An efficient synthesis of functionalized α-amino-phosphine oxides and -phosphonates by addition of aminoalcohols to 4-phosphorylated-1,2-diaza-1,3-butadienes

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Dedicated to Professor Eusebio Juaristi on the occasion of his 55th anniversary
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Abstract
Michael addition (1,4-addition) of achiral and chiral aminoalcohol derivatives to 1,2-diaza-1,3-butadienes derived from phosphine oxides and phosphonates gives functionalized α-amino-phosphine oxides and -phosphonates.

Keywords: 1,2-Diaza-1,3-butadienes, functionalized α-amino-phosphine oxides and -phosphonates, Michael addition, phosphorylated hydrazones

Introduction

1,2-Diaza-1,3-butadienes **I** (Figure 1) are widely used intermediates in organic synthesis[1,2] because they offer easy access to a broad range of heterocycles. Many of these heterodienes substituted on the terminal nitrogen (N-1) (**I**, R^1 = Me, Ar, $ArSO_2$, COR, CO_2R, $CONR_2$)[1a,3] and on the terminal carbon (C–4) (**I**, R^3 = Me, Br, Cl, COR, CO_2R, $CONR_2$, D-*arabino*-$(CHOAc)_3CH_2OAc$)[1a,2b,3,4] have been described. However, very little information about the behaviour of 1,2-diaza-1,3-butadienes **II** (Figure 1) containing phosphorus substituents at C–4 have been reported.[5] Furthermore, it is known that phosphorus substituents regulate important biological functions,[6] and the introduction of organophosphorus functionalities in simple *synthons* could be very interesting for the preparation of biologically active compounds.

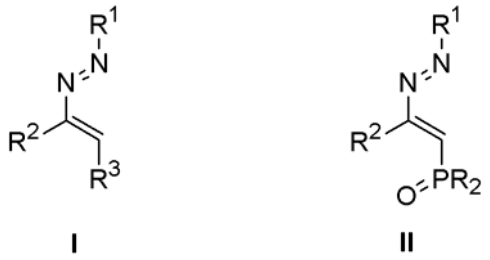
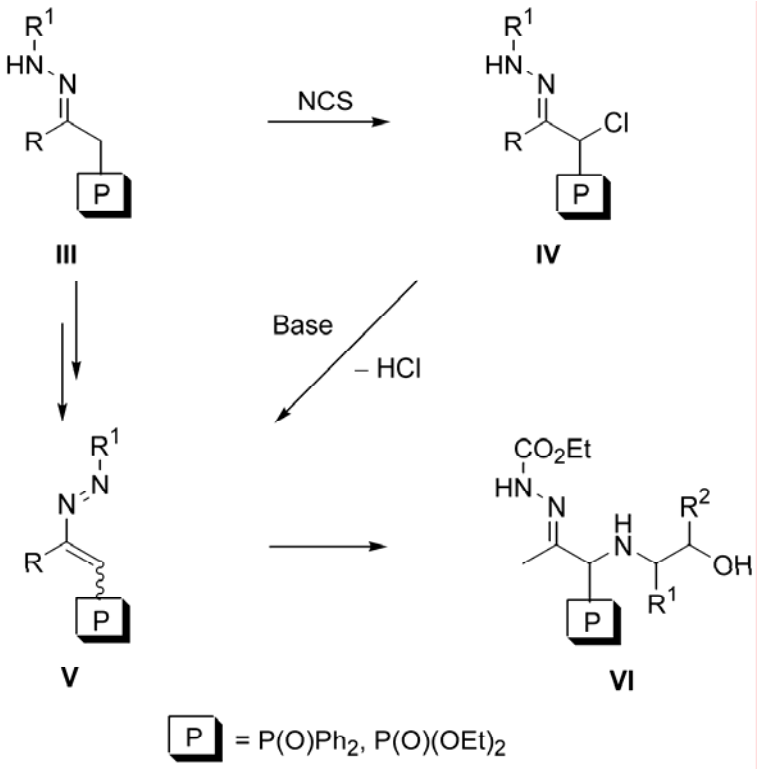


Figure 1

Recent work in our group has focused on the synthesis and the application of phosphorus substituted hydrazones[7] as starting materials for the preparation of acyclic and cyclic compounds and we have also used hydrazonoalkyl-phosphine oxides and -phosphonates **III** as starting materials for the preparation of functionalized 1,2-diaza-1,3-butadienes **V**. The sequence involves halogenation with formation of an α-halogenated hydrazone **IV**, and 1,4-dehalogenation with subsequent formation of aza-alkene **V** (Scheme 1).



Scheme 1

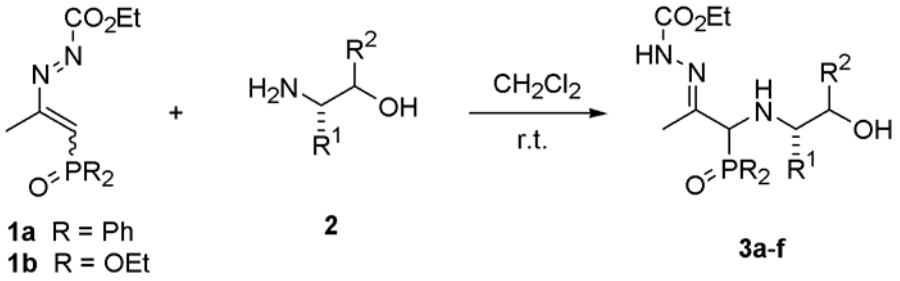
In these substrates, the presence of electron-poor groups on the terminal nitrogen atom of the azo-ene system of 1,2-diaza-1,3-butadienes favoured the Michael addition of nucleophilic reagents on the terminal carbon atom (1,4-addition). Some conjugate additions of amines to 1,2-

diaza-1,3-butadienes have been reported.[8] However, Michael additions of aminoalcohol derivatives to phosphorus substituted 1,2-diazadienes, have not been fully explored. For this reason, we wish to report a further strategy for the preparation of functionalized α-amino-phosphine oxides **VI** (P = $POPh_2$) and -phosphonates **VI** (P = $PO(OEt)_2$) through nucleophilic addition of racemic and optically pure aminoalcohols to 1,2-diaza-1,3-butadienes **V** as shown in Scheme 1. It is noteworthy that α-aminophosphonates[9,10] are important substrates in organic and medicinal chemistry because they can be considered as surrogates for α-aminoacids,[11a] and have been used as haptens for the generation of catalytic antibodies,[11b] as antibacterial agents,[11c] or as phosphapeptide enzyme inhibitors.[11d]

Results and Discussion

The required 4-phosphinyl and 4-phosphonyl-1,2-diaza-1,3-butadienes **1**, prepared through base treatment of hydrazone derivatives bearing a good leaving group in the Cα–carbon atom of the hydrazono carbon-nitrogen double bond,[5a] easily react in CH_2Cl_2 at room temperature with achiral and chiral aminoalcohol derivatives **2** to give substituted α-aminophosphine oxides and phosphonates **3** in good to excellent yield. Michael addition of ethanolamine **2a** ($R^1 = R^2 = H$) to heterodiene **1a** (R = Ph) in CH_2Cl_2 (*TLC* control) led to the formation of α-amino phosphine oxide **3a** (Scheme 2, Table 1, entry 1). α-Amino phosphine oxide **3a** proved to be not stable enough for chromatography, and the hydrochloride salt of compound **3a** was obtained in 89% yield. The hydrochloride salt of compound **3a** was characterized by its spectroscopic data. ^{31}P NMR spectrum of **3a**·HCl showed one absorption at δ_P 29.9 ppm. Likewise, the ^1H NMR spectra of **3a**·HCl gave a triplet for the methylene protons directly bonded to the nitrogen atom at δ_H 3.06 ppm ($^3J_{HH}$ = 5.2 Hz), a quadruplet for the methylene protons directly bonded to the oxygen atom at δ_H 3.68 ppm ($^3J_{HH}$ = 5.2 Hz) and a well resolved doublet for the methine proton directly bonded to the phosphorus atom at δ_H 5.27 ppm ($^2J_{PH}$ = 6.6 Hz); while in ^{13}C NMR a doublet appeared at δ_C 62.1 ppm ($^1J_{PC}$ = 63.9 Hz) for the carbon bonded to the phosphorus atom. The reaction takes place by the nucleophilic attack of the amino moiety of aminoalcohol **2** on the terminal carbon atom of the heterodiene **1** with the formation of 1,4-adducts **3** (Scheme 2).

The process was extended to 4-phosphonyl-1,2-diaza-1,3-butadienes **1b** (R = OEt), and this heterodiene **1b** reacted with ethanolamine **2a** ($R^1 = R^2 = H$) to give α-amino phosphonate **3b** (Scheme 2, Table 1, entry 2). The same strategy was used for the preparation of substituted α-aminophosphine oxides with a methyl (**3c**) or a cyclohexyl group (**3d**), when starting aminoalcohols **2b** (R^1 = H, R^2 = Me) or **2c** ($R^1R^2 = –(CH_2)_4–$), respectively, were used (Scheme 2, Table 1, entries 3 and 4).



Scheme 2

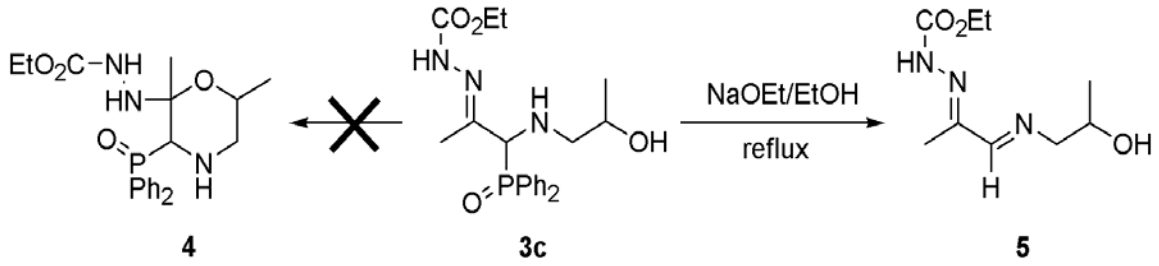
We also studied the diastereoselective addition of optically active aminoalcohols **2** to 1,2-diaza-1,3-butadiene **1a**. However, very low diastereoselectivity (<10% d.e.) was observed when (*S*)-(+)-leucinol **2d** (R^1 = ^{i}Bu, R^2 = H) was treated at r.t. with 4-phosphinyl-1,2-diaza-1,3-butadiene **1a** (R = Ph). Functionalized α-aminophosphine oxide **3e** (R = Ph, R^1 = ^{i}Bu, R^2 = H) was obtained as a non-separable diastereoisomeric mixture[12] (Scheme 2, Table 1, entry 5). However, a better diastereoselection was observed when a bulky aminoalcohol such as (*S*)-*tert*-leucinol was used. Reaction of (*S*)-*tert*-leucinol **2e** (R^1 = ^{t}Bu, R^2 = H) with **1a** gave compound **3f** as a nonseparable diastereoisomeric mixture and quite good diatereoselective excess (70%)[12] was observed (Scheme 2, Table 1, entry 6).

Table 1. Michael Addition of Aminoalcohol Derivatives to Heterodienes **1**

Entry	Product	R	R^1	R^2	de (%)[a]	Yield (%)[b]
1	**3a**	Ph	H	H	---	89
2	**3b**	OEt	H	H	---	77
3	**3c**	Ph	H	Me	<10	92
4	**3d**	Ph	$-(CH_2)_4-$		28	96
5	**3e**	Ph	^{i}Bu	H	<10	86
6	**3f**	Ph	^{t}Bu	H	70	81

[a] Diastereoselectivity was determined by ^{31}P NMR analysis on the crude reaction mixture.
[b] Isolated yields after purification.

Finally, the treatment of adducts **3** with base was explored in order to test whether further intramolecular nucleophilic attack of the hydroxyl group at the carbon-nitrogen double bond of the hydrazone in compounds **3** could be achieved to obtain substituted 3-phosphorylated morpholines **4**. Thus, compound **3c** was subjected to base (EtONa) treatment in refluxing EtOH to give the β-elimination product **5** instead of morpholine **4** (Scheme 3). Therefore, by means of this strategy functionalized imino-hydrazone **5** is obtained. Cyclization reaction of α-amino phosphine oxide **3a** in refluxing THF or by treatment with NaH/THF does not take place, recovering the starting compound **3** (Scheme 3).



Scheme 3

In summary, the procedure described here represents a convenient entry to functionalized α-amino phosphine oxides and phosphonates by Michael addition of aminoalcohols to 4-phosphorylated-1,2-diaza-1,3-butadienes in very good yields. These hydrazonoalkyl-α-aminophosphonate derivatives may be important synthons in organic synthesis and for the preparation of biologically active compounds of interest in medicinal chemistry.[9–11]

Experimental Section

General Procedures. Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC were performed with silica gel 60 F_{254} plates. Spot visualization was accomplished by UV light or $KMnO_4$ solution. Flash chromatography was carried out using silica gel 60 (230–400 mesh). Melting points were determined with a Electrothermal IA9100 digital apparatus and are uncorrected. ^{1}H (300 and 400 MHz), ^{13}C (75 and 100 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Varian Unity Plus 300 MHz spectrometer or on a Bruker Avance 400 MHz spectrometer, respectively. Tetramethylsilane (TMS) (0.00 ppm) or chloroform (7.24 ppm) as an internal reference in $CDCl_3$ solutions for ^{1}H NMR spectra, or chloroform (77.0 ppm) as an internal reference in $CDCl_3$ solutions for ^{13}C NMR spectra, or phosphoric acid (85%) in $CDCl_3$ solutions for ^{31}P NMR spectra have been used. Chemical shifts (δ) are given in ppm; multiplicities are indicated by s (singlet), bs (broad singlet), d (doublet), dd (double-doublet), t (triplet), q (quadruplet) or m (multiplet). Coupling constants (J) are reported in Hertz. Low-resolution mass spectra (MS) were obtained on a Hewlett Packard 5971 MSD Series spectrometer at 50–70 eV by electron impact (EI) or on a Hewlett Packard 1100 MSD Series spectrometer by chemical ionization (CI). Data are reported in the form *m/z* (intensity relative to base peak = 100). Infrared spectra (IR) were taken on a Nicolet FTIR Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils in NaCl. Peaks are reported in cm^{-1}. Elemental analyses were performed in a Perkin Elmer Model 240 instrument. 1,2-diaza-1,3-butadienes **1a-b**[5a] were synthesized according to literature procedures.

General procedure for the synthesis of functionalized *α*-amino-phosphine oxides and phosphonates (3)

To a stirred solution of 1,2-diaza-1,3-butadienes **1a-b** (1 mmol) in CH_2Cl_2 (10 mL), the corresponding aminoalcohols **2** (1.2 mmol) were added at room temperature and under a nitrogen atmosphere. The mixture was stirred at room temperature for 30-60 min. The crude mixture was washed with H_2O (2 x 10 mL) and the aqueous phase was extracted twice with CH_2Cl_2 (5 mL). The organic layer was dried over $MgSO_4$ and evaporated under vacuum. Finally, the crude product was purified by formation of the hydrochloride salt, by flash-chromatography (silica gel) or crystallization.

Ethyl *N′*-[2-(diphenylphosphinoyl)-2-(2-hydroxyethylamino)-1-methylethylidene] hydrazine carboxylate hydrochloride (3a). As described in the general procedure, **3a** was obtained as a white solid from 1,2-diaza-1,3-butadiene **1a** (0.34 g, 1 mmol) and ethanolamine (72 μL, 1.2 mmol) after bubbling HCl(g) and formation of hydrochloride salt, 0.43 g (89%). Data for **3a**: mp 109–110 ºC; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.99–7.46 (m, 10 H), 5.27 (d, $^2J_{PH}$ = 6.6 Hz, 1H), 4.16 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 3.68 (q, $^3J_{HH}$ = 5.2 Hz, 2H), 3.06 (t, $^3J_{HH}$ = 5.2 Hz, 2H), 1.34 (d, $^4J_{PH}$ = 2.4 Hz, 3H), 1.18 (t, $^3J_{HH}$ = 7.1 Hz, 3H) ppm; ^{13}C NMR (CD_3OD, 100 MHz) δ 157.4, 143.4 (d, $^2J_{PC}$ = 5.7 Hz) 135.3 (d, $^4J_{PC}$ = 2.8 Hz), 135.1 (d, $^4J_{PC}$ = 2.8 Hz), 133.6 (d, $^3J_{PC}$ = 10.1 Hz), 133.0 (d, $^3J_{PC}$ = 10.1 Hz), 130.9 (d, $^2J_{PC}$ = 12.5 Hz), 130.4 (d, $^2J_{PC}$ = 12.7 Hz), 129.3 (d, $^1J_{PC}$ = 101.0 Hz), 128.8 (d, $^1J_{PC}$ = 104.2 Hz), 63.5, 62.1 (d, $^1J_{PC}$ = 63.9 Hz), 57.8, 50.7 (d, $^3J_{PC}$ = 3.9 Hz), 17.9, 14.9 ppm; ^{31}P NMR (CD_3OD, 120 MHz) δ 29.9 ppm; IR (KBr) 3463, 3244, 1713, 1540, 1169 cm^{-1}; MS (CI) *m/z* 404 [(M^+ – HCl) + 1]. Anal. Calcd. for $C_{20}H_{27}ClN_3O_4P$: C, 54.61; H, 6.19; N, 9.55. Found: C, 54.50; H, 6.21; N, 9.50.

[2-(Ethoxycarbonylhydrazono)-1-(2-hydroxyethylamino)propyl] phosphonic acid diethyl ester (3b). As described in the general procedure, **3b** was obtained as a colorless oil from 1,2-diaza-1,3-butadiene **1b** (0.28 g, 1 mmol) and ethanolamine (72 μL, 1.2 mmol) after flash-chromatography (silica gel, AcOEt), 0.26 g (77%). Data for **3b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 4.31–4.09 (m, 6H), 3.80 (d, $^2J_{PH}$ = 22.4 Hz, 1H), 3.63–3.59 (m, 2H), 2.77–2.73 (m, 2H), 1.97 (d, $^4J_{PH}$ = 2.7 Hz, 3H), 1.48–1.22 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.2, 148.8, 72.3 (d, $^1J_{PC}$ = 166.7 Hz), 63.9, 63.7, 63.6, 63.5, 63.3, 63.2, 62.1, 61.9, 61.7, 61.1, 60.9, 59.9, 51.0 (d, $^3J_{PC}$ = 15.1 Hz), 25.5, 16.6–13.9 (m) ppm; ^{31}P NMR ($CDCl_3$, 120 MHz) δ 21.3 ppm; IR (NaCl) 3405, 2961, 1722, 1226, 1044 cm^{-1}; MS (CI) *m/z* 340 (M^+ + 1). Anal. Calcd. for $C_{12}H_{26}N_3O_6P$: C, 42.48; H, 7.72; N, 12.38. Found: C, 42.40; H, 7.77; N, 12.35.

Ethyl *N′*-[2-(diphenylphosphinoyl)-2-(2-hydroxypropylamino)-1-methylethylidene] hydrazine carboxylate hydrochloride (3c). As described in the general procedure, **3c** was obtained as a white solid from 1,2-diaza-1,3-butadiene **1a** (0.34 g, 1 mmol) and (±)-1-amino-2-propanol (93 μL, 1.2 mmol) after bubbling HCl(g) and formation of hydrochloride salt, 0.38 g (92%). Data for **3c**: ^{1}H NMR (CD_3OD, 300 MHz) δ 8.02–7.34 (m, 10H), 5.45 (d, $^2J_{PH}$ = 6.8 Hz, 1H), 5.26 (d, $^2J_{PH}$ = 5.9 Hz, 1H), 4.12 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 4.03–3.87 (m, 1H), 3.17–2.96 (m, 1H), 2.68–2.81 (m, 1H), 1.39 (d, $^4J_{PH}$ = 2.6 Hz, 3H), 1.18 (d, $^3J_{HH}$ = 7.1 Hz, 3H), 0.99 (d, $^3J_{HH}$ = 6.3 Hz, 3H), 0.98 (d, $^3J_{HH}$ = 6.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.8 (*major*),

150.3 (*minor*), 149.1, 132.0, 131.6, 131.6, 131.5, 131.5, 131.5, 131.4, 131.4, 131.2, 131.2, 130.9, 130.4, 130.4, 129.9, 128.8, 128.5, 128.4, 128.4, 128.3, 128.3, 65.4 (d, $^1J_{PC}$ = 80.7 Hz, *major*), 64.9 (d, $^1J_{PC}$ = 77.7 Hz, *minor*), 61.6, 60.3, 57.1 (d, $^3J_{PC}$ = 12.9 Hz, *major*), 55.1 (d, $^3J_{PC}$ = 13.7 Hz, *minor*), 20.3 (*minor*), 19.6 (*major*), 14.5 (*minor*), 14.4 (*major*), 14.3 (*major*), 13.2 (*minor*) ppm; ^{31}P NMR ($CDCl_3$, 120 MHz) δ 30.5 (*minor*), 30.2 (*major*) ppm; IR (KBr) 3399, 3052, 2971, 1717, 1530, 1434, 1236, 1119 cm^{-1}; MS (CI) *m/z* 418 (M^+ + 1). Anal. Calcd. for $C_{21}H_{29}ClN_3O_4P$: C, 55.57; H, 6.44; N, 9.55; Found: C, 55.44; H, 6.39; N, 9.45.

Ethyl *N′*-[2-(diphenylphosphinoyl)-2-(2-hydroxycyclohexylamino)-1-methylethyl- idene] hydrazine carboxylate (3d). As described in the general procedure, **3d** was obtained as a white solid from 1,2-diaza-1,3-butadiene **1a** (0.34 g, 1 mmol) and *trans*-2-aminocyclohexanol hydrochloride (0.182 g, 1.2 mmol) after recrystallization from AcOEt, 0.44 g (96%). Data for **3d**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99–7.41 (m, 10H), 4.41 (d, $^2J_{PH}$ = 13.4 Hz, 1H), 4.22 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 3.10–3.00 (m, 1H), 2.66–2.59 (m, 1H), 2.27–2.20 (m, 2H), 1.99–1.95 (m, 2H), 1.94 (d, $^4J_{PH}$ = 1.9 Hz, 3H), 1.67–1.60 (m, 2H), 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 1.11–1.07 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.7, 150.4, 133.0, 132.3, 132.2, 132.0, 131.9, 131.8, 131.6, 131.5, 129.2, 129.0, 128.9, 128.8, 128.6, 128.4, 74.0, 64.9, 64.4 (d, $^1J_{PC}$ = 80.5 Hz), 62.1, 32.9, 32.3, 25.5, 24.3, 14.4 (d, $^3J_{PC}$ = 12.0 Hz), 8.8 ppm; ^{31}P NMR ($CDCl_3$, 120 MHz) δ 31.2 (*major*), 30.2 (*minor*) ppm; IR (KBr) 3301, 3102, 1717, 1527, 1178 cm^{-1}; MS (CI) *m/z* 458 (M^+ + 1). Anal. Calcd. for $C_{24}H_{32}N_3O_4P$: C, 63.01; H, 7.05; N, 9.18. Found: C, 62.98; H, 7.01; N, 9.22.

Ethyl *N′*-[2-(diphenylphosphinoyl)-2-(1-hydroxymethyl-3-methylbutylamino)-1-methylethylidene] hydrazine carboxylate (3e). As described in the general procedure, **3e** was obtained as a white solid from 1,2-diaza-1,3-butadiene **1a** (0.34 g, 1 mmol) and (*S*)-(+)-leucinol (158 μL, 1.2 mmol) after recrystallization from AcOEt, 0.39 g (86%). Data for **3e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.60 (bs, 1H), 7.99–7.24 (m, 10H), 4.39 (d, $^2J_{PH}$ = 12.9 Hz, 1H, *minor*), 4.27 (d, $^2J_{PH}$ = 17.1 Hz, 1H, *major*), 4.14 (q, $^3J_{HH}$ = 6.8 Hz, 2H), 3.46–3.38 (m, 1H), 3.22–3.09 (m, 1H), 2.61–2.50 (m, 1H), 2.04 (d, $^3J_{PH}$ = 2.1 Hz, 3H, *minor*), 1.83 (d, $^3J_{PH}$ = 2.1 Hz, 3H, *major*), 1.54–1.40 (m, 1H), 1.27 (q, $^3J_{HH}$ = 6.8 Hz, 3H, *minor*), 1.20 (q, 3H, $^3J_{HH}$ = 6.8 Hz, *major*), 0.82–0.74 (m, 8H) ppm;^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.7 (*major*), 153.9 (*minor*), 152.2 (*minor*), 149.6 (*major*), 132.2, 131.7, 131.6, 131.3, 131.2, 131.1, 131.0, 130.7, 130.6, 130.5, 130.4, 130.3, 130.0, 129.7, 129.3, 128.6, 128.4, 128.1, 128.0, 127.9, 127.7, 64.2 (d, $^1J_{PC}$ = 82.1 Hz. *major*), 63.5, 62.8 (d, $^1J_{PC}$ = 85.6 Hz, *minor*), 61.8, 58.2 (d, $^3J_{PC}$ = 13.0 Hz, *major*), 57.2 (d, $^3J_{PC}$ = 13.0 Hz, *minor*), 41.6 (*major*), 41.4 (*minor)*, 24.7, 23.0 (d, $^3J_{PC}$ = 18.1 Hz, *major*), 22.7 (d, $^3J_{PC}$ = 19.2 Hz, *minor*), 15.8 (*major*), 14.5, 14.4, 13.9 (*minor*) ppm; ^{31}P NMR ($CDCl_3$, 120 MHz) δ 31.1 (*major*), 30.8 (*minor*) ppm; IR (KBr) 3319, 3047, 1722, 1530, 1114 cm^{-1}; MS (CI) m/z 460 (M^+ + 1). Anal. Calcd. for $C_{24}H_{34}N_3O_4P$: C, 62.73; H, 7.46; N, 9.14; Found: C, 62.71; H, 7.40; N, 9.11.

Ethyl *N′*-[2-(diphenylphosphinoyl)-2-(1-hydroxymethyl-2,2-dimethylpropylamino)-1-methylethylidene] hydrazine carboxylate (3f). As described in the general procedure, **3f** was obtained as a white solid from 1,2-diaza-1,3-butadiene **1a** (0.34 g, 1 mmol) and (*S*)-*tert*-leucinol (0.16 g, 1.2 mmol) after flash-chromatography (silica gel, AcOEt) 0.37 g (81%). Data for **3f**: ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 7.93–7.41 (m, 11H), 4.57 (d, $^2J_{PH}$ = 12.7 Hz, 1H, *major*), 4.23–4.18 (m, 2H), 3.67–3.43 (m, 2H), 2.39–2.11 (m, 2H), 1.99 (d, $^4J_{PH}$ = 2.1 Hz, 3H, *minor*), 1.73 (d, $^4J_{PH}$ = 2.1 Hz, 3H, *major*), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 0.80 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.7, 149.2, 132.9, 132.8, 132.3, 132.2, 132.1, 131.8, 131.6, 131.5, 131.4, 131.0, 130.7, 130.3, 129.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.1, 127.9, 65.9 (d, $^3J_{PC}$ = 8.6 Hz), 63.3 (d, $^1J_{PC}$ = 75.0 Hz), 61.7, 60.3, 34.0, 27.3, 14.4, 13.5 ppm; ^{31}P NMR ($CDCl_3$, 120 MHz) δ 31.8 (*minor*), 30.9 (*major*); IR (NaCl) 3350, 2959, 1725, 1434, 1222, 1043 cm^{-1}; MS (CI) m/z 460 (M^+ + 1). Anal. Calcd. for $C_{24}H_{34}N_3O_4P$: C, 62.73; H, 7.46; N, 9.14. Found: C, 62.51; H, 7.49; N, 9.12.

Synthesis of ethyl *N′*-[2-(2-hydroxypropylimino)-1-methylethylidene] hydrazine carboxylate (5). To a stirred solution of compound **3c** (0.21 g, 0.5 mmol) in EtOH (5 mL), EtONa (68 mg, 1 mmol) was added at room temperature and under a nitrogen atmosphere. The mixture was stirred at reflux for 48h. The solvent was evaporated and the crude mixture was diluted in CH_2Cl_2, washed with H_2O (2 x 10 mL) and the aqueous phase was extracted twice with CH_2Cl_2 (5 mL). The organic layer was dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash-chromatography (silica gel, AcOEt) to afford **5** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (s, 1H), 7.46 (bs, 1H), 4.86–4.81 (m, 1H), 4.07 (dd, $^2J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 9.5 Hz, 1H), 3.53 (dd, $^2J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 8.0 Hz, 1H), 2.16 (s, 3H), 1.43–1.33 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.6, 153.0, 139.2, 67.6, 61.4, 47.4, 21.0, 14.4, 9.6 ppm; MS (CI) *m/z* 216 (M^+ + 1). Anal. Calcd. for $C_9H_{17}N_3O_3$: C, 50.22; H, 7.96; N, 19.52. Found: C, 50.29; H, 7.90; N, 19.58.

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References and Footnotes

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12. Diastereoisomers ratio were determined by ^{31}P NMR on the crude reaction mixture.