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PALLADIUM(0)-CATALYZED HYDROXYLAMINATION OF ALLYL ESTERS. SYNTHESIS OF N-ALLYLHYDROXYLAMINES AND SECONDARY ALLYLAMINES

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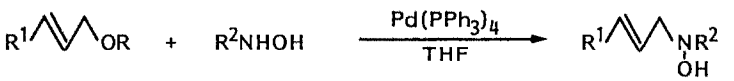
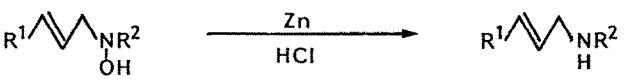
Summary: Palladium-catalyzed reaction of allyl esters with hydroxylamines gives N-allylhydroxylamines, which are readily converted into secondary allylamines upon treatment with zinc powder in a dilute HCl solution.

Palladium-catalyzed amination of allyl esters is one of the important methods for the preparation of biologically active amine compounds.[1] Tertiary allylamines can be prepared by the palladium-catalyzed amination of allyl esters with secondary amines.[2] Primary allylamines can be prepared selectively by the palladium-catalyzed azidation of allyl esters followed by treatment with PPh_3/NaOH.[3]

Selective synthesis of secondary allylamines by the amination of allyl esters is difficult, because secondary allylamines formed undergo further amination to afford tertiary allylamines. Here, we wish to report that palladium(0)-catalyzed reaction of allyl esters with hydroxylamines gives N-allylhydroxylamines, which can be readily converted into secondary allylamines upon treating with zinc powder in an aqueous HCl solution (Eqs. 1 and 2).



(1)



(2)

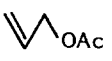
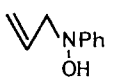
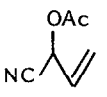
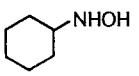
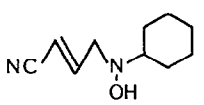
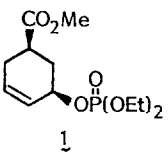
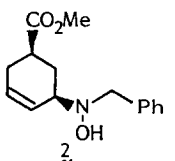
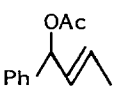
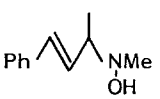
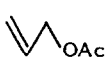
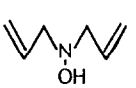
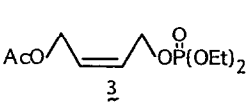
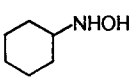
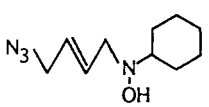
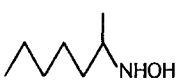
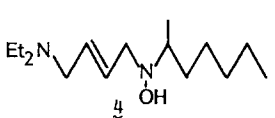
The palladium(0)-catalyzed reaction of allyl esters with hydroxylamines under argon gives the corresponding N-allylhydroxylamines regioselectively in excellent yields. The representative results are summarized in Table 1. The substrates of N-monosubstituted hydroxylamines can be readily prepared by various methods such as reduction of oximes[4] and alkylation of oximes.[5] A mixture of hydroxylamine hydrochlorides and an aqueous NaOH solution (1:1) is also utilized in place of hydroxylamines (entries 4 and 5). The reaction of (Z)-5-methoxycarbonyl-2-cyclohexenyl diethyl phosphate (1) with N-benzylhydroxylamine gave N-benzyl-N-(5-methoxycarbonyl-2-cyclohexenyl)hydroxylamine (2) in 84% yield. The Z/E ratio was determined to be 80/20 on the basis of HPLC analysis and NMR spectral data.[6] The hydroxylamination seems to proceed with retention of configuration, although the epimerization of 1 under the

reaction conditions induced loss of stereochemistry of 2.[7] Sequential substitution of 4-acetoxy-2-butenyl diethyl phosphate (3) gave various (E)-1,4-disubstituted 2-butenes.

Typically, the preparation of N-(4-diethylamino-2-butenyl)-N-(2-heptyl)-hydroxylamine (4) is as follows (entry 7). To a solution of $Pd(PPh_3)_4$ (0.092 g, 0.08 mmol) and N-(2-heptyl)hydroxylamine (0.26 g, 2.0 mmol) in THF (4.0 mL) was added acetoxy phosphate 3 (0.53 g, 2.0 mmol) under argon. The mixture was stirred at room temperature for 2 hr, then diethylamine (0.15 g, 2.2 mmol) was added. After the mixture was stirred at room temperature for 3 hr, ether and a 2N HCl solution were added. The aqueous layer was separated and made alkaline. Extraction with ether and removal of the solvent gave hydroxylamine 4 (0.46 g, 90%).

N-Allylhydroxylamines can be readily converted into secondary allylamines. Thus, the treatment of N-allylhydroxylamines with zinc powder in

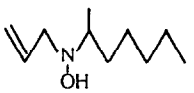
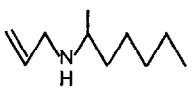
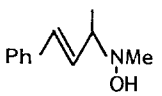
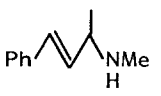
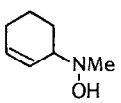
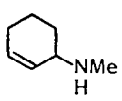
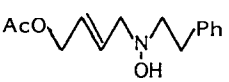
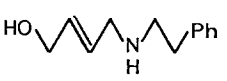
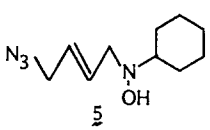
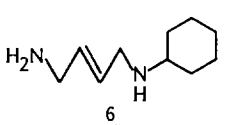
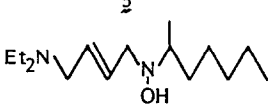
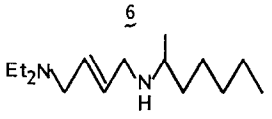
Table 1. Palladium-Catalyzed Hydroxylamination of Allyl Esters[a]

Entry	Allyl Ester	Nu^1	Nu^2	Product[b]	Isolated Yield,%
1		PhNHOH	-		91
2			-		92[c]
3	 1	Ph NHOH	-	 2	84[d]
4		MeNHOH·HCl[e]	-		99
5		$NH_2OH \cdot HCl$[e]	-		93
6	 3		NaN_3		92
7	3		Et_2NH	 4	90

[a]The reaction conditions are same to the procedure descrived in the text. [b]The products gave satisfactory IR, NMR, and Mass spectral data. [c]The product contains cis isomer(<20%). [d]The Z/E ratio is 80/20. [e]Equimolar amount of aqueous NaOH was used.

an aqueous HCl solution gave secondary allylamines.[8] The representative results of the preparation of secondary allylamines are shown in Table 2. Allylic double bonds tolerate the reduction. Ester groups are hydrolyzed (entry 4), and azido groups are reduced to primary amino groups (entry 6). Sequential substitution of 3 followed by the reduction gives various functionalyzed secondary 2-butenylamines.

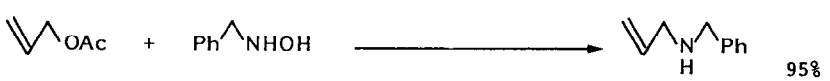
Table 2. Conversion of N-Allylhydroxylamines to Secondary Allylamines[a]

Entry	N-Allylhydroxylamine	Allylamine[b]	Isolated Yield, %
1			95
2			93
3			85
4			84
5			72
6			78

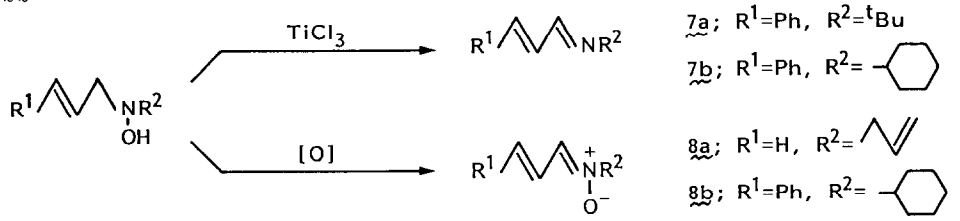
[a]The reaction conditions are same to the procedure descrived in the text. [b]The products gave satisfactory IR, NMR, and Mass spectral data.

The preparation of N-(4-amino-2-butenyl)cyclohexylamine (6) is representative (entry 5). A mixture of N-allylhydroxylamine 5 (0.18 g, 0.87 mmol) and zinc powder (0.29 g, 4.4 mmol) in an aqueous 2N HCl solution (6 mL) was stirred at 80 °C for 1 hr. Addition of excess of a dilute NaOH solution, extraction with ether followed by usual work-up gave diamine 6 (0.11 g, 72%).

Naturally, secondary allylamines can be prepared simply without isolation of N-allylhydroxylamines by direct treatment of hydroxylamines with Zn/2N HCl. For examples, N-allylbenzylamine can be prepared simply from allyl acetate and N-benzylhydroxylamine by one-pot reaction in 95% isolated yield.



N-Allylhydroxylamines can be converted into various synthetically useful key intermediates such as 1-aza-1,3-dienes[9] and α,β-unsaturated nitrones.[10] Thus, the treatment of hydroxylamines with titanium trichloride[11] gave the corresponding azadienes, such as 7a (60%) and 7b (52%). Further, the oxidation with mercuric oxide[12] gave conjugated nitrones, such as 8a (99%) and 8b (99%).



7a; R^1=Ph, R^2=^{t}Bu
7b; R^1=Ph, R^2=
8a; R^1=H, R^2=
8b; R^1=Ph, R^2=

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6) NMR spectra (500 MHz) (Z)-2: δ 3.69 (CO_2CH_3 at C^5), 3.45 (C^1H); (E)-2: 3.66 (CO_2CH_3 at C^5), 3.35 (C^1H).

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