SYNTHESIS OF ENANTIOMERICALLY PURE MONO-SUBSTITUTED 1,2λ^5-OXAPHOSPHOLANES. SYNTHESIS OF HOMOALLYLIC ALCOHOLS

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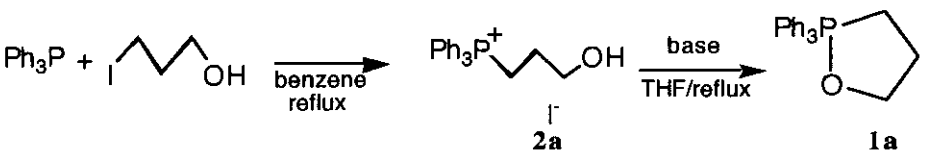
Abstract—Enantiomerically pure 5-monosubstituted 1,2λ^5-oxaphospholanes were synthesized by the reaction of sodium hydride with enantiomerically pure 3-hydroxyalkyltriphenylphosphonium salts. The reaction of 1,2λ^5-oxaphospholanes with aldehydes afforded *Z*-rich homoallylic alcohols in nearly quantitative yields. The *E*:*Z* ratio of the products was in the range of 11:89-34:66.

Wittig reaction is widely used for the olefin synthesis. Over the last 40 years, a large number of experimental and theoretical investigations have been achieved.[1] Synthesis of naturally occurring homoallylic alcohols is one of the important application of Wittig reaction.[2] High *E* stereoselectivity in the reaction of γ-oxido ylides can be induced by the method of Schlosser, which entails metalation of the Wittig intermediates.[3] *Z* stereoselectivity is maximized by polar aprotic solvents, exclusion of lithium salts, and low reaction temperatures.[4] However, relatively few reports have been made on the synthesis of homoallylic alcohols by the use of 1,2λ^5-oxaphospholanes (**1**) as substrates, which are isomers of γ-hydroxy ylides.[5] In 1967, Hands and Mercer reported the first isolation of a 1,2λ^5-oxaphospholane (**1a**) from 3-hydroxypropyltriphenylphosphonium iodide (**2a**) (Scheme 1).[6]



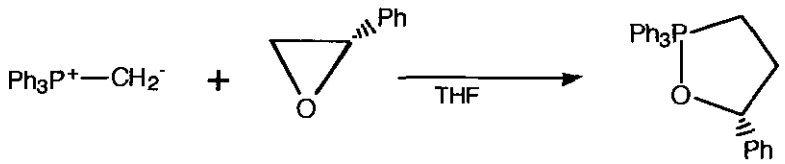
2a **1a**

Scheme 1

The reaction of **1a** with aldehyde generally affords the corresponding homoallylic alcohols (**3**) in good yields.[6] Surprisingly, there is no report on the synthesis of enantiomerically pure monosubstituted oxaphospholanes. These results prompted us to investigate the possibility of the synthesis of

enantiomerically pure monosubstituted 1,2λ^5-oxaphospholanes (**1**). We report herein a general synthesis, several reactions of optically active **1**, and their synthetic application to homoallylic alcohols.

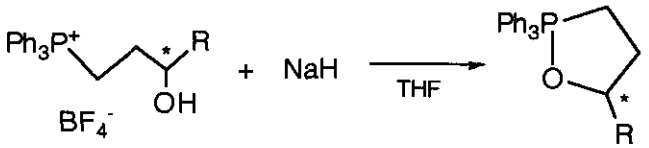
Recently, Bestmann *et al.* have shown that racemic **1** was prepared by the reaction of methylenetriphenylphosphorane with epoxides.[7] We applied this method for the synthesis of enantiomerically pure **1**. The reaction of methylenetriphenylphosphorane with (*R*)-(+)-styrene oxide (>97% ee) gave enantiomerically pure (*R*)-(–)-2,2,2,5-tetraphenyl-1,2λ^5-oxaphospholane (**1b**) in only 35% yield (Scheme 2).



(*R*)-(+) styrene oxide (*R*)-(–)-**1b**: Yield; 35%, $[\alpha]_D^{20}$ -91.1° (>97% ee)

Scheme 2

We then tried the preparation of **1** by the reaction of enantiomerically pure 3-hydroxyalkyltriphenylphosphonium salts with bases. Enantiomerically pure 3-hydroxyalkyltriphenylphosphonium salts (**2**) were prepared by optical resolution of the corresponding dibenzoyl tartrates (DBT) as described in a previous paper.[8] After extensive variation of experimental conditions, enantiomerically pure **1** has been successfully prepared by the action of sodium hydride with optically active 3-hydroxyalkyltriphenylphosphonium salts, **2** (Scheme 3, Table 1).



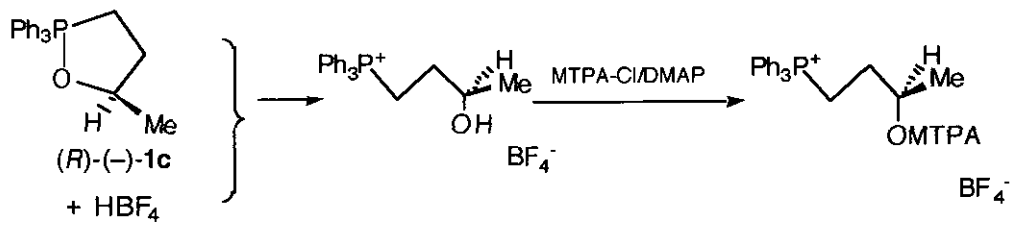
2 **1c**: R=Me **1d**: R=Et

Scheme 3

Table 1. Synthesis of 1 from Enantiomerically Pure 2

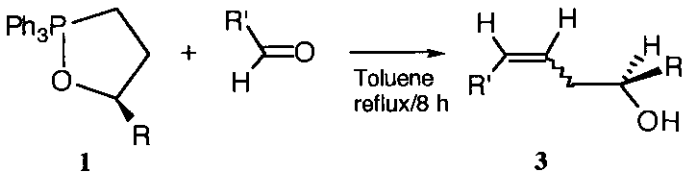
2	R	Conditions Solvent	Temp.	1,2λ^5-Oxaphospholane **1**	Yield/%	$[\alpha]_D^{20}$
(*R*)-(+)-**2b**	Me	THF	reflux	(*R*)-(–)-**1c** R=Me	53	–121.4° (c 2.0, $CHCl_3$)
(*R*)-(+)-**2b**	Me	THF	rt	(*R*)-(–)-**1c** R=Me	72	–121.4° (c 2.0, $CHCl_3$)
(*S*)-(–)-**2b**	Me	THF	rt	(*S*)-(+)-**1c** R=Me	71	+119.8° (c 2.0, $CHCl_3$)
(*R*)-(+)-**2c**	Et	THF	rt	(*R*)-(–)-**1d** R=Et	72	–98.6° (c 1.5, $CHCl_3$)

When the reaction was carried out at room temperature, **1c** and **1d** were obtained in better yields than the refluxing conditions. Enantiomeric excess of **1** was determined by ^{1}H NMR measurement of MTPA esters of **2**, after the reaction with fluoroboric acid, followed by conversion of the 3-hydroxyalkylphosphonium salts obtained into their MTPA esters and the ee's of **1** were found to be >98% (Scheme 4).



Scheme 4

The reactions of optically pure **1** with carbonyl compounds were then carried out. Hands and Mercer reported that the reaction of **1a** with benzaldehyde at 90°C without any solvent afforded 4-phenyl-3-buten-1-ol in 67% yield (*E*:*Z*=58:42).[6] We modified this method to the reaction with aldehydes by using toluene as a solvent. When the reaction was carried out in refluxing toluene, *Z*-rich **3** was obtained in nearly quantitative yields. The *E*:*Z* ratio of the products was in the range of 11:89-34:66 (Scheme 5, Table 2).



Scheme 5

Table 2. Synthesis of Enantiomerically Pure Homoallylic Alcohols

1	Aldehyde		Homoallylic Alcohol[a]			
	R	R'	3	Yield/%	*E*:*Z*	$[\alpha]_D^{20}$
(*R*)-(–)-**1c**	Me	Ph	(*R*)-(–)-**3a**	95	30:70	Z: –39.5°
(*R*)-(–)-**1b**	Ph	Pr	(*S*)-(–)-**3b**	97	11:89	Z: –36.8°
(*R*)-(–)-**1b**	Ph	Ph	(*S*)-(–)-**3c**	97	33:67	Z: –18.4°
(*R*)-(–)-**1c**	Me	PhCH=CH	(*R*)-(–)-**3d**	95	34:66	Z: –17.5°

a) When butyllithium was added in the present reaction, *E*-rich homoallylic alcohols were obtained.

The *E*:*Z* ratio was determined by their ^{1}H NMR spectra. The fact that no racemization had occurred during this reaction was ascertained by comparison of the products with authentic homoallylic alcohols. The stereoselectivity of **3** is different from that of the result of Hands and Mercer, which might be due to the solvent effect and slightly different reaction temperature. Previously, many researchers have studied the stereochemistry of olefins prepared by Wittig reaction. Kawashima *et al.* isolated pentacoordinate 1,2-oxaphosphetane drivetives, which were heated around 100°C to give the corresponding olefins. They concluded that the second step proceeds *via* a concerted mechanism.[9] Schlosser *et al.* reported that salt free oxide ylides react with aldehyde to afford *Z*-olefins preferentially.[4] Maryanoff *et al.* also described the reaction of 2-, 3-, and 4-hydroxyalkylphosphonium salts with bases followed by the addition of aldehydes.[5] They observed *Z* stereoselectivity in the reaction of 3-hydroxypropyltriphenylphosphonium bromide with sodium hydride followed by the addition of aldehydes (benzaldehyde and hexanal) in refluxing THF for 15 h. They also found that the *E* stereoselectivity increased by the addition of **2** with

aromatic aldehydes in the presence of bases, and it decreased by using aliphatic aldehydes. The present result is similar to theirs. The *Z* stereoselectivity was increased by using aliphatic aldehydes.

Optically active **3** was formerly prepared by Wittig rearrangement of the corresponding allyl silyl ether,[10] by Wittig reaction of 3-hydroxyalkylphosphonium salts,[8] or by a diastereoselective addition of allyltrimethylsilane to proline ketones.[11] The present result provides a new method on the preparation of enantiomerically pure **3**.

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EXPERIMENTAL

Material: Optically active 3-hydroxybutyl- and 3-hydroxypentyltriphenylphosphonium tetrafluoroborates were prepared by the method described before.[8] Optically active (*R*)-(+)-styrene oxide (98%, >97% ee $[\alpha]_D$ +33°) was purchased from Aldrich.

Direct Preparation of (*R*)-(–)-2,2,2,5-tetraphenyl-1,2λ^5-oxaphospholane (1b)

To a solution of methyltriphenylphosphonium bromide (1.78 g, 5 mmol) in THF (25 mL) was added a solution of sodium bis(trimethylsilyl)amide (6.0 mL, 6 mmol, 1.0 M solution in THF) at rt. After stirring for 3 min, the resulting orange solution was cooled to -78°C and (*R*)-(+)-styrene oxide (0.60 g, 5 mmol) in THF (10 mL) was added to this solution. After stirring for 2 h at –78°C, the reaction mixture was warmed up to rt. After standing for 6 h, the reaction mixture was filtered and evaporated to give colorless crystals, which was recrystallized from hexane to give colorless crystals of (*R*)-(–)-**1b** (0.693 g, 35%). $[\alpha]_D^{20}$ –91.1° (c 1.3, $CHCl_3$); mp 142-143°C (racemic; lit.,[8] mp 143-144°C); ^{1}H NMR (C_6D_6) δ=1.56 (m, 1H, C<u>H</u>H), 2.05 (m, 1H, CH<u>H</u>), 2.31 (m, 1H, C<u>H</u>H), 2.71 (m, 1H, CH<u>H</u>), 4.28 (dd, *J*=4.8 and 10.0 Hz, CH), 6.88-7.50 (m, 20H, Ph). ^{13}C NMR (C_6D_6) δ=29.89 (d, $J_{P\text{-}C}$=93.3 Hz, CH_2), 33.16 (CH_2), 71.45 (CH), 125.67, 126.61, 127.50, 127.61, 127.76, 127.81, 127.90, 128.25, 131.85, 146.89 (Ar).

Synthesis of (*R*)-(–)-5-Methyl-2,2,2-triphenyl-1,2λ^5-oxaphospholane (1c)

To a suspension of sodium hydride (0.80 g, 60% mineral oil dispersion, 20 mmol) in THF (150 mL) was added a solution of *R*-(+)-3-hydroxybutyltriphenyl phosphonium tetrafluoroborate (**2b**, 9.3 g, 20 mmol) in THF (50 mL) at rt. After refluxing for 3 h, the reaction mixture was filtered and the filtrate was evaporated to give a pale yellow solid, which was recrystallized from methanol-ether to afford colorless crystals of *R*-(–)-**1c** (3.54 g, 53%). $[\alpha]_D^{20}$ –121.4° (c 2.0, $CHCl_3$); mp 110-111°C: ^{1}H NMR (C_6D_6) δ=1.09 (d, 3H, *J*=5.9 Hz, CH_3), 1.17-1.29 (m, 1H, C<u>H</u>H), 1.62-1.79 (m, 1H, CH<u>H</u>), 2.11-2.22 (m, 1H, PC<u>H</u>H), 2.63-2.73 (m, 1H, PCH<u>H</u>), 3.27 (septet, 1H, *J* =5.1 Hz, CH), 6.98-7.07 (m, 9H, Ar),7.42-7.47 (m, 6H, Ar). ^{13}C NMR (C_6D_6) 23.27 (d, $J_{P\text{-}C}$=5.5 Hz, CH_3), 30.34 (d, $J_{P\text{-}C}$=91.9 Hz, PCH_2), 32.13 (CH_2), 64.69 ($J_{P\text{-}C}$=5.5 Hz, CH), 127.38, 127.49, 127.65, 131.86, 131.93 (Ar). Anal. Calcd for $C_{22}H_{23}OP$; C, 79.02; H, 6.93. Found. C, 79.46; H, 7.16.

Oxaphospholane (**1d**) was prepared in a similar manner by using sodium hydride (0.40g, 60% mineral oil dispersion, 10.0 mmol) in THF (100 mL) and 3-hydroxypentyltriphenylphosphonium tetrafluoroborate **2c** (4.05 g, 9.3 mmol). **1d**: colorless crystals, {*R*-(–), 2.33 g, 72%}. $[\alpha]_D^{20}$ –98.6° (c 1.5, $CHCl_3$); mp 122-123 °C; ^{1}H NMR (C_6D_6) δ=0.78 (t, *J*=7.6 Hz, 3H, CH_3), 1.21-1.40 (m, 2H, C<u>H</u>H and

CHHCH$_3$), 1.45-1.55 (m, 1H, CHHCH$_3$), 1.64-1.79 (m, 1H, CHH), 2.14-2.26 (m, 1H, PCHH), 2.63-2.78 (m, 1H, PCHH), 3.05-3.12 (m, 1H, CH), 6.98-7.07 (m, 1H, Ar), 7.43-7.48 (m, 6H, Ar). ^{13}C NMR (C_6D_6) δ=10.02 (CH_3), 29.39 (CH_2), 29.86 (d, J_{P-C}=93.8 Hz, PCH_2), 30.61 (d, J_{P-C}=5.5 Hz, CH_2CH_3), 70.08 (d, J_{P-C}=3.7 Hz, CH), 127.36, 127.47, 126.63, 131.95 (Ar). Anal. Calcd for $C_{23}H_{25}OP$; C, 79.29; H, 7.23. Found C, 79.27; H, 7.06.

Reaction of (*R*)-(–)-2,2,2,5-Tetraphenyl-1,2λ^5-oxaphospholane (1b) with Butyraldehyde

To a solution of oxaphospholane {(*R*)-(–)-**1b**} (0.46 g, 1.0 mmol) in toluene (5 mL) was added a solution of butyraldehyde (0.072 g, 1.0 mmol) in toluene (1 mL) at rt. After refluxing for 8 h, the reaction mixture was evaporated to give a pale yellow oil, which was extracted with hexane (10 mL x 3). The combined extracts were evaporated to give a pale yellow oil, which was chromatographed over silica gel by elution with dichloromethane-hexane (1:1) to give a mixture of *E*- and *Z*-1-phenyl-3-heptenols (**3b**, 0.20 g, 0.97 mmol, 97%, *E*/*Z*=11/89). HPLC (silica gel) separation gave the corresponding *Z*-isomer of (*S*)-(–)-**3b** (0.11 g, 53%). Enantiomeric excess of (–)-**3b** was determined by its MTPA ester; ee>97%. $[\alpha]_D^{20}$ –36.8° (c 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ=0.85 (t, *J*=7.3 Hz, 3H, CH_3), 1.25-1.42 (m, 2H, CH_3CH_2), 1.95-2.05 (m, 2H, CH_2CH=CH), 2.42-2.63 (m, 3H, CH_2CHPh, OH), 4.65-4.72 (t, *J*=7.9 Hz, 1H, CH_2CHPh), 5.35-5.45 (m, 1H, CH=CH), 5.52-5.60 (m, 1H, CH=CH), 7.22-7.30, 7.31-7.40 (m, 5H, Ph).^{13}C NMR ($CDCl_3$) δ=13.7 (CH_3), 22.7 (CH_2), 29.4 (CH_2), 37.3 (CH_2), 73.9 (CH), 124.8 (CH=CH), 125.9, 127.5, 128.4 (Ph), 133.6 (CH=CH), 144.1 (Ph). Found: m/z 190.1262. Calcd for $C_{13}H_{18}O$: M, 190.1357.

Other reactions were carried out in a similar manner.

(*R*)-(–)-5-phenyl-4-penten-2-ol (**3a**): (*Z* form) $[\alpha]_D^{20}$ –39.5° (c 1.80, CCl_4) {lit.,[8] $[\alpha]_D$ -39.7° (c 2.20, CCl_4)}. Enantiomeric excess of *Z*-(–)-**3a** was determined by its MTPA ester; ee>97%. (E form) $[\alpha]_D^{20}$ –33.7° (c 1.17, CCl_4) {lit.,[8] $[\alpha]_D$ -34.3° (c 0.80, CCl_4)}. Enantiomeric excess of *E*-(–)-**3a** was determined by its MTPA ester; ee>97%. Spectral data of *E*- and *Z*-**3a** are identical with the reported one.[8]

(*S*)-(–)-1,4-Diphenyl-3-buten-1-ol (**3c**): (*Z* form) $[\alpha]_D^{20}$ –18.4° (c 0.15, $CHCl_3$) Enantiomeric excess of (–)-**3c** was determined by using chiral HPLC (CHIRAL CELL OD); ee>97%. ^{1}H NMR ($CDCl_3$) δ=1.98 (s, 1H, OH), 2,75 (m, 1H, CHH), 2.88 (m, 1H, CHH), 4.81 (m, 1H, PhCH), 5.72 (dt, J=7.0 and 11.6 Hz, 1H, CH=), 6.57 (d, 1H, *J*=11.6 Hz, PhCH=), 7.20-7.38 (m, 10 H, Ph). Found: m/z 224.1178. Calcd for $C_{16}H_{16}O$: M, 224.1201.

(*R*)-(–)-7-phenyl-4,6-heptadien-2-ol (**3d**): (*Z* form) $[\alpha]_D^{20}$ –17.5° (c 0.90, CCl_4) {lit.,[8] $[\alpha]_D$ –17.3° (c 3.77, CCl_4)}. Enantiomeric excess of (*R*)-(–)-**3d** was determined by its MTPA ester; ee>97%. Spectral data of *Z*-**3d** are identical with the reported one.[8]

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