JOC Article

An Efficient Route to 4-Halophosphaisocoumarins via CuX_2-Mediated Direct Halocyclization of 2-(1-Alkynyl)phenylphosphonic Acid Diesters

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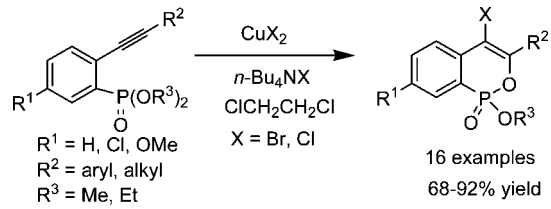

A series of 4-halophosphaisocoumarins were synthesized via CuX_2 (X = Br, Cl) -mediated direct halocyclization of 2-(1-alkynyl)phenylphosphonic acid diesters in dichloroethane with the addition of *n*-Bu_4NX or/and AgI in good to excellent yields. This reaction provides an effecient route to 4-halophosphaisocoumarins and represents the first example of bromo- and chlorocyclization of unsaturated phosphonic acid diesters.

Introduction

Electrophilic halocyclization of unsaturated carboxylic acids, carboxylates, amides, and sulfides is one of the most important procedures to construct various heterocycles. Among these, iodocyclization is the most widely studied and used reaction.[1] By contrast, there are far fewer reports on bromo- and chlorocyclization reactions,[2] probably because the stability of the corresponding halonium intermediates decreases in the order I > Br > Cl.[3] This methodology has also been used to construct cyclic phosphates and phosphonates (phostones), but direct bromo- and chlorocyclization of unsaturated phosphonic acid diesters has remained unknown. In 1977, Bartlett and Jernstedt[4] first reported iodocyclization of alkenylphosphates. In 1985, Zhao et al.[5] developed iodocyclization of alkenylphosphonic acid diesters, and they found that bromocyclization of the same substrates with Br_2 under similar conditions led only to dibromides. Subsequently, Shibuya and co-workers[6] synthesized several phostones by bromocyclization of alkenylphosphonic acid monoesters with NBS in 1997, but they have not extended it to chlorocyclization reactions thus far. We recently synthesized a series of 4-iodophosphaisocoumarins via iodocyclization of 2-(1-alkynyl)phenylphosphonic acid diesters, but reaction of the same diesters with *N*-bromosuccinimide (NBS) in $CHCl_3$ did not lead to any cyclized products, and 4-bromo- and 4-chlorophosphaisocoumarins were eventually prepared from the monoesters with NBS or *N*-chlorosuccinimide (NCS) in *N*,*N*-dimethylformamide (DMF) (Scheme 1).[7] Some of the obtained 4-halophosphaisomarins preliminarily showed medium antitumor activity and good insecticidal activity. However, the utility of our above bromo- and chlorocyclization reactions suffers from

(1) For recent selected iodocyclization reactions, see (a) Hu, T.; Liu, K.; Shen, M.; Yuan, X.; Tang, Y.; Li, C. *J. Org. Chem.* **2007**, *72*, 8555. (b) Minakata, S.; Morino, Y.; Oderatoshi, Y.; Komatsu, M. *Org. Lett.* **2006**, *8*, 3335. (c) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (d) Galeazzi, R.; Martelli, G.; Mobblili, G.; Orena, M.; Rinaldi, S. *Org. Lett.* **2004**, *6*, 2571. (e) Blot, V.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2004**, *69*, 1196. (f) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874. (g) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (h) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377. (i) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (j) Barluenga, J.; Trincado, M.; Rubio, E.; González, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (k) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067. (l) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. I* **2002**, 622. (m) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (n) Review: Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33.

(2) For electrophilic bromo- and chlorocyclization reactions, see (a) Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979. (b) Steinmann, J. G.; Phillips, J. H.; Sanders, W. J.; Kiessling, L. L. *Org. Lett.* **2001**, *3*, 3557. (c) Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem. Sect. B* **1988**, *27*, 380. (d) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459.

(3) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; Chapt. 15.

(4) Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829.

(5) Zhao, Y.-F.; Yan, S.-J.; Zhai, C. *J. Org. Chem.* **1985**, *50*, 2136.

(6) Yokomatsu, T.; Shioya, Y.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1997**, *46*, 463.

(7) (a) Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2004**, *6*, 1119. (b) Peng, A.-Y.; Ding, Y.-X. *Tetrahedron* **2005**, *61*, 10303.

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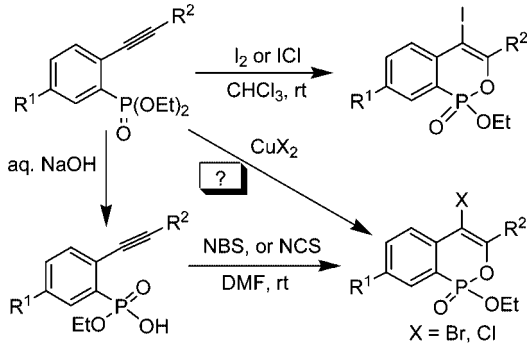
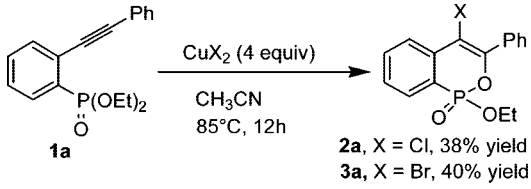
SCHEME 1. Previous Routes to 4-Halophosphaisocoumarins



SCHEME 2. Halocyclization of 1a with CuX_2 in CH_3CN



some drawbacks, including the concomitant formation of 4-unsubstituted phosphaisocoumarins and restricted generality (in some cases, no chlorocyclization products were obtained). Thus, it is highly desirable to develop a general and efficient methodology to synthesize 4-bromo- and 4-chlorophosphaisocoumarins starting from the diesters.

Halocyclization of 2,3-allenoic acids, esters, and amides,[8] 2-alkynylthioanisoles,[9] and 2-(1-alkynyl)benzoates[10] by $CuBr_2$ or $CuCl_2$ is well documented. On the basis of these results and the proposed mechanism for these transformations, we reasoned that the reaction of 2-(1-alkynyl)phenylphosphonic acid diesters with CuX_2 (X = Br, Cl) might be expected to form 4-halophosphaisocoumarins (Scheme 1).

Results and Discussions

We initiated this study with the reaction of 2-(1-phenylethynyl)phenylphosphonic acid diethyl ester **1a** with CuX_2 (X = Br, Cl) in CH_3CN. When **1a** was treated with 4 equiv of $CuCl_2$ (or $CuBr_2$) in CH_3CN at 85 °C for 12 h, **1a** disappeared completely, but the desired product **2a** (or **3a**) was obtained in only 38% (or 40%) yield along with some unidentified compounds with strong polarity (R_f = 0, petroleum ether/EtOAc = 2:1) (Scheme 2).

On the assumption that the above results might be associated with the deethylation of P-OEt by X^- in nonprotic polar solvents (e.g., CH_3CN, DMF),[11] we then turned our attention to investigate the reaction in other solvents with some additives, and the results are summarized in Table 1. It has been reported that ethanol/H_2O (3:2) is a good reaction medium for the $CuBr_2$-mediated bromolactonization of 2,3-allenoates,[8] but no reaction was detected for our substrate **1a** with $CuCl_2$ in this medium. Gratifyingly, when $ClCH_2CH_2Cl$ (dichloroethane, DCE) was used as solvent, it was found that both *n*-Bu_4NCl and AgI could accelerate the reaction, and the addition of *n*-Bu_4NCl plus AgI

TABLE 1. Halocyclization of 1a with CuX_2 under Various Conditions[a]

entry	solvent	additive (equiv)	temp, °C (time, h)	yield, %
1[b]	EtOH/H_2O		85 (12)	0 (**2a**)
2	DCE		85 (24)	30 (**2a**)[c]
3	DCE	*n*-Bu_4NCl (0.5)	85 (24)	40 (**2a**)
4	DCE	*n*-Bu_4NCl (2)	85 (24)	65 (**2a**)
5	DCE	*n*-Bu_4NCl (4)	85 (28)	66 (**2a**)
6	DCE	AgI (0.1)	85 (24)	67 (**2a**)
7	DCE	*n*-Bu_4NCl (2)/AgI (0.1)	85 (15)	86 (**2a**)
8	DCE	*n*-Bu_4NCl (0.2)/AgI (0.1)	85 (26)	75 (**2a**)
9[d]	DCE	*n*-Bu_4NCl (2)/AgI (0.1)	85 (24)	50 (**2a**)[e]
10[f]	DCE	*n*-Bu_4NCl (4)/AgI (0.1)	85 (24)	0 (**2a**)
11	DCE		85 (12)	61 (**3a**)
12	DCE	*n*-Bu_4NBr (2)	85 (5)	82 (**3a**)
13	DCE	*n*-Bu_4NBr (0.1)	85 (5)	82 (**3a**)
14	DCE	AgI (0.1)	85 (5)	81 (**3a**)
15	DCE	*n*-Bu_4NBr (2)	rt (36)	38 (**3a**)[g]

[a] **1a**:CuX_2 = 1:4 (X = Cl, Br). [b] EtOH:H_2O = 3:2. [c] 52% of **1a** was recovered. [d] With only 2 equiv. of $CuCl_2$. [e] 35% of **1a** was recovered. [f] Without $CuCl_2$. [g] 50% of **1a** was recovered.

gave better result, in which the starting material **1a** was consumed completely and **2a** was isolated in good yield (entries 2−8, Table 1). The decreased amount of *n*-Bu_4NCl would slow down the reaction, apparently; 2 equiv of *n*-Bu_4NCl proved to be appropriate for this reaction. Other additives, including LiCl, Ag_2CO_3, and $AgNO_3$, were also tested; the results showed that all of them affected the reaction slightly. Furthermore, the amount of $CuCl_2$ also affected the reaction. When the amount of $CuCl_2$ was reduced to 2 equiv, the yield of **2a** was decreased to 50% and no reaction took place in the absence of $CuCl_2$ (entries 9 and 10, Table 1). Under similar conditions, the reaction of **1a** with $CuBr_2$ (4 equiv) afforded **3a** in good yield, in which 0.1 equiv of *n*-Bu_4NBr was sufficient under heating conditions (entries 11−15, Table 1).

With these conditions in hand, the scope of this reaction was then examined. As shown in Table 2, we can see that the current reaction is extremely versatile and provides a convenient method to synthesize various 4-halophosphaisocoumarins in good to excellent yields. Functionalities, such as alkyl and aryl at the terminus of alkynes or chloro and methoxy on the benzene ring, are all tolerated under the reaction conditions. It should be pointed out that compounds **2b** and **2f** could not be obtained by our previous procedure starting from the corresponding monoesters.[7b] In addition, there are two features to be addressed about this reaction. First, $CuBr_2$ is more reactive than $CuCl_2$ by comparison of their reaction times and additives. Second, the reaction rates depend, to some extent, on the electronic and steric nature of the substrates. Alkynes with an electron-donating methoxy group on the benzene reacted faster than those with an electron-withdrawing chloro group. Alkynes bearing an aryl at the acetylic terminus reacted slower than those bearing an alkyl group, probably because of steric interactions. For example, in cases where R^2 is a phenyl group, the chlorocyclization reactions proceeded slowly and required the addition of *n*-Bu_4NCl and AgI, while for those cases where R^2 is an alkyl group, the chlorocyclization reactions needed only the addition of *n*-Bu_4NCl and the bromocyclization reactions proceeded smoothly even at room temperature at relatively slow rates.

It is noteworthy that the reaction of **1h** with $CuBr_2$ and *n*-Bu_4NBr gave the cyclization product **3h** only in 55% yield, along with 18% of the dibromide **4h** (entry 14, Table 2). By

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(9) Lu, W.-D.; Wu, M.-J. *Tetrahedron* **2007**, *63*, 356.
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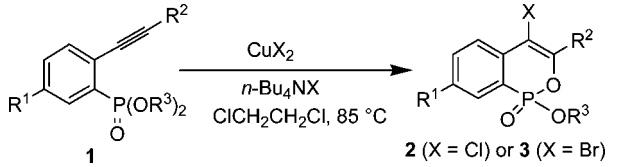
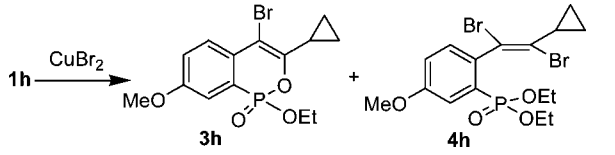
TABLE 2. Halocyclization of 1 with CuX_2[a]



	compound **1**					
entry	R^1	R^2	R^3	X	time, h	yield, %
1[b]	OMe	Ph	Et (**1b**)	Cl	10	70 (**2b**)
2	OMe	Ph	Et (**1b**)	Br	5	82 (**3b**)
3[b]	Cl	Ph	Et (**1c**)	Cl	28	73 (**2c**)
4	Cl	Ph	Et (**1c**)	Br	10	84 (**3c**)
5[b]	H	Ph	Me (**1d**)	Cl	12	68 (**2d**)
6	H	Ph	Me (**1d**)	Br	5	72 (**3d**)
7	H	*n*-Bu	Et (**1e**)	Cl	5	88 (**2e**)
8	H	*n*-Bu	Et (**1e**)	Br	1.5	88 (**3e**)
9	Cl	*n*-Bu	Et (**1f**)	Cl	8	89 (**2f**)
10	Cl	*n*-Bu	Et (**1f**)	Br	3	91 (**3f**)
11	Cl	*c*-Pr	Et (**1g**)	Cl	8	72 (**2g**)
12	Cl	*c*-Pr	Et (**1g**)	Br	1.5	92 (**3g**)
13	OMe	*c*-Pr	Et (**1h**)	Cl	5	79 (**2h**)
14	OMe	*c*-Pr	Et (**1h**)	Br	1	55 (**3h**)[c]

[a] Reaction conditions: **1** (0.5 mmol), CuX_2 (4 equiv), *n*-Bu_4NCl (2 equiv) or *n*-Bu_4NBr (0.1 equiv) in DCE (5 mL) at 85 °C unless otherwise specified. [b] Additional 0.1 equiv of AgI was added. [c] 18% of bromine addition product **4h** was isolated.

TABLE 3. Bromocyclization of 1h with $CuBr_2$[a]



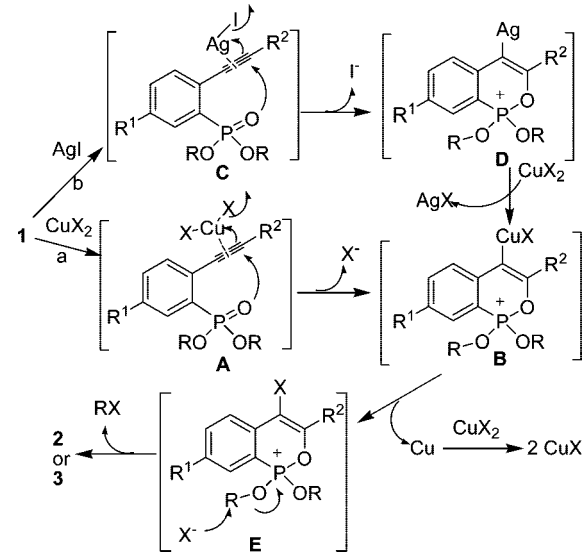
entry	solvent	additive (equiv)	temp, °C (time, h)	yield, %
1	DCE	*n*-Bu_4NBr (2)	rt (5)	50 (**3h**) + 25 (**4h**)
2	DCE	*n*-Bu_4NBr (2)	85 (4)	40 (**3h**) + 35 (**4h**)
3	DCE		rt (8)	70 (**3h**) + 10 (**4h**)
4	CH_3CN		85 (24)	20 (**3h**) + 18 (**4h**)
5[b]	CH_3CN		60 (7)	5 (**3h**) + 65 (**4h**)
6	$EtOH/H_2O$(3:2)		85 (10)	60 (**4h**)

[a] All reactions were conducted with **1h** and 4.0 equiv of $CuBr_2$ in solvent unless otherwise specified. [b] With only 2 equiv of $CuBr_2$.

contrast, other substrates appeared to be far more selective and very little of the noncyclized 1,2-addition products were detected. To improve the yield of the bromocyclized product **3h**, we examined the reaction of **1h** with $CuBr_2$ under other conditions, and the results are summarized in Table 3. When the reaction was conducted in DCE at room temperature in the absence of *n*-Bu_4NBr, the yield of **3h** could be increased to 70% (entry 3, Table 3). When the reaction was run in CH_3CN with only 2 equiv of $CuBr_2$, or in $EtOH/H_2O$ (3:2), the bromine addition adduct **4h** became the main product (entries 5 and 6, Table 3).

Based on the above results and related literature,[9,10,12] some plausible mechanisms for the formation of **2** and **3** are proposed in Scheme 3. Coordination of CuX_2 with the alkynyl moiety of **1** forms π-complex **A**.[12] Subsequently, regioselective nucleophilic attack of the activated triple bond by phosphonyl in the

SCHEME 3. Possible Reaction Mechanisms



endo mode[13] gives intermediate **B** (path a). Alternatively, a catalytic amount of AgI mediates the formation of intermediate **C**, and then **D**, which undergoes a transmetalation reaction with CuX_2 to give intermediate **B** (path b). Reductive elimination of **B** can afford intermediate **E**. Finally, removal of the alkyl group by X^- from **E** affords compound **2** or **3**. We thought that the accelerating effect of AgI might come mainly from the stronger coordination ability of Ag^+ (compared to CuX_2) and the release of a catalytic amount of I^-, which has stronger nucleophilicity (compared to Br^- and Cl^-) to remove the alkyl group from **E**. Alternatively, *n*-Bu_4NX may accelerate the reaction in the following two ways: (1) act as a phase-transfer catalyst to increase the solubility of CuX_2, or (2) provide a large amount of X^- to promote removal of the alkyl group. Furthermore, the intermediates **A** and **C** may be attacked by X^-, which would lead to the formation of dihalides **4**. Dihalogenation of alkenes or alkynes by $CuBr_2$, $CuCl_2$,[12b,c] or Br_2[14] is well documented and explained, but for the substrates we examined, the halocyclization reaction leading to the cyclized product is able to overwhelm the intermolecular process to the dihalide.

Conclusions

In conclusion, we developed a general and efficient method for the synthesis of 4-bromo- and 4-chlorophosphaisocoumarins via CuX_2-mediated direct halocyclization of 2-(1-alkynyl)phenylphosphonic acid diesters in dichloroethane. This reaction represents the first example of bromo- and chlorocyclization of unsaturated phosphonic acid diesters. Due to the easy availability of the starting material, simple procedure, and high efficiency, this methodology will show utility in the synthesis of P−O heterocycles.

Experimental Section

General Procedure for Synthesis of 2 or 3 by Halocyclization of 1 with CuX_2 (X = Cl, Br). The mixture of **1** (0.50 mmol) with $CuCl_2$ (2.0 mmol) and *n*-Bu_4NCl (1.0 mmol) [in some cases, additional AgI (0.05 mmol) was added], or with $CuBr_2$ (2.0 mmol)

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and *n*-Bu_4NBr (0.05 mmol), in DCE (5.0 mL) was stirred at 85 °C until the material **1** had completely or mostly disappeared by TLC monitoring (the reaction conditions and times were shown in Tables 1−3). The reaction mixture was then diluted with saturated brine and extracted with EtOAc. The combined organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel with petroleum ether/EtOAc (6:1−2:1) as the eluents to afford the corresponding product **2** or **3**.

Among the products, **2b**, **2e**, **2f**, **2h**, **3e**, and **3h** are new compounds; other compounds have been previously reported and their identities were confirmed by comparison with their reported spectral data.[7b,15]

4-Chloro-1-ethoxy-7-methoxy-3-phenylbenz[*c*-1,2]oxaphosphinine 1-Oxide (2b). White solid, mp 102.3−103.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.91 (m, 3H), 7.42−7.49 (m, 4H), 7.24−7.38 (m, 1H), 4.22−4.32 (m, 2H), 3.93 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7 (d, J = 18.7 Hz), 145.2 (d, J = 11.3 Hz), 133.1 (d, J = 5.4 Hz), 129.6, 129.3 (d, J = 6.8 Hz), 129.1, 128.0, 127.9 (d, J = 13.7 Hz), 122.2 (d, J = 179.7 Hz), 120.3 (d, J = 3.1 Hz), 113.9 (d, J = 12.9 Hz), 112.9 (d, J = 10.7 Hz), 63.4 (d, J = 6.6 Hz), 55.8, 16.4 (d, J = 5.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 10.7; MS (ESI) *m*/*z* (%) 373 [(M + Na)$^+$, 100]. Anal. Calcd for $C_{17}H_{16}ClO_4P$: C, 58.22; H, 4.60. Found: C, 58.07; H, 4.60. IR (KBr) 2961, 1578, 1407, 1265, 1093, 1034 cm^{-1}.

3-Butyl-4-chloro-1-ethoxybenz[*c*-1,2]oxaphosphinine 1-Oxide (2e). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.87 (m, 3H), 7.42−7.48 (m, 1H), 4.15−4.26 (m, 2H), 2.60−2.78 (m, 2H), 1.63−1.73 (m, 2H), 1.39−1.49 (m, 2H), 1.33 (t, J = 6.9 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 151.4 (d, J = 11.2 Hz), 135.9 (d, J = 7.1 Hz), 133.2, 129.2 (d, J = 4.1 Hz), 127.8 (d, J = 17.0 Hz), 124.7 (d, J = 9.7 Hz), 120.0 (d, J = 180.7 Hz), 113.0 (d, J = 10.3 Hz), 63.1 (d, J = 7.4 Hz), 32.3 (d, J = 4.4 Hz), 28.3, 22.1 (d, J = 12.2 Hz), 16.4 (d, J = 7.9 Hz), 13.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 11.0; MS (EI) *m*/*z* (%) 300 (M$^+$, 51), 302 (21), 271 (34), 243 (91), 195 (100). HRMS (EI) calcd for $C_{14}H_{18}O_3ClP$, 300.0677; found, 300.0677. Anal. Calcd for $C_{14}H_{18}ClO_3P$: C, 55.92; H, 6.03. Found: C, 55.57; H, 6.12. IR (film) 2960, 1622, 1467, 1408, 1272, 1152, 1092, 1033 cm^{-1}.

3-Butyl-4-chloro-7-chloro-1-ethoxybenz[*c*-1,2]oxaphosphinine 1-Oxide (2f). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.79 (m, 3H), 4.17−4.27 (m, 2H), 2.57−2.72 (m, 2H), 1.61−1.71 (m, 2H), 1.39−1.49 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8 (d, J = 11.6 Hz), 134.3 (d, J = 6.0 Hz), 133.9 (d, J = 20.6 Hz), 133.2 (d, J = 3.5 Hz), 128.9 (d, J = 9.9 Hz), 126.5 (d, J = 12.6 Hz), 121.9 (d, J = 179.9 Hz), 112.4 (d, J = 13.0 Hz), 63.4 (d, J = 6.2 Hz), 32.1 (d, J = 5.0 Hz), 28.1, 21.9, 16.2 (d, J = 6.3 Hz), 13.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ 7.8; MS (EI) *m*/*z* (%) 334 (M$^+$, 53), 336 (35), 306 (33), 277 (100), 229(76). HRMS (EI) calcd for $C_{14}H_{17}O_3Cl_2P$, 334.0287; found, 334.0289. Anal. Calcd for $C_{14}H_{17}Cl_2O_3P$: C, 50.17; H, 5.11. Found: C, 49.87; H, 5.25. IR (film) 2960, 1620, 1465, 1384, 1281, 1160, 1113, 1034, 999 cm^{-1}.

4-Chloro-3-cyclopropyl-1-ethoxy-7-methoxybenz[*c*-1,2]oxaphosphinine 1-Oxide (2h). White solid, mp 127.1−128.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.69 (m, 1H), 7.15−7.31 (m, 2H), 4.09−4.21 (m, 2H), 3.85 (s, 3H), 2.29−2.39 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 1.11−1.24 (m, 1H), 0.87−0.99 (m, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 158.5 (d, J = 19.8 Hz), 148.2 (d, J = 9.5 Hz), 129.3 (d, J = 5.7 Hz), 126.2 (d, J = 14.6 Hz), 120.8 (d, J = 179.3 Hz), 120.2, 112.6 (d, J = 9.9 Hz), 111.8 (d, J = 11.8 Hz), 63.0 (d, J = 6.6 Hz), 55.7, 16.4 (d, J = 3.4 Hz), 12.2 (d, J = 3.8 Hz), 6.7, 5.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ 11.4; MS (ESI) *m*/*z* 337 [(M + Na)$^+$, 100]. Anal. Calcd for $C_{14}H_{16}ClO_4P$: C, 53.43; H, 5.12. Found: C, 53.17; H, 5.15. IR (KBr) 2960, 1618, 1487, 1408, 1271, 1241, 1068, 1024 cm^{-1}.

4-Bromo-3-butyl-1-ethoxybenz[*c*-1,2]oxaphosphinine 1-Oxide (3e). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.86 (m, 3H), 7.42−7.48 (m, 1H), 4.17−4.28 (m, 2H), 2.70−2.85 (m, 2H), 1.65−1.75 (m, 2H), 1.41−1.49 (m, 2H), 1.35 (t, J = 6.9 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 152.3 (d, J = 11.2 Hz), 136.7 (d, J = 6.0 Hz), 133.3, 129.1 (d, J = 6.1 Hz), 127.9 (d, J = 14.2 Hz), 127.4 (d, J = 11.5 Hz), 120.3 (d, J = 181.9 Hz), 103.9 (d, J = 12.9 Hz), 63.2 (d, J = 6.5 Hz), 34.8 (d, J = 4.7 Hz), 28.4, 22.2, 16.5 (d, J = 5.3 Hz), 13.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 11.0; MS (EI) *m*/*z* (%) 300 (M$^+$, 51), 302 (21), 271 (34), 243 (91), 195 (100). HRMS (EI) calcd for $C_{14}H_{18}O_3BrP$, 344.0171; found, 344.0170. Anal. Calcd for $C_{14}H_{18}BrO_3P$: C, 48.72; H, 5.26. Found: C, 48.55; H, 5.19. IR (film) 2960, 1611, 1465, 1408, 1263, 1152, 1090, 1032 cm^{-1}.

4-Bromo-3-cyclopropyl-1-ethoxy-7-methoxybenz[*c*-1,2]oxaphosphinine 1-Oxide (3h). Pale yellow solid, mp 112.9−114.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.73 (m, 1H), 7.25−7.30 (m, 1H), 7.14−7.17 (m, 1H), 4.10−4.19 (m, 2H), 3.85 (s, 3H), 2.37−2.44 (m, 1H), 1.31 (t, J = 7.2 Hz, 3H), 1.11−1.17 (m, 1H), 0.84−0.98 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (d, J = 18.8 Hz), 149.1 (d, J = 10.3 Hz), 130.1 (d, J = 5.7 Hz), 128.9 (d, J = 13.4 Hz), 121.2 (d, J = 182.2 Hz), 120.3, 112.6 (d, J = 10.2 Hz), 102.6 (d, J = 12.1 Hz), 63.1 (d, J = 6.3 Hz), 55.7, 16.3 (d, J = 5.7 Hz), 14.4 (d, J = 5.3 Hz), 6.9, 5.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 11.4; MS (ESI) *m*/*z* (%) 383 [(M + H + Na)$^+$, 100]. MS (EI) *m*/*z* (%) 358 (M$^+$, 29), 360 (28), 330 (18), 251 (100), 233 (51). HRMS (EI) calcd for $C_{14}H_{16}O_4BrP$, 357.9964; found, 357.9965. Anal. Calcd for $C_{14}H_{16}BrO_4P$: C, 46.82; H, 4.49. Found: C, 46.88; H, 4.67. IR (KBr) 2962, 1575, 1405, 1265, 1155, 1089, 1031 cm^{-1}.

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Supporting Information Available: General procedure, characterization, NMR spectra of **2**, **3**, and **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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