Synthesis and Characterization of Chiral Oxazolidine-2-selones:[1] A General One-Step Procedure from Readily Available Oxazolines†

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The synthesis of a wide variety of chiral oxazolidine-2-selones from readily available 2-oxazolines has been accomplished in one step with yields ranging from 82 to 98%. A mechanistic investigation of the formation of these selones has indicated the presence of intermediate anions which have been characterized by ^{13}C and ^{77}Se NMR spectroscopy. X-ray crystallographic data suggest the chiral selones exists as dimeric pairs or networks linked by unusual selenium hydrogen bonds. These chiral reagents exhibit extraordinary ^{77}Se chemical shift sensitivity and are useful for the detection and quantitation of chirality at remotely disposed chiral centers.

Introduction

The development of convenient methods for the determination of enantiomeric excesses and absolute configurations of chiral compounds has been of growing interest for some time.[5] The demand for chiral derivatizing agents is in response to the rapid progress made in the field of asymmetric synthesis and the growing pressure on the pharmaceutical industry to market chiral drugs as pure enantiomers.[6] Chirality will, in part, determine whether or not a drug has the desired biological effect, has no effect, or has an unknown, and perhaps even dangerous, effect.

Currently, there are three instrumental methods that can be employed for chiral analysis. Optical rotation and chromatographic determinations have been used frequently.[7] Nuclear magnetic resonance (NMR) spectroscopy has become a useful method for probing the structure of molecules.[8] There are currently three classes of NMR reagents used for chiral analysis: chiral solvation agents (CSAs),[9] chiral lanthanide shift reagents (CLSRs),[10] and chiral derivatizing agents (CDAs).[11]

A large number of CDAs have been synthesized and evaluated, many of which employ the following nuclei: ^{1}H, ^{13}C, ^{19}F, ^{31}P, ^{29}Si, and ^{195}Pt.[12] Mislow and Raban first observed the chemical shift nonequivalence of optically active compounds in ^{1}H NMR spectra and proposed the possibilility of NMR spectroscopy for chiral analysis in 1965.[13,14] Following their work, a fluorine-containing CDA, α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), was introduced by Mosher in 1969.[15] Although many simple analogues of MTPA have been investigated, Mosher's reagent remains the preferred and most widely employed CDA. In a recent report, Takeuchi[16] and coworkers have described a new ^{19}F-based CDA, α-cyano-α-fluorophenylacetic acid, which has demonstrated enhanced chemical shift sensitivity over MTPA. In a related approach, several chiral phosphoryl chlorides,[17]

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(1) R & D 100 Award winner for 1993; filed in the United States Patent Office October 6, 1989. Awarded June 16, 1992. Patent No. 5,122,472. Filed in the United States Patent Office March 5, 1993. U.S. Patent Appl. S.N. 08/027,552.

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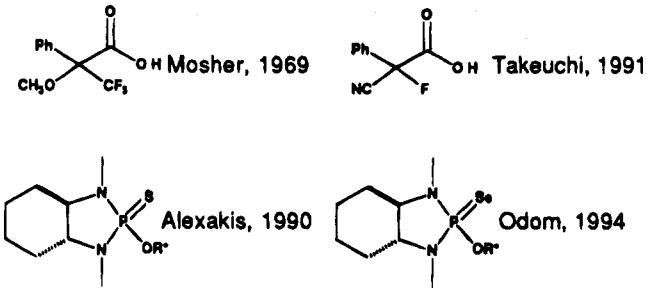
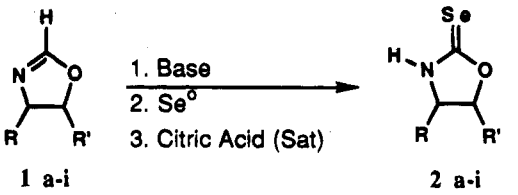
Chart 1



Alexakis's diazaphospholidine or thiophosphoramidate,[18] and Odom's selenophosphoramidate[19] (Chart 1) have been reported as useful CDAs for alcohols and amines. Most CDAs developed to date are not useful for the detection and quantitiation of remotely disposed chiral centers in compounds that contain functional groups other than alcohols and amines (*e.g.*, carboxylic acids).

There have been a number of reports of the use of the ^{77}Se nucleus as a novel spectroscopic probe for the study of various inorganic, organic, and biochemical systems.[20] The sensitivity of the ^{77}Se nucleus, its natural abundance, and its spin make it an excellent NMR reporter nucleus. The ^{77}Se nucleus possesses a large chemical shift range (~3400 ppm) and is extremely sensitive to its electronic environment.[21,22] Only one literature report prior to 1990 described the use of a Se-containing CDA. In this report (phenylseleno)propionic acid was used as an NMR CDA to resolve two racemic alcohols.[23] Ongoing studies in the application of the chemical shift sensitivity of the selenium atom prompted us to design a series of new Se-containing CDAs.

Scheme 1



1 a-i 2 a-i

In designing a selenium-containing chiral auxiliary, we wanted to take advantage of several features reported for compounds containing the selenocarbonyl group (C=Se): (1) the range of ^{77}Se chemical shifts for selenocarbonyl groups (~2600 ppm) is larger than that for any other type of selenium moiety and spans more than 80% of the current limits of the ^{77}Se chemical shift range,[24] (2) the T_1's (spin lattice relaxation times) of ^{77}Se selenocarbonyls are relatively short (1−8 s), while those for dialkyl selenides and especially the diaryl and dibenzyl selenides, are long (3−27 s),[25] and (3) selenocarbonyl groups display enhanced sensitivity toward small changes in its electronic environment as compared to selenides and diselenides.[26]

Our first efforts to construct selenocarbonyls within a rigid chiral framework resulted in the synthesis of (4*R*,5*S*)-4-methyl-5-phenyloxazolidine-2-selone.[27] To test this new selenium-containing CDA, a mixture of 2-phenyl[2-$^1H_2$]acetic acid, (*R*,*S*)-2-phenyl[2-$^2H_1$]acetic acid, and 2-phenyl[2-$^2H_2$]acetic acid was coupled to (4*R*,5*S*)-(+)-4-methyl-5-phenyloxazolidine-2-selone.[28] The ^{77}Se NMR spectrum illustrated a dramatic example of the sensitivity of the selenium nucleus by exhibiting four clearly resolved resonances. From these results we, and others,[29] were confident that oxazolidine-2-selones were a new class of sensitive CDAs for chiral interrogations.

Results and Discussion

Scheme 1 illustrates an improved method for the synthesis of multigram quantities of the various oxazolidine-2-selones via the easily accessible intermediate oxazolines.[30] Starting from commercially available chiral amino alcohols, the chiral oxazolines **1a-i** are constructed, with some modification, in excellent yield in enantiomerically pure form by the methods of Meyers *et al.*[31] We have evaluated a number of other literature methods for the generation of chiral oxazolines, and none are as generally useful for our needs. Oxazolines derived from valinol, leucinol, and *tert*-butylleucinol can be quickly and easily generated by condensing chiral 2-amino alcohols with a stoichiometric amount of formic acid. Heating the

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reaction mixtures at 90–100 °C for 30 min, followed by codistillation of oxazoline and water into a methylene chloride solution containing either sodium sulfate or activated 4-Å sieves, cleanly gives solutions of the volatile oxazolines. The oxazolines were then isolated by removing the methylene chloride via distillation. The use of diethyl ether instead of methylene chloride in the solvent trap resulted in diminished yields due to the difficulty in removal of the diethyl ether. Apparently diethyl ether and oxazolines form an azeotrope. Use of magnesium sulfate as the desiccant also resulted in diminished yields of the oxazolines, presumably because the magnesium coordinates strongly with the oxazoline nitrogen, thus promoting ring opening to the formamide. Finally, it should be noted that oxazolines are particularly water sensitive and care should be taken to exclude water during storage. Chiral amino alcohols which were not commercially available were obtained from the LAH reduction of the corresponding amino acids in 60–70% yields. In all cases reported, no racemization was observed. Metalation of the oxazolines (Scheme 1) was accomplished using lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LHMDS). Use of *n*-butyllithium resulted in inconsistent yields. After examining a variety of reagents and conditions for deprotonation, we found that when LHMDS was used, the presence of an aromatic substituent on or near the oxazoline ring led to a remarkable increase in the yield of product. Addition of selenium, followed by acidification with citric acid and reaction workup, afforded the crude product. Overall, this process represents a basic oxidation of the oxazolines. Purification was accomplished by flash chromatography using a step gradient of diethyl ether/methylene chloride as the eluent. In order to obtain consistent yields we found that the use of deoxygenated distilled diethyl ether was required. Although methylene chloride is the ideal chromatography solvent, with respect to promoting separation and purification, its use as the sole eluent resulted in longer retention times and necessarily larger quantities of solvent. The optimized yields for this series of chiral selones ranged from 82 to 98% (Table 1). We have successfully performed this synthesis to prepare 10-g lots of selone **2a**.

1. NMR Mechanistic Studies. The metalation step of the oxazolines was predicated on a previous report that *n*-butyllithium was successful in removing exclusively the C-2 proton.[32] Scheme 2 presents the proposed mechanism of lithiation of oxazolines. Due in part to our concern that the yields of the reaction of *n*-butyllithium with a number of chiral oxazolines for similar deprotonations were low and inconsistent, as well as the possibility of racemization of the monosubstituted chiral oxazolines through a pathway involving **6** and **7**, we undertook a series of experiments addressing these concerns. In a previous study of the deprotonation of oxazolines, Meyers *et al.* treated 4,4-dimethyl-2-oxazoline with *n*-butyllithium to generate the C-2 carbanion. Trapping experiments gave nearly quantitative yields of the derivatized oxazoline. In addition, it was reported that under carefully controlled conditions the lithiated carbanion **4** was in equilibrium with the open-chain isonitrile **5**. Evidently, careful hydrolysis of the reaction mixture allowed the isolation of both the oxazoline and the isonitrile alcohol. In these experiments the methyl groups at C-4 effectively served to block carbanion generation at C-4. In related studies it was demonstrated that 2-alkyl-4-(methoxymethyl)-5-phenyl-2-oxazoline is selectively deprotonated at the 2-exocyclic methylene group, not at C-4.[33] Because these systems are more closely related to our oxazolines, we initially used these data to support our contention that only the C-2 proton should be removed under proper reaction conditions.

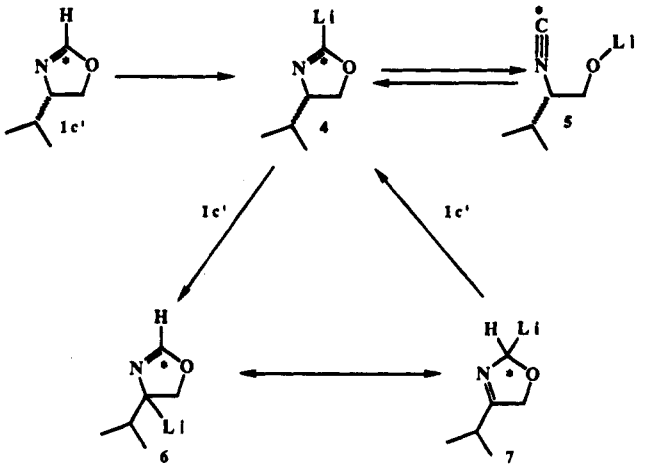
To further address these mechanistic questions, a low-temperature ^{13}C NMR study was conducted. We constructed [2-^{13}C]-4-(1-methylethyl)oxazolidine-2-selone **1c′** from formic-^{13}C acid.[34] The proton-coupled ^{13}C NMR spectrum of **1c′** in [^{1}H]THF, which exhibited a doublet centered at 155 ppm, is presented in Figure 1A. Treatment with LDA (generated from methyllithium in diethyl

Table 1. Formation of Oxazolidine-2-selones

	R[a]	R′	method[b]	yield[c] (%)
2a	Me (R)	Ph	B	91
2a′	Me	Ph (R)	B	84–99
	Me	Ph (R)	C	71
2b	CMe_3	H	A	90
2c	$CHMe_2$	H	A	92
	$CHMe_2$	H	C	35–85[d]
2d	CH_2Ph	H	A	98–99
	CH_2Ph	H	C	36, 37
2e	CH_2CHMe_2	H	A	90
2f	Ph	Ph (R)	B	83
2g	Ph (R)	H	B	85–95
	Ph (R)	H	A	29
2h	$(CH_2)_2Me$ (R)	H	A	85
2h′	$(CH_2)_2Me$	H	B	93
2i	$(CH_2)_3Me$ (R)	H	A	82
2i′	$(CH_2)_3Me$	H	A	91

[a] Unless otherwise noted the absolute configurations are *S*. [b] All reactions were performed using 1–3 g of oxazoline, 1.10 equiv of base (generated with 1.05 equiv of methyllithium), and 1.05 equiv of Se^0. Method A: LDA. Method B: LHMDS. Method C: *n*-butyllithium. [c] Isolated yields from silica gel column chromatography (using a step gradient of methylene chloride to 2% diethyl ether/methylene chloride). [d] This reaction was repeated 10× giving the stated yield range.

Scheme 2. Proposed Mechanism of Lithiation of 2-Oxazolines. Route to Intermediate Carbanions 6 and 7, with Racemization



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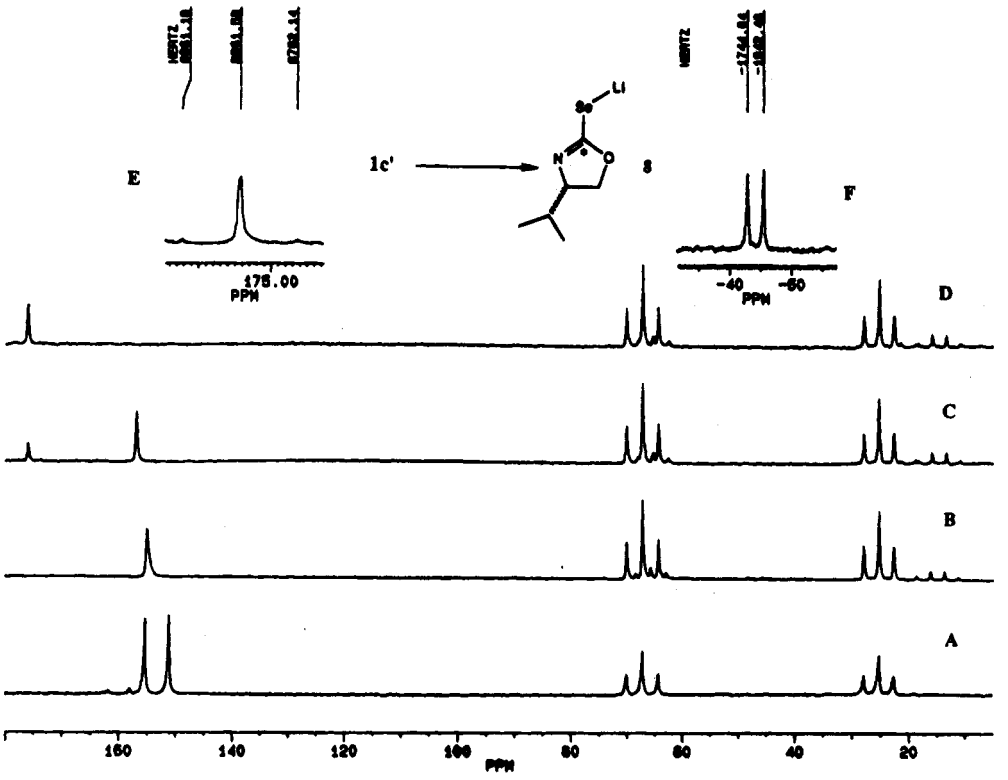

Figure 1. (A) Proton-coupled ^{13}C spectrum of **1c** in 1H THF at −78 °C. (B) Proton-coupled ^{13}C spectrum of **1c** at −78 °C with 1.05 equiv of LDA. (C) Proton-coupled ^{13}C spectrum of **1c** with Se^0, at ambient temperature. (D) Proton-coupled ^{13}C spectrum of **1c** with Se^0 after ~1 h at ambient temperature. (E) $^{13}C-^{77}Se$ ^{13}C satellites of **8** (J = 199.6 Hz). (F) ^{77}Se NMR spectrum of **8**.

ether) at −80 °C resulted in a collapse of the doublet on the proton-coupled spectrum to a broad singlet with a $1/2\upsilon$= 17 Hz (Figure 1B). Efforts to gain insight into the aggregation state of the lithiocarbanion **4** through $^7Li-^{13}C$ couplings by lowering the sample temperature through the freezing point of the solution failed. Evidently, either the ion separation is fairly great or the lithium exchange rate is sufficiently fast at −120 °C to obscure the couplings.[35] In addition, the presence of varying amounts of HMPA did not affect the resonance (at −78 °C). The resulting chemical shift of the carbanion ^{13}C nucleus is apparently not much different than the protonated version. In related trigonal lithiated carbanions, it has been reported that their ^{13}C signals showed little change[36] in chemical shift as compared to their protonated version. The ^{13}C NMR signal of **1c'**, however, is significantly broadened, which suggests the presence of $^{13}C-^7Li$ quadrupole interactions. Furthermore, it is apparent that the metalation reaction is not only clean, but upon warming it does not give rise to the ring-opened version **5**. A symmetrical triplet with the characteristic $^{13}C-^{14}N$ spin coupling centered near 150 ppm would be expected for **5**. The observed resonance, however, is possibly broad enough (at ambient temperature the $1/2h$= 7 Hz) to obscure a triplet with coupling constant ~9 Hz. All attempts to resolution enhance the resonance failed to provide any further structural elucidation. Considering that ^{13}C T_1's of isocyanides are long and the 155 ppm resonance is not truncated, it is reasonable to assume that we have not generated the isocyanide.[37] If the isocyanide were present, it could react with elemental selenium to form the isoselenocyanide. However, this process requires refluxing THF or chloroform suspensions of the isocyanide and elemental selenium. Because it is exceedingly difficult to promote alkoxide additions to isoselenocyanides, even under forcing conditions, the annulation reaction leading to the formation of the oxazolidine-2-selone would be expected to fail.[38] Under our conditions, the oxazoline anion is very likely undergoing either a facile ring opening and closing process that is extremely rapid on the NMR time scale or we have generated a stable trigonal carbanion at C-2. Alternatively, if deprotonation at C-4 had occurred, we would have observed the formation of **6** and/or **7**, accompanied by a shift of the proton coupled (doublet) C-2 resonance. There is clearly only one singlet in the spectrum, which supports the occurrence of C-2 deprotonation and the absence of racemization. Treatment of **4** with elemental selenium at −80 °C, followed by warming to ambient temperature to give **8**, caused a time dependent decrease of the singlet at 155 ppm and the concomitant appearance of a new peak at 180 ppm (Figure 1C). Complete conversion to the compound associated with the deshielded peak occurred within 2 h (Figure 1D). The time required for this process to be complete was variable,

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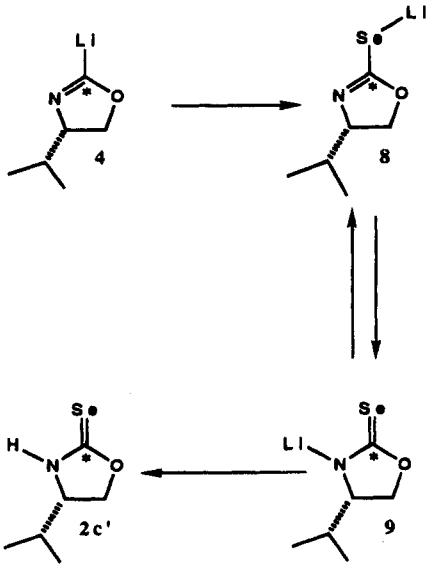
(36) O'Brien, D. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1980; Part A, Chapter 6. Reich, H. J.; Green D. P. *J. Am. Chem. Soc.* **1989**, *111*, 8729. Reich, H. J.; Borst, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1835. Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 444. Caution should be used in interpreting chemical shifts of carbanions, especially if they are trigonal. See: Lett, R.; Chassaing, G.; Marquet, A. *J. Organomet. Chem.* **1976**, *111*, C17.

(37) Often relaxation effects and lack of NOE tend to preclude detection of the isocyanide carbon resonances. See: Guy, M. P.; Coffer, J. L.; Rommel, J. S.; Bennett, D. W. *Inorg. Chem.* **1988**, *27*, 2942. Mann, B. E.; Taylor, B. F. *^{13}C NMR Data for Organometallic Compounds*; Academic: New York, 1981; p 6.

(38) Warner, J. S. *J. Org. Chem.* **1963**, *28*, 1642. Warner, J. S. In *Organic selenium compounds: their chemistry and biology*; Klayman, D. L.; Gunther, W. H. H., Eds.; Wiley-Interscience: New York, 1972.

Scheme 3. Proposed Pathway for the Insertion of the Selenium Atom into the Carbon Lithium Bond



presumably due to differences in concentration between experiments. The new resonance possessed selenium satellite peaks with a $J = 199$ Hz (Figure 1E). This is a relatively large value and compares to the protonated selones which possess J's on the order of 240 Hz. The ^{77}Se NMR spectrum exhibited a resonance at −49 ppm (Figure 1F) relative to a 60% dimethyl selenide $CDCl_3$ solution (v/v).[39] The large ^{13}C−^{77}Se coupling constant suggests a significant amount of sigma character in the selenocarbonyl bond (Figure 4).[40] Since the selenium chemical shift for selenide anions usually occurs in the region of −250 to −350 ppm relative to a 60% dimethyl selenide $CDCl_3$ solution (v/v), it is reasonable to view this intermediate as a selenocarbonyl (structure **9**, Scheme 3) with little charge on selenium and most of the negative charge residing on the nitrogen (with most of the negative charge centered at N-4, generation of an C-5 carbanion would then be highly disfavored). Treatment with a saturated solution of citric acid resulted in the shifting of the ^{13}C resonance to 182 ppm and the selenium resonance to 117 ppm, which corresponds to a conversion of **9** to **2c**. The striking feature of this series of reactions ("selenoylation") is that anionic oxidation of the C-2 carbon of the oxazolines apparently occurs in a very clean fashion, diminishing the likelihood of forming **6** and **7**.

2. Characterization of Selones. ^{77}Se, ^{13}C NMR, and ultraviolet data of the selones are provided in Table 2. All selones have a strong absorption with λ_{max} 276−280 nm. The bands are assigned to a $\pi \rightarrow \pi^*$ transition since these bands are insensitive to a change of solvent and exhibited high extinction coefficients. The electronic absorption spectrum of **2a**, as well as **2a'**, exhibited an identical characteristic absorption band at 278 nm in methylene chloride. In analogous carbonyl chromophores, the transition observed in such instances originates from the promotion of one electron from a nonbonding 2p orbital of the oxygen atom to an antibonding π^* orbital involving both the carbon and the oxygen atoms of the carbonyl group. Such absorptions (usually below 200 nm) are generally classified as $\pi \rightarrow \pi^*$ transitions. It has been

Table 2. ^{13}C NMR, ^{77}Se NMR, and UV Spectral Data of Oxazolidine-2-selones 2a−2i

	δ^{77}Se[a]	δ[b]	J[c] (Hz)	λ_{max}	ϵ[d]
2a	137	188	240	278	19,259
2a'	137	188	240	278	19,228
2b	119	189	237	278	12,703
2c	118	199	233	278	11,685
2d	137	188	237	276	13,930
2e	117	188	237	276	11,921
2f	156	189	229	280	15,113
2g	140	188	237	278	12,996
2h	118	188	232	[e]	[e]
2h'	118	188	233	276	14,005
2i	119	188	233	276	17,362
2i'	118	188	234	[e]	[e]

[a] The selenium chemical shifts are concentration, solvent, and temperature dependent. [b] Data listed are ^{13}C chemical shifts of selenocarbonyl carbons. [c] $J = {}^{13}C-{}^{77}Se$. [d] Experiments were performed in CH_2Cl_2. Data were obtained as average of three readings. [e] The measurement was performed on only one enantiomer.

Table 3. Comparison of ^{77}Se and ^{13}C Chemical Shift of Selones and *O*-Carbonyl Analogs

compd	δ ^{77}Se	Se=C, δ ^{13}C	C=O, δ ^{13}C
	1613−2134[a]	287−300[b]	204−217[c]
	915[a]	222−238[d]	171[c]
	643−733[a]	199−211[d]	170[c]
	117−156[e]	188−189[e]	161[c]

[a] References 40, 42, and 43. [b] References 42−44. [c] Reference 65. [d] References 63 and 65. [e] Reference 64.

reported that substituting sulfur or selenium for oxygen can lead to a bathochromic shift in the UV region.[41] By analogy to the carbonyl group, the electronic absorption band at 278 nm was assigned to a $\pi \rightarrow \pi^*$ transition of the selenocarbonyl chromophore. The tail of this band is due to the overlapping of a $n \rightarrow \pi^*$ transition.

The chemical shifts also exhibit some interesting trends. The ^{77}Se chemical shifts of our selones were dramatically shielded compared to selenoketones, selenoesters, and selenoamides.[40,42-44] This trend parallels the observation of ^{17}O chemical shifts in ketones, esters, amides, and oxazolidinones.[45] The shielding trend in this series of compounds is related to the increased electron density on selenium. Due to an increase in s character of the σ bond between the selenium and carbon atoms, the effect of ring-strain in oxazolidine-2-selones serves to further shield the ^{77}Se nucleus. It is noteworthy that the ^{77}Se shifts for the different types of selenocarbonyl compounds in Table 3 display remarkable sensitivity toward changes in the electronic structure of the selenium atom, with ^{77}Se resonances covering a range of more

(39) Luthra, N. P.; Dunlap, R. B.; Odom, J. D. *J. Magn. Reson.* **1983**, *52*, 318.
(40) Andersen, K. K.; Gash, D. M.; Robertson, J. D. *Tetrahedron Lett.* **1982**, *23*, 911.
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(42) Wong T. C.; Guziec, F. S., Jr.; Moustakis, C. A *J. Chem. Soc., Perkin Trans. 2* **1983**, 1471.
(43) Ishii, A.; Okazaki, R.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 861.
(44) Guziec, F. S.; Moustakis, C. A. *J. Org. Chem.* **1984**, *49*, 189. Also see, Guziec, F. S. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987.
(45) Mason, J. *J. Chem. Soc., Faraday Trans. 2* **1979**, *75*, 607.

than 2000 ppm. The ^{77}Se chemical shifts of the selone derivatives that contain aromatic substituents (137–156 ppm) were all deshielded with respect to those that contain alkyl groups (117–119). This observation suggests a possible interaction between the aromatic ring and the selenium atom. A deshielded ^{77}Se chemical shift for a cyclic selone with an aromatic group has also been observed by Wong *et al.*[42] The ^{13}C chemical shifts of the selenocarbonyl carbons show the same trend as selenium, which are summarized in Table 3. As with the ^{77}Se chemical shifts, the trend of ^{13}C chemical shifts of selenocarbonyl carbons in the order of shielding was found to be selenoketone < selenoester < selenoamide < oxazolidine-2-selone. The increased shielding of the ^{13}C shift of the selenocarbonyl moieties compared to that of carbonyl moieties can be explained as the decrease of 2p-4p π overlap that is present in selenium compounds compared to 2p-2p π overlap that is present in the oxygen analogs. The carbon–selenium coupling constants were measured from the ^{77}Se satellites (^{77}Se natural abundance = 7.5%) of the ^{13}C spectra and were in the range of 229–240 Hz, similar to those of the selone analogs previously reported. In addition, we have measured the T_1 of **2a** using the inversion/recovery sequence at 7.05 T and have determined it to be 0.95 s. This is in close agreement with other T_1's obtained with similar types of selenocarbonyls.[46]

The nuclear shielding constant σ can be viewed as the sum of two terms, σ_0 and $\sigma_{solvent}$, where σ_0 is a shielding term for the isolated molecule in the gas phase *in vacuo* and $\sigma_{solvent}$ consists of all types of shielding from medium effects. The quantity $\sigma_{solvent}$ has been proposed to be the result of the following five contributions (eq 1),

$$\sigma_{solvent} = \sigma_b + \sigma_w + \sigma_E + \sigma_a + \sigma_{HB} \quad (1)$$

where σ_b is the contribution from the bulk magnetic susceptibility of the medium, σ_w arises from the van der Waals interactions between the solute and solvent, σ_E is a shielding contribution from a polar solute-induced solvent alignment leading to an electric field E acting on the solute, σ_a is due to anisotropy in the susceptibility of the solvent; and σ_{HB} is the shielding caused by hydrogen bonding (this term is often included within σ_E).[47]

Selenium-77 NMR chemical shifts are very susceptible to changes in the electronic environment of the selenium nucleus.[48] A change of solvent can cause the ^{77}Se chemical shift of a given organoselenium compound to vary by approximately 80 ppm. A few groups have studied the solvent dependence of ^{77}Se chemical shifts. Carr and Colton demonstrated that the ^{77}Se chemical shifts of organophosphorus(V) selenides were solvent dependent.[49] The ^{77}Se solvent shifts of dimethyl selenide solutions have also been reported by two different groups.[48] Taft demonstrated that in nonchlorinated solvents, ^{77}Se chemical shifts of dimethyl selenide were influenced primarily by the dipolarity of the solvents.[50] Solvent-induced shifts were also found in alkyl selenides and alkyl diselenides.[51] It is expected, therefore, that solvent-induced shifts are significant in oxazolidine-2-selones and their derivatives.

Table 4. Solvent Effect of the ^{77}Se Chemical Shift for Selone 2a

solvent (^{1}H)	δ ^{77}Se[a]
toluene	152.6
THF	151.1
benzene	149.2
acetone	148.6
CH_2Cl_2	144.0
pyridine	143.9
DMF	140.3
$CHCl_3$	135.5

[a] The concentrations were 0.604 M. Probe temperature of 298 K. The values are in ppm. Internally referenced using a 1.21 M $CDCl_3$ solution of selone **2a**.

On the basis of eq 1, the σ_b could be expected to play a role in ^{77}Se chemical shifts. However, an examination of bulk magnetic susceptibility values and a calculation of the corrected shifts from these values reveals that these corrections (<1 ppm) are negligible compared to the experimental solvent shifts of the selones. The σ_w would be expected to contribute to the shielding because selenium is a soft atom and therefore easily polarized; thus, induced dipole solute–dipole solvent interactions in a polar solvent would be expected to be significant. The contribution from this term becomes larger with increasing solvent polarity. Since selones are polar functional groups, they should interact with the surrounding solvent molecules via van der Waals forces. The interactions arrange dipoles of polar solvent molecules around the solute dipole for maximum interaction and produce an "induced electric field" due to this alignment. The contribution of such a polar interaction has been demonstrated to be significant only with solvents of high dielectric constant in proton NMR studies. In low-dielectric constant solvents such as hexane and benzene, studies indicated that the corresponding shifts are negligibly small. It can be concluded that a high dielectric solvent causes a shielded ^{77}Se shift due to stronger solute–solvent intermolecular interactions. The solvent effect on the ^{77}Se chemical shift of the norephedrine derived selone (**2a**) in the presence of seven different solvents was studied, and the results are shown in Table 4. The solvent-induced shifts cover a range of 12.3 ppm with the extremes being defined by DMF (most shielded) and toluene (most deshielded).

Although reports of temperature studies of ^{77}Se shifts are scarce, there is no doubt that ^{77}Se chemical shifts are also temperature dependent. Lardon first noted that ^{77}Se chemical shifts change with temperature in melts of aromatic diselenides.[52] Odom *et al.* later reported the temperature dependence of ^{77}Se chemical shifts in solution for a variety of selenium compounds.[25] The ^{77}Se chemical shift of **2a** was measured over a range of 120 K. The sample was prepared as a 0.83 M solution in $CDCl_3$ in a 5-mm NMR tube. As seen in Figure 2, an increase in temperature resulted in a deshielding of the ^{77}Se resonances. Over the temperature range studied, the correlation of the ^{77}Se chemical shifts with temperature is linear, with $R^2 > 0.99$. The temperature dependencies are found to be 0.258 ppm K^{-1} at a field strength

(46) Wong, T. C.; Ang, T. T.; Guziec, F. S., Jr.; Moustakis, C. A. *J. Magn. Reson.* **1984**, *57*, 463.
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(49) Carr, S. W.; Colton, R. *Aust. J. Chem.* **1981**, *34*, 35.
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(51) Luthra, N. P.; Boccanfuso, A. M.; Dunlap, R. B.; Odom, J. D. *J. Organomet. Chem.* **1988**, *354*, 51.
(52) Lardon, M. A. *Ann. N.Y. Acad. Sci.* **1972**, *192*, 132.

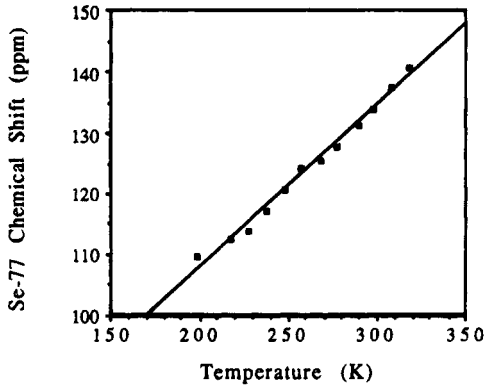


Figure 2. Temperature effect of the ^{77}Se chemical shift of selone **2a** in $CDCl_3$.

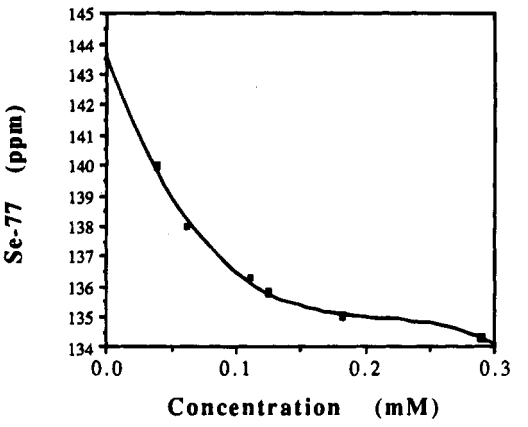


Figure 3. Concentration effect of the ^{77}Se chemical shift of selone **2a** in $CDCl_3$.

of 4.7 T. This result is similar to the value reported by Wong and co-workers (0.34–0.48 ppm K^{-1}) for selenocarbonyls (7.05 Tesla).[42]

There are many parameters that can change with temperature and give rise to temperature-induced chemical shifts. The macroscopic factors such as the shielding term σ_b from bulk susceptibility, viscosity of solvent, and the density of solution are all temperature dependent. The microscopic factors such as the shielding terms σ_w, σ_{HB}, and σ_E are also strongly affected by temperature. Raynes and co-workers proposed a statistical collision model to calculate medium effects,[53] which helps explain the ^{77}Se temperature-dependent chemical shifts. A change in temperature alters both the viscosity and density of a solution and, therefore, the collision rate of particles. At a higher temperature, as a solution becomes less viscous and has a lower density, molecules move more freely and faster in the solution, and the average lifetime of interaction between particles is shorter. This phenomenon decreases the solute–solute and solute–solvent intermolecular interactions. As found in solvent effect studies, intermolecular interactions tend to shift resonances to greater shielding; thus, an increase in temperature reduces those interactions and leads to the temperature dependent deshielding of the resonances.

Although smaller in magnitude than the effects due to solvent and temperature, a concentration dependence of ^{77}Se chemical shifts is also observed. The variation of the ^{77}Se chemical shifts of **2a** in $CDCl_3$ solutions as a function of concentration is shown in Figure 3. A chemical shift range of approximately 5.6 ppm was observed from a dilute 0.16 mM solution to a more concentrated 1.2 mM solution. As the concentration of the selone increased, the ^{77}Se resonance became more shielded. This small concentration dependence can be explained by (1) an increase in solute–solute intermolecular interactions when the solution becomes more concentrated and (2) a difference between the diamagnetic susceptibility of solutes and the solvent, $CDCl_3$.

We have evaluated the enantiomeric ratios of two different selones using Mosher's acid chloride. We chose the valinol- and phenylglycinol-derived selones for the following reasons. The valinol-derived selone is relatively inexpensive to construct and has, in general, given the best $\Delta\delta$ for the detection of remotely disposed chiral centers. The phenylglycinol derivative was chosen because it has the greatest potential of racemizing at the benzyl C-4 position.[54] Coupling of acid chlorides (1.1 equiv) to chiral selones in methylene chloride in the presence of 1.1 equiv of triethylamine has been reported to occur in 1 h in high yield.[30] However, the coupling of the **2c** and **2g** with the sterically demanding (*R*)- and (*S*)-MTPA acid chlorides required 4–12 h (thin-layer chromatography; 1:1 methylene chloride/hexane; v/v) for completion. ^{1}H, ^{19}F, and ^{77}Se NMR data for the resulting adducts is illustrated in Table 5. In all cases studied, the enantiomeric excesses were determined to be >99%. Interestingly, these adducts have given the greatest ^{77}Se $\Delta\delta$ observed (in $CDCl_3$): 113 ppm (phenylglycinol-derived selone) and 67 ppm (valinol-derived selone). The ^{1}H NMR gave a $\Delta\delta$ of 0.04 ppm for the (*R*)- and (*S*)-MTPA adducts of **2c** and the R and S-MTPA adducts of **2g** showed a $\Delta\delta$ of 1.09 ppm. Remarkably, the ^{19}F NMR spectrum gave a broad peak ($1/2h$ = 20 Hz) with a 0.0 ppm, or negligible, $\Delta\delta$ for the pairs of diastereomers. Examination of the $CFCl_3$ ^{19}F NMR standard gave a $1/2v$ line width of 0.5 Hz. In addition, we were unable to observe through-space ^{19}F–^{77}Se coupling in either the ^{19}F or ^{77}Se NMR spectrum, thereby discounting any fluorine and selenium interactions. The extremely large $\Delta\delta$ for the pairs of selenium diastereomers could possibly arise from a conformational change of the carbonyl groups from the anti to syn conformation in one diastereomer. Overall, this is an excellent example of the chemical shift sensitivity of the selenium nucleus to small perturbations in its electronic environment. The chemical shift sensitivity of the selenium atom for this pair of diastereomers is on the order of 1000 times better than that of fluorine and ~250 times better than that of proton.

Table 5. ^{1}H, ^{19}F, and ^{77}Se NMR Spectral Data of Mosher's Acid Chloride Adducts of 2c and 2g′ [a]

adduct	δ^1H (OCH_3)	δ ^{19}F	δ ^{77}Se
(*R*)-MPTA-**2c**	3.72	−73.84	540.9
(*S*)-MPTA-**2c**	3.76	−73.84	473.5
(*R*)-MPTA-**2g′**	3.81	−73.18	620.6
(*S*)-MPTA-**2g′**	2.72	−73.86	507.8

[a] **2g′** is the antipode of **2g**.

It should be noted that the synthesis of the **2i** from the corresponding amino acid resulted in ~60% enantiomeric excess, indicating partial racemization during the synthesis. The amino acid was converted to the amino

(53) Pople, J. A.; Buckingham, A. D. *Disc. Faraday Soc.* **1956**, *22*, 17.

(54) It is known that treatment of *cis*- and *trans*-4-methyl-5-phenyl oxazolidinones with excess *n*-butyllithium at 0 °C results in C-5 epimerization, via an N,C-5-dianion. See: Davies, S. G.; Doisneau, G. J.-M. *Tetrahedron Asymmetry* **1993**, *4*, 2514.

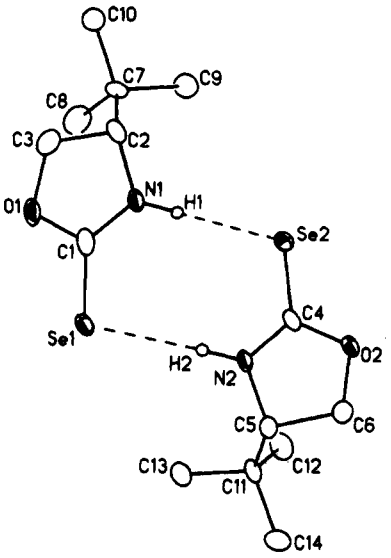


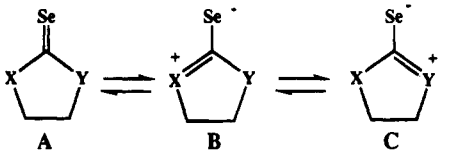
Figure 4. ORTEP of Selone **2b**.[66]

alcohol using the standard literature procedure, presumably without racemization. Conversion of the amino alcohol to the oxazoline using formic acid has occurred without racemization in all other instances. The racemization in this case presumably occurred during the metallation step and is depicted by structures **6** and **7** in Scheme 2. According to ^{13}C NMR experiments, the deprotonation occurs selectively at C-2 in a very clean reaction. It is highly probable that during this period the racemization occurred due to the presence of less than 1.0 equiv of base. The selenium insertion reaction usually takes approximately 1 h at ambient temperature, and it is possible that the allylic proton at C-4 could react with the C-2 carbanion, thereby giving rise to racemization. We must emphasize that this was the only reaction carried out to date that has given rise to any amount of detectable racemization.

The X-ray structure of **2b** is shown in Figure 4[66]and those of **2a,f** are contained in the supplementary material. To the best of our knowledge these are the first oxazolidine-2-selone structures which have been determined. The determination of the solid-state structure of these selones was critical because the only evidence that we had to support our contention that we were actually dealing with a selenocarbonyl were the $^{13}C-^{77}Se$ NMR coupling constants.

The average C=Se bond length was determined to be ~1.80 Å. Since no other oxazolidine-2-selone carbon–selenium bond lengths are available, a comparison was made with selenoureas. The selenium–carbon bond lengths in selenoureas[55] are in the range of 1.82–1.89 Å. X-ray structures for selenium-containing hydantoins have been reported, and the C=Se bond lengths in these derivatives are 1.792 and 1.805 Å. X-ray diffraction structural determination of novel cyclic selenocarbonates has recently been reported, and in these derivatives the average C=Se bond length is 1.78 Å.[56] Accordingly, the sum of the single bond covalent radii of selenium and carbon is 1.94 Å and that of selenium carbon double bond

Scheme 4. Selone Resonance Structures



radii is 1.74 Å.[57] The observed bond length of these three selones falls between these two values and also suggests the existence of a considerable contribution from structures B and C (Scheme 4). In resonance structure C, nitrogen has a positive charge, leading to retraction of much of the hydrogen electron density, and Se has a negative charge, leading to the attraction of an almost "naked" hydrogen in its neighbor molecule. In these compounds an intermolecular hydrogen bond is formed between the selenium atom Se(1) in one molecule and the N(2)-hydrogen in the second molecule. Selenium does not normally participate in hydrogen bonding; however, for these selones it is apparently common. In selenoureas the rather short Se–N distances of 3.55 and 3.56 Å were taken to indicate that hydrogen bonding was also present in these derivatives.[58] From the X-ray structures of all three selones it is evident that the five-membered ring and the exocyclic Se atom were almost in a plane, thereby placing the selenium atom in a rigid chiral environment ideally suited to allow for the reporting of remotely disposed chiral centers. Interestingly, for the *tert*-butylleucinol selone **2b**, the selone molecules exist as discrete dimeric pairs held together by selenium-hydrogen interactions of 2.4 and 2.6 Å (Se–N, 3.36 and 3.50 Å) in length. The selone molecules of **2a** and **2f** differ from **2b** in that they engage in hydrogen–selenium bonding interactions with their two nearest neighbors.

It has been reported that selones are stable indefinitely at −25 °C in the absence of light.[59] We have found that methylene chloride solutions of **2a**, in the presence of oxygen at −25 °C did not show evidence of decomposition (TLC and ^1H NMR analysis) over a period of 7 months. The appearance of a small amount of red precipitate (elemental selenium) over time is not unusual and does not affect the coupling reactions. Since these compounds are somewhat light sensitive, the storage vessels are covered with aluminun foil to avoid decomposition. In addition, we have found that storing the selones in 1% solutions of 2,6-di-*tert*-butyl-4-methylphenol increases their stability in methylene chloride.[60] Finally, selenium-containing compounds have traditionally been viewed as unpleasant to handle. We would like to emphasize that our selones are fairly nonvolatile and that **2g** possesses a particularly pleasant fragrance similar to that of lilacs (*Syringa valgaris*).

Summary

The results presented herein underscore the importance of chiral selones as a new generation of chiral auxiliary reagents which have doubled the limits of

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detection of the agents currently employed. They are complementary to most of the existing CDAs in that they are useful with a variety of different functional groups, including carboxylic acids. Overall, these data indicate that the construction of a number of enantiomerically pure selone CDAs can be accomplished in two steps from commercially available chiral 2-amino-alcohols in high yield and in bulk. Moreover, X-ray studies have uncovered an unusual selenium—hydrogen bonding event in the solid state for this class of selones.

We have demonstrated the advantages of using ^{77}Se NMR spectroscopy in detecting small nuances in the chemical and electronic environment of the selenium nucleus. Studies are ongoing to exploit this sensitivity via NMR spectroscopy and to increase the nature and number of functional groups which can be coupled and subsequently evaluated by ^{77}Se NMR spectroscopy with this new class of chiral CDAs.

Experimental Section

General. The ^{1}H, ^{13}C, ^{19}F, and ^{77}Se NMR spectra were recorded as $CDCl_3$ solutions. ^{1}H chemical shifts are expressed in parts per million deshielded with respect to tetramethylsilane at 0.0 ppm; ^{13}C chemical shifts are referenced using $CDCl_3$ (δ = 77.0 ppm with respect to tetramethylsilane at 0.0 ppm); ^{19}F NMR chemical shifts are referenced with respect to $CFCl_3$; ^{77}Se chemical shifts are expressed in ppm deshielded with respect to a 60% (v/v) solution of $(CH_3)_2Se$ in $CDCl_3$ (0 ppm).[39] Positive chemical shifts denote resonances deshielded with respect to the reference. Typically, spectra were obtained in the Fourier transform mode at 7.05 T. Measurements were made at, or near, ambient probe temperature in 5-mm NMR tubes using $CDCl_3$ as an internal lock solvent. All spectra were acquired in the proton-decoupled mode; generally, 0.15—0.30 M solutions were used and 128—1024 scans were acquired using a pulse angle of 30° and a recycle time of 2.2 s. Use of a higher field NMR instrument (500 MHz) resulted in increased peak broadening. Infrared spectra were recorded as CCl_4 solutions, unless otherwise noted. Analytical thin-layer chromatography (TLC) was carried out on glass plates (silica gel 60 Å, 250-μm thickness) obtained from Analtech. TLC visualization was accomplished with a UV lamp, I_2 staining, and an ethanolic solution of phosphomolybdic acid (PMA). Liquid chromatography separations were carried out on silica gel using the Still protocol.[61] The columns were handpacked with silica gel 60 (230—400 mesh, Merck). Pressures used were between 5 and 8 psi, and fractions were monitored by thin layer chromatography (TLC). Moisture-sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon.

Elemental selenium (200 mesh), the chiral amino alcohols, *tert*-butylleucine, *N,N*-dimethylformamide dimethyl acetal, benzene, methyllithium in diethyl ether, and 95% formic acid were obtained from Aldrich Chemical Co. and used without purification. Triethylamine was purchased from Sigma Chemical Co. and was distilled over calcium hydride and stored over KOH prior to use. Methylene chloride was distilled over calcium hydride prior to use. Tetrahydrofuran was distilled over potassium benzophenone ketyl prior to use. Methyllithium was titrated with elemental selenium.[62]

Relaxation measurements were made on **2a** in $CDCl_3$ in a 5-mm NMR tube. The sample was degassed by a series of freeze—pump—thaw cycles before being sealed under dynamic high vacuum, although a previous study has shown that dissolved oxygen does not affect the measured ^{77}Se T_1.[61] The relaxation time was measured on a Bruker AM-300 MHz spectrometer (B_o = 7.05 T) operating at 57.2 MHz for ^{77}Se at ambient temperature. All experimental data were analyzed on a Bruker 1000 data station. The saturation—recovery pulse sequence was used for T_1 measurement. Spectra were acquired using a 0.58-s acquisition time, and 11 different τ values, with the longest τ = 28 s as the infinity value were obtained. The data were analyzed by a three-parameter-fit computer program.

The concentration, temperature, and solvent studies were performed on **2a** using a wide bore Bruker 200 MHz (B_o = 4.7 T) spectrometer operating at 38.168 MHz for ^{77}Se with a 10 mm broad band probe. For the concentration studies, $CDCl_3$ solutions were placed in 5-mm NMR tubes, and the measurements were taken. Solvent studies were performed using 0.61 mM solutions of the ^{1}H solvents indicated. Stock solvents were used without purification. The temperature studies were performed with 1.2 mM solutions in $CDCl_3$. These solutions were placed in a 10-mm NMR tube and referenced using an internal tube containing a 1.2 mM solution of **2a** in $CDCl_3$.

The low-temperature NMR metalation experiments were performed using a Bruker 200-MHz spectrometer operating at 50.34 MHz for ^{13}C and fitted with a 10-mm wide bore broad band probe. The 10 mm NMR tube was flame dried and degassed prior to use. Dry deoxygenated protonated THF (2.0 mL) was added, followed by argon. [2-^{13}C]-4-(1-methylethyl)-2-oxazoline was added neat via a gas-tight Hamilton syringe. The measured ^{13}C chemical shift was referenced with respect to interal THF (23.6 ppm). Chilling the tube to −78 °C using a dry ice—acetone bath, followed by the addition of 1.05 equiv (1.0 mL) of a LDA solution (prepared from diisopropylamine and methyllithium in diethyl ether), generated the carbanion. NMR measurements were then performed both in the proton-coupled and -decoupled mode. The temperature was decreased to −178 °C in 10 °C increments with intermittent NMR measurements. After the temperature was raised to −50 °C, 1 equiv of elemental selenium was added (under argon), and the temperature of the probe was raised in 10 °C increments until the probe reached ambient temperture.

X-ray structure determinations were obtained on ENRAF-Nonius CAD4 and Seimens P3F diffractometers with crystals obtained from methylene chloride solutions. Details of data collection and structural refinement and tables of atomic cooordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Centre and are available as supplementary material.[66]

General Procedure for the Synthesis of Amino Alcohols. To a suspension of lithium aluminum hydride (2.45 g, 64.6 mmol) in 100 mL of dry THF at rt was carefully added 5.0 g (38.1 mmol) of D-norleucine. The reaction mixture was refluxed overnight and after cooling was poured into 50 mL of ether. To the ether layer was added slowly 5 mL of water, followed by 10 mL of 15% NaOH solution and 20 mL of water. The solution was filtered and the precipitate washed with ether. The organic layers were combined and dried over anhydrous K_2CO_3. The product was purified by bulb-to-bulb vacuum distillation to give 3.1 g of a white solid (69.4%).

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General Procedures for the Syntheses of 2-Oxazolines. 4-Alkyl-2-oxazolines. The synthetic protocol previously outlined for the conversion of valinol to the 2-oxazoline was repeated for the valinol, leucinol, and *tert*-butylleucinol derived 2-oxazolines. These 2-oxazolines have previously been reported, and our spectral data for these compounds are identical to that which are reported.[36]

(*R*)-(−)-4-Butyl-2-oxazoline (1i). D-Norleucinol (3.0 g, 25.6 mmol) and *N,N'*-dimethylformamide dimethyl acetal (DMF−DMA, 94%, 4.16 mL, 1.2 equiv) were combined neat. The reaction mixture was warmed, with stirring, in an oil bath at 70 °C for 7 h. The volatiles were removed by rotary evaporation, and the mixture was twice evaporated with the addition of a 30 mL portion of hexane. The residue was diluted with 30-mL of hexane, and *p*-toluenesulfonic acid (10 mg) was added. After being refluxed for 17 h, the solution was washed with 10% $KHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4. The mixture was distilled at reduced pressure to yield 2.21 g (68%) of the oxazoline as a clear, colorless liquid.

The procedures for the construction of oxazolines using DMF−DMA reported by Meyers *et al.* were utilized with the following modifications for (*R* and *S*)-4-benzyl-2-oxazoline, (*R,S* and *S,R*)-4-methyl-5-phenyl-2-oxazoline, and (*R* and *S*)-4-phenyl-2-oxazoline.[36] A typical procedure for these syntheses follows.

4(*S*)-Methyl-5(*R*)-phenyl-2-oxazoline (1a'). (1*R*,2*S*)-Norephedrine (5.00 g, 33.1 mmol) was dissolved in 150 mL of benzene. Benzenesulfonic acid (30.0 mg) was added along with 1.10 equiv of DMF−DMA (4.85 mL, 36.4 mmol), and the flask was equipped with a Dean-Stark trap and flushed with N_2. The solution was refluxed for 70 h, at which time the reaction was determined to be complete by TLC (100% diethyl ether). After being cooled to ambient temperature, the reaction was quenched with 10% $KHCO_3$. The organic layer was then washed with a 50-mL portion of saturated NaCl solution. The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness to give a purple, viscous oil. Kugelrohr distillation (120 °C, 200 mTorr) afforded 4.46 g (27.8 mmol, 84%) of the oxazoline as a clear pungent oil. (*R* and *S*)-4-Benzyl-2-oxazoline was also prepared in this manner.

The procedure described by Meyers and co-workers[36] for construction of 4-phenyl-2-oxazoline was significantly modified as follows:

4(*S*)-Phenyl-2-oxazoline (1g'). (*S*)-Phenylglycinol (3.30 g, 24.1 mmol) was dissolved in 80 mL of toluene. Benzenesulfonic acid (25 mg) was added, and 1.3 equiv of DMF−DMA (4.13 mL, 33.4 mmol) was added under N_2. An addition funnel containing a mixture of 40 g of activated 4−5-Å molecular sieves (previously desiccated under vacuum at 150 °C) was fitted onto the reaction flask, and the reaction mixture was refluxed under nitrogen for 72 h until complete by TLC (100% diethyl ether). $NaHCO_3$ (10%, 45 mL) was used to quench the reaction, and the organic layer was washed with 45 mL of brine. The organic layer was dried (Na_2SO_4), rotary evaporated, and twice azeotropically evaporated with 30-mL portions of hexanes. Short path vacuum distillation (78 °C, 75 mTorr) yielded 2.87 g (81%) of the oxazoline as a clear oil. The spectral data for the oxazolines were identical to those which are reported.[36]

General Procedure for the Synthesis of Formic-^{13}C Acid. Into a 1-L stainless steel cylinder was placed sodium hydroxide (25%, 18 mL, 0.15 mol) and carbon-^{13}C monoxide (180 psi, 0.15 mol). The mixture was swirled on a shaker bath, and the cylinder was heated to 170 °C using a heating jacket. The reaction was deemed complete when the pressure decreased to a constant value. The vessel was opened after cooling, and the contents were transferred to a round-bottom flask. The water was evaporated to give a white crystalline solid (10.2 g, 99%). The sodium formate-^{13}C was then added to phosphoric acid (85%), and the formic acid was distilled to give a mixture of product and water.

General Procedure for the Synthesis of Oxazolidine-2-selones. In a 500-mL three-neck, round-bottom flask fitted with a septum, ground glass stopper, and gas (N_2) inlet was placed 15.0 mL (71.3 mmol) of HMDS in 250 mL of dry deoxygenated THF. The solution was chilled to 0 °C, and 53 mL of methyllithium in Et_2O (1.40 M, 74.4 mmol) was added. After gas evolution ceased, the reaction mixture was chilled to −78 °C, and 10.00 g of 4(*R*)-methyl-5(*S*)-phenyl-2-oxazoline (62.0 mmol) was added neat. The resulting pale yellow solution was stirred for 30 min, and 5.60 g of elemental selenium (70.9 mmol, 200 mesh) was then added. The mixture was allowed to warm to ambient temperature, and stirring was continued for 1 h. The reaction was quenched with degassed citric acid (saturated) until the pH of the aqueous layer remained acidic (pH ~4−5). The reaction mixture was filtered through a pad of Celite, and the organic layer was isolated and dried over Na_2SO_4. Filtration, followed by removal of the volatiles *in vacuo*, afforded the crude material. The residue was dissolved in CH_2Cl_2 and filtered though a pad of SiO_2. The silica gel was then washed with 2−5% Et_2O (distilled from benzophenone ketyl)/CH_2Cl_2 until the pad was free of selone (by TLC analysis). The solvents were removed *in vacuo*. The material was subjected to flash silica gel chromatography (100% CH_2Cl_2) to give the pure selone (91%).

General Procedure for MTPA-Cl Selone Acylation. A mixture of acid chloride and selone (1.2 equiv) was stirred at 0 °C in dried (over CaH_2), distilled CH_2Cl_2. To this mixture was added dropwise 1.2 equiv of triethylamine (neat). Generally, for unhindered carbonyls the reaction solution became bright yellow and the reaction was complete within 1−5 min (the progress of the reaction was monitored by TLC). Stirring was continued for 1 h to ensure completion. Reaction of both (*R*)- and (*S*)-MTPA-Cl with **2c** and **2g** took on the order of 12 h for completion. The mixture was filtered through a pad of SiO_2, and the pad was rinsed with CH_2Cl_2 until free of the acylated selone. The mixture was then concentrated to give the bright yellow crude material. Silica gel chromatography was performed using CH_2Cl_2/hexane (usually 1:1; v/v) mixtures as the eluent.

(4*R*,5*S*)-(+)-4-Methyl-5-phenyloxazolidine-2-selone (2a): mp 119−120 °C; $[\alpha]_D$ = +166° (c = 1 × 10^{-3}, $CHCl_3$); λ_{max} ($CHCl_3$) 278 nm (ϵ = 19 254); IR ($CDCl_3$) 3446, 3136, 2982, 1526, 1476, 1445, 1385, 1347, 1275, 1155, 1104, and 938 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.7 Hz, 3 H), 4.41 (m, 1 H), 5.96 (d, J = 9.1 Hz, 1 H), 7.23−7.41 (m, 5 H); ^{13}C NMR δ 16.4, 57.0, 88.2, 126.3, 128.7, 129.0, 133.2, 187.6; ^{77}Se NMR δ 137; HRMS m/z calcd $C_{10}H_{11}NO^{76}Se$ 237.0033, found 237.0025. Anal. Calcd for $C_{10}H_{11}NOSe$: C, 50.01; H, 4.62; N, 5.83. Found: C, 49.78; H, 4.76; N, 5.96.

(4*S*,5*R*)-(−)-4-Methyl-5-phenyloxazolidine-2-selone (2a'): mp 119−120 °C; $[\alpha]_D$ = −166° (c = 1 × 10^{-3}, $CHCl_3$); λ_{max} ($CHCl_3$) 278 nm (ϵ = 19 254); IR ($CDCl_3$) 3446, 3136, 2982, 1526, 1476, 1445, 1385, 1347, 1275, 1155, 1104 and 938 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.7 Hz, 3 H), 4.41 (m, 1 H), 5.96 (d, J = 9.1 Hz, 1 H), 7.23−7.41 (m, 5 H); ^{13}C NMR δ 16.4, 57.0, 88.2, 126.3, 128.7, 129.0, 133.2, 187.6; ^{77}Se NMR δ 137; HRMS m/z calcd $C_{10}H_{11}NO^{80}Se$ 241.0006, found 241.0007.

(*S*)-(−)-4-(1,1-Dimethylethyl)oxazolidine-2-selone (2b): mp 154−155 °C; $[\alpha]_D$ = −9.8° (c = 0.25, $CHCl_3$); λ_{max} ($CHCl_3$) 277 nm (ϵ = 11 890); IR ($CDCl_3$) 3116, 2910, 1532, 1418, 1378, 1368, 1278, 1166, 926, 910 cm^{-1}; ^1H NMR($CDCl_3$) δ 0.91 (s, 9 H), 3.75 (dd, J = 6.3, 9.6 Hz, 1 H), 4.40 (dd, J = 6.3, 9.6 Hz, 1 H), 4.58 (t_{app}, J = 9.6 Hz, 1 H), 9.02 (s, br, 1 H); ^{13}C NMR δ 25.1, 33.5, 66.8, 73.1, 188.9; ^{77}Se NMR δ 118.7. Anal. Calcd for $C_7H_{13}NOSe$: C, 40.79; H, 6.36; N, 6.80. Found: C, 40.85; H, 6.54; N, 6.73.

(*S*)-(−)-4-(1-Methylethyl)oxazolidine-2-selone (2c): mp 68−71 °C; $[\alpha]_D$ = −22.7° (c = 0.67, $CHCl_3$); λ_{max} ($CHCl_3$) 278 nm (ϵ = 11 685); IR ($CDCl_3$) 3455, 31,39, 2969, 1522, 1478, 1394, 1332, 1266, 1162, 1027, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.82 (m, 1H), 3.84 (m, 1H), 4.37 (dd, J = 6.8, 9.3 Hz, 1 H), 4.68 (dd, J = 9.3, 9.3 Hz, 1 H), 9.64 (s, br, 1 H); ^{13}C NMR δ 17.8, 31.6, 63.3, 74.8, and 187.5; ^{77}Se NMR δ 112.8; HRMS m/z calcd $C_6H_{11}NO^{76}Se$ 189.0033, found 189.0035. Anal. Calcd for $C_6H_{11}NOSe$: C, 37.51; H, 5.77; N, 7.29. Found: C, 37.98; H, 5.71; N, 7.17.

(*S*)-(−)-4-Benzyloxazolidine-2-selone (2d): mp 94−96 °C; $[\alpha]_D$ = −93.2° (c = 0.31, $CHCl_3$); λ_{max} ($CHCl_3$) 276 nm (ϵ = 13 930); IR ($CDCl_3$) 3447, 3133, 2972, 1518, 1472, 1399, 1320, 1260, 1160, 1061, 949 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.93 (m, 2 H),

4.28 (m, 1 H), 4.42 (dd, J = 6.5, 9.0 Hz, 1 H), 4.70 (m, 1 H), 7.14–7.36 (m, 5 H), 9.20 (s, br, 1 H); ^{13}C NMR δ 40.2, 58.8, 76.0, 127.6, 129.0, 129.2, 134.8, 188.0; ^{77}Se NMR δ 112.8; HRMS m/z calcd $C_{10}H_{11}NO^{76}Se$ 237.0033, found 237.0027. Anal. Calcd for $C_{10}H_{11}NOSe$: C, 50.01; H, 4.62; N, 5.83. Found: C, 49.99; H, 4.68; N, 5.83.

(*S*)-(−)-(2-Methylpropyl)oxazolidine-2-selone (2e). Isolated as an oil: $[\alpha]_D$ = −23.7° (c = 0.14, $CHCl_3$); λ_{max} ($CHCl_3$) 276 nm (ϵ = 11921); IR ($CDCl_3$) 3453, 3138, 2962, 1522, 1470, 1389, 1316, 1269, 1164, 1078, 984 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 0.92 (m, 6 H), 1.42 (m, 1 H), 1.65 (m, 2 H), 4.08 (m, 1 H), 4.27 (dd, J = 7.3, 8.9 Hz, 1 H), 4.76 (dd, J = 8.9, 8.9 Hz, 1 H), 9.60 (s, br, 1 H); ^{13}C NMR δ 22.7, 25.0, 43.2, 56.2, 77.9, and 187.5; ^{77}Se NMR δ 117; HRMS m/z calcd $C_7H_{13}NO^{80}Se$ 207.0162, found 207.0163. Anal. Calcd for $C_7H_{13}NOSe$: C, 40.79; H, 6.36; N, 6.80. Found: C, 40.93; H, 6.13; N, 6.67.

(4*S*,5*R*)-(+)-4,5-Diphenyloxazolidine-2-selone (2f): mp 155–158 °C; $[\alpha]_D$ = +68.7° (c = 0.18, $CHCl_3$); λ_{max} ($CHCl_3$) 280 nm (ϵ = 15 113); IR ($CDCl_3$) 3441, 3069, 3034, 1499, 1467, 1454, 1338, 1234, 1142, 1029, 948 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.28 (d, J = 9.0 Hz, 1 H), 6.17 (d, J = 9.0 Hz, 1H), 6.87–7.14 (m, 1 H), 9.09 (s, br, 1 H); ^{13}C NMR δ 63.5, 87.4, 124.2, 124.9, 125.9, 126.3, 126.4, 126.6, 130.3, 131.3 and 188.1; ^{77}Se NMR δ 117; HRMS m/z calcd $C_{15}H_{13}NO^{80}Se$ 303.0162, found 303.0152. Anal. Calcd for $C_{15}H_{13}NOSe$: C, 59.61; H, 4.34; N, 4.63. Found: C, 59.58; H, 4.11; N, 4.43.

(*R*)-(−)-4-Phenyloxazolidine-2-selone (2g): mp 134–137 °C; $[\alpha]_D$ = −53° (c = 0.64, $CHCl_3$); λ_{max} ($CHCl_3$) 278 nm (ϵ = 12 996); IR ($CDCl_3$) 3453, 3146, 2963, 2930, 2876, 1654, 1552, 1524, 1405, 1321, 1264, 1072, 949 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 4.43 (dd, J = 6.4, 7.0 Hz, 1 H), 4.97 (t, J = 7.0 Hz, 1 H), 5.10 (dd, J = 6.4, 7.0 Hz, 1 H), 7.26–7.42 (m, 5 H), 9.23 (s, br, 1H); ^{13}C NMR δ 61.0, 78.8, 126.4, 129.3, 129.5, 137.3, 189.2; ^{77}Se NMR δ 140; HRMS m/z calcd $C_9H_9NO^{78}Se$ 224.9857, found 224.9863. Anal. Calcd for C_9H_9NOSe: C, 47.80; H, 4.01; N, 6.19. Found: C, 48.11; H, 3.84; N, 6.18.

(*R*)-(+)-4-Propyloxazolidine-2-selone (2h): isolated as an oil; λ_{max} ($CHCl_3$) 276 nm (ϵ = 14 005); IR ($CDCl_3$) 3453, 3146, 2963, 2930, 2876, 1654, 1552, 1524, 1405, 1321, 1264, 1170, 1072, 949 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3 H), 1.36 (m, 2 H), 1.62 (m, 2 H), 4.03 (m, 1 H), 4.32 (dd, J = 6.9, 9.0 Hz, 1 H) 4.76 (dd, J = 9.0, 9.0 Hz, 1 H), 9.23 (s, br, 1H); ^{13}C NMR δ 14.2, 19.0, 36.6, 58.0, 77.1, and 187.9; ^{77}Se NMR δ 118; HRMS m/z calcd $C_6H_{11}NO^{76}Se$ 189.0033, found 189.0029.

(*S*)-(+)-4-Propyloxazolidine-2-selone (2h′): isolated as an oil; λ_{max} ($CHCl_3$) 276 nm (ϵ = 14 005); IR ($CDCl_3$) 3454, 2960, 2927, 2855, 1718, 1552, 1537, 1446, 1360, 1264, 1218, 1161, 949 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3 H), 1.36 (m, 2 H), 1.62 (m, 2 H), 4.03 (m, 1 H), 4.32 (dd, J = 6.9, 9.0 Hz, 1 H) 4.76 (dd, J = 9.0, 9.0 Hz, 1 H), 9.23 (s, br, 1H); ^{13}C NMR δ 14.2, 19.0, 36.6, 58.0, 77.1, and 187.9; ^{77}Se NMR δ 118; HRMS m/z calcd $C_6H_{11}NO^{76}Se$ 189.0033, found 189.0032.

(*R*)-(+)-4-Butyloxazolidine-2-selone (2i): isolated as an oil; λ_{max} ($CHCl_3$) 276 nm (ϵ = 17 362); IR ($CDCl_3$) 3453, 3140, 2961, 2933, 2861, 1717, 1655, 1552, 1521, 1468, 1405, 1331, 1264, 1164, 1081, 951 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.9 Hz, 3 H), 1.34 (m, 4 H), 1.64 (m, 2 H), 4.01 (m, 1 H), 4.32 (dd, J = 6.9, 9.0 Hz, 1 H) 4.76 (dd, J = 9.0, 9.0 Hz, 1H), 9.0 (s, br, 1H); ^{13}C NMR δ 14.2, 22.7, 34.3, 58.3, 77.1, and 188.3; ^{77}Se NMR δ 118; HRMS m/z calcd $C_7H_{13}NO^{76}Se$ 203.0189, found 203.0195.

(*S*)-(−)-4-Butyloxazolidine-2-selone (2i′): isolated as an oil; λ_{max} ($CHCl_3$) 276 nm (ϵ = 17 362); IR ($CDCl_3$) 3453, 3141, 2962, 2933, 2862, 1737, 1709, 1552, 1526, 1468, 1402, 1320, 1264, 1164, 1081, 949 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 1.33 (m, 4 H), 1.62 (m, 2 H), 4.03 (m, 1 H), 4.31 (dd, J = 6.9, 9.0 Hz, 1 H) 4.75 (dd, J = 9.0, 9.0 Hz, 1 H), 9.0 (s, br, 1 H); ^{13}C NMR δ 14.2, 22.6, 34.2, 58.2, 77.1, and 187.9; ^{77}Se NMR δ 118; HRMS m/z calcd $C_7H_{13}NO^{76}Se$ 203.0189, found 203.0191.

(*S*)-MTPA-(*S*)-(−)-4-(1-methylethyl)oxazolidine-2-selone (3): mp 201 °C; IR (neat) 2982, 2952, 2922, 2843, 1723, 1468, 1446, 1366, 1239, 1179, 1109, 1073, 988, 928, 813, 719, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.29 (d, J = 6.4 Hz, 3 H), 0.61 (s, 3 H), 3.76 (q, J = 1.9 Hz, 3 H), 4.33 (q, J = 9.6 Hz, 2 H), 4.34 (s, 1 H), 4.65–4.67 (m, 1 H), 7.41–7.45 (m, 3 H), 7.62–7.64 (m, 2 H); ^{13}C NMR δ 13.9, 17.9, 30.1, 57.2, 63.7, 70.3, 85.3, 122.6, 126.6, 128.8, 130.4, 131.1, 167.0, 187.7; ^{19}F NMR δ −73.84; ^{77}Se NMR δ 473.5. Anal. Calcd for $C_{16}H_{18}F_3NO_3Se$: C, 47.07; H, 4.44; N, 3.43. Found: C, 46.85; H, 4.33; N, 3.35.

(*R*)-MTPA-(*S*)-(−)-4-(1-methylethyl)oxazolidine-2-selone (3′): 85%; mp 133–135 °C; IR (neat) 2968, 2874, 2844, 1796, 1733, 1695, 1474, 1364, 1256, 1209, 1164, 1113, 998, 941, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.70 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 6.9 Hz, 3 H), 2.21 (m, 1 H), 3.67 (dd, J = 9.4, 7.8 Hz, 1 H), 3.72 (q, J = 2.3 Hz, 3 H), 4.85 (ddd, J = 9.4, 4.2, 1.4 Hz, 2 H), 4.16 (dd, J = 9.4, 1.4 Hz, 1 H), 7.4–7.6 (m, 5 H); ^{13}C NMR δ 14.7, 18.1, 30.3, 56.8, 64.6, 69.8, 82.5, 122.7, 126.5, 128.7, 130.2, 131.9, 166.6, 189.1 ($J_{^{13}C-^{77}Se}$ = 244 Hz); ^{19}F NMR δ −73.84; ^{77}Se NMR δ 540.9. Anal. Calcd for $C_{16}H_{18}F_3NO_3Se$: C, 47.07; H, 4.44; N, 3.43. Found: C, 47.06; H, 4.35; N, 3.37.

(*R*)-MTPA-(*S*)-(+)-4-phenyloxazolidine-2-selone (4): 88%; isolated as an oil; IR (neat) 2930, 2846, 1803, 1720, 1440, 1319, 1266, 1215, 1170, 1102, 930, 814, 699, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.72 (q, J = 2.3 Hz, 3 H), 3.93 (dd, J = 8.7, 7.0 Hz, 1 H), 4.04 (d, J = 8.7 Hz, 1 H), 4.96 (d, J = 7.0 Hz, 1 H), 7.11–7.13 (m, 2 H), 7.34–7.4 (m, 2 H), 7.49–7.53 (m, 6 H); ^{13}C NMR δ 57.2, 62.5, 77.7, 84.5, 124.7, 124.1, 126.2, 128.0, 128.1, 128.7, 129.3, 129.8, 137.0 166.4, 187.6; ^{19}F NMR δ −73.86; ^{77}Se NMR δ 507.8; HRMS m/z calcd $C_{19}H_{16}F_3NO_3{}^{76}Se$ 439.0274, found 439.0266. Anal. Calcd for $C_{19}H_{16}F_3NO_3Se$: C, 51.60; H, 3.65; N, 3.17. Found: C, 51.24; H, 3.36; N, 3.41.

(*S*)-MTPA-(*S*)-(+)-4-phenyloxazolidine-2-selone (4′): 93%; mp 201 °C; IR (neat) 2930, 2846, 1803, 1720, 1440, 1319, 1268, 1215, 1170, 1102, 930, 814, 699, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81 (q, J = 2.3 Hz, 3 H), 3.93 (dd, J = 8.8, 1.4 Hz, 1 H), 4.69 (dd, J = 9.1, 7.8 Hz, 1 H), 5.68 (dd, J = 7.7, 1.4 Hz, 1 H), 7.11–7.13 (m, 2 H), 7.34–7.40 (m, 2 H), 7.49–7.53 (m, 6 H); ^{13}C NMR δ 56.2, 62.7, 76.8, 85.1, 122.3, 125.3, 126.4, 128.9 (2C), 129.2, 130.5, 125.3, 126.4, 128.9 (2C), 129.2, 130.5, 138.3, 165.2, 188.1; ^{19}F NMR δ −74.18; ^{77}Se NMR δ 620.6; HRMS m/z calcd $C_{19}H_{16}F_3NO_3{}^{76}Se$ 439.0274, found 439.0262. Anal. Calcd for $C_{19}H_{16}F_3NO_3Se$: C, 51.60; H, 3.65; N, 3.17. Found: C, 51.82; H, 3.65; N, 3.20.

(*S*)-4-(1-Methylethyl)-[2-^{13}C]-2-oxazoline (1c′): 88%; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 6.7 Hz, 3 H), 0.94 (d, J = 6.7 Hz, 3 H), 1.62–1.80 (m, 1 H), 3.8–3.9 (m, 2 H), 4.1–4.2 (m, 1 H), 6.8 (d, $J_{^1H-^{13}C}$ = 214 Hz); ^{13}C NMR δ 154 (d, $J_{^1H-^{13}C}$ = 214 Hz).

(*S*)-(−)-4-(1-Methylethyl)-[2-^{13}C]-oxazolidine-2-selone (2c′): 92%; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.82–1.95 (m, 1 H), 3.79–3.97 (m, 1 H), 4.37 (dd, J = 6.8, 9.3 Hz, 1 H), 4.68 (dd, J = 9.3, 9.3 Hz, 1 H), 9.64 (s, br, 1H); ^{13}C NMR δ 188.0 ($J_{^{13}C-^{77}Se}$ = 232 Hz).

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Supplementary Material Available: The atomic coordinates for **2a**, **2b**, and **2f** and ORTEPS (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.