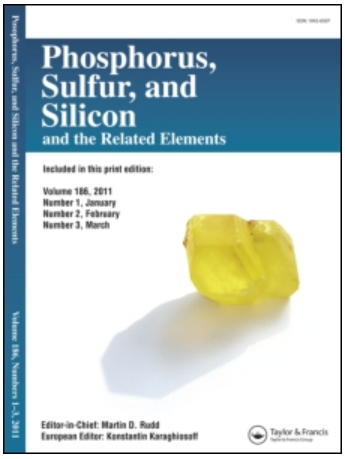

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A DIASTEREOSELECTIVE PALLADIUM-CATALYZED ACETOXYLATION OF RACEMIC ALLYL PHOSPHORUS COMPOUNDS

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The palladium-catalyzed acetoxylation of chiral racemic allyl phosphorus compounds **1** and **2** occurs diastereoselectively, showing that the presence of a chiral moiety on phosphorus can influence the stereochemical course of the reaction. Although the yield obtained from **1** is very low, the use of **2** leads to a 50% diastereomeric excess and 86% yield.

Keywords: Palladium-catalyzed acetoxylation; chiral allyl phosphorus compounds; allylic acetates; diastereoselectivity; dialkyl 3-acetoxy-1-alkenyl phosphonates

The palladium-catalyzed acetoxylation of alkenes is a useful and straightforward method for the preparation of allylic acetates[1] which have become important synthetic intermediates[2]. Therefore, an enantio-or diastereoselective version of this reaction would be a valuable tool in organic synthesis. Successful results in the enantioselective acetoxylation of cyclic olefins have been described with several chiral copper complexes and hydroperoxides or peresters as reoxidants[3]. However, the use of palladium salts in combination with benzoquinone and manganese dioxide in acetic acid has been much less studied : thus, Nicholas[4] obtained low enantiomeric excess for the acetoxylation of cyclohexene with chiral palladium complexes. On the other hand, the use of chiral acids[5] also gave unsatisfactory results.

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We have already reported the palladium-catalyzed acetoxylation of dialkyl allyl phosphonates[6] and the application of the products for the synthesis of biologically active phosphono amino acids[7], whose chirality is determinant for their activity. Therefore, with the aim of preparing chiral dialkyl (3-acetoxy 1-alkenyl) phosphonates, we felt that the use of chiral allyl phosphorus compounds would lead to successful diastereoselective acetoxylation. This study was also dictated by the fact that the presence of the phosphoryl group allows facile introduction of chirality.

We report herein the first results in this area through the palladium-catalyzed acetoxylation of racemic compounds **1** and **2** with benzoquinone and manganese dioxide in acetic acid, which enables assessment for asymmetric induction in this reaction.

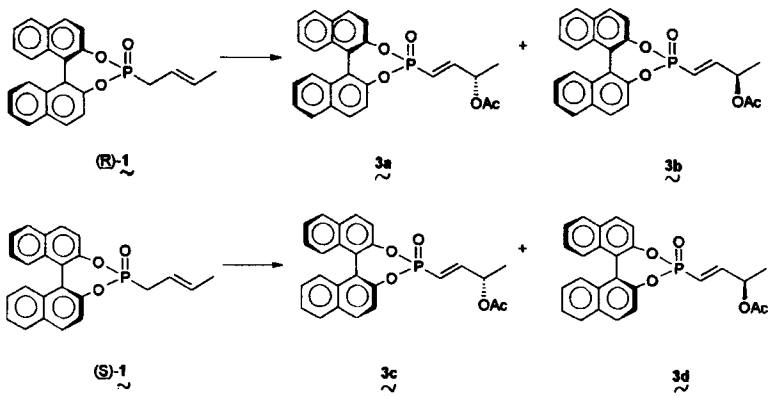
Acetoxylation of 1

The performance of a diastereoselective reaction can be assessed through the use of a racemic substrate provided that an efficient method for the measurement of the diastereomers produced can be found. Starting from a racemic allylic phosphonate, the acetoxylation products will also be racemic, but the ratio of diastereomers will be equal to the diastereomeric excess (d.e.) obtained with an enantiomerically pure substrate[8].

Thus, the use of racemic **1** in the acetoxylation reaction can lead to four compounds **3a, 3b, 3c**, and **3d** (Scheme 1), which are actually two pairs of enantiomers, **(3a/3d)** and **(3b/3c)**. Diastereomers **3a** and **3b** are obtained from (*R*)-**1** and (*S*)-**1** leads to **3c** and **3d**. If we assume that acetoxylation of (*R*)-**1** and (*S*)-**1** occurs in opposite sense but with the same d.e., the **3a+3d** : **3b+3c** ratio is the same as the diastereomer ratio obtained with only (*R*)-**1** or (*S*)-**1** as starting material.

Racemic **1** was prepared from binaphthol and crotyl phosphonic dichloride[9] and subjected to the acetoxylation reaction under various conditions.

No conversion was obtained in the presence of 5% of palladium acetate even on prolonged heating (65°C, 90 hours), and **1** was recovered only in very low amounts, indicating extensive decomposition. The same results were obtained at higher temperature (90°C, 75 hours). Finally, an increase of the amount of catalyst to 30% led to a low conversion (9%) after heating to 70°C for 30 hours. In this case, the expected 3-acetoxy-1-butenyl phosphonates **3** were isolated in 5% yield after flash chromatography. ^{31}P



SCHEME 1

NMR analysis showed the presence of two partially resolved signals ($\delta = 25.80$ ppm and $\delta = 25.95$ ppm) which can be attributed to the two pairs of enantiomers **(3a+3d)** and **(3b+3c)**, as expected. These compounds were obtained only as *E* isomers as shown by careful examination of the $^3J_{PH}$ and $^3J_{HH}$ coupling constants and comparison with published data[6].

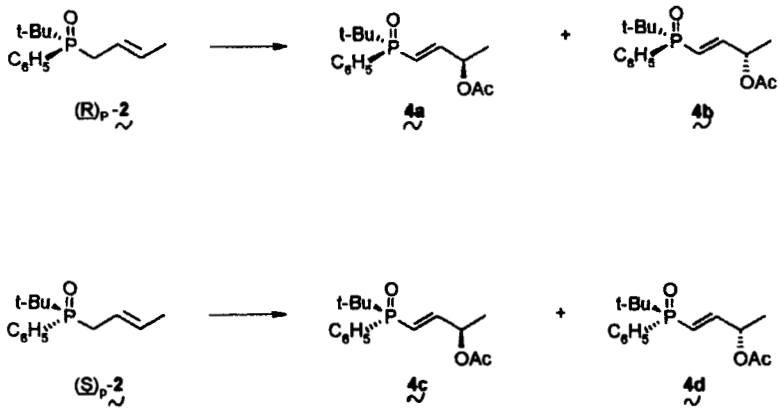
The relative amount of these diastereomers was evaluated by integration of the two ^{31}P NMR signals, and showed *ca* 19% d.e. for the reaction. However, in view of the very low conversion obtained together with the high amounts of palladium acetate needed, we did not pursue the study with this substrate.

Acetoxylation of 2

Several reports have shown that **2** is a useful substrate for Michael addition with α,β–unsaturated ketones[10]. We expected that its use in the acetoxylation reaction would give better results than **1** since the chiral center is closer to the double bond.

Racemic **2** was prepared through a Michaelis-becker reaction from *tert*-butylphenylphosphine oxide[11] and subjected to the standard acetoxylation conditions (5% $Pd(OAc)_2$, 20% benzoquinone, 125% MnO_2, HOAc, 65°C). After 25 hours, ^{31}P NMR analysis of the crude product

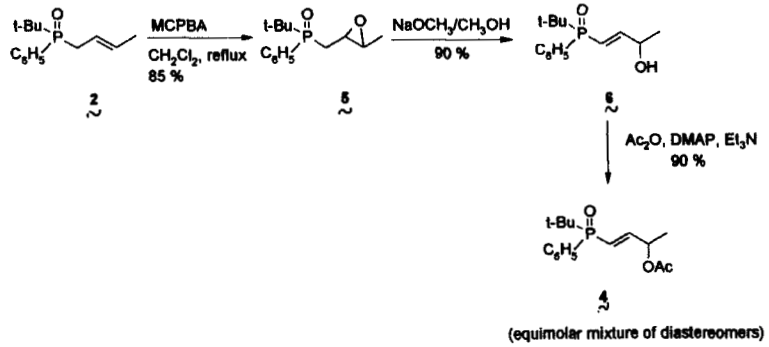
showed that all starting material was consumed and revealed the presence of two signals, attributed to the two pairs of enantiomers **4a+4d** and **4b+4c** (δ = 36.7 ppm, and δ = 36.9 ppm).



SCHEME 2

The diastereomeric excess, measured by ^{31}P NMR of the crude mixture was 50% (determined as for the **3a-3d** mixture), whereas the chemical yield of pure products was 86%. Again, ^{1}H NMR analysis showed the exclusive formation of the *E* isomers.

To confirm these results, we prepared the diastereomeric mixture by a different route, as depicted in scheme 3.



SCHEME 3

Thus, **2** was treated with metachloroperbenzoic acid (MCPBA) in refluxing dichloromethane to provide the epoxide **5** as an equimolar mixture of diastereomers. Reaction of this mixture with sodium methoxide in methanol[12] yielded (*E*)-*tert*-Butyl(3-hydroxy-1-butenyl)phenyl phosphine oxide **6**, which was acetylated to provide an equimolar mixture of diastereomers **4**. ^{1}H and ^{31}P NMR showed the presence of the same signals as those obtained from the crude product of acetoxylation of **2**.

Having established the nature of the acetoxylation products, we carried out the reaction at different temperatures. The results are collected in table I.

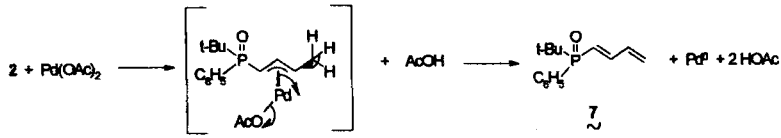
TABLE I Effect of temperature on the catalytic acetoxylation of **2**

Entry	*Temperature (°C)*	*D.e. (%)*[a]	*Time (h)*	*Conversion(%)*[a]	*Yield (%)*[b]
1	65	50	25	100	86
2	50	50	35	98	85
3	35	51	65	90	80
4	80	48	18	100	55[c]

a: Determined by ^{31}P NMR analysis of the crude product. b: Of pure product. c: The elimination product **7** is formed to the extent of 30%

These experiments clearly show that the temperature does not influence the d.e. (always close to 50%), but has an effect on the conversion and yield. Thus, the reaction rate decreases slightly on switching the temperature from 65°C to 50°C, but the yield is not significantly modified (entries 1 and 2). However, a further decrease to 35°C (entry 3) leads to an incomplete reaction, and the conversion does not exceed 90% even on prolonged reaction. On the other hand, the reaction performed at 80°C occurs with 100% conversion, but the yield is only 55% (entry 4). In this case, a by-product was isolated (up to 30%), later identified as the dienyl phosphine oxide **7** (scheme 4).

Thus, the conditions listed in entry 1 of table I are those under which the reaction gives optimized results in terms of diastereoselectivity, yield and reaction time.



SCHEME 4

Although the formation of **7** remains unclear, it can be explained if we assume that the reaction proceeds through a (π-allyl)palladium complex. This assumption has already been put forward to explain the stereoselectivity of the palladium-catalyzed acetoxylation of allylic phosphonates[6]. This complex would lead to **7** through elimination, as depicted in scheme 4 with the acetate anion acting as a base.

In conclusion, although the present study has been conducted with racemic substrates, it clearly shows that the catalytic acetoxylation of allylic phosphonates or allylic phosphine oxides using the $Pd(OAc)_2$/benzoquinone/MnO_2 system in acetic acid can be diastereoselective through the presence of a chiral organophosphorus group. This constitutes the first successful diastereoselective palladium-catalyzed acetoxylation of functionnalized alkenes. The use of the cyclic phosphonate **1** prepared from binaphthol is unsatisfactory because of its extensive decomposition under the reaction conditions, and the low d.e. obtained. However, the influence of chirality on phosphorus (as in compound **2**) leads to appreciable diastereomeric excess, probably because of the closeness of the chiral moiety to the reaction center. From these results, we can now consider the use of more efficient substrates in an enantiomerically pure form, which should provide useful information on the diastereoselection mechanism.

Experimental

Compound **1** was prepared from binaphthol as already described[9]. ^1H NMR spectra were recorded in $CDCl_3$, on a Bruker AC 100 spectrometer at 100.00 MHz (the usual abbreviations are used: s : singulet, d : doublet, t : triplet, m: multiplet). Tetramethylsilane was used as internal standard.

^{31}P NMR spectra were recorded at 40.54 MHz, using 85% H_3PO_4 as external standard.

Acetoxylation of 1

A mixture of palladium acetate (43 mg, 0.19 mmol), benzoquinone (42 mg, 0.39 mmol) and MnO_2 (70 mg, 0.80 mmol) in acetic acid (2 mL) was heated to 65°C with stirring for 20 min. Then, **1** (245 mg, 0.64 mmol) was added as a solution in acetic acid (2 mL), and the whole was stirred at 65°C for 30 hours. After cooling to room temperature, ethyl acetate (10 mL) was added, and the mixture was filtered through a short plug of celite, which was rinsed with EtOAc (3×10 mL) The solvents were removed on a rotary evaporator and acetic acid was evaporated under high vacuum (60°C/0.05 mm Hg). ^{31}P NMR analysis of the crude showed a conversion of 9%. Flash chromatography afforded 70 mg (28% recovery) of starting material and 14 mg (5% yield) of acetoxylation product as a 60/40 mixture of diastereomers (m.p. 223°C). ^1H NMR (an asterisk denotes the signals corresponding to the minor isomer): 1.36 (d, $C\underline{H}_3CH$, $^3J_{HH}$=6.9 Hz); 2.10 (s, CH_3C=O); 5.45 (m, CHOC=O); 5.86 (ddd, PC$\underline{H}$=CH, $^2J_{PH}$=23.5 Hz, $^3J_{HH}$=17.2 Hz, $^4J_{HH}$=1.7 Hz); 5.87* (ddd, PC$\underline{H}$=CH, $^2J_{PH}$=22.3 Hz, $^3J_{HH}$=17.2 Hz, $^4J_{HH}$=1.7 Hz); 6.92 (ddd, PCH=C$\underline{H}$, $^3J_{PH}$=23.3 Hz, $^3J_{HH}$=17.2 Hz, $^3J_{HH}$=4.5 Hz); 6.93* (ddd, PCH=C$\underline{H}$, $^3J_{PH}$=23.4 Hz, $^3J_{HH}$=17.2 Hz, $^3J_{HH}$=4.5 Hz); 7.2–7.8 (m, Ar). ^{31}P NMR: 25.80 and 25.95*.

(2-Butenyl)-*tert*-butyl-phenyl phosphine oxide **2** was prepared by the following procedure: In a 25 mL flask, sodium hydride (295 mg of a 60% slurry ; 7.4 mmol) was washed twice with dry pentane, suspended in THF (5 mL), and cooled with an ice bath. A solution of *tert*-butyl-phenyl phosphine oxide[11] (1.28 g; 7 mmol) in THF (5 mL) was added dropwise with stirring, and the mixture was stirred at room temperature until no more hydrogen was evolved (1 hour). After cooling to 0°C, a solution of crotyl bromide (1.05 g, 8 mmol) in THF (2 mL) was added dropwise, and the mixture was stirred at room temperature for 2 hours. Water (5 mL) was added, and THF was removed *in vacuo*. The remaining liquid was extracted with ether (3×10 mL), dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The residue was Kugelrhor distilled (130°C, 0.05 Torr, air bath temperature) to provide a colorless liquid which solidified upon standing at room temperature. There was obtained 1.08 g (67%)

of product as a white solid, m.p. 66°C. ^{1}H NMR: 1.25 (d, CH_3C, $^3J_{PH}$= 14.5 Hz); 1.62 (m, $C\underline{H}_3CH$,); 2.95 (dd, CH_2, $^2J_{PH}$=21.5, $^3J_{HH}$= 7.3 Hz); 5.30–5.75 (m, CH=CH); 7.3–7.8 (m, Ar). ^{31}P NMR: 46.7.

Acetoxylation of 2.

The reaction was performed as for **1** from 21 mg of palladium acetate (0.094 mmol), 41 mg of benzoquinone (0.38 mmol), 215 mg of MnO_2 (2.44 mmol) and 450 mg of **2** (1.95 mmol) in 4 mL of acetic acid, and the mixture was stirred at 65°C for 25 hours. The crude product obtained after work up was Kugelrhor distilled (150°C, 0.05 Torr, air bath temperature) to yield 492 mg (86%) of the acetoxylation product as viscous colorless oil. ^{31}P NMR analysis of the crude showed that the compound was constituted by a 75 : 25 mixture of acetoxylation products **4a-4d**. These two pairs were separated by HPLC (silica column, eluent : ethyl acetate/methanol (95:5), flow rate :1.3 mL/mn, UV detection). Major diastereomer : ^{1}H NMR: 1.10 (d, CH_3C, $^3J_{PH}$= 15. 1 Hz); 1.36 (d, $C\underline{H}_3CH$, $^3J_{HH}$=6.6 Hz); 2.08 (s, CH_3C=O); 5.50 (m, CHOC=O); 6.45 (ddd, PCH=CH, $^2J_{PH}$=26.0 Hz, $^3J_{HH}$=17.0 Hz, $^4J_{HH}$=1.3 Hz); 6.79 (td, PCH=C$\underline{H}$, $^3J_{PH}$=17.0 Hz, $^3J_{HH}$=17.0 Hz, $^3J_{HH}$=4.6 Hz); 7.4–7.8 (m, Ar). ^{31}P NMR: 36.7.

Minor diastereomer : ^{1}H NMR: 1.11 (d, CH_3C, $^3J_{PH}$= 15. 1 Hz); 1.38 (d, $C\underline{H}_3CH$, $^3J_{HH}$=6.6 Hz); 2.11 (s, CH_3C=O); 5.50 (m, CHOC=O); 6.48 (ddd, PC$\underline{H}$=CH, $^2J_{PH}$=22.0 Hz, $^3J_{HH}$=17. 1 Hz, $^4J_{HH}$=1.2 Hz); 6.82 (td, PCH=C$\underline{H}$, $^3J_{PH}$=17. 1 Hz, $^3J_{HH}$=17. 1 Hz, $^3J_{HH}$=4.7 Hz); 7.4–7.8 (m, Ar). ^{31}P NMR: 36.9.

Tert-butyl-(2,3-epoxybutyl)-phenyl phosphine oxide **5**: To a solution of **2** (376 mg, 1.6 mmol) in dichloromethane (5 mL) was added dropwise a solution of 70% MCPBA (600 mg, 2.4 mmol) in dichloromethane (5 mL), and the mixture was refluxed for 6 hours. It was then cooled, diluted with dichloromethane (20 mL), and washed with 5% sodium carbonate (3 × 20 mL), brine (10 mL), and dried over $MgSO_4$. Filtration, removal of solvents, and flash chromatography (EtOAc/methanol, 90 :10) afforded **5** (343 mg) as a light yellow liquid in 85% yield. ^{1}H NMR: 1.10 (d, $C\underline{H}_3CH$, $^3J_{HH}$=5.9 Hz); 1.13 (d, CH_3C, $^3J_{PH}$= 15.0 Hz); 2.12–2.30 (m, CH_2); 2.50–3.74 (m, CHO); 7.4–7.8 (m, Ar). ^{31}P NMR: 45.8 and 46.0 (equimolar mixture of diastereomers).

Tert-butyl-(3-hydroxy-1-butenyl)-phenyl phosphine oxide **6**: A solution of **5** (270 mg, 1.07 mmol) in methanol (5 mL) was treated with a saturated solution of sodium methylate in methanol (a few drops), and stirred for one hour. The reaction was quenched by addition of Dowex (5 g), the mixture was filtered, and the solvent was removed *in vacuo*. The residue was further purified by flash chromatography (ethyl acetate/methanol, 80:20) to furnish **6** (244 mg, 90%) as a light yellow oil. ^{1}H NMR: 1.12 (d, CH_3C, $^3J_{PH}$= 15.1 Hz); 1.30 (d, $C\underline{H}_3CH$, $^3J_{HH}$=6.7 Hz); 4.20–4.35 (m, CHO); 4.50 (s, OH); 6.20–6.45 (m, PCH=CH); 6.70–6.95 (m, PCH=C$\underline{H}$); 7.4–7.8 (m, Ar). ^{31}P NMR: 39.8 and 40.0 (equimolar mixture of diastereomers).

Acetylation of 6

A solution of **6** (240 mg, 1 mmol), triethylamine (0.4 mL, 2.5 mmol) and 4-(dimethylamino) pyridine (8 mg, 0.06 mmol) in dichloromethane (5 mL) was cooled to 0°C, and 0.1 mL of acetic anhydride (1.1 mmol) was added *via* syringe. The mixture was then stirred at room temperature for two hours. It was then diluted with dichloromethane (20 mL), transferred to a separatory funnel, and washed with 5% sodium carbonate (2 × 15 mL), 5% HCl (2 × 15 mL), brine (2 × 10 mL), and finally dried over $MgSO_4$. The residue obtained after filtration and removal of solvents was subjected to flash chromatography (ethyl acetate/methanol, 90:10) to yield compound **4** (238 mg) as an equimolar mixture of the two diastereomers in 81% yield. ^{1}H and ^{31}P NMR data were identical with those obtained from **4** prepared by catalytic acetoxylation.

(1,3-butadienyl)-*tert*-butyl-phenyl phosphine oxide **7**: this compound was isolated as an oil during flash chromatography when acetoxylation of **2** was performed at 80°C. ^{1}H NMR: 1.13 (d, CH_3C, $^3J_{PH}$= 15.1 Hz); 5.50 (m, CH=C$\underline{H}_2$); 6.40 (ddd, PCH, $^2J_{PH}$=25.86 Hz, $^3J_{HH}$=16.82 Hz, $^4J_{HH}$=0.6 Hz); 6.50 (m, C$\underline{H}$=CH_2); 6.79 (td, PCH=C$\underline{H}$, $^3J_{PH}$=16.4 Hz, $^3J_{HH}$=16.8 Hz, $^3J_{HH}$=10.4 Hz); 7.4–7.8 (m, Ar).^{31}P NMR: 37.2.

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