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Note

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One-step Synthesis of Isocoumarins and 3-Benzylidenephthalides via Ligandless Pd–catalyzed Oxidative Coupling of Benzoic Acids and Vinylarenes

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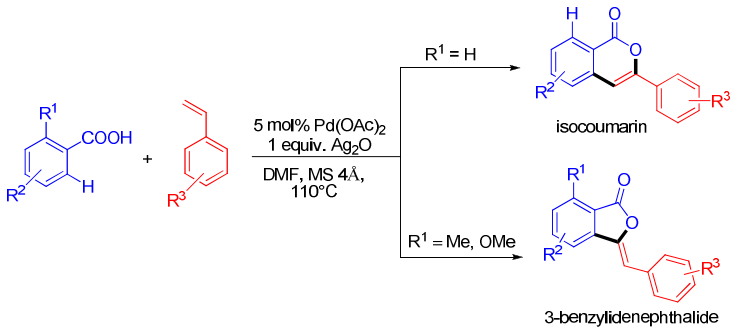
Abstract

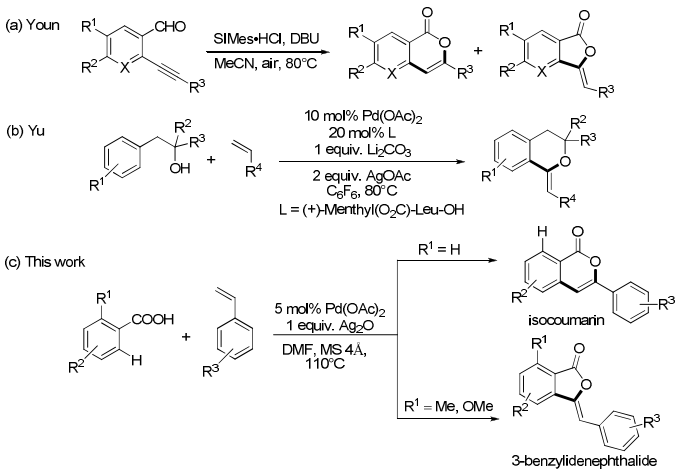


A straight-forward synthetic method for the preparation of isocoumarins and 3-benzylidenephthalides via C–H olefination and oxidative coupling of readily available benzoic acids and vinylarenes was developed. The directing effect of the substituents on the benzoic acid allows for the synthesis of both types of lactone in pure form.

Isocoumarins[1-6] and 3-benzylidenephthalides[4-7] are naturally occurring lactones which exhibit a broad range of biological activities. They are also important in medicinal chemistry as building blocks for the synthesis of bioactive compounds.[8,9] Because of their wide-range of biological activities, a number of methods have been developed for the construction of isocoumarins[10-12] and 3-benzylidenephthalide frameworks.[3,13] For isocoumarins, the most popular method is based on the catalytic cyclization of *in situ*[14-18] or preformed[19-24] *o*-alkynylbenzoic acid derivatives. For instance, Youn recently reported the oxidative cyclization of 2-alkynylbenzaldehyde catalyzed by *N*-heterocyclic carbene (Scheme 1a).[18] Synthetic methods avoiding alkyne-based substrates have also been

developed, including cyclization of 2-alkenyl or 2-allylbenzoic acid derivatives,[3,25,26] microwave-assisted reaction of homophthalic acid with acid chlorides or esters,[27] Cu(I)-catalyzed intramolecular sequential C–C coupling and rearrangement of 1-(2-halophenyl)-1,3-diones,[28] and Cu(I)-catalyzed intermolecular domino reactions from 2-halobenzoic acids or 2-halobenzoic acid derivatives with 1,3-diketones.[29-31] Despite the efficiency of these synthetic strategies for isocoumarins, they are significantly limited by substrate availability. Most often, these methods involve multistep sequences, harsh conditions, or expensive catalysts and ligands. Also in some of these syntheses, mixtures of isocoumarin and 3-benzylidenephthalide are obtained.[14,18] Comparatively, the synthesis of 3-benzylidenephthalides has received less attention and reported procedures generally require multistep synthesis via 5-exo cyclization of *o*-alkynylbenzoic acids.[3]

Recently, Yu reported the tandem Pd-catalyzed hydroxyl-directed C–H olefination reaction/oxidative cyclization.[32] In his study, mono-N-protected amino acid ligands effectively promoted C–H olefination and the olefinated intermediates of electron-deficient alkenes underwent Pd(II)-catalyzed intramolecular oxidative cyclization to give pyrans (Scheme 1b). Since *ortho* C–H activation directed by a carboxylate group is well-known,[33-36] we envisioned the feasibility of a similar Pd-catalyzed C–H olefination between benzoic acid and vinylarene (Scheme 1c).[37-40] A subsequent Pd-catalyzed intramolecular ring-closing process via attack of the carboxylate O atom on the olefin moiety should give isocoumarins or 3-benzylidenephthalides. This strategy is challenging because kinetically significant aryl C–H activation is involved. Desirably, extra synthetic steps to remove the directing group would not be required since it is part of the product.[32]

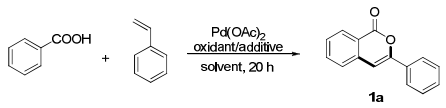


Scheme 1. Lactone and Benzopyran Synthesis

Herein, we report a straight-forward strategy to selectively obtain isocoumarins and 3-benzylidenephthalides. Unlike aforementioned syntheses, our method based on Pd-catalyzed tandem C–H olefination and oxidative cyclization is a simple one-step procedure that avoids lengthy prefunctionalization of substrates since both benzoic acid and vinylarenes are cheap and widely accessible. The practicability of this method is further manifested by the ligandless and mild reaction conditions.

The reaction between benzoic acid and styrene yielding isocoumarins **1a** was chosen for the optimization of conditions (Table 1). The best solvent was determined to be DMF (entries 1–3). The optimal temperature was 110 °C (entries 4–6), as higher temperature resulted in an inferior yield. A moderate 5 mol% Pd loading was necessary to give the product in reasonable yield (entries 5 and 7). Theoretically four H atoms were released and therefore 1–2 equiv of Ag_2O were required. Thus, reducing Ag_2O to sub-stoichiometric amount lowered the yield. However, excess Ag_2O also decreased the yield drastically (entries 5 and 9–11). Oxidants other than Ag salts were not effective (entries 12–13). Since 1 equiv of water also formed in the reaction, the addition of 4 Å molecular sieves improved the yield (entry 5 vs. 8).

Table 1. Reaction Optimization[a]



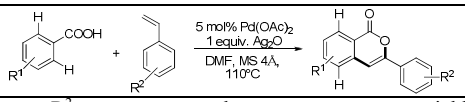
1a

entry	Pd mol%	Oxidant /additive	solvent	temp. (ºC)	yield[b] (%)
1	5	Ag_2O (1 equiv)	DCE	100	0
2	5	Ag_2O (1 equiv)	NMP	100	34
3	5	Ag_2O (1 equiv)	DMF	100	39
4	5	Ag_2O (1 equiv)	DMF	60	0
5	5	Ag_2O (1 equiv)	DMF	110	41
6	5	Ag_2O (1 equiv)	DMF	130	15
7	2.5	Ag_2O (1 equiv)	DMF	110	28
8	5	Ag_2O (1 equiv)/ MS 4 Å (0.5 g)	DMF	110	**56**
9	5	Ag_2O (15 mol%)	DMF	110	11
10	5	Ag_2O (50 mol%)	DMF	110	26
11	5	Ag_2O (2 equiv)	DMF	110	32
12	5	CuOAc (1 equiv)	DMF	110	0
13	5	$PhI(OAc)_2$ (1 equiv)	DMF	110	0

[a]Reaction conditions: 2.0 mmol benzoic acid, 2.0 mmol vinylarene, 15–200 mol% oxidant/additive, 2.5 or 5 mol% Pd(OAc)2, 5 mL dry solvent, heating, 20 h. [b]isolated yield.

Using the optimized conditions, the substrate scope of the reaction was investigated (Table 2). In general, the use of unsubstituted, *para*-, and *meta*-substituted benzoic acids afforded isocoumarins as single products. Benzoic acids with electron-donating groups (EDGs) gave higher yields than unsubstituted substrate (**1a** vs. **4a** and **1b** vs. **4b**). This reactivity pattern, together with the fact that C–H activation is disfavored when an electron-withdrawing group (EWG) is present on the benzoic acid (*vide infra*), is consistent with an electrophilic aromatic substitution mechanism (S_EAr). The reactions also went smoothly with EDGs on the vinylarene, producing **4b** and **4e**, in 70 and 56% yields, respectively. However, attempts to use vinylarenes with EWGs failed. The formation of pure **2a–c** from 3-toluic acid indicates that C–H cleavage on the benzoic acid ring selectively occurred at the less hindered *ortho* site. Sterically hindered 3-methylstyrene also successfully produced **2c**, **3c** and **4c** in satisfactory yields. The X-ray structure of **2a** was obtained (Figure S1 in supporting information).

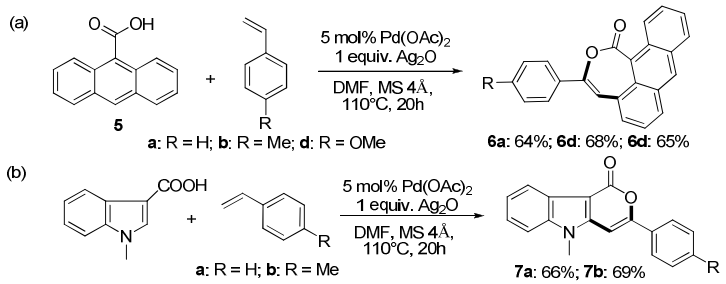
Table 2. Synthesis of 3-Substituted Isocoumarins[a,b]



entry	R^2	product	yield[b] (%)
1	--	**1a**	56
2	Me	**1b**	65
3	OMe	**1d**	68
3	H	**2a**	58
4	Me	**2b**	70
5	--	**2c**	76
6	H	**3a**	51
7	Me	**3b**	72
8	--	**3c**	72
9	--	**4c**	69
10	H	**4a**	60
11	Me	**4b**	70
12	--	**4e**	56

[a]Reaction conditions: 2.0 mmol benzoic acid, 2.0 mmol vinylarene, 1 equiv. Ag_2O, 5 mol% $Pd(OAc)_2$, 5 mL DMF, 110 ºC, 20 h, MS 4 Å (0.5 g). [b]isolated yield.

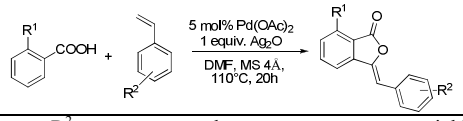
Pleasingly, the reaction can be extended to other aromatic acids. For instance, 9-anthracenecarboxylic acid (**5**) reacted with arylarenes to afford 7-membered ring lactones **6a**, **b**, and **d** in 64–68% yields (Scheme 2a). We were also pleased to find that heteroaromatic carboxylic acids can also be used as substrates. The reaction of 1-methyl-3-indolecarboxylic acid with arylarenes afforded **7a** and **b** in good yields (Scheme 2b). However, the reaction between isomeric 1-methyl-2-indolecarboxylic acid and styrene failed perhaps owing to the less acidic C3*H* of the indole.



Scheme 2. Preparation of Lactone Derivatives

When *ortho*-substituted benzoic acids were employed in the reaction with vinylarenes under identical conditions, isomeric (*z*)-3-benzylidenephthalides **8–10** were isolated instead of isocoumarins in 47–80% yields (Table 3). EDGs on the benzoic acids were essential and the yields also significantly improved if methyl or methoxy-substituted styrenes were employed (**8b** vs. **8a**). These results reveals an intriguing directing effect of the benzene ring substituents on the regioselective nucleophilic attack of the carboxylate O atom on the olefin (*vide infra*). Notably, the reactions failed with 4-acetylstyrene bearing a EWG.

Table 3. Synthesis of 3-Benzylidenephthalide[a,b]



entry	R^2	product	yield[b] (%)
1	--	**8a**	47
2	Me	**8b**	80
3	OMe	**8d**	53
3	--	**8c**	62
5	H	**9a**	62
6	Me	**9b**	74
7	--	**9c**	59
8	--	**10e**	51

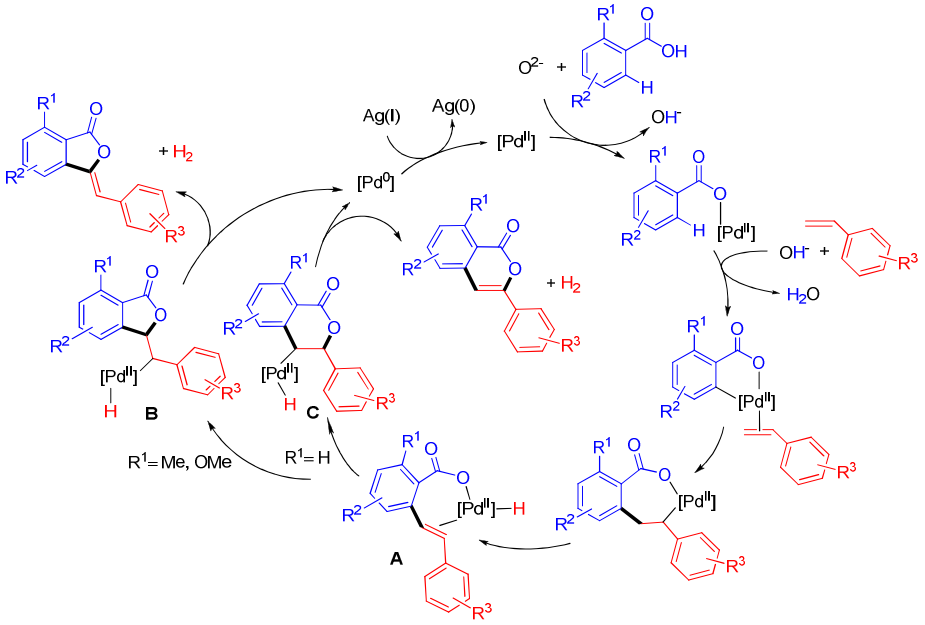
[a]Reaction conditions: 2.0 mmol benzoic acid, 2.0 mmol vinylarene, 1 equiv. Ag_2O, 5 mol% $Pd(OAc)_2$, 5 mL DMF, 110 ºC, 20 h, MS 4 Å (0.5 g). [b]isolated yield.

To confirm the aryl C–H activation via the S_EAr mechanism, we carried out reactions between vinylarenes and benzoic acids with EWGs. Various substrates including 2-acetylbenzoic acid was tested; however, mixtures of unidentified products resulted. Intriguingly, in the case of 2-nitrobenzoic acid, instead of the formation of lactone products, decarboxylative Heck coupling reaction occurred, [41,42] affording compounds **11a**, **b**, and **d** in good yields (Scheme 3). This reactivity pattern can be explained by the fact that nucleophilic attack of the phenyl ring on Pd(II) via the S_EAr mechanism is strongly disfavored. Thus, instead of *ortho* aryl C–H activation, decarboxylation occurred preferentially. A competitive experiment was also performed (Scheme S1 in supporting information). The reaction of a mixture of *o*- and *p*-toluic acids with 3-methylstyrene revealed a slight preference for the formation of 3-benzylidenephthalides. Further mechanistic information was obtained from kinetic isotopic experiments (Scheme S2 in supporting information), which gave a k_H/k_D value of 2.8, indicating that aryl C–H activation may be a rate-controlling step.

Scheme 3. Decarboxylative Heck Coupling Reaction

On the basis of the above results, we propose the mechanistic cycle (Scheme 4). Upon coordination to Pd(II), the carboxylate group directs the *ortho* C–H bond toward the metal center. A five-membered palladacycle was formed via S_EAr. Such palladacycles are common intermediates in Pd-catalyzed C–H functionalization.[37,39] Next, a Heck-type mechanism involving *β*-H elimination at C1 of the vinyl group produces intermediate **A** with a new C–C bond formed regioselectively. For *ortho*-substituted benzoic acids, intramolecular attack of the coordinated O atom on C1 of the vinyl group affords intermediate **B**. Subsequently, *β*-H elimination furnishes the

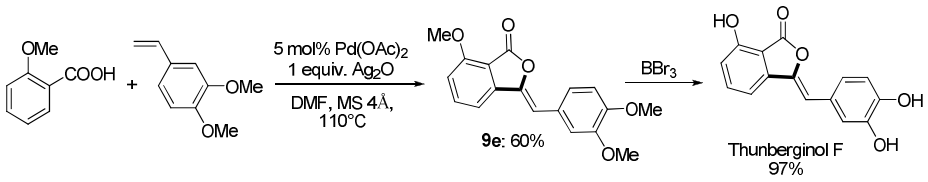
3-benzylidenephathalide. For other benzoic acids, the coordinated O atom in **A** attacks C2, leading to intermediate **C**, which undergoes *β*-H elimination to give isocoumarin. The dependence of the preferential formation of **B** and **C** on ring substitution remains to be elucidated. However, it may be related to the steric effect between the neighboring *ortho* substituent and carboxylate group, which restricts O atom from attacking the distant C2 of the vinyl group. In order to complete the catalytic cycle, Ag(I) is needed to oxidize Pd(0) back to the active Pd(II) species. The formation of metallic Ag was visually observed on the surface of the molecular sieve after the reaction.



Scheme 4. A Proposed Catalytic Cycle

Thunberginol F is a naturally occurring 3-benzylide-nephthalide isolated from *Hydrangea macrophylla* var. *thunbergii*.[6] Thunberginol F 7-O-*β*-D-glucopyranoside was also isolated from the roots of *Scorzonera judaica*.[7] The natural product exhibits antiallergic,[5,6] antimicrobial, and other biological activities,[6] and has been synthesized in three-steps from *N*,*N*-diethyl-2-methoxy-benzamide in an overall 9% yield.[5] We applied our methodology to the ligandless two-step preparation of thunberginol F (Scheme 5). Commercially available 2-methoxybenzolic acid

and 3,4-dimethoxystyrene reacted to give **9e**. Deprotection of the OH groups afforded pure thunberginol F in an overall 58% yield. The X-ray structure of **9e** was established (Figure S2 in supporting information). Our preliminary biological studies showed that thunberginol F exhibited similar cytotoxicity effect as paclitaxel. It can inhibit growth of human cancer cells above 75% at 30 μM (Figure S3 in supporting information).



Scheme 5. Total Synthesis of Thunberginol F

In summary, we have developed a straightforward synthetic method for the preparation of isocoumarins and 3-benzylidenephthalides via C–H olefination and oxidative coupling of aromatic carboxylic acids and vinylarenes. The directing effect of the substituents on benzoic acids allows the preparation of both types of lactones in pure forms. Based on easily available substrates and a simple one-step procedure, this method should receive interest in natural product synthesis and medicinal chemistry.

Experimental Section

All manipulations were performed under a dry nitrogen atmosphere using standard Schlenk techniques. Solvents were dried with standard procedures. Starting chemicals were purchased from commercial source and used as received. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 300.13 and 75.48 MHz, respectively. HRMS was carried out on a sector field mass spectrometer.

Typical Procedure for the Preparation of Coupling Products. To a 50 mL flask fitted with magnetic stirrer arene carboxylic acid (2.0 mmol), Ag_2O (2.0 mmol), $Pd(OAc)_2$ (0.023 g, 0.1 mmol) (5 mol%) and oven activated

molecular sieves 4 Å (0.5 g) were added under nitrogen. Styrene (2.00 mmol) and dry DMF (5 mL) were then added to it. The reaction mixture was stirred at 110 ºC for 20 h and then was allowed to cool at room temperature and filtered through celite bed and mother liquor was collected. After dilution with 20 mL of distilled water, the solution was extracted with ethyl acetate (3x15 mL). The organic layer was separated washed with saturated $NaHCO_3$ solution and dried over anhydrous $MgSO_4$. Removal of the solvent resulted in a residual mass which was subjected to column chromatography over silica gel using hexane and an increasing proportion of ethyl acetate as eluent to provide the corresponding products.

3-Phenyl-1*H*-isochromen-1-one (1a).[43] Yellow solid (249 mg, 56% yield); R_f= 0.43 (9:1 hexane: EtOAc), synthesized following the general procedure from benzoic acid (244 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); mp = 82.2 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (d, *J* = 7.5 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.67 (td, *J* = 7.5, 1.1 Hz, 1H), 7.47-6.90 (m, 5H), 6.91 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.3, 153.5, 137.5, 134.9, 131.9, 129.9, 129.6, 128.8, 128.1, 126.0, 125.2, 120.5, 101.8; HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{15}H_{10}O_2$ 222.0680, found 222.0683.

3-*p*-Tolyl-1*H*-isochromen-1-one (1b).[43] White solid (307 mg, 65% yield); R_f = 0.66 (8:2 hexane: EtOAc), synthesized following the general procedure from benzoic acid (244 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); mp = 109.1 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.24 (d, *J* = 8.1 Hz, 1H), 7.73-7.68 (m, 2H), 7.64 (d, *J* = 7.5 Hz, 1H), 7.45-7.40 (m, 2H), 7.21(d, *J* = 8.4 Hz, 2H), 6.84 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz): δ 162.5, 153.7, 140.3, 137.7, 134.8, 130.1, 129.5, 129.1, 127.9, 125.9, 125.1, 120.3, 101.1, 21.4; HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{16}H_{12}O_2$ 236.0837, found 236.0835.

3-(4-Methoxyphenyl)-1*H*-isochromen-1-one (1d).[44] Pale yellow solid (343 mg, 68% yield); R_f = 0.25 (9:1 hexane: EtOAc), synthesized following the general procedure from benzoic acid (244 mg, 2.0 mmol) and

1-methoxy-4-vinylbenzene (268 mg, 2.0 mmol); mp = 109.1 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.24 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.64 (m, 1H), 7.41 (td, *J* = 5.6 Hz, 3.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.77 (s, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.5, 161.1, 153.7, 137.9, 134.8, 129.5, 127.6, 126.3, 125.7, 124.5, 120.1, 144.2, 100.2, 55.4. HRMS (ESI) *m/z* calcd for $C_{16}H_{12}O_3$ $[M]^+$ 252.0786, found 252.0783.

7-Methyl-3-phenyl-1*H*-isochromen-1-one (2a).[43] White solid (273 mg, 58% yield); R_f = 0.44 (9:1 hexane: EtOAc), synthesized following the general procedure from *m*-toluic acid (272 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); mp = 143.7 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (s, 1H), 7.83 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.42-7.35 (m, 4H), 6.89 (s, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.5, 152.6, 138.4, 136.1, 134.9, 130.0, 129.7, 129.2, 128.7, 125.9, 125.0, 120.3, 101.7, 21.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}O_2$ $[M]^+$ 236.0837, found 236.0838.

7-Methyl-3-*p*-tolyl-1*H*-isochromen-1-one (2b).[43] White solid (350 mg, 70% yield); R_f = 0.91 (8:2 hexane: EtOAc); synthesized following the general procedure from 3-methylbenzoic acid (272 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); mp = 159.2 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.04 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.81 (s, 1H), 2.41 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.9, 153.0, 140.0, 138.2, 136.1, 136.2, 135.2, 129.5, 129.3, 129.3, 125.0, 120.3, 101.0, 21.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_2$ $[M]^+$ 250.0993, found 250.0997.

7-Methyl-3-*m*-tolyl-1*H*-isochromen-1-one (2c). Off-white solid (380 mg, 76% yield); R_f = 0.53 (9:1 hexane: EtOAc); synthesized following the general procedure from 3-methylbenzoic acid (272 mg, 2.0 mmol) and 1-methyl-3-vinylbenzene (236 mg, 2.0 mmol); mp = 125.4 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (s, 1H), 7.66 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.36-7.32 (m, 1H), 7.28 (d, *J* = 7.5, 1H), 7.18 (d, *J* =

7.5, 1H), 6.87 (s, 1H), 2.42 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.7, 152.3, 136.6, 136.2, 135.1, 130.6, 129.3, 128.7, 125.9, 125.7, 122.2, 120.3, 115.0, 101.7, 21.5, 21.4. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_2$ $[M]^+$ 250.0993, found: 250.1003.

6-Methyl-3-phenyl-1*H*-isochromen-1-one (3a).[18] White solid (240 mg, 51% yield); R_f = 0.67 (8:2 hexane: EtOAc); synthesized following the general procedure from 4-methylbenzoic acid (272 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); mp = 102.5 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, *J* = 7.8 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.46-7.41 (m, 3H), 7.41-7.31 (m, 2H), 6.88 (s, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.6, 150.5, 147.0, 137.6, 132.0, 129.9, 129.6, 129.6, 128.8, 125.9, 125.2, 118.1, 101.8, 29.7; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}O_2$ $[M]^+$ 236.0837, found 236.0837.

6-Methyl-3-*p*-tolyl-1*H*-isochromen-1-one (3b). White solid (360 mg, 72% yield); R_f = 0.51 (9:1 hexane: EtOAc); synthesized following the general procedure from 4-methylbenzoic acid (272 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); mp = 155.4 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.16 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.28-7.23 (m, 4H), 6.81 (s, 1H), 2.47 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.5, 153.8, 145.9, 140.1, 137.8, 130.1, 129.5, 129.3, 129.3, 125.8, 125.1, 118.0, 101.0, 22.0, 21.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_2$ $[M]^+$ 250.0993, found 250.0997.

6-Methyl-3-*m*-tolyl-1*H*-isochromen-1-one (3c). Off white solid (360 mg, 72% yield); R_f = 0.57 (9:1 hexane: EtOAc); synthesized following the general procedure from 4-methylbenzoic acid (272 mg, 2.0 mmol) and 1-methyl-3-vinylbenzene (236 mg, 2.0 mmol); mp = 112.5 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.14 (d, *J* = 6.0 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.33-7.30 (m, 1H), 7.28 (d, *J* = 3.0 Hz, 1H), 7.24-7.18 (m, 2H), 6.83 (s, 1H), 2.44 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.5, 153.8, 147.0, 138.6, 137.7, 131.9, 130.7,

129.5, 128.7, 126.0, 126.0, 125.8, 122.3, 118.1, 101.7, 22.0, 21.5. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_2$ $[M]^+$ 250.0993, found: 250.0995.

6-Methoxy-3-phenyl-1*H*-isochromen-1-one (4a).[45] White solid (304 mg, 60% yield); R_f = 0.30 (9:1 hexane: EtOAc); synthesized following the general procedure from 4-methoxybenzoic acid (304 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); mp = 133.1 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.42 (d, *J* = 7.2 Hz, 3H), 6.99 (dd, *J* = 7.5, 2.4 Hz, 1H), 6.86 (s, 1H), 6.84 (d, *J* = 3.0 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.7, 154.1, 139.8, 132.0, 131.8, 130.1, 130.0, 128.8, 125.3, 116.5, 113.6, 107.9, 101.8, 55.8; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}O_3$ $[M]^+$ 252.0786, found 252.0789.

6-Methoxy-3-*p*-tolyl-1*H*-isochromen-1-one (4b). White solid (372 mg, 70% yield); R_f = 0.60 (8:2 hexane: EtOAc); synthesized following the general procedure from 4-methoxybenzoic acid (304 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); mp = 148.3 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21 (d, *J* = 8.7 Hz, 1H), 7.78 (s, 1H), 7.75 (s, 1H), 1.26 (d, *J* = 8.7 Hz, 2H), 7.01 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.86 (d, *J* = 3.0 Hz, 1H), 6.84 (s, 1H), 3.93 (s, 3H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.7, 162.3, 140.3, 140.1, 131.8, 129.5, 129.2 125.2, 116.4, 113.6, 107.8, 101.2, 55.7, 21.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_3$ $[M]^+$ 266.0942, found 266.0948.

6-Methoxy-3-*m*-tolyl-1*H*-isochromen-1-one (4c). White solid (370 mg, 69% yield); R_f = 0.59 (8:2 hexane: EtOAc); synthesized following the general procedure from 4-methoxybenzoic acid (304 mg, 2.0 mmol) and 1-methyl-3-vinylbenzene (236 mg, 2.0 mmol); mp = 136.7 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18 (d, *J* = 9.0 Hz, 1H), 7.68 (s, 1H), 7.63-7.60 (m, 1H), 7.30-7.21 (m, 2H), 6.98 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.84 (s, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 3.89 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.8, 152.3, 139.9, 138.6, 131.9, 130.8,

128.7, 126.0, 122.4, 116.5, 113.7, 107.9, 102.6, 101.8, 56.7, 21.5. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_3$ $[M]^+$ 266.0942, found: 266.0946.

3-(3,4-Dimethoxyphenyl)-6-methoxy-1*H*-isochromen-1-one (4e). White solid (350 mg, 56% yield); R_f = 0.41 (7:3 hexane: EtOAc); synthesized following the general procedure from 4-methoxybenzoic acid (304 mg, 2.0 mmol) and 1,2-dimethoxy-4-vinylbenzene (328 mg, 2.0 mmol); mp = 118.2 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.16 (d, *J* = 8.7 Hz, 1H), 7.42 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 6.96 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.91-6.88 (m, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.75 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.8, 162.3, 158.7, 154.2, 150.7, 149.1, 140.1, 131.8, 124.9, 118.5, 116.3, 111.1, 108.1, 107.6, 100.7, 56.1, 56.0, 55.7. HRMS (ESI) *m/z* calcd for $C_{18}H_{16}O_5$ $[M]^+$ 312.0997, found: 312.1003.

(*Z*)-3-Phenyl-1*H*-anthra[9,1-*cd*]oxepin-1-one (6a). Red solid (412 mg, 64% yield); R_f = 0.71 (8:2 hexane: EtOAc); synthesized following the general procedure from anthracene-9-carboxylic acid (444 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); mp = 195.9 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.65 (d, *J* = 9.0 Hz, 1H), 8.60 (s, 1H), 7.97-7.94 (m, 3H), 7.91 (d, *J* = 2.7 Hz, 1H), 7.75-7.69 (m, 1H), 7.57-7.50 (m, 2H), 7.47-7.41 (m, 3H), 7.31-7.29 (m, 1H), 6.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.2, 146.8, 143.8, 138.5, 135.6, 134.4, 132.4, 130.2, 129.8, 129.8, 128.8, 128.7, 127.5, 126.7, 126.5, 125.7, 124.9, 121.9, 112.9, 108.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{14}O_2$ $[M]^+$ 322.0993, found 322.0996.

(*Z*)-3-*p*-Tolyl-1*H*-anthra[9,1-*cd*]oxepin-1-one (6b). Red solid (457 mg, 68% yield); R_f = 0.40 (9:1 hexane: EtOAc); synthesized following the general procedure from anthracene-9-carboxylic acid (444 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); mp = 150.8 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.63 (d, *J* = 9.0 Hz, 1H), 8.54 (s, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.86-7.83 (m, 3H), 7.73-7.67 (m, 1H), 7.54

(dd, *J* = 6.8, 1.4 Hz, 1H), 7.50-7.44 (m, 1H), 7.25 (m, 1H), 7.22 (s, 1H), 6.44 (s, 1H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.3, 146.2, 137.5, 135.5, 132.0, 131.6, 130.0, 129.7, 129.4, 129.2, 128.5, 126.7, 126.4, 125.7, 125.1, 124.9, 121.6, 112.9, 108.1, 21.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{16}O_2$ $[M]^+$ 336.1150, found 336.1153.

3-(4-Methoxyphenyl)-1*H*-anthra[9,1-*cd*]oxepin-1-one (6d). Red solid (457 mg, 65% yield); R_f = 0.64 (8:2 hexane: EtOAc); synthesized following the general procedure from anthracene-9-carboxylic acid (444 mg, 2.0 mmol) and 1-methoxy-4-vinylbenzene (268 mg, 2.0mmol); mp = 174.5 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.74 (d, *J* = 8.7 Hz, 1H), 8.71 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.01-7.94 (m, 3H), 7.78 (dd, *J* = 6.6, 1.5 Hz, 1H), 7.60-7.55 (m, 2H), 7.28 (s, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.53 (s, 1H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.0, 159.0, 145.4, 135.5, 132.2, 131.2, 130.1, 129.6, 129.2, 128.2, 127.3, 126.7, 126.4, 125.8, 121.3, 114.1, 113.9, 113.6, 107.9, 55.3. HRMS (ESI) *m/z* calcd for $C_{24}H_{16}O_3$ $[M]^+$ 352.1099, found 352.1092.

5-Methyl-3-phenylpyrano[4,3-*b*]indol-1(5*H*)-one (7a). Pale yellow solid (364 mg, 66% yield); R_f = 0.33 (8:2 hexane: EtOAc); synthesized following the general procedure from 1-methyl-1*H*-indole-3-carboxylic acid (350 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); mp = 217.1 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.16 (d, *J* = 3.6 Hz, 1H), 7.86-7.83 (m, 2H), 7.43-7.39 (m, 3H), 7.31-7.25 (m, 3H), 6.84 (s, 1H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.3, 146.2, 139.1, 132.2, 130.3, 128.8, 125.6, 124.6, 124.1, 122.59, 121.1, 109.33, 99.8, 90.8, 29.8; HRMS (ESI) *m/z* calcd for $C_{18}H_{13}NO_2$ $[M]^+$ 275.0946, found 275.0942.

5-Methyl-3-*p*-tolylpyrano[4,3-*b*]indol-1(5*H*)-one (7b). Pale yellow solid (398 mg, 69% yield); R_f = 0.41(8:2 hexane: EtOAc); synthesized following the general procedure from 1-methyl-1*H*-indole-3-carboxylic acid (350 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); mp = 205.8 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.14

(dd, *J* = 7.5, 2.1 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.30-7.25 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.78 (s, 1H), 3.72 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.2, 158.5, 140.7, 139.1, 129.5, 129.5, 129.4, 125.5, 125.5, 124.5, 124.2, 122.5, 121.1, 109.3, 90.0, 29.8, 21.4.; HRMS (ESI) *m/z* calcd for $C_{19}H_{15}NO_2$ $[M]^+$ 289.1103, found 289.1107.

(*Z*)-3-Benzylidene-7-methylisobenzofuran-1(3*H*)-one (8a). White solid (222 mg, 47% yield); R_f = 0.64 (9:1 hexane: EtOAc); synthesized following the general procedure from *o*-toluic acid (272 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); mp = 125.2 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, *J* = 9.0 Hz, 2H), 7.54 (m, 2H), 7.43-7.36 (m, 2H), 7.31-7.25 (m, 2H), 6.35 (s, 1H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 149.1, 144.5, 141.0, 139.6, 134.1, 133.3, 131,3, 130.0, 128.7, 128.2, 121.1, 117.2, 106.2, 17.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}O_2$ $[M]^+$ 236.0837, found 236.0831.

(*Z*)-7-Methyl-3-(4-methylbenzylidene)isobenzofuran-1(3*H*)-one (8b). White solid (401 mg, 80% yield); R_f = 0.68 (9:1 hexane: EtOAc); synthesized following the general procedure from 2-methylbenzoic acid (272 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); mp = 153.7 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 5.7 Hz, 2H), 7.25-7.19 (m, 3H), 6.32 (s, 1H), 2.69 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.3, 143.9, 141.1, 139.5, 138.3, 134.1, 131.1, 130.5, 130.0, 129.4, 121.0, 117.1, 106.4, 21.4, 17.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_2$ $[M]^+$ 250.0993, found 250.0990.

(*Z*)-7-Methyl-3-(3-methylbenzylidene)isobenzofuran-1(3*H*)-one (8c). Off white solid (310 mg, 62% yield); R_f= 0.48 (9:1 hexane: EtOAc); synthesized following the general procedure from 2-methylbenzoic acid (272 mg, 2.0 mmol) and 1-methyl-3-vinylbenzene (236 mg, 2.0 mmol); mp = 168.4 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (s, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.52 (s, 1H), 7.30-7.24 (m, 2H), 7.10 (d, *J* = 6.0 Hz, 1H), 6.32 (s, 1H), 2.68 (s, 3H),

2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4, 144.4, 141.1, 139.6, 138.3, 134.1, 133.2, 131.4, 130.6, 129.1, 128.7, 127.3, 117.2, 106.5, 21.5, 17.6. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_2$ $[M]^+$ 250.0993, found: 250.0985.

(*Z*)-3-(4-Methoxybenzylidene)-7-methylisobenzofuran-1(3*H*)-one (8d). Light yellow solid (280 mg, 53% yield); R_f = 0.61 (8:2 hexane: EtOAc); synthesized following the general procedure from 2-methylbenzoic acid (272 mg, 2.0 mmol) and 1-methoxy-4-vinylbenzene (268 mg, 2.0 mmol); mp = 137.1 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 3 Hz, 1H), 7.50 (s, 1H), 7.23-7.22 (m, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.30 (s, 1H), 3.82 (s, 3H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.5, 159.6, 143.0, 139.6, 134.1, 131.5, 130.9, 126.1, 123.1, 116.9, 114.3, 113.7, 106.2, 55.3, 17.6. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_3$ $[M]^+$ 266.0942, found: 266.0934.

(*Z*)-3-Benzylidene-7-methoxyisobenzofuran-1(3*H*)-one (9a). Pale yellow solid (312 mg, 62% yield); R_f = 0.33 (8:2 hexane: EtOAc); synthesized following the general procedure from 2-methoxybenzoic acid (304 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); mp = 144.2°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, *J* = 9.0 Hz, 2H), 7.59 (t, *J* = 9.0 Hz, 1H) 7.38-7.33 (m, 2H), 7.29-7.27 (m, 2H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.33 (s, 1H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.1, 158.4, 144.2, 142.9, 136.6, 133.1, 130.1, 128.7, 128.3, 111.6, 111.1, 110.8, 107.0, 56.1; HRMS (ESI) *m/z* calcd for $C_{16}H_{12}O_3$ $[M]^+$ 252.0786, found 252.0783.

(*Z*)-7-Methoxy-3-(4-methylbenzylidene)isobenzofuran-1(3*H*)-one (9b). White solid (393 mg, 74% yield); R_f = 0.54 (8:2 hexane: EtOAc); synthesized following the general procedure from 2-methoxybenzoic acid (304 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); mp = 188.1 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, *J* = 6.6 Hz, 2H), 7.61 (td, *J* = 8.2, 3.0 Hz, 1H), 7.25 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 6.88 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.33 (s, 1H), 3.98 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.3, 158.5, 143.6, 143.1,

138.6, 136.5, 130.4, 130.2, 129.5, 115.0, 111.5, 110.9, 110.7, 107.2, 56.1, 21.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_3$ $[M]^+$ 266.0942, found 266.0945.

(*Z*)-7-Methoxy-3-(3-methylbenzylidene)isobenzofuran-1(3*H*)-one (9c). Light yellow solid (310 mg, 59% yield); R_f = 0.55 (8:2 hexane: EtOAc); synthesized following the general procedure from 2-methoxybenzoic acid (304 mg, 2.0 mmol) and 1-methyl-3-vinylbenzene (236 mg, 2.0 mmol); mp = 196.3 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65-7.60 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 6.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 1H), 6.34 (s, 1H), 4.00 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.3, 158.6, 144.1, 143.1, 138.4, 136.6, 133.1, 130.7, 129.3, 128.7, 127.4, 111.6, 111.1, 107.3, 56.2, 21.5. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}O_3$ $[M]^+$ 266.0942, found: 266.0937.

(*Z*)-3-(3,4-Dimethoxybenzylidene)-7-methoxyisobenzofuran-1(3*H*)-one (9e).[46] Yellow solid (370 mg, 60% yield); R_f = 0.48 (1:1 hexane: EtOAc); synthesized following the general procedure from 2-methoxybenzoic acid (304 mg, 2.0 mmol) and 1,2-dimethoxy-4-vinylbenzene (328 mg, 2.0 mmol); mp = 118.8 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58 (t, *J* = 3.9 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.33 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 6.85 (dd, *J* = 8.2, 5.5 Hz, 2H), 6.29 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.2, 158.5, 149.4, 148.9, 143.2, 142.9, 136.5, 123.3, 123.8, 122.2, 112.6, 111.4, 111.1, 110.7, 107.1, 56.1, 56.0, 55.9. HRMS (ESI) *m/z* calcd for $C_{18}H_{16}O_5$ $[M]^+$ 312.0997, found 312.0994.

(*Z*)-3-(3,4-Dimethoxybenzylidene)-5,7-dimethoxyisobenzofurane-1(3*H*)-one (10e).[46] Yellow solid (349 mg, 51% yield); R_f = 0.39 (3:7 hexane: EtOAc); synthesized following the general procedure from 2,4-dimethoxybenzoic acid (364 mg, 2.0 mmol) and 1,2-dimethoxy-4-vinylbenzene (328 mg, 2.0 mmol); mp = 118.4 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 (d, *J* = 1.8 Hz, 1H), 7.33 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 1.8 Hz,

1H), 6.39 (s, 1H), 6.25 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 149.3, 148.9, 145.0, 143.1, 126.3, 123.7, 112.6, 111.0, 106.7, 104.3, 99.7, 94.4, 56.0, 57.0, 56.8. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}O_6$ $[M]^+$ 342.1103, found 342.1106.

(*E*)-1-Nitro-2-styrylbenzene (11a).[47] Orange oil (364 mg, 81% yield); R_f = 0.66 (9:1 hexane: EtOAc); synthesized following the general procedure from 2-nitrobenzoic acid (334 mg, 2.0 mmol) and styrene (208 mg, 2.0 mmol); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.61-7.51 (m, 4H), 7.40-7.31 (m, 4H), 7.06(d, *J* = 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 147.9, 136.5, 133.8, 133.2, 132.9, 128.8, 128.6, 128.1, 130.0, 127.1, 124.8, 123.4; HRMS (ESI) *m/z* calcd for $C_{14}H_{11}NO_2$ $[M]^+$ 225.0789, found 225.0786.

(*E*)-1-(2-Nitrostyryl)-4-methylbenzene (11b).[48] Orange oil (325 mg, 78% yield); R_f = 0.68 (9:1 hexane: EtOAc); synthesized following the general procedure from 2- nitrobenzoic acid (334 mg, 2.0 mmol) and 1-methyl-4-vinylbenzene (236 mg, 2.0 mmol); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.73 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.59-7.51 (m, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.38-7.33 (m, 1H), 7.17(d, *J* = 8.1 Hz, 2H), 7.05(d, *J* = 16.2 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.0, 138.7, 133.9, 133.8, 133.2, 138.1, 129.6, 128.1, 127.8, 127.1, 124.8, 122.4, 21.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}NO_2$ $[M]^+$ 239.0946, found 239.0943.

(*E*)-1-(4-Methoxystyryl)-2-nitrobenzene (11d).[49] Orange solid (357 mg, 70% yield); R_f = 0.48 (9:1 hexane: EtOAc); synthesized following the general procedure from 2- nitrobenzoic acid (334 mg, 2.0 mmol) and 1-methoxy-4-vinylbenzene (268 mg, 2.0mmol); mp = 69.9 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.91 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.72 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.48-7.43 (m, 3H), 7.35 (d, *J* = 9 Hz, 1H), 7.04 (d, *J* = 16.2, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.1, 147.9, 133.5, 133.3,

133.0, 129.3, 128.5, 127.9, 127.5, 124.8, 121.1, 114.3, 56.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}NO_3$ $[M]^+$ 255.08954, found 255.08951.

Thunberginol F.[50] Compound **9e** (100 mg, 0.32 mmol) of was taken in 2 mL of dry DCM in a 50 mL of reaction flask and the temperature of the reaction flask was allowed to cool down at -60º C. Then a 1M DCM solution of BBr_3 (5.2 equiv., 1.66 mL, 1.66 mmol) was dropewise added to it under nitrogen. The temperature of the reaction mixture slowly increased to room temperature and allowed to stir for another 2 h. The solution was then poured to ice cold water (20 mL), and the mixture was extracted with EtOAc (4×15 mL). The organic extract was washed with brine solution and dried over $MgSO_4$ and concentered under reduced pressure. The crude mass was washed several times with DCM to give the pure compound as light yellow solid (0.084g, 97%); R_f = 0.78 (100% EtOAc); mp = 208.9 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.76 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 3.0 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.05 (m, 1H), 6.79 (dd, *J* = 7.8, 2.1, 1H), 6.68 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 164.6, 158.4, 147.0, 145.9, 143.2, 141.6, 137.6, 126.5, 125.2, 123.1, 117.1, 116.3, 112.3, 111.8, 108.1; HRMS (ESI) *m/z* calcd for $C_{15}H_{10}O_5$ $[M]^+$ 270.0528, found 270.0526.

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Supporting Information. Crystallographic data, additional experimental details, and NMR spectra for all products. This material is available free of cost via the Internet at http://pubs.acs.org.

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