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Article

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Site-Selective Ruthenium-Catalyzed C-H Bond Arylations with Boronic Acids: Exploiting Isoindolinones as a Weak Directing Group

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

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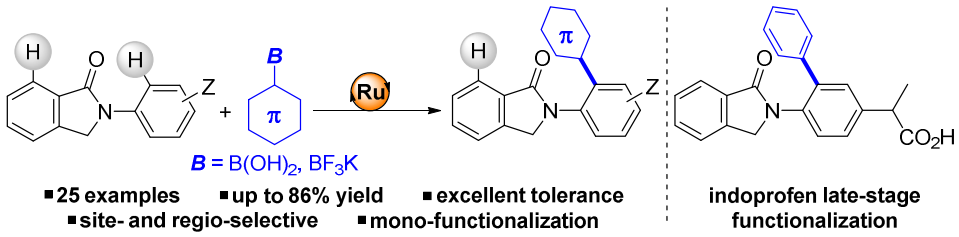
ABSTRACT:

Biologically relevant *N*-arylisoindolinones efficiently underwent arylation reactions under ruthenium catalysis *via* C-H bond functionalization. The reactions exclusively led to mono-arylated products and only *ortho* selectivity was observed in the aromatic ring connected to the nitrogen atom. Interestingly, no C-H bond functionalization was observed in the other benzene ring being in *ortho* position with respect to the carbonyl group. This ruthenium-catalyzed reaction displayed a high functional group tolerance, and it employed readily available and benchmark stable boronic acid and potassium aryltrifluoroborate derivatives as coupling partners. An appealing late-stage functionalization of indoprofen applying this methodology is showcased.



■ INTRODUCTION

Isoindolinones are an important class of compounds which combine a benzene ring fused with a five-membered cyclic tertiary amide.[1] For instance, *N*-arylisoindolinones are present in many relevant pharmaceutical and medicinal compounds[2] as well as building blocks for pigments and other molecular materials.[3] For example, indoprofen (**A**) displays anti-inflammatory activity,[4] DWP205190 (**B**) is known to be an inhibitor for the production of tumor necrosis factor TNF-α[5] and **C** behaves as a potent and selective 5-HT_{2C} antagonist (Figure 1).[6] Consequently, the access to molecular diversity arising from the isoindolinone motif is receiving increasing attention.[7]

In particular, the use of weak directing groups in transition metal-catalyzed C-H bond functionalization[8] has emerged as a powerful strategy for implementation in the late-stage derivatization of biologically active molecules in the last years.[9] In this context, transition metal-catalyzed carbon-carbon bond-forming reactions *via* C-H bond functionalization occupy a central place as they represent a sustainable approach compared to traditional Suzuki, Heck or Stille cross-coupling reactions that generate over-stoichiometric amounts of organometallic species starting from highly pre-functionalized building blocks.[10]

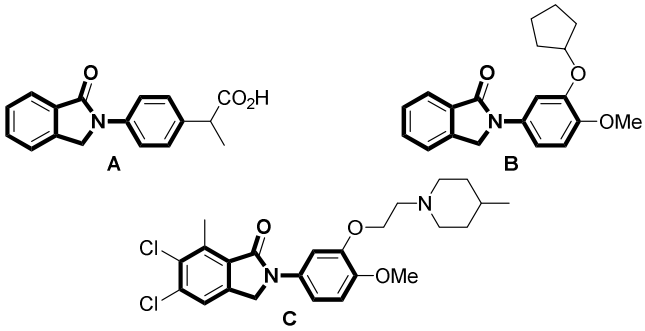


Figure 1. Examples of important *N*-arylisoindolinones.

However, the use of *N*-substituted phenylbenzamides (Ar^1-CONR-Ar^2), *the acyclic version of N-arylisoindolinones*, as weak directing groups for the formation of new carbon-carbon bonds *via* transition metal-catalyzed C-H bond functionalizations remains rare with limited examples reported to date (Figure 2). For instance, Miura and co-workers described a ruthenium-catalyzed hydroarylation of *N,N*-diphenylbenzamide with diphenylacetylene in 2012 (Figure 2A).[11] Two years later, Glorius and co-workers described an example of rhodium-catalyzed alkynylation of *N*-isopropyl phenylbenzamide with TIPS-EBX (TIPS-EBX = 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one) as reagent (Figure 2B)[12] and a ruthenium-catalyzed cyanation of *N*-methyl phenylbenzamide with NCTS (NCTS = *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide) was developed by Ackermann and co-workers (Figure 2C).[13] In these three examples,[11-13] the C-H bond belonging to the benzamide aromatic ring **A** was the one that was functionalized (Figure 2A-C). These observations highlight the challenge to reverse the site-selectivity for discriminating between two chemically similar aromatic C-H bonds where a carbon-carbon bond forming reaction can take place.[11-14] It is important to note that *secondary amides* (RCONHR) behave differently than *tertiary amides* ($RCONR_2$) when transiently coordinating to the metal catalyst throughout the catalytic cycle. Whereas in the former case the nitrogen atom strongly binds to the metal center due to amide tautomerization,[15] in the latter case it is the oxygen atom that weakly binds to the catalyst.[16]

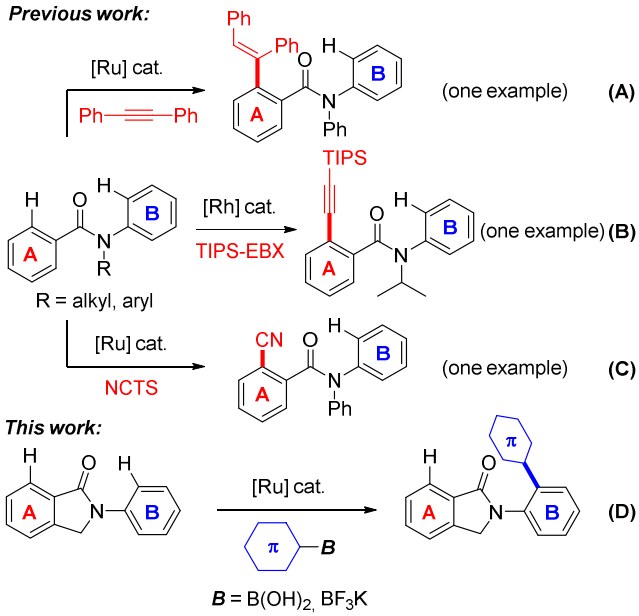


Figure 2. State-of-the-art for the site-selective transition metal-catalyzed carbon-carbon bond formations *via* aromatic C-H bond functionalizations of acyclic *vs* cyclic *N*-substituted arylbenzamides as weak coordinating groups (A-C) and present work (D).

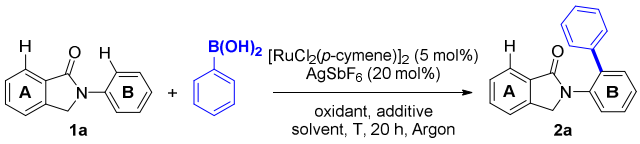
In view of the need for methodologies available to target selective C-H bond functionalizations with biologically relevant molecules, we report herein on site-selective ruthenium-catalyzed arylation reactions applied to the isoindolinone motif (Figure 2D). The carbonyl group of the cyclic tertiary amide turned out to act as an excellent weak directing group enforcing the catalysis to take place selectively at the *ortho* position of the acetanilide aromatic ring **B** employing readily available boronic acid derivatives and potassium aryltrifluoroborates as coupling partners (Figure 2D). The methodology was applied to the late-stage derivatization of a biologically relevant target: indoprofen (Figure 1). Selective C-H bond arylation reactions occurring in the acetanilide aromatic ring **B** of tertiary phenylbenzamides (Ar^1-CONR-Ar^2) are unknown to date, although ruthenium-catalyzed C-H bond arylations with boronic acid derivatives containing a single aromatic fragment using weak directing groups have been reported.[16,17]

■ RESULTS AND DISCUSSION

Encouraged by the use of aryl boronic acids as coupling partners for ruthenium-catalyzed C-H bond arylation of tertiary amides containing a sole aromatic fragment by Szostak and co-workers,[16a] *N*-phenylisoindolinone **1a** was reacted with phenylboronic acid as an aryl source under different reaction conditions in the presence of [$RuCl_2$(*p*-

cymene)]$_2$ as pre-catalyst to study the formation of arylated products (Table 1). Initially, the reaction conditions developed by Szostak were employed leading to 51% yield of the arylated product **2a**, in which the C-H bond arylation occurred at the *ortho* position of the aromatic ring **B** (Table 1, entry 1). Gratifyingly, no C-H bond arylation occurred in the benzamide aromatic ring **A** according to the NMR analyses of the reaction mixture. Whereas the reaction conditions developed by Szostak are sought to proceed via a 5-membered ruthenacycle species,[16a] in our case, a 6-membered ruthenacycle species might form considering the outcome of the reaction. In contrast to observations from Szostak,[16a] we noticed that the absence of water led to an increase of reactivity with 72% yield of the targeted compound **2a** (Table 1, entry 2). Changing THF as solvent for 2-MeTHF or NMP led to **2a** in yields as low as 34% and 10%, respectively (Table 1, entries 3 and 4). The use of DMF, DCE, dioxane, ^{t}AmOH, toluene and acetonitrile as solvents, respectively, completely inhibited the reaction (Table 1, entries 5-10). Reactions using different oxidants [Cu(OAc)$_2$•H$_2$O, (NH$_4$)$_2$S$_2$O$_8$, Ag$_2$CO$_3$, AgOAc] and triflate metal salts as additives [AgOTf, Zn(OTf)$_2$] in place of Ag$_2$O and Cu(OTf)$_2$ led to low yields of the product (Table 1, entries 11-16). In the presence of one equivalent of Cu(OTf)$_2$ instead of 20 mol%, the same reactivity was observed (Table 1, entry 17). Other ruthenium complexes such as [Ru(NC^{t}Bu)$_6$](BF$_4$)$_2$ and [Ru(*p*-cymene)(O$_2$CMes)$_2$] were catalytically unproductive (Table 1, entries 18 and 19). These observations suggest that (i) the catalytically active species could involve *para*-cymene coordinated ruthenium complexes and (ii) the carboxylate anions inhibit the reactions to some extent (see also Table 1, entries 11 and 14). The reaction performed under air atmosphere still afforded **2a** in 55% yield (Table 1, entry 20). Additionally, control experiments revealed the necessity of all reagents for the favorable outcome of the reaction (Table 1, entries 21-24). We found that the reaction was also operating at temperatures lower than 110 °C. For instance, 74% yield of **2a** was obtained in a reaction conducted at 90 °C (Table 1, entry 25), 66% at 70 °C (Table 1, entry 26) and 59% at room temperature (Table 1, entry 27). This constitutes a unique example of ruthenium-catalyzed C-H bond arylation at room temperature and mild conditions using weak directing groups.[18] We noted that the reaction did not proceed when replacing phenylboronic acid by phenylboronic acid glycol ester (Table 1, entry 28), indicating the preference of this methodology for aryl boronic acids rather than arylboronate derivatives. The catalysis performed at larger scale (starting from 1 mmol of **1a**) afforded the corresponding product **2a** in 71% isolated yield (Table 1, entry 29) using the optimal reaction conditions.

Table 1. Survey for the Optimal Reaction Conditions for the Site-Selective Ru-Catalyzed C-H Bond Arylation of 1a with Phenylboronic Acid[a]



entry	oxidant	additive	solvent	T (°C)	Yield (%)[b]
1[c]	Ag$_2$O	Cu(OTf)$_2$	THF	110	51
2	Ag$_2$O	Cu(OTf)$_2$	THF	110	72
3	Ag$_2$O	Cu(OTf)$_2$	2-MeTHF	110	34
4	Ag$_2$O	Cu(OTf)$_2$	NMP	110	10
5	Ag$_2$O	Cu(OTf)$_2$	DMF	110	<5
6	Ag$_2$O	Cu(OTf)$_2$	DCE	110	<5
7	Ag$_2$O	Cu(OTf)$_2$	dioxane	110	<5
8	Ag$_2$O	Cu(OTf)$_2$	^{t}AmOH	110	<5
9	Ag$_2$O	Cu(OTf)$_2$	toluene	110	<5
10	Ag$_2$O	Cu(OTf)$_2$	MeCN	110	<5
11	Cu(OAc)$_2$·H$_2$O	Cu(OTf)$_2$	THF	110	0
12	(NH$_4$)$_2$S$_2$O$_8$	Cu(OTf)$_2$	THF	110	0
13	Ag$_2$CO$_3$	Cu(OTf)$_2$	THF	110	34
14	AgOAc	Cu(OTf)$_2$	THF	110	9
15	Ag$_2$O	AgOTf	THF	110	0
16	Ag$_2$O	Zn(OTf)$_2$	THF	110	0
17[d]	Ag$_2$O	Cu(OTf)$_2$	THF	110	75
18[e]	Ag$_2$O	Cu(OTf)$_2$	THF	110	0
19[f]	Ag$_2$O	Cu(OTf)$_2$	THF	110	0
20[g]	Ag$_2$O	Cu(OTf)$_2$	THF	110	55
21[h]	Ag$_2$O	Cu(OTf)$_2$	THF	110	0
22[i]	Ag$_2$O	Cu(OTf)$_2$	THF	110	<5
23	-	Cu(OTf)$_2$	THF	110	<5
24	Ag$_2$O	-	THF	110	13
25	Ag$_2$O	Cu(OTf)$_2$	THF	90	74 (72)
26	Ag$_2$O	Cu(OTf)$_2$	THF	70	66
27	Ag$_2$O	Cu(OTf)$_2$	THF	25	59
28[j]	Ag$_2$O	Cu(OTf)$_2$	THF	110	<5
29[k]	Ag$_2$O	Cu(OTf)$_2$	THF	100	71

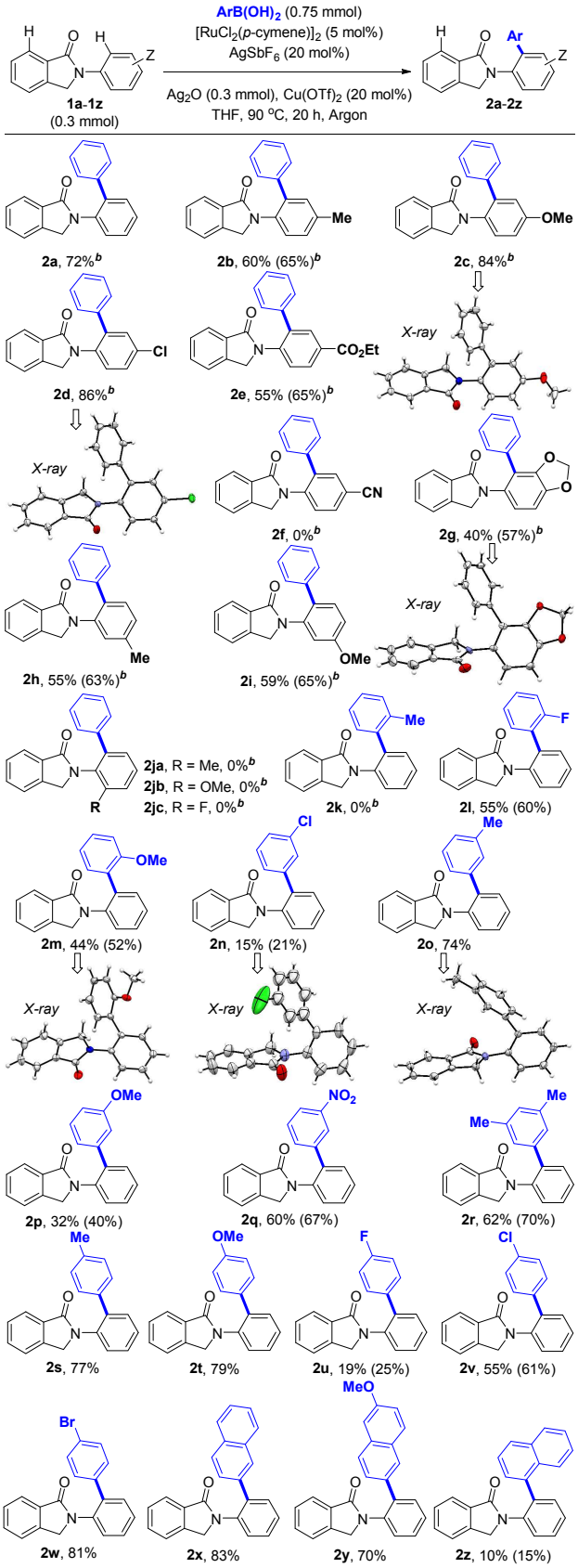
[a]Reaction conditions: **1a** (0.1 mmol, 1 equiv.), phenylboronic acid (0.25 mmol, 2.5 equiv.), [RuCl$_2$(*p*-cymene)]$_2$ (5 mol%), AgSbF$_6$ (20 mol%), oxidant (0.1 mmol, 1 equiv.), additive (20 mol%), solvent (0.5 mL), 20 h, Argon. [b]Determined by ^{1}H NMR spectroscopy analysis using dibromomethane as internal standard; isolated yields obtained after purification by column chromatograph are displayed in parentheses. [c]H$_2$O (3 equiv.). [d]Cu(OTf)$_2$ (1 equiv.). [e][Ru(NC^{t}Bu)$_6$](BF$_4$)$_2$ instead of [RuCl$_2$(*p*-cymene)]$_2$. [f][Ru(*p*-cymene)(O$_2$CMes)$_2$] instead of [RuCl$_2$(*p*-cyme-ne)]$_2$. [g]Air instead of Argon. [h]Without [RuCl$_2$(*p*-cymene)]$_2$. [i]Without AgSbF$_6$. [j]Phenylboronic acid glycol ester instead of phenylboronic acid. [k]Reaction conditions: **1a** (1 mmol, 1 equiv.), phenylboronic acid (2.5 mmol, 2.5 equiv.), [RuCl$_2$(*p*-cymene)]$_2$ (5 mol%), AgSbF$_6$ (20 mol%), Ag$_2$O (1 mmol, 1 equiv.), Cu(OTf)$_2$ (20 mol%), THF (5 mL), 20 h, Argon.

Next, we applied the optimal reaction conditions we found (Table 1, entry 25) to *N*-arylisoindolinones **1** and boronic acid derivatives containing both different substitution patterns in order to determine the scope and limitations for this transformation (Table 2). Isoindolinones

para-substituted with methyl, methoxy and chloro groups were well tolerated leading to the corresponding arylated products **2b**-**2d** in 60-86% yield. Notably, carboxylic acid ester groups were suitable for the ruthenium-catalyzed C-H bond arylation protocol affording **2e** in 55% yield. Although ester groups are known to direct some ruthenium-catalyzed C-H bond functionalizations,[19] in the present case the isoindolinone core seems to be more appropriate for coordination to ruthenium and thus, it exclusively dictates the selectivity of the reaction. Unfortunately, nitrile-containing partners are not compatible with the catalysis (**2f**) as it appeared to be the case in other ruthenium-catalyzed C-H bond functionalizations as well.[15-17] Dioxolane-containing isoindolinone led to a single isomer **2g** in 40% isolated yield. Methyl- and methoxy-substituted isoindolinones in *meta* position led exclusively to **2h** and **2i**, respectively, in 55% and 59% yield. Moreover, the reactions were sensitive to the steric hindrance found in some substrates. For instance, *ortho*-substituted coupling partners did not react as evidenced in the absence of formation of **2j**-**2k**. However, the reaction did operate using *ortho*-fluorophenylboronic acid and *ortho*-methoxyphenylboronic acid as coupling partners leading to **2l** and **2m** in 55% and 44% yield, respectively. *meta*-Substituted phenylboronic acids are overall well tolerated with the only exception of the chloride derivative, which led to **2n** in 15% yield. On the other hand, the reactions with methyl-, methoxy- and nitro-containing boronic acids afforded the corresponding products **2o**, **2p** and **2q** in 74%, 32% and 60% yields, respectively. As such, the reaction seems to be sensitive to the electronic effects imposed by the boronic acids substituted in *meta* position. The reaction for 3,5-dimethylphenylboronic acid gave rise to the corresponding arylated product **2r** in 70% yield. *para*-Substituted phenylboronic acids were also used in this C-H bond arylation protocol. Methyl- and methoxy-containing products **2s** and **2t** were formed in comparable yields of 77% and 79%. In the case of reactions with substrates containing halides in the *para* position of the phenylboronic acid, a trend was observed following the order of reactivity F < Cl < Br with **2u**, **2v** and **2w** respectively obtained in 19%, 55% and 81% yield. The main by-product observed during the formation of **2u** is the one resulting from the homocoupling of the corresponding boronic acid derivative. Naphthalene-containing boronic acids efficiently reacted leading to **2x** and **2y** in 83% and 70% yield, respectively. The reaction with very bulky 1-naphthaleneboronic acid still afforded the corresponding product **2z** but in a low yield of 10%.

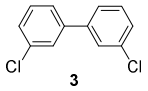
Moreover, single crystal X-ray diffraction studies established the molecular structures of **2c**, **2d**, **2g**, **2m**, **2n** and **2o** (Table 2), thus unambiguously supporting the control of the site- and regio-selectivity during the catalysis. It is worthy to mention that the traditional synthetic route towards this types of products require the use of over-stoichiometric amounts of metal zinc and highly pre-functionalized starting materials, which require an important number of additional steps that significantly decreases the overall yield and generates significant chemical waste.[20a] As such, the presented ruthenium-catalyzed arylation is appealing in terms of an atom- and step-economy methodology. Importantly, analogs to products **2** have been studied against the spinal muscular atrophy.[20b]

Table 2. Scope and Limitations for the C-H Bond Arylation of N-arylisoindolinones[a]

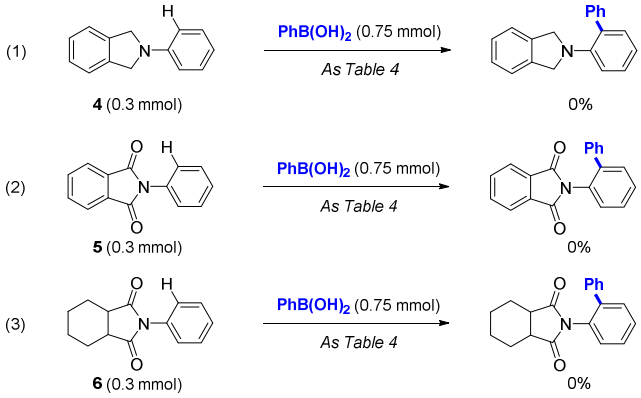


[a]Isolated yields obtained after purification by column chromatography are displayed whereas conversions are shown in parentheses. [b]110 °C instead of 90 °C.

Interestingly, no C-H bond bis-arylation was observed for any of the cases presented in Table 2. In some cases, the product resulting from the homocoupling of the boronic acid derivative was detected as illustrated by the isolation of **3** (*vide infra*) during the purification of **2n**. This homocoupling reaction appears to be a side reaction that may explain the relatively low yields obtained in some of the cases in Table 2. We noted that very challenging boronic acids such as alkyl boronic ones (e.g. 1-butylboronic acid) and heteroaromatic-containing ones (e.g. 3-thiopheneboronic acid) did not react under the studied reaction conditions illustrating the current limitations of the methodology as it has been shown before with other substrates.[16a,17]

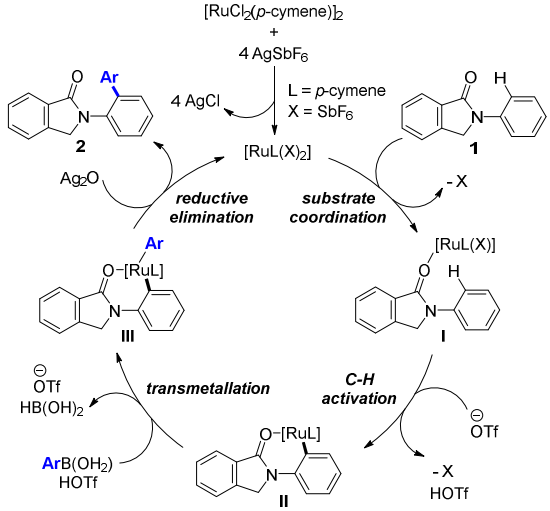


In order to study the relevance of the carbonyl group from the isoindolinone core as a weak directing group in the catalysis, we performed a control reaction employing a substrate featuring no ketone group. Under the studied reaction conditions, isoindoline **4** did no afford any arylated product (Eq. 1). The same outcome was observed in the catalysis with the cyclic imides **5** and **6** as substrates (Eq. 2 and Eq. 3). These findings suggest that (i) the carbonyl group of the isoindolinone **1** acts as a weak directing unit throughout the catalytic cycle and (ii) that the flexibility and less steric hindrance of cyclic amides (i.e. **1**) when compared to cyclic imides (i.e. **5-6**) enable to accommodate key ruthenacycle species. Deuteration experiments using *N*-phenylisoindolinone **1a** were performed and they were not conclusive at this stage.



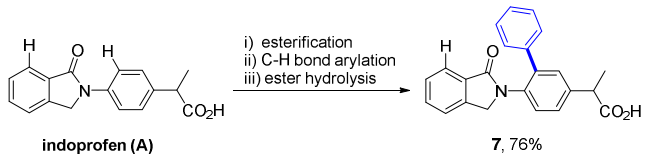
These data, combined with previous observations,[16a,17,21] enabled us to suggest a plausible reaction mechanism for the C-H bond arylation of *N*-arylisoindolinones (Scheme 1). Initially, chloride-free ruthenium(II) complexes coordinate to substrate **1** *via* the oxygen lone pair of the ketone group to from species **I**. Then, base-assisted C-H bond activation enabled by triflate anions led to a six-membered ruthenacycle species **II**. In the presence of boronic acids, intermediate **III** forms that undergoes reductive elimination giving product **2** and the resulting ruthenium(0) species were regenerated into active ruthenium(II) species upon oxidation with Ag_2O.

Scheme 1. Simplified, Plausible Catalytic Cycle for the Ru-Catalyzed C-H Bond Arylation of Isoindolinones 1



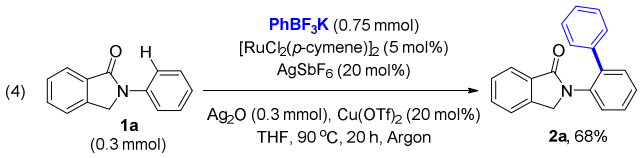
To further demonstrate the potential and utility of this methodology, we decided to apply it to the late-stage functionalization of biologically relevant indoprofen **A** (Figure 1 and Scheme 2), which is known to display anti-inflammatory activity.[4] Indoprofen **A** contains a carboxylic acid that, unfortunately, is not compatible under the standard reaction conditions. However, it can readily be converted into an ester group, which in turn, is compatible with our methodology (see **2e** in Table 2). Consequently, we performed a reaction sequence involving (1) esterification, (2) ruthenium-catalyzed C-H bond arylation and (3) ester hydrolysis. In this manner, the corresponding *ortho*-arylated indoprofen **7** was obtained in 76% overall yield starting from indoprofen over three steps (Scheme 2). The regio- and site-selectivity observed in the resulting product **7** was determined by multinuclear NMR spectroscopy studies. During the sequence, only one column chromatography was performed in the second step as the first and third steps are almost quantitative and require a trivial acid/base workup for the isolation of the products. As such, this sequence can be considered as sustainable to some extent.

Scheme 2. Application of the Ru-Catalyzed Site-Selective C-H Bond Arylation to the Late-Stage Functionalization of Indoprofen[a]

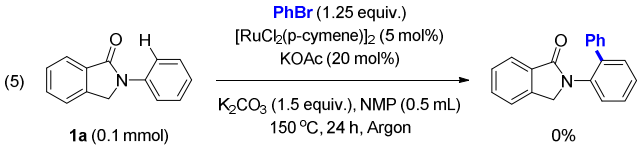


[a]Reaction conditions: (i) H_2SO_4 (cat.), EtOH, reflux, 12 h, 99%; (ii) $Ph(BOH)_2$ (2.5 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Ag_2O (1 equiv.), $Cu(OTf)_2$ (20 mol%), THF, 90 °C, 20 h, 85%; (iii) NaOH (2 M), MeOH:THF, r.t., 12 h, 90%.

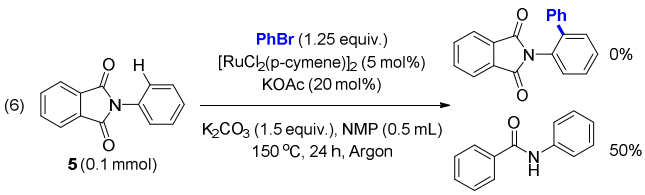
In addition, we reasoned that potassium organotrifluoroborates, which are nowadays well recognized as efficient coupling partners in cross-coupling chemistry,[22] may eventually be used for site-selective ruthenium-catalyzed C-H bond arylation reactions as well. As a proof of concept, *N*-phenylisoindolinone **1a** was submitted to our standard reaction conditions but employing potassium phenyltrifluoroborate as the aryl source for the C-H bond functionalization instead of phenylboronic acid. Gratifyingly, the reaction was equally efficient leading to the mono-arylated product **2a** in 68% yield (Eq. 4).



Finally, for comparison purposes, *N*-phenylisoindolinone **1a** was submitted to the reaction conditions traditionally used for ruthenium-catalyzed C-H bond arylation reactions with strong nitrogen-containing directing units.[23] They consist of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), KOAc (20 mol%), K_2CO_3 as base, bromobenzene as aryl source in NMP as solvent at 150 °C (Eq. 5). Under these reaction conditions, the starting material **1a** was found unreactive. This shows the true potential of boronic acids and related derivatives[17] as an alternative to replace aryl halides and aryl pseudo-halides as coupling partners for challenging C-H bond arylation reactions with transition metal catalysts, as it is the case here for weak directing groups.



Furthermore, the same reaction conditions applied to *N*-phenylphthalimide **5** did not produce any arylated product, but *N*-phenylbenzamide was formed to some extent (Eq. 6). We have previously reported improved reaction conditions, and substrate scope and limitations regarding this unexpected ruthenium-catalyzed protodecarbonylation reaction.[24]



■ CONCLUSIONS

In conclusion, we have disclosed an efficient and site-selective ruthenium-catalyzed C-H bond arylation protocol to form unique aromatic C(sp²)-C(sp²) bonds within the biologically relevant isoindolinone skeleton. A large number of number of useful functional chemical groups [e.g. fluoro, chloro, bromo, nitro, alkyl, (a)cyclic ethers, esters, polycyclic aromatic hydrocarbons] at different positions (*ortho*, *meta*, *para*) within the different coupling partners are tolerated by the catalysis due to the mild conditions employed. This catalysis represents a type of general selective functionalization in which combining a ruthenium(II) catalyst with a weak coordinating group (i.e. cyclic amide) promotes the discrimination of one out of two aromatic C-H bonds with similar bond dissociation energies. In addition, mono-arylated products were exclusively obtained in the above-described catalysis. The previously neglected homocoupling side-products observed during the C-H bond arylation reaction are likely originating from a simultaneous reaction that competes with the C-H bond arylation. Importantly, this methodology shows the relevance of ruthenium(II) pre-catalysts leading to the formation of six-membered ruthenacycles during the catalysis even when using weak coordinating groups within the substrate. In addition, and considering the availability of the developed ruthenium-based catalytic systems, one could expect manifold implementations of this strategy in the late-stage derivatization of potential drug candidates (as it is shown here with indoprofen) and (supra)molecular materials that feature such relevant organic skeleton or similar chemical motifs.

■ EXPERIMENTAL SECTION

General Methods. 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. $CDCl_3$ was stored under nitrogen over molecular sieves. NMR spectra were recorded on an AVANCE III 400 spectrometer. ¹H NMR spectra were referenced to residual protiated solvent (δ = 7.26 ppm for $CDCl_3$, δ = 2.50 ppm for DMSO-d_6 and δ = 2.05 ppm for acetone-d_6) and ¹³C chemical shifts are reported relative to deuterated solvents (δ = 77.0 ppm for $CDCl_3$, δ = 39.5 ppm for DMSO-d_6 and δ = 29.8 ppm for acetone-d_6) [Note: 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 °C for 2 minutes, then 20 °C/min until 280 °C and 280 °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*-arylisoindolinone substrates (1): A mixture of 2-formylbenzoic acid (0.751 g, 5 mmol, 1 equiv.), the corresponding aniline derivative (6 mmol, 1.2 equiv.), DABCO (1.122 g, 10 mmol, 2 equiv.), HCOOH (1.25 mL, 1.525 g, 33.1 mmol), $Pd(OAc)_2$ (0.056 g, 0.25 mmol, 5 mol%) in 1,4-dioxane (5 mL) was heated in an oil bath at 80 °C for 3 hours. 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 Na_2SO_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 (0.55 mL, 0.559 g, 6 mmol) in 98% isolated yield (1.03 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

2-(*p*-Tolyl)isoindolin-1-one (1b): starting from *p*-toluidine (0.66 mL, 0.643 g, 6 mmol) in 80% isolated yield (0.89 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

2-(*p*-Methoxyphenyl)isoindolin-1-one (1c): starting from *p*-anisidine (0.739 g, 6 mmol) in 62% isolated yield (0.74 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

2-(*p*-Chlorophenyl)isoindolin-1-one (1d): starting from *p*-chloroaniline (0.765 g, 6 mmol) in 61% isolated yield (0.74 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

Ethyl 4-(1-oxoisoindolin-2-yl)benzoate (1e): starting from ethyl 4-aminobenzoate (0.991 g, 6 mmol) in 96% isolated yield (1.35 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

4-(1-Oxoisoindolin-2-yl)benzonitrile (1f): starting from 4-aminobenzonitrile (0.709 g, 6 mmol) in 64% isolated yield (0.71 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

2-(Benzo[*d*][1,3]dioxol-5-yl)isoindolin-1-one (1g): starting from 3,4-(methylenedioxy)aniline (0.823 g, 6 mmol) in 58% isolated yield (0.73 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

2-(*m*-Tolyl)isoindolin-1-one (1h): starting from *m*-toluidine (0.64 mL, 0.643 g, 6 mmol) in 65% isolated yield (0.73 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

2-(*m*-Methoxyphenyl)isoindolin-1-one (1i): starting from *m*-anisidine (0.67 mL, 0.739 g, 6 mmol) in 80% isolated yield (0.96 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

2-(*o*-Tolyl)isoindolin-1-one (1ja): starting from *o*-toluidine (0.64 mL, 0.643 g, 6 mmol) in 68% isolated yield (0.76 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[25]

2-(2-Methoxyphenyl)isoindolin-1-one (1jb): starting from *o*-anisidine (X.XX mL, X.XX g, X mmol) in 61% isolated yield (X.XX g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.6 Hz, 1H), 7.58 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.43 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.32 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1H), 7.06-7.00 (m, 2H), 4.80 (s, 2H), 3.82 (s, 3H) ppm.. The spectral data match those previously reported.[25]

2-(2-Fluorophenyl)isoindolin-1-one (1jc): starting from *o*-fluoroaniline (0.19 mL, 0.222 g, 2 mmol) in 76% isolated yield (0.35 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.4 Hz, 1H), 7.67-7.60 (m, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.33-7.27 (m, 1H), 7.25-7.18 (m, 2H), 4.88 (s, 2H) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = -120.5 ppm. The spectral data match those previously reported.[26]

Synthesis and characterization of isoindoline (4): 1,2-Bis(bromomethyl)benzene (1.32 g, 5 mmol, 1 equiv.), DIPEA (2.18 mL, 1.62 g, 12.5 mmol, 2.5 eq.), and aniline (0.68 mL, 0.698 g, 7.5 mmol, 1.5 equiv.) were dissolved in toluene (25 mL) and added to a sealed tube before vigorously stirring at 110 °C in an oil bath under a N_2 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_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether) to obtain the desired product **4** (89%

isolated yield, 0.87 g) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[27]

Synthesis and characterization of *N*-phenylphthalimide (5): In a Schlenk tube, Phthalic anhydride (0.74 g, 5 mmol, 1 equiv.), aniline (0.47 g, 5 mmol, 1 equiv.) and acetic acid (30 mL) were refluxed in an oil bath for 2-5 h. Once at room temperature, water was added and the solid recovered by filtration. After drying under vacuum the desired phthalimide **5** (80% isolated yield, 0.89 g) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[28]

Synthesis and characterization of 2-Phenylhexahydro-1*H*-isoindole-1,3(2*H*)-dione (6): Hexahydrophthalic anhydride (1.54 g, 10 mmol, 1 equiv.) and aniline (0.91 mL, 0.93 g, 10 mmol, 1 equiv.) and THF (15 mL) were added to a 100 mL round bottom flask. The solution was stirred for 30 min. at 40 °C in an oil bath. 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 Ar for 4 h. The desired hexahydrophthalimide **6** (86% isolated yield, 1.97 g) was purified by silica gel column chromatography (petroleum ether/EtOAc gradient 10:1 to 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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.[29]

General procedure for the arylation reactions, and characterization of products 2: $[RuCl_2(p\text{-cymene})]_2$ (9.2 mg, 0.015 mmol, 5 mol%), $AgSbF_6$ (20.6 mg, 0.06 mmol, 20 mol%), Ag_2O (69.5 mg, 0.3 mmol, 1.0 equiv.), $Cu(OTf)_2$ (21.7 mg, 0.06 mmol, 20 mol%), the corresponding *N*-arylisoindolinone derivative **1** (0.3 mmol, 1.0 equiv.) and the corresponding phenylboronic acid derivative (0.75 mmol, 2.5 equiv.) were taken in a 15 mL Schlenk tube, which was equipped with a magnetic stirrer bar. THF (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 90 or 110 °C for 20 h in an oil bath. 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 gradient 10:1 to 5:1) to give the desired product **2**.

2-([1,1'-Biphenyl]-2-yl)isoindolin-1-one (2a): 61.6 mg (72% yield), white solid, Mp: < 50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.2 Hz, 1H), 7.52-7.43 (m, 6H), 7.40-7.38 (m, 2H), 7.32-7.24 (m, 4H), 4.17 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.0, 141.7, 139.9, 139.2, 135.9, 132.2, 131.7, 131.1, 129.1, 128.7, 128.6, 128.4, 128.3, 128.1, 127.6, 124.3, 122.7, 52.3 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{20}H_{15}NONa$ 308.1046, found 308.1050 (1 ppm).

2-(5-Methyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2b): 54.3 mg (60% yield), white solid, Mp: 167-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.2 Hz, 1H), 7.51-7.44 (m, 2H), 7.40-7.35 (m, 3H), 7.31-7.22 (m, 6H), 4.16 (s, 2H), 2.44 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.1, 141.7, 139.7, 139.2, 138.2, 133.3, 132.3, 131.7, 131.6, 129.4, 128.9, 128.6, 128.4, 128.1, 127.5, 124.3, 122.7, 52.4, 21.3 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{21}H_{17}NONa$ 322.1202, found 322.1202 (0 ppm).

2-(5-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2c): 79.1 mg (84% yield), white solid, Mp: 162-164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.2 Hz, 1H), 7.51-7.43 (m, 2H), 7.41-7.36 (m, 3H), 7.31-7.22 (m, 4H), 7.01-6.98 (m, 2H), 4.14 (s, 2H), 3.86 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.2, 159.2, 141.6, 141.2, 139.0, 132.2, 131.5, 130.2, 128.6, 128.3, 128.0, 127.7, 124.2, 122.6, 116.1, 114.1, 55.7, 52.6 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{21}H_{17}NO_2Na$ 338.1152, found 338.1153 (0 ppm). Single crystals suitable for X-ray diffraction studies were obtained after evaporation of a solution of **2c** in acetone.

2-(5-Chloro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2d): 82.8 mg (86% yield), white solid, Mp: 121-123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.2 Hz, 1H), 7.53-7.42 (m, 5H), 7.37-7.34 (m, 2H), 7.33-7.26 (m, 4H), 4.14 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.1, 141.6, 141.4, 137.9, 134.6, 133.8, 131.92, 131.90, 131.0, 130.4, 128.9, 128.7, 128.3, 128.24, 128.16, 124.4, 122.8, 52.1 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{20}H_{14}NO^{35}ClNa$ 342.0656, found 342.0658 (1 ppm). Single crystals suitable for X-ray diffraction studies were obtained after evaporation of a solution of **2d** in acetone.

Ethyl 6-(1-oxoisoindolin-2-yl)-[1,1'-biphenyl]-3-carboxylate (2e): 59.2 mg (55% yield), white solid, Mp: < 50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, J = 2.0 Hz, 1H), 8.12 (dd, J = 8.4, 2.0 Hz, 1H), 7.92 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.54-7.45 (m, 2H), 7.40 (dd, J = 8.0, 1.6 Hz, 2H), 7.35-7.27 (m, 4H), 4.41 (q, J = 7.2 Hz, 2H), 4.17 (s, 2H), 1.40 (t, J = 7.2 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.9, 166.0, 141.6, 140.2, 139.4, 138.5, 132.6, 132.0, 131.9, 130.0, 129.7, 129.0, 128.4, 128.3, 128.0, 124.4, 122.8, 61.3, 51.9, 14.5 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{23}H_{19}NO_3Na$ 380.1257, found 380.1259 (0 ppm).

2-(4-Phenylbenzo[d][1,3]dioxol-5-yl)isoindolin-1-one (2g): 39.8 mg (40% yield), white solid, Mp: 212-214 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.2 Hz, 1H), 7.51-7.41 (m, 4H), 7.32-7.23 (m, 4H), 6.95 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.02 (s, 2H), 4.17 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.4, 147.3, 146.2, 141.6, 132.7, 132.2, 131.7, 130.0, 129.1, 128.7, 128.2, 128.1, 124.4, 122.69, 122.65, 122.55, 108.0, 101.9, 52.9 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{21}H_{15}NO_3Na$ 352.0944, found 352.0947 (1 ppm). Single crystals suitable for X-ray diffraction studies were obtained after evaporation of a solution of **2g** in acetone.

2-(4-Methyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2h): 49.8 mg (55% yield), white solid, Mp: < 50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 6.8 Hz, 1H), 7.52-7.44 (m, 2H), 7.38-7.35 (m, 3H), 7.30-7.23 (m, 6H), 4.16 (s, 2H), 2.43 (s,

3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.2, 141.7, 139.2, 138.8, 137.0, 135.7, 132.3, 131.7, 131.0, 129.6, 129.3, 128.7, 128.5, 128.1, 127.4, 124.3, 122.7, 52.4, 21.2 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{21}H_{17}NONa$ 322.1202, found 322.1205 (1 ppm).

2-(4-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2i): 55.6 mg (59% yield), white solid, Mp: 142-144 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.2 Hz, 1H), 7.52-7.44 (m, 2H), 7.38-7.34 (m, 3H), 7.29-7.20 (m, 4H), 7.03-6.99 (m, 2H), 4.17 (s, 2H), 3.85 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.0, 159.7, 141.7, 139.0, 136.7, 132.22, 132.18, 131.9, 131.7, 128.7, 128.5, 128.1, 127.2, 124.3, 122.7, 114.7, 113.8, 55.6, 52.2 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{21}H_{17}NO_2Na$ 338.1152, found 338.1155 (1 ppm).

2-(2'-Fluoro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2l): 49.7 mg (55% yield), white solid, Mp: 153-155 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 7.6 Hz, 1H), 7.53-7.42 (m, 6H), 7.39-7.32 (m, 2H), 7.27-7.21 (m, 1H), 7.10-7.01 (m, 2H), 4.39 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.2, 159.4 (d, J_{C-F} = 245.0 Hz), 141.6, 136.9, 133.9, 132.1, 131.8 (d, J_{C-F} = 1.4 Hz), 131.7, 131.5 (d, J_{C-F} = 3.1 Hz), 129.6 (d, J_{C-F} = 8.0 Hz), 129.3, 128.4, 128.1, 127.9, 126.7 (d, J_{C-F} = 15.4 Hz), 124.4 (d, J_{C-F} = 3.6 Hz), 124.3, 122.7, 115.7 (d, J_{C-F} = 22.1 Hz), 52.3 (d, J_{C-F} = 1.4 Hz) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = -116.4 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{20}H_{14}NOFNa$ 326.0952, found 326.0952 (0 ppm).

2-(2'-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2m): 41.3 mg (44% yield), white solid, Mp: 120-122 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.6 Hz, 1H), 7.51-7.40 (m, 6H), 7.30-7.22 (m, 3H), 6.91 (dd, J = 7.6, 7.2 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.24 (s, 2H), 3.66 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.2, 156.4, 141.7, 137.0, 136.3, 132.5, 132.1, 131.5, 131.1, 129.3, 128.5, 128.4, 128.1, 128.0, 127.5, 124.2, 122.6, 120.9, 110.8, 55.6, 52.0 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{21}H_{17}NO_2Na$ 338.1152, found 338.1150 (0 ppm). Single crystals suitable for X-ray diffraction studies were obtained after evaporation of a solution of **2m** in acetone.

2-(3'-Chloro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2n): 14.8 mg (15% yield), yellow solid, Mp: 128-130 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.2 Hz, 1H), 7.55-7.44 (m, 6H), 7.40 (s, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.28-7.23 (m, 2H), 7.18 (dd, J = 7.6, 7.6 Hz, 1H), 4.23 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.1, 141.6, 141.0, 138.7, 136.1, 134.6, 132.1, 131.9, 131.0, 130.0, 129.3, 129.2, 128.6, 128.5, 128.3, 127.8, 126.8, 124.4, 122.8, 52.5 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{20}H_{14}NO^{35}ClNa$ 342.0656, found 342.0654 (1 ppm). Single crystals suitable for X-ray diffraction studies were obtained after evaporation of a solution of **2n** in acetone.

2-(3'-Methyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2o): 66.7 mg (74% yield), white solid, Mp: 146-148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 6.4 Hz, 1H), 7.52-7.40 (m, 6H), 7.27 (d, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.20-7.14 (m, 2H), 7.06 (d, J = 7.2 Hz, 1H), 4.18 (s, 2H), 2.26 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.0, 141.7, 139.9, 139.0, 138.3, 135.9, 132.2, 131.6, 131.0, 129.1, 129.0, 128.52, 128.48, 128.3, 128.2, 128.0, 125.4, 124.2, 122.7, 52.2, 21.4 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{21}H_{17}NONa$ 322.1202, found 322.1203 (0 ppm). Single crystals suitable for X-ray diffraction studies were obtained after evaporation of a solution of **2o** in acetone.

2-(3'-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2p): 30.7 mg (32% yield), white solid, Mp: < 50 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.2 Hz, 1H), 7.53-7.42 (m, 6H), 7.29 (d, J = 7.2 Hz, 1H), 7.20 (dd, J = 8.0, 8.0 Hz, 1H), 7.00-6.94 (m, 2H), 6.82-6.79 (m, 1H), 4.19 (s, 2H), 3.65 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.1, 159.7, 141.8, 140.5, 139.8, 135.9, 132.2, 131.7, 131.0, 129.8, 129.2, 128.8, 128.4, 128.2, 124.3, 122.8, 120.9, 114.0, 113.3, 55.3, 52.3 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{21}H_{17}NO_2Na$ 338.1152, found 338.1149 (1 ppm).

2-(3'-Nitro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2q): 58.8 mg (60% yield), yellow solid, Mp: 226-228 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (dd, J = 2.0, 2.0 Hz, 1H), 8.10 (dd, J = 8.0, 2.0 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.55-7.41 (m, 7H), 7.35 (d, J = 7.6 Hz, 1H), 4.36 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.7, 148.4, 141.3, 141.0, 138.0, 136.1, 134.7, 132.0, 131.8, 130.9, 129.8, 129.6, 129.0, 128.7, 128.4, 124.3, 123.3, 122.8, 122.5, 52.8 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{20}H_{14}N_2O_3Na$ 353.0897, found 353.0898 (0 ppm).

2-(3',5'-Dimethyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2r): 58.7 mg (62% yield), white solid, Mp: 169-171 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.2 Hz, 1H), 7.52-7.41 (m, 6H), 7.29 (d, J = 6.8 Hz, 1H), 6.99 (s, 2H), 6.88 (s, 1H), 4.17 (s, 2H), 2.19 (s, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.1, 141.8, 139.9, 139.1, 138.2, 135.9, 132.3, 131.6, 131.1, 129.3, 129.1, 128.4, 128.2, 128.1, 126.2, 124.3, 122.7, 52.2, 21.3 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{22}H_{19}NONa$ 336.1359, found 336.1363 (1 ppm).

2-(4'-Methyl-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2s): 68.8 mg (77% yield), white solid, Mp: 132-134 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 1H), 7.53-7.42 (m, 6H), 7.29-7.26 (m, 3H), 7.10 (d, J = 7.2 Hz, 2H), 4.20 (s, 2H), 2.30 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.0, 141.7, 139.8, 137.3, 136.2, 135.9, 132.3, 131.6, 131.2, 129.5, 129.1, 128.4, 128.29, 128.28, 128.1, 124.3, 122.8, 52.2, 21.2 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{21}H_{17}NONa$ 322.1202, found 322.1201 (0 ppm).

2-(4'-Methoxy-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2t): 74.5 mg (79% yield), white solid, Mp: < 50 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 6.8 Hz, 1H), 7.51-7.41 (m, 6H), 7.33-7.28 (m, 3H), 6.83 (dd, J = 6.8, 2.0 Hz, 2H), 4.20 (s, 2H), 3.75 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.0, 159.1, 141.7, 139.5, 135.9, 132.3, 131.6, 131.4, 131.1, 129.6, 129.1, 128.3, 128.2, 128.1, 124.2, 122.8, 114.2, 55.2, 52.2 ppm. HRMS (ESI) calcd. for [M + Na]$^+$ $C_{21}H_{17}NO_2Na$ 338.1152, found 338.1147 (1 ppm).

2-(4'-Fluoro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2u): 16.9 mg (19% yield), yellow solid, Mp: 108-110 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.6 Hz, 1H), 7.54-7.43 (m, 6H), 7.38-7.30 (m, 3H), 7.01-6.96 (m, 2H), 4.21 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.1, 162.4 (d, J_{C-F} =

245.4 Hz), 141.6, 139.1, 136.0, 135.1 (d, J_{C-F} = 3.5 Hz), 132.1, 131.8, 131.1, 130.1 (d, J_{C-F} = 8.0 Hz), 129.2, 128.9, 128.5, 128.3, 124.4, 122.8, 115.7 (d, J_{C-F} = 21.3 Hz), 52.4 ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = -114.6 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{20}H_{14}NOFNa$ 326.0952, found 326.0951 (0 ppm).

2-(4'-Chloro-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2v): 52.4 mg (55% yield), white solid, Mp: 141-143 °C. ^1H NMR (400 MHz, $CDCl_3$): δ= 7.92 (d, J = 7.6 Hz, 1H), 7.55-7.42 (m, 6H), 7.34-7.31 (m, 3H), 7.26 (d, J = 8.4 Hz, 2H), 4.23 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ= 169.0, 141.5, 138.9, 137.6, 135.9, 133.7, 132.0, 131.9, 131.0, 129.8, 129.2, 129.1, 128.9, 128.5, 128.3, 124.3, 122.8, 52.4 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{20}H_{14}NO^{35}ClNa$ 342.0656, found 342.0657 (0 ppm).

2-(4'-Bromo-[1,1'-biphenyl]-2-yl)isoindolin-1-one (2w): 88.7 mg (81% yield), white solid, Mp: 138-140 °C. ^1H NMR (400 MHz, $CDCl_3$): δ= 7.91 (d, J = 7.2 Hz, 1H), 7.55-7.40 (m, 8H), 7.32 (d, J = 7.2 Hz, 1H), 7.27 (ddd, J = 8.0, 2.8, 1.6 Hz, 2H), 4.24 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ= 169.0, 141.5, 138.8, 138.1, 135.8, 132.0, 131.9, 131.8, 130.9, 130.1, 129.2, 129.1, 128.5, 128.2, 124.3, 122.8, 122.0, 52.4 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{20}H_{14}NO^{79}BrNa$ 386.0151, found 386.0155 (1 ppm).

2-(2-(Naphthalen-2-yl)phenyl)isoindolin-1-one (2x): 83.1 mg (83% yield), white solid, Mp: 204-206 °C. ^1H NMR (400 MHz, $CDCl_3$): δ= 7.97-7.95 (m, 1H), 7.92 (s, 1H), 7.83-7.77 (m, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.60-7.57 (m, 1H), 7.56-7.44 (m, 8H), 7.19-7.17 (m, 1H), 4.17 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ= 169.1, 141.6, 139.7, 136.8, 136.2, 133.5, 132.6, 132.1, 131.6, 131.4, 129.2, 128.8, 128.34, 128.31, 128.2, 128.1, 127.7, 127.4, 126.5, 126.3, 126.2, 124.2, 122.8, 52.3 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{24}H_{17}NONa$ 358.1202, found 358.1206 (1 ppm).

2-(2-(6-Methoxynaphthalen-2-yl)phenyl)isoindolin-1-one (2y): 76.7 mg (70% yield), brown solid, Mp: 76-78 °C. ^1H NMR (400 MHz, $CDCl_3$): δ= 7.96-7.94 (m, 1H), 7.82 (s, 1H), 7.69 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.58-7.55 (m, 1H), 7.53-7.44 (m, 6H), 7.20-7.18 (m, 1H), 7.12 (dd, J = 9.2, 2.8 Hz, 1H), 7.07 (d, J = 2.8 Hz, 1H), 4.16 (s, 2H), 3.89 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.2, 158.1, 141.7, 139.8, 136.2, 134.6, 133.9, 132.2, 131.7, 131.4, 129.7, 129.2, 129.1, 128.6, 128.4, 128.1, 127.2, 127.1, 124.3, 122.8, 119.2, 105.7, 55.4, 52.3 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{25}H_{19}NO_2Na$ 388.1308, found 388.1310 (0 ppm).

2-(2-(Naphthalen-1-yl)phenyl)isoindolin-1-one (2z): 9.8 mg (10% yield), brown solid, Mp: < 50 °C. 1H NMR (400 MHz, $CDCl_3$): δ= 7.83-7.75 (m, 4H), 7.62 (d, J = 8.0 Hz, 1H), 7.58-7.35 (m, 9H), 7.09 (d, J = 8.0 Hz, 1H), 4.02 (d, J = 16.8 Hz, 1H), 3.87 (d, J = 16.8 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ= 168.6, 141.5, 137.9, 137.4, 136.7, 133.7, 132.5, 132.1, 131.7, 131.5, 128.9, 128.34, 128.30, 128.0, 127.7, 127.3, 126.4, 126.1, 125.8, 125.6, 124.2, 122.6, 52.2 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{24}H_{17}NONa$ 358.1202, found 358.1202 (0 ppm).

3,3'-Dichloro-1,1'-biphenyl (3): Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ= 7.55 (s, 2H), 7.45-7.42 (m, 2H), 7.40-7.33 (m, 4H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ= 141.7, 135.0, 130.2, 128.0, 127.4, 125.4 ppm. MS (EI): m/z 222 (M^+, 100), 152 (77), 93 (20), 75 (22). The spectral data match those previously reported.[30]

Large scale synthesis of product 2a: $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 0.05 mmol, 5 mol%), $AgSbF_6$ (68.7 mg, 0.2 mmol, 20 mol%), Ag_2O (231.7 mg, 1 mmol, 1.0 equiv.), $Cu(OTf)_2$ (72.3 mg, 0.2 mmol, 20 mol%), *N*-pheylisoindolinone **1a** (209.2 mg, 1 mmol, 1.0 equiv.) and phenylboronic acid (304.8 mg, 2.5 mmol, 2.5 equiv.) were taken in a 25 mL Schlenk tube, which was equipped with a magnetic stirrer bar. THF (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 20 h in an oil bath. 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 gradient 10:1 to 5:1) to give the desired product **2a** (202.6 mg, 71% yield).

Late-stage ruthenium-catalyzed site-selective C-H bond arylation of indoprofen (A): Indoprofen (**A**) was synthesized according to a literature procedure.[31] Esterification step: Indoprofen (140.7 mg, 0.5 mmol, 1 equiv.) and concentrated H_2SO_4 (1 drop) were stirred together in EtOH (2 mL) under reflux in an oil bath during 12 hours with a Dean-Stark condenser. Back at room temperature, solid sodium bicarbonate was added and the reaction mixture was filtered and concentrated under vacuum to afford the carboxylic acid ethyl ester indoprofen intermediate (**7a**) in quantitative yield and it was used without further purification for the next step. **Ethyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoate (7a):** 153.0 mg (99% yield), yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.6 Hz, 1H), 7.79-7.77 (m, 2H), 7.54-7.50 (m, 1H), 7.45-7.41 (m, 2H), 7.33-7.30 (m, 2H), 4.74 (s, 2H), 4.15-4.05 (m, 2H), 3.68 (q, J = 7.2 Hz, 1H), 1.47 (d, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ= 174.4, 167.3, 140.1, 138.4, 136.6, 133.0, 132.0, 128.3, 128.1, 123.9, 122.6, 119.4, 60.7, 50.6, 44.9, 18.5, 14.1 ppm ppm. The spectral data match those previously reported.[32] Ru-catalyzed C-H bond arylation: $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 0.025 mmol, 5 mol%), $AgSbF_6$ (34.4 mg, 0.1 mmol, 20 mol%), Ag_2O (115.9 mg, 0.5 mmol, 1.0 equiv.), $Cu(OTf)_2$ (36.2 mg, 0.1 mmol, 20 mol%), indoprofen derivative **7a** (153.0 mg, 0.5 mmol, 1.0 equiv.) and phenylboronic acid (152.4 mg, 1.25 mmol, 2.5 equiv.) were taken in a 15 mL Schlenk tube, which was equipped with a magnetic stirrer bar. THF (2.5 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 20 h in an oil bath. 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 gradient 10:1 to 5:1) to give the arylated product **7b**. **Ethyl 2-(6-(1-oxoisoindolin-2-yl)-[1,1'-biphenyl]-3-yl)propanoate (7b):** 160.1 mg (85% yield), colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J =

6.8 Hz, 1H), 7.52-7.39 (m, 7H), 7.32-7.23 (m, 4H), 4.23-4.10 (m, 4H), 3.81 (q, *J* = 7.2 Hz, 1H), 1.56 (d, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ= 174.2, 169.0, 141.6, 140.6, 139.8, 138.9, 134.7, 132.0, 131.6, 130.2, 129.1, 128.6, 128.3, 128.0, 127.7, 127.6, 124.2, 122.6, 60.9, 52.2, 45.3, 18.7, 14.2 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{25}H_{23}NO_3Na$ 408.1570, found 408.1573 (1 ppm). Ester hydrolysis: **7b** (106 mg, 0.27 mmol, 1 equiv.) and 2 M NaOH (1 mL) were stirred in a mixture of MeOH (1 mL) and THF (1 mL) at room temperature for 12 hours. Then, the reaction mixture was basified to pH 14 and washed with ethyl acetate three times. The aqueous layer was acidified to pH 1 with concentrated HCl and the product **7** precipitated out. After washing with pentane and drying under vacuum, product **7** was isolated. **2-(6-(1-Oxoisoindolin-2-yl)-[1,1'-biphenyl]-3-yl)propanoic acid (7):** 86.8 mg (90% yield), white solid, Mp: 208-210 °C. ^1H NMR (400 MHz, $CDCl_3$): δ= 7.92 (d, *J* = 7.6 Hz, 1H), 7.52-7.41 (m, 5H), 7.39-7.35 (m, 2H), 7.31-7.24 (m, 4H), 4.16 (s, 2H), 3.83 (q, *J* = 7.2 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 179.2, 169.4, 141.7, 140.2, 140.0, 138.9, 134.9, 132.0, 131.8, 130.5, 129.3, 128.8, 128.5, 128.2, 128.0, 127.7, 124.4, 122.7, 52.4, 45.2, 18.4 ppm. HRMS (ESI) calcd. for $[M + Na]^+$ $C_{23}H_{19}NO_3Na$ 380.1257, found 380.1263 (2 ppm).

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx.

^1H NMR spectra for known compounds, and ^1H and $^{13}C\{^1H\}$ NMR spectra for all new compounds, and X-ray crystallography data (PDF)

X-ray crystallography of **2c** (CIF)

X-ray crystallography of **2d** (CIF)

X-ray crystallography of **2g** (CIF)

X-ray crystallography of **2m** (CIF)

X-ray crystallography of **2n** (CIF)

X-ray crystallography of **2o** (CIF)

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Notes

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