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Chemoselective reaction of ethane-1,2-dithiol, hydrazines, and hydroxylamine onto γ-keto allyl phosphonates and phosphine oxides

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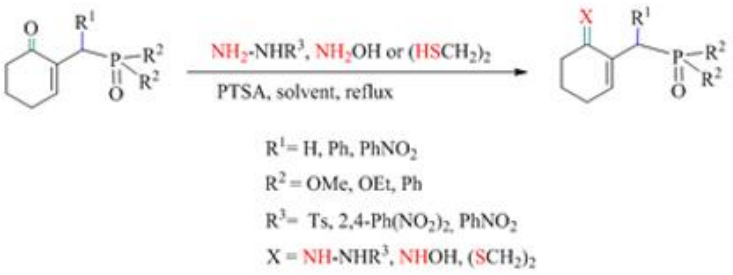
Abstract

An efficient protocol involving highly chemoselective reaction of ethane-1,2-dithiol, hydroxylamine, and hydrazine derivatives with a series of γ-keto allyl phosphonates in the presence of *p*-toluene sulfonic acid (PTSA), is described herein. All the synthesized compounds are obtained in 76-98% yields and fully characterized.



Keywords: Keto phosphonate, protection, oximophosphonate, hydrazonophosphonate, thioketal

Introduction

We have recently reported an efficient synthetic method for a new series of γ-keto allyl phosphonates **1a-e**.[1] Now, our goal is to investigate their functionalization at the α-phosphonate carbon atom as functionalized phosphonates which are well known for their interesting biological activities.[2-4] For this purpose, we first envisioned, without prior protection of the ketone moiety,[5-6] their deprotonation with an excess of strong bases including LDA and NaH then the trapping of the intermediate enolates with various electrophiles (alkyl, alkenyl or benzyl halides, bromine, and aldehydes).[7-10] Among these reactions, we intended to particularly develop the Wittig-Horner olefination using various aldehydes as electrophiles, which would afford a variety of 1,3-dienes that are employed as useful substrates in the reaction of Diels-Alder.[11]

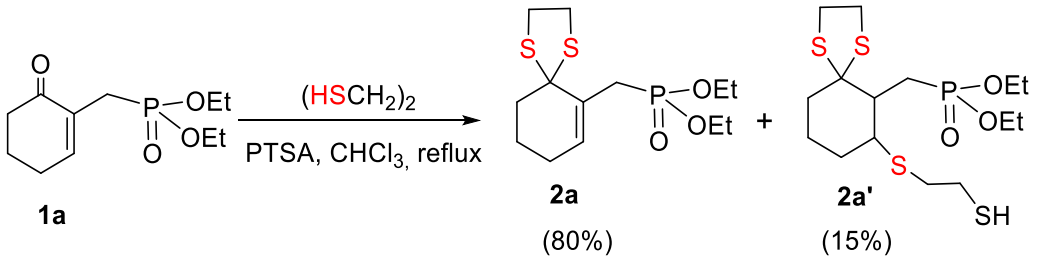
First, we attempted the deprotonation of the γ-keto allyl phosphonate **1a** at 0 °C by NaH or LDA (1-6 equiv) in THF, followed by the addition of bromine (1-2 equiv) at room temperature then at reflux for 4 h. Unfortunately, the starting material **1a** was completely recovered. Moreover, all the reactions of compound **1a** either with NBS (AIBN in CCl_4) or under the previous conditions (NaH or LDA), with the considered halogenated derivatives failed.[12]

Next, we explored the reaction of Wittig-Horner starting from the additon of the ketophosphonate **1a** to a suspension of NaH (4 equiv) in THF at 0 °C then at room temperature, followed by the addition of benzaldehyde (2 equiv). We have observed that, at room temperature, no reaction occurred but in refluxing THF, an incomplete aromatization of **1a** took place.[13-15]

On the basis of these unsuccessful preliminary results, we decided to first establish the suitable experimental conditions for the protection of the ketone moiety of the ketophosphonate **1a** using ethylene glycol or ethane-1,2-dithiol commonly used for this purpose. At the same time, we envisionned to explore the reaction of other *N*-nucleophiles including hydrazines, tosylhydrazines,[16-24] and hydroxylamine[25-31-32-33] on the enone moiety. Hence, we wish to report in this paper our results on the chemoselective reaction of these *S*- and *N*-nucleophiles on a series of γ-keto allyl phosphonates.

Results and discussion

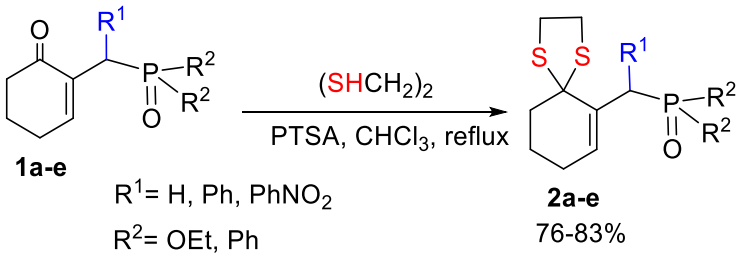
Under the conventional conditions for the protection of ketones with ethane-1,2-diol (1equiv) in the presence of 30% of PTSA, the ketophosphonate **1a** (1 equiv) in refluxing toluene, using a Dean-Stark apparatus, was partially converted, within 48 h, into a complex mixture.[12] Alternatively, on treatment of phosphonate **1a** with ethane-1,2-dithiol (1.2 equiv) and PTSA (1 equiv) in refluxing chloroform, we have observed the formation of the desired thioketal **2a** in 80% yield, together with the compound **2a'** (15%) resulting from a further conjugate addition of ethane-1,2-dithiol on the enone moiety of the ketal **2a** (Scheme 1).



1a **2a** (80%) **2a'** (15%)

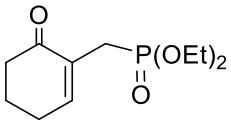
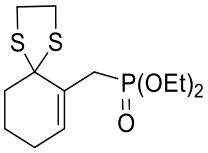
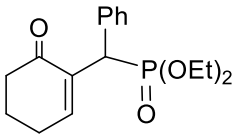
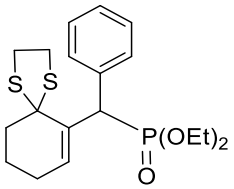
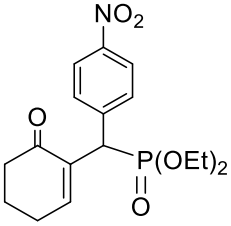
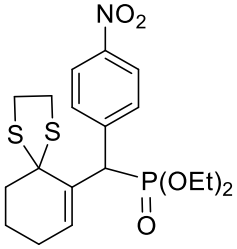
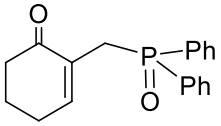
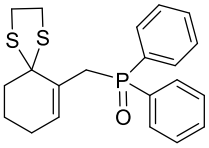
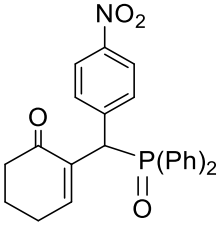
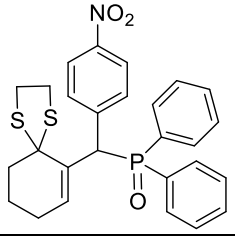
Scheme 1. Synthesis of the thioketal **2a** and its derivative **2a'**.

Next, we turned our attention to improving the selectivity of such reaction in favor of the ketal **2a**. We first focused our efforts on the ratios of the ketophosphonate **2a**/ethane-1,2-dithiol in the presence of PTSA in refluxing chloroform. After optimising the experimental conditions, we have found that the reaction of a slight excess of the ketophosphonate **1a** (1 equiv) and PTSA (1 equiv) with regard to ethane-1,2-dithiol (0.9 equiv), selectively afforded the thioketal phosphonate **2a** in 80% (Scheme 2, table 1, entry 1).



Scheme 2. Synthesis of thioketals phosphonates **2a-e**.

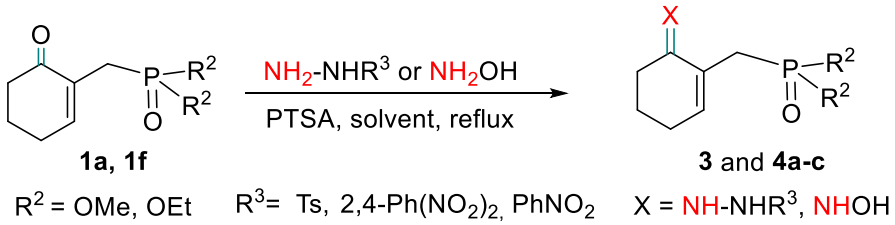
Table 1. Synthesis of thioketals phosphonates **2a-e**

Entry	Phosphonate **1**		Compound **2**		Yield **2** (%)
1	**1a**		**2a**		80
2	**1b**		**2b**		76
3	**1c**		**2c**		78
4	**1d**		**2d**		83
5	**1e**		**2e**		81

This thioketalisation reaction was successfully performed, under the above conditions (refluxing chloroform, 0.9 equiv of ethane-1,2-dithiol) on various ketophosphonates **1b-e** differently substituted at the

β'-carbon close to the phosphonate moiety. The corresponding thioketals phosphonates **2b-e** were obtained in 76-83% yields with a high selectivity (Scheme 2, table 1, entries 2-5).

Encouraged by these successful results, we next focused our efforts on screening various N-nucleophiles likely to react with carbonyl moiety of the keto phosphonates **1a** and **1f**. Interestingly, on treatment of the ketophosphonate **1f** with hydroxylamine chlorohydrate (1.2 equiv) and PTSA (1 equiv) in refluxing methanol, the oximophosphonate **3** was obtained in 83% yield (Scheme 3, table 2, entry 1).

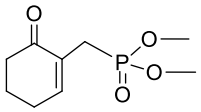
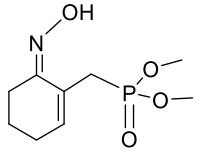
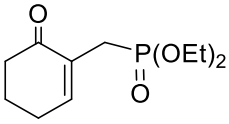
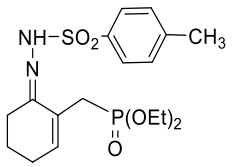
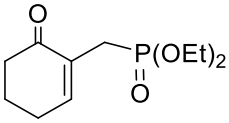
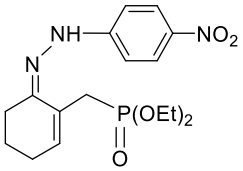
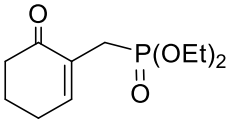
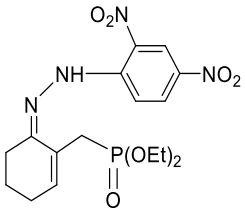


Scheme 3. Synthesis of the oximophosphonate **3** and the hydrazonophosphonates **4a-c**.

Unfortunately, under the conditions described above (PTSA, refluxing methanol), all the reactions of phosphonate **1a** with primary amines including ethylamine, methylamine, isopropylmaine and benzylamine, failed and the starting materials were recovered.

Finally, in refluxing methanol, the ketophosphonate **1a** reacted with tosylhydrazine (1.1 equiv) or phenylhydrazines (1.1 equiv) in the presence of PTSA (1 equiv), affording the corresponding hydrazonophosphonates **4b-c** in 86-96% yields**.**

Table 2. Conversion of keto phosphonates **1f** and **1a** into oximophosphonate **3** and hydrazonophosphonates **4a-c**

Entry		Phosphonate **1**		Compound **3** or **4**	Yield (%)
1	**1f**		**3**		83
2	**1a**		**4a**		93
3	**1a**		**4b**		86
4	**1a**		**4c**		96

Conclusions

We have shown that PTSA-mediated reaction of ethane-1,2-dithiol in refluxing chloroform as well as hydroxylamine and some hydrazines derivatives in refluxing methanol onto various γ-keto allyl phosphonates, affording the corresponding thioketals, oximo- and hydrazonophosphonates in good yields and with high chemoselectivity.

Experimental Section

General. All ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$ as the solvent, at 300 and 75 MHz, respectively, using tetramethylsilane. Chemical shifts □ are given in ppm and the coupling constants *J* in Hz. High resolution mass spectra (HRMS) were recorded as TOF-HRMS on a micromass mass spectrometer. The electronic impact (EI) mass spectra were recorded at 70 eV. Analytical thin layer chromatography (TLC) was carried out on aluminium plates precoated with silica gel 60 F254. The Visualization was achieved with UV light at 254 nm. Column chromatography was performed using silicagel (70-230 mesh ASTM) and a gradient solvent system (dichloromethane/ether) as eluents.

General procedure for the preparation of the thioketal phosphonates (2a-e). A mixture of the ketophosphonate **1** (1 equiv), ethane-1,2-dithiol (0.9 equiv) and PTSA (1 equiv) in 20 mL of $CHCl_3$, was heated with stirring in an oil bath at 80 °C for 4 h. The progress of the reaction was monitored by TLC using dichloromethane-ether. The mixture was neutralized with an aqueous solution of 4M hydrochloric acid and extracted with $CHCl_3$. The combined organic layers were neutralized with $NaHCO_3$ and washed with saturated NaCl solution. These layers were further dried and concentrated. The residue was purified by a column chromatography on silica gel (20% dichloromethane/ether) to give the pure thioketals phosphonates **2a-e** as solids except **2a** and **2b** that are obtained as yellow oils.

Diethyl (1,4-dithiaspiro[4.5]dec-6-en-6-ylmethyl)phosphonate (2a). Yield: 542 mg (80%), 2.03 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, *J* 6.0 Hz, 6H), 1.78 (m, 2H), 2.08 (m, 2H), 2.25 (t, *J* 6.0 Hz, 2H), 2.90 (d, $J_{P\text{-}H}$ 21.0 Hz, 2H), 3.31 (s, 4H), 4.10 (q, *J* 6.0 Hz, 2H), 4.11 (q, *J* 9.0 Hz, 2H), 6.19 (t, *J* 3.0 Hz, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 16.5, 21.9, 25.1, 28.63 (d, $J_{C\text{-}P}$ 141.5 Hz), 40.2, 43.6, 61.9, 62.0, 70.2 (d, $J_{C\text{-}P}$ 10.3 Hz), 128.5 (d, $J_{C\text{-}P}$ 5.1 Hz), 131.0 (d, $J_{C\text{-}P}$ 7.0 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) : δ 29.1 ; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{13}H_{24}O_3PS_2$: 323.0904. Found: 323.0904.

Diethyl (phenyl(1,4-dithiaspiro[4.5]dec-6-en-6-yl)methyl)phosphonate (2b). Yield: 468 mg (76%), 1. 55 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, *J* 6.0 Hz, 3H), 1.29 (t, *J* 6.0 Hz, 3H), 1.79 (m, 2H), 2.22 (m, 4H), 3.27 (m, 4H), 3.87 (q, *J* 6.0 Hz, 2H), 4.07 (q, *J* 6.0 Hz, 2H), 4.41 (d, $J_{P\text{-}H}$ 27.0 Hz, 1H), 6.81 (t, *J* 6.0 Hz, 1H), 7.21-7.48 (m, 5H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 16.5, 21.6, 25.3, 39.8, 44.0, 46.9 (d, $J_{C\text{-}P}$ 136.9 Hz), 62.2, 62.9, 71.0 (d, $J_{C\text{-}P}$ 11.3 Hz), 133.4 (d, $J_{C\text{-}P}$ 6.9 Hz), 126-132 (aromatics) , 137.3 (d, $J_{C\text{-}P}$ 6.5 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.3; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{19}H_{28}O_3PS_2$: 399.1217. Found: 399.1225.

Diethyl ((4-nitrophenyl)(1,4-dithiaspiro[4.5]dec-6-en-6-yl)methyl)phosphonate (2c). Solid: mp 136-139 °C; yield: 469 mg (78%), 1.36 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, *J* 6.0 Hz, 3H), 1.31 (t, *J* 6.0 Hz, 3H),1.8 (m, 2H), 2.26 (m, 4H), 3.28 (m, 4H), 3.88 (q, *J* 6.0 Hz, 2H), 4.12 (q, *J* 6.0 Hz, 2H), 4.56 (d, $J_{P\text{-}H}$ 27.0 Hz, 1H), 6.85 (t, *J* 3.0 Hz, 1H), 7.64-8.16 (AB, *J* 8.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 16.5, 21.6, 25.3, 39.6, 40.1, 43.9, 47.04 (d, $J_{C\text{-}P}$ 136.4 Hz), 62.2, 63.6, 70.9 (d, $J_{C\text{-}P}$ 10.9 Hz), 134.3 (d, $J_{C\text{-}P}$ 6.8 Hz), 123-145 (aromatics),

145.7 (d, $J_{C\text{-}P}$ 6.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) : δ 24.2 ; HRMS (ESI-TOF): [M + H]$^+$ calcd for $C_{19}H_{27}NO_5PS_2$: 444.1068. Found: 444.1061.

(1,4-Dithiaspiro[4.5]dec-6-en-6-ylmethyl)diphenylphosphine oxide (2d). Solid: mp 93-94 °C; yield: 515 mg (83%), 1.61 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (m, 2H), 1.95 (m, 2H), 2.17 (t, *J* 6.0 Hz, 2H), 3.24 (s, 4H), 3.46 (d, $J_{P\text{-}H}$ 12.0 Hz, 2H), 6.33 (t, *J* 3.0 Hz, 1H), 7.44-7.82 (m, 10H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 25.1, 32.1 (d, $J_{C\text{-}P}$ 71.5 Hz), 40.1, 43.5, 70.4 (d, $J_{C\text{-}P}$ 8.7 Hz), 128.9 (d, $J_{C\text{-}P}$ 4.8 Hz), 132.3 (d, $J_{C\text{-}P}$ 7.0 Hz), 128.3-134.0 (aromatics); ^{31}P NMR (121 MHz, $CDCl_3$) : δ 32.1 ; HRMS (ESI-TOF): [M + H]$^+$ calcd for $C_{21}H_{24}OPS_2$: 387.1006. Found: 387.1009.

((4-Nitrophenyl)(1,4-dithiaspiro[4.5]dec-6-en-6-yl)methyl)diphenylphosphine oxide (2e). Solid: mp 183-185 °C; yield: 588 mg (81%), 1.16 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 2H), 2.02 (m, 4H), 3.11 (m, 2H), 3.29 (m, 2H), 5.07 (d, $J_{P\text{-}H}$ 9.0 Hz, 1H), 7.11 (t, *J* 3.0 Hz, 1H), 7.30-8.05 (m, 14H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 25.4, 39.3, 40.0, 43.7, 49.3 (d, $J_{C\text{-}P}$ 62.5 Hz), 71.0 (d, $J_{C\text{-}P}$ 8.3 Hz), 135.9 (d, $J_{C\text{-}P}$ 7.2 Hz), 145.3 (d, $J_{C\text{-}P}$ 5.8 Hz), 122.0-146.4 (aromatics); ^{31}P NMR (121 MHz, $CDCl_3$) : δ 31.5 ; HRMS (ESI-TOF): [M + H]$^+$ calcd for $C_{27}H_{27}NO_3PS_2$: 508.1170. Found: 508.1179.

General procedure for the preparation of oximo- and hydrazonophosphonates 3 and (4a-c)

A mixture of the ketophosphonates **1a** or **1f** (1 equiv), hydrazine or hydroxylamine (1.1 equiv) and PTSA (1 equiv) in 20 mL of MeOH, was heated with stirring in an oil bath at 80 °C for 4h. The progress of the reaction was monitored by TLC using dichloromethane-ether. The mixture was neutralized with an aqueous solution of 4M hydrochloric acid and extracted with $CHCl_3$. The combined organic layers were neutralized with $NaHCO_3$ and washed with saturated NaCl solution. These layers further were dried and concentrated. The residue was purified by a column chromatography on silicagel (20% dichloromethane/ether), affording the pure oximo- or hydrazonophosphonate **3** and **4a-c** as solids.

Dimethyl ((6-(hydroxyimino)cyclohex-1-en-1-yl)methyl)phosphonate (3). Solid: mp 103-105 °C; yield: 442 mg (83%), 2.29 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (m, 2H), 2.13 (m, 2H), 2.56 (t, *J* 6.0 Hz, 2H), 2.93 (d, $J_{P\text{-}H}$ 21.0 Hz, 2H), 3.64 (s, 3H), 3.68 (s, 3H), 6.15 (t, *J* 6.0 Hz, 1H), 9.67 (s,1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 22.3, 25.3, 26.5 (d, $J_{C\text{-}P}$ 139.0 Hz), 52.8, 52.9, 125.4 (d, $J_{C\text{-}P}$ 10.3 Hz), 135.8 (d, $J_{C\text{-}P}$ 9.6 Hz), 154.5 (d, $J_{C\text{-}P}$ 4.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) : δ 31.5 ; (ESI-TOF): [M + H]$^+$ calcd for $C_9H_{17}NO_4P$: 234.0895. Found: 234.0892.

Diethyl ((6-(2-tosylhydrazono)cyclohex-1-en-1-yl)methyl)phosphonate (4a). Solid: mp 113-115 °C; yield: 781 mg (93%), 2.03 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, *J* 9.0 Hz, 6H), 1.74 (m, 2H), 2.17 (m, 2H), 2.31 (t, *J* 6.0 Hz, 2H), 2.41 (s, 3H), 2.88 (d, $J_{P\text{-}H}$ 21.0 Hz, 2H), 3.96 (q, *J* 6.0 Hz, 2H), 3.98 (q, *J* 6.0 Hz, 2H), 6.40 (t, *J* 3.0 Hz, 1H), 7.29-7.87 (AB, *J* 8.0 Hz, 4H), 8.09 (s,1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 16.3, 20.8, 21.4, 24.4, 26.0 (d, $J_{C\text{-}P}$ 158.4 Hz), 29.0, 61.7, 61.8, 127.2 (d, $J_{C\text{-}P}$ 7.5 Hz), 137.5 (d, $J_{C\text{-}P}$ 9.0 Hz), 153.0 (d, $J_{C\text{-}P}$ 5.25 Hz), 128.0-143.7 (aromatics); ^{31}P NMR (121 MHz, $CDCl_3$) : δ 27.8 ; HRMS (ESI-TOF): [M + H]$^+$ calcd for $C_{18}H_{28}N_2O_5PS$: 415.1457. Found: 415.1430.

Diethyl ((6-(2-(3-nitrophenyl)hydrazono)cyclohex-1-en-1-yl)methyl)phosphonate (4b). Solid: mp 214-215 °C; yield: 655 mg (86%), 2.03 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* 6.0 Hz, 6H), 1.67 (m, 2H), 1.91 (m, 2H), 2.40 (t, *J* 6.0 Hz, 2H), 3.09 (d, $J_{P\text{-}H}$ 21.0 Hz, 2H), 4.10 (q, *J* 9.0 Hz, 2H), 4.12 (q, *J* 9.0 Hz, 2H), 6.19 (t, *J* 3.0 Hz, 1H), 7.14-8.10 (AB, *J* 9.0 Hz, 4H), 9.12 (s,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 16.5, 21.0, 22.6, 23.7, 27.4 (d, $J_{C\text{-}P}$ 140.0 Hz), 29.3, 61.7, 61.8, 127.9 (d, $J_{C\text{-}P}$ 9.7 Hz), 135.3 (d, $J_{C\text{-}P}$ 11.2 Hz), 146.8 (d, $J_{C\text{-}P}$ 4.5 Hz), 111.7-150.7 (aromatics); ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.7 ; HRMS (ESI-TOF): [M + H]$^+$ calcd for $C_{17}H_{25}N_3O_5P$: 382.1532. Found: 382.1539.

Diethyl ((6-(2-(2,4-dinitrophenyl)hydrazono)cyclohex-1-en-1-yl)methyl)phosphonate (4c).

Solid: mp 170-171 °C; yield: 847 mg (98%), 2.03 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, *J* 6.0 Hz, 6H), 1.92 (m, 2H), 2.32 (m, 2H), 2.57 (t, *J* 6.0 Hz, 2H), 3.03 (d, $J_{P\text{-}H}$ 21.0 Hz, 2H), 4.03 (q, *J* 6.0 Hz, 2H), 4.05

(q, *J* 6.0 Hz, 2H), 6.49 (t, *J* 3.0 Hz, 1H), 8.03-8.06 (m, 1H), 8.26-8.30 (m, 1H), 9.05 (m, 1H), 11.21 (s,1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 16.5, 20.9, 24.4, 25.0, 28.06 (d, J_{C-P} 144.4 Hz), 61.7, 61.8, 127.8 (d, J_{C-P} 9.7 Hz), 139.3 (d, J_{C-P} 9.6 Hz), 116.7-144.8 (aromatics), 152.4 (d, J_{C-P} 4.8 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.5 ; HRMS (ESI-TOF): $[M + H]^+$ calcd for $C_{17}H_{24}N_4O_7P$: 427.1383. Found: 427.1398.

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