 131.8 (C(5)), 131.1 (C(13)), 130.7 (C(6)), 129.5 (C(15)), 128.8 (C(25)), 128.15 (C(20)), 128.14 (C(12,26)), 128.07 (C(17)), 127.8 (C(18)), 126.55 (C(16)), 126.52 (C(27)), 125.6 (C(21)), 121.6 (C(9)), 111.3 (C(7)), 71.4 (C(1)), 56.2 (C(22)), 31.1 (C(23)), 29.4 (C(4)), 29.1 (C(3)), 18.2 (C(2)).

^{77}Se NMR: (95 MHz, $CDCl_3$)

δ 246.2 (dd, J = 20.4, 4.6 Hz).

IR: (neat)

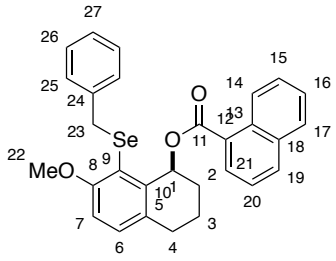
2935 (w), 2836 (w), 2051 (w), 1707 (s), 1706 (s), 1629 (w), 1598 (w), 1492 (w), 1475 (w), 1471 (m), 1438 (m), 1388 (w), 1351 (w), 1350 (w), 1318 (w), 1282 (s), 1263 (s), 1231 (m), 1230 (m), 1193 (s), 1154 (m), 1144 (w), 1127 (s), 1081 (m), 1080 (m), 1067 (m), 1063 (s), 1012 (m), 966 (m), 965 (m), 914 (m), 894 (m), 893 (m), 870 (m), 847 (w), 829 (m), 828 (m), 812 (m), 811 (m), 780 (s), 779 (s), 763 (s), 717 (w), 699 (s), 636 (w), 601 (m), 553 (m), 475 (s), 453 (m).

LRMS: (EI^+, 70 eV, TOF)

65.0 (17), 91.0 (90), 115.0 (88), 116.1 (12), 117.1 (26), 126.0 (23), 127.0 (91), 128.1 (56), 129.1 (16), 144.1 (13), 145.1 (35), 155.0 (90), 158.1 (38), 159.1 (12), 171.1 (71), 172.0 (91), 239.0 (10), 249.1 (10), 326.1 (19), 327.1 (17), 328.1 (55), 330.0 (100), 331.1 (11), 332.1 (13).

TLC: R_f 0.34 (4:1 hexanes/EtOAc) [UV/CAM]

Preparation of (*S*)-8-(Benzylselanyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl 1-Naphthoate (4.3.4) [BBG-2019-013].



4.3.4

Following General Procedure VII, DMAP (122 mg, 1.00 mmol, 2.00 equiv), toluene (2.5 mL), 1-naphthoyl chloride (191 mg, 1.00 mmol, 2.00 equiv), pyridine (403 µL, 5.00 mmol, 10.0 equiv), and **4.2.17** (174 mg, 0.500 mmol) were reacted at reflux (oil bath temperature 120 ºC) for 24 h. Purification by silica gel column chromatography (50 g silica, 3 cm ø column) eluting with hexanes/EtOAc, 19:1 afforded **4.3.4** (149 mg, 59%) as a white powder.

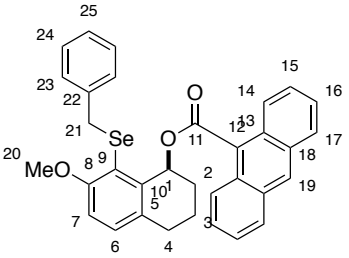
Data for **4.3.4**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.94 (dt, *J* = 8.6, 1.0 Hz, 1 H, HC(aryl)), 8.00 (dt, *J* = 7.2, 1.0 Hz, 1 H, HC(aryl)), 7.96 – 7.89 (m, 1 H, HC(aryl)), 7.84 (dd, *J* = 8.3, 1.3 Hz, 1 H, HC(aryl)), 7.58 (tt, *J* = 7.5, 1.0 Hz, 1 H, HC(aryl)), 7.51 (ddt, *J* = 7.8, 6.9, 1.0 Hz, 1 H, HC(aryl)), 7.42 – 7.33 (m, 1 H, HC(aryl)), 7.15 (d, *J* = 8.5 Hz, 1 H, HC(6)), 7.11 – 7.04 (m, 3 H, HC(26,27)), 7.01 (dd, *J* = 7.6, 1.9 Hz, 2 H, HC(25)), 6.90 (d, *J* = 8.5 Hz, 1 H, HC(7)), 6.23 (t, *J* = 3.2 Hz, 1 H, HC(1)), 4.03 (d, *J* = 11.0 Hz, 1 H, H'C(23)), 3.97 – 3.88 (m, 4 H, HC(22,23)), 2.84 (d, *J* = 16.0 Hz, 1 H, HC(4)), 2.68 (ddd, *J* = 16.9, 11.9, 5.7 Hz, 1 H, H'C(4)), 2.42 (dd, *J* = 14.4, 3.5 Hz, 1 H, H'C(2)), 1.94 – 1.66 (m, 3 H, HC(2,3)).

TLC: R_f = 0.19 (9:1 hexanes/EtOAc) [UV/CAM]

Preparation of (*S*)-8-(Benzylselanyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl Anthracene-9-carboxylate (4.3.5) [BBG-2019-037].



4.3.5

Following General Procedure VII, DMAP (122 mg, 1.00 mmol, 2.00 equiv), toluene (2.5 mL), anthracene-9-carbonyl chloride (241 mg, 1.00 mmol, 2.00 equiv), pyridine (403 µL, 5.00 mmol, 10.0 equiv), and **4.2.17** (174 mg, 0.500 mmol) were reacted at reflux (oil bath temperature 120 ºC) for 24 h. Purification by silica gel column chromatography afforded **4.3.5** (80.0 mg, 29%) as a white powder.

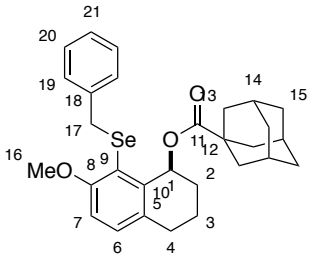
Data for **4.3.5**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.43 (s, 1 H, HC(19)), 8.24 – 8.17 (m, 2 H, HC(aryl)), 7.97 – 7.91 (m, 2 H, HC(aryl)), 7.48 – 7.40 (m, 4 H, HC(aryl)), 7.24 – 7.09 (m, 4 H, HC(aryl)), 7.05 (d, *J* = 8.5 Hz, 1 H, HC(6)), 6.81 (d, *J* = 8.5 Hz, 1 H, HC(7)), 6.51 (s, 1 H, HC(1)), 4.07 (d, *J* = 11.0 Hz, 1 H, HC(21)), 4.02 (d, *J* = 11.0 Hz, 1 H, H'C(21)), 3.83 (s, 3 H, HC(20)), 2.89 – 2.55 (m, 3 H, HC(2,4)), 2.07 – 1.85 (m, 2 H, H'C(2,3)), 1.76 (tt, *J* = 14.1, 3.4 Hz, 1 H, HC(3)).

TLC: R_f = 0.14 (9:1 hexanes/EtOAc) [UV/CAM]

Preparation of (*S*)-8-(Benzylselanyl)-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl (3*S*,5*S*,7*S*)-Adamantane-1-carboxylate (4.3.6) [BBG-2019-109].



4.3.6

Following General Procedure VII, DMAP (61.1 mg, 0.500 mmol, 0.500 equiv), CH_2Cl_2 (5.00 mL), adamantane-1-carbonyl chloride (993 mg, 5.00 mmol, 5.00 equiv), pyridine (805 µL, 10.0 mmol, 10.0 equiv), and **4.2.17** (347 mg, 1.00 mmol) were reacted at room temperature for 12 h. Purification by silica gel column chromatography (120 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 9:1 over 30 min afforded **4.3.6** (370 mg, 73%) as a pale yellow solid.

Data for **4.3.6**:

^{1}H NMR: (500 MHz, $CDCl_3$)

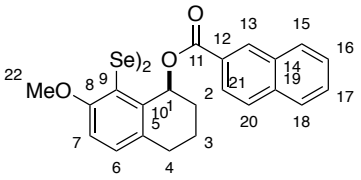
δ 7.18 – 7.12 (m, 2 H), 7.12 – 7.06 (m, 3 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 5.80 (t, *J* = 3.2 Hz, 1 H), 4.03 (d, *J* = 11.2 Hz, 1 H), 3.97 (d, *J* = 11.2 Hz, 1 H), 3.92 (s, 3 H), 2.76 (dd, *J* = 16.5, 4.0 Hz, 1 H, HC(4)), 2.59 (ddd, *J* = 16.9, 10.8, 7.2 Hz, 1 H, H'C(4)), 2.15 – 2.03 (m, 1 H, HC(2)), 1.98 – 1.88 (m, 3 H, HC(14)), 1.86 – 1.77 (m, 6 H, HC(13)), 1.72 – 1.58 (m, 9 H, HC(2,3,15)), 1.53 – 1.43 (m, 1 H, H'C(3)).

TLC: R_f = 0.13 (19:1 hexanes/EtOAc) [UV/CAM]

General Procedure VIII: Preparation of Diselenides 3.16, 3.17, 3.18, and 3.19.

To a Schlenk flask equipped with a magnetic stir bar was added **4.3.3 – 4.3.6** (0.15 – 9.0 mmol) and CH_2Cl_2 (0.10 – 0.50 M). Bromine (solution in CH_2Cl_2, 1.00 equiv) was then added dropwise at room temperature. The bromine color faded and was quickly replaced by an intense red-brown. After 5 min at room temperature, hydrazine (5.0 equiv) was added in one portion with vigorous stirring (gas evolution!). The dark red solution rapidly became an intense orange. After 5 min, the reaction mixture was transferred to a separatory funnel with CH_2Cl_2 (4 × 10 mL/mmol). The mixture was washed with 1 M HCl (2 × 5 mL/mmol), water (5 mL/mmol), sat. aq. $NaHCO_3$ (5 mL/mmol), water (5 mL/mmol) and brine (5 mL/mmol), dried over $MgsO_4$ (2 – 8 g), filtered, and concentrated under reduced pressure by rotary evaporation (25 ºC, 4 mm Hg). Purification by silica gel column chromatography afforded diselenides **3.16 – 3.19** as orange solids.

Preparation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis(2-naphthoate) (3.16) [BBG-2019-084; see also: TZL-2019-194].



3.16

Following General Procedure VIII, **4.3.3** (850 mg, 1.69 mmol), bromine (1.69 mL, 1.00 M in CH_2Cl_2, 1.00 equiv), and hydrazine (260 µL, 8.5 mmol, 5.0 equiv) were reacted. Purification by silica gel column chromatography (40 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 4:1 over 20 min afforded **3.16** as a yellow-orange solid (672 mg, 97%).

Data for **3.16**:

m.p. 114-116 ºC (hexanes)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.41 (d, *J* = 1.6 Hz, 1 H, HC(13)), 7.90 (dd, *J* = 8.6, 1.7 Hz, 1 H, HC(21)), 7.84 (d, *J* = 8.1 Hz, 1 H, HC(15)), 7.74 (d, *J* = 8.1 Hz, 1 H, HC(18)), 7.71 (d, *J* = 8.7 Hz, 1 H, HC(20)), 7.51 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1 H, HC(17)), 7.45 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1 H, HC(16)), 7.19 (d, *J* = 8.5 Hz, 1 H, HC(6)), 7.09 (d, *J* = 8.5 Hz, 1 H, HC(7)), 5.32 (t, *J* = 3.4 Hz, 1 H, HC(1)), 4.03 (s, 3 H, HC(22)), 2.83 (dt, *J* = 16.5, 3.7 Hz, 1 H, HC(4)), 2.61 (ddd, *J* = 16.8, 11.8, 5.5 Hz, 1 H, H'C(4)), 2.24 – 2.05 (m, 1 H, HC(2)), 1.85 – 1.69 (m, 1 H, HC(3)), 1.65 (ddt, *J* = 11.2, 5.9, 2.9 Hz, 1 H, H'C(3)), 1.28 (ddt, *J* = 17.5, 14.5, 3.7 Hz, 1 H, H'C(2)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 165.4 (C(11)), 159.0 (C(8)), 138.2 (C(10)), 135.5 (C(19)), 132.6 (C(14)), 131.5 (C(6)), 130.9 (C(13)), 130.5 (C(5)), 129.4 (C(15)), 128.1 (C(12)), 128.1 (C(17)), 128.0 (C(20)), 127.7 (C(18)), 126.5 (C(16)), 125.4 (C(21)), 122.4 (C(9)), 112.0 (C(7)), 70.7 (C(1)), 56.4 (C(22)), 29.5 (C(4)), 29.1 (C(2)), 18.2 (C(3)).

^{77}Se NMR: (95 MHz, $CDCl_3$)

δ 369.4

IR: (neat)

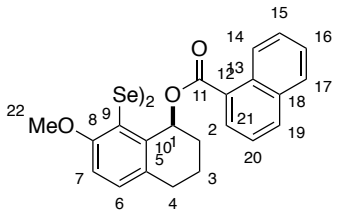
2933 (w), 2833 (w), 1708 (s), 1630 (w), 1591 (w), 1561 (w), 1508 (w), 1472 (m), 1436 (w), 1387 (w), 1350 (w), 1331 (w), 1305 (w), 1264 (s), 1223 (s), 1192 (s), 1152 (m), 1128 (m), 1086 (m), 1062 (s), 1011 (m), 963 (m), 902 (m), 865 (w), 849 (m), 823 (m), 802 (m), 777 (s), 761 (s), 718 (m), 678 (w), 635 (w), 606 (w), 592 (w), 552 (w), 474 (m).

LRMS: (EI^+, 70 eV, TOF)

51.0 (11), 63.0 (36), 65.0 (41), 74.0 (18), 75.0 (21), 76.0 (12), 77.0 (26), 89.0 (55), 90.0 (19), 91.0 (73), 92.1 (11), 101.0 (16), 102.0 (15), 104.1 (38), 105.0 (21), 115.1 (49), 116.1 (12), 117.1 (24), 118.1 (48), 120.1 (11), 121.1 (25), 126.0 (42), 127.1 (47), 128.1 (23), 129.1 (17), 132.0 (31), 139.0 (34), 143.1 (22), 144.1 (55), 145.1 (44), 148.1 (45), 155.0 (55), 155.1 (23), 158.1 (37), 159.1 (37), 160.1 (28), 172.1 (47), 209.0 (14), 236.0 (23), 237.0 (25), 238.0 (55), 239.0 (23), 240.0 (51), 251.1 (100), 252.1 (27), 406.1 (56), 407.1 (13), 474.0 (28), 475.0 (10), 476.0 (55), 478.0 (47).

TLC: R_f 0.23 (4:1 hexanes/EtOAc) [visible yellow/UV/CAM]

Preparation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis(1-naphthoate) (3.17) [BBG-2019-020].



3.17

Following General Procedure VIII, **4.3.4** (127 mg, 0.253 mmol), bromine (506 µL, 0.500 M in CH_2Cl_2, 1.00 equiv), and hydrazine (41 mg, 5.0 equiv, 1.27 mmol) were reacted. Purification by column chromatography (30 g silica, 2 cm ø column) eluting with hexanes/EtOAc, 9:1 gradient to 5:1 afforded **3.17** (86 mg, 83%) as an orange solid.

Data for **3.17**:

^{1}H NMR: (500 MHz, $CDCl_3$)

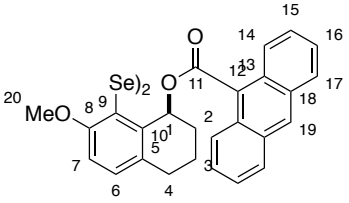
δ 8.87 (dd, *J* = 8.5, 1.1 Hz, 1 H, HC(aryl)), 7.96 – 7.76 (m, 3 H, HC(aryl)), 7.57 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1 H, HC(aryl)), 7.50 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1 H, HC(aryl)), 7.30 (dd, *J* = 8.2, 7.3 Hz, 1 H, HC(aryl)), 7.20 (d, *J* = 8.5 Hz, 1 H, HC(6)), 7.10 (d, *J* = 8.5 Hz, 1 H, HC(7)), 5.30 (s, 1 H, HC(1)), 4.05 (s, 3 H, HC(22)), 3.01 – 2.71 (m, 1 H, HC(4)), 2.60 (ddd, *J* = 16.8, 11.9, 5.6 Hz, 1 H, H'C(4)), 2.15 (dq, *J* = 12.9, 2.1 Hz, 1 H, H'C(2)), 1.87 – 1.60 (m, 2 H, HC(2,3)), 1.35 – 1.14 (m, 1 H, H'C(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 166.0 (C(11)), 159.2 (C(8)), 138.4 (C(10)), 133.8 (C(13)), 132.9 (C(18)), 131.7 (C(6)), 131.5 (C(aryl)), 130.4 (C(5)), 129.9 (C(aryl)), 128.5 (C(aryl)), 127.9 (C(aryl)), 127.6 (C(aryl)), 126.2 (C(aryl)), 125.9 (C(aryl)), 124.6 (C(aryl)), 122.0 (C(9)), 112.1 (C(7)), 70.5 (C(1)), 56.5 (C(22)), 29.5 (C(4)), 29.1 (C(2)), 18.2 (C(3)).

TLC: R_f = 0.13 (19:1 hexanes/EtOAc) [UV/CAM]

Preparation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis(anthracene-9-carboxylate) (3.18) [BBG-2019-045].



3.18

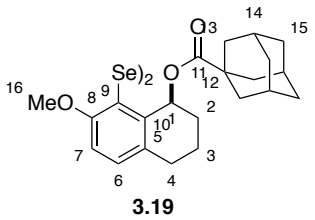
Following General Procedure VIII, **4.3.5** (80.0 mg, 0.145 mmol), bromine (290 µL, 0.500 M in CH_2Cl_2, 1.00 equiv), and hydrazine (23 mg, 5.0 equiv, 5.0 mmol) were reacted. Purification by column chromatography (30 g silica, 2 cm ø column) eluting with hexanes/EtOAc, 8:1 afforded **3.18** (4.7 mg, 7%) as an orange solid.

Data for **3.18**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.44 (s, 1 H, HC(19)), 8.24 – 8.14 (m, 2 H, HC(aryl)), 8.01 – 7.87 (m, 2 H, HC(aryl)), 7.53 (ddd, *J* = 8.8, 6.5, 1.2 Hz, 2 H, HC(aryl)), 7.44 (ddd, *J* = 7.8, 6.6, 1.0 Hz, 2 H, HC(aryl)), 7.20 (d, *J* = 8.5 Hz, 1 H, HC(6)), 7.11 (d, *J* = 8.5 Hz, 1 H, HC(7)), 5.46 (t, *J* = 3.0 Hz, 1 H, HC(1)), 4.17 (s, 3 H, HC(20)), 2.85 (d, *J* = 15.5 Hz, 1 H, HC(4)), 2.72 – 2.61 (m, 1 H, H'C(4)), 2.47 (d, *J* = 14.8 Hz, 1 H, H'C(2)), 1.99 – 1.80 (m, 2 H, HC(2,3)), 1.24 – 1.14 (m, 1 H, H'C(3)).

Preparation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis((3*S*,5*S*,7*S*)-adamantane-1-carboxylate) (3.19) [BBG-2019-114].



3.19

Following General Procedure VIII, **4.3.6** (300 mg, 0.589 mmol), bromine (1.18 mL, 0.500 M in CH_2Cl_2, 1.00 equiv), and hydrazine (94 mg, 2.9 mmol, 5.0 equiv) were reacted. Purification by column chromatography (120 g, ISCO MPLC) eluting with hexanes/EtOAc, 1:0 gradient to 9:1 over 30 min afforded **3.19** (196 mg, 79%) as an orange solid.

Data for **3.19**:

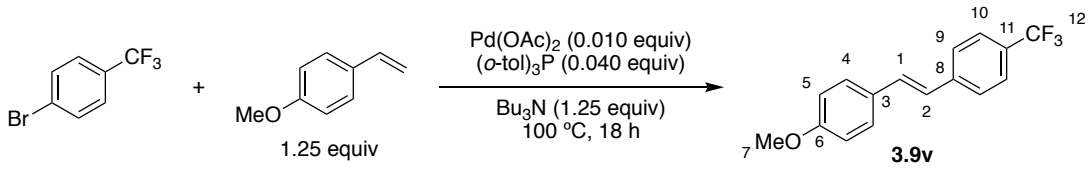
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.10 (d, J = 8.5 Hz, 1 H, HC(6)), 7.01 (d, J = 8.5 Hz, 1 H, HC(7)), 4.73 (t, J = 3.3 Hz, 1 H, HC(1)), 4.03 (s, 3 H, HC(16)), 2.72 (dt, J = 16.2, 3.9 Hz, 1 H, HC(4)), 2.57 – 2.40 (m, 1 H, H'C(4)), 1.95 – 1.87 (m, 3 H, HC(14)), 1.84 – 1.71 (m, 7 H, HC(2,13)), 1.70 – 1.57 (m, 6 H, HC(15)), 1.57 – 1.49 (m, 2 H, H'C(2,3)), 0.98 (ddt, J = 18.7, 10.9, 4.4 Hz, 1 H, HC(3)).

TLC: R_f = 0.27 (9:1 hexanes/EtOAc) [UV/CAM]

4.3.2.2. Preparation of Alkenes.

Preparation of (*E*)-1-Methoxy-4-(4-(trifluoromethyl)styryl)benzene (3.9v) [BBG-2019-150].



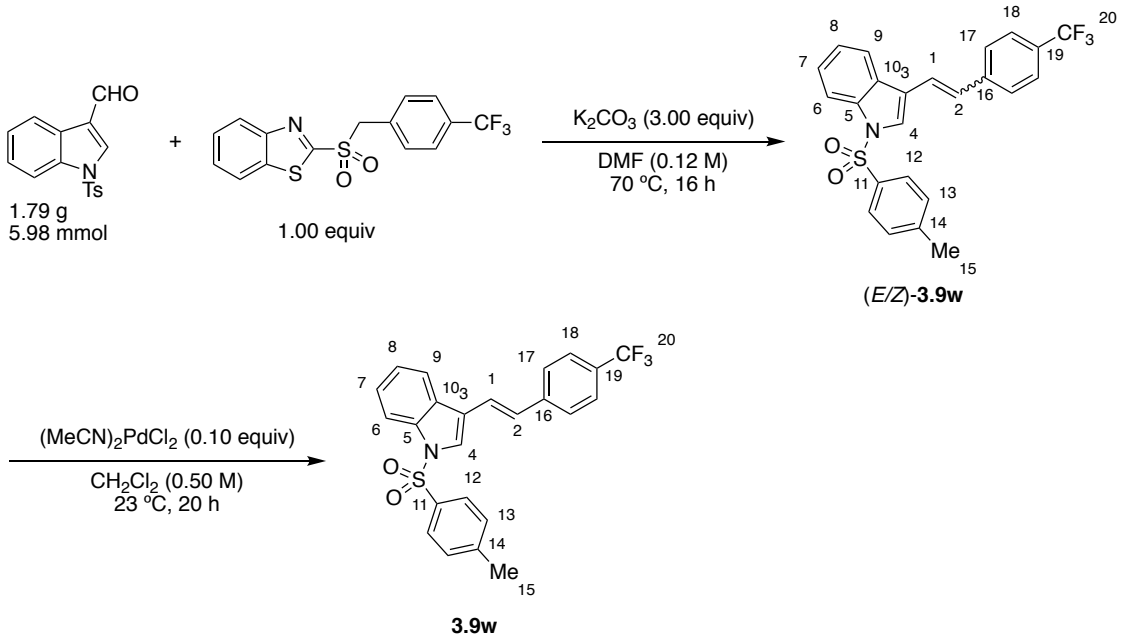
The alkene was prepared according to a literature procedure.[52] A flame-dried 10-mL Schlenk flask was brought into the glove box and charged with $Pd(OAc)_2$ (27 mg, 0.12 mmol, 0.010 equiv) and tri-*o*-tolylphosphine (146 mg, 0.480 mmol, 0.0400 equiv). The flask was removed from the glove box and connected to a Schlenk line flushed with dry nitrogen. Tributylamine (3.56 mL, 15.0 mmol, 1.25 equiv) was added, followed by 4-bromobenzotrifluoride (1.68 mL, 2.70 g, 12.0 mmol), and finally 4-methoxystyrene (1.99 mL, 15.0 mmol, 1.25 equiv). The resulting orange-brown mixture was stirred vigorously and heated to 100 ºC (bath temp.) in an oil bath. The reaction turned a red-violet color over the next 1-2 h. After ~5 h, solid product began to crash out of solution. After 18 h the reaction mixture, now mostly solid, was cooled to room temperature, taken up in EtOAc (75 mL total, 5-10 mL portions), and transferred to a 125-mL separatory funnel. The ethyl acetate solution was washed with 1 M HCl (2 × 25 mL) and water (25 mL). Combined aqueous phases were back-extracted with ethyl acetate (20 mL). Combined organic phases were then washed with water/brine, 1:1 (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure by rotary evaporation (30-35 ºC, ~20 mm Hg) to afford the crude product as a yellow solid. Recrystallization from boiling ethanol/water, 98:2 (~100 mL) afforded **3.9v** (2.65 g, 79%, >98:2 d.r.) as pale yellow crystals. The ^{1}H NMR spectrum matched those in the literature.[53]

Data for **3.9v**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.63 – 7.53 (m, 4 H, HC(9,10)), 7.48 (d, *J* = 8.6 Hz, 2 H, HC(4)), 7.15 (d, *J* = 16.3 Hz, 1 H, HC(1)), 6.99 (d, *J* = 16.3 Hz, 1 H, HC(2)), 6.92 (d, *J* = 8.8 Hz, 2 H, HC(5)), 3.84 (s, 3 H, HC(7)).

Preparation of (*E*)-1-Tosyl-3-(4-(trifluoromethyl)styryl)-1*H*-indole (3.9w) [BBG-2019-227, BBG-2019-228].



The alkene was prepared according to a literature procedure.[54] A flame-dried 100-mL Schlenk flask equipped with a magnetic stir bar and a rubber septum under nitrogen atmosphere was charged with K_2CO_3 (2.48 g, 17.9 mmol, 3.00 equiv). DMF (30 mL) was added *via* syringe, followed by the solid benzothiazole sulfone (2.14 g, 5.98 mmol, 1.00 equiv), against nitrogen back-flow, at rt. DMF (10 mL) was used to rinse down the walls of the flask. Solid *N*-tosylindole-3-carbaldehyde (1.79 g, 5.98 mmol) was added against nitrogen back-flow, followed by a second rinse with DMF (10 mL), at rt. The resulting orange-brown mixture was stirred strongly heated to 70 ºC. Larger granules of K_2CO_3 were consumed as the reaction progressed and were replaced by a fine white powder. After 16 h, the reaction mixture was cooled to room temperature and transferred to a 500-mL separatory funnel, rinsing with EtOAc (2×50 mL) and water (2 × 50 mL). The layers were shaken and separated, and the aqueous layer was extracted with EtOAc (2 × 100

mL). Combined organic layers were washed with 1:1 v/v water/brine (4 × 50 mL), dried over $MgSO_4$ (8 g), filtered, and concentrated under reduced pressure by rotary evaporation (30-35 ºC, ~20 mm Hg). The crude product, a thick, orange oil, was purified by column chromatography (silica, 5 cm ø × 16 cm column) eluting with 10:1 hexanes/EtOAc to afford (*E*/*Z*)-**3.9w** as a yellow, clear, glassy solid (1.74 g, 66%) in a ~1.3:1 *E/Z* ratio. Diagnostic proton signals were: (*E*)-**3.9w**: δ 7.85 (dd, *J* = 7.9, 1.1 Hz, 1 H, HC(9)), 7.62 (d, *J* = 8.6 Hz, 2 H, HC(18)), 7.59 (d, *J* = 8.6 Hz, 2 H, HC(17)); (*Z*)-**3.9w**: δ 6.74 (d, *J* = 12.0 Hz, 1 H, HC(1)), 6.67 (dd, *J* = 12.1, 1.1 Hz, 1 H, HC(2)).

The *E/Z* mixture was isomerized to the *E*-alkene according to a literature procedure.[55] A flame-dried 25-mL Schlenk flask equipped with a magnetic stir bar and a rubber septum under a nitrogen atmosphere was charged with (*E/Z*)-**3.9w** (1.74 g, 3.94 mmol) and CH_2Cl_2 (7.9 mL, 0.50 M) at rt. Solid $(MeCN)_2PdCl_2$ (102 mg, 0.394 mmol, 0.100 equiv) was added in one portion, against nitrogen back-flow. The solution quickly became red-orange, then slowly became burgundy over ca. 15 min. After 20 h, the reaction mixture was diluted with Et_2O (10 mL) and filtered by dry column vacuum chromatography (silica, 1.5 cm ø × 5 cm column) eluting with Et_2O (5×20 mL). The filtrate was concentrated under reduced pressure by rotary evaporation (20-25 ºC, ~20 mm Hg) to afford a thick, yellow oil. Purification by column chromatography (silica, 4.5 cm ø × 15 cm column) eluting with hexanes/EtOAc, 10:1 afforded (*E*)-**3.9w** as a white foam (1.68 g, 96%). An analytical sample was prepared from a 115-mg portion by bulb-to-bulb distillation (150 ºC, 2×10^{-5} mm Hg) (42 mg, 37% recovery).

Data for **3.9w**:

m.p. 54 ºC

b.p. 150 ºC (ABT, 2×10^{-5} mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.03 (dd, *J* = 8.3, 1.0 Hz, 1 H, HC(6)), 7.85 (dd, *J* = 7.8, 1.1 Hz, 1 H, HC(9)), 7.80 (d, *J* = 8.4 Hz, 2 H, HC(12)), 7.77 (s, 1 H, HC(4)), 7.62 (d, *J* = 8.5 Hz, 2 H, HC(17)), 7.59 (d, *J* = 8.7 Hz, 2 H, HC(18)), 7.38 (ddd, *J* = 8.8, 7.5, 1.3 Hz, 1 H, HC(7)), 7.33 (t, *J* = 7.4 Hz, 1 H, HC(8)), 7.29 – 7.22 (m, 3 H, HC(1,13)), 7.19 (d, *J* = 16.4 Hz, 1 H, HC(2)), 2.35 (s, 3 H, HC(15)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 145.4 (C(14)), 141.0 (C(16)), 135.7 (C(5)), 135.2 (C(11)), 130.1 (C(13)), 129.4 (q, J = 32.6 Hz, C(19)), 128.9 (C(10)), 128.2 (C(2)), 127.0 (C(12)), 126.4 (C(17)), 125.8 (q, J = 3.8 Hz, C(18)), 125.4 (C(7)), 124.9 (C(4)), 124.3 (q, J = 136 Hz, C(20)), 123.8 (C(8)), 122.0 (C(1)), 120.5 (C(9)), 120.3 (C(3)), 114.0 (C(6)), 21.7 (C(15)).

^{19}F NMR: (471 MHz, $CDCl_3$)

δ –62.4

IR: (neat)

3052 (w), 1640 (w), 1613 (w), 1543 (w), 1514 (w), 1494 (w), 1446 (w), 1415 (w), 1367 (w), 1321 (s), 1284 (w), 1253 (w), 1211 (w), 1188 (m), 1170 (s), 1119 (s), 1108 (s), 1086 (m), 1065 (s), 1015 (m), 975 (m), 950 (m), 866 (w), 823 (m), 811 (m), 785 (w), 758 (m), 743 (m), 702 (m), 685 (m), 676 (m), 659 (s), 606 (s), 567 (s), 536 (s), 506 (m).

LRMS: (EI^+, 70 eV, TOF)

91.1 (24), 189.1 (13), 216.1 (15), 217.1 (70), 218.1 (10), 285.1 (21), 286.1 (100), 287.1 (18), 441.1 (47), 442.1 (10).

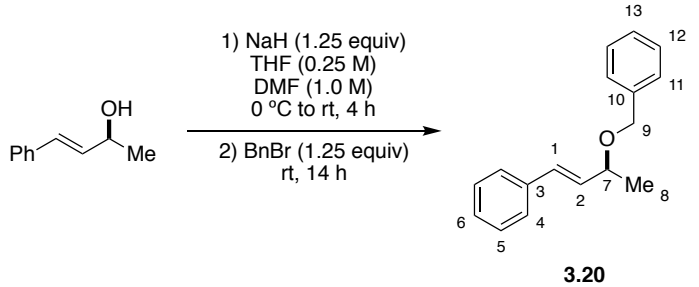
Analysis: $C_{24}H_{18}F_3NO_2S$

Calcd: C, 65.30%; H, 4.11%; N, 3.17%

Found: C, 65.17%; H, 3.91%; N, 3.16%

TLC: R_f 0.25 (9:1 hexanes/EtOAc) [UV]

Preparation of (*R*,*E*)-(3-(Benzyloxy)but-1-en-1-yl)benzene ((*R*)-3.20) and (*S*,*E*)-(3-(Benzyloxy)but-1-en-1-yl)benzene ((*S*)-3.20) [BBG-2019-133, BBG-2019-158].



3.20

A flame-dried 25-mL Schlenk flask equipped with a magnetic stir bar was brought into the glove box and charged with NaH (60.0 mg, 2.50 mmol, 1.25 equiv). The flask was capped with a

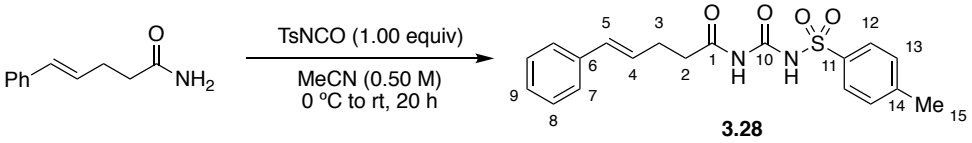
rubber septum and removed from the glove box, then connected to a Schlenk line under nitrogen. The flask was immersed in an ice-water bath and THF (8.0 mL, 0.25 M) was added. After 10 min, (*R*,*E*)-4-phenylbut-3-en-2-ol or (*S*,*E*)-4-phenylbut-3-en-2-ol (296 mg, 2.00 mmol) was added, followed by DMF (2.0 mL, 1.0 M). The reaction mixture was removed from the ice-water bath and allowed to warm to room temperature. After 4 h, benzyl bromide (296 µL, 2.50 mmol, 1.25 equiv) was added dropwise at room temperature *via* syringe. After a further 14 h, the reaction was quenched by the addition of sat. aq. NH_4Cl (5 mL). The reaction mixture was transferred to a 250-mL separatory funnel with a diethyl ether rinse (3 × 10 mL) and shaken with water (25 mL). The aqueous phase was extracted with diethyl ether (2 × 25 mL). The combined organic phases were then washed with 1:1 water/brine (3 × 25 mL), dried over $MgSO_4$ (3 g), filtered, and concentrated under reduced pressure (20-25 ºC, ~20 mm Hg). The crude product was purified by column chromatography (silica, 3 cm ø × 15 cm column) eluting with hexanes/EtOAc, 1:0 gradient to 9:1 to afford (*R*)-**3.20** (451 mg, 95%) or (*S*)-**3.20** (436 mg, 92%) as a white solid that melts near room temperature. The ^{1}H NMR spectra matched those in the literature.[56]

Data for **3.20**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.45 – 7.39 (m, 2 H, HC(4)), 7.38 – 7.31 (m, 6 H, HC(5,11,12)), 7.31 – 7.23 (m, 2 H, HC(6,13)), 6.55 (d, *J* = 16.0 Hz, 1 H, HC(1)), 6.18 (dd, *J* = 15.9, 7.7 Hz, 1 H, HC(2)), 4.63 (d, *J* = 12.0 Hz, 1 H, HC(9)), 4.45 (d, *J* = 12.0 Hz, 1 H, H'C(9)), 4.11 (tt, *J* = 7.3, 6.0 Hz, 1 H, HC(7)), 1.39 (d, *J* = 6.3 Hz, 3 H, HC(8)).

Preparation of (*E*)-5-Phenyl-*N*-(tosylcarbamoyl)pent-4-enamide (3.28) [BBG-2019-024].



3.28

To a 10-mL Schlenk flask was added (*E*)-5-phenylpent-4-enamide[51] (263 mg, 1.50 mmol) and MeCN (3.0 mL, 0.50 M). 4-Toluenesulfonyl isocyanate (229 µL, 1.50 mmol, 1.00 equiv) was then added dropwise at room temperature. The mixture was heated to 40 ºC (oil bath temperature). After 18 h, the reaction mixture was cooled to room temperature and transferred to a 100-mL round bottom flask with CH_2Cl_2 (2 × 25 mL). The resulting solution was concentrated under reduced pressure by rotary evaporation (30 – 35 ºC, 4 mm Hg) to afford a white solid. Recrystallization

from boiling $CHCl_3$ afforded **3.28** (406 mg, 73%) as white crystals.

Data for **3.28**:

^{1}H NMR: (500 MHz, $CDCl_3$)

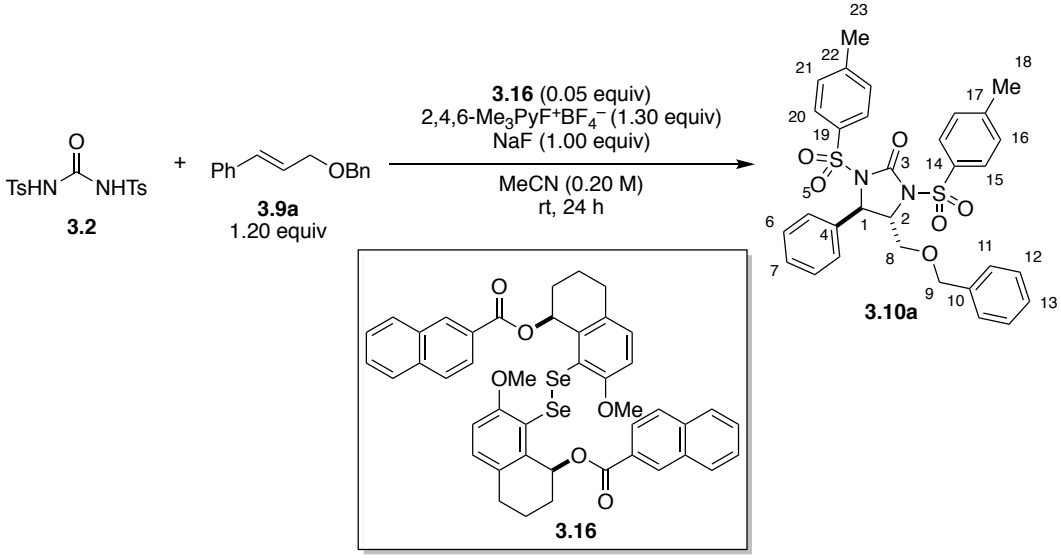
δ 11.05 (s, 1 H, CO-N**H**-SO_2), 8.22 (s, 1 H, CO-N**H**-CO), 7.94 (d, *J* = 8.3 Hz, 2 H, HC(12)), 7.34 – 7.27 (m, 6 H, HC(7,8,13)), 7.25 – 7.20 (m, 1 H, HC(9)), 6.45 (d, *J* = 15.9 Hz, 1 H, HC(5)), 6.13 (dt, *J* = 15.9, 6.8 Hz, 1 H, HC(4)), 2.60 – 2.52 (m, 2 H, HC(2)), 2.48 (ddd, *J* = 7.9, 6.9, 1.2 Hz, 2 H, HC(3)), 2.39 (s, 3 H, HC(15)).

4.3.2.3. Survey of Chiral Diselenide Catalysts.

General Procedure IX: Survey of Chiral Catalysts with (*E*)-(3-(Benzyloxy)prop-1-en-1-yl)benzene (3.9a).

An oven-dried 5-mL dram vial equipped with a magnetic stir bar and a septum-cap was charged with *N,N′*-bis-(toluenesulfonyl)urea **3.2** (36.8 mg, 0.100 mmol) and diselenide catalyst (0.0050 mmol, 0.050 equiv). The vial was subsequently taken into the glove box, and sodium fluoride (10.5 mg, 0.250 mmol, 2.50 equiv) and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (29.5 mg, 0.130 mmol, 1.30 equiv) were added. The vial was sealed and removed from the glove box. Acetonitrile (0.50 mL, 0.20 M) was added, followed by benzyl cinnamyl ether **3.9a** (26.9 mg, 0.120 mmol, 1.20 equiv). The resulting mixture was stirred at room temperature. The solution initially formed was yellow-orange, but rapidly became pale yellow after the addition of the alkene. After 24 h, the reaction mixture was diluted with dichloromethane (1 mL), transferred to a scintillation vial with a dichloromethane rinse (3 × 1 mL), and was concentrated under reduced pressure by rotary evaporation (25-30 ºC at ~20 mm Hg). The crude product was purified by silica gel column chromatography (silica, 2 cm × 12 cm column) eluting with hexanes/EtOAc, 5:1 gradient to 4:1 to afford imidazolidin-2-one products **3.10a**.

Evaluation of 1,2-Bis((*S*)-8-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-5,6,7,8-tetrahydronaphthalen-1-yl)diselane (3.16) [BBG-2019-025; see also: TZL-2019-333].



Following General Procedure II, *N,N′*-bis-(toluenesulfonyl)urea **3.2** (36.8 mg, 0.100 mmol), diselenide catalyst **3.16** (4.1 mg, 0.0050 mmol, 0.050 equiv), NaF (10.5 mg, 0.250 mmol, 2.50 equiv), 2,4,6-$Me_3PyF^+BF_4^-$ (29.5 mg, 0.130 mmol, 1.30 equiv), and benzyl cinnamyl ether **3.9a** (26.9 mg, 0.120 mmol, 1.20 equiv) in MeCN (0.50 mL, 0.20 M) were allowed to react for 24 h. The resulting suspension was worked up and purified as described in the general procedure to afford **5** (49 mg, 83%) with an e.r. of 93:7.

Data for **3.10a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.80 (d, *J* = 8.3 Hz, 2 H, HC(15)), 7.47 (d, *J* = 8.4 Hz, 2 H, HC(20)), 7.40 – 7.33 (m, 3 H, HC(12,13)), 7.30 (t, *J* = 8.0 Hz, 1 H, HC(7)), 7.29 – 7.24 (m, 3 H, HC(11,16)), 7.22 (t, *J* = 8.4 Hz, 2 H, HC(6)), 7.07 (d, *J* = 8.0 Hz, 2 H, HC(21)), 7.02 (d, *J* = 8.2, 2 H, HC(5)), 5.22 (d, *J* = 1.8 Hz, 1 H, HC(1)), 4.50 (d, *J* = 12.1 Hz, 1 H, HC(9)), 4.46 (d, *J* = 12.1 Hz, 1 H, H'C(9)), 4.21 (ddd, *J* = 6.1, 3.1, 1.7 Hz, 1 H, HC(2)), 3.73 (dd, *J* = 10.0, 3.2 Hz, 1 H, HC(8)), 3.66 (dd, *J* = 9.9, 6.1 Hz, 1 H, H'C(8)), 2.43 (s, 3 H, HC(18)), 2.36 (s, 3 H, HC(23)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.1 (C(3)), 145.5 (C(17)), 145.1 (C(22)), 138.8 (C(4)), 137.3 (C(10)), 135.3 (C(14)), 135.1 (C(19), 129.9 (C(16)), 129.4 (C(21)), 129.2 (C(6)), 129.0 (C(12)), 128.7 (C(7)), 128.4 (C(20)), 128.3 (C(15)), 128.1 (C(13)), 127.8 (C(11)), 126.1 (C(5)), 73.6 (C(9)), 70.0 (C(8)), 62.5 (C(2)), 60.9 (C(1)), 21.8 (C(18)), 21.8 (C(23)).

IR: (neat)

3061 (w), 2860 (w), 1766 (w), 1741 (m), 1595 (w), 1495 (w), 1453 (w), 1403 (w), 1363 (m), 1349 (m), 1332 (w), 1317 (w), 1297 (w), 1270 (w), 1239 (w), 1225 (w), 1214 (w), 1187 (m), 1157 (s), 1119 (m), 1101 (m), 1083 (s), 1043 (m), 1031 (w), 1017 (w), 999 (w), 960 (w), 933 (w), 914 (w), 864 (m), 841 (w), 811 (m), 778 (w), 740 (s), 716 (w), 697 (m), 662 (s), 632 (w), 614 (w), 576 (s), 541 (s), 524 (s), 500 (m), 487 (m), 470 (m), 456 (w).

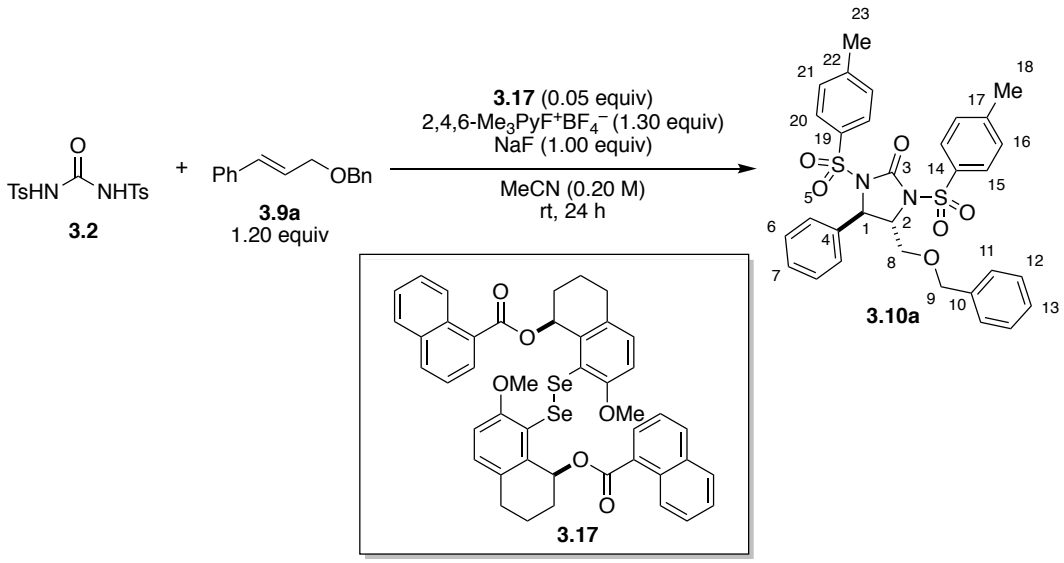
LRMS: (EI^+, 70 eV, TOF)

57.1 (10), 65.0 (13), 91.1 (100), 132.0 (24), 155.0 (88), 185.1 (19), 315.1 (15), 329.1 (28), 405.1 (11), 435.1 (37), 469.1 (16).

TLC: R_f 0.11 (4:1 hexanes/EtOAc) [UV]

HPLC: (*S,R*)-**3.10a** t_R 28.9 min (7.4%); (*R,S*)-**3.10a** t_R 32.3 min (92.6%) (Supelco Astec Cellulose, hexanes/*i*-PrOH, 80:20, 0.50 mL/min. 220 nm, 24 ºC)

Evaluation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis(1-naphthoate) (3.17) [BBG-2019-023].

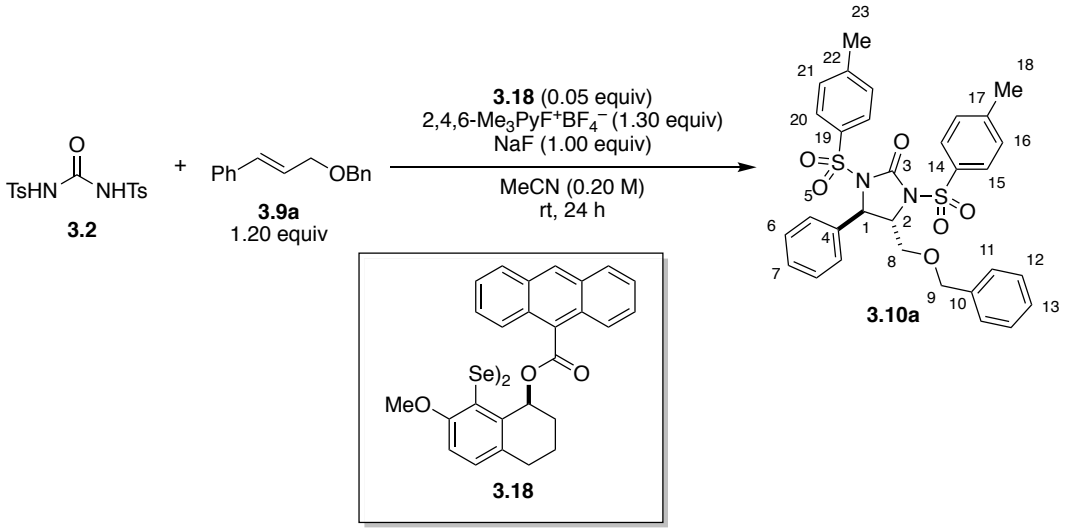


Following General Procedure II, *N,N'*-bis-(toluenesulfonyl)urea **3.2** (36.8 mg, 0.100 mmol), diselenide catalyst **3.17** (4.1 mg, 0.0050 mmol, 0.050 equiv), NaF (10.5 mg, 0.250 mmol, 2.50 equiv), 2,4,6-$Me_3PyF^+BF_4^-$ (29.5 mg, 0.130 mmol, 1.30 equiv), and benzyl cinnamyl ether **3.9a** (26.9 mg, 0.120 mmol, 1.20 equiv) in MeCN (0.50 mL, 0.20 M) were allowed to react for 24 h. The resulting suspension was worked up and purified as described in the general procedure to afford **3.10a** (58 mg, 93%, 95% pure) with an e.r. of 92:8.

Data for **3.10a**:

HPLC: (*S,R*)-**3.10a** t_R 27.4 min (7.8%); (*R,S*)-**3.10a** t_R 30.4 min (92.2%) (Supelco Astec Cellulose, hexanes/*i*-PrOH, 80:20, 0.50 mL/min. 220 nm, 24 ºC)

Evaluation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis(anthracene-9-carboxylate) (3.18) [BBG-2019-056].

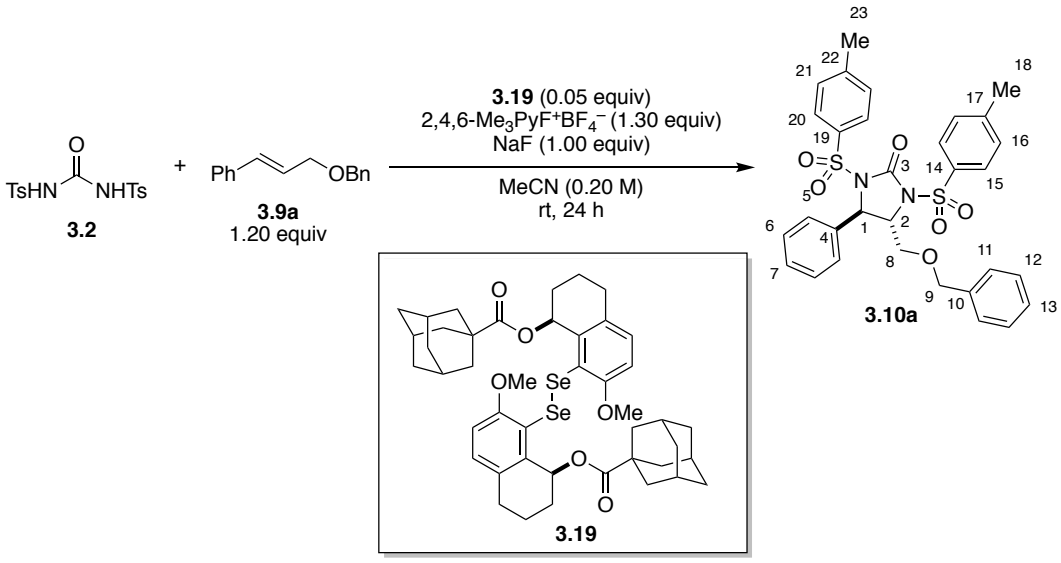


Following General Procedure II, *N,N'*-bis-(toluenesulfonyl)urea **3.2** (36.8 mg, 0.100 mmol), diselenide catalyst **3.18** (4.6 mg, 0.0050 mmol, 0.050 equiv), NaF (10.5 mg, 0.250 mmol, 2.50 equiv), 2,4,6-$Me_3PyF^+BF_4^-$ (29.5 mg, 0.130 mmol, 1.30 equiv), and benzyl cinnamyl ether **3.9a** (26.9 mg, 0.120 mmol, 1.20 equiv) in MeCN (0.50 mL, 0.20 M) were allowed to react for 24 h. The resulting suspension was worked up and purified as described in the general procedure to afford **3.10a** (47 mg, 80%) with an e.r. of 87:13.

Data for **3.10a**:

HPLC: (*S,R*)-**3.10a** t_R 29.2 min (13.0%); (*R,S*)-**3.10a** t_R 32.5 min (87.0%) (Supelco Astec Cellulose, hexanes/*i*-PrOH, 80:20, 0.50 mL/min. 220 nm, 24 ºC)

Evaluation of (1*S*,1'*S*)-Diselanediylbis(7-methoxy-1,2,3,4-tetrahydronaphthalene-8,1-diyl) Bis((3*S*,5*S*,7*S*)-adamantane-1-carboxylate) (3.19) [BBG-2019-092].



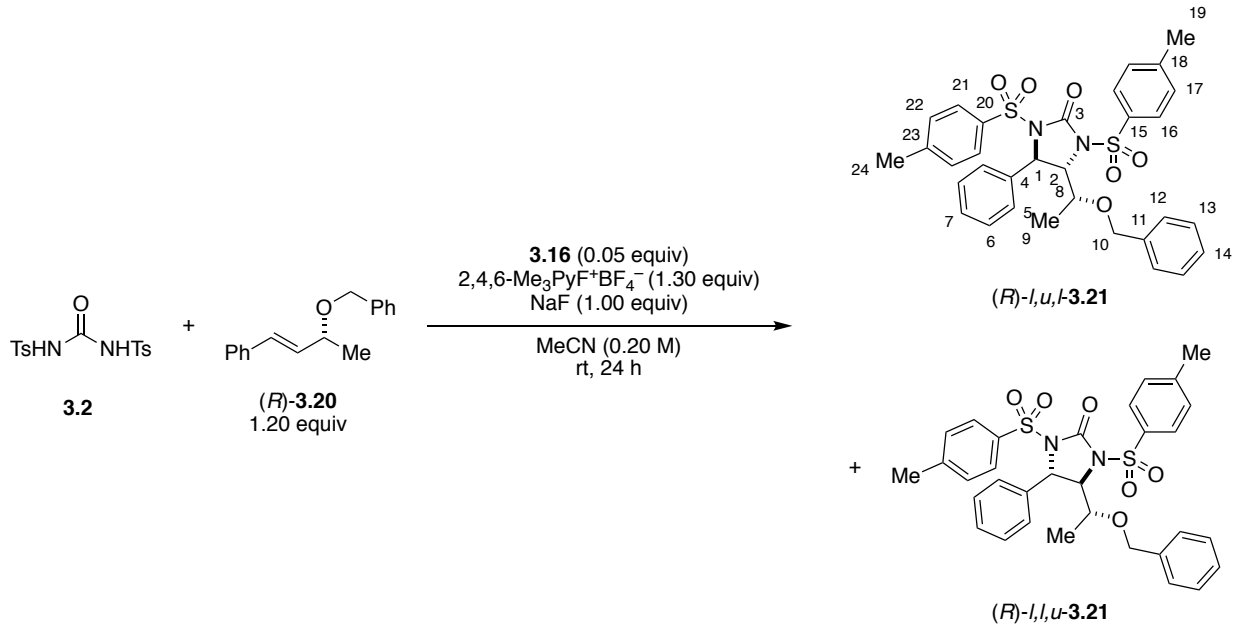
Following General Procedure II, *N,N'*-bis-(toluenesulfonyl)urea **3.2** (36.8 mg, 0.100 mmol), diselenide catalyst **3.19** (4.2 mg, 0.0050 mmol, 0.050 equiv), NaF (10.5 mg, 0.250 mmol, 2.50 equiv), 2,4,6-$Me_3PyF^+BF_4^-$ (29.5 mg, 0.130 mmol, 1.30 equiv), and benzyl cinnamyl ether **3.9a** (26.9 mg, 0.120 mmol, 1.20 equiv) in MeCN (0.50 mL, 0.20 M) were allowed to react for 24 h. The resulting suspension was worked up and purified as described in the general procedure to afford **3.10a** (52 mg, 88%) with an e.r. of 85:15.

Data for **3.10a**:

HPLC: (*S,R*)-**3.10a** t_R 30.3 min (15.1%); (*R,S*)-**3.10a** t_R 33.9 min (84.9%) (Supelco Astec Cellulose, hexanes/*i*-PrOH, 80:20, 0.50 mL/min. 220 nm, 24 ºC)

4.3.2.4. Matched and Mismatched Diastereoselective Diaminations.

Preparation of (4*S*,5*R*)-4-((*R*)-1-(Benzyloxy)ethyl)-5-phenyl-1,3-ditosylimidazolidin-2-one ((*R*)-*l,u,l*-3.21) [BBG-2019-224].



Following General Procedure III, *N,N′*-bis-(toluenesulfonyl)urea **3.2** (368 mg, 1.00 mmol), diselenide catalyst **3.16** (41.0 mg, 0.0500 mmol, 0.0500 equiv), NaF (42.0 mg, 1.00 mmol, 1.00 equiv), 2,4,6-$Me_3PyF^+BF_4^-$ (295 mg, 1.30 mmol, 1.30 equiv), and (*R*,*E*)-(3-(benzyloxy)but-1-en-1-yl)benzene (*R*)-**3.20** (291 mg, 1.20 mmol, 1.20 equiv) in MeCN (5.0 mL, 0.20 M) were allowed to react for 24 h. The resulting suspension was worked up as described in the general procedure and purified by column chromatography (silica, 4 cm ø × 16 cm column) eluting with hexanes/EtOAc, 6:1 gradient to 5:1 to afford (*R*)-*l,u,l*-**3.21** with a d.r. of >20:1. Further purification by trituration with boiling EtOH (3.0 mL) and standing in a –30 ºC freezer for 12 h afforded analytically pure material as a white solid (382 mg, 63%).

Data for (*R*)-*l,u,l*-**3.21**:

m.p. 62 ºC (EtOH)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.84 (d, *J* = 8.4 Hz, 2 H, HC(16)), 7.56 (d, *J* = 8.4 Hz, 2 H, HC(21)), 7.40 – 7.20 (m, 8 H, HC(6,7,13,14,17)), 7.12 (dd, *J* = 7.6, 1.7 Hz, 2 H, HC(12)), 7.05 (d, *J* = 7.5 Hz, 2 H, HC(5)), 7.02 (d, *J* = 8.1 Hz, 2 H, HC(22)), 5.37 (d, *J* = 1.4 Hz, 1 H, HC(1)), 4.45 (d, *J* = 12.1 Hz, 1 H, HC(10)), 4.17 (d, *J* = 12.1 Hz, 1 H, H'C(10)), 4.06 – 3.96 (m, 2 H, HC(2,8)), 2.41 (s, 3 H, HC(19)), 2.31 (s, 3 H, HC(24)), 1.28 (d, *J* = 6.3 Hz, 3 H, HC(9)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.5 (C(3)), 145.5 (C(15)), 145.0 (C(20)), 140.0 (C(4)), 137.9 (C(11)), 135.5 (C(18)), 135.2 (C(23)), 129.9 (C(17)), 129.38 (C(22)), 129.36 (C(6)), 128.8 (C(7)), 128.6 (C(21)), 128.5 (C(16)), 128.3 (C(13)), 127.7 (C(14)), 127.3 (C(12)), 125.9 (C(5)), 75.5 (C(8)), 71.8 (C(10)), 67.5 (C(2)), 58.0 (C(1)), 21.84 (C(19)), 21.78 (C(24)), 15.9 (C(9)).

IR: (neat)

2976 (w), 1749 (m), 1596 (w), 1495 (w), 1455 (w), 1362 (m), 1308 (w), 1293 (w), 1263 (w), 1215 (w), 1169 (s), 1114 (m), 1083 (s), 1027 (w), 972 (w), 887 (w), 860 (w), 812 (m), 741 (m), 710 (m), 698 (m), 663 (s), 583 (s), 564 (s), 542 (s), 531 (s).

LRMS: (EI^+, 70 eV, TOF)

65.0 (20), 77.0 (11), 91.0 (100), 92.1 (13), 132.0 (25), 139.0 (10), 155.0 (98), 250.1 (10), 315.1 (10), 343.1 (21), 405.1 (90), 406.1 (17), 449.2 (17), 469.1 (63), 470.1 (12).

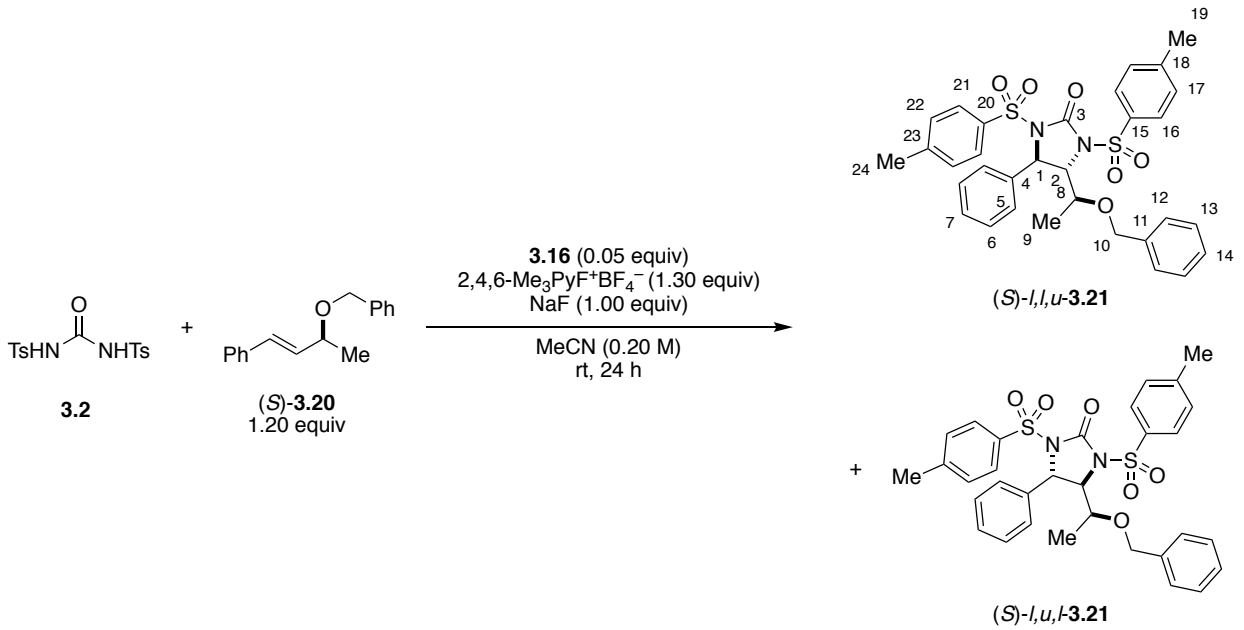
Analysis: $C_{32}H_{32}N_2O_6S_2$

Calcd: C, 63.56%; H, 5.33%; N, 4.63%

Found: C, 63.49%; H, 5.20%; N, 4.55%

TLC: R_f 0.14 (4:1 hexanes/EtOAc) [UV]

Preparation of (4*S*,5*R*)-4-((*S*)-1-(Benzyloxy)ethyl)-5-phenyl-1,3-ditosylimidazolidin-2-one and (4*R*,5*S*)-4-((*S*)-1-(Benzyloxy)ethyl)-5-phenyl-1,3-ditosylimidazolidin-2-one ((*S*)-*l,l,u*-3.21) and ((*S*)-*l,u,l*-3.21) [BBG-2019-226].



Following General Procedure III, *N,N′*-bis-(toluenesulfonyl)urea **3.2** (368 mg, 1.00 mmol), diselenide catalyst **3.16** (41.0 mg, 0.0500 mmol, 0.0500 equiv), NaF (42.0 mg, 1.00 mmol, 1.00 equiv), 2,4,6-$Me_3PyF^+BF_4^-$ (295 mg, 1.30 mmol, 1.30 equiv), and (*S*,*E*)-(3-(benzyloxy)but-1-en-1-yl)benzene (*S*)-**3.20** (291 mg, 1.20 mmol, 1.20 equiv) in MeCN (5.0 mL, 0.20 M) were allowed to react for 24 h. The resulting suspension was worked up as described in the general procedure and purified by column chromatography (silica, 4 cm ø × 16 cm column) eluting with hexanes/EtOAc, 6:1 gradient to 5:1 to afford a mixture of (*S*)-*l,l,u*-**3.21** and (*S*)-*l,u,l*-**3.21** in a ratio of 64:36. Further purification by trituration with boiling MeOH (3.0 mL) afforded (*S*)-*l,l,u*-**3.21** (201 mg, 33%) as a white solid with a d.r. of 95:5. A second crop from the filtrate afforded (*S*)-*l,u,l*-**3.21** (74.8 mg, 12%) as a white solid with a d.r. of 85:15.

Data for (*S*)-*l,l,u*-**3.21**:

m.p. 127-128 ºC (MeOH)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.79 (d, *J* = 8.3 Hz, 2 H, HC(16)), 7.50 (d, *J* = 8.3 Hz, 2 H, HC(21)), 7.39 – 7.27 (m, 8 H, HC(7,12,13,14,17)), 7.18 (t, *J* = 7.6 Hz, 2 H, HC(6)), 7.13 (d, *J* = 8.1 Hz, 2 H, HC(22)), 6.95 (dd, *J* = 7.4, 1.4 Hz, 2 H, HC(5)), 5.36 (d, *J* = 1.5 Hz, 1 H, HC(1)), 4.59 (d, *J* = 11.8 Hz, 1 H, HC(10)), 4.51 (d, *J* = 11.8 Hz, 1 H, H'C(10)), 4.27 (dd, *J* = 4.1, 1.5 Hz, 1 H, HC(2)), 4.04 (qd, *J* = 6.6, 4.1 Hz, 1 H, HC(8)), 2.46 (s, 3 H, HC(19)), 2.38 (s, 3 H, HC(24)), 1.06 (d, *J* = 6.5 Hz, 3 H, HC(9)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.3 (C(3)), 145.7 (C(15)), 145.3 (C(20)), 139.3 (C(4)), 137.8 (C(11)), 135.2 (C(23)), 135.0 (C(18)), 130.0 (C(17)), 129.5 (C(22)), 129.1 (C(6)), 128.8 (C(7)), 128.6 (C(13)), 128.5 (C(21)), 128.4 (C(16)), 128.0 (C(14)), 127.9 (C(12)), 126.0 (C(5)), 74.1 (C(8)), 71.5 (C(c10)), 63.9 (C(2)), 57.8 (C(1)), 21.9 (C(19)), 21.8 (C(24)), 13.0 (C(9)).

IR: (neat)

2974 (w), 2867 (w), 1746 (m), 1597 (w), 1496 (w), 1459 (w), 1366 (m), 1346 (m), 1322 (w), 1294 (w), 1262 (w), 1221 (m), 1186 (m), 1171 (m), 1152 (m), 1126 (m), 1104 (m), 1084 (s), 1050 (w), 1030 (w), 1017 (w), 1002 (w), 940 (w), 916 (w), 884 (w), 850 (w), 836 (w), 814 (m), 759 (w), 743 (m), 733 (m), 706 (s), 666 (s), 652 (m), 610 (w), 582 (s), 556 (m), 545 (s), 532 (s), 484 (w), 460 (w).

LRMS: (EI^+, 70eV, TOF)

65.0 (21), 91.0 (83), 92.1 (13), 132.0 (27), 139.0 (12), 155.0 (100), 250.1 (13), 405.1 (99), 406.1 (24), 449.2 (16), 469.1 (82), 470.1 (15).

Analysis: $C_{32}H_{32}N_2O_6S_2$

Calcd: C, 63.56%; H, 5.33%; N, 4.63%

Found: C, 63.43%; H, 5.10%; N, 4.86%

TLC: R_f 0.15 (4:1 hexanes/EtOAc) [UV]

Data for (*S*)-*l,u,l*-**3.21**:

m.p. 110-120 ºC (MeOH)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.84 (d, *J* = 8.4 Hz, 2 H, HC(16)), 7.56 (d, *J* = 8.4 Hz, 2 H, HC(21)), 7.40 – 7.20 (m, 8 H, HC(6,7,13,14,17)), 7.12 (dd, *J* = 7.6, 1.7 Hz, 2 H, HC(12)), 7.05 (d, *J* = 7.5 Hz, 2 H, HC(5)), 7.02 (d, *J* = 8.1 Hz, 2 H, HC(22)), 5.37 (d, *J* = 1.4 Hz, 1 H, HC(1)), 4.45 (d, *J* = 12.1 Hz, 1 H, HC(10)), 4.17 (d, *J* = 12.1 Hz, 1 H, H'C(10)), 4.06 – 3.96 (m, 2 H, HC(2,8)), 2.41 (s, 3 H, HC(19)), 2.31 (s, 3 H, HC(24)), 1.28 (d, *J* = 6.3 Hz, 3 H, HC(9)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.5 (C(3)), 145.5 (C(15)), 145.0 (C(20)), 140.0 (C(4)), 137.9 (C(11)), 135.5 (C(18)), 135.2 (C(23)), 129.9 (C(17)), 129.38 (C(22)), 129.36 (C(6)), 128.8 (C(7)), 128.6 (C(21)), 128.5 (C(16)), 128.3 (C(13)), 127.7 (C(14)), 127.3 (C(12)), 125.9 (C(5)), 75.5 (C(8)), 71.8 (C(10)), 67.5 (C(2)), 58.0 (C(1)), 21.84 (C(19)), 21.78 (C(24)), 15.9 (C(9)).

IR: (neat)

2924 (w), 1760 (m), 1597 (w), 1495 (w), 1453 (w), 1364 (s), 1307 (w), 1294 (w), 1245 (w), 1211 (w), 1170 (s), 1150 (m), 1122 (w), 1104 (m), 1084 (s), 1048 (m), 1027 (w), 973 (w), 945 (w), 888 (w), 862 (w), 832 (w), 812 (w), 804 (w), 750 (m), 736 (s), 707 (m), 696 (m), 664 (s), 633 (w), 603 (m), 585 (s), 561 (s), 543 (s), 531 (s), 480 (m), 460 (w).

LRMS: (EI^+, 70 eV, TOF)

65.0 (12), 91.0 (93), 132.0 (20), 155.0 (100), 343.1 (13), 405.1 (89), 406.1 (16), 449.2 (14), 469.1 (51), 470.1 (11).

Analysis: $C_{32}H_{32}N_2O_6S_2$

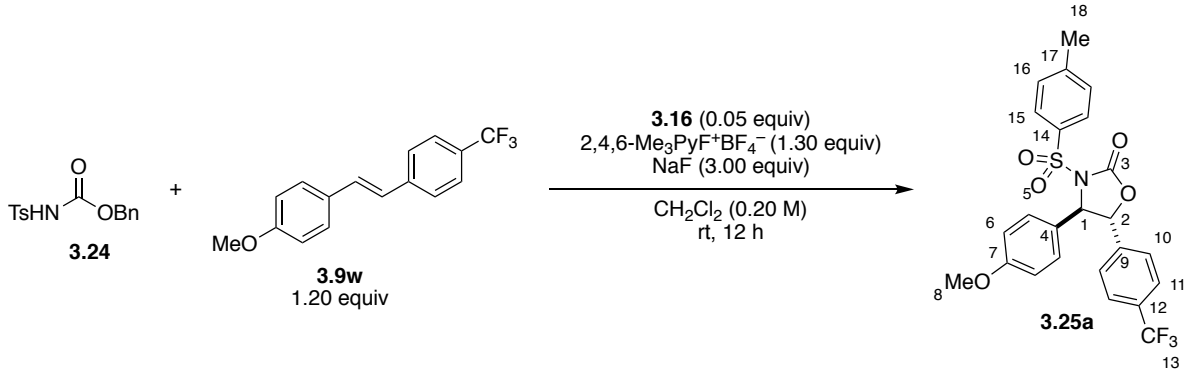
Calcd: C, 63.56%; H, 5.33%; N, 4.63%

Found: C, 63.50%; H, 5.13%; N, 4.96%

TLC: R_f 0.14 (4:1 hexanes/EtOAc) [UV]

4.3.2.5. Oxyamination.

Preparation of (4*R*,5*R*)-4-(4-Methoxyphenyl)-3-tosyl-5-(4-(trifluoromethyl)phenyl)-oxazolidin-2-one (17) [BBG-2019-217].



An oven-dried 20-mL scintillation vial equipped with a magnetic stir bar and a septum-cap was charged with benzyl tosylcarbamate **3.24** (305 mg, 1.00 mmol) and diselenide **3.16** (41.0 mg, 0.05 mmol, 0.05 equiv). The vial was subsequently taken into the glove box, and sodium fluoride (126 mg, 3.00 mmol, 3.00 equiv) and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (295 mg, 1.30 mmol, 1.30 equiv) were added. The vial was sealed and removed from the glove box. Dichloromethane (5.0 mL, 0.20 M) was added, followed by **3.9v** (334 mg, 1.20 mmol, 1.20 equiv). The resulting heterogeneous mixture was stirred vigorously at room temperature. After 12 h, the reaction mixture was diluted with dichloromethane (5 mL), transferred to a round bottom flask with dichloromethane rinse (3x 5 mL), and concentrated under reduced pressure by rotary evaporation (25-30 ºC at ~20 mm Hg). The resulting yellow viscous oil was purified by column chromatography (silica, 4 cm ø × 18 cm column) eluting with hexanes/EtOAc, 6:1 to afford **3.25a** as a white powder, 97:3 e.r. Trituration with boiling methanol afforded analytically pure material (292 mg, 59%).

Data for **3.25a**:

m.p. 129-132 ºC (MeOH)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.67 (d, *J* = 8.1 Hz, 2 H, HC(11)), 7.50 (d, *J* = 8.3 Hz, 2 H, HC(15)), 7.36 (d, *J* = 8.1 Hz, 2 H, HC(10)), 7.20 (d, *J* = 6.6 Hz, 2 H, HC(5)), 7.18 (d, *J* = 6.2 Hz, 2 H, HC(16)), 6.90 (d, *J* = 8.7 Hz, 2 H, HC(6)), 5.38 (d, *J* = 4.2 Hz, 1 H, HC(2)), 5.13 (d, *J* = 4.2 Hz, 1 H, HC(1)), 3.85 (s, 3 H, HC(8)), 2.42 (s, 3 H, HC(18)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 160.6 (C(7)), 151.6 (C(3)), 145.6 (C(14)), 141.1 (C(9)), 134.8 (C(17)), 131.8 (q, J = 32.7 Hz, C(12)), 129.6 (C(16)), 129.1 (C(4)), 128.6 (C(15)), 128.5 (C(5)), 126.4 (q, J = 3.7 Hz, C(11)), 125.5 (C(10)), 123.8 (q, J = 272.3 Hz, C(13)), 114.8 (C(6)), 82.5 (C(2)), 67.8 (C(1)), 55.6 (C(8)), 21.8 (C(18)).

^{19}F NMR: (471 MHz, $CDCl_3$)

δ –62.4

IR: (neat)

3050 (w), 2955 (w), 2929 (w), 2040 (w), 1774 (m), 1613 (w), 1599 (w), 1512 (m), 1495 (w), 1459 (w), 1436 (w), 1416 (w), 1385 (m), 1377 (m), 1322 (m), 1304 (m), 1277 (m), 1257 (m), 1218 (w), 1188 (m), 1157 (s), 1107 (s), 1091 (s), 1064 (m), 1042 (m), 1024 (m), 1011 (m), 979 (m), 955 (w), 898 (w), 850 (w), 828 (s), 811 (s), 772 (w), 758 (m), 741 (w), 734 (w), 705 (m), 666 (m), 650 (m), 640 (m), 620 (m), 598 (m), 579 (s), 562 (m), 547 (s), 527 (s), 508 (m), 453 (w).

LRMS: (EI^+, 70eV, TOF)

57.1 (29), 65.0 (23), 71.1 (31), 77.0 (28), 85.1 (29), 91.1 (27), 97.1 (14), 99.1 (16), 107.1 (38), 111.1 (12), 113.1 (11), 119.0 (20), 127.2 (12), 134.1 (38), 135.1 (29), 145.0 (10), 155.0 (12), 162.1 (100), 163.1 (11), 200.0 (18), 265.1 (16), 292.1 (22), 336.1 (20), 491.1 (43), 492.1 (11).

Analysis: $C_{24}H_{20}F_3NO_5S$

Calcd: C, 58.65%; H, 4.10%; N, 2.85%

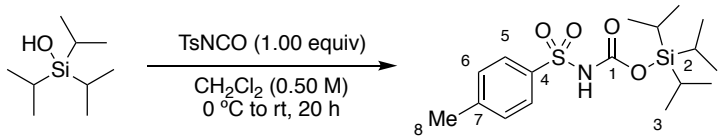
Found: C, 58.80%; H, 4.14%; N, 2.92%

TLC: R_f 0.21 (3:1 hexanes/EtOAc) [UV]

HPLC: (*R,R*)-**3.25a** t_R 15.4 min (96.7%); (*S,S*)-**3.25a** t_R 19.9 min (3.3%) (Supelco Astec Cellulose, hexanes/*i*-PrOH, 4:1, 1.0 mL/min. 220 nm, 24 ºC)

Opt. Rot.: $[\alpha]_D^{25}$ +78.1 (c = 0.94 in $CHCl_3$)

Preparation of Triisopropylsilyl Tosylcarbamate (3.27) [BBG-2019-137].



3.27

To a 50-mL Schlenk flask equipped with a magnetic stir bar was added triisopropylsilanol[50] (1.39 g, 8.00 mmol) and CH_2Cl_2 (16 mL, 0.50 M). The solution was immersed in an ice-water bath and 4-toluenesulfonyl isocyanate (1.22 mL, 8.00 mmol, 1.00 equiv) was added dropwise over 5 min. Once the addition was complete, the reaction mixture was removed from the ice bath and allowed to warm to room temperature. After 20 h the solvent was removed under reduced pressure by rotary evaporation (25 – 30 ºC, 4 mm Hg), then on high vacuum (25 ºC, 0.05 – 0.1 mm Hg) to afford **3.27** (3.04 g, 87%, 85% pure [CH_2Cl_2]) as a viscous, clear, colorless oil.

Data for **3.27**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.89 (d, *J* = 8.3 Hz, 2 H, HC(5)), 7.33 (d, *J* = 8.3 Hz, 2 H, HC(6)), 7.29 (bs, 1 H, NH), 2.44 (s, 3 H, HC(8)), 1.23 (sept, *J* = 7.5 Hz, 3 H, HC(2)), 0.98 (d, *J* = 7.5 Hz, 18 H, HC(3)).

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