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Highly Efficient [2+1] Cycloaddition Reactions of a 1-Seleno-2-silylethene to 2-Phosphonoacrylates: Synthesis of Novel Functionalized Cyclopropanephosphonic Acid Esters.

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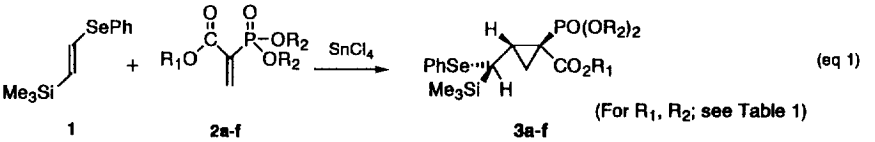
Abstract: 1-Seleno-2-silylethene **1** undergoes stereoselective $SnCl_4$-promoted [2+1] cycloaddition reactions with 2-phosphonoacrylates **2** in high yields; the resulting highly functionalized cyclopropanephosphonic acid ester products **3** are versatile starting materials for biologically important compounds. © 1997 Elsevier Science Ltd.

Cyclopropanes represent a rich source of structural and biological diversity and have attracted considerable interest from organic chemists interested in developing novel methods of cyclopropanation.[1] In this context, we have recently reported a novel [2+1] cycloaddition strategy involving reaction of (*E*)-1-phenylseleno-2-silylethenes with electrophilic olefins, to afford cyclopropane products with high stereoselectivity in the presence of Lewis acids.[2] This novel approach to cyclopropane construction is based on a hitherto unprecedented selenium-stabilized 1,2-silicon migration process that does not occur with the corresponding sulfur analogs.

As part of efforts to expand this reaction to a wide variety of substrates containing synthetically and biologically useful substituents, thus giving rise to highly functionalized cyclopropanes, we were attracted to phosphorus containing esters. The phosphonate functionality has been demonstrated to be a versatile and useful moiety for organic synthesis.[3] In addition, compounds bearing phosphonate groups have a number of useful biochemical properties.[4] 2-Phosphonoacrylates such as **2** would appear to have high reactivity towards 1-seleno-2-silylethene **1** since they are isoelectronic analogues of methylenemalonate esters.[2b] Although a number of reports on the synthesis and chemistry of **2** have appeared in the literature, only a limited number of Lewis acid-promoted reactions of **2** have been reported.[5] In this paper we wish to disclose the results of studies on the use of 2-phosphonoacrylates **2a-f** in [2+1] cycloaddition reactions with 1-seleno-2-silylethene **1** and the finding that remarkably high yields of cyclopropanes **3** result.



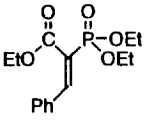
1 **2a-f** **3a-f** (eq 1)

(For R_1, R_2; see Table 1)

2-Phosphonoacrylates **2b-f** were prepared according to literature procedures from the corresponding phosphonoacetates.[6] Table 1 summarizes the [2+1] cycloaddition reactions of **1** and **2** (eq 1). Reaction of **1** (1 equiv.) and 2-phosphonoacrylates **2a-f** (1.3 equiv.) was carried out in the presence of $SnCl_4$ (1.5 equiv.) in CH_2Cl_2 at -78 °C for 3-6 h. Quenching with triethylamine (2.6 equiv.) gave [2+1] cycloadducts **3a-f** as single stereoisomeric products in high yields.[7] Steric bulk in the carboxylate moiety seems to result in lower yields (entries 3, 4), although sterically demanding phosphonic acid ester groups seem to have less effect on overall yield (entry 5). The ready formation of cyclopropanes **3c** and **3d** bearing *t*-butyl and trimethylsilylethyl protected carboxyl groups provides suitable handles for further transformations. No reaction occurred between **1** and the 3-substituted 2-phosphonoacrylates **4** and **5** under these reaction conditions, suggesting steric limitations in the acceptor moiety.[8]

Table 1. [2+1] Cycloadditions of **1** with 2-phosphonoacrylates (**2**)[a]

entry	2-phosphonoacrylate			time / h	product (yield, %)
		R_1	R_2		
1	**2a**	Me	Me	3	**3a** (96)
2	**2b**	Et	Et	6	**3b** (92)
3	**2c**	^{t}Bu	Me	4	**3c** (52)
4	**2d**	CH_2CH_2TMS	Et	4	**3d** (66)[b]
5	**2e**	Et	iPr	4	**3e** (85)[c]
6	**2f**	(*l*)-menthyl	Me	4	**3f** (70)[d]



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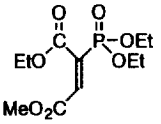

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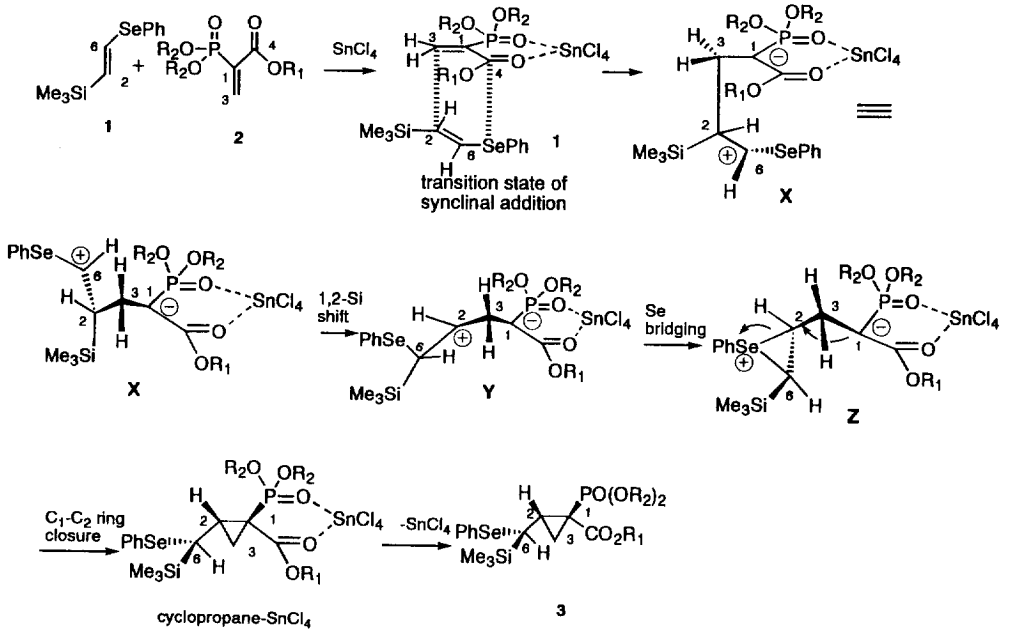
[a] Reactions were carried out at -78 °C at ~0.4 M for **1** in CH_2Cl_2.
[b] 18% recovered **1**. [c] 14% recovered **1**. [d] 12% recovered **1**.

Cyclopropanes **3a-f** were produced as single stereoisomers. Assignment of the stereochemistry was achieved for **3a** and **3c** using 2D-NOESY, which indicated that the CO_2R_1 and $CH(SePh)(SiMe_3)$ groups were orientated *cis*.[9]

The stereochemical outcome of the products may be explained in terms similar to our earlier examples. Thus, *via* a Se---C=O secondary orbital interaction in the first synclinal addition step, as illustrated in Scheme 1.[2] Thus, initially a complex of **2** with $SnCl_4$ is formed, which is then attacked by the selenosilyl nucleophile **1**. Synclinal stereoselective addition (due to a stabilizing secondary orbital interaction, Se---C=O, not Se---$PO(OR_2)_2$) may cause the observed *cis*-selectivity regarding CO_2R_1 and $CH(SePh)(SiMe_3)$ groups. Subsequent 1,2-silicon migration from the first produced zwitterion **X** leads to the second intermediate **Y**. This is followed by generation of a selenium-bridged intermediate **Z** by minimum motion; ring closure then affords cyclopropane **3**. Thus, single-bond rotation as well as C_2-C_3 rotation must be a slower process than ring closure. Since the stereochemistry of the original synclinal addition step is retained throughout this proposed mechanism, the origin of the observed *cis* selectivity in **3** arises from an Se-C_4 secondary orbital interaction between **2** and **1**. Detailed

ab initio investigation of the structure of the complex of **2** with $SnCl_4$ is in progress, and will be reported in due course.

Scheme 1. Proposed reaction mechanism for cyclopropanation. (The carbon atom numbering is the same as that in Figure 2.)



Good diastereoselectivity was obtained in the reaction of chiral olefin **2f** (entry 6); no diastereoisomer of **3f** was detected by NMR analysis. In order to account for the high diastereoselectivity, attack from the *si*-side with respect to C_1 (Figure 1) of the $SnCl_4$-coordinated **2f** in the addition step is assumed. This proposed diastereoselection is similar to the asymmetric Diels-Alder reactions involving (*l*)-menthyl acrylates.[10] Determination of the absolute stereochemistry of the product **3f** is under way.

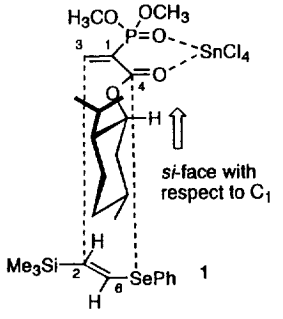


Figure 1

In summary, we have shown that 1-seleno-2-silylethene **1** and 2-phosphonoacrylates **2** undergo $SnCl_4$-promoted [2+1] cycloaddition reactions stereoselectively in high yield. We are currently investigating the transformation of **3** to biologically interesting compounds.

Acknowledgment

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6. **2a** was purchased from Aldrich. **2b**[5g] and **2d**[5f] were prepared according to literature methods. **2c**, **2e** (which included a small amount of impurity) and **2f** were prepared using similar methods to **2b** in 48%, ca. 67% and 68% yields, respectively.
7. *Typical experimental procedure.* To a solution of **1** (256 mg, 1.00 mmol) in dichloromethane (2.5 ml) was added $SnCl_4$ (0.176 ml, 391 mg, 1.50 mmol), followed by 2-phosphonoacrylate (**2a**) (0.202 ml, 252 mg, 1.30 mmol) at -78 °C. The mixture was stirred at -78 °C for 3 hours. The reaction mixture was quenched by triethylamine (0.36 ml, 260 mg, 2.6 mmol) and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with CH_2Cl_2-ether (2 : 1) to give **3a** (430 mg, 96%) (R_f = 0.3). **3a**: pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.105 (s, 9H, H_{13}), 1.61 (ddd, J = 9.9, 7.7, 4.5 Hz, 1H, H_{3b}), 1.86 (ddd, J = 14.2, 9.0, 4.5 Hz, 1H, H_{3a}), 2.24 (dddd, J = 14.1, 12.5, 9.0, 7.7 Hz, 1H, H_2), 2.59 (d, J = 12.5 Hz, 1H, H_6), 3.40 (s, 3H, H_5), 3.80 (d, J = 11.0 Hz, 3H, H_7), 3.89 (d, J = 11.0 Hz, 3H, H_8), 7.19-7.24 (m, 3H, $H_{11,12}$), 7.48-7.52 (m, 2H, H_{10}); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ (ppm) -2.114 (J_{CH} = 120 Hz, C_{13}), 23.69 (J_{CH} = 166 Hz, C_3), 25.10 (d, J_{CP} = 190.5 Hz, C_1), 28.69 (J_{CH} = 152 Hz, C_6), 33.19 (J_{CH} = 167, 10 Hz, C_2), 52.37 (J_{CH} = 148 Hz, C_5), 53.24 (d, J_{CP} = 5.9 Hz, J_{CH} = 148 Hz, $C_{7 \text{ or } 8}$), 53.36 (d, J_{CP} = 5.9 Hz, J_{CH} = 148 Hz, $C_{7 \text{ or } 8}$), 126.9 (J_{CH} = 161, 7.3 Hz, C_{12}), 128.6 (J_{CH} = 160, 5.1 Hz, $C_{10 \text{ or } 11}$), 130.3 (C_9), 133.5 (J_{CH} = 161 Hz, $C_{10 \text{ or } 11}$), 168.5 (d, J_{CP} = 7.3 Hz, C_4) (for numbering see Figure 2); IR (neat) 1721, 1251 cm^{-1}; exact mass M$^+$ 450.0536 (calcd for $C_{17}H_{27}O_5PSeSi$ 450.0530).
8. **4** and **5** were prepared according to the literature methods.[5g,5f] The stereochemistry of the respective major isomers of **4** and **5** was assigned as *E*. see: (a) Reetz, M. T.; Peter, R.; von Itzstein, M. *Chem. Ber.* **1987**, *120*, 121. (b) Sainz-Díaz, C. I.; Gálvez-Ruano, E.; Hernández-Laguna. A.; Bellanato, J. *J. Org. Chem.* **1995**, *60*, 74.
9. The relative configuration at C_2 and C_6 was deduced as (*R,R*) or (*S,S*) assuming the same stereochemical course as previously discussed.[2a,b] For **3a** and **3c**, the combination of large vicinal coupling constants ($J_{2,6}$ = 12.5 Hz for **3a** / 12.7 Hz for **3c**), which indicate that $-H_2-C_2-C_6-H_6$ is close to 180°, and the observed NOE's (H_{3b}-H_{13}, H_5-H_{10} for **3a** / H_{14}-H_{10} for **3c**, and H_5-$H_{11,12}$ for **3a** / H_{14}-H_{10} for **3c**), support the above hypothesis (Figure 2).[2b]

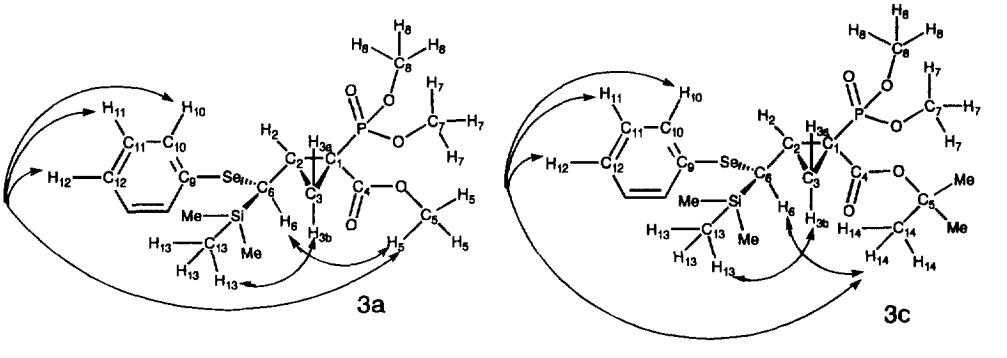

Figure 2. The atom numbering used in the assignment in notes 7 and 9 is included.

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