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The Synthesis of δ-Hydroxy Allylic Phosphine Oxides by Palladium(II)-Catalysed Allylic Transposition

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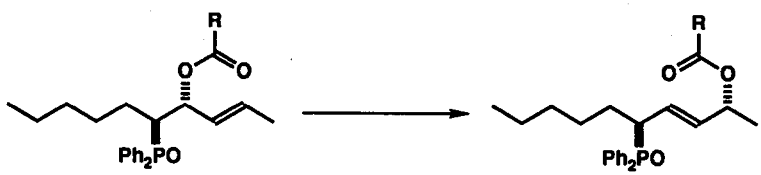
Abstract: *Palladium(II)-catalysed rearrangement of allylic acetates 5, which contain a diphenylphosphinoyl group, yields transposed acetates 6 in good yield. The reaction is mild, general for most substitution patterns, and stereospecific. The transposed acetates 6 may be hydrolysed to δ-hydroxy allylic phosphine oxides 4.*

δ-Hydroxy allylic phosphine oxides are useful intermediates in, for example, the stereocontrolled synthesis of dienols,[1,2] trienols,[3] and of β-hydroxy sulphides.[4] Currently we are making use of them as starting materials for enantio- and diastereoselective epoxidations.[5] Our published methods are a stereorandom acid-catalysed allylic transposition of an allylic acetate **1**[1] or a stereospecific thermal rearrangement of a *p*-nitrobenzoate **2**,[6] but these are quite unsuitable for our present work. Both proceed through cationic transition states, and the high temperatures or acidic conditions of the reactions lead to extensive formation of diene by-products. Moreover, unless there are substituents on the allylic system, no rearrangement is observed.



(1) R = Me Ac$_2$O, TsOH, AcOH *E* only, 65:35, *anti:syn*

(2) R = *p*-NO$_2$C$_6$H$_4$ PhCN, 180 °C *E* only, >95:5, *anti:syn*

We have now found that it is possible to transpose allylic acetates **5** under mild conditions (20 °C in THF) and in high yield without elimination using palladium(II) catalysis.[7,8] The reaction is stereospecific,[9] succeeds for a wide range of substitution patterns, and opens up new possibilities in the efficient use of allylic phosphine oxides in synthesis.

The starting materials are allylic alcohols **3** from the addition of lithium derivatives of phosphine oxides to unsaturated aldehydes. The aldehyde adducts **3** were acetylated under basic conditions to give **5**,[10] rearranged with $Pd(MeCN)_2Cl_2$,[11] and the transposed acetates **6** hydrolysed to give allylic alcohols **4** (Route A). For comparison, the same allylic alcohols **5** were also rearranged under our standard acid-catalysed conditions[1,2] and hydrolysed (Route B). Table 1 shows some results with R^1 = H for easy comparison.

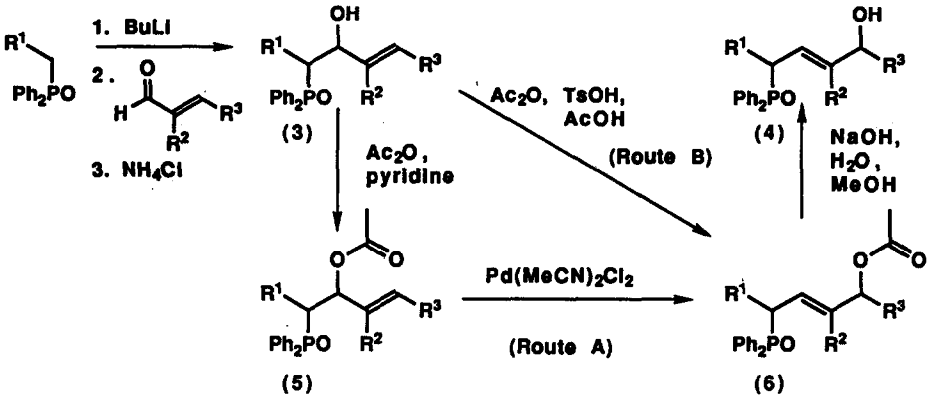


Table 1. Synthesis of Allylically Transposed Alcohols (6)

Entry	R^1	R^2	R^3	Yields (%): 3	$3 \rightarrow 5$	$5 \rightarrow 6$	$6 \rightarrow 4$	Route A $3 \rightarrow 4$	Route B $3 \rightarrow 4$
a	H	H	H	60	80	76	85	52	0[a,b]
b	H	H	Me	76	98	87	71, 99[c]	84	53
c	H	H	*n*-Pr	71	98	75	69	51	47
d	H	Me	Me	81	88	7[d]	—	0	60

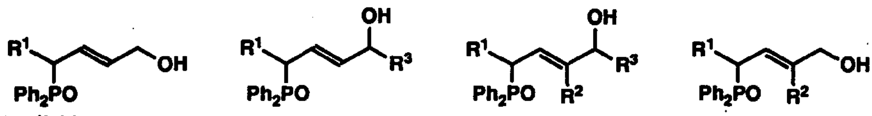
[a]1.25 eq. TsOH at 60 °C for 43 h. [b]<10% rearranged acetate **8** in crude mixture before hydrolysis; remainder unrearranged acetate **7** (by NMR). [c]hydrolysed in 1% HCl/MeOH. [d]% in crude product; remainder starting material **5** (by NMR).

The acid catalysed route fails if R^3 = H (entry **a**) because the cationic intermediate **7** requires substitution for stability.[1,2] Substitution solely at R^2 (type IV) is insufficient because of the node in the middle of an allyl cation LUMO. Allylic alcohols of types I and IV are therefore unavailable by this route. The palladium-catalysed route, on the other hand, succeeds for the two most important series of compounds for Sharpless epoxidation,[5] type I (entry **a**) and type II (entries **b** and **c**) with unbranched carbon chains. It fails, however, for compounds of types III and IV, where $R^2 \neq$ H (entry **d**),[12] presumably due to a blocking steric interaction between palladium and R^2 in the intermediate[13] **8**.

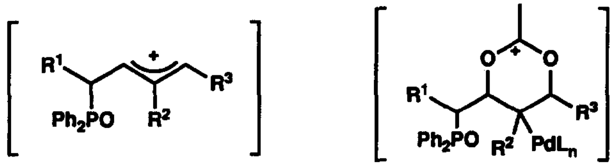
The geometry of the resulting double bonds is controlled by the steric effect of the Ph_2PO group. Some tri-substituted double bonds are formed as mixtures of geometrical isomers by method B,[1,2] but all the products from either method reported in this letter are formed solely with the *E* configuration. Indeed, the palladium catalysed route is *E*-selective whenever it is successful.

The Ph_2PO group must also be providing the driving force for the rearrangements. Most reported high yielding palladium(II)-catalysed ester rearrangements involve either the creation of a trisubstituted double bond from a monosubstituted one or a shift of the double bond into conjugation.[8,12] However, we have observed good yields even when both unrearranged and rearranged alkenes have equal numbers of substituents (entries **b** and **c**).[9,14] Presumably, as with the acid-catalysed rearrangements,[1,2] this is a steric effect. It remains to explore the question of stereochemical control in the rearrangement of single diastereoiomers of **3** to give *E* allylic alcohols for Sharpless epoxidation,[5] since the acid catalysed route is known to give mixtures of diastereomers.[1,2]

Type I | Type II | Type III | Type IV

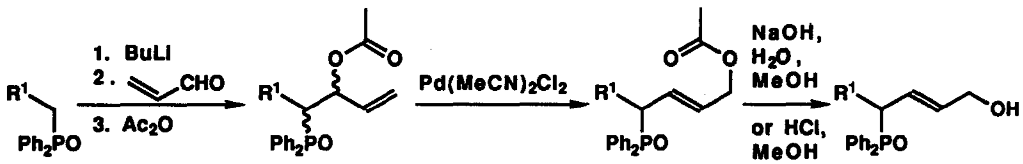


Available by route: A only | A or B | B only | Neither



(7) (8)

The palladium-catalysed rearrangement was first used to synthesise the previously unavailable type I δ-hydroxy allylic phosphine oxides **11** (Table 2). Two chiral centres in the starting material become one in the product, and both diastereoisomers of the acrolein adducts **9** rearrange to the same *E*-allyl acetate **10**. Basic hydrolysis of **10a** and of similar compounds without a branch β to phosphorus gave poor yields of allylic alcohols **11**, while hydrolysis with 2% HCl/MeOH gave consistently good results. These products **11** exhibited a remarkable kinetic resolution under Sharpless epoxidation conditions.[5]



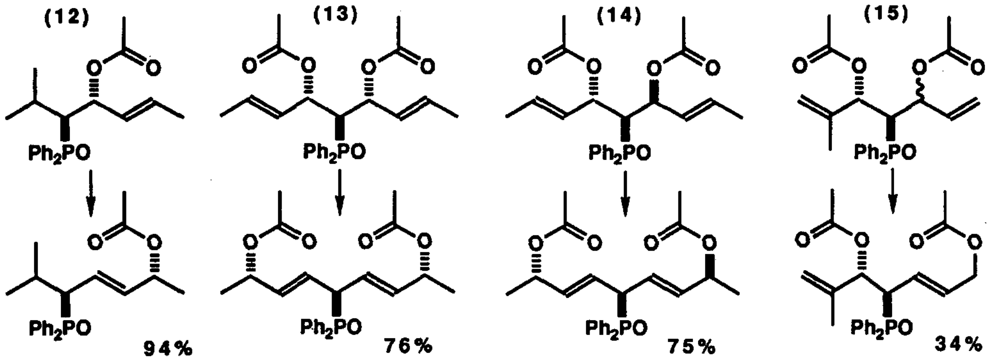
(9) (10) (11)

Table 2

entry	R^1	yield **9** (%) (*anti*:*syn*)	yield **10** (%)	yield **11** (%)
a	Me	70 (85:15)	65[a]	64[b]
b	*i*-Pr	58 (65:35)	84[c]	91[d]
c	cyclohexyl	52 (69:31)	60[a]	76[b]

[a]5-10 mol% $Pd(MeCN)_2Cl_2$, THF, reflux, 3-4 h. [b]hydrolysed with 2% HCl/MeOH. [c]5 mol% $Pd(MeCN)_2Cl_2$, THF, r.t., 78 h. [d]hydrolysed with NaOH, H_2O, MeOH

In addition to being *E*-selective in a two dimensional sense, the rearrangement is totally stereospecific in a three dimensional sense. Single rearrangement of **12** and double rearrangement of **13** and **14** with Pd(II) gave in each case a single diastereoisomer resulting from *supra*facial acetate transfer regardless of the stereochemistry of the starting material. Acid-catalysed rearrangement of compounds similar to **12** (such as **1**) gives mixtures of diastereomers, while the stereospecific *p*-nitrobenzoate rearrangement requires vigorous conditions and leads to elimination.[6] The chemoselectivity of the reaction was exploited in the rearrangement of **15**, in which only the allylic acetate without a β-substituent underwent rearrangement.



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10. Attempted acetylation of tertiary alcohols (from addition to enones) under basic conditions returned only starting material. Such alcohols have however been rearranged successfully by our acid-catalysed route.[1,2]
11. Typical procedure for rearrangement with $Pd(MeCN)_2Cl_2$: A 0.1 mol dm^{-3} solution of the allylic acetate in dry THF was stirred with 5-10 mol% $Pd(MeCN)_2Cl_2$ (Aldrich Chemical Company) under nitrogen at room temperature for 2-48 hours. Unsubstituted compounds such as **4a**, **9** and **15** required longer reaction times, but these could be shortened by refluxing in THF for 2-3 hours.
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