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UMPOLUNG IN ALLYLIC PHOSPHONATES. REGIOSELECTIVE REACTION OF ACETOXY ALLYLIC PHOSPHONATES WITH NUCLEOPHILES CATALYZED BY PALLADIUM(0) COMPLEX

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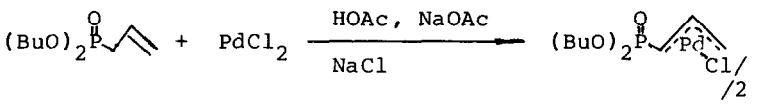
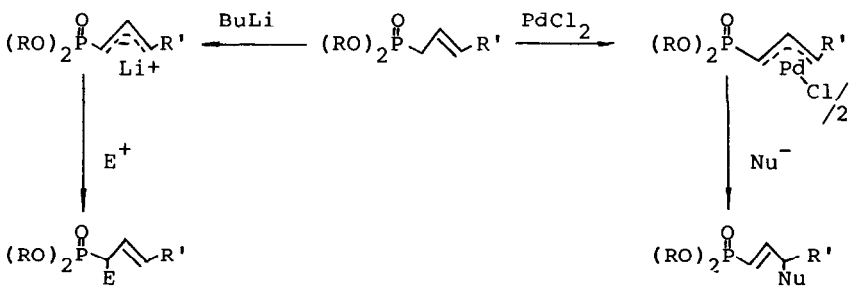
Abstract: Vinylic phosphonates with functional groups can be synthesized regioselectively by the reaction of acetoxy allylic phosphonates with soft carbon nucleophiles in the presence of bis(trimethylsilyl)acetamide (BSA) under palladium(0) catalysis with moderate to good yields.

Reactions of carbanions stablized by P=O bond with electrophiles are widely used in organic synthesis[1]. Allylic phosphonate anions could react with aldehydes and ketones to give dienes[2] and could be alkylated first with alkyl halides followed by reduction with $LiAlH_4$ to give olefins[3]. However, to the best of our knowledge, the reaction of allylic phosphonate cation, which would be rich in interesting chemistry, has not been reported.

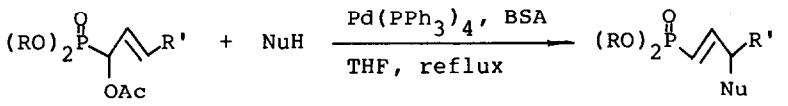
From the systematic study of the chemistry of π-allyl palladium complexes in our laboratory, it occurs to us that although the allylic phosphonate cation would be destablized by the P=O bond, the palladium complex would make it stable enough to exist. Therefore, dibutyl allylphosphonate was first tried to react with palladium chloride[4], the expected product O,O-dibutyl phosphonylated π-allyl palladium complex was formed.



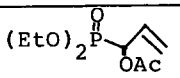
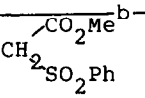
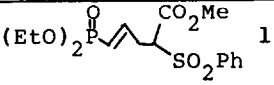
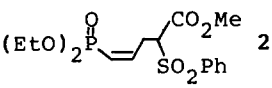
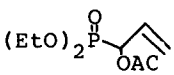
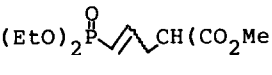
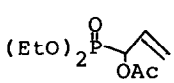
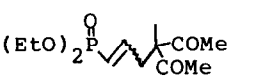
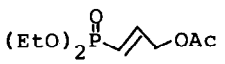
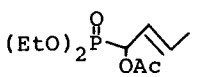
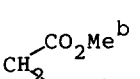
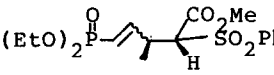
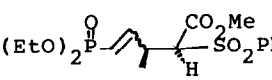
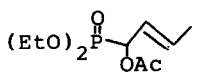
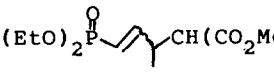
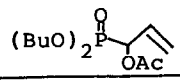
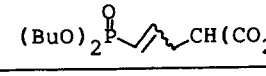
The phosphonylated π-allyl palladium complex could react smoothly with sodium dimethyl malonate in THF at mild condition to give γ-substituted vinylic phosphonate in 58% yield[5]. This interesting reaction may be considered as an umpolung in the reactivities of allylic phosphonates:



Owing to the fact that the acetoxy group is a good leaving group in palladium catalyzed reactions in allylic system, the α-acetoxy allylic phosphonate might be considered as the precusor of allylic phosphonate cation. Thus, α-acetoxy allylic phosphonates were tried to react with soft carbon nucleophiles under the catalysis of $Pd(PPh_3)_4$ in THF. It was found that α-acetoxy allylic phosphonates did react with nucleophiles such as malonate anion to give the vinylic phosphonate derivatives in moderate to good yields. α-Acetoxy allylic phosphonates are easily available from the reaction of O,O-dialkyl-O-trimethylsilyl phosphite with α,β-unsaturated aldehydes followed by hydrolysis and acetylation[6]. Therefore, this novel reaction provides a convenient way to prepare the functionalized vinylic phosphonates which are difficult to prepare. The results are shown in the Table.



Table

Entry	Reactant	Nucleophile	Time	Product[a]		Isolated yield(%)
1		 [b]	10		1(60)	76[c]
					2(40)	
2		$CH_2(CO_2Me)_2$	6		3	61
3		$MeCH(COMe)_2$	11		4	59
4		$CH_2(CO_2Me)_2$	7	3		43
5		 [b]	14		5(50)[d]	46
					6(50)[d]	
6		$CH_2(CO_2Me)_2$	5		7	65
7		$CH_2(CO_2Me)_2$[e]	9		8	88

a: All compounds gave satisfactory ^1H NMR, IR, MS data[7].
b: Equivalent amount of nucleophile was used.
c: Calculated based on the consumed nucleophile.
d: Determined by ^1H NMR.
e: Four equivalents of $CH_2(CO_2Me)_2$ were used.

The general procedure is as follows: To a solution of nucleophile(2 mmol), BSA(2 mmol) and $Pd(PPh_3)_4$ (0.04 mmol) in THF(4 ml), dialkyl α-acetoxy allylic phosphonate(1 mmol) was added with a syringe under a prepurified nitrogen atmosphere. The solution was refluxed to the disappearance of dialkyl α-acetoxy allylic phosphonate as monitored by TLC. The crude product obtained after the removal of solvent was purified by column chromatography on silica gel(petroleum ether-ethyl acetate). The products were characterized by ^1H NMR, IR, MS and elemental analysis.

It can be seen from the Table that the soft carbon nucleophiles regioselectively attack the γ-position of the allylic phosphonate cations formed in the reaction to yield the vinylic phosphonate derivatives. The steric effect, the electronic effect and the conjugate effect between P=O bond and the double bond may play the important roles in the control of the regioselectivity, but the products contain a mixture of cis and trans isomers. From the reaction of α-acetoxy allylphosphonate with methyl phenyl sulfonylacetate, the cis and trans isomers were separated with a ratio of 2:3(entry 1), while from the reaction of α-acetoxy crotylphosphonate with methyl phenyl sulfonylacetate, a mixture of isomers with threo/erythro ratio of 1:1(entry 5) was obtained. The substituents on the phosphorus atom seem to have no significant effect to the reaction. The fact that the same product **3** was obtained from α-acetoxy allylphosphonate(entry 2) or γ-acetoxy allylphosphonate(entry 4) strongly indicates that the reaction proceeds through a π-allyl palladium complex intermediate.

Further applications of this reaction are being investigated in our laboratory.

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References and notes:

1. B. J. Walker, in "Organophosphorus Reagents in Organic Synthesis", ed. J. I. G. Cadogan, Academic Press, London, 1979, p.155.
2. G. Lavielle and G. Sturtz, Bull. Soc. Chim. France, 1970, 1369.
3. K. Kondo, A. Negishi and D. Tunemoto, Angew. Chem. Internat. Ed., 1974, **13** 407.
4. R. F. Heck, "Palladium Reagents in Organic Synthesis", Academic Press, New york, 1985.
5. J. Zhu and X. Lu, to be published.
6. T. Hata, A. Hashizume, M. Nakajima and M. Sekine, Tetrahedron Lett., 1978, 363.

7. **1**: M.p.: 104.5-105.5°C; IR(KCl): 1740(s,C=O), 1310(s,SO_2), 1235(s,P=O), 1145(s,SO_2), 1025(s,P-O-C); ^{1}H NMR($CDCl_3$, 200 MHz): 1.30(t,J=7 Hz,6H), 2.86-3.03(m,2H), 3.64(s,3H), 3.98-4.09(m,5H), 5.76(q-t,J=1 Hz,J=17 Hz, J_{P-H}=19 Hz,1H), 6.57(q-t,J=7 Hz,J=17 Hz,J_{P-H}=21 Hz,1H), 7.28-7.90(m,5H); MS: 391(M^++1), 390(M^+), 249, 217; calcd. for $C_{16}H_{23}O_7PS$: C, 49.23, H,5.94, P, 7.93, S, 8.21, found: C, 49.04, H, 5.98, P, 7.61, S, 8.38.

2: IR(neat): 1740(s,C=O), 1625(m,C=C), 1325(s,SO_2), 1250(s,P=O), 1150(s, SO_2), 1010(s,P-O-C); ^{1}H NMR($CDCl_3$, 200 MHz): 1.31(t,J=7 Hz,6H), 3.03-3.45 (m,2H),3.66(s,3H), 3.99-4.22(m,5H), 5.75(q-t,J=1 Hz,J=13 Hz,J_{P-H}=18 Hz, 1H) 6.43(q-t,J=7.5 Hz,J=13 Hz,J_{P-H}=51 Hz,1H),7.27-7.92(m,5H);MS: 391(M^++1), 390(M^+), 249, 217;calcd. exact mass for $C_{16}H_{23}O_7PS$:390.090, found: 390.091.

3: IR(neat): 1740-1755(s,br.,C=O), 1635(m,C=C), 1240(s,P=O), 1010(s,P-O-C); ^{1}H NMR($CDCl_3$, 60 MHz): 1.31(t,J=7 Hz,6H), 2.63-3.01(m,2H), 3.75(s,6H), 3.41 -4.31(m,5H),5.40-7.08(m,2H); MS: 309(M^++1), 308(M^+), 276, 249; calcd. exact mass for $C_{12}H_{21}O_7P$=308.103, found: 308.100.

4: IR(neat): 1695-1720(s,br.,C=O), 1630(m,C=C), 1245(s,P=O),1010(s,P-O-C); ^{1}H NMR($CDCl_3$, 60 MHz): 1.20(t,J=7 Hz,6H), 1.38(s,3H), 2.14(s,6H), 2.46-2.81 (m,2H), 3.74-4.33(m,4H), 5.34-6.98(m,2H); MS: 291(M^++1), 290(M^+), 247, 152; calcd. exact mass for $C_{13}H_{23}O_5P$:290.128, found: 290.129.

5,6: IR(neat): 1740(s,C=O), 1630(m,C=C), 1325(s,SO_2), 1245(s,P=O), 1150(s, SO_2), 1010(s,P-O-C); ^{1}H NMR($CDCl_3$, 60 MHz): 1.09-1.51(m,9H), 2.91-3.42(m, 1H), 3.47(s,1.5H), 3.56(s,1.5H), 3.77-4.37(m,5H), 5.39-7.35(m,2H), 7.45 -8.04(m,5H); MS: 405(M^++1), 404(M^+), 263, 231; calcd. exact mass for $C_{17}H_{25}O_7PS$: 404.108, found: 404.110.

7: IR(neat): 1740-1755(s,br.,C=O), 1635(m,C=C), 1250(s,P=O),1010(s,P-O-C); ^{1}H NMR($CDCl_3$, 60 MHz): 1.19(t,J=6 Hz,6H), 1.36(d,J=7 Hz,3H), 2.71-3.22(m, 1H), 3.31-4.31(m,5H), 3.69(s,3H), 3.73(s,3H), 5.36-7.12(m,2H); MS:323 (M^++1), 322(M^+), 263, 258; calcd. exact mass for $C_{13}H_{23}O_7P$: 322.118,found: 322.120.

8: IR(neat): 1740-1755(s,br.,C=O), 1630(m,C=C), 1240(s,P=O), 1020(s,P-O-C); ^{1}H NMR($CDCl_3$, 60 MHz): 0.80-1.78(m,14H), 2.77-3.18(m,2H), 3.29-4.10(m,5H), 3.70(s,6H), 5.20-7.19(m,2H); MS: 365(M^++1), 364(M^+), 333, 305, 277, 252, 219, 193; calcd. exact mass for $C_{16}H_{29}O_7P$: 364.165, found: 364.167.

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