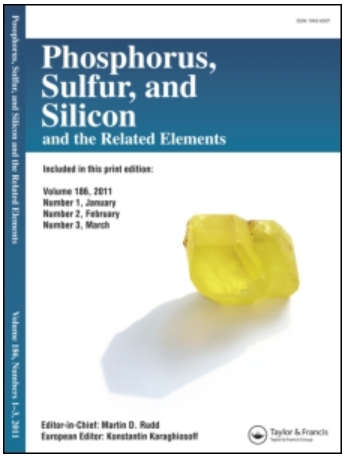

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SYNTHESIS AND APPLICATIONS OF CHIRAL SELONES

L. A. "PETE" SILKS[¶], RUILIAN WU[¶], R. BRUCE DUNLAP* AND JEROME D. ODOM*

[¶]Los Alamos National Laboratory, Bioscience and Biotechnology Group, CST-4, MS C345, Los Alamos, NM 87545. *University of South Carolina, Department of Chemistry and Biochemisty, Columbia, South Carolina, USA.

ABSTRACT The use of chiral selone derivatizing reagents (CDA's) and ^{77}Se NMR spectroscopy for the observation of remotely disposed chiral centers has proven to be a highly sensitive method for the determination of enantiomeric excesses. A variety of functional groups can be attached to these CDA's making them the most diverse class of CDA's yet developed. We are now investigating the chemistry unique to these CDA's such as new aldol reactions

Keywords: Chiral selones, chiral derivatizing agents, aldol reactions.

Selenium based chiral derivatizing agents (CDA's), "selones," have proven to be useful for the evaluation of enantiomeric excesses (ee's) of carboxylic acids, acid chlorides, protected amino acids, alcohols, alkyl halides and amines.[1] We have shown that when the chiral center is remotely disposed, up to 8 bonds removed from the observing selenium nucleus, discrimination of the diastereomeric selone adducts is

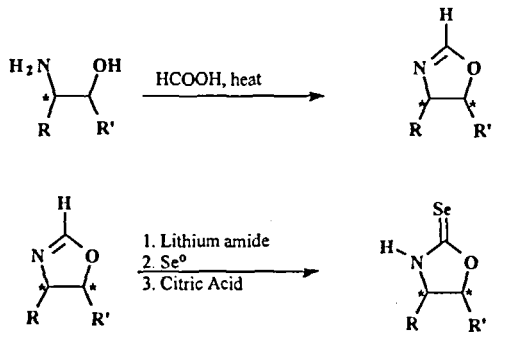
possible.[2] X-ray single crystal analysis has revealed a unique *anti* carbonyl relationship which helps in the understanding of why these selones display such extreme chemical shift sensitivity.[3]

A large number of CDAs have been developed which employ the following nuclei: ^{1}H, ^{13}C, ^{19}F, ^{31}P, ^{29}Si, and ^{195}Pt. The sensitivity of the ^{77}Se nucleus (6.93×10^{-3} with respect to ^{1}H and 2.98 compared to ^{13}C), its natural abundance (7.6%), and spin (I=1/2) make it an excellent candidate for an NMR reporter nucleus. Selenium has the special feature of possessing a large chemical shift range (~3400 ppm), and the selenium nucleus is extremely sensitive to its electronic environment. In designing a selenium-containing chiral auxiliary, we wanted to take advantage of several features reported for compounds containing the selenocarbonyl group (C=Se).[4] Scheme I illustrates the synthesis of chiral selones. Starting from commercially available chiral amino alcohols, chiral oxazolines are constructed. Metallation of the oxazolines was accomplished using lithium diisopropyl amide (LDA) or lithium bis(trimethylsilyl)amide (LHMDS). Addition of selenium, followed by citric acid, afforded the crude selone product. The optimized yields for this series of chiral selones ranged from 82-98%.

Most CDA's which have been developed to date are restricted in the nature and type of groups which can be attached. In designing a second generation CDA we have taken advantage of the unique discrimina-tory ability of our selone heteroatom system to select the functional group of choice for covalent bonding.

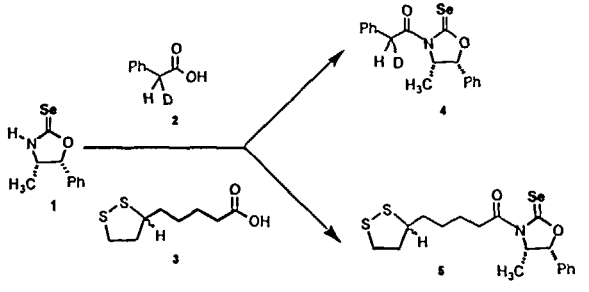
For example, removal of the nitrogen proton gives rise to an electrophilic nitrogen which can couple to an activated carboxylic acid derivative, forming an amide linkage. Alternatively, alcohol and amine functional groups can be coupled indirectly to the nitrogen atom via a carbonyl linker system. Since the selenium atom is considered to be a non-basic highly nucleophilic site, reaction of activated alkyl groups can be considered as coupling partners to the selenium atom.

Scheme 1



The coupling of the selone **1** to racemic carboxylic acids **2** and **3** is illustrated in Scheme 2. The ^{77}Se NMR spectrum of **5** illustrated that a distance of 8 bonds from the chiral center to the observing selenium atom gave rise to two clearly resolved peaks which possessed a $\Delta\delta_{Se} = 5.3$ Hz. Alternatively, the deuterated acylated selone **4** was constructed and the ^{77}Se NMR spectrum exhibited four resonances. The largest peak was assigned to the per-protonated species, which had a chemical shift at $\delta_{Se} = 471.7$ ppm. The diastereomeric monodeuterated species exhibited an observable $\Delta\delta_{Se}$ of 5 Hz. The most shielded peak has been assigned to the bis-deuterated species at $\delta_{Se} = 470.4$ ppm.

Scheme 2



We have found that alcohols can be linked to these selone CDA's. Coupling the alcohol of choice to **1** is accomplished using a carbonyl bridge derived from triphosgene. We have reacted a series of alcohols with our CDA and have found that both 1° and 2° alcohols undergo the coupling reaction in high yield. However, tertiary alcohols either do not

react under the conditions studied or do so in low yield. The ^{77}Se NMR analysis of these alcohol-based adducts indicated that the δ_{Se} sensitivity of the selenium nucleus found in our studies of carboxylic acids and acid chlorides adducts has now been extended to these systems. In general, these adducts gave a greater $\Delta\delta_{Se}$ for the same bond distances when compared to the $\Delta\delta_{Se}$ in carboxylic acid adducts.

In an effort to increase the utility of these selone CDA's we have developed a one-pot triphosgene-mediated coupling of both chiral and racemic amines to our selone CDA's. The use of both 1° and 2° amines in the coupling reaction gave good to excellent yields. However, in some cases the study of the 2° amines by ^{77}Se NMR spectroscopy has been complicated by the existence of both E and Z carbamoyl isomers (and broad peaks). This results in the appearance of four ^{77}Se resonances for the diastereomeric adducts. The $\Delta\delta_{Se}$ of our amine adducts indicated that the chemical shift sensitivity of the selenium nucleus found in our studies of carboxylic acids, alcohols and acid chlorides adducts has now been extended to these systems. In general, these adducts gave a greater $\Delta\delta_{Se}$ for the same bond distances when compared to the $\Delta\delta_{Se}$ in carboxylic acid or alcohol adducts.

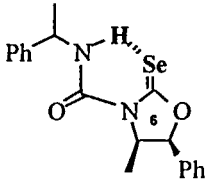


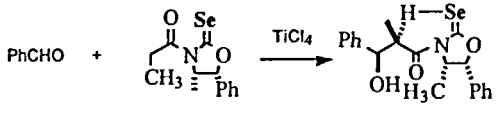
Figure 1

During the course of this work we have measured both the proton coupled and decoupled ^{77}Se spectra of a number of selone amine adducts and have determined that there exists one distinct $J_{H\text{-}Se}$ for each adduct. These coupling constants were on the order of 13 Hz. This proton coupling is too large for a $^{5}J_{Se\_H}$, and in an effort to determine the origin of this coupling we performed heteronuclear multiple quantum coherence (HMQC) ^{77}Se-^{1}H NMR spectroscopy. From the results of these

experiments on **6**, we concluded that the amine adduct assumes an *anti* carbonyl relationship and that the N-H must be hydrogen bonded to the selenium atom of the selenocarbonyl. Moreover, the selenium atom is apparently weakly interacting with the water (1.5 ppm) that arises from $CDCl_3$ that was not dried prior to use. These results may signal the potential for significant hydrogen selenium bonding interactions within biomacromolecular systems which contain either selenomethionine or selenocysteine.

To the best of our knowledge, the evaluation of chiral alkyl halides using CDA's is unknown. We were intrigued by the possibility of the coupling of alkyl halides with our CDA and were pleased that the reactions proceeded in good yield with activated alkyl halides. For unactivated halides the coupling was found to be promoted by the use of sodium iodide, giving good yields of the adduct. Interestingly, the coupling took place at the selenium atom, giving rise to selenides. The C2 $J_{C\text{-}Se}$= 130 Hz is indicative of an allylic type coupling constant. Comparison of the $\Delta\delta_{se}$ for both the selenide adducts and the selone adducts clearly indicated that the chemical shift sensitivity going from the selenocarbonyl to the selenide significantly decreases.

Scheme 3



7 8

Our current interest has been in the develop-ment of new chemistries invol-ving these se-lones. Chiral oxidations and aldol reactions have been the focus of these efforts. For example, $TiCl_4$ promoted aldol reactions have given rise, in some cases, to the desired products in good yield and stereoselectivity. As illustrated in Scheme 3 the $TiCl_4$ enolate of the acylated selone cleanly undergoes reaction with benzaldehyde to afford the aldol product in 87% yield. In addition to the aldol product, a 13% yield of the unacylated selone was obtained. Single

crystal X-ray crystallography of **8** indicated that these selone adducts gave rise to a new class of non-Evans aldol products.

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