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REGIO-AND STEREOSELECTIVE PALLADIUM CATALYZED AMINATION OF ALLYLIC SUBSTRATES. SYNTHESIS OF E-4-AMINO-2-ALKEN-1-OL DERIVATIVES

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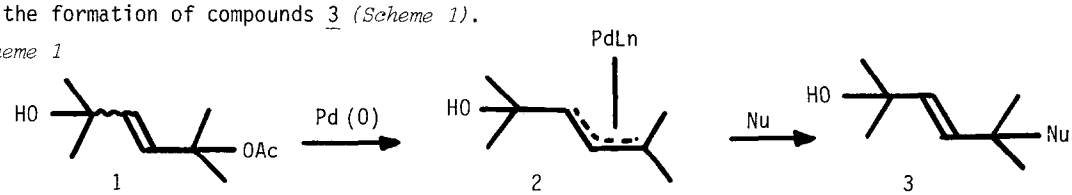
Summary : Under mild conditions 4, 5 and 6 react with primary and secondary amines in the presence of palladium phosphine complexes as catalysts to give 4-amino-2-alken-1-ols with (E) stereochemistry.

The ability of palladium complexes to catalyze allylic exchange reactions by nucleophiles is an important synthetic methodology heavily documented[1]. In addition to carbon nucleophiles the heteronucleophiles and especially those with nitrogen have recently been studied. After the first catalyzed amination described by Atkins[2] and Takahashi[3], these palladium reactions have proved efficient in syntheses of alkaloids [4], aminosugars[5], and azaspiranes[6]. These aminations are believed to proceed mainly via π-allyl palladium complexes[7], and the regio-[7] and stereochemistry[8] of the nucleophilic attack by amine depends very much on the reaction conditions.

We have previously shown[9] that π-allyl complexes 2 generated *chemoselectively* from 1,4-hydroxyacetates 1 are useful in directing nucleophilic attack by stabilized carbanions. The new carbon-carbon bond was formed exclusively in the 4-position to the hydroxy group, resulting in the formation of compounds 3 *(Scheme 1)*.

Scheme 1

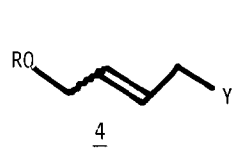


1 2 3

The same directing effect has been observed in the palladium (0)-catalyzed alkylation of 1-methoxy-4-acetoxy-2-cyclohexene[10], 1-acetoxy-4-chloro-2-alkenes[11], 1,2-epoxy-3-alkenes[12] and dicarboxylates of cyclopentene-1,4-diol[13]. A recent publication[14] also describes the activation of Z-4-acetoxybut-2-enyl dimethylphosphonate 4b related to 4-hydroxybut-2-enyl acetate 4a[9c] and 4-chlorobut-2-enyl acetate 4c[11] *(Scheme 2)*. In the latter publication the question was raised about the *unreactivity* of 4a in palladium catalyzed aminations.

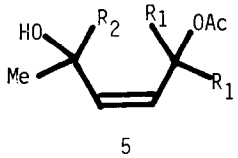
We now wish to report our initial observation[15] that Z-4-hydroxybut-2-enyl acetate 4a and related 1,4-hydroxyacetates are *highly* reactive in palladium (0)-catalyzed aminations. We also report that palladium catalyzed amination of chloroacetates 6c and 6d occurs under mild conditions.

Scheme 2



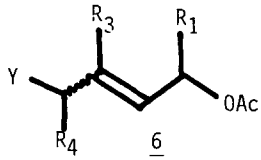
4

a : R = H Y = OAc
b : R = Ac Y = $OPO(OEt)_2$
c : R = Ac Y = Cl
d : R = Ac Y = OAc



5

a : R_1 = H R_2 = C_9H_{19}
b : R_1 = R_2 = Me



6

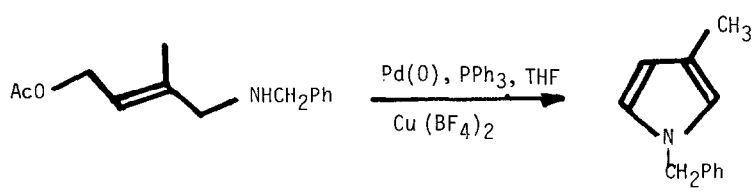
a : R_1 = R_3 = H, R_4 = Me Y = OTHP
b : R_1 = R_4 = Me, R_3 = H Y = OH
c : R_1 = R_4 = Me, R_3 = H Y = Cl
d : R_1 = R_4 = H, R_3 = Me Y = Cl

The palladium-catalyzed amination of substrates 4, 5 and 6 works well with both primary and secondary amines (Table 1) and constitutes a general synthesis of 4-amino-2-alken-1-ol derivatives. It is interesting to note that primary amines only give rise to monoalkylated products (entries 4-6 and 9-10)[16]. The E and Z diacetate 4d also underwent a smooth amination reaction and more importantly, the use of one equivalent of Et_2NH in the presence of Et_3N results in amination of *only one* of the two allylic acetoxy groups (entry 2)[17]. The new carbon-nitrogen bond was regioselectively formed in the 4-position to the hydroxy or acetoxy group in all cases studied.

The stereochemistry of the 4-amino-2-alken-1-ols was established by ^1H NMR spectroscopy at 200 or 250 MHz. In the cases of disubstituted double bonds the vicinal coupling constants of the olefinic protons J_{HH} = 15 - 16 Hz are consistent only with E configuration of the double bond. In the case of the product obtained from 6d (entry 12), mainly one geometrical isomer was observed, which was assigned as the E-isomer[18].

Our studies establish the high reactivity of allylic substrates 4, 5 and 6 in palladium catalyzed amination. The reactions of these 1,4-hydroxyacetates and the related chloroacetates are highly regio-and stereoselective. The usefulness of the reactions studied is enhanced by the allylic hydroxy or acetoxy group in the products and by the readily available starting materials[19]. The products obtained have considerable synthetic utility for cyclization reactions[20] and for incorporating a second nucleophile in the allylic oxygen position[11]The cyclization of the aminoacetate 7 to the pyrrole 8 demonstrates this point *(Scheme 3)*.

Scheme 3



7 8 (50 %)

In conclusion, our approach to 4-amino-2-alken-1-ol derivatives appears quite efficient considering the generality and simplicity in synthesis of the starting materials[19].

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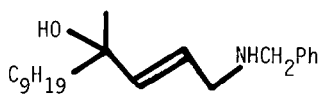
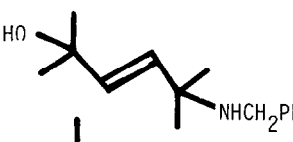
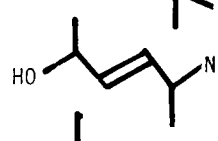
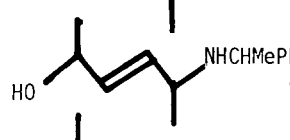
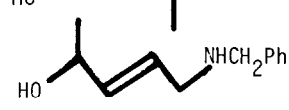
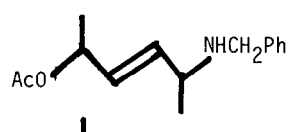
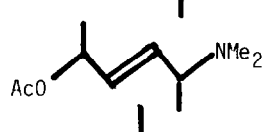
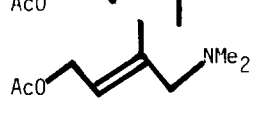
Table 1 : Amination of allylic substrates 4, 5 and 6 with primary or secondary amines[a]

entry	substrate	amine	catalyst[b]	conditions t(hr)	conditions temp(°C)	products	yield[c] %
1	4a (Z)	Et_2NH	$Pd(PPh_3)_4$	0,3	20		75
2	4d (E) or (Z)	Et_2NH[d]	$Pd(PPh_3)_4$	2	20		70
3	4a (E)		$Pd(PPh_3)_4$	1	20		65
4	4a (Z)	$PhCH_2NH_2$	$Pd(PPh_3)_4$	2	20		65
5	5a (Z)	$PhCH_2NH_2$	$Pd(DIPHOS)_2$	1	25		74
6	5b (Z)	$PhCH_2NH_2$	$Pd(DIPHOS)_2$	24	65		76
7	6b (Z)	Et_2NH	$Pd(PPh_3)_4$	4	60		68
8	6b (Z)	$PhCH(Me)NH_2$	$Pd(PPh_3)_4$	4	60		45
9	6a (Z)	$PhCH_2NH_2$	$Pd(DIPHOS)_2$	1	20		75[21]
10	6c (E)	$PhCH_2NH_2$	$Pd(acac)_2 + 4PPh_3$	9	20		56
11	6c (E)	Me_2NH	$Pd(acac)_2 + 4PPh_3$	3	20		80
12	6d (E/Z = 3.6)	Me_2NH	$Pd(acac)_2 + 4PPh_3$	4	20		71
13	6d (E/Z = 3.6)	$PhCH_2NH_2$	no catalyst	1,5	80[e]		89[f]

a) Entries 1-9 1,1 equivalent of amine was used in THF or DME with an excess of triethylamine (1,5 equivalent). Entries 10-12 in THF with 3 equivalents of amine - b) 5 - 8 % of catalyst was used in entries 1-9 and 2 - 3 % of catalyst was used in entries 10-12 - c) Isolated yield - d) Only one equivalent of amine was used - e) The reaction was performed in refluxing acetonitrile. Amination of chloroacetates 6c and 6d, in THF in the absence of catalyst was extremely slow - f) E/Z = 3.6.

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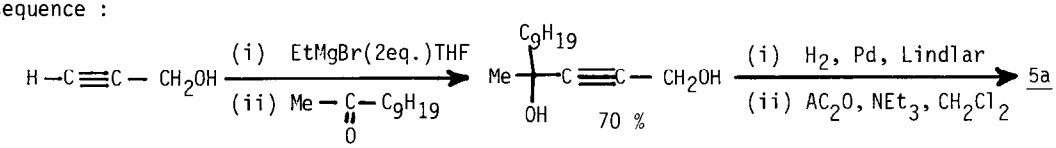
17. A similar selectivity for monosubstitution was recently observed in the palladium-catalyzed alkylation of cyclopentene-1,4-diol dicarboxylates (réf 13).
18. The assignment is based on the fact that the product is identical to the major geometrical isomer obtained from classical nucleophilic substitution of the E/Z mixture (E/Z = 3.6). In the non-catalyzed nucleophilic substitution the olefin geometry should not be affected.
19. For the syntheses of hydroxyacetates 4a, 5b, 6a and 6b see references (9a-d). The chloroacetates 6c and 6d were prepared by palladium-catalyzed 1,4-acetoxychlorination of E,Z-2,4-hexadiène and isoprène respectively (11). Hydroxyacetate 5a was prepared according to the following sequence :



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21. The aminoalcohol was obtained after hydrolysis (HCl, 2 N ; 1 hr, 25°C) of the corresponding tetrahydropyrannyl ether.

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