ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

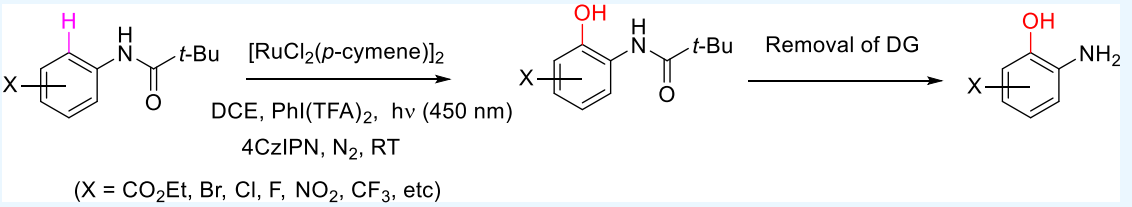
Hydroxylation of Substituted Anilides with Metallaphotocatalysis

Buddha B. Khatri,* Lu Chen, Dawei Xu, Rhys Salter, and Ronghui Lin*

Cite This: *ACS Omega* 2024, 9, 19982−19991

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: We report the combination of organo-photocatalysis with transition metal (TM) catalysis for directed *ortho*-hydroxylation of substituted anilides for the synthesis of *α*-aminophenol derivatives under mild conditions. The developed metallaphotocatalysis utilizes *N*-pivaloyl as a directing group and phenyl iodine(III) bis(trifluoroacetate) (PIFA) in the combination of the 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) photocatalyst and $[RuCl_2(p\text{-cymene})]_2$ TM catalyst under visible-light irradiation at room temperature. The hydroxylation reaction works well for a wide range of substrates containing electron-withdrawing substituents and could be applied to late-stage functionalization and *ortho*-hydroxyl metabolite generation for drug compounds-containing anilides with electron-withdrawing substituents in a single mild reaction.

INTRODUCTION

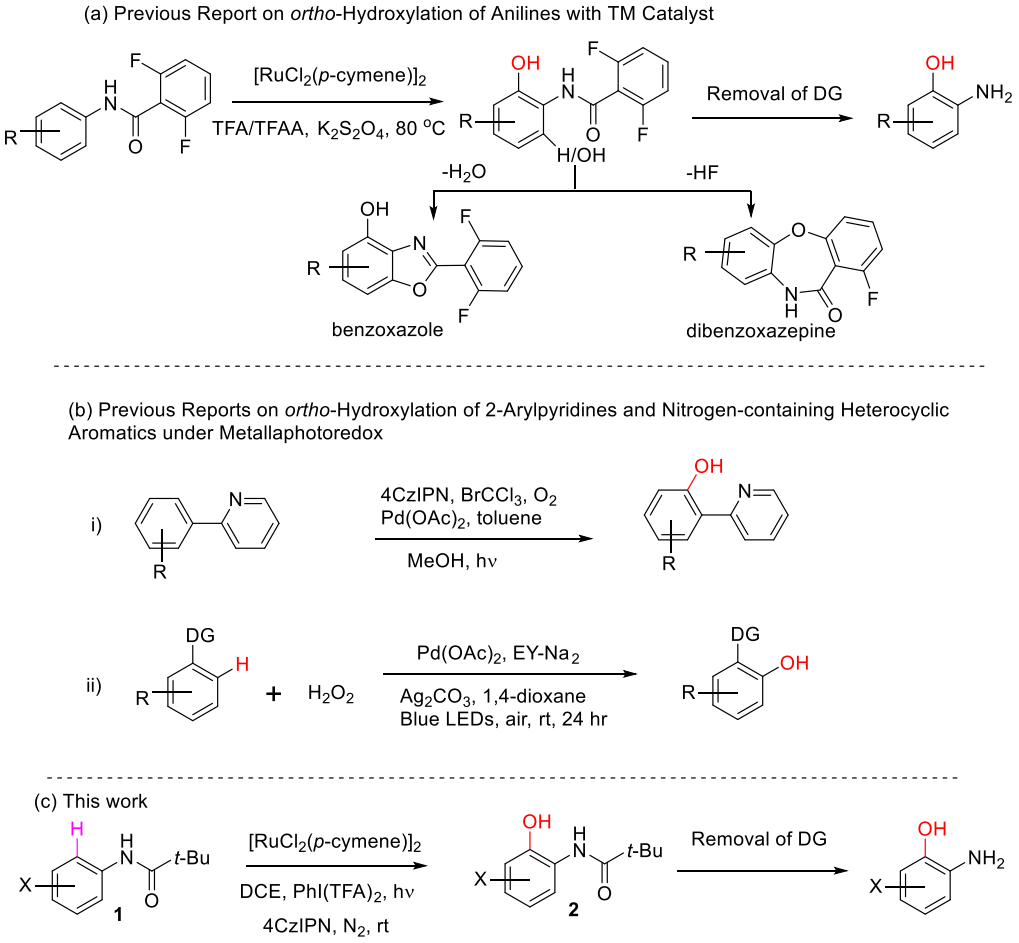
Aminophenols such as 2-aminophenols and 2-aminobenzene-1,3-diols are common structures in biologically active compounds, building blocks in material science, and metabolites in the agrochemical and pharmaceutical industries.[1] Classically, 2-aminophenols are synthesized through sequential nitration-reduction of phenols,[2] but this strategy suffers from poor regioselectivity, functional group tolerance, and tedious work up procedures. In the past decade, with notable advances in transition metal (TM)-catalyzed direct C−H activation, several research groups have utilized TM-catalyzed direct C−H oxidation, leading to hydroxylated arenes and heteroarenes as versatile synthetic intermediates. In 2009, Yu et al. demonstrated carboxylic acid group-directed *ortho*-hydroxylation of benzoic acids with a Pd catalyst in the presence of 1 atm of O_2 or air.[3] The same group also disclosed Cu(II)-mediated *ortho*-hydroxylation of aryl C−H bonds.[4] Furthermore, TM-catalyzed carbonyl directed hydroxylation of arenes and heteroarenes has been achieved successfully by the groups of Rao,[5−7] Ackermann,[8−12] and others under thermal conditions.[13,14]

Although significant progress has been made toward the *ortho*-hydroxylation of arenes and heteroarenes with a wide range of TM catalysts and oxidants and directing groups, site-selective *ortho*-hydroxylation of substituted anilines under mild conditions with a readily removable or traceless directing group (DG) remains a challenge. In 2013, Rao et al. described mono- and dihydroxylation of anilines with a Ru catalyst using 2,6-difluororobenzoyl as a DG.[15] The DG was successfully removed after the hydroxylation in a few examples, but in others, it leads to benzoxazole or dibenzoazepine (Scheme 1a). In 2020, Shi et al. reported an elegant metal-free chelation-assisted direct hydroxylation of aromatic amides that covers a wide range of substrates but does not cover some *ortho*-substituted functional groups such as ester, nitro, F, CF_3, etc.[16] The published literature utilizes high temperature, harsh reaction conditions, and DGs that are difficult to remove, which limits the scope and practicability of the developed methodologies.[15−17]

More recently, light-induced catalysis has been used in other chemical transformations beyond C−C and C−heteroatom bond-forming cross-coupling reactions due to its ability to generate reactive intermediates under mild conditions.[18,19] In 2018, Singh et al. reported a metallaphotoredox method for *ortho*-hydroxylation of 2-arylpyridines by integrating 4CzIPN photocatalyst and $Pd(OAc)_2$ as a TM metal catalyst under visible-light conditions (Scheme 1bi).[20] In 2022, *ortho*-hydroxylation of 2-arylpyridines and 2-arylbenzoxazoles has been reported by Chu and co-workers using a Pd(II) catalyst and an Eosin Y photocatalyst (EY-Na_2) under mild conditions (Scheme 1bii).[21] With the onset of hypervalent iodine(III) reagents being prevalently used as an oxidizing reagent in hydroxylation reactions of arenes and heteroarenes in thermal TM catalysis reactions,[7,10,15] and their increasing application in

Received: December 14, 2023
Revised: April 9, 2024
Accepted: April 11, 2024
Published: April 24, 2024

Scheme 1. Directed *ortho*-Hydroxylation of Anilines and 2-Arylpyridines

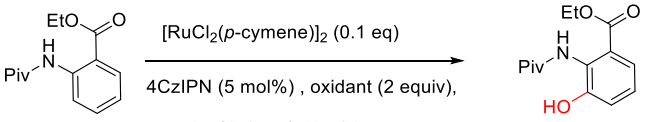


visible-light-induced organophotocatalysis,[22] we were prompted to investigate directed *ortho*-hydroxylation of substituted anilides with hypervalent iodine(III) oxidizing reagents under visible-light metallaphotocatalysis (Scheme 1c).

RESULTS AND DISCUSSION

Initially, we investigated *ortho*-hydroxylation of ethyl anthranilate with *N*-trifluoroacetyl, *N*-2,6-difluorobenzoyl, and *N*-pivaloyl as the DG under Rao's thermal conditions {[$RuCl_2$(*p*-cymene)]$_2$, TFA/TFAA, $K_2S_2O_8$, 80 °C},[15] and only *N*-pivaloyl worked well to give the desired hydroxyl product. Based on this, we hypothesized that an *N*-pivaloyl (Piv-) group may serve as an ideal DG for the *ortho*-hydroxylation of substituted anilines because it is stable under reaction conditions and can readily be removed. We began our photochemical investigations with *N*-pivaloyl ethyl anthranilate **1a**, a representative *ortho*-substituted aniline, and explored reaction conditions to find an optimal oxidizing reagent using [$RuCl_2$(*p*-cymene)]$_2$ as the TM catalyst and 4CzIPN as the organo-photocatalyst. Standard conditions utilized irradiation of the reaction mixture under visible light (450 nm) for 6 h in dichloroethane under nitrogen (Table 1). A host of oxidants including air, $K_2S_2O_8$, Cu(OAc)$_2$, PhI(OAc)$_2$, and MesI(OAc)$_2$ were evaluated and found ineffective (Table 1 entries 1−5), but we were pleased to find 60% conversion by high-performance liquid chromatography (HPLC) into the desired *ortho*-hydroxylated product **2** with PhI(TFA)$_2$ (Table 1 entry 6). The reaction profile was clean, and the conversion was

Table 1. Optimization of the Reaction Conditions



1a **2a**

entry	TM catalyst	oxidant (2 equiv)	remarks
1	[$RuCl_2$(*p*-cymene)]$_2$	air	no reaction
2	[$RuCl_2$(*p*-cymene)]$_2$	$K_2S_2O_8$	no reaction
3	[$RuCl_2$(*p*-cymene)]$_2$	Cu(OAc)$_2$	no reaction
4	[$RuCl_2$(*p*-cymene)]$_2$	PhI(OAc)$_2$	no reaction
5	[$RuCl_2$(*p*-cymene)]$_2$	MesI(OAc)$_2$	no reaction
6	[$RuCl_2$(*p*-cymene)]$_2$	PhI(TFA)$_2$	60%[a]
7	[$RuCl_2$(*p*-cymene)]$_2$	PhI(TFA)$_2$	46%[a] under air
8[b]	[$RuCl_2$(*p*-cymene)]$_2$	PhI(TFA)$_2$	90%[a]
9[c]	[$RuCl_2$(*p*-cymene)]$_2$	PhI(TFA)$_2$	complex mixture
10	$RuCl_3 \cdot H_2O$	PhI(TFA)$_2$	no reaction
11	Pd(OAc)$_2$	PhI(TFA)$_2$	no reaction

[a]Product by HPLC. [b]3 equiv of the oxidant used. [c][Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 (5 mol %) used instead of 4CzIPN.

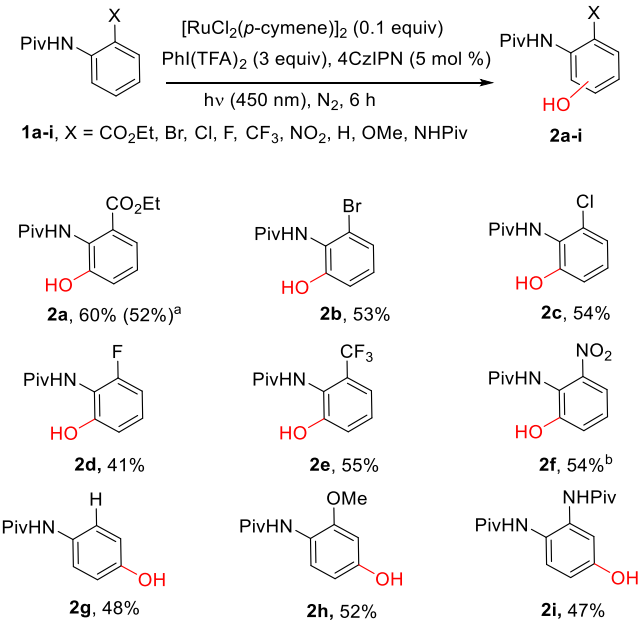
improved to 90% by HPLC with 3 equiv of the oxidant (Table 1 entry 8). Upon using the iridium photocatalyst [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 instead of 4CzIPN, although some hydroxylated products were observed on HPLC, the reaction mixture was complex (Table 1 entry 9). Alternative TM catalysts such as $RuCl_3 \cdot H_2O$ and Pd(OAc)$_2$ were found to be

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991

ineffective in this reaction (Table 1 entries 10−11). Furthermore, we examined *N*-trifluoroacetyl, *N*-2,6-difluorobenzoyl, and *N*-Boc on the amino group of ethyl anthranilate as the alternative DG, instead of the *N*-pivaloyl group in **1a**, under our current metallaphotoredox hydroxylation conditions, but all failed to give any desired product.

After identifying optimal reaction conditions, the direct *ortho*-hydroxylation of a range of anilides containing *o*-substituents was explored to establish the substrate scope of the catalytic reaction. Anilides containing electron-withdrawing groups (EWGs) such as Br, Cl, F, and CF_3 at the *ortho* position were tolerated and oxidized in modest yields (Scheme 2,

Scheme 2. Substrate Scope for *ortho*-Substituted Anilides in Isolated Yields



[a]Yield in parentheses in 1 mmol of the substrate (**1a**) while others are in 0.125−0.25 mmol. [b]Reaction required 0.2 equiv of $[RuCl_2(p\text{-cymene})]_2$, 4 equiv of $PhI(TFA)_2$, 10 mol % 4CzIPN, and 24 h of irradiation.

substrates **1a**−**1e**). In the case of the anilide containing an *ortho*-nitro substituent, a higher catalyst loading, more oxidant, and longer irradiation time were required to complete the reaction (Scheme 2, substrate **1f**). In contrast, the introduction of electron-donating groups (EDGs) or unsubstituted anilides resulted in *para*-hydroxylation as the sole outcome (Scheme 2, substrates **1g**, **1h**, and **1i**), likely by a competitive non-directed mechanism. Such *para*-selective hydroxylation was previously reported with electron-rich anilides using hypervalent iodine(III) reagents, but only under strong acidic conditions (TFA/$CHCl_3$).[23] To support the observed *para*-hydroxylation as the non-directed pathway, three reactions on **1g** were performed: (1) without the TM catalyst, (2) without the TM catalyst and photocatalyst, and (3) without the TM catalyst and photocatalyst and in the absence of light (21 h stirring at room temperature). In each case, product **2g** was obtained as the major product with HPLC yields of 60%, 71%, and 75% respectively, indicating that $PhI(TFA)_2$ directly oxidizes the substrates **1g** to **2g** without involving C−H activation and photoredox catalysis.

Substrates with substituents at the *para* and *meta* positions were also studied. Unlike *ortho*-substituted anilides, monohydroxylation was accompanied by second hydroxylation in another *ortho* position, yielding a mixture of mono- and dihydroxylated products (Scheme 3a,b). Dihydroxylation was not surprising and is useful to generate 2-aminobenzene-1,3-diols. Again, EWG substituents such as CO_2Et, Br, Cl, and F were all well tolerated. Mixtures of mono- and bis-hydroxylated products were separated and fully characterized. In the case of the *m*-Cl substituent, the *para*-hydroxylated compound was isolated as the only product, presumably formed by competitive nondirected hydroxylation mechanism described earlier.[23]

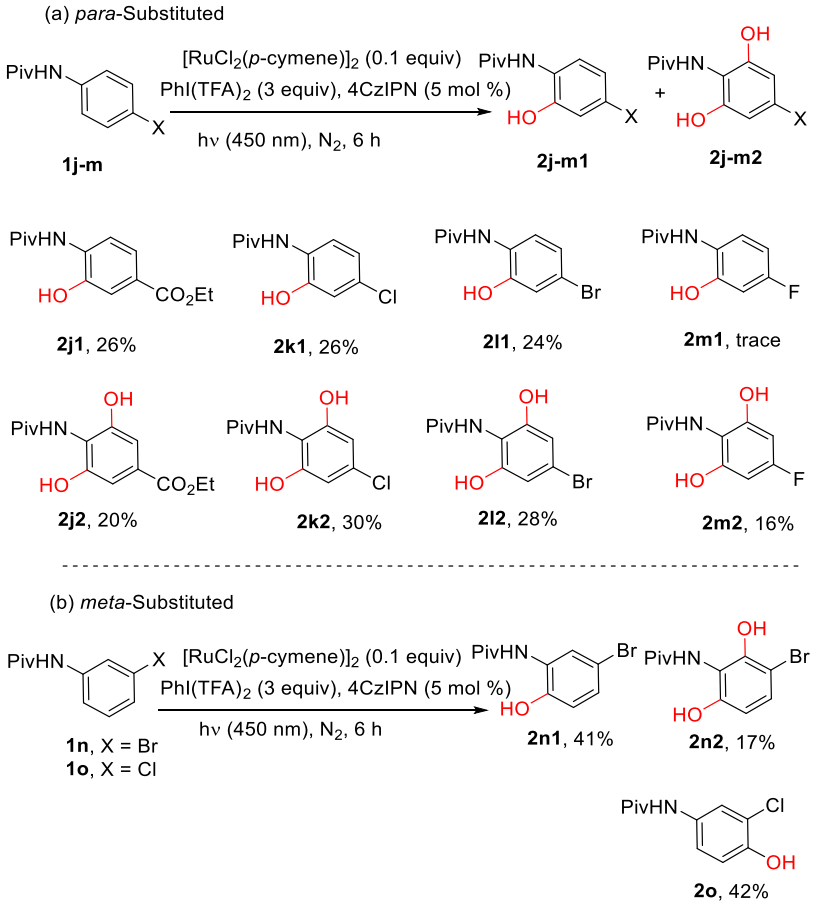
Another conventional way to access 2-aminophenols from anilines is through *ortho*-aminophenyl sulfate esters. It has been reported that aromatic amines can be oxidized to *ortho*-aminophenyl sulfate esters by sodium or potassium persulfate, which in turn can be hydrolyzed in hot acid to its corresponding 2-aminophenols, with the net result being *ortho*-hydroxylation (Boyland−Sims oxidation).[17] This procedure suffers from harsh reaction conditions, low yield, and tedious workup steps. In a separate program, we were in need of stable-isotope-labeled hydroxy anthranilic acid ([phenyl-u-$^{13}C_6$]3-HAA) **4** to track the isotope incorporation in downstream analytes of tryptophan degradation by the kynurenine pathway.[24] [Phenyl-u-$^{13}C_6$]3-HAA is not commercially available, but we were able to prepare milligram quantities of it by following the literature procedure with just 4% isolated yield, Scheme 4a.[17,25] By using our developed hydroxylation with the metallaphotocatalysis, the yield (total isolated yield 29%) and reproducibility to access [phenyl-u-$^{13}C_6$]3-HAA were greatly improved, though with extra steps (Scheme 4b).

Hydroxylation is one of the major metabolism pathways in drug compounds, and often attempts to acquire greater amounts of drug metabolites via chemical approaches to both confirm structures and assess pharmacological properties requires *de novo* synthesis. One-step synthesis of hydroxyl metabolites from drug molecules or drug candidates is much desired to potentially accelerate drug discovery and research efforts. This mild photocatalytic hydroxylation method could be applied to late-stage functionalization and *ortho*-hydroxyl metabolite generation for drug-compound-containing anilides with EWG substituents in a single, neutral, and mild reaction.

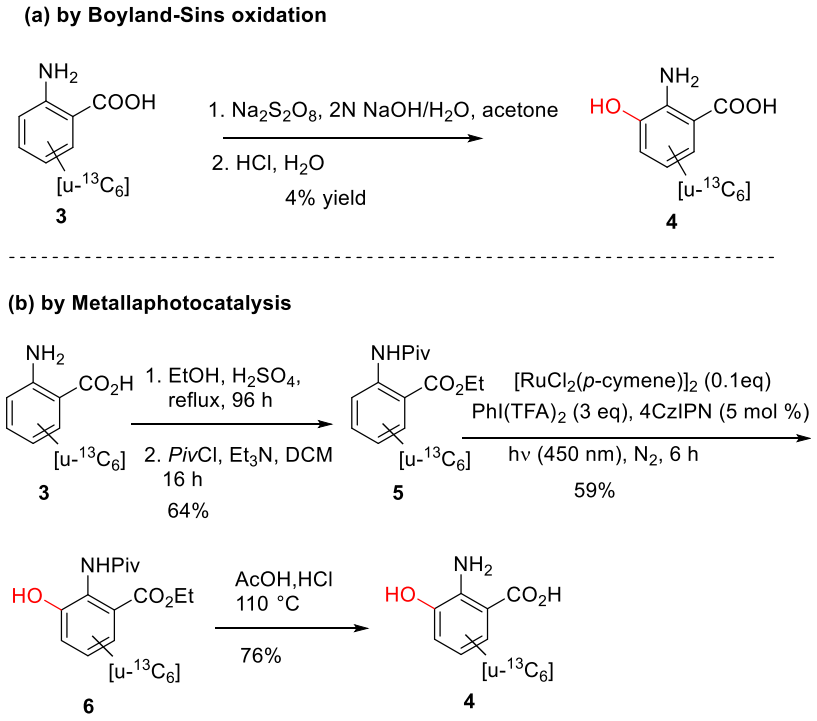
Hypervalent iodine(III) reagents act as oxidants through electron transfer mechanisms.[22,26] In consideration of the mild nature of selective *ortho*-hydroxylation of substituted anilides, we became interested in the mechanism of the optimized metallaphotocatalytic method. The reaction of **1a** did not proceed in the absence of one of the components from 4CzIPN, $[RuCl_2(p\text{-cymene})]_2$, and $PhI(TFA)_2$ or in the absence of the light, confirming the necessity of each component within the catalytic cycle. When the reaction of **1a** was performed in the presence of 3 equiv of a radical trapping agent, TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl, no product (**2a**) was detected. Likewise, no conversion was observed when $PhI(OAc)_2$ was used in place of $PhI(TFA)_2$ [calculated reference redox potential values in the literature of −0.08 V for $PhI(OAc)_2$ vs 0.63 V $PhI(TFA)_2$ in the single electron transfer (SET) mechanism[27]]. These observations support a radical reaction pathway for the Ru-catalyzed photoredox C−H activation/*ortho*-hydroxylation of substituted anilides containing various EWG substituents like

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991

Scheme 3. Substrate Scope for (a) *para*- and (b) *meta*-Substituted Anilides in Isolated Yields



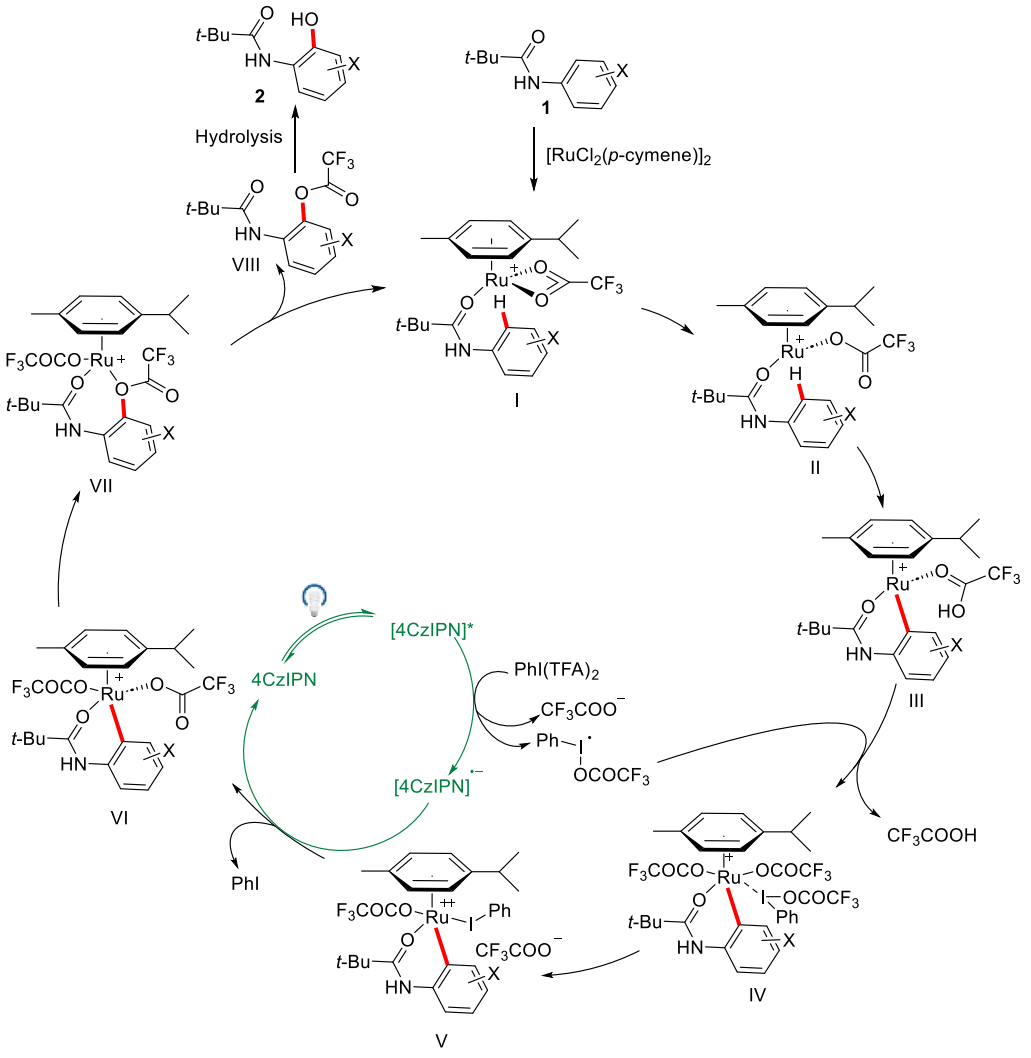
Scheme 4. Synthesis of [Phenyl-u-$^{13}C_6$]3-hydroxy Anthranilic Acid ([u-$^{13}C_6$]3-HAA)



1a. On the other hand, the hydroxylation of substituted anilides containing EDG substituents, such as substrate **1g**, proceeds via competitive direct oxidation with $PhI(TFA)_2$ without involving C−H activation and photoredox catalysis.

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991

Scheme 5. Plausible Reaction Mechanism



Based on the observed reactions and experimental data, a mechanism for the *ortho*-hydroxylation of substituted anilides containing the EWG substituents is proposed in Scheme 5. Initially, $PhI(TFA)_2$ undergoes ligand exchange with $[RuCl_2(p\text{-cymene})]_2$, where the carbonyl of the *N*-Piv group of the substrate acts as a DG and facilitates C−H activation to form intermediates I−III. Absorption of visible light by 4CzIPN generates the excited state species, 4CzIPN*, which undergoes SET to another molecule of $PhI(TFA)_2$, generating an iodanyl radical and a trifluoroacetate anion, which engage in a ruthenacycle through ligand exchange. The reduced photocatalyst $[4CzIPN]^{\bullet-}$ undergoes SET to regenerate the photocatalyst. The oxidation occurs in two steps, first by the cleavage of the I−O bond along with the formation of the Ru−I bond via intermediate IV, followed by the subsequent cleavage of the second I−O bond, forming intermediate V. Reduction of intermediate V, release of iodobenzene and trifluoroacetate coordination to the metal center, forms intermediate VI, which upon the reductive elimination to VII followed by hydrolysis gives the *ortho*-hydroxylated product. For dihydroxylation, the catalytic cycle repeats and ultimately leads to hydroxylate the other accessible *ortho* position.

In conclusion, the metallaphotocatalysis method for the *ortho*-hydroxylation of substituted anilines containing various EWG substituents operates under mild conditions using a readily removable pivaloyl DG by integrating the photocatalyst 4CzIPN and $[RuCl_2(p\text{-cymene})]_2$ and PIFA. The *ortho*-substituted pivalanilides containing EWGs such as Br, Cl, F, CF_3, and CO_2Et at the *ortho* position were hydroxylated at the *ortho* positions of the DG in 41−60% isolated yields. In comparison, the substrates with *ortho* EDGs or unsubstituted anilides resulted in *para*-hydroxylation of the anilides as the only product, likely by a nondirected hydroxylation mechanism. On the other hand, for *para*-substituted pivalanilides, monohydroxylation was accompanied by second hydroxylation in another *ortho* position, yielding a mixture of mono- and bis-hydroxylated products. For *meta*-substituted pivalanilides, with limited substrates, it might produce a mixture of mono- and bis-hydroxylated products or monohydroxylated products. This methodology was applicable to hydroxylate at the *ortho* positions of substituted anilines containing various EWG substituents, which would otherwise not be easily accessible. The utility of the developed hydroxylation method was exemplified by preparing the stable-isotope-labeled compound [phenyl-u-$^{13}C_6$]3-hydroxy anthranilic acid, which was difficult to prepare using conventional methods. The hydroxylation method could be potentially applied to late-stage functionalization and *ortho*-hydroxyl metabolite generation for drug

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991

compound-containing anilides with EWG substituents in a single, neutral, and mild reaction, offering an advantage to *de novo* synthesis.

EXPERIMENTAL SECTION

All reagents and chemicals were obtained from commercial suppliers and used as received. Reactions were monitored by thin layer chromatography (TLC) analysis on silica gel (Merck, 60 F254 plate) and/or liquid chromatography mass spectrometry (LC−MS). TLC plates were visualized by exposure to short-wave ultraviolet (254 and 366 nm) light. LC−MS analyses were performed on an Agilent 6140 quadrupole LC/MS system. Thermally heated reactions were carried out in an oil bath on a hot plate with a temperature controller. Photochemical reactions were performed on photoreactors m1 and m2 from Penn Optical Coatings LLC equipped with 450 nm LED light and an 8 mL vial holder. Purification of compounds was performed by gradient elution by specified solvents either by flash column chromatography or by preparative HPLC. Flash column chromatography was carried out on a CombiFlash R_f with prepacked silica gel (Redi Sep) columns. Preparative HPLC was conducted on a Teledyne ISCO EZ prep using a Phenomenex Gemini C18, 5 μm, 110 Å column (size: 250 × 21.2 mm). HPLC analysis was performed on an Agilent 1200 using a Waters Xbridge C18, 3.5 μm, 4.6 × 150 mm column at 25 °C with a 1 mL/min flow rate and a 5 μL injection volume. Mobile phase A: 0.1% TFA in H_2O. Mobile phase B: 0.1% TFA in CH_3CN. Gradient: 10−90% B, 0−15 min; 90% B, 15−18 min; 90−10% B, 18−19 min; and 10% B, 19−20 min ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra were recorded on a Brüker AVANCE III HD Nanobay spectrometer (400 and 500 MHz). Chemical shifts (δ) were given in ppm relative to TMS, and multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (J) are given in hertz (Hz). High-resolution mass spectrometry (HRMS) was performed on a Waters TOF LC/MS system using a Zspray electrospray ionization (ESI) and time-of-flight (TOF) analyzer in the positive-ion detection mode. The mass peak with a higher intensity of $[M + H]^+$ was chosen for accurate mass analysis.

Substrates for hydroxylation reactions were purchased from chemical suppliers, except **1a**, **1i**, and **1j**, which were prepared as described below.

Ethyl 2-Pivalamidobenzoate (1a). To a solution of ethyl anthranilate (1.669 g, 10 mmol) in dichloromethane (DCM) at 0 °C was added triethylamine (4.17 mL, 0.728 g/mL, 30 mmol), followed by pivaloyl chloride (1.462 g, 12 mmol). The reaction was slowly warmed to room temperature and stirred for 4 h before diluting with water (40 mL). Layers were separated, and the aqueous layer was extracted with DCM (2 × 20 mL). Combined organic layers were washed with water and brine, dried over Na_2SO_4, concentrated, and purified on a silica gel column with 20% EtOAc/heptane. Pure fractions were combined and concentrated to obtain the title compound (2.4 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.36 (br s, 1H), 8.78 (dd, J = 1.0, 8.8 Hz, 1H), 8.05 (dd, J = 1.7, 8.1 Hz, 1H), 7.53 (dt, J = 1.7, 7.9 Hz, 1H), 7.09−7.04 (m, 1H), 4.39 (q, J = 7.3 Hz, 2H), 1.39 (t, J = 7.3 Hz, 3H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.96, 168.41, 142.05, 134.53, 130.81, 122.14, 120.31, 115.27, 61.34, 40.39, 27.62, 14.22. HRMS (ESI) calcd for $C_{14}H_{20}NO_3$ $[M + H]^+$, 250.1443; found, 250.1447.

***N*,*N*′-(1,2-Phenylene)bis(2,2-dimethylpropanamide) (1i).** To a 0 °C solution of benzene-1,2-diamine (200 mg, 1.85 mmol) in DCM (3 mL), DMAP (22.6 mg, 0.185 mmol), and *N*,*N*-diisopropylamine (0.5 mL, 3.70 mmol) was added pivaloyl chloride (0.46 mL, 3.70 mmol). The solution was slowly warmed to room temperature and stirred for 3 h before diluting with water (5 mL). Layers were separated, and the aqueous layer was extracted with DCM (2 × 3 mL). Combined organics were dried in $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified on a silica gel column with 0−70% EtOAc/heptane. Pure fractions were combined and concentrated to get the title compound **1i** as a fluffy-white solid (439 mg, 86% yield). ^{1}H NMR data match with the literature.[28] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (br s, 2H), 7.39−7.42 (m, 2H), 7.18−7.22 (m, 2H), 1.32 (s, 18H).

Ethyl 4-Pivalamidobenzoate (1j). Prepared following the literature procedure.[29] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03−7.99 (d, J = 8.8 Hz, 2H), 7.64−7.60 (d, J = 8.8 Hz, 2H), 7.44 (br s, 1H), 4.36 (q, J = 7.3 Hz, 2H), 1.39 (t, J = 7.3 Hz, 3H), 1.33 (s, 9H).

A general representative procedure for the hydroxylation is described here using ethyl 2-pivalamidobenzoate (**1a**).

Ethyl 3-Hydroxy-2-pivalamidobenzoate (2a). To a mixture of ethyl 2-pivalamidobenzoate (**1a**) (31.2 mg, 0.125 mmol), (bis(trifluoroacetoxy)iodo)benzene (161.3 mg, 0.375 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (7.6 mg, 0.0125 mmol), and 4CzIPN (4.9 mg, 0.0062 mmol) in a vial, dichloroethane (1 mL) was added under nitrogen and irradiated at 450 nm for 6 h. The reaction was concentrated and purified on a silica gel column using 15% EtOAc/heptane to get the monohydroxylated title product **2a** (20 mg, 60% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.35 (br s, 1H), 9.83 (s, 1H), 7.55 (dd, J = 7.6, 1.7 Hz, 1H), 7.17 (dd, J = 8.2, 1.3 Hz, 1H), 7.07 (t, J = 8.2 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.36−1.31 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.55, 168.50, 150.02, 128.97, 125.73, 125.66, 122.86, 119.91, 61.73, 40.15, 27.75, 14.16. HRMS (ESI) calcd for $C_{14}H_{20}NO_4$ $[M + H]^+$, 266.1392; found, 266.1394. The isolated yield of **2a** was 52% when the reaction was scaled up to 1 mmol of the substrate (**1a**), while HPLC analysis of the reaction mixture showed that it was composed of the desired product and the starting material (**1a**) in a ratio of about 3:1.

***N*-(2-Bromo-6-hydroxyphenyl)pivalamide (2b).** Prepared following the general procedure from *N*-(2-bromophenyl)pivalamide (**1b**, 50 mg, 0.195 mmol), and 28 mg was isolated (53% yield), ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 8.75 (s, 1H), 7.08−6.99 (m, 2H), 6.86 (dd, J = 7.8, 2.0 Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.88, 155.69, 129.02, 125.49, 124.74, 122.91, 115.83, 39.06, 27.89. HRMS (ESI) calcd for $C_{11}H_{15}NO_2Br$ $[M + H]^+$, 272.0286; found, 272.0286.

***N*-(2-Chloro-6-hydroxyphenyl)pivalamide (2c).** Prepared following the general procedure from *N*-(2-chlorophenyl)pivalamide (**1c**, 50 mg, 0.236 mmol), and 27 mg was isolated (54% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.50 (s, 1H), 8.04 (br s, 1H), 7.07 (dd, J = 8.7, 7.5 Hz, 1H), 6.99−6.95 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 179.71, 150.74, 127.17, 126.17, 123.23, 120.73, 119.28, 40.06, 27.66. HRMS (ESI) calcd for $C_{11}H_{15}NO_2Cl$ $[M + H]^+$, 228.0791; found, 228.0797.

***N*-(2-Fluoro-6-hydroxyphenyl)pivalamide (2d).** Prepared following the general procedure from *N*-(2-chlorophenyl)pivalamide (**1d**, 24.4 mg, 0.125 mmol), and 11

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991

mg was isolated (42% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.76 (br s,1H), 7.07 (td, J = 8.29, 6.82 Hz 1H), 6.81−6.83 (d, J = 8.50, 7.5 Hz, 1H), 6.66−6.68 (ddd, J = 10.13, 1.13 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 179.56, 155.84, 153.43, 150.37, 126.65, 126.55, 115.67, 114.97, 114.85, 106.34, 106.13, 39.80, 27.58. ^{19}F NMR (377 MHz, $CDCl_3$): δ −128.50 (s, 1F). HRMS (ESI) calcd for $C_{11}H_{14}FNO_2$ [M + H]$^+$, 212.1087; found, 212.1087.

***N*-(2-Hydroxy-6-(trifluoromethyl)phenyl)pivalamide (2e).** Prepared following the general procedure from *N*-(2-(trifluoromethyl)phenyl)pivalamide (**1e**, 57.9 mg, 0.236 mmol), and 34 mg was isolated (55% yield), ^{1}H NMR (400 MHz, C_6D_6): δ 9.28 (s, 1H), 7.70−7.57 (m, 1H), 7.19−7.16 (m, 1H), 6.88 (d, J = 7.2 Hz, 1H), 6.68 (t, J = 8.1 Hz, 1H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.10, 151.67, 127.32, 125.36, 125.05, 123.65, 122.88, 118.30, 39.77, 27.40. ^{19}F NMR (377 MHz, $CDCl_3$): δ −60.39 (s, 3F). HRMS (ESI) calcd for $C_{12}H_{15}NO_2F_3$ [M + H]$^+$, 262.1055; found, 262.1056.

***N*-(2-Hydroxy-6-nitrophenyl)pivalamide (2f).** To a mixture of *N*-(2-nitrophenyl)pivalamide (**1f**, 55.6 mg, 0.25 mmol), (bis(trifluoroacetoxy)iodo)benzene (430 mg, 1.0 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (30.6 mg, 0.20 mmol), and 4CzIPN (19.7 mg, 0.025 mmol) in a vial, dichloroethane (1 mL) was added under nitrogen and irradiated at 450 nm for 24 h. The reaction was concentrated and purified on a silica gel column using 20% EtOAc/hexane to get the monohydroxylated title product **2f** (32 mg, 54% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.29 (br s, 1H), 9.30 (s, 1H), 7.66 (dd, J = 8.1 1.7 Hz, 1H), 7.29 (dd, J = 7.8, 1.5 Hz, 1H), 7.21−7.15 (m, 1H), 7.25−7.11 (m, 1H), 1.42−1.27 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 181.09, 151.30, 141.27, 127.14, 126.12, 122.47, 118.00, 40.31, 27.60. HRMS (ESI) calcd for $C_{11}H_{15}N_2O_4$ [M + H]$^+$, 239.1032; found, 239.1029.

***N*-(4-Hydroxyphenyl)pivalamide (2g).** Prepared following the general procedure from *N*-phenylpivalamide (**1g**, 44.3 mg, 0.25 mmol), and 23 mg was isolated (48% yield). Both ^{1}H and ^{13}C NMR spectra matched with literature data.[30] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, br, 1H), 8.94 (s, br, 1H), 7.38−7.32 (m, 2H), 6.74−6.60 (m, 2H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.32, 153.77, 131.31, 122.79, 115.20, 39.28, 27.81.

To confirm non-directed hydroxylation in example *N*-phenylpivalamide (**1g**), the following test reactions were conducted: (1) reaction without the TM catalyst, (2) reaction without the TM and photocatalyst, and (3) reaction without the TM and photocatalyst and in the absence of light (21 h stirring at room temp). In all cases, product **2g** was formed as a major product with HPLC yields of 60%, 71%, and 75% respectively, while the products were not isolated.

***N*-(4-Hydroxy-2-methoxyphenyl)pivalamide (2h).** Prepared following the general procedure from *N*-(2-methoxyphenyl)pivalamide (**1h**, 38 mg, 0.183 mmol), and 21 mg was isolated (51% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.51 Hz, 1H), 7.94 (s, 1H), 7.27 (s, 1H), 6.84 (br, s, 1H) 6.42−6.48, (m, 1H), 3.82 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.96, 153.43, 149.73, 121.14, 119.69, 106.64, 98.73, 55.70, 39.76, 27.55. HRMS (ESI) calcd for $C_{12}H_{17}NO_3$ [M + H]$^+$, 224.1287; found, 224.1288.

***N*,*N*′-(4-Hydroxy-1,2-phenylene)bis(2,2-dimethylpropanamide) (2i).** Prepared following the general procedure from *N*,*N*′-(1,2-phenylene)bis(2,2-dimethylpropanamide) (**1i**, 34.5 mg, 0.125 mmol), and 17 mg was isolated (47% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, J = 8.68 Hz, 1H), 6.97 (d, J = 2.69 Hz, 1H), 6.65 (dd, J = 8.68, 2.69 Hz, 1H), 1.28 (s, 8H) 1.28(s, 8H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 180.49, 179.86, 157.15, 134.16, 128.11, 123.77, 114.00, 112.78, 40.53, 40.26, 28.04, 27.97. HRMS (ESI) calcd for $C_{16}H_{24}N_2O_3$ [M + H]$^+$, 293.1865; found, 293.1871.

Ethyl 3-Hydroxy-4-pivalamidobenzoate (2j1). Prepared following the general procedure from ethyl 4-pivalamidobenzoate (**1j**, 62.3 mg, 0.25 mmol); two products (**2j1** and **2j2**) were isolated. 17 mg of **2j1** was isolated (26% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 7.95 (s, 1H), 7.69 (d, J = 1.5 Hz, 1H), 7.58 (dd, J = 8.3, 1.9 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 4.35 (q, J = 6.8 Hz, 2H), 1.40−1.33 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.72, 166.40, 147.18, 130.25, 127.67, 122.22, 120.96, 119.24, 61.14, 39.86, 27.63, 14.28. HRMS (ESI) calcd for $C_{14}H_{20}NO_4$ [M + H]$^+$, 266.1392; found, 266.1395.

Ethyl 3,5-Dihydroxy-4-pivalamidobenzoate (2j2). Isolated 14 mg of **2j2** (20% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 2H), 8.33 (s, 1H), 7.30−7.25 (m, 2H), 4.34 (q, J = 7.2 Hz, 2H), 1.41−1.34 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.66, 167.17, 148.30, 127.58, 119.21, 110.51, 61.55, 40.00, 27.65, 14.15. HRMS (ESI) calcd for $C_{14}H_{20}NO_5$ [M + H]$^+$, 282.1344; found, 282.1341.

***N*-(4-Chloro-2-hydroxyphenyl)pivalamide (2k1).** Prepared following the general procedure from *N*-(4-chlorophenyl)pivalamide (**1k**, 52.9 mg, 0.25 mmol); two products (**2k1** and **2k2**) were isolated. 15 mg of **2k1** was isolated (26% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.63−7.50 (m, 1H), 7.02 (d, J = 2.0 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.86−6.82 (m, 1H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.24, 149.77, 132.12, 124.39, 122.91, 120.39, 120.02, 39.53, 27.66. HRMS (ESI) calcd for $C_{11}H_{15}NO_2Cl$ [M + H]$^+$, 228.0791; found, 228.0796.

***N*-(4-Chloro-2,6-dihydroxyphenyl)pivalamide (2k2).** Isolated 18 mg of **2k2** (30% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 2H), 8.05 (br s, 1H), 6.51 (s, 2H), and 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.27, 148.83, 131.29, 113.80, 109.76, 39.82, 27.65. HRMS (ESI) calcd for $C_{11}H_{15}NO_3Cl$ [M + H]$^+$, 244.0748; found, 244.0743.

***N*-(4-Bromo-2-hydroxyphenyl)pivalamide (2l1).** Prepared following the general procedure from *N*-(4-bromophenyl)pivalamide (**1l**, 64 mg, 0.25 mmol); two products (**2l1** and **2l2**) were isolated. Isolated 16 mg of **2l1** (24% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (s, 1H), 8.48 (s, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 2.2, 8.6 Hz, 1H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.83, 149.59, 126.47, 124.01, 122.14, 118.26, 116.15, 39.68, 27.68. HRMS (ESI) calcd for $C_{11}H_{15}NO_3Br$ [M + H]$^+$, 272.0286; found, 272.0291.

***N*-(4-Bromo-2,6-dihydroxyphenyl)pivalamide (2l2).** Isolated 20 mg of **2l2** (28% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (s, 2H), 8.43 (s, 1H), 6.52 (s, 2H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 178.30, 154.41, 118.80, 114.03, 110.55, 39.24, 27.86. HRMS (ESI) calcd for $C_{11}H_{15}NO_3Br$ [M + H]$^+$, 288.0235; found, 288.0242.

***N*-(4-Fluoro-2,6-dihydroxyphenyl)pivalamide (2m2).** To a mixture of *N*-(4-fluorophenyl)pivalamide (**1m**, 48.8 mg, 0.25 mmol), (bis(trifluoroacetoxy)iodo)benzene (430 mg, 1 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (15.3 mg, 0.025 mmol), and 4CzIPN (9.9 mg, 0.0125 mmol) in a vial, dichloroethane (2 mL) was added under nitrogen and

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991

irradiated at 450 nm for 24 h, generating a mixture of **2m2** and trace **2m1**. The reaction mixture was concentrated and purified on a silica gel column using 0−30% EtOAc/hexane to get the dihydroxylated title product **2m2** (9 mg, 16% yield) as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 6.14 (d, J = 9.8 Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.71, 161.75, 152.18, 110.19, 94.63, 39.08, 26.51. ^{19}F NMR (377 MHz, CD_3OD): δ −117.09 (s, 1F). HRMS (ESI) calcd for $C_{11}H_{15}FNO_3$ $[M + H]^+$, 228.1036; found, 228.1039.

***N*-(5-Bromo-2-hydroxyphenyl)pivalamide (2n1).** Prepared following the general procedure from *N*-(3-bromophenyl)pivalamide (**1n**, 32 mg, 0.125 mmol); two products (**2n1** and **2n2**) were isolated. Isolated 14 mg of **2n1** (42% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (br s, 1H), 7.55 (br s, 1H), 7.24−7.20 (m, 2H), 6.89 (d, J = 8.8 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.23, 148.10, 129.78, 126.93, 124.80, 121.31, 111.86, 39.61, 27.65. HRMS (ESI) calcd for $C_{11}H_{15}NO_2Br$ $[M + H]^+$, 272.0286; found, 272.0290.

***N*-(3-Bromo-2,6-dihydroxyphenyl)pivalamide (2n2).** Isolated 6 mg of **2n2** (17% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (br s, 1H), 8.05 (br s, 1H), 7.16 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 9.3 Hz, 1H), 6.16 (br s, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.47, 149.39, 143.83, 128.34, 115.58, 112.81, 99.64, 39.88, 27.65. HRMS (ESI) calcd for $C_{11}H_{15}NO_3Br$ $[M + H]^+$, 288.0235; found, 288.0240.

***N*-(3-Chloro-4-hydroxyphenyl)pivalamide (2o).** Prepared following the general procedure from *N*-(3-chlorophenyl)pivalamide (**1o**, 27.2 mg, 0.125 mmol), isolated yield = 12 mg (42% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 2.4 Hz, 1H), 7.21 (s, br, 1H), 7.17−7.16 (dd, J = 8.8, 2.4 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 5.51 (s, 1H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.62, 148.20, 131.42, 121.46, 120.68, 119.83, 116.08, 39.49, 27.59. HRMS (ESI) calcd for $C_{11}H_{15}NO_2Cl$ $[M + H]^+$, 228.0791; found, 228.0793.

[Phenyl-u-$^{13}C_6$]ethyl 2-Pivalamidobenzoate (5). To an ethanol (1 mL) solution of [phenyl-u-$^{13}C_6$]anthranilic acid (**3**) (200 mg, 1.398 mmol) in a 15 mL round-bottom flask equipped with an air condenser was added concentrated sulfuric acid (0.25 mL, 4.69 mmol) at room temperature. The reaction was slowly heated to reflux for 96 h. After cooling to ambient temperature, the reaction mixture was neutralized with 2N aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 × 5 mL). Combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to get an off-white solid (240 mg), which was dissolved in DCM (2 mL) and cooled to 0 °C. To this was added triethylamine (0.58 mL) followed by the dropwise addition of pivolyl chloride (236 mg, 1.957 mmol). The reaction was slowly warmed to room temperature and, after stirring for 16 h, diluted with DCM (2.5 mL) and water (5 mL). Layers were separated, and the aqueous layer was extracted with DCM (5 mL). Combined organic layers were dried over anhydrous sodium sulfate and concentrated, and the residue was purified on a 12 g silica gel column with 0−10% EtOAc/heptane. Pure fractions were combined and concentrated to get the title compound **5** (230 mg, 64% over two steps) as a clear oil, which solidified upon storage. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.36 (br s, 1H), 9.05−8.48 (m, 1H), 8.40−7.78 (m, 1H), 7.79−7.31 (m, 1H), 7.30−6.75 (m, 1H), 4.39 (q, J = 6.8 Hz, 2H), 1.55 (s, H), 1.42 (t, J = 7.3 Hz, 3H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.95, 168.41, 142.03, 134.51, 130.79, 122.08, 120.27, 115.22, 61.33, 40.39, 27.62, 14.22. HRMS (ESI) calcd for $C_8{}^{13}C_6H_{20}NO_3$ $[M + H]^+$, 256.1644; found, 256.1647.

[Phenyl-u-$^{13}C_6$]ethyl 3-Hydroxy-2-pivalamidobenzoate (6). To a mixture of [phenyl-u-$^{13}C_6$]ethyl 2-pivalamidobenzoate (**5**) (31.9 mg, 0.125 mmol), (bis-(trifluoroacetoxy)iodo)benzene (161.3 mg, 0.375 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (7.6 mg, 0.0125 mmol), and 4CzIPN (4.9 mg, 0.0062 mmol) in a vial, dichloroethane (1 mL) was added under nitrogen and irradiated at 450 nm for 6 h. The reaction was concentrated and purified on a 12 g silica gel column using 15% EtOAc/hexane to get the title compound **6** (20 mg, 59% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.33 (br s, 1H), 9.90 (t, J = 4.2 Hz, 1H), 7.92−7.29 (m, 2H), 7.16−6.78 (m, 1H), 4.38 (q, J = 7.3 Hz, 2H), 1.45−1.37 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.55, 168.45, 150.01, 128.95, 125.72, 125.65, 122.78, 119.83, 61.73, 40.14, 27.62, 14.16. HRMS (ESI) calcd for $C_8{}^{13}C_6H_{20}NO_4$ $[M + H]^+$, 272.1593; found, 272.1596.

[Phenyl-u-1$^{13}C_6$]3-hydroxy Anthranilic Acid (4). To a solution of [phenyl-u-$^{13}C_6$]ethyl 3-hydroxy-2-pivalamidobenzoate (**6**) (18 mg, 0.067 mmol) in acetic acid (1 mL) was added 6 M HCl (2 mL), and the mixture was heated to 110 °C for 110 h. The reaction was concentrated to dryness and purified on a Teledyne ISCO EZ prep using a Gemini 5 μm C18 110 Å column (size 250 × 21.2 mm) with the following solvent gradient. Solvent A: 0.1% formic acid in water, solvent B: ACN. 0−4 min, isocratic 5% B; 4−7 min, gradient 5−38% B; 7−17 min isocratic 38% B, 17−18 min, gradient 38−95% B; 18−21 min, isocratic 95% B; 21 min, back to 35% B; 21−23 min isocratic 35% B. The flow rate was 22 mL/min. The desired product was eluted at 17.8 min. Pure fractions were combined and concentrated to dryness to give the title compound **4** (8 mg, 76% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.52 (br s, 1H), 8.25 (br s, 1H), 7.42−6.14 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.29, 144.92, 141.61, 121.80, 117.11, 114.41, 110.41. HRMS (ESI) calcd for $C^{13}C_6H_8NO_3$ $[M + H]^+$, 160.0705; found, 160.0705.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c10008.

Characterization data including ^{1}H, ^{13}C, ^{19}F, and 2D NMR spectra of the isolated compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Buddha B. Khatri − *Global Discovery Chemistry, Janssen Research & Development LLC, Johnson & Johnson, Spring House, Pennsylvania 19477, United States*; Email: bkhatri@its.jnj.com

Ronghui Lin − *Global Discovery Chemistry, Janssen Research & Development LLC, Johnson & Johnson, Spring House, Pennsylvania 19477, United States*; orcid.org/0000-0001-7951-7253; Email: rlin@its.jnj.com

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991

Authors

Lu Chen − *Global Discovery Chemistry, Janssen Research & Development LLC, Johnson & Johnson, Spring House, Pennsylvania 19477, United States*

Dawei Xu − *Global Discovery Chemistry, Janssen Research & Development LLC, Johnson & Johnson, Spring House, Pennsylvania 19477, United States*

Rhys Salter − *Global Discovery Chemistry, Janssen Research & Development LLC, Johnson & Johnson, Spring House, Pennsylvania 19477, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c10008

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Professor Paul J. Chirik (Chemistry Department, Princeton University) for his review and suggestions of the manuscript. We are also thankful to Dr. George Chiu and Dr. Fan Huang (Janssen Research & Development LLC) for their assistance in literature search and high-resolution mass spectrometry analysis, respectively.

■ REFERENCES

(1) Iqbal, Z.; Joshi, A.; Ranjan De, S. Recent advancements on transition-metal-catalyzed, helation-induced *ortho*-hydroxylation of arenes. *Adv. Synth. Catal.* **2020**, *362* (23), 5301−5351.

(2) Smith, C. J.; Ali, A.; Chen, L.; Hammond, M. L.; Anderson, M. S.; Chen, Y.; Eveland, S. S.; Guo, Q.; Hyland, S. A.; Milot, D. P.; Sparrow, C. P.; Wright, S. D.; Sinclair, P. J. 2-Arylbenzoxazoles as CETP inhibitors: substitution of the benzoxazole moiety. *Bioorg. Med. Chem. Lett.* **2010**, *20* (1), 346−349.

(3) Zhang, Y.-H.; Yu, J.-Q. Pd(II)-Catalyzed hydroxylation of arenes with 1 atm of O_2 or air. *J. Am. Chem. Soc.* **2009**, *131* (41), 14654−14655.

(4) Shang, M.; Shao, Q.; Sun, S.-Z.; Chen, Y.-Q.; Xu, H.; Dai, H.-X.; Yu, J.-Q. Identification of monodentate oxazoline as a ligand for copper-promoted ortho-C-H hydroxylation and amination. *Chem. Sci.* **2017**, *8* (2), 1469−1473.

(5) Shan, G.; Yang, X.; Ma, L.; Rao, Y. Pd-Catalyzed C-H oxygenation with TFA/TFAA: expedient access to oxygen-containing heterocycles and late-stage drug modification. *Angew. Chem., Int. Ed.* **2012**, *51* (52), 13070−13074.

(6) Yang, Y.; Lin, Y.; Rao, Y. Ruthenium(II)-Catalyzed synthesis of hydroxylated arenes with ester as an effective directing group. *Org. Lett.* **2012**, *14* (11), 2874−2877.

(7) Shan, G.; Han, X.; Lin, Y.; Yu, S.; Rao, Y. Broadening the catalyst and reaction scope of regio- and chemoselective C-H oxygenation: a convenient and scalable approach to 2-acylphenols by intriguing Rh(ii) and Ru(ii) catalysis. *Org. Biomol. Chem.* **2013**, *11* (14), 2318−2322.

(8) Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. Ruthenium-Catalyzed oxidative C(sp^2)-H bond hydroxylation: site-selective C-O bond formation on benzamides. *Org. Lett.* **2012**, *14* (16), 4210−4213.

(9) Liu, W.; Ackermann, L. *Ortho*- and *Para*-selective Ruthenium-catalyzed C(sp^2)-H oxygenations of phenol derivatives. *Org. Lett.* **2013**, *15* (13), 3484−3486.

(10) Thirunavukkarasu, V. S.; Ackermann, L. Ruthenium-Catalyzed C-H bond oxygenations with weakly coordinating ketones. *Org. Lett.* **2012**, *14* (24), 6206−6209.

(11) Bu, Q.; Kuniyil, R.; Shen, Z.; Gońka, E.; Ackermann, L. Insights into ruthenium(II/IV)-catalyzed distal C-H oxygenation by weak coordination. *Chem. -Eur. J.* **2020**, *26* (69), 16450−16454.

(12) Yang, F.; Rauch, K.; Kettelhoit, K.; Ackermann, L. Aldehyde-assisted ruthenium(II)-catalyzed C-H oxygenations. *Angew. Chem., Int. Ed.* **2014**, *53* (42), 11285−11288.

(13) Mo, F.; Trzepkowski, L. J.; Dong, G. Synthesis of *ortho*-acylphenols through the palladium-catalyzed ketone-directed hydroxylation of arenes. *Angew. Chem., Int. Ed.* **2012**, *51* (52), 13075−13079.

(14) Yan, Y.; Feng, P.; Zheng, Q.-Z.; Liang, Y.-F.; Lu, J.-F.; Cui, Y.; Jiao, N. $PdCl_2$ and *N*-Hydroxyphthalimide co-catalyzed C-H hydroxylation by dioxygen activation. *Angew. Chem., Int. Ed.* **2013**, *52* (22), 5827−5831.

(15) Yang, X.; Shan, G.; Rao, Y. Synthesis of 2-aminophenols and heterocycles by Ru-catalyzed C-H mono- and dihydroxylation. *Org. Lett.* **2013**, *15* (10), 2334−2337.

(16) Lv, J.; Zhao, B.; Yuan, Y.; Han, Y.; Shi, Z. Boron-mediated directed aromatic C-H hydroxylation. *Nat. Commun.* **2020**, *11* (1), 1316.

(17) Boyland, E.; Sims, P. The oxidation of some aromatic amines with persulphate. *J. Chem. Soc.* **1954**, 980−985.

(18) Shang, T.-Y.; Lu, L.-H.; Cao, Z.; Liu, Y.; He, W.-M.; Yu, B. Recent advances of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) in photocatalytic transformations. *Chem. Commun.* **2019**, *55* (38), 5408−5419.

(19) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. Metallaphotoredox: the merger of photoredox and transition metal catalysis. *Chem. Rev.* **2022**, *122* (2), 1485−1542.

(20) Shah, S. S.; Paul, A.; Bera, M.; Venkatesh, Y.; Singh, N. D. P. Metallaphotoredox-mediated Csp^2-H hydroxylation of arenes under aerobic conditions. *Org. Lett.* **2018**, *20* (18), 5533−5536.

(21) He, C.; Fan, X.; Ji, M.; Sun, X.; Zhang, W.; Zhu, X.; Sun, Z.; Chu, W. Visible light induced palladium catalyzed CH hydroxylation of nitrogen-containing heterocyclic aromatics in the presence of H_2O_2. *Tetrahedron Lett.* **2022**, *112*, 154225.

(22) Chen, C.; Wang, X.; Yang, T. Recent synthetic applications of the hypervalent iodine(III) reagents in visible-light-induced photoredox catalysis. *Front. Chem.* **2020**, *8*, 551159.

(23) Itoh, N.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. Introduction of a hydroxy group at the *para* position and *N*-iodophenylation of *N*-arylamides using phenyliodine(III) bis-(trifluoroacetate). *J. Org. Chem.* **2002**, *67* (21), 7424−7428.

(24) Schwarcz, R. The kynurenine pathway of tryptophan degradation as a drug target. *Curr. Opin. Pharmacol.* **2004**, *4* (1), 12−17.

(25) Khatri, B.; Lin, R.; Salter, R. Catalyzed C-H activation/hydroxylation for synthesis of [$^{13}C_6$]3-hydroxy anthranilic acid and hydroxy anilines, In. *14th International Symposium of the Synthesis and Applications of Isotopes and Isotopically Labeled Compounds*, International Isotope Society, June 12−16, 2022, Raleigh, NC, USA.

(26) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. Hypervalent iodine(III): selective and efficient single-electron-transfer (SET) oxidizing agent. *Tetrahedron* **2009**, *65* (52), 10797−10815.

(27) Radzhabov, M. R.; Sheremetev, A. B.; Pivina, T. S. Oxidative ability of organic iodine(iii) reagents: a theoretical assessment. *New J. Chem.* **2020**, *44* (17), 7051−7057.

(28) Gampe, D. M.; Schramm, S.; Ziemann, S.; Westerhausen, M.; Görls, H.; Naumov, P.; Beckert, R. From highly fluorescent donors to strongly absorbing acceptors: the tunable properties of fluorubines. *J. Org. Chem.* **2017**, *82*, 6153−6162.

(29) Mei, C.; Lu, W. Palladium(II)-catalyzed oxidative homo- and cross-coupling of aryl *ortho*-sp^2 C-H bonds of anilides at room temperature. *J. Org. Chem.* **2018**, *83*, 4812−4823.

(30) Chuang, H.-Y.; Schupp, M.; Meyrelles, R.; Maryasin, B.; Maulide, N. Redox-neutral selenium-catalysed isomerisation of *para*-hydroxamic acids into *para*-aminophenols. *Angew. Chem., Int. Ed.* **2021**, *60*, 13778−13782.

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991

NOTE ADDED AFTER ASAP PUBLICATION

This paper originally published ASAP on April 24, 2024. As the Supporting Information file was unreadable, a new version reposted on April 26, 2024.

https://doi.org/10.1021/acsomega.3c10008
ACS Omega 2024, 9, 19982−19991