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PALLADIUM(0) CATALYZED AZIDATION AND AMINATION OF ALLYL ACETATES. SELECTIVE SYNTHESIS OF ALLYL AZIDES AND PRIMARY ALLYLAMINES

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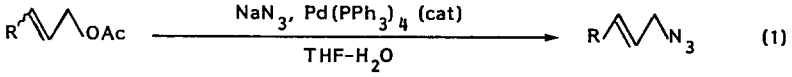
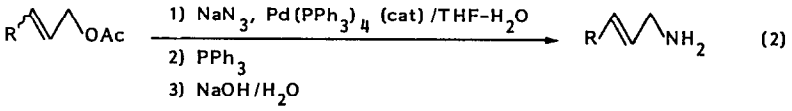
Summary: Palladium catalyzed reaction of allyl acetates with azide ion gives allyl azides, which are readily converted into the corresponding primary allylamines upon treatment with PPh_3/NaOH.

The catalytic transformation of allylic substrates via π-allyl palladium complexes is now well documented.[1] Palladium catalyzed amination of allylic compounds has been extensively studied[2-6] and proved to be efficient for synthesis of various nitrogen containing biologically active compounds[4-6] such as alkaloids[4] and amino sugars.[5] The preparation of primary allylamines by the amination of allylic substrates with ammonia was unsuccessful, and hence attention has been directed to the preparation of benzylated amines and removal of the benzyl group by catalytic hydrogenation reactions.[7]





We have found that the palladium(0) catalyzed reaction of allyl acetates with azide ion gives the corresponding allyl azides, which are versatile synthetic intermediates[8] (eq 1). Importantly, allyl azides thus obtained can be readily converted into primary allylamines, which are important synthetic intermediates of many natural products[9] upon treatment with PPh_3/NaOH, without isolation (eq 2). The palladium catalyzed azidation of allylic substrates, to our knowledge, has never been reported. Noteworthy is that π-allyl palladium complexes react with azide ion, which is a borderline nucleophile in the HSAB principle.[10]

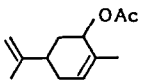
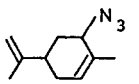
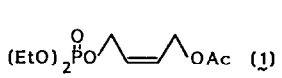
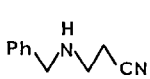
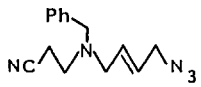
The palladium(0) catalyzed azidation reaction of allyl acetates with aqueous NaN_3 was

carried out in the presence of $Pd(PPh_3)_4$ catalyst in THF under argon. The representative results of the azidation are summarised in Table I. The present reaction affords (E)-isomer exclusively irrespective of the stereochemistry of the starting substrates (entries 4 and 5).[11] The formation of γ-substituted allylic azides is due to the characteristic 1,3-rearrangement of allyl azides (entry 3).[12]

The present reaction is particularly useful for the sequential substitution of disubstituted allylic compounds. The sequential reactions of 4-acetoxy-2-butenyl diethyl phosphate (1) give various (E)-1,4-disubstituted alkenes, which are versatile synthetic intermediates (entries 4 and 5).

A typical procedure for the preparation of 3-{N-[(E)-4-azido-2-butenyl]-N-benzylamino}-propionitrile (2), which is the precursor of spermidine, is as follows (entry 4). To a solution of $Pd(PPh_3)_4$ (0.23 g, 0.20 mmol) in THF (10 mL) was added acetoxy phosphate 1 (1.3 g, 5.0 mmol) and then β-benzylaminopropionitrile (0.80 g, 5.0 mmol) under argon.[2] The mixture was stirred for 1 hr at room temperature, and then a solution of NaN_3 (0.36 g, 5.0 mmol) in water (5 mL) was added. After the mixture was stirred for 3 hr, usual work-up followed by column chromatography (SiO_2) gave allyl azide 2 (0.97 g, 76%), which was homogeneous by TLC and GLC analyses.[13]

Table I. Palladium Catalyzed Azidation of Allyl Acetates[a]

entry	substrate	Nu^1	Nu^2	product[b]	isolated yield,[c] %
1		NaN_3	-		88
2		NaN_3	-		84
3		NaN_3	-		64[d]
4	 (1)		NaN_3	 (2)	76
5	1	$NaCH(CO_2Me)_2$	NaN_3		76

[a] The reaction was carried out following to the procedure described in the text. [b] The product gives satisfactory IR, NMR, and Mass spectral data. [c] Purified by chromatographic separation (SiO_2). [d] The product contains linalyl azide (20%).

Importantly, allyl acetates can be directly converted into primary allylamines. The allyl azides thus obtained are allowed to react with PPh_3 to give the corresponding iminophosphoranes, which are readily converted into primary allylamines upon treatment with aqueous NaOH.[14] The representative results of the preparation of primary amines are summarized in Table II.

The present reaction is highly useful for the preparation of primary (E)-allylamines, because of its high regioselectivity. Even a mixture of α- and γ-allyl azides can be converted

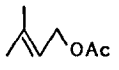
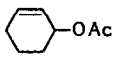
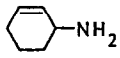
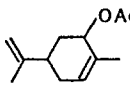
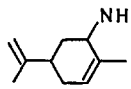
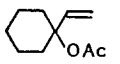
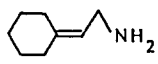
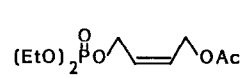
into the corresponding α-allylamines. Thus, the azidation of geranyl acetate gives a mixture of geranyl and linalyl azide (80:20) (entry 3 in Table I). However, when the above mixture was treated with PPh_3, geranylamine was obtained exclusively (entry 5 in Table II).

Following procedure for the preparation of (E)-4-(2-methylpiperidino)-2-butenylamine (3) (entry 6) is illustrative. To a solution of $Pd(PPh_3)_4$ (0.092 g, 0.080 mmol) and acetoxy phosphate 1 (0.53 g, 2.0 mmol) in THF (6 mL) was added 2-methylpiperidine (0.20 g, 2.0 mmol) at room temperature under argon, and the reaction mixture was stirred for 1 hr. A solution of NaN_3 (0.14 g, 2.0 mmol) in water (2 mL) was added under argon, and the reaction mixture was stirred at 50°C for 1 hr. Then PPh_3 (0.58 g, 2.2 mmol) was added, and the reaction mixture was stirred at 50°C for 1 hr. After the addition of a 2N NaOH solution (10 mL), the mixture was stirred for 1 hr. Extraction with a 2N HCl solution, and the acidic phase was made alkaline and extracted with CH_2Cl_2. Usual work-up followed by evaporation of the solvent gave the allylamine 3 (0.28 g, 84%), which was homogeneous by TLC and GLC analyses.[15]

Among various reducing reagents of azides[16] the reaction system of PPh_3/NaOH is chosen because the intermediate iminophosphoranes can be used as key intermediates for various nitrogen compounds, such as secondary amines,[17] amides,[18] imines,[19] nitro compounds,[20] and amino-phosphonium salts,[21] in addition to the primary amine synthesis. Here again the present reaction is highly useful for the synthesis of substituted primary (E)-allylamines by using the sequential reactions (entry 6 in Table II).

Extention of this methodology and applications in natural products synthesis are actively being pursued in our laboratory.

Table II. One-Pot Preparation of Primary Allylamines[a]

entry	allyl acetate	allylamine[b]	isolated yield, %
1			61[c]
2			70[c]
3			91
4			80
5			59
6		 (3)	84

[a] The conditions are same to the procedure described in the text. [b] The product gives satisfactory IR, NMR, and Mass spectral data. [c] Isolated as amine hydrochloride.

References and Notes

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13. 2: ^{1}H NMR ($CDCl_3$) δ 2.38 (d, J=4.3 Hz, 2H), 2.78 (t, J=4.3 Hz, 2H), 3.16 (d, J=5.0 Hz, 2H), 3.62 (s, 2H), 3.73 (d, J=5.0 Hz, 2H), 5.71 (dt, J=15.3 and 5.0 Hz, 1H), 5.75 (dt, J=15.3 and 5.0 Hz, 1H), 7.05-7.40 (m, 5H); mass spectrum m/e 255 (M^+).
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15. 3: ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J=7.0 Hz, 3H), 1.14-1.85 (m, 9H), 1.85-2.45 (m, 2H), 2.67-3.06 (m, 2H), 3.14-3.47 (m, 2H), 5.64 (dt, J=16.0 and 4.7 Hz, 1H), 5.65 (dt, J=16.0 and 4.7 Hz, 1H); mass spectrum m/e 168 (M^+).
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