

Palladium-Catalyzed Asymmetric Hydrogenation of *N*-Hydroxy- α -imino Phosphonates Using Brønsted Acid as Activator: The First Catalytic Enantioselective Approach to Chiral *N*-Hydroxy- α -amino Phosphonates

Nataliya S. Goulioukina,^{a,*} Ilya A. Shergold,^a Grigorii N. Bondarenko,^a Mikhail M. Ilyin,^b Vadim A. Davankov,^b and Irina P. Beletskaya^{a,*}

^a Department of Chemistry, Moscow State University, Leninskie Gory, GSP-1, Moscow 119991, Russia

Fax: (+7)-495-939-1854; e-mail: goulioukina@org.chem.msu.ru or beletska@org.chem.msu.ru

^b Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov str., Moscow 119991, Russia

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Abstract: The enantioselective synthesis of ring-substituted [N-(hydroxyamino)(phenyl)methylphosphonic esters *via* asymmetric hydrogenation of the corresponding *N*-hydroxy- α -imino phosphonates with up to 90% *ee* was developed using catalytic amounts of palladium(II) acetate and (*R*)-BINAP in

2,2,2-trifluoroethanol with a Brønsted acid as an activator.

Keywords: asymmetric catalysis; Brønsted acids; hydrogenation; *N*-hydroxy- α -amino phosphonates; *N*-hydroxy- α -imino phosphonates; palladium

Introduction

The interest towards the application of homogeneous palladium catalysis for asymmetric hydrogenation was generated in 2001, when Amii et al. first reported enantioselective reduction of imino esters with a Pd(OCOFCF₃)₂/(*R*)-BINAP complex.^[1] In the past decade, the method was successfully applied to a wide scope of prochiral substrates containing C=N,^[2] C=C–N,^[3] or C=O^[4] double bonds, thus promising to become an effective tool for both routine and advanced organic synthesis. In our ongoing efforts towards the development of a general synthetic approach to chiral α -functionalized phosphonates based on the enantioselective hydrogenation of carbon-carbon and especially carbon-heteroatom unsaturated precursors,^[4b,5] we became interested in exploring homogeneous Pd catalysis for a practical synthesis of optically active *N*-hydroxy- α -amino phosphonates. This task seemed particularly intriguing since successful examples of asymmetric hydrogenation of oximes are sparse.

N-Hydroxyamino phosphonic acids and their derivatives are known as biologically active organic compounds of practical significance. One bright example is the antibiotic fosmidomycin, 3-[*N*-formyl-*N*-(hydroxyamino)propylphosphonic acid, which is a prom-

ising antimalarial drug candidate that has been successfully used in clinical trials.^[6] *N*-Hydroxy- α -amino phosphonic acids are phosphorus isosters of *N*-hydroxy- α -amino acids, which are important in many metabolic and biological processes.^[7] *N*-Hydroxy- α -amino phosphonates exert herbicidal and growth-regulating activity^[8] and were announced as suitable synthons for pseudopeptides, prospective, in part, as haptens for reactive immunization.^[9] They also find synthetic applications for the preparation of α -amino phosphonates^[10] and phosphonylated nitrones. The latter are of interest as spin-trapping agents^[11] and convenient precursors for ring-substituted 2-phosphonomethylisoxazolidines.^[12,13]

Several methods have been reported for the synthesis of racemic *N*-hydroxy- α -amino phosphonic acids and esters, including phosphorylation of oximes^[14] or nitrones,^[15] borane reduction of *N*-hydroxy- or *N*-benzyloxy- α -imino phosphonates,^[16–18] controlled reduction of α -nitro or α -nitroso phosphonates,^[19] a Mitsunobu reaction of α -hydroxy phosphonates with phenyl [(*tert*-butoxycarbonyl)oxy]carbamate,^[9] S_N2 reaction of phosphonomethyl triflates with *tert*-butyldimethylsilyloxyamine,^[13] and others.^[8] To the best of our knowledge, the sole reported approach to optically active *N*-hydroxy- α -amino phosphonates relies on the addition of phosphites to chiral nitrones,^[10,20] and thus

requires the application of a stoichiometric amount of chiral auxiliary.

Herein we wish to report the first example of the catalytic synthesis of optically active *N*-hydroxy- α -amino phosphonates by homogeneous Pd-catalyzed asymmetric hydrogenation of *N*-hydroxy- α -imino phosphonates.

Results and Discussion

A model substrate – diethyl [*N*-(hydroxyimino)]-(phenyl)methylphosphonate (**1a**) – was prepared according to Berlin's method^[16,21] by condensation of diethyl benzoylphosphonate with hydroxylamine. The product was obtained as a 66:34 mixture of *E*- and *Z*-isomers which are easily distinguishable by ³¹P NMR spectroscopy. The major thermodynamically more stable *E*-isomer resonates at δ_P = 9.7 ppm whereas the signal from the minor thermodynamically less stable *Z*-isomer undergoes an upfield shift due to a shielding effect from the lone pairs of the oxime oxygen and appears at δ_P = 5.7 ppm.^[21b]

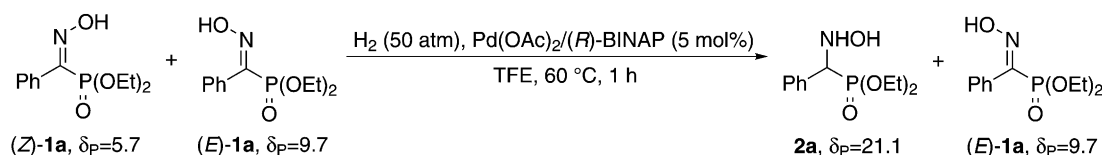
In the initial experiments, the above mixture of isomers **1a** was subjected to the reduction under 50 atm of hydrogen pressure at 60 °C in 2,2,2-trifluoroethanol (TFE) with the Pd(OAc)₂/(*R*)-BINAP system (Scheme 1). The course of the reaction was monitored by ³¹P NMR. Only (*Z*)-**1a** appeared to undergo the hydrogenation, the signal at δ_P = 5.7 ppm disappearing

completely over 1 h and the signal from diethyl [*N*-(hydroxyamino)](phenyl)methylphosphonate (**2a**) arising at δ_P = 21.1 ppm. At the same time, the more thermodynamically stable isomer (*E*)-**1a** remained unreactive (Table 1, entry 1).

Variation of the ligand [(*R*)-BINAP, (*R*)-TolBINAP, (*R*)-MeO-BIPHEP, (*S,S*)-CHIRAPHOS, (*S,S*)-MeDuPHOS], precatalyst [Pd(OAc)₂, Pd(OCOCF₃)₂, Pd₂(dba)₃·CHCl₃], solvent (TFE, MeOH, toluene, EtOAc, CH₂Cl₂), hydrogen pressure (1–100 atm), temperature (20–80 °C), addition of 4 Å molecular sieves,^[2b] or prolongation of the reaction time were to no avail. Under drastic conditions, slow degradation of (*E*)-**1a** was observed without increasing the yield of the target product **2a**. The situation changed dramatically after a catalytic amount of (1*S*)-(+)-10-camphorsulfonic acid (CSA) was added as an activator. In the presence of CSA (10 mol%) the yield of **2a** rose up to 91% at 92% conversion of **1a**, albeit, the optical yield was only 33% *ee* (Table 1, entry 2).

Since the asymmetric hydrogenation of *E*- and *Z*-isomers of prochiral oximes is known to proceed with different enantioselectivity,^[22] the examination was made as to how the *E/Z* composition of the initial substrate **1a** affects the optical purity of the product **2a**. It was found that the *ee* increases up to 69% in the case of an 86:14 *E/Z*-isomer ratio (entry 3) and achieves 85% for the individual (*E*)-**1a** (entry 4).

The observed relationship between the enantiomeric excess of the product **2a** and the *E/Z* ratio of the



Scheme 1. Comparative abilities of *Z*- and *E*-isomers of oxime **1a** for hydrogenation.

Table 1. The effect of *E/Z* ratio on the reactivity of **1a** and the enantioselectivity of the formation of **2a**.^[a]

$\text{Ph}-\text{CH}=\text{N}-\text{OH} \cdot \text{P}(\text{OEt})_2 \xrightarrow[\text{CSA (10 mol\%), TFE, 60 } ^\circ\text{C, 1 h}]{\text{H}_2 (50 \text{ atm}), \text{Pd}(\text{OAc})_2 / (R)\text{-BINAP} (5 \text{ mol}\%)} \text{Ph}-\text{CH}(\text{NHOH})-\text{P}(\text{OEt})_2$ (<i>E</i>)- and (<i>Z</i>)- 1a 2a				
Entry	<i>E/Z</i> ratio	Conversion of 1a [%] ^[b]	Yield of 2a [%] ^[b]	<i>ee</i> [%] ^[c]
1 ^[d]	66:34	35	34	n.a.
2	66:34	92	91	33
3	86:14	92	91	69
4	100:0	93	91	85

^[a] Unless otherwise stated, reactions were performed in TFE (4 mL) on a 0.144-mmol scale: Pd(OAc)₂ (7 μmol, 5 mol%), (*R*)-BINAP (7 μmol, 5 mol%), CSA (14 μmol, 10 mol%), H₂ (50 atm), 60 °C, 1 h.

^[b] Determined by ³¹P NMR analysis of the crude reaction mixture.

^[c] Determined by chiral HPLC analysis; n.a. = not analyzed.

^[d] Without CSA.

starting oxime **1a** clearly indicates that the crucial role of the Brønsted acid activator cannot be explained in terms of the lowering of the energy barrier of *Z/E* isomerization *via* protonation and the establishment of rapid equilibrium between the two forms under acidic conditions. In several recent publications^[3b–e] on Pd-catalyzed hydrogenation of C=N bonds, isotopic labeling experiments were described that agree with the reaction mechanism in which a sequential H⁺/H[−] transfer takes place. If so, the role of the Brønsted acid can be explained in terms of formation of the iminium intermediate that should exhibit enhanced reactivity towards nucleophilic attack, and the *Z/E* isomerization process is slower than hydrogenation. The similar strategy of C=N double bond activation has been previously applied in Ir-, Ru-, and Rh-catalyzed hydrogenation processes^[23] and became a hot point in the Pd-catalyzed homogeneous hydrogenation of prochiral imines and heteroaromatic compounds while the present work was in progress.^[2d,3]

In a control experiment, the chemical and configurational stability of the product **2a** under the reaction conditions was tested and proved. We further performed a systematic screening of the reaction conditions of the asymmetric hydrogenation of the individual (*E*)-**1a**, which is easily available on treating the mixture of isomers with hydrogen chloride in ethanol.^[21b] The results are summarized in Table 2. Solvent experiments revealed that no hydrogenation reaction was observed in toluene, MeOH, and CH₂Cl₂ (entries 2–4), and TFE was the only effective one. This particular solvent behaviour of TFE is widespread in homogeneous catalysis^[1,2a–d,3,4,24] and has been rationalized in some cases.^[1,24]

Other palladium precursors were also tested in the reaction. In comparison with palladium(II) acetate, Pd(OCOFCF₃)₂ exhibited lower catalytic activity with similar *ee* values (entry 5). PdCl₂ and Pd₂(dba)₃·CHCl₃ were totally ineffective (entries 6 and 7). Next, several commercially available axial chiral bidentate bisphosphine ligands were examined. Electron-rich (*S,S*)-Me-DuPhos and (*S,S*)-CHIRAPHOS forming a quite rigid five-membered chelate ring^[2f] had almost no catalytic activity (entries 8 and 9). Atropoisomeric ligands bearing a binaphthyl motif providing a larger bite angle and chelate ring flexibility, gave reasonable results (entries 1 and 10), and (*R*)-BINAP was found to be superior to the other ligands in both reactivity and enantioselectivity. The effect of the catalyst amount was also tested. Reducing the catalyst loading to 3–4 mol% led to a noticeable formation of by-products (entries 11 and 12).

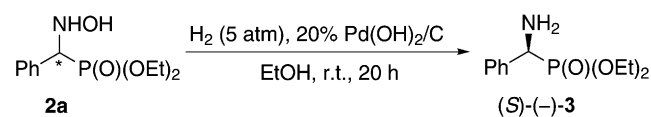
Thereafter, a number of Brønsted acids were screened. When a catalytic amount of trifluoroacetic acid was used, the conversion of (*E*)-**1a** was full but the desired product **2a** was not obtained. Benzoic or 5-sulfosalicylic acids (10 mol%) did not afford satis-

factory conversion of (*E*)-**1a**. In comparison with CSA, the use of achiral TsOH (entry 13) or racemic 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BNPA) (entry 14) gave the expected product **2a** with similar *ee* values but in decreased yields. Lower enantioselectivity, yield, and conversion were observed when the CSA loading was increased to 20 mol% (entry 15). In the presence of 5 mol% CSA the conversion decreased substantially (entry 16), so a 10 mol% amount of CSA was found to be optimal. The possible asymmetric induction from optically active CSA was also checked. When (*S*)-BINAP was used instead of (*R*)-BINAP, the optical yield stayed roughly constant within the measurement error (entry 17). Accordingly, application of (±)-BINAP furnished the racemic product **2a** (entry 18). Consequently, the stereoinduction is controlled by the chiral ligand only.

Finally, the effect of hydrogen pressure and reaction temperature on the enantioselectivity and reactivity of the hydrogenation was examined. The hydrogen pressure had only a weak effect on the conversion of (*E*)-**1a** and the yield of **2a** (entries 19–21). The optical yield slightly decreased with a pressure increase to 70–90 atm (entries 20 and 21) and significantly dropped at 30 atm (entry 19). The lowering of the temperature resulted in the enhancement of enantioselectivity (entries 25, 1, 23). The best *ee* value (90%) was obtained at 40 °C, however, the reaction almost stopped at 68% conversion (entry 23). Prolongation of the reaction time up to 6 h resulted in just an insignificant increase in yield (entry 24).

The product **2a** was isolated by column chromatography and characterized by IR, ³¹P, ¹H, and ¹³C NMR spectroscopy, which were in agreement with the literature data.^[16] The IR spectrum along with the characteristic pattern of the diethoxyphosphoryl moiety reveals a broad O–H stretching vibration band^[25] at 3240 cm^{−1}. The ¹H and ¹³C NMR spectra show two sets of signals for the diastereotopic ethoxy groups. The doublets of the methyne proton at $\delta_{\text{H}} = 4.50$ ppm (²*J*_{H,P} = 18.4 Hz) and α -C-atom at $\delta_{\text{C}} = 65.5$ ppm (¹*J*_{C,P} = 146.5 Hz) are the main characteristic features. It is noteworthy that the spectral data unambiguously indicate the product **2a** to be *N*-hydroxy- α -amino phosphonate rather than the α -amino phosphonate.^[26]

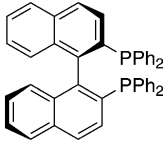
To assign the absolute configuration at the new stereogenic center, a sample of **2a** was transformed with some racemization to diethyl α -aminobenzylphosphonate (**3**) by hydrogenation in the presence of Pearlman's catalyst^[10b] (Scheme 2). The (*S*) configuration



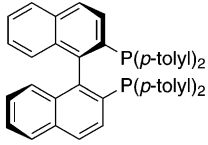
Scheme 2. Assignment of the absolute configuration.

Table 2. Screening of reaction conditions for the asymmetric hydrogenation of oxime **1a**.^[a]

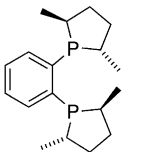
Entry	Pd-precursor	Ligand	Brønsted acid	Solvent	Pressure [atm]	<i>T</i> [°C]	Conversion of 1a [%] ^[b]	Yield of 2a [%] ^[b]	<i>ee</i> [%] ^[c]
1	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	50	60	93	91	85
2	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	toluene	50	60	20	0	n.a.
3	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	MeOH	50	60	3	0	n.a.
4	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	CH ₂ Cl ₂	50	60	8	0	n.a.
5	Pd(OCOCF ₃) ₂	(<i>R</i>)-BINAP	CSA	TFE	50	60	78	67	84
6	PdCl ₂	(<i>R</i>)-BINAP	CSA	TFE	50	60	5	0	n.a.
7	Pd ₂ (dba) ₃ ·CHCl ₃	(<i>R</i>)-BINAP	CSA	TFE	50	60	3	0	n.a.
8	Pd(OAc) ₂	(<i>S,S</i>)-Me-DuPhos	CSA	TFE	50	60	32	24	n.a.
9	Pd(OAc) ₂	(<i>S,S</i>)-CHIRA-PHOS	CSA	TFE	50	60	10	0	n.a.
10	Pd(OAc) ₂	(<i>R</i>)-TolBINAP	CSA	TFE	50	60	91	84	74
11 ^[d]	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	50	60	90	76	n.a.
12 ^[e]	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	50	60	88	69	n.a.
13	Pd(OAc) ₂	(<i>R</i>)-BINAP	TsOH	TFE	50	60	83	78	86
14	Pd(OAc) ₂	(<i>R</i>)-BINAP	BNPA	TFE	50	60	88	77	83
15	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA ^[f]	TFE	50	60	88	79	72
16	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA ^[g]	TFE	50	60	58	49	n.a.
17	Pd(OAc) ₂	(<i>S</i>)-BINAP	CSA	TFE	50	60	93	91	83
18	Pd(OAc) ₂	(±)-BINAP	CSA	TFE	50	60	84	83	0
19	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	30	60	90	88	74
20	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	70	60	88	86	82
21	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	90	60	87	85	82
22	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	50	20	43	43	n.a.
23	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	50	40	68	68	90
24 ^[h]	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	50	40	74	72	86
25	Pd(OAc) ₂	(<i>R</i>)-BINAP	CSA	TFE	50	80	88	84	80



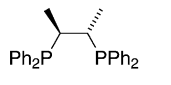
(*R*)-BINAP



(*R*)-TolBINAP



(*S,S*)-Me-DuPhos



(*S,S*)-CHIRAPHOS

^[a] Unless otherwise stated, reactions were carried out with (*E*)-**1a** (0.144 mmol), Pd precursor (7 μmol, 5 mol%), ligand (7 μmol, 5 mol%), Brønsted acid (14 μmol, 10 mol%), and 4 mL of solvent under directed conditions for 1 h.

^[b] Determined by ³¹P NMR analysis of the crude reaction mixture.

^[c] Determined by chiral HPLC analysis; n.a. = not analyzed.

^[d] (*E*)-**1a** (0.155 mmol), Pd(OAc)₂ (7 μmol, 4 mol%), (*R*)-BINAP (7 μmol, 4 mol%), CSA (15 μmol, 10 mol%) were used.

^[e] (*E*)-**1a** (0.221 mmol), Pd(OAc)₂ (7 μmol, 3 mol%), (*R*)-BINAP (7 μmol, 3 mol%), CSA (22 μmol, 10 mol%), and 6 mL of TFE were used.

^[f] 20 mol% CSA was used.

^[g] 5 mol% CSA was used.

^[h] Reaction time was 6 h.

of α-amino phosphonate **3** was proven by comparison of the sign of the optical rotation with published data,^[27] confirming that the major enantiomer of **2a** has the (*S*)-*N*-hydroxy-α-amino phosphonate structure.

Next, to explore the scope of the reaction, a series of *para*-substituted diethyl [*N*-(hydroxyimino)-(phenyl)methylphosphonates (*E*)-**1b–f** was subjected to hydrogenation under the optimal conditions, found above, and the results are summarized in Table 3. In general, high yields and good enantioselectivities

were obtained. Substitution at the *para*-position has a detrimental effect on the enantioselectivity. The reason is not clear. We can only cite similar observations in Pd-catalyzed hydrogenations of prochiral ketones^[4c] and 2,5-disubstituted pyrroles.^[3a] It is noteworthy that oxime (*E*)-**1e** reveals very low reactivity which may be ascribed to significant stabilization of the iminium intermediate by a mesomeric effect of the MeO group. In the case of the bromo-substituted substrate (*E*)-**1f** no desirable product was obtained. The competitive oxidative addition of the aryl bro-

Table 3. Pd-catalyzed asymmetric hydrogenation of oximes (*E*)-**1a–g**.^[a]

$ \begin{array}{c} \text{HO}-\text{N} \\ \diagup \\ \text{Ar}-\text{C}=\text{P}(\text{O})(\text{OR})_2 \\ \text{(E)-1a-g} \end{array} \xrightarrow[\text{CSA (10 mol\%), TFE, 60 }^\circ\text{C, 1 h}]{\text{H}_2 \text{ (50 atm), Pd(OAc)}_2 \text{ (R)-BINAP (5 mol\%)}} \begin{array}{c} \text{NHOH} \\ \diagup \\ \text{Ar}-\text{C}-\text{P}(\text{O})(\text{OR})_2 \\ \text{2a-g} \end{array} $					
Substrate	Ar	R	Conversion [%] ^[b]	Yield of 2 [%] ^[b]	ee [%] ^[c]
(<i>E</i>)- 1a	Ph	Et	94	92	85
(<i>E</i>)- 1b	<i>p</i> -FC ₆ H ₄	Et	90	89	81
(<i>E</i>)- 1c	<i>p</i> -ClC ₆ H ₄	Et	87	87	75
(<i>E</i>)- 1d	<i>p</i> -MeC ₆ H ₄	Et	85	85	72
(<i>E</i>)- 1e	<i>p</i> -MeOC ₆ H ₄	Et	61	61	78
(<i>E</i>)- 1f	<i>p</i> -BrC ₆ H ₄	Et	20	< 10	-
(<i>E</i>)- 1g	<i>p</i> -FC ₆ H ₄	<i>i</i> Pr	91	91	90

^[a] Reactions were carried out with (*E*)-**1a–g** (0.144 mmol), Pd(OAc)₂ (7 μ mol, 5 mol%), (*R*)-BINAP (7 μ mol, 5 mol%), CSA (14 μ mol, 10 mol%), and 4 mL of solvent under directed conditions for 1 h.

^[b] Determined by ³¹P NMR analysis of the crude reaction mixture.

^[c] Determined by chiral HPLC analysis.

mide onto the palladium(0) species is probably responsible for this failure.^[4a]

Stereoselectivity of the process essentially depends on the steric demands from the dialkoxyphosphoryl group, and diisopropyl ester substitution gave a substantial improvement in enantiomeric excess of up to 90% ee [*cf.* results for (*E*)-**1b** and (*E*)-**1g**]. The only inconvenience is the lability of the diisopropyl phosphonates in the presence of strong acids, such as HCl, hence column chromatography has to be used for isolating the individual (*E*)-**1g** isomer.

Conclusions

In summary, ring-substituted [*N*-(hydroxy)imino]-(phenyl)methylphosphonic esters, which are stable and easily available in the *E*-configuration, can be hydrogenated in TFE medium using Pd(OAc)₂/(*R*)-BINAP as a catalyst and a Brønsted acid as an activator with enantioselectivities of up to 90% ee. The proposed method provides the first catalytic, most straightforward, and atom-economical approach to enantioenriched *N*-hydroxy- α -amino phosphonates, as well as demonstrating the possibility to expand homogeneous asymmetric palladium catalysis to oximes hydrogenation.

Experimental Section

Typical Experimental Procedure for the Asymmetric Hydrogenation of Oxime (*E*)-**1a**

A Schlenk tube dried at 120 °C for 1 h, equipped with stirring bar and septum cap, was charged with Pd(OAc)₂ (1.6 mg, 7 μ mol), (*R*)-BINAP (4.5 mg, 7 μ mol), and 4 mL of

anhydrous TFE under an argon atmosphere. The mixture was gently heated to 70 °C with stirring until (*R*)-BINAP was completely dissolved and the solution became brownish-red. After cooling, (*E*)-**1a** (37.0 mg, 0.144 mmol) and CSA (3.2 mg, 14 μ mol) were added under Ar. The mixture was stirred until total homogenization and transferred with a syringe into a steel autoclave with a glass inlet, equipped with a stirring bar and filled with dry argon. The autoclave was sealed, pressurized with H₂ to 50 atm, the temperature was increased to 60 °C, and the reaction mixture was stirred for 1 h. After the end of the experiment, TFE was removed under reduced pressure and the residue was dissolved in CDCl₃ to be analyzed by ³¹P NMR. The product **2a** was isolated by column chromatography on silica gel (CH₂Cl₂/MeOH 40:1). The enantiomeric excess was determined by HPLC analysis in comparison with authentic racemic material.

Diethyl [N-(hydroxy)amino](phenyl)methylphosphonate (2a): White solid; 85% ee; *R*_f = 0.3 (CH₂Cl₂/MeOH 40:1), mp 117.6–119.0 °C (benzene); ³¹P NMR (162 MHz, CDCl₃): δ = 21.1; ¹H NMR (400 MHz, CDCl₃): δ = 1.17 (t, *J* = 7.0 Hz, 3H, CH₃), 1.27 (t, *J* = 7.0 Hz, 3H, CH₃), 3.85–4.07 (m, 4H, CH₂), 4.50 (d, *J* = 18.4 Hz, PCH), 5.10 and 5.79 (two br. s, each 1H, NH and OH), 7.32 (m, 1H, aryl), 7.37 (m, 2H, aryl), 7.46 (m, 2H, aryl); ¹H NMR (400 MHz, DMSO-*d*₆): δ = 1.04 (t, *J* = 7.1 Hz, 3H, CH₃), 1.18 (t, *J* = 7.1 Hz, 3H, CH₃), 3.69–3.89 (m, 2H, CH₂), 3.97 (m, 2H, CH₂), 4.33 (d, *J* = 20.4 Hz, PCH), 6.08 and 7.63 (two s, each 1H, NH and OH), 7.26 (m, 1H, aryl), 7.32 (m, 2H, aryl), 7.43 (m, 2H, aryl); ¹³C NMR (101 MHz, CDCl₃): δ = 16.2 (d, *J* = 5.7 Hz), 16.3 (d, *J* = 5.9 Hz), 62.9 (d, *J* = 6.8 Hz), 63.1 (d, *J* = 6.7 Hz), 65.5 (d, *J* = 146.5 Hz, CP), 128.3, 128.5, 128.6, 134.2 (d, *J* = 5.9 Hz); IR (Nujol): ν = 3240 (OH), 1250 (P=O), 1060 (O–C), 1040 (O–C), 980 (POC–C) cm^{–1}; HR-MS: *m/z* = 541.1839, calcd. for [2M+Na]⁺ (C₂₂H₃₆N₂O₈P₂Na): 541.1844; [α]_D: –33.5° (c 1.91, MeOH) for an enantiomerically enriched sample of 85% ee; HPLC (Kromasil Amy-Coat column, hexane/*i*-PrOH 9:1, 220 nm): *t*_r (minor enantiomer) = 9.6 min, *t*_r (major enantiomer) = 13.6 min.

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