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Stereoselective Addition of Phenyl Selenyl Chloride to Methoxy Alkenes Derived from *N*-Protected Chiral α-Amino Acids.

Mariangela Demarcus,[a] Silvia N. Filigheddu,[a] André Mann[b] and Maurizio Taddei[a]*

[a]Dipartimento di Chimica, Università di Sassari, Via Vienna 2, I-07100 Sassari, Italy, (E-mail: mtad@ssmain.uniss.it) and [b]CNRS, ERS 655, Pharmacochimie de la Communication Cellulaire, Faculte de Pharmacie, 74, route du Rhin, BP 24, 67401 Illkirch Cedex, France

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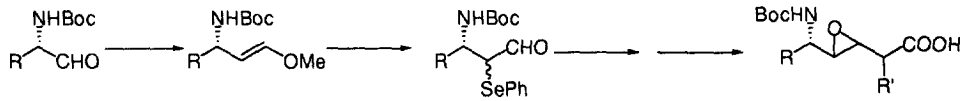
Abstract. (*E*)-Methoxy alkenes derived from N-Boc or N-Cbz α-amino acids undergo stereoselective addition of phenyl selenyl chloride in the presence of Ti(O*i*-Pr)4 and LiCl to give the corresponding phenylselenyl aldehydes that can be easily transformed into new enantiomerically pure amino acids containing an aziridine ring.

Keywords: Selenium halogen compounds, Selenonium ions, Chelation, Acetals.

The search for lead structures for the discovery of new effective proteinase inhibitors is one of the major tasks of contemporary organic chemistry.[1] Recently we described the preparation of a new class of peptidomimetics containing an epoxide in the place of the peptidic bond following the general synthetic scheme described in scheme 1.[2]



Scheme 1

The key step of the synthesis was the addition of phenyl selenyl chloride, in the presence of Na_2CO_3, to chiral vinyl ethers derived from protected α-amino aldehydes. This reaction gave a mixture of two diastereoisomers that were separated by column chromatography on silica gel and then transformed into the corresponding epoxides. As one of the two isomers showed higher activity as an inhibitor of cysteine proteases,[3] we decided to explore the possibility of controlling the diastereoselectivity during the addition of phenyl selenyl chloride.The low level of stereoselectivity observed could be related to the difference in steric hindrance between the R and the NHBoc or NHCbz groups linked to the stereogenic centre. Moreover, the rotation of the σ bond in the allylic group could be considered as another source for low selectivity.

At first, we observed that the stereochemistry of the double bond in the starting material had no influence on the diastereomeric composition of the final adduct. Starting either from the *E* or the *Z* isomers, we always obtained the corresponding selenyl aldehydes with comparable diastereomeric excess (de).

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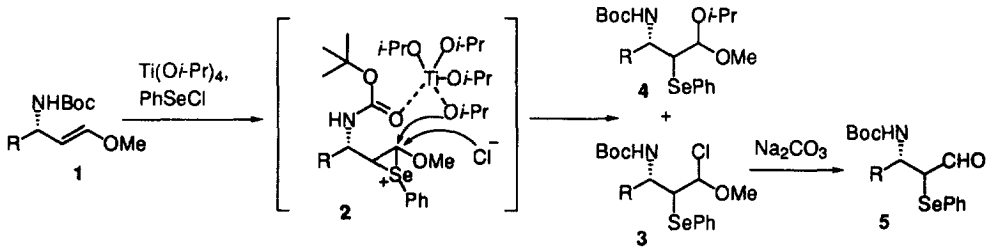
In one case (**1f**) the two diastereomeric products were separated and stirred in the presence of Na_2CO_3 for 12 h and no epimerisation was observed, demonstrating that the selenyl aldehydes are stereochemically stable to the reaction conditions.[4]

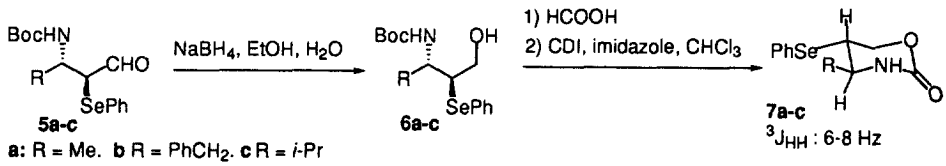
The presence in compounds **1a-f** of two groups that can behave as Lewis bases led us to try the use of a chelating Lewis acid that should prevent rotation around the σ bond. Experiments carried out with strong Lewis acids such as $ZnCl_2$, $MgCl_2$ or $TiCl_4$ were discouraging as the aldehyde **5** was not obtained. The strong competition between the Lewis acid and the Na_2CO_3 employed, indispensable in the reaction,[5] was certainly responsible for that failure. When we used Ti(O*i*-Pr)$_4$ we observed the formation of small amounts of the desired aldehyde **5** together with larger quantites of the mixed acetal **4**.



Scheme 2

These two products came from a competition, between the ligand of Ti(O*i*-Pr)$_4$ complexed to the Boc group and the chloride of the PhSeCl, in the nucleophilic opening of the selenonium intermediate **2**. While the chloride **3** was easily transformed into the aldehyde **5** by Na_2CO_3, the acetal **4** was stable to the basic conditions and was recovered unchanged at the end of the reaction.

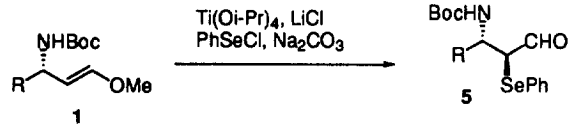
We tried to invert this unfavourable product ratio by increasing the amount of chloride ions in solution. We found that when the reaction was carried out at -78°C in THF, in the presence of 10 eq. of LiCl, we were able to isolate the desired phenyl selenyl aldehydes **5** in acceptable yield and good de (see Table). The values of de were easily determined by ^{1}H NMR analysis of the crude. The signals of the diastereomeric aldehydes at δ = 9.0-9.5 (-CHO) were always well separated and could be simply integrated to estimate the ratio. The stereochemistry of the products was determined by reduction of compounds **5a-c** into alcohols **6a-c** followed by deprotection and cyclisation with carbonyldiimidazole (CDI) and imidazole to give the cyclic urethanes **7a-c**. The ^{1}H NMR spectra of **7a-c** in $CDCl_3$-D_2O showed a vicinal coupling constant of 6 - 8 Hz, typical for an axial-axial relationship in a six membered ring.[6]

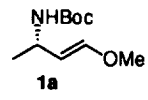
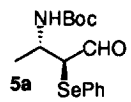
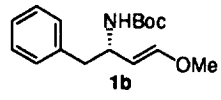
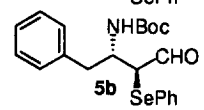
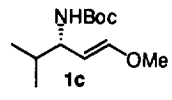
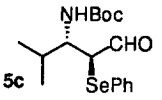
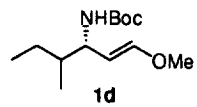
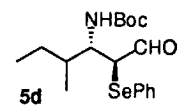
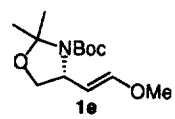
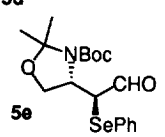
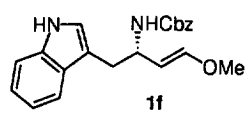
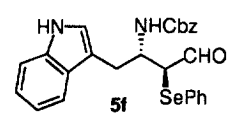
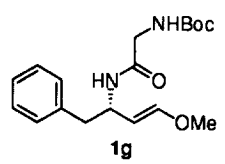
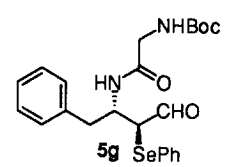


a: R = Me. **b** R = $PhCH_2$. **c** R = *i*-Pr

Scheme 3

Table 1. Stereoselective addition of PhSeCl to methoxy alkenes derived from protected α-amino acids in the presence of $Ti(Oi\text{-}Pr)_4$, LiCl and Na_2CO_3

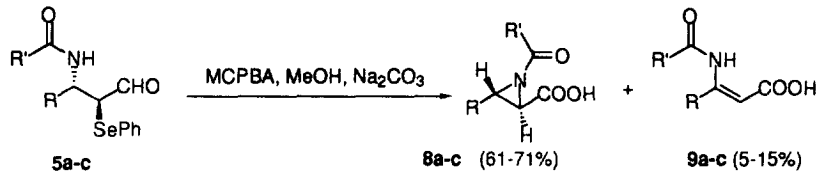


Starting amino acid	Alkene [a]	Product	yield (de)[b]
(L)-N-Boc-Ala-OH	 **1a**	 **5a**	73 % (75)
(L)-N-Boc-Phe-OH	 **1b**	 **5b**	83% (88)
(L)-N-Boc-Val-OH	 **1c**	 **5c**	71% (92)
(L)-N-Boc-Ile-OH	 **1d**	 **5d**	73% (94)
(L)-Ser-OH	 **1e**	 **5e**	77% (92)
(L)-Cbz-Trp-OH	 **1f**	 **5f**	69% (85)
(L)-N-Boc-Gly-Phe-OH	 **1g**	 **5g**	55% (90)

a) Compounds **1a-g** were prepared, according to ref. 2, from the *N*-protected amino aldehyde *via* a Wittig reaction of the ylide generated from $MeOCH_2PPh_3Cl$ and $NaN(SiMe_3)_2$. The products were always obtained as a mixture of the E/Z isomers in approximatively 8/2 ratio. b) Yields of isolated and fully characterized products. For the determination of the de see text. The relative stereochemistry of compound **5d-g** was assigned by analogy with products **5a-c**

The stereochemistry observed suggests that the $Ti(Oi\text{-}Pr)_4$ may coordinate to the protecting group of the nitrogen leaving the face opposite to the nitrogen accessible for the attack of PhSeCl.[7]

The aldehydes obtained with this reaction are valuable synthetic intermediates that can be transformed into the corresponding epoxides[2] or, as described in scheme 4 for **5a-c**, oxidized with 4 eq of MCPBA in MeOH in the presence of Na_2CO_3 at 0°C to give, after acidification and extraction with ethyl acetate, the aziridine carboxylic acids **8a-c** in acceptable yields.[8] In this case variable amounts (5-15%) of the unsaturated N-Boc amino acids **9a-c** were also isolated after column chromatography on silica gel.



Scheme 4

Compounds **8a-c** are conformationally constrained amino acid derivatives, suitable for introduction into a peptidic structure, that may have several applications in the field of peptidomimetics and enzyme inhibitors.[9]

Acknowledgements. *This work has been partially financed by CNR (Rome) as a "Contributo di Ricerca n. 98.01856.CT03".*

References and Notes.

1 See for example: Summers, J.B.; Davidsen, S.K. in: *Ann. Rep. in Med. Chem.*, J.A.Bristol Ed., Academic Press, New York, 1998, 131 and references therein.

2 Mann, A.; Quaranta, L.; Reginato, G.; Taddei, M. *Tetrahedron Lett.* **1996**, *37*, 2651

3 The results of the inhibition of papaine with peptidomimetics containing an oxirane ring will be reported elsewhere.

4 For a discussion of the stereochemical stability of related sulfenyl aldehydes see: Poli, G.; Belvisi, L.; Manzoni, L.; Scolastico, C. *J. Org. Chem.* **1993**, *58*, 3165.

5 If the addition of PhSeCl to product **1** is carried out without Na_2CO_3 the starting material is recovered unchanged.

6 The evaluation of the coupling constant was carried out under decoupling of the protons of the R groups.

7 Another possible explanation of the observed increase in stereoselectivity obtained after Lewis acid complexation is a minimisation of the allylic strain.

8 Reference data for **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J=7 Hz, 3H), 1.45 (s, 9H), 2.18 (qd, J= 7 Hz and 2 Hz, 1H), 3.11 (d, J= 2Hz, 1H), 10.1 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 23.2, 28.7, 41.4, 70.7, 156.1, 171.3. **9a** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.61 (s, 3H), 5.5 (s, 1H), 5.9 (bs, 1H), 9.1 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 28.6, 70.2, 99.6, 145.7, 153.4, 170.2.

9 Filigheddu, S.N.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 3857. Ziegler, F.E.; Belema, M. *J. Org. Chem.* **1997**, *62*, 1083. Funaki, I.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1996**, *52*, 9909. Schirmeister, T. *J. Med. Chem.* **1999**, *42*, 560.