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New phenylselanyl group activation: synthesis of aziridines and oxazolidin-2-ones †

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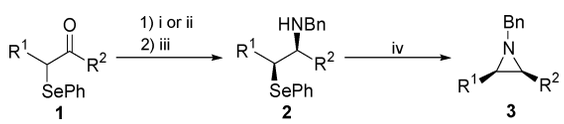
After the study of different phenylselanyl group activators, halogenation by *N*-bromosuccinimide (NBS) has been shown to be the most suitable manner for cyclizing β-phenylselanyl amines into aziridines and also enabled production of oxazolidin-2-ones from *N*-Boc β-phenylselanyl amines in excellent yield.

The conceptually simple approach of heterocycles probably relies on the cyclization of appropriate heterosubstituted precursors bearing internal leaving groups. One such group could be a selanyl group which is easily displaced under mild experimental conditions by several nucleophiles when it is activated in oxidation state IV as selenone or selenonium salt.[1] The synthesis of epoxides promoted by alkylation of β-phenylselanyl alcohols has been reported in the literature.[2] More recently, aziridines have been prepared by the oxidation of *N*-protected β-phenylselanyl amines.[3] However, a selenoxide *syn*-elimination sometimes occurs as a competing pathway. In our group, the diastereoselective preparation of β-phenylselanyl amines and their conversion into aziridines, promoted by methylation with the Meerwein salt, has been investigated (Scheme 1).[4]



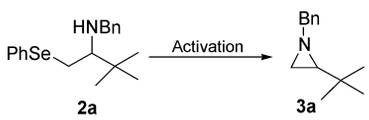
Scheme 1 *Reagents and conditions*: i. NH_2Bn, $MgSO_4$; CH_2Cl_2, 20 °C, 4 h; ii. NH_2Bn, $TiCl_4$, Et_2O, 20 °C, 4 h; iii. $NaBH_3CN$, AcOH, EtOH, −78 °C, 1 h; iv. Me_3OBF_4, CH_2Cl_2, 20 °C, 12 h.

Nevertheless with bulky R^1 groups, side reactions and formation of *N*-methylated products were observed. Herein, we report a new method to trigger the cyclization of selenenylated substrates while limiting the side reactions.

During the course of our work on the reactivity of β-phenylselanyl amines, we undertook a comparative study of the different methods promoting their cyclization into aziridines (Table 1). Treatment of the β-phenylselanyl amine **2a** with the Meerwein salt, afforded the aziridine **3a** in 58% yield (Table 1; entry 1). Resorting to an oxidant like mCPBA or hydrogen peroxide led to **3a** together with by-products derived from selenoxide *syn*-elimination (Table 1; entries 2,3). However, the cyclisation yield increased when the reaction was promoted by selenenylation (Table 1; entries 4,5). We also decided to try halogen activators. SO_2Cl_2 and Br_2 gave good yields, 63 and 75% respectively, but the best result was obtained using NBS as phenylselanyl group activator (80% yield, Table 1; entry 8). In addition, the conversion of the β-phenylselanyl amine **2a** became very rapid (5 min).

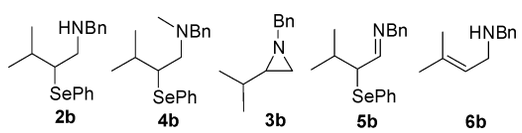
† Electronic Supplementary Information (ESI) available: experimental section. See http://www.rsc.org/suppdata/ob/b4/b406566m/

Table 1 Cyclization of **2a** induced by different phenylselanyl group activations



Entry	Activation	Yield (%)
1	MeO_3BF_4, 20 °C, 12 h	58
2	*m*CPBA, −78 °C, 20 min	32
3	H_2O_2, 20 °C, 30 min	25
4	PhSeCl, 20 °C, 5 min	64
5	PhSeBr, 20 °C, 5 min	70
6	SO_2Cl_2, 20 °C, 5 min	63
7	Br_2, 20 °C, 5 min	75
8	NBS, 20 °C, 5 min	80

Table 2 Cyclization of **2b** induced by different phenylselanyl group activations



Entry	Activation	Product (yield, %)
1	MeO_3BF_4, 20 °C, 12 h	**4b** (50), **3b** (21)
2	*m*CPBA, −78 °C, 20 min	**5b** (56), **6b** (24)
3	NBS, 20 °C, 5 min	**3b** (58)

The superiority of this new activation method became even clearer with the more hindered β-phenylselanyl amine **2b**. Promoting the reaction with the Meerwein salt afforded the *N*-methylated β-phenylselanyl amine **4b** as the major product and the aziridine **3b** in only 21% yield (Table 2; entry 1). Suprisingly, *m*CPBA converted the substrate **2b** into the α-phenylselanyl imine **5b** and a small amount of selenoxide *syn*-elimination product **6b** (Table 2; entry 2). Whereas using NBS, the aziridine **3b** was the sole product obtained in 58% yield (Table 2; entry 3).

This aziridine synthesis promoted by halogenation was successfully extended to the β-phenylselanyl amines **2d–h** (Table 3).[5] With this versatile method, the aziridines **3d–h** were obtained in 56–80% yield. Nevertheless starting from the substrate **2c**, the desired aziridine **3c** was obtained as a mixture with the β-bromo amine **7c**. An unexpected isomerisation was also observed during the cyclization of compound **2h**. Starting from a single *syn* diastereomer, the corresponding aziridine **3h** was obtained as a mixture of *cis* : *trans* diastereomers (15 : 85). The stereochemistry of the aziridines were unambigously assigned by ^1H NMR based on the characteristic $J_{H_2H_3}$ coupling constant.[6] It is assumed that intramolecular substitutions usually occur with inversion of configuration. In our case, the unexpected *trans* diastereomer may result from an

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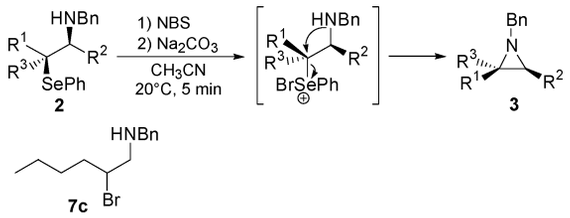
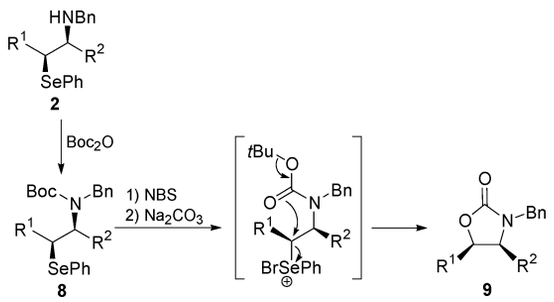
Table 3 Synthesis of aziridines **3** induced by phenylselanyl group halogenation with NBS



Substrates (*syn* : *anti*)[a]	R^1	R^2	R^3	Products (*cis* : *trans*)	Yield (%)
2c	*n*Bu	H	H	**3c** (**7c**)	36 (32)
2d	Me	H	Ph	**3d**	56
2e	H	Ph	H	**3f**	71
2f	H	Me	H	**3e**	60
2g (80 : 20)	Me	Et	H	**3g** (80 : 20)	65
2h (100 : 0)	Me	Ph	H	**3h** (15 : 85)	80

Table 4 Synthesis of oxazolidin-2-ones **9** induced by phenylselanyl group halogenation with NBS



Substrates (*syn* : *anti*)	R^1	R^2	Products (*cis* : *trans*)	Yield (%)
8f	Me	H	**9f**	87
8g (80/20)	Me	Et	**9g** (80 : 20)	91
8h (100/0)	Me	Ph	**9h** (100 : 0)[a]	85

[a] Confirmed by NOE experiment.

intermolecular substitution by a bromide anion prior to the ring closure.

We next attempted to extend the halogenation promoted cyclization to oxygenated nucleophiles. Like aziridines,[7a] oxazolidin-2-ones[7b] are attractive targets due to their occurence in biologically active compounds, synthetic intermediates or chiral auxiliaries. One method of preparing oxazolidin-2-ones consists of an intramolecular nucleophilic substitution of carbamates bearing an internal leaving group.[8] In the literature, the cyclization of selenenylated carbamates by phenylselanyl sulfate has been evoked by Tiecco *et al*. to rationalize the one-pot transformation of alkenes into 4-substituted oxazolidin-2-ones.[9] We decided to adopt a comparable strategy. Thus, a Boc protection of compounds **2f**–**h** led to new cyclization substrates **8f**–**h** which reacted with NBS to afford oxazolidin-2-ones **9f**–**h** in 85–91% yield (Table 4). The stereochemistry of the products **9f**–**h** has been assigned in accordance to the literature data.[10] Only an intramolecular S_N2 reaction with inversion of configuration at the carbon bearing the selenium group were observed.

In conclusion, resorting to NBS as an activator of the phenylselanyl group constitutes a very simple and rapid new method for cyclizing β-phenylselanyl amines **2** into aziridines **3**. It gives access to a wide variety of aziridines, some of which could not be obtained by previous routes. The developed activation method also transforms stereospecifically selenenylated carbamates **8** into oxazolidin-2-ones in excellent yield.

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5 Typical procedure: To the β-phenylselanyl amine (1 mmol) in acetonitrile (15 ml) was added NBS (195 mg, 1.1 mmol) at room temperature. After 5 min of stirring the mixture became red–brown and sodium bicarbonate (212 mg, 2 mmol) was introduced. The mixture turned rapidly yellow. Water (15 ml) was added and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 ml). The combined organic phases were dried with $MgSO_4$ and concentrated. The crude product was purified by column chromatography (cyclohexane : Et_2O, 8 : 2) to afford the desired aziridine.

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