Electrochemical Generation and Catalytic Use of Selenium Electrophiles

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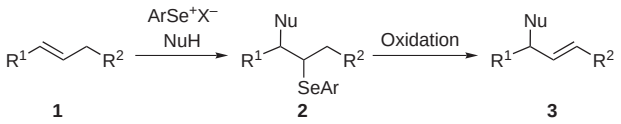
Received 7 November 2005

Abstract: The generation and use of selenium electrophiles in catalytic, electrochemically driven selenenylation–elimination sequences is described.

Key words: electrochemistry, electrophilic addition, elimination, selenium, stereoselective synthesis

Organoselenium compounds are known to be very useful reagents in organic synthesis.[1] The reaction of carbon–carbon double bonds with selenium electrophiles is performed under mild reaction conditions and the reaction products can be used in a variety of subsequent functionalizations. A general protocol for selenenylations of alkenes **1** is shown in Scheme 1. Selenide **2** is then oxidized and, after elimination, compounds **3** are obtained. The use of enantiomerically pure selenium electrophiles can lead to addition products in high diastereomeric ratios and to highly enantiomerically enriched elimination products **3**.[2]

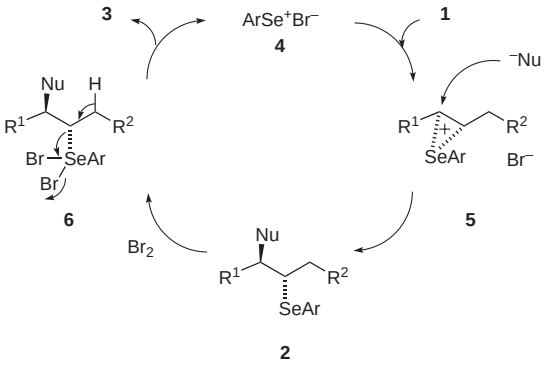


Scheme 1 Functionalization of double bonds with selenium electrophiles and subsequent oxidative elimination

Due to the necessity to use these reagents in stoichiometric quantities in addition reactions to double bonds, the development of alternative methods is becoming increasingly important. We already developed a series of polymer-supported selenium electrophiles which allow easy purification of the addition products (filtration) and, after cleavage of the reaction products from the solid support, a recycling of the reagent for the next reaction.[3] A superior solution is the development of a protocol using only catalytic amounts of selenium electrophiles. We[4] and other research groups[5] have already reported the use of peroxodisulfates as oxidants in such reactions, but the turnover numbers are still small and the amount of selenium reagent as catalyst relatively high.

Various transformations of organoselenium compounds have been performed using electrochemical methods.[6] The reaction of a electrochemically generated selenium electrophile (Ar = Ph) with a variety of substrates has featured prominently in the literature.[7] Most notably, the catalytic use of diphenyl diselenide in an oxyselenenylation–deselenenylation sequence for the conversion of alkenes **1** into allylic compounds **3** has been reported.[8] Herein we describe the application of catalytic amounts of diphenyl diselenide in electrochemical alkoxyselenenylation–deselenenylation sequences.

Conditions were established for the electrochemical conversion of alkenes of type **1** with R^2 being an acceptor substituent to the addition–elimination products **3** using 10 mol% diphenyl diselenide in methanol. Tetraethylammonium bromide was employed to act both as a redox catalyst and as an electrolyte. Dry methanol was used as the solvent and the reaction was carried out using platinum foil electrodes. Graphite electrodes can be used with similar efficiency.

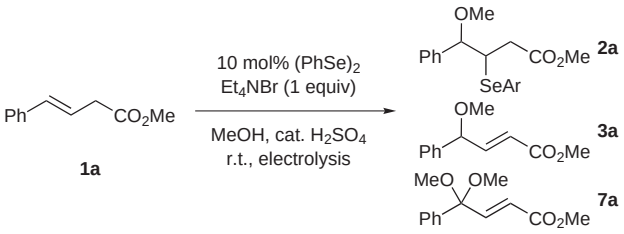


Scheme 2 Electrochemical oxyselenenylation–elimination of alkenes

The reaction is initiated by anodic oxidation of bromide to bromine and subsequent reaction with diaryl diselenide to form arylselenenyl bromide **4** (Scheme 2). Reagent **4** reacts with alkene **1** to form the seleniranium cation **5**, which undergoes reaction with the nucleophile giving selenide **2**. The next equivalent of bromine is electrochemically generated and this reacts with **2** to give the unstable tetravalent selenenylbromide **6**. Elimination of the selenium moiety produces the allylic ether **3** and arylselenenyl bromide, thus completing the catalytic cycle. In an independent reaction we showed that the reaction of **2** with bromine generates the elimination product **3** and arylselenenyl bromide, which was isolated as diaryl diselenide after the aqueous work up. The deselenenylation of **2** to **3** is traditionally achieved by selenoxide elimination.[5f] Electrochemical eliminations by oxidation of selenides via the corresponding selenoxides have been described.[8]

SYNLETT 2006, No. 2, pp 0251–0254
Advanced online publication: 23.12.2005
DOI: 10.1055/s-2005-923585; Art ID: D33405ST

The reaction conditions for the methoxyselenenylation of **1a**[9] (R^1 = Ph, R^2 = CO_2Me) using 10 mol% diphenyl diselenide were optimized.[10] At low currents the addition product **2a** was the main product (Table 1, entry 1) and at very high currents the elimination product **3a**[11] was further oxidized to **7a**[12] as shown in Scheme 3 and Table 1. This was also confirmed by an independent experiment where **3a** as a starting material was converted to **7a** under similar high current reaction conditions.



Scheme 3 Addition–elimination sequence leading to various products depending on reaction conditions

Table 1 Addition–Elimination Reaction Using **1a**

Entry	Current (mA)	Product ratio[a] **2a**:**3a**:**7a**:other[b]
1	0.5	19:64:0:17
2	3	5:83[c]:0:12
3	10	0:46:36:18
4	30	0:10:85[d]:5

[a] Determined by ^{1}H NMR.
[b] Other compounds identified as reaction products are methyl 4-phenyl-4-oxo-butanoate and methyl 4-hydroxy-4-phenyl-(*E*)-but-2-enoate.
[c] Isolated yield: 50%.
[d] Isolated yield: 42%.

The use of other nucleophiles in the addition–elimination sequence led to compounds **3b**–**d**[13] in moderate yields. A replacement of tetraethylammonium bromide with ammonium peroxodisulfate was only advantageous when using acetic acid as nucleophile in the synthesis of **3e** (Figure 1).[14]

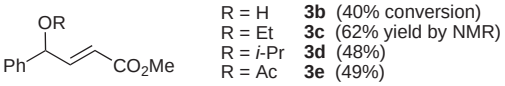


Figure 1 Addition–elimination products **3** using different nucleophiles

The development of organoselenium reagents for asymmetric synthesis has produced a range of chiral reagents such as diselenides, which are efficient in the transfer of chiral information.[2] Enantiomerically pure selenium electrophiles, easily prepared from the corresponding diselenides of type **8** (Figure 2), have proven themselves as powerful reagents for the stereoselective functionalization of non-activated carbon–carbon double bonds (**1** → **2**, Scheme 1). Diastereoselectivities of up to 96% have been obtained in the addition products **2**.

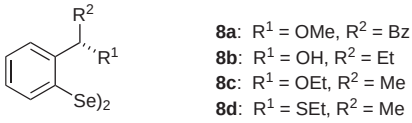


Figure 2 Enantiomerically pure diselenides **8**

Catalytic quantities of several enantiomerically pure diselenides **8**[15] were then used in this reaction in place of diphenyl diselenide. For each diselenide it was necessary to adjust the conditions to achieve the highest yields. The functionality present in the side chain R^1 of the chiral selenium reagent was the determining factor in optimizing these conditions. For example, the use of sulfuric acid proved unsurprisingly incompatible with diselenides containing a methoxymethyl-protected alcohol in the chiral side chain. Some selected results are shown in Table 2.

Table 2 Electrochemical Selenenylation–Elimination Sequence to Allylic Ether **3a**[a]

Entry	**8** (R^1)	**8** (R^2)	Yield (%) of **3a**	ee (%) of **3a**[b]
1[c]	OMe	Bz	56	18 (*S*)
2[c]	OH	Et	29	44 (*S*)
3[d]	OEt	Me	55	5 (*S*)
4[e]	SEt	Me	38	66 (*S*)

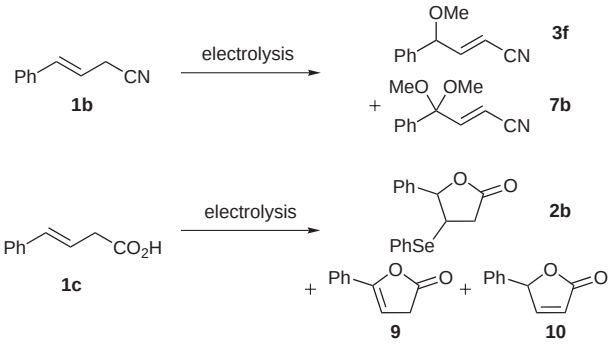
[a] Conditions: 10 mol% diselenide, cat. H_2SO_4.
[b] Determined by HPLC: Chiracel OD-H, hexane–*i*-PrOH 98:2, 0.5 mL/min, 254 nm, R_f (*R*) = 18.3 min, R_f (*S*) = 20.2 min.
[c] 20 mol% Et_4NBr.
[d] 10 mol% Et_4NBr.
[e] 50 mol% Et_4NBr, 5 mol% diselenide.

Traces of sulfuric acid were found to be essential for the success of this reaction. Previous workers have described the use of sulfuric acid to prevent the elimination from **2** to **3** from occurring, enabling isolation of the selenide. We found, however, that while sulfuric acid enhances the rate and yield of the reaction, it does not prevent the elimination step proceeding. The increased rate and yield is probably due to the free proton acting as an excellent electrolyte.

The effect of various electrolytes in place of sulfuric acid on this reaction was studied in order to overcome the acid dependence, but neither tetraethylammonium hexafluorophosphate, tetraethylammonium tetrafluoroborate nor an excess of tetraethylammonium bromide proved as effective as sulfuric acid using enantiomerically pure diselenides **8**. Previous workers have used a range of salts to prevent disproportionation of phenylselenenic acid into the inert phenylseleninic acid, leading to enhanced yields. We have found that the use of these salts ($MgSO_4$, $CaSO_4$ and Na_2SO_4) has no effect on the above reactions other than to increase the reaction times. The use of tetraethyl-

ammonium chloride and tetraethylammonium iodide has also been investigated in a variety of different conditions but yields were lower than with tetraethylammonium bromide.

The restriction on temperature imposed by the electrochemical approach accounts for the low selectivities when selenium reagents optimized for much lower temperatures are employed. Varying the amount of tetraethylammonium bromide had no effect on selectivity. In the absence of any tetraethylammonium bromide, the increased cell potential required for the direct oxidation of the diselenide resulted in a multitude of side reactions. Highest selectivities are obtained with a sulfur-containing diselenide (Table 2, entry 4) leading to product **3a** in 66% ee. This is in agreement with the results using similar sulfur-containing selenium electrophiles reported recently by Tiecco et al.[5e] These results are quite remarkable as the diselenides investigated previously that have been designed for low-temperature reactions but the electrochemical reactions are performed at room temperature.



Scheme 4 Catalytic electrochemical reactions of other alkenes

Other alkenes have also been investigated in the addition–elimination sequence. Compound **1b**[16] (R^1 = Ph, R^2 = CN) and **1c**[5e] (R^1 = Ph, R^2 = CO_2H) were subjected to similar reaction conditions and the formation of compounds **3f**/**7b** and **2b**/**9**/**10** was observed (Scheme 4).

The expected methoxyselenenylation–elimination compound **3f**[17] was formed in 50% yield and at higher currents (30 mA), the corresponding dimethoxylated product **7b**[18] was isolated in 43% yield. Cyclizations were studied using **1c** as substrate. After initial formation of **2b**,[19] elimination to 5-phenylfuran-2(3*H*)-one (**9**)[20] together with small amounts of 5-phenylfuran-2(5*H*)-one (**10**,[21] ratio **9**:**10** = 85:15) was observed by using tetraethylammonium bromide in acetonitrile. The use of acetonitrile–methanol (40:1) as solvent mixture and ammonium peroxodisulfate instead of tetraethylammonium bromide allowed a complete suppression of the formation of **9** and only **10** was isolated in 32% yield.

β-Methyl styrene **1** (R^1 = Ph, R^2 = H) has also been used in this reaction. The catalytic use of diphenyl diselenide produces allylic ether **3**[22] (R^1 = Ph, R^2 = H, Nu = OMe) in low yields, with most of the β-methyl styrene undergoing direct transformation to 1,2-dimethoxy-1-phenylpropane[23] or, in the presence of a bromide source, 2-bromo-1-methoxy-1-phenylpropane.[24] We conclude that the oxidation potential of β-methyl styrene is too low to enable the selective oxidation of either the diselenide or a redox catalyst.

Work is currently underway to broaden the scope of this reaction by the development of efficient chiral selenium reagents optimized for room temperature reactions. We were able to demonstrate the catalytic use of chiral diselenides in an electrochemical selenenylation–deselenenylation sequence.

Acknowledgment

We thank Prof. R. Breinbauer, University of Leipzig, Germany, for fruitful discussions and for graphite electrodes. We thank the Royal Society for a fellowship (O.N.), EPSRC for support and the National Mass Spectrometry Service Centre, Swansea, for mass spectrometric data.

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(10) **Typical Experimental Procedure.** The alkene (0.1 mmol) was dissolved in MeOH (7 mL) and tetraethylammonium bromide (0.1 mmol), diselenide (0.01 mmol) and H_2SO_4 (1 μL) were added. The electrodes were inserted into the reaction mixture and constant current of 3 mA applied. After 6 h, electrolysis was stopped and the MeOH removed in vacuo. The mixture was dissolved in Et_2O, washed with $NaHCO_3$ solution and H_2O before drying over $MgSO_4$. The products were purified by preparative TLC or column chromatography.

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(12) Spectroscopic data for **7a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12 (s, 6 H), 3.65 (s, 3 H), 6.24 (d, *J* = 15.7 Hz, 1 H), 6.73 (d, *J* = 15.7 Hz, 1 H), 7.20–7.28 (m, 3 H), 7.38–7.40 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.7, 51.7, 100.9, 122.0, 126.9, 128.31, 128.33, 139.0, 147.8, 166.7 ppm. IR (NaCl): ν = 2950, 2832, 1727, 1659, 1449, 1436, 1304, 1276, 1192, 1167, 1072, 1046, 988, 700 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{16}O_4$: 259.0941; found: 259.0941.
(13) Spectroscopic data for **3d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.1 Hz, 3 H), 1.13 (d, *J* = 6.1 Hz, 3 H), 3.57 (sept, *J* = 6.1 Hz, 1 H), 3.64 (s, 3 H), 4.95 (dd, *J* = 5.4, 1.4 Hz, 1 H), 6.02 (dd, *J* = 15.6, 1.4 Hz, 1 H), 6.91 (dd, *J* = 15.6, 5.4 Hz, 1 H), 7.19–7.30 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 22.6, 51.6, 69.5, 77.8, 120.1, 127.3, 128.0, 128.7, 140.0, 148.8, 166.9 ppm. IR (NaCl): ν = 2971, 1725, 1659, 1453, 1435, 1298, 1272, 1167, 1120, 978, 699 cm^{-1}. HRMS: *m/z* calcd for $C_{14}H_{18}O_3$: 252.1594; found: 252.1593.
(14) Spectroscopic data for **3e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 3.67 (s, 3 H), 5.97 (dd, *J* = 15.7, 1.5 Hz, 1 H), 6.32 (dd, *J* = 5.0, 1.5 Hz, 1 H), 6.95 (dd, *J* = 15.7, 5.0 Hz, 1 H), 7.27–7.31 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 51.8, 74.2, 121.2, 127.4, 128.83, 128.86, 137.1, 144.9, 166.4, 169.7. IR (NaCl): ν = 2952, 2918, 2849, 1738, 1727, 1662, 1436, 1372, 1310, 1279, 1228, 1197, 1171, 1069, 1022, 980, 699 cm^{-1}. HRMS: *m/z* calcd for $C_{13}H_{14}O_4$: 252.1230; found: 252.1229.
(15) Diselenides **8** were synthesized according to literature procedures: (a) Compounds **8a**,**c**: Wirth, T.; Fragale, G. *Chem.–Eur. J.* **1997**, *3*, 1894. (b) Compound **8b**: Uehlin, L.; Fragale, G.; Wirth, T. *Chem.–Eur. J.* **2002**, *8*, 1125. (c) For compound **8d** see ref. 5e.
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(18) Spectroscopic data for **7b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.11 (s, 6 H), 5.85 (d, *J* = 16.2 Hz, 1 H), 6.43 (d, *J* = 16.2 Hz, 1 H), 7.25–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.8, 100.2, 101.4, 116.8, 126.9, 128.6, 128.8, 137.8, 154.0 ppm. IR (NaCl): ν = 2916, 2848, 2228, 1732, 1450, 1261, 1226, 1191, 1159, 1071, 1047, 972, 774, 746, 702 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{13}NO_2$: 221.1285; found: 221.1283.
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