JOC Article

CuX_2-Mediated Halolactonization Reaction of Monoesters of 1,2-Allenyl Phosphonic Acids and Their Suzuki Cross-Coupling Reaction

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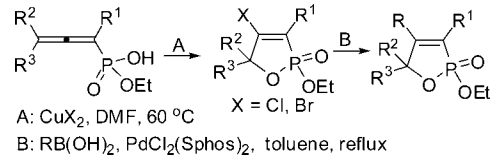
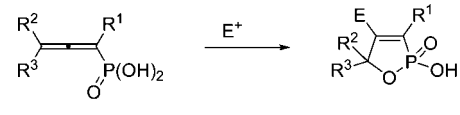


CuX_2-mediated (X = Cl, Br) halolactonization of monoesters of 1,2-allenyl phosphonic acids is presented. The reaction proceeded smoothly under the mild condition for differently substituted allenic substrates giving the 4-halo-2,5-dihydro[1,2]oxaphosphole 2-oxides in good yields. The Suzuki cross-coupling reaction of these bromides and even chlorides with organic boronic acids under the catalysis of $PdCl_2(Sphos)_2$ afforded 4-substitueted-2,5-dihydro[1,2]oxaphosphole 2-oxides in moderate to good yields.

Introduction

The phosphorus-containing compounds are always attractive due to their various biological activities[1] and catalytic properties.[2] So far, the phosphorylated heterocycles and related compounds have shown their superiorities and are already widely used in the field of agrochemistry and pharmaceuticals such as pesticides, insecticides, fungicides, bactericides, and growth regulators.[3] Phosphonates have better physiological stability because the carbon−phosphorus bond is not susceptible to enzymatic degradation by phosphatases, and have better cell permeability due to the more lipophilic nature of the phosphonate esters.[4] Among them the oxaphospholenes had been extensively studied not only for their potential biological activities but also as useful precursors for the synthesis of organophosphorous derivatives.[5] Methods have been developed using the allenic phosphonates or phosphonic acids: for example, Macomber and co-workers have disclosed cyclization of allenic phosphonic acids with different electrophiles (eq 1),[6] which provides a convenient method for the preparation of 1,2-oxaphosphol-3-enes. Subsequent reports[7] from other groups showed that the 2,5-dihydro[1,2]oxaphosphole 2-oxide derivatives would be formed directly via dialkyl phosphonates by treating with certain electrophilic reagents, such as Cl^+, I^+, SO_2Cl_2, etc.



(1)

We have previously described a convenient and efficient method for the synthesis of β-halobutenolides. Both β-chloro- and β-bromobutenolides can be obtained in high to excellent yields by the

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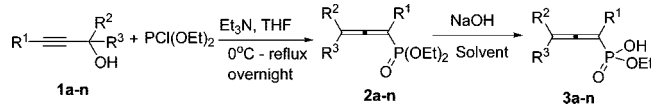
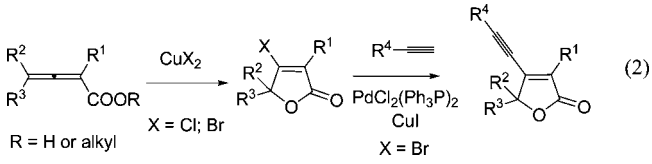
TABLE 1. Preparation of the Starting Materials 3a−n



entry	R^1	R^2	R^3		yield of **2** (%)	yield of **3** (%)
1	*n*-Bu	Me	Me	(**1a**)	72 (**2a**)	93 (**3a**)[a]
2	Bn	Me	Me	(**1b**)	51 (**2b**)	85 (**3b**)[b]
3	allyl	Me	Me	(**1c**)	98 (**2c**)	75 (**3c**)[c]
4	2-methylallyl	Me	Me	(**1d**)	81 (**2d**)	81 (**3d**)[c]
5	n-C_6H_{13}	Et	Et	(**1e**)	52 (**2e**)	82 (**3e**)[c]
6	*n*-Bu	$-(CH_2)_4-$		(**1f**)	32 (**2f**)	66 (**3f**)[c]
7	*n*-Bu	$-(CH_2)_5-$		(**1g**)	74 (**2g**)	55 (**3g**)[c]
8	Me	$-(CH_2)_5-$		(**1h**)	80 (**2h**)	57 (**3h**)[c]
9	*n*-Bu	Me	Et	(**1i**)	96 (**2i**)	85 (**3i**)[c]
10	*n*-Bu	H	*n*-Pr	(**1j**)	78 (**2j**)	42 (**3j**)[c,d]
11	allyl	H	H	(**1k**)	73 (**2k**)	64 (**3k**)[b]
12	Me	H	H	(**1*l***)	62 (**2*l***)	69 (**3*l***)[b]
13	*n*-Bu	H	H	(**1m**)	63 (**2m**)	99 (**3m**)[b]
14	H	Me	Me	(**1n**)	66 (**2n**)	99 (**3n**)[b]

[a] The reaction was conducted in H_2O under reflux overnight. [b] The reaction was conducted in H_2O at 80 °C overnight. [c] The reaction was conducted in a mixed solvent of H_2O and MeOH in a ratio of 1:1 under reflux. [d] 55% of **2j** was recovered.

reaction of 2,3-allenoic acids or ester with CuX_2 in aqueous acetone.[8] Subsequent metal-mediated coupling reactions[9] made the β-bromobutenolides an important class of building blocks for the introduction of different types of R′ at the β-position (eq 2).



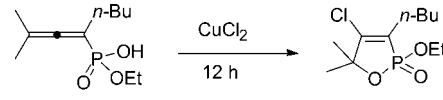
(2)

To complement our earlier work in this area,[10] we examined the CuX_2-mediated cyclization reaction of monoesters of 2,3-allenic phosphonic acids. To avoid using the relatively active eletrophiles such as I_2, Br_2, Cl_2, etc., the reaction with CuX_2 may be much easier to handle and should have better substituent compatibility.[8,11] Herein we present our recent results on halolactonization of monoesters of 1,2-allenyl phosphonic acids with CuX_2 and the subsequent of Pd-catalyzed Suzuki cross-coupling reaction of the corresponding bromides or even chlorides with Sphos as the ligand.

Results and Discussion

Preparation of the Starting Materials 3. The monoesters of 1,2-allenyl phosphonic acids **3** were prepared from hydrolysis of diethyl 1,2-allenyl phosphonates **2** with excess NaOH,[12] which, in turn, were afforded by the reaction of propargylic alcohols **1** with $P(OEt)_2Cl$ (Table 1).[13]

TABLE 2. $CuCl_2$-Mediated Chlorocyclization Reaction of Ethyl (2-Methylocta-2,3-dien-4-yl)phosphonate 3a



entry	$CuCl_2$ (equiv)	solvent	*T* (°C)	yield (%)
1	2	DMF	80	48
2	3	DMF	80	66
3	4	DMF	80	75
4	5	DMF	80	75
5	4	DMF	60	88
6	4	DMF	100	41
7	4	DMF	40	81
8	4	CH_2Cl_2	reflux	70
9	4	THF	60	76
10	4	CH_3CN	60	69
11	4	toluene	60	77

CuX_2-Mediated Halolactonization Reaction of Monoesters of 1,2-Allenyl Phosphonic Acids 3. Our initial study began with the reaction of the monoester of 1,2-allenyl phosphonic acid **3a** with $CuCl_2$ (Table 2). The reaction of **3a** with 2 equiv of $CuCl_2$ in DMF at 80 °C for 12 h smoothly afforded 3-butyl-4-chloro-2-ethoxy-5,5-dimethyl-2,5-dihydro-[1,2]oxaphosphole 2-oxide **4a** in 48% yield (entry 1, Table 2). After screening some reaction conditions, it was observed that the temperature is important, cyclic product **4a** was isolated in 88% yield in DMF at 60 °C by applying 4 equiv of $CuCl_2$ (entry 5, Table 2). When other solvents were used, no better results can be achieved (entries 8−11, Table 2).

With the optimized reaction conditions in hand, we studied the reaction of differently substituted monoesters of 1,2-allenyl phosphonic acids under the optimized conditions (Table 3). The bromolactonization products **5** were also smoothly formed from the reaction of the monoester of 1,2-allenyl phosphonic acid **3**

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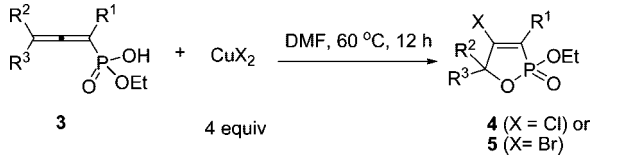
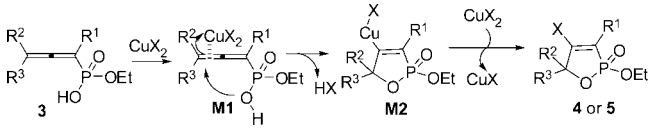
TABLE 3. CuX_2-Mediated Halocyclization Reaction of Monoesters of 1,2-Allenyl Phosphonic Acids 3



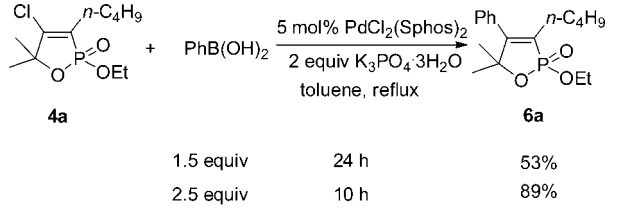
entry	R^1	R^2	R^3		X	yield (%)
1	*n*-Bu	Me	Me	(**3a**)	Cl	88 (**4a**)
2	(**3a**)				Br	84 (**5a**)
3	Bn	Me	Me	(**3b**)	Cl	68 (**4b**)
4	(**3b**)				Br	69 (**5b**)
5	allyl	Me	Me	(**3c**)	Cl	77 (**4c**)
6	(**3c**)				Br	82 (**5c**)
7	2-methylallyl	Me	Me	(**3d**)	Cl	82 (**4d**)
8	(**3d**)				Br	66 (**5d**)
9	n-C_6H_{13}	Et	Et	(**3e**)	Cl	83 (**4e**)
10	(**3e**)				Br	80 (**5e**)
11	*n*-Bu	$-(CH_2)_4-$		(**3f**)	Cl	73 (**4f**)
12	(**3f**)				Br	73 (**5f**)
13	*n*-Bu	$-(CH_2)_5-$		(**3g**)	Cl	84 (**4g**)
14	(**3g**)				Br	76 (**5g**)
15	Me	$-(CH_2)_5-$		(**3h**)	Cl	73 (**4h**)
16	(**3h**)				Br	94 (**5h**)
17	*n*-Bu	Me	Et	(**3i**)	Cl	38; 23 (**4i**)[a]
18	(**3i**)				Br	36; 26 (**5i**)[a]
19	*n*-Bu	*n*-Pr	H	(**3j**)	Cl	17; 12 (**4j**)[a]
20	(**3j**)				Br	15; 20 (**5j**)[a]

[a] Two diastereoisomers were isolated.

SCHEME 1



SCHEME 2



with $CuBr_2$ (Table 3). With fully substituted substrates **3**, the halolactonization products **4** or **5** could be smoothly prepared in good yields (entries 1−18, Table 3). When R^3 is H, the yield is relatively lower (entries 19 and 20, Table 3). It should be noted that two diastereoisomers were formed as a mixture when R^2 was different from R^3 (entries 17−20, Table 3). However, no reaction was observed with 1-monosubstituted substrates **3k**, **3*l***, **3m**, and 3,3-disubstituted substrate **3n**, possibly owing to the low electron density and, thus, low reactivity of the allene moieties toward CuX_2.

A plausible mechanism was proposed for this CuX_2-mediated halolactonization reaction (Scheme 1): in the presence of CuX_2, the 1,2-allenyl phosphonic acids undergo an oxy-metalation to generate a five-membered intermediate **M2**, which undergoes a C−X bond formation reaction to afford product **4** or **5** in the presence of another molecule of CuX_2 with the generation of two molecules of CuX.

Pd-Catalyzed Suzuki Cross-Coupling of 4-Halo-2,5-dihydro[1,2]oxaphosphole 2-Oxides with Organic Bronic Acids. Next we studied the Suzuki cross-coupling reaction[14] of 4-bromo-3-butyl-2-ethoxy-5,5-dimethyl-2,5-dihydro[1,2]oxaphosphole 2-oxide **5a** with phenyl boronic acid (Table 4). Our initial experiments were conducted using $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, or $PdCl_2(PhCN)_2$ as the catalyst; however, the cross-coupling product **6a** was formed in very low isolated yield (entries 1−5, Table 4).[15] Recently, Buchwald et al. developed a very practical and efficient catalyst system based on the ligand: Sphos.[16] We also have achieved the activation of the C−Cl bond of α-chloroalkylidene-β-lactones and furnished the Suzuki cross-coupling reaction in the presence of $PdCl_2(Sphos)_2$.[17] When we used the preprepared $PdCl_2(Sphos)_2$[17] (5 mol %) as the catalyst, the yield of **6a** was improved significantly (entries 6−8, Table 4). The best result was obtained by conducting the reaction in refluxing toluene for 1 h affording **6a** in 96% yield (entry 8, Table 4).

In addition, the cross-coupling reaction of the carbon−chlorine bond in 3-butyl-4-chloro-2-ethoxy-5,5-dimethyl-2,5-dihydro[1,2]oxaphosphole 2-oxide **4a** with 2.5 equiv of Ph-$B(OH)_2$ could also proceed smoothly to afford **6a** in 89% yield under the catalysis of $PdCl_2(Sphos)_2$ for 10 h (Scheme 2).

More examples of the Suzuki coupling of 4-halo-2-ethoxy-5,5-dimethyl-2,5-dihydro[1,2]oxaphosphole with phenyl boronic acid to afford the coupling products **6** in high yields were shown in Table 5. The structure of **6h** was further confirmed by the single-crystal X-ray diffraction study.[18]

The reactions of 4-bromo-3-butyl-2-ethoxy-5,5-dimethyl-2,5-dihydro[1,2]oxaphosphole 2-oxide **5a** with various different organic boronic acids were also examined (Table 6). Both electron-donating (entries 1−5, Table 6) and electron-withdrawing (entries 6−9, Table 6) aryl boronic acids could smoothly react with **5a** to afford the products **6** in high yields. *n*-Butyl boronic acid reacted with **5a** to afford product **6x** in 58% yield (entry 10, Table 6).

Conclusion

In conclusion, we have developed a convenient and efficient method for the synthesis of 4-bromo- or 4-chloro-2,5-dihydro[1,2]oxaphosphole 2-oxides in high yields by the reaction of monoesters of 1,2-allenyl phosphonic acids with CuX_2. $PdCl_2(Sphos)_2$ was shown to be an excellent catalyst for the Suzuki cross-coupling reaction of these products with organic boronic acids to afford 4-substituted-2,5-dihydro[1,2]oxaphosphole 2-oxides in moderate to excellent yields. It should be a very useful synthetic strategy for construction of relatively more complex phosphorus-containing compounds and provide a possibility for finding potentially bioactive hits in medicinal chemistry. Further studies in this area are being conducted in our laboratory.

Experimental Section

Synthesis of Starting Materials:

Synthesis of Diethyl 1,2-Allenyl Phosphonates 2a−n. Compounds **2a−n** were prepared from Horner−Mark [2,3]-sigmatropic rearrangement of propargylic alcohols **1** with $P(OEt)_2Cl$.[13]

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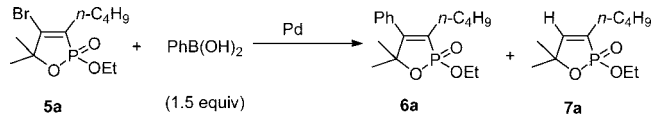
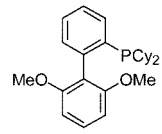
TABLE 4. The Suzuki Coupling Reaction of 4-Bromo-3-butyl-2-ethoxy-5,5-dimethyl-2,5-dihydro[1,2]oxaphosphole 2-Oxide 5a with Phenyl Boronic Acid



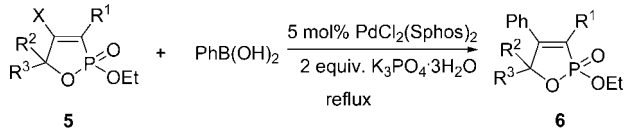


Sphos

entry	Pd complex (mol %)	base (equiv)	solvent	*T* (°C)	time (h)	yield of **6a** (%)
1	$Pd(PPh_3)_4$ (3)	Na_2CO_3[a] (2)	*b*	reflux	22	5[c]
2	$Pd(PPh_3)_4$ (3)	$K_3PO_4 \cdot 3H_2O$ (2)	toluene	100	8	34
3	$Pd(PPh_3)_4$ (3)	$K_3PO_4 \cdot 3H_2O$ (1)	toluene	100	24	29
4	$PdCl_2(PPh_3)_2$ (3)	$K_3PO_4 \cdot 3H_2O$ (2)	toluene	100	24	24
5	$PdCl_2(PhCN)_2$ (3)	$K_3PO_4 \cdot 3H_2O$ (2)	toluene	100	24	trace
6	$PdCl_2$(Sphos)$_2$ (3)	$K_3PO_4 \cdot 3H_2O$ (2)	toluene	100	2	84
7	$PdCl_2$(Sphos)$_2$ (3)	$K_3PO_4 \cdot 3H_2O$ (2)	toluene	reflux	1	89
8	$PdCl_2$(Sphos)$_2$ (5)	$K_3PO_4 \cdot 3H_2O$ (2)	toluene	reflux	1	96

[a] Aqueous solution (2 M). [b] Toluene:EtOH = 4:1. [c] Cycloisomerzation product **7a** (9%) was also isolated.

TABLE 5. The Suzuki Cross-Coupling Reaction of 4-Halo-2-ethoxy-5,5- dimethyl-2,5-dihydro[1,2]oxaphosphole 2-Oxide 5 with Phenyl Boronic Acid

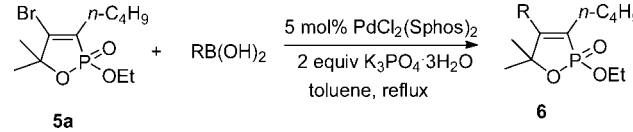


5 6

entry	R^1	R^2	R^3	X		time (h)	yield of **6** (%)
1[a]	Bn	Me	Me	Br	(**5b**)	4	96 (**6b**)
2[a]	allyl	Me	Me	Br	(**5c**)	7	80 (**6c**)
3[a]	n-C_6H_{13}	Et	Et	Br	(**5e**)	1	77 (**6e**)
4[a]	n-Bu	$-(CH_2)_5-$		Br	(**5g**)	2	81 (**6g**)
5[a]	Me	$-(CH_2)_5-$		Br	(**5h**)	1	81 (**6h**)
6[b]	Bn	Me	Me	Cl	(**4b**)	9	91 (**6b**)
7[b]	allyl	Me	Me	Cl	(**4c**)	9	65 (**6c**)
8[b]	n-C_6H_{13}	Et	Et	Cl	(**4e**)	9	73 (**6e**)
9[b]	n-Bu	$-(CH_2)_5-$		Cl	(**4f**)	1	73 (**6f**)
10[b]	Me	$-(CH_2)_5-$		Cl	(**4h**)	9	61 (**6h**)

[a] 1.5 equiv of $PhB(OH)_2$ was used. [b] 2.5 equiv of $PhB(OH)_2$ was used.

TABLE 6. The Suzuki Cross-Coupling Reaction of 4-Bromo-3-butyl-2-ethoxy-5,5-dimethyl-2,5-dihydro[1,2]oxaphosphole 2-Oxide 5a with Different Organic Bronic Acids



5a 6

	$RB(OH)_2$			
entry	R	equiv	time (h)	yield of **6** (%)
1	*p*-methylphenyl	1.5	1	91 (**6o**)
2	*p*-methoxyphenyl	1.5	1	71 (**6p**)
3	*m*-methoxyphenyl	1.5	2	66 (**6q**)
4	*o*-methoxyphenyl	1.5	2	93 (**6r**)
5	benzo[1,3]dioxol-5-yl	1.5	2	90 (**6s**)
6	*m*-nitrophenyl	2.5	20	69 (**6t**)
7	*p*-acetylphenyl	2.5	20	47 (**6u**)
8	cyclopropyl	2.5	64	84 (**6v**)
9	hex-1(*E*)-en-1-yl	2.5	48	90 (**6w**)
10	*n*-butyl	1.5	68	58 (**6x**)

Synthesis of Diethyl (2-Methylocta-2,3-dien-4-yl)phosphonate (2a). Typical procedure I: To a solution of 2-methylocta-3-yn-2-ol **1a** (4.255 g, 30.4 mmol) and Et_3N (6 mL, d = 0.726 g/cm^3, 4.32 g, 42.9 mmol) in THF (110 mL) was added a solution of $P(OEt)_2Cl$ (7.117 g, 45.5 mmol) in THF (50 mL) dropwise at −78 °C. After the addition the resulting mixture was warmed to rt and then heated under reflux. After complete conversion of the corresponding propargylic alcohol as monitored by TLC (petroleum ether/ether = 1:1), the mixture was filtered off. Evaporation of the solvent and flash chromatography on silica gel (eluent: petroleum ether/ether = 1:1) afforded 5.699 g (72%) of **2a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10−4.00 (m, 4 H), 2.15−2.07 (m, 2 H), 1.74 (d, J = 6.3 Hz, 6 H), 1.45−1.25 (m, 10 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 206.1 (d, J_{PC} = 5.7 Hz), 97.1 (d, J_{PC} = 16.7 Hz), 91.1 (d, J_{PC} = 188.0 Hz), 61.3 (d, J_{PC} = 5.7 Hz), 29.7 (d, J_{PC} = 6.3 Hz), 27.8 (d, J_{PC} = 8.0 Hz), 21.5, 19.1 (d, J_{PC} = 6.9 Hz), 15.7 (d, J_{PC} = 6.1 Hz), 13.3 (d, J_{PC} = 1.1 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 20.2; IR (neat, cm^{-1}) 1959, 1444, 1379, 1245, 1028; MS *m*/*z* 260 (M^+, 4.90), 218 ($M^+ - C_3H_6$, 56.41), 79 (100); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{25}O_3PNa$ [M^+ + Na] 283.1434, found 283.1433.

Synthesis of Monoesters of 1,2-Allenyl Phosphonic Acids 3a−n. Compounds **3a−n** were prepared by the hydrolysis of the diethyl 1,2-allenyl phosphonates **2** with excess NaOH.[12]

Synthesis of the Monoethyl Ester of (2-Methylocta-2,3-dien-4-yl)phosphonic Acid (3a). Typical procedure II: A solution of diethyl (2-methylocta-2,3-dien-4-yl)phosphonate **2a** (12.566 g, 47.2 mmol) and NaOH (11.596 g, 289.9 mmol) in 300 mL of H_2O was stirred under reflux overnight. After extraction with ethyl acetate, the aqueous phase was acidified with 1 N HCl and extracted with ether. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford 10.227 g (93%) of **3a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (br s, 1 H), 4.09−3.96 (m, 2 H), 2.18−2.03 (m, 2 H), 1.74 (d, J = 7.2 Hz, 6 H), 1.49−1.23 (m, 7 H), 0.89 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 206.4 (d, J_{PC} = 6.3 Hz), 97.9 (d, J_{PC} = 17.3

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(17) Ma, S.; Jiang, X.; Cheng, X.; Hou, H. *Adv. Synth. Catal.* **2006**, *348*, 2114.

(18) For the crystal data for **6h**, see the Supporting Information.

Hz), 92.0 (d, J_{PC} = 193.3 Hz), 61.8 (d, J_{PC} = 6.3 Hz), 30.1 (d, J_{PC} = 6.9 Hz), 28.0 (d, J_{PC} = 8.6 Hz), 21.9, 19.5 (d, J_{PC} = 7.5 Hz), 16.1 (d, J_{PC} = 6.9 Hz), 13.8; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 23.4; IR (neat, cm^{-1}) 1958, 1450, 1377, 1230, 1046; MS *m/z* 233 (M^+ + 1, 21.38), 232 (M^+, 9.69), 217 ($M^+ - CH_3$, 6.25), 190 ($M^+ - C_3H_6$, 47.13), 79 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{21}O_3P$ [M^+] 232.1228, found 232.1222.

Synthesis of the Monoethyl Ester of (2-Methylhepta-2,3,6-trien-4-yl)phosphonic Acid (3c). Typical procedure III: A solution of diethyl (2-methylhepta-2,3,6-trien-4-yl)phosphonate **2c** (9.318 g, 38.8 mmol) and NaOH (9.644 g, 241.1 mmol) in a mixed solvent of 240 mL of H_2O and 240 mL of MeOH was stirred under reflux for 3 days. After extraction with ethyl acetate, the aqueous phase was acidified with 1 N HCl and extracted with ether. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated. Then the residue was diluted again with ether, washed with water, dried over anhydrous Na_2SO_4, and evaporated to afford 6.284 g (75%) of **3c**. This compound was used for the cyclization reaction directly. **3c**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84−5.65 (m, 1 H), 5.09−4.95 (m, 2 H), 4.11−3.94 (m, 2 H), 2.84 (dd, J = 11.1, 6.9 Hz, 2 H), 1.70 (d, J = 6.9 Hz, 6 H), 1.27 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 207.3 (d, J_{PC} = 6.0 Hz), 134.9 (d, J_{PC} = 7.5 Hz), 116.0, 98.9 (d, J_{PC} = 15.9 Hz), 90.5 (d, J_{PC} = 195.5 Hz), 62.1 (d, J_{PC} = 6.6 Hz), 32.8 (d, J_{PC} = 9.4 Hz), 19.3 (d, J_{PC} = 6.9 Hz), 16.0 (d, J_{PC} = 6.7 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 22.1; IR (neat, cm^{-1}) 1961, 1642, 1445, 1377, 1211; MS *m/z* 216 (M^+, 5.97), 187 ($M^+ - C_2H_5$, 19.42), 91 (100); HRMS (EI) *m/z* calcd for $C_{10}H_{17}O_3P$ [M^+] 216.0915, found 216.0923.

CuX_2-Mediated Halocyclization of Monoesters of 1,2-Allenyl Phosphonic Acids—Synthesis of 4-Halo-2-ethoxy-2,5-dihydro[1,2]oxaphosphole 2-Oxides:

Synthesis of 3-Butyl-4-chloro-5,5-dimethyl-2-ethoxy-2,5-dihydro[1,2]oxa-phosphole 2-Oxide(4a).[10b] Typical procedure IV: A mixture of the monoethyl ester of (2-methylocta-2,3-dien-4-yl)phosphonic acid **3a** (69 mg, 0.30 mmol) and $CuCl_2$ (162 mg, 1.2 mmol) was stirred at 60 °C in 2 mL of DMF for 12 h. After 12 h, ether (50 mL) was added. The reaction mixture was washed with brine (three times) and dried over Na_2SO_4. After evaporation, the residue was subjected to column chromatography on silica gel (petroleum ether/ether acetate = 3/1) to afford 70 mg (88%) of **4a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (dq, J = 6.9, 9.3 Hz, 2 H), 2.42−2.18 (m, 2 H), 1.60−1.45 (m, 2 H), 1.51 (s, 3 H), 1.47 (s, 3 H), 1.38−1.24 (m, 2 H), 1.30 (t, J = 6.9 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 150.6 (d, J_{PC} = 50.6 Hz), 124.7 (d, J_{PC} = 157.7 Hz), 85.4 (d, J_{PC} = 2.9 Hz), 63.1 (d, J_{PC} = 6.3 Hz), 29.4 (d, J_{PC} = 1.7 Hz), 26.8 (d, J_{PC} = 2.9 Hz), 26.2 (d, J_{PC} = 2.3 Hz), 25.4 (d, J_{PC} = 9.2 Hz), 22.4, 16.5 (d, J_{PC} = 5.7 Hz), 13.6; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 32.7; IR (neat, cm^{-1}) 1630, 1464, 1368, 1272, 1151, 1042; MS *m/z* 269 ($M^+(^{37}Cl)$ + 1, 28.14), 267 ($M^+(^{35}Cl)$ + 1, 81.43), 240 ($M^+(^{37}Cl) - C_2H_4$, 4.91), 238 ($M^+(^{35}Cl) - C_2H_4$, 12.79), 226 ($M^+(^{37}Cl) - C_3H_6$, 19.15), 224 ($M^+(^{35}Cl) - C_3H_6$, 49.73), 43 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{20}O_3{}^{35}ClP$ [M^+] 266.0839, found 266.0844.

Synthesis of 4-Bromo-3-butyl-5,5-dimethyl-2-ethoxy-2,5-dihydro[1,2]oxaphosphole 2-Oxide (5a). Typical procedure V: A mixture of the monoethyl ester of (2-methylocta-2,3-dien-4-yl)phosphonic acid **3a** (71 mg, 0.31 mmol) and $CuBr_2$ (269 mg, 1.2 mmol) was stirred at 60 °C in 2 mL of DMF for 12 h. After 12 h, ether (50 mL) was added. The reaction mixture was washed with brine (three times) and dried over Na_2SO_4. After evaporation, the residue was subjected to column chromatography on silica gel (petroleum ether/ether acetate = 3/1) to afford 80 mg (84%) of **5a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22−4.05 (m, 2 H), 2.42−2.20 (m, 2 H), 1.79−1.61 (m, 1 H), 1.60−1.42 (m, 1 H), 1.56 (s, 3 H), 1.52 (s, 3 H), 1.41−1.27 (m, 5 H), 0.93 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 143.5 (d, J_{PC} = 47.7 Hz), 128.4 (d, J_{PC} = 152.5 Hz), 86.3 (d, J_{PC} = 4.0 Hz), 63.1 (d, J_{PC} = 6.9 Hz), 29.3 (d, J_{PC} = 1.7 Hz), 27.5, 27.4 (d, J_{PC} = 3.5 Hz), 26.7 (d, J_{PC} = 1.7 Hz), 22.4, 16.4 (d, J_{PC} = 5.7 Hz), 13.6; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 32.6; IR (neat, cm^{-1}) 1621, 1461, 1368, 1257, 1147, 1080; MS *m/z* 313 ($M^+(Br^{81})$ + 1, 1.53), 311 ($M^+(Br^{79})$ + 1, 1.09), 242 ($M^+(Br^{81}) - C_3H_6 - C_2H_4$, 57.84), 240 ($M^+(Br^{79}) - C_3H_6 - C_2H_4$, 58.76), 43 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{20}O_3{}^{79}BrP$ [M^+] 310.0333, found 310.0323.

$PdCl_2(Sphos)_2$-Catalyzed Suzuki Cross-Coupling Reaction of 4-Halo-2-ethoxy-2,5-dihydro[1,2]oxaphosphole 2-Oxides with Organic Boronic Acids—Synthesis of 4-Substituted-2,5-dihydro[1,2]oxaphosphole 2-Oxides:

Synthesis of 3-Butyl-5,5-dimethyl-2-ethoxy-4-phenyl-2,5-dihydro[1,2]oxaphosphole 2-Oxide (6a). Typical procedure VI: A mixture of 4-bromo-3-butyl-5,5-dimethyl-2-ethoxy-2,5-dihydro[1,2]oxaphosphole 2-oxide **5a** (95 mg, 0.31 mmol), phenyl boronic acid (54 mg, 0.45 mmol), $K_3PO_4 \cdot 3H_2O$ (160 mg, 0.60 mmol), and $PdCl_2(Sphos)_2$[17] (15 mg, 5 mol%) was stirred under reflux in 2 mL of toluene. When the reaction was complete as monitored by TLC, ether (50 mL) was added. The reaction was washed with brine (three times) and dried over Na_2SO_4. After evaporation, the residue was subjected to column chromatography on silica gel (petroleum ether/ether acetate = 3/2) to afford 90 mg (96%) of **6a**: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 3 H), 7.09−7.00 (m, 2 H), 4.18−4.04 (m, 2 H), 2.17−1.82 (m, 2 H), 1.45−1.38 (m, 8 H), 1.15 (t, J = 7.5 Hz, 3 H), 1.20−1.06 (m, 2 H), 0.72 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 161.1 (d, J_{PC} = 24.7 Hz), 133.7 (d, J_{PC} = 21.9 Hz), 128.4, 128.2, 127.8 (d, J_{PC} = 1.7 Hz), 125.9 (d, J_{PC} = 155.4 Hz), 85.9 (d, J_{PC} = 9.3 Hz), 62.4 (d, J_{PC} = 6.3 Hz), 30.3 (d, J_{PC} = 2.3 Hz), 27.3 (d, J_{PC} = 2.9 Hz), 26.7 (d, J_{PC} = 1.7 Hz), 25.4 (d, J_{PC} = 12.7 Hz), 22.3, 16.5 (d, J_{PC} = 5.7 Hz), 13.5; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 38.5; IR (neat, cm^{-1}) 1637, 1598, 1465, 1264, 1232, 1149, 1044; MS *m/z* 309 (M^+ + 1, 24.22), 308 (M^+, 27.83), 307 (M^+ − 1, 21.48), 293 ($M^+ - CH_3$, 17.83), 279 ($M^+ - C_2H_5$, 13.16), 266 ($M^+ - C_3H_6$, 100); HRMS (EI) *m/z* calcd for $C_{17}H_{25}O_3P$ [M^+] 308.1541, found 308.1534.

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Supporting Information Available: Typical experimental procedure, analytical data for all new products not listed in the text, ^{1}H, ^{13}C NMR, and ^{31}P spectra of all new compounds, and cif file of **6h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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