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Note

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Copper-catalyzed oxidative *sp*^{3}-carbon radical cross-coupling with trialkylphosphites leading to α-phosphonyl 1,3-dicarbonyl compounds

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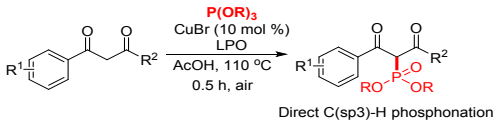


ABSTRACT: A copper-catalyzed radical C_{sp3}-H/$P(OR)_3$ cross-coupling reaction for the formation of C_{sp3}–P bonds is described. A range of 1,3-dicarbonyl compounds and trialkylphosphites were coupled in this fashion to give the corresponding products in moderate to good yields. This protocol provides direct access to α-phosphonyl 1,3-dicarbonyl compounds.

The construction of carbon-phosphorus bonds have become a topic of immense interest due to their importance as versatile intermediates in chemical synthesis.[1] In recent years,

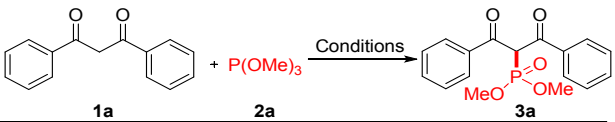
significant efforts have been made towards the development of methods for the making of this kind of bond. Among these, the transition-metal-catalyzed cross-coupling strategy for C_{sp2}-P bond formation has attracted attention due to its high efficiency.[2] In line with this strategy, some important methods including the coupling of C_{sp2}-H/P-H bonds to form C_{sp3}-P bonds have emerged in recent times.[1f,3] Nevertheless, the formation of C_{sp3}-P bonds *via* the direct cross coupling reaction of C_{sp3}-H/P-H bonds still remains a great challenge.[4] In 2015, Lei's group reported a rare example involving the copper catalyzed radical C_{sp3}-H/P-H cross-coupling reaction between aryl ketone O-acetyloximes and phosphine oxides to afford *β*-ketophosphonates.[5] In continuation of our research on C_{sp2}-P bond formation,[2a, 6] we envisioned that the direct coupling of C_{sp3}-H bonds with trialkylphosphite could lead to the formation of C_{sp3}-P bonds.[7] Herein, we report the first example of copper-catalyzed radical cross-coupling reaction of α-C_{sp3}-H bond of 1,3-dicarbonyl compounds and trialkylphosphites. This protocol provides a direct and convenient access to α-phosphonyl 1,3-dicarbonyl compounds.

Initial studies began by investigating the reaction between 1,3-diphenylpropane-1,3-dione (**1a**) and trimethylphosphite (**2a**) in the presence of copper iodide (CuI, 10 mol %) and di-*tert*-butyl peroxide (DTBP, 6 equiv) in acetic acid (AcOH, 5 mL) at 100 °C.

Fortunately, the desired product **3a** was formed after 6 hours, albeit in 10% yield (Table 1, entry 1). This was likely due to the ease of oxidation of the trimethylphosphite **2a** to trimethylphosphate ($PO(OMe)_3$) during the course of the reaction. Consequently, excess amounts of DTBP (12 equiv) and **2a** (12 equiv) were employed and this led to an increase in the yield of **3a** to 42% (Table 1, entry 2). However, when the reaction was carried out at lower temperature, only trace amounts of the product **3a** was observed (Table 1, entries 3-4); whereas at a higher temperature (110 °C), a better yield (48%) of **3a** was obtained (Table 1, entry 5). Other oxidants such as *tert*-butyl peroxybenzoate (TBPB) and *tert*-butyl hydroperoxide (TBHP) were completely ineffective (Table 1, entries 6-7). However, the use of lauroyl peroxide (LPO) did not only give a slightly better yield (50%), but the reaction was also completed in 30 minutes (Table 1, entry 8). Next, attention was turned to the screening of other catalysts with LPO as the oxidant. While the use of other Cu^{I} catalysts afforded product **3a** in good yields (Table 1, entries 9-10), CuBr proved to be the most effective (85%). At this point, an attempt was made to improve the reaction output by further increasing the amount of **2a**; however this resulted in a dramatic lowering of the yield of **3a** to 30% (Table 1, entry 11). In order to avoid excessive use of reagents, the amounts of **2a**, LPO and AcOH were systematically reduced. After some trials (Table 1, entries 12-17), it

was found that the use of 7 equiv. each of **2a** and LPO in 1 mL AcOH could lead to an optimal 84% yield of product **3a** (Table 1, entry 16). Furthermore, Cu^{II} reagents such as $CuBr_2$, $CuCl_2$ and CuI_2 as catalyst were also explored; the results were not so effective as CuBr (Table 1, entries 18-20). Interestingly, the desired product **3a** could also be obtained in 25% yield in the absence of copper catalyst (Table 1, entry 21). More importantly, the yield of **3a** increased to 56% when the reaction time was prolonged, and to 65% when the amount of **2a** and LPO were increased (Table 1, entries 22-23, supporting information Tables S1). Therefore, the role of CuBr catalyst is probably to accelerate the decomposition of LPO[8] into radical intermediates in time for the next reaction cycle (see Scheme 5). Finally, the screening of solvent confirmed AcOH to be the best reaction medium (see supporting information Table S2).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

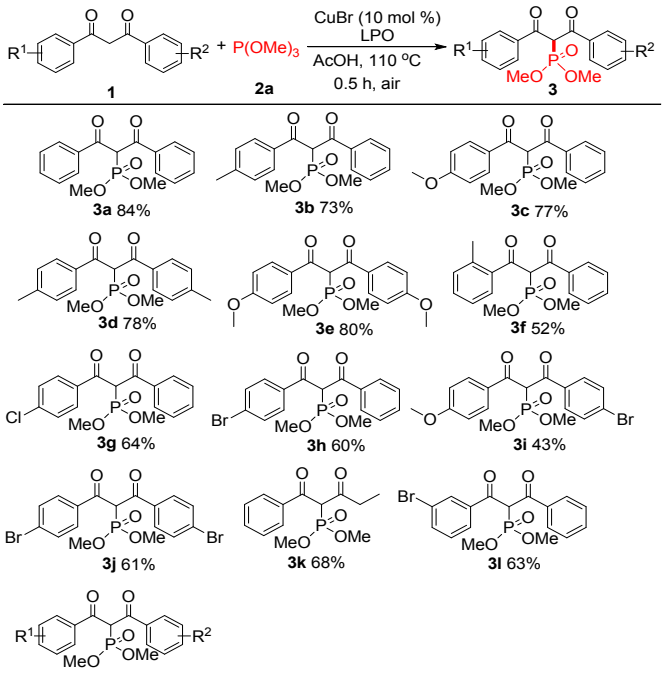
entry	catalyst	oxidant	**1a**:**2a**:oxi.	temp.(°C)	yield (%)[b]
1[c]	CuI	DTBP	1:6:6	100	10
2[c]	CuI	DTBP	1:12:12	100	42
3	CuI	DTBP	1:12:12	30	Trace
4	CuI	DTBP	1:12:12	60	Trace
5[c]	CuI	DTBP	1:12:12	110	48
6[c]	CuI	TBPB	1:12:12	110	N.R.[d]
7[c]	CuI	TBHP	1:12:12	110	N.R.[d]
8[e]	CuI	LPO	1:12:12	110	50
9[e]	CuBr	LPO	1:12:12	110	85
10[e]	CuCl	LPO	1:12:12	110	69
11[e]	CuBr	LPO	1:25:12	110	30
12[e]	CuBr	LPO	1:8:12	110	75
13[e]	CuBr	LPO	1:4:12	110	25
14[e]	CuBr	LPO	1:1:12	110	N.R.[d]
15[e,f]	CuBr	LPO	1:8:8	110	80
16[e,f]	CuBr	LPO	1:7:7	110	84
17[e,f]	CuBr	LPO	1:6:6	110	45
18[e,f]	$CuBr_2$	LPO	1:7:7	110	54
19[e,f]	$CuCl_2$	LPO	1:7:7	110	50
20[e,f]	CuI_2	LPO	1:7:7	110	42
21[e,f]	--	LPO	1:7:7	110	25
22[e,f,g]	--	LPO	1:7:7	110	56
23[e,f,g]	--	LPO	1:14:14	110	65

[a] Reaction conditions: **1a** (0.25 mmol), catalyst (10 mol %), and oxidant (di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), *tert*-butyl hydroperoxide (TBHP), Lauroyl peroxide (LPO) in HOAc (5 mL) for 3 hours in air. [b] Isolated yield. [c] reaction for 6 hours. [d] N.R. means no reaction. [e] reaction for 0.5 hours. [f] 0.25 mmol **1a** in 1 mL AcOH. [g] reaction for 1.5 hours.

With the optimized reaction conditions in hand (Table 1, entry 16), we focused on investigating the scope and limitations of the reaction. The reaction proceeded smoothly with a variety of 1,3-diketones, affording the products in moderate to good yields (Scheme 1, **3a**-**3l**). In general, the reaction outcome was influenced by the electronic nature of the substrates. For instance, diketones bearing electron-donating groups such as methyl and methoxy gave high yields of corresponding products (**3b-e**). Meanwhile, substrates containing halo-groups produced moderate to good yields of product (**3g-j**, **3l**). However, electron-deficient substrates such as those substituted by the strongly electron-withdrawing

nitro and cyano groups either did not react or could only furnish trace amount of desired product (**3p** and **3q**). The reaction was also sensitive to steric hindrance as observed with the *ortho*-substituted substrates (compare **3b** *vs* **3f**, **3d** *vs* **3n**, **3e** *vs* **3o**, **3h** *vs* **3m**). Fortunately, the reaction of substrate **1k** having an alkyl moiety at one end occurred smoothly to afford product **3k** in 68% yield. Unfortunately, no products were obtained with aliphatic 1,3-diketone compounds including cyclic substrates possibly due to the instability of the formed radical intermediates (see supporting information Scheme S1).

Scheme 1. Scope of 1, 3-diketones[a,b]

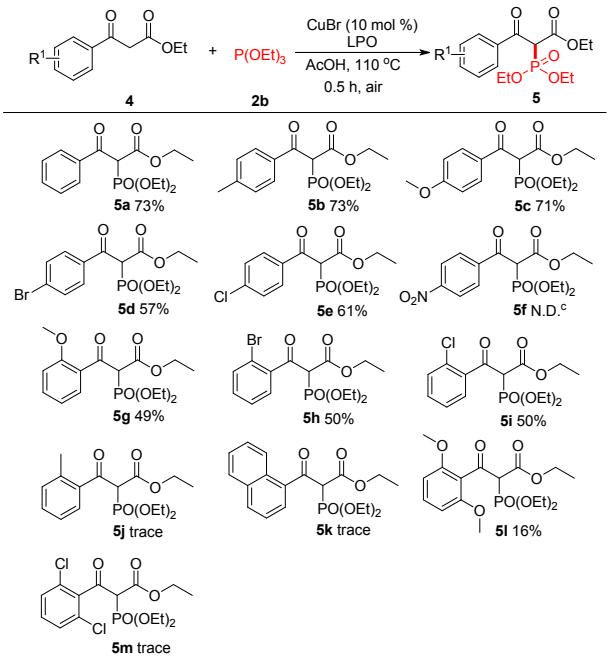


3m, R^1 = 2-Br; R^2 = H (trace)
3n, R^1 = 2-Me; R^2 = 2-Me (trace)
3o, R^1 = 2-OMe; R^2 = 2-OMe (N.D.[c])
3p, R^1 = 4-NO_2; R^2 = H (N.D.[c])
3q, R^1 = 4-CN; R^2 = H (trace)

[a] Unless the otherwise noted, reactions were performed using **1a** (0.50 mmol), **2a** (3.50 mmol), CuBr (10 mol %) and LPO (3.50 mmol) in HOAc (2 mL) at 110 °C for 0.5 h in air. [b] Isolated yield. [c] N.D. means not detected. [d] N.R. means no reaction.

Furthermore, we examined the scope of the reactions of β-ketoesters with triethylphosphite (**2b**) (Scheme 2). Ethyl benzoylacetate reacted smoothly with **2b** to give 73% yield of the expected product **5a**. As observed with 1,3-diketones, the reactions of ethyl benzoylacetate derivatives were sensitive to both steric and electronic effects. Notably, electron-rich substrates provided the corresponding products in good yields (**5b** and **5c**) while the halo-containing substrates furnished moderate yields of product (**5d** and **5e**). The electronic effect was more pronounced with the nitro-containing β-ketoester which remained unreactive (**5f**). As a result of steric hindrance, *ortho*-substituted β-ketoesters could only afford trace to modest amounts of desired products (**5g-k**). The effect was more severe with substrates containing two *ortho*-substituents as observed with products **5l** and **5m**. Unfortunately, no reactions were observed with aliphatic substrates including cyclic β-ketoesters probably due to the lower stability of the intermediate radicals. Meanwhile, the electron-pulling effect of the *O*-atom of the phenoxy group might be responsible for the inertness of phenyl 3-oxo-3-phenylpropanoate (**4r**) (see supporting information Scheme S2).

Scheme 2. Scope of β-ketoesters[a,b]



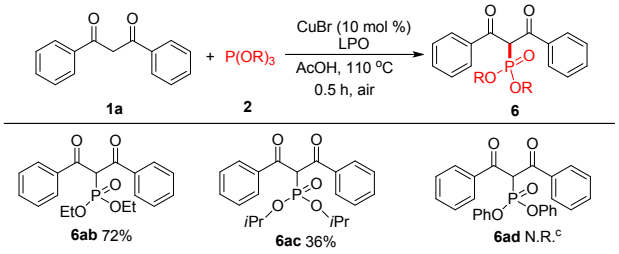
[a] Unless the otherwise noted, reactions were performed using **4** (0.50 mmol), **2b** (3.50 mmol), CuBr (10 mol %) and LPO (3.50 mmol) in HOAc (2 mL) at 110 °C for 0.5 h in air. [b] Isolated yield. [c] N.D. means not detected. [d] N.R. means no reaction.

In a bid to extend the scope of this protocol, the reactions of a variety of trialkyl/triaryl phosphites **2** were examined. As observed in Scheme 3, the reactions were largely influenced by the bulkiness of the phosphites. The bulkier the size of the alkyl/aryl component of phosphite **2** was, the lower the yield of the product obtained. For example, the reaction of **1a** with triethylphosphite (**2b**) gave the desired product **6ab** in 72% yield while triisopropylphosphite (**2c**) could only afford 36% yield of product **6ac**. In fact, no reaction occurred with triphenylphosphite (**2d**) due to the obvious steric hindrance (**6ad**).

In order to unravel the mechanism of this reaction, radical-trapping experiments were conducted (Scheme 4). Although, the addition of 2 equivalents of the radical-scavenger,

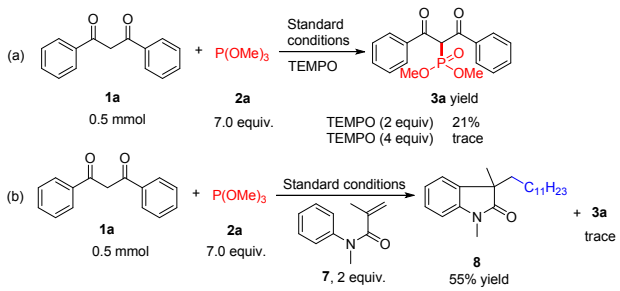
2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) partially inhibited the formation of **3a**, the reaction was completely shut down by simply increasing the amount to 4 equivalents (Scheme 4a). While the suppressed formation of **3a** might suggest the involvement of radical species, no TEMPO-radical adduct was observed. Delightfully, the inclusion of *N*-methyl-*N*-phenylmethacrylamide (**7**) in the standard reaction mainly furnished the undecanyl radical adduct **8** in 55% yield (Scheme 4b).

Scheme 3. Scope of trialkyl/triaryl phosphites [a,b]



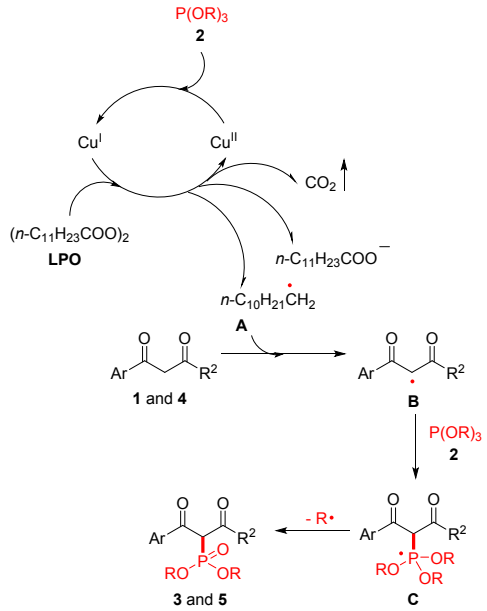
[a] Unless the otherwise noted, reactions were performed using **1a** (0.50 mmol), **2** (3.50 mmol), CuBr (10 mol %) and LPO (3.50 mmol) in HOAc (2 mL) at 110 °C for 0.5 h in air. [b] Isolated yield. [c] N.R. means no reaction.

Scheme 4. Radical trapping experiments



On the basis of experimental results and previous studies, a mechanism for the copper-catalyzed cross-coupling of 1,3-dicarbonyl compounds with trialkylphosphites is proposed (Scheme 5). Upon heating, LPO rapidly decomposes in the presence of Cu^{I} to form radical **A** and Cu^{II}. Meanwhile, Cu^{I} can be regenerated *via* the reduction of Cu^{II} by trialkylphosphite **2**.[8a] Furthermore, **A** could abstract H-atom from 1,3-dicarbonyl compound **1** or **4** to form the C_{sp3}-centered radical **B**, which further reacts with trialkylphosphite **2** to generate the radical intermediate **C**. This is followed by the *β*-scission of one of the alkoxy groups of intermediate **C** to release the product **3** or **5** and alkyl radical.[9]

Scheme 5. Proposed Mechanism for the Reaction of 1,3-Dicarbonyl Compounds with Trialkylphosphites



In conclusion, we have developed a new method for the formation of C_{sp3}–P bond based on the Cu-catalyzed cross-coupling reaction of 1,3-dicarbonyl compounds with trialkyl phosphites. The mechanistic study indicates that undecanyl radicals generated from lauroyl peroxide (LPO) could oxidize 1,3-dicarbonyl compounds to produce α-C_{sp3} radical species, which could selectively couple with trialkyl phosphites to form α-phosphonyl dicarbonyl compounds. A variety of 1,3-diketones, β-ketoesters and trialkylphosphites were shown to be compatible with this reaction. This protocol offers direct access to compounds, which can be easily transformed to other important organic compounds and bioactive molecules.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were determined with $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal standard or 85% H_3PO_4 as external standard for ^{31}P NMR (162 MHz). Chemical shifts were reported in ppm from internal TMS (δ), all coupling constants (J values) were reported in Hertz (Hz). High resolution mass spectra were recorded on a TOF machine (ESI). Column chromatography was performed with 300-400 mesh silica gel using flash column techniques. All of the reagents were used directly as obtained commercially unless otherwise noted. The substrates of **1a-1q**, **4a-4m** were synthesized according to the reported procedures, the details are: **1a-1c**,[10] **1g-1h**,[10] **1k-1l**,[10] **4a-4d**,[10] **1d**,[11] **1e**,[12] **1f**,[13] **1i-1m**,[14] **1j**,[15] **1n**,[16] **1o**,[17] **1p**,[18] **1q**,[19] **4e-4f**,[20] **4i-4j**,[20] **4k**,[21] **4g**,[22] **4l**,[22] **4h**,[23] **4m**.[24]

Preparation of 1,3-Diketo phosphonates 3. *Typical Procedure for the Preparation of Dimethyl (1,3-dioxo-1,3-diphenylpropan-2-yl)phosphonate (**3a**).* To a mixture of 1,3-diphenyl-propane-1,3-dione (0.112 g, 0.5 mmol), trimethylphosphite (0.434 g，3.5 mmol), and CuBr (0.007 g, 0.05 mmol) in AcOH (2 mL) was added lauroyl peroxide (LPO) (1.40 g，3.5 mmol). After the reaction mixture was stirred at 110 °C in oil bath for 30 minutes in air, it was allowed to cool to room temperature, and diluted with dichloromethane (5 mL). The mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/dimethyl acetone 10:1 to 6:1) to afford the dimethyl (1,3-dioxo-1,3-diphenylpropan-2-yl)phosphonate (**3a**).

*Dimethyl (1,3-dioxo-1,3-diphenylpropan-2-yl)phosphonate (**3a**)*

Yellow oil, 84% yield (139.4 mg); ^{1}H NMR (400 MHz, DMSO-d_6,): δ 8.05 (d, J = 7.4 Hz, 4H), 7.67 (t, J = 7.4 Hz, 2H), 7.54 (t, J = 7.7 Hz, 4H), 7.13 (d, J = 23.2 Hz, 1H), 3.67 (d, J = 11.3 Hz, 6H). ^{13}C{1H} NMR (101 MHz, DMSO-d_6): δ 190.6 (d, J = 6.4 Hz), 135.5 (d, J = 3.5 Hz), 134.1, 128.9

(d, J = 3.5 Hz), 58.9, 57.6, 53.3 (d, J = 6.4 Hz). $^{31}P\{1H\}$ NMR (162 MHz, DMSO-d_6): δ 17.84; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{18}O_5P$ 333.0892, found 333.0894.

*Dimethyl(1,3-dioxo-1-phenyl-3-(p-tolyl)propan-2-yl)phosphonate (**3b**)*

Yellow oil, 73% yield (126.2 mg); ^1H NMR (400 MHz, DMSO-d_6): δ 7.99 (dd, J = 25.2, 7.9 Hz, 4H), 7.67 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.7 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 23.0 Hz, 1H), 3.67 (d, J = 11.3 Hz, 6H), 2.37 (s, 3H). $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 190.7 (d, J = 6.4 Hz), 190.0 (d, J = 6.3 Hz), 144.9, 135.5 (d, J = 3.8 Hz), 134.1, 133.0 (d, J = 3.3 Hz), 129.5, 129.1, 128.9, 128.8, 58.1 (d, J = 130.7 Hz), 53.3 (d, J = 1.0 Hz), 53.2 (d, J = 1.0 Hz), 21.2; $^{31}P\{1H\}$ NMR (162 MHz, DMSO-d_6): δ 18.04; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{18}H_{20}O_5P$ 347.1048, found 347.1050.

*Dimethyl(1-(4-methoxyphenyl)-1,3-dioxo-3-phenylpropan-2-yl)phosphonate (**3c**)*

White solid, mp 128-129 °C, 77% yield (139.3 mg); ^1H NMR (400 MHz, DMSO-d_6): δ 8.07 – 8.02 (m, 4H), 7.66 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.7 Hz, 2H), 7.10-7.01 (m, 3H), 3.85 (s, 3H), 3.69 (d, J = 11.3 Hz, 6H). $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 190.7 (d, J = 6.4 Hz), 188.7 (d, J = 6.3 Hz), 163.9, 135.6 (d, J = 4.1 Hz), 134.0, 131.6, 128.9, 128.8, 128.3 (d, J = 3.1 Hz), 114.2, 58.0 (d, J = 131.0 Hz), 55.7, 53.3 (d, J = 0.9 Hz), 53.2 (d, J = 0.9 Hz); $^{31}P\{1H\}$ NMR (162 MHz, DMSO-d_6): δ 18.28; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{18}H_{20}O_6P$ 363.0997, found 363.0998.

*Dimethyl(1,3-dioxo-1,3-di-p-tolylpropan-2-yl)phosphonate (**3d**).*

White solid, mp 163-165 °C, 78% yield (140.4 mg); ^1H NMR (400 MHz, DMSO-d_6): δ 7.94 (d, J = 8.0 Hz, 4H), 7.33 (d, J = 7.9 Hz, 4H), 7.02 (d, J = 22.8 Hz, 1H), 3.67 (d, J = 11.3 Hz, 6H), 2.36 (s, 6H); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 190.0 (d, J = 6.4 Hz), 144.8, 133.1 (d, J = 3.6 Hz), 129.5, 129.1, 58.0 (d, J = 131.0 Hz), 53.2 (d, J = 6.4 Hz), 21.2; $^{31}P\{1H\}$ NMR(162 MHz, DMSO-d_6): δ 18.38; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{19}H_{22}O_5P$ 361.1205, found 361.1206.

*Dimethyl(1,3-bis(4-methoxyphenyl)-1,3-dioxopropan-2-yl)phosphonate (**3e**)*

White solid, mp 165-166 °C, 80% yield (156.8 mg); ^1H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, J = 8.8 Hz, 4H), 7.05 (d, J = 8.8 Hz, 4H), 6.95 (d, J = 22.7 Hz, 1H), 3.84 (s, 6H), 3.67 (d, J = 11.2 Hz,

6H); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 188.8 (d, J = 6.4 Hz), 163.8, 131.4, 128.4 (d, J = 3.7 Hz), 114.2, 57.7 (d, J = 131.5 Hz), 55.7, 53.1 (d, J = 6.3 Hz); $^{31}P\{1H\}$ NMR (162 MHz, DMSO-d_6): δ 18.66; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{19}H_{22}O_7P$ 393.1103, found 393.1108.

Dimethyl(1,3-dioxo-1-phenyl-3-(o-tolyl)propan-2-yl)phosphonate ***(3f)***

Yellow oil, 52% yield (88.2 mg); ^1H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 12.29 (s, 0.19H, enol), 8.09-7.99 (m, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.43 (t, J = 7.1 Hz, 1H), 7.37-7.10 (m, 3H), 6.97 (d, J = 23.9 Hz, 0.77H, keto), 3.64 (dd, J = 11.3, 2.7 Hz, 6H), 2.34 (d, J = 16.2 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 193.9 (d, J = 6.0 Hz), 191.1 (d, J = 5.8 Hz), 138.2, 136.7 (d, J = 3.4 Hz), 135.8 (d, J = 3.1 Hz), 134.0, 132.0, 131.8, 130.1, 128.9 (d, J = 2.8 Hz), 128.8, 128.4, 128.1, 125.8, 125.1, 60.5 (d, J = 129.3 Hz), 53.3 (d, J = 8.3 Hz), 53.2 (d, J = 8.3 Hz), 20.4, 19.4; $^{31}P\{1H\}$ NMR (162 MHz, DMSO-d_6): δ 17.84; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{18}H_{19}NaO_5P$ 369.0868, found 369.0853.

Dimethyl(1-(4-chlorophenyl)-1,3-dioxo-3-phenylpropan-2-yl)phosphonate ***(3g)***

Yellow oil, 64% yield (117.1 mg); ^1H NMR (400 MHz, DMSO-d_6): δ 8.12-7.96 (m, 4H), 7.73-7.60 (m, 3H), 7.54 (t, J = 7.7 Hz, 2H), 7.12 (d, J = 23.3 Hz, 1H), 3.69 (d, J = 4.7 Hz, 3H), 3.66 (d, J = 4.8 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 190.6 (d, J = 6.3 Hz), 189.76 (d, J = 6.06 Hz), 189.67 (d, J = 6.06 Hz), 139.3 (d, J = 4.2 Hz), 135.4 (d, J = 3.6 Hz), 134.2, 134.1 (d, J = 3.4 Hz), 130.8, 129.1, 129.0, 128.9, 58.34 (d, J = 130.29 Hz), 58.29 (d, J = 130.29 Hz), 53.42, 53.39, 53.36, 53.33, 53.27; $^{31}P\{1H\}$ NMR (162 MHz, DMSO-d_6): δ 17.38 (d, J = 50.8 Hz); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{17}ClO_5P$ 367.0502, found 367.0516.

Dimethyl(1-(4-bromophenyl)-1,3-dioxo-3-phenylpropan-2-yl)phosphonate ***(3h)***

Yellow oil, 60% yield (122.7 mg); ^1H NMR (400 MHz, DMSO-d_6): δ 8.07-7.93 (m, 4H), 7.78 (d, J = 8.6 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.11 (d, J = 23.3 Hz, 1H), 3.69 (d, J = 5.0 Hz, 3H), 3.66 (d, J = 5.0 Hz, 3H); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 190.6 (d, J = 6.3 Hz), 190.0 (d, J = 6.4 Hz), 135.4 (d, J = 3.6 Hz), 134.5 (d, J = 3.3 Hz), 134.2, 132.1, 130.9, 128.9 (d, J = 8.8 Hz), 128.6, 58.3 (d, J = 130.1 Hz), 53.4 (d, J = 6.4 Hz), 53.3 (d, J = 6.4 Hz); $^{31}P\{1H\}$ NMR (162

MHz, DMSO-d_6): δ 17.35 (d, J = 53.9 Hz); HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{17}BrO_5P$ 410.9997, found 410.9987.

*Dimethyl(1-(4-bromophenyl)-3-(4-methoxyphenyl)-1,3-dioxopropan-2-yl)phosphonate (**3i**)*

White solid, mp 167-168 °C, 43% yield (94.6 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.10-6.99 (m, 3H), 3.84 (s, 3H), 3.69 (d, J = 5.0 Hz, 3H), 3.66 (d, J = 5.0 Hz, 3H); ^{13}C{1H} NMR (101 MHz, DMSO-d_6): δ 190.1 (d, J = 6.5 Hz), 188.6 (d, J = 6.2 Hz), 163.9, 134.6 (d, J = 3.9 Hz), 132.1, 131.5, 130.8, 128.4, 128.2 (d, J = 3.3 Hz), 114.2, 58.0 (d, J = 130.7 Hz), 55.7, 53.3 (d, J = 6.2 Hz), 53.2 (d, J = 6.2 Hz); ^{31}P{1H} NMR (162 MHz, DMSO-d_6): δ 17.93; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{18}H_{19}BrO_6P$ 441.0103, found 441.0105.

*Dimethyl(1,3-bis(4-bromophenyl)-1,3-dioxopropan-2-yl)phosphonate (**3j**)*

White solid, mp 165-166 °C, 61% yield (148.5 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, J = 8.6 Hz, 4H), 7.78 (d, J = 8.6 Hz, 4H), 7.11 (d, J = 23.5 Hz, 1H), 3.68 (d, J = 11.3 Hz, 6H); ^{13}C{1H} NMR (101 MHz, DMSO-d_6): δ 189.9 (d, J = 6.4 Hz), 134.4 (d, J = 3.4 Hz), 132.1, 130.8, 128.6, 58.28 (d, J = 129.8 Hz), 53.4 (d, J = 6.5 Hz); ^{31}P{1H} NMR (162 MHz, DMSO-d_6): δ 17.17; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{16}Br_2O_5P$ 488.9102, found 488.9101.

*Dimethyl (1,3-dioxo-1-phenylpentan-2-yl)phosphonate (**3k**)*

Yellow oil, 68% yield (96.6 mg); ^{1}H NMR (400 MHz, DMSO-d_6):δ 8.04-7.98 (m, 2H), 7.75 (t, J = 7.4 Hz, 1H), 7.61 (t, J = 7.7 Hz, 2H), 6.22 (d, J = 23.3 Hz, 1H), 3.72 (d, J = 1.7 Hz, 3H), 3.70 (d, J = 1.7 Hz, 3H), 2.75 (qd, J = 7.2, 2.8 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C{1H} NMR (101 MHz, DMSO-d_6): δ 200.2 (d, J = 5.7 Hz), 190.5 (d, J = 6.2 Hz), 136.0 (d, J = 3.9 Hz), 134.1, 128.9, 128.8, 61.6 (d, J = 126.8 Hz), 53.4 (d, J = 2.9 Hz), 53.3 (d, J = 2.9 Hz), 36.0, 7.6. ^{31}P{1H} NMR (162 MHz, DMSO-d_6): δ 17.84; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{13}H_{18}O_5P$ 285.0892, found 285.0890.

*Dimethyl(1-(3-bromophenyl)-1,3-dioxo-3-phenylpropan-2-yl)phosphonate(**3l**)*

Yellow oil, 63% yield (135.7 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.28 (t, J = 1.7 Hz, 1H), 8.09

(d, J = 8.0 Hz, 3H), 7.96-7.86 (m, 1H), 7.73 (t, J = 7.4 Hz, 1H), 7.64-7.53 (m, 3H), 7.20 (d, J = 23.4 Hz, 1H), 3.74 (d, J = 3.4 Hz, 3H), 3.72 (d, J = 3.4 Hz, 3H); ^{13}C{1H} NMR (101 MHz, DMSO-d_6): δ 190.6 (d, J = 6.3 Hz), 189.7 (d, J = 6.5 Hz), 137.4 (d, J = 3.3 Hz), 136.7, 135.4 (d, J = 3.4 Hz), 134.2, 131.4, 131.1, 129.0, 128.9, 127.8, 122.3, 58.34 (d, J = 129.8 Hz), 53.4 (d, J = 4.4 Hz), 53.3 (d, J = 4.4 Hz); ^{31}P{1H} NMR (162 MHz, DMSO-d_6): δ 15.14; HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for $C_{17}H_{16}BrNaO_5P$ 432.9816, found 432.9806.

*Ethyl 2-(diethoxyphosphoryl)-3-oxo-3-phenylpropanoate (**5a**)*

Yellow oil, 73% yield (119.7 mg); ^{1}H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 8.03 (d, J = 7.4 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.7 Hz, 2H), 5.83 (d, J = 23.1 Hz, 0.82H, enol), 4.23-3.95 (m, 6H), 3.11 (d, J = 21.4 Hz, 0.18H, keto), 1.29-1.10 (m, 9H); ^{13}C{1H} NMR (101 MHz, DMSO-d_6): δ 189.9 (d, J = 5.8 Hz), 164.5 (d, J = 5.3 Hz), 135.9 (d, J = 3.0 Hz), 134.0 128.9, 128.7, 62.8 (d, J = 0.9 Hz), 62.7 (d, J = 0.9 Hz), 61.6, 55.1 (d, J = 130.5 Hz), 16.04 (d, J = 6.06 Hz), 13.8; ^{31}P{1H} NMR (enol+ keto) (162 MHz, DMSO-d_6): δ 20.13, 14.25; MS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{22}O_6P$ 329.1, found 329.1.

*Ethyl2-(diethoxyphosphoryl)-3-oxo-3-(p-tolyl)propanoate (**5b**)*

Yellow oil, 73% yield (124.8 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 5.76 (d, J = 22.9 Hz, 1H), 4.17-4.01 (m, 6H), 2.39 (s, 3H), 1.20-1.11(m, 9H); ^{13}C{1H} NMR (101 MHz, DMSO-d_6): δ 189.3 (d, J = 5.8 Hz), 164.6 (d, J = 5.3 Hz), 144.7, 133.4 (d, J = 3.1 Hz), 129.3, 129.1, 62.73 (d, J = 6.2 Hz), 62.67 (d, J = 6.2 Hz), 61.5, 55.0 (d, J = 130.7 Hz), 21.2, 16.1 (d, J = 1.2 Hz), 16.0 (d, J = 1.2 Hz), 13.8; ^{31}P{1H} NMR (162 MHz, DMSO-d_6): δ 14.41; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{24}O_6P$ 343.1311, found 343.1301.

*Ethyl2-(diethoxyphosphoryl)-3-(4-methoxyphenyl)-3-oxopropanoate (**5c**)*

Yellow oil, 71% yield (127.0 mg); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 5.74 (d, J = 22.8 Hz, 1H), 4.18-4.04 (m, 6H), 3.86 (s, 3H), 1.22-1.12 (m, 9H); ^{13}C{1H} NMR (101 MHz, DMSO-d_6): δ 188.0 (d, J = 5.7 Hz), 164.7 (d, J = 5.2 Hz), 163.8, 131.6, 128.7 (d, J = 3.0 Hz), 114.0, 62.7 (d, J = 6.2 Hz), 62.6 (d, J = 6.2 Hz), 61.5, 55.7, 54.8 (d, J = 131.1

Hz), 16.12 (d, J = 1.7 Hz), 16.06 (d, J = 1.7 Hz), 13.8; $^{31}P\{1H\}$ NMR (162 MHz, DMSO-d_6): δ 14.61; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{16}H_{24}O_7P$ 359.1260, found 359.1265.

*Ethyl3(4-bromophenyl)-2-(diethoxyphosphoryl)-3-oxopropanoate (**5d**)*

Yellow oil, 57% yield (115.7 mg); ^1H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 7.96 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 5.85 (d, J = 23.3 Hz, 0.81H, enol), 4.18-3.99 (m, 6H), 3.10 (d, J = 21.4 Hz, 0.22H, keto), 1.30-1.10 (m, 9H); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 189.3 (d, J = 5.8 Hz), 164.4 (d, J = 5.2 Hz), 134.9 (d, J = 3.0 Hz), 131.9, 131.7, 131.0, 130.9, 128.4, 62.92 (d, J = 1.8 Hz), 62.86 (d, J = 1.8 Hz), 61.7, 55.2 (d, J = 130.2 Hz), 16.14, 16.08, 13.8; $^{31}P\{1H\}$ NMR (enol+ keto) (162 MHz, DMSO-d_6): δ 20.12, 13.95; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{21}BrO_6P$ 407.0259, found 407.0245.

*Ethyl3-(4-chlorophenyl)-2-(diethoxyphosphoryl)-3-oxopropanoate (**5e**)*

Yellow oil, 61% yield (110.4 mg); ^1H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 8.04 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 5.86 (d, J = 23.3 Hz, 0.79H, enol), 4.20-3.80 (m, 6H), 3.10 (d, J = 21.4 Hz, 0.25H, keto), 1.27-1.10 (m, 9H); $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$-d_6): δ 189.1 (d, J = 5.8 Hz), 164.4 (d, J = 5.2 Hz), 139.1, 134.6 (d, J = 2.9 Hz), 130.9, 128.9, 62.9, 62.8, 61.7, 55.2 (d, J = 130.0 Hz), 16.06 (d, J = 6.06 Hz), 13.8. $^{31}P\{1H\}$ NMR (enol+ keto) (162 MHz, DMSO-d_6): δ 20.12, 13.96; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{21}ClO_6P$ 363.0764, found 363.0761.

*Ethyl2-(diethoxyphosphoryl)-3-(2-methoxyphenyl)-3-oxopropanoate (**5g**)*

Yellow oil, 49% yield (87.7 mg); ^1H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 13.38 (s, 0.2H, enol), 7.66 -7.38 (m, 2H), 7.32-7.15 (m, 1H), 7.11-6.97 (m, 1H), 5.33 (d, J = 22.4 Hz, 0.72H, keto), 4.22-3.92 (m, 6H), 3.86 (s, 2.48H, keto), 3.73 (s, 0.64H, enol), 1.28 (t, J = 7.0 Hz, 1.45H, enol), 1.21 -1.14 (m, 6.64H, keto), 0.88 (t, J = 7.1 Hz, 0.67H, enol); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 189.9 (d, J = 6.4 Hz), 164.0 (d, J = 5.9 Hz), 158.3, 155.9, 134.9, 131.4, 130.2, 128.4, 126.5 (d, J = 3.2 Hz), 120.7, 120.0, 112.5, 111.1, 62.63 (d, J = 6.3 Hz), 62.57 (d, J = 6.3 Hz), 61.4, 59.2 (d, J = 127.8 Hz), 55.8, 16.08 (d, J = 6.06 Hz, keto), 15.93 (d, J = 6.06 Hz, enol), 13.9 (keto), 13.6 (enol); $^{31}P\{1H\}$ NMR (enol+ keto) (162 MHz, DMSO-d_6): δ 24.24, 14.72; HRMS (ESI-TOF) *m/z*: $(M+H)^+$

Calcd for $C_{16}H_{24}O_7P$ 359.1260, found 359.1268.

*Ethyl3-(2-bromophenyl)-2-(diethoxyphosphoryl)-3-oxopropanoate (**5h**)*

Yellow oil, 50% yield (101.5 mg); ^{1}H NMR (enol+keto) (400 MHz, DMSO-d_6): δ 13.82 (s, 0.72H, enol), 7.84-7.64 (m, 1H), 7.54-7.34 (m, 3H), 5.60 (d, J = 24.1 Hz, 0.14H, keto), 4.23-4.10 (m, 3.31H, enol), 4.09-3.99 (m, 0.8H, keto), 3.85 (q, J = 7.1 Hz, 1.65H, enol), 1.30 (t, J = 7.0 Hz, 4.71H, enol), 1.23-1.08 (m, 2.25H, keto), 0.86 (t, J = 7.1 Hz, 2.35H, enol); ^{13}C{1H} NMR (enol+keto) (101 MHz, DMSO-d_6): δ 191.4 (d, J = 5.9 Hz), 180.5 (d, J = 6.9 Hz), 163.9 (d, J = 4.6 Hz), 163.6 (d, J = 9.8 Hz), 138.7, 138.0 (d, J = 15.8 Hz), 133.9, 133.1, 132.1, 130.9, 130.1, 128.7, 127.5 (d, J = 11.2 Hz), 119.5, 119.1, 93.38, 91.64, 63.3, 63.0 (d, J = 6.3 Hz), 62.9 (d, J = 6.5 Hz), 61.7, 59.8, 58.7 (d, J = 127.2 Hz), 16.04 (d, J = 6.06 Hz), 13.8, 13.5; ^{31}P{1H} NMR (enol+keto) (162 MHz, DMSO-d_6): δ 23.50, 13.21; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{21}BrO_6P$ 407.0259, found 407.0265.

*Ethyl3-(2-chlorophenyl)-2-(diethoxyphosphoryl)-3-oxopropanoate (**5i**)*

Yellow oil, 50% yield (90.5 mg); ^{1}H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 13.80 (s, 0.6H, enol), 7.82 (t, J = 7.4 Hz, 0.29H), 7.60-7.36 (m, 4H), 5.59 (d, J = 24.1 Hz, 0.17H, keto), 4.25-3.94 (m, 4.48H), 3.91-3.78 (m, 1.86H), 1.30 (t, J = 7.0 Hz, 4.58H), 1.22-1.08 (m, 2.41H), 0.87 (t, J = 7.1 Hz, 2.24H); ^{13}C{1H} NMR (enol+ keto) (101 MHz, DMSO-d_6): δ 193.8 (d, J = 6.4 Hz), 190.8 (d, J = 5.9 Hz), 179.1 (d, J = 6.9 Hz), 163.9 (d, J = 4.7 Hz), 163.7 (d, J = 9.7 Hz), 137.8 (d, J = 1.9 Hz), 137.0 (d, J = 2.1 Hz), 136.0, 135.8, 133.0, 132.7, 130.8, 130.2 (d, J = 3.9 Hz), 130.0, 129.0, 128.8, 127.2 (d, J = 1.4 Hz), 127.0, 93.7, 92.0, 63.3 (d, J = 5.0 Hz), 62.98 (d, J = 6.3 Hz), 62.83 (d, J = 6.4 Hz), 61.84 (d, J = 6.2 Hz), 61.64, 59.8, 58.8 (d, J = 127.3 Hz), 15.97 (d, J = 6.06 Hz), 13.7, 13.5; ^{31}P{1H} NMR (enol+ keto) (162 MHz, DMSO-d_6): δ 23.35, 19.32, 13.22; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{21}ClO_6P$ 363.0764, found 363.0758.

*Ethyl2-(diethoxyphosphoryl)-3-(2,6-dimethoxyphenyl)-3-oxopropanoate (**5l**)*

Yellow oil, 16% yield (31.0 mg); ^{1}H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 13.44 (s, 0.78H, enol), 7.43-7.27 (m, 1H), 6.80-6.62 (m, 2H), 4.87 (d, J = 23.2 Hz, 0.21H), 4.18-3.77 (m, 6H), 3.76 – 3.66 (m, 6H), 1.29 (t, J = 7.0 Hz, 4.31H), 1.21-1.04 (m, 2.87H), 0.84 (t, J = 7.1 Hz, 2.1H); ^{13}C{1H}

NMR (enol+ keto) (101 MHz, $CDCl_3$): δ 194.2 (d, J = 6.4 Hz), 189.4 (d, J = 6.2 Hz), 178.0 (d, J = 7.4 Hz), 164.1 (d, J = 10.5 Hz), 163.6 (d, J = 4.7 Hz), 157.3, 156.7, 156.4, 132.5, 131.6, 130.7, 115.1 (d, J = 14.7 Hz), 104.2 (d, J = 28.6 Hz), 94.0, 92.1, 63.0 (d, J = 5.1 Hz), 62.8 (d, J = 6.3 Hz), 62.5 (d, J = 6.4 Hz), 59.3, 55.9, 18.6, 15.9 (d, J = 6.1 Hz), 13.9, 13.5. $^{31}P\{1H\}$ NMR (enol+ keto) (162 MHz, DMSO-d_6): δ 24.50, 13.49; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{17}H_{26}O_8P$ 389.1365, found 389.1362.

*Diethyl (1,3-dioxo-1,3-diphenylpropan-2-yl)phosphonate (**6ab**)*

Yellow oil, 72% yield (129.6 mg); ^1H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 12.74 (s, 0.04H, enol), 8.07 (d, J = 7.3 Hz, 4H), 7.67 (t, J = 7.4 Hz, 2H), 7.54 (t, J = 7.7 Hz, 4H), 7.08 (d, J = 23.2 Hz, 0.93H, keto), 4.16-4.02 (m, 4H), 1.09 (t, J = 7.0 Hz, 6H); $^{13}C\{1H\}$ NMR (enol+ keto) (101 MHz, DMSO-d_6): δ 190.9 (d, J = 6.3 Hz), 135.7 (d, J = 3.4 Hz), 134.0, 128.94, 128.85, 62.41 (d, J = 7.07 Hz), 58.6 (d, J = 130.3 Hz), 15.95 (d, J = 6.06 Hz) ; $^{31}P\{1H\}$ NMR (enol+ keto) (162 MHz, DMSO-d_6): δ 22.50, 14.94; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{19}H_{22}O_5P$ 361.1205, found 361.1206.

*Diisopropyl(1,3-dioxo-1,3-diphenylpropan-2-yl)phosphonate (**6ac**)*

Yellow oil, 36% yield (69.8 mg); ^1H NMR (enol+ keto) (400 MHz, DMSO-d_6): δ 12.90 (s, 0.07H, enol), 8.06 (d, J = 7.4 Hz, 4H), 7.66 (t, J = 7.4 Hz, 2H), 7.53 (t, J = 7.7 Hz, 4H), 6.99 (d, J = 23.3 Hz, 0.90H, keto), 4.83-4.67 (m, 2H), 1.11 (dd, J = 5.9, 4.8 Hz, 12H); $^{13}C\{1H\}$ NMR (101 MHz, DMSO-d_6): δ 191.0 (d, J = 6.2 Hz), 135.8 (d, J = 3.4 Hz), 133.9, 129.0, 128.8, 71.1 (d, J = 6.7 Hz), 59.1 (d, J = 131.5 Hz), 23.7 (d, J = 3.0 Hz), 23.2 (d, J = 5.9 Hz); $^{31}P\{1H\}$ NMR (162 MHz, DMSO-d_6): δ 12.88; HRMS (ESI-TOF) *m/z*: $(M+H)^+$ Calcd for $C_{21}H_{26}O_5P$ 389.1518, found 389.1519.

*3-Dodecyl-1,3-dimethylindolin-2-one (**8**)*

Colorless oil, 55% yield (43 mg); ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 -7.16 (m, 1H), 7.11 - 7.07 (m, 1H), 7.02 - 6.96 (m, 1H), 6.78 - 6.74 (m, 1H), 3.14 (s, 3H), 1.91 - 1.74 (m, 1H), 1.69 - 1.58 (m, 1H), 1.27 (s, 3H), 1.22 – 1.02 (m, 20H), 0.80 (t, J = 6.9 Hz, 3H). $^{13}C\{1H\}$ NMR (101 MHz, $CDCl_3$): δ 181.01, 143.46, 134.47, 127.67, 122.59, 122.52, 107.96, 48.59, 38.68, 32.05, 29.89, 29.74, 29.70, 29.68, 29.47, 29.45, 26.23, 24.60, 23.92, 22.82, 14.26. HRMS (ESI-TOF) *m/z*: $(M+Na)^+$ Calcd for

$C_{22}H_{35}NNaO$ 352.2616, found 352.2612.

ASSOCIATED CONTENT

Supporting Information

^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **3**, **5**, **6** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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