Communication

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Cyclopropyl thioethers, new inputs for Palladium catalyzed ring-opening of cyclopropanes

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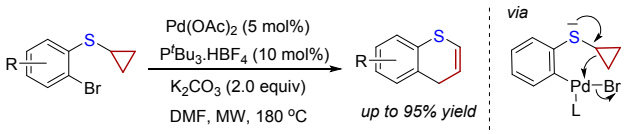
TOC


Pd(OAc)2 (5 mol%)
PtBu3.HBF4 (10 mol%)
K2CO3 (2.0 equiv)
DMF, MW, 180 °C
up to 95% yield
via

ABSTRACT. We present herein a new palladium-catalyzed ring-opening of cyclopropane-substituted thioethers. The study involves an intramolecular trapping of an intermediate aryl palladium to afford thiochromene derivatives. In contrast to the analogous cyclopropylamines which led to efficient ring-opening using triphenylphosphine as ligand for palladium, good yields for cyclopropyl thioethers required the use of bulkier electron-donating phosphines, such as tri-*tert*butylphosphine.

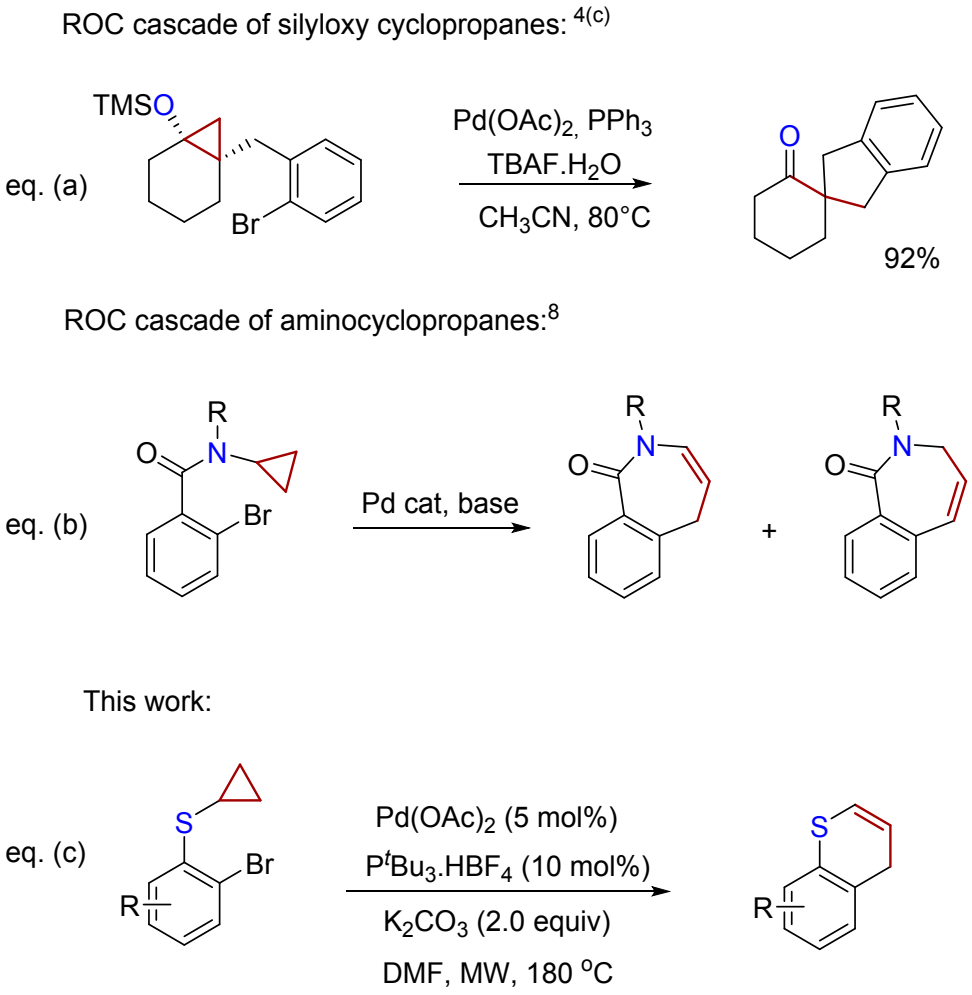
KEYWORDS : Cyclopropane, ring-opening, thioether, palladium catalysis, thiochromene.

Introduction

Due to high steric constraint with angles close to 60° instead of the standard tetrahedral geometry around the carbon atom, cyclopropanes constitute a unique class of reactive alkanes. According to their substitution pattern, a wide range of experimental conditions has been disclosed for their ring-opening and subsequent trapping by a nucleophile, an electrophile or a dipolarophile.[1] Among the various methods, metal-catalyzed processes

were highly successful for the ring-opening of alkylidene- or vinyl-cyclopropanes.[2] Since the 70s, alkoxycyclopropanes[3] have attracted much attention with the pioneering work of Nakamura and Kuwajima who disclosed the first Pd-catalyzed opening of a silylated alkoxycyclopropane and trapping of the resulting homoenolate.[4] Comparatively, the metal-catalyzed ring-opening of aminocyclopropanes[5] has significantly received less attention. Along with some acid-triggered[6] and oxidative ring-openings,[7] Pd-catalyzed conditions have been reported a few years ago by our group and others to propose efficient syntheses of benzo-fused oxa- and aza-heterocycles (Scheme 1, eq. (a) & (b)).[8] In contrast, the corresponding ring-opening of cyclopropyl thioethers has been scarcely reported[9] and, to the best of our knowledge, there is no example of such a metal-catalyzed approach.

Considering this lack, we decided to study the likelihood of an intramolecular trapping of cyclopropyl thioethers, as previously disclosed for oxa- and aza- analogues,[4c,8] as a means to generate valuable 4*H*-thiochromenes in a very efficient and straightforward manner (Scheme 1, eq. (c)).



Scheme 1. Palladium triggered ring-opening/cyclization of RO, R_2N and RS-tethered cyclopropanes

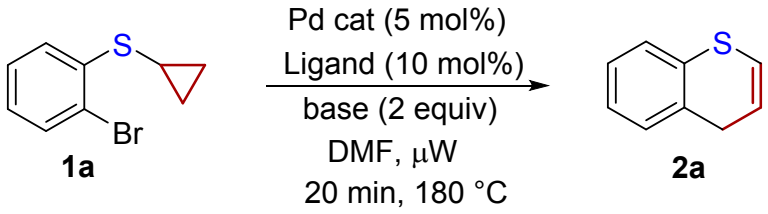
Results and Discussion

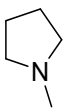
Following our past interest in the ring-opening of aminocyclopropanes, experimental conditions close to those developed previously were tested first. For this purpose, 2-

bromophenyl cyclopropyl thioether **1a** was prepared through the alkylation of the 2-bromo thiophenol under classical basic reaction conditions.[10] The mercaptocyclopropane **1a** was then treated in the presence of 5 mol% of $PdCl_2(PPh_3)_2$ in wet acetonitrile with 2 equiv of cesium carbonate under microwave irradiation at 130 °C for 20 min (entry 1, Table 1).[11] Nevertheless, no reaction occurred under these conditions, even when increasing the reaction temperature up to 180 °C. Faced to such an absence of reactivity, we thus decided to use a commercially available Pd(0) source, with the hope to boost the expected catalytic activity. For this purpose, $Pd_2(dba)_3$ was selected as catalyst and different ligands were tested next. In order to perform the reaction at higher temperature, *N,N*-dimethylformamide was selected as solvent. Poor conversions were observed at 180 °C with common phosphines such as triphenylphosphine, tri-*ortho*-tolylphosphine and dppf (entries 2-4, Table 1). Based on the hypothesis that these disappointing results could result from a sluggish oxidative addition arising from the electron-donating effect of the thiocyclopropyl moiety, conditions close to those reported for the cross-coupling of aryl chlorides[12] were enforced (entry 5, Table 1). To our delight, the use of tri(*tert*-butyl)phosphine turned out to be highly beneficial, leading to a 66% of conversion after

only 20 min. Unfortunately, longer reaction time induced a significantly higher level of competititive decomposition. Several bases were then assessed (entries 8-10, Table 1) and potassium carbonate turned out to give the best results. Indeed, tertiary amine bases showed prone to partially induce the undesired isomerization of C=C bond (entries 8 and 10, Table 1). *N,N*-dimethylformamide and *N,N*-dimethylacetamide gave similar results (entries 5-6, Table 1) but acetonitrile reduced conversion (entry 7, Table 1). Finally, sources of Pd(II) were tested with tri-*tert*butylphosphine (entries 11-12, Table 1) and, pleasingly, complete conversion was achieved starting with $Pd(OAc)_2$. With these optimized conditions, the desired thiochromene **2a** was isolated in 70% yield. Surprisingly, all trials to give higher yields failed, even when the crude NMR of the reaction mixture was very clean. This behavior was attributed to the air sensitivity of the **2a** during the purification process. Indeed, after 24 h at room temperature, the ^{1}H NMR spectrum unmistakably showed a prominent level of product decomposition.

Table 1. Optimization of the reaction conditions.



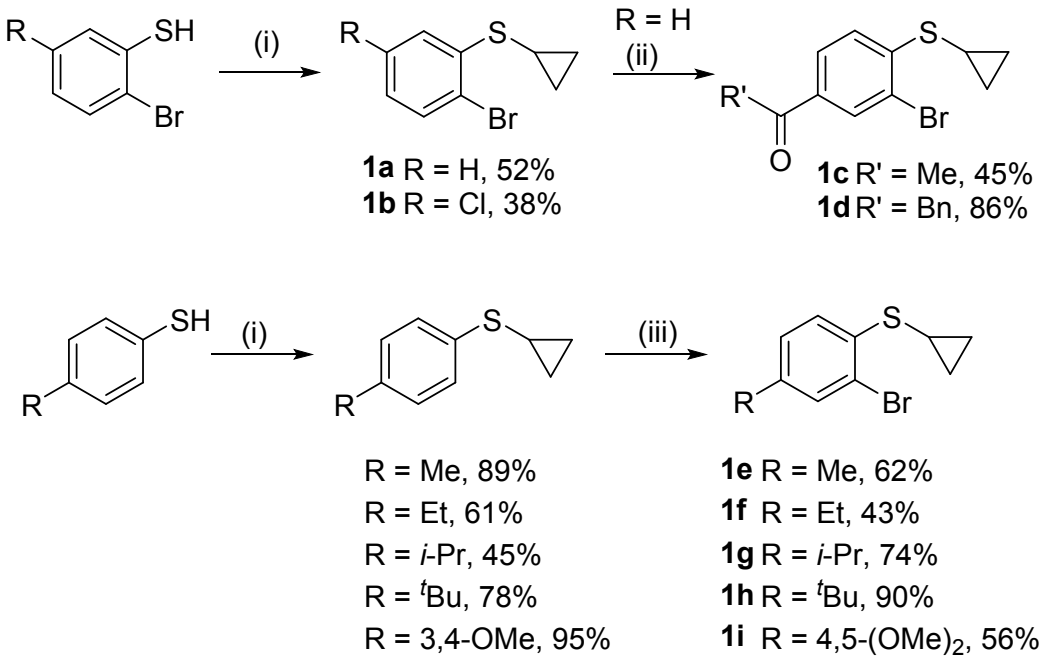
Entry	Cat.	Ligand	Base	Conversion[a] (isolated yields %)
1	$PdCl_2(PPh_3)_2$	-	Cs_2CO_3	0%[b]
2	$Pd_2(dba)_3$	PPh_3	K_2CO_3	4%
3	$Pd_2(dba)_3$	P(*o*-tol)$_3$	K_2CO_3	14%
4	$Pd_2(dba)_3$	dppf	K_2CO_3	0%
5	$Pd_2(dba)_3$	P(^{t}Bu)$_3$.HBF_4	K_2CO_3	66%
6	$Pd_2(dba)_3$	P(^{t}Bu)$_3$.HBF_4	K_2CO_3	68%[c]
7	$Pd_2(dba)_3$	P(^{t}Bu)$_3$.HBF_4	K_2CO_3	<5%[d]
8	$Pd_2(dba)_3$	P(^{t}Bu)$_3$.HBF_4		60%[e]

9	$Pd_2(dba)_3$	$P(^tBu)_3.HBF_4$	TMEDA	46%
10	$Pd_2(dba)_3$	$P(^tBu)_3.HBF_4$	$^iPr_2NEt$	66%[f]
11	$PdCl_2$	$P(^tBu)_3.HBF_4$	K_2CO_3	6%
12	$Pd(OAc)_2$	$P(^tBu)_3.HBF_4$	K_2CO_3	100% (70%)[g]

[a] Evaluated by ^1H NMR. [b] performed in MeCN at 130 °C. [c] performed in DMA instead of DMF. [d] performed in MeCN. [e] Product obtained as a 1:1 mixture of two regiomers. [f] Product obtained as a 2:1 mixture of two regioisomers. [g] Yields did not exceed 20% when performed under thermic conditions (oil bath).

In order to assess the scope of this new Pd-catalyzed ring-opening of cyclopropyl thioethers, a wider set of starting materials were prepared. They were synthesized by either direct alkylation of *o*-bromothiophenol derivatives with bromo cyclopropane[10] or bromination of the corresponding cyclopropane arylthioether[13] (Scheme 2). After

electrophilic aromatic acylation of products **1c** and **1d**, substrates **1b** an **1e-i** were thereby obtained.

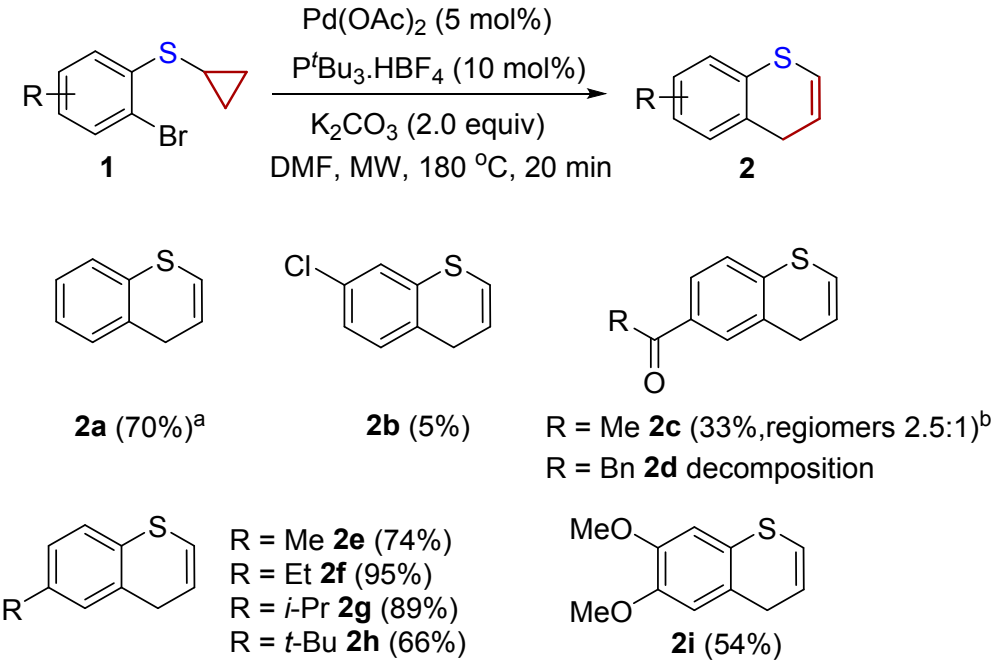


Conditions: (i) bromocyclopropane (1.3 equiv), K_2CO_3 (1.5 equiv), DMF, 24h (ii) R'COCl (5 equiv), $AlCl_3$ (1.2 equiv), $CHCl_3$, 0 ^oC to rt, 3h. (iii) Br_2 (1.6 equiv), $CHCl_3$, 0 ^oC to rt, 6h.

Scheme 2. Starting material syntheses.

With the set of optimized conditions in hand, we investigated the scope and limitations of the Pd-catalyzed reaction (scheme 3). Electron-poor starting materials afforded the

corresponding thiochromenes in low yields due to fast decomposition of the crude mixture. Indeed, compounds **2b** and **2c** gave very low isolated yields of the corresponding thiochromenes and **2d** -obtained from **1d**- decomposed under the reaction conditions. The presence of an acyl group in **2c** provoked the isomerization of the double bond in the final product probably due to enhanced conjugation of the resulting regiomer. However, for electron-rich arylthioethers, the desired thiochromenes **2e-2i** were obtained in fair to good yields. Moreover, the reaction can be performed on the gram scale and **2a** was isolated with a slightly reduced 55% yield.



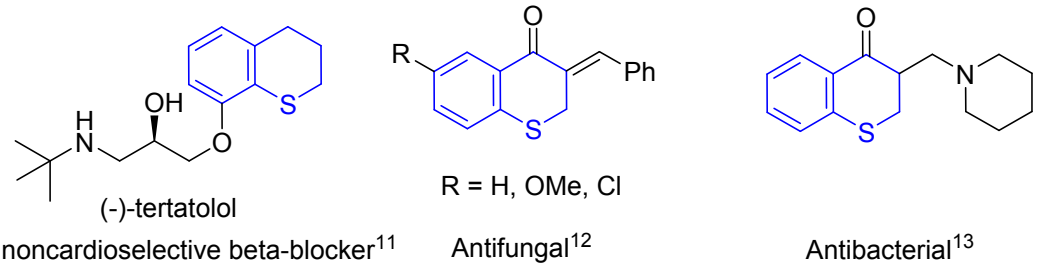
[a] 55% for gram scale of starting material

[b] The minor regiomer is the one with the C=C bond conjugated with the aromatic core

Scheme 3. Scope of the reaction.

To the best of our knowledge, this reaction constitutes the first example of metal triggered ring-opening of non-substituted cyclopropyl thioethers. The reaction turned out to be less general than those relying on oxygen- or nitrogen-based derivatives. However, this method provides an unparalleled and straightforward access to thiochromenes, structures that have been narrowly reported in the literature so far and for which scarce synthetic routes have been described.[14] Worthy of note, thiochromenes are direct precursors of thiochromane derivatives, many of which possess interesting biological

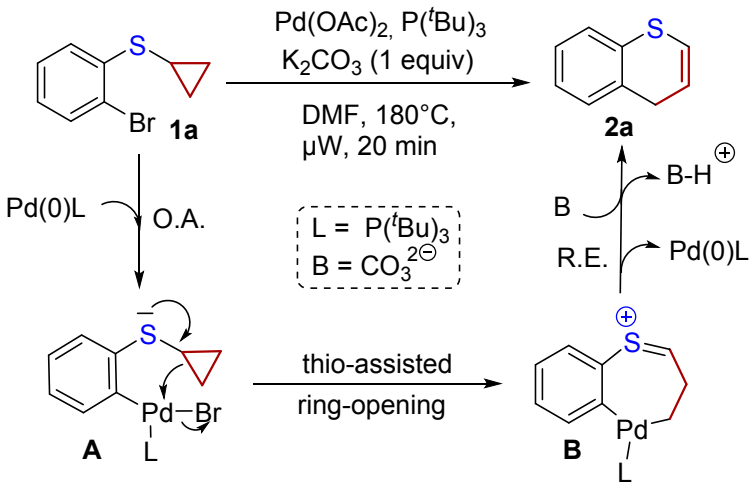
properties encompassing anti-hypertensive ((-)-tertatolol), antibacterial and antifungal activities (Scheme 4).[15-17]



Scheme 4. Thiochromanes with biological activities.

Finally, by analogy to our previous work and related studies,[8] we propose the following mechanistic scenario (Scheme 5). Upon oxidative addition of the starting arylbromide **1a** onto an *in situ* generated monoligated Pd(0) complex, the resulting aryl-Pd(II) intermediate **A** would then evolve through an intramolecular ring-enlargement process, which would likely be assisted by the nucleophilic character of the neighbouring sulfur atom. This key event would induce the formation of the 7-membered palladacycle **B** which, upon reductive elimination and carbonate-promoted proton abstraction, would

allow the formation of the thiochromene **2a**. While we previsouly demonstrated that the palladium-catalyzed ring opening of aminocyclopropyl derivatives is rather facile as compared to that of the cyclopropyl thioethers,[8(b)] we suggest that, in the latter case, the oxidative addition onto Pd(0) is rather a sluggish step. Indeed, as often observed in the case of reluctant oxidative additions, the very electron-rich phosphine ligand $P(^tBu)_3$ is compulsory for obtaining satisfactory results. Hence, the presence of the sulfur atom in ortho position of the bromine atom probably increases the electron density of the aromatic ring to such an extent that the oxidative addition is dramatically hampered. On the other hand, the necessity of using an electron rich phosphine ligand such as $P(^tBu)_3$ may decrease the electrophilic character of the palladium center in intermediate **A** and, consequently, might render the rearrangement process more difficult. Further mechanistic studies are ongoing and will be reported in due course.



Scheme 5. Mechanistic proposal.

Conclusions

To conclude, we have reported here the first Pd-catalyzed ring opening of thiocyclopropanes. The ability of sulfur to act as ligand for transition metals and potentially disturb the ring opening process was among some of the questions raised by the project. The moderate yield and lower scope of the fragmentation of thiocyclopropanes compared to the related nitrogen derivatives may be related to such interactions. Anyhow our results shed the light on an unusual fragmentation process that could find further applications using either palladium for the formation of monocyclic thioheterocycles or even other transition metals. Further directions involving competing CH activations of

thiocyclopropanes as observed for amino analogues might be also interesting to follow.[8a,8c,18]

Experimental Section

All reactions were performed under argon atmosphere. Solvents were distilled or purified with a purification system using activated alumina columns before use. All products were purified by flash chromatography using silica gel (230-400 mesh). ^{1}H-NMR and ^{13}C-NMR were recorded in $CDCl_3$ with chemical shifts reported for ^{1}H NMR relative to residual $CHCl_3$ peak (7.26 ppm). For ^{13}C NMR, chemical shifts were reported relative to the central peak of $CDCl_3$ (77.16 ppm). HRMS data for new compounds were obtained electrospray ionization method coupled to a LTQ-Orbitrap high resolution detector in positive mode. All microwave reactions were carried out using Anton Paar Microwave Synthesis Reactor (Monowave 300). Unless otherwise noted, all the reagents were ordered and used without further purification.

General procedure for the alkylation reaction:[10] To a stirred solution of substituted thiophenol (1.0 mmol) and K_2CO_3 (1.50 equiv) in dry DMF (2 mL) under argon atmosphere

was added bromocyclopropane (1.3 equiv). The mixture was heated at 120 ^{o}C for 24 h and then cooled to room temperature. After TLC shows complete conversion of thiols the crude reaction mixture was diluted with methyl *tert*-butyl ether, excess K_2CO_3 was removed by filtration and washed with saturated Na_2CO_3 solution (3 x 5 mL). After separation of organic layer the aqueous phase was then extracted with methyl *tert*-butyl ether (2 x 20 mL) and the combined organic extracts washed by water (5 x 40 mL) and brine (40 mL) before being dried over $MgSO_4$. After filtration and evaporation of the solvents under reduced pressure, the crude material was purified by flash column chromatography on silica gel to afford the desired cyclopropyl(phenyl)sulfane derivative **1**.

General procedure for bromination reaction:[13] Under argon atmosphere cyclopropyl(phenyl)sulfane derivative (1.0 mmol) was dissolved in 2 mL $CHCl_3$ and stirred at 0 ^{o}C for 10 minutes. To this ice cold solution, Br_2 (1.6 equiv) was added dropwise and after addition the reaction mixture was stirred at room temperature for further 6 h. After TLC showed complete conversion of cyclopropyl(phenyl)sulfane derivative, the crude reaction mixture was quenched with saturated $Na_2S_2O_3$ solution (10 mL) and diluted with

CH_2Cl_2 (15 mL). After separation of organic layer the aqueous phase was then extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts washed by water (40 mL) and brine (40 mL) before being dried over $MgSO_4$. After filtration and evaporation of the solvents under reduced pressure, the crude material was purified by flash column chromatography on silica gel to afford the desired brominated product **1**.

General procedure for acylation reaction: In an oven dried flask under argon atmosphere were sequentially introduced $AlCl_3$ (1.2 equiv), acyl chloride (5.0 equiv), 2 mL $CHCl_3$ and stirred at 0 °C for 15 minutes. To this ice cold solution (2-bromophenyl)(cyclopropyl)sulfane (1.0 mmol) was added dropwise and after addition the reaction mixture was stirred at room temperature for further 3 h. After TLC shows complete conversion of (2-bromophenyl)(cyclopropyl)sulfane derivative, the crude reaction mixture was quenched with ice water (5 mL) and neutralized by HCl until pH = 2. The whole mixture was diluted with CH_2Cl_2 (10 mL) and after separation of organic layer the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts washed by water (40 mL) and brine (40 mL) before being dried over $MgSO_4$. After filtration and evaporation of the solvents under reduced pressure, the crude material

was purified by flash column chromatography on silica gel to afford the desired acylated product.

(2-Bromophenyl)(cyclopropyl)sulfane (1a): Starting from 2-bromothiophenol (189 mg, 118 µL, 1.0 mmol) and bromocyclopropane (157 mg, 104 µL, 1.3 mmol) and following the general procedure of cyclopropanation reaction, the desired (2-bromophenyl)(cyclopropyl)sulfane **1a** was obtained as a colorless oil (120 mg, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.48 (m, 2H), 7.30 (td, J = 7.8, 1.2 Hz, 1H), 7.00 (td, J = 7.7, 1.5 Hz, 1H), 2.14 (tt, J = 7.4, 4.4 Hz, 1H), 1.14 (td, J = 6.6, 4.9 Hz, 2H), 0.78-0.69 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 132.6, 127.7, 126.4, 125.7, 120.7, 11.9, 8.5; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for C_9H_9BrS 227.9608, found: 227.9609.

(2-Bromo-5-chlorophenyl)(cyclopropyl)sulfane (1b): Starting from 2-bromo-5-chlorobenzenethiol (223.5 mg, 1.0 mmol) and bromocyclopropane (157 mg, 104 µL, 1.3 mmol) and following the general procedure of cyclopropanation reaction, the desired (2-bromo-5-chlorophenyl)(cyclopropyl)sulfane **1b** was obtained as colorless oil (100 mg, 38% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.4 Hz,

1H), 6.97 (dd, J = 8.4, 2.4 Hz, 1H), 2.18-2.06 (m, 1H), 1.24-1.13 (m, 2H), 0.80-0.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 134.0, 133.5, 125.9, 125.8, 118.3, 11.9, 8.6; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for C_9H_8BrClS 261.9219, found: 261.9218.

1-(3-Bromo-4-(cyclopropylthio)phenyl)ethanone (1c): Starting from acetyl chloride (392 mg, 355 µL, 5.0 mmol) and following the general procedure of acylation reaction, the desired 1-(3-bromo-4-(cyclopropylthio)phenyl)ethanone **1c** was obtained as grey colored crystalline solid (121 mg, 45% yield), mp 66-68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 1.8 Hz, 1H), 7.87 (dd, J = 8.3, 1.8 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 2.56 (s, 3H), 2.15 (tt, J = 7.4, 4.4 Hz, 1H), 1.24-1.15 (m, 2H), 0.81-0.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 147.8, 134.7, 132.4, 127.4, 125.6, 120.3, 26.5, 11.8, 8.6; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{11}H_{11}BrOS$ 269.9714, found: 269.9715.

1-(3-Bromo-4-(cyclopropylthio)phenyl)-2-phenylethanone (1d): Starting from phenylacetyl chloride (773 mg, 622 µL, 5.0 mmol) and following the general procedure of acylation reaction, the desired 1-(3-bromo-4-(cyclopropylthio)phenyl)-2-phenylethanone **1d** was obtained as a grey colored crystalline solid (298 mg, 86% yield), mp 92-94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 1.8 Hz, 1H), 7.91 (dd, J = 8.3, 1.8 Hz, 1H), 7.59 (d,

J = 8.3 Hz, 1H), 7.39-7.19 (m, 5H), 4.21 (s, 2H), 2.22-2.05 (m, 1H), 1.23-1.13 (m, 2H), 0.80-0.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 148.0, 134.4, 134.1, 132.7, 129.5, 128.9, 127.8, 127.1, 125.6, 120.4, 45.5, 11.8, 8.6; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{17}H_{15}BrOS$ 346.0027, found: 346.0018.

(2-Bromo-4-methylphenyl)(cyclopropyl)sulfane (1e): Starting from 4-methylthiophenol (500 mg, 4.03 mmol) and following the general procedure of cyclopropanation reaction, the desired cyclopropyl(*p*-tolyl)sulfane was obtained as colorless oil (590 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 2.33 (s, 3H), 2.20 (tt, J = 7.4, 4.4 Hz, 1H), 1.09-0.99 (m, 2H), 0.76-0.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 129.6, 127.4, 21.0, 12.8, 8.6; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{10}H_{12}BrS$ 164.0660, found: 164.0660. Starting from cyclopropyl(*p*-tolyl)sulfane (490 mg, 2.98 mmol) and following the general procedure of bromination reaction, the desired (2-bromo-4-methylphenyl)(cyclopropyl)sulfane **1e** was obtained as colorless oil (453 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 1.0 Hz, 1H), 7.11 (ddd, J = 8.0, 1.8, 0.7 Hz, 1H), 2.30 (s, 3H), 2.14 (tt, J = 7.4, 4.4 Hz, 1H), 1.17-1.05 (m, 2H), 0.79-0.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 136.1, 133.2, 128.7,

126.7, 120.9, 20.6, 12.2, 8.5; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{10}H_{11}BrS$ 241.9765, found: 241.9759.

(2-Bromo-4-ethylphenyl)(cyclopropyl)sulfane (1f): Starting from 4-ethylthiophenol (1.00 g, 7.20 mmol) and following the general procedure of cyclopropanation reaction, the desired cyclopropyl(4-ethylphenyl)sulfane was obtained as colorless oil (785 mg, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 2.64 (q, J = 7.6 Hz, 2H), 2.20 (tt, J = 7.4, 4.4 Hz, 1H), 1.25 (t, J = 7.6 Hz, 3H), 1.10-1.00 (m, 2H), 0.75-0.66 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 135.2, 128.3, 127.1, 28.3, 15.6, 12.5, 8.5 ; HRMS (APPI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{11}H_{14}S$: 178.0816, found:178.0813. Starting from cyclopropyl(4-ethylphenyl)sulfane (763 mg, 4.30 mmol) and following the general procedure of bromination reaction, the desired (2-bromo-4-ethylphenyl)(cyclopropyl)sulfane **1f** was obtained as colorless oil (471 mg, 43% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 1H), 7.37 (d, 1.8 Hz, 1H), 7.14 (dd, J = 8.0, 1.8 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 2.19-2.09 (m, 1H), 1.22 (t, J = 7.6 Hz, 3H), 1.16-1.07 (m, 2H), 0.78-0.69 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 136.8, 131.9, 127.3,

126.5, 120.7, 27.9, 15.4, 11.9, 8.4 ; HRMS (APPI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{11}H_{13}BrS$: 255.9921, found : 255.9922.

(2-Bromo-4-*iso*propylphenyl)(cyclopropyl)sulfane (1g): Starting from 4-*iso*propylthiophenol (1.00 g, 6.60 mmol) and following the general procedure of cyclopropanation reaction, the desired cyclopropyl(4-*iso*propylphenyl)sulfane was obtained as colorless oil (565 mg, 45% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 2.90 (hept, J = 6.9 Hz, 1H), 2.21 (tt, J = 7.4, 4.4 Hz, 1H), 1.27 (d, J = 6.9 Hz, 6H), 1.10-1.01 (m, 2H), 0.76-0.68 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 135.3, 127.0, 126.8, 33.6, 24.0, 12.4, 8.4 ; HRMS (APPI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{12}H_{16}S$: 192.0973, found: 192.0971. Starting from cyclopropyl(4-*iso*propylphenyl)sulfane (487 mg, 2.50 mmol) and following the general procedure of bromination reaction, the desired (2-bromo-4- *iso*propylphenyl)(cyclopropyl)sulfane **1g** was obtained as colorless oil (507 mg, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 1.9, 1H), 7.17 (dd, J = 8.1, 1.9 Hz, 1H), 2.85 (hept, J = 6.9 Hz, 1H), 2.17-2.10 (m, 1H), 1.23 (d, J = 6.9 Hz, 6H), 1.16-1.07 (m, 2H), 0.77-0.69 (m,

2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 136.9, 130.6, 126.5, 125.9, 120.7, 33.4, 23.8, 11.9, 8.4 ; HRMS (APPI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{12}H_{15}BrS$: 270.0078, found: 270.0082.

(2-Bromo-4-*tert*-butylphenyl)(cyclopropyl)sulfane (1h): Starting from 4-*tert*-butylbenzenethiol (1.34 mL, 8.0 mmol) and following the general procedure of cyclopropanation reaction, the desired (4-*tert*-butylphenyl)(cyclopropyl)sulfane was obtained as colorless oil (1.28 g, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 4H), 2.19 (tt, *J* = 7.4, 4.4 Hz, 1H), 1.32 (s, 9H), 1.10-1.00 (m, 2H), 0.74-0.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 135.3, 126.9, 125.9, 34.5, 31.5, 27.1, 12.6, 8.6; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{13}H_{18}S$ 206.1129, found: 206.1124. Starting from (4-*tert*-butylphenyl)(cyclopropyl)sulfane (400 mg, 1.94 mmol) and following the general procedure of bromination reaction, the desired (2-bromo-4-*tert*-butylphenyl)(cyclopropyl)sulfane **1h** was obtained as colorless oil (496 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.2 Hz, 1H), 7.51 (dd, *J* = 8.2 Hz, 1H), 7.34 (dd, *J* = 8.2, 2.2 Hz, 1H), 2.14 (tt, *J* = 7.4, 4.4 Hz, 1H), 1.31 (s, 9H), 1.17-1.08 (m, 2H), 0.78-0.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 136.9, 129.8, 126.4, 125.0, 120.8, 34.5,

31.4, 31.3, 12.1, 8.5; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{13}H_{17}BrS$ 284.0234, found: 284.0228.

(2-Bromo-4,5-dimethoxyphenyl)(cyclopropyl)sulfane (1i): Starting from 3,4-dimethoxybenzenethiol (170 mg, 145 µL, 1.0 mmol) and following the general procedure of cyclopropanation reaction, the desired cyclopropyl(3,4-dimethoxyphenyl)sulfane was obtained as slightly grey colored crystalline solid (200 mg, 95% yield), mp 82-84 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01-6.90 (m, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.19 (tt, *J* = 7.4, 4.4 Hz, 1H), 1.00 (td, *J* = 6.5, 4.8 Hz, 2H), 0.73-0.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 147.8, 129.5, 120.9, 112.3, 112.0, 56.2, 56.0, 13.9, 8.6; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{11}H_{14}O_2S$ 210.0715, found: 210.0705. Starting from cyclopropyl(3,4-dimethoxyphenyl)sulfane (200 mg, 0.95 mmol) and following the general procedure of bromination reaction, the desired (2-bromo-4,5-dimethoxyphenyl)(cyclopropyl)sulfane **1i** was obtained as white colored amorphous solid (496 mg, 56% yield), mp 93-95 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 1H), 7.02 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.19 (tt, *J* = 7.4, 4.4 Hz, 1H), 1.14-1.04 (m, 2H), 0.81-0.68

(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 147.8, 130.7, 116.2, 112.4, 111.7, 56.4, 56.3, 13.1, 8.6; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{11}H_{13}BrO_2S$ 287.9820, found: 287.9826.

General procedure for Pd-catalyzed cyclopropane ring opening reaction (2): In an oven dried microwave glass vial reactor under argon atmosphere sequentially introduced substituted (2-bromophenyl)(cyclopropyl)sulfane **1** (1.0 mmol), DMF (2 mL) and degassed with argon for 20 minutes. To this reaction mixture $Pd(OAc)_2$ (0.05 equiv), $P^tBu_3.HBF_4$ (0.1 equiv), K_2CO_3 (2 equiv) were carefully introduced. The whole reaction mixture was heated under microwave irradiation at 180 °C for 20 minutes. After TLC shows complete conversion of (2-bromophenyl)(cyclopropyl)sulfane derivative the crude reaction mixture was diluted with Et_2O (10 mL) and H_2O (10 mL). After separation of organic layer the aqueous phase was further extracted with Et_2O (2 x 20 mL) and the combined organic extracts washed by water (5 x 40 mL) and brine (40 mL) before being dried over $MgSO_4$. After filtration and evaporation of the solvents under reduced pressure, the crude material was purified by flash column chromatography on silica gel to afford the desired thiopyran derivative **2**.

4*H*-Thiochromene (2a): Starting from (2-bromophenyl)(cyclopropyl)sulfane **1a** (100 mg, 0.436 mmol), $Pd(OAc)_2$ (4.9 mg, 0.021 mmol), $P^tBu_3.HBF_4$ (12.6 mg, 0.044 mmol), K_2CO_3 (121 mg, 0.872 mmol) and following the general procedure of cyclopropane ring opening reaction, the desired 4*H*-thiochromene **2a** was obtained as colorless oil (45 mg, 70% yield). The same reaction performed using 1g of **1a**, $Pd(OAc)_2$ (49 mg, 0.22 mmol) and $P^tBu_3.HBF_4$ (128 mg, 0.44 mmol), K_2CO_3 (1.20g, 8.72 mmol) to give 356 mg of **2a** (55%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.20-7.16 (m, 1H), 7.11-7.00 (m, 3H), 6.32 (dt, *J* = 9.1, 1.1 Hz, 1H), 5.95 (dt, *J* = 9.1, 4.7 Hz, 1H), 3.30 (d, *J* = 4.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.6, 132.2, 128.7, 126.7, 126.6, 126.5, 122.4, 120.9, 31.7; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for C_9H_8S 148.0347, found: 148.0332.

7-Chloro-4*H*-thiochromene (2b): Starting from (2-bromo-5-chlorophenyl)(cyclopropyl)sulfane **1b** (150 mg, 0.57 mmol), $Pd(OAc)_2$ (12.8 mg, 0.057 mmol), $P^tBu_3.HBF_4$ (33.0 mg, 0.114 mmol), K_2CO_3 (157 mg, 1.14 mmol) and following the general procedure of cyclopropane ring opening reaction for 1 h, the desired 7-chloro-4*H*-thiochromene **2b** was obtained as colorless oil (5 mg, 5% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.44 (d, *J* = 9.8

Hz, 1H), 5.94 (dt, *J* = 9.8, 5.0 Hz, 1H), 3.45 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.7, 133.3, 130.7, 129.1, 128.5, 126.9, 125.8, 122.0, 25.1; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for C_9H_7ClS 181.9957, found: 181.9952.

6-Methyl-4*H*-thiochromene (**2e**): Starting from (2-bromo-4-methylphenyl)(cyclopropyl)sulfane **1e** (120 mg, 0.493 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $P^tBu_3.HBF_4$ (14.3 mg, 0.049 mmol), K_2CO_3 (136 mg, 0.986 mmol) and following the general procedure of cyclopropane ring opening reaction, the desired 6-methyl-4*H*-thiochromene **2e** was obtained as colorless oil (59 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.9 Hz, 1H), 6.91-6.83 (m, 2H), 6.31 (dd, *J* = 9.0, 1.0 Hz, 1H), 5.95-5.90 (m, 1H), 3.25 (d, *J* = 4.5 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 132.5, 129.4, 128.7, 127.3, 126.4, 122.3, 121.0, 31.6, 21.0; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{10}H_{10}S$ 162.0503, found: 162.0497.

6-Ethyl-4*H*-thiochromene (**2f**): Starting from (2-bromo-4-ethylphenyl)(cyclopropyl)sulfane **1f** (202 mg, 0.79 mmol), $Pd(OAc)_2$ (8.8 mg, 0.039 mmol), $P^tBu_3.HBF_4$ (22.9 mg, 0.079 mmol), K_2CO_3 (217 mg, 1.57 mmol) and following the general procedure of cyclopropane ring opening reaction, the desired 6-ethyl-4*H*-thiochromene **2f**

was obtained as colorless oil (133 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 7.9 Hz, 1H), 7.02 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.99 (s, 1H), 6.42 (dt, *J* = 9.1, 1.1 Hz, 1H), 6.04 (dt, *J* = 9.1, 4.7 Hz, 1H), 3.38 (d, *J* = 4.7 Hz, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 132.4, 128.8, 128.1, 126.3, 126.0, 122.1, 120.9, 31.6, 28.3, 15.6 ; HRMS (APPI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{11}H_{12}S$: 176.0660, found: 176.0661.

6-Isopropyl-4*H*-thiochromene (**2g**): Starting from (2-bromo-4-isopropylphenyl)(cyclopropyl)sulfane **1g** (205 mg, 0.76 mmol), $Pd(OAc)_2$ (8.5 mg, 0.038 mmol), $P^tBu_3.HBF_4$ (22.0 mg, 0.076 mmol), K_2CO_3 (209 mg, 1.51 mmol) and following the general procedure of cyclopropane ring opening reaction, the desired 6-isopropyl-4*H*-thiochromene **2g** was obtained as colorless oil (130 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.99 (d, *J* = 1.5 Hz, 1H), 6.40 (dt, *J* = 9.1, 1.1 Hz, 1H), 6.03 (dt, *J* = 9.1, 4.7 Hz, 1H), 3.37 (d, *J* = 4.7 Hz, 2H), 2.87 (hept, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 132.3, 128.9, 126.7, 126.3, 124.6, 122.2, 120.9, 33.7, 31.7, 24.0 ; HRMS (APPI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{12}H_{14}S$: 190.0816, found:190.0824.

6-*tert*-Butyl-4*H*-thiochromene (**2h**): Starting from (2-bromo-4-*tert*-butylphenyl)(cyclopropyl)sulfane **1h** (200 mg, 0.70 mmol), $Pd(OAc)_2$ (7.9 mg, 0.035 mmol), $P^tBu_3.HBF_4$ (20.0 mg, 0.070 mmol), K_2CO_3 (194 mg, 1.40 mmol) and following the general procedure of cyclopropane ring opening reaction, the desired 6-*tert*-butyl-4*H*-thiochromene **2h** was obtained as colorless oil (95 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 2H), 7.21 (s, 1H), 6.47 (d, J = 8.9 Hz, 1H), 6.10 (dt, J = 8.9, 4.8 Hz, 1H), 3.45 (d, J = 4.8 Hz, 2H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 132.1, 128.8, 126.2, 125.7, 123.7, 122.3, 121.0, 34.5, 32.0, 31.5; HRMS (ESI) *m*/*z*: $[M]^{+\bullet}$ calcd for $C_{13}H_{16}S$ 204.0973, found: 204.0974.

6,7-Dimethoxy-4*H*-thiochromene (**2i**): Starting from (2-bromo-4,5-dimethoxyphenyl)(cyclopropyl)sulfane **1i** (231 mg, 0.80 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), $P^tBu_3.HBF_4$ (23.0 mg, 0.08 mmol), K_2CO_3 (220 mg, 1.60 mmol) and following the general procedure of cyclopropane ring opening reaction, the desired 6,7-dimethoxy-4*H*-thiochromene **2i** was obtained as colorless oil (90 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.61 (s, 1H), 6.38 (d, J = 9.1 Hz, 1H), 5.99 (dt, J = 9.1, 4.6 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.34 (d, J = 4.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1,

147.8, 124.2, 122.4, 121.9, 120.6, 111.9, 109.5, 56.1, 31.1; HRMS (ESI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{11}H_{12}O_2S$ 208.0558, found: 208.0560.

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds included.

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