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One-Pot Two-Step Synthesis of Optically Active α-Amino Phosphonates by Palladium-Catalyzed Hydrogenation/Hydrogenolysis of α-Hydrazono Phosphonates

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Abstract: An efficient and convenient *one-pot* procedure for the stereoselective catalytic synthesis of ring-substituted [amino(phenyl)methyl]phosphonates has been developed. The enantioselective hydrogenation of easily available diisopropyl (*Z*)-[aryl(phenylhydrazono)methyl]phosphonates using palladium(II) acetate as a precatalyst, (*R*)-2,2′-bis (diphenylphosphino)-5,5′-dichloro-6,6′-dimethoxy-1,1′-biphenyl [(*R*)-Cl–MeO-BIPHEP] as a ligand, and (1*S*)-(+)-10-camphorsulfonic acid as an activator in a mixture of 2,2,2-trifluoroethanol and methylene chloride at ambient temperature results in the formation of corresponding [aryl(2-phenylhydrazino)methyl]phosphonates. The subsequent cleavage of the N–N bond has been accomplished with molecular hydrogen after the addition of palladium on carbon and methanol into crude reaction mixture to afford the optically active [amino(aryl)methyl]phosphonates. The method is operationally simple and provides an appreciable enantioselectivity up to 98% *ee*.

Keywords: α-amino phosphonates; asymmetric catalysis; α-hydrazono phosphonates; hydrogenation; palladium

α-Amino phosphonates, particularly nonracemic ones, have been a topic for decades due to a wide spectrum of their possible applications.[1] Nevertheless, the stereocontrolled formation of α-amino phosphonates remains a challenge in chemical synthesis. Among catalytic concepts for the enantioselective synthesis of α-amino phosphonates, two methodologies are leading, namely, asymmetric hydrophosphonylation of aldimines and ketimines and asymmetric reduction of α,β-dehydroaminophosphonates.[2] Several years ago we reported on the feasibility of Rh-catalyzed asymmetric hydrogenation of α-imino phosphonates as a straightforward access to optically active α-amino phosphonates containing the quaternary β-carbon atom.[3] Subsequently, this approach was extended on oxazaborolidine catalyzed reduction of (2,2,2-trifluoro-1-iminoethyl)phosphonates with catecholeborane.[4] Along with all apparent advantages, some pitfalls of this method should be mentioned. First, α-imino phosphonates are actually an equilibrium mixture of *Z*/*E*-isomers, which may have an adverse effect on the overall stereoselectivity of the process. In addition, these starting substrates are slowly hydrolyzed on storage. Finally, the common synthesis of α-imino phosphonates *via* the Michaelis-Arbuzov rearrangement requires the usage of labile imidoyl chlorides under harsh reaction conditions.[5] When the present paper was in preparation, Zhou et al. communicated on excellent results in Pd-catalyzed asymmetric hydrogenation of α-tosylimino phosphonates.[6] However, the latter precursors cannot be considered the best choice, because they are synthesized from the same racemic α-tosylamino phosphonates by *N*-chlorination/dehydrochlorination procedure.[7]

Readily accessible α-oxo phosphonates[8] are important reagents for the preparation of elaborate phosphonates. Unfortunately, they cannot be used for the synthesis of the corresponding α-imino phosphonates since the interaction of simple nucleophiles like ammonia and amines as well as water, alcohols and thiols with α-oxo phosphonates leads to C–P bond cleavage.[9] On the contrary, nucleophiles with an α-heteroatom, such as hydroxylamine and substituted hydrazines, smoothly react with α-oxo phosphonates

to yield the corresponding oximes and hydrazones. α-Hydrazono phosphonates are quite stable, easy to handle, and can be isolated as individual *Z*- or *E*-isomers. In general terms, hydrazones (in particular *N*-acylhydrazones) are recognized as stable imine surrogates and versatile electrophiles for the synthesis of various nitrogen-containing compounds.[10] As for the chemistry of organophosphorus compounds, the use of α-C=N unsaturated precursors in the synthesis of racemic α-amino phosphonates originated from reduction of α-hydrazono phosphonates.[11]

Over the recent fifteen years, palladium complexes have been successfully applied in asymmetric hydrogenation of various prochiral substrates bearing C=N double bond,[6,12] including hydrazones.[12e,13] Considerable advances in this field and our previous experience[14] prompted us to study an application of palladium catalysis for the synthesis of optically active α-amino phosphonates using α-hydrazono phosphonates as convenient precursors. Herein we report our results.

We prepared three model precursors (*Z*)-**1**, (*Z*)-**2a**, and (*E*)-**2a** distinguished by substituent at the nitrogen atom and by the configuration of the C=N double bond (Figure 1). *N*-Benzoylated α-hydrazono phosphonate was synthesized according to a known procedure[15] and was isolated by column chromatography as an individual *Z*-isomer [(*Z*)-**1**]. We unambiguously proved the conformation across the C=N bond by the X-ray diffraction data (Figure 2).[16]

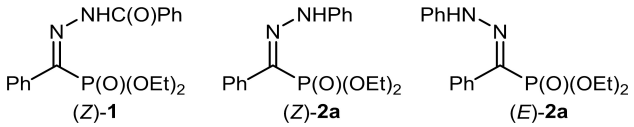


Figure 1. Model substrates screened in palladium-catalyzed asymmetric hydrogenation.

We strongly hoped to use (*Z*)-**1** as a prochiral precursor, this compound being the only α-hydrazono phosphonate for which the possibility of stereoselective catalytic hydrogenation had been mentioned in the literature with the Rh(I) catalyst derived from 1,2-bis[(2*R*,5*R*)-2,5-diethylphospholano]benzene [(*R*,*R*)-Et-DUPHOS].[15,17] The concept of substrate chelation in highly enantioselective rhodium catalyzed hydrogenation is well known,[18] and phosphonate (*Z*)-**1**, containing an additional carbonyl group capable of capturing the catalytic center fits in this concept. Unfortunately, all our attempts to reduce (*Z*)-**1** under the palladium catalysis conditions (including those listed below in Table 1) were unsuccessful: the reaction either did not occur at all or resulted in unidentified products.

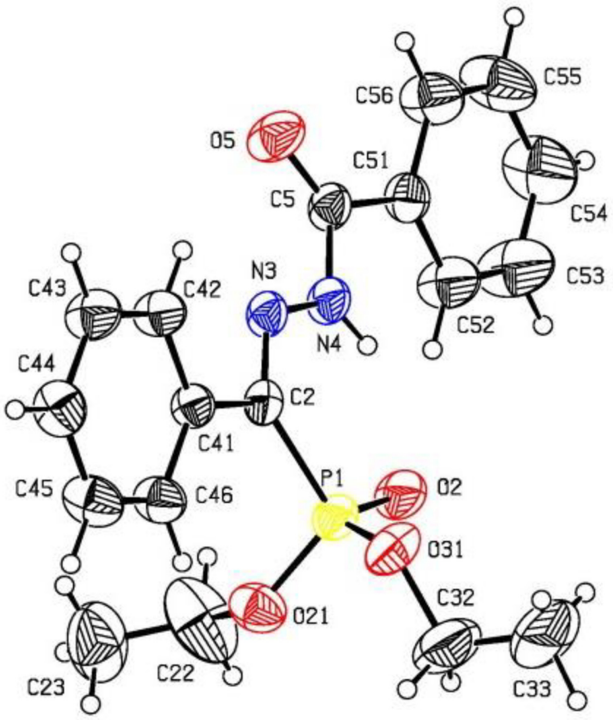
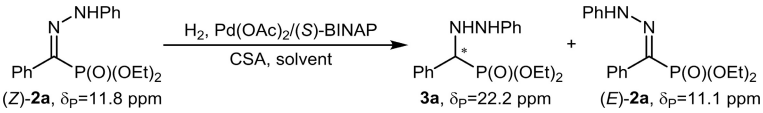


Figure 2. The molecular structure[16] of hydrazone (*Z*)-**1**, with atom labels. Displacement ellipsoids are drawn at 30% probability level. The H atoms are presented as small spheres of arbitrary radius.

α-Hydrazono phosphonate **2a** was synthesized using a modified literature procedure[19] by the condensation of diethyl benzoylphosphonate with phenylhydrazine hydrochloride in ethanol in the presence of pyridine[20] as a mixture of *Z*- and *E*-isomers in a ratio of 75:25. Individual isomer (*Z*)-**2a** was obtained by simple crystallization from ethanol. The second isomer (*E*)-**2a** was isolated in a pure state by chromatography. The stabilization of isomer (*Z*)-**2a** by intramolecular hydrogen bond had previously been assumed in the literature on the basis of comparative analysis of the spectral data[19,21] and the chromatographic mobility[19] of isomers **2a.** This assumption was unambiguously confirmed by the X-ray diffraction data (Figure 3).[22]

Preliminary experiments on the homogeneous enantioselective hydrogenation of isomers **2a** were carried out using 5 mol% palladium acetate as a precatalyst, 5 mol% ligand (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BINAP] in 2,2,2-trifluoroethanol (TFE) in the presence of 10 mol% (1*S*)-(+)-10-camphorsulfonic acid (CSA) as an activator, and hydrogen pressure of 50 atm. We found these conditions to be optimal for the enantioselective hydrogenation of α-oxyimino phosphonates.[14] The reaction course was monitored by the ^{31}P NMR method. It turned out that under these conditions α-

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



Entry	Pressure [atm]	T [°C]	Solvent	Conversion of (*Z*)-**2a** [%][b]	Yield of **3a** [%][b]	Yield of (*E*)-**2a** [%][b]	*ee* [%][c]
1[d]	50	60	TFE	–	0	95	n.a.
2	50	20	TFE	100	93	6	78
3[e]	50	20	TFE	25	0	18	n.a.
4[f]	50	20	TFE	37	33	4	n.a.
5	50	20	TFE/PhMe (1:1)	99	71	20	n.a.
6	50	20	TFE/CH_2Cl_2 (1:1)	96	90	6	89
7	50	20	TFE/CH_2Cl_2 (1:2)	100	96	4	90
8	50	20	TFE/CH_2Cl_2 (1:3)	100	98	2	91
9	50	20	TFE/CH_2Cl_2 (1:4)	99	95	4	89
10	50	40	TFE/CH_2Cl_2 (1:3)	100	90	10	80
11	50	60	TFE/CH_2Cl_2 (1:3)	100	86	14	71
12	20	20	TFE/CH_2Cl_2 (1:3)	98	80	18	82
13	30	20	TFE/CH_2Cl_2 (1:3)	100	90	10	88
14	40	20	TFE/CH_2Cl_2 (1:3)	100	92	8	90
15	60	20	TFE/CH_2Cl_2 (1:3)	100	88	12	84
16	70	20	TFE/CH_2Cl_2 (1:3)	100	88	12	82

[a] Unless otherwise stated, reactions were carried out with (*Z*)-**2a** (0.14 mmol), $Pd(OAc)_2$ (7 μmol, 5 mol%), (*S*)-BINAP (7 μmol, 5 mol%), CSA (14 μmol, 10 mol%), and 4 mL of solvent under directed conditions for 1.5 h.
[b] Determined by ^{31}P NMR analysis of the crude reaction mixture.
[c] Determined by ^{1}H NMR analysis of the crude reaction mixture after addition of CSA (1 equiv.); n.a. – not analysed.
[d] (*E*)-**2a** was used as a substrate; 5% of (*Z*)-**2a** was detected in the crude reaction mixture by ^{31}P NMR analysis.
[e] 1 equiv. of CSA was used.
[f] 5 mol% CSA was used.

hydrazono phosphonate (*E*)-**2a** ($\delta_P = 11.1$ ppm) did not undergo hydrogenation either at room temperature or at 60 °C (Table 1, entry 1). On the contrary, in the case of substrate (*Z*)-**2a** ($\delta_P = 11.8$ ppm), the reaction completed within 1.5 h and afforded diethyl [phenyl(2-phenylhydrazino)methyl]phosphonate (**3a**) as the major product in 93% yield.[23] Besides, the formation of a minor amount (6%) of (*E*)-**2a** was detected (entry 2). This is not surprising because the mutual transformation of *Z*/*E*-isomers of α-hydrazono phosphonate **2a** is known to be catalyzed by acid, and the more polar and sterically less hindered *E*-isomer becomes predominant in a polar protonic solvent.[19,21b] The yield of (*E*)-**2a** increased and hence the yield of **3a** decreased with an increase in the amount of CSA used. In the presence of 1 equiv. of CSA, the reaction was mainly reduced to the isomerization of the substrate (*Z*)-**2a** to the *E*-form (entry 3). An attempt to decrease the amount of the Brønsted acid to 5 mol% resulted in a drastic decrease in conversion (entry 4).

The enantiomeric excess of product **3a** was estimated by the ^{1}H NMR method from the ratio of integral intensities of doublets of the methinic α-CH protons ($\delta_H = 4.77$ ppm ($^{2}J_{PH} = 13.1$ Hz) and $\delta_H = 4.82$ ppm ($^{2}J_{PH} = 13.0$ Hz)) corresponding to two diastereomeric salts formed after the reaction mixture was treated with 1 equiv. of CSA.[24] The stereoselectivity of the process in entry 2 was 78% *ee*. It must be noted that the same *ee* value was obtained when antipodal ligand (*R*)-BINAP was applied. The usage of (±)-BINAP afforded the racemic product **3a.** These results indicate that the chirality of CSA plays no role in stereodifferentiation which is controlled solely by the chiral ligand.

It is known that TFE[25] serves as a "magic" solvent in homogeneous enantioselective Pd-catalyzed hydrogenation.[12a–e,13,14,26] However, it has been shown that its dilution with such low-polarity solvents as toluene[27] or dichloromethane[6,12g,28] have had a good effect in some cases. As applied to substrate (*Z*)-**2a**, the use of a TFE/PhMe (1:1) mixture as solvent led to a noticeable decrease in the chemiselectivity of the process (entry 5). On the contrary, the dilution of TFE with dichloromethane exerted almost no effect on the yield of target product **3a**, but the stereoselectivity of hydrogenation increased substantially (entries 6–9). When using a TFE/CH_2Cl_2 (1:3) mixture, the enantiomeric excess of α-hydrazino phosphonate **3a** was 91% (entry 8). An increase in the reaction temperature to

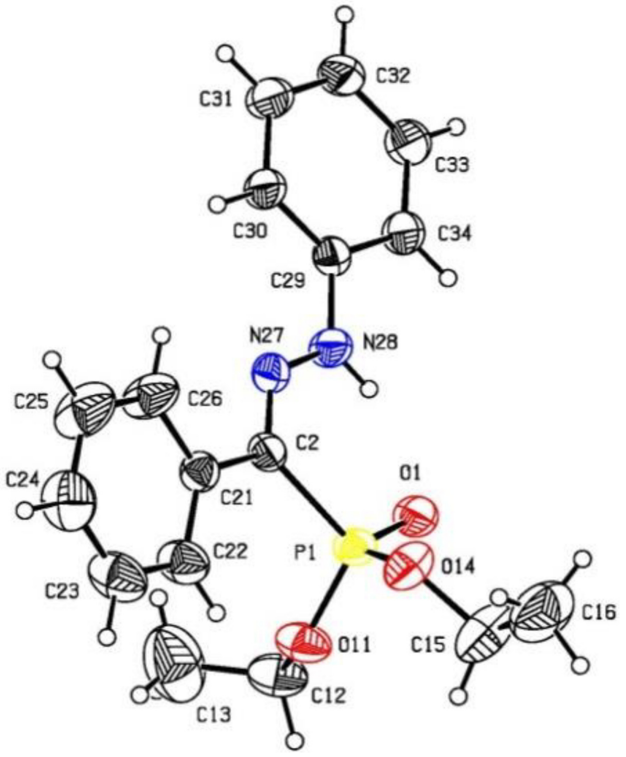
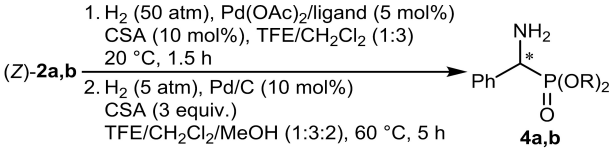


Figure 3. The molecular structure[22] of hydrazone (*Z*)-**2a**, with atom labels. Displacement ellipsoids are drawn at 30% probability level. The H atoms are presented as small spheres of arbitrary radius.

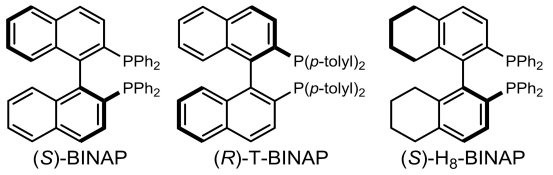
40 or 60 °C induced a sharp drop in *ee* to 80 and 71%, respectively (entries 10 and 11). Both the yield and the enantiomeric excess of product **3a** exhibit pronounced bell-shaped dependence on the hydrogen pressure in a range of 20–70 atm (entries 8 and 12–16) attaining the maximum at 50 atm.

At the next stage we had to find conditions for the reduction of α-hydrazino phosphonate **3a** in order to obtain target optically active diethyl [amino(phenyl)-methyl]phosphonate (**4a**). Palladium on carbon (Pd/C) is a common catalyst of N–N bond hydrogenolysis,[29] and the reaction is carried out, as a rule, in acidic medium by adding hydrochloric or acetic acid to prevent catalyst inactivation by the amines formed.[30] We preferred to use Pd/C in combination with CSA.[31] The optimization of conditions of this step included the variation of solvent (TFE, CH_2Cl_2, MeOH), substrate concentration (0.014–0.035 M), hydrogen pressure (5–40 atm), temperature (20–80 °C), and amount of the catalyst (5–30 mol%) and CSA (0–3 equiv.). α-Hydrazino phosphonate **3a** is easily oxidized in air to form α-hydrazono phosphonates **2a**,[11d,32] and hence the hydrogenation (under the conditions of entry 8, Table 1) and hydrogenolysis were carried out *one-pot* by adding the necessary amounts of Pd/C, CSA, and solvent to the reaction mixture. Under the optimal hydrogenolysis conditions found (10 mol% Pd/C and 3 equiv. of CSA in a TFE/CH_2Cl_2/MeOH (1:3:2) mixture of solvents (substrate concentration 0.023 M) at 60 °C and at hydrogen pressure of 5 atm for 5 h), we succeeded in achieving an 86% yield of amino phosphonate **4a** (entry 1, Table 2).

Table 2. Ligand screening for the asymmetric hydrogenation of hydrazone (*Z*)-**2b.**



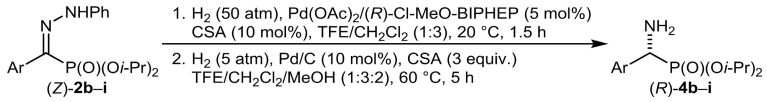
Entry	R	Ligand	Yield [%][a]	*ee* [%][b]
1	Et	(*S*)-BINAP	86	89
2	*i*-Pr	(*S*)-BINAP	92	90
3	*i*-Pr	(*R*)-T-BINAP	94	88
4	*i*-Pr	(*S*)-H_8-BINAP	83	80
5	*i*-Pr	(*S*)-SEGPHOS	92	90
6	*i*-Pr	(*S*)-MeO-BIPHEP	89	92
7	*i*-Pr	(*R*)-Cl-MeO-BIPHEP	96	92



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

The enantiomeric excess of product **4a** was determined by ^{31}P NMR from the ratio of integral intensities of well resolved signals at $\delta_P = 21.26$ and 21.53 ppm of two diastereomeric amides **5a** formed after the reaction mixture treatment with (*S*)-naproxen chloride in pyridine.[33] The stereoselectivity of the process in entry 1 was 89% *ee*, which is lower than the expected value of 91% *ee* (entry 8, Table 1). The decrease in the optical purity of α-amino phosphonate **4a** compared to α-hydrazino phosphonate **3a** is likely caused by the hydrogenation of trace amounts of (*E*)-**2a** (formed in the first step of the process) in the presence of Pd/C and is not related to the racemization of **3a** or **4a** in the course of hydrogenolysis.[30b,c,34]

Table 3. Two-step palladium-catalyzed asymmetric hydrogenation of hydrazones **2b–i.**[a]



Entry	Substrate	Ar	Yield of (*R*)-**4** [%][b]	*ee* [%][c]	δ_P of (*S*)-naproxen deriv. of **4** [ppm][d]	Optical rotation sign[e]
1	(*Z*)-**2b**	Ph	96(82)	92	**20.16**, 20.42	(+), (*R*)[f]
2	(*Z*)-**2c**	4-FC_6H_4	92(82)	95	**19.14** (J_{PF} = 4.1 Hz), 19.36 (J_{PF} = 4.0 Hz)	(+)
3	(*Z*)-**2d**	4-ClC_6H_4	80(72)	91	**18.95**, 19.16	(+)
4	(*Z*)-**2e**	4-MeC_6H_4	82(72)	90	**19.61**, 19.84	(+)
5	(*Z*)-**2f**	4-PhC_6H_4	72(69)	93	**19.34**, 19.59	(+)
6	(*Z*)-**2g**	3-FC_6H_4	62(57)	92	**18.70**, 18.90	(+)
7	(*Z*)-**2h**	2-MeC_6H_4	60(55)	97	**20.49**, 20.70	(+)
8	(*Z*)-**2i**	1-naphthyl	57(52)	98	**19.88**, 20.10	(+)

[a] Reactions were performed on a 0.56-mmol scale: 1) (*R*)-Cl–MeO-BIPHEP (28 μmol, 5 mol%), Pd(OAc)$_2$ (28 μmol, 5 mol%), CSA (56 μmol, 10 mol%), CH_2Cl_2 (12 mL), TFE (4 mL); 2) 10% Pd/C (56 μmol, 10 mol%), CSA (1.68 mmol, 3 equiv.), MeOH (8 mL).
[b] Determined by ^{31}P NMR analysis of the crude reaction mixture; isolated yields are given in parentheses.
[c] Determined by ^{31}P NMR analysis of the corresponding (*S*)-naproxen amides.
[d] The signals of major diastereomers are given in bold.
[e] Solvent $CHCl_3$.
[f] The absolute configuration was determined by single-crystal X-ray diffraction of the corresponding (*S*)-naproxen amide (*R*,*S*)-**5b.**

Previously it had been shown that in the homogeneous palladium-catalyzed hydrogenation of α-oxo, α-oxyimino, and α-tosylimino phosphonates the enantioselectivity of the process increased substantially on going from ethyl to isopropyl esters[6,14,35] (although opposite examples are also known).[36] We synthesized diisopropyl (*Z*)-[phenyl(phenylhydrazono)methyl]-phosphonate [(*Z*)-**2b**], however, this replacement led only to a slight increase in the degree of stereodifferentiation, but noticeably increased the yield of the corresponding product **4b** (entries 1 and 2, Table 2).

We also screened a series of ligands which showed the best results in homogeneous Pd-catalyzed hydrogenation.[26,28,35,37] Among atropoisomeric C_2-symmetric bidentate ligands of the triarylphosphine type only (*S*)-2,2′-bis(diphenylphospino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl [(*S*)-H_8-BINAP] (entry 4) showed an unsatisfactory result. It is worth mentioning that a characteristic feature of (*S*)-H_8-BINAP is an appreciably increased dihedral angle between the planes of the aromatic fragments.[38] On the whole, the ligands of the biphenyl type, namely, (*S*)-5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole [(*S*)-SEGPHOS] (entry 5), (*S*)-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl [(*S*)-MeO-BIPHEP] (entry 6), and (*R*)-2,2′-bis(diphenylphosphino)-5,5′-dichloro-6,6′-dimethoxy-1,1′-biphenyl [(*R*)-Cl–MeO-BIPHEP] (entry 7) turned out to be more efficient than the ligands of the binaphthyl type (*S*)-BINAP (entry 2) and (*R*)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl [(*R*)-T-BINAP] (entry 3). Both the highest enantiomeric excess (92% *ee*) and the best yield of α-amino phosphonate **4b** (96%) were obtained using (*R*)-Cl–MeO-BIPHEP (entry 7). These conditions were chosen as optimal. Note that the yield of α-hydrazino phosphonate **3b** in the first step did not exceed 20% in the case of bidentate phosphines (2*S*,3*S*)-2,3-bis(diphenylphosphino)butane [(*S*,*S*)-CHIRAPHOS] and 1,2-bis[(2*S*,5*S*)-2,5-dimethylphospholano]benzene [(*S*,*S*)-Me–DUPHOS] forming rigid five-membered chelates.

Under the optimal reaction conditions, a series of diisopropyl (*Z*)-[aryl(phenylhydrazono)methyl]-phosphonates (*Z*)-**2c–i** was explored to examine the reaction scope. The obtained results presented in Table 3 show that the electronic effect of the substituent in the *para*-position of the benzene ring exerts only a slight effect on both the stereoselectivity of the process and the yield of the product (entries 1–5). The corresponding *para*-substituted α-amino phosphonates **4c–f** were isolated with an optical purity of 90–95% and a 69–82% yield. The yield of the product substantially decreased for *meta*- and *ortho*-substituted substrates (*Z*)-**2g,h** (entries 6 and 7) or their 1-naphthyl analog (*Z*)-**2i** (entry 8). It can be asserted on the basis of the ^{31}P NMR monitoring data that the reactivity decreases in these cases in the hydrogenolysis step. For highly sterically hindered substrates (*Z*)-**2h,i**, the degree of stereodifferentiation simultaneously increases in the step of asymmetric hydrogenation: the enantiomeric excess of products **4h,i** attains 97–98% *ee* (entries 7 and 8).

It is known that on the derivatization of chiral α-amino phosphonates by enantiopure naproxen

chloride the resonance of phosphorus in the ^{31}P NMR spectrum of the corresponding diastereomeric amide with opposite configurations of the C*–P and C*–C(O) stereocenters shifted upfield in relation to the signal corresponding to the diastereomer with the coinciding configurations of two asymmetric carbon atoms.[39] In the ^{31}P NMR spectra of (*S*)-naproxen derivatives of products **4b–i**, the signal of the major diastereomer is always shifted upfield (Table 3). This means that for the hydrogenation of α-hydrazono phosphonates (*Z*)-**2b–i** in the presence of (*R*)-Cl–MeO-BIPHEP the arising stereogenic center adopts the (*R*)-configuration and, as a consequence, products (*R*)-**4b–i** are formed. It is worth noting that all ligands with the (*R*)-configuration listed in Table 2 led to the formation of product (*R*)-**4b** and, on the contrary, (*S*)-**4a,b** were formed when (*S*)-ligands were used.

The validity of the spectral correlations presented above was also confirmed by the X-ray diffraction data. With this aim in view, a racemic sample of α-amino phosphonate (±)-**4b** obtained by the modified Kabachnik–Fields reaction[40] was acylated by (*S*)-naproxen chloride. The chromatographically less mobile diastereomer of α-amido phosphonate (*S*,*S*)-**5b** (δ_P = 20.42 ppm) was isolated as an oil using column chromatography, while the chromatographically more mobile diastereomer (*R*,*S*)-**5b** (δ_P = 20.16 ppm) was acquired in crystalline form. The absolute configuration of the C*–P stereocenter was established as (*R*) by anomalous dispersion effects in diffraction measurements on a single crystal (Figure 4).[41]

Speaking of regularities observed, we can sum up that the homogeneous palladium-catalyzed hydrogenation of α-oxo phosphonates[35] and *E*-isomers of the corresponding oximes[14] and tosylimines[6] using (*R*)-ligands of the binaphthyl and biphenyl types provides (*S*)-enantiomers of the products, but the hydrogenation of *Z*-oximes and *Z*-phenylhydrazones affords (*R*)-enantiomers. A tentative mechanism for homogeneous Pd(II)-catalyzed asymmetric hydrogenation can be outlined on the basis of previous investigations of Zhou et al.,[12c] which include isotope-labeling tests,[26,28,42] NMR experiments, and DFT calculations[28] and taking into account general mechanistic aspects.[43] Initially, the heterolytic activation of molecular hydrogen results in the production of monohydride palladium complex **A** (Scheme 1). Then, dissociation equilibriums in solution[28] would enable the formation of metal–substrate complex **B.** The next stage of the inner-sphere migratory insertion of the bound substrate into the metal hydride bond (Pd–H) leads to Pd amide (or alkoxide) intermediate **C.** Finally, the reaction with a proton donor (for instance, HX) furnishes the final product and re-forms the (diphosphine)PdX_2 complex. The postulated catalytic cycle involved exclusively Pd(II) species. Although this scheme requires further systematic study and

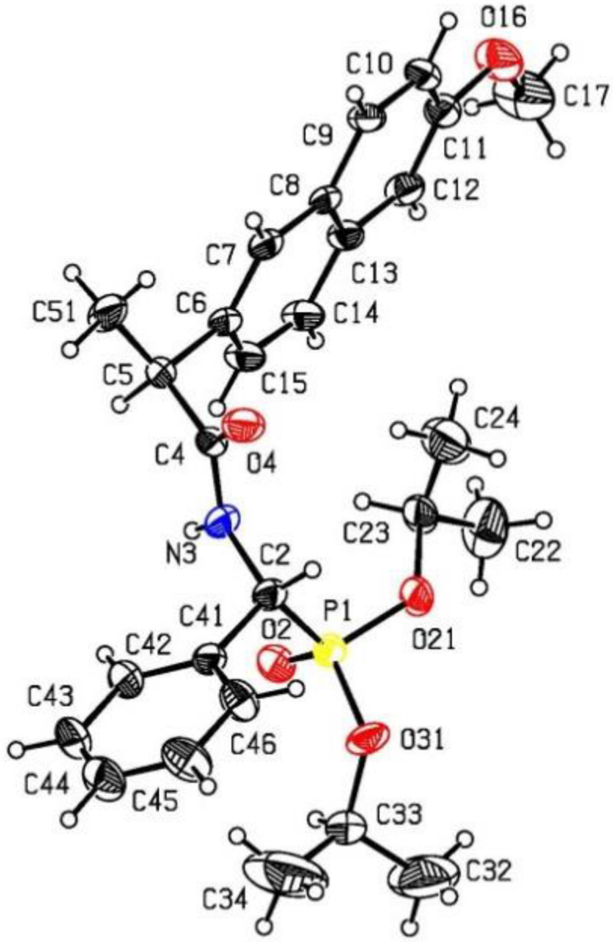
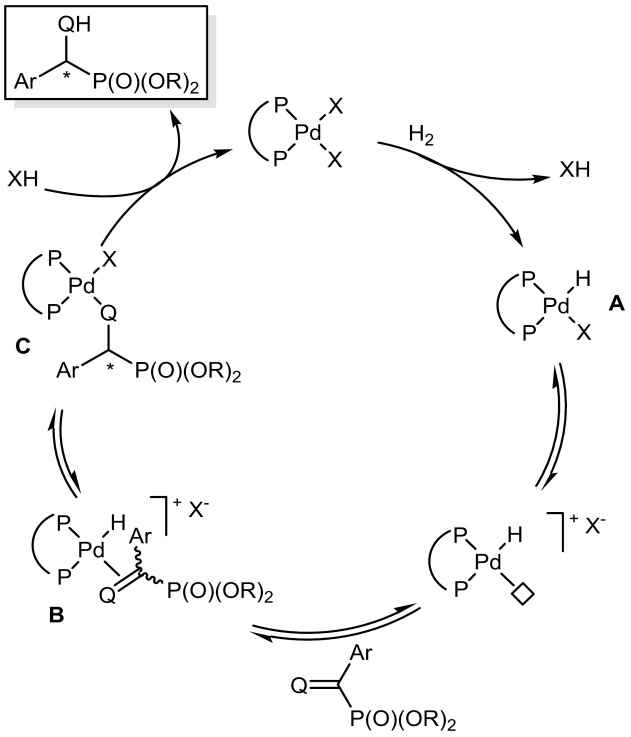


Figure 4. The molecular structure[41] of (*S*)-naproxen amide (*R*,*S*)-**5b**, with atom labels. Displacement ellipsoids are drawn at 30% probability level. The H atoms are presented as small spheres of arbitrary radius.

complete kinetic analysis, it allows for the interpretation of the above mentioned stereoselectivity of the process in terms of the quadrant model (Scheme 2).

The substituent on the imine nitrogen atom seems to be the most important factor determining the *Re*-face coordination of *E*-substrates (leading to (*S*)-products) and *Si*-face coordination of *Z*-substrates (leading to (*R*)-products). In the case of *E*-isomers like *E*-oximes[14] and *E*-tosylimines,[6] the impacts of the dialkoxyphosphoryl group and *N*-substituent are matched, so the change of diethyl phosphonates to diisopropyl phosphonates improves the enantioselectivity of the process. On the contrary, in the case of α-hydrazono phosphonates (*Z*)-**2** a similar effect was not observed because the influences of the phosphonate group and *N*-substituent are mismatched. Without a substituent at a heteroatom, a poor stereocontrol can be expected because the preference of *Re*-face coordination of the prochiral substrate depends only on the bulkiness of the dialkoxyphosphoryl group. Indeed,



Scheme 1. A plausible catalytic cycle for homogeneous hydrogenation of α-oxo phosphonates (Q=O) and corresponding oximes (Q=NOH), tosylimines (Q=NTs), and phenylhydrazones (Q=NNHPh), catalyzed by (diphosphine) PdX_2 complexes (X=OAc or $OC(O)CF_3$).

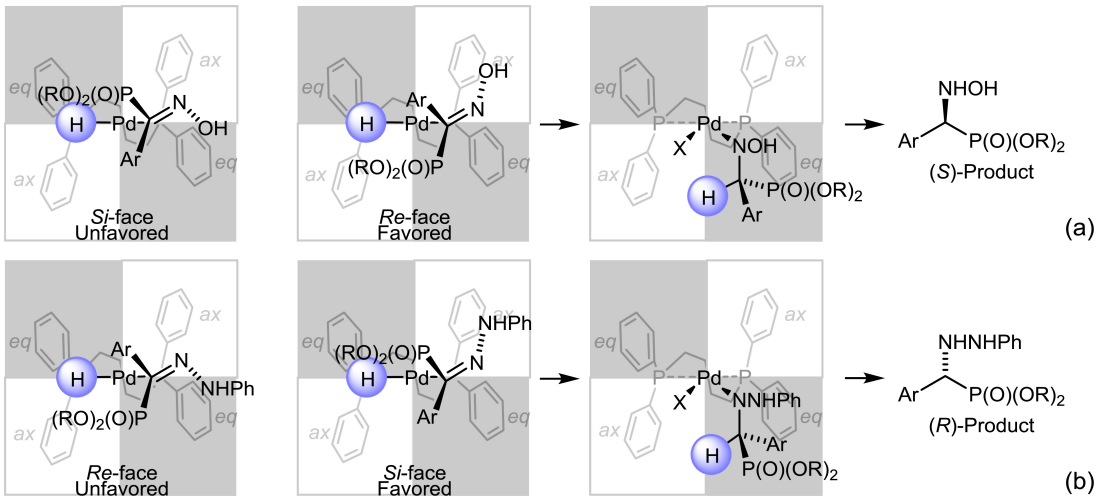
we have observed that the enantioselectivity in palladium catalyzed hydrogenation of α-oxo phosphonates appreciably increased on going from diethyl to diisopropyl esters, nevertheless, enantiomeric excess did not exceed 55 %.[35]

In summary, we have developed a convenient, highly efficient, general method for a direct catalytic synthesis of optically active α-amino phosphonates bearing an aryl substituent in the α-position employing *Z*-isomers of α-phenylhydrazono phosphonates as the prochiral precursors. The usability of these starting substrates and the fact that they are readily available make the present approach particularly attractive and practical. The proposed two-step *one-pot* procedure combines advantages of both homogeneous and heterogeneous palladium catalysis and includes asymmetric hydrogenation in the TFE/CH_2Cl_2 medium using Pd $(OAc)_2$/(*R*)-Cl–MeO-BIPHEP as a catalyst and CSA as an activator, followed by hydrogenolysis over Pd/C. This protocol provides a rapid access to α-amino phosphonates in high yields and enantioselectivity up to 98 % *ee*. It appeared that configuration of the C=N double bond in substrate and the substituent at the nitrogen atom played a remarkable role in the origin of enantioselectivity in asymmetric palladium-catalyzed hydrogenation. Further mechanistic studies are underway and will be reported in due course.

Experimental Section

Synthesis of diisopropyl (*R*)-[amino(phenyl)methyl]phosphonate [(*R*)-(4b)] as a representative example for the syntheses of α-amino phosphonates (*R*)-4b–i:

A Schlenk tube dried at 120 °C for 1 h, equipped with a stirring bar and a septum cap, was charged with (*R*)-Cl–MeO-BIPHEP (18.2 mg, 28 μmol, 5 mol%), $Pd(OAc)_2$ (6.3 mg, 28 μmol, 5 mol%) and anhydrous CH_2Cl_2 (12 mL). The mixture was stirred under argon until (*R*)-Cl–MeO-BIPHEP completely dissolved. Then (*Z*)-**2b** (201.8 mg, 0.56 mmol), CSA (13.0 mg, 56 μmol, 10 mol%) and anhydrous TFE (4 mL) were added. The mixture was stirred under argon until complete homogenization and transferred



Scheme 2. Origin of enantioselectivity in asymmetric hydrogenation of *E*-isomers of α-oxyimino phosphonates[14] (a) and α-hydrazono phosphonates (*Z*)-**2** (b) catalyzed by palladium complexes with (*R*)-ligands of biaryl diphosphine type.

with a syringe into a stainless-steel autoclave with a glass liner, equipped with a stirring bar and filled with dry argon. The autoclave was sealed, pressurized with H_2 to 50 atm and the reaction mixture was stirred at ambient temperature for 1.5 h. After the end of the hydrogenation the pressure was reduced to atmospheric and the autoclave was flushed with argon. 10% Pd/C (59.6 mg, 56 μmol, 10 mol%), CSA (390.3 mg, 1.68 mmol, 3 equiv.) and anhydrous MeOH (8 mL) were added to the reaction mixture under an argon flux. The autoclave was sealed, pressurized with H_2 to 5 atm and the reaction mixture was stirred at 60 °C for 5 h. After the end of hydrogenolysis, the autoclave was cooled to the ambient temperature and the solid components of the reaction mixture were filtered off and washed with anhydrous MeOH. An aliquot of the combined organic layers was taken to be analyzed by ^{31}P NMR and thereafter was returned to the main bulk of the reaction mixture. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed successively with concentrated aqueous K_2CO_3 (6 mL × 3) and brine (6 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by preparative TLC on silica gel (CH_2Cl_2/MeOH/Et_3N 80:2:1, R_f 0.25) to afford amino phosphonate (*R*)-**4b** as pale yellow oil (124.9 mg) in 82% yield. A sample of (*R*)-**4b** (11.0 mg, 40 μmol) was treated with anhydrous pyridine (65 μL, 0.80 mmol, 20 equiv.) and (*S*)-(+)-2-(6-methoxy-2-naphthyl)propanoyl chloride (15 mg, 60 μmol, 1.5 equiv.) and analyzed by ^{31}P NMR to determine the enantiomeric excess. IR (film): ν = 3380, 3297, 2979, 2935, 1454, 1386, 1375, 1237, 1105, 1008, 990, 699, 560 cm^{-1}; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.2 ppm; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.2 Hz, 3H, CH_3), 1.22 (d, J = 6.2 Hz, 3H, CH_3), 1.23 (d, J = 6.2 Hz, 3H, CH_3), 1.26 (d, J = 6.2 Hz, 3H, CH_3), 2.10 (br. s, 2H, NH_2), 4.15 (d, J = 17.1 Hz, 1H, PCH), 4.49 (m, 1H, CH(*i*-Pr)), 4.60 (m, 1H, CH(*i*-Pr)), 7.25 (m, 1H, CH(Ph)), 7.31 (m, 2H, CH(Ph)), 7.43 (m, 2H, CH(Ph)) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.4 (J = 5.5 Hz, CH_3), 23.8 (J = 5.2 Hz, CH_3), 24.0 (J = 3.5 Hz, CH_3), 24.1 (J = 3.2 Hz, CH_3), 54.4 (J = 150.4 Hz, CP), 71.0 (J = 7.5 Hz, CH(*i*-Pr)), 71.3 (J = 7.3 Hz, CH(*i*-Pr)), 127.6 (J = 3.1 Hz, CH(Ph)), 127.9 (J = 6.2 Hz, 2CH(Ph)), 128.2 (J = 2.4 Hz, 2CH(Ph)), 137.8 (J = 3.3 Hz, C(Ph)) ppm; HR-MS: m/z = 294.1230, calcd. for $[M+Na]^+$ ($C_{13}H_{22}NO_3PNa$): 294.1230; $[\alpha]_D^{25}$: +12.3° (*c* 1.54, $CHCl_3$) for an enantiomerically enriched sample of 92% *ee*.

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