Active metallic indium-mediated ring-opening of epoxides with diphenyl diselenides: a novel one-pot synthesis of β-hydroxy selenides in aqueous media

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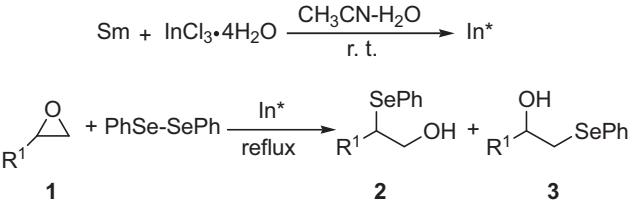
An efficient and simple one-pot procedure for the synthesis of β-hydroxy selenides in aqueous media through highly regioselective ring-opening of epoxides with diphenyl diselenide in the presence of active metallic indium is described.

Keywords: β-hydroxy selenides, diphenyl diselenide, epoxides, active metallic indium

β-Hydroxy selenides are highly valuable intermediates in organic synthesis.[1] They can be transformed into allylic alcohols, olefins, halohydrins, vinyl selenides, epoxides and heterocyclic compounds.[2] Consequently, several methods have been developed for the synthesis of β-hydroxy selenides.[3] The most common method is the ring-opening of epoxides with phenyl selenide anion generated from diphenylselenide with tributyphosphine in alkaline medium,[4] sodium borohydride,[2a] Sm–TMSCl,[5] indium(I) iodide[6] or zinc.[7] Although ring-opening of epoxides involving some of the above-mentioned methods have their own advantages, each suffers from one or more drawbacks such as unsatisfactory regioselectivity,[4] long reaction periods[2a,7] and excessive reagents.[4-7] Furthermore, most of above mentioned procedures are carried out in anhydrous organic solvents. Thus, the development of new reagents, capable of promoting the ring opening reaction under mild conditions (including aqueous or neutral media) is highly desirable.

Recently, indium metal and selected indium(III) compounds have emerged as an attractive and promising tool in organic synthesis. This is largely due to their high reactivity in promoting various reactions, low toxiãty and high stability toward water and air compared with other metals.[8] Aiming at the development of green and more effiãent organic methodologies, recently we have been focusing our research on the application of active metallic indium in organic synthesis.[9] As a continuation of our research in this area, we report here an effiãent and convenient one-pot synthesis of



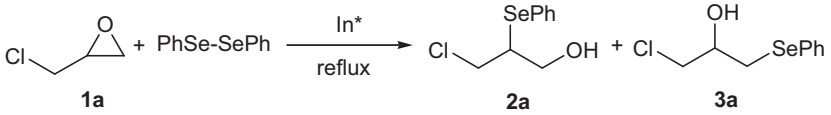
Scheme 1

β-hydroxy selenides (**2** and/or **3**, Scheme 1) through a regio- and steroselective ring opening of epoxides with diphenyl diselenide mediated by active metallic indium generated *in situ* from $Sm/InCl_3•4H_2O$ under neutral conditions in aqueous media.

Initially, as an optimisation process, the reaction of epichlorohydrin **1a** with PhSeSePh under various conditions was investigated. The results are summarised in Table 1.

As shown in Table 1, these preliminary results lead to the following conclusions: First of all, in the presence of the *in situ* formed active indium, epichlorohydrin reacts smoothly with PhSeSePh and affords the corresponding β-hydroxy selenide with excellent regioselectivity and in good yield. Of the two possible products, **2a** and **3a**, only **3a** was obtained. Secondly, among the solvents studied, CH_3CN/H_2O was found to be most suitable for this reaction from the point view of yields (entries 1–4). Thirdly, long reaction times (>0.5 h) do not necessarily result in higher yields (entries 1, 6).

Table 1 Reaction of epichlorohydrin with PhSeSePh under various conditions



1a **2a** **3a**

Entry[a]	Solvent[b]	Temperature	Time/h	Yield/%[c,d]
1	CH_3CN/H_2O (9/1)	reflux	0.5	86
2	THF/H_2O (9/1)	reflux	0.5	75
3	C_2H_5OH/H_2O (9/1)	reflux	0.5	80
4	CH_2Cl_2/H_2O(9/1)	reflux	0.5	81
5	CH_3CN/H_2O(9/1)	r.t.	2	70
6	CH_3CN/H_2O(9/1)	reflux	2	87
7	CH_3CN/H_2O(3/1)	reflux	0.5	79

[a]Amount of reagents: Epicholorohydrin (2 mmol) and PhSeSePh (1 mmol).
[b]v/v ratio.
[c]Ratio of **3a**/**2a** > 99/1.
[d]Isolated yields based on PhSeSePh.

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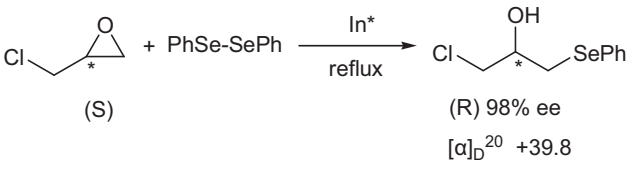
This is probably due to the gradual loss of activity of the indium reagent over longer periods of time. Lastly, while increasing the amount of water causes a decrease in the yield (entries 1, 7), it should be highlighted that this reaction still gives a fairly good yield even with as much as 33% water in the solvent system (entry 7). After exploring a wide array of conditions, we arrived at a best result that the reaction should be carried out under refluxing for 0.5 h in CH_3CN/H_2O (9/1).

The mild reaction conditions, excellent regioselectivity and good yields encouraged us to examine the scope and generality of the present method. Thus, several structurally diverse epoxides were studied and the results are listed in Table 2.

The results in Table 2 reveal that various epoxides react readily with diphenyldiselenide under the present reaction conditions to give the desired products with impressive yields. Interestingly, no evidence was found for the formation of the corresponding diols in aqueous media. In the case of alkyl-substituted unsymmetrical epoxides, the reaction proceeds with a remarkable regio-selectivity to give only **3** of the two possible regio-isomers (**2** and **3**, Scheme 1) as a result of the exclusive attack of the selenide anions on the less hindered carbon of the epoxide (entries 1–4). On the contrary, with aryl-substituted epoxides (entries 5 and 6), the attack occurs preferentialy at the benzylic carbon atom, the more hindered carbon of the epoxide, to give another regioisomer, **2e** or **2f** as main products respectively. However, for 3-OR-1,2-epoxypropane, R groups affect the regioselectivity remarkably (entries 7–9). Interestingly, ring-opening of 1,2-epoxy-3-naphthaleneoxy-propane gave only one isomer **3h**, which shows excellent regioselectivity (entry 9).

Furthermore, some insight into the stereoselectivity of the present method was obtained from reactions carried out on two cyclic epoxides (entries 10 and 11), which exclusively give the corresponding *anti*-β-hydroxy selenides in 73% and 69% yields respectively. No trace of the *syn*-adducts was detected by ^{1}H NMR spectroscopy.[4]

To extend the scope of the ring-opening reaction, (*S*)-epichlorohydrin[12] was studied under similar conditions (Scheme 2). The reaction was found to be highly regioselective and stereospeãfic, which demonstrated that original chirality in the epoxides was retained. The corresponding products were obtained in good yield (85%) and high ee (98%). Enantiopure β-hydroxy selenides are important intermediates in organic synthesis.[13]



Scheme 2

In conclusion, a faãle and effiãent one-pot procedure for the preparation of β-hydroxy selenides is described. Compared with previously reported methods for the ring-opening of epoxides, this method has several advantages, such as good regioselectivity, short reaction times, relatively environmentally friendly processes and neutral reaction conditions. Studies to extend the application of active metallic indium in green organic synthesis are currently underway in our laboratory.

Experimental

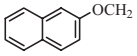
Diphenyl diselenide (m.p 59–61°C; Lit. 60–62°C) was prepared through a known procedure.[14] Melting points were uncorrected. IR spectra were recorded on a Bruker-EQUINOX55 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AC 300 instrument using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. Elemental analyses were carried out using a Carlo-Erba EA1112 instrument. Chiral LC's were obtained on a chiracel OJ-H column with a mobile phase of *iso*-PrOH/hexane (1/99) at a flow rate of 0.8 ml/min and UV detection at 254 nm.

General procedure for preparation of β-hydroxy selenides

To a flask containing $InCl_3$•$4H_2O$ (1 mmol), samarium powder (1 mmol) and CH_3CN (9 ml) was slowly added 1 ml H_2O. Upon adding of H_2O, vigorous reaction took place to give a light black speães (active metallic indium) in several minutes. Then PhSeSePh (1 mmol) was added and the mixture was refluxed for 10 min to give an almost colourless solution. To this solution was then added the epoxide substrate (2 mmol) and it was stirred for a certain period of time as indicated in Tables 1 and 2. Upon completion (monitored by TLC), the solution was aãdified with 10% HCl until the pH value was about 5. The aqueous solution was extracted with Et_2O (2 × 15 ml) and the combined organic phases were dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the resulting crude product was purified by silica gel column chromatography eluting with petroleum ether and ethyl acetate (9:1) to give the corresponding β-hydroxy selenides. The physical and spectroscopic data of all compounds are as follows.

1-chloro-3-(phenylselanyl)propan-2-ol (**3a**)[5]: ^{1}H NMR: δ 2.73 (d, J = 5.1 Hz, 1H), 3.05 (dd, J = 12.9, 7.1 Hz, 1H), 3.14 (dd, J = 12.9,

Table 2 Reaction of epoxides with PhSeSePh mediated by active indium

Entry[a]	R^1	Products[b]	Regioselectivity/β/α[c]	Yield/%[d]
1	$ClCH_2$	**3a**[5]	99/1	86
2	CH_3	**3b**[10]	99/1	85
3	$CH_3(CH_2)_4CH_2$	**3c**[10]	99/1	81
4	CH_2 =$CH(CH_2)_5CH_2$	**3d**	99/1	80
5	Ph	**3e**/**2e**[4]	24/76	82
6	4-$Cl(C_6H_4)$	**3f**/**2f**[6]	32/68	80
7	$PhCH_2OCH_2$	**3g**/**2g**[2h]	31/69	82
8	4-$Cl(C_6H_4)OCH_2$	**3h**/**2h**[11]	75/25	83
9		**3i**	99/1	86
10		**2j**[4]	–	73
11		**2k**[4]	–	69

[a]Reaction conditions: CH_3CN/H_2O (9/1, v/v), reflux, 0.5 h.
[b]All products are known compounds except for **3d** and **3i**.
[c]The ratio of two regio-isomers was determined by ^{1}H NMR.
[d]Isolated yields.

5.5 Hz, 1H), 3.66 (m, 2H), 3.92 (m, 1H), 7.26–7.30 (m, 3H), 7.52–7.56 (m, 2H). IR ν (cm^{-1}): 3438 (OH).

(*R*)-(+)-*1-chloro-3-(phenylselanyl)propan-2-ol*: $[\alpha]_D^{20}$ + 39.8 (c 1.01, $CHCl_3$). HPLC analysis using a Chiracel OJ-H column [*iso*-PrOH/hexane: 1/99; flow rate: 0.8 ml/min; detector: 254 nm] showed it to 98% ee. Retention time: 15.04 min (major), 16.47 min (minor).

1-(phenylselanyl)propan-2-ol (**3b**)[10]: ^{1}H NMR: δ 1.27 (d, *J* = 6.2 Hz, 3H), 2.59 (br s, 1H), 2.88 (dd, *J* = 12.7, 7.7 Hz, 1H), 3.09 (dd, *J* = 12.7, 4.0 Hz, 1H), 3.86 (m, 1H), 7.24–7.27 (m, 3H), 7.50–7.54 (m, 2H). IR ν (cm^{-1}): 3466 (OH).

1-(phenylselanyl)octan-2-ol (**3c**)[10]: ^{1}H NMR: δ 0.84 (t, *J* = 6.3 Hz, 3H), 1.25–1.54 (m, 10H), 2.41 (d, *J* = 3.8 Hz, 1H), 2.88 (dd, *J* = 12.7, 5.7 Hz, 1H), 3.14 (dd, *J* = 12.7, 3.4 Hz, 1H), 3.64 (m, 1H), 7.24–7.27 (m, 2H), 7.50–7.53 (m, 3H). IR ν (cm^{-1}): 3434 (OH).

1-(phenylselanyl)dec-9-en-2-ol (**3d**): ^{1}H NMR: δ 1.25–1.55 (m, 10H), 2.02 (q, *J* = 6.7 Hz, 2H), 2.35 (d, *J* = 3.57 Hz, 1H), 2.87 (dd, *J* = 12.7, 8.6 Hz, 1H), 3.15 (dd, *J* = 12.7, 3.4 Hz, 1H), 3.66 (m, 1H), 4.96 (m, 2H), 5.80 (m, 1H), 7.25–7.27 (m, 3H), 7.51–7.55 (m, 2H). ^{13}C NMR: δ 25.7, 28.8, 28.9, 29.4, 33.7, 36.6, 37.3, 69.8, 114.2, 127.3, 129.2, 129.4, 133.0, 139.1. MS(EI): 312 (M^+), 310, 172, 170, 158, 141, 123, 95, 81, 79, 81,67, 55. IR ν (cm^{-1}): 3422 (OH). Anal. Calcd for $C_{16}H_{24}OSe$: C, 61.73; H, 7.77. Found: C, 61.6; H, 7.7.

1-phenyl-2-(phenylselanyl)ethanol (**3e**)[4]: ^{1}H NMR: δ 2.33 (br s, 1H), 4.02–4.07 (m, 2H), 4.99 (dd, *J* = 7.1, 5.9 Hz, 1H), 7.25–7.50 (m, 10H).

2-phenyl-2-(phenylselanyl)ethanol (**2e**)[4]: ^{1}H NMR: δ 2.04 (br s, 1H), 3.93–4.05 (m, 2H), 4.40 (t, *J* = 7.1 Hz, 1H), 7.06–7.48 (m, 10H). IR ν (cm^{-1}): Mixture of **3e** and **2e** (24/76): 3446 (OH).

1-(4-chlorophenyl)-2-(phenylselanyl)ethanol (**3f**)[6]: ^{1}H NMR: δ 2.28 (t, *J* = 6.9 Hz 1H), 3.87–3.92 (m, 2H), 4.94 (dd, *J* = 7.0, 5.9 Hz, 1H), 7.12–7.47 (m, 9H).

2-(4-chlorophenyl)-2-(phenylselanyl)ethanol (**2f**)[6]: ^{1}H NMR: δ 2.13 (t, *J* = 6.4 Hz 1H), 3.91–3.97 (m, 2H), 4.40 (t, *J* = 7.0 Hz, 1H), 7.11–7.46 (m, 9H). IR ν (cm^{-1}): Mixture of **3f** and **2f** (32/68): 3397 (OH).

1-(benzyloxy)-3-(phenylselanyl)propan-2-ol (**3g**)[2h]: ^{1}H NMR: δ 2.82 (d, *J* = 4.7 Hz, 1H), 3.15 (dd, *J* = 12.9, 7.0 Hz, 1H), 3.24 (dd, *J* = 12.9, 5.7 Hz, 1H), 3.52–3.57 (m, 2H), 3.94–3.96 (m, 1H), 4.50(s, 2H), 7.25–7.55 (m, 10H).

3-(benzyloxy)-2-(phenylselanyl)propan-1-ol (**2g**)[2h]: ^{1}H NMR: δ 2.75 (d, *J* = 5.7 Hz, 1H), 3.58–3.67 (m, 4H), 3.96–4.03 (m, 1H), 4.57 (s, 2H), 7.21–7.47 (m, 10H). IR ν (cm^{-1}): Mixture of **3g** and **2g** (31/69): 3423 (OH).

1-(4-chlorophenoxy)-3-(phenylselanyl)propan-2-ol (**3h**)[11]: ^{1}HNMR: δ 2.69 (d, *J* = 4.7 Hz, 1H), 3.12 (dd, *J* = 12.9, 6.9 Hz, 1H), 3.21 (dd, *J* = 12.9, 5.6 Hz, 1H), 3.96–4.00 (m, 2H), 4.04–4.06 (m, 1H), 6.76–6.79 (m, 2H), 7.19–7.26 (m, 7H).

3-(4-chlorophenoxy)-2-(phenylselanyl)propan-1-ol (**2h**)[11]: ^{1}HNMR: δ 2.54 (d, *J* = 6.0 Hz, 1H), 3.73–3.77 (m, 2H), 4.09–4.13 (m, 2H), 4.21 (m, 1H), 6.83–6.87 (m, 2H), 7.18–7.56 (m, 7H). IR ν (cm^{-1}): Mixture of **3h** and **2h** (75/25): 3425 (OH).

1-(naphthalen-2-yloxy)-3-(phenylselanyl)propan-2-ol (**3i**): M.p: 82–83°C. ^{1}H NMR: δ 2.76 (d, *J* = 4.4 Hz, 1H), 3.19 (dd, *J* = 12.9, 6.6 Hz, 1H), 3.28 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.10–4.22 (m, 3H), 7.07–7.78 (m, 12H).). ^{13}C NMR: δ32.0, 69.0, 70.5, 106.87, 118.60, 123.8, 126.4, 126.8, 127.4, 127.6, 129.1, 129.2, 129.3, 129.5, 133.0, 134.4, 156.2. MS(EI): 358 (M^+), 356, 354, 217, 215, 213, 211, 171, 169, 157, 155, 144, 127, 115, 91, 77. IR ν (cm^{-1}): 3448 (OH). Anal. Calcd for $C_{19}H_{18}O_2Se$: C, 63.87; H, 5.08. Found: C, 63.8; H, 5.0.

Anti-2-(phenylselanyl)cyclohexanol (**2j**)[4]: ^{1}H NMR: δ 1.21–1.38 (m, 4H), 1.61–1.75 (m, 2H), 2.15 (m, 2H), 2.88 (ddd, *J* = 12.0, 10.0, 4.0 Hz, 1H), 2.93 (s, 1H), 3.32 (dt, *J* = 9.9, 4.1 Hz, 1H), 7.25–7.36 (m, 3H), 7.57–7.61 (m, 2H). IR ν(cm^{-1}): 3444 (OH).

Anti-2-(phenylselanyl)cyclooctanol (**2k**)[4]: ^{1}H NMR: δ 1.25–2.31 (m, 12H), 2.62 (br s, 1H), 3.31 (ddd, *J* = 12.0, 10.0, 4.0 Hz), 3.69 (dt, *J* = 10.1, 2.9 Hz, 1H), 7.25-7.32 (m, 3H), 7.58–7.61 (m, 2H). IR ν (cm^{-1}): 3444 (OH).

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