JOC The Journal of Organic Chemistry

Note

Isoindolinone Synthesis: Selective Dioxane-Mediated Aerobic Oxidation of Isoindolines

Pawan Thapa, Esai Corral, Sinjinee Sardar, Brad S. Pierce, and Frank W. Foss

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01920 • Publication Date (Web): 20 Dec 2018

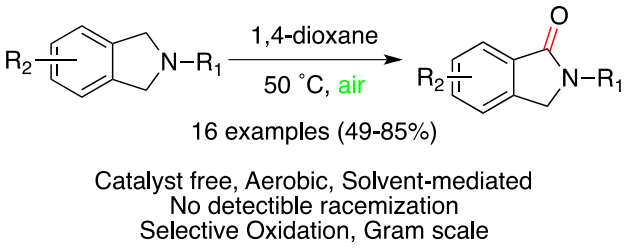
ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Isoindolinone Synthesis: Selective Dioxane-Mediated Aerobic Oxidation of Isoindolines

Pawan Thapa, Esai Corral, Sinjinee Sardar, Brad S. Pierce, Frank W. Foss Jr.*

Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington 76019, TX, USA



ABSTRACT: N-alkyl and N-aryl-isoindolinones were prepared by a dioxane-mediated oxidation of isoindoline precursors. The transformation exhibits unique chemoselectivity for isoindonlines. A chiral 3º-benzylic position was not racemized during oxidation, and methyl indoprofen was prepared by late stage oxidation. Mechanistic studies suggest a selective H-atom transfer, which avoids many known oxidation (by)products of isoindolinones.

Isoindolinones (phthalimidines) represent a growing class of benzofused γ-lactam natural products.[1-8] Synthetic and natural isoindolinones are medicinally relevant,[9-11] and valuable building blocks for materials[9] (**Figure 1**).

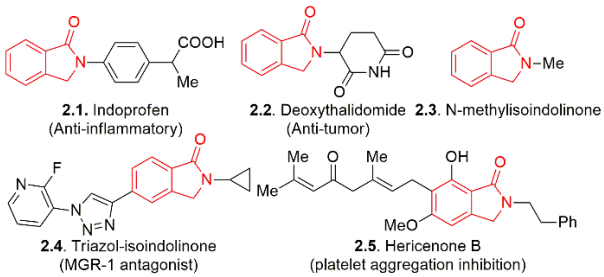
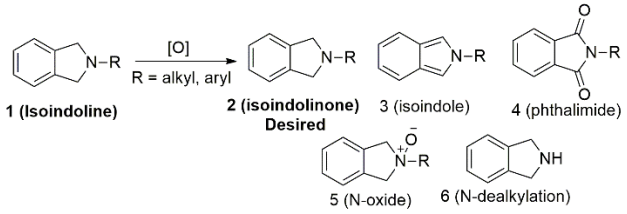


Figure 1: Valuable Isoindolinones

Approaches to isoindolinones overcome a variety of synthetic challenges derived from desired substitution patterns. Phthalimide mono-reductions were directed by ortho-aromatic substituents, as in the total syntheses of staurosporine.[8,10,11] A variety of cyclization strategies build the lactam ring, including the halogenation or direct C-H activation and cyclization of *o*-methylbenzamides,[12-20] reductive/condensative cyclizations,[21-29] carbonylative strategies.[30-36] Parham acylations, [37-39] cross-dehydrogenative coupling,[40] and aryne mediated substitutions. [41] A recent Bischler-Napieralski-type cyclization[42] allowed the late stage construction of an isoindolinone in the total synthesis of

lactonamycin.[43] Recently, a method for 1º and 2º amine oxidation prepared unsubstituted isoindolinone in good yield.[44] However, the oxidation of N-substituted isoindolines, **1**, as demonstrated in this note, is an underexplored approach to isoindolinones, **2**. Many isoindoline **1** preparations involve reductions, which may caution those attempting to improve redox economy; however, the accessibility of isoindoline precursors are rarely more elaborate than current preparations of isoindolinones and recent [2+2+2] cycloadditions access isoindolines (and some isoindolinones) with a variety of functionalization patterns.[45]

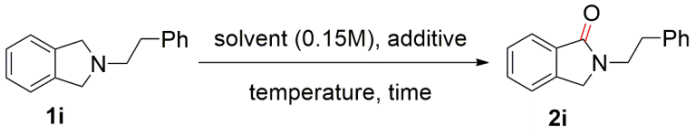
Scheme 1: Isoindoline Oxidations

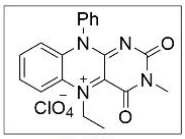


The conversion of isoindolines to isoindolinones presents a variety of potential oxidation byproducts—including overoxidation to phthalimides,[11,32-37] *N*-oxide formation,[46,47] *N*-dealkylation,[48-52] or isoindole[53-57] formation (**Scheme 1**). Here, we describe an unexpected catalyst-free and solvent-enhanced oxidation method that provides synthetically useful yields of isoindolinones for a range of substrates. Significant selectivity was found over phthalimide formation, which can form aerobically under basic conditions from isoindolinones.[23]

We initially considered flavoperoxide mimics to examine the catalytic oxidation of isoindoline derivatives, since flavoproteins oxidize amines to iminium intermediates in many monoamine oxidases.[58] Furthermore, flavoperoxides occupy a space in oxidation potential between alkylperoxides and more powerful peroxyacids.[59] The successful oxidation of a single benzylic site of isoindoline (**1i)** with isoalloxazinium $FLClO_4$ was observed in oxygenated DMF (table 1, entry 1)—with no over-oxidization after 48 h at 100 °C; however, control reactions gave similar results Table 1, entry 2). In fact, many polar aprotic solvents afforded positive results without catalyst (see also **Table S1**). 1,4-Dioxane was best (91% yield in eight hours, 0% neat). The addition of various terminal oxidants did not improve the initial dioxane conditions and bases shut down the production of desired product. Interestingly, O_2 atmospheres produced greater consumption of starting materials, but lower overall yields than open air reactions. Dioxane autoxidation is a known process sometimes involved in fine catalytic methods,[60-62] therefore other peroxides were investigated in dioxanes and various polar aprotic solvents. No additive performed better than 1,4-dioxane alone (**see SI**).

Table 1: Select Reaction Condition Screening[a]





FLClO$_4$

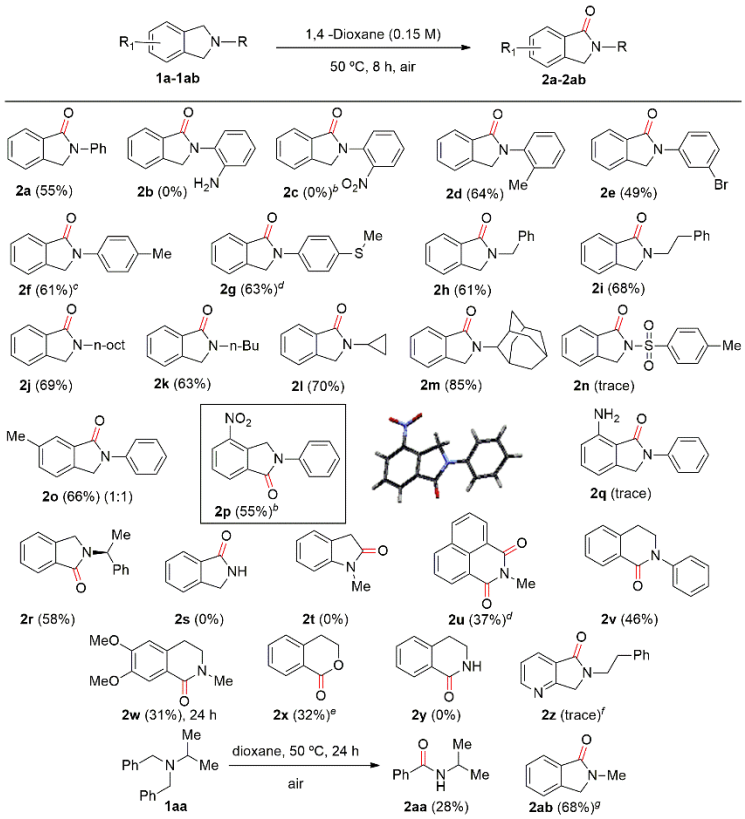
Entry	solvent	Temp. (°C)	Time (h)	Atmosphere	FLClO$_4$ (equiv)	Conversion	Yield
1	DMF	90	8	air	0.1	NA	48
2	DMF	90	8	air	0.0	NA	35
3	DMSO	50	6	air	0.0	100	53
4	THF	50	8	air	0.0	43	38
5	Dioxane	50	8	air	0.0	100	**91[b], 86[c], 83[d]**
6	Dioxane	50	6	Ar	0.0	0	0
7	Dioxane	50	2	O_2	0.0	100	61

[a]Unless otherwise stated, substrate **1i** (0.2 mmol) in given solvent (0.15 M) in open air at given condition. CH_2Br_2 added as NMR internal standard for conversion and yield calculations. [b]ACS grade dioxane 1. [c]ACS grade dioxane 2. [d]extra dry dioxane.

Several isoindolines were prepared and oxidized in the air/dioxane system (**Table 2**). While 2-arylisoindolines (**1a-1g**) gave moderate yields, 2-alkylisoindolines (**1h-1m**) provided more significant yields in eight hours. Strongly electron withdrawing substrates, (**1c**, **1n**) and protic substrates, (**1b**, **1s**, and **1y**) afforded trace amounts of product on these time scales. Amino-substituted substrates were unproductive with full consumption of substrate (e.g. **1b)**. *Ortho*-substitution on 2-aryl moieties had little effect on reactivity (**1d** vs. **1f**). Contrary to 2-(*o*-nitrophenyl)isoindoline (**1c**), 4-nitro-2-phenylisoindoline (**1p**) formed isoindolinone in moderate yields and good selectivity. 5-methyl-2-phenylisoindolinone (**2o**), unlike **2p**, was formed in ca. 1:1 mixture of isomers. Again, amino substitution of isoindoline (**1q**) decomposed under the reaction conditions. Chiral **1r**, which contains a competing tertiary-benzylic position, was oxidized to **2r** with no significant racemization of the N-benzyl chiral center (**2r** $[\sigma]_D^{22}$ = -164.7 (0.1, $CHCl_3$); lit.[63] -161.3 (c 1.33, $CHCl_3$). While bond dissociation energies dominate H-atom abstraction rates, the relief of strain energy and relative sterics cannot be overlooked; 2º C-H's within cyclopentane have enhanced reactivity, while 3º-neopentyl C-H's in acyclic systems are nearly unreactive. [64] Furthermore, changes in degrees of freedom can effect relative activation barriers, H-atom abstraction from cumene's benzylic position has an *A* factor that is ca. a log order lower than that of the 3º hydrogen of 3-methylpentane.[65] The special reactivity of isoindolines is further demonstrated by the poor reactivity of **1s**-**1y**. Secondary amines and tertiary amines with non-benzylic substrates (**1s**, **1t** and **1y**) were non-productive substrates. Tetrahydroisoquinoline derived substrates, containing a 6-membered ring, (**1v** and **1w)** and isochroman (**1x**) produced modest yields, even with increased temperatures and reactions times. Dibenzylisopropylamine **1aa** gave low

conversions to amide **2aa**, with loss of one benzylic group. *N*-methylisoindolinone **2ab** was formed in 68% after five hours at 6.0 mmol scale.

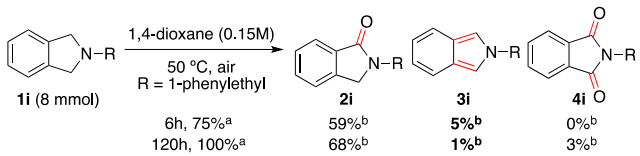
Table 2: Substrate Scope[a]



[a]**Reaction conditions**: Isoindoline substrates **1a-1ab** (0.25 mmol) in 0.15 M extra dry 1,4-dioxane, isolated yield in parenthesis. [b]O_2 balloon, 12 h. [c]O_2 balloon, 4 h. [d]0.5 mmol scale. [e]68 h, 80 °C. [f]30% isoindole product observed by NMR spectroscopy. [g]6.0 mmol scale reaction, O_2 balloon, 5 h.

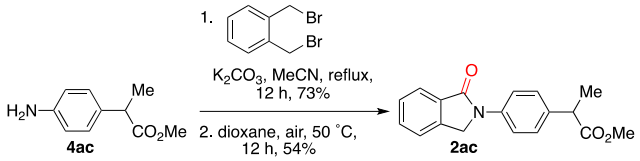
To explore the synthetic use of this process, a gram scale synthesis of **2i** was performed (investigating six and 120 h reaction times) with good yields and little isolated byproduct (**Scheme 2**). Methyl indoprofen (**2ac),** a precursor to the discontinued analgesic and potential neuronal protectants,[66] was also prepared using this selective oxidation process (**Scheme 3**).

Scheme 2: N-phenylethylIsoindolinone synthesis



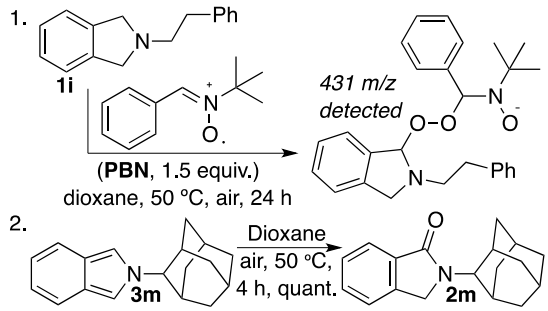
[a]NMR conversion of **1i**, [b]isolated yields

Scheme 3: Synthesis of Methyl Indoprofen



To understand the mechanism, various species were added to oxidations of substrate **1i** (**Scheme S1,** TEMPO, BHT, NBS, and *N*-tert-butyl-α-phenylnitrone (**PBN**)). TEMPO inhibited the transformation at lower concentrations and formed isoindole (**3i**) with four equivalents. BHT, an H-atom donor capable of suppressing autoxidation, formed no detectable product. Various sub-stoichiometric equivalents of NBS were well tolerated. GC-MS analysis of the reaction progress revealed a **1i-O-O-PBN** adduct mass (**m/z 431.0** and predictable fragments (**Scheme 4, entry 1**). Because NMR and TLC experiments suggested the presence of isoindoles, isoindole **3m** (serendipitously isolated as a stable material from the preparation of **1m**) was resubmitted to the reaction conditions, yielding isoindolinone **2m** quantitatively (**entry 2**).Together, H-atom abstraction and conversion to isoindoles **3** was considered.

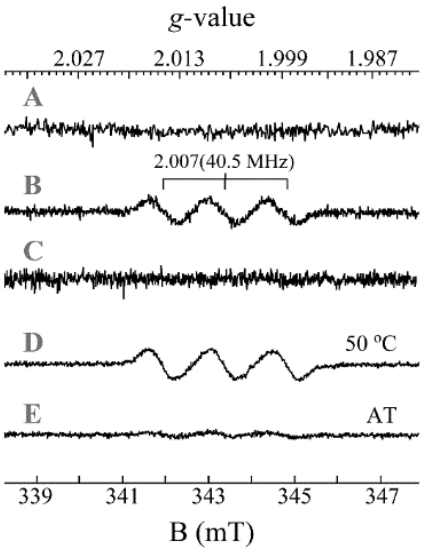
Scheme 4: Intermediate/Byproduct Investigation



Radical involvement was confirmed by a series of EPR experiments illustrated in **Scheme 5**. Reactions carried out with excess (0.09 M) PBN spin-trap in dioxane formed a radical when heated. The characteristic ^{14}N-triplet (I = 1; 40.5 MHz) centered at a g-value of 2.007 (**trace B**) was typical of the nitrogen-centered PBN-radical.[67] Control reactions were performed in solvents where product formation was not observed (ethyl acetate) with no PBN-radicals observed (**trace C**). When a reaction mixture containing substrate **1i** (0.022 mmol), dioxane (0.3 mL), and spin trap PBN (0.028 mmol) was heated, an EPR analysis of aliquots taken from the reaction showed the PBN-radical. As compared to similar

reactions performed at ambient temperature (AT), the amount of PBN-radical is greatly increased at elevated temperatures (**traces D** and **E**). Double integration of these spectra indicates that the amount of PBN-radical formed at AT is attenuated by nearly 85% relative to 50 °C reactions. Collectively, these observations are consistent with the formation of radical reaction intermediates in reaction conditions that lead to the isoindolinone product; while the **1i**-OO-PBN adduct was detected, the exact identity of the EPR observable radical specie has yet to be determined. A parallel kinetic isotope study (**Scheme S3**) of **1i** and 1,1,3,3-tetradeutero-**1i** (**1i-D_4)** revealed a primary kinetic isotope effect (K_H/K_D=3.88±0.11), indicating likely C1-H bond breaking in the rate determining step, which is consistent with autoxidation processes.

Scheme 5. EPR spectra for selected reaction conditions[a]



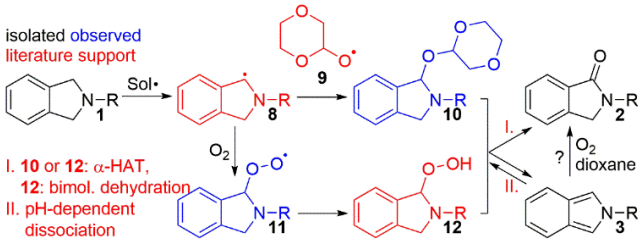
(**A**) dioxane at 50 °C; (**B**) dioxane and PBN at 50 °C; (**C**) ethyl acetate, isoindoline, and PBN at 50 °C; (**D**) dioxane, isoindoline, and PBN at 50 °C; (**E**) dioxane, isoindoline, and PBN at ambient temperature (AT). Instrumental conditions: frequency, 9.65 GHz; modulation power, 20 mW; modulation frequency, 0.3 mT.

Potentially operative mechanisms are summarized in **Scheme 6** . Dioxane autooxidation products likely form **8,** initiating oxidation. Independent of additional solvent interactions, isoindoline radical **8** should form 1-hydroperoxyisoindoline **12** (leading to the **1i-OO-PBN** adduct). Alkylperoxide **12**, like many other secondary hydroperoxy species could proceed to the product **2** by a second H-atom transfer and elimination of hydroxy radical, or by a non-radical intermolecular dehydration reaction between two molecules of **12**. When considering the TEMPO additive data, which shuts down product production, one may favor a radical transformation over dimeric dehydration, which is slow in the presence of trace protic species.[68] Isoindole **3** formation is observed under autoxidation conditions. In a study of N-

butylisoindole and O_2 in methyl isopropyl ketone, a mixture of phthalimide, isoindolinone, and hydroxyisoindolinone products were formed,[69] whereas re-subjection of isoindole **3m** to air/dioxane reaction conditions quantitatively yields isoindolinone **2m**. Whether isoindole **3** is part of the productive pathway or a reversible thermodynamic sink is yet unknown.

Dioxane is uniquely autooxidized compared to other ethers, due to the β-effect from the additional ring oxygen. This results in the relatively slow formation of bulk oxidants compared to THF and Et_2O (see SI), and rapid formation of **9** and O_2 from two dioxane-OO·, whereas, two THF-OO· molecules decompose to lactone and acetal intermediates. Indeed, dioxane-O-1i adduct (**10**) is detected by GC-MS of reactions, while THF reactions formed more peroxide content, a detectable dialkylperoxide **THF-OO-1i,** and significantly lower yields of isoindolinone **2**. Ether **10** is not isolated as a byproduct, and could undergo elimination to **3,** or a second H-atom transfer at the α-C1 carbon, which can convert to **2**. Regardless, a general mechanism can be deduced from the bulk reaction investigation, leading to future kinetic investigation.

Scheme 6: Potential Mechanisms for Isoindoline Oxidation



In conclusion, we report a simple and synthetically useful oxidative strategy for the preparation of isoindolinones from isoindolines. The solvent-mediated method uses O_2 as the terminal oxidant and requires no catalyst, it is selective (even over teriary-benzylic C-H's and larger heterocyclic rings) and avoids common (over)oxidation byproducts related to many other oxidants. Initial mechanistic studies indicate an H-atom transfer rate-limiting process with potential for future catalyst/reagent design and application to selective late stage oxidations of isoindolines to produce functional isoindolinones.

EXPERIMENTAL SECTION:

General Comments:

^{1}H NMR spectra were recorded on 300 MHz and 500 MHz spectrometers and referenced to the internal solvent signals (7.26 ppm in $CDCl_3$). ^{13}C NMR spectra were recorded on 75 MHz and 125 MHz spectrometers referenced to the internal solvent signals (central peak 77.16 ppm in $CDCl_3$). Dibromomethane was used as internal standard for screening reaction condition ($CDCl_3$, 4.8 ppm). NMR data are reported as follows: chemical shift (in ppm, δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (in Hz, *J*). Reactions were monitored by thin layer chromatography (TLC) on silica gel coated aluminum plates (EMD Merck F254, 250 mm

thickness). Column chromatography was carried out with Silicycle Silicaflash P60 silica gel (mesh 230-400). Melting points were measured in capillary tubes on a Mel-Temp II apparatus and were uncorrected. IR spectra were collected in Bruker Alpha-P FT-IR Spectrometer by attenuated total reflectance on a diamond sample plate. Electron Paramagnetic Spectroscopy (EPR) experiments were recorded on a Bruker (Billerica, MA) EMX Plus spectrometer equipped with a bimodal resonator (Bruker model 4116DM). High resolution mass spectrometry (HRMS) experiments were performed in electrospray ionization (ESI) mass spectrometry measurements using a TOF mass analyzer. GC-MS experiments were obtained in Shimadzu Scientific Instruments, GCMS-QP2010, using electron impact ionization (EI) at 150 eV and a mass selective detector. All reagents were weighed and handled in air at room temperature. Various grades of 1,4-Dioxane were purchased from Acros Organics, Alfa Aesar, and Sigma Aldrich, and used without further purification, unless otherwise specified. Starting materials **1s**, **1t**, **1x** and **1y** are commercially available and purchased from VWR and Fisher Scientific. **N. B. Explosive peroxide intermediates are known to form and accumulate due to heating and evaporation of peroxide forming solvent.** As such, appropriate safety measures should be taken into consideration. Larger scale reactions were performed behind blast shield as a safety measure. Though reaction systems were tested at elevated temperatures, for long periods, in oxygenated atmospheres, no explosions or accidents were encountered during this study. All peroxide forming reagents were less than 12 months old, often freshly purchased, and were tested with peroxide test strips prior to use.

General Procedure for the Synthesis of Substrates 1a-n, **1r** and **1ac:**[70]

α,α'-dibromo-*o*-xylene (500 mg, 1.76 mmol) and aniline derivatives (1.76 mmol) were dissolved in 10 mL acetonitrile. Potassium carbonate (690 mg, 5.0 mmol) was then added to the reaction mixture. This resulting mixture was stirred and heated at 60 °C for 18 hours under Argon atmosphere. After the completion of reaction as indicated by TLC analysis, the precipitate was filtered, and the residue was washed with 5 mL of acetonitrile. The filtrate was concentrated under reduced pressure, giving the crude product, which was purified by column chromatography.

2-phenylisoindoline (1a):[70]

Yield 59% (202 mg); R_f = 0.44 (SiO_2; hexanes: ethyl acetate, 10:1); White solid; **mp** 160-162 °C; **IR** (neat, cm^{-1}): 3038, 3040, 2923, 1588, 1463, 1181, 1091; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 6H), 6.79 (t, *J* = 7.1 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 2H), 4.68 (s, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 147.2, 138.0, 129.5, 127.2, 122.7, 116.2, 111.6, 53.8.

2-(2-amino)phenylisoindoline (1b):[71]

Yield 54% (200 mg); R_f = 0.26 (SiO_2; hexanes: ethyl acetate, 10:1); Pale brown solid; **mp** 100-101 °C; **IR** (neat, cm^{-1}): 3414, 3392, 2802, 1614, 1500, 1469; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 5H), 7.21 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.99 – 6.95 (m, 1H), 6.83 – 6.76 (m, 2H), 4.48 (s, 4H), 3.99 (br, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.4, 139.9, 136.9, 127.0, 124.5, 122.4, 121.4, 120.5, 118.9, 115.8, 56.5.

2-(2-nitro)phenylisoindoline (1c):[71]

Yield 51% (215 mg); R_f = 0.37 (SiO_2; hexanes: ethyl acetate, 10:1); Orange solid; **mp** 105-107 °C; **IR** (neat, cm^{-1}): 3055, 2922, 2902, 1512, 1512, 1463, 1377, 1255, 1174**; ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.44 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.29 (s, 4H), 7.02 (dd, *J* = 8.6, 1.0 Hz, 1H), 6.79 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 4.66 (s, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.4, 138.08, 136.5, 133.0, 127.6, 126.7, 122.3, 116.4, 55.6.

2-(2-methyl)phenylisoindoline (1d):[72]

Yield 60% (220 mg); R_f = 0.47 (SiO_2; hexanes: ethyl acetate, 10:1); White solid; **mp** 114-115 °C; **IR** (neat, cm^{-1}): 3043, 2911, 2852, 1520, 1371, 1254, 1163; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.30 – 7.24 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 4.69 (s, 4H), 2.53 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.3, 139.2, 132.2, 129.4, 127.1, 126.8, 122.4, 121.2, 117.3, 56.6, 21.1.

2-(3-bromo)phenylisoindoline (1e):

Yield 49% (236 mg); R_f = 0.40 (SiO_2; hexanes: ethyl acetate, 10:1); Pale yellow liquid; **IR** (neat, cm^{-1}): 3045, 2966, 1589, 1489, 1479, 1467, 1388, 1217, 993; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 4H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.80 (s, 1H), 6.58 (d, *J* = 6.7 Hz, 1H), 4.63 (s, 4H); **^{13}C NMR**(125 MHz, $CDCl_3$) δ 148.3, 137.5, 134.7, 130.6, 127.4, 122.7, 119.0, 114.4, 110.3, 53.8; **HRMS** (ESI) calcd for **$C_{14}H_{13}BrN$** $[M+H]^+$, 274.0226; found, 274.0232

2-benzylisoindoline (1h):[72]

Yield 66% (243 mg); R_f = 0.2 (SiO_2; hexanes: ethyl acetate, 10:1); Pale brown liquid; **IR** (neat, cm^{-1}): 3044, 2962, 1505, 1361, 1135; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, *J*= 7.3 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.31 (dt, *J* = 4.5, 1.8 Hz, 1H), 7.21 – 7.17 (m, 4H), 4.01 (s, 4H), 3.96 (s, 2H);**^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.3, 139.2, 128.9, 128.5, 127.2, 126.7, 122.4, 60.4, 59.0.

2-phenethylisoindoline (1i):[73]

Yield 69% (271 mg); R_f = 0.26 (SiO_2; hexanes: ethyl acetate, 10:1); White solid; **mp** 60-61°C; **IR** (neat, cm^{-1}): 3026, 2949, 2882, 1495, 1357, 1120; ^{1}H NMR (300 MHz, $CDCl_3$-D) δ 7.85 (dd, *J* = 6.8, 1.0 Hz, 1H), 7.51 (td, *J* = 7.3, 1.4 Hz, 1H), 7.45 (td, *J* = 7.4, 0.9 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.33 – 7.21

(m, 5H), 4.21 (s, 2H), 3.91 – 3.84 (m, 2H), 3.04 – 2.97 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.3, 140.1, 128.7, 128.5, 126.7, 126.1, 122.3, 59.2, 58.0, 35.8

2-octylisoindoline (1j):[74]

Yield 63% (256 mg); R_f = 0.18 (SiO_2; hexanes: ethyl acetate, 5:1); Pale brown liquid; **IR** (neat, cm^{-1}): 3027, 2926, 2854, 1465, 1364, 1324, 1149; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.19 (m, 4H), 3.95 (s, 4H), 2.74 – 2.70 (m, 2H), 1.63 – 1.57 (m, 2H), 1.40 – 1.25 (m, 10H), 0.89 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.8, 126.9, 122.4, 59.2, 56.4, 31.9, 29.7, 29.4, 28.8, 27.5, 22.8, 14.2.

2-butylisoindoline (1k):[75]

Yield 61% (188 mg); R_f = 0.25 (SiO_2; hexanes: ethyl acetate, 2:1); Pale brown liquid; **IR** (neat, cm^{-1}): 3038, 2955, 2929, 1463, 1325, 1152; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 – 7.17 (m, 4H), 3.92 (s, 4H), 2.74 – 2.69 (m, 2H), 1.62 – 1.55 (m, 2H), 1.42 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.35, 126.7, 122.3, 59.2, 56.1, 31.2, 20.7, 14.2.

2-cyclopropylIsoindoline (1l):[76]

Yield 46% (129 mg); R_f = 0.4 (SiO_2; hexanes: ethyl acetate, 5:1); Colorless liquid; **IR** (neat, cm^{-1}): 3082, 3007, 2935, 2796, 1462, 1348, 1016; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 0.8 Hz, 4H), 4.06 (s, 4H), 2.08 – 1.99 (m, 1H), 0.58 – 0.49 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.3, 126.8, 122.5, 58.9, 35.6, 6.1.

2-adamantylisoindoline (1m):[75]

Yield 65% (290 mg); R_f = 0.25 (SiO_2; hexanes: ethyl acetate, 5:1); White solid; **mp** 202-203 °C; **IR** (neat, cm^{-1}): 2900, 2846, 2770, 1486, 1356, 1282, 1149, 1081; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 4H), 4.11 (s, 4H), 2.14 (m, 3H), 1.82 (d, *J* = 2.7 Hz, 6H), 1.74 – 1.63 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.6, 126.6, 122.6, 53.2, 50.2, 44.3, 39.2, 37.0, 36.3, 29.8, 29.5.

2-tosylisoindoline (1n):[77]

Prepared from corresponding monosodium salt of tosyl amide.

Yield 78% (355 mg); R_f = 0.36 (SiO_2; hexanes: ethyl acetate, 10:1); White solid; **mp** 174-175 °C; **IR** (neat, cm^{-1}): 3074, 2974, 1720, 1469, 1344, 1170, 1080; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.25 – 7.21 (m, 2H), 7.19 – 7.15 (m, 2H), 4.62 (s, 4H), 2.40 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.8, 136.2, 133.8, 129.9, 127.8, 127.7, 122.7, 53.8, 21.6.

(S)-2-(1-phenylethyl)isoindoline (1r):

Yield 59% (231 mg); R_f = 0.22 (SiO_2; hexanes: ethyl acetate, 10:1); Pale pink solid; **mp** 42-44 °C; **IR** (neat, cm^{-1}): 3025, 2970, 2928, 1598, 1366, 1077; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.22 – 7.16 (m, 4H), 3.98 (d, *J* = 11.3 Hz, 2H), 3.84 (d, *J* = 11.3 Hz, 2H), 3.67 (q, *J* = 6.5 Hz, 1H), 1.53 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (125 MHz,

$CDCl_3$) δ 145.3, 140.1, 128.6, 127.4, 127.2, 126.7, 122.4, 65.5, 58.1, 23.4; **HRMS** (ESI) calcd for **$C_{16}H_{18}N$** $[M+H]^+$, 224.1434; found, 224.1434

methyl 2-(4-(isoindolin-2-yl)phenyl)propanoate (1ac):

Yield 62% (306 mg); R_f = 0.33 (SiO_2; hexanes: ethyl acetate, 10:1); White solid; **mp** 124-126 °C; **IR** (neat, cm^{-1}): 3041, 2978, 2944, 1726, 1520, 1373, 1159, 1067; **^{1}H NMR** (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 2H), 7.33 – 7.29 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 4.65 (s, 2H), 3.68 (q, 1H), 3.67 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.8, 146.3, 138.0, 128.5, 128.1, 127.3, 122.7, 111.7, 53.9, 52.0, 44.6, 18.8; **HRMS** (ESI) calcd for **$C_{18}H_{20}NO_2$** $[M+H]^+$, 282.1489; found, 282.1485

General Procedure for the Synthesis of Substrates 1f-g, 1o-q, 1u, 1z, and 1ab:[70]

An *N*-phenylpthalimide derivative (2.0 mmol) was dissolved in 10 mL distilled THF and stirred in an ice/water bath at 0 °C. Over five minutes, 6 mL of 1M BH_3 in THF (8 mmol) was added dropwise, to the reaction mixture. The resulting solution was heated under reflux for 6 hours. After cooling the reaction mixture to room temperature, methanol was carefully added dropwise until the residual solid was dissolved. The resulting solution was diluted with 10 mL ethyl acetate. The combined organic solution was washed with brine solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography.

2(4-methyl)phenylisoindoline (1f):[70]

Yield 71% (297 mg); R_f = 0.43 (SiO_2; hexanes: ethyl acetate, 10:1); White solid; **mp** 120-121 °C; **IR** (neat, cm^{-1}): 3045, 2914, 2854, 1523, 1371, 1255, 1165; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 4H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 4.65 (s, 4H), 2.30 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.1, 142.1, 138.1, 130.0, 127.2, 122.6, 111.9, 54.3, 20.4.

2-(4-thiomethyl)phenylisoindoline (1g):

Yield 68% (328 mg); R_f = 0.32 (SiO_2; hexanes: ethyl acetate, 10:1); Pale yellow solid; **mp** 210-211 °C; **IR** (neat, cm^{-1}): 3043, 2846, 2825, 1608, 1502, 1467, 1377, 1249, 1166; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 6H), 6.67 (d, *J* = 8.2 Hz, 2H), 4.66 (s, 4H), 2.44 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 146.0, 137.6, 132.0, 127.4, 123.7, 122.7, 112.6, 54.3, 19.5; **HRMS** (ESI) calcd for $C_{15}H_{16}NS$ $[M+H]^+$, 241.0812; found, 241.0803

5-methyl-2-phenylisoindoline (1o):[70]

Yield 87% (364 mg); R_f = 0.4 (SiO_2; hexanes: ethyl acetate, 10:1); White solid; **mp** 136-138 °C; **IR** (neat, cm^{-1}): 3060, 2951, 2853, 1596, 1496, 1374, 1160; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.68

(d, J = 8.0 Hz, 2H), 4.62 (s, 4H), 2.40 (s, 3H); **^{13}C NMR**(125 MHz, $CDCl_3$) δ 147.3, 138.2, 137.0, 135.0, 129.5, 128.1, 123.3, 122.4, 116.1, 111.6, 53.7, 53.6, 21.5.

2-phenyl-4-nitroisoindoline (1p):[70]

Yield 61% (293 mg); R_f = 0.5 (SiO_2; hexanes: ethyl acetate, 5:1); Orange solid; **mp** 128-130 °C; **IR** (neat, cm^{-1}): 3053, 3036, 2953, 2922, 1692, 1593, 1524, 1489, 1381, 1344, 1297, 1276; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.6 Hz, 1H), 7.74 – 7.61 (m, 1H), 7.53 (m, 1H), 7.34 (m, 2H), 6.89 – 6.67 (m, 3H), 5.10 (s, 2H), 4.74 (s, 2H); **^{13}CNMR** (75 MHz, $CDCl_3$) δ 146.4, 141.9, 135.1, 130.0, 129.6, 128.8, 123.0, 122.7, 117.0, 111.8, 55.1, 53.4; **HRMS** (ESI) calcd for **$C_{14}H_{13}N_2O_2$** $[M+H]^+$, 241.0972; found, 241.0966

2-methyl-2,3-dihydro-1H-benzo[de]isoquinoline (1u):[78]

Yield 60% (220 mg); R_f = 0.26 (SiO_2; hexanes: ethyl acetate, 2:1); Pale brown solid; **mp** 60-61 °C; **IR** (neat, cm^{-1}): 3065, 2988, 2886, 1591, 1465, 1400, 1371, 1280; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.40 (dd, J = 8.1, 7.1 Hz, 2H), 7.21 (d, J = 6.8 Hz, 2H), 3.93 (s, 4H), 2.60 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 133.3, 133.2, 127.8, 126.3, 125.7, 122.1, 58.7, 45.5.

6-phenethyl-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (1z):

Yield 33% (74 mg at 1.0 mmol scale of corresponding phthalimide); R_f = 0.15 (SiO_2; dichloromethane: methanol, 19:1); Yellow viscous oil; **IR** (neat, cm^{-1}): 3059, 3025, 2927, 1663, 1602, 1495; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.39 (d, J = 4.6 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.33 – 7.25 (m, 4H), 7.22 (t, J = 7.1 Hz, 1H), 7.10 (dd, J = 7.5, 5.1 Hz, 1H), 4.06 (s, 2H), 4.04 (s, 2H), 3.06 – 3.00 (m, 2H), 2.97 – 2.86 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.4, 148.1, 140.0, 133.5, 130.2, 128.7, 128.5, 126.3, 121.8, 59.6, 57.9, 57.6, 35.4; **HRMS** (ESI) calcd for $C_{15}H_{17}N_2$ $[M+H]^+$, 225.1386; found, 225.1382

2-methylisoindoline(1ab):[73]

Caution, peroxide formation was not evaluated at various scales. Though no mishaps occurred during the presented work, all substrates may undergo oxidation differently and should be scaled with caution. Methods for evaluating total peroxide load can be found in the SI. Yield 80% (1.06 g at 10.0 mmol scale of corresponding phthalimide); R_f = 0.24 (SiO_2; hexanes: ethyl acetate, 1:1); Brown liquid; **IR** (neat, cm^{-1}): 3029, 2945, 2919, 1466, 1354, 1177; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (s, 4H), 3.89 (s, 4H), 2.58 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.5, 126.4, 121.9, 60.7, 42.1

General Procedure for the Synthesis of Substrate 1q:

To a cold solution of 2-phenyl-4-nitropthalimide (536 mg, 2.0 mmol) in dry THF (15 mL), was added lithium aluminum hydride (304 mg, 8.0 mmol) in small portion. The resulting mixture was warmed to room temperature and then refluxed under nitrogen. After the completion of reaction in 4 hours, the reaction mixture was cooled to 0 °C, and carefully quenched with water (0.5 mL) and saturated Na_2CO_3 solution (1 mL). The white precipitate formed was filtered out and the filtrate was concentrated under

reduced pressure. The crude product was purified by column chromatography (SiO_2; hexanes: ethyl acetate; 5:1; R_f=0.34) which afforded 58% (244 mg, 1.16 mmol) of 2-phenylsoindolin-4-amine (**1q**) as brown solid.

Similarly, deuterated substrate **1i-D$_4$** was synthesized using $LiAlD_4$ (1.0 mmol) reducing agent and corresponding phthalimide (0.25 mmol) following similar procedure described above.

2-phenylisoindolin-4-amine (1q):

Yield 58% (244 mg); R_f = 0.34 (SiO_2; hexanes: ethyl acetate, 5:1); Brown solid; **mp** 120-122 °C; **IR** (neat, cm^{-1}): 3422, 3374, 3203, 3047, 3020, 2805, 1592, 1458, 1377, 1342, 1155; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.85 (dd, *J* = 15.8, 7.5 Hz, 2H), 6.74 (dd, *J* = 8.7, 0.9 Hz, 2H), 6.65 (dd, *J* = 7.9, 0.7 Hz, 1H), 4.66 (s, 2H), 4.51 (s, 2H), 3.64 (br, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 147.1, 141.2, 139.1, 129.3, 128.5, 123.0, 116.0, 113.4, 112.7, 111.5, 54.1, 51.4; **HRMS** (ESI) calcd for $C_{14}H_{15}N_2$ $[M+H]^+$, 211.1120; found, 211.1124

1,1,3,3-tetradeuterated-2-phenethylisoindoline (1i-D4):

Yield 87% (49 mg); White solid; **mp** 71-72 °C; **IR** (neat, cm^{-1}): 3057, 2948, 2901, 2387, 2171, 1600, 1454, 1303, 1260; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 4H), 3.12 – 3.03 (m, 2H), 3.02 – 2.95 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.1, 139.7, 128.8, 128.5, 126.9, 126.3, 122.4, 57.9, 35.6; **HRMS** (ESI) calcd for $C_{16}H_{14}D_4N$ $[M+H]^+$, 228.1690; found, 228.1677

General Procedure for the Synthesis of Substrate 1v:[79]

CuI (95 mg, 0.5 mmol), K_3PO_4 (2.1 g, 10 mmol), and a stir bar were charged into a flame-dried (100 mL) round-bottom flask. The flask was evacuated and back filled with argon. This process was repeated three times. At room temperature, 5 mL of isopropanol, ethylene glycol (560 µL, 10 mmol), tetrahydroisoquinoline (1.0 g, 950 µL, 7.5 mmol) and iodobenzene (1.0 g, 557 µL, 5 mmol) were then added successively via syringe. The reaction mixture was heated to 90 °C and stirred for a day. After completion of the reaction, 10 mL diethyl ether followed by 10 mL water was added to the reaction flask. The aqueous layer was extracted by Et_2O (2x10 mL). The combined organic phase was washed with brine solution, dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2; hexanes: ethyl acetate, 15:1; R_f= 0.33) to afford 82% (257.3 mg, 4.1 mmol) of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1v)** as colorless liquid.

***N*-phenyl-1,2,3,4-tetrahydroisoquinoline (1v):[79]**

Yield 82% (257.3 mg); R_f = 0.33 (SiO_2; hexanes: ethyl acetate, 15:1); Colorless liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 11.7, 4.3 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.85 (t, *J*

= 7.3 Hz, 1H), 4.43 (s, 0H), 3.58 (t, *J* = 5.7 Hz, 1H), 3.01 (t, *J* = 5.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 150.6, 135.0, 134.6, 129.3, 128.6, 126.6, 126.4, 126.1, 118.7, 115.2, 50.8, 46.6, 29.2.

General Procedure for the Synthesis of Substrate 1w:[80]

To a mixture of 2-(3,4-dimethoxyphenyl)-*N*-methylethanamine (975 mg, 5.0 mmol) and 37% aqueous solution of formaldehyde (1.4 mL, 29.0 mmol), was added 5 mL formic acid at room temperature. The resulting mixture was heated at 100 °C for 4 hours. The solution was poured into ice-water and adjusted to pH =11 by the addition of 2M sodium hydroxide solution. The solid formed was extracted with dichloromethane (15 mL x 2). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified with column chromatography (SiO_2; ethyl acetate: methanol, 4:1; $R_{f=}$ 0.24) to afford 88% (910 mg, 4.4 mmol) of (**1w**) as pale-yellow solid.

6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1w):[80]

Yield 88% (910 mg); $R_{f=}$ 0.24 (SiO_2; ethyl acetate: methanol, 4:1); Pale yellow solid; **mp** 70-71 °C; **IR** (neat, cm^{-1}): 3045, 2968, 1485, 1375, 1220, 1004; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.48 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.49 (s, 2H), 2.82 (t, *J* = 5.8 Hz, 2H), 2.64 (t, *J* = 5.9 Hz, 2H), 2.43 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 147.5, 147.1, 126.4, 125.6, 111.3, 109.2, 57.5, 55.9, 55.9, 52.9, 46.0, 28.7

General procedure for synthesis of isoindolinone derivatives:

To a flame dried and cooled to room temperature 10 mL round bottomed flask was added i**soindoline** (0.25 mmol) followed by 1.5 mL 1,4-dioxane. The reaction mixture was heated for 8 hours at 50 °C in open air. After the completion of the reaction, as determined by thin layered chromatography, the mixture was directly concentrated under reduced pressure. The crude product was purified by column chromatography.

Note: In one particular example of isoindolinone 2i, work up procedure was slightly modified. After the reaction was complete, the reaction solution was diluted by adding 2 mL deionized water. The resulting solution was extracted using 2 mL dichloromethane twice. The combined organic layer was dried in anhydrous Na_2SO_4. The dried organic layer was concentrated and purified by column chromatography in silica gel using hexanes and ethyl acetate as mobile phase to afford 2i in 63% isolated yield.

Reactions under O_2 balloon were set up like the procedure described above except that the flask was purged with O_2 for three cycles and sealed properly with the septum.

For a gram scale reaction with substrate **1i**, **1i** (1.78 g, 8.0 mmol) was added into flame-dried 100 mL round bottom flask. 50 mL of 1,4-dioxane was added in the flask. The resulting solution was then heated

in oil bath at 50 °C in open air for 6 hours. The solution was concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2; hexanes: ethyl acetate; 5:1; R_f = 0.1) to afford 59% (1.12 g, 4.72 mmol) of 2-phenethylisoindolin-1-one (**2i)** as white solid.

2-phenylisoindolin-1-one (2a):[12]

Yield 55% (28.7 mg); R_f = 0.25 (SiO_2; hexanes: ethyl acetate, 10:1); White solid; **mp** 161-162 °C; **IR** (neat, cm^{-1}): 3042, 2924, 1683, 1594, 1491,1329, 1265, 1222,1151; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 1H), 7.87 (dd, *J* = 8.8, 1.1 Hz, 2H), 7.62 – 7.58 (m, 1H), 7.53 – 7.49 (m, 2H), 7.45 – 7.41 (m, 2H), 7.18 (tt, *J* = 7.6, 1.1 Hz, 1H), 4.87 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.6, 140.2, 139.5, 133.3, 132.1, 129.2, 128.4, 124.5, 124.2, 122.7, 119.5, 50.8.

2-(o-tolyl)isoindolin-1-one (2d):[12]

Yield 64% (35.7 mg); R_f = 0.28 (SiO_2; hexanes: ethyl acetate; 10:1); White solid; **mp** 129-130 °C; **IR** (neat, cm^{-1}): 3053, 2955, 2924, 1685,1602, 1451, 1388, 1302, 1213, 1123; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.60 (ddd, *J* = 6.9, 6.5, 1.3 Hz, 1H), 7.55-7.48 (m, 2H), 7.33-7.23 (m, 4H), 4.72 (s, 2H), 2.25 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7, 141.6, 137.0, 136.4, 132.5, 131.7, 131.3, 128.3, 128.3, 127.5, 126.9, 124.3, 122.9, 53.1, 18.3.

2-(3-bromophenyl)isoindolin-1-one (2e):[12]

Yield 49% (35.2 mg); R_f = 0.41 (SiO_2; hexanes: ethyl acetate; 10:1); Pale brown solid; **mp** 178-180 °C; **IR** (neat, cm^{-1}): 3113, 3044, 2950, 1689, 1561,1432, 1374, 1299, 1197, 1091; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, 1H), 7.92 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.89 (dt, *J* = 6.8, 2.2 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.54 – 7.50 (m, 2H), 7.31 – 7.28 (m, 2H), 4.84 (s, 2H); **^{13}C NMR**(125 MHz, $CDCl_3$) δ 167.6, 140.9, 139.9, 132.9, 132.5, 130.5, 128.6, 127.3, 124.4, 123.0, 122.7, 122.0, 117.7, 50.6.

2-(p-tolyl)isoindolin-1-one (2f):[81]

Yield 61% (34 mg); R_f = 0.24 (SiO_2; hexanes: ethyl acetate; 10:1); White solid; **mp** 125-126 °C; **IR IR** (neat, cm^{-1}): 3140, 2918, 1660, 1512, 1390, 1305; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.3 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.53 – 7.48 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 4.84 (s, 2H), 2.36 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.4, 140.2, 137.0, 134.3, 133.4, 132.0, 129.7, 128.4, 124.2, 122.6, 119.7, 50.9, 20.9.

2-(4-(methylthio)phenyl)isoindolin-1-one (2g):[12]

Yield 63% (80.3 mg); R_f = 0.19 (SiO_2; hexanes: ethyl acetate; 5:1); Pale yellow solid; **mp** 168-170 °C; **IR** (neat, cm^{-1}): 2922, 1685, 1492, 1440, 1386, 1336, 1222, 1155, 1060; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.81 (d, *J* = 8.9 Hz, 2H), 7.62 – 7.58 (m, 1H), 7.51 (m, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 4.84 (s, 1H), 2.51 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.5, 140.1, 137.2, 134.0, 133.3, 132.2, 128.5, 128.1, 124.2, 122.7, 120.1, 50.8, 16.7.

2-benzylisoindolin-1-one (2h):[10]

Yield 61% (34 mg); R_f = 0.15 (SiO_2; hexanes: ethyl acetate; 10:1); White solid; **mp** 86-87 °C; **IR** (neat, cm^{-1}): 3028, 2977, 1670, 1567,1494, 1316, 1255, 1158; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.5 Hz, 1H), 7.52 (td, *J* = 7.5, 1.0 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.35 – 7.27 (m, 5H), 4.81 (s, 2H), 4.27 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.6, 141.3, 137.1, 132.7, 131.4, 128.9, 128.3, 128.1, 127.8, 124.0, 122.8, 49.5, 46.5.

2-phenethylisoindolin-1-one (2i):[82]

Yield 68% (40.3 mg); R_f = 0.1 (SiO_2; hexanes: ethyl acetate; 5:1); White solid; **mp** 93-95 °C; **IR** (neat, cm^{-1}): 3059, 2913, 1671, 1448, 1409, 1303, 1211, 1127; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.2 Hz, 1H), 7.51 (td, *J* = 7.3, 1.4 Hz, 1H), 7.45 (t, *J* = 7.1 Hz, 1H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.33 – 7.21 (m, 5H), 4.21 (s, 2H), 3.88 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.6, 141.2, 138.9, 133.0, 131.3, 128.8, 128.7, 128.1, 126.6, 123.7, 122.7, 50.7, 44.2, 35.0.

2-octylisoindolin-1-one (2j):[33]

Yield 69% (42.3 mg); R_f = 0.2 (SiO_2; hexanes: ethyl acetate; 5:1); Pale yellow liquid; **IR** (neat, cm^{-1}): 3038, 2923, 1680, 1468, 1226, 1105; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.51 (td, *J* = 7.5, 1.2 Hz, 1H), 7.46 – 7.42 (m, 2H), 3.60 (t, *J* = 7.4 Hz, 2H), 1.71 – 1.60 (m, 2H), 1.34 – 1.23 (m, 10H), 0.86 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.5, 141.2, 133.2, 131.1, 128.0, 123.7, 122.7, 50.0, 42.5, 31.9, 29.4, 29.3, 28.5, 27.0, 22.7, 14.2.

2-butylisoindolin-1-one (2k):[75]

Yield 63% (30 mg); R_f = 0.2 (SiO_2; hexanes: ethyl acetate; 5:1); Pale yellow liquid; **IR** (neat, cm^{-1}): 3047, 2957, 1675, 1469, 1377, 1210, 1172, 1094; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.5, 2.2 Hz, 1H), 7.52 (td, *J* = 7.5, 1.2 Hz, 1H), 7.47 – 7.42 (m, 2H), 4.37 (s, 2H), 3.62 (t, *J* = 7.3 Hz, 2H), 1.70 – 1.59 (m, 2H), 1.44 – 1.32 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.5, 141.2, 133.2, 131.2, 128.1, 123.7, 122.7, 50.0, 42.2, 30.6, 20.2, 13.9.

2-cyclopropylisoindolin-1-one (2l):[75]

Yield 70% (30.2 mg); R_f = 0.28 (SiO_2; hexanes: ethyl acetate; 5:1); Pale yellow solid; **mp** 51-52 °C; **IR** (neat, cm^{-1}): 3088, 3014, 2914, 2868, 1678,1409, 1371, 1213, 1155, 1056; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.50 (td, *J* = 7.4, 1.2 Hz, 1H), 7.45 – 7.38 (m, 2H), 4.31 (s, 2H), 2.96 – 2.90 (m, 1H), 0.94 – 0.89 (m, 2H), 0.88 – 0.83 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.8, 141.1, 133.3, 131.4, 128.1, 123.6, 122.7, 50.5, 25.2, 5.7.

2-(adamantan-1-yl)isoindolin-1-one (2m):

Yield 85% (56 mg); R_f = 0.18 (SiO_2; hexanes: ethyl acetate; 5:1); White solid; **mp** 221-222 °C; **IR** (neat, cm^{-1}): 2940, 2892, 1688, 1483, 1402, 1330; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz,

1H), 7.49 (td, *J* = 7.4, 1.2 Hz, 1H), 7.41 (m, 2H), 4.46 (s, 2H), 2.31 (d, *J* = 2.7 Hz, 6H), 2.18 – 2.14 (m, 3H), 1.80 – 1.69 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.9, 141.0, 134.8, 130.9, 127.9, 123.3, 122.4, 55.6, 47.6, 40.2, 36.5, 29.7; **HRMS** (ESI) calcd for $C_{18}H_{21}NONa$ $[M+Na]^+$, 290.1515; found, 290.1509

5(6)-methyl-2-phenylisoindolin-1-one (2o):[12]

Yield 66% (36.8 mg) (*45:55*); R_f = 0.38 (SiO_2; hexanes: ethyl acetate; 5:1); White solid; **IR** (neat, cm^{-1}): 3060, 3041, 2923, 1679, 1620, 1493, 1453, 1375, 1294, 1165, 1122;

I: 6-methyl-2-phenylisoindolin-1-one: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 2H), 7.73 (s, 1H), 7.45 – 7.41 (m, 4H), 7.20 – 7.15 (m, 1H), 4.82 (s, 2H), 2.49 (s, 3H); **^{13}C NMR** (125 MHz,$CDCl_3$) δ 167.8, 139.8, 138.5, 137.4, 133.5, 133.2, 129.5, 124.4, 124.4, 122.4, 119.5, 50.7, 22.1.

II: 5-methyl-2-phenylisoindolin-1-one: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 2H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.40 (s, 2H), 7.31 (d, *J* = 6.4 Hz, 2H), 7.20 – 7.15 (m, 1H), 4.82 (s, 2H), 2.47 (s, 3H); **^{13}C NMR** (125 MHz,$CDCl_3$) δ 167.7, 142.9, 140.6, 139.7, 130.8, 129.2, 124.5, 124.1, 123.2, 120.4, 119.5, 50.7, 21.5.

4-nitro-2-phenylisoindolin-1-one (2p):

Yield 55% (34.9 mg); R_f = 0.22 (SiO_2; hexanes: ethyl acetate; 5:1); Orange solid; **mp** 142-143 °C; **IR** (neat, cm^{-1}): 3051, 3036, 2919, 2851, 1692, 1523, 1344, 1145; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 2H), 7.76 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 2H), 5.35 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.9, 138.6, 136.7, 135.9, 130.5, 130.2, 129.5, 127.4, 126.7, 125.5, 119.9, 51.9; **HRMS** (ESI) calcd for **$C_{14}H_{11}N_2O_3$** $[M+H]^+$, 255.0764; found, 255.0763

(S)-2-(1-phenylethyl)isoindolin-1-one (2r):[63]

Yield 58% (34.4 mg); R_f = 0.18 (SiO_2; hexanes: ethyl acetate; 5:1); Pale brown solid; **mp** 144-145 °C; **IR** (neat, cm^{-1}): 3087, 2986, 1668, 1497, 1347,1161; **1H NMR** (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.4 Hz, 1H), 7.50 (td, *J* = 7.4, 1.3 Hz, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.39 – 7.32 (m, 5H), 7.28 (dt, *J* = 4.7, 2.1 Hz, 1H), 5.82 (q, *J* = 7.3 Hz, 1H), 4.33 (d, *J* = 17.0 Hz, 1H), 4.00 (d, *J* = 17.0 Hz, 1H), 1.70 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.2, 141.4, 140.8, 133.0, 131.3, 128.8, 128.1, 127.7, 127.2, 123.9, 122.9, 49.2, 45.7, 17.4; **$[\alpha]_D$ -167 (c 0.1, CH_2Cl_2)** and **-164.7 (c 0.1, $CHCl_3$)** *{Ref: -161.3 (c 1.33, $CHCl_3$)}*[46]

2-methyl-1H-benzo[de]isoquinoline-1,3(2H)-dione (2u):[83]

Yield 37% (39 mg); R_f = 0.3 (SiO_2; hexanes: ethyl acetate; 5:1); White solid; **mp** 206-207 °C; **IR** (neat, cm^{-1}): 3070, 2954,1697,1588,1439, 1397,1279, 1232, 1201, 1182, 1033; **^{1}H NMR** (500 MHz, $CDCl_3$) δ

8.61 (dd, *J* = 7.3, 1.1 Hz, 2H), 8.21 (dd, *J* = 8.4, 1.0 Hz, 2H), 7.76 (dd, *J* = 8.2, 7.2 Hz, 2H), 3.57 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.6, 134.1, 131.7, 131.3, 128.1, 127.0, 122.7, 27.1.

2-phenyl-3,4-dihydroisoquinolin-1(2H)-one (2v):[84]

Yield 46% (25.7 mg); R_f =0.13 (SiO_2; hexanes: ethyl acetate; 5:1); Pale brown solid; **mp** 100-101 °C; **IR** (neat, cm^{-1}): 3059, 3036, 2926, 1647, 1594, 1466, 1456, 1407, 1316, 1307, 1276, 1254, 1220, 1169, 1064; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 1H), 7.47 (td, *J* = 7.5, 1.3 Hz, 1H), 7.44 – 7.36 (m, 5H), 7.28 – 7.23 (m, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.14 (t, *J* = 6.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.3, 143.2, 138.4, 132.1, 129.8, 129.0, 128.8, 127.2, 127.0, 126.3, 125.4, 49.5, 28.7.

6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolin-1(2H)-one (2w):[85]

Yield 31% (17 mg); R_f = 0.15 (SiO_2; hexanes: ethyl acetate; 2:1); White solid; **mp** 123-125 °C; **IR** (neat, cm^{-1}): 2924, 2886, 1640, 1508, 1435, 1275, 1016; **^{1}H NMR** (301 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.62 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.13 (s, 3H), 2.93 (t, *J* = 6.7 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.1, 151.8, 148.0, 131.7, 121.9, 110.6, 109.3, 56.2, 56.1, 48.5, 35.4, 27.6.

isochroman-1-one (2x):[86]

Yield 32% (11.8 mg); R_f = 0.35 (SiO_2; hexanes: ethyl acetate; 5:1); Pale yellow liquid; **IR** (neat, cm^{-1}): 3071, 2990,1714, 1605, 1470, 1391, 1291, 1193, 1118, 1089; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.53 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 4.55 – 4.51 (m, 2H), 3.06 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.2, 139.6, 133.7, 130.5, 127.8, 127.3, 125.4, 67.4, 27.9.

***N*-isopropylbenzamide (2aa):[87]**

Yield 28% (11.4 mg); R_f = 0.1 (SiO_2; hexanes: ethyl acetate; 5:1); White solid; **mp** 100-101 °C; **IR** (neat, cm^{-1}): 3292, 3029, 2930, 1627, 1577, 1346, 1168; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 2H), 4.34 – 4.26 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.8, 135.1, 131.4, 128.6, 126.9, 42.0, 23.0.

2-methylisoindolin-1-one (2ab):[10]

Yield= 68% (600 mg, 0.6 mmol scale); R_f= 0.18 (SiO_2; hexanes: ethyl acetate; 2:1); Pale brown solid; **mp** 106-108 °C; **IR** (neat, cm^{-1}): 3053, 2953, 2918,1665, 1590, 1480,1396,1275, 1053; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.52 (td, *J* = 7.4, 1.2 Hz, 1H), 7.46 – 7.41 (m, 2H), 4.37 (s, 2H), 3.20 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 168.8, 141.1, 133.0, 131.3, 128.1, 123.7, 122.7, 52.1, 29.6.

methyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoate (2ac):[12]

Yield 54% (40 mg); R_f = 0.16 (SiO_2; hexanes: ethyl acetate; 2:1); Pale brown solid; **mp** 120-122 °C; **IR** (neat, cm^{-1}): 3039, 2978, 2950, 1730, 1683, 1608, 1513, 1467, 1442, 1245, 1015; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.62 – 7.58 (m, 1H), 7.53 – 7.49 (m, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 4.85 (s, 2H), 3.74 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.52 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.1, 167.6, 140.2, 138.6, 136.7, 133.2, 132.2, 128.5, 128.3, 124.3, 122.7, 119.8, 52.2, 50.8, 44.9, 18.6.

2-phenethylisoindole (3i):

Yield 54% (30 mg); R_f = 0.9 (SiO_2; hexanes: ethyl acetate; 5:1); Pale brown liquid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 6.4, 3.1 Hz, 2H), 7.32 – 7.22 (m, 3H), 7.12 – 7.07 (m, H), 7.04 (s, 2H), 6.91 (dd, *J* = 6.6, 3.0 Hz, 2H), 4.40 (t, *J* = 7.5 Hz, 2H), 3.19 (t, *J* = 7.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 128.7, 128.7, 126.9, 124.4, 123.3, 120.7, 119.6, 110.6, 52.7, 38.7; **GC/MS**: t_R= 7.89 min, 221.0 m/z

Note: This compound is highly sensitive to heat, light, and moisture. As such, other analytical data were not presented due to inconsistent results.

2-((3s,5s,7s)-adamantan-1-yl)-2H-isoindole (3m):

Substrate **3m** was obtained in first fraction during preparation of substrate **1m**.

Yield 17% (75 mg); Pale pink solid**; mp** 170-172 °C; **IR** (neat, cm^{-1}): 3058, 2915, 2848, 1627, 1585, 1458, 1347, 1154; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 6.4, 3.0 Hz, 2H), 7.33 (s, 2H), 6.91 (dd, *J* = 6.5, 2.9 Hz, 2H), 2.25 (m, 9H), 1.82 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 123.5, 120.4, 119.7, 106.8, 44.4, 40.1, 36.3, 29.8; Anal. Calcd for **$C_{18}H_{21}N$**: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.97; H, 8.38; N, 5.5

ASSOCIATED CONTENT

Supporting Information

NMR spectra of starting compounds and final products, details of the EPR sample preparation, detailed screening of reaction conditions, GC-MS sample preparation, and deuterium KIE measurement. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* Frank W. Foss Jr. ffoss@uta.edu

ACKNOWLEDGEMENT

Partial support for this work from the National Science Foundation, CHE-1303803 (ICC) and CHE-0840509 (CRIF: MU), and from the University of Texas at Arlington is acknowledged. We thank Delphin

Gout for performing X-ray crystallography experiments in UTA's Shimadzu Center for Nanostructured Materials.

REFERENCE

(1) Parsons, P. J.; Jones, D. R.; Walsh, L. J.; Allen, L. A. T.; Onwubiko, A.; Preece, L.; Board, J.; White, A. J. P. An Approach to the Core of Lactonamycin. *Org. Lett.* **2017**, *19* (10), 2533–2535.

(2) Fouseki, M. M.; Damianakos, H.; Karikas, G. A.; Roussakis, C.; P Gupta, M.; Chinou, I. Chemical Constituents From Cordia Alliodora and C. Colloccoca (Boraginaceae) and Their Biological Activities. *Fitoterapia* **2016**, *115*, 9–14.

(3) Hu, S.; Yuan, L.; Yan, H.; Li, Z. Design, Synthesis and Biological Evaluation of Lenalidomide Derivatives as Tumor Angiogenesis Inhibitor. *Bioorg. Med. Chem. Lett.* **2017**, *27* (17), 4075–4081.

(4) Flores, B.; Molinski, T. F. Assembly of the Isoindolinone Core of Muironolide a by Asymmetric Intramolecular Diels–Alder Cycloaddition. *Org. Lett.* **2011**, *13* (15), 3932–3935.

(5) Augner, D.; Schmalz, H.-G. Biomimetic Synthesis of Isoindolinones Related to the Marilines. *Synlett* **2015**, *26* (10), 1395–1397.

(6) Choomuenwai, V.; Beattie, K. D.; Healy, P. C.; Andrews, K. T.; Fechner, N.; Davis, R. A. Entonalactams a–C: Isoindolinone Derivatives From an Australian Rainforest Fungus Belonging to the Genus Entonaema. *Phytochemistry* **2015**, *117*, 10–16.

(7) Lowinger, T. B.; Chu, J.; Spence, P. L. The Total Synthesis of (±)K252a. *Tetrahedron Lett.* **1995**, *36* (46), 8383–8386.

(8) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. Staurosporine and Ent-Staurosporine: the First Total Syntheses, Prospects for a Regioselective Approach, and Activity Profiles 1. *J. Am. Chem. Soc.* **1996**, *118* (12), 2825–2842.

(9) Karanatsios, D. 4,5,6,7-Tetrahalo-Isoindolin-1-One Derivatives. *US Patent Office*. US Patent Office November 1, 1983.

(10) Das, S.; Addis, D.; Knöpke, L. R.; Bentrup, U.; Junge, K.; Brückner, A.; Beller, M. Selective Catalytic Monoreduction of Phthalimides and Imidazolidine-2,4-Diones. *Angew. Chem.* **2011**, *123* (39), 9346–9350.

(11) Link, J. T.; Danishefsky, S. J. Regioselective Imide Reduction: an Issue in the Total Synthesis of Staurosporine. *Tetrahedron Lett.* **1994**, *35* (49), 9135–9138.

(12) Verma, A.; Patel, S.; Meenakshi; Kumar, A.; Yadav, A.; Kumar, S.; Jana, S.; Sharma, S.; Prasad, C. D.; Kumar, S. Transition Metal Free Intramolecular Selective Oxidative C(Sp3)-N Coupling: Synthesis of N-Aryl-Isoindolinones From 2-Alkylbenzamides. *Chem. Commun.* **2015**, *51* (7), 1371–1374.

(13) Nozawa-Kumada, K.; Kadokawa, J.; Kameyama, T.; Kondo, Y. Copper-Catalyzed Sp 3C–H Aminative Cyclization of 2-Alkyl- N-Arylbenzamides: an Approach for the Synthesis of N-Aryl-Isoindolinones. *Org. Lett.* **2015**, *17* (18), 4479–4481.

(14) Yamamoto, C.; Takamatsu, K.; Hirano, K.; Miura, M. Copper-Catalyzed Intramolecular Benzylic C–H Amination for the Synthesis of Isoindolinones. *J. Org. Chem.* **2016**, *81* (17), 7675–7684.

(15) Wertjes, W. C.; Wolfe, L. C.; Waller, P. J.; Kalyani, D. Nickel or Phenanthroline Mediated Intramolecular Arylation of Sp3 C–H Bonds Using Aryl Halides. *Org. Lett.* **2013**, *15* (23), 5986–5989.

(16) Bhakuni, B. S.; Yadav, A.; Kumar, S.; Patel, S.; Sharma, S.; Kumar, S. KOtBu-Mediated Synthesis of Dimethylisoindolin-1-Ones and Dimethyl-5-Phenylisoindolin-1-Ones: Selective C–C Coupling of an Unreactive Tertiary Sp3 C–H Bond. *J. Org. Chem.* **2014**, *79* (7), 2944–2954.

(17) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. Investigation of the Mechanism of C(Sp3)−H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation Adjacent to Amides and Sulfonamides. *J. Am. Chem. Soc.* **2010**, *132* (31), 10692–10705.

(18) Xia, C.; White, A. J. P.; Hii, K. K. M. Synthesis of Isoindolinones by Pd-Catalyzed Coupling Between N-Methoxybenzamide and Styrene Derivatives. *J. Org. Chem.* **2016**.

(19) Miura, H.; Terajima, S.; Tsutsui, K.; Shishido, T. Ruthenium-Catalyzed Addition of Aromatic Amides to Internal Alkynes and Subsequent Intramolecular Cyclization for the Atom-Economical Synthesis of Isoindolinones. *J. Org. Chem.* **2017**, *82* (2), 1231–1239.

(20) Ji, W.-W.; Lin, E.; Li, Q.; Wang, H. Heteroannulation Enabled by a Bimetallic Rh(III)/Ag(I) Relay Catalysis: Application in the Total Synthesis of Aristolactam BII. *Chem. Commun.* **2017**, *53* (41), 5665–5668.

(21) Do Minh, T.; Johnson, A. L.; Jones, J. E.; Senise, P. P. Reactions of Phthalaldehyde with Ammonia and Amines. *J. Org. Chem.* **1977**, *42* (26), 4217–4221.

(22) Comins, D. L.; Schilling, S.; letters, Y. Z. O.; 2005. Asymmetric Synthesis of 3-Substituted Isoindolinones: Application to the Total Synthesis of (+)-Lennoxamine. *Org. Lett.* **2005**, *7*, 95–98.

(23) Wehlan, H.; Jezek, E.; Lebrasseur, N.; Pavé, G.; Roulland, E.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. Studies on the Total Synthesis of Lactonamycin: Synthesis of the CDEF Ring System. *J. Org. Chem.* **2006**, *71* (21), 8151–8158.

(24) Ghosh, U.; Bhattacharyya, R.; Keche, A. Mild and Efficient Syntheses of Diverse Isoindolinones From Ortho-Phthaldehydic Acid Methylthiomethyl Ester. *Tetrahedron* **2010**, *66* (12), 2148–2155.

(25) Dhanasekaran, S.; Bisai, V.; Unhale, R. A.; Suneja, A.; Singh, V. K. A General Catalytic Route to Isoindolinones and Tetrahydroisoquinolines: Application in the Synthesis of (±)-Crispine A. *Org. Lett.* **2014**, *16* (23), 6068–6071.

(26) Di Mola, A.; Tiffner, M.; Scorzelli, F.; Palombi, L.; Filosa, R.; De Caprariis, P.; Waser, M.; Massa, A. Bifunctional Phase-Transfer Catalysis in the Asymmetric Synthesis of Biologically Active Isoindolinones. *Beilstein J. Org. Chem.* **2015**, *11* (1), 2591–2599.

(27) Mun, B.; Kim, S.; Yoon, H.; Kim, K. H.; Lee, Y. Total Synthesis of Isohericerin, Isohericenone, and Erinacerin a: Development of a Copper-Catalyzed Methylboronation of Terminal Alkynes. *J. Org. Chem.* **2017**, *82* (12), 6349–6357.

(28) Tian, Y.; Wei, J.; Wang, M.; Li, G.; Xu, F. Hantzsch Ester Triggered Metal-Free Cascade Approach to Isoindolinones. *Tetrahedron Lett.* **2018**, *59* (19), 1866–1870.

(29) Tian, Y.; Liu, Q.; Liu, Y.; Zhao, R.; Li, G.; Xu, F. Catalyst-Free Mannich-Type Reactions in Water: Expedient Synthesis of Naphthol-Substituted Isoindolinones. *Tetrahedron Lett.* **2018**, *59* (15), 1454–1457.

(30) Mori, M.; Chiba, K.; Ban, Y. Reactions and Syntheses with Organometallic Compounds. 7. Synthesis of Benzolactams by Palladium-Catalyzed Amidation. *J. Org. Chem.* **2002**, *43* (9), 1684–1687.

(31) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. Preparation of Benzolactams by $Pd(OAc)_2$-Catalyzed Direct Aromatic Carbonylation. *J. Am. Chem. Soc.* **2004**, *126* (44), 14342–14343.

(32) Zhang, C.; Ding, Y.; Gao, Y.; Li, S.; Li, G. Palladium-Catalyzed Direct C–H Carbonylation of Free Primary Benzylamines: a Synthesis of Benzolactams. *Org. Lett.* **2018**, *20* (9), 2595–2598.

(33) Cho, C. S.; Ren, W. X. Palladium-Catalyzed Carbonylative Cyclization of 2-Bromobenzaldehyde with Primary Amines Leading to Isoindolin-1-Ones. *Tetrahedron Lett.* **2009**, *50* (18), 2097–2099.

(34) Liu, B.; Wang, Y.; Liao, B.; Zhang, C.; Zhou, X. Palladium-Catalyzed Cycloaminocarbonylation of 2-Aminomethyl- and 2-Alkylcarbamoylaryl Tosylates with CO. *Tetrahedron Lett.* **2015**, *56* (42), 5776–5780.

(35) Gómez-Prado, R. A.; Miranda, L. D. Concise Total Synthesis of Hericerin Natural Product. *Tetrahedron Lett.* **2013**, *54* (17), 2131–2132.

(36) Xu, Y.; Liu, X.-Y.; Wang, Z.-H.; Tang, L.-F. Synthesis of 3-Acyl, Methylene and Epoxy Substituted Isoindolinone Derivatives via the Ortho-Lithiation/Cyclization Procedures of Aromatic Imines with Carbon Monoxide. *Tetrahedron* **2017**, *73* (52), 7245–7253.

(37) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. A New Approach to Isoindoloisoquinolinones. a Simple Synthesis of Nuevamine. *Tetrahedron* **2004**, *60* (29), 6169–6176.

(38) Moreau, A.; Lorion, M.; Couture, A.; Deniau, E.; Grandclaudon, P. A New Total Synthesis of Porritoxin. *J. Org. Chem.* **2006**, *71* (8), 3303–3305.

(39) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. A Concise First Total Synthesis of Narceine Imide. *Org. Biomol. Chem.* **2007**, *5* (9), 1466–1471.

(40) Wang, P.-M.; Fan, P.; Yan, L. K.; Jun, L. C.; Wen, L. Z.; Ying, S. X.; Juan, F.; Yu, Y. M.; Fa, W. J. Catalyst-Free Three-Component Tandem CDC Cyclization: Convenient Access to Isoindolinones From Aromatic Acid, Amides, and DMSO by a Pummerer-Type Rearrangement. *Chem.-Eur. J.* **2016**, *22* (18), 6262–6267.

(41) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. Total Syntheses of Taliscanine, Velutinam, and Enterocarpam II. *J. Org. Chem.* **1998**, *63* (9), 3128–3132.

(42) Adachi, S.; Onozuka, M.; Yoshida, Y.; Ide, M.; Saikawa, Y.; Nakata, M. Smooth Isoindolinone Formation From Isopropyl Carbamates via Bischler–Napieralski-Type Cyclization. *Org. Lett.* **2014**, *16* (2), 358–361.

(43) Adachi, S.; Watanabe, K.; Iwata, Y.; Kameda, S.; Miyaoka, Y.; Onozuka, M.; Mitsui, R.; Saikawa, Y.; Nakata, M. Total Syntheses of Lactonamycin and Lactonamycin Z with Late-Stage a-Ring Formation and Glycosylation. *Angew. Chem. Int. Ed.* **2013**, *52* (7), 2087–2091.

(44) Ghosh, S.; Jana, C. K. Metal-Free Thermal Activation of Molecular Oxygen Enabled Direct A-CH2-Oxygenation of Free Amines. *J. Org. Chem.* **2018**, *83* (1), 260–266.

(45) Kotha, S.; Sreevani, G. [2 + 2 + 2] Cyclotrimerization with Propargyl Halides as Copartners: Formal Total Synthesis of the Antitumor Hsp90 Inhibitor AT13387. *ACS Omega* **2018**, *3* (2), 1850–1855.

(46) Cai, X.; Sha, M.; Guo, C.; Pan, R. M. Synthesis of Tertiary Amine N-Oxides-a Review. *Asian J. Chem.* **2012**, *24* (9), 3781–3784.

(47) Cymerman Craig, J.; Purushothaman, K. K. Improved Preparation of Tertiary Amine N-Oxides. *J. Org. Chem.* **1970**, *35* (5), 1721–1722.

(48) Ling, Z.; Yun, L.; Liu, L.; Wu, B.; Fu, X. Aerobic Oxidative N-Dealkylation of Tertiary Amines in Aqueous Solution Catalyzed by Rhodium Porphyrins. *Chem. Commun.* **2013**, *49* (39), 4214–4216.

(49) Galliani, G.; Rindone, B.; Scolastico, C. Selective Demethylation in the Oxidation of Arylalkylmethylamines with Metal Acetates. *Tetrahedron Lett.* **1975**, *16* (15), 1285–1288.

(50) Wu, X.; Seo, M. S.; Davis, K. M.; Lee, Y. M.; Chen, J.; Cho, K. B.; Pushkar, Y. N.; Nam, W. A Highly Reactive Mononuclear Non-Heme Manganese(IV)–Oxo Complex That Can Activate the Strong C–H Bonds of Alkanes. *J. Am. Chem. Soc.* **2011**, *133* (50), 20088–20091.

(51) Debabrata Maiti; Amy A Narducci Sarjeant, A.; Karlin, K. D. *Copper(II)−Hydroperoxo Complex Induced Oxidative N-Dealkylation Chemistry*; American Chemical Society, 2007; Vol. 129, pp 6720–6721.

(52) Botla, V.; Barreddi, C.; Daggupati, R. V.; Malapaka, C. Base-Oxidant Promoted Metal-Free N-Demethylation of Arylamines. *J. Chem. Sci.* **2016**, *128* (9), 1469–1473.

(53) Hui, B. W.-Q.; Chiba, S. Orthogonal Synthesis of Isoindole and Isoquinoline Derivatives From Organic Azides. *Org. Lett.* **2009**, *11* (3), 729–732.

(54) Duen-Ren Hou; Ming-Shiang Wang; Ming-Wen Chung; Yih-Dar Hsieh, A.; Tsai, H.-H. G. Formation of 4,5,6,7-Tetrahydroisoindoles by Palladium-Catalyzed Hydride Reduction. *J. Org. Chem.* **2007**, *72* (24), 9231–9239.

(55) Anderson, P. S.; Christy, M. E.; Colton, C. D.; Halczenko, W.; Ponticello, G. S.; Shepard, K. L. Synthesis of 9,10-Dihydroanthracen-9,10-Imines. *J. Org. Chem.* **1979**, *44* (9), 1519–1533.

(56) Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. Synthesis of Isoindoles and Related Iso-Condensed Heteroaromatic Pyrroles. *Chem. Soc. Rev.* **2012**, *41* (17), 5626–5640.

(57) Ding, G.; Wu, X.; Jiang, L.; Zhang, Z.; Xie, X. Reduction of Benzolactams to Isoindoles via an Alkoxide-Catalyzed Hydrosilylation. *Org. Lett.* **2017**, *19* (22), 6048–6051.

(58) Fitzpatrick, P. F. Oxidation of Amines by Flavoproteins. *Arch. Biochem. Biophys.* **2010**, *493* (1), 13–25.

(59) Kemal, C.; Chan, T. W.; Bruice, T. C. Chemiluminescent Reactions and Electrophilic Oxygen Donating Ability of 4a-Hydroperoxyflavins: General Synthetic Method for the Preparation of N5-Alkyl-1,5-Dihydroflavins. *Proc. Nat. Acad. Sci.* **1977**, *74* (2), 405–409.

(60) Mimoun, H. The Role of Peroxymetallation in Selective Oxidative Processes. **1980**, *7* (1), 1–29.

(61) Weinstein, A. B.; Stahl, S. S. Palladium Catalyzed Aryl C-H Amination with O2 via in Situ Formation of Peroxide-Based Oxidant(S) From Dioxane. *Catal. Sci. Technol.* **2014**, *4* (12), 4301–4307.

(62) Clark, D. E. Peroxides and Peroxide-Forming Compounds. *Chemical Health and Safety* **2001**, *8* (5), 12–22.

(63) Ordonez, M.; Tibhe, G. D.; Zamudio-Medina, A.; Viveros-Ceballos, J. L. An Easy Approach for the Synthesis of N-Substituted Isoindolin-1-Ones. *Synthesis* **2012**, *44* (4), 569–574.

(64) Chenier, J. H. B.; Tong, S. B.; Howard, J. A. Absolute Rate Constants for Hydrocarbon Autoxidation. 25. Rate Constants for Hydrogen Atom Abstraction from Alkanes by the Tert-Butylperoxy Radical. *Can. J. Chem.* **2011**, *56* (24), 3047–3053.

(65) Howard, J. A.; Chenier, J. H. B.; Holden, D. A. Absolute Rate Constants for Hydrocarbon Autoxidation. 24. Rate Constants and Arrhenius Parameters for Reaction of Tert-Butylperoxy Radicals with 3-Methylpentane. *Can. J. Chem.* **1978**, *56* (2), 170–175.

(66) Lunn, M. R.; Root, D. E.; Martino, A. M.; Flaherty, S. P.; Kelley, B. P.; Coovert, D. D.; Burghes, A. H.; Man, N. T.; Morris, G. E.; Zhou, J.; et al. Indoprofen Upregulates the Survival Motor Neuron Protein Through a Cyclooxygenase-Independent Mechanism. *Chem. Biol.* **2004**, *11* (11), 1489–1493.

(67) Sankar, M.; Nowicka, E.; Carter, E.; Murphy, D. M.; Knight, D. W.; Bethell, D.; Hutchings, G. J. The Benzaldehyde Oxidation Paradox Explained by the Interception of Peroxy Radical by Benzyl Alcohol. *Nat. Comms.* **2014**, *5*.

(68) Khatmullin, R.; Zhou, D.; Corrigan, T.; Mirzakulova, E.; Glusac, K. D. Thermolysis and Photolysis of 2-Ethyl-4-Nitro-1(2H)-Isoquinolinium Hydroperoxide. *J. Phys. Org. Chem.* **2013**, *26* (5), 440–450.

(69) Kochi, J. K.; Singleton, E. A. Autoxidation of N-Alkylisoindolines : Solvent Effects and Mechanisms. *Tetrahedron* **1968**, *24* (13), 4649–4665.

(70) Lin, C.; Zhen, L.; Cheng, Y.; Du, H.-J.; Zhao, H.; Wen, X.; Kong, L.-Y.; Xu, Q.-L.; Sun, H. Visible-Light Induced Isoindoles Formation To Trigger Intermolecular Diels–Alder Re actions in the Presence of Air. *Org. Lett.* **2015**, *17* (11), 2684–2687.

(71) Xue, D.; Long, Y.-Q. Metal-Free TEMPO-Promoted C(sp^3)–H Amination To Afford Mul tisubstituted Benzimidazoles. *J. Org. Chem.* **2014**, *79* (10), 4727–4734.

(72) Watanabe, Y.; Shim, S.C.; Uchida, H.; Mitsudo, T.; Takegami, Y. The reducive amination of phthalaldehyde by tetracarbonylhydridoferrate : Synthesis of 2-arylisoindoles. *Tetrahe dron* **1979**, *35* (11), 1433–1436.

(73) Ohmura, T.; Kijima, A.; Suginome, M. Synthesis of 1-Borylisoindoles via Palladium-Catalyzed Dehydrogenation/C−H Borylation of Isoindolines. *J. Am. Chem. Soc.* **2009**, *131* (17), 6070–6071.

(74) Subbarayappa, A.; Patoliya, P. U. An efficient method for the synthesis of 2,3-dihydro-1*H*-isoindoles *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2009**, *48B*, 545–552.

(75) Jeffrey, J. L.; Bartlett, E.S.; Sarpong, R. Intramolecular C(sp^3)–N Coupling by Oxidation of Benzylic C,N-Dianions. *Angew. Chem., Int. Ed.* **2013**, *52* (8), 2194–2197.

(76) Bénard, S.; Neuville, L.; Zhu, J. Copper-promoted *N*-cyclopropylation of anilines and amines by cyclopropylboronic acid. *Chem. Commun.* **2010**, *46* (19), 3393–3395.

(77) Bottino, F.; Grazia, M. D.; Finocchiaro, P. Fronczek, F. R.; Mamo, A.; Pappalardo, S. Reaction of tosylamide monosodium salt with bis(halomethyl) compounds: an easy entry to symmetrical N-tosyl aza macrocycles *J. Org. Chem*. **1988**, *53* (15), 3521–3529.

(78) Azzena, U.; Demartis, S.; Pilo, L.; Piras, E. Reductive Cleavage of Benzannelated Cyclic Ethers and Amines: Synthetic Applications. *Tetrahedron* **2000**, *56* (42), 8375–8382.

(79) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. Copper-Catalyzed Coupling of Alkylamines and Aryl Iodides: An Efficient System Even in an Air Atmosphere. *Org. Lett*. **2002**, *4* (4), 581–584.

(80) Crestey, F.; Jensen, A.; Borch, M.; Andreasen, J. T.; Andersen, J.; Balle, T.; Kristensen, J. L. Design, Synthesis, and Biological Evaluation of *Erythrina* Alkaloid Analogues as Neuronal Nicotinic Acetylcholine Receptor Antagonists. *J. Med. Chem.* **2013**, *56* (23), 9673− 9682.

(81) Shi, L.; Hu, L.; Wang, J.; Cao, X.; Gu, H. Highly Efficient Synthesis of *N*-Substituted Isoindolinones and Phthalazinones Using Pt Nanowires as Catalysts. *Org. Lett.* **2012**, *14* (7), 1876–1879.

(82) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. $Pd(OAc)_2$-Catalyzed Carbonylation of Amines. *J. Org. Chem*. **2006**, *71* (16), 5951–5958.

(83) Yan, X.; Fang, K.; Liua, H.; Xi, C. Copper-catalyzed oxidation of arene-fused cyclic amines to cyclic imides. *Chem. Commun*. **2013**, *49* (90), 10650–10652.

(84) Espelt, L. R.; Wiensch, E.M.; Yoon, T.P. Brønsted Acid Cocatalysts in Photocatalytic Radical Addition of α-Amino C–H Bonds across Michael Acceptors. *J. Org. Chem.* **2013**, *78* (8), 4107–4114.

(85) Huang, W.J.; Singh, O.V.; Chen, C.H.; Chiou, S.Y.; Lee, S.S. Activation of Iodosobenzene by Catalytic Tetrabutylammonium Iodide and Its Application in the Oxidation of Some Isoquinoline Alkaloids. *Helv. Chim. Acta* **2002**, *85* (4), 1069–1078.

(86) Ang, W. J.; Chng, Y. S.; Lam, Y. Fluorous bispidine: a bifunctional reagent for copper-catalyzed oxidation and knoevenagel condensation reactions in water. *RSC Adv*. **2015**, *5*, 81415–81428.

(87) Liu, Y.; Shi, S.; Achtenhagen, M.; Liu, R.; Szostak, M. Metal-Free Transamidation of Secondary Amides via Selective N–C Cleavage under Mild Conditions. *Org. Lett*. **2017**, *19* (7), 1614–1617.