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Cu(II)-Promoted Transformations of α-Thienylcarbinols into Spirothienooxindoles: Regioselective Halogenation of Dienyl Sulfethers Containing Electron-Rich Aryl Rings

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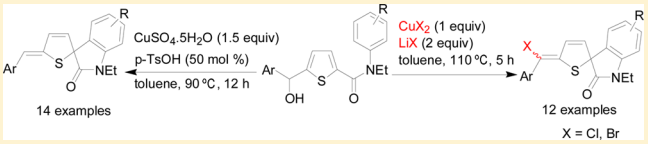
Supporting Information

ABSTRACT: Under the promotion of Cu(II) salts, the α-thienylcarbinols with an *N*-phenyl carbonyl group at the other α-position are converted into three different ranges of spirothienooxindoles involving dearomatizing Friedel–Crafts reaction. In addition, the unprecedented regioselective CuX_2-mediated C–H functionalization/halogenation of dienyl sulfether containing electron-rich aryl rings is presented.



The heterocyclic spirooxindoles **1** (Figure 1) with diverse B ring, of synthetic or natural origin, are a class of important

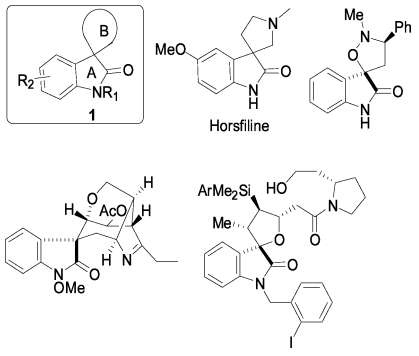
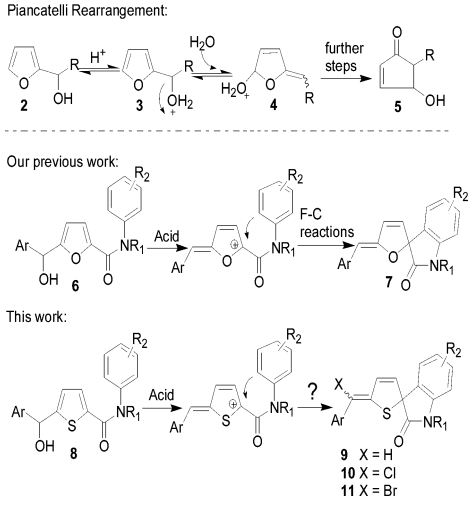


Figure 1. Bioactive spirooxindoles with variable B-rings.

compounds.[1] Spirooxindoles **1** have been identified as potent MDM2-inhibitors,[2] adjuvants of the actin polymerization inhibitor latrunculin B,[3] antimalarial agent,[4] inhibitors of lung adenocarcinoma (A549) cells and hepatocellular carcinoma (HepG2) cells,[5] and so on.[6] Presently, spirooxindoles known as "privileged structure" in synthetic and medicinal chemistry have emerged as attractive synthetic targets. Thus, a variety of strategies have been developed for them, mostly employing indoles or isatin as the starting material. These strategies include cycloadditions,[7] addition–cyclizations,[8] oxidative rearrangements,[9] intramolecular Heck reaction,[10] and others.[11] It is still highly desirable to develop alternative methods using simple materials that allow the introduction of heteroatom at the B-ring efficiently.

Piancatelli[12] once reported an acid-catalyzed rearrangement of certain α-furylcarbinols into 4-hydroxycyclopentenone derivatives (Scheme 1). This rearrangement involved protonation of the hydroxyl group, formation of carbocation **3**, a nucleophilic attacking on the other α-position of furan ring

Scheme 1. Synthesis of Spirooxindoles by Piancatelli Rearrangement



forming enol ethers and further steps. Recently, we and other groups have investigated this reaction from an intramolecular persepective[13] and used an electron-rich phenyl ring as the nucleophile (Friedel–Crafts reaction), which result in an access to structurally new spirofurooxindoles **7**.[14] In order to deliver a comprehensive library of heterocyclic spirooxindoles with the structural diversity of the B-ring, our aim is to replace the furan ring of **6** by other five-membered aromatic rings. In this article, we would like to employ α-thienylcarbinols **8** as the substrates and report their acid-catalyzed transformation into unprecedented sulfether-containing spirooxindoles. To the best of our knowledge, such type of Friedel–Crafts reaction using

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thiocarbenium adjacent to an electron-withdrawing carbonyl group as an alkylation agent has never been reported.

At the outset, the precursor **8** was prepared from 2-benzylthiophene **12** over five successive steps including the simple Vilsmeier−Haack reaction, simultaneous oxidation of the methylene and aldehyde group, acid chloride preparation, amidation, and reduction (Scheme 2). To optimize the reaction conditions for cyclization, **8aa** was used as the substrate under the influence of various acids. As demonstrated in Table 1, the strong Lewis acids such as $SnCl_4$ and $BF_3{\cdot}Et_2O$ were not suitable for this conversion and led to complicated reaction mixture (entries 1 and 2). Weaker Lewis acids $Dy(OTf)_3$, $CuSO_4{\cdot}5H_2O$, and $FeCl_3{\cdot}6H_2O$ were also proven to be ineffective (entries 3−5). In addition to Lewis acids, a series of Bronsted acids such as AcOH, CF_3COOH, CSA, and *p*-TsOH were also screened. Among them, *p*-TsOH gave the best yield (40%) (entries 6−9). Gratifyingly, a combination of $CuSO_4{\cdot}5H_2O$ (1.5 equiv)/*p*-TsOH (0.5 equiv) afforded **9aa** in 68% yield (entry 11). Further studies on solvent variation and increasing the reaction temperature to 110 °C resulted in lower yields (entries 12−14).

With the optimized reaction conditions in hand, various α-thienylcarbinol **8** with different Ar and R groups were tested to investigate the reaction scope. As shown in Table 2, with the exception of **8bd** and **8be,** all the α-thienylcarbinol amides **8** were cyclized to the corresponding spirothienooxindoles **9** in moderate to good yields. The failure of **9bd** and **9be** might result from lower electron density of their *N*-phenyl rings (entries 7 and 8). Generally the *N*-phenyl ring of higher electron density gave rise to a higher yield (entry 1 > entry 2 > entry 3).

In order to increase the molecular diversity of spirooxindoles, we aimed at the modification of the dienyl sulfether segment of **9**. The selective introduction of the halogen atom into the two double bonds of **9** is very interesting both from the points of view of medicinal chemistry and synthetic chemistry, since the halogen atom can increase the lipophilicity of the molecules and vinyl halides are common substrates for many coupling reactions. Recently, transition-metal-mediated Aryl C−H functionalization/halogenation has attracted much attention.[15] However, to the best of our knowledge, there have been no related reports for the dienyl sulfether.

The selective halogenation of **9** is exceedingly challenging because of its multiple halogenable reactive cites including four olefinic carbons and two electron-rich phenyl rings. To test the possibility, **9aa** was treated with $CuCl_2$ (1 equiv) in AcOH at 110 °C for 5 h. Unfortunately, the reaction system was extremely complicated, and simultaneous chlorination of *N*-Ar ring and the 1-position of dienyl sulfether was observed. The situation did not improve when the solvent was changed to acetonitrile or DCE. We were delighted to observe that when the nonpolar solvent of toluene was used, chlorination occurred exclusively at the 1-position of dienyl sulfether, resulting in chlorinated spirothienooxindoles **10aa** in 35% yield. The addition of LiCl (2 equiv) improved the yield to 68% (Scheme 3). The product **10aa** was formed as a mixture of *Z*/*E* isomers (*Z*/*E* = 1:2), and the stereochemistry of product **10aa** was

Scheme 2. Synthesis of the Precursor 8 for Cyclization

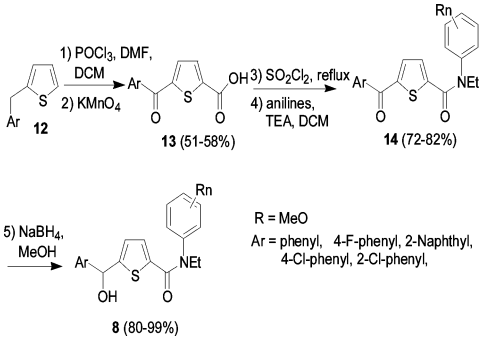
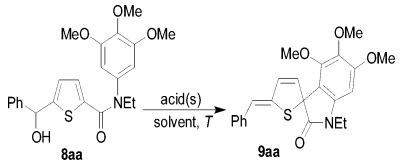


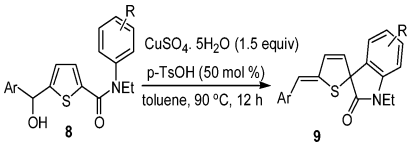
Table 1. Optimization of the Reaction Conditions[a,b]



entry	acid(s)	solvent	*T* (°C)	yield (%)[c]
1	$SnCl_4$[d]	DCM	−78	ND[f]
2	$BF_3{\cdot}Et_2O$[d]	DCM	−78	ND
3	$Dy(OTf)_3$[e]	toluene	90	trace
4	$CuSO_4{\cdot}5H_2O$[e]	toluene	90	ND
5	$FeCl_3{\cdot}6H_2O$[e]	toluene	90	ND
6	AcOH[e]	toluene	90	NR[g]
7	CF_3COOH[e]	toluene	90	35
8	CSA[e]	toluene	90	trace
9	*p*-TsOH[e]	toluene	90	40
10	$CuSO_4{\cdot}5H_2O$[e]/AcOH[d]	toluene	90	0
11	$CuSO_4{\cdot}5H_2O$[e]/*p*-TsOH[d]	toluene	90	68
12	$CuSO_4{\cdot}5H_2O$[e]/*p*-TsOH[d]	DCE	90	20
13	$CuSO_4{\cdot}5H_2O$[e]/*p*-TsOH[d]	THF	90	trace
14	$CuSO_4{\cdot}5H_2O$[e]/*p*-TsOH[d]	toluene	110	53

[a]Unless otherwise noted, the reaction time was 12 h. [b]All reactions were carried out on a 0.3 mmol scale. [c]Isolated yield. [d]0.5 equiv was used. [e]1.5 equiv was used. [f]ND: not detected. [g]NR: no reaction.

Table 2. Synthesis of Spirothienooxindoles 9[a]



entry	**8** (Ar; R)	product	yield[b] (%)
1	**8aa** (Ph; 3,4,5-tri-MeO)	**9aa**	66
2	**8ab** (Ph; 3,5-di-MeO)	**9ab**	63
3	**8ac** (Ph; 3,4-di-MeO)	**9ac**	56
4	**8ba** (4-F-Ph; 3,4,5-tri-MeO)	**9ba**	59
5	**8bb** (4-F-Ph; 3,5-di-MeO)	**9bb**	56
6	**8bc** (4-F-Ph; 3,4-di-MeO)	**9bc**	52
7	**8bd** (4-F-Ph; 3,4-di-Me)	**9bd**	ND
8	**8be** (4-F-Ph; 3-MeO)	**9be**	ND
9	**8ca** (2-Np; 3,4,5-tri-MeO)	**9ca**	62
10	**8cb** (2-Np; 3,5-di-MeO)	**9cb**	56
11	**8cc** (2-Np; 3,4-di-MeO)	**9cc**	56
12	**8da** (4-Cl-Ph; 3,4,5-tri-MeO)	**9da**	54
13	**8ea** (2-Cl-Ph; 3,4,5-tri-MeO)	**9ea**	72
14	**8eb** (2-Cl-Ph; 3,4-di-MeO)	**9eb**	68

[a]All reactions were carried out on a 0.3 mmol scale. [b]Isolated yield.

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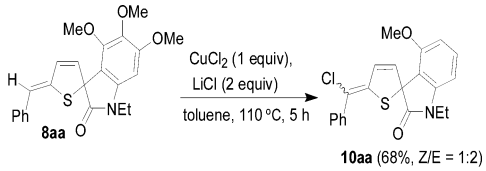
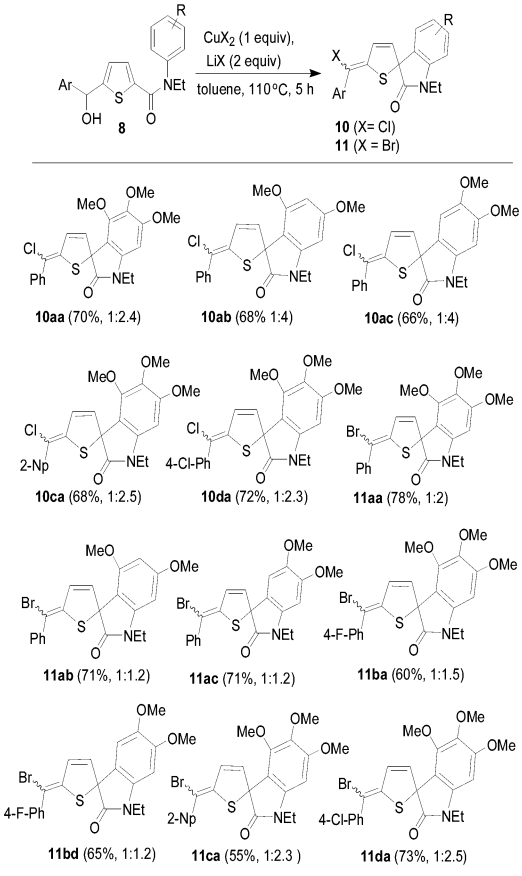
Scheme 3. Synthesis 10aa from 8aa



assigned by 400 MHz NOESY experiments in $CDCl_3$. Given that Cu(II) salts are able to catalyze the dehydration−cyclization of **8** into **9**, we also anticipated that **10** could be prepared directly from α-thienylcarbinol **8**. As shown in Table 3, under the same reaction condition as the chlorination of **9aa**,

Table 3. Synthesis of Halogenated Spirothienooxindoles 10 and 11[a]

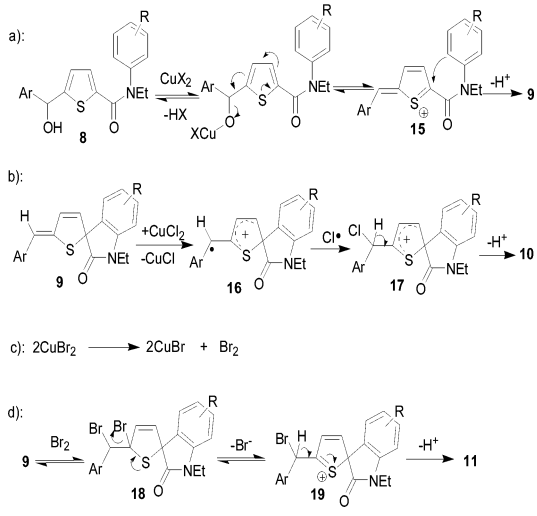


[a]All reactions were performed on a 1 mmol scale. Yields of isolated products were given. The ratios of Z/E in parentheses were based on ^{1}H NMR

a series of **8** could be converted into the corresponding chlorinated spirothienooxindoles **10** in moderate to good yields and moderate Z/E ratios. The formation of brominated spirothienooxindoles **11** was also achieved when $CuCl_2$ (1 equiv)/LiCl (2 equiv) was replaced by $CuBr_2$ (1 equiv)/LiBr (2 equiv). Because of the relatively larger size of bromine compared to chlorine, the ratios Z/E of brominated products **11** are generally lower than those of chlorinated products.

On the basis of the experimental outcomes shown above, tentative mechanisms for the formation of halogenated spirothienooxindoles were proposed in Scheme 4. Initially, the coordination of CuX_2 with the hydroxyl group produced

Scheme 4. Plausible Mechanism for the Formation of 10 and 11



sulfonium ion **15**. Intermediate **15** then underwent an intramolecular Friedel−Crafts reaction to form **9** (Scheme 4a). For the chlorination process, a single electron transfer (SET) mechanism was suggested (Scheme 4b).[16] A single electron transfer from electron-rich dienyl thioether to $CuCl_2$ led to the cation-radical intermediate **16**, which reacted with another equivalent of $CuCl_2$ via chlorine-atom transfer yielding the carboncation **17**. **17** was then deprotonated to form **10**. For bromination, the decomposition of $CuBr_2$ into CuBr and Br_2 has been reported previously (Scheme 4c).[17] The electrophilic addition of the Br_2 generated in situ toward the exocyclic double bond of **9** produced the intermediate **18**, which was converted into **11** after the elimination of HBr (Scheme 4d). Notably, treatment of **8aa** with NBS (1equiv) in toluene at 110 °C for 5 h furnished **11aa** in a comparable yield to treatment under $CuBr_2$/LiBr system. This observation brought additional proof of the molecular bromine-mediated mechanism.

In summary, we have developed the Cu(II)-promoted transformation of α-thienylcarbinols, with an *N*-phenyl carbonyl group at the other α-position, into unprecedented spirothienooxindoles with thioether segment at their B-rings. Apart form the dearomatizing Friedel−Crafts reaction employing thiocarbenium adjacent to an electron-withdrawing carbonyl group as an alkylation agent, the regioselective halogenations of dienyl thioether containing electron-rich *N*-phenyl rings are also interesting.

EXPERIMENATAL SECTION

General Procedure for Preparation of 9 from 8. The mixture of **8** (0.3 mmol), toluene (5 mL), $CuSO_4{\cdot}5H_2O$ (112.5 mg, 0.45 mmol), and *p*-TsOH (25.8 mg, 0.15 mmol) was stirred at 90 °C. After the disappearance of **8** according to the TLC, the mixture was cooled to room temperature, and the solid was filtered off. Removal of the organic solvent provided the crude product, which then was purified by column chromatography to give **9.**

*(Z)-5′-Benzylidene-1-ethyl-4,5,6-trimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one (**9aa**).* Brown syrup (81 mg, 66%): IR (KBr) 2935, 1717, 1611, 1470, 1342, 1286, 1221, 1129, 1041, 792, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2H), 7.34−7.30 (m, 2H), 7.19−7.15 (m, 1H), 6.72 (d, J = 6.0 Hz, 1H), 6.70 (s, 1H), 6.25 (s, 1H), 5.82 (d, J = 6.0 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.76 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 155.7, 152.1, 143.0, 138.4, 138.3, 137.5, 136.9,

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131.4, 128.4, 128.2, 126.5, 120.5, 111.8, 90.1, 68.9, 61.3, 61.1, 56.6, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{24}NO_4S$ $[M + H]^+$ 410.1426, found 410.1415.

(Z)-5′-Benzylidene-1-ethyl-4,6-dimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one ***(9ab)***. Brown syrup (71 mg, 63%): IR (KBr) 2833, 1702, 1620, 1520, 1458, 1378, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2H), 7.34−7.29 (m, 2H), 7.17−7.14 (m, 1H), 6.68 (d, J = 6.0 Hz, 1H), 6.66 (s, 1H), 6.14 (s, 1H), 6.12 (s, 1H), 5.78 (d, J = 6.0 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.74 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.01, 162.91, 157.91, 144.19, 143.55, 137.56, 137.12, 131.47, 128.36, 128.17, 126.40, 119.97, 105.77, 92.68, 88.93, 68.88, 55.86, 55.69, 35.71, 12.89; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{22}NO_3S$ $[M + H]^+$ 380.1320, found 380.1310.

(Z)-5′-Benzylidene-1-ethyl-5,6-dimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one ***(9ac)***. Brown syrup (64 mg, 56%): IR (KBr) 2835, 1714, 1619, 1503, 1460, 1375, 1285, 1214, 1104, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2H), 7.33−7.26 (m, 2H), 7.20−7.17 (m, 1H), 6.87 (s, 1H), 6.73 (s, 1H), 6.69 (d, J = 6.0 Hz, 1H), 6.48 (s, 1H), 5.80 (d, J = 6.0 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H), 3.78 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 150.8, 145.8, 142.8, 137.3, 136.7, 135.7, 132.4, 128.5, 128.1, 126.8, 121.0, 119.5, 109.8, 94.5,70.2, 56.7, 56.5, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{22}NO_3S$ $[M + H]^+$ 380.1320, found 380.1308.

(Z)-1-Ethyl-5′-(4-fluorobenzylidene)-4,5,6-trimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one ***(9ba)***. Brown syrup (75 mg, 59%): IR (KBr) 2931, 1715, 1615, 1468, 1341, 1226, 1128, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.40 (m, 2H), 7.03−6.99 (m, 2H), 6.70 (d, J = 6.0 Hz, 1H), 6.66 (s, 1H), 6.26 (s, 1H), 5.82 (d, J = 6.0 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.79 (s, 3H), 3.76 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 162.5, 160.0, 155.8, 152.1, 142.7, 142.6, 138.4, 138.3, 137.34, 133.3, 133.2, 131.5, 129.7, 129.6, 119.2, 115.5, 115.3, 111.7, 90.1, 68.9, 61.3, 61.1, 56.6, 38.8, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{23}FNO_4S$ $[M + H]^+$ 428.1332, found 428.1320.

(Z)-1-Ethyl-5′-(4-fluorobenzylidene)-4,6-dimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one ***(9bb)***. Brown syrup (67 mg, 56%): IR (KBr) 2938, 1719, 1617, 1505, 1459, 1345, 1283, 1151, 1081, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.40 (m, 2H), 7.02−6.98 (m, 2H), 6.66 (d, J = 6.0 Hz, 1H), 6.62 (s, 1H), 6.14 (s, 1H), 6.12 (s, 1H), 5.77 (d, J = 6.0 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.75 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 162.9, 162.4, 159.9, 157.9, 144.2, 143.2, 137.3, 133.4, 131.5, 129.7, 129.7, 118.7, 115.4, 115.2, 105.6, 92.7, 88.9, 68.8, 55.8, 55.7, 35.7, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{21}FNO_3S$ $[M + H]^+$ 398.1226, found 398.1218.

(Z)-1-Ethyl-5′-(4-fluorobenzylidene)-5,6-dimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one ***(9bc)***. Brown syrup (62 mg, 52%): IR (KBr) 2936, 1714, 1616, 1504, 1460, 1375, 1285, 1216, 1104, 850, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.41 (m, 2H), 7.04−7.00 (m, 2H), 6.87 (s, 1H), 6.69 (s, 1H), 6.68 (d, J = 6.0 Hz, 1H), 6.48 (s, 1H), 5.80 (d, J = 6.0 Hz, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 3.78 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 162.6, 160.2, 150.8, 145.8, 142.4, 137.1, 135.8, 132.9, 132.4, 129.8, 129.7, 119.8, 119.3, 115.6, 115.4, 109.7, 94.5, 70.1, 56.7, 56.5, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{21}FNO_3S$ $[M + H]^+$ 398.1226, found 398.1214.

(Z)-1-Ethyl-4,5,6-trimethoxy-5′-(naphthalen-1-ylmethylene)-5′H-spiro[indoline-3,2′-thiophen]-2-one ***(9ca)***. Brown syrup (85 mg, 62%): IR (KBr) 2934, 1717, 1612, 1470, 1392, 1341, 1227, 1129, 1038, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.78−7.76 (m, 3H), 7.58−7.56(m, 1H), 7.43−7.40 (m, 2H), 6.85 (s, 1H), 6.79 (d, J = 6.0 Hz, 1H), 6.27 (s, 1H), 5.86 (d, J = 6.0 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.79 (s, 3H), 3.80 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 155.8, 152.1, 143.6, 138.4, 138.3, 137.6, 134.6, 133.5, 132.1, 131.6, 128.0, 127.9, 127.5, 126.8, 126.7, 126.2, 125.8, 120.5, 111.7, 90.1, 69.1, 61.4, 61.1, 56.6, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{27}H_{26}NO_4S$ $[M + H]^+$ 460.1583, found 460.1567.

(Z)-1-Ethyl-4,6-dimethoxy-5′-(naphthalen-1-ylmethylene)-5′H-spiro[indoline-3,2′-thiophen]-2-one ***(9cb)***. Brown syrup (72 mg, 56%): IR (KBr) 2931, 1719, 1617, 1505, 1457, 1342, 1206, 1147, 1080, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.77−7.75 (m, 3H), 7.58−7.56 (m, 1H), 7.42−7.40 (m, 2H), 6.82 (s, 1H), 6.74 (d, J = 6.0 Hz, 1H), 6.14 (s, 1H), 6.15 (s, 1H), 5.82 (d, J = 6.0 Hz, 1H), 3.84 (s, 3H), 3.77 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 162.9, 157.9, 144.2, 144.2, 137.6, 134.7, 133.5, 132.0, 131.6, 128.0, 127.8, 127.5, 126.8, 126.7, 126.1, 125.7, 120.0, 105.7, 92.7, 89.0, 69.0, 55.8, 55.7, 35.7, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{26}H_{24}NO_3S$ $[M + H]^+$ 430.1477, found 430.1466.

(Z)-1-Ethyl-5,6-dimethoxy-5′-(naphthalen-1-ylmethylene)-5′H-spiro[indoline-3,2′-thiophen]-2-one ***(9cc)***. Brown syrup (72 mg, 56%): IR (KBr) 2930, 1714, 1619, 1504, 1460, 1375, 1214, 1102, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.79−7.76 (m, 3H), 7.58−7.56 (m, 1H), 7.43−7.42 (m, 2H), 6.90 (s, 1H), 6.88 (s, 1H), 6.75 (d, J = 6.0 Hz, 1H), 6.49 (s, 1H), 5.84 (d, J = 6.0 Hz, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 3.80 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 150.8, 145.8, 143.3, 137.3, 135.8, 134.3, 133.5, 132.5, 132.3, 128.1, 128.0, 127.6, 126.8, 126.6, 126.3, 125.9, 121.1, 119.4, 109.7, 94.5,70.3, 56.7, 56.6, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{26}H_{24}NO_3S$ $[M + H]^+$ 430.1477, found 430.1461.

(Z)-5′-(4-Chlorobenzylidene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one ***(9da)***. Brown syrup (71 mg, 54%): IR (KBr) 2935, 1720, 1611, 1473, 1343, 1229, 1088, 1040, 852, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 6.0 Hz, 1H), 6.64 (s, 1H), 6.26 (s, 1H), 5.84 (d, J = 6.0 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.76 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 155.8, 152.0, 143.8, 138.4,138.3, 137.3, 135.5, 132.0, 131.9, 129.3, 128.5, 119.1, 111.5, 90.1, 69.1, 61.3, 61.1, 56.6, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{23}ClNO_4S$ $[M + H]^+$ 444.1036, found 444.1020.

(Z)-5′-(2-Chlorobenzylidene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one ***(9ea)***. Brown syrup (95 mg, 72%): IR (KBr) 2938, 1718, 1612, 1471, 1343, 1227, 1130, 1039, 749, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.72 (m, 1H), 7.38−7.35 (m, 1H), 7.22−7.19 (m, 1H), 7.12−7.08 (m, 1H), 7.02 (s, 1H), 6.79 (d, J = 6.0 Hz, 1H), 6.25 (s, 1H), 5.88 (d, J = 6.0 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.78 (s, 3H), 3.75 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 155.8, 152.7, 145.7, 138.4, 138.3, 137.4, 134.9, 133.4, 132.5, 129.6, 128.1, 127.7, 126.6, 116.4, 111.5, 90.1, 68.7, 61.3, 61.1, 56.6, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{23}ClNO_4S$ $[M + H]^+$ 444.1036, found 444.1027.

(Z)-5′-(2-Chlorobenzylidene)-1-ethyl-5,6-dimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one ***(9eb)***. Brown syrup (84 mg, 68%): IR (KBr) ν2936, 1715, 1616, 1503, 1463, 1376, 1215, 1102, 1033, 748, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.72 (m, 1H), 7.38−7.36 (m, 1H), 7.24−7.20 (m, 1H), 7.14−7.10 (m, 1H), 7.04 (s, 1H), 6.87 (s, 1H), 6.75 (d, J = 6.0 Hz, 1H), 6.48 (s, 1H), 5.86 (d, J = 6.0 Hz, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 3.77 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 150.8, 145.8, 145.5, 137.2, 135.7, 134.7, 133.4, 133.4, 129.7, 128.0, 127.9, 126.7, 119.1, 116.9, 109.7, 94.5, 69.9, 56.7, 56.5, 35.6, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{21}ClNO_3S$ $[M + H]^+$ 414.0931, found 414.0920.

General Procedure (V) for the Preparation of 10 and 11 from 8. The mixture of **8** (0.3 mmol), toluene (5 mL), CuX_2 (0.45 mmol), and LiX (2 mmol) was stirred at 110 °C for 5 h. After the disappearance of **9** according to the TLC, the mixture was cooled to room temperature, and the solid was filtered off. Removal of the organic solvent provided the crude product, which then was purified by flash chromatography to give **10** or **11**.

5′-(Chloro(phenyl)methylene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one ***(10aa)***. Brown syrup (93 mg, 70%, Z/E = 1:2.4): IR (KBr) 2935, 1717, 1612, 1472, 1342, 1227, 1130, 793, 756, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.2 Hz, 0.58H), 7.50 (d, J = 7.2 Hz, 1.42H), 7.40−7.31 (m, 3H), 7.13 (d, J = 6.0 Hz, 0.29H), 6.72 (d, J = 6.0 Hz, 0.71H), 6.26 (s, 0.71H),

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6.22 (s, 0.29H), 5.94 (d, J = 6.0 Hz, 0.29H), 5.86 (d, J = 6.0 Hz, 0.71H), 3.97 (s, 2.13H), 3.92 (s, 3H), 3.90 (s, 0.87H), 3.82 (s, 2.13H), 3.80 (s, 0.87H), 3.78−3.72 (m, 2H), 1.31−1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 155.8, 155.8, 152.0, 152.0, 143.6, 140.2, 138.4, 138.3, 138.12, 137.6, 135.6, 134.6, 133.8, 131.2, 128.8, 128.5, 128.3, 128.2, 128.0, 120.8, 116.5, 111.5, 111.2, 90.1, 90.0, 68.6, 66.8, 61.4, 61.3, 61.1, 61.1, 56.6, 35.6, 35.6, 12.9, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{23}ClNO_4S$ $[M + H]^+$ 444.1036, found 444.1027.

*5′-(Chloro(phenyl)methylene)-1-ethyl-4,6-dimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one (**10ab**).* Brown syrup (84 mg, 68%, Z/E = 1:4): IR (KBr) 2938, 1721, 1617, 1460, 1345, 1282, 1209, 1150, 1080, 902, 816, 756, 628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1.6H), 7.45 (d, J = 8.0 Hz, 0.4H), 7.39−7.29 (m, 3H), 6.69−6.66 (m, 1H), 6.16 (s, 0.8H), 6.14 (s, 0.2H), 6.12 (s, 1H), 5.82 (d, J = 6.0 Hz, 0.8H), 5.78 (d, J = 6.0 Hz, 0.2H), 3.84 (s, 3H), 3.82 (s, 2.4H), 3.75 (s, 0.6H), 3.74 (q, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 162.9, 157.9, 144.2, 144.1, 143.9, 143.6, 137.7, 137.5, 135.8, 131.2, 128.8, 128.3, 128.2, 128.1, 120.2, 119.9, 105.4, 92.7, 92.6, 89.0, 88.9, 66.7, 55.9, 55.8, 55.7, 35.7, 35.7, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{21}ClNO_3S$ $[M + H]^+$ 414.0931, found 414.0923.

*5′-(Chloro(phenyl)methylene)-1-ethyl-5,6-dimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one (**10ac**).* Brown syrup (82 mg, 66%, Z/E = 1:4): IR (KBr) 2933, 1716, 1616, 1503, 1462, 1376, 1345, 1216, 1033, 783, 756, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.2 Hz, 0.4H), 7.51 (d, J = 7.2 Hz, 1.6H), 7.41−7.33 (m, 3H), 7.11 (d, J = 6.0 Hz, 0.2H), 6.93 (s, 0.8H), 6.89 (s, 0.2H), 6.69 (d, J = 6.0 Hz, 0.8H), 6.48 (s, 0.8H), 6.45 (s, 0.2H), 5.92 (d, J = 6.0 Hz, 0.2H), 5.83 (d, J = 6.0 Hz, 0.8H), 3.94 (s, 2.4H), 3.92 (s, 0.6H), 3.87 (s, 2.4H), 3.85 (s, 0.6H), 3.78 (q, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 150.9, 145.9, 143.3, 137.5, 136.7, 135.9, 135.5, 130.9, 128.8, 128.5, 128.4, 128.2, 128.0 121.4, 119.0, 109.8, 109.7, 94.5, 94.4, 68.1, 56.8, 56.5, 35.6, 35.5, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{21}ClNO_3S$ $[M + H]^+$ 414.0931, found 414.0922.

*5′-(Chloro(naphthalen-2-yl)methylene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one (**10ca**).* Brown syrup (100 mg, 68%, Z/E = 1:2.5): IR (KBr) 2932, 1718, 1610, 1470, 1340, 1225, 1132, 1097, 798 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 0.29H), 7.95 (s, 0.71H), 7.86−7.80 (m, 3H), 7.62−7.60 (m, 0.87H), 7.53−7.45 (m, 2.13H), 7.19 (d, J = 6.0 Hz, 0.29H), 6.79 (d, J = 6.0 Hz, 0.71H), 6.26 (s, 0.71H), 6.22 (s, 0.29H), 5.97 (d, J = 6.0 Hz, 0.29H), 5.89 (d, J = 6.0 Hz, 0.71H), 4.00 (s, 2.13H), 3.92 (s, 3H), 3.89 (s, 0.87H), 3.83 (s, 2.13H), 3.80 (s, 0.87H), 3.77 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 155.8, 152.0, 144.0, 138.4, 138.3, 135.8, 134.9, 134.6, 133.8, 133.0, 132.9, 132.8, 132.7, 131.3, 128.3, 128.2, 128.1, 127.9, 127.6, 127.6, 127.5, 126.7, 126.6, 126.4, 126.3, 125.4, 120.9, 111.4, 90.1, 90.0, 66.9, 61.4, 61.3, 61.1, 56.6, 56.5, 35.6, 35.6, 12.9, 12.8. Ion-trap-HRMS (ESI) calcd for $C_{27}H_{25}BrClNO_4S$ $[M + H]^+$ 494.1193, found 494.1185.

*5′-(Chloro(4-chlorophenyl)methylene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one (**10da**).* Brown syrup (103 mg, 72%, Z/E = 1:2.3): IR (KBr) 2932, 1721, 1611, 1474, 1343, 1229, 1130, 1090, 1040, 797 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 0.6H), 7.43 (d, J = 8.4 Hz, 1.4H), 7.35 (d, J = 8.4 Hz, 1.4H), 7.30 (d, J = 8.4 Hz, 0.6H), 7.11 (d, J = 6.0 Hz, 0.3H), 6.67 (d, J = 6.0 Hz, 0.7H), 6.25 (s, 0.7H), 6.22 (s, 0.3H), 5.96 (d, J = 6.0 Hz, 0.3H), 5.89 (d, J = 6.0 Hz, 0.7H), 3.96 (s, 2.1H), 3.92 (s, 2.1H), 3.91 (s, 1.8H), 3.82 (s, 2.1H), 3.80(s, 0.9H), 3.76 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 155.9, 152.0, 144.3, 138.3, 136.7, 136.3, 136.0, 135.1, 135.0, 134.3, 133.7, 130.8, 130.0, 129.4, 128.6, 128.4, 119.3, 111.1, 90.1, 90.0, 68.8, 66.9, 61.4, 61.3, 61.1, 61.1, 56.6, 35.6, 12.9, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{22}Cl_2NO_4S$ $[M + H]^+$ 478.0647, found 478.0638.

*5′-(Bromo(phenyl)methylene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one (**11aa**).* Brown syrup, (114 mg, 78%, Z/E = 1:2): IR (KBr) 2932, 1718, 1610, 1471, 1341, 1227, 1129, 1082, 1038, 793, 749, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 0.66H), 7.43 (d, J = 8.0 Hz, 1.34H), 7.38−7.24 (m, 3H), 7.08 (d, J = 6.0 Hz, 0.33H), 6.63 (d, J = 6.0 Hz, 0.67H), 6.25 (s, 0.67H), 6.21 (s, 0.33H), 5.97−5.95 (m, 1H), 3.98 (s, 2.0H), 3.93 (s, 1.0H), 3.92 (s, 2.0H), 3.89 (s, 1.0H), 3.82 (s, 2.0H), 3.80 (s, 1.0H), 3.75 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 155.8, 155.8, 152.0, 152.0, 146.7, 142.2, 140.0, 139.2, 138.4, 138.3, 138.2, 138.1, 136.0, 135.8, 135.4, 130.9, 129.4, 128.8, 128.5, 128.4, 128.3, 128.2, 111.4, 111.2, 111.1, 105.2, 90.1, 90.0, 68.7, 66.4, 61.3, 61.3, 61.1, 61.1, 56.6, 56.6, 35.6, 35.6, 12.9, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{23}BrNO_4S$ $[M + H]^+$ 488.0531, found 488.0518.

*5′-(Bromo(phenyl)methylene)-1-ethyl-4,6-dimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one (**11ab**).* Brown syrup (97 mg, 71%, Z/E = 1:1.2): IR (KBr) 2925, 1717, 1616, 1458, 1237, 911, 811, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.44 (m, 2H), 7.37−7.29(m, 3H), 6.69−6.66 (m, 1H), 6.16−6.12 (m, 2H), 5.93 (d, J = 6.0 Hz, 0.55H), 5.78 (d, J = 6.0 Hz, 0.45H), 3.84−3.81 (br, 4.55H), 3.75 (s, 1.45H), 3.74 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 174.4, 163.0, 162.9, 157.9, 144.1, 143.5, 137.5, 137.1, 136.1, 135.9, 131.4, 131.0, 129.4, 128.8, 128.3, 128.2, 128.2, 128.1, 126.3, 119.9, 105.8, 105.3, 92.7, 92.7, 88.9, 88.9, 68.8, 68.3, 55.9, 55.8, 55.6, 35.7, 35.7, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{21}BrNO_3S$ $[M + H]^+$ 458.0426, found 458.0413.

*5′-(Bromo(phenyl)methylene)-1-ethyl-5,6-dimethoxy-5′H-spiro-[indoline-3,2′-thiophen]-2-one (**11ac**).* Brown syrup (97 mg, 71%, Z/E = 1:5.6): IR (KBr) 2927, 1713, 1617, 1503, 1374, 1214, 1103, 1032, 782, 749, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.6 Hz, 0.3H), 7.49 (d, J = 7.6 Hz, 1.7H), 7.37−7.31(m, 3H), 7.06 (d, J = 6.0 Hz, 0.15H), 6.94 (s, 0.85H), 6.73 (s, 0.15H), 6.61 (d, J = 6.0 Hz, 0.85H), 6.48 (s, 1H), 5.94 (d, J = 6.0 Hz, 0.85H), 5.80 (d, J = 6.0 Hz, 0.15H), 3.94 (s, 3H), 3.88 (s, 2.55H), 3.85 (s, 0.45H), 3.80 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 173.9, 150.9, 146.4, 145.8, 139.0, 137.1, 135.9, 130.7, 129.3, 128.4, 128.3, 128.1, 118.9, 111.7, 109.8, 94.5, 94.4, 67.7, 56.8, 56.8, 56.5, 35.6, 35.5, 12.9; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{21}BrNO_3S$ $[M + H]^+$ 458.0426, found 458.0420.

*5′-(Bromo(4-fluorophenyl)methylene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one (**11ba**).* Brown syrup (91 mg, 60%, Z/E = 1:1.5): IR (KBr) ν3749, 2936, 1714, 1502, 1460, 1375, 1217, 782 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.60 (m, 0.8H), 7.46−7.43 (m, 1.2H), 7.07−6.97 (m, 2.4H), 6.56 (d, J = 6.0 Hz, 0.6H), 6.25 (s, 0.6H), 6.21 (s, 0.4H), 5.97 (d, J = 6.0 Hz, 1H), 3.97 (s, 1.8H), 3.92 (s, 1.2H), 3.92 (s, 1.8H), 3.89 (s, 1.2H), 3.81 (s, 1.8H), 3.79 (s, 1.2H), 3.77−3.70 (m, 2H), 1.30−1.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 155.9, 155.8, 152.0, 152.0, 147.0, 142.2, 138.3, 138.3, 138.1, 136.3, 135.6, 135.4, 135.3, 131.2, 131.1, 130.9, 130.8, 130.6, 115.4, 115.3, 115.2, 115.1, 111.2, 111.0, 109.1, 103.8, 90.1, 90.0, 68.8, 66.5, 61.4, 61.3, 61.1, 56.6, 56.5, 35.6, 35.6, 12.9, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{22}BrFNO_4S$ $[M + H]^+$ 506.0437, found 506.0423.

*5′-(Bromo(4-fluorophenyl)methylene)-1-ethyl-5,6-dimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one (**11bd**).* Brown syrup (92 mg, 65%, Z/E = 1:1.2): IR (KBr) 3749, 2929, 1717, 1614, 1341, 1228, 1037, 794 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 7.65−7.62 (m, 0.9H), 7.48−7.44 (m, 1.1H), 7.07−6.99 (m, 2.45H), 6.92 (s, 0.55H), 6.88 (s, 0.45H), 6.54 (d, J = 6.0 Hz, 0.55H), 6.47 (s, 0.55H), 6.44 (s, 0.45H), 6.95 (d, J = 6.0 Hz, 1H), 3.93 (s, 1.65H), 3.91 (s, 1.35H), 3.86 (s, 1.65H), 3.85 (s, 1.35H), 3.79−3.72 (m, 2H), 1.31−1.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0,173.9, 161.3, 161.1, 151.0, 150.9, 146.7, 145.8, 141.9, 137.4, 136.6, 135.9, 135.6, 135.5, 131.2, 131.1, 130.9, 130.8, 130.4, 118.7, 118.6, 115.5, 115.4, 115.3, 115.2, 110.3, 109.8, 109.7, 104.6, 94.5, 94.5, 94.5, 70.0, 67.8, 56.8, 56.8, 56.5, 56.5, 35.6, 35.6, 12.9, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{22}H_{20}BrFNO_3S$ $[M + H]^+$ 476.0331, found 476.0315.

*5′-(Bromo(naphthalen-2-yl)methylene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one (**11ca**).* Brown syrup (88 mg, 55%, Z/E = 1:2.3): IR (KBr) 2935, 1720, 1611, 1472, 1342, 1229, 1130, 1099, 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 0.3H), 7.92 (s, 0.7H), 7.86−7.76 (m, 3H), 7.60−7.44 (m, 3H), 7.14 (d, J = 6.0 Hz, 0.3H), 6.70 (d, J = 6.0 Hz, 0.7H), 6.26 (s, 0.7H), 6.21 (s, 0.3H), 6.01 (d, J = 6.0 Hz, 0.3H), 5.99 (d, J = 6.0 Hz, 0.7H), 4.02 (s, 2.1H), 3.94 (s, 0.9H), 3.92 (s, 2.1H), 3.88 (s, 0.9H), 3.83 (s, 2.1H),

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380 (s, 0.9H), 3.78 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 174.0, 155.8, 152.0, 147.1, 142.5, 138.4, 138.3, 138.0, 137.4, 136.5, 136.2, 135.8, 135.5,132.9, 132.8, 132.7, 131.1, 128.5, 128.2, 128.2, 128.0, 128.0, 127.6, 127.6, 127.0, 126.7, 126.6, 126.4, 126.3, 111.3, 111.2, 90.1, 90.0, 68.7, 68.5, 61.4, 61.3, 61.1, 61.1, 56.6, 35.6, 35.6, 12.9, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{27}H_{25}BrNO_4S$ $[M + H]^+$ 538.0688, found 538.0668.

*5′-(Bromo(4-chlorophenyl)methylene)-1-ethyl-4,5,6-trimethoxy-5′H-spiro[indoline-3,2′-thiophen]-2-one (**11da**).* Brown syrup (114 mg, 73%, Z/E = 1:2.5): IR (KBr) ν2930, 1722, 1612, 1340, 1229, 1132, 1092, 1038, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.8 Hz, 0.58H), 7.41 (d, J = 8.4 Hz, 1.42H), 7.33 (d, J = 8.4 Hz, 1.42H), 7.28 (d, J = 8.8 Hz, 0.58H), 7.06 (d, J = 6.0 Hz, 0.29H), 6.58 (d, J = 6.0 Hz, 0.71H), 6.25 (s, 0.71H), 6.22 (s, 0.29H), 5.99 (d, J = 6.0 Hz, 1H), 3.97 (s, 2.13H), 3.92 (s, 3H), 3.90 (s, 0.87H), 3.82 (s, 2.13H), 3.80 (s, 0.87H), 3.75 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 155.9, 155.9, 152.0, 147.5, 138.3, 138.3, 137.6, 136.7, 135.9, 135.7, 134.2, 130.6, 130.5, 130.2, 128.5, 128.4, 111.1, 109.3, 90.1, 90.0, 66.5, 61.3, 61.2, 61.1, 61.1, 56.6, 56.5, 35.6, 35.6, 12.8, 12.8; Ion-trap-HRMS (ESI) calcd for $C_{23}H_{21}BrClNO_4S$ $[M + H]^+$ 522.0141, found 522.0151.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (c) Dasilva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273. (d) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060.

(2) (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. *J. Am. Chem. Soc.* **2005**, *127*, 10130. (b) Yu, S.; Qin, D.; Shangary, S.; Chen, J.; Wang, G.; Ding, K.; McEachern, D.; Qiu, S.; Nikolovska-Coleska, Z.; Miller, R.; Kang, S.; Yang, D.; Wang, S. *J. Med. Chem.* **2009**, *52*, 7970.

(3) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077.

(4) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175.

(5) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020.

(6) (a) Lopez-Gresa, M. P.; Gonzalez, M. C.; Ciavatta, L.; Ayala, I.; Moya, P.; Primo, J. *J. Agric. Food Chem.* **2006**, *54*, 2921. (b) Mugishima, T.; Tsuda, M.; Yuu, K.; Haruaki, I.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430. (c) Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skeltonb, B. W.; White, A. H. *Tetrahedron* **2007**, *63*, 5579.

(7) (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (b) Muthusamy, S.; Gunanathan, C.; Nethaji, M. *J. Org. Chem.* **2004**, *69*, 5631. (c) Zhang, Y.; Wang, L.; Zhang, M.; Fun, H. K.; Xu, J. H. *Org. Lett.* **2004**, *6*, 4893. (d) Chen, X.; Wei, Q.; Luo, S.; Xiao, H.; Gong, L. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (e) Galliford, C. V.; Martenson, J. S.; Stern, C.; Scheidt, K. A. *Chem. Commun.* **2007**, 631. (f) Helan, V.; Mills, A.; Drewry, D.; Grant, D. *J. Org. Chem.* **2010**, *75*, 6693.

(8) (a) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2006**, *71*, 2346. (b) Basavaiah, D.; Reddy, K. M. *Org. Lett.* **2007**, *9*, 57. (c) Alcaide, B.; Almendros, P.; Campo, T. M.; Quirós, M. T. *Chem.—Eur. J.* **2009**, *15*, 3344. (d) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (e) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem.—Eur. J.* **2011**, *17*, 2842. (f) Albertshofer, K.; Tan, B.; Barbas, C. F. *Org. Lett.* **2012**, *14*, 1834.

(9) (a) Knueppel, D.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4623.

(10) (a) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596. (b) Overman, L. E.; Watson, D. *J. Org. Chem.* **2006**, *71*, 2587.

(11) (a) Kyei, A. S.; Tchabanenko, K.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 8931. (b) Jaegli, S.; Dufour, J.; Wei, H.-L.; Piou, T.; Duan, X.-H.; Vors, J.-P.; Neuville, L.; Zhu, J. P. *Org. Lett.* **2010**, *12*, 4498. (c) Zhang, Y.; Panek, J. S. *Org. Lett.* **2009**, *11*, 3366.

(12) (a) Piancatelli, G.; Scettri, A.; Barbadoro, S. *Tetrahedron Lett.* **1976**, *17*, 3555. (b) Piancatelli, G.; Scettri, A. *Tetrahedron Lett.* **1977**, *13*, 1131. (c) Piancatelli, G.; Scettri, A.; David, G.; D'Auria, V. M. *Tetrahedron* **1978**, *34*, 2775.

(13) (a) Gao, Y.; Wu, W.-L.; Ye, B.; Zhou, R.; Wu, Y.-L. *Tetrahedron Lett.* **1996**, *37*, 893. (b) Yin, B.-L.; Wu, Y.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1.* **2002**, 1746. (c) Yin, B.-L.; Fan, J.-F.; Gao, Y.; Wu, Y.-L. *Synlett* **2003**, 399. (d) Yin, B.-L.; Yang, Z.-M.; Hu, T.-S.; Wu, Y.-L. *Synthesis* **2003**, 1995. (e) Yin, B.-L.; Hu, T.-S.; Y., H.-J.; Gao, Y.; Wu, W.-M.; Wu, Y.-L. *Synlett* **2004**, 306. (f) Yin, B.-L.; Hu, T.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2004**, *45*, 2017. (g) Veits, G. K.; Wenz, D. R.; Read de Alanz, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9484. (h) Palmer, L. I.; Read de Alaniz, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7167.

(14) Yin, B.-L.; Lai, J.-Q.; Zhang, Z.-R.; Jiang, H.-F. *Adv. Synth. Catal.* **2011**, *353*, 1961.

(15) For selected reference concerning transition-metal-catalyzed regioselective halogenation of sp^2 C−H, see: (a) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (b) Qiu, D.; Mo, F.; Zheng, Z.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 5474. (c) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523.

(16) Selected examples concerning SET pathway for Cu(II)-catalyzed functionalizations of Aryl C−H bond, see: (a) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Menini, L.; Gusevskaya, E. V. *Chem. Commun.* **2006**, 209.

(17) Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009**, 6460.