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On the Allyl Protection of the Imidazole Ring of Histidine[1]

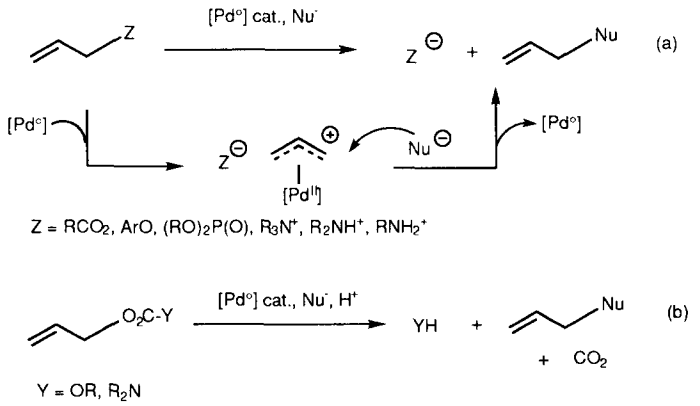
A. Malanda Kimbonguila,[a] S. Boucida,[a] F. Guibé[a]* and A. Loffet[b,c]

[a] *Laboratoire des Réactions Organiques Sélectives, URA 1497, bât 420, Université Paris-Sud, F-91405, Orsay, France*
[b] *Propeptide Co., BP 12, F-91710 Vert-le-Petit, France*
[c] *Present address: Senn Chemicals international, 11 rue Jean-Baptiste Clément F-94250 Gentilly, France*

Abstract: The regiospecific synthesis of the *N*(π)-allyl and the *N*(τ)-allyl derivatives of *N*(α)-*tert*-butoxycarbonyl-histidine is described. The DCC-mediated coupling of *N*(α)-*tert*-butoxycarbonyl-*N*(π)-allyl-(L)-histidine with (L)-prolinamide, used as a test reaction to probe the extent of racemization during coupling processes, was found to occur with good (*ca.* 97%) conservation of enantiomeric purity. Three methods have been devised, all of them based on catalytic palladium π-allyl chemistry, for the selective removal under mild conditions of the *N*-imidazolic allyl groups. Finally it is shown that the allyl group at N(τ)–position may be used as a temporary protection in the synthesis of N(π)-substituted derivatives of histidine. © 1997 Elsevier Science Ltd.

Introduction

Allylic protecting groups, especially the allyl (All) and the allyloxycarbonyl (Alloc) groups which in many instances may be cleaved under mild and selective conditions through catalytic palladium π-allyl chemistry (scheme 1, equations a and b) are orthogonal to a wide range of other protecting entities including



Scheme 1

E-mail: fraguibe@icmo.u-psud.fr FAX: (33) 1 69 15 46 80

the acid labile Boc/*t*-Bu and base labile Fmoc protecting groups. For that reason, they have become increasingly popular in amino acid and peptide chemistry. Allylic linkers have been devised for use in solid phase peptide synthesis and the All or Alloc groups may be used for protection, either in a temporary or semi-permanent way, of α-amino or α-carboxyl groups and of various side-chain reactive functionalities, such as those of lysine, tryptophan, aspartic acid, glutamic acid and tyrosine.[2] Taking full advantage of the permanent allylic side-chain protection strategy however would require to have at one's disposal a whole set of allylic protections which span the entire series of natural amino acid side-chain functionalities, a condition which is not fulfilled at the present time. We recently proposed[3] the allyloxycarbonyl-aminomethyl (Allocam) group as an alternative for side-chain protection of cysteine for which both the All and the Alloc group are unsuitable. This paper deals with the problem of allylic protection of the imidazole ring of histidine.

Side-chain protection of histidine during peptide synthesis is highly recommended, especially to avoid racemization at the α-carbon of the corresponding acyl-activated species during peptide coupling.[4,5] Despite the fact that many protecting groups have already been proposed towards this end, the continuing interest in devising new ones with different properties and compatibilities is attested by recent reports concerning the 2-adamantyloxycarbonyl (2-Adoc)[6], the 2,4-dimethylpent-3-yloxycarbonyl (Doc)[7] and the 2-adamantyloxy-methyl (Adom)[8] groups. From a general point of view, protecting groups used so far for the imidazole ring of histidine essentially fall into two categories.[4,5] Those with electron-withdrawing character, such as the tosyl or the 2,4-dinitrophenyl groups or the above mentioned 2-Adoc and Doc groups, are generally introduced at the $N(\tau)$ position and reduce the risks of racemization by decreasing the electron density of the imidazole nucleus; those which are devoid of electron-withdrawing properties, namely the phenacyl[9], the benzyloxymethyl[10] and the *tert*-butyloxymethyl groups[11], all developed by Jones and his coworkers, as well as the recently devised 2-adamantyloxymethyl group cited above must imperatively be introduced at the N^{π}-position. If so, they are very efficient against racemization.

As far as allylic groups are concerned, protection of the imidazole nucleus by the electron-withdrawing Alloc group is unsuitable due to the excessive lablity of the corresponding *N*-acyl-imidazole compounds towards nucleophilic species.[2d] On the contrary, protection by the allyl group, provided that it was selectively introduced at the $N(\pi)$ position, seemed attractive. Indeed, *N*-allyl derivatives of imidazole may be supposed to be quite stable under both acidic and basic conditions. In the meantime, owing to recent precedents[12,13] in the literature concerning the deallylation of allylamines in general, it could be reasonably expected that very specific π-allyl palladium based procedures could be devised for deprotection of *N*-allyl imidazole compounds. Here is a report on our first investigations on that subject.

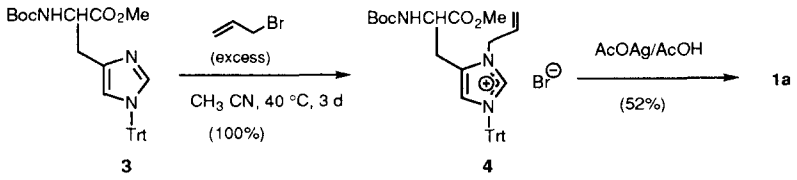
Results and Discussion

We have carried out the synthesis, both in the L and the D,L (racemic) series, of the $N(\pi)$-allyl and the $N(\tau)$-allyl derivatives **1a** and **2a** of $N(\alpha)$-*tert*-butoxycarbonyl-histidine methyl ester, from which the carboxylic acids **1b** and **2b** were further obtained by saponification. On the carboxylic acids **1b**, **2b**, we have tested the configurational stability during coupling processes conferred by the allyl group on imidazole, while the methyl esters have been used to work out proper procedures for deallylation of the imidazole ring. Finally, the allyl group at the $N(\tau)$-position has been used as a temporary protection for the introduction of other groups at the $N(\pi)$-position of histidine.

Selective introduction of the allyl group at the N-π and the N-τ positions of the imidazole ring of histidine.

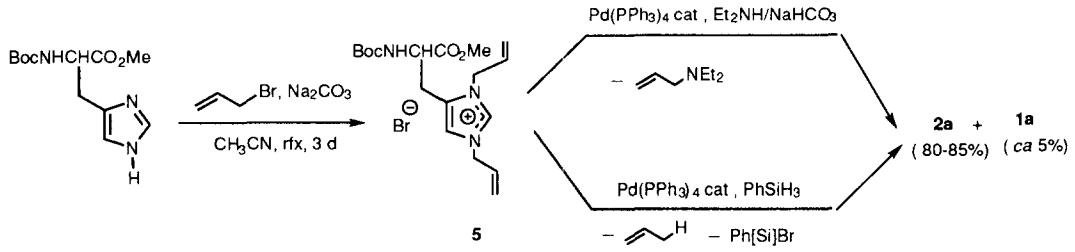
First attempts to prepare *N(α)–tert*-butoxycarbonyl-*N(π)*-allyl-histidine methyl ester **1a** by allylating *N(α)-tert*-butoxycarbonyl-*N(π)-tert*-butoxycarbonyl-histidine methyl ester with allyl triflate, following the

procedure described by Hodges[14] for introduction of other alkyl groups, resulted in low (<30%) and poorly reproducible yields. **1a** was more conveniently obtained by using a strategy previously described by Jones and coworkers for regioselective *N(π)*-introduction of the phenacyl group,[9] that is by allylation of the *N(τ)*-trityl derivative **3** of *N(α)-tert*-butoxycarbonyl-histidine methyl ester with excess allyl bromide (100% yield) followed by selective detritylation (52% yield) of the *N(π)*-allyl-*N(τ)*-trityl-imidazolium salt **4** with AcOH/AcOAg (scheme 1).



Scheme 1

The *N(τ)*-allyl derivative of *N(α)-tert*-butoxycarbonyl-histidine methyl ester **2a** was obtained in an unexpected manner while trying to devise another route to the *N(π)*-isomer (scheme 2).



Scheme 2

N(α)-tert-butoxycarbonyl-histidine methyl ester was treated with excess allyl bromide in the presence of $NaHCO_3$ in dry acetonitrile to give in a quantitative manner the corresponding diallyl imidiazolium bromide **5**. Contrary to quaternary allylammonium salts[15], allylamines are not cleaved by palladium in the absence of protonating agents.[12] Chemoselective monodeallylation was therefore carried out on the diallylimidazolium salt **5** in the presence of catalytic amounts (4 mol%) of $Pd(PPh_3)_4$ in dichloromethane at reflux using diethylamine/$NaHCO_3$ or $PhSiH_3$/$NaHCO_3$[16,17] as allyl group scavengers. As expected, selective monodeallylation of **5** was achieved, but, contrary to our expectations, it was found to take place mainly (90-95%) at the *N(π)*-allyl group despite its more sterically crowded environment . The *N(α)-tert*-butoxycarbonyl-*N(τ)*-allyl-histidine methyl ester **2a** thus formed was easily purified from the small amounts of the *N(π)*-isomer **1a** by flash chromatography and obtained in 80-85% yield. Such regioselectivity which was also observed in the palladium catalysed mono-deallylation of the *N(π), N(τ)*-diallylimidazolium bromide of *N(α)*-Boc-histamine[18] is probably the result of a coordination of the palladium atom by the *N(α)-tert*-butoxycarbonyl group during the catalytic process.

1a and **2a** were finally converted by saponification (aqueous 1M-NaOH/methanol) to free acids **1b** and **2b** in *ca.* 90% yield. In the L series, the enantiomeric purity of **1b** and **2b** was checked by HPLC after reconversion to methyl esters with diazomethane. In neither cases, could any D-enantiomers be detected (detection limit: *ca.* 2%). Saponification of *N(α)-tert*-butoxycarbonyl-*N(π), N(τ)*-diallyl-histidine methyl ester imidazolium bromide **5** was also found to give the corresponding acid in quantitative yield and pure by NMR standard. However, all efforts to obtain it in crystalline form, in particular by exchange of the Br^- counter-anion by TsO^-, BF_4^- or PF_6^- through metathetical exchange with the corresponding silver salts were unsuccessful.

Racemization studies

The resistance towards racemization conferred by the *N(im)*-allyl groups was studied on the DCC mediated coupling reaction with L-prolinamide in DMF, a test reaction previously used by Jones and co-workers in the case of the *N(im)*-phenacyl derivatives[9] of histidine and which is known[9] to favour racemization. The diastereoisomeric Boc-D-His(π-All)-L-Pro-NH_2 and Boc-L-His(π-All)-L-Pro-NH_2 dipeptides are readily separated by HPLC. Under the above-mentioned conditions, good conservation of enantiopurity was observed with Boc-L-His(π–All)-OH **1a**, as attested by the high diastereoisomeric excess obtained for the dipeptide ((L,L)/(L,L) + (D,L) = 97.5/100 (fig 1). On the contrary, gross racemization seemed to have occured

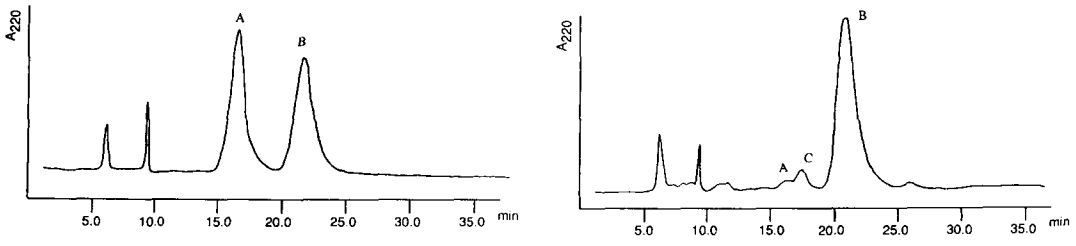


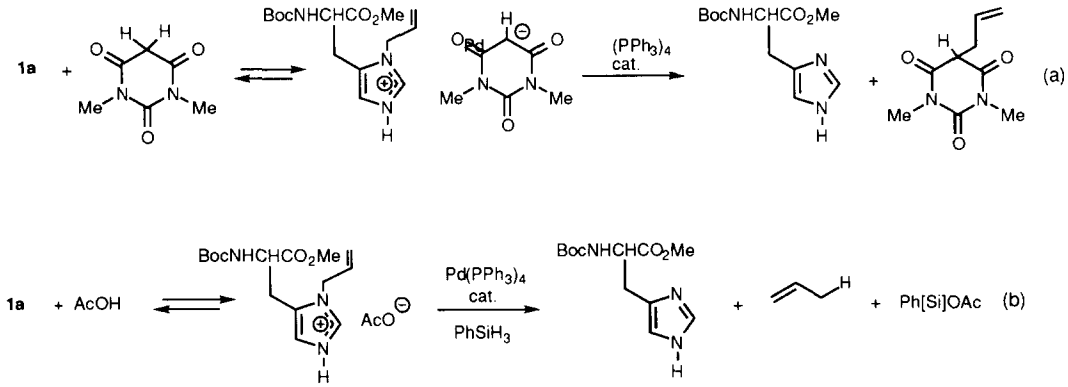
Figure 1. HPLC of crude coupling products of Boc-D,L-His(π-All)-OH (left) and Boc-L-His(π-All)-OH (right) with L-prolinamide: Daicel Chiracel OD column; isocratic mode hexane/2-propanol 90:10; flow rate, 0.5 mL/min. A: Boc-D-His(π-All)-L-Pro-NH_2, B: Boc-L-His(π-All)-L-Pro-NH_2, C: impurity.

with the $N(\tau)$-isomer **2a** although its extent could not be properly quantified due to the poor separation of the HPLC peaks of the corresponding diastereoisomeric dipeptides. Such results are consistent with those reported by Jones and coworkers for the corresponding *N(im)*-phenacyl derivatives and underline the necessity to use regiospecific $N(\pi)$-protection with the allyl group.

Deallylation of N(im)-allyl derivatives of histidine

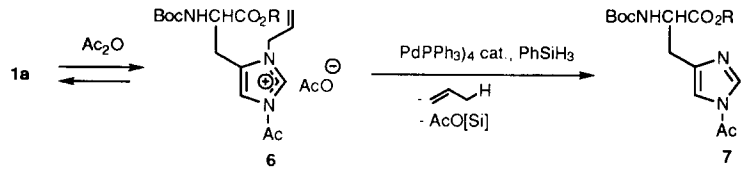
We next adressed the problem of the deallylation of the *N(im)*-allyl derivatives of histidine. Three different procedures were devised to achieve this goal.

First, the allyl groups in **1a** and **2a** were found to be totally removed through palladium catalysed transfer to *N*, *N'*-dimethylbarbituric acid (NDMBA) in dichloromethane at reflux within *ca.* 3 h for **1a** and 8 h for **2a**. In this procedure previously developed in our laboratory for the deallylation of *N*-allylamines in general,[12] NDMBA ($pK_a(H_2O)$ = 4.7) acts as a protonating agent of the imidazole nucleus (a necessary condition for transfer of the allyl group to the zerovalent palladium catalyst) while its enolate serves as the allyl group scavenger (Nu^- in eq. 1). Deallylation of **1a** and **2a** could also be achieved under milder conditions (dichloromethane, room temperature, 3 h for **1a**, 7 h for **2a**) by use of $PhSiH_3$ as the allyl group scavenger and acetic acid as the protonating agent. The principles of these two first deprotection procedures, as applied to **1a**, are represented in equations a and b of scheme 3.



Scheme 3

In a third method, **1a** was totally converted at room temperature and in less than 1h to $N(\alpha)$-*tert*-butoxycarbonyl-$N(\tau)$-acetyl-histidine methyl ester (Boc-His(τ-Ac)OMe **7**) by palladium catalysed reaction with $PhSiH_3$ in dichloromethane/Ac_2O 9:1. This reaction was run in the presence of diisopropylethylamine to ensure neutralization of any adventitious acetic acid. The formation of the $N(\tau)$–acetyl derivative is believed to proceed through transient formation of the $N(\pi)$-allyl, $N(\tau)$-acetyl imidazolium cationic species **6** which then undergoes allylic cleavage by palladium(0) (scheme 4). When applied to **2a**, the same reaction leads to

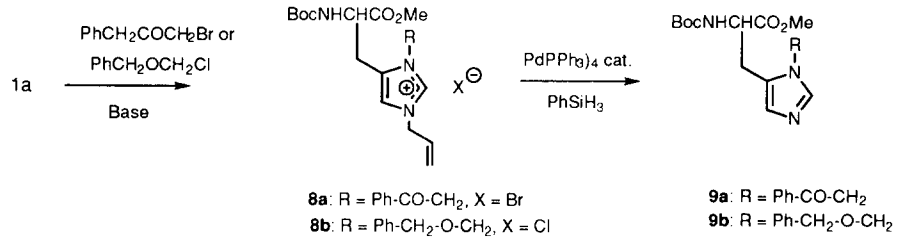


Scheme 4

N(α)-*tert*-butoxycarbonyl-*N*(π)-acetyl-histidine methyl ester (Boc-His(π-Ac)-OMe) but not surprisingly is much more sluggish. After 48 h at room temperature, only 40% of starting material was found to be converted to acetyl derivative. Both the *N*(τ)- and *N*(π)-acetyl derivatives of *N*(α)-*tert*-butoxycarbonyl-histidine methyl ester were characterized by NMR spectroscopy on the crude reaction mixtures. They are readily converted to free imidazole compounds by hydrolysis under mild acidic (aqueous citric acid/methanol) or basic (aqueous $NaHCO_3$/methanol) conditions.

Use of the allyl group at N(τ)-position as a temporary protection on the way to N(π)-substituted histidine derivatives.

The possible obtention of *N*(α)-*tert*-butoxycarbonyl-*N*(τ)-allyl-histidine methyl ester **2a** by chemo- and regioselective mono-deallylation of the *N*(π), *N*(τ)-diallylimidazolium precursor **5** makes attractive the use of temporary *N*(τ)-allyl protection for regioselective introduction of other groups at the *N*(π)-position. To illustrate this possibility, we have carried out the alkylation of *N*(α)-*tert*-butoxycarbonyl-*N*(τ)-allyl-histidine methyl ester **2a** with phenacyl bromide and with benzyloxymethyl chloride. The imidazolium salts **8a** and **8b**, formed in quantitative or near-to-quantitative yields, were then submitted to palladium catalysed deallylation using $PhSiH_3$ as the allyl group scavenger. The already known *N*(α)-*tert*-butoxycarbonyl-*N*(π)-phenacyl-histidine[9] and *N*(α)-*tert*-butoxycarbonyl-*N*(π)-benzyloxymethyl histidine-methyl[10] esters **9a**, **9b** were obtained in fair to good yields (respectively 72% and 62%) after chromatographic purification (scheme 5).



8a: R = Ph-CO-CH_2, X = Br
8b: R = Ph-CH_2-O-CH_2, X = Cl

9a: R = Ph-CO-CH_2
9b: R = Ph-CH_2-O-CH_2

Scheme 5

Conclusion

The *N(π)*-allyl- and *N(τ)*-allyl-derivatives of *N(α)-tert*-butoxycarbonyl-L-histidine have been prepared, the first one through temporary protection of the *N(τ)*-position by the trityl group, the second one through palladium-catalysed chemo- and regioselective mono-deallylation of a *N(π), N(τ)*-diallyl-imidazolium derivative. The possibility of using the allyl group at *N(τ)*-position as a temporary protection for regioselective introduction of other groups at *N(π)* has been illustrated in the preparation of *N(α)-tert*-butoxycarbonyl-*N(π)*-phenacyl-L-histidine and *N(α)-tert*-butoxycarbonyl-*N(π)*-benzyloxymethyl-L-histidine methyl esters.The allyl group at *N(π)*-position is shown to efficiently prevent the risk of racemization associated with carboxy-activation of histidine during peptidic coupling. The *N(π)*-allyl- and *N(τ)*-allyl-derivatives of *N(α)-tert*-butoxycarbonyl-L-histidine methyl ester are easily and selectively deallylated by the use of π-allyl palladium chemistry, either under very mild acidic conditions or in the presence of acetic anhydride. On the basis of these encouraging preliminary results, it is believed that *N*-allyl substitution of the imidazole ring, especially because it should be compatible[19] both with temporary N(α)-Fmoc protection and with temporary N(α)-Boc protection, should constitute a new form of histidine side-chain protection very useful in peptide synthesis.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or in other solvents as indicated at 250 MHz and 63 MHz respectively. Chemical shifts are quoted in ppm relative to TMS. All solvents were used dried and freshly distilled under nitrogen atmosphere. Tetrakis(triphenylphosphine)palladium(0) was prepared as previously described.[20] All manipulations involving this catalyst were carried out under argon atmosphere. $PhSiH_3$ is commercially available or may be easily synthesized by $LiAlH_4$ reduction of trichlorophenylsilane.[21] *N(α)-tert*-butoxycarbonyl-histidine methyl ester[22] was prepared by refluxing *N(α)-tert*-butoxycarbonyl-*N(τ)-tert*-butoxycarbonyl-histidine methyl ester[14] in methanol for 3 days in the presence of 0.5 equiv. of pyridinium tosylate.

***N(α)-tert*-Butoxycarbonyl-*N(τ)*-triphenylmethyl-L-histidine Methyl Ester (3).** This compound was prepared according to the procedure described by Hartter.[23] It was used without recrystallisation in the following step.

***N(α)-tert*-Butoxycarbonyl-*N(τ)*-triphenylmethyl-*N*(π)-allyl-L-histidine Methyl Ester Imidazolium Bromide (4).** An excess of allyl bromide (1.75 mL, 20 mmmol) was added to a solution of *N(α)-tert*-butoxycarbonyl-*N(τ)*-triphenylmethyl-L-histidine methyl ester (**2b**) (2 g, 4 mmol) in 50 mL of acetonitrile. The reaction mixture was stirred for 72 h at 40 °C. The solvent was then evaporated and the residual salt was rinsed several times with diethyl ether. 2.42 g (90% yield) of crude *N(α)-tert*-butoxycarbonyl-*N(π)*-allyl-*N(τ)*-triphenylmethyl-L-histidine methyl ester imidazolium bromide were thus obtained and used without further purification in the following step. ^1H NMR δ 1.39 (s, 9H), 3.2 (m, 2H), 3.7 (s, 3H), 4.5 (m, 1H), 4.8 (m, 2H), 5.5 (m, 2H), 5.9 (m, 1H), 7.2-7.4 (m, 15H), 8.7 (s, 1H), 9.2 (s, 1H).

***N(α)-tert*-Butoxycarbonyl-*N(π)*-allyl-L-histidine Methyl Ester (1a).** *N(α)-tert*-butoxycarbonyl-*N(π)*-allyl-*N(τ)*-triphenylmethyl-L-histidine methyl ester imidazolium bromide **4** (2.4 g, 3.8 mmol) was dissolved in 40 mL of 80% acetic acid and one equivalent (0.634 g) of silver acetate was added to this solution. The precipitated silver bromide was filtered off and the filtrate was stirred at room temperature for 48 h. The solvent was then evaporated and the residue was taken up in diethyl ether. The ethereal solution was washed with saturated aqueous $NaHCO_3$ (3 x 50 mL), dried on $MgSO_4$ and evaporated. The residue (1.64 g) was purified by flash chromatography on silica (chloroform/methanol 98:2) to give 0.59 g (52%) of *N(α)-tert*-butoxycarbonyl-*N(π)*-allyl-L-histidine methyl ester as an oil. ^1H NMR δ 1.43 (s, 9H), 3.06 (m, 2H), 3.74 (s, 3H), 4.5 (d, 2H, J=5 Hz), 4.54 (q, 1H, J=6Hz), 5.2 (m, 2H), 5.3 (d, 1H, NH, J=6Hz), 5.95 (m, 1H, J=5 Hz), 6.81 (s, 1H), 7.43 (s, 1H); ^{13}C NMR δ 26.4, 27.96, 46.76, 52.1, 52.79, 79.65, 117.62, 126.2, 127.73, 132.63, 137.39, 154.2, 171.8; HRMS (EI) calcd for $C_{15}H_{23}O_4N_3$ (M^+) 309.1681, found 309.1688; $[\alpha]_D^{20}$ = + 40,1 (c = 1.0, $CHCl_3$) .

***N(α)-tert*-Butoxycarbonyl-*N(π)*-allyl-L-histidine (1b).** *N(α)-tert*-Butoxycarbonyl-*N(π)*-allyl-L-histidine methyl ester (**1a**) (3 g, 10 mmol) was dissolved in 4 mL of methanol. 15 mL of 1.0M-NaOH were added and the reaction mixture was stirred at room temperature until complete disappearance (TLC monitoring, *ca.* 90 min) of starting ester. The reaction mixture was then diluted with 50 mL of water and the pH of the solution was adjusted to 5 with 1.0M-HCl. The aqueous phase was exhaustively extracted with chloroform (10 x 15mL). The organic phase was dried on $MgSO_4$ and evaporated. Upon trituration of the residue in diethyl ether, 2.15 g (75% yield) of *N(α)-tert*-butoxycarbonyl-*N(π)*-allyl-L-histidine were obtained in crystalline form. A small portion of the acid was converted back to methyl ester by reaction with diazomethane. The esters, in the D,L and the L series were analysed by chiral HPLC ("Chiralcel OD (250 x 4.6 mm, isocratic mode with hexane/2-propanol 90:10, flow rate 0.5 mL/min ; retention times: D-isomer: 47.4 min ; L-isomer: 72.16 min). No contamination by the D-isomer could be evidenced in the L series (detection limit 2%).
^1H NMR ($CD_3OD/CDCl_3$),δ 1.39 (s, 9H), 3.16 (m, 2H), 4.26 (q, 1H), 4.58 (m, 2H), 5.2 (m, 2H), 5.4 (d, 1H, NH), 5.85 (m, 1H), 6.96 (s, 1H), 7.95 (s, 1H) ; ^{13}C NMR ($CD_3OD/CDCl_3$) δ 27.8, 54.79, 119.7, 120.6, 130.2, 130.7, 134.5, 155.5, 174.4 ; HRMS (EI) calcd for $C_{14}H_{21}O_4N_3$ (M^+) 295.15342, found 295.15320 ; Anal. Calcd for $C_{14}H_{21}O_4N_3$: C: 56.94 ; H: 07.16 ; N:14.23. Found: C: 57.03 ; H: 06.84 ; N:14.38 ; $[\alpha]_D^{20}$= + 9,7 (c = 1.0, MeOH) ; mp 118-122 °C.

***N(α)-tert*-Butoxycarbonyl-*N(π)*, *N(τ)*-diallyl-L-histidine Methyl Ester Imidazolium Bromide (5).** A solution of *N(α)-tert*-butoxycarbonyl-L-histidine methyl ester (10 g, 37 mmol), allyl bromide (16 mL, 185 mmol, excess) and 12 g (150 mmol) of $NaHCO_3$ in dry acetonitrile was refluxed for 16 h. After cooling, the inorganic salts were filtered off and the filtrate was evaporated first on a Rotovap under 15 mmHg and then overnight on a vacuum line under 0.05 mmHg. *N(α)-tert*-butoxycarbonyl-*N(π)*, *N(τ)*-diallyl-L-histidine methyl ester imidazolium bromide was thus obtained in 93% yield (14.9 g) and used as such, without further purification, in the following step. ^1H NMR δ 1.42 (s, 9H), 3.24 (d, 2H, J=7Hz), 3.75 (s, 3H), 4.55 (m, 1H), 4.95 (m, 4H), 5.42 (m, 4H), 5.90 (m, 2H), 6.04 (m, 1H, NH), 7.35 (s, 1H), 10.17 (s, 1H) ; ^{13}C NMR δ 26.1, 27.7, 49.5, 51.8, 52.7, 80.1, 120.3, 121.2, 122.3, 129.6, 129.9, 131.4, 136.5, 155.3, 170.7 .

***N*(α)-*tert*-Butoxycarbonyl-*N*(τ)-allyl-L-histidine Methyl Ester (2a).** *Method A (Palladium /diethylamine):* 0.1 g (0. 089 mmol) of tetrakis(triphenylphosphine)palladium and 0.35 g (4.46 mmol) of solid $NaHCO_3$ were put together under argon atmosphere in a Schlenk tube fitted with a rubber septum cap. Into this Schlenk tube were successively syringed a solution of 0.32 mL (9 mmol) of diethylamine in 4 mL of degassed dichloromethane and a solution of the *N*(π), *N*(τ)-diallyl imidazolium salt **5** (0.96 g, 2.23 mmol) in 4 mL of degassed dichloromethane. The reaction mixture was then refluxed for 16 h. After cooling, the reaction mixture was filtered, the filtrate was evaporated and the residue was taken up in diethyl ether. The ethereal solution was washed three times with small portions of water and dried over $MgSO_4$. After evaporation, the residue was found by ^1H NMR spectroscopy to contain *N*(α)-*tert*-butoxycarbonyl-*N*(τ)-allyl-L-histidine methyl ester (**2a**) and *N*(α)-*tert*-butoxycarbonyl-*N*(π)-allyl-L-histidine methyl ester (**1a**) in *ca.* 90-95% and 10-5% respective amounts. Pure *N*(α)-*tert*-butoxycarbonyl-*N*(τ)-allyl-L-histidine methyl ester was obtained after flash chromatography ($CHCl_3$/MeOH 98:2) in 80% yield (0.56 g). TLC (silica) R_f 0.3 for the τ-isomer and R_f 0.25 for the π-isomer ; ^1H NMR δ 1.43 (s, 9H), 3.06 (m, 2H), 3.69 (s, 3H), 4.5 (m, 2H), 4.55 (q, 1H), 5.27 (m, 2H), 5.95 (m, 2H), 6.66 (s, 1H), 7.38 (s, 1H) ; ^{13}C NMR δ 28.2, 30.12, 49.2, 53.5, 79.4, 116.6, 118.3, 132.6, 136.8, 137.5, 155.5, 172.5; HRMS (EI) calcd for $C_{14}H_{21}O_4N_3$ (M^+) 309.1688, found 309.1683; $[\alpha]_D^{20}$ = + 14,2 (c = 1.0, $CHCl_3$).

Method B (Palladium /$PhSiH_3$). In a Schlenk tube and under argon atmosphere, 0.2 g (0.46 mmol) of *N*(π), *N*(τ)-diallyl imidazolium salt **5** and 0.021 g (0.04 mol. equiv.) of tetrakis(triphenylphosphine)palladium were mixed in 4 mL of a degassed 95:5 mixture of dichloromethane/water with 0.22 mL (1.86 mmol) of phenylsilane ($PhSiH_3$) and 0.077 g (0.22 mmol) of $NaHCO_3$.[17] The heterogeneous mixture was then refluxed for 2 h, upon which its initially yellow colour had turned to deep red. Dichloromethane was evaporated and replaced with 15 mL of diethyl ether. The ethereal solution was extracted three times with 10 mL of water. After drying over $MgSO_4$ and evaporation, the residue was found, by NMR, to contain a mixture of *N*(α)-*tert*-butoxycarbonyl-*N*(τ)-allyl-L-histidine methyl ester (**2a**) and *N*(α)-*tert*-butoxycarbonyl-*N*(π)-allyl-L-histidine methyl ester (**1a**) in proportions similar to those observed with method A. After flash chromatography ($CHCl_3$/MeOH 98: 2), the pure *N*-τ isomer was obtained in 91% yield (0.13 g).

***N*(α)-*tert*-Butoxycarbonyl-*N*(τ)-allyl-L-histidine (2b).** *N*(α)-*tert*-Butoxycarbonyl-*N*(τ)-allyl-L-histidine methyl ester (**2a**) (5 g, 16.2 mmol) was saponified according to the procedure described above for the *N*(π)-allyl isomer to give 4.2 g (88% yield) of *N*(α)-*tert*-butoxycarbonyl-*N*(τ)-allyl-L-histidine as a crystalline product. The enantiomeric purity (ee>98%) of the acid was checked after reconversion to methyl ester with diazomethane as described above for the π-isomer, using the same HPLC conditions: retention times: D-isomer: 58.65 min; L-isomer: 61.50 min). ^1H NMR ($CD_3OD/CDCl_3$) δ 1.38 (s, 9H), 3.25 (2dd, 2H, J=14.1, 5Hz), 4.3 (q, 1H, J=5.3Hz), 4.44 (d, 2H, J=6Hz), 5.25 (m, 2H), 5.5 (d, 1H, NH, J=5.5Hz), 5.85 (m, 1H), 6.63 (s, 1H), 7.76 (s, 1H) ; ^{13}C NMR ($CD_3OD/CDCl_3$) δ 28.4, 29.3, 50.25, 53.4, 79.2, 117.9, 120, 131.43, 134.65, 135.78, 155.25, 174; HRMS (EI) calcd for $C_{14}H_{21}O_4N_3$ (M^+) 295.1532, found 295.1532; $[\alpha]_D^{20}$= + 156,9 (c = 1.0, $CHCl_3$) ; mp 129-131 °C.

***N*(α)-*tert*-Butoxycarbonyl-*N*(π), *N*(τ)-diallyl-L-histidine Imidazolium Bromide ([Boc-His(All)$_2$-OH]$^+$, Br$^-$)** *N*(α)-*tert*-Butoxycarbonyl-*N*(π), *N*(τ)-diallyl-L-histidine methyl ester imidazolium bromide **5** (1 g, 2.32 mmol) was dissolved in 10 mL of methanol. To this solution cooled to 0 °C were added, under magnetic stirring, 5 mL

of aqueous 1.0M-NaOH. The reaction mixture was further stirred at 25 °C for 1 h. 25 mL of water were then added and the methanol was evaporated on a Rotovap. The pH of the solution was then adjusted to 3.8 (pH meter) with 1.0M-HBr. After having been washed with diethyl ether (3 x 10mL), the aqueous solution solution was evaporated under 0.05 mmHg. The solid residue was dried by azeotropic evaporation with toluene (3 x 75 mL). 0.947 g of *N(α)-tert*-butoxycarbonyl-*N(π)*, *N(τ)*-diallyl-L-histidine imidazolium bromide (**4b**) were thus obtained as an hygroscopic viscous oil: ^{1}H NMR (D_2O) δ 1.4 (s, 9H), 3.1 (m, 2H), 4.25 (m, 1H), 4.8 (m, 4H), 5.4 (m, 4H), 6.1 (m, 2H), 7.35 (s, 1H), 8.8 (s, 1H) ; ^{13}C RMN (D_2O) δ 28.2, 49.1, 51.6, 54.2, 79.1, 120.6, 121.7, 125.0, 128.0, 128.8, 130.3, 132.7, 135.3, 155.5, 174.2.

Test Relative to the Optical Stability of *N(α)-tert*-Butoxycarbonyl-*N(π)*-allyl-L-histidine and *N(α)-tert*-Butoxycarbonyl-*N(τ)*-allyl-L-histidine. The protocol used for the coupling of *N(α)-tert*-butoxycarbonyl-*N(π)*-allyl-L-histidine and *N(α)-tert*-butoxycarbonyl-*N(τ)*-allyl-L-histidine with L-prolinamide was essentially the same as the one described by Jones and coworkers for the corresponding *N(π)*- and *N(τ)*-phenacyl derivatives[9]. To an ice-bath cooled solution of dicyclohexylcarbodiimide (0.55 mmol) in 4 mL of DMF was added under stirring 0.5 mmol of the *N*(α)-*tert*-butoxycarbonyl-*N*(*im*)-allyl derivative of histidine under study. After stirring for 2 h, a precooled solution of L-prolinamide (0.5 mmol) and triethylamine (0.5 mmol) in 2 mL of DMF was added. The reaction mixture was further stirred for 2 h at 0 °C and then left at room temperature for 16 h. The precipitated dicyclohexylurea was filtered off and the filtrate was evaporated under vacuum (0.05 mmHg). The residue was taken up in chloroform and the chloroform solution was successively washed with saturated aqueous $NaHCO_3$ (3x15mL) and with saturated aqueous NaCl. The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was then pumped out for 16 h under 0.05 mmHg and analysed by HPLC. The coupling reactions were performed with the *N(π)*- and *N(τ)*- derivatives of *N(α)-tert*-butoxycarbonyl-histidine, both in the L and the D,L series. The HPLC profiles for coupling of the *N*(π)-isomers are shown in fig 1. With the *N(τ)*-isomers, the peaks of the corresponding diastereoisomeric dipeptides were insufficiently resolved and the extent of racemization, albeit seemingly important, could not be properly quantified.

Palladium-Catalysed Deallylation of *N(α)-tert*-Butoxycarbonyl-*N(π)*-allyl-L-histidine Methyl Ester (1a) and of *N(α)-tert*-Butoxycarbonyl-*N(τ)*-allyl-L-histidine Methyl Ester (2a). *Method A (Palladium/ N, N'-dimethylbarbituric acid)*: In a Schlenk tube under argon atmosphere, a solution of 0.2 g (0.65 mmmol) of *N(α)-tert*-butoxycarbonyl-*N(π)*-allyl-L-histidine methyl ester, 30 mg (0.026 mmol, 0.04 mol. equiv.) of tetrakis(triphenylphosphine)palladium and 0.31 g (1.94 mmol, 3 equiv.) of *N, N'*-dimethylbarbituric acid (NDMBA) in 4 mL of degassed dichloromethane was refluxed for 3 h , the reaction being monitored by TLC. After cooling, the solvent was evaporated and the residue taken up in diethyl ether. The precipitate formed was triturated , collected by filtration and dissolved again in ethyl acetate. The organic phase was extracted with aqueous $NaHCO_3$ to eliminate the NDMBA in excess. Upon flash chromatography (CH_2Cl_2/MeOH 96: 4), 0.13 g (77% yield) of pure *N(α)-tert*-butoxycarbonyl-L-histidine methyl ester were collected.

Starting with *N(α)-tert*-butoxycarbonyl-*N(τ)*-allyl-L-histidine methyl ester, the deallylation process according to method A requires *ca.* 8h. *N(α)-tert*-butoxycarbonyl-L-histidine methyl ester was obtained in 72% yield after chromatography. ^{1}H NMR δ 1.42 (s, 9H), 3.1(d, 2H, J=7Hz), 3.69 (s, 3H), 4.56 (q, 1H, J=7Hz), 5.89 (d, 1H, NH, J=6Hz), 6.81 (s, 1H), 7.55 (s, 1H) ; ^{13}C NMR δ 28.02, 29.31, 52.02, 53.52, 79.68, 116.31, 133.43, 134.25, 135.27, 155.47, 172.39; HRMS (EI) calcd for $C_{12}H_{19}O_4N_3$ (M^+) 269.1358 found 269.1358;

Anal. Calcd for $C_{12}H_{19}O_4N_3$: C: 53.52 ; H: 07.11 ; N: 15.60. Found: C: 53.81 ; H: 07.24 ; N:15.85 ; $[\alpha]_D^{20}$= -09.7 (c = 1.0, MeOH) ; mp 110-114°C ; TLC R_f 0.3 ($CHCl_3$/MeOH 95: 5).

Method B (Palladium/$PhSiH_3$/AcOH): In a Schlenk tube and under argon atmosphere, 0.2 g (0.65 mmol) of *N(α)-tert*-butoxycarbonyl-*N*(π)-allyl-L-histidine methyl ester, 30 mg (0.026 mmol, 0.04 mol. equiv.) of tetrakis(triphenylphosphine)palladium and 0.15 mL (2.6 mmol) of acetic acid were dissolved in 4 mL of degassed dichloromethane. To this solution was added dropwise with a syringe 0.16 mL (1.3 mmol) of phenylsilane and the reaction was allowed to proceed with magnetic stirring and at room temperature for 3 h, upon which the deallylation process was found to be complete (TLC). The solvent was evaporated and *N(α)-tert*-butoxycarbonyl-L-histidine was obtained in 89% yield after flash chromatography. In another experiment, after completion of the reaction, D-camphorsulfonic acid (0.15 g, 0.65 mmol) was added to the reaction mixture. The solvent was evaporated. The salt was rinsed several times in diethyl ether to eliminate the catalyst, the silyl compounds and triphenylphosphine. After drying under vacuum, 0.31 g (97%) of *N*(α)-*tert*-butoxycarbonyl-L-histidine methyl ester camphor sulfonate was thus obtained. ^1H NMR (only the peaks of the histidine moiety are given) δ 1.45 (s, 9H), 3.2 (m, 2H), 3.8 (s, 3H), 4.5 (q, 1H, J=7Hz), 6.1 (d, 1H, NH), 7.2 (s, 1H), 8.6 (s, 1H).

When applied to the *N(τ)*-isomer, the deallylation process according to method B requires *ca.* 7 h.

Method C (Palladium/$PhSiH_3$/Ac_2O): *N*(α)-*tert*-butoxycarbonyl-*N*(π)-allyl-L-histidine methyl ester **1a** (0.1 g, 0.32 mmol) was dissolved in 9 mL of degassed dichloromethane together with 0.16 mL (1.3 mmol) of $PhSiH_3$, 15 mg (4 mol%) of tetrakis(triphenylphosphine)palladium and 1 mL of acetic anhydride. Diisopropylethylamine (0.5 mL) was further added to ensure neutralisation of any adventitious acetic acid. The reaction mixture was stirred at room temperature until completion of the reaction (1 h by TLC). After evaporation of the solvent, acetic anhydride and diisopropylethylamine were removed under vacuum (0.05 mmHg, overnight). NMR analysis of the crude residue showed that all starting *N(α)-tert*-butoxycarbonyl-*N(π)*-allyl-L-histidine had been converted to *N(α)-tert*-butoxycarbonyl-*N(τ)*-acetyl-L-histidine **7**. The *N(τ)*-acetyl derivative may be further deacylated under mild acidic (aqueous citric acid/methanol) or basic (aqueous HCO_3Na/methanol) conditions.

When similar conditions were applied to *N(α)-tert*-butoxycarbonyl-*N(τ)*-allyl-L-histidine, a mixture of 60% of starting material and of 40% of *N(α)-tert*-butoxycarbonyl-*N(π)*-acetyl-L-histidine was obtained after 48 h at room temperature.

Boc-L-His(τ-Ac)-OMe (**7**): ^1H NMR δ 1.43 (s, 9H), 2.6 (s, 3H), 3.1(d, 2H, J=7Hz), 3.72 (s, 3H), 4.6 (q, 1H, J=7Hz), 5.8 (d, 1H, NH, J=7Hz), 7.3 (s, 1H), 8.1 (s, 1H) ; IR (CCl_4) ν(CO) cm^{-1}: 1743, 1712 ; TLC (silica, CH_2Cl_2/MeOH 95:5) R_f 0.48.

Boc-L-His(π-Ac)-OMe: ^1H RMN δ 1.44 (s, 9H), 2.54 (s, 3H), 3.1(d, 2H, J=6Hz), 3.7 (s, 3H), 4.6 (q, 1H, J=6Hz), 5.7 (d, 1H, NH, J=6Hz), 7.4 (s, 1H), 8.05 (s, 1H) ; IR (CCl_4) ν(CO) cm^{-1}: 1754, 1715 ; TLC (silica, $CHCl_3$/MeOH 95: 5) R_f 0.56.

***N(α)-tert*-Butoxycarbonyl-*N(π)*-phenacyl-*N(τ)*-allyl-L-histidine Methyl Ester Imidazolium Bromide (8a).** 0.1 g (0.32 mmol) of *N(α)-tert*-butoxycarbonyl-*N(τ)*-allyl-L-histidine methyl ester **2a** and 0.064 g (0.32 mmol) of 2-bromoacetophenone were stirred in 2 mL of anhydrous diethyl ether at room temperature during 72 h. The

solvent was evaporated, the solid residue was rinsed with diethyl ether and dried to give 0.19 g (100%) of *N(α)-tert*-butoxycarbonyl-*N(π)*-phenacyl-*N(τ)*-allyl-L-histidine methyl ester imidazolium bromide **8a** as hygroscopic crystals. ^{1}H NMR δ 1.36 (s, 9H), 3.1 (m, 2H), 3.7 (s, 3H), 4.5 (q, 1H, J=6Hz), 4.8 (d, 2H, J=6Hz), 5.4 (m, 2H), 5.95 (m, 1H), 6.4 (q, 2H, AB system, J=18Hz,NCH_2CO), 7.5-7.7 (m, 3H, Ar-H + 1H im.), 8.1 (m, 2H Ar-H), 10.02 (s, 1H) ; ^{13}C NMR δ 28, 51.92, 52.82, 53.85, 80.35, 119.58, 122.4, 128.5, 128.7, 128.9, 129.4, 132.8, 133.26, 134.6, 137.4, 155.4, 170.8, 190.6.

***N(α)-tert*-Butoxycarbonyl-*N(π)*-benzyloxymethyl-*N(τ)*-allyl-L-histidine Methyl Ester Imidazolium Chloride (8b).** 0.6 g (1.94 mmol) of *N(α)-tert*-butoxycarbonyl-*N(τ)*-allyl-L-histidine methyl ester **2a** were dissolved in 5 mL of anhydrous diethyl ether. 1.35 mL (excess) of chloromethyl benzyl ether were added to this solution and the reaction mixture was stirred for 72 h at room temperature. The solvent was evaporated ; the residue was triturated in diethyl ether and rapidly collected by filtration on a sintered glass. After drying under vacuum, 0.85 g (94%) of *N(α)-tert*-butoxycarbonyl-*N(π)*-benzyloxymethyl-*N(τ)*-allyl-L-histidine methyl ester imidazolium chloride **8b** were obtained as very hygroscopic crystals. ^{1}H NMR δ 1.45 (s, 9H), 3.3 (m, 2H), 3.75 (s, 3H), 4.6 (q, 1H), 4.85 (m, 4 H allylic and benzylic H), 5.4 (m, 2H), 6.1 (m, (2 + 1) H, internal vinylic H and $N\underline{CH_2}O$), 6.6 (d, 1H, NH), 7.3 (m, 5H), 7.5 (s, 1H), 10.5 (s, 1H). ^{13}C NMR δ 14.6, 27.6, 51.3, 52.1, 65.1, 65.8, 71.7, 79.3, 120.1, 121.8, 127.4, 127.8, 129.2, 131.2, 135.5, 134.6, 137.0, 155.0, 170.6

***N(α)-tert*-Butoxycarbonyl-*N(π)*-phenacyl-L-histidine Methyl Ester.** In a Schlenk tube and under argon atmosphere, 100 mg (0.2 mmol) of *N(α)-tert*-butoxycarbonyl-*N(π)*-phenacyl-*N(τ)*-allyl-L-histidine methyl ester imidazolium bromide **8a** were dissolved in 2 mL of degassed dichloromethane together with 9 mg (0.008 mmol, 0.04 mol equiv.) of tetrakis(triphenylphosphine)palladium. Phenylsilane (0.1 mL, 0.8 mmol) was then added. The reaction mixture was stirred for 16 h at room temperature . The solvent was evaporated and the residue was dissolved in ethyl acetate. The organic solution was washed once with aqueous $NaHCO_3$ and three times with water and dried over $MgSO_4$. After evaporation of the solvent and flash chromatography (silica, CH_2Cl_2/MeOH 97: 3), 54 mg (72%) of *N(α)-tert*-butoxycarbonyl-*N(π)*-phenacyl-L-histidine methyl ester[9] were obtained as a solid: ^{1}H NMR δ 1.43 (s, 9H), 3.07 (m, 2H), 3.67 (s, 3H), 4.52 (q, 1H), 5.36 (s, 2H), 6.07 (m, 1H, NH), 6.72 (s, 1H), 7.39 (s, 1H), 7.5 (m, 3H, Ar-H), 7.9 (d, 2H, Ar-H) ; ^{13}C RMN δ 28.3, 30.2, 52, 52.4, 53.6, 79.5, 117.9, 127.9, 129.04, 134.1, 134.3, 137.5, 137.9, 155.6, 172.6, 191.7.

***N(α)-tert*-Butoxycarbonyl-*N(π)*-benzyloxymethyl-L-histidine Methyl Ester.** To a solution of 0.7 g (1.5 mmol) of *N(α)-tert*-butoxycarbonyl-*N(π)*-benzyloxymethyl-*N(τ)*-allyl-L-histidine methyl ester imidazolium chloride **8b** and 0.069 g (0.06 mmol, 0.04 mol. equiv.) of tetrakis(triphenylphosphine)palladium in 7 mL of degassed dichloromethane contained in a Schlenk tube and under argon atmosphere, were added 0.9 mL (*ca.* 6 mmol, 4 mol. equiv.) of phenylsilane. The reaction was then conducted as described above for the deallylation of *N(α)-tert*-butoxycarbonyl-*N(π)*-phenacyl-*N(τ)*-allyl-L-histidine methyl ester imidazolium bromide. Upon purification by flash chromatography (silica, CH_2Cl_2/MeOH: 97: 3), 0.37 g (62%) of *N(α)-tert*-butoxycarbonyl-*N(π)*-benzyloxymethyl-L-histidine methyl ester[10] were collected. ^{1}H NMR δ 1.41 (s, 9H), 3.1 (2dd, 2H, ABX system J=15Hz, 7Hz and 5Hz), 3.72 (s, 3H), 4.4 (s, 2H), 4.6 (q, 1H, J=7Hz), 5.3(s, 2H), 5.4 (d, 1H, NH, J=7Hz), 6.87 (s, 1H), 7.4 (m, 5H), 7.5 (s, 1H) ; ^{13}C NMR δ 26.6, 28.1, 52.3, 52.9, 69.5, 72.9, 79.9, 126.5, 127.9, 128.2, 128.6, 129.2, 135.9, 138.3, 155.0, 171.8.

Notes and References

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17. $PhSiH_3$ acts formally as an hydride donor in this reaction[16] and propene is therefore formed as by-product. Silicon bromides are supposed to be the other by-products of deallylation of the imidazolium bromide **5** with $PhSiH_3$. For fear that those latter reactive species could cause poisoning of the catalyst, the reaction was run in the presence of small amounts of water and $NaHCO_3$ to bring about their hydrolysis. As a matter of fact, we were, later on (see scheme 5), able to carry out the catalytic

hydrosilylosis of the *N(π)*-phenacyl-*N(τ)*-allyl imidazolium bromide **8a** and of the *N(π)*-benzyloxymethyl-*N(τ)*-allyl-imidazolium chloride **8b** without these additives which therefore do not appear to be necessary.

18. Unpublished results from our laboratory.
19. We have checked (NMR, HPLC) that the N(*im*)-allyl derivatives of *N(α)-tert*-butoxycarbonyl-histidine methyl ester are completely stable in DMF/piperidine 5:1. Similarly, the N(*im*)-allyl derivatives of histamine were found to be totally stable in dichloromethane/CF_3CO_2H 1:1.
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