JOC The Journal of Organic Chemistry

Note

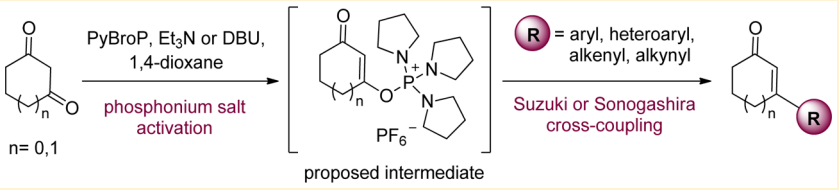
pubs.acs.org/joc

# Synthesis of β-Substituted Cyclic Enones via Phosphonium Salt-Activated, Palladium-Catalyzed Cross-Coupling of Cyclic 1,3-Diones

Shyh-Ming Yang,* Gee-Hong Kuo, Michael D. Gaul, and William V. Murray

Cardiovascular and Metabolism Research, Janssen Research and Development, LLC, Welsh & McKean Roads, Spring House, Pennsylvania 19477, United States

Supporting Information

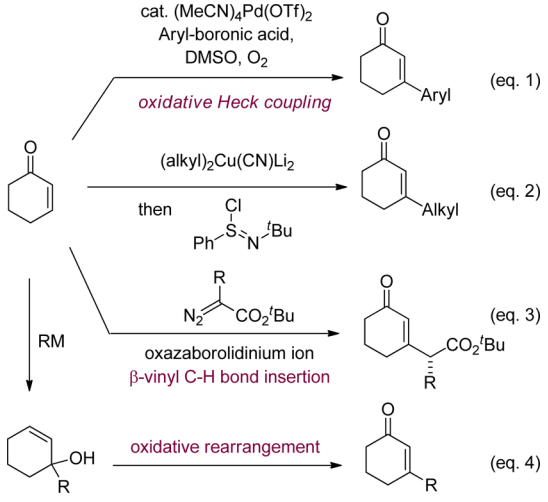



**ABSTRACT:** Phosphonium salt-activated, Pd-catalyzed Suzuki−Miyaura and Sonogashira cross-coupling reactions of cyclic 1,3-diones in the synthesis of β-substituted cyclic enones are described. These transformations exhibit good isolated yield and high generality with respect to both substrates and coupling partners. Extension of the substrate scope to cyclic 1,3-dione equivalents, such as 2-cyanocyclohexanone (**4**), is also briefly examined.

β-Substituted cyclic enones are versatile building blocks and often exhibit biological activity in small molecule drug design.[1] Examples of approaches to afford β-substituted enones include alkali base-mediated cyclization of diketones[2] and gold-catalyzed intramolecular cyclization of alkynyl ketones.[3] These transformations, however, require synthetic manipulation to generate prefunctionalized acyclic substrates that ultimately limit the generality of the scope. An aerobic double dehydrogenative cross-coupling protocol in the synthesis of β-aryl-substituted cyclic enones from saturated cyclic ketones and arenes has been recently developed.[4] Several direct β-position functionalizations from cyclic enones have also been discovered recently. These include palladium-catalyzed oxidative Heck coupling (Scheme 1, eq 1),[5] the addition−olefination protocol (eq 2),[6] the β-vinyl C−H bond insertion with high enantiomeric excess obtained in the presence of chiral oxazaborolidinium ion (eq 3),[7] and the oxidative rearrangement of tertiary allylic alcohols that originally derived from cyclic enones (eq 4).[8]

In view of other practical methodologies, cyclic 1,3-diones are facile building blocks often used to generate β-substituted cyclic enones. These transformations typically require two-step manipulation with isolation of intermediates, such as β-bromo, ethoxy, OTf, or carbamate. Those intermediates could subsequently undergo Pd- or Ni-catalyzed cross-coupling or utilize the addition−elimination protocol to furnish β-substituted cyclic enones (Scheme 2).[9] In our drug discovery programs, we are particularly interested in the β-substituted cyclic enones as useful synthons for developing novel compounds exhibiting significant biological activity. We envisioned the *enolizable* cyclic 1,3-diones is suited for generating activated intermediates, such as **A**, in situ with phosphonium salts. These intermediates could undergo a Pd-catalyzed cross-coupling reaction to yield β-substituted cyclic enones in a one-pot manner, without handling of potential moisture sensitive material and isolation of intermediates.[10]

**Scheme 1. Synthesis of β-Substituted Cyclic Enones from Corresponding Cyclic β-C−H Enones**




The direct functionalization of tautomerizable hetreocycles utilizing phosphonium salts, such as PyBrop, have been developed recently by Kang and others.[11−13] To test the feasibility of this transformation, we adopted the optimized conditions from those reported studies. Typical conditions would include using PyBroP as an activation reagent,[14] $PdCl_2(PPh_3)_2$ as the catalyst, triethyl amine as the base for activation, and 1,4-dioxane as the solvent. The initial attention

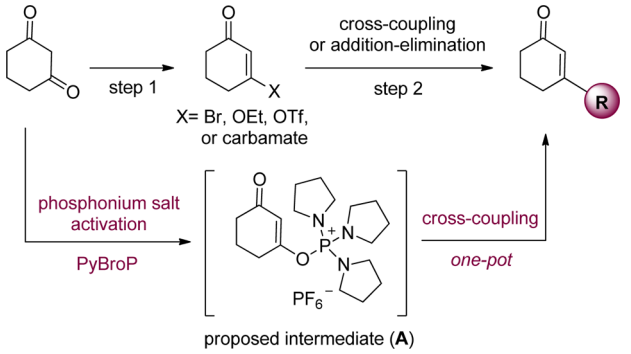
**Received:** February 22, 2016
**Published:** April 7, 2016





DOI: 10.1021/acs.joc.6b00317
J. Org. Chem. 2016, 81, 3464−3469

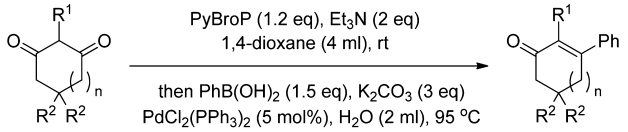
**Scheme 2. Synthesis of $\beta$-Substituted Cyclic Enones from Cyclic 1,3-Diones**

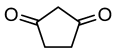
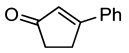
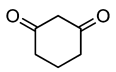
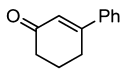
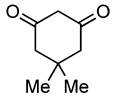
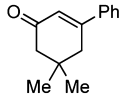
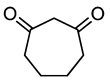
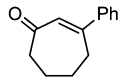
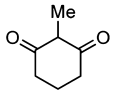
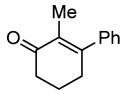



was mainly focused on the scope of cyclic 1,3-diones **1** (Table 1). To our delight, both the activation and subsequent Suzuki–Miyaura coupling of 5- or 6-membered diones (**1a–c**) proceeded effectively and efficiently to afforded enones **2a–c**, respectively, in 74–90% isolated yield (entries 1–3, respectively). In contrast, only ~15% of 7-membered enone **2d** was obtained under these conditions (entry 4). The sterically hindered 2-methyl-cyclohexane-1,3-dione **1e** was also problematic in the production of tetrasubstituted cyclohexenone **2e**, albeit in lower yield (entry 5). Prolonged activation times with or without an elevated temperature (50 °C) were ineffective, with an only slight improvement in yield (entries 6 and 7). This issue was solved by using DBU as the base, under typical reaction conditions, which afforded **2e** in 63% yield (entry 8).[12c] It should be noted that no improvement was observed for substrate **1d** by using DBU as the base, which indicates the low yield of **2d** presumably due to the difficulty in forming the activated phosphonium intermediate.

With a feasible protocol in hand, our attention was then focused on the scope of $\beta$-substitution. In general, the results compiled in Table 2 reveal this transformation exhibits good generality with a high isolated yield. No significant electronic effect was observed, though an electron-donating group (for example, OMe) typically gave slightly better yields (entries 1–4). The steric influence of the ortho substitution, such as 2-methoxy, 2-hydroxymethyl, and even 2,6-dimethyl, is minimal without a significant effect on the efficiency (entries 5–7, 72–85% yield). Moreover, heteroarylboronic acids, including 1-methylpyrazole (a pinacol boronic ester, entry 8), thiophene (entry 9), and isoxazole (a pinacol boronic ester, entry 10), are also effective coupling partners and give **3h–j** in 69–89% yield. Finally, the alkenyl boronic pinacol ester employed successfully

**Table 1. Scope of Cyclic 1,3-Diones in Phosphonium Salt-Activated, Pd-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction**[a]



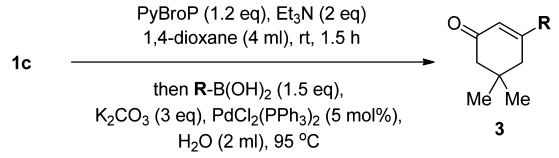

| entry | substrate | | time/time (PyBroP activation/cross-coupling) | **2** (yield, %) | |
|---|---|---|---|---|---|
| 1 | **1a** |  | 1.5 h/1 h |  | **2a** (74) |
| 2 | **1b** |  | 1.5 h/1 h |  | **2b** (85) |
| 3 | **1c** |  | 1.5 h/1 h |  | **2c** (90) |
| 4 | **1d** |  | 1.5 h/3 h |  | **2d** (15)[b] |
| 5 | **1e** |  | 1.5 h/1 h |  | **2e** (14) |
| 6 | **1e** | | 24 h/2 h | | **2e** (20) |
| 7[c] | **1e** | | 24 h/2 h | | **2e** (26) |
| 8[d] | **1e** | | 1.5 h/1 h | | **2e** (63) |

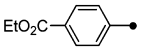
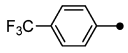
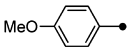
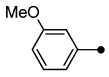
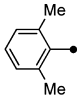
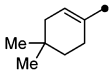
[a]All reactions were performed on 2 mmol scale. [b]Approximately 85% purity. [c]The PyBroP activation was performed at 50 °C. [d]DBU (2 equiv) as the base for PyBroP activation was employed.



DOI: 10.1021/acs.joc.6b00317
J. Org. Chem. 2016, 81, 3464–3469

**Table 2. Synthesis of β-Substituted Cyclic Enones Using Phosphonium Salt-Activated, Pd-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction**[a]

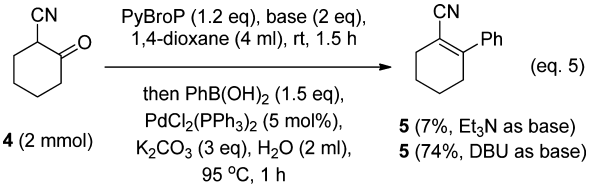



| entry | R | time (cross-coupling) | 3 (yield, %) |
|---|---|---|---|
| 1 |  | 2 h | **3a** (69) |
| 2 |  | 1 h | **3b** (82) |
| 3 |  | 1 h | **3c** (95) |
| 4 |  | 1 h | **3d** (95) |
| 5 |  | 1 h | **3e** (84) |
| 6 |  | 1 h | **3f** (72) |
| 7 |  | 1 h | **3g** (85) |
| 8[b] |  | 2 h | **3h** (69) |
| 9 |  | 2 h | **3i** (76) |
| 10[b] |  | 1.5 h | **3j** (89) |
| 11[b] |  | 1 h | **3k** (71) |
| 12 |  | 3 h | **3l** (8) |

[a]All reactions were performed on 2 mmol scale. [b]The corresponding boronic acid pinacol ester was employed.

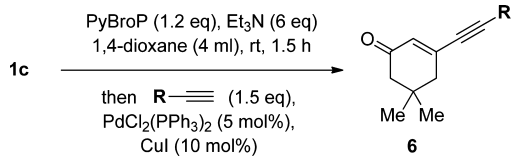
produced coupling product **3k** (71%), while the alkyl type boronic acid, exemplified as cyclopropyl boronic acid, is less effective and gave **3l** in only 8% yield.

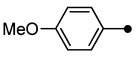
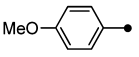
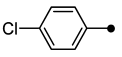
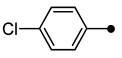
Other cyclic 1,3-dione equivalents such as 2-cyanocyclohexanone (**4**) with the capability of being easily enolized were tested under the same directed activation, cross-coupling protocol. This substrate required a stronger base, i.e., DBU, to preserve good yields (74%), while an only 7% isolated yield was obtained when triethylamine was employed as the base (eq 5)




Given the successful demonstration of the phosphonium salt-activated, Pd-catalyzed Suzuki–Miyaura cross-coupling reaction, we then tested the Sonogashira coupling with representative alkynes to generate corresponding β-alkynyl-substituted cyclic enones (Table 3). This transformation

**Table 3. Synthesis of β-Alkynyl-Substituted Cyclic Enones Using Phosphonium Salt-Activated, Pd-Catalyzed Sonogashira Cross-Coupling Reaction**[a]




| entry | R | conditions (cross-coupling) | 6 (yield, %) |
|---|---|---|---|
| 1 |  | 60 °C/2 h | **6a** (61) |
| 2 |  | rt/16 h | **6b** (64) |
| 3 |  | 60 °C/2 h | **6b** (78) |
| 4 |  | rt/16 h | **6c** (27) |
| 5 |  | 60 °C/2 h | **6c** (54) |

[a]All reactions were performed on 2 mmol scale.

required a slightly elevated temperature (60 °C) to afford moderate to good yields (54–78%) with similar efficiencies (2 h) for both cycloalkyl and aryl acetylene (entries 1, 3, and 5). The aryl acetylene with an electron-donating group (OMe) could produce the desired product at room temperature and with an extended reaction time (16 h) with a comparable yield (entry 2). Similarly, the electron-donating group is still preferred as the Cl-phenylacetylene typically gave a slightly lower yield (entry 2 vs entry 4 and entry 3 vs entry 5).

In conclusion, a simple extension of phosphonium salt-activated, Pd-catalyzed Suzuki–Miyaura and Sonogashira cross-coupling reactions of cyclic 1,3-diones in the synthesis of β-substituted cyclic enones is demonstrated. These transformations exhibited high yield and good generality with respect to both substrates and coupling partners. Further expanding the substrate scope to other cyclic 1,3-dione equivalent, such as **4**, is highly desirable.

## EXPERIMENTAL SECTION

**General Methods.** All reactions were performed under a positive pressure of nitrogen with oven-dried glassware. Chemical reagents and anhydrous solvents were obtained from commercial sources and used as is. $^1$H NMR spectra were recorded on 400 MHz spectrometers. All



DOI: 10.1021/acs.joc.6b00317
J. Org. Chem. 2016, 81, 3464–3469

NMR analyses were recorded using $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in parts per million with reference to TMS ($\delta$ 0.00). Data are presented as follows: chemical shift, multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (hertz), and integration. $^{13}C$ NMR spectra were recorded on 100 MHz spectrometers with reference to $CDCl_3$ ($\delta$ 77.0). Masses were recorded on a LC/MS system. High-resolution mass spectra (HRMS) were recorded on a Time-of-Flight (TOF, ESI mode) LC/HRMS system.

**General Procedure A for the Phosphonium Salt-Activated, Pd-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction.** *Preparation of 3-Phenylcyclopent-2-en-1-one (**2a**).*[1a] In a two-neck flask were placed cyclopentane-1,3-dione (196 mg, 2 mmol) and PyBroP (1118 mg, 2.4 mmol). The air was removed and the flask refilled with $N_2$ (twice). Then, 1,4-dioxane (4 mL) and $Et_3N$ (0.56 mL, 4 mmol) were added. The mixture was stirred at rt for 1.5 h. A mixture of phenylboronic acid (366 mg, 3 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), and $K_2CO_3$ (829 mg, 6 mmol) was added under $N_2$, and then $H_2O$ (2 mL) was added. The mixture was stirred at 95 °C for 1 h. The mixture was poured into an EtOAc/$H_2O$ solvent (10 mL/10 mL), and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layer was dried ($Na_2SO_4$) and then filtered. After removal of solvent, the product was purified by silica gel chromatography (24g column) using a 0 to 30% EtOAc/heptane gradient as the eluent to give 234 mg of 3-phenylcyclopent-2-en-1-one (**2a**, 74%): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (dd, $J$ = 7.3, 2.3 Hz, 2 H), 7.40–7.54 (m, 3 H), 6.59 (s, 1 H), 3.06 (dd, $J$ = 4.8, 2.8 Hz, 2 H), 2.52–2.66 (m, 2 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 209.5, 174.0, 134.1, 131.3, 128.9, 127.5, 126.8, 35.3, 28.7; MS $m/z$ $(M + H)^+$ 159 (100%).

*3-Phenylcyclohex-2-en-1-one (**2b**).*[8a] According to general procedure A described above, compound **2b** was prepared from cyclohexane-1,3-dione (224 mg, 2 mmol) and phenylboronic acid (366 mg, 3 mmol) in 85% yield (292 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (dd, $J$ = 6.6, 3.0 Hz, 2 H), 7.33–7.48 (m, 3 H), 6.43 (s, 1 H), 2.78 (t, $J$ = 5.3 Hz, 2 H), 2.44–2.57 (m, 2 H), 2.06–2.23 (m, 2 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.0, 159.8, 138.8, 130.0, 128.8, 126.1, 125.4, 37.3, 28.1, 22.8; MS $m/z$ $(M + H)^+$ 173 (100%).

*5,5-Dimethyl-3-phenylcyclohex-2-en-1-one (**2c**).*[1a] According to general procedure A described above, compound **2c** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and phenylboronic acid (366 mg, 3 mmol) in 90% yield (360 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (dd, $J$ = 6.6, 3.0 Hz, 2 H), 7.35–7.48 (m, 3 H), 6.42 (s, 1 H), 2.66 (s, 2 H), 2.35 (s, 2 H), 1.14 (s, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 157.7, 139.1, 130.0, 128.8, 126.2, 124.4, 51.0, 42.4, 33.8, 28.5; MS $m/z$ $(M + H)^+$ 201 (100%).

*3-Phenylcyclohept-2-en-1-one (**2d**).*[8a] According to general procedure A described above, compound **2d** was prepared from cycloheptane-1,3-dione (252 mg, 2 mmol) and phenylboronic acid (366 mg, 3 mmol) in ∼15% yield (65 mg, ∼85% purity): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.30–7.50 (m, 5 H), 6.31 (s, 1 H), 2.80–2.96 (m, 2 H), 2.61–2.78 (m, 2 H), 1.80–2.05 (m, 4 H); MS $m/z$ $(M + H)^+$ 187 (100%).

*2-Methyl-3-phenylcyclohex-2-en-1-one (**2e**).*[3] According to general procedure A described above, compound **2e** was prepared from 2-methylcyclohexane-1,3-dione (252 mg, 2 mmol) and phenylboronic acid (366 mg, 3 mmol) in 63% yield (234 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.29–7.47 (m, 3 H), 7.20 (d, $J$ = 7.1 Hz, 2 H), 2.58–2.71 (m, 2 H), 2.45–2.58 (m, 2 H), 2.00–2.18 (m, 2 H), 1.72 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.1, 156.6, 141.3, 131.9, 128.4, 127.9, 127.1, 37.8, 33.0, 22.8, 12.9; MS $m/z$ $(M + H)^+$ 187 (100%).

*3-(4-Ethoxycarbonylphenyl)-5,5-dimethylcyclohex-2-en-1-one (**3a**).* According to general procedure A described above, compound **3a** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 4-ethoxycarbonylphenylboronic acid (582 mg, 3 mmol) in 69% yield (378 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.08 (m, $J$ = 8.6 Hz, 2 H), 7.58 (d, $J$ = 8.6 Hz, 2 H), 6.45 (s, 1 H), 4.40 (q, $J$ = 7.1 Hz, 2 H), 2.66 (s, 2 H), 2.37 (s, 2 H), 1.41 (t, $J$ = 7.3 Hz, 3 H), 1.15 (s, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.9, 166.0, 156.3, 143.3, 131.5, 129.9, 126.1, 125.7, 61.2, 50.9, 42.3, 33.8, 28.4, 14.3; MS $m/z$ $(M + H)^+$ 273 (100%); HRMS (ESI/TOF) calcd for $C_{17}H_{21}O_3$ $[M + H]^+$ 273.1485, found 273.1499.

*5,5-Dimethyl-3-(4-trifluoromethylphenyl)cyclohex-2-en-1-one (**3b**).* According to general procedure A described above, compound **3b** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 4-trifluoromethylphenylboronic acid (570 mg, 3 mmol) in 82% yield (441 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (d, $J$ = 8.6 Hz, 2 H), 7.63 (d, $J$ = 8.6 Hz, 2 H), 6.43 (s, 1 H), 2.65 (s, 2 H), 2.37 (s, 2 H), 1.15 (s, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.8, 156.0, 142.7, 131.6 (q, $^2J_{C-F}$ = 32.6 Hz), 126.5, 125.9, 125.7 (q, $^3J_{C-F}$ = 3.6 Hz), 123.8 (q, $^1J_{C-F}$ = 270.6 Hz), 50.9, 42.4, 33.9, 28.4; MS $m/z$ $(M + H)^+$ 269 (100%); HRMS (ESI/TOF) calcd for $C_{15}H_{16}F_3O$ $[M + H]^+$ 269.1148, found 269.1157.

*5,5-Dimethyl-3-(4-methoxyphenyl)cyclohex-2-en-1-one (**3c**).*[1a] According to general procedure A described above, compound **3c** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 4-methoxyphenylboronic acid (456 mg, 3 mmol) in 95% yield (438 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$ = 9.1 Hz, 2 H), 6.93 (d, $J$ = 8.6 Hz, 2 H), 6.40 (s, 1 H), 3.85 (s, 3 H), 2.63 (s, 2 H), 2.33 (s, 2 H), 1.13 (s, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 161.2, 157.0, 131.1, 127.7, 122.7, 114.2, 55.5, 50.9, 42.1, 33.7, 28.5; MS $m/z$ $(M + H)^+$ 231 (100%).

*5,5-Dimethyl-3-(3-methoxyphenyl)cyclohex-2-en-1-one (**3d**).*[1a] According to general procedure A described above, compound **3d** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 3-methoxyphenylboronic acid (456 mg, 3 mmol) in 95% yield (439 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 8.0 Hz, 1 H), 7.12 (dd, $J$ = 7.7, 1.7 Hz, 1 H), 7.01–7.06 (m, 1 H), 6.95 (dd, $J$ = 8.2, 2.6 Hz, 1 H), 6.40 (t, $J$ = 1.5 Hz, 1 H), 3.84 (s, 3 H), 2.63 (d, $J$ = 1.5 Hz, 2 H), 2.34 (s, 2 H), 1.13 (s, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.1, 159.8, 157.5, 140.5, 129.7, 124.5, 118.6, 115.3, 111.8, 55.3, 51.0, 42.4, 33.7, 28.4; MS $m/z$ $(M + H)^+$ 231 (100%); HRMS (ESI/TOF) calcd for $C_{15}H_{19}O_2$ $[M + H]^+$ 231.1380, found 231.1397.

*5,5-Dimethyl-3-(2-methoxyphenyl)cyclohex-2-en-1-one (**3e**).*[1a] According to general procedure A described above, compound **3e** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 2-methoxyphenylboronic acid (456 mg, 3 mmol) in 84% yield (386 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.33 (td, $J$ = 7.4, 1.8 Hz, 1 H), 7.14–7.20 (m, 1 H), 6.97 (t, $J$ = 7.5 Hz, 1 H), 6.92 (d, $J$ = 8.3 Hz, 1 H), 6.17 (t, $J$ = 1.3 Hz, 1 H), 3.83 (s, 3 H), 2.62 (d, $J$ = 1.5 Hz, 2 H), 2.33 (s, 2 H), 1.11 (s, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 159.7, 156.6, 130.2, 129.9, 128.6, 127.1, 120.7, 111.1, 55.4, 51.2, 44.0, 34.2, 28.2; MS $m/z$ $(M + H)^+$ 231 (100%).

*5,5-Dimethyl-3-(2-hydroxymethylphenyl)cyclohex-2-en-1-one (**3f**).* According to general procedure A described above, compound **3f** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 2-hydroxymethylphenylboronic acid (456 mg, 3 mmol) in 72% yield (330 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$ = 7.1 Hz, 1 H), 7.29–7.44 (m, 2 H), 7.14 (d, $J$ = 7.1 Hz, 1 H), 6.02 (s, 1 H), 4.68 (d, $J$ = 5.6 Hz, 2 H), 2.53 (s, 2 H), 2.36 (s, 2 H), 1.88 (t, $J$ = 5.6 Hz, 1 H), 1.15 (s, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.8, 160.1, 140.0, 136.9, 128.72, 128.69, 127.9, 127.7, 127.1, 62.8, 50.9, 45.8, 34.2, 28.3; MS $m/z$ $(M + H)^+$ 231 (100%); HRMS (ESI/TOF) calcd for $C_{15}H_{19}O_2$ $[M + H]^+$ 231.1380, found 231.1386.

*5,5-Dimethyl-3-(2,6-dimethylphenyl)cyclohex-2-en-1-one (**3g**).* According to general procedure A described above, compound **3g** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 2,6-dimethylphenylboronic acid (450 mg, 3 mmol) in 85% yield (292 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.09–7.19 (m, 1 H), 7.01–7.09 (m, 2 H), 5.94 (s, 1 H), 2.30–2.44 (m, 4 H), 2.22 (s, 6 H), 1.17 (s, 6 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 198.1, 159.7, 138.0, 131.8, 126.1, 125.9, 125.8, 49.3, 42.6, 32.1, 26.8, 17.9; MS $m/z$ $(M + H)^+$ 229 (100%); HRMS (ESI/TOF) calcd for $C_{16}H_{21}O$ $[M + H]^+$ 229.1587, found 229.1599.

*5,5-Dimethyl-3-(1-methylpyrazol-4-yl)cyclohex-2-en-1-one (**3h**).* According to general procedure A described above, compound **3h** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (624 mg, 3 mmol) in 69% yield (280 mg): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (s, 1 H), 7.61 (s, 1 H), 6.28 (s, 1 H), 3.94 (s, 3



DOI: 10.1021/acs.joc.6b00317
J. Org. Chem. 2016, 81, 3464–3469

H), 2.51 (s, 2 H), 2.31 (s, 2 H), 1.11 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.7, 149.8, 137.8, 128.8, 122.0, 120.4, 51.0, 41.9, 39.4, 33.4, 28.5; MS $m/z$ $(M + H)^+$ 205 (100%); HRMS (ESI/TOF) calcd for $C_{12}H_{17}N_2O$ $[M + H]^+$ 205.1335, found 205.1344.

*5,5-Dimethyl-3-(4-methylthiophen-3-yl)cyclohex-2-en-1-one (**3i**).* According to general procedure A described above, compound **3i** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and (4-methylthiophen-3-yl)boronic acid (426 mg, 3 mmol) in 76% yield (335 mg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35 (d, $J$ = 3.0 Hz, 1 H), 7.01 (d, $J$ = 2.5 Hz, 1 H), 6.20 (s, 1 H), 2.58 (s, 2 H), 2.33 (s, 5 H), 1.13 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.2, 154.0, 141.1, 136.0, 125.4, 125.3, 123.5, 50.9, 44.2, 33.9, 28.4, 16.7; MS $m/z$ $(M + H)^+$ 221 (100%); HRMS (ESI/TOF) calcd for $C_{13}H_{17}OS$ $[M + H]^+$ 221.0995, found 221.1010.

*5,5-Dimethyl-3-(3,5-dimethylisoxazol-4-yl)cyclohex-2-en-1-one (**3j**).* According to general procedure A described above, compound **3j** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (669 mg, 3 mmol) in 89% yield (390 mg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.97 (t, $J$ = 1.6 Hz, 1 H), 2.41 (d, $J$ = 1.6 Hz, 2 H), 2.40 (s, 3 H), 2.29 (s, 2 H), 2.26 (s, 3 H), 1.08 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 198.9, 166.5, 157.7, 149.4, 127.6, 115.8, 50.8, 43.7, 34.1, 28.2, 12.5, 11.6; MS $m/z$ $(M + H)^+$ 220 (100%); HRMS (ESI/TOF) calcd for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1332, found 220.1341.

*5,5-Dimethyl-3-(4,4-dimethylcyclohex-1-en-1-yl)cyclohex-2-en-1-one (**3k**).* According to general procedure A described above, compound **3k** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (708 mg, 3 mmol) in 71% yield (330 mg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.28 (t, $J$ = 4.3 Hz, 1 H), 6.05 (s, 1 H), 2.39 (s, 2 H), 2.14–2.32 (m, 4 H), 1.94–2.08 (m, 2 H), 1.47 (t, $J$ = 6.3 Hz, 2 H), 1.06 (s, 6 H), 0.92 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.1, 156.8, 134.8, 131.3, 121.5, 51.1, 40.5, 39.9, 35.3, 33.2, 28.6, 28.4, 28.1, 23.2; MS $m/z$ $(M + H)^+$ 233 (100%); HRMS (ESI/TOF) calcd for $C_{16}H_{25}O$ $[M + H]^+$ 233.1900, found 233.1914.

*3-Cyclopropyl-5,5-dimethylcyclohex-2-en-1-one (**3l**).*[2] According to general procedure A described above, compound **3l** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and cyclopropylboronic acid (258 mg, 3 mmol) in 8% yield (25 mg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.86 (s, 1 H), 2.21 (s, 2 H), 2.00 (s, 2 H), 1.49–1.60 (m, 1 H), 1.02 (s, 6 H), 0.85–0.96 (m, 2 H), 0.69–0.79 (m, 2 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.5, 166.2, 122.2, 51.2, 41.0, 33.3, 28.3, 18.0, 7.8 MS $m/z$ $(M + H)^+$ 165 (100%).

*2-Phenyl-1-cyclohexenecarbonitrile (**5**).*[3] In a two-neck flask was placed PyBroP (1118 mg, 2.4 mmol). The air was removed and then the flask refilled with $N_2$ (twice). Then, 2-oxocyclohexanecarbonitrile (246 mg, 2 mmol) in 1,4-dioxane (4 mL) and then DBU (0.6 mL, 4 mmol) were added. The mixture was stirred at rt for 1.5 h. A mixture of phenylboronic acid (366 mg, 3 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), and $K_2CO_3$ (829 mg, 6 mmol) was added under $N_2$, and then $H_2O$ (2 mL) was added. The mixture was stirred at 95 °C for 1 h. The mixture was poured into an EtOAc/$H_2O$ solvent (10 mL/10 mL), and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layer was dried ($Na_2SO_4$) and then filtered. After removal of solvent, the product was purified by silica gel chromatography (40g column) using a 0 to 5% EtOAc/heptane gradient as the eluent to give 270 mg of **5** (74%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.29–7.48 (m, 5 H), 2.45–2.58 (m, 2 H), 2.35–2.45 (m, 2 H), 1.77 (ddd, $J$ = 11.6, 8.8, 2.8 Hz, 4 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.6, 140.1, 128.8, 128.5, 127.2, 119.8, 107.9, 31.3, 28.3, 21.9, 21.4; MS $m/z$ $(M + H)^+$ 184 (100%).

**General Procedure B for the Phosphonium Salt-Activated, Pd-Catalyzed Sonogashira Cross-Coupling Reaction.** *Preparation of 3-(Cyclohexylethynyl)-5,5-dimethylcyclohex-2-en-1-one (**6a**).*[1a] In a two-neck flask were placed 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and PyBroP (1118 mg, 2.4 mmol). The air was removed and the flask refilled with $N_2$ (twice). Then, 1,4-dioxane (4 mL) and $Et_3N$ (1.67 mL, 12 mmol) were added. The mixture was stirred at rt for 1.5 h. Cyclohexylethyne (324 mg, 3 mmol) was added, and then a mixture of $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol) and CuI (38 mg, 0.2 mmol) was added under $N_2$. The mixture was stirred at 60 °C for 2 h. The mixture was poured into an EtOAc/$H_2O$ solvent (10 mL/10 mL), and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layer was dried ($Na_2SO_4$) and then filtered. After removal of solvent, the product was purified by silica gel chromatography (80g column) using a 0 to 15% EtOAc/heptane gradient as the eluent to give 280 mg of **6a** (61%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.14 (s, 1 H), 2.51–2.63 (m, 1 H), 2.30 (s, 2 H), 2.24 (s, 2 H), 1.77–1.91 (m, 2 H), 1.71 (dd, $J$ = 9.3, 3.8 Hz, 2 H), 1.41–1.58 (m, 3 H), 1.26–1.41 (m, 3 H), 1.05 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.3, 142.5, 130.7, 105.9, 80.6, 51.0, 44.9, 33.7, 32.2, 30.0, 28.2, 25.8, 24.8; MS $m/z$ $(M + H)^+$ 231 (100%).

*5,5-Dimethyl-3-(4-methoxyphenylethynyl)cyclohex-2-en-1-one (**6b**).*[1a] According to general procedure B described above, compound **6b** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and (4-methoxyphenyl)ethyne (0.39 mL, 3 mmol) in 78% yield (398 mg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44 (d, $J$ = 8.6 Hz, 2 H), 6.88 (d, $J$ = 9.1 Hz, 2 H), 6.27 (s, 1 H), 3.84 (s, 3 H), 2.43 (s, 2 H), 2.29 (s, 2 H), 1.09 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.1, 160.6, 141.7, 133.7, 130.6, 114.2, 114.0, 100.1, 88.0, 55.4, 51.1, 44.5, 33.8, 28.2; MS $m/z$ $(M + H)^+$ 255 (100%).

*3-(4-Chlorophenylethynyl)-5,5-dimethylcyclohex-2-en-1-one (**6c**).* According to general procedure B described above, compound **6c** was prepared from 5,5-dimethylcyclohexane-1,3-dione (280 mg, 2 mmol) and (4-chlorophenyl)ethyne (410 mg, 3 mmol) in 54% yield (280 mg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42 (d, $J$ = 8.6 Hz, 2 H), 7.34 (d, $J$ = 8.6 Hz, 2 H), 6.30 (s, 1 H), 2.43 (s, 2 H), 2.30 (s, 2 H), 1.10 (s, 6 H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 199.0, 140.8, 135.7, 133.2, 131.6, 129.0, 120.5, 98.0, 89.6, 51.1, 44.2, 33.9, 28.2; MS $m/z$ $(M + H)^+$ 259 (100%); HRMS (ESI/TOF) calcd for $C_{16}H_{16}ClO$ $[M + H]^+$ 259.0884, found 259.0893.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00317.

$^1$H and/or $^{13}$C NMR spectra of all compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: shyhyang99@yahoo.com.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors thank Scott Ballentine and Mike Kolpak for HRMS determination.

## ■ REFERENCES


(1) (a) Khalaf, J.; Estrella-Jimenez, M. E.; Shashack, M. J.; Phatak, S. S.; Zhang, S.; Gilbertson, S. R. *ACS Comb. Sci.* **2011**, *13*, 351–356. (b) Jimenez, M. E.; Bush, K.; Pawlik, J.; Sower, L.; Peterson, J. W.; Gilbertson, S. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4215–4218.

(2) Grieco, P. A.; Ohfune, Y. *J. Org. Chem.* **1978**, *43*, 2720–2721.

(3) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259–5262.

(4) Gigant, N.; Bäckvall, J.-E. *Chem.–Eur. J.* **2014**, *20*, 5890–5894.

(5) (a) Walker, S. E.; Boehnke, J.; Glen, P. E.; Levey, S.; Patrick, L.; Jordan-Hore, J. A.; Lee, A.-L. *Org. Lett.* **2013**, *15*, 1886–1889. (b) Chung, L. G. Y.; Juwaini, N. A. B.; Seayad, J. *ChemCatChem* **2015**, *7*, 1270–1274.

(6) Matsuo, J.; Aizawa, Y. *Chem. Commun.* **2005**, 2399–2401.

(7) (a) Lee, S. I.; Kang, B. C.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2013**, *15*, 1428–1431. (b) For enantioselective insertion, see: Lee, S. I.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2013**, *135*, 7126–7129.

(8) (a) Shibuya, M.; Ito, S.; Takahashi, M.; Iwabuchi, Y. *Org. Lett.* **2004**, *6*, 4303–4306. (b) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J.*




DOI: 10.1021/acs.joc.6b00317
*J. Org. Chem.* 2016, 81, 3464–3469

*Org. Chem.* **2008**, *73*, 4750−4752. (c) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *Org. Lett.* **2008**, *10*, 4715−4718. (d) Uyanik, M.; Fukatsu, R.; Ishihara, K. *Org. Lett.* **2009**, *11*, 3470−3473. (e) Li, J.; Tan, C.; Gong, J.; Yang, Z. *Org. Lett.* **2014**, *16*, 5370−5373.

(9) (a) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376−1378. (b) Kehrli, S.; Martin, D.; Rix, D.; Mauduit, M.; Alexakis, A. *Chem.−Eur. J.* **2010**, *16*, 9890−9904. (c) Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 884−887. (d) Carpenter, R. D.; Verkman, A. S. *Org. Lett.* **2010**, *12*, 1160−1163. The 3-oxocycloalken-1-yl triflate is rarely used directly for Suzuki−Miyaura coupling. For a few examples, see: (e) Raghavan, S.; Schmidt, D. R.; Colletti, S. L.; Smenton, A. L. PCT Patent WO 2007092364, 2007. (f) Abad, A.; Agulló, C.; Cuñat, A. C.; Jiménez, D.; Perni, R. H. *Tetrahedron* **2001**, *57*, 9727−9735. Instead, the triflate can be converted to the corresponding pinacol boronic ester and serve as a coupling donor. See: (g) Ishiyama, T.; Takagi, J.; Kamon, A.; Miyaura, N. *J. Organomet. Chem.* **2003**, *687*, 284−290. For the 3-oxocycloalken-1-yl triflate for Sonogashira coupling, see: (h) Jiang, C.; Zhang, Z.; Xu, H.; Sun, L.; Liu, L.; Wang, C. *Appl. Organomet. Chem.* **2010**, *24*, 208−214.

(10) During the preparation of this work, Guchhait and Priyadarshani reported a Pd-catalyzed enolic C−O bond activation−Suzuki coupling for accessing *β*-substituted enones. See: (a) Guchhait, S. K.; Priyadarshani, G. *J. Org. Chem.* **2015**, *80*, 6342−6349. Another similar transformation involved *p*-toluenesulfonyl chloride (TsCl) activation. See: (b) Luo, Y.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 2103−2105.

(11) For a review, see: Kang, F.-A.; Sui, Z.; Murray, W. V. *Eur. J. Org. Chem.* **2009**, *2009*, 461−479.

(12) For representative phosphonium-mediated $S_NAr$ reactions, see: (a) Kang, F.-A.; Kodah, J.; Guan, Q.; Li, X.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 1957−1960. (b) Wan, Z.-K.; Binnun, E.; Wilson, D. P.; Lee, J. *Org. Lett.* **2005**, *7*, 5877−5880. (c) Wan, Z.-K.; Wacharasindhu, S.; Binnun, E.; Mansour, T. *Org. Lett.* **2006**, *8*, 2425−2428. (d) Wan, Z.-K.; Wacharasindhu, S.; Levins, C. G.; Lin, M.; Tabei, K.; Mansour, T. S. *J. Org. Chem.* **2007**, *72*, 10194−10210. (e) Levins, C. G.; Wan, Z.-K. *Org. Lett.* **2008**, *10*, 1755−1758. (f) Bae, S.; Lakshman, M. K. *Org. Lett.* **2008**, *10*, 2203−2206. (g) Bae, S.; Lakshman, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 782−789. (h) Kang, F.-A.; Murray, W. V. *Abstracts of Papers*; 228th ACS National Meeting, Philadelphia, PA, August 22−26, 2004; American Chemical Society: Washington, DC, ORGN-702.

(13) For Suzuki−Miyaura coupling, see: (a) Kang, F.-A.; Sui, Z.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300−11302. (b) Mehta, V. P.; Modha, S. G.; Van der Eycken, E. V. *J. Org. Chem.* **2010**, *75*, 976−979. (c) Li, S.-M.; Huang, J.; Chen, G.-J.; Han, F.-S. *Chem. Commun.* **2011**, *47*, 12840−12842. For Sonogashira coupling, see: (d) Kang, F.-A.; Lanter, J. C.; Cai, C.; Sui, Z.; Murray, W. V. *Chem. Commun.* **2010**, *46*, 1347−1349. (e) Shi, C.; Aldrich, C. C. *Org. Lett.* **2010**, *12*, 2286−2289 For a proposed mechanism for phosphonium salt-activated, Pd-catalyzed Suzuki−Miyaura and Sonogashira cross-coupling reactions, see refs 13a and 13d, respectively.

(14) The Br phosphonium salts (e.g., PyBroP and BroP) are more effective activation reagents as OBt phosphonium salts (e.g., PyBOP and BOP) could produce OBt ether side product that is not a reactive intermediate for the coupling reaction (see ref 13a).



DOI: 10.1021/acs.joc.6b00317
*J. Org. Chem.* 2016, 81, 3464−3469