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On the Mechanism of the Selenolactonization Reaction with Selenenyl Halides

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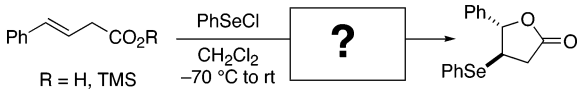

The mechanism of selenocyclization reactions of β,γ-unsaturated acids and their derivatives has been studied. The reactions of (*E*)-4-phenyl-3-butenoic acid **10** and its silyl and alkyl esters with benzeneselenenyl chloride (PhSeCl) and bromide (PhSeBr) have been examined by VT-NMR and in situ IR spectroscopic methods. Whereas the reactions of the acid **10** in the presence of a base were irreproducible and complicated, reactions of the silyl esters were clean and spontaneously and quantitatively afforded a chloroselenylation adduct at −70 °C as a single (Markovnikov) isomer. This adduct underwent three processes as the temperature was raised: (1) reversal to the starting materials, (2) isomerization to the anti-Markovnikov product, and (3) cyclization to the selenolactone **12**. All of these processes are believed to proceed via a seleniranium ion the intermediacy of which was established by independent synthesis and spectroscopic identification. The reversible formation of chloro selenide adducts was unambiguously established by crossover experiments. The reaction of **10** with PhSeBr was found to be rapid but thermodynamically unfavorable at room temperature.

Introduction

It can be safely argued that nowhere in the Periodic Table is chemical reactivity so diverse and useful synthetic transformations so abundant as in the Main Group.[1] Considering the expanse of organometallic chemistry from lithium to lead and nonmetallic chemistry from boron to iodine, the scope, development, and understanding of the chemistry of these elements is truly breathtaking. Yet, at this advanced vantage point, the number of catalytic enantioselective variants of the powerful transformations of these organoelement compounds pales in comparison to the edifice of accomplishments in this arena for the d-block elements, i.e., those in the transition-metal series.[2]

As part of our continuing interest to develop new concepts of catalysis for reactions in the Main Group,[3] we have embarked on a broadly based program to identify those uncharted regions of the p-block for which the potential for catalysis has yet to be realized. We have identified the heavier chalcogens (S, Se, and Te) as elements for which a rich and diverse chemistry is extant with the simultaneous and surprising absence of catalytic (asymmetric) variants. The focus of this report is a mechanistic investigation of the functionalization reactions of alkenes electrophilically triggered by organoselenium(II) reagents.

Background

The incorporation of organoselenium chemistry in organic synthesis was stimulated by the seminal work of Sharpless[4] and Reich[5] on the α-selenylation of carbonyl compounds with subsequent oxidation and elimination to generate α,β-unsaturated carbonyl compounds. This represented the first useful application of selenium derivatives in organic synthesis and led to the development of new methods and reagents that are now used routinely in synthetic organic chemistry. The development

(1) (a) *Main Group Metals in Organic Synthesis*; Yamamoto, H., Oshima, K., Eds.; Wiley-VCH: Weinheim, 2005; Vols. 1 and 2. (b) *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; Wiley-VCH: Weinheim, 1999. (c) Finet, J.-P. *Ligand Coupling Reactions with Heteroatomic Compounds*; Pergamon: Oxford, 1998.

(2) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Volumes I−III. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-Interscience: New York, 2000. (c) *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vols. 1 and 2. (d) *Handbook of Enantioselective Catalysis*; Brunner, H., Zettlemeier, W., Eds.; Wiley-VCH: Weinheim, 1993; Vols. 1 and 2.

(3) Denmark, S. E.; Fujimori, S. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, Chapter 7. (b) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432−440.

(4) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2967−2699. (b) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, *14*, 1979−1982. (c) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137−6139.

(5) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813−5815.

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of the second major strand of organoselenium chemistry, namely the electrophilic addition of selenenyl halides to alkenes, was stimulated by the successful advancement of α-selenylation chemistry. Although the first reported addition reactions of this type were reported in 1958,[6] they were of limited utility until the pioneering advances of Sharpless and Reich prompted a reexamination of this chemistry. Subsequently, the simple addition of a selenium(II) halide to an alkene to afford a *β*-halo selenide became the basis for many useful transformations. This is exemplified by Sharpless's development of a practical method for the preparation of allylic alcohols via alkoxyselenylation of alkenes and subsequent oxidative elimination of benzeneselenenic acid.[7]

Perhaps the most important subset of electrophilic selenium(II) additions to alkenes are the selenocyclization reactions. Selenocyclizations constitute a subset of the class of reactions termed *cyclofunctionalizations*,[8] in which electrophilic addition to a double bond triggers capture of the resulting intermediate by a pendant nucleophilic group to generate a cyclic product. The first example of a selenocyclization was reported in 1960[9] and involved the formation of a selenolactone from an unsaturated carboxylic acid. These reactions were extensively developed in the 1970s[10,11] and became useful tools in organic synthesis because of the further elaboration of the resulting selenides to alkenes (via oxidation and elimination) or to addition products (via radical chemistry).[12] The versatility of these reactions is enhanced by the wide range of pendant nucleophiles can be utilized in these reactions, e.g., carboxylic acids, alcohols, amines, amides, enol ethers, and vinylstannanes have all been employed as nucleophiles in selenocyclizations.[13] Not surprisingly, these reactions have also found widespread use in natural product synthesis;[14] in particular, seleno etherification reactions have been used in the preparation of prostaglandin analogues.[15]

The mechanism of the addition of benzeneselenenyl halides to alkenes has been the subject of considerable study (Scheme 1). Stereospecific anti-addition to the alkene occurs to afford a *β*-halo selenide product. Stopped-flow kinetic studies with both PhSeCl[16] and PhSeBr[17] demonstrated that this process is a bimolecular reaction which is first order in both the alkene and arylselenium halide components. The *β*-halo selenide products can arise from either or both of two intermediates on this reaction pathway, seleniranium ion **2** and episelenurane **3**, both of which have been isolated and characterized (Chart 1). In 1974, Garratt and Schmid[18] reported that reaction of ethylene with *p*-tolueneselenenyl chloride affords episelenurane **4**, the only known example of such a species. The same authors were also the first to demonstrate the existence of stable seleniranium ions by the generation of several seleniranium hexafluoroantimonates, e.g., **5**,[19] from *p*-tolueneselenenyl hexafluoroantimonate. It is noteworthy that these species, when treated with halide, afford the same *β*-halo selenide obtained from the direct reaction with benzeneselenenyl halide and is also suggestive of the intermediacy of seleniranium ions on the reaction pathway. The seleniranium ion **6** (generated by treatment of 1,2-dimethylacenaphthalene with a combination of aluminum chloride, thionyl chloride, and benzeneselenenyl chloride) could be isolated and the structure confirmed by X-ray crystallography.[20] Further indirect evidence for the formation of seleniranium ions as intermediates has been obtained from a careful study of cumulative substituent effects upon the rate of reaction.[16] Furthermore, a computational study by Houk and Wirth on the asymmetric alkoxyselenylation with chiral selenium electrophiles demonstrated that the formation of a seleniranium ion from the corresponding reagents is both highly exothermic and rapid—at least in the case of selenium(II) reagents featuring "non-coordinating" counterions such as triflate or hexafluorophosphate.[21] It is also known that for simple *β*-halo selenides, the addition reaction can be reversible. The reversibility of addition for simple alkenes was proven by a clever crossover experiment in which in situ generated adduct **7** was combined with alkenoic acid **8** to obtain selenolactonization product **9** (Scheme 2).[10a]

SCHEME 1

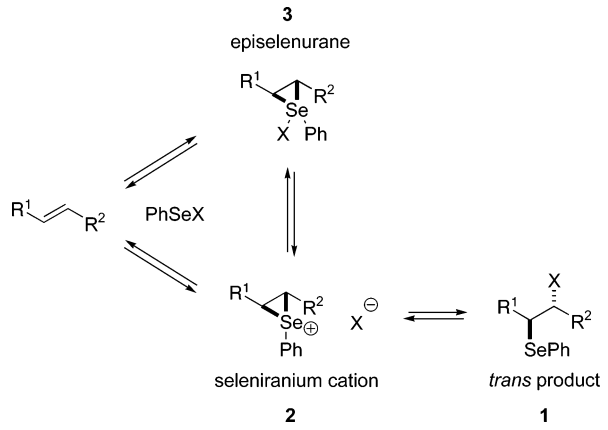
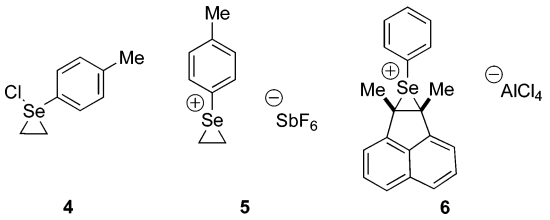
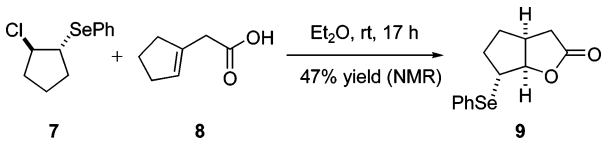


CHART 1



SCHEME 2



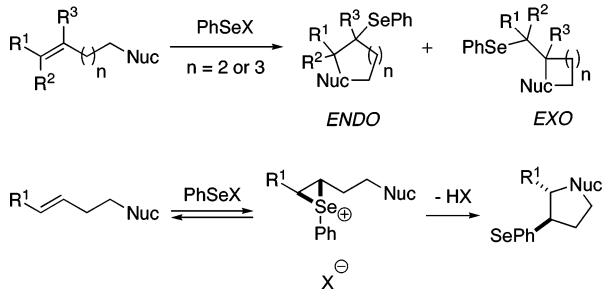
In the formation of *β*-halo selenides from alkenes and benzeneselenenyl halides, electronic factors generally predomi-

(6) Holze, G.; Jenny, W. *Helv. Chim. Acta*. **1958**, *41*, 593.
(7) Sharpless, K. B.; Lauer, R. F. *J. Org. Chem.* **1974**, *39*, 429−430.
(8) Clive, D. J. L.; Chittattu, G.; Curtis, N. J.; Kiel, W. A.; Wong, C. K. *J. Chem. Soc. Chem. Commun.* **1977**, 725−727.
(9) Campos, M. M.; Petragnani, N. *Chem. Ber.* **1960**, *93*, 317.
(10) (a) Clive, D. J. L.; Russell, C. G.; Chittattu, G.; Singh, A. *Tetrahedron*, **1980**, *36*, 1399−1408. (b) Clive, D. J. L.; Chittattu, G. *J. Chem. Soc., Chem. Commun*. **1977**, 484−485.
(11) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc*. **1979**, *101*, 3884−3893. (b) Nicolaou, K. C.; Lysenko, Z. *J. Am. Chem. Soc.* **1977**, *99*, 3185−3187.
(12) See, for example: (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986. (b) Liotta, D. *Organoselenium Chemistry*; John Wiley: New York, 1986.
(13) For recent reviews on the subject, see: (a) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273−5308. (b) Petragnani, N.; Stefani, H. A.; Valduga, C. J. *Tetrahedron* **2001**, *57*, 1411−1448. (c) Tiecco, M. *Electrophilic Selenium, Selenocyclization*, in *Topics in Current Chemistry: Organoselenium Chemistry*; Springer, Heidelberg, 2000; pp 7−54.
(14) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Product Synthesis*; CIS: Philadelphia, 1984.

nate over steric factors and result in the formation of the Markovnikov adduct at low temperature (conditions of kinetic control).[22] The formation of these adducts is, however, reversible, and at higher temperatures both isomers can be observed.[23,24]

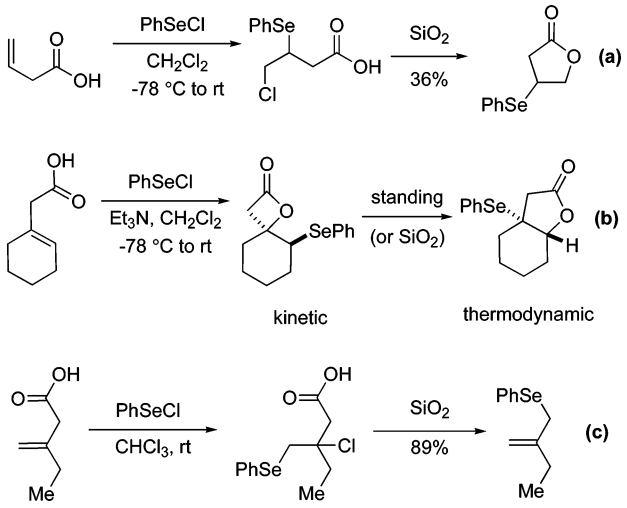
The mechanistic aspects of the seleno*cyclization* process are less well understood. These reactions are typically used for the synthesis of four- to seven-membered rings from substrates that contain a pendant nucleophile and either a γ,δ or δ,ω-alkene (Scheme 3). Depending upon the reaction conditions, the cyclization can proceed via 4-*exo-trig* and 5-*endo-trig* (γ,δ-alkene) or 5-*exo-trig* and 6-*endo-trig* (δ,ω-alkene) pathways. Fortunately, the conditions required to obtain either adduct are well-understood conditions and have been reviewed recently.[22b,c]

SCHEME 3



Selenocyclization reactions are usually depicted as the simple process illustrated in Scheme 3; the pendant nucleophile captures the seleniranium ion to afford the cyclization product. However, the primary literature contains many indications that these reactions are more complex than this simple picture. For example, the primary formation of chloroselenylation adducts that subsequently lactonize to the selenolactones upon exposure to silica gel has been reported (Scheme 4, eq a). Moreover, in a reaction of cyclohexene-1-carboxylic acid, kinetic formation of a β-lactone that later isomerized to the γ-lactone was observed (Scheme 4, eq b).[11] The reactivity of β,γ-unsaturated acids depends on the alkene substitution pattern. Thus, the expected selenolactonization reaction is competitive with a process of decarboxylative elimination to generate allyl selenides (Scheme 4, eq c).[25] Other than these empirical observations, no studies on the mechanism or the kinetics of these cyclizations are available. In line with our long-term objectives, a clear mechanistic understanding of the reaction would facilitate the development of a viable, catalytic, enantioselective selenocyclization method.[26]

SCHEME 4



Accordingly we elected to undertake a thorough study of the mechanism of selenocyclization using VT-NMR and React-IR spectroscopic analysis. In designing a system for study, the choice of the substrate was crucial. We decided that a substrate known to be site-selective and that affords a single cyclization product was essential. Both Tiecco[26d] and Wirth[26e] showed that γ,δ-unsaturated nucleophiles bearing a δ-phenyl substituent cyclize cleanly to the 5-*endo* product, and thus, we chose this substrate class. Initially, we considered the seleno etherification reaction as a suitable starting point for our investigation, but preliminary experiments with 4-phenyl-3-buten-1-ol showed that the reaction was too fast to study and lacked a suitable IR absorbance for study by in situ React-IR analysis. Consequently, we turned instead to studying the selenolactonization of (*E*)-4-phenyl-3-butenoic acid, a substrate amenable to study by both IR and VT-NMR spectroscopy. The objectives of this study were as follows: (1) to identify the intermediates (if any) involved on the reaction pathway; (2) to determine whether each (or indeed any) of the reaction steps was reversible; and (3) to gain a better understanding of the overall reaction mechanism. Herein we describe, in full, our insights into these reactions and the resulting mechanistic implications.

Results

1. Preparation of Unsaturated Acid 10. The chosen substrate (*E*)-4-phenyl-3-butenoic acid **10** (Scheme 5) was prepared

(15) (a) Nicolaou, K. C.; Barnette, W. E.; Magolda, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 3480−3485. (b) Corey, E. J.; Keck, G. E.; Szekely, I.; Ishigura, M. *Tetrahedron Lett.* **1978**, *19*, 1023−1026.

(16) Schmid, G. H.; Garratt, D. G. *Tetrahedron* **1978**, *34*, 2869−2872.

(17) Luh, T.-Y.; So, W.-H.; Cheung, K. S.; Tam, S. W. *J. Org. Chem.* **1985**, *50*, 3051−3053.

(18) Schmid, G. H.; Garratt, D. G. *Can J. Chem.* **1974**, *52*, 1027−1028.

(19) Schmid, G. H.; Garratt, D. G. *Tetrahedron Lett.* **1975**, *16*, 3991−3994.

(20) Borodkin, G. I.; Chernyak, E. I.; Shakirov, M. M.; Gatilov, Y. V.; Rybalova, T. V.; Shubin, V. G. *J. Org. Chem. USSR* **1990**, *26*, 1163−1179.

(21) Wang, X.; Houk, K. N.; Spichty, M.; Wirth, T. *J. Am. Chem. Soc.* **1999**, *121*, 8567−8576.

(22) See, for example: (a) Garratt, D. G.; Kabo, A. *Can. J. Chem.* **1980**, *58*, 1030−1041. (b) Back, T. G. In *The Chemistry of organic selenium and tellurium compounds*; Patai, S., Ed.; Wiley: New York, 1987; Vol. 2, pp 94−215. (c) Schmid, G. H.; Garratt, D. G. In *The Chemistry of double bonded functional groups*; Patai, S., Ed.; Wiley: New York, 1977; Supplement A, Part 2, pp 854−866.

(23) Raucher, S. *J. Org. Chem.* **1977**, *42*, 2950−2951.

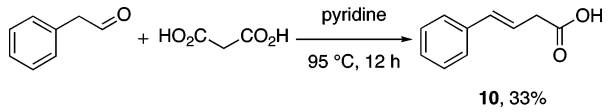
(24) Pannecouke, X.; Outurquin, F.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 995−1006.

(25) Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. *Tetrahedron Lett.* **1979**, *20*, 4801−4804.

(26) There are several reported examples of stoichiometric, asymmetric selenocyclization reactions with chiral selenium reagents. For reviews, see: (a) Tiecco, M.; Testaferri, L.; Marini, F.; Bagnoli, L.; Santi, C.; Temperini, A.; Sternativo, S.; Tomasssini, C. *Phosphorus, Sulfur Silicon* **2005**, *180*, 729−740. (b) Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3741−3749. (c) Wirth, T. *Tetrahedron* **1999**, *55*, 1−28. For more recent reports of these reactions, see: (d) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Chem. Eur. J.* **2002**, 1118−1124. (e) Fragale, G.; Wirth, T. *Eur, J. Org. Chem.* **1998**, 1361−1369.

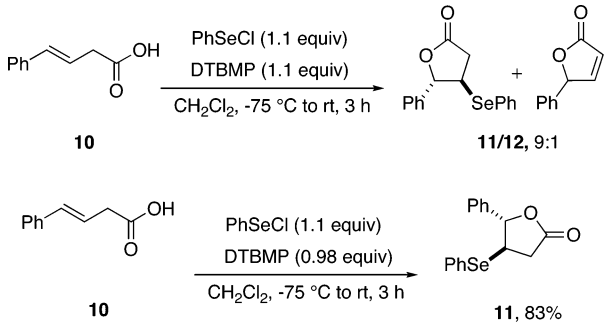
by modification of the procedure of Hoye and Richardson.[27] Although Knoevenagel condensation between phenylacetaldehyde and malonic acid in the presence of pyridine proceeded in high yield and was highly selective for the *E*-isomer, the crude product was a 9:1 mixture of β,γ/α,β-isomers. Careful distillation and recrystallization twice from heptane afforded isomerically pure **10** in 33% yield.

SCHEME 5



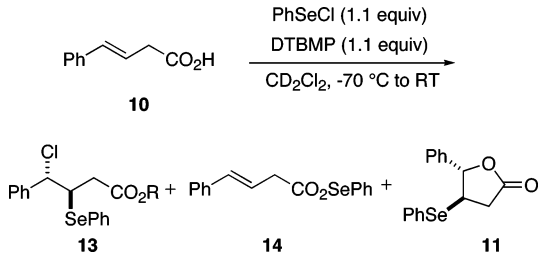
1.1. Selenocyclization of Unsaturated Acid 10 in the Presence of Base. The starting point for this investigation was to prepare the selenolactone product derived from acid **10** and to establish the reaction conditions required for its preparation from benzeneselenenyl chloride. The selenolactone product, (±)-(4*RS*,5*SR*)-dihydro-4-(phenylseleno)-5-phenylfuran-2(3*H*)-one **11**, has previously been prepared by the in situ oxidation of diphenyl diselenide to the benzeneselenenyl cation with DDQ.[28] However, this selenolactone has never been prepared by a classical selenolactonization reaction with benzeneselenenyl chloride. Thus, the reaction of acid **10** with 1.1 equiv of benzeneselenenyl chloride in the presence of 1.1 equiv of the hindered base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in methylene chloride solution was conducted (Scheme 6). Under these conditions, complete consumption of the starting material was observed and a 9:1 mixture of selenolactone **11** and butenolide **12** was produced (Scheme 6). The sole function of the base was to neutralize the HCl generated; in the absence of base an undesired acid-promoted cyclization was competitive.[29] The identity of the base was not important to prevent of the protiocyclization process—Et_3N, *i*-Pr_2EtN, 1,2,2,6,6-pentamethylpiperidine, and DTBMP were all successful in this regard—however, in some cases, sterically unencumbered bases also retarded the desired cyclization reaction. In this respect, 2,6-di-*tert*-butyl-4-methylpyridine was unique in having no effect upon the rate of cyclization. Although we ultimately found that these reactions could in fact be run on a small scale in the absence of base, poor and irreproducible solubility led us to run preparative reactions in the presence of 0.98 equiv of DTBMP. Under these conditions, both the problems of acid-mediated cyclization and butenolide formation were eliminated. Thus, selenolactone **11** was prepared in 83% yield as illustrated in Scheme 6.

SCHEME 6



Armed with the conditions required for the preparation of selenolactone **11**, in situ React-IR studies were commenced using reaction conditions identical to those employed in the preparation of selenolactone **11**. The aims of these studies were to gauge the rate of cyclization and identify whether intermediates were formed in the reaction. The conversion of the starting acid **10** into selenolactone **11** was observed by monitoring the decrease of the acid carbonyl absorbance at 1704 cm^{-1} and the corresponding increase in the lactone carbonyl absorbance at 1784 cm^{-1}. At lower temperatures (−70 to −40 °C), an initial burst of product formation was observed followed by stalling until the reaction reached ambient temperature. Surprisingly, the lower the initial temperature, the greater the initial burst of product formation.[30] This curious observation prompted further examination of the reaction by VT-NMR analysis. It was important to determine whether the initial burst was a function of some contamination or whether stalling was the result of forming a deactivated intermediate. A mixture of carboxylic acid **10**, benzeneselenenyl chloride, and DTBMP in CD_2Cl_2 solution cooled to −70 °C showed the formation of three products: the lactone **11**, an intermediate chloroselenylation adduct **12** (bearing an unknown carboxylate substituent), and a third species which proved difficult to identify by NMR spectroscopy, but appeared to be selenenyl carboxylate **13** (Scheme 7). Upon warming, only the desired product **11** was obtained, indicating that both **13** and **14** must be intermediates on the reaction pathway to the selenolactone. Many experiments were performed to identify the putative selenenyl carboxylate species **14** (as well as other selenenyl carboxylates), but these species were found to be unstable with respect to disproportionation into diphenyl diselenide, benzeneseleninic acid and the corresponding acid anhydride.[31] Given the reported instability of the analogous sulfur derivatives this is perhaps not surprising.[32] It is noteworthy that in none of these reactions was any formation of the β-lactone product seen. The complexity of these reactions in the presence of a Brønsted base led to the examination of alternate sources of the pendant carboxylate nucleophile.

SCHEME 7



1.2. Selenocyclization of Ester Derivatives of 10. To avoid the problems of carboxylate salt insolubility, HCl generation, and the irreproducible burst of product formation at low temperature, a more soluble nonacidic precursor was sought. The cyclization of *n*-butylalkenamide substrates to afford selenoimidates through attack of the carbonyl oxygen has been reported.[33] Accordingly, (*E*)-*N*-butyl-4-phenyl-3-butenamide was prepared, and its reactions with both benzeneselenenyl chloride and bromide were examined. Unfortunately, no reaction was

(27) Hoye, T. R.; Richardson, W. S. *J. Org. Chem.* **1989**, *54*, 688−693.

(28) Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Synlett* **2001**, 1767−1771.

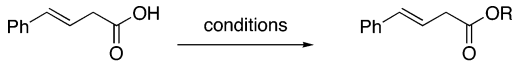
(29) This phenomenon was mainly a problem with the selenoetherification reaction.

(30) We were not able to quantify the amount of product formed by the in-situ IR monitoring. The amount varied from run to run between ca. 10 and 25%.

observed under a wide range of conditions, not even the formation of the β-halo selenide.

Our attention next turned to the use of silyl esters as cyclization precursors in view of their solubility and the fact that the chlorosilane generated would be an innocuous byproduct. To the best of our knowledge, the use of silyl esters in selenocyclization is unprecedented. Thus, from carboxylic acid **10**, a series of five silyl esters with varying steric demand was prepared in 68−94% yield as illustrated in Table 1. We also prepared the methyl (**15g**) and neopentyl (**15h**) ester derivatives as silyl ester surrogates in 94 and 81% yield, respectively.

TABLE 1. Preparation of Ester Derivatives of Unsaturated Acid 10



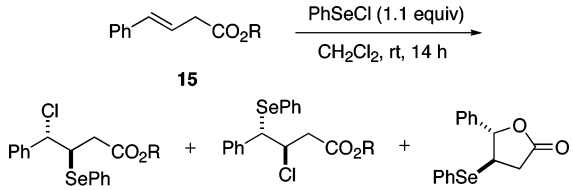
10 **15**

entry	R	conditions	product	yield,[a] %
1	TMS	HMDS, cat. saccharin, CH_2Cl_2, Δ	**15b**	82
2	TES	Et_3SiOAc, Δ, vacuum	**15c**	68
3	TBS	TBSCl, imidazole, DMF, rt	**15d**	94
4	TIPS	TIPSCl, imidazole, DMF, rt	**15e**	72
5	TBDPS	TBDPSCl, imidazole, DMF, rt	**15f**	71
6	Me	CH_2N_2, Et_2O, −75 °C to rt	**15g**	94
7	CH_2*t*-Bu	*t*-$BuCH_2OH$, EDC, DMAP, CH_2Cl_2, rt	**15h**	81

[a] Yield of analytically pure material obtained after bulb-to-bulb distillation.

The silyl ester substrates were all subjected to standard reaction conditions to probe their reactivity toward benzeneselenenyl chloride (1.1 equiv of PhSeCl, CH_2Cl_2, 14 h, rt). The results from these reactions are compiled in Table 2. The ^{1}H NMR spectra of the crude reaction mixtures showed that the starting silyl ester, selenolactone **11**, and both the Markovnikov **16a** and anti-Markovnikov **17a** adducts were present. In addition, IR spectroscopic analysis showed the presence of both the lactone product **11** (1787 cm^{-1}) and a species shifted a few wavenumbers (2−5 cm^{-1})[34] from the silyl ester starting materials. These were assigned as the Markovnikov and anti-Markovnikov β-chloro selenide adducts **16a** and **17a**. Again, no evidence for β-lactone formation was gleaned from either NMR or IR spectroscopic analysis. Interestingly, the rate of conversion of silyl esters into selenolactone **11** correlates with the increasing bulk of the silyl ester substituent as the substituent is varied. Both the TMS and TES esters (entries 1 and 2, Table 2) underwent rapid and complete reaction, affording selenolactone **11**. In both of these reactions, a small amount of an unidentifiable byproduct (∼10%) was observed (vide infra). For the three other silyl esters, none of the reactions went to completion and the conversion decreased in the order TBS > TIPS ≈ TBDPS, following the steric demand of the silyl ester. Interestingly, for all three of these entries, the reaction mixture contained a greater amount of anti-Markovnikov adduct **17** than Markovnikov adduct **16**. Chromatographic purification of each of these reaction mixtures yielded only selenolactone **11** and no trace of either **16** or **17**. The yields obtained in entries 3−5 indicate that cyclization of adducts **16** and **17** must have occurred upon exposure to silica gel (vide supra).[25]

TABLE 2. Reaction of Ester Derivatives of 10 with PhSeCl



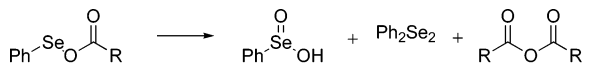
entry	R	conversion,[a] %	series	**16**,[b] %	**17**,[c] %	**11**,[d] %	yield,[e] %
1	TMS (**15b**)	100	**b**	0	0	100	77
2	TES (**15c**)	100	**c**	0	0	100	72
3	TBS (**15d**)	97	**d**	6	25	66	73
4	TIPS (**15e**)	85	**e**	16	46	23	65
5	TBDPS (**15f**)	70	**f**	10	43	17	48
6[f]	Me (**15g**)	92	**g**	52	40	0	
7[g]	*t*-$BuCH_2$ (**15h**)	72	**h**	32	40	0	

[a] Total conversion of silyl ester starting material into **16**, **17**, and **11** as determined by ^{1}H NMR. [b] Integration of the C(4) doublet at ∼5.20 ppm. [c] Integration of the C(3) doublet at ∼4.55 ppm. [d] Integration of the C(3) quartet at 3.75 ppm. [e] Isolated yield of chromatographically homogeneous **11**. [f] Reaction was run for 2 h at rt. [g] Reaction was run for 3 h at rt.

Study of these reactions by in situ React-IR spectroscopy showed that consumption of the TMS ester was complete within 6 min at room temperature. In contrast, the corresponding TBS ester reacted only slowly at room temperature and was less than 50% complete at the 6 h time point. Once more, only the γ-lactone product could be observed. To correlate the formation of the Markovnikov and anti-Markovnikov adducts and to obtain proof of structure, the reactions of ester substrates **15g** and **15h** with benzeneselenenyl chloride were examined (Table 2, entries 6 and 7). Reactions of these substrates proceeded more slowly than the corresponding silyl esters and in both cases, mixtures of **16** and **17** were obtained. Unfortunately, the adducts from these reactions could not be isolated. Distillation or chromatographic purification of the mixture derived from either methyl ester **15g** or neopentyl ester **15h** led only to cyclization and isolation of selenolactone **11**.[35] Fortunately, the adducts obtained from these reactions could be characterized by 2D-NMR techniques (COSY, HMQC and HMBC) to assign the structures of both isomers, and composition of matter was secured by HRMS measurement of the mixture of **16** and **17** adducts (see the Supporting Information).

1.3. VT-NMR Analysis of the Selenocyclization of 10 and Its Derivatives. To obtain a more accurate measure of the rate of the cyclization process, a series of VT-NMR experiments with acid **10** and its ester derivatives was performed. These experiments were all conducted as follows: a CD_2Cl_2 solution

(31) For example, the species illustrated in the following scheme, prepared in situ from PhSeCl and the anion of the corresponding carboxylic acid, disproportionated as shown. This illustrates that steric bulk has no effect upon attenuating this process.



R = Me, adamantyl, Ph, 2,4,6-*i*-Pr-Ph

(32) (a) Bell, P. A.; Hogg, D. R.; Robertson, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1246−1248. (b) Putnam, R. E.; Sharkey, W. H. *J. Am. Chem. Soc.* **1957**, *79*, 6526−6529.

(33) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1987**, *52*, 2018−2026.

(34) The IR spectroscopic data for all of these reactions is reported in the Supporting Information.

(35) The selenocyclization reaction of ester substrates has previously been observed on exposure to silica gel: Garratt, D. G.; Ryan, D. M.; Kabo, A. *Can. J. Chem.* **1980**, *58*, 2329−2339.

of benzeneselenenyl halide was cooled to −70 °C, whereupon a solution of the required alkene in CD_2Cl_2 was added such that the overall concentration was 0.2 M in alkene (the same concentration as used in all the preparative runs). The ^1H NMR and ^{13}C NMR spectra were then recorded at −70 °C, and then following a standard protocol of 30 min at each temperature (−50, −20, 0, and +20 °C), the ^1H NMR spectra were recorded. The data from these experiments (Scheme 8) are collected in Tables 3−6.

SCHEME 8

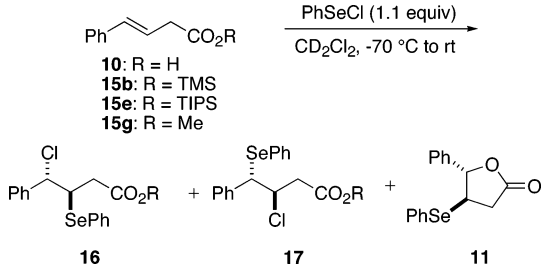


TABLE 3. VT-NMR Experiment with 10

entry	*T*, °C[a]	conversion,[b] %	**16a**,[c] %	**17a**,[d] %	**11**,[e] %
1	−70	100	100	0	0
2	−50	100	100	0	0
3	−20	98	50	0	48
4	0	98	21	1	79
5	20[f]	100	0	<1	99

[a] The sample was held for 30 min at each temperature before recording the NMR spectra. [b] Total conversion of carboxylic acid **10** into **16a**, **17a**, and **11** as determined by ^1H NMR analysis. [c] Integration of the C(4) doublet at 5.03 ppm. [d] Integration of the C(4) doublet at 4.51 ppm. [e] Integration of the C(3) quartet at 3.75 ppm. [f] The sample was held at 20 °C for 12 h before recording the NMR spectra.

TABLE 4. VT-NMR Experiment with 15b

entry	*T*,[a] °C	conversion,[b] %	**16b**,[c] %	**17b**,[d] %	**11**,[e] %
1	−70	100	100	0	0
2	−50	100	100	0	0
3	−20	100	72	0	28
4	0	100	7	<1	93
5	20[f]	100	<1	<1	99

[a] The sample was held for 30 min at each temperature before recording the NMR spectra. [b] Total conversion of TMS ester **15b** into **16b**, **17b**, and **11** as determined by ^1H NMR analysis. [c] Integration of the C(4) doublet at 5.03 ppm. [d] Integration of the C(4) doublet at 4.51 ppm. [e] Integration of the C(3) quartet at 3.75 ppm. [f] The sample was held at 20 °C for 12 h before recording the NMR spectra.

TABLE 5. VT-NMR Experiment with 15e

entry	*T*,[a] °C	conversion,[b] %	**16e**,[c] %	**17e**,[d] %	**11**,[e] %
1	−70	100	100	0	0
2	−50	100	100	0	0
3	−20	97	97	0	0
4	0	94	92	2	0
5	20[f]	90	14	35	41

[a] The sample was held for 30 min at each temperature before recording the NMR spectra. [b] Total conversion of TIPS ester **15e** into **16e**, **17e**, and **11** as determined by ^1H NMR analysis. [c] Integration of the C(4) doublet at 5.03 ppm. [d] Integration of the C(4) doublet at 4.51 ppm. [e] Integration of the C(3) quartet at 3.75 ppm. [f] The sample was held at 20 °C for 12 h before recording the NMR spectra.

For 4-phenyl-3-butenoic acid **10** (Table 3), complete formation of the Markovnikov adduct **16a** was observed as a single isomer at low temperature (Figure 1); at this temperature, none

TABLE 6. VT-NMR Experiment with 15g

entry	*T*,[a] °C	conversion,[b] %	**16g**,[c] %	**17g**,[d] %	**11**,[e] %
1	−70	100	100	0	0
2	−50	100	100	0	0
3	−20	97	97	0	0
4	0	97	95	2	0
5	20[f]	89	26	63	<1

[a] The sample was held for 30 min at each temperature before recording the NMR spectra. [b] Total conversion of methyl ester **15g** into **16g**, **17g**, and **11** as determined by ^1H NMR analysis. [c] Integration of the C(4) doublet at 5.03 ppm. [d] Integration of the C(4) doublet at 4.51 ppm. [e] Integration of the C(3) quartet at 3.75 ppm. [f] The sample was held at 20 °C for 12 h before recording the NMR spectra.

of the corresponding anti-Markovnikov **17a** was found. This behavior was consistent for all of the ester derivatives examined with benzeneselenenyl chloride as the electrophile. Upon warming the reaction mixtures, the Markovnikov adducts **16a** transformed via two competing processes: (1) isomerization of the Markovnikov adduct **16a** into the anti-Markovnikov adduct **17a** and (2) cyclization of these isomers into the selenolactone product **11**. Depending upon the steric demand of the ester group, different rates of change were observed for different substrates. For the carboxylic acid **10** (Table 3) and its TMS ester **15b** (Table 4), cyclization occurs much faster than does isomerization upon warming. Thus, at −20 °C, large amounts of the lactone product **11** are observed. Upon warming to 20 °C almost complete conversion into the lactone **11** occurs. The small amount of β-chloro selenide remaining is evenly distributed between the **16b** and **17b**. In contrast, the bulkier TIPS ester **15e** (Table 5) does not isomerize or cyclize until the temperature reaches 0 °C and not until the temperature reaches 20 °C is the same composition obtained as in the preparative run (Table 2, entry 4). Certainly the most interesting observation with TIPS ester **15e** is that formation of the β-chloro selenide is reversible; at −70 °C, all of the starting material is consumed and formation of **16e** observed. However, upon warming, significant amounts of starting material reappear (10% at 20 °C) in the NMR spectrum. Methyl ester **15g** clearly illustrates the trend toward isomerization and equilibration in the formation of β-chloro selenide adducts (Table 6). Upon warming, the reaction mixture **16g** (which is formed exclusively at −70 °C) undergoes isomerization into **17g**. At room temperature, it is evident that the anti-Markovnikov adduct **17g** is preferred in the mixture at equilibrium.

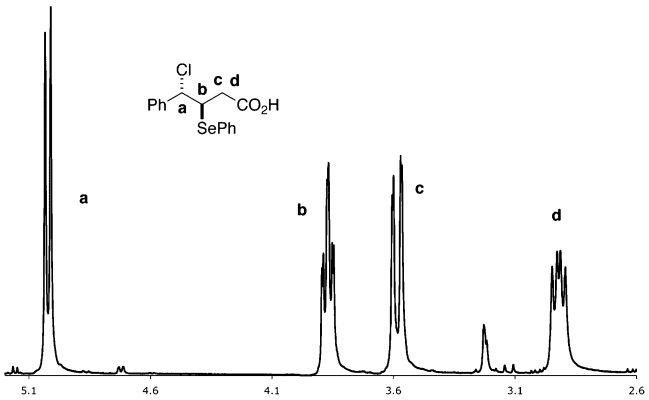
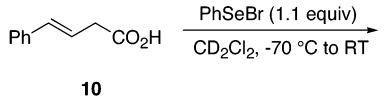


FIGURE 1. ^1H NMR spectrum of the Markovnikov adduct **16a** recorded at −70 °C in CD_2Cl_2.

The most striking illustration of the reversibility of the addition was seen in the reaction of carboxylic acid **10** with

benzeneselenenyl *bromide* (Table 7). At low temperature (−70 °C), the adduct **18a** (88%) and the unreacted acid **10** (12%) were detected by ^{1}H NMR analysis. Upon warming the mixture, the expected cyclization was not observed but rather a reverse of the initial addition and the increasing reappearance of acid **10** and benzeneselenenyl bromide! This result was reproducible, and no selenolactone **11** was isolated from a preparative reaction after 18 h at room temperature.

TABLE 7. VT-NMR Experiment with Acid 10 and PhSeBr



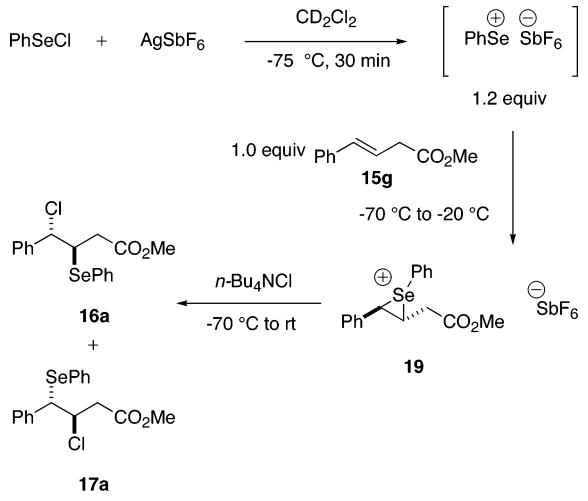
entry	*T*,[a] °C	conversion,[b] %	**18a**,[c] %	**19a**,[d] %	**11**, %
1	−70	88	88	0	0
2	−50	68	65	3	0
3	−20	37	28	9	0
4	0	23	11.5	11.5	0
5	20[e]	low	ND[f]	ND[f]	0

[a] The sample was held for 30 min at each temperature before recording the NMR spectra. [b] Total conversion of carboxylic acid **10** into **18a**, **19a**, and **11** as determined by ^{1}H NMR analysis. [c] Integration of the C(4) doublet at 5.12 ppm. [d] Integration of the C(4) doublet at 4.57 ppm. [e] The sample was held at 20 °C for 12 h before recording the NMR spectra. [f] Not determined due to complexity of the NMR spectra.

1.4. Formation of the Intermediate Seleniranium Ion. The successful demonstration of the intermediacy of chloroselenylation adducts **16a** and **17a** in the selenocyclization reaction prompted experiments to identify the putative seleniranium ion that is responsible for their formation, interconversion, and capture. Seleniranium ions, although frequently postulated, have never been observed in selenocyclization reactions. Thus, the intention was to generate such a species in situ and demonstrate its transformation into the corresponding β-chloro selenide. Following the method of Garratt and Schmid,[19] benzeneselenenyl hexafluoroantimonate (generated in situ from the metathesis reaction of $AgSbF_6$ with PhSeBr) was added by syringe to a dry NMR tube cooled to −70 °C under an argon atmosphere and then was treated with methyl ester **15g**. This reaction led to the formation of a single species that is consistent with the desired seleniranium salt **19** (Table 8). The ^{1}H, ^{13}C, and ^{19}F NMR spectra of this adduct were recorded at −70, −50, and −20 °C. Figure 2 illustrates the ^{1}H NMR spectrum of this species in CD_2Cl_2 at −20 °C. Interestingly, only a single diastereomer was formed from the addition even though two isomers might be expected from the slow inversion of the selenium center. Significant broadening was observed in both the ^{1}H and ^{13}C spectra, and this is presumably indicative of a dynamic process occurring. Furthermore, the ^{19}F NMR signal was very broad and indicative of a nonsymmetrical ion pair. When this species was treated with a solution of 1.2 equiv of *n*-Bu_4NCl in CD_2Cl_2 the initial signals (shown in Figure 2) disappeared and a 5:1 mixture of Markovnikov adduct chloroselenylation adduct **16g** and starting material **16g** was formed.

1.5. Selenocyclization Crossover Experiments. 1.5.1. Analysis. The results described in the previous sections suggest that

TABLE 8. Formation and Trapping of Seleniranium Salt 19



entry	*T*, °C	conversion,[d] %	**19**,[e] %	**16g**,[f] %	**17g**,[g] %
1	−70[a]	100	100	0	0
2	−50[a]	100	100	0	0
3	−20[a]	100	100	0	0
recooled to −70 °C then added 1.2 equiv *n*-Bu_4NCl in CD_2Cl_2					
4	−70[b]	83	0	83	0
5	−50[b]	83	0	83	0
6	−20[b]	83	0	83	0
7	0[b]	53	0	52	<1
8	20[c]	ND[h]	ND[h]	ND[h]	ND[h]

[a] The sample was held for 10 min at this temperature before recording the NMR spectra. [b] The sample was held for 20 min at this temperature before recording the NMR spectra. [c] The sample was held for 12 h at this temperature before recording the NMR spectra. [d] Total conversion of methyl ester **15g** into **19**, **16g** and **17g** as determined by ^{1}H NMR analysis. [e] Integration of the C(4) doublet at 6.58 ppm. [f] Integration of the C(4) doublet at 5.10 ppm. [g] Integration of the C(4) doublet at 4.55 ppm. [h] Because of the complexity of the NMR spectrum, these numbers were not determined.

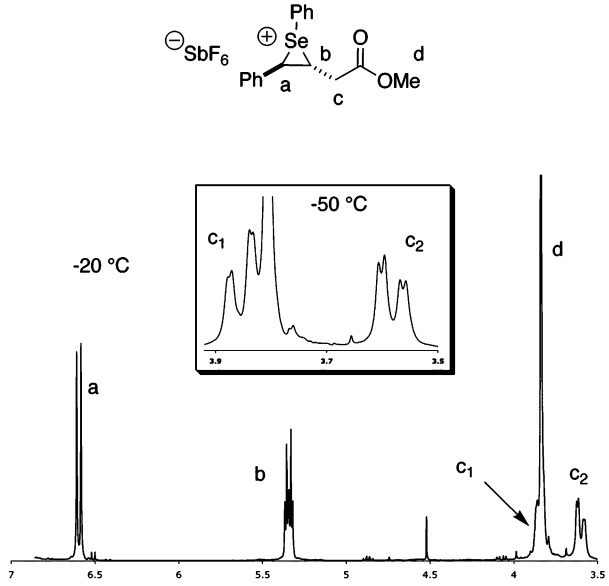
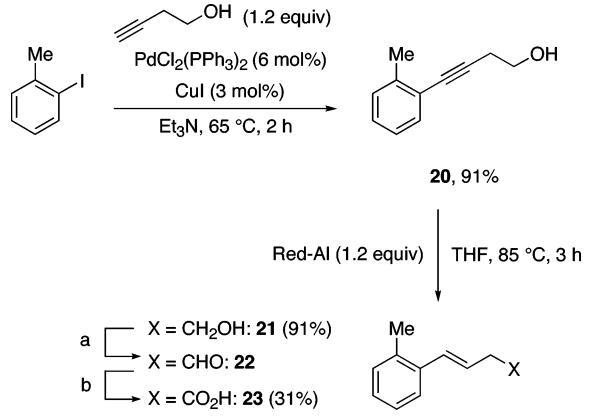


FIGURE 2. ^{1}H NMR spectrum of the seleniranium species **19** in CD_2Cl_2.

adduct formation is clearly reversible and that isomerization of the Markovnikov and anti-Markovnikov chloroselenylation adducts **16a** and **17a** and selenocyclization are competitive processes depending upon the substrate. This observation leads

naturally to question which of the steps are reversible. To probe this question, a crossover experiment was devised wherein the initially formed adduct **16a** would be treated with an equimolar amount of a closely related β,γ-unsaturated acid and the progress of any exchange would be monitored by ^{1}H NMR analysis.[36] 4-(2-Methylphenyl)-3-butenoic acid **23** (Scheme 9) was chosen as the crossover substrate because there is no significant steric or electronic difference between this substrate and **10** and the 2-methyl group provides a label to decipher the results by ^{1}H NMR spectroscopy.

SCHEME 9[a]

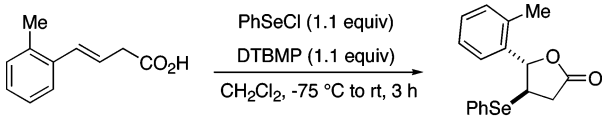


[a] Conditions: (a) DMP (1.5 equiv), CH_2Cl_2, rt, 5 h; (b) $NaClO_2$ (3.0 equiv), KH_2PO_4 (3.0 equiv), 12:5:3 *t*-BuOH/H_2O/2-methyl-2-butene, rt, 15 h.

1.5.2. Preparation of Crossover Substrate 23. The required acid **23** was prepared by the four-step reaction sequence shown in Scheme 9. Sonogashira coupling of 3-butyn-1-ol with 2-tolyl iodide was accomplished in 91% yield to afford alkyne **20**. This alkyne was then selectively reduced with Red-Al to afford alkene (*E*)-**21** in >99/<1 diastereoselectivity and 80% yield. The oxidation of the primary alcohol to the required carboxylic acid proved to be troublesome initially but could be achieved successfully by a stepwise oxidation sequence. Thus, Dess−Martin periodinane oxidation of **21** provided the unstable β,δ-enal **22** that was immediately oxidized to the required carboxylic acid **23** by the action of sodium chlorite in the presence of 3-methyl-2-butene as a chlorine scavenger. This two-step transformation could be achieved in 31% yield to obtain analytically pure, crystalline material.

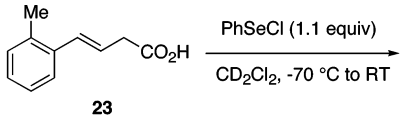
1.5.3. Control Experiments with Acid 23. With this material in hand, the preparative selenolactonization was performed under standard conditions to yield the selenolactone product (±)-(4*RS*,5*SR*)-dihydro-4-(phenylseleno)-5-(2-methylphenyl)furan-2(3*H*)-one **24** in 81% yield (Scheme 10). A control reaction was also performed with VT-NMR analysis to enable assignment of the chloroselenylation Markovnikov and anti-Markovnikov adducts **25a** and **26a** (Table 9). These results are similar to those obtained with the styryl analogue (Table 2), except it is clear this 2-tolyl substrate is slightly more reactive. This is reflected in the observation of some isomerization and cyclization already at −50 °C compared to the corresponding styryl analogue for which no reaction occurs until the temperature reaches −20 °C.

SCHEME 10

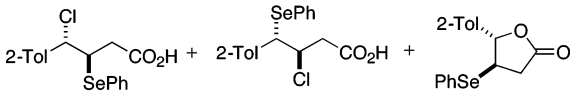


23 **24**, 81%

TABLE 9. VT-NMR Experiment with Acid 23



23



25a **26a** **24**

entry	*T*,[a] °C	conversion,[b] %	**25a**,[c] %	**26a**,[d] %	**24**,[e] %
1	−70	100	100	0	0
2	−50	100	94	0	6
3	−20	100	69	0	31
4	0	100	19	9	72
5	20[f]	100	6	13	81

[a] The sample was held for 30 min at each temperature before recording the NMR spectra. [b] Total conversion of carboxylic acid **23** into **25a**, **26a**, and **24** as determined by ^{1}H NMR analysis. [c] Integration of the C(3) multiplet at 3.90 ppm. [d] Integration of the C(4) doublet at 4.71 ppm. [e] Integration of the C(4) doublet at 5.65 ppm. [f] The sample was held at 20 °C for 12 h before recording the NMR spectra.

The initial crossover experiment was executed by mixing 1.1 equiv of benzeneselenenyl chloride with 1 equiv of 4-phenyl-3-butenoic acid **10** at −70 °C, observing complete formation of adduct **16a** by ^{1}H NMR analysis, adding an equimolar amount of 4-(2-methylphenyl)-3-butenoic acid **23** and observing the effect of warming the mixture through the standard warming cycle (−70, −50, −20, 0, and +20 °C) (Scheme 11). To ensure consistency, the same experiment was repeated in the other direction with the two acids reversed. The results of these experiments are shown in Tables 10 and 11. Figure 3 illustrates the alkenic region for the data collected in Table 8. The data collected from these two experiments show that in either case little or no-crossover occurs at −70 °C, and that crossover begins to occur at −50 °C. In the case of the tolyl substrate (Table 11), the amount of crossover is greater in both cases than that observed with the styryl substrate (Table 10). At −20 °C, almost complete equilibration is observed with an approximate 1:1 ratio of the two acids slightly favoring the tolyl substrate **23**. At the equilibrium position (20 °C, 14 h), it is evident that the relative amounts of the two lactone products **11** and **24** and also the two starting materials **10** and **23** are nearly equal. The differences in these numbers may arise from the excess of PhSeCl used in the experiment and the small inherent error in the NMR integration. Nevertheless, the observation that crossover occurs between the two acid substrates which is competitive with the processes of cyclization and isomerization at −20 °C unambiguously establishes the reversibility of the selenylation.

(36) Although Clive's crossover experiment (Scheme 2) indicates that benzeneselenenyl chloride exchange can occur between a simple alkene and a β,γ-unsaturated acid to afford a selenolactone product, we felt this experiment was unsatisfactory for our purposes for two reasons. First, this experiment is inherently biased because of the thermodynamic driving force provided by the formation of the lactone in relation to simple adduct formation. Second, we desired a crossover experiment that approximated the kinetic reaction conditions used in the VT-NMR experiments.

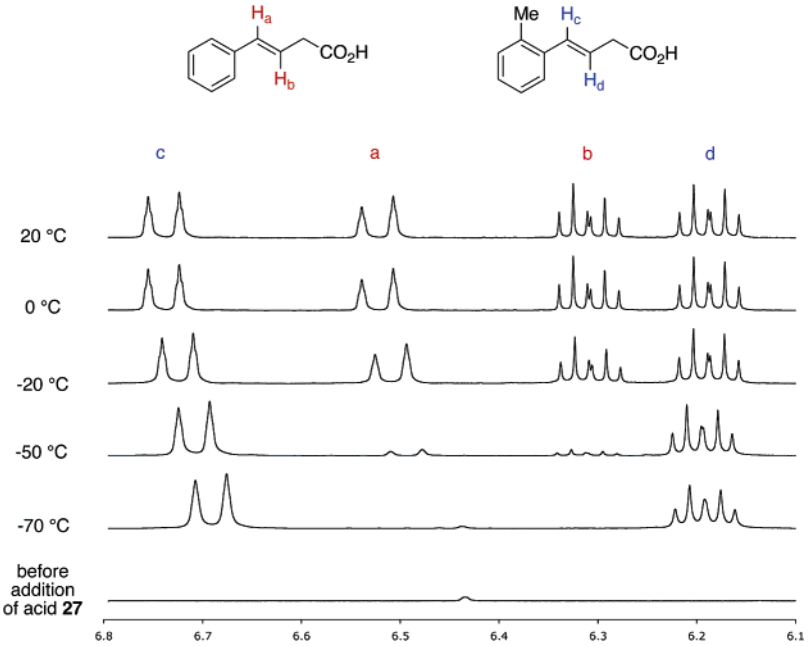


FIGURE 3. Alkenic region for VT-NMR crossover experiment shown in Table 8.

SCHEME 11

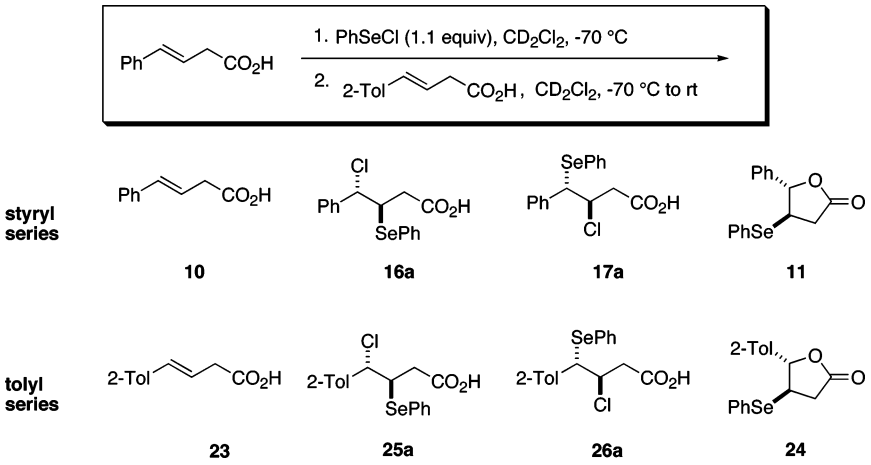


TABLE 10. Crossover Experiment Commencing with Acid 10

		styryl series,[a] %				tolyl series,[b] %				crossover,[c] %
entry	*T*,[d] °C	**10**[e]	**16a**[f]	**17a**[g]	**11**[h]	**23**[i]	**25a**[j]	**26a**[k]	**24**[l]	styryl → tolyl
1	−70	0	100	0	0	100	0	0	0	0
2	−50	11	89	0	0	90	10	0	0	10
3	−20	39	29	0	32	44	28	0	28	56
4	0	48	25	0	26	44	19	0	37	56
5	20[m]	40	0	0	60	48	0	0	52	52

[a] Styryl series refers to the four components (**10**, **16a**, **17a**, and **11**) derived from carboxylic acid **10** that sum to 100%. [b] Tolyl series refers to the four components (**23**, **25a**, **26a**, and **24**) derived from carboxylic acid **23** that sum to 100%. [c] Crossover refers to the % of crossover between the styryl and tolyl series as determined by integration of the peaks in the tolyl series. [d] The sample was held for 30 min at each temperature before recording the NMR spectra. [e] Integration of the C(4) doublet at 6.54 ppm. [f] Integration of the C(4) doublet at 5.03 ppm. [g] Integration of the C(4) doublet at 4.51 ppm. [h] Integration of the C(3) quartet at 3.75 ppm. [i] Integration of the C(4) doublet at 6.68 ppm. [j] Integration of the C(4) doublet at 5.40 ppm. [k] Integration of the C(4) doublet at 4.71 ppm. [l] Integration of the C(4) doublet at 5.65 ppm. [m] The sample was held at 20 °C for 12 h before recording the NMR spectra.

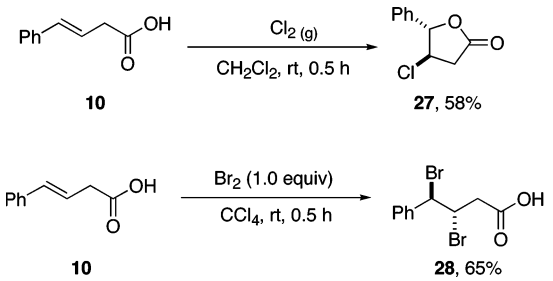
TABLE 11. Crossover Experiment Commencing with Acid 23

		styryl series,[a] %				tolyl series,[b] %				crossover,[c] %
entry	*T*, °C[d]	**10**[e]	**16a**[f]	**17a**[g]	**11**[h]	**23**[i]	**25a**[j]	**26a**[k]	**24**[l]	tolyl → styryl
1	−70	89	11	0	0	5	95	0	0	5
2	−50	60	40	0	0	22	78	0	0	22
3	−20	32	37	0	31	39	34	0	27	39
4	0	33	18	0	49	43	18	0	39	43
5	20[m]	36	0	0	64	45	0	0	55	45

[a] Styryl series refers to the four components (**10**, **16a**, **17a**, and **11**) derived from carboxylic acid **10** that sum to 100%. [b] Tolyl series refers to the four components (**23**, **25a**, **26a**, and **24**) derived from carboxylic acid **23** that sum to 100%. [c] Crossover refers to the % of crossover between the styryl and tolyl series as determined by integration of the peaks in the tolyl series. [d] The sample was held for 30 min at each temperature before recording the NMR spectra. [e] Integration of the C(4) doublet at 6.54 ppm. [f] Integration of the C(4) doublet at 5.03 ppm. [g] Integration of the C(4) doublet at 4.51 ppm. [h] Integration of the C(3) quartet at 3.75 ppm. [i] Integration of the C(4) doublet at 6.68 ppm. [j] Integration of the C(4) doublet at 5.40 ppm. [k] Integration of the C(4) doublet at 4.71 ppm. [l] Integration of the C(4) doublet at 5.65 ppm. [m] The sample was held at 20 °C for 12 h before recording the NMR spectra.

1.6. Halolactonization. When benzeneselenenyl chloride was used as the electrophile, the consistent formation of 8−15% of an unidentified adduct was observed in the NMR experiments. The NMR data indicated that this species is an alkene adduct because of the clear ABX_2 pattern observed and the presence of two diasterotopic and geminally coupled X protons. Moreover, this species does not contain selenium,[37] and the chemical shifts of the A and B protons are consistent with the presence of two electronegative substituents. This species might have resulted from chlorination, but this conclusion could be experimentally ruled this out by the experiments illustrated in Scheme 12.

SCHEME 12



Bubbling chlorine gas through a methylene chloride solution of **10** resulted in spontaneous chlorolactonization[38] to afford chloro lactone **27**, with no evidence for the formation of an intermediate dichloride adduct. Even at −70 °C in CD_2Cl_2, chlorolactonization was found to be rapid and the corresponding dichloride adduct could not be observed. In contrast, when acid **10** is treated with bromine, the dibromide adduct **28** was formed. This confirms the observation by Fittig and co-workers that to effect bromolactonization the dibromide adduct must be boiled in water.[39] This divergent behavior is a key indicator of the importance of the halide counterion in cyclization reactions (vide infra).

The unknown species formed in the NMR experiments is stable up to −20 °C, but above this temperature it cyclizes to a second unknown species that is consistent with a γ-lactone that contains heteroatom substituents in both the 3 and 4-positions. The NMR data demonstrates that this product is not chlorolactone **27**, and upon purification no trace of this species can be detected. The NMR data is consistent with oxygen substituents in both the 3- and 4-positions, but since this species is not a dimer of the starting material, the identity of the species remains obscure.

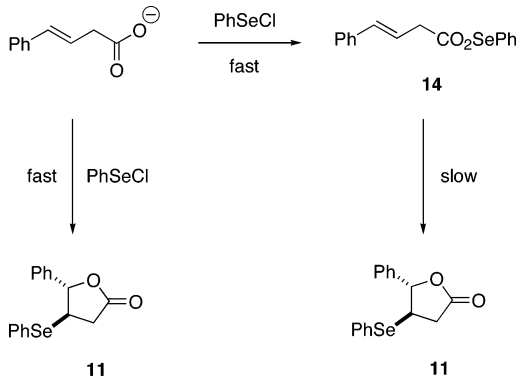
Discussion

1. Summary. The results obtained clearly indicate the reversibility of some of the key steps and identify the intermediates involved on the reaction pathway. To construct a mechanism for the overall transformation it is necessary to discuss each series of experiments in turn and highlight their role in formulating a mechanism.

2. The Role of External Base. The function of external base in these selenocyclization reactions was initially viewed to neutralize the HCl generated upon cyclization. Interestingly, although the asymmetric selenocyclizations reported by Wirth and Tiecco construct similar substrates, none of these reactions are run in the presence of base, despite the generation of triflic acid in the reaction.[26d,e] The nature of the base in these reactions also proved to be important. The observation that only the very hindered base DTBMP did not attenuate the rate of cyclization is consistent with an intermolecular coordination between the amines and the selenium center. Presumably, sterically unencumbered bases (or their ammonium salts) compete with the alkene nucleophile to retard the desired cyclization reaction.

The initial burst of product observed by both in situ React-IR and NMR spectroscopy is consistent with the formation of an intermediate selenenyl carboxylate species **14** that subsequently undergoes intramolecular selenocyclization upon warming to ambient temperature. However, there is no definitive evidence to support this argument. Most likely upon addition of the acid substrate to the basic reaction mixture, deprotonation occurs to afford a carboxylate nucleophile. Then, two competitive steps result in the formation of the species observed by VT-NMR (Scheme 13); selenocyclization and nucleophilic displacement of chloride by the carboxylate at the selenium center.[40] Nevertheless, the postulated formation of the selenenyl carboxylate **14** explains the slower rate of consumption of **10** in the presence of base and the observation of unreacted alkene at −70 °C in the VT NMR experiment, whereas the alkene is consumed in absence of base. Thus, it appears that the base is an unnecessary complication.

SCHEME 13



3. β-Halo Selenide Adducts: Formation and Isomerization. The results from VT-NMR experiments unambiguously demonstrate that the formation of a chloroselenylation adduct is the first step in the cyclization reaction. Furthermore, the intermediacy of a seleniranium ion was substantiated by observation of its subsequent conversion into the Markovnikov adduct **16a** upon addition of chloride (Scheme 14). An interesting aspect of the species **19** was the identification of a single diastereomer in its NMR spectrum. As noted previously, based up the slow inversion of the selenium center, the formation of two diastereomers would be expected. Selenium(II) derivatives are known to undergo intramolecular coordination of an *n*-type lone pair into the PhSe-X σ^* orbital;[41] thus, a possible explanation for this observation is that coordination of the methyl ester carbonyl group to selenium results in the formation of a single diastereomer. Nevertheless, the transformation of

(37) None of the signals in the ^{1}H NMR spectrum showed the characteristic ^{77}Se satellites.

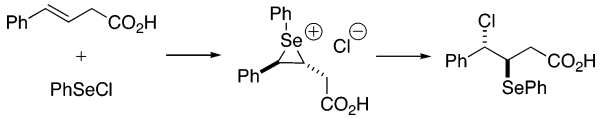
(38) Woodward, R. B.; Singh, G. *J. Am. Chem. Soc.* **1950**, *72*, 5351−5352.

(39) Fittig, R.; Obermuller, P.; Schiffer, C. *Liebigs Ann. Chem.* **1892**, *268*, 71.

(40) The formation of a selenenyl carboxylate is inconsistent with the results of Garratt and Kabo who demonstrated that chloride displacement at the selenium is orders of magnitude faster with an alkene nucleophile than with an alcohol nucleophile (albeit in methanolic solution).[22a]

19 into **16a** upon addition of chloride demonstrates that this species must be a seleniranium ion and an intermediate on the reaction pathway.

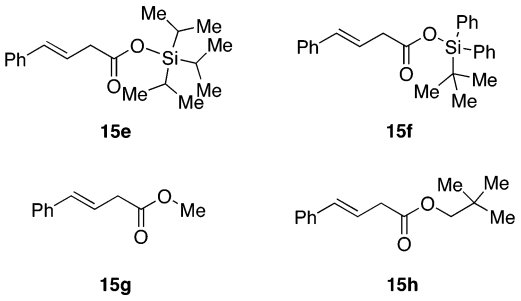
SCHEME 14



Previous reports have shown[11,15] that, in certain cases, chloroselenylation adducts were formed and that cyclization proceeds only with subsequent assistance with, e.g., silica gel or a base. In these cases, no evidence was presented for the formation of intermediate β-chloro selenide adducts prior to the formation of the selenolactone product. From the data presented above, we conclude that the initial step in *all* selenocyclization reactions with benzeneselenenyl chloride (not just those in which cyclization is slow, e.g., Scheme 4, eq a) is formation of a β-chloro selenide adduct. Although the inability to purify the β-halo selenide adducts was disappointing, this is perhaps not surprising given the previous unsuccessful attempts to isolate these adducts.[17,25,35]

The observation that a single (Markovnikov) adduct is formed at low temperature which then isomerizes to the anti-Markovnikov adduct is well documented.[23−25] In all of the experiments undertaken it is evident that exclusive formation of the Markovnikov adduct occurs at −70 °C and that isomerization occurs only upon warming. The data obtained from the VT-NMR experiments afford an insight into the relative rate of isomerization. With carboxylic acids **10** and **23**, cyclization is much faster than isomerization. However, in the substrates wherein cyclization is either slow (TIPS ester **15e** and TBDPS ester **15f**) or precluded (methyl ester **15g** and neopentyl ester **15h**), considerable amounts of anti-Markovnikov adduct are observed. Upon standing, a continuing enrichment of the mixture toward the anti-Markovnikov adduct was seen, but never to exclusivity.

CHART 2



15e **15f** **15g** **15h**

The VT-NMR data show that regardless of the steric bulk of the silyl group, complete adduct formation occurs even at low temperature. However, this does not translate into complete cyclization upon warming because the steric bulk of ester substituent does influence the rate of cyclization. In the case of small substituents, e.g., TMS or TES, cyclization is rapid upon warming and thus out competes the constitutional isomerization. However, when the silyl substituent is increased to TIPS, both isomerization and cyclization are slowed. Perhaps the best illustration of the relative rate of isomerization is to consider the percent fraction of each of the total chloroselenylation adducts that remains as the Markovnikov adduct after 14 h at room temperature (Table 1). For the TBS, TIPS, and TBDPS examples, 19−25% of the total chloroselenylation adduct formed is the kinetic Markovnikov adduct. This suggests that, as is the case for the initial addition, steric bulk does not hinder isomerization significantly. In contrast, the effect of bulk upon the retardation of the rate of cyclization is clear from the decreased conversion in the ratio TMS ≈ TES > TBS > TIPS ≈ TBDPS.

4. Reversibility of the Chloroselenylation Addition Process. One of the most interesting facets of the chloroselenylation process is the ease of reversibility and the pronounced temperature dependence of the thermodynamics of the addition. This phenomenon results from closely matched contributions from both the enthalpic and entropic components of the Gibbs energy for this reaction ($\Delta G° = \Delta H° - T\Delta S°$). The reactivity of PhSeBr shows how delicate this balance is. Predominant (88%) adduct formation at −70 °C and then complete reversal in the equilibrium upon warming is indicative of the fact that both the change in enthalpy and entropy of reaction are negative and that the temperature is the controlling factor between the two closely balanced terms. It is noteworthy that incomplete formation of adducts (and subsequent cyclization) with ester and silyl ester substrates occurs for thermodynamic and not kinetic reasons; counterintuitive to what might be expected if only the end result were known.

The demonstration that the seleniranium ion is an intermediate in the formation of the β-chloro selenide gives valuable insight into how the processes of isomerization and reversibility must precede. Since the β-chloro selenide is formed via the seleniranium ion then the process of microscopic reversal to starting material must also occur through the same intermediate. Similarly, that the process of isomerization from the Markovnikov adduct into the anti-Markovnikov adduct must occur through the seleniranium ion. However, because starting material is observed before the onset of isomerization for some substrates, it is clear that reversal of addition through the seleniranium ion does not necessarily lead to isomerization.

The two VT-NMR crossover experiments give clear insight into the process of reversibility. Because products from both series are observed in both experiments, crossover must occur and therefore the initial addition is reversible. The question thus arises if cyclization is competitive with crossover under the reaction conditions. Because cyclization and crossover both begin to occur at the same temperature (Table 10, −20 °C; Table 11, −50 °C), it is clear that crossover, the reversion of adduct formation, is at least competitive with cyclization and indeed it may be faster. Because complete scrambling is observed to give the almost statistical mixture of products, it would appear that both of the processes occur at similar rates.

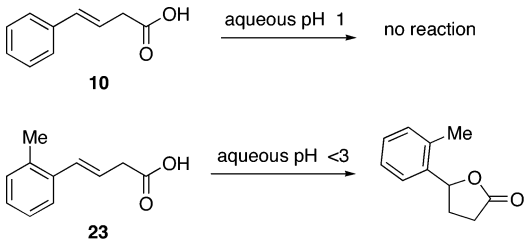
The conversion of the chloroselenylation adducts to the selenolactone must occur through the seleniranium ion (the same process that can leads to reversion and isomerization) and not through direct S_N2 displacement because the products are of *trans*-configuration. Therefore, taking all of the results into

(41) See, for example: (a) Iwaoka, M.; Komatsu, H.; Katsuda, T.; Tomoda, S. *J. Am. Chem. Soc.* **2004**, *126*, 5309−5317. (b) Panda, A.; Mugesh, G.; Singh, H. B.; Butcher, R. J. *Phosphorus, Sulfur Silicon* **2001**, *171*, 187−205. (c) Mugesh, G.; Singh, H. B.; Butcher, R. J. *Tetrahedron: Asymmetry*, **1999**, *10*, 237−242. (d) Mugesh, G.; Panda, A.; Singh, H. B.; Butcher, R. J. *Chem. Eur. J.* **1999**, 1411−1421. (e) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1996**, *118*, 8077−8084. (f) Barton, D. H. R.; Hall, M. B.; Lin, Z.; Parekh, S. I.; Reibenspies, J. *J. Am. Chem. Soc.* **1993**, *115*, 5056−5059.

consideration it is clear that several steps in the reaction are reversible and that the starting material, Markovnikov adduct, and anti-Markovnikov adduct are in equilibrium and interconvertible through the seleniranium ion. Furthermore, this means that the rate-determining step for the reaction must be either trapping of the seleniranium ion by the carboxylic acid or deprotonation of the carboxylic acid by the halide counterion (vide infra).

The crossover experiments also indicate that the tolyl substrate **23** is more reactive than the corresponding styryl substrate **10**. This outcome is a direct result of the steric effect of the *o*-methyl substituent. The steric interaction of this group and the alkene causes a torsion of the double bond and reduces conjugation with the aryl ring, thus rendering the alkene more reactive. This effect is reflected in the chemical shift change of the two alkenic protons relative to the styryl analogue. It also explains why the process of isomerization and cyclization are observed at −50 °C rather than at −20 °C when the experiment is performed with acid **23**. Presumably, this also explains the increased sensitivity of acid **23** to protiocyclization compared to acid **10**; whereas acid **10** is unchanged on exposure to pH 1 conditions, acid **23** undergoes acid-promoted cyclization below pH 3 (Scheme 15). In contrast, there is a thermodynamic preference for the formation of the lactone **11** compared to lactone **24**, expressed in the greater amount of lactone **11** formed in both series. This must be indicative of a steric interaction in the lactone product **24** created by the *ortho*-methyl group that destabilizes this product.

SCHEME 15

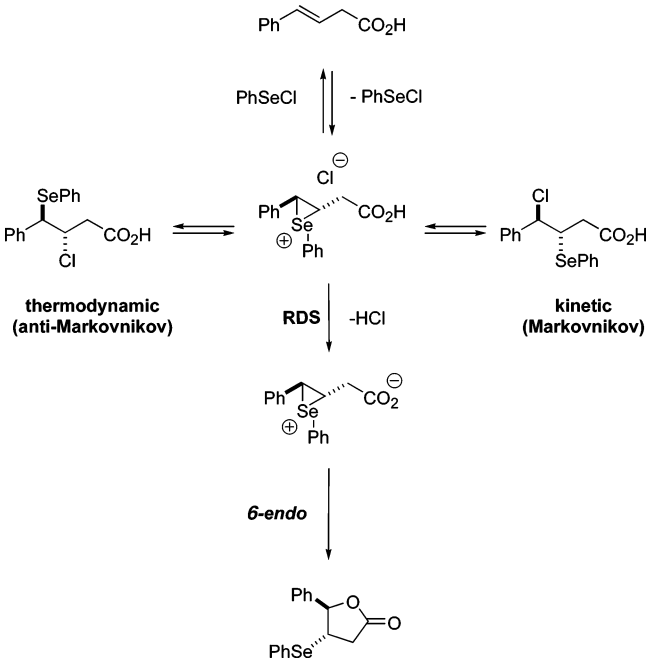


5. The Halide Counterion. Perhaps the most significant finding is the role of the halide in these selenocyclization reactions. In the absence of an external base, the halide counterion must fulfill this role. As noted above, deprotonation can occur before or after cyclization has taken place. These data indicate that the rate-limiting step must be either deprotonation by the halide counterion or cyclization. On the basis of the difference in reactivity observed with PhSeCl and PhSeBr, we suggest that deprotonation precedes cyclization and is the rate-determining step. If cyclization occurred before deprotonation then the pK_a of the resulting protonated lactone is sufficiently low that it should protonate bromide readily. Presumably, chloride facilitates cyclization in the absence of external base whereas bromide cannot. This effect is also observed in the different reactivity of acid **10** toward bromine and chlorine. In the presence of chlorine spontaneous cyclization affords chlorolactone **27** as the product whereas treatment with bromine provides the dibromide adduct **28**.

For the silyl ester substrates, the effect of the halide counterion is manifested in the cleavage of the silyl substituent and again this could occur before or after cyclization. It is clear that the rate-determining event must involve a step in which the silyl ester is involved since increasing steric bulk results in slower reaction; however, this could conceivably be cyclization of the silyl ester onto the seleniranium ion or chloride induced cleavage of the silyl ester to reveal a carboxylate. None of the results presented enable either of these possibilities to be eliminated.

5. Overall Reaction Mechanism. On the basis of all of the experiments undertaken, the following mechanistic pathway (Scheme 16) for the selenocyclization reaction with carboxylic acids and benzeneselenenyl chloride can be constructed. Initial attack of the alkene upon benzeneselenenyl chloride affords a seleniranium salt that is then trapped by the chloride ion to afford the Markovnikov chloroselenylation product as the kinetic adduct. As the reaction mixture is warmed to a temperature at which cyclization can proceed, then the Markovnikov adduct can react in one of three different ways, all of which proceed through the seleniranium intermediate: (1) reversion to the starting alkene and benzeneselenenyl chloride, (2) isomerization into the anti-Markovnikov adduct, or (3) deprotonation of the carboxylic acid by the halide counterion to afford a zwitterionic seleniranium carboxylate species.[42] The first two possibilities are both reversible through the seleniranium ion, and it is the deprotonation by the halide that represents the rate determining step. The final step in the reaction is then the rapid collapse of the zwitterionic seleniranium carboxylate species. Cyclization through nucleophilic attack of the carboxylate affords the observed selenolactone product with the *trans*-configuration.

SCHEME 16

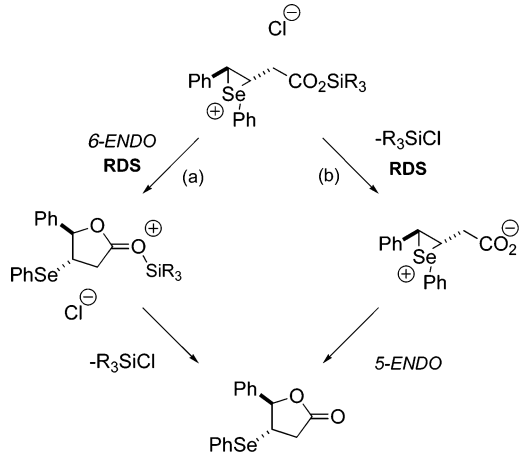


For the silyl ester substrates, a similar mechanistic picture can be drawn. In this case, however, there are two possible rate-determining steps which we cannot distinguish (Scheme 17, paths a and b). Because the steric demand of the silyl ester affects the observed rate of cyclization, it is evident that the silyl group must be involved in the rate-limiting step. For path a, initial *6-endo* cyclization of the silyl ester onto the seleniranium ion would be the rate-determining step which is then be followed by rapid desilylation by the chloride anion.[43] For path

(42) We cannot unambiguously rule out an association between the seleniranium ion and the carboxylate to form an episelenurane, but such a species was never detected and would be formed after a rate-determining deprotonation.

b, chloride cleaves the silyl ester in the rate-determining step to afford a zwitterionic seleniranium carboxylate that rapidly cyclizes to the observed product. Weinberg and Wooley studied the transilylation reaction between trimethylsilyl esters and trialkylsilyl chlorides in THF solution. Their results demonstrated that additives such as trimethylammonium chloride promoted this exchange reaction, but only at elevated temperatures (reflux).[44] This evidence suggests that path b is unlikely (under the reaction conditions employed) and leads us to suggest that path a is the more likely mechanism for this reaction.

SCHEME 17



Conclusion

Mechanistic studies of the selenocyclization reaction have allowed the determination of the reaction mechanism and identified the intermediates along the mechanistic path for the selenocyclization reaction with benzeneselenenyl chloride. The reaction proceeds via an initial formation of a Markovnikov β-chloro selenide adduct that ultimately cyclizes to afford the selenolactone product. Along the reaction pathway this adduct can also reverse to starting material or form an anti-Markovnikov adduct. Reversibility of the initial addition reaction was demonstrated by two crossover experiments that also indicated that reversibility and cyclization were competitive processes under the reaction conditions. The key role of the halide counterion as a base in the reaction was also demonstrated by reactions contrasting benzeneselenenyl chloride and bromide. In the absence of a sufficiently basic counterion, the cyclization is unable to proceed and no product is obtained. This study also demonstrated through the use of silyl and alkyl ester substrates that the processes of addition and isomerization were finely balanced thermodynamically and an equilibrium process that could be shifted by manipulation of the reaction temperature.

These studies have provided a firm mechanistic foundation on which to further pursue opportunities for (asymmetric) catalysis of electrophile-initiated reactions. Such investigations are ongoing and the results will be reported in due course.

Experimental Section

General Experimental Procedures. See the Supporting Information.

Preparative Selenolactonization. Preparation of (±)-(4*RS*,5*SR*)-Dihydro-4-(phenylseleno)-5-(2-methylphenyl)furan-2(3*H*)-one (24). A flame-dried, 10-mL, Schlenk flask equipped with a stir bar under an atmosphere of argon was charged with benzeneselenenyl chloride (211 mg, 1.1 mmol, 1.1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (201 mg, 0.98 mmol, 0.98 equiv). CH_2Cl_2 (4 mL) was added via syringe and the resulting solution cooled to −75 °C (bath temperature) with an external *i*-PrOH/CO_2 cold bath. A solution of 4-(2-methylphenyl)but-3-enoic acid (176 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added dropwise via cannula to the orange suspension; the immediate formation of a homogeneous yellow solution was observed. The reaction mixture was stirred for 2 h at −75 °C, the cooling bath removed, and the mixture stirred for an additional 1 h. The resulting dark yellow solution was transferred to a 25-mL round-bottom flask with CH_2Cl_2 (3 × 1 mL) and then was concentrated in vacuo to afford 354 mg of a dark yellow oil. The crude material was preadsorbed onto silica gel (1 g) and purified by column chromatography (SiO_2, 20 g, 20 mm i.d. × 12 cm, hexanes/Et_2O, 9:1, 400 mL) to afford 291 mg of a pale pink liquid. Bulb-to-bulb distillation afforded 266 mg (81%) of (±)-**24** as a viscous, pink liquid. Data for (±)-**24**: bp 150 °C (5 × 10^{-5} mmHg, ABT); ^{1}H NMR (500 MHz, $CDCl_3$) 7.53−7.56 (m, 2 H, CH(13)), 7.36 (dt, J = 7.3, 1.4 Hz, 1 H, CH(15)), 7.29 (2H, dt, J = 7.3, 1.5 Hz, 1 H, 2 H, CH(14)), 7.22−7.25 (m, 3 H, CH(3,4,5)), 7.17 (d, J = 7.1 Hz, 1 H, CH(6)), 5.68 (d, J = 5.0 Hz, 1 H, CH(8)), 3.83 (ddd, J = 8.0, 6.0, 5.0, 1 H, CH(9)), 3.05 (dd, J = 18.2, 8.0 Hz, 1 H, CH_2(10a), 2.67 (dd, J = 18.1, 6.0 Hz, CH_2-(10b), 2.29 (s, 3 H, CH_3(1)); ^{13}C NMR (126 MHz, $CDCl_3$) 175.0 (C(11)), 135.9 (C(13)), 135.5 (C(7)), 135.3 (C(2)), 131.0 (C(3)), 129.5 (C(14)), 129.0 (C(15)), 128.7 (C(4)), 126.4 (C(5)), 126.4 (C(12)), 124.7 (C(6)), 83.6 (C(8)), 41.1 (C(10)), 35.8 (C(10)), 19.3 (C(1)); ^{77}Se NMR (143 MHz, $CDCl_3$) 390.1; IR (neat) 3056 (m), 3026 (w), 2923 (w), 1782 (s), 1606 (w), 1578 (m), 1477 (m), 1462 (m), 1438 (m), 1412 (m), 1361 (w), 1301 (w), 1254 (m), 1209 (s), 1157 (m), 1110 (m), 1068 (m), 1048 (m), 1021 (m), 999 (s), 977 (m), 866 (m), 837 (m), 742 (s), 692 (s); MS (EI, 70 eV) 332 (($M^{\bullet+}$, 34), 330 (17), 186 (22), 185 (15), 184 (100), 183 (28), 182 (55), 181 (30), 180 (26), 176 (15), 175 (50), 174 (18), 158 (26), 157 (22), 156 (14), 147 (18), 145 (18), 132 (10), 131 (71), 129 (25), 128 (14), 119 (37), 117 (24), 116 (26), 115 (35), 105 (21), 104 (29), 103 (17), 91 (62), 86 (78), 84 (11), 78 (50), 77 (46), 65 (23), 55 (10); TLC R_f 0.14 (hexanes/Et_2O, 9:1) [CAM/Δ]. Anal. Calcd for $C_{17}H_{16}O_2Se$ (331.27): C, 61.64; H, 4.87. Found: C, 61.90; H, 4.83.

VT-NMR Experiment between (*E*)-Trimethylsilyl 4-Phenyl-3-butenoate 15b and Benzeneselenenyl Chloride. An oven-dried NMR tube was cooled in a desiccator and then charged with benzeneselenenyl chloride (35.8 mg, 0.187 mmol, 1.1 equiv), capped with a rubber septum, and attached to a vacuum manifold via an inlet needle. The tube was purged three times with a vacuum/argon cycle and then was maintained under an atmosphere of argon. CD_2Cl_2 (0.5 mL) was added via syringe, and the tube was vortexed for 15 s to afford an orange/brown solution. The tube was immersed in a −75 °C cold bath (bath temperature, acetone/CO_2) which resulted in precipitation of the majority of the benzeneselenenyl chloride. A solution of (*E*)-trimethylsilyl 4-phenyl-3-butenoic acid **15b** (39.8 mg, 0.17 mmol) in CD_2Cl_2 (0.25 mL) was added via cannula, and the tube was momentarily removed from the cooling bath and revortexed to afford a homogeneous dark yellow solution. The tube was taken to the precooled (−70 °C) NMR magnet and inserted. The mixture was aged for 30 min at −70 °C, and then both the ^{1}H NMR (64 scans) and ^{13}C NMR (1024 scans) spectra were recorded. The temperature was then increased to −20 °C, and after 30 min of aging, the ^{1}H NMR (64 scans) spectrum was recorded. This process was repeated at 0 °C, and then the tube was removed from the NMR spectrometer and was allowed to stand at

(43) For a formally endocyclic process on an sp^3 carbon, the leaving group must be included in the ring. Tenud, M.; Farooq, S.; Seibel, J.; Eschenmoser, A. *Helv. Chem. Acta* **1970**, *53*, 2059−2069.

(44) Weinberg, J. M.; Wooley, K. L. *J. Organomet. Chem.* **1997**, *542*, 235−240.

room temperature for 12 h. Then, a final ^{1}H NMR spectrum was recorded. Under these conditions, the data recorded in Table 4 were obtained. Data for **16b**: ^{1}H NMR (500 MHz, CD_2Cl_2, −70 °C, selected signals) 5.03 (d, 1 H, J = 11.4 Hz, CH(1)), 3.81 (ddd, J = 11.2, 10.1, 3.3 Hz, CH(2)), 3.46 (dd, J = 17.1, 3.3 Hz, 1 H, CH_2(3a)), 2.82 (dd, J = 17.1, 9.8 Hz, 1 H, CH(3b)), 0.32 (s, 9 H, CH_3(5)); ^{13}C NMR (126 MHz, CD_2Cl_2, −70 °C, selected signals) 171.6 (C(4)), 66.1 (C(1)), 46.6 (C(2)), 39.7 (C(3)), −0.9 (C(5)).

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Note Added after ASAP Publication. Line 4 of the Abstract erroneously contained the words “absence of” in the version published ASAP August 15, 2006; the corrected version was published ASAP August 16, 2006.

Supporting Information Available: Detailed procedures for the preparation and characterization of all new compounds along with variable-temperature NMR and IR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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