Multi-component Coupling Reaction Using Arynes: Synthesis of Xanthene Derivatives

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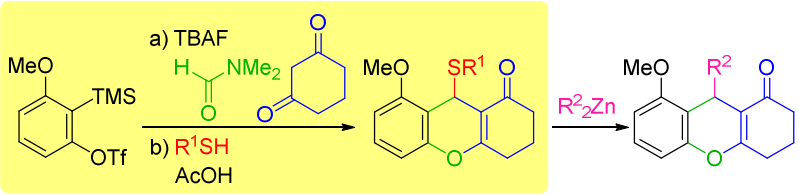
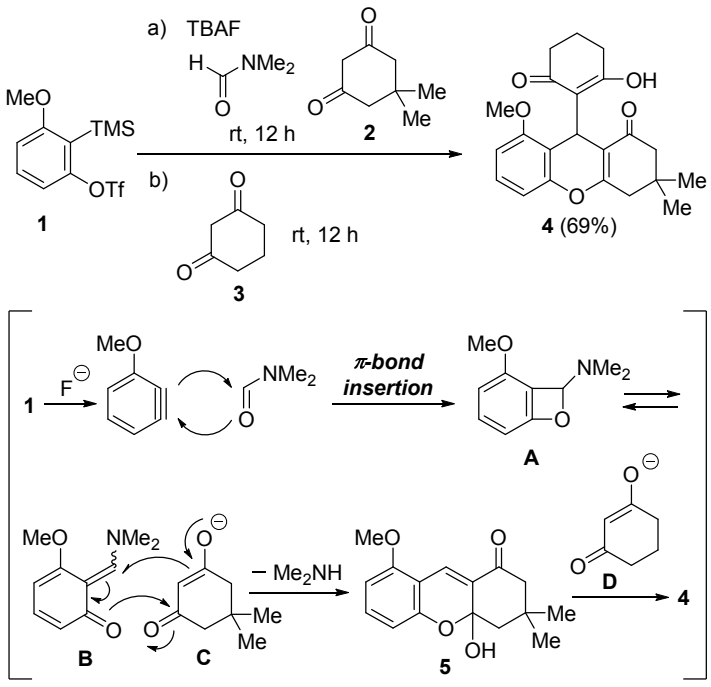
ABSTRACT

One-pot synthesis of xanthene derivatives was achieved by a route involving the cascade three-component coupling reaction of arynes with DMF and active methylenes followed by the S_N2' reaction of three-component coupling products with thiols. The reactivity of three-component coupling products toward nucleophiles and the further conversion of oxygen heterocycles allowing facile incorporation of structural variety were studied.



Synthetic strategies involving cascade/domino/tandem process offer the advantage of multiple carbon-carbon and/or carbon-heteroatom bond formations in a single operation.[1,2] In recent years, arynes have gained increased attention as highly reactive species for constructing the multi-substituted arenes.[3] In particular, the multi-component

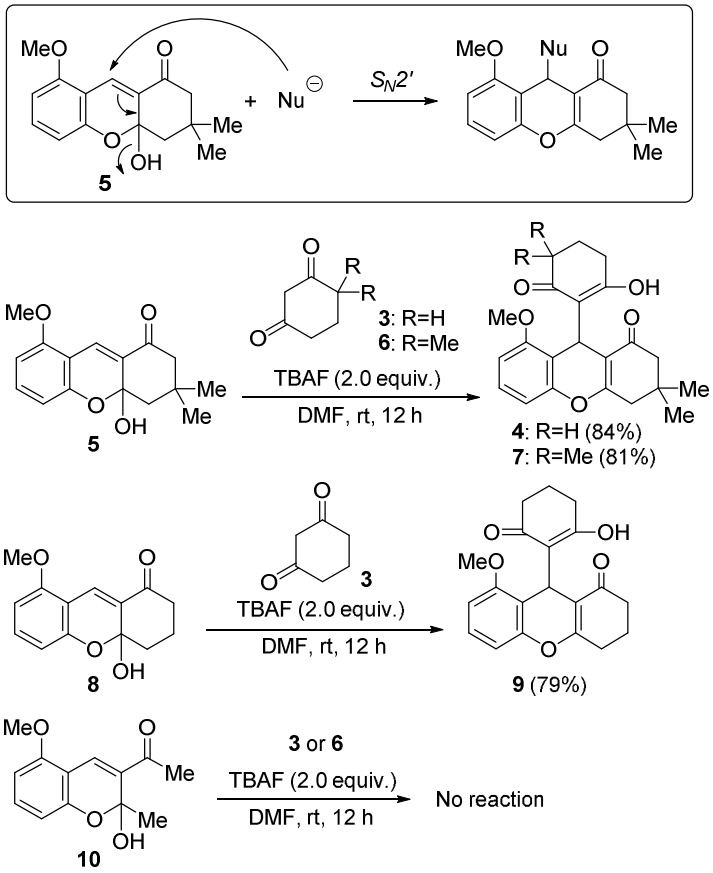
coupling reactions using arynes continue to attract much interest.[4,5] Recently, we reported the insertion of arynes into the C=O bond of formamides[6,7] and its application to the cascade process trapping the transient intermediates with nucleophiles or dienophiles.[8] In this paper, we describe the synthetic application to prepare the oxygen heterocycles such as xanthene derivatives *via* a route involving three-component coupling reaction of arynes with *N*,*N*-dimethylformamide (DMF) and active methylenes followed by the S_N2' reaction of three-component coupling products with thiols. We also report the further conversion of xanthene derivatives allowing facile incorporation of structural variety.



Scheme 1. One-pot four-component coupling reaction.[8a]

In our previous study,[8a] we reported that four-component coupling reaction using two different 1,3-diketones

2 and **3** gave the xanthene derivative **4** by a one-pot procedure (Scheme 1). This transformation involves the insertion of aryne into the C=O of DMF giving benzoxetene **A** and *ortho*-quinone methide **B**,[9] which are trapped by anion **C**. The xanthene **4** is formed by the S_N2' reaction of three-component coupling product **5** and anion **D**.



Scheme 2. Reaction of three-component coupling products **5**, **8** and **10** with second nucleophiles.

However, the structural variety of oxygen heterocycles prepared by this four-component coupling reaction is limited as shown below. For further expansion of this multi-step sequential transformation, we first directed our attention to the reactivity of three-component coupling products such as **5** and the adaptability of second nucleophiles

in the S_N2' reaction trapping **5**. Our experiments began with the investigation of the reactivity of **5**, **8** and **10** (Scheme 2). The S_N2' reaction of **5** with 1,3-diketones **3** or **6** proceeded effectively to give xanthenes **4** and **7** in good chemical yields. Similarly, tricyclic substrate **8** has shown the excellent reactivity toward 1,3-diketone **3**. In marked contrast, no reaction was observed when bicyclic substrate **10** was employed. Next, the adaptability of second nucleophiles was studied. Under the similar conditions, the acyclic active methylenes such as acetylacetone and diethyl malonate did not work as a second nucleophile trapping **5**. Consequently, the usable nucleophile is limited to cyclic 1,3-diketones.

To understand the different reactivities between tricyclic substrates and bicyclic substrate, we calculated the stable conformations of **8** and **10** (Figure 1).[10] In the optimized structure of **8**, the hydroxyl group occupies pseudo-axial direction which would be crucial for the efficiency of S_N2' process. In contrast, the computational structure optimization of **10** supported the formation of stable intramolecular hydrogen bond between the hydroxyl group and the carbonyl group.

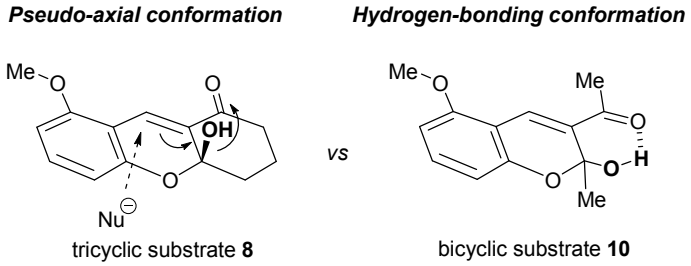
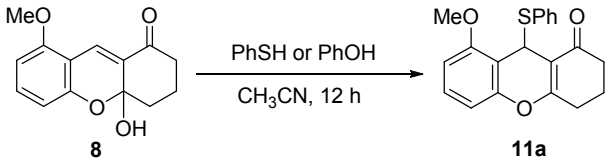


Figure 1. Stable conformations of substrates **8** and **10**.

With these results in mind, the reactive tricyclic substrate **8** was used in further investigations screening the usable nucleophiles. We found that thiophenol acted as a second nucleophile in S_N2' reaction of tricyclic substrate **8**

(Table 1). Initially, we allowed tricyclic substrate **8** to react with 2 equivalents of thiophenol in CH_3CN at room temperature (entry 1). The desired xanthene derivative **11a** having a phenylthio group at 9 position was obtained in 22% yield, accompanied by 43% yield of the recovered starting material **8**. The chemical yield of **11a** increased to 51% when the reaction was carried out under reflux conditions (entry 2). The further improvement in the chemical yield was observed by employing acetic acid as an additive at room temperature (entry 3), although the use of trifluoroacetic acid (TFA) was less effective (entry 4). These results indicate that the mild Brønsted acid is suitable for the activation of the hydroxyl group as a leaving group. In contrast, the reaction of bicyclic substrate **10** with thiophenol did not proceed effectively (entry 5). For comparison, phenol did not work even under the acidic conditions (entries 6 and 7).

Table 1. Reaction with thiophenol or phenol [a]



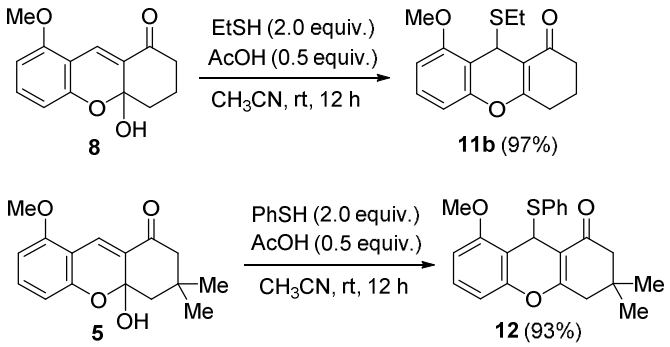
8 **11a**

Enrty	Substrate	Nucleophile (2.0 equiv.)	Additive (0.5 equiv.)	Temp.	Yield (%)[b]
1	**8**	PhSH	none	rt	22 (43)
2	**8**	PhSH	none	reflux	51 (10)
3	**8**	PhSH	AcOH	rt	89
4	**8**	PhSH	TFA	rt	complex mixture
5	**10**	PhSH	AcOH	rt	not detected
6	**8**	PhOH	none	rt	trace
7	**8**	PhOH	AcOH	rt	trace

[a] Reactions were carried out with **8** or **10** (1.0 equiv.) and nucleophile (2.0 equiv.) in CH_3CN.
[b] Isolated yield. The yield in parentheses is for the recovered substrate **8**.

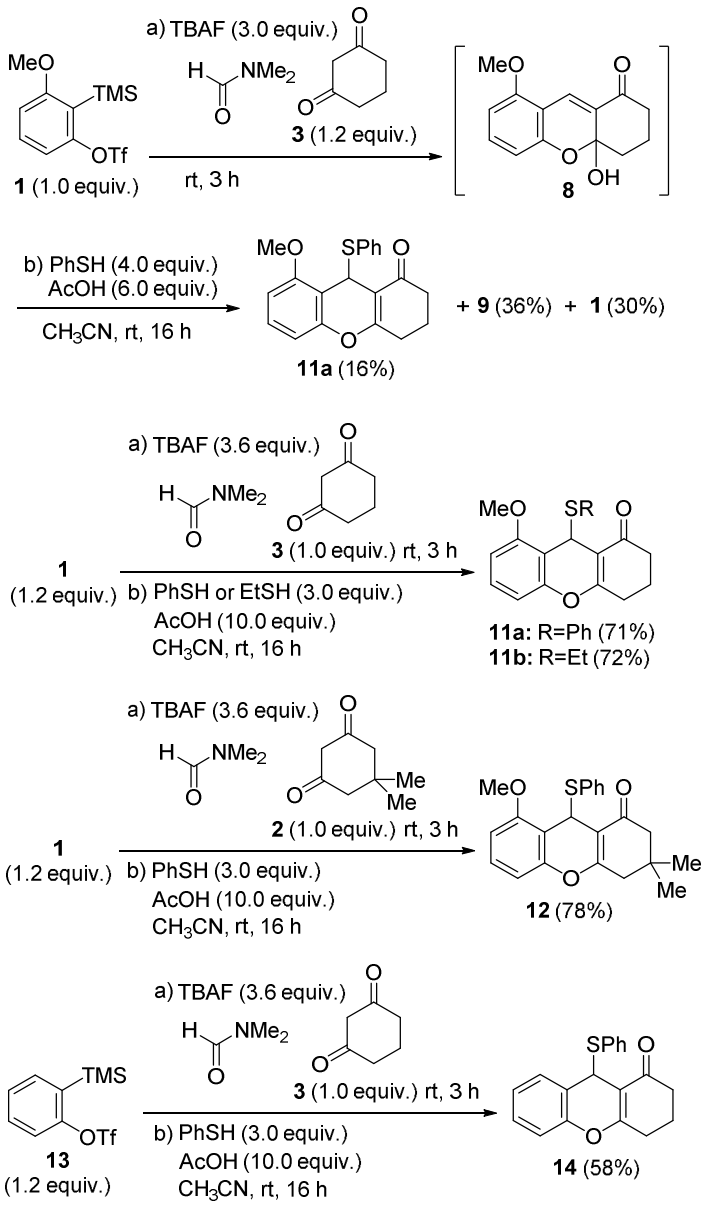
Next, we allowed tricyclic substrate **8** to react with ethanethiol (EtSH) in the presence of acetic acid (Scheme 3). As expected, the xanthene derivative **11b** was isolated in 97% yield. Good yield was obtained when tricyclic

substrate **5** was employed.



Scheme 3. Reaction of **8** or **5** with thiols.

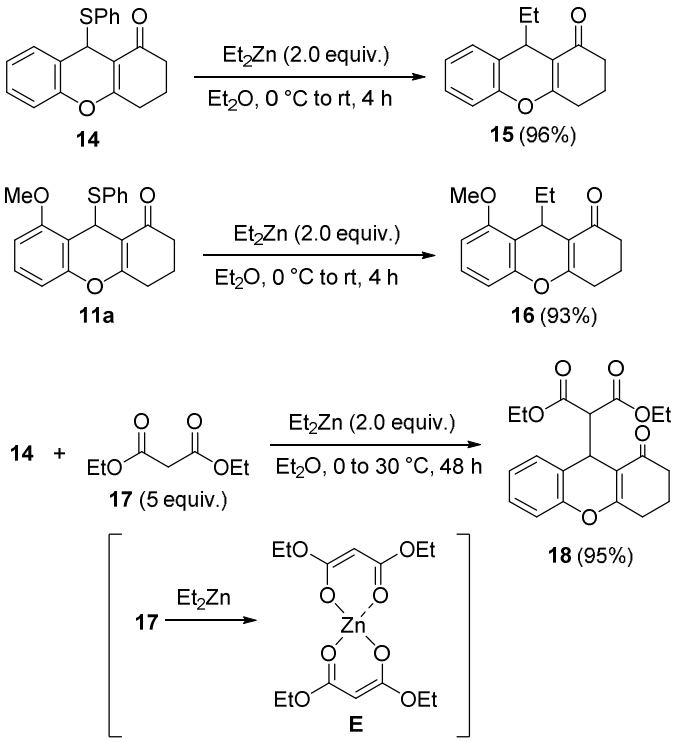
We were gratified to observe the sufficient nucleophilicity of thiols toward tricyclic substrates under mild acidic conditions. Therefore, the S_N2' reaction with thiols was next applied to the one-pot four-component coupling reaction starting from the insertion of arynes to DMF (Scheme 4).[11] After a solution of triflate **1** (1.0 equiv.), 1,3-diketone **3** (1.2 equiv.) and anhydrous TBAF (3.0 equiv.) in DMF was stirred at room temperature for 3 h, a solution of thiophenol (4.0 equiv.) and acetic acid (6.0 equiv.) in CH_3CN was added to the reaction mixture. Although the desired xanthene **11a** was obtained in 16% yield, xanthene **9**, generated by the reaction of **8** with 1,3-diketone **3**, was a major product. Improvement in the chemical yield of xanthene **11a** was observed by changing the amounts of triflate **1** and 1,3-diketone **3**. When triflate **1** (1.2 equiv.) and 1,3-diketone **3** (1.0 equiv.) were employed, the fromation of **9** was mostly suppressed to afford **11a** in 71% yield. Under the similar reaction conditions, four-component coupling reactions giving xanthenes **11b**, **12** and **14** proceeded effectively by a one-pot procedure. These transformations involve the formation of two C–C, two C–O and C–S bonds.



Scheme 4. One-pot four-component coupling reactions.

To synthesize xanthene derivatives with structural variety, we finally investigated the further conversion of the four-component coupling products **14** and **11a** having a phenylthio group at 9 position (Scheme 5). To introduce the alkyl group, the nucleophilic substitution of **14** with organometallic reagents was evaluated. Among several reagents,[12]

the use of diethylzinc led to the formation of the ethylated xanthene **15** in 96% yield. Similarly, the ethylated xanthene **16** was formed form **11a**. This conversion was successfully applied to the reaction using diethyl malonate **17** and Et_2Zn *via* the formation of zinc complex **E**.[12] As expected, the desired product **18** was obtained in 95% yield, allowing facile incorporation of structural variety. It is important to note that the obtained xanthene derivatives **15**, **16** and **18** could not be synthesized by the direct S_N2'reaction of three-component coupling products such as **8** with Et_2Zn or diethyl malonate **17**.



Scheme 5. Further conversion of **14** and **11a** using dialkylzincs.

In conclusion, we have developed the multi-component coupling reaction for the synthesis of xanthene derivatives. Most of the synthetic approaches to the benzo-fused oxygen heterocycles have involved the use of phenol

derivatives.[13] Therefore, new approaches using transition metal-catalyzed aromatic C–O bond formation continues to attract much interest.[14] This cascade reaction is important as an alternative approach involving the aromatic C–O bond-forming process using arynes and DMF.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were measured at 400 or 600 MHz with $CDCl_3$ or C_6D_6 as an internal standard (7.26 or 7.15 ppm, respectively). ^{13}C NMR spectra were measured at 101 or 151 MHz with $CDCl_3$ or C_6D_6 as an internal standard (77.0 or 128.0 ppm, respectively). HRMS measurements using electrospray ionization (ESI) were performed with a time-of-flight (TOF) mass analyzer.

We reported the experimental procedure for preparing of 2*H*-chromenes **8** and **10** in our previous paper.[8a] According to this procedure, 2*H*-chromene **5** was prepared.[8e]

2,3,4,4a-Tetrahydro-4a-hydroxy-8-methoxy-3,3-dimethyl-1*H*-xanthen-1-one (5). Colorless crystals. Sublimated decomposition Mp 118-120 °C (CH_2Cl_2–*i*-PrOH). IR (KBr) 3417, 2957, 1671, 1603, 1566, 1467 cm^{-1}. ^{1}H NMR (C_6D_6) δ 8.21 (1H, s), 6.94 (1H, br t, *J* = 8.0 Hz), 6.73 (1H, br d, *J* = 8.0 Hz), 6.03 (1H, br d, *J* = 8.0 Hz), 3.20 (3H, s), 2.39 (1H, br s), 2.32 (1H, dd, *J* = 16.0, 1.5 Hz), 2.13 (1H, dd, *J* = 14.0, 1.0 Hz), 2.03 (1H, br d, *J* = 14.0 Hz), 1.91 (1H, br d, *J* = 16.0 Hz), 0.94 (3H, s), 0.69 (3H, s). ^{13}C NMR (C_6D_6) δ 196.1, 158.2, 153.9, 132.2, 128.7, 124.7, 111.0, 110.3, 103.4, 96.7, 55.2, 52.6, 48.7, 31.4, 30.3, 27.8. HRMS (ESI^+) calcd for $C_{16}H_{18}O_4Na$ ($M+Na^+$): 297.1097, Found: 297.1095.

General procedure for the reaction of 5, 8 and 10 with 1,3-diketones 3 or 6. To a solution of **5**, **8** or **10** (0.10 mmol) and 1,3-diketones **3** or **6** (0.10 mmol) in DMF (1.0 mL) was added a solution of anhydrous TBAF (63 mg, 0.20 mmol) in DMF (0.10 mL) under argon atmosphere at room temperature. After being stirred at room temperature for 12 h, silica gel (0.50 g) was added to the reaction mixture, which was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:10–1:0 with 2% CH_2Cl_2) afforded the products **4** (31 mg, 84%), **7** (32 mg, 81%) and **9** (27 mg, 79%). We reported the characterization data of **4** in our previous paper.[8a]

2,3,4,9-Tetrahydro-9-(2-hydroxy-5,5-dimethyl-6-oxo-1-cyclohexen-1-yl)-8-methoxy-3,3-dimethyl-1*H*-xanthen-1-one (**7**)**.** Brown solid. IR (KBr) 3179, 2960, 1713, 1618, 1588, 1469, 1381 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.49 (1H, s), 7.11 (1H, br dt, *J* = 8.2, 1.4 Hz), 6.68 (1H, br dd, *J* = 8.2, 1.0 Hz), 6.54 (1H, br d, *J* = 8.2 Hz), 4.69 (1H, s), 3.72 (3H, s), 2.78-2.44 (2H, m), 2.34 (1H, d, *J* = 17.9 Hz), 2.31 (1H, d, *J* = 17.9 Hz), 2.00 (1H, d, *J* = 17.4 Hz), 1.91 (1H, d, *J* = 17.4 Hz), 1.90-1.75 (2H, m), 1.12 (3H, s), 1.11 (3H, s), 0.97 (3H, s), 0.93 (3H, s). ^{13}C NMR ($CDCl_3$) δ 205.9, 196.8, 170.9, 168.4, 156.3, 151.9, 127.5, 116.8, 112.5, 110.4, 108.2, 105.7, 55.3, 50.7, 43.1, 40.1, 33.5, 30.6, 30.0, 25.4, 25.1, 24.9, 24.3, 23.9. HRMS (ESI^+) calcd for $C_{24}H_{29}O_5$ ($M+H^+$): 397.2010, Found: 397.2005.

2,3,4,9-Tetrahydro-9-(2-hydroxy-6-oxo-1-cyclohexen-1-yl)-8-methoxy-1*H*-xanthen-1-one (**9**)**.** Colorless crystals. Mp 182.5-184 °C (CH_2Cl_2–*i*-PrOH). IR (KBr) 3072, 2945, 1646, 1617, 1588, 1469 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.55 (1H, s), 7.13 (1H, t, *J* = 8.0 Hz), 6.69 (1H, dd, *J* = 8.0, 1.0 Hz), 6.57 (1H, dd, *J* = 8.0, 1.0 Hz), 4.73 (1H, s), 3.75 (3H, s), 2.74 (1H, dt, *J* = 18.0, 5.0 Hz), 2.60-2.50 (3H, m), 2.43-2.36 (2H, m), 2.13 (1H, m), 2.06-1.99 (3H, m), 1.82 (1H, m), 1.72

(1H, m). ^{13}C NMR ($CDCl_3$) δ 201.2, 197.2, 172.7, 170.7, 156.8, 151.9, 127.6, 118.2, 112.9, 112.6, 108.3, 106.4, 55.7, 37.2, 36.0, 29.6, 27.8, 23.7, 20.0, 19.9. HRMS (ESI^+) calcd for $C_{20}H_{21}O_5$ ($M+H^+$): 341.1384, Found: 341.1383.

General procedure for the reaction of 5 and 8 with thiols. To a solution of **5** or **8** (0.10 mmol) in CH_3CN (0.85 mL) were added thiophenol or ethanethiol (0.20 mmol) and acetic acid (3.0 μL, 0.050 mmol) under argon atmosphere at room temperature. After being stirred at room temperature for 12 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:20–1:0 with 2% CH_2Cl_2) afforded the products **11a** (30 mg, 89%), **11b** (28 mg, 97%) and **12** (34 mg, 93%).

2,3,4,9-Tetrahydro-8-methoxy-9-(phenylthio)-1*H*-xanthen-1-one (11a). Colorless crystals. Mp 130-133 °C (CH_2Cl_2–hexanes). IR (KBr) 2943, 2892, 1641, 1585, 1482, 1470, 1382 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.30 (1H, br t, *J* = 7.8 Hz), 7.14 (3H, br t, *J* = 7.8 Hz), 7.00 (2H, br dd, *J* = 7.8, 1.0 Hz), 6.68 (1H, d, *J* = 8.2 Hz), 6.41 (1H, d, *J* = 8.2 Hz), 5.49 (1H, s), 3.89 (3H, s), 2.52 (1H, dt, *J* = 17.6, 1.0 Hz), 2.41-2.32 (2H, m), 2.22 (1H, dt, *J* = 17.6, 1.0 Hz), 2.02-1.89 (2H, m). ^{13}C NMR ($CDCl_3$) δ 195.8, 167.7, 156.9, 151.3, 137.1, 131.9, 128.8, 128.1, 127.8, 111.8, 110.7, 108.2, 106.5, 55.9, 36.9, 35.6, 27.4, 20.2. HRMS (ESI^+) calcd for $C_{20}H_{18}O_3SNa$ ($M+Na^+$): 361.0869, Found: 361.0872.

2,3,4,9-Tetrahydro-8-methoxy-9-(ethylthio)-1*H*-xanthen-1-one (11b). Colorless oil. IR (KBr) 2959, 1643, 1589, 1483, 1379 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.18 (1H, br t, *J* = 8.2 Hz), 6.68 (1H, br d, *J* = 8.2 Hz), 6.67 (1H, br d, *J* = 8.2 Hz), 5.20 (1H, s), 3.89 (3H, s), 2.72 (1H, dt, *J* = 17.9, 5.0 Hz), 2.62-2.34 (5H, m), 2.34-2.05 (2H, m), 1.12 (3H, t, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 196.4, 167.5, 156.9, 151.5, 128.0, 112.6, 112.3, 108.5, 106.8, 55.9, 37.0, 30.2, 27.7, 24.3, 20.4, 14.0. HRMS (ESI^+) calcd for $C_{16}H_{18}O_3SNa$ ($M+Na^+$): 313.0869, Found: 313.0868.

2,3,4,9-Tetrahydro-8-methoxy-3,3-dimethyl-9-(phenylthio)-1*H*-xanthen-1-one (12). Colorless crystals. Mp 147-148 °C (CH_2Cl_2–hexanes). IR (KBr) 2958, 1664, 1647, 1585, 1469, 1382 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.29-7.25 (1H, m), 7.17-7.12 (3H, m), 7.05 (2H, br dt, *J* = 8.2, 1.6 Hz), 6.66 (1H, br d, *J* = 8.2 Hz), 6.45 (1H, br d, *J* = 8.2 Hz), 5.50 (1H, s), 3.83 (3H, s), 2.32 (1H, d, *J* = 16.0 Hz), 2.31 (1H, d, *J* = 16.0 Hz), 2.25 (1H, d, *J* = 17.4 Hz), 2.19 (1H, d, *J* = 17.4 Hz), 1.12 (3H, s), 1.03 (3H, s). ^{13}C NMR ($CDCl_3$) δ 195.8, 166.0, 156.9, 151.5, 136.5, 132.5, 128.5, 128.2, 127.9, 111.8, 110.2, 108.4, 106.4, 55.8, 50.9, 41.3, 35.9, 32.1, 28.9, 28.1. HRMS (ESI^+) calcd for $C_{22}H_{22}O_3SNa$ ($M+Na^+$): 389.1182, Found: 389.1184.

General procedure for the one-pot four-component coupling reaction. To a solution of triflates **1** or **13** (0.24 mmol) and 1,3-diketones **2** or **3** (0.20 mmol) in DMF (2.0 mL) was added a solution of anhydrous TBAF (227 mg, 0.72 mmol) in DMF (0.36 mL) under argon atmosphere at room temperature. After being stirred at room temperature for 3 h, a solution of thiophenol or ethanethiol (0.60 mmol) and acetic acid (114 μL, 2.0 mmol) in CH_3CN (2.0 mL) was added to the reaction mixture. After being stirred at room temperature for 16 h, silica gel (2.0 g) was added to the reaction mixture, which was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:20–1:0 with 2% CH_2Cl_2) afforded the products **11a** (48 mg, 71%), **11b** (42 mg, 72%), **12** (57 mg, 78%) and **14** (36 mg, 58%).

2,3,4,9-Tetrahydro-9-(phenylthio)-1*H*-xanthen-1-one (14).[13a] Colorless crystals. Mp 86-87 °C (CH_2Cl_2–hexanes). IR (KBr) 3058, 2950, 1663, 1640, 1579, 1483, 1458, 1382 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.36-7.34 (1H, m), 7.31 (1H, br t, *J* = 7.8 Hz), 7.19-7.13 (4H, m), 6.99 (2H, br d, *J* = 7.8 Hz), 6.78-6.73 (1H, m), 5.32 (1H, s), 2.57 (1H, dt, *J* = 17.0, 5.0

Hz), 2.48-2.31 (3H, m), 2.08-1.99 (2H, m). ^{13}C NMR ($CDCl_3$) δ 196.1, 168.0, 150.5, 137.0, 131.1, 129.6, 129.0, 128.1 (2C), 125.1, 122.5, 115.8, 110.5, 40.4, 36.8, 27.5, 20.2. HRMS (ESI^+) calcd for $C_{19}H_{16}O_2SNa$ ($M+Na^+$): 331.0763, Found: 331.0764.

General procedure for the reaction of 11a and 14 with Et_2Zn. To a solution of xanthenes **11a** or **14** (0.10 mmol) in diethyl ether (2.0 mL) was added Et_2Zn (1.05 M in hexane, 0.19 mL, 0.20 mmol) under argon atmosphere at 0 °C. After being stirred at room temperature for 4 h, the reaction mixture was diluted with diethyl ether and 0.1 M HCl, and then extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:6–1:0 with 2% CH_2Cl_2) afforded the products **15** (22 mg, 96%) and **16** (24 mg, 93%).

2,3,4,9-Tetrahydro-9-ethyl-1*H*-xanthen-1-one (15). Colorless crystals. Mp 73-74 °C (hexanes). IR (KBr) 2959, 2871, 1643, 1581, 1486, 1456, 1388 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.20-7.08 (3H, m), 6.99 (1H, br d, J = 8.3 Hz), 3.94 (1H, t, J = 5.0 Hz), 2.65 (1H, dt, J = 17.4, 5.0 Hz), 2.60-2.33 (2H, m), 2.37 (1H, m), 2.11-2.00 (2H, m), 1.74-1.55 (2H, m), 0.67 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 197.6, 167.8, 150.7, 129.0, 127.2, 125.4, 124.6, 115.9, 113.6, 37.1, 32.2, 29.9, 27.8, 20.6, 9.1. HRMS (ESI^+) calcd for $C_{15}H_{16}O_2Na$ ($M+Na^+$): 251.1043, Found: 251.1048.

2,3,4,9-Tetrahydro-9-ethyl-8-methoxy-1*H*-xanthen-1-one (16). Colorless crystals. Mp 132-133 °C (hexanes). IR (KBr) 2959, 4647, 1586, 1482, 1466, 1388 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.12 (1H, br t, J = 8.2 Hz), 6.62 (2H, br d, J = 8.2 Hz), 4.24 (1H, t, J = 4.6 Hz), 3.81 (3H, s), 2.63 (1H, dt, J = 17.4, 5.0 Hz), 2.57-2.47 (2H, m), 2.35 (1H, m), 2.08-2.00 (2H, m), 1.75-1.58 (2H, m), 0.60 (3H, t, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 197.5, 167.8, 157.3, 151.7, 127.2, 114.2,

113.7, 108.4, 106.1, 55.5, 37.1, 27.7, 27.2, 26.9, 20.6, 8.9. HRMS (ESI^+) calcd for $C_{16}H_{18}O_3Na$ ($M+Na^+$): 281.1148, Found: 281.1142.

Procedure for the reaction of 14 with diethyl malonate 17 and Et_2Zn. To a solution of diethyl malonate **17** (76 μL, 0.50 mmol) in diethyl ether (2.0 mL) was added Et_2Zn (1.05 M in hexane, 0.19 mL, 0.20 mmol) under argon atmosphere at 0 °C. After being stirred at 0 °C for 30 min, a solution of xanthene **14** (31 mg, 0.10 mmol) in diethyl ether (2.0 mL) was added to the reaction mixture at 0 °C. After being stirred at 30 °C for 48 h, the reaction mixture was diluted with diethyl ether and 0.1 M HCl, and then extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:6–1:0 with 2% CH_2Cl_2) afforded the product **18** (34 mg, 95%).

2-(2,3,4,9-Tetrahydro-1-oxo-1*H*-xanthen-9-yl)-propanedioic acid, 1,3-diethyl ester (**18**). Colorless crystals. Mp 57-58 °C (hexanes). IR (KBr) 2981, 2939, 1730, 1644, 1458, 1386 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.48 (1H, dd, *J* = 7.8, 1.4 Hz), 7.21 (1H, m), 7.08 (1H, m), 7.00 (1H, dd, *J* = 8.2, 0.9 Hz), 4.74 (1H, d, *J* = 3.7 Hz), 4.19 (2H, q, *J* = 7.1 Hz), 3.92 (2H, br d, *J* = 7.1 Hz), 3.68 (1H, d, *J* = 3.7 Hz), 2.71-2.48 (3H, m), 2.38 (1H, m), 2.10-2.03 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz), 1.06 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 197.1, 169.0, 168.2, 167.8, 151.0, 129.9, 128.3, 124.7, 121.5, 116.1, 111.5, 61.4, 61.0, 57.6, 36.9, 31.4, 28.0, 20.4, 14.0, 13.7. HRMS (ESI^+) calcd for $C_{20}H_{22}O_6Na$ ($M+Na^+$): 381.1309, Found: 381.1295.

Procedure for the reaction of 14 with EtMgBr. To a solution of xanthenes **14** (62 mg, 0.20 mmol) in diethyl ether (4.0 mL) was added EtMgBr (1.0 M in THF, 0.80 mL, 0.80 mmol) under argon atmosphere at 0 °C. After being stirred

at room temperature for 14 h, the reaction mixture was diluted with AcOEt and 0.1 M HCl, and then extracted with AcOEt. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by preparative TLC (AcOEt:hexane = 1:6) afforded the product **19** (21 mg, 44%).

(1*E*)-9-Ethyl-1-ethylidene-2,3,4,9-tetrahydro-1*H*-xanthene (**19**). Colorless oil. IR (KBr) 2965, 2931, 1712, 1604, 1577, 1475, 1452 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.14 (1H, dd, *J* = 8.1, 0.9 Hz), 7.11 (1H, m), 7.01 (1H, td, *J* = 8.1, 0.9 Hz), 6.94 (1H, br d, *J* = 7.8 Hz), 5.47 (1H, q, *J* = 6.9 Hz), 3.69 (1H, t, *J* = 4.8 Hz), 2.53 (1H, dt, *J* = 15.1, 4.8 Hz), 2.44 (1H, dt, *J* = 16.5, 5.0 Hz), 2.34 (1H, ddd, *J* = 16.5, 9.2, 5.0 Hz), 2.15 (1H, br m), 1.85 (1H, m), 1.79-1.54 (3H, m), 1.74 (3H, d, *J* = 6.9 Hz), 0.70 (3H, t, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 151.8, 148.8, 133.4, 128.6, 126.7, 125.5, 122.8, 115.4, 113.5, 110.6, 35.1, 29.5, 27.8, 25.4, 21.9, 13.6, 9.5. HRMS (ESI) calcd for $C_{17}H_{20}ONa$ ($M+Na^+$): 263.1406, Found: 263.1420. HRMS (ESI) calcd for $C_{17}H_{22}O_2Na$ ($M+H_2O+Na^+$): 281.1512, Found: 281.1530.

Procedure for the reaction of 14 with diethyl α-bromomalonate 20 and Et_2Zn. To a solution of diethyl α-bromomalonate **20** (165 μL, 1.0 mmol) in diethyl ether (2.0 mL) was added Et_2Zn (1.0 M in hexane, 0.50 mL, 0.50 mmol) under argon atmosphere at 0 °C. After being stirred at 0 °C for 30 min, a solution of xanthene **14** (31 mg, 0.10 mmol) in diethyl ether (2.0 mL) was added to the reaction mixture at 0 °C. After being stirred at room temperature for 24 h, the reaction mixture was diluted with diethyl ether and 0.1 M HCl, and then extracted with diethyl ether. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (AcOEt:hexane = 1:2 with 2% CH_2Cl_2) afforded the products **18** (7.2 mg, 20%) and **21** (15 mg, 34%).

2-Bromo-2-(2,3,4,9-tetrahydro-1-oxo-1*H*-xanthen-9-yl)-propanedioic acid, 1,3-diethyl ester (**21**). Colorless

crystals. Mp 73-74 °C (hexanes). IR (KBr) 2981, 2938, 1738, 1663, 1642, 1457, 1380 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.56 (1H, dd, *J* = 8.2, 1.4 Hz), 7.26 (1H, td, *J* = 8.2, 1.4 Hz), 7.14-7.07 (2H, m), 5.35 (1H, s), 4.25-4.11 (4H, m), 2.81 (1H, dt, *J* = 17.9, 3.9 Hz), 2.60-2.52 (2H, m), 2.32-2.11 (2H, m), 2.05 (1H, m), 1.29 (3H, t, *J* = 7.1 Hz), 1.25 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 196.8, 170.1, 165.8, 165.6, 152.5, 130.5, 128.7, 124.7, 121.0, 116.3, 110.1, 71.2, 63.5, 63.0, 37.7, 36.8, 28.3, 19.7, 13.7; One carbon peak was missing due to overlapping. HRMS (ESI^+) calcd for $C_{20}H_{22}{}^{79}BrO_6$ ($M+H^+$): 437.0594, Found: 437.0597. HRMS (ESI^+) calcd for $C_{20}H_{22}{}^{81}BrO_6$ ($M+H^+$): 439.0577, Found: 439.0577.

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Supporting Information

The computationally optimized structures, tables of atom coordinates and absolute energies of **8** and **10**, the reaction of **14** with organometallic reagents and ^1H and ^{13}C NMR spectra of newly obtained products are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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