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Palladacycle-Catalyzed Methylenecyclopropanation of Bicyclic Alkenes with Propiolates

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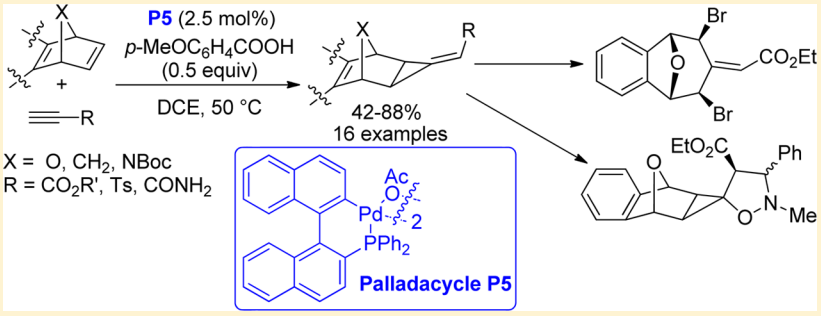
Supporting Information



ABSTRACT: An efficient way to access functionalized methylenecyclopropanes has been developed by palladacycle-catalyzed cyclopropanation of bicyclic alkenes with propiolates in high yields. The structure of the palladacycle was kept intact in the reaction, shown by ^{31}P NMR spectrum studies. A rational mechanism has been proposed with a deuterium-labeled experiment. The usefulness of the functionalized methylenecyclopropanes has also been demonstrated.

INTRODUCTION

Methylene- and alkylidenecyclopropanes having a strained three-membered carbocyclic ring and an *exo*-methylene moiety are found in many natural-occurring and artificial biologically active molecules.[1] They have also served as highly versatile synthons in organic synthesis and received intensive attention from synthetic chemists over the past decade.[2] To date, a variety of methodologies for their synthesis have been reported, such as elimination of cyclopropane derivatives,[3] Wittig olefinations,[4] the addition of carbenes to allenes,[5] the addition of alkylidenecarbenes to olefins,[6] and other cyclization reactions.[7] These procedures, however, suffer from a multistep synthesis, harsh reaction conditions, lower yields, or limited substrate scope. The preparation of alkylidenecyclopropanes has also been realized by transition-metal-catalyzed reaction of alkynes with alkenes. However, phenyl- and alkyl-substituted alkynes were used in most cases.[8] In the course of our research on the development of palladacycles as the real transition metal catalyst,[9−11] we realized the selectivity switch in the reaction of bicyclic alkenes with terminal alkynes, affording addition and ring-opening products selectively using palladacycles with an sp^3 and sp^2 C−Pd bond respectively.[12] When terminal ynones were the substrates, polysubstituted furans were obtained regioselectively under palladacycle catalysis.[13] Further research showed that an alkylidenecyclopropane was produced if propiolates were used to react with bicyclic alkenes. In this paper, we report the reaction of bicyclic alkenes with propiolates by using a phosphapalladacycle as the catalyst to provide alkoxycarbonyl substituted alkylidenecyclopropanes in high yields. The usefulness of the products is also demonstrated.

RESULTS AND DISSCUSSION

The research was initiated by our findings in the mechanistic studies on the reaction of bicyclic alkenes with ynones. In that study, we found that the alkylidenecyclopropanes should be the reaction intermediate, which was then transformed to furan products (Scheme 1A). We reasoned that the latter rearrangement may be attributed to the easy enolization of ketone. We envisioned that alkylidenecyclopropanes should be afforded in the presence of a palladacycle catalyst if we use a reactant that does not enolize (Scheme 1B). Thus, the ethyl propiolate (**2a**) (2.0 equiv) was reacted with 7-oxabenzonorbornadiene (**1a**) in the presence of palladacycle **P1** (2.5 mol %) as the catalyst in 1,2-dichloroethane (DCE) at 50 °C for 5 h. Indeed, expected alkylidenecyclopropanes **3a** was obtained in 51% yield, and its structure was established by X-ray diffraction. The control experiments with some common palladium species, such as $Pd(OAc)_2$, $Pd(OAc)_2/PPh_3$, $Pd(OAc)_2/(R)$-BINAP, $Pd_2(dba)_3{\cdot}CHCl_3$, $Pd(CH_3CN)_2Cl_2$, and $Pd(PPh_3)_2Cl_2$, resulted in no reaction or low conversion (<10%), which revealed the efficiency of a palladacycle in this reaction. A series of palladacycles (Figure 1) were then examined under the conditions shown in Table 1. Both the scaffold and donor atom of palladacycles affected the reaction greatly. The reaction

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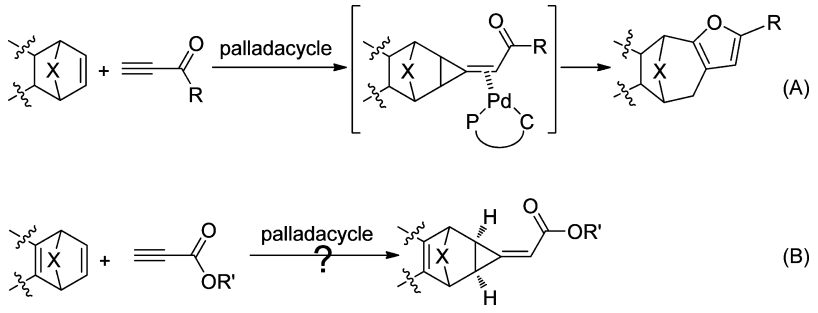
Scheme 1. Reaction of Bicyclic Alkenes with Ynones or Propiolates Catalyzed by a Palladacycle



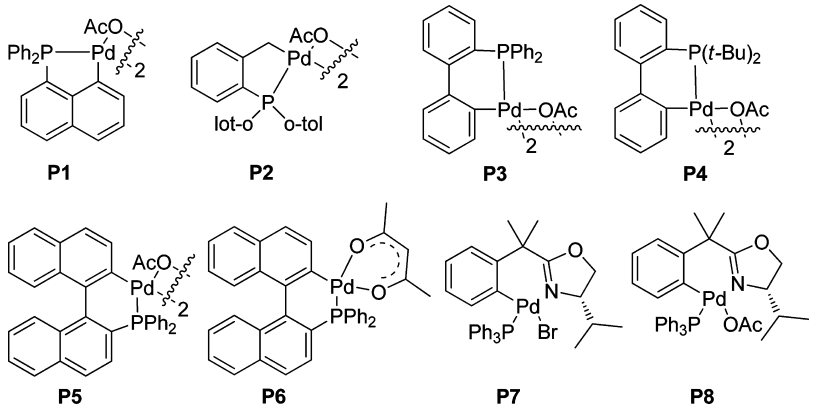
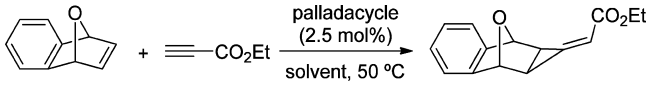


Figure 1. Palladacycles with different scaffolds and donor atoms.

Table 1. Optimizations for Cyclopropanation of Bicyclic Alkene 1a with Propiolate 2a[a]



entry	solvent	palladacycle	**3a**, yield (%)
1	DCE	**P1**	51
2	DCE	**P2**	43
3	DCE	**P3**	56
4	DCE	**P4**	5
5	DCE	**P5**	64
6	DCE	**P6**	38
7	DCE	**P7**	–
8	DCE	**P8**	–
9	toluene	**P5**	58
10	$CHCl_3$	**P5**	49
11	DME	**P5**	6
12	THF	**P5**	10
13	CH_3CN	**P5**	12
14	EtOH	**P5**	Trace[b]

[a]Reaction conditions: **1a** (28.8 mg, 0.2 mmol), **2a** (40 μL, 0.4 mmol), palladacycle (0.005 mmol), DCE (3.0 mL). [b]Determined by ^{1}H NMR.

usually proceeded smoothly by using *P*-containing palladacycles **P1**−**3** and **P5**−**6** (entries 1−3 and entries 5−6) while no reaction took place if *N*-containing palladacycles **P7** and **P8** were the catalysts (entries 7−8). Palladacycles **P1**−**3** gave product **3a** in moderate yield (entries 1−3). In contrast, the reaction became sluggish with palladacycle **P4** although it has the same scaffold as that of **P3**, perhaps due to its steric hindrance (entry 4). Palladacycle **P5** showed the highest activity, affording **3a** in 64% yield (entry 5). When the acetate group in palladacycle **P5** was replaced with acetylacetonate, the yield of **3a** decreased dramatically to 38% (entry 6 vs 5). With the palladacycle **P5** in hand, the influence of solvents on the reaction was evaluated. The reaction in toluene or $CHCl_3$ afforded **3a** in moderate yield (entries 9 and 10), while the yield dropped sharply when tetrahydrofuran (THF), dimethoxyethane (DME), or CH_3CN was used as the solvent (entries 11−13 vs 5). The use of EtOH hampered the reaction; only trace amount of product **3a** was observed from ^{1}H NMR (entry 14).

To further improve the reaction, the effect of additives was investigated with palladacycle **P5** as the catalyst and DCE as the solvent (Table 2). We observed that the addition of a base, such as NEt_3 or Cs_2CO_3, shut down the reaction completely while the starting material **1a** was almost fully recovered (entries 2 and 3). In contrast, the acid additive had great impact on the reaction. A strong acid such as CF_3COOH fully inhibited the reaction (entry 4), while AcOH gave a lower yield than that without any additive (entry 5 vs 1). Delightfully, the addition of 50 mol % of benzoic acid led to an increased yield of product **3a** (entry 6 vs 1). We then examined the effect of the quantity of benzoic acid on the reaction. These experiments indicated the use of a catalytic amount of benzoic acid resulted in a dramatic decrease of yield, while the use of a stoichiometric amount of benzoic acid did not improve the reaction (entries 7 and 8 vs 6). Also, the substituents at the *para*-position of benzoic acid have a great effect on the reaction (entries 9−12). The presence of an electron withdrawing group diminished the yield noticeably (entries 9 vs 6). In contrast, the introduction of an electron donating group is beneficial for the reaction and the best result was obtained when *p*-$MeOC_6H_4COOH$ was used as the additive, providing **3a** in 84% yield (entry 12).

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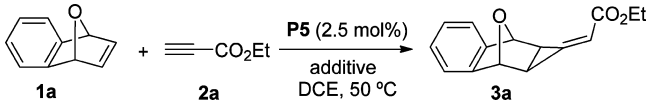
Table 2. Evaluation of Additive for Palladacycle P5-Catalyzed Cyclopropanation of Bicyclic Alkene 1a with Propiolate 2a[a]



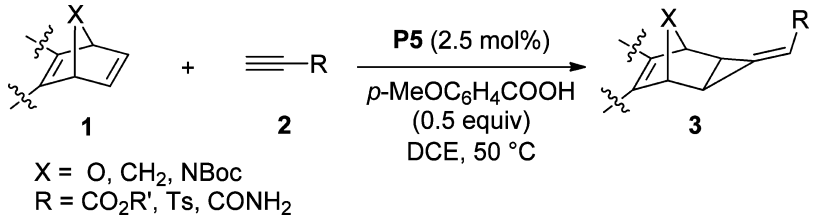
entry	additive	equiv.	3a, yield (%)
1	–	–	64
2	NEt_3	0.5	N.o.[b]
3	Cs_2CO_3	0.5	N.o.[b]
4	CF_3COOH	0.5	N.o.[b]
5	AcOH	0.5	57
6	PhCOOH	0.5	77
7	PhCOOH	0.05	60
8	PhCOOH	1.0	73
9	*p*-$NO_2C_6H_4COOH$	0.5	53
10	*p*-BrC_6H_4COOH	0.5	74
11	*p*-MeC_6H_4COOH	0.5	81
12	*p*-$MeOC_6H_4COOH$	0.5	84

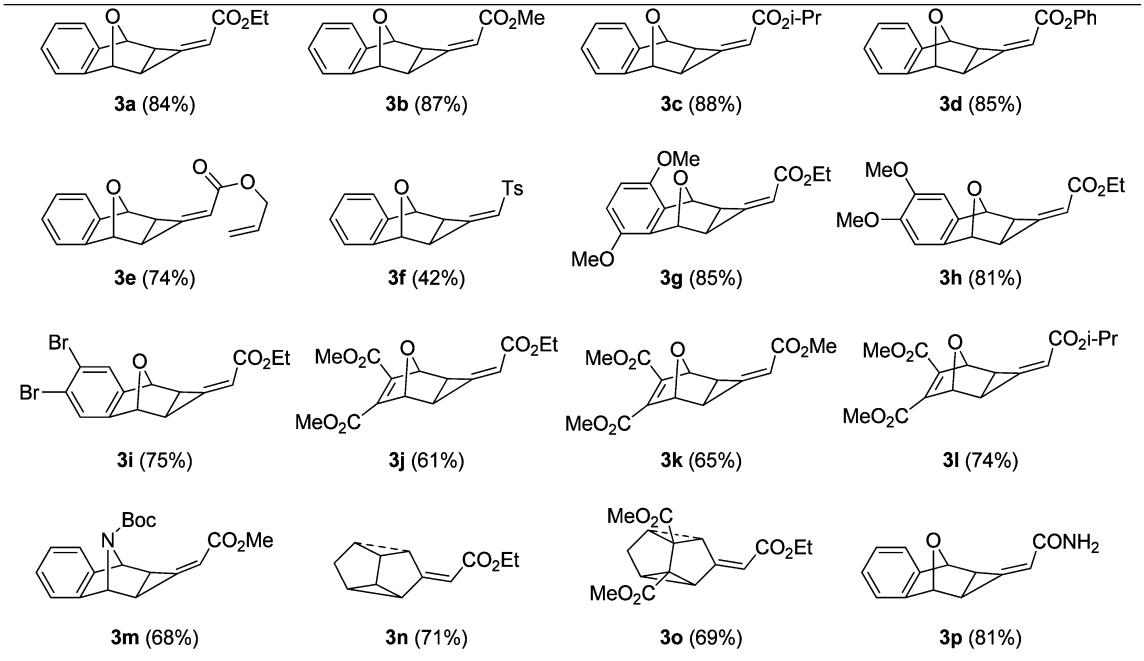
[a]Reaction conditions: **1a** (28.8 mg, 0.2 mmol), **2a** (40 μL, 0.4 mmol), **P5** (0.005 mmol), DCE (3.0 mL). [b]N.o. = Not observed.

Under the optimized conditions, the substrate scope of the reaction was evaluated (Table 3). Various oxabicyclic alkenes with a methoxy group and Br atom as the substituent were suitable substrates to afford products **3** in high yields (**3a** and **3g–i**). In addition, some other bicyclic alkenes, such as dimethyl oxanorbornadiene-2,3-dicarboxylate and 7-azabenzonorbornadiene, could also be used in the reaction, providing corresponding alkylidenecyclopropanes in good yields (**3j–m**). It is worthwhile to note that no cyclopropanes were obtained when norbornadiene derivates were used as the reactant; instead, polycyclic products **3n** and **3o** were afforded in 71% and 69% yield respectively.[14] The examination of alkyne substrates revealed that different alkyl and phenyl propiolates reacted with oxa-bicyclicalkenes, providing the corresponding alkylidenecyclopropanes in good yields (**3a–e**). Especially, cyclopropanation product **3f** was delivered in moderate yield when tosylacetylene was the reagent. Propiolamide was also applicable to the cyclopropanation reaction to give alkylidenecyclopropanes **3p** in 81% yield. Further studies of substrate scope revealed that the reaction is only applicable to terminal propiolates. When methyl-2-butynoate was subjected to the standard reaction conditions, no reaction occurred (not shown in table).

To investigate the reaction mechanism, the reaction was traced by a ^{31}P NMR spectrum using palladacycle **P2** as the catalyst (Figure 2). The ^{31}P NMR spectrum of palladacycle **P2** shows the peak at δ 34.9 ppm (sample A), which disappeared, and a new peak was observed at δ 30.6 ppm if 1.0 equiv of methyl propiolate (**2a**) was added after 10 min (sample B).[15] When bicyclic alkene **1a** (1.0 equiv) was added into sample B, the peak at δ 34.9 ppm appeared accompanied by two small peaks at δ 25.0 and 24.6 ppm (Sample C). The peaks at δ 30.6,

Table 3. Substrate Scope for Palladacycle P5-Catalyzed Cyclopropanation of Bicyclic Alkenes with Propiolates[a]





[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), **P5** (0.005 mmol), *p*-$MeOC_6H_4COOH$ (15.2 mg, 0.1 mmol), DCE (3.0 mL).

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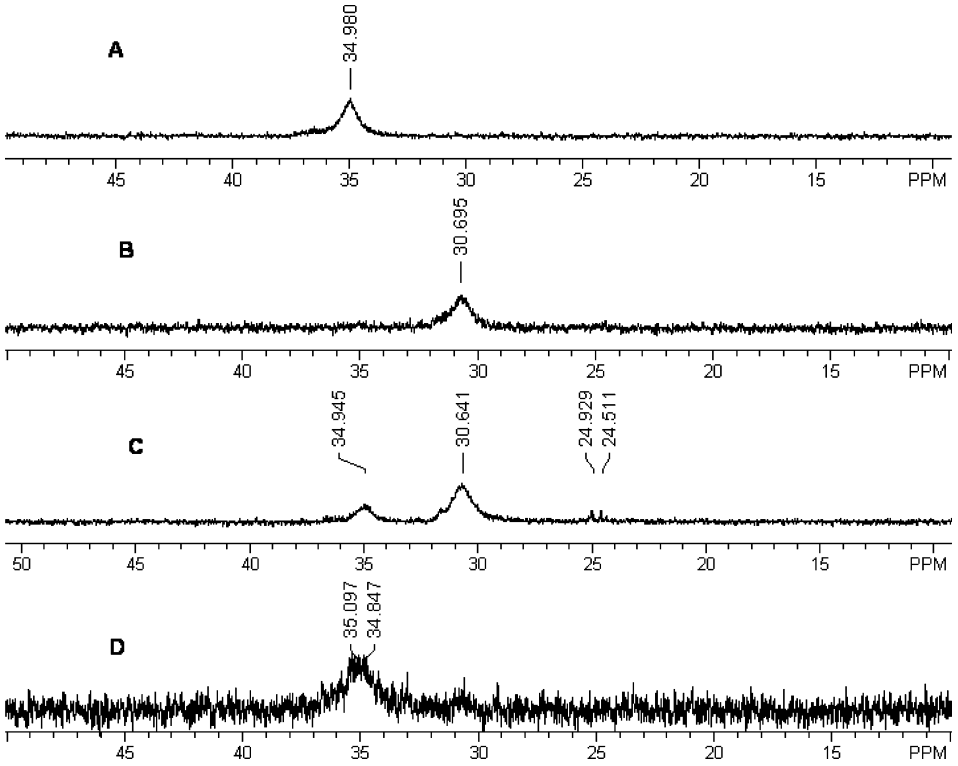
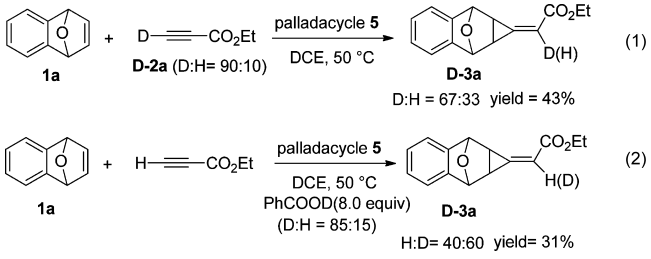


Figure 2. ^{31}P NMR spectrum studies of the reaction (sample A: ^{31}P NMR of palladacycle **P2** in DCE; sample B: ^{31}P NMR was detected when **2a** (1.0 equiv) was added to A after 10 min; sample C: ^{31}P NMR was detected when **1a** (1.0 equiv) was added to B after 1 h; sample D: ^{31}P NMR was detected after 5 h when **1a** was consumed by TLC).

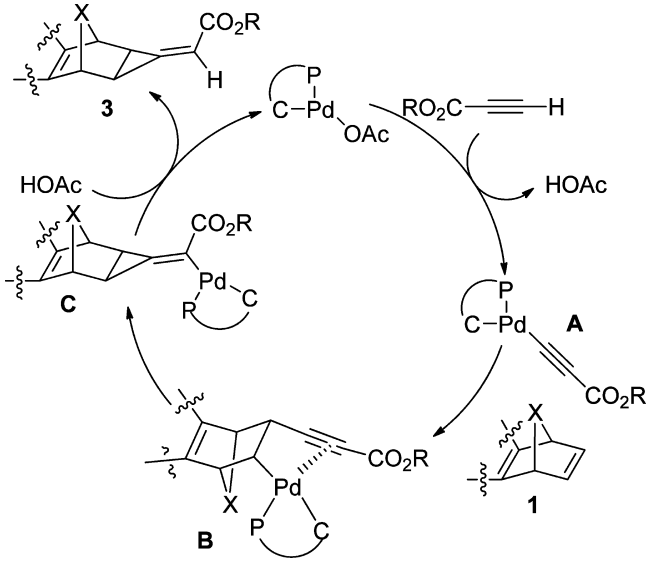
25.0, and 24.6 ppm disappeared completely, and only the peak of palladacycle **P2** was found at δ 35.0 ppm after 5 h (Sample D). Product **3a** was separated by column chromatography in 56% yield from sample D. These results showed that the palladacycles served as a real transition metal catalyst in the reaction, which was supported further by mass spectra (ESI) study. It was found that palladacycle **P2** gave a peak at m/z 409.0 (sample A), which could also be obtained when the reaction completed (sample D).[16]

A further clue concerning the reaction mechanism comes from deuterium labeling experiments. It demonstrated that product **3a** partially deuterium-labeled at the *exo*-vinyl carbon was afforded by the reaction using either a deuterium-labeled terminal alkyne or deuterium-labeled acid as an additive (eqs 1 and 2).



Based upon the above evidence and the literature,[8h,10a] a plausible mechanism was proposed (Scheme 2). The reaction of a palladacycle with propiolate **2** produces alkynylpalladium(II) **A**, which adds to the oxabicyclic alkene to form intermediate **B**. Intermediate **B** goes through an intramolecular insertion to form intermediate **C**, which undergoes intermolecular protonolysis to release product **3** and the palladacycle catalyst. The acid additive may accelerate this protonolysis step.

Scheme 2. A Plausible Mechanism for the Palladacycle-Catalyzed Cyclopropanation of Bicyclic Alkenes with Propiolates



The usefulness of the alkoxycarbonyl substituted alkylidenecyclopropane product **3** was also investigated. The reaction of alkylidenecyclopropanes **3a** with 4.0 equiv of $CuBr_2$ under 85 °C produced dibromide **4** in 53% yield,[17] and its structure was determined by X-ray diffraction (Scheme 3, eq 3). Furthermore, when **3a** was treated with nitrone in toluene at 100 °C, [3 + 2] cycloaddition products isoxazolidine **5a** and **5b** were obtained

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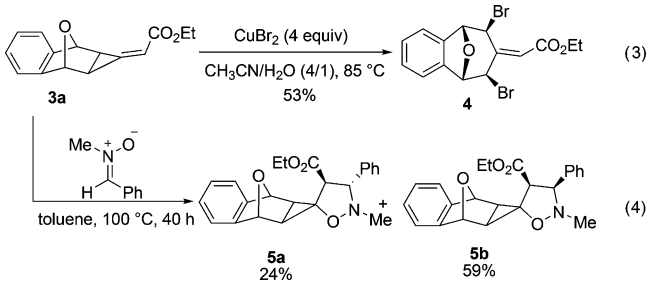
Scheme 3. Transformation of Product 3a



in 24% and 59% yield respectively (Scheme 3, eq 4).[18] Isoxazolidines have been demonstrated as valuable building blocks which were readily converted to γ-amino alcohols, β-amino acids, and β-lactams in recent decades.[19]

CONCLUSION

In summary, we have developed a simple and efficient method for preparing functionalized methylenecyclopropanes via cyclopropanation of bicyclic alkenes with propiolates catalyzed by a phosphapalladacycle. The mechanism investigations demonstrate that the palladacycle was the real transition metal catalyst in the reaction. The usefulness of the products is also demonstrated. Further investigations on the applications of the protocol as well as the palladacycles in organic synthesis are in progress.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under an atmosphere of either dry argon or nitrogen using oven-dried glassware. Solvents were treated using standard procedures and were distilled under an atmosphere of nitrogen before use. Commercially available reagents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on an NMR instrument operated at 300, 400 MHz respectively. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet or unresolved), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on an NMR instrument operated at 75, 100 MHz respectively with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm). IR spectra were recorded from thin films of pure samples. MS and HRMS were measured in EI or ESI mode, and the mass analyzer of the HRMS was TOF. Flash column chromatography was performed on silica gel (300−400 mesh). The palladacycles **P1**,[20] **P2**,[21] **P3**, **P4**,[22] **P5**,[11b] **P6**,[13] **P7**,[11a] and **P8**[23] were prepared according to literature methods, and their spectral data matched literature values.

General Procedure for Cyclopropanation of Oxabicyclic Alkenes with Propiolates Catalyzed by Palladacycle P5. In a Schlenk tube, palladacycle **P5** (2.5 mol %), oxabicyclic alkenes **1** (0.2 mmol), and *p*-$MeOC_6H_4COOH$ (15.2 mg, 0.1 mmol) were dissolved in DCE (3 mL) under argon. Terminal alkyne **2** (0.4 mmol) was added slowly to the mixture. Then, the mixture was stirred at 50 °C until the substrate **1** disappeared (monitored by TLC). The solvent was removed, and the residue was purified by flash chromatography on silica gel using PE/EtOAc (10/1−5/1) as the eluent to give product **3**.

3a. 40.6 mg, yield 84%. White solid. Mp: 60−62 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 6.9 Hz, 3H), 1.97 (d, J = 6.9 Hz, 1H), 2.21 (d, J = 6.9 Hz, 1H), 4.20 (q, J = 6.9 Hz, 2H), 5.52 (s, 1H), 5.61 (s, 1H), 6.19 (s, 1H), 7.18−7.21 (m, 2H), 7.35−7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 25.9, 28.4, 60.2, 80.0, 80.1, 112.1, 119.6, 119.7, 126.5, 126.59, 146.3, 146.4, 150.9, 165.5; MS (EI) m/z (rel): 242 (M^+, 2), 213 (18), 185 (59), 168 (48), 157 (45), 141 (100), 129 (62), 115 (46), 77(10); IR (KBr, neat): 3052, 3003, 2971, 2907, 1756, 1706, 1459, 1373, 1191, 746, 665 cm^{-1}; HRMS (EI) m/z for $C_{15}H_{14}O_3$: Calcd 242.0943; Found 242.0959.

3b. 39.6 mg, yield 87%. White solid. Mp: 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.98 (d, J = 7.2 Hz, 1H), 2.23 (d, J = 7.2 Hz, 1H), 3.78 (s, 3H), 5.52 (s, 1H), 5.62 (s, 1H), 6.20 (s, 1H), 7.19−7.21 (m, 2H), 7.37−7.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0, 28.5, 51.5, 80.1, 80.2, 111.7, 119.6, 119.7, 126.5, 126.6, 146.3, 146.4, 151.2, 165.9; MS (EI) m/z (rel): 228 (M^+, 6), 199 (16), 185 (12), 168 (76), 155 (25), 141 (100), 128 (34), 115 (52), 77 (8); IR (KBr, neat): 3045, 3013, 2949, 2841, 1755, 1694, 1458, 1434, 1288, 1040, 757, 669 cm^{-1}; HRMS (EI) m/z for $C_{14}H_{12}O_3$: Calcd 228.0786; Found 228.0784.

3c. 69.8 mg, yield 88%. White solid. Mp: 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, J = 4.4 Hz, 3H), 1.31 (d, J = 4.4 Hz, 3H), 1.96 (d, J = 7.2 Hz, 1H), 2.21 (d, J = 7.2 Hz, 1H), 5.06−5.15 (m, 1H), 5.51 (s, 1H), 5.59 (s, 1H), 6.16 (s, 1H), 7.19−7.21 (m, 2H), 7.35−7.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 25.8, 28.4, 67.5, 80.0, 80.1, 112.5, 119.6, 119.7, 126.5, 126.6, 146.4, 146.5, 150.5, 165.0; MS (ESI) m/z (rel): 257.4 $(M+H)^+$; IR (KBr, neat): 2986, 1752, 1706, 1461, 1369, 1190, 1110, 746 cm^{-1}; HRMS(ESI) m/z for $C_{16}H_{17}O_3$ $(M+H)^+$: Calcd 257.1178; Found 257.1174.

3d. 49.3 mg, yield 85%. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.06 (d, J = 7.2 Hz, 1H), 2.30 (d, J = 7.2 Hz, 1H), 5.57 (s, 1H), 5.64 (s, 1H), 6.38 (s, 1H), 7.15−7.23 (m, 5H), 7.35−7.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.6, 28.9, 80.3, 80.4, 111.5, 119.7, 119.8, 121.7, 125.7, 126.6, 126.7, 129.4, 146.3, 146.4, 150.8, 153.6, 163.8; MS (ESI) m/z (rel): 313 $(M+Na)^+$; IR (KBr, neat): 3056, 1721, 1593, 1492, 1458, 1197, 1144, 883, 759, 668 cm^{-1}; HRMS (ESI) m/z for $C_{19}H_{14}NaO_3$ $(M+Na)^+$: Calcd 313.0841; Found 313.0836.

3e. 37.6 mg, yield 74%. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (d, J = 7.2 Hz, 1H), 2.23 (d, J = 7.2 Hz, 1H), 4.68 (d, J = 4.8 Hz, 2H), 5.25 (d, J = 10.4 Hz, 1H), 5.35 (d, J = 17.2 Hz, 1H), 5.51 (s, 1H), 5.60 (s, 1H), 5.94−6.03 (m, 1H), 6.21 (s, 1H), 7.19−7.20 (m, 2H), 7.36−7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 28.5, 64.9, 80.1, 80.2, 111.8, 117.9, 119.6, 119.7, 126.5, 126.6, 132.3, 146.3, 146.4, 151.5, 165.0; MS (EI) m/z (rel): 254 (M^+, 0.5), 213 (6), 185 (93), 169 (24), 157 (58), 141 (100), 129 (66), 115 (56), 77 (7); IR (KBr, neat): 3051, 3001, 1712, 1647, 1458, 1370, 1171, 881, 759, 668 cm^{-1}; HRMS (EI) m/z for $C_{16}H_{14}O_3$: Calcd 254.0943; Found 254.0948.

3f. 27.2 mg, yield 42%. Yellow solid. Mp: 135−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (d, J = 7.2 Hz, 1H), 2.37 (d, J = 7.2 Hz, 1H), 2.43 (s, 3H), 5.51 (s, 1H), 5.53 (s, 1H), 6.67 (s, 1H), 7.19−7.22 (m, 2H), 7.33−7.36 (m, 4H), 7.80 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 26.3, 28.6, 80.2, 80.3, 119.8, 119.9, 121.5, 126.7, 126.8, 127.7, 129.8, 138.1, 144.3, 145.9, 146.0, 148.0; MS (ESI) m/z (rel): 325.1 $(M+H)^+$; IR (KBr, neat): 3047, 3003, 1745, 1598, 1458, 1341, 1289, 1140, 1083, 756, 675 cm^{-1}; HRMS (ESI) m/z for $C_{19}H_{17}O_3S$ $(M+H)^+$: Calcd 325.0898; Found 325.0892.

3g. 51.3 mg, yield 85%. White solid. Mp: 121−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 6.6 Hz, 3H), 2.02 (d, J = 6.9 Hz, 1H), 2.26 (d, J = 6.9 Hz, 1H), 3.82 (s, 6H), 4.23 (q, J = 6.6 Hz, 2H), 5.69 (s, 1H), 5.79 (s, 1H), 6.16 (s, 1H), 6.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 25.5, 28.1, 56.0, 56.1, 60.2, 78.3, 78.4, 111.5, 111.6, 111.8, 135.5, 147.3, 147.4, 150.9, 165.5; MS (EI) m/z (rel): 302 (M^+, 69), 274 (40), 259 (43), 245 (53), 228 (42), 215 (100), 199 (58), 171 (54), 115 (69), 77 (30); IR (KBr, neat): 3009, 2841, 1755, 1702, 1500, 1458, 1262, 1082, 807, 712 cm^{-1}; HRMS (EI) m/z for $C_{17}H_{18}O_5$: Calcd 302.1154; Found 302.1146.

3h. 49.1 mg, yield 81%. White solid. Mp: 119−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 6.9 Hz, 3H), 1.96 (d, J = 7.2 Hz, 1H), 2.20 (d, J = 7.2 Hz, 1H), 3.89 (s, 6H), 4.20 (q, J = 6.9 Hz, 2H), 5.48 (s, 1H), 5.78 (s, 1H), 6.15 (s, 1H), 7.00 (d, J = 5.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 26.3, 28.8, 56.3, 60.2, 80.5, 80.6, 104.7, 104.8, 111.6, 139.0, 139.1, 147.5, 147.6, 150.9, 165.6; MS (ESI) m/z (rel): 303 $(M+H)^+$; IR (KBr, neat): 2937, 2834, 1707, 1500, 1462, 1204, 1078, 847, 667 cm^{-1}; HRMS (ESI) m/z for $C_{17}H_{18}NaO_5$ $(M+Na)^+$: Calcd 325.1052; Found 325.1052.

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3i. 59.7 mg, yield 75%. Yellow solid. Mp: 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J = 6.8 Hz, 3H), 1.98 (d, J = 6.8 Hz, 1H), 2.22 (d, J = 6.4 Hz, 1H), 4.21 (q, J = 6.8 Hz, 2H), 5.45 (s, 1H), 5.53 (s, 1H), 6.19 (s, 1H), 7.61 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.3, 25.3, 27.8, 60.4, 79.5, 79.6, 113.0, 122.4, 122.5, 125.1, 125.2, 147.3, 147.4, 148.9, 165.2; MS (EI) m/z (rel): 398 (M^+, 4), 372 (19), 356 (15), 299 (25), 262 (8), 207 (17), 167 (4), 139 (100), 69 (15); IR (KBr, neat): 2986, 2851, 1697, 1183, 831, 675 cm^{-1}; HRMS (EI) m/z for $C_{15}H_{12}Br_2O_3$: Calcd 397.9153; Found 397.9155.

3j. 37.5 mg, yield 61%. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H), 2.27 (d, J = 6.8 Hz, 1H), 2.51 (d, J = 6.8 Hz, 1H), 3.85 (s, 6H), 4.20 (q, J = 7.2 Hz, 2H), 5.41 (s, 1H), 5.49 (s, 1H), 6.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 26.0, 28.5, 52.3, 60.3, 82.0, 82.1, 111.9, 146.6, 147.0, 149.8, 162.4, 162.5, 165.1; MS (EI) m/z (rel): 308 (M^+, 1), 248 (9), 220 (18), 203 (57), 191 (12), 176 (100), 161 (13), 153 (18), 96 (27), 79 (42); IR (KBr, neat): 2985, 2957, 2906, 1717, 1630, 1438, 1263, 1185, 733, 692 cm^{-1}; HRMS (EI) m/z for $C_{15}H_{16}O_7$: Calcd 308.0896; Found 308.0898.

3k. 38.2 mg, yield 65%. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (d, J = 7.2 Hz, 1H), 2.52 (d, J = 7.2 Hz, 1H), 3.77 (s, 3H), 3.85 (s, 6H), 5.42 (s, 1H), 5.50 (s, 1H), 6.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 28.5, 51.5, 52.3, 82.0, 82.1, 111.5, 146.6, 147.0, 150.1, 162.4, 162.5, 165.5; MS (ESI) m/z (rel): 317.0 (M+Na)$^+$; IR (KBr, neat): 2961, 1738, 1719, 1704, 1440, 1238, 1132, 856, 696 cm^{-1}; HRMS (ESI) m/z for $C_{14}H_{14}NaO_7$ (M+Na)$^+$: Calcd 317.0637; Found 317.0636.

3l. 51.0 mg, yield 74%. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, J = 5.2 Hz,6H), 2.27 (d, J = 7.2 Hz, 1H), 2.50 (d, J = 7.2 Hz, 1H), 3.85 (s, 6H), 5.05−5.11 (m, 1H), 5.41 (s, 1H), 5.48 (s, 1H), 6.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 25.9, 28.5, 52.2, 52.3, 67.7, 82.0, 82.1, 112.3, 146.6, 147.0, 149.5, 162.5, 162.6, 164.6; MS (ESI) m/z (rel): 345 (M+Na)$^+$; IR (KBr, neat): 2983, 2956, 2849, 1740, 1712, 1629, 1438, 1266, 1110, 896, 691 cm^{-1}; HRMS (ESI) m/z for $C_{16}H_{18}NaO_7$ (M+Na)$^+$: Calcd 345.0950; Found 345.0949.

3m. 44.4 mg, yield 68%. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 1.96 (d, J = 7.2 Hz, 1H), 2.17 (d, J = 7.2 Hz, 1H), 3.79 (s, 3H), 5.46 (s, 1H), 5.49(s, 1H), 6.23 (s, 1H), 7.15−7.17 (m, 2H), 7.35−7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.0, 27.9, 29.6, 51.5, 61.8, 62.2, 80.2, 114.3, 119.9, 120.2, 120.4, 126.2, 126.3, 146.0, 146.2, 152.8, 165.7; MS (ESI) m/z (rel): 350.1 (M+Na)$^+$; IR (KBr, neat): 3033, 2979, 2952, 1753, 1706, 1390, 1369, 1174, 913, 732, 669 cm^{-1}; HRMS (ESI) m/z for $C_{19}H_{21}NNaO_4$ (M+Na)$^+$: Calcd 350.1368; Found 350.1364.

3n. 27.0 mg, yield 71%. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 3H), 1.68−1.73 (m, 2H), 1.78 (m, 1H), 1.85−1.88 (m, 1H), 1.93−1.98 (m, 1H), 2.21−2.25 (m, 1H), 2.27−2.31 (m, 1H), 3.01−3.06 (m, 1H), 4.08 (dd, J = 11.4, 7.2 Hz, 2H), 5.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 26.1, 27.1, 28.3, 29.2, 31.0, 31.4, 32.9, 59.2, 109.9, 164.6, 167.2; MS (EI) m/z (rel): 190 (M^+, 18), 161 (6), 145 (14), 117 (94), 86 (65), 84 (100), 47 (55); IR (KBr, neat): 3059, 3039, 2927, 2858, 1709, 1643, 1447, 1383, 1211, 1145, 1041, 862, 740, 617 cm^{-1}; HRMS (EI) m/z for $C_{12}H_{14}O_2$: Calcd 190.0994; Found 190.0992.

3o. 42.2 mg, yield 69%. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H), 1.76 (d, J = 13.6 Hz, 1H), 2.25−2.29 (m, 1H), 2.35−2.37 (m, 1H), 2.51−2.53 (m, 1H), 2.65−2.68 (m, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 3.77−3.78 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 5.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 24.9, 37.2, 38.4, 38.5, 40.7, 41.4, 43.5, 52.0, 52.1, 59.9, 113.3, 155.4, 166.3, 169.5; MS (EI) m/z (rel): 306 (M^+, 13), 291 (1), 275 (6), 246 (7), 201 (10), 115 (20), 43 (100); IR (KBr, neat): 2985, 2955, 1733, 1654, 1440, 1216, 1151, 1035 cm^{-1}; HRMS (EI) m/z for $C_{16}H_{18}O_6$: Calcd 306.1103; Found 306.1100.

3p. 34.5 mg, yield 81%. White solid. Mp: 188−191 °C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ 1.94 (d, J = 7.2 Hz, 1H), 2.19 (d, J = 7.2 Hz, 1H), 5.53 (s, 1H), 5.57 (s, 1H), 6.09 (s, 1H), 7.05 (brs, 1H),7.16−7.19 (m, 2H), 7.25 (brs, 1H), 7.39−7.43 (m, 2H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 24.8, 27.6, 79.5, 79.7, 115.5, 120.1, 120.2, 126.5, 126.6, 145.4, 147.2, 147.3, 166.7; IR (KBr, neat): 3339, 3158, 1760, 1665, 1623, 1422, 880, 754, 670 cm^{-1}; HRMS (ESI) m/z for $C_{13}H_{12}NO_2$ (M+H)$^+$: Calcd 214.0863; Found 214.0896.

Reaction of 3a with $CuBr_2$. The Synthesis of Product 4. In a Schlenk tube with a condenser, substrate **3a** (48 mg, 0.2 mmol) and $CuBr_2$ (176 mg, 0.8 mmol) were dissolved in the mixed solvent of CH_3CN (4 mL) and H_2O (1 mL) under argon. Then, the mixture was stirred at 85 °C for about 10 h. The solvent was removed, and the residue was purified by flash chromatography on silica gel using PE/EtOAc (10/1−5/1) as the eluent to give product **4** as a white solid; yield 53%. Mp: 166−167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, J = 1.5 Hz, 3H), 4.09−4.13 (m, 2H), 4.52 (s, 1H), 5.44 (s, 1H), 5.46 (s, 1H), 5.85 (s, 1H), 5.89 (s, 1H), 7.30−7.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 40.6, 46.6, 60.7, 82.6, 83.0, 121.4, 121.8, 126.6, 129.0, 129.2, 140.0, 140.4, 149.7, 163.8; MS (ESI) m/z (rel): 422.9 (M+Na)$^+$; IR (KBr, neat): 2981, 2966, 2936, 2854, 1714, 1647, 1464, 1254, 1212, 1178, 1045, 736, 679 cm^{-1}; HRMS (ESI) m/z for $C_{15}H_{14}Br_2O_3Na$ (M+Na)$^+$: Calcd 422.9207; Found 422.9186.

Reaction of 3a with Nitrone. The Synthesis of Products 5a and 5b. In a Schlenk tube, (*Z*)-*N*-benzylidenemethanamine oxide (308 mg, 2.28 mmol) was added to a solution of compound **3a** (415 mg, 1.71 mmol) in toluene (4 mL), and the reaction mixture was stirred for 40 h at 100 °C. Evaporation of the solvent under reduced pressure and purification of the crude product by chromatography on silica gel (ethyl acetate/petroleum ether = 1/8) afforded product **5a** (158 mg, 24%) and product **5b** (379.6 mg, 59%).

5a. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H), 1.69 (d, J = 8.0 Hz, 1H), 1.85 (d, J = 8.0 Hz, 1H), 2.59 (s, 3H), 3.61 (d, J = 8.8 Hz, 1H), 3.71 (d, J = 8.8 Hz, 1H), 4.08−4.19 (m, 2H), 5.24 (s, 1H), 5.27 (s, 1H), 7.14−7.17 (m, 2H), 7.29−7.44 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 28.0, 30.2, 42.8, 59.1, 60.6, 77.2, 77.5, 78.9, 119.2, 119.7, 126.1, 126.2, 127.7, 128.4, 128.7, 145.9, 146.3, 172.1; MS (EI) m/z (rel): 377 (M^+, 3), 205 (44), 160 (45), 144 (77), 132 (100), 118 (63); IR (KBr, neat): 2959, 1731, 1175, 980, 754, 698 cm^{-1}; HRMS (ESI) m/z for $C_{23}H_{24}NO_4$ (M+H)$^+$: Calcd 378.1705; Found 378.1706.

5b. White solid. Mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, J = 7.2 Hz, 3H), 1.57 (d, J = 8.0 Hz, 1H), 1.94 (d, J = 8.0 Hz, 1H), 2.66 (s, 3H), 3.52−3.57 (m, 1H), 3.66−3.71 (m, 1H), 3.88 (d, J = 7.6 Hz, 1H), 4.11 (d, J = 8.4 Hz, 1H), 5.19 (s, 1H), 5.29 (s, 1H), 7.13−7.17 (m, 2H), 7.29−7.34 (m, 5H), 7.37−7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 27.3, 30.1, 43.5, 55.5, 60.1, 75.8, 77.2, 77.8, 119.2, 119.6, 126.1, 126.2, 127.9, 128.1, 135.5, 145.8, 146.0, 169.9; IR (KBr, neat): 2961, 1738, 1173, 848, 700, 672 cm^{-1}; HRMS (ESI) m/z for $C_{23}H_{24}NO_4$ (M+H)$^+$: Calcd 378.1705; Found 378.1705.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra of compounds **3a**−**3p**, **4**, and **5**, and X-ray analysis data of **3a** and **4** in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) This peak can be attributed to that of the adduct of palladacycle **P2** and alkyne **2a** because the same peak was detected if **P2**, **1a**, and **2a** was mixed.

(16) Please see Supporting Information for details.

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