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Michael Addition of Amine Derivatives to Conjugate Phosphinyl and Phosphonyl Nitrosoalkenes. Preparation of α-Amino Phosphine Oxide and Phosphonate Derivatives[#]

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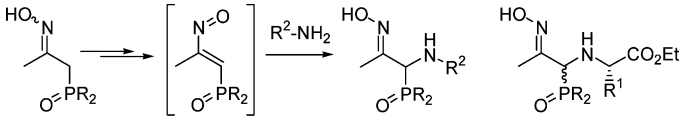

R = Ph, OEt

The synthesis of nitrosoalkenes derived from phosphine oxides and phosphonates generated through base-mediated dehydrohalogenations of readily available α-halooximes is reported. These highly reactive intermediates act as Michael acceptors toward nucleophilic reagents such as ammonia, amines, and optically active amino esters, furnishing α-amino phosphine oxides and phosphonates in a highly regioselective fashion.

Introduction

Oximes have great potential not only as intermediates in organic synthesis[1,2] and in the preparation of natural products such as erythromycin derivatives[3a] and perhydrohistrionicotoxin[3b] but also for their industrial applications in the areas of agrochemicals,[4a] medicinal chemistry,[4b] toxicology,[4c,d] and in the preparation of cephalosporin derivatives with potent antibacterial activity.[4e] Likewise, there has been a great deal of recently renewed interest in nitroso compounds due to their applications in catalytic or cycloaddition processes.[5] Nitrosoalkenes (**I**, see Figure 1) are functionalized nitroso derivatives, and the presence of an adjacent double bond in conjugation with the nitroso moiety introduces new reactivity centers in these substrates and then increases the synthetic value of these compounds. Therefore, the usefulness of nitrosoalkenes[6] (**I**) as conjugate addition acceptors,[7] coupled with the easy conversion of the nitroso group into other functionalities, such as oximes and ketones,[8] or their ability to act as dienes in hetero-Diels−Alder reactions for the preparation of 1,2-oxazine derivatives,[9] has been reported. Examples of nitrosoalkenes with substitution

[#] Dedicated to Prof. Vicente Gotor on the occasion of his 60th birthday.

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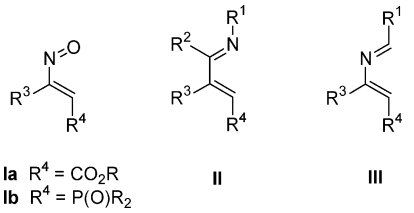
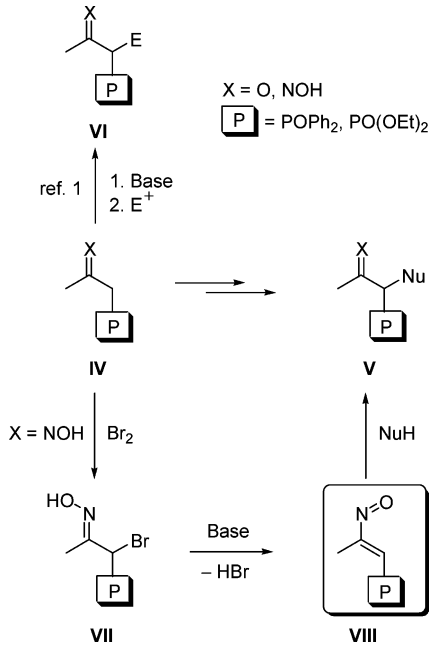


FIGURE 1. Nitrosoalkenes **I** and azadienes **II** and **III**.

at C-3, mainly alkyl, aryl, and carboxylate groups, of the heterodiene system[6,9] have been described. However, to the best of our knowledge, only one report for the preparation of nitrosoalkenes containing a carboxylate group at C-4 of the heterodiene system (**Ia**, $R^4 = CO_2R$, Figure 1) and its behavior in [4 + 2] cycloaddition processes has been previously reported.[10]

We have been involved in the chemistry of functionalized 1- (**II**)[11] and 2-azadienes (**III**)[12] (Figure 1) derived from amino esters and amino phosphonates and in the application of phosphorus-substituted oximes[13] as starting materials for the preparation of acyclic and cyclic compounds as well as in the synthesis of α-[14] and β-amino phosphonate[15] derivatives. Oximes not only serve as protecting groups for carbonyl compounds[16] but they can also be used as starting materials for the preparation of nitrosoalkenes, and it is well-known that molecular modifications involving the introduction of organophosphorus functionalities in organic substrates could increase their biological activity or their interest as synthetic intermediates in organic and medicinal chemistry.[17] Moreover, to date, the synthesis of nitrosoalkenes containing phosphorus substituents at C-4 (**Ib**, $R^4 = P(O)R_2$, Figure 1) and the study of these highly reactive intermediates as Michael acceptors toward nucleophilic reagents remain unexplored.

SCHEME 1. Umpolung Reactions at the Cα Atom of α-Phosphorylated Oximes



The Cα functionalization of ketones **IV** (X = O) or oximes **IV** (X = NOH) with electrophilic reagents to obtain Cα-substituted compounds **VI** (X = O, NOH) is known[1] (Scheme 1). Bearing this in mind, we envisaged the use of oximinoalkyl phosphine oxides and phosphonates (**IV**, X = NOH, P = $POPh_2$ or $PO(OEt)_2$, Scheme 1) as starting materials for the preparation of functionalized oximes containing a nucleophilic substituent (**V**, X = NOH), through a sequence involving halogenation with formation of an α-halooxime **VII**, subsequent formation of nitrosoalkene **VIII** through base-mediated dehydrohalogenation, and Michael addition of nucleophiles to the heterodiene system (Scheme 1). Therefore, by means of this strategy, the umpolung reaction in the Cα of the phosphonate (phosphine oxide) moiety could be achieved, favoring the introduction of nucleophiles in order to prepare functionalized oximes (**V**, X = NOH) or their synthetic equivalent carbonyl compounds (**V**, X = O, Scheme 1). This strategy could be of particular interest since the introduction of amino substituents (Scheme 1, NuH = RNH_2) at the Cα carbon atom could produce α-amino phosphonates,[18] which are important substrates in organic and medicinal chemistry.[19,20]

As a continuation of our work on the preparation of new α-amino phosphorus compounds, here we disclose the preparation of new species such as 2-nitrosoprop-1-enyl phosphine oxides (**Ib**, R = Ph, Figure 1) or phosphonates (**Ib**, R = OEt,

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SCHEME 2. Preparation of Highly Reactive Nitrosoalkenes 5 through Base-Mediated Dehydrohalogenation

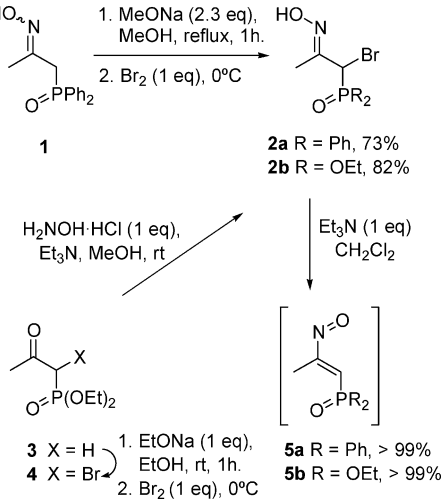


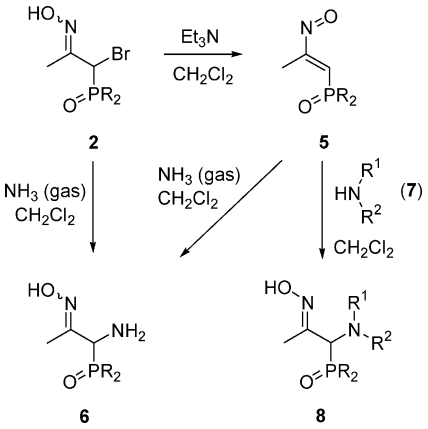
Figure 1), as well as the results of the conjugate addition of nitrogen nucleophiles to these highly reactive phosphorylated nitrosoalkenes.

Results and Discussion

As outlined in Scheme 2, for the preparation of phosphorylated nitrosoalkenes, the required α-halooxime **2a** derived from phosphine oxide (R = Ph) is in turn easily accessible from the reaction of functionalized *β*-oxime **1**[13d,e] with a base followed by addition of bromine. Treatment of compound **1** with an excess (2.3 equiv) of MeONa in MeOH at reflux and subsequent addition of bromine at 0 °C led to the formation of α-bromooxime phosphine oxide **2a** (Scheme 2). A different process was applied to the preparation of the corresponding α-bromooxime phosphonate **2b**, which was synthesized in two steps from *β*-ketophosphonate **3** (X = H). Treatment of compound **3** with a base such as EtONa in EtOH at rt followed by addition of bromine at 0 °C gave α-bromoketophosphonate **4** (X = Br) in excellent yield.[21] Condensation reaction of compound **4** with hydroxylamine hydrochloride in MeOH and in the presence of base (Et_3N) at room temperature led to the formation of α-bromooxime phosphonate **2b** (Scheme 2).

Addition of 1 equiv of triethylamine to a solution of functionalized α-bromooxime **2a** derived from phosphine oxide in dichloromethane caused 1,4-elimination of HBr and led to the formation of the highly colored 4-phosphinyl-1,2-oxaza-1,3-butadiene **5a** (R = Ph) in almost quantitative yield (>99%, Scheme 2). The presence of nitrosoalkene **5a** in the crude reaction mixtures was confirmed by NMR spectroscopy at −40 °C. Thus, the ^{31}P NMR spectrum of **5a** showed only an absorption at δ_P 23.1 ppm, and the ^{13}C NMR spectrum of **5a** showed an absorption at δ_C 7.65 ppm as a doublet with a coupling constant ($^3J_{PC}$ = 2.8 Hz) for the methyl group, indicating the presence of only one isomer and that the phosphorus atom and the methyl group are related *cis*[22] and confirming the *E*-stereochemistry of the carbon−carbon double bond of heterodiene **5a**. Similarly, 4-phosphonyl-1,2-oxaza-1,3-butadiene **5b** was obtained in very high yield (δ_P 15.4 ppm). Nitrosoalkenes **5** proved to be unstable, and they were not isolated and but were, therefore, used in situ without isolation in subsequent Michael additions. As far as we know, this is the first reported example of the preparation of phosphorus-containing nitrosoalkenes **5** using this methodology.

SCHEME 3. Michael Addition of Ammonia and Amine Reagents to Phosphorylated Nitrosoalkenes 5



Electron-withdrawing groups on the terminal carbon atom may enhance the electrophilic character of this atom, and the Michael addition of nucleophilic reagents on this carbon atom (1,4-addition) may be favored. Some conjugate addition of amines to 1,2-oxaza-1,3-butadienes have been reported.[6,7] However, to date, Michael addition of nucleophilic reagents to phosphorus-substituted nitrosoalkenes remains unexplored, and by means of this strategy, a wide range of α-amino phosphorus derivatives could be obtained. For this reason, we first studied the reaction between ammonia and amines with phosphorus-containing nitrosoalkenes **5** (Scheme 3).

We explored the addition of ammonia to nitrosoalkene **5a** (R = Ph) generated in situ from α-bromooxime **2a**. When ammonia gas was bubbled through a solution of α-bromooxime **2a** in CH_2Cl_2, the reaction mixture became deep green, showing the formation of 1,2-oxazadiene **5a**. The green color disappeared very fast, showing the end of the reaction with the formation of only one stereoisomer corresponding to the α-amino phosphine oxide **6a** in good yield (Scheme 3, Table 1, entry 1). Compound **6a** was characterized on the basis of its spectroscopic data. Mass spectrometry of **6a** supported the molecular ion peak, while the ^{31}P NMR spectrum of the phosphinyl group resonated at δ_P 31.3 ppm. The ^1H NMR spectrum showed an absorption at δ_H 4.35 ppm as a doublet with coupling constant $^2J_{PH}$ = 8.1 Hz for the methine proton, and the ^{13}C NMR spectrum showed an absorption at δ_C 56.7 ppm as a doublet with coupling constant $^1J_{PC}$ = 73.5 Hz for the carbon atom directly bonded to the phosphorus atom. Then, the process was extended to 4-phosphonyl nitrosoalkene **5b** (R = OEt). Although, in this case α-amino phosphonate **6b** (R = OEt) was very unstable, it could be isolated as a mixture of *syn*- and *anti*-α-amino phosphonate **6b** and further characterized (Scheme 3, Table 1, entry 2). α-Amino phosphonates[18] are very interesting substrates in medicinal chemistry,[19] with a wide range of biological activities such as haptens of catalytic antibodies,[20a] peptide mimetics,[20b] enzyme inhibitors,[20c] and antibacterial[20d] or antihypertensive agents.[20e]

Functionalized nitrosoalkenes **5** can also act as Michael acceptors toward primary and secondary amines. The addition

(21) A modified procedure of the Sturtz method was used: Haelters, J. P.; Corbel, B.; Sturtz, G. *Phosphorus Sulfur Relat. Elem.* **1988**, *37*, 65−85.

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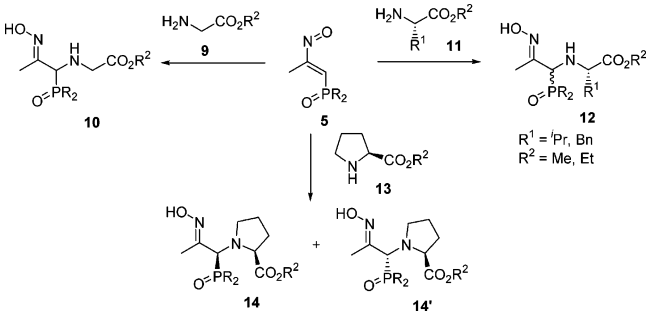
TABLE 1. α-Amino Phosphine Oxides and Phosphonates 6 and 8 Obtained through Conjugate Addition of Ammonia and Amines to Nitrosoalkenes 5

entry	product	R	R^1	R^2	yield (%)[a,b]
1	**6a**	Ph	-	-	71
2	**6b**	OEt	-	-	66
3	**8a**	Ph	*p*-MeO-C_6H_4	H	90
4	**8b**	Ph	Ph	H	72
5	**8c**	Ph		H	70
6	**8d**	Ph		H	95
7	**8e**	Ph	Et	Et	94
8	**8f**	OEt	*p*-MeO-C_6H_4	H	89
9	**8g**	OEt		H	90
10	**8h**	OEt	Et	Et	88

[a] After chromatography. [b] Yields of pure compounds **6** and **8** are based on 1,2-oxazadienes **5**.

SCHEME 4. Michael Addition of α-Amino Esters to Phosphorylated Nitrosoalkenes 5



of primary or secondary amines **7** to functionalized nitrosoalkenes **5** containing a phosphine oxide or a phosphonate group[23] led to the formation of functionalized *anti*-α-amino phosphine oxide[24] **8** (R = Ph) and phosphonate **8** (R = OEt) derivatives in moderate to excellent yields (Scheme 3, Table 1, entries 3−10). The scope of the reaction was not limited to aliphatic (Table 1, entries 7 and 10) and aromatic amines (Table 1, entries 3, 4, and 8) since amines containing double or triple bonds can also be used (Table 1, entries 5, 6, and 9).

Finally, we studied the addition of α-amino esters because this strategy could afford a new alternative for the preparation of phospha-depsipeptide derivatives.[25] The addition of ethyl glycinate **9** (R^2 = Et) to nitrosoalkene phosphine oxide[23] **5a** led to the formation of functionalized α-amino phosphine oxide derivative **10** (R = Ph, R^2 = Et) in good yield (Scheme 4, Table 2, entry 1). Compound **10** was characterized by its spectroscopic data, which indicated that it was isolated as the *anti*-oxime[24] **10**. The ^{31}P NMR spectrum of **10** showed one absorption at δ_P 29.5 ppm. Likewise, the ^1H NMR spectra of **10** gave a well-resolved doublet for the methine proton at δ_H 4.31 ppm ($^2J_{PH}$ = 11.4 Hz), while in the ^{13}C NMR spectra, a doublet appeared

(23) In these processes, nitrosoalkenes **5** were generated in situ from α-halooximes **2** and triethylamine.

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TABLE 2. α-Amino Phosphine Oxides and Phosphonates Obtained through Conjugate Addition of α-Amino Esters to Nitrosoalkenes 5

entry	product	R	R^1	R^2	yield (%)[a,b]
1	**10**	Ph	−	Et	58
2	**12a**	Ph	*i*Pr	Et	90
3	**12b**	OEt	*i*Pr	Et	82
4	**12c**	Ph	Bn	Me	83
5	**12d**	OEt	Bn	Me	80
6	**14a**[c]	Ph	−	Me	87
7	**14b**[c]	OEt	−	Me	79

[a] After chromatography. [b] Yields of pure compounds **10**, **12**, and **14** are based on 1,2-oxazadienes **3**. [c] Both isomers can be separated and isolated from the diastereomeric mixture.

at δ_C 61.9 ppm ($^1J_{PC}$ = 80.1 Hz) for the carbon bonded to the phosphorus atom.

Then the reaction was extended to the diastereoselective addition of optically active α-amino esters **11** to phosphorylated nitrosoalkenes **5**. A slight diastereoselection was observed when L-valine ethyl ester hydrochloride **11a** (R^1 = *i*Pr, R^2 = Et) or L-phenylalanine methyl ester hydrochloride **11b** (R^1 = Bn, R^2 = Me) was used in the reaction with nitrosoalkenes **5**. Thus, reaction of L-valine ethyl ester hydrochloride **11a** with **5a** and **5b** gave α-amino phosphorus derivatives **12a** and **12b**, respectively, as nonseparable diastereomeric mixtures, and light diastereoselective excess (51% in the case of **12a** and 28% in the case of **12b**)[26] was observed (Scheme 4, Table 2, entries 2 and 3). Michael addition of L-phenylalanine methyl ester hydrochloride **11b** to nitrosoalkenes **5a** and **5b** gave adducts **12c** and **12d**, respectively, obtained as before as nonseparable diastereomeric mixtures and diastereoselective excess rising from 13% for compound **12c** and 65% for compound **12d** (Scheme 4, Table 2, entries 4 and 5).[26]

However, no diastereoselection was observed when L-proline methyl ester hydrochloride **13** was treated with nitrosoalkene phosphine oxide **5a** (R = Ph) or when treated with nitrosoalkene phosphonate **5b** (R = OEt). Adducts **14a** and **14b** were obtained as an equimolecular mixture of both isomers.[26] However, in these cases, both isomers **14** and **14′** (see Scheme 4) could be separated and isolated from the diastereomeric mixture (Scheme 4, Table 2, entries 6 and 7). This new family of functionalized α-amino phosphonates **10**, **12**, and **14** derived from α-amino esters can be considered as "phospha-depsipeptides" and could be interesting substrates in medicinal chemistry.[25] As far as we know, this novel strategy is the first example of conjugate addition of nitrogen nucleophiles to phosphorylated nitrosoalkenes to be reported.

Conclusion

In conclusion, the first synthesis of 1,2-oxaza-1,3-butadienes containing a phosphine oxide group **5a** or a phosphonate group **5b** at the C-4 position of the heterodiene system is reported. This is also the first example reported for the conjugate addition of ammonia, amines, and optically active amino esters to phosphorylated nitrosoalkenes **5** for the preparation of functionalized α-amino phosphorus compounds **6**, **8**, **10**, **12**, and **14**. It should be also emphasized that the use of these very reactive phosphorylated heterodienes **5** also opens a novel route to other functionalized phosphorus compounds due to the

(26) Diastereoisomer ratios were determined by ^{31}P NMR on the crude reaction mixture.

marked ability of compounds **5** to add nucleophiles. These α-amino phosphorus derivatives may be important synthons in organic synthesis for the preparation of biologically active compounds of interest to medicinal chemistry.[18−20]

Experimental Section

General Methods. Reagent and solvent purification, workup procedures, and analyses were performed in general as describe in the Supporting Information.

General Procedure for the Preparation of 1-Bromo-1-(diphenylphosphinoyl)propan-2-one Oxime (2a). To a stirred solution of sodium methoxide (0.62 g, 11.5 mmol) in methanol (50 mL) was added the *β*-oximino phosphine oxide **1**[13d,e] (1.37 g, 5.0 mmol). The mixture was refluxed for 1 h, and then it was cooled at 0 °C. Then bromine (256 *μ*L, 5.0 mmol) was added with a syringe pump. Once added, the reaction mixture was allowed to reach room temperature and stirred for 1 h. The crude product was washed with water and extracted twice with dichloromethane (20 mL). Organic layers were dried over $MgSO_4$, filtered, and the crude product was purified by flash-column chromatography (silica gel, AcOEt/pentane 50:50) to afford **2a** (1.29 g, 73%) as a colorless oil: IR (NaCl) ν_{max} 3183, 1728, 1436, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.40 (1H, br s), 8.09−7.27 (10H, m), 5.31 (1H, s), 2.09 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 132.9, 132.6, 132.5, 132.4, 132.3, 131.8, 131,7, 131.6, 131.5, 131.4, 131.3, 131.2, 131.0, 130.9, 130.3, 129.9, 129.5, 129.3, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.2, 47.0 (d, $^1J_{PC}$ = 68.8 Hz), 12.1; ^{31}P NMR (160 MHz, $CDCl_3$) δ 27.9; MS (CI) *m*/*z* 352 (M^+, 100). Anal. Calcd for $C_{15}H_{15}BrNO_2P$: C, 51.16; H, 4.29; N, 3.98. Found: C, 51.18; H, 4.33; N, 4.00.

General Procedure for the Addition of Ammonia to Phosphorylated Nitrosoalkenes. To an ice-cooled solution of α-bromooxime **2a** or **2b** (1.0 mmol) in dichloromethane (5 mL) was bubbled ammonia gas for 1 min. The reaction was allowed to stir at room temperature for 30 min. The solvent was removed by rotary evaporation, the residue was stirred with diethyl ether, and then it was filtered through a sintered glass vacuum filtration funnel. The solid was washed twice with ether, and the filtrate was concentrated to dryness in vacuum. The crude products were purified by flash-column chromatography (silica gel, AcOEt) to afford α-amino phosphine oxide **6a** or α-amino phosphonate **6b**.

1-Amino-1-(diphenylphosphinoyl)propan-2-one Oxime (6a) (205 mg, 71%) was obtained as a colorless oil as described in the general procedure: IR (NaCl) ν_{max} 3383, 3246, 1728, 1236, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.14 (1H, br s), 7.43−7.88 (10H, m), 4.35 (1H, d, $^2J_{PH}$ = 8.1 Hz), 1.85 (3H, d, $^4J_{PH}$ = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 132.1, 132.1, 132.0, 131.8, 131.6, 131.5, 128.7, 128.5, 128.4, 56.7 (d, $^1J_{PC}$ = 73.5 Hz), 12.7; ^{31}P NMR (120 MHz, $CDCl_3$) δ 31.3; MS (EI) *m*/*z* 288 (M^+, 12), 201 (100), 124 (30), 77 (30). Anal. Calcd for $C_{15}H_{17}N_2O_2P$: C, 62.49; H, 5.94; N, 9.72. Found: C, 62.51; H, 5.97; N, 9.71.

General Procedure for the Addition of Amines to Phosphorylated Nitrosoalkenes. To an ice-cooled solution of α-bromooxime **2a** or **2b** (1.0 mmol) in dichloromethane (5 mL) was added triethylamine (140 *μ*L, 1.0 mmol). Then the corresponding amine (1.0 mmol) (*p*-anisidine, aniline, allylamine, propargylamine, or diethylamine) was added at once. The reaction was allowed to stir at room temperature for 30 min. The solvent was removed by rotary evaporation, the residue was stirred with diethyl ether, and then it was filtered through a sintered glass vacuum filtration funnel. The solid was washed twice with ether, and the filtrate was concentrated to dryness in vacuum. The crude products were purified by flash-column chromatography (silica gel, AcOEt) to afford α-amino phosphine oxides or phosphonates **8**.

1-(Diphenylphosphinoyl)-1-(4-methoxyphenylamino)propan-2-one Oxime (8a) (354 mg, 90%) was obtained as a colorless oil as described in the general procedure; IR (NaCl) ν_{max} 3341, 2929, 2673, 1514, 1434, 1242, 1167, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.84 (1H, br s), 7.80−7.31 (10H, m), 6.60 (4H, s), 4.94−4.89 (1H, m), 4.82 (1H, dd, $^3J_{PH}$ = 9.9 Hz, $^3J_{HH}$ = 7.0 Hz), 3.62 (3H, s), 1.78 (3H, d, $^4J_{PH}$ = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 152.8, 140.1, 140.0, 132.2, 132.2, 132.1, 132.0, 131.7, 131.6, 131.2, 131.1, 130.4, 129.8, 128.6, 128.5, 128.4, 128.2, 115.4, 114.7, 58.3 (d, $^1J_{PC}$ = 76.1 Hz), 55.5, 11.4; ^{31}P NMR (120 MHz, $CDCl_3$) δ 32.1; MS (CI) *m*/*z* 395 (M^+ + 1, 100). Anal. Calcd for $C_{22}H_{23}N_2O_3P$: C, 67.00; H, 5.88; N, 7.10. Found: C, 67.01; H, 5.90; N, 7.09.

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Supporting Information Available: Full characterization data and procedures for the synthesis of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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