JOC The Journal of Organic Chemistry

Note

Cu(I)-Catalyzed Domino Reaction of 3-Cyclopropylideneprop-2-en-1-ones

Maozhong Miao, Jian Cao, Jingjing Zhang, Xian Huang, and Luling Wu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo302312y • Publication Date (Web): 15 Feb 2013

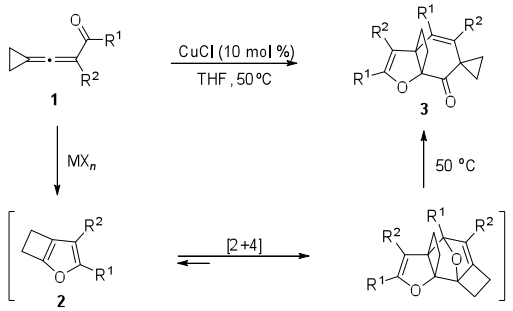
Cu(I)-Catalyzed Domino Reaction of 3-Cyclopropylideneprop-2-en-1-ones

Maozhong Miao[†], Jian Cao[†], Jingjing Zhang[†], Xian Huang[†,‡,§] and Luling Wu*[,†]

[†] *Department of Chemistry, Zhejiang University, Hangzhou 310028, P. R. China*

[‡] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China*

wululing@zju.edu.cn

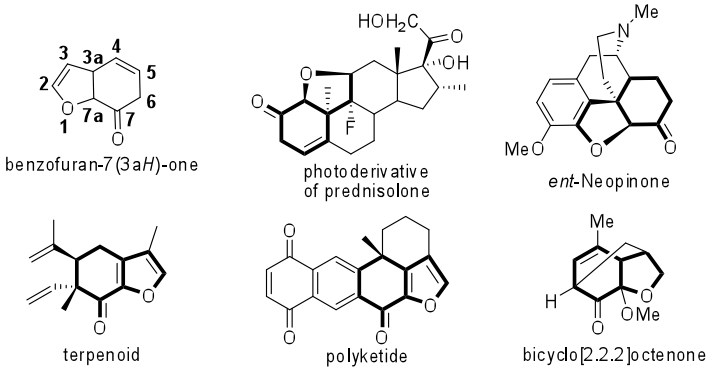


CuCl-catalyzed cyclization-dimerization reactions of 3-cyclopropylideneprop-2-en-1-ones provide an interesting route to benzofuran-7(3a*H*)-one derivatives with one highly strained three-membered ring and one four-membered ring via intramolecular cycloisomerization, sequential bimolecular [4+2] cycloaddition, opening of the oxa-bridge and ring-contraction. Furthermore, the reaction was monitored by NMR experiments to unveil some key intermediates.

Furans are important five-membered heterocycles in non-natural and natural organic compounds.[1] They are also important intermediates in synthetic transformations.[2] In addition, benzofuran-7(3a*H*)-one and its analogs are present in bioactive natural products,[3] pharmaceuticals[4] and intermediates for synthesis of natural products[5] (Figure 1). Some methods have been well developed for the synthesis of the

benzofuran-7(3a*H*)-one core;[6] however, the development of conceptually different synthetic approaches is still of great interest.

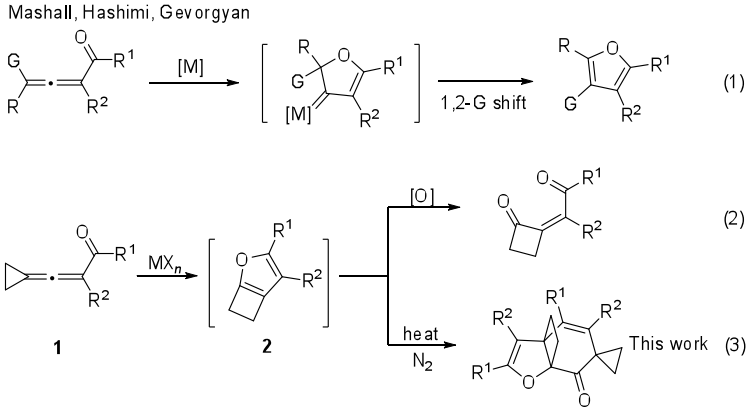
Figure 1. Bioactive compounds containing a common motif that consists of a benzofuran-7(3a*H*)-one core



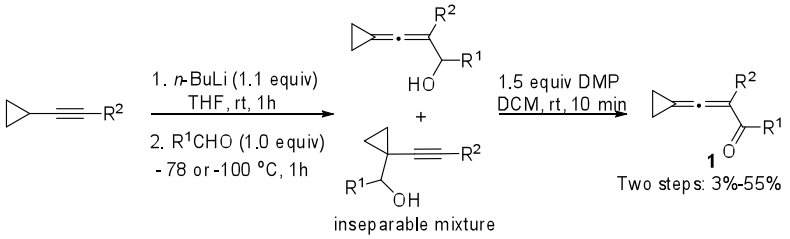
In recent years, increasing attention has been paid to metal-catalyzed cyclization/1,2-migration domino methodology which provides rapid access to complex molecular frameworks.[7] Specifically, cyclization of allenyl ketones via 1,2-migration of various groups is an efficient approach for the assembly of the furan ring.[8] Marshall and Hashmi have shown an efficient approach for the assembly of the furan ring via a formal 1,2-hydrogen shift of allenyl ketones (eq 1, Scheme 1).[8b-d] Gevorgyan has reported the metal-catalyzed cyclization of allenyl ketones with 1,2-alkyl migration as a key step in the formation of highly substituted furans (eq 1, Scheme 1).[8e] In this regard, we have reported a $PdCl_2$-catalyzed oxidative cycloisomerization of 3-cyclopropylideneprop-2-en-1-ones which can be prepared from substituted ethynylcyclopropane according to the known procedure (Scheme 2), providing a facile synthesis of highly strained functionalized 2-alkylidenecyclobutanones (eq 2, Scheme 1).[9] As a continuing exploration of the synthetic utility of 3-cyclopropylideneprop-2-en-1-ones, herein we wish to disclose our unexpected observation of a copper-catalyzed cyclization-dimerization reaction of 3-cyclopropylideneprop-2-en-1-ones, which resulted in a complex molecular structure of benzofuran-

7(3a*H*)-ones with one highly strained three-membered ring and one four-membered ring (eq 3, Scheme 1).

Scheme 1. Transition metal catalyzed cycloisomerization of 1,2-allenylketones and 3-cyclopropylideneprop-2-en-1-ones **1**



Scheme 2. The procedures for the synthesis of starting materials



In a preliminary experiment, we were successfully able to convert 3-cyclopropylideneprop-2-en-1-one **1a** into the 2-alkylidenecyclobutanone upon treatment with 10% $PdCl_2$ as the catalyst and 2.5 equiv Dess-Martin periodinane (DMP) as the oxidant in the open air.[9] Next, we observed that the reaction of **1a** in the presence of 10 mol % CuI in THF at 50 ^{o}C in a N_2 atmosphere gave a structurally very different complex product. Finally, careful examination of the single crystal X-ray diffraction study of product **3c**[10] (Table 2, entry 3) and **3i**[11] (Table 2, entry 9) revealed that the structurally very different complex product is the benzofuran-7(3a*H*)-one with a highly strained spiro-three-membered ring at the 6-position and a highly strained four-membered ring on the bridge (Figure 2). Both three-membered ring and four-membered ring are useful functional groups because of the inherent ring strains.

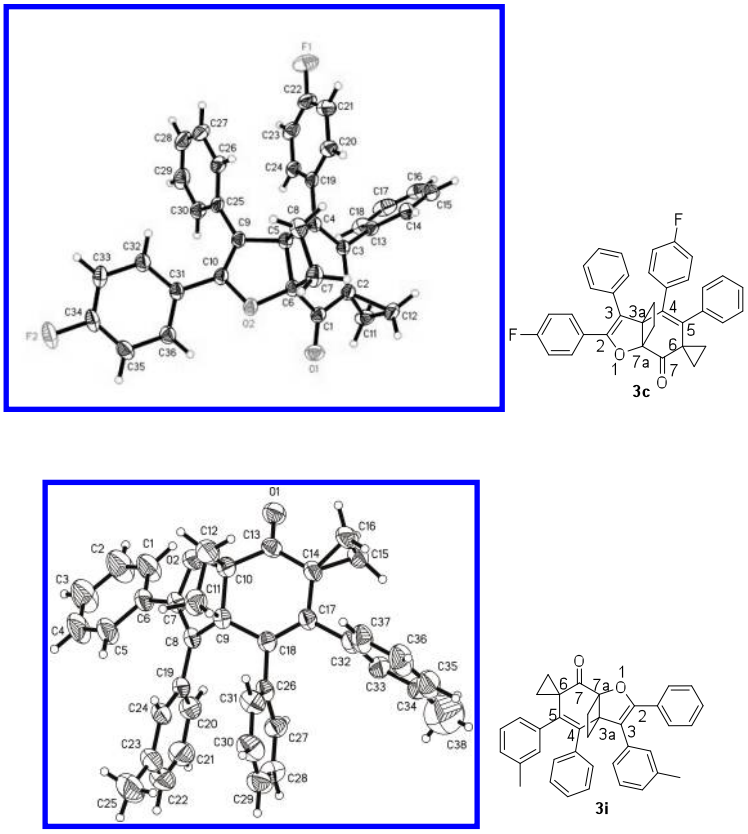
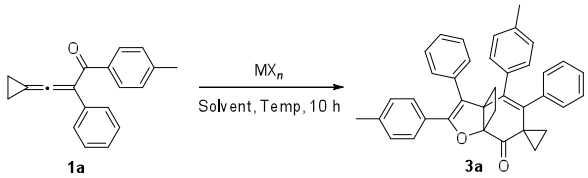


Figure 2. ORTEP representation of **3c** (top) and **3i** (bottom)

With these encouraging results, a further study on optimizing the reaction conditions for the selective formation of **3a** was immediately undertaken. We first investigated the effect of metal salts on the reaction. The best result was obtained when 10 mol % CuCl was used as the catalyst, and **3a** could be obtained in 87% yield (Table 1, entry 3). Examination of the solvent effects indicated that THF is most suitable (Table 1, entry 3). Further experiments showed that the temperature had a dramatic effect on the reaction (Table 1, entries 9-10). Finally, we were able to define the best conditions for this transformation: the reaction in THF at 50 ^{o}C using 10 mol % CuCl as the catalyst (Table 1, entry 3).

Table 1. Reaction conditions optimization for the formation of **3a**[a]

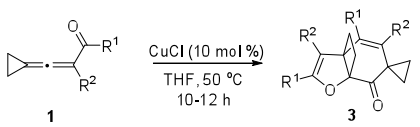


Entry	MX_n (10 mol %)	Temp (°C)	Solvent	Yield of **3a** (%)[b]
1	CuI	50	THF	78
2	CuBr	50	THF	83
3	CuCl	50	THF	87
4	AgOTf	50	THF	31
5	$PdCl_2$	50	THF	66
6	$AgNO_3$	50	THF	70
7	CuCl	50	toluene	82
8	CuCl	50	CH_3CN	75
9	CuCl	rt	THF	21
10	CuCl	reflux	THF	86

[a] Unless otherwise specified, the reaction was carried out using **1a** (0.15 mmol) in 3 mL of solvent in a N_2 atmosphere. [b] Isolated yields.

Inspired by these results, derivatives of **1** in which R^1 or R^2 are varied as shown in Table 2. The nature and position of substituents on the aromatic R^1 or R^2 have a limited effect on this reaction. Interestingly, when we examined the reaction of **1m** by treating with 10 mol % CuCl at 50 °C, furan-fused cyclobutene **2m** can be obtained in 91% yield by flash chromatography on neutral Al_2O_3 (Table 2, entry 13). However, no dimer was isolated from the reaction of **1m** in the presence of CuCl even after 10 hours heating at 50 °C.

Table 2. The scope of the reaction for the formation of **3**[a]



1 3

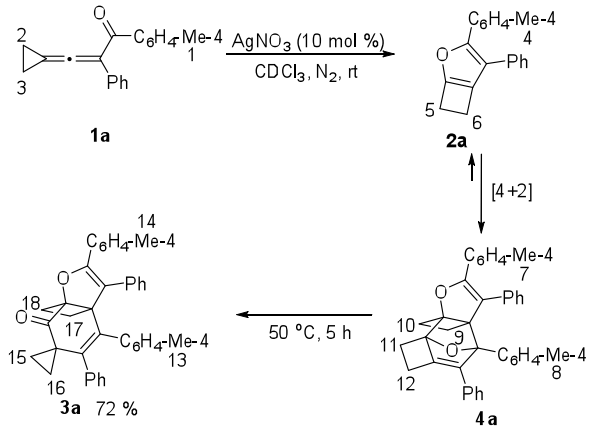
Entry	1		Yield of **3** (%)[b]
	R^1	R^2	
1	4-MeC_6H_4	Ph (**1a**)	87 (**3a**)
2	Ph	Ph (**1b**)	83 (**3b**)
3	4-FC_6H_4	Ph (**1c**)	61 (**3c**)
4	4-$MeOC_6H_4$	Ph (**1d**)	91 (**3d**)
5	3,4,5-$(MeO)_3C_6H_2$	Ph (**1e**)	64 (**3e**)
6	2-furyl	Ph (**1f**)	86 (**3f**)
7	2-thienyl	Ph (**1g**)	63 (**3g**)
8	4-MeC_6H_4	4-MeC_6H_4 (**1h**)	78 (**3h**)
9	Ph	3-MeC_6H_4 (**1i**)	93 (**3i**)
10	Ph	4-$MeOC_6H_4$ (**1j**)	86 (**3j**)[c]
11	Ph	4-FC_6H_4 (**1k**)	85 (**3k**)
12	Ph	2-naphthyl (**1l**)	78 (**3l**)
13	*i*-Bu	Ph (**1m**)	91 (**2m**)[d]

[a] Unless otherwise specified, the reaction was carried out using **1** (0.15 mmol) in presence of 10 mol % CuCl in 3 mL of THF at 50 ^oC in a N_2 atmosphere. [b] Isolated yields. [c] When the reaction was carried out using **1j** in 1 mmol, 276 mg scale catalyzed by 10% CuCl, the product **3j** was obtained in 89% yield (246 mg). [d] The reaction was carried out for 10 min and the structure of **2m** is 3-isobutyl-4-phenyl-2-oxabicyclo[3.2.0]hepta-1(5),3-diene.

The reaction was slow at room temperature when we used the CuCl as the catalyst. In order to elucidate the mechanism, we conducted the reaction of **1a** in the presence of 10 mol % $AgNO_3$ instead of 10 mol % CuCl as the catalyst in $CDCl_3$ under N_2 atmosphere. This reaction was then monitored by NMR experiments to detect the formation of any intermediates (Scheme 3). Initially, the reaction gave

rise to two sets of CH_2 signals Nos. 6 and 5 at 3.39 (t, J = 2.8 Hz, 2H), 3.01 (t, J = 2.8 Hz, 2H) together with one methyl resonance signal No. 4 at 2.33 ppm (3H, s) in the high field region (*Figure S1* b, c), and these two sets of characteristic CH_2 shifts 6, 5 are similar to the furan-fused cyclobutene **2m** (for the ^{1}H NMR spectra of **2m** see Supporting Information). This result indicates that **1a** was converted to furan-fused cyclobutene **2a** at first. Subsequent transformation of **2a** at room temperature gave the [4+2] intermediate **4a**, which was identified by the four sets of characteristic CH_2 signals in the two four-membered rings Nos. 9, 10, 11 and 12 at 3.32-3.45 (m, 1H), 3.07-3.21 (m, 1H), 2.84-3.06 (m, 2H), 2.55-2.75 (m, 2H), 2.36-2.51 (m, 1H), 2.04-2.21 ppm (m, 1H) and two methyl signals Nos. 7 and 8 at 2.27 (3H, s), 2.24 ppm (3H, s) in the high field region (*Figure S1* d-g). Meanwhile, the structure of [4+2] intermediate **4a** was further supported by ^{13}C NMR, DEPT 135 (*Figure S1* h, i) and ESI-MS spectra (see Supporting Information). Finally, the transformation of bimolecular **4a** to **3a** at 50 ^{o}C (*Figure S1* j, k) indicated that the [4+2] product **4a** was the key intermediate for this reaction.

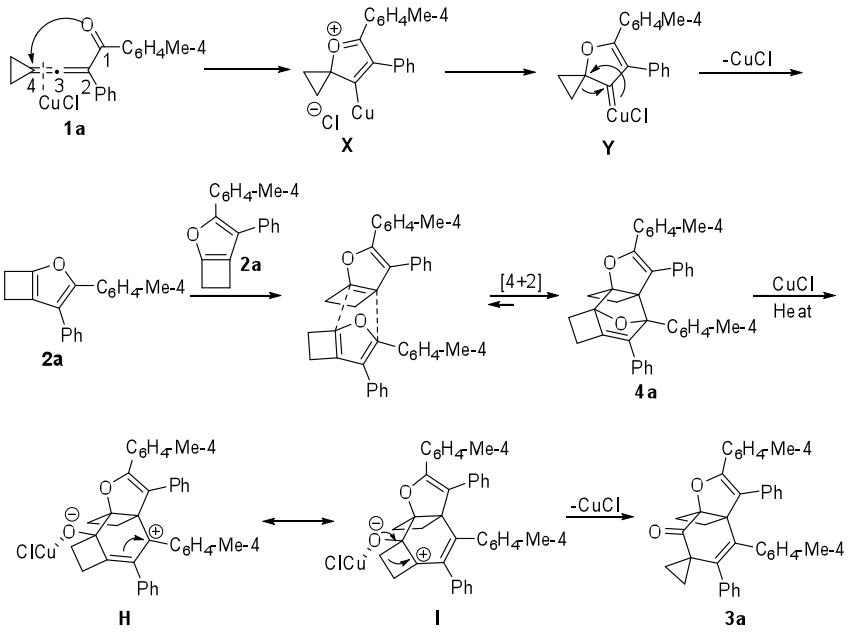
Scheme 3. Controlled experiment in the NMR tube.



On the basis of the above results, we proposed a plausible pathway for the formation of product **3a** as shown in Scheme 4. At first, CuCl may activate the relatively electron-rich C3-C4 double bond and trigger the nucleophilic attack of the carbonyl oxygen at the C4 atom of the allenone moiety to form the spirocyclic oxonium salt X. The latter intermediate would evolve into the Cu(I) carbenoid Y, and

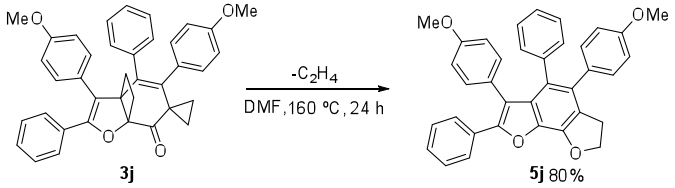
subsequent bond cleavage followed by elimination of the metal would provide the intermediate compound **2a**. The next dimerization of intermediate **2a** via [4+2] cycloaddition may afford the bimolecular intermediate **4a**. Subsequent cleavage of the oxa-bridge catalyzed by CuCl gives the allylic cationic mesomeric forms **H** and **I**. The ring-contraction reaction of the cyclobutyloxyl anion **I** furnishes the product **3a** and regenerates the catalyst CuCl.

Scheme 4. Plausible mechanism for the formation of 6,7a-dihydrobenzofuran-7(3a*H*)-one derivatives **3a**



Both three-membered ring and four-membered ring have shown interesting reactivity in organic synthesis. Considering the readily available bifuctional (three-membered ring and four-membered ring) benzofuran-7(3a*H*)-one derivatives **3** with our protocol, thus, we observed an interesting route to substituted 2,3-dihydrobenzofuro[7,6-*b*]furan **5j** from **3j** in 80% yield at elevated temperature (Scheme 5). The overall sequence of reactions can be described as proceeding by an initial ethylene elimination and a subsequent Cloke-Wilson cyclopropyl ketone rearrangement.[12] The facility of the process might be related to the aromaticity gained in the final step.

Scheme 5. Synthesis of tricyclic compound **5j**



In conclusion, a new copper (I) catalyzed dimerization pathway of 3-cyclopropylideneprop-2-en-1-ones into spirocyclic-oxa-[4,3,2]propellanes containing benzofuran-7(3a*H*)-one core has been revealed. In this process, the intermediate furan-fused cyclobutenes demonstrate a new type of reactivity; it involves the unusual [4+2] cycloaddition which can present as diene and dienophile in one reaction. The reaction is accompanied by the formation of bridged four-menbered ring and spiro-three-membered ring. Also, the propellane scaffolding can be easily transformed to substituted 2,3-dihydrobenzofuro[7,6-*b*]furan in high yield.

1. Experimental Procedures

1.1 General Methods

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively using tetramethylsilane as the internal standard. Chemical shifts are expressed in ppm and *J* values are given in Hz. Organic solvents used were dried by standard methods when necessary. The THF and toluene were distilled from sodium-benzophenone; The DCM and CH_3CN were distilled from CaH_2. Commercially obtained available reagents were used without further purification. Petroleum ether refers to the fraction with boiling point in the range 60~90 °C. All reactions were monitored by TLC with GF 254 silica gel coated plates. Flash column chromatography was carried out using 300-400 mesh silica gel or 200-300 mesh Al_2O_3 at increased pressure.

1.2 Procedure for Synthesis of **3a-3l**

(1) 2,4-Bis(4-methylphenyl)-3a,7a-ethylene-3,5-diphenyl-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3a)

Typical procedure: Under an atmosphere of dry nitrogen, CuCl (1.5 mg, 0.015 mmol, 10 mol %) was added to a solution of **1a** (39 mg, 0.150 mmol) in 3 mL of anhydrous THF at 50 ^{o}C. After being stirred for 10-12 hours (monitored by TLC), the mixture was quenched with 5 mL of water and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After filtration and removal of the solvent in vacuo, the residue was purified with flash silica gel chromatography (petroleum ether/ethyl acetate 15:1 v/v) to afford **3a** (34 mg, 87%) as a white solid: M.p. 179-180 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.89-7.06 (m, 6H), 6.82 (t, *J* = 8.0 Hz, 2H), 6.72-6.76 (m, 2H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.29-6.35 (m, 4H), 3.04-3.15 (m, 1H), 2.85-2.99 (m, 2H), 2.73-2.83 (m, 1H), 2.24 (s, 3H), 1.96 (s, 3H), 1.74-1.82 (m, 1H), 1.45-1.53 (m, 1H), 1.08-1.16 (m, 1H), 0.88-0.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 18.9, 20.8, 21.2, 30.5, 30.8, 34.4, 61.8, 83.8, 117.0, 125.5, 126.3, 126.9, 127.2, 127.5, 127.6, 128.2, 128.4, 129.5, 130.3, 130.6, 130.8, 134.7, 135.0, 135.7, 137.1, 138.2, 138.2, 151.4, 205.4; IR (neat): 1698, 1626, 1510, 1084, 900, 825, 764, 701 cm^{-1}; MS (70 eV, EI) m/z: 520 (M^+), 492 (100); TOF HRMS (EI): calcd for $C_{38}H_{32}O_2$ (M^+): 520.2402. Found, 520.2407.

The following compounds **3b-3l** were prepared similarly.

(2) 3a,7a-Ethylene-2,3,4,5-tetraphenyl-3a*H*-spiro[benzofuran-6,1'-cyclo- propan]-7(7a*H*)-one (3b)

The reaction of **1b** (40 mg, 0.163 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 ^{o}C afforded **3b** (33 mg, 83%) as white solid: M.p. 177-179 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 7.6 Hz, 2H), 7.06-7.21 (m, 4H), 6.86-7.06 (m, 4H), 6.83 (t, *J* = 7.2 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.58-6.70 (m, 2H), 6.55 (t, *J* = 7.2 Hz, 2H), 6.46 (d, J = 7.6 Hz, 2H), 3.08-3.20 (m, 1H), 2.90-3.02 (m, 2H), 2.75-2.88 (m, 1H), 1.75-1.84 (m, 1H), 1.47-1.55 (m, 1H), 1.10-1.20 (m,

1H), 0.90-1.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 19.0, 30.6, 30.7, 34.4, 61.6, 83.9, 117.7, 125.4, 126.0, 126.4, 126.5, 126.9, 127.6, 127.7, 127.7, 127.8, 128.4, 129.7, 130.2, 130.5, 130.7, 131.1, 134.6, 135.6, 136.8, 138.1, 138.8, 151.4, 205.2; IR (neat): 1687, 1638, 1491, 1442, 1072, 764, 694 cm^{-1}; MS (70 eV, EI) m/z: 492 (M^+), 464 (100); TOF HRMS (EI): calcd for $C_{36}H_{28}O_2$ (M^+): 492.2089. Found, 492.2086.

(3) 2,4-Bis(4-fluorophenyl)-3a,7a-ethylene-3,5-diphenyl-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3c)

The reaction of **1c** (41 mg, 0.155 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 °C afforded **3c** (25 mg, 61%) as white solid: M.p. 208-209 °C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 8.4 Hz, 5.6 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.93-7.05 (m, 4H), 6.79-6.91 (m, 4H), 6.75 (d, *J* = 7.2 Hz, 2H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.41 (dd, *J* = 8.4 Hz, 6.0 Hz, 2H), 6.23 (t, *J* = 8.8 Hz, 2H), 3.09-3.21 (m, 1H), 2.87-3.02 (m, 2H), 2.75-2.88 (m, 1H), 1.77-1.86 (m, 1H), 1.46-1.55 (m, 1H), 1.10-1.19 (m, 1H), 0.92-1.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 19.5, 30.7, 34.7, 61.5, 83.9, 113.4 (d, $^2J_{C-F}$ = 21 Hz), 114.8 (d, $^2J_{C-F}$ = 21 Hz), 117.1, 126.3, 126.6, 127.1, 127.1, 127.8, 127.9, 129.7 (d, $^3J_{C-F}$ = 9 Hz), 130.1, 130.4, 130.6, 131.1 (d, $^3J_{C-F}$ = 8 Hz), 134.5, 134.7 (d, $^4J_{C-F}$ = 4 Hz), 136.2, 136.6, 137.0, 150.6, 160.6 (d, $^1J_{C-F}$ = 243 Hz), 162.5 (d, $^1J_{C-F}$ = 247 Hz), 204.9; IR (neat): 1702, 1638, 1506, 1226, 1081, 1063, 902, 844, 700 cm^{-1}; MS (70 eV, EI) m/z: 528 (M^+), 500 (100); TOF HRMS (EI): calcd for $C_{36}H_{26}O_2F_2$ (M^+): 528.1901. Found, 528.1899.

(4) 2,4-Bis(4-methoxyphenyl)-3a,7a-ethylene-3,5-diphenyl-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3d)

The reaction of **1d** (43 mg, 0.156 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 °C afforded **3d** (39 mg, 91%) as white solid: M.p. 178-179 °C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22-7.28 (m, 2H), 7.12 (t, *J* = 6.8 Hz, 1H), 6.90-7.06 (m, 4H), 6.87 (t, *J* = 7.2 Hz, 2H),

6.76 (d, *J* = 8.0 Hz, 2H), 6.63-6.71 (m, 3H), 6.35 (d, *J* = 8.0 Hz, 2H), 6.09 (d, *J* = 8.0 Hz, 2H), 3.72 (s, 3H), 3.53 (s, 3H), 3.04-3.16 (m, 1H), 2.84-2.99 (m, 2H), 2.72-2.83 (m, 1H), 1.73-1.84 (m, 1H), 1.44-1.54 (m, 1H), 1.07-1.17 (m, 1H), 0.89-0.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 19.1, 30.6, 30.8, 34.4, 54.9, 55.1, 61.7, 83.8, 112.1, 113.1, 116.0, 123.7, 125.8, 126.4, 126.9, 127.6, 129.1, 130.3, 130.6, 130.7, 130.8, 131.3, 135.1, 135.2, 137.1, 137.8, 151.1, 157.1, 159.5, 205.5; IR (neat): 1685, 1605, 1509, 1246, 1178, 1094, 1028, 909, 833, 734, 716 cm^{-1}; MS (70 eV, EI) m/z: 552 (M^+), 524 (100); TOF HRMS (EI): calcd for $C_{38}H_{32}O_4$ (M^+): 552.2301. Found, 552.2296.

(5) 3a,7a-Ethylene-3,5-diphenyl-2,4-bis(3,4,5-trimethoxy- phenyl)-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3e)

The reaction of **1e** (50 mg, 0.149 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 ^{o}C afforded **3e** (32 mg, 64%) as white solid: M.p. 177-178 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16-7.24 (m, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.96-7.04 (m, 4H), 6.86-6.91 (m, 2H), 6.66 (d, *J* = 7.2 Hz, 1H), 6.54 (s, 2H), 5.76 (s, 2H), 3.77 (s, 3H), 3.60 (s, 3H), 3.51 (s, 6H), 3.38 (s, 6H), 3.11-3.22 (m, 1H), 2.97-3.10 (m, 1H), 2.85-2.96 (m, 1H), 2.72-2.84 (m, 1H), 1.82-1.92 (m, 1H), 1.45-1.55 (m, 1H), 1.20-1.25 (m, 1H), 0.94-1.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 20.0, 30.9, 31.0, 33.9, 55.5, 55.6, 60.4, 60.7, 61.5, 83.5, 104.6, 107.5, 117.1, 126.0, 126.5, 126.7, 126.8, 127.6, 128.2, 130.5, 130.6, 134.1, 135.0, 135.5, 135.7, 137.0, 137.5, 137.9, 150.6, 151.4, 152.3, 205.0; IR (neat): 1708, 1575, 1504, 1411, 1350, 1241, 1121, 1001, 833, 700 cm^{-1}; MS (70 eV, EI) m/z: 672 (M^+), 644 (100); TOF HRMS (EI): calcd for $C_{42}H_{40}O_8$ (M^+): 672.2723. Found, 672.2726.

(6) 2,4-Di(furan-2-yl)-3a,7a-ethylene-3,5-diphenyl-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3f)

The reaction of **1f** (35 mg, 0.148 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 ^{o}C afforded **3f** (30 mg, 86%) as white solid: M.p. 187-188 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 7.24-7.42 (m, 4H), 7.06-7.17 (m, 4H), 6.90-7.05 (m, 3H), 6.41 (s, 1H), 6.23 (t, *J* = 1.6 Hz, 1H), 5.98 (d, *J* = 7.2 Hz, 1H), 5.63 (t, *J* = 1.6 Hz, 1H), 4.65 (d, *J* = 7.2 Hz, 1H), 3.01-3.12 (m, 1H), 2.78-2.98 (m, 2H), 2.62-2.75 (m, 1H), 1.55-1.64 (m, 2H), 1.15-1.23 (m, 1H), 0.89-0.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2, 20.6, 29.3, 30.9, 33.6, 61.1, 84.2, 109.7, 110.1, 110.2, 110.9, 118.2, 126.4, 126.5, 127.6, 127.7, 128.1, 129.0, 129.4, 129.8, 134.0, 134.6, 137.5, 139.6, 142.5, 144.1, 145.7, 151.0, 204.0; IR (neat): 1698, 1163, 1090, 1007, 977, 867, 745, 702 cm^{-1}; MS (70 eV, EI) m/z: 472 (M^+), 444 (100); TOF HRMS (EI): calcd for $C_{32}H_{24}O_4$ (M^+): 472.1675. Found, 472.1677.

(7) 3a,7a-Ethylene-3,5-diphenyl-2,4-di(thiophen-2-yl)-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3g)

The reaction of **1g** (38 mg, 0.151 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 ^{o}C afforded **3g** (24 mg, 63%) as white solid: M.p. 176-177 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04-7.32 (m, 8H), 6.96-7.04 (m, 3H), 6.86 (dd, *J* = 8.4 Hz, 4.4 Hz, 2H), 6.63 (d, *J* = 4.8 Hz, 1H), 6.17 (t, *J* = 4.4 Hz, 1H), 5.98 (d, *J* = 3.6 Hz, 1H), 2.99-3.08 (m, 1H), 2.88-2.98 (m, 1H), 2.70-2.88 (m, 2H), 1.55-1.70 (m, 2H), 1.19-1.29 (m, 1H), 0.84-0.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 20.3, 29.2, 31.3, 33.4, 62.4, 84.1, 117.1, 124.6, 125.0, 126.5, 126.6, 126.8, 127.0, 127.4, 127.5, 128.1, 128.2, 128.5, 130.2, 130.5, 130.8, 132.8, 134.0, 136.3, 136.9, 139.5, 147.5, 204.3; IR (neat): 1701, 1638, 1248, 1197, 1082, 694 cm^{-1}; MS (70 eV, EI) m/z: 504 (M^+), 476 (100); TOF HRMS (EI): calcd for $C_{32}H_{24}O_2S_2$ (M^+): 504.1218. Found, 504.1223.

(8) 2,3,4,5-Tetrakis(4-methylphenyl)-3a,7a-ethylene-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3h)

The reaction of **1h** (41 mg, 0.150 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 ^{o}C afforded **3h** (32 mg, 78%) as white solid: M.p. 172-173 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.0 Hz, 2H), 6.86-6.97 (m, 4H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.53-6.67 (m, 5H),

6.33 (q, *J* = 8.0 Hz, 4H), 3.01-3.12 (m, 1H), 2.82-2.98 (m, 2H), 2.70-2.80 (m, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H), 2.00 (s, 3H), 1.70-1.79 (m, 1H), 1.42-1.50 (m, 1H), 1.05-1.15 (m, 1H), 0.87-0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 18.9, 20.8, 21.0, 21.1, 21.2, 30.5, 30.9, 34.4, 61.8, 83.7, 117.0, 127.2, 127.6, 127.6, 128.3, 128.4, 128.4, 128.5, 130.0, 130.4, 130.6, 132.0, 134.1, 134.6, 134.8, 135.2, 135.8, 136.0, 138.1, 138.1, 150.9, 205.6; IR (neat): 1705, 1509, 1339, 1071, 1036, 893, 812, 721 cm^{-1}; MS (70 eV, EI) m/z: 548 (M^+), 520 (100); TOF HRMS (EI): calcd for $C_{40}H_{36}O_2$ (M^+): 548.2715. Found, 548.2712.

(9) 3,5-Bis(3-methylphenyl)-3a,7a-ethylene-2,4-diphenyl-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3i)

The reaction of **1i** (40 mg, 0.154 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 ^{o}C afforded **3i** (37 mg, 93%) as white solid: M.p. 170-172 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 7.2 Hz, 2H), 6.42-7.20 (m, 16H), 3.08-3.20 (m, 1H), 2.88-3.01 (m, 2H), 2.74-2.86 (m, 1H), 2.13 (d, J = 71.2 Hz, 3H), 1.96 (s, 3H), 1.73-1.84 (m, 1H), 1.45-1.55 (m, 1H), 1.11-1.20 (m, 1H), 0.91-1.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 19.1, 19.3, 21.1, 21.3, 30.5, 30.6, 30.7, 34.5, 61.5, 83.8, 117.8, 125.4, 126.2, 126.7, 126.9, 127.1, 127.1, 127.3, 127.4, 127.5, 127.6, 127.7, 127.7, 127.8, 128.3, 129.6, 130.9, 131.2, 131.2, 131.4, 134.4, 135.5, 135.6, 136.3, 136.7, 137.0, 137.8, 137.8, 138.9, 151.0, 205.4; IR (neat): 1701, 1494, 1447, 1242, 1090, 900, 768, 696, 667 cm^{-1}; MS (70 eV, EI) m/z: 520 (M^+), 492 (100); TOF HRMS (EI): calcd for $C_{38}H_{32}O_2$ (M^+): 520.2402. Found, 520.2404.

(10) 3,5-Bis(4-methoxyphenyl)-3a,7a-ethylene-2,4-diphenyl-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3j)

The reaction of **1j** (42 mg, 0.152 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 ^{o}C to afford **3j** (36 mg, 86%) as white solid: M.p. 159-160 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 7.35 (d, *J* = 6.8 Hz, 2H), 7.10-7.21 (m, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.53-6.71 (m, 7H), 6.43-6.51 (m, 3H), 6.38 (d, J = 8.4 Hz, 2H), 3.67 (s, 3H), 3.64 (s, 3H), 3.03-3.15 (m, 1H), 2.86-3.00 (m, 2H), 2.72-2.83 (m, 1H), 1.73-1.83 (m, 1H), 1.45-1.55 (m, 1H), 1.09-1.19 (m, 1H), 0.89-0.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 19.1, 30.5, 31.0, 34.3, 54.9, 55.1, 61.4, 83.6, 112.4, 112.9, 113.3, 117.3, 125.2, 126.6, 126.9, 127.6, 127.7, 128.2, 129.1, 129.7, 131.1, 131.7, 131.7, 135.1, 138.3, 139.1, 150.8, 157.8, 157.8, 205.5; IR (neat): 1702, 1604, 1509, 1284, 1242, 1175, 1031, 907, 728, 696 cm^{-1}; MS (70 eV, EI) m/z: 552 (M^+), 524 (100); TOF HRMS (EI): calcd for $C_{38}H_{32}O_4$ (M^+): 552.2301. Found, 552.2297.

(11) 3,5-Bis(4-fluorophenyl)-3a,7a-ethylene-2,4-diphenyl-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3k)

The reaction of **1k** (40 mg, 0.152 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 °C afforded **3k** (34 mg, 85%) as white solid: M.p. 163-164 °C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 6.8 Hz, 2H), 7.11-7.23 (m, 3H), 6.97-7.05 (m, 1H), 6.83 (t, *J* = 8.4 Hz, 1H), 6.71 (dt, *J* = 8.6 Hz, 5.2 Hz, 3H), 6.62 (t, *J* = 7.6 Hz, 4H), 6.51 (t, *J* = 8.8 Hz, 2H), 6.45 (d, *J* = 6.8 Hz, 2H), 3.05-3.16 (m, 1H), 2.90-3.03 (m, 2H), 2.74-2.87 (m, 1H), 1.78-1.88 (m, 1H), 1.47-1.56 (m, 1H), 1.06-1.16 (m, 1H), 0.89-0.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 19.3, 30.6, 30.7, 34.5, 61.3, 83.8, 114.1 (d, $^2J_{C\text{-}F}$ = 21 Hz), 114.5, 114.7 (d, $^2J_{C\text{-}F}$ = 21 Hz), 114.7, 116.3, 125.6, 126.8, 127.7, 127.8, 128.6, 129.6, 130.5 (d, $^4J_{C\text{-}F}$ = 3 Hz), 130.8, 131.6 (d, $^3J_{C\text{-}F}$ = 7 Hz), 132.2 (d, $^3J_{C\text{-}F}$ = 8 Hz), 132.6 (d, $^4J_{C\text{-}F}$ = 3 Hz), 134.6, 138.6, 138.7, 151.7, 161.3 (d, $^1J_{C\text{-}F}$ = 245 Hz), 204.8; IR (neat): 1705, 1599, 1507, 1225, 1069, 902, 834, 766, 694 cm^{-1}; MS (70 eV, EI) m/z: 528 (M^+), 500 (100); TOF HRMS (EI): calcd for $C_{36}H_{26}O_2F_2$ (M^+): 528.1901. Found, 528.1897.

(12) 3a,7a-Ethylene-3,5-di(naphthalen-2-yl)-2,4-diphenyl-3a*H*-spiro[benzofuran-6,1'-cyclopropan]-7(7a*H*)-one (3l)

The reaction of **1l** (45 mg, 0.152 mmol) and CuCl (1.5 mg, 0.015 mmol, 10 mol %) at 50 ^{o}C afforded **3l** (35 mg, 78%) as white solid: M.p. 141-142 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.74 (m, 3H), 6.76-7.51 (m, 16H), 6.49 (d, *J* = 7.2 Hz, 2H), 6.10-6.26 (m, 3H), 3.20-3.40 (m, 1H), 2.99-3.17 (m, 2H), 2.80-2.96 (m, 1H), 1.75-1.91 (m, 1H), 1.45-1.57 (m, 1H), 1.06-1.35 (m, 1H), 0.80-1.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 18.8, 19.0, 19.8, 30.4, 30.9, 31.0, 34.4, 35.0, 61.6, 61.8, 83.7, 84.2, 117.4, 117.6, 125.2, 125.3, 125.7, 125.7, 125.8, 126.3, 126.4, 126.5, 127.1, 127.2, 127.4, 127.6, 127.7, 127.7, 127.8, 127.9, 128.4, 128.5, 128.6, 128.9, 129.0, 129.3, 129.6, 131.0, 131.0, 131.7, 131.8, 132.1, 132.2, 132.6, 133.0, 134.2, 134.4, 135.2, 135.4, 138.2, 138.5, 138.6, 138.7, 151.7, 151.8, 205.1, 205.2; IR (neat): 1705, 1495, 1339, 1069, 1020, 894, 855, 819, 744, 695 cm^{-1}; MS (70 eV, EI) m/z: 592 (M^+), 564 (100); TOF HRMS (EI): calcd for $C_{44}H_{32}O_2$ (M^+): 592.2402. Found, 592.2405.

1.3 Syntheis of furan-fused cyclobutenes **2m** from **1m** in the presence of 10 mol % CuCl

Under an atmosphere of dry nitrogen, CuCl (1.5 mg, 0.015 mmol, 10 mol %) was added to a solution of **1m** (34 mg, 0.15 mmol) in 3 mL of dry THF at 50 ^{o}C. After being stirred for 10 min (monitored by TLC), filtration and removal of the solvent in vacuo, flash chromatography on Al_2O_3 (petroleum ether) afforded **2m** in 91% yield as yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.35-7.42 (m, 4H), 7.20-7.30 (m, 1H), 3.29-3.34 (m, 2H), 2.95-2.30 (m, 2H), 2.71 (d, *J* = 2.8 Hz, 2H), 1.92-2.05 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.2, 24.7, 28.1, 34.0, 36.3, 120.1, 122.9, 126.3, 127.1, 128.7, 133.1, 149.6, 153.6. Known compound see Rf. 9.

1.4 Syntheis of 4,6-bis(4-methoxyphenyl)-5,7-diphenyl-2,3-dihydrobenzofuro[7,6-b]furan **5j**

Under an atmosphere of dry nitrogen, a solution of **3j** (35 mg, 0.06 mmol) in 2 mL of DMF was stirred at 160 ^{o}C for 24 hour (monitored by TLC). The mixture was quenched with 5 mL of water and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After filtration and removal of the solvent in vacuo, the residue was purified with flash silica gel chromatography (petroleum ether/ethyl acetate 15:1 v/v) to afford **5j** (28 mg, 80%) as a white solid:

M.p. 206-208 ^{o}C (petroleum ether/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.56 (m, 2H), 7.18-7.24 (m, 3H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.60-6.76 (m, 8H), 6.47 (d, *J* = 8.8 Hz, 2H), 4.79 (t, *J* = 8.8 Hz, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 3.19 (t, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9, 55,0, 55.2, 73.1, 112.9, 113.5, 118.8, 123.4, 125.1, 125.2, 126.4, 126.9, 127.3, 127.8, 128.1, 129.7, 130.8, 131.09, 131.12, 131.3, 131.9, 133.2, 136.9, 137.7, 142.1, 151.0, 157.7, 158.2 ; IR (neat): 2957, 2835, 1607, 1512, 1454, 1413, 1381, 1337, 1285, 1243, 1179, 1148, 1098, 1033 cm^{-1}; MS (70 eV, EI) m/z: 524 (M^+), 524 (100); TOF HRMS (EI): calcd for $C_{36}H_{28}O_4$ (M^+): 524.1988. Found, 524.1986.

Notes

[§] Professor Huang passed away on March 6, 2010. He was fully in charge of this project. Professor Luling Wu is helping to finish all the projects with assistance from Professor Shengming Ma.

ACKNOWLEDGMENT:

We are grateful to the National Natural Science Foundation of China (Project Nos. 20872127, 20732005, and J0830431) and National Basic Research Program of China (973 Program, 2009CB825300) and CAS Academician Foundation of Zhejiang Province and the Fundamental Research Funds for the Central Universities for financial support.

Supporting Information.

Copies of ^{1}H and ^{13}C NMR spectra for **3**, **2m**, X-ray crystallographic data (CIF file) for **3c** and **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES:

(1) (a) Graening, T.; Thrun, F. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ed.; Elsevier: New York, **2008**; Vol. *3*, p 497-569. (b) Dudnik, A. S.; Gevorgyan, V. In *Catalyzed Carbon−Heteroatom Bond Formation*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, **2011**; Chapter 8, p 227-316. (c) Patil, N. T.; Yamamoto, Y. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley-VCH: Weinheim, Germany, **2009**; Vol. *1*, Chapter 10, pp 457-525. (d) Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, **2003**; Vol. *15*, p 167-205. (e) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42-64.

(2) (a) Lee, H.-K.; Chan, K.-F.; Hui, C.-W.; Yim, H.-K.; Wu, X.-W.; Wong, H. N. C. *Pure Appl. Chem.* **2005**, *77*, 139-143. (b) Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, Germany, **1995**; p 231-242.

(3) (a) Nakamura, H.; Kobayashi, J.; Kobayashi, M.; Ohizumi, Y.; Hirata, Y. *Chem. Lett.* **1985**, 713-716. (b) Endo, J.; *Yakugaku Zasshi (J. Pharm. Soc. Jpn.)*, **1975**, *95*, 1321-1326. (c) Duchek, J.; Piercy, T. G.; Gilmet, J.; Hudlicky, T. *Can. J. Chem.* **2011**, *89*, 709-728.

(4) DellaGreca, M.; Fiorentino, A.; Isidori, M.; Lavorgna, M.; Previtera, L.; Rubino, M.; Temussi, F. *Chemosphere* **2004**, *54*, 629-637.

(5) (a) Juo, W.-J.; Lee, T.-H.; Liu, W.-C.; Ko, S.; Chittimalla, S. K.; Rao C. P.; Liao, C.-C. *J. Org. Chem.* **2007**, *72*, 7992-8004. (b) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107-124. (c) Paquette, L. A.; Maleczka, R. E., Jr. *J. Org. Chem.* **1992**, *57*, 7118-7122.

(6) (a) Hagiwara, H.; Sato, K.; Nishino, D.; Hoshi, T.; Suzuki, T.; Ando, M., *J. Chem. Soc. Perkin Trans. 1*, **2001**, 2946-2957. (b) Arai, S.; Nakayama, K.; Suzuki, Y.; Hatano, K.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 9739-9742.

(7) (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395-3442. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49-92. (c) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244-9245. (d) Kirsch, S. F.; Binder, J. T.; Liébert, C; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878-5880. (e) Trost, B. M; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231-6242.

(8) (a) Sheng, H.; Lin, S.; Huang, Y. Z. *Tetrahedron Lett*. **1986**, *27*, 4893-4894. (b) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450-3451. (c) Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796-797. (d) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285-2288. (e) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195-5197. (f) Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98-101. (g) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500-10501. (h) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280-2282. (i) Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645-7655.

(9) Miao, M.; Cao, J.; Zhang, J.; Huang, X.; Wu L. *Org. Lett.* **2012**, *14*, 2718-2721.

(10) X-ray crystal data for **3c**: $C_{36}H_{26}F_2O_2$; M=528.57; crystal system: triclinic; space group: *P-1*; final R indices [$I > 2\sigma(I)$] $R1$=0.0558, $wR2$=0.1508, R indices (all data) $R1$=0.0659, $wR2$=0.1600; a=7.8825(8) Å, b=10.8228(11) Å, c=15.9897(17) Å; α=87.010(2), β=88.663(2), γ=76.653(2), V=1325.4(2) Å^3, T=293(2) K, Z=2; F(000) 552; reflections collected/unique: 7036/4871 [R(int)=0.1084]; number of observations [$I > 2\sigma(I)$]: 3909; parameters: 362. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 807078.

(11) X-ray crystal data for **3i**: $C_{38}H_{32}O_2$; M=520.64; crystal system: triclinic; space group: *P-1*; final R indices [$I > 2\sigma(I)$] $R1$=0.0756, $wR2$=0.2222, R indices (all data) $R1$=0.1499, $wR2$=0.2521; a=8.0059(5) Å, b=13.2066(8) Å, c=14.6206(11) Å; α=79.046(6), β=75.191(6), γ=81.987(5), V=1460.53(17) Å^3, T=293(2) K, Z=2; F(000) 552; reflections collected/unique: 12425/5337 [R(int)=0.1084]; number of observations [$I > 2\sigma(I)$]: 2232; parameters: 358. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 807081.

(12) (a) Curtis, E. A.; Sandanayaka, V. P.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 1989-1992. (b) Gould, N. P.; Lee, T.-J. *J. Org. Chem.* **1980**, *45*, 4530-4532.