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Pd(II)-catalyzed coupling–cyclization reaction of *o*-ethylnylphenyl-phosphonamides monoesters with allyl halide

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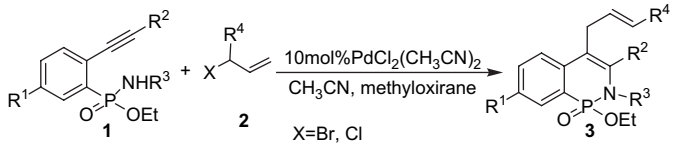
ABSTRACT

4-Allyl-phosphaisoquinolin-1-ones were synthesized by palladium-catalyzed coupling–cyclization of *o*-ethynylphenylphosphonamide monoethyl esters with allyl halides with high regioselectivity and good yields. The synthesized 4-allyl-phosphaisoquinolin-1-ones show bioactivity as inhibitor of MCH-1R.

1. Introduction

Isoquinolin-1-ones, a structural unit in many natural products, are important intermediates in organic synthesis.[1] For a long time, isoquinolin-1-one compounds have gained considerable synthetic and pharmacological interest because of their potential antitumor activity, such as potential antitumor activity,[2] cytotoxicity,[3] cardiovascular activity,[4] antineoplastic,[5] antimicrobial,[6] inhibition of human thymidylate synthase,[7] inhibition of PARP activity,[8] and reduction of systolic blood pressure,[9] etc. Phosphaisoquinolin-1-ones are phosphorus analogues of isoquinolin-1-ones that can be anticipated to have bioactivities.[10] So, the synthesis of phosphaisoquinolin-1-one derivatives and the assessment of their biological properties are very attractive. Here we would like to report the research of 4-allyl-phosphaisoquinolin-1-one.

Transition metal-catalyzed methodology has been proven to be one of the most powerful pathways for the formation of carbocycles as well as nitrogen-containing heterocycles.[11,12] Recently, we reported[13] an intramolecular cyclization reaction of *o*-ethynylphenylphosphonamides monoethyl ester catalyzed by $PdCl_2(CH_3CN)_2$, which provides a convenient method of preparing 3-substituted phosphaisoquinolin-1-ones. In continuation of the above investigation, we recently decided to search for a new procedure of coupling–cyclization with a carbon–carbon bond-forming reaction, which would allow us to synthesize 3,4-disubstituted phosphaisoquinolin-1-ones and permit further elaboration of more complex derivatives to study its bioactivity. On the other hand, palladium-catalyzed allylation is a practical tool for introducing the allyl group into the products.[14] The coupling–cyclization of *o*-ethynylphosphonamide with allyl halides may provide an efficient pathway to the allyl-substituted cyclic compounds. In this paper, we wish to present a full account of our observation on the coupling–cyclization of *o*-ethynylphosphonamide **1** with allyl halides **2** (Scheme 1).



Scheme 1. Coupling–cyclization of *o*-ethynylphenylphosphonamides (**1**) with allyl halides (**2**).

2. Results and discussion

The reaction of *o*-(2-phenylethynyl)phenylphosphonamides monoethyl ester (**1a**) and allyl bromide **2a** was used to optimize the reaction conditions and some representative results are listed in

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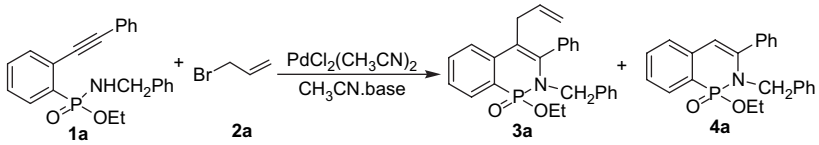
Table 1
Pd(II)-catalyzed coupling–cyclization of the *o*-(1-phenylethynyl)phenylphosphonamides monoethyl ester (**1a**) with allyl bromide **2a**[a]



Entry	Equiv of **2a**	Base	Equiv of base	Temperature (°C)	Time (h)	**3a** (%)	**4a** (%)
1	**2**	K_2CO_3	3	25–80	12	0	0
2	**2**	Et_3N	3	25–80	12	0	0
3	**2**	$P(OEt)_3$	3	25–80	12	0	0
4	**2**	Methyloxirane	10	25–80	12	65[b]	12
5	**5**	Methyloxirane	50	80	4	85[c]	0
6	**10**	Methyloxirane	50	80	4	90	0

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (0.01 mmol), anhydrous solvent (3 mL).
[b] Compound **1a** (25%) was recovered.
[c] Compound **1a** (11%) was recovered.

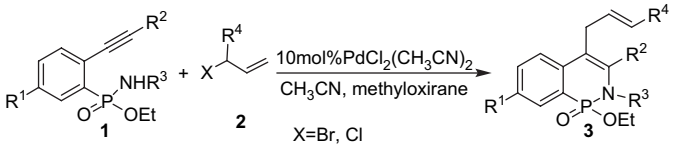
Table 1. Through control experiments, we found that the use of $PdCl_2$ or $PdCl_2(CH_3CN)_2$ as a catalyst, in the presence of a large excess of methyloxirane,[15] the reaction proceeds smoothly and product **3a** was isolated in 85% yield with 10% recovery of the reactant **1a** (Table 1, entry 5). Other palladium catalysts (e.g., $Pd(PPh_3)_4$ and $Pd(OAc)_2$) were less effective and gave only unchanged starting materials. The use of K_2CO_3, Et_3N, or $P(OEt)_3$ as a base proved to be ineffective and none of the desired product was detected; while the reaction employing proton scanvenger, such as methyloxirane, in place of base, proceeded smoothly. Only use of 10 equiv methyloxirane afforded the desired product **3a** in 65% yield and the cyclized product **4a** in 12% yield. Use of a large excess of methyloxirane (about 50 equiv), the cyclized product **4a** was not detected. Moreover, use of fewer equivalents of allyl bromide resulted in lower yields (Table 1, entries 4 and 5). Subsequently, the effects of employing various solvents were studied. We found that CH_3CN or THF as the solvent was effective, and the reaction couldn't proceed in DMF, DMSO, or DCM. The best result was obtained when 10 mol % of $PdCl_2(CH_3CN)_2$ and 10 equiv of allyl bromide (**2a**) in the presence of 50 equiv methyloxirane in CH_3CN were used, leading to a 90% yield of **3a**.

Based on the above optimization efforts, this method was applied to the synthesis of other 4-allylic phosphaisoquinolin-1-ones. The results are summarized in Table 2. A variety of 4-allylphosphaisoquinolin-1-ones were obtained in good to excellent yields. Functionalities such as aryl, alkyl, ether on the alkyne moiety and chloro, methoxy substituents on the benzene ring are tolerated.

In addition, the *N*-unsubstituted phosphamide compound (Table 2, entry 2) can also afford the corresponding product in good yield. Under the same reaction conditions, the reaction of *o*-ethynylphenylphosphonamides monoethyl ester (**1**) with 3-chloro-1-butene were also examined (Table 2, entries 8, 9, 10, 11, and 12), the reaction afforded desired products (**3**) as an *E* and *Z* mixture (*E*/*Z*=77:23) in good combined yields. Under the above standard conditions, product **3h** was isolated in 85% yield. The result indicated that vinylpalladium intermediate (**B**) firstly inserts the carbon–carbon bond of allyl chloride to give a carbon–palladium intermediate, which undergoes β-chloride elimination to afford desired product **3h** (Scheme 2).

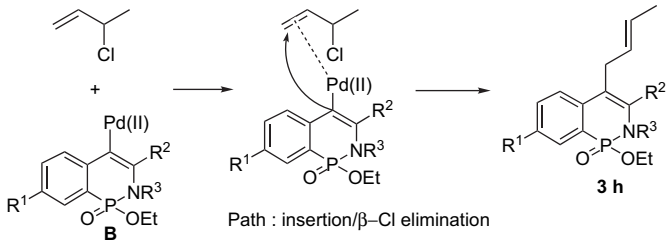
On the basis of the observed regioselectivity of the 3-chloro-1-butene reaction and the related literature,[16] proposed mechanism is shown in Scheme 3. It presumably involves (i) the formation of the complex through coordination of the ethynyl moiety of **1** with $PdCl_2(CH_3CN)_2$; (ii) regioselective nucleophilic attack of the activated triple bond by nitrogen in the *endo* mode would give the

Table 2
Coupling–cyclization of the *o*-ethynylphenylphosphonamides monoethyl esters **1** with allyl halide **2** employing $PdCl_2(CH_3CN)_2$[a]



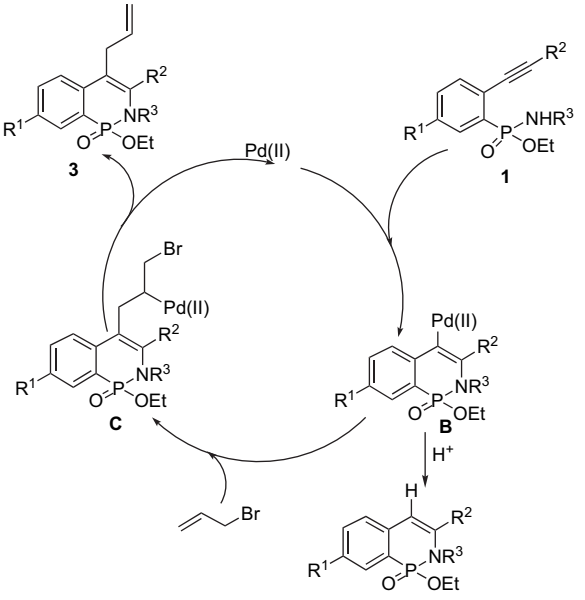
Entry	R^1	R^2	R^3	R^4	X	Time (h)	Product	Yield (%)
1	H	C_6H_5	$C_6H_5CH_2$	H	Br	4	**3a**	90
2	H	C_6H_5	H	H	Br	6	**3b**	69
3	Cl	C_6H_5	$C_6H_5CH_2$	H	Br	4	**3c**	92
4	Cl	C_6H_5	*n*-Pr	H	Br	4	**3d**	87
5	Cl	*p*-EtC_6H_5	$C_6H_5CH_2$	H	Br	4	**3e**	88
6	Cl	*n*-Bu	$C_6H_5CH_2$	H	Br	6	**3f**	82
7	MeO	C_6H_5	$C_6H_5CH_2$	H	Br	4	**3g**	85
8	H	C_6H_5	$C_6H_5CH_2$	CH_3	Cl	4	**3h**	85
9	H	*n*-Bu	$C_6H_5CH_2$	CH_3	Cl	6	**3i**	78
10	Cl	C_6H_5	$C_6H_5CH_2$	CH_3	Cl	4	**3j**	86
11	Cl	C_6H_5	*n*-Pr	CH_3	Cl	4	**3k**	81
12	Cl	*p*-EtC_6H_5	*n*-Pr	CH_3	Cl	4	**3l**	83
13	H	C_6H_5	C_6H_5	H	Br	4	**3m**	83
14	Cl	C_6H_5	C_6H_5	H	Br	4	**3n**	80
15	OCH_3	C_6H_5	C_6H_5	H	Br	4	**3o**	78
16	H	C_6H_5	CH_2CO_2Et	H	Br	4	**3p**	82
17	Cl	C_6H_5	CH_2CO_2Et	H	Br	4	**3q**	85

[a] Reaction conditions: **1** (0.1 mmol), catalyst (0.01 mmol), anhydrous solvent (3 mL), methyloxirane (5 mmol) and allyl halide **2** (1 mmol) at 80 °C in CH_3CN.



Scheme 2. Reaction of *o*-ethynylphenylphosphonamides monoester (**1**) with 3-chloro-1-butene.

vinylpalladium species **B**; (iii) in the presence of a large excess of methyloxirane, followed by insertion of the carbon–carbon bond of allylic halide to give a carbon–palladium intermediate **C**, which subsequently undergoes β-elimination affording desired product **3** with regeneration of the Pd(II) catalyst. On the other hand, the vinylpalladium species **B** could also undergo protonation and lead to the cyclized product, which is competitive with the allylation.



Scheme 3. A proposed mechanism of cyclized coupling reaction.

To probe whether the synthesized 4-allyl-phosphaisoquinolin-1-ones are of biological activities, these compounds underwent a preliminary screening. We firstly tested their inhibitory activity against the enzyme SHP-1 (Src homology 2-containing phosphatase-1), one of the protein tyrosine phosphatases (PTPs). At a concentration of 20 μg/mL, the SHP-1 inhibition ratios of **3c**, **3d**, **3e**, **3g**, **3h**, **3i**, **3j**, **3k**, and **3l** are 20.2%, 21.8%, 24.7%, 36.6%, 23.5%, 54.3%, 33.8%, 23.3%, and 39.6%, respectively. Then their inhibitory activity against the MCH-1R (molanin-concentrating hormone receptor-1) was also tested, with IC_{50} value of **3c**, **3d**, **3e 3n** are 4.30, 3.78, 10.23, and 7.6 μmol, respectively. In comparison, 4-allylphosphaisocoumarins[17] have no MCH-1R activities, and 4-unsubstituted phosphaisoquinolin-1-ones[13] showed low MCH-1R activities. 4-Allyl group and N atom may be the basic factor. This represents the first example using the phosphorus analogues of heterocyclic natural products as MCH-1R inhibitors.

3. Conclusion

In summary, we have developed a novel $PdCl_2(CH_3CN)_2$-catalyzed coupling–cyclization of *o*-ethylnylphenylphosphonamide monoethyl esters with allyl halides to 4-allyl-phosphaisoquinolin-1-ones with high regioselectivity and good yields. These compounds show some bioactivities as inhibitor of MCH-1R. This reaction represents the first example of phosphonamides coupling–cyclization reaction with allyl halides, the olefin moiety of the resulting 4-allylic phosphaisoquinolin-1-ones provides possibilities for further functionalization for more complex derivatives to research its bioactivity. The synthesis of more derivatives and further biochemical evaluations are underway.

4. Experimental

4.1. General

NMR spectra were all recorded on a Varian Mercury 300 spectrometer using $CDCl_3$ as the solvent. The ^1H NMR spectra used $CDCl_3$ (with TMS) as the internal reference at 7.27 ppm. MS spectra were determined using a HP5989A mass spectrometer. IR spectra were measured on a Y-Zoom Cursor instrument. Starting materials **1** were prepared as described previously.[13]

4.2. General procedure for the preparation of 4-allyl-phosphaisoquinolin-1-ones (3)

A mixture of *o*-ethylnylphenylphosphonamide monoethyl esters (**1**) (0.1 mmol), allyl bromide (1.0 mmol), methyloxirane (5.0 mmol), and $PdCl_2(CH_3CN)_2$ (0.01 mmol) in 3 ml CH_3CN was stirred at 80 °C in a 25 ml flask for 4 h under nitrogen. The reaction mixture was then diluted with EtOAc and washed with brine, dried (Na_2SO_4), and evaporated in vacuo. Chromatography of the residue on silica gel using hexane/EtOAc as eluent gave the corresponding product 4-allyl-phosphaisoquinolin-1-ones (**3**).

4.3. Characterization data for products 3

*4.3.1. Compound **3a***

Oily. Yield: 90%. ^1H NMR: δ 8.06–7.98 (m, 1H), 7.59–7.27 (m, 6H), 7.08–7.02 (m, 5H), 6.67–6.65 (m, 2H), 5.83–5.72 (m, 1H), 5.07 (dd, J=9, 15.9 Hz, 1H), 4.92 (dd, J=2.1, 10.5 Hz, 1H), 4.78 (dd, J=2.1, 17.4 Hz, 1H), 4.13–4.06 (m, 2H), 3.97 (dd, J=7.5, 15.9 Hz, 1H), 3.07 (d, J=2.4 Hz, 2H), 1.29 (t, J=7.2 Hz, 3H); MS (EI): m/z: 415 (M^+, 100), 361 (69), 304 (30), 291 (24), 165 (7), 105 (9), 91 (90), 77 (10), 65 (12); IR (film, cm^{-1}): 3060, 2926, 1591, 1472, 1241, 1028, 950, 701. Anal. Calcd for $C_{26}H_{26}NO_2P$: C, 75.16; H, 6.31; N, 3.37. Found: C, 74.83; H, 6.39; N, 3.46.

*4.3.2. Compound **3b***

Oily. Yield: 69%. ^1H NMR: δ 7.95–7.88 (m, 1H), 7.61–7.35 (m, 8H), 6.10 (s, 1H), 5.99–5.86 (m, 1H), 5.08–4.94 (m, 2H), 4.01–3.93 (m, 2H), 3.22–3.20 (m, 2H), 1.25 (t, J=6.9 Hz, 3H); MS (EI): m/z: 325 (M^+, 100), 296 (43), 278 (27), 252 (43), 220 (14), 128 (18), 104 (14), 77 (27), 44 (50); IR (film, cm^{-1}): 3120, 2981, 1616, 1594, 1478, 1409, 1223, 1043, 958, 783, 697. Anal. Calcd for $C_{19}H_{20}NO_2P$: C, 70.14; H, 6.20; N, 4.31. Found: C, 69.97; H, 6.37; N, 4.21.

*4.3.3. Compound **3c***

A pale yellow solid; mp: 88–89 °C. Yield: 92%. ^1H NMR: δ 8.01–7.95 (m, 1H), 7.51–7.27 (m, 5H), 7.10–7.03 (m, 5H), 6.65 (d, J=6.6 Hz, 2H), 5.81–5.67 (m, 1H), 5.05 (dd, J=9.0, 15.6 Hz, 1H), 4.93 (dd, J=1.8, 10.5 Hz, 1H), 4.75 (dd, J=1.8, 17.4 Hz, 1H), 4.20–4.08 (m, 2H), 3.95 (dd, J=8.1, 15.6 Hz, 1H), 3.05 (d, J=3.6 Hz, 2H), 1.31 (t, J=6.9 Hz, 3H); MS (EI): m/z: 449 (M^+, 58), 358 (4), 330 (7), 128 (7), 91 (100), 77 (4), 65 (11); IR (film, cm^{-1}): 3061, 2926, 1637, 1587, 1472, 1242, 1156, 1027, 953, 701. Anal. Calcd for $C_{26}H_{25}ClNO_2P$: C, 69.41; H, 5.60; N, 3.11. Found: C, 69.79; H, 5.80; N, 2.95.

4.3.4. Compound ***3d***

Oily. Yield: 87%. ^{1}H NMR: δ 7.93–7.88 (m, 1H), 7.51–7.36 (m, 7H), 5.88–5.57 (m, 1H), 5.02 (dd, J=1.8, 10.2 Hz, 1H), 4.92 (dd, J=1.8, 17.4 Hz, 1H), 4.13–3.98 (m, 2H), 3.63–3.50 (m, 1H), 3.16–3.14 (m, 2H), 2.91–2.81 (m, 1H), 1.31–1.23 (m, 5H), 0.55 (t, J=7.2 Hz, 3H); MS (EI): m/z: 401 (M^+, 100), 372 (28), 344 (35), 303 (26), 215 (10), 104 (15), 91 (7), 77 (18), 65 (6); IR (film, cm^{-1}): 3060, 2968, 1638, 1587, 1474, 1240, 1158, 1022, 954, 829, 703. Anal. Calcd for $C_{22}H_{25}ClNO_2P$: C, 65.75; H, 6.27; N, 3.49. Found: C, 66.08; H, 6.38; N, 3.48.

4.3.5. Compound ***3e***

Oily. Yield: 88%. ^{1}H NMR: δ 8.00–7.95 (m, 1H), 7.54–7.44 (m, 2H), 7.14–6.95 (m, 7H), 6.67–6.65 (m, 2H), 5.82–5.70 (m, 1H), 5.03 (dd, J=9.0, 15.9 Hz, 1H), 4.93 (dd, J=1.8, 10.2 Hz, 1H), 4.75 (dd, J=1.8, 17.1 Hz, 1H), 4.19–4.08 (m, 2H), 3.99 (dd, J=8.1, 15.9 Hz, 1H), 3.07 (d, J=3.6 Hz, 2H), 2.69 (q, J=7.8 Hz, 2H), 1.33–1.24 (m, 6H); MS (MALDI): m/z: 477 (M^+, 100), 478 (M^++1, 42); IR (film, cm^{-1}): 3030, 2968, 1715, 1589, 1473, 1245, 1157, 1027, 953, 697. Anal. Calcd for $C_{28}H_{29}ClNO_2P$: C, 70.36; H, 6.12; N, 2.93. Found: C, 70.38; H, 6.17; N, 2.83.

4.3.6. Compound ***3f***

A pale yellow solid; mp: 111–112 °C. Yield: 82%. ^{1}H NMR: δ 7.93–7.87 (m, 1H), 7.50–7.46 (m, 1H), 7.35–7.30 (m, 1H), 7.16–7.14 (m, 3H), 6.91–6.89 (m, 2H), 5.97–5.84 (m, 1H), 5.30 (dd, J=10.2, 15.9 Hz, 1H), 4.90 (d, J=10.2 Hz, 1H), 4.63 (d, J=17.7 Hz, 1H), 4.48 (dd, J=6.9, 16.5 Hz, 1H), 4.05–3.95 (m, 2H), 3.32–3.15 (m, 2H), 2.32–2.13 (m, 2H), 1.63–1.60 (m, 2H), 1.52–1.30 (m, 2H), 1.23 (t, J=6.9 Hz, 3H), 0.924 (t, J=6.9 Hz, 3H); MS (MALDI): m/z: 429 (M^+, 40), 430 (M^++1, 100); IR (film, cm^{-1}): 3030, 2927, 1596, 1475, 1245, 1029, 949, 821. Anal. Calcd for $C_{24}H_{29}ClNO_2P$: C, 67.05; H, 6.80; N, 3.26. Found: C, 67.09; H, 6.57; N, 2.98.

4.3.7. Compound ***3g***

Oily. Yield: 85%. ^{1}H NMR: δ 7.52–7.46 (m, 2H), 7.36–7.27 (m, 4H), 7.16–7.03 (m, 5H), 6.65 (d, J=7.2 Hz, 2H), 5.82–5.70 (m, 1H), 5.07 (dd, J=9.0, 16.2 Hz, 1H), 4.92 (d, J=10.2 Hz, 1H), 4.76 (d, J=17.4 Hz, 1H), 4.17–4.04 (m, 2H), 3.98–3.91 (m, 1H), 3.93 (s, 3H), 3.05 (d, J=4.2 Hz, 2H), 1.33 (t, J=6.9 Hz, 3H); MS (EI): m/z: 445 (M^+, 100), 354 (17), 326 (30), 308 (20), 159 (7), 115 (11), 91 (56), 77 (4), 65 (14); IR (film, cm^{-1}): 3030, 2980, 1737, 1604, 1490, 1233, 1029, 952, 701. Anal. Calcd for $C_{27}H_{28}NO_3P$: C, 72.79; H, 6.34; N, 3.14. Found: C, 72.59; H, 6.64; N, 2.91.

4.3.8. Compound ***3h***

Z/*E*=77:23. Oily. Yield: 85%. ^{1}H NMR: δ 8.05–7.98 (m, 1H), 7.70–7.27 (m, 6H), 7.08–7.00 (m, 5H), 6.66–6.62 (m, 2H), 5.37–5.27 (m, 1H), 5.19–5.12 (m, 1H), 5.06 (dd, J=9.3, 15.3 Hz, 1H), 4.17–4.03 (m, 2H), 3.96 (dd, J=8.1, 15.3 Hz, 1H), 3.09–3.00 (m, 2H), 1.63–1.37 (m, 3H), 1.28 (t, J=7.2 Hz, 3H); MS (MALDI): m/z: 429 (M^+, 100), 430 (M^++1, 40); IR (film, cm^{-1}): 3028, 2933, 1591, 1473, 1241, 1164, 1028, 950, 701. Anal. Calcd for $C_{27}H_{28}NO_2P$: C, 75.51; H, 6.57; N, 3.26. Found: C, 75.69; H, 6.54; N, 3.17.

4.3.9. Compound ***3i***

Z/*E*=77:23. Oily. Yield: 78%. ^{1}H NMR: δ 7.96–7.89 (m, 1H), 7.67–7.35 (m, 3H), 7.13–7.12 (m, 3H), 6.92–6.89 (m, 1H), 5.61–5.44 (m, 1H), 5.30 (dd, J=9.3, 16.5 Hz, 1H), 5.09–5.01 (m, 1H), 4.48 (dd, J=6.9, 16.5 Hz, 1H), 4.01–3.90 (m, 2H), 3.27–3.14 (m, 2H), 2.33–2.11 (m, 2H), 1.74–1.49 (m, 3H), 1.66–1.55 (m, 1H), 1.47–1.29 (m, 3H), 1.22 (t, J=7.2 Hz, 3H), 0.94 (t, J=7.2 Hz, 3H); MS (EI): m/z: 410 (M^++1, 14), 366 (9), 338 (3), 289 (3), 247 (5), 106 (6), 91 (100), 77 (4), 65 (12); IR (film, cm^{-1}): 3063, 2931, 1594, 1473, 1245, 1094, 1034, 954, 738, 697. Anal. Calcd for $C_{25}H_{32}NO_2P$: C, 73.33; H, 7.88; N, 3.42. Found: C, 73.17; H, 7.74; N, 3.21.

4.3.10. Compound ***3j***

Z/*E*=77:23. Oily. Yield: 86%. ^{1}H NMR: δ 8.01–7.96 (m, 1H), 7.56–7.30 (m, 5H), 7.08–7.02 (m, 5H), 6.66–6.61 (m, 2H), 5.36–5.00 (m, 3H), 4.19–4.04 (m, 2H), 3.95 (dd, J=8.1, 15.6 Hz, 1H), 3.07–2.97 (m, 2H), 1.53–1.51 (m, 2.3H), 1.38 (d, J=6.6 Hz, 0.7H), 1.29 (t, J=6.9 Hz, 3H); MS (MALDI): m/z: 463 (M^+, 100), 464 (M^++1, 28); IR (film, cm^{-1}): 3063, 3029, 2982, 1715, 1588, 1473, 1243, 1157, 1028, 955, 701. Anal. Calcd for $C_{27}H_{27}ClNO_2P$: C, 69.90; H, 5.87; N, 3.02. Found: C, 69.55; H, 5.77; N, 3.01.

4.3.11. Compound ***3k***

Z/*E*=77:23. A yellow solid; mp: 92–93 °C. Yield: 81%. ^{1}H NMR: δ 7.92–7.86 (m, 1H), 7.56–7.34 (m, 7H), 5.42–5.22 (m, 2H), 4.12–3.96 (m, 2H), 3.61–3.48 (m, 1H), 3.15–3.06 (m, 2H), 2.92–2.79 (m, 1H), 1.58 (dd, J=1.2, 6 Hz, 2.3H), 1.44–1.42 (m, 0.7H), 1.27–1.23 (m, 5H), 0.54 (t, J=2.4 Hz, 3H); MS (MALDI): m/z: 415 (M^+, 100), 416 (M^++1, 33); IR (film, cm^{-1}): 3018, 2968, 1587, 1476, 1237, 1162, 1025, 958, 705. Anal. Calcd for $C_{23}H_{27}ClNO_2P$: C, 66.42; H, 6.54; N, 3.37. Found: C, 66.58; H, 6.64; N, 3.31.

4.3.12. Compound ***3l***

Z/*E*=77:23. Oily. Yield: 83%. ^{1}H NMR: δ 7.91–7.86 (m, 1H), 7.56–7.45 (m, 2H), 7.27–7.23 (m, 4H), 5.43–5.24 (m, 2H), 4.12–3.94 (m, 2H), 3.61–3.49 (m, 1H), 3.16–3.09 (m, 2H), 2.91–2.75 (m, 1H), 2.71 (q, J=7.5 Hz, 2H), 1.59 (d, J=5.7 Hz, 2.3H), 1.45 (d, J=6.6 Hz, 0.7H), 1.29–1.22 (m, 8H), 0.54 (t, J=7.5 Hz, 3H); MS (MALDI): m/z: 443 (M^+, 100), 444 (M^++1, 32); IR (film, cm^{-1}): 3024, 2967, 2876, 1587, 1472, 1243, 1157, 1025, 954, 830, 773. Anal. Calcd for $C_{25}H_{31}ClNO_2P$: C, 67.64; H, 7.04; N, 3.16. Found: C, 67.68; H, 7.07; N, 2.95.

4.3.13. Compound ***3m***

A pale yellow solid; mp: 130–131 °C. Yield: 83%. ^{1}H NMR: δ 7.96–7.89 (m, 1H), 7.72–7.59 (m, 2H), 7.35–7.32 (m, 3H), 7.19–6.95 (m, 8H), 5.99–5.87 (m, 1H), 5.10–5.05 (ddd, J=1.9, 1.9, 1.4 Hz, 2H), 4.23–4.13 (m, 2H), 3.36_3.35 (d, J=2.1 Hz), 1.27 (t, J=14.0 Hz, 3H); IR (film, cm^{-1}): 3060, 2977, 1609, 1589, 1549, 1490, 1249, 1238, 1022, 946, 784, 695; MS (EI) m/z: 402 (M^++1, 26), 401 (M^+, 100), 372 (28), 354 (17), 328 (19), 280 (17), 180 (20), 77 (47). Anal. Calcd for $C_{25}H_{24}NO_2P$: C, 74.08; H, 6.03; N, 3.49. Found: C, 74.53; H, 6.14; N, 3.49.

4.3.14. Compound ***3n***

Oily. Yield: 80%. ^{1}H NMR: δ 7.92–7.86 (m, 1H), 7.64–7.53 (m, 2H), 7.33–7.29 (m, 2H), 7.21–6.95 (m, 8H), 5.93–5.82 (m, 1H), 5.11–5.01 (ddd, J=1.4, 1.4 Hz, 2.0 Hz, 2H), 4.22–4.14 (m, 2H), 3.31 (dd, J=0.5, 1.4 Hz, 2H), 1.28 (t, J=14.0 Hz, 3H); IR (film, cm^{-1}): 3060, 2929, 1639, 1492, 1256, 1025, 956, 785, 696; MS (EI) m/z: 437 (M^++2, 36), 436 (M^++1, 36), 435 (M^+, 100), 407 (12), 406 (17), 314 (10), 180 (27), 77 (37). Anal. Calcd for $C_{25}H_{23}ClNO_2P$: C, 68.89; H, 5.32; N, 3.21. Found: C, 68.47; H, 5.46; N, 3.06.

4.3.15. Compound ***3o***

Oily. Yield: 78%. ^{1}H NMR: δ 7.65–7.60 (m, 1H), 7.43–7.33 (m, 3H), 7.19–6.90 (m, 9H), 5.98–5.84 (m, 1H), 5.10–5.04 (t, J=18.5 Hz, 2H), 4.25–4.14 (m, 2H), 3.87 (s, 3H), 3.34 (s, 2H), 1.31 (t, J=14.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 16.3, 34.4, 55.6, 61.0, 111.3, 116.1, 118.9, 119.6, 123.8, 125.3, 126.1, 127.5, 127.6, 127.8, 128.1, 130.2, 132.3, 136.3, 137.5, 138.3, 138.9, 158.4; IR (film, cm^{-1}): 3059, 2980, 1638, 1559, 1552, 1490, 1261, 1028, 957, 759, 696; MS (EI) m/z: M=431, 354 (30), 233 (17), 221 (17), 205 (24), 197 (13), 191 (13), 105 (100), 91 (46); HRMS (EI). Calcd for $C_{20}H_{21}ClNO_4P$ (M^+): 431.1650. Found: 431.1651.

4.3.16. Compound ***3p***

Oily. Yield: 82%. ^{1}H NMR: δ 7.97–7.89 (m, 1H), 7.60–7.31 (m, 8H), 5.89–5.76 (m, 1H), 5.02–4.94 (ddd, J=3.6, 1.4 Hz, 1.5 Hz, 2H), 4.20–

4.12 (m, 3H), 3.96–3.77 (m, 3H), 3.19–3.14 (m, 2H), 1.30 (t, J=14.1 Hz, 3H), 0.99 (t, J=14.5 Hz, 3H); IR (film, cm^{-1}): 3078, 2982, 1819, 1753, 1638, 1553, 1246, 1186, 1030, 656, 705; MS (EI) m/z: 412 (M^++1, 28), 411 (M^+, 100), 338 (24), 310 (26), 294 (19), 292 (14), 269 (21), 268 (17). Anal. Calcd for $C_{23}H_{26}NO_4P$: C, 67.14; H, 6.37; N, 3.40. Found: C, 66.80; H, 6.56; N, 3.55.

*4.3.17. Compound **3q***

Oily. Yield: 85%. ^1H NMR: δ 7.92–7.879 (d, J=15.4 Hz, 1H), 7.53–7.27 (m, 7H), 5.85–5.76 (m, 1H), 4.99 (ddd, J=1.8, 3.1, 1.7 Hz, 2H), 4.23–4.12 (m, 3H), 3.95–3.73 (m, 3H), 3.14 (m, 2H), 1.31 (t, J=14.0 Hz, 3H), 1.01 (t, J=14.3 Hz, 3H); IR (film, cm^{-1}): 3061, 2982, 1752, 1607, 1496, 1246, 1029, 958, 104; MS (EI) m/z: 447 (M^++2, 35), 446 (M^++1, 30), 445 (M^+, 100), 372 (21), 344 (33), 328 (16), 303 (23), 302 (16). Anal. Calcd for $C_{23}H_{25}ClNO_4P$: C, 61.96; H, 5.65; N, 3.14. Found: C, 61.74; H, 5.42; N, 2.92.

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