Highly Selective Thioselenation of Olefins Using Disulfide–Diselenide Mixed System

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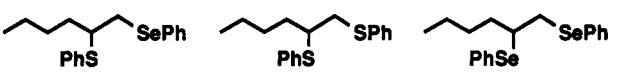
A highly selective thioselenation of olefins has been attained by using a disulfide–diselenide mixed system. Upon irradiation through Pyrex with a tungsten lamp in the absence of solvent, the thioselenation of olefins **1** with diphenyl disulfide (**2**) and diphenyl diselenide (**3**) takes place to provide 1-(phenylthio)-2-(phenylseleno)alkanes **4** as a sole product in good yields. In the cases of terminal olefins, the thioselenation proceeds regioselectively. The cyclic olefins like cyclopentene and cyclohexene also undergo thioselenation to give corresponding *E* isomers stereoselectively. The reaction of the conjugate diene with diphenyl disulfide and diphenyl diselenide produces the 1,4-thioselenation adduct in good yield. The excellent regioselectivity observed in the thioselenation of the terminal olefins is due to the higher reactivity of PhS•, compared with PhSe•, toward carbon–carbon double bonds and the higher capturing ability of $(PhSe)_2$, compared with $(PhS)_2$, toward carbon radicals.

The addition of heteroatom-centered radicals to unsaturated compounds is one of the basic reactions in organic chemistry.[1] It is well-known that disulfides and diselenides undergo photolysis to generate thiyl radicals and seleno radicals, respectively, as labile intermediates.[2] However, there are no examples reported up to date of the efficient free-radical addition of disulfides and diselenides to olefins.[3-5] Indeed, the attempted reactions of diphenyl disulfide (**2**) and diphenyl diselenide (**3**) with olefins like 1-hexene (**1a**) hardly proceeded upon irradiation with a tungsten lamp (500 W) through Pyrex.[6]

It has been reported that the addition rate constants of PhSe• to an olefinic double bond are smaller than those of PhS• by a factor of about 10–50,[7] whereas the rate constants of the S_H2 reaction of alkyl radicals with diphenyl diselenide (**3**) are known to be much larger than those with diphenyl disulfide (**2**) by a factor of ca. 160.[8] These facts suggest that the difficulty in realizing the addition of disulfides to carbon–carbon double bond is conceivably due to the lower capturing ability of disulfides toward carbon radicals formed by the addition of thiyl radical to the double bond and, in contrast, that the difficulty of the addition of diselenides may be based on the lower reactivity of seleno radicals toward double bond. Accordingly, if the addition would be performed in coexistence of $(PhS)_2$ and $(PhSe)_2$, the high reactivity of PhS• toward olefins and the excellent capturing ability of $(PhSe)_2$ for carbon radicals may realize the simultaneous addition of two different heteroatom groups to double bond. These considerations prompted us to examine the reaction of 1-hexene (**1a**) with equimolar amounts of $(PhS)_2$ and $(PhSe)_2$ by irradiation with a tungsten lamp at 45 °C[9] for 30 h, which successfully provided 1-(phenylthio)-2-(phenylseleno)hexane (**4a**) as a sole product and 1-(phenylseleno)-2-(phenylthio)hexane (**5a**) as the regioisomer; the disulfide adduct **6a** and the diselenide adduct **7a** were not formed at all (Scheme I and entry 1 in Table I).



5a **6a** **7a**

The stoichiometric reaction of **1a** (1 mmol) with **2** (0.5 mmol) and **3** (0.5 mmol) at 45 °C for 30 h provided **4a** in 70% yield (entry 2, Table I). The regiochemistry of the thioselenation product was determined by ^{13}C NMR (OFR or INEPT) because the signals of the α-carbon of selenium can be assigned on the basis of satellite caused by ^{77}Se (see the thioselenation of **1a** in the Experimental Section).

Table I summarizes the results of the thioselenation of several olefins in the $(PhS)_2/(PhSe)_2$ mixed system. A variety of functional groups such as hydroxy (entry 3), trimethylsilyl (entry 4), alkoxy (entry 5), cyano (entry 6), and carbonyl groups (entries 7 and 8) did not affect the thioselenation with $(PhS)_2$ and $(PhSe)_2$. In each case of terminal olefins examined, the excellent regioselectivity was observed. Again, the regioisomer, the disulfide adduct, and the diselenide adduct were not formed in all cases except for butyl vinyl ether (**1d**). The thioselenation of **1d** was exceptionally accompanied by the formation of 1,2-bis(phenylthio)ethyl butyl ether as a byproduct (11%).

(1) Kochi, J. K. *Free Radicals*; Wiley: New York, 1973; Vol. II.
(2) Schmidt, U.; Müller, A.; Markau, K. *Chem. Ber.* **1964**, *97*, 405.
(3) For the radical addition of organic disulfides to acetylenes, see: Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1967**, *32*, 3837.
(4) For the radical addition of organic diselenides to acetylenes and allenes, see: (a) Back, T. G.; Krishna, M. V. *J. Org. Chem.* **1988**, *53*, 2533. (b) Ogawa, A.; Yokoyama, K.; Yokoyama, H.; Sekiguchi, M.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1990**, *31*, 5931. (c) Ogawa, A.; Yokoyama, H.; Yokoyama, K.; Masawaki, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **1991**, *56*, 5721. (d) Ogawa, A.; Takami, N.; Sekiguchi, M.; Yokoyama, H.; Kuniyasu, H.; Ryu, I.; Sonoda, N. *Chem. Lett.*, in press. For the palladium-catalyzed addition of organic disulfides and diselenides to acetylenes, see: (e) Kuniyasu, H.; Ogawa, A.; Miyazaki, S.-I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.*, in press.
(5) For the radical addition of *S*-benzoyl phenylseleno sulfide to olefins, see: Toru, T.; Seko, T.; Maekawa, E. *Tetrahedron Lett.* **1985**, *26*, 3263.
(6) The yields of the disulfide adduct and the diselenide adduct are 7% and 9%, respectively, upon irradiation for 30 h. Prolonged reaction time did not improve the yields of 1,2-adducts (330 h, 18% for the disulfide adduct; 270 h, 21% for the diselenide adduct).
(7) In the case of styrene, for example, the addition rate constants of PhS• and PhSe• are 5.1×10^7 and 2.2×10^6 M^{-1} s^{-1}, respectively. See: (a) Ito, O. *J. Am. Chem. Soc.* **1983**, *105*, 850. (b) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1979**, *101*, 1815. (c) Ito, O.; Matsuda, M. *J. Org. Chem.* **1984**, *49*, 17. (d) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1981**, *103*, 5871. (e) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1979**, *101*, 5732. (f) Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* **1982**, *104*, 1701. (g) McPhee, D. J.; Campredon, M.; Lesage, M.; Griller, D. *J. Am. Chem. Soc.* **1989**, *111*, 7563.
(8) The rate constants for the S_H2 reaction of 5-hexenyl radical with $(PhS)_2$ and $(PhSe)_2$ are 7.6×10^4 and 1.2×10^7 M^{-1} s^{-1}, respectively. See: (a) Russell, G. A.; Tashtoush, H. *J. Am. Chem. Soc.* **1983**, *105*, 1398. (b) Perkins, M. J.; Turner, E. S. *J. Chem. Soc., Chem. Commun.* **1981**, 139. (c) Russell, G. A.; Ngoviwatchai, P.; Tashtoush, H. I.; Pla-Dalmau, A.; Khanna, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 3530.
(9) The diphenyl disulfide (mp 58–60 °C)/diphenyl diselenide (mp 63 °C)/olefin mixture becomes homogeneous above that temperature (45 °C).

0022-3263/92/1957-0111$03.00/0

Scheme I

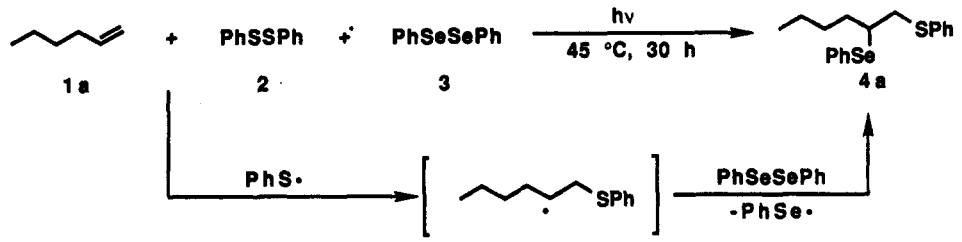
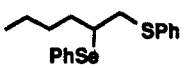
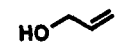
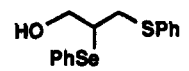
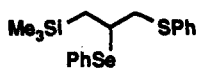
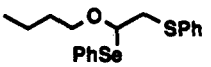
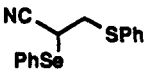
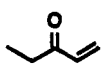
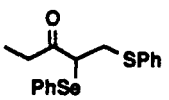
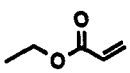
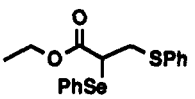
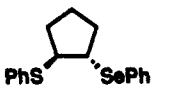
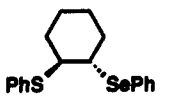
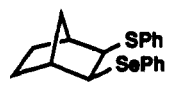
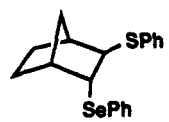
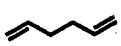
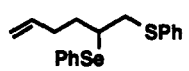
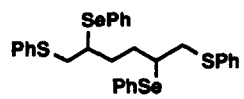


Table I. Photoinitiated Thioselenation of Olefins with $(PhS)_2$ and $(PhSe)_2$[a]

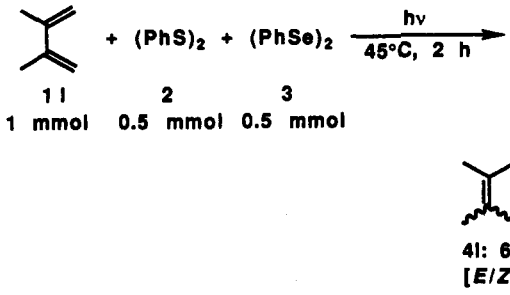
entry	olefin		temp	time	product		yield, %[b]
1		1a	45 °C	30 h		4a	74 (89)
2			45 °C	30 h			(70)[c]
3		1b	45 °C	31 h		4b	67 (80)
4		1b	45 °C	73 h		4c	51 (71)
5		1d	45 °C	20 h		4d	41 (61)[d]
6		1e	45 °C	34 h		4e	75 (80)
7		1f	40 °C	40 h		4f	66 (80)
8		1g	45 °C	83 h		4g	83 (91)
9		1h	45 °C	30 h		4h[e]	(65)
10			45 °C	57 h			74 (82)
11		1i	45 °C	30 h		4i[e]	(38)
12			45 °C	121 h			69 (71)
13		1j	40 °C	26 h		4j	55 (66)
						4j'	32 (38)
14[c]		1k	45 °C	20 h		4k	40[f]
						4k'	11[f]

[a] Reaction conditions: olefin (1 mmol), PhSSPh (1 mmol), PhSeSePh (1 mmol), $h\nu$; tungsten lamp (500 W, Pyrex). [b] Isolated (NMR) yield. [c] PhSSPh (1 mmol) and PhSeSePh (0.5 mmol) were used. [d] Along with disulfide adduct (11%). [e] Only *E* isomer. [f] Yield based on **1k**.

The thioselenation of cyclic olefins **1h** and **1i** proceeded stereoselectively to give only *E* isomers **4h** and **4i** (entries 10 and 12).[10] Norbornene (**1j**) provided a mixture of stereoisomers (entry 13). The stoichiometric reaction of 1,5-hexadiene (**1k**) with the disulfide and the diselenide led to the formation of the single thioselenation product **4k** and the double thioselenation product **4k'**. Noteworthy is that some side reactions of reactive olefins under radical conditions (e.g., dimerization and polymerization) were completely suppressed in the presence of $(PhSe)_2$. An application of this thioselenation with $(PhS)_2$ and $(PhSe)_2$

(10) The stereochemistry of **4h** and **4i** was determined from the following experiment: The oxidation of **4h** and **4i** with excess H_2O_2 provided not allylic sulfones but vinylic sulfones in 76% and 90% yields, respectively, *via* the selenoxide *syn* elimination.

to the conjugated diene **11** was examined: When irradiated with a tungsten lamp for 2 h, the reaction of 2,3-dimethyl-1,3-butadiene (**11**) with stoichiometric amounts of the disulfide and the diselenide selectively produced 1,4-adduct **41** in good yield (eq 1).[11]



(1)

In conclusion, the highly selective thioselenation of olefins has been attained by using a disulfide–diselenide mixed system. The excellent regioselectivity observed is due to the high reactivity of PhS• toward the carbon–carbon double bond and the high capturing ability of $(PhSe)_2$ toward carbon radicals. Investigations along these lines are continuing.

Experimental Section

General Comments. Unless otherwise noted, materials were obtained commercially and were purified by distillation or recrystallization. Diphenyl diselenide (**3**) was prepared according to the literature[12] and was recrystallized from *n*-hexane.

^1H NMR spectra of $CDCl_3$ solutions were recorded with a JEOL JNM-GSX-270 (270 MHz) spectrometer. Me_4Si served as the internal standard. ^{13}C NMR spectra of $CDCl_3$ solutions were recorded with a JEOL JNM-GSX-270 instruments. Chemical shifts in the ^{13}C NMR spectra were determined relative to $CDCl_3$ but are reported in ppm downfield from Me_4Si (δ_{CDCl_3} = 76.9 ppm). IR spectra were recorded with a Perkin Elmer Model 1600 spectrometer. Mass spectra were recorded with a JEOL JMS-DX303. Elemental analyses were performed in the Instrumental Analysis Center of the Faculty of Engineering, Osaka University.

1-(Phenylthio)-2-(phenylseleno)hexane (4a). In a Pyrex glass tube (ϕ = 5 mm) were placed 1-hexene (**1a**, 1 mmol), diphenyl disulfide (**2**, 1 mmol), and diphenyl diselenide (**3**, 1 mmol). The tube was filled with Ar and was sealed under reduced pressure. The mixture was irradiated at 45 °C for 30 h with a tungsten lamp (500 W) positioned approximately 8 cm from the tube. The NMR yield of the thioselenation product (89%) was determined by ^1H NMR measurement of the reaction mixture using trioxane (δ = 5.15) as an internal standard. Unreacted 1-hexene and $CDCl_3$ as the NMR solvent were evaporated in vacuo, and the residue was chromatographed on silica gel eluted with *n*-hexane to remove diphenyl disulfide, diphenyl diselenide, and diphenyl selenosulfide.[13] Purification by preparative TLC on silica gel (Wakogel B-5F (through 325 mesh 75% up), *n*-hexane/Et_2O = 200/1, R_f = 0.091) yielded 258 mg (74%) of 1-(phenylthio)-2-(phenylseleno)hexane (**4a**, a pale yellow oil): ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, 3 H, J = 7 Hz), 1.30 (m, 3 H), 1.57 (m, 2 H), 1.97 (m, 1 H), 3.00 (dd, 1 H, J = 10, 13 Hz), 3.20 (m, 1 H), 3.37 (dd, 1 H, J = 13, 4 Hz), 7.14–7.49 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.91, 22.37, 29.65, 32.66, 40.08 (t, *C*SPh), 44.48 (d, *C*SePh), 126.02, 127.69, 128.50, 128.82, 128.99, 129.43, 135.19, 135.83. The satellite caused by ^{77}Se can be used to distinguish clearly between the signal of the α-carbon of selenium and that of sulfur. So the measurement of ^{13}C NMR (OFR or INEPT) unambiguously indicated that the phenylthio group bonded to the methylene group ($-CH_2$) and the phenylseleno group bonded to the methyne group (–CH): IR (NaCl) 2927, 1579, 1478, 1437, 1023, 736, 690 cm^{-1}; MS m/e = 350 (M^+, 15). Anal. Calcd for $C_{18}H_{22}SSe$: C, 61.88; H, 6.35. Found: C, 61.69; H, 6.59.

3-(Phenylthio)-2-(phenylseleno)-1-propanol (4b). The reaction of allyl alcohol (**1b**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 45 °C for 31 h with a tungsten lamp (500 W) through Pyrex. After the NMR yield (80%) was determined in the same manner as described above, the residual mixture was purified by flash chromatography on silica gel using *n*-hexane and then diethyl ether as eluents to provide 215 mg (67%) of 3-(phenylthio)-2-(phenylseleno)-1-propanol (**4b**, a pale yellow oil): ^1H NMR (270 MHz, $CDCl_3$) δ 2.32 (br s, 1 H), 3.17 (dd, 1 H, J = 10.7, 14.6 Hz), 3.32–3.38 (m, 2 H), 3.83 (d, 2 H, J = 4.0 Hz), 7.16–7.53 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 35.98 (t, CSPh), 47.20 (d, CSePh), 62.88, 126.50, 127.11, 128.33, 129.11, 129.31, 129.71, 135.33, 135.53; IR (NaCl) 3418, 3055, 2934, 1579, 1478, 1438, 1071, 1023, 738, 691 cm^{-1}; MS m/e = 324 (M^+, 6). Anal. Calcd for $C_{15}H_{16}OSSe$: C, 55.72, H, 4.99. Found: C, 56.01; H, 5.25.

1-(Phenylthio)-2-(phenylseleno)-3-(trimethylsilyl)propane (4c). The thioselenation of allylsilane (**1c**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 45 °C for 73 h[14] with a tungsten lamp (500 W) through Pyrex. After determination of the NMR yield (71%), the residual mixture was purified by preparative TLC (silica gel, *n*-hexane/Et_2O = 200/1) to provide 193 mg (51%) of 1-(phenylthio)-2-(phenylseleno)-3-(trimethylsilyl)propane (**4c**, a pale yellow oil): ^1H NMR (270 MHz, $CDCl_3$) δ 0.10 (s, 9 H), 0.91 (dd, 1 H, J = 9.8, 15.3 Hz), 1.58 (dd, 1 H, J = 4.3, 15.3 Hz), 2.98 (dd, 1 H, J = 9.5, 13.1 Hz), 3.30 (m, 1 H), 3.36 (dd, 1 H, J = 3.4, 13.1 Hz), 7.09–7.46 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ –0.71, 21.36, 39.72 (d, *C*SePh), 43.49 (t, *C*SPh), 126.17, 127.69, 128.84, 129.07, 129.30, 129.82, 134.92, 135.67; IR (NaCl) 3057, 2952, 2894, 1579, 1478, 1438, 1248, 848, 737, 691 cm^{-1}; MS m/e = 380 (M^+, 0.3). Anal. Calcd for $C_{18}H_{24}SSeSi$: C, 56.97; H, 6.37. Found: C, 57.41; H, 6.62.

2-(Phenylthio)-1-(phenylseleno)-1-butoxyethane (4d). The thioselenation of butyl vinyl ether (**1d**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 45 °C for 20 h with a tungsten lamp (500 W) through Pyrex. Measurement of ^1H NMR spectrum of the reaction mixture indicated the formation of the desired thioselenation product **4d** (61%) and the disulfide adduct (11%). Purification by column chromatography on silica gel followed by preparative TLC on silica gel provided 150 mg (41%) of 2-(phenylthio)-1-(phenylseleno)-1-butoxyethane (**4d**, a pale yellow oil): ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 7.3 Hz), 1.38 (m, 2 H), 1.56 (m, 2 H), 3.37 (dd, 1 H, J = 9.2, 13.7 Hz), 3.38 (m, 1 H), 3.44 (dd, 1 H, J = 3.9, 13.7 Hz), 3.89 (dt, 1 H, J = 6.4, 9.5 Hz), 4.97 (dd, 1 H, J = 3.9, 9.2 Hz), 7.14–7.57 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.84, 19.32, 31.08, 41.44 (t, CSPh), 70.24, 85.50 (d, CSePh), 126.09, 127.55, 127.96, 128.82, 129.00, 129.49, 134.31, 135.94; IR (NaCl) 3057, 2957, 2931, 2870, 1579, 1477, 1438, 1106, 738, 691 cm^{-1}; MS m/e = 257 (M^+ – PhS, 5.7), 209 (M^+ – PhSe, 100). Anal. Calcd for $C_{18}H_{22}OSSe$: C, 59.17; H, 6.07. Found: C, 59.54; H, 6.26.

2-(Phenylthio)-1-(phenylseleno)-1-cyanoethane (4e). The thioselenation of acrylonitrile (**1e**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 45 °C for 34 h with a tungsten lamp (500 W) through Pyrex. After the NMR yield was determined, the reaction mixture was purified by preparative TLC on silica gel (*n*-hexane/Et_2O = 200/1) to yield 239 mg (75%) of 2-(phenylthio)-1-(phenylseleno)-1-cyanoethane (**4e**, a pale yellow oil): ^1H NMR (270 MHz, $CDCl_3$) δ 3.11 (dd, 1 H, J = 10.4, 14.0 Hz), 3.28 (dd, 1 H, J = 5.5, 14.0 Hz), 3.62 (dd, 1 H, J = 5.5, 10.4 Hz), 7.26–7.70 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.24 (d, CSePh), 37.32 (t, CSPh), 118.51, 124,98, 127.87, 129.41, 129.65, 129.99, 131.56, 132.92, 136.76; IR (NaCl) 3056, 2929, 2233, 1580, 1477, 1438, 1023,

(11) Further irradiation (24 h) caused the selenide–sulfide exchange reaction of once-formed thioselenation product **41** with $(PhS)_2$, giving 1,4-disulfide; this suggests the possibility of the addition of $(PhS)_2$ to 1,3-diene catalyzed by $(PhSe)_2$. This catalytic reaction is now under investigation.

(12) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(13) When a mixture of $(PhS)_2$ and $(PhSe)_2$ (1:1) was irradiated with a tungsten lamp, PhSSePh was formed in situ (the ratio of $(PhS)_2$/$(PhSe)_2$/PhSSePh was ca. 1/1/1.4 during the thioselenation of olefins).

(14) Irradiation for 25 h provided 23% of the desired thioselenation product **4c** and 72% of allysilane was recovered.

742, 691 cm^{-1}; MS m/e = 319 (M$^+$, 7). Anal. Calcd for $C_{15}H_{13}NSSe$: C, 56.60; H, 4.12; N, 4.40. Found: C, 56.59; H, 4.26; N, 4.42.

1-(Phenylthio)-2-(phenylseleno)pentan-3-one (4f). The thioselenation of ethyl vinyl ketone (**1f**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 40 °C for 40 h with a tungsten lamp (500 W) through Pyrex. After the NMR yield was determined, the reaction mixture was purified by preparative TLC on silica gel (n-hexane/Et_2O = 200/1) to yield 230 mg (66%) of 1-(phenylthio)-2-(phenylseleno)pentan-3-one (**4f**, a pale yellow oil): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.07 (t, 3 H, J = 7.3 Hz), 2.41 (dq, 1 H, J = 7.3, 17.7 Hz), 2.80 (dq, 1 H, J = 7.3, 17.7 Hz), 3.27 (dd, 1 H, J = 4.3, 13.7 Hz), 3.38 (dd, 1 H, J = 10.4, 13.7 Hz), 3.81 (dd, 1 H, J = 4.3, 10.4 Hz), 7.16–7.48 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 8.15, 34.27 (t), 34.74 (t), 48.29 (d, *C*SePh), 126.37, 126.52, 129.05, 129.26, 129.79, 135.11, 136.03, 205.03; IR (NaCl) 2973, 1706, 1472, 1438, 1023, 740, 691 cm^{-1}; MS m/e = 350 (M$^+$, 3). Anal. Calcd for $C_{17}H_{18}OSSe$: C, 58.45; H, 5.19. Found: C, 58.50; H, 5.35.

Ethyl 3-(Phenylthio)-2-(phenylseleno)propiolate (4g). The thioselenation of ethyl acrylate (**1g**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 45 °C for 83 h with a tungsten lamp (500 W) through Pyrex. After the NMR yield was determined, the reaction mixture was purified by preparative TLC on silica gel (n-hexane/Et_2O = 200/1) to yield 303 mg (83%) of ethyl 3-(phenylthio)-2-(phenylseleno)propiolate (**4g**, a pale yellow oil): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.10 (t, 3 H, J = 7.0 Hz), 3.19 (dd, 1 H, J = 5.5, 13.7 Hz), 3.27 (dd, 1 H, J = 10.1, 13.7 Hz), 3.64 (dd, 1 H, J = 5.5, 10.1 Hz), 4.02 (q, 2 H, J = 7.0 Hz), 7.10–7.48 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.92, 36.03 (t, *C*SPh), 41.72 (d, *C*SePh), 61.19, 126.80, 128.77, 128.93, 128.98, 129.05, 130.55, 134.47, 135.87, 171.10; IR (NaCl) 2980, 1728, 1477, 1438, 1255, 1207, 1151, 1022, 740, 691 cm^{-1}; MS m/e = 366 (M$^+$, 6). Anal. Calcd for $C_{17}H_{18}O_2SSe$: C, 55.89; H, 4.97. Found: C, 55.60; H, 4.88.

(*E*)-1-(Phenylthio)-2-(phenylseleno)cyclopentane (4h). The thioselenation of cyclopentene (**1h**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 45 °C for 57 h with a tungsten lamp (500 W) through Pyrex. Measurement of ^{1}H NMR spectrum of the reaction mixture indicated the formation of only one isomer (*E*)[11] of the desired thioselenation product **4h**. Purification by preparative TLC on silica gel (n-hexane/Et_2O = 200/1) yielded 246 mg (74%) of (*E*)-1-(phenylthio)-2-(phenylseleno)cyclopentane (**4h**, a pale yellow oil): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.75–1.88 (m, 4 H), 2.38 (m, 2 H), 3.65 (m, 2 H), 7.16–7.41 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.26, 30.69, 31.14, 48.17 (*C*SePh), 53.13 (*C*SPh), 126.44, 127.42, 128.80, 128.99, 129.69, 130.84, 134.33, 135.58; IR (NaCl) 2954, 1578, 1478, 1437, 1023, 738, 691 cm^{-1}; MS m/e = 334 (M$^+$, 20). Anal. Calcd for $C_{17}H_{18}SSe$: C, 61.25; H, 5.44. Found: C, 60.96; H, 5.53.

(*E*)-1-(Phenylthio)-2-(phenylseleno)cyclohexane (4i). The thioselenation of cyclohexene (**1i**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 45 °C for 121 h with a tungsten lamp (500 W) through Pyrex. Measurement of ^{1}H NMR spectrum of the reaction mixture indicated the formation of only one isomer (*E*)[11] of the desired thioselenation product **4i**. Purification by preparative TLC on silica gel (n-hexane/Et_2O = 200/1) yielded 239 mg (69%) of (*E*)-1-(phenylthio)-2-(phenylseleno)cyclohexane (**4i**, a pale yellow oil): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.44 (m, 2 H), 1.67 (m, 4 H), 2.27 (m, 2 H), 3.40 (m, 2 H), 7.18–7.47 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.40, 24.28, 30.15, 30.29, 46.51 (*C*SePh), 50.50 (*C*SPh), 126.88, 127.53, 128.85, 128.96, 129.31, 132.05, 134.78, 134.96; IR (NaCl) 3056, 2930, 2853, 1578, 1476, 1437, 1023, 737, 691 cm^{-1}; MS m/e = 348 (M$^+$, 2). Anal. Calcd for $C_{18}H_{20}SSe$: C, 62.24; H, 5.80. Found: C, 61.97; H, 5.80.

Thioselenation of Norbornene (1j) with Diphenyl Disulfide and Diphenyl Diselenide. The thioselenation of norbornene (**1j**, 1 mmol) with diphenyl disulfide (**2**, 1 mmol) and diphenyl diselenide (**3**, 1 mmol) was performed by irradiation at 40 °C for 26 h with a tungsten lamp (500 W) through Pyrex. After the NMR yields were determined, the reaction mixture was purified by preparative TLC on silica gel (n-hexane/Et_2O = 200/1) to give 197 mg (55%) of 1-*exo*-(phenylthio)-2-*exo*-(phenylseleno)norbornane (**4j**, R_f = 0.19) and 115 mg (32%) of 1-*exo*-(phenylthio)-2-*endo*-(phenylseleno)norbornane (**4j'**, R_f = 0.28). The product **4j** was obtained as white needles, whereas **4j'** was isolated as a pale yellow oil, but was crystallized by keeping overnight in refrigerator. **4j**: mp 82.5–83.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17–1.27 (m, 3 H), 1.61 (m, 2 H), 2.04 (d, 1 H, J = 9.1 Hz), 2.44 (s, 2 H), 3.53 (d, 1 H, J = 6.7 Hz), 3.73 (dd, 1 H, J = 1.0, 7.9 Hz), 7.13–7.55 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 28.88, 29.15, 34.61, 44.92, 45.06, 53.76 (*C*SePh), 55.97 (*C*SPh), 125.93, 126.75, 128.80, 128.95, 129.34, 132.66, 132.94, 138.24; IR (NaCl) 3051, 2957, 2862, 1578, 1476, 1438, 1020, 738, 690 cm^{-1}; MS m/e = 360 (M$^+$, 12). Anal. Calcd for $C_{19}H_{20}SSe$: C, 63.50; H, 5.61. Found: C, 63.68; H, 5.65. **4j'**: mp 62.0–63.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25–1.32 (m, 1 H), 1.39–1.53 (m, 2 H), 1.65 (tt, 1 H, J = 4.3, 12.2 Hz), 1.79 (d, 1 H, J = 10.4 Hz), 1.92–2.01 (m, 1 H), 2.31 (br d, 1 H, J = 4.0 Hz), 2.39 (br s, 1 H), 2.99 (dd, 1 H, J = 4.3, 12.2 Hz), 3.33 (m, 1 H), 7.15–7.60 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.55, 28.69, 36.16, 42.22, 43.89, 52.75 (*C*SePh), 57.37 (*C*SPh), 126.32, 127.31, 128.85, 128.96, 130.10, 130.30, 134.12, 136.54; IR (NaCl) 3055, 2959, 2869, 1579, 1478, 1437, 1300, 1023, 736, 691 cm^{-1}; MS m/e = 360 (M$^+$, 16). Anal. Calcd for $C_{19}H_{20}SSe$: C, 63.50; H, 5.61. Found: C, 63.28; H, 5.63.

Thioselenation of 1,5-Hexadiene (1k) with Diphenyl Disulfide and Diphenyl Diselenide. The thioselenation of 1,5-hexadiene (**1k**, 1 mmol) with diphenyl disulfide (**2**, 0.5 mmol) and diphenyl diselenide (**3**, 0.5 mmol) was performed by irradiation at 45 °C for 20 h with a tungsten lamp (500 W) through Pyrex. After the reaction was complete, the reaction mixture was purified by preparative TLC on silica gel (n-hexane) to give 142 mg (40%) of 1-(phenylthio)-2-(phenylseleno)-5-hexene (**4k**, R_f = 0.20) and 67 mg (11%) of 1,6-bis(phenylthio)-2,5-bis(phenylseleno)hexane (**4k'**, R_f = 0.01). **4k** (a pale yellow oil): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.53–1.70 (m, 1 H), 2.04–2.36 (m, 3 H), 3.00 (dd, 1 H, J = 10, 13 Hz), 3.15–3.25 (m, 1 H), 3.39 (dd, 1 H, J = 4, 13 Hz), 4.95 (d, 1 H, J = 9.7 Hz), 5.02 (dd, 1 H, J = 2, 17 Hz), 5.68–5.82 (m, 1 H), 7.12–7.31 (m, 8 H), 7.47 (dd, 2 H, J = 2, 8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 31.65, 32.04, 40.20 (t, *C*SPh), 43.78 (d, *C*SePh), 115.27, 126.08, 127.77, 128.21, 128.83, 129.01, 129.54, 135.28, 135.68, 137.48; IR (NaCl) 3072, 2928, 1639, 1579, 1478, 1438, 1023, 914, 738, 691 cm^{-1}; MS m/e = 348 (M$^+$, 3). Anal. Calcd for $C_{18}H_{20}SSe$: C, 62.24; H, 5.80. Found: C, 62.06; H, 5.76. **4k'** (white needles): mp 75–76 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.61 (m, 1 H), 1.86 (m, 1 H), 2.20 (m, 1 H), 2.37 (m, 1 H), 2.91–3.01 (m, 2 H), 3.14 (m, 2 H), 3.39 (dd, 2 H, J = 2, 13 Hz), 7.14–7.33 (m, 8 H), 7.44–7.49 (m, 2 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 30.87, 31.11, 40.05 (t, *C*SPh), 40.11 (t, *C*SPh), 43.88 (d, *C*SePh), 44.01 (d, *C*SePh), 126.10, 126.18, 127.91, 127.92, 128.01, 128.89, 128.92, 129.06, 129.48, 129.63, 135.50, 135.54; IR (NaCl) 3072, 2933, 1581, 1480, 1436, 1222, 1020, 736, 691 cm^{-1}; MS m/e = 614 (M$^+$, 1). Anal. Calcd for $C_{30}H_{30}S_2Se_2$: C, 58.82; H, 4.94. Found: C, 58.65; H, 4.74.

Thioselenation of 2,3-Dimethyl-1,3-butadiene (1l) with Diphenyl Disulfide and Diphenyl Diselenide. The thioselenation of 2,3-dimethyl-1,3-butadiene (**1l**, 1 mmol) with diphenyl disulfide (**2**, 0.5 mmol) and diphenyl diselenide (**3**, 0.5 mmol) was performed by irradiation at 45 °C for 2 h with a tungsten lamp (500 W) through Pyrex. Measurement of ^{1}H NMR spectrum of the reaction mixture indicated that the 1,4-thioselenation products were formed exclusively (*Z* isomer: 49%; *E* isomer: 34%). Purification of the reaction mixture by preparative TLC on silica gel (n-hexane/Et_2O = 200/1) provided 118 mg (68%) of 1-(phenylthio)-4-(phenylseleno)-2,3-dimethyl-2-butene (**4l**) as a mixture of stereoisomers (*E*/*Z* = 41/59).[15] *E* isomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.75 (s, 3 H), 1.79 (s, 3 H), 3.22 (s, 2 H), 3.35 (s, 2 H), 7.16–7.48 (m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.86, 18.08, 33.39 (*C*SePh), 39.59 (*C*SPh), 126.38, 127.42, 127.70, 127.89, 128.72, 128.82, 129.64, 130.44, 134.27, 136.80; IR (NaCl) 3070, 3056, 2996, 2914, 1579, 1478, 1437, 737, 691 cm^{-1}; MS m/e = 348 (M$^+$, 2). Anal. Calcd for $C_{18}H_{20}SSe$: C, 62.24; H, 5.80. Found: C, 61.78; H, 5.98. *Z* isomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.59 (s, 3 H), 1.67 (s, 3 H), 3.51 (s, 2 H), 3.56 (s, 2 H), 7.16–7.53

(15) (*E*)-**4l** and (*Z*)-**4l** could not be separated. So, the elemental analyses were performed using the *E* and *Z* mixture of **4l**.

(m, 10 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.57, 18.70, 32.60 (CSePh), 38.47 (CSPh), 126.50, 127.34, 128.78, 128.88, 129.61, 130.88, 134.36, 136.60; MS m/e = 348 (M^+, 1).

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Registry No. **1a**, 592-41-6; **1b**, 107-18-6; **1c**, 762-72-1; **1d**, 111-34-2; **1e**, 107-13-1; **1f**, 1629-58-9; **1g**, 140-88-5; **1h**, 142-29-0; **1i**, 110-83-8; **1j**, 498-66-8; **1k**, 592-42-7; **1l**, 513-81-5; **2**, 882-33-7; **3**, 1666-13-3; **4a**, 137258-85-6; **4b**, 137258-86-7; **4c**, 137258-87-8; **4d**, 137258-88-9; **4e**, 137258-89-0; **4f**, 137258-90-3; **4g**, 137258-91-4; **4h**, 137258-92-5; **4i**, 137258-93-6; **4j**, 137429-16-4; **4j'**, 137258-94-7; **4k**, 137258-95-8; **4k'**, 137258-96-9; (*E*)-**4l**, 137258-97-0; (*Z*)-**4l**, 137258-98-1.

S_N2' Addition of Cuprates to Acyclic Vinyloxiranes. Synthesis of Tylactone and Tylonolide Subunits

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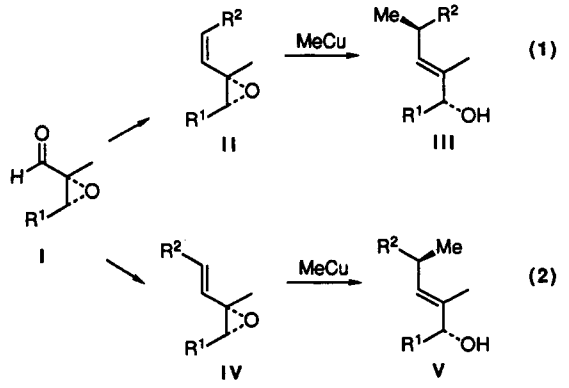
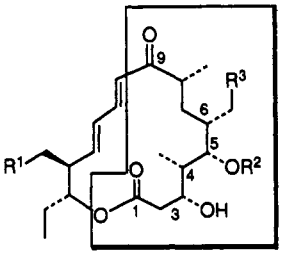
The chiral acyclic vinyloxiranes **8** and **18** undergo highly anti selective S_N2' additions upon treatment with Et_2CuLi and (*S*)-PMBOMOCH$_2$CH(CH$_3$)CH$_2$Cu(CN)Li, respectively. The product of the former addition, diol **9**, affords the α-epoxide **12** upon epoxidation with *m*-CPBA. Conversion to acetonide **15**, a possible C-1–C-7 segment of tylactone, was effected by hydrogenation of the methylene acetonide **14** obtained from epoxide **12** through $LiNEt_2$ elimination and ketalization with 2,2-dimethoxypropane (2,2-DMP). Allylic alcohol **24b**, a close analogue of diol **9**, gave only the β-epoxide **25b** upon treatment with *m*-CPBA. Epoxidation with magnesium monoperoxyphthalic acid (MMPP), however, yielded a separable 53:47 mixture of β- and α-epoxides **25b** and **26b**. The former was carried on to acetonide **29** by a sequence involving basic elimination ($LiNEt_2$), treatment with 2,2-DMP, and hydrogenation. Acetonide **30**, a diastereomer of **29**, was prepared from epoxide **26b** by a parallel sequence. Acetonide **30** was converted to the lactol methyl ether **48**, an intermediate in Nicolaou's synthesis of *O*-micinosyl tylonolide, through displacement of tosylate **43** with KCN and then reduction (DIBAH), methanolysis (HCl, MeOH), silylation (TBSOTf, 2,6-lutidine), and finally PMBOM cleavage (DDQ). An identical sequence was applied to acetonide **29** resulting in the isomeric lactol methyl ether **37**.

The macrolide antibiotics have been the focus of extensive synthetic investigation for over two decades.[1] The quest for synthetically viable routes to these medicinally important natural products has stimulated important methodological developments in acyclic and macrocyclic stereocontrol. In connection with a program on the synthesis of such compounds we undertook studies on the S_N2' addition of organocopper reagents to chiral acyclic vinyloxiranes.[2] Our initial investigations showed that, with certain structural constraints, additions of methylcuprates proceed with high anti diastereoselectivity to afford mainly *E* S_N2' substitution products (eqs 1 and 2). By varying the double-bond geometry or epoxide stereochemistry all diastereomers of a given product can be prepared.



The present study was initiated to examine these S_N2' additions with more complex cuprates as a possible route to subunits of tylactone (VI) or tylonolide (VII).[3] The former is the biosynthetic precursor and the latter the aglycon of tylosin (VIII), a commercially important antibiotic.[4]



VI Tylactone $R^1 = R^2 = H$, $R^3 = CH_3$
VII Tylonolide $R^1 = OH$, $R^2 = H$, $R^3 = CHO$
VIII Tylosin R^1 = Osugar, R^2 = sugar, $R^3 = CHO$

The goal of the tylactone investigation was to optimize ethylcuprate additions to a vinyloxirane such as IX, a modest extension of our previous work, and to develop methodology for further elaborating the S_N2' product X

(1) Cf.: Boeckman, R. K.; Goldstein, S. W. The Total Synthesis of Macrocyclic Lactones In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, 1988; Vol. 8, pp 1–140.

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