Efficient Ring Opening of Protected and Unprotected Aziridines Promoted by Stable Zinc Selenolate in Ionic Liquid

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Abstract: A highly efficient protocol is reported for the synthesis of chiral β-seleno amines via the ring-opening reaction of aziridines. Under neutral conditions, employing a stable phenyl selenolate specie (PhSeZnBr) and (BMIM)BF_4 as solvent, β-seleno amines were obtained in good to excellent yields. Reuse of the ionic liquid was also possible, and four runs were performed with no decrease in the yields.

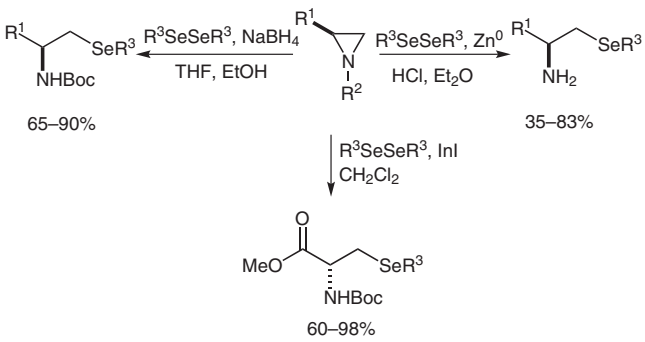
Key words: chiral β-seleno amines, ring opening reaction, aziridine, ionic liquid

Organoselenium chemistry is a field of continuous interest in modern organic synthesis.[1] Organoselenides are versatile tools in many synthetic transformations, and have found a broad range of applications as radical precursors, in elimination and oxidation reactions, and as selenium-stabilized carbanions.[2] Moreover, chiral selenide- and diselenide-containing ligands offer attractive and practical options in the development of asymmetric transformations.[3]

The biological and medicinal properties of selenium and organoselenium compounds are also increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[4] In this context, synthetic methods for the preparation of selenocysteine,[5] selenium-based peptides,[6] selenoglycosides,[7] selenonucleosides,[8] and other important natural coumpounds[9] is nowadays an area of intensive research.

The development of new methods for the introduction of selenium-containing groups into organic molecules, particularly in a stereocontrolled manner, remains a significant challenge. Many reports appeared in the literature describing the use of selenium as a nucleophilic agent through the reduction of Se–Se bond, especially cleaveage of diaryl diselenides. Such procedures commonly employed $NaBH_4$,[10] Zn,[11] Zn/In(III),[12] and InI[13] among others.[14]

In recent years our group has been working extensively towards the development of protocols to prepare organoselenium compounds. Although synthesis of chiral β-seleno amines and selenocysteine derivatives has been successful accomplished, most procedures often require basic or acid reaction conditions and the use of undesirable, from an environmental point of view, organic solvents (Scheme 1).[15] In this context, we recently reported the synthesis of unsymmetrical diorganyl selenides using ionic liquid as an efficient and recyclable medium.[16] The advantages of employing ionic liquids, such as the high reactivity, their readily commercial availability, ease of preparation and handling as well the environmental aspects, justified our choice to employ them in our work.[17]



Scheme 1 Examples of ring opening of aziridines with R^3SeSeR^3 using different reducing agents and conditions

In the course of our pursuit of the synthesis and application of functionalized organoselenium compounds in organic synthesis,[18] we report herein a new methodology to prepare β-seleno amines in a neutral and smooth protocol. Using a bench-stable phenyl selenolate specie (PhSeZnBr), recently described by Santi et al.[19] to promote the ring-opening reaction of protected and unprotected aziridines in (BMIM)BF_4, the desired products were obtained in good to excellent yields, in really short time and with the advantage of recycle the reaction media, which represents an environmentally benign approach.

Aiming to achieve the optimum conditions, Boc-protected aziridine **1a** was selected as a model substrate. Our studies started by comparing the feasibility of ionic liquids to promote the reaction efficiently, compared with the well-known organic solvents applied for this purpose (Table 1). We selected (BMIM)BF_4, (BMIM)PF_6, and (BMIM)NTf_2 to be evaluated. Using THF under reflux, the product **2a** was obtained with higher yield than when

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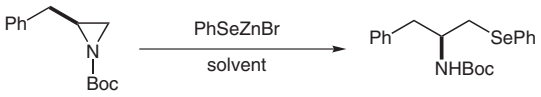
the reaction was carried out at room temperature (entries 1 and 2). When CH_2Cl_2 was used, a decrease in the yield was observed, affording the corresponding product in 70% yield (entry 3). Acetonitrile, EtOAc, and EtOH were also used and they were less effective than THF: 67%, 50% and 62%, respectively (entries 4–6). Water was also used (entry 7), but unfortunately the product was obtained in a lower yield. By using (BMIM)BF_4, (BMIM)PF_6, and (BMIM)NTf_2 at 90 °C for 24 hours, the product was formed in 86%, 26%, and 31% yields, respectively (entries 8–10). With these results in hands, (BMIM)BF_4 was chosen for the subsequent reactions. When the reaction was conduced at room temperature, a significant decrease in the yield was found (entry 11). The reaction time was also evaluated, and it was noted that, when the time was reduced to 12 hours, 4 hours, and 1 hour (entries 12–14), the yields were at the same level as those in 24 hours. We also used PhSeZnCl as nucleophile, however, the product was obtained in a lower yield when compared with PhSeZnBr (entry 15).

With the optimal conditions in hands,[20] and in order to evaluate the scope and limitations of the reaction procedure, the present protocol was extended to a broader range of protected and unprotected aziridines **1a**–**g** (Table 2).

Table 1 Optimization of the Solvent in the Ring-Opening Reaction of Aziridine **1a** by PhSeZnBr



1a **2a**

Entry[a]	Solvent	Time (h)	Temp (°C)	Yield (%)[b]
1	THF	24	r.t.	65
2	THF	24	reflux	85
3	CH_2Cl_2	24	reflux	70
4	MeCN	24	reflux	67
5	EtOAc	24	reflux	50
6	EtOH	24	reflux	62
7	H_2O	24	reflux	42
8	(BMIM)BF_4	24	90	86
9	(BMIM)PF_6	24	90	26
10	(BMIM)NTf_2	24	90	31
11	(BMIM)BF_4	24	r.t.	50
12	(BMIM)BF_4	12	90	84
13	(BMIM)BF_4	4	90	82
14	(BMIM)BF_4	1	90	81
15[c]	(BMIM)BF_4	1	90	68

[a] Reaction conditions: solvent, PhSeZnBr (0.5 mmol), and aziridine (0.5 mmol).
[b] Isolated yields.
[c] PhSeZnCl was used as nucleophile instead of (PhSeZnBr).

Table 2 Ring-Opening Reaction of Aziridines **1a**–**g**

1a–g **2a–g**

Entry[a]	R^1	R^2	Product	Yield (%)[b]
1	Bn	Boc	**2a**	81
2	*i*-Pr	Boc	**2b**	60
3	Bn	Ts	**2c**	99
4	*i*-Pr	Ts	**2d**	90
5	*i*-Bu	Ts	**2e**	85
6	*i*-Pr	H	**2f**	70
7	*i*-Bu	H	**2g**	52

[a] Reaction conditions: (BMIM)BF_4 (1 mL), PhSeZnBr (0.5 mmol), and aziridine (0.5 mmol).
[b] Isolated yields.

The *N*-Boc-protected aziridine **1b**, derived from L-valine gave the product in 60% yield (entry 2). For *N*-Ts-protected aziridines **1c**–**e** better yields were obtained, the β-seleno amine **2c**, derived from L-phenylalanine, was achieved in quantitative yield (entry 3). Unprotected aziridines **2f** and **2g** also underwent the reaction, furnishing the desired products in goods yields (entries 6 and 7). These aziridines commonly require severe reaction conditions to underwent ring opening (e.g., use of Lewis acid and reflux for several hours) affording the products in low yield and with poor regioselectivity.[21]

An important feature of ionic liquids is that they are readily recyclable, which makes their use an excellent alternative, mainly considering economic and environmental aspects.[17] Thus, as a further extension to our work, we verified the possibility to recycle the ionic liquid. The data shown in Figure 1 illustrate that the medium can be reused for at least four times without loss of yield in the ring-opening reaction of aziridine **1c**.

We also extended our protocol to other electrophiles (Scheme 2) and useful compounds such as seleno ester **3**[22] and diorganyl selenides **4** and **5**[23] were synthesized in good to excellent yields.

In summary, we have described a practical and concise synthesis of structurally diverse chiral β-seleno amines via the ring-opening reaction of protected and unprotected aziridines. In a straightforward and flexible synthetic route, using PhSeZnBr as a nucleophile in BMIM(BF_4), which was susceptible for further reuse without loss of efficiency for at least four runs. Notable features of our approach are the use of bench-stable phenyl selenolate specie in neutral conditions, the recycling of the reaction media and the high reactivity towards unprotected aziridines, making this an efficient and desirable approach. We

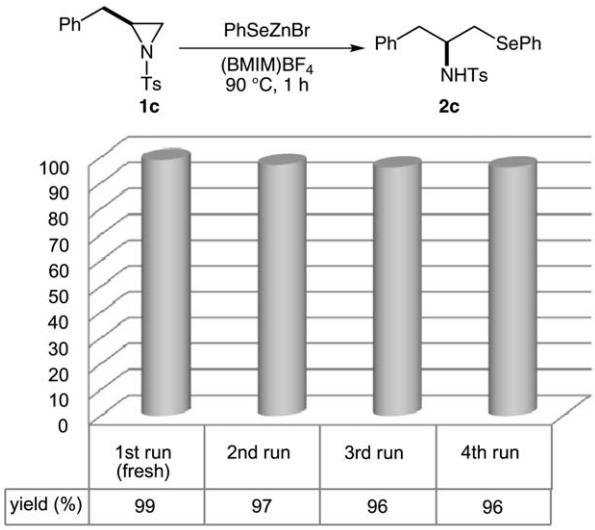
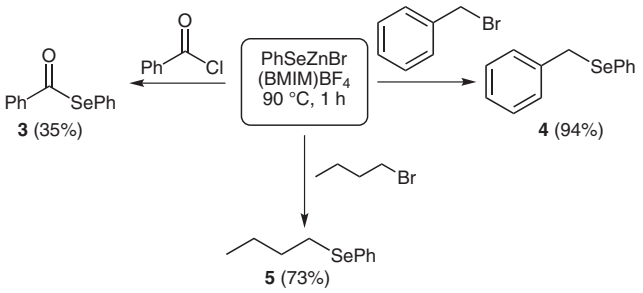


Figure 1 Reuse of the reaction media for the ring-opening reaction of aziridine **1c**



Scheme 2 Synthesis of selenoester **3** and diorganyl selenides **4** and **5**

believe that the chemistry described herein represents a new route for the synthesis of chiral organoselenium compounds containing nitrogen, among several applications, these coumpounds are useful chiral ligands in asymmetric catalysis. Intensive research in this area is in progress in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are general procedures and ^{1}H and ^{13}C NMR spectra of all compounds.

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