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Graphical abstract

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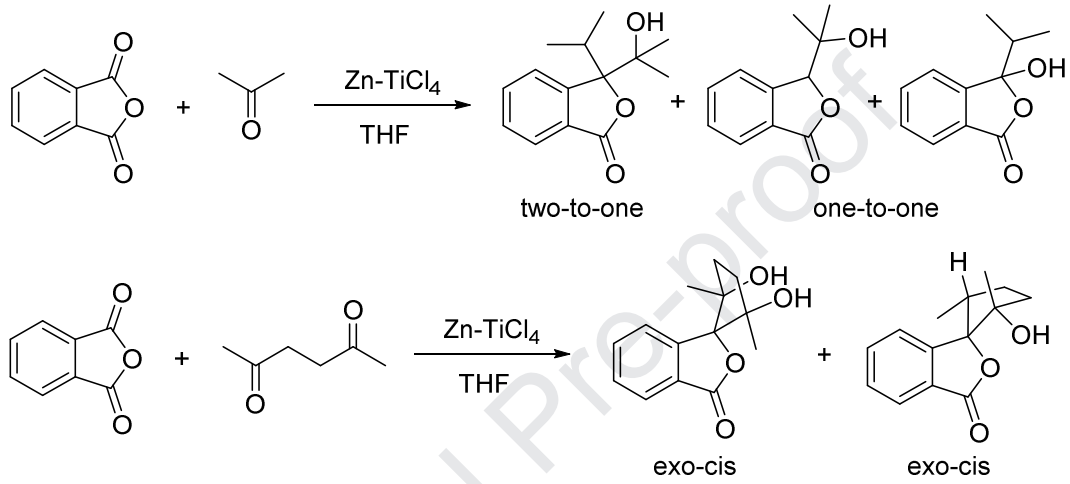

Reductive coupling of phthalic anhydrides with aliphatic ketones by low-valent titanium: Unusual two-to-one coupling for preparation of 3,3-disubstituted phthalides

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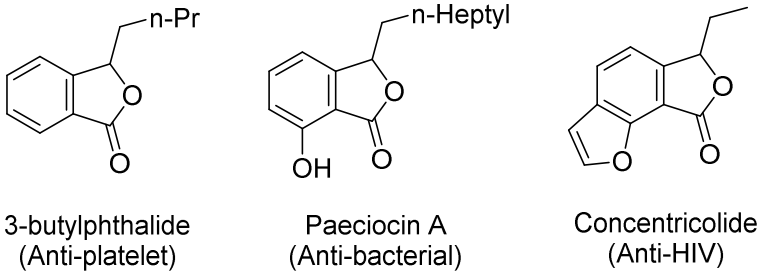
ABSTRACT:

The reductive coupling of phthalic anhydrides with acetone by Zn-$TiCl_4$ in THF gave two-to-one and one-to-one coupled products. The coupled products were transformed to 3,3-diisopropyl-, 3-isopropylidene-, and 3-isopropylphthalides. In addition, the reductive coupling of phthalic anhydrides with acetonylacetone by Zn-$TiCl_4$ in THF gave 3-spirocyclopentanylphtalides stereoselectively.

Keywords: Reductive coupling; Low-valent titanium; Phthalic anhydrides; 3,3-disubstituted phthalides; 3-isopropylidenephthalides; 3-spirocyclopentanylphtalides.

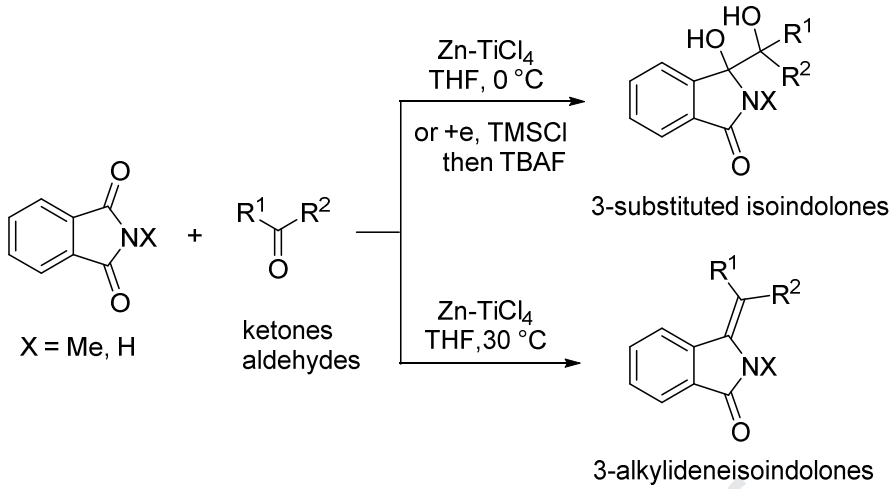
1. Introduction

Phthalides (isobenzofuran-1(3H)-ones) are found in many biologically active naturally occurring compounds (Figure 1).[1] Therefore, the synthesis of 3-substituted,[2] 3,3-disubstituted,[3] and 3-alkylidenephthalides[4] has attracted much attention from organic chemists. On the other hand, we have reported that the reductive coupling of phthalimides with ketones and aldehydes by low-valent titanium ($Zn\text{-}TiCl_4$)[5a] or electroreduction[5b] is a promising method for the synthesis of 3-substituted and 3-alkylideneisoindolones (Scheme 1). From these results, we examined the reductive coupling of phthalic anhydrides with ketones, since 3-substituted phthalides and 3-alkylidenephthalides might be synthesized by this reaction. As far as we know, this type of reductive coupling has not so far been reported at all. In this paper, we report our study on the reductive coupling of phthalic anhydrides with acetone and acetonylacetone by $Zn\text{-}TiCl_4$ (Scheme 2). Unlike our expectation, two-to-one coupled products were formed mainly from the reaction of 4,7-unsubstituted phthalic anhydrides with acetone. In particular, 3-spirocyclopentanylphthalides were obtained stereoselectively from the reaction with acetonylacetone. Reaction mechanism of the reductive coupling was also discussed.

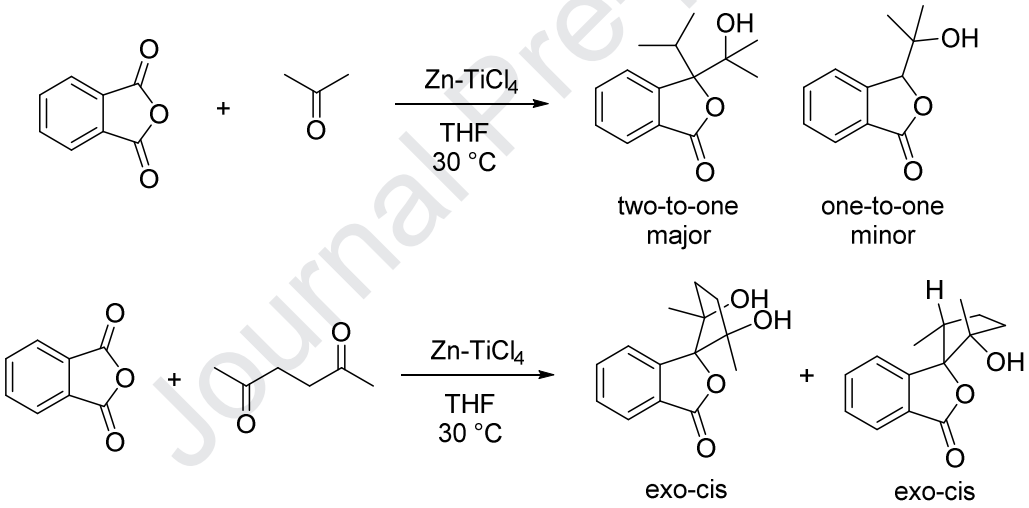


3-butylphthalide (Anti-platelet) | Paeciocin A (Anti-bacterial) | Concentricolide (Anti-HIV)

Figure 1. Examples of biologically active natural phthalides.



Scheme 2. Reductive coupling of phthalimides with aldehydes and ketones by Zn-$TiCl_4$[5a] or electroreduction[5b] (our previous works).



Scheme 2. Reductive coupling of phthalic anhydride with acetone and acetonylacetone by Zn-$TiCl_4$ (this work).

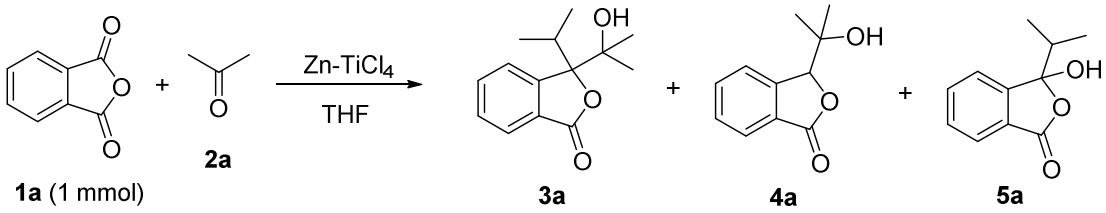
2. Results and discussion

2.1. Reductive coupling of phthalic anhydrides with acetone by Zn-$TiCl_4$

The reductive coupling of phthalic anhydride (**1a**) with acetone (**2a**) was carried out with the molar ratio of **1a**/**2a**/$TiCl_4$ as 1/3/3 (run 1) or 1/5/5 (run 2) at 30 °C (Table 1). The molar ratio of Zn/$TiCl_4$ was fixed as 2/1. The two-to-one coupled product **3a** was obtained in 29% and 38% yields, respectively, together with a small amount (7% and 10% yields) of one-to-one coupled product **4a**. Other than these cross-coupled products, homo-coupled product of **2a**, 2,3-dimethylbutane-2,3-diol, was also formed as by-product. The reaction with the ratio of **1a**/**2a**/$TiCl_4$ as 1/10/5 at 30 °C (run 3) brought about some improvement in the yield of **3a** (41% yield). It gave almost the same result to double the quantity of **2a** in run 3 (run 4). The reaction at 50 °C with the same ratio as run 3 somewhat lowered the yield of **3a** (run 5). To obtain one-to-one coupled product **4a** as the major product, the reaction was carried out with the molar ratio of **1a**/**2a**/$TiCl_4$ as 1/10/2 at 0 °C (run 6). Although **3a** was not formed, one-to-one products were isolated as a 1:1 mixture of **4a** and **5a** in 60% total yield. The mixture of **4a** and **5a** was subjected to the reductive coupling with **2a** under the same conditions in run 3 to give **3a** (66% yield) with some recovered **4a** (Scheme 3). This result shows that **3a** was formed from **4a** and **5a** by the reductive coupling with **2a**. The two-to-one coupled product **3a** was transformed to 3,3-diisopropylphthalide (**7a**) by dehydration in refluxing PTSA/toluene and subsequent hydrogenation of resultant **6a** (Scheme 4). In a similar manner, the mixture of **4a** and **5a** was converted to 3-isopropylidenephthalide (**8a**)[4c] and 3-isopropylphthalide (**9a**).

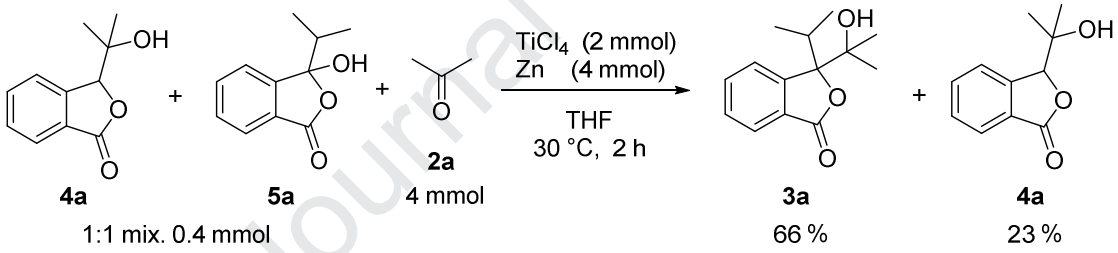
Table 1

Reductive coupling of **1a** with **2a** by Zn-$TiCl_4$.

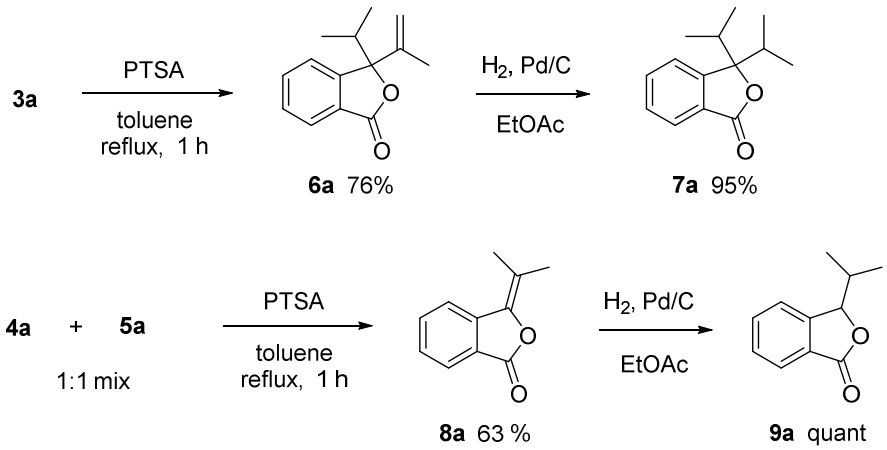


run	**2a**	$TiCl_4$ (mmol)	Zn	Temp. (°C)	Time (h)	% Yield[a] **3a**	**4a**	**5a**
1	3	3	6	30	2	29	7	-
2	5	5	10	30	2	38	10	-
3	10	5	10	30	2	41	13	-
4	20	5	10	30	2	41	15	-
5	10	5	10	50	1	37	10	-
6	10	2	4	0	1	-	60 (1:1)	

[a]Isolated yields.

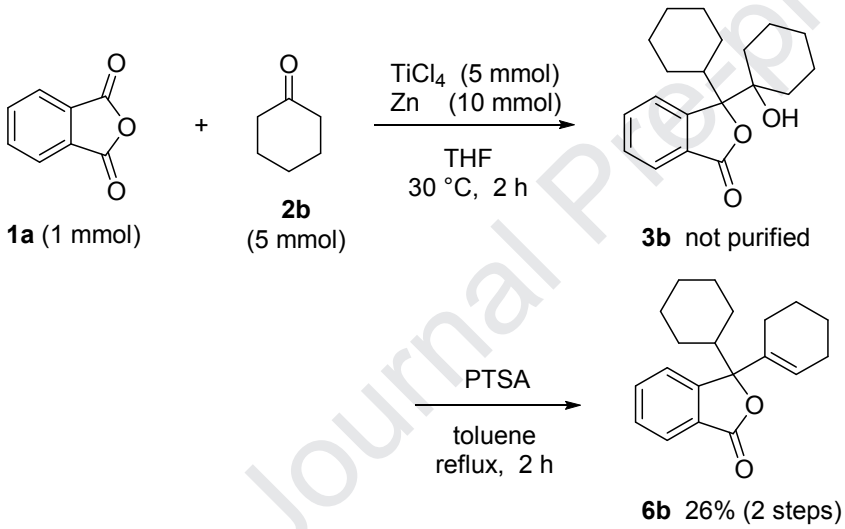


Scheme 3. Reductive coupling of **4a** and **5a** with **2a** by Zn-$TiCl_4$.



Scheme 4. Dehydration and subsequent hydrogenation of **3a** and 1:1 mixture of **4a** and **5a**.

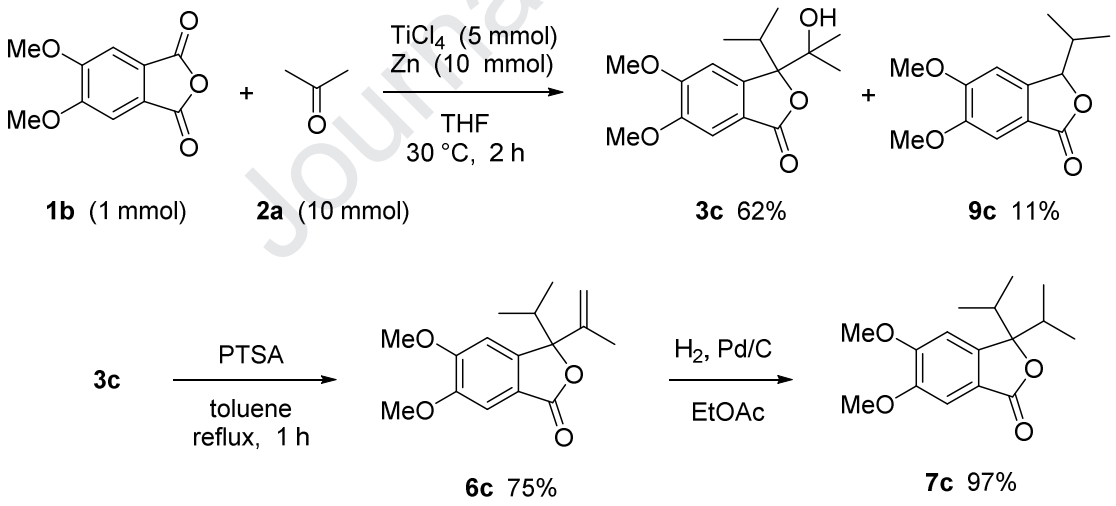
Next, the reductive coupling of **1a** with other ketones such as 3-pentanone, acetophenone, and benzophenone was examined using the same conditions as run 3 in Table 1. However, cross-coupled products of **1a** with ketones could not be obtained from these ketones. Although the yield was low, two-to-one coupling product **3b** was formed from **1a** and cyclohexanone (**2b**) (Scheme 5). Since **3b** could not be purified, the product was isolated as **6b** in 26% overall yield after dehydration of **3b**. From these results, it is suggested that the reductive coupling of **1a** with ketones strongly inhibited by the steric bulkiness of ketones.



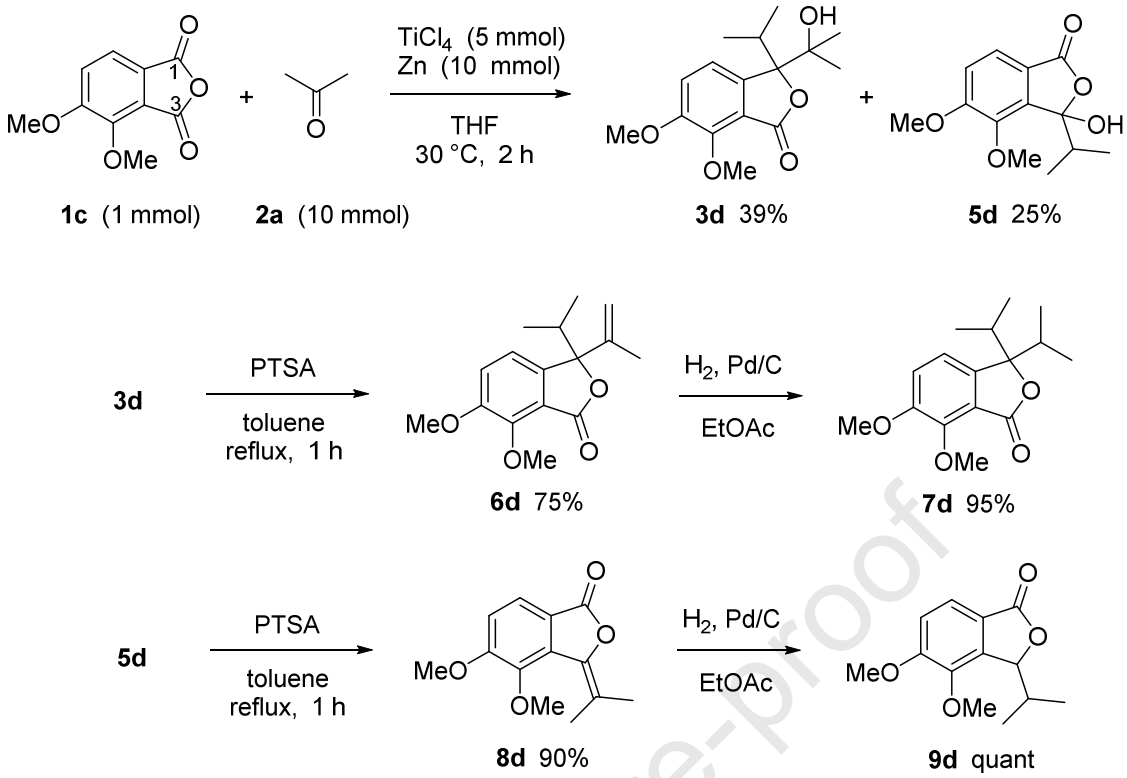
Scheme 5. Reductive coupling of **1a** with **2b** by Zn-$TiCl_4$ and subsequent dehydration to **6b**.

On the other hand, the reductive coupling of 5,6-dimethoxyphthalic anhydride (**1b**) with **2a** gave two-to-one coupled product **3c** in 62% yield (Scheme 6). In this case, a small amount (11% yield) of one-to-one coupled product was formed as 3-isopropylphthalide **9c**. The dehydration of **3c** and following hydrogenation of resultant **6c** afforded 3,3-diisopropylphthalide (**7c**). It is noted that the reductive coupling of 4,5-dimethoxyphthalic anhydride (**1c**) with **2a** gave two-to-one coupled product **3d** (39%

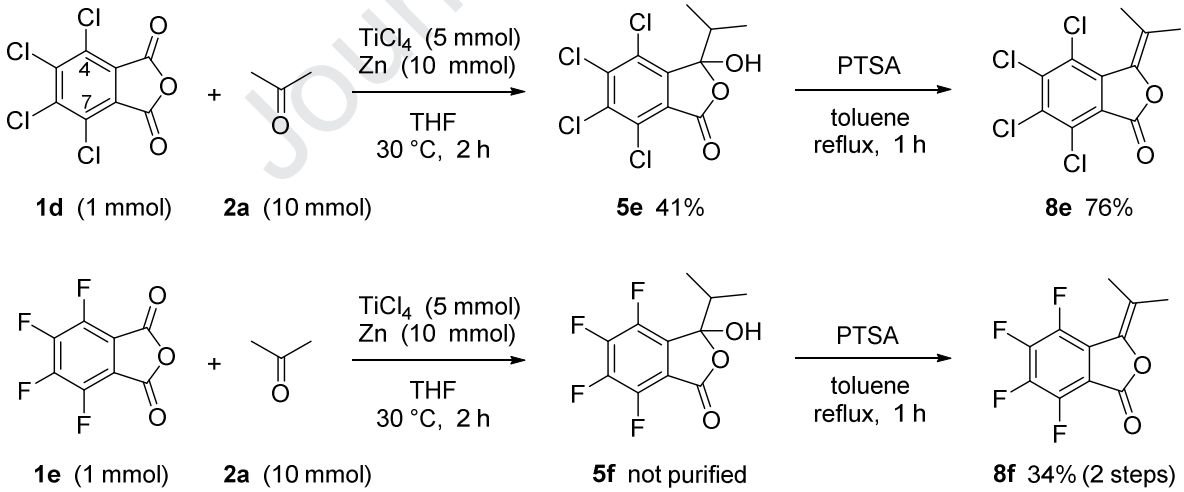
yield) and one-to-one coupled product **5d** (25% yield) (Scheme 7). This result shows that two-to-one coupled product was not formed by the reaction at the 3-position of **1c** probably due to steric hindrance of 4-methoxy group but formed by the reaction at the 1-position of **1c**. The products **3d** and **5d** were transformed to **7d** and **9d** through **6d** and **8d** in a similar manner as above. The regio-chemistry of **3d** was determined by 2D-NMR (NOESY) analysis and that of **5d** was confirmed by X-ray crystallography of **8d**. In addition, the reductive coupling of 4,5,6,7-tetrachlorophthalic anhydride (**1d**) with **2a** gave one-to-one coupled product **5e** as a sole product (41% yield) and **5e** was dehydrated to **8e**[4c] (Scheme 8). Similarly, the one-to-one coupled product of 4,5,6,7-tetrafluorophthalic anhydride (**1e**) with **2a** was isolated as **8f** (34% overall yield) after dehydration, since **5f** could not be purified. These results suggest that two-to-one coupled products are not formed from 4- and 7-disubstituted phthalic anhydrides owing to the steric hindrance of 4- and 7-substituents.



Scheme 6. Reductive coupling of **1b** with **2a** by Zn-$TiCl_4$ and transformation of **3c** to **7c**.



Scheme 7. Reductive coupling of **1c** with **2a** by Zn-$TiCl_4$ and transformation of **3d** and **5d** to **7d** and **9d**.

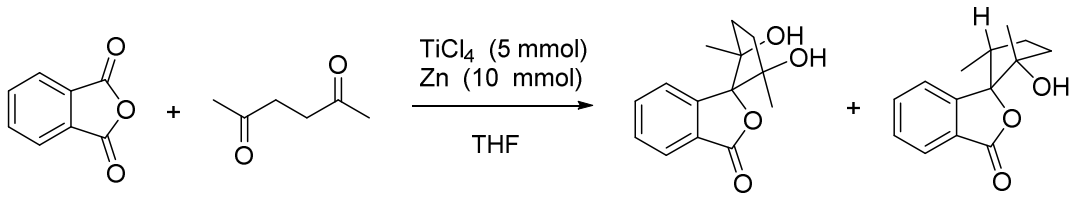


Scheme 8. Reductive coupling of **1d,e** with **2a** by Zn-$TiCl_4$ and dehydration of **5e,f** to **8e,f**.

2.2. Reductive coupling of phthalic anhydrides with acetonylacetone by Zn-$TiCl_4$

Expecting the synthesis of spiro compounds by the two-to-one reductive coupling, the reductive coupling of **1a** with acetonylacetone (**2c**) was examined. As shown in Table 2, 3-spirocyclopentanylphthalides **10a** (exo-cis) and **11a** (exo-cis) were obtained stereoselectively. The reaction at 30 °C gave diol **10a** as the major product (run 1), while **11a** was the major product by the reaction at 50 °C (run 2). The reaction at 0 °C, however, decreased the total yield of **10a** and **11a** (run 3). In all cases, no one-to-one coupled product could be isolated and intramolecular homo-coupled product of **2c**, 1,2-dimethylcyclobutane-1,2-diol, was formed as by-product. The stereochemistries of **10a** and **11a** were both determined to be exo-cis by X-ray crystallographic analysis (Figure 2). Similarly, the reductive coupling of **1b** and **1c** with **2c** afforded **10b**, **11b**, and **10c** stereoselectively (Scheme 9). It is assumed that the stereostructures of **10b,c** and **11b** are the same as those of **10a** and **11a**, respectively. In the latter case, **10c** was formed from the reaction at the 1-position of **1c** and no coupled product at the 3-position of **1c** could be detected. The regio-chemistry of **10c** was determined by 2D-NMR (NOESY) analysis.

Table 2. Reductive coupling of **1a** with **2c** by Zn-$TiCl_4$.



1a (1 mmol) **2c** (5 mmol) **10a** (exo-cis) **11a** (exo-cis)

run	Temp. (°C)	Time (h)	% Yield[a]	
			10a	**11a**
1	30	1	37	19
2	50	1	16	30
3	0	6	24	9

[a]Isolated yields.

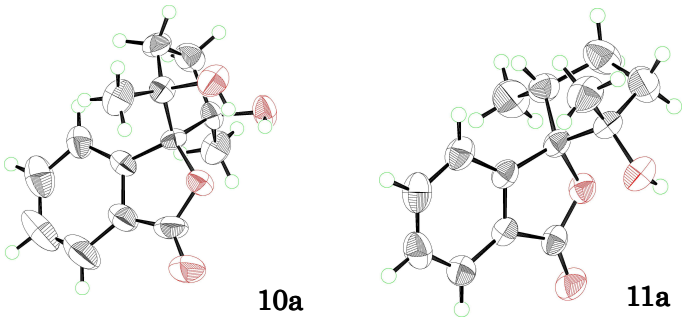
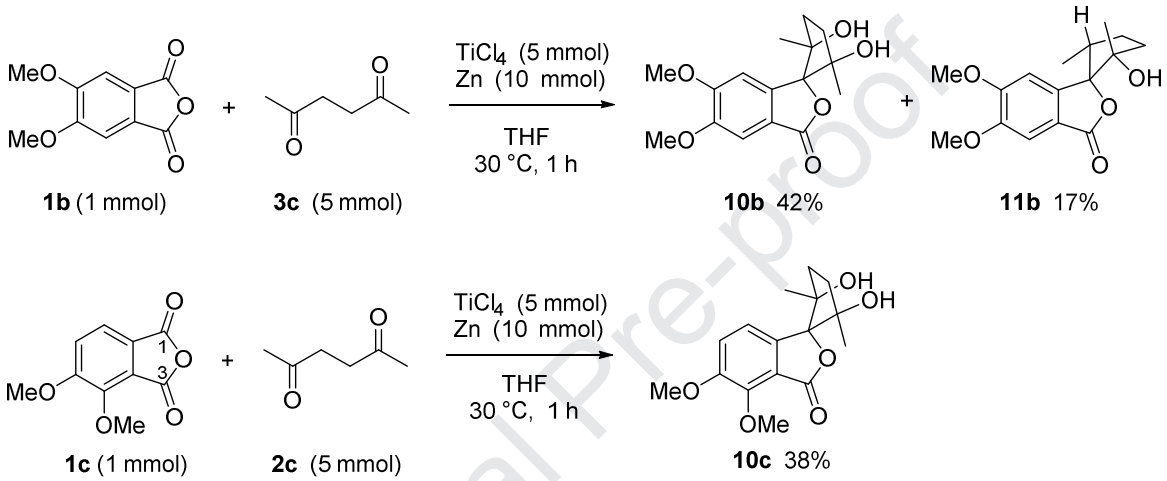


Figure 2. X-ray crystal structures of **10a** and **11a**.



Scheme 9. Reductive coupling of **1b,c** with **2c** by Zn-$TiCl_4$.

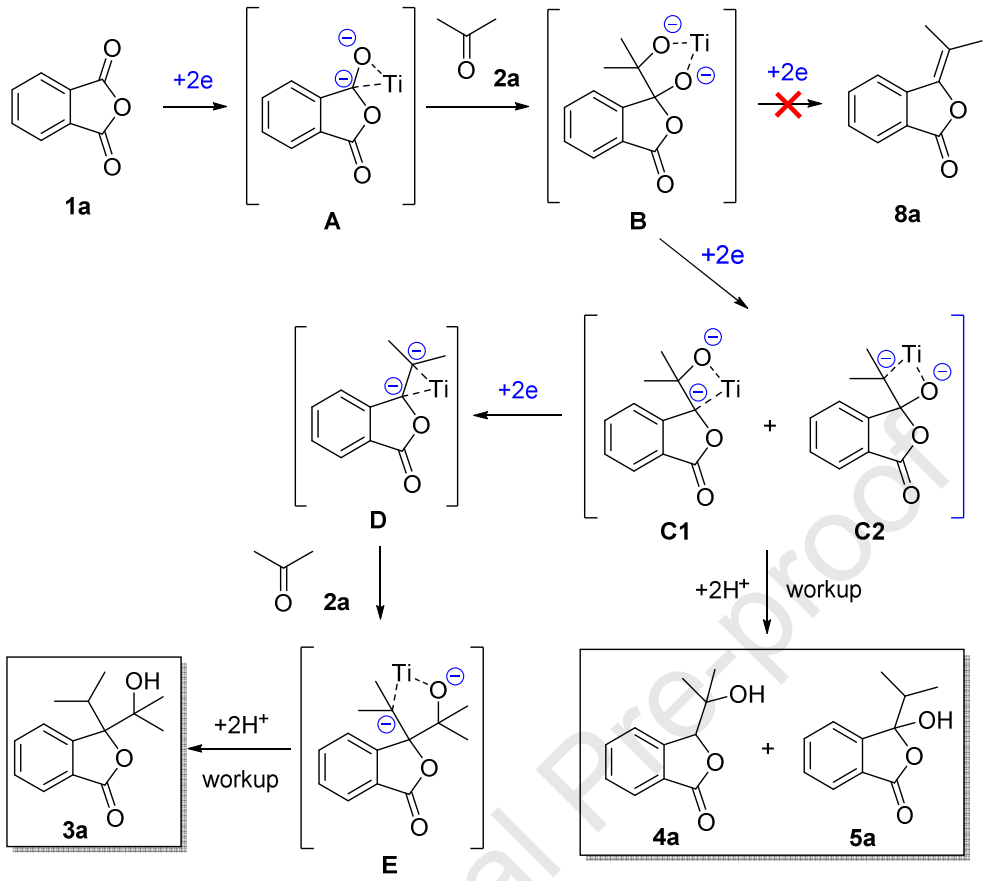
2.3. Reaction mechanism of reductive coupling of phthalic anhydrides with ketones

The cyclic voltammogram of **1a** in 0.03 M Bu_4NClO_4 on a platinum cathode showed a first reduction peak at −1.30 V versus SCE, although that of **2a** did not show a reduction peak to −2.50 V under the same conditions. This result shows that **1a** is much more reducible than **2a**. Therefore, the presumed reaction mechanism of the reductive coupling of **1a** with **2a** can be illustrated in Scheme 10. First, **1a** is reduced by low-valent titanium to dianion intermediate **A**. The nucleophilic addition of **A** to **2a** and subsequent further reduction of adduct **B** give dianions **C1** and **C2**. When the reaction was conducted and quenched with water at 0 °C, one-to-one coupled products **4a** and **5a** are formed from **C1** and **C2**, respectively. At 30 °C, further reduction of **C1** and **C2** proceeds to give **D** and following

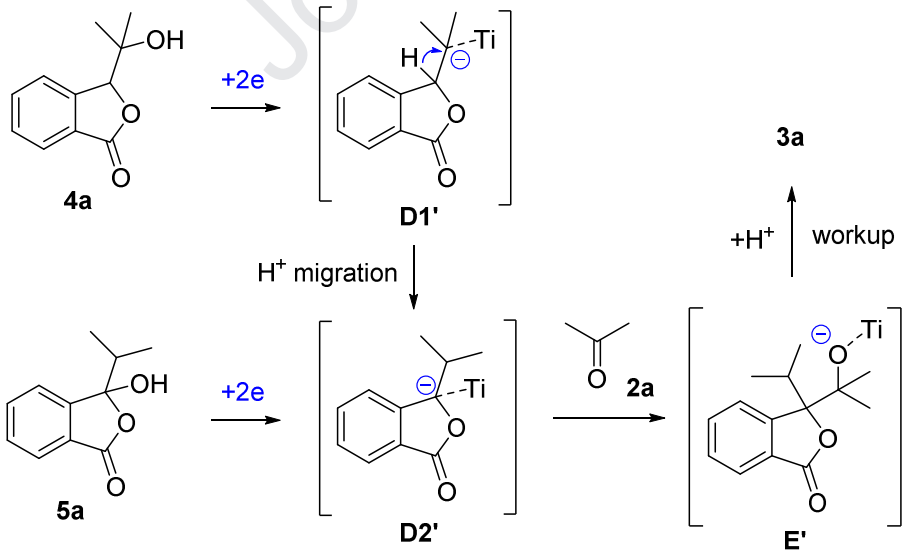
nucleophilic addition of **D** to **2a** produces adduct **E**. From the results in Table 1 and Scheme 3, it is supposed that the reduction of **C2** is much faster than that of **C1** with low-valent titanium at this temperature and, therefore, **C2** is immediately reduced to **D**. Finally, two-to-one coupled product **3a** is formed from **E** after workup with water. At first, we expected that 3-alkylidenephthalide **8a** was formed as an one-to-one coupled product like the previously reported coupling of phthalimides.[5a] However, mono-alcohols **4a** and **5a** were formed as four-electron reduced products in this reaction. Although the reason is not clear at present, we have found that the similar reductive C-O bond cleavage occurred in the reductive coupling of isatins[6a] and hydantoins.[6b]

Incidentally, the presumed reaction mechanism of reductive coupling of **4a** and **5a** with **2a** (Scheme 3) is shown in Scheme 11. Mono-alcohols **4a** and **5a** are reduced by low-valent titanium to anion intermediates **D1'** and **D2'**, respectively. Unstable anion **D1'** is immediately isolated to more stable benzylic anion **D2'**. The nucleophilic addition of **D2'** to **2a** and following workup of resultant **E'** give **3a**.

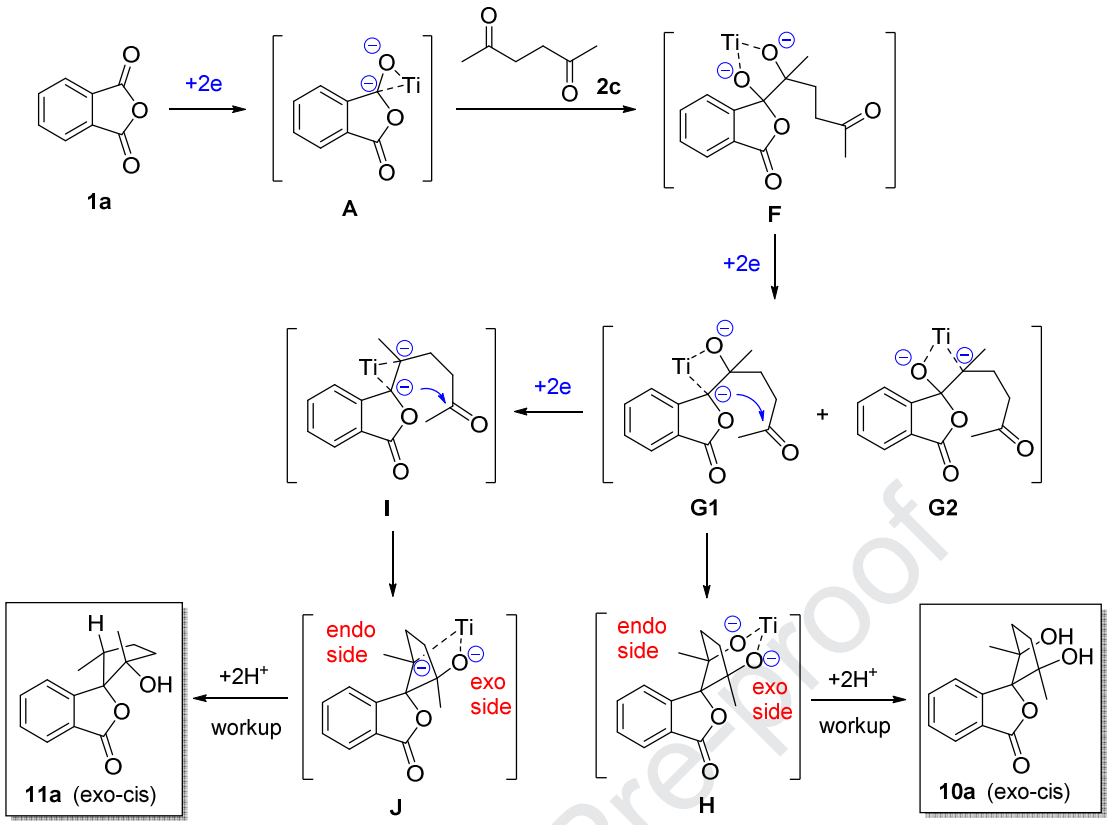
Similarly to Scheme 10, the presumed reaction mechanism of the reductive coupling of **1a** with **1c** is depicted in Scheme 12. The nucleophilic addition of **A** to **2c** and following reduction of adduct **F** afford dianions **G1** and **G2**. Even at 0 °C, intramolecular nucleophilic addition of **G1** proceeds to give adduct **H**. At the same time, **G1** and **G2** are subjected further reduction and subsequent intramolecular addition of resultant **I** gives adduct **J**. Similarly to dianion **C2** in Scheme 10, it seems that dianion **G2** is immediately reduced to **I**. Finally, coupled products **10a** and **11a** are obtained from **H** and **J** by workup with water. Since the titanium ions in dianions **H** and **J** are located in less hindered side (exo side), *exo*-diol **10a** and *exo*-alcohol **11a** are produced stereoselectively. In addition, protonation to *C*-anion of **J** occurs from the opposite side of the titanium ion (endo side) to give *exo*-*cis*-alcohol **11a** selectively.



Scheme 10. Presumed reaction mechanism of reductive coupling of **1a** with **2a**.



Scheme 11. Presumed reaction mechanism of reductive coupling of **4a** and **5a** with **2a**.



Scheme 12. Presumed reaction mechanism of reductive coupling of **1a** with **2c**.

3. Conclusion

The reduction of phthalic anhydrides **1a-c** and acetone (**2a**) with Zn-$TiCl_4$ in THF at 30 °C gave unusual two-to-one coupled products **3a,c,d** with small amounts of one-to-one coupled products **4a** and **5d**. On the contrary, the reduction of 4,5,6,7-tetrahalophthalic anhydrides **1d,e** and **2a** under the same conditions afforded one-to-one coupled products **5e,f**. The two-to-one coupled products **3a,c,d** were transformed to 3,3-diisopropylphthalides **7a,c,d** by dehydration and subsequent hydrogenation. The dehydration of one-to-one coupled products **4a** and **5d-f** produced 3-isopropylidenephthalides **8a,d-f**. In addition, the reductive coupling of phthalic anhydrides **1a-c** and acetonylacetone (**2c**) with Zn-$TiCl_4$ in THF at 30 °C gave 3-spirocyclopentanylphthalides **10a-c** and **11a-b**. These products were obtained as exo-cis isomers with complete stereoselectivity.

4. Experimental section

4.1. General

Column chromatography was performed on silica gel 60. THF was freshly distilled from sodium benzophenone ketyl. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured on a JEOL JNM-ECP500 spectrometer with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu IRAffinity-1 infrared spectrometer. HRMS were measured on a Thermo Scientific Exactive FTMS spectrometer. Melting points were uncorrected.

4.2. Starting materials

5,6- and 4,5-Dimethoxyisobenzofuran-1,3-diones (**1b** and **1c**) were prepared by the reported methods.[7,8] 4,5,6,7-Tetrachloro- and tetrafluoroisobenzofuran-1,3-diones (**1d** and **1e**) are commercially available.

*4.2.1. 5,6-Dimethoxyisobenzofuran-1,3-dione (**1b**)*[7]

White solid; mp 175 □; *Rf* 0.5 (hexanes-ethyl acetate, 2:1); ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 6H), 7.37 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 56.9 (q), 106.1 (d), 124.9 (s), 155.7 (s), 163.1 (s).

*4.2.2. 4,5-Dimethoxyisobenzofuran-1,3-dione (**1c**)*[8]

White solid; mp 166-167 □; *Rf* 0.35 (hexanes-ethyl acetate, 2:1); ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H), 4.22 (s, 3H), 7.28 (d, 1H, *J* = 8.3 Hz), 7.68 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 56.9 (q), 62.6 (q), 118.2 (d), 120.5 (s), 121.5 (d), 122.9 (s), 148.5 (s), 158.6 (s), 160.6 (s), 162.4 (s).

*4.3. Typical procedure for the reductive coupling of **1a** with **2a** (Table 1, run 3)*

To a solution of **1a** (148 mg, 1 mmol), **2a** (0.75 mL, 10 mmol), and zinc powder (0.65 g, 10 mmol) in THF (10 mL) was added $TiCl_4$ (0.55 mL, 5 mmol) dropwise at 0 ºC and then the dark blue suspension was stirred for 2 h at 30 ºC. To the mixture was added 1 M HCl (20 mL) and the mixture was stirred for 15 min at 25 ºC. The clear solution was extracted with ethyl acetate three times. The organic layer was washed with aqueous NaCl and dried over $MgSO_4$. After the solvent was removed *in vacuo*, the residue was purified by column chromatography on silica gel to give **3a** (96 mg, 41%) and **4a** (25 mg, 13%).

*4.3.1. 3-(2-Hydroxypropan-2-yl)-3-isopropylisobenzofuran-1(3H)-one (**3a**)*

White solid (CCDC 1958789); *Rf* 0.55 (hexanes-ethyl acetate, 2:1); mp 125-126 °C; IR (ATR) 3466 (br), 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 1.18 (s, 3H), 1.23 (s, 3H), 1.97 (brs, 1H), 2.59-2.68 (m, 1H), 7.51-7.57 (m, 2H), 7.63-7.67 (m, 1H), 7.86-7.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.50 (q), 18.52 (q), 25.5 (q), 26.5 (q), 32.4 (d), 75.2 (s), 94.7 (s), 123.4 (d), 125.5 (d), 127.5 (s), 129.0 (d), 133.6 (d), 149.9 (s), 170.7 (s); HRMS (ESI, ion trap) calcd for $C_{14}H_{19}O_3$ ($M + H^+$) 235.1334, found 235.1324.

*4.3.2. 3-(2-Hydroxypropan-2-yl)isobenzofuran-1(3H)-one (**4a**)*

Colorless paste; *Rf* 0.5 (hexanes-ethyl acetate, 1:1); IR (ATR) 3424 (br), 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.35 (s, 3H), 2.19 (brs, 1H), 5.29 (s, 1H), 7.54-7.58(m, 1H), 7.65-7.71 (m, 2H), 7.90-7.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.0 (q), 26.3 (q), 72.5 (s), 86.6 (d), 123.7 (d) 125.7 (d), 126.6 (s), 129.4 (d), 133.9 (d), 146.9 (s), 170.5 (s); HRMS (ESI, ion trap) calcd for $C_{11}H_{13}O_3$ ($M + H^+$) 193.0865, found 193.0863.

*4.3.3. 3-(2-Hydroxypropan-2-yl)-3-isopropyl-5,6-dimethoxyisobenzofuran-1(3H)-one (**3c**)*

Colorless paste; *Rf* 0.4 (hexanes-ethyl acetate 1:1); IR (ATR) 3428 (br), 1749, 1713, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, 3H, *J* = 6.8 Hz), 0.97 (d, 3H, *J* = 7.0 Hz), 1.20 (s, 3H), 1.22 (s, 3H), 1.98 (brs, 1H), 2.56-2.64 (m, 1H), 3.95 (s, 3H), 3.99 (s, 3H), 6.95 (s, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.38 (q), 18.44 (q), 25.6 (q), 26.4 (q), 32.3 (d), 56.0 (q), 56.3 (q),

75.2 (s), 93.7 (s), 105.1 (d), 105.7 (d), 119.4 (s), 144.4 (s), 150.1 (s), 154.0 (s), 170.9 (s); HRMS (ESI, ion trap) calcd for $C_{16}H_{23}O_5$ (M + H^+) 295.1545, found 295.1540.

*4.3.4. 3-Isopropyl-5,6-dimethoxyisobenzofuran-1(3H)-one (**9c**)*

Colorless paste; *Rf* 0.55 (hexanes-ethyl acetate 1:1); IR (ATR) 1742, 1601, 1503 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 3H, *J* = 6.8 Hz), 1.14 (d, 3H, *J* = 7.0 Hz), 2.22-2.28 (m, 1H), 3.94 (s, 3H), 3.98 (s, 3H), 5.28 (d, 1H, *J* =3.4 Hz), 6.83 (s, 1H), 7.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.3 (q), 18.8 (q), 32.3 (d), 56.2 (q), 56.3 (q), 85.0 (d), 103.3 (d), 106.0 (d), 118.6 (s), 143.4 (s), 150.3 (s), 154.6 (s), 171.1 (s); HRMS (ESI, ion trap) calcd for $C_{13}H_{17}O_4$ (M + H^+) 237.1127, found 237.1122.

*4.3.5. 3-(2-Hydroxypropan-2-yl)-3-isopropyl-6,7-dimethoxyisobenzofuran-1(3H)-one (**3d**)*

Colorless paste; *Rf* 0.55 (hexanes-ethyl acetate 1:1); IR (ATR) 3476 (br), 1736, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 6H, *J* = 6.8 Hz), 1.17 (s, 3H), 1.23 (s, 3H), 1.64 (brs, 1H), 2.51-2.60 (m, 1H), 3.92 (s, 3H), 4.09 (s, 3H), 7.12-7.15 (m, 1H), 7.17-7.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.5 (q), 18.6 (q), 25.5 (q), 26.5 (q), 32.7 (d), 56.7 (q), 62.3 (q), 75.4 (s), 93.0 (s), 117.7 (d), 118.7 (d), 119.9 (s), 143.0 (s), 148.2 (s), 152.5 (s), 168.0 (s); HRMS (ESI, ion trap) calcd for $C_{16}H_{23}O_5$ (M + H^+) 295.1545, found 295.1539.

*4.3.6. 3-(2-Hydroxypropan-2-yl)-4,5-dimethoxyisobenzofuran-1(3H)-one (**5d**)*

Colorless paste; *Rf* 0.4 (hexanes-ethyl acetate 1:2); IR (ATR) 3389 (br), 1736, 1706 1597 1574 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11-1.33 (m, 6H), 2.64-2.84 (brs, 1H), 3.89 (brs, 3H), 3.96 (s, 3H), 4.55 (brs, 1H), 6.98-7.10 (m, 1H), 7.48-7.69 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.5 (brq), 17.2 (brs), 34.6 (brd), 56.2 (brq), 61.4 (brq), 109.0 (brs), 114.5 (brd), 119.7 (brs), 121.9 (brd), 141.0 (brs), 143.6 (brs), 157.8 (brs), 168.7 (brs); HRMS (ESI, ion trap) calcd for $C_{13}H_{17}O_6$ (M + H^+) 253.1076, found 253.1068.

*4.3.7. 4,5,6,7-Tetrachloro-3-hydroxy-3-isopropylisobenzofuran-1(3H)-one (**5e**)*

White solid; *Rf* 0.4 (hexanes-ethyl acetate 2:1); mp 215 □; IR (ATR) 3443 (br), 1751,

1744, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.67 (d, 3H, *J* = 6.9 Hz), 1.30 (d, 3H, *J* = 6.9 Hz), 2.87-2.96 (m, 1H), 3.83 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 15.2 (q), 16.9 (q), 33.5 (d), 107.7 (s), 124.1 (s), 127.6 (s), 131.3 (s), 136.9 (s), 140.3 (s), 145.5 (s), 163.0 (s); HRMS (ESI, ion trap) calcd for $C_{11}H_7Cl_4O_2$ ($M + H^+ - H_2O$) 310.9200, found 310.9195.

4.3.8.

(1s,2R*,5S*)-2,5-Dihydroxy-2,5-dimethyl-3'H-spiro[cyclopentane-1,1'-isobenzofuran]-3'-on e (**10a**)*

White solid (CCDC 1958792); *Rf* 0.4 (hexanes-ethyl acetate, 1:1); mp 160 □; IR (ATR) 3391, 1759 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 6H), 2.13-2.19 (m, 2H), 2.38-2.43 (m, 2H), 4.19 (brs, 2H), 7.29 (d, 1H, *J* = 8.0 Hz), 7.56 (t, 1H, *J* = 7.5 Hz), 7.67-7.72 (m, 1H), 7.93 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 22.9 (q), 34.9 (t), 82.1 (s), 96.9 (s), 122.3 (d), 125.7 (s), 126.3 (d), 129.5 (d), 134.5 (d), 147.9 (s), 169.8 (s); HRMS (ESI, ion trap) calcd for $C_{14}H_{17}O_4$ ($M + H^+$) 249.1127, found 249.1123.

4.3.9.

(1R,2R*,5S*)-2-Hydroxy-2,5-dimethyl-3'H-spiro[cyclopentane-1,1'-isobenzofuran]-3'-one (**11a**)*

White solid (CCDC 1958793); *Rf* 0.6 (hexanes-ethyl acetate, 1:1); mp 172-173 □; IR (ATR) 3445, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.77 (d, 3H, *J* = 6.9 Hz), 1.43 (s, 3H), 1.64-1.74 (m, 1H), 2.02-2.16 (m, 3H), 2.17 (brs, 1H), 2.58-2.68 (m, 1H), 7.38-7.41 (m, 1H), 7.52-7.56 (m, 1H), 7.65-7.69 (m, 1H), 7.89-7.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4 (q), 24.3 (q), 27.5 (t), 39.5 (t), 39.7 (d), 81.3 (s), 98.4 (s), 123.0 (d), 125.6 (d), 127.8 (s), 129.2 (d), 133.6 (d), 147.2 (s), 170.0 (s); HRMS (ESI, ion trap) calcd for $C_{14}H_{17}O_3$ ($M + H^+$) 233.1178, found 233.1172.

4.3.10.

(1s,2R*,5S*)-2,5-Dihydroxy-5',6'-dimethoxy-2,5-dimethyl-3'H-spiro[cyclopentane-1,1'-isobe*

*nzofuran]-3'-one (**10b**)*

Colorless paste; *Rf* 0.25 (hexanes-ethyl acetate 1:2); IR (ATR) 3393 (br), 1748, 1597, 1503 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 6H), 2.09-2.14 (m, 2H), 2.38-2.43 (m, 2H), 3.96 (s, 3H), 3.97 (s, 3H), 4.29 (s, 2H), 6.61 (s, 1H), 7.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.8 (q), 35.0 (t), 56.2 (q), 56.4 (q), 81.9 (s), 96.3 (s), 103.6 (d), 106.3 (d), 118.0 (s), 142.2 (s), 150.6 (s), 155.0 (s), 170.1 (s); HRMS (ESI, ion trap) calcd for $C_{18}H_{21}O_6$ ($M + H^+$) 309.1338, found 309.1337.

4.3.11.

(1R,2R*,5S*)-2-Hydroxy-5',6'-dimethoxy-2,5-dimethyl-3'H-spiro[cyclopentane-1,1'-isobenzo furan]-3'-one (**11b**)*

colorless paste; *Rf* 0.4 (hexanes-ethyl acetate 1:2); IR (ATR) 3451 (br), 1736, 1599, 1503 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.78 (d, 3H, *J* = 6.9 Hz), 1.44 (s, 3H), 1.63-1.70 (m, 1H), 2.02-2.15 (m, 3H), 2.20 (brs, 1H), 2.53-2.62 (m,1H), 3.94 (s, 3H), 3.98 (s, 3H), 6.75 (s, 1H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4 (q), 24.3 (q), 27.4 (t), 39.46 (t), 39.54 (d), 56.2 (q), 56.4 (q), 81.1 (s), 97.6 (s), 104.5 (d), 106.1 (d), 120.0 (s), 141.5 (s), 150.6 (s), 154.3 (s), 170.1 (s); HRMS (ESI, ion trap) calcd for $C_{16}H_{21}O_5$ ($M + H^+$) 293.1389, found 293.1387.

4.3.12.

(1s,2R*,5S*)-2,5-Dihydroxy-4',5'-dimethoxy-2,5-dimethyl-3'H-spiro[cyclopentane-1,1'-isobe nzofuran]-3'-one (**10c**)*

Pale yellow solid; *Rf* 0.3 (hexanes-ethyl acetate 1:1); mp 130-131 □; IR (ATR) 3285 (br), 1753, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 6H), 2.08-2.14 (m, 2H), 2.38-2.44 (m, 2H), 3.92 (s, 3H), 4.11 (s, 3H), 4.49 (brs, 2H), 6.87 (d, 1H, *J* = 8.5 Hz), 7.22 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 22.7 (q), 34.7 (t), 56.7 (q), 62.4 (q), 82.6 (s), 95.5 (s), 116.8 (d), 118.0 (s), 119.5 (d), 140.6 (s), 148.4 (s), 152.7 (s), 167.5 (s); HRMS (ESI, ion trap) calcd for $C_{16}H_{21}O_6$ ($M + H^+$) 309.1338, found 309.1331.

*4.4. Typical procedure for the dehydration of **3** to **6***

A solution of **3a** (117 mg, 0.5 mmol) in toluene (10 mL) was refluxed in the presence of cat. *p*-TsOH for 1 h using Dean-Stark apparatus. After the solvent was removed *in vacuo*, the residue was purified by column chromatography on silica gel to give **6a** (82 mg, 76%).

*4.4.1. 3-Isopropyl-3-(prop-1-en-2-yl)isobenzofuran-1(3H)-one (**6a**)*

Colorless paste; *Rf* 0.45 (hexanes-ethyl acetate, 10:1); IR (ATR) 1757 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.67 (d, 3H, *J* = 6.9 Hz), 1.00 (d, 3H, *J* = 6.9 Hz), 1.88 (s, 3H), 2.52-2.61 (m, 1H), 4.97 (s, 1H), 5.19 (s, 1H), 7.45-7.48 (m, 1H), 7.49-7.53 (m, 1H), 7.63-7.67 (m, 1H), 7.86-7.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.1 (q), 16.9 (q), 19.2 (q), 33.0 (d), 94.0 (s), 113.2 (t), 122.2 (d), 125.7 (d), 126.2 (s), 128.9 (d), 133.6 (d), 143.1 (s), 151.1 (s), 170.4 (s); HRMS (ESI, ion trap) calcd for $C_{14}H_{17}O_2$ ($M + H^+$) 217.1229, found 217.1223.

*4.4.2 3-(Propan-2-ylidene)isobenzofuran-1(3H)-one (**8a**)*[4c]

Colorless paste; *Rf* 0.45 (hexanes-ethyl acetate, 5:1); IR (ATR) 1755, 1717, 1674, 1603, 1586 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.20 (s, 3H), 7.48 (t, 1H, *J* = 7.5 Hz), 7.67-7.71 (m, 1H), 7.80 (d, 1H, *J* = 8.0 Hz), 7.93 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 18.7 (q), 20.2 (q), 119.5 (s), 122.5 (d), 125.4 (d), 125.5 (s), 128.3 (d), 134.1 (d), 138.8 (s), 141.4 (s), 167.1 (s); HRMS (ESI, ion trap) calcd for $C_{11}H_{11}O_2$ ($M + H^+$) 175.0759, found 175.0756.

*4.4.3. 3-(Cyclohex-1-en-1-yl)-3-cyclohexylisobenzofuran-1(3H)-one (**6b**)*

Colorless paste; *Rf* 0.5 (hexanes-ethyl acetate, 5:1); IR (ATR) 1757, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86-1.28 (m, 6H), 1.43-1.78 (m, 8H), 1.97-2.20 (m, 5H), 5.82-5.85 (m, 1H), 7.41-7.46 (m, 1H), 7.46-7.51 (m, 1H), 7.60-7.64 (m, 1H), 7.84-7.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9 (t), 22.7 (t), 24.6 (t), 25.1 (t), 26.0 (t), 26.3 (t), 26.35 (t), 26.39 (t), 26.9 (t) 42.6 (d), 94.4 (s), 122.6 (d), 124.4 (d), 125.6 (d), 126.5 (s), 128.6 (d), 133.2 (d), 135.1 (s), 151.1 (s), 170.5 (s); HRMS (ESI, ion trap) calcd for $C_{20}H_{25}O_2$ ($M + H^+$) 297.1855, found

297.1849.

*4.4.4. 3-Isopropyl-5,6-dimethoxy-3-(prop-1-en-2-yl)isobenzofuran-1(3H)-one (**6c**)*

Colorless paste; *Rf* 0.65 (hexanes-ethyl acetate 1:1) IR (ATR) 1748, 1705, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.68 (d, 3H, *J* = 6.7 Hz), 1.01 (d, 3H, *J* = 6.7 Hz), 1.85 (s, 3H), 2.48-2.57 (m, 1H), 3.94 (s, 3H), 3.98 (s, 3H), 4.98 (s, 1H), 5.18 (s, 1H), 6.80 (s, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.1 (q), 16.9 (q), 19.2 (q), 32.8 (d), 56.1 (q), 56.3 (q), 93.2 (s), 103.6 (d), 105.9 (d), 112.9 (t), 118.1 (s), 143.4 (s), 145.6 (s), 150.2 (s), 154.3 (s), 170.6 (s); HRMS (ESI, ion trap) calcd for $C_{16}H_{21}O_4$ ($M + H^+$) 277.1440, found 277.1434.

*4.4.5. 3-Isopropyl-6,7-dimethoxy-3-(prop-1-en-2-yl)isobenzofuran-1(3H)-one (**6d**)*

Colorless paste; *Rf* 0.5 (hexanes-ethyl acetate 2:1); IR (ATR) 1751, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.68 (d, 3H, *J* = 6.7 Hz), 0.98 (d, 3H, *J* = 6.7 Hz), 1.86 (s, 3H), 2.44-2.52 (m, 1H), 3.91 (s, 3H), 4.10 (s, 3H), 4.94 (s, 1H), 5.18 (s, 1H), 7.05 (d. 1H, *J* = 8.2 Hz), 7.19 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 16.0 (q), 16.9 (q), 19.1 (q), 33.0 (d), 56.7 (q), 62.2 (q), 92.3 (s), 112.7 (t), 116.7 (d), 118.3 (s), 118.7 (d), 143.4 (s), 144.1 (s), 148.1 (s), 152.3 (s), 167.7 (s); HRMS (ESI, ion trap) calcd for $C_{16}H_{21}O_4$ ($M + H^+$) 277.1440, found 277.1435.

*4.4.6. 4,5-Dimethoxy-3-(propan-2-ylidene)isobenzofuran-1(3H)-one (**8d**)*

White solid (CCDC 1958790); *Rf* 0.5 (hexanes-ethyl acetate 2:1); mp 89-90 □; IR (ATR) 1749, 1659, 1612, 1578 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.35 (s, 3H), 3.82 (s, 3H), 3.99 (s, 3H), 7.08 (d, 1H, *J* = 8.2 Hz), 7.68 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 19.3 (q), 21.4 (q), 56.5 (q), 61.1 (q), 113.4 (d), 119.8 (s), 122.2 (s), 122.3 (d), 131.6 (s), 140.1 (s), 142.2 (s), 158.3 (s), 166.5 (s); HRMS (ESI, ion trap) calcd for $C_{13}H_{15}O_4$ ($M + H^+$) 235.0970, found 235.0965.

*4.4.7. 4,5,6,7-Tetrachloro-3-(propan-2-ylidene)isobenzofuran-1(3H)-one (**8e**)*[4c]

Pale yellow solid; *Rf* 0.55 (hexanes-ethyl acetate 10:1); mp 117 □; IR (ATR) 1757, 1636, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H), 2.31(s, 3H); ^{13}C NMR ($CDCl_3$) δ 22.6 (q), 23.3

(q), 123.2 (s), 125.3 (s), 126.3 (s), 131.2 (s), 134.8 (s), 137.2 (s), 138.4 (s), 140.4 (s), 161.3 (s); HRMS (ESI, ion trap) calcd for $C_{11}H_7Cl_4O_2$ (M + H^+) 310.9200, found 310.9195.

*4.4.8. 4,5,6,7-Tetrafluoro-3-(propan-2-ylidene)isobenzofuran-1(3H)-one (**8f**)*

Yellow solid (CCDC 1958791); *Rf* 0.5 (hexanes-ethyl acetate 10:1); mp 92 □; IR (ATR) 1761, 1670, 1518 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.23 (s, 1.5H), 2.24 (s, 1.5H); ^{13}C NMR δ 19.1 (q), 19.3 (q), 21.4 (q), 109.7 (s, J_{CCF} = 12.0 Hz), 121.4 (s, J_{CCF} = 15.6 Hz), 126.1 (s), 137.3 (s), 139.0 (s, J_{CF} = 257.3 Hz, J_{CCF} = 13.8 Hz, J_{CCCF} = 4.8 Hz), 140.4 (s, J_{CF} = 258.5 Hz, J_{CCF} = 14.4 Hz), 144.1 (s, J_{CF} = 265.1 Hz, J_{CCF} = 11.4 Hz, J_{CCCF} = 3.6 Hz), 145.6 (s, J_{CF} = 261.5 Hz, J_{CCF} = 13.8 Hz, J_{CCCF} = 2.4 Hz); HRMS (ESI, ion trap) calcd for $C_{11}H_7F_2O_2$ (M + H^+) 247.0382, found 247.0375.

*4.5. Typical procedure for the hydrogenation of **6** to **7***

A solution of **6a** (54 mg, 0.25 mmol) in ethyl acetate (10 mL) was stirred in the presence of cat. Pd/C (10%) under H_2 (1 atm) for 2 h. After the solution was filtered, the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel to give **7a** (52 mg, 95%).

*4.5.1. 3,3-Diisopropylisobenzofuran-1(3H)-one (**7a**)*

Colorless paste; *Rf* 0.45 (hexanes-ethyl acetate, 10:1); IR (ATR) 1751 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, 6H, *J* = 6.9 Hz), 0.84 (d, 6H, *J* = 6.9 Hz), 2.45-2.54 (m, 2H), 7.34-7.39 (m, 1H), 7.48-7.53 (m, 1H), 7.61-7.66 (m, 1H) 7.85-7.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6 (q), 16.8 (q), 32.4 (d), 94.9 (s), 121.9 (d), 125.5 (d), 127.9 (s), 128.7 (d), 133.4 (d), 150.6 (s), 170.9 (s); HRMS (ESI, ion trap) calcd for $C_{14}H_{19}O_2$ (M + H^+) 219.1385, found 219.1380.

*4.5.2. 3-Isopropylisobenzofuran-1(3H)-one (**9a**)*

Colorless paste; *Rf* 0.4 (hexanes-ethyl acetate, 5:1); IR (ATR) 1757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (d, 3H, *J* = 6.9 Hz), 1.13 (d, 3H, *J* = 6.9Hz), 2.25-2.32 (m, 1H), 5.37 (d, 1H, *J*

= 3.9 Hz), 7.45 (d, 1H, *J* = 7.7 Hz), 7.53 (t, 1H, *J* = 7.7 Hz), 7.65-7.69 (m, 1H), 7.90 (d, 1H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 15.6 (q), 18.6 (q), 32.3 (d), 85.6 (d) 122.1 (d), 125.6 (d), 126.7 (s), 129.0 (d), 133.8 (d), 148.8 (s), 170.8 (s); HRMS (ESI, ion trap) calcd for $C_{11}H_{13}O_2$ (M + H^+) 177.0916, found 177.0912.

*4.5.3. 3,3-Diisopropyl-5,6-dimethoxyisobenzofuran-1(3H)-one (**7c**)*

Colorless paste; *Rf* 0.55 (hexanes-ethyl acetate 2:1), IR (ATR) 1736, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 6H, *J* = 6.6 Hz), 0.85 (d, 6H, *J* = 6.3 Hz), 2.41-2.50 (m, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 6.72 (s, 1H), 7.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.5 (q), 16.8 (q), 32.3 (d), 56.1 (q), 56.3 (q), 94.1 (s), 103.4 (d), 105.9 (d), 119.9 (s), 144.9 (s), 150.0 (s), 154.2 (s), 171.1 (s); HRMS (ESI, ion trap) calcd for $C_{16}H_{23}O_4$ (M + H^+) 279.1596, found 279.1587.

*4.5.4. 3,3-Diisopropyl-6,7-dimethoxyisobenzofuran-1(3H)-one (**7d**)*

Colorless paste; *Rf* 0.6 (hexanes-ethyl acetate 2:1), IR (ATR) 1749, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 6H, *J* = 7.2 Hz), 0.84 (d, 6H, *J* = 6.9 Hz), 2.38-2.46 (m, 2H), 3.91 (s, 3H), 4.10 (s, 3H), 6.95 (d, 1H, *J* = 8.2 Hz), 7.18 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 16.5 (q), 16.7 (q), 32.5 (d), 56.6 (q), 62.3 (q), 93.2 (s), 116.3 (d), 118.5 (d), 120.1 (s), 143.6 (s), 148.0 (s), 152.1 (s), 168.2 (s); HRMS (ESI, ion trap) calcd for $C_{16}H_{23}O_4$ (M + H^+) 279.1596, found 279.1594.

*4.5.5. 3-Isopropyl-4,5-dimethoxyisobenzofuran-1(3H)-one (**9d**)*

Colorless paste; *Rf* 0.5 (hexane-ethyl acetate 2:1); IR (ATR) 1751, 1612, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.59 (d, 3H, *J* = 7.0 Hz), 1.26 (d, 3H, *J* = 7.0 Hz), 2.50-2.59 (m, 1H), 3.91 (s, 3H), 3.97 (s, 3H), 5.46 (d, 1H, *J* = 2.3 Hz), 7.08 (d, 1H, *J* = 8.4 Hz), 7.61 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 20.1 (q), 30.6 (d), 56.3 (q), 60.4 (q), 84.1 (d), 113.8 (d), 119.8 (s), 121.8 (d), 141.4 (s), 142.8 (s), 157.0 (s), 170.5 (s); HRMS (ESI, ion trap) calcd for $C_{13}H_{17}O_4$ (M + H^+) 237.1127, found 237.1123.

4.6. X-ray crystallographic analysis

All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SIR-97 and refined with SHELXL-97. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. All calculations were performed using the YADOKARI-XG software package. Crystal data of **3a**, **8d**, **8f**, **10a**, and **11a** are deposited into CCDC 1958789-1958793, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.ac.uk/data/cif.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.XXXX.

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Highlights

► Reductive coupling of phthalic anhydrides with acetone and acetonylacetone by Zn-$TiCl_4$. ► Unusual two-to-one coupled products for preparation of 3,3-disubstituted phthalides. ► Stereoselective synthesis of 3-spirocyclopentanylphtalides. ► One-to-one coupled products for preparation of 3-isopropylidene- and 3-isopropylphthalides.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: