Tetrahedron: Asymmetry Vol. 1, No. 10, pp. 737-742, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Preparation of 2-Hydroxy-1,2-Diphenylethyl Phenylphosphinate: a Chiral Reagent for Asymmetric Reduction of Ketones

Remi Chauvin

Massachusetts Institute of Technology, Department of Chemistry, 77 Massachusetts Avenue, Cambridge, M.A. 02139, U.S.A.

(*Received* 31 *August* 1990)

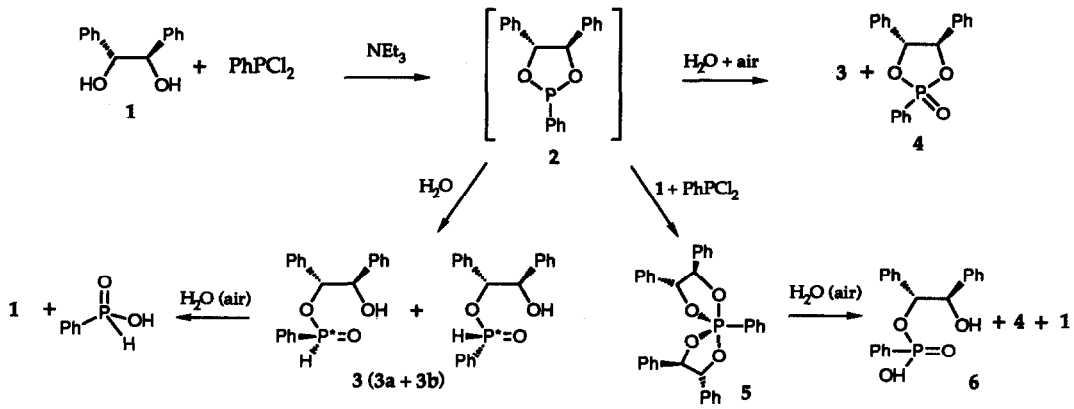
Abstract. *2-hydroxy-1,2-diphenylethyl phenylphosphinate has been prepared in 85% yield and 84% d.e. at the phosphorus atom from (R,R)-hydrobenzoin, and has been found to reduce electron-deficient ketones under mild conditions in up to 95% yield and 43% e.e.*

Hydrogen-P^V compounds HP(O)XY (X,Y=alkyl or alkoxide) are chemically and configurationally stable.[1] Tautomerism with the corresponding P^{III} acids HO-PXY makes them useful nucleophilic and reducing reagents.[2] In particular, hydrogen phosphinates have been widely used in asymmetric synthesis.[3] We report here a diastereoselective preparation of the β-hydroxyalkyl-hydrogenphosphinate **3** from *(R,R)*-hydrobenzoin **1**, and an unprecedented asymmetric reaction of this compound with ketones.

Preparation 2-hydroxy-1,2-diphenylethyl phenylphosphinate 3.

Cyclic phosphonites of chiral 1,4-diols were characterized and used in asymmetric Arbuzov reactions.[4] By contrast, cyclic phosphonites of 1,2-diols undergo facile oxidation, hydrolysis, and polymerization.[5] Reaction of *(R,R)*-hydrobenzoin with dichlorophenylphosphine followed by work-up in air does not yield 2-hydroxy-1,2-diphenylethylen phenylphosphonite **2**,[6] but the two diastereoisomers of 2-hydroxy-1,2-diphenylethyl phenylphosphinate **3** and the cyclic phosphonate **4**. If the reaction is performed under an inert atmosphere, and if water is added, **3** is afforded quantitatively (Scheme 1). In toluene or deuterochloroform some oxidation (probably due to $PhPCl_2$) was observed, providing by-products **5** and **6**. Compound **3** is stable towards oxidation, but must be stored under an inert atmosphere in order to prevent hydrolysis in the solid state by moist air (Scheme 1).[7]

It is noteworthy that under similar conditions, 1,1,2-triphenyl-1,2-ethanediol and PCl_3 have been reported to provide the β-hydroxyalkyl-phosphonate $Ph_2COHCHPh-OPO_2H$ without a stereogenic phosphorus atom.[8]

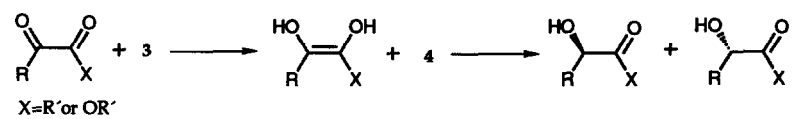


Scheme 1. Formation of 2-hydroxy-1,2-diphenylethylen phenylphosphonite 2, and its reactions with water and oxidizing agents.

At 25°C with water at pH=7, the reaction requires several hours, and the final d.e. does not exceed 20% (after 6 hours, a 50:50 **3a**:**3b** mixture is crystallized in 70% yield). The exchange $HP(O)Ph(OR)+HO(CH_2)_nOH \rightleftarrows HP(O)Ph(O(CH_2)_nOH)+ROH$ has been used to prepare other β-hydroxyalkyl-phosphinates,[9] and should be enhanced in an intramolecular process: the epimerization **3a** ⇄ **3b** can be evidenced by NMR (a $CDCl_3$ solution of 100% pure **3a** leads to a 50:50 **3a**:**3b** mixture in less than 48 hours at 25°C). However, in the presence of a THF–soluble acid, the reaction can be completed in 85% yield and 84% d.e. (**3a**:**3b**=92:8) in two hours between –78 and 0°C. One crystallization affords the pure epimer **3a**, which configuration has not been unambigously assigned so far.

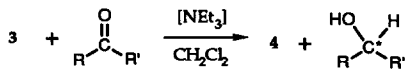
Reaction of 2-hydroxy-1,2-diphenylethyl phenylphosphinate with ketones.

We found that **3** reacts with electron-deficient ketones in the presence of triethylamine, giving the corresponding alcohols and the phosphonate **4** (Table). Trifluoroacetophenone is quickly reduced. 1,2–Diketones and 2–ketoesters react as well, but acetophenone and ethylacetoacetate do not. 4-Nitroacetophenone does not yield the alcohol, but it is slowly reduced at 40°C to the nitroso dimer, possibly through a photochemical catalysis by ambient light.[10]



Scheme 2. Possible enediol intermediate in the reduction of 1,2-dicarbonyl compounds by **3**, resulting in poor asymmetric induction.

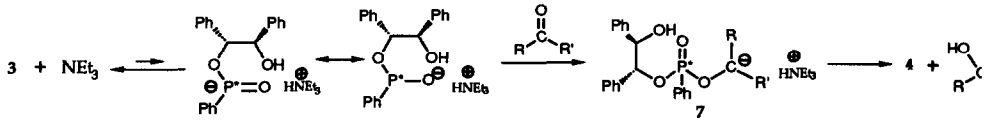
Enolizable trifluoromethyl ketones like $CF_3COCH_2CO_2Et$ or CF_3COCH_2COPh react very slowly with pure **3a**, giving racemic alcohols. By contrast, the reaction of trifluoroacetophenone with the 50:50 mixture **3a**:**3b** affords the (+)-alcohol in 21% e.e. Starting from the pure epimer **3a**, the e.e. in (+)-alcohol is improved to 43%, but no improvement is achieved with the 50:50 mixture performing the reaction at 0°C. 1,2–Diketones and 2–ketoesters are reduced in poor optical yields. This can be explained by a 1,4–hydrogen transfer to the 1,2–dicarbonyl compound, followed by a tautomeric transformation of the enediol intermediate to the α–hydroxycarbonyl compound far from the chiral center (Scheme 2).



Ketone	3a:3b	T(°C)	Time(h)	Product	Yield[a](%)	e.e.[b](%)
PhCOCOPh	50:50	25	2	PhCHOHCOPh	57	1(R)
$PhCOCO_2Me$	50:50	25	2	$PhCHOHCO_2Me$	80	0
"	100:0	25	2	"	90	7(R)
$MeCOCO_2Et$	100:0	25	1	$MeCHOHCO_2Et$	74	2(S)
" [c]	38:62	25	1	"	79	7(R)
$PhCOCF_3$	100:0	25	2	$PhCHOHCF_3$	95	43(S)
"	50:50	25	2	"	95	21(S)
"	50:50	0	6	"	71	19(S)
$4\text{-}NO_2C_6H_4COMe$	50:50	40	5	$[4\text{-}NOC_6H_4COMe]_2$	28	–

Table. Reaction of **3** in various diastereoisomeric ratios **3a**:**3b** with ketones in the presence of 0.2 equivalent of triethylamine. **a)** Products are purified by distillation or by preparative TLC. **b)** Enantiomeric excess are measured from optical rotation by comparison to known $[\alpha]_{Dmax}$ values,[11] except for ethyl lactate, for which the e.e. is accurately determined from G.C. analysis of the Mosher ester (complete disappearance of the starting alcohol being checked on the G.C. spectrum).[12] **c)** 1.2 equivalents of triethylamine were used.

Reaction of hydrogen–P^V compounds with aldehydes and ketones generally proceeds through nuc attack of the tautomeric P^{III} atom to the carbonyl carbon atom.[2,3,13] Since no P–C bond is formed her $O{=}P^{-}{\rightarrow}C{=}O$ attack is ruled out. On the other hand, either a $P{-}O^{-}{\rightarrow}C{=}O$ attack follow rearrangement,[13] or a direct $O{=}P^{-}{\rightarrow}O{=}C$ attack, would result in the intermediate **7**, which is stab electron–withdrawing substituents (R=CF_3, CO_2R'', COR''). Analogous intermediates could be envi the reaction of trialkylphosphites with electron-deficient ketones.[14] Moreover, structure **7** is closely r the postulated intermediate in the reaction of trifluoroacetophenone with hydridotetraaminophosphora therefore proposed as intermediate before intramolecular asymmetric protonation (Scheme 3 framework of this mechanism, the reduction does not involve any hydride transfer.



Scheme 3. Proposed intermediates in the reaction of **3** with ketones in the presence of triethylamine.

Since optically pure hydrobenzoin is afforded by dihydroxylation of *trans*-stilbene,[16] 2-hydrc diphenylethyl phenylphosphinate is a readily available chiral reagent. Therefore the scope of t procedure for asymmetric reduction of ketones deserves to be investigated further: reduction of non– ketones at higher temperature or in the presence of a Lewis acid and a proton sponge could be examin

Experimental.

(R,R)-hydrobenzoin **1** was prepared according to the procedure described in reference [16]. NMR spec recorded in $CDCl_3$ solution: at 300 MHz for ^1H (chemical shifts relative to TMS as internal standarc MHz for ^{13}C (chemical shifts relative to TMS: $\delta(CDCl_3)$=77.20 ppm), at 101 MHz for ^{31}P (chemic relative to 85% H_3PO_4 as external standard). IR spectra were recorded in KBr pelets using a Fourier tr infrared spectrometer.

2-hydroxy-1,2-diphenylethyl phenylphosphinates 3a and 3b. 0.535 g (2.5 mmol) of (+)-(*R,R*)-hydrc **1** and 0.70 mL (5 mmol) of triethylamine are dissolved in 20 mL THF under argon. A solution of 0.34 mmol) of $PhPCl_2$ in 10 mL THF is added dropwise at 25°C with stirring. After 10 minutes, the susp cooled to –78°C. 0.46 mL of 2N aqueous HCl in 8 mL THF is added dropwise. The temperature is al rise to 0°C over a 2 hour period. The solvent is removed under reduced pressure, and the white analysed immediately by NMR: 85% yield of **3a+3b**, with **3a** in 84% d.e.

The crude product is dissolved in CH_2Cl_2, and extracted with 1N aqueous HCl. The organic phase is separated and dried over $MgSO_4$. One crystallization from CH_2Cl_2/ether, affords pure **3a**. Mp=170–171°C. $[\alpha]_D^{25}$=+27 (c=1; CH_2Cl_2). ^1H NMR: 3.35 ppm (1H, broad : OH), 4.97 ppm (1H, d, $^3J_{HH}$=8 Hz: CHOH), 5.23 ppm (1H, dd, $^3J_{HP}$=10 Hz: CHOP), 6.95–7.70 ppm (15 aromatic H), 7.68 ppm (1H, d, $^1J_{PH}$=586 Hz). ^{31}P NMR: +157 ppm (d, $^1J_{PH}$=585Hz). ^{13}C NMR: 78.2 ppm (s), 84.3 ppm (d, $^2J_{CP}$=7Hz), 127.5–139.2 ppm. IR: 499, 553, 691, 750, 942, 1014, 1068, 1127, ν(P=O)=1211, 1439, 1456, ν(P–H)=2409, 2863, 3031, ν(OH)=3234 cm^{-1}. NMR data of **3b**: ^1H NMR : 3.61ppm (1H broad), 4.94 ppm (1H,d, $^3J_{HH}$=8 Hz), 5.41 (1H, t, J=8 Hz), 7.57 ppm (1H, d, $^1J_{HP}$=560 Hz), 6.94-7.77 ppm; ^{31}P NMR : +155 ppm (d, $^1J_{PH}$=561Hz).

Characterization of by-products 5 and 6. If the reaction is performed at 25°C in toluene using neutral water, one of the products **5** can be purified on chromatography column and crystallized from hexane: mp 128-134°. $[\alpha]_D^{25}$=–10 (c=0.66; CH_2Cl_2); ^1H NMR: 4.44 ppm (2H, d, $^3J_{HH}$=9Hz), 4.95 ppm (2H, dd, $^3J_{HP}$=1 Hz), 6.98–7.61 ppm (23 H), 8.25 ppm (2H, m). ^{31}P NMR: +103.4 ppm. ^{13}C NMR: 79.93 ppm (d, $^2J_{CP}$=5Hz), 82.32 ppm (s), 127.39–137.99 ppm. IR: 697, 759, 800, 862, 887, 1015, 1036, 1118, 1210, 1456, 1497, 2903, 3036 cm^{-1}. Hydrolysis of **5** produces hydrobenzoin **1**, 2-hydroxy-1,2-diphenylethylen phenylphosphonate **4** (see below), and 2-hydroxy-1,2-diphenylethyl phenylphosphonic acid monoester **6**; spectral data of **6** : ^1H NMR: 4.89 ppm (1H, d, $^3J_{HH}$=8 Hz); 5.41 ppm (1H, t, $^3J_{HH}$=$^3J_{HP}$=8 Hz), 6.63 ppm (2H broad), 6.80–7.63 (15 H). ^{31}P NMR: +149.0 ppm. ^{13}C NMR: 78.64 ppm (s), 84.66 ppm (d, $^2J_{CP}$=6 Hz). IR: 503, 568, 697, 756, 985, 1209, 1238, 1438, 1455, 2908, 3026, 3061, 3461 cm^{-1}.

Procedure for asymmetric reduction of ketones by 3. 0.338 g (1 mmol) of **3a** and 0.03 mL of NEt_3 (0.2 mmol) are dissolved in 5 mL CH_2Cl_2 under argon. 0.14 mL (1 mmol) of trifluoroacetophenone is added. After 2 hours stirring at 25°C (G.C. monitoring), the solvent is removed. 1–Phenyl–2,2,2–trifluoroethanol is purified on preparative SiO_2-TLC plate or by distillation: 0.167 g, 95% yield; $[\alpha]_D^{25}$=+12.8 (c=1.5; $CHCl_3$), 43% e.e. The oxidation product **4** is purified on chromatography column and crystallized from CH_2Cl_2/ether: mp 139-141°C; $[\alpha]_D^{25}$=+47 (c=1; CH_2Cl_2); ^1H NMR : 5.40 ppm (1H, dd, $^3J_{HH}$=8Hz), 5.55 ppm (1H, d, $^3J_{HP}$=2Hz), 7.15–8.09 ppm (15 H). ^{31}P NMR: +162.4 ppm. ^{13}C NMR: 85.59 ppm + aromatic C. IR: 600, 697, 749, 887, 959, 995, 1005, 1133, 1256, 1441, 1456, 2923 cm^{-1}.

Acknowledgements.

I greatly thank Professor K.B. Sharpless for permitting me to achieve this project, with the support of the National Institute of Health (GM-28384). I am grateful to the Elf-Aquitaine company for financial support.

References and notes

1 W.B. Fanham, R.A. Lewis, R.K. Murray Jr., K. Mislow, *J. Am. Chem. Soc.* **1970**, *92* , 5808.

2 R. Engel, *Synthesis of Carbon–Phosphorus Bonds*, CRS Press, **1988**; Y. Xu, H. Wei, J. Xia, *Liebigs Ann. Chem.* **1988**, 1139; M. Tazaki, S. Nagahama, M. Takagi, *Chem. Lett.* **1988**, 1619; Purnamand, B.S. Batra, B.P. Pant, *Tetrahedron Lett.*, **1989**, *30*, 1687; F. Hammerschmidt, H. Völlenkle, *Liebigs Ann. Chem.* **1989**, 577. Thottathil, C.A. Przybyla, J.L. Moniot, *Tetrahedron Lett.* **1984**, *25*, 4737; Thottathil, D. E. Ryono, C.A. Przybyla, J.L. Moniot, R. Neubeck, *Tetrahedron Lett.* **1984**, *25*, 4741.

3 L.P. Reif, H.S. Aaron, *J. Am. Chem. Soc.* **1970**, *92*, 5275; W.B. Fanham, R.A. Lewis, R.K. Murray Jr., K. Mislow, *J. Am. Chem. Soc.* **1970**, *92*, 5809; G.R. Van den Berg, D.H.J.M. Platenburg, H.P. Benschop, *J. Chem. Soc. Chem. Commun.* **1971**, 606; L.J. Szafraniec, L.L. Szafraniec, H.S, Aaron, *J. Org. Chem.* **1982**, *47*, 1936; K.M. Pietrusiewicz, W. Wisniewski, M. Zablocka, *Tetrahedron*, **1989**, *45*, 337; Y. Xu, H. Wei, J. Zhang, G. Huang, *Tetrahedron Lett.* **1989**, *30*, 949.

4 T. Kato, K. Kobayashi, S. Masuda, M. Segi, T. Kakajima, S. Suga, *Chem. Letters*, **1987**, 1915.

5 T. Mukaiyama, T. Fujisawa, Y. Tamura, Y. Yokota, *J. Org. Chem.* **1964**, *29*, 2572. J.P. Dutasta, A. Grand, A.C. Guimaraes, J.B. Robert, *Tetrahedron*, **1979**, *35*, 197.

6 In anhydrous and degassed $CDCl_3$ solution, the assumed structure **2** can be observed by ^1H NMR in mixture with **5**: 4.87 and 4.95 ppm (2d, J=10 Hz).

7 The same observation was done with the phenyloxazaphospholidine of (-)-ephedrine, which is hydrolyzed twice by moist air in the solid state into (-)-ephedrinium phenylphosphinate (R. Chauvin, unpublished result).

8 B. Brodesser, M. Braun, *Phosphorus, Sulfur and Silicon* , **1989**, *44*, 217.

9 E.E. Nifant'ev, A.I. Zavalishina, I.V. Komlev, *Zh. Obshch. Khim.* **1967**, *37*, 2497 (C.A. **68** 87347u).

10 R.J. Sundberg, B.P. Das, R.H. Smith Jr., *J. Am. Chem. Soc.* **1969**, *91*, 658; W.C. Petersen, R.L. Letsinger, *Tetrahedron Lett.* **1971**, *24*, 2197.

11 P. Newman, *Optical Resolution Procedures for Chemical Compounds*, Vol. 3, **1984**, Optical Resolution Information Center, N.Y.

12 J.A. Dale, D.L. Dull, H.S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543.

13 Y. Vannoorenberghe, G. Buono, *J. Am. Chem. Soc.* **1990**, *112*, 6142.

14 F. Ramirez, S.B. Bathia, C.P. Smith, *Tetrahedron* **1967**, 23, 2067; F. Ramirez, A.V. Patwardan, H.J. Kugler, C.P. Smith, *J. Am. Chem. Soc.* **1967**, *89*, 6276; F. Ramirez, A.S Gulati, C.P. Smith, *J. Am. Chem. Soc.* **1967**, *89*, 6283; N. Weferling, R. Schmutzler, *Z. Naturforsh. B* , **1988**, *43*, 1524. See also: A. Bulpin, S. Masson, A. Sene, *Tetrahedron Lett.* **1990**, *31*, 1151, and references cited.

15 F. Bouvier, P. Vierling, J.M. Dupart, *Inorg. Chem.* **1988**, *27*, 1099.

16 E.N. Jacobsen, I. Markó, W.S. Mungall, G. Schröder, K.B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968 ; B.H. McKee, K.B. Sharpless, *Org. Synth.* , submitted for publication.