Hydrothiolation and Intramolecular Cyclization Sequence for the Synthesis of 1,3-Oxathiine Frameworks

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Abstract: 1,3-Oxathiine frameworks can be prepared via the sequential addition and intramolecular cyclization of thiosalicylic acid onto alkynes. A substituent on the alkyne and the presence of a palladium catalyst can allow product regioselectivity control. This strategy is applicable to the synthesis of heterocycles comprising sulfur and oxygen atoms, namely 3,1-benzoxathiines, without any unwanted byproduct.

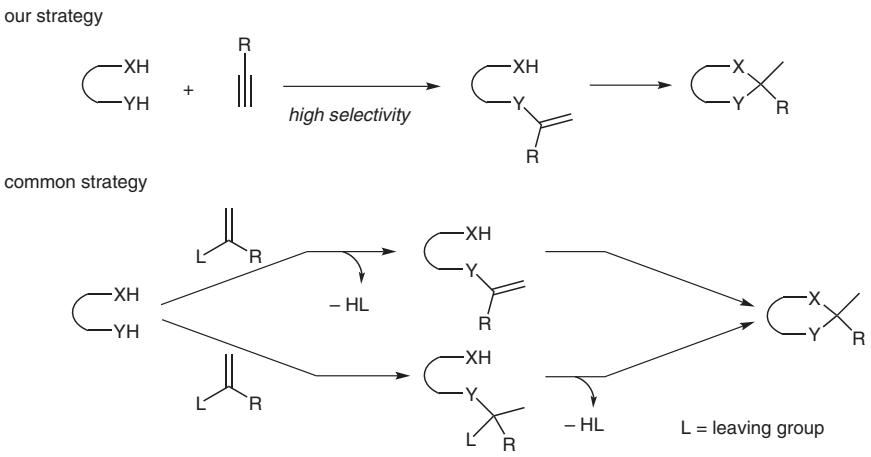
Key words: heterocycles, hydrothiolation, palladium, sequential reaction, alkynes, 3,1-benzoxathiines

Heterocycles containing two different heteroatoms are widely observed in natural and biologically active compounds. Though there have been many methods for their preparation, the annulation of two different molecules has been particularly effective in terms of molecular diversity. Sequential addition–cyclizations are a typical approach, but they often require one or more leaving groups.[1] However, the introduction of two heteroatoms via sequential hydroheterofunctionalizations on an alkyne would be atom-economical. Hydroheterofunctionalizations both with and without catalysts have been developed to date, but two types of hydroheterofunctionalization occurring in one pot is rare.[2] The regioselectivity of the initial hydroheterofunctionalization presents another challenge.[3] Asymmetric alkynes can lead to three types of alkenes (*cis*, *trans*, and *geminal*) via hydroheterofunctionalization. On the other hand, cross-coupling reactions that employ a leaving group bearing substrate usually proceed to give one exclusive regioisomer. Thus, predominantly, coupling or substitution protocols have been adopted to generate the desired cyclic product (Scheme 1).

We have focused on the regioselective addition of a thiol to an alkyne (hydrothiolation)[4] and intramolecular cyclization via the addition of a carboxylic acid to the resulting alkene (hydrooxycarbonylation).[5] Although these reactions have each been previously investigated independently, there has been no report of a sequential one-pot protocol.[6]

Initially, we investigated different catalysts and reaction conditions for the model reaction of thiosalicylic acid (**1a**) with dodec-1-yne (**2a**) (Table 1). A wide variety of transition metals promoted the hydrothiolation/intramolecular cyclization sequence. However, most of them led to mixtures of uncharacterized products, including regioisomers of **3a**.[7] Of these catalysts, palladium(II) acetate and bis(benzonitrile)dichloropalladium selectively produced the 1,3-oxathiine derivative **3a**.[8–10]

The scope of the reaction, with respect to the alkyne **2** was also examined (Table 2). Alkynes with alkyl or aryl substituents gave the corresponding 1,3-oxathiine derivatives



Scheme 1 Synthesis of heterocyclic compounds

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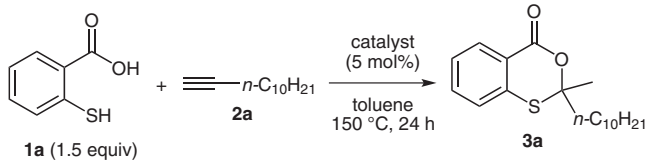
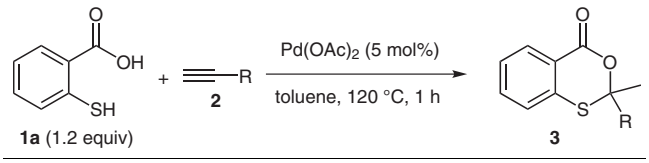
Table 1 Examination of Catalysts for the Formation of **3a**[a]



Entry	Catalyst	Yield[b] (%)
1	$HAuCl_4$	2.0
2	$IrCl_3 \cdot n\ H_2O$	7.2
3[c]	$RuCl_3 \cdot n\ H_2O$	9.1
4	H_2PtCl_4	24
5	$RhCl_3 \cdot n\ H_2O$	27
6	$NiCl_2$	47
7	$PdCl_2$	51
8	$PdCl_2(PPh_3)_2$	60
9	$Pd(dba)_2$	82
10	$PdCl_2(PhCN)_2$	97
11	$Pd(OAc)_2$	96
12[c]	$Pd(OAc)_2$	91

[a] Reaction conditions: catalyst (5 mol%), **1a** (0.30 mmol), **2a** (0.20 mmol), toluene (1 mL), argon atmosphere.
[b] The yield was determined by GC using *n*-dodecane as an internal standard.
[c] 120 °C, 1 h.

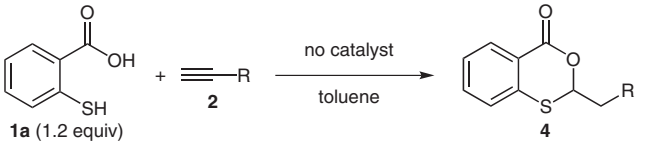
Table 2 Survey of Unactivated Alkynes[a]



Entry	Alkyne	R	Product	Yield[b] (%)
1	**2a**	*n*-$C_{10}H_{21}$	**3a**	72 (86)
2[c]				83 (99)
3	**2b**	$(CH_2)_2Ph$	**3b**	42 (56)
4	**2c**	CH_2OBn	**3c**	40 (44)
5	**2d**	Ph	**3d**	72 (83)
6	**2e**	4-MeC_6H_4	**3e**	65 (73)
7	**2f**	4-$MeOC_6H_4$	**3f**	20 (25)
8[c]	**2g**	4-$F_3CC_6H_4$	**3g**	59 (78)
9	**2h**	3-pyridyl	**3h**	9 (9)
10[c]				39 (39)
11	**2i**	2-furyl	**3i**	56 (68)
12[d]				64 (77)

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), **1a** (0.24 mmol), **2** (0.20 mmol), toluene (1 mL), argon atmosphere.
[b] Isolated yield. NMR yield is given in parenthesis. Due to hydrolysis of the product during column chromatography, the isolated yield was lower than the NMR yield.
[c] 150 °C, 3 h.
[d] 80 °C.

Table 3 Survey of Activated Alkynes[a]



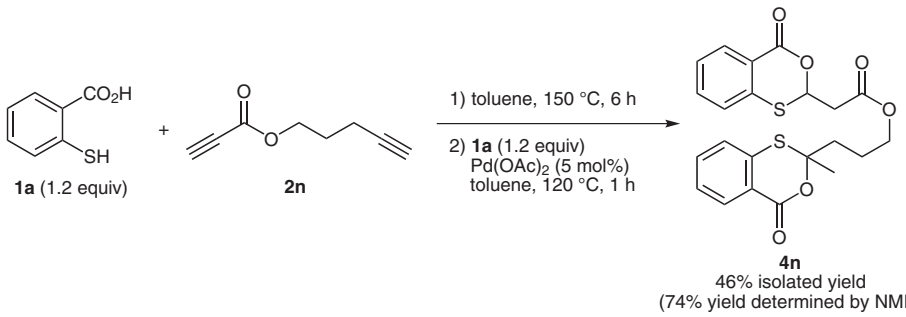
Entry	Alkyne	R	Temp (°C)	Time (h)	Product	Yield (%)
1	**2j**	CO_2Et	135	7	**4j**	86
2	**2k**	CO_2Ph	135	4	**4k**	97
3	**2l**	Ac	120	1	**4l**	84
4	**2m**	2-pyridyl	120	1	**4m**	98

[a] Reaction conditions: **1a** (0.24 mmol), **2** (0.20 mmol), toluene (1 mL), argon atmosphere.

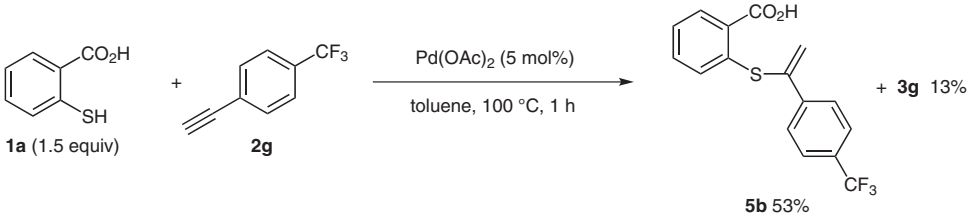
3a–**g** (entries 1–8). Since an alkyne with an electron-donating aryl group **2f** is susceptible to oligomerization, **3f** was only obtained in low yield (entry 7). Although the pyridyl-substituted alkyne **2h** required high temperatures to form the corresponding 1,3-oxathiine **3h** (entries 9 and 10), the furyl-substituted alkyne **2i** gave the corresponding product **3i** under mild conditions (entry 12). However, internal alkynes, dodec-6-yne, and diphenylacetylene, did not give the desired products.

When activated alkynes are employed, a similar reaction occurs, even in the absence of a catalyst. It was recently reported that a thiol can add to such alkynes selectively via a Michael-type reaction,[11,12] but a further cyclization step has not been explored. More recently, the ruthenium-catalyzed alkenylation of a C–H bond, and successive intramolecular Michael addition has been reported,[13] but metal-free reaction conditions were not examined. Alkynes with a β-carbonyl group **2j**–**l** provided their 1,3-oxathiine derivatives **4j**–**l**, but with different regioselectivities to that observed for the formation of **3** (Table 3). The ester moiety slowed down the intramolecular cyclization, therefore, higher temperatures and longer reaction times were necessary (entries 1 and 2).[14] Despite the result obtained for 3-ethynylpyridine (**2h**) (Table 2, entry 9), 2-ethynylpyridine (**2m**) gave the corresponding 1,3-oxathiine **4m** with no methyl group at the 2-position (entry 4).[15]

Pent-4-ynyl propiolate (**2n**) was subjected to reaction under catalyst-free conditions with **1a** at 150 °C for six hours, followed by addition of catalytic palladium(II) acetate and an additional amount of **1a** with heating at 120 °C



Equation 1



Equation 2

for one hour. This successfully generated the bis-1,3-oxathiine derivative **4n** (Equation 1).[16]

We then monitored the profile of the reaction with thiosalicylic acid (**1a**) and dodec-1-yne (**2a**) in the presence of a catalytic amount of palladium(II) acetate. To slow down the reaction rate for a finer analysis, the reaction temperature was lowered to 80 °C; **1a**, **3a**, and intermediate **5a** were measured using ^{1}H NMR after 0.5, 1, 2, 3, 6, 9, and 18 hours. The intramolecular cyclization is slower than hydrothiolation, since after 0.5 hours, more **5a** (33%) is observed than **3a** (11%) (Figure 1).

The proposed mechanism is further supported by the following investigations. The reaction of thiosalicylic acid (**1a**) and 1-(trifluoromethyl)-4-vinylbenzene (**2g**),[17] in the presence of palladium(II) acetate provided the corresponding vinyl sulfide **5b** in 53% yield, along with 1,3-oxathiine **3g** in 13% yield (Equation 2).

We went on to investigate further the mechanism of the intramolecular hydrooxycarbonylation of the vinyl sulfide **5b** (Table 4). The reaction did not occur at 120 °C in the absence and presence of palladium(II) acetate, suggesting that the palladium catalyst does not promote the cyclization (entries 1 and 2). A catalytic amount of thiosalicylic acid (**1a**) enhanced the reaction conversion (entry 3). To determine the active moiety of **1a** for the cyclization, the addition of a catalytic amount of thiophenol and benzoic acid was investigated, as a result, the thiol group was found to be necessary (entries 4 and 5). The reaction was also promoted by the radical initiator, 2,2′-azobisisobutyronitrile (entry 6), and inhibited by the radical inhibitor, galvinoxyl free radical (entry 7). These results suggest a radical-mediated initiation. The same behavior was observed for the intramolecular cyclization of a vinyl sulfide bearing an electron-withdrawing group **5c**;[18] a catalytic

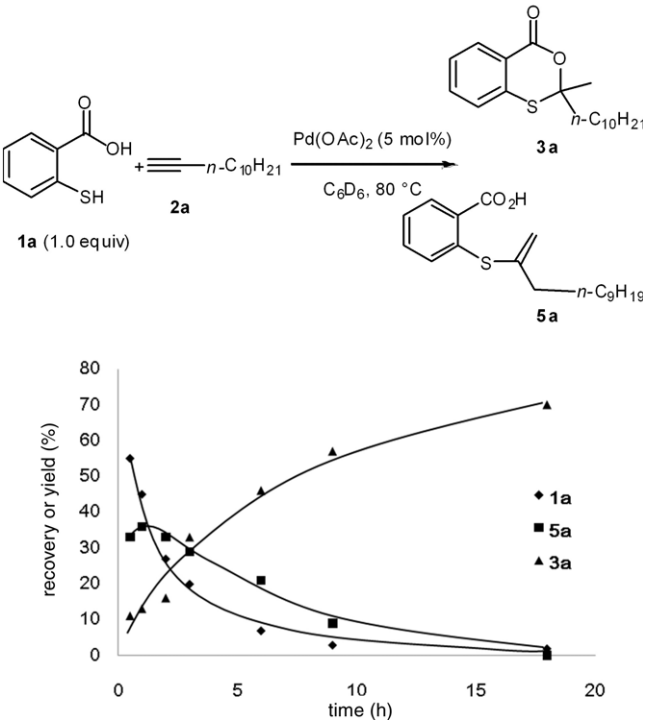
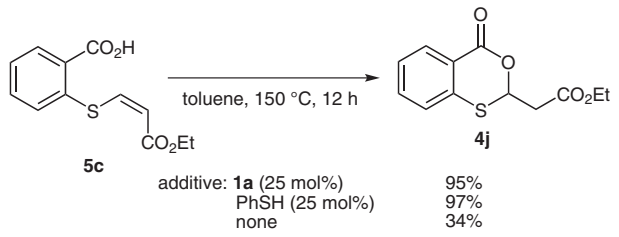


Figure 1 Reaction profile. *Reaction conditions*: $Pd(OAc)_2$ (5.0 mol%), **1a** (1.0 mmol), **2a** (1.0 mmol), benzene-d_6 (3 mL), $CHCl_2CHCl_2$ (1.0 mmol, internal standard), argon atmosphere, 80 °C. Small portions of the reaction mixture were taken at designated time points for NMR analysis.

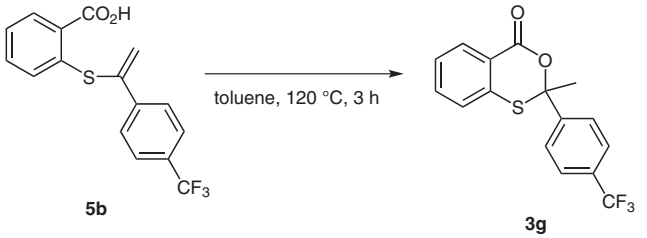
amount of **1a** and thiophenol also accelerated the formation of **4j** (Equation 3).[19]

In an attempt to broaden the scope of our strategy, other hydroheterofunctionalizations were examined (Equation 4). Under similar reaction conditions, as shown in Table 1, 2-(hydroxymethyl)thiophenol (**1b**) underwent sequen-



Equation 3

Table 4 Reaction Conditions for Intramolecular Cyclization[a]



Entry	Catalyst	Yield (%)
1	none	0
2	$Pd(OAc)_2$ (5 mol%)	0
3	**1a** (25 mol%)	67
4	PhSH (25 mol%)	59
5	$PhCO_2H$ (25 mol%)	7
6	AIBN (25 mol%)	53
7	galvinoxyl free radical (25 mol%) + PhSH (25 mol%)	3

[a] Reaction conditions: **5b** (0.05 mmol), toluene (0.3 mL), argon atmosphere, 120 °C, 3 h. The yields were determined by ^{1}H NMR using $CHCl_2CHCl_2$ as an internal standard.

tial hydrothiolation/hydroalkoxylation with alkyne **2a** in the presence of palladium(II) acetate, to give 1,3-oxathiine **6** in 81% yield. When performed at 120 °C, the yield of **6** was low (30%) and the hydrothiolation product was observed in 50% yield. This indicates that the intramolecular hydroalkoxylation is slower than not only the hydrothiolation, but also the intramolecular addition of carboxylic acid to the alkene.

In conclusion, we have developed an atom-economical protocol for the synthesis of heterocycles via two sequential hydroheterofunctionalizations. Regioselective hydrothiolations of the unactivated alkynes **2a**–**i** with a palladium catalyst, and of activated alkynes **2j**–**m** without a catalyst, led to the selective synthesis of 1,3-oxathiines **3** and **4**. This strategy was applicable to the synthesis of heterocycles containing sulfur and oxygen atoms.

All reactions were carried out in dry solvent under an argon atmosphere. Toluene was purchased from Wako Pure Chemical Industries, dried with molecular sieves 4A, and degassed before use. $Pd(OAc)_2$ was purchased from Wako Pure Chemical Industries. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using a Jeol JNM-LA400 spectrometer relative to solvent peaks [$CHCl_3$: δ = 7.26 (^{1}H), δ = 77.00 (^{13}C)]. IR (ATR) spectra were measured with a Jasco ATR PRO450-S with Ge. HRMS were measured by Jeol JMS-700 or Jeol JMS-T100LP AccuTOF LC-Plus (ESI) spectrometers with a Jeol MS-5414DART attachment.

2-Substituted 2-Methyl-3,1-benzoxathiine-4*H*-ones 3; General Procedure

Thiosalicylic acid (**1a**, 0.240 mmol), alkyne **2** (0.200 mmol), and $Pd(OAc)_2$ (0.01 mmol) were added to toluene (1 mL) under an argon atmosphere. The mixture was stirred at the temperature and for the time indicated in Table 2. The mixture was concentrated in vacuo, and the residue was purified by column chromatography to give 1,3-oxathiin **3**.

When unreacted **1a** was observed after the reaction, the mixture was washed with aq K_2CO_3, and purified by column chromatography.

2-Decyl-2-methyl-4*H*-3,1-benzoxathiin-4-one (3a)

Colorless oil; yield: 53.2 mg (0.166 mmol, 83%).

IR: 2923, 2852, 1723, 1441, 1282, 1108, 1031, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.16 (m, 1 H), 7.48–7.44 (m, 1 H), 7.29–7.25 (m, 2 H), 2.04–1.98 (m, 2 H), 1.77 (s, 3 H), 1.60–1.48 (m, 2 H), 1.24 (s, 14 H), 0.87 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 136.8, 133.8, 132.0, 127.9, 126.1, 123.6, 89.5, 41.2, 31.8, 29.5, 29.4, 29.4, 29.3, 29.2, 26.9, 24.4, 22.6, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{29}O_2S$: 321.18883; found: 321.18849.

2-Methyl-2-phenethyl-4*H*-3,1-benzoxathiin-4-one (3b)

Pale yellow oil; yield: 23.9 mg (0.084 mmol, 42%).

IR: 3062, 3027, 1716, 1441, 1284, 1113, 1031, 740, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.16 (m, 1 H), 7.53–7.46 (m, 1 H), 7.33–7.27 (m, 3 H), 7.25–7.12 (m, 4 H), 2.94–2.86 (m, 2 H), 2.38–2.30 (m, 2 H), 1.86 (s, 3 H).

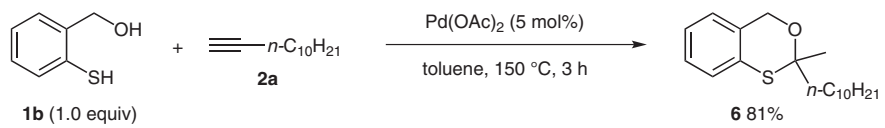
^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 140.5, 136.5, 134.0, 132.1, 128.5, 128.3, 128.0, 126.3, 126.2, 123.5, 88.9, 43.0, 30.8, 27.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_2S$: 285.09493; found: 285.09330.

2-[(Benzyloxy)methyl]-2-methyl-4*H*-3,1-benzoxathiin-4-one (3c)

Pale yellow oil; yield: 24.1 mg (0.080 mmol, 40%).

IR: 3063, 2925, 1724, 1590, 1442, 1286, 1090, 743, 698 cm^{-1}.



Equation 4

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.09 (m, 1 H), 7.46–7.41 (m, 1 H), 7.33–7.19 (m, 7 H), 4.56 (s, 2 H), 3.78–3.68 (m, 2 H), 1.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 137.2, 136.4, 133.9, 132.0, 128.4, 127.8, 127.6, 127.6, 126.2, 123.4, 87.7, 74.6, 73.6, 25.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}O_3S$: 301.08825; found: 301.08984.

2-Methyl-2-phenyl-4*H*-3,1-benzoxathiin-4-one (3d)
Pale yellow solid; yield: 36.9 mg (0.144 mmol, 72%); mp 68.5–69.3 °C.

IR: 3060, 1720, 1590, 1441, 1279, 1027, 741, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.05 (m, 1 H), 7.65–7.61 (m, 2 H), 7.42–7.37 (m, 1 H), 7.32–7.24 (m, 4 H), 7.24–7.16 (m, 1 H), 2.07 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 142.3, 136.6, 133.8, 132.0, 128.5, 128.4, 127.4, 126.5, 125.6, 124.4, 90.3, 31.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{13}O_2S$: 257.06363; found: 257.0619.

2-Methyl-2-(*p*-tolyl)-4*H*-3,1-benzoxathiin-4-one (3e)
Pale yellow oil; yield: 35.1 mg (0.130 mmol, 65%).

IR: 3029, 2925, 1721, 1592, 1441, 1279, 1112, 1084, 1030, 818, 741, 686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.04 (m, 1 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 7.42–7.36 (m, 1 H), 7.27–7.22 (m, 1 H), 7.21–7.09 (m, 1 H), 7.09 (d, *J* = 8.2 Hz, 2 H), 2.28 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 139.4, 138.4, 136.8, 133.7, 132.0, 129.1, 127.4, 126.4, 125.5, 124.4, 90.3, 31.4, 21.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}O_2S$: 271.07928; found: 271.07979.

2-(4-Methoxyphenyl)-2-methyl-4*H*-3,1-benzoxathiin-4-one (3f)
Pale yellow solid; yield: 11.4 mg (0.040 mmol, 20%); mp 80.5–81.3 °C.

IR: 2932, 2836, 1718, 1607, 1509, 1252, 1179, 1029, 832, 742, 686, 583 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.04 (m, 1 H), 7.56–7.47 (m, 2 H), 7.42–7.36 (m, 1 H), 7.28–7.16 (m, 2 H), 6.82–6.76 (m, 2 H), 3.76 (s, 3 H), 2.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 159.5, 136.8, 134.2, 133.7, 132.0, 127.4, 127.0, 126.4, 124.4, 113.7, 90.2, 55.2, 31.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{15}O_3S$: 287.07419; found: 287.07882.

2-Methyl-2-[4-(trifluoromethyl)phenyl]-4*H*-3,1-benzoxathiin-4-one (3g)
Pale yellow solid; yield: 38.3 mg (0.118 mmol, 59%); mp 59.0–59.9 °C.

IR: 3072, 2935, 1723, 1325, 1278, 1115, 1075, 745, 674 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.03 (m, 1 H), 7.75 (d, *J* = 8.2 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.44–7.38 (m, 1 H), 7.27–7.18 (m, 2 H), 2.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 146.4, 136.0, 134.0, 132.1, 130.7 (q, *J* = 32.7 Hz), 127.5, 126.8, 126.0, 125.6, 125.5, 124.1, 123.7 (q, *J* = 270.9 Hz), 89.5, 31.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{12}F_3O_2S$: 325.05101; found: 325.05493.

2-Methyl-2-(pyridin-3-yl)-4*H*-3,1-benzoxathiin-4-one (3h)
Pale yellow solid; yield: 20.0 mg (0.078 mmol, 39%); mp 81.5–82.6 °C.

IR: 3064, 2980, 2929, 1718, 1587, 1441, 1284, 1226, 1084, 1021, 957, 815, 740, 714, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (s, 1 H), 8.56 (d, *J* = 4.0 Hz, 1 H), 8.20–8.00 (m, 2 H), 7.46–7.41 (m, 1 H), 7.35 (dd, *J* = 4.8, 5.2 Hz, 1 H), 7.31–7.18 (m, 2 H), 2.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 148.7, 146.1, 138.8, 135.6, 134.5, 134.2, 132.3, 127.7, 127.1, 124.0, 123.6, 88.3, 31.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}NO_2S$: 258.05887; found 258.05913.

2-(Furan-2-yl)-2-methyl-4*H*-3,1-benzoxathiin-4-one (3i)
Yellow oil; yield: 31.5 mg (0.128 mmol, 64%).

IR: 3064, 2925, 2825, 1714, 1588, 1441, 1283, 1014, 741, 687 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.10 (m, 1 H), 7.48–7.41 (m, 1 H), 7.32–7.29 (m, 1 H), 7.28–7.22 (m, 2 H), 6.35–6.32 (m, 1 H), 6.23–6.20 (m, 1 H), 2.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 152.3, 143.0, 136.2, 133.9, 132.0, 127.3, 126.5, 123.5, 110.4, 109.1, 84.4, 28.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{11}O_3S$: 247.04289; found: 247.04298.

2-Decyl-2-methyl-4*H*-3,1-benzoxathiin (6)
2-(Hydroxymethyl)thiophenol (**1b**, 0.200 mmol), alkyne **2a** (0.200 mmol), and $Pd(OAc)_2$ (0.01 mmol) were added to toluene (1 mL) under an argon atmosphere. The mixture was stirred at 150 °C for 3 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography to give benzoxathiine **6**.

Pale yellow oil; yield: 49.7 mg (0.162 mmol, 81%).

IR: 2923, 2852, 1593, 1571, 1465, 1440, 1371, 1211, 1084, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.10 (m, 2 H), 7.10–7.00 (m, 2 H), 4.83 (d, *J* = 2.8 Hz, 2 H), 1.96–1.80 (m, 2 H), 1.63 (s, 3 H), 1.54–1.43 (m, 2 H), 1.31–1.15 (m, 14 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.6, 130.8, 128.0, 127.3, 125.5, 124.4, 85.3, 64.1, 42.4, 31.9, 29.8, 29.6, 29.6, 29.5, 29.3, 26.9, 23.9, 22.7, 14.1.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{31}OS$: 306.2017; found: 306.2006.

2-Substituted 3,1-Benzoxathiin-4*H*-ones 4; General Procedure
Thiosalicylic acid (**1a**, 0.240 mmol) and alkyne **2** (0.200 mmol) were added to toluene (1 mL) under an argon atmosphere. The mixture was stirred following the conditions shown in Table 3. The mixture was concentrated in vacuo, and the residue was purified by column chromatography to give 1,3-oxathiines **4**.

Ethyl 4-Oxo-4*H*-3,1-benzoxathiin-2-ylacetate (4j)
Pale yellow solid; yield: 43.4 mg (0.172 mmol, 86%); mp 54.9–55.9 °C.

IR: 2985, 2941, 1730, 1587, 1443, 1270, 1102, 1010, 740, 680 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.15 (m, 1 H), 7.52–7.46 (m, 1 H), 7.37–7.30 (m, 2 H), 6.00 (t, *J* = 6.6 Hz, 1 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 3.18 (dd, *J* = 7.2, 7.6 Hz, 1 H), 2.96 (dd, *J* = 5.6, 5.6 Hz, 1 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 163.3, 137.5, 133.7, 132.6, 127.6, 126.9, 123.9, 78.3, 61.5, 39.4, 14.0;

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}O_4S$: 253.05345; found: 253.05157.

Phenyl 4-Oxo-4*H*-3,1-benzoxathiin-2-ylacetate (4k)
Pale yellow solid; yield: 58.3 mg (0.194 mmol, 97%); mp 83.8–84.1 °C.

IR: 3065, 2929, 1722, 1589, 1378, 1333, 1113, 1019, 838, 741, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.42–7.25 (m, 4 H), 7.21–7.16 (m, 1 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 6.04 (t, *J* = 6.6 Hz, 1 H), 3.37 (dd, *J* = 7.2, 7.2 Hz, 1 H), 3.16 (dd, *J* = 5.2, 5.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 163.1, 150.2, 137.3, 133.8, 132.7, 129.5, 127.7, 127.0, 126.2, 123.9, 121.3, 78.1, 39.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}O_4S$: 301.05345; found: 301.05271.

2-(2-Oxopropyl)-4*H*-3,1-benzoxathiin-4-one (4l)
Pale yellow oil; yield: 37.3 mg (0.168 mmol, 84%).

IR: 3064, 2923, 1705, 1588, 1442, 1291, 1116, 1028, 741, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.16 (m, 1 H), 7.53–7.46 (m, 1 H), 7.37–7.29 (m, 2 H), 6.07 (dd, *J* = 5.2, 4.8 Hz, 1 H), 3.35 (dd, *J* = 7.2, 7.2 Hz, 1 H), 3.02 (dd, *J* = 4.8, 5.2 Hz, 1 H), 2.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.2, 163.5, 137.7, 133.6, 132.6, 127.6, 126.8, 123.9, 77.6, 47.1, 30.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{11}O_3S$: 223.04289; found: 223.04122.

2-(Pyridin-2-ylmethyl)-4*H*-3,1-benzoxathiin-4-one (4m)
Pale yellow solid; yield: 50.4 mg (0.196 mmol, 98%); mp 52.5–53.8 °C.

IR: 3062, 2925, 1719, 1588, 14391, 1279, 1110, 1029, 741, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 4.8 Hz, 1 H), 7.58–7.55 (m, 1 H), 7.13–7.06 (m, 1 H), 6.90–6.83 (m, 1 H), 6.76–6.69 (m, 3 H), 6.66–6.60 (m, 1 H), 5.52 (t, *J* = 6.6 Hz, 1 H), 3.05 (dd, *J* = 6.8, 7.2 Hz, 1 H), 2.88 (dd, *J* = 6.4, 6.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 154.7, 149.5, 138.3, 136.8, 133.5, 132.5, 127.6, 126.6, 124.4, 124.1, 122.5, 82.0, 42.6.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}NO_2S$: 258.05887; found: 258.05886.

3-(2-Methyl-4-oxo-4*H*-3,1-benzoxathiin-2-yl)propyl 4-Oxo-4*H*-3,1-benzoxathiin-2-ylacetate (4n); One-Pot Synthesis
Thiosalicylic acid (**1a,** 0.240 mmol) and pent-4-ynyl propiolate (**2n**, 0.200 mmol) were added to toluene (1 mL) under an argon atmosphere. The mixture was stirred at 150 °C for 6 h and then $Pd(OAc)_2$ (0.01 mmol) and thiosalicylic acid (**1a**, 0.240 mmol) were added. The mixture was heated at 120 °C for 3 h, and concentrated under reduced pressure. The residue was added $CHCl_2CHCl_2$ (0.200 mmol) as an internal standard for NMR analysis. The crude NMR yield was determined by comparison with integration values of the protons of $CHCl_2CHCl_2$ (δ = 5.93, 2 H) and the methyl moiety of **4n** (δ = 1.81, 3 H). The crude mixture was purified by column chromatography (silica gel) to give **4n** as a pale yellow oil; yield: 40.9 mg (0.092 mmol, 46%).

IR: 3064, 2928, 1720, 1589, 1440, 1330, 1281, 1241, 1167, 1112, 1017, 914, 741, 685 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 6.8 Hz, 2 H), 7.56–7.43 (m, 2 H), 7.40–7.32 (m, 2 H), 7.32–7.25 (m, 2 H), 6.05–5.92 (m, 1 H), 4.20 (t, *J* = 6.2 Hz, 2 H), 3.23–3.12 (m, 1 H), 2.96 (dd, *J* = 6.0, 5.2 Hz, 1 H), 2.18–2.05 (m, 2 H), 2.03–1.92 (m, 2 H), 1.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 163.2, 163.1, 137.4, 136.4, 134.0, 133.8, 132.6, 132.0, 128.0, 127.7, 126.9, 126.4, 123.9, 123.3, 88.7, 78.1, 64.7, 39.3, 37.6, 27.1, 23.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}O_6S_2$: 445.07795; found: 445.07988.

Pent-4-ynyl 4-Oxo-4*H*-3,1-benzoxathiin-2-ylacetate (4n′)
Thiosalicylic acid (**1a,** 0.240 mmol) and pent-4-ynyl propiolate (**2n**, 0.200 mmol) were added to toluene (1 mL) under an argon atmosphere. The mixture was stirred at 150 °C for 6 h. Then, the mixture was concentrated under reduce pressure. The residue was purified by column chromatography (silica gel) to give **4n′** as a pale yellow oil; yield: 48.2 mg (0.166 mmol, 83%).

IR: 3291, 2961, 1725, 1589, 1441, 1332, 1276, 1216, 1166, 1110, 1016, 743, 641 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.15 (m, 1 H), 7.55–7.43 (m, 1 H), 7.37–7.32 (m, 2 H), 6.00 (dd, *J* = 5.6, 5.6 Hz, 1 H), 4.28 (t, *J* = 6.4 Hz, 2 H), 3.19 (dd, *J* = 7.2, 7.6 Hz, 1 H), 2.98 (dd, *J* = 5.6, 5.6 Hz, 1 H), 2.38–2.22 (m, 2 H), 1.97 (t, *J* = 2.6 Hz, 1 H), 1.94–1.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 163.2, 137.4, 133.7, 132.6, 127.6, 126.9, 123.9, 82.7, 78.1, 69.1, 63.9, 39.3, 27.2, 15.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}O_4S$: 291.06910; found: 291.06954.

2-({1-[4-(Trifluoromethyl)phenyl]vinyl}sulfanyl)benzoic Acid (5b)
Thiosalicylic acid (**1a**, 3.00 mmol), 1-(trifluoromethyl)-4-vinylbenzene (**2g**, 2.00 mmol), and $Pd(OAc)_2$ (0.1 mmol) were added to toluene (10 mL) under an argon atmosphere. The mixture was stirred at 100 °C for 1 h. Then, the mixture was concentrated under reduce pressure. The residue was purified by column chromatography (silica gel) to give **5b** and **3g** in 53% and 13% yields, respectively.

Benzoic Acid 5b
Pale yellow solid; yield: 344 mg (1.06 mmol, 53%); mp 73.2–74.9 °C.

IR: 2960, 1678, 1408, 1323, 1260, 1167, 1114, 1064, 846, 742, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.1 Hz, 2 H), 7.74 (d, *J* = 8.1 Hz, 2 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.38–7.31 (m, 2 H), 6.38 (s, 1 H), 6.29 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 141.8, 140.6, 140.6, 133.1, 132.3, 130.3 (t, *J* = 32.8 Hz), 128.7, 127.3, 126.4, 126.3, 125.5 (d, *J* = 3.6 Hz), 125.0, 123.9 (q, *J* = 270.9 Hz).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}O_2S$: 325.05101; found: 325.05137.

(*Z*)-2-{[2-(Ethoxycarbonyl)vinyl]sulfanyl}benzoic Acid (5c)
Methyl thiosalicylate (4.00 mmol) and ethyl propiolate (**2j**, 4.00 mmol) were added to H_2O (10 mL) under an argon atmosphere. The mixture was stirred at 25 °C for 3 h. Then, the mixture was extracted with EtOAc, concentrated in vacuo, and the residue was purified by column chromatography to give the corresponding vinyl sulfide. The product was hydrolyzed with aq KOH to give **5c** as a pale yellow solid; yield: 434 mg (1.72 mmol, 43%); mp 111.5–112.1 °C.

IR: 3074, 2988, 2646, 1687, 1583, 1469, 1267c, 1227, 1187, 1030, 820, 748, 649 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.0 Hz, 1 H), 7.57–7.43 (m, 2 H), 7.43–7.32 (m, 1 H), 7.29 (d, *J* = 10.4 Hz, 1 H), 6.00 (d, *J* = 10.4 Hz, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 1.33 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 166.4, 148.1, 148.1, 139.4, 133.2, 131.6, 130.3, 127.4, 115.0, 60.5, 14.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{13}O_4S$: 253.05345; found: 253.05335.

(*E*)-{[2-(Ethoxycarbonyl)vinyl]sulfanyl}benzoic Acid (5c′)
Methyl thiosalicylate (4.00 mmol) and ethyl propiolate (**2j**, 4.00 mmol) were added to toluene (10 mL) under an argon atmosphere. The mixture was stirred at 150 °C for 3 h. Then, the mixture was extracted with EtOAc, concentrated in vacuo, and the residue was purified by column chromatography to give the corresponding vinyl sulfides. The product was hydrolyzed with aq KOH to give a mixture of **5c** and **5c′**. The mixture was separated by column chromatography (silica gel).

(*E*)-Isomer 5c′
Pale yellow solid; yield: 595 mg (2.36 mmol, 59%); mp 134.5–135.3 °C.

IR: 3072, 2979, 2649, 1685, 1596, 1463, 1413, 1260, 1157, 1027, 920, 741, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.11 (m, 1 H), 7.88 (d, *J* = 15.2 Hz, 1 H), 7.65–7.55 (m, 1 H), 7.53–7.47 (m, 1 H), 7.41–7.35 (m, 1 H), 6.16 (d, *J* = 15.2 Hz, 1 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 165.3, 144.3, 137.4, 133.6, 132.2, 130.2, 128.3, 126.9, 119.8, 60.6, 14.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}O_4S$: 253.05345; found: 253.05335.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(7) Conversion of **1a** is more than 80%; we detected isomers of **3a** and a dimer of **1a** by GC-MS.

(8) In the $Pd(OAc)_2$ catalyzed reaction, various solvents were investigated; DMSO, 0%; EtOH, 9%, DMF, 27%; 1,4-dioxane, 60%; 1,2-dichloroethane, 90%; hexane, 88%.

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(14) When the reactions were stopped after 1 h, **4j** and **4k** were obtained in 48% and 69% yields, respectively.

(15) Even in the presence of the palladium catalyst, a product with a structure like **3** was not observed.

(16) We also obtained the intermediate. If the reaction is stopped before the addition of the palladium catalyst, the activated alkyne moiety is selectively functionalized to give 1,3-oxathiine **4n′** in 83% yield (Figure 2).

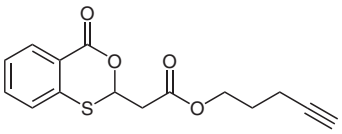

Figure 2

(17) We chose **2g** to isolate a vinyl sulfide intermediate, since intramolecular cyclization of **5b** was slow. Other alkynes also gave the corresponding vinyl sulfides, but with a low yield.

(18) The *trans*-vinyl sulfides **5c′** (see Supporting Information) were also transformed into **4j** under the same reaction conditions of Equation 2.

(19) In this case, AIBN did not work as an appropriate promoter; **4j** was obtained in 52% yield and unknown mixture of products was observed.