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A convenient metal-free synthesis of (*E*)-3-styrylisocoumarins through annulation of (*E*)-1,4-diarylenynes

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This manuscript is dedicated to Professor Jean-François Normant for his 80th birthday

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Abstract: A metal-free procedure for the cyclization of (*E*)-1,4-diarylenynes is described. The reaction promoted by a catalytic amount of PTSA takes place in EtOH at 160 °C under microwaves irradiation and afforded stereoselectively (*E*)-3-styrylisocoumarins in good to excellent yields.

Key words styrylisocoumarins, cyclization, enynes, *para*-toluene sulfonic acid, Suzuki couplings

Isocoumarins represent an important class of heteroaromatic compounds that exhibit a variety of pharmacological properties.¹ In addition, they are endowed as a pivotal intermediate in the synthesis of several other heterocyclic structures such as isoquinolines and isochromenes.¹ One of the most important subfamilies of isocoumarins is 3-styrylisocoumarins, whose derivatives are the key structural units of a variety of natural products.² While the synthesis of 3-arylisocoumarins is well documented,^{1,3} a careful examination of the literature reveals that general methods for the preparation of stereodefined 3-styrylisocoumarins remain under-developed.

Only three reports described the synthesis of 3-styryl-isocoumarins, and within each work only one example is reported. Saeed⁴ and Rama⁵ have disclosed the construction of polyoxygenated 3-styrylisocoumarins through the cyclocondensation of homophthalic acids with phenyl acrylate⁴ or phenylacryloyl chloride derivatives⁵ under extremely harsh conditions (Scheme 1). Recently, Kapur *et al.*⁶ have described, as

a single example, the Pd-catalyzed arylation of triethylsilylenol ethers of enones followed by a cyclization to provide the simple unfunctionalized 3-styrylisocoumarin. Therefore, there remains a need for the development of novel metal-free transformations tolerating a wide variety of substitution patterns on the styryl component, and proceeding with a high stereoselectivity.

As part of our medicinal chemistry program directed to the synthesis of heterocombretastatins,⁷ combined with our interest to the construction of novel substituted heterocycles through metal-free cyclization reactions,⁸ we required an efficient access to (*E*)-3-styryl-isocoumarins **1** containing several elements of structural diversity on the styryl unit. In our previous work, a metal-free annulation of diarylalkynes in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA), under mild conditions, to afford a series of 3-arylisocoumarins has been successfully established.⁹ Inspired by these works, PTSA-catalyzed cyclization of alkyne-tethered olefin units bearing an aryl ester to synthesize targeted 3-styrylisocoumarins was proposed (Figure 1). The major challenge associated with this transformation is to achieve the cyclization reaction while keeping intact the stereochemistry of the C–C double bond. Herein we report our success on the development of such a protocol that extends the scope of our previous work.⁹

Scheme 1. Conventional strategies to 3-styryl-isocoumarins

Figure 1 Access of (*E*)-3-styrylisocoumarins **1** from the cyclization of (*E*)-1,4-diarylenynes **2**.

As depicted in Scheme 2, the required 1,4-diarylenyne derivatives **2a-n** were synthesized in a two-step sequence from 2-methoxycarbonyl phenylacetylene **3**. In details, Pd-catalyzed reaction with (*E*)-1,2-dichloroethylene and alkyne **3** afforded the desired (*E*)-chloroenyne **4** according to Sonogashira-Linstrumelle coupling.¹⁰ Next, Suzuki coupling reactions¹¹ between (*E*)-**4** and a variety of boronic acids was achieved, using Pd(PPh₃)₄ (5 mol%) as a catalyst, K₂CO₃ as a base in a refluxing combination of toluene/MeOH as a solvent. Accordingly, (*E*)-1,4-diarylenynes **2** were formed stereo-selectively with satisfactory isolated yields (Scheme 2). Under these conditions, we were pleased to observe that the coupling process was efficient regardless the electronic nature of the boronic acids having electron-rich or electron-poor substituents in the *ortho*-, *meta*- or *para*-position.

We have next studied the cyclization of enyne (*E*)-**2a** into isocoumarin (*E*)-**1a**, as a model substrate to establish the best reaction conditions. The influence of several parameters were examined including, the solvent (EtOH, MeOH or BnOH), the quantities of PTSA, and the reaction temperature (conventional or MW heating). The best conditions required the use of 30 mol% of PTSA in EtOH and heating under microwave irradiation (MWI) at 160 °C to accelerate the reaction. Accordingly, isocoumarin **1a** was formed in an almost a quantitative yield of 95% within 1.5 h (Table 1, entry 1). It should be noted that the optimal temperature was 160 °C, as lower temperatures resulted in a low conversion and inferior yields.

With this encouraging result in hand, we next turned our attention to examining the scope and limitations of this cyclization under the optimized reaction conditions. As shown in Table 1, we were able to transform a panel of (*E*)-1,4-diarylenynes **2** bearing various functional groups into their corresponding isocoumarin derivatives **1**. (*E*)-Enynes **2a-f** bearing electron-donating substituents (OMe, Me or SMe) on *ortho*-, *meta*- and *para*-positions on the aromatic nucleus were successfully transformed into the expected (*E*)-styryl-isocoumarins **1a-f** with satisfactory yields ranging from 63% to 90% (entries 1-6). A naphthyl aromatic ring was also well tolerated by the PTSA-catalyzed cyclization process and **2g** was transformed into isocoumarin **1g** with a good 86% yield (entry 7). Enynes **2h-n** with an electron-withdrawing group on the aromatic ring were next evaluated in the above cyclization methodology (entries 8-14). Altogether, the process was still efficient and led to the expected isocoumarins **1h-n** with yields ranging from 20% to 99%, depending on the nature and the position of the electron-withdrawing substituent on the aromatic ring. It should be noted that the cyclization-reaction of enyne **2n**

Table 1. Synthesis of 3-styrylisocoumarins **1a-n**

Entry	1,4-diarylenyne 2	3-styrylisocoumarin 1	Yield (%) ^a
1			95
2			81
3			63
4			78
5			77
6			90
7			86
8			95
9			67
10			99
11			41
12			67
13			30
14			20

^a Yield of isolated product.

gave isocoumarin **1n** but with a low 20% yield (entry 14), probably because the CN-function of **2n** reacted with PTSA, as we had previously reported with other CN-containing substrates under similar conditions.⁹

We next focused our attention whether the developed protocol would be applicable with (*Z*)-1,4-diarylenynes to provide the corresponding (*Z*)-3-styrylisocoumarins. A Pd-coupling reaction between alkyne **3** and (*Z*)-1,2-dichloroethylene in the presence of PdCl₂(PPh₃)₂, CuI, and *n*-butylamine

Scheme 3. Synthesis of 3-styrylisocoumarin **1** from arylalkyne **3**. *Reagents and conditions:* (i) (Z)-1,2-dichloroethylene (2 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (10 mol%), CuI (10 mol%), *n*-butylamine (2 equiv); Et_2O , rt. (ii) $\text{ArB}(\text{OH})_2$ (1.2 equiv), $\text{Pd}(\text{PPh}_3)_4$ (5 mol%), K_2CO_3 (2 equiv), toluene/MeOH : 2/1, 60 °C; (iii) PTSA (30 mol%), EtOH, 160 °C, microwaves.

afforded stereoselectively the (Z)-chloroenyne **4**¹⁰ in a 52% yield (Scheme 3). Subsequent Suzuki-coupling reactions furnished selectively the expected (Z)-1,4-diarylenynes (Z)-**2a**, (Z)-**2d**, (Z)-**2g** with no trace of isomerization of their (Z)-double bond. When 1,4-diarylenynes (Z)-**2** were treated under the optimized reaction conditions, we were pleased to observe that the cyclization reaction was still efficient but led to a mixture of non-separable Z/E isocoumarins **1** in nearly equivalent proportions (Scheme 3).

On the basis of the results depicted in Table 1, we believe that this annulation process proceeds as shown in Scheme 4 by a sequence involving (i) activation of the triple bond by PTSA, (ii) nucleophilic attack by the oxygen of the ester group to the more electrophilic acetylenic carbon according to a favored 6-endo-dig process,¹² and (iii) loss of the methyl group of the oxonium species promoted by the solvent^{8b} to afford the 3-styrylisocoumarin **1** together with one equivalent of EtOMe.

Scheme 4. Proposed mechanism for the PTSA-catalyzed annulation of **2**.

We next examined the possibility of preparing (E)-3-styrylisocoumarins **1** from isocoumarin **5** bearing a vinyl chloride function on the 3-position. Accordingly, the PTSA-catalyzed annulation of (E)-chloroenyne **4** was investigated. Thus, heating (E)-**4** under our optimized conditions (EtOH, 160 °C, MWI, 1 h) yielded the expected isocoumarin (E)-**5** in a 60% yield (Table 2, entry 1). It should be noted that achieving the annulation under conventional heating (EtOH, 78 °C) required longer reaction time (24 h) and gave (E)-**5** in a lower yield (30%, entry 2). One notes that little improvement was realized with increasing the amount of PTSA (entry 3). The effects of Lewis acids (e.g., FeBr_3 , InCl_3 , PdCl_2) were then briefly studied in refluxing EtOH or under microwave irradiation (entries 4–7). No improvement in yield was observed using these metal catalysts; the best result (50%, entry 7) was obtained using a catalytic amount of PdCl_2 (10 mol%) after refluxing in EtOH for a long reaction time of 30 h.

By combining the use of catalytic amounts of PdCl_2 (10 mol%) and PTSA (10 mol%) in refluxing EtOH for 24 h, we were pleased to observe that (E)-chloroenyne **4a** undergo the annulation process successfully providing the expected isocoumarin **5** with a good 70% yield (entry 8).

Table 2. Effect of additives mediated cyclization of (E)-chloroenyne **4a**

Entry	Reactants	Yield of (E)-5 (%) ^a
1	PTSA (10 mol%), MWI, 160 °C, 1 h	60
2	PTSA (10 mol%), reflux, 24 h	30
3	PTSA (50 mol%), reflux, 24 h	42
4	FeBr_3 (20 mol%), reflux, 15 h	17
5	FeBr_3 (20 mol%), MWI, 160 °C, 1 h	Nd
6	InCl_3 (20 mol%), reflux, 30 h	20
7	PdCl_2 (10 mol%), reflux, 30 h	50
8	PdCl_2 (10 mol%), PTSA (10 mol%), reflux, 24 h	70
9	PdCl_2 (30 mol%), PTSA (30 mol%), reflux, 1 h	75

^a Yield of isolated product. ^b Nd not determined.

Finally, we found that increasing the quantities of PTSA and PdCl_2 (from 10% to 30%) allowed to prepare 3-(chlorovinyl)isocoumarin **5** in a good 75% yield after 1 h refluxing in EtOH (entry 9). By applying these experimental conditions to the chloroenyne (Z)-**4** (Scheme 5), we have observed the formation of the expected (Z)-3-(chlorovinyl)isocoumarin **5** but with a very low yield of 15% accompanied by its (E)-isomer **5** (21%).

Scheme 5. Synthesis of (Z)-3-(chlorovinyl)isocoumarin **5** by cyclization of (Z)-chloroenyne **4**. *Reagents and conditions:* (i) PdCl_2 (30 mol%), PTSA (30 mol%), EtOH reflux, 1 h.

With (E)-**5** in hand, its Suzuki coupling with boronic acids under the conditions described in Scheme 2, however, failed, clearly demonstrating that the $\text{C}_{\text{sp}^2}\text{-Cl}$ bond of chloroenyne **4** and 3-(chlorovinyl)isocoumarin **5** displayed different reactivity. After several attempts, we found that the protocol¹³ involving the use of $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ as the catalyst, and $\text{P}(t\text{-Bu})_3$ as the ligand in the presence of KF as the base proved to be suitable furnishing the desired (E)-3-styrylisocoumarin **1a** in a good 73% yield (Scheme 6).

Scheme 6. Synthesis of (E)-**1a** from (E)-3-(chlorovinyl)isocoumarin **5**. *Reagents and conditions:* (i) 4-methoxyphenylboronic acid (4 equiv), KF (3.3 equiv), $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ (5 mol%), $\text{P}(t\text{-Bu})_3$ (10 mol%), THF, 65 °C, 7 h.

In summary, we demonstrated that chloroenynes of type **4** constitutes a common starting material for the synthesis of various 3-styrylisocoumarins **1** having several elements of structural diversity on the styryl unit. The strategy developed is general and involves two different and complementary pathways: (i) a Suzuki coupling reaction of boronic acids with (E)-chloroenynes of type **4** followed by cyclization in the presence of catalytic amounts of PTSA, or (ii) a PTSA/ PdCl_2 -catalyzed the cyclization of (E)-chloroenynes **4** followed by Suzuki couplings on the resulting 3-chlorovinylisocoumarin **5**. Some of these new derivatives **1**, having a great resemblance to biologically active heteroaromatic analogs¹⁴ of combretastatins

will be evaluated later in our lab for their possible antitumor activities.

All glasswares were oven-dried at 140 °C and all reactions were conducted under a nitrogen atmosphere. Solvents: cyclohexane, ethyl acetate (EtOAc), for chromatography, were technical grade. All new compounds were characterized by ¹H-NMR, ¹³C-NMR, IR spectroscopy and HRMS. ¹H and ¹³C NMR spectra were measured in CDCl₃ with a Bruker Avance 300. ¹H chemical shifts are reported in ppm from an internal standard TMS or of residual chloroform (7.26 ppm). The following abbreviation are used: m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublet), td (triplet of doublet), ddd (doublet of doublet of doublet). ¹³C chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm⁻¹). High-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF-Q instrument. Analytical TLC was performed on Merck precoated silica gel 60 F-254 plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography. The plates were visualized by either UV light (254 nm), or by a solution of phosphomolybdic acid in ethanol.

Methyl (E)-2-(4-chlorobut-3-en-1-yn-1-yl)benzoate 4 (55%)

To a solution of alkyne **3** (160 mg, 1 mmol) in Et₂O (15 mL) was added successively (E)-1,2-dichloroethylene (0.8 mL, 10 mmol), PdCl₂(PPh₃)₂ (70 mg, 0.1 mmol), piperidine (0.2 mL, 2 mmol) and CuI by portions (19 mg, 0.1 mmol). After 7 h of stirring at rt, the solution was filtered on a pad of SiO₂ using EtOAc. Organic layer was successively washed with a saturated NH₄Cl, saturated NaHCO₃ and HCl 1M solutions. After drying on Na₂SO₄ and evaporation *in vacuo*, the crude was purified by chromatography on SiO₂ to give **4** (121 mg, 0.55 mmol).

IR (neat): 3466, 2339, 2219, 2151, 2104, 1974, 1936, 1727 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.95 (dd, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.54 (dd, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.46 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.37 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 6.68 (d, *J* = 13.6 Hz, 1H), 6.22 (d, *J* = 13.6 Hz, 1H), 3.92 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.3 (Cq), 134.0 (CH), 131.8 (CH), 131.6 (Cq), 130.9 (CH), 130.5 (CH), 128.2 (CH), 123.2 (Cq), 114.0 (CH), 90.6 (Cq), 89.3 (Cq), 52.2 (CH₃).

HRMS Calcd for C₁₂H₁₀O₂Cl [M+H]⁺ 221.0369, found 221.0363.

Methyl (Z)-2-(4-chlorobut-3-en-1-yn-1-yl)benzoate 4 (52%)

The protocol was identical to that developed for (E)-**4** but *n*BuNH₂ (200 μL mg, 2 mmol) replaced piperidine and 800 μL (20 mmol) of (Z)-1,2-dichloroethylene were used. The crude was purified by chromatography on SiO₂ to give **4** (114 mg, 0.52 mmol).

IR (neat): 3087, 2951, 1729, 1711, 1582, 1565, 1484, 1447, 1432, 1335, 1294, 1277, 1252, 1190, 1164, 1128, 1083, 1043, 962, 831, 801, 756, 724, 697, 660, 634 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.95 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.47 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.37 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 6.47 (d, *J* = 7.5 Hz, 1H), 6.16 (d, *J* = 7.5 Hz, 1H), 3.93 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.6 (Cq), 134.4 (CH), 131.8 (Cq), 131.7 (CH), 130.4 (CH), 128.8 (CH), 128.4 (CH), 123.1 (Cq), 112.3 (CH), 96.0 (Cq), 88.0 (Cq), 52.3 (CH₃).

HRMS Calcd for C₁₂H₁₀O₂Cl [M+H]⁺ 221.0369, found 221.0363.

General procedure for the synthesis of diarylenynes 2

To a solution of **4** (220 mg, 1 mmol) in toluene/MeOH: 2/1 (10 mL) were added the boronic acid (1.2 mmol), K₂CO₃ (373 mg, 2 mmol) and

Pd(PPh₃)₄ (58 mg, 0.05 mmol). The mixture was stirred under reflux until the disappearance of **4** (judged by TLC). After concentration, the crude was diluted in CH₂Cl₂ and washed with water. After drying on Na₂SO₄ and evaporation *in vacuo*, the crude was purified by chromatography on SiO₂.

Methyl (E)-2-(4-(4-methoxyphenyl)but-3-en-1-yn-1-yl)benzoate 2a
(Yield: 213 mg, 0.73 mmol, 73%)

IR (neat): 3033, 3001, 2951, 2837, 2360, 2192, 1729, 1603, 1563, 1511, 1483, 1462, 1445, 1433, 1343, 1308, 1289, 1243, 1174, 1128, 1084, 1031, 954, 848, 815, 757, 735, 699, 658 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.97 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.0 Hz, 1H), 7.33–7.42 (m, 3H), 7.07 (d, *J* = 16.0 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.34 (d, *J* = 16.0 Hz, 1H), 3.98 (s, 3H, CH₃), 3.85 (s, 3H, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ = 160.2 (Cq), 141.6 (CH), 134.0 (CH), 131.7 (CH), 131.4 (Cq), 130.4 (CH), 129.2 (Cq), 127.8 (2CH), 127.6 (CH), 124.2 (Cq), 114.2 (2CH), 105.9 (CH), 94.5 (Cq), 89.8 (Cq), 55.3 (CH₃), 52.2 (CH₃), one C not seen.

HRMS Calcd for C₁₉H₁₇O₃ [M+H]⁺ 293.1178, found 293.1178.

Methyl (E)-2-(4-(2-methoxyphenyl)but-3-en-1-yn-1-yl)benzoate 2b
(Yield: 277 mg, 0.95 mmol, 95%)

IR (neat): 3439, 3153, 2839, 2359, 2005, 1729, 1711 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.90 (dd, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.42–7.36 (m, 2H), 7.30–7.17 (m, 3H), 6.90–6.80 (m, 2H), 6.47 (d, *J* = 16.2 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.7 (Cq), 157.1 (Cq), 137.4 (CH), 134.0 (CH), 131.6 (CH), 131.5 (Cq), 130.4 (CH), 129.8 (CH), 127.6 (CH), 127.0 (CH), 125.3 (Cq), 124.2 (Cq), 120.7 (CH), 111.1 (CH), 108.8 (CH), 94.9 (Cq), 90.0 (Cq), 55.5 (CH₃), 52.2 (CH₃).

HRMS Calcd for C₁₉H₁₇O₃ [M+H]⁺ 293.1178, found 293.1169.

Methyl (E)-2-(4-(3-methoxyphenyl)but-3-en-1-yn-1-yl)benzoate 2c
(Yield: 225 mg, 0.77 mmol, 77%)

IR (neat): 2950, 2836, 2194, 1729, 1711, 1596, 1578, 1483, 1432, 1292, 1274, 1252, 1191, 1156, 1134, 1086, 1046, 952, 827, 783, 757, 687 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.96 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.47 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.09–7.03 (m, 2H), 6.97 (s, 1H), 6.86 (dd, *J* = 8.2 Hz, *J* = 2.5 Hz, 1H), 6.46 (d, *J* = 16.2 Hz, 1H), 3.96 (s, 3H), 3.83 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.6 (Cq), 159.9 (Cq), 141.8 (CH), 137.7 (Cq), 134.1 (CH), 131.7 (CH), 131.5 (Cq), 130.4 (CH), 129.7 (CH), 127.8 (CH), 124.0 (Cq), 119.2 (CH), 114.5 (CH), 111.6 (CH), 108.6 (CH), 93.9 (Cq), 90.6 (Cq), 55.3 (CH₃), 52.2 (CH₃).

HRMS Calcd for C₁₉H₁₆O₃Na [M+Na]⁺ 315.0997, found 315.0993.

Methyl (E)-2-(4-(3,4,5-trimethoxyphenyl)but-3-en-1-yn-1-yl)benzoate 2d
(Yield: 211 mg, 0.6 mmol, 60%)

IR (neat): 3000, 2943, 2839, 2192, 1729, 1578, 1505, 1484, 1465, 1450, 1418, 1343, 1298, 1282, 1252, 1233, 1188, 1154, 1126, 1086, 1045, 1005, 951, 853, 812, 758, 701, 628 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.95 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.46 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.35 (dd, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.01 (d, *J* = 16.2 Hz, 1H), 6.66 (s, 2H), 6.37 (d, *J* = 16.2 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 6H), 3.86 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.5 (Cq), 153.4 (2Cq), 141.8 (CH), 138.9 (Cq), 134.0 (CH), 132.0 (Cq), 131.7 (CH), 131.4 (Cq), 130.4 (CH), 127.7

(CH), 124.0 (Cq), 107.7 (CH), 103.6 (2CH), 93.9 (Cq), 90.5 (Cq), 60.9 (CH₃), 56.1 (2CH₃), 52.2 (CH₃).

HRMS Calcd for C₂₁H₂₁O₅ [M+H]⁺ 353.1389, found 353.1385.

Methyl (E)-2-(4-(2,5-dimethylphenyl) but-3-en-1-yn-1-yl) benzoate 2e (Yield: 154 mg, 0.53 mmol, 53%)

IR (neat): 2949, 2194, 1730, 1712, 1592, 1564, 1482, 1447, 1432, 1292, 1249, 1190, 1163, 1132, 1083, 1045, 952, 882, 810, 756, 699, 660 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.97 (dd, *J* = 7.5 Hz, *J* = 0.6 Hz, 1H), 7.59 (dd, *J* = 7.5 Hz, *J* = 0.6 Hz, 1H), 7.48 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.05 (m, 2H), 6.37 (d, *J* = 16.2 Hz, 1H), 3.97 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.7 (Cq), 139.9 (CH), 135.6 (Cq), 135.0 (Cq), 134.0 (CH), 132.9 (Cq), 131.7 (CH), 130.5 (CH), 130.4 (CH), 129.5 (CH), 127.7 (CH), 125.6 (CH), 124.0 (Cq), 108.9 (CH), 94.4 (Cq), 90.0 (Cq), 52.2 (CH₃), 21.0 (CH₃), 19.3 (CH₃), one C not seen.

HRMS Calcd for C₂₀H₁₉O₂ [M+H]⁺ 291.1385, found 291.1386.

Methyl (E)-2-(4-(4-thiomethylphenyl)but-3-en-1-yn-1-yl)benzoate 2f (Yield: 154 mg, 0.5 mmol, 50%)

IR (neat): 3028, 2949, 2192, 1729, 1709, 1670, 1590, 1564, 1482, 1432, 1405, 1293, 1249, 1188, 1163, 1134, 1083, 1045, 1014, 954, 852, 803, 756, 699, 655 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.96 (dd, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.58 (dd, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.47 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.38 – 7.32 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 16.2 Hz, 1H), 6.41 (d, *J* = 16.2 Hz, 1H), 3.95 (s, 3H), 2.49 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.6 (Cq), 141.3 (CH), 139.6 (Cq), 134.0 (CH), 133.1 (Cq), 131.7 (CH), 131.5 (Cq), 130.4 (CH), 127.7 (CH), 126.8 (2CH), 126.4 (2CH), 124.1 (Cq), 107.5 (CH), 94.1 (Cq), 90.5 (Cq), 52.2 (CH₃), 15.5 (CH₃).

HRMS Calcd for C₁₉H₁₇O₂S [M+H]⁺ 309.0949, found 309.0945.

Methyl (E)-2-(4-(naphthalen-2-yl)but-3-en-1-yn-1-yl) benzoate 2g (Yield: 165 mg, 0.53 mmol, 53%)

IR (neat): 3058, 2949, 2193, 1728, 1708, 1633, 1591, 1563, 1483, 1432, 1364, 1290, 1273, 1250, 1189, 1162, 1128, 1084, 1046, 952, 910, 862, 811, 756, 699, 659, 625 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.98 (dd, *J* = 7.8, *J* = 1.0 Hz, 1H), 7.85 – 7.79 (m, 4H), 7.65 – 7.61 (m, 2H), 7.51 – 7.46 (m, 3H), 7.37 (td, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.27 (d, *J* = 16.2 Hz, 1H), 6.60 (d, *J* = 16.2 Hz, 1H), 3.99 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.6 (Cq), 142.1 (CH), 134.1 (CH), 133.8 (Cq), 133.6 (Cq), 133.5 (Cq), 131.7 (CH), 131.6 (Cq), 130.5 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.2 (CH), 126.5 (CH), 126.4 (CH), 124.0 (Cq), 122.8 (CH), 108.6 (CH), 94.2 (Cq), 90.9 (Cq), 52.2 (CH₃).

HRMS Calcd for C₂₂H₁₇O₂ [M+H]⁺ 313.1229, found 313.1226.

Methyl (E)-2-(4-(4-fluorophenyl)but-3-en-1-yn-1-yl)benzoate 2h (Yield: 185 mg, 0.66 mmol, 66%)

IR (neat): 2951, 2195, 1729, 1712, 1600, 1565, 1509, 1484, 1448, 1433, 1296, 1285, 1252, 1228, 1191, 1159, 1133, 1085, 1045, 955, 935, 852, 815, 791, 757, 699, 659 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, *J* = 7.1 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.53 – 7.36 (m, 4H), 7.11 – 7.02 (m, 3H), 6.39 (d, *J* = 16.2 Hz, 1H), 3.98 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.5 (Cq), 163.0 (d, *J* = 247.5 Hz, Cq), 140.6 (CH), 134.1 (CH), 132.5 (Cq), 131.7 (CH), 131.5 (Cq), 130.5 (CH), 128.1 (d,

J = 7.5 Hz, CH), 127.8 (CH), 124.0 (Cq), 115.8 (d, *J* = 21.8 Hz, CH), 108.1 (CH), 93.7 (Cq), 90.4 (Cq), 52.2 (CH₃).

¹⁹F NMR (188 MHz, CDCl₃) δ = -110.42.

HRMS Calcd for C₁₈H₁₄O₂F [M+H]⁺ 281.0978, found 281.0975.

Methyl (E)-2-(4-(2-fluorophenyl)but-3-en-1-yn-1-yl)benzoate 2i (Yield: 179 mg, 0.64 mmol, 64%)

IR (cm⁻¹): 2950, 1729, 1711, 1593, 1565, 1481, 1448, 1432, 1286, 1251, 1228, 1189, 1164, 1133, 1082, 1046, 953, 885, 827, 803, 751, 698, 660.

¹H NMR (300 MHz, CDCl₃) δ = 7.88 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.28 (td, *J* = 7.8, 1.1 Hz, 1H), 7.22 – 7.09 (m, 2H), 7.07 – 6.92 (m, 2H), 6.48 (d, *J* = 16.4 Hz, 1H), 3.85 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.6 (Cq), 160.3 (d, *J* = 250.5 Hz, Cq), 134.5 (d, *J* = 2.3 Hz, CH), 134.1 (CH), 131.7 (CH), 131.6 (Cq), 130.5 (CH), 130.0 (d, *J* = 8.3 Hz, CH), 127.9 (CH), 127.2 (d, *J* = 3.0 Hz, CH), 124.3 (d, *J* = 3.0 Hz, CH), 124.2 (Cq), 123.8 (Cq), 116.0 (d, *J* = 22.5 Hz, CH), 110.9 (d, *J* = 6.8 Hz, CH), 93.9 (Cq), 91.1 (Cq), 52.2 (CH₃).

¹⁹F NMR (188 MHz, CDCl₃) δ = -114.74.

HRMS Calcd for C₁₈H₁₄O₂F [M+H]⁺ 281.0978, found 281.0974.

Methyl (E)-2-(4-(4-trifluoromethylphenyl)but-3-en-1-yn-1-yl) benzoate 2j (Yield: 132 mg, 0.4 mmol, 40%)

IR (neat): 1729, 1711, 1612, 1592, 1564, 1484, 1433, 1412, 1322, 1289, 1250, 1189, 1163, 1123, 1108, 1084, 1066, 1045, 1014, 962, 945, 861, 815, 755, 699, 664, 645 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.98 (d, *J* = 7.8 Hz, 1H), 7.61 – 7.46 (m, 6H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 16.2 Hz, 1H), 6.55 (d, *J* = 16.2 Hz, 1H), 3.96 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.4 (Cq), 140.1 (CH), 139.6 (Cq), 134.1 (CH), 131.8 (CH), 131.6 (Cq), 130.5 (CH), 130.1 (Cq), 129.7 (CH), 128.1 (CH), 126.5 (2CH), 125.7 (2CH), 123.7 (Cq), 122.2 (Cq), 111.1 (CH), 93.2 (Cq), 91.80 (Cq), 52.2 (CH₃).

¹⁹F NMR (188 MHz, CDCl₃) δ = -63.04.

HRMS Calcd for C₁₉H₁₄O₂F₃ [M+H]⁺ 331.0946, found 331.0953.

Methyl (E)-2-(4-(3-nitrophenyl)but-3-en-1-yn-1-yl)benzoate 2k (Yield: 166 mg, 0.54 mmol, 54%)

IR (neat): 2951, 1729, 1711, 1565, 1528, 1485, 1433, 1351, 1293, 1254, 1190, 1135, 1086, 1046, 952, 824, 803, 758, 734, 699, 674 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.28 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 16.2 Hz, 1H), 6.60 (d, *J* = 16.2 Hz, 1H), 3.96 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 164.3 (Cq), 148.7 (Cq), 139.0 (CH), 138.0 (2Cq), 134.2 (CH), 131.9 (CH), 131.8 (CH), 130.5 (CH), 129.7 (CH), 128.2 (CH), 123.5 (Cq), 123.0 (CH), 120.9 (CH), 111.8 (CH), 92.7 (Cq), 92.3 (Cq), 52.3 (CH₃).

HRMS Calcd for C₁₈H₁₄NO₄ [M+H]⁺ 308.0923, found 308.0922.

Methyl (E)-2-(4-(3,4-dichlorophenyl)but-3-en-1-yn-1-yl)benzoate 2l (Yield: 142 mg, 0.43 mmol, 43%)

IR (neat): 2008, 1729, 1592, 1565, 1473, 1432, 1389, 1294, 1275, 1252, 1190, 1133, 1085, 1046, 1029, 945, 880, 809, 756, 698, 673, 656 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.99 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.44 – 7.37 (m, 2H), 7.27 (dd, *J* = 8.1, *J* = 2.1 Hz, 1H), 6.99 (d, *J* = 16.2 Hz, 1H), 6.46 (d, *J* = 16.2 Hz, 1H), 3.97 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.4 (Cq), 139.1 (CH), 136.4 (Cq), 134.1 (CH), 133.0 (Cq), 132.4 (Cq), 131.8 (CH), 131.6 (Cq), 130.7 (CH), 130.5 (CH), 128.1 (CH), 128.0 (CH), 125.4 (CH), 123.7 (Cq), 110.4 (CH), 93.1 (Cq), 91.8 (Cq), 52.2 (CH₃).

HRMS Calcd for C₁₈H₁₃O₂Cl₂ [M+H]⁺ 331.0293, found 331.0294.

Methyl (E)-2-(4-(4-acetylphenyl)but-3-en-1-yn-1-yl)benzoate 2m
(Yield: 195 mg, 0.64 mmol, 64%)

IR (neat): 1729, 1712, 1679, 1599, 1564, 1484, 1432, 1410, 1358, 1290, 1269, 1250, 1183, 1134, 1085, 1046, 1015, 959, 861, 814, 758, 699 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.98 – 7.91 (m, 3H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.51 – 7.48 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 16.2 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 3.95 (s, 3H), 2.59 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 197.3 (Cq), 166.4 (Cq), 140.7 (Cq), 140.5 (CH), 136.8 (Cq), 134.1 (CH), 131.8 (CH), 131.6 (Cq), 130.5 (CH), 128.8 (2CH), 128.1 (CH), 126.4 (CH), 123.7 (Cq), 111.2 (CH), 93.4 (Cq), 92.1 (Cq), 52.2 (CH₃), 26.6 (CH₃).

HRMS Calcd for C₂₀H₁₇O₃ [M+H]⁺ 305.1178, found 305.1171.

Methyl (E)-2-(4-(4-cyanophenyl)but-3-en-1-yn-1-yl)benzoate 2n
(Yield: 164 mg, 0.57 mmol, 57%)

IR (neat): 2951, 2226, 1728, 1709, 1601, 1565, 1484, 1448, 1432, 1412, 1296, 1251, 1191, 1133, 1085, 963, 945, 863, 815, 757, 699, 658 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.90 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.40 (m, 6H), 7.31 (td, *J* = 7.7, 1.2 Hz, 1H), 6.98 (d, *J* = 16.2 Hz, 1H), 6.49 (d, *J* = 16.2 Hz, 1H), 3.87 (s, 3H), an impurity was observed between 7.60 and 7.75 ppm.

¹³C NMR (75 MHz, CDCl₃) δ = 166.3 (Cq), 140.6 (Cq), 139.6 (CH), 134.2 (CH), 131.8 (2CH), 131.6 (Cq), 130.5 (CH), 128.3 (CH), 126.8 (2CH), 123.5 (Cq), 118.7 (Cq), 112.3 (CH), 111.7 (Cq), 93.0 (Cq), 92.8 (Cq), 52.2 (CH₃).

HRMS Calcd for ¹⁹H₁₄O₂ [M+H]⁺ 288.1025, found 288.1022.

Methyl (Z)-2-(4-(4-methoxyphenyl)but-3-en-1-yn-1-yl) benzoate 2a
(Yield: 146 mg, 0.5 mmol, 50%)

IR (neat): 2951, 2837, 2182, 1728, 1711, 1605, 1565, 1510, 1484, 1432, 1408, 1326, 1304, 1279, 1248, 1172, 1132, 1083, 1031, 962, 835, 789, 756, 699, 653 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.98 – 7.94 (m, 3H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.67 (d, *J* = 12.0 Hz, 1H), 5.88 (d, *J* = 12.0 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.7 (Cq), 159.9 (Cq), 138.8 (CH), 134.1 (CH), 131.7 (CH), 131.5 (Cq), 130.5 (3CH), 129.5 (Cq), 127.8 (CH), 124.1 (Cq), 113.7 (2CH), 104.9 (CH), 94.1 (Cq), 93.6 (Cq), 55.3 (CH₃), 52.2 (CH₃).

HRMS Calcd for C₁₉H₁₇O₃ [M+H]⁺ 293.1178, found 293.1179.

Methyl (Z)-2-(4-(3,4,5-trimethoxyphenyl)but-3-en-1-yn-1-yl) benzoate 2d
(Yield: 204 mg, 0.58 mmol, 58%) accompanied with less than 2% of (*E*)-2d.

IR (neat): 2838, 1728, 1574, 1506, 1483, 1450, 1422, 1404, 1330, 1299, 1279, 1251, 1238, 1188, 1126, 1083, 1043, 1006, 963, 846, 758, 700, 644 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.97 (dd, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H), 7.57 (dd, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H), 7.47 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.38 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.22 (s, 2H), 6.64 (d, *J* = 12.0 Hz, 1H), 5.96 (d, *J* = 12.0 Hz, 1H), 3.86 (s, 6H), 3.80 (s, 6H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.4 (Cq), 152.9 (Cq), 138.9 (CH), 138.6 (Cq), 133.8 (CH), 132.1 (Cq), 131.8 (CH), 131.5 (Cq), 130.6 (CH), 128.0

(CH), 123.8 (Cq), 106.7 (CH), 106.2 (2CH), 94.7 (Cq), 93.1 (Cq), 60.9 (CH₃), 56.1 (2CH₃), 52.1 (CH₃), one C not seen.

HRMS Calcd for C₂₁H₂₁O₅ [M+H]⁺ 353.1389, found 353.1395.

Methyl (Z)-2-(4-(naphthalen-2-yl)but-3-en-1-yn-1-yl)benzoate 2g
(Yield: 181 mg, 0.58 mmol, 58%)

IR (neat): 1728, 1593, 1564, 1504, 1484, 1432, 1294, 1277, 1251, 1190, 1164, 1134, 1082, 1043, 964, 950, 895, 861, 822, 757, 737, 698 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.44 (s, 1H), 8.20 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.92 – 7.82 (m, 3H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 12.0 Hz, 1H), 6.11 (d, *J* = 12.0 Hz, 1H), 3.89 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.6 (Cq), 139.3 (CH), 134.2 (CH), 134.1 (Cq), 133.4 (Cq), 133.3 (Cq), 131.8 (CH), 131.5 (Cq), 130.6 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.6 (CH), 126.5 (2CH), 126.2 (CH), 124.0 (Cq), 107.8 (CH), 94.9 (Cq), 93.3 (Cq), 52.3 (CH₃).

HRMS Calcd for C₂₂H₁₇O₂ [M+H]⁺ 313.1229, found 313.1231.

General procedure for the synthesis of isocoumarins 1

To a solution of **2** (0.5 mmol) in EtOH (4 mL) was added PTSA (26 mg, 0.15 mmol). The mixture was stirred at 160 °C under microwave irradiation (for time see for each compounds). After concentration *in vacuo*, the crude mixture was diluted in EtOAc, washed with water and dried over Na₂SO₄ and purified by chromatography on SiO₂.

(E)-3-(4-Methoxystyryl)-1H-isochromen-1-one 1a (Yield: 132 mg, 0.48 mmol, 95%)

Reaction time 1.5 h, (yellow solid, m.p. 142.8 – 143.5 °C)

IR (neat) : 3070, 2957, 2837, 1728, 1720, 1635, 1599, 1574, 1560, 1511, 1481, 1456, 1441, 1421, 1363, 1330, 1300, 1264, 1247, 1223, 1175, 1159, 1111, 1058, 1026, 976, 959, 911, 881, 863, 829, 790, 755, 732, 688, 641 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.25 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.36 (m, 5H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.38 (s, 1H), 3.83 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 162.2 (Cq), 160.3 (Cq), 153.0 (Cq), 137.8 (Cq), 134.8 (CH), 132.6 (CH), 129.8 (CH), 128.6 (2CH), 127.7 (CH), 125.6 (CH), 120.7 (Cq), 117.2 (CH), 114.3 (2CH), 104.8 (CH), 55.4 (CH₃), one C not seen.

HRMS Calcd for C₁₈H₁₅O₃ [M+H]⁺ 279.1021, found 279.1015.

(*E*)-**1a** was also prepared from chloroenyne **5** (see after) and 4-(methoxyphenyl)boronic acid according to the following protocol: To a solution of **5** (206 mg; 1 mmol) in THF (10 mL) were added successively, 4-(methoxyphenyl)boronic acid (608 mg, 4 mmol), KF (192 mg, 3.3 mmol), Pd₂dba₃·CHCl₃ (52 mg, 0.05 mmol), P(*t*-Bu)₃ (20 mg, 0.1 mmol). The mixture was stirred at 65 °C for 7 h. After concentration, the crude was diluted in CH₂Cl₂ and washed with water. After drying on Na₂SO₄ and evaporation *in vacuo*, the crude was purified by chromatography on SiO₂ to give (*E*)-**1a** (203 mg, 0.73 mmol, 73%).

(E)-3-(2-Methoxystyryl)-1H-isochromen-1-one 1b (Yield: 113 mg, 0.41 mmol, 81%)

Reaction time 2.5 h, (yellow solid, m.p. 129.4 – 130.3 °C).

IR (neat): 3048, 3350, 3250, 3216, 2361, 2328, 2192, 2169, 2150, 2034, 1895, 1483, 1245, 754, 688 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.30 (d, *J* = 7.8 Hz, 1H), 7.80 – 7.66 (m, 2H), 7.56 – 7.41 (m, 3H), 7.35 – 7.26 (m, 2H), 7.02 – 6.92 (m, 2H), 6.84 (d, *J* = 16.2 Hz, 1H), 6.47 (s, 1H), 3.94 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 162.2 (Cq), 157.8 (Cq), 153.3 (Cq), 137.8 (Cq), 134.7 (CH), 129.9 (CH), 129.8 (CH), 128.5 (CH), 127.8 (2 CH), 125.7 (CH), 124.9 (Cq), 120.7 (CH), 120.3 (CH), 111.1 (CH), 105.4 (CH), 55.4 (CH₃).

HRMS Calcd for C₁₈H₁₅O₃ [M+H]⁺ 279.1021, found 279.1024.

(E)-3-(3-Methoxystyryl)-1H-isochromen-1-one 1c (Yield: 88 mg, 0.32 mmol, 63%)

Reaction time 3 h, (yellow solid, m.p. 115.0 – 115.5 °C).

IR (neat): 2835, 1720, 1635, 1615, 1596, 1577, 1561, 1481, 1454, 1432, 1363, 1328, 1291, 1272, 1244, 1218, 1164, 1056, 1023, 977, 956, 918, 879, 847, 820, 779, 756, 729, 688 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.27 (d, *J* = 7.8 Hz, 1H), 7.67 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.48 – 7.38 (m, 3H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 6.87 (dd, *J* = 8.1 Hz, *J* = 2.4 Hz, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.45 (s, 1H), 3.84 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 162.0 (Cq), 160.0 (Cq), 152.5 (Cq), 137.5 (Cq), 137.2 (Cq), 134.8 (CH), 132.9 (CH), 129.8 (2CH), 128.1 (CH), 125.8 (CH), 120.9 (Cq), 119.8 (2CH), 114.6 (CH), 112.3 (CH), 105.8 (CH), 55.3 (CH₃).

HRMS Calcd for C₁₈H₁₅O₃ [M+H]⁺ 279.1021, found 279.1019.

(E)-3-(3,4,5-Trimethoxystyryl)-1H-isochromen-1-one 1d (Yield: 128 mg, 0.38 mmol, 76%)

Reaction time 1.5 h, (yellow solid, m.p. 231.7 – 232.6 °C).

IR (neat): 3002, 2938, 1728, 1634, 1616, 1578, 1560, 1504, 1481, 1368, 1342, 1329, 1244, 1220, 1184, 1149, 1123, 1057, 1023, 1005, 969, 890, 844, 814, 768, 732, 716, 691, 663, 638 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.27 (d, *J* = 7.8 Hz, 1H), 7.67 (td, *J* = 8.1 Hz, *J* = 1.0 Hz, 1H), 7.48 – 7.34 (m, 3H), 6.74 (s, 2H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.45 (s, 1H), 3.90 (s, 6H), 3.88 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 162.0 (Cq), 153.5 (Cq), 152.6 (Cq), 139.0 (Cq), 137.6 (Cq), 134.9 (CH), 133.0 (CH), 131.4 (Cq), 129.8 (CH), 128.0 (CH), 125.8 (CH), 120.8 (Cq), 118.8 (CH), 105.5 (CH), 104.3 (2 CH), 61.0 (CH₃), 56.1 (2CH₃).

HRMS Calcd for C₂₀H₁₉O₅ [M+H]⁺ 339.1232, found 339.1227.

(E)-3-(2,5-Dimethylstyryl)-1H-isochromen-1-one 1e (Yield: 106 mg, 0.39 mmol, 77%)

Reaction time 2 h, (yellow solid, m.p. 120.3 – 121.5 °C).

IR (neat): 1730, 1635, 1615, 1561, 1482, 1455, 1363, 1329, 1286, 1220, 1162, 1057, 1025, 959, 820, 755, 688 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.29 (d, *J* = 7.8 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.49 – 7.38 (m, 3H), 7.11 – 7.38 (m, 2H), 6.61 (d, *J* = 15.6 Hz, 1H), 6.46 (s, 1H), 2.42 (s, 3H), 2.35 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 162.2 (Cq), 152.9 (Cq), 137.6 (Cq), 135.6 (Cq), 134.8 (CH), 134.6 (Cq), 134.0 (Cq), 130.7 (CH), 130.6 (CH), 129.9 (CH), 129.5 (CH), 128.0 (CH), 126.0 (CH), 125.7 (CH), 120.9 (Cq), 120.5 (CH), 105.6 (CH), 21.0 (CH₃), 19.5 (CH₃).

HRMS Calcd for C₁₉H₁₇O₂ [M+H]⁺ 277.1229, found 277.1219.

(E)-3-(4-(Methylthio)styryl)-1H-isochromen-1-one 1f (Yield: 132 mg, 0.45 mmol, 90%)

Reaction time 3 h, (yellow solid, m.p. 148.2 – 148.6 °C).

IR (neat): 2920, 1720, 1632, 1615, 1588, 1561, 1480, 1437, 1405, 1363, 1331, 1282, 1224, 1186, 1161, 1093, 1057, 1027, 976, 957, 910, 880, 860, 825, 805, 754, 730, 688, 638 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.25 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.46 – 7.34 (m, 5H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.41 (s, 1H), 2.49 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 162.0 (Cq), 152.7 (Cq), 139.8 (Cq), 137.6 (Cq), 134.8 (CH), 132.5 (Cq), 132.3 (CH), 129.8 (CH), 128.0 (CH), 127.5 (2CH), 126.4 (2CH), 125.7 (CH), 120.8 (Cq), 118.6 (CH), 105.5 (CH), 15.5 (CH₃).

HRMS Calcd for C₁₈H₁₅O₂S [M+H]⁺ 295.0793, found 295.0789.

(E)-3-(2-(Naphthalen-2-yl)vinyl)-1H-isochromen-1-one 1g (Yield: 128 mg, 0.43 mmol, 86%)

Reaction time 5 h, (yellow solid, m.p. 223.1 – 223.9 °C).

IR (neat): 1740, 1632, 1480, 1364, 1224, 1159, 1054, 1024, 962, 854, 817, 747, 686 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.30 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.58 (m, 4H), 7.71 – 7.41 (m, 3H), 7.50 – 7.41 (m, 4H), 6.81 (d, *J* = 15.9 Hz, 2H), 6.49 (s, 2H).

¹³C NMR (75 MHz, CDCl₃) δ = 165.0 (Cq), 162.1 (Cq), 152.7 (Cq), 137.6 (Cq), 134.8 (CH), 133.6 (Cq), 133.3 (Cq), 133.0 (CH), 129.9 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 127.7 (CH), 126.6 (2CH), 125.8 (CH), 123.3 (CH), 120.9 (Cq), 119.7 (CH), 105.8 (CH).

HRMS Calcd for C₂₁H₁₅O₂ [M+H]⁺ 299.1072, found 299.1074.

(E)-3-(4-Fluorostyryl)-1H-isochromen-1-one 1h (Yield: 126 mg, 0.48 mmol, 95%)

Reaction time 5 h, (yellow solid, m.p. 164.4 – 165.1 °C).

IR (neat): 1728, 1723, 1639, 1618, 1599, 1562, 1509, 1482, 1415, 1366, 1329, 1293, 1234, 1222, 1160, 1098, 1058, 1027, 977, 959, 832, 801, 755, 689 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.27 (d, *J* = 7.5 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.50 – 7.37 (m, 5H), 7.06 (t, *J* = 8.7 Hz, 2H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.44 (s, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 163.0 (d, *J* = 247.9 Hz, Cq), 162.0 (Cq), 152.4 (Cq), 137.5 (Cq), 134.9 (CH), 132.1 (d, *J* = 3.1 Hz, Cq), 131.7 (CH), 129.8 (CH), 128.8 (d, *J* = 8.1 Hz, CH), 128.1 (CH), 125.8 (CH), 120.8 (Cq), 119.2 (CH), 115.9 (d, *J* = 21.7 Hz, CH), 105.8 (CH).

¹⁹F NMR (188 MHz, CDCl₃) δ = -110.06.

HRMS Calcd for C₁₇H₁₂O₂F [M+H]⁺ 267.0821, found 267.0824.

(E)-3-(2-Fluorostyryl)-1H-isochromen-1-one 1i (Yield: 91 mg, 0.34 mmol, 67%)

Reaction time 5 h, (yellow solid, m.p. 164.9 – 165.5 °C).

IR (neat): 3134, 2334, 2202, 2157, 1995, 1725, 1707, 1496 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.31 (d, *J* = 8.1 Hz, 1H), 7.68-7.40 (m, 1H), 7.43-7.56 (m, 4H), 7.26 – 7.31 (m, 2H), 7.07-7.20 (m, 2H), 6.86 (dd, *J* = 16.2, *J* = 1.6 Hz, 1H), 6.51 (s, 1H).

¹³C NMR (101 MHz, CDCl₃) δ = 162.0 (Cq), 161.1 (d, *J* = 253.1 Hz, Cq), 152.6 (Cq), 137.5 (Cq), 134.9 (CH), 130.1 (d, *J* = 8.5 Hz, CH), 130.0 (CH), 128.8 (d, *J* = 2.9 Hz, CH), 128.3 (CH), 126.0 (d, *J* = 6.7 Hz, CH), 124.5 (d, *J* = 3.1 Hz, CH), 124.0 (Cq), 123.9 (Cq), 122.4 (d, *J* = 8.1 Hz, CH), 121.1 (Cq), 116.2 (d, *J* = 22.1 Hz, CH), 106.5 (CH).

¹⁹F NMR (188 MHz, CDCl₃) δ = -115.4.

HRMS Calcd for C₁₇H₁₂FO₂ [M+H]⁺ 267.0821, found 267.0821.

(E)-3-(4-(Trifluoromethyl)styryl)-1H-isochromen-1-one 1j (Yield: 156 mg, 0.49 mmol, 99%)

Reaction time 5 h, (yellow solid, m. p. 181.7 – 182.5 °C).

IR (neat): 1783, 1729, 1618, 1482, 1414, 1371, 1324, 1260, 1163, 1107, 1067, 1015, 967, 872, 837, 754, 686, 638 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.29 (d, *J* = 7.8 Hz, 1H), 7.70 (td, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.64 – 7.57 (m, 4H), 7.52 – 7.42 (m, 3H), 6.76 (d, *J* = 16.2 Hz, 1H), 6.52 (s, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.1 (Cq), 161.8 (Cq), 151.9 (Cq), 139.3 (Cq), 137.2 (Cq), 134.9 (CH), 131.2 (CH), 129.9 (CH), 128.5 (CH), 127.2 (2CH), 126.0 (CH), 125.8 (2CH), 121.8 (CH), 121.1 (Cq), 106.9 (CH).

¹⁹F NMR (188 MHz, CDCl₃) δ = -63.01.

HRMS Calcd for C₁₉H₁₄O₂F₃ [M+H]⁺ 317.0789, found 317.0793.

(*E*)-3-(3-Nitrostyryl)-1H-isochromen-1-one 1k (Yield: 62 mg, 0.21 mmol, 41%)

Reaction time 6 h, (yellow solid, m.p. 248.0 – 249.0 °C).

IR (neat): 1782, 1737, 1620, 1563, 1528, 1482, 1352, 1327, 1225, 1169, 1056, 1026, 964, 833, 803, 755, 735, 686, 674 cm⁻¹.

¹H NMR (400 MHz, DMSO) δ = 8.48 (s, 1H), 8.18 – 8.07 (m, 3H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 16.0 Hz, 1H), 7.25 (d, *J* = 16.0 Hz, 1H), 6.94 (s, 1H).

¹³C NMR (101 MHz, DMSO) δ = 170.9 (Cq), 160.4 (Cq), 151.2 (Cq), 137.4 (Cq), 136.5 (Cq), 134.8 (CH), 132.8 (CH), 129.8 (CH), 128.9 (CH), 128.6 (CH), 128. (CH), 126.1 (CH), 122.9 (CH), 122.4 (CH), 120.8 (CH), 120.1 (Cq), 106.8 (CH), one C not seen.

HRMS Calcd for C₁₈H₁₄NO₄ [M+H]⁺ 308.0923, found 308.0922.

(*E*)-3-(3,4-dichlorostyryl)-1H-isochromen-1-one 1l (Yield: 106 mg, 0.34 mmol, 67%)

Reaction time 5 h, (yellow solid, m.p. 223.3 – 224.2 °C).

IR (neat): 1721, 1617, 1477, 1369, 1226, 1134, 1064, 1027, 958, 823, 750, 685 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 7.99 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.44 – 7.37 (m, 2H), 7.27 (dd, *J* = 8.1, *J* = 2.1 Hz, 1H), 6.99 (d, *J* = 16.2 Hz, 1H), 6.46 (d, *J* = 16.2 Hz, 1H), 3.97 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 166.4 (Cq), 139.1 (CH), 136.4 (Cq), 134.1 (CH), 133.0 (Cq), 132.4 (Cq), 131.8 (CH), 131.6 (Cq), 130.7 (CH), 130.5 (CH), 128.1 (CH), 128.0 (CH), 125.4 (CH), 123.7 (Cq), 110.4 (CH), 93.1 (Cq), 91.8 (Cq), 52.2 (CH₃).

HRMS Calcd for C₁₇H₁₁O₂Cl₂ [M+H]⁺ 317.0136, found 317.0134.

(*E*)-3-(4-acetylstyryl)-1H-isochromen-1-one 1m (Yield: 44 mg, 0.15 mmol, 30%)

Reaction time 3.5 h, (yellow solid, m. p. 225.9 – 227.3 °C).

IR (neat): 1723, 1673, 1616, 1598, 1563, 1483, 1410, 1357, 1298, 1268, 1181, 1065, 1027, 958, 837, 812, 768, 718, 690, 636 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.29 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.52 – 7.43 (m, 3H), 6.80 (d, *J* = 15.9 Hz, 1H), 6.53 (s, 1H), 2.61 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ = 197.3 (Cq), 161.8 (Cq), 152.0 (Cq), 140.3 (Cq), 137.2 (Cq), 136.8 (Cq), 134.9 (CH), 131.5 (CH), 129.9 (CH), 128.9 (2CH), 128.5 (CH), 127.2 (CH), 126.0 (CH), 121.9 (CH), 121.1 (Cq), 107.0 (CH), 26.6 (CH₃).

HRMS Calcd for C₁₉H₁₅O₃ [M+H]⁺ 291.1021, found 291.1017.

(*E*)-4-(2-(1-oxo-1H-isochromen-3-yl)vinyl)benzonitrile 1n (Yield: 27 mg, 0.1 mmol, 20%)

Reaction time 5 h, (yellow solid, m.p. 196.3 – 197.6 °C).

IR (neat): 1723, 1655, 1616, 1599, 1481, 1411, 1373, 1327, 1229, 1108, 1061, 1023, 960, 871, 837, 753, 730, 686, 634 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.31 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.41 (m, 8H), 6.79 (d, *J* = 15.4 Hz, 1H), 6.55 (s, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 161.6 (Cq), 151.6 (Cq), 140.2 (Cq), 137.1 (Cq), 135.0 (CH), 132.6 (CH), 130.7 (CH), 130.0 (CH), 128.7 (CH), 127.4 (CH), 126.1 (CH), 122.8 (CH), 121.3 (Cq), 111.8 (Cq), 107.6 (CH), 105.7 (Cq).

HRMS Calcd for C₁₈H₁₂NO₂ [M+H]⁺ 274.0868, found 274.0867.

(*E*)-3-(2-Chlorovinyl)-1H-isochromen-1-one 5 (Yield: 155 mg, 0.75 mmol, 75%)

To a solution of (*E*)-4 (220 mg, 1 mmol) in EtOH (4 mL) was added 52mg (0.3 mmol) of PTSA and 53 mg (0.3 mmol) of PdCl₂. The solution was stirred for 1 h under reflux and concentrated. The crude was then dissolved in EtOAc and washed with water. After extraction and drying, the crude was purified by chromatography on SiO₂ to give (*E*)-5 (155 mg, 0.75 mmol, 75%) as a white solid yellow solid, m.p. 91.2 – 91.4 °C.

IR (neat): 3401, 3385, 3246, 3139, 3100, 2365, 2191, 1966 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.26 (d, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 13.2 Hz, 1H), 6.46 (d, *J* = 13.2 Hz, 1H), 6.34 (s, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 161.3 (Cq), 149.9 (Cq), 136.9 (Cq), 135.0 (CH), 129.9 (CH), 128.6 (CH), 126.0 (CH), 125.1 (CH), 124.7 (CH), 121.0 (Cq), 105.5 (CH).

HRMS Calcd for C₁₁H₇ClNaO₂ [M+Na]⁺ 229.0032, found 229.0041.

(*Z*)-3-(2-Chlorovinyl)-1H-isochromen-1-one 5 (Yield: 31 mg, 0.15 mmol, 15%)

To a solution of (*Z*)-4 (220 mg, 1 mmol) in EtOH (4 mL) was added 52 mg (0.3 mmol) of PTSA and 53 mg (0.3 mmol) of PdCl₂. The solution was stirred for 1 h under reflux and concentrated. The crude was then dissolved in EtOAc and washed with water. After extraction and drying, the crude mixture was purified by chromatography to furnish (*Z*)-5 (31 mg, 0.15 mmol, 15%) and (*E*)-5 (43 mg, 0.21 mmol, 21%) which could be separated on SiO₂.

(*Z*)-5

IR (neat): 1751, 1728, 1631, 1483, 1288, 1200, 1161, 1139, 1052, 1023, 971, 838, 791, 756, 688 cm⁻¹.

¹H NMR (300 MHz, CDCl₃) δ = 8.29 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.19 (s, 1H), 6.46 (d, *J* = 8.7 Hz, 1H), 6.41 (d, *J* = 8.7 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ = 161.8 (Cq), 149.4 (Cq), 136.8 (Cq), 134.9 (CH), 129.6 (CH), 128.9 (CH), 126.4 (CH), 122.5 (CH), 122.4 (CH), 121.0 (Cq), 108.1 (CH).

Calculated for C₁₁H₈O₂³⁵Cl [M+H]⁺ 207.0213, found 207.0217.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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