Ru-Catalyzed Selective C-H Bond Hydroxylation of Cyclic Imides

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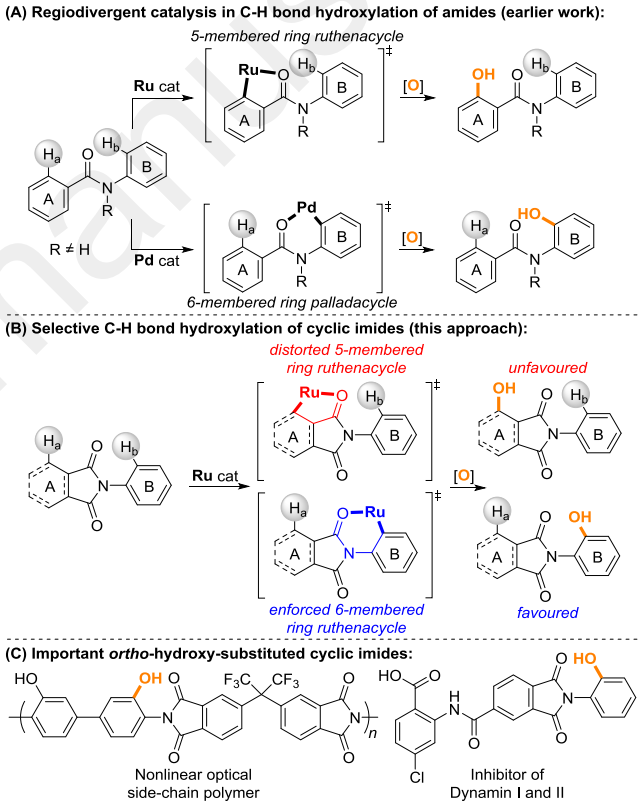
Supporting Information Placeholder

ABSTRACT: We report on cyclic imides as weak directing groups for selective mono-hydroxylation reactions using ruthenium catalysis. Whereas acyclic amides are known to promote the hydroxylation of the C(sp^2)-H bond enabling 5-membered ring ruthenacycle intermediates, the cyclic imides studied herein enabled the hydroxylation of the C(sp^2)-H bond *via* a larger 6-membered ruthenacycle intermediates. Furthermore, mono-hydroxylated products were exclusively obtained (even in the presence of over-stoichiometric amounts of reagents), which was rationalized by the difficulty to accommodate co-planar intermediates once the first hydroxyl group was introduced into the substrate. The same reactivity was observed in the presence of palladium catalysts.

■ INTRODUCTION

Catalytic oxidations have become increasingly important in the last decades with the aim of replacing toxic and hazardous reagents in industrial and academic laboratories.[1] Additionally, they provide a plethora possibilities to achieve selectivity patterns that are *per se* difficult or impossible to tackle with non-catalyzed reactions that traditionally require harsher reaction conditions than the catalytic ones.[2] In this context, particular focus has been devoted to catalytic oxidations such as hydroxylation, epoxidation, acetoxylation and benzoxylation of C-H bonds sought to be traditionally unreactive.[3] Bio-inspired iron, copper and manganese complexes are the prevalent catalysts for aliphatic and alkene C-H bond oxidations as they promote oxygen atom transfer mechanisms *via* key oxo species.[4] On the other hand, the aromatic C-H bond oxidations are usually accomplished with palladium and ruthenium catalysts that enable the key C-H bond activation step *via* a key metallacycle intermediate assisted by a directing group.[5] In the former case, most of the examples have been performed with substrates containing a single aromatic fragment, which significantly decreases and simplifies the number of the products that can be formed.[6] Indeed, in the case where two aromatic fragments are present around the same directing group, undesired regio-selectivity issues as well as over-oxidation reactions are encountered.[7] An interesting strategy to circumvent this problem was reported by Rao and co-workers who demonstrated the regio-divergent catalytic behavior of ruthenium and palladium towards flexible, acyclic tertiary amides containing two aromatic fragments (Scheme 1A).[8] Whereas the ruthenium catalyst formed the 5-membered metallacycle intermediate enabling the hydroxylation at the *ortho* C-H_a bond of the phenyl ring A attached to the carbonyl group, the palladium catalyst favored the 6-membered metallacycle intermediate that promoted the hydroxylation at the *ortho* C-H_b bond of the phenyl ring B attached to the nitrogen atom. The carbonyl group behaved in both cases as a weak directing group for this type of flexible substrates.[8]

Scheme 1.



With this in mind, we wondered what the hydroxylation reaction outcome could be by swapping the weak directing group into a more rigid, although synthetically useful, cyclic imides (Scheme 1B). We reasoned that cyclic imides containing two aromatic moieties, such as phthalimide-like molecules, may have difficulties to accommodate a 5-membered ruthenacycle intermediate (activation of C-H_a) due to important ring strain, and consequently, the 6-membered ring (activation of C-H_b) could preferentially form due to the specific pre-disposed orientation of the carbonyl group within the cyclic imide backbone (Scheme 1B). If so, the behavior of the ruthenium catalysts would be the same as the palladium ones for this type of synthetically appealing directing groups in hydroxylation reactions. Herein, we report such strategy, which enables a straightforward access to *ortho*-hydroxylated cyclic imides together with

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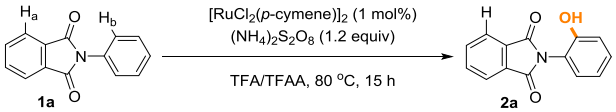
preliminary mechanistic studies to understand the unexpected absence of di-hydroxylated products. *N*-Phenyl-substituted cyclic imides containing hydroxyl groups in the *ortho* position represent an important class of compounds for polymer sciences[9] as well as biology and pharmacology (Scheme 1C).[10] So far, the use of cyclic imides as weak directing groups[11] in transition metal-catalyzed C-H bond functionalizations has been exclusively limited to selected examples of carbon-carbon bond forming reactions.[12] Oxygenation reactions *via* 6-membered ruthenacycle intermediates with 2-pyridyloxy and 2-amino-pyrimidine substituents as strong directing group have been reported respectively.[13]

■ RESULTS AND DISCUSSION

N-Phenylphthalimide (**1a**) was selected as the model substrate for the optimization of the hydroxylation reaction with ruthenium complexes as the pre-catalysts. After screening a number of parameters (Table S1), we found suitable reaction conditions that afforded exclusively the targeted phenol derivative **2a**, in which the C-H bond oxidation occurred in the hydrogen atom H_b (*ortho* position with respect to the nitrogen atom), with no evidence of the C-H bond functionalization taking place at the other possible hydrogen atom H_a (Table 1). The reaction conditions consist of 1 or 2.5 mol% of $[RuCl_2(p\text{-cymene})]_2$, $(NH_4)_2S_2O_8$ as oxidant in a mixture of TFA/TFAA (TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride) as solvents at 80 °C during 15 h (Table 1, entries 1-2). In this way, **2a** was obtained in 82% isolated yield and the same results were obtained when conducting the catalysis at large scale (starting with 2 mmol of **1a**). In the presence of $[RuCl_3.xH_2O]$, the reaction afforded **2a** in only 39% yield (Table 1, entry 3); whereas the reaction using $[Ru(O_2CMes)_2(p\text{-cymene})]$ (O_2CMes = 2-mesitylenecarboxylate anion) gave the same yield as using $[RuCl_2(p\text{-cymene})]_2$ (Table 1, entry 4). **1a** was unreactive in the absence of any ruthenium complex (Table 1, entry 5); and other oxidants and solvents did not lead to better results (Table S1). Shortening the time (8 h) and decreasing the temperature (60 °C) of the reaction, respectively, led to lower yields of **2a** (Table 1, entries 6-7). On the other hand, raising the temperature of the reaction to 100 °C provided similar yields of **2a** as when conducted at 80 °C (Table 1, entry 8). In the absence of TFAA, almost no reaction took place (Table 1, entry 9) which indicated the key role of TFAA as a source of trifluoroacetate anions during the catalytic cycle.[5-8] Interestingly, the use of over-stoichiometric amounts of the oxidant did not afford any di-hydroxylation product during the catalysis (Table 1, entry 10). The mono-selectivity observed in this reaction contrasts with other types of carbonyl-containing substrates that do afford di-hydroxylated products as side-products at some extent.[7] Using $[Pd(OAc)_2]$ as the pre-catalyst provided **2a** in 84% yield (Table 1, entry 11), showing that the selectivity is exclusively controlled by the structure and coordinating properties of the directing group as it was anticipated (Scheme 1B). From a sustainable and economic point of view, however, ruthenium seems more appealing than palladium for this type of transformations.

The scope of the reaction was evaluated with different *N*-substituted cyclic imides (Scheme 2). *para*-Substituted *N*-phenylphthalimides containing different functional groups such as methyl, diethylamino, fluoro, chloro, bromo, iodo and ester followed the protocol leading to the corresponding phenols **2a-2h** in 80-90% isolated yields, respectively. The molecular structure of **2b** and **2d** was further established by single crystal X-ray diffraction studies. The very electron withdrawing group nitro provided the corresponding phenol **2i** in a moderate yield of 53%. *N*-Phenylphthalimides substituted with bromo and iodo groups in the *meta* position selectively afforded the phenols **2j** and **2k** in 75% and 87% yields, respectively. The reaction was sensitive to the *ortho* substitution pattern of the *N*-phenyl side of the substrates. For instance, *N*-phenylphthalimide containing the small fluoro substituent at the *ortho* position afforded the corresponding phenol **2l** in

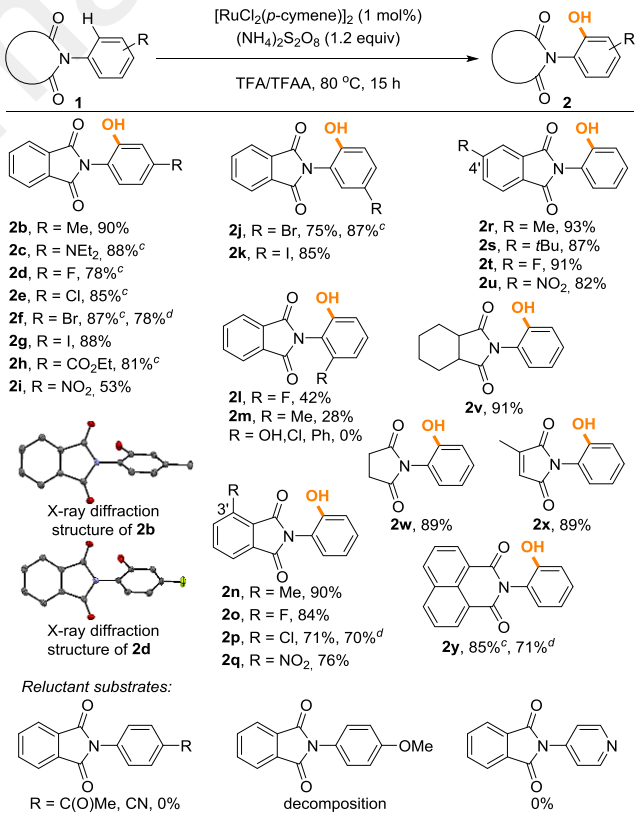
Table 1. Optimization of the Reaction Conditions[a]



entry	deviation from standard conditions	**2a** (%)[b]
1	none	85 (82)[c]
2	2.5 mol% of $[RuCl_2(p\text{-cymene})]_2$	83
3	2.5 mol% $[RuCl_3{\bullet}xH_2O]$	39
4	2.5 mol% $[Ru(O_2CMes)_2(p\text{-cymene})]$	86
5	no $[RuCl_2(p\text{-cymene})]_2$	0
6	8 h instead of 15 h	79
7	60 °C instead of 80 °C	50
8	100 °C instead of 80 °C	85
9	no TFAA	<5
10	2-10 equiv of $(NH_4)_2S_2O_8$	85
11	$[Pd(OAc)_2]$ instead of $[RuCl_2(p\text{-cymene})]_2$	80[d]

[a]**1a** (0.1 mmol), $(NH_4)_2S_2O_8$ (0.12 mmol), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%) in TFA/TFAA (0.5 mL, *v*/*v* 3:1) at 80 °C for 15 h under air. [b]Yield calculated by ^1H NMR spectroscopy analysis using dibromomethane as internal standard. [c]Isolated yield. [d]2 mol%.

Scheme 2. Substrate Scope[a,b]

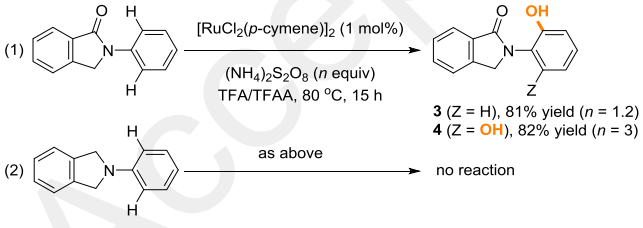


[a]Reaction conditions: **1** (0.3 mmol), $(NH_4)_2S_2O_8$ (0.36 mmol), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%) in TFA/TFAA (1 mL, *v*/*v* 3:1) at 80 °C for 15 h under air. [b]Isolated yields. [c]2.5 mol% of $[RuCl_2(p\text{-cymene})]_2$. [d]$[Pd(OAc)_2]$ (2 mol%) instead of $[RuCl_2(p\text{-cymene})]_2$ (1 mol%).

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42% yield, whereas a substrate with the methyl group afforded the phenol **2m** in only 28% yield. No reaction was observed for substrates containing the hydroxyl, chloro and phenyl substituents at the *ortho* position. The reaction of *ortho*-substituted phthalimides seem to be affected not only by the bulkiness of the substituents but also by the electrostatic repulsion between the substituents and the imide carbonyl group. In addition, there was no impact for the reactivity of *N*-phenylphthalimides substituted at 3' or 4' position with different functional groups such as alkyl (Me, *t*Bu), halide (F, Cl), and nitro, and the corresponding phenols **2n**-**2u** were obtained in 71-93% yields. Interestingly, other cyclic imides behaved as excellent directing groups as the phthalimides. A cyclohexane-containing cyclic imide afforded the corresponding phenol **2v** in 91% yield and, *N*-phenyl-substituted succinimide and 2-methylmaleimide gave rise to the corresponding phenols **2w** and **2x** in 89% yield in both cases. The catalysis was also applicable (85% yield) to *N*-phenylnaphthalimide (**2y**), which is an appealing motif for material sciences.[14] Similar reactivity was observed using 2 mol% of $[Pd(OAc)_2]$ instead of $[RuCl_2(p\text{-cymene})]_2$ as the pre-catalyst as it was exemplified in the synthesis of phenols **2a**, **2f**, **2p**, and **2y** in 70-80% isolated yields (Scheme 2). In all cases (**2a**-**2y**), no di-hydroxylated products were observed. Unfortunately, no reactivity was found for *N*-(4-acetylphenyl)phthalimide, *N*-(4-cyanophenyl)phthalimide and *N*-(4-pyridyl)phthalimide (Scheme 2) neither for C(sp^3)-H bond hydroxylation of *N*-alkylphthalimides. *N*-(4-methoxyphenyl)phthalimide decomposed under the studied reaction conditions leading to an unidentified mixture of species (Scheme 2).

To gain further insights into the reaction mechanism, we performed the catalysis with substrates lacking one and two carbonyl groups, respectively (Eq. 1-2). Under the standard reaction conditions, the selective mono-hydroxylation reaction took place with a cyclic amide (81% yield of **3**, Eq. 1) with traces of the di-hydroxylated product **4** detected by TLC and GC-MS analysis. However, increasing the number of equivalents of oxidant to three afforded exclusively the di-hydroxylated product **4** in 82% yield (Eq. 1) whereas the excess of oxidant has no impact when a cyclic imide was used (Table 1, entry 10). On the other hand, no reaction occurred with a cyclic amine (Eq. 2), which indicates the coordinating role of the carbonyl group throughout the catalytic cycle. Consequently, the selectivity observed for di- *vs* mono-hydroxylation in the resulting products is likely controlled by an increase in the steric bulk when going from cyclic amides to cyclic imides as the weak directing groups.



The above described findings together with previous contributions[5-8] enabled us to propose a catalytic cycle (Figure 1a). Initially, one of the carbonyl groups of the imide substrate coordinated to a chloride-free ruthenium species leading to **A** that followed C-H bond activation at the *ortho* position to form the 6-membered ruthenacycle intermediate **B**. After oxidation and reductive elimination, the trifluoroacetate product **D** was formed followed by hydrolysis releasing the final product **2**. The nature of **D** was evidenced by GC-MS analysis of the crude reaction mixture using **1a** as substrate, which showed a peak at *m/z* = 335 corresponding to the trifluoroacetate-containing *N*-phenylphthalimide (Figure S1 in the Supporting Information). After hydrolysis, this peak disappeared and the peak corresponding to the phenol **2a** (*m/z* = 239) was observed (Figure S2 in the Supporting Information). The origin of the selectivity for the exclusive mono-hydroxylation and the fact that the catalysis was sensitive to the *ortho* substitution pattern was addressed as well (Figure 1b). The rotational barrier around the *N*-phenyl axis of non-substituted *N*-phenylphthalimide was estimated to be *ca.* 10 kJ/mol (see Supporting Information), which suggests a fast interconversion between the staggered and the eclipsed conformations. This translates into an accessible pathway (blue arrows, Figure 1b) for the catalytically productive intermediate $\mathbf{A_E}$ (where the C-H bond is in close proximity of the ruthenium center) and ruthenacycle $\mathbf{B_E}$ (co-planar 6-membered ring). On the other hand, a substitution pattern in the *ortho* position favors the staggered conformation at a higher extent with a rotational barrier around the *N*-phenyl axis estimated to be, at least, higher than 20 kJ/mol for R = OH or $OC(O)CF_3$ (see Supporting Information). Consequently, the catalytically unproductive intermediates $\mathbf{A_S}$ **(**where the C-H bond is far away from the ruthenium center**)** and $\mathbf{B_S}$ (distorted 6-membered ruthenacycle) dominate in this catalytically unproductive case (red arrows, Figure 1b).

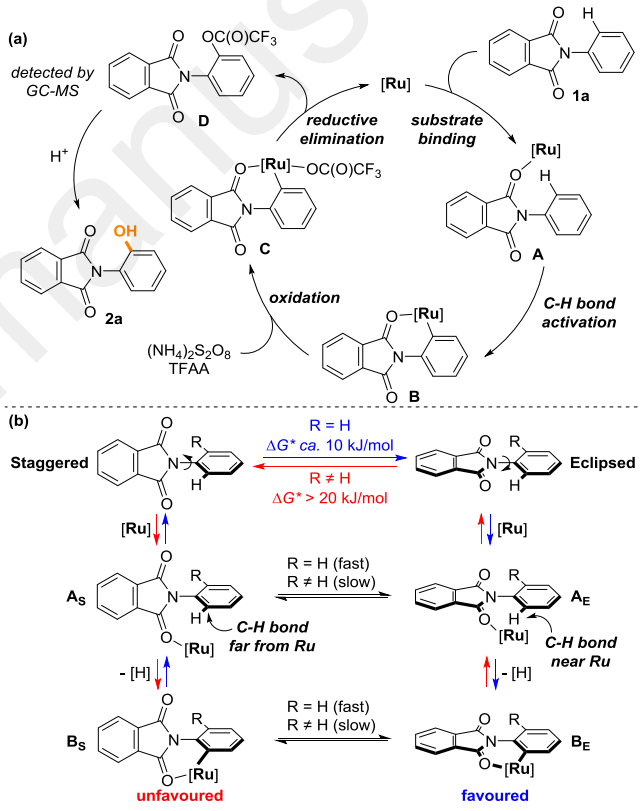
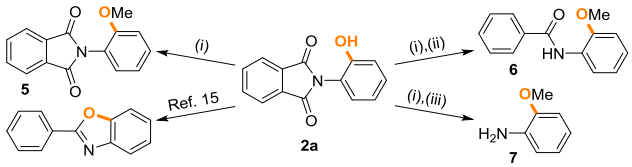


Figure 1. (a) Proposed catalytic cycle. (b) Stereochemical model explaining the selectivity for mono-hydroxylation.

Finally, a brief applicability of the transformation was demonstrated (Scheme 3). The *ortho*-hydroxylated phthalimides were alkylated leading to the methoxy-containing product **5** in almost quantitative yield. They could be transformed into a benzoxazole upon thermal treatment[15] and into amide **6** *via* ruthenium catalsyis.[16] Deprotection with hydrazine led to the corresponding 2-aminoanisole (**7**), highlighting the great potential of the phthalimide ring as a traceless directing group for the transition metal-catalyzed C-H bond functionalizations.

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Scheme 3. Postfunctionalization Reactions[a]



[a]Reaction conditions: (i) MeI (1.5 equiv), K_2CO_3 (1.5 equiv), DMF (0.2 M), 20 °C, 2 h, 96% yield; (ii) H_2O (1.5 equiv), K_2CO_3 (3 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NMP (0.2 M), 150 °C, 48 h, 78% yield; (iii)$N_2H_4.H_2O$ (7.75 equiv), EtOH (0.2 M), reflux, 2 h, 83% yield.

■ CONCLUSION

In summary, we have developed a selective C(sp^2)-H bond hydroxylation reaction of a large variety of functionalized phthalimides, succinimides, maleimides, naphthalimides, and cyclic amides. The reactions proceeded under relatively mild conditions with as low as 1 mol% of readily-available ruthenium or palladium catalysts affording the corresponding mono-hydroxylated products at the *ortho* position with respect to the nitrogen atom of the directing group. As such, cyclic imides can now be further exploited as easily-removable, weak directing groups for other types of C-H bond functionalizations leading to useful shortcuts in the synthesis of fine chemicals.

■ EXPERIMENTAL SECTION

General information. 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 ^{13}C 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 rate 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 substrates (1). Method A: Phthalic anhydride (5 mmol, 0.74 g, 1 eq.) and the corresponding aniline (5 mmol, 1 eq.) were refluxed in acetic acid (30 mL) for 2-5 hours. Once at room temperature, water was added and the solid recovered by filtration. After drying under vacuum the desired phthalimide was obtained. **Method B:** A mixture of 2-formylbenzoic acid (5.0 mmol, 1 eq.), amine (6.0 mmol, 1.2 eq.), DABCO (10.0 mmol, 2 eq.), HCOOH (1.25 mL), $Pd(OAc)_2$ (0.25 mmol, 5 mol%) in 1,4-dioxane (5 mL) was heated to 80 °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 filter, 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. **Method C:** 1,2-Bis(bromomethyl)benzene (5.0 mmol, 1 eq.), DIPEA (12.5 mmol, 2.5 eq.), and aniline (7.50 mmol, 1.5 eq.) dissolved in toluene (25 mL) were added to a tube sealing before vigorously stirring at 110 °C under a Ar atmosphere. The resulting mixture was cooled 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 as a light yellow solid. **Method D:** Hexahydrophthalic anhydride (10 mmol, 1.54 g, 1 eq.), aniline (10 mmol, 1 eq.) and THF (15 mL) were added to a 100 mL round bottom flask. The solution was stirred for 30 min at 40 °C. Removal of the solvent using a rotary evaporator gave the corresponding carboxylic acid-amide as white solid. The white solid was then heated at 190 °C under Ar for 4 h. The desired phthalimide was purified by silica gel column chromatography with a mixture of petroleum ether and ethyl acetate as eluent. **Method E:** A solution of succinic acid (10 mmol, 1 eq.) and aniline (10 mmol, 1 eq.) were dissolved in water (5.0 mL) in a flask and stirred and maintained at boiling for 2 h. The reaction progress was monitored by TLC (1:1 *n*-hexane/acetone). The reaction mixture was cooled to room temperature and the product was filtered, washed with water and recrystallized from methanol.

*N-Phenylphthalimide (**1a**).* Prepared according to Method A starting from aniline in 80% isolated yield (891 mg). ^1H 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.[17]

*N-(p-Tolyl)phthalimide (**1b**).* Prepared according to Method A starting from *p*-toluidine in 72% isolated yield (1.2 g). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.78 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.31 (s, 4H), 2.41 (s, 3H) ppm. The spectral data match those previously reported.[17]

*N-((p-Diethylamino)phenyl)phthalimide (**1c**).* Prepared according to Method A starting from *N*,*N*-diethyl-1,4-phenylenediamine in 90% isolated yield (1.58 g). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.75 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.20 (dd, *J* = 6.8, 2.4 Hz, 2H), 6.73 (dd, *J* = 6.8, 2.4 Hz, 2H), 3.38 (q, *J* = 7.2 Hz, 4H), 1.19 (t, *J* = 7.2 Hz, 6H) ppm. The spectral data match those previously reported.[18]

*N-(p-Fluorophenyl)phthalimide (**1d**).* Prepared according to Method A starting from 4-fluoroaniline in 82% isolated yield (1.59 g). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.71 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.34 (dd, *J* = 9.2, 4.8 Hz, 2H), 7.11 (dd, *J* = 8.8, 8.8 Hz, 2H) ppm. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ = -113.8 ppm. The spectral data match those previously reported.[19]

*N-(p-Chlorophenyl)phthalimide (**1e**).* Prepared according to Method A starting from 4-chloroaniline in 91% isolated yield (1.17 g). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.81 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.48 (dd, *J* = 6.4, 2.4 Hz, 2H), 7.42 (dd, *J* = 6.4, 2.4 Hz, 2H) ppm. The spectral data match those previously reported.[20]

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*N-(p-Bromophenyl)phthalimide (**1f**)*. Prepared according to Method A starting from 4-bromoaniline in 88% isolated yield (1.61 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.80 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H) ppm. The spectral data match those previously reported.[21]

*N-(p-Iodophenyl)phthalimide (**1g**)*. Prepared according to Method A starting from 4-iodoaniline in 80% isolated yield (1.39 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96-7.94 (m, 2H), 7.84-7.79 (m, 4H), 7.23 (d, *J* = 8.4 Hz, 2H) ppm. The spectral data match those previously reported.[22]

*N-(p-Ethoxycarbonylphenyl)phthalimide (**1h**)*. Prepared according to Method A starting from benzocaine in 50% isolated yield (801 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.97 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.82 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.59 (dd, *J* = 6.8, 1.6 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H) ppm. The spectral data match those previously reported.[23]

*N-(p-Nitrophenyl)phthalimide (**1i**)*. Prepared according to Method A starting from 4-nitroaniline in 63% isolated yield (758 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (dd, *J* = 7.2, 2.0 Hz, 2H), 8.00 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.85 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.78 (dd, *J* = 7.2, 2.0 Hz, 2H) ppm. The spectral data match those previously reported.[17]

*N-(m-Bromophenyl)phthalimide (**1j**)*. Prepared according to Method A starting from 3-bromoaniline in 70% isolated yield (1.69 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.65 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.55-7.52 (m, 1H), 7.44-7.41 (m, 1H), 7.37 (dd, *J* = 8.0, 8.0 Hz, 1H) ppm. The spectral data match those previously reported.[24]

*N-(m-Iodophenyl)phthalimide (**1k**)*. Prepared according to Method A starting from 3-iodoaniline in 88% isolated yield (1.50 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.83-7.80 (m, 3H), 7.74 (ddd, *J* = 8.0, 2.4, 2.4 Hz, 1H), 7.45 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.24 (dd, *J* = 8.0, 8.0 Hz, 1H) ppm. The spectral data match those previously reported.[21]

*N-(o-Fluorophenyl)phthalimide (**1l**)*. Prepared according to Method A starting from 2-fluoroaniline in 91% isolated yield (1.53 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.81 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.48-7.43 (m, 1H), 7.39-7.35 (m, 1H), 7.31-7.25 (m, 2H) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = -118.7 ppm. The spectral data match those previously reported.[25]

*N-o-Tolylphthalimide (**1m**)*. Prepared according to Method A starting from *o*-toluidine in 43% isolated yield (1.2 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.6, 2.8 Hz, 2H), 7.39-7.31 (m, 3H), 7.21 (d, *J* = 7.6 Hz, 1H), 2.21 (s, 3H) ppm. The spectral data match those previously reported.[26]

*N-Phenyl-3-methylphthalimide (**1n**)*. Prepared according to Method A starting from 3-methylphthalic anhydride in 95% isolated yield (1.13 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.2 Hz, 1H), 7.63 (dd, *J* = 7.6 Hz, 1H), 7.54-7.49 (m, 3H), 7.45-7.38 (m, 3H), 2.75 (s, 3H) ppm. The spectral data match those previously reported.[27]

*N-Phenyl-3-fluorophthalimide (**1o**)*. Prepared according to Method A starting from 3-fluorophthalic anhydride in 91% isolated yield (1.09 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82-7.77 (m, 2H), 7.53-7.49 (m, 2H), 7.47-7.40 (m, 4H) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = -112.3 ppm. The spectral data match those previously reported.[28]

*N-Phenyl-3-chlorophthalimide (**1p**)*. Prepared according to Method A starting from 3-chlorophthalic anhydride in 94% isolated yield (1.2 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 4.8, 3.6 Hz, 1H), 7.71-7.70 (m, 2H), 7.53-7.48 (m, 2H), 7.45-7.41 (m, 3H) ppm. The spectral data match those previously reported.[29]

*N-Phenyl-3-nitrophthalimide (**1q**)*. Prepared according to Method A starting from 3-nitrophthalic anhydride in 78% isolated yield (972 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.15 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.98 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.54-7.50 (m, 2H), 7.46-7.42 (m, 3H) ppm. The spectral data match those previously reported.[30]

*N-Phenyl-4-methylphthalimide (**1r**)*. Prepared according to Method A starting from 4-methylphthalic anhydride in 97% isolated yield (1.15 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.6 Hz, 1H), 7.75 (dd, *J* = 0.8, 0.8 Hz, 1H), 7.59-7.56 (m, 1H), 7.52-7.48 (m, 2H), 7.45-7.37 (m, 3H), 2.55 (s, 3H) ppm. The spectral data match those previously reported.[31]

*N-Phenyl-4-tert-butylphthalimide (**1s**)*. Prepared according to Method A starting from 4-tert-butylphthalic anhydride in 93% isolated yield (1.3 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.88 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.81 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.53-7.48 (m, 2H), 7.44-7.38 (m, 3H), 1.41 (s, 9H) ppm. The spectral data match those previously reported.[28]

*N-Phenyl-4-fluorophthalimide (**1t**)*. Prepared according to Method A starting from 4-fluorophthalic anhydride in 89% isolated yield (1.07 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.62 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.54-7.47 (m, 2H), 7.46-7.39 (m, 4H) ppm. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ = -101.1 ppm. The spectral data match those previously reported.[28]

*N-Phenyl-4-nitrophthalimide (**1u**)*. Prepared according to Method A starting from 4-nitrophthalic anhydride in 98% isolated yield (1.85 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (dd, *J* = 6.0, 0.8 Hz, 1H), 8.67 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.16 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.56-7.52 (m, 2H), 7.48-7.43 (m, 3H) ppm. The spectral data match those previously reported.[32]

*2-Phenylhexahydro-1H-isoindole-1,3(2H)-dione (**1v**)*. Prepared according to Method D in 86% isolated yield (1.69 g). ^{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.[33]

*N-Phenylsuccinimide (**1w**)*. Prepared according to Method E starting from succinic acid in 10% isolated yield (35.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.45 (m, 2H), 7.41-7.37 (m, 1H), 7.29-7.26 (m, 2H), 2.87 (s, 4H) ppm. The spectral data match those previously reported.[34]

*3-Methyl-1-phenyl-1H-pyrrole-2,5-dione (**1x**)*. Prepared according to Method A starting from citraconic anhydride in 77% isolated yield (1.15 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.43 (m, 2H), 7.36-7.32 (m, 3H), 6.46 (q, *J* = 2.0 Hz, 1H), 2.15 (d, *J* = 2.0 Hz, 3H) ppm. The spectral data match those previously reported.[35]

*2-Phenyl-1H-benzo[de]isoquinoline-1,3(2H)-dione (**1y**)*. Prepared according to Method A starting from 1,8-naphthalic anhydride in 78% isolated yield (1.49 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (dd, *J* = 7.2, 1.2 Hz, 2H), 8.26 (dd, *J* = 8.4, 0.8 Hz, 2H), 7.78 (dd, *J* = 8.0, 7.2 Hz, 2H), 7.59-7.54 (m, 2H), 7.51-7.47 (m, 1H), 7.34 (dd, *J* = 4.0, 1.2 Hz, 2H) ppm. The spectral data match those previously reported.[32]

*2-Phenylisoindolin-1-one (**1z**)*. Prepared according to the previous literature[36] in 78% isolated yield (1.4 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.[37]

*2-Phenyl-2,3-dihydro-1H-isoindole (**1aa**)*. Prepared according to Method C starting from 1,2-bis(bromomethyl)benzene in 89% isolated yield (869 mg). ^{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.[38]

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*N-(p-Methoxyphenyl)phthalimide (**1ab**).* Prepared according to Method A starting from *p*-anisidine in 80% isolated yield (1.01 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.78 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.34 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H) ppm. The spectral data match those previously reported.[17,24]

*p-Phthalimidoacetophenone (**1ac**).* Prepared according to Method A starting from 4-aminoacetophenone in 79% isolated yield (1.67 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.97 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.82 (dd, *J* = 5.6, 3,2 Hz, 2H), 7.63 (dd, *J* = 6.8, 2.0 Hz, 2H), 2.64 (s, 3H) ppm. The spectral data match those previously reported.[17]

*N-(p-Cyanophenyl)phthalimide (**1ad**).* Prepared according to Method A starting from 4-aminobenzonitrile in 93% isolated yield (2.3 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.84 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.80 (dd, *J* = 6.4, 2.0 Hz, 2H), 7.69 (dd, *J* = 6.4, 2.0 Hz, 2H) ppm. The spectral data match those previously reported.[39]

*N-(o-Chlorophenyl)phthalimide (**1ae**).* Prepared according to Method A starting from 2-chloroaniline in 70% isolated yield (1.4 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.59-7.55 (m, 1H), 7.46-7.38 (m, 2H), 7.37-7.35 (m, 1H) ppm. The spectral data match those previously reported.[40]

*N-(2-Biphenyl)phthalimide (**1af**).* Prepared according to Method A starting from 2-chloroaniline in 50% isolated yield (878 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.70 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.55-7.48 (m, 3H), 7.35-7.32 (m, 1H), 7.29-7.20 (m, 5H) ppm. The spectral data match those previously reported.[12c]

*N-(4-pyridyl)phthalimide (**1ag**).* Prepared according to Method A starting from 4-aminopyridine in 76% isolated yield (1.19 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (dd, *J* = 4.8, 1.6 Hz, 2H), 7.99 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.84 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.61 (dd, *J* = 4.8, 1.6 Hz, 2H) ppm. The spectral data match those previously reported.[41]

General procedure for the ruthenium-catalysed hydroxylation reaction and characterization of products (2-4). $[RuCl_2(p\text{-cymene})]_2$ (0.003 mmol, 1.8 mg, 0.01 eq.), ammonium persulfate (0.36 mmol, 82.2 mg, 1.2 eq.), substrate **1** (0.3 mmol, 1 eq.) and TFA/TFAA (1.0 mL, 3:1, *v*/*v*) were introduced in a flame-dried Schlenk tube under air atmosphere. The reaction mixture was stirred at 80 °C during 15 hours. Then, the reaction mixture was cooled down to room temperature and diluted with H_2O (50 mL) followed by extraction with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuo, the crude product was purified by column chromatography on silica gel (*n*-heptane/EtOAc: 4/1, *v*/*v*) to give product **2**.

*2-(2-Hydroxyphenyl)isoindoline-1,3-dione (**2a**).* Yellow solid, yield = 82%, 60.9 mg. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.81 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.36-7.30 (m, 2H), 7.11-7.07 (m, 2H), 5.80 (br, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.9, 154.9, 135.2, 133.5, 131.3, 131.2, 124.0, 120.6, 120.4, 117.5 ppm. MS (EI): *m/z* = 239 (M^+, 52), 195 (100), 104 (39), 76 (64). The spectral data match those previously reported.[42]

*2-(2-Hydroxy-4-methylphenyl)isoindoline-1,3-dione (**2b**).* Colorless solid, yield = 90%, 68.4 mg. Mp > 250 °C dec. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.80 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 5.71 (br, 1H), 2.36 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 168.1, 154.6, 141.4, 135.1, 133.5, 130.9, 124.0, 121.4, 118.0, 117.7, 21.3 ppm. HRMS (ESI) calcd. for $[M+Na]^+$ $C_{15}H_{11}NO_3Na$ 276.0631, found 276.0635 (1 ppm).

*2-(4-Diethylamino-2-hydroxyphenyl)isoindoline-1,3-dione (**2c**).* Brown oil, yield = 88%, 65.0 mg. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.95-7.88 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.02 (q, *J* = 7.2 Hz, 4H), 0.99 (t, *J* = 7.2 Hz, 6H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.8, 155.0, 137.2, 135.3, 132.8, 130.6, 124.1, 124.0, 119.1, 113.6, 49.8, 13.0 ppm. HRMS (ESI) calcd. for $[M+Na]^+$ $C_{18}H_{18}N_2O_3Na$ 333.1210, found 333.1213 (1 ppm).

*2-(4-Fluoro-2-hydroxyphenyl)isoindoline-1,3-dione (**2d**).* Colorless solid, yield = 78%, 45.5 mg. Mp: 225-228 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.27 (br, 1H), 7.95-7.89 (m, 4H), 7.37 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.85-6.75 (m, 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.9, 164.4 (d, $J_{C\text{-}F}$ = 243.9 Hz), 156.3 (d, $J_{C\text{-}F}$ = 12.5 Hz), 135.2, 133.4, 132.6 (d, $J_{C\text{-}F}$ = 10.8 Hz), 124.1, 116.8 (d, $J_{C\text{-}F}$ = 3.3 Hz), 107.4 (d, $J_{C\text{-}F}$ = 22.9 Hz), 104.6 (d, $J_{C\text{-}F}$ = 25.2 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, acetone-d_6): δ = -112.3 ppm. HRMS (ESI) calcd. for $[M+Na]^+$ $C_{14}H_8NO_3FNa$ 280.0380, found 280.0381 (0 ppm).

*2-(4-Chloro-2-hydroxyphenyl)isoindoline-1,3-dione (**2e**).* Colorless solid, yield = 85%, 60.6 mg. ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.24 (br, 1H), 7.96-7.90 (m, 4H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 7.03 (dd, *J* = 8.4, 2.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.7, 155.7, 135.8, 135.2, 133.3, 132.5, 124.1, 120.7, 119.4, 117.6 ppm. MS (EI): *m/z* = 273 (M^+, 44), 229 (100), 104 (46), 76 (78). The spectral data match those previously reported.[42]

*2-(4-Bromo-2-hydroxyphenyl)isoindoline-1,3-dione (**2f**).* Colorless solid, yield = 87%, 83.0 mg. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.95-7.89 (m, 4H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.6, 155.9, 135.2, 133.3, 132.8, 124.1, 123.70, 123.69, 120.5, 119.9 ppm. MS (EI): *m/z* = 317 (M^+, 52), 275 (94), 104 (61), 76 (100), 50 (35). The spectral data match those previously reported.[42]

*2-(2-Hydroxy-4-iodophenyl)isoindoline-1,3-dione (**2g**).* Yellow solid, yield = 88%, 96.3 mg. Mp: 184-187 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.15 (br, 1H), 7.95-7.89 (m, 4H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.6, 155.7, 135.2, 133.3, 133.0, 129.9, 126.6, 124.1, 120.6, 95.3 ppm. HRMS (ESI) calcd. for $[M+Na]^+$ $C_{14}H_8NO_3INa$ 387.9441, found 387.9445 (1 ppm).

*2-(4-Ethoxycarbonyl-2-hydroxyphenyl)isoindoline-1,3-dione (**2h**).* Colorless solid, yield = 81%, 47.8 mg. Mp: 210-213 °C. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.97-7.91 (m, 4H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.5, 166.1, 154.8, 135.3, 133.40, 133.37, 131.5, 124.7, 124.2, 121.4, 118.2, 61.7, 14.5 ppm. HRMS (ESI) calcd. for $[M+Na]^+$ $C_{17}H_{13}NO_5Na$ 334.0686, found 334.0686 (0 ppm).

*2-(2-Hydroxy-4-nitrophenyl)isoindoline-1,3-dione (**2i**).* Colorless solid, yield = 53%, 45.2 mg. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.01 (br, 1H), 8.01-7.92 (m, 4H), 7.82-7.78 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 166.3, 154.7, 148.4, 134.8, 131.8, 131.5, 125.3, 123.5, 113.9, 111.1 ppm. MS (EI): *m/z* = 248 (M^+, 100), 204 (85), 104 (30), 76 (85), 50 (31). The spectral data match those previously reported.[43]

*2-(5-Bromo-2-hydroxyphenyl)isoindoline-1,3-dione (**2j**).* Colorless solid, yield = 87%, 71.5 mg. ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.08 (br, 1H), 7.96-7.90 (m, 4H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.6, 154.5, 135.3, 134.0, 133.8, 133.3, 124.1, 121.9, 119.4, 111.0 ppm. MS (EI): *m/z* = 317 (M^+, 34), 273 (82), 104 (60), 76 (100), 50 (34). The spectral data match those previously reported.[42]

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*2-(2-Hydroxy-5-iodophenyl)isoindoline-1,3-dione (**2k**)*. Brown solid, yield = 85%, 93.0 mg. Mp > 250 ºC dec. ^{1}H NMR (400 MHz, acetone-d^6): δ = 9.10 (br, 1H), 7.96-7.90 (m, 4H), 7.71 (d, J = 2.4 Hz, 1H), 7.66 (dd, J = 8.8, 2.4 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.6, 155.2, 140.0, 139.7, 135.3, 133.4, 124.1, 122.2, 119.9, 80.2 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{14}H_8NO_3INa$ 387.9441, found 387.9443 (0 ppm).

*2-(6-Fluoro-2-hydroxyphenyl)isoindoline-1,3-dione (**2l**)*. Yellow solid, yield = 42%, 32.4 mg. Mp: 204-207 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 9.31 (br, 1H), 8.01-7.94 (m, 4H), 7.39 (dd, J = 8.4, 6.8 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.84 (dd, J = 8.4, 8.4 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.2, 160.6 (d, $J_{C\text{-}F}$ = 246.5 Hz), 156.9 (d, $J_{C\text{-}F}$ = 3.6 Hz), 135.6, 133.2, 131.9 (d, $J_{C\text{-}F}$ = 10.5 Hz), 124.4, 113.3 (d, $J_{C\text{-}F}$ = 3.0 Hz), 108.8 (d, $J_{C\text{-}F}$ = 16.0 Hz), 107.3 (d, $J_{C\text{-}F}$ = 20.0 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, acetone-d_6): δ = -122.0 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{14}H_8NO_3FNa$ 280.0380, found 280.0383 (1 ppm).

*2-(2-Hydroxy-6-methylphenyl)isoindoline-1,3-dione (**2m**)*. Colorless solid, yield = 28%, 21.1 mg. Mp: 145-148 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.75 (br, 1H), 7.97-7.91 (m, 4H), 7.22 (dd, J = 8.0, 8.0 Hz, 1H), 6.88 (dd, J = 8.0, 8.0 Hz, 2H), 2.14 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.9, 155.1, 139.4, 135.3, 133.4, 130.8, 124.1, 122.0, 119.7, 114.8, 17.9 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{15}H_{11}NO_3Na$ 276.0631, found 276.0635 (1 ppm).

*2-(2-Hydroxyphenyl)-4-methylisoindoline-1,3-dione (**2n**)*. Colorless solid, yield = 90%, 68.3 mg. Mp: 187-190 ºC. 1H NMR (400 MHz, acetone-d_6): δ = 8.77 (br, 1H), 7.74-7.72 (m, 2H), 7.65-7.63 (m, 1H), 7.35-7.29 (m, 2H), 7.07 (dd, J = 8.0, 1.2 Hz, 1H), 6.98 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 2.70 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 168.7, 167.8, 154.9, 138.6, 137.2, 134.6, 133.8, 131.3, 131.1, 129.9, 121.6, 120.5, 120.4, 117.5, 17.6 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{15}H_{11}NO_3Na$ 276.0631, found 276.0634 (1 ppm).

*4-Fluoro-2-(2-hydroxyphenyl)isoindoline-1,3-dione (**2o**)*. Colorless solid, yield = 84%, 64.7 mg. Mp: 200-203 ºC. 1H NMR (400 MHz, acetone-d_6): δ = 8.82 (br, 1H), 7.95 (ddd, J = 8.0, 8.0, 4.4 Hz, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.63 (dd, J = 8.8, 8.8 Hz, 1H), 7.37-7.32 (m, 2H), 7.07 (dd, J = 8.0, 1.2 Hz, 1H), 6.99 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 166.8 (d, $J_{C\text{-}F}$ = 3.1 Hz), 164.6 (d, $J_{C\text{-}F}$ = 1.6 Hz), 158.4 (d, $J_{C\text{-}F}$ = 261.1 Hz), 154.8, 138.1 (d, $J_{C\text{-}F}$ = 7.7 Hz), 135.7 (d, $J_{C\text{-}F}$ = 1.8 Hz), 131.3 (d, $J_{C\text{-}F}$ = 18.7 Hz), 123.2 (d, $J_{C\text{-}F}$ = 19.8 Hz), 120.6, 120.4 (d, $J_{C\text{-}F}$ = 3.7 Hz), 120.0, 119.0 (d, $J_{C\text{-}F}$ = 12.5 Hz), 117.6 ppm. ^{19}F{^{1}H} NMR (376 MHz, acetone-d_6): δ = -115.7 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{14}H_8NO_3FNa$ 280.0380, found 280.0383 (1 ppm).

*4-Chloro-2-(2-hydroxyphenyl)isoindoline-1,3-dione (**2p**)*. Colorless solid, yield = 71%, 58.1 mg. Mp: 209-212 ºC. 1H NMR (400 MHz, acetone-d_6): δ = 8.82 (br, 1H), 7.91-7.84 (m, 3H), 7.37-7.32 (m, 2H), 7.07 (dd, J = 8.0, 1.2 Hz, 1H), 6.99 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 166.5, 165.5, 154.9, 136.6, 136.5, 135.6, 131.39, 131.36, 131.2, 129.0, 122.8, 120.6, 120.0, 117.6 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{14}H_8NO_3ClNa$ 296.0085, found 296.0086 (0 ppm).

*2-(2-Hydroxyphenyl)-4-nitroisoindoline-1,3-dione (**2q**)*. Colorless solid, yield = 76%, 64.8 mg. Mp: 226-229 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.87 (br, 1H), 8.30-8.25 (m, 2H), 8.18 (dd, J = 7.6, 7.6 Hz, 1H), 7.38-7.34 (m, 2H), 7.08 (ddd, J = 7.6, 1.2, 1.2 Hz, 1H), 6.99 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 165.9, 163.3, 154.8, 146.1, 137.1, 135.2, 131.6, 131.1, 129.1, 127.6, 124.4, 120.7, 119.7, 117.7 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{14}H_8N_2O_5Na$ 307.0325, found 307.0327 (0 ppm).

*2-(2-Hydroxyphenyl)-5-methylisoindoline-1,3-dione (**2r**)*. Colorless solid, yield = 93%, 70.6 mg. Mp: 216-219 ºC. 1H NMR (400 MHz, acetone-d_6): δ = 8.71 (br, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.75 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.35-7.27 (m, 2H), 7.05 (dd, J = 8.0, 1.2 Hz, 1H), 6.97 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 2.56 (s, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 168.0, 167.9, 154.9, 146.5, 135.6, 133.8, 131.3, 131.1, 130.9, 124.4, 123.9, 120.6, 117.5, 21.8 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{15}H_{11}NO_3Na$ 276.0631, found 276.0632 (0 ppm).

*5-(tert-Butyl)-2-(2-hydroxyphenyl)isoindoline-1,3-dione (**2s**)*. Colorless solid, yield = 87%, 77.0 mg. Mp: 116-119 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.96-7.95 (m, 2H), 7.86 (d, J = 8.4 Hz, 1H), 7.36-7.29 (m, 2H), 7.07 (dd, J = 8.4, 1.2 Hz, 1H), 6.98 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 1.44 (s, 9H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 168.2, 167.8, 159.4, 154.9, 133.6, 132.1, 131.2, 131.1, 130.8, 123.9, 121.0, 120.54, 120.47, 117.5, 36.3, 31.4 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{18}H_{17}NO_3Na$ 318.1101, found 318.1104 (1 ppm).

*5-Fuloro-2-(2-hydroxyphenyl)isoindoline-1,3-dione (**2t**)*. Colorless solid, yield = 91%, 70.2 mg. Mp: 190-193 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.00 (dd, J = 8.4, 4.4 Hz, 1H), 7.71-7.63 (m, 2H), 7.36-7.30 (m, 2H), 7.07 (dd, J = 8.0, 1.2 Hz, 1H), 6.98 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 167.2 (d, $J_{C\text{-}F}$ = 252.5 Hz), 166.9, 166.6 (d, $J_{C\text{-}F}$ = 2.9 Hz), 154.8, 136.3 (d, $J_{C\text{-}F}$ = 9.5 Hz), 131.3 (d, $J_{C\text{-}F}$ = 17.7 Hz), 129.4 (d, $J_{C\text{-}F}$ = 2.8 Hz), 126.8 (d, $J_{C\text{-}F}$ = 9.5 Hz), 122.0 (d, $J_{C\text{-}F}$ = 23.8 Hz), 120.6, 120.2, 117.5, 111.6 (d, $J_{C\text{-}F}$ = 25.0 Hz) ppm. ^{19}F{^{1}H} NMR (376 MHz, acetone-d_6): δ = -104.5 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{14}H_8NO_3FNa$ 280.0380, found 280.0382 (1 ppm).

*2-(2-Hydroxyphenyl)-5-nitroisoindoline-1,3-dione (**2u**)*. Yellow solid, yield = 82%, 69.9 mg. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.96 (br, 1H), 8.76 (dd, J = 8.4, 2.0 Hz, 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.39-7.33 (m, 2H), 7.09 (dd, J = 8.0, 1.2 Hz, 1H), 7.00 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 166.2, 166.0, 154.7, 152.9, 137.8, 134.7, 131.6, 131.0, 130.4, 125.6, 120.7, 119.8, 119.0, 117.6 ppm. MS (EI): m/z = 248 (M$^+$, 100), 204 (85), 104 (30) 76 (84), 50 (31). The spectral data match those previously reported.[44]

*2-(2-Hydroxyphenyl)hexahydro-1H-isoindole-1,3(2H)-dione (**2v**)*. Colorless solid, yield = 91%, 66.9 mg. Mp: 232-235 ºC. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.62 (br, 1H), 7.25 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.09 (dd, J = 8.0, 1.6 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.91 (dd, J = 7.6, 7.6 Hz, 1H), 3.13-3.07 (m, 2H), 1.91-1.86 (m, 4H), 1.50-1.47 (m, 4H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 179.1, 154.2, 130.8, 130.5, 121.5, 120.5, 117.3, 41.0, 24.6, 22.6 ppm. HRMS (ESI) calcd. for [M+Na]$^+$ $C_{14}H_{15}NO_3Na$ 268.0944, found 268.0947 (1 ppm).

*1-(2-Hydroxyphenyl)pyrrolidine-2,5-dione (**2w**)*. Yellow solid, yield = 89%, 33.9 mg. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.47 (br, 1H), 7.28-7.24 (m, 1H), 7.08 (dd, J = 8.0, 1.6 Hz, 1H), 6.98 (dd, J = 8.4, 1.2 Hz, 1H), 6.91 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 2.84 (s, 4H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 177.2, 154.2, 130.9, 130.5, 121.3, 120.5, 117.5, 29.4 ppm. MS (EI): m/z = 191 (M$^+$, 100), 146 (88), 136 (54), 109 (100), 55 (84). The spectral data match those previously reported.[45]

*1-(2-Hydroxyphenyl)-3-methyl-1H-pyrrole-2,5-dione (**2x**)*. Colorless solid, yield = 89%, 54.2 mg. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.61 (br, 1H), 7.28 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H), 7.15 (dd, J = 8.0, 2.0 Hz, 1H), 7.00 (dd, J = 8.0, 1.2 Hz, 1H), 6.92 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.62 (q, J = 2.0 Hz, 1H), 2.11 (d, J = 2.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ = 171.5, 170.4, 154.9, 147.0, 131.2, 130.9, 128.7, 120.52, 120.47, 117.4, 11.0 ppm. MS (EI): m/z = 203 (M$^+$, 94), 159 (100), 133 (44), 68 (80), 52 (40). The spectral data match those previously reported.[36]

*2-(2-Hydroxyphenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**2y**)*. Colorless solid, yield = 85%, 59.8 mg. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.62 (br, 1H), 8.50 (d, J = 7.6 Hz, 4H), 7.90

(dd, *J* = 7.6, 7.6 Hz, 2H), 7.29 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.24 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.92 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 163.3, 153.4, 134.3, 131.4, 130.6, 130.3, 129.5, 127.9, 127.1, 122.9, 122.7, 119.0, 116.4 ppm. MS (EI): *m/z* = 289 (M^+, 72), 272 (74), 244 (100), 126 (66). The spectral data match those previously reported.[46]

*2-(2-Hydroxyphenyl)isoindolin-1-one (**3**).* Colorless solid, yield = 81%, 54.6 mg. ^1H NMR (400 MHz, acetone-d_6): δ = 9.00 (br, 1H), 7.28 (ddd, *J* = 7.6, 1.2, 1.2 Hz, 1H), 7.70-7.68 (m, 2H), 7.60-7.56 (m, 1H), 7.46 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.22 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.98 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 5.08 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 169.2, 152.5, 143.8, 133.1, 132.8, 129.1, 128.8, 128.0, 125.9, 124.3, 124.1, 121.2, 120.0, 53.2 ppm. MS (EI): *m/z* = 225 (M^+, 84), 196 (30), 132 (100), 120 (45). The spectral data match those previously reported.[47]

*2-(2,6-Dihydroxyphenyl)isoindolin-1-one (**4**).* Colorless solid, yield = 82%, 39.5 mg. Mp > 250 °C dec. ^1H NMR (400 MHz, acetone-d_6): δ = 8.46 (br, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.65-7.62 (m, 2H), 7.55-7,51 (m, 1H), 7.05 (dd, *J* = 8.4, 8.4 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 2H), 4.83 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 169.3, 155.8, 144.4, 133.6, 132.4, 129.7, 128.5, 124.15, 124.10, 114.8, 108.8, 51.9 ppm. HRMS (ESI) calcd. for $[M+Na]^+$ $C_{14}H11NO3Na$ 264.0631, found 264.0632 (0 ppm).

Scale-up experiment: $[RuCl_2(p\text{-cymene})]_2$ (0.02 mmol, 12.2 mg, 0.01 eq.), ammonium persulfate (2.4 mmol, 548 mg, 1.2 eq.), substrate **1a** (2 mmol, 1 eq.) and TFA/TFAA (6 mL, 3:1, *v*/*v*) were introduced in a flame-dried Schlenk tube under air atmosphere. The reaction mixture was stirred at 80 °C during 15 hours. Then, the reaction mixture was cooled down to room temperature and diluted with H_2O (200 mL) followed by extraction with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuo, the crude product was purified by column chromatography on silica gel (*n*-heptane/EtOAc: 4/1, *v*/*v*) to give product **2a** as a solid in 82% yield (396 mg).

Synthesis and characterization of 5. A solution of **2a** (0.4 mmol, 1 eq.) and K_2CO_3 (0.6 mmol, 1.5 eq.) in DMF (2 mL) was stirred at room temperature, then iodomethane (0.6 mmol, 1.5 eq.) was added. After 2 h, the reaction mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (3 x 20 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 (*n*-heptane/EtOAc: 5/1, *v*/*v*) to obtain product **5** in 96% yield as a white solid.

*N-o-Methoxyphenylphthalimide (**5**).* Colorless solid, yield = 96%, 48.6 mg. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.77 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.46-7.42 (m, 1H), 7.27-7.25 (m, 1H), 7.10-7.04 (m, 2H), 3.80 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.3, 155.4, 134.1, 132.2, 130.6, 130.0, 123.6, 120.8, 120.2, 112.1, 55.8 ppm. The spectral data match those previously reported.[24]

Synthesis and characterization of 6. $[RuCl_2(p\text{-cymene})]_2$ (0.002 mmol, 1.2 mg, 0.01 eq.), potassium carbonate (0.6 mmol, 82.9 mg, 3 eq.), distilled water (0.3 mmol, 5.4 mg, 5.4 µL, 1.5 eq.), substrate **1a** (0.2 mmol, 1 eq.) and *N*-methyl-2-pyrrolidine (1.0 mL) were introduced in a flame-dried Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C during 6 hours. Then, the reaction mixture was cooled down to room temperature and diluted with water (10 mL) followed by addition of HCl (1.0 M) until pH reached 7. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. After solvents evaporation under vacuum, product **6** was purified by column chromatography (petroleum ether/EtOAc: 5/1, *v*/*v*) in 78% yield.

*N-(o-Methoxyphenyl)benzamide (**6**).* Colorless solid, yield = 78%, 70.9 mg. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.90 (dd, *J* = 6.8, 1.6 Hz, 2H), 7.57-7.48 (m, 3H), 7.11-7.01 (m, 2H), 6.93 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.93 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.2, 148.1, 135.3, 131.6, 128.7, 127.8, 127.0, 123.8, 121.2, 119.8, 109.9, 55.8 ppm. MS (EI): *m/z* = 227 (M^+, 29), 105 (100), 77 (46). The spectral data match those previously reported.[48]

Synthesis and characterization of 7. A solution of **5** (0.2 mmol) and $NH_2NH_2{\cdot}H_2O$ (80 µL) in ethanol (1 mL) was heated under reflux for 2 h. The reaction mixture was cooled to room temperature, and the mixture was filtered through Celite. The solvent was removed, and the crude product was purified using column chromatography (*n*-heptane/EtOAc: 10/1, *v*/*v*) to give a red oil **7** in 83% yield.

*o-Anisidine (**7**).* Red oil, yield = 83%, 20.4 mg. ^1H NMR (400 MHz, acetone-d_6): δ = 6.79 (d, *J* = 7.6 Hz, 1H), 6.69 (dd, *J* = 5.2, 1.2 Hz, 2H), 6.57 (ddd, *J* = 8.0, 4.8, 4.8 Hz, 1H), 4.32 (br, 2H), 3.80 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6): δ = 147.9, 138.4, 121.8, 117.8, 115.0, 111.3, 55.7 ppm. The spectral data match those previously reported.[49]

■ ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website at DOI: XXX.
Screening of reaction conditions, computational details and NMR spectra (PDF)
Crystallographic data for **2b** (CCDC-187307, CIF)
Crystallographic data for **2d** (CCDC-1873708, CIF)

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Notes

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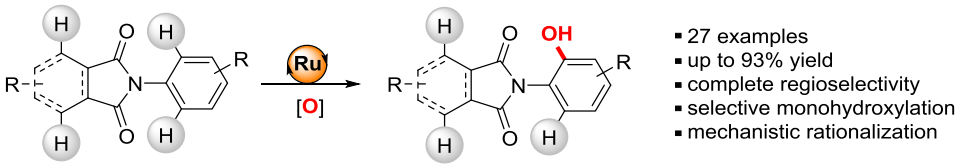
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