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Rhodium-Catalyzed Hydroacylation of *para*-Quinone Methides with Salicylaldehydes: An Approach to α,α-Diaryl-2-Hydroxy Acetophenones

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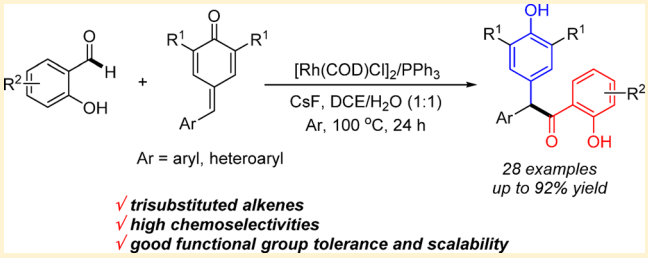
Supporting Information

ABSTRACT: A rhodium-catalyzed hydroacylation of *para*-quinone methides (*p*-QMs) with salicylaldehydes has been disclosed. This method allows for the construction of α,α-diaryl-2-hydroxy acetophenones through tandem C−H activation/C−C bond formation/aromatization process. Moreover, this unprecedented hydroacylation of trisubstituted alkenes exhibits good yields with broad functional group tolerance as well as gram-scale capacity.



The transition-metal-catalyzed hydroacylation of alkenes, allenes, and alkynes with aldehydes represents an atom-economic approach to construct ketones through a direct C−H activation/C−C bond formation process.[1] In 1997, Miura's group first reported a rhodium-catalyzed hydroacylation of alkynes with salicylaldehydes.[2] It was proposed that employing chelating salicylaldehydes could stabilize the five-membered cyclometal intermediates that were formed, prevent the potential decarbonylation pathway, and increase the transformation efficiency. From then on, salicylaldehydes were frequently used in the intermolecular hydroacylation for coupling with various olefins.

Normally, unfunctionalized terminal olefins give linear adduct products (Scheme 1a),[3] whereas branch isomers are unavoidable when 1,4- or 1,5-dienes are used (Scheme 1b).[4] By introducing heteroatoms as directing groups to the homoallylic position of the olefins, the branch products can be realized smoothly (Scheme 1c).[5] Hydroacylation of the strained cyclic olefins such as norbornenes and related bicyclic alkenes[6] as well as cyclopropenes[7] are also feasible (Scheme 1d). Hydroacylation of allenes can be achieved in good yields, albeit the selectivities are not well controlled (Scheme 1e).[2,8] Despite the fact that the aforementioned methods are very interesting, transition-metal-catalyzed hydroacylation of multisubstituted and steric hindrance olefins with salicylaldehydes has not been reported so far. Therefore, the development of hydroacylation of complex olefins is still highly desirable for constructing functional molecules. In 2015, Anand's group[9g] reported an organocatalyzed formal 1,6-conjugative addition of *para*-quinone methides (*p*-QMs) with aromatic aldehydes to prepare α,α-diaryl-acetophenones.[9] It is well-known that the *ortho*-hydroxyl or *ortho*-alkoxyl arylcarbonyl frameworks are widely found in natural products or pharmaceutical molecules, and introducing hydroxyl to the *ortho*-position of carbonyl has the potential to dramatically expedite the discovery and optimization of biologically active molecules.[10] However, the direct catalytic hydroacylation of *p*-QMs with salicylaldehydes is challenging due to the potentially competitive phenolic hydroxyl conjugative addition side reaction[11] and the steric effect embodied in *p*-QMs. To continue our research interests on *p*-QMs and rhodium-catalyzed C−H activation reactions,[12] herein we will describe our results on the rhodium-catalyzed hydroacylation of *p*-QMs with salicylaldehydes, leading to the direct synthesis of α,α-diaryl-2-hydroxy acetophenones (Scheme 1f). It is worth noting that the reaction was achieved through tandem C−H activation/C−C bond formation/aromatization process with high chemoselectivity.

We began our investigation with *para*-quinone methide **1a** and salicylaldehyde **2a** as model substrates. Preliminary attempts using $[Rh(COD)Cl]_2$ as a catalyst and 1,1′-bis(diphenylphosphino)ferrocene (dppf) as a ligand in the presence of CsF in CH_3CN at 100 °C led to the hydroacylation product **3aa** in 18% yield (Table 1, entry 1). Evaluation of commercially available rhodium catalysts revealed that $[Rh(COD)Cl]_2$ was the best choice (Table 1, entries 2−4). Screening of solvents suggested that 1,2-dichloroethane (DCE) could afford **3aa** in 46% yield (Table 1, entries 5−9). The yield was further improved to 67% when DCE and H_2O were chosen as the cosolvents (Table 1, entry 10) (see Table S1 for details). Other additives such as CsOAc, DIPEA, K_3PO_4, and $KHCO_3$ were also tested and exhibited inferior performance (Table 1, entries 11−14). Increasing the loading amount of **1a** to 1.5 equiv, **3aa** could be obtained in 72% yield (Table 1, entry 15). Finally, a significant improvement was noticed when PPh_3 was employed as the ligand (Table 1, entry 17). When electron-withdrawing, electron-donating, and diphosphine ligands were used, a sudden drop of the yield was observed (Table 1, entries 18−20). Various chiral ligands were

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Scheme 1. Transition-Metal-Catalyzed Intermolecular Hydroacylation of Alkenes with Salicylaldehydes

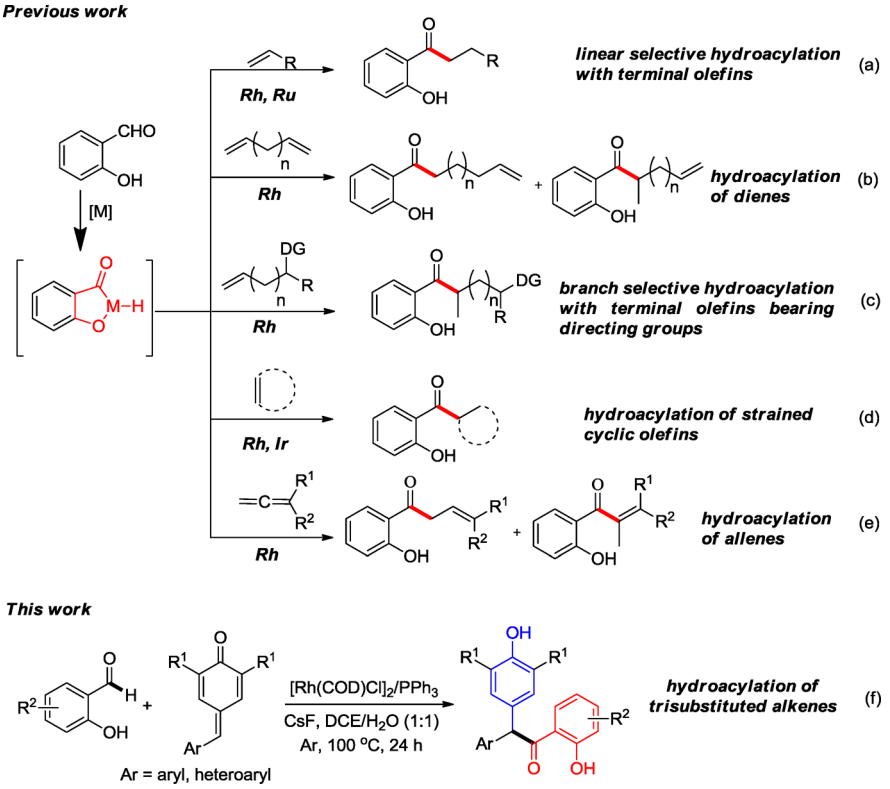
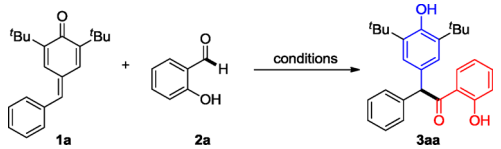


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	additive	solvent	yield [%][b]
1	$[Rh(COD)Cl]_2$	dppf	CsF	CH_3CN	18
2	$[Rh(CO)_2Cl]_2$	dppf	CsF	CH_3CN	trace
3	$Rh_2(OAc)_4$	dppf	CsF	CH_3CN	trace
4	$[RhCp^*Cl_2]_2$	dppf	CsF	CH_3CN	trace
5	$[Rh(COD)Cl]_2$	dppf	CsF	DCM	41
6	$[Rh(COD)Cl]_2$	dppf	CsF	THF	22
7	$[Rh(COD)Cl]_2$	dppf	CsF	toluene	21
8	$[Rh(COD)Cl]_2$	dppf	CsF	DMF	trace
9	$[Rh(COD)Cl]_2$	dppf	CsF	DCE	46
10	$[Rh(COD)Cl]_2$	dppf	CsF	DCE/H_2O	67
11	$[Rh(COD)Cl]_2$	dppf	CsOAc	DCE/H_2O	32
12	$[Rh(COD)Cl]_2$	dppf	DIPEA	DCE/H_2O	trace
13	$[Rh(COD)Cl]_2$	dppf	K_3PO_4	DCE/H_2O	8
14	$[Rh(COD)Cl]_2$	dppf	$KHCO_3$	DCE/H_2O	trace
15[c]	$[Rh(COD)Cl]_2$	dppf	CsF	DCE/H_2O	72
16[c]	$[Rh(COD)Cl]_2$	dppf	CsF	DCE/H_2O	57
17[c]	**$[Rh(COD)Cl]_2$**	**PPh_3**	**CsF**	**DCE/H_2O**	**98(92)**[d]
18[c]	$[Rh(COD)Cl]_2$	$(p\text{-}CF_3C_6H_4)_3P$	CsF	DCE/H_2O	20
19[c]	$[Rh(COD)Cl]_2$	$(p\text{-}CH_3C_6H_4)_3P$	CsF	DCE/H_2O	14
20[c]	$[Rh(COD)Cl]_2$	(±)-BINAP	CsF	DCE/H_2O	trace

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), catalyst (2.5 mol %), additive (0.2 mmol) in solvent (2 mL) at 100 °C for 24 h under argon atmosphere. The ratio of DCE/H_2O (v/v) was 1:1. [b]^1H NMR yields using dibromomethane (δ = 4.80) as an internal standard. [c]Used 0.3 mmol **1a** and 0.2 mmol **2a**. [d]Isolated yields.

tested with our catalyst system,[13] and no ee value was detected (see Table S2 for more details).

With the optimized conditions in hand, the substrate scope of *p*-QMs was examined, and the results are shown in Table 2.

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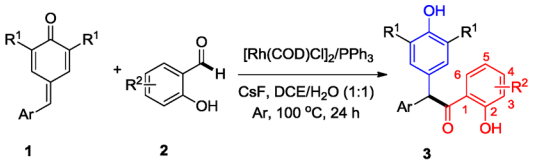
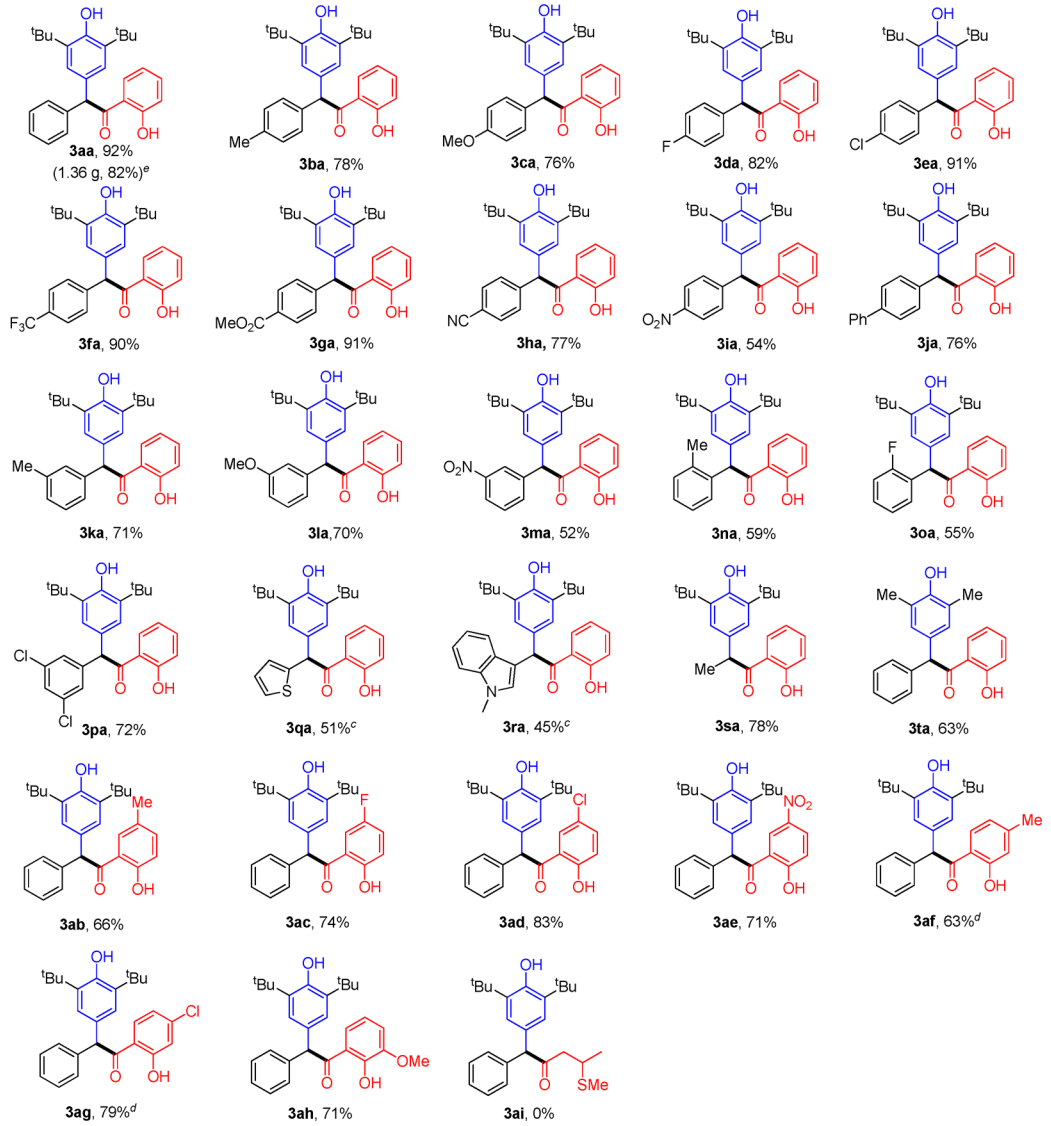
Table 2. Substrate Scope[a,b]





[a]Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), $[Rh(COD)Cl]_2$ (2.5 mol %), PPh_3 (5 mol %), CsF (0.2 mmol) in DCE/H_2O = 1:1 (2 mL) at 100 °C for 24 h under argon atmosphere. [b]Isolated yields. [c]$[Rh(COD)Cl]_2$ (5 mol %) and PPh_3 (10 mol %). [d]At 120 °C. [e]Used 6 mmol **1a** and 4 mmol **2a**.

The substrates containing electron-donating groups, such as methyl and methoxy groups at the *para*-position of the phenyl ring afforded desired products **3ba** and **3ca** in 78 and 76% yields, respectively. Substrates containing electron-withdrawing groups (-F, -Cl, $-CF_3$, $-CO_2Me$, -CN, $-NO_2$) produced **3da**–**ia** in 54–91% yields. The phenyl group-substituted **1j** furnished **3ja** in 76% yield. Moreover, the reaction could become more complicated with substituents at the *meta* or *para* positions of the phenyl ring, resulting in **3ka**–**oa** in 52–71% yields. Disubstituted substrate **1p** gave **3pa** in 72% yield. Replacing the phenyl group with heteroaromatic groups, such as thiophen-2-yl and indol-3-yl, offered **3qa** in 51% yield and **3ra** in 45% yield. Varying the phenyl group to an alkyl group, hydroacylation product **3sa** could be obtained in 78% yield. Replacing the *tert*-butyl group with a methyl group, **3ta** was isolated in 63% yield. Moreover, the reaction could proceed smoothly on gram-scale (4 mmol), offering **3aa** (1.36 g) in 82% yield, which highlighted the synthetic utility of this reaction. After the examination of the substrate scope of *p*-QMs, we then explored the scope of salicylaldehydes. A series of salicylaldehydes with electron-donating and -withdrawing groups at the C5-position gave **3ab**–**ae** in 66–83% yields. Salicylaldehydes with a methyl or chloro group at the C4-position gave **3af** in 63% yield and **3ag** in 79% yield. When the methoxy group was introduced to the *ortho* position of the phenolic hydroxyl group,

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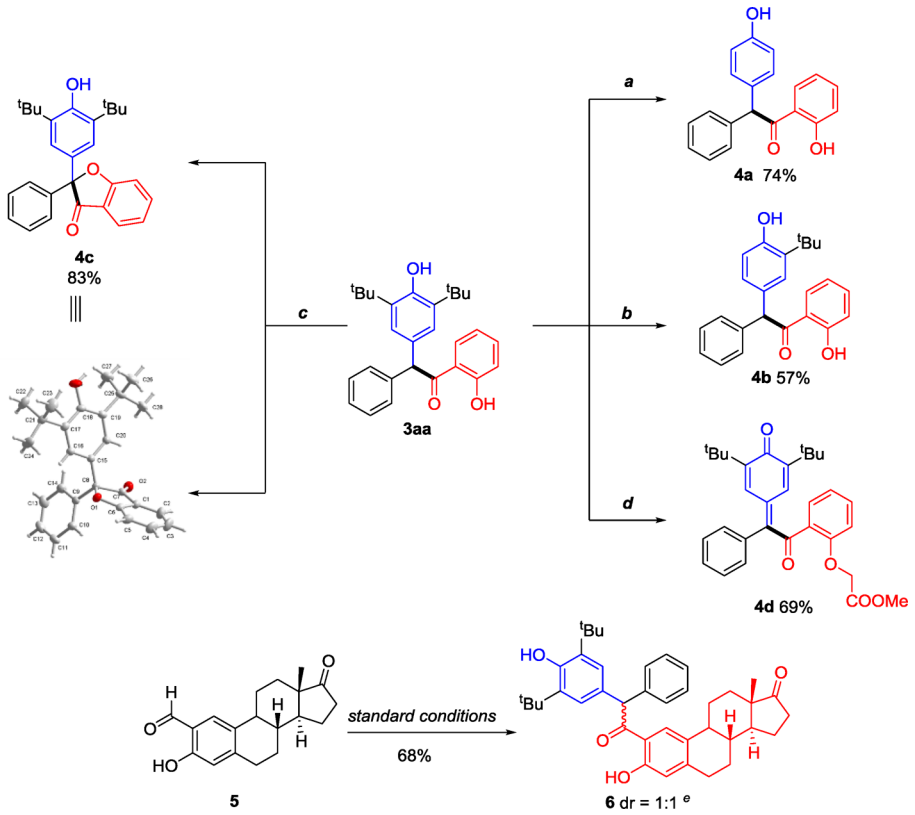
Scheme 2. Synthetic Transformations of 3aa



[a]$AlCl_3$ (10 equiv), benzene, 80 °C. [b]$AlCl_3$ (5 equiv), anisole, 10 °C. [c]$BrCH(CO_2Et)_2$, K_2CO_3 (2 equiv), acetone, 80 °C. [d]$BrCH_2CO_2Me$, K_2CO_3 (2 equiv), acetone, 80 °C. [e]Ratio determined by ^1H NMR.

3ah was achieved in 71% yield. C6-Methoxy-substituted salicylaldehyde failed to deliver the corresponding product due to the steric effect. A *β*-S-substituted aldehyde[14] was also tested under our standard conditions, but no corresponding product was detected.

With the aim of expanding the application of the reaction, the transformations of **3aa** were carried out as outlined in Scheme 2. The bulky *tert*-butyl group could easily be removed, affording **4a** in 72% yield or **4b** in 57% yield as prompted by $AlCl_3$.[15] When **3aa** was treated with diethyl 2-bromomalioonate and K_2CO_3, cyclic product **4c** was obtained in 83% yield, and the structure was identified by single-crystal X-ray analysis.[16] With methyl 2-bromoacetate as alkylating agent, **3aa** could be alkylated and oxidized in situ to deliver **4d** in 69% yield. This strategy could also be successfully applied to the late-stage diversification of estrone **5**, affording hydroacylation product **6** in 68% yield with 1:1 dr, which allowed the rapid generation of new analogues of estrone.

For gaining insight into the mechanism of the reaction, parallel experiments were performed as shown in Scheme 3a and b. With benzaldehyde **7** and 2-methoxy benzaldehyde **8** as substrates, no corresponding products were detected, indicating that the hydroxyl group was essential to the hydroacylation process. According to the previous report[3b] and our control experiments, a plausible catalytic cycle was proposed as outlined in Scheme 3c. Combining $[Rh(COD)Cl]_2$ with PPh_3 generates the initial active catalyst. Then, a hydroxyl-assisted C−H activation of aldehyde group occurs to form intermediate **A**. *para*-Quinone methide **1a** chelates with intermediate **A**, leading to the formation of metal−organic intermediate **B**. Migratory insertion of hydride in intermediate **B** to *exo*-methylene delivers intermediate **C**. At this stage, two pathways were possible. In pathway "a", intermediate **C** could isomerize to **D**, which offers product **3aa** through reductive elimination and regenerates the active catalyst to enter in the next catalytic cycle. In pathway "b", reductive elimination of intermediate **C** furnishes intermediate **E**, which then isomerizes to product **3aa** and regenerates the active catalyst.

In conclusion, an unprecedented rhodium-catalyzed hydroacylation of *para*-quinone methides (*p*-QMs) with salicylaldehydes to construct *α*,*α*-diaryl-2-hydroxy acetophenones through a tandem C−H activation/C−C bond formation/aromatization process has been achieved. This methodology exhibits high chemoselectivity, good functional group tolerance, and gram-scale capacity. Moreover, the formed products could be further transformed to a series of useful synthetic motifs.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were collected on a 300 MHz spectrometer using $CDCl_3$ as solvent. Infrared (IR) spectra were recorded using a thin film supported on KBr disks. High-resolution mass measurement was performed with an electrospray ionization (ESI) method on a Q-TOF mass spectrometer operating in positive or negative ion mode. Melting point (mp) was measured on a microscopic melting point apparatus. PE refers to petroleum ether (bp 60−90 °C) and EA refers to ethyl acetate. Flash column chromatography was carried out using commercially available 200−300 mesh under pressure unless otherwise indicated. Gradient flash chromatography was conducted eluting with PE/EA. All other starting materials and solvents were commercially available and were used without further purification unless otherwise stated.

General Procedure for the Preparation of *para*-Quinone Methides. Aldehydes (10 mmol) were added to a solution of phenols

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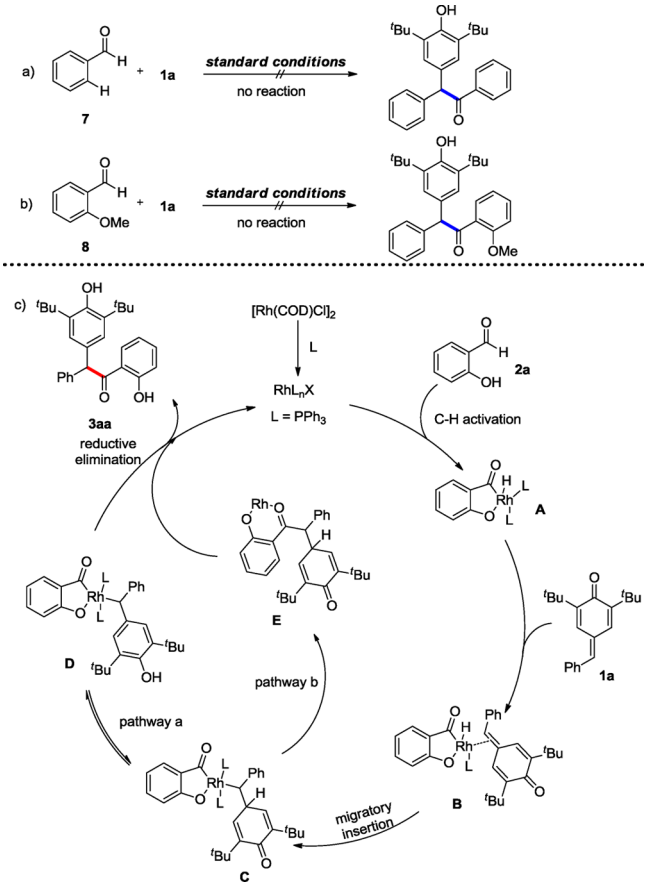
Scheme 3. Plausible Mechanism



(10 mmol) in toluene (40 mL). The reaction mixture was heated in a Dean−Stark apparatus to reflux. Piperidine (20 mmol) was added dropwise in 1 h, and the reaction mixture was refluxed for 3 h. After the mixture cooled to just below the boiling point of toluene, acetic anhydride (20 mmol) was added, and then the solution was stirred for 15 min. The residue was extracted with dichloromethane (DCM) three times. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to afford the corresponding products. Compounds **1a−r** were synthesized by the general procedure. Compounds **1s** and **1t** were prepared according to our previous work.[10a]

General Procedure for Preparing α,α-Diaryl-2-hydroxy Acetophenones. In a 10 mL Schlenk tube were sequentially added salicylaldehydes (0.2 mmol, 1 equiv), *p*-QMs (0.3 mmol, 1.5 equiv), $[Rh(COD)Cl]_2$ (2.5 mol %), PPh_3 (5 mol %), CsF (0.2 mmol, 1 equiv), DCE (1 mL), and H_2O (1 mL). The tube was frozen by liquid nitrogen and then connected to an argon-vacuum line and evacuated and backfilled with argon three times. The reaction mixture was stirred for 24 h at 120 °C. Then, the mixture was cooled to room temperature, and 20 mL of DCM was added. The mixture was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residues were purified by flash column chromatography on silica gel to afford the corresponding products.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-phenylethanone (**3aa**).* Purified by column chromatography (PE:EA = 200:1) to give **3aa** as a white solid (76.5 mg, 92% yield); mp 139−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.38 (s, 1H), 7.88 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.46−7.37 (m, 1H), 7.37−7.28 (m, 3H), 7.27 (d, *J* = 3.7 Hz, 1H), 7.24 (d, *J* = 5.5 Hz, 1H), 7.05 (s, 2H), 6.97 (dd, *J* = 8.4, 0.7 Hz, 1H), 6.87−6.77 (m, 1H), 5.99 (s, 1H), 5.17 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 163.3, 153.1, 139.3, 136.3, 136.0, 130.1, 129.0, 128.8, 128.7, 127.2, 125.9, 119.2, 119.0, 118.7, 58.6, 34.4, 30.3; IR (KBr) 3596, 3448, 2956, 2873, 1636, 1588, 1433, 1296, 751, 711, 685 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{32}O_3 + H]^+$ 417.2424, found 417.2424.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(p-tolyl)ethanone (**3ba**).* Purified by column chromatography (PE:EA = 150:1) to give **3ba** as a white solid (67.1 mg, 78% yield); mp 128−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, 1H), 7.90 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.43−7.38 (m, 1H), 7.18−7.11 (m, 4H), 7.05 (s, 2H), 6.97 (dd, *J* = 8.4, 0.7 Hz, 1H), 6.90−6.77 (m, 1H), 5.95 (s, 1H), 5.16 (s, 1H), 2.31 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 163.3, 153.0, 136.9, 136.2, 136.0, 130.7, 129.5, 129.0, 128.9, 125.8, 119.2, 118.9, 118.7, 58.3, 34.4, 30.3, 21.1; IR (KBr) 3629, 3490, 2956, 2871, 1693, 1578, 1434, 1120, 792, 752, 703 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_3 - H]^-$ 429.2435, found 429.2425.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(4-methoxyphenyl)ethanone (**3ca**).* Purified by column chromatography (PE:EA = 150:1) to give **3ca** as a white solid (67.8 mg, 76% yield); mp 126−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.39 (s, 1H), 7.88 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.41 (ddd, *J* = 8.5, 7.3, 1.5 Hz, 1H), 7.23−7.18 (m, 2H), 7.04 (s, 2H), 6.97 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.98−6.88 (m, 1H), 6.86 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.84−6.79 (m, 1H), 5.94 (s, 1H), 5.16 (s, 1H), 3.77 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 163.3, 158.7, 153.0, 136.3, 136.0, 131.3, 130.7, 130.1, 129.2, 125.8, 119.2, 118.9, 118.7, 114.2, 57.8, 55.3, 34.4, 30.3; IR (KBr) 3620, 3457, 2956, 2906, 2867, 1637, 1510, 1460, 1176, 1030, 821, 632 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_4 - H]^-$ 445.2384, found 445.2391.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(4-fluorophenyl)-1-(2-hydroxyphenyl)ethanone (**3da**).* Purified by column chromatography (PE:EA = 150:1) to give **3da** as a white solid (71.2 mg, 82% yield); mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.32 (s, 1H), 7.87 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.48−7.37 (m, 1H), 7.24 (dd, *J* = 8.1, 5.4 Hz, 2H), 7.01 (m, 5H), 6.89−6.79 (m, 1H), 5.98 (s, 1H), 5.19 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 161.5 (d, *J* = 244.6 Hz), 162.8, 159.8, 152.7, 136.0, 135.7, 134.6 (d, *J* = 3.4 Hz), 130.2, 130.1, 128.2, 125.2, 118.5, 118.3, 115.1 (d, *J* = 21.4 Hz), 57.2, 33.9, 29.8; IR (KBr) 3636, 3474, 2961, 2873, 1639, 1505, 1463, 1153, 809, 747, 609 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}FO_3 - H]^-$ 433.2184, found 433.2172.

*2-(4-Chlorophenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)ethanone (**3ea**).* Purified by column chromatography (PE:EA = 150:1) to give **3ea** as a white solid (81.9 mg, 91% yield); mp 101−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.29 (s, 1H), 7.86−7.82 (m, 1H), 7.43−7.32 (m, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.03 (s, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 5.96 (s, 1H), 5.19 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.7, 163.3, 153.2 137.9, 136.5, 136.3 133.1, 130.6, 130.4, 128.8, 128.4, 125.7, 119.0, 118.8, 57.9 34.4, 30.3; IR (KBr) 3598, 3439, 2956, 2920, 2861, 1621, 1572, 1304, 1121, 1082, 911, 880, 783 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}ClO_3 - H]^-$ 450.1962, found 450.1951.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)ethanone (**3fa**).* Purified by column chromatography (PE:EA = 150:1) to give **3fa** as a white solid (87.1 mg, 90% yield); mp 59−60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.24 (s, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.48−7.42 (m, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.06 (s, 2H), 6.99 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.88−6.83 (m, 1H), 6.03 (s, 1H), 5.22 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 162.9, 152.9, 142.9, 136.1, 135.9, 130.0, 129.1, 128.9, 128.7, 127.4, 125.2, 125.0 (q, *J* = 3.8 Hz), 118.6, 118.5, 118.4, 57.8, 33.9, 29.7; IR (KBr) 3623, 3433, 2955, 2861, 1621, 1612, 1458, 1259, 1155, 1121, 1001, 850, 759, 653 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{31}F_3O_3 - H]^-$ 483.2153, found 483.2155.

*Methyl 4-(1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(2-hydroxyphenyl)-2-oxoethyl)benzoate (**3ga**).* Purified by column chromatography (PE:EA = 100:1) to give **3ga** as a white solid (86.3 mg, 91% yield); mp 143−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.29 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.86 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.48−7.42 (m, 1H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.05 (s, 2H), 7.01−6.98 (m, 1H), 6.87−6.82 (m, 1H), 6.05 (s, 1H), 5.22 (s, 1H), 3.90 (s, 3H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 166.8, 163.3, 153.3, 144.6, 136.6, 136.3, 130.6, 130.0, 129.1, 129.0, 128.1, 126.5, 125.8, 123.9, 119.1, 118.8, 58.5, 52.1, 34.4, 30.3; IR (KBr) 3597, 3439, 2964, 1715, 1633, 1575, 1436,

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1286, 1117, 1021, 833, 747 cm^{-1}; HRMS (ESI) calcd for $[C_{30}H_{34}O_5 - H]^-$ 473.2333, found 473.2341.

*4-(1-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(2-hydroxyphenyl)-2-oxoethyl)benzonitrile (**3ha**).* Purified by column chromatography (PE:EA = 150:1) to give **3ha** as a white solid (67.9 mg, 77% yield); mp 134−135 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.16 (s, 1H), 7.81 (dd, J = 8.2, 1.4 Hz, 1H), 7.62−7.59 (m, 2H), 7.44−7.41 (m, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.02 (s, 2H), 6.97 (dd, J = 8.4, 0.9 Hz, 1H), 6.87−6.71 (m, 1H), 6.01 (s, 1H), 5.22 (s, 1H), 1.37 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 163.4, 153.5, 144.9, 136.8, 136.6, 132.3, 130.4, 130.0, 127.5, 125.6, 119.2, 118.9, 118.8, 111.1, 58.4, 34.4, 30.2; IR (KBr) 3615, 3433, 2953, 2230, 1715, 1637, 1606, 1575, 1484, 1236, 1155, 997, 850, 793, 658 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{31}NO_3 - H]^-$ 440.2231, found 440.2227.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(4-nitrophenyl)ethanone (**3ia**).* Purified by column chromatography (PE:EA = 150:1) to give **3ia** as a white solid (49.8 mg, 54% yield); mp 151−152 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.19 (d, J = 8.8 Hz, 2H), 7.83 (dd, J = 8.1, 1.1 Hz, 1H), 7.49−7.41 (m, 3H), 7.06 (s, 2H), 7.02−6.99 (m, 1H), 6.90−6.84 (m, 1H), 6.08 (s, 1H), 5.25 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 163.4, 153.6, 146.9, 136.9, 136.7, 134.6, 130.4, 130.1, 127.5, 125.6, 123.7, 122.5, 119.2, 119.0, 58.2, 34.5, 30.2; IR (KBr) 3626, 3445, 2958, 2914, 1715, 1637, 1577, 1518, 1345, 1259, 1154, 841, 787, 752, 697 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}NO_5 - H]^-$ 460.2129, found 460.2118.

*2-([1,1′-Biphenyl]-4-yl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)ethanone (**3ja**).* Purified by column chromatography (PE:EA = 100:1) to give **3ja** as a white solid (74.8 mg, 76% yield); mp 173−174 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.31 (s, 1H), 7.90−7.78 (m, 1H), 7.49 (d, J = 8.0 Hz, 4H), 7.37−7.27 (m, 4H), 7.23 (s, 1H), 7.02 (s, 2H), 6.92−6.89 (m, 1H), 6.77 (dd, J = 11.2, 7.2 Hz, 1H), 5.95 (s, 1H), 5.10 (s, 1H), 1.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 163.4, 153.2, 140.7, 140.1, 138.4, 136.4, 136.1, 130.7, 129.5, 128.8, 128.7, 127.4, 127.3, 127.1, 125.9, 119.2, 119.0, 118.8, 58.3, 34.5, 30.3; IR (KBr) 3636, 3410, 2955, 2861, 1695, 1610, 1575, 1483, 1259, 1151, 827, 747, 700, 644 cm^{-1}; HRMS (ESI) calcd for $[C_{34}H_{36}O_3 - H]^-$ 491.2592, found 491.2587.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(m-tolyl)ethanone (**3ka**).* Purified by column chromatography (PE:EA = 150:1) to give **3ka** as a white solid (61.1 mg, 71% yield); mp 151−152 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.40 (s, 1H), 7.90 (dd, J = 8.1, 1.2 Hz, 1H), 7.46−7.40 (m, 1H), 7.22 (d, J = 7.3 Hz, 1H), 7.11 (d, J = 4.3 Hz, 2H), 7.06 (d, J = 4.2 Hz, 3H), 6.98 (dd, J = 8.4, 0.8 Hz, 1H), 6.87−6.82 (m, 1H), 5.96 (s, 1H), 5.17 (s, 1H), 2.34 (s, 3H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 163.3, 153.0, 139.1, 138.4, 136.2, 135.9, 130.7, 129.7, 128.8, 128.6, 128.0, 126.0, 125.9, 119.2, 118.9, 118.7, 58.6, 34.4, 30.3, 21.5; IR (KBr) 3627, 3421, 2958, 1637, 1604, 1566, 1484, 1444, 1358, 1155, 786, 769, 753 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_3 - H]^-$ 429.2435, found 429.2441.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(3-methoxyphenyl)ethanone (**3la**).* Purified by column chromatography (PE:EA = 150:1) to give **3la** as a white solid (62.5 mg, 70% yield); mp 131−132 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.37 (s, 1H), 7.90−7.88 (m, 1H), 7.45−7.39 (m, 1H), 7.25 (dd, J = 9.4, 6.3 Hz, 1H), 7.06 (s, 2H), 6.97 (d, J = 8.3 Hz, 1H), 6.88−6.78 (m, 4H), 5.95 (s, 1H), 5.17 (s, 1H), 3.77 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 163.3, 159.8, 153.1, 140.7, 136.3, 136.0, 130.7, 130.0, 128.6, 125.9, 121.4, 119.2, 119.0, 118.7, 115.0, 112.4, 58.6, 55.2, 34.4, 30.3; IR (KBr) 3620, 3448, 2954, 2865, 1701, 1603, 1583, 1486, 1256, 1138, 1050, 778, 769, 705 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_4 - H]^-$ 445.2384, found 445.2383.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(3-nitrophenyl)ethanone (**3ma**).* Purified by column chromatography (PE:EA = 150:1) to give **3ma** as a white solid (47.9 mg, 52% yield); mp 161−162 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.17 (s, 1H), 8.17−8.13 (m, 2H), 7.86 (d, J = 7.0 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.49 (m, 2H), 7.09 (s, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.87 (m, 1H), 6.07 (s, 1H), 5.25 (s, 1H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 163.4, 153.6, 141.5, 136.8, 136.2, 135.3, 130.4, 129.3, 127.6, 125.5, 125.1, 124.3, 122.3, 119.2, 119.0, 118.9, 58.0, 34.5, 30.2; IR (KBr) 3622, 3439, 2955, 2910, 1634, 1575, 1518, 1345, 1196, 1155, 1021, 849, 787 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}NO_5 - H]^-$ 460.2129, found 460.2141.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(o-tolyl)ethanone (**3na**).* Purified by column chromatography (PE:EA = 150:1) to give **3na** as a white solid (50.8 mg, 59% yield); mp 155−156 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.37 (s, 1H), 7.72 (dd, J = 8.1, 1.1 Hz, 1H), 7.44−7.38 (m, 1H), 7.23−7.11 (m, 3H), 7.04−7.01 (m, 1H), 6.97 (d, J = 5.6 Hz, 3H), 6.81 (dd, J = 11.2, 4.0 Hz, 1H), 6.05 (s, 1H), 5.17 (s, 1H), 2.34 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 163.1, 153.0, 139.5, 138.2, 136.2, 135.6, 130.8, 130.3, 128.6, 127.4, 127.3, 126.4, 126.3, 119.0, 119.1, 118.7, 56.1, 34.4, 30.3, 20.2; IR (KBr) 3597, 3439, 2964, 2856, 1633, 1617, 1579, 1446, 1286, 1121, 823, 777, 625 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_3 - H]^-$ 429.2435, found 429.2429.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(2-fluorophenyl)-1-(2-hydroxyphenyl)ethanone (**3oa**).* Purified by column chromatography (PE:EA = 150:1) to give **3oa** as a white solid (47.3 mg, 55% yield); mp 134−135 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.27 (s, 1H), 7.89 (dd, J = 8.1, 1.1 Hz, 1H), 7.45−7.39 (m, 1H), 7.29−7.24 (m, 1H), 7.12−7.04 (m, 5H), 6.97 (dd, J = 8.3, 0.6 Hz, 1H), 6.87−6.81 (m, 1H), 6.25 (s, 1H), 5.21 (s, 1H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 160.1 (d, J = 245.8 Hz), 158.4, 153.4, 136.4, 130.6, 130.5, 129.0 (d, J = 8.3 Hz), 127.1 (d, J = 15.0 Hz), 126.7, 126.0, 124.2 (d, J = 3.5 Hz), 119.0, 118.9, 118.7, 115.3 (d, J = 22.1 Hz), 51.3 (d, J = 2.7 Hz), 34.4, 30.3; IR (KBr) 3592, 3441, 3002, 2884, 1639, 1583, 1487, 1449, 1232, 1157, 998, 856, 760, 651 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}FO_3 - H]^-$ 433.2184, found 433.2182.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-(3,5-dichlorophenyl)-1-(2-hydroxyphenyl)ethanone (**3pa**).* Purified by column chromatography (PE:EA = 150:1) to give **3pa** as a pale yellow solid (69.7 mg, 72% yield); mp 140−141 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.20 (s, 1H), 7.81 (dd, J = 8.1, 1.0 Hz, 1H), 7.48−7.43 (m, 1H), 7.26 (t, J = 1.7 Hz, 1H), 7.16 (d, J = 1.6 Hz, 2H), 7.05 (s, 2H), 7.00−6.98 (m, 1H), 6.87 (dd, J = 11.3, 4.1 Hz, 1H), 5.90 (s, 1H), 5.24 (s, 1H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 163.4, 153.6, 142.7, 136.8, 136.5, 135.0, 130.4, 127.7, 127.5, 127.4, 125.6, 119.2, 118.9, 57.7, 34.5, 30.2; IR (KBr) 3604, 3451, 2963, 2867, 1636, 1582, 1447, 1232, 1155, 1121, 1007, 818, 797, 747, 674 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{30}Cl_2O_3 - H]^-$ 483.1499, found 483.1493.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(thiophen-2-yl)ethanone (**3qa**).* Purified by column chromatography (PE:EA = 150:1) to give **3qa** as a yellow solid (43.0 mg, 51% yield); mp 111−112 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.18 (s, 1H), 7.89−7.86 (m, 1H), 7.40−7.34 (m, 1H), 7.18−7.16 (m, 1H), 7.11 (s, 2H), 6.92−6.77 (m, 4H), 6.12 (s, 1H), 5.12 (s, 1H), 1.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 163.4, 153.4, 142.1, 136.6, 136.2, 130.4, 128.8, 126.6, 126.5, 125.5, 125.4, 119.0, 118.8, 118.7, 53.2, 34.4, 30.3; IR (KBr) 3617, 3262, 2960, 2861, 1636, 1575, 1489, 1433, 1239, 1156, 859, 750, 712, 705 cm^{-1}; HRMS (ESI) calcd for $[C_{26}H_{30}O_3S - H]^-$ 421.1843, found 421.1835.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-(1-methyl-1H-indol-3-yl)ethanone (**3ra**).* Purified by column chromatography (PE:EA = 100:1) to give **3ra** as a yellow solid (42.2 mg, 45% yield); mp 160−161 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.45 (s, 1H), 8.01 (d, J = 7.1 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.42 (dd, J = 11.3, 4.2 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.22 (s, 1H), 7.20 (s, 1H), 7.09 (t, J = 6.9 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 6.89−6.79 (m, 2H), 6.20 (s, 1H), 5.14 (s, 1H), 3.74 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 163.3, 153.0, 136.2, 135.9, 130.5, 128.7, 128.4, 125.63, 125.62, 125.2, 121.9, 119.3, 118.92, 118.85, 118.6, 113.3, 109.4, 49.9, 34.4, 32.9, 30.3; IR (KBr) 3595, 3439, 2954, 1633, 1565, 1507, 1436, 1286, 1197, 1114, 1025, 833, 747, 693 cm^{-1}; HRMS (ESI) calcd for $[C_{31}H_{35}NO_3 - H]^-$ 468.2544, found 468.2539.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-propan-1-one (**3sa**).* Purified by column chromatography (PE:EA = 60:1) to give **3sa** as a white solid (55.2 mg, 78% yield); mp 130−131 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.52 (s, 1H), 7.88 (dd, J = 8.1, 1.2 Hz, 1H), 7.44−7.38 (m, 1H), 7.10 (s, 2H), 6.96 (d, J = 8.4 Hz, 1H), 6.84 (t, J = 7.6 Hz, 1H), 5.13 (s, 1H), 4.68 (q, J = 6.8 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H), 1.41 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 163.2, 152.9, 136.3, 136.0, 131.3, 130.4, 124.3, 118.9, 118.7, 118.6, 46.6, 34.4, 30.3,

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19.4; IR (KBr) 3626, 3447, 2954, 2861, 1631, 1609, 1433, 1372, 1244, 1203, 1158, 1118, 966, 892, 757 cm^{-1}; HRMS (ESI) calcd for $[C_{23}H_{30}O_3 - H]^-$ 353.2122, found 353.2126.

*2-(4-Hydroxy-3,5-dimethylphenyl)-1-(2-hydroxyphenyl)-2-phenylethanone (**3ta**).* Purified by column chromatography (PE:EA = 150:1) to give **3ta** as a white solid (41.8 mg, 63% yield); mp 145−146 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.33 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H), 7.33 (dd, J = 14.7, 7.3 Hz, 3H), 7.25 (t, J = 6.9 Hz, 3H), 6.98 (d, J = 8.3 Hz, 1H), 6.86 (s, 2H), 6.81 (t, J = 7.7 Hz, 1H), 5.95 (s, 1H), 4.68 (s, 1H), 2.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 163.3, 151.6, 139.1, 136.4, 130.7, 129.9, 129.8, 129.2, 129.1, 128.7, 127.3, 123.5, 119.0, 118.7, 58.2, 16.1; IR (KBr) 3466, 2923, 2852, 1637, 1612, 1487, 1446, 1325, 1196, 1155, 1031, 754, 698, 648 cm^{-1}; HRMS (ESI) calcd for $[C_{22}H_{20}O_3 - H]^-$ 331.1340, found 331.1345.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxy-5-methylphenyl)-2-phenylethanone (**3ab**).* Purified by column chromatography (PE:EA = 150:1) to give **3ab** as a white solid (56.7 mg, 66% yield); mp 130−131 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.13 (s, 1H), 7.59 (s, 1H), 7.29−7.14 (m, 6H), 6.99 (s, 2H), 6.80 (d, J = 8.5 Hz, 1H), 5.91 (s, 1H), 5.09 (s, 1H), 2.17 (s, 3H), 1.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 161.2, 153.1, 139.3, 137.4, 136.0, 130.4, 129.0, 128.9, 128.7, 127.9, 127.2, 125.9, 118.8, 118.4, 58.5, 34.4, 30.3, 20.7; IR (KBr) 3629, 3433, 2962, 2849, 1639, 1617, 1481, 1434, 1361, 1262, 1179, 1162, 1121, 824, 777, 701, 656 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_3 - H]^-$ 429.2435, found 429.2443.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(5-fluoro-2-hydroxyphenyl)-2-phenylethanone (**3ac**).* Purified by column chromatography (PE:EA = 150:1) to give **3ac** as a white solid (64.2 mg, 74% yield); mp 136−137 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.02 (s, 1H), 7.44 (dd, J = 9.2, 3.1 Hz, 1H), 7.29−7.24 (m, 2H), 7.21−7.14 (m, 3H), 7.07 (ddd, J = 9.1, 7.7, 2.9 Hz, 1H), 6.96 (s, 2H), 6.85 (dd, J = 9.2, 4.6 Hz, 1H), 5.79 (s, 1H), 5.12 (s, 1H), 1.31 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 157.9 (d, J = 241.5 Hz), 153.2, 153.1, 138.9, 136.3, 128.9 (d, J = 13.0 Hz), 128.5, 127.4, 125.8, 124.1, 123.8, 120.0 (d, J = 7.3 Hz), 118.7, 115.5 (d, J = 23.5 Hz), 59.0, 34.4, 30.3; IR (KBr) 3628, 3448, 2956, 2920, 2855, 1647, 1628, 1433, 1247, 1238, 1157, 1008, 841, 785, 706 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}FO_3 - H]^-$ 433.2184, found 433.2173.

*1-(5-Chloro-2-hydroxyphenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-phenylethanone (**3ad**).* Purified by column chromatography (PE:EA = 150:1) to give **3ad** as a white solid (74.7 mg, 83% yield); mp 130−131 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.17 (s, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.29−7.25 (m, 3H), 7.21−7.15 (m, 3H), 6.99 (d, J = 5.6 Hz, 2H), 6.84 (d, J = 8.9 Hz, 1H), 5.82 (s, 1H), 5.12 (s, 1H), 1.32 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 161.3, 152.8, 138.2, 135.7, 129.4, 128.5, 128.3, 127.7, 127.3, 126.9, 125.4, 123.0, 119.9, 119.2, 58.4, 33.9, 29.8; IR (KBr) 3602, 3415, 2996, 2872, 1637, 1466, 1434, 1375, 1316, 1263, 1171, 1122, 991, 831, 742, 695, 643 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}ClO_3 - H]^-$ 449.1889, found 449.1889.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxy-5-nitrophenyl)-2-phenylethanone (**3ae**).* Purified by column chromatography (PE:EA = 150:1) to give **3ae** as a white solid (65.4 mg, 71% yield); mp 180−181 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.89 (s, 1H), 8.90 (d, J = 2.6 Hz, 1H), 8.27 (dd, J = 9.2, 2.6 Hz, 1H), 7.35 (dt, J = 16.9, 7.7 Hz, 5H), 7.13 (s, 2H), 7.06 (d, J = 9.2 Hz, 1H), 6.00 (s, 1H), 5.24 (s, 1H), 1.41 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 167.9, 153.5, 139.5, 138.0, 136.6, 130.8, 129.0, 128.9, 127.7, 127.6, 127.5, 125.8, 119.8, 117.8, 59.3, 34.5, 30.2; IR (KBr) 3601, 3574, 2949, 2867, 1648, 1623, 1578, 1431, 1371, 1299, 1238, 1108, 850, 700, 681 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}NO_5 - H]^-$ 460.2129, found 460.2128.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxy-4-methylphenyl)-2-phenylethanone (**3af**).* Purified by column chromatography (PE:EA = 150:1) to give **3af** as a white solid (54.2 mg, 63% yield); mp 162−163 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.42 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.35−7.24 (m, 5H), 7.04 (s, 2H), 6.78 (s, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.96 (s, 1H), 5.16 (s, 1H), 2.30 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 162.9, 152.5, 147.5, 138.9, 135.4, 130.0, 128.5, 128.2, 126.7, 125.4, 123.2, 119.8, 118.2, 116.5, 58.0, 33.9, 29.8, 21.4; IR (KBr) 3589, 3433, 2955, 2932, 2867, 1633, 1572, 1433, 1305, 1208, 1130, 1120, 1015, 942, 780, 703, 653 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_3 - H]^-$ 429.2435, found 429.2441.

*1-(4-Chloro-2-hydroxyphenyl)-2-(3,5-ditert-butyl-4-hydroxyphenyl)-2-phenylethanone (**3ag**).* Purified by column chromatography (PE:EA = 150:1) to give **3ag** as a white solid (71.1 mg, 79% yield); mp 135−136 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.49 (s, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.33 (d, J = 6.9 Hz, 2H), 7.24 (s, 1H), 7.02 (s, 2H), 6.98 (d, J = 1.8 Hz, 1H), 6.80 (dd, J = 8.7, 1.9 Hz, 1H), 5.90 (s, 1H), 5.18 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 163.9, 153.2, 142.0, 138.9, 136.1, 131.7, 129.0, 128.8, 128.5, 127.4, 125.8, 119.7, 118.7, 58.9, 34.4, 30.3; IR (KBr) 3629, 3445, 2956, 2923, 2911, 1643, 1611, 1576, 1434, 1303, 1257, 1223, 1187, 1120, 1083, 850, 749, 659 cm^{-1}; HRMS (ESI) calcd for $[C_{28}H_{31}ClO_3 - H]^-$ 449.1889, found 449.1898.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2-hydroxy-3-methoxyphenyl)-2-phenylethanone (**3ah**).* Purified by column chromatography (PE:EA = 150:1) to give **3ah** as a white solid (63.3 mg, 71% yield); mp 135−136 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 12.71 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.30 (dq, J = 13.7, 7.0 Hz, 5H), 7.04 (s, 2H), 6.99 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 5.99 (s, 1H), 5.17 (s, 1H), 3.87 (s, 3H), 1.39 (d, J = 5.9 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 153.8, 153.1, 149.1, 139.2, 136.0, 129.1, 128.8, 128.7, 127.2, 125.9, 121.9, 118.2, 116.7, 59.0, 56.2, 34.4, 30.3; IR (KBr) 3594, 3438, 2946, 2923, 2859, 1644, 1628, 1559, 1480, 1337, 1157, 996, 805, 771, 669 cm^{-1}; HRMS (ESI) calcd for $[C_{29}H_{34}O_4 - H]^-$ 445.2384, found 445.2385.

General Procedure for Preparing 1-(2-Hydroxyphenyl)-2-(4-hydroxyphenyl)-2-phenylethanone. A 25 mL dried round-bottom flask was charged with **3aa** (83.2 mg, 0.2 mmol, 1 equiv), $AlCl_3$ (270 mg, 10 equiv), and benzene (5 mL). The flask was connected to an argon-vacuum line and evacuated and backfilled with argon three times. Then, the mixture was heated to 70 °C for 12 h. After the reaction mixture was cooled to room temperature, water was added to quench the reaction. The aqueous phase was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (PE:EA = 20:1) to afford **4a**.

*1-(2-Hydroxyphenyl)-2-(4-hydroxyphenyl)-2-phenylethanone (**4a**).* Purple oil, 45.0 mg, 74% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 12.31 (s, 1H), 7.72−7.69 (m, 1H), 7.31−7.28 (m, 1H), 7.24−7.10 (m, 5H), 6.97 (m, 2H), 6.85 (m, 1H), 6.71−6.64 (m, 3H), 5.90 (s, 1H), 5.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 163.1, 155.0, 138.9, 136.6, 130.8, 130.6, 130.4, 129.1, 128.9, 127.4, 119.2, 119.0, 118.8, 115.8, 58.1; IR (KBr) 3622, 3384, 3020, 1612, 1512, 1489, 1447, 1238, 1174, 1015, 881, 773, 696, 612 cm^{-1}; HRMS (ESI) calcd for $[C_{20}H_{16}O_3 - H]^-$ 303.1027, found 303.1022.

General Procedure for Preparing 2-(3-(*tert*-Butyl)-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-phenylethanone. A 25 mL dried round-bottom flask was charged with **3aa** (83.2 mg, 0.2 mmol, 1 equiv), $AlCl_3$ (135 mg, 5 equiv), and anisole (5 mL). The flask was connected to an argon-vacuum line and evacuated and backfilled with argon three times. Then, the mixture was reacted at 10 °C for 12 h. Then, water was added to quench the reaction. The aqueous phase was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (PE:EA = 60:1), and **4b** was obtained in 57% yield.

*2-(3-(tert-Butyl)-4-hydroxyphenyl)-1-(2-hydroxyphenyl)-2-phenylethanone (**4b**).* Red oil, 41.1 mg, 57% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 12.35 (s, 1H), δ 7.85 (dd, J = 8.1, 1.6 Hz, 1H), 7.46−7.41 (m, 1H), 7.37−7.27 (m, 3H), 7.26−7.24 (m, 2H), 7.14 (d, J = 2.3 Hz, 1H), 7.02−6.91 (m, 2H), 6.87−6.78 (m, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.00 (d, J = 6.4 Hz, 1H), 4.89 (s, 1H), 1.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 163.2, 153.5, 139.1, 136.5, 136.4, 130.7, 130.2, 129.0, 128.8, 128.1, 127.6, 127.3, 119.0, 118.7, 116.8, 115.0, 58.4, 34.6, 29.5; IR (KBr) 3599, 3458, 2955, 2889, 1636, 1617, 1558, 1446, 1433, 1296, 1230, 1115, 881, 755, 713, 685 cm^{-1}; HRMS (ESI) calcd for $[C_{24}H_{24}O_3 - H]^-$ 359.1653, found 359.1652.

General Procedure for Preparing 2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-phenylbenzofuran-3(2*H*)-one. Compound **3aa** (83.2 mg, 0.2 mmol, 1 equiv), diethyl 2-bromomalonate (48 mg, 0.2 mmol, 1 equiv), and K_2CO_3 (56 mg, 0.4 mmol, 2 equiv) were dissolved in 2 mL of acetone in a 25 mL dried tube. The reaction mixture were stirred and refluxed at 80 °C for 12 h. Solvent was directly removed

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under reduced pressure, and the crude mixture was purified by flash column chromatography (PE:EA = 150:1) on silica gel to afford **4c** in 83% yield.

*2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-phenylbenzofuran-3(2H)-one (**4c**).* White solid, 68.8 mg, 83% yield; mp 167−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.60 (m, 2H), 7.59−7.50 (m, 2H), 7.38−7.28 (m, 5H), 7.24 (d, J = 6.1 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 5.27 (s, 1H), 1.37 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3, 171.5, 154.1, 138.6, 138.2, 135.8, 128.9, 128.4, 128.2, 126.6, 125.3, 124.0, 122.1, 120.5, 113.3, 92.9, 34.5, 30.3; IR (KBr) 3627, 3067, 2962, 2873, 1702, 1609, 1496, 1477, 1434, 1357, 1312, 1251, 1154, 983, 965, 883, 753, 671 cm^{-1}; HRMS (ESI) calcd for $[C_{23}H_{30}O_3 - H]^-$ 353.2122, found 353.2126.

General Procedure for Preparing Methyl 2-(2-(2-(3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)-2-phenylacetyl)-phenoxy)acetate. Compound **3aa** (83.2 mg, 0.2 mmol, 1 equiv), methyl bromoacetate (30.4 mg, 0.2 mmol, 1 equiv), and K_2CO_3 (56 mg, 0.4 mmol, 2 equiv) were dissolved in 2 mL of acetone in a 25 mL dried tube. The reaction mixture were stirred and refluxed at 60 °C for 12 h. The solvent was directly removed under reduced pressure, and the crude mixture was purified by flash column chromatography (PE:EA = 100:1) on silica gel to afford **4d** in 69% yield.

*Methyl 2-(2-(2-(3,5-Di-tert-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)-2-phenylacetyl)phenoxy)acetate (**4d**).* Yellow solid, 67.2 mg, 69% yield; mp 145−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 7.7, 1.8 Hz, 1H), 7.48−7.35 (m, 6H), 7.20 (d, J = 2.6 Hz, 1H), 7.13 (d, J = 2.6 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 4.52 (s, 2H), 3.65 (s, 3H), 1.21 (d, J = 13.3 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 186.5, 168.2, 156.9, 149.5, 148.4, 134.8, 134.6, 131.6, 130.7, 130.5, 130.1, 129.1, 128.2, 122.1, 112.8, 65.8, 52.3, 35.5, 35.3, 29.5, 29.4; IR (KBr) 3621, 3085, 2958, 2870, 1759, 1676, 1597, 1484, 1437, 1308, 1292, 1250, 1164, 1065, 840, 717, 698, 642 cm^{-1}; HRMS (ESI) calcd for $[C_{31}H_{34}O_5 + H]^+$ 487.2412, found 487.2406.

General Procedure for the Late-Stage Diversification of Estrone. In a 10 mL Schlenk tube was sequentially added estrone **5** (0.2 mmol, 1 equiv), *p*-QMs **1a** (0.3 mmol, 1.5 equiv), $[Rh(COD)Cl]_2$ (2.5 mol %), PPh_3 (5 mol %), CsF (0.2 mmol, 1 equiv), DCE (1 mL), and H_2O (1 mL). The tube was frozen by liquid nitrogen and then connected to an argon-vacuum line and evacuated and backfilled with argon three times. The reaction mixture was stirred for 24 h at 120 °C. After the mixture was cooled to room temperature, 10 mL of DCM was added to the mixture and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residues were purified by flash column chromatography (PE:EA = 40:1) on silica gel to afford hydroacylation product **6**.

*(8R,13S,14S)-2-(2-(3,5-Di-tert-butyl-4-hydroxyphenyl)-2-phenylacetyl)-3-hydroxy-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (**6**).* Yellow powder, 80.6 mg, 68% yield, dr 1:1; $[\alpha]_D^{20}$ 131.7 (*c* 0.3, EA); mp 233−234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.10 (s, 1H), 7.80 (s, 1H), 7.36−7.23 (m, 6H), 7.11 (s, 2H), 6.99 (s, 1H), 5.91 (s, 1H), 5.18 (s, 1H), 2.89−2.83 (m, 2H), 2.48 (d, J = 2.53 Hz, 1H), 2.24−1.94 (m, 8H), 1.56−1.49 (m, 6H), 1.39 (s, 18H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.7, 204.3, 161.0, 153.1, 146.6, 139.3, 136.3, 130.7, 129.1, 128.6, 127.7, 127.2, 125.8, 117.8, 117.1, 115.4, 59.6, 50.4, 43.5, 37.9, 35.9, 34.4, 31.4, 30.3, 26.2, 25.9, 21.6, 13.8; IR (KBr) 3596, 3451, 2956, 2924, 2876, 1730, 1642, 1569, 1491, 1432, 1365, 1273, 1121, 886, 768, 697 cm^{-1}; HRMS (ESI) calcd for $[C_{40}H_{48}O_4 - H]^-$ 591.3480, found 519.3488.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01859.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

X-ray crystallographic data for **4c** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on transition-metal-catalyzed hydroacylation of olefins, see: (a) Ghosh, A.; Johnson, K. F.; Vickerman, K. L.; Walker, J. A. J.; Stanley, L. M. *Org. Chem. Front.* **2016**, *3*, 639. (b) Liu, B.; Hu, F.; Shi, B.-F. *ACS Catal.* **2015**, *5*, 1863. (c) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (d) Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, *2007*, 1869. (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (f) Willis, M. C. *Comprehensive Organic Synthesis II* **2014**, *4*, 961. (g) *Homogeneous Catalysis for Unreactive Bond Activation*, Chapter 6, 1st ed.; Shi, Z.-J., Ed.; John Wiley & Sons, Inc., 2015; p 441.

(2) Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303.

(3) (a) Shi, Z.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8092. (b) von Delius, M.; Le, C. M.; Dong, V. M. *J. Am. Chem. Soc.* **2012**, *134*, 15022. (c) Imai, M.; Tanaka, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2007**, *72*, 2543.

(4) (a) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2004**, *69*, 1144. (b) Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *Org. Lett.* **2003**, *5*, 1365.

(5) (a) Murphy, S. K.; Coulter, M. M.; Dong, V. M. *Chem. Sci.* **2012**, *3*, 355. (b) Murphy, S. K.; Petrone, D. A.; Coulter, M. M.; Dong, V. M. *Org. Lett.* **2011**, *13*, 6216. (c) Zhang, H.-J.; Bolm, C. *Org. Lett.* **2011**, *13*, 3900.

(6) (a) Nagamoto, M.; Nishimura, T. *Chem. Commun.* **2015**, *51*, 13791. (b) Tanaka, K.; Tanaka, M.; Suemune, H. *Tetrahedron Lett.* **2005**, *46*, 6053. (c) Stemmler, R. T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 1185.

(7) Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354.

(8) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4564.

(9) For selected examples on the synthesis of α,α-diaryl-acetophenones, see: (a) Zhu, Y.-P.; Jia, F.-C.; Liu, M.-C.; Wu, L.-M.; Cai, Q.; Gao, Y.; Wu, A.-X. *Org. Lett.* **2012**, *14*, 5378. (b) More, N. Y.; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 804. (c) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2002**, *4*, 1591. (d) Padmanaban, M.; Biju, A. T.; Glorius, F. *Org. Lett.* **2011**, *13*, 98. (e) Danoun, G.; Tlili, A.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 12815. (f) Zhang, X.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 10794. (g) Ramanjaneyulu, B. T.; Mahesh, S.; Anand, R. V. *Org. Lett.* **2015**, *17*, 3952.

(10) For selected examples on bioactive molecules containing *ortho*-hydroxyl or *ortho*-alkoxyl arylcarbonyl frameworks, see: (a) Rücker, H.; Al-Rifai, N.; Rascle, A.; Gottfried, E.; Brodziak-Jarosz, L.; Gerhäuser, C.; Dick, T. P.; Amslinger, S. *Org. Biomol. Chem.* **2015**, *13*, 3040. (b) Al-Rifai, N.; Rucker, H.; Amslinger, S. *Chem. - Eur. J.* **2013**, *19*, 15384. (c) Nowakowska, Z. *Eur. J. Med. Chem.* **2007**, *42*, 125. (d) Alaimo, P. J.; Knight, Z. A.; Shokat, K. M. *Bioorg. Med. Chem.* **2005**, *13*, 2825. For selected examples on the construction of *ortho*-hydroxyl or *ortho*-alkoxyl arylcarbonyl frameworks, see: (e) Sun, S.-Z.; Shang, M.; Wang, H.-L.; Lin, H.-X.; Dai, H.-X.; Yu, J.-Q. *J. Org. Chem.* **2015**, *80*, 8843. (f) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070. (g) Sun, Y.-H.; Sun, T.-Y.; Wu, Y.-D.; Zhang, X.; Rao, Y. *Chem. Sci.* **2016**,

DOI: 10.1021/acs.joc.6b01859
J. Org. Chem. 2016, 81, 11956−11964

7, 2229. (h) Mo, F.; Trzepkowski, L. J.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 13075 and references cited therein.
(11) For selected examples, see: (a) Munro-Leighton, C.; Delp, S. A.; Blue, E. D.; Gunnoe, T. B. *Organometallics* **2007**, *26*, 1483. (b) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696. (c) Karodia, N.; Liu, X.; Ludley, P.; Pletsas, D.; Stevenson, G. *Tetrahedron* **2006**, *62*, 11039. (d) Guo, S.-H.; Xing, S.-Z.; Mao, S.; Gao, Y.-R.; Chen, W.-L.; Wang, Y.-Q. *Tetrahedron Lett.* **2014**, *55*, 6718.
(12) (a) Gai, K.; Fang, X.; Li, X.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Chem. Commun.* **2015**, *51*, 15831. (b) Li, X.; Xu, X.; Wei, W.; Lin, A.; Yao, H. *Org. Lett.* **2016**, *18*, 428. (c) Yuan, Z.; Fang, X.; Li, X.; Wu, J.; Yao, H.; Lin, A. *J. Org. Chem.* **2015**, *80*, 11123. (d) Gao, S.; Xu, X.; Yuan, Z.; Zhou, H.; Yao, H.; Lin, A. *Eur. J. Org. Chem.* **2016**, *2016*, 3006. (e) Yuan, Z.; Wei, W.; Lin, A.; Yao, H. *Org. Lett.* **2016**, *18*, 3370.
(13) Inui, Y.; Tanaka, M.; Imai, M.; Tanaka, K.; Suemune, H. *Chem. Pharm. Bull.* **2009**, *57*, 1158.
(14) Moxham, H. G.; Randell-Sly, H. E.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7618.
(15) Saleh, S. A.; Tashtoush, H. I. *Tetrahedron* **1998**, *54*, 14157.
(16) Crystallographic data for **4c** has been deposited with the Cambridge Crystallographic Data Centre as Deposition Numbers CCDC 1507252. Detailed information can be found in the Supporting Information.

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