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COMMUNICATION

A general phosphoric acid-catalyzed desymmetrization of *meso*-aziridines with silylated selenium nucleophiles†

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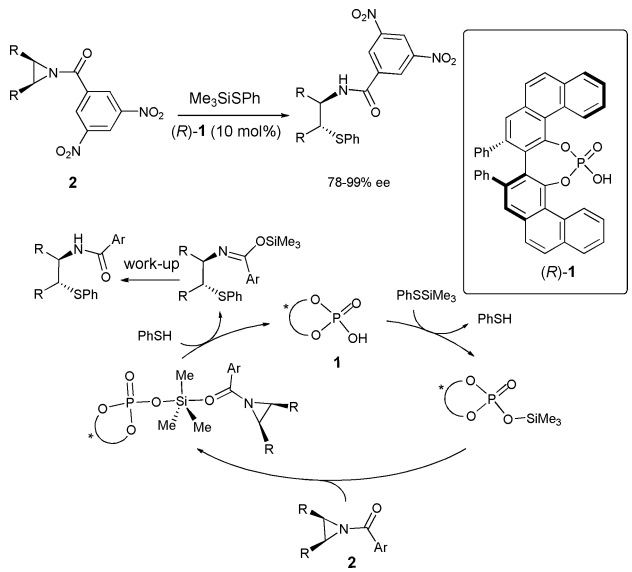
The first example of *meso*-aziridine desymmetrization with selenium nucleophiles is reported. The reaction, promoted by VAPOL-hydrogen phosphate using (phenylseleno)trimethylsilane as the nucleophile, proves to be very general and highly enantioselective (84–99% ee).

Chiral enantiopure β-aminoselenium compounds play a very significant role in organic chemistry thanks to their biological activity and reactivity. A broad range of medicinal properties has recently been established.[1] Although selenocysteine and its derivatives are in a position of prominence as building blocks for the synthesis of selenoproteins and as biologically active compounds,[2] interesting properties were also shown by different chiral β-aminoselenides.[3] These compounds, in non-racemic form, were successfully employed as chiral ligands, especially in association with late transition metal catalysts.[4] In addition, the unique reactivity of organoselenium compounds, compared to their sulfur analogues, makes them highly versatile intermediates for organic synthesis.[5] In particular, chiral non-racemic β-aminoselenium compounds, have been converted stereospecifically into enantioenriched aziridines,[6–8] oxazolines,[8,9] thiazolines,[10] saturated amine derivatives,[9] allylic amine derivatives,[11] and pyrrolidines.[12]

The most straightforward method for the synthesis of enantioenriched 1,2-disubstituted β-aminoselenides, with two adjacent stereogenic carbons, is based on the chiral pool.[4,7,11,13] However, in spite of the great relevance of these products, to our knowledge only one example of an asymmetric catalytic method has been reported to date.[14]

The catalytic desymmetrization of *meso*-aziridines with different nucleophiles is a highly convenient method for the synthesis of enantioenriched β-functionalized amine derivatives, owing to the use of a small amount of catalyst and the simultaneous formation of two adjacent stereocenters with the desired relative configuration. Although many highly enantioselective processes of desymmetrization of activated *meso*-aziridines have been described,[15,16] and some of them are based on sulfur nucleophiles,[17,18] surprisingly no example has been reported with selenium nucleophiles. Recently we reported a highly enantioselective desymmetrization of *meso*-*N*-acylaziridines **2** with the readily available enantiopure VAPOL-derived phosphoric acid **1**[19] as the catalyst and (phenylthio)trimethylsilane as the nucleophile (Scheme 1).[18] The presence of 2,3-dinitrobenzoyl as the activating group proved to furnish the best enantioselectivities in this process. A plausible catalytic cycle, analogous to that reported previously for the desymmetrization with trimethylsilyl azide catalysed by **1**,[16e] is presented in Scheme 1.



Scheme 1 Desymmetrization of *meso*-aziridines **2** with silylated sulfur nucleophiles and a plausible mechanism.

The excellent results achieved in the desymmetrization of aziridines with thiosilanes prompted us to investigate the analogous process featuring a selenosilane as nucleophile. Initially we opted for the air- and moisture-stable selenosilane **4a**.[20] In general, in the reaction of **4a** with aziridine **2a** catalysed by (*R*)-**1**, good conversions were accomplished only after a very long reaction time, but the enantioselectivity level was encouraging. After an extensive screening of solvents we observed an unexpected behaviour. In fact, unlike the related process with sulfur nucleophiles, some aromatic solvents led to better enantioselectivies than halogenated ones (Table 1). In toluene, in particular, full

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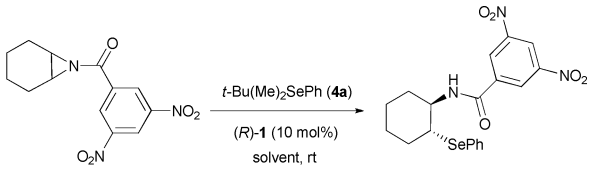
† Electronic supplementary information (ESI) available: Experimental details, characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra for all the unknown compounds. See DOI: 10.1039/c1ob05837a

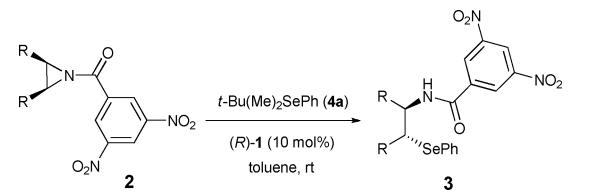
Table 1 Effect of solvent in the desymmetrization of aziridine **2a** with nucleophile **4a**[a]



Entry	Solvent	Time/days	Yield (%)[b]	ee (%)[c]
1	$ClCH_2CH_2Cl$	4	68	50
2	$CHCl_3$	1	41	40
3	CCl_3CH_3	4	50	49
4	benzene	5	74	36
5	PhCl	4	65	56
6	*o*-xylene	4	72	79
7	toluene	4	96	85

[a] Reaction performed at 0.08 mmol scale using **2a** (1 equiv.), **4a** (1.5 equiv.) and **1** (0.10 equiv.) in solvent (0.1 M concentration). [b] Isolated yields. [c] Determined by chiral HPLC.

Table 2 Scope of the desymmetrization of aziridines **2** with **4a**[a]



Entry	2	Time/days	Yield (%)[b]	ee (%)[c]
1	**2a**	4	96	85
2	**2b**	7	63	99
3	**2c**	7	46	82
4	**2d**	4	38	37
5	**2e**	12	61	85

[a] Reaction performed at 0.08 mmol scale using **2** (1 equiv.), **4a** (1.5 equiv.) and **1** (0.10 equiv.) in toluene (0.1 M concentration). [b] Isolated yields. [c] Determined by chiral HPLC.

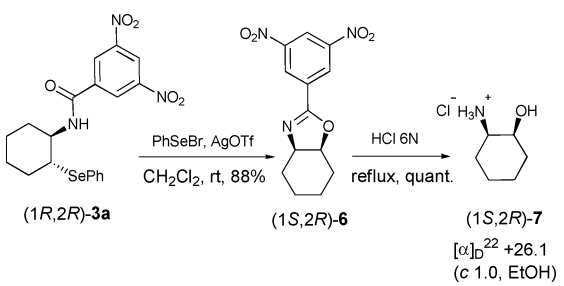
conversion was achieved at room temperature after 4 days, and the β-aminoselenide **3a** was obtained in 85% ee (entry 7).

The above reaction conditions were applied to different 3,5-dinitrobenzoyl aziridines **2** (Table 2). However, although in most cases the enantioselectivities varied from good to excellent, partial conversions were obtained even after several days. The five membered product **3d** was obtained in both disappointing yield and ee (entry 4).

We attributed the poor reactivity of **4a**, to the steric hindrance of the TBS group. With this in view, we submitted the substrate **2a** to the same reaction conditions (see Tables 1 and 2), using the less hindered (phenylseleno)trimethylsilane (**4b**) in place of (phenylseleno)*t*-butyldimethylsilane (**4a**). As expected, the opening of aziridine **2a**, at 20 °C in toluene, was almost complete after 5 h, affording **3a** with 92% yield and 64% ee. In 1,1,1-trichloroethane after 7 h, **3a** was obtained with 78% yield and 49% ee. Differently from the previous reported analogous desymmetrization with (phenylthio)trimethylsilane,[18] the reaction appeared to slow down severely after some hours. This different behaviour could be ascribed to the lability of the actual nucleophile, PhSeH (**5**), that was formed in small amount in the induction step of the catalytic cycle (see Scheme 1). Accordingly, a modified protocol based on the use of the mixture **4b**/**5** as the nucleophile was developed (method A, Table 3). Under the latter conditions the reaction of **2a** turned out to be very fast, giving **3a** in high yield (93%) and enantioselectivity (92% ee) after 30 min. The ee was further improved at 0 °C (entry 1, Table 3). When the same reaction was ten-fold scaled up, the ee was increased up to 99%. It is worth noting that the presence of a silylated nucleophile resulted to be essential. In fact, unlike the desymmetrization with thiols studied by Antilla and coworkers,[17c] the reaction of aziridine **2a** with PhSeH (**6**) catalysed by (*R*)-**1**, afforded **3a** with only 45% ee and 93% yield, after 2 h at room temperature in toluene.

A good reactivity and excellent enantioselectivity was observed at 0 °C also for cyclic aziridines **2b–d** (95–98% ee, entries 2–4). The acyclic aziridines **2e,f** and the seven-membered aziridine **2g** turned out to be less reactive and required the reaction to be performed at 20 °C. However, while the acyclic products **3e,f** were obtained in good yields (entries 5 and 6), a double amount of catalyst and nucleophile was needed in order to obtain an acceptable yield (method B, entry 7). Method A gave an unsatisfactory enantioselectivity only with aromatic aziridine **2h** (66% ee at 0 °C). In that case, reverse molar ratio between nucleophile and substrate proved to be advantageous (method C, entries 8 and 9).

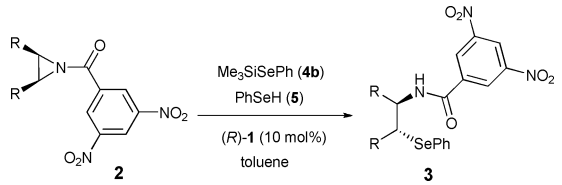
The absolute configuration of product **3a** was determined by transformation into the known aminoalcohol hydrochloride **7** in two steps (Scheme 2). The almost enantiopure material was subjected to typical conditions of cyclization[9,21] affording *cis*-oxazoline **6**, which was then hydrolysed affording **7**. The positive $[\alpha]_D$ measured for **7** allowed us to attribute the (1*S*,2*R*) configuration, by comparison with literature data,[22] and consequently, the (1*R*,2*R*) configuration to **3a**. This assignment is in agreement with the configuration previously established for the products of desymmetrization with Me_3SiSPh and with Me_3SiN_3 catalyzed by phosphoric acid (*R*)-**1**.

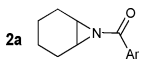
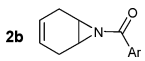
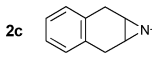
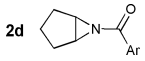
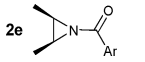
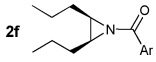
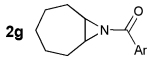
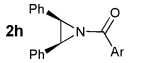


Scheme 2 Determination of the absolute configuration of **3a**.

In conclusion, we have developed the first method for the enantioselective synthesis of β-aminoselenides based on asymmetric catalysis, specifically on the desymmetrization of *meso*-aziridines.

Table 3 Scope of the desymmetrization of aziridines **2** with the **4b/5** mixture[a]



Entry	2	T/°C	Time/h	Yield (%)[b]	ee (%)[c]
1		0	1	94	97 (99)[d]
2		0	6	73	95
3		0	8	74	98
4		0	2	90	96
5		20	3	72	92
6		20	4	66	84
7[e]		20	30	46	96
8[f]		20	7	97	72
9[f]		0	6	46	84

[a] Except where otherwise specified, reaction performed at 0.08 mmol scale using method A: **2a** (1 equiv.), **4b** (0.5 equiv.), **5** (1 equiv.) and **1** (0.10 equiv.) in toluene (0.1 M concentration). [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reaction performed at 0.8 mmol scale. [e] Method B was used: **2a** (1 equiv.), **4b** (1 equiv.), **5** (2 equiv.) and **1** (0.20 equiv.) in toluene (0.1 M concentration). [f] Method C was used: **2a** (1.5 equiv.), **4b** (0.5 equiv.), **5** (0.5 equiv.) and **1** (0.10 equiv.) in toluene (0.1 M concentration).

The process proved to be general in scope and highly enantioselective. The procedure employs a readily available enantiopure phosphoric acid as the catalyst and (phenylseleno)trimethylsilane as the nucleophile. This approach allows us to obtain β-aminoselenium compounds that are hardly accessible from the chiral pool and can be easily elaborated, through known chemistry, to a number of enantioenriched products. Mechanistic investigations into this process are currently underway by our group and will be reported in the due course.

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