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# 纯水及空气中芳香羧酸和丙烯酸酯氧化偶联构筑苯酞的绿色方法

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**摘要** 苯酞是一类重要的杂环化合物, 广泛存在于药物和天然产物中, 其合成备受关注. 本研究发展了一种水促进、铑催化芳香酸和丙烯酸酯通过[3+2]串联环化反应构筑苯酞的绿色方法, 反应在空气和纯水介质中进行, 无需任何添加剂. 与文献相比, 该方法具有反应条件方便、操作简单、无添加剂等特点. 机理研究表明, 催化循环中, 除了外部氧化剂氧化 Rh(I)外, 还包含丙烯酸酯作为氢受体的氢转移过程使活性 Rh(III)再生, 这一机理与文献报道的金属催化苯酞的合成机理不同. 利用该方法, 可一步合成具有生物活性的(4-羟基-3-氧亚基-1,3-二氢异苯并呋喃-1-基)乙酸.
**关键词** 水相反应; 串联环化; 氧化偶联; 苯酞

# Green Method for Constructing Phthalides via Oxidative Coupling of Aromatic Acids and Acrylates in Neat Water and Air

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**Abstract** Phthalides represent an important class of bioactive heterocycle extensively found in pharmaceuticals and natural products, their syntheses have attracted extensively attention. A water-promoted and rhodium-catalyzed [3+2] tandem cyclization of aromatic acids and acrylates has been developed in air and neat water free of any additives, which provides an environmentally benign approach for constructing phthalide motifs. Compared with previous literatures, this methodology features quite simple reaction conditions, simple operation and additive-free. Mechanistic studies indicate that apart from the many other well-known oxidations of Rh(I) by external oxidant, hydrogen transfer with the acrylate being a hydrogen acceptor is involved to regenerate the active Rh species, which is different from documented metal-catalyzed phthalides syntheses. The application of this protocol is further demonstrated by the green synthesis of biologically active isoochracinic acid in one step.
**Keywords** on water reaction; tandem cyclization; oxidative coupling; phthalides

## 1 Introduction

Catalytic tandem cyclization via C—H bond functionalizations has provided a powerful and an atom-economical strategy for the direct access to complex heterocycles in one step.[1] In this regard, remarkable progress has been achieved in methodologies for the construction of significant heterocycle motifs.[2] However, most of these reactions took place in organic solvents with additives. As for oxidative tandem cyclization, the stoichiometric amounts of metal oxidants such as Cu(II) and Ag(I) salts have been frequently employed.[3] As a consequence, a great deal of chemical waste is generated. From the view of green chemistry and sustainable development, the exploration of oxidative tandem cyclization utilizing green solvent and oxidant free of any additive is highly desirable.

Phthalides represent an important class of bioactive heterocycle extensively found in pharmaceuticals and natural products, especially 3-substituted phthalide.[4] As demonstrated in Figure 1, herbaric acid and isoochracinic acid known as fungal metabolites present antibacterial activity.[5] 7-Methoxyphthalide-3-acetic acid was isolated from *Alternaria sp.* (Figure 1).[6] Therefore, great efforts have been devoted to the development of efficient methods to this significant heterocyclic compounds.[7] Over the past two decades, several catalytic systems based on C—H activation have been developed for the formation of phthalides by employing aromatic acids and acrylates as starting materials (Scheme 1).[8] However, many procedures generally suffer from utilizing the stoichiometric amounts of

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metal oxidants, additives and/or organic solvents. Although metal oxidants replaced by oxygen or electricity to complete the reactions were reported by Ackermann, Su and Baidya,[9] the reactions were performed in organic solvents with additives. In addition, it is noteworthy that all reported mechanisms realized closed cycle by external oxidants without exception, in which the oxidation of $M^{n-2}$ (M=metal) to $M^n$ is well known in catalytic cycle.

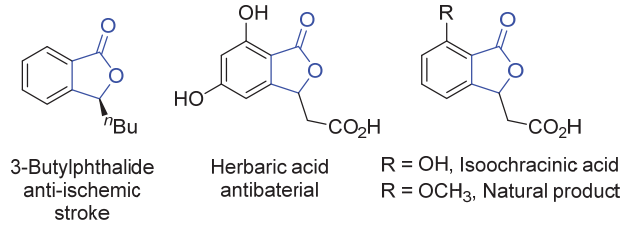
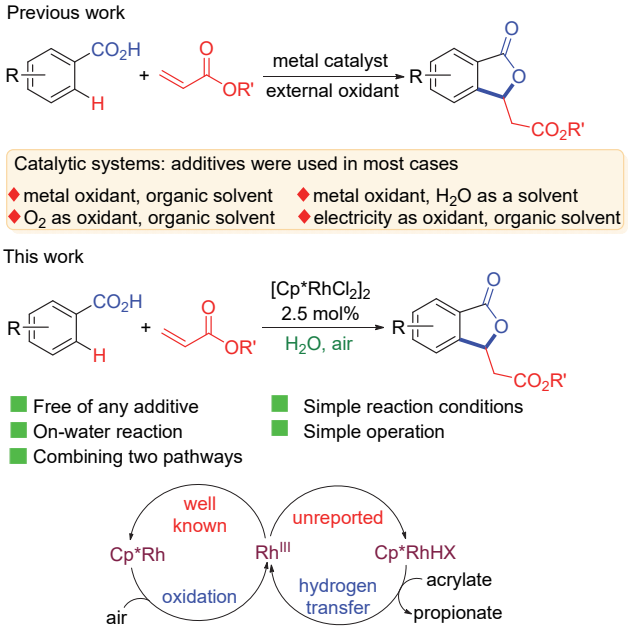



**Figure 1** Representative examples with phthalide scaffold



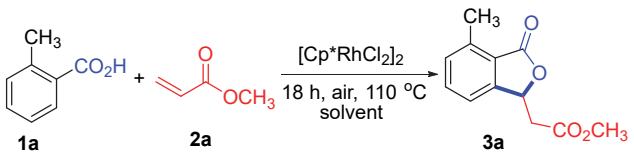

**Scheme 1** Catalytic reactions between aromatic acids and acrylates

Our keen interests in C—H functionalization in water and tandem cyclization reactions prompt us to explore greener approach to synthesize phthalides.[10] Herein, a rhodium(III)-catalyzed additive-free oxidative coupling of aromatic acids and acrylates for the environmental benign synthesis of phthalides in air and neat water is described. The notable features of this on-water protocol include free of any additive, quite simple reaction conditions and operation. During the mechanism investigation, there are two plausible pathways in the catalytic cycle. Apart from the well-known oxidation of Cp*Rh by external oxidant,[8] hydrogen transfer with the acrylate being a hydrogen acceptor is involved to regenerate the active Rh species, which is different from documented metal-catalyzed phthalide syntheses, and provides a new insight, *i.e.* probable coexistence of two pathways, into the mechanism of the transition-metal-catalyzed oxidative coupling of C—H bond with alkenes. It is noteworthy that to the best of our knowledge, acrylate as a hydrogen acceptor in rhodium-catalyzed oxidative cyclization reaction has not been reported so far. Moreover, there are only few reports on oxidative tandem cyclization occurring in neat water and air without any metal oxidants and additives.

## 2 Results and discussion

Our investigations were started by employing 2-methylbenzoic acid (**1a**) and methyl acrylate (**2a**) as model substrates (Table 1). To our delight, 84% yield of tandem cyclization product **3a** was observed in the presence of catalyst $[Cp^*RhCl_2]_2$ in neat water and air free of any additives (Table 1, Entry 1). The control experiment displayed that the reaction did not take place without water (Table 1, Entry 2). The evaluation of organic solvents demonstrates that the option of solvents is crucial to this additive-free transformation. Only four solvents such as $CH_3OH$, hexafluoroisopropanol (HFIP), acetone and *N*,*N*-dimethylformamide (DMF) afforded low yield of desired product (Table 1, Entries 3～6). Other commonly used solvents including EtOH, 1,2-dichloroethane (DCE), EtOAc, dimethoxyethane (DME), trifluoroethanol (TFE), $CH_3CN$, tetrahydrofuran (THF), 1,4-dioxane, $PhCH_3$ and PhCl failed to deliver the targeted product (Table 1, Entries 7～16). Then, several parameters affecting reactions such as the amounts

**Table 1** Selected results for optimizing reaction conditions[a]




| Entry | Solvent | Yield[b]/% |
|---|---|---|
| 1 | $H_2O$ | 84 |
| 2 | — | ND[c] |
| 3 | $CH_3OH$ | 6 |
| 4 | HFIP | 13 |
| 5 | Acetone | 12 |
| 6 | DMF | 17 |
| 7 | EtOH | ND |
| 8 | DCE | ND |
| 9 | EtOAc | ND |
| 10 | DME | ND |
| 11 | TFE | ND |
| 12 | $CH_3CN$ | ND |
| 13 | THF | ND |
| 14 | Dioxane | ND |
| 15 | $PhCH_3$ | ND |
| 16 | PhCl | ND |

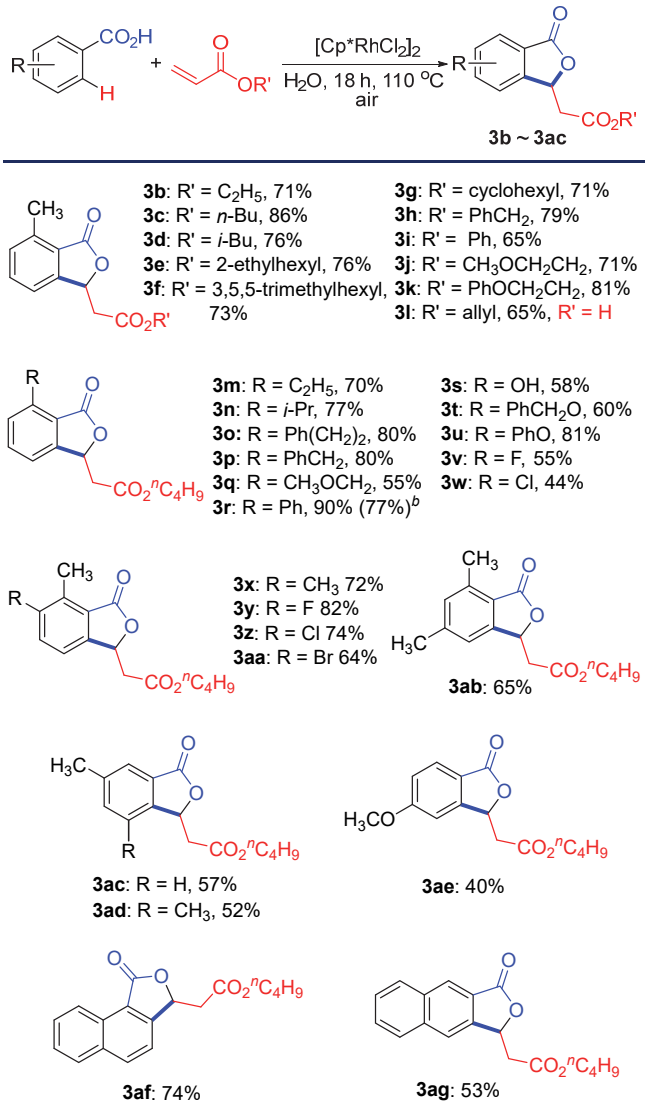
[a] **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), deionized water (0.5 mL), 110 ℃, 18 h, under air. [b] Determined by $^1H$ NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c] ND=not detected.

of catalyst, reaction temperature and reaction time, the yield of **3a** did not further be enhanced. Thus, the optimal reaction conditions were identified as follows: 2.5 mol% $[RhCp^*Cl_2]_2$ in neat water at 110 ℃ under air for 18 h.

After determining the efficient reaction conditions for the formation of phthalide **3a**, the substrate scope of acrylates was studied with 2-methylbenzoic acid firstly to demonstrate the applicability of this approach (Table 2). Acrylates formed from primary alcohols with or without branched chain all underwent the cyclization reactions successfully giving rise to good to excellent yields of products (**3b**～**3f**, 71%～86%). Cyclohexyl acrylate was also tolerated and gave the corresponding phthalide in good yield (**3g**, 71%). Acrylates bearing aryl ring and oxygen could be transformed smoothly into the cyclization products in satisfactory yields (**3h**～**3k**, 65%～81%). Interestingly, the reaction of 2-methylbenzoic acid with allyl acrylate provided the hydrolysis product instead of expected product (**3l**, 65%). Unfortunately, replacing acrylate by other active alkenes such as acrylic acid, vinylsulfonylbenzene, *N*,*N*-dimethylacrylamide, acrylonitrile and diethyl vinylphosphonate, resulted in rather low yields of phthalides. No cyclization product was observed using acrylaldehyde or styrene.

**Table 2** Substrate scope for tandem cyclization reaction[a]




[a] Reaction conditions: aromatic acids (0.1 mmol), acrylates (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), deionized water (0.5 mL), 110 ℃, 18 h, under air, isolated yield; [b] 1 mmol of biphenyl-2-carboxylic acid.

To further investigate the generality of this methodology, the substrate scope of different aromatic acids reacting with butyl acrylate was assessed. The results indicate that both electronic factor and the position of substituents have significant influence on the reactivity. Unsubstituted benzoic acid only generated 38% NMR yield of product. In generally, *ortho*-substituents favor the reaction process. *Ortho*-monosubstituted aromatic acids with electron-donating alkyl and aryl substituents such as $C_2H_5$, *iso*-Pr, $Ph(CH_2)_2$, $PhCH_2$ and $CH_3OCH_2$, Ph, all reacted efficiently with butyl acrylate to deliver the desired phathalides in good to excellent yields (**3m**～**3r**, 55%～90%). Gratifyingly, aromatic acids with unmasked OH, $PhCH_2O$ and PhO at the *ortho* position participated in this cyclization process well to produce the corresponding products in moderate to good isolated yields (**3s**～**3u**, 58%～81%). Fluoro and chloro groups were also discovered to be compatible with this transformation delivering moderate yields (**3v**～**3w**, 44%～55%). 2,3- and 2,4-disubstuted aromatic acids all worked well and furnished good yields of **3x**～**3ab** (64%～82%). However, strong electronic-withdraw groups such as $CF_3$, $NO_2$ and CN retarded the reaction. The reason may lie in that electron-withdrawing groups make the aryl ring highly electron deficient and retard the attacking of the electrophilic rhodium. 38% NMR yield of product was detected using 2-(trifluoromethyl)benzoic acid.

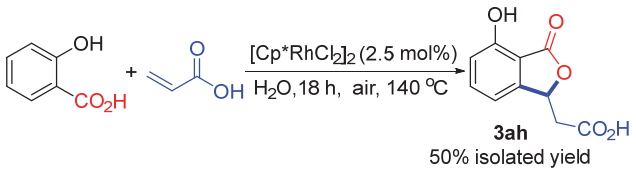
It is delighted to find that *meta*- and *para*-substituted benzoic acids were also favorably converted to phthalides. For 3-methylbenzoic acid, C—H activation took place selectively at the less sterically hindered position (**3ac**, 57%). Moderate yield was obtained with 3,5-dimethylbenzoic acid (**3ad**, 52%). 4-Methoxybenzoic acid was found to be less reactive than *ortho*-substituted benzoic acids, offering 40% yield of **3ae**. As for fused-ring type substrate, 1-naphthoic acid and 2-naphthoic acid afforded 74% and 53% isolated yields, respectively (**3ag** and **3af**). Piperic acid gave 15% NMR yield. Regrettably, this transformation could not be extended to heteroaromatic acid. No desired products were detected utilizing 1-methyl-1*H*-indole-2-carboxylic acid and thiophene-2-carboxylic acid, respectively.

Moreover, contrary to our expectations, biphenyl-2-carboxylic acid, 2-phenoxybenzoic acid and 2-benzylbenzoic acid with poor water solubility displayed higher reactivity than salicylic acid (**3p**, **3r**, **3u** *vs* **3s**). The reaction is also pretty inefficient in organic solvent listed in Table 1. These results indicate that this additive-free oxidative tandem reaction probably proceeds on water, and the trans-phase interactions of water with transition states

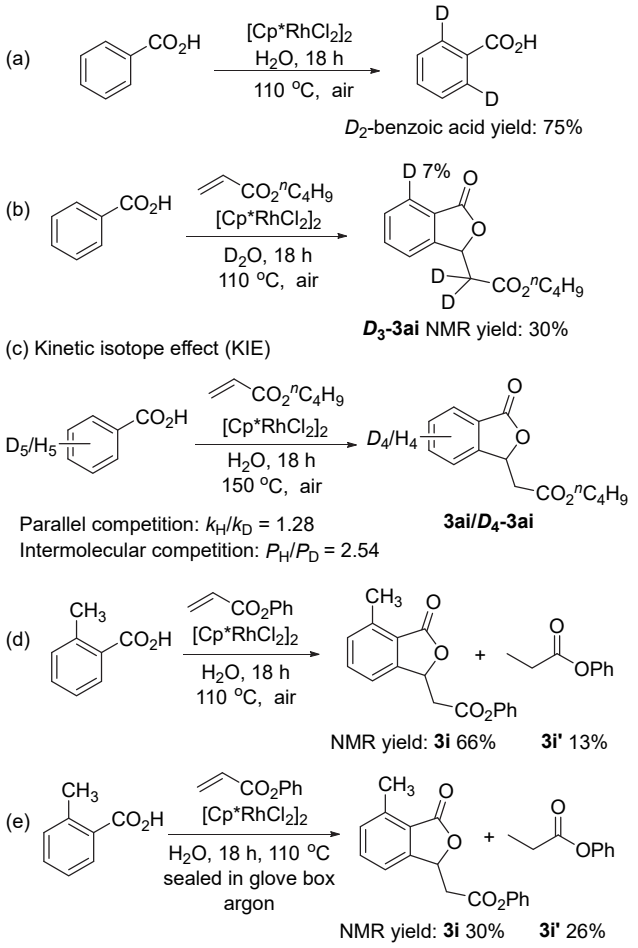
and reactants probably play an important role in increasing the reaction rates.[11] There is no this effect under solvent-free or organic solvent conditions. Thus, no desired product or rather low yield was observed. In addition, this reaction can be successfully scaled up to 1 mmol. The scale-up reaction of biphenyl-2-carboxylic acid with butyl acrylate furnished targeted product **3r** in 77% isolated yield.

The convenience and simplicity of this approach to afford phthalides can be handily utilized in the preparation of bioactive compound isoochracinic acid. It is pleased to find that the isoochracinic acid can be effectively formed from commercially available salicylic acid and acrylic acid (Scheme 2). It is worth to note that isoochracinic acid was previously prepared by multistep syntheses, in which harsh conditions such as high pressure and hazardous lithium reagent were necessary.[13]



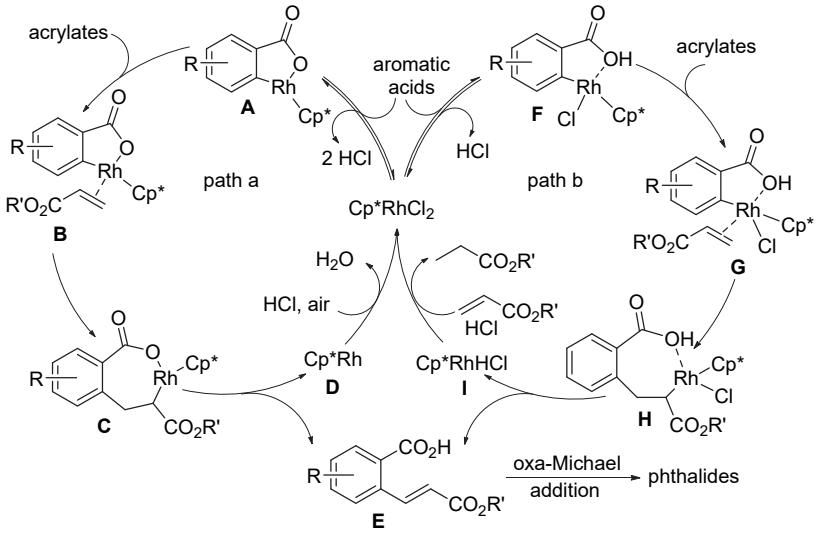

**Scheme 2** Synthesis of isoochracinic acid

To gain detailed insights into the mechanism, several experiments were performed (Scheme 3). Treating benzoic acid under optimized reaction conditions in $D_2O$ generated 75% deuterated compound in the *ortho* position of carboxyl (Scheme 3a), indicating the C—H activation step in this reaction is reversible. When benzoic acid reacted with butyl acrylate in $D_2O$ under standard conditions, only 7% deuterium was observed in the cyclization product (Scheme 3b), which implied that the step after C—H activation was much faster than the protonation of cyclometalation intermediate.[13] No isotope effect (KIE value = 1.28) was determined from the parallel experiment (Scheme 3c). However, a small isotope effect of 2.54 was observed in the intermolecular competition experiment (Scheme 3c), which indicate that the rate-limiting step may occur before the C—H bond cleavage, and an intramolecular electrophilic metalation may be involved in the formation of intermediates **A** and **F** (Scheme 4).[14]




**Scheme 3** Mechanistic studies

To our surprise, 13% yield of phenyl propionate was




**Scheme 4** Plausible reaction mechanism

detected when 2-methylbenzoic acid reacted with phenyl acrylate (Scheme 3d). This result demonstrates that acrylate not only participated in the reaction as a substrate, but also as a hydrogen acceptor. 30% yield of **3i** can be obtained under inert atmosphere of argon. It proved that the reaction can be realized without external oxidant, and acrylate can be acted as hydrogen acceptor (Scheme 3e).

According to the above experimental results and the previous mechanism of rhodium-catalyzed carboxyl-directed oxidation tandem cyclization,[15] this reaction probably involves two possible pathways as depicted in Scheme 4. In pathway a, the catalytic reaction initiates with Rh(III)-catalyzed carboxyl deprotonation and reversible *ortho* C—H activation, generating a five-membered rhodacycle intermediate **A**, which goes through coordination with acrylates followed by migratory insertion leading to intermediate **C**. *β*-Hydride elimination of **C** releases *ortho*-alkenylated product **E** and Cp*Rh(I). Cp*Rh(I) is oxidized by air to give rise to Rh(III) species. Alkenylation product is subjected to an intramolecular Michael addition to give the final product. To our knowledge, the path **a** is documented mechanism without exception in transition-metal-catalyzed oxidative cyclization reactions of aromatic acids with active alkenes.

In pathway b, with the assistance of carboxyl, the intermediate **F** is formed via Rh(III)-catalyzed *ortho* C—H activation. The intermediate **G** also undergoes the sequential steps of coordination with acrylates, migratory insertion and *β*-hydride elimination to produce *ortho*-alkenylated product **E** and rhodium hydride Cp*Rh(I)HCl. Cp*Rh(I)HCl is reoxidized by acrylate via the addition of Cp*Rh(I)HCl to double bonds and subsequent protonolysis by HCl.[16] Taking the yields of different propionates into consideration, the pathway **a** may be the dominant way to form the final products. It is noteworthy that rhodium-catalyzed directed C(alkenyl)—H alkenylation by hydrogen transfer is rarely reported, and It is not reported that the acrylate serves as a hydrogen acceptor so far in oxidative cyclization reactions.

## 3 Conclusions

In conclusion, an environmentally benign method for preparing 3-substituted phthalides from commercially available aromatic acids and acrylates catalyzed by rhodium(III) has been demonstrated. The reaction proceeds readily in air and neat water without the use of any additives, and affords a broad range of 3-substituted phthalides in moderate to excellent yields. Notably, the green synthesis of active compound isoochracinic acid further manifests the synthetic potential of this protocol. Two plausible catalytic cycles are discovered to complete the transformation. This investigation provides a new insight into the mechanism of the transition-metal-catalyzed oxidative coupling of C—H bond with alkenes. It is believed that both simple operation and simple reaction conditions make this method be practical for application.

## 4 Experimental section

### 4.1 General information

All reagents were utilized directly without further purification. All work-up and purification procedures were performed with analytical reagent solvents. $^1$H NMR and $^{13}$C NMR spectra were recorded on a 400 MHz or 600 MHz spectrometer with tetramethylsilane (TMS) as internal standard at room temperature. High-resolution mass spectra (HRMS) were measured by a Bruker Compass-Maxis instrument (ESI). Melting points were detected using a WRX-4 without correction.

### 4.2 General procedure for the synthesis of phthalides

A 5 mL microwave vial was charged with aromatic acids (0.1 mmol), acrylates (0.2 mmol), $[Cp^*RhCl_2]_2$ (1.6 mg, 0.0025 mmol), deionic water (0.5 mL), and sealed under air. Then, the mixture was stirred at 110 ℃ (oil bath temperature) for 18 h. The resulting mixture was cooled to room temperature, diluted with EtOAc and filtered. The solution was concentrated under vacuum, and the residue was purified by a preparative thin-layer chromatography (TLC) to give the corresponding product.

Methyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3a**): White solid, 16.5 mg, yield 75%. m.p. 85.8～86.6 ℃; $^1$H NMR (600 MHz, $CDCl_3$) *δ*: 7.53 (t, *J*=7.6 Hz, 1H), 7.29 (t, *J*=8.0 Hz, 2H), 5.82 (t, *J*=6.6 Hz, 1H), 3.76 (s, 3H), 2.87 (d, *J*=6.8 Hz, 2H), 2.69 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ*: 169.9, 169.8, 149.1, 139.9, 133.9, 131.1, 123.3, 119.2, 75.9, 52.1, 39.5, 17.3; HRMS (ESI-TOF) calcd for $C_{12}H_{12}NaO_4$ $[M+Na]^+$ 243.0628, found 243.0630.

Ethyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3b**): White solid, 16.7 mg, yield 71%. m.p. 48.2～49.3 ℃; $^1$H NMR (400 MHz, $CDCl_3$) *δ*: 7.53 (t, *J*=7.6 Hz, 1H), 7.28 (t, *J*=11.8, 4.3 Hz, 2H), 5.82 (t, *J*=6.5 Hz, 1H), 4.21 (q, *J*=7.1 Hz, 2H), 2.87 (d, *J*=6.8 Hz, 2H), 2.69 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) *δ*: 170.1, 169.4, 149.2, 139.9, 133.9, 131.1, 123.3, 119.2, 76.0, 61.2, 39.7, 17.3, 14.1; HRMS (ESI-TOF) calcd for $C_{13}H_{14}NaO_4$ $[M+Na]^+$ 257.0784, found 257.0786.

Butyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3c**): Yellow liquid, 22.7 mg, yield 86%. $^1$H NMR (600 MHz, $CDCl_3$) *δ*: 7.45 (t, *J*=7.6 Hz, 1H), 7.21 (t, *J*=7.8 Hz, 2H), 5.74 (t, *J*=6.5 Hz, 1H), 4.08 (t, *J*=6.7 Hz, 2H), 2.80 (d, *J*=6.6 Hz, 2H), 2.61 (s, 3H), 1.57～1.52 (m, 2H), 1.28 (dt, *J*=14.7, 7.4 Hz, 2H), 0.85 (t, *J*=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) *δ*: 170.0, 169.4, 149.2, 139.8, 133.9, 131.0, 123.3, 119.2, 76.0, 65.0, 39.7, 30.4, 19.0, 17.3, 13.6; HRMS (ESI-TOF) calcd for $C_{15}H_{18}NaO_4$ $[M+Na]^+$ 285.1097, found 285.1099.

Isobutyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3d**): Yellow solid, 19.8 mg, yield 76%. m.p. 85.4～86.5 ℃; $^1$H NMR (400 MHz, $CDCl_3$) *δ*: 7.53 (t, *J*=7.6 Hz, 1H), 7.30～7.28 (m, 2H), 5.82 (t, *J*=6.5 Hz, 1H),

4.00～3.90 (m, 2H), 2.96～2.82 (m, 2H), 2.69 (s, 3H), 2.00～1.87 (m, 1H), 0.93 (dd, $J$=6.7, 2.5 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 170.1, 169.4, 149.2, 139.9, 133.9, 131.1, 123.4, 119.2, 76.1, 71.3, 39.7, 27.6, 19.0, 17.3; HRMS (ESI-TOF) calcd for $C_{15}H_{18}NaO_4$ $[M+Na]^+$ 285.1097, found 285.1099.

2-Ethylhexyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3e**): White solid, 24.1 mg, yield 76%. m.p. 55.4～56.1 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.45 (ddd, $J$=11.1, 7.5, 3.3 Hz, 1H), 7.26～7.15 (m, 2H), 5.74 (t, $J$=5.9 Hz, 1H), 4.06～3.94 (m, 2H), 2.81 (dd, $J$=4.0, 2.1 Hz, 2H), 2.61 (d, $J$=4.3 Hz, 3H), 1.50 (d, $J$=5.3 Hz, 1H), 1.27～1.18 (m, 8H), 0.81 (dd, $J$=8.8, 3.8 Hz, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 170.0, 169.6, 149.3, 139.9, 133.9, 131.1, 123.4, 119.2, 76.0, 67.6, 39.8, 38.6, 30.3, 28.9, 23.6, 22.9, 17.3, 14.0, 10.9; HRMS (ESI-TOF) calcd for $C_{19}H_{26}NaO_4$ $[M+Na]^+$ 341.1723, found 341.1725.

3,5,5-Trimethylhexyl2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3f**): Yellow liquid, 24.2 mg, yield 73%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.52 (t, $J$=7.6 Hz, 1H), 7.28 (t, 2H), 5.81 (t, $J$=6.5 Hz, 1H), 4.17 (t, $J$=6.7 Hz, 2H), 2.86 (d, $J$=6.0 Hz, 2H), 2.68 (s, 3H), 1.67～1.55 (m, 2H), 1.52～1.43 (m, 1H), 1.23～1.17 (m, 1H), 1.11～1.04 (m, 1H), 0.94 (d, $J$=5.6 Hz, 3H), 0.87 (d, $J$=1.7 Hz, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 170.0, 169.5, 149.3, 139.9, 133.9, 131.1, 123.4, 119.2, 76.0, 63.9, 50.9, 39.8, 37.6, 31.1, 29.9, 26.1, 22.6, 17.3; HRMS (ESI- TOF) calcd for $C_{20}H_{28}NaO_4$ $[M+Na]^+$ 355.1880, found 355.1876.

Cyclohexyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3g**): White solid, 22.5 mg, yield 71%. m.p. 69.7～70.1 ℃; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.45 (t, $J$=7.4 Hz, 1H), 7.21 (d, $J$=7.3 Hz, 2H), 5.73 (t, $J$=6.1 Hz, 1H), 4.76 (s, 1H), 2.80 (d, $J$=4.7 Hz, 2H), 2.62 (s, 3H), 1.76 (d, $J$=12.9 Hz, 2H), 1.64 (s, 2H), 1.46 (s, 1H), 1.31 (s, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 170.1, 168.7, 149.3, 139.8, 133.9, 131.0, 123.4, 119.2, 76.1, 73.8, 40.0, 31.48, 34.47, 25.2, 23.7, 17.3; HRMS (ESI-TOF) calcd for $C_{17}H_{20}NaO_4$ $[M+Na]^+$ 311.1254, found 311.1253.

Benzyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3h**): White solid, 23.5 mg, yield 79%. m.p. 60.6～61.2 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.40 (t, $J$=7.6 Hz, 1H), 7.31～7.22 (m, 5H), 7.18 (d, $J$=7.6 Hz, 1H), 7.12 (d, $J$=7.6 Hz, 1H), 5.72 (t, $J$=6.5 Hz, 1H), 5.10 (q, $J$=12.2 Hz, 2H), 2.83 (d, $J$=6.9 Hz, 2H), 2.58 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.9, 169.1, 149.1, 139.8, 135.2, 133.9, 131.0, 128.5, 128.4, 128.3, 123.3, 119.2, 75.9, 66.9, 39.7, 17.2; HRMS (ESI-TOF) calcd for $C_{18}H_{16}NaO_4$ $[M+Na]^+$ 319.0941, found 319.0937.

Phenyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3i**): White solid, 18.4 mg, yield 65%. m.p. 112.1～112.3 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.48 (t, $J$=7.5 Hz, 1H), 7.31 (t, $J$=7.6 Hz, 2H), 7.26 (d, $J$=7.5 Hz, 1H), 7.24 (d, $J$=7.4 Hz, 1H), 7.17 (t, $J$=7.2 Hz 1H), 7.02 (d, $J$=7.8 Hz, 2H), 5.83 (t, $J$=6.3 Hz, 1H), 3.10～3.01 (m, 2H), 2.62 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.9, 167.9, 150.2, 148.9, 140.0, 134.0, 131.3, 129.5, 126.1, 123.4, 121.3, 119.3, 75.8, 39.8, 17.3; HRMS (ESI-TOF) calcd for $C_{17}H_{14}NaO_4$ $[M+Na]^+$ 305.0784, found 305.0782.

2-Methoxyethyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3j**): Colorless liquid, 18.7 mg, yield 71%. m.p. 72.5～73.6 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.52 (t, $J$=7.6 Hz, 1H), 7.31～7.27 (m, 2H), 5.82 (t, $J$=6.6 Hz, 1H), 4.32 (t, $J$=4.6 Hz, 2H), 3.61 (t, $J$=4.6 Hz, 2H), 3.39 (s, 3H), 2.96～2.88 (m, 2H), 2.69 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 170.0, 169.3, 149.2, 139.9, 133.9, 131.1, 123.4, 119.3, 75.9, 70.2, 64.1, 58.9, 39.6, 17.3; HRMS (ESI-TOF) calcd for $C_{14}H_{16}NaO_5$ $[M+Na]^+$ 287.0890, found 287.0891.

2-Phenoxyethyl 2-(4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3k**): Yellow liquid, 26.5 mg, yield 81%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.49 (t, $J$=7.6 Hz, 1H), 7.32～7.26 (m, 4H), 6.97 (t, $J$=7.3 Hz, 1H), 6.90 (d, $J$=8.0 Hz, 2H), 5.82 (t, $J$=6.5 Hz, 1H), 4.52 (dd, $J$=5.3, 3.3 Hz, 2H), 4.18 (dd, $J$=5.0, 4.3 Hz, 2H), 2.92 (d, $J$=6.6 Hz, 2H), 2.67 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.9, 169.2, 158.3, 149.1, 139.9, 133.9, 131.1, 129.5, 123.3, 121.2, 119.2, 114.6, 75.8, 65.5, 63.5, 39.6, 17.3; HRMS (ESI-TOF) calcd for $C_{19}H_{18}NaO_5$ $[M+Na]^+$ 349.1046, found 349.1044.

2-(4-Methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetic acid (**3l**): White solid, 13.3 mg, yield 65%. m.p. 125.3～125.9 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.56 (t, $J$=7.5 Hz, 1H), 7.31 (d, $J$=7.5 Hz, 2H), 5.82 (t, $J$=6.5 Hz, 1H), 2.94 (qd, $J$=16.8, 6.6 Hz, 2H), 2.70 (s, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 175.0, 170.1, 148.9, 140.1, 134.1, 131.3, 123.3, 119.2, 75.7, 39.6, 17.3; HRMS (ESI-TOF) calcd for $C_{11}H_{10}NaO_4$ $[M+Na]^+$ 229.0471, found 229.0468.

Butyl 2-(4-ethyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3m**): Colorless liquid, 19.3 mg, yield 70%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.56 (t, $J$=7.6 Hz, 1H), 7.32 (d, $J$=7.5 Hz, 1H), 7.27 (d, $J$=7.8 Hz, 1H), 5.80 (t, $J$=6.5 Hz, 1H), 4.15 (t, $J$=6.7 Hz, 2H), 3.12 (ddd, $J$=14.7, 7.2, 3.6 Hz, 2H), 2.86 (d, $J$=6.6 Hz, 2H), 1.66～1.56 (m, 2H), 1.36 (dt, $J$=14.9, 7.4 Hz, 2H), 1.27 (t, $J$=7.5 Hz, 3H), 0.92 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 169.8, 169.5, 149.4, 146.3, 134.2, 129.4, 122.7, 119.3, 76.0, 65.1, 39.8, 30.5, 24.1, 19.0, 15.0, 13.7; HRMS (ESI-TOF) calcd for $C_{16}H_{20}NaO_4$ $[M+Na]^+$ 299.1254, found 299.1253.

Butyl 2-(4-isopropyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3n**): Colorless liquid, 22.3 mg, yield 77%. $R_f$=0.44 [$V$(hexane) ∶ $V$(EtOAc) ∶ $V$(HOAc)=5 ∶ 1 ∶ 0.05); $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.59 (t, $J$=7.6 Hz, 1H), 7.44 (d, $J$=7.7 Hz, 1H), 7.27 (d, $J$=7.2 Hz, 1H), 5.80 (t, $J$=6.6 Hz, 1H), 4.18～4.09 (m, 3H), 2.87 (d, $J$=7.2 Hz, 2H), 1.65～1.58 (m, 2H), 1.37 (p, $J$=7.4 Hz, 2H), 1.29 (t, $J$=7.0 Hz, 6H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.7, 169.5, 151.2, 149.4, 134.3, 126.1, 122.0, 119.1, 75.8, 65.1, 39.8, 30.5, 27.2, 23.2, 22.9, 19.0, 13.6; HRMS (ESI-TOF) calcd for $C_{17}H_{22}NaO_4$ $[M+Na]^+$ 313.1410, found 313.1406.

Butyl 2-(3-*oxo*-4-phenethyl-1,3-dihydroisobenzofuran-1-yl) acetate (**3o**): Colorless liquid, 28.0 mg, yield 80%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.52 (t, $J$=7.6 Hz, 1H), 7.31～7.22 (m, 6H), 7.19 (t, $J$=7.1 Hz, 1H), 5.83 (t, $J$=6.6 Hz, 1H), 4.17 (t, $J$=6.7 Hz, 2H), 3.38 (qdd, $J$=13.2, 9.2, 7.0 Hz, 2H), 2.99～2.92 (m, 2H), 2.91～2.84 (m, 2H), 1.65～1.60 (m, 2H), 1.41～1.34 (m, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 169.7, 169.4, 149.6, 143.6, 141.2, 134.0, 130.4, 128.6, 128.3, 126.0, 122.9, 119.6, 76.1, 65.1, 39.7, 37.2, 33.3, 30.5, 19.0, 13.7; HRMS (ESI-TOF) calcd for $C_{22}H_{24}NaO_4$ $[M+Na]^+$ 375.1567, found 375.1563.

Butyl 2-(4-benzyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3p**): Colorless solid, 27.1 mg, yield 80%. m.p. 74.8～77.5 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.53 (t, $J$=7.6 Hz, 1H), 7.31～7.25 (m, 6H), 7.20 (dt, $J$=8.5, 4.4 Hz, 1H), 5.82 (t, $J$=6.5 Hz, 1H), 4.50 (q, $J$=15.1 Hz, 2H), 4.16 (t, $J$=6.7 Hz, 2H), 2.93～2.84 (m, 2H), 1.64～1.59 (m, 2H), 1.37 (dq, $J$=14.8, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.8, 169.4, 149.5, 143.0, 139.6, 134.2, 130.6, 129.2, 128.5, 126.3, 122.8, 119.7, 76.0, 65.1, 39.7, 36.0, 30.5, 19.0, 13.6; HRMS (ESI-TOF) calcd for $C_{21}H_{22}NaO_4$ $[M+Na]^+$ 361.1410, found 361.1404.

Butyl 2-(4-(methoxymethyl)-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3q**): Colorless liquid, 13.8 mg, yield 55%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.69～7.62 (m, 2H), 7.37 (d, $J$=6.4 Hz, 1H), 5.86 (t, $J$=6.5 Hz, 1H), 4.98 (s, 2H), 4.16 (t, $J$=6.7 Hz, 2H), 3.51 (s, 3H), 2.93～2.84 (m, 2H), 1.64～1.59 (m, 2H), 1.37 (dq, $J$=14.8, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 169.6, 169.4, 149.1, 140.1, 134.4, 127.5, 122.2, 120.6, 69.2, 65.2, 58.9, 39.6, 30.5, 19.0, 13.7; HRMS (ESI-TOF) calcd for $C_{16}H_{20}NaO_5$ $[M+Na]^+$ 315.1203, found 315.1199.

Butyl 2-(3-*oxo*-4-phenyl-1,3-dihydroisobenzofuran-1-yl) acetate (**3r**): Colorless liquid, 29.2 mg, yield 90%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.70 (t, $J$=7.6 Hz, 1H), 7.53 (d, $J$=7.2 Hz, 2H), 7.49～7.40 (m, 5H), 5.87 (t, $J$=6.5 Hz, 1H), 4.18 (t, $J$=6.7 Hz, 2H), 2.98～2.89 (m, 2H), 1.65～1.60 (m, 2H), 1.38 (dq, $J$=14.8, 7.4 Hz, 2H), 0.94 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.4, 168.6, 150.1, 142.9, 136.2, 134.0, 131.3, 129.5, 128.4, 128.0, 121.9, 120.7, 75.5, 65.1, 39.8, 30.5, 19.0, 13.6; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NaO_4$ $[M+Na]^+$ 347.1254, found 347.1250.

Butyl 2-(4-hydroxy-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3s**): Yellow liquid, 15.2 mg, yield 58%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.75 (s, 1H), 7.56 (t, $J$=7.9 Hz, 1H), 6.96 (d, $J$=7.9 Hz, 2H), 5.89 (t, $J$=6.6 Hz, 1H), 4.16 (t, $J$=6.7 Hz, 2H), 2.98～2.84 (m, 2H), 1.67～1.58 (m, 2H), 1.37 (dq, $J$=14.7, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 171.5, 169.1, 156.6, 149.0, 137.2, 115.9, 113.4, 111.0, 78.3, 65.2, 39.4, 30.5, 19.0, 13.6; HRMS (ESI-TOF) calcd for $C_{14}H_{16}NaO_5$ $[M+Na]^+$ 287.0890, found 287.0888.

Butyl 2-(4-(benzyloxy)-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3t**): Colorless liquid, 21.2 mg, yield 60%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.53 (t, $J$=7.9 Hz, 1H), 7.49 (d, $J$=7.4 Hz, 2H), 7.38 (t, $J$=7.6 Hz, 2H), 7.30 (t, $J$=7.4 Hz, 1H), 6.99 (d, $J$=7.5 Hz, 1H), 6.94 (d, $J$=8.3 Hz, 1H), 5.79 (t, $J$=6.6 Hz, 1H), 5.32 (s, 2H), 4.16 (t, $J$=6.7 Hz, 2H), 2.86 (qd, $J$=16.4, 6.6 Hz, 2H), 1.64～1.59 (m, 2H), 1.37 (dq, $J$=14.8, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.4, 167.5, 157.7, 151.6, 136.2, 136.0, 128.7, 128.0, 126.7, 114.0, 113.8, 113.0, 75.8, 70.5, 65.1, 39.7, 30.5, 19.0, 13.6; HRMS (ESI-TOF) calcd for $C_{21}H_{22}NaO_5$ $[M+Na]^+$ 377.1359, found 377.1356.

Butyl 2-(3-*oxo*-4-phenoxy-1,3-dihydroisobenzofuran-1-yl) acetate (**3u**): Colorless liquid, 27.6 mg, yield 81%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.50 (t, $J$=7.9 Hz, 1H), 7.41 (t, $J$=7.8 Hz, 2H), 7.23 (t, $J$=7.3 Hz, 1H), 7.11 (dd, $J$=14.3, 7.8 Hz, 3H), 6.75 (d, $J$=8.3 Hz, 1H), 5.86 (t, $J$=6.5 Hz, 1H), 4.17 (t, $J$=6.7 Hz, 2H), 2.99～2.85 (m, 2H), 1.68～1.59 (m, 2H), 1.38 (dq, $J$=14.8, 7.4 Hz, 2H), 0.94 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.3, 167.2, 157.2, 154.9, 151.5, 136.1, 130.0, 125.1, 120.7, 116.3, 115.4, 114.8, 76.0, 65.2, 39.7, 30.5, 19.1, 13.6; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NaO_5$ $[M+Na]^+$ 363.1203, found 363.1201.

Butyl 2-(4-fluoro-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3v**): Colorless liquid, 14.7 mg, yield 55%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.67 (td, $J$=7.9, 4.6 Hz, 1H), 7.28 (d, $J$=7.6 Hz, 1H), 7.18 (t, $J$=8.5 Hz, 1H), 5.87 (t, $J$=6.5 Hz, 1H), 4.16 (t, $J$=6.7 Hz, 2H), 2.92 (ddd, $J$=43.6, 16.6, 6.5 Hz, 2H), 1.62 (dt, $J$=14.6, 6.8 Hz, 2H), 1.36 (dq, $J$=14.8, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.0, 165.9, 159.6 (d, $J_{C\text{-}F}$=264.9 Hz), 151.4, 136.8 (d, $J_{C\text{-}F}$=7.5 Hz), 118.0 (d, $J_{C\text{-}F}$=4.3 Hz), 116.6 (d, $J_{C\text{-}F}$=18.7 Hz), 113.8 (d, $J_{C\text{-}F}$=14.6 Hz), 76.6, 65.3, 39.3, 30.5, 19.0, 13.6; HRMS (ESI-TOF) calcd for $C_{14}H_{15}FNaO_4$ $[M+Na]^+$ 289.0847, found 289.0844.

Butyl 2-(4-chloro-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3w**): Colorless liquid, 12.5 mg, yield 44%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.60 (t, $J$=7.8 Hz, 1H), 7.50 (d, $J$=7.9 Hz, 1H), 7.40 (d, $J$=7.6 Hz, 1H), 5.82 (t, $J$=6.5 Hz, 1H), 4.15 (t, $J$=6.7 Hz, 2H), 2.91 (ddd, $J$=41.9, 16.6, 6.5 Hz, 2H), 1.63～1.58 (m, 2H), 1.36 (dq, $J$=14.8, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.1, 166.7, 151.1, 135.2, 133.5, 130.9, 122.7, 120.5, 75.6, 65.3, 39.4, 30.5, 19.0, 13.6; HRMS (ESI-TOF) calcd for $C_{14}H_{15}ClNaO_4$ $[M+Na]^+$ 305.0551, found 305.0544.

Butyl 2-(4,5-dimethyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3x**): White solid, 19.9 mg, yield 72%. m.p. 61.2～65.1 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.41 (d, $J$=7.7 Hz, 1H), 7.16 (d, $J$=7.7 Hz, 1H), 5.75 (t, $J$=6.5 Hz, 1H), 4.15 (t, $J$=6.7 Hz, 2H), 2.90～2.79 (m, 2H), 2.63 (s, 3H), 2.35 (s, 3H), 1.65～1.57 (m, 2H), 1.36 (dq, $J$=14.8, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 170.4, 169.5, 147.0, 138.7, 138.4, 135.5, 123.3, 118.6, 75.3, 65.1, 39.9, 30.5, 19.2, 19.0, 13.6, 13.2;

HRMS (ESI-TOF) calcd for $C_{16}H_{20}NaO_4$ $[M+Na]^+$ 299.1254, found 299.1250.

Butyl 2-(5-fluoro-4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3y**): White solid, 22.9 mg, yield 82%. m.p. 94.3～95.1 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.31 (t, $J$=8.8 Hz, 1H), 7.26～7.24 (m, 1H), 5.78 (t, $J$=6.5 Hz, 1H), 4.16 (t, $J$=6.7 Hz, 2H), 2.88 (ddd, $J$=22.6, 16.5, 6.5 Hz, 2H), 2.60 (s, 3H), 1.71～1.53 (m, 2H), 1.44～1.30 (m, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.3, 169.1, 161.5 (d, $J_{C\text{-}F}$=246.9 Hz), 144.5, 126.4 (d, $J_{C\text{-}F}$=19.9 Hz), 125.4 (d, $J_{C\text{-}F}$=6.7 Hz), 121.2 (d, $J_{C\text{-}F}$=25.1 Hz), 120.2 (d, $J_{C\text{-}F}$=8.8 Hz), 75.6, 65.2, 39.6, 30.5, 19.0, 13.6, 9.0 (d, $J_{C\text{-}F}$=3.8 Hz); HRMS (ESI-TOF) calcd for $C_{15}H_{17}FNaO_4$ $[M+Na]^+$303.1003, found 303.0999.

Butyl 2-(5-chloro-4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3z**): White solid, 21.8 mg, yield 74%. m.p. 121.1～122.1 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.63 (d, $J$=8.1 Hz, 1H), 7.26 (d, $J$=6.6 Hz, 1H), 5.77 (t, $J$=6.4 Hz, 1H), 4.15 (t, $J$=6.7 Hz, 2H), 2.88 (ddd, $J$=38.8, 16.5, 6.5 Hz, 2H), 2.74 (s, 3H), 1.66～1.58 (m, 2H), 1.36 (dq, $J$=14.8, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.2, 169.0, 147.6, 138.0, 136.2, 134.6, 125.0, 120.1, 75.3, 65.2, 39.5, 30.5, 19.0, 13.8, 13.6; HRMS (ESI-TOF) calcd for $C_{15}H_{17}Cl$- $NaO_4$ $[M+Na]^+$ 319.0708, found 319.0700.

Butyl 2-(5-bromo-4-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3aa**): White solid, 21.8 mg, yield 64%. m.p. 125.3～125.9 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.80 (d, $J$=8.1 Hz, 1H), 7.18 (d, $J$=8.1 Hz, 1H), 5.74 (t, $J$=6.5 Hz, 1H), 4.15 (t, $J$=6.7 Hz, 2H), 2.87 (ddd, $J$=38.9, 16.6, 6.5 Hz, 2H), 2.76 (s, 3H), 1.65～1.57 (m, 2H), 1.40～1.32 (m, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.2, 168.9, 148.4, 140.0, 137.9, 126.9, 125.0, 120.5, 75.3, 65.2, 39.4, 30.5, 19.0, 16.7, 13.7; HRMS (ESI-TOF) $[M+Na+2]^+$ calcd for $C_{15}H_{17}{}^{79}BrNaO_4$ $[M+Na]^+$ 363.0202, found 363.0198; HRMS (ESI-TOF) calcd for $C_{15}H_{17}{}^{81}BrNaO_4$ $[M+Na]^+$ 365.0202, found 365.0177.

Butyl 2-(4,6-dimethyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3ab**): Yellow liquid, 17.9 mg, yield 65%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.07 (d, $J$=17.3 Hz, 2H), 5.75 (t, $J$=6.5 Hz, 1H), 4.15 (t, $J$=6.6 Hz, 2H), 2.84 (d, $J$=6.5 Hz, 2H), 2.63 (s, 3H), 2.42 (s, 3H), 1.68～1.57 (m, 2H), 1.36 (dq, $J$=14.7, 7.4 Hz, 2H), 0.92 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 170.1, 169.5, 149.9, 145.1, 139.5, 132.2, 120.9, 119.7, 75.8, 65.1, 39.8, 30.5, 21.9, 19.0, 17.2, 13.6; HRMS (ESI-TOF) calcd for $C_{16}H_{20}NaO_4$ $[M+Na]^+$ 299.1254, found 299.1251.

Butyl 2-(5-methyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3ac**): Colorless liquid, 15.0 mg, yield 57%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.69 (s, 1H), 7.48 (d, $J$=7.7 Hz, 1H), 7.37 (d, $J$=7.8 Hz, 1H), 5.84 (t, $J$=6.6 Hz, 1H), 4.15 (t, $J$=6.7 Hz, 2H), 2.87 (qd, $J$=16.4, 6.6 Hz, 2H), 2.46 (s, 3H), 1.67～1.56 (m, 2H), 1.36 (dq, $J$=14.7, 7.4 Hz, 2H), 0.93 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 170.1, 169.4, 146.2, 139.9, 135.4, 126.1, 125.8, 121.7, 65.1, 39.6, 30.5, 29.7, 21.3, 19.0, 13.7; HRMS (ESI-TOF) calcd for $C_{15}H_{18}NaO_4$ $[M+Na]^+$285.1097, found 285.1094.

Butyl 2-(5,7-dimethyl-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3ad**): Colorless liquid, 14.4 mg, yield 52%. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 7.52 (s, 1H), 7.26 (s, 1H), 5.83 (d, $J$=6.9 Hz, 1H), 4.09 (t, $J$=6.6 Hz, 2H), 3.13 (dd, $J$=16.3, 2.4 Hz, 1H), 2.61 (dd, $J$=16.3, 8.7 Hz, 1H), 2.38 (d, $J$=21.9 Hz, 6H), 1.60～1.52 (m, 2H), 1.32 (dq, $J$=14.6, 7.3 Hz, 2H), 0.90 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$: 170.3, 169.2, 144.0, 140.0, 136.7, 131.8, 126.3, 123.4, 76.9, 65.1, 38.4, 30.4, 21.1, 19.0, 17.9, 13.6; HRMS (ESI-TOF) calcd for $C_{16}H_{20}NaO_4$ $[M+Na]^+$ 299.1254, found 299.1253.

Butyl 2-(6-methoxy-3-*oxo*-1,3-dihydroisobenzofuran-1-yl) acetate (**3ae**): Colorless liquid, 10.9 mg, yield 39%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 7.80 (d, $J$=8.4 Hz, 1H), 7.04 (d, $J$=8.0 Hz, 1H), 6.93 (s, 1H), 5.79 (t, $J$=6.5 Hz, 1H), 4.16 (t, $J$=6.6 Hz, 2H), 3.89 (s, 3H), 2.88 (ddd, $J$=22.7, 16.5, 6.6 Hz, 2H), 1.65～1.59 (m, 2H), 1.37 (dq, $J$=14.6, 7.2 Hz, 2H), 0.93 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.6, 169.4, 164.8, 151.6, 127.3, 118.2, 116.7, 106.2, 76.3, 65.1, 55.8, 39.6, 30.5, 19.0, 13.6; HRMS (ESI-TOF) calcd for $C_{15}H_{18}NaO_5$ $[M+Na]^+$301.1046, found 301.1043.

Butyl 2-(1-*oxo*-1,3-dihydronaphtho[1,2-*c*]furan-3-yl) acetate (**3af**): White solid, 22.1 mg, yield 74%. m.p. 81.0～81.6 ℃; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 9.00 (d, $J$=8.2 Hz, 1H), 8.14 (d, $J$=8.3 Hz, 1H), 7.97 (d, $J$=8.1 Hz, 1H), 7.73 (t, $J$=7.5 Hz, 1H), 7.64 (t, $J$=7.4 Hz, 1H), 7.52 (d, $J$=8.3 Hz, 1H), 5.95 (t, $J$=6.4 Hz, 1H), 4.17 (t, $J$=6.6 Hz, 2H), 2.96 (d, $J$=5.8 Hz, 2H), 1.66～1.56 (m, 2H), 1.35 (dq, $J$=14.4, 7.0 Hz, 2H), 0.91 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 170.1, 169.4, 150.4, 135.7, 133.5, 129.2, 128.4, 127.5, 123.5, 120.2, 118.4, 76.3, 65.2, 39.4, 30.5, 19.0, 13.6; HRMS (ESI) calcd for $C_{18}H_{18}NaO_4$ $[M+Na]^+$ 321.1097, found 321.1095.

Butyl 2-(3-*oxo*-1,3-dihydronaphtho[2,3-*c*]furan-1-yl) acetate (**3ag**): Colorless liquid, 15.7 mg, yield 53%. $^1$H NMR (600 MHz, $CDCl_3$) $\delta$: 8.49 (s, 1H), 8.05 (d, $J$=8.2 Hz, 1H), 7.97～7.90 (m, 2H), 7.67 (t, $J$=7.4 Hz, 1H), 7.61 (t, $J$=7.4 Hz, 1H), 6.04 (t, $J$=6.5 Hz, 1H), 4.18 (t, $J$=6.7 Hz, 2H), 3.01 (ddd, $J$=39.4, 16.6, 6.5 Hz, 2H), 1.63～1.60 (m, 2H), 1.36 (dt, $J$=15.1, 7.4 Hz, 2H), 0.92 (t, $J$=7.4 Hz, 3H); $^{13}$C NMR (150 MHz, $CDCl_3$) $\delta$: 169.8, 169.4, 142.4, 136.2, 133.3, 129.9, 129.1, 128.3, 127.2, 123.6, 121.1, 77.0, 65.2, 40.1, 30.5, 19.0, 13.6; HRMS (ESI) calcd for $C_{18}H_{18}NaO_4$ $[M+Na]^+$ 321.1097, found 321.1094.

2-(4-Hydroxy-3-*oxo*-1,3-dihydroisobenzofuran-1-yl)-acetic acid (**3ah**): White solid, 10.4 mg, yield 50%. m.p. 150.3～151.3 ℃; $^1$H NMR (600 MHz, Acetone) $\delta$: 7.61 (t, $J$=7.7 Hz, 1H), 7.15 (d, $J$=7.4 Hz, 1H), 6.95 (d, $J$=8.1 Hz, 1H), 5.98～5.78 (m, 1H), 3.11 (dd, $J$=16.8, 4.4 Hz, 1H), 2.86 (dd, $J$=16.8, 7.9 Hz, 1H); $^{13}$C NMR (150 MHz, Acetone) $\delta$: 171.0, 170.3, 157.2, 151.4, 137.4, 116.6, 114.3, 112.3, 78.3, 39.5; HRMS (ESI-TOF) calcd for $C_{10}H_8NaO_5$ $[M+Na]^+$ 231.0264, found 231.0258.

### 4.3 Experimental procedure for the reaction of biphenyl-2-carboxylic acid with butyl acrylate on 1 mmol scale

A 25 mL Schlenk tube was charged with biphenyl-2-carboxylic acid (1 mmol, 202.0 mg), butyl acrylate (2 mmol, 285 μL), $[Cp^*RhCl_2]_2$ (0.025 mmol, 16.0 mg), deionic water (5 mL). The reaction vessel was sealed under air. Then, the mixture was reacted at 110 ℃ (oil bath temperature) for 18 h. The resulting mixture was cooled to room temperature and concentrated under vacuum to give a crude product, which is purified by silica-gel column chromatography using hexane/EtOAc ($V$∶$V$=25∶1) to yield compound **3r** (0.25 g, 77%).

### 4.4 Experimental procedure for the synthesis of **3ah**

A 5 mL microwave vial was charged with $[Cp^*RhCl_2]_2$ (1.6 mg, 0.0025 mmol), salicylic acid (0.1 mmol, 14.0 mg), acrylic acid (0.2 mmol, 14.0 μL), deionic water (0.5 mL). The mixture was sealed in air and stirred at 140 ℃ (oil bath temperature) for 18 h. Then the mixture was diluted with EtOAc and filtered. The solvent was removed under vacuum. The resulting residue was purified by a preparative TLC using hexane/EtOAc/HOAc ($V$∶$V$∶$V$=2∶1∶0.05) to yield compound **3ah**.

**Supporting Information** Mechanistic studies, $^1$H NMR and $^{13}$C NMR spectra for **3a**～**3ah**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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