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Palladium (0) Catalyzed Amination with N,O-bis-*ter*-Boc Hydroxylamine. Synthesis of (+)-N^6-Hydroxylysine

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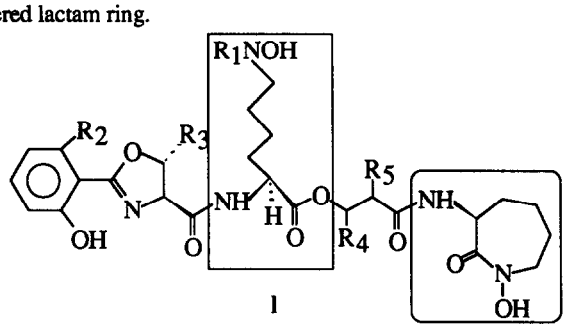
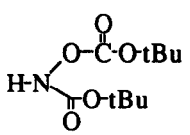
Key words : Allylic amination, Palladium (0), N,O-protected hydroxylamine, (+) N^6-hydroxylysine.

Abstract : Palladium-catalyzed reaction of allyl esters with (N,O)-bis-*ter*-Boc hydroxylamine **2** gives protected N-allylhydroxylamines. A synthetic application to (+)-N^6-hydroxylysine component of mycobactin T is also described.

Interest in the synthesis of N-alkylhydroxylamines stems from the fact that α-amino-ω-hydroxyamino acids are the constituent of various peptides of biological interest. N^5-hydroxyornithine has been found in the antibiotic albomycin[1]. Mycobactin T **1**, a potent chelator of ferric ion or *Siderophore*, is the simplest member of the family of mycobactins which are important in the study of iron metabolism[2]. This siderophore consist of two hydroxamates residues derived from N^6-hydroxylysine, one residue is acyclic whereas the other is present as a seven-membered lactam ring.



1



2

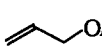
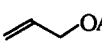
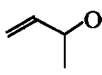
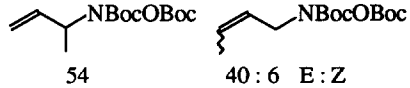
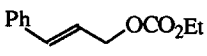
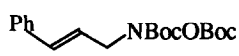
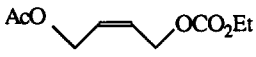
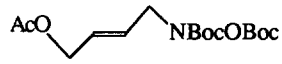
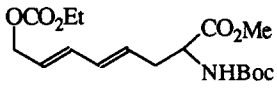
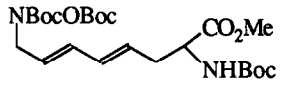
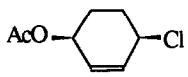
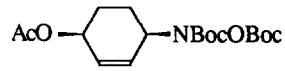
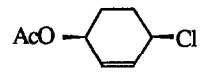
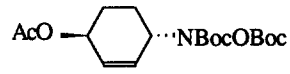
R_1 = $COCH_3$, R_2=R_3=R_5= H, R_4= CH_3

Palladium-catalyzed amination of allylic compounds with primary amines[3], secondary amines[4] and several equivalents of ammonia (e.g. phtalimide[5] sodium azide[6] di-*tert*-butyl imino-dicarbonate[7] etc..) has been extensively used[8] for the synthesis of allylic amines[9] and nitrogen containing alkaloids[10]. In contrast, to our knowledge, there is only one example of palladium-catalyzed hydroxylamination of allyl esters with N-alkyl hydroxylamines for the synthesis of N,N-disubstituted hydroxylamine[11]. This palladium technology for a selective synthesis of N-allylhydroxylamines was unsuccessful, because the amination of allyl esters with hydroxylamine undergoes double allylation[11].

Based on the successful use of stabilized nucleophiles such as anions derived from α-imino carboxylates[12] and phosphonic esters[13] in palladium-catalyzed reaction as part of our ongoing interest in the synthesis of α-amino-N^6-hydroxylamino acids, we sought to develop a method for conversion of allylic ester into mono N-substituted hydroxylamines. Thus, our attention has been directed to the use of N,O-bis-*ter*-Boc protected hydroxylamine **2**[14] as nucleophile. We report the use of this efficient nitrogen nucleophile in palladium-catalyzed amination and the synthesis of (+)-N^6-hydroxylysine, component of mycobactins.

The palladium(0)-catalyzed reaction of allyl derivatives with **2** under argon gives the expected protected N-allylhydroxylamines in good yields. The typical examples are given in table.

Conversion of allylic substrates to protected N-allylhydroxylamine with HNBocOBoc 2.

Entry	allyl derivative	Reactions conditions[a]	Yield (%)[b]	Products
1		**2** / K_2CO_3 24 h R.T.[c]	77	
2		$LiN(OBoc)Boc$ 1.5 h R.T.[c]	70	
3		**2** 15 h R.T.[d]	74	 54 40 : 6 E : Z
4		**2** 15 h R.T.[d]	80	
5		**2** 5 h 45°C[d]	86	
6		**2** 5 h 45°C[d]	63	
7		$NaN(OBoc)Boc$ 3 h R.T.[c, e]	87	
8		$NaN(OBoc)Boc$ 15 h R.T.[c, f]	75	

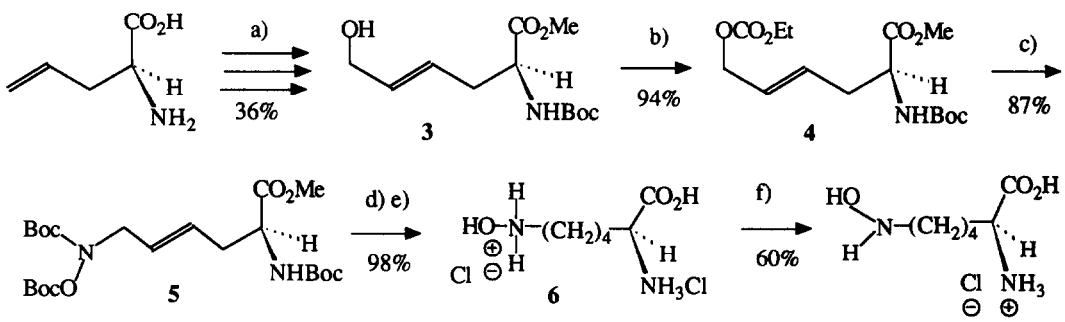
a) $Pd(dppe)_2$ 3%; b) Isolated yield; c) Solvent THF/DMF; d) Solvent THF; e) $Pd(OAc)_2$ 3%, PPh_3 12%; f) Without catalyst.

In all cases, (except entry 7, 8), the active catalyst was performed in situ by adding dppe to 3% of $Pd(dba)_2$. The reaction of **2** or lithium, potassium salts with allylic derivatives were run in THF or mixture of THF and DMF at room temperature. The reaction of simple allylic acetate or chloride proceeded at room temperature giving the substituted product in good yields (70-87 %) (entries 1, 2, 7). When the allylic carbonate is substituted, mixture of regioisomers was obtained (entry 3). However with cinnamyl carbonate and functionalized allylic derivatives a

high selectivity was obtained giving in good yields allylic derivatives (entrie 4, 5, 6). The stereochemical course of palladium-catalyzed amination was examined precisely with cis-1,4-chloroacetoxycyclohex-2-ene[15,16]. The sodium salt of **2** in THF proceeded with retention of configuration in 87% yield (entry 7). The uncatalyzed reaction provided after longer reaction time the trans product in 75% yield (entry 8).

The usefulness of this hydroxylamination was examplified by the synthesis of (+)-N^6-hydroxylysine as shown in scheme: the functionalized allylic alcohol **3** was easily prepared in five steps [17] from (L)-allyl glycine. Treatment with ethyl chloroformate gave the allylic carbonate **4**. The key reaction was the palladium-catalyzed amination of **4** with the (N,O)-protected hydroxylamine **2** under neutral conditions giving **5**. Simultaneous removal of methylester and N-*ter*-Boc groups was accomplished by the reaction of hydrogen chloride (6N) reflux for 1 h.; hydrogenation over palladium/carbon in ethanol provided the (+)-N^6-hydroxylysine dihydrochloride. The resulting solution gave after basification with pyridine (pH 4-5) the desired (+)-N^6-hydroxylysine monohydrochloride as an amorphous powder. $[\alpha]_D$= +22 (C=0.25, 1N HCl), Litt. $[\alpha]_D$= +25.5 (C=0.20, 1N HCl).

Synthesis of the (+)-N^6-Hydroxylysine



a) ref.17; b) $ClCO_2Et$, pyridine, CH_2Cl_2, 4h, 0 to 25°C; c) NHBocOBoc, $Pd(dppe)_2$ 5%,THF, 45°C, 4h; d) HCl, 6N reflux, 1h30; e) H_2,1 atm, Pd/ C, R.T.; f) pyridine pH 4-5.

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(16) **(Cis)-1-acetoxy-4-(N,O-diterbutyloxycarbonyl-hydroxylamino)-cyclohex-2-ene:**
General method: A solution of HNBocOBoc (233 mg, 1 mmol) in THF/DMF 1/1 (1 mL) was added to a suspension of NaH (40 mg, 1 mmol) in THF (1 mL). After 30 min. was added a solution of $Pd(OAc)_2$ (3mol %), PPh_3 (12 mol %) and (Cis)-1,4-chloroacetoxy-cyclohex-2-ene (180 mg, 1.03 eq) in THF (1 mL). After 3h was added aqueous NH_4Cl (2 mL). The solution was extracted with ether (2x10 mL), the organic layer washed with brine (2x2 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure followed by chromatography (1:9 cyclohexane: AcOEt) yielded to 323 mg (87%) of white needles.(m.p.: 75°C)
$C_{18}H_{29}NO_7$ calc. C 58.21 H 7.87 N 3.77 found C 58.31 H 7.83 N 3.73.
^1H NMR ($CDCl_3$, 500 MHz, δppm): 5.94 (m, 2 H, HC=CH), 5.17 (m, 1 H, CHOAc), 4.70 (m, 1 H, CHN), 2.07 (s, 3 H, CO_2CH_3), 1.91 (m, 4 H), 1.54 (s, 9 H), 1.51 (s, 9 H).
^{13}C NMR ($CDCl_3$, 50 MHz, δppm): δ = 170.5 (OCOMe), 154.4 (NCO_2tBu), 152.5 (OCO_2tBu), 131.3, 129.0 (HC=CH), 84.4 ($NCO_2C(CH_3)_3$), 82.6 ($OCO_2C(CH_3)_3$), 65.7 (CHOAc), 55.4 (CHN), 28.0 ($NCO_2C(CH_3)_3$), 27.5 ($OCO_2C(CH_3)_3$), 26.5 (CH_2CHOAc), 21.2 ($OCOCH_3$), 21.1 (CH_2CHN).
IR($HCCl_3$, cm^{-1}): ν = 2995, 2930, 1787, 1733, 1707, 1371, 1256, 1240, 1147.
(Trans)-1-acetoxy-4-(N,O-diterbutyloxycarbonyl-hydroxylamino)-cyclohex-2-ene:
$C_{18}H_{29}NO_7$ calc. C 58.21 H 7.87 N 3.77 found C 57.57 H 7.92 N 3.90. (m.p.: 72-73°C)
^1H NMR ($CDCl_3$, 500 MHz, δppm): 5.81 (s br, 2 H, CH=CH), 5.34 (ddd, 1 H, *J* = 9.0, 5.5, 2.5 Hz, CHOAc), 4.80 (mt, 1 H, *J* = 7.0 Hz, CHN), 2.23-1.93 (m, 2 H), 2.04 (s, 3 H, CH_3CO_2), 1.83-1.58 (m, 2 H), 1.49 (s, 9 H), 1.47 (s, 9 H).
^{13}C NMR ($CDCl_3$, 50 MHz, δppm): 170.6 (OCOMe), 154.4 (NCO_2tBu), 152.4 (OCO_2tBu), 131.0, 129.6 (HC=CH), 84.5 ($NCO_2C(CH_3)_3$), 82.6 ($OCO_2C(CH_3)_3$), 68.5 (CHOAc), 55.3 (CHN), 28.0 ($NCO_2C(CH_3)_3$), 27.5 ($OCO_2C(CH_3)_3$), 26.8 (CH_2CHOAc), 23.7 (CH_2CHN), 21.1 ($OCOCH_3$).
IR($HCCl_3$, cm^{-1}): ν = 2981, 2937, 1788, 1736, 1714, 1371, 1242, 1151.

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