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One-pot Domino Friedel-Crafts Acylation/Annulation between Alkynes and 2-Methoxybenzoyl Chlorides: Synthesis of 2,3-Disubstituted Chromen-4-one Derivatives

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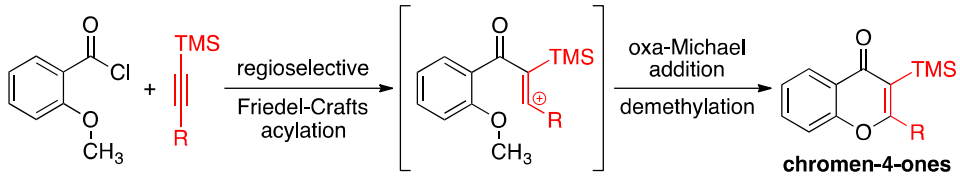


ABSTRACT: A highly regioselective synthesis of 2,3-disubstituted chromen-4-one derivatives is accomplished from readily available internal alkynes and 2-methoxybenzoyl chlorides. The reaction proceeds via a domino intermolecular Friedel-Crafts acylation/intramolecular vinyl carbocation trapping (or oxa-Michael addition)/demethylation reaction sequence. This Lewis acid promoted method features relatively mild reaction conditions to synthesize a variety of 2,3-disubstituted chromen-4-one derivatives in one-pot with up to 93% yield. Chromen-2-one (coumarin) product was obtained when 2,6-dimethoxybenzoyl chloride was used as a starting material via an electrophilic aromatic substitution/rearrangement process.

INTRODUCTION

Chromen-4-ones and their derivatives are secondary metabolites that are ubiquitous in nature.[1] The rigid chromen-4-one structure has been identified as an important structure in drug discovery due to its pharmacologically active properties, such as antiviral,[2] antimicrobial,[3] anticancer,[4] anti-oxidative,[5] cardioprotective,[6] and many other biological properties.[1a, 7] The prenylated flavonoid, kuwanon C, isolated from the root bark of *Morus lhou*, inhibits the activity of β-secretase, which is a potential target for the treatment of Alzheimer's disease (Figure 1).[8] The chromen-4-one alkaloid schumannificine, isolated from root bark of *Schumanniophyton magnificum*, was found to be active against the human immunodeficiency virus (HIV) and herpes simplex virus (HSV).[9]

It has been found that the baicalein (5,6,7-tryhydrooxyflavone) is active against a variety of cancer cells, especially human breast cancer cells.[10]

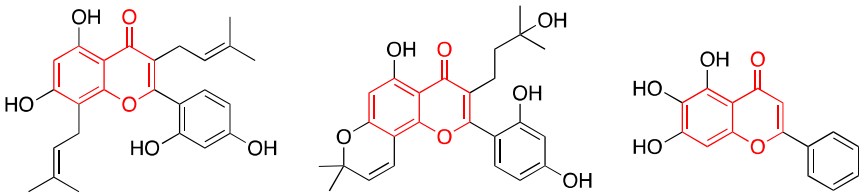


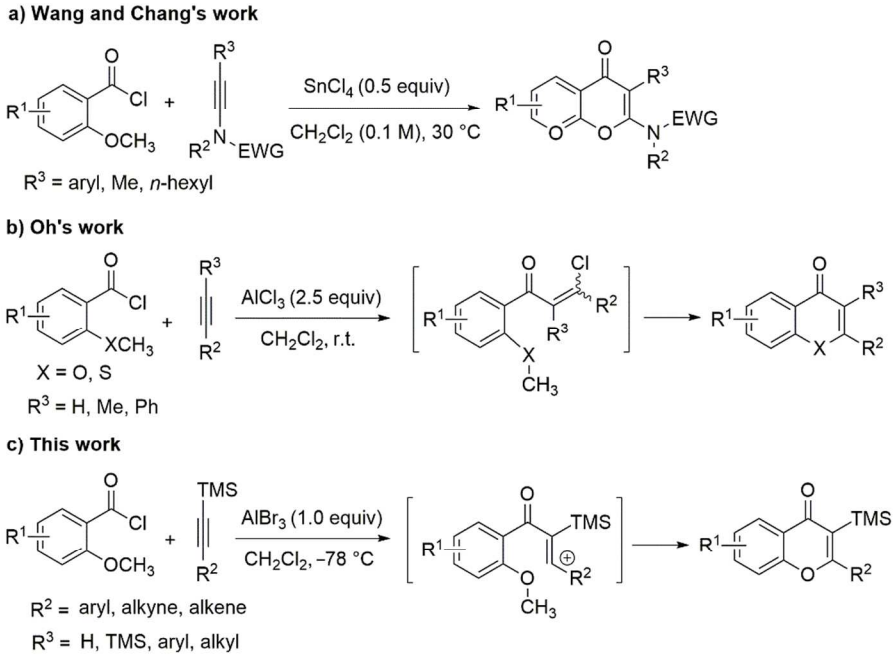
Figure 1. Examples of some biologically active chromen-4-one derivatives.

Chromen-4-one derivatives can be prepared from salicylic acids,[11] phenols[12] and *o*-hydroxyaryl ketones.[13] The most common synthetic approaches to make chromen-4-one derivatives includes Baker-Venkatamaran,[14] Kostanecki-Robinson[15] and Vilsmeier-Haack reactions.[1a,16] More recently, microwave irradiation has been used for the synthesis of several chromen-4-one derivatives.[17] Although several methods have been established for the construction of simple chromen-4-one derivatives, most of them suffer from serious disadvantages such as harsh conditions, multi-step procedures, long reaction times, unexpected side-reactions and poor yields.

The Friedel-Crafts reaction is an important tool to form C-C bonds.[18] Friedel-Crafts acylation of trialkylsilyl-substituted alkynes has been used in the preparation of ynones.[19] These high energy ynones are very important intermediates for the synthesis of oligoynes, molecules that have been used to study the properties of the elusive sp-hybridized carbon allotrope, carbyne.[20] They can also serve as useful substrates for multicomponent and domino cyclizations to afford terpenoid scaffolds.[21] Recently, our group reported the synthesis of 1-acyl-2-alkynyl-1,4-cyclohexadienes via a regioselective Diels–Alder cycloaddition of conjugated 2,4-diynones and a variety of dienes.[22] During that study, the formation of an interesting annulated side product was observed when attempting to make a 2-methoxyphenyl ynone derivative. Interestingly, the side reaction of the Friedel-Crafts acylation reaction turned out to be annulation to give a chromen-4-one. A very convenient method to make substituted chromen-4-ones is via a Lewis acid catalyzed Friedel-Crafts acylation of alkynes with suitable benzoyl chlorides. For example, a $SnCl_4$-catalyzed synthesis of 2-substituted aminochromen-4-ones via an annulation reaction of ynamides with 2-methoxybenzoyl chlorides was recently reported by Chang and co-workers (Scheme 1a).[23] Oh and co-workers recently reported the synthesis of (thio)chromen-4-ones via a Friedel-Crafts

acylation/cyclization (Scheme 1b).[24] A TMS group is a very useful functional handle that can easily be converted to other functionalities.[25] However, to date, TMS-substituted internal alkynes have rarely been used to make TMS-functionalized chromen-4-ones.[25] Thus, the development of new methods for the direct synthesis of TMS-functionalized chromen-4-ones would be of significant value in terms of probing chemical space. Herein, we report a one-pot synthesis of various 2,3-disubstituted chromen-4-ones via the annulation reaction between 2-methoxybenzoyl chlorides and internal alkynes, including terminal TMS-substituted alkynes, under relatively mild conditions.[26]

Scheme 1: One-pot Synthesis of Chromen-4-ones

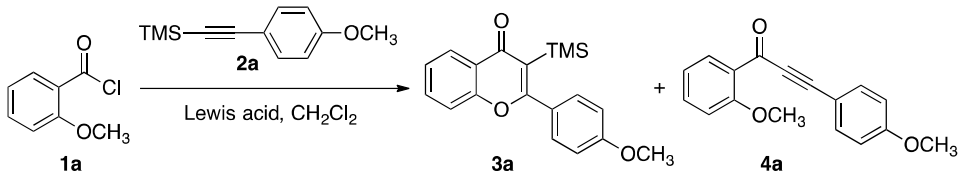


RESULTS AND DISCUSSION

2-Methoxybenzoyl chloride **1a** and (4-methoxyphenylethynyl)trimethylsilane **2a** were used as substrates to optimize the reaction conditions (Table 1). As expected, neither desired product **3a** nor ketone **4a** were observed in the absence of Lewis acid at room temperature (entry 1). When Lewis acids such as $EtAlCl_2$, $SnCl_4$, $Sc(OTf)_3$, and $FeCl_3$ were used in the reaction, only ynone **4a** was observed as a product (entries 2-5). Neither **3a** nor **4a** were observed in the presence of $BF_3{\cdot}OEt_2$ (entry 6) or BBr_3 (entry 7). A 1:3 ratio of **3a**:**4a** was obtained when $TiCl_4$ was used as a Lewis acid at low temperature (entries 8). When $AlCl_3$ was employed at low temperature, a

significant increase in the formation of **3a** was observed (entry 9). Increasing the temperature resulted in a slight decrease in the amount of **3a** formed (entry 10). We hypothesized that switching to $AlBr_3$ would increase the amount of **3a** being formed in the reaction relative to **4a**. The idea here is that increasing the bromide ion concentration in the reaction would increase the rate of demethylation and favor the formation of product **3a**. This is because the bromide anion is a better nucleophile for the demethylation step of the mechanism (vide infra) relative to chloride.[27] At the same time, the rate of desilylation would decrease, disfavoring the alternate reaction pathway leading to **4a**, since bromide is slower than chloride for desilylation.[28] To our delight, the annulated product **3a** was formed exclusively in the presence of $AlBr_3$ in 56% yield (entry 11). This result suggests that one of these steps demethylation or desilylation is the rate determining step under these reaction conditions.

Table 1. Reaction Optimization for 3a



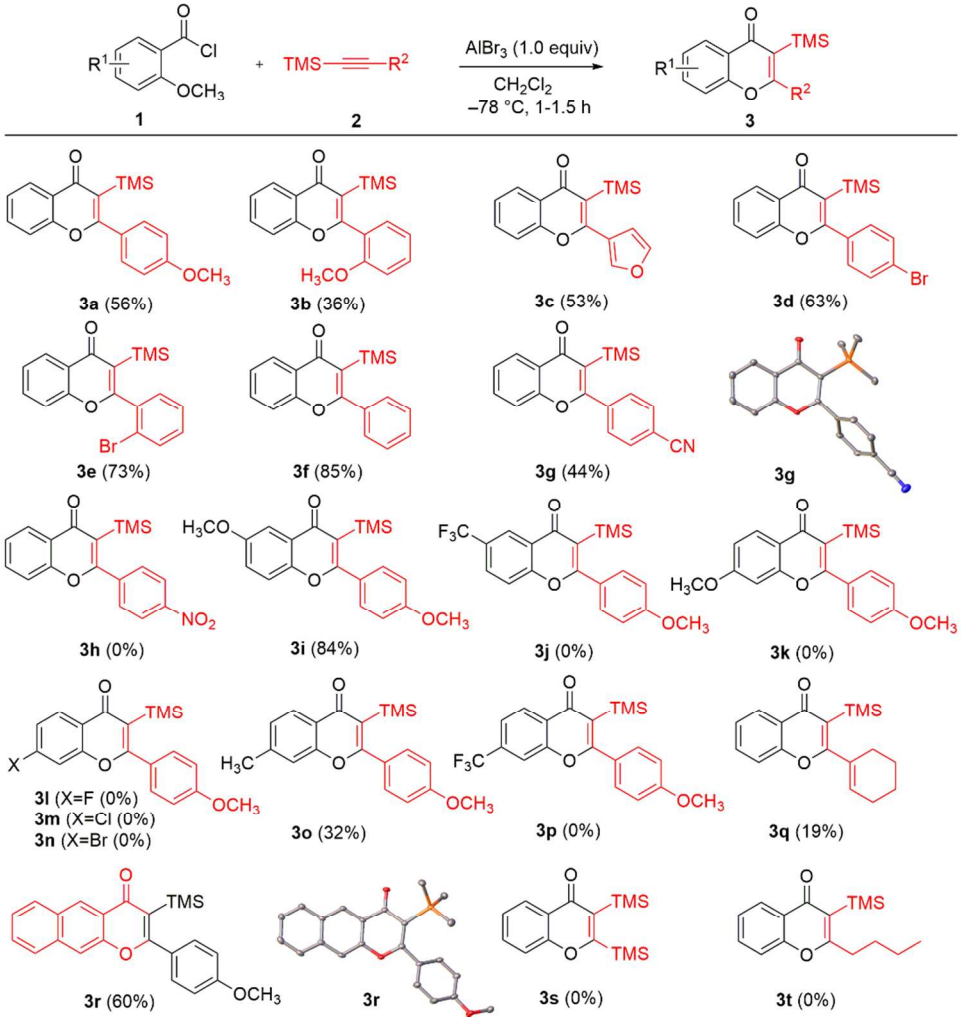
entry	Lewis acid	temperature (°C)	yield **3a** (%)	**3a**:**4a**[a]
1	-	–78 to r.t	0	0
2	$EtAlCl_2$	–78	0	0:1
3	$SnCl_4$	–78	0	0:1
4	$Sc(OTf)_3$	–78	0	0:1
5	$FeCl_3$	–78	0	0:1
6	BF_3•OEt_2	–78	0	0
7	BBr_3	–78	0	0
8	$TiCl_4$	–78	N/A[b]	1:3
9	$AlCl_3$	–78	45	3:2
10	$AlCl_3$	r.t.	N/A[b]	1:1
11	$AlBr_3$	–78	56	1:0

[a]Determined by ^{1}H NMR. [b]Not isolated.

With optimized conditions in hand, a series of TMS-substituted alkynes were studied, and the results are summarized in Scheme 2. Alkynes substituted with electron-rich and electron-poor

aryl groups (R^2) as well as heteroaryl groups provided desired products (**3a-g**). The very electron-poor 2-(*p*-nitrophenyl)-1-(TMS)acetylene failed to provide either **3h** or **4h**. The reaction is fast and clean when an electron-donating group is *para* to the methoxy substituent, providing **3i** in 84% yield. Placing an electron-withdrawing trifluoromethyl group *para* to the methoxy group gave only ketone product **4j**. Having an electron-donating methoxy group *para* to the carbonyl resulted in the formation of many spots, by TLC, with no desired product **3k** or acyclic ketone **4k** being isolated. Interestingly, other *ortho*/*para* directing groups in this position – such as a fluoro, chloro or bromo – produced the respective ketone products **4l**, **4m**, and **4n** but failed to provide any desired chromen-4-one products **3l**, **3m** and **3n**. Having a weakly electron-donating methyl group *para* to the carbonyl did give desired product **3o,** albeit in modest yield. Having an electron-withdrawing CF3 group *para* to the carbonyl group did not provide **3p** but did produce ketone **4p** as the major product. It seems from these results that increasing the nucleophilicity of the methoxy group that is participating in the cyclization step (i.e., placing an electron-donating substituent *para* to it), improves the formation of the cyclic chromen-4-one product **3**. However, deactivating the methoxy group by substituting the with inductively withdrawing substituents *para* to the methoxy group, such as in **3j**, seems to retard the cyclization step, leading to larger amounts of ketone product **4** being observed. Placing the electron-withdrawing group *para* to the carbonyl group, such as in **3p**, would increase the rate of the Friedel-Crafts step but it likely slows down the cyclization step by inductively deactivating the methoxy group leading to desilylation being favored. It was found that a conjugated enyne was tolerated to provide **3q**, albeit in low yield. We were excited that the larger naphthyl derivative worked to provide benzochromone derivative **3r** in good yield. Neither bis(TMS)acetylene or 1-(TMS)-1-hexyne gave desired products **3s** or **3t**, respectively. This may be attributed to a less stabilized vinyl cation intermediate. Single crystals of **3g** and **3r**, suitable for X-ray crystallographic analysis, were obtained and their structures unambiguously confirmed (Scheme 2).

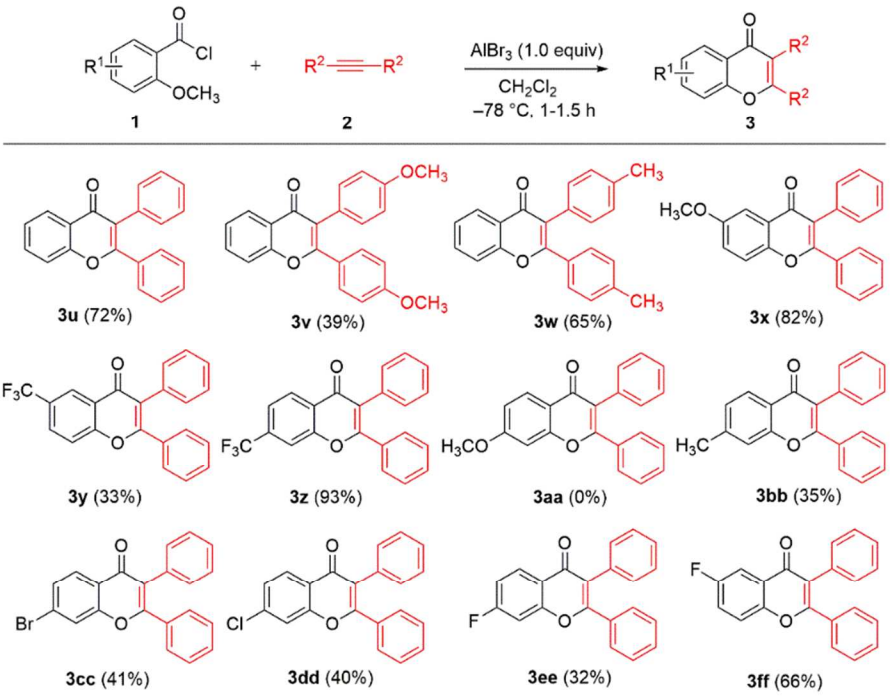
Scheme 2: Scope of Reaction with TMS-alkynes



After demonstrating that TMS-substituted alkynes worked well for this transformation, various symmetrical tolans were explored. To our delight, tolan gave compound **3u** in 72% yield (Scheme 3). Further, electron-rich tolans provided products **3v** and **3w** in 39% and 65% yields, respectively. It was found that the substituents on the benzoyl chloride significantly affected its reactivity, following a similar trend as seen in Scheme 2. For instance, having an electron-donating group *para* to the methoxy substituent resulted in formation of desired chromen-4-one product **3x** in **82**% yield; whereas, having an electron-withdrawing group in this position significantly slowed down the reaction and gave only 33% yield of product **3y,** along with an intractable mixture of other side products. However, placing the CF_3 group *para* to carbonyl

resulted in a fast reaction and provided **3z** in 93% yield. This result would seem to contrast the analogous result seen for **3p** (Scheme 2); however, since tolans are now being used in the Friedel-Crafts step, there is no option for desilylation to afford ketone **4** as an alternative pathway, thus chromen-4-one **3z** is favored. Having a methoxy group *para* to carbonyl resulted in no desired product **3aa** (as was also seen for **3j**, Scheme 2), whereas the weakly electron-donating methyl group *para* to the carbonyl gives moderate yield of the desired product **3bb**. In contrast to the results when using alkyne **2a** (Scheme 2), the halogen-substituted (Br, Cl and F) benzoyl chlorides did react with tolan to give moderate yields of chromen-4-one products **3cc-3ff**. The lower yield could be attributed to these groups being *ortho*/*para* directors (via their lone pairs) and thus they will retard the Friedel-Crafts step in a similar way as seen in **3aa** (although to a lesser extent).

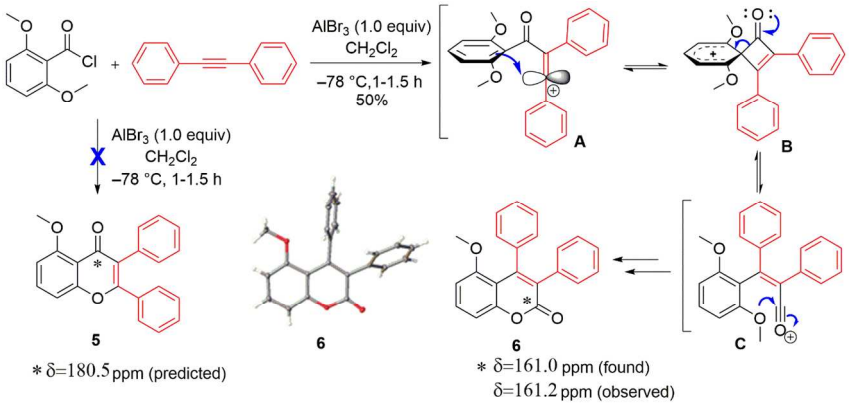
Scheme 3: Scope of the Reaction with Internal Alkynes



Interestingly, when 2,6-dimethoxybenzoyl chloride and tolan were used under the optimized reaction conditions, we observed in the $^{13}C\{^{1}H\}$ NMR spectrum that the carbonyl peak of the isolated product was significantly shifted upfield (δ=161.2 ppm) relative to the other chromen-4-one products (176-183.5 ppm) and the predicted value of 180.5 ppm.[29] X-ray crystallographic analysis of the product showed that a rearrangement had occurred to provide compound **6** as the major product (Scheme 4). We propose that this alternate reaction pathway is the result of steric

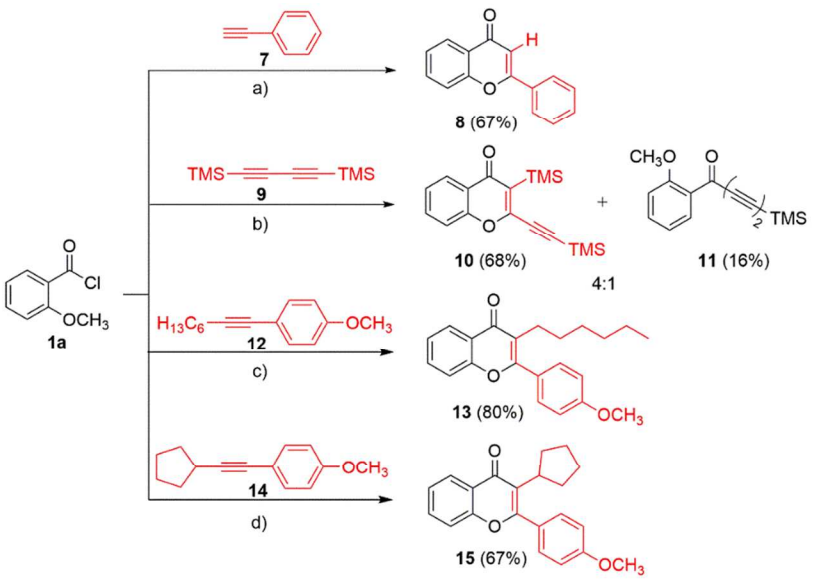
inhibition of resonance,[30] where the carbonyl group in intermediate **A** is forced to be out-of-plane relative to the aryl group due to the steric repulsion of the two *ortho*-methoxy groups. This results in the methoxy group being further away from the vinyl cation. However, the highly activated *ipso*-carbon of the dimethoxy aryl group in intermediate **A** is poised to capture the vinyl cation to form a spirocyclic intermediate **B**.[31] This strained 4-membered spirocyclic intermediate would undergo ring opening to generate the more conjugated intermediate **C**. This intermediate can then participate in a cyclization/demethylation step to form 3,4-diphenylcoumarin **6**.

Scheme 4: Proposed Rearrangement Pathway towards Compound 6



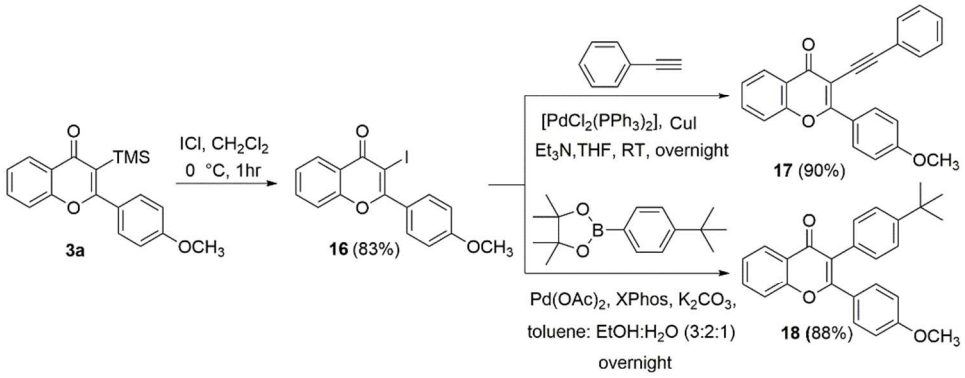
The reaction of phenylacetylene **7** required a higher temperature (25 °C) but also gave desired annulation product **8** in 67% yield (Scheme 5a). Using the optimized reaction conditions, the reaction between 2-methoxybenzoyl chloride and 1,4-bis(trimethylsilyl)buta-1,3-diyne **9** provided a 4:1 mixture of the 2-ethynyl(TMS)-substituted product **10** and acyclic ketone **11**, respectively (Scheme 5b). These could be easily separated to provide **10** and **11** in 68% and 16% yields, respectively. Unsymmetrical internal alkynes with *n*-hexyl and cyclopentyl substituents were also investigated and shown to work, providing **13** and **15** in 80% and 67% yields, respectively.

Scheme 5: Regioselective Annulation Reaction of Benzoyl Chloride Derivatives and other Alkynes



To demonstrate the utility of TMS-functionalized chromen-4-one derivatives, product **3a** was converted into the iodochromenone intermediate **16** by iododesilylation with ICl (Scheme 6). Alkyne functionalized chromen-4-one derivative **17** was obtained in a very good yield (90%) via a Sonogashira cross-coupling reaction. In addition to that, iodochromenone intermediate **16** was utilized to obtain the 1,2-disubstituted chromen-4-one derivatives **18** in good yield (88%) by a Suziki cross-coupling reaction. This demonstrates that this method provides an easy route to desirable unsymmetrical and highly functionalized disubstituted chromen-4-one derivatives.

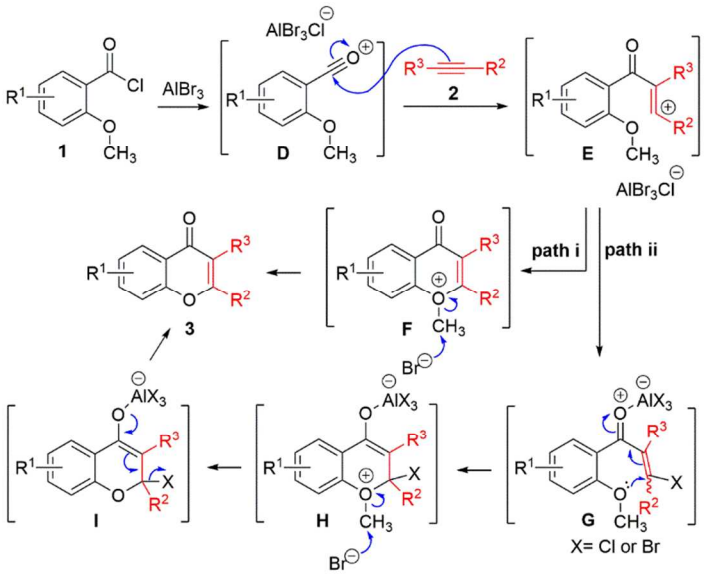
Scheme 6: Synthetic Utility of TMS-functionalized Chromen-4-one Products



We propose that the formation of the chromen-4-one product proceeds by way of initial acylium ion **D** formation followed by nucleophilic attack by internal alkyne **2** to form vinyl

carbocation intermediate **E** (Scheme 7). This carbocation is stabilized by resonance via the aryl substituent (R^2) and by the trimethylsilyl group (R^3), via the β-silyl effect, when alkyne substrates **2** and **9** are used. We propose that there are two possible pathways from here that the reaction can follow. In **path i**, there can be a direct intramolecular nucleophilic attack of the carbocation by the methoxy substituent to provide intermediate **F**. Demethylation of **F** by the bromide anion would result in compound **3**. Although the formation of vinyl bromide intermediates **G** was not observed,[24] **path ii** cannot be ruled as a plausible route to chromen-4-one product **3**. This would involve an oxa-Michael addition on intermediate **G** followed by demethylation and halogen elimination.

Scheme 7: Proposed Reaction Pathway of Annulation Reaction to Chromen-4-ones



CONCLUSION

In summary, highly functionalized chromen-4-one derivatives have been synthesized in moderate to high yields by a domino Friedel-Crafts acylation/oxa-Michael addition/elimination pathway. A wide scope of both benzoyl chloride and internal alkyne substrates were studied, and the regioselectively was unambiguously determined by X-ray crystallography. The regiochemistry observed in the final annulated products can be rationalized by the resonance stabilization of the vinyl carbocation intermediate. In addition, electronic effects played a vital role on benzoyl chloride substrate, particularly when the substituents were *para* relative to the methoxy group or the carbonyl group. Moreover, an interesting rearrangement reaction was observed when

employing 2,6-dimethoxybenzoyl chlorides in the reaction, resulting in the formation of a functionalized coumarin product. Additionally, this method would allow the synthesis of regiocontrolled 2,3-disubstituted chromen-4-one derivatives through cross-coupling. Overall, this one-pot synthetic methodology provides an effective way to synthesize biologically relevant chromen-4-ones and coumarin derivatives from inexpensive starting materials.

EXPERIMENTAL SECTION

General Experimental Methods

2-Methoxybenzoyl chloride was purchased from commercial suppliers and used without further purification. Dichloromethane was purified using a PureSolv MD 5 solvent purification system. Evaporation and concentration in vacuo was performed using rotary evaporation. Where appropriate, reactions were performed in standard, dry glassware under an inert atmosphere of N_2. Column chromatography: Silica gel irregular 60 Å (40-60 micron) from VWR International. Thin-layer chromatography (TLC): glass sheets covered with silica gel 60 F254 from Millipore a Corporation; visualization by UV light. Mp: Mel-Temp apparatus; uncorrected. IR spectra (cm^{-1}): Thermo Nicolet 6700 FT-IR (diamond ATR), data are reported as cm^{-1}. ^1H and $^{13}C\{^1H\}$ NMR (Varian NMR 400 MHz and 500 MHz) spectra were recorded in deuterated chloroform ($CDCl_3$). Tetramethylsilane (TMS, set to 0 ppm) was used as an internal standard for chemical shifts or referenced to the residual protio-solvent peaks (7.26 ppm for ^1H and 77.16 ppm for $^{13}C\{^1H\}$, respectively). ESI-TOF MS: Agilent G6230A instrument with purine and HP-Ø921 as internal calibrants.

General Procedure A

To a solution of benzyol chloride **1** (1.1 equiv) in dichloromethane (20 mL) at –78 ºC under N_2 atmosphere was added aluminum bromide (1.0 equiv) followed by addition of alkyne **2** (1.0 equiv). After stirring for 1-1.5 hours at –78 ºC, the reaction was quenched with saturated aqueous $NaHCO_3$ at –78 ºC, then warmed to room temperature. The reaction mixture was extracted with Et_2O (100 mL × 2). The layers were separated, the organic phase was washed with H_2O, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography.

General Procedure B

The carboxylic acid (1.0 ~ 1.6 equiv) was dissolved in $SOCl_2$ (2 mL). After refluxing for two hours, the excess $SOCl_2$ was removed by vacuum distillation. The resulting crude acid chloride was used without further purification. To a solution of crude acid chloride in dichloromethane (20 mL) at –78 ºC under N_2 atmosphere was added aluminum bromide (1.0 equiv) and alkyne **2** (1.0 equiv). The reaction was quenched after 1-1.5 hours at –78 ºC with saturated aqueous $NaHCO_3$, then warmed to room temperature. The reaction mixture was extracted with Et_2O (100 mL × 2). The organic layer was washed with H_2O, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography.

2-(4-Methoxyphenyl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3a) was prepared following the general procedure A using 2-methoxybenzoyl chloride **1a** (274 mg, 1.60 mmol) and alkyne **2a** (300 mg, 1.47 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 5:1, v/v) yielded pure **3a** as a white solid (219 mg, 56%). R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 110-111 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.8 Hz, 1H), 7.61 (dd, J = 9.6, 6.8 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.40 – 7.31 (m, 2H), 7.01 – 6.93 (m, 2H), 3.87 (s, 3H), 0.05 ppm (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.7, 169.3, 161.5, 156.4, 133.5, 131.0, 128.4, 125.8, 125.0, 123.0, 118.2, 117.8, 113.7, 55.6, 0.8 ppm; IR (film): 3008, 2953, 2891, 1627, 1614, 1503, 1463 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{19}H_{21}O_3Si$ $[M+H]^+$ 325.1254; found 325.1252.

2-(2-Methoxyyphenyl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3b) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (137 mg, 0.810 mmol) and alkyne **2b** (150 mg, 0.735 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 10:1, v/v) yielded pure **3b** as a yellow oil (85 mg, 36%). R_f = 0.20 (hexane:EtOAc = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 9.0 Hz, 1H), 7.66 – 7.58 (m, 1H), 7.54 – 7.41 (m, 1H), 7.40 – 7.34 (m, 2H), 7.30 (d, J = 7.3 Hz, 1H), 7.08 – 7.01 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), -0.02 ppm (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.4, 166.3, 157.4, 156.8, 133.4, 131.8, 130.9, 125.8, 125.0, 124.9, 123.2, 120.3, 120.2, 118.0, 111.1, 55.6, -0.1 ppm; IR

(film): 2951, 1631, 1613, 1464, 1348, 1245 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{21}O_3Si$ $[M+H]^+$ 325.1254; found 325.1241.

2-(2-Furanyl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3c) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (228 mg, 1.34 mmol) and alkyne **2c** (200 mg, 1.22 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 15:1, v/v) yielded pure **3c** as a colorless crystalline solid (150 mg, 53%). R_f = 0.39 (hexane:EtOAc = 10:1); Mp = 137-138 ºC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.64 – 7.59 (m, 1H), 7.53 (s, 1H), 7.38 – 7.33 (m, 2H), 6.66 (s, 1H), 0.17 ppm (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 181.4, 160.7, 155.3, 142.7, 142.4, 132.6, 124.8, 124.1, 122.1, 120.6, 118.7, 116.7, 110.1, -0.1 ppm; IR (film): 2946, 1613, 1603, 1543, 1461, 1352 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{17}O_3Si$ $[M+H]^+$ 285.0941; found 285.0929.

2-(4-Bromoyphenyl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3d) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (148 mg, 0.868 mmol) and alkyne **2d** (200 mg, 0.790 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 6:1, v/v) yielded pure **3d** as a light yellow solid (184 mg, 63%). R_f = 0.20 (hexane:CH_2Cl_2 = 1:1); Mp = 169-171 ºC; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 7.8 Hz, 1H), 7.67 – 7.61 (m, 3H), 7.43 – 7.35 (m, 4H), 0.05 ppm (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.3, 167.9, 156.3, 134.7, 133.7, 131.6, 131.0, 125.8, 125.2, 125.1, 122.9, 119.0, 117.8, 0.7 ppm; IR (film): 3062, 2950, 1628, 1611, 1464, 1347 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{18}BrO_2Si$ $[M+H]^+$ 373.0254; found 373.0245.

2-(2-Bromoyphenyl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3e) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (370 mg, 2.17 mmol) and alkyne **2e** (500 mg, 1.97 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 10:1, v/v) yielded pure **3e** as a yellow oil (540 mg, 73%). R_f = 0.20 (hexane: EtOAc = 8:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 1H), 7.72 – 7.57 (m, 2H), 7.50 – 7.27 (m, 5H), 0.00 ppm (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 182.1, 166.9, 156.5, 136.7, 133.7, 132.8, 131.5, 131.1, 127.2, 125.7, 125.2, 123.2, 123.1, 119.9, 117.9, -0.2 ppm; IR (film): 2979, 1626, 1611, 1558, 1461, 1340 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{18}BrO_2Si$ $[M+H]^+$ 373.0254; found 373.0234.

2-Phenyl-3-(trimethylsilyl)-*4H*-chromen-4-one (3f) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (188 mg, 1.10 mmol) and alkyne **2f** (174 mg, 1.00 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 4:1, v/v) yielded pure **3f** as a colorless crystalline solid (250 mg, 85%). R_f = 0.20 (hexane:CH_2Cl_2 = 3:1); Mp = 136-137 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.4 Hz, 1H), 7.63 (dd, J = 8.8, 6.7 Hz, 1H), 7.58 – 7.45 (m, 5H), 7.43 – 7.34 (m, 2H), 0.05 ppm (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.5, 169.3, 156.4, 135.9, 133.6, 130.6, 129.4, 128.4, 125.8, 125.1, 123.0, 118.7, 117.8, 0.6 ppm; IR (film): 2944, 1623, 1607, 1546 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{19}O_2Si$ $[M+H]^+$ 295.1149; found 295.1135.

2-(4-Cyanophenyl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3g) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (141 mg, 0.830 mmol) and alkyne **2g** (149 mg, 0.750 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 15:1, v/v) yielded pure **3g** as a white solid (106 mg, 44%). R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 161-163 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.8 Hz, 1H), 7.83– 7.75 (m, 2H), 7.70 – 7.57 (m, 3H), 7.50 – 7.34 (m, 2H), 0.03 ppm (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.0, 164.6, 154.3, 137.8, 132.0, 130.2, 128.2, 123.9, 123.5, 120.9, 117.7, 116.2, 115.8, 112.4, -1.4 ppm; IR (film): 2957, 2917, 2849, 2230, 1629, 1602, 1464 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{18}NO_2Si$ $[M+H]^+$ 320.1101; found 320.1085.

6-Methoxy-2-(4-methoxyphenyl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3i) was prepared following general procedure B using 2,5-dimethoxybenzoic acid (250 mg, 1.37 mmol) and alkyne **2a** (150 mg, 0.734 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 8:1, v/v) yielded pure **3i** as a light yellow solid (219 mg, 84%). R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 126-127 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 3.1 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.32 (d, J = 9.1, Hz, 1H), 7.22 (dd, J = 9.1, 3.1 Hz, 1H), 7.03 – 6.95 (m, 2H), 3.887 (s, 3H), 3.878 (s, 3H), 0.05 ppm (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.6, 169.2, 161.4, 156.8, 151.2, 130.9, 128.4, 123.6, 123.4, 119.3, 117.1, 113.7, 104.8, 56.0, 55.5, 0.8 ppm; IR (film): 3005, 2967, 1625, 1609, 1503, 1481 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{23}O_4Si$ $[M+H]^+$ 355.1360; found 355.1371.

7-Methyl-2-(4-methoxyphenyl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3o) was prepared following general procedure B using 2-methoxy-4-methylbenzoic acid (250 mg, 1.51 mmol) and alkyne **2a** (200 mg, 0.980 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 8:1, v/v) yielded pure **3o** as a yellow solid (106 mg, 32%). R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 138-139 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.21 – 7.11 (m, 2H), 7.04 – 6.92 (m, 2H), 3.88 (s, 3H), 2.46 (s, 3H), 0.05 ppm (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.5, 169.0, 161.4, 156.5, 144.7, 130.9, 128.5, 126.4, 125.5, 120.8, 117.9, 117.5, 113.7, 55.5, 21.9, 0.8 ppm; IR (film): 2959, 2923, 1652, 1607, 1504, 1245 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{23}O_3Si$ $[M+H]^+$ 339.1411; found 339.1393.

2-(1-Cyclohexen-1-yl)-3-(trimethylsilyl)-*4H*-chromen-4-one (3q) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (263 mg, 1.55 mmol) and alkyne **2i** (250 mg, 1.40 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 10:1, v/v) yielded pure **3q** as a brown sticky solid (80 mg, 19%). R_f = 0.20 (hexane:EtOAc = 15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.9, 1.4 Hz, 1H), 7.59 (ddd, J = 8.8, 7.2, 1.7, 1H), 7.34 (d, J = 8.5, 1H), 7.32 (ddd, J = 8.1, 7.1, 1.0, 1H), 5.96 (tt, J = 3.72, 1.75 Hz, 1H), 2.46 – 2.29 (m, 2H), 2.29 – 2.10 (m, 2H), 1.83 – 1.73 (m, 2H), 1.72 – 1.64 (m, 2H), 0.28 ppm (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 183.1, 172.3, 156.1, 134.3, 134.1, 133.4, 125.7, 124.7, 123.1, 117.6, 116.5, 26.7, 25.4, 22.1, 21.5, 1.2 ppm; IR (film): 2933, 2858, 1629, 1610, 1544 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{23}O_2Si$ $[M+H]^+$ 299.1462; found 299.1456.

2-(4-Methoxyphenyl)-3-(trimethylsilyl)-Naphtho[2,3-b]-*4H*-chromen-4-one (3r) was prepared following general procedure B using 3-methoxy-2-naphthoic acid (296 mg, 1.46 mmol) and alkyne **2a** (250 mg, 1.22 mmol). Purification by flash column chromatography (silica gel, hexane:CH_2Cl_2 = 1:1, v/v) yielded pure **3r** as a white solid (274 mg, 60%). R_f = 0.20 (hexane:CH_2Cl_2 = 2:1); Mp = 149-151 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.83 (s, 1H), 7.57 (dd, J = 8.4, 6.8 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.49 (dd, J = 8.4, 6.9 Hz, 1H), 7.08 – 6.98 (m, 2H), 3.90 (s, 3H), 0.10 ppm (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 183.5, 170.2, 161.6, 152.9, 136.0, 131.0, 130.5, 129.9, 128.6, 128.5, 127.3, 126.8, 125.7, 122.2, 116.3, 113.8, 113.7, 55.6, 0.9 ppm; IR (film): 3054,

2839, 1644, 1612, 1452, 1244 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{23}SiO_3$ $[M+H]^+$ 375.1411; found 375.1391.

2,3-Diphenyl-*4H*-chromen-4-one (3u) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (210 mg, 1.24 mmol) and alkyne **2l** (200 mg, 1.12 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 6:1, v/v) yielded pure **3u** as a white solid (240 mg, 72%). R_f = 0.30 (hexane:EtOAc = 8:1); Mp = 146-147 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.9 Hz, 1H), 7.69 (dd, *J* = 9.3, 6.3 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.36 (m, 3H), 7.36 – 7.19 ppm (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.4, 161.6, 156.2, 133.8, 133.4, 133.0, 131.3, 130.2, 129.7, 128.4, 128.2, 127.7, 126.5, 125.2, 123.7, 123.1, 118.1 ppm; IR (film): 3052, 1632, 1615, 1599, 1560 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{15}O_2$ $[M+H]^+$ 299.1067; found 299.1055.

2,3-Bis(4-methoxyphenyl)-*4H*-chromen-4-one (3v) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (150 mg, 0.880 mmol) and alkyne **2m** (150 mg, 0.630 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 5:1, v/v) yielded pure **3v** as a white solid (87 mg, 39%). R_f = 0.20 (hexane:EtOAc = 8:1); Mp = 157-158 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.4 Hz, 1H), 7.68 (dd, *J* = 9.2, 6.3 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.44 – 7.35 (m, 3H), 7.21 – 7.13 (m, 2H), 6.92 – 6.84 (m, 2H), 6.84 – 6.76 (m, 2H), 3.82 (s, 3H), 3.81 ppm (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.6, 161.2, 160.9, 159.0, 156.0, 133.5, 132.4, 131.3, 126.4, 125.7, 125.5, 124.9, 123.5, 121.7, 117.9, 114.0, 113.6, 55.4, 55.3 ppm; IR (film): 2933, 2837, 1637, 1607, 1506 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{19}O_4$ $[M+H]^+$ 359.1278; found 359.1257.

2,3-Bis(4-methylphenyl)-*4H*-chromen-4-one (3w) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (455 mg, 2.68 mmol) and alkyne **2n** (500 mg, 2.43 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 6:1, v/v) yielded pure **3w** as a white solid (510 mg, 65%). R_f = 0.30 (hexane:EtOAc = 8:1); Mp = 145-146 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.9 Hz, 1H), 7.71 – 7.66 (dd, *J* =7.8, 6.3 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.16 – 7.06 (m, 6H), 2.35 (s, 3H), 2.34 ppm (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 177.6, 161.5, 156.1, 140.4, 137.3, 133.6, 131.1, 130.7, 130.1, 129.6, 129.2, 128.9, 126.5, 125.0, 123.6, 122.6,

118.0, 21.54, 21.45 ppm; IR (film): 2918, 1640, 1609, 1462 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{23}H_{19}O_2$ $[M+H]^+$ 327.1380; found 327.1363.

6-Methoxy-2,3-diphenyl-*4H*-chromen-4-one (3x) *w*as prepared following general procedure B using 2-methoxy-5-methoxybenzoic acid (100 mg, 1.64 mmol) and alkyne **2l** (100 mg, 0.561 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 10:1, v/v) yielded pure **3x** as a white solid (151 mg, 82%). R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 181-182 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 3.1 Hz, 1H), 7.48 (d, J = 9.1 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.34 – 7.19 (m, 9H), 3.92 ppm (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.3, 161.5, 157.1, 151.1, 133.6, 133.2, 131.4, 130.1, 129.7, 128.4, 128.2, 127.7, 124.3, 123.9, 122.4, 119.6, 105.6, 56.1 ppm; IR (film): 3054, 2971, 1627, 1601, 1566, 1482, 1437 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{17}O_3$ $[M+H]^+$ 329.1172; found 329.1166.

6-(Trifluoromethyl)-2,3-diphenyl-*4H*-chromen-4-one (3y) was prepared following general procedure B using, 2-methoxy-5-(trifluoromethyl)-benzoic acid (429 mg, 1.95 mmol) and alkyne **2l** (250 mg, 1.40 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 12:1, v/v) yielded pure **3y** as a white solid (169 mg, 33%). R_f = 0.40 (hexane:EtOAc = 10:1); Mp = 144-146 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.89 (d, J = 10.7 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.42 – 7.17 ppm (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.5, 162.0, 157.6, 132.7, 132.3, 131.2, 130.6, 130.1 (q, J = 3.3 Hz), 129.7, 128.5, 128.3, 128.0, 127.6 (q, J = 33.7 Hz), 124.6 (q, J = 4.0 Hz), 123.7 (q, J = 272.4 Hz), 123.52, 123.46, 119.3 ppm; IR (film): 3062, 1638, 1621, 1562 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{14}F_3O_2$ $[M+H]^+$ 367.0940; found 367.0934.

7-(Trifluoromethyl)-2,3-diphenyl-*4H*-chromen-4-one (3z) was prepared following general procedure B using 2-methoxy-4-(trifluoromethyl)-benzoic acid (150 mg, 0.682 mmol) and alkyne **2l** (110 mg, 0.617 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 15:1, v/v) yielded pure **3z** as a white solid (210 mg, 93%). R_f = 0.40 (hexane:EtOAc = 10:1); Mp = 145-146 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 7.9 Hz, 1H), 7.85 (s, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.44 – 7.15 ppm (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.6, 162.3, 155.6, 135.4 (q, J = 33.0 Hz), 132.8, 132.4, 131.2, 130.6, 129.7, 128.5, 128.3, 128.1, 127.9, 125.8, 123.7, 123.3 (q, J = 271.0 Hz), 121.5 (q, J = 3.0 Hz), 116.1 ppm (q, J

= 4.0 Hz); IR (film): 3056, 1639, 1629, 1554, 1435 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{14}F_3O_2$ $[M+H]^+$ 367.0940; found 367.0937.

7-Methyl-2,3-diphenyl-*4H*-chromen-4-one (3bb) was prepared following general procedure B using 2-methoxy-4-methylbenzoic acid (300 mg, 1.80 mmol) and alkyne **2l** (61 mg, 0.195 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 10:1, v/v) yielded pure **3bb** as a white solid (61 mg, 35%). R_f = 0.30 (hexane:EtOAc = 10:1); Mp = 241-243 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.35 – 7.19 (m, 12H), 2.51 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) *δ* 177.3, 161.3, 156.3, 145.1, 133.6, 133.1, 131.4, 130.1, 129.7, 128.3, 128.2, 127.6, 126.7, 126.3, 123.0, 121.4, 117.8, 22.0 ppm; IR (film): 3055, 2923, 1706, 1604, 1442 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{17}O_2$ $[M+H]^+$ 313.1223; found 313.1221.

7-Bromo-2,3-diphenyl-*4H*-chromen-4-one (3cc) was prepared following general procedure B using 2-methoxy-4-bromobenzoic acid (190 mg, 0.757 mmol) and alkyne **2l** (100 mg, 0.562 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 8:1, v/v) yielded pure **3cc** as a white solid (87 mg, 41%). R_f = 0.30 (hexane:EtOAc = 10:1); Mp = 129-131 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.13 (d, *J* = 8.5 Hz, 1H), 7.72 (s, 1H), 7.52 (d, *J* = 9.8 Hz, 1H), 7.41 – 7.16 ppm (m, 10H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 176.6, 161.5, 156.1, 132.8, 132.5, 131.1, 130.3, 129.5, 128.7, 128.3, 128.1, 127.9, 127.82, 127.79, 123.2, 122.4, 121.1 ppm; IR (film): 3054, 1640, 1599, 1559, 1420 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{14}BrO_2$ $[M+H]^+$ 377.0172; found 377.0164.

7-Chloro-2,3-diphenyl-*4H*-chromen-4-one (3dd) was prepared following general procedure B using 2-methoxy-4-chlorobenzoic acid (250 mg, 1.34 mmol) and alkyne **2l** (150 mg, 0.843 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 8:1, v/v) yielded pure **3dd** as a white solid (112 mg, 40%). R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 110-111 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.21 (d, *J* = 8.6 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.40 – 7.17 ppm (m, 11H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) *δ* 176.6, 161.6, 156.2, 139.7, 132.9, 132.5, 131.2, 130.3, 129.6, 128.4, 128.2, 127.9, 127.8, 126.0, 123.2, 122.1, 118.1 ppm; IR (film): 2924, 1639, 1595 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{14}ClO_2$ $[M+H]^+$ 333.0677; found 333.0671.

7-Fluoro-2,3-diphenyl-*4H*-chromen-4-one (3ee) was prepared following general procedure B using 4-fluoro-2-methoxy-benzoic acid (300 mg, 1.76 mmol) and alkyne **2l** (200 mg, 1.12 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 8:1, v/v) yielded pure **3ee** as a white solid (114 mg, 32%). R_f = 0.35 (hexane:EtOAc = 10:1); Mp = 155-157 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, J = 8.9, 6.3 Hz, 1H), 7.42 – 7.08 ppm (m, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.6, 165.9 (d, J = 253.3 Hz), 161.8, 157.1 (d, J = 13.4 Hz), 133.0, 132.6, 131.3, 130.3, 129.6, 129.1 (d, J = 10.5 Hz), 128.4, 128.3, 127.9, 123.2, 120.5 (d, J = 2.4 Hz), 114.0 (d, J = 22.7 Hz), 104.7 ppm (d, J = 25.0 Hz); IR (film): 3058, 2920, 1732, 1709, 1644, 1606, 1559 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{14}FO_2$ $[M+H]^+$ 317.0972; found 317.0964.

6-Fluoro-2,3-diphenyl-*4H*-chromen-4-one (3ff) was prepared following general procedure B using 5-fluoro-2-methoxybenzoic acid (300 mg, 1.76 mmol) and alkyne **2l** (280 mg, 1.57 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 8:1, v/v) yielded pure **3ff** as a white solid (330 mg, 66%). R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 169-170 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s 1H), 7.91 (dd, J = 8.8, 2.3 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.44 – 7.15 ppm (m, 10H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.7, 161.9, 159.7 (d, J = 245.0 Hz), 152.4 (d, J = 1.6 Hz), 133.1, 132.6, 131.3, 130.3, 129.7, 128.4, 128.2, 127.9, 124.8 (d, J = 7.3 Hz), 122.4, 122.1 (d, J = 25.5 Hz), 120.2 (d, J = 8.0 Hz), 111.2 ppm (d, J = 23.6 Hz); IR (film): 3059, 1626, 1528, 1563, 1480 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{14}FO_2$ $[M+H]^+$ 317.0972; found 317.0965.

3,4-Diphenyl-*2H*-chromen-2-one (6) was prepared following general procedure A using 2,6-dimethoxybenzoyl chloride **1a** (124mg, 0.37 mmol) and alkyne **2l** (100 mg, 0.67 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 10:1, v/v) yielded pure **6** as a crystalline solid (109 mg, 50%). R_f = 0.10 (hexane:EtOAc = 10:1); Mp = 201-204 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 1H), 7.18 – 7.10 (m, 6H), 7.08 – 6.96 (m, 5H), 6.73 – 6.55 (m, 1H), 3.34 ppm (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.2, 157.8, 154.5, 151.2, 138.6, 134.1, 132.0, 130.6, 128.0, 127.6, 127.3, 127.2, 127.1, 126.8, 110.5, 109.8, 107.1, 55.9 ppm; IR (film): 3097, 3054, 3027, 2928, 1712, 1590, 1466, 1263 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{17}O_3$ $[M+H]^+$ 329.1172; found 329.1154.

2-Phenyl-*4H*-chromen-4-one (8)*:* To a solution of 2-methoxybenzoyl chloride **1a** (230 mg, 1.35 mmol) in dichloromethane (20 mL) at room temperature under N_2 atmosphere, aluminum bromide (330 mg, 1.24 mmol) was added, which was followed by addition of phenylacetylene **7** (128 mg, 1.25 mmol). After stirring for 1.5 hours, the reaction was quenched by saturated aqueous $NaHCO_3$ and extracted with Et_2O (100 mL x 2). The layers were separated, the organic phase was washed with H_2O, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane:EtOAc = 6:1, v/v) yielded pure **8** as a white solid (187 mg, 67%). R_f = 0.20 (hexane:EtOAc = 8:1); Mp = 97-98 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 7.9 Hz, 1H), 7.98 – 7.90 (m, 2H), 7.72 – 7.69 (m, 1H), 7.63 – 7.48 (m, 4H), 7.46 – 7.40 (m, 1H), 6.84 ppm (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 178.6, 163.6, 156.4, 133.9, 131.9, 131.8, 129.2, 126.5, 125.9, 125.4, 124.1, 118.2, 107.7 ppm; IR (film): 3053, 1640, 1607, 1465 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{11}O_2$ $[M+H]^+$ 223.0754; found 223.0755.

3-(Trimethylsilyl)-2-[2-(trimethylsilyl)ethynyl]-*4H*-chromen-4-one (10) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (483 mg, 2.83 mmol) and 1,4-bis(trimethylsilyl)buta-1,3-diyne **9** (500 mg, 2.57 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 10:1, v/v) yielded pure **10** as a brown sticky solid (549 mg, 68%). R_f = 0.30 (hexane:EtOAc = 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.1, Hz, 1H), 7.64 – 7.57 (m, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.35 – 7.30 (m, 1H), 0.40 (s, 9H), 0.30 ppm (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 181.6, 156.6, 149.8, 133.8, 125.8, 125.2, 123.4, 123.3, 117.7, 104.7, 98.3, 0.6, -0.6 ppm; IR (film): 2961, 2900, 2099, 1626, 1611, 1534 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{23}Si_2O_2$ $[M+H]^+$ 315.1231; found 315.1215.

3-Hexyl-2-(4-methoxyphenyl)-*4H*-chromen-4-one (13) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (147 mg, 0.865 mmol) and alkyne **12** (170 mg, 0.785 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 6:1, v/v) yielded pure **13** as a colorless oil (210 mg, 80%). R_f = 0.30 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 8.0, Hz, 1H), 7.65 – 7.6 (m, 1H), 7.59 – 7.52 (m, 2H), 7.45 – 7.40 (m, 1H), 7.39 – 7.34 (m, 1H), 7.06 – 7.00 (m, 2H), 3.89 (s, 3H), 2.60 – 2.50 (m, 2H), 1.62 – 1.52 (m, 2H), 1.36 – 1.18 (m, 6H), 0.85 ppm (t, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 178.6, 161.7, 161.1, 156.2, 133.3, 130.3, 126.2, 126.0, 124.7, 123.1, 122.1, 117.9, 114.0, 55.6, 31.6,

29.6, 29.2, 26.0, 22.7, 14.2 ppm; IR (film): 2955, 2926, 1619, 1609, 1510 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{25}O_3$ $[M+H]^+$ 337.1798; found 337.1776.

3-Cyclopentyl-2-(4-methoxyphenyl)-*4H*-chromen-4-one (15) was prepared following general procedure A using 2-methoxybenzoyl chloride **1a** (190 mg, 1.12 mmol) and alkyne **14** (215 mg, 1.08 mmol). Purification by flash column chromatography (silica gel, hexane:EtOAc = 10:1, v/v) yielded pure **15** as a white solid (230 mg, 67%). R_f = 0.20 (hexane:EtOAc = 15:1); Mp = 123-124 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.61– 7.56 (m, 1H), 7.53 – 7.49 (m, 2H), 7.39 – 7.30 (m, 2H), 7.03 – 6.98 (m, 2H), 3.87 (s, 3H), 3.01 – 2.88 (m, 1H), 2.25 – 2.14 (m, 2H), 1.99 – 1.97 (m, 2H), 1.72 – 1.63 (m, 2H), 1.59 – 1.49 ppm (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.3, 162.0, 161.0, 155.9, 133.1, 130.5, 126.4, 125.7, 124.6, 123.9, 123.4, 117.8, 113.9, 55.5, 39.3, 30.7, 27.2 ppm; IR (film): 2952, 2930, 2872, 2833, 1690, 1625, 1611, 1509 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{21}O_3$ $[M+H]^+$ 321.1485; found 321.1481.

3-Iodo-2-(4-methoxyphenyl)-*4H*-chromen-4-one (16): A procedure in the literature was modified.[32] A solution of ICl in dry CH_2Cl_2 (1.00 g, 6.16 mmol) was added dropwise to a solution of **3a** (1.60 g, 4.90 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C. After stirring for 1 h, the reaction was quenched with aqueous $Na_2S_2O_3$. The organic layer was extracted using CH_2Cl_2/water, and dried using Na_2CO_3. Purification by flash chromatography on silica gel to afford the compound **16** as a light yellow solid (1.5g, 83%); R_f = 0.30 (hexane:EtOAc = 15:1); Mp = 127-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.69 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.53 – 7.37 (m, 2H), 7.06 – 6.96 ppm (m, 2H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.8, 164.5, 161.8, 156.0, 134.2, 131.5, 127.3, 126.9, 125.9, 120.1, 117.7, 113.7, 87.8, 55.6 ppm; IR (film): 3069, 3014, 2841, 1657, 1608, 1558, 1504, 1465 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{11}IKO_3$ $[M+K]^+$ 416.9384; found 416.9366.

2-(4-Methoxyphenyl)-3-(2-phenylethynyl)-*4H*-chromen-4-one (17)*:* Compound **16** (210 mg, 0.555 mmol), and phenylacetylene (68 mg, 0.67 mmol) were dissolved in dry THF (2 mL) and Et_3N (5 mL). Then $(Ph_3P)_2PdCl_2$ (20 mg, 0.028 mmol), CuI (10 mg, 0.053 mmol) were added to the solution after degassing the reaction mixture via bubbling nitrogen for 30 min. The solution was allowed to stir at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the

compound **17** as a light yellow solid (179 mg, 90%); R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 142-144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 – 8.26 (m, 3H), 7.69 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.43 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.09 – 7.03 (m, 2H), 3.92 ppm (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.8, 165.4, 162.3, 155.5, 134.0, 131.7, 131.0, 128.5, 128.4, 126.3, 125.5, 124.9, 123.5, 122.4, 118.0, 113.8, 106.1, 97.9, 82.6, 55.7 ppm; IR (film): 3060, 2935, 2838, 2361, 1647, 1604, 1576, 1510 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{24}H_{17}O_3$ $[M+H]^+$ 353.1172; found 353.1201.

3-[4-(1,1-Dimethylethyl)phenyl]-2-(4-methoxyphenyl)-*4H*-chromen-4-one (18): Compound **16** (300 mg, 0.970 mmol), 4-tert-butylphenylboronic acid pinacol ester (379 mg, 1.46 mmol) and K_2CO_3 (340 mg, 2.50 mmol) were dissolved in the mixture of toluene (9 mL), EtOH (6 mL), and H_2O(3 mL). Then $Pd(OAc)_2$ (22.0 mg, 0.097 mmol) and XPhos (92.0 mg, 0.193 mmol) were added to the solution after degassing the reaction mixture via bubbling nitrogen for 30 min. The resulting mixture was stirred under a N_2 atmosphere at 80 °C overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the compound **18** as a white solid (310 mg, 88%); R_f = 0.20 (hexane:EtOAc = 10:1); Mp = 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.68 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.52 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.41 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.19 – 7.14 (m, 2H), 6.87 – 6.72 (m, 2H), 3.80 (s, 3H), 1.32 ppm (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.6, 160.2, 159.9, 155.1, 149.4, 132.5, 130.4, 129.8, 129.2, 125.5, 124.8, 124.4, 124.0, 122.6, 121.1, 116.9, 112.5, 54.4, 33.7, 30.5 ppm; IR (film): 2960, 2867, 2838, 1637, 1606, 1578, 1503 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{26}H_{25}O_3$ $[M+H]^+$ 385.1798; found 385.1797.

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Notes

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ASSOCIATED CONTENT

Supporting Information

NMR spectra, crystallographic data, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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