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PALLADIUM(0)-CATALYZED ALLYLIC ALKYLATION AND AMINATION OF ALLYLIC PHOSPHATES[1]

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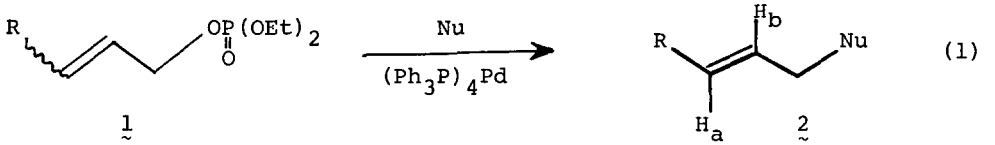
Allyl diethyl phosphates (1) can be easily substituted with malonates and amines in the presence of palladium(0) catalyst. Synthetic utility of the reaction is demonstrated by the sequential amination-amination and alkylation-amination of (Z)-4-acetoxybut-2-enyl diethyl phosphate (1b) with high regio- and stereoselectivity.

Allylic transformations catalyzed by palladium are of great value, since an allylic moiety is important for organic synthesis[2]. The most common and useful approach to such purpose led to the development of palladium-catalyzed reactions of allylic acetates and ethers with various nucleophiles[3]. However, palladium-induced allylic transformation of allylic phosphates, to our knowledge, has never been reported[4]. We now wish to report that allyl diethyl phosphate (1) is the most efficient substrate for allylic alkylation[2,3] and amination[5] catalyzed by palladium(0) catalyst as depicted in eq 1.

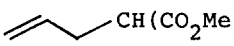
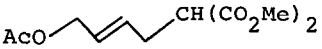
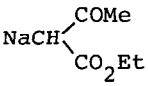
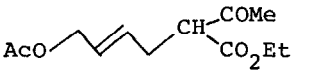
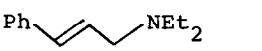
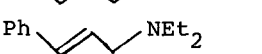
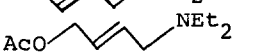
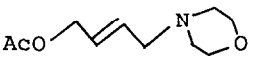
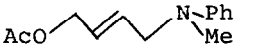


1 2 (1)

The reaction proceeds rapidly and cleanly at room temperature. General procedure for alkylation and amination reactions of the phosphate 1 is as follows: To a mixed solution of 1 and tetrakis(triphenylphosphine)palladium (2-4 mol %) in THF was added a nucleophile (1.0 equivalent) such as malonates and amines, then the reaction mixture was stirred at room temperature for 1 h. Monitoring the reaction by tlc and/or glc showed that the substrate 1 disappears within 1 h. After usual work-up, distillation and/or preparative tlc gave the corresponding alkenoates and allylic amines (2).

High reactivity of allylic phosphates was verified by the following facts. The competitive reaction of allyl diethyl phosphate (1a) and allyl acetate with sodium dimethyl malonate showed that the relative rate of the alkylation of the phosphate to that of the acetate is about 11[6]. Furthermore, the reaction of

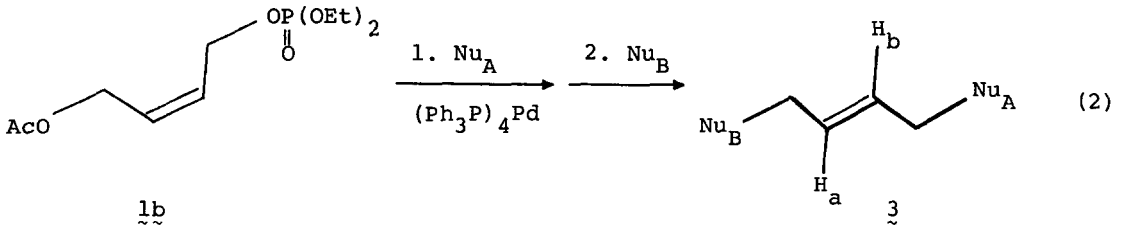
Table 1. Alkylation and Amination of Allylic Phosphates 1[a]

Entry	R in the substrate (1)	Nucleophile	Product (2)[b]	E/Z[c]	Isolated Yield (%)	$J_{H_a-H_b}$ (Hz)
1	H (1a)	$NaCH(CO_2Me)_2$		—	81	—
2	(Z)-CH_2OAc (1b)	$NaCH(CO_2Me)_2$		87/13	83	15.2
3	(Z)-CH_2OAc (1b)			93/7	68	15.2
4	(E)-Ph (1c)	Et_2NH		100/0	68	16.5
5	(Z)-Ph (1d)	Et_2NH		100/0	63	16.5
6	(Z)-CH_2OAc (1b)	Et_2NH		100/0	88	15.2
7	(Z)-CH_2OAc (1b)			100/0	75	15.2
8	(Z)-CH_2OAc (1b)	Ph(Me)NH		100/0	84	15.4

a) All reactions were carried out on 1-3 mmol scale at room temperature in THF for 1 h using 2-4 mol% of $(Ph_3P)_4Pd$ under nitrogen. b) All products have been fully characterized by spectral data and elemental analyses. c) Determined by NMR analysis.

(E)-cinnamyl diethyl phosphate (1c) with diethylamine proceeds much faster than that of (E)-cinnamyl acetate and alcohol[6]. Consequently, the reactivity of allylic substrates is in the order of $-OP(O)(OEt)_2 > -OC(O)CH_3 > -OH$[7].

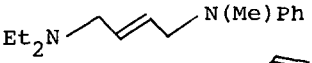
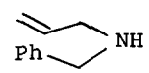
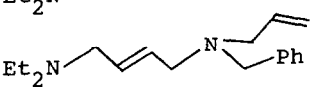
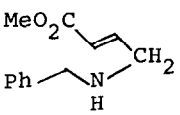
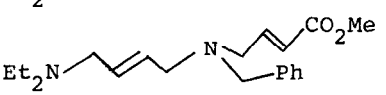
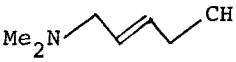
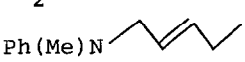
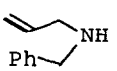
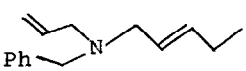
Typical examples of the alkylation (entries 1-3) and amination (entries 4-8) are summarized in the Table 1. Synthetic utility of the reaction is enhanced by both high reactivity of the phosphoryl group of 1b and lability of the acetoxy group of 2 to other nucleophiles via organopalladium chemistry (eq 2). Thus, the diethyl phosphoryl group of (Z)-4-acetoxybut-2-enyl diethyl phosphate 1b[8] is selectively substituted with various nucleophiles to give (E)-4-substituted-2-butenyl acetates 2 which are synthetically valuable intermediates (entries 2,3,6,7, and 8 in Table 1). The sequential amination and amination of 1b is achieved to give (E)-N,N-dialkyl(4-N',N'-dialkylamino)but-2-enylamine (3) with high selectivity (entries 1-3 in Table 2). In this reaction, excess of triethylamine is required to trap the liberating diethyl phosphoric acid, since the acid produces the corresponding ammonium salt of 2 which undergoes complexed substitution reactions. Furthermore, the sequential alkylation and amination of 1b is also performed to give (E)-6-N,N-dialkylamino-4-alkenoate[9] highly selectively (entries 4-6 in Table 2). In this case, the precedence of amination



(2)

1b 3

Table 2 Sequential Amination-Amination and Alkylation-Amination of the Acetoxyphosphate 1b (eq 2)[a]

Entry	Nucleophile Nu_A	Nucleophile Nu_B	Product (3)[b]	Isolated Yield (%)[c]	$J_{H_a-H_b}$ (Hz)
1	Ph(Me)NH	Et_2NH		70	15.4
2		Et_2NH		65	20.8
3		Et_2NH		50	15.6
4	$NaCH(CO_2Me)_2$	Me_2NH		79	15.5
5	$NaCH(CO_2Me)_2$	Ph(Me)NH		67	18.1
6	$NaCH(CO_2Me)_2$			80	15.6

a) The reaction was carried out as follows: A mixture of the phosphate 1b, a nucleophile (Nu_A), $(Ph_3P)_4Pd$, and Et_3N (1:1:0.04:10) (without Et_3N in the case of sequential alkylation and amination) in THF was stirred at room temperature for 1 h under nitrogen. To the resulting solution was added one equivalent of the second nucleophile (Nu_B), and the reaction mixture was stirred at room temperature for 4-8 h. b) All products have been fully characterized by spectral data and elemental composition. c) Yields were not optimized.

should be avoided to prevent the formation of diethyl phosphoric acid.

Generally, the present reaction affords (E)-isomer exclusively independent of the stereochemistry of starting substrates (entries 4 and 5 in Table 1). It is noteworthy that the Pd(0)-catalyzed alkylation of 4-hydroxybut-2-enyl acetate (4) with malonates gives the (Z)-isomer of 6-hydroxy-4-alkenoate[7,10]. The assignment of (E)-stereochemistry of the compounds 2 and 3 was established by analyzing the coupling constants ($J_{H_a-H_b}$) of the olefinic protons H_a and H_b

by the decoupling method.

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References and Notes

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4. The reactions of allylic phosphates with aluminum reagents; see: Y. Kitagawa, S. Hashimoto, S. Iemura, H. Yamamoto, and H. Nozaki, ibid., 98, 5030 (1976).
5. (a) S.-I. Murahashi, T. Shimamura, and I. Moritani, J. Chem. Soc., Chem. Commun., 931 (1974); (b) B. M. Trost and E. Keinan, J. Org. Chem., 44, 3451 (1979); (c) J.-E. Bäckvall, R. E. Nordberg, and J.-E. Nyström, ibid., 46 3479 (1981).
6. For alkylation: The reaction of 1a and allyl acetate with sodium dimethyl malonate gave allyl dimethyl malonate (92%) and 1a (10%) in addition to the acetate (92%) (GLC analysis). For amination: The reaction of 1c and (E)-cinnamyl acetate with diethylamine gave (E)-N,N-diethylcinnamylamine (95%) and the acetate (98%), and switching of the acetate to the alcohol afforded the allyl amine (93%) and the alcohol (100%) (GLC analysis).
7. J. P. Genet, M. Balabane, and Y. Legras, Tetrahedron Lett., 23, 331 (1982).
8. The acetoxyphosphate 1b was prepared by the sequential treatment of (Z)-2-butene-1,4-diol with BuLi-acetyl chloride in THF and diethylphosphorochloridate in pyridine followed by distillation (b.p. 140°C/1.0 mmHg) in 72% yield. IR(neat): 1735, 1250, 1020, 970 cm^{-1} (strong); ^1H NMR 100 MHz($CDCl_3$, δ): 1.36 (t, J=7Hz, 6H), 2.06(s, 3H), 4.12(q-d, J=7Hz, 4H), 4.65(d-d, J=5, 10Hz, 4H), 5.85-5.96(m, 2H). Doublet-doublet signals at δ5.73 and 5.84 with coupling constant, J=11.4 Hz, were observed on the irradiation of the signals at δ4.65.
9. Stepwise nucleophilic substitutions of 1,4-acetoxychloro-2-butene; see: J.-E. Bäckvall, R. E. Norbera, and J.-E. Nyström, Tetrahedron Lett., 23, 1617 (1982).
10. It should be noted that the hydroxy acetate 4 does not undergo the Pd(0)-catalyzed amination to give the corresponding 1,4-hydroxyamino-2-butene.

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