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Iodide-Catalyzed Ring-Opening Cyclization of Cyclohexane-1,3-dione-2-spirocyclopropanes

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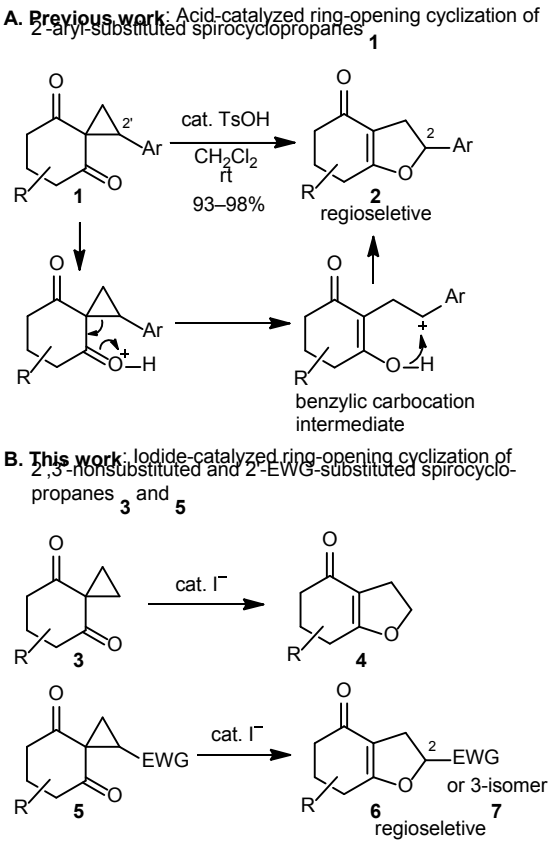
Abstract. The ring-opening cyclization of 2',3'-nonsubstituted and 2'-electron-withdrawing group (EWG)-substituted cyclohexane-1,3-dione-2-spirocyclopropanes was accomplished using iodide as a catalyst. The nonsubstituted derivatives afforded 3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-ones in high yields in the presence of trimethylsilyl iodide at room temperature. The EWG-substituted spirocyclopropanes, in turn, underwent regioselective ring opening followed by cyclization, which gave rise to 2-substituted tetrahydrobenzofuran-4-ones when a combination of tetrabutylammonium iodide catalyst and trifluoromethanesulfonic acid was used, whereas calcium iodide afforded the 3-substituted derivatives.

Keywords: iodide catalysts; cyclopropanes; ring opening; cyclization; benzofurans

Doubly activated cyclopropanes are known to be versatile synthetic intermediates for the synthesis of a wide variety of carbo- and heterocyclic compounds.[1,2] In this context, we recently reported the ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes for the construction of indole[3] and benzofuran[4] skeletons. In the case of the benzofuran derivatives, we disclosed that the acid-catalyzed ring-opening cyclization of 2'-aryl-substituted cyclohexane-1,3-dione-2-spirocyclopropanes **1** afforded 2-aryl-3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-ones **2** in a regioselective manner in excellent yields (Scheme 1, A).[4] Both Brønsted and Lewis acids, such as *p*-toluenesulfonic acid monohydrate (TsOH·H_2O), boron trifluoride (BF_3·OEt_2), trimethylsilyl trifluoromethanesulfonate (TMSOTf), and scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$], proved to be effective activators for the reaction. The reaction was proposed to proceed through a stable benzylic carbocation intermediate, which provided excellent regioselectivity. As a logical extension of this catalytic process, we investigated the ring-opening cyclization of a variety of nonsubstituted and electron-withdrawing group (EWG)-substituted spirocyclopropanes **3** and **5** to find that the presence of an iodide ion was crucial for the ring-opening cyclization. Consequently, we herein report the iodide-catalyzed ring-opening cyclization of 2',3'-nonsubstituted and 2'-EWG-substituted cyclohexane-1,3-dione-2-spirocyclopropanes **3** and **5** (Scheme 1, B).

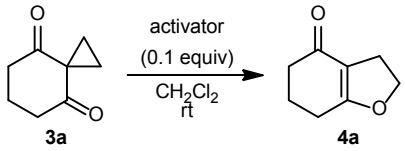


Scheme 1. Ring-opening cyclization of a variety of cyclohexane-1,3-dione-2-spirocyclopropanes **1**, **3** and **5**.

Initially, we examined the ring-opening cyclization of 2',3'-nonsubstituted cyclohexane-1,3-dione-2-

spirocyclopropane **3a**[5] (Table 1). The reaction with 0.1 equiv of Brønsted or Lewis acids such as $TsOH·H_2O$, trifluoromethanesulfonic acid (TfOH), TMSOTf, or $BF_3·OEt_2$ in CH_2Cl_2 at room temperature hardly progressed even after 24 h (entries 1–4). Therefore, the use of activators was investigated.[6] The reaction of **3a** with a catalytic amount of MgI_2 proceeded smoothly at room temperature, giving 3,5,6,7-tetrahydro-1-benzofuran-4(2*H*)-one **4a** within 5.5 h in 79% yield (entry 5). In contrast, the reaction with $MgBr_2$ required significantly longer times (10 h) to achieve completion and provided **4a** in 75% yield (entry 6), indicating that the iodide ion is a more effective activator of the present reaction than its bromide counterpart is. Then, after screening various activators, trimethylsilyl iodide (TMSI) was established as the most effective activator for this reaction, affording **4a** in 96% yield (entry 7).[7]

Table 1. Ring-opening cyclization of 2',3'-nonsubstituted spirocyclopropane **3a**.



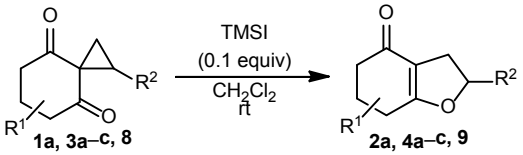
Entry	Activator	Time (h)	Yield (%)[a]
1	$TsOH·H_2O$	24	trace
2	TfOH	24	7
3	TMSOTf	24	4
4	$BF_3·OEt_2$	24	7
5	MgI_2	5.5	79
6	$MgBr_2$	10	75
7	TMSI	2.5	96

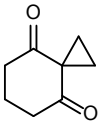
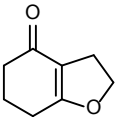
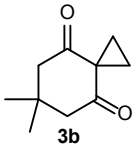
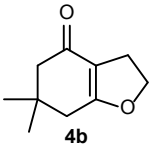
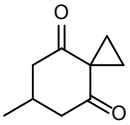
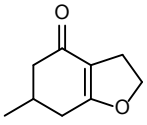
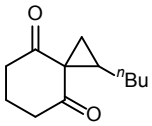
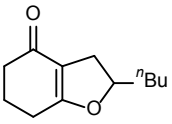
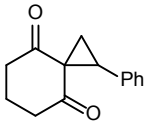
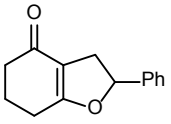
[a] Isolated yield.

With the optimal activator in hand, we investigated the reactions of a range of spirocyclopropanes (Table 2). The reaction of 2',3'-nonsubstituted spirocyclopropanes **3b** and **3c** provided the corresponding tetrahydrobenzofuran-4-ones **4b** and **4c** in 82% and 90% yields, respectively (entries 2 and 3).[8] TMSI was also effective for the reaction of alkyl- and aryl-substituted spirocyclopropanes **8** and **1a**. Thus, the reaction of *n*-butyl-substituted spirocyclopropane **8** under the same conditions (0.1 equiv of TMSI in CH_2Cl_2 at room temperature) proceeded smoothly to completion within 1.5 h, affording the corresponding product **9** in 84% yield (entry 4). To provide comparison, the result of the TsOH-catalyzed version has been included in the table; in this case **9** was obtained in 72% yield after 24 h. Finally, the reaction of **1a**[9] finished within 0.5 h to give **2a** in 98% yield (entry 5).[10]

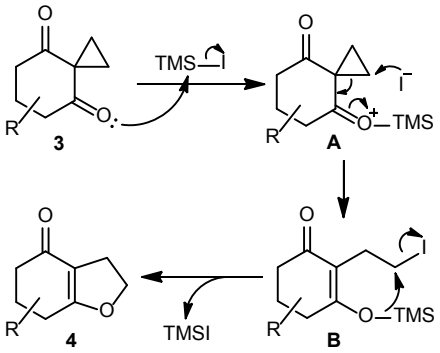
A plausible mechanism for the TMSI-catalyzed ring-opening cyclization of 2',3'-nonsubstituted spirocyclopropane **3** is shown in Scheme 2. Accordingly, spirocyclopropane **3** would be activated by silylation on the carbonyl oxygen atom with TMSI, resulting in the cleavage of the cyclopropane moiety by the nucleophilic attack of the iodide ion on the cyclopropane intermediate **A** to provide the alkyl iodide intermediate **B**. Cyclization of **B** would, then, occur rapidly to form tetrahydrobenzofuran-4-one **4**, with the concomitant regeneration of TMSI. It is worth noting that the iodide ion would serve as a good nucleophile to open the cyclopropane and as a good leaving group to prompt the cyclization that leads to the dihydrofuran.[11]

Table 2. TMSI-catalyzed ring-opening cyclization of various spirocyclopropanes **1a**, **3a–c**, and **8**.



Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **3a**	2.5 (24)[b]	 **4a**	96 (trace)[b]
2	 **3b**	3	 **4b**	82
3	 **3c**	3.5	 **4c**	90
4	 **8**	1.5 (24)[b]	 **9**	84 (72)[b]
5	 **1a**	0.5 (1)[b]	 **2a**	98 (98)[b]

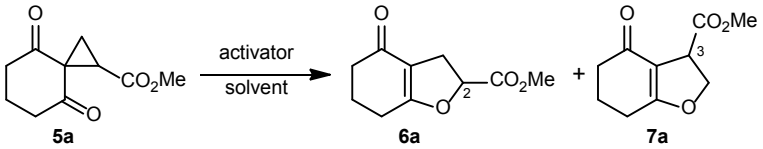
[a] Isolated yield.
[b] $TsOH·H_2O$ (0.1 equiv) instead of TMSI was used as an activator.[4]



Scheme 2. Plausible mechanism for 2',3'-nonsubstituted spirocyclopropanes **3**.

Next, we turned our attention to the ring-opening cyclization of 2'-EWG-substituted spirocyclopropanes (Table 3). The acid-induced reactions of 2'-methoxycarbonyl-substituted cyclohexane-1,3-dione-2-spirocyclopropane **5a** were first examined. The reaction of **5a** with 1.0 equiv of $TsOH·H_2O$ in CH_2Cl_2 at room temperature did not proceed at all (entry 1). In contrast, a stronger Brønsted acid, TfOH, provided a mixture of 2- and 3-methoxycarbonyl-substituted tetrahydrobenzofuran-4-ones **6a** and **7a** in 49% combined yield after 24 h (entry 2). Interestingly, this reaction showed the opposite regioselectivity to that of the acid-catalyzed reaction of 2'-aryl-substituted spirocyclopropane **1**[4] and gave 3-substituted tetrahydrobenzofuran-4-one **7a** as the major product (**6a**:**7a** = 10:90). Next, we investigated the iodide-catalyzed reactions of **5a** (entries 3–5). The reaction with TMSI afforded **6a** and **7a** in 87% yield after 7.5 h. The regioselectivity was the same as that of the reaction with TfOH; however, **7a** was obtained as the major product with lower selectivity (**6a**:**7a** = 25:75, entry 3). On the other hand, the use of MgI_2 was found to accelerate the reaction strongly, affording products **6a** and **7a** in 90% yield after 4 h with poor regioselectivity that followed the opposite trend (**6a**:**7a** = 59:41, entry 4). In the case of the reaction of **5a** with tetrabutylammonium iodide (TBAI), the reaction required 24 h to give a 46:54 mixture of **6a** and **7a** (entry 5). This longer reaction time most likely stems from the lower Lewis acidity of TBAI compared to that of TMSI and MgI_2. We investigated a combination of an iodide catalyst and a strong acid to obtain good yield and regioselectivity.[12] When **5a** was reacted with 0.2 equiv of TBAI and 1.0 equiv of TfOH, a 20:80 mixture of **6a** and **7a** was produced in 87% yield after 22 h (entry 6). Increasing the TBAI amount to 1.0 equiv was found to enhance the reaction rate; however, a decrease in the regioselectivity was observed (**6a**:**7a** = 27:73, entry 7). In contrast, the addition of 2.0 equiv of TfOH resulted in an acceleration of the reaction (12 h) and an improvement of the regioselectivity (**6a**:**7a** = 6:94, entry 8). When 3.0 equiv of TfOH was used, the 3-isomer **7a** was obtained with the highest yield and selectivity (87% yield, **6a**:**7a** = 4:96, entry 9). Further addition of TfOH (a total of 3.5 equiv) led to a decrease in the yield (entry 10).

Table 3. Ring-opening cyclization of 2'-methoxycarbonyl-substituted cyclohexane-1,3-dione-2-spirocyclopropane **5a**.



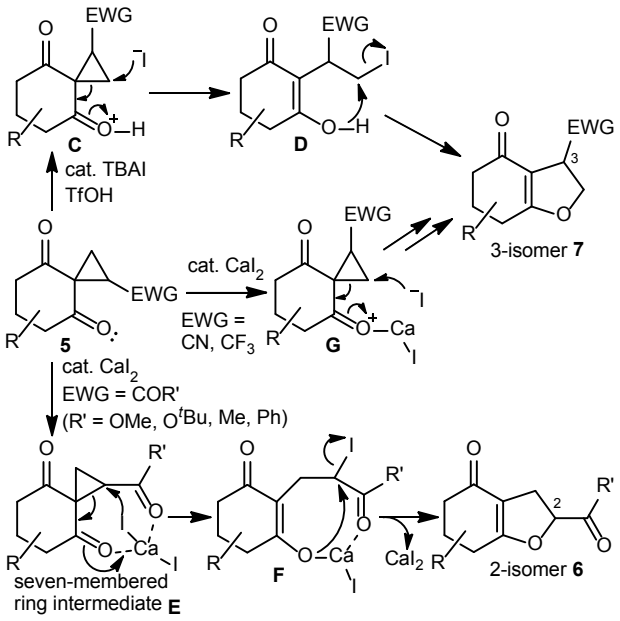
Entry	Activator (equiv)	Solvent	Temp.	Time (h)	Yield (%)[a]	**6a**:**7a**[b]
1	$TsOH·H_2O$ (1.0)	CH_2Cl_2	rt	24	No reaction	
2	TfOH (1.0)	CH_2Cl_2	rt	24	49	10:90
3	TMSI (0.2)	CH_2Cl_2	rt	7.5	87	25:75
4	MgI_2 (0.2)	CH_2Cl_2	rt	4	90	59:41
5	TBAI (0.2)	CH_2Cl_2	rt	24	85	46:54
6	TBAI (0.2) + TfOH (1.0)	CH_2Cl_2	rt	22	87	20:80
7	TBAI (1.0) + TfOH (1.0)	CH_2Cl_2	rt	1.5	85	27:73
8	TBAI (0.2) + TfOH (2.0)	CH_2Cl_2	rt	12	87	6:94
9	**TBAI (0.2) + TfOH (3.0)**	**CH_2Cl_2**	**rt**	**4**	**87**	**4:96**
10	TBAI (0.2) + TfOH (3.5)	CH_2Cl_2	rt	2	82	4:96
11	MgI_2 (0.2)	EtOAc	rt	0.5	92	73:27
12	MgI_2 (0.2)	DMF	rt	12	82	77:23
13	MgI_2 (0.2)	THF	rt	0.5	95	83:17
14	$BaI_2·2H_2O$ (0.2)	THF	rt	0.5	95	70:30
15	ZnI_2 (0.2)	THF	rt	24	8	50:50
16	CaI_2 (0.2)	THF	rt	0.5	91	93:7
17	CaI_2 (0.1)	THF	rt	0.5	97	96:4
18	**CaI_2 (0.1)**	**THF**	**0 °C**	**0.5**	**95**	**97:3**
19	CaI_2 (0.05)	THF	0 °C	1.5	92	96:4

[a] Combined yield of **6a** and **7a**.
[b] Determined by ^{1}H NMR analysis of the crude product.

Once the regioselective formation of the 3-isomer **7a** was accomplished, we tackled the optimization of the conditions for the synthesis of the 2-isomer **6a**.[13] Since MgI_2 had been shown to favor the formation of **6a** over **7a** (entry 4), we examined a series of solvents with MgI_2 and found that tetrahydrofuran (THF) gave the best results for the selective formation of the 2-isomer **6a** (**6a**:**7a** = 83:17, entry 13 vs entries 4, 11, and 12). After screening of other iodides such as $BaI_2{\cdot}2H_2O$, ZnI_2, and CaI_2 (entries 14–16), CaI_2 was found to be the most effective catalyst for the selective synthesis of the 2-isomer **6a** (91% yield, **6a**:**7a** = 93:7, entry 16).[14] Furthermore, the optimal conditions were established as 0.1 equiv of CaI_2 at 0 °C of reaction temperature, which furnished the combined product of **6a** and **7a** in 95% yield with excellent regioselectivity (**6a**:**7a** = 97:3, entry 18 vs entries 16, 17, and 19).

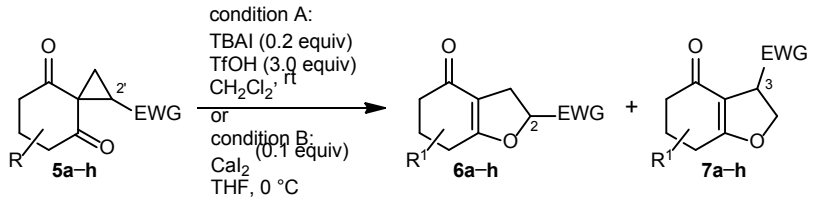
Having optimized the reaction conditions for the selective formation of the 2- and 3-isomers, we then addressed the reaction of a variety of 2'-EWG-substituted spirocyclopropanes **5** under either conditions A or B (Table 4). The reaction of methyl esters **5b** and **5c** under condition A (cat. TBAI and TfOH in CH_2Cl_2 at rt) provided 3-substituted tetrahydrobenzofuran-4-ones **7b** and **7c** as major products, respectively (entries 3 and 5), whereas the reaction of **5b** and **5c** under condition B (cat. CaI_2 in THF at 0 °C) afforded the respective 2-substituted products **6b** and **6c** as major products (entries 4 and 6). Although *tert*-butyl ester **5d** led to decomposition under condition A (entry 7), the reaction of **5d** under condition B resulted in an excellent regioselectivity (**6d**:**7d** = 98:2), and the 2-isomer **6d** was obtained in 81% yield (entry 8). Moreover, the reaction of methyl and phenyl ketones **5e** and **5f** under condition A furnished a 19:81 mixture of 2-isomers (**6e** and **6f**) and 3-isomers (**7e** and **7f**) in 76% and 81% combined yields, respectively (entries 9 and 11). On the other hand, the 2-isomers **6e** and **6f** were obtained as sole products in 93% and 91% yields from **5e** and **5f**, respectively, under condition B (entries 10 and 12). Unfortunately, nitrile **5g** quickly decomposed under condition A (entry 13). In surprising contrast, the reaction of **5g** under condition B provided 3-isomer **7g** as the major product (85% combined yield, **6g**:**7g** = 17:83, entry 14). Furthermore, trifluoromethyl-substituted spirocyclopropane **5h**[15] afforded the 3-isomer **7h** as a sole product under both conditions A and B in 85% and 80% yields, respectively (entries 15 and 16). These results suggested that the presence of a carbonyl group in the 2'-EWG substitution strongly affects the regioselectivity.

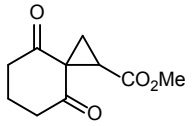
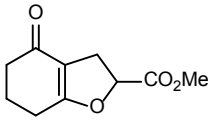
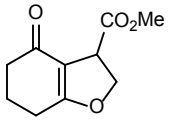
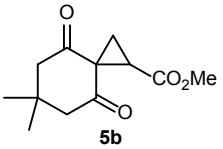
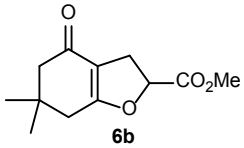
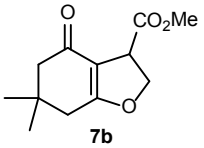
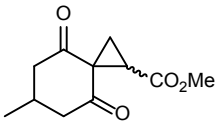
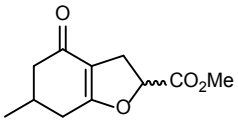
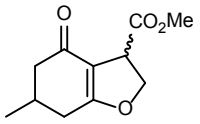
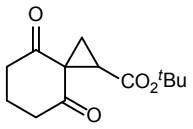
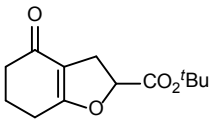
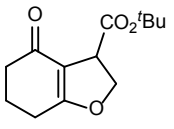
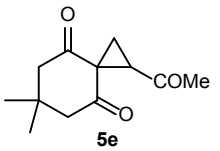
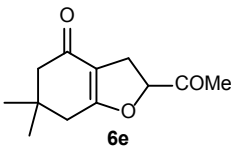
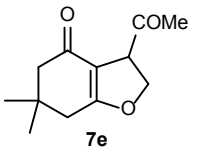
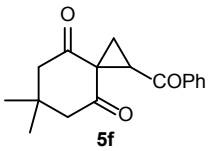
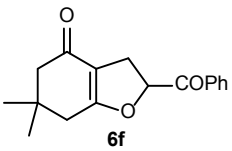
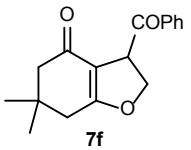
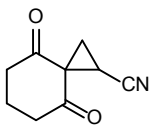
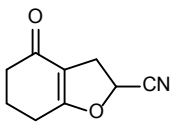
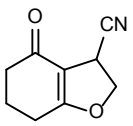
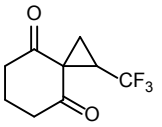
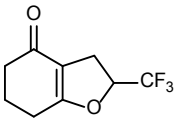
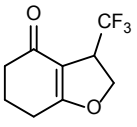
For the iodide-catalyzed ring-opening cyclization of 2'-EWG-substituted spirocyclopropanes **5**, we envisaged the mechanism depicted in Scheme 3. Under condition A (cat. TBAI and TfOH), spirocyclopropane **5** would be activated by protonation on the carbonyl oxygen atom with TfOH, followed by the nucleophilic attack of the iodide ion from TBAI on the less hindered carbon atom in intermediate **C**, which would trigger the regioselective cleavage of the cyclopropane to provide an alkyl iodide intermediate **D**. The subsequent cyclization of **D** would proceed smoothly to form the 3-substituted product **7**, along with the release of the iodide ion. In contrast, the reaction of 2'-carbonyl group-substituted spirocyclopropanes **5**, such as ester and ketone, under condition B (cat. CaI_2) would generate a seven-membered ring intermediate **E** formed by the bidentate chelation of the two carbonyl oxygen atoms by CaI_2. The intramolecular attack of the iodide ion of CaI_2 on the carbon atom next to the substituted carbonyl group would lead to the regioselective cleavage of the cyclopropane to provide the α-iodo carbonyl compound **F**. Subsequently, cyclization of **F** would occur, affording the 2-substituted product **6**, with the concomitant regeneration of CaI_2. On the other hand, the reactions of cyano and trifluoromethyl-substituted **5g** and **5h** would take place without the formation of the seven-membered ring intermediate, providing the 3-isomers **7** by the nucleophilic attack of an intermolecular iodide ion from CaI_2 on the less hindered carbon atom in **G**. Again, according to the proposed mechanism, the iodide ion would act in the reaction of EWG-substituted spirocyclopropanes **5** as a good nucleophile to open the cyclopropane and as a good leaving group to trigger the cyclization that ultimately affords the dihydrofuran.[16]



Scheme 3. Plausible mechanism for EWG-substituted spirocyclopropanes **5**.

Table 4. Ring-opening cyclization of 2'-EWG-substituted cyclohexane-1,3-dione-2-spirocyclopropane **5a**–**h**.



Entry	Substrate	Conditions	Products		Time (h)	Yield (%)[a]	**6**:**7**[b]
1	 **5a**	A	 **6a**	 **7a**	4	87	4:96
2		B			0.5	95	97:3
3	 **5b**	A	 **6b**	 **7b**	4	91	5:95
4		B			0.5	98	97:3
5[c]	 **5c**	A	 **6c**	 **7c**	4	83[d]	4:96
6[c]		B			0.5	93[d]	95:5
7	 **5d**	A	 **6d**	 **7d**	0.5	Decomp.	
8		B			0.5	81[e]	98:2
9	 **5e**	A[f]	 **6e**	 **7e**	0.3	76	19:81
10		B			0.5	93	100:0
11	 **5f**	A	 **6f**	 **7f**	1.5	81	19:81
12		B			0.5	91	100:0
13	 **5g**	A	 **6g**	 **7g**	0.5	Decomp.	
14		B[g]			2.5	85	17:83
15	 **5h**	A	 **6h**	 **7h**	1	85	0:100
16		B			24	80	0:100

[a] Combined yield of **6** and **7**.
[b] Determined by ^{1}H NMR analysis of the crude product.
[c] A diastereomeric mixture (ca. 1:1) of starting material **5c** was used.
[d] The products **6c** and **7c** were isolated as a diastereomeric mixture (ca. 1:1).
[e] Isolated yield of **6d**.
[f] Performed at 0 °C.
[g] Performed at room temperature.

In summary, we have developed an iodide-catalyzed ring-opening cyclization of 2',3'-nonsubstituted and 2'-EWG-substituted cyclohexane-1,3-dione-2-spirocyclopropanes. The reaction of nonsubstituted spirocyclopropanes provided tetrahydrobenzofuran-4-ones in high yields in the presence of a catalytic amount of trimethylsilyl iodide at room temperature. Moreover, the regioselective ring-opening of 2'-carbonyl group-substituted spirocyclopropanes followed by cyclization was achieved by using an iodide catalyst. In this case, a combination of tetrabutylammonium iodide catalyst and trifluoromethanesulfonic acid afforded the 2-substituted products, whereas calcium iodide gave the 3-substituted derivatives. Further application of this method to the synthesis of a variety of benzofuran and 2,3-dihydrobenzofuran natural products is currently in progress.

Experimental Section

Typical Procedure for the Ring-Opening Cyclization of 2',3'-Nonsubstituted Spirocyclopropane 3a with TMSI

TMSI (4 mg, 0.020 mmol) was added to a solution of spiro[2.5]octane-4,8-dione (**3a**) (28 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) at room temperature. After stirring for 2.5 h, the reaction was quenched by addition of water (3 mL), and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 60% EtOAc in hexane) to provide **4a** (27 mg, 96%).

Typical Procedure for the Selective Synthesis of 3-Substituted Tetrahydrobenzofuran-4-one 7a with a Combination of TBAI Catalyst and TfOH (condition A)

A solution of 1-methoxycarbonylspiro[2.5]octane-4,8-dione (**5a**) (39 mg, 0.20 mmol) in CH_2Cl_2 (0.3 mL) was added to a solution of TBAI (15 mg, 0.040 mmol) and TfOH (90 mg, 0.60 mmol) in CH_2Cl_2 (0.7 mL) at room temperature. After stirring for 4 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (3 mL), and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous $MgSO_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 80% EtOAc in hexane) to provide a 4:96 mixture of **6a** and **7a** (34 mg, 87%).

Typical Procedure for the Selective Synthesis of 2-Substituted Tetrahydrobenzofuran-4-one 6a with CaI_2 Catalyst (condition B)

CaI_2 (6 mg, 0.020 mmol) was added to a solution of **5a** (39 mg, 0.20 mmol) in THF (1 mL) at 0 °C. After stirring at 0 °C for 0.5 h, the reaction was quenched by addition of water (3 mL), and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography (silica gel, 80% EtOAc in hexane) to provide a 97:3 mixture of **6a** and **7a** (37 mg, 95%).

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Iodide-Catalyzed Ring-Opening Cyclization of Cyclohexane-1,3-dione-2-spirocyclopropanes

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