Tetrahedron Letters 51 (2010) 4437–4440

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regioselective synthesis of azetidines or pyrrolidines by selenium-induced cyclization of secondary homoallylic amines

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ARTICLE INFO

Article history:
Received 28 May 2010
Revised 14 June 2010
Accepted 16 June 2010
Available online 20 June 2010

Keywords:
Azetidines
Pyrrolidines
Selenocyclization
^{77}Se NMR

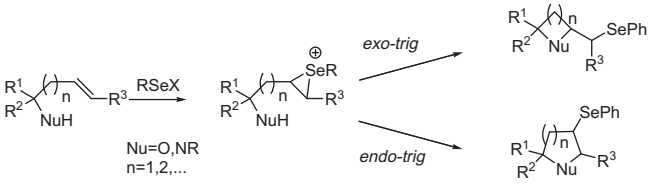
ABSTRACT

Azetidines or pyrrolidines can be regioselectively obtained by selenocyclization of homoallylic amines, according to the double bond substitution.

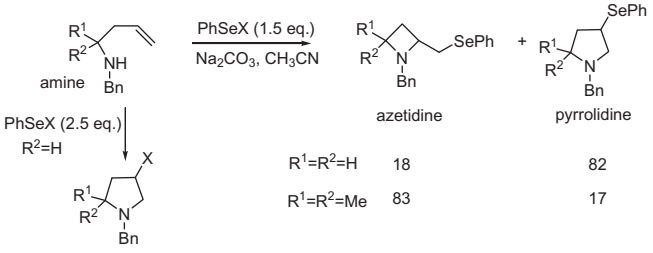
Cyclofunctionalizations are cyclizations mediated by an electrophilic reagent and are called selenocyclizations, in the case of selenenylated reagents. The reaction of selenium electrophiles with olefins is a stereospecific anti addition and internal nucleophiles lead to cyclic products. Selenocyclizations of unsaturated alcohols and amines (Scheme 1) are efficient methods for the synthesis of oxygenated or nitrogenated heterocycles.[1] Numerous studies concerning the influence of the nature of the electrophilic selenium species have been reported. These include [benzeneselenyl halides, *N*-(phenylseleno)phthalimides, and benzeneselenyl triflates or sulfates], including their counter-ion.[2] Asymmetric use of selenium reagents has also been developed recently.[3] The synthetic interest of the presence of an organoselenium function is obvious as it is one of the easiest functional groups to be transformed, either to double bond (*syn*-elimination of selenoxide) or to generate a stabilized carbanion or radical.

Some years ago, we showed for the first time that azetidines could be formed as a mixture with pyrrolidines from simple homoallylic secondary amines by selenium-induced ring closure, according to a 4-*exo-trig* process, when treated with 1.5 equiv of benzeneselenyl halide, whereas, the use of 2.5 equiv yielded only the halo-pyrrolidine ring when $R^2 = H$ (Scheme 2).[4] We also showed that the regioselectivity was dependent on the R^1, R^2 substitutions. Until now, no regioselective 4-*exo-trig* selenocyclization has been reported. We now report on the control of the regioselectivity of this cyclization, according to the substitution on the double bond and mainly focus on the synthesis of azetidines. Few reports describe that the regioselective obtention of azetidines[5] occurs by the cyclization of 4-haloamines, δ-aminoalcohols, or diols.[6] The development of new methods is therefore of high importance, due to the biological relevance of such moiety.[7]

Homoallylic amines **1** bearing different substituents in the γ- or δ-position of the double bond and with various R^1, R^2 substituents (Scheme 3) were prepared. The application of Barbier conditions



Scheme 1. Selenocyclizations of alcohols and amines.



Scheme 2. Azetidine/pyrrolidine formation.

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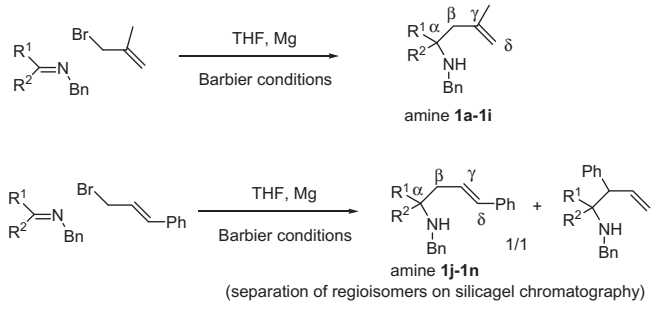
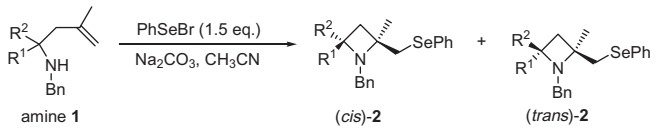
doi:10.1016/j.tetlet.2010.06.087



Scheme 3. Preparation of amines **1**.



Scheme 4. Regioselective synthesis of azetidines **2**.

(in situ generation and addition of Grignard reagent on preformed imines)[4b] allowed us to obtain amines **1a–1i** with methallyl bromide (in 50–70% average yield); amines **1j–n** were obtained (in 10–30% average yield) from cinnamyl bromide after separation from their regioisomer.

Having in hand homoallylic amines substituted at position γ or δ, we studied the regioselectivity of the selenium-induced cyclization. The reaction of homoallylic amines **1a–j** with 1.5 equiv of phenylselenium bromide afforded azetidines **2** as the only regioisomer (Scheme 4, Table 1).

Azetidines **2** were obtained as mixtures of cis (between R^1 and CH_2SePh) and trans isomers, with a large preference for the *cis* one (*cis*/*trans* > 80:20) regardless of the substituents R^1 and R^2. Yields of **2** increased when the size of R^1, R^2 substituents increased. From **1b** R^1 = Me to **1f** R^1 = *t*Bu, keeping R^2 = H, the yields increased from 45% to 68% (entries 2–5). Also, when $R_1 = R_2$ = H, a moderate 35% yield was obtained (entry 1). The Thorpe Ingold effect is therefore very important in order to achieve this transformation in good yields, but has no effect on the stereoselectivity.

We have determined the relative stereochemistry of cis/trans azetidines by the use of nOe correlations on compound **2d** (Fig. 1). According to the literature, we have represented the *trans* isomer like a nearly planar ring and the *cis* isomer like a puckered ring.[10] We could also generalize and attribute the relative abundance of each *cis*/*trans* diastereomer by using ^{77}Se NMR which is a very powerful tool we have already used for the determination of diastereomeric ratios of cyclopropanes and dienes.[11] In the azetidine series, homogeneous values for cis and trans azetidines **2** were observed with ^{77}Se δ 242–244 ppm and ^{77}Se δ 249–252 ppm, respectively.

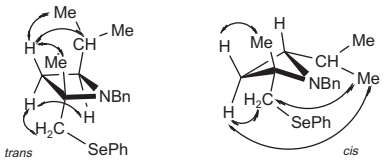
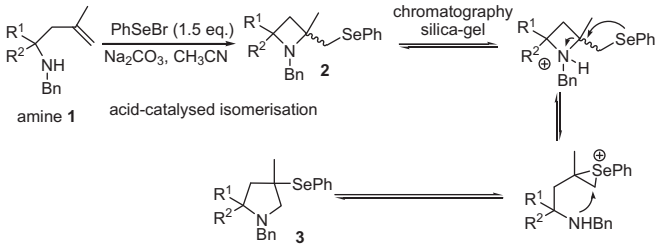
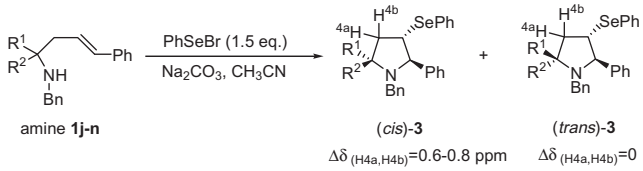


Figure 1. NOe correlations on **2d**.



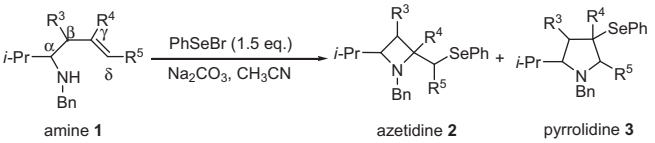
Scheme 5. Acid-catalyzed isomerization of azetidine **2** into pyrrolidine **3**.



Scheme 6. Regioselective synthesis of pyrrolidines **3**.

Table 2
Regioselective synthesis of pyrrolidines **3**

Entry	amine **1**	R^1, R^2	Yield% of **3** (*cis* + *trans*)	Pyrrolidines **3**	
				2,4-*cis*	2,4-*trans*
1	**1j**[14]	H, H	55	(373.5)	
2	**1k**	Et, H	73	80 (392.6)	20 (367.2)
3	**1l**	*i*Pr, H	80	85 (403.4)	15 (359.7)
4	**1m**	Ph, H	72	84 (397.5)	16 (376.6)
5	**1n**	Me, Me	88	(375.2)	



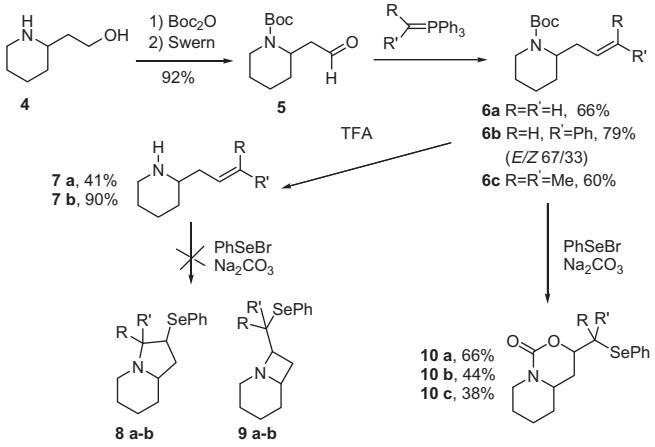
Scheme 7. Influence of the position of a methyl on the regioselectivity of the cyclization.

Table 1
Regioselective synthesis of azetidines

Entry	Amine **1**	R^1, R^2	Yield% of **2** (*cis* + *trans*)	Azetidines **2**%, (^{77}Se NMR δ ppm)	
				cis	*trans*
1	**1a**[8]	H, H	35	(244.2)	
2	**1b**	Me, H	45	82 (244.3)	18 (252.1)
3	**1c**	Et, H	58	82 (243.1)	18 (251.1)
4	**1d**	*i*Pr, H	65	82 (242.5)	18 (250.6)
5	**1f**	*t*Bu, H	68	81 (243.2)	19 (248.8)
6	**1g**[9]	Ph, H	67	82 (244.3)	18 (252.6)
7	**1h**	Me, Me	72	(245.4)	
8	**1i**[9]	$(CH_2)_5$	69	(244.4)	

Table 3
Variation of the regioselectivity

Entry	Amine **1**	R^3, R^4, R^5	Azetidine **2**% (^{77}Se NMR δ ppm)		Pyrrolidine **3**% (^{77}Se NMR δ ppm)	
			cis	*trans*	*cis*	*trans*
1	**1o**[15]	H, H, H	46 (252.0)	22 (251.2)	19 (407.3)	13 (372.7)
2	**1p**[16]	Me, H, H	51 (247.2)	25 (249.7)	24 (393.7)	—
3	**1d**	H, Me, H	82 (242.4)	18 (250.2)	—	—
4	**1q**	H, H, Me	56 (356.7)	22 (367.1)	22 (414.4)	—



Scheme 8. Synthesis of bicyclic carbamates **10**.

It should be noted that partial rearrangement of azetidine **2** into pyrrolidine **3** occurred during silica gel chromatography of the crude material (Scheme 5). Couty has reported in the literature the similar ring expansion under thermal condition.[12] This acid-catalyzed rearrangement could be totally suppressed by adding 1% Et_3N to the eluent but the separation became harder. On the other hand, the use of alumina column chromatography proved to be efficient with neither Et_3N nor rearrangement.[13]

We then modified the substitution of the double bond and introduced a phenyl group in the δ-position in order to drive the selenocyclization of homoallylic amines **1j–n** in favor of the 5-*endo-trig* mode (Scheme 6, Table 2).

In this case, only pyrrolidines **3** were obtained in yields ranging from 55% to 88% and, as with azetidines, better yields were obtained in the case of bulky R^1 substituents (entries 2–4). 2,4-*Cis* isomers (between R^1 and SePh) were also obtained in higher amount than the *trans* one (usually >80/20 ratio). The *cis*/*trans* relative configuration of pyrrolidines **3** was determined by ^{1}H NMR. Indeed, the chemical shifts of geminal H-4 protons are similar in the *trans* configuration (between R^1 and SePh) whereas they are very different ($0.6 < \Delta\delta < 0.8$ ppm) in the case of the *cis* configuration. The same observation has already been reported in the case of N-tosylated pyrrolidine.[1a] Again, ^{77}Se NMR also proved very useful for the determination of *cis*/*trans* ratio as δ ^{77}Se for *cis* isomer is comprised between 393–403 ppm whereas *trans* isomers show ^{77}Se NMR chemical shifts ranging from 360 to 377 ppm. Phenyl group in the δ-position directs the cyclization reaction toward the 5-*endo* mode exclusively.

We have also studied the influence of only one methyl substituent migrating from position β to position δ of the side chain (Scheme 7, Table 3). Without any substituent, selenocyclization of amine **1o** gave a mixture of azetidine **2** (68%) and pyrrolidine **3** (32%, entry 1). Introducing a methyl in the β-position, amine **1p** increased proportions of azetidine **2** (77%, entry 2). In the case of amine **1d**, no pyrrolidine was obtained (entry 3) as already shown in Scheme 4 and Table 1. With amine **1q** having a methyl in the δ-position, only 22% of pyrrolidine **3** was obtained after selenocyclization (entry 4). This relatively low yield in pyrrolidine compared to that in entry 1 (δ-carbocation should be stabilized by δ-methyl, thus expected to increase pyrrolidine formation) can be explained by steric interaction between nucleophilic nitrogen and δ-methyl, increasing the azetidine formation.

To further increase molecular diversity, we tried to prepare bicyclic azetidines or pyrrolidines by selenocyclization of 2-allylpiperidines **7**, which are constrained analogues of homoallylic amines **1** (where R^1 and N-substituents are joined in a six-membered ring). 2-allylpiperidines **7a–b**[17,18] were prepared from 2-hydroxyethyl piperidine **4**[19] by *N*-Boc protection, Swern oxidation[20], Wittig reaction, and TFA removal of the Boc group (Scheme 8). Unfortunately, addition of PhSeBr in the presence of Na_2CO_3 to allylpiperidines **7a–b** did not afford any bicyclic amines **8** or **9**. This unreactivity may be explained by the cyclic strain allowing less freedom for the nitrogen to add onto seleniranium ion. On the other hand, the reaction of *N*-Boc allylpiperidines **6a–c**[21,22] with PhSeBr resulted in an oxyselenenylation of the double bond giving rise to bicyclic carbamates **10a–c**, precursors of sedum alkaloids. In the case of **10a** (R = R′ = H) and **10c** (R = R′ = Me), a mixture of inseparable cis and trans isomers was obtained.[23] In the case of **10b**, a mixture of 4 isomers was obtained, as the starting alkene **6b**[20] was a *cis*/*trans* mixture.

To conclude, in this Letter, we have described an efficient method to obtain regioselectively selenofunctionalized azetidine with a good diastereoselectivity in favor toward the cis diastereomer.[24] It was demonstrated that Thorpe Ingold effect plays an important role for the yield of the selenocyclization reaction. And when a phenyl group is located in the δ-position, the regioselectivity of selenocyclization was completely reversed to furnish pyrrolidine products with a preference for cis diastereomer. Further studies in order to broaden the scope of this reaction, including the influence of the nitrogen-protecting group, will be reported in due course.

Acknowledgment

We gratefully acknowledge the Région Haute Normandie for funding.

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23. cis and trans mixture could only be evidenced by ^{13}C NMR, all signals overlapped on ^{1}H NMR and diastereomers could not be distinguished. Same observation was already reported on similar structures: Szakonyi, Z.; D'Hooge, M.; Kanizsai, I.; Fülöp, F.; De Kimpe, N. *Tetrahedron* **2005**, *61*, 1595–1602.
24. *Typical procedure*: To a solution of amine **1** (10 mmol) in freshly distilled acetonitrile (30 ml) containing anhydrous sodium carbonate (2 g) was added, dropwise at rt and under inert atmosphere, a solution of PhSeBr (15 mmol) in acetonitrile (50 ml). The mixture was stirred for16 h at rt and then treated with a saturated aq NaCl solution. After separation, the aqueous layer was extracted with CH_2Cl_2 (3×20 ml) and the organic phases were collected, dried with anhydrous $MgSO_4$, and concentrated in vacuo. Purification of the residue was carried out by flash chromatography on alumina gel (199:1–99:1 of cyclohexane/ethyl acetate) providing successively diphenyldiselenide, *cis* azetidine followed by *trans* azetidine, without isomerization to pyrrolidine.