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

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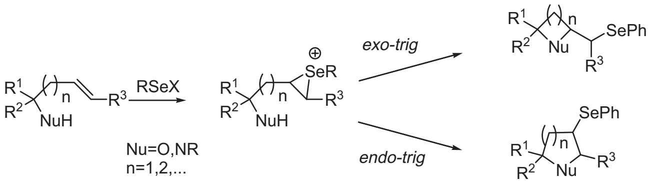
ABSTRACT

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

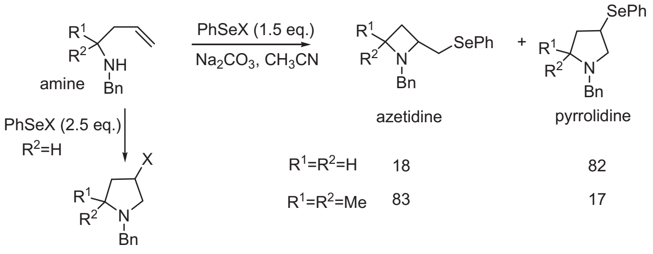
Cyclofunctionalizations are cyclizations mediated by an electrophilic reagent and are called selenocyclizations, in the case of selenenylated reagents. The reaction of selenium electrophiles with olefins is a stereospecific anti addition and internal nucleophiles lead to cyclic products. Selenocyclizations 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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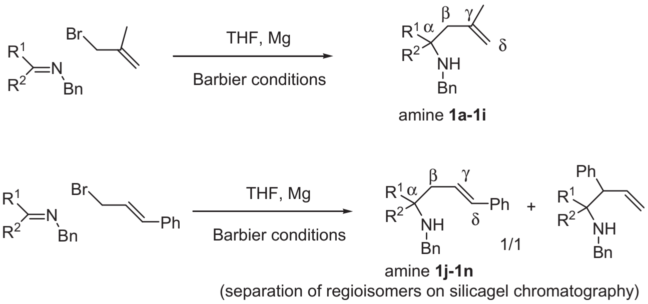
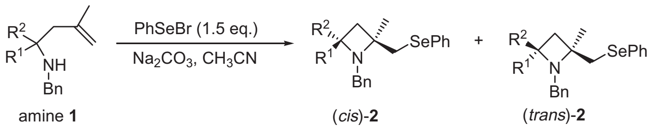


Scheme 3. Preparation of amines **1**.



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.

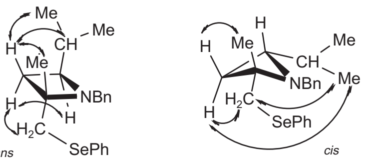
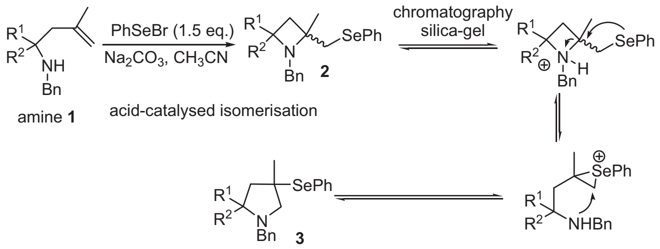
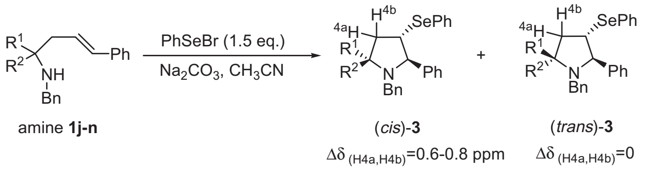


Figure 1. NOe correlations on **2d**.



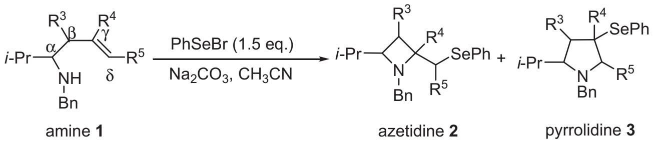
Scheme 5. Acid-catalyzed isomerization of azetidine **2** into pyrrolidine **3**.



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)	