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Allyltrichlorostannane additions to chiral dipeptide aldehydes†

Luiz C. Dias* and Edílson Ferreira

Instituto de Química-Universidade Estadual de Campinas/UNICAMP, CP 6154, CEP 13083-970, Campinas, SP, Brazil

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Abstract—The first examples of successful allylsilane additions to chiral dipeptide aldehydes are described. Treatment of allylsilanes with tin tetrachloride at room temperature affords allyltrichlorostannane intermediates that reacts with dipeptide aldehydes to give 1,2-*syn*-homoallylic alcohols, potential intermediates for the synthesis of hydroxyethylene dipeptide isosteres.

In the last several years there has been a major research effort towards the development of clinically useful inhibitors of HIV-1 protease.[1] This world-wide search has led to various peptide isosteres, wherein the scissile peptide bond is replaced by a hydrolytically more stable isosteric functional group. In this context, the hydroxy amino acid framework **B** in Fig. 1, where the peptidic linkage of the sequence in structure **A** is replaced by a $CH(OH)CH_2$ group, constitute a useful class of HIV protease inhibitors.[1–3]

We recently communicated that a chiral allylsilane reacts with *N*-Boc-α-aminoaldehydes in the presence of $SnCl_4$ to give 1,2-*syn* *N*-Boc-α-aminoalcohols that are key intermediates (molecules of type **C**) for the preparation of hydroxyethylene dipeptide isosteres.[4] The stereoselectivity of these tin(IV) chloride-promoted reactions is consistent with a mechanism involving transmetallation of the chiral allylsilane to give an intermediate allyltintrichloride which is stabilized by tin–oxygen interaction.[4] A synthetic methodology which allows compounds with programmed variations of substituents to be synthesized is particularly important in the screening of the pharmacological activity and in a study of structure–activity relationships

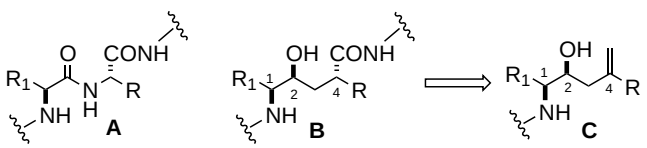

Figure 1. Core units of HIV protease inhibitors.

directed toward the design of the best substituents for positions 1 and 4 in structure **C** (R and R_1 groups).

Taddei and co-workers reported that allylchromium(III) organometallics react with dipeptide aldehydes to give the corresponding homoallylic alcohols with predominantly *syn*-selectivity.[5] They observed that any attempt to react allylsilanes, trialkylstannanes and allylcuprates with dipeptide aldehydes in the presence of Lewis acids or fluoride ions failed, mainly giving the product of protodesilylation, poor yields and a complex mixture of products.[5]

We wish to report here our initial results towards the synthesis of more complex dipeptide isosteres by reaction of allylsilanes with dipeptide aldehydes in the presence of $SnCl_4$. The present methodology is useful for the preparation of molecules of type **C** and consists, in the first step, of the preparation of molecules of type **B** (Fig. 1). To the best of our knowledge, these are the first examples of successful allylsilane additions to chiral dipeptide aldehydes.

The corresponding dipeptide amides **7a–e** were obtained in excellent yields by treatment of *N*-Boc-L-amino acids **1** and **2** and *N*-deprotected-L-Weinreb amides **3–6** with HOBt, DCC and $NaHCO_3$ in CH_2Cl_2 (Scheme 1).

The dipeptide aldehydes **8a–e** were obtained in good isolated yields for the two-step sequence by $LiAlH_4$ reduction of the corresponding Weinreb amides **7a–e** (Scheme 1).[5–10]

The dipeptide aldehyde **8f** was obtained after the following sequence: coupling between *N*-Boc-phenylala-

* Corresponding author. Fax: +55-019-3788-3023; e-mail: ldias@iqm.unicamp.br

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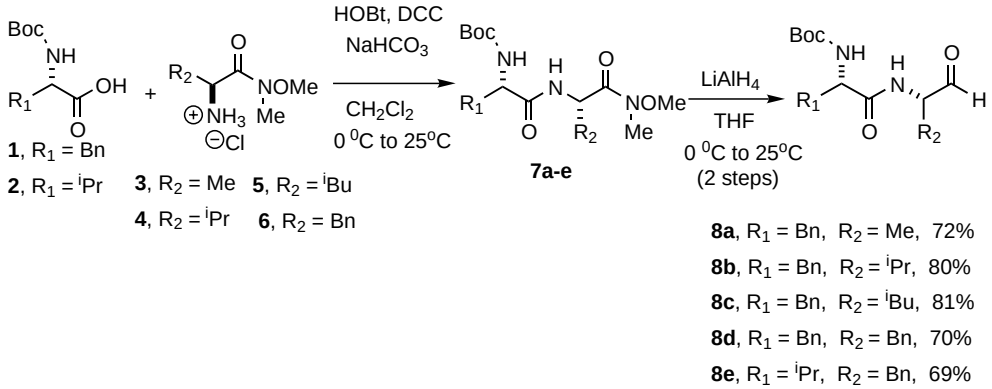


Scheme 1. Dipeptide aldehydes **8a**–**e**.

nine **1** and hydrochloride **9** (74%), protection of **10** with TBSCl (95%), reduction with 2 M $LiBH_4$ in THF to produce **11** (100%), followed by Dess–Martin oxidation (88%) (Scheme 2).[6–10]

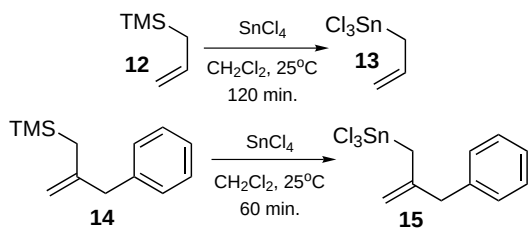
The next step is allyltrichlorostannane addition to these dipeptide aldehydes. According to a previously established experimental procedure, allylsilanes **12** and **14** and $SnCl_4$ (0.5 M solution in CH_2Cl_2) were mixed before the addition of a solution of the aldehyde in order to promote ligand exchange, leading to the corresponding allyltrichlorostannanes.[4b] For allyltrimethylsilane **12** (0.5 M in CH_2Cl_2) the ligand exchange affording allyltrichlorostannane **13** is complete after 120 min (Scheme 3). For allylsilane **14** (0.5 M in CH_2Cl_2) the metathesis is faster, as expected for a 1,1-disubstituted olefin, being complete after 60 min at room temperature, furnishing **15**.

The results of allyltrichlorostannane additions to dipeptide aldehydes **8a**–**f** are shown in Table 1. In all cases, the major product results from a chelation controlled reaction that mainly gives the 1,2-*syn* isomer, showing that the (*S*)-α-amino dipeptide aldehydes have a preference for *anti*-Felkin addition (*Si*-face attack). Increased steric bulk of the R_2 group ($R_2 = {}^{i}Pr$, ${}^{i}Bu$) in the aldehydes gives better diastereoselection.

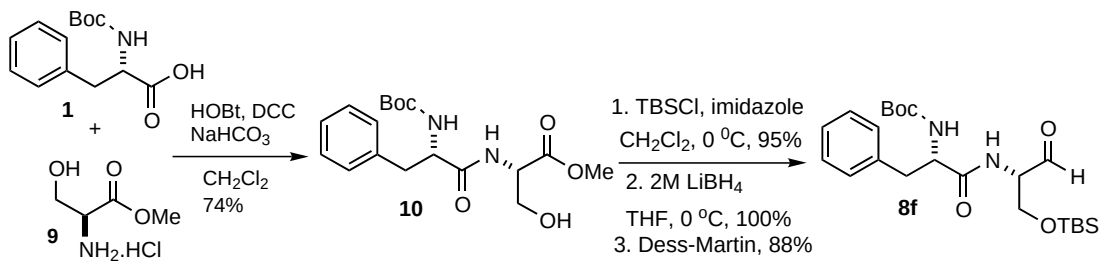
With small R_2 groups ($R_2 = CH_3$, Bn, CH_2OTBS) the diastereoselectivity is poor, although the reaction occurs in very good yields. It is essential to promote the ligand-exchange reaction before addition of the aldehyde in order to obtain good yields and selectivities. This reaction benefits from the fact that the real nucleophile is the allyltrichlorostannane and not the allylsilane itself.[11] It is interesting to point out that, if the allyltrichlorostannane addition reaction is carried out from −78°C to room temperature, we have observed loss of the Boc protecting group with the corresponding deprotected homoallylic alcohols being isolated in very good yields and having essentially the same selectivities.

The 1,2-*syn* relative stereochemistry of the major products was unambiguously established by spectroscopic analysis of the corresponding *trans* oxazolidines (upon irradiation of the hydrogens adjacent to H_a and H_b). Observed average coupling constants ($^3J = 1.0$ Hz) indicate that protons H_a and H_b are on opposite faces of the heterocyclic ring and, therefore, the oxazolidines are derived from 1,2-*syn* adducts (Scheme 4).[12]

Although the remote stereogenic center may influence the stereochemical course of C–C bond formation, we

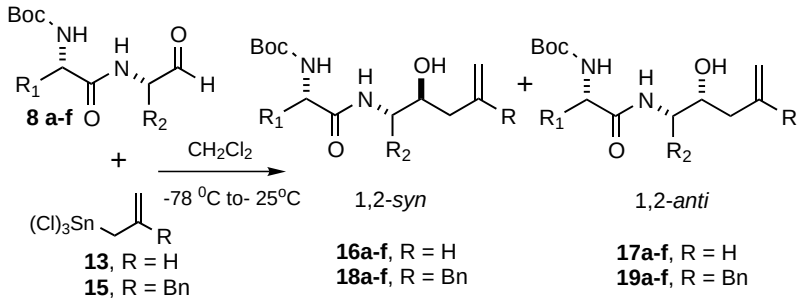


Scheme 3. Metathesis of allylsilanes **12** and **14**.



Scheme 2. Dipeptide aldehyde **8f**.

Table 1. Allyltrichlorostannane additions to dipeptide aldehydes[a,b]



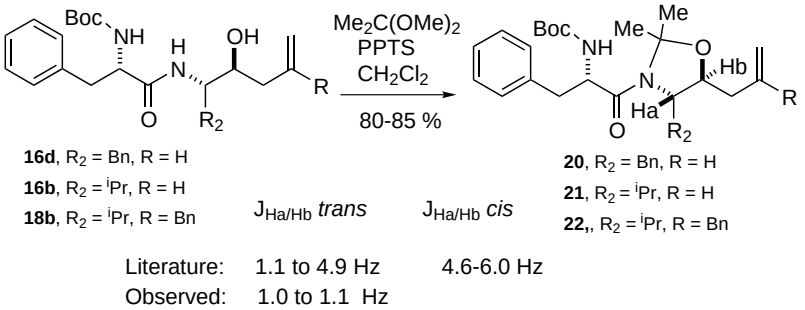
Dipeptide aldehydes **8**			R = H		R = Bn	
	R_1	R_2	**16**:**17**[b,c]	Yield (%)[d]	**18**:**19**[b,c]	Yield (%)[d]
a	Bn	Me	78:22	87	68:32	80
b	Bn	^{i}Pr	95:5	89	95:5	89
c	Bn	^{i}Bu	90:10	83	90:10	83
d	Bn	Bn	60:40	79	60:40	70
e	^{i}Pr	Bn	53:47	74	60:40	75
f	Bn	CH_2OTBS	66:34	86	60:40	74

[a] Reactions were carried out in dichloromethane from −78 to −25°C using molar equivalents of allylsilane, $SnCl_4$ and aldehyde in the presence of MS 4 Å.

[b] The ratios were determined by ^1H and ^{13}C NMR spectroscopic analysis of the crude mixtures of *syn* and *anti* products.

[c] Averages of at least three runs with ratios ±3%.

[d] Combined yields of products isolated chromatographically (SiO_2), after two steps (preparation of the aldehyde and coupling with allyltrichlorostannane).



Scheme 4. Coupling constants analysis.

expect such reactions to be dominated by the stereogenic center next to the aldehyde function. We believe that the observed selectivity can be explained by an equilibrium between the intramolecular hydrogen bond conformer **D** and a non-bonded conformer **E** (Fig. 2).[13] When the form **D** predominates (bulkier R groups), the *syn* isomer is favored, whereas the prevalence of the **E**-like conformer (smaller R groups) leads to the *anti* isomer. The nucleophile selects the less hindered *Si*-face, forming a six-membered transition state **F** where the chiral residue of the aldehyde occupies a *pseudo*-equatorial position.

We have reported herein the first examples of allylsilane additions to chiral dipeptide aldehydes. Treatment of allylsilanes with tin tetrachloride at room temperature affords allyltrichlorostannane intermediates that react with dipeptide aldehydes to give 1,2-*syn*-homoallylic

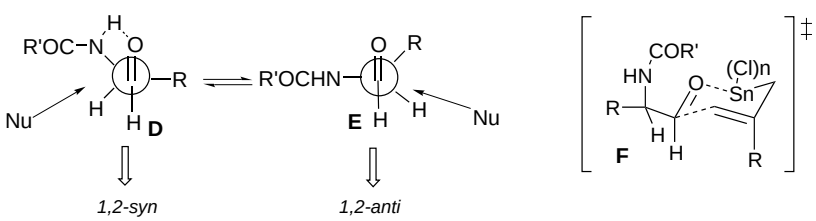


Figure 2. Transition state model.

alcohols, potential intermediates for the synthesis of hydroxyethylene dipeptide isosteres, with little or no undesired α-epimerization at the stereogenic center next to the aldehyde function.[14]

These resulting homoallylic alcohols are versatile intermediates for the introduction of different functional groups in intermediates aimed at the synthesis of hydroxyethylene isosteres. The examples show that the levels of π-facial selection depend on the substituents of the dipeptide aldehydes. We believe that this chemistry is truly significant in the context of acyclic diastereoselection and will prove to be exceptionally useful in the synthesis of more complex hydroxyethylene isosteres. Further exploration of these reagents and their applications is now underway in our laboratory.[14,15]

Acknowledgements

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6. (a) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676; (b) Saari, W. S.; Fisher, T. E. *Synthesis* **1990**, 453. These aldehydes should be used freshly prepared. Attempts to purify dipeptide aldehydes **8a**–**f** by silica-gel chromatography resulted in partial epimerization. Since the diastereoselectivity of the reactions of these aldehydes with allylsilanes depends on their diastereomeric purity, crude aldehydes were used in all of the studies described in the text. All the freshly prepared dipeptide aldehydes show single sets of signals in their respective ^1H and ^{13}C NMR spectra (DMSO-d_6), which proves the absence of appreciable epimerization.
7. For optical stability studies of *N*-protected α-amino aldehydes, see: (a) Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081; (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361; (c) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149; (d) Myers, A. G.; Zhong, B. Y.; Movassaghi, M.; Kung, D. W.; Lannan, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359.
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9. When aldehydes **8d** and **8e** (R_2 = Bn) were prepared from Swern oxidation of the corresponding peptide alcohols and used in coupling reactions with allyltrichlorostannanes **13** and **15**, we observed the formation of all four possible diastereomers. We have not observed this α-epimerization at the aldehyde stage when the corresponding primary alcohols derived from amides **7a**–**c** were submitted to Swern conditions, in agreement with the observations by Reetz and Griebenow. See Ref. 8.
10. We believe that partial epimerization of these dipeptide aldehydes does not occur in the allyltrichlorostannane addition reactions, since we have observed very clean ^1H and ^{13}C NMR spectra for all the corresponding products with signals for only two products.
11. Attempts to use allylsilanes **12** and **14** with other Lewis acids ($TiCl_4$, $BF_3{\cdot}OEt_2$) as well as attempts at mixing allylsilanes and dipeptide aldehydes before addition of $SnCl_4$ lead to poor yields, loss of the Boc protecting group and recovered starting material.
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13. The influence of an intramolecular hydrogen bond in the stereoselection of α-amino carbonyl compounds has been described. See: Pace, R. D.; Kabalka, G. W. *J. Org. Chem.* **1995**, *60*, 4838.
14. All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^1H and ^{13}C NMR, IR, MS, and HRMS spectral data.
15. **General procedure for the allyltrichlorostannane additions**: To a solution of 2.5 mmol of the corresponding allylsilane in 5 mL of dry CH_2Cl_2 at 25°C suspended with powdered molecular sieves 4 Å (50 mg) was added 2.5 mmol of $SnCl_4$. The resulting solution was stirred at 25°C for 1 h, then cooled to −78°C and 2.5 mmol of aldehyde in 2.5 mL of CH_2Cl_2 were added. This mixture was stirred for 30 min (−78 to −25°C) and quenched by the slow addition of 0.2 mL of Et_3N, followed by 10 mL of saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (40% EtOAc/hexanes) afforded the corresponding homoallylic alcohols.