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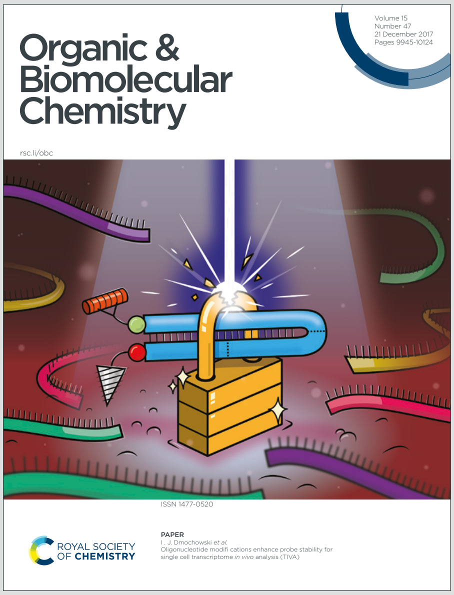

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ARTICLE

Acid-base-sensitive allylic oxidation of 2-allylbenzoic acids to form phthalides†

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Allylic oxidation of 2-allylbenzoic acids to phthalides, instead of Wacker-type isocoumarins, was achieved with 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate (White catalyst) and oxygen in DMSO. The selective formation of 3-ethylidenephthalides or 3-vinylphthalides was controlled by the addition of acids or bases, and the reaction conditions were applied to substituted 2-allylbenzoic acids to generate correspodning phthalides selectively. Mechanistic studies, including the corresponding reaction of (*E*)-2-(1-propenyl)benzoic acid to 3-methylisocoumarin, isomerization reaction of 3-vinylphthalide to 3-ethylidenephthalide, and the kinetic isotope effect using 2-(1,1-d_2-allyl)benzoic acid, revealed the competition between Wacker-type oxidation and allylic C-H cleavage, which is the key step to generating phthalides. A natural product, 3-ethyl-6-hydroxyphthalide, was prepared by this method.

Introduction

The framework of isobenzofuran-1(3H)-one, also known as phthalide, is widely found in natural products,[1-7,8-11] pharmaceutical compounds,[12-14] and synthetic building blocks (Figure 1).[15-22] In 2018, more than fifteen new natural products containing the phthalide moiety have been reported,[1, 7, 23-27] and the number of naturally occurring phthalides isolated from various plants, bacteria, and fungi has exceeded two hundred.[28, 29] Because of the pervasiveness and broad biological activities of phthalides and their function as synthetic precursors, the preparation of phthalides has attracted much attention from organic chemists.[28, 30-32]

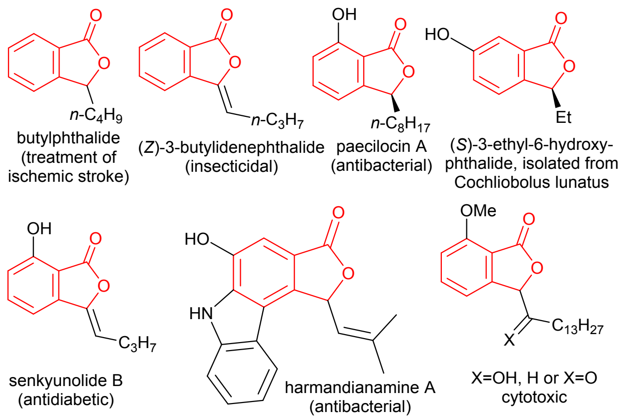
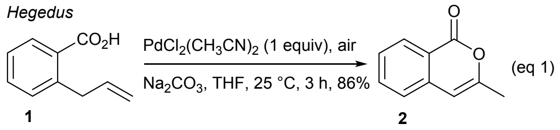


Figure 1 Selected phthalide derivatives having biological activity

Many elegant methods have been developed to prepare phthalides.[33-41] In this regard, Hegedus' and Larock's groups reported the formation of 3-methylisocoumarin (**2**) and 3-ethylidenephthalide (**3**) from 2-allylbenzoic acid (**1**) by palladium(II) catalysts and oxygen (eqs 1 and 2).[42, 43] This direct oxidative lactonization of 2-allylbenzoic acid is attractive because it is commercially available or conveniently prepared by the one-pot sequence of magnesiation and allylation of 2-iodobenzoic acid.[44, 45] However, the formation of 3-vinylphthalide by this approach has not been achieved; instead, 3-vinylphthalides were produced by the intramolecular condensation of the corresponding allylic alcohols (eq 3).[46] Stoltz's and Sasai's groups prepared substituted 3-vinylphthalide and γ-lactones by the oxidative cyclization of 2-(2-butenyl)benzoic acid and 4-alkenoic acids, respectively (eq 4).[47, 48] Breder's group recently reported that a catalytic amount of diphenyldiselenide and *N*-fluorobenzenesulfonimide (NFSI) as the oxidant converted 2-allylbenzoic acids to the corresponding lactones (eq 5).[49] However, this reaction is limited to olefins conjugated with an aromatic ring. Li's group also reported a copper-catalysed, aerobic lactonization of alkenoic acids (eq 6) recently.[50-52]

The recent development of allylic C-H activation, especially by using 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate (White catalyst), has become a powerful tool for furnishing allyl amides, esters, lactones, carbamates, imidazolidinones, and oxazolidinones inter- or intramolecularly.[53-64] We surmised that the challenge in preparing 3-vinylphthalides from 2-allylbenzoic acids could be met by using this palladium catalyst (eq 7).



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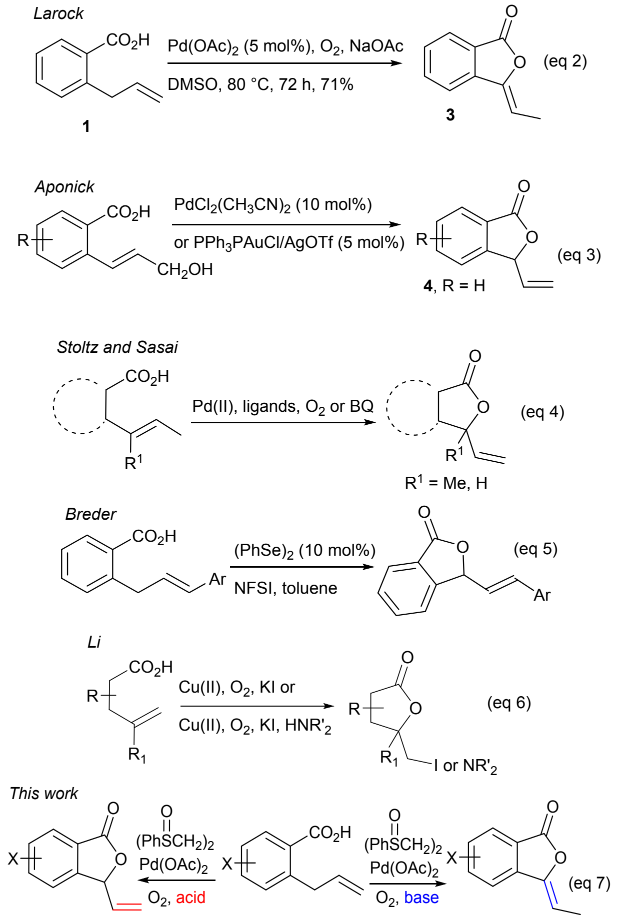
†Electronic Supplementary Information (ESI) available: [^{1}H and ^{13}C{^{1}H} NMR spectra for compounds **2-4**, **3a-3h**, **4d**, **6** and all the new compounds]. See DOI: 10.1039/x0xx00000x



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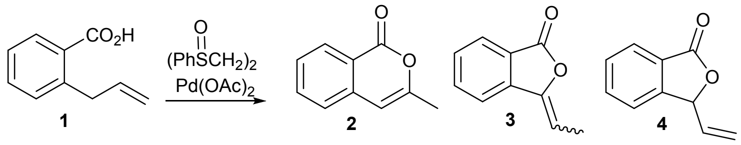
Results and discussion

Our results for preparing lactones utilizing allylic C-H cleavage, *i.e.,* 3-ethylidenephthalide (**3**) or 3-vinylphthalide (**4**) from 2-allylbenzoic acid (**1**), are summarized in Table 1. The initial experiments using White catalyst, *p*-benzoquinone (BQ) and the reported reaction conditions (SI Table 1 in Supporting Information) were not satisfactory,[53, 55-58, 65] as isocoumarin **2**, derived from Wacker-type oxidation, was the major product. Utilizing DMSO, acetic acid, or their 1:1 mixture, solvents often applied in allylic C-H cleavages, also gave isocoumarin **2** as the major product (entries 1–3). Although White catalyst is known for promoting allylic oxidation rather than Wacker-type reactions, these results indicate that the reported conditions are not effective for suppressing Wacker oxidation and activating the allylic/benzylic C-H bond of **1**. However, we noticed that the addition of sodium azide, a reagent often applied to attack the intermediate palladium allyl complex,[66] afforded a 74% yield of 3-ethylidenephthalide (**3**) mainly as the *Z* diastereomer (entry 4), and a similar yield (72%) was obtained when benzoquinone was replaced with oxygen (entry 5). Simply adding sodium hydroxide solution (1 *N*) to the reaction mixture further improved the yield of **3** to 87% (entry 6), suggesting that the reaction pathway could be altered by base. This finding prompted us to further study the effect of acid and base on the reaction. As the pH values of the reaction media decreased by adding different buffered solutions (pH 9.8–4.7), the yields of **3** also decreased (entries 7–9). We were glad to find that the desired 3-vinylphthalide (**4**) was produced in high yields when hydrochloric acid (1 *N*) or acetic acid was applied (entries 10 and 11). To our knowledge, the direct allylic oxidation of

Table 1 Reaction Conditions for the Oxidation of 2-Allylbenzoic acids (**1**)



Entry[a]	reagents	Solvent	Time (h)	Yield (%)[b] 2	3 (E:Z)[c]	4	Recovered 1
1	White catalyst, BQ	DMSO	24	80			
2	White catalyst, BQ	AcOH	24	75		8	
3	White catalyst, BQ	DMSO/AcOH (1:1)	24	95			
4	White catalyst, BQ, NaN_3 (1.5 equiv)	DMSO	24		74 (1:8)[c]		
5	White catalyst, O_2, NaN_3 (1.5 equiv)	DMSO	24		72 (1:9)[c]		
6	White catalyst, O_2, $NaOH_{(aq)}$ (1 *N*, 50 μL, 0.5 equiv)	DMSO	12		87 (1:14)[c]		
7	White catalyst, O_2, $Na_2HPO_{4(aq)}$ (pH 9.8, 2 *M*, 100 μL)	DMSO	12	15	85 (1:10)[c]		
8	White catalyst, O_2, phosphate buffer (pH 7.0, 2 *M*, 100 μL)	DMSO	12	39	50 (1:5)[c]		
9	White catalyst, O_2, $KH_2PO_{4(aq)}$ (pH 4.7, 2 *M*, 100 μL)	DMSO	12		29 (1:10)[c]		71
10	White catalyst,[d] O_2, $HCl_{(aq)}$ (1 *N*, 50 μL, 0.5 equiv)	DMSO	24	5		92	
11	White catalyst,[d] O_2, AcOH (1.5 equiv)	DMSO	24	3		94	
12	$Pd(OAc)_2$, O_2, $NaOH_{(aq)}$ (1 *N*, 50 μL, 0.5 equiv)	DMSO	12	14	82 (1:10)[c]		
13	$Pd(OAc)_2$, O_2, $HCl_{(aq)}$ (1 *N*, 50 μL, 0.5 equiv)	DMSO	24	11		29	60
14	$PdCl_2$, O_2, $HCl_{(aq)}$ (1 *N*, 50 μL, 0.5 equiv)	DMSO	24	47		53	

[a] 2-Allylbenzoic acid (1.0 mmol), Pd catalyst (5 mol%), solvent (1.0 mL), benzoquinone (BQ, 2.0 mmol) or O_2 (1 atm) at 100 °C. [b] Isolated yields. [c] *E*- to *Z*-ratio based on ^1H NMR analysis. [d] 10 mol%.

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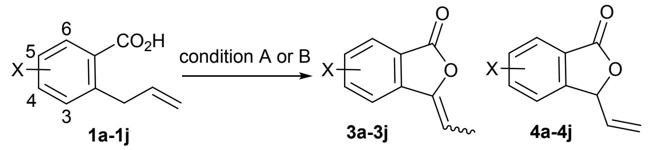
2-allylbenzoic acid to give 3-vinylphthalide with high purity is achieved for the first time. Replacing White catalyst with palladium acetate, the basic condition provided fewer **3**, accompanied with byproduct **2** (entry 12 versus 6). Comparing with Larock's condition to generate **3** (eq 2), the White catalyst and basic condition reported in entry 6 has the advantages of a shorter reaction time and a better yield. Under the acidic condition, the reaction of $Pd(OAc)_2$ also provided an inferior result (entry 13 versus 11). Palladium(II) chloride gave nearly 1:1 ratio of **4** and **2** under the same acidic conditions (1 *N* $HCl_{(aq)}$, entry 14). These results suggest that benzoquinone is not required to produce phthalides **3** and **4**; rather their ratio is affected by the acidity of the environment and White catalyst is a better choice for activation/oxidation of the allylic C-H bond.

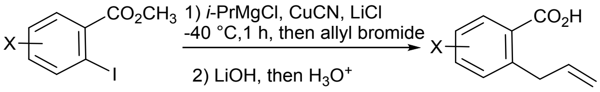
The optimized conditions were applied to convert various 2-allylbenzoic acids to the corresponding phthalide derivatives using White catalyst. The starting 2-allylbenzoic acids **1a**–**1j** were prepared according to eq 8.[45] The standard conditions we used for preparing the 3-ethylidenephthalide **3**, *i.e.*, White catalyst (5 mol%), oxygen gas (1 atm), in DMSO (0.1 *M*) with 0.5 equivalent of sodium hydroxide (Condition A), provided the corresponding phthalides **3a**–**3h** and **3j**, with the *Z*-diastereomer predominating. On the other hand, replacing the base with hydrochloric acid (Condition B) gave the 3-vinylphthalides **4a**–**4h** and **4j** as the major product (Table 2).

Table 2 Selective Formation of Phthalides



Entry	X, reactant	Condition[a]	Product	Yield (%)[b]	*E*:*Z*[c]
1	4-F, **1a**	A	**3a**	63	1:15
2	4-F, **1a**	B	**4a**	65	-
3	4-Cl, **1b**	A	**3b**	65	1:10
4	4-Cl, **1b**	B	**4b**	86	-
5	5-Cl, **1c**	A	**3c**	26	1:5.4
6	5-Cl, **1c**	B	**4c**	56	-
7	5-Br, **1d**	A	**3d**	65	1:3
8	5-Br, **1d**	B	**4d**	85	-
9	5-OMe, **1e**	A	**3e**	71	1:4.5
10	5-OMe, **1e**	B	**4e**	42	-
11	4,5-(OMe)$_2$, **1f**	A[d]	**3f**	86	1:14
12	4,5-(OMe)$_2$, **1f**	B	**4f**	63	-
13	5-Me, **1g**	A	**3g**	75	1:16
14	5-Me, **1g**	B	**4g**	25	-
15	6-Me, **1h**	A[d]	**3h**	69	1:6.3
16	6-Me, **1h**	B	**4h**	20	-
17	5-CN, **1i**	A	**5i**	93[e]	-
18	5-CN, **1i**	B	-	95[f]	-
19	5-OH, **1j**	A	**3j**	80	1:4.8
20	5-OH, **1j**	B	**4j**	50	-

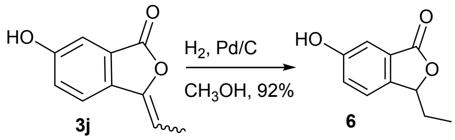
[a] A: Substituted benzoic acid **1** (0.1 mmol), White catalyst (5 mol%), O_2 (1 atm), $NaOH_{(aq)}$ (1 *N*, 50 μL) in DMSO (1 mL), 100 °C, 12 h; B: Substituted benzoic acid **1** (0.1 mmol), White catalyst (10 mol%), O_2 (1 atm), $HCl_{(aq)}$ (1 *N*, 50 μL) in DMSO (1 mL), 100 °C, 24 h. [b] Isolated yields. [c] *E*- to *Z*-ratio based on ^1H NMR analysis. [d] NaN_3 (0.15 mmol) instead of $NaOH_{(aq)}$, 24 h. [e] (*E*)-5-Cyano-2-(1-propenyl)benzoic acid (**5i**) produced. [f] Starting material **1i** recovered.



(eq 8)

In general, the reactions carried out under Condition A were completed in 12 h and provided better yields of 3-ethylidenephthalides than those under Condition B to yield 3-vinylphthalides. All the halogenated substrates (**1a**–**1d**) provided the corresponding phthalides with yields up to 86% (entries 1–8). The reactions of 4- or 5-methoxy-substituted benzoic acids **1e** and **1f** also went smoothly in good yields (entries 9–12), although addition of sodium azide provided a better yield (86%) for the formation of **3f** (entry 11). The corresponding reactions of the methyl-substituted 2-allylbenzoic acids **1g** and **1h** were more challenging. 3-Ethylidenephthalides **3g** and **3h** were prepared in good yields using Condition A (entries 13 and 15), but Condition B produced low yields of the 3-vinylphthalides **4g** and **4h**, and the phthalides were contaminated with Wacker-type products (entries 14 and 16). The 5-cyano-substituted benzoic acid **1i** gave only the isomerized, (*E*)-5-cyano-2-(1-propenyl)benzoic acid (**5i**) under Condition A (entry 17), suggesting that the electron-withdrawing 5-cyano group not only facilitates the isomerization but suppresses further oxidation of the olefin.

We also found that **1i** was stable under Condition B (entry 18). The reactions of 5-hydroxyl-substituted benzoic acid **1j** provided slightly better yields of **3j** and **4j**, comparing with its 5-methoxy counterpart **1e** (entries 19 and 20). Hydrogenation of **3j** achieved the racemic synthesis of 3-ethyl-6-hydroxyphthalide (**6**, eq 9), a natural product recently discovered.[7]



(eq 9)

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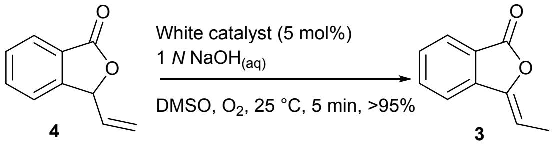
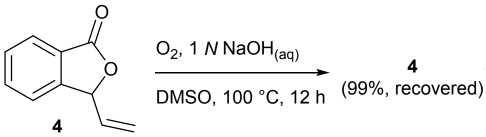
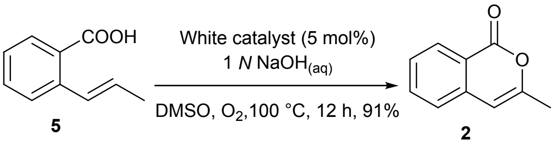
Mechanistic insights were obtained from the following reactions (eqs 10–13). We found that 3-vinylphthalide (**4**) were rapidly converted to 3-ethylidenephthalide (3) under the basic condition and White catalyst (25 °C, 5 min, eq 10). In the absence of White catalyst, 3-vinylphthalide (**4**) was stable in the basic reaction media, indicating that the isomerization of **4** to **3** requires palladium (eq 11). No trace of thermodynamically stable isocoumarin 2 was found in these isomerization studies,[67] which suggests that the formation of phthalides and isocoumarins are two independent processes, viz., allylic C-H oxidation and Wacker-type oxidation, respectively. When (*E*)-2-(1-propenyl)benzoic acid (**5**)[42] was subjected to the allylic C-H oxidation, both Conditions A and B yielded only isocoumarin **2** (eqs 12 and 13). These results also indicate that phthalides **3** and **4** are only derived from 2-allylbenzoic acids (**1**) through allylic C-H cleavage, which competes with the processes of Wacker oxidation/isomerization leading to isocoumarin **2**.



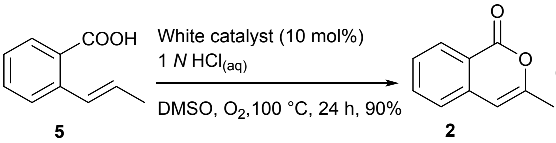
(eq 10)



(eq 11)



(eq 12)



(eq 13)

Based on our experimental results, a reaction mechanism for the formation of phthalides can be proposed (Scheme 1). Previous studies using White catalyst and benzoquinone indicated that the quinone facilitates the functionalization of π-allylpalladium intermediates with incoming nucleophiles such as acetate, carboxylates and carbamates, etc. to achieve allylic C-H activation efficiently.[53-56, 59] However, this effect should not be critical for the reaction of **1**, as the functionalization step now is an intramolecular, kinetically favored *5-exo-tect* process to form intermediates **B** and **D**.[68, 69] The fact that isocoumarin **2** was always generated in the reactions using benzoquinone (entries 1–3, Table 1 and SI Table 1) suggests that its presence may also increase the reaction rate of the Wacker-type oxidation. Under basic conditions, the resulting carboxylate-palladium complex allows facile allylic C-H oxidation; however, the basic environment also promotes migration of the terminal double bond to give product **3** as seen in eq 10. On the other hand, the acidic condition not only slows down all the reactions but makes the allylic C-H cleavage/functionalization a dominant pathway to give **4**.

To better understand the reaction mechanism, 2-(1,1-$d_2$allyl)benzoic acid (**1-D$_2$**, 98% CD_2) was prepared (SI Scheme 1 in Supporting Information). Under the basic condition, two parallel, oxidative lactonizations of **1** and **1-D2** were performed to determine the kinetic isotope effect (Scheme 2). As monitored by *in situ* ^{1}H NMR, a substantial KIE was observed using the initial rates method for each reaction at the onset of product formation (k_H/k_D = 4.3–4.4, see Supporting Information for details). The KIE value is consistent with primary isotope effects[70] and indicates that the cleavage of the allylic C-H bond should be the rate-determining step.[71, 72] We also observed that the methyl group of 3-D derived from **1-D$_2$** contained only 10% deuterium according to ^{1}H NMR analysis. The loss of deuterium can be attributed to the extensive exchange between Pd-D and protons of the reaction media during the isomerization step **B** to afford **3** (Scheme 1).

We also measured the reaction rate of **1** under the acidic condition, which was only 15% of the reaction rate of **1** under the basic condition (see Supporting Information). In addition, the reaction of **1-D$_2$** in the acidic media provided Wacker-type product **2-D** as the major product (67% yield) with traces of phthalide **4-D** (7% yield, eq 14). This result indicates that the competing Wacker-type oxidation seems less influenced by the acidic media and results in the isocoumarin **2-D** being the major product. The slow and negligible formation of **4-D** makes the measurement of this KIE unlikely. However, the remaining deuterium of **1-D$_2$** was well retained (>95%) in the two products **2-D** and **4-D**, which is in agreement with the speculation that isomerization and hydrogen exchange, catalyzed by palladium-hydride species generated from allylic C-H activations,[73, 74] are prevalent under basic conditions, but very limited under acidic conditions.

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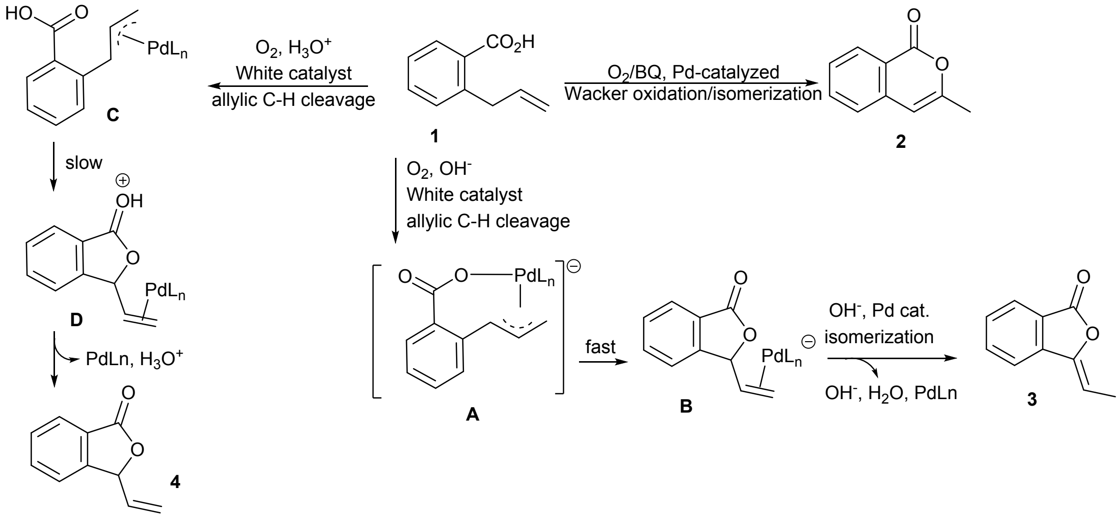
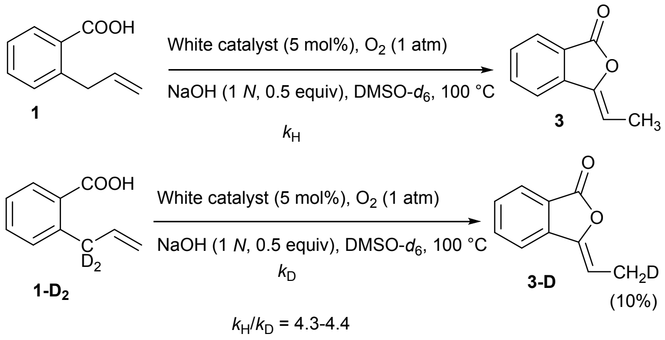
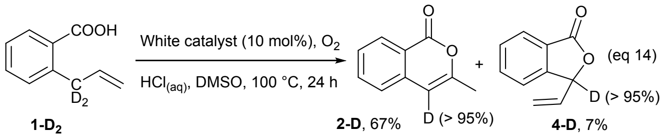


Scheme 1 Proposed reaction mechanism



Scheme 2 Kinetic Isotope Effect of the Oxidative Lactonization



Experimental

General experimental details

Dichloromethane and dimethyl sulfoxide (DMSO) were dried over calcium hydride and distilled prior to use. Tetrahydrofuran and diethyl ether were dried over sodium, monitored with benzophenone ketyl radicals and distilled prior to use. DMF was dried over molecular sieves (3 Å). TLC was conducted using pre-coated silica gel 60 F254 plates containing a fluorescent indicator; purification by chromatography was conducted using silica gel (230–400 mesh). Chemical shifts for ^{1}H-NMR and ^{13}C{^{1}H} NMR spectra are reported in δ units (parts per million) with reference to residual solvent peaks. All spectra were obtained at 25 °C. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, td = triplet of doublets. High-resolution mass spectrometry (HRMS) data were recorded on a JMS-700 quadrupole mass spectrometer. 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (White catalyst)[55] and 2-allylbenzoic acids **1, 1a, 1b, 1d, 1e, 1f, 1g**, **1h** and **1i**[45] were prepared according to the literature.

2-Allyl-5-chlorobenzoic Acid (1c)

i-PrMgCl (1 *M* in THF, 10 mL, 10.0 mmol) was added dropwise to a solution of methyl 5-chloro-2-iodobenzoate[75, 76] (1.0 g, 3.37 mmol) and THF (34 mL) at -40 °C. The reaction mixture was added with a solution of CuCN·2LiCl in THF (0.34 *M* in THF, 10 mL, 3.37 mmol), stirred for 30 min at -40 °C, added with a solution of allyl bromide (1.1 mL, 13.50 mmol) and stirred for another 1 h at -40 °C. The reaction mixture was allowed to warm to room temperature overnight, quenched with sat. NH$_4$Cl$_{(aq)}$ (25 mL), and extracted with ethyl acetate (45 mL × 3). The combined organic layers were washed with sat. NaCl$_{(aq)}$ (25 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was re-dissolved in THF (24 mL), methanol (6 mL) and water (6 mL), added with lithium hydroxide monohydrate (0.71 g, 16.8 mmol) and stirred at rt for 16 h. The reaction mixture was concentrated, washed with diethyl ether (15 mL × 2), acidified

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with $HCl_{(aq)}$ (2 *N*, 5 mL) and extracted with diethyl ether (15 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq)}$ (15 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, ethyl acetate/hexanes,1:3; R_f 0.50) to give **1c** (517.0 mg, 2.63 mmol, 78% over two steps) as a white amorphous solid. Mp: 54.5–56.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77 (d, *J* = 6.5 Hz, 2H), 4.99–5.07 (m, 2H), 5.94–6.02 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.44 (dd, *J* = 2.5 Hz, 8.3 Hz, 1H), 8.02 (d, *J* = 2.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 37.8, 116.2, 129.5, 131.4, 132.1, 132.5, 133.0, 136.6, 141.2, 171.9; HRMS (ESI) calcd for $[M + H]^+$ ($C_{10}H_{10}ClO_2$) 197.0369, found 197.0393.

2-Allyl-5-cyanobenzoic acid (1i)

A solution of methyl 2-amino-5-cyanobenzoate[77] (2.6 g, 14.7 mmol) in water (24 mL) was added $HCl_{(aq)}$ (0.7 *M*, 21 mL, 14.7 mmol), sodium nitrite (1.2 g, 17.7 mmol) in water (5.5 mL) slowly at 0 °C. The resulting solution was stirred for 30 min and added with a solution of potassium iodide (4.90 g, 29.5 mmol) in water (12.4 mL). The reaction mixture was heated at 30 °C (oil bath) for 16 h, quenched with a sat. $Na_2S_2O_{3(aq)}$ (65 mL) and extracted with ethyl acetate (70 mL × 3). The combined organic layers were dried over $NaSO_4$, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:10; R_f 0.50) to give methyl 5-cyano-2-iodobenzoate (2.4 g, 8.36 mmol, 57%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.94 (s, 3H), 7.35 (dd, *J* = 2.0 Hz, 8.3 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 53.0, 100.3, 112.4, 117.2, 133.9, 134.6, 136.1, 142.5, 165.0; HRMS (ESI) calcd for $[M + H]^+$ ($C_9H_7INO_2$) 287.9521, found 287.9506.

i-PrMgCl (1 *M* in THF, 10 mL, 10.0 mmol) was added dropwise to a solution of 5-cyano-2-iodobenzoate (0.50 g, 1.74 mmol) and THF (17 mL) at -40 °C. The reaction mixture was added with a solution of CuCN·2LiCl in THF (0.34 *M* in THF, 5.1 mL, 1.74 mmol), stirred for 30 min at -40 °C, added with a solution of allyl bromide (0.45 mL, 5.22 mmol) and stirred for another 1 h at -40 °C. The reaction mixture was warmed to room temperature overnight, quenched with sat. $NH_4Cl_{(aq)}$ (12 mL), and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq)}$ (12 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was re-dissolved in THF (8 mL), methanol (1 mL) and water (1 mL), added with lithium hydroxide monohydrate (0.37 g, 8.5 mmol) and stirred at rt for 16 h. The reaction mixture was concentrated, washed with diethyl ether (2 mL), acidified with $HCl_{(aq)}$ (2 *N*, 0.5 mL) and extracted with diethyl ether (5 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq)}$ (5 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was further purified by column chromatography (SiO_2, ethyl acetate/hexanes,1:3; R_f 0.35) to give **1i** (227.0 mg, 1.21 mmol, 70% over two steps) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.58 (d, *J* =6.5 Hz, 2H), 5.02–5.11 (m, 2H), 5.92–6.00 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.73 (dd, *J* = 1.5 Hz, 8.0 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 38.4, 110.6, 117.2, 117.7, 129.3, 132.1, 135.3, 135.4, 135.7, 148.0, 170.8; HRMS (ESI) calcd for $[M + H]^+$ ($C_{11}H_{10}NO_2$) 188.0711, found 188.0704.

3-Methylisocoumarin (2)

A reaction mixture of 2-allylbenzoic acid (**1**, 16.2 mg, 99.9 µmol), White cat (5.0 mg, 10 µmol) and p-benzoquinone (22.0 mg, 201 µmol) in DMSO (1 mL) was stirred at 100 °C (oil bath) for 24 h, added with water (1 mL) and extracted with diethyl ether (2 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.50) to give **2** (12.8 mg, 0.08 mmol, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 3H), 6.23 (s, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 7.5 Hz,1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 19.6, 103.5, 119.9, 124.8, 127.5, 129.4, 134.7, 137.6, 154.5, 162.9. The NMR spectroscopic data were consistent with the literature.[78]

(*Z*)-3-Ethylidenephthalide (3)

A solution of 2-allylbenzoic acid (**1**, 16.2 mg, 99.9 µmol), White cat (2.5 mg, 5 µmol) and DMSO (1 mL) was added with $NaOH_{(aq)}$ (1 *N*, 50 µL, 50 µmol). The reaction mixture was stirred at 100 °C (oil bath) for 12 h under an atmosphere of oxygen, added with water (1 mL) and extracted with diethyl ether (2 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.55) to give **3** (14 mg, 0.087 mmol, 87%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.97 (d, *J* = 7.5 Hz, 3H), 5.61 (q, *J* = 7.0 Hz, 1H), 7.44–7.47 (m, 1H), 7.57–7.64 (m, 2H), 7.82 (d, *J* = 7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 11.1, 104.1, 119.4, 124.3, 125.1, 129.2, 134.1, 139.4, 146.3, 167.0. The NMR spectroscopic data were consistent with the literature.[79]

3-Vinylphthalide (4)

A solution of 2-allylbenzoic acid (**1**, 16.2 mg, 99.9 µmol), White catalyst (5.0 mg, 10 µmol) and DMSO (1 mL) was added with $HCl_{(aq)}$ (1 *N*, 50 µL, 50 µmol). The reaction mixture was stirred at 100 °C (oil bath) for 24 h under an atmosphere of oxygen, added with water (1 mL) and extracted with diethyl ether (2 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.45) to give **4** (14 mg, 0.092 mmol, 92%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.37–5.41 (m, 1H), 5.56-5.61 (m, 1H), 5.80–5.87 (m, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 82.0, 119.9, 122.4, 125.7, 129.3, 130.2, 133.3, 134.1, 148.5, 170.2. The NMR spectroscopic data were consistent with the literature.[80]

(*Z*)-3-Ethylidene-5-fluoroisobenzofuran-1(3H)-one (3a)

The procedure to prepare **3** was followed. Starting with **1a** (19.6 mg, 0.10 mmol), $NaOH_{(aq)}$ (1 *N*, 50 µL, 50 µmol), and White cat (2.5 mg, 5 µmol) in DMSO (1 mL), compound **3a** (11.2 mg, 0.063 mmol, 63%) was produced after column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.50) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.99 (d, *J* = 7.5 Hz, 3H), 5.61 (q, *J* = 7.0

Hz, 1H), 7.14–7.21 (m, 1H), 7.22–7.25 (m, 1H), 7.84 (q, J = 4.5 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz) δ 11.3, 105.6, 106.3 (d, $^{2}J_{\text{C-F}}$ = 24.8 Hz), 117.7 (d, $^{2}J_{\text{C-F}}$ = 24.3 Hz), 120.6, 127.7 (d, $^{3}J_{\text{C-F}}$ = 10.3 Hz), 142.0 (d, $^{3}J_{\text{C-F}}$ = 11.3 Hz), 145.5, 166.7 (d, $^{1}J_{\text{C-F}}$ = 253.3 Hz), 165.9. The NMR spectroscopic data were consistent with the literature.[81]

5-Fluoro-3-vinylisobenzofuran-1(3H)-one (4a)

The procedure to prepare **4** was followed. Starting with **1a** (19.6 mg, 0.10 mmol), HCl$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (5.0 mg, 10 µmol) in DMSO (1 mL), compound **4a** (11.5 mg, 0.065 mmol, 65%) was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.45) as a colourless liquid. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.39 (d, J = 15.3 Hz, 1H), 5.62 (d, J = 20.0 Hz, 1H), 5.75–5.87 (m, 2H), 7.39 (s, 1H), 7.18 (dd, J = 7.5 Hz, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz) δ 81.3, 109.8 (d, $^{2}J_{\text{C-F}}$ = 24.2 Hz), 117.7 (d, $^{2}J_{\text{C-F}}$ = 23.9 Hz), 120.5, 121.7, 128.1 (d, $^{3}J_{\text{C-F}}$ = 10.1 Hz), 132.7, 151.3 (d, $^{3}J_{\text{C-F}}$ = 9.6 Hz), 166.6 (d, $^{1}J_{\text{C-F}}$ = 255.0 Hz), 169.0; HRMS (ESI) calcd for [M + H]$^+$ (C$_{10}$H$_8$FO$_2$) 179.0508, found 179.0502.

(*Z*)-5-Chloro-3-ethylideneisobenzofuran-1(3H)-one (3b)

The procedure to prepare **3** was followed. Starting with **1b** (19.7 mg, 0.10 mmol), NaOH$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (2.5 mg, 5 µmol) in DMSO (1 mL), compound **3b** (12.6 mg, 0.065 mmol, 65%) as a colourless liquid was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.50). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.99 (d, J = 7.3 Hz, 3H), 5.63 (q, J = 7.2 Hz, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.58 (s, 1H), 7.78 (d, J = 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz) δ 11.3, 105.7, 119.7, 122.8, 126.5, 129.9, 140.9, 141.0, 145.3, 166.0. The NMR spectroscopic data were consistent with the literature.[81]

5-Chloro-3-vinylisobenzofuran-1(3H)-one (4b)

The procedure to prepare **4** was followed. Starting with **1b** (19.7 mg, 0.10 mmol), HCl$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (5.0 mg, 10 µmol) in DMSO (1 mL), compound **4b** (16.7 mg, 0.086 mmol, 86%) was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.45) as a colourless liquid. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.41 (m, 1H), 5.57 (m, 1H), 5.75–5.86 (m, 2H), 7.39 (s, 1H), 7.48 (dd, J = 1.2 Hz, J = 8.1 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz) δ 81.4, 120.6, 122.9, 126.9, 128.0, 130.2, 132.7, 140.9, 150.1, 169.0; HRMS (ESI) calcd for [M + H]$^+$ (C$_{10}$H$_8$ClO$_2$) 195.0213, found 195.0202.

(Z)-6-Chloro-3-ethylideneisobenzofuran-1(3H)-one (3c)

The procedure to prepare **3** was followed. Starting with **1c** (19.7 mg, 0.10 mmol), NaOH$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (2.5 mg, 5 µmol) in DMSO (1 mL), compound **3c** (5 mg, 0.026 mmol, 26%) was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.50) as a colourless liquid. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.03 (d, J = 7.2 Hz, 3H), 5.63 (q, J = 7.5 Hz, 1H), 7.27 (m, 2H), 7.87 (d, J = 0.6 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz) δ 11.3, 105.2, 120.7, 125.1, 125.9, 134.6, 135.4, 137.7, 145.6, 165.6; HRMS (ESI) calcd for [M+H]$^+$ (C$_{10}$H$_8$ClO$_2$) 195.0213, found 195.0204.

6-Chloro-3-vinylisobenzofuran-1(3H)-one (4c)

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The procedure to prepare **4** was followed. Starting with **1c** (19.7 mg, 0.10 mmol), HCl$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (5.0 mg, 10 µmol) in DMSO (1 mL), compound **4c** (10.9 mg, 0.056 mmol, 56%) was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.45) as a colourless liquid. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.39 (m, 1H), 5.55 (m, 1H), 5.76–5.83 (m, 2H), 7.39 (s, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.61 (dd, J = 1.4 Hz, 8.0 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz) δ 29.6, 81.8,120.3, 123.7, 125.6, 132.8, 134.4, 135.8, 146.6, 168.6; HRMS (ESI) calcd for [M + H]$^+$ (C$_{10}$H$_8$ClO$_2$) 195.0213, found 195.0205.

(*Z*)-6-Bromo-3-ethylideneisobenzofuran-1(3H)-one (3d). The procedure to prepare **3** was followed. Starting with **1d** (24.0 mg, 0.10 mmol), NaOH$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (2.5 mg, 5 µmol) in DMSO (1 mL), and compound **3d** (15.5 mg, 0.065 mmol, 65%) was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.50) as a colourless liquid. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.98 (d, J = 7.2 Hz, 3H), 5.63 (q, J = 7.2 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.73 (dd, J = 1.8 Hz, J = 8.4 Hz, 1H), 7.99 (d, J = 1.5 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz) δ 11.3, 105.3, 120.8, 120.9, 123.1, 126.1, 128.1, 137.3, 137.4, 138.1, 145.7, 165.5. The NMR spectroscopic data were consistent with the literature.[82]

6-Bromo-3-vinylisobenzofuran-1(3H)-one (4d)

The procedure to prepare **4** was followed. Starting with **1d** (24.0 mg, 0.10 mmol), HCl$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (5.0 mg, 10 µmol) in DMSO (1 mL), compound **4d** (20.3 mg, 0.085 mmol, 85%) was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.45) as a colourless liquid. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.40 (d, J = 9.2 Hz, 1H), 5.60 (d, J = 16.5 Hz, 1H), 5.75–5.83 (m, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.76 (dd, J = 1.7 Hz, J = 8.1 Hz, 1H), 8.01 (d, J = 1.7 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz) δ 81.8, 120.4, 123.4, 124.0, 127.7, 128.7, 132.7, 137.2, 147.1, 168.5; HRMS (ESI) calcd for [M + H]$^+$ (C$_{10}$H$_8$BrO$_2$) 238.9707, found 238.9690. The NMR spectroscopic data were consistent with the literature.[46]

(*Z*)-3-Ethylidene-6-methoxyisobenzofuran-1(3H)-one (3e)

The procedure to prepare **3** was followed. Starting with **1e** (19.0 mg, 0.10 mmol), NaOH$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (2.5 mg, 5 µmol) in DMSO (1 mL), compound **3e** (13.5 mg, 0.071 mmol, 71%) as a colourless liquid was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.50). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.96 (d, J = 7.2 Hz, 3H), 3.85 (s, 3H), 5.46 (q, J = 7.2 Hz, 1H), 7.19–7.27 (m, 2H), 7.47 (d, J = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz) δ 11.1, 55.8, 102.4, 106.3, 120.7, 123.7, 125.8, 132.7, 146.1, 160.8, 167.2. The NMR spectroscopic data were consistent with the literature.[83]

6-Methoxy-3-vinylisobenzofuran-1(3H)-one (4e)

The procedure to prepare **4** was followed. Starting with **1e** (19.0 mg, 0.10 mmol), HCl$_{(aq)}$ (1 N, 50 µL, 50 µmol), and White cat (5.0 mg, 10 µmol) in DMSO (1 mL), compound **4e** (7.9 mg, 0.042 mmol, 42%) was produced after column chromatography (SiO$_2$, ethyl acetate/hexanes, 1:20; R$_f$ 0.45) as a colourless liquid. ^{1}H

NMR ($CDCl_3$, 500 MHz) δ 3.85 (s, 3H), 5.35 (d, *J* = 8.4 Hz, 1H), 5.38 (d, *J* = 8.4 Hz, 1H), 5.57–5.86 (m, 2H), 7.19–7.31 (m, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 11.1, 55.8, 102.4, 106.3, 120.7, 123.7, 125.8, 132.7, 146.1, 160.8, 167.2; HRMS (ESI) calcd for $[M + H]^+$ ($C_{11}H_{11}O_3$) 191.0708, found 191.0700.

(*Z*)-3-Ethylidene-5,6-dimethoxyisobenzofuran-1(3H)-one (3f)

The procedure to prepare **3** was followed. Starting with **1f** (19.0 mg, 0.10 mmol), $NaOH_{(aq)}$ (1 *N*, 50 μL, 50 μmol), White cat (2.5 mg, 5 μmol) in DMSO (1 mL), compound **3f** (18.9 mg, 0.086 mmol, 86%) was produced after column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.50) as a colourless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.96 (d, *J* = 7.3 Hz, 3H), 3.91(s, 3H), 3.96 (s, 3H), 5.47 (q, *J* = 7.0 Hz, 1H), 6.95 (s, 1H), 6.21 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 11.2, 56.3, 56.4, 100.5, 102.5, 105.2, 116.9, 134.2, 146.2, 151.1, 155.1, 167.3. The NMR spectroscopic data were consistent with the literature.[84]

5,6-Dimethoxy-3-vinylisobenzofuran-1(3H)-one (4f)

The general procedure for the lactonization was followed. Starting with **1f** (19 mg, 0.10 mmol), $HCl_{(aq)}$ (1 *N*, 50 μL, 50 μmol), and White cat (5.0 mg, 10 μmol) in DMSO (1 mL), compound **4f** (13.8 mg, 0.063 mmol, 63%) as a colourless liquid was purified by column chromatography (C18-reversed phase silica gel, H_2O/MeOH, 1:3; R_f 0.42). ^1H NMR ($CDCl_3$, 500 MHz) 3.92 (s, 3H), 3.94 (s, 3H), 5.38 (d, *J* = 7.5 Hz, 1H), 5.56 (d, *J* = 17.0 Hz, 1H), 5.68 (d, *J* = 7.8 Hz, 1H), 5.75 (m, 1H), 6.76 (s, 1H), 7.27 (s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 56.3, 56.4, 81.5, 103.7, 106.1, 117.6, 119.8, 133.8, 143.1, 150.7, 155.0, 170.4. HRMS (ESI) calcd for $[M + H]^+$ ($C_{12}H_{13}O_4$) 221.0814, found 221.0801.

(*Z*)-3-Ethylidene-6-methylisobenzofuran-1(3H)-one (3g)

The procedure to prepare **3** was followed. Starting with **1g** (17.6 mg, 0.10 mmol), $NaOH_{(aq)}$ (1 *N*, 50 μL, 50 μmol), and White cat (2.5 mg, 5 μmol) in DMSO (1 mL), compound **3g** (13.0 mg, 0.075 mmol, 75%) as a colourless liquid was produced after column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.50). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.96 (d, *J* = 7.5 Hz, 3H), 2.44 (s, 3H), 5.53 (q, *J* = 7.2 Hz, 1H), 7.43–7.50 (m, 2H), 7.64 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 11.2, 21.4, 103.1, 119.2, 124.2, 125.0, 135.5, 137.2, 139.8, 146.4, 167.3. The NMR spectroscopic data were consistent with the literature.[81]

6-Methyl-3-vinylisobenzofuran-1(3H)-one (4g)

The procedure to prepare **4** was followed. Starting with **1g** (17.6 mg, 0.10 mmol), $HCl_{(aq)}$ (1 *N*, 50 μL, 50 μmol), and White cat (5.0 mg, 10 μmol) in DMSO (1 mL), compound **4g** (4.3 mg, 0.025 mmol, 25%) was produced after column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.45) as a colourless liquid. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 5.35 (d, *J* = 9.9 Hz, 1H), 5.53 (d, *J* = 16.4 Hz, 1H), 5.74-5.87 (m, 2H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H). 7.67 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 21.2, 81.9, 119.6, 122.1, 125.6, 133.6, 135.3, 139.7, 142.1, 145.9, 170.4; HRMS (ESI) calcd for $[M + H]^+$ ($C_{11}H_{11}O_2$) 175.0759, found 175.0752**.**

(*Z*)-3-Ethylidene-7-methylisobenzofuran-1(3H)-one (3h)

The procedure to prepare **3** was followed. Starting with **1h** (17.6 mg, 0.10 mmol), $NaOH_{(aq)}$ (1 *N*, 50 μL, 50 μmol), and White cat (2.5 mg, 5 μmol) in DMSO (1 mL), compound **3h** (12.0 mg, 0.069 mmol, 69%) as a colourless liquid was produced after column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.50). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.97 (d, *J* = 7.5 Hz, 3H), 2.65 (s, 3H), 5.57 (q, *J* = 7.0 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 11.1, 17.4, 103.2, 116.8, 122.1, 130.8, 133.9, 139.2, 139.9, 146.1, 167.3. The NMR spectroscopic data were consistent with the literature.[81]

7-Methyl-3-vinylisobenzofuran-1(3H)-one (4h)

The procedure to prepare **4** was followed. Starting with **1h** (17.6 mg, 0.10 mmol), $HCl_{(aq)}$ (1 *N*, 50 μL, 50 μmol), and White cat (5.0 mg, 10 μmol) in DMSO (1 mL), compound racemic **4h** (3.4 mg, 0.02 mmol, 20%) was produced after column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.45) as a colourless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.67 (s, 3H), 5.35 (d, *J* = 10.0 Hz, 1H), 5.55 (d, *J* = 15.9 Hz, 1H), 5.72 (d, *J* = 7.3 Hz, 1H), 5.78–5.85 (m, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H). 7.49 (t, *J* = 7.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 17.2, 81.0, 119.4, 119.7, 123.1, 130.9, 133.7, 133.8, 139.8, 149.0, 170.4; HRMS (ESI) calcd for $[M + H]^+$ ($C_{11}H_{11}O_2$) 175.0759, found 175.0752.

(*E*)-5-Cyano-2-(1-propen-yl)benzoic acid (5i)

A solution of **1i** (19.0 mg, 100.0 μmol), White cat (2.5 mg, 5 μmol) and DMSO (1 mL) was added with $NaOH_{(aq)}$ (1 *N*, 50 μL, 50 μmol). The reaction mixture was stirred at 100 °C (oil bath) for 12 h under an atmosphere of oxygen, added with water (1 mL) and extracted with diethyl ether (2 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:3; R_f 0.50) to give **5i** (14.9 mg, 0.093 mmol, 93%) as a colourless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.95 (dd, *J* = 2.0 Hz, *J* = 7.0 Hz, 3H), 6.29 (tq, *J* = 7.0 Hz, *J* = 13.5 Hz, 1H), 7.26 (d, *J* = 14.5 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.70 (dd, *J* = 1.5 Hz, *J* = 8.5 Hz, 1H), 8.27 (d, *J* = 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 19.0, 110.3, 117.8, 127.3, 128.1, 128.4, 133.3, 135.3, 135.4, 144.7, 170.9; HRMS (ESI) calcd for $[M + H]^+$ ($C_{11}H_{10}NO_2$) 188.0711, found 188.0708.

(*Z*)-3-Ethylidene-6-hydroxyisobenzofuran-1(3H)-one (3j)

The procedure to prepare **3** was followed. Starting with **1j** (50.0 mg, 0.28 mmol), $NaOH_{(aq)}$ (1 *N*, 140 μL, 140 μmol) and White cat (7.1 mg, 14.0 μmol) in DMSO (2.8 mL), compound **3j** (39.4 mg, 0.22 mmol, 80%) was prepared after column chromatography (SiO_2, ethyl acetate/hexanes, 1:3; R_f 0.60) as a colourless liquid. ^1H NMR ($CDCl_3$/ $(CD_3)_2CO$, 6:1 (v/v), 300 MHz) δ 1.87 (d, *J* = 7.3 Hz, 3H), 5.38 (q, *J* = 7.3 Hz, 1H), 7.12-7.19 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$/$(CD_3)_2CO$, 6:1 (v/v), 75 MHz) δ 10.4, 100.7, 109.2, 120.5, 122.8, 125.3, 131.1, 145.9, 158.1, 166.6. HRMS (ESI) calcd for $[M + H]^+$ ($C_{10}H_9O_3$) 177.0552, found 177.0554.

6-Hydroxy-3-vinylisobenzofuran-1(3*H*)-one (4j)

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The general procedure to prepare **4** was followed. Starting with **1j** (50 mg, 0.28 mmol), $HCl_{(aq)}$ (1 *N*, 140 μL, 140 μmol), and White catalyst (14.1 mg, 28 μmol) in DMSO (2.8 mL), compound racemic **4j** (24.5 mg, 0.14 mmol, 50%) was produced after column chromatography (SiO_2, ethyl acetate/hexanes, 1:2; R_f 0.43) as a colourless liquid. ^1H NMR ($CDCl_3$ +$(CD_3)_2CO$, 6:1 (v/v), 300 MHz) δ 5.34-5.40 (m, 1H), 5.51-5.591 (m, 1H), 5.73-5.85 (m, 2H), 7.19-7.26 (m, 2H), 7.51 (d, *J* = 1.5 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$ +$(CD_3)_2CO$, 6:1 (v/v), 75 MHz) δ 82.5, 110.9, 119.9, 123.1, 123.5, 126.8, 133.4, 140.5, 157.6, 171.2. HRMS (ESI) calcd for $[M + H]^+$ ($C_{10}H_8O_3$) 177.0552, found 177.0553.

3-Ethyl-6-hydroxyphthalide (6)

A suspension of **3j** (17.6 mg, 0.10 mmol) and palladium on activated charcoal (10%, 5.3 mg) in methanol (2 mL) was stirred under an atmosphere of hydrogen (500 psi) at 30 °C for 5 h and then concentrated. The crude product was purified by column chromatography (ethyl acetate/hexanes, 1:2; R_f 0.45) to give **6** (16.3 mg, 0.092 mmol, 92%). ^1H NMR ($CDCl_3$/ $(CD_3)_2CO$, 6:1 (v/v), 500 MHz) δ 0.91 (t, *J* = 7.3 Hz, 1H), 1.68-1.76 (m, 1H), 1.98-2.03 (m, 1H), 5.30-5.33 (m, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.26 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$/$(CD_3)_2CO$, 6:1 (v/v), 125 MHz) δ 8.7, 27.7, 82.8, 110.9, 122.7, 122.8, 127.4, 141.7, 157.5, 171.5. The NMR spectroscopic data were consistent with the literature.[7]

The reaction scheme to prepare **1-D₂** is shown in Supporting Information (SI Scheme 1).

2-(Methyl-d₃)benzoic acid (7)

n-BuLi (2.5 M in hexanes, 73.4 mL, 183.6 mmol) was added dropwise to a solution of 2-methylbenzoic acid (5.0 g, 36.72 mmol), THF (250 mL), and hexamethylphosphoramide (HMPA; 26 mL, 147 mmol) at -60 °C. The reaction mixture was stirred at -60 °C for 1 h, added with D_2O (6.6 mL, 367.2 mmol), diluted with $HCl_{(aq)}$ (5 N, 30 mL) and extracted with diethyl ether (50 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq)}$ (60 mL), dried over Na_2SO_4, filtered, and concentrated. The deprotonation and deuteriation was repeated five times, and the crude product was further purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:3; R_f 0.43) to give **7** (1.51 g, 10.86 mmol, 30% with 94% deuteriated methyl group). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25 (t, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 125.8, 128.3, 131.5, 131.9, 132.9, 141.2, 173.1; HRMS (EI+) calcd for $[M]^+$ ($C_8H_5D_3O_2$) 139.0712, found 139.0713.

Methyl 2-(methyl-d₃)benzoate (8)

Dimethyl sulfate (3.1 mL, 32.6 mmol) was added to a solution of 2-(methyl-d₃)benzoic acid (**7**, 1.51 g, 10.86 mmol), potassium carbonate (4.5 g, 32.6 mmol) and acetone (54 mL). The reaction mixture was stirred at rt for 8 h, filtered over a pad of celite and concentrated. The crude product was further purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.50) to give **8** (1.36 g, 8.90 mmol, 82%) as a colourless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ 3.86 (m, 3H), 7.20–7.23 (m, 2H), 7.35–7.38 (dt, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.88 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 51.7, 125.6, 129.5, 130.4, 131.6, 131.8, 140.0, 168.0; HRMS (ESI) calcd for $[M + H]^+$ ($C_9H_8D_3O_2$) 154.0947, found 154.0919.

Methyl 2-(bromomethyl-d₂)benzoate (9)

N-Bromosuccinimide (384 mg, 2.14 mmol) was added to a solution of **8** (300 mg, 1.94 mmol), benzoyl peroxide (480 mg, 0.08 mmol) and benzene (4 mL). The reaction mixture was heated in an oil bath to reflux for 48 h, added with sat. $NaHCO_{3(aq)}$ (4 mL) and extracted with diethyl ether (8 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq)}$ (25 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.55) to give **9** (190 mg, 0.82 mmol, 42%; 98.7% CD_2Br) as a colourless liquid. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.91 (m, 3H), 4.91 (m, 0.027H), 7.32–7.37 (m, 1H), 7.41–7.51 (m, 2H), 7.93 (dd, *J* = 8.0 Hz, *J* = 0.9 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 52.2, 128.4, 129.0, 131.2, 131.6, 132.4, 139.0, 166.9. HRMS (ESI) calcd for $[M + H]^+$ ($C_9H_8BrD_2O_2$) 230.9989, found 230.9953.

2-(Allyl-1,1-d₂)benzoic acid (1-D₂)

Vinylmagnesium bromide (1 *M* in THF, 1.1 mL, 1.1 mmol) was added dropwise to a solution of **9** (120 mg, 0.51 mmol), CuI (19.4 mg, 0.1 mmol), 2,2'-bipyridyl (15.6 mg, 0.1 mmol) and THF (3.0 mL) at -60 °C. The reaction mixture was stirred at -60 °C for 1 h, another 12 h at rt, quenched with sat. $NH_4Cl_{(aq)}$ (2 mL) and extracted with diethyl ether (3 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq)}$ (10 mL), dried over Na_2SO_4, filtered, and concentrated. Lithium hydroxide (107.0 mg, 2.55 mmol) in THF/ MeOH/H_2O (4: 1: 1, 5 mL) was added to the residue, and the solution was stirred at rt for 16 h, acidified with $HCl_{(aq)}$ (1 *N*, 1.5 mL) and extracted with diethyl ether (3 mL × 3). The combined organic layers were washed with sat. $NaCl_{(aq)}$ (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:3; R_f 0.50) to give **1-D₂** (39.4 mg, 0.24 mmol, 47% two steps; 98% CD_2) as a colorless solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.01-5.04 (m, 2H), 5.99 (q, *J* = 10.8 Hz, 1H), 7.28 (m, 2H), 7.46 (dt, *J* = 7.9 Hz, *J* =1.4 Hz, 1H), 8.03 (dd, *J* = 7.9 Hz, *J* =1.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 115.7, 126.3, 128.2, 131.1, 131.6, 133.0, 137.2, 142.7, 172.7; HRMS (ESI) calcd for $[M + H]^+$ ($C_{10}H_9D_2O_2$) 165.0884, found 165.0887.

3-Methyl-1H-isochromen-1-one-4-d (2-D) and 3-vinylisobenzofuran-1(3H)-one-3-d (4-D)

A solution of **1-D₂** (16.4 mg, 010 mmol), White cat (5.0 mg, 10 μmol) and DMSO (1 mL) was added with $HCl_{(aq)}$ (1 *N*, 50 μL, 50 μmol). The reaction mixture was stirred at 100 °C (oil bath) for 12 h under an atmosphere of oxygen, added with water (1 mL) and extracted with diethyl ether (2 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography to give a mixture of **2-D** and **4-D** (9:1, 12.0 mg, 0.074 mmol, 74%) as a colourless liquid. HRMS (ESI) calcd for $[M + H]^+$ ($C_{10}H_8DO_2$) 162.0665, found 162.0659.

(*E*)-3-(Ethylidene-2-d)isobenzofuran-1(3H)-one (3-D)

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A solution of **1-D$_2$** (16.4 mg, 010 mmol), White cat (2.5 mg, 5 μmol) and DMSO (1 mL) was added with sodium azide (10.0 mg, 0.15 mmol). The reaction mixture was stirred at 100 °C (oil bath) for 12 h under an atmosphere of oxygen, added with water (1 mL) and extracted with diethyl ether (2 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 1:20; R_f 0.55) to give **3-D** (10.0 mg , 0.062 mmol, 62%; 10% CH_2D) as a colourless liquid. HRMS (ESI) calcd for $[M + H]^+$ ($C_{10}H_8DO_2$) 162.0665, found 162.0649.

Conclusions

We have developed a practical allylic oxidation of 2-allylbenzoic acids to yield phthalides. Using White catalyst and environmentally benign oxygen,[85] the Wacker oxidation to form isocoumarins is suppressed, and the selective formation of 3-ethylidenephthalidesor 3-vinylphthalidesis achieved by adjusting the acidity of the reaction media. A natural product is prepared after hydrogenation of the generated 3-ethylidenephthalide. The mechanistic study using 2-(1-propenyl)benzoic acid and deuterated 2-allylbenzoic acid reveals that the oxidative cleavage of allylic C-H bond to form phthalides is competing with Wacker-type oxidation and is sensitive to the reagents and the pH values of the reaction media.

Conflicts of interest

There are no conflicts to declare.

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