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Cascade Annulation of 2-Alkynylthioanisoles with Unsaturated α-Bromocarbonyls Leading to Thio-Benzobicyclic Skeletons

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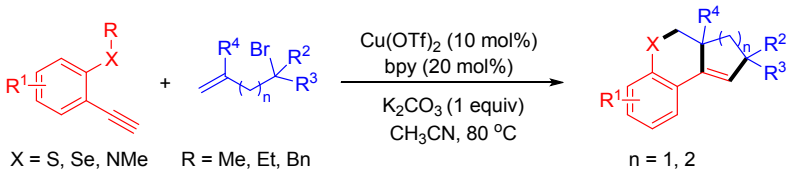


ABSTRACT: A protocol of Cu-catalyzed annulation of phenylethynylsulfanes with unsaturated α-bromocarbonyls for the construction of thio-benzobicyclic skeletons is described. In this single reaction, three new bonds and two new rings can be established, highlighting the step-economics and high efficiency of this protocol.

INTRODUCTION

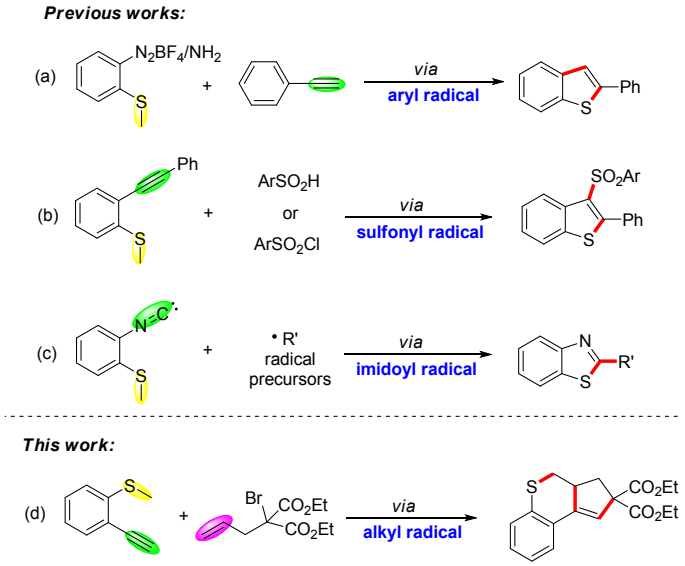
In recent years, thioanisole derivatives have been applied for the construction of benzothiophenes *via* radical cascade reactions.[1, 2] In these transformations, the radical cyclization process was terminated by the addition of a radical to a sulfur atom along with the release of a methyl group. In elegant works, Zanardi's, Schiesser's, König's, Maulide's, McDonald's and Zhang's groups revealed the synthesis of benzothiophenes *via* tandem radical annulations between *o*-methylthioarenediazonium salts/anilines and alkynes (Scheme 1a).[1] Subsequently, Song's group developed a tandem radical addition−cyclization reaction between 2-alkynylthioanisoles and sulfinic acids/sulfonyl chlorides for the formation of 3-(arylsulfonyl)benzothiophenes (Scheme 1b).[2] Very recently, Wu's group disclosed a radical cascade reaction between (2-isocyanophenyl)(methyl)sulfanes and radical precursors, providing a method for the construction of benzothiazole derivatives (Scheme 1c).[3]

Meanwhile, readily available α-bromocarbonyls are important organic building blocks in synthesis and chemical industries.[4] Generally, alkyl radicals are provided by α-bromocarbonyls to react with unsaturated hydrocarbons for the construction of diverse polycyclic compounds in concise process with highly atom economic and simple operation.[5, 6] However, monocyclic compounds were formed through this strategy in most cases, probably because such approaches were terminated by halogen atoms which is known as atom transfer radical cyclization (ATRC) process.[7] Thus, it still

remains great challenge to employ α-bromocarbonyls for the synthesis of polycyclic compounds.

Herein, we considered that α-bromocarbonyls containing unsaturated functional groups could react with 2-alkynylthioanisoles *via* a radical addition to the sulfur atom, leading to the construction of thio-benzobicyclic skeletons (Scheme 1d). In this one-pot reaction, three new bonds can be formed, as well as polycyclic rings can be constructed, highlighting the step-economics and high efficiency of this protocol.

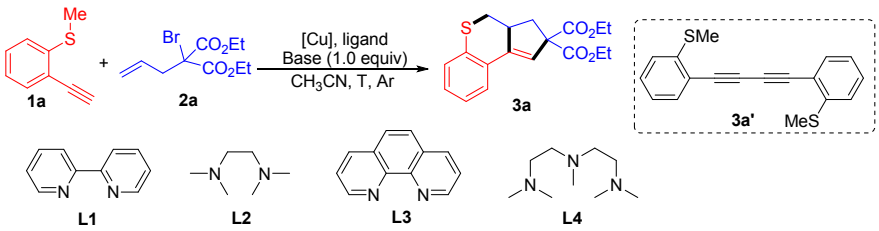
Scheme 1. Studies on Intermolecular Radical Cascade Reactions of Thioanisole Derivatives



RESULTS AND DISCUSSION

To test this hypothesis, (2-ethynylphenyl)(methyl)sulfane (**1a**) and diethyl 2-allyl-2-bromomalonate (**2a**) were chosen as reaction partners (Table 1). Thus far, copper-based catalysts have been the common agents to induced the cascade radical reactions.[8] Hence, copper salts were first employed as the catalyst. Pleasingly, when using 10 mol% of $Cu(OAc)_2 \cdot 5H_2O$ as the catalyst, 20 mol% bipy (**L1)** as the ligand, and 1 equiv of K_2CO_3 as the base, **3a** was isolated in 22% yield, after being heated at 80 °C for 8 h (entry 1). Subsequently, various copper salts were further checked and showed that $Cu(OTf)_2$ was the most effective and gave **3a** in 71% yield (entries 1–10). Screening a few other ligands, such as TMEDA (**L2**), 1,10-phenanthroline (**L3**) and pentamethyldiethylenetriamine (**L4**), revealed that **L1** was the most efficient one (entries 11–13). The influence of base was also investigated and K_2CO_3 was found to be the most suitable base (entries 14−17). The reaction was inhibited in the absence of copper salt, base or ligand (entries 18–20). Moreover, the yield of **3a** decreased when the loading of $Cu(OTf)_2$ was reduced (entry 21) or the temperature was changed (entries 22−23). Under the optimal reaction conditions, **3a'** was found as the major byproduct.

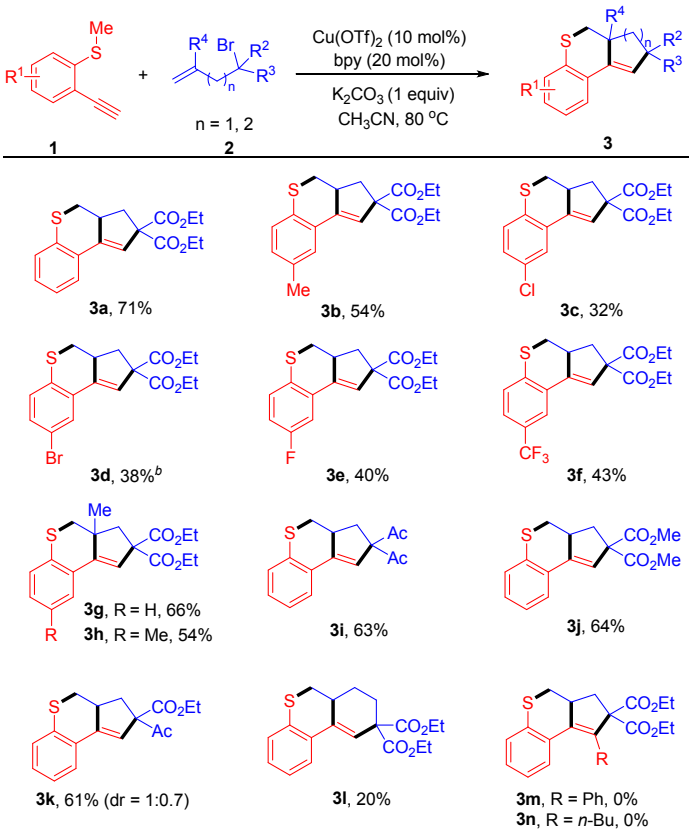
Table 1. Optimization of Reaction Conditions[a]



entry	[Cu]	ligand	base	yield (%)
1	$Cu(OAc)_2·5H_2O$	**L1**	K_2CO_3	22
2	**$Cu(OTf)_2$**	**L1**	**K_2CO_3**	**71**
3	$Cu(acac)_2$	**L1**	K_2CO_3	50
4	CuCl	**L1**	K_2CO_3	24
5	CuI	**L1**	K_2CO_3	54
6	$Cu(NO_3)_2·6H_2O$	**L1**	K_2CO_3	62
7	CuBr	**L1**	K_2CO_3	32
8	$Cu(SO_4)_2·5H_2O$	**L1**	K_2CO_3	66
9	$CuCl_2·2H_2O$	**L1**	K_2CO_3	24
10	$Cu(CH_3CN)_4PF_6$	**L1**	K_2CO_3	52
11	$Cu(OTf)_2$	**L2**	K_2CO_3	trace
12	$Cu(OTf)_2$	**L3**	K_2CO_3	56
13	$Cu(OTf)_2$	**L4**	K_2CO_3	46
14	$Cu(OTf)_2$	**L1**	CsF	18
15	$Cu(OTf)_2$	**L1**	*t*-BuOK	32
16	$Cu(OTf)_2$	**L1**	Et_3N	24
17	$Cu(OTf)_2$	**L1**	Cs_2CO_3	60
18	-	**L1**	K_2CO_3	0
19	$Cu(OTf)_2$	**L1**	-	8
20	$Cu(OTf)_2$	**-**	K_2CO_3	trace
21	$Cu(OTf)_2$	**L1**	K_2CO_3	51[b]
22	$Cu(OTf)_2$	**L1**	K_2CO_3	44[c]
23	$Cu(OTf)_2$	**L1**	K_2CO_3	33[d]

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), [Cu] (10 mol%), ligand (20 mol%) and base (0.3 mmol) in CH_3CN (2 mL) stirring under argon in 80 °C for 8 h. Oil bath temperature. Yield of the isolated product. [b] $Cu(OTf)_2$ (5 mol%), L1 (10 mol%). [c]100 °C. [d]60 °C.

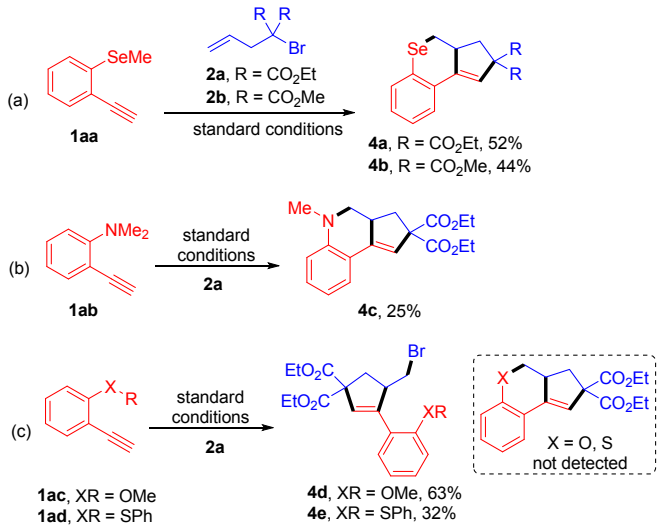
Table 2. Substrates Scope[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), $Cu(OTf)_2$ (10 mol %), bpy (20 mol %), and K_2CO_3 (0.3 mmol) in CH_3CN (2 mL), with stirring under argon at 80 °C for 8 h. [b]12 h.

With the optimized reaction conditions in hand, the scope of this Cu-catalyzed annulation was investigated, and the results are summarized in Table 2. With methyl substituted on benzene, **3b** and **3h** were obtained both in 54% yields. Halogen atoms such as chloro, bromo and fluoro on the aromatic ring were also suitable to the present reaction conditions to afford the corresponding products **3c**–**3e** in moderate yields, which giving opportunities for further elaboration through the transition-metal-catalyzed coupling reactions. Substrate bearing electron-withdrawing (CF_3) group on the benzene was also investigated and converted into product **3f** in 43% yield. The process was extended to various unsaturated α-halogenocarbonyl compounds **2**. The products **3g** and **3h** with a quaternary carbon center were obtained by employing the methyl-substited analogue. Other activated organobromides were also performed well in this Cu-catalyzed cascade annulation reaction, as exemplified by the formation of **3i**–**3k**. Moreover, the structure of **3j** was confirmed by X-ray crystal structure analysis (details see Supporting Information).[9] Gratifyingly, the 6-6-6-tricyclic product **3l** was afforded when diethyl 2-bromo-2-(but-3-en-1-yl)malonate (**2l**) was employed instead of **2a**. Internal alkynes were also examined, unfortunately, no desired products were detected under the reaction conditions.

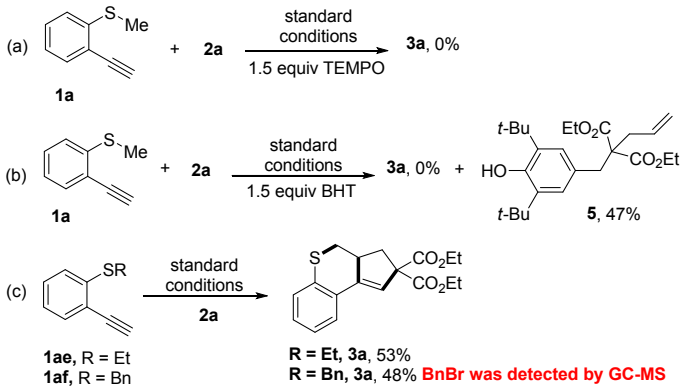
Scheme 2. Scope of Alkynes



Importantly, (2-ethynylphenyl)(methyl)selane **1aa** was also suitable to this reaction to deliver tetrahydrocyclopentaselenochromene derivatives (**4a**, **4b**) in 52-44% yields (Scheme 2a). When 2-ethynyl-*N*,*N*-dimethylaniline **1ab** was used as the substrate, **4c** was obtained in 25% yield, providing a optional pathway for the synthesis of tetrahydro-2*H*-cyclopentaquinoline derivatives which is a useful core in bioactive natural products and pharmaceuticals (Scheme 2b).[10] Moreover, no desired products were afforded when 1-ethynyl-2-methoxybenzene **1ac** or (2-ethynylphenyl)(phenyl)sulfane **1ad** were employed as the substrates and ATRA products were obtained in 63% and 32% yields, respectively (Scheme 2c).[8a]

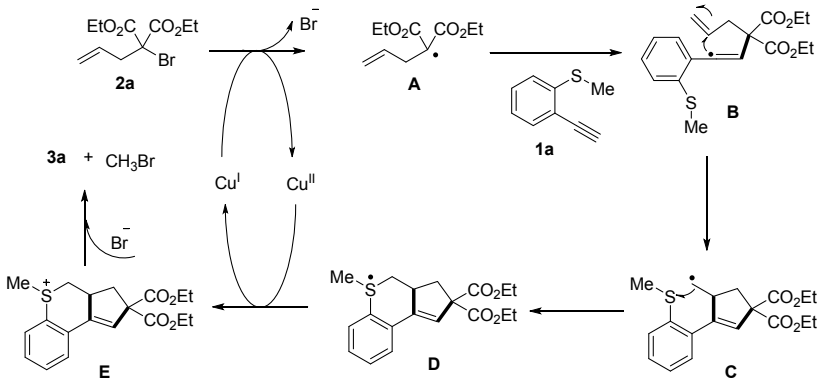
To gain insights into the reaction mechanism, some control experiments were carried out (Scheme 3). The reaction between **1a** and **2a** was inhibited by adding 1.5 equiv of 2,2,6,6-tetra-methylpiperidinooxy (TEMPO) or butylated hydroxytoluene (BHT). Instead, compound **5** was obtained in 47% yield in the presence of BHT (Scheme 3b). These results indicated that the Cu-catalyzed annulation might *via* a radical pathway.[8a, 11] Additional, when changed the methyl in the sulfur atom into ethyl and benzyl, **3a** was also afforded in 53% and 48% yields, respectively (Scheme 3c). Remarkably, in our reaction mixtures, (bromomethyl)benzene (BnBr) was detected by GC-MS when **1af** was employed as the substrate, which provide evidence for the mechanism of this transformation.

Scheme 3. Control Experiments



In accordance to literature reports[1a, 8a] and the control experiments, a tentative pathway was proposed for this transformation (Scheme 4). Initially, the alkyl radical **A** is formed by a SET process from **2a**, which then adds to **1a** to give the alkenyl radical **B**. The resulting alkenyl radical **B** participates in an intramolecular radical substitution yielding the corresponding intermediate **C**, which then cyclizes to give the sulphuranyl radical **D**. Intermediate **D** could be oxidized by the Cu(II) species to the corresponding cation **E** with the formation of a Cu(I) species to re-enter the catalytic cycle. Finally, desired product **3a** is produced from cation **E** *via* an E_2 process and bromomethane is released as the byproduct.

Scheme 4. A Tentative Mechanistic Pathway



■ SUMMARY

In summary, we have developed an efficient protocol for the construction of thio-benzobicyclic skeletons by copper-mediated cascade annulation of 2-alkynylthioanisoles with unsaturated α-bromocarbonyls under mild conditions. In this single reaction, three new bonds and two new rings can be established, highlighting the step-economics and high efficiency of this protocol.

■ EXPERIMENTAL SECTION

All reactions were carried out under Ar. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III spectrometer (400 MHz and 100 MHz, respectively), and a JEOL ECZ600S (600 MHz and 150 MHz, respectively). Chemical shifts are reported parts per million (ppm) referenced to $CDCl_3$ (δ 7.26 ppm), tetramethylsilane (TMS, δ 0.00 ppm) for ^{1}H NMR, $CDCl_3$ (δ 77.23 ppm) for ^{13}C NMR. All coupling constants (*J* values) were reported in Hertz (Hz). Column chromatography was performed on silica gel 300-400 mesh. High-resolution mass spectra (HRMS) were obtained on an Impact IIUHR-TOF mass spectrometry equipped with an ESI source from Bruker at Fujian Institute of Research on the Structure of Matter.

General Procedures for the Synthesis of Substrates 1. Procedure A[12a]**:** To a mixture of corresponding (2-iodophenyl)(methyl)sulfane and derivatives (3.0 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%) and Et_3N (1.5 equiv) in dry THF was slowly added trimethylsilylacetylene (1.5 equiv). After the reaction mixture was stirred at room temperature for overnight, the reaction was quenched by addition of water and the whole mixture was extracted with Et_2O. The organic layer was dried over anhydrous $MgSO_4$ and filtered the solid off. After evaporation of the solvent,

the crude was purified by silica gel column chromatography using petroleum ether as the eluent to afford the trimethyl((2-(methylthio)phenyl)ethynyl)silane and derivatives. **Procedure B**[12b]**:** To a solution of trimethyl((2-(methylthio)phenyl)ethynyl)silane or derivatives in methanol and CH_2Cl_2 (*v/v* = 2:1) was added K_2CO_3 (3.0 equiv) and stirred at room temperature for 12 h. Then, the mixture was extracted with $CHCl_3$ and dried over anhydrous $MgSO_4$. After filtration of the solid, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography using petroleum ether as the eluent to provide substrates **1**.

Characterization Data of Products 1. *(2-ethynylphenyl)(methyl)Sulfane(**1a**, known compound)*[13a] Yellow oil. 337 mg, 76% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.46 (dd, *J* = 1.0 Hz, *J* = 7.6 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.11 – 7.07 (m, 1H), 3.48 (s, 1H), 2.49 (s, 3H).

*(2-ethynyl-4-methylphenyl)(methyl)Sulfane (**1b**, New Compound)* Yellow oil. 364 mg, 75% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.30 (s, 1H), 7.14 – 7.08 (m, 2H), 3.43 (s, 1H), 2.48 (s, 3H), 2.29 (s, 3H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 138.4, 134.6, 134.0, 130.5, 125.4, 120.8, 83.1, 81.5, 20.8, 15.8. Anal. Calcd for $C_{10}H_{10}S$: C, 74.05; H, 6.22. Found: C, 73.62; H, 6.14.

*(4-chloro-2-ethynylphenyl)(methyl)Sulfane (**1c**, New Compound)* Yellow oil. 371 mg, 68% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.43 (d, *J* = 2.3 Hz, 1H), 7.28 (dd, *J* = 2.4 Hz, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 3.50 (s, 1H), 2.49 (s, 3H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 140.8, 132.9, 130.2, 129.7, 125.9, 121.9, 84.8, 80.0, 15.6. Anal. Calcd for C_9H_7ClS: C, 59.34; H, 3.88. Found: C, 58.08; H, 4.08.

*(4-bromo-2-ethynylphenyl)(methyl)Sulfane (**1d**, New Compound)* Yellow oil. 393 mg, 58% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.57 (d, *J* = 1.7 Hz, 1H), 7.42 (dd, *J* = 1.7 Hz, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 3.51 (s, 1H), 2.47 (s, 3H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 141.5, 135.7, 132.5, 126.0, 122.2, 117.6, 85.0, 79.9, 15.5. Anal. Calcd for C_9H_7BrS: C, 47.80; H, 3.12. Found: C, 47.67; H, 3.15.

*(2-ethynyl-4-fluorophenyl)(methyl)Sulfane (**1e**, New Compound)* Yellow oil. 324 mg, 65% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.20 – 7.14 (m, 2H), 7.07 – 7.02 (m, 1H), 3.49 (s, 1H), 2.49 (s, 3H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 160.3 (d, *J* = 244.9 Hz), 137.2 (d, *J* = 3.4 Hz), 127.4 (d, *J* = 8.4 Hz), 122.6 (d, *J* = 9.5 Hz), 120.2 (d, *J* = 23.6 Hz), 117.1 (d, *J* = 21.8 Hz), 84.4, 80.3 (d, *J* = 3.1 Hz), 16.3. **^{19}F NMR (377 MHz, d-CDCl3):** δ -118.1. Anal. Calcd for C_9H_7FS: C, 65.05; H, 4.25. Found: C, 65.45; H, 4.33.

*(2-ethynyl-4-(trifluoromethyl)phenyl)(methyl)Sulfane (**1f**, New Compound)* Yellow oil. 460 mg, 71% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.68 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 3.54 (s, 1H), 2.52 (s, 3H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 147.4, 129.9 (q, *J* = 3.9 Hz), 126.6 (q, *J* = 33.2 Hz),

125.9 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 271.7 Hz), 123.7, 119.9, 85.4, 79.8, 15.0. **^{19}F NMR (377 MHz, d-CDCl3):** δ -62.5. Anal. Calcd for $C_{10}H_7F_3S$: C, 55.55; H, 3.27. Found: C, 55.98; H, 3.24.

*(2-ethynylphenyl)(methyl)Selane (**1aa**, known compound)* Yellow oil. 341 mg, 58% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.45 (d, *J* = 7.7 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.16 – 7.12 (m, 1H), 3.44 (s, 1H), 2.35 (s, 3H).

*2-Ethynyl-N,N-dimethylaniline (**1ab**, known compound)*[13b] Yellow oil. 226 mg, 52% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.45 (dd, *J* = 1.5 Hz, *J* = 7.6 Hz, 1H), 7.27 – 7.23 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.88 – 6.84 (m, 1H), 3.40 (s, 1H), 2.92 (s, 6H).

*1-Ethynyl-2-methoxybenzene (**1ac**, known compound)*[13c] Yellow oil. 289 mg, 73% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.49 (dd, *J* = 1.2 Hz, *J* = 7.4 Hz, 1H), 7.36 – 7.32 (m, 1H), 6.95 – 6.90 (m, 2H), 3.92 (s, 3H), 3.33 (s, 1H).

*(2-ethynylphenyl)(phenyl)Sulfane (**1ad**, known compound)*[13d] Yellow solid. 391 mg, 62% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$)** δ 7.50 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.47 – 7.45 (m, 2H), 7.38 – 7.32 (m, 3H), 7.19 – 7.09 (m, 2H), 6.97 (dd, *J* = 1.3, 8.0 Hz, 1H), 3.43 (s, 1H).

*Ethyl(2-ethynylphenyl)sulfane (**1ae**, known compound)*[13e] Yellow oil. 316 mg, 65% total yield of Procedures A and B. **^{1}H NMR (600 MHz, d-CDCl$_3$)** δ7.47 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.30 – 7.28 (m, 1H), 7.25 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.12 – 7.09 (m, 1H), 3.45 (s, 1H), 3.00 (q, J = 7.4 Hz, 2H), 1.36 (t, J = 7.4 Hz, 3H).

*Benzyl(2-ethynylphenyl)sulfane (**1af**, known compound)*[13f] Yellow solid. 470 mg, 70% total yield of Procedures A and B. **^{1}H NMR (400 MHz, d-CDCl$_3$)** δ 7.48 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.34 (m, 2H), 7.31 – 7.27 (m, 2H), 7.25 – 7.22 (m, 3H), 7.13 – 7.09 (m, 1H), 4.19 (s, 2H), 3.45 (s, 1H).

General Procedures for the Synthesis of Substrates 2[14]**.** To a stirred solution of γ,δ-unsaturated carbonyls (3.0 mmol) in EtOAc (50 mL) was added Lewis acid $Mg(ClO_4)_2$ (0.9 mmol) at room temperature. Then NBS (3.3 mmol) was added to the above mixture carefully 20 min later. After the reaction was finished, the reaction mixture was extracted with diethylether (3 x 15 mL). The organic phases were washed with brine (15 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified by silica gel chromatography using a petroleum ether/AcOEt (50:1-20:1, v/v) as the eluent to afford substrates **2**.

Characterization Data of Products 2. *Diethyl 2-allyl-2-bromomalonate (**2a**, known compound)*[5b] Colourless oil. 684 mg, 82% yield. **^{1}H NMR (600 MHz, d-CDCl$_3$)** δ 5.85 – 5.78 (m, 1H), 5.23 – 5.21 (m, 1H), 5.20 – 5.18 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 4H), 3.05 (dt, *J* = 7.0, 1.2 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 6H).

*Diethyl 2-bromo-2-(2-methylallyl)malonate (**2b**, known compound)*[5b] Light yellow oil. 675 mg, 77% yield. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 4.96 (s, 1H), 4.86 (s, 1H), 4.31 – 4.26 (m, 4H), 3.10 (s, 2H), 1.79 (s, 3H), 1.31 (t, *J* = 7.0 Hz, 6H).

*3-Allyl-3-bromopentane-2,4-dione (**2c**, known compound)*[5b] Light yellow oil. 536 mg, 82% yield. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 5.79 – 5.69 (m, 1H), 5.17 (s, 1H), 5.14 – 5.13 (m, 1H), 2.94 (d, *J* = 7.1 Hz, 2H), 2.37 (s, 6H).

*Dimethyl 2-allyl-2-bromomalonate (**2d**, known compound)*[8a] Colourless oil. 375 mg, 80% yield. **^{1}H NMR (600 MHz, d-CDCl$_3$)** δ 5.84 – 5.77 (m, 1H), 5.22 (t, *J* = 1.2 Hz, 1H), 5.21 – 5.18 (m, 1H), 3.82 (s, 6H), 3.05 (dt, *J* = 7.1, 1.2 Hz, 2H).

*Ethyl 2-acetyl-2-bromopent-4-enoate (**2e**, known compound)*[5b] Light yellow oil. 580 mg, 78% yield. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 5.85 – 5.74 (m, 1H), 5.20 (s, 1H), 5.17 (d, *J* = 3.4 Hz, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.05 – 2.92 (m, 2H), 2.41 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H).

*Diethyl 2-bromo-2-(but-3-en-1-yl)malonate (**2f**, known compound)*[5b] Light yellow oil. 702 mg, 81% yield. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 5.86 – 5.76 (m, 1H), 5.10 (dd, *J* = 1.0 Hz, *J* = 17.1 Hz, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 4H), 2.40 – 2.36 (m, 2H), 2.24 – 2.19 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 6H).

Experimental Procedure for the Synthesis of Products 3 and 4. A Schlenk tube containing $Cu(OTf)_2$ (0.03 mmol, 10 mol%), bpy (0.06 mmol, 20 mol%) and K_2CO_3 (0.30 mmol, 1.0 eq) were evacuated and purged with argon three times. **1** (0.3 mmol, 1.0 eq), **2** (0.45 mmol, 1.5 eq) and CH_3CN (2.0 mL) were sequentially added to the system at room temperature. The reaction mixture was heated with stirring at 80 °C for 8 hours. Upon completion, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt (40:1-10:1, v/v) as the eluent to give the corresponding products.

Characterization Data of Products 3 and 4. *Diethyl 3a, 4-dihydrocyclopenta[c]thiochromene-2, 2(3H)-dicarboxylate (**3a,** New Compound)* 70.7 mg, 71% yield, yellow oil. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.18 – 7.11 (m, 2H), 7.07 – 7.03 (m, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 4.27 – 4.16 (m, 4H), 3.42 – 3.34 (m, 1H), 3.06 (dd, *J* = 7.4 Hz, *J* = 13.3 Hz, 1H), 3.01 – 2.89 (m, 2H), 2.04 (dd, *J* = 8.3 Hz, *J* = 13.3 Hz, 1H), 1.32 – 1.26 (m, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.2, 170.5, 143.8, 133.8, 128.7, 128.5, 127.1, 127.0, 124.6, 121.6, 65.2, 61.9, 61.8, 43.0, 39.4, 32.7, 14.2. **HRMS** Calcd for $C_{18}H_{20}NaO_4S^+$ $[M+Na]^+$ 355.0975, found 355.0982.

*1,4-Bis(2-(methylthio)phenyl)buta-1,3-diyne (**3a'**, known compound)*[13e] Light yellow solid. **^{1}H NMR (600 MHz, d-CDCl$_3$):** δ 7.50 (dd, *J* = 7.6, 1.4 Hz, 2H), 7.32 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.10 (td, *J* = 7.5, 1.1 Hz, 2H), 2.51 (s, 6H).

*Diethyl 8-methyl-3a, 4-dihydrocyclopenta[c]thiochromene-2, 2(3H)-dicarboxylate (**3b,** New Compound)* 56.1 mg, 54% yield, yellow solid, melt point: 74.7 – 76.3 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.49 (s, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 1.1 Hz, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 4.27 – 4.17 (m, 4H), 3.40 – 3.33 (m, 1H), 3.06 (dd, *J* = 7.5 Hz, *J* = 13.3 Hz, 1H), 2.97 (dd, *J* = 4.3 Hz, *J* = 12.2 Hz, 1H), 2.90 (t, *J* = 12.3 Hz, 1H), 2.30 (s, 3H), 2.03 (dd, *J* = 8.4 Hz, *J* = 13.2 Hz, 1H), 1.32 – 1.27 (m, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.2, 170.5, 144.0, 134.2, 130.3, 129.8, 128.2, 127.4, 127.0, 121.3, 65.2, 61.9, 61.8, 43.1, 39.5, 32.7, 21.0, 14.23, 14.22. **HRMS** Calcd for $C_{19}H_{22}NaO_4S^+$ $[M+Na]^+$ 369.1131, found 369.1161.

*Diethyl 8-chloro-3a,4-dihydrocyclopenta[c]thiochromene-2,2(3H)-dicarboxylate (**3c,** New Compound)* 35.1 mg, 32% yield, yellow solid, melt point: 99.2 – 101.1 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.61 (s, 1H), 7.08 (d, *J* = 0.9 Hz, 2H), 6.28 (d, *J* = 2.2 Hz, 1H), 4.27 – 4.15 (m, 4H), 3.37 – 3.29 (m, 1H), 3.05 (dd, *J* = 7.5 Hz, *J* = 13.4 Hz, 1H), 2.98 (dd, *J* = 4.3 Hz, *J* = 12.4 Hz, 1H), 2.88 (t, *J* = 12.3 Hz, 1H), 2.02 (dd, *J* = 8.3 Hz, *J* = 13.3 Hz, 1H), 1.28 (q, *J* = 7.1 Hz,

6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.0, 170.3, 142.9, 132.3, 130.3, 129.9, 128.7, 128.4, 126.7, 123.0, 65.2, 62.1, 62.0, 42.7, 39.4, 32.5, 14.3. **HRMS** Calcd for $C_{18}H_{19}ClNaO_4S^+$ $[M+Na]^+$ 389.0585, found 389.0583.

*Diethyl 8-bromo-3a,4-dihydrocyclopenta[c]thiochromene-2,2(3H)-dicarboxylate (**3d,** New Compound)* 46.9 mg, 38% yield, yellow solid, melt point: 101.4 – 102.6 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.75 (d, *J* = 2.1 Hz, 1H), 7.22 (dd, *J* = 2.1 Hz, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.27 (d, *J* = 2.3 Hz, 1H), 4.27 – 4.15 (m, 4H), 3.37 – 3.28 (m, 1H), 3.05 (dd, *J* = 7.5 Hz, *J* = 13.3 Hz, 1H), 2.98 (dd, *J* = 4.3 Hz, *J* = 12.4 Hz, 1H), 2.88 (t, *J* = 12.4 Hz, 1H), 2.02 (dd, *J* = 8.3 Hz, *J* = 13.4 Hz, 1H), 1.28 (dd, *J* = 7.0 Hz, *J* = 13.4 Hz, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.0, 170.3, 142.8, 133.0, 131.5, 130.3, 129.7, 128.6, 123.1, 118.0, 65.2, 62.1, 62.0, 42.6, 39.4, 32.5, 14.3. **HRMS** Calcd for $C_{18}H_{19}BrNaO_4S^+$ $[M+Na]^+$ 433.0080, found 433.0076.

*Diethyl 8-fluoro-3a, 4-dihydrocyclopenta[c]thiochromene-2,2 (3H)-dicarboxylate (**3e,** New Compound)* 42.0 mg, 40% yield, yellow solid, melt point: 75.2 – 76.6 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.35 (dd, *J* = 2.7 Hz, *J* = 10.0 Hz, 1H), 7.13 (dd, *J* = 5.5 Hz, *J* = 8.8 Hz, 1H), 6.91 – 6.86 (m, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 4.27 – 4.16 (m, 4H), 3.40 – 3.32 (m, 1H), 3.07 (dd, *J* = 7.4 Hz, *J* = 13.3 Hz, 1H), 2.99 (dd, *J* = 4.3 Hz, *J* = 12.3 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H), 2.04 (dd, *J* = 8.4 Hz, *J* = 13.3 Hz, 1H), 1.32 – 1.26 (m, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.0, 170.3, 160.4 (d, *J* = 243.7 Hz), 143.32 (d, *J* = 2.3 Hz), 129.94 (d, *J* = 7.2 Hz), 128.93 (d, *J* = 2.7 Hz), 128.55 (d, *J* = 7.6 Hz), 123.1, 116.44 (d, *J* = 22.8 Hz), 113.25 (d, *J* = 22.5 Hz), 65.2, 62.0, 61.9, 42.8, 39.5, 32.5, 14.2. **^{19}F NMR (377 MHz, d-CDCl3):** δ -133.6. **HRMS** Calcd for $C_{18}H_{20}FO_4S^+$ $[M+H]^+$ 351.1061, found 351.1053.

*Diethyl 8-(trifluoromethyl)-3a, 4-dihydrocyclopenta[c]thiochromene-2, 2(3H)-dicarboxylate (**3f,** New Compound)* 51.6 mg, 43% yield, yellow solid, melt point: 76.4 – 78.5 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.87 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.29 – 7.27 (m, 1H), 6.37 (d, *J* = 2.1 Hz, 1H), 4.29 – 4.18 (m, 4H), 3.42 – 3.34 (m, 1H), 3.12 – 3.03 (m, 2H), 2.95 (t, *J* = 12.3 Hz, 1H), 2.08 (dd, *J* = 8.1 Hz, *J* = 13.4 Hz, 1H), 1.33 – 1.28 (m, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 170.9, 170.3, 142.8, 138.7, 128.8 127.5 127.0 (d, *J* = 32.7 Hz), 125.6 (q, *J* = 271.7 Hz), 124.82 (d, *J* = 3.7 Hz), 128.91 (d, *J* = 3.8 Hz), 123.5, 65.3, 62.2, 62.1, 42.5, 39.4, 32.6, 14.28, 14.27. **^{19}F NMR (377 MHz, d-CDCl3):** δ -78.0. **HRMS** Calcd for $C_{19}H_{19}F_3NaO_4S^+$ $[M+Na]^+$ 423.0848, found 423.0849.

*Diethyl 3a-methyl-3a, 4-dihydrocyclopenta[c]thiochromene-2, 2(3H)-dicarboxylate (**3g,** New Compound)* 68.5 mg, 66% yield, yellow oil. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.61 (d, *J* = 7.6 Hz, 1H), 7.17 – 7.12 (m, 2H), 7.07 – 7.03 (m, 1H), 6.11 (s, 1H), 4.31 – 4.20 (m, 4H), 3.20 (d, *J* = 12.3 Hz, 1H), 2.81 (dd, *J* = 5.7 Hz, *J* = 13.7 Hz, 2H), 3.37 (d, *J* = 13.7 Hz, 1H), 1.33 – 1.27 (m, 9H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.3, 171.2, 147.5, 132.9, 128.6, 128.1, 127.9, 126.5, 124.4, 120.8, 64.7, 61.99, 61.96, 46.6, 43.2, 39.9, 23.9, 14.3. **HRMS** Calcd for $C_{19}H_{22}NaO_4S^+$ $[M+Na]^+$ 369.1131, found 369.1137.

*Diethyl 3a,8-dimethyl-3a,4-dihydrocyclopenta[c]thiochromene-2,2(3H)-dicarboxylate (**3h,** New Compound)* 58.3 mg, 54% yield, yellow solid, melt point: 59.3 – 61.6 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.43 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.98 (dd, *J* = 1.3 Hz, *J* = 8.1 Hz, 1H), 6.10 (s, 1H), 4.31 – 4.20 (m, 4H), 3.18 (d, *J* = 12.4 Hz, 1H), 2.79 (dd, *J* = 6.4 Hz, *J* = 13.7 Hz, 2H), 2.39 – 2.32 (m, 1H), 2.30 (s, 3H), 1.31 – 1.27 (m, 9H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.33, 171.25, 147.6, 133.9, 129.8, 129.4, 128.2, 127.8, 126.4, 120.5, 64.6, 62.0, 61.9, 46.6, 43.3, 39.8, 23.9, 21.0, 14.3. **HRMS** Calcd for $C_{20}H_{24}NaO_4S^+$ $[M+Na]^+$ 383.1288, found 383.1288.

*1, 1'-(2, 3, 3a, 4-tetrahydrocyclopenta[c]thiochromene-2, 2-diyl) Diethanone (**3i,** New Compound)* 51.4 mg, 63% yield, yellow solid, melt point: 105.1 – 107.2 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.66 (dd, *J* = 1.0 Hz, *J* = 7.8 Hz, 1H),

7.20 – 7.14 (m, 2H), 7.09 – 7.06 (m, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 3.32 – 3.25 (m, 1H), 3.09 (dd, *J* = 7.4 Hz, *J* = 13.1 Hz, 1H), 3.01 (dd, *J* = 4.3 Hz, *J* = 12.3 Hz, 1H), 2.90 (t, *J* = 12.3 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H), 1.89 (dd, *J* = 8.4 Hz, *J* = 13.1 Hz, 1H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 205.6, 203.7, 144.8, 134.0, 129.0, 128.4, 127.3, 126.9, 124.8, 121.0, 79.4, 43.0, 37.3, 32.8, 27.3, 27.1. **HRMS** Calcd for $C_{16}H_{16}NaO_2S^+$ $[M+Na]^+$ 295.0763, found 295.0751.

*Dimethyl 3a, 4-dihydrocyclopenta[c]thiochromene-2, 2(3H)-dicarboxylate (**3j,** New Compound)* 58.3 mg, 64% yield, yellow solid, melt point: 122.3 – 124.1 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.66 (dd, *J* = 0.7 Hz, *J* = 7.9 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.08 – 7.05 (m, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.43 – 3.36 (m, 1H), 3.08 (dd, *J* = 7.5 Hz, *J* = 13.3 Hz, 1H), 2.99 (dd, *J* = 4.4 Hz, *J* = 12.2 Hz, 1H), 2.93 (t, *J* = 12.3 Hz, 1H), 2.05 (dd, *J* = 8.4 Hz, *J* = 13.3 Hz, 1H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.7, 171.0, 144.0, 133.9, 128.8, 128.4, 127.2, 127.1, 124.7, 121.4, 65.0, 53.12, 53.06, 43.0, 39.6, 32.6. **HRMS** Calcd for $C_{16}H_{16}NaO_4S^+$ $[M+Na]^+$ 327.0662, found 327.0672.

*Ethyl 2-acetyl-2, 3, 3a, 4-tetrahydrocyclopenta[c]thiochromene-2-carboxylate (**3k,** New Compound)* 55.3 mg, 61% yield, yellow solid, melt point: 53.8 – 55.7 °C. dr = 1:0.7; data of the mixture. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.67 – 7.64 (m, 1H), 7.19 – 7.13 (m, 2H), 7.08 – 7.05 (m, 1H), 6.34 – 6.31 (m, 1H), 4.28 – 4.18 (m, 2H), 3.43 – 3.24 (m, 1H), 3.07 – 2.88 (m, 3H), 2.26 (s, 3H), 2.06 – 1.89 (m, 1H), 1.33 – 1.27 (m, 3H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 204.0, 202.2, 171.7, 171.0, 144.6, 144.2, 134.0, 133.9, 128.9, 128.8, 128.44, 128.36, 127.3, 127.2, 127.00, 126.97, 124.7, 121.4, 121.3, 72.1, 71.9, 62.02, 61.95, 43.01, 42.94, 38.2, 38.1, 32.8, 32.7, 26.8, 14.29, 14.27. **HRMS** Calcd for $C_{17}H_{18}NaO_3S^+$ $[M+Na]^+$ 325.0869, found 325.0842.

*Diethyl 7, 8-dihydro-6H-benzo[c]thiochromene-9, 9(6aH)-dicarboxylate (**3l,** New Compound)* 20.8 mg, 20% yield, yellow solid, melt point: 70.8 – 72.1 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.14 – 7.10 (m, 2H), 7.08 – 7.05 (m, 1H), 6.48 (s, 1H), 4.28 – 4.17 (m, 4H), 2.96 (t, *J* = 12.1 Hz, 1H), 2.83 (dd, *J* = 3.5 Hz, *J* = 12.3 Hz, 1H), 2.73 – 2.68 (m, 1H), 2.43 – 2.37 (m, 1H), 2.16 – 2.08 (m, 1H), 2.03 – 1.96 (m, 1H), 1.62 – 1.60 (m, 1H), 1.32 – 1.26 (m, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.1, 170.6, 138.1, 133.4, 132.4, 128.3, 127.0, 126.9, 124.6, 119.5, 61.95, 61.92, 56.0, 34.3, 32.6, 27.4, 27.3, 14.31, 14.28. **HRMS** Calcd for $C_{19}H_{22}NaO_4S^+$ $[M+Na]^+$ 369.1131, found 369.1132.

*Diethyl 3a,4-dihydrocyclopenta[c]selenochromene-2, 2(3H)-dicarboxylate (**4a,** New Compound)* 59.3 mg, 52% yield, yellow solid, melt point: 35.9 – 37.8 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.67 – 7.64 (m, 1H), 7.30 – 7.28 (m, 1H), 7.12 – 7.07 (m, 2H), 6.29 (d, *J* = 1.9 Hz, 1H), 4.27 – 4.17 (m, 4H), 3.53 – 3.45 (m, 1H), 3.10 – 3.03 (m, 2H), 2.94 (dd, *J* = 4.2 Hz, *J* = 11.1 Hz, 1H), 2.12 (dd, *J* = 7.3 Hz, *J* = 13.5 Hz, 1H), 1.32 – 1.27 (m, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.2, 170.6, 145.1, 131.1, 129.5, 128.84, 128.76, 127.7, 125.4, 122.7, 65.2, 61.9, 61.8, 43.5, 40.1, 25.3, 14.2. **HRMS** Calcd for $C_{18}H_{20}NaO_4Se^+$ $[M+Na]^+$ 403.0419, found 403.0448.

*Dimethyl 3a,4-dihydrocyclopenta[c]selenochromene-2,2(3H)-dicarboxylate (**4b,** New Compound)* 46.5 mg, 44% yield, yellow solid, melt point: 107.0 – 109.2 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.65 – 7.63 (m, 1H), 7.30 – 7.26 (m, 1H), 7.11 – 7.06 (m, 2H), 6.27 (d, *J* = 2.1 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.52 – 3.44 (m, 1H), 3.08 – 3.02 (m, 2H), 2.92 (dd, *J* = 4.2 Hz, *J* = 11.0 Hz, 1H), 2.10 (dd, *J* = 7.4 Hz, *J* = 13.5 Hz, 1H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.6, 171.1, 145.3, 131.0, 129.6, 128.91, 128.89, 127.7, 125.5, 122.5, 65.0, 53.12, 53.08, 43.5, 40.3, 25.2. **HRMS** Calcd for $C_{16}H_{16}NaO_4Se^+$ $[M+Na]^+$ 375.0106, found 375.0105.

*Diethyl 5-methyl-3,3a,4,5-tetrahydro-2H-cyclopenta[c]quinoline-2,2-dicarboxylate (**4c,** New Compound)* 24.7 mg, 25% yield, yellow solid, melt point: 43.3 – 45.2 °C. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.49 (dd, *J* = 1.5 Hz, *J* = 7.7 Hz,

1H), 7.19 – 7.15 (m, 1H), 6.70 – 6.64 (m, 2H), 6.00 (d, *J* = 2.4 Hz, 1H), 4.26 – 4.14 (m, 4H), 3.40 (dd, *J* = 5.4 Hz, *J* = 10.7 Hz, 1H), 3.31 – 3.22 (m, 1H), 2.97 – 2.90 (m, 5H), 1.89 (dd, *J* = 8.9 Hz, *J* = 13.0 Hz, 1H), 1.29 – 1.24 (m, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.7, 171.0, 146.4, 144.3, 130.2, 126.1, 117.5, 117.1, 116.4, 112.5, 65.8, 61.72, 61.66, 57.7, 41.3, 39.9, 37.6, 17.29, 17.27. **HRMS** Calcd for $C_{19}H_{23}NNaO_4^+$ $[M+Na]^+$ 352.1519, found 352.1519.

Diethyl 4-(bromomethyl)-3-(2-methoxyphenyl)cyclopent-2-ene-1, 1-dicarboxylate ***(4d,*** *New Compound)* 77.5 mg, 63% yield, yellow oil. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 7.30 – 7.26 (m, 2H), 6.95 – 6.88 (m, 2H), 6.14 (d, *J* = 1.7 Hz, 1H), 4.28 – 4.14 (m, 4H), 4.01 – 3.95 (m, 1H), 3.82 (s, 3H), 3.46 (dd, *J* = 3.1 Hz, *J* = 10.0 Hz, 1H), 3.23 (t, *J* = 8.9 Hz, 1H), 2.92 (dd, *J* = 8.2 Hz, *J* = 13.9 Hz, 1H), 2.45 (dd, *J* = 5.7 Hz, *J* = 13.9 Hz, 1H), 1.32 – 1.23 (m, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.3, 170.9, 157.1, 146.9, 130.4, 129.7, 128.4, 123.8, 121.0, 111.2, 65.3, 61.80, 61.77, 55.6, 48.4, 37.4, 36.9, 14.3, 14.2. **HRMS** Calcd for $C_{19}H_{23}BrNaO_5^+$ $[M+Na]^+$ 433.0621, found 433.0647.

Diethyl 4-(bromomethyl)-3-(2-(phenylthio)phenyl)cyclopent-2-ene-1,1-dicarboxylate ***(4e,*** *New Compound)* 46.8 mg, 32% yield, yellow oil. **^{1}H NMR (600 MHz, d-CDCl$_3$):** 7.30 – 7.26 (m, 3H), 7.26 – 7.19 (m, 6H), 5.98 (d, *J* = 2.1 Hz, 1H), 4.27 – 4.22 (m, 2H), 4.18 – 4.08 (m, 2H), 4.03 – 3.99 (m, 1H), 3.39 (dd, *J* = 10.1, 3.4 Hz, 1H), 3.25 (dd, *J* = 10.2, 8.0 Hz, 1H), 2.93 (dd, *J* = 13.9, 8.2 Hz, 1H), 2.44 (dd, *J* = 13.9, 5.8 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (150 MHz, d-CDCl$_3$):** δ 171.0, 170.4, 147.9, 136.8, 135.6, 134.7, 132.3, 131.3, 130.7, 130.4, 129.4, 128.9, 127.3, 65.5, 61.9, 49.1, 36.8, 14.3, 14.2. **HRMS** Calcd for $C_{24}H_{25}BrNaO_4S^+$ $[M+Na]^+$ 511.0549, found 511.0549.

Radical trapping experiments for the synthesis of 5. A Schlenk tube containing BHT (0.45 mmol, 1.5 eq), $Cu(OTf)_2$ (0.03 mmol, 10 mol%), bpy (0.06 mmol, 20 mol%) and K_2CO_3 (0.30 mmol, 1.0 eq) were evacuated and purged with argon three times. **1a** (0.3 mmol, 1.0 eq), **2a** (0.45 mmol, 1.5 eq) and CH_3CN (2.0 mL) were sequentially added to the system at room temperature. The reaction mixture was heated with stirring at 80 °C for 8 hours. Upon completion, the reaction mixture was concentrated under vacuum. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt to afford the corresponding compound **5** (yield were determined by **2a**).

Characterization Data of Product 5. *Diethyl 2-allyl-2-(3,5-di-tert-butyl-4-hydroxybenzyl)malonate* (**5**, known compound)[8a] 88.4 mg, 47% yield, yellow soild. **^{1}H NMR (400 MHz, d-CDCl$_3$):** δ 6.89 (s, 2H), 5.81 – 5.71 (m, 1H), 5.16 (s, 1H), 5.14 – 5.13 (m, 1H), 5.09 (s, 1H), 4.24 – 4.11 (m, 4H), 3.16 (s, 2H), 2.55 (d, *J* = 7.2 Hz, 2H), 1.40 (s, 18H), 1.24 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR (100 MHz, d-CDCl$_3$):** δ 171.1, 152.9, 135.7, 133.2, 126.74, 126.70, 119.1, 61.3, 59.1, 38.1, 36.5, 34.4, 30.5, 14.2.

■ ASSOCIATED CONTENT

Supporting Information Available: Copies of NMR spectrum detail are available free of charge *via* the Internet at http://pubs.acs.org.

NMR spectra for all compounds. (PDF)

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■ **REFERENCES**

(1) (a) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. Reaction pathways for the cyclization of *ortho*-thioalkyl and *ortho*-thioaryl substituted phenyl radicals with alkynes. Reaction of *o*-Methylthioarenediazonium Tetrafluoroborates with Alkynes to Give 2-Substituted Benzo[*b*]thiophenes. *J. Chem. Soc., Chem. Commun.* **1985**, 1390-1391. (b) Staples, M. K.; Grange, R. L.; Angus, J. A.; Ziogas, J.; Tan, N. P. H.; Taylor, K. T.; Schiesser, C. H. Tandem Free-Radical Addition/Substitution Chemistry and Its Application to the Preparation of Novel AT_1 Receptor Antagonists. *Org. Biomol. Chem.* **2011**, *9*, 473-479. (c) Hari, D. P.; Hering, T.; König, B. Visible Light Photocatalytic Synthesis of Benzothiophenes. *Org. Lett.* **2012**, *14*, 5334-5337. (d) Zang, H.; Sun, J.-G.; Dong, X.; Li, P.; Zhang, B. Preparation of Benzothiophenes and Benzoselenophenes from Arylamines and Alkynes *via* Radical Cascade Reactions. *Adv. Synth. Catal*. **2016**, *358*, 1746-1752. (e) Shaaban, S.; Jolit, A.; Petkova, D.; Maulide, N. A Family of Low Molecular-Weight, Organic Catalysts for Reductive C–C Bond Formation. *Chem. Commun.* **2015**, *51*, 13902-13905. (f) McDonald, F. E.; Burova, S. A.; Huffman Jr, L. G. Sulfur-Alkyne Cyclizations for Formation of Dihydrothiophenes and Annulated Thiophenes. *Synthesis* **2000**, 970-974.

(2) (a) Xu, J.; Yu, X.; Yan, J.; Song, Q. Synthesis of 3-(Arylsulfonyl)benzothiophenes and Benzoselenophenes *via* TBHP-Initiated Radical Cyclization of 2-Alkynylthioanisoles or -Selenoanisoles with Sulfinic Acids. *Org. Lett.* **2017**, *19*, 6292-6295. (b) Yan, J.; Xu, J.; Zhou, Y.; Chen, J.; Song, Q. Photoredox-Catalyzed Cascade Annulation of Methyl(2-(phenylethynyl)phenyl)sulfanes and Methyl(2-(phenylethynyl)phenyl)selanes with Sulfonyl Chlorides: Synthesis of Benzothiophenes and Benzoselenophenes. *Org. Chem. Front.* **2018**, *5*, 1483-1487.

(3) Yang, W.-C.; Wei, K.; Sun, X.; Zhu, J.; Wu, L. Cascade C(sp^3)–S Bond Cleavage and Imidoyl C–S Formation: Radical Cyclization of 2-Isocyanoaryl Thioethers toward 2-Substituted Benzothiazoles. *Org. Lett.* **2018**, *20*, 3144-3147.

(4) For a review on α-bromocarbonyls, see: Ouyang, X.-H.; Song, R.-J.; Li, J.-H. Developments in the Chemistry of α-Carbonyl Alkyl Bromides. *Chem. Asian J.* **2018**, *13*, 2316-2332.

(5) For recent reports between the unsaturated α-bromocarbonyls and alkynes to form polycyclic compounds, see: (a) Zhou, N.; Cheng, Y.; Xie, J.; Zhu, C. Harnessing Sunlight without A Photosensitizer for Highly Efficient Consecutive [3+2]/[4+2] Annulation to Synthesize Fused Benzobicyclic Skeletons. *Chem. Commun.* **2017**, *53*, 10707-10710. (b) Lu, D.; Wan, Y.; Kong, L.; Zhu, G. Copper-Catalyzed Cascade Annulation between α-Bromocarbonyls and Biaryl or (*Z*)-Arylvinylacetylenes Enabling A Direct Synthesis of Dibenzocycloheptanes and Related Compounds. *Chem. Commun.* **2016**, *52*, 13971-13974. (c) Zhou, N.; Liu, J.; Yan, Z.; Wu, Z.; Zhang, H.; Lia, W.; Zhu, C. Synthesis of Cyclohexylidenehydrazine-Fused Polycyclics *via* A Photocatalytic Radical Cascade Reaction of 2-Ethynylaldehyde Hydrazones. *Chem. Commun.* **2017**, *53*, 2036-2039. (d) Che, C.; Huang, Q.; Zheng, H.; Zhu, G. Copper-Catalyzed Cascade Annulation of Unsaturated α-Bromocarbonyls with Enynals: A Facile Access to Ketones from Aldehydes. *Chem. Sci.* **2016**, *7*, 4134-4139. (e) Liu, B.; Yu, J.-X.; Li, Y.; Li, J.-H.; He, D.-L. Copper-Catalyzed Annulation Cascades of Alkyne-Tethered α-Bromocarbonyls with Alkynes: An Access to Heteropolycycles. *Org. Lett*. **2018**, *20*, 2129-2132. (f) Sun, X.; Li, J.; Ni, Y.; Ren, D.; Hu, Z.; Yu, S. Synthesis of Fused Quinoline and Quinoxaline

Derivatives Enabled by Domino Radical Triple Bond Insertions. *Asian J. Org. Chem.* **2014**, *3*, 1317-1325.

(6) For recent reports on the reaction of 2-bromo-1,3-dicarbonyls to form polycyclic compounds, see: (a) Li, Y.; Liu, B.; Song, R.-J.; Wang, Q.-A.; Li, J.-H. Visible Light-Initiated C(sp^3)–Br/C(sp^3)–H Functionalization of α-Carbonyl Alkyl Bromides through Hydride Radical Shift. *Adv. Synth. Catal.* **2016**, 358, 1219-1228. (b) Hu, M.; Song, R.-J.; Ouyang, X.-H.; Tan, F.-L.; Wei, W.-T.; Li, J.-H. Copper-Catalyzed Oxidative [2+2+1] Annulation of 1,*n*-Enynes with α-Carbonyl Alkyl Bromides through C–Br/C–H Functionalization. *Chem. Commun*. **2016**, *52*, 3328-3331. (c) Wei, P.-S.; Wang, M.-X.; Xu, D.-C.; Xie, J.-W. Synthesis of 2,3-Dihydrothieno(2,3-*b*)quinolines and Thieno(2,3-*b*)-quinolines *via* An Unexpected Domino Aza-MBH/Alkylation/Aldol Reaction. *J. Org. Chem.* **2016**, *81*, 1216-1222.

(7) For selected reviews on ATRA, see: (a) Iqbal, J.; Bhatia, B.; Nayyar, N. K. Transition Metal-Promoted Free-Radical Reactions in Organic Synthesis: The Formation of Carbon-Carbon Bonds. *Chem. Rev.* **1994**, *94*, 519-564. (b) Clark, A. J. Copper Catalyzed Atom Transfer Radical Cyclization Reactions. *Eur. J. Org. Chem.* **2016**, 2231-2243. (c) Studer, A.; Curran, D. P. Catalysis of Radical Reactions: A Radical Chemistry Perspective. *Angew. Chem. Int. Ed.* **2016**, *55*, 58-102. (d) Pintauer, T.; Matyjaszewski, K. Atom Transfer Radical Addition and Polymerization Reactions Catalyzed by ppm Amounts of Copper Complexes. *Chem. Soc. Rev.* **2008**, *37*, 1087-1097.

(8) For selected reports, see: (a) Gao, Y.; Zhang, P.; Ji, Z.; Tang, G.; Zhao, Y. Copper-Catalyzed Cascade Radical Addition–Cyclization Halogen Atom Transfer between Alkynes and Unsaturated α-Halogenocarbonyls. *ACS Catal*. **2017**, *7*, 186-190. (b) Bull, J. A.; Hutchings, M. G.; Quayle, P. A Remarkably Simple and Efficient Benzannulation Reaction. *Angew. Chem., Int. Ed*. **2007**, *46*, 1869-1872. (c) Sebren, L. J.; Devery, J. J., III; Stephenson, C. R. J. Catalytic Radical Domino Reactions in Organic Synthesis. *ACS Catal*. **2014**, *4*, 703-716. (d) Ram, R. N.; Kumar, N.; Singh, N. Synthesis of Chlorinated Bicyclic C-Fused Tetrahydrofuro[3,2-*c*]azetidin-2-ones. *J. Org. Chem.* **2010**, *75*, 7408-7411. (e) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. Visible Light-Mediated Atom Transfer Radical Addition *via* Oxidative and Reductive Quenching of Photocatalysts. *J. Am. Chem. Soc.* **2012**, *134*, 8875-8884. (f) Xu, T.; Hu, X. Copper-Catalyzed 1,2-Addition of α-Carbonyl Iodides to Alkynes. *Angew. Chem., Int. Ed.* **2015**, *54*, 1307-1311.

(9) CCDC 1859515 (**3j**) contains the supplementary crystallographic data for this paper. See the Supporting Information for details.

(10) (a) Bosco, E. E.; Kumar, S.; Marchioni, F.; Biesiada, J.; Kordos, M.; Szczur, K.; Meller, J.; Seibel, W.; Mizrahi, A.; Pick, E.; Filippi, M. D.; Zheng, Y. Rational Design of Small Molecule Inhibitors Targeting the Rac GTPase-p67^{phox} Signaling Axis in Inflammation. *Chem. Biol.* **2012**, *19*, 228-242. (b) Neelamegam, R.; Hellenbrand, T.; Schroeder, F. A.; Wang, C.-N.; Hooker, J. M. Imaging Evaluation of $5HT_{2C}$ Agonists, [^{11}C]WAY-163909 and [^{11}C]Vabicaserin, Formed by Pictet–Spengler Cyclization. *J. Med. Chem*. **2014**, 57, 1488-1494. (c) Upadhayaya, R. S.; Lahore, S. V.; Sayyed, A. Y.; Dixit, S. S.; Shinde, P. D.; Chattopadhyaya, J. Conformationally-Constrained Indeno[2,1-*c*]quinolines – A new Class of Anti-Mycobacterial Agents. *Org. Biomol. Chem*. **2010**, *8*, 2180-2197.

(11) (a) Gao, Y.; Lu, G.; Zhang, P.; Zhang, L.; Tang, G.; Zhao, Y. A Cascade Phosphinoylation/Cyclization/Desulfonylation Process for the Synthesis of 3-Phosphinoylindoles. *Org. Lett*. **2016**, *18*, 1242-1245. (b) Egami, H.; Ide, T.; Kawato, Y.; Hamashima, Y. Benzylic C–H Trifluoromethylation of Phenol Derivatives. *Chem. Commun*. **2015**, *51*, 16675-16678.

(12) (a) Thorand, S.; Krause, N. Improved Procedures for the Palladium-Catalyzed Coupling of Terminal Alkynes with Aryl Bromides (Sonogashira Coupling). *J. Org. Chem.* **1998**, *63*, 8551-8553. (b) Pearson, A. J.; Kim, J. B.

Cyclopentadienones as Intermediates for the Synthesis of Highly Functionalized Biaryls. *Tetrahedron Lett*. **2003**, *44*, 8525-8527.

(13) (a) Chen, C.-C.; Chen, C.-M.; Wu, M.-J. Transition Metal-Catalyzed Cascade Cyclization of Aryldiynes to Halogenated Benzo[*b*]naphtho[2,1-*d*]thiophene Derivatives. *J. Org. Chem.* **2014**, *79*, 4704-4711. (b) Chen, C.-C.; Chin, L.-Y.; Yang, S.-C.; Wu, M.-J. Synthetic Development and Mechanistic Study on Pd(II)-Catalyzed Cyclization of Enediynes to Benzo[*a*]carbazoles. *Org. Lett.* **2010**, *12*, 5652-5655. (c) Chen, C.-C.; Wu, M.-Y.; Chen, H.-Y.; Wu, M.-J. Halogen-Mediated Cascade Cyclization Reaction of Aryldiynes to Indeno[1,2-*c*]chromene Derivatives. *J. Org. Chem.* **2017**, *82*, 6071-6081. (d) Wang, Y.; Zheng, Z.; Zhang, L. Ruthenium-Catalyzed Oxidative Transformations of Terminal Alkynes to Ketenes By Using Tethered Sulfoxides: Access to β-Lactams and Cyclobutanones. *Angew. Chem., Int. Ed.* **2014**, *53*, 9572. (e) Takashi, M.; Chihoko, Y.; Hitomi, K.; Makoto, K.; Shuichi, O. Novel Pyrrolopyrimidine Compound of Salt Thereof, Pharmaceutical Composition Containing Same, Especially Agent for Prevention and/or Treatment of Tumors etc Based on Nae Inhibitory Effect. US2017/66772, **2017**. (f) Lin, C.-H., Chen, C.-C., Wu, M.-J. Mercury(II)-Catalyzed Cyclization of 2-Alkynylphenyl Alkyl Sulfoxides Provides 3-Acylbenzo[*b*]thiophenes. *Chem. Eur. J.* **2013**, *19*, 2578-2581.

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(14) Yang, D.; Yan, Y.-L.; Lui, B. Mild α-Halogenation Reactions of 1,3-Dicarbonyl Compounds Catalyzed by Lewis Acids. *J. Org. Chem.* **2002**, *67*, 7429-7431.

(15) Gupta, A.; Flynn, B. L. Linear and Angular Heteroacenes from Double-Electrophilic Cyclization (DEC) and DEC-Reductive Elimination of Diynes. *Org. Lett.* **2017**, *19*, 1939-1941.