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Synthesis of Phosphaisoquinolin-1-ones by Pd(II)-Catalyzed Cyclization of *o*-(1-Alkynyl)phenylphosphonamide Monoesters

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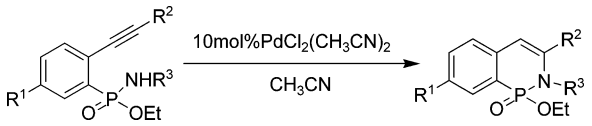

A Pd(II)-catalyzed intramolecular cyclization of *o*-(1-alkynyl)phenylphosphonamide monoethyl esters was examined, and a new class of six-membered phosphorus heterocycles (phosphaisoquinolin-1-ones) were formed with high regioselectivity and good yields. The present reaction is the first example of intramolecular addition of P−NH to substituted alkynes, which provides a valuable way to synthesize novel phosphorus heterocycles with potential bioactivities.

Introduction

Isoquinolin-1-ones have gained considerable synthetic and pharmacological interest for a long time because of their diverse bioactivities, such as antitumor activity,[1] cytotoxicity,[2] cardiovascular activity,[3] antineoplastic property,[4] antimicrobial property,[5] inhibition of human thymidylate synthase,[6] inhibition of PARP activity,[7] and reduction of systolic blood pressure.[8] Organophosphorus compounds continue to receive widespread attention due to their ubiquity in biological systems[9] and their potential to serve as novel pharmaceuticals.[10] Recent studies have indicated that a lot of heterocycle analogues containing phosphorus show the expected bioactivity. For example, phosphacoumarins showed good inhibitory activity against SHP-1,[11] and phosphaisocoumarins served as inhibitors of protein tyrosine phosphatase 1B (PTP1B).[12] Because there is a remarkable similarity in reactivity and bioactivities between the carbon species and their phosphorus counterparts,[13] one can anticipate that the phosphonamide analogues of isoquinolin-1-ones (i.e., phosphaisoquinolin-1-ones) would have potential bioactivities similar to those of isoquinolin-1-ones (Figure 1). To the best of our knowledge, phosphaisoquinolin-1-ones are a new type of phosphorus heterocycles that have never been synthesized thus far. So, the synthesis of phosphaisoquinolin-1-ones and the assessment of their biological properties are very attractive.

The transition-metal-catalyzed cyclization of alkynes possessing a nucleophile in proximity to the triple bond is an important process in organic synthesis, which can construct various heterocycles in an efficient and atom-economic way. Over the past few years, the intramolecular annulations of amines,[14] amides,[15] imines,[16] carboxylic acids,[17] alcohols,[18] and phosphonic acid monoesters[12] to a triple bond have been

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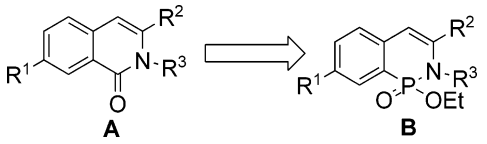
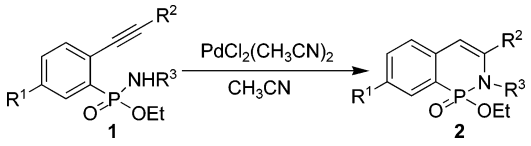


FIGURE 1. Isoquinolin-1-one (**A**) and the designed phosphaisoquinolin-1-ones (**B**).

SCHEME 1. Approach to Synthesize 2



extensively investigated using transition-metal reagents as effective catalysts. However, analogous intramolecular cyclization of P−NH to alkynes has never been reported thus far. In this paper, we report a mild and efficient palladium-catalyzed intramolecular cyclization of *o*-(1-alkynyl)phenylphosphonamide monoethyl esters **1**, leading to the formation of the phosphaisoquinolin-1-ones **2** (Scheme 1).

Results and Discussion

A two-step approach to phosphaisoquinolin-1-ones has been examined involving (i) preparation of the key starting materials **1** by the amination of phosphonyl chloride and (ii) the Pd(II)-catalyzed cyclization of the starting materials **1**.

The *o*-(1-alkynyl)phenylphosphonamide monoethyl esters **1** were prepared according to the known method[19] by treatment of **3** with thionyl chloride and subsequent amination of phosphonyl chloride with an amine such as benzylamine or *n*-propylamine in CH_2Cl_2 at 0 °C (Scheme 2). The *o*-(1-alkynyl)-phenylphosphonic acid monoethyl esters **3** were prepared as described previously.[12]

SCHEME 2. Synthesis of *o*-(1-Alkynyl)phenylphosphonamide Monoesters

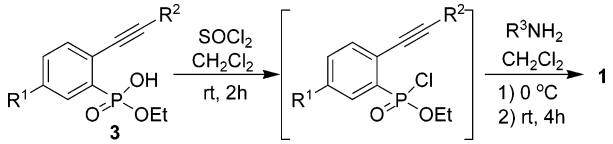
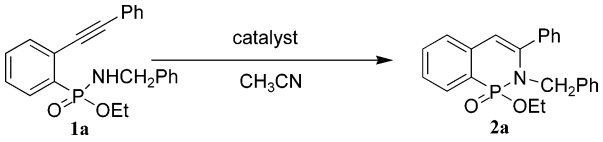


TABLE 1. Transition-Metal-Catalyzed Cyclization of the *o*-(1-Alkynyl)phenylphosphonamide Monoethyl Ester (1a)[a]



entry	catalyst (10 mol %)	time (h)	temp (°C)	yield (**2a**) (%)[b]
1	none	24	reflux	0
2	$PdCl_2$	24	25−80	65
3	$PdCl_2(CH_3CN)_2$	4	25−80	80
4	$PdCl_2(PPh_3)_2$	24	80	trace
5	$Pd(PPh_3)_4$	12	80	0
6	$Pd(OAc)_2$	12	80	0
7	AgI	12	reflux	0
8	$AgNO_3$	12	reflux	0
9	CuI	12	reflux	0
10	$CuCl_2$	24	60	trace
11	AcOH	72	reflux	0

[a] Reaction conditions: **1a** (0.1 mmol), catalyst (0.01 mmol), anhydrous solvent (1 mL). [b] Isolated yield.

The intramolecular cyclization of the *o*-(1-alkynyl)phenylphosphonamide monoethyl ester (**1a**) was first examined (Table 1). Through control experiments, we found that the use of $PdCl_2$ as a catalyst gave the product **2a** in only 65% yield, and $PdCl_2(CH_3CN)_2$ improved the yield to 80%; other palladium catalysts (e.g., $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, and $Pd(OAc)_2$) gave only unchanged starting materials. Next, silver salts (AgI, $AgNO_3$) and copper salts (CuI, $CuCl_2$) were tested, and no improvement was observed. $PdCl_2(CH_3CN)_2$ was an excellent catalyst for the current reaction, but the catalyst CuI showed less activities for this reaction. Although CuI was an excellent catalyst for intramolecular cyclization of 2-alkynylphenylphosphonic acid monoesters,[12] the catalyst $PdCl_2(CH_3CN)_2$ was less effective for intramolecular cyclization of 2-alkynylphenylphosphonic acid monoesters. All facts showed that the palladium catalyst $PdCl_2(CH_3CN)_2$ was crucial for this reaction. We also examined the reaction of **1a** to **2a** in the presence of AcOH without Pd catalysts; however, none of the desired product was detected, and only salt was formed for a long time.

In the presence of $PdCl_2(CH_3CN)_2$ (10 mol %), the reaction of **1a** was performed at room temperature for 24 h in CH_3CN, and product **2a** was isolated in 55% yield with 36% recovery of the reactant **1a**. While the reaction was run at 80 °C for 4 h, the reactant **1a** disappeared completely and gave product **2a** in 80% good isolated yield.

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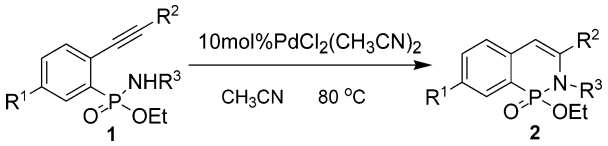
TABLE 2. $PdCl_2(CH_3CN)_2$-Catalyzed Cyclization of the *o*-(1-Alkynyl)phenylphosphonamide Monoethyl Esters 1[a]



entry	substrate	R^1	R^2	R^3	time (h)	product	yield (%)[c]
1	**1a**	H	C_6H_5	$C_6H_5CH_2$	4	**2a**	80
2	**1b**	H	C_6H_5	H	8	**2b**	68
3	**1c**	H	C_6H_5	*n*-Pr	4	**2c**	72
4	**1d**	H	*n*-Bu	$C_6H_5CH_2$	6	**2d**	87
5	**1e**	Cl	C_6H_5	$C_6H_5CH_2$	4	**2e**	85
6	**1f**	Cl	C_6H_5	*n*-Pr	4	**2f**	67
7	**1g**	Cl	*n*-Bu	$C_6H_5CH_2$	4	**2g**	85
8	**1h**	Cl	*p*-EtC_6H_5	$C_6H_5CH_2$	4	**2h**	72
9	**1i**	Cl	*p*-EtC_6H_5	*n*-Pr	4	**2i**	70
10	**1j**	Cl	cyclopropyl	$C_6H_5CH_2$	4	**2j**	90
11[b]	**1k**	Cl	CH_3OCH_2	*n*-Pr	6	**2k**	65
12	**1l**	OMe	C_6H_5	$C_6H_5CH_2$	6	**2l**	79

[a] The reaction of **1** was carried out in the presence of 10 mol % of $PdCl_2(CH_3CN)_2$ at 80 °C in CH_3CN for 4 h. [b] The addition of a few drops of CH_3CO_2H was essential for the reactant **1k**. [c] Isolated yield.

The reaction solvents were next studied. The use of DMF, DMSO, toluene, and DCM as the solvent proved to be ineffective, and none of the desired product was detected; only with CH_3CN or THF as the solvent did the cyclization reaction proceed smoothly, and CH_3CN proved to be the most suitable solvent. Moreover, it is particularly noteworthy that the reaction proceeded well without rigorously anhydrous or oxygen-free conditions, which will be a great advantage for practical use.

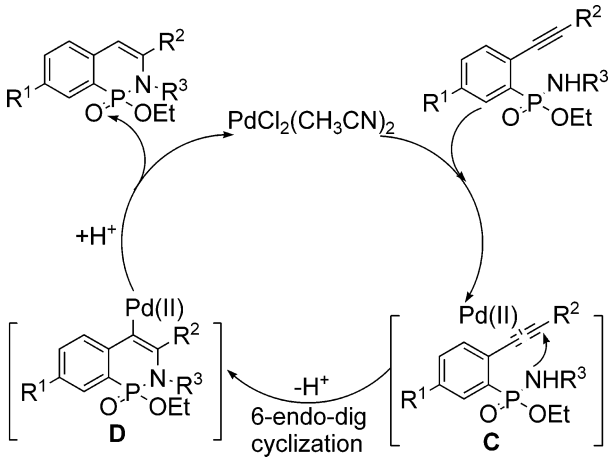
On the basis of the above optimization efforts, this method was applied to the synthesis of a variety of 2-, 3-, and 7-substituted phosphaisoquinolin-1-ones, and results are summarized in Table 2. In the presence of catalytic amounts of $PdCl_2(CH_3CN)_2$, *o*-(1-alkynyl)phenylphosphonamide monoethyl esters **1** with a variety of substituents (R^1, R^2, and R^3) could be cyclized to form phosphaisoquinolin-1-ones **2** in CH_3CN with moderate heating in good to excellent yields.

The chemical properties of substituents (R^2) on the acetylene terminal did not affect the yields of the phosphaisoquinolin-1-ones. Both aryl-substituted (entries 1−3, 5, 6, 8, 9, and 12) and alkyl-substituted (entries 4, 7, and 10) alkynes were able to tolerate the reaction conditions. However, the methoxymethyl-substituted alkyne (entry 11) has a significant effect on the yield of the phosphaisoquinolin-1-one. The reactant **1k** only gave 15% of product **2k** under the typical reaction conditions. However, with a few drops of CH_3CO_2H added, the reaction could give **2k** in 65% yield. In this instance, an external proton source presumably facilitated the cleavage of vinylpalladium species **D** to afford **2k** and to regenerate a reactive Pd(II) species (see proposed reaction mechanism in Scheme 3).

Functionalities such as chloro and methoxy on the aromatic ring also did not affect the reaction efficiency. In addition, the unsubstituted phosphonamide compound (entry 2) can also afford the cyclization product in good yields. The current reaction is extremely versatile and provides a convenient method for the synthesis of various phosphaisoquinolin-1-ones.

In contrast with the cyclization of *o*-(1-alkynyl)benzamides, which gave a 5-exo-dig cyclization predominantly in the presence of transition-metal catalysts, the current reaction shows very high regioselectivity to give the 6-endo-dig[20] cyclization product. In each case, only the six-membered endocyclic phosphaisoquinolin-1-ones were obtained, and the reaction

SCHEME 3



monitored by TLC and ^1H NMR spectra indicated that no other regioisomers had been observed during the reaction progress. Factors affecting the above regioselectivity are not yet very clear. A possible explanation is that the longer C−P and P−N bond lengths would be less favorable for the transition state leading to five-membered ring products than that leading to six-membered ring products. The structures of **2** were assigned on the basis of ^1H NMR and ^{13}C NMR spectra and X-ray crystallographic analysis (see Supporting Information).

On the basis of the above results and the related literature,[21] a plausible reaction mechanism is shown in Scheme 3. It presumably involves (i) the formation of the complex **C** through coordination of the alkynyl moiety of **1** with $PdCl_2(CH_3CN)_2$; (ii) regioselective nucleophilic attack of the activation triple bond by nitrogen in the endo mode to give the vinylpalladium species **D** (iii) which subsequently undergoes in situ protonation with regeneration of the Pd(II) catalyst to product **2**.

To probe whether the synthesized phosphaisoquinolin-1-ones possessed biological activities, their in vitro antitumor properties

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were evaluated in an A-549 lung cell line by the SRB assay. At a concentration of 10^{-4} mol/L, the A-549 lung cell growth inhibition ratios of **2a**, **2c**, **2d**, **2e**, **2f**, **2h**, **2j**, and **2l** are 97.2%, 74.7%, 83.2%, 97.0%, 97.2%, 97.2%, 97.5%, and 97.2%, respectively, but their biological activities drop obviously with the decrease of concentration. So, further studies are needed to confirm this possibility.

Conclusion

In summary, we have developed a novel $PdCl_2(CH_3CN)_2$-catalyzed cyclization reaction of *o*-(1-alkynyl)phenylphosphonamide monoethyl esters to phosphaisoquinolin-1-ones with high regioselectivity and good yields. The present reaction represents the first example of intramolecular addition of P−NH to alkynes, which provides a new approach to synthesize phosphorus heterocycles. The further biochemical evaluation of them and the extension of this reaction are underway.

Experimental Section

General Procedure for the Preparation of *o*-(1-Alkynyl)-phenylphosphonamide Monoethyl Esters 1. At ambient temperature, a solution of *o*-(1-alkynyl)phenylphosphonic acid monoethyl ester **3** (2 mmol) in CH_2Cl_2 (5 mL) was treated with thionyl chloride (6 mmol). After 2 h, the mixture was concentrated and the resultant opaque oil was exposed to a high vacuum (1 mmHg) for 3 h. The crude phosphonyl chloride was dissolved in CH_2Cl_2 (5 mL), and then Et_3N (2.2 mmol) and amine (10 mmol) were added at 0 °C; the solution was stirred for 4 h at ambient temperature. Concentration afforded a residue that was purified by column chromatography using hexane/EtOAc as eluent to give the corresponding **1**. The isolated yield and the physical data for **1** are as follows.

***N*-Benzyl (2-Phenylethynylphenyl)phosphonamide Monoethyl Ester (1a).** Purification by flash chromatography (1:1 hexane/EtOAc) afforded 375 mg of the product as a yellow solid. Mp: 96−97 °C. Yield: 50%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14−8.05 (m, 1H), 7.66−7.32 (m, 8H), 7.26−7.20 (m, 5H), 4.31−4.02 (m, 4H), 3.53 (q, J = 8.4 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H). MS (EI): *m/z* 375 (M^+, 100). Anal. Calcd for $C_{23}H_{22}NO_2P$: C, 73.59; H, 5.91; N, 3.73. Found: C, 73.29; H, 6.02; N, 3.63.

(2-Phenylethynylphenyl)phosphonamide Monoethyl Ester (1b). Purification by flash chromatography (1:1 hexane/EtOAc) afforded 273 mg of the product as a yellow solid. Mp: 115−116 °C. Yield: 48%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13−8.06 (m, 1H), 7.65−7.31 (m, 8H), 4.20−3.95 (m, 2H), 3.50 (d, J = 2.7 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). MS (EI): *m/z* 285 (M^+, 100). Anal. Calcd for $C_{16}H_{16}NO_2P$: C, 67.36; H, 5.65; N, 4.91. Found: C, 67.15; H, 5.68; N, 4.72.

***N*-Propyl (2-Phenylethynylphenyl)phosphonamide Monoethyl Ester (1c).** Purification by flash chromatography (2:1 hexane/EtOAc) afforded 294 mg of the product as oil. Yield: 45%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12−8.05 (m, 1H), 7.65−7.38 (m, 8H), 4.17−4.00 (m, 2H), 3.24 (q, J = 7.5 Hz, 1H), 3.01−2.89 (m, 2H), 1.47−1.40 (m, 2H), 1.33 (t, J = 9.6 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H). MS (EI): *m/z* 327 (M^+, 1). Anal. Calcd for $C_{19}H_{22}NO_2P$: C, 69.71; H, 6.77; N, 4.28. Found: C, 69.35; H, 6.70; N, 4.05.

General Procedure for the Preparation of Phosphaisoquinolin-1-ones 2. To a solution of *o*-(1-alkynyl)phenylphosphonamide monoethyl esters **1** (1 mmol) and acetonitrile (5 mL) was added $PdCl_2(CH_3CN)_2$ (0.1 mmol), and the mixture was heated at 80 °C for 4 h. The reaction mixture was diluted with EtOAc and washed with brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The resulting residue was purified by column chromatography using hexane/EtOAc as eluent to give the corresponding **2**. The isolated yield and the physical data for **2** are as follows.

2-Benzyl-1-ethoxy-3-phenyl-benzo[c][1,2] Azaphosphinine 1-Oxide (2a). Purification by flash chromatography (4:1 hexane/EtOAc) afforded 300 mg of the product as a pale yellow solid. Mp: 95−96 °C. Yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (dd, J = 13.2 Hz, J = 7.5 Hz, 1H), 7.57−7.27 (m, 8H), 7.07−6.96 (m, 3H), 6.67(d, J = 6.9 Hz, 2H), 6.20 (d, J = 2.1 Hz, 1H), 5.17 (dd, J = 15 Hz, J = 8.1 Hz, 1H), 4.42 (dd, J = 15.3 Hz, J = 9.6 Hz, 1H), 4.17−4.07 (m, 2H), 1.30 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.1, 138.2 (d, J = 6.9 Hz), 137.8 (d, J = 1.8 Hz), 136.4 (d, J = 5.1 Hz), 131.9 (d, J = 2.6 Hz), 128.7, 128.4 (d, J = 8.4 Hz), 128.3 (2 C), 128.2 (2 C), 127.9 (2 C), 127.7 (2 C), 126.9 (d, J = 11.6 Hz), 126.8, 126.5 (d, J = 15.5 Hz), 122.0 (d, J = 171.0 Hz), 112.6 (d, J = 10.2 Hz), 60.4 (d, J = 6.3 Hz), 48.7 (d, J = 3.4 Hz), 16.4 (d, J = 6.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 17.83. MS (EI): *m/z* 375 (M^+, 90), 91 (100). HRMS (EI): Calcd for $C_{23}H_{22}NO_2P$ ($M^+ + 1$), 376.1458; found, 376.1460.

2-Benzyl-7-chloro-1-ethoxy-3-phenyl-benzo[c][1,2] Azaphosphinine 1-Oxide (2e). Purification by flash chromatography (4:1 hexane/EtOAc) afforded 347 mg of the product as a yellow solid. Mp: 126−127 °C. Yield: 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (dd, J = 14.1 Hz, J = 2.1 Hz, 1H), 7.50−7.46 (m, 1H), 7.38−7.28 (m, 5H), 7.27−7.19 (m, 1H), 7.05−6.97 (m, 3H), 6.67−6.64 (m, 2H), 6.17 (d, J = 1.5 Hz, 1H), 5.15 (dd, J = 15.3 Hz, J = 8.1 Hz, 1H), 4.40 (dd, J = 15.6 Hz, J = 9.9 Hz, 1H), 4.16−4.10 (m, 2H), 1.28 (t, J = 3.9 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.5, 137.5, 136.5 (d, J = 5.7 Hz), 136.1 (d, J = 5.1 Hz), 132.2 (d, J = 17.2 Hz), 132.1, 129.0, 128.5 (d, J = 15.4 Hz), 128.4 (2 C), 128.3 (d, J = 4.2 Hz), 128.2 (2 C), 128.0 (2 C), 127.7 (2 C), 127.0, 123.6 (d, J = 170.4 Hz), 111.9 (d, J = 8.9 Hz), 60.8 (d, J = 6.1 Hz), 48.9 (d, J = 3.5 Hz), 16.4 (d, J = 6.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ 16.07. MS (EI): *m/z* 409 (M^+, 36), 380 (3), 91 (100), 77 (6), 43 (9). IR (film, cm^{-1}): 2926, 1714, 1609, 1472, 1248, 1123, 1028, 955. HRMS (EI): Calcd for $C_{23}H_{21}ClNO_2P$ ($M^+ + 1$), 410.1086; found, 410.1071.

7-Chloro-1-ethoxy-3-methoxylmethyl-2-propyl-benzo[c]-[1,2] Azaphosphinine 1-Oxide (2k). A few drops of CH_3CO_2H were added, and purification by flash chromatography (4:1 hexane/EtOAc) afforded 213 mg of the product as oil. Yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84−7.82 (m, 1H), 7.47−7.44 (m, 1H), 7.26−7.17 (m, 1H), 6.07 (d, J = 1.8 Hz, 1H), 4.47 (d, J = 12.9 Hz, 1H), 4.01−3.87 (m, 3H), 3.82−3.73 (m, 1H), 3.71−3.40 (m, 1H), 3.39 (s, 3H), 1.63−1.53 (m, 2H), 1.25 (t, J = 6.6 Hz, 3H), 0.87−0.82 (t, J = 7.8 Hz, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 140.0, 136.1 (d, J = 4.6 Hz), 132.1 (d, J = 15.0 Hz), 132.0, 128.1 (d, J = 7.2 Hz), 127.9 (d, J = 9.1 Hz), 123.0 (d, J = 127.3 Hz), 108.5 (d, J = 7.6 Hz), 72.2 (d, J = 3.4 Hz), 60.9 (d, J = 4.7 Hz), 57.6, 44.8 (d, J = 1.4 Hz), 24.9, 16.2 (d, J = 5.0 Hz), 11.1. ^{31}P NMR (121 MHz, $CDCl_3$): δ 17.47. MS (EI): *m/z* 329 (M^+, 100), 314 (4), 300 (29), 256 (28), 229 (28), 97 (5), 57 (11), 41 (22). IR (film, cm^{-1}): 2964, 1621, 1471, 1245, 1158, 1029, 959, 843, 788. HRMS (EI): Calcd for $C_{15}H_{21}ClNO_3P$ ($M^+ + 1$), 330.1029; found, 330.1020.

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Supporting Information Available: Typical experimental procedures and spectral data for **1** and **2** and the CIF for **2e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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