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Note

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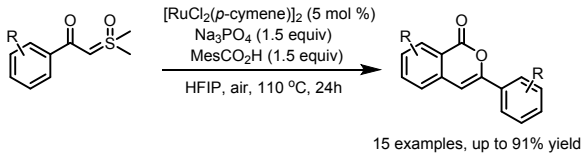
Ruthenium(II)-Catalyzed Construction of Isocoumarins via Dual C−H/C−C Activation of Sulfoxonium Ylides

Si Wen, Yanhui Chen, Zemin Zhao, Dan Ba, Weiwei Lv, and Guolin Cheng*

College of Materials Science & Engineering, Huaqiao University, Xiamen 361021, China
E-mail: glcheng@hqu.edu.cn

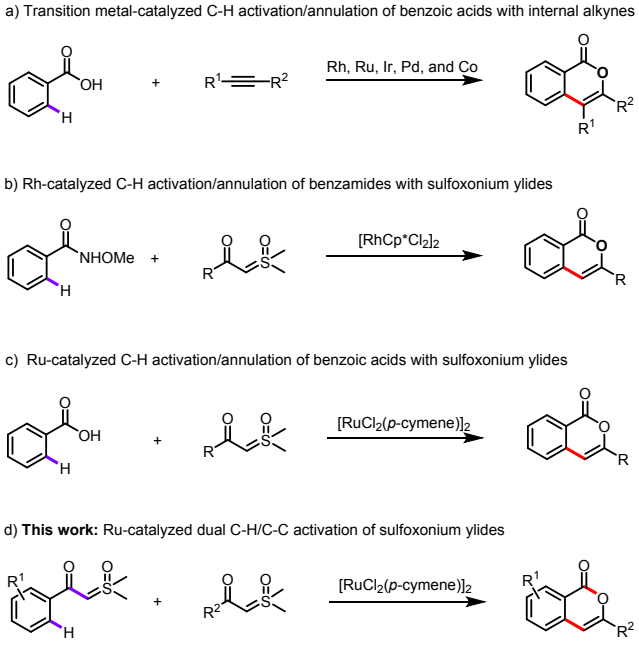


ABSTRACT: A ruthenium(II)-catalyzed annulation between two molecules of sulfoxonium ylides is achieved, generating a variety of substituted isocoumarins in reasonable yields. This strategy features dual C−H/C−C activation in one pot, and has a wide substrate scope and good functional group tolerance.

Isocoumarin and its derivatives are important natural lactones, which are generally found in natural products as a basic structure.[1] It was found that compounds with isocoumarin structure have a certain physiological activity,[2] which are widely used in the treatment of cancer,[3] allergy,[4] sterilization,[5] and other aspects.[6] In addition, they could be used as key synthetic intermediates in drug discovery.[7] Thus, the synthesis of compounds with such a skeleton has attracted great interesting.[8] Among the many synthetic methods to access of these compounds, the transition metal-catalyzed C−H activation/annulation cascade reactions of benzoic acid derivatives with coupling partners represent one of the most powerful and straightforward methods to isocoumarins. However, the coupling partners are commonly limited to internal alkynes (Scheme 1a).[9] The use of coupling partners other than internal alkynes will greatly enhance the scope of metal-catalyzed synthesis of isocoumarins.

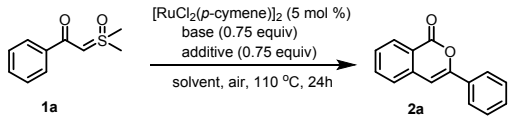
Sulfoxonium ylides are carbene precursors that are easier to prepare, and more stable and safer than diazonium compounds.[10] Sulfoxonium ylides have been used as alkylating reagents in a variety of reactions.[11-15] Since the first example of rhodium(III)-catalyzed C−H alkylation of arenes with sulfoxonium ylides was independently discovered by Aïssa[11] and Li,[12] sulfoxonium ylides have been widely used as alkylating reagents in transition metal-catalyzed C−H functionalization of a range of arenes.[13] Recently, Li's work illuminated the method of synthesizing isocoumarins from N-methoxybenzamides, using sulfoxonium ylides as coupling partners and rhodium(III) as a catalyst (Scheme 1b).[14] Subsequently, a method for the formation of isocoumarins *via* ruthenium(II)-catalyzed C−H activation/annulation of benzoic acids and sulfoxonium ylides was reported by Ackermann (Scheme 1c).[15] Inspired by the works of Li and Ackermann, we questioned whether sulfoxonium ylides could be able to serve as both arenes[16] and coupling partners in transition metal-catalyzed C−H activation. As our ongoing interest in C−H activation[17] and C−C cleavage,[18] herein, we disclose a ruthenium(II)-catalyzed dual C−H/C−C activation of sulfoxonium ylides for the synthesis of isocoumarins (Scheme 1d).[19]

Scheme 1. Synthesis of Isocoumarins *via* C–H Activation



We initiated our investigation on the model reaction of sulfoxonium ylide (1a) to optimize various reaction parameters. The results are summarized in Table 1. To our delight, under reaction conditions using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, 2,4,6-trimethylbenzoic acid ($MesCO_2H$) being an additive, and Na_3PO_4 as the base in HFIP at 110 °C under an air atmosphere for 24 h, the desired product (2a) was obtained in 78% yield (entry 1). Investigations on various solvents indicated that other solvents did not perform as well as HFIP (entries 1−6). Probably, protic solvents with low pKa values, such as HFIP (pKa = 9.3) and 2,2,2-trifluoroethanol (TFE, pKa = 12.4),[19] are favored in this transformation. Substituting other inorganic bases for Na_3PO_4 decreased the productivity, giving 2a in yields of 20–76% (entries 7−14). Removal of Na_3PO_4 from the reaction significantly reduced the reaction efficiency (entry 15). Only 20% yield of products was obtained in the absence of an additive (entry 16). These experiments indicated that both the base and additive were essential for this reaction. Ac-Gly-OH was not as a suitable additive as $MesCO_2H$ for this reaction, and the yield of 2a reduced to 64% (entry 17). Val-Boc-OH almost inhibited the reaction, and only trace of 2a was observed (entry 18). Further screening the reaction temperature showed that the reaction profile did not improve (entries 19 and 20). Finally, no reaction occurred in the absence of $[RuCl_2(p\text{-cymene})]_2$ (entry 21). Then, the optimized reaction conditions were identified as follows: 1a (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), Na_3PO_4 (0.75 equiv) and $MesCO_2H$ (0.75 equiv) in HFIP (1 mL) at 110 °C under an air atmosphere for 24 h (entry 1).

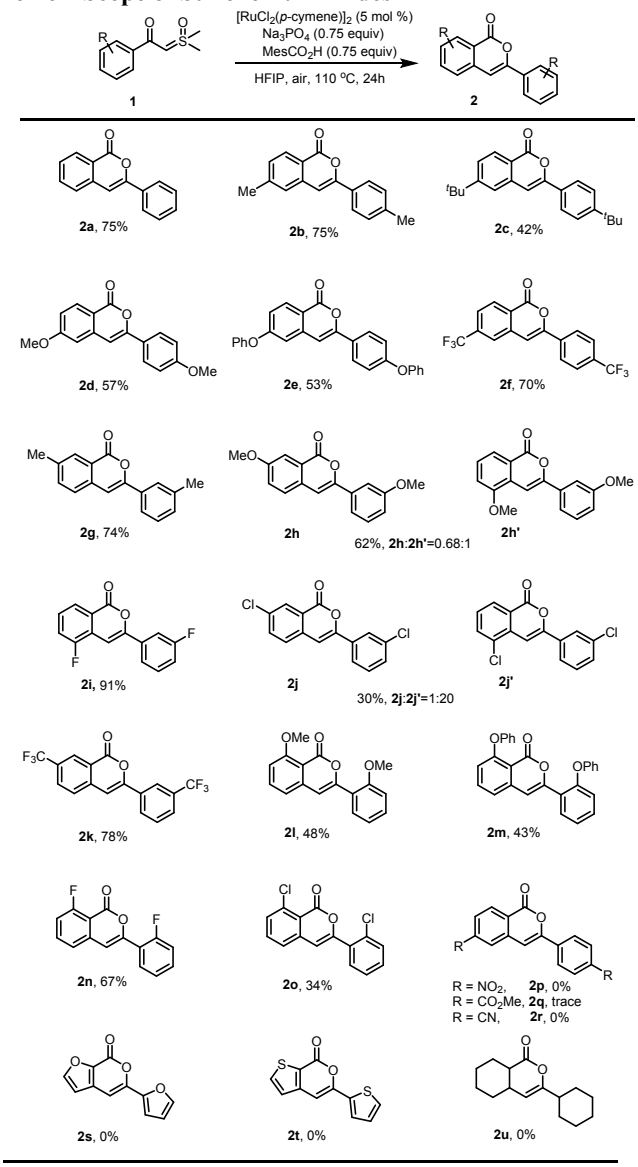
Table 1. Screen of the Reaction Conditions[a]



Entry	Solvent	Base	Additive	Yield(%)[b]
1	HFIP	Na_3PO_4	$MesCO_2H$	78 (75)[c]
2	^{i}PrOH	Na_3PO_4	$MesCO_2H$	15
3	DMF	Na_3PO_4	$MesCO_2H$	30
4	CH_3CN	Na_3PO_4	$MesCO_2H$	14
5	DCE	Na_3PO_4	$MesCO_2H$	0
6	toluene	Na_3PO_4	$MesCO_2H$	20
7	HFIP	Na_2CO_3	$MesCO_2H$	30
8	HFIP	K_2CO_3	$MesCO_2H$	20
9	HFIP	Cs_2CO_3	$MesCO_2H$	30
10	HFIP	$NaHCO_3$	$MesCO_2H$	76
11	HFIP	$KHCO_3$	$MesCO_2H$	60
12	HFIP	NaH_2PO_4	$MesCO_2H$	52
13	HFIP	K_3PO_4	$MesCO_2H$	20
14	HFIP	KH_2PO_4	$MesCO_2H$	44
15	HFIP	-	$MesCO_2H$	40
16	HFIP	Na_3PO_4	-	20
17	HFIP	Na_3PO_4	Ac-Gly-OH	64
18	HFIP	Na_3PO_4	Val-Boc-OH	trace
19[d]	HFIP	Na_3PO_4	$MesCO_2H$	72
20[e]	HFIP	Na_3PO_4	$MesCO_2H$	70
21[f]	HFIP	Na_3PO_4	$MesCO_2H$	0

[a]Reaction conditions: **1a** (0.2 mmol), base (0.15 mmol), additive (0.15 mmol), and $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) in solvent (1 mL) at 110 °C under an air atmosphere for 24 h. [b]The yields were determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c]Isolated yield. [d]Reaction was carried out at 100 °C. [e]Reaction was carried out at 120 °C. [f]Without $[RuCl_2(p\text{-cymene})]_2$. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. DMF = *N,N*-dimethylformamide. DCE = 1,2-dichloroethane.

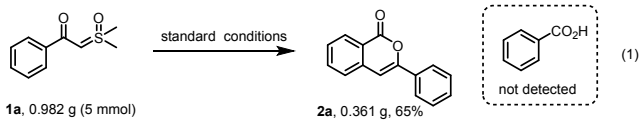
Scheme 2 Scope of Sulfoxonium Ylides



With the optimized reaction conditions in hand, we paid our attention to the scope of a series of benzoyl sulfoxonium ylides (Scheme 2). The sulfoxonium ylide derivatives bearing electron-donating or electron-withdrawing groups on benzoyl moieties, all could be smoothly carried out to give the substituted isocoumarin products in moderate to good yields (**2a−o**). The reactivity of this transformation was not sensitive to the electronic properties of the benzoyl groups. For sulfoxonium ylides with a *para*-substituent on phenyl rings, such as methyl, *tert*-butyl, methoxyl, phenoxyl, and trifluoromethyl, showed moderate to good reactivity, giving products (**2b−f**) in 42-75% yields. For *meta*-methyl and

trifluoromethyl benzoyl sulfoxonium ylides, the C−H activation occurred at the sterically less hindered position, giving the desired products in 74% and 78% yields, respectively (**2g** and **2k**). However, *meta*-methoxyl and *meta*-chloro substituted substrates led to mixtures of two regioisomers (**2h**/**2h′** and **2j**/**2j′**). Interestingly, exclusively *ortho*-to-fluorine and highly *ortho*-to-chlorine selectivities were obtained when *meta*-halogen substituted substrates were used (**2i** and **2g**). The reaction efficiency was slightly retarded by steric hindrance, and *ortho*-substituted substrates only gave the desired products (**2l**−**o**) in 34-67% yields. This reaction was not applicable to 4-nitro, 4-ester, and 4-cyano substituted substrates, as well as furyl and thienyl substituted substrates(**2p**−**t**). Finally, the sulfoxonium ylides with an alkanoyl group failed to produce the desired product, probably due to the difficulty to active the C(sp^3)−H bond (**2u**).

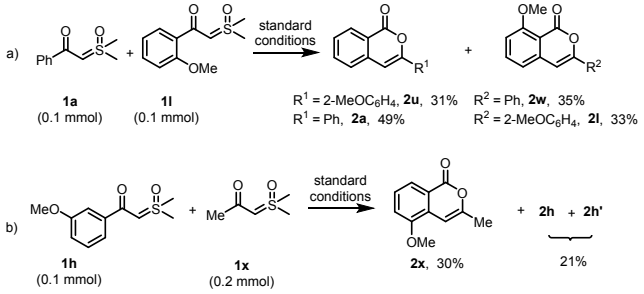
To demonstrate the applicability of the method, a gram-scale experiment of 1a was also feasible, giving **2a** in 65% yield (eq. 1).



(1)

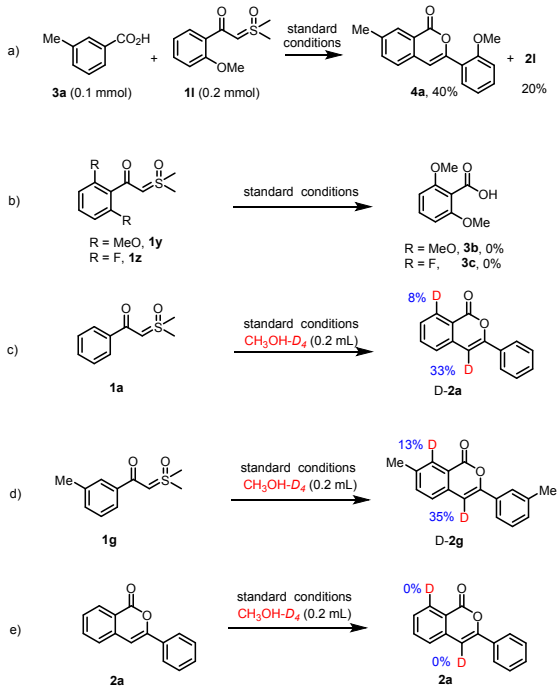
In addition, we found that under the standard reaction conditions, the cross-over reaction of **1a** and **1l** could generate isocoumarins (**2v**), (**2w**), (**2a**), and (**2l**) in 31%, 35%, 49%, and 33% yields, respectively (Scheme 3a). Significantly, the cross-coupling reaction could be carried out using an aroyl substrate (**1h**) and an alkanoyl substrate (**1x**) to give the corresponding product **2x** in 30% yield together with a mixture of **2h** and **2h'** in 21% combined yield (Scheme 3b).

Scheme 3 Cross-Over Reactions

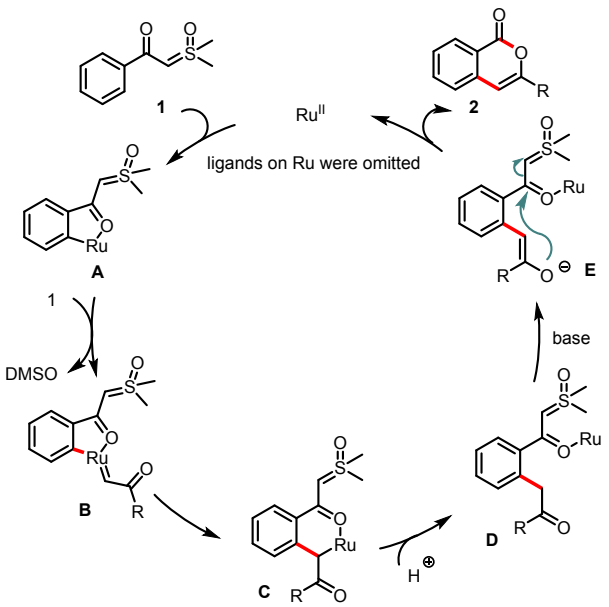


In order to further understand the reaction mechanism, several control experiments were performed. The reaction of 3-methylbenzoic acid (**3a**) and sulfoxonium ylide (**1l**) could deliver isocoumarin (**4a**) in 40% yield (Scheme 4a).[15] However, the reaction of 2,6-disubstituted benzoyl sulfoxonium ylides (**1y** or **1z**) under the standard reaction conditions failure to give 2,6-disubstituted benzoic acids, which indicated that benzoic acids may not be involved in this reaction (Scheme 4b). Furthermore, the compounds (**1a**) and (**1g**) were subjected to the standard reaction conditions independently using CH_3OH-D_4 (0.2 mL) as a co-solvent, leading to H/D exchange occurred at the C4 and C8 positions of the corresponding products, which suggested that the *ortho*-C−H cleavage process is reversible (Scheme 4c and 4d). Since the incorporation of deuterium (D) on the aromatic ring at C3 position of the product was not occurred, we proposed that the coordination of sulfoxonium ylide with Ru catalyst is irreversible (Scheme 4c and 4d). Moreover, no deuterated incorporation was observed, when isocoumarin (**2a**) was allowed to undergo H/D exchange (Scheme 4e). These experiments indicated that the H/D exchange process is slightly faster than the formation of the final isocoumarins.

Scheme 4 Control Experiments



Scheme 5 Plausible Catalytic Cycle



On the basis of the above results and literature reports,[15,16] a plausible catalytic cycle is proposed as shown in Scheme 5. Initially, the coordination of carbonyl oxygen of sulfoxonium ylide (**1**) to a Ru(II) catalyst is followed by *ortho*-C−H activation to give a five-membered Ru(II) complex (**A**). Then

A is captured by **1** to form Ru(II) carbene complex (**B**), which could deliver a six-membered Ru(II) complex (**C**) *via* carbene migratory insertion. The protonolysis of **C** leads the alkylated intermediate (**D**). Finally, the enolization of **D** under basic condition forms intermediate (**E**), following by intramolecular cyclization of **E**, affording the isocoumarins (**2**) along with the cleavage of a C−C bond.

CONCLUSION

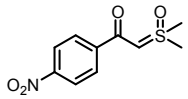
In summary, we have demonstrated a strategy for the formation of isocoumarins *via* ruthenium(II)-catalyzed dual C−H/C−C activation of sulfoxonium ylides. This novel method has a broad substrates scope, and a range of substituted isocoumarins have been synthesized with moderate to good yields.

EXPERIMENTAL SECTION

General Information. All the solvents were used without further purification. The other commercial chemicals were used without further purification. All reactions were performed under an inert atmosphere of nitrogen in flame-dried glassware, unless otherwise stated. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. Preparative TLC was performed on 1.0 mm silica gel. ^{1}H NMR spectra were recorded on Bruker DRX-500 instrument (500 MHz). ^{13}C NMR spectra were recorded on Bruker DRX-500 instrument (126 MHz) were fully decoupled by broad band proton decoupling. High-resolution mass spectra (HRMS) were recorded on an Agilent 1290 Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). NMR spectra were recorded in $CDCl_3$. ^{1}H NMR spectra were referenced to residual $CHCl_3$ at 7.26 ppm, and ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at 77.0 ppm. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

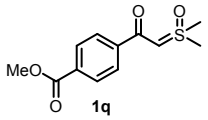
Procedure for the Synthesis of 1

1 was synthesized following a literature procedure[20]



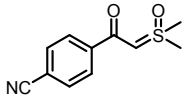
1p

2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-(4-nitrophenyl)ethan-1-one (1p)[21] as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 – 8.27 (m, 2H), 8.06 – 8.03 (m, 2H), 5.85 (s, 1H), 3.65 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 177.6, 148.4, 145.2, 127.6, 123.5, 74.5, 40.5.



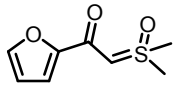
1q

Methyl-4-(2-(dimethyl(oxo)-λ^6-sulfanylidene)acetyl)benzoate (1q)[21] as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.08 – 8.02 (m, 2H), 7.88 – 7.80 (m, 2H), 5.04 (s, 1H), 3.95 – 3.90 (m, 3H), 3.55 – 3.52 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 181.0, 166.6, 142.8, 131.8, 129.4, 126.5, 69.6, 52.1, 42.3.



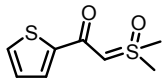
1r

4-(2-(dimethyl(oxo)-λ^6-sulfanylidene)acetyl)benzonitrile (1y) as a white solid, m.p. 216 - 218 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 – 7.92 (m, 2H), 7.90 – 7.87 (m, 2H), 5.78 (s, 1H), 3.59 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 177.9, 143.4, 132.2, 127.1, 118.7, 112.5, 74.0, 40.5; HRMS (ESI-TOF) m/z: calcd for $C_{11}H_{12}NO_2S^+$: 222.0583 $(M + H)^+$, found: 222.0584.



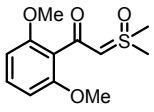
1s

2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-(furan-2-yl)ethan-1-one (1s)[22] as a brown solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.36 (m, 1H), 6.95 – 6.87 (m, 1H), 6.47 – 6.39 (m, 1H), 5.03 (s, 1H), 3.50 (d, *J* = 14.9 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 172.2, 153.3, 143.3, 111.4, 111.2, 68.4, 42.3.



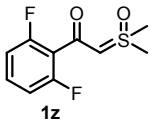
1t

2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-(thiophen-2-yl)ethan-1-one (1v)[21] as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.49 – 7.37 (m, 2H), 7.05 (s, 1H), 4.89 (s, 1H), 3.51 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 175.6, 145.6, 129.0, 127.5, 127.0, 67.1, 42.8.



1y

1-(2,6-dimethoxyphenyl)-2-(dimethyl(oxo)-λ^6-sulfanylidene)ethan-1-one (1y) as a white solid, m.p. 146 – 147 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.22 – 7.15 (m, 1H), 6.56 – 6.50 (m, 2H), 4.53 (s, 1H), 3.82 – 3.75 (m, 6H), 3.55 – 3.46 (m, 6H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 182.2, 156.9 (d, *J* = 2.2 Hz), 129.2, 121.2, 103.9, 72.2, 55.9, 42.4; HRMS (ESI-TOF) m/z: calcd for $C_{12}H_{17}O_4S^+$: 257.0842 $(M + H)^+$, found: 257.0845.



1z

1-(2,6-difluorophenyl)-2-(dimethyl(oxo)-λ^6-sulfanylidene)ethan-1-one (1z) as a white solid, m.p. 135 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.20 (m, 1H), 6.87 (q, *J* = 8.3 Hz, 2H), 4.71 (d, *J* = 2.9 Hz, 1H), 3.54 (d, *J* = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 175.0, 160.8 (d, *J* = 7.7 Hz), 158.8 (d, *J* = 7.6 Hz), 130.0 (d, *J* = 20.4

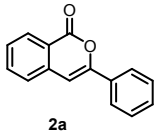
Hz), 130.0, 111.6 (d, J = 5.2 Hz), 111.5 (d, J = 5.1 Hz), 74.2, 42.2; HRMS (ESI-TOF) m/z: calcd for $C_{10}H_{11}F_2O_2S^+$: 233.0442 $(M + H)^+$, found: 233.0445.

Procedure for the Synthesis of 2.

A dried 10 mL Schlenk tube was charged with sulfoxonium ylide **1** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) (3.1 mg, 0.005 mmol, 5 mol %), Na_3PO_4 (24.6 mg, 0.15 mmol), $MesCO_2H$ (24.6 mg, 0.15 mmol), and HFIP (1 mL). This mixture was heated to 110 °C on a heating plate for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated under vacuum, and the resulting residue was purified by preparative thin layer chromatography (PTLC) with ethyl acetate: hexane to give the corresponding products.

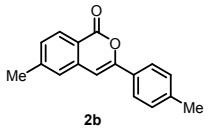
Safety Precaution of High-Pressure Reactions

We have NOT encountered any explosion during the synthesis of all isocoumarins. However, for safety concerns, we recommend using a plastic shield.



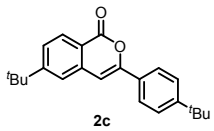
2a

3-phenyl-1*H*-isochromen-1-one (**2a**)[9k] (16.7 mg, 75%) as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.32 (d, J = 8.2 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.75 – 7.71 (m, 1H), 7.54 – 7.42 (m, 5H), 6.97 (s, 1H) ; ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 162.3, 153.6, 137.5, 134.9, 131.9, 130.0, 129.6, 128.8, 128.1, 126.0, 125.2, 120.5, 101.8.



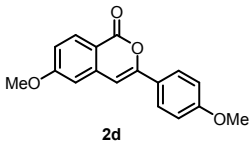
2b

6-methyl-3-(*p*-tolyl)-1*H*-isochromen-1-one (**2b**) (18.7 mg, 75%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as yellow solid, m.p. 150 - 152 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.30 – 7.24 (m, 4H), 6.84 (s, 1H), 2.47 (s, 3H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 162.5, 153.8, 145.9, 140.1, 137.8, 129.5, 129.5, 129.3, 129.2, 125.8, 125.1, 118.0, 101.0, 22.0, 21.4; HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{15}O_2^+$: 251.1067 $(M + H)^+$, found: 251.1070.



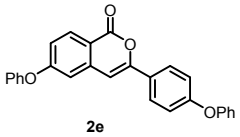
2c

6-(*tert*-butyl)-3-(4-(*tert*-butyl)phenyl)-1*H*-isochromen-1-one (**2c**) (14.1 mg, 42%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as light yellow solid, m.p. 143 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.23 (d, J = 8.4 Hz, 1H), 7.85 – 7.81 (m, 2H), 7.56 – 7.53 (m, 1H), 7.50 – 7.46 (m, 3H), 6.94 (s, 1H), 1.39 (s, 9H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 162.5, 158.8, 153.7, 153.2, 137.7, 129.4, 129.3, 125.9, 125.8, 125.0, 122.2, 118.0, 101.6, 35.4, 34.8, 31.2, 31.0; HRMS (ESI-TOF) m/z: calcd for $C_{23}H_{27}O_2^+$: 335.2006 $(M + H)^+$, found: 335.2010.



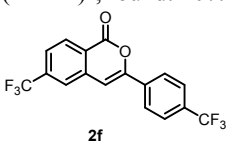
2d

6-**methoxy-3-(4-methoxyphenyl)-1*H*-isochromen-1-one** (**2d**) (15.7 mg, 57%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 10) as orange solid, m.p. 147 - 148 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.20 (d, J = 8.8 Hz, 1H), 7.84 – 7.79 (m, 2H), 7.01 – 6.98 (m, 1H), 6.98 – 6.95 (m, 2H), 6.84 (d, J = 2.4 Hz, 1H), 6.77 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 164.7, 162.3, 161.0, 154.2, 140.2, 131.8, 126.8, 124.5, 116.1, 114.2, 113.3, 107.6, 100.3, 55.6, 55.4; HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{15}O_4^+$: 283.0965 $(M + H)^+$, found: 283.0968.



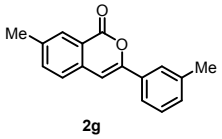
2e

6-phenoxy-3-(4-phenoxyphenyl)-1*H*-isochromen-1-one (**2e**) (21.5 mg, 53%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as yellow solid, m.p. 125 - 126 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.24 (d, J = 8.7 Hz, 1H), 7.82 – 7.78 (m, 2H), 7.47 – 7.42 (m, 2H), 7.40 – 7.36 (m, 2H), 7.28 – 7.24 (m, 1H), 7.19 – 7.15 (m, 1H), 7.14 – 7.11 (m, 2H), 7.09 – 7.02 (m, 5H), 6.87 (d, J = 2.4 Hz, 1H), 6.74 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 163.5, 161.8, 159.2, 156.1, 154.8, 153.9, 139.9, 132.2, 130.2, 129.9, 127.0, 126.5, 125.1, 124.1, 120.6, 119.6, 118.3, 118.1, 114.7, 111.8, 100.7; HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{19}O_4^+$: 407.1278 $(M + H)^+$, found: 407.1277.



2f

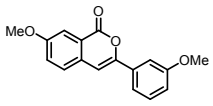
6-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-1*H*-isochromen-1-one (**2f**) (24.9 mg, 70%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as white solid, m.p. 170 - 172 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.46 (d, J = 8.2 Hz, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.83 (s, 1H), 7.77 (t, J = 7.7 Hz, 3H), 7.11 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 160.6, 153.4, 137.3, 136.6 (q, J = 33.0 Hz), 134.6, 132.2 (q, J = 32.9 Hz), 130.8, 126.7 (q, J = 68.0 Hz), 126.0 (q, J = 3.8 Hz), 125.7, 125.0 (q, J = 3.5 Hz), 123.7 (q, J = 272.4 Hz), 123.4 (q, J = 4.0 Hz), 123.1 (q, J = 273.4 Hz), 102.6; HRMS (ESI-TOF) m/z: calcd for $C_{17}H_9F_6O_2^+$: 359.0501 $(M + H)^+$, found: 359.0502.



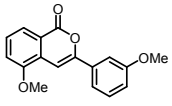
2g

7-methyl-3-(*m*-tolyl)-1*H*-isochromen-1-one (**2g**) (18.6 mg, 74%) was prepared from typical procedure (ethyl acetate:

hexane = 1 : 30) as yellow white solid, m.p. 120 - 122 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 7.72 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 6.93 (s, 1H), 2.48 (s, 3H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 162.6, 152.9, 138.5, 138.4, 136.2, 135.1, 132.0, 130.5, 129.3, 128.7, 125.9, 125.7, 122.2, 120.4, 101.7, 21.5, 21.4; HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{15}O_2^+$: 251.1067 (M + H)$^+$, found: 251.1064.

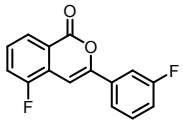


2h



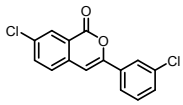
2h'

2h and **2h'** (17.4 mg, 62%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 10) as cream solid, m.p. 120 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 2.7 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.45 – 7.29 (m, 8H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.91 (s, 1H), 3.96 (s, 3H), 3.92 (s, 2H), 3.88 (d, *J* = 2.3 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 162.4, 162.2, 159.9, 159.9, 159.5, 154.3, 152.6, 151.4, 133.6, 133.4, 131.1, 129.8, 129.7, 128.4, 128.0, 127.6, 124.7, 121.6, 121.3, 120.9, 117.6, 117.3, 115.7, 115.5, 114.3, 110.2, 110.1, 109.9, 101.9, 96.5, 55.9, 55.7, 55.4, 55.4. HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{15}O_4^+$: 283.0965 (M + H)$^+$, found: 283.0964; （**2h:2h'**=0.68:1）

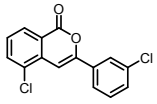


2i

5-fluoro-3-(3-fluorophenyl)-1*H*-isochromen-1-one (**2i**) (23.4 mg, 91%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as yellowish white solid, m.p. 157 - 160 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.15 – 8.11 (m, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.52 – 7.43 (m, 3H), 7.19 (s, 1H), 7.18 – 7.13 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 163.1 (d, *J* = 246.8 Hz), 160.7, 157.3 (d, *J* = 252.8 Hz), 152.8, 133.8 (d, *J* = 8.1 Hz), 130.5 (d, *J* = 8.3 Hz), 128.9 (d, *J* = 7.8 Hz), 126.3 (d, *J* = 16.8 Hz), 125.4 (d, *J* = 3.7 Hz), 122.0 (d, *J* = 4.1 Hz), 121.0 (d, *J* = 2.9 Hz), 120.4 (d, *J* = 19.8 Hz), 117.2 (d, *J* = 21.3 Hz), 112.5 (d, *J* = 23.9 Hz), 95.2 (d, *J* = 4.9 Hz); HRMS (ESI-TOF) m/z: calcd for $C_{15}H_9F_2O_2^+$: 259.0565 (M + H)$^+$, found: 259.0570.

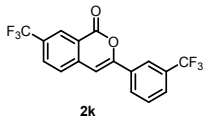


2j



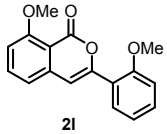
2j'

2j and **2j'** (8.6 mg, 30%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as white solid, m.p. 172 - 173 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 7.9 Hz, 1H), 7.92 (q, *J* = 1.5 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.45 – 7.43 (m, 2H), 7.34 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 161.1, 153.0, 135.2, 135.2, 135.1, 133.4, 130.8, 130.4, 130.2, 128.7, 128.5, 125.6, 123.6, 122.1, 98.8; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_9Cl_2O_2^+$: 290.9974 (M + H)$^+$, found: 290.9979. (**2j:2j'**=1:20).



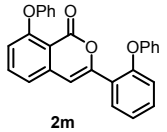
2k

7-(trifluoromethyl)-3-(3-(trifluoromethyl)phenyl)-1*H*-isochromen-1-one (**2k**) (28 mg, 78%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as white solid, m.p. 168 - 169 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 (s, 1H), 8.15 (s, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 8.00 – 7.96 (m, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.09 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 160.7, 154.0, 139.7, 132.1, 131.6 (q, *J* = 32.8 Hz), 131.3 (q, *J* = 3.3 Hz), 130.7 (q, *J* = 33.7 Hz), 129.6, 128.6, 127.3 (q, *J* = 4.1 Hz), 127.1 (q, *J* = 3.7 Hz), 127.0, 123.7 (q, *J* = 272.6 Hz), 123.3 (q, *J* = 272.4 Hz), 122.3 (q, *J* = 3.8 Hz), 120.7, 102.0; HRMS (ESI-TOF) m/z: calcd for $C_{17}H_9F_6O_2^+$: 359.0501 (M + H)$^+$, found: 359.0500.



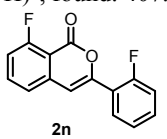
2l

8-methoxy-3-(2-methoxyphenyl)-1*H*-isochromen-1-one (**2l**) (13.2 mg, 48%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 6) as brown solid, m.p. 172 - 173 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 8.1 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.30 (s, 1H), 7.09 – 7.03 (m, 2H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 161.5, 159.4, 157.2, 150.7, 141.0, 135.5, 130.7, 128.9, 120.8, 120.6, 118.4, 111.2, 109.6, 109.4, 107.0, 56.3, 55.6; HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{15}O_4^+$: 283.0965 (M + H)$^+$, found: 283.0970.



2m

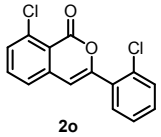
8-phenoxy-3-(2-phenoxyphenyl)-1*H*-isochromen-1-one (**2m**) (17.3 mg, 43%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as brown solid, m.p. 127 - 128 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 – 8.06 (m, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.40 – 7.31 (m, 6H), 7.25 – 7.21 (m, 1H), 7.18 – 7.13 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.09 – 7.05 (m, 4H), 6.95 – 6.92 (m, 1H), 6.85 – 6.81 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 159.2, 158.4, 156.3, 156.3, 154.8, 150.1, 140.6, 135.3, 130.8, 130.0, 129.8, 129.1, 124.1, 123.8, 123.7, 123.2, 121.0, 119.7, 119.3, 119.0, 117.5, 111.6, 107.0; HRMS (ESI-TOF) m/z: calcd for $C_{27}H_{19}O_4^+$: 407.1278 (M + H)$^+$, found: 407.1280.



2n

8-fluoro-3-(2-fluorophenyl)-1*H*-isochromen-1-one (**2n**) (17.1 mg, 67%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as white solid, m.p. 169- 171 °C. ^{1}H

NMR (500 MHz, Chloroform-*d*) δ 8.04 – 7.99 (m, 1H), 7.72 – 7.67 (m, 1H), 7.44 – 7.39 (m, 1H), 7.32 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*) δ 162.8 (d, *J* = 266.8 Hz), 160.1 (d, *J* = 253.3 Hz), 157.5 (d, *J* = 5.4 Hz), 149.0 (d, *J* = 5.2 Hz), 139.9, 136.2 (d, *J* = 10.2 Hz), 131.5 (d, *J* = 9.0 Hz), 128.5 (d, *J* = 1.7 Hz), 124.6 (d, *J* = 3.6 Hz), 122.3 (d, *J* = 4.4 Hz), 119.6 (d, *J* = 9.8 Hz), 116.4 (d, *J* = 22.8 Hz), 115.6 (d, *J* = 21.3 Hz), 109.5 (d, *J* = 7.2 Hz), 106.50 (dd, *J* = 16.0, 3.0 Hz); HRMS (ESI-TOF) m/z: calcd for $C_{15}H_9F_2O_2^+$: 259.0565 (M + H)$^+$, found: 259.0567.

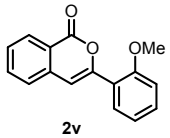


2o

8-chloro-3-(2-chlorophenyl)-1*H*-isochromen-1-one (**2o**) (9.6 mg, 34%) was prepared from typical procedure (ethyl acetate: hexane = 1 : 30) as cream solid, m.p. 153 - 154 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.75 – 7.72 (m, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.52 – 7.48 (m, 1H), 7.42 – 7.36 (m, 3H), 6.97 (s, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*) δ 158.8, 152.0, 140.0, 137.2, 134.6, 132.3, 131.4, 131.0, 130.9, 130.7, 130.6, 127.1, 125.2, 117.7, 107.4; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_9Cl_2O_2^+$: 290.9974 (M + H)$^+$, found: 290.9977.

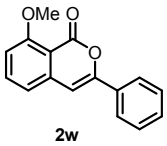
Procedure for Synthesis of 2v, 2w

A dried 10 mL Schlenk tube was charged with **2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-phenylethan-1-one** (**1a**) (0.1 mmol, 19.6 mg), **2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-(2-methoxyphenyl)ethan-1-one** (**1l**) (0.1 mmol, 22.6 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) (3.1 mg, 0.005 mmol, 5 mol %), Na_3PO_4 (24.6 mg, 0.15 mmol), $MesCO_2H$ (24.6 mg, 0.15 mmol), and HFIP (1 mL). This mixture was heated to 110 °C on a heating plate for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated under vacuum, and the resulting residue was purified by preparative thin layer chromatography (PTLC) with (ethyl acetate: hexane) to give the (**2v**, 7.8 mg, 31%), (**2w**, 9.0 mg, 35%), (**2a**, 10.9 mg, 49%), and (**2l**, 9.1 mg, 33%).



2v

3-(2-methoxyphenyl)-1*H*-isochromen-1-one (**2v**) was prepared from typical procedure (ethyl acetate: hexane=1:20) as a yellow solid, m.p. 120 - 121 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 7.9 Hz, 1H), 8.01 – 7.95 (m, 1H), 7.75 – 7.67 (m, 1H), 7.53 – 7.47 (m, 2H), 7.42 – 7.37 (m, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 3.97 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*) δ 162.7, 157.1, 150.4, 138.0, 134.6, 130.7, 129.4, 128.8, 128.0, 126.3, 120.8, 120.7, 120.6, 111.3, 107.0, 55.6; HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{13}O_3^+$: 253.0859 (M + H)$^+$, found: 253.0856.

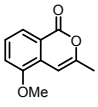


2w

8-methoxy-3-phenyl-1*H*-isochromen-1-one (**2w**) was prepared from typical procedure (ethyl acetate: hexane=1:10) as a yellowish solid, m.p. 144 - 145 °C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.92 – 7.86 (m, 2H), 7.63 (t, *J* = 8.1 Hz, 1H), 7.5 – 7.4 (m, 3H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 1H), 4.03 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*) δ 161.6, 159.1, 153.9, 140.4, 135.8, 131.8, 129.9, 128.7, 125.3, 118.1, 109.8, 109.2, 101.8, 56.3; HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{13}O_3^+$: 253.0859 (M + H)$^+$, found: 253.0861.

Procedure for Synthesis of 2x

A dried 10 mL Schlenk tube was charged with **2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-(3-methoxyphenyl)ethan-1-one** (**1h**) (0.1 mmol, 22.6 mg), **1-(dimethyl(oxo)-λ^6-sulfanylidene)propan-2-one** (**1x**) (0.2 mmol, 26.8mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) (3.1 mg, 0.005 mmol, 5 mol %), Na_3PO_4 (24.6 mg, 0.15 mmol), $MesCO_2H$ (24.6 mg, 0.15 mmol), and HFIP (1 mL). This mixture was heated to 110 °C on a heating plate for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated under vacuum, and the resulting residue was purified by preparative thin layer chromatography (PTLC) with ethyl acetate: hexane to give the corresponding products.



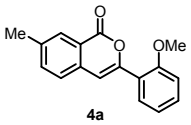
2x

5-methoxy-3-methyl-1*H*-isochromen-1-one (**2x**) (5.7 mg, 30%) was prepared from typical procedure (ethyl acetate: hexane=1:50) as a white solid, m.p. 41 - 43 °C ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.85 – 7.82 (m, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.14 – 7.10 (m, 1H), 6.63 (t, *J* = 1.0 Hz, 1H), 3.92 (s, 3H), 2.29 (d, *J* = 1.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*) δ 162.9, 153.9, 153.5, 128.3, 127.7, 120.9, 120.7, 114.3, 97.8, 55.9, 19.8; HRMS (ESI-TOF) m/z: calcd for $C_{11}H_{11}O_3^+$: 191.0703 (M + H)$^+$, found: 191.0706.

Procedure for Synthesis of 4a

A dried 10 mL Schlenk tube was charged with **3-methylbenzoic acid** (**3a**) (0.1 mmol, 13.6 mg), **2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-(2-methoxyphenyl)ethan-1-one** (**1l**) (0.2 mmol, 45.3mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) (3.1 mg, 0.005 mmol, 5 mol %), Na_3PO_4 (24.6 mg, 0.15 mmol), $MesCO_2H$ (24.6 mg, 0.15 mmol), and HFIP (1 mL). This mixture was heated to 110 °C on a heating plate for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated under vacuum, and the resulting residue was

purified by preparative thin layer chromatography (PTLC) with ethyl acetate: hexane to give the corresponding products.



4a

3-(2-methoxyphenyl)-7-methyl-1*H*-isochromen-1-one (4a)[23] (10.7 mg, 40%) was prepared from typical procedure (ethyl acetate: hexane=1:20) as a white solid. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 7.99 – 7.95 (m, 1H), 7.54 – 7.51 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.10 – 7.03 (m, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 3.96 (s, 3H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 162.8, 157.1, 149.6, 138.3, 136.0, 135.5, 130.5, 129.1, 128.7, 126.2, 120.8, 120.5, 111.3, 107.0, 55.6, 21.4.

Gram-Scale reaction experiment

A dried 100 mL Schlenk tube was charged with **2-(dimethyl(oxo)-λ^6-sulfanylidene)-1-phenylethan-1-one 1a** (0.981 g, 5.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (76.5 mg, 0.125 mmol, 5 mol %), $MesCO_2H$ (0.615 g, 3.75 mmol), Na_3PO_4 (0.615 g, 3.75 mmol) and HFIP (50 mL). This mixture was heated to 110 °C on a heating plate for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated under vacuum, and the resulting residue was purified by flash chromatography on silica gel with ethyl acetate/hexane (1 : 30) to give the corresponding products **3-phenyl-1*H*-isochromen-1-one** (**2a**) (360.9 mg, 65%) as a white solid.

ASSOCIATED CONTENT

Supporting Information.

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

^{1}H and ^{13}C NMR spectra of new compounds.

AUTHOR INFORMATION

Corresponding Author

*E-mail: glcheng@hqu.edu.cn

Notes

The authors declare no competing financial interest.

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