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Diastereoselectivity in the alkylation of 4-fluoroproline methyl esters

Rosanna Filosa,* Claude Holder and Yves P. Auberson

Novartis Institutes for BioMedical Research, Klybeckstrasse 141, 4002 Basel, Switzerland

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Abstract—The reaction of alkylation of *cis*- and *trans*-4-fluoro-*N*-Boc-L-proline methyl esters has been examined by exposing their lithium enolates to a range of alkylating agents. The process showed a high degree of facial diastereoselectivity (except when methyl iodide was used as alkylating agent), invariably giving rise to products bearing the alkyl group in *anti* with respect to the fluorine atom. A tentative model to account for the observed stereoselectivity is also proposed.

1. Introduction

The stereo-selective alkylation of *N*-Boc-L-proline esters is recognized as a synthetically important process in the construction of a variety of natural products[1] as well as of conformationally restricted building blocks for the synthesis of peptidomimetics.[2] Over the last years, much effort has been expended in attempting to rationalize the stereochemical outcome of the alkylation of heterocyclic enolates such as those produced by 4-silyloxy-*N*-Boc-L-proline methyl esters.[3]

Sato et al.[3c] synthesized a series of 2-alkyl proline derivatives with the aim of shedding more light on the factors controlling the diastereoselectivity in this type of reaction (Fig. 1). They report that the steric and/or electronic factors of the *N*-Boc group would be more crucial rather than that of the silyloxy or ester moieties in the attack on the electrophilic carbon centre. Thus, the preferential formation of **3a** might be due to a shielding of the *syn*-face of the enolate by the *N*-Boc group.

On the other hand, quite recently Kawahara and co-workers[3d] found that the diastereoselectivity of the alkylation of 4-silyloxy-*N*-Boc-L-proline methyl esters is strongly dependent on the alkylating reagents. In their hands, alkylation with benzylic iodide preferentially gave products substituted at the β face (**3b**), whereas allylic or aliphatic halides, furnished the corresponding α-epimers (**3a**) as major products. They interpreted their stereochemical results in terms of a balance between two opposite effects: (a) the stereoelectronic interaction of N-lone pair with the forming C–C bond orbital (*anomeric effect*), independent of the type of alkylating agent, favouring substitution at the α-face, and (b) the interaction of the N-lone pair with π-orbitals of benzyl or allyl halide (n–π *interaction*), leading to the preferential formation of β-epimers.

In light of the preceding results, we embarked on a programme designed to readily examine the stereochemical behaviour of the corresponding 4-fluoro-*N*-Boc-L-proline methyl ester derivatives via classical alkylation conditions. More particularly, we demonstrated the strong influence of the fluorine atom in directing the reactivity of these heterocyclic lithium enolates, leading to a particularly high degree of facial diastereoselectivity.

In this letter, we describe the reaction of alkylation of *cis*- and *trans*-4-fluoro-*N*-Boc-L-proline methyl esters, by exposing their lithium enolates to a range of alkylating agents, leading to a series of alkylated *N*-Boc-L-prolines (**13**–**16**).

Our synthesis (Scheme 1) commenced with the readily available 2-allyl-4-silyloxy-*N*-Boc-L-proline methyl esters **5** and **6** which were converted to the corresponding fluorinated L-proline derivatives **9** and **10** whose absolute configuration at C-2 was formerly assigned.[3c]

Keywords: Diastereoselectivity; Proline derivatives; Fluorinated organic compounds; Alkylation.
* Corresponding author at present address: Dipartimento di Scienze Farmaceutiche, Università degli Studi di Salerno, Via Ponte don Melillo, 84084 Fisciano, SA, Italy. Tel.: +39 89962822; fax: +39 89962828; e-mail: rfilosa@unisa.it

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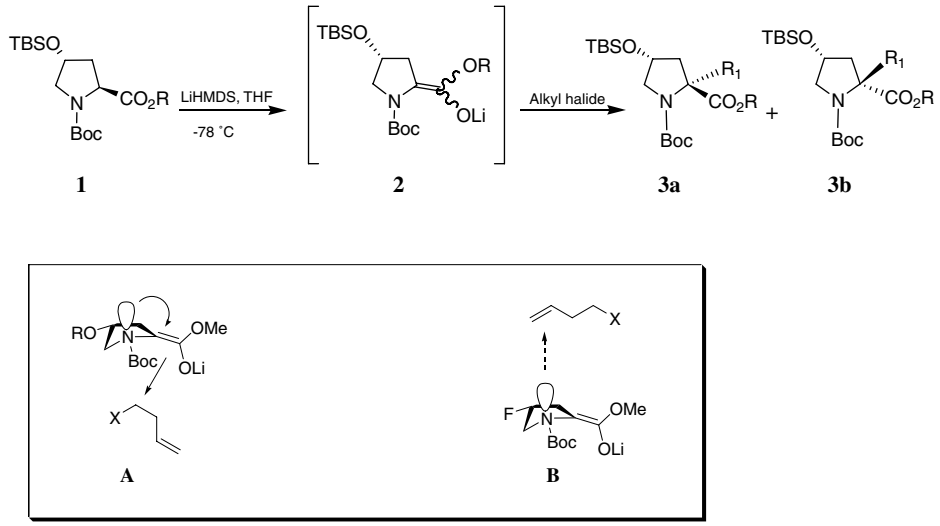
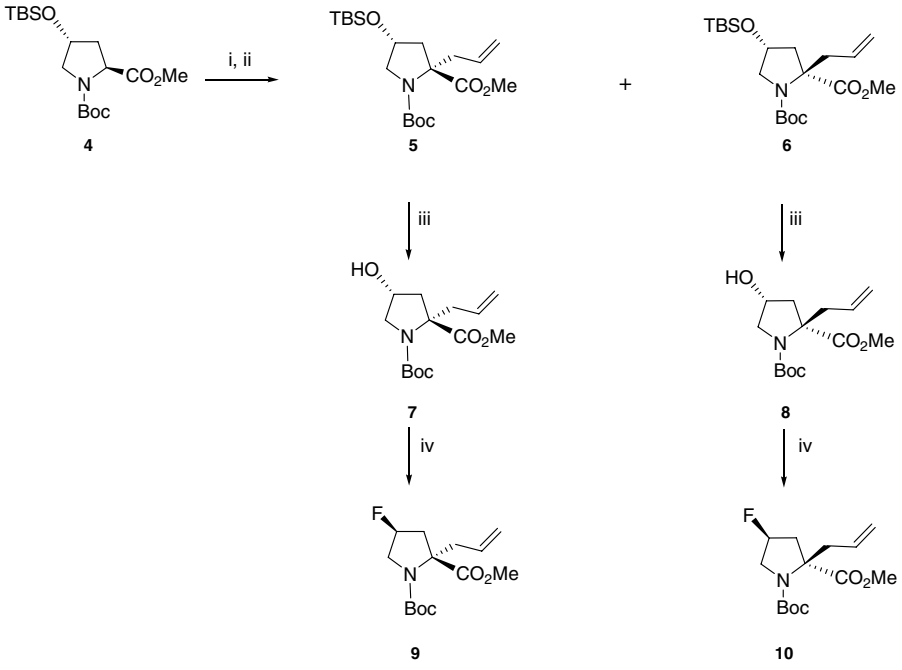


Figure 1. Alkylation of 4-siloxy-*N*-Boc-L-proline methyl esters, and transition state's hypothesis.

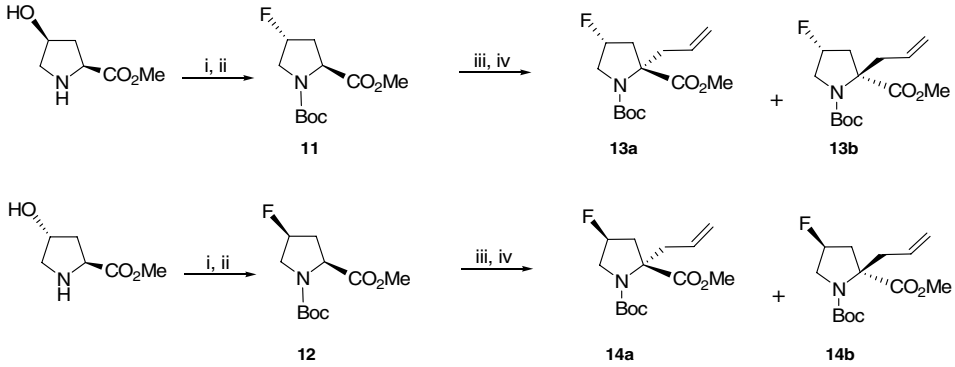


Scheme 1. Reagents and conditions: (i) LiHMDS, THF, −78 °C, 30 min; (ii) allyl bromide; (iii) TBAF, THF, rt; (iv) DAST, CH_2Cl_2, rt.

Each diastereoisomer (**5** and **6**) previously separated by flash silica gel chromatography, was deprotected with TBAF in THF to give the corresponding derivatives **7** and **8**. Thus, exposure to diethylamino sulfur trifluoride (DAST), as fluorinating agent, under mild conditions (rt, under CH_2Cl_2, 8 h), of **7** and **8** yielded the desired compounds (2*S*,4*S*)-2-allyl-4-fluoro-*N*-Boc-L-proline methyl ester **9** ($[\alpha]_D^{20}$ +42 (*c* 0.55, $CHCl_3$)) and (2*R*,4*S*)-2-allyl-4-fluoro-*N*-Boc-L-proline methyl ester **10** ($[\alpha]_D^{20}$ −30 (*c* 0.7, $CHCl_3$)), respectively. Their configuration was assigned on the basis of mechanistic arguments, namely considering that hydroxyl/fluorine substitution promoted by DAST is a typical S_N2 reaction,[4] and confirmed for derivative **9** by two-dimensional (2D) homonuclear chemical shift correlation (ROESY) spectra that show a crosspeak between $C^{\alpha}H_4$ 5.22, (m, 1H, H_4) and $^{\alpha}H$ 2.55 (1H, $C^{\alpha}H$, br dd $J = 14.3$ and 7.5) of the methylene group of the allyl substituent.

Prompted by these reports, and by general focus on evaluating the experimental influence of fluorine in organic chemistry, it appeared appropriate to also examine the alkylation of also β-4-silyloxyproline enolates.

Comparison with the results of the alkylation with allyl bromide which gave 47% of (2*S*,4*S*)-2-allyl-product and 53% of (2*R*,4*S*)-2-allyl-product, confirms the lack of diastereoselectivity with this substrate.



Substrate	RX	Products	Yield	Ratio
11	CH_2=$CHCH_2Br$	**13a, 13b**	93%	3:97
12	CH_2=$CHCH_2Br$	**14a, 14b**	95%	96:4

Scheme 2. Reagents and conditions: (i) Et_3N, $(Boc)_2O$; (ii) DAST, CH_2Cl_2, rt; (iii) LiHMDS, THF, −78 °C, 30 min; (iv) allyl bromide. Yields and diastereomeric ratios observed in the allylation of **11** and **12**.

In the second step of our investigation, the allylation of (4*R*)-4-fluoro-*N*-Boc-L-proline methyl ester **11** and (4*S*)-4-fluoro-*N*-Boc-L-proline methyl ester **12** was examined (Scheme 2).

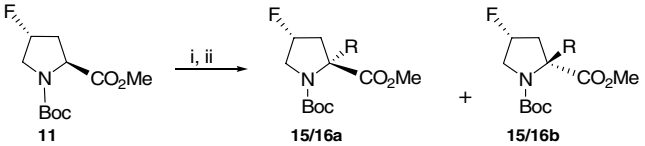
Hence, treatment of **11** and **12** with allyl bromide and 1.25 M equiv of lithium bis-(trimethylsilyl)amide in THF at −78 °C, directly gave the enantiopure alkylation products **13b** ($[\alpha]_D^{20}$ −46 (*c* 0.84, $CHCl_3$)) and **14a** ($[\alpha]_D^{20}$ +45 (*c* 0.865, $CHCl_3$)) in high stereoselectivity ratio (3:97 and 96:4), respectively (Scheme 2).

The diastereomeric ratios were determined by HPLC analysis and independently confirmed by analysis of the relative intensities of appropriate signals in their ^{1}H NMR spectra, while the configuration of **14a** and **13b** was deduced by comparison of $[\alpha]_D^{20}$ values with those of an authentic sample of **9**, synthesized starting from D-proline (Scheme 1).

Intrigued by these results, we next examined the alkylation of compound **11** with benzyl and methyl halides.

The outcome of these experiments highlights, again the substantially different behaviour of 4-fluoro-prolines, under Cα alkylation conditions, as opposed to those with a 4-hydroxy-substituent. In both aforementioned cases, diastereomeric ratios were determined by HPLC analysis and by measuring the relative intensities of signals in their ^{1}H NMR spectra (Scheme 3).

In practice, alkylation with benzyl halides proceeds much along the same line as that with allyl halides displaying a high yield and almost quantitative diastereofacial discrimination and basically furnishing compound **15a** as the sole product. Conversely, the same reaction with methyl halide led to a ca. 1:1 mixture of the two diastereoisomers. Actually, the latter results were not fully unexpected. In fact, whatever are the stereoelectronic factors (steric hindrance, orbital interactions,



Substrate	RX	Products	Yield	Ratio
11	$PhCH_2Br$	**15a, 15b**	97%	98:2
11	CH_3I	**16a, 16b**	72%	53:47

Scheme 3. Reagents and conditions: (i) LiHMDS, THF, −78 °C, 30 min; (ii) alkyl bromide. Yields and diastereomeric ratios observed in the benzylation of **11**.

etc.) controlling the process, they are likely to be very small in magnitude in this particular case.

Taken together, our results indicate that the reaction of enolates produced from 4-fluoroproline methyl ester does not proceed in the same way as those coming from O-protected 4-hydroxyprolines, as shown by Nagumo et al.[3d] (Fig. 1).

It is apparent that the particularly relevant feature of this reaction is its strong dependence on the final orientation of the incoming alkyl group upon the initial position (α or β) of the fluorine atom in the five-membered Pro ring system. We wish to point out that this aspect seems to be a somewhat distinctive attribute of 4-fluoro-Pro which does not appear to be shared by other similar systems. Moreover, the influence of fluorine atoms (positioned in 3 with respect to carbonyl group) on the final outcome of enolate alkylation reactions has very recently been examined, in light of the possibility that the fluorine may participate in the metal (lithium) coordination, therefore shielding one face of the enolate.[5]

On the other hand, meaningful comparisons with other Pro systems are not always straightforward, as—for

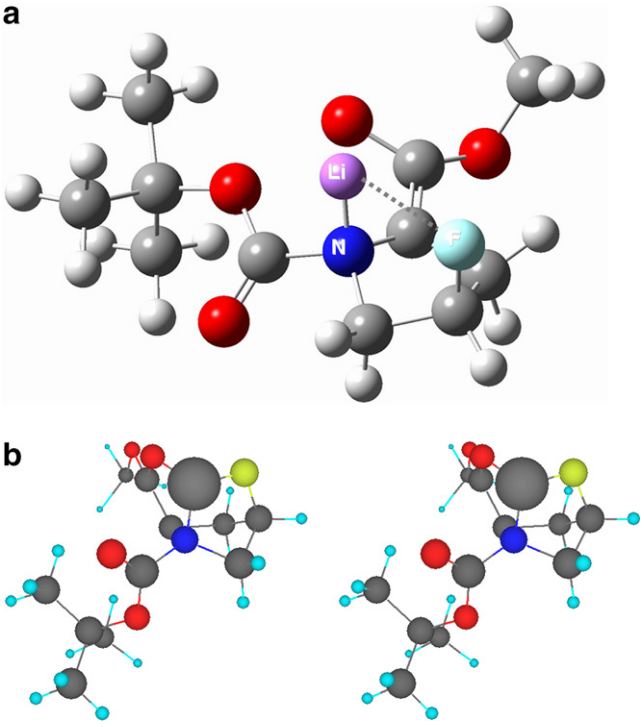


Figure 2. (a) Representation of the postulated transition states formed in the course of alkylation of O-protected 4-hydroxy-*N*-Boc-proline ester enolates. (b) Stereo view of the enolate highlighting the statement of the shielding of the syn face by the Boc.

instance—the literature data refer to reactions effected *only* on a α-oriented 4-OH group. For this reason, in the attempt of rationalizing the outcome of this series of 4-fluoro-*N*-Boc-L-Pro alkylation reaction, we prefer to discuss separately from each other the case of the two 4-fluoro epimers **11** and **12**. A preliminary consideration is that, since the presence of the fluorine atom at C4 is likely to induce in compounds **11** and **12** a decrease in the pK_a of the Hα, the corresponding enolates should be considered more stabilized species than other similar heterocyclic enolates.

Thus, in the case of 4α-fluoro-substituted **11**, the transition states (TS) may benefit of further stabilization by interaction of the n-lone pair orbital of *N*-Boc moiety with the π-system of the incoming alkylating reagent, and we can assume that the n–π interaction becomes the predominant factor determining the diastereofacial differentiation, leading to a lower energy TS for the alkylation of the β-face affording **13b**.

On the other hand, in the case of derivative **12**, the fluorine is in a pseudo-axial orientation, and we can argue that fluorine may chelate lithium in a sort of bicycle [3.3.0] TS, as shown in the model (Fig. 2) in analogy with what was recently found in acyclic systems.[5]

In this chelate species the nitrogen becomes a tertiary centre and its steric influence is clearly significant and will certainly contribute to the efficiency of diastereoselectivity of the reactions.

In conclusion, we found that alkylation of 4-fluoro-*N*-Boc-L-Pro methyl esters proceeds in high yield and diastereoselectivity. The influence of the fluorine atom on the final outcome of these reactions appears to be quite relevant. Except when MeI is used, our data suggest that the major product is a compound in which the incoming alkyl group is invariably oriented from the other side of the fluorine atom. Very likely, the factors governing such process depend on the possibility to form a chelate in which there is an active participation of fluorine.

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References and notes

1. (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*; Wiley: New York, 1987; (b) Confalone, P. N.; Huie, E. M.; Cole, G. M. *J. Org. Chem.* **1988**, *53*, 482; (c) Ikeda, M.; Matsubayashi, K.; Imoto, T.; Kitao, K.; Ishibashi, H.; Sato, T. *Heterocycles* **1994**, *38*, 1237.
2. (a) Thairivongs, D. T.; Pals, J. A.; Lawson, S. R.; Harris, D. W. *J. Med. Chem.* **1987**, *30*, 536; (b) Khalil, E. M.; Ojala, W. H.; Pradhan, A.; Nair, V. D.; Gleason, W. B.; Mishara, R. K.; Johnson, R. L. *J. Med. Chem.* **1999**, *42*, 626.
3. (a) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704; (b) Noe, R.; Knollmuller, H.; Vollenkle, N. *Pharmazie* **1996**, *51*, 800; (c) Sato, T.; Kugo, Y.; Nakaumi, E.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1801; (d) Nagumo, S.; Mizukami, M.; Akutsu, N.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1999**, *40*, 3209.
4. Doi, M.; Nishi, Y.; Kiritoshi, N.; Iwata, T.; Nago, M.; Nakano, H.; Uchiyama, S.; Nakazawa, T.; Wakamiya, T.; Kobayashi, Y. *Tetrahedron* **2002**, *58*, 8453.
5. Yamazaki, T.; Kitazume, M. T.; Kubota, T.; Omura, M. *Org. Lett.* **1999**, *1*, 905.