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Generation of 1,3-Dimethylene-Substituted Isobenzofurans *via* Pd(II)-Catalyzed Selective *oxo*-Cyclization/SO_2 Insertion Cascade of *β*-Alkynyl Ketones

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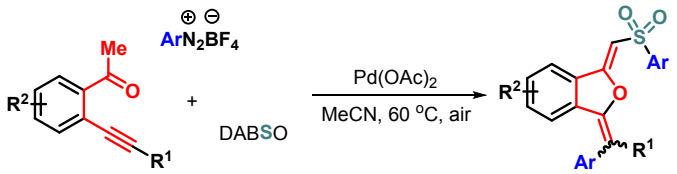


ABSTRACT. A new palladium(II)-catalyzed cyclization-radical addition cascade enables the direct construction of 1,3-dimethylene-substituted isobenzofuran derivatives containing vinyl aryl sulfone unit in good yields by treating with *β*-alkynyl ketones, aryl diazonium salts and DABCO·$(SO_2)_2$ (DABSO). The oxidant-free multicomponent reaction features good substrate scope and functional group tolerance, which proceeds through a sequence of by Heck coupling, *oxo*-cyclization and SO_2 insertion

Introduction

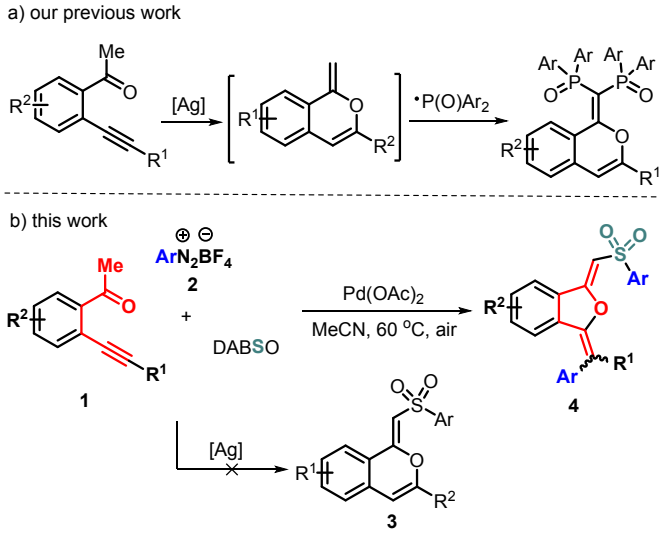
Isobenzofuran is a privileged oxygen-containing bicyclic motif that widely presents in a myriad of pharmaceuticals, chemicals and bioactive natural products as well as functional materials.[1]

Furthermore, such molecules could behave as key intermediates for the preparation of natural products as well as pharmaceutically important products.[2] Among the family of isobenzofurans, 1,3-disubstituted derivatives have been found to display a broad spectrum of extraordinary biologically and pharmaceutically properties, such as anti-inflammatory,[3] antihistaminic,[4] anti-HIV activity,[5] and act as farnesyl transferase inhibitor,[6] Accordingly, substantial effort has been paid for identifying powerful and reliable synthetic methodologies for the construction of isobenzofuran framework, especially with 1,3-disubstituted patterns. Generally, strategies for assembling1,3-disubstituted isobenzofurans include iodocyclization of 2-(1-alkynyl)benzylic alcohols,[7] radical-triggered cycloetherification,[8] nucleophilic epoxide ring-opening,[9] rhodium-catalyzed triazole denitrogenation,[10] oxo-Michael reaction of *o*-formyl chalcones,[11] 5-*exo-dig* oxo-cyclization of *β*-alkynyl ketones,[12] transition metal-catalyzed cyclization reactions of *o*-bromobenzyl alcohols,[13] and so on. Despite these significant achievements, synthetic approaches for installing 1,3-disubstituted isobenzofurans are still rather limited, thus requiring the development of new and efficient strategies for their syntheses.

Over the years, radical cyclization cascades have been emerged as a powerful tool toward cyclic molecule system in the organic community which have enabled previously inaccessible transformations.[14] Specifically, radical addition-cyclization cascades have been extensively investigated.[15] In sharp contrast, the studies on new reactivity modes of cyclization-radical additions are quite less and pose a particular challenge in the field of radical transformations due to the inherent difficulty of controlling radicals' behavior.[16] Recently, our group have established an attractive cyclization-radical addition cascade in which silver-mediated C(sp^3)-H biphosphinylation of *β*-alkynyl ketones was realized to access functionalized isochromenes through 6-*endo-dig*

cyclization/phosphinyl radical addition (Scheme 1a).[16a] In view of this successful transformation and recent findings on SO_2 insertion.[17] We envisaged that under silver-catalyzed conditions, *β*-alkynyl ketones **1** could procced through 6-*endo-dig* cyclization to generate methyleneisochromenes, trapped by sulfonyl radical from aryldiazonium tetrafluoroborates **2** and DABCO·$(SO_2)_2$ (DABSO), providing sulfonylated isochromenes **3**. Unluckily, this transformation did not work. Interestingly, changing the silver catalyst to palladium salt drove the reaction to furnish the unexpected sulfone-containing isobenzofurans **4** through 5-*exo-dig* cyclization/*S*-centered radical addition sequence. The current protocol represents the first palladium(II)-catalyzed *oxo*-cyclization/*S*-centered radical addition cascade together with SO_2 insertion for the stereoselective synthesis of 1,3-disubstituted isobenzofurans in generally good yields without additional oxidants. Herein, we elaborate this unprecedented and attractive multicomponent transformation of *β*-alkynyl ketones, which also provides a useful method for constructing vinyl aryl sulfone scaffold.

Scheme 1. Profiles of Cyclization-Radical Additions

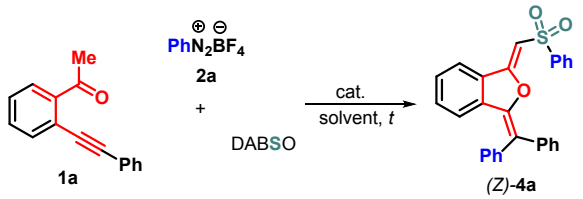


Results and Discussion

Initially, we commenced our investigation by mixing easily available *β*-alkynyl ketone **1a**, phenyldiazonium tetrafluoroborate (**2a**) and DABSO in 1:2.5:2 mole ratio at 50 °C with acetonitrile

(MeCN) as the solvent, catalyst, but the transformation did not proceed (Table 1, entry 1). AgTFA was employed as the silver catalyst to improve the transformation by taking advantage of our previous discovery, but a complex mixture was observed (entry 2). The use of $Cu(TFA)_2$ did not drive this transformation (entry 3). To our delight, the reaction worked well when $Pd(TFA)_2$ was added into the above system, and the unexpected sulfone-containing isobenzofuran **4a** was obtained in 61% yield, in which the geometry of the exocyclic olefin attached by sulfonyl group is the *Z*-configuration confirmed by the analogy of X-ray structure **4f**. Inspired by these satisfactory results, several others palladium salts such as $PdCl_2$, $Pd(dba)_2$ and $Pd(OAc)_2$ that are often employed in the catalytic transformations, were subsequently tested for this transformation (entries 5–7). The former two led to relatively lower conversions as compared with $Pd(TFA)_2$ (entries 5–6 vs 4) whereas the latter one showed the best catalytic performance in this transformation, affording higher yield of **4a** (75%, entry 7). Lowering the Pd-catalyst loading resulted in the remarkably dropped yield of **4a** (65%, entry 8). As the next optimization step, we conducted the screening of a variety of reaction media, such as 1,4-dioxane, tetrahydrofuran (THF), 1,2-dichloroethane (DCE), toluene, and *N,N*-dimethylformamide (DMF), for this cyclization-radical addition cascade by using $Pd(OAc)_2$ as the catalyst. The experimental results indicate that all these attempts did not show any improvements with respect to the obtainable yield of **3a** (entries 9-13). The reaction efficiency was proven to display an important temperature dependence. An increase of the temperature to 60 °C could accelerate the conversion into **4a** in the rising yield of 81% (entry 15), whereas the lower conversion was observed as the reaction was conducted at either room temperature or 70 °C (entries 14 and 16).

Table 1. Optimization of Reaction Conditions[a]



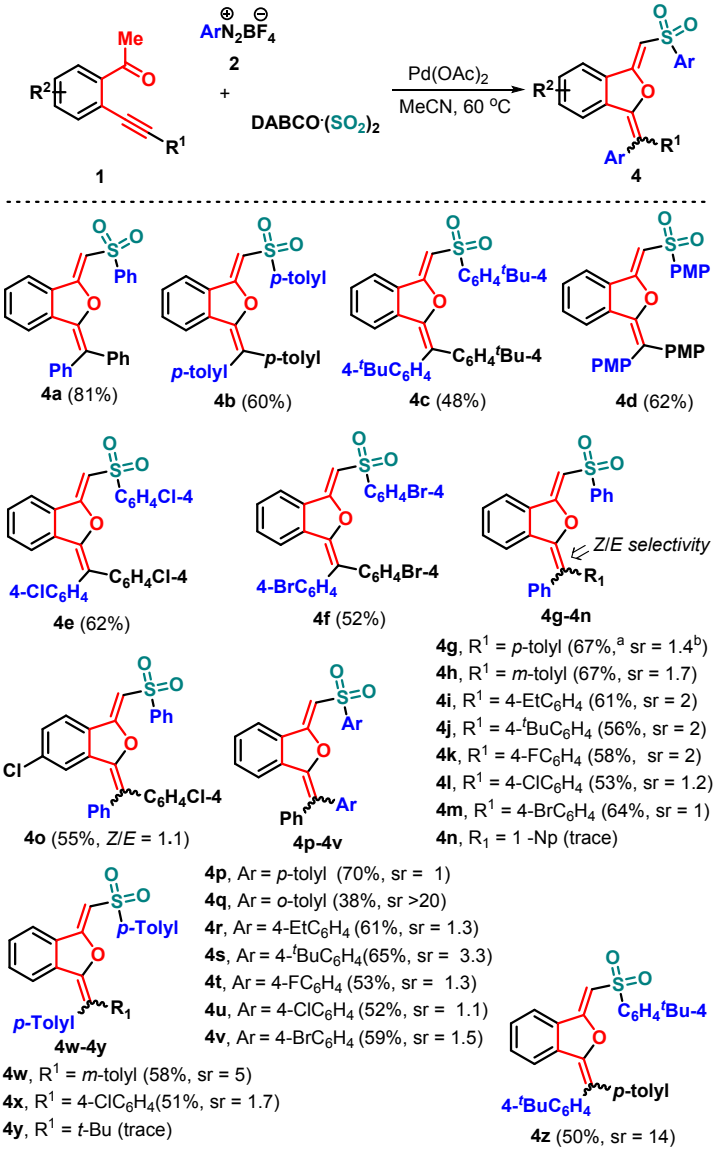
entry	cat (mol %)	solvent	temp (°C)	yield[b] (%)
1	-	MeCN	50	NR[c]
2	AgTFA (10)	MeCN	50	ND[d]
3	$Cu(TFA)_2$ (10)	MeCN	50	NR
4	$Pd(TFA)_2$ (10)	MeCN	50	61
5	$PdCl_2$ (10)	MeCN	50	54
6	$Pd(dba)_2$ (10)	MeCN	50	51
7	$Pd(OAc)_2$ (10)	MeCN	50	75
8	$Pd(OAc)_2$ (5)	MeCN	50	65
9	$Pd(OAc)_2$ (10)	1,4-dioxane	50	25
10	$Pd(OAc)_2$ (10)	THF	50	45
11	$Pd(OAc)_2$ (10)	DCE	50	ND
12	$Pd(OAc)_2$ (10)	toluene	50	NR
13	$Pd(OAc)_2$ (10)	DMF	50	ND
14	$Pd(OAc)_2$ (10)	MeCN	25	51
15	$Pd(OAc)_2$ (10)	MeCN	60	81
16	$Pd(OAc)_2$ (10)	MeCN	70	72

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), DABSO (0.4 mmol), catalyst, solvent (3.0 mL), under the air conditions, 6 h. [b]Isolated yield based on substrate **1a**. [c]No reaction (NR). [d]No detected (ND).

With the optimized conditions in hand, we sought to explore the scope and generality of this palladium(II)-catalyzed cyclization-radical addition for accessing functionalized isobenzofuran derivatives **4** (Scheme 2). Due to the products have two exocyclic alkene units, we first directed the *Z*-selectivity of exocyclic alkene associated with sulfonyl group by introducing two same aryl groups into the other exocyclic alkene unit. *β*-Alkynyl ketones **1** bearing aryl substituents at the alkynyl moiety were subjected to the reaction of substrates **2** having same aryl groups under the standard conditions, and the corresponding *Z*-products **4b-4f** were generated with acceptable yields and high stereoselectivity. Both electron-donating (*e.g.* methyl, *tert*-butyl and methoxy (*p*-methoxyphenyl = PMP) and electron-withdrawing (*e.g.* chloride and bromide) groups were proven to be compatible in the present cyclization-radical addition condition. Next, the different aryl substituents residing in substrates **1** and **2** were evaluated to explore the stereoselectivity of exocyclic alkene linked by two different aryl substituents. As expected, the reaction occurred readily to deliver the corresponding products **4g-4m**, **4p-4x** and **4z** in generally good yields but with very poor stereoselectivity except for **4q**. Electronic nature of substituents on both arylalkynyl (R^1) of substrates **1** and aryl (Ar) of substrates **2** moieties was also systematically investigated. Either electronically rich, neutral, or poor groups would be accommodated, confirming the success of this transformation, as the corresponding products **4** were generated in 35%-70% yields. Unluckily, *β*-alkynyl ketone having a 1-naphthyl (1-Np, **1j**) or *tert*-butyl (*t*-Bu, **1l**) group on the alkynyl moiety was not an appropriate candidate, as only a trace amount of products **4n** and **4y** were detected under the standard conditions, respectively (Scheme 2). Notably, *o*-tolyl diazonium tetrafluoroborate has been found to show the high stereoselectivity, albeit with a lower 38% yield (**4q**). The structures of these isobenzofuran derivatives **4** were characterized by their NMR spectroscopy and HRMS. In the

case of **4f**, its structure was unequivocally confirmed by carrying out single crystal X-ray diffraction (see Supporting Information).

Scheme 2. Substrate Scope for Synthesis of Products 4[a]

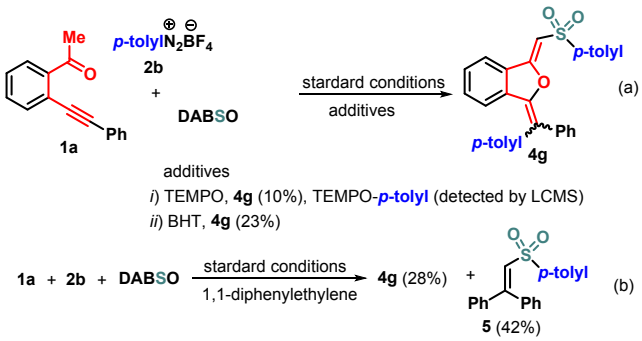


[a]Isolated total yields based on substrates **1**. [b]The stereoisomeric ratio (sr) value determined by its ^{1}H NMR analysis

To gain more mechanistic insight into this transformation, several control experiments were performed. When 3.0 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were subjected with the reaction of *β*-alkynyl ketone **1a** with DABSO and *p*-tolyldiazonium tetrafluoroborate **2b** under the standard conditions, the generation of the desired product **4g** was dramatically suppressed

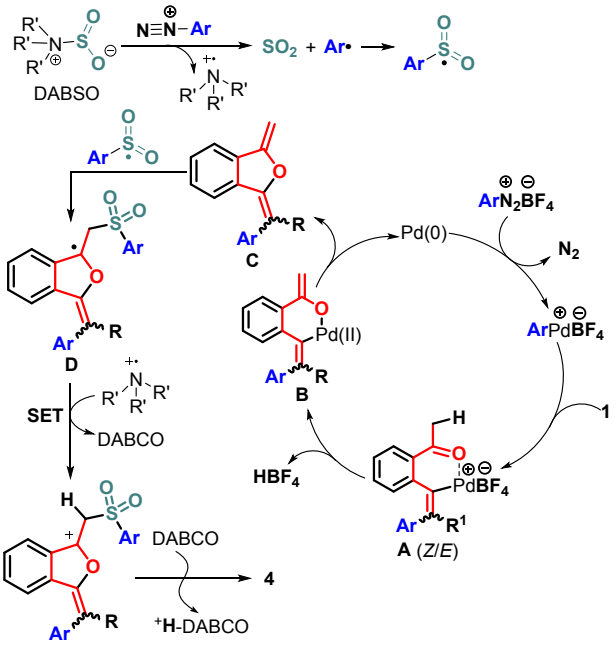
and only 10% yield of **4g** was obtained (Scheme 3a), in which a TEMPO–*p*-tolyl adduct was detected by LC–MS analysis. The presence of 3.0 equivalents of butylhydroxytoluene (BHT) lowered the yield of **4g** to 23%. These results indicate that the reaction might include a radical process. Then, 1,1-diphenylethylene was added into the above reaction system, and the product **4g** and (2-tosylethene-1,1-diyl)dibenzene **5** were isolated in 28% and 42% yields, respectively, suggesting that the transformation could involve the *in-situ*-generation of sulfonyl radicals from the combination of DABSO and aryldiazonium tetrafluoroborates (Scheme 3b).

Scheme 3. Control Experiments



On the basis of these mechanistic studies and related literature,[18] a plausible cyclization-radical addition process was proposed as depicted in Scheme 4. Initially, the oxidative addition of the active Pd(0) species, which is in situ generated from $PdCl_2$, to substrates **2** yields Pd(II) species,[17] which undergoes the addition to the carbon–carbon triple bond of **1** to give intermediate **A** with poor stereoselectivity. Intermediate **A** loses a proton to afford intermediate **B**, followed by reductive elimination to construct isobenzofuran intermediate **C** and regenerate the active Pd(0) species. Subsequently, the addition of *in-situ* generated sulfonyl radical from DABSO and aryldiazonium tetrafluoroborates into the alkene unit of **C** occurs, leading to radical intermediate **D** which is converted into the final products **4** through SET and deprotonation process.

Scheme 4. Plausible Reaction Pathways



In conclusion, we have illustrated the first palladium(II)-catalyzed cyclization-radical addition cascade of *β*-alkynyl ketones, enabling a multicomponent strategy to access 1,3-disubstituted isobenzofurans under mild and neutral redox conditions. The current protocol allows the direct formation of multiple chemical bonds including the C–S and C–O bonds in a single step through Heck-type addition, *oxo*-cyclization, and SO_2 insertion cascades. Importantly, the results broaden the scope and concept of transition-metal-catalyzed multicomponent reactions, and the significance of the isobenzofuran skeleton may make this radical strategy attractive for organic and medical syntheses, thereby offering a new potential entry for the preparation of other heterocyclic architectures. Further investigations on its mechanism and application are currently underway in our laboratories.

Experimental Section

General Information.

All melting points are uncorrected. The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 400 MHz instrument with TMS as internal standard. Chemical shifts (δ) were reported in ppm with respect to TMS. Data are represented as follows: chemical shift, mutiplicity (s = singlet, d = doublet, t = triplet,

m = multiplet), coupling constant (*J*, Hz) and integration. HRMS analyses were carried out using a TOF-MS instrument with an ESI source. X-ray crystallographic analysis was performed with a SMART CCD and a P4 diffractometer.

General Procedure for the Preparation of *β*-Alkynyl Ketones 1a−l (Known Compounds).

$PdCl_2(PPh_3)_2$ (2 mol%) and CuI (5 mol%) were added to a solution of 2-bromobenzaldehyde or 2-iodoacetophenone (5.0 mmol), phenylacetylene (6 mmol), and Et_3N (5 mL). The mixture was heated at 60 °C under N_2. The system was filtered by short silica, then the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography with petroleum to afford the desired products **1**.[19] Yields of the *β*-alkynyl ketones **1** are ranged from 78% to 90%

General Procedure for the Preparation of Aryldiazonium Salts 2a−k (Known Compounds).

Aniline **1** (10 mmol) was added to a mixture of 50% fluoroboric acid (3 mL) and distilled water (3 mL)

in ice bath. To this solution, an ice-cold solution of sodium nitrite (704 mg, 10.2 mmol) in distilled water (3 mL) was added. After stirring for 30 mins, the precipitate was collected on a hirch funnel and washed with small amount of ice-cold distilled water. The solid was dissolved in acetone and precipitated with slow addition of ethyl ether. White crystalline solids were obtained after repeat this trituration two to three times.[20] Yields of the aryldiazonium salts **2** are ranged from 70% to 88%.

General Procedure for the Synthesis of 4

*Example for the synthesis of **4a***

A mixture of 1-(2-(phenylethynyl)phenyl)ethanone (**1a**, 0.2 mmol, 44.0 mg), phenyldiazonium tetrafluoroborate (**2a**, 0.5 mmol, 96.2 mg), 1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct (DABSO) (**3**, 0.4 mmol, 96.2 mg), $Pd(OAc)_2$ (10 mol %, 4.5 mg) and 3.0 mL acetonitrile (MeCN) were added in a 10-mL reaction vial, which was sealed and heated at 60 °C for 6 h until TLC (petroleum ether: ethyl acetate= 5:1) revealed that conversion of the starting material **1a** was completed. Then the reaction mixture was concentrated by vacuum distillation and was purified by

flash column chromatography (silica gel, mixtures of petroleum ether / acetic ester, 15:1, v/v) to afford the desired pure products (**4a**, 70.6 mg, 81% yield) as yellow solid.

*Amplification Reaction for the Synthesis of **4a***

A mixture of **1a** (1.0 mmol, 220.0 mg), **2a** (2.5 mmol, 481 mg), DABSO (**3**, 2.0 mmol, 480 mg), $Pd(OAc)_2$ (10 mol %, 22.5 mg) and 8.0 mL acetonitrile (MeCN) were added in a 25-mL reaction vial, which was sealed and heated at 60 °C for 6 h. Then the reaction mixture was concentrated by vacuum distillation and was purified by flash column chromatography (silica gel, mixtures of petroleum ether / acetic ester, 15:1, v/v) to afford the desired pure products (**4a**, 331.4 mg, 76% yield) as yellow solid.

(Z)-1-(diphenylmethylene)-3-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4a)

70.6 mg, 81% yield; yellow solid, mp 217-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.07 (d, J = 7.6 Hz, 1H), 7.90-7.85 (m, 2H), 7.67-7.62 (m, 1H), 7.61-7.55 (m, 5H), 7.52-7.46 (m, 5H), 7.42 (d, J = 7.2 Hz, 1H), 7.39-7.32 (m, 3H), 7.01 (s, 1H), 6.08 (d, J = 8.0 Hz, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$; δ, ppm) 159.4, 147.9, 143.4, 137.7, 137.3, 134.1, 133.7, 132.8, 131.7, 130.7, 130.4, 130.2, 130.0, 129.6, 129.2, 128.7, 128.5, 127.0, 123.2, 122.1, 99.1. IR (KBr, ν, cm^{-1}). 3052, 1621, 1444, 1305, 1144, 1047, 760, 672. HR-MS (APCI) m/z calcd for $C_{28}H_{19}O_3S$ $[M-H]^-$ 435.1055, found 435.1061.

(Z)-1-(di-p-tolylmethylene)-3-(tosylmethylene)-1,3-dihydroisobenzofuran (4b)

57.4 mg, 60% yield; yellow solid, mp 231-232 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.82 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 5H), 7.19 (d, J = 8.0 Hz, 3H), 7.09 (d, J = 8.0 Hz, 2H), 6.33 (d, J = 8.0 Hz, 1H), 6.20 (s, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.34 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$; δ, ppm) 159.6, 147.5, 143.4, 140.4, 138.3, 138.0, 135.2, 134.9, 134.6, 131.7, 131.5, 130.5, 130.0, 129.5, 129.3, 129.0, 128.9, 128.8, 127.3, 123.5, 123.0, 121.2, 97.8, 21.6, 21.4(4), 21.4(6). IR (KBr, ν, cm^{-1}). 3087, 1618, 1458, 1310, 1141, 1044, 762, 669. HR-MS (APCI) m/z calcd for $C_{31}H_{25}O_3S$ $[M-H]^-$ 477.1524, found 477.1526.

(Z)-1-(bis(4-(tert-butyl)phenyl)methylene)-3-(((4-(tert-butyl)phenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4c)

58.0 mg, 48% yield; yellow solid, mp 236-237 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.86-7.82 (m, 2H), 7.68-7.64 (m, 2H), 7.54-7.47 (m, 5H), 7.30 (d, J = 7.2 Hz, 1H), 7.26-7.21 (m, 4H), 7.18-7.14 (m, 1H), 6.22 (s, 2H), 1.40 (s, 9H), 1.39 (s, 9H), 1.26 (s, 9H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$; δ, ppm) 159.6, 156.3, 151.6, 151.1, 147.6, 140.1, 135.1, 134.9, 134.5, 131.7, 131.6, 130.2, 130.2, 128.9, 127.2, 126.0, 125.7, 125.6, 125.1, 123.6, 122.9, 121.2, 97.9, 35.0, 34.8, 34.8, 31.4(3), 31.4(8), 31.1. IR (KBr, ν, cm^{-1}). 3047, 1621, 1438, 1306, 1141, 1044, 761, 671. HR-MS (APCI) m/z calcd for $C_{40}H_{43}O_3S$ $[M-H]^-$ 603.2933, found 603.2940.

(Z)-1-(bis(4-methoxyphenyl)methylene)-3-(((4-methoxyphenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4d)

65.2 mg, 62% yield; yellow solid, mp 192-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.92-7.88 (m, 2H), 7.70-7.67 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.29 (s, 1H), 7.23-7.20 (m, 2H), 7.19-7.16 (m, 1H), 7.01 (d, J = 8.4 Hz, 4H), 6.78-6.76 (m, 2H), 6.33 (d, J = 8.0 Hz, 1H), 6.20 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$; δ, ppm) 158.3, 155.0, 154.7, 154.7, 142.3, 130.5, 130.2, 127.3, 127.2, 126.9, 126.6, 126.0, 125.1, 124.6, 124.0, 118.6, 117.5, 116.4, 109.9, 109.1, 108.8, 93.1, 50.8, 50.7, 50.6. IR (KBr, ν, cm^{-1}). 3062, 1616, 1445, 1307, 1139, 1047, 758, 689. HR-MS (APCI) m/z calcd for $C_{31}H_{25}O_6S$ $[M-H]^-$ 525.1372, found 525.1369.

(Z)-1-(bis(4-chlorophenyl)methylene)-3-(((4-chlorophenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4e)

66.9 mg, 62% yield; yellow solid, mp 233-234 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.82-7.79 (m, 2H), 7.60-7.54 (m, 3H), 7.51-7.45 (m, 4H), 7.40 (d, J = 7.2 Hz, 1H), 7.30-7.26 (m, 5H), 6.43 (d, J = 8.0 Hz, 1H), 6.24 (s, 1H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$; δ, ppm) 159.6, 148.2, 141.4, 139.4, 135.9, 135.4, 135.0, 134.3, 134.1, 132.3, 132.1, 131.7, 131.6, 129.8(0), 129.8(6), 129.0, 128.6, 128.5, 123.5, 121.6, 120.5, 98.2. IR (KBr, ν, cm^{-1}). 3083, 1618, 1455,1318, 1142, 1044, 763, 690. HR-MS (APCI) m/z calcd for $C_{28}H_{16}Cl_3O_3S$ $[M-H]^-$ 536.9886, found 536.9887.

(Z)-1-(bis(4-bromophenyl)methylene)-3-(((4-bromophenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4f)

70.1 mg, 52% yield; yellow solid, mp 243-244 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.07 (d, J = 7.6 Hz, 1H), 7.80-7.73 (m, 6H), 7.70-7.66 (m, 2H), 7.55-7.50 (m, 1H), 7.49-7.42 (m, 3H), 7.38-7.34 (m, 2H), 7.05 (s, 1H), 6.29 (d, J = 8.0 Hz, 1H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6; δ, ppm) 159. 5, 148. 3, 142.6, 136.7, 136.1, 133.7, 133.2, 133.1, 132.8, 132.2, 131.9, 131.7, 130.8, 128.9, 127.7, 123.4, 123.2, 122.9, 121.9, 119.7, 98.9. IR (KBr, ν, cm^{-1}). 3089, 1618, 1472, 1307, 1141, 1044, 763, 689. HR-MS (APCI) m/z calcd for $C_{28}H_{16}Br_3O_3S$ [M-H]$^-$ 670.8350, found 670.8355.

(3Z)-1-(phenyl(p-tolyl)methylene)-3-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4g)

60.3 mg, 67% yield; yellow solid, mp 195-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.05 (d, J = 7.6 Hz, 1H), 7.93-7.90 (m, 2H), 7.58-7.54 (m, 5H), 7.50-7.47 (m, 4H), 7.36-7.33 (m, 3H), 7.29 (d, J = 8.0 Hz, 2H), 6.98 (s, 1H), 6.03 (d, J = 8.0 Hz, 1H), 2.39 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$; δ, ppm) 159.5, 147.5, 143.5, 138.1, 137.4, 134.8, 134.2, 133.7, 132.8, 131.5, 130.7, 130.6, 130.2, 130.0, 129.6, 129.3, 128.6, 126.9, 123.2, 122.2, 98.7, 21.3. IR (KBr, ν, cm^{-1}). 3065, 1616, 1444, 1309, 1138, 1048, 759, 688. HR-MS (APCI) m/z calcd for $C_{29}H_{21}O_3S$ [M-H]$^-$ 449.1211, found 449.1217.

(3Z)-1-(phenyl(m-tolyl)methylene)-3-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4h)

60.3 mg, 67% yield; yellow solid, mp 185-186 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.05 (d, J = 7.6 Hz, 1H), 7.87-7.84 (m, 2H), 7.72 (s, 1H), 7.58-7.55 (m, 3H), 7.49-7.46 (m, 4H), 7.39-7.35 (m, 4H), 7.24 (s, 1H), 7.18 (s, 1H), 6.98 (s, 1H), 6.07 (d, J = 8.0 Hz, 1H), 2.40 (s, 3H). ^{13}C{1H} NMR (100 MHz, $CDCl_3$; δ, ppm) 159.4, 147.8, 143.6, 137.8, 137.6, 137.3, 134.1, 133.7, 132.8, 131.6, 130.9, 130.7, 130.2, 130.0, 129.6, 129.2, 128.7, 128.5, 127.3, 126.9, 126.8, 123.2, 122.3, 99.0, 21.6. IR (KBr, ν, cm^{-1}). 3058, 1611, 1444, 1308, 1141, 1408, 763, 687. HR-MS (APCI) m/z calcd for $C_{29}H_{21}O_3S$ [M-H]$^-$ 449.1211, found 449.1209.

(3Z)-1-((4-ethylphenyl)(phenyl)methylene)-3-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4i)

56.6 mg, 61% yield; yellow solid, mp 181-182 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.04 (s, 1H), 7.93-7.89 (m, 2H), 7.57-7.55 (m, 3H), 7.52-7.48 (m, 5H), 7.38-7.31 (m, 6H), 6.98 (s, 1H), 6.04 (d, J = 8.0 Hz, 1H), 2.71-2.66 (m, 2H), 1.28 (t, J = 6.8 Hz, 2H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6; δ, ppm) 159.5, 147.5, 144.4, 143.5, 137.4, 135.1, 134.2, 133.7, 132.8, 131.5, 130.7, 130.3, 130.0, 129.6, 129.3, 128.6, 128.1, 127.0, 123.2, 122.2, 98.8, 28.4, 16.1. IR (KBr, ν, cm^{-1}). 3081, 1620, 1445, 1309, 1141, 1047, 759, 688. HR-MS (APCI) m/z calcd for $C_{30}H_{23}O_3S$ [M-H]$^-$ 463.1368, found 463.1372.

(3Z)-1-((4-(tert-butyl)phenyl)(phenyl)methylene)-3-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4j)

55.1 mg, 56% yield; yellow solid, mp 194-195 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.06 (d, J = 7.6 Hz, 1H), 7.89 (m, 2H), 7.57-7.54 (m, 5H), 7.50-7.45 (m, 5H), 7.36-7.32 (m, 3H), 7.27 (d, J = 8.0 Hz, 1H), 7.00 (s, 1H), 6.04 (d, J = 8.0 Hz, 1H), 1.34 (s, 9H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6; δ, ppm) 159.5, 151.2, 147. 6, 143.4, 137.3, 134.8, 134.2, 133.7, 132.8, 131.5, 130.7, 130.3, 130.1, 129.9, 129.5, 129.2, 128.7, 127.0, 126.6, 125.4, 123.2, 123.1, 122.1, 98.9, 34.9, 31.5.IR (KBr, ν, cm^{-1}). 3079, 1617, 1445, 1307, 1140, 1046, 760, 670. HR-MS (APCI) m/z calcd for $C_{32}H_{27}O_3S$ [M-H]$^-$ 491.1681, found 491.1685.

(3Z)-1-((4-fluorophenyl)(phenyl)methylene)-3-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4k)

52.7 mg, 58% yield; yellow solid, mp 211-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.06 (d, J = 8.0 Hz, 1H), 7.92-7.88 (m, 2H), 7.60-7.54 (m, 6H), 7.50-7.46 (m, 3H), 7.44-7.40 (m, 3H), 7.35-7.32 (m, 2H), 7.03 (s, 1H), 6.05 (d, J = 8.0 Hz, 1H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6; δ, ppm) 162.4 ($^1J_{CF}$ = 247.9 Hz), 148.1, 142.9, 137.3, 134.4, 133.4 ($^4J_{CF}$ = 3.5 Hz), 132.8 ($^3J_{CF}$ = 7.5 Hz), 132.4, 132.3, 132.0, 131.7, 131.5, 130.4, 129.4, 129.3, 128.8, 128.3, 127.3, 123.6, 123.4, 121.8, 121.5, 115.1 ($^2J_{CF}$ = 21.2 Hz), 98.3. IR (KBr, ν, cm^{-1}). 3045, 1620, 1446, 1307, 1144, 1047, 760, 667. HR-MS (APCI) m/z calcd for $C_{28}H_{18}FO_3S$ [M-H]$^-$ 453.0961, found 453.0962.

(3Z)-1-((4-chlorophenyl)(phenyl)methylene)-3-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4l)

49.8 mg, 53% yield; yellow solid, mp 218-219 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.06 (d, J = 7.6 Hz, 1H), 7.92-7.88 (m, 2H), 7.60-7.53 (m, 9H), 7.51-7.46 (m, 5H), 7.03 (s, 1H), 6.06 (d, J = 8.0 Hz, 1H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6; δ, ppm) 159.2, 148.3, 143.4, 136.8, 136.6, 133.9, 133.7, 133.0, 132.9, 132.7, 131.9, 131.8, 130.7, 130.3, 130.1, 129.7, 129.4, 128.7, 128.6, 126.9, 123.3, 123.1, 120.6, 99.3. IR (KBr, ν, cm^{-1}). 3057, 1619, 1444, 1310, 1143, 1047, 761, 687. HR-MS (APCI) m/z calcd for $C_{28}H_{18}ClO_3S$ [M-H]$^-$ 469.0665, found 469.0666.

(3Z)-1-((4-bromophenyl)(phenyl)methylene)-3-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4m)

66.0 mg, 64% yield; yellow solid, mp 193-194 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.06 (d, J = 8.0 Hz, 1H), 7.92-7.87 (m, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.59-7.53 (m, 8H), 7.38-7.33 (m, 4H), 7.01 (s, 1H), 6.07 (d, J = 8.0 Hz, 1H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6; δ, ppm) 159.3, 147.9, 143.4, 137.5, 136.8, 133.9, 133.8, 133.0, 132.9, 132.2, 131.6, 130.8, 130.3, 129.7, 129.6, 123.3, 123.2, 122.7, 120.9, 99.4. IR (KBr, ν, cm^{-1}). 3063, 1616, 1444, 1307, 1142, 1046, 759, 689. HR-MS (APCI) m/z calcd for $C_{28}H_{18}BrO_3S$ [M-H]$^-$ 513.0160, found 513.0162.

(3Z)-5-chloro-3-((4-chlorophenyl)(phenyl)methylene)-1-((phenylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4o)

55.4 mg, 55% yield; yellow solid, mp 214-215 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.25 (d, J = 2.0 Hz, 1H), 7.91-7.87 (m, 2H), 7.61-7.55 (m, 7H), 7.53-7.47 (m, 6H), 7.11 (s, 1H), 6.01 (d, J = 8.6 Hz, 1H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6; δ, ppm) 158.0, 147.4, 143.2, 137.4, 136.6, 136.4, 136.0, 135.2, 133.9, 133.6, 133.2, 131.9, 130.3, 130.2, 129.8, 128.7, 126.9, 124.7, 123.1, 121.1, 100.4. IR (KBr, ν, cm^{-1}). 3074, 1615,1445, 1308, 1144, 1044, 763, 668. HR-MS (APCI) m/z calcd for $C_{28}H_{17}Cl_2O_3S$ [M-H]$^-$ 503.0275, found 503.0278.

(3Z)-1-(phenyl(p-tolyl)methylene)-3-(tosylmethylene)-1,3-dihydroisobenzofuran (4p)

65.0 mg, 70% yield; yellow solid, mp 191-192 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.03 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.38-7.33 (m, 6H), 7.31-7.23 (m, 7H), 6.95 (s, 1H), 6.21 (d, J = 8.0 Hz, 1H), 2.43 (s, 3H), 2.34 (s, 3H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6; δ, ppm) 159.5, 151.2,

147.6, 143.4, 137.3, 134.8, 134.2, 133.7, 132.8, 131.5, 130.7, 130.3, 130.1, 129.9, 129.5, 129.2, 128.7, 127.0, 126.6, 125.4, 123.2, 123.1, 122.1, 98.9, 34.9, 31.5. IR (KBr, ν, cm^{-1}). 3051, 1618, 1443, 1310, 1141, 1045, 761, 668. HR-MS (APCI) m/z calcd for $C_{30}H_{23}O_3S$ $[M-H]^-$ 463.1368, found 463.1367.

(3Z)-1-(phenyl(o-tolyl)methylene)-3-((o-tolylsulfonyl)methylene)-1,3-dihydroisobenzofuran (4q)

35.3 mg, 38% yield; yellow solid, mp 186-187 °C; ^1H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.15 (d, J = 8.0 Hz, 1H), 8.09-8.06 (m, 1H), 7.61-7.57 (m, 2H), 7.53-7.44 (m, 6H), 7.40 (m, 3H), 7.42-7.37 (m, 3H), 7.12 (s, 1H), 5.82 (d, J = 8.0 Hz, 1H), 2.66 (s, 3H), 1.97 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6; δ, ppm) 159.5, 147.8, 141.2, 137.4, 137.3, 136.4, 136.3, 134.2, 133.7, 133.1, 133.0, 131.6, 131.4, 131.0, 130.4, 129.8, 129.5, 128.8, 128.5, 128.4, 127.6, 126.4, 123.3, 122.8, 120.5, 98.5, 20.3, 19.4. IR (KBr, ν, cm^{-1}). 3062, 1613, 1446, 1299, 1146, 1045, 762, 669. HR-MS (APCI) m/z calcd for $C_{30}H_{23}O_3S$ $[M-H]^-$ 463.1368, found 463.1371.

(3Z)-1-((4-ethylphenyl)(phenyl)methylene)-3-(((4-ethylphenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4r)

60.0 mg, 61% yield; yellow solid, mp 175-176 °C; ^1H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.03 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.61- 7.53 (m, 7H), 7.35-7.31 (m, 6H), 6.95 (s, 1H), 6.16 (d, J = 8.0 Hz, 1H), 2.67-2.61 (m, 4H), 1.27 (m, 6H). $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6; δ, ppm) 159.2, 150.1, 147.9, 144.8, 141.0, 137.9, 137.4, 135.1, 134.6, 134.12, 132.8, 131.7, 130.7, 130.3, 130.0, 129.3, 128.6, 127.1, 123.1, 122.1, 99.3, 28.5, 28.4, 15.9, 15.6. IR (KBr, ν, cm^{-1}). 3062, 1611, 1455, 1308, 1145, 1043, 762, 688. HR-MS (APCI) m/z calcd for $C_{32}H_{27}O_3S$ $[M-H]^-$ 491.1681, found 491.1685.

(3Z)-1-((4-(tert-butyl)phenyl)(phenyl)methylene)-3-(((4-(tert-butyl)phenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4s)

71.2 mg, 65% yield; yellow solid, mp 237-238 °C; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.81 (d, J = 8.4 Hz, 2H), 7.71-7.68 (m, 2H), 7.51-7.47 (m, 5H), 7.31- 7.26 (m, 4H), 7.25-7.23 (m, 2H), 7.19-7.16 (m, 1H), 6.29 (d, J = 8.0 Hz, 1H), 6.23 (s, 1H), 1.40 (s, 9H), 1.27 (s, 9H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 154.8, 151.6, 147.0, 142.9, 135.3, 132.9, 130.1, 129.7, 127.0, 125.9, 125.4, 124.5, 124.3, 123.7,

123.4, 122.4, 121.3, 120.8, 120.4, 118.8, 118.0, 116.5, 93.3, 26.6, 26.3. IR (KBr, ν, cm^{-1}). 3089, 1619, 1456, 1306, 1146, 1048, 762, 669. HR-MS (APCI) m/z calcd for $C_{36}H_{35}O_3S$ $[M-H]^-$ 547.2307, found 547.2312.

(3Z)-1-((4-fluorophenyl)(phenyl)methylene)-3-(((4-fluorophenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4t)

50.0 mg, 53% yield; yellow solid, mp 203-204 °C; ^1H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.05 (d, J = 8.0 Hz, 1H), 7.97-7.92 (m, 2H), 7.63-7.61 (m, 1H), 7.59-7.55 (m, 5H), 7.45-7.41 (m, 4H), 7.36-7.33 (m, 3H), 7.02 (s, 1H), 6.07 (d, J = 8.0 Hz, 1H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 165.1 ($^1J_{CF}$ = 252.9 Hz), 162.6 ($^2J_{CF}$ = 248.2 Hz), 159.7, 148.0, 138.9 ($^8J_{CF}$ = 3.0 Hz), 137.1, 134.3, 133.8 ($^7J_{CF}$ = 3.3 Hz), 132.4 ($^6J_{CF}$ = 8.0 Hz), 132.05, 131.6, 130.4, 129.8 ($^5J_{CF}$ = 9.4 Hz), 129.4, 128.3, 123.4, 122.0, 121.4, 116.4 ($^3J_{CF}$ = 21.4 Hz), 115.2 ($^4J_{CF}$ = 21.2 Hz), 97.9. IR (KBr, ν, cm^{-1}). 3073, 1621, 1444, 1315, 1156, 1046, 762, 668. HR-MS (APCI) m/z calcd for $C_{28}H_{17}F_2O_3S$ $[M-H]^-$ 471.0866, found 471.0869.

(3Z)-1-((4-chlorophenyl)(phenyl)methylene)-3-(((4-chlorophenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4u)

52.4 mg, 52% yield; yellow solid, mp 190-191 °C; ^1H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.06 (d, J = 7.6 Hz, 1H), 7.90-7.87 (m, 2H), 7.65-7.56 (m, 9H), 7.45-7.39 (m, 4H), 7.04 (s, 1H), 6.08 (d, J = 8.0 Hz, 1H). $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6; δ, ppm) 159.6, 148.3, 148.0, 142.3, 138.6, 136.8, 136.6, 133.2, 133.1, 133.0, 132.7, 131.9, 130.7, 130.3, 130.1, 129.9, 129.7, 128.8, 128.7, 123.4, 123.3, 120.8, 98.8. IR (KBr, ν, cm^{-1}). 3089, 1617, 1473, 1321, 1145, 1046, 762, 693. HR-MS (APCI) m/z calcd for $C_{28}H_{17}Cl_2O_3S$ $[M-H]^-$ 503.0275, found 503.0280.

(3Z)-1-((4-bromophenyl)(phenyl)methylene)-3-(((4-bromophenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4v)

70.1 mg, 59% yield; yellow solid, mp 206-207 °C;^1H NMR (400 MHz, DMSO-d_6; δ, ppm) 8.07 (d, J = 8.0 Hz, 1H), 7.82-7.72 (m, 7H), 7.59-7.56 (m, 2H), 7.53-7.49 (m, 6H), 7.02 (s, 1H), 6.32 (d, J = 8.0 Hz, 1H). $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6; δ, ppm) 159.7, 148.0, 142.7, 137.6, 136.8, 136.6, 133.8, 133.0, 132.8, 132.6, 132.1, 131.7, 130.7, 130.6, 130.3, 130.1, 129.0, 128.8, 127.6, 123.4, 122.7, 121.8,

121.2, 98.7. IR (KBr, ν, cm^{-1}). 3089, 1618, 1472, 1307, 1141, 1044, 763, 689. HR-MS (APCI) m/z calcd for $C_{28}H_{17}Br_2O_3S$ $[M-H]^-$ 592.9245, found 592.9248.

(3Z)-1-(m-tolyl(p-tolyl)methylene)-3-(tosylmethylene)-1,3-dihydroisobenzofuran (4w)

55.4 mg, 58% yield; yellow solid, mp 246-247 °C; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.83 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.33-7.27 (m, 5H), 7.22-7.15 (m, 2H), 7.13-7.09 (m, 3H), 6.25 (d, J = 8.4 Hz, 1H), 6.21 (s, 1H), 2.43 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6; δ, ppm) 154.9, 142.7, 138.7, 135.7, 134.3, 133.3, 132.7, 130.2, 130.1, 127.0, 126.8, 126.4, 125.7, 124.6, 124.4, 124.3, 124.2, 124.1, 122.9, 122.5, 118.8, 118.3, 116.5, 93.1, 16.8, 16.7, 16.6. IR (KBr, ν, cm^{-1}). 3083, 1619, 1455, 1320, 1141, 1048, 766, 687. HR-MS (APCI) m/z calcd for $C_{31}H_{25}O_3S$ $[M-H]^-$ 477.1524, found 477.1529.

(3Z)-1-((4-chlorophenyl)(p-tolyl)methylene)-3-(tosylmethylene)-1,3-dihydroisobenzofuran (4x)

50.8 mg, 51% yield; yellow solid, mp 233-234 °C; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.82 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.44-7.41 (m, 2H), 7.31-7.28 (m, 4H), 7.19-7.13 (m, 4H), 6.32 (d, J = 8.0 Hz, 1H), 6.23 (s, 1H), 2.47 (s, 3H), 2.36 (s, 3H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 159.3, 148.1, 143.7, 140.3, 138.7, 136.4, 134.6, 134.0, 132.2, 131.8(3), 131.7(8), 130.5, 130.4, 130.1, 129.5, 129.4, 129.3, 129.0, 128.3, 127.3, 127.1, 123.7, 121.4, 121.3, 98.4, 21.6, 21.4. IR (KBr, ν, cm^{-1}). 3088, 1619, 1473, 1311, 1141, 1043, 763, 668. HR-MS (APCI) m/z calcd for $C_{30}H_{22}ClO_3S$ $[M-H]^-$ 497.0978, found 497.0979.

(3Z)-1-((4-(tert-butyl)phenyl)(p-tolyl)methylene)-3-(((4-(tert-butyl)phenyl)sulfonyl)methylene)-1,3-dihydroisobenzofuran (4z)

56.2 mg, 50% yield; yellow solid, mp 208-209 °C; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.85 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H),7.54-7.45(m, 4H), 7.31-7.28 (m, 4H), 7.24-7.21 (m, 2H), 7.18-7.14 (m, 1H), 6.23 (d, J = 8.0 Hz, 1H), 6.20 (s, 1H), 2.43 (s, 3H), 1.40 (s, 9H), 1.27 (s, 9H). $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$; δ, ppm) 159.6, 156.3, 151.2, 147.6, 140.1, 138.3, 135.1, 134.9, 134.6, 131.7, 130.4, 130.2, 129.9, 128.9, 127.2, 127.1, 126.0, 125.7, 125.6, 125.1, 123.6, 122.8, 121.2, 97.9, 34.8, 31.1, 21. 4. IR

(KBr, ν, cm^{-1}). 2960, 1617, 1457, 1315, 1146, 1048, 762, 688. HR-MS (APCI) m/z calcd for $C_{37}H_{37}O_3S$ $[M-H]^-$ 561.2463, found 561.2466.

ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for all pure products, and X-ray crystal data (CIF) for **4f**. This material is available free of charge via the Internet at http//pubs.acs.org.

Notes

The authors declare no competing financial interest.

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REFERENCES

[1] (a) Harper, J. K.; Arif, A. M.; Ford, E. J.; Strobel, G. A.; Porco, J. A.; Tomer, D. P.; Oneill, K. L.; Heider, E. M.; Grant, D. M. Pestacin: a 1,3-dihydro isobenzofuran from *Pestalotiopsis microspora* possessing antioxidant and antimycotic activities. *Tetrahedron* **2003**, *59*, 2471-2476. (b) Moore, N.; Verdoux, H.; Fantino, B. Prospective, multicentre, randomized, double-blind study of the efficacy of escitalopram versus citalopram in outpatient treatment of major depressive disorder. *Int. Clin. Psychopharmacol.* **2005**, *20*, 131-137. (c) Kwon, Y. J.; M. J. Sohn, C. J. Kim, H. Koshino, W. G. Kim, Flavimycins A and B, Dimeric 1,3-Dihydroisobenzofurans with Peptide Deformylase Inhibitory Activity from Aspergillus flavipes. *J. Nat. Prod.* **2012**, *75*, 271-274. (d) Abdelfattah, M. S.; Arai, M. A.; Ishibashi, M. Bioactive Secondary Metabolites with Unique Aromatic and Heterocyclic Structures Obtained from Terrestrial Actinomycetes Species. *Chem. Pharm. Bull.* **2016**, *64*, 668-675. (e) Peters, M. K.; Herges, R. Preparation and isolation of isobenzofuran. *Beilstein J. Org. Chem.* **2017**, *13*, 2659-2662.

[2] (a) Snieckus, V. Directed Ortho Metalation. Tertiary Amide and O-Carbamate Directors in Synthetic Strategies for Polysubstituted Aromaticst. *Chem. Rev.* **1990**, *90*, 879-933. (b) Mal, D.; Pahari, P. Recent Advances in the Hauser Annulation. *Chem. Rev.* **2007**, *107*, 1892-1918. (c) Karmakar, R.; Pahari, P.; Mal, D. Phthalides and Phthalans: Synthetic Methodologies and Their Applications in the Total Synthesis. *Chem. Rev.* **2014**, *114*, 6213-6284. (d) Donner, C. D. Tandem Michael-Dieckmann/Claisen reaction of ortho-toluates-the Staunton-Weinreb annulation. *Tetrahedron* **2013**, *69*, 3747-3773. (e) Hernández, E.; Vélez, J. M.; Vlaar, C. P. Synthesis of 1, 4-dihydro-benzo[*d*][1,3]oxazin-2-ones from phthalides via an aminolysis-Hofmann rearrangement protocol. *Tetrahedron Lett.* **2007**, *48*, 8972-8975. (f) Rathwell, K.; Brimble, M. A. Use of stabilized phthalide anion annulation reactions in synthesis: an update. *Synthesis* **2007**, *2007*, 643-662.

[3] (a) Goezler, B.; Goezler, T.; Shamma, M. Egenine: a possible intermediate in phthalideisoquinoline biogenesis. *Tetrahedron* **1983**, *39*, 577-580. (b) Jing, L.; Wenzao, L.; Guoshi, T. Two phthalideisoquinoline hemiacetal alkaloids from Corydalis decumbens. *Planta Med.* **1994**, *60*, 486-487.

[4] Coote, S. J.; Davies, S. G. Stereoselective synthesis of *cis*-1,3-disubstituted 1,3-dihydroisobenzofurans via arenechromium tricarbonyl methodology. *J. Organomet. Chem.* **1989**, *379*, 81-88.

[5] Len, C.; Selouane, A.; Postel, D.; Villa, P.; Aubertin, A. M.; Egron, D.; Gosselin, G.; Périgaud. C. Synthesis, Stability, and Biological Evaluation of 1,3-Dihydrobenzo[*c*]furan Analogue of d4T and Its SATE Pronucleotide. *Nucleosides, Nucleotides Nucleic Acids* **2003**, *22*, 943-945.

[6] Martin, C.; Mailliet, P.; Maddaluno, J. Synthesis of Oxa-Bridged Analogues of Farnesyltransferase Inhibitor RPR 115135. *J. Org. Chem.* **2001**, *66*, 3797-3805.

[7] Mancuso, R.; Mehta, S.; Gabriele, B.; Salerno, G.; Jenks, W. S.; Larock, R. C. A Simple and Mild Synthesis of 1*H*-Isochromenes and (*Z*)-1-Alkylidene-1,3-dihydroisobenzofurans by the Iodocyclization of 2-(1-Alkynyl)benzylic Alcohols. *J. Org. Chem.* **2010**, *75*, 897-901.

[8] (a) Sha, W.; Ni, S.; Han, J.; Pan, Y. Access to Alkyl-Substituted Lactone via Photoredox-Catalyzed Alkylation/Lactonization of Unsaturated Carboxylic Acids. *Org. Lett.* **2017**, *19*, 5900-5903. (b) Sha, W.; Zhang, W.;

Ni, S.; Mei, H.; Han, J.; Pan, Y. Photoredox-Catalyzed Cascade Difluoroalkylation and Intramolecular Cyclization for Construction of Fluorinated γ-Butyrolactones. *J. Org. Chem.* **2017**, *82*, 9824-9831.

[9] Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone. A. Synthesis of 1,3-Dihydrobenzo[c]furans from Ortho-Lithiated Aryloxiranes. *J. Org. Chem.* **2006**, *71*, 3984-3987.

[10] (a) Shen, H.; Fu, J.; Gong, J.; Yang, Z. Tunable and Chemoselective Syntheses of Dihydroisobenzofuransand Indanones via Rhodium-Catalyzed Tandem Reactions of 2-Triazole-benzaldehydes and 2-Triazole-alkylaryl Ketones. *Org. Lett.* **2014**, *16*, 5588-5591. (b) Yuan, H.; Gong, J.; Yang, Z. Stereoselective Synthesis of Oxabicyclo[2.2.1]heptenes via a Tandem Dirhodium(II)-Catalyzed Triazole Denitrogenation and [3 + 2] Cycloaddition. *Org. Lett.* **2016**, *18*, 5500-5503.

[11] (a) Maity, S.; Saha, M.; Hazra, G.; Ghorai, P. Switchable Chemoselectivity for Organocatalytic, Asymmetric Malononitrile Addition to ortho-Formyl Chalcones. *Org. Lett.* **2017**, *19*, 5872-5875. (b) Yang, X.; Pang, S.; Cheng, F.; Zhang, Y.; Lin, Y.-W.; Yuan, Q.; Zhang, F.-L.; Huang, Y.-Y. Enantioselective Synthesis of 1,3-Disubstituted 1,3-Dihydroisobenzofurans via a Cascade Allylboration/Oxo-Michael Reaction of o-Formyl Chalcones Catalyzed by a Chiral Phosphoric Acid. *J. Org. Chem.* **2017**, *82*, 10388-10397.

[12] (a) Bantreil, X.; Bourderioux, A.; Mateo, P.; Hagerman, C. E.; Selkti, M.; Brachet, E.; Belmont, P. Phosphine-Triggered Selectivity Switch in Silver-Catalyzed *o*-Alkynylbenzohydroxamic Acid Cycloisomerizations. *Org. Lett.* **2016**, *18*, 4814-4817. (b) Mehta, S.; Yao, T.; Larock, R. C. Regio- and Stereoselective Synthesis of Cyclic Imidates via Electrophilic Cyclization of 2-(1-Alkynyl)benzamides. A Correction. *J. Org. Chem.* **2012**, *77*, 10938-10944. (c) Jithunsa, M.; Ueda, M.; Miyata, O. Copper(II) Chloride-Mediated Cyclization Reaction of *N*-Alkoxy-ortho-alkynylbenzamides. *Org. Lett.* **2011**, *13*, 518-521. (d) Sekine, K.; Takayanagi, A.; Kikuchi, S.; Yamada, T. Silver-catalyzed C-C bond formation with carbon dioxide: significant synthesis of dihydroisobenzofurans. *Chem. Commun.* **2013**, *49*, 11320-11322. (e) Zhang, W.-Z.; Yang, M.-W.; Yang, X.-T.; Shi, L.-L.; Wang, H.-B.; Lu, X.-B. Double carboxylation of *o*-alkynyl acetophenone with carbon dioxide. *Org. Chem. Front.* **2016**, *3*, 217-221.

[13] (a) Mahendar, L.; Satyanarayana, G. Domino [Pd]-Catalysis: One-Pot Synthesis of Isobenzofuran-1(3H)-ones. *J. Org. Chem.* **2016**, *81*, 7685-7691. (b) Mahendar, L.; Satyanarayana, G. Domino One-Pot Process for the Synthesis of Isobenzofuran-1(3*H*)-ones via [Cu]-Catalysis Using Water as the Green Solvent. *J. Org. Chem.* **2015**, *80*, 7089-7098.

[14] For selected reviews, examples, see: (a) Snider, B. B. Manganese(III)-Based Oxidative Free-Radical Cyclizations. *Chem. Rev.* **1996**, *96*, 339-361. (b) Clark, A. J. Atom transfer radical cyclisation reactions mediated by copper complexes. *Chem. Soc. Rev.* **2002**, *31*, 1-11. (c) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K. Lei, A. Recent Advances in Radical C-H Activation/Radical Cross-Coupling. *Chem. Rev.* **2017**, *117*, 9016-9085. (d) Miyabe, H.; Kawashima, A.; Yoshioka, E.; Kohtani, S. Progress in Enantioselective Radical Cyclizations. *Chem. - Eur. J.* **2017**, *23*, 6225-6236. (e) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Exploration of Visible-Light Photocatalysis in Heterocycle Synthesis and Functionalization: Reaction Design and Beyond. *Acc. Chem. Res.* **2016**, *49*, 1911-1923. (f) Xuan, J.; Studer, A. Radical cascade cyclization of 1,n-enynes and diynes for the synthesis of carbocycles and heterocycles. *Chem. Soc. Rev.* **2017**, *46*, 4329-4346. (g) Studer, A.; Curran, D. P. Catalysis of Radical Reactions: A Radical Chemistry Perspective. *Angew. Chem. Int. Ed.* **2016**, *55*, 58-102. (h) Alpers, D.; Gallhof, M.; Witt, J.; Hoffmann, F.; Brasholz, M. A Photoredox-Induced Stereoselective Dearomative Radical (4+2)-Cyclization/1,4-Addition Cascade for the Synthesis of Highly Functionalized Hexahydro-*1H*-carbazoles. *Angew. Chem. Int. Ed.* **2017**, *56*, 1402-1406.

[15] For selected reviews, see: (a) Clark, A. J. Copper Catalyzed Atom Transfer Radical Cyclization Reactions. *Eur. J. Org. Chem.* **2016**, *13,* 2231-2243. (b) Yu, J.-T.; Pan, C. Radical C–H functionalization to construct heterocyclic compounds. *Chem. Commun.* **2016**, *52,* 2220-2236. (c) Huang, M.-H.; Hao, W.-J.; Jiang, B. Recent Advances in Radical Enabled Bicyclization and Annulation /1,n-Bifunctionalization Reactions, *Chem. Asian J.* **2018**, *13*, 2958-2977. (d) Huang, M.-H.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Recent advances in radical transformations of internal alkynes, *Chem. Commun.* **2018**, *54*, 10415-10418. For selected examples, see: (e) Hu, M.; Fan, J.-H.; Liu, Y.; Ouyang, X.-H.; Song, R.-J.; Li, J.-H. Metal-Free Radical [2+2+1] Carbocyclization of Benzene-Linked 1,n-Enynes: Dual C(sp3)-H Functionalization Adjacent to a Heteroatom. *Angew. Chem. Int. Ed.* **2015**, *54*, 9577-9580. (f) Hu, M.; Song, R.-J.; Li. J.-H. Metal-Free Radical 5-exo-dig Cyclizations of Phenol-Linked 1,6-Enynes for the Synthesis of Carbonylated Benzofurans. *Angew. Chem. Int. Ed.* **2015**, *54*, 608-612. (g) Qiu, J.-K.; Jiang, B.; Zhu, Y.-L.; Hao, W.-J.;

Wang, D.-C.; Sun, J.; Wei, P.; Tu, S.-J.; Li, G. Catalytic Dual 1,1-H-Abstraction/Insertion for Domino Spirocyclizations. *J. Am. Chem. Soc.* **2015**, *137*, 8928-8931. (h) Fuentes, N.; Kong, W.; Fernández-Sánchez, L.; Merino, E.; Nevado, C. Cyclization Cascades via *N*-Amidyl Radicals toward Highly Functionalized Heterocyclic Scaffolds. *J. Am. Chem. Soc.* **2015,** *137*, 964-973. (i) Huang, M.-H.; Zhu, Y.-L.; Hao, W.-J.; Wang, A.-F.; Wang, D.-C.; Liu, F.; Wei, P.; Tu, S.-J.; Jiang, B. Visible-light photocatalytic bicyclization of 1,7-enynes toward functionalized sulfone-containing benzo[*a*]fluoren-5-ones. *Adv. Synth. Catal.* **2017**, *359*, 2229-2234.

[16] (a) Sun, J.; Qiu, J.-K.; Wu, Y.-N.; Hao, W.-J.; Guo, C.; Li, G.; Tu, S.-J.; Jiang, B. Silver-mediated radical C(sp^3)-H biphosphinylation and nitration of *β*-alkynyl ketones for accessing functional isochromenes. *Org. Lett.* **2017**, *19*, 754-757. (b) Liu, F.; Wang, J.-Y.; Zhou, P.; Li, G.; Hao, W.-J.; Tu, S.-J.; Jiang, B. Merging [2 + 2] cycloaddition with radical 1,4-addition: Metal-free access to functionalized cyclobuta[a]naphthalen-4-ols. *Angew. Chem. Int. Ed.* **2017**, *56*, 15570-15574.

[17] For recent reviews see (a) Qiu, G.; Lai, L.; Cheng, J.; Wu, J. Recent advances in the sulfonylation of alkenes with the insertion of sulfur dioxide via radical reactions. *Chem. Commun.* **2018**, *54*, 10405-10414. (b) Qiu, G.; Zhou, K.; Gao, L.; Wu, J. Insertion of sulfur dioxide via a radical process: an efficient route to sulfonyl compounds. *Org. Chem. Front.* **2018**, *5*, 691-705. For selected examples, see: (c) Wang, A.-F.; Hao, W.-J.; Zhu, Y.-L.; Li, G.; Zhou, P.; Tu, S.-J.; Jiang, B. Double SO_2 insertion into 1,7-diynes leading to functionalized naphtho[1,2-*c*]thiophene 2,2-dioxides. *ACS Omega*, **2018**, *3*, 1482-1491. (d) Zhou, K.; Zhang, J.; Lai, L.; Cheng, J.; Sun, J.; Wu, J. C-H bond sulfonylation of anilines with the insertion of sulfur dioxide under metal-free conditions. *Chem. Commun.* **2018**, *54*, 7459-7462. (e) Liu, T.; Li, Y.; Lai, L.; Cheng, ; Sun, J.; Wu, J. Photocatalytic Reaction of Potassium Alkyltrifluoroborates and Sulfur Dioxide with Alkenes. *Org. Lett.* **2018**, *20*, 3605-3608. (f) Zhang, F.; Zheng, D.; Lai, L.; Cheng, J.; Sun, J.; Wu, J. Synthesis of Aromatic Sulfonamides through a Copper-Catalyzed Coupling of Aryldiazonium Tetrafluoroborates, DABCO·$(SO_2)_2$, and *N*-Chloroamines. *Org. Lett.* **2018**, *20*, 1167-1170. (g) An, Y.; Wu, J. Synthesis of Tetrahydropyridine Derivatives through a Reaction of 1,6-Enynes, Sulfur Dioxide, and Aryldiazonium Tetrafluoroborates. *Org. Lett.* **2017**, *19*, 6028-6031. (h) Shen, Z.-J.; Wu, Y.-N.; He, C.-L.; He, L.; Hao, W.-J.; Wang, A.-F.; Tu, S.-J.; Jiang, B. Stereoselective synthesis of sulfonated 1-indenones via radical-triggered multi-component cyclization of *β*-alkynyl propenones. *Chem. Commun.* **2018**, *54*, 445-448.

[18] For selected papers on the metal-catalyzed cross-coupling with aryl diazonium salts: (a) Fabrizi, G.; Goggiamani, A. A. Sferrazza, S. Cacchi, Sonogashira Cross-Coupling of Arenediazonium Salts. *Angew. Chem. Int. Ed.* **2010**, *49*, 4067-4070. (b) Yamamoto, E.; Hilton, M. J.; Orlandi, M.; Saini, V.; Toste, F. D.; Sigman, M. S. Development and Analysis of a Pd(0)-Catalyzed Enantioselective 1,1-Diarylation of Acrylates Enabled by Chiral Anion Phase Transfer. *J. Am. Chem. Soc.* **2016**, *138,* 15877-15880. (c) Yang, K.; Song, Q. Pd-Catalyzed Regioselective Arylboration of Vinylarenes. *Org. Lett.* **2016**, *18*, 5460-5463. (d) Liu, Y.; Song, R.-J.; Li, J.-H. Palladium-catalyzed dearomatizative [2 + 2 + 1] carboannulation of 1,7-enynes with aryldiazonium salts and H_2O: facile synthesis of spirocyclohexadienone-fused cyclopenta[*c*]quinolin-4(5*H*)-ones. *Chem. Commun.* **2017**, *53*, 8600-8603. (e) Huang, L.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. Photosensitizer-Free Visible-Light-Mediated Gold-Catalyzed 1,2-Difunctionalization of Alkynes. *Angew. Chem., Int. Ed.* **2016**, *55*, 4808-4813. (f) Huang, L.; Rominger, F.; Rudolph, M.; Hashmi, A. S. K. A general access to organogold(iii) complexes by oxidative addition of diazonium salts. *Chem. Commun.* **2016**, *52*, 6435-6438. (g) Witzel, S.; Sekine, K.; Rudolph, M.; Hashmi, A. S. K. New transmetalation reagents for the gold-catalyzed visible light-enabled C(sp or sp^2)-C(sp^2) cross-coupling with aryldiazonium salts in the absence of a photosensitizer. *Chem. Commun.* **2018**, *54*, 13802-13804. (h) Xie, J.; Li, J.; Weingand, V.; Rudolph, M.; Hashmi, A. S. K. Intermolecular Photocatalyzed Heck-like Coupling of Unactivated Alkyl Bromides by a Dinuclear Gold Complex. *Chem.-Eur. J.* **2016**, *22*, 12646-12650. (i) Witzel, S.; Xie, J.; Rudolph, M.; Hashmi, A. S. K. Photosensitizer-Free, Gold-Catalyzed C-C Cross-Coupling of Boronic Acids and Diazonium Salts, *Adv. Synth. Catal.* **2017**, *359*, 1522-1528.

[19] The preparation of *β*-alkynyl ketones see: (a) Zhu, S.; Huang, H.; Zhang, Z.; Ma, T.; Jiang H.; Mechanistic insight into transition metal-catalyzed reaction of enynal/enynone with alkenes: Metal-dependent reaction pathway. *J. Org. Chem.* **2014**, *79*, 6113−6122. (b) Zhu, Y.-L.; Wang, A.-F.; Du, J.-Y.; Leng, B.-R.; Tu, S.-J.; Wang, D.-C.; Wei, P.; Hao, W.-J.; Jiang, B. Ag-Catalyzed difluorohydration of *β*-alkynyl ketones for diastereoselective synthesis of 1,5-dicarbonyl compounds. *Chem. Commun.* **2017**, *53*, 6397-6400. (c) Liu, S.; Lan, X.-C.; Chen, K.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Ag/Bronsted acid co-catalyzed spiroketalization of β-alkynyl ketones toward spiro[chromane-2,1'-isochromene] derivatives. *Org. Lett.* **2017**, *19*, 3831-3834. (d) Wang, Z.-Q.; Zhang, W.-W.; Gong, L.-B. Copper-catalyzed intramolecular oxidative 6-exo-trig cyclization of 1,6-enynes with H_2O and O_2. *Angew. Chem., Int. Ed.* **2011**, *50*, 8968-8973. (e) Too, P.-C.; Chiba, S. A CuBr-mediated aerobic reaction of 2-alkynylbenzaldehydes and primary amines: synthesis of 4-bromoisoquinolones. *Chem. Commun.* **2012**, *48*, 7634-7636.