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ARTICLE

# A mild and efficient method for the synthesis of a new optically active diallyl selenide and its catalytic activity in allylic chlorination of natural terpenes

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A mild and convenient method for the synthesis of the new optically active di(6,6-Dimethyl-bicyclo[3.1.1]hept-2-ene-2-selenide **1** from the corresponding bicyclic terpene is described. The structure of the obtained organoselenium compound was established using $^{1}H$, $^{13}C$, $^{77}Se$-NMR spectroscopy and X-ray diffraction studies. Its application as a catalyst in allylic chlorination of terpenic olefins has been successfully carried out under mild conditions. The reaction showed a high selectivity affording the corresponding chlorides in good to excellent yields. The use of enantiomerically pure monoterpenes as starting materials allowed the preparation of asymmetric allyl chlorides through a process controlled by the substrate.

## Introduction

In recent years, organoselenium chemistry has received much attention from the whole chemical community because of its potential applications in various fields. Selenium reagents have been extensively used in a variety of organic reactions.[1] Other major applications are: coordination chemistry,[2-4] precursors for the preparation of thin films in metal-organic chemical vapor deposition[5,6] and biochemistry.[7-10] In addition, selenides have played an important role in biochemical processes serving as therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplement.[11, 12] The two most important classes of organoselenium compounds are selenides and diselenides. It's noteworthy to mention that the optically active monoselenides are still limited despite the fact that it possesses potential applicability to asymmetric syntheses. Though methods for the preparation of dialkyl monoselenides have been reported,[13-15] sometimes they suffer from difficulties in handling the selenide reagent used as the selenium source, strongly basic or acidic reaction conditions and low yields of tertiary alkyl phenyl selenides.[16, 17]

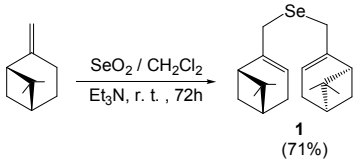
In organic synthesis, diselenides were successfully used as catalysts for the allylic chlorination of olefins. In fact, Sharpless reported that diphenyldiselenide catalyzes the chlorination of olefins in the presence of N-chlorosuccinimide (NCS)[18, 19] in process in which the electrophilic PhSeCl is initially involved. However, the study was limited in scope and the reaction lacked selectivity. Moreover, the reaction of simple olefins in the presence of diselenide catalysts provided mixtures of allyl halides, vinyl halides, and dihalides.[18-20]

Continuing with our interest in the valorization of natural terpenes,[21-23] herein we report an efficient and pertinent method for the preparation of new organoselenide **1** starting from β-pinene. Its application as a catalyst in the allylic chlorination of a various terpenic olefins in the presence of NCS under mild conditions has been investigated. The results show that monoterpenic olefins react to form the corresponding allylic chlorides in good to excellent yields. As the course of the reaction could be in principle enantioselective, attention was paid to the optical purity of the corresponding allylic chlorides, when starting from optically active monoterpenes.

## Results and discussion,

### Synthesis of the organoselenide Se(β-pinene)$_2$ 1

As shown in scheme 1, Se(β-pinene)$_2$ derivative **1** was easily prepared in 71% yield at room temperature by reacting β-pinene with an equimolar amount of selenium oxide in $CH_2Cl_2$ in the presence of triethylamine.




**Scheme 1**. Synthesis of Se(β-pinene)$_2$ **1**

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[c] *Institute of Physics, University of Neuchâtel, CH-2000 Neuchâtel, Switzerland*
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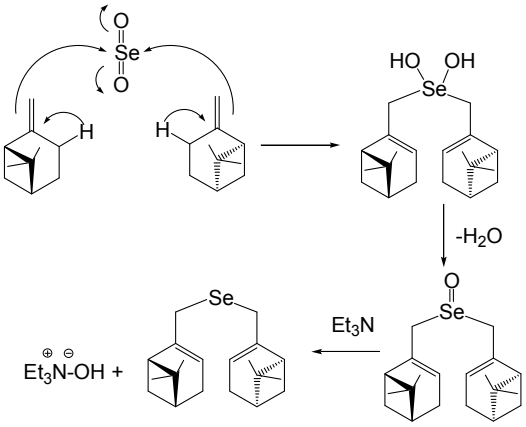
[e] **corresponding author (hous_soufiane@hotmail.com)*

**Table1.** Effect of solvent and $SeO_2$ ratio on the synthesis of Se(β-pinene)$_2$ **1**

| Entry | Equiv. of $SeO_2$ | Solvent | Conversion (%) | Isolated Yield (%) |
|---|---|---|---|---|
| 1 | 1 | MeCN | 53 | 30 |
| 2 | 1 | THF | 72 | 53 |
| 3 | 1 | $CH_2Cl_2$ | 100 | 71 |
| 4 | 1 | $CH_3Cl$ | 74 | 67 |
| 5 | 1 | $CCl_4$ | 69 | 62 |
| 6 | 0.7 | $CH_2Cl_2$ | 100 | 69 |
| 7 | 0.6 | $CH_2Cl_2$ | 100 | 66 |
| 8 | 0.5 | $CH_2Cl_2$ | 100 | 58 |
| 9a | 0.6 | $CH_2Cl_2$ | 0 | 0 |

Reaction conditions : β-pinene (7.35 mmol); solvent (15 mL); triethylamine (5.5 mmol); room temperature; reaction time : 72h.
[a] without triethylamine

The effects of different solvents and of the selenium oxide amount has been evaluated and the results are summarized in Table 1. Equimolar amount of selenium oxide, dichloromethane, chloroform and tetrachloromethane showed good efficiencies (entries 3-5). Dichloromethane appears to be the best solvent (entry 3). Acetonitrile seems to be the less reactive (entry 1). In the absence of triethylamine practically no reaction took place (entry 9). In the presence of dichloromethane as solvent, a reduced amount of selenium oxide gave good results (entries 6-8). Selenide **1** was purified by flash chromatography using hexane as eluent and fully characterize on the basis of $^{1}H$, $^{13}C$ and $^{77}Se$ NMR spectroscopy and X-Ray analysis. The suggested formation mechanism is given below (scheme 2).




**Scheme 2.** *Proposed mechanism for the preparation of **1**.*

**X-ray Crystal Structure of Se (β-pinene)$_2$ 1**

The X-ray crystal structure analysis of the selenium complex **1** indicated that the molecule possesses two-fold rotation symmetry, with the selenium atom located on the two-fold axis. In the crystal, there are no significant intermolecular interactions present. A summary of selected crystal data and refinement details are given in Table 2, and an ORTEP representation for complex 1 is given in Figure 1.

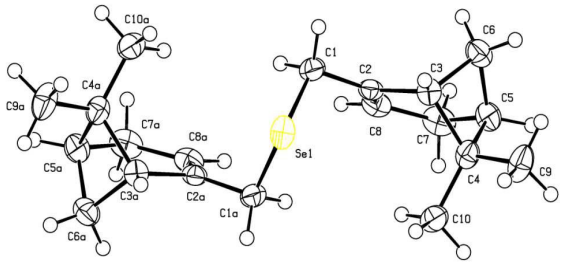



**Figure 1.** *A view of the molecular structure of compound **1**, with atom labelling and displacement ellipsoids drawn at the 50% probability level [symmetry code: (a) = –x, y, -z]. CCDC No 1430591.*

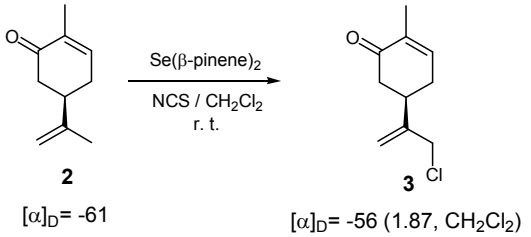
***Table 2.** Crystal Data and Structure Refinement for Compound **1***

| | |
|---|---|
| formula | $C_{20}H_{30}Se$ |
| Fw | 349.40 |
| crys sys | Monoclinic |
| space group | C 2 |
| unit cell dimensions (Å, °) | a = 11.4153(8)<br>b = 6.8490(7)<br>c = 12.4992(12)<br>β = 110.314(6) |
| volume (Å$^3$) | 916.45(14) |
| Z | 2 |
| density (calcd, g/cm$^3$) | 1.266 |
| F(000) | 368 |
| wavelength (Å) | 0.71073 |
| abs coeff (mm-1) | 2.042 |
| crystal size | 0.45 x 0.26 x 14 mm |
| temp (K) | 173(2) |
| diffractometer | |
| θ (°) range for data collection | 1.74 – 26.03 |
| index ranges | -13 h 13, -8 k 8, -15 l 15 |
| scan method | ϕ and ω scans |
| scan width (°, in ω) | 1.0 |
| no. of total data collected | 4842 |
| no. of unique data / Rint | 1710 / 0.031 |
| no. of unique obsd. data [I > 2σ(I)] | 1695 |
| max. and min. transmission | 1.000, 0.8204 |
| weighting scheme | w=1/[σ2(Fo2)+(0.0259P)<br>2+0.3056P]<br>where P=(Fo2+2Fc2)/3 |
| no. of data/restraints/parameters | 1719/9971 |

| | |
|---|---|
| GOF on F2 | 1.003 |
| final R1, wR1 indices [I > 2σ(I)] | 0.0195, 0.0457 |
| final R1, wR1 indices (all data) | 0.0200, 0.0458 |
| largest diff peak and hole (e Å-3) | 0.395 and -0.344 |

**Catalytic chlorination of monoterpenes**

With the aim to explore the synthetic application and limitations of the selenide **1**, we investigated its use as a catalyst for the allylic chlorination of terpenic olefins. As a model reaction the allylic chlorination of carvone **2** (scheme 3) has been carried using 1.1 equivalents of NCS and 5 mol% of **1** in dichloromethane at room temperature. The reaction resulted to be chemospecific and the primary allylic chloride **3** was obtained in 87 % yield after 1h.




**Scheme 3.** Catalytic chlorination of carvone **2**

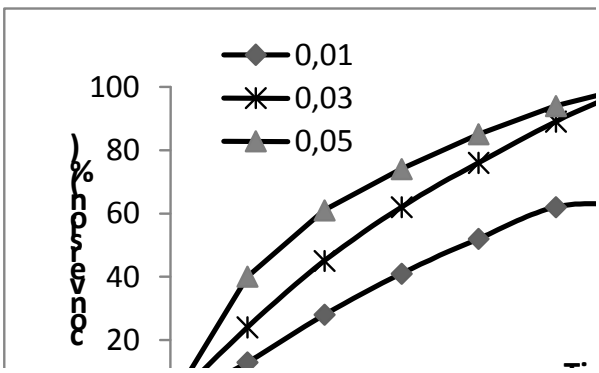



**Figure 2**. *Effect of Se(β-pinene)2 ratio on the allylic chlorination of carvone **2**.*

In order to investigate the effect of the catalyst amount on promoting the allylic chlorination of carvone, we studied the conversion rate effecting the reaction at different ratios of substrate **2** and selenide **1** in the presence of NCS at room temperature in dichlorometane. The results are depicted in Figure 2.

The best results has been achieved using 5 mol% of Se(β-pinene)$_2$, with a conversion of 70% after 30 minutes and almost quantitative after one hour. Using 1 mol% of Se(β-pinene)$_2$, the desired product was obtained for the first 50 min but the rate dropped dramatically and the conversion reached a plateau at around 63 %. We also investigated the effect of the solvents in the allylic chlorination of carvone. These results are summarized in the Table 3. Among the solvents studied, dichloromethane appears to be the most suitable (entry 1).

In the attempt to identify, the actual species that are involved in the catalytic chlorination the selenide **1** and NCS were made reacted in a NMR tube and analysed by $^{77}$Se-NMR spectroscopy. The spectra reported in Figure 3 evidenced the presence of two peaks at 470 and 334 ppm, respectively. The low field peak (470ppm) can be assigned to the hypervalent dialkyl selenium dichloride, according to the chemical shift reported for similar derivatives.[24] The other peak could be envisioned to be the monochloride derivatives or the adduct coordinated with succinamide. On the basis of this results the allylic chlorination can proceed following a radical pathway.

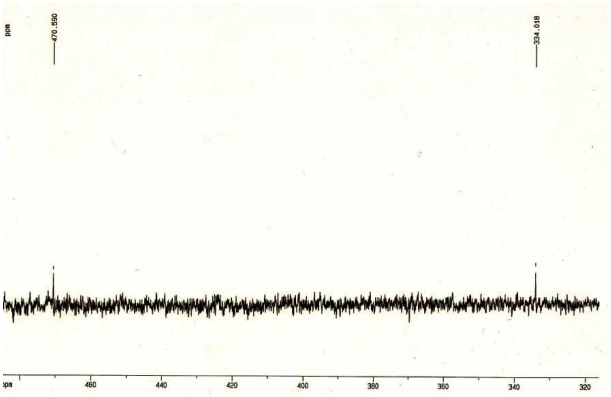


**Figure 3**. *$^{77}$Se-NMR spectra of selenide **1** and NCS reaction*

In order to extend the scope and limitation of the reaction, the protocol optimized to chlorination of carvone was then performed using a variety of terpenic olefins (Table 4). Using 5 mol% of Se(β-pinene)$_2$ in dichloromethane under optimized conditions, all the substrates are converted to the corresponding chlorinated products in good to excellent yields. As shown in Table 4, β-pinene gave selectively the trans secondary allylic chloride **5** (entry 1), as major diastereoisomer, in a good yield. It's important to note that the transformation of β-pinene took place without the opening ring as it was the case when using lewis acid catalyst.[21] However, mono and dichlorinated products **7** and **8** were obtained in the allylic chlorination of limonene **6** (entry 2). Performing the reaction with methylstyrene **9** resulted in an excellent yield (entry 3).

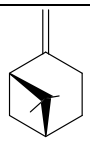
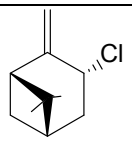
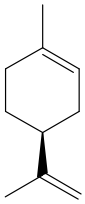
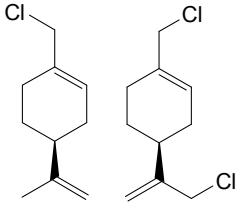
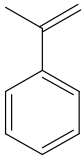
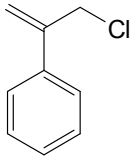
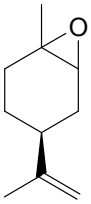
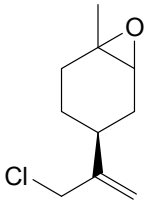
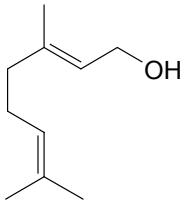
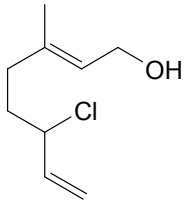
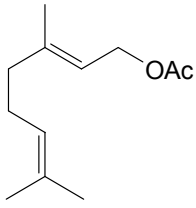
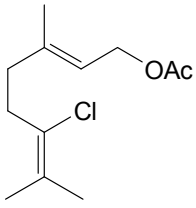
We have also checked the allylic chlorination of limonene oxide **11**, geraniol **13**, and geranyl acetate **15**. The resulting corresponding chlorides were obtained in good yields (entries 4-6). It is noteworthy that all chlorinated products derived from optically active monoterpenes exhibit optical activities (entries 1, 2, 4).

**Table 3**. Solvent effect on the chlorination of carvone catalyzed by Se(β-pinene)$_2$

| Entry | Solvent | Conversion (%)[a] | Yield (%)[a] |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 100 | 92 |
| 2 | $CH_3Cl$ | 95 | 87 |
| 3 | $CCl_4$ | 79 | 68 |

Reaction conditions: Carvone (0.5 mmol); Se(β-pinene)$_2$ (0.005 mmol), NCS (0.55 mmol) in 20 ml of solvent at room temperature, dodecane (200 mg).
[a]Conversions and yields are determined by GC using dodecane as internal standard

**Table 4**: Allylic chlorination of terpenic olefins

| Entry | Terpene | Allyl chloride | Time (h) | $\alpha_{[D]}$ | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 |  $[\alpha]_D$= -20 *β-pinene* |  **5** | 5 | –20 (1.92, $CH_2Cl_2$) | 83 |
| 2 |  **6** $[\alpha]_D$= -94 |  **7** **8** | 5 | **7** : –53 (2.0, $CH_2Cl_2$)<br>**8** : -68 (1.82,$CH_2Cl_2$) | 7 : 34<br>8 : 61 |
| 3 |  **9** |  **10** | 3 | ---- | 92 |
| 4 |  **11** $[\alpha]_D$= -69 (cis /trans) |  **12** (cis /trans) | 5 | -46 (1.50, $CH_2Cl_2$)<br>(cis /trans) | 85 |
| 5 |  **13** |  **14** | 5 | ---- | 73 |
| 6 |  **15** |  **16** | 5 | ---- | 85 |

## Conclusion

A new organoselenium compound, Se(β-pinene)$_2$ **1**, has been synthesized and investigated in the allylic chlorination of alkenes under mild conditions. The chlorination of terpenic olefins using Se(β-pinene)$_2$ as catalyst, has been successfully carried out, and led to the terpenic chlorides in good to excellent yields. The reaction shows a high degree of efficiency and selectivity. When the reaction was performed with optically active monoterpenes, asymmetric allylic chlorides were obtained.

## Acknowledgements

This work is a part of the activities of the multidisciplinary Network SeS Redox and Catalysis; LS and CS contributed to the NMR characterization of the organoselenium compounds (selenide **1** and organoselenium intermediates) to the discussion around the reaction mechanism and to write the paper.

## Experimental

### Materials and methods

NMR studies were performed on a Bruker Avance 300 and Bruker Avance DRX 400 spectrometer in $CDCl_3$, chemicals shifts are given in ppm relative to external TMS and coupling constant (J) in Hz. Mass spectra were recorded on AMD 402 spectrometer (70 ev, EI). All the spectroscopic data of the known products were compared with those reported in the literature. The reaction mixtures were analyzed on a Trace GC Thermo Finnigan chromatograph equipped with an FID detector. GC parameters for capillary columns BP (25m x 0.25mm, SGE): injector 250 °C; detector 250 °C; oven 70 °C for 5 min then 3 °C/min until 250 °C for 30 min; column pressure 20 kPa, column flow 6.3 mL/min; linear velocity 53.1 cm/s; total flow 138 mL/min. Liquid chromatography was performed on silica gel (Merk 60, 220-440 mesh; eluent: hexane). Analytical thin-layer chromatography (TLC) was conducted on Merck aluminium plates with 0.2 mm of silica gel 60F-254. All the reagents and solvents used in the experiments were purchased from commercial sources.

### Synthesis of Se(β-pinene)$_2$ 1

0.81 g (7.35 mmol) of $SeO_2$ was dissolved in 15 mL of dichloromethane and stirred for 15 min. Then, 1g (7.35 mmol) of β-pinene and 0.55 g (5.5 mmol) of triethylamine were added. After stirring for 72 h, the reaction mixture was diluted with 50 mL of water and extracted 3 times with 20 mL of ethyl acetate. The organic layer was dried over $Na_2SO_4$. The filtrate was concentrated with a rotary evaporator and the residue was purified by flash chromatography leading to the organoselenium **1** in 71% of yield.

m.p. 63-65 °C. $^1$H NMR ($CDCl_3$, 400 MHz)) δ : 5.36 (ddq, 2H, *J* = 4.4, 2.9 and 1.3 Hz); 3.12 (dq, 2H, *J* = 11.7 and 1.3 Hz); 3.03 (dq, 2H, *J* = 11.7 and 1.3 Hz); 2.43 (dt, 2H, *J* = 8.6 and 5.6 Hz); 2.35-2.27 (m, 2H); 2.26-2.20 (m, 2H): 2.18 (dt, 2H, *J* = 1.6 and 5.6 Hz); 2,13-2.08 (m, 2H); 1.31 (s, 6H); 1.16 (d, 2H, *J* = 8.6 Hz), 0.85 (s, 6H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 144.3(Cq), 119.1 (=CH), 45.8 (-CH), 40.4 (-CH), 38.0 (Cq), 31.8 ($CH_2$), 31.2 ($CH_2$), 29.8 ($CH_2$), 26.1 (CH3), 21.0 ($CH_3$) ppm. $^{77}$Se NMR ($CDCl_3$, 76 MHz) δ 162.5 ppm. Mass (M+) 350.

### General procedure for allylic chlorination of terpenic olefins

Se(β-pinene)$_2$ (5 mol %, 0.005 mmol) was dissolved in 20 mL of $CH_2Cl_2$, producing an yellow solution. To this solution, terpenic olefin (0.5 mmol) was added. The addition of the olefin resulted in immediate color change from yellow to pale yellow. N-chlorosuccinimide (0.55 mmol) was then added and the resultant mixture was stirred at room temperature for the indicated reaction time. The reaction was monotired by GC. The reaction mixture was concentrated to 2 mL and dissolved in 10 mL of diethyl ether. The mixture was washed tow time with 10 mL of water and the organic layer was dried over $Na_2SO_4$. The filtrate was concentrated and purified by flash chromatography leading to virtually pure isolated chlorides. All isolated pure products were fully characterized by $^1$H and $^{13}$C NMR and MS, and then compared to the already know compounds.[21,25]

### X-ray Crystallographic Analysis.

Suitable crystals of the selenium complex were grown from $CH_2Cl_2$. The intensity data were collected at 173K (-100°C) on a Stoe Mark II-Image Plate Diffraction System[26] equiped with a two-circle goniometer and using MoKα graphite monochromated radiation (λ = 0.71073 Å). Image plate distance 130mm, ω rotation scans 0 - 180° at ϕ = 0°, and 0 - 90° at ϕ = 90°, step Δ ω = 1.0°, exposures of 3 mins per image, 2θ range 1.76 - 52.59°, dmin – dmax = 23.107 - 0.802 Å. The structure was solved by direct methods with SHELXS-97.[27] The refinement and all further calculations were carried with SHELXL-97.[27] The C-bound H-atoms were included in calculated positions and treated as riding atoms: C-H = 0.95, 1.00, 0.99 and 0.98 Å for CH(allyl), CH(methine), $CH_2$ and $CH_3$, respectively, with Uiso(H) = 1.5Ueq(C-methyl) and = 1.2Ueq(C) for all other H-atoms. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F2. A semi-empirical absorption correction was applied using the MULscanABS routine in PLATON.[28]

## Notes and references

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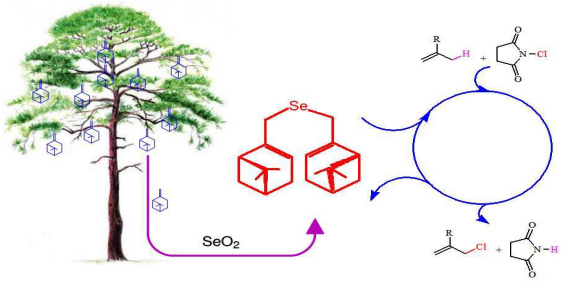
**Graphical Abstract**




An organoselenide compound was synthesized starting from β-pinene. The activity of this complex towards the allylic chlorination has been studied.