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Enzymatic Synthesis of Enantiopure Precursors of Chiral Bidentate and Tridentate Phosphorus Catalysts

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Abstract: The *Candida antarctica* lipase (CAL-B)-catalyzed acetylation of racemic 2-hydroxymethylphenyl(methyl)phenylphosphine oxide, performed in diethyl ether, led to kinetic resolution with an unusually high enantioselectivity ($E = 3000$). The CAL-B-mediated desymmetrization of prochiral bis(2-hydroxymethylphenyl)methylphosphine oxide gave, *via* its enantioselective monoacetylation, the corresponding monoacetate in 80% yield and with $ee > 98\%$. The latter transformation allowed us to efficiently transform the prochiral substrate into the enantiomerically pure product in one single step. In both cases the stereogenic or prostereogenic phosphorus atom and the reacting hydroxy oxygen are distant from each other by four bonds. The absolute configurations of all the products were determined by a chemical correlation and X-ray analysis. The products will be used as enantiopure substrates in the preparation of a variety of chiral organophosphorus ligands/catalysts for asymmetric synthesis.

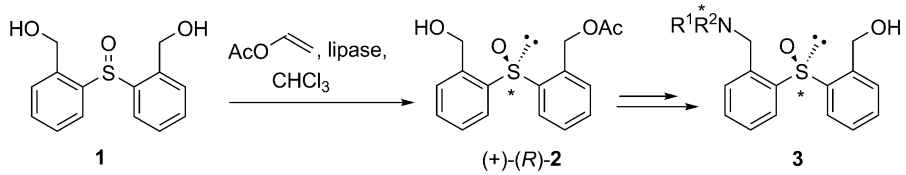
Keywords: biotransformations; configuration determination; desymmetrization; enzyme catalysis; kinetic resolution; phosphorus

Introduction

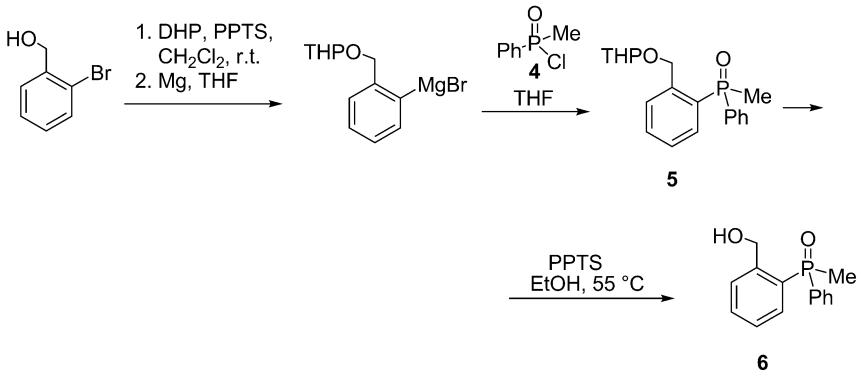
Racemic and prochiral organosulfur and organophosphorus compounds have proved to be good substrates for various types of enzymes and many useful transformations leading to non-racemic products have been described by us and others.[1a] In this way, enantiomerically enriched products were obtained, having a stereogenic centre located either on sulfur,[1b,c] phosphorus[1d] or on a carbon atom of an organic substituent.[1e]

These positive results prompted us to continue investigations on the use of biocatalysis in heteroatom chemistry. One of our long-term goals is to use enzymatic methodology in the synthesis of non-racemic heteroorganic derivatives having a desired structure and serving desired purposes. Our recent work has been focused on the preparation of enantiopure heteroatom compounds that could be used as chiral catalysts in asymmetric synthesis. Thus, we have recently succeeded in the chemoenzymatic synthesis of a variety of tridentate ligands **3**, containing a stereogenic sulfinyl moiety, an enantiomeric amine fragment and the hydroxy group (Scheme 1).[2] The crucial step was the enzyme-promoted desymmetrization of the prochiral sulfoxide **1**, which allowed us to obtain the desired precursor **2** in one step in high yield and in an almost enantiomerically pure form. The ligands **3** proved to be excellent catalysts for the asymmetric organozinc additions to aldehydes,[3,4] Michael additions to enones[5] and in the nitroaldol (Henry) reaction.[6] In all cases the products were obtained in the yields up to 98% and with *ee*s up to 98%.

The results presented above encouraged us to consider a possibility of replacing the stereogenic sulfinyl moiety in the catalysts with a stereogenic phosphorus-containing group in the hope of getting new classes of chiral catalysts. It should be stressed that the phosphorus atom, in comparison with the sulfur atom, creates more possibilities of functionalization – from



Scheme 1. Synthesis of chiral sulfinyl tridentate ligands.



Scheme 2. Synthesis of 2-hydroxymethylphenyl(methyl)phenylphosphine oxide (**6**).

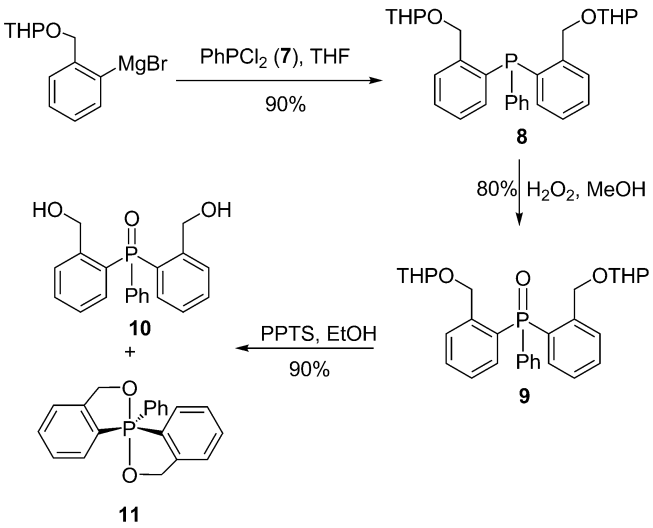
phosphines [P(III)] through phosphine oxides to phosphine sulfides and selenides [P(V)]. Although we were very lucky in the desymmetrization of the hydoxy sulfoxide **1**, in which the reacting site, the OH group, is in the γ position with respect to the stereogenic sulfur atom (thus the distance between the stereogenic sulfinyl centre and the hydroxy group is equal to four bonds) (for other examples of similar transformations: kinetic resolutions of γ, and ε-hydoxy sulfoxides with $E=10$ and 35, respectively, see refs.[7,8]), no such literature example can be found in the case of P-chiral hydroxyphosphoryl analogues (for an example of a kinetic resolution of β-hydroxyphosphines and phosphine oxides, thus with the hydroxy group located at a distance of three bonds from the stereogenic phosphorus atom, with E up to 81, see ref.[9]). To check whether the same procedure, as for the transformation of the sulfoxide **1**, will be effective for the phosphoryl analogues, we decided to investigate both the enzymatic kinetic resolution of racemic and the desymmetrization of prochiral phosphine oxides, bearing the reacting hydroxy group distant from the stereogenic or prostereogenic phosphorus atom by four bonds.

Results and Discussion

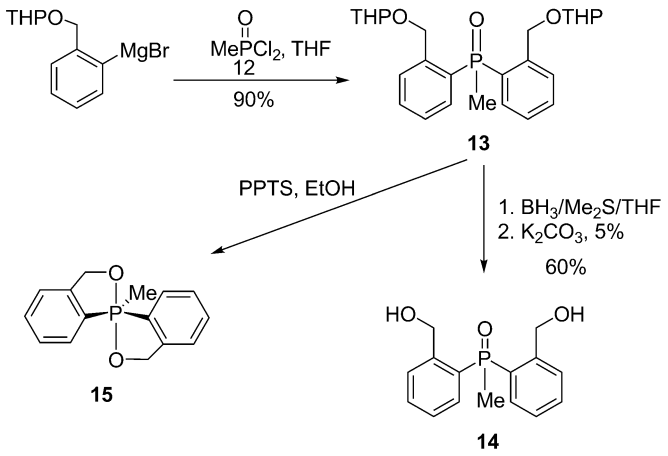
Synthesis of Substrates

The 2-2ydroxymethylphenyl(methyl)phenylphosphine oxide **6** was synthesized in the reaction of 2′-(2-tetrahydropyranyloxymethyl)phenylmagnesium bromide with methylphenylphosphinyl chloride **4**, followed by acidic removal of the tetrahydropyranyl protecting group from **5** (Scheme 2).

To synthesize prochiral bis(2-hydroxymethylphenyl)phosphine oxides a similar approach was planned in which 2′-(2-tetrahydropyranyloxymethyl)phenylmagnesium bromide was subjected to a reaction with dichlorophenylphosphine **7** (Scheme 3) or dichloromethylphosphine oxide **12** (Scheme 4). While the synthesis of bis(2-hydroxymethylphenyl)phenylphosphine



Scheme 3. Synthesis of bis(2-hydroxymethylphenyl)phenylphosphine oxide (**10**).



Scheme 4. Synthesis of bis(2-hydroxymethylphenyl)methylphosphine oxide (**14**).

oxide **10** proceeded smoothly, with only slight formation of the undesired spirophosphorane **11**, which was produced during the removal of the THP protecting group using pyridinium *p*-toluenesulfonate, PPTS, (Scheme 3), the analogous deprotection of the methyl analogue **13** led to the exclusive formation of spirophosphorane **15** (Scheme 4). After several unsuccessful attempts, the desired bis(2-hydroxymethylphenyl)-methylphosphine oxide **14** was unexpectedly obtained when **13** was treated with a THF solution of the borane/dimethyl sulfide complex, followed by a basic work-up. The latter was crucial, since the presence of even traces of acids caused immediate formation of **15.**

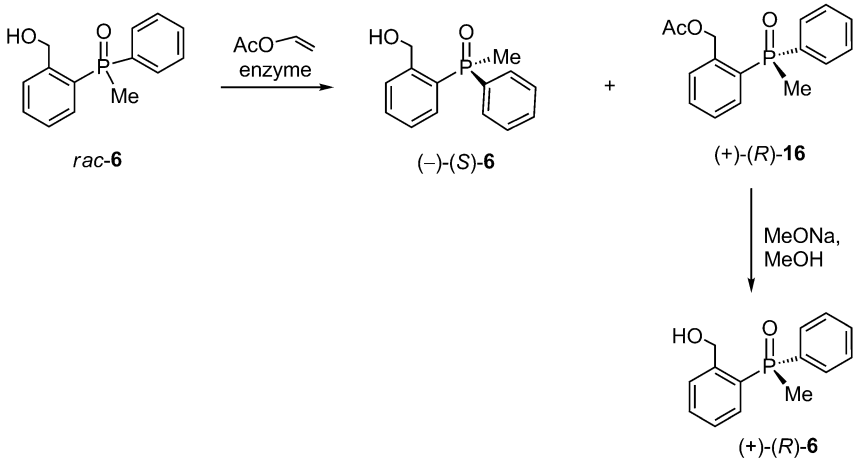
Kinetic Resolution of 2-Hydroxymethylphenyl-(methyl)phenylphosphine Oxide 6

To achieve kinetic resolution of **6**, several lipases were screened for the enantioselective acetylation of **6** (Scheme 5). All the reactions were carried out in organic solvents as reaction media. The acetate (+)-**16** was separated from the unreacted alcohol (−)-**6** using column chromatography. The results are collected in Table 1. Enantiomeric (+)-**6** was obtained from (+)-**16** *via* its deacetylation using MeONa/MeOH. An enantiomerically pure crystalline sample of (−)-**6** was subjected to X-ray analysis. On the basis of the molecular structure (Figure 1) its absolute configuration was determined as (−)-(*S*).

Inspection of the data shown in Table 1 reveals that the reaction time, yields and enantioselectivity strongly depended on the lipase and the solvent used. Except for the two experiments shown in entries 1 and 3, where no reaction was observed, in all other cases the reaction proceeded quite smoothly. The best results were obtained using lipase from *Candida antarctica* CAL-B. From the point of view of stereoselectivity, chloroform proved to be inferior to ethers. Although diisopropyl ether gave satisfactory results, a breakthrough was achieved when diethyl ether was applied as solvent. In this case, a certain trick was used which rests upon the fact that the starting alcohol **6** is almost insoluble in diethyl ether while the acetate **16** dissolves in it reasonably well. Combination of two effects – intrinsic stereoselectivity of the enzyme and physical separation based on the difference in solubility between the substrate and the product, resulted in the full enantioselectivity of the reaction ($E = 3000$).

Desymmetrization of Bis(2-hydroxymethylphenyl)-methylphosphine Oxide 14

Prochiral phosphine oxides **10** and **14** were subjected to acetylation with an excess of vinyl acetate in various solvents at 30 °C, using a number of lipases. Much to our surprise, the phosphine oxide **10** did not under-

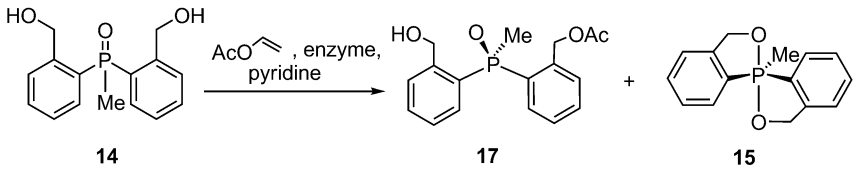


Scheme 5. Kinetic resolution of 2-hydroxymethylphenyl(methyl)phenylphosphine oxide (**6**).

Table 1. Kinetic resolution of 2-hydroxymethylphenyl(methyl)phenylphosphine oxide (**6**)

Entry	Enzyme	Time [days]	Solvent	Recovered substrate **6**			Acetate **16**			E
				Yield [%]	$[\alpha]_D$[a]	*ee* [%][b]	Yield [%]	$[\alpha]_D$[a]	*ee* [%][b]	
1	LPL	58	$CHCl_3$	–	–	–	–	–	–	–
2	LPL	28	$(i\text{-Pr})_2O$	44	−6.7	83.6	41	+15	81.7	26
3	PS	56	$(i\text{-Pr})_2O$	–	–	–	–	–	–	–
4	AK	32	$CHCl_3$	43	−0.3	2.6	39	+10.4	56.5	4
5	AK	18	$(i\text{-Pr})_2O$	43	−6.9	72	40	+14.2	78.2	17
6	CAL-B	100	$CHCl_3$	65	−0.7	8.4	28	+15.8	77	9
7	CAL-B	6	$(i\text{-Pr})_2O$	47.5	−7.5	93.4	47	+16.3	88.5	64
8	CAL-B	2	Et_2O	48	−8.1	99.9	46	+20.3	99.5	3000

[a] In chloroform (*c* 1).
[b] The *ee* values were determined by chiral HPLC



Scheme 6. Desymmetrization of bis(2-hydroxymethylphenyl)methylphosphine oxide (**14**).

go the desired reaction under any conditions applied. This may be due the a large steric hindrance created by three phenyl groups connected with phosphorus. On the contrary, acetylation of phosphine oxide **14** proceeded relatively smoothly (Scheme 6).

However, the use of a basic additive, for example, pyridine, proved crucial, since in its absence spirophosphorane **15** was the only product. This was due to the fact that vinyl acetate is partially hydrolyzed by the water that is constitutionally bound in the enzyme molecule, to form acetic acid. The latter, in turn, causes cyclization of the substrate (as discussed above). The reactions were monitored by ^{31}P NMR. After completion, the enzymes were filtered off, the solvents and excess of vinyl acetate were evaporated and the residue which, besides the desired monoacetate **17**, contained also phosphorane **15**, unreacted substrate **14** and the corresponding diacetate, was separated *via* column chromatography. The results are collected in Table 2. Inspection of Table 2 clearly shows that the best result was again obtained using CAL-B as the biocatalyst, but this time the solvent of choice was dichloromethane. It is noteworthy that application of the biocatalytic methodology made it possible to obtain the desired product in high yield and with almost full stereoselectivity in one step. Such a result could not be achieved using traditional chemical methods.

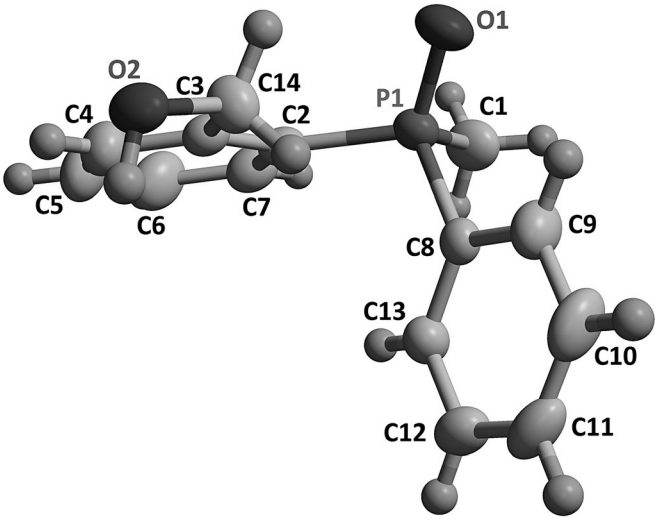


Figure 1. Molecular structure of the recovered alcohol (−)-(*S*)-**6**.

Since it turned out to be impossible to obtain the product **17** in a crystalline form and to determine its absolute configuration by an X-ray analysis, we had to resort to a chemical correlation. To this end, the enantiomerically enriched sample of (−)-**17** was treated with methanesulfonic anhydride in the presence of triethylamine to give the mesyl derivative **18**. Its reaction with sodium iodide in acetone led to the corresponding iodo derivative **19**, which was reduced under radical conditions[10] to yield the acetate **20**. This product was purified by chiral HPLC using a recycling chromatograph. Hence, the enantomeric excess of this sample was increased to 100% at the expense of its chemical yield. Finally, **20** was transformed into the alcohol **21** (Scheme 7). Its absolute configuration was determined in two ways. First, the CD spectrum of (−)-**21** was compared with the CD spectra of both

Table 2. Desymmetrization of bis(2-hydroxymethylphenyl)-methylphosphine oxide (**14**).

Entry	Enzyme	Solvent	Monoacetate **17**			
			Yield [%]	$[\alpha]_D$[a]	*ee* [%][b]	Abs. conf.
1	AK	$(i\text{-Pr})_2O$	30	−2.1	35	(*R*)
2	PS	$(i\text{-Pr})_2O$	15	−2.6	42	(*R*)
3	CAL-B	$(i\text{-Pr})_2O$	42	−4.3	66	(*R*)
4	CAL-B	$CHCl_3$	60	−5.6	85	(*R*)
5	CAL-B	CH_2Cl_2	80	−6.6	>98	(*R*)

[a] In acetone (*c* 1).
[b] Determined by chiral HPLC.

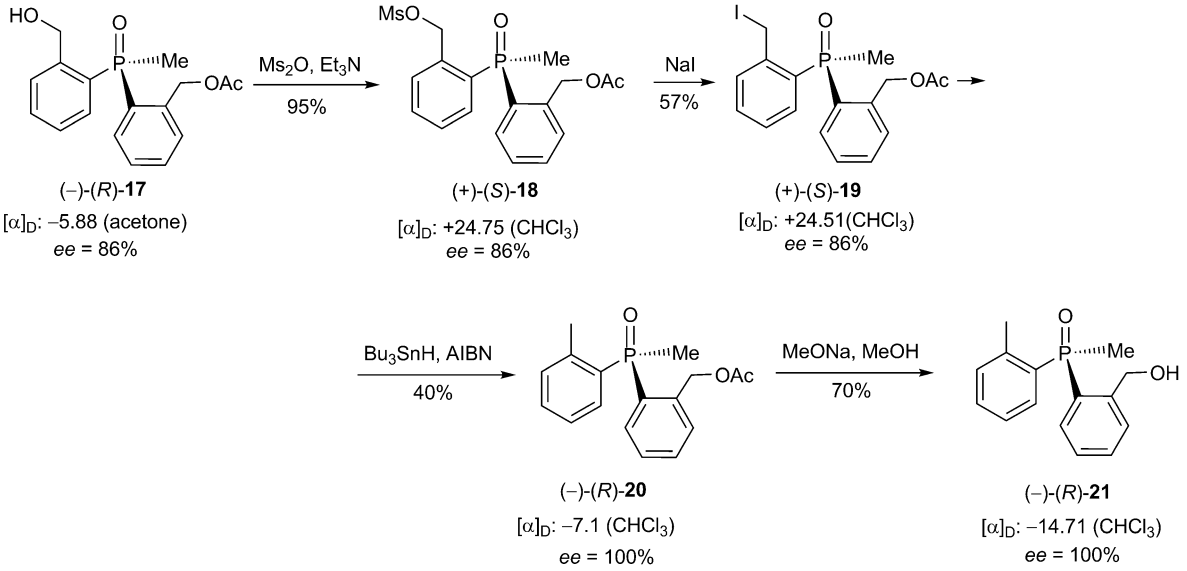
enantiomers of the alcohol **6**. It turned out that the CD curves of (+)-(*R*)-**6** and the levorotatory **21** were of the same shape and exhibited the same sign of the Cotton effect (Figure 2). Since both compounds are closely related (the phosphorus atom is in each case linked to three identical substitutents, and the fourth one, that is, the aryl group, differs only by the presence of the *ortho*-methyl group), it seems very reasonable to assume that the absolute configuration of (−)-**21** is also (*R*).

The ultimate proof was provided by the X-ray analysis of the enantiopure sample of (−)-**21**, which undoubtedly confirmed the above considerations (Figure 3). Since all the transformations presented in Scheme 7 proceeded outside of the stereogenic phosphorus atom, its absolute configuration must have remained unchanged. Hence, the absolute configuration of the enzymatic desymmetrization product (−)-**17** must be (*R*).

The investigations of the transformation of the enantiopure products, (−)-(*S*)-**6**, (+)-(*R*)-**6** and (−)-(*R*)-**17** into of a variety of chiral organophosphorus ligands/catalysts and their use in asymmetric synthesis are under way and the results will be published elsewhere.

Conclusions

Biocatalytic transformations proved again to be a valuable synthetic methodology in the synthesis of enantiomerically pure P-chiral organophosphorus derivatives. Kinetic resolution of racemic 2-hydroxymethylphenyl(methyl)phenylphosphine oxide *via* its CAL-B-catalyzed acetylation, performed in the properly selected solvent – diethyl ether in which the substrate was insoluble and the product dissolved quite well – resulted in an unusually high enantioselectivity ($E=3000$). In turn, CAL-B-mediated desymmetrization of prochiral bis(2-hydroxymethylphenyl)-methylphosphine oxide gave, *via* its enantioselective monoacetylation, the corresponding monoacetate in high yield and with *ee* > 98%. It is noteworthy that in both cases the distance between the stereogenic or prostereogenic phosphorus atom and the reacting hydroxy oxygen was equal to four bonds, which proves that the enzymes are capable of recognizing remote heteroatom centres of chirality. Moreover, in the case of the desymmetrization the biocatalytic procedure made it possible to efficiently transform a prochiral substrate into an enatiomerically pure product in one single step – a transformation which would be very difficult to achieve by traditional chemical methods. The products obtained, whose absolute configurations



Scheme 7. Determination of the absolute configuration of **17** by chemical correlation.

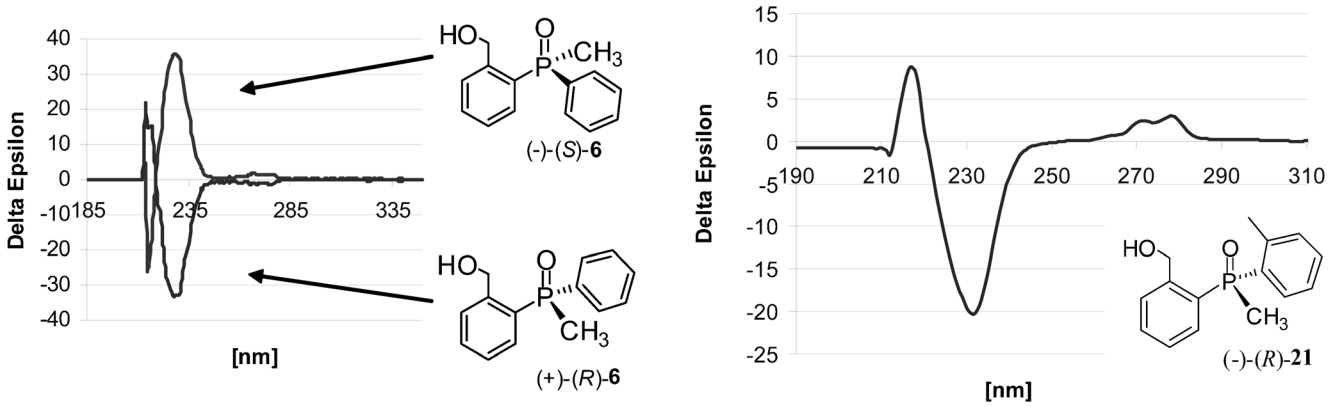


Figure 2. Comparison of CD curves of **6** and **21**.

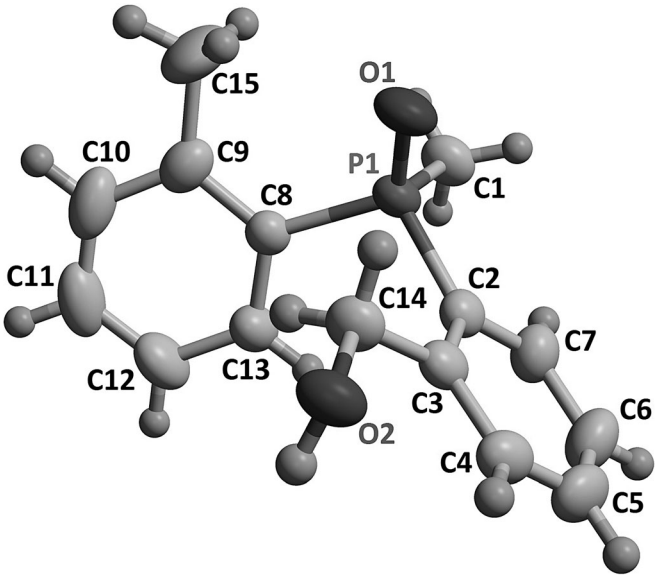


Figure 3. Molecular structure of (−)-(*R*)-**21**.

were determined by a chemical correlation and X-ray analysis, will be used as enantiopure substrates in the preparation of a variety of chiral organophosphorus ligands/catalysts for asymmetric synthesis.

Experimental Section

General Remarks

The enzymes were purchased from AMANO or SIGMA. NMR spectra were recorded on a Bruker instrument at 200 MHz with $CDCl_3$ and CD_3OD as solvents. Mass spectra including HR-MS were measured on a Finnigan MAT instrument Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter ($c=1$). Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 F254 silica gel plates. The enantiomeric excess (*ee*) values were determined by chiral HPLC (Varian Pro Star 210, Chiralpak AS, Chiralcel OD).

Lipases: CAL-B *Candida antarctica* lipase B (Novozym 435), AK Lipase AK (AMANO), PS Lipase PS (AMANO), LPL Lipoprotein lipase were used.

The X-ray data for compounds (−)-(*S*)-**6** and (−)-(*R*)-**21** were collected with a Bruker APEX-II CCD diffractometer at room temperature using CuKα radiation, and the crystal structures and absolute configurations were determined with SHELXL-97.[11]

Synthesis of Methylphenylphosphinyl Chloride (4)

To methyl methylphenylphosphinate[12] (16.5 g, 0.097 mol), placed in a two-neck round-bottom flask equipped with a mechanical stirrer, dropping funnel and reflux condenser with a $CaCl_2$ tube, $SOCl_2$ (11.54 g, 0.097 mol) was slowly added. After the addition, the mixture was stirred and heated (oil bath temperature 60 °C) for 2 h. The reaction was monitored by ^{31}P NMR. After cooling to room temperature, the excess of $SOCl_2$ was evaporated under vacuum and the residue was distilled at 103–104° (0.1 mm Hg). The product **4** was obtained as a colourless liquid; yield: 13.2 g (78%). ^1H NMR ($CDCl_3$): $\delta=2.16$ (d, $J=14.01$ Hz, 3H), 7.41–7.89 (m, 5H, Ar-H); ^{31}P NMR ($CDCl_3$): $\delta=51.72$.

Synthesis of 2-Hydroxymethylphenyl(methyl)-phenylphosphine Oxide (6)

To a stirred solution of 2-bromobenzyl alcohol (11.6 g, 0.062 mol) in dichloromethane (200 mL) was added dihydropyran (7.81 g, 0.093 mol) and PPTS (1.55 g, 0.0062 mol). The solution was stirred for 4 h. After this time the solvent was removed under vacuum and brine was added. The aqueous layer was extracted with diethyl ether (3×50 mL). The phases were separated and the organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was distilled (96–100°; 0.2 mm Hg) to give *2′-(2-tetrahydropyranyloxymethyl)bromobenzene*; yield: 5.15 g (90%). ^1H NMR ($CDCl_3$): $\delta=1.51$–1.93 (m, 6H), 3.50–3.97 (m, 2H), 4.53–4.86 (m, 3H), 7.05–7.59 (m, 4H, Ar-H).

Magnesium (1.4 g, 0.055 mol) and THF (10 mL) were placed in a three-neck round-bottom flask equipped with a mechanical stirrer, reflux condenser, and argon inlet. 10 mL of a solution of the total amount of 2′-(2-tetrahydropyranyloxymethyl)bromobenzene (15.15 g, 0.055 mol) in THF (100 mL) were added, followed by a small crystal of iodine.

The mixture was heated until the formation of the Grignard reagent began. Then, the next portions of the solution of 2′-(2-tetrahydropyranyloxymethyl)bromobenzene in THF were added and the reaction mixture was refluxed until magnesium disappeared. The solution was cooled to room temperature and methylphenylphosphinyl chloride **4** (8.02 g, 0.046 mol) was added in small portions. The reaction was monitored by ^{31}P NMR. After the reaction was completed THF was evaporated, the residue was dissolved in dichloromethane (60 mL) and washed with a solution of NH_4Cl (3× 30 mL). After drying over anhydrous $MgSO_4$ and evaporation of the solvent, the residue was purified by column chromatography (dichloromethane/methanol in gradient from 100:1 to 1:1) to give pure *2′-(2-tetrahydropyranyloxymethylphenyl)(methyl)phenylphosphine oxide* (**5**); yield: 12.72 g (70%); white powder; m.p. 87–90 °C. ^{1}H NMR ($CDCl_3$): δ = 1.27–1.69 (m, 6H), 2.02 (d, J = 13.27 Hz, 3H), 3.31–3.79 (m, 2H), 4.37–4.95 (m, 3H), 7.22–7.68 (m, 9H, Ar-H); ^{31}P NMR ($CDCl_3$): δ = 31.92.

Product **5** (12.72 g, 0.0385 mol) was dissolved in ethanol (110 mL), PPTS (0.97 g, 0.00385 mol) was added and the reaction mixture was stirred at 55 °C for 4 h and monitored by TLC. After this time, ethanol was evaporated, the residue was dissolved in dichloromethane and washed with a solution of Na_2CO_3 (2×20 mL). After drying over anhydrous $MgSO_4$ and evaporation of CH_2Cl_2, the residue was purified by column chromatography (dichloromethane/methanol in gradient from 200:1 to 1:1) to afford **6**; yield: 8.24 g (87%); white powder; m.p. 168–171 °C. ^{1}H NMR ($CDCl_3$): δ = 2.04 (d, J = 13.23 Hz, 3H), 4.57 (AB, 2H), 7.39–7.68 (m, 9H, Ar-H); ^{31}P NMR ($CDCl_3$): δ = 36.52; MS (CI): m/z = 247 (M+H); HRMS (CI): m/z = 247.0885, calcd for $C_{14}H_{16}PO_2$ (M+H), 247.0887.

Kinetic Resolution of Racemic 2-Hydroxymethylphenyl(methyl)phenylphosphine Oxide (6); General Procedure

Racemic substrate **6** (0.20 g, 0.00081 mol) was dissolved in a solvent (5 mL) and an enzyme (50 mg) and vinyl acetate (1.5 mL) were added. The mixture was stirred at room temperature and the reaction was monitored by ^{31}P NMR and stopped at the 50% conversion. The enzyme was filtered off and the solvent was removed under vacuum. The residue was purified by column chromatography (dichloromethane/isopropanol in gradient from 80:1 to 1:1) to give unreacted alcohol (−)-(*S*)-**6** and (+)-(*R*)-2-acetoxymethylphenyl-(methyl)phenylphosphine oxide [(+)-(*R*)-**16**]. The results are shown in Table 1.

(+)-(*R*)-2-Acetoxymethylphenyl(methyl)phenylphosphine oxide [(+)-(*R*)-16]: ^{1}H NMR ($CDCl_3$): δ = 1.84 (s, 3H), 2.05 (d, J = 13.2 Hz, 3H), 5.35 (s, 2H), 7.34–7.7 (m, 9H, Ar-H); ^{31}P NMR ($CDCl_3$): δ = 32.08; MS (CI): m/z = 289 (M+H).

Synthesis of (+)-(*R*)-2-Hydroxymethylphenyl-(methyl)phenylphosphine Oxide [(+)-(*R*)-6]

To the acetyl derivative (+)-(*R*)-**16** (0.656 g, 0.00228 mol) MeONa/MeOH (2 mL) was added. After the addition, the mixture was stirred for 2 h. After this time TLC indicated completion of the reaction. Methanol was evaporated and the residue was purified by column chromatography (chloroform/methanol in gradient from 70:1 to 1:1) to give (+)-(*R*)-**6**; yield: 0.494 g (88%).

Synthesis of Bis[2-(2′-tetrahydropyranyloxy)methylphenyl]phenylphosphine Oxide (9)

To magnesium (0.264 g, 0.01 mol) under argon was added a solution of 2′-(2-tetrahydropyranyloxymethyl)bromobenzene (3 g, 0.01 mol) in THF (8 mL) followed by a small crystal of iodine. The mixture was gently heated to initiate the Grignard reagent formation. After magnesium had completely dissolved, dichlorophenylphosphine **7** (0.985 g, 0.0055 mol) was added and the solution was stirred for 3 h. THF was evaporated, water was added to the residue and the mixture was extracted with Et_2O (3×10 mL). The organic solution was dried over $MgSO_4$ and the solvent was removed to give crude phosphine **8**; yield: 2.42 g (90%).

This was dissolved in methanol (20 mL) and a 30% solution of H_2O_2 was slowly added with external cooling. After 30 min MeOH was evaporated, water was added and the mixture was extracted with $CHCl_3$. The organic solution was dried over $MgSO_4$, and the solvent evaporated to give **9**; yield: 2.43 g (85%). ^{31}P NMR ($CDCl_3$): δ = 34.8; ^{1}H NMR ($CDCl_3$): δ = 1.7–2.1 (m, 12H), 3.57 (m, 2H), 3.89 (m, 2H), 4.72 (AB, 2H), 5.1 (m, 2H), 7.48–7.56 (m, 13H). The crude product was used in the ensuing reaction.

Synthesis of Bis-(2-hydroxymethylphenyl)phenylphosphine Oxide (10)

To a solution of crude phosphine oxide **9** (2.74 g, 0.0054 mol) in EtOH (40 mL) PPTS (2.7 g, 0.0108 mol) was added and the mixture was stirred at 55 °C for 7 h. EtOH was evaporated and the residue was separated and purified by column chromatography using $CHCl_3$ as eluent to give the product **10**; yield: 1.56 g (85%). ^{31}P NMR ($CDCl_3$): δ = 40.7; ^{1}H NMR ($CDCl_3$): δ = 4.49–4.68 (m, 4H), 5.25 (t,„J = 6.98 Hz, 2H; OH), 6.83–7.78 (m, 13H); MS (CI): m/z = 339 (M+H); HR-MS (CI): m/z = 339.3378, calcd for $C_{20}H_{20}PO_3$ (M+H), 339.3369.

Spirophosphorane 11[13]: ^{1}H NMR ($CDCl_3$): δ = 4.92–5.13 (2×AB, 4H), 7.26–7.65 (m, 11H), 8.31–8.40 (m, 2H); ^{31}P NMR ($CDCl_3$): δ = −38.1; MS (CI): m/z = 321 (M+H).

Synthesis of Bis[2-(2′-tetrahydropyranyloxy)methylphenyl]methylphosphine Oxide (13)

Magnesium (0.73 g, 0.03 mol) and THF (5 mL) were placed under argon and 5 mL of a solution of the total amount of 2′-(2-tetrahydropyranyloxymethyl)bromobenzene (8.27 g, 0.03 mol) in THF (60 mL) were added, followed by a few drops of 1,2-dibromoethane. The mixture was heated until the formation of the Grignard reagent began. Then, the next portions of the solution of 2′-(2-tetrahydropyranyloxymethyl)bromobenzene in THF were added and the reaction mixture was refluxed for 2 h. After cooling the solution to room temperature, dichloromethylphosphine oxide **12** (1.9 g, 0.015 mol) in THF (10 mL) was added dropwise and the resulting mixture was stirred for 24 h. THF was removed under vacuum. To the residue aqueous NH_4Cl solution was added and the mixture was extracted with dichloromethane (3×25 mL). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated to give the crude prod-

uct **13** as a diastereomer mixture; yield: 6.189 g (98%). ^{31}P NMR ($CDCl_3$): $\delta = 32.50, 32.89, 33.08$. The crude product was used in the ensuing reaction.

Synthesis of Bis-(2-hydroxymethylphenyl)methylphosphine Oxide (14)

To **13** (6.397 g, 0.0144 mol) was added BH_3/Me_2S (2 M in THF, 29.4 mL, 0.3312 mol; 23 equiv.) and the solution was stirred at room temperature for 50 h. The reaction was quenched by a slow addition of 5% K_2CO_3 (12 mL). The organic solvents were evaporated, water was added and the mixture was extracted with chloroform (3×50 mL). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated and the residue was purified by column chromatography using dichloromethane/acetone in gradient from 10:1 to 1:1 to afford **14**; yield: 2.39 g (60%); white powder; m.p. 153–155 °C. ^{1}H NMR ($CDCl_3$): $\delta = 1.2$ (br. s, 2H), 2.16 (d, $J = 13.22$ Hz, 3H), 4.60–4.80 (AB, 4H), 7.23–7.69 (m, 8H, Ar-H); ^{31}P NMR ($CDCl_3$): $\delta = 42.49$; MS (CI): $m/z = 277$ (M+H); HR-MS (FAB): $m/z = 277.09893$, calcd. for $C_{15}H_{18}PO_3$ (M+H), 277.099358; anal. calcd. for $C_{15}H_{17}O_3P$: C 65.22, H 6.16, P 11.23, O 17.39; found: C 65.03, H 6.11, P 10.97, O 17.51.

Spirophosphorane 15: ^{1}H NMR ($CDCl_3$): $\delta = 1.96$ (d, $J = 16.33$ Hz, 3H), 4.88–5.22 (m, 4H), 7.25–7.56 (m, 6H, Ar-H), 8.08 (m, 2H); ^{31}P NMR ($CDCl_3$): $\delta = -30.19$; MS (CI): $m/z = 259$ (M+H).

Enzymatic Desymmetrization of Bis-(2-hydroxymethylphenyl)methylphosphine Oxide (14)

To the diol **14** (2.12 g, 7.69 mmol), dissolved in CH_2Cl_2 (50 mL), were added pyridine (1.86 mL, 23.07 mmol, 3 equiv), CAL-B (immobilized, Novozym 435; 500 mg) and vinyl acetate (5 mL). The mixture was stirred at room temperature and the reaction was monitored by ^{31}P NMR. After 5 days the enzyme was filtered off, the solvents were evaporated and the crude reaction mixture was purified by column chromatography using CH_2Cl_2/acetone in gradient from 10:1 to 1:1 to give pure (−)-(*R*)-**17** as an oil; yield: 1.96 g (80%); $[\alpha]_D$: −6.6; *ee* > 98% (for other examples see Table 2). ^{1}H NMR ($CDCl_3$): $\delta = 1.88$ (s, 3H), 2.13 (d, $J = 13.24$ Hz, 3H), 4.55–4.73 (m, 2H), 5.39–5.51 (m, 2H), 7.26–7.55 (m, 8H, Ar-H); ^{31}P NMR ($CDCl_3$): $\delta = 38.62$; MS (CI): $m/z = 319$ (M+H); HR-MS (CI): $m/z = 319.109170$, calcd. for $C_{17}H_{20}PO_4$ (M+H): 319.109923.

Chemical Correlations

Synthesis of (+)-(*S*)-18: To a solution of (−)-(*R*)-**17** (263 mg,0.826 mmol, $[\alpha]_D$: −5.88 (*c* 1.7, acetone; *ee* = 86%) in dichlorometane (10 mL) were added methanesulfonic anhydride (288 mg, 1.653 mmol) and triethylamine (167 mg, 1.653 mmol) and the mixture was stirred at room temperature for 3 h [TLC (CH_2Cl_2:acetone 3:2) and ^{31}P NMR control]. Then the solution was washed with water and dried with $MgSO_4$. The solvent was evaporated to give pure **18**; yield: 311 mg (95%); $[\alpha]_D$: +24.75 (*c* 1.6, $CHCl_3$); *ee* = 86%. ^{31}P NMR ($CDCl_3$): $\delta = 35.44$; ^{1}H NMR ($CDCl_3$): $\delta = 1.85$ (s, 3H, Ac), 2.14 (d, $J = 13.23$ Hz, 3H, P-Me), 2.99 (s, 3H, CH_3SO_2), 5.37 (s, 2H, CH_2OAc), 5.68 (AB, 2H, CH_2OMs), 7.31–7.62 (m, 8H, aromat.).

Synthesis of (+)-(*S*)-19: A mixture of (+)-(*S*)-**18** (291 mg, 0.735 mmol) and sodium iodide (441 mg, 2.939 mmol) in acetone (10 mL) was stirred overnight at room temperature (TLC control: CH_2Cl_2:acetone 3:2). Acetone was removed under vacuum, the residue was dissolved in dichloromethane and washed with H_2O and an aqueous solution of $Na_2S_2O_3$. The organic layer was dried with $MgSO_4$ and evaporated. The crude product was purified by preparative TLC (CH_2Cl_2:acetone 3:2) to give pure **19**; yield: 179 mg (57%); $[\alpha]_D$: +24.51 (*c* 1.22, $CHCl_3$); *ee* = 86%. ^{31}P NMR ($CDCl_3$): $\delta = 34.17$; ^{1}H NMR ($CDCl_3$): $\delta = 1.88$ (s, 3H, Ac), 2.18 (d, $J = 13.24$ Hz, 3H, P-Me), 4.97 (AB, 2H, CH_2I), 5.34 (d, $J = 2.52$ Hz, 2H, CH_2OAc), 7.30–7.68 (m, 8H, aromat.); MS (CI): $m/z = 429$ (M+H); HR-MS: $m/z = 429.011653$, calcd. for $C_{17}H_{19}IPO_3$: 429.01055.

Synthesis of (−)-(*R*)-20: A mixture of (+)-(*S*)-**19** (164 mg, 0.735 mmol), AIBN (a few milligrams) and Bu_3SnH (133 mg, 0.460 mmol) in dry benzene (20 mL) was refluxed for 6 days [TLC (CH_2Cl_2:acetone 3:2) and ^{31}P NMR control]. After evaporation of the solvent the residue was purified by preparative chiral HPLC [CYCLOBOND DMT hexane (*i*-PrOH-EtOH 4:1) 15%; flow 3.6 mL min^{-1}] to give pure **20**; yield: 46 mg (40%); $[\alpha]_D$: −7.31 (*c* 1.34, $CHCl_3$); *ee* = 100%. ^{31}P NMR ($CDCl_3$): $\delta = 32.76$; ^{1}H NMR ($CDCl_3$): $\delta = 1.93$ (s, 3H, Ac), 2.11 (d, $J = 13.12$ Hz, 3H, P-Me), 2.34 (s, 3H, CH_3), 5.29 (AB, 2H, CH_2OAc), 7.30–7.68 (m, 8H, aromat.); MS (CI): $m/z = 303$ (M+H); HR-MS: $m/z = 303.115008$, calcd. for $C_{17}H_{20}PO_3$ 303.11598.

Synthesis of (−)-(*R*)-21: To a solution of (−)-(*R*)-**20** (22 mg, 0.073 mmol) in MeOH (2 mL) was added NaOMe (a few milligrams in methanol) and the mixture was stirred at room temperature for several minutes until the substrate disappeared (TLC control: CH_2Cl_2:acetone 3:2). After evaporation of the solvent the residue was purified by preparative TLC (CH_2Cl_2:acetone 3:2) to give pure **21**; yield:12 mg (60%); $[\alpha]_D$: −9.56 (*c* 1.13, $CHCl_3$); *ee* = 100%. ^{31}P NMR ($CDCl_3$): $\delta = 38.54$; ^{1}H NMR ($CDCl_3$): $\delta = 2.10$ (d, $J = 13.10$ Hz, 3H, P-Me), 2.43 (s, 3H, CH_3), 4.71(d, $J = 7.5$ Hz, 2H, CH_2OH), 5.82 (t, $J = 7.52$ Hz, 1H, OH), 7.18–7.75 (m, 8H, aromat.); MS (CI): $m/z = 261$ (M+H); HR-MS: $m/z = 261.104444$, calcd. for $C_{15}H_{18}PO_2$: 261.10391.

Crystallographic Data

See Supporting Information. Crystallographic data for (−)-(*S*)-**6** and (−)-(*R*)-**21** have been deposited with the Cambridge Crystallographic Data Centre as entries CCDC 785937 and CCDC 810782, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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