ChemInform Abstract: An Efficient Route to 4-Halophosphaisocoumarins via CuX2-Mediated Direct Halocyclization of 2-(1-Alkynyl)phenylphosphonic Acid Diesters

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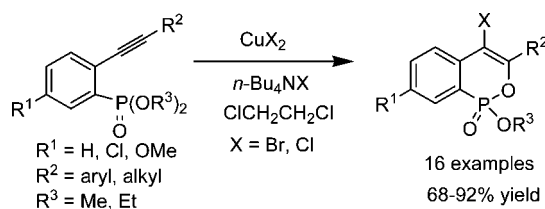Chinese Academy of Sciences

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An Efficient Route to 4-Halophosphaisocoumarins via CuX₂-Mediated Direct Halocyclization of 2-(1-Alkynyl)phenylphosphonic Acid Diesters

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A series of 4-halophosphaisocoumarins were synthesized via CuX₂ (X = Br, Cl) -mediated direct halocyclization of 2-(1-alkynyl)phenylphosphonic acid diesters in dichloroethane with the addition of *n*-Bu₄NX 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 Br₂ 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 CHCl₃ 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

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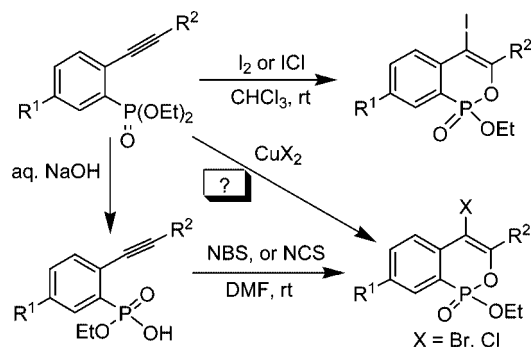
(4) Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829.

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

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SCHEME 1. Previous Routes to 4-Halophosphaisocoumarins

SCHEME 2. Halocyclization of 1a with CuX₂ in CH₃CN

2a, X = Cl, 38% yield
3a, X = Br, 40% yield
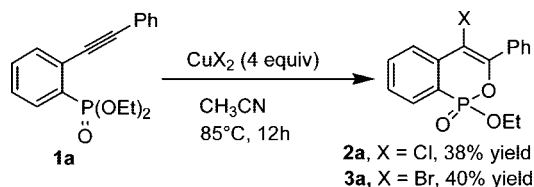
some drawbacks, including the concomitant formation of 4-unsubstituted phosphaisocoumarins and restricted generality (in some cases, no chlorocyclization products were obtained). Thus, it is highly desirable to develop a general and efficient methodology to synthesize 4-bromo- and 4-chlorophosphaiso-coumarins starting from the diesters.

Halocyclization of 2,3-allenoic acids, esters, and amides,[8] 2-alkynylthioanisoles,[9] and 2-(1-alkynyl)benzoates[10] by CuBr₂ or CuCl₂ 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 CuX₂ (X = Br, Cl) might be expected to form 4-halo-phosphaisocoumarins (Scheme 1).

Results and Discussions

We initiated this study with the reaction of 2-(1-phenylethy-nyl)phenylphosphonic acid diethyl ester **1a** with CuX₂ (X = Br, Cl) in CH₃CN. When **1a** was treated with 4 equiv of CuCl₂ (or CuBr₂) in CH₃CN 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., CH₃CN, 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/H₂O (3:2) is a good reaction medium for the CuBr₂-mediated bromolactonization of 2,3-allenoates,[8] but no reaction was detected for our substrate **1a** with CuCl₂ in this medium. Gratifyingly, when ClCH₂CH₂Cl (dichloroethane, DCE) was used as solvent, it was found that both n-Bu₄NCl and AgI could accelerate the reaction, and the addition of n-Bu₄NCl plus AgI

(8) Review: Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701 and references therein.
(9) Lu, W.-D.; Wu, M.-J. *Tetrahedron* **2007**, *63*, 356.
(10) Liang, Y.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2007**, 400.
(11) (a) Polozov, A. M.; Cremer, S. E. *J. Organomet. Chem.* **2002**, *646*, 153. (b) Peng, A.-Y.; Li, B.; Guo, Y.-J. Chinese Patent CN 101143880, 2008 (*Chem. Abstr.* **2008**, *148*, 449764).

TABLE 1. Halocyclization of 1a with CuX₂ under Various Conditions[a]

entry	solvent	additive (equiv)	temp, °C (time, h)	yield, %
1[b]	EtOH/H₂O		85 (12)	0 (**2a**)
2	DCE		85 (24)	30 (**2a**)[c]
3	DCE	n-Bu₄NCl (0.5)	85 (24)	40 (**2a**)
4	DCE	n-Bu₄NCl (2)	85 (24)	65 (**2a**)
5	DCE	n-Bu₄NCl (4)	85 (28)	66 (**2a**)
6	DCE	AgI (0.1)	85 (24)	67 (**2a**)
7	DCE	n-Bu₄NCl (2)/AgI (0.1)	85 (24)	86 (**2a**)
8	DCE	n-Bu₄NCl (0.2)/AgI (0.1)	85 (26)	75 (**2a**)
9[d]	DCE	n-Bu₄NCl (2)/AgI (0.1)	85 (24)	50 (**2a**)[e]
10[f]	DCE	n-Bu₄NCl (4)/AgI (0.1)	85 (24)	0 (**2a**)
11	DCE		85 (12)	61 (**3a**)
12	DCE	n-Bu₄NBr (2)	85 (5)	82 (**3a**)
13	DCE	n-Bu₄NBr (0.1)	85 (5)	82 (**3a**)
14	DCE	AgI (0.1)	85 (5)	81 (**3a**)
15	DCE	n-Bu₄NBr (2)	rt (36)	38 (**3a**)[g]

[a] **1a**:CuX₂ = 1:4 (X = Cl, Br). [b] EtOH:H₂O = 3:2. [c] 52% of **1a** was recovered. [d] With only 2 equiv. of CuCl₂. [e] 35% of **1a** was recovered. [f] Without CuCl₂. [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-Bu₄NCl would slow down the reaction, apparently; 2 equiv of n-Bu₄NCl proved to be appropriate for this reaction. Other additives, including LiCl, Ag₂CO₃, and AgNO₃, were also tested; the results showed that all of them affected the reaction slightly. Furthermore, the amount of CuCl₂ also affected the reaction. When the amount of CuCl₂ was reduced to 2 equiv, the yield of **2a** was decreased to 50% and no reaction took place in the absence of CuCl₂ (entries 9 and 10, Table 1). Under similar conditions, the reaction of **1a** with CuBr₂ (4 equiv) afforded **3a** in good yield, in which 0.1 equiv of n-Bu₄NBr 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, CuBr₂ is more reactive than CuCl₂ 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 R² is a phenyl group, the chlorocy-clization reactions proceeded slowly and required the addition of n-Bu₄NCl and AgI, while for those cases where R² is an alkyl group, the chlorocyclization reactions needed only the addition of n-Bu₄NCl and the bromocyclization reactions proceeded smoothly even at room temperature at relatively slow rates.
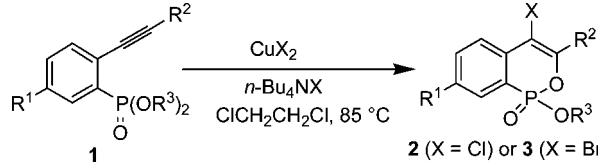
It is noteworthy that the reaction of **1h** with CuBr₂ and n-Bu₄NBr gave the cyclization product **3h** only in 55% yield, along with 18% of the dibromide **4h** (entry 14, Table 2). By
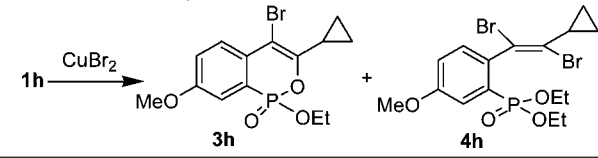
TABLE 2. Halocyclization of 1 with CuX$_2$[a]

		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$_4$NCl (2 equiv) or *n*-Bu$_4$NBr (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$_4$NBr (2)	rt (5)	50 (3h) + 25 (4h)
2	DCE	*n*-Bu$_4$NBr (2)	85 (4)	40 (3h) + 35 (4h)
3	DCE		rt (8)	70 (3h) + 10 (4h)
4	CH$_3$CN		85 (24)	20 (3h) + 18 (4h)
5[b]	CH$_3$CN		60 (7)	5 (3h) + 65 (4h)
6	EtOH/H$_2$O(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$_4$NBr, the yield of 3h could be increased to 70% (entry 3, Table 3). When the reaction was run in CH$_3$CN with only 2 equiv of CuBr$_2$, or in EtOH/H$_2$O (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
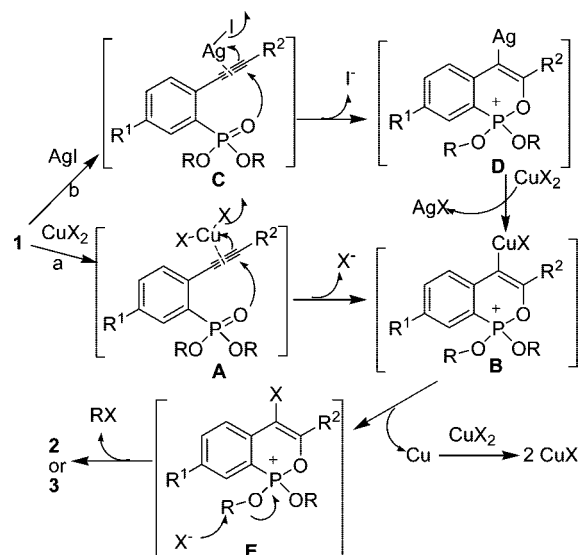
endo mode[13] gives intermediate B (path a). Alternatively, a catalytic amount of AgI mediates the formation of intermediate C, and then D, which undergoes a transmetalation reaction with CuX$_2$ to give intermediate B (path b). Reductive elimination of B can afford intermediate E. Finally, removal of 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$_4$NX 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$_4$NCl (1.0 mmol) [in some cases, additional AgI (0.05 mmol) was added], or with CuBr$_2$ (2.0 mmol)

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(14) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068.

and *n*-Bu$_4$NBr (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$_2$SO$_4$. 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$_4$P: 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$_3$ClP, 300.0677; found, 300.0677. Anal. Calcd for C$_{14}$H$_{18}$ClO$_3$P: 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$_3$Cl$_2$P, 334.0287; found, 334.0289. Anal. Calcd for C$_{14}$H$_{17}$Cl$_2$O$_3$P: 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$_4$P: 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$_3$BrP, 344.0171; found, 344.0170. Anal. Calcd for C$_{14}$H$_{18}$BrO$_3$P: 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$_4$BrP, 357.9964; found, 357.9965. Anal. Calcd for C$_{14}$H$_{16}$BrO$_4$P: C, 46.82; H, 4.49. Found: C, 46.88; H, 4.67. IR (KBr) 2962, 1575, 1405, 1265, 1155, 1089, 1031 cm^{-1}.

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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