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## Palladium-Catalyzed Indirect and Regioselective Phosphonation of Azobenzenes: Toward the Design of Water-Soluble Photoswitches

Ivanna Amarsy,<sup>[a]</sup> Nicolas Gigant,<sup>[a]</sup> Izel Erturk,<sup>[a]</sup> Nicolas Bogliotti,<sup>[b]</sup> Delphine Joseph,\*<sup>[a]</sup> and Sandrine Delarue-Cochin\*<sup>[a]</sup>

An efficient palladium-catalyzed *ortho* C–H acyloxylation of azobenzenes, allowing the introduction of the difunctionalised substituent, diethylphosphonoacetate, is reported. Thanks to the mild reaction conditions implemented, this regioselective late-stage *ortho*-functionalization tolerates a wide range of functional groups and permits the access of diversely sub-

#### Introduction

Azobenzenes have been proven to be valuable scaffolds in numerous domains, from organic dyes<sup>[1]</sup> and photochemical switches<sup>[2]</sup> to responsive polymers, liquid crystals,<sup>[3]</sup> and molecular machines.<sup>[4]</sup> In the fields of optogenetics and photopharmacology, they have emerged as powerful tools for visualizing and manipulating biological processes with high spatiotemporal resolution. However, while their unique photochemical properties have made azobenzenes inescapable,<sup>[5]</sup> one of their major drawbacks is their lipophilic nature for wideranging biological applications. Indeed, the water-solubility of optochemical probes is a key physicochemical property that influences their behavior in vivo by affecting their biodistribution and pharmacokinetics. As aqueous environments dominate biological systems, the solubility of probes is crucial by profoundly impacting their performance and applicability in living organisms.<sup>[6]</sup>

To overcome the azobenzene aqueous solubility issue, several examples of functionalization were reported. They

 [a] Dr. I. Amarsy, Dr. N. Gigant, I. Erturk, Prof. D. Joseph, Dr. S. Delarue-Cochin BioCIS Université Paris-Saclay, CNRS 91400, Orsay, France E-mail: delphine.joseph@universite-paris-saclay.fr sandrine.delarue-cochin@universite-paris-saclay.fr

 [b] Dr. N. Bogliotti PPSM Université Paris-Saclay, ENS Paris-Saclay, CNRS 91190, Gif-sur-Yvette, France

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stituted azobenzenes in good to excellent yields. Selective hydrolysis of the diethyl phosphonate group leads to stable water-soluble azo-photoswitches with interesting photophysical properties such as an extended Z-isomer half-life, opening new opportunities in the design of optochemical tools for the exploration of living organisms.

proceed through the introduction of hydrophilic functional units such as phosphate,<sup>[7–9]</sup> phosphonate,<sup>[10–13]</sup> or sulfonate,<sup>[14–16]</sup> and more recently sugars.<sup>[17]</sup> Although phosphonates are considered to be bioisosters of phosphates with greater metabolic stability, the efficient functionalization of azobenzenes, enabling the introduction of a phosphonate group either directly or indirectly via a carbon chain, is still scarcely described. Indeed, azobenzene phosphonates are typically synthesized by building up the azo unit from phosphonatesubstituted anilines or phenols.[10-12,18-20] A more versatile alternative that provide access to diversity is the late-stage functionalization of preformed azobenzenes. Direct phosphonation methods have been described in the literature in the presence of phosphite via a Cu(II)-promoted nucleophile displacement from halogenated azobenzenes<sup>[21]</sup> or via a Pd(II)catalyzed ortho-regioselective C-H phosphonation<sup>[22]</sup> (Figure 1). As C-H activation has recently emerged as one of the most

 $\textbf{Direct phosphonation: nucleophiles displacement^{[21]} or regioselective C-H phosphonation^{[22]}}{}$ 



Figure 1. Methods for direct and indirect phosphonation of azobenzenes.

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attractive atom-economic approach for the regioselective functionalization of azobenzenes,<sup>[23]</sup> we set out to reproduce it. However, despite being described as efficient and tolerant of a wide range of substituents, our attempts were unsuccessful.

We therefore turned to indirect phosphonation methods enabling the introduction of a phosphonated side chain (Figure 1). Only two methods have been reported in the literature for very specific scaffolds. The first allowed the introduction of a  $\alpha,\alpha$ -difluoromethylphosphonate group via a Cu(II)-promoted Burton's coupling of iodoazobenzenes using previously prepared (diethylphosphono)difluoromethyl cadmium bromide.<sup>[13]</sup> The second was reported in 2015 by Kim *et al.*, who described the unique example of Rh(III)-catalyzed C–H phosphonoalkylations using diethyl 2-diazo-2-diethylphosphonoacetate starting from the symmetrical di(*m*-tolyl)diazene (Figure 1).<sup>[24]</sup>

Inspired by these reports and pursuing our interest in transition-metal catalyzed C--H activation, we focused our attention on the design of water-soluble azobenzenes by exploring the indirect phosphonation of azobenzenes.

#### **Results and Discussion**

Based on the literature of ortho-alkylation of azobenzenes using organic hypervalent iodine oxidants,<sup>[25-31]</sup> the model azobenzene 2a, was subjected to Premi's reaction conditions<sup>[27]</sup> using a functionalized acetic acid as an alkylating agent in the presence of PIDA 1a and Pd(OAc)<sub>2</sub> (Scheme 1). After 1 h at 80 °C under solvent-free conditions, two compounds 4a and 5, resulting from a competitive ortho-acetoxylation involving diethylphosphonoacetic acid and PIDA as sources of acetates, were obtained in 34% and 50% yields respectively. Attempts to promote the formation of the expected alkyl compound 3a by using the more substituted 2-methyl or 2,2-dimethyl diethylphosphonoacetic acid gave similar results. Only the acyloxylated azobenzenes 4'a or 4", respectively, and 5 were isolated (Scheme 1). It can be noticed that the increase in reactant steric hindrance induces a significant viscosity in the reaction medium considerably and slows down the transformation: the reaction remains incomplete with the recovery of 50% of the unchanged



Scheme 1. Synthesis of *ortho*-acyloxylated azobenzenes under solvent-free Premi's conditions.

starting azobenzene **2 a** and the isolation of compounds **4**' **a** or **4**" **a** in a modest 18% or 21% yield respectively.

With these encouraging results in hand and given that the introduction of a functionalized acyloxy group has never been reported before, we explored this new transformation further. The first part of the work was devoted to optimizing the conditions to promote the phosphonoacetyloxylation reaction.

The effect of temperature was evaluated by carrying out reactions at different temperatures up to the total consumption of the starting material 2a (Table 1, entries 1-3). A temperature of 80°C with a short reaction time seemed to be the best compromise, degradation being observed after 1h30 whatever the reaction temperature. In addition, at the 50°C lower temperature, the higher viscosity of diethylphosphonoacetic acid causes the reaction to slow down significantly. To reduce the formation of the undesired acetoxylated compound 5, we took into account the mechanism proposed by Fu et al. for the Pd(II)-catalyzed ortho-acetoxylation of azobenzenes in the presence of PIDA 1a,<sup>[29]</sup> and explored the replacement of the latter by its diethylphosphonoacetate analog 1 b. The latter was prepared by acetate/diethylphosphonoacetate easily exchange.<sup>[32]</sup> After 1 h of reaction at 80°C, the formation of compound 5 is considerably reduced, but not eliminated due to the presence of acetate ligands on the Pd-catalyst (Table 1, entry 4). If the expected compound 4a was isolated in a similar 37% yield, 52% of the unreacted azobenzene 2a was recovered showing a lower efficiency of 1b compared with PIDA 1a (Table 1, entries 1 and 4). Increasing the reaction time did not improve the azobenzene conversion because of the degradation of the reaction medium, as previously observed (Table 1, entries 4 and 5).



[a] Reaction conditions: azobenzene 2a (0.5 mmol, 1 eq.), Pd(OAC)<sub>2</sub> (10 mol%), oxidant **1 a** or **1 b** (1 mmol, 2 eq), diethylphosphonoacetic acid (1 mmol, 2 eq). [b] Reaction carried out without (diethylphosphonoacetic acid.

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As the mechanism proposed for *ortho*-acetoxylation in the presence of PIDA<sup>[29]</sup> seems to show that the additional use of the acetic acid derivative is not necessary, the reaction was carried out in the absence of diethylphosphonoacetic acid. Only a slight slowing down of the transformation was observed, confirming that the use of the carboxylic acid derivative as additive is useful but not crucial to the reaction (Table 1, entries 5 and 6).

Facing numerous difficulties associated with solvent-free conditions, such as high reaction mixture viscosity, elevated reaction temperature, limited reactivity, and degradation, we investigated the influence of solvent dilution. Inspired by Fu's acyloxylation conditions,<sup>[29]</sup> we examined the effect of using HFIP as solvent with the oxidant **1b** at 45 °C. Under these mild reaction conditions, consumption of the starting azobenzene **2a** was achieved after just 1 h, and the desired compound **4a** was obtained in an attractive 47% yield (Table 2, entry 1). Unexpectedly, the disubstituted compound **6a** was also isolated in 15% yield. Analysis of the <sup>1</sup>H and <sup>13</sup>C NMR spectra shows that the diacyloxylation took place on the same benzene

Table 2. Optimization of the reaction conditions.							
2a catalyst (10 mol%) solvent, temperature (EtO) <sub>2</sub> OP							
Entry <sup>[a]</sup>	Catalyst	Solvent	Temp (°C)	Time (min)	Yield 2 a	(%) <sup>[b]</sup> 4a	бa
1	Pd(OAc) <sub>2</sub>	HFIP	45	60	2	47	15
2	Pd(OAc) <sub>2</sub>	TFE	45	60	85	5	-
3	Pd(OAc) <sub>2</sub>	DCE	45	60	95	2	-
4	Pd(OAc) <sub>2</sub>	AcN	45	60	91	5	-
5	Pd(OAc) <sub>2</sub>	<sup>t</sup> AmOH	45	60	75	6	-
6	PdCl <sub>2</sub>	HFIP	45	60	94	-	-
7	Pd(dba) <sub>2</sub>	HFIP	45	60	38	43	4
8	$Pd(AcN)_2Cl_2$	HFIP	45	60	43	35	-
9	Pd(OAc) <sub>2</sub>	HFIP	58	20	-	72	-
10	Pd(OAc) <sub>2</sub>	HFIP	58	30	-	55	18
11 <sup>[c]</sup>	Pd(OAc) <sub>2</sub>	HFIP	58	120	5	41	-
12	Pd(OAc) <sub>2</sub>	HFIP/	58	20	45	39	-
13	Pd(OAc) <sub>2</sub>	DMSO 3:1	58	40	27	17	-
14	Pd(OAc) <sub>2</sub>	HFIP/ DMF 3:1	58	20	20	43	-

[a] Reaction conditions: azobenzene 2a (0.5 mmol, 1 eq.), catalyst (10 mol%), oxidant 1b (1 mmol, 2 eq.), solvent (1.5 mL). [b] Up to 10% of isolated *ortho*-acetylated compound 5. [c] 0.75 mmol (1.5 eq.) of oxidant 1b.

ring, despite the increasing steric hindrance caused by the first functionalization.

A range of solvents conventionally used in C-H activation was also evaluated, but only traces of compound 4a were isolated, confirming the remarkable effect played by HFIP (Table 2, entries 2 to 5).<sup>[33,34]</sup> This could be explained by the generation of active palladium species,<sup>[35]</sup> and/or by the enhanced oxidizing abilities of hypervalent iodine reagents<sup>[36]</sup> induced by specific HFIP bindings. Other classically used palladium catalysts were found to be ineffective, highlighting the key role of Pd(OAc)<sub>2</sub> for the transformation (Table 2, entries 6 to 8). We next carefully investigated both the effect of temperature and the reaction time on the transformation. Carrying out the reaction at refluxing HFIP (58°C), compound 4a is obtained in an excellent 72% yield in just 20 minutes with the full conversion of the starting azobenzene 2a (Table 2, entry 9). It is important to note that a slight increase of only 10 min leads to non-negligible formation of the difunctionalised compound 6a up to 18% (Table 2, entry 10). Attempts to favour the formation of the difunctionalised compound 6a by increasing reaction time or by submitting monofunctionalised 4a to the initial reaction conditions failed. Compound 6a was always obtained as a secondary product up to 20% yield, probably due to degradation of the reactive medium.

As a part of a systematic approach to waste reduction, the amount of **1b** was reduced, but the reaction efficiency was strongly impacted requiring a longer reaction time, accompanied by degradation of the reaction medium (Table 2, entry 11). It is noteworthy that the addition of cosolvents such as DMSO or DMF has a considerable impact on the reaction efficiency with incomplete consumption of **2a** and formation of **4a** in lower yield (Table 2, entries 12 and 14). This phenomenon could be explained by a plausible detrimental interaction of the cosolvent with the palladium catalyst and/or the oxidant, reducing the effect of HFIP. Increasing the reaction time did not improve the yield of compound **4a**, as the degradation of the reactive medium was faster than the consumption of starting azobenzene **2a** (Table 2, entry 13).

With the optimized conditions in hand, the substrate scope was explored starting with variously substituted azobenzenes. Reactions were carried out in refluxing HFIP and monitored by TLC until full consumption of the starting azobenzene but not beyond 24 hours to avoid degradation (Scheme 2). Initially, we probed the scope of symmetric *para-* and *meta-*disubstituted azobenzenes **2b–e**, **2g**, and **2j**. The substitution pattern affected the reaction time, from 30 min for electron-enriched azobenzenes **2b** and **2c** to 21 h for electron-poor *meta-*difluoro azobenzene **2g**, leading to the targeted azobenzenes in 39% to 64% yields.

The reactivity of the sparingly HFIP-soluble deactivated *para*-disubstituted azobenzenes 2f, 2i, 2l, and 2m and the *ortho*-disubstituted ones 2h and 2k was also evaluated. In refluxing HFIP, reactions either did not lead to the desired product or gave poor yields of up to 28% after 24 hours with a large amount of starting material remaining. A few optimizations were necessary to obtain the desired compounds by heating the reaction to  $120^{\circ}$ C in a sealed tube. However, the

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[a] Reaction conditions: azobenzene 2a-m (0.5 mmol, 1 eq.), catalyst (10 mol%), oxidant 1b (1 mmol, 2 eq.), HFIP (1.5 mL). <sup>[b]</sup> Unreacted starting material was recovered. <sup>[c]</sup> Reaction performed in a sealed tube at 120°C. <sup>[d]</sup> Reaction performed in a sealed tube at 90°C.
[e] Reaction performed with oxidant 1c.

Scheme 2. (Dialkoxyphosphinyl)acetoxylation of diversely substituted symmetrical azobenzenes.

higher temperature again leads to degradation as well as to an HFIP-ester by-product **7**, making purification more complex. The best compromise between temperature and time for each azobenzene is shown in Scheme 2. Finally, the use of the dimethylphosphonoacetate oxidant **1c** afforded compound **8a**, albeit in a lower 48% yield due to extensive decomposition (Scheme 2).

Of special note, compared with the azobenzenes **2a**–m, 4,4'-dimethoxy azobenzene **2n** exhibits atypical behavior. As confirmed by 2D NMR analyses, in particular nOesy experiments (See Figure S1 in SI), its functionalization mainly occurs in the *ortho* position of the methoxy moiety and not of the azo group (Scheme 3). This *meta*-functionalized compound is isolated in a



Scheme 3. Regioselectivity switch for the *p*-methoxy azobenzene 2 n.

50% yield. An inseparable and complex mixture of difunctionalized regioisomers was also obtained in about 24% yield. This switch in regioselectivity was not common and has only been described in the case of Pd(II)-catalyzed bromination of **2 n** with *N*-bromosuccinimide.<sup>[37]</sup>

A control experiment, performed without metal catalyst, yielded the compound 4'n, suggesting a different mechanism entirely governed by the methoxy group as the directing group. Under these conditions, difunctionalized regioisomers were not observed.

To gain some insights on the reaction mechanism, we evaluated the intermolecular isotope effect starting from an equimolar mixture of 2a and  $[D_{10}]$ -2a (Scheme 4).

A moderate primary isotope effect  $(k_H/k_D = 1.44)$  was measured, and this result was confirmed by determining the intramolecular isotope effect starting from  $[D_s]$ -2 a  $(k_H/k_D = 1.33)$  (Scheme 4). The aromatic C–H bond cleavage by Pd may be involved in the rate-determining step of the reaction, which is in accordance with previous results of palladium catalyzed hydroxylation of azobenzenes using PIFA as oxidant.<sup>[28]</sup>

The synthetic utility of the method was illustrated through the chemoselective hydrolysis of diethylphophonate **4a** into the corresponding phosphonic acid **9a** in an excellent 90% yield by using trimethylsilyl iodide (TMSI) in the presence of Research Article doi.org/10.1002/ejoc.202400406



Scheme 4. Kinetic isotope effect studies.

*N,O*-bis(trimethylsilyl)-trifluoroacetamide (BSTFA) as hydrogen iodide quencher (Scheme 5).<sup>[38]</sup> The acid **9a** has a good water-solubility of around 2 g/L, compared with that of simple azobenzene **2a** of 6.4 mg/L,<sup>[39]</sup> highlighting the remarkable effect of such functionalization on water-solubility and opening up new opportunities for biological applications. It also proved stable in aqueous solution at pH 4.7, 7.0 and 9.0, with no phosphonoacetic acid detected in the reactive medium after 96 hours by <sup>1</sup>H NMR analysis (Supporting Information - Figures S2A–S2C).

The photochemical behavior of compound **9a** was then evaluated.

The UV-Vis absorption spectrum of **9a**, which was in a pure E conformation (initial state PSS dark), was measured in water at pH 4.7, 7.0 and 9.0 and showed a  $\pi$ - $\pi$ \* maxima band at 324 nm and a  $n-\pi^*$  slight band at 424 nm for the pH tested (Figure 2 and SI Figures S3 and S4).<sup>[40]</sup> Irradiation with UV light at 320 nm induced  $E \rightarrow Z$  isomerisation in less than 20 seconds, causing the intense decrease of  $\pi$ - $\pi$ \* band and a slight increase of  $n-\pi^*$  band. A photostationary state (PSS 320 nm) was observed with a 2:3 E/Z ratio, determined by irradiation of an NMR tube containing compound 9a in D<sub>2</sub>O. Noteworthy, the Eisomer can be regenerated to around 80% in 3 minutes with 405 nm irradiation at all three pH values (Figure 2 and SI Figures S3 and S4). Moreover, the presence of isosbestic points indicates that no secondary reaction occurs under UV irradiation during the time range of E to Z and Z to E isomerisation.<sup>[41]</sup> Thermal  $Z \rightarrow E$  isomerisation was monitored in the dark by UV absorption at 324 nm. Measurements were taken until the modification in UV absorption indicated the beginning of compound degradation, after 220 h, 350 h, and 320 h for pH 4.7, 7, and 9 respectively (Figure 2 and SI Figure S5). The thermal back-isomerisation of (Z)-9a appeared to be monoexponential for the pH tested with good to excellent correlation. It gave us access to an estimated half-life of (Z)-9a at 20°C around 600 h depending on the pH solution (Figure 3). The



Scheme 5. Chemoselective phosphonate hydrolysis of 4a.

 $E \rightarrow Z$  isomerisation of **9a** by 320 nm irradiation



 $Z \rightarrow E$  isomerisation of **9a** by 405 nm irradiation



Figure 2. Optical spectra of 9a in water at pH 7 and 20 °C in a 1.0 cm quartz cuvette.



Figure 3. Half-life estimation of 9a at pH 7.

thermal stability of (*Z*)-**9** $\mathbf{a}$  is thus found to be equivalent to this of (*Z*)-**2** $\mathbf{a}$ , which presents a 600 h half-life in water.<sup>[42]</sup>

#### Conclusions

In conclusion, we have developed an efficient method of C–H functionalization of azobenzenes, allowing the regioselective introduction of a dialkylphosphonoacetate pattern under mild reaction conditions. Subsequent chemoselective hydrolysis of the phosphonate group into the corresponding phosphonic acid leads to an azobenzene with improved aqueous solubility, of interest for potential applications in living organisms. In

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addition, this azobenzene also exhibits encouraging physicochemical and photophysical properties, such as long-time stability in water, an isomerisation of E to Z and Z to E upon irradiation with near UV and blue light, respectively, and a prolonged thermal lifetime of the (Z)-isomer.

## **Experimental Section**

All chemicals were obtained from commercial sources and used without further purification unless otherwise stated. Azobenzenes 2a-2n were prepared according to literature procedures.[43-45] Melting points were recorded on an electrothermal digital apparatus and were uncorrected. Infrared (IR) spectra were obtained as neat films on Bruker Vector22 spectrophotometer. <sup>1</sup>H, and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance 300 apparatus respectively at 300 and 75 MHz unless otherwise specified. <sup>19</sup>F spectra were recorded on a Bruker Avance 200 apparatus at 188 MHz. The chemical shifts for <sup>1</sup>H NMR and for <sup>13</sup>C NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Coupling constants (J) are reported in Hz and refer to apparent peak multiplications. High-resolution mass spectra were realized on an HPLC-MS 6830 Agilent Technologies spectrometer using electrospray impact (ESI) mode. Analytical thin layer chromatography was performed on 60F-254 precoated silica (0.2 mm) on glass and was revealed by UV light. Flash chromatography separations were performed on Kieselgel (40-63 µm).

(Bis[diethyl phosphonoacetoxy]iodo)benzene (1 b). A mixture of diethylphosphonoacetic acid (3.92 g, 20.0 mmol, 2 eq.) and PIDA (3.22 g, 10.0 mmol, 1 eq) was stirred in toluene (30 mL) for 30 min and concentrated under vacuum. The procedure was repeated 6 times until the total exchange of the acetate groups by the diethylphosphonoacetate moieties. The crude product was finally diluted in DCM and concentrated to remove the last traces of toluene giving 1b as a colorless viscous oil (5.94 g, 99% yield). 1b was used as a crude product in further experiments. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.23 + 1.29 (2 t, <sup>3</sup>*J* = 7.2 Hz, 12H, 2 PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2.92 (d, <sup>2</sup>*J*<sub>*p*</sub> = 21.0 Hz, 4H, 2 CH<sub>2</sub>P), 3.95-4.20 (m, 8H, 2 PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 7.40-7.60 (m, 3H, H<sub>arom</sub>), 8.10 (d, <sup>3</sup>*J* = 7.5 Hz, 2H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.3 (d, <sup>3</sup>*J*<sub>*p*</sub> = 6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 122.0 (Cq<sub>arom</sub>), 131.0 (CH<sub>arom</sub>), 132.0 (CH<sub>arom</sub>), 135.0 (CH<sub>arom</sub>), 170.1 (d, <sup>2</sup>*J*<sub>*p*</sub> = 5.6 Hz, CO).

(Bis[dimethyl phosphonoacetoxy]iodo)benzene (1 c). To a solution of trimethylphosphonoacetate (4.89 g, 26.9 mmol, 1 eq.) in water (10 mL) was added dropwise, at 10 °C, a solution of NaOH (1.16 g, 29.0 mmol, 1.1 eq) in water (3 mL). After stirring at r.t. for 2 h, the medium was acidified by adding conc. HCl at  $0^{\circ}$ C until pH < 2, then NaCl was added to saturation. The saturated aqueous layer was extracted with THF (3 $\times$ 30 mL), and the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated to yield dimethyl phosphonoacetic acid as a colorless oil (3.70 g, 82% yield). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.00 (d, <sup>2</sup>J<sub>p</sub>=21.6 Hz, 2H, CH<sub>2</sub>P), 3.79 (d, <sup>3</sup>J<sub>p</sub>=11.4 Hz, 6H, PO(OCH<sub>3</sub>)<sub>2</sub>), 8.74 (bs, 1H, COOH); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  33.1 (d, <sup>1</sup>J<sub>p</sub> = 135.3 Hz, CH<sub>2</sub>P), 53.7 (d,  ${}^{2}J_{p} = 6.4$  Hz, PO(OCH<sub>3</sub>)<sub>2</sub>), 167.6 (d,  ${}^{2}J_{p} =$ 5.3 Hz, CO). Then, a mixture of dimethyl phosphonoacetic acid (1.69 g, 10.0 mmol, 2 eq) and PIDA 1a (1.62 g, 5.0 mmol, 1 eq) was stirred in toluene (15 mL) for 30 min and concentrated. The procedure was repeated 6 times until the total exchange of the acetate groups by the dimethyl phosphonoacetate moieties. The crude product was finally diluted in DCM and concentrated to remove the last traces of toluene giving 1 c as a colorless viscous oil (2.63 g, 92% yield). The latter was used as a crude product in further experiments. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.93 (d, <sup>2</sup>J<sub>p</sub>=21.0 Hz, 4H, 2

CH<sub>2</sub>P), 3.66 + 3.74 (2 d,  ${}^{3}J_{p}$  = 11.4 Hz, 6H, 2 PO(OCH<sub>3</sub>)<sub>2</sub>), 7.40–7.60 (m, 3H, H<sub>arom</sub>), 8.10 (d,  ${}^{3}J$  = 7.8 Hz, 2H, H<sub>arom</sub>);  ${}^{13}$ C NMR (CDCl<sub>3</sub>)  $\delta$  32.4 + 33.3 (2d,  ${}^{1}J_{p}$  = 134.3 Hz, CH<sub>2</sub>P), 53.2 (d,  ${}^{2}J_{p}$  = 5.9 Hz, PO(OCH<sub>3</sub>)<sub>2</sub>), 122.2 (Cq<sub>arom</sub>), 131.1 (CH<sub>arom</sub>), 132.1 (CH<sub>arom</sub>), 135.0 (CH<sub>arom</sub>), 169.8 (d,  ${}^{2}J_{p}$  = 5.4 Hz, CO).

General procedure for the synthesis of compounds 4a, 4a', and 4"a using PIDA as oxidant. To a solution of PIDA 1a (322 mg, 1 mmol, 2 eq.) and a diethylphosphonoacetic acid derivative (1 mmol, 2 eq.) was added azobenzene 2a (mg, 0.5 mmol, 1 eq.) and Pd(OAc)<sub>2</sub> (11 mg, 0.05 mmol, 0.1 eq.). After stirring at 80 °C for 1 h, the reaction mixture was filtered through Celite, and the latter was then washed with ethyl acetate (20 mL). The filtrate was washed with a saturated aqueous solution of NaHCO<sub>3</sub> (20 mL), a 1 M HCl aqueous solution (20 mL), and brine (20 mL), and then, dried over MgSO<sub>4</sub>, filtered, and concentrated under vacuum. The residue was finally purified by column chromatography (DCM/ MeOH from 100/0 to 99/1) to yield the desired compound 4a, 4'a or 4"a. The acetylated compound 5, usually obtained as a reaction by-product, was isolated and characterized by way of example.

**Diethyl** [2-(phenyldiazenyl)phenyloxycarbonyl]-methylphosphonate (4a). Obtained as a red viscous oil in 34% yield (64.3 mg) starting from diethylphosphonoacetic acid (196 mg). Rf=0.25 (DCM/MeOH 98:2); IR  $v_{max}/cm^{-1}$  2982, 1769, 1264, 1194, 1013, 976; *E/Z* ratio = 85:15 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.33 (t, <sup>3</sup>*J*=6.9 Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.20 + 3.31 (d, <sup>2</sup>*J*<sub>p</sub>=21.6 Hz, 2H, CH<sub>2</sub>P *Z* + *E*), 4.23 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 6.95–7.95 (m, 9H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.5 (d, <sup>3</sup>*J*<sub>p</sub>=6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 34.2 (d, <sup>1</sup>*J*<sub>p</sub>=133.5 Hz, CH<sub>2</sub>P), 63.1 (d, <sup>2</sup>*J*<sub>p</sub>=6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 117.8 (CH<sub>arom</sub>), 123.3 (3 CH<sub>arom</sub>), 127.1 (CH<sub>arom</sub>), 129.2 (2 CH<sub>arom</sub>), 131.6 (CH<sub>arom</sub>), 132.2 (CH<sub>arom</sub>), 144.0 (Cq<sub>arom</sub>), 148.7 (Cq<sub>arom</sub>), 152.9 (Cq<sub>arom</sub>), 164.6 (d, <sup>2</sup>*J*<sub>p</sub>=6.8 Hz, CO); HRMS (TOF MS ES+) m/z: Calcd for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>P [M+H]<sup>+</sup> 377.1265, Found 377.1260.

Diethyl 1-[2-(phenyldiazenyl)phenyloxycarbonyl]-ethylphosphonate (4'a). Obtained as a red viscous oil in 18% yield (36.1 mg) starting from diethyl 2-phosphonopropanoic acid (216.2 mg). Rf = 0.20 (DCM/MeOH 98:2); IR v<sub>max</sub>/cm<sup>-1</sup> 2968, 1759, 1255, 1195, 1015, 972; *E/Z* ratio = 85:15 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.33 (m, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 1.56 + 1.62 (dd, <sup>3</sup>J = 7.2 Hz, <sup>3</sup>J<sub>p</sub> = 17.7 Hz, 3H, CH<sub>3</sub>CHP *Z* + *E*), 3.30 + 3.40 (qd, <sup>3</sup>J = 7.1 Hz, <sup>2</sup>J<sub>p</sub> = 23.1 Hz, 1H, CHP *Z* + *E*), 4.21 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 6.95–7.90 (m, 9H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 12.2 (d, <sup>2</sup>J<sub>p</sub> = 6.1 Hz, *CH*<sub>3</sub>CHP), 16.5 (d, <sup>3</sup>J<sub>p</sub> = 3.7 Hz, PO-(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 39.6 (d, <sup>1</sup>J<sub>p</sub> = 133.3 Hz, CHP), 63.1 (d, <sup>2</sup>J<sub>p</sub> = 6.3 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 117.6 (CH<sub>arom</sub>), 123.2 (2 CH<sub>arom</sub>), 123.3 (CH<sub>arom</sub>), 126.9 (CH<sub>arom</sub>), 129.1 (2 CH<sub>arom</sub>), 131.5 (CH<sub>arom</sub>), 132.1 (CH<sub>arom</sub>), 144.2 (Cq<sub>arom</sub>), 148.9 (Cq<sub>arom</sub>), 153.0 (Cq<sub>arom</sub>), 168.4 (d, <sup>2</sup>J<sub>p</sub> = 4.5 Hz, CO); HRMS (TOF MS ES +) m/z: Calcd for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>P [M + H]<sup>+</sup> 391.1417, Found 391.1418.

**Diethyl** 1-methyl-1-[2-(phenyldiazenyl)phenyloxycarbonyl]ethylphosphonate (4"a). Obtained as a red viscous oil in 21% yield (41.0 mg) starting from diethyl 2-methyl-2-phosphonopropanoic acid (224.6 mg). Rf=0.20 (DCM/MeOH 98:2); IR  $v_{max}/cm^{-1}$  2964, 1759, 1253, 1115, 1025, 972; *E/Z* ratio=85:15 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.33 + 1.35 (t, <sup>3</sup>J=7.1 Hz, 6H, PO-(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> Z + E), 1.62 + 1.67 (d, <sup>3</sup>J<sub>p</sub> = 16.2 Hz, 6H, (CH<sub>3</sub>)<sub>2</sub>CqP Z + E), 4.22 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 6.90-7.90 (m, 9H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 16.6 (d, <sup>3</sup>J<sub>p</sub>=5.6 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 21.5 (d, <sup>2</sup>J<sub>p</sub>=6.9 Hz, PO-(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 117.4 (CH<sub>arom</sub>), 123.2 (2 CH<sub>arom</sub>), 123.3 (CH<sub>arom</sub>), 126.8 (CH<sub>arom</sub>), 129.2 (2 CH<sub>arom</sub>), 131.4 (CH<sub>arom</sub>), 132.1 (CH<sub>arom</sub>), 144.4 (Cq<sub>arom</sub>), 149.2 (Cq<sub>arom</sub>), 153.0 (Cq<sub>arom</sub>), 171.1 (d, <sup>2</sup>J<sub>p</sub>=2.8 Hz, CO); HRMS (TOF MS ES +) m/z: Calcd for C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>P [M+H]<sup>+</sup> 405.1574, Found 405.1582.



**2-Acetoxyazobenzene (5).** Reaction by-product isolated as an orange viscous oil. Rf = 0.8 (DCM/MeOH 99:1); *E/Z* ratio = 85:15 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  2.30 + 2.40 (2 s, 3H, COCH<sub>3</sub> *Z* + *E*), 7.05–7.95 (m, 9H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  20.8 + 20.9 (COCH<sub>3</sub> *Z* + *E*), 117.7 (CH<sub>arom</sub> *E*), 119.2 (CH<sub>arom</sub> *Z*), 120.6 (2 CH<sub>arom</sub> *Z*), 123.0 (2 CH<sub>arom</sub> *E*), 123.3 (CH<sub>arom</sub> *E*), 125.7 (CH<sub>arom</sub> *Z*), 126.6 (CH<sub>arom</sub> *E*), 128.3 (CH<sub>arom</sub> *Z*), 128.5 (CH<sub>arom</sub> *Z*), 128.4 (2 CH<sub>arom</sub> *Z*), 129.1 (2 CH<sub>arom</sub> *E*), 131.4 (CH<sub>arom</sub> *E*), 132.1 (CH<sub>arom</sub> *E*), 144.0 (Cq<sub>arom</sub>), 149.0 (Cq<sub>arom</sub>), 152.8 (Cq<sub>arom</sub>), 169.6 (CO); HRMS (TOF MS ES +) m/z: Calcd for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup> 241.0979, Found 241.0971. Analytical data are conformed to the literature.<sup>[45]</sup>

General procedure for the synthesis of compounds 4a-m, 4'n and 8a. To a solution of oxidant 1b or 1c (1.0 mmol, 2 eq.) in HFIP (1.5 mL), were added azobenzene 2a-n (0.5 mmol, 1 eq.) and Pd(OAc)<sub>2</sub> (11 mg, 0.05 mmol, 0.1 eq.). After stirring at the given temperature until the disappearance of the starting azobenzene (followed by TLC), the reaction mixture was filtered through Celite, and the latter was washed with ethyl acetate (20 mL). The filtrate was then washed with a saturated solution of NaHCO<sub>3</sub> (20 mL), a 1 M aqueous HCI solution (20 mL), and brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by column chromatography (DCM/MeOH from 100:0 to 98:2) to yield the desired compound 4a-m, 4'n or 8a. Dual-function compounds such as compound 6a are sometimes observed. Compound 6a has been isolated and characterized as an example.

**Diethyl** [2-(phenyldiazenyl)phenyloxycarbonyl]methyl-phosphonate (4a). Obtained as a red viscous oil in 79% yield (147.8 mg) by reacting azobenzene 2a (91.2 mg) and oxidant 1b (598.4 mg) at 60 °C for 20 min.

**Diethyl** [5-methyl-2-(4-methylphenyldiazenyl)phenyloxycarbonyl]methylphosphonate (4b). Obtained as a red viscous oil in 39% yield (78.7 mg) by reacting from azobenzene 2b (104.9 mg) and oxidant 1b (597.8 mg) at 60 °C for 30 min. Rf = 0.25 (DCM/MeOH 98:2); IR  $v_{max}/cm^{-1}$  2985, 1770, 1602, 1504, 1262, 1197, 1111, 1050, 1019, 976; *E/Z* ratio = 9:1 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.34 (t, <sup>3</sup>*J* = 6.9 Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2.30 + 2.37 + 2.42 (3 s, 6H, CH<sub>3</sub> *Z* + *E*), 3.19 + 3.29 (d, <sup>2</sup>*J*<sub>*p*</sub> = 21.3 Hz, 2H, CH<sub>2</sub>P *Z* + *E*), 4.23 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 7.00–7.80 (m, 7H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.5 (d, <sup>3</sup>*J*<sub>*p*</sub> = 6.1 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 21.5 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 34.1 (d, <sup>1</sup>*J*<sub>*p*</sub> = 134.2 Hz, CH<sub>2</sub>P), 63.2 (d, <sup>2</sup>*J*<sub>*p*</sub> = 5.9 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 115.6 (CH<sub>arom</sub>), 123.1 (2 CH<sub>arom</sub>), 123.5 (CH<sub>arom</sub>), 127.8 (CH<sub>arom</sub>), 129.8 (2 CH<sub>arom</sub>), 141.9 (Cq<sub>arom</sub>), 143.0 (Cq<sub>arom</sub>), 148.4 (Cq<sub>arom</sub>), 151.1 (Cq<sub>arom</sub>), 154.1 (Cq<sub>arom</sub>), 164.6 (d, <sup>2</sup>*J*<sub>*p*</sub> = 6.2 Hz, CO); HRMS (TOF MS ES +) m/z: Calcd for C<sub>20</sub>H<sub>26</sub>N<sub>20</sub>SP [M+H]<sup>+</sup> 405.1574, Found 405.1583.

Diethyl [4-methyl-2-(3-methylphenyldiazenyl)phenyloxycarbonyl]methylphosphonate (4c). Obtained as a red viscous oil in 53% yield (106.3 mg) by reacting azobenzene 2c (105.4 mg) and oxidant 1 b (593.8 mg) at 60  $^\circ\text{C}$  for 30 min. Rf=0.30 (DCM/ MeOH 98/2); IR v<sub>max</sub>/cm<sup>-1</sup> 2985, 1765, 1515, 1257, 1191, 1081, 1044, 1022, 971; E/Z ratio = 85:15 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.33 (t,  ${}^{3}J = 6.9$  Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2.28+2.36+2.40+2.44  $(2 \text{ s}, 2x3\text{H}, 2 \text{ CH}_3 Z + E), 3.15 + 3.29 \text{ (d}, {}^2J_p = 21.3 \text{ Hz}, 2\text{H}, \text{CH}_2\text{P} Z + E),$ 4.21 (m, 4H,  $PO(OCH_2CH_3)_2$ ), 6.90–7.75 (m, 7H,  $H_{arom}$ ); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.4 (d,  ${}^{3}J_{p} = 6.0$  Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 21.0 (CH<sub>3</sub>), 21.3 (CH<sub>3</sub>), 34.1 (d,  ${}^{1}J_{p} = 133.7$  Hz, CH<sub>2</sub>P), 63.0 (d,  ${}^{2}J_{p} = 6.0$  Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 117.9 (CH<sub>arom</sub>), 120.2 (CH<sub>arom</sub>), 122.8 (CH<sub>arom</sub>), 123.8 (CH<sub>arom</sub>), 128.9 (CH<sub>arom</sub>), 132.2 (CH<sub>arom</sub>), 132.6 (CH<sub>arom</sub>), 136.9 (Cq<sub>arom</sub>), 139.0 (Cq<sub>arom</sub>), 143.5 (Cq<sub>arom</sub>), 146.4 (Cq<sub>arom</sub>), 152.9 (Cq<sub>arom</sub>), 164.6 (d,  ${}^{2}J_{P}$ =5.9 Hz, CO); HRMS (TOF MS ES+) m/z: Calcd for  $C_{20}H_{26}N_2O_5P$  [M+H]<sup>+</sup> 405.1574, Found 405.1584.

Diethyl [5-(ethyloxycarbonyl)-2-(4-(ethyloxycarbonyl)phenyldiazenyl)phenyloxycarbonyl]methylphosphonate (4d). Obtained as a red solid in 64% yield (165.2 mg) by reacting azobenzene **2d** (161.2 mg) and oxidant **1b** (595.0 mg) at 60 °C for 1 h. Rf = 0.30 (DCM/MeOH 98:2); mp = 90–92 °C; IR v<sub>max</sub>/cm<sup>-1</sup> 2980, 1770, 1765, 1715, 1272, 1242, 1218, 1020, 1011, 975, 959; *E/Z* ratio > 95:5 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.34 (t, <sup>3</sup>*J*=6.9 Hz, 6H, 2 x CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.42 + 1.43 (2 t, <sup>3</sup>*J*=6.9 Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.31 (d, <sup>2</sup>*J*<sub>*p*</sub>=21.6 Hz, 2H, CH<sub>2</sub>P *Z* + *E*), 4.24 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 4.42 (q, <sup>3</sup>*J*=7.1 Hz, 4H, 2 x CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 7.80–8.25 (m, 7H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  14.3 (2×CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 16.3 (d, <sup>3</sup>*J*<sub>*p*</sub>=6.0 Hz, PO-(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 34.0 (d, <sup>1</sup>*J*<sub>*p*</sub>=133.7 Hz, CH<sub>2</sub>P), 61.4 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 61.6 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 63.0 (d, <sup>2</sup>*J*<sub>*p*</sub>=6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 117.5 (CH<sub>arom</sub>), 123.2 (2 CH<sub>arom</sub>), 124.7 (CH<sub>arom</sub>), 128.1 (CH<sub>arom</sub>), 130.6 (2 CH<sub>arom</sub>), 133.1 (Cq<sub>arom</sub>), 134.1 (Cq<sub>arom</sub>), 146.4 (Cq<sub>arom</sub>), 148.5 (Cq<sub>arom</sub>), 154.9 (Cq<sub>arom</sub>), 164.2 (d, <sup>2</sup>*J*<sub>*p*</sub>=6.0 Hz, CO), 164.9 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 165.8 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>). HRMS (TOF MS ES +) m/z: Calcd for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>9</sub>P [M + H]<sup>+</sup> 521.1683, Found 521.1686.

[5-acetyl-2-(4-acetylphenyldiazenyl)phenyloxy-Diethvl carbonyl]methylphosphonate (4e). Obtained as a red solid in 51% yield (116.5 mg) by reacting azobenzene 2e (133.1 mg) and oxidant 1b (603.2 mg) at 60 °C for 2.5 h. Rf=0.35 (DCM/MeOH 98:2); mp= 102–104°C; IR v<sub>max</sub>/cm<sup>-1</sup> 2983, 1765, 1682, 1263, 1221, 1048, 1019, 962; E/Z ratio > 95:5 (estimated by  $^1\text{H}$  NMR);  $^1\text{H}$  NMR (CDCl\_3)  $\delta$  1.33 (t, <sup>3</sup>J=7.1 Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 2.63 (s, 3H, CH<sub>3</sub>CO), 2.65 (s, 3H, CH<sub>3</sub>CO), 3.30 (d, <sup>2</sup>J<sub>p</sub>=21.6 Hz, 2H, CH<sub>2</sub>P), 4.22 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 7.80–8.10 (m, 7H,  $H_{arom}$ ); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.5 (d, <sup>3</sup>J<sub>p</sub>=5.9 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 26.9 (COCH<sub>3</sub>), 27.0 (COCH<sub>3</sub>), 34.2 (d, <sup>1</sup>J<sub>p</sub>=133.9 Hz, CH<sub>2</sub>P), 63.2 (d,  ${}^{2}J_{p} = 6.1$  Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 117.9 (CH<sub>arom</sub>), 123.6  $(CH_{arom})$ , 123.7 (2  $CH_{arom}$ ), 127.0  $(CH_{arom})$ , 129.5 (2  $CH_{arom}$ ), 139.3  $(Cq_{arom})$ , 140.2  $(Cq_{arom})$ , 146.5  $(Cq_{arom})$ , 148.9  $(Cq_{arom})$ , 155.0  $(Cq_{arom})$ , 164.4 (d, <sup>2</sup>*J*<sub>*p*</sub>=6.3 Hz, CO), 196.2 (COCH<sub>3</sub>), 197.4 (COCH<sub>3</sub>); HRMS (TOF MS ES+) m/z: Calcd for  $C_{22}H_{26}N_2O_7P\ [M+H]^+$  461.1472, Found 461.1473.

Diethyl [5-fluoro-2-(4-fluorophenyldiazenyl)phenyloxy-carbonyl] methylphosphonate (4f). Obtained as a red solid in 34% yield (46.5 mg) by reacting azobenzene 2f (72.4 mg) and oxidant 1b (398.4 mg) at 120 °C for 4 h in a sealed tube. Rf = 0.40 (DCM/MeOH 98:2); mp = 82–83 °C; IR  $v_{max}/cm^{-1}$  2985, 1763, 1593, 1500, 1490, 1263, 1231, 1105, 1048, 974; *E/Z* ratio = 90:10 (estimated by <sup>1</sup>H and <sup>19</sup>F NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.33 (t, <sup>3</sup>*J*=7.1 Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.18 + 3.28 (d,  ${}^{2}J_{p} = 21.6$  Hz, 2H, CH<sub>2</sub>P Z+E), 4.22 (m, 4H, PO- $(OCH_2CH_3)_2$ ), 6.25–7.30 (m, 4H, H<sub>arom</sub>), 7.80–8.00 (m, 3H, H<sub>arom</sub>); <sup>19</sup>F NMR (CDCl\_3)  $\delta$  -106.4 (E), -108.4 (E), -110.2 (Z), -111.8 (Z);  $^{13}\text{C}$ NMR (CDCl<sub>3</sub>)  $\delta$  16.3 (d,  ${}^{3}J_{p}$ =6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 34.0 (d,  ${}^{1}J_{p}$ = 133.7 Hz, CH<sub>2</sub>P), 63.0 (d,  ${}^{2}J_{p}$ =6.1 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 110.8 (d,  ${}^{2}J_{F}$ = 25.0 Hz, CH<sub>arom</sub>), 114.3 (d,  ${}^{2}J_{F} = 22.5$  Hz, CH<sub>arom</sub>), 116.1 (d,  ${}^{2}J_{F} =$ 22.8 Hz, 2 CH<sub>arom</sub>), 119.0 (d, <sup>3</sup>J<sub>F</sub>=9.8 Hz, CH<sub>arom</sub>), 125.2 (d, <sup>3</sup>J<sub>F</sub>=8.9 Hz, 2 CH<sub>arom</sub>), 140.6 (Cq<sub>arom</sub>), 149.1 (Cq<sub>arom</sub>), 149.5 (d, <sup>3</sup>J<sub>F</sub> = 11.6 Hz, Cq<sub>arom</sub>), 164.0 (d,  ${}^{2}J_{p}$ =6.3 Hz, CO), 164.3 (d,  ${}^{1}J_{F}$ =252.7 Hz, Cq<sub>arom</sub>), 164.6 (d,  $J_F = 251.5 \text{ Hz}$ , Cq<sub>arom</sub>); HRMS (TOF MS ES+) m/z: Calcd for  $C_{18}H_{20}F_2N_2O_5P [M+H]^+$  413.1072, Found 413.1066.

Diethvl [4-fluoro-2-(3-fluorophenyldiazenyl)phenyloxycarbonyl]methylphosphonate (4g). Obtained as a red solid in 47% yield (96.5 mg) by reacting azobenzene 2g (108.2 mg) and oxidant **1 b** (600.1 mg) at 60 °C for 21 h. Rf = 0.30 (DCM/MeOH 98:2); IR  $v_{max}$ cm<sup>-1</sup> 2984, 1765, 1593, 1495, 1479, 1254, 1231, 1112, 1095, 1048, 1014, 961; E/Z ratio = 80:20 (estimated by <sup>1</sup>H and <sup>19</sup>F NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.35 (t, <sup>3</sup>*J*=7.1 Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.31+3.36 (d, <sup>2</sup>*J*<sub>p</sub>= 21.8 Hz, 2H, CH<sub>2</sub>P E+Z), 4.24 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 6.75-7.80 (m, 7H,  $H_{arom}$ ); <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  -113.8 (*E*+*Z*), -111.8 (*Z*), -111.7 (*E*); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.4 (d, <sup>3</sup> $J_p$  = 5.8 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 33.8 (d, <sup>1</sup> $J_p$  = 133.7 Hz, CH<sub>2</sub>P Z), 34.1 (d, <sup>1</sup> $J_p$  = 133.6 Hz, CH<sub>2</sub>P E), 63.1 (d, <sup>2</sup> $J_p$  = 5.9 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 104.1 (d,  ${}^{2}J_{F}$ =24.8 Hz, CH<sub>arom</sub>), 108.1 (d,  ${}^{2}J_{F}$ = 22.7 Hz, CH<sub>arom</sub>), 118.7 (d,  ${}^{2}J_{F} = 22.1$  Hz, CH<sub>arom</sub>), 119.2 (d,  ${}^{2}J_{F} =$ 24.4 Hz, CH<sub>arom</sub>), 121.7 (d,  ${}^{4}J_{F}$  = 2.3 Hz, CH<sub>arom</sub>), 124.6 (d,  ${}^{3}J_{F}$  = 8.5 Hz,  $CH_{arom}$ ), 130.4 (d,  ${}^{3}J_{F} = 8.4 Hz$ ,  $CH_{arom}$ ), 144.6 (d,  ${}^{3}J_{F} = 6.1 Hz$ ,  $Cq_{arom}$ ), 145.1 (d,  ${}^{4}J_{F} = 2.7$  Hz, Cq<sub>arom</sub>), 153.9 (d,  ${}^{3}J_{F} = 7.0$  Hz, Cq<sub>arom</sub>), 160.9 (d,

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 $^1J_F{=}$  246.5 Hz, Cq\_arom), 163.3 (d,  $^1J_F{=}$  246.5 Hz, Cq\_arom), 164.5 (d,  $^2J_P{=}$  6.3 Hz, CO); HRMS (TOF MS ES +) m/z: Calcd for C\_{18}H\_{20}F\_2N\_2O\_5P [M + H]^+ 413.1072, Found 413.1081.

Diethyl [3-fluoro-2-(2-fluorophenyldiazenyl)phenyloxycarbonyl]methylphosphonate (4h). Obtained as a red viscous oil in 34% yield (69.6 mg) by reacting azobenzene 2h (108.9 mg) and oxidant 1b (594.0 mg) at 90 °C for 6 h in a sealed tube. Rf=0.35 (DCM/MeOH 98:2); IR  $\nu_{max}/cm^{-1}$  2990, 1765, 1484, 1466, 1266, 1232, 1093, 1048, 1010, 975; *E/Z* ratio = 60:40 (estimated by <sup>19</sup>F NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.34 (t, <sup>3</sup>*J*=6.5 Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.19+3.25 (d, <sup>2</sup>J<sub>p</sub>=21.3 Hz, 2H, CH<sub>2</sub>P Z+E), 4.21 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 6.75–7.80 (m, 7H, H<sub>arom</sub>); <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  -123.6 (d, <sup>7</sup>J<sub>FP</sub>=2.6 Hz, *E*), -122.5 (d,  ${}^{7}J_{FF} = 4.1$  Hz, Z), -120.0 (E), -118.4 (d,  ${}^{7}J_{FF} = 4.1$  Hz, Z);  ${}^{13}C$  NMR (CDCl<sub>3</sub>)  $\delta$  16.3 (d,  ${}^{3}J_{p}$ =6.8 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> Z), 16.4 (d,  ${}^{3}J_{p}$ =6.1 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> E), 34.0 (dd,  ${}^{1}J_{p} = 133.5$  Hz,  ${}^{6}J_{F} = 3.5$  Hz, CH<sub>2</sub>P), 63.0 (d,  $^{2}J_{p} = 6.2$  Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2 E</sub>), 63.2 (d,  $^{2}J_{p} = 5.9$  Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> Z), 114.0 (d,  ${}_{2}J_{F}$ =20.0 Hz, CH<sub>arom</sub> Z), 115.3 (d,  ${}^{2}J_{F}$ =20.6 Hz, CH<sub>arom</sub> E), 116.7 (d,  ${}^{2}J_{F}$  = 19.1 Hz, CH<sub>arom</sub> Z), 117.2 (d,  ${}^{2}J_{F}$  = 22.4 Hz, CH<sub>arom</sub> E), 117.4 (CH<sub>arom</sub> E), 118.9 (d,  ${}^{4}J_{F}$  = 3.2 Hz, CH<sub>arom</sub> Z), 119.5 (CH<sub>arom</sub> Z), 119.6 (d,  ${}^{4}J_{F}$  = 3.2 Hz, CH<sub>arom</sub> E), 124.0 (d,  ${}^{4}J_{F}$  = 3.5 Hz, CH<sub>arom</sub> Z), 124.6 (d,  ${}^{4}J_{F} = 3.5$  Hz, CH<sub>arom</sub> E), 129.1 (d,  ${}^{3}J_{F} = 8.9$  Hz, CH<sub>arom</sub> Z), 130.5 (d,  ${}^{3}J_{F} = 7.4$  Hz, CH<sub>arom</sub> Z), 131.5 (d,  ${}^{3}J_{F} = 10.1$  Hz, CH<sub>arom</sub> E), 133.7 (d,  ${}^{3}J_{F} =$ 8.5 Hz, CH<sub>arom</sub> E), 141.3 (d, <sup>3</sup>J<sub>F</sub>=7.0 Hz, Cq<sub>arom</sub>), 142.1 (Cq<sub>arom</sub>), 157.9 (d,  ${}^{1}J_{F} = 136.1$  Hz, Cq<sub>arom</sub>), 161.4 (d,  ${}^{1}J_{F} = 134.1$  Hz, Cq<sub>arom</sub>), 164.3 (d,  ${}^{2}J_{P} = 5.9$  Hz, CO), the hindered CqN=N is missing; HRMS (TOF MS ES +) m/z: Calcd for  $C_{18}H_{20}F_2N_2O_5P$  [M+H]<sup>+</sup> 413.1072, Found 445,1081.

[4-chloro-2-(3-chlorophenyldiazenyl)phenyloxy-Diethvl carbonyl]methylphosphonate (4j). Obtained as a red viscous oil in 48% yield (105.5 mg) by reacting azobenzene 2j (124.2 mg) and oxidant 1b (599.8 mg) at 60 °C for 1 h. Rf = 0.35 (DCM/MeOH 98:2); IR  $v_{max}/cm^{-1}$  2981, 1771, 1472, 1250, 1195, 1113, 1094, 1048, 1013, 975; *E/Z* ratio = 90:10 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.37 (t,  ${}^{3}J = 7.1$  Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.21 + 3.33 (d,  ${}^{2}J_{p} = 21.6$  Hz, 2H, CH<sub>2</sub>P Z+E), 4.27 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 7.10-7.90 (m, 7H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.4 (d,  ${}^{3}J_{p}$ =6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 34.1 (d,  ${}^{1}J_{p}$ = 133.4 Hz, CH<sub>2</sub>P), 63.1 (d,  ${}^{2}J_{p} = 6.1$  Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 117.7 (CH<sub>arom</sub>), 122.2 ( $CH_{arom}$ ), 123.1 ( $CH_{arom}$ ), 124.6 ( $CH_{arom}$ ), 130.3 ( $CH_{arom}$ ), 131.7 (CH\_{arom}), 132.2 (CH\_{arom}), 132.9 (Cq\_{arom}), 135.3 (Cq\_{arom}), 144.2 (Cq\_{arom}), 147.4 (Cq<sub>arom</sub>), 153.3 (Cq<sub>arom</sub>), 164.3 (d, <sup>2</sup>J<sub>P</sub>=6.2 Hz, CO); HRMS (TOF MS ES+) m/z: Calcd for  $C_{18}H_{20}Cl_2N_2O_5P\ [M+H]^+$  445.0481, Found 445.0490.

Diethvl [3-chloro-2-(2-chlorophenyldiazenyl)phenyloxycarbonyl]methylphosphonate (4k). Obtained as a red viscous oil in 36% yield (43.1 mg) by reacting azobenzene 2k (66.8 mg) and oxidant 1b (329.2 mg) at 90°C for 6 h in a sealed tube. Rf=0.45 (DCM/MeOH 98:2); IR  $\nu_{max}/cm^{-1}$  2931, 1770, 1268, 1230, 1048, 1019, 953; *E/Z* ratio = 70:30 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$ 1.31 + 1.33 (t,  ${}^{3}J = 7.1$  Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> Z+E), 3.16 + 3.19 (d,  $^{2}J_{p} = 21.3$  Hz, 2H, CH<sub>2</sub>P Z+E), 4.18 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 6.95-7.75 (m, 7H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.5 (d, <sup>3</sup>J<sub>p</sub> = 5.9 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 34.4 (d, <sup>1</sup>J<sub>p</sub>=131.8 Hz, CH<sub>2</sub>P Z), 34.5 (d, <sup>1</sup>J<sub>p</sub>=132.8 Hz, CH<sub>2</sub>P E), 63.0 (d, <sup>2</sup>J<sub>p</sub>=6.3 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 117.4 (CH<sub>arom</sub> Z), 117.9 (CH<sub>arom</sub> E), 121.8 (CH<sub>arom</sub> Z), 123.0 (CH<sub>arom</sub> E), 126.8 (CH<sub>arom</sub> Z), 127.6 (CH<sub>arom</sub> E), 128.3 (CH<sub>arom</sub> Z), 128.8 (CH<sub>arom</sub> E), 129.4 (CH<sub>arom</sub> Z), 130.4 (CH<sub>arom</sub> Z), 130.5 (CH<sub>arom</sub> E), 130.8 (CH<sub>arom</sub> Z), 130.9 (CH<sub>arom</sub> E), 132.9 (CH<sub>arom</sub> E), 134.1 (Cq<sub>arom</sub>), 135.8 (Cq<sub>arom</sub>), 140.4 (Cq<sub>arom</sub>), 149.3 (Cq<sub>arom</sub>), 163.6 (Cq<sub>arom</sub>), 164.2 (d,  ${}^{2}J_{P}$ =6.2 Hz, CO); HRMS (TOF MS ES+) m/z: Calcd for  $C_{18}H_{20}CI_2N_2O_5P$  [M + H]<sup>+</sup> 445.0481, Found 445.0493.

Diethyl [5-(trifluoromethyl)-2-(4-(trifluoromethyl)phenyldiazenyl)phenyloxycarbonyl]methylphosphonate (41). Obtained as a red viscous oil in 44% yield (140.8 mg) by reacting **21** (159.2 mg) and oxidant **1b** (594.7 mg) at 90 °C for 23 h in a sealed tube. Rf=0.30 (DCM/MeOH 98:2); IR  $v_{max}$ /cm<sup>-1</sup> 2989, 1771, 1321, 1126, 1013; *E/Z* ratio > 95:5 (estimated by <sup>1</sup>H and <sup>19</sup>F NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.34 (t, <sup>3</sup>*J*=7.1 Hz, 6H, PO(OCH<sub>2</sub>*CH*<sub>3</sub>)<sub>2</sub>), 3.30 (d, <sup>2</sup>*J*<sub>p</sub>=21.6 Hz, 2H, CH<sub>2</sub>P), 4.22 (m, 4H, PO(O*CH*<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 7.57 (d, <sup>4</sup>*J*=1.5 Hz, 1H, H<sub>arom</sub>), 7.64 (dd, <sup>3</sup>*J*=8.7 Hz, <sup>4</sup>*J*=1.5 Hz, 1H, H<sub>arom</sub>), 7.80 (d, <sup>3</sup>*J*=8.1 Hz, 2H, H<sub>arom</sub>), 7.91 (d, <sup>3</sup>*J*=8.4 Hz, 1H, H<sub>arom</sub>), 8.04 (d, <sup>3</sup>*J*=8.1 Hz, 2H, H<sub>arom</sub>), 7.91 (d, <sup>3</sup>*J*=8.4 Hz, 1H, H<sub>arom</sub>), 8.04 (d, <sup>3</sup>*J*=8.1 Hz, 2H, H<sub>arom</sub>), 7.91 (d, <sup>3</sup>*J*=8.4 Hz, 1H, H<sub>arom</sub>), 8.04 (d, <sup>3</sup>*J*=8.1 Hz, 2H, H<sub>arom</sub>), <sup>19</sup>F NMR (CDCl<sub>3</sub>)  $\delta$  -62.87, -62.78; <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.5 (d, <sup>3</sup>*J*<sub>p</sub>=6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 34.2 (d, <sup>1</sup>*J*<sub>p</sub>=133.8 Hz, CH<sub>2</sub>P), 63.2 (d, <sup>2</sup>*J*<sub>p</sub>=6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 118.4 (CH<sub>arom</sub>), 121.2 (q, <sup>3</sup>*J*<sub>F</sub>=3.5 Hz, CH<sub>arom</sub>), 123.8 (2CH<sub>arom</sub>), 124.2 (q, <sup>3</sup>*J*<sub>F</sub>=3.4 Hz, CH<sub>arom</sub>), 126.6 (q, <sup>3</sup>*J*<sub>F</sub>=3.5 Hz, 2CH<sub>arom</sub>), 133.9 (q, <sup>2</sup>*J*<sub>F</sub>=31.4 Hz, 2Cq<sub>arom</sub>), 145.9 (Cq<sub>arom</sub>), 148.8 (Cq<sub>arom</sub>), 154.4 (Cq<sub>arom</sub>), 164.2 (d, <sup>2</sup>*J*<sub>p</sub>=5.4 Hz, CO), the CF<sub>3</sub> is missing; HRMS (TOF MS ES+) m/z: Calcd for C<sub>20</sub>H<sub>20</sub> F<sub>6</sub>N<sub>2</sub>O<sub>5</sub>P [M+H]<sup>+</sup> 413.1009, Found 413.1015.

Diethyl [5-nitro-2-(4-nitrophenyldiazenyl)phenyloxycarbonyl]methylphosphonate (4m). Obtained as a red solid in 13% yield (30.4 mg) by reacting azobenzene 2m (136.3 mg) and oxidant 1b (593.9 mg) at 90 °C for 6 h in a sealed tube. Rf=0.40 (DCM/MeOH 98:2); mp = 184–186 °C; IR v<sub>max</sub>/cm<sup>-1</sup> 2995, 1765, 1524, 1350, 1253, 1200, 1163, 1016; *E/Z* ratio=90:10 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.36 (t, <sup>3</sup>*J*=7.1 Hz, 6H, PO(OCH<sub>2</sub>*CH*<sub>3</sub>)<sub>2</sub>), 3.20 + 3.32 (d, <sup>2</sup>*J*<sub>p</sub>=21.6 Hz, 2H, CH<sub>2</sub>P *E/Z*), 4.24 (m, 4H, PO(OCH<sub>2</sub>*CH*<sub>3</sub>)<sub>2</sub>), 7.95–8.45 (m, 7H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 16.5 (d, <sup>3</sup>*J*<sub>p</sub>=5.7 Hz, PO(OCH<sub>2</sub>*CH*<sub>3</sub>)<sub>2</sub>), 34.2 (d, <sup>1</sup>*J*<sub>p</sub>=133.5 Hz, CH<sub>2</sub>P), 63.4 (d, <sup>2</sup>*J*<sub>p</sub>=6.1 Hz, PO(OCH<sub>2</sub>*CH*<sub>3</sub>)<sub>2</sub>), 118.5 (CH<sub>arom</sub>), 119.8 (CH<sub>arom</sub>), 122.4 (CH<sub>arom</sub>), 124.6 (2CH<sub>arom</sub>), 125.0 (2CH<sub>arom</sub>), 164.0 (d, <sup>2</sup>*J*<sub>p</sub>=5.7 Hz, CO); HRMS (TOF MS ES +) m/z: Calcd for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>9</sub>P [M+H]<sup>+</sup> 467.0962, Found 467.0970.

Diethyl [6-methoxy-3-(4-methoxyphenyldiazenyl)phenyloxycarbonyl]methylphosphonate (4'n). Obtained as a red solid in 50% yield (109.7 mg) by reacting azobenzene 2n (121.0 mg) and oxidant 1 b (605.8 mg) at 60  $^\circ\text{C}$  for 20 min. Rf = 0.50 (DCM/MeOH 95:5); mp = 73–75 °C; IR  $\nu_{max}\!/cm^{-1}$  2983, 1770, 1600, 1504, 1261, 1195, 1106, 1050, 1021, 975; E/Z ratio > 95:5 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.36 (t, <sup>3</sup>J=7.2 Hz, 6H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.22 (d, <sup>2</sup>J<sub>p</sub> = 21.6 Hz, 2H, CH<sub>2</sub>P), 3.82 (s, 3H, OCH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 4.22 (m, 4H, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 6.95 (d, <sup>3</sup>J=8.8 Hz, 2H,  $H_{arom}$ ), 7.03 (d,  ${}^{3}J = 8.8$  Hz, 1H,  $H_{arom}$ ), 7.64 (d,  ${}^{4}J = 2.2$  Hz, 1H,  $H_{arom}$ ), 7.80 (dd,  ${}^{3}J = 8.8$  Hz,  ${}^{4}J = 2.2$  Hz, 1H,  $H_{arom}$ ), 7.83 (d,  ${}^{3}J = 9.2$  Hz, 2H,  $H_{arom}$ ); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  16.4 (d, <sup>3</sup>J<sub>p</sub>=6.0 Hz,  $PO(OCH_2CH_3)_2)$ , 34.0 (d,  ${}^1J_p = 133.0 \text{ Hz}$ ,  $CH_2P$ ), 55.5 (OCH<sub>3</sub>), 56.1 (OCH<sub>3</sub>), 62.9 (d, <sup>2</sup>J<sub>p</sub>=6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 111.9 (CH<sub>arom</sub>), 114.2 (2 CH<sub>arom</sub>), 114.9 (CH<sub>arom</sub>), 124.4 (CH<sub>arom</sub>), 124.5 (2 CH<sub>arom</sub>), 140.0 (Cq<sub>arom</sub>), 146.7 (Cq $_{arom}$ ), 146.8 (Cq $_{arom}$ ), 152.9 (Cq $_{arom}$ ), 161.8 (Cq $_{arom}$ ), 163.7 (d,  $^{2}J_{P}$  = 6.0 Hz, CO). HRMS (TOF MS ES +) m/z: Calcd for C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>P [M +H]<sup>+</sup> 437.1472, Found 437.1469.

**Diethyl** [2-(2-(diethylphosphonacetoxy)phenyldiazenyl)phenyloxycarbonyl]methylphosphonate (6a). Obtained as a red viscous oil in up to 18% yield by reacting azobenzene 2 a (91.3 mg) and oxidant 1b (596.3 mg), in the case of a prolonged reaction time. Rf = 0.10 (DCM/MeOH 98:2); IR  $v_{max}/cm^{-1}$  2985, 1770, 1261, 1229, 1046, 961 ; *E/Z* ratio > 95:5 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.32 (t, <sup>3</sup>*J*=7.1 Hz, 12H, 2 PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.20 (d, <sup>2</sup>*J*<sub>p</sub>=21.3 Hz, 4H, CH<sub>2</sub>P), 4.19 (m, 8H, 2 PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 7.15-7.80 (m, 8H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  16.4 (d, <sup>3</sup>*J*<sub>p</sub>=5.9 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 34.0 (d, <sup>1</sup>*J*<sub>p</sub>=134.4 Hz, CH<sub>2</sub>P), 63.0 (d, <sup>2</sup>*J*<sub>p</sub>=6.0 Hz, PO(OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 121.9 (2 CH<sub>arom</sub>), 122.8 (2 CH<sub>arom</sub>), 129.2 (2 CH<sub>arom</sub>), 130.6 (CH<sub>arom</sub>), 132.0 (CH<sub>arom</sub>), 144.3 (Cq<sub>arom</sub>), 153.0 (Cq<sub>arom</sub>), 164.1 (d, <sup>2</sup>*J*<sub>p</sub>=5.9 Hz, CO), the hindered CqN=N is missing; HRMS (TOF MS ES +) m/z: Calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>10</sub>NaP<sub>2</sub> [M+Na]<sup>+</sup> 593.1424, Found 593.1431.

**Dimethyl [2-(phenyldiazenyl)phenyloxycarbonyl]-methylphosphonate (8a)**. Obtained as a red viscous oil in 48% yield (83.4 mg) by reacting azobenzene **2a** (91.3 mg) and oxidant **1c** (567.2 mg) for 20 min at 60 °C. Rf=0.29 (DCM/MeOH 98:2); IR  $v_{max}/cm^{-1}$  2958,

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1765, 1452, 1402, 1263, 1195, 1101, 1054; *E/Z* ratio = 85:15 (estimated by <sup>1</sup>H NMR); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  3.22+3.32 (d, <sup>2</sup> $J_p$ = 21.6 Hz, 2H, CH<sub>2</sub>P Z+E), 3.83 + 3.85 (d, <sup>3</sup> $J_p$ =11.4 Hz,6H, PO(OCH<sub>3</sub>)<sub>2</sub> Z +E), 6.90-7.95 (m, 9H, H<sub>arom</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  33.2 (d, <sup>1</sup> $J_p$ = 135.2 Hz, CH<sub>2</sub>P), 53.5 (d, <sup>2</sup> $J_p$ =6.2 Hz, PO(OCH<sub>3</sub>)<sub>2</sub>), 117.7 (CH<sub>arom</sub>), 123.2 (3 CH<sub>arom</sub>), 127.1 (CH<sub>arom</sub>), 129.1 (2 CH<sub>arom</sub>), 131.5 (CH<sub>arom</sub>), 132.1 (CH<sub>arom</sub>), 143.9 (Cq<sub>arom</sub>), 148.5 (Cq<sub>arom</sub>), 152.8 (Cq<sub>arom</sub>), 164.3 (d, <sup>2</sup> $J_p$ = 5.9 Hz, CO); HRMS (TOF MS ES +) m/z: Calcd for C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>NaO<sub>5</sub>P [M + Na]<sup>+</sup> 371.0767, Found 371.0775.

[2-(Phenyldiazenyl)phenyloxycarbonyl]methylphospho-nic acid (9a). To a solution of compound 4a (188 mg, 0.5 mmol, 1 eq.) in anhydrous DCE (5 mL) was added BSTFA (0.4 mL, 1.5 mmol, 3 eq.). After stirring at r.t. for 1 h, the reactive medium was cooled to -10°C then TMSI (0.2 mL, 1.5 mmol, 3 eq.) was added. After further stirring of the mixture from 0°C to r.t. for 3 h, the solvent was evaporated under reduced pressure then the crude mixture was diluted in MeOH (5 mL) and filtered. The filtrate was concentrated then the residue triturated in Et<sub>2</sub>O and the supernatant was removed to yield compound 8a as a red solid (155 mg, 90% yield). mp = 121-123 °C; IR  $v_{max}$ /cm<sup>-1</sup> 2952, 1759, 1258, 1221, 1113, 1099, 954; <sup>1</sup>H NMR (Acetone d6)  $\delta$  3.42 (d, <sup>2</sup>J<sub>p</sub>=21.3 Hz, 2H, CH<sub>2</sub>P), 7.40 (m, 2H, H<sub>arom</sub>), 7.54 (m, 4H, H<sub>arom</sub>), 7.81 (d, <sup>3</sup>J=7.8 Hz, 1H, H<sub>arom</sub>), 7.96 (d,  $^{3}J$  = 7.2 Hz, 2H, H<sub>arom</sub>), 10.17 (bs, 2H, PO<sub>3</sub>H<sub>2</sub>); <sup>13</sup>C NMR (Acetone d6)  $\delta$ 36.0 (d,  ${}^{1}J_{p} = 132.8$  Hz, CH<sub>2</sub>P), 117.7 (CH<sub>arom</sub>), 124.0 (2 CH<sub>arom</sub>), 124.6  $({\rm CH}_{\rm arom}), \ 127.6 \ ({\rm CH}_{\rm arom}), \ 130.2 \ (2 \ {\rm CH}_{\rm arom}), \ 132.4 \ ({\rm CH}_{\rm arom}), \ 132.2$ (CH<sub>arom</sub>), 144.8 (Cq<sub>arom</sub>), 150.0 (Cq<sub>arom</sub>), 153.6 (Cq<sub>arom</sub>), 165.8 (d,  ${}^{2}J_{P} =$ 5.0 Hz, CO); HRMS (TOF MS ES+) m/z: Calcd for  $C_{14}H_{14}N_2O_5P$  [M+ H]<sup>+</sup> 321.0635, Found 321.0641.

Aqueous stability of compound 9 a at pH 7, 5 and 9.3. For aqueous stability at pH 7, compound 9 a (2 mg) was dissolved in  $D_2O$  (500 µL) then <sup>1</sup>H NMR was realized regularly up to 96 h at room temperature. For aqueous stability at pH 5 and 9.3, compound 9 a (2 mg) was dissolved in  $D_2O$  (490 µL). Then 10 µL of a solution of TFA in  $D_2O$  (5.10<sup>-4</sup> M) or LiOH in  $D_2O$  (10<sup>-3</sup> M) was added respectively and <sup>1</sup>H NMR of this mixture was realized regularly up to 96 h at room temperature. <sup>1</sup>H NMR of phosphonoacetic acid was used as a reference for the estimation of the hydrolysis phenomenon.

Photoisomerisation study of compound 9a. UV-visible absorption spectra were recorded using quartz cuvettes on a Cary 4000 Agilent UV-Vis spectrophotometer. Spectrophotometric-grade water was used as solvent. Irradiation experiments were performed in a 1 cm path length quartz cuvette using a Hg/Xe lamp (Hamamatsu, LC6 Lightningcure, 200 W) equipped with a narrow band interference filter of the appropriate wavelength (Semrock FF01-320/40-25 for  $\lambda$ irr  $\approx$  320 nm, FF01-406/15-25 for  $\lambda$ irr = 405 nm). The sample of compound 9a in water solutions at pH 4.7, 7 and 9 in the quartz cuvette was irradiated with light at 320 nm (for  $E \rightarrow Z$  isomerisation) and 405 nm (for  $Z \rightarrow E$  isomerisation) until no further evolution in absorbance was observed. For the half-life determination a solution of 9a (1 mg) in water (2 mL) at pH 4.7, 7 and 9 in a 1 cm pathlength quartz cuvette was irradiated with UV light (320 nm, for 30 sec.). The solution was then left in the dark at 20  $^\circ\text{C},$  and the absorbance at 324 nm was monitored for two to three days until degradation was observed. The kinetic constants of the thermal isomerisation processes were extracted by exponential fitting of the absorbance at 324 nm, according to a first-order kinetic model. PSS compositions were determined by <sup>1</sup>H NMR analyses. A sample of compound 9a (2 mg) in  $D_2O$  (500  $\mu$ L) was placed in an NMR tube and irradiated. Then, a <sup>1</sup>H NMR spectrum was acquired. The Z/E ratio was estimated by comparing the CH<sub>2</sub>P <sup>1</sup>H-NMR integrations of the cis and trans isomers at 3.10 and 3.30 ppm respectively.

### **Supporting Information**

The data that support the findings of this study are available in the supplementary material of this article.

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### **Conflict of Interests**

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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