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Activation of Marginally Reactive Boron Enolates by MeLi for the Formation of Enol Phosphates and Synthesis of the Δ⁹-THC Intermediate

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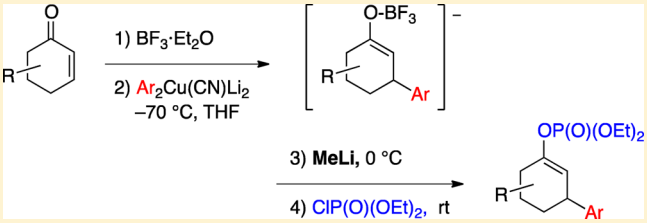
Supporting Information

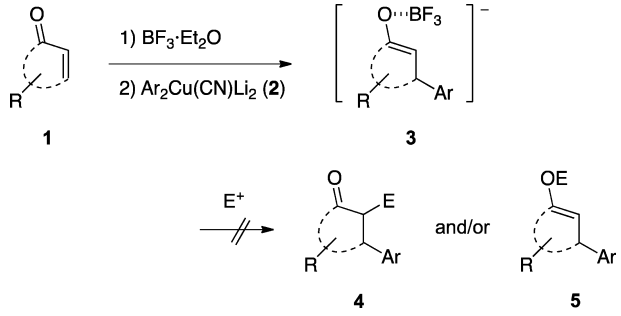
ABSTRACT: The addition of MeLi to boron enolates produced by the 1,4-addition of $Ar_2Cu(CN)Li_2$ to $BF_3{\cdot}OEt_2$-activated enones was followed by the reaction with $ClP(O)(OEt)_2$ to afford the corresponding enol phosphates in moderate to good yields. The scope of this method was examined with sterically hindered or electronically biased enones and/or reagents. This activation of boron enolates was successfully applied to the synthesis of the methyl ether of Δ⁹-tetrahydrocannabinol.



INTRODUCTION

The primary advantages of the 1,4-addition of organometallic reagents to enones are the formation of a new C−C bond at the β-position of the enone and the subsequent reaction with electrophiles (enolate trapping). 1,4-Addition−enolate trapping, especially using copper reagents, has been utilized extensively in organic synthesis.[1,2] Furthermore, recent studies have shown enantioselective 1,4-addition with several types of organometallics,[3] using catalysts such as copper,[4] rhodium,[5,6] palladium,[7] and nickel[8] catalysts, etc. Among them, alkylation and aldol reactions, as well as the formation of TMS ethers, have been demonstrated. However, studies using sterically demanding reagents have only been reported in a few cases. Thus, 1,4-addition has been studied with reagents possessing *sec*-alkyls[4a,b,j,v] such as *i*-Pr, or substituted aryl groups[4i,k,5,6c,i,k,7b,c] such as 2-MeC_6H_4, 2-$MeOC_6H_4$, and 2,4,6-$Me_3C_6H_2$, whereas the enolate trapping has only been shown with enolates derived from less sterically hindered reagents[4a,b,6i] except for one report with *i*-Pr.[4v] The activation of enones by adding a Lewis acid such as $BF_3{\cdot}OEt_2$[9] or TMSCl[10] is an effective method for achieving 1,4-addition with sterically demanding organocopper reagents and/or enones (Scheme 1). However, the addition of $BF_3{\cdot}OEt_2$ yields boron enolates **3**[11] with low reactivity toward electrophiles (E^+), which is probably due to the strong stabilization of the enolate caused by the electron-withdrawing fluorine atoms attached to the boron atom. In accordance with this fact, trialkylboron enolates prepared by adding BEt_3 to lithium or potassium enolates have shown to undergo Pd-catalyzed or Pd-free alkylation with allylic halides.[12] Similarly, dialkylboron enolates are activated with BuLi for alkylation with a simple allyl bromide.[6d] The use of TMSCl yields neutral enol ethers, which can be converted to enolates upon reaction with MeLi. Furyl and thienyl anions are marginally reactive toward 1,4-addition due to electronic factors, and thus the $BF_3{\cdot}OEt_2$ activation of enones is an effective method.[13] Recently, a rhodium-catalyzed version has been developed.[6l,14] However, reaction of the corresponding enolates with E^+ has been not reported except for hydrolysis.

Scheme 1. A Problem Associated with the $BF_3{\cdot}OEt_2$-Assisted 1,4-Addition of Enones with Copper Reagents



To circumvent the problem associated with the boron enolates **3**, an indirect method through α-iodo enones has been developed.[15] However, this indirect method requires additional steps for the synthesis of α-iodo enones and the generation of reactive enolates from the α-iodo ketone intermediates; hence direct activation of the boron enolates generated by $BF_3{\cdot}OEt_2$-assisted 1,4-addition is certainly advantageous for organic synthesis. Herein, we present the results of our work on this challenging issue.

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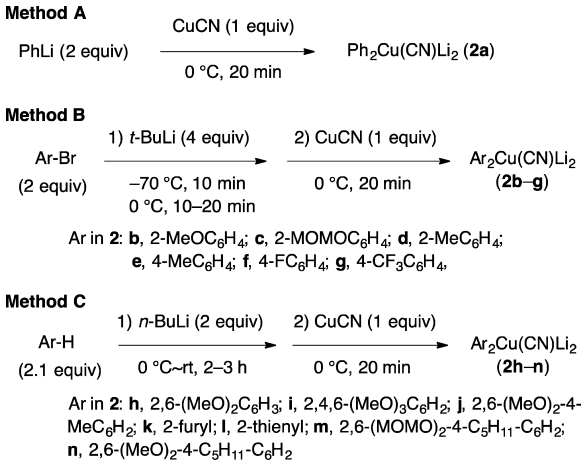
RESULTS AND DISCUSSION

We prepared $Ph_2Cu(CN)Li_2$ (**2a**) according to Method A in Scheme 2, and 1.5 equiv and 1.1 equiv of **2a** were added to

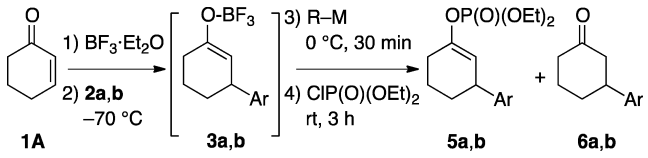
Scheme 2. Preparation of $Ar_2Cu(CN)Li_2$



the $BF_3{\cdot}OEt_2$-activated cyclohexenone (**1A**) at −78 °C for 1 h in THF. Without isolation the resulting boron enolate **3a** was subjected to phosphorylation with $ClP(O)(OEt)_2$ (5 equiv) at room temperature for 3 h to yield mixtures of enol phosphate **5a** and ketone **6a** in 62:38 and 26:74 ratios for 1.5 equiv and 1.1 equiv of **2a**, respectively (Table 1, entries 1 and 2).

Although the above experiments clearly indicated decreased reactivity of the boron enolate **3a** toward $ClP(O)(OEt)_2$,[16] we

Table 1. Examination of R−M for Activation of the Boron Enolate[a,b]



entry	Ar	R−M (equiv)	solvent	5:6	yield of 5[c]
1	Ph	–	THF	62:38	nd
2[d]	Ph	–	THF	26:74	nd
3	Ph	PhLi (6)	THF	100:0	72%
4	Ph	MeLi (6)	THF	100:0	76%
5	Ph	MeLi (4)	THF	100:0[e]	54%
6	Ph	MeLi (6)	Et_2O	(66:34)[e,f]	nd
7	2-$MeOC_6H_4$	–	THF	18:82	nd
8	2-$MeOC_6H_4$	MeLi (6)	THF	100:0	75%
9	2-$MeOC_6H_4$	MeLi (7)	Et_2O	nd[g]	46%
10	2-$MeOC_6H_4$	MeMgCl (6)	THF	100:0	35%
11	2-$MeOC_6H_4$	Et_2Zn (6)	THF	100:0	53%
12	2-$MeOC_6H_4$	MeZnCl (9)	THF	72:28	nd
13	2-$MeOC_6H_4$	Et_3Al (6)	THF	33:67	nd

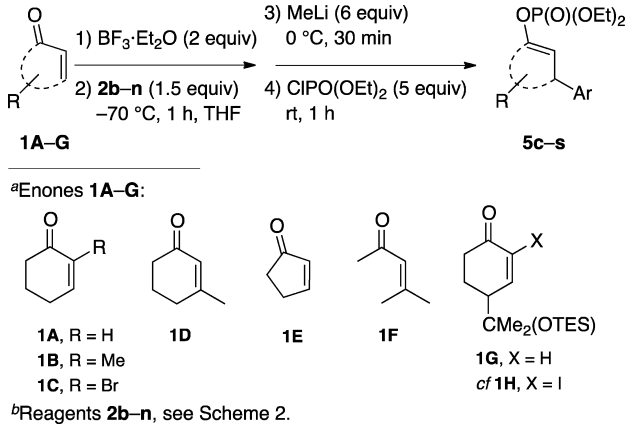
[a]Ar in **2**, **5**, and **6**: **a**, Ph; **b**, 2-$MeOC_6H_4$. [b]Unless otherwise noted, a mixture of **1A** (1.0 equiv) and $BF_3{\cdot}OEt_2$ (2 equiv) was added to **2a** or **2b** (1.5 equiv) in THF or Et_2O at −70 °C and stirred for 1 h. The boron enolate was reacted with R−M (4−9 equiv) at 0 °C for 30 min and then with $ClP(O)(OEt)_2$ (5 equiv) at rt. [c]nd: Not determined. [d]**2a** (1.1 equiv) was used. [e]An unidentified byproduct (entry 5) and another byproduct (entry 6), respectively, were detected by ^1H NMR spectroscopy. [f]Ratio of **5a**/byproduct. [g]A byproduct(s) similar to that of entry 5 was produced.

focused on the different ratios of **5a** and **6a** observed with 1.5 and 1.1 equiv of **2a** and deduced the following: (1) conversion of the B−F bond(s) to the B−Ph bond(s) with the remaining **2a** and/or $PhLi{\cdot}BF_3$ being regenerated from **2a** and $BF_3{\cdot}OEt_2$, similar to a previous report,[9a] and (2) the increased reactivity of the enolate derivative with Ph group(s) bound to the boron atom.[17] Based on these suppositions, we postulated that the reactivity of **3a** would be increased upon adding an organometallic reagent (R−M) to **3a**. Indeed, the addition of PhLi (6 equiv) followed by reaction with $ClP(O)(OEt)_2$ resulted in a complete reaction to afford enol phosphate **5a** in 72% isolated yield (entry 3). We then switched our attention to the use of MeLi, because the mass of the reagent residue(s) produced using excess MeLi after quenching would be less than that with PhLi. In practice, 6 equiv of MeLi produced **5a**, which was easily purified by chromatography in 76% yield (entry 4), whereas the use of 4 equiv of MeLi produced a mixture of **4a** (54% isolated yield) and an unidentified byproduct (entry 5). This indicated that the use of 6 equiv of MeLi was optimal for successful activation. In contrast to THF, an attempted reaction in Et_2O, which has been used successfully as the solvent for the 1,4-additions, produced a mixture of products (entry 6). Instead of using $BF_3{\cdot}OEt_2$, a reaction with BEt_3 gave a mixture of **5a** and unidentified product(s) (data not shown).

Next, a moderately sterically hindered reagent, $(2\text{-}MeOC_6H_4)_2Cu(CN)Li_2$ (**2b**), was synthesized via Br−Li exchange with *t*-BuLi (Method B, Scheme 2), and 1,4-addition to the $BF_3{\cdot}OEt_2$-activated enone **1A** followed by reaction with $ClP(O)(OEt)_2$ under the same reaction conditions was examined, affording a mixture of enol phosphate **5b** and ketone **6b** in a ratio of 18:82 (entry 7). This result clearly indicated that steric hindrance lowered the reactivity of boron enolate **3b** compared to **3a**. This observation is a rare case showing the influence of an Ar group on the reactivity of enolates. In contrast, the reaction with $ClP(O)(OEt)_2$ after the activation of **3b** by adding MeLi proceeded to completion and produced enol phosphate **5b** in 75% yield (entry 8). The reaction was also examined in Et_2O, which gave a mixture of enol phosphate **5b** and byproduct(s) (entry 9) as in the case of **2a**. Other organometallics (R−M) attempted in entries 10−13 were less effective than MeLi.

The method used for the formation of enol phosphates **5a** and **5b** was applied to several substrates and copper reagents to establish the generality of the method (Scheme 3). The

Scheme 3. Synthesis of Enol Phosphates[a,b]



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results are shown in Figures 1 and 2 along with the yields. The 2-MOMOC$_6$H$_4$ reagent **2c** afforded enol phosphate **5c** in

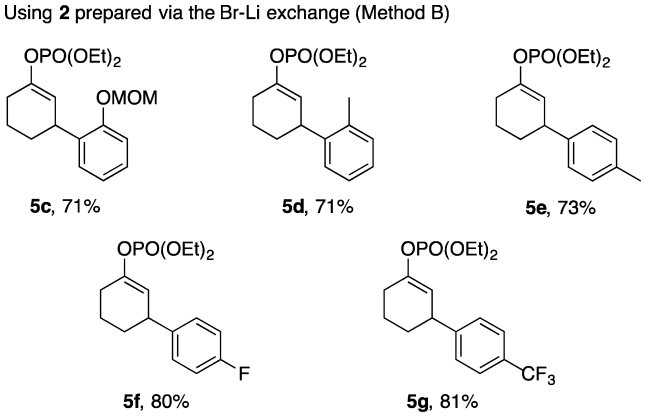


Figure 1. Synthesis of enol phosphates from enone **1A** and reagents **2c–l**.

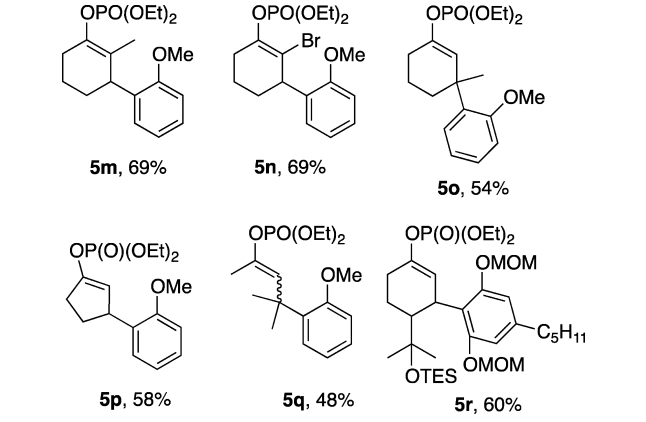


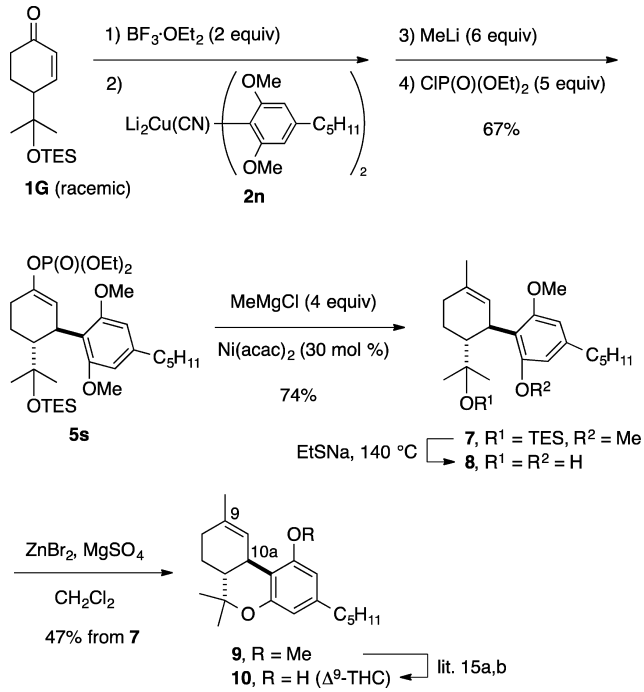
Figure 2. More examples of synthesized enol phosphates.

71% yield, which is similar to the yield of **2b**. The 2-Me- and 4-MeC$_6$H$_4$ reagents **2d** and **2e** gave **5d** and **5e** in good yields. These results indicate almost no steric influence by substitution at the ortho position. 4-Fluoro- and 4-CF$_3$C$_6$H$_4$ reagents **2f** and **2g** also furnished **5f** and **5g**, respectively. The more sterically demanding reagent **2h** (Ar = 2,6-(MeO)$_2$C$_6$H$_3$) prepared by Method C afforded **5h** in good yield. As the BF$_3$·OEt$_2$ activation of enone **1A** is inevitably necessary for the 1,4-addition of **2h** (our observation), this result is a good example for demonstrating the advantage of the present method for synthesizing enol phosphates with a sterically demanding Ar group. Phosphates **5i** (Ar = 2,4,6-(MeO)$_3$C$_6$H$_2$) and **5j** (Ar = 2,6-(MeO)$_2$-4-MeC$_6$H$_2$) were produced from bulky reagents **2i** and **2j**, respectively, in good yields. The syntheses of enol phosphates **5k** and **5l** are another set of reactions demonstrating the efficiency of the present method. Previously, the 1,4-addition of furyl copper reagents to enones was reported to proceed only with BF$_3$·OEt$_2$.[13,18] The Rh-catalyzed 1,4-addition of furyl and thienyl reagents described in the literature gives the corresponding ketones, but no further reaction of the intermediary enolates is reported.[6l,14]

Further demonstration of the present method is delineated in Figure 2, wherein enones in Scheme 3, i.e. substituted cyclohexenones **1B–D**, cyclopentenone (**1E**), and acyclic enone **1F** were subjected to reaction with reagents **2b** (Ar = 2-MeOC$_6$H$_4$) to afford enol phosphates **5m–5q**, whereas an attempted 1,4-addition of enone **1D** with **2b** did not proceed without the activation of the enone by BF$_3$·OEt$_2$. Furthermore, the reaction of enone **1G** with **2m** (Ar = 2,6-(MOMO)$_2$-4-C$_5$H$_{11}$-C$_6$H$_2$) afforded **5r** in 60% yield. Previously, **5r** was synthesized in 35% yield in three steps from **1G** through α-iodo enone **1H**.[15b]

The method was successfully applied to the synthesis of enol phosphate **5s** in 67% yield from enone **1G** and cuprate **2n** (Scheme 4). Furthermore, **5s** was subjected to a Ni-

Scheme 4. Synthesis of Δ^9-THC



catalyzed coupling reaction with MeMgCl to afford 1-methyl-1-cyclohexene derivative **7** in 74% yield. Exposure of **7** to EtSNa at 140 °C followed by reaction with ZnBr$_2$/MgSO$_4$ gave methyl ether **9**, which was transformed[19] to Δ^9-THC (**10**).[15a,b,20] The ^{1}H and ^{13}C NMR spectra of **9** were consistent with those reported previously.[15b] The relative trans stereochemistry on the cyclohexene ring of **9** was confirmed by the hydrogen at C-10a appearing at δ 3.17 ppm as a doublet (J = 11.4 Hz). The J value indicated pseudoaxial hydrogen, while the chemical shift is close to the characteristic signal of Δ^9-THC (**10**) (3.14 ppm) and distant from that of the cis isomer of **10** (3.59 ppm).[21] The trans stereochemistry is consistent with the steric approach control of cuprates to 4-substituted cyclohexenones in the 1,4-addition.

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Recently, the demand for a method to synthesize Δ^9-THC analogues has increased not only for developing a ligand with high affinity to the Δ^9-THC receptor subtype but also as the standard for analyzing the Δ^9-THC family in plants.[22] On the basis of the results shown in Figures 2 and 3 and Scheme 3, Δ^9-THC analogues such as those delineated in Figure 3 would be synthesized in short steps.[23]

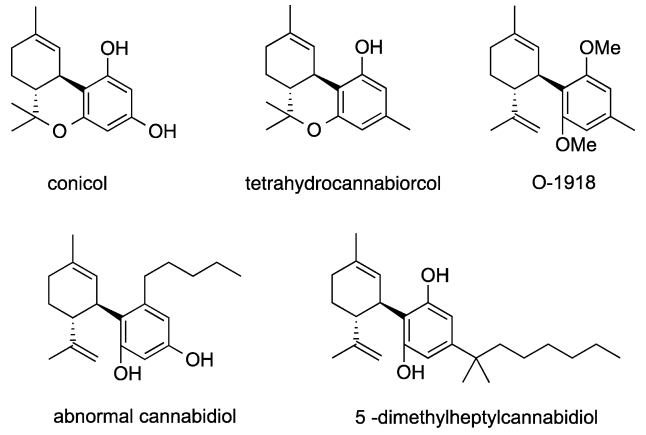
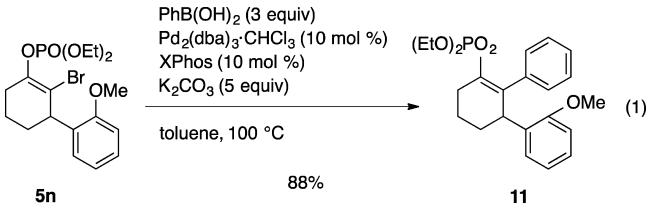


Figure 3. Δ^9-THC analogues to be synthesized.

Finally, a coupling reaction of enol phosphate **5n** with $PhB(OH)_2$ was examined. Among the two possible reaction sites, the C−Br bond selectively participated in the Pd-catalyzed reaction under Buchwald conditions[24] to afford compound **11** in 88% yield (eq 1).



CONCLUSION

The addition of $BF_3{\cdot}OEt_2$ to enones is a convenient method for their activation in 1,4-addition reactions with bulky aryl copper reagents, although the derived boron enolates cannot be used for further reactions. To resolve this inconvenience, we developed a new method to activate unreacted boron enolates for phosphorylation by simply adding MeLi to the boron enolates before the phosphorylation with $ClP(O)(OEt)_2$. The generality of this one-pot method, consisting of 1,4-addition to $BF_3{\cdot}OEt_2$-activated enones, addition of MeLi to the boron enolates, and phosphorylation, was proven by the products shown in Figures 1 and 2. Furthermore, the method was applied to furyl and thienyl copper reagents, which were unreactive toward 1,4-addition to enones in the absence of $BF_3{\cdot}OEt_2$. To demonstrate the applicability of the method, the methyl ether of Δ^9-THC was successfully synthesized.

EXPERIMENTAL SECTION

General Remarks. The ^1H (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectroscopic data were recorded in $CDCl_3$ using Me_4Si (δ = 0 ppm) and the centerline of the triplet (δ = 77.1 ppm), respectively, as internal standards. Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (J) are given in hertz (Hz). Chemical shifts of carbons are accompanied by negative (for C and CH_2) and positive (for CH and CH_3) signs of the attached proton test (APT) experiments. High-resolution mass spectroscopy (HRMS) was performed with a double-focusing mass spectrometer. The solvents that were distilled prior to use are THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). After extraction of the products, the extracts were concentrated by using an evaporator, and then the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60N).

General Procedures for the Synthesis of Enol Phosphates (5a−s). *(1). Using Copper Reagent **2a** prepared by Method A. Synthesis of Diethyl 3-Phenyl-1-cyclohexen-1-yl Phosphate (**5a**) from Enone **1A** and $Ph_2Cu(CN)Li_2$ (**2a**).* To an ice-cold mixture of CuCN (53.7 mg, 0.60 mmol) and THF (3 mL) was added PhLi (1.09 M in cyclohexane−Et_2O, 1.10 mL, 1.20 mmol) dropwise. The mixture was stirred at 0 °C for 20 min and cooled to −70 °C. A solution of enone **1A** (38.5 mg, 0.40 mmol) and $BF_3{\cdot}Et_2O$ (0.100 mL, 0.796 mmol) in THF (2 mL) was added to the mixture over 5 min. The reaction mixture was stirred at −70 °C for 1 h, and MeLi (1.08 M in Et_2O, 2.20 mL, 2.38 mmol) was added. After 30 min of stirring at 0 °C, $ClP(O)(OEt)_2$ (0.290 mL, 2.02 mmol) was added. The mixture was stirred at room temperature for 1 h and poured into saturated NH_4Cl. The resulting mixture was extracted with Et_2O twice. The organic layers were washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to afford **5a** (94.9 mg, 76%): R_f = 0.34 (hexane/EtOAc 2:1); IR (neat) 1681, 1272, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J = 7.2 Hz, 6 H), 1.32−2.03 (m, 4 H), 2.18−2.42 (m, 2 H), 3.48−3.58 (m, 1 H), 4.12−4.25 (m, 4 H), 5.56−5.58 (m, 1 H), 7.17−7.34 (m, 5 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 21.0 (−), 27.7 (−) (d, J = 4 Hz), 31.9 (−), 40.9 (+), 64.2 (−) (d, J = 6 Hz), 114.0 (+) (d, J = 5 Hz), 126.3 (+), 127.7 (+), 128.4 (+), 145.6 (−), 149.0 (−) (d, J = 8 Hz); HRMS (FAB) m/z: $[M + H]^+$ Calcd for $C_{16}H_{24}O_4P$ 311.1412; Found 311.1415.

*(2). Using Copper Reagents **2b−g** prepared by Method B. Synthesis of Diethyl 3-(2-Methoxyphenyl)-1-cyclohexen-1-yl Phosphate (**5b**) from Enone **1A** and $(2\text{-}MeOC_6H_4)_2Cu(CN)Li_2$ (**2b**).* To a solution of 2-bromoanisol (0.150 mL, 1.22 mmol) in THF (2 mL) was added *t*-BuLi (1.77 M in *n*-pentane, 1.36 mL, 2.40 mmol) dropwise at −70 °C. The solution was stirred at −70 °C for 10 min and at 0 °C for 20 min before addition of CuCN (55.2 mg, 0.616 mmol). The mixture was stirred at 0 °C for 20 min and cooled to −70 °C. A solution of enone **1A** (38.9 mg, 0.405 mmol) and $BF_3{\cdot}Et_2O$ (0.100 mL, 0.796 mmol) in THF (2 mL) was added to the mixture over 5 min. The reaction mixture was stirred at −70 °C for 1 h, and MeLi (1.13 M in Et_2O, 2.10 mL, 2.37 mmol) was added. After 30 min of stirring at 0 °C, $ClP(O)(OEt)_2$ (0.290 mL, 2.02 mmol) was added. After 1 h of stirring at room temperature, the solution was poured into saturated NH_4Cl. The resulting mixture was extracted with Et_2O twice. The organic layers were washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to afford **5b** (103.0 mg, 75%): R_f = 0.10 (hexane/EtOAc 3:1); IR (neat) 1682, 1272, 1030, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 6 H), 1.40−1.51 (m, 1 H), 1.63−1.81 (m, 2 H), 1.89−1.99 (m, 1 H), 2.21−2.38 (m, 2 H), 3.83 (s, 3 H), 3.93−4.02 (m, 1 H), 4.12−4.24 (m, 4 H), 5.46−5.52 (m, 1 H), 6.85 (d, J = 7.6 Hz, 1 H), 6.91 (dt, J = 1.2, 7.6 Hz, 1 H), 7.19 (dt, J = 1.6, 7.6 Hz, 1 H), 7.20 (d, J = 7.6 Hz, 1 H); ^{13}C−APT NMR (100 MHz, $CDCl_3$): δ 16.1 (+) (d, J = 7 Hz), 20.8 (−), 27.8 (−) (d, J = 4 Hz), 29.1 (−), 33.5 (+), 55.3 (+) (d, J = 4 Hz), 64.1 (−) (d, J = 5 Hz), 110.2 (+), 114.0 (+) (d, J = 5 Hz), 120.3 (+), 127.2 (+), 128.5 (+), 133.4 (−) (d, 2 Hz), 149.0 (−) (d, J = 9 Hz), 156.7 (−); HRMS (FAB) m/z: $[M + H]^+$ Calcd for $C_{17}H_{26}O_5P$ 341.1518; Found 341.1524.

*(3). Using Copper Reagents **2h−n** prepared by Method C. Synthesis of Diethyl 3-((2,6-Dimethoxy)phenyl)-1-cyclohexen-1-yl*

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*Phosphate (**5h**) from Enone **1A** and (2,6-(MeO)$_2$C$_6$H$_3$)$_2$Cu(CN)Li$_2$ (**2h**).* To an ice-cold solution of 1,3-dimethoxybenzene (0.17 mL, 1.30 mmol) in THF (3 mL) was added *n*-BuLi (1.60 M in hexane, 0.75 mL, 1.20 mmol) dropwise. The mixture was stirred at room temperature for 4 h, and CuCN (54.0 mg, 0.603 mmol) was added to the solution. The mixture was stirred at 0 °C for 20 min and cooled to −70 °C. A solution of enone **1A** (37.8 mg, 0.393 mmol) and BF_3·Et_2O (0.100 mL, 0.796 mmol) in THF (1 mL) was added to the mixture over 5 min. The reaction mixture was stirred at −70 °C for 1 h, and then MeLi (1.13 M in Et_2O, 2.10 mL, 2.37 mmol) was added to the solution. After 30 min of stirring at 0 °C, $ClP(O)(OEt)_2$ (0.290 mL, 2.02 mmol) was added. The solution was stirred at room temperature for 1 h and poured into saturated NH_4Cl. The resulting mixture was extracted with Et_2O twice. The organic layers were washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by column chromatography (hexane/EtOAc) to afford enol phosphate **5h** (111.3 mg, 76%): R_f = 0.15 (hexane/EtOAc 3:1); IR (neat) 1683, 1270, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 6 H), 1.64−1.87 (m, 3 H), 1.87−1.99 (m, 1 H), 2.14−2.27 (m, 1 H), 2.32−2.48 (m, 1 H), 3.78 (s, 6 H), 4.08−4.21 (m, 5 H), 5.40 (br s, 1 H), 6.53 (d, J = 8.4 Hz, 2 H), 7.14 (t, J = 8.4 Hz, 1 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 23.3 (−), 26.8 (−), 27.5 (−) (d, J = 4 Hz), 31.2 (+), 55.8 (+), 63.9 (−) (d, J = 6 Hz), 104.2 (+), 116.3 (+) (d, J = 6 Hz), 121.0 (−), 127.3 (+), 145.6 (−) (d, J = 9 Hz), 158.7 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{18}H_{28}O_6P$ 371.1624; Found 371.1626.

Data of Enol Phosphates. *Diethyl 3-((2-Methoxymethoxy)-phenyl)-1-cyclohexen-1-yl Phosphate (**5c**) from Enone **1A** and (2-MOMOC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2c**) Prepared by Method B.* Yield 71%; R_f = 0.18 (hexane/EtOAc 3:1); IR (neat) 1681, 1600, 1585, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J = 7.2 Hz, 6 H), 1.40−1.53 (m, 1 H), 1.64−1.85 (m, 2 H), 1.91−2.02 (m, 1 H), 2.26−2.35 (m, 2 H), 3.49 (s, 3 H), 3.95−4.04 (m, 1 H), 4.13−4.25 (m, 4 H), 5.22 (s, 2 H), 5.48−5.52 (m, 1 H), 6.96 (dt, J = 7.5, 1.4 Hz, 1 H), 7.07 (dd, J = 8.3, 1.1 Hz, 1 H), 7.13−7.24 (m, 2 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 20.8 (−), 27.8 (−) (d, J = 4 Hz), 29.4 (−), 33.7 (+), 56.1 (+), 64.2 (−) (d, J = 6 Hz), 94.4 (−), 113.7 (+), 113.9 (+) (d, J = 5 Hz), 121.6 (+), 127.3 (+), 128.7 (+), 134.0 (−) (d, J = 1 Hz), 149.1 (−) (d, J = 9 Hz), 154.4 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{18}H_{28}O_6P$ 371.1624; Found 371.1634.

*Diethyl 3-(2-Methylphenyl)-1-cyclohexen-1-y Phosphate (**5d**) from Enone **1A** and (2-MeC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2d**) Prepared by Method B.* Yield 71%; R_f = 0.26 (hexane/EtOAc 3:1); IR (neat) 1681, 1367, 1273, 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J = 7.2 Hz, 6 H), 1.33−2.01 (m, 4 H), 2.22−2.43 (m, 2 H), 2.35 (s, 3 H), 3.70−3.80 (m, 1 H), 4.13−4.25 (m, 4 H), 5.48−5.52 (m, 1 H), 7.07−7.24 (m, 4 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 19.2 (+), 21.0 (−), 27.7 (−) (d, J = 4 Hz), 29.7 (−), 36.9 (+), 64.2 (−) (d, J = 5 Hz), 114.3 (+) (d, J = 5 Hz), 126.1 (+), 126.2 (+), 127.7 (+), 130.4 (+), 135.3 (−), 143.4 (−), 149.0 (−) (d, J = 9 Hz); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{17}H_{26}O_4P$ 325.1569; Found 325.1572.

*Diethyl 3-(4-Methylphenyl)-1-cyclohexen-1-yl Phosphate (**5e**) from Enone **1A** and (4-MeC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2e**) Prepared by Method B.* Yield 73%; R_f = 0.24 (hexane/EtOAc 3:1); IR (neat) 1680, 1513, 1270, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 6 H), 1.19−2.02 (m, 4 H), 2.20−2.41 (m, 2 H), 2.32 (s, 3 H), 3.44−3.55 (m, 1 H), 4.10−4.27 (m, 4 H), 5.51−5.56 (m, 1 H), 7.11 (s, 4 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.1 (+) (d, J = 7 Hz), 20.9 (−), 27.6 (−) (d, J = 4 Hz), 31.8 (−), 40.4 (+), 64.1 (−) (d, J = 6 Hz), 114.1 (+) (d, J = 5 Hz), 127.5 (+), 129.0 (+), 135.7 (−), 142.5 (−), 148.8 (−) (d, J = 9 Hz); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{17}H_{26}O_4P$ 325.1569; Found 325.1565.

*Diethyl 3-(4-Fluorophenyl)-1-cyclohexen-1-yl Phosphate (**5f**) from Enone **1A** and (4-FC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2f**) Prepared by Method B.* Yield 80%; R_f = 0.17 (hexane/EtOAc 3:1); IR (neat) 1681, 1604, 1508, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 6 H), 1.40−1.51 (m, 1 H), 1.62−2.01 (m, 3 H), 2.20−2.42 (m, 2 H), 3.47−3.58 (m, 1 H), 4.12−4.24 (m, 4 H), 5.50−5.54 (m, 1 H), 6.94−7.02 (m, 2 H), 7.14−7.22 (m, 2 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 20.9 (−), 27.6 (−) (d, J = 4 Hz), 31.9 (−), 40.2 (+), 64.2 (−) (d, J = 6 Hz), 113.8 (+) (d, J = 5 Hz), 115.1 (+) (d, J = 21 Hz), 129.1 (+) (d, J = 8 Hz), 141.3 (−) (d, J = 4 Hz), 149.2 (−) (d, J = 9 Hz), 161.5 (−) (d, J = 242 Hz); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{16}H_{23}FO_4P$ 329.1318; Found 329.1317.

*Diethyl 3-(4-(Trifluoromethyl)phenyl)-1-cyclohexen-1-yl Phosphate (**5g**) from Enone **1A** and (4-CF$_3$C$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2g**) Prepared by Method B.* Yield 81%; R_f = 0.15 (hexane/EtOAc 3:1); IR (neat) 1680, 1619, 1327, 1275 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J = 6.9 Hz, 6 H), 1.40−1.53 (m, 1 H), 1.64−2.06 (m, 3 H), 2.27−2.37 (m, 2 H), 3.55−3.65 (m, 1 H), 4.13−4.25 (m, 4 H), 5.51−5.55 (m, 1 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.55 (d, J = 8.0 Hz, 2 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.1 (+) (d, J = 7 Hz), 20.9 (−), 27.6 (−) (d, J = 4 Hz), 31.7 (−), 40.8 (+), 64.3 (−) (d, J = 6 Hz), 112.9 (+) (d, J = 5 Hz), 124.3 (−) (q, J = 270 Hz), 125.4 (+) (q, J = 4 Hz), 128.1 (+), 128.7 (−) (q, J = 32 Hz), 149.6 (−), 149.7 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{17}H_{23}F_3O_4P$ 379.1286; Found 379.1285.

*Diethyl 3-((2,4,6-Trimethoxy)phenyl)-1-cyclohexen-1-yl Phosphate (**5i**) from Enone **1A** and (2,4,6-(MeO)$_3$C$_6$H$_2$)$_2$Cu(CN)Li$_2$ (**2i**) Prepared by Method C.* Yield 73%; R_f = 0.15 (hexane/EtOAc 3:1); IR (neat) 1683, 1606, 1037, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 6 H), 1.56−1.85 (m, 3 H), 1.88−1.97 (m, 1 H), 2.15−2.24 (m, 1 H), 2.30−2.44 (m, 1 H), 3.76 (s, 6 H), 3.79 (s, 3 H), 3.96−4.06 (m, 1 H), 4.08−4.20 (m, 4 H), 5.34−5.39 (m, 1 H), 6.11 (s, 2 H); ^{13}C−APT NMR (100 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 23.4 (−), 27.2 (−), 27.5 (−) (d, J = 3 Hz), 31.0 (+), 55.3 (+) (m), 55.8 (+) (m), 63.9 (−) (d, J = 6 Hz), 91.1 (+) (m), 113.7 (−), 116.7 (+) (m), 145.6 (−) (d, J = 9 Hz), 159.3 (−), 159.6 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{19}H_{30}O_7P$ 401.1729; Found 401.1724.

*Diethyl 3-((2,6-Dimethoxy)-3-methylphenyl)-1-cyclohexen-1-yl Phosphate (**5j**) from Enone **1A** and (2,6-(MeO)$_2$-4-MeC$_6$H$_2$)$_2$Cu(CN)Li$_2$ (**2j**) Prepared by Method C.* Yield 77%; R_f = 0.19 (hexane/EtOAc 3:1); IR (neat) 1683, 1608, 1582, 1044 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 6 H), 1.62−1.98 (m, 4 H), 2.14−2.47 (m, 2 H), 2.32 (s, 3 H), 3.76 (s, 6 H), 4.01−4.21 (m, 5 H), 5.36−5.40 (m, 1 H), 6.35 (s, 2 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 21.9 (+), 23.3 (−), 27.0 (−), 27.5 (−) (d, J = 3 Hz), 31.0 (+), 55.7 (+), 63.9 (−) (d, J = 6 Hz), 105.1 (+), 116.5 (+) (d, J = 6 Hz), 117.9 (−), 137.4 (−), 145.5 (−) (d, J = 9 Hz), 158.5 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{19}H_{30}O_6P$ 385.1780; Found 385.1787.

*Diethyl 3-(Furan-2-yl)-1-cyclohexen-1-yl Phosphate (**5k**) from Enone **1A** and (Furan-2-yl)$_2$Cu(CN)Li$_2$ (**2k**) Prepared by Method C.* Yield 76%; R_f = 0.16 (hexane/EtOAc 3:1); IR (neat) 3114, 1684, 1267, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, J = 7.1 Hz, 6 H), 1.56−1.98 (m, 4 H), 2.20−2.32 (m, 2 H), 3.56−3.66 (m, 1 H), 4.11−4.24 (m, 4 H), 5.57−5.63 (m, 1 H), 6.02 (dt, J = 3.3, 0.9 Hz, 1 H), 6.28 (dd, J = 3.3, 2.1 Hz, 1 H), 7.30−7.33 (m, 1 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 20.3 (−), 27.3 (−), 27.7 (−) (d, J = 4 Hz), 34.2 (+), 64.3 (−) (d, J = 6 Hz), 105.2 (+), 110.1 (+), 111.1 (+) (d, J = 5 Hz), 141.2 (+), 149.4 (−) (d, J = 9 Hz), 157.8 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{14}H_{22}O_5P$ 301.1205; Found 301.1213.

*Diethyl 3-(Thiophen-2-yl)-1-cyclohexen-1-yl Phosphate (**5l**) from Enone **1A** and (Thiophen-2-yl)$_2$Cu(CN)Li$_2$ (**2l**) Prepared by Method C.* Yield 59%; R_f = 0.21 (hexane/EtOAc 3:1); IR (neat) 3070, 1679, 1273 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 6 H), 1.58−1.92 (m, 3 H), 1.95−2.08 (m, 1 H), 2.24−2.33 (m, 2 H), 3.79−3.89 (m, 1 H), 4.12−4.24 (m, 4 H), 5.62−5.67 (m, 1 H), 6.84 (dt, J = 3.3, 0.9 Hz, 1 H), 6.93 (dd, J = 5.1, 3.3 Hz, 1 H), 7.15 (dd, J = 5.1, 0.9 Hz, 1 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 20.4 (−), 27.6 (−) (d, J = 4 Hz), 31.7 (−), 35.9 (+), 64.3 (−) (m), 113.5 (+) (d, J = 5 Hz), 123.3 (+), 123.9 (+), 126.7 (+), 149.1 (−) (d, J = 9 Hz), 149.4 (−) (d, J = 1 Hz); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{14}H_{22}O_4PS$ 317.0976; Found 317.0983.

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*Diethyl 3-(2-Methoxyphenyl)-2-methyl-1-cyclohexen-1-yl Phosphate (**5m**) from Enone **1B** and (2-MeOC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2b**) Prepared by Method B.* Yield 69%; R_f = 0.15 (hexane/EtOAc 3:1); IR (neat) 1697, 1489, 1031, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J = 7.1 Hz, 6 H), 1.52−1.67 (m, 3 H), 1.56 (t, J = 1.8 Hz, 3 H), 1.72−1.90 (m, 1 H), 2.34−2.44 (m, 2 H), 3.80−3.86 (m, 1 H), 3.84 (s, 3 H), 4.15−4.26 (m, 4 H), 6.84−6.94 (m, 2 H), 7.09 (dd, J = 7.5, 1.5 Hz, 1 H), 7.19 (dt, J = 7.5, 1.8 Hz, 1 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 15.5 (+), 16.3 (+) (d, J = 7 Hz), 19.3 (−), 28.1 (−), 29.1 (−), 38.9 (+), 55.3 (+), 63.9−64.2 (−) (m), 110.3 (+), 120.1 (−) (d, J = 8 Hz), 120.2 (+), 127.2 (+), 129.3 (+), 132.0 (−) (d, J = 2 Hz), 144.3 (−) (d, J = 9 Hz), 157.2 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{18}H_{28}O_5P$ 355.1674; Found 355.1673.

*2-Bromo-3-(2-methoxyphenyl)-1-cyclohexen-1-yl Diethyl Phosphate (**5n**) from Enone **1C** and (2-MeOC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2b**) Prepared by Method B.* Yield 69%; R_f = 0.12 (hexane/EtOAc 3:1); amorphous; IR (nujol) 1675, 1596, 1459, 1022, 759 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J = 7.1 Hz, 6 H), 1.58−1.83 (m, 3 H), 1.93−2.07 (m, 1 H), 2.44−2.65 (m, 2 H), 3.84 (s, 3 H), 4.22−4.34 (m, 4 H), 6.88 (dd, J = 8.1, 1.0 Hz, 1 H), 6.94 (dt, J = 7.5, 1.0 Hz, 1 H), 7.16 (dd, J = 7.5, 1.5 Hz, 1 H), 7.24 (dt, J = 8.1, 1.5 Hz, 1 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 6 Hz), 18.6 (−), 29.5 (−), 30.2 (−), 42.6 (+), 55.4 (+), 64.7 (−) (d, J = 6 Hz), 110.1 (−) (d, J = 10 Hz), 110.4 (+), 120.3 (+), 127.8 (+), 129.2 (+), 130.4 (−) (d, J = 2 Hz), 146.9 (−) (d, J = 7 Hz), 156.9 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{17}H_{25}BrO_5P$ 419.0623; Found 419.0617.

*Diethyl 3-(2-Methoxyphenyl)-3-methyl-1-cyclohexen-1-yl Phosphate (**5o**) from Enone **1D** and (2-MeOC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2b**) Prepared by Method B.* Yield 54%; R_f = 0.15 (hexane/EtOAc 3:1); IR (neat) 1682, 1272, 1031, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J = 7.2 Hz, 6 H), 1.46−1.51 (m, 1 H), 1.49 (s, 3 H), 1.52−1.71 (m, 2 H), 2.10−2.30 (m, 2 H), 2.35−2.45 (m, 1 H), 3.83 (s, 3 H), 4.14−4.26 (m, 4 H), 5.64 (br s, 1 H), 6.84−6.91 (m, 2 H), 7.19 (dt, J = 1.8, 7.8 Hz, 1 H), 7.29 (dd, J = 8.0, 1.8 Hz, 1 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 19.8 (−), 27.7 (+), 27.9 (−) (d, J = 4 Hz), 33.7 (−), 40.3 (−), 55.0 (+), 64.1 (−) (d, J = 6 Hz), 111.6 (+), 120.1 (+), 120.4 (+) (d, J = 5 Hz), 127.4 (+), 129.7 (+), 135.6 (−) (d, J = 1 Hz), 147.3 (−) (d, J = 9 Hz), 157.8 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{18}H_{28}O_5P$ 355.1674; Found 355.1673.

*Diethyl 3-(2-Methoxyphenyl)-1-cyclopenten-1-yl Phosphate (**5p**) from Enone **1E** and (2-MeOC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2b**) Prepared by Method B.* Yield 58%; R_f = 0.26 (hexane/EtOAc 3:1); IR (neat) 1657, 1600, 1491, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J = 7.2 Hz, 6 H), 1.63−1.74 (m, 1 H), 2.42−2.60 (m, 3 H), 3.83 (s, 3 H), 4.16−4.33 (m, 5 H), 5.32−5.37 (m, 1 H), 6.86 (dd, J = 8.4, 1.2 Hz, 1 H), 6.91 (dt, J = 7.6, 1.2 Hz, 1 H), 7.15−7.23 (m, 2 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.2 (+) (d, J = 7 Hz), 30.2 (−), 31.2 (−) (d, J = 5 Hz), 40.2 (+), 55.4 (+), 64.4 (−) (d, J = 6 Hz), 110.2 (+), 112.2 (+) (d, J = 5 Hz), 120.5 (+), 127.0 (+), 127.2 (+), 134.2 (−), 151.0 (−) (d, J = 9 Hz), 156.8 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{16}H_{24}O_5P$ 327.1361; Found 327.1358.

*Diethyl 4-(2-Methoxyphenyl)-4-methylpent-2-en-2-yl Phosphate (**5q**) from Enone **1F** and (2-MeOC$_6$H$_4$)$_2$Cu(CN)Li$_2$ (**2b**) Prepared by Method B.* Yield 48%; R_f = 0.13 (hexane/EtOAc 5:1); IR (neat) 1686, 1490, 1285, 1243 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 6 H), 1.49 (s, 6 H), 2.01 (t, J = 1.1 Hz, 3 H), 3.75−3.87 (m, 4 H), 3.80 (s, 3 H), 4.96−4.99 (m, 1 H), 6.85 (dd, J = 8.1, 1.2 Hz, 1 H), 6.88 (dt, J = 7.5, 1.2 Hz, 1 H), 7.15 (dt, J = 8.1, 1.7 Hz, 1 H), 7.32 (dd, J = 7.5, 1.7 Hz, 1 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.0 (+) (d, J = 7 Hz), 20.7 (+), 28.7 (+), 37.2 (−), 55.5 (+), 63.6 (−) (d, J = 6 Hz), 111.9 (+), 120.2 (+), 122.4 (+) (d, J = 10 Hz), 126.2 (+), 126.9 (+), 137.7 (−), 141.2 (−) (d, J = 7 Hz), 157.9 (−); HRMS (FAB) m/z: [M + H]$^+$ Calcd for $C_{17}H_{28}O_5P$ 343.1674; Found 343.1680.

*Diethyl (3-(2,6-Methoxymethoxy)-4-pentylphenyl)-(4-(2-((triethylsilyl)oxy)propan-2-yl)-1-cyclopenten-1-yl Phosphate (**5r**) from Enone **1G** and (2,6-(MOMO)$_2$-4-C$_5$H$_{11}$C$_6$H$_2$)$_2$Cu(CN)Li$_2$ (**2m**) Prepared by Method C.* Yield 60%; R_f = 0.35 (hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.51 (q, J = 8.0 Hz, 6 H), 0.85−0.98 (m, 15 H), 1.12 (s, 3 H), 1.28 (t, J = 7.2 Hz, 6 H), 1.17−1.40 (m, 3 H), 1.50−1.68 (m, 4 H), 2.20−2.58 (m, 4 H), 2.50 (t, J = 8.0, 2 H), 3.48 (s, 6 H), 4.02−4.15 (m, 5 H), 5.04−5.22 (m, 5 H), 6.57 (s, 2 H); ^{13}C NMR−APT (75 MHz, $CDCl_3$): δ 6.8 (−), 7.2 (+), 14.1 (+), 16.1 (+), (d, J = 7 Hz), 22.5 (−), 25.2 (−), 26.2 (+), 28.2 (−) (d, J = 3 Hz), 30.1 (+), 31.1 (−), 31.7 (−), 32.8 (+), 36.2 (−), 46.9 (+), 56.1 (+), 63.90 (−) (d, J = 6 Hz), 63.93 (−) (d, J = 6 Hz), 76.1 (−), 94.9 (−), 108.5 (+), 108.8 (+), 115.2 (+), (d, J = 6 Hz), 121.0 (−), 142.7 (−), 147.2 (−) (d, J = 9 Hz). The ^{1}H NMR spectrum was consistent with that reported,[15b] whereas the ^{13}C NMR spectrum was updated.

Synthesis of the Δ^9-THC Methyl Ether (9). *((2-(2′,6′-Dimethoxy-5-methyl-4′-pentyl-1,2,3,4-tetrahydro-[1,1′-biphenyl]-2-yl)propan-2-yl)oxy)triethylsilane (**7**).* To an ice-cold solution of bis methyl ether of olivetol (201.1 mg, 0.965 mmol) in THF (2 mL) was added *n*-BuLi (0.58 mL, 1.55 M in hexane, 0.899 mmol) dropwise. The mixture was stirred at room temperature for 2 h, and CuCN (40.9 mg, 0.457 mmol) was added to the solution. The mixture was stirred at 0 °C for 20 min and cooled to −70 °C. A solution of enone **1G** (77.9 mg, 0.290 mmol) and BF_3·Et_2O (0.075 mL, 0.597 mmol) in THF (1 mL) was added to the mixture over 5 min. The reaction mixture was warmed up to −50 °C over 1 h, and then MeLi (1.60 mL, 1.13 M in Et_2O, 1.81 mmol) was added to the solution. After 30 min of stirring at 0 °C, ClP(O)(OEt)$_2$ (0.220 mL, 1.53 mmol) was added. The solution was stirred at room temperature for 1 h and poured into saturated NH_4Cl. The resulting mixture was extracted with Et_2O twice. The organic layers were washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to furnish enol phosphate **5s** (119.0 mg, 67%): R_f = 0.27 (hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.50 (q, J = 7.9 Hz, 6 H), 0.86−0.95 (m, 15 H), 1.06 (s, 3 H), 1.24−1.37 (m, 3 H), 1.28 (t, J = 7.1 Hz, 6 H), 1.50−1.66 (m, 4 H), 2.16−2.27 (m, 2 H), 2.30−2.44 (m, 2 H), 2.53 (t, J = 7.8 Hz, 2 H), 3.76 (s, 6 H), 4.01−4.16 (m, 5 H), 5.03−5.07 (m, 1 H), 6.30 (s, 2 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 6.80 (−), 7.21 (+), 14.1 (+), 16.1 (+) (d, J = 7 Hz), 22.6 (−), 25.3 (−), 26.4 (+), 28.1 (−) (d, J = 4 Hz), 30.0 (+), 31.2 (−), 31.7 (−), 32.2 (+), 36.5 (−), 46.6 (+), 55.5 (+), 63.9 (−) (d, J = 6 Hz), 76.2 (−), 104.8 (+) (br s), 115.1 (+) (d, J = 6 Hz), 119.5 (−), 142.2 (−), 147.1 (−) (d, J = 9 Hz). To an ice-cold solution of Ni(acac)$_2$ (26.6 mg, 0.10 mmol) in THF (1.5 mL) was added MeMgCl (0.27 mL, 3.0 M in THF, 0.81 mmol). The mixture was stirred at 0 °C for 10 min, and a solution of enol phosphate **5s** (122.5 mg, 0.20 mmol) in THF (0.5 mL) was added. The solution was stirred at room temperature overnight and poured into saturated NH_4Cl. The resulting mixture was extracted with Et_2O twice. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to furnish **7** (70.1 mg, 74%): R_f = 0.88 (hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.50 (q, J = 8.0 Hz, 6 H), 0.84−0.95 (m, 15 H), 1.06 (s, 3 H), 1.23−1.67 (m, 7 H), 1.62 (s, 3 H), 1.84−1.96 (m, 1 H), 2.03−2.20 (m, 2 H), 2.32−2.43 (m, 1 H), 2.54 (t, J = 8.1 Hz, 2 H), 3.74 (br s, 6 H), 3.90 (dm, J = 8.0 Hz, 1 H), 4.92−4.98 (m, 1 H), 6.32 (s, 2 H); ^{13}C NMR−APT (75 MHz, $CDCl_3$): δ 6.86 (−), 7.25 (+), 14.2 (+), 22.7 (−), 23.4 (+), 25.3 (−), 26.4 (+), 30.0 (+), 30.6 (−), 31.2 (−), 31.8 (−), 33.9 (+), 36.5 (−), 47.0 (+), 55.7 (+), 76.6 (−), 104.1, 105.7, 121.7 (−), 125.5 (+), 132.4 (−), 141.7 (−). The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[12b]

*1-Methoxy-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromene (**9**).* To an ice-cold solution of NaH (24.3 mg, 60% in oil, 0.61 mmol) in DMF (1 mL) was added EtSH (0.069 mL, 0.798 mmol). The solution was stirred for 30 min at 0 °C, and dimethyl ether **7** (37.9 mg, 0.080 mmol) in DMF (1 mL) was added. The mixture was stirred at 140 °C overnight, cooled to room temperature, and diluted with saturated NH_4Cl. The resulting mixture was extracted with Et_2O twice. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to

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furnish **8** (16.2 mg, 60%): R_f = 0.52 (hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 6.9 Hz, 3 H), 1.12 (s, 3 H), 1.14 (s, 3 H), 1.23−1.38 (m, 4 H), 1.45−1.64 (m, 3 H), 1.76 (s, 3 H), 1.90−2.27 (m, 5 H), 2.50 (t, J = 7.7 Hz, 2 H), 3.82 (s, 3 H), 3.98−4.10 (m, 1 H), 5.37−5.46 (m, 1 H), 6.03 (br s, 1 H), 6.29 (d, J = 1.5 Hz, 1 H), 6.35 (d, J = 1.5 Hz, 1 H); ^{13}C NMR−APT (75 MHz, $CDCl_3$): δ 14.1 (+), 22.6 (−), 23.4 (+), 25.2 (−), 26.1 (+), 28.8 (+), 30.1 (−), 30.9 (−), 31.6 (−), 33.1 (+), 36.1 (−), 48.0 (+), 55.8 (+), 73.8 (−), 103.6 (+), 110.8 (+), 116.3 (−), 124.9 (+), 139.2 (−), 143.5 (−), 156.0 (−), 156.4 (−). The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[15b] To a mixture of $ZnBr_2$ (84.6 mg, 0.376 mmol) and $MgSO_4$ (66.1 mg, 0.549 mmol) in CH_2Cl_2 (1 mL) was added **8** (15.3 mg, 0.044 mmol) in CH_2Cl_2 (1 mL). After being stirred at room temperature overnight, the mixture was diluted with saturated $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 twice. The organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography (hexane/EtOAc) to furnish **9** (11.3 mg, 78%): R_f = 0.82 (hexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3 H), 1.07 (s, 3 H), 1.23−1.74 (m, 8 H), 1.41 (s, 3 H), 1.67 (s, 3 H), 1.85−1.95 (m, 1 H), 2.10−2.20 (m, 2 H), 2.50 (t, J = 7.7 Hz, 2 H), 3.17 (dm, J = 11.4 Hz, 1 H), 3.84 (s, 3 H), 6.20−6.25 (m, 1 H), 6.26 (d, J = 1.5 Hz, 1 H), 6.30 (d, J = 1.5 Hz, 1 H); ^{13}C NMR−APT (75 MHz, $CDCl_3$): δ 14.1 (+), 19.2 (+), 22.7 (−), 23.5 (+), 25.2 (−), 27.7 (+), 30.9 (−), 31.4 (−), 31.7 (−), 34.0 (+), 36.1 (−), 46.0 (+), 55.3 (+), 77.3 (−), 103.0 (+), 110.3 (+), 110.4 (−), 124.9 (+), 133.6 (−), 142.7 (−), 154.4 (−), 158.4 (−). The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[15b]

Diethyl 3-(2-Methoxyphenyl)-2-phenyl-1-cyclohexen-1-yl Phosphate (11). To a mixture of K_3PO_4 (261.7 mg, 1.23 mmol), XPhos (12.2 mg, 0.026 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (25.2 mg, 0.024 mmol), and phenyl boronic acid (89.3 mg, 0.732 mmol) in toluene (2 mL) was added a solution of enol phosphate **5n** (100.3 mg, 0.239 mmol) in toluene (1 mL). The mixture was stirred at 100 °C overnight and filtered through a pad of Celite. The filtrate was concentrated to leave a residue, which was purified by column chromatography (hexane/EtOAc) to afford enol phosphate **11** (87.9 mg, 88%): R_f = 0.12 (hexane/EtOAc 3:1); IR (neat) 1677, 1599, 1489, 1281 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (dt, J = 7.2, 1.2 Hz, 3 H), 1.19 (dt, J = 7.2, 1.2 Hz, 3 H), 1.63−1.84 (m, 3 H), 1.90−2.04 (m, 1 H), 2.53−2.62 (m, 2 H), 3.67−3.93 (m, 4 H), 3.76 (s, 3 H), 4.32−4.39 (m, 1 H), 6.77 (dd, J = 8.1, 0.9 Hz, 1 H), 6.86 (dt, J = 7.5, 1.2 Hz, 1 H), 7.03−7.20 (m, 4 H), 7.22−7.34 (m, 3 H); ^{13}C−APT NMR (75 MHz, $CDCl_3$): δ 16.0 (+) (dd, J = 7, 2 Hz), 18.5 (−), 28.4 (−), 29.0 (−), 38.6 (+), 55.3 (+), 63.7 (−) (d, J = 7 Hz), 63.8 (d, J = 7 Hz), 110.2 (+), 119.9 (+), 124.5 (−), 124.6 (−), 126.4 (+), 127.1 (+), 127.6 (+), 129.1 (+), 130.0 (+), 131.5 (−) (d, J = 2 Hz), 138.7 (−), 145.5 (−) (d, J = 8 Hz), 156.8 (−); HRMS (FAB) m/z: $[M + H]^+$ Calcd for $C_{23}H_{30}O_5P$ 417.1831; Found 417.1832.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01630.

The ^{1}H and ^{13}C NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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