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## Ruthenium(II)-catalysed selective C(sp<sup>2</sup>)-H bond benzylation of biologically appealing *N*-arylisindolinones

Yu-Chao Yuan, Christian Bruneau, Thierry Roisnel and Rafael Gramage-Doria\*

Site- and regio-selective aromatic C-H bond benzylation reactions were found to take place using biologically appealing *N*-arylisindolinones under ruthenium(II) catalysis in the presence of (hetero)aromatic carboxylic acid derivatives as coupling partners. Besides the presence of two potential C(sp<sup>2</sup>)-H sites available for functionalization in the substrates, exclusive *ortho* selectivity was achieved in the phenyl ring attached to the nitrogen atom. Notably, the reactions occurred in a selective manner as only mono-functionalized products were formed and they tolerated a large number of functional chemical groups. The ability of the cyclic tertiary amide within the isoindolinone skeleton to act as a weak directing group in order to accommodate six-membered ring ruthenacycle intermediates appears to be the key to reach such high levels of selectivity. In contrast, the more sterically demanding cyclic imides were unreactive under identical reaction conditions.

### Introduction

Since the pioneering contributions from Crabtree and Sanford on palladium-catalysed C-H bond acyloxylation reactions,<sup>1</sup> metal-catalysed C-H bond oxidations has represented an important entry to form new C-O bonds in valuable organic molecules.<sup>2</sup> Indeed, it enables to rapidly access molecular diversity using different transition metal catalysts derived from Pd, Rh, Ir, Ru, Fe, Cu, Co, etc.<sup>3</sup> The main advantage of the transition metal-catalysed C-H bond acyloxylation reactions is that they traditionally operate under mild reaction conditions, thus avoiding the use of harsh oxidizing reagents which are not always compatible with many sensitive functional groups.<sup>4</sup> So far, most of the research in this area has been devoted to the use of nitrogen-containing directing groups that are capable to strongly coordinate to the metal catalyst leading to the formation of key metallacycle species.<sup>4</sup> Making these methodologies compatible with weak directing groups is rather attractive<sup>5</sup> as they can be further implemented in the late stage functionalization of chemicals relevant for medicine, pharmacology, agrochemistry and material sciences.<sup>6</sup>

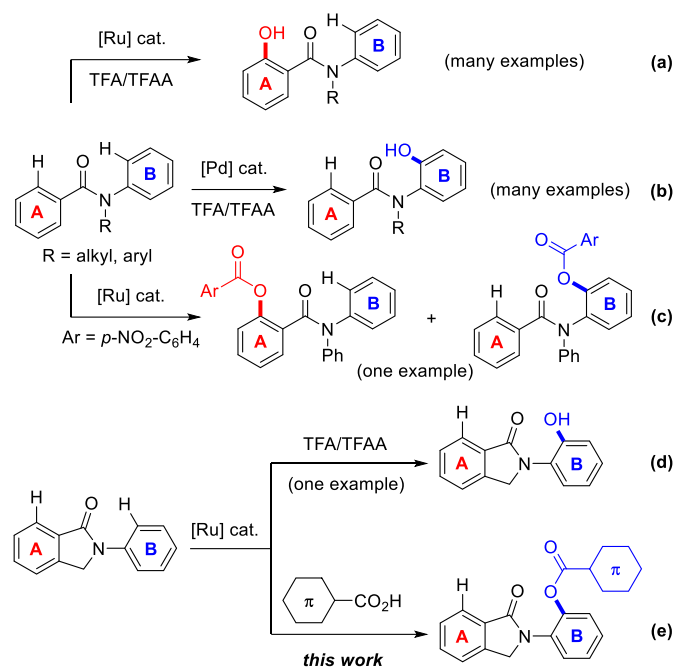
A particular class of useful weak directing groups are amides. They have been used in many transition metal-catalysed C-H bond functionalization reactions,<sup>7</sup> although their use in C-O bond forming reactions is rare.<sup>8</sup> In addition, *N*-substituted phenylbenzamides (Ar<sup>1</sup>-CONR-Ar<sup>2</sup>) are a sub-family of amides that present two aromatic fragments with two types of C-H bonds that can *a priori* react in a similar manner.<sup>9-11</sup> In the case of C-O bond forming reactions *via* transition metal-catalysed C-H bond functionalizations, Rao *et al.* showed that

ruthenium catalysts enabled the hydroxylation to take place in a C-H bond from the benzamide ring **A** (Fig. 1a) while palladium catalysts hydroxylated the C-H bond from the acetanilide ring **B** (Fig. 1b) in TFA/TFAA medium (TFA = trifluoroacetic acid, TFAA = trifluoroacetic acid anhydride).<sup>9</sup> Additionally, Jegannathan *et al.* described the difficulty to perform selective C-H bond benzylation reactions with *N*-substituted phenylbenzamides as both possible products are formed in a 1:1 ratio (Fig. 1c).<sup>10</sup> We recently applied a modified Rao's methodology to one example of *N*-arylisindolinone,<sup>11</sup> which is the simplest cyclic version of *N*-substituted phenylbenzamides and the skeleton of which is found in many biologically relevant compounds.<sup>12</sup> For *N*-phenylisoindolinone, the C-H bond hydroxylation exclusively occurred in the aromatic ring **B** either with palladium or ruthenium catalysts (Fig. 1d).<sup>11</sup> These examples show the current limitations and challenges encountered in C-H bond acyloxylation reactions in order to discriminate between two aromatic C-H sites for tertiary amides as weak directing groups. It is relevant to note that ruthenium-catalysed C(sp<sup>2</sup>)-H bond benzylation reactions using strong directing groups have been studied recently.<sup>13</sup> Herein, we report the development and scope of ruthenium catalysis enabling C-H bond benzylation reactions exclusively in the acetanilide ring **B** from the biologically relevant *N*-arylisindolinone (Fig. 1e).

Univ Rennes, CNRS, ISCR – UMR6226, F-35000 Rennes, France.

CCDC 1910244 (**2a**), 1910245 (**2b**), 1910246 (**2c**), 1910247 (**2o**), and 1910248 (**2t**), contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Electronic Supplementary Information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. See DOI: 10.1039/x0xx00000x



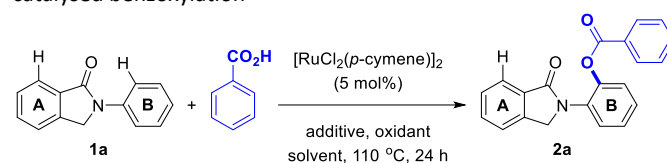
**Fig. 1** State-of-the-art for the transition metal-catalysed C-H bond hydro/benzoxylation of *N*-substituted phenylbenzamides as weak directing groups (a-d) and present work (e).

## Results and discussion

Initially, we focused on the ruthenium-catalysed benzoxylation of isoindolinone **1a** in the presence of benchmark benzoic acid (1.5 equiv.) as coupling partner (Table 1). A systematic study was performed using the air and moisture stable  $[\text{RuCl}_2(p\text{-cymene})]_2$  complex as pre-catalyst (5 mol%) in combination with different additives and oxidants (Table 1). First, we tested the reaction conditions employed by Jegamohan and co-workers for the benzoxylation of acyclic tertiary amides (Fig. 1c),<sup>10</sup> namely,  $\text{AgSbF}_6$  (20 mol%) as chloride scavenger and  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (2 equiv.) as oxidant in 1,2-dichloroethane (DCE) as solvent at 100 °C. After 24 h, only trace amounts of the product **2a** were detected (entry 1). Interestingly, raising the temperature of the reaction to 110 °C, afforded **2a** in 66% yield (entry 2), with no functionalization in the benzene ring **A**. A similar result (69% yield) was observed when the reaction was conducted with  $\text{Ag}_2\text{CO}_3$  as oxidant (entry 3). However, the use of  $\text{K}_2\text{S}_2\text{O}_8$  or  $\text{PhI}(\text{OAc})_2$  as oxidant, respectively, was detrimental to the formation of **2a** (entries 4-5) as was the use of  $\text{KPF}_6$  or  $\text{AgOTf}$  as additives, respectively (entries 6-7). The use of 2-MeTHF as solvent provided **2a** in 66% yield (entry 8) and other solvents such as 1,4-dioxane, *N,N*-dimethylformamide (DMF) and toluene were not as high yielding as DCE (entries 9-11). Decreasing the amount of benzoic acid to 1.2 equiv. afforded **2a** in 56% yield (entry 12). Conversely, using a slight excess of substrate **1a** (1.1 equiv.) with respect to benzoic acid (1 equiv.) gave rise to **2a** in 74% yield of isolated product (entry 13), which constituted the highest yielding reaction conditions so far obtained. Furthermore, no bis-functionalization was observed. The starting substrate **1a** was recovered unreacted when the reaction was carried out in the absence of  $[\text{RuCl}_2(p\text{-cymene})]_2$ ,

$\text{AgSbF}_6$  and  $\text{Ag}_2\text{CO}_3$ , respectively (entries 14-16), thus, supporting the need of all reagents for this transformation.

**Table 1** Optimization of reaction conditions for the ruthenium-catalysed benzoxylation<sup>a</sup>



| Entry           | Additive         | Oxidant                               | Solvent     | Yield (%) <sup>b</sup> |
|-----------------|------------------|---------------------------------------|-------------|------------------------|
| 1 <sup>c</sup>  | $\text{AgSbF}_6$ | $(\text{NH}_4)_2\text{S}_2\text{O}_8$ | DCE         | traces                 |
| 2               | $\text{AgSbF}_6$ | $(\text{NH}_4)_2\text{S}_2\text{O}_8$ | DCE         | 66                     |
| 3               | $\text{AgSbF}_6$ | $\text{Ag}_2\text{CO}_3$              | DCE         | 69 (67)                |
| 4               | $\text{AgSbF}_6$ | $\text{K}_2\text{S}_2\text{O}_8$      | DCE         | traces                 |
| 5               | $\text{AgSbF}_6$ | $\text{PhI}(\text{OAc})_2$            | DCE         | traces                 |
| 6               | $\text{KF}_6$    | $\text{Ag}_2\text{CO}_3$              | DCE         | traces                 |
| 7               | $\text{AgOTf}$   | $\text{Ag}_2\text{CO}_3$              | DCE         | traces                 |
| 8               | $\text{AgSbF}_6$ | $\text{Ag}_2\text{CO}_3$              | 2-MeTHF     | 66                     |
| 9               | $\text{AgSbF}_6$ | $\text{Ag}_2\text{CO}_3$              | 1,4-dioxane | 36                     |
| 10              | $\text{AgSbF}_6$ | $\text{Ag}_2\text{CO}_3$              | DMF         | 0                      |
| 11              | $\text{AgSbF}_6$ | $\text{Ag}_2\text{CO}_3$              | toluene     | 49                     |
| 12 <sup>d</sup> | $\text{AgSbF}_6$ | $\text{Ag}_2\text{CO}_3$              | DCE         | 56                     |
| 13 <sup>e</sup> | $\text{AgSbF}_6$ | $\text{Ag}_2\text{CO}_3$              | DCE         | 77 (74)                |
| 14 <sup>f</sup> | $\text{AgSbF}_6$ | $\text{Ag}_2\text{CO}_3$              | DCE         | 0                      |
| 15              | -                | $\text{Ag}_2\text{CO}_3$              | DCE         | 0                      |
| 16              | $\text{AgSbF}_6$ | -                                     | DCE         | 0                      |

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol, 1 equiv.), benzoic acid (0.15 mmol, 1.5 equiv.),  $[\text{RuCl}_2(p\text{-cymene})]_2$  (5 mol%), additive (20 mol%), oxidant (0.2 mmol, 2 equiv.), solvent (0.5 mL), 110 °C, 24 h, Argon.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy analysis using dibromomethane as internal standard; isolated yields obtained after purification by column chromatograph are displayed in parentheses.

<sup>c</sup> 100 °C.

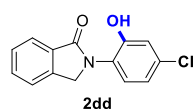
<sup>d</sup> Benzoic acid (0.12 mmol, 1.2 equiv.).

<sup>e</sup> **1a** (0.11 mmol, 1.1 equiv.), benzoic acid (0.1 mmol, 1 equiv.).

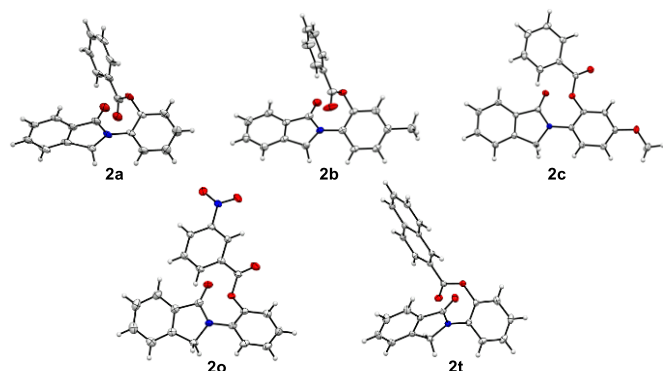
<sup>f</sup> Without  $[\text{RuCl}_2(p\text{-cymene})]_2$ .

With the developed reaction conditions in hand (Table 1, entry 13), we evaluated the scope for this transformation (Table 2). The catalysis was compatible with different *para*- and *meta*-substitution patterns in the phenyl ring **B** of the *N*-arylisindolinone backbone. As such, benzoxyated products **2b-2g** that contain methyl, methoxy, chloro and dioxolane functional groups were obtained in 35%-68% yields. During the purification of **2d**, the debenzoylated alcohol product **2dd** was isolated in 19%, and in the case of **2g**, small amounts of the other regioisomer were obtained as well. The formation of debenzoylated product was also observed in other cases (*vide infra* for discussion). Isoindolinone bearing an *ortho*-tolyl substituent attached to the nitrogen atom was unreactive under catalytic conditions (**2h**), indicating that the sterically hindered substrates are significantly less reactive than

unhindered substrates. Benzoic acids containing different *para*- and *meta*-substituted functional groups as useful as fluoride, chloride, bromide, iodide, trifluoromethyl, nitro and methoxy were reactive, and they provided the corresponding products **2i-2p** in 50%-73% yields. Nitrile-substituted isoindolinones, however, did not afford the corresponding product **2q**. On the other hand, *ortho*-substituted benzoic acids afforded the corresponding products with yields depending on the steric bulk of the substituent as shown in the synthesis of the fluoro derivative **2r** in 63% yield and the chloro derivative **2s** in 36% yield. Polycyclic aromatic hydrocarbon fragments such as naphthalene were also compatible with the catalysis leading to **2t** in 62% yield. Gratifyingly, heteroaromatic-containing carboxylic acids were also compatible with the reaction. Thiophene-containing **2u** and furan-containing **2v** were obtained in 38% and 77% yields, respectively. In the latter case, 21% of debenzoylated alcohol product was also isolated. We also noted that the catalysis was not compatible with oxidation-sensitive formyl groups.

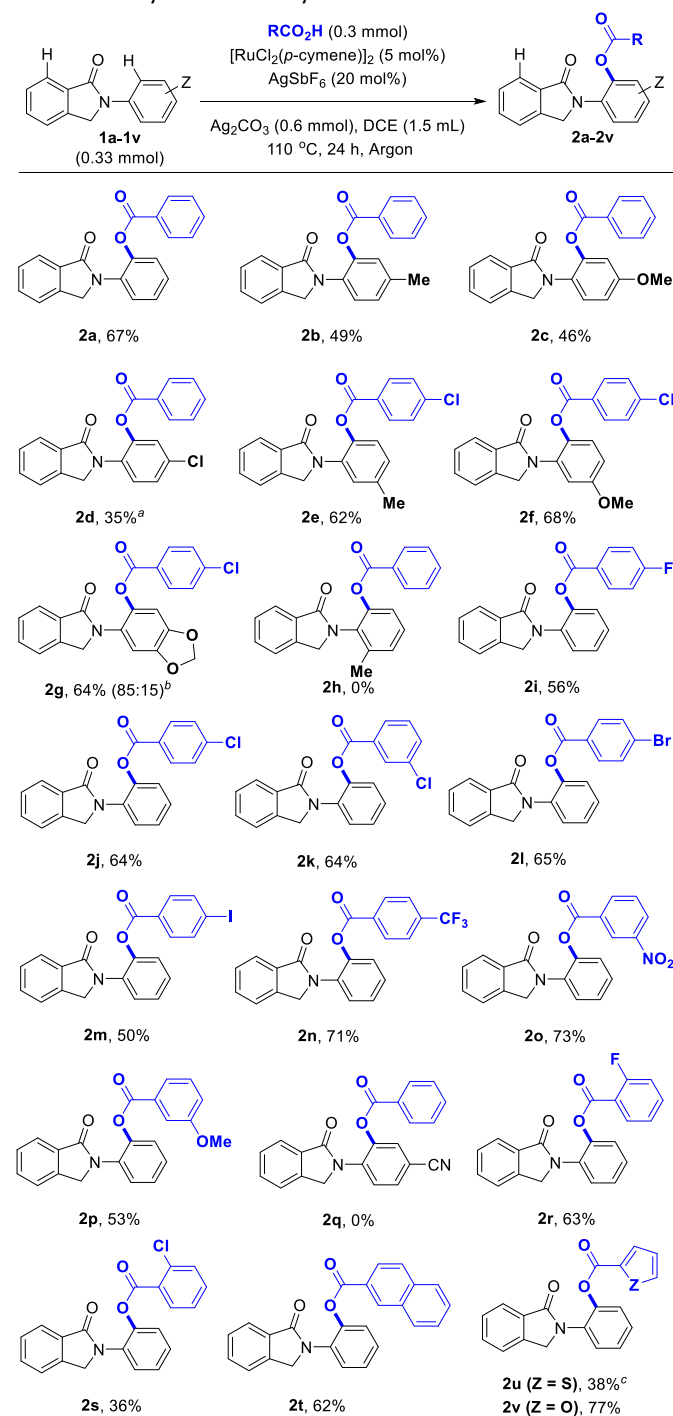


Additionally, the molecular structures of **2a**, **2b**, **2c**, **2o**, and **2t** were unambiguously confirmed by single-crystal X-ray diffraction (SCXRD) studies which further supported the regio- and site-selectivity of the reaction (Figure 2). Unfortunately, carboxylic acids containing nitrile, dimethylamino, pyridine and pyrrole functional groups were not viable for this reaction, in analogy to reactions reported before for substrates containing strong nitrogen-containing directing groups.<sup>13</sup> Neither acrylic acid nor trifluoroacetic acid formed any product in our hands.



**Fig. 2** SCXRD molecular structures of **2a**, **2b**, **2c**, **2o** and **2t**.

**Table 2.** Scope and limitations for the ruthenium-catalysed C-H bond benzylation of *N*-arylisoindolinones **1**.

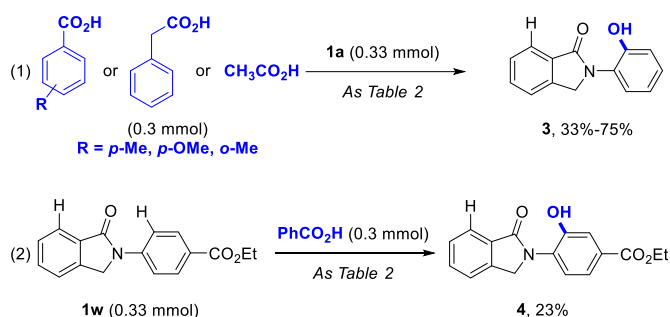


<sup>a</sup> 19% of debenzoylated product **2dd** was isolated.

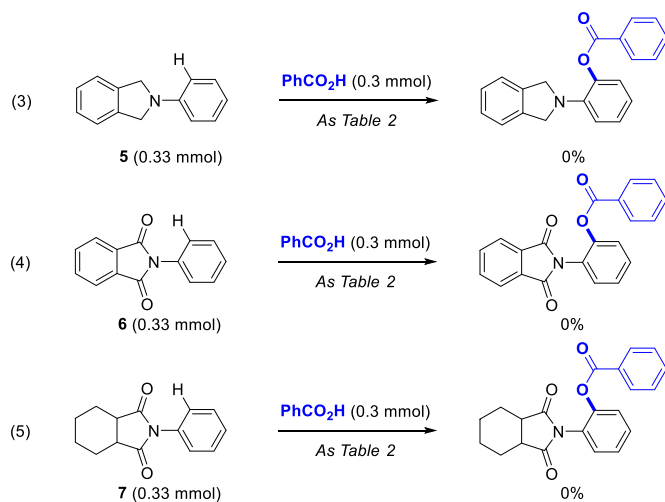
<sup>b</sup> The minor *ortho*-regioisomer is not represented.

<sup>c</sup> 21% of debenzoylated product was isolated.

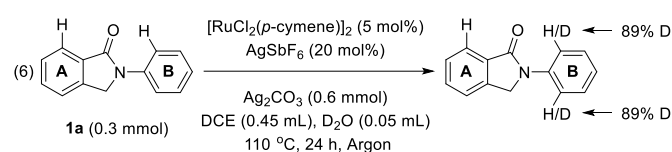
In general, trace amounts of starting material remained once the reaction was stopped. However, during the purification of **2d** and **2u**, small amounts of debenzoylated product were observed. This feature was observed in another set of carboxylic acids as coupling partners in which no acyloxylated products were detected so far and debenzoylated phenol **3** was the only product that was formed (Eq. 1). For example, *N*-phenylisoindolinone **1a** reacted under the standard reaction conditions with *para*-toluic acid, *para*-methoxybenzoic acid, *ortho*-toluic acid, phenylacetic acid and acetic acid, respectively, leading exclusively to phenol **3** in variable yields (Eq. 1). The same behaviour was identified when using ester substituted isoindolinone **1w**, which afforded **4** in 23% yield besides unreacted starting material **1w** (Eq. 2). Although we do not have any reason to explain such findings, it can be suggested that the corresponding benzoylated products that transiently form are rather unstable under the conditions used in the catalysis and they are readily hydrolysed.



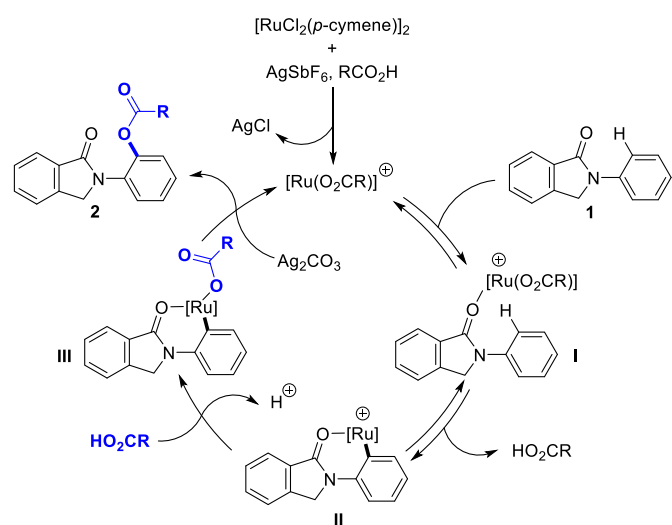
Next, we evaluated whether the carbonyl group of the isoindolinone fragment **1** might behave as a weak coordinating group to ruthenium during the reaction. For that, we performed a control experiment with a substrate lacking any carbonyl group, isoindoline **5**. With this substrate no benzoylated product was observed with the reaction conditions employed in the catalysis (Eq. 3). The same observations were made using cyclic imides **6** and **7** as substrates, respectively (Eq. 4-5).<sup>14</sup> The lack of reactivity in these cases likely arises from the rigidity and/or bulkiness of the directing groups that prevent the accommodation of catalytically productive ruthenacycle intermediates.



To further verify that the carbonyl group in **1** plays a key role for the C-H bond activation step, we performed the ruthenium-based catalysis in the absence of benzoic acid using a mixture of solvents DCE:D<sub>2</sub>O (Eq. 6). Under these reaction conditions, 89% deuterium was incorporated in both *ortho* C-H bonds of the phenyl ring **B**. This indicates the ease and reversibility of the C-H bond activation step in the presence of the ruthenium catalyst.

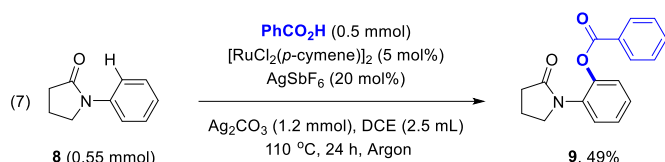


Based on the above-described data and previous reports,<sup>10,13,15</sup> a catalytic cycle is proposed in Scheme 1. First, chloride-free carboxylate-containing ruthenium species are formed, which coordinate to the carbonyl group of the isoindolinone core (**I**). Then, base-assisted C-H bond metalation gives rise to a six-membered ruthenacycle intermediate **II**. Due to the large amount of carboxylic acid in the reaction media, intermediate **III** can form which undergoes reductive elimination towards product formation and oxidation of the metal centre to regenerate a ruthenium(II) species.



**Scheme 1** Proposed catalytic cycle for the ruthenium-catalysed C-H bond benzoylation of *N*-arylisindolinones **1**.

Finally, to investigate whether other cyclic amides can act as weak directing groups for this transformation, we performed the catalysis with *N*-phenylpyrrolidinone (**8**) as substrate (Eq. 7). Under our standard reaction conditions, the ruthenium-catalyzed benzoylation gave rise to the *ortho*-substituted product **9** in 49% isolated yield (56% conversion of **8**) with no evidences of bis-functionalization. For this type of transformation, the pyrrolidinone motif seems not to be as appropriate directing group as the isoindolinone motif. Probably, subtle stereoelectronic properties associated to each directing group are responsible for these observations.



## Experimental

All reagents were obtained from commercial sources and used as supplied. All reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Catalytic experiments were performed in Schlenk-type flasks under argon atmosphere unless otherwise noted. Organic solutions were concentrated under reduced pressure using a rotary evaporator. Thin-layer chromatography (TLC) were carried out on 0.25 mm Merck silica gel (60-F254). Flash column chromatography was performed using silica gel Silica 60 M, 0.04-0.063 mm. Technical grade petroleum ether (40-60), *n*-heptane and ethyl acetate were used for column chromatography.  $\text{CDCl}_3$  was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer.  $^1\text{H}$  NMR spectra were referenced to residual protiated solvent ( $\delta = 7.26$  ppm for  $\text{CDCl}_3$ ,  $\delta = 2.50$  ppm for  $\text{DMSO}-d_6$  and  $\delta = 2.05$  ppm for  $\text{acetone}-d_6$ ) and  $^{13}\text{C}$  chemical shifts are reported relative to deuterated solvents ( $\delta = 77.0$  ppm for  $\text{CDCl}_3$ ,  $\delta = 39.5$  ppm for  $\text{DMSO}-d_6$  and  $\delta = 29.8$  ppm for  $\text{acetone}-d_6$ ) [Note:  $\text{acetone}-d_6$  contains traces of water at *ca.* 3 ppm]. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br. for broad. GC-MS analyses were performed with a GCMS-QP2010S (Shimadzu) instrument with a GC-2010 equipped with a 30 m capillary column (Supelco, SLBTM-5ms, fused silica capillary column, 30 m x 0.25 mm x 0.25 mm film thickness), which was used with helium as the vector gas. The following GC conditions were used: initial temperature  $80^\circ\text{C}$  for 2 minutes, then rate  $20^\circ\text{C}/\text{min}$  until  $280^\circ\text{C}$  and  $280^\circ\text{C}$  for 28 minutes. HRMS were recorded on a Waters Q-ToF 2 mass spectrometer at the corresponding facilities of the CRMPO, Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1.

**Synthesis and characterization of N-arylisindolinone substrates (1).** A mixture of 2-formylbenzoic acid (5.0 mmol, 1 equiv.), aniline derivative (6.0 mmol, 1.2 equiv.), DABCO (10.0 mmol, 2 equiv.),  $\text{HCOOH}$  (1.25 mL),  $\text{Pd}(\text{OAc})_2$  (0.25 mmol, 5 mol%) in 1,4-dioxane (5 mL) was heated at  $80^\circ\text{C}$  for 3 h. After completion of the reaction, the mixture was cooled to room temperature, and diluted with DCM (50 mL). The solid was removed by filtration, and the filtrate was washed with water (50 mL) and brine (50 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/acetone = 5/1, v/v) to afford the desired product **1**.

**2-Phenylisoindolin-1-one (1a):** Starting from aniline in 98% isolated yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.93$  (d,  $J = 7.6$  Hz, 1H), 7.89-7.86 (m, 2H), 7.62-7.58 (m, 1H), 7.53-7.49 (m, 2H), 7.43 (dd,  $J = 8.4, 7.2$  Hz, 2H), 7.18 (dd,  $J = 7.2, 7.2$  Hz, 1H), 4.87 (s, 2H) ppm. The spectral data match those previously reported.<sup>16</sup>

**2-(*p*-Tolyl)isoindolin-1-one (1b):** starting from *p*-toluidine in 80% isolated yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.92$  (d,  $J = 7.2$  Hz, 1H), 7.74 (d,  $J = 8.4$  Hz, 2H), 7.59 (dd,  $J = 7.6, 7.6$  Hz, 1H), 7.50 (dd,  $J = 6.8, 6.8$  Hz, 2H), 7.24 (d,  $J = 8.4$  Hz, 2H), 4.84 (s, 2H), 2.36 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

**2-(*p*-Methoxyphenyl)isoindolin-1-one (1c):** starting from *p*-anisidine in 62% isolated yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.92$  (d,  $J = 7.6$  Hz, 1H), 7.74 (d,  $J = 9.2$  Hz, 2H), 7.58 (dd,  $J = 7.6, 7.6$  Hz, 1H), 7.52-7.48 (m, 2H), 6.97 (d,  $J = 9.2$  Hz, 2H), 4.83 (s, 2H), 3.83 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

**2-(*p*-Chlorophenyl)isoindolin-1-one (1d):** starting from *p*-chloroaniline in 61% isolated yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.92$  (d,  $J = 7.2$  Hz, 1H), 7.74 (dd,  $J = 9.2, 2.4$  Hz, 2H), 7.61 (ddd,  $J = 7.6, 7.6, 1.2$  Hz, 1H), 7.54-7.50 (m, 2H), 7.39 (dd,  $J = 9.2, 2.4$  Hz, 2H), 4.84 (s, 2H) ppm. The spectral data match those previously reported.<sup>16</sup>

**2-(*m*-Tolyl)isoindolin-1-one (1e):** starting from *m*-toluidine in 65% isolated yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.93$  (d,  $J = 6.8$  Hz, 1H), 7.73 (s, 1H), 7.65-7.58 (m, 2H), 7.51 (dd,  $J = 7.2, 6.8$  Hz, 2H), 7.32 (dd,  $J = 8.0, 8.0$  Hz, 1H), 7.01 (d,  $J = 7.6$  Hz, 1H), 4.86 (s, 2H), 2.41 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

**2-(*m*-Methoxyphenyl)isoindolin-1-one (1f):** starting from *m*-anisidine in 80% isolated yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.93$  (d,  $J = 7.2$  Hz, 1H), 7.69 (dd,  $J = 2.0, 1.6$  Hz, 1H), 7.62-7.58 (m, 1H), 7.51 (dd,  $J = 7.6, 7.6$  Hz, 2H), 7.34-7.32 (m, 2H), 6.76-6.73 (m, 1H), 4.86 (s, 2H), 3.87 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

**2-(Benzo[*d*][1,3]dioxol-5-yl)isoindolin-1-one (1g):** starting from 3,4-(methylenedioxy)aniline in 58% isolated yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.92$  (d,  $J = 8.0$  Hz, 1H), 7.61-7.57 (m, 2H), 7.51 (dd,  $J = 6.4, 5.6$  Hz, 2H), 7.11 (dd,  $J = 8.4, 2.0$  Hz, 1H), 6.85 (d,  $J = 8.4$  Hz, 1H), 5.99 (s, 2H), 4.81 (s, 2H) ppm. The spectral data match those previously reported.<sup>16</sup>

**2-(*o*-Tolyl)isoindolin-1-one (1h):** starting from *o*-toluidine in 68% isolated yield.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.96$  (d,  $J = 7.6$  Hz, 1H), 7.61 (ddd,  $J = 7.2, 7.2, 1.2$  Hz, 1H), 7.55-7.50 (m, 2H), 7.35-7.32 (m, 1H), 7.30-7.24 (m, 3H), 4.74 (s, 2H), 2.27 (s, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

**4-(1-Oxoisindolin-2-yl)benzotrile (1q):** starting from 4-aminobenzotrile in 64% isolated yield.  $^1\text{H}$  NMR (400 MHz,

CDCl<sub>3</sub>):  $\delta$  = 8.06 (d,  $J$  = 9.2 Hz, 2H), 7.94 (d,  $J$  = 7.2 Hz, 1H), 7.71 (d,  $J$  = 8.8 Hz, 2H), 7.65 (dd,  $J$  = 7.6, 7.2 Hz, 1H), 7.54 (dd,  $J$  = 7.6, 7.2 Hz, 2H), 4.89 (s, 2H) ppm. The spectral data match those previously reported.<sup>16</sup>

**Ethyl 4-(1-oxoisindolin-2-yl)benzoate (1w):** starting from ethyl 4-aminobenzoate in 96% isolated yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.11 (d,  $J$  = 8.4 Hz, 2H), 7.99 (d,  $J$  = 8.8 Hz, 2H), 7.94 (d,  $J$  = 7.6 Hz, 1H), 7.63 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 7.53 (dd,  $J$  = 7.6, 7.6 Hz, 2H), 4.90 (s, 2H), 4.39 (q,  $J$  = 7.2 Hz, 2H), 1.41 (t,  $J$  = 7.2 Hz, 3H) ppm. The spectral data match those previously reported.<sup>16</sup>

**Synthesis and characterization of isoindoline (5):** 1,2-Bis(bromomethyl)benzene (5.0 mmol, 1 equiv.), DIPEA (12.5 mmol, 2.5 eq.), and aniline (7.50 mmol, 1.5 equiv.) were dissolved in toluene (25 mL) and added to a sealed tube before vigorously stirring at 110 °C under an Argon atmosphere. The resulting mixture was cooled to down to room temperature and extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether) to obtain the desired product **5** (89% isolated yield) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.38-7.31 (m, 6H), 6.78 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 6.71 (d,  $J$  = 7.6 Hz, 2H), 4.68 (s, 4H) ppm. The spectral data match those previously reported.<sup>17</sup>

**Synthesis and characterization of N-phenylphthalimide (6):** Phthalic anhydride (5 mmol, 0.74 g, 1 equiv.) and aniline (5 mmol, 1 equiv.) were refluxed in acetic acid (30 mL) for 2-5 h. Once at room temperature, water was added and the solid recovered by filtration. After drying under vacuum the desired phthalimide **6** (80% isolated yield) was obtained. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (dd,  $J$  = 5.6, 3.2 Hz, 2H), 7.80 (dd,  $J$  = 5.2, 3.2 Hz, 2H), 7.52 (dd,  $J$  = 7.6, 7.6 Hz, 2H), 7.34-7.27 (m, 3H) ppm. The spectral data match those previously reported.<sup>18</sup>

**Synthesis and characterization of 2-phenylhexahydro-1H-isoindole-1,3(2H)-dione (7):** Hexahydrophthalic anhydride (10 mmol, 1.54 g, 1 equiv.) and aniline (10 mmol, 1 equiv.) and THF (15 mL) were added to a 100 mL round bottom flask. The solution was stirred for 30 minutes at 40 °C. Removal of the solvent using a rotary evaporator gave the corresponding carboxylic acid-amide as a white solid. The white solid was then heated at 190 °C under Argon for 4 h. The desired phthalimide **7** (86% isolated yield) was purified by silica gel column chromatography with a mixture of petroleum ether and ethyl acetate as eluent. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.48-7.44 (m, 2H), 7.39-7.35 (m, 1H), 7.30-7.27 (m, 2H), 3.06-3.00 (m, 2H), 1.95-1.85 (m, 4H), 1.53-1.50 (m, 4H) ppm. The spectral data match those previously reported.<sup>19</sup>

**General procedure for the ruthenium-catalysed C-H bond benzylation reaction, and synthesis and characterization of products 2:** [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (0.2 mmol, 2.0 equiv.), *N*-arylisindolinone **1** (0.33 mmol, 1.1 equiv.) and the corresponding benzoic acid derivative

(0.3 mmol, 1.0 equiv.) were taken in a 15 mL Schlenk tube, which was equipped with a magnetic stirrer bar. 1,2-Dichloroethane (1.5 mL) was added to the Schlenk tube *via* a syringe, and the reaction mixture was degassed with Argon three times. The reaction mixture was allowed to stir at 110 °C for 24 h. After being cooled to ambient temperature, the reaction mixture was diluted with DCM and then filtered through Celite. After evaporation of the solvent in vacuo, the crude product was purified by column chromatography on silica gel (*n*-heptane/EtOAc: 10:1 to 5:1, *v/v*) to give the desired product **2**.

**2-(1-Oxoisindolin-2-yl)phenyl benzoate (2a):** 73.1 mg (74% yield), white solid, Mp: 139-141 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.08 (d,  $J$  = 8.0 Hz, 2H), 7.85 (d,  $J$  = 7.6 Hz, 1H), 7.56-7.49 (m, 3H), 7.46-7.36 (m, 7H), 4.76 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.7, 164.9, 146.8, 141.7, 133.8, 132.0, 131.9, 131.0, 130.3, 129.0, 128.73, 128.66, 128.33, 128.27, 126.9, 124.3, 124.0, 122.9, 52.5 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>15</sub>NO<sub>3</sub>Na 352.0944, found 352.0948 (1 ppm).

**5-Methyl-2-(1-oxoisindolin-2-yl)phenyl benzoate (2b):** 50.7 mg (49% yield), white solid, Mp: 158-160 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.07 (d,  $J$  = 7.2 Hz, 2H), 7.84 (d,  $J$  = 7.6 Hz, 1H), 7.55-7.49 (m, 2H), 7.43-7.35 (m, 5H), 7.18 (d,  $J$  = 7.6 Hz, 2H), 4.72 (s, 2H), 2.42 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.8, 165.0, 146.6, 141.7, 139.2, 133.7, 132.0, 131.8, 130.3, 129.0, 128.6, 128.2, 128.0, 127.6, 124.3, 124.2, 122.8, 52.5, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>17</sub>NO<sub>3</sub>Na 366.1101, found 366.1104 (1 ppm).

**5-Methoxy-2-(1-oxoisindolin-2-yl)phenyl benzoate (2c):** 60.4 mg (56% yield), white solid, Mp: 111-113 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.06 (d,  $J$  = 8.0 Hz, 2H), 7.83 (d,  $J$  = 7.6 Hz, 1H), 7.54-7.48 (m, 2H), 7.43-7.34 (m, 5H), 6.91 (d,  $J$  = 7.6 Hz, 2H), 4.70 (s, 2H), 3.84 (s, 3H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.9, 164.8, 159.8, 147.8, 141.7, 133.8, 132.0, 131.7, 130.3, 129.0, 128.9, 128.6, 128.2, 124.2, 123.6, 122.8, 112.8, 109.2, 55.8, 52.7 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>22</sub>H<sub>17</sub>NO<sub>4</sub>Na 382.1050, found 382.1054 (1 ppm).

**5-Chloro-2-(1-oxoisindolin-2-yl)phenyl benzoate (2d):** 38.1 mg (35% yield), yellow solid, Mp: <50 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.06 (d,  $J$  = 7.6 Hz, 2H), 7.84 (d,  $J$  = 7.6 Hz, 1H), 7.58-7.52 (m, 2H), 7.46-7.35 (m, 7H), 4.74 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 167.8, 164.5, 147.1, 141.6, 134.1, 133.7, 132.1, 131.7, 130.4, 129.8, 129.0, 128.8, 128.6, 128.4, 127.1, 124.5, 124.4, 122.9, 52.4 ppm. HRMS (ESI) calcd. for [M + Na]<sup>+</sup> C<sub>21</sub>H<sub>14</sub>NO<sub>3</sub><sup>35</sup>ClNa 386.0554, found 386.0555 (0 ppm).

**2-(4-Chloro-2-hydroxyphenyl)isoindolin-1-one (2dd):** 14.8 mg (19% yield), white solid, Mp: 243-245 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 10.31 (br, 1H), 7.77 (d,  $J$  = 7.6 Hz, 1H), 7.69-7.63 (m, 2H), 7.54 (ddd,  $J$  = 7.6, 7.6, 1.6 Hz, 1H), 7.36 (d,  $J$  = 8.4 Hz, 1H), 7.01 (d,  $J$  = 2.4 Hz, 1H), 6.95 (dd,  $J$  = 8.4, 2.4 Hz, 1H), 4.82 (s, 2H) ppm. <sup>13</sup>C{<sup>1</sup>H} NMR (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  = 167.1, 154.0, 142.4, 132.0, 131.8, 130.2, 127.9, 124.6, 123.4, 123.2, 119.1,

116.4, 51.5 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{14}H_{10}NO_2^{35}ClNa$  282.0292, found 282.0291 (0 ppm).

**4-Methyl-2-(1-oxoisindolin-2-yl)phenyl 4-chlorobenzoate (2e):** 70.4 mg (62% yield), yellow solid, Mp: < 50 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.99 (d,  $J$  = 8.0 Hz, 2H), 7.82 (d,  $J$  = 7.6 Hz, 1H), 7.52 (dd,  $J$  = 7.6, 7.2 Hz, 1H), 7.44-7.40 (m, 2H), 7.34 (d,  $J$  = 8.0 Hz, 2H), 7.27 (s, 1H), 7.25-7.20 (m, 2H), 4.73 (s, 2H), 2.40 (s, 3H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.5, 164.2, 144.3, 141.6, 140.2, 136.9, 131.9, 131.6, 130.4, 129.3, 128.9, 128.6, 128.2, 127.5, 124.2, 123.3, 122.8, 52.4, 21.0 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{22}H_{16}NO_3^{35}ClNa$  400.0711, found 400.0708 (1 ppm).

**4-Methoxy-2-(1-oxoisindolin-2-yl)phenyl 4-chlorobenzoate (2f):** 79.8 mg (68% yield), yellow solid, Mp: < 50 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.00 (d,  $J$  = 8.4 Hz, 2H), 7.83 (d,  $J$  = 7.6 Hz, 1H), 7.54 (dd,  $J$  = 7.6, 7.2 Hz, 1H), 7.44 (dd,  $J$  = 8.8, 8.0 Hz, 2H), 7.35 (d,  $J$  = 8.4 Hz, 2H), 7.27 (d,  $J$  = 8.8 Hz, 1H), 7.02 (s, 1H), 6.96 (d,  $J$  = 8.4 Hz, 1H), 4.75 (s, 2H), 3.83 (s, 3H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.5, 164.3, 157.9, 141.6, 140.1, 139.9, 132.0, 131.8, 131.6, 131.4, 128.9, 128.3, 127.5, 124.22, 124.19, 122.9, 114.0, 113.2, 55.8, 52.4 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{22}H_{16}NO_4^{35}ClNa$  416.0660, found 416.0659 (0 ppm).

**6-(1-Oxoisindolin-2-yl)benzo[d][1,3]dioxol-5-yl 4-chlorobenzoate (2g):** 77.8 mg (64% yield), yellow solid, Mp: < 50 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.95 (d,  $J$  = 8.4 Hz, 2H), 7.82 (d,  $J$  = 7.2 Hz, 1H), 7.51 (dd,  $J$  = 7.6, 7.2 Hz, 1H), 7.44-7.38 (m, 2H), 7.32 (d,  $J$  = 8.4 Hz, 2H), 6.88 (s, 1H), 6.84 (s, 1H), 6.04 (s, 2H), 4.65 (s, 2H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.8, 164.2, 147.6, 146.0, 141.6, 141.2, 140.3, 131.9, 131.6, 129.0, 128.3, 127.3, 124.2, 123.7, 122.9, 107.8, 104.6, 102.4, 52.6 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{22}H_{14}NO_5^{35}ClNa$  430.0453, found 430.0458 (1 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 4-fluorobenzoate (2i):** 58.7 mg (56% yield), white solid, Mp: 125-127 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.09 (m, 2H), 7.82 (d,  $J$  = 7.6 Hz, 1H), 7.54-7.34 (m, 7H), 7.04 (dd,  $J$  = 8.4, 8.4 Hz, 2H), 4.74 (s, 2H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.5, 166.2 (d,  $J_{C-F}$  = 253.6 Hz), 163.8, 146.7, 141.7, 132.9 (d,  $J_{C-F}$  = 9.5 Hz), 131.9, 131.8, 130.9, 128.7, 128.3, 128.1, 126.9, 125.2 (d,  $J_{C-F}$  = 3.0 Hz), 124.2, 123.8, 122.9, 115.8 (d,  $J_{C-F}$  = 22.0 Hz), 52.4 ppm.  $^{19}F\{^1H\}$  NMR (376 MHz,  $CDCl_3$ ):  $\delta$  = -104.1 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{21}H_{14}NO_3FNa$  370.0850, found 370.0850 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 4-chlorobenzoate (2j):** 69.8 mg (64% yield), yellow solid, Mp: 58-60 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.00 (d,  $J$  = 8.8 Hz, 2H), 7.83 (d,  $J$  = 7.6 Hz, 1H), 7.54 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 7.49-7.35 (m, 8H), 4.75 (s, 2H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.6, 164.0, 146.7, 141.7, 140.3, 132.0, 131.9, 131.7, 130.9, 129.0, 128.8, 128.4, 128.2, 127.5, 127.0, 124.3, 123.8, 122.9, 52.5 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{21}H_{14}NO_3^{35}ClNa$  386.0554, found 386.0553 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 3-chlorobenzoate (2k):** 70.3 mg (64% yield), yellow solid, Mp: < 50 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.02 (s, 1H), 7.96 (d,  $J$  = 7.6 Hz, 1H), 7.83 (d,  $J$  = 7.2 Hz, 1H), 7.55-7.35 (m, 8H), 7.32 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 4.76 (s, 2H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.5, 163.6, 146.5, 141.6, 134.7, 133.7, 131.9, 131.8, 130.9, 130.8, 130.2, 129.9, 128.6, 128.33, 128.28, 128.1, 127.0, 124.2, 123.7, 122.9, 52.4 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{21}H_{14}NO_3^{35}ClNa$  386.0554, found 386.0555 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 4-bromobenzoate (2l):** 79.9 mg (65% yield), yellow solid, Mp: 54-56 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.92 (d,  $J$  = 8.4 Hz, 2H), 7.83 (d,  $J$  = 7.6 Hz, 1H), 7.55-7.51 (m, 3H), 7.49-7.42 (m, 4H), 7.40-7.36 (m, 2H), 4.75 (s, 2H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.5, 164.2, 146.6, 141.7, 132.00, 131.98, 131.86, 131.76, 130.9, 129.1, 128.7, 128.4, 128.1, 128.0, 127.0, 124.3, 123.8, 122.9, 52.4 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{21}H_{14}NO_3^{79}BrNa$  430.0049, found 430.0050 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 4-iodobenzoate (2m):** 68.5 mg (50% yield), yellow solid, Mp: 61-63 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.83 (d,  $J$  = 7.6 Hz, 1H), 7.78-7.72 (m, 4H), 7.53 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 7.48-7.35 (m, 6H), 4.75 (s, 2H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.5, 164.4, 146.6, 141.6, 138.0, 132.0, 131.8, 131.6, 130.9, 128.7, 128.5, 128.3, 128.1, 127.0, 124.3, 123.8, 122.9, 101.9, 52.4 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{21}H_{14}NO_3I Na$  477.9911, found 477.9913 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 4-(trifluoromethyl)benzoate (2n):** 84.6 mg (71% yield), yellow solid, Mp: < 50 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.18 (d,  $J$  = 8.0 Hz, 2H), 7.81 (d,  $J$  = 8.0 Hz, 1H), 7.65 (d,  $J$  = 8.0 Hz, 2H), 7.54 (ddd,  $J$  = 7.6, 7.6, 1.2 Hz, 1H), 7.49-7.37 (m, 6H), 4.77 (s, 2H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.4, 163.7, 146.5, 141.7, 135.0 (q,  $J_{C-F}$  = 32.5 Hz), 132.3, 132.0, 131.8, 130.9, 130.7, 128.7, 128.4, 128.0, 127.1, 125.6 (q,  $J_{C-F}$  = 3.7 Hz), 124.2, 123.8, 123.6 (q,  $J_{C-F}$  = 270.1 Hz), 122.9, 52.4 ppm.  $^{19}F\{^1H\}$  NMR (376 MHz,  $CDCl_3$ ):  $\delta$  = -63.2 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{22}H_{14}NO_3F_3Na$  420.0818, found 420.0820 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 3-nitrobenzoate (2o):** 82.4 mg (73% yield), yellow solid, Mp: 111-113 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 8.82 (s, 1H), 8.40 (d,  $J$  = 8.0 Hz, 1H), 8.36 (dd,  $J$  = 8.0, 8.0 Hz, 1H), 7.76 (d,  $J$  = 7.6 Hz, 1H), 7.60 (dd,  $J$  = 8.0, 8.0 Hz, 1H), 7.53 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 7.48-7.37 (m, 6H), 4.80 (s, 2H) ppm.  $^{13}C\{^1H\}$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 167.3, 162.7, 148.3, 146.2, 141.6, 135.8, 132.0, 131.7, 130.9, 130.8, 130.0, 128.6, 128.3, 128.0, 127.8, 127.2, 125.1, 124.1, 123.7, 123.0, 52.4 ppm. HRMS (ESI) calcd. for  $[M + Na]^+$   $C_{21}H_{14}N_2O_5Na$  397.0795, found 397.0799 (1 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 3-methoxybenzoate (2p):** 57.5 mg (53% yield), white solid, Mp: 142-144 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 7.85 (d,  $J$  = 7.6 Hz, 1H), 7.68 (d,  $J$  = 7.6 Hz, 1H), 7.58 (s, 1H), 7.55-7.49 (m, 2H), 7.45-7.35 (m, 5H), 7.29 (dd,  $J$  = 8.0, 8.0 Hz, 1H), 7.08 (dd,  $J$  = 8.0, 2.4 Hz, 1H), 4.76 (s, 2H), 3.76 (s,



3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 167.6, 164.7, 159.7, 146.8, 141.7, 132.0, 131.9, 130.9, 130.3, 129.6, 128.7, 128.3, 128.2, 126.8, 124.2, 123.9, 122.9, 122.7, 120.8, 114.2, 55.5, 52.5 ppm. HRMS (ESI) calcd. for  $[\text{M} + \text{Na}]^+ \text{C}_{22}\text{H}_{17}\text{NO}_4\text{Na}$  382.1050, found 382.1051 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 2-fluorobenzoate (2r):** 65.6 mg (63% yield), white solid, Mp: 88-90 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.01 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 7.85 (d,  $J$  = 7.6 Hz, 1H), 7.56-7.35 (m, 8H), 7.15 (dd,  $J$  = 7.6, 7.6 Hz, 1H), 7.06 (dd,  $J$  = 8.4, 8.4 Hz, 1H), 4.80 (s, 2H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 167.6, 166.2 (d,  $J_{\text{C-F}}$  = 259.9 Hz), 162.0 (d,  $J_{\text{C-F}}$  = 3.9 Hz), 146.5, 141.8, 135.3 (d,  $J_{\text{C-F}}$  = 9.0 Hz), 132.6, 132.0, 131.9, 130.9, 128.6, 128.3, 128.2, 127.0, 124.24 (d,  $J_{\text{C-F}}$  = 4.1 Hz), 124.22, 123.9, 122.9, 117.6 (d,  $J_{\text{C-F}}$  = 9.2 Hz), 117.1 (d,  $J_{\text{C-F}}$  = 21.8 Hz), 52.4 ppm.  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -108.8 ppm. HRMS (ESI) calcd. for  $[\text{M} + \text{Na}]^+ \text{C}_{21}\text{H}_{14}\text{NO}_3\text{FNa}$  370.0850, found 370.0852 (1 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 2-chlorobenzoate (2s):** 38.9 mg (36% yield), yellow solid, Mp: 110-112 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.95 (d,  $J$  = 7.6 Hz, 1H), 7.87 (d,  $J$  = 7.6 Hz, 1H), 7.55 (dd,  $J$  = 7.6, 7.2 Hz, 1H), 7.48-7.37 (m, 8H), 7.29-7.23 (m, 1H), 4.80 (s, 2H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 167.6, 163.4, 146.7, 141.9, 134.3, 133.3, 133.2, 132.1, 132.04, 131.96, 131.2, 131.0, 128.89, 128.86, 128.3, 127.1, 126.9, 124.3, 123.8, 123.0, 52.5 ppm. HRMS (ESI) calcd. for  $[\text{M} + \text{Na}]^+ \text{C}_{21}\text{H}_{14}\text{NO}_3^{35}\text{ClNa}$  386.0554, found 386.0555 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl 2-naphthoate (2t):** 70.3 mg (62% yield), yellow solid, Mp: < 50 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.67 (s, 1H), 8.07 (d,  $J$  = 8.4 Hz, 1H), 7.88-7.82 (m, 4H), 7.60-7.37 (m, 9H), 4.80 (s, 2H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 167.8, 165.0, 146.9, 141.7, 135.9, 132.5, 132.2, 131.94, 131.89, 131.0, 129.6, 128.8, 128.5, 128.4, 128.2, 127.8, 126.8, 126.2, 125.4, 124.3, 124.0, 122.9, 52.5 ppm. HRMS (ESI) calcd. for  $[\text{M} + \text{Na}]^+ \text{C}_{25}\text{H}_{17}\text{NO}_3\text{Na}$  402.1101, found 402.1099 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl thiophene-2-carboxylate (2u):** 73.8 mg (77% yield), yellow solid, Mp: < 50 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.86 (d,  $J$  = 7.6 Hz, 1H), 7.57-7.36 (m, 8H), 7.29 (d,  $J$  = 7.6 Hz, 1H), 6.47 (dd,  $J$  = 2.8, 2.0 Hz, 1H), 4.79 (s, 2H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 167.6, 156.3, 147.5, 145.9, 143.4, 141.8, 131.9, 130.9, 128.5, 128.24, 128.20, 126.9, 124.2, 123.7, 122.9, 120.1, 112.2, 52.4 ppm. HRMS (ESI) calcd. for  $[\text{M} + \text{Na}]^+ \text{C}_{19}\text{H}_{13}\text{NO}_3\text{SNa}$  358.0508, found 358.0510 (0 ppm).

**2-(1-Oxoisindolin-2-yl)phenyl furan-2-carboxylate (2v):** 73.8 mg (77% yield), yellow solid, Mp: < 50 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.86 (d,  $J$  = 7.6 Hz, 1H), 7.57-7.36 (m, 8H), 7.29 (d,  $J$  = 7.6 Hz, 1H), 6.47 (dd,  $J$  = 2.8, 2.0 Hz, 1H), 4.79 (s, 2H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 167.6, 156.3, 147.5, 145.9, 143.4, 141.8, 131.9, 130.9, 128.5, 128.24, 128.20, 126.9, 124.2, 123.7, 122.9, 120.1, 112.2, 52.4 ppm. HRMS (ESI) calcd. for  $[\text{M} + \text{Na}]^+ \text{C}_{19}\text{H}_{13}\text{NO}_4\text{Na}$  392.0737, found 392.0740 (1 ppm).

**2-(2-Hydroxyphenyl)isoindolin-1-one (3):** 40.9 mg (63% yield), colourless solid,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.82 (br, 1H), 7.93 (d,  $J$  = 7.6 Hz, 1H), 7.64 (dd,  $J$  = 7.6, 7.2 Hz, 1H), 7.56-7.52 (m, 2H), 7.25-7.21 (m, 2H), 7.14 (dd,  $J$  = 8.4, 1.6 Hz, 1H), 6.99 (ddd,  $J$  = 8.0, 8.0, 1.6 Hz, 1H), 4.96 (s, 2H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 169.1, 150.9, 141.9, 132.6, 131.8, 128.8, 128.1, 127.5, 124.4, 122.8, 122.5, 121.3, 121.1, 52.7 ppm. MS (EI):  $m/z$  = 225 ( $\text{M}^+$ , 84), 196 (30), 132 (100), 120 (45). The spectral data match those previously reported.<sup>11</sup>

**Ethyl 3-hydroxy-4-(1-oxoisindolin-2-yl)benzoate (4):** 20.1 mg (23% yield), white solid, Mp: 205-207 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.09 (br, 1H), 7.94 (d,  $J$  = 7.6 Hz, 1H), 7.79 (d,  $J$  = 1.6 Hz, 1H), 7.68-7.64 (m, 2H), 7.58-7.54 (m, 2H), 7.27 (d,  $J$  = 8.0 Hz, 1H), 5.00 (s, 2H), 4.37 (q,  $J$  = 7.2 Hz, 2H), 1.40 (t,  $J$  = 7.2 Hz, 3H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 169.4, 166.0, 150.5, 141.9, 133.0, 131.5, 130.0, 129.0, 124.6, 122.9, 122.6, 122.3, 122.0, 61.2, 52.8, 14.4 ppm. HRMS (ESI) calcd. for  $[\text{M} + \text{Na}]^+ \text{C}_{17}\text{H}_{15}\text{NO}_4\text{Na}$  320.0893, found 320.0888 (2 ppm).

**2-(2-oxopyrrolidin-1-yl)phenyl benzoate (9):** 68.8 mg (49% yield), brown oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.18 (d,  $J$  = 7.6 Hz, 2H), 7.62 (dd,  $J$  = 7.6, 7.2 Hz, 1H), 7.49 (dd,  $J$  = 7.6, 7.6 Hz, 2H), 7.38-7.27 (m, 4H), 3.71 (t,  $J$  = 7.2 Hz, 2H), 2.36 (t,  $J$  = 8.0 Hz, 2H), 2.05-1.97 (m, 2H) ppm.  $^{13}\text{C}\{^1\text{H}\}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 174.3, 164.7, 146.4, 133.8, 131.3, 130.2, 129.0, 128.7, 128.4, 127.5, 126.7, 123.7, 50.1, 31.1, 19.3 ppm. HRMS (ESI) calcd. for  $[\text{M} + \text{Na}]^+ \text{C}_{17}\text{H}_{15}\text{NO}_3\text{Na}$  304.0944, found 309.0946 (1 ppm).

## Conclusions

In summary, we have developed an efficient benzoylation reaction to selectively form unprecedented C-O bonds within the isoindolinone core. The catalysis tolerates an important number of functional groups at different positions within both coupling partners. This ruthenium(II) catalysis constitutes an example of site-selective transformation where the combination of the weak directing group (cyclic amide) with the ruthenium catalyst enables to discriminate between two aromatic C-H bonds having comparable bond dissociation energies. Moreover, mono-functionalized products are exclusively obtained for this C-O bond-forming reaction. Overall, this methodology highlights the uniqueness of ruthenium catalysts enabling formation of six-membered ring intermediates throughout the catalysis even with very weak directing groups.

## Conflicts of interest

There are no conflicts to declare.

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## TOC

A general site- and regio-selective aromatic C-H bond benzylation reaction using biologically-relevant isoindolinones as weak directing groups has been developed.

