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Synthesis of 2,3,4-Trisubstituted 2-Cyclopentenones via Sequential Functionalization of 2-Cyclopentenone

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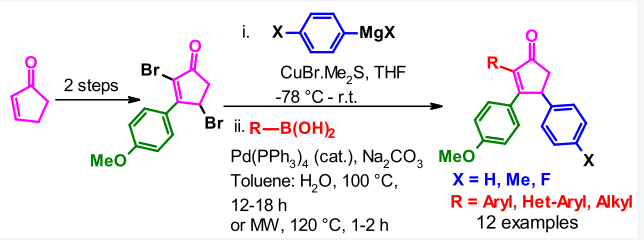
ABSTRACT: The synthesis of differently substituted 2,3,4-triarylcyclopent-2-en-1-ones from 2-cyclopentenone via sequential functionalization of a novel 2,4-dibromo-3-(4-methoxyphenyl) cyclopent-2-en-1-one intermediate has been developed. The process provides access to selective arylation at C-4 and C-2 with a broader substrates scope, which includes heteroaryl and alkyl substitution at C-2.



Substituted cyclopentenones are highly versatile building blocks for the synthesis of bioactive natural products, pharmaceuticals, agrochemicals, and synthetic materials.[1] Substituted 2-cyclopentenones have gained importance in recent times because of their multiple functional centers along with pre-established dense substituents.[2] These are also useful intermediates for the synthesis of rocaglaol and flavaglines group of natural products and their analogues.[3] There is an ample number of methods available for the synthesis of mono- or diarylcyclopentenones, most commonly via Pauson-Khand and Nazarov reaction.[4] However, only a few reports are available for the synthesis of triaryl 2-cyclopentenones, especially where all the aryl substituents are different. The first synthesis of differently substituted 2,3,4-triaryl cyclopentenone was reported in the year 2004 by Thede et al. via formation of 3,4-diaryl cyclopentenones-5-ethylcarboxylate from diaryl-α-bromoketones and allyldienetriphenylphosphorane.[5] Barluenga and co-workers have demonstrated the use of nickel(0)-catalyzed [3+2] cyclization reaction of chromium alkenyl(methoxy)carbene complexes for the construction of 3,4-diphenyl-2-tributylstannyl-cyclopent-2-en-1-one, which was finally converted to 2,3,4-triaryl cyclopentenones.[6] Recently, Basmadjian's group published differently substituted 2,3,4-triaryl 2-cyclopentenones by using gold(I)-catalyzed intramolecular alkyne-ether cyclization as the key step.[7] However, starting materials used in these processes are quite complex and with a limited substrate scope. Importantly, all of these methods for the construction of cyclopentanone derivatives are rely on cyclization of the highly functionalized starting material as a key step (Scheme 1), which is often low yielding and catalyzed by expensive metal catalysts. For the construction of the rocaglaol basic cage, which is the lead for our current agrochemical research project, we needed access to differently substituted 2,3,4-triaryl 2-cyclopentenones. To the best of our knowledge, the synthesis of 2,3,4-triaryl 2-cyclopentenones from 2-cyclopentenone is not known. Herein, we report a convenient and general synthesis of differently substituted 2,3,4-triaryl 2-cyclopentenones via sequential functionalization of easily available 2-cyclopentenone.

We commenced our studies with 3-(4-methoxyphenyl)-cyclopent-2-en-1-one (**2**), which was prepared in a single step from 2-cyclopentenone in 68% yield via the Heck reaction following our previously reported condition.[8] Our initial plan was two sequential brominations, each followed by arylation at the C-2 and C-4 position of **2** to afford the desired 2,3,4-triaryl 2-cyclopentenones (Scheme 2). Selective C-2 bromination was achieved with NBS in the presence of pyridine-*N*-oxide in acetonitrile at 0 °C to afford bromo compound **3** in 85% yield. Then we tried α-arylation of 2-bromo-3-(4-methoxyphenyl) cyclopent-2-en-1-one (**3**) via Suzuki coupling with (2-benzyloxyphenyl)boronic acid using $PdCl_2(PPh_3)_2$ as a catalyst reported for a similar moiety.[5] However, the yield obtained for desired coupling product **4** was not satisfactory (30%). Therefore, we quickly screened a few Pd catalysts under different conditions.[9] The best yields were obtained with $Pd(PPh_3)_4$ (5.0 mol %) using of 3.0 equiv of Na_2CO_3 in a toluene and water mixture (4:1) at 110 °C (Scheme 2).

Next, we planned the synthesis of 2,3,4-trisubstituted derivatives (**11**), starting from C-4 bromo intermediate **5**. However, our attempts to brominate the C-4 position of compound **4** to prepare **5** under various conditions were unsuccessful.

At this point, we decided to explore the feasibility of reversing the proposed reaction sequence, i.e., the first

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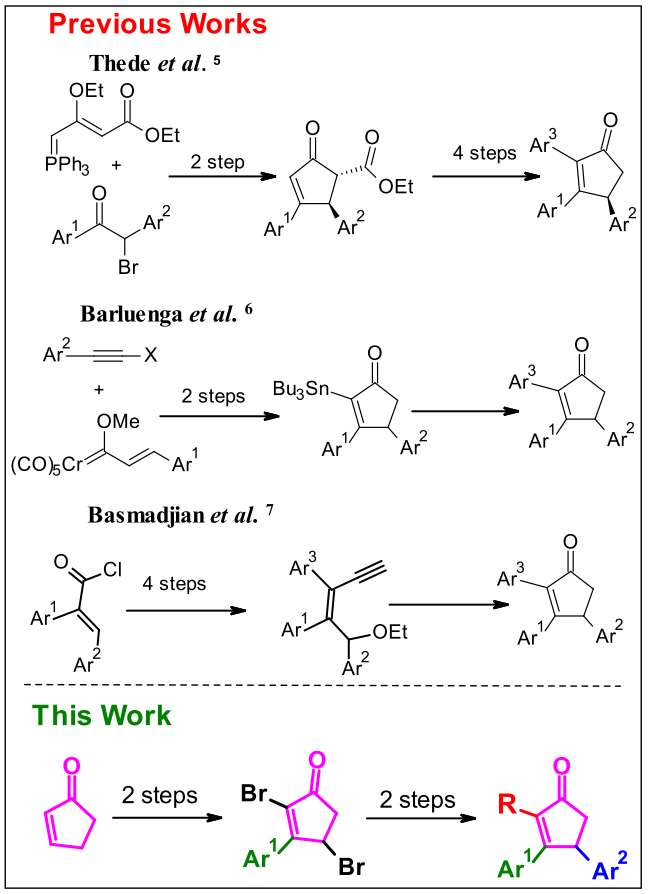
Scheme 1. Previous Work in the Context of Present Work

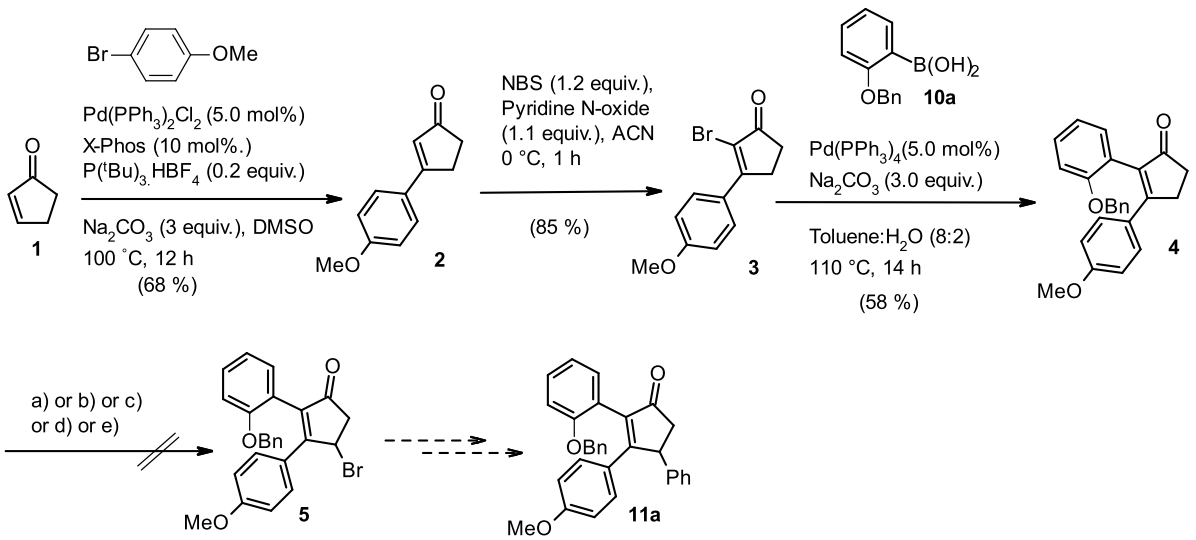


introduction of the aryl moiety at the C-4 position via bromination, then the introduction of aryl at the C-2 position. During the initial attempts for C-4 bromination of 3-(4-methoxyphenyl)cyclopent-2-en-1-one (**2**), a substantial amount of dibromo **6** was obtained as a side product, which triggered a new idea that if we can use the dibromo intermediate instead of monobromo so that we can reduce one step in the synthetic scheme. Therefore, we optimized the di bromination of **2** with excess NBS (2.2 equiv) to afford dibromo cyclopentenone **6** in 80% yield (Scheme 3).[9] Next, we explored C-4 arylation of dibromo-2-cyclopentenone **6**. We expected that treatment of excess arylmagnesium bromide would in situ convert **6** to the corresponding cyclopentadieneone intermediate **9**, following which, upon the 1,4-addition of an aryl moiety, would afford aryl addition product **8**. To our delight, treatment of **6** with excess PhMgBr and Cu(I)Br·Me_2S at −78 °C in THF afforded desired phenyl addition product **8a** in 62% yield (Scheme 3).[9]

To generalize the reaction, we then treated dibromo-2-cyclopentenone **6** with two other aryl Grignard reagents 4-fluorophenylmagnesium bromide and 4-methylphenylmagnesium bromide solutions under the optimized condition and afforded the desired products **8b** and **8c** in 54% and 58% yields, respectively (Scheme 3).

After successful synthesis of 3,4-diaryl-2-bromo-cyclopentenone **8**, the feasibility of C-2 arylation by Suzuki coupling with 2-(benzyloxy)phenylboronic acid was explored. Our previously optimized condition[9] for the synthesis of **4** was proven to be the best for this coupling as well. The reaction of **8a** with (2-benzyloxyphenyl)boronic acid in the presence $Pd(PPh_3)_4$ (5.0 mol %) and Na_2CO_3 in toluene and water mixture (4:1) at 110 °C furnished the desired triarylcyclopentenone **11a** in 58% yield (Table 1; entry 1). Several other arylboronic acids were conveniently reacted with **8** under the same reaction condition to afford the desired 2,3,4-triaryl-2-cyclopentenones (**11b**–**11h**) in moderate to good yields. The scope of aryl boronic acids for C-4 aryl substitution on Suzuki coupling was briefly examined. Aryl boronic acid bearing an electron-withdrawing or electron-donating aryl group was found equally efficient toward the coupling reaction and afforded a comparable yield (Table 1, entry 1 vs entry 4, entry 2 vs entry 5, and entry 6 vs entry 7). Notably, boronic acid having a free hydroxyl group was well tolerated in the reaction condition (Table 1, entry 8).

Scheme 2. Initial Approach Toward the Synthesis of 2,3,4-Trisubstituted Cyclopent-2-en-1-ones[a]



[a]Reagents and conditions: (a) NBS (1.2 equiv), AIBN (0.2 equiv), $CHCl_3$, 80 °C, 2 h; (b) NBS (1.2 equiv), Bn_2O_2 (0.2 equiv), $CHCl_3$ 80 °C, 2 h; (c) NBS (1.2 equiv), AIBN (0.2 equiv), ACN, 80 °C, 2 h; (d) bromohydantoin (0.6 equiv), AIBN (0.2 equiv), $CHCl_3$, 80 °C, 2 h; (e) bromohydantoin (0.6 equiv), Bn_2O_2 (0.2 equiv), $CHCl_3$, 80 °C, 2 h.

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Scheme 3. Synthesis of 2-Bromo-3-(4-methoxyphenyl)-4-aryl-cyclopent-2-en-1-ones 8a−c

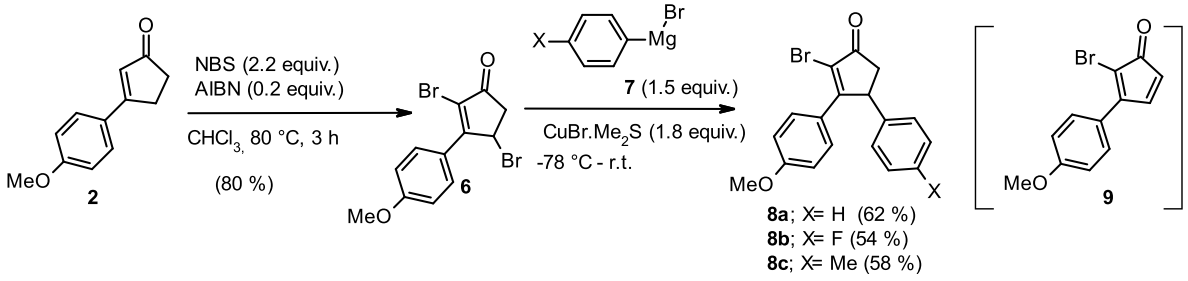
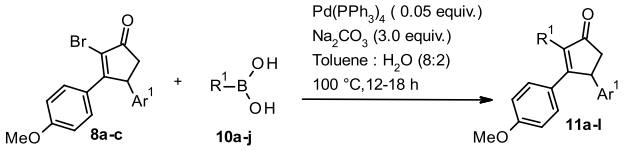


Table 1. Synthesis of 2,3,4-Trisubstituted Cyclopent-2-en-1-ones 11a−l



Entry	Ar[1]	R[1]	Product	Yield[a] (%)
1	Ph	10a	11a	58 (62)[b]
2	Me	10a	11b	55 (60)[b]
3	F	10a	11c	62 (65)[b]
4	Ph	10b	11d	65
5	Me	10b	11e	60
6	Ph	10c	11f	65
7	Ph	10d	11g	62
8	Ph	10f	11h	52
9	Ph	10g	11i	0
10	Ph	13h	11j	56
11	Ph	10i	11k	48
12	Ph	14j	11l	< 5 (35)[c]

[a]2-Bromo 3,4-biaryl cyclopent-2-en-1-one **8a** (1.46 mmol) and boronic acid (1.89 mmol) were used for the reaction. [b]Standard conditions were performed in a microwave reactor at 120 °C, 1−2 h. [c]Reaction conditions: $Pd(^tBu_3P)_2$ (5.0 mol %), CsF (2.0 equiv), THF (10 mL), 65 °C, 12 h.

However, highly electron-rich 2,4,6-trimethoxybenzene boronic acid failed to give the desired coupling product under optimal conditions (Table 1, entry 9). It seems **10g** underwent a proto deborylation reaction due to its rich electronic nature, which was indicated by the formation of 1,3,5-trimethoxybenzene as a major byproduct.[10]

Importantly, the reaction is not limited to simple aryl boronic acids. Alkyl boronic acid (Table 1, entry 10) and heteroaryl boronic acid (Table 1, entry 11) also underwent a coupling reaction to give the desired products in moderate yields. However, 2-furyl boronic acid provided only a trace amount (<5%) of the desired coupled product under the optimized condition (Table 1, entry 12). However, in the presence of cat. $Pd(^tBu_3P)_2$ (5 mol %), CsF (2.0 equiv) in THF at 65 °C, 2-furyl boronic acid successfully reacted with **8a** to afford the desired coupling product **11l** (Table 1, entry 12) though in a moderate yield (35%).[9] In general, the time required for these coupling reactions was 12−18 h. It is worth mentioning that the reaction time could be reduced to 1−2 h without compromising the yield under microwave irradiation (Table 1, entry 1−3).

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In summary, we have demonstrated a convenient and general route to the construction of differently substituted 2,3,4-triarylcyclopent-2-en-1-ones from 2-cyclopentenone via synthesis of a novel building block, 2,4-dibromo-3-(4-methoxyphenyl)cyclopent-2-en-1-one. The strategy is also suitable for the synthesis of 2-heteroaryl-3,4-diaryl- and 2-alkyl-3,4-diaryl-2-cyclopentenones. Further functionalization of 2,3,4-triarylcyclopent-2-en-1-ones to generate a library of rocaglaol analogues toward the optimization of agrochemical lead is in progress in our laboratory.

EXPERIMENTAL SECTION

General. Unless otherwise indicated, all reactions were carried out under an inert atmosphere of a nitrogen and in oven-dried flasks. Materials were purchased from commercial sources and used without additional purification. Anhydrous tetrahydrofuran and toluene were obtained via passage through an activated alumina column. All heating reactions were carried out using Heidolph heating blocks. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker Avance II-400 spectrometer in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. The HRMS analyses were performed on an Agilent QTOF 6520 mass spectrometer and LCMS on a THERMO MSQ PLUS mass spectrometer. Melting points were determined with an SRS-OptiMelt digital melting point apparatus and were uncorrected. Column chromatographic purifications were performed on a CombiFlash Rf (Teledyne Isco) with silica gel using the mobile phase indicated.

*2-Bromo-3-(4-methoxyphenyl)cyclopent-2-en-1-one (**3**).* To a stirred solution of 3-(4-methoxyphenyl)cyclopent-2-en-1-one (**2**) (1.0 g, 5.32 mmol) and pyridine-*N*-oxide (5.85 mmol) in CH_3CN (30 mL) was added NBS (6.38 mmol) at 0 °C. The stirring was continued at the same temperature for 1 h. The reaction mixture was quenched with water (30 mL) and extracted with DCM (3 × 50 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:9) to provide **3** as a pale-yellow solid: 1.20 g, 85% yield; mp 99−101 °C; IR (KBr) cm^{-1} 2934, 2914, 2840, 1730, 1604, 1584, 1508, 1460, 1323, 1180, 1026, 931, 842; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.80 Hz, 2H), 7.00 (d, J = 8.93 Hz, 2H), 3.88 (s, 3H) 3.10−3.08 (m, 2H) 2.69−2.66 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 201.7, 166.4, 161.9, 129.8, 126.3, 119.5, 114.0, 55.5, 32.3, 30.3; HRMS (EI) m/z [M + H]$^+$ calcd for $C_{12}H_{12}BrO_2$ 267.0022, found 267.0015.

*2-(2-Benzyloxyphenyl)-3-(4-methoxyphenyl)cyclopent-2-en-1-one (**4**).* To a stirred solution of 2-bromo-3-(4-methoxyphenyl) cyclopent-2-en-1-one (**3**) (1.0 g, 3.75 mmol) in toluene and water (8:2) mixed solvents (10 mL) were added (2-benzyloxyphenyl)-boronic acid (5.62 mmol) and Na_2CO_3 (11.25 mmol). The mixture was degassed with nitrogen for 10 min followed by the addition of $Pd(PPh_3)_4$ (0.187 mmol) and stirred at 100 °C for 14 h. The reaction mixture was cooled to an ambient temperature, diluted with water (30 mL), and extracted with AcOEt (3 × 50 mL). The combined organic layer was washed with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, and filtered, and the volatiles were evaporated. The crude was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:4) to get **4** as a white solid: 800 mg, 58% yield; mp 152−154 °C; IR (KBr) cm^{-1} 2956, 2926, 1692, 1604, 1594, 1514, 1354, 1260, 1178, 1045, 1030, 941, 842; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.29 (m, 3H), 7.28−7.24 (m, 3H), 7.14−7.10 (m, 3H), 7.01 (t, J = 7.24 Hz, 1H), 6.96 (d, J = 8.01 Hz, 1H), 6.78 (d, J = 8.00 Hz, 2H), 4.97 (br s, 1H), 4.90 (br s, 1H), 3.81 (s, 3H), 3.07 (br d, J = 5.38 Hz, 2H), 2.70−2.68 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 207.7, 167.3, 161.0, 156.2,137.2, 135.9, 131.1, 129.4, 129.3, 128.5, 128.3, 127.5, 127.1, 123.1, 121.3, 113.7, 112.9, 70.1, 55.3, 34.6, 29.0; HRMS (EI) m/z [M + H]$^+$ calcd for $C_{25}H_{23}O_3$ 371.1648, found 371.1639.

*2,4-Dibromo-3-(4-methoxyphenyl)cyclopent-2-en-1-one (**6**).* To a stirred solution of 3-(4-methoxyphenyl)cyclopent-2-en-1-one (**2**) (5.0 g, 26.59 mmol) in chloroform (150 mL) under a nitrogen atmosphere were added NBS (58.58 mmol) and AIBN (5.31 mmol), and the solution was heated at 80 °C for 6 h. The reaction mixture was cooled to an ambient temperature, quenched with water (100 mL), and extracted with DCM (3 × 150 mL). The combined organic layer was washed with brine (1 × 100 mL), dried over anhydrous Na_2SO_4, and filtered and the volatiles were evaporated. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:9) to afford **6** as a pale-yellow solid: 7.30 g, 80% yield; mp 122−124 °C; IR (KBr) cm^{-1} 2932, 2837, 1720, 1606, 1508, 1260, 1240, 1174, 1018, 937, 839; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 5.57 (dd, J = 6.60, 1.34 Hz, 1H), 3.90 (s, 3H), 3.38 (dd, J = 19.44, 6.60 Hz, 1H), 3.13 (dd, J = 19.44, 1.34 Hz, 1H); ^{13}C{^{1}H} NMR(101 MHz, $CDCl_3$) δ 195.5, 165.4, 162.1, 130.5, 124.0, 123.0, 114.1, 55.5, 44.3, 43.6; HRMS (EI) m/z [M + H]$^+$ calcd for $C_{12}H_{11}Br_2O_2$ 344.9127, found 344.9125.

General Procedure for the Synthesis of 2-Bromo-3-(4-methoxyphenyl)-4-aryl-cyclopent-2-en-1-one 8a−c. To a stirred solution of Cu (I)Br·Me_2S (5.20 mmol) in THF (15 mL) under a nitrogen atmosphere at −78 °C was added the appropriate arylmagnesium bromide in THF solution (4.33 mmol) dropwise (exotherm observed), and the reaction mixture was stirred for 1 h at the same temperature. 2,4-Dibromo-3-(4-methoxyphenyl)cyclopent-2-en-1-one (**6**) (1.0 g, 2.89 mmol) in THF (5 mL) was then added to the reaction dropwise at −78 °C over a period of 20 min (exotherm observed), and the reaction was brought to an ambient temperature slowly. The reaction mixture was quenched with saturated NH_4Cl at 0 °C and extracted with AcOEt (3 × 100 mL). The combined organic layer was washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, and filtered and the volatiles were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:4) to give **8a−c**.

*2-Bromo-3-(4-methoxyphenyl)-4-phenyl-cyclopent-2-en-1-one (**8a**):* 620 mg, 62% yield; pale-yellow gummy solid; IR (film) cm^{-1} 3011, 2931, 1713, 1698, 1605, 1587, 1504, 1450, 1255, 1180, 1028, 938, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.6 Hz, 2H), 7.28−7.18 (m, 3H), 7.13−7.11 (m, 2H), (d, J = 8.6 Hz, 2H), 4.62 (dd, J = 7.34, 1.96 Hz, 1H), 3.80 (s, 3H), 3.21 (dd, J = 18.89, 7.40 Hz, 1H), 2.57 (dd, J = 18.89, 2.02 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.8, 170.0, 161.3, 141.8, 130.6, 129.1, 127.2, 127.1, 125.4, 121.4, 113.8, 55.3, 48.0, 43.6; HRMS (EI) m/z [M + H]$^+$ calcd for $C_{18}H_{16}BrO_2$ 343.0328, found 343.0329.

*2-Bromo-4-(4-fluorophenyl)-3-(4-methoxyphenyl)cyclopent-2-en-1-one (**8b**):* 545 mg, 54% yield; pale-yellow gummy solid; IR (film) cm^{-1} 3010, 2839, 1712, 1697, 1605, 1587, 1504, 1454, 1254, 1178, 1028, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.6 Hz, 2H), 7.07- 7.05 (m, 2H), 6.95−6.86 (m, 4H), 4.61 (dd, J = 7.40, 1.90 Hz, 1H), 3.81 (s, 3H), 3.20 (dd, J = 18.89, 7.40 Hz, 1H), 2.52 (dd, J = 18.89, 2.02 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.4, 168.9, 163.0 (C−F, $^1J_{C-F}$ = 246.10 Hz), 161.4 (C−F, $^1J_{C-F}$ = 246.10 Hz), 160.5, 137.5, 130.5, 128.7 (C−F, $^3J_{C-F}$ = 8.09 Hz), 128.6 (C−F, $^3J_{C-F}$ = 8.09 Hz), 125.2, 121.6, 116.1 (C−F, $^2J_{C-F}$ = 21.69 Hz), 115.9 (C−F, $^2J_{C-F}$ = 21.69 Hz), 113.9, 55.3, 47.2, 43.5; HRMS (EI) m/z [M + H]$^+$ calcd for $C_{18}H_{15}BrFO_2$ 361.0239, found 361.0230.

*2-Bromo-3-(4-methoxyphenyl)-4-(p-tolyl)cyclopent-2-en-1-one (**8c**):* 600 mg, 58% yield, pale-yellow gummy solid; IR (film) cm^{-1} 3012, 2928, 1715, 1698, 1605, 1584, 1500, 1450, 1255, 1028, 940, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.93 Hz, 2H), 7.05−6.98 (m, 4H), 6.86 (br d, J = 8.80 Hz, 2H), 4.59−4.57 (m, 1H), 3.79 (s, 3H), 3.18 (dd, J = 18.89, 7.40 Hz, 1H), 2.56−2.51 (m, 1H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 200.8, 169.2, 161.3, 138.8, 136.8, 130.6, 129.8, 127.0, 125.5, 121.3, 113.8, 55.3, 47.6, 43.7, 26.9; HRMS (EI) m/z [M + H]$^+$ calcd for $C_{19}H_{18}BrO_2$ 357.0484, found 357.0471.

General Procedure for the Synthesis of 11a−l. *Method A.* To a stirred solution of 2-bromo-3-(4-methoxyphenyl)-4-aryl-cyclopent-2-en-1-one **8** (1.46 mmol) in toluene and water (8:2) mixed (5 mL) were added appropriate arylboronic acid (1.89 mmol) and Na_2CO_3

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(4.38 mmol), and the reaction mixture was degassed with nitrogen for 10 min. To the above mixture was added $Pd(PPh_3)_4$ (0.073 mmol), and the solution was stirred at 100 °C for 12−18 h. The reaction mixture was cooled to an ambient temperature. All volatiles were evaporated under reduced pressure and then diluted with water (15 mL) and extracted with AcOEt (3 × 30 mL). The combined organic layer was washed with brine (1 × 30 mL), dried over anhydrous Na_2SO_4, and filtered and all volatiles were evaporated. The crude was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to afford the corresponding coupling product.

Method B. To a stirred solution of 2-bromo-3-(4-methoxyphenyl)-4-aryl-cyclopent-2-en-1-one **8** (1.46 mmol) in THF (10 mL) were added appropriate arylboronic acid (1.89 mmol) and CsF (2.96 mmol), and the mixture was degassed with nitrogen for 10 min. To the above mixture was added $Pd(^tBu_3P)_2$ (0.073 mmol), and the mixture was stirred at 65 °C for 12 h. The reaction mixture was cooled to an ambient temperature. All volatiles were evaporated under reduced pressure, diluted with water (15 mL), and extracted with AcOEt (3 × 30 mL). The combined organic layer was washed with brine (1 × 30 mL) and dried over anhydrous Na_2SO_4, and the volatiles were evaporated. The crude was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:2) to afford the corresponding coupling product.

*2-(2-Benzyloxyphenyl)-3-(4-methoxyphenyl)-4-phenyl-cyclopent-2-en-1-one (**11a**).* The reaction was performed with 500 mg (1.46 mmol) of **8a**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to afford **11a** as a white solid: 380 mg, 58% yield; mp 65−67 °C; IR (KBr) cm^{-1} 2835, 1693, 1602, 1514, 1454, 1348, 1253, 1180, 1029, 837; ^1H NMR (400 MHz, DMSO-d_6) δ 7.33 (br d, J = 5.62 Hz, 5H), 7.26−7.20 as(m, 5H), 7.11 (br d, J = 7.21 Hz, 2H), 7.03−6.86 (m, 4H) 6.70 (br d, J = 8.68 Hz, 2H), 5.15−4.82 (m, 3H), 3.63 (s, 3H), 3.13 (brdd, J = 18.58 Hz, 7.34 Hz, 1H), 2.21 (br d, J = 18.71 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 206.1, 168.7, 160.5, 157.1, 114.2, 137.7, 137.4, 130.7, 130.4, 129.8, 129.0, 128.8, 128.2, 127.5, 126.9, 126.7, 123.7, 121.3, 114.0, 112.9, 70.2, 55.5, 46.0, 45.9; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{31}H_{27}O_3$ 447.1960, found 447.1926.

*2-(2-Benzyloxyphenyl)-3-(4-methoxyphenyl)-4-(p-tolyl)-cyclopent-2-en-1-one (**11b**).* The reaction was performed with 520 mg (1.46 mmol) of **8c**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to give **11b** as a white solid: 370 mg, 55% yield; mp 70−72 °C; IR (KBr) cm^{-1} 2840, 1702, 1600, 1530, 1454, 1348, 1253, 1180, 1040, 830; ^1H NMR (400 MHz, DMSO-d_6) δ 7.34 (br s, 4H), 7.24−7.18 (m, 5H), 7.06−6.86 (m, 5H), 6.78 (br d, J = 7.46 Hz, 1H), 6.70 (br d, J = 8.56 Hz, 2H), 5.13−4.76 (m, 3H), 3.64 (s, 3H), 3.11 (brdd, J = 18.58, 7.34 Hz, 1H), 2.22−2.16 (m, 1H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 204.6, 167.4, 158.9, 155.5 139.5, 135.9, 134.1, 129.1, 128.8, 128.2, 128.0, 127.2, 126.6, 126.6, 125.8, 125.3, 122.2, 119.7, 116.8, 112.4, 111.3, 68.5, 53.9, 44.3, 44.1, 19.3; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{32}H_{29}O_3$ 461.2111, found 461.2106.

*2-(2-Benzyloxyphenyl)-4-(4-fluorophenyl)-3-(4-methoxyphenyl)-cyclopent-2-en-1-one (**11c**).* The reaction was performed with 525 mg (1.46 mmol) of **8b**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to get **11c** as a brown solid: 420 mg, 62% yield; mp 131−133 °C; IR (KBr) cm^{-1} 2830, 1691, 1598, 1587, 1510, 1440, 1342, 1257, 1238, 1182, 844; ^1H NMR (400 MHz, DMSO-d_6) δ 7.38−7.17 (m, 9H), 7.12−6.87 (m, 5H), 6.73−6.69 (m, 3H), 5.16−4.70 (m, 3H), 3.65 (s, 3H), 3.12 (brdd, J = 18.52, 7.40 Hz, 1H), 2.19 (br d, J = 18.71 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 206.0, 168.5, 162.2 (C−F, $^1J_{C-F}$ = 244.40 Hz), 160.6, 159.8 (C−F, $^1J_{C-F}$ = 244.40 Hz), 157.0, 140.3, 137.6, 137.4, 130.7, 130.4, 129.9, 129.3 (C−F, $^3J_{C-F}$ = 7.90 Hz), 129.2 (C−F, $^3J_{C-F}$ = 7.90 Hz), 128.8, 128.4, 128.3, 127.2, 126.7, 123.6, 121.4, 115.8 (C−F, $^2J_{C-F}$ = 21.19 Hz), 115.6 (C−F, $^2J_{C-F}$ = 21.19 Hz), 114.1, 112.9, 70.2, 55.6, 45.8, 45.1; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{31}H_{26}FO_3$ 465.1865, found 465.1853.

*2-(2-Benzyloxy-4-fluoro-phenyl)-3-(4-methoxyphenyl)-4-phenyl-cyclopent-2-en-1-one (**11d**).* The reaction was performed with 500 mg (1.46 mmol) of **8a**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to give **11d** as a pale-yellow solid: 440 mg, 65% yield; mp 64−66 °C; IR (KBr) cm^{-1} 2930, 1697, 1593, 1514, 1496, 1417, 1339, 1256, 1180, 1153, 1026, 968; ^1H NMR (400 MHz, DMSO-d_6) δ 7.34 (br s, 4H), 7.30−7.18 (m, 5H), 7.13−6.95 (m, 4H), 6.90−6.78 (m, 2H), 6.74 (br d, J = 8.68 Hz, 2H), 5.17−4.82 (m, 3H), 3.66 (s, 3H), 3.14 (br dd, J = 18.40, 7.03 Hz, 1H), 2.34−2.19 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 205.1, 168.4, 163.5 (C−F, $^1J_{C-F}$ = 244.40 Hz), 161.1 (C−F, $^1J_{C-F}$ = 244.40 Hz), 159.7, 157.4, 143.2, 136.0, 130.5 (2C−F, $^3J_{C-F}$ = 8.80 Hz), 129.7, 128.2, 128.0, 127.4, 126.6, 126.4, 125.9, 118.9, 113.2, 106.9 (C−F, $^2J_{C-F}$ = 21.30 Hz), 106.7 (C−F, $^2J_{C-F}$ = 21.30 Hz), 100.6 (C−F, $^2J_{C-F}$ = 27.60 Hz), 100.4 (C−F, $^2J_{C-F}$ = 27.60 Hz), 69.8, 54.7, 45.1, 44.9; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{31}H_{26}FO_3$ 465.1860, found 465.1879.

*2-(2-Benzyloxy-4-fluoro-phenyl)-3-(4-methoxyphenyl)-4-(p-tolyl)cyclopent-2-en-1-one (**11e**).* The reaction was performed with 520 mg (1.46 mmol) of **8c**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to afford **11e** as a yellow solid: 418 mg, 60% yield; mp 72−74 °C; IR (KBr) cm^{-1} 2920, 2362, 1697, 1593, 1508, 1458, 1340, 1256, 1180, 1155, 1026, 837; ^1H NMR (400 MHz, DMSO-d_6) δ 7.34 (br s, 4H), 7.28−7.11 (m, 4H), 7.05−6.96 (m, 2H), 6.96−6.84 (m, 2H), 6.82−6.68 (m, 4H), 5.15−4.77 (m, 3H), 3.66 (s, 3H), 3.19−3.05 (m, 1H), 2.32−2.11 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 205.6, 169.0, 163.9 (C−F, $^1J_{C-F}$ = 244.10 Hz), 161.5 (C−F, $^1J_{C-F}$ = 244.10 Hz), 160.1, 157.8, 140.5, 136.4, 135.3, 131.4 (2C−F, $^3J_{C-F}$ = 9.1 Hz), 130.2, 129.2, 128.4, 127.8, 126.9, 126.8, 126.4, 119.3, 113.6, 107.3 (C−F, $^2J_{C-F}$ = 19.14 Hz), 107.1 (C−F, $^2J_{C-F}$ = 19.14 Hz), 101.0 (C−F, $^2J_{C-F}$ = 21.30 Hz), 100.8 (C−F, $^2J_{C-F}$ = 21.30 Hz), 70.1, 55.1, 45.4, 45.1, 20.5; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{32}H_{28}FO_3$ 479.2016, found 479.2036.

*2,3-Bis(4-methoxyphenyl)-4-phenyl-cyclopent-2-en-1-one (**11f**).* The reaction was performed with 500 mg (1.46 mmol) of **8a**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to get **11f** as a pale-yellow solid: 350 mg, 65% yield; mp 82−84 °C; IR (KBr) cm^{-1} 2845, 1706, 1602, 1535, 1450, 1348, 1253, 1040, 850; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18−7.14 (m, 4H), 7.10−7.05 (m, 5H), 6.82 (d, J = 7.84 Hz, 2H), 6.56 (d, J = 8.03 Hz, 2H), 4.46 (dd, J = 7.40, 2.02 Hz, 1H), 3.74 (s, 3H), 3.62 (s, 3H), 3.12 (dd, J = 18.83, 7.46 Hz, 1H), 2.49 (dd, J = 18.77, 2.14 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.0, 168.6, 160.3, 159.3, 143.0, 139.2, 130.9, 130.7, 129.0, 127.4, 127.2, 126.8, 124.6, 114.0, 113.6, 55.2, 55.1, 46.9, 46.0; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{25}H_{23}O_3$ 371.1641, found 371.1469.

*2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-4-phenyl-cyclopent-2-en-1-one (**11g**).* The reaction was performed with 500 mg (1.46 mmol) of **8a**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to afford **11g** as a pale-yellow solid: 340 mg, 62% yield; mp 78−80 °C; IR (KBr) cm^{-1} 2833, 1690, 1602, 1516, 1460, 1348, 1250, 1180, 1029, 830; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.33 (m, 2H), 7.28−7.24 (m, 4H), 7.18−7.11 (m, 5H), 6.67 (d, J = 7.40 Hz, 2H), 4.57 (dd, J = 7.40, 2.02 Hz, 1H), 3.72 (s, 3H), 3.22 (dd, J = 18.89, 7.40 Hz, 1H), 2.60 (dd, J = 18.83, 2.08 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 206.3, 170.2, 160.6, 142.5, 138.4, 133.9, 131.1, 130.9, 130.7, 129.0, 128.8, 127.4, 126.9, 126.6, 113.8, 55.2, 47.0, 46.0; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{24}H_{20}ClO_2$ 375.1146; found 375.1143.

*2-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-4-phenyl-cyclopent-2-en-1-one (**11h**).* The reaction was performed with 500 mg (1.46 mmol) of **8a**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to give **11h** as brown solid: 270 mg, 52% yield; mp 192−194 °C; IR (KBr) cm^{-1} 3157, 2837, 2647, 1798, 1662, 1600, 1564, 1450, 1346, 1261, 1185, 1031, 839; ^1H NMR (400 MHz, DMSO-d_6) δ 9.34 (br s, 1H), 7.31−7.14 (m, 8H), 6.96 (br d, J = 7.09 Hz, 1H), 6.88−

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6.84 (m, 2H), 6.71 (d, J = 8.80 Hz, 2H), 4.86 (br d, J = 5.99 Hz, 1H), 3.65 (s, 3H), 3.14 (dd, J = 18.52, 7.52 Hz, 1H), 2.30−2.25 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 206.3, 168.9, 160.4, 155.6, 144.4, 137.7, 131.2, 130.5, 129.5, 129.2, 127.7, 127.4, 126.9, 121.2, 119.5, 116.0, 113.9, 55.5, 45.9, 41.0; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{24}H_{21}O_3$ 357.1490, found 357.1496.

2-Cyclopropyl-3-(4-methoxyphenyl)-4-phenyl-cyclopent-2-en-1-one (11j). The reaction was performed with 500 mg (1.46 mmol) of **8a**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to get **11j** as pale-yellow gummy mass: 250 mg, 56% yield; IR (film) cm^{-1} 2852, 1688, 1605, 1514, 1348, 1263, 1200, 1039, 839; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.80 Hz, 2H), 7.28−7.02 (m, 5H), 6.82 (d, J = 8.68 Hz, 2H), 4.34 (d, J = 6.60 Hz, 1H), 3.77 (s, 3H), 3.00 (dd, J = 18.83, 7.34 Hz, 1H), 2.44−2.33 (m, 1H), 1.71−1.68 (m, 1H), 1.10−1.06 (m, 1H), 1.02−0.98 (m, 1H), 0.92- 0.88 (m, 1H), 0.72−0.69 (m, 1H); $^{13}C\{^1H\}$ NMR(101 MHz, $CDCl_3$) δ 208.2, 170.0, 160.0, 143.0, 139.7, 130.0, 128.8, 127.7, 127.4, 126.6, 113.6, 55.2, 46.7, 45.9, 8.3, 6.6, 5.5; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{21}H_{21}O_2$ 305.1541, found 305.1533.

3-(4-Methoxyphenyl)-4-phenyl-2-(3-pyridyl)cyclopent-2-en-1-one (11k). The reaction was performed with 500 mg (1.46 mmol) of **8a**, following general method A. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:3) to afford the desired product **11k** as a brown solid: 240 mg, 48%; yield; mp 80−82 °C; IR (KBr) cm^{-1} 2835, 1693, 1602, 1514, 1454, 1348, 1253, 1180, 1029, 837; ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (br d, J = 3.67 Hz, 1H), 8.36 (s, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.43 (dd, J = 7.89, 4.95 Hz, 1H), 7.25−7.22 (m, 4H), 7.17 (d, J = 8.80 Hz, 2H), 7.16−7.12 (m, 1H), 6.77 (d, J = 8.93 Hz, 2H), 4.89 (dd, J = 7.15, 1.77 Hz, 1H), 3.67 (s, 3H), 3.27−3.19 (m, 1H), 2.45−2.39 (m, 1H) ;$^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 205.8, 171.7, 160.6, 150.3, 149.0, 143.2, 137.6, 136.3, 130.9, 130.1, 129.2, 128.0, 127.0, 126.6, 124.0, 114.3, 55.6, 46.4, 45.9; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{23}H_{20}NO_2$ 342.1488, found 342.1488.

2-(2-Furyl)-3-(4-methoxyphenyl)-4-phenyl-cyclopent-2-en-1-one (11l). The reaction was performed with 500 mg (1.46 mmol) of **8a**, following general method B. The crude product was purified by flash chromatography on silica gel (AcOEt/cyclohexane, 1:2) to afford **11l** as a pale-yellow gummy solid: 170 mg, 35% yield; IR (film) cm^{-1} 2832, 1695, 1600, 1512, 1455, 1340, 1252, 1180, 1029, 837; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.23 (m, 1H), 7.16−7.07 (m, 7H), 6.95 (d, J = 3.30 Hz, 1H), 6.69−6.66 (m, 2H), 6.41 (dd, J = 3.36, 1.77 Hz, 1H), 4.42 (dd, J = 7.40, 2.02 Hz, 1H) 3.69 (s, 3H), 3.12 (dd, J = 18.89, 7.52 Hz, 1H), 2.50 (dd, J = 18.83, 2.20 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.8, 160.4, 146.3, 142.5, 142.1, 130.8, 130.4, 128.9, 127.5, 127.4, 126.9, 113.5, 113.3, 111.9, 11.3, 55.1, 47.8, 46.1; HRMS (EI) m/z $[M + H]^+$ calcd for $C_{22}H_{19}O_3$ 331.1328, found 331.1328.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01039.

Optimization tables, additional experimental procedure, analytical data, and copies of spectra (^1H NMR spectra and $^{13}C\{^1H\}$ NMR spectra) (PDF)

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Notes

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