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2-Hydroxyalkyl Diphenylphosphines: Biocatalytic Resolution and Use as Ligands for Transition-metal Catalysts

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Abstract· Kinetic resolution of 2-hydroxyalkyldiphenylphosphines **1** by acylation with isopropenyl acetate was carried out under rabbit gastric lipase (RGL) catalysis to give optically active **1** and the corresponding acetate, the enantioselectivity factors E ranging from 10 to 20

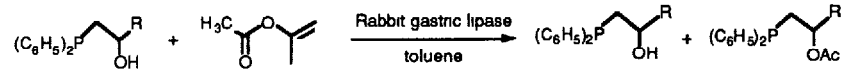
Chelating biphosphines are among the most widely used optically active ligands in asymmetric transition-metal catalyzed organic reactions [1] In some of these reactions the presence of a functional group in the phosphine has been reported to be of some benefit as long as the enantioselectivity is concerned Introduction of a hydroxyl group in the bis-(diphenylphosphino)-ferrocenyl ligand brought about a high enantioselectivity in the Pd-catalyzed alkylation[2] or amination[3] of allylic acetates and in the Rh-catalyzed hydrogenation of aminoketones or pyruvic acid [4] Gold-catalyzed asymmetric aldol reaction required the participation of the terminal amino group in the chiral ferrocenylaminephosphine ligands [5]

Monophosphine ligands have been less useful in transition-metal catalysis [1] However, optically active monophosphines have been shown to be efficient chiral inductors (up to 80%ee) in Ziegler-Natta type nickel complexes for the hydrovinylation reaction (codimerization between ethylene and cycloocta-1,3-diene or norbornene) [6] In palladium-catalyzed coupling of allyl acetates and phenylzinc chloride, monophosphines showed higher reactivity and enantioselectivity than chelating diphosphines [7] In nickel-catalyzed cross-coupling reactions between (2-methyl-1-naphthyl)magnesium bromide and 1-naphthyl bromide a ferrocenylphosphine with a methoxy group gave the coupling product with 83% ee, whereas the same ligand but lacking the alkoxy group showed only 1% ee [8]

We want to describe a general route to enantiomerically enriched 2-hydroxyphosphines These monophosphines may serve either as functional ligands for transition metal-catalyzed reactions or as synthons to prepare further functionalized phosphines or diphosphines

Successful lipase-catalyzed enantioselective preparations of many hydroxylated organic compounds have been carried out through either acylation of the OH group or hydrolysis of an ester derivative [9] Unless a great variety of chiral alcohols have been resolved through such procedures, no optically active hydroxyphosphine has been obtained in such way

We report the preparation of optically active β-hydroxyphosphines **1** and the corresponding enantiomeric acetates **2** through lipase-catalyzed acylation of racemic **1** with isopropenyl acetate in toluene As enzymatic catalyst, we selected the rabbit gastric lipase (RGL)[10] the use of which in organic synthesis has never been described till now

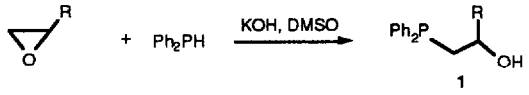


racemic 1 — optically active-1 — optically active-2

a R = CH_3 d R = -i-C_3H_7 g R = $-CH_2-O-CH_3$
b R = $-C_2H_5$ e R = $-C_6H_5$
c R = -n C_3H_7 f R = $-CH_2-Ph$

enantioselectivity factor E 10-20

Racemic substrates **1** were prepared in good yield according to a slightly modified Kabachnik procedure,[11] involving regioselective ring opening of the suitable epoxide by $(C_6H_5)_2PH$ / KOH in DMSO Racemic epoxides were either commercially available (giving access to **1a, 1b, 1e, 1f, 1g**) or prepared *via* the bromhydrin obtained through hydrobromination of the corresponding alkene (and used to reach **1c, 1d**) [12]



1

Table
Rabbit Gastric Lipase catalyzed Resolution of **1**[a)]

Racemic hydroxy-phosphine **1**	Reaction time (h)	Conversion[b)] (%)	Recovered[c)] substrate ee(%)	Ester[e)] produced ee(%)	E value[f)]
1a	1 5	56	88[d)]	69	16± 5
1b	3 5	38	47	76	12 ± 2
1c	8	44	66	84	20 ± 3
1d	8 days	44	- g)	- g)	
1e	6	0			
1f	36	0			
1g	26	51	80	77	18 ± 3

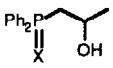
a) Experimental conditions see text
b) Determined by glc, by comparison with an internal standard
c) Determined from the $[\alpha]_D$ of the enantiomers obtained through successive resolutions until constant (< 1% variation) value $[\alpha]_D^{25}$ (c=2, AcOEt) **1a** - 7 2 ± 0 3°, **1b** + 9 8 ± 0 3°, **1c** + 3 9 ± 0 2°, **1g** + 8 5 ± 0 3°
d) Determined by ^1H NMR and HPLC measurement of the diastereomeric ratio of the urethane derivative made from (R)-(-)-1-(1-naphthyl)ethyl isocyanate,[14] and by ^1H NMR of the Mosher's esters [15] The two methods gave the same result
e) Determined on the alcohol obtained after saponification of the ester
f) Calculated from the conversion c and substrate's ee_S value, taking $E = \ln [(1- c) (1- ee_S)] / \ln [(1- c) (1+ ee_S)]$ [16] The reported value is the average of figures recorded from at least two different c values
g) Not determined

A typical procedure for the resolution is as follows to a solution of racemic hydroxyphosphine (1 mmol) in dry toluene (0 8 mL) and isopropenyl acetate (200 μL, 2 eq), placed under nitrogen or argon were added 0 25 g rabbit gastric lipase (RGL) [13] The resulting suspension was stirred (magnetic stirrer) and the reaction mixture was monitored by dilution of samples with toluene, filtration and analysis by glc to estimate the conversion When the desired conversion has been reached, the reaction mixture was filtered on a diatomaceous earth plug, washed with ethyl acetate or toluene Unreacted starting material **1** and acetate **2** were isolated in yields usually over 90% by column chromatography (SiO_2, hexane/AcOEt 80/20 as eluent) Results are collected in the table and indicate that the size of the R group controls the rate of reaction Neither lengthening of the R chain (going from Me to n-Pr) nor replacement of a CH_2 group by an oxygen atom (CH_2-O-CH_3 instead of n-Pr CH_2-CH_2-CH_3) did modify noticeably the reactivity or the enantioselectivity No acylation however was recorded for R= Ph or Ph-CH_2

Acylation may be conducted either in toluene or in neat isopropenyl acetate, without significant variation in the recorded enantioselectivity Minor amounts (usually < 5%) of phosphine oxides were produced during the acylation Running the kinetic resolution on a higher scale allowed a better mixing and hence a better enantioselectivity starting from 10 mmol **1a** (10 mL toluene, 2 mL isopropenyl acetate, ‡2 5 g RGL) afforded at 56% conversion, after purification, 1 05 g (43%) of (-)-**1a** (98%ee) The configuration of the more reactive enantiomer **1a** has been shown to be R, by correlation with the (S)-(-)-hydroxyphosphine obtained through ring opening of the commercial (S)-(-)-epoxy propane according to Kabachnik's procedure

Experiments carried out on **1a** with various acylating agents show the following sequence for acylation rate isopropenyl acetate ~ vinyl acetate > vinyl valerate >> ethyl acetate The stereoselectivity displayed by isopropenyl acetate is higher than vinyl valerate

Substitution of the phosphorus atom in phosphines by a P=O or P=S group has a deleterious effect on the reactivity a 50% conversion in 2 7 h was recorded for acylation of **1a** with isopropenyl acetate while 10 h were required to reach 48% conversion of **3a** into the corresponding acetate, no acylation was detected after 4 h exposure of **3b** to the same reaction conditions



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a X = O

b X = S

Pig pancreatic lipase and lipases from *Candida cylindracea* and *Pseudomonas fluorescens* showed a much lower activity in acylation of **1a** We are currently investigating the scope of RGL, a new comer in the area of lipases, as catalyst for asymmetric transformation

Use of chiral β-hydroxyphosphines **1** as ligands in transition-metal complexes, and evaluation of the catalytic activity and enantioselectivity of these complexes in organic transformations are under current investigation As an encouraging example, ketopantoylactone was fully (>99%) converted by hydrogenation to pantolactone (65%ee) using as catalytic system ([RhCl(COD)]$_2$ + 4 equiv (S)-(-)-**1a** (98%ee)) in a molar ratio Rh / substrate =2x10^{-2}, in THF, at 20°C and 40 atm H_2 (initial pressure) for 20 h

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