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Catalytic Hydrogenation of α-Iminophosphonates as a Method for the Synthesis of Racemic and Optically Active α-Aminophosphonates

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Abstract: It was shown that the catalytic hydrogenation of α-iminophosphonates by molecular hydrogen can serve as a convenient method for the synthesis of racemic and optically active α-aminophosphonates. Up to 94% *ee* was achieved in the rhodium-catalyzed enantioselective hydrogenation using chiral ligand (*R*)-BINAP.

Keywords: α-aminophosphonates; asymmetric catalysis; hydrogenation; α-iminophosphonates

Introduction

α-Aminophosphonic acids are among the most intensively studied classes of biologically active compounds.[1] A wide range of possibilities of practical use of α-aminophosphonates has stimulated considerable interest in the development of methods for their synthesis. Much experimental material, which is summarized in the monograph[1] and reviews,[2–6] has been accumulated in this area. Considerable recent attention has been focused on the most straightforward approach to α-aminophosphonates based on the rhodium- and ruthenium-catalyzed hydrogenation (first of all, enantioselective[7–14]) of the corresponding olefinic precursors, and excellent results have been achieved. Nevertheless, the limitation of this method is evident, as it cannot be used for the synthesis of α-aminophosphonic acids containing a quaternary β-carbon atom, for instance, α-aminobenzylphosphonic or α-amino-2,2,2-trifluoroethylphosphonic acids. Both latter types are particularly interesting. By analogy to aminocarboxylic acids, the introduction of fluorine atoms into the molecule of aminophosphonic acids can extend the spectrum of their biological activity and make possible the application of ^{19}F NMR spectroscopy to study the metabolism of these substances.[15] Some ring-substituted α-aminobenzylphosphonic acids were found to exhibit antifungal activity,[16] to be potent inhibitors of phenylalanine ammonia-lyase,[17] human prostatic acid phosphatase,[18] as well as promising structural units for the design of antithrombotic tripeptides.[19]

Optically active α-aminobenzylphosphonic acids are of special interest. For instance, it was shown that (+)-α-amino-3,4-dichlorobenzylphosphonic acid inhibits phenylalanine ammonia-lyase almost forty times more efficiently than its laevorotatory enantiomer.[17] Optically active substituted α-aminobenzylphosphonates are used as chiral eluents for enantiomeric analysis of amino acids by ligand-exchange chromatography.[20]

Possibilities of hydrogenation of prochiral α-C=N-unsaturated precursors for the synthesis of optically active α-aminophosphonic acids remained largely unexplored until recently. Only a few examples of the catalytic enantioselective hydrophosphorylation of Schiff's bases in the presence of quinine,[21] an optically active thiourea derivative,[22] a chiral Brønsted acid, derived from (*R*)-BINOL,[23] heterobimetallic BINOL complexes,[24] and the aluminum complex containing an [ONN(Me)O] tetradentate ligand of the hybrid salane/salene type[25] were described. The purpose of the present work is to develop new methods for the synthesis of racemic and optically active esters of α-

aminophosphonic acids by the catalytic reduction of the corresponding α-iminophosphonates.

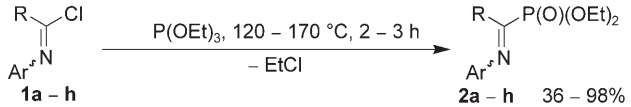
Results and Discussion

Diethyl α-iminomethylphosphonates containing aryl, heteroaryl, *tert*-butyl, and trifluoromethyl residues in the α-position were chosen as model substrates. To avoid possible 1,3-prototropic rearrangements,[26,27] phenyl and *p*-anisyl groups were used as substituents at the nitrogen atom. The *p*-anisyl protective group can be removed by the action of cerium ammonium nitrate; this procedure is well established and used in the chemistry of aminophosphonic acids.[28–30]

The starting diethyl α-iminophosphonates **2a–h** were synthesized *via* the Arbuzov reaction of triethyl phosphite with the corresponding imidoyl chlorides **1a–h** (for the synthesis see Experimental Section) similarly to a described procedure[31] (Scheme 1). The reaction takes place upon heating at 120–170 °C for 2–3 h; preparative yields of the target products **2a–d**, **f–h** are 56–98%. Noticeable tarring of the reaction mixture was observed only in the case of imidoyl chloride **1e** containing the furyl fragment, and diethyl (*p*-anisylimino)(2-furyl)methylphosphonate (**2e**) was isolated in 36% yield.

Six (**2b–g**) of the eight thus prepared α-iminophosphonates are novel compounds, which we have completely characterized spectrally. The ^{31}P NMR spectra of all synthesized α-iminophosphonates **2a–h** contain two signals, indicating the formation of *Z*- and *E*-isomers (Figure 1).

Predominant formation of the *Z*-isomer should be expected for diethyl 1-(*p*-anisylimino)-2,2-dimethylpropylphosphonate (**2g**) containing the bulky *tert*-butyl substituent. In this case, the diethoxyphosphoryl group of the major isomer and the *tert*-butyl group of the minor isomer should be exposed to the shielding effect of the aromatic substituent at the nitrogen



Ar = Ph (**a**), 4-MeOC$_6$H$_4$ (**b – h**);
R = Ph (**a**,**b**), 4-MeC$_6$H$_4$ (**c**), 4-FC$_6$H$_4$ (**d**), 2-furyl (**e**), 2-thienyl (**f**), *t*-Bu (**g**), F$_3$C (**h**)

Scheme 1. Synthesis of α-iminophosphonates **2a–h**.

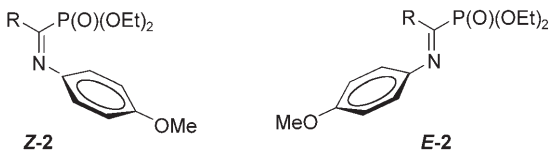


Figure 1. *Z*- and *E*-isomers of α-iminophosphonates **2b–h**.

atom. Indeed, in the ^{31}P NMR spectrum the signal of the major isomer at 3.4 ppm is shifted upfield relative to the signal of the minor isomer by 3.5 ppm (the ratio of integral intensities is 96/4). Intense signals of the methyl protons and carbon atoms of the *tert*-butyl fragment of both isomers are well discernible in the ^{1}H and ^{13}C NMR spectra of α-iminophosphonate **2g**; their chemical shifts for the major *Z*-isomer are $\delta_H =$ 1.36 ppm and $\delta_C = 27.9$ ppm. For the minor *E*-isomer the resonances of the same nuclei exhibit upfield shifts to 1.30 and 27.5 ppm, respectively.

A similar pattern of the signals is also observed for diethyl 1-(*p*-anisylimino)-2,2,2-trifluoroethylphosphonate (**2h**), although with a substantial decrease in the selectivity: the ratio of the *Z*- and *E*-isomers is 88/12.

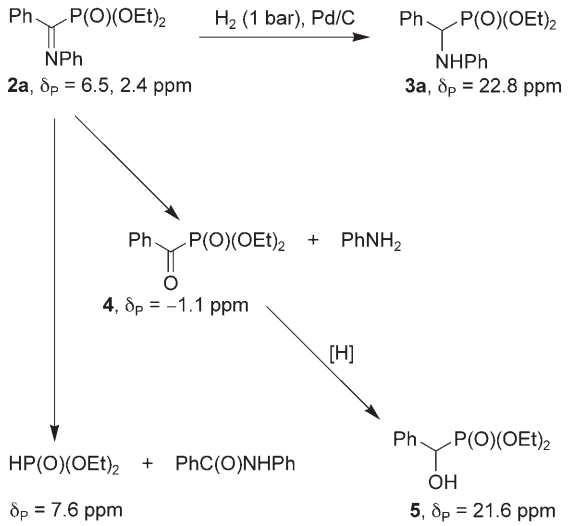
For α-iminophosphonates **2a–f** containing an aromatic fragment in the α-position, the ^{31}P NMR resonance of the major isomer is observed at 6.4–7.2 ppm. The signal of the minor isomer exhibits an upfield shift of 1.6–2.9 ppm. Simultaneously in the ^{1}H and ^{13}P NMR spectra the upfield shift is observed for the triplets of the methyl protons ($\Delta\delta = 0.22$–0.29 ppm) and signals of the methylene ($\Delta\delta = 1.1$–1.2 ppm) and methyl ($\Delta\delta = 0.3$–0.4 ppm) carbon atoms of the diethoxyphosphoryl groups of the minor isomers. These data indicate that the major isomer for **2a–f** has the *E*-configuration and in the minor *Z*-isomer the diethoxyphosphoryl group experiences the shielding effect of the aromatic N-substituent. Anisotropy of the aryl α-substituent in compounds **2b–d** results in the upfield shift of signals of the methyl group of the *p*-anisyl substituent at the nitrogen atom of the major isomers: $\Delta\delta_H = 0.07$–0.10 ppm, $\Delta\delta_C = 0.2$ ppm.

The predominant formation of the *E*-isomers of α-iminophosphonates **2a–f** and *Z*-isomers of α-iminophosphonates **2g**, **h** has been additionally verified by the analysis of the spin-spin coupling constants. It is known[32] that in unsaturated systems the $^{3}J_{C,P}$ constants for a *trans*-arrangement are higher than for a *cis*-arrangement of the interacting nuclei. In fact, the observed value of the vicinal spin-spin coupling constant between the phosphorus nuclei and the nodal carbon of the aromatic substituent at the nitrogen atom in the major isomers of α-iminophosphonates **2a–f** is 31.5–33.7 Hz, whereas for the major isomers of **2g**, **h** this value is 13.9–17.6 Hz.

To prove the predominant *E*-configuration of the imine bond for α-iminophosphonates **2a–f** and the *Z*-configuration for **2g**, **h** NOE difference experiments were performed for compounds **2d** and **g**. In the ^{1}H NMR spectrum of **2d**, the assignment of the signals of the aromatic protons is unambiguous due to characteristic ^{1}H-^{19}F spin-spin coupling constants (see Supporting Information). Irradiation of the aromatic protons of the *p*-anisyl group reveals an NOE enhancement of the *ortho* protons of the 4-fluorophenyl substituent [$\eta_{H(2,6)}(CH_{p\text{-anisyl}}) = 1.9\%$], but no effect on

the protons of the diethoxyphosphoryl group. On the contrary, in the case of α-iminophosphonate **2g** the irradiation of the aromatic protons at $\delta = 6.70$ ppm reveals an NOE enhancement of the methylene and methyl protons of the diethoxyphosphoryl group [$\eta_{Harom}(CH_2) = 0.2\%$, $\eta_{Harom}(CH_3) = 0.2\%$], but no effect on the protons of the *tert*-butyl group.

The IR spectra of α-iminophosphonates **2a–h** exhibit a characteristic set of bands corresponding to vibrations of the diethoxyphosphoryl fragment.[33] The stretching vibration of the P=O bonds appears in the region of 1225–1260 cm^{-1}. The prominent band at 1015–1040 cm^{-1} corresponds to ν(C–O) vibrations. An intense band at 1580–1615 cm^{-1} corresponds to the C=N stretching vibration. For diethyl (*p*-anisylimino)(2-thienyl)methylphosphonate (**2f**), two bands are observed in this region. They correspond, probably, to the *E*- and *Z*-isomers formed in a ratio of 78/22. Intense absorptions at 1135 and 1155 cm^{-1} in the spectrum of α-iminophosphonate **2h** correspond to vibrations of the CF_3 group.



Scheme 2. Hydrogenation of **2a** catalyzed by palladium on carbon and possible side reactions.

A characteristic feature of the mass spectra of α-iminophosphonates **2b–h** is a considerable intensity of the $[M-P(O)(OEt)_2]^+$ ion peaks. The fragmentation of aliphatic α-iminophosphonates **2g**, **h** is accompanied by both C^{α}–P bond cleavage, and C^{α}–C^{β} bond cleavage, thus the $[M-R]^+$ peaks are observed.

The reduction of α-iminophosphonates is rather scarcely described in literature. As a rule, the reduction is accomplished by sodium borohydrides $NaBH(OAc)_3$[34] or $NaBH_3CN$.[35–37] The reductive amination of α-ketophosphonic acids was carried out using $NaBH_4$[38] or its tritium analogue NaB^3H_4.[39] An attempt to hydrogenate diethyl 1-(benzhydrylimino)-2,2-difluoroethylphosphonate by hydrogen in the presence of palladium on carbon was unsuccessful,[35] perhaps for steric reasons. The catalytic hydrogenation of γ-substituted α-iminopropenylphosphonates was published[30] while the present publication was in preparation.

The conditions for hydrogenation of α-iminophosphonates in the presence of palladium on carbon were optimized on the model substrate **2a**, by varying the solvent (methanol or chloroform), reaction temperature (ambient or reflux), palladium content in the catalyst (5 or 10 wt%), and the amount of the latter (S/Pd mol ratio 100/1 or 20/1). The reaction course was monitored using ^{31}P NMR for the disappearance of the signals of the initial phosphonate **2a** at $\delta_P = 6.5$ and 2.4 ppm and the increase of the signal from diethyl α-(phenylamino)benzylphosphonate (**3a**) at $\delta_P = 22.8$ ppm (Scheme 2).

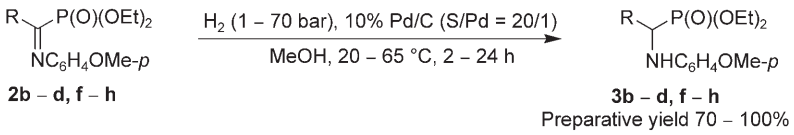
The obtained results (Table 1) show that under 1 bar hydrogen pressure the reduction of α-iminophosphonate **2a** in boiling methanol in the presence of 10% Pd/C (S/Pd mol ratio 20/1) occurs smoothly within 2 h and affords aminophosphonate **3a** as a single reaction product for both microscale (entry 1) and preparative scale experiments (entry 2).

A decrease of the catalyst amount (S/Pd mol ratio 100/1, entry 3) or the use of other catalyst with a lower content of metal (5% Pd/C instead of 10% Pd/C, entry 4) noticeably decreases the rate and selectivi-

Table 1. Hydrogenation of **2a** catalyzed by palladium on carbon (1 bar H_2, $c = 0.03$ mol/L).

Entry	Solvent	Catalyst	S/Pd	Temperature [°C]	Time [h]	Yield [%][a]				
						3a	**2a**	$HP(O)(OEt)_2$	**4**	**5**
1	MeOH	10% Pd/C	20/1	65	2	100	0	0	0	0
2[b]	MeOH	10% Pd/C	20/1	65	2	100[c]	0	0	0	0
3	MeOH	10% Pd/C	100/1	65	2	80	7	1	8	4
4	MeOH	5% Pd/C	20/1	65	1	84	13	0	3	0
5	MeOH	10% Pd/C	100/1	20	1	38	11	1	22	28
6	$CHCl_3$	10% Pd/C	20/1	61	1	9	56	0	35	0

[a] Determined by ^{31}P NMR.
[b] Preparative experiment ($c = 0.1$ mol/L).
[c] Preparative yield 86%.



Scheme 3. Hydrogenation of **2b–d**, **f–h** catalyzed by palladium on carbon.

ty of the process. The decrease of reaction temperature to ambient (entry 5), or the use of chloroform as solvent (entry 6) results in the predominant formation of decomposition products – diethyl phosphite (δ_P = 7.6 ppm) and diethyl benzoylphosphonate (**4**) (δ_P = −1.1 ppm), as well as the reduction product of the latter, diethyl α-hydroxybenzylphosphonate (**5**) (δ_P = 21.6 ppm).

The results of the hydrogenation of α-iminophosphonates **2b–d**, **f–h** are presented in Scheme 3 and Table 2. The reduction of α-iminophosphonates **2b–d**, **h** in dilute solutions (c = 0.03 mol/L) takes place as readily as the reduction of **2a**: within 2–2.5 h at 100% conversion the yields of α-aminophosphonates **3b–d**, **h** are 92–100%. However, under the conditions of the preparative experiment with an increase in the substrate concentration (c = 0.07–0.08 mol/L) the rate and selectivity of the process decrease considerably. α-Aminophosphonates **3b–d**, **h** were synthesized in quantitative yields when the hydrogenation was carried out under 50 bar at room temperature.

For the reduction of α-iminophosphonate **2g** containing a bulky *tert*-butyl substituent, the conversion and the yield of the target product under 1 bar hydrogen pressure remained low with an increase in the catalyst amount (S/Pd mol ratio 10/1) and when methanol was replaced by higher boiling ethanol. We succeeded to hydrogenate **2g** in good yield only by increasing of the hydrogen pressure to 70 bar and prolonging the reaction time to 20 h.

The hydrogenation of α-iminophosphonates **2e**, **f** containing heteroaromatic fragments met with difficulties. In the case of the furyl derivative **2e**, the reaction is complicated by the formation of many side products, including, probably, products of the hydrogenation of the heteroaromatic ring. We failed to isolate and characterize the target product. In the case of the thienyl derivative **2f**, the maximal yield of α-aminophosphonate **3f** estimated by ^{31}P NMR is 70% at 90% conversion. The target product **3f** was isolated with a low preparative yield and characterized spectrally.

Table 2. Hydrogenation of α-iminophosphonates **2b–d**, **f–h** catalyzed by palladium on carbon (MeOH, 10% Pd/C, S/Pd mol ratio 20/1).

Substrate **2**	R	Concentration [mol/L]	Pressure [bar]	Temperature [°C]	Time [h]	Conversion [%][a]	Yield of **3** [%][a]
2b	Ph	0.03	1	65	2	100	92
		0.08	1	65	3	88	72
		0.10	50	20	3	100	100
2c	4-MeC_6H_4	0.03	1	65	2	100	94
		0.07	1	65	2.5	75	50
		0.09	50	20	3	100	100
2d	4-FC_6H_4	0.03	1	65	2.5	100	100
		0.08	1	65	2	90	86
		0.09	50	20	3	100	100
2f	2-thienyl	0.03	1	65	2.5	34	17
		0.015	70	20	24	90	70
2g	*t*-Bu	0.03	1	65	2.5	32	22
		0.03	1	65	2.5	48	37[b]
		0.03	1	78	3	34	21[c]
		0.02	50	20	3	70	69
		0.02	70	20	20	100	100
		0.10	70	20	20	100	100
2h	F_3C	0.03	1	65	2	100	93
		0.10	50	20	3	100	91

[a] Determined by ^{31}P NMR.
[b] S/Pd mol ratio 10/1.
[c] In EtOH.

The purity and structures of the isolated α-aminophosphonates **3a–d**, **g**, **h** were confirmed by the elemental analysis and spectral data. In the IR spectra of α-aminophosphonates **3a–d**, **f–h** vibrational bands of the diethoxyphosphoryl fragment are observed, in particular, the band of ν(P=O) vibrations at 1240–1250 cm^{-1} and the band in the region of 1030–1060 cm^{-1} corresponding to vibrations of the O–C bond. On the contrary, the stretching band of the C=N bond at 1580–1615 cm^{-1} disappears, and a broad band at 3300–3340 cm^{-1}, typical for ν(N–H) vibrations, is observed.

In the ^{1}H NMR spectra of α-aminophosphonates **3a–d**, **f–h** the doublet of the methine proton at 3.3–5.0 ppm ($^2J_{P,H}$ = 18.7–24.3 Hz) is a main characteristic feature. In the ^{13}C NMR spectra, the doublet of the α-carbon atom of α-aminophosphonates lies at 56.0–61.2 ppm ($^1J_{C,P}$ = 147.1–152.2 Hz) (for α-iminophosphonates, it lies at 150.7–171.4 ppm). Through the nascent α-C* stereocenter the ethoxy groups become diastereotopic and appear in the ^{13}C and ^{1}H NMR spectra as two sets of signals.

Compared to the asymmetric hydrogenation of C=C and C=O multiple bonds, the homogeneous stereoselective hydrogenation of the C=N bond remains poorly studied, although considerable progress in this area has been achieved recently.[40–42] The success is related, first of all, to the application of chiral Ti, Ru, Rh, and especially Ir complexes. In the last case, good results are provided by the use of ligands of the phosphino-oxazoline type.[40,41,43–50] The iridium(I) cationic complex ([Ir(COD)(**L1**)]$^+$[BAr_F]$^-$, Figure 2) containing chiral ligand **L1** of the phosphino-oxazoline type has been used by us previously[51] in the homogeneous enantioselective hydrogenation of 1-arylethenylphosphonates, which gave phosphorus analogues of Naproxen and Ibuprofen with *ee*s of 95 and 88%, respectively. However, our attempts to use the same complex in the hydrogenation of α-iminophosphonates failed. In dichloromethane or chloroform (commonly used solvents for this type of catalysts) the hydrogenation of α-iminophosphonate **2a** does not take place at all or is too slow in the whole ranges of temperature (20–80 °C) and pressure (10–110 bar) studied. When methanol is used as solvent under drastic conditions (110 bar, 80 °C), conversion was 95% and the yield of α-aminophosphonate **3a** was 76% after 10 h, but the isolated sample of **3a** was optically inactive.

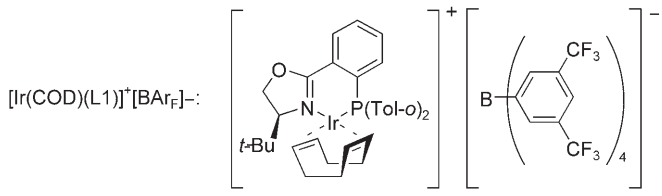
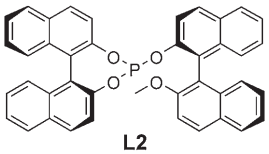
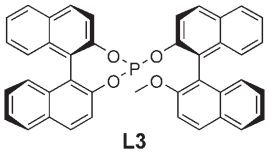
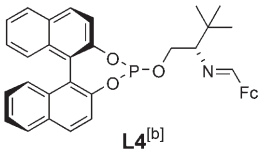
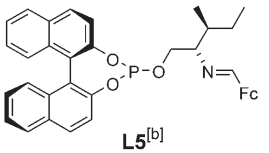
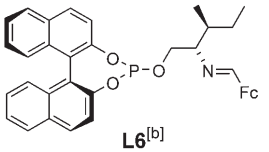
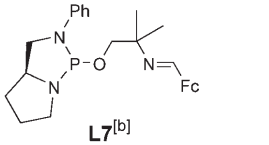
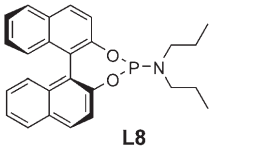


Figure 2. Structure of the complex [Ir(COD)(**L1**)]$^+$[BAr_F]$^-$.

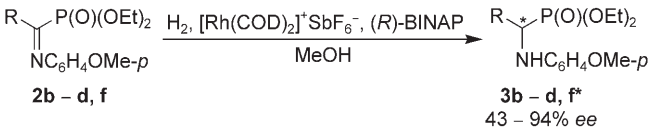
Iridium complexes with ligands involving a phosphite donor center showed good results in the asymmetric hydrogenation of *N*-(1-arylethylidene)aniline.[52,53] The chiral amidophosphite MonoPhos[54] was successfully applied in the Ir(I)-catalyzed hydrogenation of the model 2,3,3-trimethylindolenine.[55] Having in hand a family of ligands of phosphite (**L2–6**)[56–58]

Table 3. Ligands **L2–8** in the catalytic asymmetric hydrogenation of **2b** (CH_2Cl_2, 50 bar H_2, 20 °C, 24 h, [Ir(COD)$_2$]$^+$$SbF_6^-$ as precatalyst, S/Ir/L = 100/3/6 for mono- or 100/3/3 for bidentate ligands).

L	Conversion of **2b** [%][a]	Yield of **3b*** [%][a]	*ee* [%]
 **L2**	74	26	7
 **L3**	68	30	3
 **L4**[b]	62	19	23
 **L5**[b]	70	31	38
 **L6**[b]	57	13	37
 **L7**[b]	66	14	69
 **L8**	46 44 68	16 6 24	80 –[c] 12[d]

[a] Determined by ^{31}P NMR.
[b] Fc = ferrocenyl.
[c] [Rh(COD)$_2$]$^+$$SbF_6^-$ as precatalyst.
[d] [Rh(COD)$_2$]$^+$$BF_4^-$ as precatalyst.

and amidophosphite (**L7**, **8**)[59,60] types, we tested them in the hydrogenation of α-iminophosphonate **2b**. The results obtained are presented in Table 3. Both the monodentate **L2**, **3** and P,N-bidentate **L4–6** BINOL-derived phosphite ligands revealed a low stereo-differentiating ability: the optical yield of the product **3b*** did not exceed 38% *ee*. A satisfactory asymmetric induction was revealed by the bidentate P-chiral diamidophosphite **L7** containing an additional sp^2-*N*-donor center and, especially, the monodentate BINOL-based amidophosphite **L8** (analogue of MonoPhos) (69 and 80% *ee*, respectively). Unfortunately, the hydrogenation rate of α-iminophosphonate **2b** using the ligands **L2–8** turned out to be very low, as the yield of the target product **3b*** was 13–31% even after a day, and decomposition products, such as diethyl benzoylphosphonate (**4**) and diethyl phosphite, were formed in considerable amounts. Our attempts to optimize the reaction conditions by using the ligand **L8** (variation of the hydrogen pressure from 10 to 100 bar and temperature in the 20–80 °C interval) were unsuccessful, as the increase in the yield of α-aminophosphonate **3b*** was inevitably accompanied by a substantial decrease in the stereoselectivity of the process. The replacement of the iridium precatalyst $[Ir(COD)_2]^+SbF_6^-$ by the rhodium ones $[Rh(COD)_2]^+SbF_6^-$ or $[Rh(COD)_2]^+BF_4^-$ gave no positive effect as well.



2b – d, f **3b – d, f***
43 – 94% *ee*

Scheme 4. Rh-catalyzed asymmetric hydrogenation of **2b–d**, **f**.

The chiral bisphosphines present the widest group of ligands used in Rh(I)- and Ir(I)-catalyzed stereoselective hydrogenation of the C=N bond.[40,41,61–63] We have also turned our attention to the classical BINAP ligand (Scheme 4).

It was found that the hydrogenation of the model substrate **2b** at room temperature and hydrogen pressure of 50 bar in the presence of the cationic rhodium complex prepared in situ by the slow addition of a solution of the $[Rh(COD)_2]^+SbF_6^-$ precatalyst in methanol to a solution of a stoichiometric amount of (*R*)-BINAP in the same solvent resulted in the formation of α-aminophosphonate **3b*** in quantitative yield after 6 h, with enantiomeric excess reaching 94% *ee* (Table 4, entry 1). When the S/Rh mol ratio was changed from 20/1 to 100/3 (entry 2), the optical yield stays roughly constant within the measurement error, but decreases substantially at S/Rh = 100/1 (entry 3). The yield of by-products simultaneously increases noticeably. The reaction rate as well as chemo- and stereoselectivity decrease significantly when the SbF_6^- counterion is replaced by BF_4^- (entry 4).

The variation of pressure from 10 to 70 bar (at 20 °C) exerts no substantial effect on the stereoselectivity of the process when S/Rh = 20/1 (entries 1, 5–7) and 100/3 (entries 2, 8, 9). In the latter case, however, trace amounts of by-products were formed under hydrogen pressures below 70 bar (entries 2, 9). Under 10 bar pressure, the target product **3b*** is formed in a quantitative yield at 60–80 °C, the optical yield being 94–92% *ee* (entries 10, 11).

It turned out that the order of reagent mixing during the catalyst preparation is of principal significance. The catalyst sample prepared by the inverse order of mixing, i.e., by a slow addition of a methanol solution of (*R*)-BINAP to a solution of

Table 4. Rh-catalyzed asymmetric hydrogenation of **2b** {MeOH, $[Rh(COD)_2]^+SbF_6^-$ as precatalyst, (*R*)-BINAP}.

Entry	S/Rh[a]	Pressure [bar]	Temperature [°C]	Time [h]	Conversion of **2b** [%][b]	Yield of **3b*** [%][b]	*ee* [%]
1	20/1	50	20	6	100	100	94
2	100/3	50	20	6	100	98	91
3	100/1	50	20	6	100	92	79
4	100/1[c]	50	20	6	88	79	51
5	20/1	70	20	24	100	100	91
6	20/1	20	20	24	100	100	91
7	20/1	10	20	24	100	100	92
8	100/3	70	20	6	100	100	91
9	100/3	10	20	6	93	90	90
10	100/3	10	60	6	100	100	94
11	100/3	10	80	6	100	100	92
12	20/1[d]	50	20	24	100	92	65

[a] Unless otherwise stated, the catalyst was prepared by addition of the solution of $[Rh(COD)_2]^+SbF_6^-$ precatalyst to (*R*)-BINAP.
[b] Determined by ^{31}P NMR.
[c] $[Rh(COD)_2]^+BF_4^-$ as precatalyst.
[d] The catalyst was prepared by addition of the solution of (*R*)-BINAP to $[Rh(COD)_2]^+SbF_6^-$ precatalyst.

$[Rh(COD)_2]^+SbF_6^-$, showed a low stereo-differentiating ability of 65% *ee* (entry 12). The replacement of methanol by CH_2Cl_2 increases the enantiomeric excess to 73% *ee*; however, the yield of the target product **3b*** decreases to 34%, and the decomposition products **4** (37%) and $HP(O)(OEt)_2$ (10%) are accumulated in significant amounts, which agrees well with published data (see, e.g.[64]) on the participation of the MeOH molecule in the catalytic cycle. The iridium precatalyst $[Ir(COD)_2]SbF_6$ exhibited no activity.

Under the optimal conditions found (MeOH, 10 bar H_2, 60 °C, S/Rh = 100/3), we tested the hydrogenation of a series of α-iminophosphonates **2c**, **d**, **f–h** (Table 5). The reduction of Me-subsituted α-iminophosphonate **2c** gave α-aminophosphonate **3c*** in quantitative yield and 94% *ee* after 6 h. The hydrogenation rate of α-iminophosphonates **2d**, **f** containing more π-donor aromatic substituents at the α-C atom decreases noticeably, which is consistent with the mechanism proposed earlier,[63,65] including the hydride transfer from Rh to the α-C atom of η^2-(C=N)-coordinated imine with formation of the Rh–N bond. The completion of the reaction in the case of fluorine-substituted α-iminophosphonate **2d** requires 10 h, the enantiomeric excess being 75%. The conversion of thienyl α-iminophosphonate **2f** comes to 88% after 12 h and remains virtually unchanged with the prolongation of the reaction time, which is due, probably, to the inhibition of the catalyst during the reaction course. Approximately the same conversion is achieved with S/Rh = 20/1; the yield of the target product **3f*** increases to 82% with 43% *ee*.

Attempts at the homogeneous hydrogenation of α-iminophosphonates **2g**, **h** with predominant *Z*-configuration have not been successful. For the sterically hindered *tert*-butyl α-iminophosphonate **2g** the maximum achieved yield of the target product is 17% at a conversion of 23% (70 bar H_2, 60 °C, 6 h, S/Rh = 100/3). No result was obtained by the variation of the pressure and temperature, an increase in the catalyst amount, and prolongation of the reaction time. The hydrogenation of trifluoromethyl α-iminophosphonate **2h** is non-selective and most probably complicated by C–F bond cleavage; the structure of the by-product deserves further clarification.

Conclusions

In summary, we have shown that the palladium-catalyzed hydrogenation of diethyl α-iminomethyl phosphonates bearing aryl, heteroaryl, *tert*-butyl or trifluoromethyl substituents in the α-position can serve as a convenient synthetic approach to α-aminophosphonates of practical interest. Asymmetric hydrogenation of the α-iminophosphonates with a predominant *E*-configuration of the imine bond using the $[Rh(COD)_2]^+SbF_6^-$/(*R*)-BINAP complex was demonstrated to provide a new general method for the synthesis of optically active α-aminophosphonates containing the quaternary β-carbon atom with enantiomeric excesses up to 94%.

Experimental Section

Chloroform and dichloromethane were distilled over P_2O_5, stored in the dark under argon and distilled over CaH_2 prior to use. Methanol was dried over magnesium methoxide followed by distillation. Palladium on carbon (10% Pd) (Aldrich) and (*R*)-BINAP (97%, Aldrich) were used without purification. The $[Rh(COD)_2]^+BF_4^-$, $[Rh(COD)_2]^+SbF_6^-$, and $[Ir(COD)_2]^+SbF_6^-$ precatalysts were prepared by the reported methods.[66] The $[Ir(COD)\mathbf{L1}]^+[BAr_F]^-$ complex was

Table 5. Rh-catalyzed asymmetric hydrogenation of **2b–d**, **f–h** {MeOH, 60 °C, $[Rh(COD)_2]^+SbF_6^-$ as precatalyst, S/Rh/(*R*)-BINAP = 100/3/3}.

Substrate **2**	R	Pressure [bar]	Time [h]	Conversion of **2** [%][a]	Yield of **3*** [%][a]	*ee* [%]
2b	Ph	10	6	100	100	94
2c	4-MeC_6H_4	10	6	100	100	94
2d	4-FC_6H_4	10	8	90	84	
		10	10	100	94	75
2f	2-thienyl	10	12	88	69	
		10	12	84	82[b]	43
2g	*t*-Bu	10	6	11	8	
		70	8	23	17	
		75	13	35	13[c,d]	
2h	F_3C	10	6	40	21	
		100	6	85	47[c]	

[a] Determined by ^{31}P NMR.
[b] S/Rh/(*R*)-BINAP = 20/1/1.
[c] At 80 °C.
[d] S/Rh/(*R*)-BINAP = 100/6/6.

synthesized in the research group of Prof. A. Pfaltz and kindly presented to the authors. Triethyl phosphite was treated with Na, then distilled under reduced pressure. Amides were prepared by the standard Schotten–Baumann procedure. *N*-Phenylbenzenecarboxyimidoyl chloride (**1a**) was synthesized as published.[67] The melting points of products were measured with Electrothermal 9100 indicator in a sealed capillary.

***N*-(*p*-Anisyl)benzenecarboxyimidoyl chloride (1b):** Synthesized by a procedure similar to[67] by stirring of a mixture of *N*-(*p*-anisyl)benzamide (3.964 g, 17.44 mmol) with thionyl chloride (2.5 mL, 34.27 mmol) at 80 °C for 2.5 h. Excess $SOCl_2$ was removed under reduced pressure, and the residue was distilled under vacuum affording **1b** as pale yellow crystals; yield: 3.641 g (85%); bp 174–176 °C (2 Torr).

***N*-(*p*-Anisyl)-4-methylbenzenecarboxyimidoyl chloride (1c):** Synthesized similarly to **1b** from 3.457 g (14.33 mmol) of *N*-(*p*-anisyl)-4-methylbenzamide and 4.0 mL (54.84 mmol) of $SOCl_2$ as pale yellow crystals; yield: 87%; bp 180–188 °C (2 Torr).

***N*-(*p*-Anisyl)-4-fluorobenzenecarboxyimidoyl chloride (1d):** Synthesized similarly to **1b** from 4.100 g (16.72 mmol) of *N*-(*p*-anisyl)-4-fluorobenzamide and 6.5 mL (89.11 mmol) of $SOCl_2$ as pale yellow crystals; yield: 91%; bp 160–164 °C (2 Torr).

***N*-(*p*-Anisyl)furan-2-carboxyimidoyl chloride (1e):** Synthesized similarly to **1b** from 5.000 g (23.02 mmol) of *N*-(*p*-anisyl)-2-furamide and 5.1 mL (69.92 mmol) of $SOCl_2$ as pale yellow crystals; yield: 78%; bp 152 °C (2 Torr).

***N*-(*p*-Anisyl)thiophene-2-carboxyimidoyl chloride (1f):** Synthesized similarly to **1b** from 2.500 g (10.72 mmol) of *N*-(*p*-anisyl)thiophene-2-carboxamide and 4.0 mL (54.84 mmol) of $SOCl_2$ as a pale yellow oil; yield: 92%; bp 180–185 °C (2 Torr).

***N*-(*p*-Anisyl)-2,2-dimethylpropanimidoyl chloride (1g):** Synthesized similarly to **1b** from 6.000 g (28.95 mmol) of *N*-(*p*-anisyl)-2,2-dimethylpropanamide and 2.6 mL (35.65 mmol) of $SOCl_2$ as pale yellow crystals; yield: 87%; bp 108 °C (2 Torr).

***N*-(*p*-Anisyl)-2,2,2-trifluoroethanimidoyl chloride (1h):** Synthesized by the method described in the literature.[68] Pale yellow viscous liquid; bp 126 °C (12 Torr).[37,68]

Diethyl α-(Phenylimino)benzylphosphonate (2a)

A Claisen flask equipped with a magnetic stirrer and filled with dry argon was loaded with **1a** (6.289 g, 29.16 mmol) and triethyl phosphite (5.0 mL, 29.16 mmol). The reaction mixture was stirred at 160 °C for 2 h and then distilled under vacuum in an argon flow affording **2a** as a yellow oil; yield: 6.542 g (71%); bp 175–180 °C (10^{-1} Torr).[31]

Diethyl α-(*p*-anisylimino)benzylphosphonate (2b): Synthesized similarly to **2a** by stirring a mixture of 3.641 g (14.82 mmol) of **1b** and 3.0 mL (17.15 mmol) of triethyl phosphite at 140–150 °C for 3 h and obtained as a yellow oil; yield: 79%; bp 204–210 °C (10^{-1} Torr).

Diethyl α-(*p*-anisylimino)-4-methylbenzylphosphonate (2c): Synthesized similarly to **2a** by stirring a mixture of 3.222 g (12.40 mmol) of **1c** and 4.1 mL (23.91 mmol) of triethyl phosphite at 140–165 °C for 2.5 h and obtained as a dark yellow oil; yield: 79%; bp 185–190 °C (10^{-1} Torr).

Diethyl α-(*p*-anisylimino)-4-fluorobenzylphosphonate (2d): Synthesized similarly to **2a** by stirring a mixture of 3.951 g (14.98 mmol) of **1d** and 3.6 mL (20.99 mmol) of triethyl phosphite at 120–150 °C for 3 h and obtained as a yellow oil; yield: 98%; bp 171–182 °C (10^{-1} Torr).

Diethyl (*p*-anisylimino)(2-furyl)methylphosphonate (2e): Synthesized similarly to **2a** by stirring a mixture of 2.368 g (10.05 mmol) of **1e** and 2.0 mL (11.66 mmol) of triethyl phosphite at 120–130 °C for 3 h and obtained as a purple oil; yield: 36%; bp 180 °C (10^{-1} Torr).

Diethyl (*p*-anisylimino)(2-thienyl)methylphosphonate (2f): Synthesized similarly to **2a** by stirring a mixture of 2.483 g (9.86 mmol) of **1f** and 1.7 mL (9.91 mmol) of triethyl phosphite at 160 °C for 2 h and obtained as an orange oil; yield: 56%; bp 185–190 °C (10^{-1} Torr).

Diethyl 1-(*p*-anisylimino)-2,2-dimethylpropylphosphonate (2g): Synthesized similarly to **2a** by stirring a mixture of 5.000 g (22.15 mmol) of **1g** and 3.8 mL (22.16 mmol) of triethyl phosphite at 170 °C for 2 h and obtained as a yellow oil; yield: 80%; bp 150–156 °C (10^{-1} Torr).

Diethyl 1-(*p*-anisylimino)-2,2,2-trifluoroethylphosphonate (2h): Synthesized similarly to **2a** by stirring a mixture of 0.717 g (3.02 mmol) of **1h** and 0.5 mL (2.92 mmol) of triethyl phosphite at 120–135 °C for 2 h and obtained as a yellow oil; yield: 59%; bp 145–155 °C (10^{-1} Torr).

Diethyl α-(Phenylamino)benzylphosphonate (3a)

α-Iminophosphonate **2a** (0.500 g, 1.58 mmol) in dry methanol (50 mL) was placed in a flask equipped with a magnetic stirrer, reflux condenser with a three-way adapter, gas bubbler, and long gas inlet tube passing through the condenser to the bottom of the flask. The device was filled with dry argon, and 0.083 g of 10% Pd/C (S/Pd = 20/1) was added. The argon supply was stopped, and hydrogen was passed through the device using the same inlet tube. The reaction mixture was refluxed with stirring for 2 h in a weak hydrogen current and then cooled. The catalyst was filtered off using a short pad of silica gel. The mother liquor was evaporated to dryness under vacuum to furnish spectrally pure α-aminophosphonate **3a** as colorless crystals, turning dark in the air; yield: 0.431 g (86%). After recrystallization from alcohol the yield of **3a** was 0.300 g (60%), mp 89–90 °C.[69–72]

Diethyl α-(*p*-Anisylamino)benzylphosphonate (3b)

Compound **2b** (1.000 g, 2.88 mmol) in dry methanol (30 mL) and 10% Pd/C (0.153 g, S/Pd = 20/1) were placed in a steel autoclave with a glass inset equipped with a magnetic stirrer and filled with dry argon. The autoclave was sealed and pressurized with H_2 (50 bar), and the reaction mixture was stirred at room temperature for 3 h. The catalyst was filtered off using a celite pad, the mother liquor was evaporated to dryness under vacuum to furnish spectrally pure α-aminophosphonate **3b** as a yellow oil; yield: 0.989 g (98%). Colorless crystals, turning dark in air, were obtained in 83% yield after crystallization from petroleum ether, mp 70–73 °C.

Diethyl α-(*p*-anisylamino)-4-methylbenzylphosphonate (3c): Synthesized similarly to **3b** as a yellow oil by the hydrogenation of **2c** (0.500 g, 1.38 mmol) in dry methanol (15 mL) in the presence of 10% Pd/C (0.073 g, S/Pd = 20/1); yield: 95%. Colorless crystals, turning dark in air, were ob-

tained in 81% yield after crystallization from petroleum ether, mp 69–73 °C.

Diethyl α-(p-anisylamino)-4-fluorobenzylphosphonate (3d): Synthesized similarly to **3b** as a yellow oil by the hydrogenation of **2d** (1.000 g, 2.74 mmol) in dry methanol (30 mL) in the presence of 10% Pd/C (0.145 g, S/Pd = 20/1); yield: 99%. Colorless crystals, turning dark in air, were obtained in 71% yield after crystallization from petroleum ether, mp 45–48 °C.

Diethyl (*p*-anisylamino)(2-thienyl)methylphosphonate (3f): Synthesized similarly to **3b** by the hydrogenation of **2f** (0.055 g, 0.15 mmol) in dry methanol (10 mL) in the presence of 10% Pd/C (0.008 g, S/Pd = 20/1). Hydrogen pressure 70 bar, reaction time 24 h.

Diethyl (p-anisylamino)-2,2-dimethylpropylphosphonate (3g): Synthesized similarly to **3b** as a yellow oil by the hydrogenation of **2g** (1.000 g, 3.05 mmol) in dry methanol (30 mL) in the presence of 10% Pd/C (0.162 g, S/Pd = 20/1). Hydrogen pressure 70 bar, reaction time 20 h; yield: 100%. Beige crystals of **3g** were obtained in 54% yield after crystallization from petroleum ether, mp 59–61 °C.

Diethyl 1-(*p*-anisylamino)-2,2,2-trifluoroethylphosphonate (3h): Synthesized similarly to **3b** as a yellow oil by the hydrogenation of **2h** (0.520 g, 1.53 mmol) in dry methanol (16 mL) in the presence of 10% Pd/C (0.082 g, S/Pd = 20/1); yield: 98%. Colorless crystals, turning dark in air, were obtained in 48% yield after crystallization from petroleum ether, mp 57–60 °C.[37]

Asymmetric Hydrogenation of 2b (Typical Example)

The Schlenk flask was dried at 150 °C for 40 min, filled with dry argon, and loaded with (*R*)-BINAP (2.7 mg, 4.34 μmol) dissolved in 4 mL of deaerated dry methanol. A solution of $[Rh(COD)_2]^+SbF_6^-$ (2.6 mg, 4.68 μmol) in MeOH (4 mL) was added dropwise with vigorous stirring for 30 min. After 10 min, α-iminophosphonate **2b** (50.0 mg, 0.14 mmol) was introduced in an argon flow. The resultant homogeneous, weakly yellow solution was stirred for 10 min more and transferred by a syringe into a steel autoclave washed with MeOH and filled with argon. The Schlenk flask was washed with MeOH (2 mL), which was added to the main solution. The autoclave was sealed, pressurized with H_2 to 10 bar, the temperature was increased to 60 °C, and the reaction mixture was stirred for 6 h. After the end of the experiment, the solution was evaporated under reduced pressure. The residue was dissolved in $CDCl_3$ and analyzed by ^{31}P and ^1H NMR. The enantiomeric excess was determined by HPLC on a Bischoff liquid chromatograph [chiral column (*R,R*)-WHELK-01, hexane/*i*-PrOH, 9/1, 1.0 mL min^{-1}, 254 nm]. The retention times of the enantiomers of **3b*** were 12.1 and 13.1 min (ratio 1/31).

Experiments on the optimization of reaction conditions of enantioselective hydrogenation of α-iminophosphonate **2b** and hydrogenation of other α-iminophosphonates **2** were carried out similarly. The retention times of the two enantiomers were: **3c***, 12.5 and 14.0 min (ratio 1/31); **3d***, 12.1 and 13.5 min (ratio 1/7), **3f***, 7.4 and 8.3 min (ratio 1/2.5).

Supporting Information

Spectral and analytical data of compounds **1b**, **e**, **h**, **2** and **3a–d**, **f–h** are given in the Supporting Information.

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