[d002]

Catalyst-controlled Asymmetric Syntheses of Organoselenium Compounds.

β-Hydroxyselenides by Desymmetrization of *meso* Epoxides

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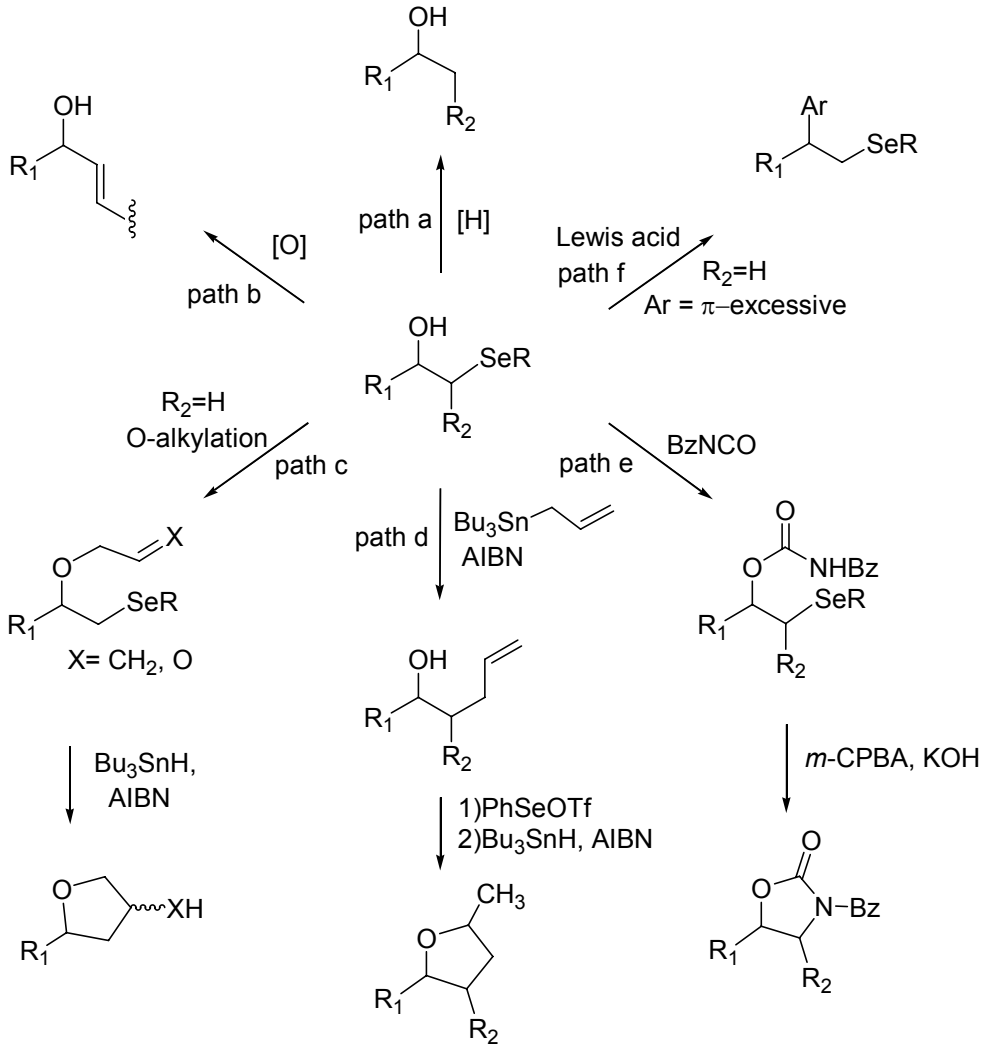
Introduction:

β-Hydroxy selenides are efficient intermediates for a variety of synthetic transformations. As depicted in Scheme 1 together with classical reactions, such as the reduction to alcohols[1] (path a) or the oxidation to allylic alcohols[1] (path b), simple and convenient conversions into tetrahydrofurans,[2] 1,3-oxazolidinones,[3] amino alcohols[3] and β-aryl selenides[4] have been recently reported in the literature. The key step of most of these multi-step procedures consists in the removal of the organoselenium moiety which occurs in radical or ionic conditions and generates substitution (path d) or cyclization products (path c and e). The interesting selenium-assisted substitution of the hydroxyl group by an aromatic compound (path f) or by other carbon nucleophiles[5] has also been recently described. It must be underlined that the products generated from enantiomerically enriched β-hydroxy selenides are obtained without any loss of the enantiomeric purity.

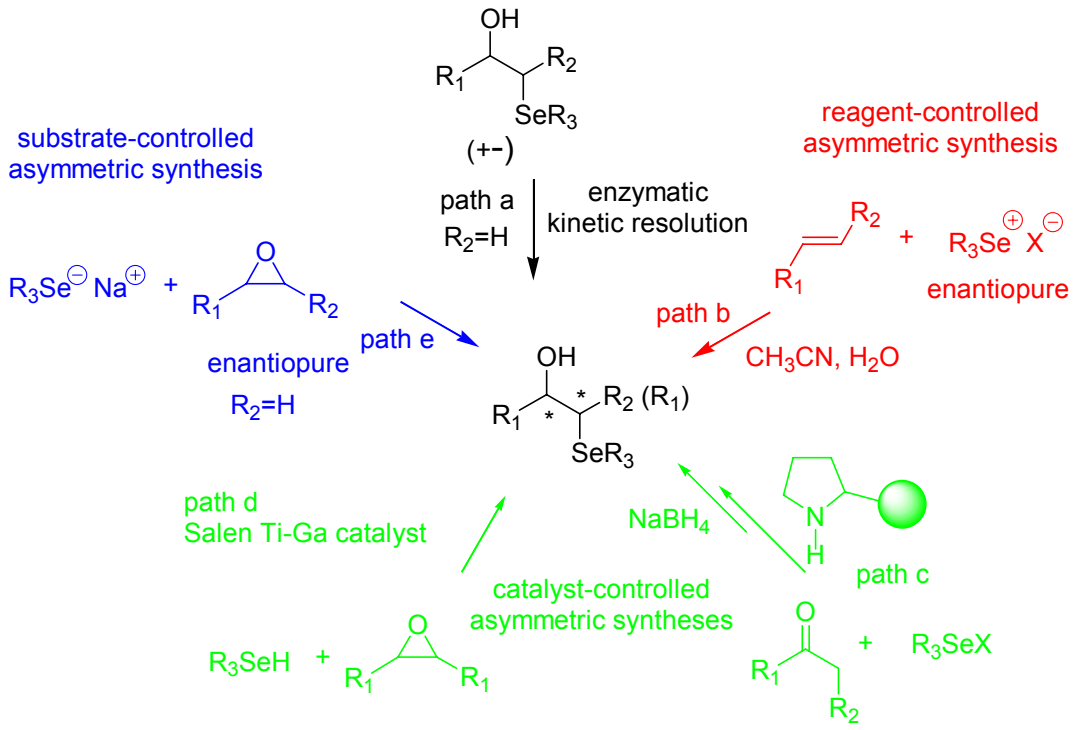
Scheme 1



Because of their importance as chiral intermediates several syntheses of enantiomerically enriched 1,2-hydroxy selenides have been developed (Scheme 2). The most common procedures are the lipase-promoted kinetic resolutions of racemic 1,2-hydroxy selenides (path a),[6] the regio and stereospecific ring opening of commercial enantiopure epoxides by arylselenolates (path e) [2c-d,3,4] and the asymmetric seleno-hydroxylation of alkenes promoted by enantiomerically pure electrophilic selenium reagents (path b).[7] Catalyst-controlled asymmetric syntheses have also been investigated. Very recently β-hydroxy selenides have been prepared with excellent enantiomeric excesses by chiral amine catalyzed α-selenenylation of aldehydes followed by reduction (path c).[8] The enantioselective ring opening of *meso*-epoxides with benzeneselenol in the presence of the heterobimetallic Salen Titanium-Gallium complex is another useful approach to 1,2-hydroxy selenides with two contiguous chiral centers (path d).[9] We now report the first desymmetrization of *meso* epoxides with commercial or easily accessible Salen catalysts[10]

and the (phenylseleno)silane **2a**. This nucleophilic selenium source is more stable and easy to handle than the oxidizable and malodorous benzeneselenol.

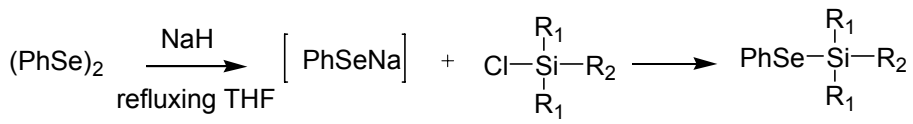
Scheme 2



Results and discussion

The (phenylseleno)silanes **2a-c** have been prepared according to the literature procedure (Scheme 3).[11] Diphenyl diselenide has been treated with NaH in refluxing THF and the resulting sodium phenylselenolate has been allowed to react with the appropriate chlorosilane. The sterically hindered (phenylseleno)silanes **2a-c** have a good stability and can be prepared, purified by distillation or crystallization and stored for several days without particular precautions.

Scheme 3

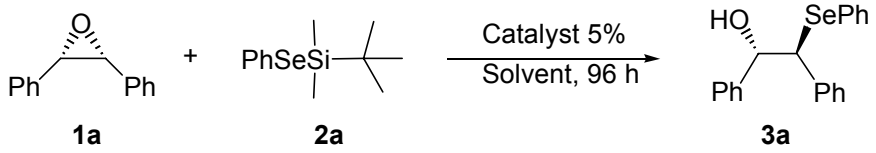


	R_1	R_2
2a	Me	*tert*-Bu
2b	*i*-Pr	*i*-Pr
2c	Ph	*tert*-Bu

Preliminary ring-opening experiments were performed at room temperature (R.T.) and under air atmosphere on stilbene oxide in order to evaluate **2a-c**[12] and several

Salen(metal)complexes in different undistilled solvents. **2a** appeared as the more suitable reagent because **2b** gave poorer results, while **2c** was inactive under the same reaction conditions. The results of selected experiments carried out with *tert*-butyl(dimethyl)(phenylseleno)silane **2a** using the following general procedure are reported in Table 1. Stilbene oxide **1a** (0.5 mmol) and the Salen(metal)complex (0.025 mmol) have been dissolved in the indicated solvent (0.5 M) and **2a** (0.61 mmol) was added. The resulting mixture was stirred for 96 h, then filtered *under vacuo* through a plug of silica gel and washed with light petroleum/diethyl ether 70:30. The crude mixture was analyzed by NMR and chiral HPLC. The β-hydroxy selenide **3a** was then purified by flash chromatography (light petroleum/ethyl ether 90:10 as eluant). As indicated in Table 1 these reactions afforded the alcohol **3a**. The best results in terms of yield and enantiomeric ratio were obtained with Salen(Cr)BF_4 in *tert*-butylmethyl ether (entry 9). Further optimization of the reaction was then attempted. The effects of the temperature and of the addition of one equivalent of *tert*-butanol,[1] tetrabutylammonium fluoride[13] or tetramethyethylendiamine (TMEDA)[14] as activating agents for the organosilicon selenium reagents, have been studied (entries 10-13). The results of these experiments demonstrated that the use of a low temperature and of TMEDA as additive can dramatically improve the yield and the selectivity of the reaction (entry 11). In fact **3a** was obtained with 92% yield and 96:4 er. This result is better than that previously obtained with benzenselenol and Salen Titanium-Gallium complex (70% yield; 86:14 er).[9] Further improvements were not observed by using 10% of the catalyst, more concentrated solutions (2 M) or lower reaction temperatures.

Table 1



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

entry	catalyst	T	solvent[a] (additive)	yield[b]	e.r.[c]
1	Salen(Ti)$(OiPr)_2$	R.T.	hexane	46%	64:36
2	Salen(Zn)II	R.T.	hexane	69%	50:50
3	Salen(Cr)SbF_6	R.T.	TBME	73%	69:31

4	Salen(Cr)Cl	R.T.	hexane	69%	82:18
5	Salen(Cr)Cl	R.T.	toluene	60%	77:23
6	(Salen)CrCl	R.T.	TBME	60%	63:37
7	Salen(Cr)BF_4	R.T.	hexane	60%	84:16
8	Salen(Cr)BF_4	R.T.	toluene	67%	89:11
9	Salen(Cr)BF_4	R.T.	TBME	82%	89:11
10	Salen(Cr)BF_4	R.T.	TBME (TMEDA)	99%	73:27
11	Salen(Cr)BF_4	-10 °C	TBME (TMEDA)	92%	96:4
12	Salen(Cr)BF_4	-10 °C	TBME, (*t*-BuOH)	99%	77:23
13	Salen(Cr)BF_4	-10 °C	TBME (Bu_4NF)	35%	87:13

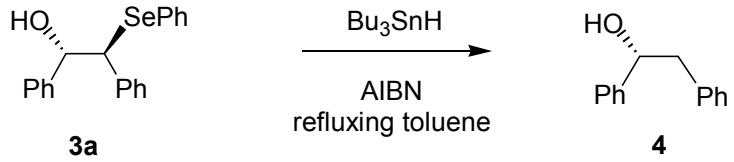
[a] The asymmetric ring opening reaction of **1a** was performed with **2a** in the presence of 5 % of catalyst in the indicated solvent (0.5 M solutions). Reaction times: 96h.

[b] Yields determined on isolated compounds.

[c] Enantiomeric ratio determined by HPLC on a Chiralpack AD-H column.

The stereochemical assignment of compound **3a** was determined after radical deselenenylation with tributyltin hydride and catalytic AIBN in refluxing toluene. This reaction generated the (*R*)-1,2-diphenylethanol **4** as demonstrated by the comparison of the specific optical rotation with the value reported in the literature.[15] Considering that **3a** is formed from **1a** by a stereospecific *anti* ring opening it can be confidently assumed that **3a** has the absolute configuration indicated in Scheme 4.

Scheme 4

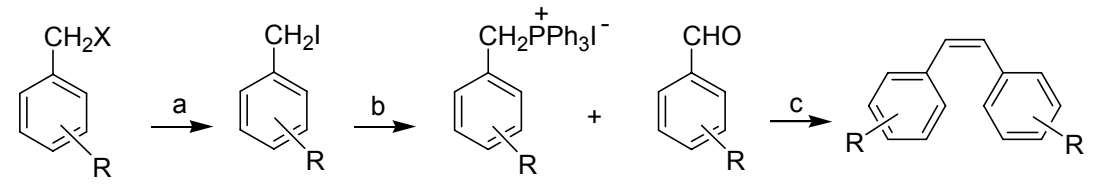


4 er 82:18 $[\alpha]_D^{23}$= -31.8 (c 1.0% in EtOH)

***(R)*-4** er 93:17 $[\alpha]_D^{20}$= -42.3 (c 1.9% in EtOH)

We next examined the scope of this ring opening reaction by carrying out desymmetrization reactions on other *cis* epoxides. Aryl epoxides **1b-d** have been prepared without any purification of the intermediates according to the four-steps sequence reported in Scheme 5. The substituted benzyl iodides **5b-d**, obtained from the corresponding bromide or chloride by using the Finkelstein reaction, react with the appropriate commercial benzaldehydes **8b-d** *via* Wittig reactions. The mixtures of the alkenes **9b-d** were treated with *m*-CPBA and converted into the corresponding epoxides. Under the reaction conditions employed the *cis* epoxides are the major or the sole reaction products. The commercial cyclic or alkyl epoxides **1e-g** were also used as substrates.

Scheme 5

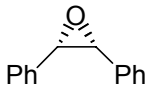
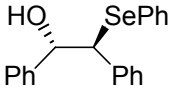
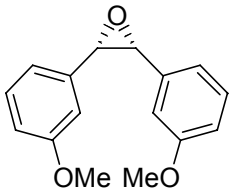
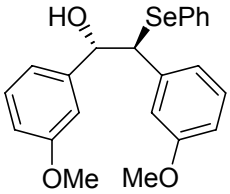
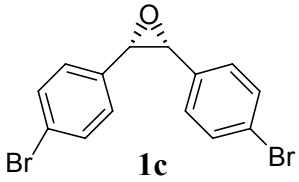
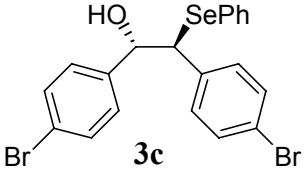
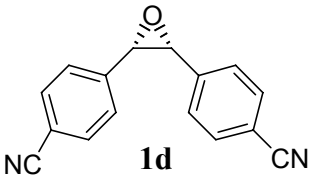
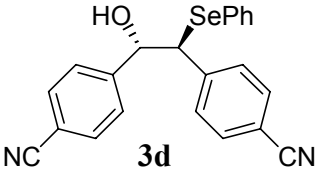
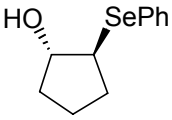
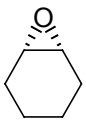
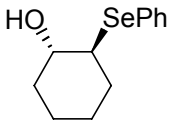


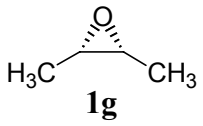
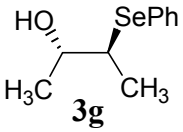
	Z/*E* Ratio		Overall Yield *cis*	Overall Yield *trans*
9b	72:28	**1b**	26%	10%
9c	69:31	**1c**	36%	16%
9d	100:0	**1d**	28%	0%

a) NaI, acetone, T.A.,1h; b) PPh_3, toluene, T.A., 16h;
c)18-Crown-6, KOH, CH_2Cl_2, -50°C-T.A., 20h; d) *m*-CPBA, CH_2Cl_2, 0°C, 6-12h.

The results of these experiments are reported in Table 2 which shows the starting epoxides, the reaction products, the yields and the enantiomeric ratios. For comparison the result obtained on stilbene oxide **1a** under optimized reaction conditions (method A) is also reported. All the reactions were carried out at room temperature or at -10 °C and stopped after 96 h. The absolute configurations of compounds **3b-d** were assigned by analogy with **3a**, those of compounds **3e-g** by comparison of the HPLC retention times obtained with a Chiralcel OD-H column with those previously reported in the literature.[9]

Table 2

epoxide	product	T	yield	e.r.
 **1a**	 **3a**	-10 °C	**A** 92%	96:4
 **1b**	 **3b**	-10 °C	**A** 50%	72:28
		R.T.	**A** 94%	66:34
		R.T.	**A** 34%[a]	64:36
 **1c**	 **3c**	-10 °C	**A** 53%	84:16
		R.T.	**A** 31%[a]	72:28
 **1d**	 **3d**	-10 °C	**A** 25%[b]	84:16
		R.T.	**A** 70%[b]	80:20
		R.T.	**A** 53%[a,b]	81:19
 **1e**	 **3e**	-10 °C	**A** 52%	64:36
		-10 °C	**B** 71%	76:24
 **1f**	 **3f**	-10 °C	**A** 70%	67:33
		-10 °C	**B** 88%	80:20

 1g	 3g	-10 °C	**B** 60%	76:24

Method A: 5% Salen(Cr)BF_4 in TBME (0.5M) with 1 eq. of TMEDA for 96 h

Method B: 5% Salen(Cr)Cl in Et_2O (0.5M) for 96 h

a) reaction effected without TMEDA; b) reaction effected in CH_2Cl_2

For all the examined epoxides the ring opening reaction is completely diastereoselective. In order to obtain good levels of enantioselectivity it is essential to use low reaction temperatures. Notably the enantioselectivity of the process depends on the structure of the starting epoxide. In fact the *p*-substituted aryl epoxides **1c-d** gave at -10 °C higher enantiomeric ratios than the other epoxides, although in moderate yields**.** Furthermore TMEDA is a good additive only for aryl epoxides in fact the experiments effected on cyclic or alkyl epoxides gave better results using method B.

In conclusion we have described the first catalytic enantioselective ring opening reactions of *meso* epoxides with (phenylseleno)silanes using commercial or easily available Salen(chromium)complexes as catalysts. These reactions constitute a simple and convenient approach to synthetically versatile, optically active β-hydroxy selenides. The enantioselectivity of the process depends on the structure of the starting epoxide. Excellent results have been obtained on stilbene oxide (92% yield and 96:4 er) and on its *p*-substituted derivatives in the presence of TMEDA as additive.

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