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Rhodium complexes of (*R*)-Me-CATPHOS and (*R*)-(*S*)-JOSIPHOS: highly enantioselective catalysts for the asymmetric hydrogenation of (*E*)- and (*Z*)-β-aryl-β-(enamido)phosphonates

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ABSTRACT

Rhodium complexes of (*R*)-Me-CATPHOS and (*R*)-(*S*)-JOSIPHOS form a complementary pair of catalysts for the highly efficient asymmetric hydrogenation of a selection of (*E*)- and (*Z*)-β-aryl-β-(enamido)phosphonates, respectively, in the majority of cases giving excellent yields and ee's in excess of 99%; the highest to be reported for this class of substrate.

1. Introduction

Enantiopure β-amino acids and their derivatives are key structural components of a number of biologically important compounds, which exhibit antibacterial and antifungal activities or find use as building blocks for the synthesis of β-peptides and β-lactam antibiotics.[1] Although numerous approaches to the synthesis of this class of molecules have been developed,[2] including the homologations of α-amino acids,[3] Mannich-type reactions of aldimines with silyl enolates,[4] Henry reactions of α-keto esters,[5] conjugate additions of nitrogen nucleophiles to α,β-unsaturated acceptors[6], and α-aminations of α-keto esters,[7] asymmetric hydrogenations of β-dehydroamino acid derivatives are among the most efficient.[8] While early studies have revealed that the hydrogenation of *Z*-β-dehydroamino acids was markedly more challenging than their *E*-counterparts,[9] catalysts have recently been developed that give high enantioselectivities for both isomers.[10] As isosters or bioisosters of their β-amino acid counterparts,[11] β-amino phosphonic acids are interesting and potentially useful synthetic targets with applications as antibacterial and antifungal agents,[12] proteolytic enzyme inhibitors,[13] haptens for catalytic antibodies[14], and as anti-HIV agents.[15] Despite recent advances in the asymmetric hydrogenation of β-dehydroamino acids, it is surprising that the corresponding hydrogenation of their phosphonate counterparts has received such limited attention, even more so considering that several highly efficient ruthenium- and rhodium-based catalysts have been developed for the asymmetric hydrogenation of α-aminophosphonates.[16] Indeed, prior to our work we are aware of only one report on the asymmetric hydrogenation of β-enamidophosphonates in which rhodium catalysts based on JOSIPHOS, BoPHOZ, SYNPHOS, and DPPF^{t}BP gave ee's of up to 92%, although catalyst performance exhibited a marked non-uniform dependence on the reaction conditions as well as substrate structure.[17] The disclosure of this preliminary study has prompted us to report full details of our work in this area, which has revealed that rhodium complexes of (*R*)-CATPHOS and (*R*)-(*S*)-JOSIPHOS catalyze the highly efficient asymmetric hydrogenation of *E*- and *Z*-β-aryl-β-(enamido)phosphonates, respectively, in both cases giving excellent yields and ee's in excess of 99%, the highest to be reported for this class of substrates.

2. Results and discussion

The substrates for this study were prepared according to the procedure described by Palacios (Scheme 1),[18] which involved deprotonation of dimethyl methylphosphonate **1**, reaction of the resulting lithium salt with substituted aryl nitriles **2a**–**f** to afford *Z*-β-aryl-β-(enamino)phosphonates **3a**–**f** and subsequent acylation with acetyl chloride to generate the corresponding β-aryl-β-(acylamino)-vinylphosphonates **4a**–**f**, typically as an approximately 3:1 mixture of *E*/*Z* isomers. Interestingly, the use of acetyl bromide for the acylation of **3a** gave β-aryl-β-(enamido)phosphonate **4a** as a *Z*-enriched isomer (*E*:*Z*, 1:2). While the *E*-isomer could only be isolated by separation of an *E*/*Z*-mixture using flash column chromatography, the *Z*-isomer was typically obtained by isomerization of an *E*/*Z*-mixture in the presence of potassium *tert*-butoxide, by analogy with the sodium methoxide-promoted isomerization of

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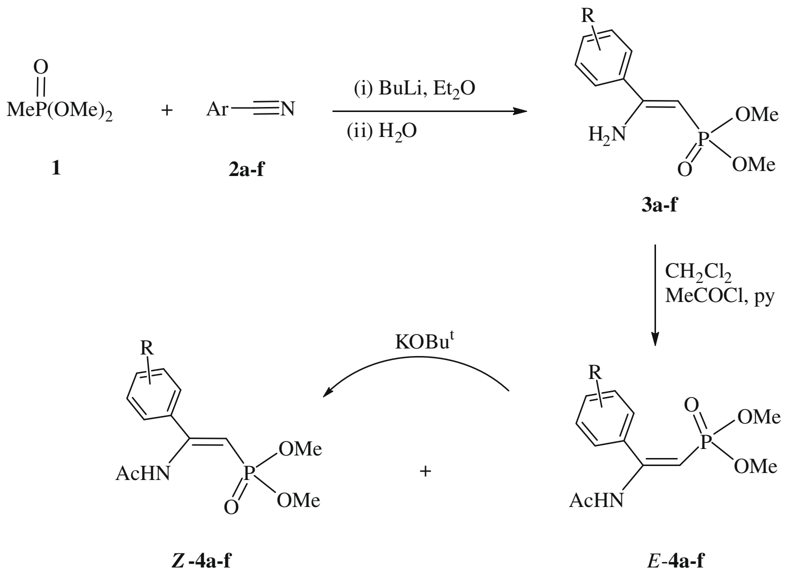


Scheme 1. Synthesis of *E*- and *Z*-β-aryl-β-(enamido)phosphonates **4a**–**f**.

β-dehydroamino acids reported by Carrie et al.[19] Each substrate (*E*)- and (*Z*)-**4a**–**f** was characterized by conventional spectroscopic and analytical methods and the stereochemistry was unequivocally assigned by a single-crystal X-ray structure determination of (*E*)-**4a**.

Reasoning that β-aryl-β-dehydroamino phosphonates **4a**–**f** resemble their β-amino acid counterparts we began catalyst screening to identify the best ligand and reaction conditions by screening the selection of phosphines shown in Chart 1 using 1 mol % catalyst generated from [Rh(cycloocta-1,5-diene)₂][BF₄] and 1 equiv of phosphine in methanol, under 5 atm of H_2 at room temperature (Table 1). Even though DUPHOS[10a,b] and TANGPHOS[10g,i] form extremely efficient catalysts for the asymmetric hydrogenation of β-dehydroamino acids, both proved to be relatively poor ligands for the rhodium-catalyzed hydrogenation of *E*- and *Z*-**4a** (R = 4-Me), the former gave β-amino phosphonate **5a** in 25% and 60% ee, respectively (entries 4 and 10), while the latter gave ee's of 66% and 10%, respectively (entries 5 and 11). Similarly, a catalyst based on PHANEPHOS[20] also gave **5a** with disappointingly low ee's of 34% and 42% from *E*- and *Z*-**4a**, respectively (entries 6 and 12). Gratifyingly, (*R*)-Me-CATPHOS[21] proved to be an exceptional ligand for the rhodium-catalyzed hydrogenation of *E*-**4a** in dichloromethane and gave the desired amino phosphonate in near quantitative yield and greater than 99% ee (entry 1). In contrast, there was no evidence for hydrogenation in methanol, which we believe to be due to the low solubility of the catalyst in this solvent. For comparison, Rh/(*R*)-BINAP is also an efficient system for hydrogenation of *E*-**4a** in dichloromethane, giving excellent conversion to **5a** in 77% ee (entry 2) and with the same absolute stereochemistry as that obtained with (*R*)-Me-CATPHOS, by comparison of the sign of the specific rotation. Under the same conditions, Rh/(*R*)-Me-CATPHOS was a poor catalyst for the hydrogenation of the *Z*-isomer, giving **5a** in reasonable yield but only 17% ee and with the opposite absolute stereochemistry to that obtained from its *E*-counterpart (entry 7). Fortunately, (*R*)-(*S*)-JOSIPHOS is a complementary ligand to (*R*)-Me-CATPHOS in that it

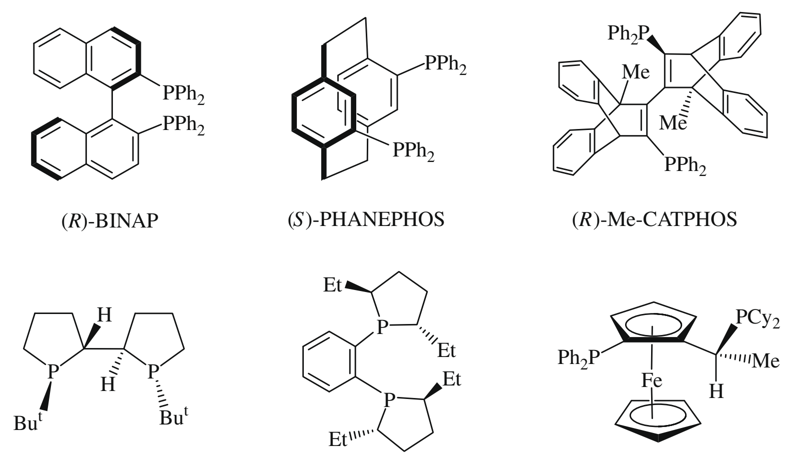
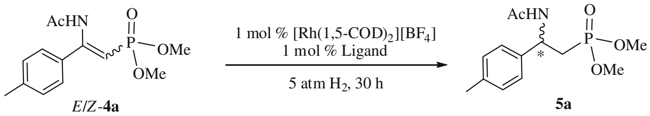


Chart 1.

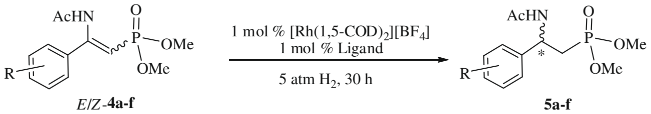
Table 1
Asymmetric hydrogenation of (*E*)- and (*Z*)-dimethyl-2-acetylamino-2-*p*-tolylvinylphosphonate (**4a**)[a]



Entry	Ligand	*E*/*Z*	Yield[d] (%)	ee[e,f] (%)
1[b]	(*R*)-Me-CATPHOS	*E*	94	>99 (+)
2[b]	(*R*)-BINAP	*E*	66	77 (+)
3[c]	(*R*)-(*S*)-JOSIPHOS	*E*	45	23 (−)
4[c]	(*S*,*S*)-Et-DUPHOS	*E*	64	25 (−)
5[c]	(*S*,*S*,*R*,*R*)-TANGPHOS	*E*	69	66 (+)
6[c]	(*S*)-PHANEPHOS	*E*	80	34 (−)
7[b]	(*R*)-Me-CATPHOS	*Z*	68	17 (−)
8[b]	(*R*)-BINAP	*Z*	37	4 (−)
9[c]	(*R*)-(*S*)-JOSIPHOS	*Z*	77	99 (+)
10[c]	(*S*,*S*)-Et-DUPHOS	*Z*	54	60 (−)
11[c]	(*S*,*S*,*R*,*R*)-TANGPHOS	*Z*	49	10 (+)
12[c]	(*S*)-PHANEPHOS	*Z*	62	42 (+)

[a] Reaction conditions: 1 mol % [Rh(COD)$_2$][BF$_4$], 1 mol % ligand, substrate (0.1765 mmol), 5 atm H$_2$, 7.0 mL of solvent, rt, 30 h.
[b] Conducted in CH$_2$Cl$_2$.
[c] Conducted in MeOH.
[d] Isolated yield.
[e] Determined by chiral HPLC using a Chiralcel OD-H column.
[f] Specific rotations were measured on an Optical Activity PolAAr 2001 digital polarimeter.

Table 2
Asymmetric hydrogenation of (*E*)- and (*Z*)-β-aryl-β-(enamido)phosphonates **4a–f** using the catalyst generated from (*R*)-Me-CATPHOS or (*R*)-(*S*)-JOSIPHOS[a]



Entry	Ligand	*E*/*Z*	R	4	Yield[d] (%)	ee[e,f] (%)
1[b]	(*R*)-Me-CATPHOS	*E*	4-Me	**4a**	94	>99 (+)
2[b]	(*R*)-Me-CATPHOS	*E*	H	**4b**	97	99 (+)
3[b]	(*R*)-Me-CATPHOS	*E*	4-F	**4c**	78	>99 (+)
4[b]	(*R*)-Me-CATPHOS	*E*	4-Cl	**4d**	80	99 (+)
5[b]	(*R*)-Me-CATPHOS	*E*	4-Br	**4e**	87	99 (+)
6[b]	(*R*)-Me-CATPHOS	*E*	4-MeO	**4f**	79	99 (+)
7[c]	(*R*)-(*S*)-JOSIPHOS	*Z*	4-Me	**4a**	77	99 (+)
8[c]	(*R*)-(*S*)-JOSIPHOS	*Z*	H	**4b**	72	97 (+)
9[c]	(*R*)-(*S*)-JOSIPHOS	*Z*	4-F	**4c**	66	96 (+)
10[c]	(*R*)-(*S*)-JOSIPHOS	*Z*	4-Cl	**4d**	81	94 (+)
11[c]	(*R*)-(*S*)-JOSIPHOS	*Z*	4-Br	**4e**	79	>99 (+)
12[c]	(*R*)-(*S*)-JOSIPHOS	*Z*	4-MeO	**4f**	82	>99 (+)

[a] Reaction conditions: 1 mol % [Rh(COD)$_2$][BF$_4$], 1 mol % (*S*)-**2b** or (*R*)-(*S*)-JOSIPHOS, substrate (0.1765 mmol), 5 atm H$_2$, 6.0 mL of solvent, rt, 30 h.
[b] Conducted in CH$_2$Cl$_2$.
[c] Conducted in MeOH.
[d] Isolated yield.
[e] Determined by chiral HPLC using a Chiralcel OD-H column.
[f] Specific rotations were measured on an Optical Activity PolAAr 2001 digital polarimeter.

forms a highly efficient catalyst for the asymmetric hydrogenation of *Z*-**4a** in methanol at 5 atm H$_2$ giving **5a** in near quantitative yield and 99% ee (entry 9). However, Rh/(*R*)-(*S*)-JOSIPHOS was only a poor catalyst for the hydrogenation of *E*-**4a**, which gave **5a** in 23% ee and with the opposite absolute configuration to that obtained with its *Z*-isomer (entry 3). A marked solvent effect was also observed for this catalyst–substrate combination with hydrogenation of *Z*-**4a** in dichloromethane also giving complete conversion but with only 86% ee; as a result all remaining studies with this system were performed in methanol.

Having identified (*R*)-Me-CATPHOS and (*R*)-(*S*)-JOSIPHOS to be a complementary pair of ligands that form highly enantioselective catalysts for the asymmetric hydrogenation of *E*- and *Z*-**4a**, respectively, a range of substrates were investigated, the results of which are listed in Table 2. Under the same conditions as those described above, Rh/(*R*)-Me-CATPHOS catalyzes the hydrogenation of *E*-**4b–f**, to give the corresponding β-aryl β-(amido)phosphonate in good to excellent yield and enantioselectivity (>99%), regardless of the electronic properties of the β-aryl group (entries 1–6). Excellent enantioselectivities (94–99% ee) and conversions were also obtained for the corresponding *Z*-isomers using catalysts based on (*R*)-(*S*)-JOSIPHOS (entries 7–12), which gave the same sense of stereocontrol as (*R*)-Me-CATPHOS, according to the sign of the specific rotation.

Even though the absolute configuration of phosphonates **5a–f** has not been unequivocally established the high ee's obtained with (*R*)-Me-CATPHOS and (*R*)-(*S*)-JOSIPHOS can be accounted for using the traditional quadrant diagram in which pseudo equatorial and axial groups occupy alternating quadrants.[22] Since enantiopure Me-CATPHOS forms a highly efficient catalyst for the asymmetric hydrogenation of *E*-**4a–f** a single-crystal X-ray determination of [Rh{(*S*)-Me-CATPHOS}(acac)] **6**, as a representative rhodium complex of (*S*)-Me-CATPHOS, was undertaken; the molecular structure is shown in Figure 1. Although the (*S*)-enantiomer of Me-CATPHOS was used for this study, the structure clearly shows the asymmetric environment created by the alternating edge-face arrangement of P–Ph rings which resembles that in [Rh{(*S*)-BIPHEP}(2-(4-*tert*-butylphenyl)-8-methoxy-1,8-dimethyl-bicyclo[2.2.2]octa-2,5-diene)][SbF$_6$][23] and [Rh{(*S*)-H$_8$-BINAP}(cycloocta-1,5-diene)][ClO$_4$][24] and as such a catalyst based on enantiopure Me-CATPHOS would be expected to exert the same sense of enantiocontrol as its BINAP counterpart. According to the quadrant model, the two equatorial phenyl rings of (*R*)-Me-CATPHOS provide effective shielding of the upper left and lower right quadrants (gray), which determines the absolute stereochemistry of the product. By direct analogy with the application of this model to the asymmetric hydrogenation of their β-(acylamino)acrylate counterparts by Imamoto et al., in which the hydride and oxygen atoms were proposed to adopt a *trans*-arrangement around octahedral rhodium with the alkene in

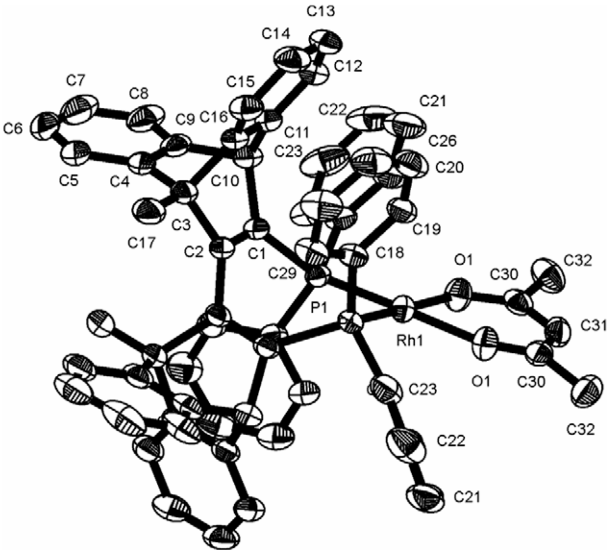


Figure 1. Molecular structure of [Rh{(*S*)-Me-CATPHOS)(acac)] **6** illustrating the spatial arrangement of P–Ph rings and the absolute stereochemistry of the buta-1,3-diene axis. Hydrogen atoms have been omitted for clarity.

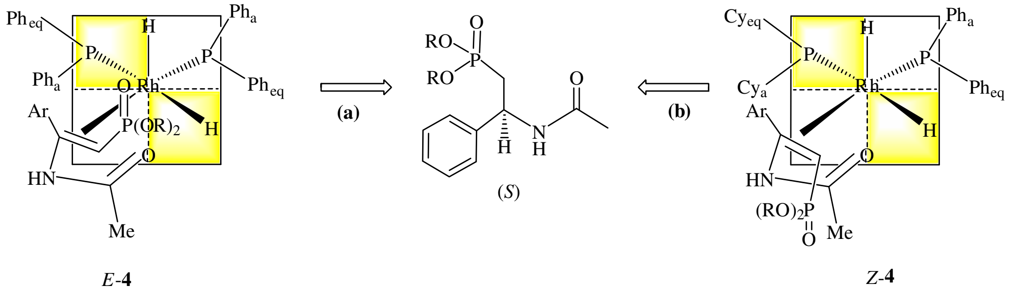


Figure 2. Quadrant diagrams of Rh/(*R*)-Me-CATPHOS (a) and Rh/(*R*)-(*S*)-JOSIPHOS (b) used to account for the absolute configuration obtained in the hydrogenation of *E*-**4a–f** and *Z*-**4a–f**, respectively.

the RhP_2H plane,[25] the chelate ring formed by coordination of the oxygen atom of the enamide carbonyl minimizes its interaction with the pseudo equatorial phenyl rings to afford product with (*S*)-absolute configuration, as shown in Figure 2a. This model also accounts for the same sense of enantioinduction obtained for the hydrogenation of *Z*-**4a–f** with catalyst based on (*R*)-(*S*)-JOSIPHOS. Examination of the molecular structure of [Rh{(*R*)-(*S*)-JOSIPHOS}(norbornadiene)][BF_4][26] reveals a pseudo C_2-symmetric arrangement of the phenyl and cyclohexyl rings such that the bottom right and upper left quadrants are hindered by pseudo equatorial phenyl and cyclohexyl rings, respectively, and placing the enamide chelate in the least hindered quadrant affords product of (*S*)-absolute configuration (Fig. 2b). However, this model does not explain why Rh/(*R*)-Me-CATPHOS affords high ee's with *E*-**4a–f** only, while its (*R*)-(*S*)-JOSIPHOS counterpart is highly enantioselective for the hydrogenation of the *Z*-substrates only; clearly a more sophisticated model is required to account for the *E*/*Z* specific nature of these systems.

3. Conclusions

In conclusion, we have shown that rhodium complexes of (*R*)-CATPHOS and (*R*)-(*S*)-JOSIPHOS diphosphines form a pair of complementary catalysts for the highly efficient asymmetric hydrogenation of (*E*)- and (*Z*)-β-aryl-β-(acylamino)vinylphosphonates, respectively. In both cases ee's in excess of 99% were obtained, which are the highest reported for this class of substrate. With an unequivocal determination of the absolute stereochemistry of the product it will be possible to provide a more definitive and sound rationale for the sense of asymmetric induction obtained with this catalyst–substrate combination.

4. Experimental

4.1. General procedures

All manipulations involving air-sensitive materials were carried out using standard Schlenk line techniques under an atmosphere of nitrogen or argon in oven-dried glassware. Dichloromethane was distilled from calcium hydride, diethyl ether from Na/K alloy, THF from sodium/benzophenone and, methanol from magnesium. 9-Methylanthracene and methyl-2-acetamido acrylate were purchased from Lancaster and used without further purification. $[RhCl(1,5\text{-}COD)]_2$,[27] and $[Rh(1,5\text{-}COD)_2][BF_4]$[28], $[Rh(acac)(coe)_2]$,[29] and **3b**[17a] were prepared as previously described. ^1H, $^{13}C\{^1H\}$, and ^{31}P NMR spectra were recorded on a JEOL LAMBDA 500 or a Bruker AMX 300 instrument. Optical rotations were measured on an Optical Activity PolAAr 2001 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{20}$ (*c* g/100 mL, solvent). Thin-layer chromatography (TLC) was carried out on aluminum sheets pre-coated with Silica Gel 60F 254 and column chromatography was performed using Merck Kieselgel 60. Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 110 Series HPLC equipped with a variable wavelength detector using a Daicel Chiralcel OD-H column. Enantiomeric excesses were calculated from the HPLC profile.

4.2. Synthesis of dimethyl 2-amino-2-arylvinylphosphonates 3a–f

4.2.1. Dimethyl 2-amino-2-*p*-tolylvinylphosphonate 3a

To a solution of dimethyl methylphosphonate (5.0 mL, 35 mmol) in diethyl ether (100 mL) cooled to −78 °C was added BuLi (14 mL, 2.5 M, 35 mmol) dropwise with vigorous stirring. The resulting solution was stirred for 1 h at −78 °C, after which time 4-methylbenzonitrile was added (4.095 g, 35 mmol) and stirring continued at the same temperature for a further 15 min. The reaction mixture was allowed to warm to 0 °C, stirred for a further 2 h, and then quenched by the addition of water (100 mL). The organic fraction was separated, washed with saturated $NaHCO_3$ (3×50 mL), brine (3×50 mL), dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the residue purified by column chromatography eluting with $CHCl_3$/MeOH (100:4) to afford **3a** in 86% yield (7.28 g). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 28.8; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.41 (d, $J = 8.1$ Hz, 2H, C_6H_4), 7.16 (d, $J = 8.0$ Hz, 2H, C_6H_4), 5.88 (s, 2H, NH_2), 4.05 (d, $J = 12.5$ Hz, 2H, CH), 3.67 (d, $J = 11.3$ Hz, 2H, OMe), 2.0 (s, 3H, $ArCH_3$). $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 163.0 (d, $J = 6.6$ Hz, $=CNH_2$), 140.5 (C_6H_4), 136.0 (d, $J = 20.7$ Hz C_6H_4), 129.4 (C_6H_4), 126.3 (C_6H_4), 72.4 (d, $J = 193$ Hz, =CHP), 51.6 (d, $J = 5.0$ Hz, OCH_3), 21.4 ($C_6H_4CH_3$). HRMS (ESI^+) exact mass calcd for $C_{11}H_{17}PO_3N$ $[M+H]^+$ requires *m*/*z* 242.0946, found *m*/*z* 242.0949.

4.2.2. Dimethyl 2-amino-2-*p*-fluorophenylvinylphosphonate 3c

Enamino phosphonate **3c** was prepared according to the procedure described above for **3a** on the same scale and isolated as an analytically and spectroscopically pure solid in 72% yield (6.19 g) after purification by column chromatography eluting with $CHCl_3$/MeOH (100:4). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 28.9; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.47 (dd, $J = 8.6$, 5.3 Hz, 2H, C_6H_4), 7.00 (m, 2H, C_6H_4), 5.89 (S,2H, NH_2), 3.96 (d, $J = 12.0$ Hz, 1H, =CH), 3.63 (d, $J = 11.3$ Hz, 6H, OCH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 165.9 ($=CNH_2$), 162.1 (m, C_6H_4), 135.1 (d, $J = 21.1$ Hz, C_6H_4), 128.1 (d, $J = 8.4$ Hz, C_6H_4), 115.6 (d, $J = 21.8$ Hz, C_6H_4), 73.6 (d, $J = 193.7$ Hz, PC=C), 51.7 (d, $J = 5.1$ Hz, OCH_3); LRMS (ESI^+) *m*/*z* 246 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{10}H_{14}FNO_3P$ $[M+H]^+$ requires *m*/*z* 246.0695, found *m*/*z* 242.0690.

4.2.3. Dimethyl 2-amino-2-*p*-chlorophenylvinylphosphonate 3d

Enamino phosphonate **3d** was prepared according to the procedure described above for **3a** on the same scale and isolated as an analytically and spectroscopically pure solid in 67% yield (6.14 g) after purification by column chromatography eluting with $CHCl_3$/

MeOH (100:4). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 28.8; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.48 (d, *J* = 8.5 Hz, 2H, C_6H_4), 7.36 (d, *J* = 8.5 Hz, 2H, C_6H_4), 5.86 (s, 2H, NH_2), 4.06 (d, *J* = 11.9 Hz, 1H, =CH), 3.70 (d, *J* = 11.3 Hz, 6H, OCH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 161.8 (d, *J* = 7.0 Hz, =CNH_2), 137.5 (d, *J* = 21.1 Hz, C_6H_4), 136.2 (C_6H_4), 129.0 (C_6H_4), 127.5 (C_6H_4), 74.1 (d, *J* = 193 Hz, PC=C), 51.8 (d, *J* = 5.1 Hz, OCH_3); LRMS (ESI^+) *m*/*z* 262 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{10}H_{14}ClNO_3P$ $[M+H]^+$ requires *m*/*z* 262.0400, found *m*/*z* 262.0397.

4.2.4. Dimethyl 2-amino-2-*p*-bromophenylvinylphosphonate 3e

Enamino phosphonate **3e** was prepared according to the procedure described above for **3a** on the same scale and isolated as an analytically and spectroscopically pure solid in 66% yield (7.07 g) after purification by column chromatography eluting with $CHCl_3$/MeOH (100:4). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 28.6; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.43 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.35 (d, *J* = 8.5 Hz, 2H, C_6H_4), 5.94 (s, 2H, NH_2), 3.95 (d, *J* = 12.0 Hz, 1H, =CH), 3.61 (d, *J* = 11.3 Hz, 6H, OCH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 161.7 (d, *J* = 6.9 Hz, =CNH_2), 137.6 (d, *J* = 21.1 Hz, C_6H_4), 131.7 (C_6H_4), 127.6 (C_6H_4), 124.0 (C_6H_4), 73.3 (d, *J* = 195.0 Hz, PC=C), 51.5 (d, *J* = 5.1 Hz, OCH_3); LRMS (ESI^+) *m*/*z* 306 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{10}H_{14}BrNO_3P$ $[M+H]^+$ requires *m*/*z* 305.9895, found *m*/*z* 305.9898.

4.2.5. Dimethyl 2-amino-2-*p*-methoxyphenylvinylphosphonate 3f

Enamino phosphonate **3f** was prepared according to the procedure described above for **3a** on the same scale and isolated as an analytically and spectroscopically pure solid in 54% yield (4.86 g) after purification by column chromatography eluting with $CHCl_3$/MeOH (100:4). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 28.8; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.47 (d, *J* = 6.7 Hz, 2H, C_6H_4), 6.88 (d, *J* = 7.7 Hz, 2H, C_6H_4), 5.85 (s, 2H, NH_2), 4.01 (d, *J* = 12.3 Hz, 1H, =CH), 3.83 (s, 3H, CH_3O), 3.69 (d, *J* = 11.3 Hz, 6H, OCH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 162.7 (d, *J* = 6.7 Hz, =CNH_2), 161.4 (C_6H_4), 131.3 (d, *J* = 20.8 Hz, C_6H_4), 127.5 (C_6H_4), 114.1 (C_6H_4), 72.1 (d, *J* = 194.2 Hz, PC=C), 55.3 (*p*-OMe) 51.7 (d, *J* = 5.0 Hz, OCH_3); LRMS (ESI^+) *m*/*z* 258 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{11}H_{17}NO_4P$ $[M+H]^+$ requires *m*/*z* 258.0895, found *m*/*z* 258.0899.

4.3. Synthesis of (*E*)- and (Z)-dimethyl 2-acetylamino-2-arylvinylphosphonate 4a–f

4.3.1. (*E*)- and (*Z*)-Dimethyl 2-acetylamino-2-*p*-tolylvinylphosphonate 4a

Enamino phosphonate **4a** (1.96 g, 10 mmol) was dissolved in a mixture of dichloromethane (20 mL) and pyridine (3.96 mL, 50 mmol) and cooled to −78 °C. Acetyl chloride (2.36 g, 30 mmol) was added dropwise with vigorous stirring and the resulting solution stirred for 2 h. The suspension was filtered through a pad of Celite, washed with $CuSO_{4(aq)}$ (3 × 50 mL) and brine (3 × 50 mL), and dried over sodium sulfate. The solvent was removed in vacuo and the residue purified by column chromatography by eluting with $CHCl_3$/MeOH (100:4). (*E*)-**4a**: R_f-value 0.3; 1.53 g (54%) pale yellow oil. $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.3; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 8.03 (s, 1H, NH), 7.27 (d, *J* = 7.9 Hz, 2H, C_6H_4), 7.13 (d, *J* = 7.9 Hz, 2H, C_6H_4), 6.66 (d, *J* = 12.1 Hz, 1H, =CH), 3.33 (d, *J* = 11.2 Hz, 6H, OCH_3), 2.32 (s, 3H, CH_3), 1.98 (s, 3H, $C_6H_4CH_3$); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.5 (C=O), 151.3 (d, *J* = 16.7 Hz, C=CP), 139.7 (C_6H_4), 133.5 (d, *J* = 6.2 Hz, C_6H_4), 128.7 (C_6H_4), 128.4 (C_6H_4), 97.4 (d, *J* = 202 Hz, C=CP), 51.6 (m, OCH_3), 24.5 (CH_3), 21.1 ($C_6H_4CH_3$); LRMS (ESI^+) *m*/*z* 284 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{13}H_{19}NO_4P$ $[M+H]^+$ requires *m*/*z* 284.1052, found *m*/*z* 284.1049. (*Z*)-**4a**. $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.1; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 9.89 (s, 1H, NH), 7.16 (d, *J* = 7.9 Hz, 2H, C_6H_4), 7.01 (d, *J* = 7.6 Hz, 2H, C_6H_4), 4.75 (d, *J* = 11.7 Hz, 1H, =CH), 3.58 (d, *J* = 11.4 Hz, 6H, OCH_3), 2.22 (s, 3H, CH_3), 1.98 (s, 3H, $C_6H_4CH_3$); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 168.1 (C=O), 157.3 (d, *J* = 3.0 Hz, C=CP), 140.3 (C_6H_4), 134.7 (d, *J* = 18.9 Hz, C_6H_4), 129.3 (C_6H_4), 127.0 (C_6H_4), 94.1 (d, *J* = 185 Hz, C=CP), 51.9 (d, *J* = 5.4 Hz, OCH_3), 23.9 (CH_3), 20.8 ($C_6H_4CH_3$); LRMS (ESI^+) *m*/*z* 284 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{13}H_{19}NO_4P$ $[M+H]^+$ requires *m*/*z* 284.1052, found *m*/*z* 284.1049. Anal. Calcd for $C_{13}H_{18}NO_4P$: C, 55.12; H, 6.41; N, 4.94. Found: C, 55.32; H, 6.69; N, 5.12.

4.3.2. (*E*)- and (*Z*)-Dimethyl 2-acetylamino-2-phenylvinylphosphonate 4b

(*E*)- and (*Z*)-**4b** were prepared according to the procedure described above for **4a** on the same scale and isolated as an analytically and spectroscopically pure oil after purification by column chromatography eluting with $CHCl_3$/MeOH (100:4). (*E*)-**4b**: R_f-value 0.3; 1.13 g (42%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.7; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.90 (s, 1H, NH), 7.38 (m, 5H, C_6H_5), 6.74 (d, *J* = 12.0 Hz, 1H, =CH), 3.33 (d, *J* = 11.2 Hz, 6H, OCH_3), 2.01 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 167.9 (C=O), 149.6 (d, *J* = 16.7 Hz, C=CP), 134.7 (d, *J* = 6.2 Hz, C_6H_5), 129.5 (C_6H_5), 128.5 (C_6H_5), 128.1 (C_6H_5), 95.2 (d, *J* = 202 Hz, C=CP), 50.1 (d, *J* = 6.1 Hz, OCH_3), 24.6 (CH_3); LRMS (ESI^+) *m*/*z* 270 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{12}H_{17}NO_4P$ $[M+H]^+$ requires *m*/*z* 270.0895, found *m*/*z* 270.0898. (*Z*)-**4b**: R_f-value 0.3; 0.59 g (22%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.6; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 10.1 (s, 1H, NH), 7.35 (m, 5H, C_6H_5), 4.81 (d, *J* = 11.6 Hz, 1H, =CH), 3.73 (d, *J* = 11.4 Hz, 6H, OCH_3), 2.12 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 168.3 (C=O), 157.8 (d, *J* = 3.1 Hz, C=CP), 137.1 (d, *J* = 18.9 Hz, C_6H_5), 129.4 (C_6H_5), 128.0 (C_6H_5), 126.7 (C_6H_5), 94.7 (d, *J* = 184 Hz, C=CP), 52.2 (d, *J* = 5.3 Hz, OCH_3), 24.2 (CH_3); LRMS (ESI^+) *m*/*z* 270 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{12}H_{16}NO_4PNa$ $[M+H]^+$ requires *m*/*z* 270.0895, found *m*/*z* 270.0903. Anal. Calcd for $C_{12}H_{16}NO_4P$: C, 53.53; H, 5.99; N, 5.20. Found: C, 53.91; H, 6.22; N, 5.51.

4.3.3. (*E*)- and (*Z*)-Dimethyl 2-acetylamino-2-*p*-fluorophenylvinylphosphonate 4c

(*E*)- and (*Z*)-**4c** were prepared according to the procedure described above for **4a** on the same scale and isolated as an analytically and spectroscopically pure oil after purification by column chromatography eluting with $CHCl_3$/MeOH (100:4). (*E*)-**4c**: R_f-value 0.3; 1.49 g (52%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.3; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.85 (s, 1H, NH), 7.38 (m, 2H, C_6H_4), 7.04 (m, 2H, C_6H_4), 6.72 (d, *J* = 11.9 Hz, 1H, =CH), 3.39 (d, *J* = 11.2 Hz, 6H, OCH_3), 2.04 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 170.0 (C=O), 163.6 (d, *J* = 250 Hz, C_6H_4), 150.1 (d, *J* = 16.3 Hz, C=CP), 132.7 (C_6H_4), 130.7 (d, *J* = 8.8 Hz, C_6H_4), 115.2 (d, *J* = 21.9 Hz, C_6H_4), 98.3 (d, *J* = 202 Hz, PC=C), 51.8 (d, *J* = 5.9 Hz, OCH_3), 24.9 (CH_3); LRMS (ESI^+) *m*/*z* 288 $[M+H]^+$; HRMS (ESI^+) exact mass calcd for $C_{12}H_{15}FNO_4P$ $[M+H]^+$ requires *m*/*z* 288.0801, found *m*/*z* 288.0804. (*Z*)-**4c**: R_f-value 0.3; 0.48 g (17%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.3; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 10.5 (s, 1H, NH), 7.30 (m, 2H, C_6H_4), 6.97 (m, 2H, C_6H_4), 4.79 (d, *J* = 11.2 Hz, 1H, =CH), 3.77 (d, *J* = 11.3 Hz, 6H, OCH_3), 2.08 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 167.5 (C=O), 162.7 (d, *J* = 250 Hz, C_6H_4), 155.7 (d, *J* = 3.2 Hz, C=CP), 132.3 (d, *J* = 19.3 Hz, C_6H_4), 127.9 (d, *J* = 8.4 Hz, C_6H_4), 114.2 (d, *J* = 22.0 Hz, C_6H_4), 93.9 (d, *J* = 185 Hz, PC=C), 51.9 (d, *J* = 5.4 Hz, OCH_3), 24.3

(CH_3); LRMS (ESI$^+$) *m*/*z* 288 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{16}FNO_4P$ [M+H]$^+$ requires *m*/*z* 288.0801, found *m*/*z* 288.0804. Anal. Calcd for $C_{12}H_{15}FNO_4P$: C, 50.18; H, 5.26; N, 4.88. Found: C, 50.33; H, 5.53; N, 5.09.

4.3.4. (*E*)- and (*Z*)-Dimethyl 2-acetylamino-2-*p*-chlorophenylvinylphosphonate 4d

(*E*)- and (*Z*)-**4d** were prepared according to the procedure described above for **4a** on the same scale and isolated as an analytically and spectroscopically pure oil after purification by column chromatography eluting with $CHCl_3$/MeOH (100:4). (*E*)-**4d**: R_f-value 0.3; 1.0 g (33%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.5; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 8.54 (s, 1H, N*H*), 7.30 (m, 4H, C_6H_4), 6.67 (d, *J* = 12.0 Hz, 1H, =C*H*), 3.34 (d, *J* = 11.3 Hz, 6H, OCH_3), 1.98 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 170.0 (C=O), 150.7 (d, *J* = 15.7 Hz, C=CP), 136.1 (C_6H_4), 135.0 (d, *J* = 6.3 Hz, C_6H_4), 130.4 (C_6H_4), 128.2 (C_6H_4), 98.4 (d, *J* = 200 Hz, PC=C), 52.2 (d, *J* = 6.1 Hz, OCH_3), 24.8 (CH_3); LRMS (ESI$^+$) *m*/*z* 304 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{16}ClNO_4P$ [M+H]$^+$ requires *m*/*z* 304.0505, found *m*/*z* 304.0511. (*Z*)-**4d**: R_f-value 0.3; 0.61 g (20%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.2; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 10.13 (s, 1H, N*H*), 7.28 (m, 4H, C_6H_4), 4.77 (d, *J* = 11.1 Hz, 1H, =C*H*), 3.69 (d, *J* = 11.4 Hz, 6H, OCH_3), 2.11 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 168.7 (C=O), 156.9 (d, *J* = 3.4 Hz, C=CP), 135.7 (m, 2 × C_6H_4), 128.3 (C_6H_4), 128.1 (C_6H_4), 95.2 (d, *J* = 185 Hz, PC=C), 52.3 (d, *J* = 5.5 Hz, OCH_3), 24.6 (CH_3); LRMS (ESI$^+$) *m*/*z* 304 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{16}ClNO_4P$ [M+H]$^+$ requires *m*/*z* 304.0505, found *m*/*z* 304.0507. Anal. Calcd for $C_{12}H_{15}ClNO_4P$: C, 47.46; H, 4.98; N, 4.61. Found: C, 47.91; H, 5.37; N, 6.91.

4.3.5. (*E*)- and (*Z*)-Dimethyl 2-acetylamino-2-*p*-bromophenylvinylphosphonate 4e

(*E*)- and (*Z*)-**4e** were prepared according to the procedure described above for **4a** on the same scale and isolated as an analytically and spectroscopically pure oil after purification by column chromatography eluting with $CHCl_3$/MeOH (100:4). (*E*)-(**4e**): R_f-value 0.3; 1.48 g (43%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.2; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 8.52 (s, 1H, N*H*), 7.42 (d, *J* = 8.4 Hz, 2H, C_6H_4), 7.18 (d, *J* = 8.4 Hz, 2H, C_6H_4), 6.63 (d, *J* = 12.0 Hz, 1H, =C*H*), 3.30 (d, *J* = 11.2 Hz, 6H, OCH_3), 1.94 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.7 (C=O), 150.4 (d, *J* = 16.6 Hz, C=CP), 135.5 (C_6H_4), 131.8 (C_6H_4), 130.6 (C_6H_4), 124.4 (C_6H_4), 98.7 (d, *J* = 199 Hz, PC=C), 52.2 (d, *J* = 6.1 Hz, OCH_3), 25.0 (CH_3); LRMS (ESI$^+$) *m*/*z* 369 [M+Na]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{15}BrNO_4PNa$ [M+Na]$^+$ requires *m*/*z* 369.9820, found *m*/*z* 369.9828. (*Z*)-(**4e**): R_f-value 0.3; 0.66 g (19%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 22.2; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 10.04 (s, 1H, N*H*), 7.39 (d, *J* = 10.8 Hz, 2H, C_6H_4), 7.16 (d, *J* = 8.7 Hz, 2H, C_6H_4), 4.74 (d, *J* = 11.1 Hz, 1H, =C*H*), 3.67 (d, *J* = 11.4 Hz, 6H, OCH_3), 2.09 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 168.3 (C=O), 156.5 (d, *J* = 3.4 Hz, C=CP), 136.0 (d, *J* = 19.3 Hz, C_6H_4), 131.2 (C_6H_4), 128.3 (C_6H_4), 123.7 (C_6H_4) 95.2 (d, *J* = 185 Hz, PC=C), 52.3 (d, *J* = 5.4 Hz, OCH_3), 24.3 (CH_3); LRMS (ESI$^+$) *m*/*z* 348 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{16}BrNO_4P$ [M+H]$^+$ requires *m*/*z* 348.0000, found *m*/*z* 348.0005. Anal. Calcd for $C_{12}H_{15}BrNO_4P$: C, 41.40; H, 4.34; N, 4.02. Found: C, 41.66; H, 4.45; N, 4.20.

4.3.6. (*E*)- and (*Z*)-Dimethyl 2-acetylamino-2-*p*-methoxyphenylvinylphosphonate 4f

(*E*)- and (*Z*)-**4f** were prepared according to the procedure described above for **4a** on the same scale and isolated as an analytically and spectroscopically pure oil after purification by column chromatography eluting with $CHCl_3$/MeOH (100:4). (*E*)-**4f**: R_f-value 0.3; 1.07 g (36%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 23.3; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.44 (d, *J* = 8.6 Hz, 2H, C_6H_4), 7.28 (s, 1H, N*H*), 6.93 (d, *J* = 8.6 Hz, 2H, C_6H_4), 6.77 (d, *J* = 11.7 Hz, 1H, =CH), 3.84 (s, 3H, ArO*Me*), 3.49 (d, *J* = 11.2 Hz, 6H, OCH_3), 2.11 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.7 (C=O), 161.0 ($ArOCH_3$) 150.8 (d, *J* = 16.9 Hz, C=CP), 129.9 (C_6H_4), 128.7 (d, *J* = 6.2 Hz, C_6H_4), 114.0 (C_6H_4), 97.6 (d, *J* = 206 Hz, PC=C), 55.6 (OCH_3), 51.8 (d, *J* = 5.9 Hz, OCH_3), 25.0 (CH_3); LRMS (ESI$^+$) *m*/*z* 300 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{13}H_{19}NO_5P$ [M+H]$^+$ requires *m*/*z* 300.1001, found *m*/*z* 300.1006. (*Z*)-**4f**: R_f-value 0.3; 0.63 g (21%). $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 23.0; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 9.98 (s, 1H, N*H*), 7.33 (d, *J* = 8.8 Hz, 2H, C_6H_4), 6.86 (d, *J* = 8.8 Hz, 2H, C_6H_4), 4.79 (d, *J* = 11.6 Hz, 1H, =C*H*), 3.81 (s, 3H, $ArOCH_3$), 3.73 (d, *J* = 11.4 Hz, 6H, OCH_3), 2.10 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 168.9 (*C*=O), 161.5 (C_6H_4), 157.7 (d, *J* = 3.4 Hz, *C*=CP), 129.7 (d, *J* = 19.0 Hz, C_6H_4), 128.7 (C_6H_4), 114.0 (C_6H_4), 93.8 (d, *J* = 186 Hz, P*C*=C), 55.6 ($ArOCH_3$), 52.5 (d, *J* = 5.3 Hz, OCH_3), 24.7 (CH_3); LRMS (ESI$^+$) *m*/*z* 300 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{13}H_{19}NO_5P$ [M+H]$^+$ requires *m*/*z* 300.1001, found *m*/*z* 300.0997. Anal. Calcd for $C_{13}H_{18}NO_5P$: C, 52.18; H, 6.06; N, 4.68. Found: C, 52.34; H, 6.29; N, 4.79.

4.4. General procedure for the rhodium-catalyzed hydrogenation of (*E*)- and (*Z*)-β-*N*-acetylaminovinylphosphonates 4a–f

A flame-dried Schlenk flask was charged with [Rh(cycloocta-1,5-diene)$_2$][BF_4] (3.6 mg, 0.008825 mmol), (*S*)-**2** (7.1 mg, 0.008825 mmol), and CH_2Cl_2 (5.0 mL), and the resulting orange solution stirred for 15 min. The substrate (0.1765 mmol) was added followed by additional CH_2Cl_2 (3.0 mL) and the resulting solution was transferred to a 50-mL Parr stainless steel bench-top reactor. The vessel was pressurized to 5 atm with hydrogen and left to stand for 10 s before releasing the gas through an outlet valve. After this sequence had been repeated six times the reactor was pressurized to 5 atm and the solution stirred vigorously at 20–22 °C for 30 h. After releasing the pressure the mixture was diluted with dichloromethane, extracted from the reactor, and the solvent was removed to leave a pale orange oil. The pure product was isolated after purification by column chromatography eluting with $CHCl_3$/MeOH (96:4).

4.4.1. Dimethyl 2-acetylamino-2-*p*-tolylethylphosphonate 5a

$^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 30.0; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.83 (d, *J* = 7.8 Hz, 2H, C_6H_4), 7.10 (d, *J* = 8.0 Hz, 2H, C_6H_4), 7.05 (s, 1H, N*H*), 5.32 (m, 1H, C*H*), 3.65 (d, *J* = 10.9 Hz, 3H, OCH_3), 3.39 (d, *J* = 11.0 Hz, 3H, OCH_3), 2.43–2.20 (m, 2H, CH_2), 2.29 (s, 3H, $C_6H_4CH_3$), 1.98 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.1 (*C*=O), 138.4 (d, *J* = 8.5 Hz, C_6H_4), 137.1 (C_6H_4), 129.2 (C_6H_4), 126.1 (C_6H_4), 52.2 (d, *J* = 6.6 Hz, OCH_3), 52.0 (d, *J* = 6.7 Hz, OCH_3), 48.2 (d, *J* = 4.1 Hz, $CHCH_2$), 31.7 (d, *J* = 139 Hz, $CHCH_2$), 23.2 (CH_3), 20.8 ($C_6H_4CH_3$); LRMS (ESI$^+$) *m*/*z* 308 [M+Na]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{13}H_{20}NO_4PNa$ [M+Na]$^+$ requires *m*/*z* 308.1028, found *m*/*z* 308.1032. Anal. Calcd for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.97; H, 7.03; N, 5.08. $[\alpha]_D = +45.2$ (*c* 1.0, CH_2Cl_2). The enantiomeric excess was calculated from the HPLC profile (Daicel Chiracel OD-H, flow rate: 0.5 mL/min, hexane/2-propanol = 85:15). Retention times: t_R (+)-enantiomer 20.2 min; t_R of (−)-enantiomer 50.2 min.

4.4.2. Dimethyl 2-acetylamino-2-phenylethylphosphonate 5b

$^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 30.1; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.31–7.24 (m, 5H, C_6H_5), 7.09 (br d, *J* = 6.7 Hz, 1H, N*H*), 5.39 (ddd, *J* = 23.9, 13.3, 7.2 Hz, 1H, C*H*), 3.67 (d, *J* = 11.0 Hz, 3H, OCH_3), 3.37 (d, *J* = 11.0 Hz, 3H, OCH_3), 2.34 (m, 2H, CH_2), 2.02 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.2 (C=O), 141.4 (d, *J* = 8.2 Hz, C_6H_5), 128.6 (C_6H_5), 127.5 (C_6H_5), 126.2 (C_6H_5), 52.3 (d, *J* = 6.8 Hz, OCH_3), 52.1 (d, *J* = 6.7 Hz, OCH_3), 48.5 (d, *J* = 4.3 Hz, $CHCH_2$), 31.7 (d, *J* = 139 Hz, $CHCH_2$), 23.2 (CH_3); LRMS (ESI$^+$) *m/z* 294 [M+Na]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{18}NO_4PNa$ [M+Na]$^+$ requires *m/z* 294.0871, found *m/z* 294.0868. Anal. Calcd for $C_{12}H_{18}NO_4P$: C, 53.14; H, 6.69; N, 5.16. Found: C, 53.27; H, 6.39; N, 5.29. $[\alpha]_D$ = +38.3 (*c* 1.0, CH_2Cl_2). The enantiomeric excess was calculated from the HPLC profile (Daicel Chiracel OD-H, flow rate: 0.5 mL/min, hexane/2-propanol = 85:15). Retention times: t_R of (+)-enantiomer 22.6 min; t_R of (−)-enantiomer 28.6 min.

4.4.3. Dimethyl 2-acetylamino-2-*p*-flourophenylethylphosphonate 5c

$^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 30.6; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.30 (m, 2H, C_6H_4), 7.18 (d, *J* = 6.9 Hz, 1H, NH), 7.03 (d, *J* = 6.9 Hz, 2H, C_6H_4), 5.38 (m, 1H, CH), 3.75 (d, *J* = 11.0 Hz, 3H, OCH_3), 3.44 (d, *J* = 11.0 Hz, 3H, OCH_3), 2.31 (m, 2H, CH_2), 2.04 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.6 (C=O), 162.6 (d, *J* = 248 Hz, C_6H_4), 137.6 (d, *J* = 9.2 Hz, C_6H_4), 128.3 (d, *J* = 7.5 Hz, C_6H_4), 115.6 (d, *J* = 20.1 Hz, C_6H_4), 52.6 (m, OCH_3), 48.4 (d, *J* = 4.1 Hz, CHNAc), 32.0 (d, *J* = 140 Hz, CH_2P), 23.6 (CH_3); LRMS (ESI$^+$) *m/z* 290 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{18}FNO_4P$ [M+H]$^+$ requires *m/z* 290.0957, found *m/z* 290.0957. Anal. Calcd for $C_{12}H_{17}FNO_4P$: C, 49.83; H, 5.92; N, 4.84. Found: C, 50.36; H, 6.13; N, 5.03. $[\alpha]_D$ = +26.4 (*c* = 1.1, CH_2Cl_2). The enantiomeric excess was calculated from the HPLC profile (Daicel Chiracel OD-H, flow rate: 0.5 mL/min, hexane/2-propanol = 85:15). Retention times: t_R (+)-enantiomer 23.1 min; t_R of (−)-enantiomer 28.0 min.

4.4.4. Dimethyl 2-acetylamino-2-*p*-chlorophenylethylphosphonate 5d

$^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 30.6; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.21 (m, 4H, C_6H_4), 7.04 (d, *J* = 7.2 Hz, 2H, C_6H_4), 5.30 (ddd, *J* = 25.9, 13.1, 6.9 Hz, 1H, CH), 3.64 (d, *J* = 11.0 Hz, 3H, OCH_3), 3.37 (d, *J* = 11.1 Hz, 3H, OCH_3), 2.23 (m, 2H, CH_2), 1.98 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.6 (C=O), 140.0 (d, *J* = 7.9 Hz, C_6H_4), 133.5 (C_6H_4), 128.8 (C_6H_4), 127.7 (C_6H_4), 52.6 (d, *J* = 10.1 Hz, OCH_3), 48.4 (CHNAc), 31.5 (d, *J* = 138 Hz, CH_2P), 23.5 (CH_3); LRMS (ESI$^+$) *m/z* 306 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{18}ClNO_4P$ [M+H]$^+$ requires *m/z* 306.0662, found *m/z* 306.0662. Anal. Calcd for $C_{12}H_{17}ClNO_4P$: C, 47.15; H, 5.61; N, 4.58 Found: C, 47.48; H, 4.97; N, 4.67. $[\alpha]_D$ = +23.8 (*c* 1.2, CH_2Cl_2). The enantiomeric excess was calculated from the HPLC profile (Daicel Chiracel OD-H, flow rate: 0.5 mL/min, hexane/2-propanol = 85:15). Retention times: t_R (+)-enantiomer 23.3 min; t_R of (−)-enantiomer 39.2 min.

4.4.5. Dimethyl 2-acetylamino-2-*p*-bromophenylethylphosphonate 5e

$^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 30.5; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.45 (d, *J* = 8.7 Hz, 2H, C_6H_4), 7.19 (d, *J* = 8.3 Hz, 2H, C_6H_4), 7.09 (d, *J* = 7.8 Hz, 1H, NH), 5.33 (m, 1H, CH), 3.69 (d, *J* = 11.0 Hz, 3H, OCH_3), 3.42 (d, *J* = 11.0 Hz, 3H, OCH_3), 2.29 (m, 2H, CH_2), 2.04 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.6 (C=O), 140.8 (d, *J* = 8.7 Hz, C_6H_4), 132.0 (C_6H_4), 128.3 (C_6H_4), 121.7 (C_6H_4), 52.5 (dd, *J* = 15.0, 6.6 Hz, OCH_3), 48.5 (CHNAc), 31.7 (d, *J* = 140 Hz, CH_2P), 23.5 (CH_3); LRMS (ESI$^+$) *m/z* 350 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{12}H_{18}NO_4PBr$ [M+H]$^+$ requires *m/z* 350.0157, found *m/z* 350.0151. Anal. Calcd for $C_{12}H_{17}BrNO_4P$: C, 41.16; H, 4.89; N, 4.00. Found: C, 41.51; H, 5.11; N, 4.33. $[\alpha]_D$ = +44.1 (*c* 1.0, CH_2Cl_2). The enantiomeric excess was calculated from the HPLC profile (Daicel Chiracel OD-H, flow rate: 0.5 mL/min, hexane/2-propanol = 85:15). Retention times: t_R (+)-enantiomer 23.6 min; t_R of (−)-enantiomer 47.3 min.

4.4.6. Dimethyl 2-acetylamino-2-*p*-methoxyphenylethylphosphonate 5f

$^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$, δ): 30.5; ^1H NMR (300.0 MHz, $CDCl_3$, δ): 7.21 (d, *J* = 8.7 Hz, 2H, C_6H_4), 6.98 (d, *J* = 7.3 Hz, 1H, NH), 6.83 (d, *J* = 8.7 Hz, 2H, C_6H_4) 5.31 (m, 1H, CH), 3.75 (s, 3H, $ArOCH_3$), 3.65 (d, *J* = 11.0 Hz, 3H, OCH_3), 3.39 (d, *J* = 11.0 Hz, 3H, OCH_3), 2.30 (m, 2H, CH_2), 1.99 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (75.8 MHz, $CDCl_3$, δ): 169.4 (C=O), 159.6 (C_6H_4), 133.9 (d, *J* = 7.9 Hz, C_6H_4), 127.7 (C_6H_4), 114.5 (C_6H_4), 55.6 ($ArOCH_3$), 52.2 (dd, *J* = 9.1, 6.8 Hz, OCH_3), 48.4 (CHNAc), 32.1 (d, *J* = 138 Hz, CH_2P), 23.5 (CH_3); LRMS (ESI$^+$) *m/z* 302 [M+H]$^+$; HRMS (ESI$^+$) exact mass calcd for $C_{13}H_{21}NO_5P$ [M+H]$^+$ requires *m/z* 302.1157, found *m/z* 302.1165. Anal. Calcd for $C_{13}H_{20}NO_5P$: C, 51.83; H, 6.69; N, 4.65. Found: C, 52.12; H, 7.02; N, 4.79. $[\alpha]_D$ = +45.4 (*c* 0.65, CH_2Cl_2). The enantiomeric excess was calculated from the HPLC profile (Daicel Chiracel OD-H, flow rate: 0.5 mL/min, hexane/2-propanol = 85:15). Retention times: t_R (+)-enantiomer 30.3 min; t_R of (−)-enantiomer 50.2 min.

4.5. Synthesis of [Rh(acac){(*S*)-Me-CATPHOS}] 6

To a stirred THF-d_8 (0.5 mL) solution of $Rh(acac)(coe)_2$ (52 mg, 0.12 mmol) was added dropwise a THF-d_8 (0.5 mL) solution of (*S*)-Me-CATPHOS (100 mg, 0.12 mmol). The reaction was allowed to proceed for 18 h at rt at which point the reaction mixture was analyzed by multinuclear NMR spectroscopy. Crystals suitable for an X-ray study were grown from a saturated solution of diethyl ether stored at room temperature. $^{31}P\{^1H\}$ NMR (109 MHz, THF-d_8, δ): 47.5 (d, J_{RH-P} = 201 Hz); ^1H NMR (270 MHz, THF-d_8, δ): 7.58 (m, 2H), 7.43 (m, 2H), 7.35–7.28 (ov m, 14H), 7.08 (t, *J* = 7.4 Hz, 4H), 7.02-6.81 (ov m, 8H), 6.70 (t, *J* = 7.4 Hz, 2H), 6.43 (t, *J* = 7.4 Hz, 2H), 6.07 (d, *J* = 7.4 Hz, 2H), 4.93 (s, 1H, CH=C), 4.78 (app t, *J* = 2.9 Hz, 2H, bridgehead CH), 1.52 (s, 6H, CH_3), 1.13 (s, 6H, acac-CH_3); $^{13}C\{^1H\}$ NMR (67 MHz, THF-d_8, δ): 183.0 (C=O), 156.2 (t, J_{C-P} = 7.7 Hz), 148.3, 146.6, 146.5, 146.0 (t, J_{C-P} = 20.5 Hz), 144.6, 138.3 (t, J_{C-P} = 22.0 Hz), 134.7 (2C), 133.5 (t, J_{C-P} = 18.9 Hz), 128.4, 128.0 (br t, J_{C-P} = 4.1 Hz), 126.4 (t, J_{C-P} = 4.6 Hz), 124.9, 124.1, 123.9, 122.9, 122.4, 121.6, 120.9, 120.7, 97.8 (C=CH), 55.6 (br t, J_{C-P} = 2.0 Hz, bridgehead CH), 54.7 (bridgehead Q), 25.9 (br t, J_{C-P} = 3.1 Hz, acac-CH_3), 13.9 (CH_3). Anal. Calcd for $C_{63}H_{51}O_2P_2Rh$ (1005.04): C, 75.28; H, 5.13. Found: C, 75.53; H, 5.34.

4.6. X-ray crystallography

Crystals of [Rh(acac){(*S*)-Me-CATPHOS}] were grown from a saturated solution of diethyl ether stored at rt. Single crystals were coated with Paratone-N oil, mounted using a polyimide MicroMount and frozen in the cold nitrogen stream of the goniometer. A hemisphere of data was collected on a Bruker AXS P4/SMART 1000 diffractometer using ω and θ scans with a scan width of 0.3° and 10 s exposure times.[30] The detector distance was 5 cm. The data were reduced (SAINT) and corrected for absorption (SADABS). The structure was solved by direct methods and refined by full-matrix least squares on F^2(SHELXTL). All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms were included in calculated positions and refined using a riding model. Data (excluding structure factors) for compound **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC# 723511. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 lEZ, UK [fax: +44(0)-1223-336033 or e-mail:deposit@ccdc.cam.ac.uk].

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