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Synthesis of Functionalized Isoindolinones via Calcium Catalyzed Generation and Trapping of N-Acyliminium Ions

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ABSTRACT: Herein we report our full investigation into the calcium catalyzed generation and trapping of N-acyliminium ions from readily available 3-hydroxyisoindolinones. We have successfully employed a range of traditional nucleophiles including carbon, nitrogen and sulfur containing reactive partners. The reaction is tolerant to a wide range of functionalities and provides high value scaffolds in good to excellent yields.

INTRODUCTION

N-acyliminium ions represent a highly useful reactive intermediate that has found use in a plethora of synthetic methodologies and total synthesis alike.1-2 Over the course of several decades, these reactive intermediates have been employed to form new carbon-carbon and carbon-heteroatom bonds with great success. In particular, N-acyliminium ions have shown utility in the synthesis of fused ring systems through intramolecular trapping of the generated reactive intermediate.3-6 This strategy has been thoroughly explored over the last two decades with noted examples such as in the total syntheses of stemoamide,7 crispine A,8 and minfiensine (Fig 1).9

Traditionally, N-acyliminium ions are generated via the activation and release of a suitable leaving group under acidic conditions. There is a wide range of these suitable leaving groups including hydroxyl,10 alkyl- and arylxoy,11 acetato12-13 and carbamates14-15 however sulfur containing and sulfoxide based groups have also found use.16 As the synthetic utility of these intermediates becomes more obvious, the need to generate them using more functionally tolerant reagents remains high. Success using stoichiometric Lewis acids such as BF3·OEt2,17 Sc(OTf)3,18 TiCl4,19 and AlCl320 have all recently been reported. Furthermore, organic acids such as p-TsOH and TFA have also been shown to generate N-acyliminium ions efficiently under notably milder conditions.21 Although great successes have been described employing stoichiometric reagents, there is a clear need to develop catalytic processes by which these important intermediates can be generated. This need is twofold; firstly, catalytic generation inherently produces less waste, with the byproducts using hydroxyl or akyloxy leaving groups being water or innocuous alcohols. Secondly, from a reactivity point of view, catalytic generation will result in a more controlled reaction profile, with a much-reduced propensity for side reactions. Unsurprisingly, there has been noted successes in this endeavor (Scheme 1), with elegant examples using Bronsted acids,22-24 thiourea organocatalysts25-28 and Lewis acids.29-33

Figure 1. Synthesis of complex natural products employing N-acyliminium ions

![Figure 1. Synthesis of complex natural products employing N-acyliminium ions](image-url)
Other methods including protonation of enamides\textsuperscript{34} and anodic (Shono)oxidation\textsuperscript{35} have also been described with varying success. Our group has a growing interest in developing methodology to catalytically generate reactive intermediates,\textsuperscript{36} and in particular using calcium complexes to mediate these processes.\textsuperscript{37,38} Calcium represents a relatively underexplored metal in catalysis,\textsuperscript{39} however over the past decade there has been an increase in interest in exploring the reactivity of calcium, which has resulted in a wealth of innovative uses for this abundant element.\textsuperscript{40-60} We,\textsuperscript{37} and others,\textsuperscript{61} have recently reported the use of Ca(NTf\textsubscript{2})\textsubscript{2} as an excellent catalyst to produce N-acyliminium ions from readily available 3-hydroxyisoidolones. Due to the importance of these scaffolds in both total synthesis\textsuperscript{62-64} and medicinal chemistry,\textsuperscript{65} we wanted to explore this reaction further. In particular, we set out to probe the limits of the reaction towards traditional carbon, amine and sulfur nucleophiles. In particular, we wanted to focus our attention on the synthesis of functionalized isoidolones, due to their importance in an ongoing medicinal chemistry campaign within our group. Unsurprisingly, due to their range of interesting biological activities,\textsuperscript{66-68} the synthesis of these scaffolds has attracted much attention in the literature (Scheme 2). In particular, the use of Bronsted and Lewis acids catalysts have been shown to be well tolerated. Although these examples provide the desired products in typically good yields, the use of tertiary hydroxyisoidolones remains underexplored. This somewhat limits the use of the more complex catalytic systems, as it results in less than optimum substrate availability. Thus we wanted to explore these tertiary alcohols, and to probe the limits of the reactions.

**RESULTS AND DISCUSSION**

We began our investigation employing indoles as nucleophiles. We rationalized that due to its importance in medicinal chemistry, paired with the availability of the motif, we could provide high value scaffolds bearing pendant functional groups in a controlled and high yielding manner. Furthermore, due to the ubiquitous nature of functionalized indoles in natural products, functionally tolerant catalytic methods to afford these types of compounds are constantly required. Indeed, upon treating 3-hydroxyisoidolone with 10 mol% Ca(NTf\textsubscript{2})\textsubscript{2} /nBu\textsubscript{4}NPF\textsubscript{6} in the presence of 5-bromoindole, the desired product was formed in high yield (83%). Reducing the catalyst loading to 1 mol% had little effect on the reaction, providing the product in identical yield. Further optimization including varying the solvent, temperature and concentration had a deleterious effect on the yield of the reaction (Table 1). Finally, lowering the catalyst loading to below 1 mol% resulted in a noticeably more sluggish reaction, and we decided that in the interest between balancing catalyst loading and reaction time, 1 mol% was optimum. Importantly, we also performed a series of control experiments, most notable of which was using 2,6-diterbutylpyridine (entry 9), a known inhibitor of Bronsted acid catalysis. The reaction proceeded unhindered, and proves that the reaction is indeed calcium catalyzed.

![Scheme 2. Recent Successes in N-acyliminium chemistry](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Calcium source</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>MeCN</td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>THF</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>Toluene</td>
<td>n.r.</td>
</tr>
<tr>
<td>4</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>79%</td>
</tr>
<tr>
<td>5</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>1,2-DCE</td>
<td>82%</td>
</tr>
<tr>
<td>6</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>1,2-DCE</td>
<td>39%</td>
</tr>
<tr>
<td>7</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>DCE:DME</td>
<td>n.r.</td>
</tr>
<tr>
<td>8</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>HFIP</td>
<td>n.r.</td>
</tr>
<tr>
<td>9</td>
<td>Ca(NTf\textsubscript{2})\textsubscript{2}</td>
<td>nBu\textsubscript{4}NPF\textsubscript{6}</td>
<td>1,2-DCE</td>
<td>82%</td>
</tr>
</tbody>
</table>

*Isolated Yield b 2,6-diterbutylpyridine added*

**Table 1. Optimization study**

With these conditions in hand we probed the substrate scope of the reaction (Scheme 3). We observed excellent conversion to the products in all cases, providing a wide variety of complex scaffolds quickly. As shown, the reaction is tolerant to 5-bromo and 5-pinacolboronate indoles, affording a range of highly useful building blocks, including electron electron-withdrawing (3b) and donating groups (3c, 3h) as well as further heterocyclic substrates (3d, 3e, 3i).

![Scheme 3. Indole Substituted Isoindolines](image)
As many catalytic processes are tolerant to carbon based functional groups, but show limited reactivity when heterocyclic reaction partners are used, we wanted to explore the limits of the calcium system to these coupling partners. We decided to therefore move onto sulfur containing fragments, and in particular, aromatic and aliphatic thiols. N(acyl)S-acetals are found in numerous pharmacologically relevant natural products and APIs alike. The most well-known of these being β-lactam antibiotics and HIV-1 Reverse Transcriptase inhibitors. Several methods have been developed for their synthesis, including a range of Brønsted acid catalyzed transformations, however they typically require long reaction times and showed a limited scope towards certain functional groups. We reasoned that the use of calcium to mediate these reactions would have several advantages including much shorter reaction times, a wider functional group tolerance and overall easier reaction set up i.e. no requirement for anhydrous or air free condition. Traditionally, it would be expected that that the nucleophilic nature of these species would poison the catalyst, or at the very least, drastically hinder the catalytic turnover. However, to our delight, we found that the reaction using thiophenol proceeded well, with the reaction complete in under 15 minutes. Once again, we probed the substrate scope of the reaction, and a range of substituted hydroxyisoindolinones were subjected to our reaction conditions, resulting in a library of 3,3-disubstituted lactams. As shown, the reaction was again tolerant of a range of functional groups with electron donating or withdrawing anilines were tolerated, however we could never manage to isolate the products in useful yields. Phenyl ring substituents was also well tolerated, with ortho and meta substituents proceeding smoothly. Finally, heterocyclic substrates also worked well, providing the lactam products in high yields.

We next turned our attention to amine nucleophiles, as we envisaged that they would be more problematic in the reaction, mainly through direct Lewis acid-Lewis base interactions. Additionally, in contrast to their sulfur counterparts, aminoisoindolinones are relatively underexplored in synthesis, with very few reports focusing on the synthesis of carbamate and sulfonamide derivatives. This is somewhat surprising, given the fact that many isoindolinones have exhibited marked activity against a range of bacterial infections as well as interesting anticancer properties. Due to this, we initially focused on delivering a robust method to produce these potentially high value molecules from readily available starting materials. We started our investigation employing our optimized conditions and simple amine nucleophiles. We observed a clear trend in reactivity, in which only electron withdrawing amines were tolerated, however we could never manage to isolate the products in useful yields. Additionally, the reaction was highly variable, and in our hands, remained unrepeatable. On the small amount of material we did isolate, we observed a rapid degradation profile, with complete degradation after 2 hours, regardless of storage temperature. After some investigation, that the reaction employing N-Bn substituted hydroxyisoindolinones were much more user friendly, reproducibly providing the desired product in good yield. As shown, the reaction proceeded well, with substrates bearing contrasting electronics being also worked well.
Therefore provides potentially new avenues of biological activities to be uncovered. The reactivity pattern remained, with only unsubstituted 11, providing reproducible reactivity and good yields throughout. Probing the variability of the sulfonamides produced a range of useful scaffolds using 5 mol% of the catalyst system. As shown above (Scheme 9), the reaction was once again tolerant to a range of synthetically useful functional groups including electron donating (14a, 14b) withdrawing (14c) halides (14d-f) thiophene (14g). Furthermore, saturated groups (14h) also worked well, providing access to 3-dimensional scaffolds.

Scheme 6. 3-Amino substituted isoindolinones

Once complete, we probed the applicability of using less nucleophilic amine sources, such as the previously mentioned amide and sulfonamide moieties. Once again employing our optimized conditions, and using 1a as our model substrate, we screened a range of carbamate nucleophiles. Unfortunately, all of these proved unsuccessful, with the reactions plateauing at 25% conversion (Scheme 7).

Scheme 7. Reaction with Benzylcarbamate

After extensive experimentation in which we screened a wide range of conditions including solvent, temperature, time and nucleophile, we were unsuccessful in delivering a reliable reaction that produced these compounds in synthetically useful yields. Although unsuccessful for compounds such as 1a, we were successful in performing the reaction on 11 using a small range of carbamate and amide nucleophiles, as shown (Scheme 8). This provides a range of differentially protected amines (12a-12c), which has the potential to find use in target synthesis.

Scheme 8. Carbamate and amide substitution reactions

Due to the limited scope of these carbamates, we moved our attention to the more useful sulfonamides. Once again these have been seemingly ignored by the synthetic community, and

Scheme 9. Functionalized isoindolinones bearing pendant sulfonamides

As observed, the reaction is generally tolerant to a wide range of functional groups and nucleophiles. However, during the course of this work, we noted some limitations which we believe the community will find useful when deciding to use this methodology. Firstly, when employing amine nucleophiles, the reactions were very sluggish with tertiary alcohols such as 1a, with many reactions not going to completion. This was consistent across all amine nucleophiles used in this study. In a similar vein, we also observed that the choice of amine was important, with secondary amines such as piperidine and morpholine providing variable reactivity patterns, with irreproducible results being obtained. Secondly, carbon based nucleophiles (outside indole and allylsilane) were unreactive towards the conditions described here. We are currently working on this, and hope to report on it soon.

A proposed general mechanism is provided below (Fig. 2). The postulated active catalyst, [CaPF₆NTf₂] A, is formed between Ca(NTf₂)₂ and nBuNPF₆ which in turn produces N-acyliminium ion B and complex C via loss of the non-coordinating PF₆⁻ ligand. Following nucleophilic attack, the aforementioned displaced PF₆⁻ re-enters the cycle, providing the product, water byproduct and reforming the active catalyst.
peak. Multiplicities are denoted as s- singlet, d- doublet, t- triplet, q- quartet and quin- quintet and derivatives thereof (br denotes a broad resonance peak). Coupling constants recorded as Hz and round to the nearest 0.1 Hz. High Resolution Mass Spectrometry (HRMS) was recorded using an Agilent Technologies® 6540 Ultra-High-Definition (UHD) AccurateMass equipped with a time of flight (Q-TOF) analyzer and the samples were ionized by ESI techniques and introduced through a high pressure liquid chromatography (HPLC) model Agilent Technologies® 1260 Infinity Quatery LC system.

In conclusion, we have developed a robust and high yield methodology to afford a range of substituted isoindolinones. Using low loadings of catalyst, the reaction proceeded smoothly, with reaction times ranging from 15 minutes to 12 hours. The reaction is tolerant towards a series of traditional nucleophiles including carbon, nitrogen and sulfur containing moieties. We envisage that this methodology will find use within medicinal chemistry campaigns due to the range of biological activities these scaffolds have shown.

**EXPERIMENTAL SECTION**

**Solvents and Reagents.** All solvents were purchased from commercial sources and used without purification (HPLC or analytical grade). Anhydrous solvent was obtained from a The Solv™ Solvent Purification System. Standard vacuum line techniques were used and glassware was oven dried prior to use. Organic solvents were dried during workup using anhydrous Na2SO4. All calcium catalyzed reactions where done without the need for anhydrous or air free conditions. All reaction were performed using DrySyn™ heating mantles and pressure regulated vials.

**Purification and chromatography.** Thin Layer Chromatography (TLC) was carried out using aluminum plates coated with 60 F254 silica gel. Plates were visualized using UV light (254 or 365 nm) or staining with 1% aq. KMnO4 or ninhydrin. Normal-phase silica gel chromatography was carried out using either a Biotage Isola One flash column chromatography system (LPLC) or traditional flash column chromatography using Geduran® Silica gel 60, 40–63 microns.

**Characterization.** Infrared spectroscopy was carried out with a Nicolet® 380 FT/IR – Fourier Transform Infrared Spectrometer. Only the most significant frequencies have been considered during the selection and characterized absorption maxima (vmax) recorded in wavenumbers (cm⁻¹). NMR spectra were recorded using a JEOL® ECS-400 MHz spectrometer using the deuterated solvent stated. Chemical shifts (δ) quoted in parts per million (ppm) and referenced to the residual solvent peak. Multiplicities are denoted as s- singlet, d- doublet, t- triplet, q- quartet and quin- quintet and derivatives thereof (br denotes a broad resonance peak). Coupling constants recorded as Hz and round to the nearest 0.1 Hz. High Resolution Mass Spectrometry (HRMS) was recorded using an Agilent Technologies® 6540 Ultra-High-Definition (UHD) AccurateMass equipped with a time of flight (Q-TOF) analyzer and the samples were ionized by ESI techniques and introduced through a high pressure liquid chromatography (HPLC) model Agilent Technologies® 1260 Infinity Quatery LC system.

3-(5-bromo-1H-indol-3-yl)-3-phenyl-2,3-dihydro-1H-isoindol-1-one (3a). To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.22 mmol), Ca(NTf2)2 (1.3 mg, 0.0022 mmol) and nBu4NPF6 (1 mg, 0.0022 mmol) in DCE (1 mL) at 80 ℃. The reaction was stirred for 1 minute and 5-bromoindole (65 mg, 0.33 mmol) was added in a single portion and stirred at 80 ℃ for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (3:1 EtOAc:Hex) to afford a cream solid (73 mg, 82%). IR (3:1 EtOAc:Hex) νmax (cm⁻¹): 3209, 3058, 1978, 1671, 1491, 1314. HRMS (ESI) m/z: [M+H]^+ Calc for C22H14BrN2O: 403.0446; found 403.0441. 1H NMR (400 MHz, DMSO-d6): δ 11.30 (s, 1H), 9.73 (s, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.53 (dq, J = 4.7, 4.1 Hz, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.40 – 7.25 (m, 4H), 7.16 (dd, J = 8.6, 1.6 Hz, 1H), 6.94 (dd, J = 15.7, 1.8 Hz, 2H). 13C{1H} NMR (101 MHz, DMSO-d6): δ 168.6, 150.6, 142.5, 135.8, 132.1, 130.9, 128.5, 126.9, 126.3, 125.9, 124.2, 123.9, 123.3, 122.1, 116.5, 113.8, 111.4, 65.9.

Reaction also performed on a 2.2 mmol from 3-hydroxy-3-phenylisoindolin-1-one (500 mg, 2.20 mmol), Ca(NTf2)2 (13 mg, 0.02 mmol) and nBu4NPF6 (9 mg, 0.02 mmol) with 5-bromoindole (653 mg, 3.33 mmol) in DCE (10 mL) for 2.5 h. Purification (3:1 EtOAc:Hex) afforded the product as a cream solid (880 mg, 98%).
was added in a single portion and stirred at 80 °C for 30 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash chromatography (1:1, EtOAc/Hex) to afford a white solid (92 mg, 98%).

To a 4 mL vial was added 3-hydroxy-3-(furan-2-yl)-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindol-1-one (50 mg, 0.20 mmol), nBuNPF₅ (0.8 mg, 0.0019 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaboran-2-yl)-1H-indole (70 mg, 0.29 mmol) was added in a single portion and stirred at 80 °C for 30 mins. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc/Hex) to afford an off white solid (92 mg, 98%).

RF (1.1 EtOAc/Hex) = 0.19. IR νmax (cm⁻¹): 3237, 2977, 1673, 1619, 1352. HRMS (ESI) m/z: [M+H⁺] Calcd for C₂₃H₂₁BCINO₅ 485.1803; found 485.1815. \(^{1}H\) NMR (400 MHz, DMSO-d₆): δ 11.24 (d, J = 1.9 Hz, 1H), 9.77 (s, 1H), 7.74 (d, J = 7.3 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.46 – 7.29 (m, 7H), 6.89 (d, J = 2.1 Hz, 1H), 1.23 (s, 12H). \(^{13}C\)(H) NMR (101 MHz, DMSO-d₆): δ 168.6, 150.7, 142.0, 139.2, 132.2, 132.1, 129.0, 128.5, 127.6, 126.7, 124.9, 124.7, 124.1, 123.3, 116.7, 111.3, 83.0, 65.8, 24.8, 24.7.

1-(2-methoxyphenyl)-3-(4-iodophenyl)-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)-3a,7a-dihydro-1H-indol-2-yl]-2,3-dihydro-1H-isooindol-1-one (3h). To a 4 mL vial was added 3-(2-methoxyphenyl)-3-hydroxyisooindolin-1-one (50 mg, 0.20 mmol), Ca(NTf₂)₂ (1.2 mg, 0.0020 mmol) and nBuNPF₅ (0.8 mg, 0.0020 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaboran-2-yl)-1H-indole (71 mg, 0.29 mmol) was added in a single portion and stirred at 80 °C for 30 mins. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc/Hex) to afford an off white solid (92 mg, 98%).

RF (2:1 EtOAc/Hex) = 0.17. IR νmax (cm⁻¹): 3414, 3264, 3008, 1680, 1612, 1351. HRMS (ESI) m/z: [M+H⁺] Calcd for C₂₃H₂₁BCINO₅ 481.2299; found 481.2314. \(^{1}H\) NMR (400 MHz, DMSO-d₆): δ 11.06 (d, J = 1.9 Hz, 1H), 9.16 (s, 1H), 7.79 – 7.69 (m, 1H), 7.58 – 7.46 (m, 4H), 7.40 – 7.28 (m, 3H), 7.21 (dd, J = 7.7, 1.5 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 6.93 – 6.85 (m, 1H), 6.82 (d, J = 2.4 Hz, 1H), 3.51 (s, 3H), 1.23 (s, 12H). \(^{13}C\)(H) NMR (101 MHz, DMSO-d₆): δ 168.6, 157.9, 150.7, 139.0, 131.6, 131.4, 129.7, 129.5, 128.1, 127.1, 127.4, 127.2, 126.7, 126.4, 124.7, 124.1, 123.3, 116.7, 111.3, 83.0, 65.8, 24.8, 24.7.

3-(4-chlorophenyl)-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaboran-2-yl)-3a,7a-dihydro-1H-indol-2-yl]-2,3-dihydro-1H-isooindol-1-one (3g). To a 4 mL vial was added 3-(4-chlorophenyl)-3-hydroxyisooindolin-1-one (50 mg, 0.19 mmol), Ca(NTf₂)₂ (1mg, 0.0019 mmol) and nBuNPF₅ (0.8 mg, 0.0019 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaboran-2-yl)-1H-indole (70 mg, 0.29 mmol) was added in a single portion and stirred at 80 °C for 30 mins. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc/Hex) to afford a white solid (87 mg, 93%).

RF (1.1 EtOAc/Hex) = 0.19. IR νmax (cm⁻¹): 3237, 2977, 1673, 1619, 1352. HRMS (ESI) m/z: [M+H⁺] Calcd for C₂₃H₂₁BCINO₅ 481.1803; found 481.1815. \(^{1}H\) NMR (400 MHz, DMSO-d₆): δ 11.24 (d, J = 1.9 Hz, 1H), 9.77 (s, 1H), 7.74 (d, J = 7.3 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.46 – 7.29 (m, 7H), 6.89 (d, J = 2.1 Hz, 1H), 1.23 (s, 12H). \(^{13}C\)(H) NMR (101 MHz, DMSO-d₆): δ 168.6, 150.7, 142.0, 139.2, 132.2, 132.1, 129.0, 128.5, 127.6, 126.7, 124.9, 124.7, 124.1, 123.3, 116.7, 111.3, 83.0, 65.8, 24.8, 24.7.
(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (85 mg, 0.35 mmol) was added in a single portion and stirred at 80 °C for 30 min. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1 EtOAc:Hex) to afford a pale orange solid (84 mg, 82%). RF (2:1 EtOAc/Hex) = 0.35. IR \( \nu \) max (cm\(^{-1}\): 3295, 3059, 2869, 1679, 1614, 1377. HRMS (ESI) m/z: [M+H]\(^+\) Calcd for C\(_{21}\)H\(_{18}\)NO\(_{3}\) 381.1214; found 381.1213. H\(_{11}\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.41 – 7.30 (m, 3H), 7.69 (d, \( J = 7.5 \) Hz, 1H), 7.31 – 7.28 (m, 1H), 7.18 (s, 1H), 1.25 (s, 12H). \(^{13}\)C\(^{1}\)H NMR (101 MHz, DMSO-d\(_6\)): \( \delta \) 169.0, 155.3, 149.5, 143.7, 139.4, 132.6, 131.6, 129.2, 127.9, 127.5, 125.0, 124.4, 123.6, 115.5, 111.8, 110.9, 107.5, 83.5, 62.6, 25.3, 25.2.

3-(3,5-bis(trifluoromethyl)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3a,7a-dihydro-1H-indol-2-yl-2,3-dihydro-1H-isoindol-1-one (3j). To a 4 mL vial was added 3-hydroxy-3-(3,5-bis(trifluoromethyl)isoindolin-1-one (50 mg, 0.14 mmol), Ca\(\left(\text{NTf}_2\right)_2\) (0.8 mg, 0.0014 mmol) and nBu\(\text{NPF}_3\) (0.5 mg, 0.0014 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (51 mg, 0.21 mmol) was added in a single portion and stirred at 80 °C for 30 min. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford an off-white solid (66 mg, 81%). RF (1:1 EtOAc/Hex) = 0.30. IR \( \nu \) max (cm\(^{-1}\): 3273, 2980, 1695, 1535, 1275, 1131. HRMS (ESI) m/z: [M+H]\(^+\) Calcd for C\(_{33}\)H\(_{21}\)BF\(_{2}\)N\(_2\)O\(_{3}\) 587.1941; found 587.1947.

3-phenyl-3-phenylsulfanyl-2,3-dihydro-isoindolin-1-one (4a). To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (50 mg, 0.22 mmol), Ca\(\left(\text{NTf}_2\right)_2\) (3 mg, 0.0022 mmol) and nBu\(\text{NPF}_3\) (1.7 mg, 0.0022 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 5 minutes and thiophenol (29 mg, 0.27 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a white solid (54 mg, 77%). RF (1:1 EtOAc/Hex) = 0.43. IR \( \nu \) max (cm\(^{-1}\): 3062, 2848, 1696, 1494, 1345, 742. HRMS (ESI) m/z: [M+H]\(^+\) Calcd for C\(_{27}\)H\(_{23}\)BF\(_2\)N\(_2\)O\(_{3}\) 515.1351; found 515.1350. H\(_{11}\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.59 – 7.57 (m, 2H), 7.57 – 7.48 (m, 1H), 7.43 (d, \( J = 7.6 \) Hz, 1H), 7.41 – 7.29 (m, 2H), 7.18 (s, 1H), 1.28 (s, 12H). \(^{13}\)C\(^{1}\)H NMR (101 MHz, CDCl\(_3\)): \( \delta \) 170.2, 149.6, 145.3, 139.4, 133.2 (q, \( J_F = 33.4 \) Hz), 132.0, 130.1, 129.3, 129.3, 126.8, 126.8, 125.0, 124.7, 124.6, 123.8, 123.6, 122.2, 121.9, 116.3, 111.6, 83.75, 66.24, 24.9, 24.8.

4-(1-Hydroxy-3-oxoisoxindolin-1-yl)benzonitrile (4d). To a 4 mL vial was added 4-(1-hydroxy-3-oxoisoxindolin-1-yl)benzonitrile (50 mg, 0.20 mmol), Ca\(\left(\text{NTf}_2\right)_2\) (1.2 mg, 0.002 mmol) and nBu\(\text{NPF}_3\) (0.8 mg, 0.002 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 5 minutes and thiophenol (33 mg, 0.33 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (54 mg, 78%). RF (1:1 EtOAc/Hex) = 0.50. IR \( \nu \) max (cm\(^{-1}\): 3215, 3075, 2229, 1714, 1679, 1497. HRMS (ESI) m/z: [M+H]\(^+\) Calcd for C\(_{27}\)H\(_{21}\)NO\(_3\) 433.0905; found 433.0907. H\(_{11}\) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.93 (d, \( J = 8.5 \) Hz, 2H), 7.71 (d, \( J = 8.5 \) Hz, 2H), 7.68 – 7.57 (m, 2H), 7.54 – 7.46 (m, 2H), 7.38 (t, \( J = 7.3 \) Hz, 1H), 7.25 – 7.21 (m, 1H), 7.14 (d, \( J = 6.9 \) Hz, 2H), 7.11 – 7.04 (m, 2H). \(^{13}\)C\(^{1}\)H NMR (101 MHz, CDCl\(_3\)): \( \delta \) 169.3, 147.7, 144.5, 135.7, 133.0, 132.9, 130.2, 129.3, 128.9, 128.7, 127.2, 123.8, 123.7, 118.4, 112.9, 75.1.

3-(4-trifluoromethylphenyl)-3-(phenylthio)isoindolin-1-one (4e). To a 4 mL vial was added 3-hydroxy-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (60 mg, 0.21 mmol), Ca\(\left(\text{NTf}_2\right)_2\) (1.2 mg, 0.0021 mmol) and nBu\(\text{NPF}_3\) (0.8 mg,
0.0021 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 5 minutes and thiophenol (34 mg, 0.353 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a light brown solid (70 mg, 98%). RF (1:1 EtOAc/CycHex) = 0.6. IR ν max (cm⁻¹): 1515, 1490, 1430, 1310, 1292, 1284, 1254, 1234, 1214, 1196, 1152, 1136, 1116, 1092, 1076, 1016, 982, 944, 928, 896, 854, 820, 796, 780, 720. HRMS (ESI) m/z: [M+H]+ Calcd for C₃₁H₂₅NO₅S 684.1282; found 684.1280.

To a 4 mL vial was added 3-hydroxy-3-(furan-2-yl)-3-(phenylthio)isoindolin-1-one (1 mg, 0.0023 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 5 minutes and thiophenol (38 mg, 0.35 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a light brown solid (70 mg, 98%). RF (1:1 EtOAc/CycHex) = 0.6. IR ν max (cm⁻¹): 1515, 1490, 1430, 1310, 1292, 1284, 1254, 1234, 1214, 1196, 1152, 1136, 1116, 1092, 1076, 1016, 982, 944, 928, 896, 854, 820, 796, 780, 720. HRMS (ESI) m/z: [M+H]+ Calcd for C₃₁H₂₅NO₅S 684.1282; found 684.1280.
3-(4-(trifluoromethyl)phenoxy)-3-phenylisoindolin-1-one (6b). To a 4 mL vial was added 3-iodo-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), Ca(NTf₂)₂ (2.7 mg, 0.0044 mmol) and nBuNPF₆ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 4-(trifluoromethyl)thiophenol (95 mg, 0.533 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1 EtOAc:Hex) to afford a cream solid (98 mg, 67%). IR (1:1 EtOAc:Hex) δ 7.98 (d, J = 5.2 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.42 (d, J = 6.2 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.26 – 7.19 (m, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.75 (dd, J = 8.8 Hz, 2H), 6.68 (d, J = 7.7 Hz, 2H), 6.64 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.42 – 7.27 (m, 2H), 6.87 (s, 1H), 6.68 (s, 2H), 2.04 (s, 6H). ¹³C{¹H} NMR (101 MHz, DMSO-d₆): δ 167.8, 148.0, 139.5, 137.2, 134.2, 132.0; 129.8, 130.0, 129.0, 128.9, 128.5, 128.0, 127.5, 124.0, 122.4, 75.8.

3-(4-(chlorophenyl)-3-phenylisoindolin-1-one (6c). To a 4 mL vial was added 3-iodo-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), Ca(NTf₂)₂ (2.67 mg, 0.0044 mmol) and nBuNPF₆ (1.72 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 4-chlorothiophenol (77 mg, 0.533 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1 EtOAc:Hex) to afford a cream solid (143 mg, 78%). RF (1:1 EtOAc:Hex) = 0.85. IR (1:1 EtOAc:Hex) = 3288, 3057, 2924, 1693, 1609, 1377. HRMS (ESI): m/z [M+Na⁺]: Calcd for C₁₂H₁₀N₄O₄S 342.0672; found 342.0671. ¹HNMR (400 MHz, CDCl₃): 8.81 (s, 1H), 8.42 (d, J = 4.9 Hz, 2H), 7.90 (d, J = 7.1 Hz, 1H), 7.86 – 7.81 (m, 2H), 7.62 – 7.42 (m, 3H), 7.32 – 7.26 (m, 2H), 7.26 – 7.19 (m, 1H), 6.96 (t, J = 4.9 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 167.4, 157.5, 147.7, 140.2, 133.1, 130.2, 129.7, 128.8, 128.3, 126.2, 124.6, 117.2, 74.3.

3-(5-dimethylphenoxy)-3-phenylisoindolin-1-one (6d). To a 4 mL vial was added 3-iodo-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), Ca(NTf₂)₂ (3 mg, 0.0044 mmol) and nBuNPF₆ (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 ºC. The reaction was stirred for 5 minutes and 3,5-dimethylthiophenol (74 mg, 0.533 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1 EtOAc:Hex) to afford a cream solid (143 mg, 78%). RF (1:1 EtOAc:Hex) = 0.39. IR (1:1 EtOAc:Hex) = 3288, 3057, 2924, 1693, 1609, 1377. HRMS (ESI): m/z [M+Na⁺]: Calcd for C₁₂H₁₀N₄O₄S 342.0672; found 342.0671. ¹HNMR (400 MHz, CDCl₃): 8.81 (s, 1H), 8.42 (d, J = 4.9 Hz, 2H), 7.90 (d, J = 7.1 Hz, 1H), 7.86 – 7.81 (m, 2H), 7.62 – 7.42 (m, 3H), 7.32 – 7.26 (m, 2H), 7.26 – 7.19 (m, 1H), 6.96 (t, J = 4.9 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 167.4, 157.5, 147.7, 140.2, 133.1, 130.2, 129.7, 128.8, 128.3, 126.2, 124.6, 117.2, 74.3.
3-(benzylthio)-3-phenylisoindolin-1-one (6h). To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), Ca(NTf₂)₂ (3 mg, 0.0044 mmol) and nBu₄NF (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 °C. The reaction was stirred for 5 minutes and benzylmercaptan (66 mg, 0.53 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a yellow product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a cream solid (135 mg, 92%). RF (1:1 EtOAc:Hex) = 0.46. IR νmax (cm⁻¹): 3127, 3056, 2943, 1694, 1312. HRMS (ESI) m/z: [M+H]+Calcd for C₂₀H₁₈N₂O₂S: 344.1185; found 344.1183. νmax (cm⁻¹): 3146, 3031, 2956, 1698, 1310. HRMS (ESI) m/z: [M+H]+Calcd for C₂₀H₁₈N₂O₂S: 344.1185; found 344.1183. νmax (cm⁻¹): 3127, 2943, 1694, 1312. HRMS (ESI) m/z: [M+H]+Calcd for C₂₀H₁₈N₂O₂S: 344.1185; found 344.1183.

3-(butanethio)-3-phenylisoindolin-1-one (6i). To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), Ca(NTf₂)₂ (3 mg, 0.0044 mmol) and nBu₄NF (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 °C. The reaction was stirred for 5 minutes and butanethiol (48 mg, 0.53 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a yellow oil which solidified upon standing (120 mg, 91%). RF (1:1 EtOAc:Hex) = 0.70. IR νmax (cm⁻¹): 3185, 3066, 2956, 1698, 1310. HRMS (ESI) m/z: [M+H]+ Calcd for C₂₀H₂₂O₂S: 328.1309; found 328.1317. IR νmax (cm⁻¹): 3185, 3066, 2956, 1698, 1310. HRMS (ESI) m/z: [M+H]+ Calcd for C₂₀H₂₂O₂S: 328.1309; found. 328.1307. νmax (cm⁻¹): 3185, 3066, 2956, 1698, 1310. HRMS (ESI) m/z: [M+H]+ Calcd for C₂₀H₂₂O₂S: 328.1309; found. 328.1307.

3-(cyclohexanethio)-3-phenylisoindolin-1-one (6j). To a 4 mL vial was added 3-hydroxy-3-phenylisoindolin-1-one (100 mg, 0.44 mmol), Ca(NTf₂)₂ (3 mg, 0.0044 mmol) and nBu₄NF (1.7 mg, 0.0044 mmol) in DCE (2 mL) at 80 °C. The reaction was stirred for 5 minutes and cyclohexanethiol (77 mg, 0.66 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1, EtOAc:Hex) to afford a yellow oil which solidified upon standing (134 mg, 93%). RF (1:1 EtOAc:Hex) = 0.52. IR νmax (cm⁻¹): 3156, 3061, 2926, 1690, 1464, 1312. HRMS (ESI) m/z: [M+H]+ Calcd for C₂₀H₂₂O₂S: 322.1452; found 322.1451. HRMS (ESI) m/z: [M+H]+ Calcd for C₂₀H₂₂O₂S: 322.1452; found 322.1451. HRMS (ESI) m/z: [M+H]+ Calcd for C₂₀H₂₂O₂S: 322.1452; found 322.1451.
2-benzyl-3-[2-methoxy-5-(trifluoromethyl)anilino]-2,3-dihydro-1H-isoindol-1-one (8e). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoindol-1-one (50 mg, 0.21 mmol), Ca(NTf$_2$)$_2$ (13 mg, 0.021 mmol) and nBuNPF$_6$ (8 mg, 0.021 mmol) in DCE (1 mL) at room temperature. 2-methoxy-5-(trifluoromethyl)aniline (60 mg, 0.31 mmol) was added in a single portion and the reaction was stirred at 80 °C overnight.

Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (0 to 5% EtOAc/DCM) to afford the desired product as a colorless oil (64 mg, 93%). RF (1:1 EtOAc/Hex) = 0.48. HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{24}$H$_{22}$F$_4$N$_2$O$_2$: 413.1477; found 413.1487. 1H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.81 (d, $J$ = 6.5 Hz, 1H), 7.70 – 7.52 (m, 2H), 7.48 (d, $J$ = 6.8 Hz, 1H), 7.28 – 7.05 (m, 5H), 6.95 – 6.82 (m, 2H), 6.44 (d, $J$ = 8.1 Hz, 1H), 6.21 (s, 1H), 6.12 (d, $J$ = 8.3 Hz, 1H), 4.79 (d, $J$ = 15.4 Hz, 1H), 4.28 (d, $J$ = 15.5 Hz, 1H), 3.81 (s, 3H). 13C{H} NMR (101 MHz, DMSO-d$_6$): $\delta$ 166.6, 149.6, 143.0, 137.6, 136.7, 132.3, 131.7, 129.4, 128.6, 128.0, 127.8, 127.2, 123.5, 122.7, 65.9, 65.8, 43.1.

b-tert-butyl (2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)carbamate (12b). To a 4 mL vial was added 2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-one (50 mg, 0.21 mmol) and nBuNPF$_6$ (8 mg, 0.021 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and tert-butyllcarbamate (29 mg, 0.25 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1 EtOAc:Hex) followed by trituration with Et$_2$O to afford the product as a white solid (65 mg, 86%). RF (1:1 EtOAc/Hex) = 0.50. IR $\nu_{max}$ (cm$^{-1}$): 3270, 2985, 2929, 1712, 1684, 1519. HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{23}$H$_{22}$N$_2$O$_2$: 343.1709; found 343.1696. 1H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.81 (d, $J$ = 9.1 Hz, 1H), 7.71 (d, $J$ = 7.4 Hz, 1H), 7.63 (t, $J$ = 7.2 Hz, 1H), 7.58 – 7.46 (m, 1H), 7.39 – 7.18 (m, 1H), 6.03 (d, $J$ = 9.0 Hz, 1H), 4.83 (d, $J$ = 15.3 Hz, 1H), 4.28 (d, $J$ = 15.5 Hz, 1H), 1.39 (s, 3H). 13C{H} NMR (101 MHz, DMSO-d$_6$): $\delta$ 166.6, 155.6, 143.3, 137.8, 132.2, 129.3, 128.5, 127.6, 127.1, 123.5, 122.6, 79.0, 65.5, 43.1, 28.1.

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)benzamide (12c). To a 4 mL vial was added 2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-one (50 mg, 0.21 mmol) Ca(NTf$_2$)$_2$ (1.3 mg, 0.0021 mmol) and nBuNPF$_6$ (0.8 mg, 0.0021 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and benzamide (38 mg, 0.3 mmol) was added in a single portion and stirred at 80 °C for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:1 EtOAc:Hex) to afford a white solid (68 mg, 95%). RF (1:1 EtOAc/Hex) = 0.41. IR $\nu_{max}$ (cm$^{-1}$): 3548, 3278, 3031, 2933, 1705, 1270. HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{26}$H$_{24}$N$_2$O$_2$: 399.1709; found 398.1709. 1H NMR (400 MHz, DMSO-d$_6$): $\delta$ 8.23 (d, $J$ = 9.2 Hz, 1H), 7.73 (d, $J$ = 7.4 Hz, 1H), 7.64 (t, $J$ = 7.3 Hz, 1H), 7.55 (dd, $J$ = 13.5, 7.3 Hz, 2H), 7.46 – 7.20 (m, 10H), 6.09 (d, $J$ = 9.1 Hz, 1H), 5.20 – 4.98 (m, 2H), 4.80 (d, $J$ = 15.4 Hz, 1H), 4.32 (d, $J$ = 15.4 Hz, 1H). 13C{H} NMR (101 MHz, DMSO-d$_6$): $\delta$ 166.5, 153.6, 143.0, 137.6, 136.7, 132.3, 131.7, 129.4, 128.4, 128.0, 127.8, 127.7, 127.2, 123.5, 122.7, 65.9, 65.8, 43.1.
2-benzyl-3-(2-oxo-1,3-oxazolidin-3-yl)-2,3-dihydro-1H-isoidol-1-one (12d). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoidol-1-one (50 mg, 0.21 mmol), Ca(NTf$_2$)$_2$ (1.3 mg, 0.0021 mmol) and nBuNPFe (1 mg, 0.0021 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 2-oxazolidinone (27 mg, 0.31 mmol) was added in a single portion and stirred at 80 ºC for 15 minutes. Once TLC analysis indicated conversion to the product, the product was concentrated and purified by flash column chromatography (1:9, EtOAc:DCM) to afford a white semi-solid (49 mg, 76%).

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-4-methylbenzene-1-sulfonamide (14a). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoidol-1-one (50 mg, 0.21 mmol), Ca(NTf$_2$)$_2$ (6.3 mg, 0.0104 mmol) and nBuNPF$_6$ (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and p-toluenesulfonamide (36 mg, 0.21 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (68 mg, 85%). IR (1:5 EtOAc/DCM) = 0.57. IR $\nu$ max (cm$^{-1}$): 3125, 2935, 2884, 1674, 1495, 1162. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C$_{39}$H$_{39}$NO$_7$S 671.2207; found 671.2205.

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-4-fluorobenzene-1-sulfonamide (14c). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoidol-1-one (50 mg, 0.21 mmol), Ca(NTf$_2$)$_2$ (6.2 mg, 0.0104 mmol) and nBuNPFe (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 2-fluorobenzene-1-sulfonamide (55 mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (55 mg, 78%). IR (1:5 EtOAc/DCM) = 0.56. IR $\nu$ max (cm$^{-1}$): 3106, 3063, 1687, 1592, 1444, 1163. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C$_{39}$H$_{39}$FNO$_7$S 697.2265; found 697.2263.

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-4-chlorobenzene-1-sulfonamide (14d). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoidol-1-one (50 mg, 0.21 mmol), Ca(NTf$_2$)$_2$ (6.3 mg, 0.0104 mmol) and nBuNPFe (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 3-chlorobenzene-1-sulfonamide (44 mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC for 2h. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (65 mg, 75%). IR (1:5 EtOAc/DCM) = 0.60. IR $\nu$ max (cm$^{-1}$): 3181, 3056, 1687, 1494, 1468, 1157. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C$_{39}$H$_{39}$ClNO$_7$S 723.0907; found 723.0909. NMR (400 MHz, DMSO-d$_6$): $\delta$ 8.97 – 8.76 (m, 1H), 7.80 (d, $J = 8.5$ Hz, 2H), 7.70 (s, 1H), 7.57 – 7.47 (m, 2H), 7.35 – 7.09 (m, 7H), 6.77 (s, 1H), 5.86 – 5.65 (m, 1H), 4.82 (d, $J = 15.6$ Hz, 1H), 4.24 (d, $J = 15.5$ Hz, 1H), 3.87 (s, 3H). $^{13}$C($^1$H) NMR (101 MHz, DMSO-d$_6$): $\delta$ 170.7, 157.1, 139.7, 137.4, 132.7, 132.4, 131.3, 130.7, 130.4, 129.8, 128.5, 127.8, 127.3, 127.2, 123.0, 122.9, 121.1, 67.2, 42.2, 21.1.

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-4-methoxybenzene-1-sulfonamide (14b). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoidol-1-one (50 mg, 0.21 mmol), Ca(NTf$_2$)$_2$ (6.2 mg, 0.0104 mmol) and nBuNPFe (4.05 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 4-methoxybenzenesulfonyl (39 mg, 0.21 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (78 mg, 91%). IR (1:5 EtOAc/DCM) = 0.30. IR $\nu$ max (cm$^{-1}$): 3130, 2929, 2843, 1677, 1594, 1495. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C$_{39}$H$_{39}$NO$_7$S 667.2207; found 667.2205.

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-4-fluorobenzene-1-sulfonamide (14e). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isoidol-1-one (50 mg, 0.21 mmol), Ca(NTf$_2$)$_2$ (6.3 mg, 0.0104 mmol) and nBuNPFe (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 3-fluorobenzene-1-sulfonamide (6.3 mg, 0.0104 mmol) in DCE (1 mL) at 80 ºC. The reaction was stirred for 1 minute and 3-fluorobenzene-1-sulfonamide (55 mg, 0.23 mmol) was added in a single portion and stirred at 80 ºC overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (75 mg, 78%). IR (1:5 EtOAc/DCM) = 0.56. IR $\nu$ max (cm$^{-1}$): 3160, 3063, 1687, 1592, 1444, 1163. HRMS (ESI) m/z: $[M+H]^+$ Calcd for C$_{39}$H$_{39}$FNO$_7$S 697.2265; found 697.2263.
N-(2-benzyl-3-oxo-2,3-dihydro-1H-isooindol-1-yl)-2,4-difluorobenzene-1-sulfonamide (14f). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isooindol-1-one (43 mg, 0.18 mmol), Ca(NTf₂)₂ (6 mg, 0.00906 mmol) and nBuNP(N)₂ (4 mg, 0.0096 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and 2,4-difluorobenzene-1-sulfonamide (35 mg, 0.18 mmol) was added in a single portion and stirred at 80 °C overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (62 mg, 77%). RF (1:5 EtOAc/DCM) = 0.58. IR ν max (cm⁻¹): 3345, 3105, 2894, 1681, 1431. HRMS (ESI) m/z: [M+H]⁺ 385.0681; found 385.0680.

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isooindol-1-yl)cyclopropanesulfonamide (14h). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isooindol-1-one (50 mg, 0.21 mmol), Ca(NTf₂)₂ (6.3 mg, 0.0104 mmol) and nBuNP(N)₂ (4 mg, 0.0104 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and cyclopropanesulfonamide (28 mg, 0.23 mmol) was added in a single portion and stirred at 80 °C overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (44 mg, 61%). RF (1:5 EtOAc/DCM) = 0.35. IR ν max (cm⁻¹): 3387, 3277, 3125, 1671, 1470, 1295. HRMS (ESI) m/z: [M+H]⁺ Calcd for C₁₉H₁₀₅N₂O₆S 343.1116; found 343.1118.

DMSO-d₆): δ 9.17 (d, J = 8.8 Hz, 1H), 7.80 – 7.57 (m, 5H), 7.52 (p, J = 7.7 Hz, 2H), 7.35 – 7.14 (m, 5H), 6.73 (d, J = 6.0 Hz, 1H), 5.90 (d, J = 8.8 Hz, 1H), 4.83 (d, J = 15.6 Hz, 1H), 4.25 (d, J = 15.6 Hz, 1H). ¹³C{¹H} NMR (101 MHz, DMSO-d₆): δ 166.3, 163.1, 160.6, 143.9 (d, J = 6.6 Hz), 142.5, 137.3, 132.4, 132.1 (d, J = 7.9 Hz), 131.2, 129.8, 128.5, 127.5, 127.1, 123.1, 122.9, 122.6, 120.2 (d, J = 21.1 Hz), 113.6 (d, J = 24.5 Hz), 67.7, 42.5.

N-(2-benzyl-3-oxo-2,3-dihydro-1H-isooindol-1-yl)-2,4-difluorobenzene-1-sulfonamide (14f). To a 4 mL vial was added 2-benzyl-3-hydroxy-2,3-dihydro-isooindol-1-one (43 mg, 0.18 mmol), Ca(NTf₂)₂ (6 mg, 0.00906 mmol) and nBuNP(N)₂ (4 mg, 0.0096 mmol) in DCE (1 mL) at 80 °C. The reaction was stirred for 1 minute and 2,4-difluorobenzene-1-sulfonamide (35 mg, 0.18 mmol) was added in a single portion and stirred at 80 °C overnight. Once TLC analysis indicated conversion to the product, hexane (2 mL) was added and the product was collected by filtration as a white solid (45 mg, 60%). RF (1:5 EtOAc/DCM) = 0.35. IR ν max (cm⁻¹): 3345, 3105, 2894, 1664, 1467, 1198. . HRMS (ESI) m/z: [M+H]⁺ 334.0928; found 334.0924.

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