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Metal-Free Synthesis of 4-Chloroisocoumarins by TMSCl-Catalyzed NCS-Induced Chlorinative Annulation of 2-Alkynylaryloate Esters

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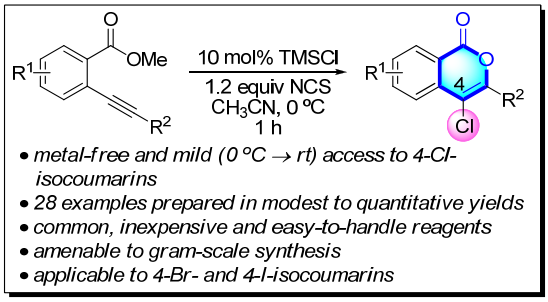


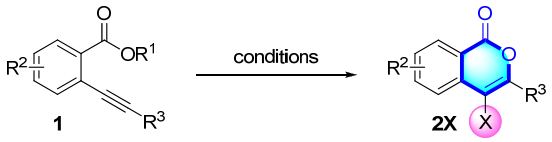
ABSTRACT: 4-Chloroisocoumarins can be conveniently prepared from 2-alkynylaryloate esters *via* the activation of alkyne by electrophilic chlorine, generated *in situ* from NCS in the presence of 10 mol% of TMSCl, which led to 6-*endo*-dig-selective chlorinative annulation to give the desired products in moderate to quantitative yields. The procedure employed readily available reagents and can be conveniently carried out on a wide scope of substrates under

mild conditions (0 °C to rt). Furthermore, the reaction was scalable for gram-scale preparation of 4-chloroisocoumarins. Additionally, 4-bromo- and 4-iodoisocoumarins can be prepared in moderate to good yields by replacing NCS with NBS and NIS, respectively.

INTRODUCTION

Isocoumarins[1] are generally an important and prevalent core structure in both natural and synthetic compounds of biological, pharmacological, and medicinal importance.[2-4] Several methods have been devised for their preparation. These methods are mostly relying on the use of transition metal compounds as the promoters or catalysts[5] in the halogenative annulation strategy of 2-alkynylaryloate esters **1** (Scheme 1). For 4-Cl-isocoumarins (**2Cl**), almost all methods are usually mediated by transition metal reagents, including $Hg(OAc)_2/CuCl_2$ combination,[6a] $CuCl_2$,[6b-e] $ZnCl_2$,[6f] both as promoters and sources of Cl atom. More recently, InX_3 and GaX_3 were utilized for the synthesis of **2X**, however, only **2Br** and **2I** could be prepared using this method.[6g] Metal-free methods for preparing **2Cl** are far less common. Earlier related examples of a cascade process starting from 2-alkynylaryl carboxylic acid derivatives were elegantly illustrated by Du and co-workers,[7d] which utilized $BF_3{\cdot}Et_2O$ in conjunction with $PhI(OAc)_2$ to affect divergent transformations of the isocoumarin intermediate to provide fused and spiro polycyclic heterocycles. The same research group also recently reported the first metal-free method for directly preparing **2Cl** from esters **1**[7e] by employing $PhICl_2$ as the chlorinating agent in CH_3CN at 70 °C. However, the uncommon $PhICl_2$ was difficult to prepare and handle[8] while the commercially available material was rather expensive. Additionally, this reagent could only be used to prepare **2Cl**, but not **2Br** and **2I**, thus rendering this procedure rather inflexible and less versatile.

Scheme 1. Previously reported methods for the synthesis of 4-chloro- and other 4-haloisocoumarins from 1.



Previous work: Conditions	X	Refs
Transition metal-mediated methods:		
$Hg(OAc)_2$ (1.0 equiv), AcOH; $CuCl_2$ (2.0 equiv), THF, reflux (or Br_2 or I_2)	Cl, Br, I	6a
CuX_2 (2.0 equiv), $Cy_2NH{\cdot}HX$ (0.1 equiv), DCE, 80 °C	Cl, Br	6b, 6d
CuX_2 (2.0 equiv), CH_3CN, reflux	Cl, Br	6c
CuX_2 (2.5 equiv), NCS (2.0 equiv), CH_3CN, reflux	Cl	6e
ZnX_2 (2.0 equiv), Oxone (2.0 equiv), DCE:H_2O (1:1), 80 °C	Cl, Br, I	6f
InX_3 or GaX_3 (1.0 equiv), toluene, 50 °C; $PhI(OAc)_2$, Et_2O, rt	Br, I	6g
Transition metal-free methods:		
Br_2 (2.0 equiv), LiBr (1.5 equiv), HOAc, rt	Br	7a
ICl (1.2 equiv) or I_2 (1.2 equiv), DCM, rt	I	6d, 7b-c
$PhICl_2$ (1.2 equiv), MeCN, 70 °C	Cl	7k

4-Cl-isocoumarins have long been recognized as an important class of potent irreversible inhibitors of serine proteases and esterases,[9] a large and important family of enzymes with crucial roles including blood coagulation, fertilization and protein turnover.[10] Undesired activities of these enzymes may lead to several disease states in human, including viral infections,[11a] stroke and inflammation,[11b-c] arthritis,[11d] cancer,[11e] and Alzheimer's disease.[11f] Examples of some bioactive 4-Cl-isocoumarins are illustrated in Figure 1. 3,4-Dichloroisocoumarin (DCI, **I**) is a general inhibitor of several serine proteases.[12a] 3-Alkoxy-7-amino-4-Cl-isocoumarin (**II**), 3-alkoxy-4-Cl-7-guanidino-isocoumarin (**III**) and 7-amino-4-Cl-3-(3-isothioureidopropoxy)isocoumarin (NH_2-CiTPrOIC, **IV**) have been found to be suicide substrates for serine proteases,[12b] anti-coagulants[12c-d] and inhibitors of Aβ 40/42 amyloid peptides production.[12e-f] 3-Cyclohexylbutoxy-4-Cl-isocoumarin (**V**) could effectively bind and inhibit cholesterol esterase in the nM-range.[9g] More recently, 3-propyloxy-7-amino-4-Cl-isocoumarin (JCP174, **VI**) was identified as an enhancer of the host-cell invasion of parasite *Toxoplasma gondii via* the covalent inhibition of human APT1 palmitoyl protein thioesterase-1 (TgPPT1).[12g]

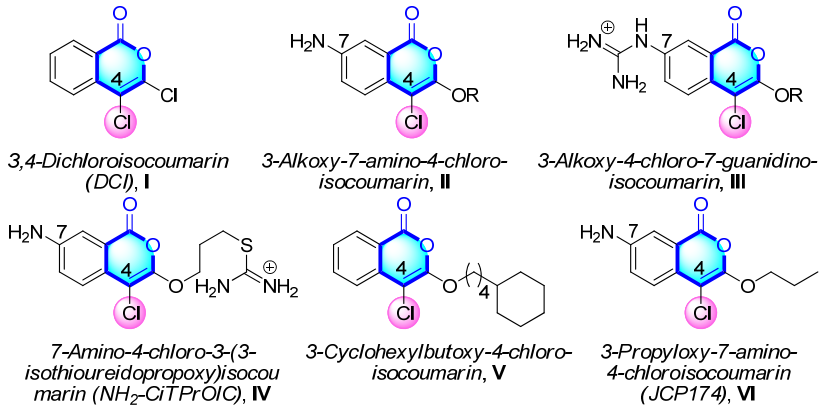


Figure 1. Examples of biologically active 4-Cl-isocoumarins.

We previously reported that the combination of *N*-halosuccinimide (NXS; X = Cl, Br, I) and catalytic TMSCl could lead to the generation of halogen (X-Cl) species which could be utilized in electrophilic aromatic halogenation[13a] and in the synthesis of 4-haloisoxazoles from alkynyl-*O*-methyloximes.[13b] Due to the limitations encountered by other methods in preparing 4-Cl-isocoumarins, herein we were compelled to report our development of a metal-free chlorinative annulation method for direct conversion of 2-alkynylaryloate esters (**1**) to 4-Cl-isocoumarins (**2Cl**) under very mild conditions (0 °C to rt), employing readily available, inexpensive and easy-to-handle NCS and TMSCl. The current protocol was efficient and general in a wide range of substrates. It was also suitable for gram-scale synthesis of **2Cl**. In addition, 4-Br- and 4-I-isocoumarins (**2Br** and **2I**) could be prepared by this method in good yields, simply by switching NCS to NBS and NIS, respectively, thus greatly widened the current repertoire of metal-free methods for the synthesis of 4-haloisocoumarins in general.

RESULTS AND DISCUSSION

Substrate **1a** (R^1 = Me, R^2 = H, R^3 = Ph) was prepared and employed in the optimization study as shown in Table 1.

Table 1. Optimization study of conversion of substrate 1a to isocoumarins 2aCl.[a,b]

Entry	Equiv of NCS	Equiv of TMSCl	Solvent	Temp.	Yield[c]
1	1.5	1.5	CH_3NO_2	rt	69%
2	1.5	1.5	CH_3CN	rt	77%
3	1.5	1.5	THF	rt	44%
4	1.5	1.5	CH_2Cl_2	rt	29%
5	1.5	1.0	CH_3CN	rt	68%
6	1.5	0.5	CH_3CN	rt	68%
7	1.5	0.1	CH_3CN	rt	73%
8	1.5	-	CH_3CN	rt	NR
9	1.2	0.1	CH_3CN	rt	80%
10	1.2	0.1	CH_3CN	0 °C	93%
11	1.2	0.1	CH_3CN	-30 °C	89%

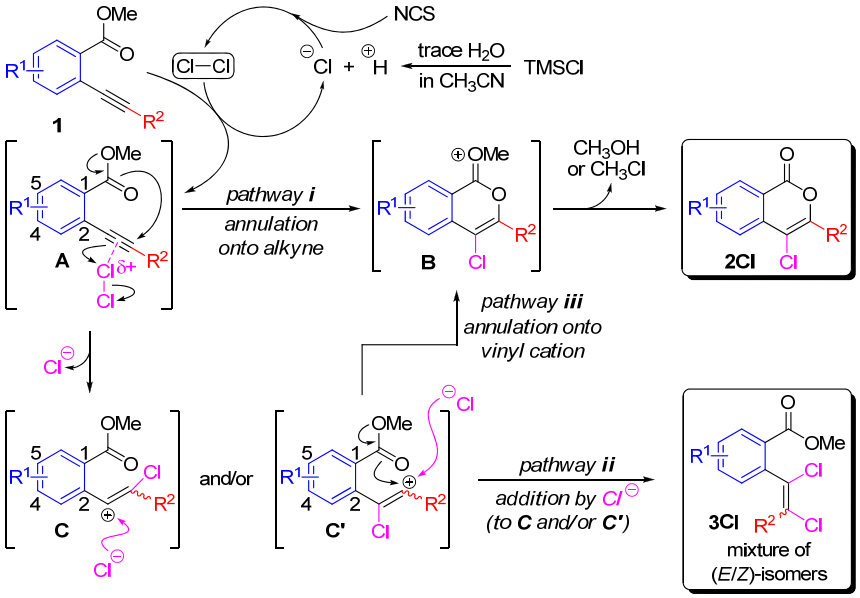
[a]Reactions were all conducted at 0.2–0.3 M of **1a**. [b]All reactions were complete within 1 h. [c]Isolated yields.

Using the combination of TMSCl and NCS, compound **1a** was subjected to these reagents under a variety of conditions. During the optimization, we also observed the formation of side-product **3aCl** in various amounts, resulted from dichlorination of the alkyne moiety (Scheme 2). Compound **1a** was first subjected to 1.5 equiv each of NCS and TMSCl in CH_3NO_2 at rt. The reaction proceeded smoothly to give 69% of the desired product after 1 h (**2aCl**) (entry 1). We next attempted to study the effect of different solvents. As shown in entries 2–4, when conducting the reactions with 1.5 equivalents of both NCS and TMSCl in CH_3CN, THF and CH_2Cl_2 at ambient temperature for 1 h, the reactions afforded the desired product in 77%, 44% and 29% yields, respectively. The results in entries 1–4 showed that the reaction proceeded most optimally in CH_3CN. We next investigated amounts of both NCS

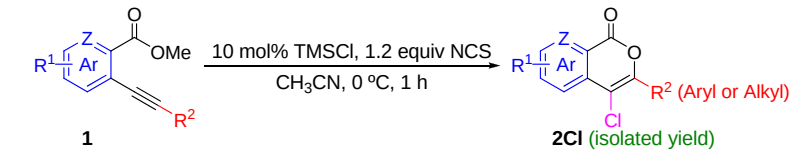
and TMSCl employed in the reaction using CH_3CN as the solvent. As shown in entry 5, when the reaction was conducted with 1.5 equiv of NCS and 1.0 equiv of TMSCl, product **2aCl** was obtained in lower yield (68%) compared to entry 2. When the amount of TMSCl was reduced further to 0.5 equiv, identical yield of compound **2aCl** was obtained (entry 6). However, the yield became slightly better with 0.1 equiv (10 mol%) of TMSCl, providing product **2aCl** in 73% yield (entry 7). Using 1.5 equiv of NCS alone in the reaction without TMSCl afforded no reaction, thus proving that TMSCl was crucial for the conversion (entry 8). We attempted to reduce the amount of NCS to 1.2 equiv while TMSCl was maintained at 0.1 equiv. As shown in entry 9 for the reaction conducted at rt, the conversion was complete within 1 h to furnish the desired product in 80% yield. We continued to examine the effect of temperature by conducting the reaction at 0 °C, while maintaining 1.2 equiv of NCS and 0.1 equiv of TMSCl, and found that the reaction went to completion within 1 h to afford the desired product in 93% yield (entry 10). Decreasing the reaction temperature further to -30 °C resulted in slightly lower yield (entry 11). The optimal conditions were therefore identified as requiring 10 mol% of TMSCl and 1.2 equiv of NCS to react with **1a** in CH_3CN (0.2–0.3 M) at 0 °C which resulted in the complete conversion within 1 h to give **2aCl** in 93% yield while minimizing the formation of **3aCl**. Importantly, these conditions were much milder and more convenient than those reported previously (Scheme 1). The proposed mechanism of this transformation (Scheme 2) commenced with the generation of Cl_2 in the reaction mixture which then activated substrate **1** to probably give the alkyne–chlorine complex **A**. The neighboring methyl ester group participation then ensued, leading to the intramolecular annulation (pathway **i**) to give desired product **2Cl**. However, it was also possible for a vinyl cation **C** or **C'** to form without the participation of the ester group. A competing chloride ion addition to vinyl cation **C** or **C'** (pathway **ii**) could take place non-selectively to give side-product **3Cl** as a mixture of (*E*)- and (*Z*)-isomers. However, addition

of the ester group could also compete with addition of a chloride ion in the case of intermediate **C'** (i.e. pathway **iii**), which would eventually lead to product **2Cl**.

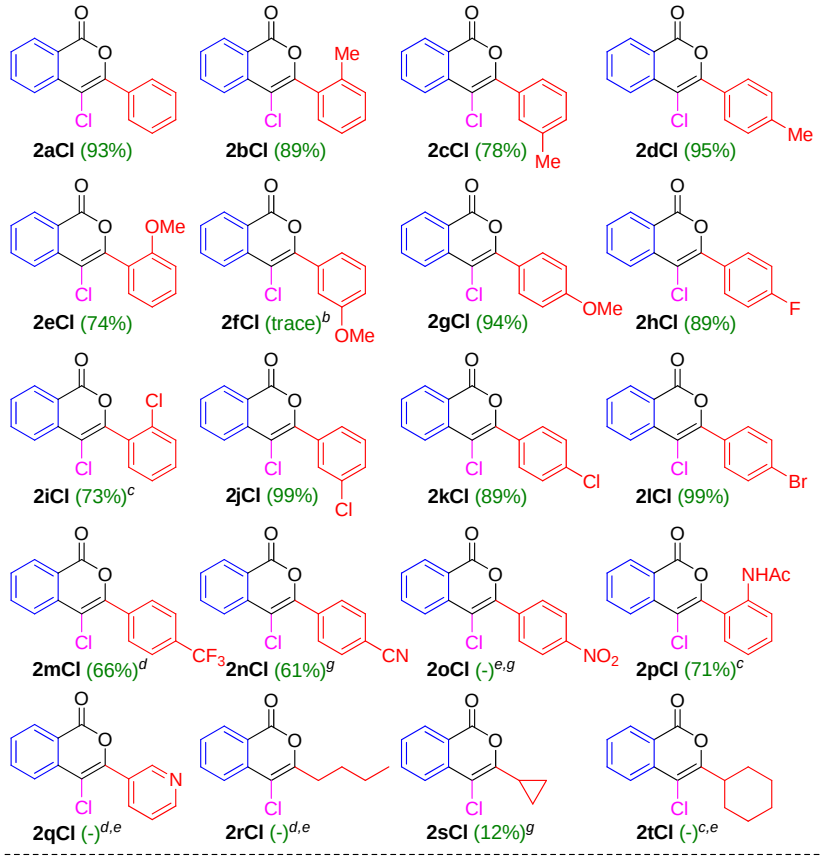
Scheme 2. Proposed mechanism of the chlorinative annulation of compound 1.

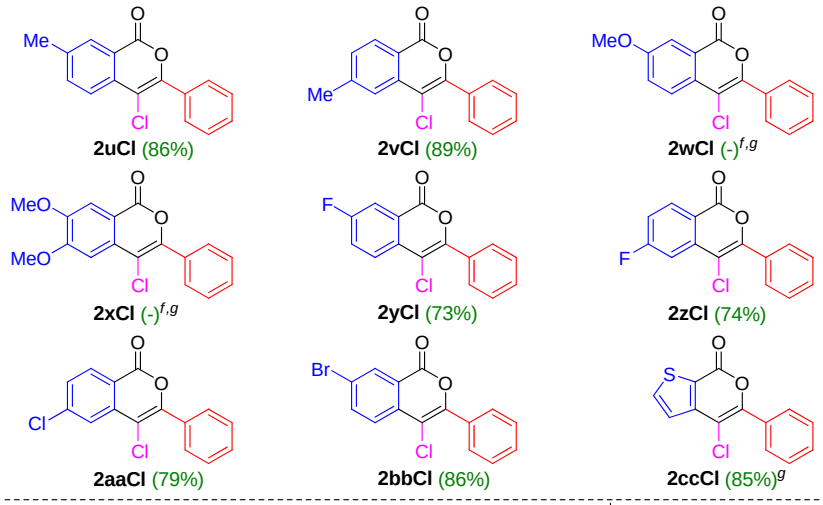


Scheme 3. Substrate scope of the chlorinative annulation.[a]



1 **2Cl** (isolated yield)

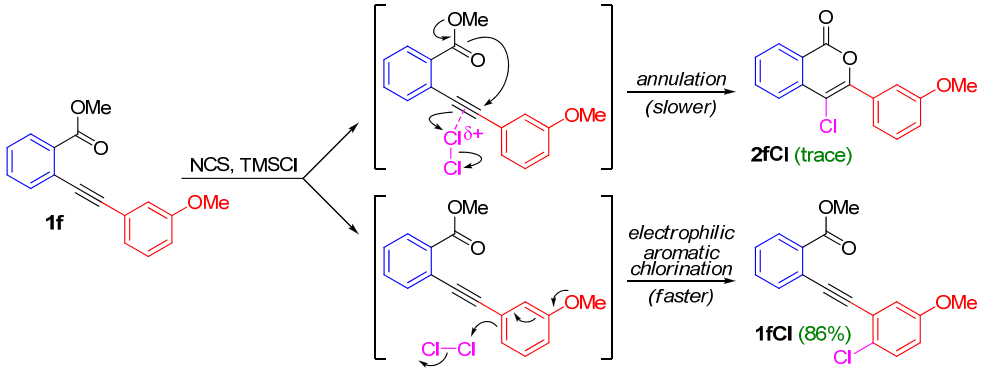




[a]Reaction was conducted at 0.2–0.3 M of **1**. [b]Chlorination occurred *para* to OMe group to afford side-product **1fCl**. [c]Reaction was warmed to rt. [d]Reaction was heated at reflux. [e]Complex reaction mixture. [f]Chlorination side-product **3Cl** was obtained. [g]Starting material was recovered. [h]Methyl 2-(2,2-dichloroacetyl)benzoate was obtained as a side-product (8%).

The generality of our method was next examined with other substrates as shown in Scheme 3. Substrates **1b**–**d** containing electronically neutral tolyl groups of different regioisomers on the alkyne were tested. The reactions proceeded to give products **2bCl**–**2dCl** in good to excellent yields. The reactions of 2-tolyl- and 4-tolyl-substrates provided better yields of products (89% and 95%, respectively) than 3-tolyl-substrate **1c**. Next, substrates with strongly electron-donating OMe group (**1e**–**g**) were investigated. The reaction of **1e** (R^2 = 2-OMe-Ph) proceeded moderately well to give the desired product in 74% yield. However for substrate **1f** (R^2 = 3-OMe-Ph), only trace amount of **2fCl** was observed even after allowing a prolonged reaction time (7 h); electrophilic chlorination on the 3-OMe-Ph ring *para* to the OMe group became the major pathway to provide the corresponding aryl chloride (**1fCl**) in 86% yield. The strongly electron-donating 3-OMe group rendered the aryl ring more reactive towards electrophilic chlorine than the alkyne, thus side-product **1fCl** was obtained *via* electrophilic aromatic chlorination (Scheme 4). Interestingly, this type of side-product was not observed in the case of substrate **1e**, perhaps due to the faster rate of intramolecular annulation by the ester group than the electrophilic aromatic chlorination. Substrate **1g** (R^2 = 4-OMe-Ph) was smoothly converted to product **2gCl** in excellent yield (94%). These results corroborated well with the mechanism proposed in Scheme 2 that strong electron-donating groups at the 2- and 4-positions of the alkynylaryl ring facilitated the desired annulation more efficiently, possibly due to better stabilization of the cationic intermediate **A**.

Scheme 4. Reaction pathways of substrate 1f.

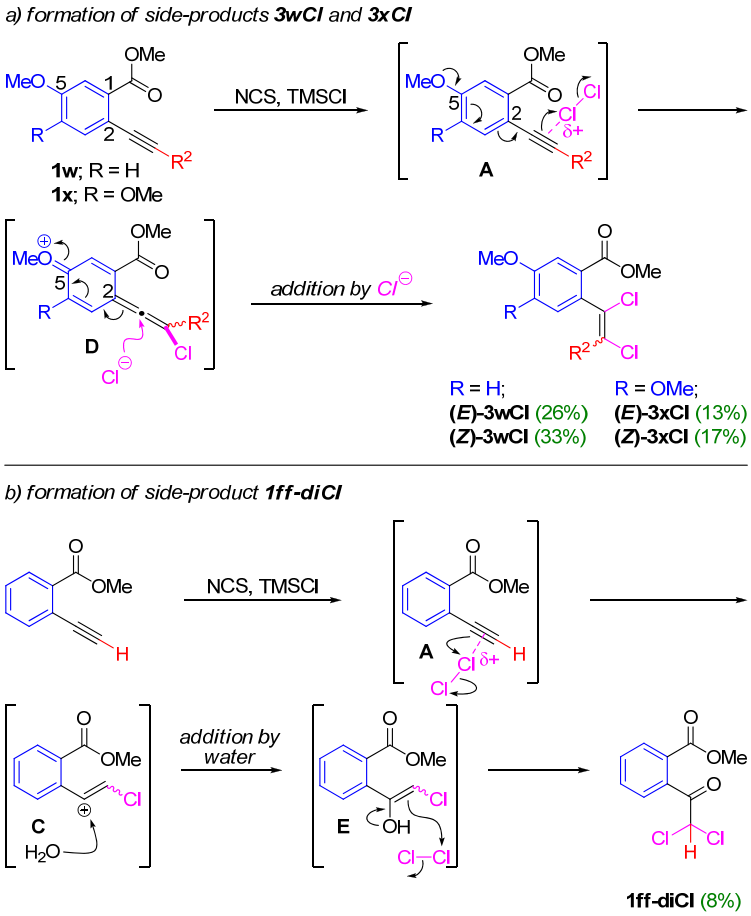


Halogen-substituted R^2 aryl rings were next investigated. The reaction of **1h** (R^2 = 4-F-Ph) proceeded excellently to give the desired product in 89% yield. Reactions were also attempted with substrates carrying Cl- and Br-substituted Ph rings (**1i–l**), all of which afforded the desired products in good to excellent yields (73–99%). Among these, reaction of **1i** (R^2 = 2-Cl-Ph) gave lower yield when compared to the others and the reaction also required longer time (3 h) at rt, possibly due to steric effect imposed by the 2-Cl atom during the annulation. The reactions were less efficient when R^2 were electron-deficient aryl rings. Compound **1m** (R^2 = 4-CF_3-Ph) was converted to **2mCl** in 66% yield while a similar efficiency was also observed with **1n** (R^2 = 4-CN-Ph) which produced **2nCl** in 61% yield along with recovered **1n**. With very strong electron-withdrawing NO_2 group (**1o**), the desired reaction was completely inhibited as only trace amount of **2oCl** was detected. Among the complex reaction mixture, unreacted **1o** was also recovered. For compound **1p** (R^2 = 2-NHAc-Ph), the reaction smoothly afforded **2pCl** in 71% yield. The reaction was then attempted with 3-pyridyl-containing **1q**. Under standard conditions, no reaction was observed even at rt. However, when the reaction was heated at reflux, a complex mixture resulted. The basicity of the pyridine ring was suspected to interfere with the reaction conducted under acidic conditions, thus adversely affecting the reaction outcome. In addition to substrates containing aryl and heteroaryl alkynes, those with alkyl and cycloalkyl alkynes were also investigated (**1r–t**). The reactions were sluggish at 0 °C; for **1r** the reaction mixture was

heated at reflux which resulted in decomposition while for substrate **1t** the reaction went to a complex reaction mixture even at rt. Only the reaction of **1s** could furnish the desired **2sCl**, albeit in low yield (12%) while unreacted **1s** was recovered.

The Ar rings were next varied in substrates **1u**–**cc** while keeping R^2 as Ph group. Most substrates gave the desired products in good to excellent yields, including the thiophene substrate (**1cc**) which was converted to **2ccCl** in 85% yield with 15% of **1cc** recovered. The reactions were not successful with compounds **1w** and **1x** having strong electron-donating OMe group *para*- to the alkyne moiety (C-5). These results were in a stark contrast to substrate **1u** having less electron-donating methyl group at C-5, which was successfully converted to product **2uCl** in excellent yield. It was suspected that in these two cases the delocalization of electron density from the OMe group to the C-2 alkyne moiety effectively competed with the annulation by the *ortho*-ester group and possibly led to the formation of allenyl *para*-quinone methide-type intermediate **D** which further reacted with a chloride anion to provide the corresponding (*E*/*Z*)-isomers of **3wCl** and **3xCl** along with the recovery of the starting compounds (Scheme 5a). The results of substrates **1w** and **1x** were consistent with the result obtained by Du and co-workers[7e] who also proposed a similar mechanism in the formation of an intermediate of type **D**. The reactions of **1dd** and **1ee**, with variations on both Ar rings and R^2 aryl groups, proceeded uneventfully to the corresponding products in excellent yields in both cases. Furthermore, substrate **1ff** containing terminal alkyne moiety was also attempted. However, incomplete conversion was observed and dichloroacetyl methyl ester side-product **1ff-diCl** was obtained in 8% along with 66% of recovered **1ff**. The ketone product (**1ff-diCl**) was presumed to arise from the vinyl cation of type **C** which in this case was intercepted faster with a molecule of water to give the corresponding chloroenol (**E**). This chloroenol intermediate then reacted further with another chlorine molecule to give product **1ff-diCl** (Scheme 5b).

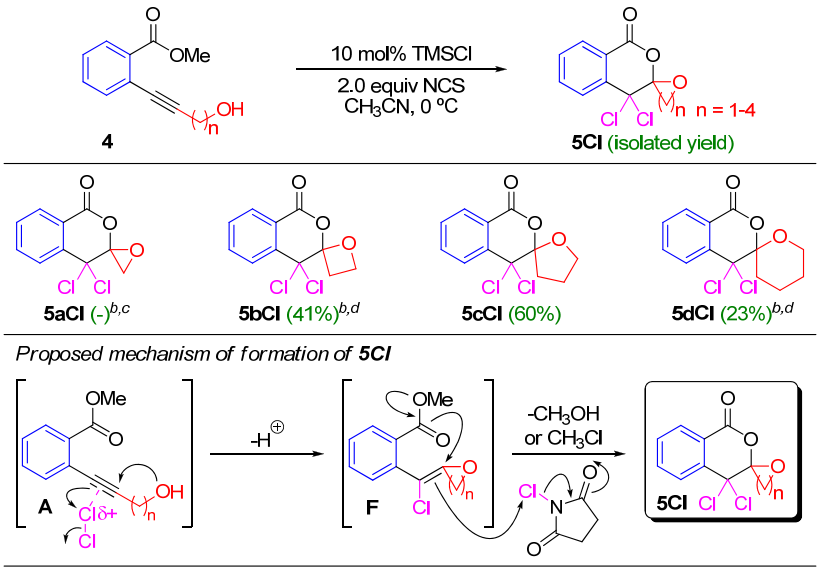
Scheme 5. Formation of side-products 3wCl, 3xCl and 1ff-diCl.



Moreover, substrates **4** bearing pendant alkylhydroxy group on the alkyne moiety, in the presence of 2.0 equiv of NCS, could be converted to spirocyclic ethers **5Cl**. The mechanism was proposed in Scheme 6. Intermediate **A** (from Scheme 2) was believed to undergo chlorinative cyclization with the pendant hydroxy group to give intermediate **F** which further underwent chlorinative spirocyclic lactonization by the nearby methyl ester and upon demethylation, **5Cl** was obtained. The reaction failed in the case of substrate **4a** while substrate **4b** was successfully converted to the 4-membered spirocyclic ether **5bCl**[14a] in moderate yield (41%) after the reaction was warmed to stir at rt. The reaction provided the highest yield from substrate **4c** (n = 3) to give the 5-membered spirocyclic ether **5cCl**[14b] (60%) while the reaction of **4d** (n = 4) proceeded to give the corresponding 6-membered spirocycle **5dCl**[14c] in low yield (23%) only after warming the reaction to rt and unreacted **4d**

was also recovered. However, the reactions of **4e**, **4f**, and **4g** (n = 5, 6, and 8, respectively) failed to give any 7-, 8- and 10-membered spirocyclic ether products.

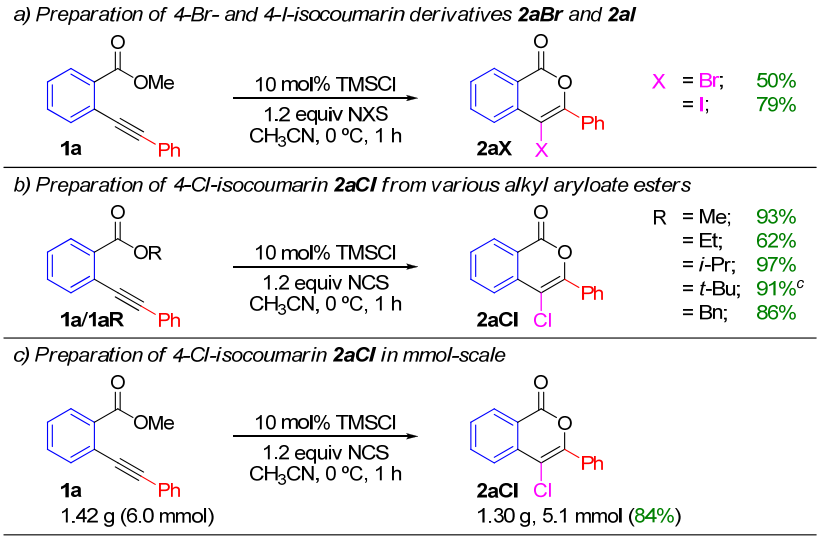
Scheme 6. Substrate scope of the chlorinative spirocyclic lactonization[a] and proposed mechanism of formation of 5Cl.



[a]Reaction was conducted at 0.2 M of **4**. [b]Reaction was warmed to rt. [c]Complex reaction mixture. [d]Starting material was recovered.

The current protocol could be adapted to preparing **2aBr** and **2aI** from **1a** by using NBS and NIS in place of NCS which produced products **2aBr** and **2aI** in 50% and 79% yields, respectively (Scheme 7a). Substrates with other alkyl ester groups were also suitable (Scheme 7b); ethyl (**1aEt**; R = Et), isopropyl (**1a*i*-Pr**; R = *i*-Pr), *tert*-butyl (**1a*t*-Bu**; R = *t*-Bu) and benzyl (**1aBn**; R = Bn) aryloate esters were all successfully converted to the desired product **2aCl** in moderate to excellent yields. Furthermore, gram-scale preparation of product was exemplified with conversion of 1.42 g (6.0 mmol) of **1a** to 1.30 g (5.1 mmol, 84%) of **2aCl** (Scheme 7c).

Scheme 7. Practical features of our method.[a,b]



[a]Reactions were carried out at 0.2-0.3 M of **1a**/**1aR**. [b]Isolated yields. [c]The reaction was carried out at 0 °C for 1 h followed by at rt for 3 h.

CONCLUSIONS

In conclusion, we disclosed a convenient procedure for the preparation of 4-Cl-isocoumarins **2Cl** from 2-alkynylaryloate esters **1** *via* chlorinative annulation. Several significant advantages over the existing methods were revealed, including very mild and metal-free conditions and 6-*endo*-dig-selective cyclization to give the desired products in moderate to excellent yields with wide substrate scope. Additional advantages were the use of readily available, inexpensive and convenient-to-handle TMSCl as the catalyst and NCS as the chlorinating reagents, adaptability to preparing 4-Br- and 4-I-isocoumarins (**2Br** and **2I**) and amenability to preparing the desired isocoumarin products in gram-scale. With modification of substrate structure and conditions, the reaction could be used to prepare spirocyclic ether derivatives containing the isocoumarin scaffold. This method should be of great value to synthetic and medicinal chemists for the preparation of 4-Cl-isocoumarins as well as other 4-haloisocoumarin derivatives.

EXPERIMENTAL SECTION

General Procedure. Commercial grade chemicals were used without further purification, unless otherwise indicated. All solvents were used as received. Oven-dried glassware (110 °C at least for 2 h) was used in all reactions. Crude reaction mixtures were concentrated under reduced pressure on a rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.06–0.2 mm; 70–230 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254 aluminum sheets. Nuclear magnetic resonance (NMR) spectra were recorded in deuteriochloroform ($CDCl_3$) with 300 and 400 MHz spectrometers. Chemical shifts for ^1H NMR and ^{13}C NMR spectra are reported in parts per million (ppm, δ), relative to tetramethylsilane (TMS) as the internal reference. Coupling constants (J) are reported in Hertz (Hz). Infrared spectra were measured using an FT-IR spectrometer and are reported in cm^{-1}. High resolution mass spectra (HRMS) were obtained using a time-of-flight (TOF) instrument.

General Procedure for the Synthesis of Methyl-, Ethyl- and Isopropyl 2-iodobenzoate. A 250-mL round-bottomed flask with a magnetic stir bar was charged with 2-iodobenzoic acid (10 g, 40 mmol) and 0.10 L of 2.0 M aq. H_2SO_4 solution in MeOH. The resulting mixture was allowed to stir at reflux. Upon completion, the reaction mixture was diluted with 20 mL of water and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with saturated aq NaCl solution (10 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure to give 11 g (40 mmol) of crude methyl 2-iodobenzoate which was used in the next step without further treatment.

Note: ~~ethyl 2-iodobenzoate was obtained when EtOH was used and~~ EtOH and *i*-PrOH were used instead of MeOH to obtain ethyl 2-iodobenzoate and isopropyl 2-iodobenzoate, respectively. *tert*-Butyl 2-iodobenzoate and benzyl 2-iodobenzoate were obtained from the procedures below. These materials were then used in Sonogashira cross-coupling with terminal alkynes.

General Procedure for the Synthesis of *t*-Butyl 2-iodobenzoate. A 50-mL round-bottomed flask with a magnetic stir bar was charged with 2-iodobenzoic acid (443.5 mg, 1.79 mmol, 1.0 equiv) and 10.0 mL of CH_2Cl_2 and cooled to 0 °C. The solution was added with *N*,*N'*-dicyclohexylcarbodiimide (DCC) (410.0 mg, 1.99 mmol, 1.1 equiv), followed by 4-*N*,*N*-dimethylaminopyridine (112.9 mg, 0.92 mmol, 0.52 equiv). After 10 min, the reaction was added with *tert*-butanol (0.25 mL, 197.5 mg, 2.66 mmol, 1.5 equiv) by syringe. The reaction mixture was allowed to warm and stir at rt overnight (18 h). After completion, the reaction mixture was filtered through a pad of Celite® and the crude material was directly purified by SiO_2 column chromatography, eluting with 5% EtOAc-hexanes to give the desired product (423.0 g, 1.39 mmol, 78%) as a colorless oil; IR (neat): υ_{max} 2951, 1727, 1286, 1247, 1098, 1015, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 7.8, 1.2 Hz), 7.82 (dd, 1H, J = 7.5, 1.5 Hz,), 7.48–7.45 (m, 2H), 7.42–7.31 (m, 4H), 7.14 (td, 1H, J = 7.5, 1.5 Hz), 5.37 (s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.2, 141.3, 135.4, 134.9, 132.6, 131.0, 128.6, 128.5, 128.4, 127.8, 94.1, 67.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{11}IO_2Na$ 360.9696; found 360.9688.

General Procedure for the Synthesis of Benzyl 2-iodobenzoate. A 10-mL round-bottomed flask with a magnetic stir bar was charged with 2-iodobenzoic acid (0.50 g, 2.0 mmol, 1.0 equiv) and 1.0 mL of CH_2Cl_2. The solution was added with *N*,*N'*-dicyclohexylcarbodiimide (DCC) (0.46 g, 2.2 mmol, 1.1 equiv), followed by 4-*N*,*N*-dimethylaminopyridine (25 mg, 0.20 mmol, 0.10 equiv). After 5 min, the reaction was added with benzyl alcohol (0.22 mL, 0.23 g, 2.12 mmol, 1.06 equiv) by syringe. The reaction mixture was allowed to stir at rt overnight (18 h) then quenched with aq HCl (6 M, 1 mL) and extracted with EtOAc (3 x 1 mL). The combined organic phases were washed with saturated aq NaCl solution (1 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude extract which was purified by SiO_2 column chromatography, eluting with 5–10% EtOAc-

hexanes to give the desired product (0.62 g, 1.8 mmol, 91%) as a colorless oil; IR (neat): υ_{max} 2951, 1727, 1286, 1247, 1098, 1015, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 7.8, 1.2 Hz), 7.82 (dd, 1H, J = 7.5, 1.5 Hz,), 7.48–7.45 (m, 2H), 7.42–7.31 (m, 4H), 7.14 (td, 1H, J = 7.5, 1.5 Hz), 5.37 (s, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.2, 141.3, 135.4, 134.9, 132.6, 131.0, 128.6, 128.5, 128.4, 127.8, 94.1, 67.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{11}IO_2Na$ 360.9696; found 360.9688.

General Procedure for the Synthesis of Compounds 1a–o, 1q–ee, 1aEt, 1a*i*-Pr, 1a*t*-Bu, and 1aBn.

A 250-mL round-bottomed flask with a magnetic stir bar was charged with the crude methyl 2-iodobenzoate from the previous step, followed by 0.10 L of Et_3N. The resulting solution was then added with $Pd(PPh_3)_2Cl_2$ (1.4 g, 2.1 mmol), followed by CuI (0.23 g, 2.1 mmol) to give a yellow solution with solid suspension. The reaction mixture was degassed by a steady stream of argon for 15 min, after which it was kept under argon atmosphere. Phenylacetylene (5.5 mL, 5.1 g, 50 mmol) was then added into the reaction flask by a syringe. The reaction mixture immediately turned black. The reaction mixture was then allowed to stir at rt under argon atmosphere overnight (11 h). The reaction mixture was then diluted with saturated aq NH_4Cl solution (20 mL), followed by extraction with EtOAc (3 x 20 mL). The combined organic phases were washed with saturated aq NaCl solution (20 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by SiO_2 column chromatography, eluting 5% EtOAc-hexanes to give the desired product **1a** (9.6 g, 41 mmol, 98%) as a yellow oil.

Procedure for the Synthesis of Compound 1p. A 25-mL round-bottomed flask with a magnetic stir bar was charged with 2-iodoaniline (0.65g, 3.0 mmol, 1.0 equiv), followed by 5.0 mL of Et_3N. The resulting solution was then added with $Pd(PPh_3)_2Cl_2$ (22 mg, 0.032 mmol, 0.010 equiv), followed by CuI (13 mg, 0.068 mmol, 0.023 equiv) to give a yellow

solution with solid suspension. The reaction mixture was degassed by a steady stream of argon for 15 min, after which it was kept under argon atmosphere. Ethynyltrimethylsilane (0.50 mL, 0.35 g, 3.6 mmol, 1.2 equiv) was then added into the reaction flask by a syringe. The reaction mixture immediately turned black. The reaction mixture was then allowed to stir at rt under argon atmosphere overnight (16 h). The reaction mixture was diluted with saturated aq NH_4Cl solution, followed by extraction with EtOAc. The combined organic phases were washed with saturated aq NaCl solution, dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give 0.63 g of crude product. This crude material was taken up in 20 mL of MeOH in a 150-mL round-bottomed flask and K_2CO_3 (0.49 g, 3.6 mmol, 1.2 equiv) was added to the reaction mixture. The resulting cloudy mixture was allowed to stir at rt until the reaction was judged complete by TLC. Upon completion, the reaction mixture was diluted with water followed by extraction with EtOAc. The combined organic phases were washed with saturated aq NaCl solution, dried over anh. Na_2SO_4, filtered and concentrated to crude orange oil. The crude material was purified by SiO_2 column chromatography, eluting with 10–15% EtOAc-hexanes to give the desired 2-ethynylaniline (0.33 mg, 2.8 mmol, 93%) as pale orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, 1H, J = 7.8, 1.8 Hz), 7.11 (ddd, 1H, J = 8.1, 7.5, 1.5 Hz), 6.73–6.25 (m, 2H), 4.22 (s, 2H), 3.37 (s, 1H). Spectroscopic data for this compound were identical to those reported.[15a]

A 100-mL round-bottomed flask with a magnetic stir bar was charged with methyl 2-iodobenzoate (0.64 g, 2.4 mmol, 1.1 equiv), 2-ethynylaniline (0.26 g, 2.2 mmol, 1.0 equiv) and 10 mL of Et_3N. The resulting solution was then added with $Pd(PPh_3)_2Cl_2$ (30 mg, 0.042 mmol, 0.020 equiv) and the resulting yellow cloudy mixture was degassed by a steady stream of argon for 15 min, after which it was kept under argon atmosphere. CuI (22 mg, 0.11 mmol, 0.052 equiv) was then quickly added to the cloudy reaction mixture which quickly turned greenish yellow. This mixture was allowed to stir at rt under argon atmosphere overnight (16

h) before it was diluted with saturated aq NH_4Cl solution (5 mL) followed by extraction with EtOAc (3 x 5 mL). The combined organic phases were washed with saturated aq NaCl solution (5 mL), dried over anh. Na_2SO_4, filtered, and concentrated to crude greenish yellow oil. The crude material was purified by SiO_2 column chromatography, eluting with 10–20% EtOAc-hexanes to give the desired aniline product (*methyl 2-((2-aminophenyl)ethynyl)benzoate*) (0.51 g, 2.0 mmol, 91%) as bright yellow solid; mp. 62.5–63.0 °C; IR (neat): υ_{max} 3310 (br), 2925, 2854, 1738, 1525, 1294, 1079, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, 1H, J = 7.8, 1.2 Hz), 7.61 (dd, 1H, J = 7.8, 1.2 Hz), 7.43 (td, 1H, J = 7.5, 1.5 Hz), 7.37 (dd, 1H, J = 7.5, 1.5 Hz), 7.33–7.18 (m, 1H), 7.10 (ddd, 1H J = 8.1, 7.5, 1.5 Hz), 6.72–6.59 (m, 2H), 5.04 (br s, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.0, 149.6, 133.4, 131.8, 130.3, 130.0, 129.9, 127.1, 124.4, 116.8, 113.9, 106.9, 93.5, 92.5, 52.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{13}NO_2Na$ 274.0838; found 274.0836.

A 10-mL round-bottomed flask with a magnetic stir bar was charged with the starting aniline compound (96 mg, 0.38 mmol, 1.0 equiv) and 3.0 mL of CH_2Cl_2 to give a clear yellow solution. The solution was cooled to 0 °C and then added with Et_3N (60 μL, 44 mg, 43 mmol, 1.1 equiv), followed by acetyl chloride (42 μL, 46 mg, 0.59 mmol, 1.5 equiv), by syringes. After 15 min, the reaction was complete as judged by TLC. The reaction mixture was diluted with CH_2Cl_2 (1 mL) and water (1 mL). The combined organic phases were washed with saturated aq NaCl solution (1 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure to give crude pale yellow solid which was purified by SiO_2 column chromatography, eluting with 10–20 % EtOAc-hexanes to give the desired **1p** (0.11 g, 0.37 mmol, 95%) as pale yellow solid.

Procedure for the Synthesis of Compound 1ff. A 50-mL round-bottomed flask with a magnetic stir bar was charged with methyl 2-iodobenzoate (931.0 mg, 3.55 mmol, 1.0 equiv),

followed by 10.0 mL of Et_3N. The resulting solution was then added with $Pd(PPh_3)_2Cl_2$ (50.6 mg, 0.072 mmol, 0.020 equiv), followed by CuI (26.5 mg, 0.139 mmol, 0.040 equiv) to give a yellow solution with solid suspension. The reaction mixture was degassed by a steady stream of argon for 15 min, after which it was kept under argon atmosphere. Ethynyltrimethylsilane (0.54 mL, 382.9 mg, 3.90 mmol, 1.10 equiv) was then added into the reaction flask by a syringe. The reaction mixture immediately turned black. The reaction mixture was then allowed to stir at rt under argon atmosphere overnight (18 h). Upon completion, the reaction mixture was diluted with saturated aq NH_4Cl solution, followed by extraction with EtOAc. The combined organic phases were washed with saturated aq NaCl solution, dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give crude product which was purified by SiO_2 column chromatography eluting with 5% EtOAc-hexanes to yield 814.1 mg (99%) of methyl 2-((trimethylsilyl)ethynyl)benzoate as brown oil; IR (neat): υ_{max} 2956, 2159, 1718, 1248, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, 1H, J = 7.8, 0.8 Hz), 7.57 (d, 1H, J = 7.6 Hz), 7.42 (td, 1H, J = 7.6, 1.2 Hz), 7.34 (td, 1H, J = 7.8, 1.2 Hz), 3.91 (s, 3H), 0.28 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 134.3, 132.5, 131.3, 130.1, 128.0, 123.1, 103.2, 99.5, 51.8, -0.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{16}O_2Si$ 233.0992; found 233.0994.

A 50-mL round-bottomed flask containing a magnetic stir bar was charged with methyl 2-((trimethylsilyl)ethynyl)benzoate (1.314 g, 5.65 mmol, 1.00 equiv) and 10.0 mL of MeOH. The reaction solution was then added with K_2CO_3 (790.0 mg, 5.72 mmol, 1.01 equiv) and the resulting heterogeneous mixture was allowed to stir at rt for 1.5 h. The reaction was then diluted with water and extracted with DCM. The combined organic phases were washed with saturated aq NaCl solution, dried over anh. Na_2SO_4, filtered and concentrated under reduced pressure to give 851.1 mg (94%) of the desired product **1ff** as brown oil. This product was

analytically pure as indicated by ^{1}H NMR and was used in the reaction without further treatment.

*Methyl 2-(phenylethynyl)benzoate (**1a**)*: Yield 9.6 g (98%, yellow oil); IR (neat): υ_{max} 2949, 2219, 1727, 1600, 1493, 1250, 1078, 754 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, 1H, J = 8.0, 0.8 Hz), 7.64 (dd, 1H, J = 7.6, 1.3 Hz), 7.59–7.57 (m, 2H), 7.48 (t, 1H, J = 7.6 Hz), 7.39–7.33 (m, 4H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 134.0, 131.9, 131.8, 131.7, 130.5, 128.5, 128.4, 127.9, 123.7, 123.3, 94.4, 88.3, 52.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{13}O_2$ 237.0910; found 237.0911.

*Methyl 2-(o-tolylethynyl)benzoate (**1b**)*: Yield 165.1 mg (72%, dark orange oil); IR (neat): υ_{max} 2950, 2213, 1729, 1492, 1249, 1077, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H, J = 7.8, 1.2 Hz), 7.65 (dd, 1H, J = 7.8, 0.9 Hz), 7.54 (d, 1H, J = 7.5 Hz), 7.49 (dt, 1H, J = 7.5, 1.5 Hz), 7.38 (td, 1H, J = 7.8, 1.2 Hz), 7.26–7.15 (m, 3H), 3.95 (s, 3H), 2.56 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.6, 140.3, 134.0, 132.1, 131.6, 131.5, 130.3, 129.4, 128.5, 127.7, 125.5, 123.8, 123.0, 93.3, 91.9, 52.1, 20.6.; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_2$ 251.1067; found 251.1070.

*Methyl 2-(m-tolylethynyl)benzoate (**1c**)*: Yield 165.1 mg (72%, dark orange oil); IR (neat): υ_{max} 2950, 2210, 1729, 1599, 1490, 1250, 1078, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H, J = 7.8, 1.2 Hz), 7.64 (dd, 1H, J = 7.8, 0.9 Hz), 7.49 (td, 1H, J = 7.5, 1.5 Hz), 7.40–7.35 (m, 3H), 7.25 (t, 1H, J = 7.5 Hz), 7.16 (d, 1H, J = 7.5 Hz), 3.97 (s, 3H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.6, 137.9, 133.9, 132.2, 131.8, 131.6, 130.4, 129.4, 128.8, 128.2, 127.7, 123.8, 123.1, 94.5, 87.8, 52.1, 21.2.; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_2$ 251.1067; found 251.1070.

*Methyl 2-(p-tolylethynyl)benzoate (**1d**)*: Yield 367.0 mg (99%, yellow oil); IR (neat): υ_{max} 2950, 2217, 1716, 1510, 1249, 1077, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, 1H, J = 8.0, 0.8 Hz), 7.63 (dd, 1H, J = 8.0, 0.8 Hz), 7.50–7.46 (m, 3H), 7.36 (td, 1H, J = 7.6, 1.2

Hz), 7.16 (d, 2H, J = 7.6 Hz), 3.96 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 138.7, 133.9, 131.8, 131.6, 130.4, 129.1, 127.7, 123.9, 120.2, 94.6, 87.6, 52.1, 21.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_2$ 251.1067; found 251.1069.

*Methyl 2-((2-methoxyphenyl)ethynyl)benzoate (**1e**)*: Yield 177.0 mg (86%, yellow oil); IR (neat): υ_{max} 2216, 1726, 1244, 1022, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, 1H, J = 7.8, 1.3 Hz), 7.67 (dd, 1H, J = 7.8, 1.3 Hz), 7.55 (dd, 1H, J = 7.6, 1.8 Hz), 7.46 (td, 1H, J = 7.6, 1.4 Hz), 7.37–7.27 (m, 2H), 6.94 (td, 1H, J = 7.5, 1.0 Hz), 6.89 (d, 1H, J = 8.4 Hz), 3.95 (s, 3H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 159.9, 134.0, 133.7, 131.6, 131.5, 130.3, 129.9, 127.6, 123.9, 120.4, 112.4, 110.6, 92.1, 90.8, 55.7, 52.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{14}O_3Na$ 289.0835; found 289.0844.

*Methyl 2-((3-methoxyphenyl)ethynyl)benzoate (**1f**)*: Yield 307.7 mg (≥99%, yellow oil); IR (neat): υ_{max} 2950, 2837, 2210, 1728, 1251, 1077, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, 1H, J = 7.8, 1.2 Hz), 7.62 (dd, 1H, J = 7.8, 1.5 Hz), 7.44 (td, 1H, J = 7.8, 1.5 Hz), 7.33 (td, 1H, J = 7.8, 1.5 Hz), 7.24 (t, 1H, J = 7.8 Hz), 7.17 (d, 1H, J = 7.8 Hz), 7.10 (s, 1H), 6.88 (ddd, 1H, J = 8.1, 2.4, 1.2 Hz), 3.93 (s, 3H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.4, 159.2, 133.8, 131.7, 131.5, 130.3, 129.3, 127.8, 124.1, 123.4, 116.4, 114.9, 94.1, 87.9, 55.1, 52.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{14}O_3Na$ 289.0835; found 289.0834.

*Methyl 2-((4-methoxyphenyl)ethynyl)benzoate (**1g**)*: Yield 216.3 mg (69%, yellow oil); IR (neat): υ_{max} 2215, 1727, 1245, 1077, 830, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, 1H, J = 7.8, 1.4 Hz), 7.62 (dd, 1H, J = 7.7, 1.3 Hz), 7.57–7.41 (m, 3H), 7.35 (td, 1H, J = 7.6, 1.4 Hz,), 6.89 (d, 2H, J = 8.8 Hz), 3.96 (s, 3H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.8, 159.8, 133.7, 133.2, 131.6, 130.4, 127.5, 124.1, 115.4, 114.0, 94.5, 87.1, 55.3, 52.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_3$ 267.1016; found 267.1020.

*Methyl 2-((4-fluorophenyl)ethynyl)benzoate (**1h**)*: Yield 191.3 mg (94%, orange oil); IR (neat): υ_{max} 2951, 1728, 1717, 1507, 1251, 1224, 1077, 835, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (ddd, 1H, J = 7.9, 1.5, 0.6 Hz), 7.66–7.60 (m, 1H), 7.60–7.52 (m, 2H), 7.48 (td, 1H, J = 7.6, 1.5 Hz), 7.37 (td, 1H, J = 7.6, 1.4 Hz), 7.11–6.99 (m, 2H), 3.95 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.9, 162.6 (d, J = 248 Hz), 161.0, 133.9, 133.6 (d, J = 8 Hz), 131.7, 131.7, 130.4, 127.9, 123.6, 119.4 (d, J = 4 Hz), 115.62 (d, J = 22 Hz), 93.2, 87.91 (d, J = 2 Hz), 52.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}FO_2Na$ 277.0635; found 277.0637.

*Methyl 2-((2-chlorophenyl)ethynyl)benzoate (**1i**)*: Yield 256.7 mg (97%, yellow oil); IR (neat): υ_{max} 2951, 1756, 1489, 1253, 1079, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, 1H, J = 7.9, 1.5 Hz), 7.68 (dd, 1H, J = 7.8, 1.4 Hz), 7.63–7.58 (m, 1H), 7.47 (td, 1H, J = 7.6, 1.5 Hz), 7.42–7.33 (m, 2H), 7.27–7.19 (m, 2H), 3.94 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.5, 135.7, 134.2, 133.4, 131.7, 131.5, 130.3, 129.4, 129.1, 128.1, 126.3, 123.1, 123.1, 93.1, 90.8, 52.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}{}^{35}ClO_2Na$ 293.0340; found 293.0336.

*Methyl 2-((3-chlorophenyl)ethynyl)benzoate (**1j**)*: Yield 220.3 mg (90%, yellow oil); IR (neat): υ_{max} 2950, 1728, 1251, 1077, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H, J = 7.8, 1.1 Hz), 7.61 (dd, 1H, J = 7.7, 1.0 Hz), 7.58–7.52 (m, 1H), 7.50–7.41 (m, 2H), 7.36 (td, 1H, J = 7.7, 1.4 Hz), 7.32–7.21 (m, 2H), 3.94 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.3, 134.1, 133.9, 131.8, 131.6, 131.4, 130.4, 129.7, 129.5, 128.6, 128.1, 125.0, 123.1, 92.7, 89.3, 52.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}{}^{35}ClO_2Na$ 293.0340; found 293.0348.

*Methyl 2-((4-chlorophenyl)ethynyl)benzoate (**1k**)*: Yield 187.2 mg (86%, yellow oil); IR (neat): υ_{max} 1729, 1492, 1252, 1078, 821, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, 1H, J = 7.8, 1.4 Hz), 7.64 (dd, 1H, J = 7.7, 1.4 Hz), 7.56–7.44 (m, 3H), 7.39 (td, 1H, J = 7.7,

1.4 Hz), 7.39–7.28 (m, 2H), 3.96 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 166.5, 134.5, 134.0, 132.9, 131.8, 131.7, 130.5, 128.7, 128.1, 123.4, 121.8, 93.1, 89.1, 52.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{11}{}^{35}ClO_2$ 271.0520; found 271.0515.

*Methyl 2-((4-bromophenyl)ethynyl)benzoate (**1l**)*: Yield 437.0 mg (93%, yellow oil); IR (neat): υ_{max} 2219, 1727, 1716, 1492, 1077, 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, 1H, J = 7.8, 1.5 Hz), 7.61 (dd, 1H, J = 7.7, 1.4 Hz), 7.51–7.30 (m, 6H), 3.93 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 166.3, 133.8, 133.0, 132.9, 131.6, 131.5, 130.4, 128.0, 123.3, 122.7, 122.2, 93.1, 89.3, 52.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}{}^{79}BrO_2Na$ 336.9835; found 336.9830.

*Methyl 2-((4-(trifluoromethyl)phenyl)ethynyl)benzoate (**1m**)*: Yield 515.6 mg (99%, orange solid); mp. 51.4–51.9 °C; IR (neat): υ_{max} 1730, 1320, 1122, 841, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, 1H, J = 7.8, 1.2 Hz), 7.69–7.60 (m, 5H), 7.52 (td, 1H, J = 7.5, 1.5 Hz), 7.42 (td, 1H, J = 7.8, 1.5 Hz), 3.96 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 166.4, 134.1, 132.0, 131.9, 131.8, 130.6, 130.1, (q, J = 33 Hz), 128.5, 127.2, 125.3, (q, J = 4 Hz), 123.9 (q, J = 272 Hz), 123.1, 92.7, 90.5, 52.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{11}F_3O_2Na$ 327.0603; found 327.0600.

*Methyl 2-((4-cyanophenyl)ethynyl)benzoate (**1n**)*: Yield 197.0 mg (95%, orange solid); mp. 95.9–96.1 °C; IR (neat): υ_{max} 2223, 1705, 1292, 1125, 946, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, 1H, J = 7.8 Hz), 7.71–7.58 (m, 5H), 7.53 (tt, 1H, J = 7.6, 1.6 Hz), 7.44 (tt, 1H, J = 7.7, 1.6 Hz), 3.96 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 166.0, 134.0, 132.1, 131.9, 131.8, 131.7, 130.5, 128.6, 128.1, 122.6, 118.4, 111.6, 92.4, 92.2, 52.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{11}NO_2Na$ 284.0682; found 284.0688.

*Methyl 2-((4-nitrophenyl)ethynyl)benzoate (**1o**)*: Yield 220.3 mg (90%, yellow solid); mp. 118.8–119.3 °C; IR (neat): υ_{max} 2443, 2217, 1708, 1588, 1341, 1105, 752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.06 (m, 2H), 7.91 (dd, 1H J = 7.8, 1.4 Hz), 7.61–7.57 (m, 2H), 7.55

(dd, 1H, J = 7.7, 1.3 Hz), 7.42 (td, 1H, J = 7.6, 1.4 Hz), 7.34 (td, 1H, J = 7.7, 1.4 Hz,), 3.86 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 146.9, 134.0, 132.2, 131.8, 130.5, 130.1, 128.7, 123.4, 122.4, 93.3, 92.0, 52.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}NO_4$ 282.0761; found 282.0758.

*Methyl 2-((2-acetamidophenyl)ethynyl)benzoate (**1p**)*: Yield 0.11 mg (95%, white solid); mp. 100.0–101.0 °C; IR (neat): υ_{max} 3329, 2949, 2213, 1716, 1686, 1522, 1255, 1079, 748 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.30 (br s, 1H), 8.61 (d, 1H, J = 8.4 Hz), 8.02 (dd, 1H, J = 7.8, 0.9 Hz), 7.61 (dd, 1H, J = 7.8, 0.9 Hz), 7.53–7.42 (m, 2H), 7.42–7.24 (m, 2H), 7.00 (td, 1H, J = 7.6, 1.1 Hz), 3.85 (s, 3H), 2.40 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 169.7, 165.8, 140.8, 133.6, 132.2, 131.7, 130.4, 129.8, 129.3, 127.8, 123.9, 122.5, 119.2, 111.2, 94.5, 90.7, 52.1, 24.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{15}NO_3Na$ 316.0944; found 316.0939.

*Methyl 2-(pyridin-3-ylethynyl)benzoate (**1q**)*: Yield 234.2 mg (97%, yellow oil); IR (neat): υ_{max} 2951, 2346, 1782, 1254, 1079, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, 1H, J = 1.2 Hz), 8.56 (dd, 1H, J = 5.2, 1.6 Hz), 8.01 (dd, 1H, J = 8.0, 1.6 Hz), 7.67 (dd, 1H, J = 8.0, 0.8 Hz), 7.52 (td, 1H, J = 7.6, 1.6 Hz), 7.42 (td, 1H, J = 7.6, 1.2 Hz), 7.31 (dd, 1H, J = 4.8, 0.4 Hz), 7.29 (dd, 1H, J = 4.8, 0.8 Hz), 3.97 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 152.2, 152.2, 148.7, 138.5, 134.0, 131.8, 131.7, 130.5, 128.4, 123.0, 122.9, 120.4, 91.4, 90.7, 52.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{12}NO_2$ 238.0863; Found 238.0864.

*Methyl 2-(hex-1-ynyl)benzoate (**1r**)*: Yield 100.2 mg (44%, yellow oil); IR (neat): υ_{max} 2929, 2161, 1718, 1285, 1082, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, 1H, J = 7.6, 0.8 Hz), 7.51 (dd, 1H, J = 7.6, 0.8 Hz), 7.42 (td, 1H, J = 7.6, 1.6 Hz), 7.30 (td, 1H, J = 7.6, 1.2 Hz), 3.91, (s, 3H), 2.48 (t, 2H, J = 6.8 Hz), 1.66–1.59 (m, 2H), 1.55–1.46 (m, 2H), 0.96 (t, 3H, J = 7.6 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.0, 134.2, 131.9, 131.4, 130.1,

127.1, 124.4, 95.9, 79.1, 52.0, 30.7, 22.0, 19.4, 13.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{16}O_2Na$ 239.1043; found 239.1044.

*Methyl 2-(cyclopropylethynyl)benzoate (**1s**)*: Yield 314.9 mg (99%, pale yellow oil); IR (neat): υ_{max} 2951, 2230, 1728, 1248, 1077, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, 1H, J = 7.8, 1.2 Hz), 7.48 (dd, 1H, J = 7.5, 1.2 Hz), 7.40 (td, 1H, J = 7.5, 1.2 Hz), 7.29 (td, 1H, J = 7.5, 1.2 Hz), 3.91 (s, 3H), 1.56–1.47 (m, 1H), 0.95–0.81 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.8, 134.0, 131.8, 131.4, 130.1, 126.9, 124.4, 99.1, 74.4, 51.9, 8.9, 0.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{12}O_2Na$ 223.0730; found 223.0736.

*Methyl 2-(cyclohexylethynyl)benzoate (**1t**)*: Yield 110.3 mg (99%, yellow oil); IR (neat): υ_{max} 2927, 1727, 1251, 1082, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, 1H, J = 7.8, 1.4 Hz), 7.50 (dd, 1H, J = 7.7, 1.3 Hz), 7.41 (t, 1H, J = 7.5 Hz), 7.30 (t, 1H, J = 7.6 Hz), 3.91 (s, 3H), 2.66 (tt, 1H, J = 8.8, 3.8 Hz), 1.95–1.85 (m, 2H), 1.83–1.72 (m, 2H), 1.66–1.47 (m, 3H), 1.42–1.31 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.1, 134.1, 132.0, 131.4, 130.1, 127.0, 124.3, 99.8, 79.2, 52.0, 32.5, 29.9, 25.9, 24.8; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{18}O_2Na$ 265.1199; found 265.1198.

*Methyl 5-methyl-2-(phenylethynyl)benzoate (**1u**)*: Yield 184.0 mg (99%, yellow oil); IR (neat): υ_{max} 1730, 1500, 1205, 1078, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.77 (m, 1H), 7.59–7.54 (m, 2H), 7.52 (d, 1H, J = 7.9 Hz), 7.39–7.31 (m, 3H), 7.28 (ddd, 1H, J = 7.9, 1.9, 0.9 Hz), 3.95 (s, 3H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 138.1, 133.8, 132.5, 131.6, 130.9, 128.2, 123.4, 120.6, 93.4, 88.3, 52.1, 21.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_2$ 251.1067; found 251.1067.

*Methyl 4-methyl-2-(phenylethynyl)benzoate (**1v**)*: Yield 190.2 mg (99%, yellow oil); IR (neat): υ_{max} 2950, 1727, 1291, 1254, 1080, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 1H, J = 8.0 Hz), 7.59–7.56 (m, 2H), 7.46 (d, 1H, J = 0.4 Hz), 7.37–7.32 (m, 3H), 7.17 (d, 1H, J = 8.0 Hz), 3.94 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 142.3,

34.5, 131.7, 139.6, 128.9, 128.8, 128.4, 128.3, 123.6, 123.4, 93.8, 88.5, 52.0, 21.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{14}O_2Na$ 273.0886; found 273.0894.

*Methyl 5-methoxy-2-(phenylethynyl)benzoate (**1w**)*: Yield 349.9 mg (79%, orange oil); IR (neat): υ_{max} 2924, 1740, 1232, 1089, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.53 (m, 3H), 7.48 (d, 1H, J = 2.8 Hz), 7.36–7.31 (m, 3H), 7.02 (dd, 1H, J = 8.8, 2.8 Hz), 3.96 (s, 3H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 159.0, 135.3, 133.1, 131.5, 128.3, 128.1, 123.6, 118.2, 115.8, 115.0, 92.5, 88.1, 55.5, 52.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{14}O_3Na$ 289.0835; found 289.0830.

*Methyl 4,5-dimethoxy-2-(phenylethynyl)benzoate (**1x**)*: Yield 278.3 mg (99%, orange solid); mp. 89.6–89.8 °C; IR (neat): υ_{max} 2949, 1722, 1518, 1209, 1002, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.53 (s, 1H), 7.39–7.33 (m, 3H), 7.09 (s, 1H), 3.97 (s, 3H), 3.96 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 151.6, 148.6, 131.6, 128.32, 128.30, 124.5, 123.5, 117.5, 115.7, 112.9, 93.0, 88.6, 56.12, 56.06, 52.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{16}O_4Na$ 319.0941; found 319.0941.

*Methyl 5-fluoro-2-(phenylethynyl)benzoate (**1y**)*: Yield 140.7 mg (99%, orange oil); IR (neat): υ_{max} 2952, 2217, 1717, 1497, 1067, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 1H d, J = 9.2, 2.8 Hz), 7.62 (dd, 1H, J = 8.6, 5.5 Hz), 7.59–7.53 (m, 2H), 7.40–7.31 (m, 3H), 7.20 (td, 1H, J = 8.2, 2.8 Hz), 3.96 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.5 (d, J = 3 Hz), 165.4, 161.5 (d, J = 249 Hz), 135.8 (d, J = 8 Hz), 133.7 (d, J= 8 Hz), 131.6, 128.5, 128.3, 123.1, 119.9 (d, J = 4 Hz), 119.2 (d, J = 22 Hz), 117.5 (d, J = 24 Hz), 94.0, 87.1, 52.4; HRMS (ESI-TOF) *m/z*: [M + Na]+ calcd for $C_{16}H_{11}FNaO_2$ 277.0635; Found 277.0635.

*Methyl 4-fluoro-2-(phenylethynyl)benzoate (**1z**)*: Yield 386.4 mg (97%, orange oil); IR (neat): υ_{max} 2952, 2216, 1716, 1248, 1116, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, 1H, J = 8.8, 5.6 Hz), 7.59–7.57 (m, 2H), 7.39–7.36 (m, 3H), 7.33 (dd, 1H, J = 9.2, 2.8 Hz), 7.33 (td, 1H, J = 8.4, 2.4 Hz), 3.96 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 164.3 (d, J =

236 Hz), 133.1 (d, J = 10 Hz), 131.8, 128.9, 128.4, 128.0 (d, J = 3 Hz), 126.4 (d, J = 10 Hz), 122.8, 120.6 (d, J = 23 Hz), 115.3 (d, J = 22 Hz), 95.6, 87.1 (d, J = 3 Hz), 52.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}FO_2Na$ 277.0635; found 277.0630.

*Methyl 4-chloro-2-(phenylethynyl)benzoate (**1aa**)*: Yield 304.3 mg (91%, yellow oil); IR (neat): υ_{max} 2221, 1732, 1716, 1285, 1101, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, 1H, J = 8.5 Hz), 7.63 (d, 1H, J = 2.2 Hz), 7.61–7.53 (m, 2H), 7.40–7.32 (m, 4H), 3.95 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 165.8, 138.0, 133.6, 131.8, 131.8, 130.0, 128.8, 128.4, 128.1, 125.5, 122.8, 95.6, 87.0, 52.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{11}{}^{35}ClO_2Na$ 293.0340; found 293.0337.

*Methyl 5-bromo-2-(phenylethynyl)benzoate (**1bb**)*: Yield 190.2 mg (99%, yellow oil); IR (neat): υ_{max} 2950, 1727, 1291, 1254, 1080, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 1H, J = 2.0 Hz), 7.61–7.55 (m, 3H), 7.49 (d, 1H, J = 8.4 Hz), 7.37–7.34 (m, 3H), 3.96 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.3, 135.1, 134.7, 133.4, 133.2, 131.7, 128.7, 128.4, 122.9, 122.7, 121.8, 95.5, 87.3, 52.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{79}BrO_2$ 315.0015; found 315.0014.

*Methyl 3-(phenylethynyl)thiophene-2-carboxylate (**1cc**)*: Yield 686.6 mg (99%, orange solid); mp. 69.0–70.0 °C; IR (neat): υ_{max} 2952, 1714, 1236, 1073, 880, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59–7.58 (m, 2H), 7.44 (d, 1H, J = 5.2 Hz), 7.35–7.34 (m, 3H), 7.19 (d, 1H, J = 5.2 Hz), 3.92 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.7, 133.2, 132.0, 131.7, 130.4, 128.7, 128.3, 127.3, 122.8, 95.2, 83.9, 52.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{11}O_2S$ 243.0474; found 243.0472.

*Methyl 5-methyl-2-(p-tolylethynyl)benzoate (**1dd**)*: Yield 146.0 mg (83%, yellow crystal); mp. 61.3–61.8 °C; IR (neat): υ_{max} 2921, 2216, 1729, 1513, 1203, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.50 (d, 1H, J = 8.0 Hz), 7.46 (d, 2H, J = 8.4 Hz), 7.25 (dd, 1H, J = 7.8, 1.2 Hz), 7.14 (d, 2H, J = 8.0 Hz), 3.94 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR

(100 MHz, $CDCl_3$) δ 166.8, 138.3, 137.8, 133.7, 132.4, 131.4, 130.9, 129.0, 120.8, 120.3, 93.6, 87.6, 52.0, 21.4, 21.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{16}NaO_2$ 287.1043; Found 287.1050.

*Methyl 5-fluoro-2-((4-methoxyphenyl)ethynyl)benzoate (**1ee**)*: Yield 280.0 mg (90%, yellow oil); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 1H, J = 9.2 Hz), 7.62–7.56 (m, 1H), 7.50 (d, 2H, J = 8.2 Hz), 7.19 (t, 1H, J = 8.1 Hz), 6.88 (d, 2H, J = 8.2 Hz), 3.96 (s, 3H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.6, 161.4 (d, J = 249 Hz), 159.9, 135.6 (d, J = 8 Hz), 133.4 (d, J = 8 Hz), 133.2, 120.4 (d, J = 4 Hz), 119.2 (d, J = 22 Hz), 117.5 (d, J = 24 Hz), 115.2, 114.0, 94.2, 86.0, 55.3, 52.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{14}O_3F$ 285.0922; Found 285.0919.

*Methyl 2-ethynylbenzoate (**1ff**)*: Yield 851.1 mg (94%, brown oil); IR (neat): υ_{max} 3265, 2951, 1717, 1254, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95-7.92 (m, 1H), 7.62 (dd, 1H, J = 7.7, 1.2 Hz), 7.47 (td, 1H, J = 7.5, 1.5 Hz), 7.40 (td, 1H, J = 7.5, 1.5 Hz), 3.93 (s, 3H)), 3.41 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.3, 134.9, 132.4, 131.6, 130.2, 128.4, 122.6, 82.2, 81.9, 52.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_9O_2$ 161.0597; found 161.0597.

*Ethyl 2-(phenylethynyl)benzoate (**1aEt**)*: Yield 465.5 mg (99%, dark orange oil); IR (neat): υ_{max} 2982, 2218, 2164, 1725, 1721, 1247, 753, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (ddd, 1H, J = 7.8, 1.5, 0.3 Hz), 7.65 (ddd, 1H J = 7.8, 1.2, 0.3 Hz), 7.59–7.57 (m, 2H), 7.49 (td, 1H, J = 7.8, 1.5 Hz), 7.41–7.34 (m, 4H), 4.43 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.4, 134.0, 132.2, 131.7, 131.5, 130.4, 128.4, 128.3, 127.9, 123.5, 123.3, 94.2, 88.2, 61.2, 14.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}O_2$ 251.1067; found 251.1062.

*Isopropyl 2-(phenylethynyl)benzoate (**1ai-Pr**)*: Yield 324.1 mg (99%, yellow oil); IR (neat): υ_{max} 2980, 2218, 1708, 1493, 1289, 1250, 1105, 1072, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 7.94 (dd, 1H, J = 7.5, 0.9 Hz), 7.64-7.55 (m, 3H), 7.45 (td, 1H, J = 7.5, 1.5 Hz), 7.38-7.33 (m, 4H), 5.36-5.23 (m, 1H), 1.37 (d, 6H, J = 6.3 Hz); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 165.9, 134.0, 132.6, 131.5, 131.3, 130.2, 128.33, 128.26, 127.8, 123.3, 94.0, 88.3, 68.7, 21.9; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{16}O_2Na$ 287.1043; found 287.1046.

*tert-Butyl 2-(phenylethynyl)benzoate (**1at-Bu**)*: Yield 218.9 mg (82%, brown oil); IR (neat): υ_{max} 2977, 2217, 1706, 1130, 757 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (δ 7.86 (dd, 1H, J = 7.7, 0.9 Hz), 7.62-7.59 (m, 1H), 7.57-7.54 (m, 2H), 7.43 (td, 1H, J = 7.5, 1.5 Hz), 7.37-7.32 (m, 4H), 1.60 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) (δ 165.9, 134.1, 133.9, 131.5, 130.9, 130.0, 128.3, 127.8, 123.5, 122.9, 93.7, 88.4, 81.6, 28.2; HRMS (ESI-TOF) (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{19}O_2$ 279.1380; found 279.1379.

*Benzyl 2-(phenylethynyl)benzoate (**1aBn**)*: Yield 163.6 mg (36%, yellow oil); IR (neat): υ_{max} 2216, 1723, 1714, 1494, 1243, 1069, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, 1H, J = 7.8, 1.4 Hz), 7.64 (dd, 1H, J = 7.7, 1.3 Hz), 7.54–7.27 (m, 12H), 5.41 (s, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 166.1, 135.8, 134.1, 131.7, 131.7, 130.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 123.8, 123.2, 94.5, 88.2, 67.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{16}O_2Na$ 335.1043; found 335.1033.

General Procedure for the Synthesis of Isocoumarins 2Cl, 2Br, and 2I. A 10-mL round-bottomed flask with a magnetic stir bar was charged with a solution of compound **1a** (46.9 mg, 0.20 mmol, 1.0 equiv) in 1.0 mL of CH_3CN (0.20 M) and cooled to 0 °C in an ice bath. To this solution, NCS (32.8 mg, 0.24 mmol, 1.2 equiv) was added in one portion, followed by TMSCl (2.5 μL, 2.2 mg, 0.020 mmol, 0.10 equiv). The resulting solution was allowed to stir at 0 °C until the reaction was judged complete by TLC (usually within 1 h). Then the reaction was warmed to rt and diluted with water (1 mL) which resulted in a bi-layer mixture. The mixture was extracted with EtOAc (3 x 1 mL) and the combined organic phases were washed

with saturated aq NaCl solution (1 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by SiO_2 column chromatography, eluting with 2–5% EtOAc-hexanes to give the desired product **2aCl** (47.6 mg, 0.19 mmol, 93%) as white solid.

Note: for **2Br** and **2I**, NBS and NIS, respectively, were used instead of NCS.

*4-Chloro-3-phenyl-1H-isochromen-1-one (**2aCl**)*: Yield 47.6 mg (93%, white solid); mp. 139.4–139.6 °C; IR (neat): υ_{max} 2926, 1739, 1233, 1091, 753, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1H, J = 8.0 Hz), 7.97 (d, 1H, J = 8.0 Hz), 7.89–7.86 (m, 3H), 7.62 (t, 1H, J = 7.6 Hz), 7.50–7.48 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.9, 150.5, 136.0, 135.4, 131.5, 130.2, 129.9, 129.4, 129.2, 128.2, 124.1, 120.6, 111.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_9{}^{35}ClO_2Na$ 279.0183; found 279.0180.

*4-Chloro-3-o-tolyl-1H-isochromen-1-one (**2bCl**)*: Yield 93.1 mg (89%, white solid); mp. 113.0–114.0 °C; IR (neat): υ_{max} 2926, 1739, 1632, 1479, 1231, 1076, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, 1H, J = 7.6, 0.4 Hz), 7.93–7.85 (m, 2H), 7.65–7.61 (m, 1H), 7.43–7.37 (m, 2H), 7.32–7.25 (m, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0, 151.5, 137.4, 135.4, 135.3, 131.2, 130.4, 130.2, 129.91, 129.89, 129.2, 125.7, 123.8, 120.6, 112.7, 19.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}{}^{35}ClO_2Na$ 293.0340; found 293.0335.

*4-Chloro-3-m-tolyl-1H-isochromen-1-one (**2cCl**)*: Yield 80.5 mg (78%, white solid); mp. 89.0–90.0 °C; IR (neat): υ_{max} 2923, 1745, 1606, 1478, 1095, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, 1H, J = 7.8 Hz), 7.92 (d, 1H, J = 8.1 Hz), 7.85–7.80 (m, 1H), 7.67–7.64 (m, 2H), 7.60–7.55 (m, 1H), 7.38–7.33 (m, 1H), 7.26 (d, 1H, J = 7.2 Hz), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.8, 150.5, 137.9, 135.9, 135.2, 131.2, 130.9, 129.7, 128.9, 128.0, 126.4, 123.9, 120.4, 111.0, 21.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}{}^{35}ClO_2Na$ 293.0340; found 293.0338.

*4-Chloro-3-p-tolyl-1H-isochromen-1-one (**2dCl**)*: Yield 54.3 mg (95%, white solid); mp. 141.1–141.9 °C; IR (neat): υ_{max} 2948, 1742, 1234, 1087, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, 1H, J = 8.0 Hz), 7.96 (d, 1H, J = 8.0 Hz), 7.86 (t, 1H, J = 7.6 Hz), 7.78 (d, 2H, J = 7.2 Hz), 7.60 (t, 1H, J = 7.6 Hz), 7.30 (d, 2H, J = 7.2 Hz), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0, 150.6, 140.5, 136.1, 135.3, 129.8, 129.2, 129.1, 128.9, 128.6, 123.9, 120.4, 110.9, 21.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClO_2$ 271.0520; found 271.0518.

*4-Chloro-3-(2-methoxyphenyl)-1H-isochromen-1-one (**2eCl**)*: Yield 26.5 mg (74%, white solid); mp. 122.8–123.3 °C; IR (neat): υ_{max} 1737, 1633, 1255, 1077, 1021, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1H, J = 7.6 Hz), 7.92 (d, 1H, J = 8.4 Hz), 7.86 (td, 1H, J = 7.6, 1.2 Hz), 7.64–7.60 (m, 1H), 7.50–7.43 (m, 2H), 7.06 (td, 1H, J = 7.2, 0.8 Hz), 7.01 (d, 1H, J = 8.4 Hz), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4, 157.5, 149.3, 135.8, 135.1, 131.9, 131.2, 129.9, 129.0, 123.8, 120.8, 120.3, 113.4, 111.4, 55.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClO_3$ 287.0469; found 287.0467.

*4-Chloro-3-(4-methoxyphenyl)-1H-isochromen-1-one (**2gCl**)*: Yield 57.5 mg (94%, white solid); mp. 139.7–140.0 °C; IR (neat): υ_{max} 2943, 2841, 1740, 1615, 1511, 1023, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, 1H, J = 7.8 Hz), 7.93 (d, 1H, J = 7.8 Hz), 7.87–7.81 (m, 3H), 7.58 (t, 1H, J = 7.8 Hz), 6.99 (d, 2H, J = 9.0 Hz), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 161.0, 160.9, 150.3, 136.2, 135.2, 130.9, 129.7, 128.7, 123.8, 123.7, 120.3, 113.6, 110.3, 55.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClO_3$ 287.0469; found 287.0464.

*4-Chloro-3-(4-fluorophenyl)-1H-isochromen-1-one (**2hCl**)*: Yield 41.8 mg (89%, white solid); mp. 166.3–166.5 °C; IR (neat): υ_{max} 2233, 1742, 1607, 1233, 1090, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (dd, 1H, J = 7.8, 1.2 Hz), 7.97 (d, 1H, J = 8.1 Hz), 7.92–7.85 (m, 3H), 7.65–7.60 (m, 1H), 7.18 (t, 2H, J = 8.7 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.5 (d, J =

252 Hz), 160.7, 149.5, 135.8, 135.4, 131.5 (d, J = 9 Hz), 129.9, 129.2, 127.5 (d, J = 3 Hz), 124.0, 120.5, 115.4 (d, J = 22 Hz), 111.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_8{}^{35}ClFO_2Na$ 297.0089; found 297.0084.

*4-Chloro-3-(2-chlorophenyl)-1H-isochromen-1-one (**2iCl**)*: Yield 51.6 mg (73%, white solid); mp. 92.0–92.2 °C; IR (neat): υ_{max} 1737, 1636, 1478, 1231, 1051, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1H, J = 7.6 Hz), 7.95–7.87 (m, 2H), 7.66 (t, 1H, J = 7.6 Hz), 7.54–7.51 (m, 2H), 7.45 (t, 1H, J = 7.6 Hz), 7.39 (t, 1H, J = 7.6 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8, 148.9, 135.4, 135.2, 134.1, 131.52, 131.47, 130.9, 130.1, 129.9, 129.5, 126.8, 124.0, 120.9, 113.9; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_8{}^{35}Cl_2O_2Na$ 312.9794; found 312.9794.

*4-Chloro-3-(3-chlorophenyl)-1H-isochromen-1-one (**2jCl**)*: Yield 38.9 mg (99%, white solid); mp. 182.2–182.3 °C; IR (neat): υ_{max} 2925, 1742, 1476, 1232, 1077, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, 1H, J = 8.0, 1.2 Hz), 7.98 (d, 1H, J = 7.6 Hz), 7.91–7.87 (m, 2H), 7.77 (tt, 1H, J = 7.2, 1.6 Hz), 7.67–7.63 (m, 1H), 7.48–7.41 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 148.9, 135.6, 135.5, 134.3, 133.0, 130.3, 129.9, 129.51, 129.49, 129.4, 127.5, 124.2, 120.6, 112.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_8{}^{35}Cl_2O_2Na$ 312.9794; found 312.9794.

*4-Chloro-3-(4-chlorophenyl)-1H-isochromen-1-one (**2kCl**)*: Yield 40.9 mg (89%, white solid); mp. 153.8–154.1 °C; IR (neat): υ_{max} 2924, 1740, 1232, 1089, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, 1H, J = 7.8 Hz), 7.96 (d, 1H, J = 7.8, Hz), 7.89 (dd ,1H, J = 7.2, 1.2 Hz) 7.83 (d, 2H, J = 8.7, Hz), 7.65–7.60 (m, 1H), 7.46 (d, 2H, J = 8.7 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.6, 149.2, 136.3, 135.7, 135.4, 130.6, 129.9, 129.8, 129.3, 128.5, 124.1, 120.5, 111.6; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_8{}^{35}Cl_2O_2Na$ 312.9794; found 312.9790.

*3-(4-Bromophenyl)-4-chloro-1H-isochromen-1-one (**2lCl**)*: Yield 65.0 mg (99%, white solid); mp. 195.4–195.7 °C; IR (neat): υ_{max} 2953, 1717, 1290, 1089, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, 1H, J = 7.8 Hz), 7.96 (d, 1H, J = 7.8 Hz), 7.90–7.84 (m, 1H), 7.56 (d, 2H, J = 8.7 Hz), 7.65–7.61 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.6, 149.3, 135.7, 135.4, 131.5, 130.9, 130.3, 129.9, 129.4, 124.7, 124.1, 120.6, 111.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9{}^{79}Br^{35}ClO_2$ 334.9469; found 334.9468.

*4-Chloro-3-(4-(trifluoromethyl)phenyl)-1H-isochromen-1-one (**2mCl**)*: Yield 55.0 mg (66%, white solid); mp. 144.6–145.1 °C; IR (neat): υ_{max} 1718, 1324, 1125, 1071, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1H, J = 8.0 Hz), 8.02–7.97 (m, 3H), 7.91–7.87 (m, 1H), 7.75 (d, 2H, J = 8.0 Hz), 7.67–7.63 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.4, 148.7, 135.5, 135.4, 134.8, 131.8 (q, J = 33 Hz), 129.9, 129.7, 129.6, 125.2 (q, J = 4 Hz), 124.2, 123.7 (q, J = 289 Hz), 120.6, 112.4; HRMS (ESI-TOF) *m/z*: $[M - H]^+$ calcd for $C_{16}H_7{}^{35}ClF_3O_2$ 323.0081; found 323.0083.

*4-(4-Chloro-1-oxo-1H-isochromen-3-yl)benzonitrile (**2nCl**)*: Yield 30.8 mg (61%, white solid); mp. 183.8–184.0 °C; IR (neat): υ_{max} 2233, 1742, 1607, 1233, 1090, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1H, J = 7.6 Hz), 8.01 (t, 3H, J = 8.8 Hz), 7.94–7.90 (m, 1H), 7.79 (d, 2H, J = 8.4 Hz), 7.68 (t, 1H, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 148.2, 135.7, 135.4, 133.1, 132.2, 132.1, 130.1, 130.0, 124.5, 120.8, 118.2. 113.8, 113.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_9{}^{35}ClNO_2$ 282.0314; found 282.0313.

*N-(2-(4-Chloro-1-oxo-1H-isochromen-3-yl)phenyl)acetamide (**2pCl**)*: Yield 82.1 mg (71%, white solid); mp. 163.0–164.0 °C; IR (neat): υ_{max} 3310 (br), 2925, 2854, 1738, 1525, 1294, 1079, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17–8.05 (m, 2H), 7.98–7.81 (m, 3H), 7.52 (t, 1H, J = 7.5 Hz), 7.42 (t, 2H, J = 8.1 Hz), 7.19 (t, 1H, J = 7.5 Hz), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.8, 161.0, 148.5, 136.0, 135.4, 135.2, 131.0, 130.4, 129.5,

129.4, 124.3, 123.9, 123.6, 122.6, 120.3, 113.8, 24.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{12}{}^{35}ClNO_3Na$ 336.0398; found 336.0396.

*4-Chloro-3-cyclopropyl-1H-isochromen-1-one (**2sCl**)*: Yield 12.4 mg (12%, colorless crystal); mp. 119.1–119.8 °C; IR (neat): υ_{max} 1725, 1621, 1320, 1079, 1002, 763, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, 1H, J = 7.5 Hz), 7.83–7.75 (m, 2H), 7.52–7.47 (m, 1H), 2.43–2.35 (m, 1H), 1.25–1.20 (m, 2H), 1.07–1.00 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.8, 153.9, 136.0, 135.3, 129.8, 127.9, 122.7, 119.8, 110.1, 11.5, 7.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_9{}^{35}ClO_2Na$ 243.0183; found 243.0181.

*4-Chloro-7-methyl-3-phenyl-1H-isochromen-1-one (**2uCl**)*: Yield 50.8 mg (86%, white solid); mp. 161.1–161.3 °C; IR (neat): υ_{max} 1742, 1627, 1497, 1095, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.89–7.85 (m, 3H), 7.68 (dd, 1H, J = 8.4, 1.2 Hz), 7.51–7.45 (m, 3H), 2.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1, 149.6, 139.7, 136.5, 133.6, 131.5, 130.0, 129.6, 129.3, 128.2, 124.0, 120.4, 111.4, 21.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}{}^{35}ClO_2Na$ 293.0340; found 293.0338.

*4-Chloro-6-methyl-3-phenyl-1H-isochromen-1-one (**2vCl**)*: Yield 89.0 mg (89%, white solid); mp. 147.5–147.6 °C; IR (neat): υ_{max} 1732, 1615, 1240, 1040, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, 1H, J = 8.0 Hz), 7.89–7.85 (m, 2H), 7.74 (s, 1H), 7.51–7.47 (m, 3H), 7.41 (d, 1H, J = 8.4, 1.5 Hz), 2.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9, 150.4, 146.7, 135.9, 131.5, 130.4, 130.1, 129.9, 129.3, 128.1, 124.0, 118.1, 111.2, 22.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{11}{}^{35}ClO_2Na$ 293.0340; found 293.0337.

*4-Chloro-7-fluoro-3-phenyl-1H-isochromen-1-one (**2yCl**)*: Yield 40.3 mg (73%, white solid); mp. 156.6–157.2 °C; IR (neat): υ_{max} 2956, 1729, 1491, 1257, 1090, 987, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.96 (m, 2H), 7.86–7.84 (m, 2H), 7.60–7.55 (m, 1H), 7.51–7.48 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J = 252 Hz), 160.0 (d, J = 3 Hz), 149.9 (d, J = 3 Hz), 132.5 (d, J = 3 Hz), 131.1, 130.3, 129.3, 128.2, 126.8 (d, J = 8 Hz),

123.5, (d, J = 23 Hz), 122.2 (d, J = 8 Hz), 115.5 (d, J = 24 Hz), 110.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9{}^{35}ClFO_2$ 275.0270; found 275.0272.

*4-Chloro-6-fluoro-3-phenyl-1H-isochromen-1-one (**2zCl**)*: Yield 49.2 mg (74%, white solid); mp. 160.9–161.1 °C; IR (neat): υ_{max} 1750, 1612, 1233, 1089, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, 1H, J = 8.8, 5.6 Hz), 7.87–7.85 (m, 2H), 7.61 (dd, 1H, J = 9.6, 2.4 Hz), 7.50–7.49 (m, 3H), 7.29 (td, 1H, J = 8.4, 2.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.2 (d, J = 258 Hz), 159.9, 151.7, 139.1 (d, J = 11 Hz), 133.3 (d, J = 10 Hz), 131.0, 130.5, 129.3, 128.3, 117.3 (d, J = 23 Hz), 116.9 (d, J = 2 Hz), 110.5 (d, J = 25 Hz), 110.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9{}^{35}ClFO_2$ 275.0270; found 275.0263.

*4,6-Dichloro-3-phenyl-1H-isochromen-1-one (**2aaCl**)*: Yield 55.1 mg (79%, white solid); mp. 174.2–174.7 °C; IR (neat): υ_{max} 2951, 1733, 1587, 1245, 1101, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, 1H, J = 8.4 Hz), 7.95 (d, 1H, J = 1.8 Hz), 7.88–7.85 (m, 2H), 7.57 (dd, 1H, J = 8.4, 1.8 Hz), 7.50 (t, 3H, J = 3.3 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 160.1, 151.7, 142.5, 137.5, 131.5, 131.1, 130.5, 129.6, 129.3, 128.3, 124.0, 118.8, 110.1; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9{}^{35}Cl_2O_2$ 290.9974; found 290.9979.

*7-Bromo-4-chloro-3-phenyl-1H-isochromen-1-one (**2bbCl**)*: Yield 44.0 mg (86%, white solid); mp. 153.4–154.0 °C; IR (neat): υ_{max} 2926, 2857, 1744, 1473, 1216, 1090, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, 1H J = 2.0 Hz), 7.95 (dd, 1H, J = 8.8, 2.0 Hz), 7.88–7.82 (m, 3H), 7.50–7.47 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.6, 150.8, 138.4, 134.8, 132.3, 131.1, 130.4, 129.3, 128.3, 125.9, 123.0, 121.8, 110.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9{}^{79}Br{}^{35}ClO_2$ 334.9469; found 334.9464.

*4-Chloro-5-phenyl-7H-thieno[2,3-c]pyran-7-one (**2ccCl**)*: Yield 64.0 mg (85%, white solid); mp. 130.5–131.0 °C; IR (neat): υ_{max} 2928, 1720, 1593, 1082, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.87 (m, 3H), 7.50–7.44 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.9,

152.4, 147.1, 137.1, 130.8, 130.3, 129.1, 128.3, 124.4, 123.0, 109.2; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_7{}^{35}ClO_2SNa$ 284.9748; found 284.9748.

*4-Chloro-7-methyl-3-p-tolyl-1H-isochromen-1-one (**2ddCl**)*: Yield 67.9 mg (92%, white solid); mp. 178.0–179.0 °C; IR (neat): υ_{max} 2923, 1729, 1620, 1089, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.83 (d, 1H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.66 (d, 1H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz), 2.51 (m, 3H), 2.42 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2, 149.7, 140.3, 139.4, 136.5, 133.7, 129.6, 129.2, 128.9, 128.7, 123.9, 120.3, 110.9, 21.5, 21.2; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{14}{}^{35}ClO_2$ 285.0677; found 285.0680.

*4-Chloro-7-fluoro-3-(4-methoxyphenyl)-1H-isochromen-1-one (**2eeCl**)*: Yield 61.1 mg (99%, white solid); mp. 166.0–167.0 °C; IR (neat): υ_{max} 2929, 2840, 1737, 1308, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.93 (m, 2H), 7.84 (d, 2H, J = 9.0 Hz), 7.56 (td, 1H, J = 8.0, 2.7 Hz), 7.00 (d, 2H, J = 9.0 Hz), 3.88 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.9, 161.0, 160.6, 160.1, 133.3 (d, J = 69 Hz), 130.9, 126.6 (d, J = 8 Hz), 123.5 (d, J = 23 Hz), 123.4, 122.0 (d, J = 8 Hz), 115.4 (d, J = 24 Hz), 113.9, 113.7, 55.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{10}{}^{35}ClFO_3Na$ 327.0195; found 327.0185.

*4-Bromo-3-phenyl-1H-isochromen-1-one (**2aBr**)*: Yield 37.0 mg (50%, white solid); mp. 115.6–115.9 °C; IR (neat): υ_{max} 1736, 1601, 1231, 1086, 757, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (dd, 1H, J = 7.8, 0.9 Hz), 8.00 (d, 1H, J = 8.1 Hz), 7.91–7.86 (m, 1H), 7.84–7.81 (m, 2H), 7.63 (td, 1H, J = 7.2, 1.2 Hz), 7.51 (t, 3H, J = 3.3 Hz); ^{13}C NM (75 MHz, $CDCl_3$) δ 161.1, 151.8, 136.6, 135.5, 132.8, 130.2, 129.8, 129.7, 129.2, 128.1, 126.7, 120.6, 101.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{10}{}^{79}BrO_2$ 300.9859; found 300.9858.

*4-Iodo-3-phenyl-1H-isochromen-1-one (**2aI**)*: Yield 51.9 mg (79%, white solid); mp. 125.0–125.3 °C; IR (neat): υ_{max} 1730, 1601, 1472, 1225, 1072, 753, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (dd, 1H, J = 8.1, 1.2 Hz), 7.90 (dd, 1H, J = 8.1, 1.2 Hz), 7.82 (ddd, 1H, J =

8.1, 7.2, 1.2 Hz), 7.74–7.64 (m, 2H), 7.58 (ddd, 1H, J = 8.2, 7.2, 1.2 Hz), 7.52–7.43 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 161.5, 154.81, 138.2, 135.7, 135.3, 131.5, 130.2, 130, 129.7, 129.2, 128.1, 120.3, 76.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{10}IO_2$ 348.9720; found 348.9720.

*Methyl 2-((2-chloro-5-methoxyphenyl)ethynyl)benzoate (**1fCl**)*: Yield 51.4 mg (86%, yellow oil); IR (neat): υ_{max} 2923, 2852, 1727, 1467, 1293, 1080, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 7.6 Hz), 7.51 (td, 1H, J = 7.2, 1.2 Hz), 7.41 (td, 1H, J = 7.6, 1.2 Hz), 7.31 (d, 1H, J = 8.8 Hz), 7.13 (d, 1H, J = 2.8 Hz), 6.84 (dd, 1H, J = 8.8, 2.8 Hz), 3.97 (s, 3H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 157.9, 134.4, 131.9, 131.7, 130.5, 130.0, 128.3, 127.6, 123.7, 123.2, 117.9, 116.4, 92.9, 91.0, 55.7, 52.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{13}{}^{35}ClO_3Na$ 323.0445; found 323.0446.

*(Z)-Methyl 2-(1,2-dichloro-2-phenylvinyl)-5-methoxybenzoate ((Z)-**3wCl**)*: Yield 41.6 mg (33%, white solid); mp. 81.1–81.9 °C; IR (neat): υ_{max} 2951, 2929, 1727, 1078, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 2H, J = 7.6 Hz), 7.55 (d, 1H, J = 2.8 Hz), 7.46–7.38 (m, 4H), 7.14 (dd, 1H, J = 8.4, 2.8 Hz), 3.95 (s, 3H), 3.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 159.7, 137.0, 131.7, 131.0, 130.6, 129.1, 129.0, 128.2, 128.0, 126.7, 118.5, 115.4, 55.6, 52.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{15}{}^{35}Cl_2O_3$ 337.0393; found 337.0399. Spectroscopic data for this compound were identical to those reported.[7e]

*(E)-Methyl 2-(1,2-dichloro-2-phenylvinyl)-5-methoxybenzoate ((E)-**3wCl**)*: Yield 33.2 mg (26%, colorless oil); IR (neat): υ_{max} 2945, 2831, 2222, 1726, 1493, 1291, 1228, 1077, 753, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, 1H, J = 2.6 Hz), 7.23–7.21 (m, 2H), 7.15–7.14 (m, 3H), 7.03 (d, 1H, J = 8.4 Hz), 6.82 (dd, 1H, J = 8.4, 2.8 Hz), 3.92 (s, 3H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 159.5, 137.0, 132.8, 131.9, 130.5, 130.1, 129.6, 129.2, 128.4, 128.0, 117.8, 115.4, 55.5, 52.6; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd

for $C_{17}H_{15}{}^{35}Cl_2O_3$ 337.0393; found 337.0392. Spectroscopic data for this compound were identical to those reported.[7e]

*(Z)-Methyl 2-(1,2-dichloro-2-phenylvinyl)-4,5-dimethoxybenzoate ((Z)-**3xCl**)*: Yield 11.2 mg (17%, white solid); mp. 129.9–131.2 °C; IR (neat): υ_{max} 2926, 1716, 1517, 1265, 1215, 1160, 1006, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, J = 7.2 Hz), 7.57 (s, 1H), 7.47–7.37 (m, 3H), 6.91 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 152.2, 148.9, 136.9, 132.7, 129.11, 129.05, 128.2, 127.9, 126.7, 121.3, 113.1, 112.4, 56.3, 56.1, 52.3; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}{}^{35}Cl_2O_4$ 367.0498; found 367.0497.

*(E)-Methyl 2-(1,2-dichloro-2-phenylvinyl)-4,5-dimethoxybenzoate ((E)-**3xCl**)*: Yield 8.3 mg (13%, white solid); mp. 123.6–124.6 °C; IR (neat): υ_{max} 2952, 1718, 1519, 1350, 1265, 1159, 1008, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.23–7.19 (m, 2H), 7.17–7.13 (m, 3H), 6.56 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.2, 151.4, 148.7, 137.0, 132.1, 130.2, 129.8, 129.0, 128.6, 128.0, 122.8, 113.9, 112.9, 56.0, 52.4; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{17}{}^{35}Cl_2O_4$ 367.0498; found 367.0495.

*Methyl 2-(2,2-dichloroacetyl)benzoate (**1ff-diCl**)*: Yield 9.0 mg (8%); IR (neat): υ_{max} 3278, 2954, 1707, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, 1H, J = 7.8, 0.9 Hz), 7.68 (td, 1H, J = 7.5, 1.2 Hz), 7.59 (td, 1H, J = 7.5, 1.5 Hz), 7.51 (dd, 1H, J = 7.4, 1.2 Hz), 6.42 (s, 1H), 3.94 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 192.3, 166.3, 138.6, 133.1, 130.7, 130.1, 129.3, 127.6, 70.4, 53.1,; HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd for $C_{10}H_7{}^{35}Cl_2O_3$ 244.9767; found 244.9772. Spectroscopic data for this compound were identical to those reported.[15b]

General Procedure for the Synthesis of Compounds 4a–g. A 25-mL round-bottomed flask with a magnetic stir bar was charged with methyl 2-iodobenzoate (0.24 g, 0.90 mmol, 1.0

equiv), followed by 4.5 mL of Et_3N. The resulting solution was added with $Pd(PPh_3)_2Cl_2$ (13 mg, 0.018 mmol, 0.020 equiv), followed by CuI (6.9 mg, 0.036 mmol, 0.04 equiv) to give a yellow solution with solid suspension. The reaction mixture was degassed by a steady stream of argon for 15 min, after which it was kept under argon atmosphere. Homopropargyl alcohol (83 mL, 78 mg, 1.1 mmol, 1.2 equiv) was then added into the reaction flask by a syringe. The reaction mixture immediately turned black. The reaction mixture was then allowed to stir at rt overnight (15 h) under argon atmosphere before it was diluted with saturated aq NH_4Cl solution (2.0 mL), followed by extraction with EtOAc (3 x 2 mL). The combined organic phases were washed with saturated aq NaCl solution (2 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by SiO_2 column chromatography, eluting with 20–50% EtOAc-hexanes to give the desired product **4b** (0.17 g, 0.83 mmol, 92%) as orange oil.

*Methyl 2-(3-hydroxyprop-1-ynyl)benzoate (**4a**)*: Yield 123.3 mg (66%, orange oil); IR (neat): υ_{max} 3423 (br), 2952, 2861, 1714, 1279, 1084, 1024, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, 1H, J = 7.8 Hz), 7.53 (d, 1H, J = 7.8 Hz), 7.44 (t, 1H, J = 7.5 Hz), 7.35 (t, 1H, J = 7.5 Hz), 4.55 (s, 2H), 3.91 (s, 3H), 32.6 (br s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.6, 134.1, 131.7, 131.5, 130.2, 127.9, 123.3, 92.9, 83.9, 52.2, 51.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{10}O_3Na$ 213.0522; found 213.0525.

*Methyl 2-(4-hydroxybut-1-ynyl)benzoate (**4b**)*: Yield 169.7 mg (92%, orange oil); IR (neat): υ_{max} 3458 (br), 2952, 2230, 1714, 1252, 1085, 1043, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 1H, J = 7.8 Hz), 7.51 (d, 1H, J = 7.5 Hz), 7.45 (t, 1H, J = 7.5 Hz), 7.35 (t, 1H, J = 7.5 Hz), 3.91 (s, 3H), 3.85 (q, 2H, J = 5.4 Hz), 3.56 (br s, 1H), 2.71 (t, 2H, J = 5.7 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.5, 133.5, 131.9, 131.3, 130.4, 127.4, 124.3, 93.1, 81.8, 60.9, 52.3, 24.3; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{12}O_3Na$ 227.0679; found 227.0686.

*Methyl 2-(5-hydroxypent-1-ynyl)benzoate (**4c**)*: Yield 169.7 mg (99%, orange oil); IR (neat): υ_{max} 3394 (br), 2950, 2236, 1716, 1251, 1084, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, 1H, J = 7.8, 0.9 Hz), 7.51 (dd, 1H, J = 7.5, 0.9 Hz), 7.43 (td, 1H, J = 7.5, 1.5 Hz), 7.32 (td, 1H, J = 7.8, 1.5 Hz), 3.92 (s, 3H), 3.87 (t, 2H, J = 6.0 Hz), 2.63 (t, 2H, J = 6.6 Hz), 2.21 (br s, 1H), 1.89 (q, 2H, J = 6.0 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.7, 133.9, 131.4, 129.9, 127.0, 124.1, 95.0, 79.4, 61.0, 51.9, 30.8, 16.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{14}O_3Na$ 241.0835; found 241.0834.

*Methyl 2-(6-hydroxyhex-1-ynyl)benzoate (**4d**)*: Yield 189.0 mg (70%, orange oil); IR (neat): υ_{max} 3442 (br), 2951, 2202, 1716, 1279, 1083, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, 1H, J = 8.0, 1.2 Hz), 7.50 (dd, 1H, J = 8.0, 1.2 Hz), 7.42 (td, 1H, J = 7.6, 1.6 Hz), 7.30 (td, 1H, J = 7.6, 1.2 Hz), 3.90 (s, 3H), 3.71 (t, 2H, J = 6.0 Hz), 3.52 (t, 2H, J = 6.8 Hz), 2.38 (br s, 1H), 1.82–1.69 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 134.1, 131.6, 131.5, 130.0, 127.1, 124.3, 95.6, 79.4, 62.0, 52.0, 31.6, 24.6, 19.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{16}O_3Na$ 255.0992; found 255.0990.

*Methyl 2-(7-hydroxyhept-1-ynyl)benzoate (**4e**)*: Yield 200.9 mg (99%, yellow oil); IR (neat): υ_{max} 3395 (br), 2938, 2222, 1715, 1431, 1250, 1083, 756 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, 1H, J = 7.8, 0.9 Hz), 7.51 (dd, 1H, J = 7.8, 0.9 Hz), 7.42 (td, 1H, J = 7.5, 1.5 Hz), 7.30 (td, 1H, J = 7.8, 1.2 Hz), 3.91 (s, 3H), 3.68 (t, 2H, J = 5.6 Hz), 2.50 (t, 2H, J = 6.5 Hz), 1.90 (br s, 1H), 1.90–1.60 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.9, 134.2, 131.7, 131.5, 130.1, 127.1, 124.5, 95.7, 79.4, 62.6, 52.1, 32.2, 28.2, 24.8, 19.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{18}O_3Na$ 269.1148; found 269.1154.

*Methyl 2-(8-hydroxyoct-1-ynyl)benzoate (**4f**)*: Yield 128.0 mg (58%, yellow oil); IR (neat): υ_{max} 3469 (br), 2934, 2853, 2227, 1716, 1250, 1083, 757, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (td, 1H, J = 7.8, 0.9 Hz), 7.50 (dd, 1H, J = 7.8, 0.9 Hz), 7.40 (td, 1H, J = 7.5, 1.5 Hz), 7.29 (td, 1H, J = 7.5, 1.2 Hz), 3.90 (s, 3H), 3.62 (t, 2H, J = 6.6 Hz), 2.60 (br s, 1H),

2.47 (t, 2H, J = 6.9 Hz), 1.68–1.34 (m, 8H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.8, 133.9, 131.6, 131.3, 129.8, 126.9, 124.2, 95.7, 79.0, 62.3, 51.8, 32.3, 28.4, 28.3, 25.0, 19.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{20}O_3Na$ 283.1305; found 283.1304.

*Methyl 2-(10-hydroxydec-1-ynyl)benzoate (**4g**)*: Yield 257.8 mg (89%, yellow oil); IR (neat): υ_{max} 3362 (br), 2929, 2856, 2226, 1717, 1249, 1083, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 1H, J = 7.8 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.41 (td, 1H, J = 7.5, 1.2 Hz), 7.30 (t, 1H J = 7.5 Hz), 3.91 (s, 3H), 3.62 (t, 2H, J = 6.5 Hz), 2.47 (t, 2H, J = 7.0 Hz), 1.68–1.35 (m, 12H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.0, 134.1, 131.8, 131.4, 130.0, 127.0, 124.4, 95.9, 79.1, 62.8, 51.9, 32.6, 29.2, 29.0, 28.7, 28.5, 25.6, 19.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{24}O_3Na$ 311.1618; found 311.1620.

General Procedure for the Synthesis of Spirocyclic Ethers 5Cl. A 10-mL round-bottomed flask with a magnetic stir bar was charged with compound **4c** (0.11 mg, 0.53 mmol, 1.0 equiv) in 2.6 mL of CH_3CN (0.20 M). The resulting solution was stirred and cooled to 0 °C in an ice bath. NCS (0.14 mg, 1.1 mmol, 2.0 equiv) was added to the reaction mixture in one portion, followed by addition of TMSCl (6.6 μL, 5.7 mg, 0.052 mmol, 0.10 equiv) by a syringe. The reaction mixture was allowed to stir at 0 °C until the reaction was judged complete by TLC. Upon completion, the reaction mixture was diluted with water (1 mL), followed by extraction with EtOAc (3 x 1 mL). Combined organic phases were washed with saturated aq NaCl solution (1 mL), dried over anh. Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained crude material was purified on SiO_2 column chromatography, eluting with 10–50% EtOAc-hexanes to give the desired spirocyclic ether **5cCl** (86 mg, 31 mmol, 60%) as white solid.

Note: for substrates **4b** and **4d**, the reactions were conducted first at 0 °C for 1 h before warming to stir at rt for 1 h.

*4,4-Dichlorospiro[isochroman-3,2'-oxetan]-1-one (**5bCl**)*: Yield 68.3 mg (41%, white solid); mp. 124.4–125.0 °C; IR (neat): υ_{max} 2925, 1775, 1282, 1103, 909, 883, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95–7.92 (m, 2H), 7.78–7.66 (m, 2H), 4.49–4.38 (m, 2H), 3.26–3.16 (m, 1H), 3.06–2.99 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 166.4, 140.2, 134.0, 131.8, 129.3, 126.5, 125.3, 112.5, 89.1, 67.4, 43.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_8{}^{35}Cl_2O_3Na$ 280.9743; found 280.9744.

*4',4'-Dichloro-4,5-dihydro-3H-spiro[furan-2,3'-isochroman]-1'-one (**5cCl**)*: Yield 85.8 mg (60%, white solid); mp. 128.2–129.1 °C; IR (neat): υ_{max} 2941, 1782, 1276, 1096, 950, 805, 759, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, 1H, J = 7.8 Hz), 7.89 (d, 1H, J = 7.2 Hz), 7.73 (td, 1H, J = 7.5, 1.2 Hz), 7.65 (td, 1H, J = 7.5, 1.2 Hz), 4.31–4.21 (m, 1H), 4.01 (dd, 1H, J = 11.6, 5.6 Hz), 2.99 (td, 1H, J = 13.8, 4.2 Hz), 2.70–2.63 (m, 1H), 2.58–2.42 (m, 1H), 1.83–1.75 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 167.1, 144.1, 134.2, 131.3, 127.8, 125.6, 125.2, 106.1, 88.3, 64.1, 40.3, 23.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{10}{}^{35}Cl_2O_3Na$ 294.9899; found 294.9900.

*4,4-Dichloro-3',4',5',6'-tetrahydrospiro[isochroman-3,2'-pyran]-1-one (**5dCl**)*: Yield 24.8 mg (23%, colorless oil); IR (neat): υ_{max} 2954, 2925, 1783, 1466, 1266, 1148, 924, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 1H, J = 7.6 Hz), 7.86 (d, 1H, J = 7.6 Hz), 7.73 (td, 1H, J = 7.6, 1.2 Hz), 7.62 (td, 1H, J = 7.6, 0.8 Hz), 4.20 (dt, 1H, J = 12.0, 5.2 Hz), 3.98–3.91 (m, 1H), 2.91–2.83 (m, 1H), 2.74 (dt, 1H, J = 15.2, 4.0 Hz), 2.19–1.87 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.8, 147.8, 134.6, 130.7, 126.2, 125.3, 124.4, 108.6, 93.4, 67.4, 45.7, 27.9, 22.0; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{12}{}^{35}Cl_2O_3Na$ 309.0056; found 309.0052.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of all prepared products (PDF)

High-resolution mass spectra (HR-MS) of all prepared products (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Hussain, H.; Green, I. R. A Patent Review of Two Fruitful Decades (1997–2016) of Isocoumarin Research. *Expert Opin. Ther. Targets* **2017**, *27*, 1267–1275. (b) Saddiqa, A.; Usman, M.; Akmak, O. C. Isocoumarins and 3,4-dihydroisocoumarins, amazing natural products: a review. *Turk. J. Chem.* **2017**, *41*, 153–178. (c) Ghosh, A. K.; Gemma, S. *Structure-Based Design of Drugs and Other Bioactive Molecules;* Wiley-VCH: Weinheim, Germany, 2014.

(2) (a) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.-I.; Nakajima, S. Antifungal Activity of Oosponol, Oospolactone, Phyllodulcin, Hydrangenol, and Some Other Related Compounds. *Chem. Pharm. Bull.* **1981**, *29*, 2689–2691. (b) Sonnenbichler, J.; Sonnenbichler I.; Schwar, D. Biosynthesis of Oosponol and Oospoglycol Elucidated by ^{13}C NMR.

Phytochemistry **1997**, *44*, 267–269. (c) Simic, M.; Paunovic, N.; Boric, I.; Randjelovic, J.; Vojnovic, S.; Nikodinovic-Runic, J.; Pekmezovic, M.; Savic, V. Functionalised isocoumarins as antifungal compounds: Synthesis and biological studies. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 235–239.

(3) (a) Sonnenbichler, J.; Peipp, H.; Dietrich, J. Secondary Fungal Metabolites and Their Biological Activities, III. Further Metabolites from Dual Cultures of the Antagonistic Basidiomycetes *Heterobasidion annosum* and *Gloeophyllum abietinum*. *Biol. Chem. Hoppe-Seyler* **1993**, *374*, 467–473. (b) Hussain, M.; Hussain, M. T.; Rama, N. H.; Hameed, S.; Malik, A.; Khan, K. M. Synthesis and Antimicrobial Activities of Some Isocoumarin and Dihydroisocoumarin Derivatives. *Nat. Prod. Res.* **2003**, *17*, 207–214. (c) Devienne, K. F.; Raddi, M. S. G.; Coelho, R. G.; Vilegas, W. Structure-antimicrobial activity of some natural isocoumarins and their analogues. *Phytomedicine* **2005**, *12*, 378–381. (d) Zhang, H. W.; Huang, W. Y.; Chen, J. R.; Yan, W. Z.; Xie, D. Q.; Tan, R. X. Cephalosol: An Antimicrobial Metabolite with an Unprecedented Skeleton from Endophytic *Cephalosporium acremonium* IFB-E007. *Chem. Eur. J.* **2008**, *14*, 10670–10674.

(4) Hideaki, N.; Hiroyuki, T.; Hitoshi, I.; Heterocyclic amine derivatives, their production and use. EP0481383B1, April 22, 1992.

(5) (a) Le Bras, G.; Hamze, A.; Messaoudi, S.; Provot, O.; Le Calvez, P.-B.; Brion, J.-D.; Alami, M. Synthesis of Isocoumarin via PTSA-Catalyzed Annulation of Diarylalkynes. *Synthesis* **2008**, 1607–1611. (b) Cai, S.; Wang, F.; Xi, C. Assembly of 3-Substituted Isocoumarins via a CuI-Catalyzed Domino Coupling/Addition/Deacylation Process. *J. Org. Chem.* **2012**, *77*, 2331–2336. (c) Kavala, V.; Wang, C.-C.; Barange, D. K.; Kuo, C.-W.; Lei, P.-M.; Yao, C.-F. Synthesis of Isocoumarin Derivatives via the Copper-Catalyzed Tandem Sequential Cyclization of 2-Halo-*N*-phenyl Benzamides and Acyclic 1,3-Diketones. *J. Org. Chem.* **2012**, *77*, 5022–5029. (d) Ge, Z.-Y.; Fei, X.-D.; Tang, T.; Zhu, Y.-M.; Shen, J.-K.

Synthesis of 3-Substituted Isocoumarins via a Cascade Intramolecular Ullmann-Type Coupling-Rearrangement Process. *J. Org. Chem.* **2012**, *77*, 5736–5743. (e) Guo, X.-X. Synthesis of Isocoumarin Derivatives by Copper-Catalyzed Addition of *o*-Halobenzoic Acids to Active Internal Alkynes. *J. Org. Chem.* **2013**, *78*, 1660–1664. (f) Yoo, W.-J.; Nguyen, T. V. Q.; Kobayashi, S. Synthesis of Isocoumarins through Three-Component Couplings of Arynes, Terminal Alkynes, and Carbon Dioxide Catalyzed by an NHC-Copper Complex. *Angew. Chem. Int. Ed.* **2014**, *53*, 10213–10217. (g) Liu, H.; Yang, Y.; Wu, J.; Wang, X.-A.; Chang, J. Regioselective synthesis of 3,4-disubstituted isocoumarins through the Pd-catalyzed annulation of 2-iodoaromatic acids with ynamides. *Chem. Commun.* **2016**, *52*, 6801–6804. (h) Saeed, A.; Haroon, M.; Muhammad, F.; Larik, F. A.; Hesham, E.-S.; Channar, P. A. Advances in transition-metal-catalyzed synthesis of 3-substituted isocoumarins. *J. Organomet. Chem.* **2017**, *834*, 88–103.

(6) (a) Nagarajan, A.; Balasubramanian, T. R. Organomercury Mediated Synthesis of Isocoumarins. *Indian J. Chem. Sect. B* **1987**, *26*, 917–919. (b) Liang, Y.; Xie, Y.-X.; Li, J.-H. $Cy_2NH{\cdot}HX$-Promoted Cyclizations of *o*-(Alk-1-ynyl)benzoates and (*Z*)-Alk-2-en-4-ynoate with Copper Halides to Synthesize Isocoumarins and α-Pyrone. *Synthesis* **2007**, 400–406. (c) Chin, L.-Y.; Lee, C.-Y.; Lo, Y.-H.; Wu, M.-J. Halocyclization of Methyl 2-Alkynylbenzoates to Isocoumarins Using Cupric Halides. *J. Chin. Chem. Soc.* **2008**, *55*, 643–648. (d) Peuchmaur, M.; Lisowski, V.; Gandreuil, C.; Maillard, L. T.; Martinez, J.; Hernandez, J.-F. Solid-Phase Synthesis of Isocoumarins: A Traceless Halocyclization Approach. *J. Org. Chem.* **2009**, *74*, 4158–4165. (e) Jithunsa, M.; Ueda, M.; Miyata, O. Copper(II) Chloride-Mediated Cyclization Reaction of *N*-Alkoxy-*ortho*-alkynylbenzamides. *Org. Lett.* **2011**, *13*, 518–521. (f) Yuan, S. T.; Zhou, H.; Zhang, L.; Liu, J.-B.; Qiu, G. Synthesis of benzil-*o*-carboxylate derivatives and isocoumarins through neighboring ester-participating bromocyclizations of *o*-alkynylbenzoates. *Org. Biomol. Chem.* **2017**, *15*, 4867–4874. (g)

Kita, Y.; Yata, T.; Nishimoto, Y.; Chiba, C.; Yasuda, M. Selective oxymetalation of terminal alkynes *via* 6-*endo* cyclization: mechanistic investigation and application to the efficient synthesis of 4-substituted isocoumarins. *Chem. Sci.* **2018**, *9*, 6041–6052.

(7) (a) Oliver, M. A.; Gandour, R. D. The Identity of 4-Bromo-3-phenylisocoumarin. A Facile Preparation by Bromolactonization of Alkyl 2-(2-Phenylethyny1)benzoates. *J. Org. Chem.* **1984**, *49*, 558–559. (b) Yao, T.; Larock, R. C. Synthesis of Isocoumarins and α-Pyrones via Electrophilic Cyclization. *J. Org. Chem.* **2003**, *68*, 5936–5942. (c) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. C. Iodine-catalyzed and solvent-controlled selective electrophilic cyclization and oxidative esterification of *ortho*-alkynyl aldehydes. *Chem. Commun.* **2010**, *46*, 4064–4066. (d) Zhang, X.; Hou, W.; Zhang-Negrerie, D.; Zhao, K.; Du, Y. Hypervalent Iodine-Mediated Intramolecular *trans*-Aminocarboxylation and Oxoaminocarboxylation of Alkynes: Divergent Cascade Annulations of Isocoumarins under Metal-Free Conditions. *Org. Lett.* **2015**, *17*, 5252–5255. (e) Xing, L.; Zhang, Y.; Li, B.; Du, Y. Synthesis of 4-Chloroisocoumarins via Intramolecular Halolactonization of *o*-Alkynylbenzoates: $PhICl_2$-Mediated C−O/C−Cl Bond Formation. *Org. Lett.* **2019**, *21*, 1989–1993.

(8) (a) Lucas, H. J.; Kennedy, E. R. Iodobenzene Dichloride. *Org. Synth.* **1942**, *22*, 69–70. (b) Zanka, A.; Takeuchi, H.; Kubota, A. Large-Scale Preparation of Iodobenzene Dichloride and Efficient Monochlorination of 4-Aminoacetophenone. *Org. Process. Res. Dev.* **1998**, *2*, 270–273. (c) Zhao, X.-F.; Zhang, C. Iodobenzene Dichloride as a Stoichiometric Oxidant for the Conversion of Alcohols into Carbonyl Compounds; Two Facile Methods for Its Preparation. *Synthesis* **2007**, 551–557. (d) Tao, J.; Tran, R.; Murphy, G. K. Dihaloiodoarenes: *α,α*-Dihalogenation of Phenylacetate Derivatives. *J. Am. Chem. Soc.* **2013**, *135*, 16312−16315. (e) Cornel, V. *e-EROS Encyclopedia of Reagents for Organic Synthesis,* 2001, DOI: 10.1002/047084289X.rp071.

(9) (a) Harper, J. W.; Powers, J. C. Reaction of Serine Proteases with Substituted 3-Alkoxy-4-chloroisocoumarins and 3-Alkoxy-7-amino-4-chloroisocoumarins: New Reactive Mechanism-Based Inhibitors. *Biochemistry* **1985**, *24,* 7200–7213. (b) Powers, J. C.; Kam, C.-M.; Narasimhan, L.; Oleksyszyn, J.; Hernandez, M. A.; Ueda, T. Mechanism-Based Isocoumarin Inhibitors for Serine Proteases: Use of Active Site Structure and Substrate Specificity in Inhibitor Design. *J. Cell. Biochem.* **1989**, *39*, 33–46. (c) Powers, J. C.; Wade, H. Use of Heterocyclic Inhibitors of Serine Proteases. US005109018A, April 28, 1992. (d) Powers, J. C.; Kam, C.-M. Isocoumarin Inhibitors of Serine Peptidases. *Method Enzymol.* **1994**, *244*, 442–457. (e) Powers, J. C.; Asgian, J. L.; Ekici, O. D.; James, K. E. Irreversible Inhibitors of Serine, Cysteine, and Threonine Proteases. *Chem. Rev.* **2002**, *102*, 4639–4750. (f) Pochet, L.; Frédérick, R.; Masereel, B. Coumarin and Isocoumarin as Serine Protease Inhibitors. *Curr. Pharm. Des.* **2004**, *10*, 3781–3796. (g) Heynekamp, J. J.; Hunsaker, L. A.; Vander Jagt, T. A.; Royer, R. E.; Deck, L. M.; Vander Jagt, D. L. Isocoumarin-based inhibitors of pancreatic cholesterol esterase. *Bioorg. Med. Chem.* **2008**, *16*, 5285–5294.

(10) (a) López-Otín, C.; Bond, J. S. Proteases: Multifunctional Enzymes in Life and Disease. *J. Biol. Chem.* **2008**, *283*, 30433–30437. (b) Di Cera, E. Serine Proteases. *IUBMB Life*, **2009**, *61*, 510‑515. (c) *Proteases: Structure and Function;* Brix, K., Stöcker, W., Eds.; Springer-Verlag: Wien, 2013.

(11) (a) Li, G.; Zhou, Q.; Qiu, L.; Yao, Q.; Chen, K.; Tang, Q.; Hu, Z. Serine protease *Bm-SP142* was differentially expressed in resistant and susceptible *Bombyx mori* strains, involving in the defence response to viral infection. *PLoS ONE* **2017**, *12*(4): e0175518. https://doi.org/10.1371/journal.pone.0175518. (b) Sharony, R.; Yu, P.-J.; Park, J.; Galloway, A. C.; Mignatti, P.; Pintucci, G. Protein targets of inflammatory serine proteases and cardiovascular disease. *J. Inflamm.* **2010** *7*(45): http://www.journal-inflammation.com/content/7/1/45. (c) Gelderblom, M.; Neumann, M,; Ledewig, P.;

Bernreuther, C.; Krasemann, S.; Arunachalam, P.; Gerloff, C.; Glatzel, M.; Magnus, T. Deficiency in Serine Protease Inhibitor Neuroserpin Exacerbates Ischemic Brain Injury by Increased Postischemic Inflammation. *PLoS ONE* **2013**, *8*(5): e63118. doi.org/10.1371/journal.pone.0063118. (d) Milner, J. M.; Patel, A.; Rowan, A. D. Emerging Roles of Serine Proteinases in Tissue Turnover in Arthritis. *Arthritis. Rheum.* **2008**, *58*, 3644–3656. (e) Miller, G. S.; Zoratti, G. L.; Murray, A. S.; Bergum, C.; Tanabe, L. M.; List, K. HATL5: A Cell Surface Serine Protease Differentially Expressed in Epithelial Cancers. *PLoS ONE* **2014**, *9*(2): e87675. doi:10.1371/journal.pone.0087675. (f) Muñoz, S. S.; Li, H.; Ruberu, K.; Chu, Q.; Saghatelian, A.; Ooi, L.; Garner, B. The serine protease HtrA1 contributes to the formation of an extracellular 25-kDa apolipoprotein E fragment that stimulates neuritogenesis. *J. Biol. Chem.* **2018**, *293*, 4071–4084.

(12) (a) Harper, J. W.; Hemmi, K.; Powers, J. C. Reaction of Serine Proteases with Substituted Isocoumarins: Discovery of 3,4-Dichloroisocoumarin, a New General Mechanism Based Serine Protease Inhibitor. *Biochemistry* **1985**, *24*, 1831–1841. (b) Harper, J. W.; Powers, J. C. 3-Alkoxy-7-amino-4-chloroisocoumarins: A New Class of Suicide Substrates for Serine Proteases. *J. Am. Chem. Soc.* **1984**, *106*, 7618–7619. (c) Kam, C.-H.; Fujikawa, K.; Powers, J. C. Mechanism-Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants. *Biochemistry* **1988**, *27*, 2547–2557. (d) Kam, C.-H.; Kerrigan, J. E.; Plaskon, R. R.; Duffy, E. J.; Lollar, P.; Suddath, F. L.; Powers, J. C. Mechanism-Based Isocoumarin Inhibitors for Blood Coagulation Serine Proteases. Effect of the 7-Substituent in 7-Amino-4-chloro-3-(isothioureidoalkoxy)isocoumarins on Inhibitory and Anticoagulant Potency. *J. Med. Chem.* **1994**, *37*, 1298–1306. (e) Bihel, F.; Faure, R.; Kraus, J.-L. Reactivity studies of 3-alkoxy-7-amino-4-chloroisocoumarins (β-amyloid peptide inhibitors) *versus* different classes of amines. *Org. Biomol. Chem.* **2003**, *1*, 800–802. (f) Bihel, F.; Quéléver, G.; Lelouard, H.; Petit, A.; da Costa, C. A.; Pourquié, O.; Checler, F.;

Thellend, A.; Pierre, P.; Kraus, J.-L. Synthesis of New 3-Alkoxy-7-amino-4-chloro-isocoumarin Derivatives as New β-Amyloid Peptide Production Inhibitors and Their Activities on Various Classes of Protease. *Bioorg. Med. Chem.* **2003**, *11*, 3141–3152. (g) Child, M. A.; Hall, C. I.; Beck, J. R. Ofori, L. O.; Albrow, V. E.; Garland, M.; Bowyer, P. W.; Bradley, P. J.; Powers, J. C.; Boothroyd, J. C.; Weerapana, E.; Bogyo, M. Small-molecule inhibition of a depalmitoylase enhances *Toxoplasma* host-cell invasion. *Nat. Chem. Biol.* **2013**, *9*, 651–656.

(13) (a) Maibunkaew, T.; Thongsornkleeb, C.; Tummatorn, J.; Bunrit, A.; Ruchirawat, S. Practical and Metal-Free Electrophilic Aromatic Halogenation by Interhalogen Compounds Generated In Situ from *N*-Halosuccinimide and Catalytic TMSCl. *Synlett* **2014**, *25*, 1769–1775. (b) Kaewsri, W.; Thongsornkleeb, C.; Tummatorn, J.; Ruchirawat, S. Isomerizable (*E*/*Z*)-alkynyl-*O*-methyl oximes employing TMSCl-NCS in chlorinative cyclization for the direct synthesis of 4-chloroisoxazoles. *RSC Adv.* **2016**, *6*, 48666–48675.

(14) NMR spectral data of spirocyclic ethers **5bCl-5dCl** were comparable to similar compounds reported, respectively, in the following references: (a) Morgan, K. F.; Hollingsworth, I. A.; Bull, J. A. 2-(Aryl-sulfonyl)oxetanes as designer 3-dimensional fragments for fragment screening: synthesis and strategies for functionalisation. *Chem. Commun.* **2014**, *50*, 5203–5205. (b) Devi, R.; Das, S. K. Combining spiro-fused cyclohexadienone – tetrahydrofuran ring system with glycine: Asymmetric synthesis of a new class of a-amino acid derivatives. *Tetrahedron Lett.* **2018**, *59*, 2281–2283. (c) Quach, R.; Furkert, D. P.; Brimble, M. A. Total Synthesis of the Resorcyclic Acid Lactone Spiroketal Citreoviranol. *J. Org. Chem.* **2016**, *81*, 8343–8350.

(15) (a) Dhanasekaran, S.; Kannaujiya, V. K.; Biswas, R. G.; Singh, V. K. Enantioselective A^3-Coupling Reaction Employing Chiral Cu^{I}-^{i}PrpyboxdiPh/*N*-Boc-(L)-Proline Complex under Cooperative Catalysis: Application in the Synthesis of (Indol-2-yl)methanamines. *J.*

Org. Chem. **2019**, *84*, 3275–3292. (b) Barluenga, J.; Llavona, L.; Yus, M.; Concellón, J. M. Reactivity of *in situ* Generated Dihalomethyllithium towards Dicarboxylic Acid Diesters and Lactones: Synthetic Applications. *Tetrahedron* **1991**, *47*, 7875–7886.