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Reaction of alcohols (via the Mitsunobu reaction) and alkyl halides with chiral selone derivatizing agents[1]

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Abstract

Coupling of a selone chiral derivatizing agent (CDA) to D,L-alkyl halides gives Se-alkylated adducts in yields ranging from 76–97%. Reaction of D,L-alcohols with the selone CDAs via the Mitsunobu reaction has given rise to Se-alkylated adducts in yields ranging from 82–92%. Examination of the ^{77}Se NMR spectra of the resulting diastereomeric adducts indicates that discrimination of remotely disposed chiral centers is possible using this technique.

1. Introduction

The development of new chiral derivatizing agents (CDAs) for the determination of the chiral enrichment of chemical and enzymatic processes is an area that is being actively investigated.[2] We have developed chiral selone CDAs which allow for the determination of enantiomeric excesses (ees) of carboxylic acids,[3] acid chlorides,[4] alcohols,[5] amines[6] and amino acids[7] by ^{77}Se NMR spectroscopy. In addition, the use of these CDAs allows the assessment of the absolute configuration of the chiral center in some cases.[8] In an effort to increase the versatility of this method we have examined the reaction of alkyl halides and the direct coupling of alcohols via the Mitsunobu reaction to these selone CDAs.[9]

Usually the ee determination of optically active organohalides is accomplished by measuring the optical rotation and comparing the value obtained to the literature value. This method gives rise to accurate determinations; however, it has some known drawbacks.[2] Development of a CDA capable of delivering the same information would be useful.

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2. Results and discussion

Reaction of acyl groups with **1** gives rise to selective *N*-acylation (Fig. 1). This has been found for acid chlorides, carbonyl chlorides, carbamoyl chlorides, and DCC activated acids. However, with softer electrophiles it was expected that alkylation would take a different course. We reported that reaction of ethyl bromoacetate with **1** afforded the Se-alkylated product.[3] The chemoselectivity of the reaction was confirmed by the observation of a J_{C-Se}=~140 Hz which is indicative of an sp^2 carbon selenium coupling.[10] Based on this result a series of alkyl halides were reacted with **1**, giving rise to the corresponding selenides. Again, observation of J_{C-Se}=~140 Hz for the alkyl halide adducts studied to date demonstrates that alkylation had taken place at the selenium atom. In addition, the selenium chemical shifts of the adducts are within the range reported for selenides.[10] As illustrated in Table 1, for activated systems such as the α-bromo-γ-butyrolactone and the 3-bromocyclohexene, the reaction proceeds in acetone over a period of 12 h. However, for unactivated systems the alkylation required the presence of NaI in acetone. After 12 h the reaction was concentrated and the selenide was purified by flash column chromatography.

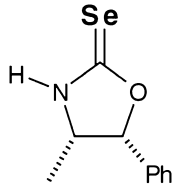
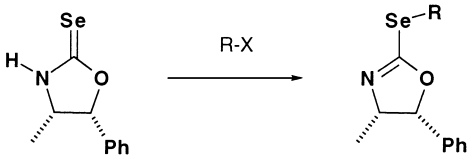


Figure 1. Chiral selone **1** structure

The use of the Mitsunobu reaction to effect the coupling of alcohols directly to the selone CDA was investigated next. There are a few reports of the use of the Mitsunobu reaction to selenides.[11] Despite this relatively unknown adaptation of the type of Mitsunobu reaction, we proceeded to evaluate conditions to effect the direct coupling of alcohols to the selenium atom of these CDAs. Simply mixing the alcohol, selone, and the triphenylphosphine, followed by the dropwise addition of the diisopropyl

Table 1
Yields and ^{77}Se NMR data of (±) alkyl halide adducts with (4*S*,5*R*)-4-methyl-5-phenyl-oxazolidin-2-selone

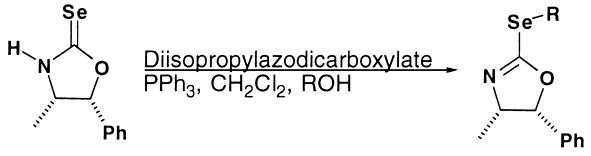


Compound	Racemic Alkyl Halide	Yield (%)	δ_{se} ($CDCl_3$)[b]	$\Delta\delta_{Se}$ ($CDCl_3$) Hz
1	$CH_3(Ph)CHCH_2CH_2$-Br	91	268.56	19
2	$CH_3CH_2(CH_3)CHCH_2Br$	76	233.91	8.1
3	$CH_3(CH_2)_3(CH_2CH_3)CHCH_2Br$	97	225.47	70
4	-OCOCH(Br)CH_2CH_2-	84	379.81	200
5	-CHCHCH(Br)$CH_2CH_2CH_2$-	80	359.62	0(202)[a]

[a]In [$^2H_6$]benzene. [b]Averaged chemical shift

azodicarboxylate at ambient temperature gave rise to the adducts in fair to good yield. The yields and $\Delta\delta_{Se}$ values are given in Table 2.

Table 2
Yields and ^{77}Se NMR data of (±)-alcohol adducts with (4*S*,5*R*)-4-methyl-5-phenyl-oxazolidin-2-selone



Compound	Racemic Alcohols	Yield(%)	δ_{se} ($CDCl_3$)[a]	$\Delta\delta_{se}$ ($CDCl_3$) Hz
2	$CH_3CH_2CH(CH_3)CH_2OH$	82	233.91	10
6[b]	PhCHDOH	92	344.89	5.6

[a]Averaged chemical shift. [b]The (4S)-4-Phenyl-Oxazolidin-2-Selone was used instead of **1**.

The sensitivity of the ^{77}Se nucleus (0.07 with respect to ^{1}H and 2.98 compared to ^{13}C), its natural abundance (7.5%), and spin (I=1/2) make it an excellent NMR probe. Selenium has the special feature of possessing a large chemical shift range (~3400 ppm) and it is extremely sensitive to its electronic environment. This chemical shift sensitivity has been observed for the mono-deuterated racemic benzyl alcohol. The NMR analysis of the Mitsunobu coupled product gave $\Delta\delta_{Se}$=5 Hz. In contrast, attachment of the alcohol through a carbonyl linker to the selone CDA nitrogen (an adduct possessing an intact selenocarbonyl) has not given rise to any resolution of the diastereomers by ^{77}Se NMR spectroscopy. Fig. 2 is the 1D spectrum of the selenide (Table 1, Entry 1) in which the chiral center is 3 atoms removed from the observed selenium nucleus. The $\Delta\delta_{Se}$ was 19 Hz.

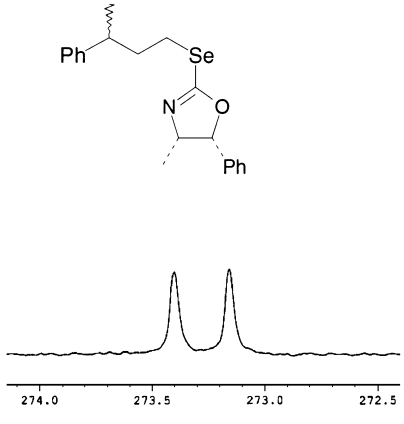


Figure 2. ^{77}Se 1D NMR spectrum of 1-bromo-3-phenylbutane selone adduct

The ability of the selone to undergo selective reaction with halides where the reacting carbon is also the chiral center has not been evaluated. However, in cases where the chiral center is remotely disposed from the reaction site, the evaluation of the diastereomeric mixtures via the measurement of the ^{77}Se NMR spectrum allows for the enantiomeric excess of the parent halide or alcohol to be determined.

3. Experimental

3.1. General

The ^{1}H, ^{13}C, and ^{77}Se NMR spectra were recorded as [^{2}H]chloroform or [^{2}H]benzene solutions on Bruker WM-300 or AMX-500 NMR spectrometers. The δ_H values are expressed in parts per million with respect to tetramethylsilane at 0.0 ppm; δ_C values are referenced with respect to internal [^{2}H]chloroform (δ=77.0 ppm with respect to tetramethylsilane at 0.0 ppm); and δ_{Se} values are expressed in parts per million with respect to a 60% (v/v) solution of $(CH_3)_2Se$ in [^{2}H]chloroform (0 ppm).[12] Positive chemical shifts denote resonances deshielded with respect to the reference. IR spectra were recorded on a BioRad FTS-40 spectrometer. Microanalyses were performed on a Perkin–Elmer Series II CHNS/O Analyzer #2400 (CST-11, Los Alamos National Laboratory). Analytical thin-layer chromatography (TLC) was carried out on glass plates (silica gel 60, 250 mu thickness) with a UV lamp, I_2 staining, and an ethanolic solution of phosphomolybdic acid. Liquid chromatography separations were carried out on silica gel (230–400 mesh, Merck).

3-Bromocyclohexene, 1-bromo-2-ethylhexane, α-bromo-γ-butyrolactone, sodium iodide, and diisopropyl azodicarboxylate were purchased from Aldrich Chemical Co. and used without purification. Triphenylphosphine was purchased from Sigma Chemical Co. and used without purification. Acetone was purchased from Aldrich Chemical Co., as a sure-seal product, and used without purification. Dichloromethane was distilled from calcium hydride. Triethylamine, and *N*,*N*-diisopropylethylamine were purchased from Aldrich Chemical Co. and distilled from calcium hydride before use. 1-Bromo-2-methylbutane, and 1-bromo-3-phenylbutane were synthesized from their corresponding alcohols by standard procedures. Monodeuterated benzyl alcohol was synthesized by reduction of benzaldehyde with sodium borodeuteride in ethanol. The chiral selones were constructed in two steps from commercially available amino alcohols.[13]

3.1.1. General procedure for unactivated alkyl bromides

To a solution of selone (0.128 g, 0.534 mmol) and sodium iodide (1.198 g, 7.99 mmol) in acetone (5.0 mL) was added 1-bromo-2-ethylhexane (0.067 g, 0.330 mmol) followed by *N*,*N*-diisopropylethylamine (0.138 g, 1.068 mmol) dropwise at room temperature. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified on silica gel (50% v/v EtOAc/hexane) to provide 0.113 g (97%) of the product as a colorless oil.

3.1.2. Oxazole, 2-[(3-phenyl)-butan-1-ylseleno]-4,5-dihydro-4-methyl-5-phenyl-,[4S-(4R*,5S*)] (**1**)

Yield 91%; IR (neat) 3192, 3104, 3082, 3061, 3027, 2970, 2927, 2868, 1606, 1494, 1452, 1377, 1358, 1334, 1291, 1255, 1212, 1110, 1080, 1040, 1029, 955, 934, 913, 879, 762, 748, 725, 699, 639, 540 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33–7.11 (m, 20H), 5.57 (d, *J*=9.3 Hz, 1H), 5.56 (d, *J*=9.3 Hz, 1H), 4.43–4.36 (m, 2H), 2.98–2.76 (m, 6H), 2.10–2.03 (m, 4H), 1.23 (d, *J*=7.5 Hz, 6H), 0.72 (d, *J*=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 159.16, 146.02, 136.53, 128.59, 128.46, 128.23, 127.91, 127.03, 126.19, 126.15, 85.43, 65.84, 39.99, 38.69, 25.17, 22.14, 17.71; ^{77}Se NMR ($CDCl_3$) δ 268.66, 268.46. Anal. calcd for $C_{20}H_{23}NOSe$: C, 64.51; H, 6.23; N, 3.76. Found: C, 64.44; H, 6.31; N, 3.94.

3.1.3. Oxazole, 2-[(2-methyl)-butan-1-ylseleno]-4,5-dihydro-4-methyl-5-phenyl-,[4S-(4R*,5S*)] (**2**)

Yield 76%; IR (neat) 3087, 3062, 3028, 2958, 2926, 2872, 1605, 1494, 1454, 1377, 1333, 1289, 1256, 1222, 1130, 1105, 1079, 1040, 1029, 958, 934, 875, 749, 698, 639 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.23 (m, 5H), 5.68 (d, *J*=9.5 Hz, 1H), 4.54–4.46 (m, 1H), 3.27–3.18 (m, 1H), 3.12–3.03 (m, 1H),

1.83 (sex, *J*=7.0 Hz, 1H), 1.62–1.49 (m, 1H), 1.38–1.26 (m, 1H), 1.07 (d, *J*=7.0 Hz, 3H), 0.96 (t, *J*=7.0 Hz, 3H), 0.83 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.53 ($^1J_{C-Se}$=140.8 Hz), 136.55, 128.19, 127.84, 126.10, 85.44, 65.78, 35.37, 35.31, 34.71 ($^1J_{C-Se}$=55.8 Hz), 29.24, 29.21, 19.42, 17.67, 11.35; ^{77}Se NMR ($CDCl_3$) δ 233.95, 233.87. Anal. calcd for $C_{15}H_{21}NOSe$: C, 58.06; H, 6.82; N, 4.51. Found: C, 58.16; H, 6.88; N, 4.61.

*3.1.4. Oxazole, 2-[(2-ethyl)-hex-1-ylseleno]-4,5-dihydro-4-methyl-5-phenyl-,[4*S*-(4*R**,5*S**)] (**3**)*

Yield 97%; IR (neat) 3064, 3030, 2959, 2928, 2872, 2858, 1607, 1454, 1378, 1290, 1256, 1110, 1080, 1040, 956, 934, 747, 699, 639 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31–7.10 (m, 5H), 5.55 (d, *J*=9.3 Hz, 1H), 4.38 (dq, *J*=6.9, 9.3 Hz, 1H), 3.17–3.06 (m, 2H), 1.60 (sept, *J*=6.2 Hz, 1H), 1.38–1.17 (m, 8H), 0.83 (t, *J*=7.5 Hz, 6H), 0.70 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.58 ($^1J_{C-Se}$=140.5 Hz), 136.57, 128.17, 127.84, 126.11, 85.45, 65.78, 39.72, 39.70, 33.14, 32.38 ($^1J_{C-Se}$=55.5 Hz), 28.88, 28.85, 26.42, 22.86, 17.66, 13.99, 10.94; ^{77}Se NMR ($CDCl_3$) δ 225.83, 225.10. Anal. calcd for $C_{18}H_{27}NOSe$: C, 61.35; H, 7.72; N, 3.97. Found: C, 61.23; H, 7.77; N, 4.30.

3.2. General procedure for activated alkyl bromides

To a solution of selone (0.058 g, 0.24 mmol) in acetone (2.0 mL) was added α-bromo-γ-butyrolactone (0.040 g, 0.24 mmol) dropwise at room temperature. To this was added triethylamine (0.049 g, 0.48 mmol) dropwise at room temperature. The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified on silica gel (50% v/v EtOAc/hexane) giving 0.065 g (84%) of the product as a colorless oil.

*3.2.1. 2(3*H*)-Furanone, 3-[(4,5-dihydro-4-methyl-5-phenyl-2-oxazolyl)seleno]dihydro-,[4*S*-(4*R**,5*S**)] (**4**)*

Yield 84%; IR (neat) 3202, 3109, 3087, 3063, 3030, 2974, 2928, 1776, 1611, 1495, 1453, 1375, 1335, 1291, 1259, 1171, 1110, 1080, 1020, 1000, 947, 935, 916, 879, 749, 728, 700, 684, 639 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31–7.09 (m, 10H), 5.61 (d, *J*=9.3 Hz, 1H), 5.59 (d, *J*=9.3 Hz, 1H), 4.43–4.27 (m, 6H), 4.27–4.20 (m, 2H), 2.87–2.78 (m, 2H), 2.59–2.47 (m, 2H), 0.69 (d, *J*=6.9 Hz, 3H), 0.68 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.82, 157.18, 135.89, 128.32, 128.10, 126.10, 126.07, 86.20, 67.24, 65.96, 65.90, 36.35, 36.25, 31.36, 31.32, 17.64; ^{77}Se NMR ($CDCl_3$) δ 380.86, 378.76. Anal. calcd for $C_{14}H_{15}NO_3Se$: C, 51.86; H, 4.66; N, 4.32. Found: C, 51.57; H, 4.79; N, 4.21.

*3.2.2. Oxazole, 2-(2-cyclohexen-1-ylseleno)-4,5-dihydro-4-methyl-5-phenyl-,[4*S*-(4*R**,5*S**)] (**5**)*

Yield 80%; IR (neat) 3187, 3085, 3060, 3025, 2971, 2925, 2831, 1602, 1494, 1453, 1376, 1290, 1252, 1210, 1181, 1107, 1079, 1035, 998, 953, 934, 914, 878, 865, 736, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31–7.10 (m, 10H), 5.86–5.80 (m, 2H), 5.77–5.72 (m, 2H), 5.55 (d, *J*=9.3 Hz, 2H), 4.43–4.34 (m, 4H), 2.12–2.04 (m, 4H), 2.04–1.97 (m, 4H), 1.81–1.71 (m, 2H), 1.70–1.61 (m, 2H), 0.71 (d, *J*=6.9 Hz, 3H), 0.70 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.80 ($^1J_{C-Se}$=140.5 Hz), 159.78 ($^1J_{C-Se}$=140.5 Hz), 136.56, 136.52, 130.78, 130.75, 128.19, 127.84, 126.82, 126.12, 85.28, 85.24, 65.80, 41.23 ($^1J_{C-Se}$=55.5 Hz), 41.21 ($^1J_{C-Se}$=55.5 Hz), 30.20, 30.03, 24.85, 19.84, 17.71; ^{77}Se NMR ($CDCl_3$) δ 363.15. (C_6D_6) δ 360.68, 358.56. Anal. calcd for $C_{16}H_{19}NOSe$: C, 60.00; H, 5.98; N, 4.37. Found: C, 59.84; H, 6.11; N, 4.30.

3.3. General procedure for Mitsunobu reactions

To a solution of selone (0.113 g, 0.500 mmol), monodeuterated benzyl alcohol (0.037 g, 0.333 mmol), and triphenylphosphine (0.131 g, 0.500 mmol) in dichloromethane (5.0 mL) was added diisopropyl azodicarboxylate (0.106 g, 0.500 mmol) dropwise at room temperature. The mixture was stirred at room temperature for 2–3 h. The solvent was removed under reduced pressure and the residue was purified on silica gel with dichloromethane giving 0.973 g (92%) of the product as a colorless oil.

3.3.1. Oxazole, 2-[2-phenyl-1-(^{2}H)ethyl-1-ylseleno]-4,5-dihydro-4-(R)-phenyl (**6**)

Yield 92%; IR (neat) 3174, 3103, 3082, 3059, 3026, 2961, 2894, 1600, 1582, 1493, 1451, 1333, 1255, 1121, 1076, 1029, 941, 890, 791, 758, 739, 697, 643, 589, 546 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.31–6.95 (m, 20H), 4.89 (d, *J*=9.3 Hz, 1H), 4.87 (d, *J*=9.3 Hz, 1H), 4.23 (br s, 1H), 4.20 (br s, 1H), 4.03 (d, *J*=9.3 Hz, 2H), 3.71 (apparent t, *J*=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 161.51, 141.82, 137.66, 128.99, 128.64, 128.55, 127.62, 127.27, 126.56, 76.17, 70.14, 30.39 (t, *J*=22.5 Hz); ^{77}Se NMR ($CDCl_3$) δ 344.92, 344.86. (C_6D_6) δ 351.47, 351.42. Anal. calcd for $C_{16}H_{14}DNOSe$: C, 60.57; H, 4.45; N, 4.41. Found: C, 60.19; H, 4.84; N, 4.39.

Acknowledgements

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