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Pd- and Rh-Catalyzed Hydroarylation of γ-(2-Methoxycarbonylphenyl)propargylic Alcohols: Approaches to 4- or 5-Substituted Seven-Membered Benzolactones and 3,3-Disubstituted Phthalides

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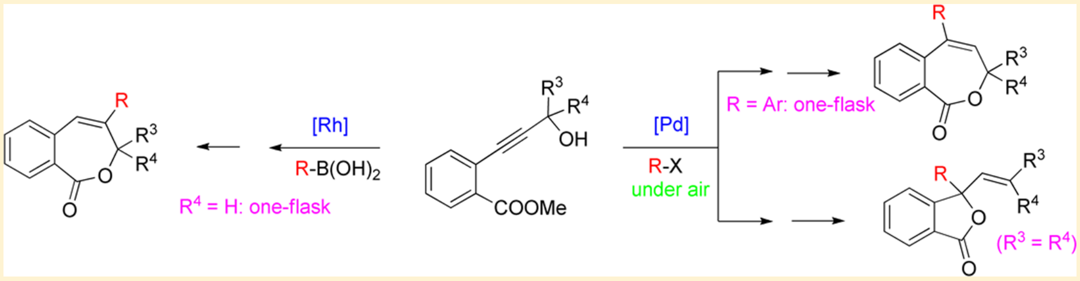
S Supporting Information

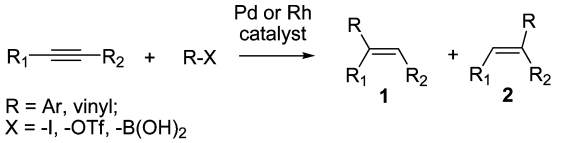


ABSTRACT: A study of the palladium-catalyzed hydroarylation/hydrovinylation reaction of γ-(2-methoxycarbonylphenyl)-propargylic alcohols with aryl iodides/vinyl triflates and of the rhodium-catalyzed one with organoboron derivatives is described. The opposite regiochemical outcome of the two processes allows an easy selective approach to 5- or 4-substituted benzoxepin-1(3*H*)-ones by combining the hydroarylative/hydrovinylative step with cyclocondensation between −OH and −COOMe groups in the intermediate γ,γ-disubstituted or β,γ-disubstituted allylic alcohols. A one-flask procedure to give benzo[c]oxepin-1(3*H*)-ones directly from the starting alkyne has been also developed. Treatment of crude γ,γ-disubstituted allylic alcohols with NaOH, followed by acidification, affords 3,3-disubstituted phthalides.

■ INTRODUCTION

Transition-metal-catalyzed hydroarylation/hydrovinylation of internal alkynes represents a powerful tool to build up substituted arylalkenes and dienes with a high degree of regio- and stereoselectivity.[1] A variety of approaches to trisubstituted alkene derivatives have been developed by means of palladium- and rhodium-catalyzed reactions (Scheme 1).

Scheme 1



Palladium-catalyzed reductive addition reactions of aryl/vinyl halides/triflates to disubstituted acetylenes with formate acting as reducing agent has been thoroughly investigated,[2] and the regiochemical outcome of the process appears directed by a variety of factors, such as the relative hindrance of R^1 and R^2 alkyne substituents, the aryl/vinyl nature of electrophilic R-X, coordination effects, and reaction conditions. The study of the reaction mechanism by a combination of experimental and theoretical methods has provided insights on these aspects.[3] The *syn* stereochemistry of the reaction allows sequential cyclization to occur in the presence of suitable nucleophilic/electrophilic groups in the alkyne substituents. Therefore, applications to the synthesis of a variety of heterocyclic systems such as butenolides,[4] quinolines,[5] and chromenes[6] have been reported.

The Pd-catalyzed hydroarylation/hydrovinylation reaction of alkynes with organoboron compounds has been also investigated, and its regiochemistry has been the object of a thorough study.[7a,b] Hydroarylation of nitriles with boron derivatives has also been reported.[7c]

More recently, following pioneering investigation by Hayashi and co-workers,[8] research activities have been devoted to the application of rhodium catalysis to the hydroarylation/hydrovinylation reaction of alkynes with organoboron derivatives. The regioselectivity of this process is determined by an intriguing combination of steric, coordinating, and electronic effects; however, the latter seem to play a more relevant role with respect to the Pd-catalyzed methodology that employs

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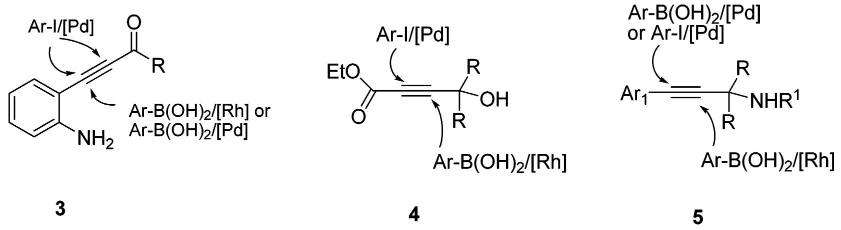
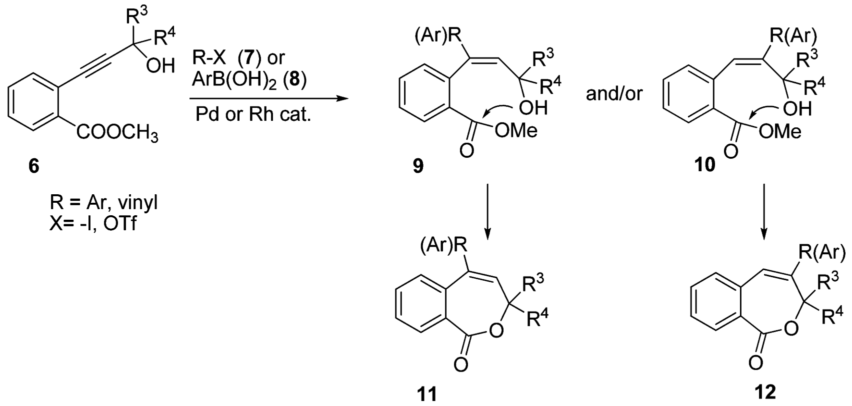
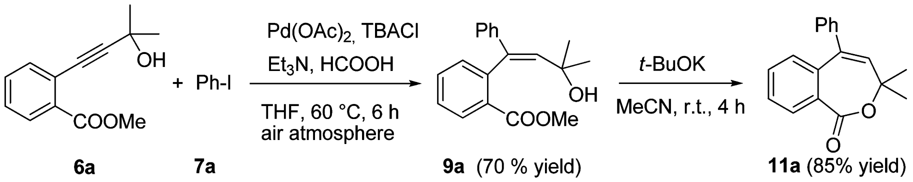
Scheme 2



Scheme 3



Scheme 4



halides/triflates as organic electrophiles. We have previously investigated the outcome of these different methodologies using alkynes **3**−**5** as starting materials: differences in the regiochemical behavior are highlighted in Scheme 2.

The sequential hydroarylation/cyclization reaction of α,β-ynones **3** with aryl iodides in the presence of a palladium catalyst afforded a mixture of 3- and 4-arylquinolines,[9] while selective β-arylation was observed in the reaction of **3** with $ArB(OH)_2$, both under palladium and rhodium catalysis.[10] Moreover, starting from 4-hydroxy-2-alkynoates **4**, regioselectivity can be switched through the suitable choice of the catalyst and the organic electrophile.[11]

In the hydroarylation of propargylamines **5** with $ArB(OH)_2$, the use of palladium catalysis resulted in a complete inversion of the regioselectivity with respect to rhodium catalysis;[12] a similar trend has been recently observed by Zhu and colleagues[13] and Lam and colleagues[14]starting from ynamides.

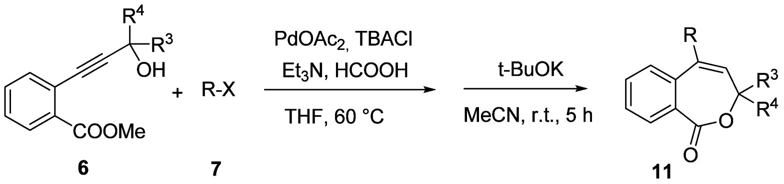
Then, as part of our ongoing interest in the use of alkynes bearing a carbonyl functional group in organic synthesis,[15] we decided to extend our investigation on the palladium- and rhodium-catalyzed hydroarylation processes to the γ-(2-methoxycarbonylphenyl)propargylic alcohols **6** as valuable building blocks to seven-membered unsaturated benzolactones **11** and/or **12** (Scheme 3).

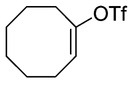
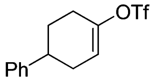
The benzolactone ring represents a prominent structural motif of various bioactive natural products and pharmaceutically important molecules.[16] Whereas five-membered,[17] and especially six-membered, benzolactones are easily accessible,[18] seven-membered benzolactones are less studied.[16a,19] Although a variety of polycyclic lactones are available through oxidative[20] or dehydrogenative lactonization of diols,[21] functionalized benzoxepin-1(3*H*)-ones **11** and **12** are much less known.[22] Therefore, the synthesis of these medium-sized unsaturated lactones remains a challenging task. Herein, we report the results of our investigation.

■ RESULTS AND DISCUSSION

We initiated our studies by investigating the palladium-catalyzed hydroarylation of the alkyne **6a** with iodobenzene **7a**. The reaction carried out in THF under a N_2 atmosphere led to the allylic alcohol **9a** in 70% yield with high regioselectivity (**9a**:**10a** = 96:4 in the crude reaction mixture by NMR analysis) (Scheme 4). Similar results were observed by carrying out the reaction under air. The use of MeCN as solvent afforded **9a** in a slightly lower yield (65%). The expected formation of the lactone **11a** through *in situ* cyclization of **9a** was observed only in trace (less than 5% by GC−MS analysis) both in THF or in MeCN, even after prolonged reaction time (24 h) at higher temperature (80 °C). Likely, the unfavorable formation of the seven-membered ring (compared with more common 5−6 membered rings)[23] requires a stronger oxygen nucleophile. Indeed, **9a** gave the desired **11a** in 85% yield in the presence of *t*-BuOK (1 equiv) at room temperature (Scheme 4).

Table 1. Synthesis of 5-Substituted Benzoxepin-1(3*H*)-ones **11**[a]



Entry	R^3, R^4 (**6**)	RX (**7**)	Procedure[b]	Time (h)[c]	**11** (Yield %)[d]
1	Me, Me (**6a**)	PhI (**7a**)	A	6	**11a** (61)
2	**6a**	3-CF_3-C_6H_4I (**7b**)	A	15	**11b** (62)
3	**6a**	4-F-C_6H_4I (**7c**)	A	15	**11c** (60)
4	**6a**	3-Cl-C_6H_4I (**7d**)	A	16	**11d** (52)
5	**6a**	1-Naphthyliodide (**7e**)	A	26	**11e** (60)
6	Me, Et (**6b**)	4-Cl-C_6H_4I (**7f**)	A	15	**11f** (50)
7	$R^3 = R^4 =$ -$(CH_2)_5$- (**6c**)	4-Me-C_6H_4I (**7g**)	A	8	**11g** (63)[e, f]
8	**6a**	4-MeO-C_6H_4I (**7h**)	B	8	**11h , 13h** (79, 60)[g, h]
9	**6a**	 (**7i**)	B	6	**11i**(95, 60)[g, i]
10	**6a**	 (**7j**)	B	5	**11j** (78, 82)[g, i]

[a] Reactions were carried out on 0.50 mmol scale in THF (2 mL) at 60 °C under air, using 2 equiv of **7**, 0.04 equiv of $Pd(OAc)_2$, 3 equiv of Et_3N, 2 equiv of HCOOH, and 1 equiv of TBACl. [b] Procedure A (one-flask): 2 mL of MeCN and 4 equiv of *t*-BuOK were added to the crude reaction mixture after hydroarylation; then, the mixture was stirred at room temperature for 5 h. Procedure B: 0.3 mmol of isolated **9**, 1 equiv of *t*-BuOK, 2 mL of MeCN, rt, 5 h. [c] Time of the hydroarylation/hydrovinylation step. [d] Unless otherwise stated: isolated overall yield of one-pot procedure. [e] Yield after crystallization of the 90:10 mixture of **11k**−**13k** obtained by chromatography. [f] Reaction time of cyclization: 20 h. [g] Data in parentheses refer to the hydrovinylation/hydroarylation step and to the cyclization step, respectively. [h] 3:1 unseparable mixture of **11i**−**13i**. [i] Hydrovinylation was carried out at 50 °C using 1.1 equiv of triflate.

Encouraged by this result, we attempted to combine the hydroarylation with the cyclization in the same flask by adding *t*-BuOK and MeCN to the crude reaction mixture after the hydroarylation step. This procedure allowed us to isolate **11a** in 60% overall yield avoiding any intermediate workup. Then, the one-flask methodology was extended to include different alkynes and aryl halides (Table 1, procedure A). Lactones **11a**−**g** were obtained in satisfactory overall yield, under an air atmosphere (entries 1−7).

In some cases, during the purification on the column, a partial rearrangement of seven-membered lactones **11** to 5-membered phthalides **13** occurred (see Scheme 5).[24] An unseparable 9:1 mixture of lactones **11g** and **13g** (NMR analysis) was obtained after the chromatographic process (Table 1, entry 8); crystallization of the mixture (diethyl ether/hexane) allowed the isolation of pure **11g**. Products **11h**−**j** resulted in being even more prone to undergo rearrangement; in these cases, a two-step procedure (that avoids chromatographic purification of lactones) afforded better results. Intermediate allylic alcohols **9h**−**j** were isolated; in the case of **9i** and **9j**, cyclization in the presence of 1 equiv of *t*-BuOK (followed by standard extractive workup) afforded crude seven-membered lactones, which were crystallized (diethyl ether/hexane) to give pure **11i**−**j** (procedure B, entries 10−11). In the case of **1h**, even this procedure failed to avoid rearrangement (Table 1, entry 9), and we isolated a 3:1 unseparable mixture of **11h** and **13h** (NMR analysis). These results demonstrate that the features of the substituent -R at the

Scheme 5

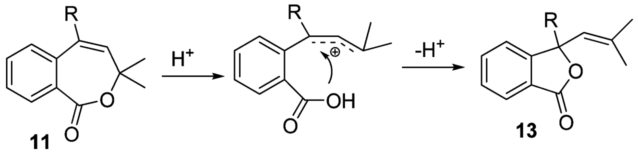
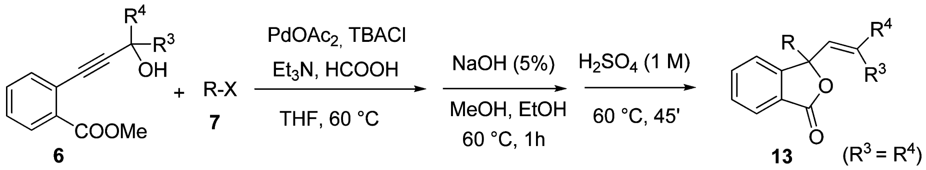


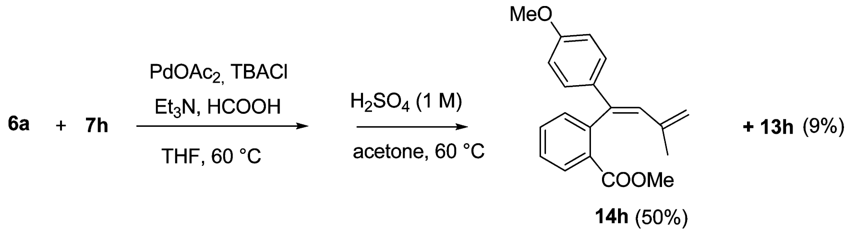
Table 2. Synthesis of 3-Substituted 3-Vinyl-isobenzofuran-1(3*H*)-ones **13**[a]



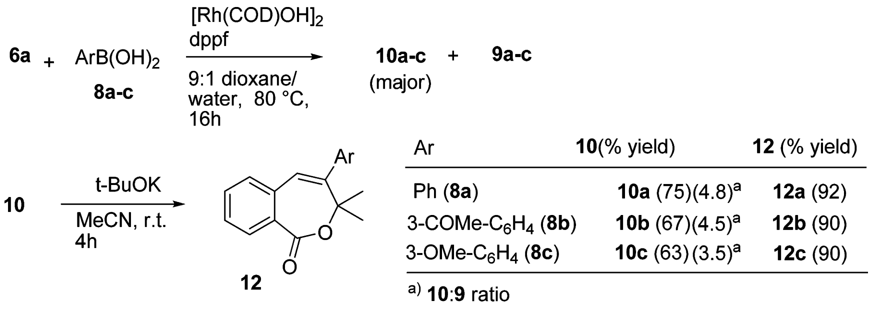
entry[a]	**6**	**7**	**13** (yield %)[b]
1	**6a**	**7a**	**13a** (40)
2	**6a**	**7b**	**13b** (65)
3	**6a**	**7c**	**13c** (70)
4	**6c**	**7g**	**13g** (62)
5	**6a**	**7h**	**13h** (70)
6	**6a**	**7i**	**13i** (45)
7	**6a**	4-NC-C_6H_4I **7k**	**13k** (58)[c,d]
8	**6a**	4-MeCO-C_6H_4I **7l**	**13l** (61)[c]

[a]Hydroarylation/hydrovinylation reactions were carried out as reported in Table 1; then MeOH (2 mL), EtOH (1 mL), 5% NaOH (3 equiv), 60 °C, 1.15 h; then 1 M H_2SO_4, (5 equiv), 60 °C, 45 min. [b]Isolated overall yield of one-flask procedure. [c]Reaction time: 18 h. [d]Carried out with 3 equiv of **7k**.

Scheme 6



Scheme 7



Ar	**10**(% yield)	**12** (% yield)
Ph (**8a**)	**10a** (75)(4.8)[a]	**12a** (92)
3-COMe-C_6H_4 (**8b**)	**10b** (67)(4.5)[a]	**12b** (90)
3-OMe-C_6H_4 (**8c**)	**10c** (63)(3.5)[a]	**12c** (90)

[a] **10**:**9** ratio

-5 position of benzoxepin-1(3*H*)-one derivatives **11** strongly affect their tendency to rearrange. Although the mechanism of the rearrangement was not thoroughly investigated, acid-catalyzed cleavage of **11**, followed by cyclization, can give phthalides **13** (Scheme 5). According to this hypothesis, we observed the complete rearrangement of **11h** to **13h** by adding a drop (20 μL) of 1 M HCl to the NMR tube containing the 3:1 mixture of **11h** and **13h** in deuterated acetone after 14 h at room temperature.

Since the phthalide core is present in some interesting natural products,[25] we explored then the possibility of obtaining selectively products **13**. As reported in Table 2, these compounds were isolated in moderate to good overall yields by saponification and subsequent acidification of the crude reaction mixture (after the hydroarylation step).[26]

Hydrolytic cleavage of COOMe in the intermediate allylic alcohols **9**, followed by acid-catalyzed cyclization, could account for the formation of **13** under these conditions. An alternative path based on cyclization of **9** to **11**, followed by acid-catalyzed rearrangement to **13**, was ruled out: when **9a** was treated with NaOH under the reaction conditions of Table 2, **11a** was not detected in the reaction mixture.[27]

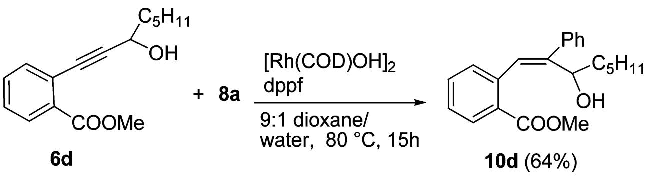
Cyclization of **9** with *t*-BuOK and subsequent rearrangement of **11** under acidic conditions can also be used to prepare **13**. Indeed, treatment of the reaction mixture (procedure A) containing crude **11b** with 1 M H_2SO_4 (6 equiv) at 60 °C for 1.5 h afforded **13b** in 61% yield. Conversely, our attempts to prepare **13** avoiding basic reaction conditions were unsuccessful; the reaction of crude **9h** with 1 M H_2SO_4 gave **14h** as the main isolated product, according to Scheme 6.

Next, on the basis of the complementary regioselectivity observed in the rhodium-catalyzed hydroarylation of propargylic amines with arylboronic acids,[12] we addressed our efforts to access 4-substituted 2-benzoxepin-1(3*H*)-ones **12** by means of rhodium-catalyzed hydroarylation/hydrovinylation of γ-(2-methoxycarbonylphenyl)propargylic alcohols **6** with organoboron derivatives **8**. The alkyne **6a** was reacted in dioxane/water (9/1 mixture) at 80 °C using 3 equiv of arylboronic acids

8a−c in the presence of the [Rh(COD)OH]$_2$/dppf catalytic system to give hydroarylation derivatives **10a−c** as main products, together with regioisomers **9a−c** (Scheme 7); cyclization of **10a−c** under usual conditions in the presence of *t*-BuOK led in high yield to the corresponding lactones **12a−c**. In all cases, we observed an opposite regiochemical outcome compared to the palladium-catalyzed reaction with aryl iodides/vinyl triflates.[28] One-flask cyclization, without isolation of **10a−c**, resulted in being not practical, due to the difficult separation of products **12a−c** from minor regioisomers **11a−c**.

Interestingly, the substrate **6d** bearing a secondary alcoholic group (which exhibited a lower directing ability in comparison with a tertiary one in the palladium-catalyzed reaction with aryl iodides)[2c] afforded only the isomer **10d** when reacted with **8a** under rhodium catalysis (Scheme 8).

Scheme 8



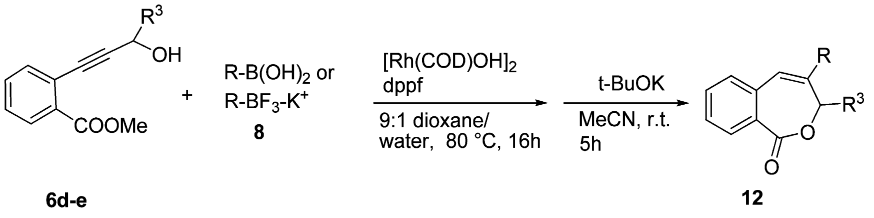
Therefore, one-flask preparation of 4-substituted 2-benzoxepin-1(3*H*)-ones **12d−k** appeared feasible. Indeed, alkynes **6d−e** were converted to **12d−k** by adding *t*-BuOK (4 equiv) and MeCN (2 mL) to the reaction mixture, after the hydroarylation step, without intermediate workup. The results of this procedure are summarized in Table 3: products were obtained as single isomers in satisfactory overall yield and, besides arylboronic acids, also potassium *β*-stiryltrifluoroborate **8f** afforded the target lactone **12i** (entry 7).

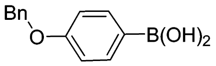
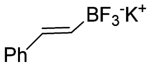
It is worth noting that isomerization of **12** to the corresponding five-membered lactones was never observed during chromatographic workup. Attempts to obtain selectively the latter products (using a procedure similar to that used for the synthesis of **13**) met with failure, and mixtures of five- and seven-membered lactones were obtained.

■ CONCLUSIONS

In summary, we have described the selective synthesis of different lactones from the same starting material, *γ*-(2-methoxycarbonylphenyl)propargylic alcohols **6**. Hydroarylation/hydrovinylation with aryl iodides/vinyl triflates under Pd catalysis resulted, after cyclization with *t*-BuOK, in the formation of 5-substituted benzo[c]oxepin-1(3*H*)-ones **11**; Rh-catalyzed hydroarylation/hydrovinylation with boron derivatives/cyclization led to regioisomeric 4-substituted benzo[c]oxepin-1(3*H*)-ones **12**. Moreover, 3,3-disubstituted phthalides **13** (isobenzofuran-(3*H*)-ones) were obtained by acid-promoted cyclization after the Pd-catalyzed reaction. In many cases, a convenient one-flask procedure led to easy isolation of target products in satisfactory yields. The Pd-catalyzed procedure can be carried out under air, without the use of an inert atmosphere.

Table 3. One-Flask Synthesis of 4-Substituted 2-Benzoxepin-1(3*H*)-ones 12[a]



Entry	R^3	**8**	**12** (yield %)[b]
1	C_5H_{11} (**6d**)	**8a**	**12d** (57)
2	**6d**	**8b**	**12e** (58)
3	**6d**	**8c**	**12f** (52)
4	**6d**	4-F-$C_6H_4B(OH)_2$ (**8d**)	**12g** (57)
5	**6d**	 (**8e**)	**12h** (56)
7	**6d**	 (**8f**)	**12i** (50)
8	Ph (**6e**)	**8a**	**12j** (64)
9	**6e**	4-OMe-$C_6H_4B(OH)_2$ (**8g**)	**12k**(53)

[a] Reactions were carried out on 0.50 mmol scale in 9:1 dioxane/water (2.5 mL) at 80 °C, under a N_2 atmosphere, using 3 equiv of **8**, 0.015 equiv of [Rh(COD)OH]$_2$, 0.03 equiv of dppf, 15 h; then 2 mL of MeCN and 4 equiv of *t*-BuOK, rt, 5 h. [b] Isolated overall yield of one-flask procedure.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, in $CDCl_3$ (unless otherwise stated). Chemical shifts are reported in ppm relative to tetramethylsilane or referenced to the chemical shifts of residual solvent resonances ($CDCl_3$ at 77.04 ppm for ^{13}C). ESI accurate mass measurements were recorded with a TOF mass spectrometer. Unless otherwise stated, all starting materials, catalysts, and solvents were commercially available and were used as purchased. Reaction products were purified by flash chromatography on silica gel (34−70 μ) by elution with *n*-hexane/EtOAc mixtures. Alkynes **6a**, **6b**, **6c**, and **6e** are known compounds.[29]

Synthesis of Methyl 2-(3-Hydroxyoct-1-ynyl)benzoate 6d. To a solution of methyl-2-iodobenzoate (0.35 mL, 2.38 mmol) in THF (4 mL) were added 1-octyn-3-ol (0.418 mL, 2.86 mmol), Et_3N (1.67 mL, 11.9 mmol), $PdCl_2(PPh_3)_2$ (0.025 g, 0.035 mmol), and CuI (0.014 g, 0.07 mmol). The mixture was stirred at room temperature under a N_2 atmosphere for 4 h and then extracted with 1 M NH_4Cl (100 mL) and ethyl acetate (3 × 50 mL). The combined organic layers were dried with Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate 85:15 v/v) to give **6d** (0.572 g, 92% yield). HRMS (ESI) *m*/*z* calcd. for $C_{16}H_{20}O_3$ $[M - H_2O + H]^+$: 243.1385; found: 243.1389. ^{1}H NMR: δ = 7.94−7.91 (m, 1H); 7.54−7.33 (m, 3H), 4.66 (t, *J* = 6.6 Hz, 1H), 3.91 (s, 3H), 1.82−1.80 (m, 2H), 1.60−1.52 (m, 2H), 1.38−1.33 (m, 4H), 0.91 (s, *J* = 7.2 Hz, 3H). ^{13}C NMR: δ = 166.7, 134.1, 131.8, 131.7, 130.3, 127.9, 123.4, 95.9, 83.3, 63.0, 52.2, 37.7, 31.6, 24.9, 22.6, 14.0.

Typical Procedure for the Synthesis 9a and 9h. *Methyl 2-[(1Z)-3-Hydroxy-3-methyl-1-phenylbut-1-enyl]benzoate* ***(9a)***. To a solution of **6a** (0.091 g, 0.42 mmol) in THF (2 mL) were added iodobenzene (0.094 mL, 0.84 mmol), Et_3N (0.176 mL, 1.26 mmol), TBACl (0.124 g, 0.42 mmol), and $Pd(OAc)_2$ (0.004 g, 0.0017 mmol). The mixture was stirred at 60 °C for 7.5 h and then extracted with water (50 mL) and ethyl acetate (3 × 30 mL). The combined organic layers were dried with Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate 80:20 v/v) to give **9a** (0.087 g, 70% yield). HRMS (ESI) *m*/*z*: calcd. for $C_{19}H_{20}O_3$ $[M - H_2O + H]^+$ 279.1385; found: 279.1381. ^{1}H NMR (acetone-d_6):[30] δ = 7.92−7.89 (m, 1H), 7.58 (dt, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H), 7.45−7.42 (m, 1H), 7.36−7.34 (m, 1H), 7.24−7.14 (m, 5H), 6.22 (s, 1H), 3.64 (s, 3H), 1.20 (bs, 3H), 1.15 (bs, 3H). ^{13}C NMR (acetone-d_6): δ = 167.9, 143.9, 142.0, 139.1, 137.4, 132.9, 132.1, 131.4, 130.8, 128.6, 128.0, 127.6, 127.4, 71.2, 51.9, 31.3, 30.7.

Methyl 2-[(1Z)-3-Hydroxy-1-(4-methoxyphenyl)-3-methylbut-1-enyl]benzoate ***(9h)***. Yield: 0.180 g (79%) from 0.153 g of **6a**. HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{22}O_4$ $[M - H_2O + H]^+$: 309.1491; found: 309.1496. ^{1}H NMR (acetone-d_6): δ = 7.90−7.88 (m, 1H), 7.58 (dt, *J* = 7.6 Hz, *J* = 1.4 Hz, 1H), 7.45−7.40 (m, 1H), 7.34−7.31 (m, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.13 (s, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (acetone-d_6): δ = 168.1, 159.7, 142.4, 138.7, 136.5, 135.9, 132.9, 132.1, 131.6, 130.8, 128.7, 127.9, 114.1, 71.2, 55.4, 52.0, 31.4, 30.8.

Methyl 2-[(1*Z*)-1-Cyclooct-1-en-1-yl-3-hydroxy-3-methylbut-1-enyl]benzoate (9i). This compound was obtained according to the preparation of **9j** reported below in Procedure B. Yield: 0.157 g (95%) from 0.110 g of **6a**. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{28}O_3$ $[M - H_2O + H]^+$: 311.2011; found: 311.2014. ^{1}H NMR: δ = 7.80−7.77 (m, 1H), 7.49−7.44 (m, 1H), 7.37−7.32 (m, 1H), 7.14−7.11 (m, 1H), 5.90 (s, 1H), 4.93 (t, *J* = 8.3 Hz, 1H), 3.81 (s, 3H), 2.51−2.45 (m, 2H), 2.11−2.01 (m, 2H), 1.66−1.37 (m, 8H), 1.29 (s, 3H), 1.14 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 166.7, 142.0, 141.0, 138.6, 132.6, 131.6, 131.1, 131.0, 130.9, 129.4, 126.8, 71.0, 52.1, 32.2, 30.4, 30.2, 28.7, 27.7, 27.1, 26.0, 25.4.

Typical Procedure for the Synthesis of 10b−d. *Methyl 2-[(1Z)-2-(3-Acetylphenyl)-3-hydroxy-3-methylbut-1-enyl]benzoate* ***(10b)***. To a solution of **6a** (0.140 g, 0.64 mmol) in 9:1 dioxane/water (3 mL) were added 3-acetylphenylboronic acid (0.316 g, 1.93 mmol), $[Rh(COD)OH]_2$, (0.0044 g, 0.0096 mmol) and dppf (0.0107 g, 0.019 mmol). The mixture was then stirred under N_2 at 80 °C for 15 h. After extraction with water (80 mL) and EtOAc (3 × 30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 75/25 v/v to afford **10b** (0.145 g, 67% yield). HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{22}O_4$ $[M - H_2O + H]^+$: 321.1491; found: 321.1487. ^{1}H NMR: δ = 8.02−8.01 (bs, 1H), 7.94−7.88 (m, 2H), 7.68−7.65 (m, 1H), 7.53−7.44 (m, 2H), 7.39−7.31 (m, 2H), 6.57 (s, 1H), 3.95 (s, 3H), 2.66 (s, 3H), 1.29 (s, 6H). ^{13}C NMR: δ = 198.3, 168.0, 147.6, 144.2, 140.5, 136.7, 133.8, 131.7, 130.2, 130.1, 129.7, 128.64, 128.55, 128.1, 126.9, 73.8, 52.2, 31.0, 26.8.

Methyl 2-[(1Z)-3-Hydroxy-2-(3-methoxyphenyl)-3-methylbut-1-enyl]benzoate ***(10c)***. Yield: 0.123 g (63%) from 0.130 g of **6a**. HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{22}O_4$ $[M - H_2O + H]^+$: 309.1491; found: 309.1485. ^{1}H NMR: δ = 7.90 (dd, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H), 7.50−7.46 (m, 1H), 7.37−7.25 (m, 3H), 7.02−6.96 (m, 2H), 6.86−6.82 (m, 1H), 6.55 (s, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 1.29 (s, 6H). ^{13}C NMR: δ = 168.2, 159.0, 148.4, 145.0, 140.8, 131.6, 130.2, 130.1, 128.8, 128.7, 126.7, 121.4, 115.1, 111.8, 73.9, 55.2, 52.2, 31.0.

Methyl 2-[(1Z)-3-Hydroxy-2-phenyloct-1-enyl]benzoate ***(10d)***. Yield: 0.109 g (64%) from 0.110 g of **6a**. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{26}O_3$ $[M - H_2O + H]^+$: 321.1855; found: 321.1852. ^{1}H NMR (acetone-d_6): δ = 8.02−8.00 (m, 1H), 7.84−7.80 (m, 2H), 7.65−7.58 (m, 2H), 7.47−7.42 (m. 1H), 7.39−7.34 (m, 2H), 7.32−7.29 (m, 1H), 7.09 (s, 1H), 4.59−4.54 (m, 1H), 3.24 (s, 3H), 1.51−1.35 (m, 2H), 1.15−1.01 (m, 4H), 1.01−0.91 (m, 2H), 0.72 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (acetone-d_6): δ = 167.8, 143.5, 142.2, 140.1, 132.8, 132.6, 131.8, 131.2, 130.3, 129.5, 128.6, 128.0, 127.7, 70.6, 52.3, 36.1, 32.3, 25.8, 23.2, 14.2.

General Experimental Procedure for the One-Flask Preparation of 5-Substituted 2-Benzoxepin-1(3*H*)-ones 11 (Table 1, Procedure A). *Synthesis of 3,3-Dimethyl-5-phenyl-2-benzoxepin-1(3H)-one* ***11a***. To a solution of **6a** (0.105 g, 0.48 mmol) in THF (2 mL) were added iodobenzene (0.108 mL, 0.96 mmol), Et_3N (0.203 mL, 1.44 mmol), TBACl (0.142 g, 0.48 mmol), $Pd(OAc)_2$ (0.004 g, 0.018 mmol), and, after stirring for 3 min at rt, HCOOH (0.036 mL, 0.96 mmol). The mixture was then stirred under air at 60 °C for 7.5 h and cooled to rt. Then, MeCN (2 mL) and *t*-BuOK (0.215 g, 1.92 mmol) were added and the mixture was stirred at room temperature for 5 h. After extraction with water (80 mL) and EtOAc (3 × 30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 96:4 v/v to afford **11a** (0.077 g, 61% yield). HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{16}O_2$ $[M + H]^+$: 265.1229; found: 265.1222. ^{1}H NMR ($CDCl_3$): δ 7.99−7.96 (m, 1H); 7.44−7.41 (m, 2H); 7.36−7.34 (m, 3H); 7.26−7.23 (m, 2H); 7.05−7.02 (m, 1H); 6.19 (s, 1H); 1.52 (s, 3H). ^{13}C NMR ($CDCl_3$): 169.4, 144.0, 141.1, 136.4, 135.2, 131.8, 131.6, 129.8, 128.7, 128.6, 128.5, 128.3, 125.7, 77.5, 27.8.

3,3-Dimethyl-5-[3-(trifluoromethyl)phenyl]-2-benzoxepin-1(3H)-one ***(11b)***. Yield: 0.106 g (62%) from 0.112 g of **6a**. HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{15}F_3O_2$ $[M + H]^+$: 333.1102; found: 333.1110. ^{1}H NMR: δ = 8.03−7.99 (m, 1H), 7.65−7.60 (m, 1H), 7.55 (s, 1H), 7.48−7.40 (m, 4H), 6.98−6.95 (m, 1H), 6.24 (s, 1H), 1.55 (s, 6H). ^{13}C NMR: δ = 169.1, 142.8, 141.9, 136.5, 135.5, 133.5, 132.12 (q, *J* = 1.4 Hz), 132.10, 131.9, 131.1 (q, *J* = 32.5 Hz,), 129.5, 129.04, 129.01, 125.4 (q, *J* = 3.9 Hz), 125.1 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 271 Hz), 77.4, 27.7.

5-(4-Fluorophenyl)-3,3-dimethyl-2-benzoxepin-1(3H)-one ***(11c)***. Yield: 0.085 g (60%) from 0.109 g of **6a**. HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{15}FO_2$ $[M + H]^+$: 283.1134; found: 283.1127. ^{1}H NMR: = δ 7.98−7.96 (m, 1H), 7.47−7.41 (m, 2H), 7.25−7.21 (m, 2H), 7.07−7.00 (m, 3H), 6.17 (s, 1H), 1.52 (s, 6H). ^{13}C NMR: δ = 169.3, 162.8 (d, *J* = 248 Hz), 143.0, 137.1 (d, *J* = 3 Hz), 136.1, 135.2, 133.4, 131.9, 131.7, 130.4 (d, *J* = 8.1 Hz), 129.6, 128.7, 115.5 (d, *J* = 21.5 Hz), 77.4, 27.8.

5-(3-Chlorophenyl)-3,3-dimethyl-2-benzoxepin-1(3H)-one ***(11d)***. Yield: 0.078 g (52%) from 0.110 g of **6a**. HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{15}ClO_2$ $[M + H]^+$: 299.0839; found: 299.0846. ^{1}H NMR: δ = 8.00−7.97−7.96 (m, 1H), 7.48−7.41 (m, 2H), 7.35−7.26 (m, 3H), 7.13–7.10 (m, 1H), 7.02–7.00 (m, 1H), 6.21 (s, 1H), 1.52 (s, 6H). ^{13}C NMR: δ = 169.0, 142.9, 142.7, 136.0, 135.6, 134.4, 133.3, 131.9, 131.8, 129.7, 129.6, 128.8, 128.7, 128.3, 126.9, 77.4, 27.6.

*5-(1-Naphthyl)-3,3-dimethyl-2-benzoxepin-1(3H)-one (**11e**).* Yield: 0.095 g (60%) from 0.110 g of **6a**. HRMS (ESI) *m/z* calcd. for $C_{22}H_{18}O_2$ $[M + H]^+$: 315.1385; found: 315.1378. ^{1}H NMR: = δ 8.05 (dd, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H), 7.86 (bt, *J* = 7.6 Hz, 2H), 7.59–7.24 (m, 7H), 6.79 (dd, *J* = 7.9 Hz, *J* = 1.1 Hz, 1H), 6.25 (s, 1H), 1.66 (bs, 3H), 1.56 (bs, 3H). ^{13}C NMR: = δ 169.3, 142.6, 130.4, 138.1, 137.0, 133.8, 132.3, 132.1, 131.5, 129.0, 128.7, 128.4, 127.6, 126.5, 126.0, 125.8, 125.3, 77.5, 29.5, 26.2.

*5-(4-Chlorophenyl)-3-ethyl-3-methyl-2-benzoxepin-1(3H)-one (**11f**).* Yield: 0.081 g (50%) from 0.120 g of **6b**. HRMS (ESI) *m/z* calcd. for $C_{19}H_{17}ClO_2$ $[M + H]^+$: 313.0995; found: 313.0987. ^{1}H NMR: δ = 7.92–7.88 (m, 1H), 7.38–7.33 (m, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.93–6.91 (m, 1H), 6.08 (s, 1H), 1.79–1.71 (m, 2H), 1.35 (s, 3H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR: δ = 169.2, 143.1, 139.7, 135.9, 134.9, 134.3, 133.5, 131.9, 131.7, 130.0, 129.6, 128.8, 128.7, 79.9, 33.5, 24.0, 8.4.

*5-(4-Methylphenyl)-1H-spiro[2-benzoxepine-3,1′-cyclohexan]-1-one (**11g**).* Yield: 0.097 g (63%) from 0.105 g of **6a**. HRMS (ESI) *m/z* calcd. for $C_{22}H_{22}O_2$ $[M + H]^+$: 319.1698; found: 319.1705. ^{1}H NMR: δ = 7.96–7.94 (m, 1H), 7.43–7.37 (m, 2H), 7.18–7.13 (overlapping AA′BB′ system, 4H), 7.06–7.03 (m, 1H), 6.10 (s, 1H), 2.38 (s, 3H), 1.89–1.65 (m, 6H), 1.49–1.42 (m, 4H). ^{13}C NMR: δ = 169.4, 143.7, 138.6, 138.1, 136.6, 133.9, 133.4, 131.5, 129.8, 129.1, 128.6, 128.4, 79.3, 35.7, 25.2, 22.7, 21.2.

General Experimental Procedure for the Two-Step Preparation of 11 (Table 1, Procedure B). *Synthesis of 3,3-Dimethyl-5-(4-phenylcyclohex-1-en-1-yl)-2-benzoxepin-1(3H)-one **11j**.* To a solution of **6a** (0.110 g, 0.50 mmol) in THF (2 mL) were added 4-phenylcyclohex-1-en-1-yl triflate **7j** (0.168 g, 0.55 mmol), Et_3N (0.210 mL, 1.50 mmol), TBACl (0.148 g, 0.50 mmol), $Pd(OAc)_2$ (0.005 g, 0.02 mmol), and, after stirring for 3 min at rt, HCOOH (0.038 mL, 1.00 mmol). The mixture was stirred under air at 50 °C for 6 h. After extraction with water (80 mL) and EtOAc (3 × 30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 80:20 v/v to afford allylic alcohol **9j** (0.147 g, 78% yield). HRMS (ESI) *m/z* calcd. for $C_{25}H_{28}O_3$ $[M - H_2O + H]^+$: 359.2011; found: 359.2016. ^{1}H NMR (DMSO-d_6, 80 °C[31]): δ 7.81–7.78 (m, 1H), 7.52–7.47 (m, 1H), 7.39–7.35 (m, 1H), 7.27–7.13 (m, 6H), 5.79 (s, 1H), 5.03 (bs, 1H), 3.72 (s, 3H), 2.75–2.66 (m, 1H), 2.42–1.92 (m, 5H), 1.76–1.67 (m, 1H), 0.96 (s, 6H). ^{13}C NMR (DMSO-d_6, 80 °C): 166.6, 146.0, 140.2, 133.0, 131.6, 130.5, 130.3, 129.0, 127.8, 126.4, 126.2, 125.4, 124.9, 69.4, 51.0, 38.7, 33.0, 30.1, 29.5, 26.2. To a solution of **9j** (0.113 g, 0.30 mmol) in MeCN (2 mL) was added *t*-BuOK (0.034 g, 0.30 mmol). The mixture was stirred at room temperature for 5 h. After extraction with water (80 mL) and EtOAc (2 × 30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure, to give crude **11j** (0.085 g). Crystallization from acetone/hexane afforded analytically pure **11j** (0.075 g, 73% yield after crystallization). HRMS (ESI) *m/z*: calcd. for $C_{24}H_{24}O_2$ $[M + H]^+$ 345.1855; found: 345.1853; ^{1}H NMR ($CDCl_3$): δ 7.82 (dd, *J* = 7.8 Hz, *J* = 1.1 Hz, 1H), 7.44 (dt, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 7.33–7.14 (m, 7H), 5.95 (s, 1H), 5.80 (broad triplet, 1H), 2.81–2.73 (m, 1H), 2.41–1.70 (m, 6H), 1.37 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 169.6, 146.4, 145.4, 137.6, 135.3, 133.3, 131.8, 131.6, 131.5, 129.0, 128.5, 128.4, 128.2, 126.8, 126.2, 77.8, 39.6, 33.8, 29.9, 28.2, 28.0, 27.7.

*5-Cyclooct-1-en-1-yl-3,3-dimethyl-2-benzoxepin-1(3H)-one (**11i**).* Yield: 0.065 g (60%) from 0.120 g of **9i**. HRMS (ESI) *m/z* calcd. for $C_{20}H_{24}O_2$ $[M + H]^+$: 297.1855; found: 297.1852. ^{1}H NMR: = δ 7.91–7.88 (m, 1H), 7.48 (dt, *J* = 7.7 Hz, *J* = 1.6 Hz, 1H), 7.37 (dt, *J* = 7.5 Hz, *J* = 1.3 Hz, 1H), 7.30–7.28 (m, 1H), 5.97 (s, 1H), 5.76 (t, *J* = 7.7 Hz, 1H), 2.27–2.16 (m, 4H), 1.60–1.45 (m, 8H), 1.44 (s, 6H). ^{13}C NMR: δ = 169.6, 146.2, 141.1, 135.4, 133.3, 132.6, 131.7, 131.6, 131.3, 129.1, 128.2, 77.7, 29.8, 28.4, 28.0, 27.9, 26.9, 26.6, 26.1.

General Experimental Procedure for the One-Flask Preparation of 3-Substituted 3-Vinyl-isobenzofuran-1(3*H*)-ones 13 (Table 2). *Synthesis of 3-(4-Methoxyphenyl)-3-(2-methylprop-1-enyl)-2-benzofuran-1(3H)-one **13h**.* To a solution of **6a** (0.150 g, 0.69 mmol) in THF (3 mL) were added 4-iodoanisole (0.321 g, 1.38 mmol), Et_3N (0.289 mL, 2.06 mmol), TBACl (0.203 g, 0.69 mmol), $Pd(OAc)_2$ (0.007 g, 0.031 mmol), and, after stirring for 3 min at rt, HCOOH (0.052 mL, 1.38 mmol). The mixture was then stirred under air at 60 °C for 7 h. Then, MeOH (2 mL), EtOH (1 mL), and 5% NaOH (1.65 mL, 2.06 mmol) were added to the flask, and the reaction mixture was stirred at 60 °C for 1.15 h. Next, 1 M H_2SO_4 (3.43 mL, 3.43 mmol) was added, and the reaction mixture was further stirred at 60 °C for 45 min. After extraction with 5% Na_2CO_3 (100 mL) and EtOAc (3 × 40 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 96:4 v/v to afford **13h** (0.142 g, 70% yield). HRMS (ESI) *m/z* calcd. for $C_{19}H_{18}O_3$ $[M + H]^+$: 295.1334; found: 295.1340. ^{1}H NMR ($CDCl_3$): δ 7.88–7.86 (m, 1H), 7.62 (dt, *J* = 7.6 Hz, *J* = 1.0 Hz, 1H), 7.47 (dt, *J* = 7.4 Hz, *J* = 0.8 Hz, 1H), 7.38–7.35 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.77 (quintuplet, *J* = 1.4 Hz, 1H), 3.78 (s, 3H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.62 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 170.5, 159.4, 155.0, 142.4, 134.5, 133.3, 128.8, 127.3, 125.6, 124.9, 123.9, 122.3, 114.0, 89.2, 55.3, 26.9, 20.1.

*3-(2-Methylprop-1-enyl)-3-phenyl-2-benzofuran-1(3H)-one (**13a**).* Yield: 0.063 g (40%) from 0.130 g of **6a**. HRMS (ESI) *m/z*: calcd. for $C_{18}H_{16}O_2$ $[M + H]^+$: 265.1229; found: 265.1220. ^{1}H NMR: δ = 7.88–7.86 (m, 1H), 7.64–7–66 (m, 1H), 7.50–7.39 (m, 4H), 7.34–7.25 (m, 3H), 5.81 (quintuplet, *J* = 1.3 Hz, 1H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.59 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR: δ = 170.5, 154.9, 143.0, 141.6, 134.5, 128.9, 128.7, 128.0, 125.7, 125.6, 124.8, 123.8, 122.3. 89.0, 26.8, 20.1.

*3-(2-Methylprop-1-enyl)-3-[3-(trifluoromethyl)phenyl]-2-benzofuran-1(3H)-one (**13b**).* Yield: 0.119 g (65%) from 0.120 g of **6a**. HRMS (ESI) *m/z* calcd. for $C_{19}H_{15}F_3O_2$ $[M + H]^+$: 333.1102; found: 333.1098. ^{1}H NMR: δ = 7.91–7.89 (m, 1H), 7.72–7.71 (bs, 1H), 7.68–7.62 (m, 2H), 7.56–7.43 (m, 3H), 7.41 (dt, *J* = 7.7 Hz, *J* = 0.8 Hz, 1H), 5.82 (quintuplet, *J* = 1.4 Hz, 1H), 1.84 (d, *J* = 1.4 Hz, 3H),1.58 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR: δ = 170.1, 154.2, 144.0, 143.0, 134.9, 131.2 (q, *J* = 32.5 Hz), 129.33, 129.31, 129.1 (q, *J* = 1.4 Hz), 125.9, 125.0 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 271 Hz), 123.4, 122.5 (q, *J* = 3.9 Hz), 122.2, 88.2, 26.8, 20.2.

*3-(4-Fluorophenyl)-3-(2-methylprop-1-enyl)-2-benzofuran-1(3H)-one (**13c**).* Yield: 0.104 g (70%) from 0.115 g of **6a**. HRMS (ESI) *m/z* calcd. for $C_{18}H_{15}FO_2$ $[M + H]^+$: 283.1134; found: 283.1140. ^{1}H NMR: δ = 7.89–7.87 (m, 1H), 7.66–7.62 (m, 1H), 7.51–7.47 (m, 4H), 7.03–6.97 (m, 2H), 5.79 (quintuplet, *J* = 1.4 Hz, 1H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.60 (d, *J* = 1.2 Hz, 3H).^{13}C NMR ($CDCl_3$): δ = 170.3, 162.5 (d, *J* = 251 Hz), 154.6, 143.0, 137.3 (d, *J* = 2.4 Hz), 129.0, 127.7 (d, *J* = 8.3 Hz), 124.8, 123.7, 122.3, 115.6 (d, *J* = 21.6 Hz), 88.6, 26.8, 20.1.

*3-(Cyclohexylidenemethyl)-3-(4-methylphenyl)-2-benzofuran-1(3H)-one (**13g**).* Yield: 0.099 g (62%) from 0.130 g of **6c**. HRMS (ESI) *m/z* calcd. for $C_{22}H_{22}O_2$ $[M + H]^+$: 319.1698; found: 319.1696. ^{1}H NMR: δ = 7.89 (dt, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.65–7.61 (m, 1H), 7.50–7.46 (m, 1H), 7.40–7.38 (m, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 5.75 (bs, 1H), 2.33 (s, 3H), 2.21–2.03 (m, 4H), 1.71–1.42 (m, 6H). ^{13}C NMR: δ = 170.6, 155.2, 150.5, 138.8, 137.8, 134.5, 129.2, 128.7, 125.7, 125.5, 124.8, 122.3, 120.9, 89.1, 37.5, 30.9, 28.6, 26.9, 26.1, 21.0.

*3-Cyclooct-1-en-1-yl-3-(2-methylprop-1-enyl)-2-benzofuran-1(3H)-one (**13i**).* Yield: 0.067 g (45%) from 0.110 g of **6a**. HRMS (ESI) *m/z* calcd. for $C_{20}H_{24}O_2$ $[M + H]^+$: 297.1855; found: 297.1849. ^{1}H NMR: δ = 7.86–7.83 (m, 1H), 7.66–7.62 (m, 1H), 7.48 (dt, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 7.37–7.35 (m, 1H), 6.00 (t, *J* = 8.3 Hz, 1H), 5.47 (quintuplet, *J* = 1.4 Hz, 1H), 2.20–2.04 (m, 3H), 1.82 (d, *J* = 1.2 Hz, 3H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.80–1.75 (m, 1H), 1.56–1.32 (m, 8H). ^{13}C NMR: δ = 170.6, 153.5, 140.7, 138.5, 133.9, 130.3, 128.7, 126.2, 125.2, 122.8, 122.3, 92.4, 29.9, 29.0 26.7, 26.5, 26.3, 26.1, 25.2, 20.3.

*4-[1-(2-Methylprop-1-enyl)-3-oxo-1,3-dihydro-2-benzofuran-1-yl]benzonitrile (**13k**).* Yield: 0.086 g (58%) from 0.112 g of **6a**. HRMS

(ESI) *m*/*z* calcd. for $C_{19}H_{15}NO_2$ $[M + H]^+$: 290.1181; found: 290.1173. ^{1}H NMR: δ = 7.91−7.88 (m, 1H), 7.69−7.65 (m, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.52 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.43−7.40 (m, 1H), 5.82 (quintuplet, J = 1.4 Hz, 1H), 1.84 (d, J = 1.4 Hz, 3H), 1.57 (d, J = 1.2 Hz, 3H). ^{13}C NMR: δ = 169.8, 153.7, 147.1, 144.5, 134.9, 132.5, 129.4, 126.3, 125.9, 124.4, 123.0, 122.0, 118.3, 112.0, 87.7, 26.6, 20.2.

*3-(4-Acetylphenyl)-3-(2-methylprop-1-enyl)-2-benzofuran-1(3H)-one (**13l**).* Yield: 0.097 g (61%) from 0.114 g of **6a**. HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{18}O_3$ $[M + H]^+$: 307.1334; found: 307.1331. ^{1}H NMR: δ = 7.93 (d, J = 8.7 Hz, 2H), 7.90−7.87 (m, 1H), 7.67−7.63 (m, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.50 (dt, J = 7.5 Hz, J = 0.9 Hz, 1H), 7.44−7.42 (m, 1H), 5.83 (quintuplet, J = 1.4 Hz, 1H), 2.57 (s, 3H), 1.84 (d, J = 1.4 Hz, 3H), 1.58 (d, J = 1.2 Hz, 3H). ^{13}C NMR: δ = 197.4, 170.1, 154.2, 146.9, 144.0, 136.6, 134.8, 129.2, 128.7, 125.8, 125.7, 124.5, 123.4, 122.1, 88.2, 26.7, 26.6, 20.2

General Experimental Procedure for the Two-Step Preparation of 4-Substituted 2-Benzoxepin-1(3*H*)-ones 12a−c (Scheme 6). *Synthesis of 3,3-Dimethyl-4-phenyl-2-benzoxepin-1(3H)-one **12a**.* To a solution of **6a** (0.110 g, 0.50 mmol) in 9:1 dioxane/water (2.5 mL) were added $PhB(OH)_2$ (0.185 g, 1.51 mmol), $[Rh(COD)OH]_2$ (0.0035 g, 0.0076 mmol), and dppf (0.0084 g, 0.015 mmol). The mixture was then stirred under N_2 at 80 °C for 15 h. After extraction with water (80 mL) and EtOAc (3 × 30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 80/20 v/v to afford **10a** (0.112 g, 75% yield). HRMS (ESI) *m*/*z*: calcd. for $C_{19}H_{20}O_3$ $[M - H_2O + H]^+$: 279.1385; found: 279.1382. ^{1}H NMR ($CDCl_3$): δ 7.91 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 7.50−7.46 (m, 1H), 7.43−7.40 (m, 2H), 7.38−7.28 (m, 5H), 6.54 (s, 1H), 3.93 (s, 3H), 1.29 (s, 6H). ^{13}C NMR ($CDCl_3$): δ = 167.1, 147.6, 142.6, 139.8, 130.6, 129.2, 129.1, 127.8, 127.8, 126.8, 125.73, 125.67, 73.0, 51.1, 27.9. To a solution of **10a** (0.104 g, 0.35 mmol) in MeCN (2 mL) was added *t*-BuOK (0.039 g, 0.35 mmol). The mixture was stirred at room temperature for 5 h. After extraction with water (80 mL) and EtOAc (3 × 30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 96:4 v/v to afford **12a** (0.085 g, 92% yield). mp: 94−95 °C. HRMS (ESI) *m*/*z* calcd. for $C_{18}H_{16}O_2$ $[M + H]^+$: 265.1229; found: 265.1237. ^{1}H NMR ($CDCl_3$): δ 8.13 (dd, J = 7.9 Hz, J = 1.5 Hz, 1H), 7.54 (dt, J = 7.6 Hz, J = 1.4 Hz, 1H), 7.40−7.33 (m, 4H), 7.24−7.21 (m, 3H), 6.55 (s, 1H), 1.49 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 168.7, 150.0, 141.2, 135.2, 132.8, 132.7, 131.1, 130.4, 130.1, 128.13, 128.11, 127.9, 127.6, 81.1, 28.0.

*4-(3-Acetylphenyl)-3,3-dimethyl-2-benzoxepin-1(3H)-one (**12b**).* Yield: 0.096 g (90%) from 0.118 g of **10b**. HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{18}O_3$ $[M + H]^+$: 307.1334; found: 307.1320. ^{1}H NMR: δ = 8.14 (dd, J = 7.9 Hz, J = 1.4 Hz, 1H), 7.96−7.94 (m, 1H), 7.83−7.82 (m, 1H), 7.57 (dt, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.52−7.40 (m, 3H), 7.29−7.24 (m, 1H), 6.58 (s, 1H), 2.65 (s, 3H), 1.50 (s, 6H). ^{13}C NMR: δ = 197.8,168.5, 148.9, 141.6, 137.0, 134.8, 132.9, 132.81, 132.80, 131.9, 130.5, 130.2, 128.5, 128.2, 127.8, 127.7, 80.7, 28.1, 26.8.

*4-(3-Methoxyphenyl)-3,3-dimethyl-2-benzoxepin-1(3H)-one (**12c**).* Yield: 0.101 g (90%) from 0.125 g of **10c**. HRMS (ESI) *m*/*z* calcd. for $C_{19}H_{18}O_3$ $[M + H]^+$: 295.1334; found: 295.1329. ^{1}H NMR: δ = 8.13 (dd, J = 7.9 Hz, J = 1.4 Hz, 1H), 7.55 (dt, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.41−7.37 (m, 1H), 7.31−7.23 (m, 2H), 6.90−6.87 (m, 1H), 6.81−6.76 (m, 2H), 6.57 (s, 1H), 3.83 (s, 3H), 1.50 (s, 6H). ^{13}C NMR: δ = 168.6, 159.2, 149.8, 142.5, 135.1, 132.8, 132.7, 130.9, 130.4, 130.1, 129.2, 127.8, 120.5, 114.1, 112.9, 81.0, 55.3, 27.9.

General Experimental Procedure for the One-Flask Preparation of 4-Substituted 2-Benzoxepin-1(3*H*)-ones 12d−k (Table 3). *Synthesis of 3-Pentyl-4-phenyl-2-benzoxepin-1(3H)-one **12d**.* To a solution of **6d** (0.133 g, 0.51 mmol) in 9:1 dioxane/water (3 mL) were added $PhB(OH)_2$ (0.187 g, 1.53 mmol), $[Rh(COD)OH]_2$ (0.0035 g, 0.0076 mmol), and dppf (0.0085 g, 0.015 mmol). The mixture was then stirred under N_2 at 80 °C for 15 h and cooled to rt. Then, MeCN (2 mL) and *t*-BuOK (0.229 g, 2.04 mmol) were added and the mixture was stirred at rt for 5 h. After extraction with water (80 mL) and EtOAc (3 × 30 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 97:3 v/v to afford **12d** (0.089 g, 57% yield). HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{22}O_2$ $[M + H]^+$: 307.1698; found: 307.1705; ^{1}H NMR ($CDCl_3$): δ 8.07 (dd, J = 7.9 Hz, J = 1.4 Hz, 1H), 7.58 (dt, J = 7.7 Hz, J = 1.4 Hz, 1H), 7.46−7.33 (m, 7H), 6.82 (s, 1H), 4.89−4.85 (m, 1H), 1.97−1.87 (m, 1H), 1.58−1.43 (m, 2H), 1.24−1.11 (m, 5H), 0.77 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 169.8, 146.0, 138.8, 135.3, 132.31, 132.29, 131.1, 129.4, 128.4, 128.1, 128.0, 127.9, 77.7, 31.9, 31.3, 25.7, 22.3, 13.9.

*4-(3-Acetylphenyl)-3-pentyl-2-benzoxepin-1(3H)-one (**12e**).* Yield: 0.097 g (58%) from 0.125 g of **6d**. HRMS (ESI) *m*/*z* calcd. for $C_{23}H_{24}O_3$ $[M + H]^+$: 349.1804; found: 349.1811. ^{1}H NMR: δ = 8.08 (dd, J = 7.9 Hz, J = 1.5 Hz, 1H), 7.98−7.94 (m, 2H), 7.63−7.58 (m, 2H), 7.54−7.45 (m, 2H), 7.39−7.36 (m, 1H), 6.87 (s, 1H), 2.66 (s, 3H), 1.95−1.84 (m, 1H), 1.54−1.45 (m, 2H), 1.25−1.10 (m, 5H), 0.78 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ = 197.8, 169.7, 145.0, 139.2, 137.3, 134.9, 133.3, 132.6, 132.40, 132.35, 131.1, 129.4, 128.7, 128.5, 127.9, 127.6, 77.3, 32.0, 31.3, 26.8, 25.7, 22.3, 13.9.

*4-(3-Methoxyphenyl)-3-pentyl-2-benzoxepin-1(3H)-one (**12f**).* Yield: 0.087 g (52%) from 0.130 g of **6d**. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{24}O_3$ $[M + H]^+$: 337.1804; found: 337.1810. ^{1}H NMR: δ = 8.07 (dd, J = 7.9 Hz, J = 1.5 Hz, 1H), 7.58 (dt, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.46−7.41 (m, 1H), 7.36−7.27 (m, 2H), 6.97−6.94 (m, 1H), 6.92−6.88 (m, 2H), 6.82 (s, 1H), 4.88−4.84 (m, 1H), 3.84 (s, 3H), 1.98−1.87 (m, 1H), 1.62−1.42 (m, 2H), 1.24−1.10 (m, 5H), 0.79 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ = 169.8, 159.4, 145.8, 140.1, 135.2, 132.3, 132.23, 132.19, 131.0, 129.38, 129.35, 128.1, 120.3, 113.4, 77.7, 55.3, 31.8, 31.3, 25.7, 22.3, 13.9.

*4-(4-Fluorophenyl)-3-pentyl-2-benzoxepin-1(3H)-one (**12g**).* Yield: 0.091 g (57%) from 0.128 g of **6d**. HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{21}FO_2$ $[M + H]^+$: 325.1604; found: 325. 1606. ^{1}H NMR: δ = 8.07 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 7.59 (dt, J = 7.7 Hz, J = 1.4 Hz, 1H), 7.38−7.32 (m, 3H), 7.10 (t, J = 8.7 Hz, 2H), 6.80 (s, 1H), 4.85−4.80 (m, 1H), 1.94−1.81 (m, 1H), 1.56−1.39 (m, 2H), 1.23−1.10 (m, 5H), 0.79 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ = 169.8, 162.5 (d, J = 246 Hz), 145.0, 135.1, 134.7, 132.6, 132.3, 131.1, 129.7 (d, J = 8.1 Hz), 129.3, 128.3, 115.4 (d, J = 21.5 Hz), 77.5, 31.9, 31.3, 25.7, 22.3, 13.9.

*4-(4-Benzyloxyphenyl)-3-pentyl-2-benzoxepin-1(3H)-one (**12h**).* Yield: 0.116 g (56%) from 0.131 g of **6d**. HRMS (ESI) *m*/*z* calcd. for $C_{28}H_{28}O_3$ $[M + H]^+$: 413.2117; found: 413.2110. ^{1}H NMR: δ = 8.06−8.04 (m, 1H), 7.55 (dt, J = 7.6 Hz, J = 1.5 Hz, 1H), 7.46−7.37 (m, 5H), 7.35−7.29 (m, 4H), 7.00 (d, J = 8.8 Hz, 2H), 6.77 (s, 1H), 5.09 (s, 2H), 4.88−4.85 (m, 1H), 1.97−1.86 (m, 1H), 1.60−1.40 (m, 2H), 1.27−1.09 (m, 5H), 0.79 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ = 169.8, 158.7, 145.6, 136.8, 135.5, 132.3, 131.5, 131.4, 131.0, 129.3, 129.0, 128.6, 128.1, 127.9, 127.5, 114.7, 78.0, 70.1, 31.9, 31.3, 25.8, 22.3, 13.9.

*3-Pentyl-4-[(E)-2-phenylvinyl]-2-benzoxepin-1(3H)-one (**12i**).* Yield: 0.086 g (50%) from 0.135 g of **6d**. HRMS (ESI) *m*/*z* calcd. for $C_{23}H_{24}O_2$ $[M + H]^+$: 333.1855; found: 333.1841. ^{1}H NMR: δ = 8.06 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 7.55 (dt, J = 7.6 Hz, J = 1.4 Hz, 1H), 7.49−7.46 (m, 2H), 7.42−7.26 (m, 5H), 6.97 (s, 1H), 6.89 (s, 2H), 4.92−4.89 (m, 1H), 2.06−1.95 (m, 1H), 1.80−1.70 (m, 1H), 1.63−1.52 (m, 1H), 1.36−1.24 (m, 5H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C NMR: δ = 169.4, 142.2, 136.7, 135.5, 132.5, 132.4, 131.1, 130.7, 129.8, 129.6, 128.8, 128.3, 127.9, 126.8, 125.8, 76.1, 31.4, 31.3, 25.8, 22.4, 13.9.

*3,4-Diphenyl-2-benzoxepin-1(3H)-one (**12j**).* Yield: 0.098 g (64%) from 0.131 g of **6e**. HRMS (ESI) *m*/*z* calcd. for $C_{22}H_{16}O_2$ $[M + H]^+$: 313.1229; found: 313.1234. ^{1}H NMR: δ = 7.90−7.87 (m, 1H), 7.50 (dt, J = 7.7 Hz, J = 1.3 Hz, 1H), 7.32−7.28 (m, 9H), 7.18−7.12 (m, 4H), 6.26 (s, 1H). ^{13}C NMR: δ = 169.3, 144.8, 139.3, 136.2, 135.3, 132.4, 132.3, 132.2, 130.9, 129.4, 128.4, 128.2, 128.1, 128.04, 128.01, 127.09, 126.9, 78.6.

*4-(4-Methoxyphenyl)-3-phenyl-2-benzoxepin-1(3H)-one (**12k**).* Yield: 0.092 g (53%) from 0.135 g of **6d**. HRMS (ESI) *m*/*z* calcd. for $C_{23}H_{18}O_3$ $[M + H]^+$: 343.1334; found: 343.1345. ^{1}H NMR: δ = 7.87 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 7.49−7.45 (m, 1H), 7.31−7.13

(m, 9H), 7.05 (s, 1H), 6.82 (d, $J = 8.9$ Hz, 2H), 6.24 (s, 1H), 3.79 (s, 3H). ^{13}C NMR: $\delta = 169.4$, 159.5, 144.3, 136.3, 135.5, 132.3, 132.2, 131.7, 130.9, 130.7, 129.3, 128.4, 128.2, 128.0, 127.8, 126.9, 113.8, 78.6, 55.3.

Preparation of 13b through Acid-Catalyzed Rearrangement of 11b. To a solution of **6a** (0.100 g, 0.46 mmol) in THF (2 mL) were added **7b** (0.133 mL, 0.92 mmol), Et_3N (0.193 mL, 1.38 mmol), TBACl (0.135 g, 0.46 mmol), $Pd(OAc)_2$ (0.004 g, 0.018 mmol), and, after stirring for 3 min at rt, HCOOH (0.035 mL, 0.92 mmol). The mixture was stirred under air at 60 °C for 15 h. Then, MeCN (3 mL) and *t*-BuOK (0.206 g, 1.84 mmol) were added and the mixture was stirred at room temperature for 5 h. Next, 1 M H_2SO_4 (2.76 mL, 2.76 mmol) was added, and the reaction mixture was stirred at 60 °C for 1.5 h. After extraction with 5% Na_2CO_3 (100 mL) and EtOAc (3 × 40 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 95:5 v/v to afford **13b** (0.093 g, 61% yield).

Preparation of Methyl 2-[(1*Z*)-1-(4-Methoxyphenyl)-3-methylbuta-1,3-dienyl]benzoate 14h. To a solution of **6a** (0.105 g, 0.48 mmol) in THF (2 mL) were added **7h** (0.225 g, 0.96 mmol), Et_3N (0.202 mL, 1.44 mmol), TBACl (0.142 g, 0.48 mmol), $Pd(OAc)_2$ (0.004 g, 0.018 mmol), and, after stirring for 3 min at rt, HCOOH (0.036 mL, 0.96 mmol). The mixture was stirred under air at 60 °C for 8 h. Then, acetone (3 mL) and 1 M H_2SO_4 (2.41 mL, 2.41 mmol) were added, and the reaction mixture was stirred at 60 °C for 2 h. After extraction with 5% Na_2CO_3 (100 mL) and EtOAc (3 × 40 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography, eluting with *n*-hexane/ethyl acetate 97:3 v/v to afford, in the order, **14h** (0.074 g, 50% yield) and **13h** (0.013 g, 9% yield). **14h**: HRMS (ESI) *m*/*z* calcd. for $C_{20}H_{20}O_3$ $[M + H]^+$: 309.1491; found: 309.1488. ^{1}H NMR: $\delta = 7.92$–7.88 (m, 1H), 7.50 (dt, $J = 7.5$ Hz, $J = 1.4$ Hz, 1H), 7.40 (dt, $J = 7.5$ Hz, $J = 1.5$ Hz, 1H), 7.27–7.25 (m, 1H), 7.11 (d, $J = 8.9$ Hz, 2H), 6.57 (d, $J = 8.9$ Hz, 2H), 6.57 (bs, 1H), 4.91–4.88 (m, 2H), 3.76 (s, 3H), 3.63 (s, 3H), 1.41 (bs, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 167.5$, 158.8, 142.2, 141.8, 140.3, 135.5, 132.1, 131.5, 130.2, 128.5, 128.0, 127.5, 118.3, 113.5, 55.2, 51.9, 21.9.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds. NOESY spectra of **11a**, **12a**, **13a**, and **14h**. HMQC spectra of **11a** and **13a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00663.

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Notes

The authors declare no competing financial interest.

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(24) The structure of five-membered lactones **13** was determined by NMR analysis. ^{1}H and ^{13}C spectra of **13a−c** and **13h−l** showed the presence of two nonequivalent allylic $-CH_3$. Moreover, HMQC experiments on **13a** showed a significant long-range heteronuclear coupling between quaternary C-3 and the phenyl substituent bonded to it, while the same experiment carried out on **11a** did not show a correlation between quaternary C-3 and phenyl substituent bonded to C-5 (see the Supporting Information).

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(26) With aryl halides **7b**, **7c**, **7k**, and **7l**, careful column purification is required, since the corresponding biaryls (formed as byproducts in the hydroarylation step) have R_f values similar to target phthalides **13**. Alternatively, easy isolation of intermediate alcohols **9** and their cyclization under similar reaction conditions (2 mL of MeOH, 1 mL of EtOH, 2 equiv of 5% NaOH, 60 °C, 1.15 h; then 3 equiv of 1 M H_2SO_4, 60 °C, 45 min) afforded **13** in comparable yields.

(27) Likely, carboxylate was formed under these conditions. Attempts to isolate the corresponding carboxylic acid were unsuccessful, since it was very prone to cyclize to **13a** during purification on silica. The IR spectrum of the crude reaction mixture (after acidic workup) showed a broad absorption in the region of 3400−2700 cm^{-1}.

(28) The regiochemistry of **11a**, **12a**, and **13a** was confirmed by NOESY experiments (see the Supporting Information).

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(30) **9a** is very sensitive to traces of HCl eventually present in $CDCl_3$.

(31) The NMR spectrum at rt showed the presence of two rotational isomers.