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C–H Activation

Synthesis of Phthalides through Tandem Rhodium-Catalyzed C–H Olefination and Annulation of Benzamides

Neeraj Kumar Mishra,[a][‡] Jihye Park,[a][‡] Miji Choi,[a] Satyasheel Sharma,[a] Hyeim Jo,[a] Taejoo Jeong,[a] Sangil Han,[a] Saegun Kim,[a] and In Su Kim*[a]

Abstract: The rhodium(III)-catalyzed tandem C–H olefination and cyclization of benzamides with various alkenes is described. This protocol provides direct access to highly substituted phthalides, which are known as crucial frameworks of biologically active compounds. In particular, the amide directing group containing a benzimidazole group facilitates the activation of aromatic *ortho*-C–H bonds leading to olefination intermediates, and is spontaneously converted into an acid moiety, which can further undergo the intramolecular annulation process.

Introduction

With considerable progress in medicinal chemistry, the construction of O-heterocycles has received increasing attention in the past decades.[1] In particular, phthalides are widely found to be biologically relevant scaffolds in natural products, pharmaceuticals, agrochemicals, and functional materials.[2] For example, *n*-butylphthalide (NBP) is currently on the market as an antiplatelet drug for ischemia-cerebral apoplexy, and has led to the development of phthalides as a class of pharmaceutically important natural products (Figure 1).[3] In addition, mycophenolic acid is under clinical trial for the prevention and reversal of transplant rejection and as anticancer agent.[4]

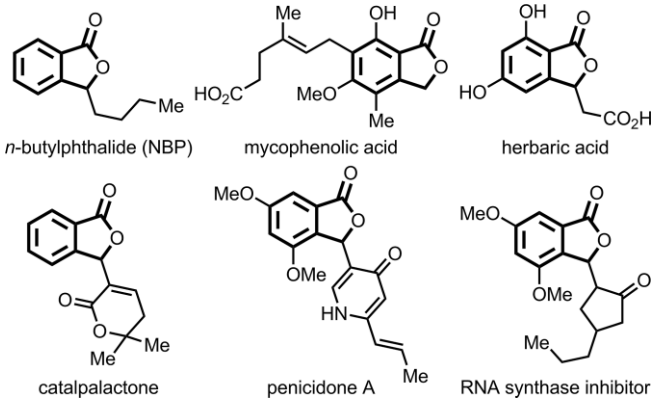

Figure 1. Selected bioactive examples containing a phthalide scaffold.

Owing to its diverse biological activities and unique structural features, the preparation of phthalide frameworks has been widely studied. Various synthetic routes include the reduction of phthalic anhydrides, oxidation of phthalan, addition of *o*-metallated aromatic compounds to carbonyl compounds, condensation reactions, cyclocarbonylations, and benzannulation/cycloaddition reactions.[5]

The transition-metal-catalyzed C–H activation reactions have been recognized as a powerful tool in organic and medicinal chemistry.[6] In this context, the direct formation of heterocycles has recently been studied using various metal catalysts.[7] Among them, secondary amide groups have been intensively used for the formation of isoindolinones,[8] dihydroisoquinolones,[9] 2-quinolinones,[10] phenanthridinones,[11] isoquinolones/pyridiones,[12] azepinones,[13] benzoisoxazoles,[14] etc.

In sharp contrast to the annulation reaction of secondary amide groups, tertiary amide groups have been rarely used for the formation of cyclic compounds. For instance, Shi et al. demonstrated the Rh/Cu-catalyzed annulation of benzimides with internal alkynes to give indenones by sequential C–H and C–N cleavage reactions (Scheme 1).[15] Ackermann et al. reported the direct synthesis of phthalimides by Ru^{II}-catalyzed tandem cyclization of tertiary benzamides with isocyanates.[16] Li et al. disclosed the efficient synthesis of (4-benzylidene)isochroman-1-ones by a hydroarylation and lactonization sequence of tertiary benzamides with propargylic alcohols.[17] Based on the previous annulation reactions using tertiary benzamides, we initially envisioned that the sequential C–H and C–N cleavage reaction using benzamides and olefins could afford indanone products by C–H olefination followed by intramolecular cyclization. After extensive screening of different *N*-benzoyl heterocycles such as PhCO-imidazole, PhCO-pyrazole, and PhCO-benzimidazole, all reactions were found to provide phthalides as major products, instead of carbocyclic indanones. Particularly, benzamides containing a benzimidazole group provided exclusively the corresponding phthalides in moderate yields (40–55 %). In this regard, Miura et al. reported the formation of phthalides and isocoumarins using benzoic acids with olefins and alkynes under Rh^{III} catalysis.[18] Jeganmohan et al. have re-

[a] *School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea*
E-mail: insukim@skku.edu
http://pharmasyn.skku.edu/
[‡] These authors contributed equally.
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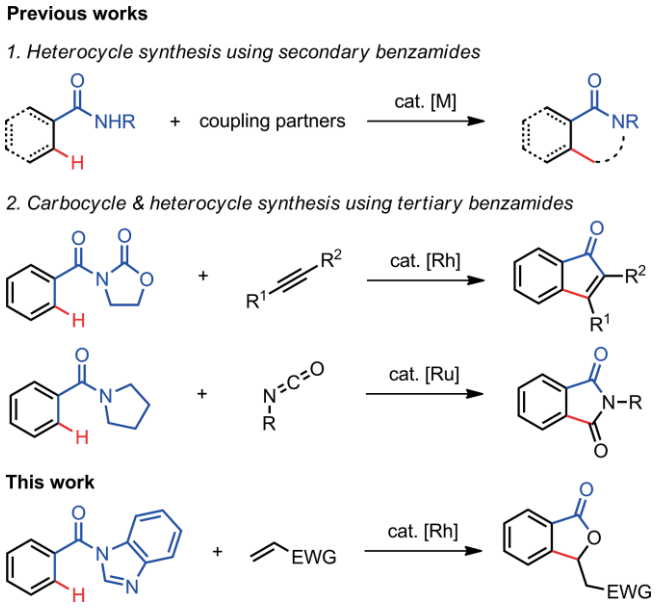
ported the ruthenium-catalyzed oxidative cyclization of aromatic acids or aromatic nitriles using alkynes and alkenes, respectively.[19] In continuation of our recent studies on the synthesis of heterocycles by C–H activation reactions,[20] we herein describe the synthesis of phthalides by tandem rhodium-catalyzed C–H olefination and annulation of benzamides.

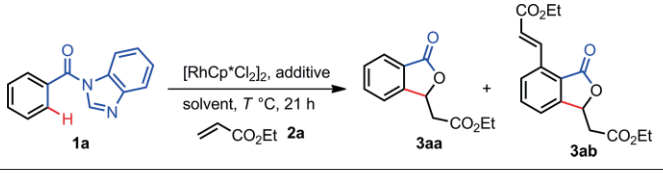


Scheme 1. Annulation reactions using benzamide directing groups.

Results and Discussion

Benzamide derivative **1a** containing a benzimidazole group was chosen as a substrate for the optimization of the reaction conditions, as shown in Table 1. A mixture of phthalide **3aa** and olefinated phthalide **3ab** was formed in 50 % combined yield in a 1:5 ratio (Table 1, Entry 1). Screening of solvents and Cu additive showed that a mixture of DMF and AcOH in the presence of 2 equiv. of $Cu(OAc)_2{\cdot}H_2O$ was found to be highly effective to give phthalide **3aa** as the major product in moderate yield (Table 1, Entries 2–5). A cationic rhodium complex derived from $[RhCp^*Cl_2]_2$ and $AgSbF_6$ provided a similar reactivity (Table 1, Entry 6). Further optimization revealed that decreasing the Rh catalyst amount (2.5 mol-%) and increasing the reaction temperature (130 °C) in DCE/AcOH co-solvents were found to facilitate a high level of the coupling reaction providing **3aa** (86 %) and **3ab** (12 %), respectively (Table 1, Entries 7–13). Further, we screened other acids such as TFA and PivOH, which were found to be less effective for the formation of **3aa** (Table 1, Entries 14 and 15). In addition, other acetate additives such as AgOAc, NaOAc and $Cu(OAc)_2$ were found to be less effective in this transformation (Table 1, Entries 16–18). However, Ru^{II}, Co^{III} and Ir^{III} catalysts provided a significant decrease

Table 1. Selected optimization of reaction conditions.[a]

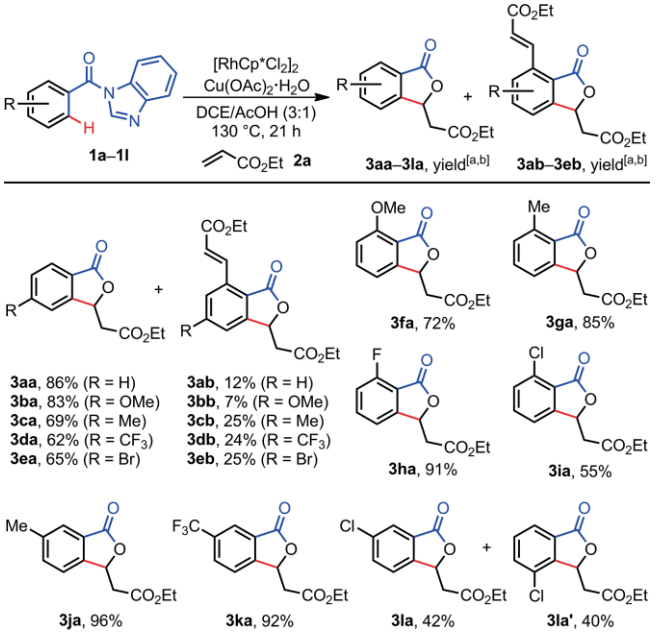


Entry	Additive (equiv.)	Solvent	Yield [%][b] (**3aa**/**3ab**)
1	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE	50 (1:5)
2	$Cu(OAc)_2{\cdot}H_2O$ (2)	DMF	20 (5:1)
3	$Cu(OAc)_2{\cdot}H_2O$ (2)	DMF/AcOH (3:1)	60 (6:1)
4	$Cu(OAc)_2{\cdot}H_2O$ (1)	DMF/AcOH (3:1)	48 (6:1)
5	$Cu(OAc)_2{\cdot}H_2O$ (0.5)	DMF/AcOH (3:1)	28 (8:1)
6[c]	$Cu(OAc)_2{\cdot}H_2O$ (2)	DMF/AcOH (3:1)	60 (5:1)
7[d]	$Cu(OAc)_2{\cdot}H_2O$ (2)	DMF/AcOH (3:1)	73 (6:1)
8[d,e]	$Cu(OAc)_2{\cdot}H_2O$ (2)	DMF/AcOH (3:1)	90 (4:1)
9[d,e]	**$Cu(OAc)_2{\cdot}H_2O$ (2)**	**DCE/AcOH (3:1)**	**98 (7:1)**
10[d,e]	$Cu(OAc)_2{\cdot}H_2O$ (2)	THF/AcOH (3:1)	90 (1:1)
11[d,e]	$Cu(OAc)_2{\cdot}H_2O$ (2)	MeCN/AcOH (3:1)	63 (>20:1)
12[d,e]	$Cu(OAc)_2{\cdot}H_2O$ (2)	MeOH/AcOH (3:1)	34 (4:1)
13[d,e]	$Cu(OAc)_2{\cdot}H_2O$ (2)	AcOH	6 (>20:1)
14[d,e]	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE/TFA (3:1)	trace
15[d,e]	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE/PivOH (3:1)	85 (1:1.8)
16[d,e]	AgOAc (2)	DCE/AcOH (3:1)	60 (10:1)
17[d,e]	NaOAc (2)	DCE/AcOH (3:1)	32 (15:1)
18[d,e]	$Cu(OAc)_2$ (2)	DCE/AcOH (3:1)	98 (4.5:1)
19[e,f]	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE/AcOH (3:1)	10 (>20:1)
20[e,g]	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE/AcOH (3:1)	trace
21[e,h]	$Cu(OAc)_2{\cdot}H_2O$ (2)	DCE/AcOH (3:1)	8 (>50:1)

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (5 mol-%), additive (quantity given), solvent (1 mL) under air in pressure tubes at 110 °C for 21 h. DCE = 1,2-dichloroethane; TFA = trifluoroacetic acid. [b] Isolation by flash column chromatography. [c] $AgSbF_6$ (20 mol-%) was used. [d] $[RhCp^*Cl_2]_2$ (2.5 mol-%) was used. [e] The reaction was carried out at 130 °C. [f] $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol-%) was used. [g] $[CoCp^*(CO)I_2]$ (5 mol-%) was used. [h] $[IrCp^*Cl_2]_2$ (5 mol-%) was used.

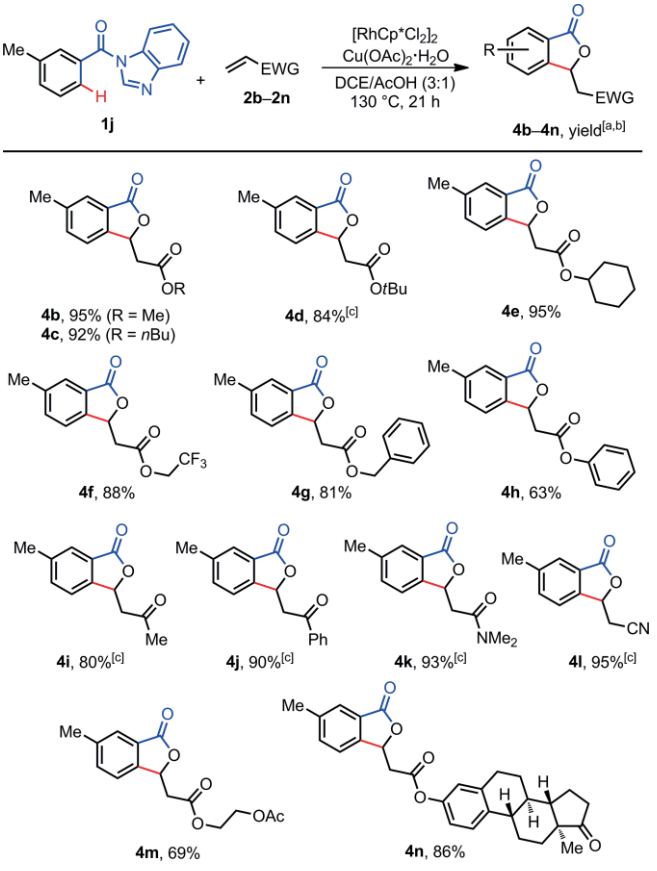
in the formation of our desired products (Table 1, Entries 19–21).

To evaluate the substrate scope of this process, a range of benzamides was subjected under the optimal reaction conditions (Scheme 2). The coupling reaction of acrylate **2a** with benzamides containing *para* substituents, such as OMe, Me, CF_3 and Br, delivered the corresponding phthalides **3aa**–**3ea** as major product in good to high yields, along with olefinated phthalides **3ab**–**3eb**. In addition, this coupling reaction was found to be compatible with both electron-rich and -deficient substituents in the *ortho* position of benzamides **1f**–**1i**. Moreover, *meta*-substituted benzamides **1j** and **1k** were smoothly coupled with **2a** at less-hindered positions to give the phthalide products **3ja** and **3ka** in high yields. However, *meta*-chloro-substituted benzamide **1l** was found to afford a mixture of regioisomeric phthalides **3la** and **3la′** in combined high yield.



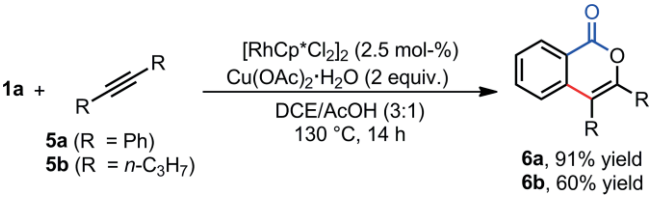
Scheme 2. Scope of benzamides. [a] Reaction conditions: **1a**–**1l** (0.2 mmol), **2a** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol-%), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv.), DCE/AcOH (3:1, 1 mL) under air in pressure tubes at 130 °C for 21 h. [b] Isolation by flash column chromatography.

To further explore the substrate scope of this transformation, various olefins **2b**–**2n** were screened to be coupled with **1j** (Scheme 3). To our pleasure, acrylates **2b**–**2h** proved to be good substrates for this transformation affording the corresponding products **4b**–**4h** in good to high yields. Interestingly, α,β-unsaturated ketones (**2i** and **2j**), *N*,*N*-dimethylacrylamide (**2k**), and acrylonitrile (**2l**) gave the corresponding phthalide products in low yields under the optimal reaction conditions. After further screening of the reaction conditions, we found that MeCN as solvent provided our desired products **4i**–**4l** in high yields. Interestingly, 2-hydroxyethyl acrylate (**2m**) containing a primary hydroxy group also participated in this coupling reaction. However, instead of phthalide product with a primary hydroxy group, acetylated derivative **4m** was obtained in 69 % yield. Finally, this protocol offers the possibility of late-stage functionalization of bioactive compounds incorporating the olefin functional groups. For an example, estrone-containing acrylate **2n** was smoothly coupled with benzamide **1j** to afford **4n** in 86 % yield.



Scheme 3. Scope of olefins. [a] Reaction conditions: **1j** (0.2 mmol), **2b**–**2n** (0.4 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol-%), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv.), DCE/AcOH (3:1, 1 mL) under air in pressure tubes at 130 °C for 21 h. [b] Isolation by flash column chromatography. [c] MeCN was used as a solvent.

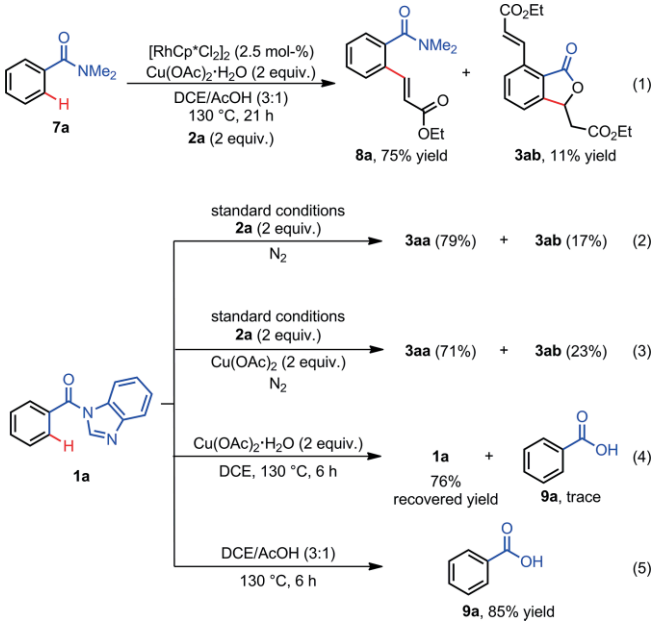
Next, we envisioned the synthesis of isocoumarins by the coupling of alkynes and benzamides containing a benzimidazole moiety as a bifunctional directing group according to the previous literature.[18a] Thus, benzamide **1a** was subjected to the optimal reaction conditions with 1,2-diphenylethyne (**5a**) and 4-octyne (**5b**), as shown in Scheme 4. To our delight, we found that benzamide **1a** smoothly reacted with alkynes **5a** and **5b** to provide the corresponding isocoumarins **6a** (91 %) and **6b** (60 %), respectively.



Scheme 4. Synthesis of isocoumarins by coupling of benzamide and alkynes.

To understand the effect of a benzimidazole group, we carried out the reaction of *N*,*N*-dimethylbenzamide (**7a**) with **2a** under the standard reaction conditions [Scheme 5, Equation (1)]. Olefinated product **8a** was obtained as the major

product along with phthalide **3ab** in 11 % yield. This result indicates that a benzimidazole group plays an important role as a leaving group. To find the source of oxygen for the formation of phthalides, various control experiments were performed. The reactions of **1a** with **2a** under an inert gas in the presence of either $Cu(OAc)_2{\cdot}H_2O$ or $Cu(OAc)_2$ provided similar results for the formation of phthalide products [Scheme 5, Equations (2) and 3]. These results show that air and H_2O can be excluded as oxygen sources in the reaction media. After further investigations, we found that AcOH might be the source of oxygen, which is supported by the conversion of **1a** into benzoic acid (**9a**). Thus, we believe that benzoic acid intermediates may undergo a tandem rhodium-catalyzed C–H olefination and annulation reaction [Scheme 5, Equation (4) and 5].



Scheme 5. Control experiments.

Conclusions

We described the site-selective rhodium(III)-catalyzed C–H olefination and cyclization of benzamides with various alkenes by C–H bond activation. These transformations allow the generation of an array of C3-substituted phthalides, which are known to be crucial scaffolds of biologically active compounds. Furthermore, this approach can be readily applied to the synthesis of isocoumarins using internal alkynes. A detailed mechanistic study is currently underway.

Experimental Section

Experimental Procedure for the Synthesis of Phthalides 3aa–3la, 3ab–3eb and 4b–4n: To an oven-dried sealed tube charged with (1*H*-benzo[*d*]imidazol-1-yl)(phenyl)methanone (**1a**) (44.4 mg, 0.2 mmol, 100 mol-%), $[RhCp^*Cl_2]_2$ (3.1 mg, 0.005 mmol, 2.5 mol-%) and $Cu(OAc)_2{\cdot}H_2O$ (79.9 mg, 0.4 mmol, 2 equiv.) in DCE/AcOH (3:1, 1 mL) was added ethyl acrylate (**2a**) (40.4 mg, 0.4 mmol, 200 mol-%) under air at ambient temperature. The reaction mixture was stirred at 130 °C for 21 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with water. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc, 6:1) to afford **3aa** (37.9 mg, 86 % yield) and **3ab** (7.8 mg, 12 % yield).

Ethyl 2-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3aa): 37.9 mg (86 %); light yellow solid; m.p. 70.0–71.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.6 Hz, 1 H), 7.68 (t, *J* = 7.2 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 5.88 (t, *J* = 6.8 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 2.94–2.83 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 169.2, 148.7, 134.2, 129.5, 125.9, 125.8, 122.0, 76.9, 61.2, 39.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2928, 1758, 1727, 1612, 1466, 1376, 1288, 1211, 1175, 1095, 1000, 746 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{12}H_{13}O_4$ $[M + H]^+$ 221.0814, found 221.0812.

Ethyl (*E*)-3-[1-(2-Ethoxy-2-oxoethyl)-3-oxo-1,3-dihydroisobenzofuran-4-yl]acrylate (3ab): 7.8 mg (12 %); light yellow sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 16.0 Hz, 1 H), 7.75 (d, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 6.58 (d, *J* = 16.0 Hz, 1 H), 5.83 (t, *J* = 6.4 Hz, 1 H), 4.26 (q, *J* = 6.8 Hz, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 2.92–2.85 (m, 2 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 168.8, 166.0, 149.6, 137.2, 134.9, 134.2, 126.6, 123.2, 123.1, 123.0, 76.0, 61.2, 60.7, 39.4, 14.2, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2982, 2928, 1758, 1707, 1641, 1592, 1361, 1302, 1220, 1165, 1078, 1047, 1008, 804, 791 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{17}H_{19}O_6$ $[M + H]^+$ 319.1182, found 319.1184.

Ethyl 2-(6-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3ba): 41.6 mg (83 %); light yellow solid; m.p. 66.8–68.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.4 Hz, 1 H), 7.02 (d, *J* = 8.8 Hz, 1 H), 6.92 (s, 1 H), 5.78 (t, *J* = 6.8 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 3.87 (s, 3 H), 2.89 (dd, *J* = 16.4, 7.2 Hz, 1 H), 2.84 (dd, *J* = 16.4, 6.0 Hz, 1 H), 1.26 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 169.3, 164.8, 151.5, 127.2, 118.1, 116.7, 106.2, 76.2, 61.2, 55.8, 39.6, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 2852, 1753, 1729, 1605, 1490, 1464, 1377, 1348, 1326, 1289, 1250, 1176, 1153, 1106, 1056, 1003, 839, 773 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{15}O_5$ $[M + H]^+$ 251.0919, found 251.0919.

Ethyl (*E*)-3-[1-(2-Ethoxy-2-oxoethyl)-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-4-yl]acrylate (3bb): 4.9 mg (7 %); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 16.4 Hz, 1 H), 7.22 (s, 1 H), 6.94 (s, 1 H), 6.57 (d, *J* = 16.4 Hz, 1 H), 5.77 (t, *J* = 6.4 Hz, 1 H), 4.28 (q, *J* = 6.8 Hz, 2 H), 4.21 (q, *J* = 6.8 Hz, 2 H), 3.91 (s, 3 H), 2.92 (dd, *J* = 16.8, 6.8 Hz, 1 H), 2.84 (dd, *J* = 16.4, 6.0 Hz, 1 H), 1.35 (t, *J* = 7.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 168.6, 166.0, 164.5, 152.4, 137.4, 136.5, 123.2, 115.8, 113.1, 107.7, 75.6, 61.3, 60.8, 55.9, 39.6, 14.2, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 2853, 1752, 1706, 1643, 1590, 1464, 1377, 1337, 1269, 1179, 1152, 1067, 1014, 862, 796 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{18}H_{21}O_7$ $[M + H]^+$ 349.1287, found 349.1288.

Ethyl 2-(6-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3ca): 32.3 mg (69 %); white solid; m.p. 92.1–94.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.27 (s, 1 H), 5.81 (t, *J* = 6.4 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 2.88 (dd, *J* = 16.8, 7.2 Hz, 1 H), 2.83 (dd, *J* = 16.8, 6.4 Hz, 1 H), 2.47 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 169.3, 149.3, 145.5, 130.6, 125.5, 123.3, 122.3, 76.6, 61.2, 39.5, 22.0, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2928, 1750, 1731, 1617, 1463, 1377, 1341, 1280, 1212, 1177, 1126, 1053, 1011, 906, 836, 769 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{15}O_4$ $[M + H]^+$ 235.0970, found 235.0969.

Ethyl (*E*)-3-[1-(2-Ethoxy-2-oxoethyl)-6-methyl-3-oxo-1,3-dihydroisobenzofuran-4-yl]acrylate (3cb): 16.7 mg (25 %); yellowish viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, J = 16.0 Hz, 1 H), 7.55 (s, 1 H), 7.26 (s, 1 H), 6.57 (d, J = 16.4 Hz, 1 H), 5.78 (t, J = 6.4 Hz, 1 H), 4.26 (q, J = 7.2 Hz, 2 H), 4.21 (q, J = 6.8 Hz, 2 H), 2.88 (dd, J = 16.8, 6.8 Hz, 1 H), 2.84 (dd, J = 16.8, 6.4 Hz, 1 H), 2.48 (s, 3 H), 1.33 (t, J = 7.2 Hz, 3 H), 1.28 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 168.9, 166.1, 150.2, 145.4, 137.4, 134.6, 127.6, 123.5, 122.7, 120.7, 75.8, 61.2, 60.7, 39.5, 22.0, 14.2, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2925, 2854, 1753, 1708, 1640, 1596, 1474, 1367, 1346, 1271, 1240, 1175, 1092, 1054, 1013, 906, 859, 802, 718 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{18}H_{21}O_6$ $[M + H]^+$ 333.1338, found 333.1342.

Ethyl 2-[3-Oxo-6-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl]acetate (3da): 35.8 mg (62 %); white solid; m.p. 116.0–117.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 8.4 Hz, 1 H), 7.83–7.81 (m, 2 H), 5.93 (t, J = 6.4 Hz, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 3.01 (dd, J = 16.8, 6.4 Hz, 1 H), 2.93 (dd, J = 16.8, 6.4 Hz, 1 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 168.3, 149.1, 135.8 (q, $J_{C,F}$ = 32.5 Hz), 129.2, 126.8 (q, $J_{C,F}$ = 3.4 Hz), 126.5, 123.2 (q, $J_{C,F}$ = 272.0 Hz), 119.7 (q, $J_{C,F}$ = 3.8 Hz), 76.9, 61.4, 39.0, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3049, 2992, 1755, 1716, 1626, 1438, 1383, 1326, 1286, 1223, 1186, 1163, 1123, 1074, 1052, 1020, 1003, 903, 852, 806, 778 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{12}F_3O_4$ $[M + H]^+$ 289.0688, found 289.0688.

Ethyl (*E*)-3-[1-(2-Ethoxy-2-oxoethyl)-3-oxo-6-(trifluoromethyl)-1,3-dihydroisobenzofuran-4-yl]acrylate (3db): 18.6 mg (24 %); white solid; m.p. 109.9–112.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, J = 16.0 Hz, 1 H), 7.99 (s, 1 H), 7.76 (s, 1 H), 6.67 (d, J = 16.4 Hz, 1 H), 5.89 (t, J = 6.4 Hz, 1 H), 4.30 (q, J = 6.8 Hz, 2 H), 4.21 (q, J = 7.2 Hz, 2 H), 3.01 (dd, J = 16.8, 6.4 Hz, 1 H), 2.92 (dd, J = 16.8, 6.8 Hz, 1 H), 1.35 (t, J = 6.8 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 167.5, 165.5, 150.3, 136.3, 136.1, 136.0, 135.8, 124.8, 124.0 (q, $J_{C,F}$ = 271.8 Hz), 123.8 (q, $J_{C,F}$ = 3.4 Hz), 119.9 (q, $J_{C,F}$ = 4.0 Hz), 76.0, 61.5, 61.0, 39.0, 14.2, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2922, 2853, 2374, 2320, 1773, 1731, 1438, 1378, 1327, 1315, 1211, 1170, 1130, 1066, 1008, 904, 852, 740 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{18}H_{18}F_3O_6$ $[M + H]^+$ 387.1055, found 387.1057.

Ethyl 2-(6-Bromo-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3ea): 38.9 mg (65 %); white solid; m.p. 115.1–117.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.4 Hz, 1 H), 7.69–7.67 (m, 2 H), 5.84 (t, J = 6.4 Hz, 1 H), 4.21 (q, J = 7.2 Hz, 2 H), 2.98 (dd, J = 16.8, 6.8 Hz, 1 H), 2.86 (dd, J = 16.8, 6.4 Hz, 1 H), 1.27 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 168.8, 150.5, 133.1, 129.5, 127.0, 125.8, 124.9, 76.3, 61.4, 39.2, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2930, 2373, 2320, 1764, 1729, 1607, 1589, 1464, 1377, 1337, 1289, 1263, 1209, 1181, 1122, 1063, 1005, 898, 838, 784 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{12}H_{12}BrO_4$ $[M + H]^+$ 298.9919, found 298.9920.

Ethyl (*E*)-3-[6-Bromo-1-(2-ethoxy-2-oxoethyl)-3-oxo-1,3-dihydroisobenzofuran-4-yl]acrylate (3eb): 19.9 mg (25 %); light yellow solid; m.p. 109.2–113.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (d, J = 16.4 Hz, 1 H), 7.89 (s, 1 H), 7.66 (s, 1 H), 6.59 (d, J = 16.4 Hz, 1 H), 5.81 (t, J = 6.8 Hz, 1 H), 4.28 (q, J = 7.2 Hz, 2 H), 4.21 (q, J = 7.2 Hz, 2 H), 2.96 (dd, J = 16.8, 6.4 Hz, 1 H), 2.85 (dd, J = 16.8, 6.4 Hz, 1 H), 1.34 (t, J = 7.2 Hz, 3 H), 1.28 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 168.9, 168.0, 165.6, 151.4, 136.5, 135.9, 130.0, 129.3, 126.3, 124.3, 122.1, 75.5, 61.5, 61.0, 39.1, 14.2, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3077, 2982, 2929, 1760, 1714, 1640, 1583, 1452, 1339, 1219, 1181, 1086, 1052, 1014, 863, 802 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{17}H_{18}BrO_6$ $[M + H]^+$ 397.0287, found 397.0291.

Ethyl 2-(4-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3fa): 36.1 mg (72 %); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (t, J = 8.0 Hz, 1 H), 6.99 (d, J = 7.6 Hz, 1 H), 6.93 (d, J = 8.4 Hz, 1 H), 5.78 (t, J = 6.4 Hz, 1 H), 4.18 (q, J = 6.8 Hz, 2 H), 3.97 (s, 3 H), 2.83 (d, J = 6.4 Hz, 2 H), 1.25 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 167.8, 158.6, 151.5, 136.5, 113.5, 113.2, 111.0, 75.8, 61.2, 56.0, 39.6, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2940, 2844, 1759, 1729, 1602, 1486, 1375, 1314, 1276, 1198, 1178, 1078, 1034, 1008, 968, 920, 800, 779, 744 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{15}O_5$ $[M + H]^+$ 251.0919, found 251.0922.

Ethyl 2-(4-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3ga): 39.9 mg (85 %); light yellow solid; m.p. 49.2–52.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (t, J = 7.6 Hz, 1 H), 7.25 (t, J = 6.4 Hz, 2 H), 5.79 (t, J = 6.4 Hz, 1 H), 4.18 (q, J = 6.8 Hz, 2 H), 2.84 (d, J = 6.4 Hz, 2 H), 2.66 (s, 3 H), 1.24 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 169.3, 149.2, 139.9, 133.9, 131.1, 123.4, 119.2, 76.0, 61.2, 61.1, 39.8, 39.7, 17.3, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2929, 1753, 1730, 1601, 1481, 1377, 1290, 1260, 1238, 1200, 1175, 1090, 1046, 1005, 904, 860, 832, 787 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{15}O_4$ $[M + H]^+$ 235.0970, found 235.0969.

Ethyl 2-(4-Fluoro-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3ha): 43.4 mg (91 %); colorless solid; m.p. 85.2–87.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (t, J = 7.6 Hz, 1 H), 7.49 (d, J = 7.6 Hz, 1 H), 7.40 (d, J = 7.6 Hz, 1 H), 5.81 (t, J = 6.4 Hz, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 2.91 (dd, J = 16.8, 6.8 Hz, 1 H), 2.85 (dd, J = 16.8, 6.4 Hz, 1 H), 1.25 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 165.8 (d, $J_{C,F}$ = 2.9 Hz), 160.9, 158.2, 151.3 (d, $J_{C,F}$ = 1.1 Hz), 136.8 (d, $J_{C,F}$ = 7.7 Hz), 118.0 (d, $J_{C,F}$ = 4.4 Hz), 116.5 (d, $J_{C,F}$ = 18.6 Hz), 113.7 (d, $J_{C,F}$ = 14.3 Hz), 76.6, 61.3, 39.3, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2983, 2930, 1764, 1729, 1625, 1603, 1481, 1378, 1350, 1312, 1291, 1258, 1203, 1178, 1071, 0144, 1000, 931, 904, 863, 837, 797 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{12}H_{12}FO_4$ $[M + H]^+$ 239.0720, found 239.0721.

Ethyl 2-(4-Chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3ia): 28.1 mg (55 %); white solid; m.p. 70.5–73.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (t, J = 7.6 Hz, 1 H), 7.49 (d, J = 7.6 Hz, 1 H), 7.40 (d, J = 7.6 Hz, 1 H), 5.81 (t, J = 6.4 Hz, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 2.94 (dd, J = 16.4, 6.8 Hz, 1 H), 2.86 (dd, J = 16.8, 6.4 Hz, 1 H), 1.25 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 166.7, 151.1, 135.2, 133.4, 130.9, 122.6, 120.5, 75.5, 61.3, 39.3, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2959, 2925, 2854, 1761, 1730, 1601, 1466, 1377, 1288, 1254, 1211, 1176, 1061, 1015, 1003, 912, 849, 747 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{12}H_{12}ClO_4$ $[M + H]^+$ 255.0424, found 255.0425.

Ethyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3ja): 45.0 mg (96 %); light yellow solid; m.p. 65.6–68.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (s, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.35 (d, J = 7.6 Hz, 1 H), 5.81 (t, J = 6.4 Hz, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 2.87 (dd, J = 16.4, 7.2 Hz, 1 H), 2.84 (dd, J = 16.8, 6.4 Hz, 1 H), 2.43 (s, 3 H), 1.24 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.4, 146.2, 139.9, 135.5, 126.2, 125.8, 121.8, 76.8, 61.3, 39.7, 21.3, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2927, 1761, 1729, 1625, 1594, 1494, 1376, 1342, 1288, 1254, 1230, 1153, 1055, 1006, 916, 838, 778 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{15}O_4$ $[M + H]^+$ 235.0970, found 235.0970.

Ethyl 2-[3-Oxo-5-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-yl]acetate (3ka): 53.1 mg (92 %); light yellow solid; m.p. 49.5–53.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 5.93 (t, J = 6.4 Hz, 1 H), 4.20 (q, J = 6.8 Hz, 2 H), 3.01 (dd, J = 16.8, 6.4 Hz, 1 H), 2.91 (dd, J = 16.8, 6.4 Hz, 1 H), 1.27 (t, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 168.8, 168.2, 151.9, 132.4 (q, $J_{C,F}$ = 33.1 Hz), 131.1 (q, $J_{C,F}$ = 3.6 Hz), 127.0, 123.2 (q, $J_{C,F}$ = 271.2 Hz), 123.1 (q, $J_{C,F}$ = 3.9 Hz), 76.9, 61.4, 39.0, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2985, 2930, 1770, 1730, 1634, 1379, 1327, 1263, 1166, 1123, 1081, 1051, 1004, 910, 846, 776, 743 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{12}F_3O_4$ $[M + H]^+$ 289.0688, found 289.0690.

Ethyl 2-(5-Chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3la): 21.4 mg (42 %); white solid; m.p. 95.5–97.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (s, 1 H), 7.64 (dd, J = 8.0, 1.6 Hz, 1 H), 7.46 (d, J = 8.4 Hz, 1 H), 5.85 (t, J = 6.4 Hz, 1 H), 4.20 (q, J = 6.8 Hz, 2 H), 2.96 (dd, J = 16.4, 6.4 Hz, 1 H), 2.84 (dd, J = 16.4, 6.4 Hz, 1 H), 1.27 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 168.4, 146.9, 135.9, 134.5, 127.8, 125.7, 123.5, 76.8, 61.4, 39.3, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2853, 1764, 1730, 1471, 1425, 1378, 1340, 1291, 1253, 1202, 1178, 1128, 1088, 1052, 1021, 1004, 897, 835, 774 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{12}H_{12}ClO_4$ $[M + H]^+$ 255.0424, found 255.0425.

Ethyl 2-(7-Chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (3la′): 20.4 mg (40 %); colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.6 Hz, 1 H), 7.64 (d, J = 8.0 Hz, 1 H), 7.52 (t, J = 7.6 Hz, 1 H), 5.90 (d, J = 7.2 Hz, 1 H), 4.15 (q, J = 6.8 Hz, 2 H), 3.42 (d, J = 15.6 Hz, 1 H), 2.76 (q, J = 8.0 Hz, 1 H), 1.22 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 168.5, 145.3, 134.5, 131.2, 128.7, 128.5, 124.3, 76.7, 61.2, 37.0, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2854, 1771, 1730, 1608, 1589, 1462, 1377, 1345, 1300, 1253, 1174, 1141, 1070, 1046, 1007, 946, 916, 885, 842, 812, 754 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{12}H_{12}ClO_4$ $[M + H]^+$ 255.0424, found 255.0426.

Methyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (4b): 41.9 mg (95 %); light yellow solid; m.p. 73.0–74.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H), 5.82 (t, J = 6.6 Hz, 1 H), 3.73 (s, 3 H), 2.87 (dd, J = 16.6, 7.0 Hz, 1 H), 2.84 (dd, J = 16.8, 6.2 Hz, 1 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.9, 146.2, 140.0, 135.6, 126.1, 125.9, 121.9, 76.9, 52.3, 39.6, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 1764, 1737, 1639, 1594, 1494, 1437, 1379, 1342, 1307, 1292, 1231, 1202, 1155, 1131, 1056, 1009, 834, 778 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{12}H_{13}O_4$ $[M + H]^+$ 221.0814, found 221.0812.

Butyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (4c): 48.3 mg (92 %); light yellow sticky oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 1 H), 5.82 (t, J = 6.5 Hz, 1 H), 4.13 (t, J = 6.6 Hz, 2 H), 2.88 (dd, J = 16.4, 6.9 Hz, 1 H), 2.83 (dd, J = 16.4, 6.2 Hz, 1 H), 2.44 (s, 3 H), 1.62–1.55 (m, 2 H), 1.38–1.31 (m, 2 H), 0.90 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 169.5, 146.3, 140.0, 135.5, 126.2, 125.9, 121.9, 76.9, 65.2, 39.7, 30.6, 21.4, 19.2, 13.8 ppm. IR (KBr): $\tilde{\nu}$ = 2959, 2932, 2873, 2360, 2294, 1765, 1730, 1495, 1460, 1395, 1341, 1287, 1230, 1170, 1153, 1130, 1056, 1006, 913, 835, 778 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{15}H_{19}O_4$ $[M + H]^+$ 263.1283, found 263.1284.

***tert*-Butyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)-acetate (4d):** 44.1 mg (84 %); white solid; m.p. 104.3–106.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.47 (d, J = 7.7 Hz, 1 H), 7.36 (d, J = 7.7 Hz, 1 H), 5.78 (t, J = 6.4 Hz, 1 H), 2.83 (dd, J = 16.2, 6.7 Hz, 1 H), 2.77 (dd, J = 16.2, 6.1 Hz, 1 H), 2.44 (s, 3 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 168.6, 146.6, 139.9, 135.4, 126.4, 125.8, 121.9, 82.0, 76.9, 40.9, 28.1, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 2976, 2931, 2373, 2321, 1765, 1728, 1624, 1594, 1495, 1455, 1367, 1343, 1306, 1292, 1256, 1232, 1150, 1057, 1007, 953, 915, 838, 781 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{15}H_{19}O_4$ $[M + H]^+$ 263.1283, found 263.1285.

Cyclohexyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)-acetate (4e): 54.8 mg (95 %); pale yellow solid; m.p. 101.7–105.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.36 (d, J = 7.8 Hz, 1 H), 5.82 (t, J = 6.5 Hz, 1 H), 4.84–4.78 (m, 1 H), 2.89 (dd, J = 16.3, 6.8 Hz, 1 H), 2.83 (dd, J = 16.3, 6.2 Hz, 1 H), 2.44 (s, 3 H), 1.86–1.18 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 168.9, 146.4, 139.9, 135.5, 126.3, 125.9, 121.9, 76.9, 73.9, 40.1, 31.6, 25.4, 23.8, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 2935, 2858, 1765, 1729, 1624, 1593, 1494, 1453, 1385, 1343, 1305, 1287, 1256, 1231, 1171, 1154, 1129, 1055, 1008, 913, 836, 779 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{17}H_{21}O_4$ $[M + H]^+$ 289.1440, found 289.1443.

2,2,2-Trifluoroethyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (4f): 50.7 mg (88 %); pale yellow solid; m.p. 73.0–75.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.49 (d, J = 7.8 Hz, 1 H), 7.36 (d, J = 7.8 Hz, 1 H), 5.83 (t, J = 6.4 Hz, 1 H), 4.62–4.43 (m, 2 H), 3.03 (dd, J = 16.8, 5.7 Hz, 1 H), 2.94 (dd, J = 16.8, 7.2 Hz, 1 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 167.9, 145.6, 140.3, 135.7, 126.2, 126.1, 122.8 (q, $J_{C,F}$ = 275.5 Hz), 76.3, 60.8 (q, $J_{C,F}$ = 36.8 Hz), 39.1, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 2929, 1758, 1625, 1594, 1495, 1412, 1343, 1304, 1274, 1150, 1057, 1008, 977, 912, 832, 779 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{12}F_3O_4$ $[M + H]^+$ 289.0688, found 289.0688.

Benzyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (4g): 48.0 mg (81 %); white viscous oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H), 7.34 (d, J = 7.7 Hz, 1 H), 7.26–7.17 (m, 6 H), 5.75 (t, J = 6.3 Hz, 1 H), 5.09 (t, J = 13.3 Hz, 2 H), 2.86 (dd, J = 16.4, 7.0 Hz, 1 H), 2.79 (dd, J = 16.4, 6.0 Hz, 1 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.2, 146.1, 140.0, 135.5, 135.4, 128.8, 128.7, 128.6, 126.2, 125.9, 121.9, 76.9, 67.1, 39.8, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 3033, 2925, 1763, 1731, 1624, 1593, 1495, 1455, 1388, 1342, 1306, 1285, 1230, 1152, 1130, 1054, 996, 912, 827, 779, 736 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{18}H_{17}O_4$ $[M + H]^+$ 297.1127, found 297.1127.

Phenyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (4h): 35.6 mg (63 %); white solid; m.p. 98.8–100.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.54 (d, J = 7.7 Hz, 1 H), 7.46 (d, J = 7.8 Hz, 1 H), 7.41 (t, J = 7.4 Hz, 2 H), 7.29–7.26 (m, 1 H), 7.12 (d, J = 7.6 Hz, 2 H), 5.96 (t, J = 6.3 Hz, 1 H), 3.19 (dd, J = 17.3, 6.9 Hz, 1 H), 3.14 (dd, J = 17.3, 6.3 Hz, 1 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 168.1, 150.4, 146.0, 140.2, 135.7, 129.7, 126.4, 126.3, 126.1, 122.0, 121.5, 76.8, 39.9, 21.4 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 1758, 1591, 1493, 1382, 1341, 1306, 1285, 1230, 1193, 1144, 1070, 1007, 947, 757 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{17}H_{15}O_4$ $[M + H]^+$ 283.0970, found 283.0971.

6-Methyl-3-(2-oxopropyl)isobenzofuran-1(3*H*)-one (4i): 32.7 mg (80 %); yellowish oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 7.45 (d, J = 7.9 Hz, 1 H), 7.33 (d, J = 7.8 Hz, 1 H), 5.85 (t, J = 6.5 Hz, 1 H), 3.08 (dd, J = 17.4, 6.8 Hz, 1 H), 2.88 (dd, J = 17.4, 6.2 Hz, 1 H), 2.43 (s, 3 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.7, 170.3, 146.9, 139.9, 135.5, 126.0, 125.8, 122.1, 76.8, 48.3, 30.8, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 2923, 2359, 2341, 1755, 1710, 1625, 1592, 1494, 1422, 1343, 1306, 1285, 1228, 1154, 1130, 1082, 1059, 1038, 1001, 949, 912, 827, 775 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{12}H_{13}O_3$ $[M + H]^+$ 205.0865, found 205.0862.

6-Methyl-3-(2-oxo-2-phenylethyl)isobenzofuran-1(3*H*)-one (4j): 47.9 mg (90 %); light yellow solid; m.p. 137.3–141.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.5 Hz, 2 H), 7.68 (s, 1 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.49–7.42 (m, 4 H), 6.11 (t, J = 6.2 Hz, 1 H), 3.74 (dd, J = 17.5, 5.6 Hz, 1 H), 3.36 (dd, J = 17.6, 7.2 Hz, 1 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3, 170.4, 147.3, 139.9, 136.4, 135.5, 133.9, 128.9, 128.3, 126.2, 125.8, 122.6, 76.9, 43.9,

21.4 ppm. IR (KBr): $\tilde{\nu}$ = 3059, 2923, 1754, 1719, 1683, 1595, 1494, 1448, 1368, 1306, 1288, 1230, 1213, 1155, 1131, 1076, 1000, 977, 828, 754 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{17}H_{15}O_3$ $[M + H]^+$ 267.1021, found 267.1021.

***N*,*N*-Dimethyl-2-(5-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetamide (4k):** 43.4 mg (93 %); white solid; m.p. 116.8–120.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 5.96 (t, *J* = 6.7 Hz, 1 H), 3.06 (dd, *J* = 15.9, 6.0 Hz, 1 H), 3.00 (s, 3 H), 2.96 (s, 3 H), 2.67 (dd, *J* = 15.9, 7.4 Hz, 1 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 168.8, 147.4, 139.7, 135.5, 126.1, 125.6, 123.0, 76.9, 39.0, 37.5, 35.6, 21.3 ppm. IR (KBr): $\tilde{\nu}$ = 2925, 1758, 1643, 1494, 1401, 1341, 1305, 1263, 1153, 1131, 1078, 1056, 993, 782 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{13}H_{16}NO_3$ $[M + H]^+$ 234.1130, found 234.1130.

2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetonitrile (4l): 35.6 mg (95 %); white solid; m.p. 179.5–181.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (s, 1 H), 7.57–7.51 (m, 2 H), 5.62 (t, *J* = 5.9 Hz, 1 H), 3.06 (dd, *J* = 16.7, 5.1 Hz, 1 H), 2.92 (dd, *J* = 16.7, 6.7 Hz, 1 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 144.1, 141.2, 136.1, 126.5, 126.1, 121.9, 115.0, 74.7, 24.1, 21.5 ppm. IR (KBr): $\tilde{\nu}$ = 2933, 1153, 1761, 1624, 1594, 1495, 1418, 1340, 1303, 1284, 1154, 1129, 1062, 1010, 993, 897, 831, 764 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{11}H_{10}NO_2$ $[M + H]^+$ 188.0712, found 188.0710.

2-Acetoxyethyl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (4m): 40.3 mg (69 %); white viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 7.8 Hz, 1 H), 5.83 (t, *J* = 6.5 Hz, 1 H), 4.36–4.34 (m, 2 H), 4.27–4.25 (m, 2 H), 2.91 (d, *J* = 6.5 Hz, 2 H), 2.46 (s, 3 H), 2.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.1, 169.3, 146.1, 140.2, 135.6, 126.3, 126.1, 121.9, 76.9, 63.1, 62.1, 39.6, 21.4, 20.9 ppm. IR (KBr): $\tilde{\nu}$ = 3418, 2954, 2923, 2853, 1764, 1732, 1625, 1593, 1495, 1455, 1375, 1284, 1227, 1154, 1130, 1055, 1005, 965, 915, 836, 778 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{15}H_{17}O6$ $[M + H]^+$ 293.1025, found 293.1027.

(8*R*,9,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl 2-(5-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (4n): 78.9 mg (86 %); white solid; m.p. 211.3–214.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.43 (d, *J* = 7.8 Hz, 1 H), 7.29–7.26 (m, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 6.81 (s, 1 H), 5.92 (t, *J* = 6.4 Hz, 1 H), 3.11 (d, *J* = 6.4 Hz, 2 H), 2.89 (br. s, 2 H), 2.53–1.94 (m, 10 H), 1.67–1.38 (m, 6 H), 0.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 168.3, 148.2, 146.0, 140.2, 138.3, 137.9, 135.6, 126.6, 126.2, 126.0, 122.0, 121.5, 118.6, 76.8, 50.5, 48.0, 44.2, 39.8, 38.0, 35.9, 31.6, 29.5, 26.4, 25.8, 21.7, 21.4, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 2927, 2858, 2364, 1764, 1736, 1623, 1493, 1381, 1341, 1307, 1285, 1224, 1153, 1056, 1007, 955, 917, 839, 779, 754 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{29}H_{31}O_5$ $[M + H]^+$ 459.2171, found 459.2171.

Typical Procedure for the Synthesis of Isocoumarins 6a and 6b: To an oven-dried sealed tube charged with (1*H*-benzo[*d*]imidazol-1-yl)(phenyl)methanone (**1a**) (44.4 mg, 0.2 mmol, 100 mol-%), $[RhCp^*Cl_2]_2$ (3.1 mg, 0.005 mmol, 2.5 mol-%) and $Cu(OAc)_2{\cdot}H_2O$ (79.9 mg, 0.4 mmol, 2 equiv.) in DCE/AcOH (3:1, 1 mL) was added diphenylacetylene (**5a**) (71.2 mg, 0.4 mmol, 200 mol-%) under air at ambient temperature. The reaction mixture was stirred at 130 °C for 14 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with water. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc, 12:1) to afford **6a** (54.3 mg) in 91 % yield.

3,4-Diphenyl-1*H*-isochromen-1-one (6a): 54.3 mg (91 %); pale yellow solid; m.p. 168.7–171.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 8.0 Hz, 1 H), 7.70 (t, *J* = 6.8 Hz, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 7.49–7.46 (m, 3 H), 7.42–7.39 (m, 2 H), 7.34–7.30 (m, 2 H), 7.29–7.26 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 150.9, 138.8, 134.6, 134.2, 132.8, 131.2, 129.5, 129.1, 129.0, 128.9, 128.1, 128.0, 127.8, 125.3, 120.4, 116.8 ppm. IR (KBr): $\tilde{\nu}$ = 3057, 3024, 2925, 1956, 1734, 1722, 1604, 1561, 1480, 1444, 1315, 1241, 1195, 1112, 1076, 1023, 961, 920, 779, 760 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{21}H_{15}O_2$ $[M + H]^+$ 299.1072, found 299.1071.

3,4-Dipropyl-1*H*-isochromen-1-one (6b): 27.6 mg (60 %); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.72 (t, *J* = 7.2 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H), 2.58 (q, *J* = 8.0 Hz, 4 H), 1.77–1.72 (m, 2 H), 1.62–1.56 (m, 2 H), 1.03 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 154.1, 138.0, 134.5, 129.8, 127.0, 122.6, 120.8, 112.2, 32.7, 28.1, 22.8, 21.1, 14.1, 13.8 ppm. IR (KBr): $\tilde{\nu}$ = 2960, 2931, 2871, 1719, 1638, 1604, 1563, 1485, 1455, 1318, 1245, 1182, 1148, 1114, 1079, 1025, 888, 767 cm^{-1}. HRMS (Orbitrap, ESI): calcd. for $C_{15}H_{19}O_2$ $[M + H]^+$ 231.1357, found 231.1356.

Ethyl (*E*)-3-[2-(Dimethylcarbamoyl)phenyl]acrylate (8a): 37.0 mg (75 %); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.60 (m, 2 H), 7.39–7.37 (m, 2 H), 7.27–7.26 (m, 1 H), 6.40 (d, *J* = 15.6 Hz, 1 H), 4.22 (q, *J* = 6.8 Hz, 2 H), 3.14 (s, 3 H), 2.76 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 166.4, 140.8, 137.3, 131.1, 130.1, 129.2, 126.8, 126.7, 120.6, 60.5, 38.5, 34.8, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 3063, 2925, 2855, 1709, 1630, 1503, 1445, 1392, 1366, 1314, 1266, 1175, 1108, 1068, 1037, 978 cm^{-1}. HRMS (quadrupole, EI): calcd. for $C_{14}H_{17}NO_3$ $[M]^+$ 247.1208, found 247.1204.

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C–H Activation

The site-selective rhodium(III)-catalyzed C–H olefination and cyclization of benzamides with various alkenes by C–H bond activation is described. These transformations allow the generation of an array of C3-substituted phthalides known to be crucial scaffolds of biologically active compounds.

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