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Asymmetric Hydrogenation of α-Keto Phosphonates with Chiral Palladium Catalysts

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Under atmospheric hydrogen pressure, a catalytic amount of palladium(II) trifluoroacetate and (*R*)-MeO-BIPHEP in 2,2,2-trifluoroethanol promoted the asymmetric hydrogenation of diisopropyl α-keto phosphonates **1** to afford the corresponding α-hydroxy phosphonates **2** in excellent yields and with a moderate enantioselectivities of up to 55 % *ee*. Racemic α-aryl-α-hydroxy phosphonates can be prepared by using palladium on carbon as the catalyst.

Introduction

Chiral nonracemic α-hydroxy phosphonates are an important class of biologically active compounds that have a wide range of activities and are of interest in the design of drugs and bioregulators.[1] They also serve as convenient precursors for a variety of biologically significant α-substituted phosphonates,[2] in particular, chiral α-amino phosphonates.[3]

Among the catalytic methods for the asymmetric synthesis of α-hydroxy phosphonates[4] the enantiofacial hydrophosphonylation of carbonyl compounds with dialkyl phosphite (the Pudovik reaction) is the best elaborated.[5,6] The alternative approach based on the enantioselective reduction of easily available α-keto phosphonates is less studied and limited to oxazaborolidine-catalyzed borane reduction.[2a,3b,7] Surprisingly, the catalytic enantioselective reduction of α-keto phosphonates with cheap hydrogen gas has not been described, notwithstanding the fact that the asymmetric hydrogenation of β-keto phosphonates[8] and α- and β-keto esters[9] using chiral Ru and Rh catalysts has been very successful. The possible reason for this may be the lability of α-keto phosphonates in the presence of some transition-metal complexes.[10] In the case of enolizable α-keto phosphonates, high *ee*s were obtained in the Rh-catalyzed hydrogenation of the corresponding enol ester phosphonates,[11] but the asymmetric hydrogenation of non-enolizable α-keto phosphonates still remains a challenging task.

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Recently we reported[12a] the enantioselective hydrogenation of α-imino phosphonates using $[Rh(COD)_2]^+SbF_6^-$/(*R*)-BINAP as the catalyst, but all our attempts to extend the method to α-keto phosphonates have been unsuccessful because in these cases P–C bond cleavage became the predominant process.[12b] However, we have shown that the hydrogenation of ring-substituted diethyl benzoylphosphonates can be performed by using heterogeneous Pd catalysts.[13] This result inspired us to explore palladium catalysis in the homogeneous asymmetric hydrogenation of α-keto phosphonates. Herein we wish to report our preliminary results.

Results and Discussion

Chiral palladium complexes are especially potent for a broad range of enantioselective transformations,[14] but until recently very little attention has been paid to their application in homogeneous hydrogenation reactions. In the last decade $Pd(OCOCF_3)_2$/bis-phosphane has emerged as a highly efficient catalytic system for the asymmetric hydrogenation of the imine bond[15] as well as functionalized ketones,[16] so we become interested in exploring its use in the hydrogenation of α-keto phosphonates.

We chose diethyl benzoylphosphonate (**1a**) as a representative substrate for a preliminary screening of chiral ligands (Figure 1) and carried out the initial experiments in 2,2,2-trifluoroethanol (TFE) under 50 bar of hydrogen at room temp. The reactions were monitored by ^{31}P NMR spectroscopy: The disappearance of the signal of **1a** at δ_P = –0.7 ppm and the emergence of the peak of diethyl [hydroxy(phenyl)methyl]phosphonate (**2a**) at δ_P = 22.1 ppm indicated a smooth reaction with no appreciable side-products.

The results obtained (Table 1) showed that of the tested C_2-symmetric bis-phosphane ligands the atropoisomeric

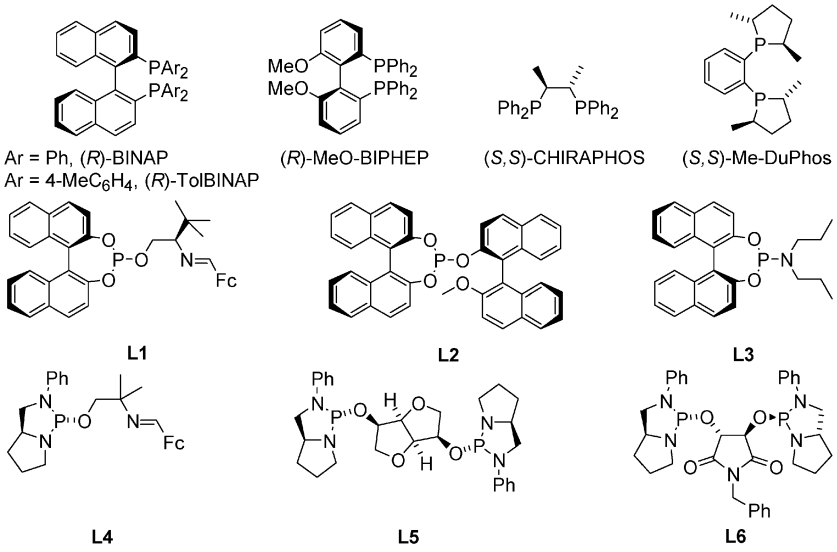
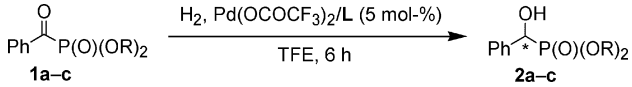


Figure 1. Ligands screened for the asymmetric hydrogenation reaction.

(*R*)-BINAP, (*R*)-TolBINAP, and (*R*)-MeO-BIPHEP, which form rather flexible seven-membered chelate rings, lead to enantioselective induction, albeit rather poor, with excellent conversion (>95% within 6 h) (entries 1–3). The stereodifferentiability of the catalytic system is noticeably sensitive to the electronic properties of the ligand (compare entries 1 and 2). Application of the electron-rich bis-phosphane (*S*,*S*)-CHIRAPHOS or the bis-phospholane (*S*,*S*)-Me-DuPhos with the more rigid five-membered-ring chelate structure gave nearly racemic **2a** (entries 4 and 5), although the latter ligand was the best in the enantioselective Pd-catalyzed hydrogenation of α-phthalimido ketones.[16]

Chiral ligands bearing a phosphite or phosphoramidite donor center have revealed high stereodifferentiability in Rh-catalyzed hydrogenation reactions of enol ester phosphonates.[11d–f] Phosphite and phosphoramidite ligands were also found to be effective in some Pd-catalyzed stereoselective transformations: hydrosilylation, carbonylation, and allylic substitution.[14,17,18a–18d] Therefore we also tested a set of phosphite (**L1**,**2**) and phosphoramidite (**L3**–**6**) type ligands.[18] Some of them, especially the *P*,*N*-bidentate ligands **L1**,**4**, provide good catalyst activity (entries 6 and 9), but all of them turned out to be ineffective in terms of stereoselectivity (entries 6–11).

Table 1. Optimization of reaction conditions for the Pd-catalyzed asymmetric hydrogenation reaction of benzoylphosphonates **1a**–**c**.



Entry	Substrate **1**	$(OR)_2$	L	Pressure [bar]	*T* [°C]	Yield of **2** [%][a]	*ee* [%][b]
1	**1a**	$(OEt)_2$	(*R*)-BINAP	50	20	99	22
2	**1a**	$(OEt)_2$	(*R*)-TolBINAP	50	20	96	14
3	**1a**	$(OEt)_2$	(*R*)-MeO-BIPHEP	50	20	100	26
4	**1a**	$(OEt)_2$	(*S*,*S*)-CHIRAPHOS	50	20	61	3
5	**1a**	$(OEt)_2$	(*S*,*S*)-Me-DuPhos	50	20	96	1
6	**1a**	$(OEt)_2$	**L1**	50	20	98	4
7	**1a**	$(OEt)_2$	**L2**	50	20	12	1
8	**1a**	$(OEt)_2$	**L3**	50	20	67	1
9	**1a**	$(OEt)_2$	**L4**	50	20	100	1
10	**1a**	$(OEt)_2$	**L5**	50	20	86	0
11	**1a**	$(OEt)_2$	**L6**	50	20	59	4
12	**1b**	$(OiPr)_2$	(*R*)-BINAP	50	20	97	33
13	**1c**	$(OCMe_2CMe_2O)$	(*R*)-BINAP	50	20	73	9
14	**1b**	$(OiPr)_2$	(*R*)-BINAP	1	20	16	38
15	**1b**	$(OiPr)_2$	(*R*)-BINAP	70	20	91	31
16	**1b**	$(OiPr)_2$	(*R*)-BINAP	50	0	13	31
17	**1b**	$(OiPr)_2$	(*R*)-BINAP	50	60	95	32
18	**1b**	$(OiPr)_2$	(*R*)-BINAP	1	80	99	39
19	**1b**	$(OiPr)_2$	(*R*)-MeO-BIPHEP	1	80	97	45

[a] Determined by ^{31}P NMR spectroscopy of the crude reaction mixture. [b] Determined by ^{31}P NMR analysis of the corresponding (*S*)-naproxen esters.

Further optimization of the conditions was carried out by using the $Pd(OCOCF_3)_2$/(*R*)-BINAP catalytic system. A strong solvent-dependent effect was observed, in agreement with some previous reports:[15a,15d,16,19] In nonfluorinated solvents ($CHCl_3$ and MeOH) the reaction did not occur. Within the series of dialkyl benzoylphosphonates **1a**–**c**, the diisopropyl ester **1b** gave an appreciably higher enantiomeric excess than diethyl ester **1a** (33 vs. 22% *ee*, entries 12 and 1), whereas only 9% *ee* was achieved when the conformationally constrained analogue **1c** was used (entry 13).

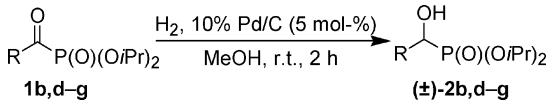
In the next set of experiments, pressure and temperature effects were studied with the model substrate **1b**. Variation of the hydrogen pressure from 1 to 70 bar caused a slight drop in the *ee* value (compare entries 14, 12 and 15), but no noticeable temperature dependence of the enantioselectivity was observed at either 50 (entries 16, 12 and 17) or 1 bar (entries 14 and 18). The rate of the hydrogenation reaction was found to increase significantly with an increase in pressure from 1 to 50 bar (entries 14 and 12) and slightly decrease at 70 bar (entry 15). Across the whole range of pressures and temperatures investigated, the chemoselectivity of the process was rather good; the formation of by-products was detected by ^{31}P NMR[20] (to the greatest extent in entry 17), but their total amount did not exceed 5%. The optimized conditions thus found were 1 bar of hydrogen at 80 °C (39% *ee* with 99% yield, entry 18). Under these conditions the best result (45% *ee* with 97% yield) was achieved with the $Pd(OCOCF_3)_2$/(*R*)-MeO-BIPHEP catalytic system (entry 19). Further purification of the crystalline product **2b** can be performed by recrystallization from dichloromethane/hexane, which led to the optically pure material.[5b,7a,21]

Under the optimized conditions, various α-keto phosphonates were subjected to the asymmetric hydrogenation reaction: Ring-substituted diisopropyl benzoylphosphonates **1d**–**g**, non-enolizable aliphatic diisopropyl (1-adamantylcarbonyl)phosphonate (**1h**), as well as diisopropyl acetylphosphonate (**1i**) (Table 2). The hydrogenation of these substrates proceeded as smoothly as the hydrogenation of **1b** providing the corresponding products **2d**–**i** in excellent yields. The stereochemical outcome of the reaction is markedly higher for α-aryl-α-keto phosphonates (45–55% *ee*, entries 1–5) than for α-alkyl-α-keto phosphonates (33–34% *ee*, entries 6 and 7). Within the series of aroylphosphonates **1b**,**d**–**f**, the electron-donating ability of the ring substituents had a noticeable beneficial effect on the enantioselectivity (entries 1–4), the best result (55% *ee*) being achieved in the hydrogenation of the most electron-rich substrate **1e** (entry 3). No perceptible influence of steric effects was observed for either the aromatic or the aliphatic substrates (compare entries 4 and 5, 6 and 7).

In all cases the (*R*)-MeO-BIPHEP/Pd catalyst leads to the (*S*) configuration at the new stereogenic center. The absolute configurations of the phosphonates (*S*)-(–)-**2b**,**e**,**g** and (*S*)-(+)-**2i** were unequivocally proven by comparison of the sign of the optical rotation with published data.[7a–7c,21,22] The (*S*) configurations of the α-hydroxy phosphonates (–)-**2d**,**f** and (+)-**2h** were assigned on the basis of ^{31}P NMR spectroscopic data for the corresponding (*S*)-naproxen derivatives (listed in Table 2) as it is known that the phosphorus signal of the diastereomeric (*S*)-naproxen ester of (*S*)-α-hydroxy phosphonate should be shifted downfield in relation to the signal of the (*R*) enantiomer.[23]

Racemic samples of (±)-**2b**,**d**–**g** were easily prepared in 69–100% isolated yields by the heterogeneous hydrogenation of the corresponding **1b**,**d**–**g** using 5 mol-% of 10% palladium on carbon in MeOH at room temperature and 15–

Table 3. Hydrogenation of α-keto phosphonates **1b**,**d**–**g** catalyzed by palladium on carbon.

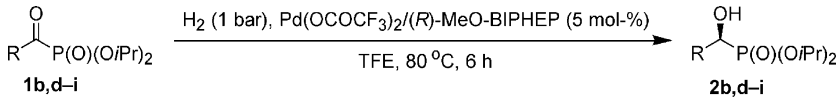


1b,d–g **(±)-2b,d–g**

Entry	Substrate **1**	R in **1**	Pressure [bar]	Yield of **2** [%][a]
1	**1b**	Ph	30	91(69)
2	**1d**	4-FC_6H_4	30	96(87)
3	**1e**	4-$MeOC_6H_4$	30	100(100)
4	**1f**	4-MeC_6H_4	15	100(100)
5	**1g**	2-MeC_6H_4	60	94(81)

[a] Determined by ^{31}P NMR spectroscopy of the crude reaction mixture; isolated yields are given in parentheses.

Table 2. Asymmetric hydrogenation of α-keto phosphonates **1b**,**d**–**i** catalyzed by the $Pd(OCOCF_3)_2$/(*R*)-BINAP system.



1b,d–i **2b,d–i**

Entry	Substrate **1**	R in **1**	Yield of **2** [%][a]	*ee* [%][b]	δ_P (ppm) of (*S*)-naproxen derivative of **2**[c]	Configuration[d]
1	**1b**	Ph	97(79)	45	**16.0**, 15.6	*S* (–)
2	**1d**	4-FC_6H_4	99(96)	50	**15.7** ($J_{P,F}$ = 4 Hz), 15.4 ($J_{P,F}$ = 4 Hz)	(–)
3	**1e**	4-$MeOC_6H_4$	99(76)	55	**16.4**, 16.0	*S* (–)
4	**1f**	4-MeC_6H_4	98(94)	51	**16.2**, 15.9	(–)
5	**1g**	2-MeC_6H_4	95(95)	50	**16.9**, 16.6	*S* (–)
6	**1h**	1-Ad	100(95)	34	**18.2**, 17.3	(+)
7	**1i**	CH_3	96(73)	33	**19.6**, 19.1	*S* (+)

[a] Determined by ^{31}P NMR spectroscopy of the crude reaction mixture; isolated yields are given in parentheses. [b] Determined by ^{31}P NMR analysis of the corresponding (*S*)-naproxen esters. [c] The major diastereomer is given in bold. [d] The absolute configuration was determined by comparison of the sign of the optical rotation with reported data.[7a–7c,21,22]

60 bar of hydrogen (Table 3). As we have previously reported for diethyl acetylphosphonate,[13] the hydrogenation of aliphatic **1h**,**i** does not occur in the presence of Pd/C; these substrates slowly decomposed with the formation of diisopropyl phosphite.

Conclusions

We have demonstrated a conceptually new approach to the synthesis of racemic and optically active α-hydroxy phosphonates by palladium-catalyzed hydrogenation of easily available α-keto phosphonates by molecular hydrogen. Palladium on carbon can be used as the catalyst for the synthesis of racemic ring-substituted α-hydroxybenzylphosphonates. The use of a catalytic amount of Pd(OCOCF$_3$)$_2$/(*R*)-MeO-BIPHEP in TFE resulted in the homogeneous asymmetric hydrogenation of α-aryl-α-keto and α-alkyl-α-keto phosphonates in excellent yields and with moderate enantioselectivities even at atmospheric hydrogen pressure, the procedure being very easy to handle. This method appears to be particularly promising for the preparation of optically active α-hydroxy phosphonates containing a quaternary β-carbon atom. Our ongoing experiments are focused on the fine-tuning of the structure of chiral ligands to improve the optical yield of the reaction and will be reported in due course.

Experimental Section

General: Optical rotations were measured with a VNIEKI-Prodmush AI-EPO polarimeter in a 0.25 dm cell at 20 °C. Mass spectra (EI) were recorded with a Varian MAT 311 spectrometer. Elemental analyses were performed by using a Carlo–Erba autoanalyzer. The melting points were measured with an Electrothermal 9100 indicator in a sealed capillary. TLC was carried out on 0.20 mm thick Macherey–Nagel plates (ALUGRAM® SIL G/UV$_{254}$).

Methanol was dried with magnesium methoxide followed by distillation. 2,2,2-Trifluoroethanol (TFE) (P&M-Invest) was distilled from anhydrous $CaSO_4$ and THF from sodium benzophenone ketyl. Triethyl phosphite (Merck) and triisopropyl phosphite[24] were treated with Na and then distilled under reduced pressure. (*S*)-(+)-2-(6-Methoxy-2-naphthyl)propanoyl chloride was obtained from (*S*)-(+)-2-(6-methoxy-2-naphthyl)propanoic acid {(*S*)-naproxen, $[a]_D^{20}$ = +66 (*c* = 1, $CHCl_3$), Akrihin} following a previously procedure.[25] Palladium(II) trifluoroacetate was prepared according to a literature procedure.[26] Palladium on carbon (10% Pd; Aldrich), (*R*)-(+)-BINAP (Dalchem), (*R*)-(+)-TolBINAP (Dalchem), (*R*)-(+)-MeO-BIPHEP (Aldrich), (*S*,*S*)-(–)-CHIRAPHOS (Dalchem) and (*S*,*S*)-(+)-Me-DuPhos (Aldrich) were used without purification.

(3*R*,4*R*)-3,4-Bis[(2′*R*,5′*S*)-3′-phenyl-1′,3′-diaza-2′-phosphabicyclo-[3.3.0]oct-2′-yloxy]-1-benzylpyrrolidine-2,5-dione (L6): A solution of (3*R*,4*R*)-1-benzyl-3,4-dihydroxypyrrolidine-2,5-dione[27] (1.11 g, 5 mmol) in THF (15 mL) was added dropwise at 20 °C over 20 min to a vigorously stirred solution of (2*R*,5*S*)-2-chloro-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane[28] (2.41 g, 10 mmol) and Et_3N (1.45 mL, 10.4 mmol) in THF (25 mL). The mixture was then heated to the boiling point, stirred for 1.5 h and cooled to 20 °C. Solid Et_3N·HCl was filtered off and the filtrate was concentrated in vacuo (40 Torr). The residue was purified by flash chromatography (silica gel, hexane/EtOAc, 5:1) to furnish the product as a light-yellow solid; yield: 2.20 g (70%). MS: *m*/*z* (%) = 629 (8) $[M]^+$, 408 (100) $[M - C_{11}H_{14}N_2OP]^+$. $C_{33}H_{37}N_5O_4P_2$ (629.63): calcd. C 62.95, H 5.92, N 11.12; found C 63.21, H 6.0, N 10.96.

α-Keto phosphonates **1a**–**i** were synthesized by standard Arbuzov reaction of acyl chlorides with trialkyl phosphites[7a,29] and purified by distillation or recrystallization; their spectral characteristics are given in the Supporting Information.

Optimization of the Reaction Conditions for the Asymmetric Hydrogenation Reaction. General Procedure: A Schlenk vessel was charged with palladium(II) trifluoroacetate (2.4 mg, 7.2 μmol), a chiral ligand (7.4 μmol if bidentate or 14.8 μmol if monodentate), and anhydrous acetone (3 mL) under argon. The mixture was stirred at room temp. for about 30–40 min. The solvent was removed under vacuum. Deaerated TFE (3 mL) and substrate **1a**–**c** (0.144 mmol) were added under argon to the colored solid residue and the mixture was stirred for 10 min. The resulting solution was transferred with a syringe into a stainless-steel autoclave filled with hydrogen. The Schlenk vessel was washed with TFE (0.5 mL), which was added to the main solution. The autoclave was sealed, pressurized with H_2, and the reaction mixture stirred under the desired conditions (pressure and temperature) for 6 h. At the end of the experiment, the reaction mixture was evaporated on a rotavapor and the residue was dissolved in $CDCl_3$ (1 mL). The resulting solution was divided into two equal portions. The first one was analyzed by ^{31}P NMR spectroscopy to determine the conversion and the yield of the desired product **2a**–**c**. The second one was treated with anhydrous pyridine (0.2 mL) and (*S*)-(+)-2-(6-methoxy-2-naphthyl)propanoyl chloride (45 mg, 0.181 mmol) and analyzed by ^{31}P NMR to determine the enantiomeric excess.

Asymmetric hydrogenation under atmospheric hydrogen pressure (including preparative experiments) was performed in a similar manner, a simple reactor, outlined below, being used instead of the autoclave.

Diisopropyl (*S*)-(–)-[Hydroxy(phenyl)methyl]phosphonate (2b): Deaerated TFE (3 mL) and substrate **1b** (39.0 mg, 0.144 mmol) were added under argon to a sample of the catalyst prepared in a Schlenk vessel from Pd(OCOCF$_3$)$_2$ (2.4 mg, 7.2 μmol) and (*R*)-(+)-MeO-BIPHEP (4.3 mg, 7.4 μmol), as described above, and the mixture was stirred for 10 min. The resulting solution was transferred into the hydrogenation unit composed of a round-bottomed flask equipped with a magnetic stirrer, a reflux condenser with a three-way adapter, a gas bubbler, and a long gas inlet tube passing through the condenser to the bottom of the flask, and filled with dry argon. The Schlenk vessel was washed with TFE (0.5 mL), which was added to the main solution. The argon supply was stopped and hydrogen was passed through the reactor using the same inlet tube. The reaction mixture was stirred at 80 °C for 6 h under a weak flow of hydrogen and then cooled. The solvent was removed under reduced pressure. The residue was dissolved in $CDCl_3$ and analyzed by ^{31}P NMR spectroscopy. The yield of **2b** thus determined was 97%. The product **2b** was purified by preparative TLC (CH_2Cl_2/MeOH, 40:1, R_f = 0.20). Isolated yield: 30.9 mg (79%), 45% *ee* [determined for the (*S*)-naproxen ester]. $[a]_D^{20}$ = –12.0 ($CHCl_3$, *c* = 1.0) {lit.: $[a]_D^{20}$ = –12.0 ($CHCl_3$, *c* = 1.0) for 45% *ee* (*S*),[7a] $[a]_D^{20}$ = –16.0 ($CHCl_3$, *c* = 1.0) for 60% *ee* (*S*),[22] $[a]_D^{20}$ = –17.3 ($CHCl_3$, *c* = 1.0) for 65% *ee* (*S*)[7b]}.

Diisopropyl (*S*)-(–)-[Hydroxy(4-fluorophenyl)methyl]phosphonate (2d): Synthesized similarly to **2b** in 99% yield by the hydrogenation of **1d** (41.5 mg, 0.144 mmol). Isolated yield: 40.1 mg (96%), 50%

ee, $[a]_D^{20}$ = –112.8 ($CHCl_3$, *c* = 1.0), R_f = 0.19 (CH_2Cl_2/MeOH, 40:1).

Diisopropyl (*S*)-(–)-[Hydroxy(4-methoxyphenyl)methyl]phosphonate (2e): Synthesized similarly to **2b** in 99% yield by the hydrogenation of **1e** (43.2 mg, 0.144 mmol). Isolated yield: 33.2 mg (76%), 55% *ee*, $[a]_D^{20}$ = –12.3 ($CHCl_3$, *c* = 0.8) {lit.: $[a]_D^{20}$ = –10.0 {$CHCl_3$, *c* = 0.8} for 45% *ee* (*S*),[7a] $[a]_D^{20}$ = –12.3 ($CHCl_3$, *c* = 0.8) for 55% *ee* (*S*)[7b]}, R_f = 0.14 (CH_2Cl_2/MeOH, 40:1).

Diisopropyl (*S*)-(–)-[Hydroxy(4-methylphenyl)methyl]phosphonate (2f): Synthesized similarly to **2b** in 98% yield by the hydrogenation of **1f** (41.0 mg, 0.144 mmol). Isolated yield: 39.0 mg (94%), 51% *ee*, $[a]_D^{20}$ = –13.4 ($CHCl_3$, *c* = 0.8), R_f = 0.17 (CH_2Cl_2/MeOH, 40:1).

Diisopropyl (*S*)-(–)-[Hydroxy(2-methylphenyl)methyl]phosphonate (2g): Synthesized similarly to **2b** in 95% yield by the hydrogenation of **1g** (41.0 mg, 0.144 mmol). Isolated yield: 39.2 mg (95%), 50% *ee*, $[a]_D^{20}$ = –35.2 ($CHCl_3$, *c* = 0.9) {lit.: $[a]_D^{20}$ = –25.3 ($CHCl_3$, *c* = 0.8) for 41% *ee* (*S*),[7c] $[a]_D^{20}$ = –47.0 ($CHCl_3$, *c* = 0.9) for 76% *ee* (*S*),[7a,c] $[a]_D^{20}$ = –60.0 ($CHCl_3$, *c* = 0.9) for 97% *ee* (*S*)[7b,c]}, R_f = 0.19 (CH_2Cl_2/MeOH, 40:1).

Diisopropyl (*S*)-(+)-[Hydroxy(1-adamantyl)methyl]phosphonate (2h): Synthesized similarly to **2b** in 100% yield by the hydrogenation of **1h** (47.3 mg, 0.144 mmol). Isolated yield: 45.2 mg (95%), 34% *ee*, $[a]_D^{20}$ = +4 (MeOH, *c* = 1.0).

Diisopropyl (*S*)-(+)-1-Hydroxyethylphosphonate (2i): Synthesized similarly to **2b** in 96% yield by the hydrogenation of **1i** (40.0 mg, 0.192 mmol) in TFE (5 mL) in the presence of a catalyst prepared from $Pd(OCOCF_3)_2$ (3.2 mg, 9.2 μmol) and (*R*)-(+)-MeO-BIPHEP (5.7 mg, 9.8 μmol). Isolated yield: 29.6 mg (73%), 33% *ee*, $[a]_D^{20}$ = +2.2 (acetone, *c* = 0.9) {lit.[21] $[a]_D^{20}$ = +1.46 (acetone) for 20% *ee* (*S*), $[a]_D^{20}$ = +5.81 (acetone) for 87% *ee* (*S*), $[a]_D^{20}$ = +5.92 (acetone) for 89% *ee* (*S*), $[a]_D^{20}$ = –1.21 (acetone) for 19% *ee* (*R*), $[a]_D^{20}$ = –6.03 (acetone) for 90% *ee* (*R*)}.

Diisopropyl (±)-[Hydroxy(phenyl)methyl]phosphonate [(±)-2b]: Compound **1b** (400 mg, 1.48 mmol) in dry methanol (32 mL) and 10% Pd/C (80 mg, 5 mol-%) were placed in a stainless-steel autoclave with a glass insert equipped with a magnetic stirrer and filled with dry argon. The autoclave was sealed, flushed three times with hydrogen, and pressurized with H_2 to 30 bar. The reaction mixture was stirred at room temperature for 2 h. At the end of the experiment the catalyst was filtered off using a short pad of silica gel. The mother liquor was evaporated under reduced pressure and the residue was dissolved in $CDCl_3$. ^{31}P NMR analysis showed a 91% yield of (±)-**2b**. After recrystallization from diethyl ether the yield of spectrally pure (±)-**2b** was 279 mg (69%), m.p. 92 °C.[30]

Diisopropyl (±)-[Hydroxy(4-fluorophenyl)methyl]phosphonate [(±)-2d]: Compound (±)-**2d** was synthesized similarly to (±)-**2b** in 96% yield by the hydrogenation of **1d** (400 mg, 1.39 mmol) in dry methanol (32 mL) in the presence of 10% Pd/C (74 mg, 5 mol-%). After recrystallization from diethyl ether the yield of pure (±)-**2d** was 351 mg (87%), m.p. 93 °C.[31] $C_{13}H_{20}FO_4P$ (290.27): calcd. C 53.79, H 6.94; found C 53.55, H 6.83.

Diisopropyl (±)-[Hydroxy(4-methoxyphenyl)methyl]phosphonate [(±)-2e]: Compound (±)-**2e** was synthesized similarly to (±)-**2b** by the hydrogenation of **1e** (400 mg, 1.33 mmol) in dry methanol (32 mL) in the presence of 10% Pd/C (71 mg, 5 mol-%). The yield of spectrally pure (±)-**2e** was 402 mg (100%), m.p. 141–142 °C.[30b]

Diisopropyl (±)-[Hydroxy(4-methylphenyl)methyl]phosphonate [(±)-2f]: Compound (±)-**2f** was synthesized similarly to (±)-**2b** by the hydrogenation of **1f** (100 mg, 0.35 mmol) in dry methanol (8 mL) in the presence of 10% Pd/C (19 mg, 5 mol-%). The reaction was performed at 15 bar hydrogen pressure. The yield of spectrally pure (±)-**2f** was 101 mg (100%), m.p. 115–116 °C.[32]

Diisopropyl (±)-[Hydroxy(2-methylphenyl)methyl]phosphonate [(±)-2g]: Compound (±)-**2g** was synthesized similarly to (±)-**2b** in 94% yield by the hydrogenation of **1g** (50 mg, 0.18 mmol) in dry methanol (4 mL) in the presence of 10% Pd/C (19 mg, 5 mol-%). The reaction was performed at 60 bar hydrogen pressure. Spectrally pure (±)-**2g** (41 mg, 81%) was isolated by TLC (CH_2Cl_2/MeOH, 40:1), m.p. 92 °C.[33]

The spectroscopic data for (±)-**2b**,**d**–**g** were in agreement with those for **2b**,**d**–**g**.

Supporting Information (see also the footnote on the first page of this article): Spectral data of compounds **1**, **2b**,**d**–**i** and **L6**.

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