Article

Carboxylate-directed Addition of Aromatic C-H Bond to Aromatic Aldehydes under Ruthenium Catalysis

Hiroki Miura, Sachie Terajima, and Tetsuya Shishido

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.8b00680 • Publication Date (Web): 31 May 2018

Carboxylate-directed Addition of Aromatic C-H Bond to Aromatic Aldehydes under Ruthenium Catalysis

Hiroki Miura[a,b,c*], Sachie Terajima[a], Tetsuya Shishido[a,b,c*]

[a] Department of Applied Chemistry, Graduate School of Urban Environmental Sciences, Tokyo Metropolitan University, 1-1 Minami-Osawa, Hachioji, Tokyo 192-0397, Japan

[b] Research Center for Hydrogen Energy-based Society, Tokyo Metropolitan University, 1-1 Minami-Osawa, Hachioji, Tokyo 192-0397, Japan

[c] Elements Strategy Initiative for Catalysts & Batteries, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8520, Japan

* Corresponding author: Tel: +81-42-677-2851 Fax: +81-42-677-2850 (H. Miura)

* Corresponding author: Tel: +81-42-677-2850 Fax: +81-42-677-2850 (T. Shishido)

E-mail address: miura-hiroki@tmu.ac.jp (H. Miura)

E-mail address: shishido-tetsuya@tmu.ac.jp (T. Shishido)

Abstract

We report that ruthenium complexes effectively catalyzed the carboxylate-directed addition of aromatic C-H bonds to aldehydes. The reactions of aromatic acids with a variety of aromatic aldehydes including unactivated ones proceeded efficiently to give the corresponding isobenzofuranone derivatives in high yields. The combination of ruthenium(II) complexes with tricyclohexylphosphine led to highly nucleophilic aryl-metal species, which enabled versatile [3+2] cycloaddition in the absence of a Lewis acid. This paper also demonstrates the application of supported ruthenium catalysts to the title reaction.

Keywords

Ruthenium, C-H activation, hydroxyalkylation, aromatic acids, aldehydes, isobenzofuranones

1. Introduction

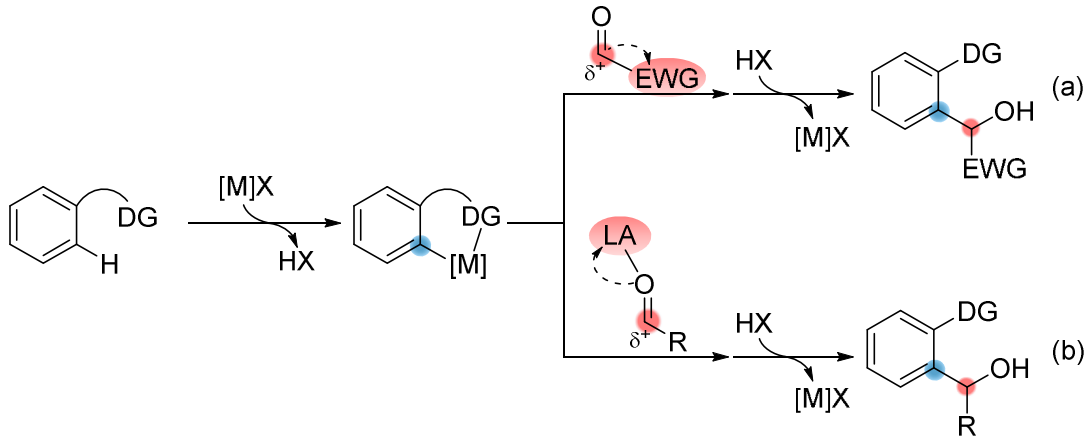
The addition of an organometallic reagent to a carbon electrophile is one of the most important tools for forming new C-C bonds. Grignard and related alkaline metallic reagents are most commonly used for the lab-scale syntheses of organic compounds due to their ease of preparation from organohalides. However, these stoichiometric reactions form undesired metallic wastes, which reduces their environmental compatibility. In contrast, direct metalation of an aromatic C-H bond with the aid of chelating functionalities has recently been regarded as a general method for the generation of aryl-metal species, and subsequent functionalization by treatment with electrophiles and regeneration of an active metallic reagent enables *catalytic* C-C bond formation.[1] These concepts revolutionized the field of arene functionalization since they avoid not only the formation of unwanted metallic waste but also preactivation of the starting materials. In this context, direct aromatic C-H addition to a carbonyl moiety by transition-metal catalysts can access step- and atom-economical hydroxyalkylation.[2–6] However, there are still remain some problems to be solved in this area. The potentially low nucleophilicity of aryl-transition metal species requires highly electrophilic coupling partners to achieve satisfactory catalytic turnover. In fact, substrates with an electron-withdrawing substituent on the carbonyl moiety have mainly been used in examples of catalytic C-H hydroxyalkylation,[7–12] which reduces the generality of this strategy (Scheme 1(a)). Alternatively, the addition of Lewis acids to enhance the electrophilicity of the carbonyl moiety improves the reaction efficiency and substrate scope (Scheme 1(b)).[13,14] Nevertheless, the use of excess (more than 0.5 equivalents to substrate) of toxic metals would still be undesirable from the perspective of green chemistry.

On the other hand, much attention has been focused on the use of a carboxylate as a chelating group in C-H activation,[15] since this ubiquitous functionality can be introduced into benzo-fused heterocycles by subsequent intramolecular cyclization.[16–18] It can also be readily removed from the products under transition-metal catalysis.[19] However, the

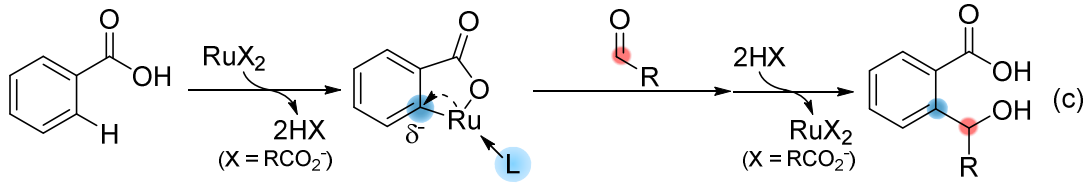
electron-withdrawing nature of the carboxylate group decreases the rate of electrophilic C-H metalation and the nucleophilicity of the generated aryl-metal species. Li's group reported a pioneering work on the Rh-catalyzed [3+2] cycloaddition of aromatic acid with aldehyde,[8] which realized the atom- and step-economical synthesis of isobenzofuranones, which are a ubiquitous framework in natural products showing a broad range of bioactivity.[20] Unfortunately, this catalysis is still severely limited with respect to the scope of aldehyde. On the other hand, ruthenium complexes have been used as one of the most effective catalysts for aromatic C-H functionalization.[21,22] Particularly, $[RuCl_2(p\text{-cymene})]_2$ showed high utility in this synthetic method with the aid of bases. Very recently, the groups of Kim[11], Ding[12] and Zhou[14] independently demonstrated Ru-catalyzed addition of aromatic C-H bond to aldehydes. In these cases, however, the applicable aldehydes were limited to activated or less-hindered ones. These facts suggest that a novel strategy should be developed to establish a method for efficient C-H addition to C-O multiple bonds with high generality regarding the substrate and high environmental compatibility.

Herein, we report ruthenium-catalyzed the addition of an aromatic C-H bond to aldehydes. A series of aromatic aldehydes, including unactivated ones, could be used under Ru catalysis in the absence of a Lewis acid to give the corresponding isobenzofuranones in high yield. Kinetic studies revealed that the combination of Ru catalysts with tricyclohexylphosphine generated aryl-metal species with high nucleophilicity, which promoted the insertion of a carbonyl moiety into an aryl-metal bond (Scheme 1(c)).

Preceding work: Increasing electrophilicity strategy



This work: Increasing nucleophilicity strategy

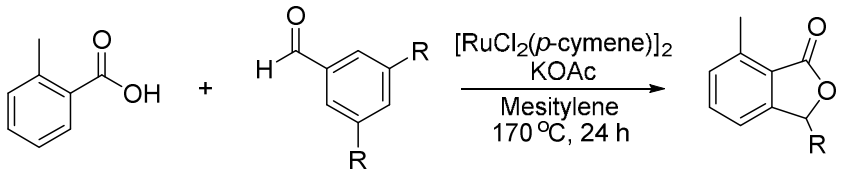


Scheme 1. Transition metal-catalyzed C-H addition to C=O bond.

2. Results and discussion

Initially, the catalytic effect of a ruthenium complex toward the carboxylate-directed C-H addition to an activated carbonyl moiety was investigated (Table 1). The combination of *o*-toluic acid (**1a**) and an aromatic aldehyde bearing a bistrifluoromethyl group (**2a**) in the presence of a catalytic amount of base underwent functionalization of an aromatic C-H bond and subsequent intramolecular cyclization to give isobenzofuranone **3aa** as a sole product in a moderate yield (entry 1). No reaction took place in the absence of KOAc (entry 2). The addition of $AgSbF_6$ significantly retarded the progress of the reaction (entry 3). Zinc salts as a Lewis acid did not affect positively the present Ru catalysis (entries 4 and 5). In contrast, a phosphine ligand enhanced the activity of Ru catalysts, and the reaction in the presence of PPh_3 gave **3aa** in an improved yield (entry 6). Screening of the ligand showed that PCy_3 was the ligand of choice for the present Ru catalysis to provide **3aa** in excellent yield (entry 7). Air-stable HBF_4 salt of PCy_3 was also effective for the present catalytic reaction (entry 8). In contrast, the addition of $P(C_6F_5)_3$ did not result in the formation of any **3aa** (entry 13), indicating that strong electron donation from phosphine to the Ru center was crucial for the present reaction. With the Ru/PCy_3 catalytic system, the reaction of unactivated aldehyde (**2b**) was carried out. Although the desired isobenzofuranone **3ab** was obtained in only a very low yield in the reaction under a diluted condition (entry 14), the reaction conducted under a higher concentration of a Ru catalyst and **2b** gave **3ab** in an excellent yield of 96% (entry 17). Despite the fact that organometallic reagents with high nucleophilicity generally exhibit poor water-tolerance, Ru catalysts often exhibit the high utility even for the reaction in aqueous media.[23–25] The present Ru/PCy_3 system also showed high activity for the catalytic C-H hydroxyalkylation even in the presence of 0.1 mL of water (entry 18). The reaction also proceeded at 150 ^{o}C to give **3ab** in good yield (entry 19), and an improved yield was obtained under further concentrated condition (entry 20).

Table 1. Optimization of reaction conditions[a]



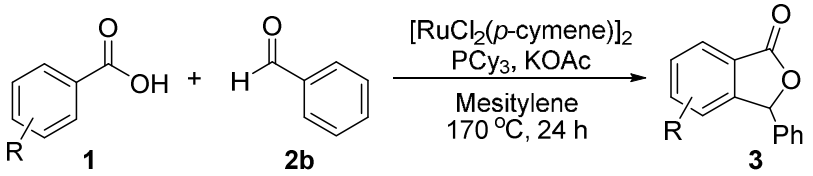
1a **2a** (R = CF_3) **2b** (R = H) **3aa** (R = 3,5-CF_3-C_6H_3) **3ab** (R = Ph)

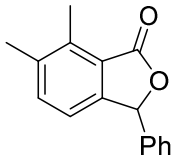
entry	additive	aldehyde / eq. to **1a**	product	Yield (%)[b]
1	-	**2a** / 1.5	**3aa**	30
2[c]	-	**2a** / 1.5	**3aa**	0
3[d]	$AgSbF_6$	**2a** / 1.5	**3aa**	4
4[d]	$ZnCl_2$	**2a** / 1.5	**3aa**	26
5[d]	$ZnBr_2$	**2a** / 1.5	**3aa**	6
6	PPh_3	**2a** / 1.5	**3aa**	52
7	PCy_3	**2a** / 1.5	**3aa**	99
8	PCy_3•HBF_4	**2a** / 1.5	**3aa**	85
9	P^nBu_3•HBF_4	**2a** / 1.5	**3aa**	37
10	P^tBu_3•HBF_4	**2a** / 1.5	**3aa**	35
11	XPhos	**2a** / 1.5	**3aa**	61
12	SPhos	**2a** / 1.5	**3aa**	2
13	$P(C_6F_5)_3$	**2a** / 1.5	**3aa**	0
14	PCy_3	**2b** / 1.5	**3ab**	7
15	PCy_3	**2b** / 2.0	**3ab**	31
16	PCy_3	**2b** / 3.0	**3ab**	47
17[e]	PCy_3	**2b** / 3.0	**3ab**	96
18[e,f]	PCy_3	**2b** / 3.0	**3ab**	86
19[e,g]	PCy_3	**2b** / 3.0	**3ab**	76
20[g,h]	PCy_3	**2b** / 3.0	**3ab**	90

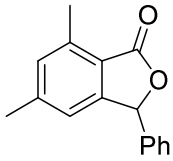
[a]Reaction conditions: **1a** (0.50 mmol), **2** (1.5–3.0 eq. to **1a**), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), KOAc (0.15 mmol), additive (0.05 mmol), mesitylene (1.0 mL), at 170 °C, 24 h, under Ar. [b]Yields were determined by GLC by using *o*-terphenyl as internal standard. [c]Reaction without KOAc. [d]Additive (0.15 mmol) was used. [e]Mesitylene (0.5 mL) was used. [f]Water (0.1 mL) was added to the reaction mixture. [g]Reaction at 150 °C. [h]Mesitylene (0.25 mL) was used.

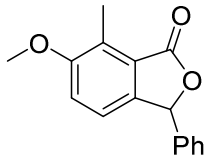
With the present Ru/PCy_3 catalytic system in hand, the scope of aromatic acid in the reaction of unactivated aldehyde **2b** was investigated (Table 2). The reactions of a series of *ortho* methyl-substituted aromatic acids (**1b**–**1e**) with unactivated aldehyde (**2b**) proceeded efficiently to give the corresponding isoindolinones (**3bb–3eb**) in good to excellent yields. 1-Naphthoic acid participated as a good coupling partner to produce **3fb** in a good yield. The reactions of *meta*-substituted aromatic acids also took place to afford **3gb** and **3hb** in excellent yields. In these cases, functionalization predominantly occurred on the less-hindered *ortho* C-H bond. Both *para*-substituted aromatic acids and the simplest aromatic acid, benzoic acid, were also converted efficiently to **3ib–3mb**. The double-functionalization of aromatic C-H bonds was not observed under the present Ru catalysis. Furthermore, *ortho*-fluoro-substituted isobenzofuranone **3ob** was obtained in a satisfactory yield. Next, the generality of aldehyde in the Ru/PCy_3-catalyzed aromatic C-H addition was surveyed (Table 3). As demonstrated in the preceding study, aromatic aldehydes bearing electron-withdrawing groups on benzene rings were efficiently converted to the corresponding isobenzofuranones (**3ac–3ah**) in the reaction with **1a**. Very recently, Gooßen and coworkers reported an elegant study on carboxylate-directed C-H arylation with aryl halide using a similar Ru catalytic system,[26] while the reactive bromo and iodo group on the arene remained intact during the present C-H hydroxyalkylation. Isobenzofuranone with alkenyl and naphthyl group (**3ai** and **3aj**) were obtained in high yield. The most intriguing feature of the present Ru catalysis is reflected in the reaction of aromatic aldehydes with electron-donating groups. The reaction of *para*-tolualdehyde efficiently proceeded to give **3ak** in high yield. Furthermore, the present Ru catalysis was effective even for the reaction of anisaldehydes to provide the corresponding products (**3al–3an**) in high yields. Interestingly, steric hindrance by an *ortho*-methoxy group of aldehyde did not affect the reaction efficiency at all. Unfortunately, the reaction of aliphatic aldehydes such as 1-decanal could not be used in the present catalytic system.

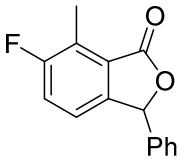
Table 2. Scope of aromatic acid[a]

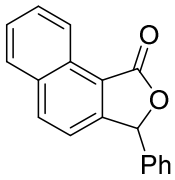


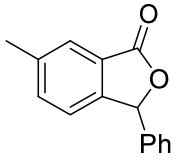

3bb 92%

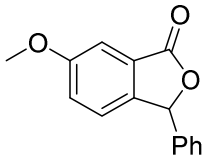

3cb: 66%

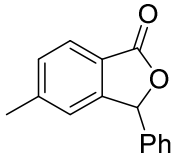

3db: 59%

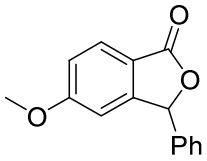

3eb: 92%

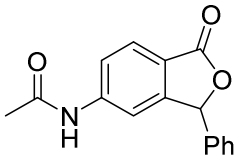

3fb: 66%

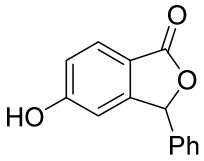

3gb: 88%

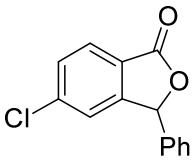

3hb: 93%

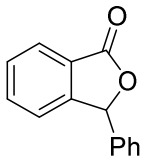

3ib: 84%

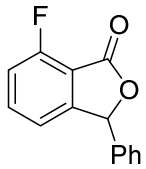

3jb: 89%


3kb: 42%


3lb: 38%

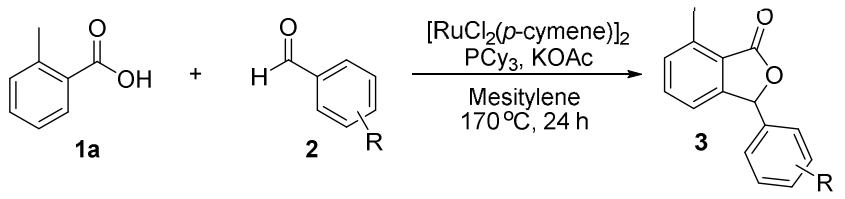

3mb: 43%

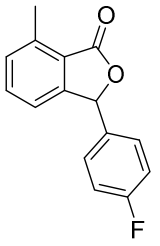

3nb: 95%


3ob: 37%

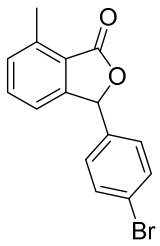
[a] Reaction conditions: **1** (0.50 mmol), **2b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), PCy_3 (0.05 mmol), KOAc (0.15 mmol), mesitylene (0.5 mL), at 170 °C, 24 h, under Ar. Isolated yields are given.

Table 3. Scope of aldehyde[a]

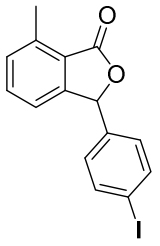




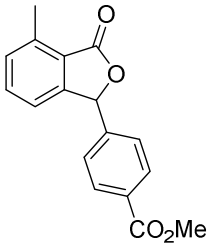
3ac: 87%



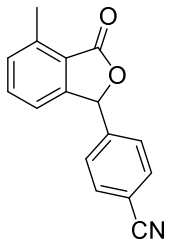
3ad: 96%



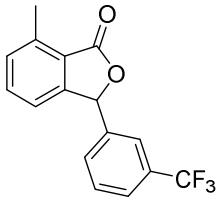
3ae: 63%



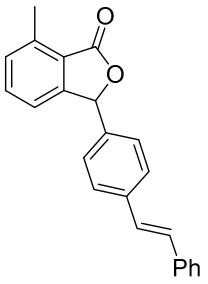
3af: 73%



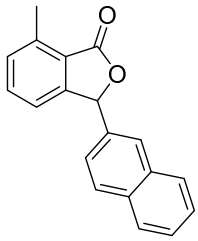
3ag: 34%



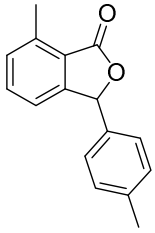
3ah: 87%



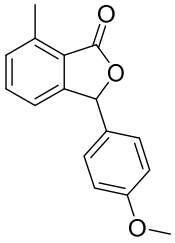
3ai: 47%



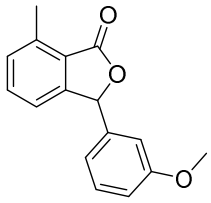
3aj: 77%



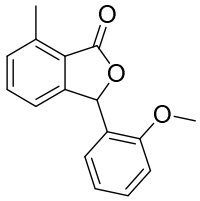
3ak: 74%



3al: 65%



3am: 75%

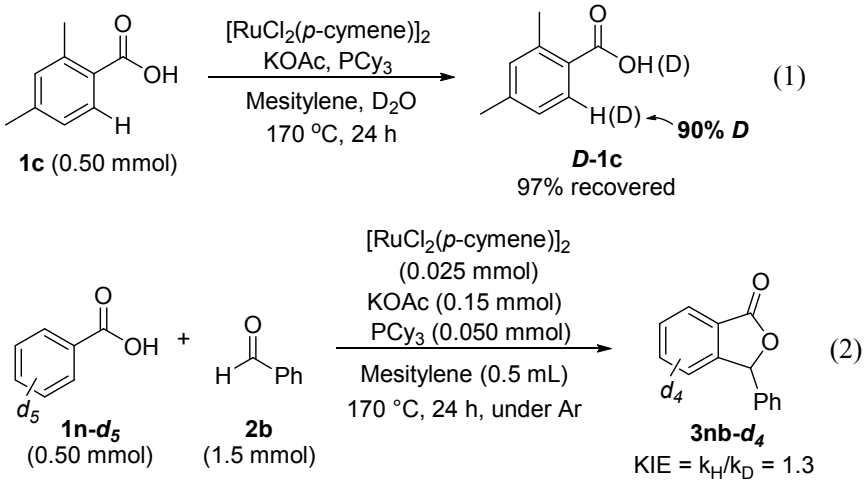


3an: 74%

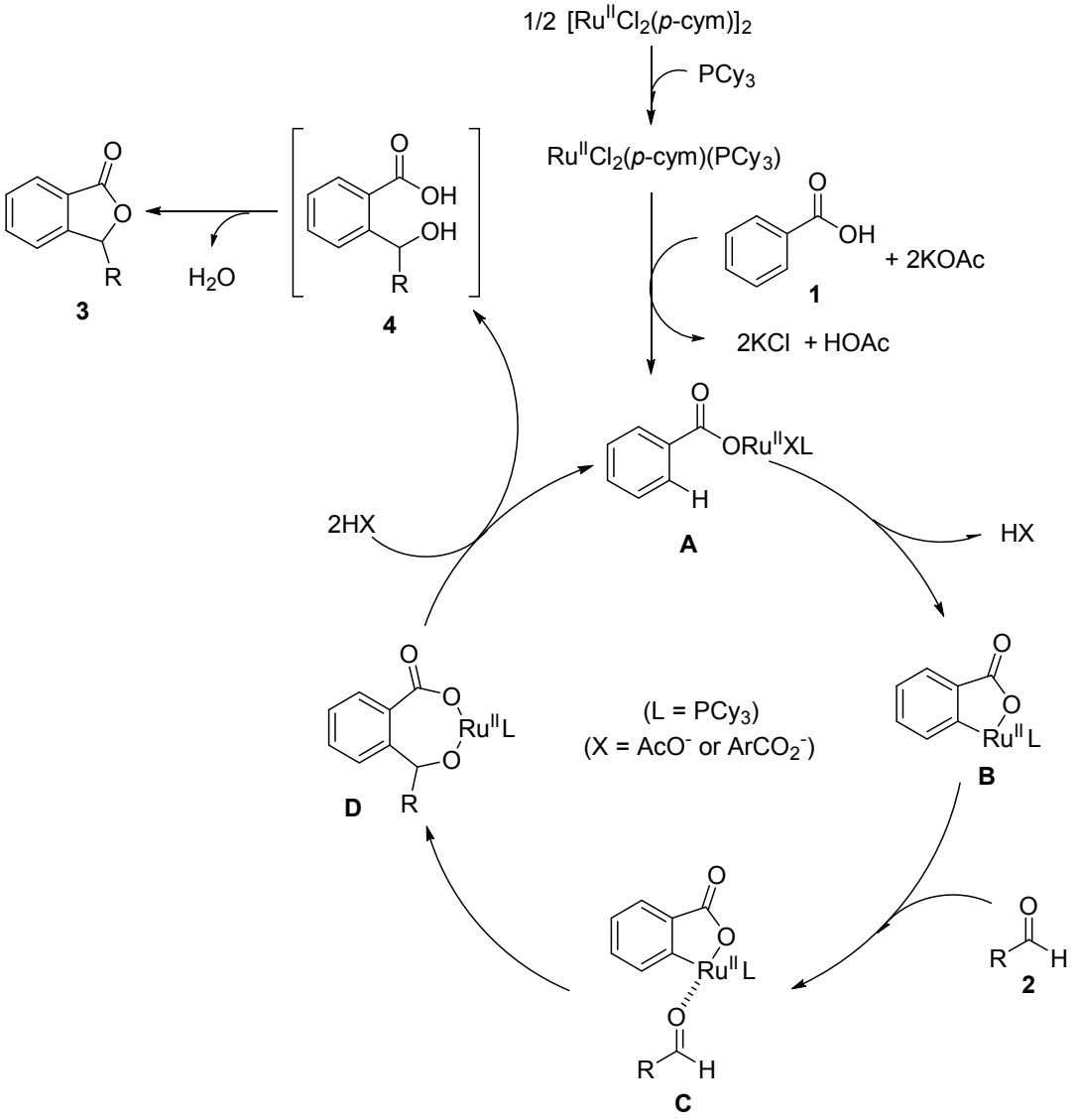
[a] Reaction conditions: **1** (0.50 mmol), **2b** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), PCy_3 (0.05 mmol), KOAc (0.15 mmol), mesitylene (0.25 mL), at 170 °C, 24 h, under Ar. Isolated yields are given.

To learn more about the reaction mechanism, several kinetic studies on the C-H addition to aldehydes were examined (Scheme 2). When **1c** was treated with D_2O in the presence of Ru cat., KOAc and PCy_3, 90% of the deuterium was incorporated at the *ortho*-position of **1c** (Scheme 2, eq. (1)). This clearly indicates that the reaction involves the formation of a ruthenacycle intermediate via carboxylate-directed electrophilic metalation of an aromatic C-H bond. Based on this result as well as the previous literature,[2–8] a plausible mechanism for the reaction under Ru catalysis is depicted in Scheme 3. Initially, the treatment of $[RuCl_2(p\text{-cymene})]_2$ with 2 equiv. of PCy_3 gives mononuclear $RuCl_2(p\text{-cymene})(PCy_3)$.[27] Then, ruthenium benzoate **A** is formed by treatment with potassium acetate. Subsequently, carboxylate-directed *ortho*-ruthenation takes place to give ruthenacycle **B**, which undergoes nucleophilic C-C bond formation to provide ruthenium alkoxide species **D**. Protonation of two Ru-O bonds by acids completes the catalytic cycle while generating *ortho*-hydroxyalkylated aromatic acid. Finally, intramolecular dehydrative cyclization provides isobenzofuranone as a final product. The remarkable effect of the addition of PCy_3 on the catalytic activity should be reflected in the rate-limiting step. The intermolecular kinetic isotope effect as estimated by the reaction of [D5]-benzoic acid (**1k-*d*$_5$**) was found to be 1.3 (Scheme 2, eq. (2)). This suggests that the formation of ruthenacycle via C-H bond cleavage was not involved in the rate-limiting step under the present Ru catalysis,[28-30] which is also supported by the reaction order of zero with respect to the benzoic acid concentration (Figure 1(a)). In sharp contrast, the reaction orders for aldehyde and Ru catalyst were estimated to be 0.8 and 1.3, respectively (Figures 1(b) and 1(c)). This indicates that the nucleophilic addition of aryl-metal species to a carbonyl moiety should be the rate-determining step in the present Ru-catalyzed reaction. In general, Lewis acids are used to increase the electrophilicity of a carbonyl moiety, which promotes coupling with a weakly nucleophilic aryl-metal reagent. In contrast, a highly basic phosphine ligand was helpful for enhancing the reaction rate under the present Ru catalysis. These results therefore suggest that

the coordination of PCy_3 to a Ru center should increase the nucleophilicity of the aryl-metal species generated during the catalytic cycle, which remarkably promote the rate-limiting C-C bond formation step instead of activating aldehyde. Therefore, the generality of aromatic aldehydes and environmental compatibility were improved. Preferential conversion of the aromatic acid with an electron-donating substituent in the intermolecular competition reaction (Scheme 4) implies that electron-rich arenes are advantageous not only for the rapid generation of ruthenacycle via electrophilic C-H metalation, but also for enhancing the reactivity of aryl-metal nucleophiles.



Scheme 2. Deuterium labeling experiments



Scheme 3. A plausible reaction mechanism

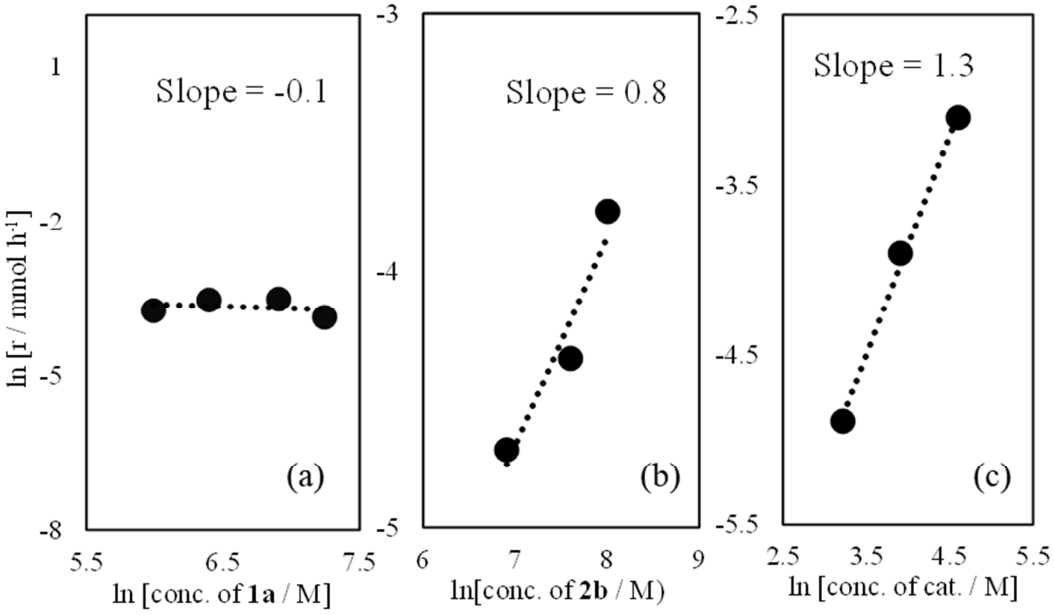
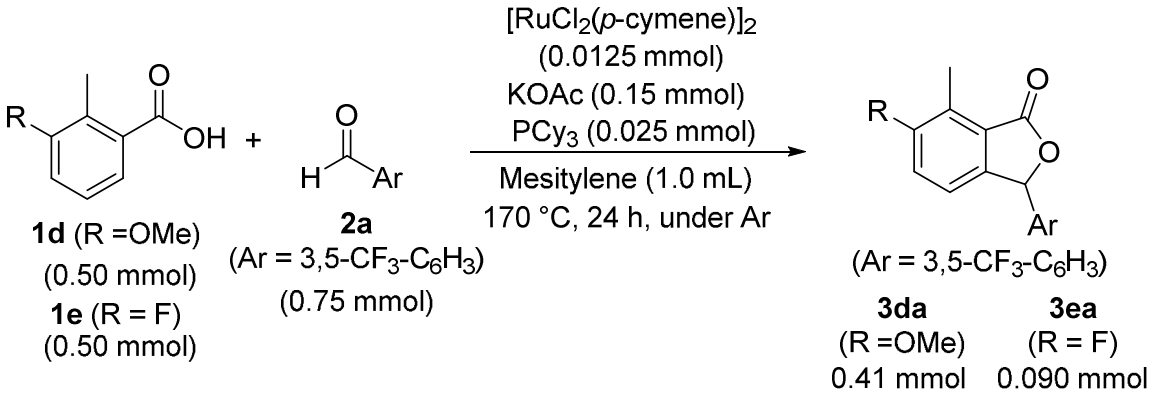
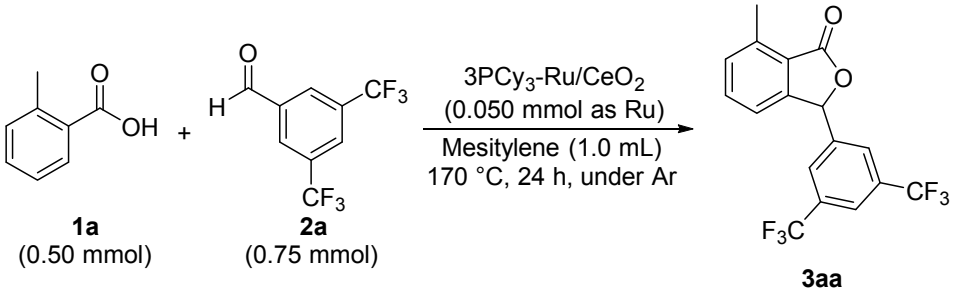


Figure 1. Effects of concentration of **1a**, **2b** and Ru cat. on reaction-rate



Scheme 4. Intermolecular competition experiment

On the other hand, considerable attention has recently focused on the use of supported metal catalysts for organic transformations from the viewpoint of green chemistry due to the ease of separation from the reaction mixture and recycling of the catalyst.[31–34] In the course of our study on the development of supported Ru catalysts that are effective for organic synthesis,[35–39] we demonstrated that phosphine-modified Ru/CeO_2 catalysts efficiently promoted various kinds of C-C bond-forming reactions involving C-H bond activation.[40–42] Fortunately, we found that Ru/CeO_2 catalysts modified with 3 equivalents of PCy_3 to Ru ($3PCy_3$-Ru/CeO_2) promoted the coupling reaction of **1a** with **2a** to give **3aa** in a good yield (Scheme 5). Notably, the supported Ru catalyst required no external base for the reaction to proceed thanks to the basic surface of CeO_2. Furthermore, the solid Ru catalyst could be reused for the reaction to furnish **3aa**. Even though the present supported Ru catalyst still presents some problems concerning the activity and durability of the catalyst and substrate scope, further studies to optimize the catalysts and reaction conditions are expected to lead to a practical synthesis of isobenzofuranones under Ru catalysis.



1a (0.50 mmol) **2a** (0.75 mmol) **3aa**

fresh : 64%
1st reuse : 64%
2nd reuse : 34%

Scheme 5. Supported Ru-catalyzed reaction

3. Conclusion

In summary, we have demonstrated a carboxylate-directed C-H addition to aldehydes under Ru catalysis. The reactions of a series of aromatic aldehydes including unactivated ones in the absence of a Lewis acid proceeded to give isobenzofuranones in an atom-economical and green manner. Moreover, we successfully applied a reusable supported Ru catalyst to C-H hydroxyalkylation. The addition of a highly basic phosphine ligand was crucial for generating aryl-metal species with high nucleophilicity, which promoted the rate-limiting step of the catalytic reaction. Further investigations on the underlying mechanism and the development of novel catalytic reactions using this strategy are underway in our laboratory.

4. Experimental

4.1. Materials

All manipulations were performed under an argon atmosphere using standard Schlenk techniques. $[RuCl_2(p\text{-cymene})]_2$ (Aldrich), all of the aromatic acids and aldehydes (TCI), sodium salt, mesitylene (Wako), cerium(III) nitrate hexahydrate, potassium hydroxide, and tetrahydrofuran (THF; Wako) were obtained commercially and used without further purification. Cerium dioxide (CeO_2) was prepared by treating a solution of cerium(III) nitrate hexahydrate (12.6 g, 29 mmol) in 400 mL of deionized water with 40 mL of 3M KOH aqueous solution with stirring for 1 h at room temperature. The resulting precipitates were collected by centrifugation, washed thoroughly with deionized water and then air-dried overnight at 80 ^oC. The product was heated in a box furnace at a rate of 10 $^oC\ min^{-1}$ and maintained at 400 ^oC for 30 min to afford ceria in an excellent ceramic yield. **1k-*d5*** was prepared from bromobenzene-d5 according to the reported literature.[43]

4.2. Preparation of $3PCy_3$-Ru/CeO_2 catalyst

Supported Ru catalysts were prepared through the method reported in our previous literature.[33–37] 1.0 g of a support was added to a solution of $[RuCl_2(p\text{-cymene})]_2$ (0.20 mmol) in 10 mL of methanol in air at 50 ^oC After impregnation, the resulting powder was calcined in air for 30 min to afford the Ru(2.0 wt%)/CeO_2 catalyst. The modification of Ru/CeO_2 catalyst by 3 eq. of PCy_3 to Ru was performed as follows: 250 mg (0.050 mmol as Ru) of Ru/CeO_2 and PCy_3 (0.15 mmol) were heated at 100 °C for 20 min under hydrogen atmosphere (1 atm) without any solvent. Thus prepared catalysts are designated as $3PCy_3$-Ru/ CeO_2.

4.3. Physical and analytical measurements

The products of the catalytic runs were analyzed by GC-MS (Shimadzu GCMS-QP2010, CBP-1 capillary column, i.d. 0.25 mm, length 30 m, at 50–250 ^oC) and gas chromatography

(Shimadzu GC-2014, CBP-10 capillary column, i.d. 0.25 mm, length 30 m at 50–250 ^{o}C). NMR spectra were recorded on a JMN-ECS400 (FT, 400 MHz (^{1}H), 100 MHz (^{13}C)) instrument. Chemical shifts (δ) of ^{1}H and ^{13}C{^{1}H} NMR spectra are referenced to $SiMe_4$. High-resolution mass spectra (FAB) were recorded on a JEOL JMS-700 spectrometer with *m*-nitrobenzyl alcohol (*m*-NBA) as a matrix.

4.4 General Procedure for the carboxylate-directed addition of aromatic C-H bonds to aldehydes in the presence of Ru catalysts

A 20 mL Schlenk tube was charged with aromatic carboxylic acids **1** (0.50 mmol), aldehyde **2** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol), potassium acetate (0.15 mmol), tricyclohexylphosphine (0.050 mmol), and mesitylene (1.0 mL) under an argon atmosphere. The reaction mixture was stirred at 170 ^{o}C for 24 h on a hot stirrer with a cooling block. After the reaction, the reaction solution was concentrated under reduced pressure. The products were isolated by silica-gel column chromatography (hexane/EtOAc).

4.5 Recycling of the $3PCy_3$-Ru/CeO_2 catalyst

After the reaction, the solid was separated from the reaction mixture by centrifugation and washed with 10 mL of diethyl ether, methanol/H_2O (1:1), and again by diethyl ether. The resulting solid was dried overnight at 80 °C and calcined in air at 400 °C for 30 min to recover the Ru/CeO_2 catalyst for reuse. Modification by 3 eq. of PCy_3 to Ru was then performed through the aforementioned procedure to give the $3PCy_3$-Ru/CeO_2 catalyst for reuse.

4.6 Characterization data of the products

3-(3,5-bis(trifluoromethyl)phenyl)-7-methylisobenzofuran-1(*3H*)-one (**3aa**): white solid; yield 94 %, 161 mg (0.50 mmol scale); hexane/EtOAc = 10/1; IR (Zn/Se-ATR, neat) 1745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.90 (s, 1H), 7.78 (s, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.44 (s, 1H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.1. 145.6, 137.3 (d, J_{C-F} = 80 Hz), 131.8, 129.7 (d, J_{C-F} = 43.4 Hz), 128.9, 124.1, 121.4, 120.3, 119.8, 118.7, 117.0, 77.0, 14.6; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{17}H_{11}F_6O_2$ 361.0663, found 361.0670.

7-methyl-3-phenylisobenzofuran-1(*3H*)-one (**3ab**): white solid; yield 67 %, 147 mg (1.0 mmol scale); hexane/EtOAc = 10/1; IR (Zn/Se-ATR, neat) 1756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.49 (t, *J* = 7.4 Hz, 1H), 7.36-7.37 (m, 3H), 7.26-7.29 (m, 3H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.32 (s, 1H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 150.2, 139.6, 136.8, 134.0, 130.9, 129.1, 128.9, 126.9, 123.0, 120.2, 81.8, 17.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{13}O_2$ 225.0916, found 225.0918.

6,7-dimethyl-3-phenylisobenzofuran-1(*3H*)-one (**3bb**) : white solid; yield 92 %, 108 mg (0.50 mmol scale); hexane/EtOAc = 10/1; IR (Zn/Se-ATR, neat) 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.35-7.39 (m, 4H), 7.26-7.28 (m, 2H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.27 (s, 1H), 2.69 (s, 3H), 2.36 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 148.0, 138.5, 138.1, 137.1, 135.6, 129.0, 128.8, 126.9, 122.9, 119.6, 81.1, 19.2, 13.3; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{16}H_{15}O_2$ 239.1072, found 239.1067.

5,7-dimethyl-3-phenylisobenzofuran-1(*3H*)-one (**3cb**) :yellow oil ; yield 66 %, 78.5 mg (0.50 mmol scale); hexane/EtOAc = 10/1; IR (Zn/Se-ATR, neat) 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.36-7.38 (m, 3H), 7.26-7.29 (m, 2H), 7.09 (s, 1H), 6.89 (s, 1H), 6.26 (s, 1H),

2.69 (s, 3H), 2.37 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 150.8, 145.2, 139.2, 137.0, 132.0, 129.0, 128.8, 126.9, 120.5, 120.4, 81.6, 21.9, 17.3; HRMS (FAB) m/z $[M - H]^-$ calcd for $C_{16}H_{13}O_2$ 237.0921, found 237.0931.

6-methoxy-7-methyl-3-phenylisobenzofuran-1(3*H*)-one (**3db**) : white solid ; yield 59 %, 74.7 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.35-7.36 (m, 3H), 7.26-7.28 (m, 2H), 7.04-7.10 (m, 2H), 6.26 (s, 1H), 3.87 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 158.3, 141.4, 137.3, 129.0, 128.8, 127.9, 126.9, 124.0, 120.3, 116.1, 81.2, 56.2. 9.9; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{16}H_{15}O_3$ 255.1021, found 255.1022.

6-fluoro-7-methyl-3-phenylisobenzofuran-1(*3H*)-one (**3eb**) : yellow solid ; yield 92 %, 111 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.36-7.38 (m, 3H), 7.25-7.29 (m, 3H), 7.08 (dd, $J_{C\text{-}F}$ = 4.2 Hz, 1H), 6.30 (s, 1H), 2.66 (d, $J_{H\text{-}F}$ = 2.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.7, 161.4 (d, $J_{C\text{-}F}$ = 246 Hz), 145.4, 136.4, 129.3, 1289.0, 126.9, 126.0 (d, $J_{C\text{-}F}$ = 20 Hz), 124.9 (d, $J_{C\text{-}F}$ = 6.5 Hz), 121.4 (d, $J_{C\text{-}F}$ = 25 Hz), 121.1 (d, $J_{C\text{-}F}$ = 8.7 Hz), 81.4, 9.1 (d, $J_{C\text{-}F}$ = 3.7 Hz) ; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{12}FO_2$ 243.0821, found 243.0810.

3-phenylnaphtho[1,2-*c*]furan-1(*3H*)-one (**3fb**) : white solid ; yield 66 %, 84.5 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.07 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 7.2 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.30-7.39 (m, 6H), 6.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ170.8, 151.3, 136.0, 135.7, 133.4, 129.3, 129.2, 129.0, 128.5, 127.5, 127.2, 127.0, 123.7, 119.7, 119.3, 82.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{18}H_{13}O_2$ 261.0916, found 261.0925.

6-methyl-3-phenylisobenzofuran-1(*3H*)-one (**3gb**) : white solid ; yield 88 %, 95.8 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.75 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.36-7.37 (m, 3H), 7.26-7.28 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 6.37 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 147.1, 139.6, 136.6, 135.5, 129.2, 128.9, 126.9, 125.7, 125.5, 122.8, 122.5, 82.6, 21.3; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{13}O_2$ 225.0916, found 225.0907.

6-methoxy-3-phenylisobenzofuran-1(*3H*)-one (**3hb**) : white solid ; yield 93 %, 108 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.36-7.38 (m, 4H), 7.25-7.27 (m, 2H), 7.20 (d, *J* = 1.6 Hz, 2H), 6.35 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ170.6, 160.8, 142.1, 136.6, 134.3, 129.2, 128.9, 1267.0, 123.7, 123.3, 107.2, 82.6, 55.8 ; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{13}O_3$ 241.0865, found 241.0867.

5-methyl-3-phenylisobenzofuran-1(*3H*)-one (**3ib**) : white solid ; yield 84 %, 94.6 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.34-7.39 (m, 4H), 7.26-7.29 (m, 2H), 7.11 (s, 1H), 6.34 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 150.2, 145.6, 136.6, 130.5, 129.2, 128.9, 126.9, 125.4, 123.1, 122.9, 82.4, 22.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{13}O_2$ 225.0916, found 225.0911.

5-methoxy-3-phenylisobenzofuran-1(*3H*)-one (**3jb**) : white solid ; yield 89 %, 109 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.85 (d, *J* = 8.4 Hz, 1H), 7.37-7.39 (m, 3H), 7.26-7.29 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.72 (s, 1H), 6.31 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ

170.2, 164.9, 152.5, 136.5, 129.2, 129.0, 127.1, 127.0, 117.8, 116.9, 106.6, 82.1, 55.8; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{13}O_3$ 241.0865, found 241.0868.

N-(1-oxo-3-phenyl-1,3-dihydroisobenzofuran-5-yl)acetamide (**3kb**) : yellow solid ; yield 42%, 50.3 mg (0.50 mmol scale); hexane/EtOAc = 1/1; IR (Zn/Se-ATR, neat) 1760 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm) δ 7.45 (t, *J* = 7.6 Hz, 1H), 7.29-7.33 (m, 1H), 7.22-7.26 (m, 2H), 7.06-7.08 (m, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.80 (s, 1H), 3.92 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO, ppm) δ 169.6, 169.3, 151.8, 145.0, 137.1, 129.1, 129.0, 126.9, 126.0, 119.9, 118.6, 111.7, 81.5, 24.3; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{16}H_{14}NO_3$ 268.0974, found 268.0984.

5-hydroxy-3-phenylisobenzofuran-1(3*H*)-one (**3lb**) : brown solid ; yield 38%, 44.4 mg (0.50 mmol scale); hexane/EtOAc = 2/1; IR (Zn/Se-ATR, neat) 1760 cm^{-1}; ^1H NMR (400 MHz, DMSO, ppm) δ 10.77 (s (br), 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.41-7.45 (m, 3H), 7.33-7.35 (m, 2H), 7.01 (dd, *J* = 8.4 and 2.0 Hz,1H), 6.72 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (100 MHz, DMSO, ppm) δ 1169.7, 163.5, 153.0, 137.4, 129.0, 127.0, 126.7, 117.7, 115.2, 108.7, 80.9; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{11}O_3$ 227.0708, found 227.0705.

5-chloro-3-phenylisobenzofuran-1(3*H*)-one (**3mb**) : brown solid ; yield 43 %, 53.4 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.30-7.32 (m, 3H), 7.22-7.23 (m, 1H), 7.17-7.20 (m, 2H), 6.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.3, 151.2, 141.0, 135.6, 130.1, 129.5, 129.1, 126.8, 126.7, 124.0, 123.2, 82.1; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{10}ClO_2$ 245.0369, found 245.0378.

3-phenylisobenzofuran-1(*3H*)-one (**3nb**) : white solid ; yield 95 %, 102 mg (0.50 mmol

scale); hexane/EtOAc = 10/1; IR (Zn/Se-ATR, neat) 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.37-7.39 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.26-7.29 (m, 2H), 6.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.5, 149.6, 136.4, 134.3, 129.3, 129.3, 129.0, 127.0, 125.6, 125.5, 122.8, 82.7; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{11}O_2$ 211.0759, found 211.0749.

7-fluoro-3-phenylisobenzofuran-1(*3H*)-one (**3ob**) : yellow solid ; yield 37 %, 43.3 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61-7.66 (m, 1H), 7.38-7.40 (m, 3H), 7.27-7.29 (m, 2H), 7.18 (t, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.5, 159.4 (d, $J_{C\text{-}F}$ = 264 Hz), 152.2, 136.9 (d, $J_{C\text{-}F}$ = 7.8 Hz), 135.8, 129.5, 129.0, 126.9, 118.8 (d, $J_{C\text{-}F}$ = 4.2 Hz), 116.3(d, $J_{C\text{-}F}$ = 18.5 Hz), 113.4 (d, $J_{C\text{-}F}$ = 14.3 Hz), 82.3 ; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{14}H_{10}FO_2$ 229.0655, found 229.0661.

3-(4-fluorophenyl)-7-methylisobenzofuran-1(*3H*)-one (**3ac**) : yellow solid ; yield 87 %, 100 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.51 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.24-7.27 (m, 2H), 7.03-7.11 (m, 3H), 6.31 (s, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.4, 163.1 (d, $J_{C\text{-}F}$ = 271 Hz), 149.9, 139.7, 134.1, 132.6 (d, $J_{C\text{-}F}$ = 3.1 Hz), 131.0, 129.0 (d, $J_{C\text{-}F}$ = 8.5 Hz), 123.0, 120.1, 115.9 (d, $J_{C\text{-}F}$ = 21.8 Hz), 81.1, 17.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{12}FO_2$ 243.0821, found 243.0810.

3-(4-bromophenyl)-7-methylisobenzofuran-1(*3H*)-one (**3ad**) : yellow solid ; yield 96 %, 142 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.49-7.52 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.28 (s, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ

170.4, 149.6, 139.8, 135.9, 134.1, 132.1, 131.1, 128.6, 123.2, 122.8, 120.0, 80.9, 17.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{12}BrO_2$ 303.0021, found 303.0022.

3-(4-iodophenyl)-7-methylisobenzofuran-1(3*H*)-one (**3ae**) : brown solid ; yield 63 %, 118.5 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ7.70 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.26 (s, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.4, 149.6, 139.8, 138.0, 136.5, 134.1, 131.1, 128.7, 122.8, 120.0, 95.0, 81.0, 17.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{15}H_{12}IO_2$ 350.9882, found 350.9897.

methyl 4-(4-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)benzoate (**3af**) : white solid ; yield 73 %, 101 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.37 (s, 1H), 3.92 (s, 3H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.4, 166.4, 149.6, 141.7, 139.9, 134.2, 131.2, 130.8, 130.2, 126.6, 122.7, 120.0, 80.9, 52.3, 17.4; HRMS (FAB) m/z $[M - H]^-$ calcd for $C_{17}H_{13}O_4$ 281.0819, found 281.0813.

4-(4-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)benzonitrile (**3ag**) : yellow solid ; yield 34 %, 43.8 mg (0.50 mmol scale); hexane/EtOAc = 3/1; IR (Zn/Se-ATR, neat) 1760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.69 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.38 (s, 1H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.1, 149.0, 142.0, 140.1, 134.3, 132.7, 131.4, 127.3, 122.5, 119.9, 118.2, 112.9, 80.3, 17.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{16}H_{12}NO_2$ 250.0868, found 250.0860.

7-methyl-3-(3-(trifluoromethyl)phenyl)isobenzofuran-1(3*H*)-one (**3ah**) : yellow solid ; yield 97 %, 141.6 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.63 (d, J = 7.6 Hz, 1H), 7.57 (s, 1H), 7.50-7.54 (m, 3H), 7.33 (d, J = 7.2 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.38 (s, 1H), 2.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.3, 149.3, 140.0, 138.0, 134.3, 131.5, 131.3, 131.2, 130.2, 129.5, 126.0 (d, J_{C-F} = 3.5 Hz), 123.7 (q, J_{C-F} = 3.7 Hz), 122.8, 120.0, 80.8, 17.4 ; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{16}H_{15}O_3$ 293.0789, found 293.0778.

(*E*)-7-methyl-3-(4-styrylphenyl)isobenzofuran-1(3*H*)-one (**3ai**) : yellow; yield 47 %, 77.0 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ7.48-7.52 (m, 5H), 7.36 (t, J = 8.0 Hz, 2H), 7.23-7.30 (m, 4H), 7.08-7.14 (m, 3H), 6.32 (s, 1H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 150.1, 139.7, 138.2, 136.9, 135.8, 134.0, 130.9, 129.6, 128.7, 127.9, 127.7, 127.4, 126.9, 126.6, 123.0, 120.5, 81.6, 17.4; HRMS (FAB) m/z $[M]^+$ calcd for $C_{23}H_{18}O_2$ 326.1307, found 326.1311.

7-methyl-3-(naphthalen-2-yl)isobenzofuran-1(*3H*)-one (**3aj**) : yellow solid ; yield 77 %, 100 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.81-7.84 (m, 4H), 7.46-7.52 (m, 3H), 7.29 (d, J = 7.6 Hz, 1H), 7.24-7.25 (m, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.48 (s, 1H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.8, 150.2, 139.7, 134.1, 134.0, 133.5, 133.0, 131.0, 129.0, 128.0, 127.8, 126.7, 126.6, 123.8, 123.0, 120.2, 82.0, 17.5; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{19}H_{15}O_2$ 275.1072, found 275.1063.

7-methyl-3-(p-tolyl)isobenzofuran-1(*3H*)-one (**3ak**) : yellow oil ; yield 74 %, 85.0 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1755 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$, ppm) δ 7.48 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.14-7.19 (m, 4H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.30 (s, 1H), 2.74 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 150.3, 139.5, 139.1, 133.9, 133.8, 130.8, 129.5, 127.0, 123.1, 120.2, 81.8, 21.2, 17.4; HRMS (FAB) m/z $[M - H]^-$ calcd for $C_{16}H_{13}O_2$ 237.0921, found 237.0931.

3-(4-methoxyphenyl)-7-methylisobenzofuran-1(*3H*)-one (**3al**) : white solid ; yield 65 %, 80.0 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.49 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.16-7.18 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.87-6.89 (m, 2H), 6.29 (s, 1H), 3.80 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 160.2, 153.5, 150.2, 139.5, 133.9, 130.8, 128.7, 123.2, 120.2, 114.2, 81.7, 55.2, 17.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{16}H_{15}O_3$ 255.1021, found 255.1022.

3-(3-methoxyphenyl)-7-methylisobenzofuran-1(*3H*)-one (**3am**) : white solid ; yield 75 %, 91.0 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.49 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.87-6.89 (m, 2H), 6.79 (s, 1H), 6.29 (s, 1H), 3.78 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7,159.9, 150.1, 139.6, 138.3, 134.0, 130.9, 130.0, 122.8, 120.1, 119.1, 114.5, 112.3, 81.6, 55.3, 17.4; HRMS (FAB) m/z [M] calcd for $C_{16}H_{14}O_3$ 254.0943, found 254.0942.

3-(2-methoxyphenyl)-7-methylisobenzofuran-1(*3H*)-one (**3an**) : yellow solid ; yield 74 %, 87.4 mg (0.50 mmol scale); hexane/EtOAc = 5/1; IR (Zn/Se-ATR, neat) 1760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.45 (t, *J* = 7.6 Hz, 1H), 7.29-7.33 (m, 1H), 7.22-7.26 (m, 2H), 7.06-7.08 (m, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.80 (s, 1H), 3.92 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.1, 156.9, 150.9, 139.4, 133.8, 130.6,

129.9, 126.8, 125.4, 123.0, 120.8, 120.2, 110.9, 77.3, 55.6, 17.4; HRMS (FAB) m/z $[M + H]^+$ calcd for $C_{16}H_{15}O_3$ 255.1021, found 255.1026.

Author information

Corresponding Authors

*E-mail: miura-hiroki@tmu.ac.jp.

*E-mail: shishido-tetsuya@tmu.ac.jp.

ORCID

Hiroki Miura: 0000-0002-2488-4432

Tetsuya Shishido: 0000-0002-8475-4226

Notes

The authors declare no competing financial interest.

Supporting Information

Detailed optimization of reaction conditions and ^{1}H and ^{13}C NMR spectra for the products **3** (PDF)

Acknowledgement

This study was supported in part by the Program for Element Strategy Initiative for Catalysts & Batteries (ESICB). This work was also supported in part by Grants-in-Aid for Scientific Research (B) (Grant 17H03459) and Scientific Research on Innovative Areas (Grant 17H06443) commissioned by MEXT of Japan. We thank Ms. Yuriko Kimura for her kind assistance to carry out experiments.

References

(1) Crabtree, R. H. Introduction: CH Activation. *Chem. Rev.* **2017**, *117*, 8481−8482, and references cited therein.

(2) Yan, G. B.; Wu, X. M.; Yang, M. H. Transition-Metal-Catalyzed Additions of C−H Bonds to C−X (X = N, O) Multiple Bonds via C−H Bond Activation. *Org. Biomol. Chem.* **2013**, *11*, 5558−5578.

(3) Zhang, X. S.; Chen, K.; Shi, Z. J. Transition Metal-Catalyzed Direct Nucleophilic Addition of C−H Bonds to Carbon-Heteroatom Double Bonds. *Chem. Sci.* **2014**, *5*, 2146−2159.

(4) Yang, L.; Huang, H. M. Transition-Metal-Catalyzed Direct Addition of Unactivated C−H Bonds to Polar Unsaturated Bonds. *Chem. Rev.* **2015**, *115*, 3468−3517.

(5) Shi, X. Y.; Han, W. J.; Li, C. J. Transition-Metal-Catalyzed Direct Addition of Aryl C–H Bonds to Unsaturated Electrophiles. *Chem. Rec.* **2016**, *16*, 1178–1190.

(6) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Transition-Metal-Catalyzed C–H Bond Addition to Carbonyls, Imines, and Related Polarized π Bonds *Chem. Rev.* **2017**, *117*, 9163−9227.

(7) Yang, L.; Correia, C. A.; Li, C. J. Grignard-Type Arylation of Aldehydes via a Rhodium-Catalyzed C−H Activation under Mild Conditions. *Adv. Synth. Catal.* **2011**, *353*, 1269−1273.

(8) Shi, X. Y.; Li, C. J. A Novel Rhodium-Catalyzed Cascade Cyclization: Direct Synthesis of 3-Substituted Phthalides from Aldehydes and Aromatic Acids. *Adv. Synth. Catal.* **2012**, *354*, 2933−2938.

(9) Li, Y.; Zhang, X. S.; Zhu, Q. L.; Shi, Z. J. Olefinic C−H Bond Addition to Aryl Aldehyde and Its *N*-Sulfonylimine via Rh Catalysis. *Org. Lett.* **2012**, *14*, 4498−4501.

(10) Li, Y.; Zhang, X. S.; Chen, K.; He, K. H.; Pan, F.; Li, B. J.; Shi, Z. J. *N*-Directing Group Assisted Rhodium-Catalyzed Aryl C−H Addition to Aryl Aldehydes. *Org.*

Lett. **2012**, *14*, 636−639.

(11) Jo, H.; Park, J.; Choi, M.; Sharma, S.; Jeon, M.; Mishra, N. K.; Jeong, T.; Han, S.; Kim, I. S. Ruthenium(II)- or Rhodium(III)-Catalyzed Grignard-Type Addition of Indolines and Indoles to Activated Carbonyl Compounds. *Adv. Synth. Catal.* **2016**, *358*, 2714−2720.

(12) Zhang, G. F.; Li, Y.; Xie, X. Q.; Ding, C. R. Ru-Catalyzed Regioselective Direct Hydroxymethylation of (Hetero)Arenes via C–H Activation. *Org. Lett.* **2017**, *19*, 1216−1219.

(13) Zhou, B.; Hu, Y.; Wang, C. Manganese-Catalyzed Direct Nucleophilic C(sp^2)−H Addition to Aldehydes and Nitriles. *Angew. Chem., Int. Ed.* **2015**, *54*, 13659−13663.

(14) Wu, Y.; Zhou, B. Ruthenium-Catalyzed Direct Hydroxymethylation of Aryl C–H Bonds. *ACS Catal.* **2017**, *7*, 2213−2217.

(15) Drapeau, M. P.; Gooßen, L. J. Carboxylic Acids as Directing Groups for C−H Bond Functionalization. *Chem. - Eur. J.* **2016**, *22*, 18654−18677.

(16) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. Oxidative Cross-Coupling of *N*-(2‘-Phenylphenyl)benzene- sulfonamides or Benzoic and Naphthoic Acids with Alkenes Using a Palladium−Copper Catalyst System under Air. *J. Org. Chem.* **1998,** *63,* 5211−5215.

(17) Ueura, K.; Satoh, T.; Miura, M. An Efficient Waste-Free Oxidative Coupling via Regioselective C–H Bond Cleavage: Rh/Cu-Catalyzed Reaction of Benzoic Acids with Alkynes and Acrylates under Air. *Org. Lett.*, **2007**, *9*, 1407−1409.

(18) Bechtoldt, A.; Tirler, C.; Raghuvanshi, K.; Warratz, S.; Kornhaaß, C.; Ackermann, L. Ruthenium Oxidase Catalysis for Site-Selective C–H Alkenylations with Ambient O_2 as the Sole Oxidant. *Angew. Chem. Int. Ed.* **2016**, *55*, 264–267.

(19) Gooßen, L. J.; Rodríguez, N.; Linder, C.; Lange, P. P.; Fromm, A. Comparative Study of Copper- and Silver-Catalyzed Protodecarboxylations of Carboxylic Acids.

ChemCatChem **2010**, *2*, 430–442, and references cited therein.

(20) Karmakar, R.; Pahari, P.; Mal, D. Phthalides and Phthalans: Synthetic Methodologies and Their Applications in the Total Synthesis. *Chem. Rev.*, **2014**, *114*, 6213–6284, and references cited therein.

(21) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C–H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *114*, 1315−1345.

(22) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalyzed C–H Bond Activation and Functionalization. *Chem. Rev.* **2012**, *112*, 5879−5918.

(23) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. C–H Bond Functionalization in Water Catalyzed by Carboxylato Ruthenium(II) Systems. *Angew. Chem., Int. Ed.*, **2010**, *49*, 6629–6632.

(24) Singh, S. K.; Sawant, S. G.; Dixneuf, P. H. Ruthenium(II)-Catalyzed Synthesis of Pyrrole- and Indole-Fused Isocoumarins by C–H Bond Activation in DMF and Water. *ChemCatChem* **2016**, *8*, 1046–1050.

(25) Zhang, G.; Gooßen, L. J. Regioselective C–H Alkylation via Carboxylate-Directed Hydroarylation in Water. *Chem. Eur. J.* **2018**, *24*, 4537–4541.

(26) Biafora, A.; Krause, T.; Hackenberger, D.; Belitz, F.; Gooßen, L. J. *ortho*-C–H Arylation of Benzoic Acids with Aryl Bromides and Chlorides Catalyzed by Ruthenium. *Angew. Chem. Int. Ed.* **2016**, *55*, 14752–14755.

(27) Solari, E.; S Gauthier, S.; Scopelliti, R.; Severin, K. Multifaceted Chemistry of $[(Cymene)RuCl_2]_2$ and PCy_3. *Organometallics* **2009**, *28*, 4519–4526.

(28) Lapointe, D.; Fagnou K. Overview of the Mechanistic Work on the Concerted Metallation Deprotonation Pathway. *Chem. Lett.* **2010**, *39*, 1118–1126.

(29) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. Mechanistic Insight into Direct Arylations with Ruthenium(II) Carboxylate Catalysts. *Org. Lett.* **2010**, *12*, 5032–5035.

(30) Ferrer-Flegeau, E.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. Autocatalysis for C_H Bond Activation by Ruthenium(II) Complexes in Catalytic Arylation of Functional Arenes. *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170.

(31) Anastas, P. T.; Warner, J. C. 12 Principles of Green Chemistry. *Green Chemistry: Theory and Practice*; Oxford University Press: New York **1998**.

(32) Sheldon, R. A.; Downing, R. S. Heterogeneous Catalytic Transformations for Environmentally Friendly Production. *Appl. Catal. A: General,* **1999**, 189, 163–183.

(33) Schlögl, R.; Heterogeneous Catalysis. *Angew. Chem. Int. Ed.* **2015**, *54*, 3465–3520.

(34) Anastas, P. T.; Allen, D. T. Twenty-Five Years of Green Chemistry and Green Engineering: The End of the Beginning. *ACS Sustainable Chem. Eng.* **2016**, *4*, 5820–5820.

(35) Wada, K.; Miura, H.; Hosokawa, S.; Inoue, M. Development of Ceria-supported Ruthenium Catalysts for Green Organic Transformation Processes. *J. Jpn. Petro. Inst.* **2013**, *56*, 69–79.

(36) Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. Ruthenium-Catalyzed Intermolecular Hydroacylation of Internal Alkynes: The Use of Ceria-Supported Catalyst Facilitates the Catalyst Recycling. *Chem. Eur. J.* **2013**, *19*, 861–864.

(37) Miura, H.; Tsutsui, K.; Wada, K.; Shishido, T. Coupling of Carboxylic Acids with Internal Alkynes by Supported Ruthenium Catalysts: Direct and Selective Syntheses of Multi-Substituted Phthalide Derivatives. *Chem. Commun.* **2015**, *51*, 1654–1657.

(38) Miura, H.; Takeuchi, K.; Shishido, T. Intermolecular [2+2+1] Carbonylative Cycloaddition of Aldehydes with Alkynes, and Subsequent Oxidation to γ-Hydroxybutenolides by a Supported Ruthenium Catalyst. *Angew. Chem. Int. Ed.* **2016**, *55*, 278–282.

(39) Miura, H.; Terajima, S.; Tsutsui, K.; Shishido, T. Ruthenium-Catalyzed Addition of Aromatic Amides to Internal Alkynes and Subsequent Intramolecular Cyclization for

the Atom-Economical Synthesis of Isoindolinones. *J. Org. Chem.* **2017**, *82*, 1231−1239.

(40) Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. Recyclable Solid Ruthenium Catalysts for the Direct Arylation of Aromatic C–H Bonds. *Chem. Eur. J.* **2010**, *16*, 4186–4189.

(41) Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. Catalytic Addition of Aromatic C-H Bonds to Vinylsilanes in the Presence of Ru/CeO_2. *ChemCatChem* **2010**, *2*, 1223–1225.

(42) Nishiumi, M.; Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. Active Ruthenium Catalysts Based on Phosphine-Modified Ru/CeO_2 for the Selective Addition of Carboxylic Acids to Terminal Alkynes. *ACS Catal.* **2012**, *2*, 1753–1759.

(43) Liu, S.-L.; Li, X.-H.; Shi, T.-H.; Yang, G.-C.; Wang, H.-L.; Gong, J.-F.; Song, M.-P. Copper-Promoted Thiolation of C(sp^2)–H Bonds Using a 2-Amino Alkylbenzimidazole Directing Group. *Eur. J. Org. Chem.* **2017**, *2017*, 2280–2289.

Graphical Abstract