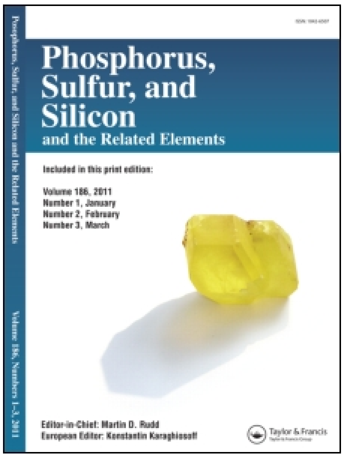

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Diastereomeric Quantification by ^{77}Se NMR

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Diastereomeric Quantification by ^{77}Se NMR

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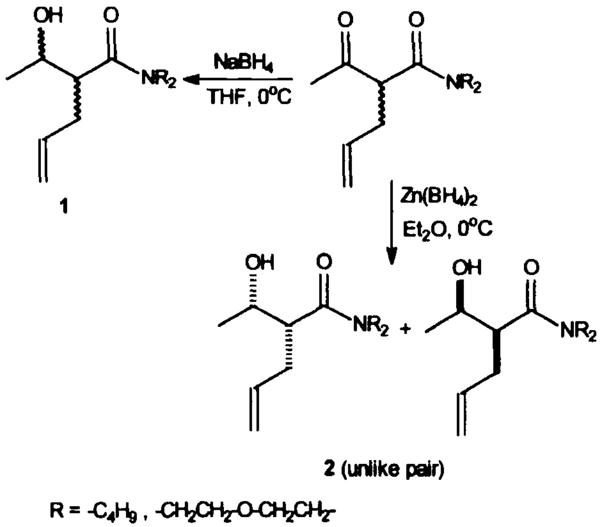
The reduction of α-substituted-β-ketoamides with either $NaBH_4$or $Zn(BH_4)_2$ yielded the respective β-hydroxyamides in different diastereomeric ratios. Selenocyclofunctionalization of these compounds yielded the corresponding tetrahydrofurans in good yields and the ratio of the diastereomers were determined by ^{77}Se NMR.

Keywords: tetrahydrofurans; ^{77}Se NMR; stereomeric quantification

Selenium compounds with a general structure RSeX undergo 1,2-additions to olefins and related unsaturated substrates *via* a seleniranium ion intermediate. When this addition is performed in the presence of an internal nucleophile, an intramolecular attack takes place, leading to a cyclized product in a diastereoselective ring closure reaction yielding the corresponding heterocycle derivatives.[1]

In this communication, we wish to report the use of ^{77}Se NMR as an alternative method to determine the diastereomeric ratio of the products and compare it with the gas chromatography analysis.

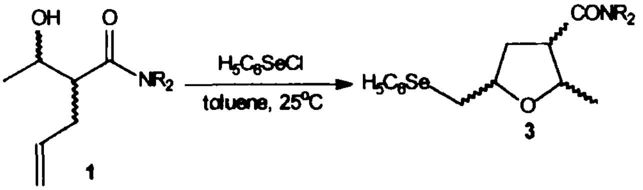
Accordingly, the reduction of α-allyl-β-ketoamides with either $NaBH_4$ and $Zn(BH_4)_2$ yielded the desired α-allyl-β-hydroxyamides **1** and **2** in good yields[2] (Scheme 1).



SCHEME 1

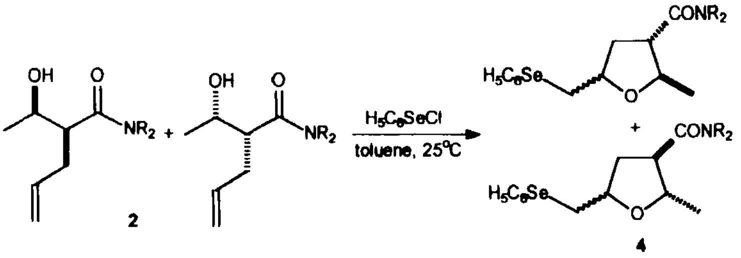
The diastereoselective control in the reduction with $Zn(BH_4)_2$ is probably due to formation of a complex between the zinc ion and the two carbonyl groups, that leaves the less hindered face for the hydride addition.

The selenocyclofunctionalization of 1 yielded a complex mixture of isomeric products due the formation of chiral centers in a non stereocontrolled reaction (Scheme 2).



SCHEME 2

However, when the α-allyl-β-hydroxyamides 2 were used, the desired tetrahydrofurans 4 were obtained in a diastereoselective manner. The diastereomeric ratio (dr) of the products was determined by ^{77}Se NMR analysis[3] (Figures 1 and 2) and further compared to the GC and leads to similar results (Scheme 3, Table 1).



SCHEME 3

TABLE 1. Diastereomeric ratio (dr) of the products determined by GC and ^{77}Se NMR

Compound	**R**	**dr by GC**	**dr by ^{77}Se NMR**
3a	-*n*-C_4H_9	1.0 : 1.2 : 1.6 : 1.7	1.0 : 1.1 : 1.6 : 1.8
3b	-CH_2-CH_2-O-CH_2-CH_2-	1.0 : 1.0 : 1.1 : 1.4	1.0 : 1.1 : 1.2 : 1.4
4a	-*n*-C_4H_9	1.0 : 1.1	1.0 : 1.1
4b	-CH_2-CH_2-O-CH_2-CH_2-	1.0 : 1.0	1.0 : 1.2

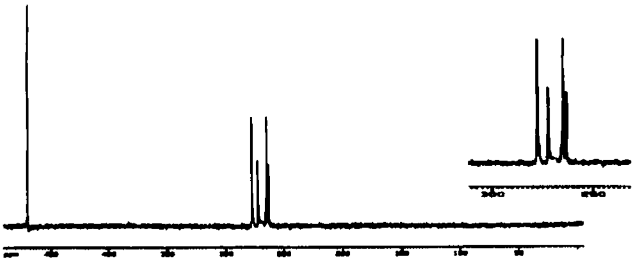


FIGURE 1. ^{77}Se NMR spectra of compound **3a**

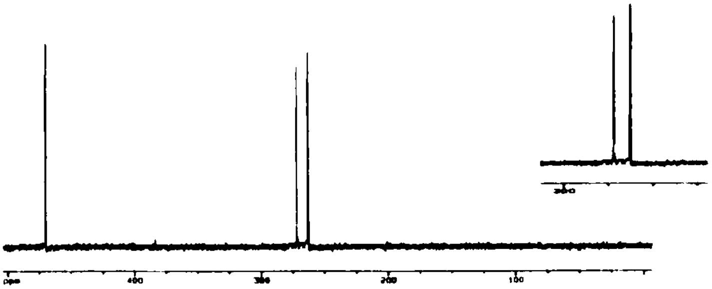


FIGURE 2. ^{77}Se NMR spectra of compound **4a**

In conclusion, we reported a general and reliable ^{77}Se NMR methodology for the analysis of isomeric mixtures obtained from a cyclofunctionalization reaction using selenium electrophiles.

EXPERIMENTAL

^{77}Se NMR spectra were recorded at 57.2 MHz, on Brüker DPX300 NMR spectrometer. The samples were diluted in $CDCl_3$ and diphenyl diselenide was used as internal reference. Gas chromatography analysis were performed on a Hewlett Packard-6890 chromatograph with a flame-ionization detector using a HP-5 capillary column (30 m x 0.32 mm x 0.25 μm).

Reduction with $NaBH_4$ (1)

To a two-necked round-bottom flask equipped with a magnetic stirring bar under inert atmosphere was added $NaBH_4$ (1.2 mmol) followed by THF (3.0 mL). The suspension was cooled to 0°C and a solution of α-substituted β-ketoamide was slowly added. After 1 hour reaction, ethanol (1.0 mL) was added and the reaction was allowed to reach the room temperature. The product was extracted with ethyl ether (2 x 20.0 mL) and washed with a NH_4Cl solution, brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography column using a mixture of hexane/ethyl acetate as eluent.

Reduction with $Zn(BH_4)_2$ (2)

Preparation of $Zn(BH_4)_2$ – Ethereal solution: $ZnCl_2$ was added to a 250 mL round-bottom flask and fused 3 to 4 times under reduced pressure. The flask was allowed to reach the room temperature and anhydrous ether (100.0 mL) was added. The mixture was then refluxed for 2 hours under argon atmosphere and cooled back to room temperature. The supernatant, an approximately 0.7 M solution of $ZnCl_2$ in ether (80.0 mL, 55.0 mmol) was added to a stirred suspension of $NaBH_4$ (3.97g, 105.0 mmol) in anhydrous ether (300.0 mL). The mixture was stirred for 2 days and stored at room temperature under argon. The supernatant solution was used for reductions.

Reduction: To a two-necked round-bottom flask equipped with a magnetic stirring bar under inert atmosphere containing the α-allyl-β-ketoamide (1.2 mmol) in ethyl ether (3.0 mL) cooled to 0°C was added a solution of $Zn(BH_4)_2$ in ether (5.0 mL). After 1 hour, the reaction was quenched by the addition of 10% HCl (15.0 mL). The product was extracted with ethyl ether (2 x 20.0 mL) and washed with a $NaHCO_3$ solution, brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography column using a mixture of hexane/ethyl acetate as eluent.

Selenocyclofunctionalization (3 and 4)

To a round-bottomed flask equipped with a magnetic stirring bar under inert atmosphere containing a suspension of sodium carbonate (1.0 mmol) and the appropriate α-substituted β-hydroxyamide (1.0 mmol) in toluene (5.0 mL) at room temperature was added the appropriate phenylselenenyl halide (2.0 mmol). The reaction was monitored by GC and TLC. The product was extracted with ethyl acetate (2 x 20.0 mL), washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue purified by silica gel chromatography column using a mixture of hexane/ethyl acetate as eluent.

ACKNOWLEDGMENTS

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