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Article

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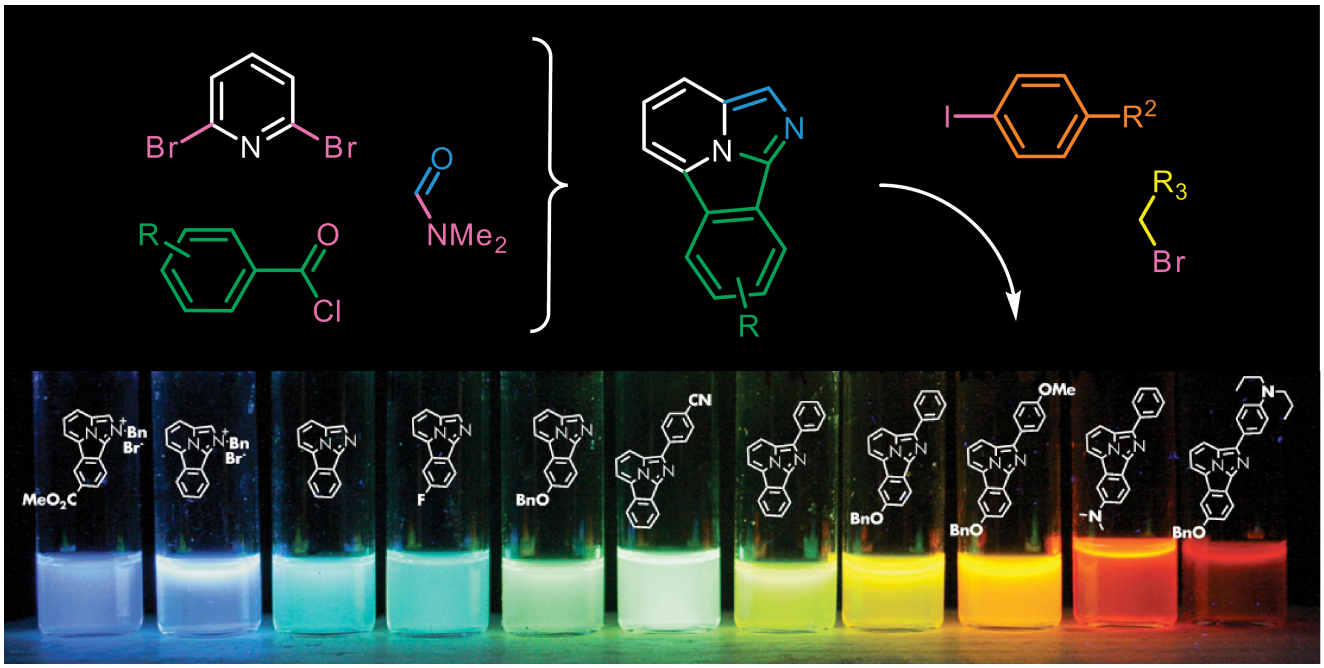
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R2
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Br-
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OMe
N
BnO
N

# General C–H Arylation Strategy for the Synthesis of Tunable Visible Light Emitting Benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizine Fluorophores

Éric Lévesque, William S. Bechara†, Léa Constantineau-Forget†, Guillaume Pelletier, Natalie M. Rachel, Joelle N. Pelletier and André B. Charette*

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ABSTRACT: Herein we report the discovery of the benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizine motif displaying tunable emission covering most of the visible spectrum. The polycyclic core is obtained from readily available amides *via* a chemoselective process involving $Tf_2O$-mediated amide cyclodehydration followed by intramolecular C–H arylation. Additionally, these fluorescent heterocycles are easily functionalized using electrophilic reagents, enabling divergent access to varied substitution. The effects of said substitution on the compounds' photophysical properties were rationalized by DFT calculations. For some compounds, emission wavelengths are directly correlated to the substituent's Hammett constants. Easily introduced non-conjugated reactive functional groups allow the labelling of biomolecules without modification of emissive properties. This work provides a straightforward platform for the synthesis of new moderately bright fluorescent dyes remarkable for their chemical stability, predictability and unusually high excitation-emission differential.

## INTRODUCTION

Organic fluorophores are privileged structures that have found pivotal applications in biological imaging, clinical diagnosis, and drug discovery.[1] Such small molecules are employed in stimulated emission depletion (STED) microscopy[2] and single-molecule microscopy,[3] tools extensively used in biochemistry for the precise tracking of specific molecules in complex biological systems.[4] In addition, the handling of small-molecule fluorophores[5] (i.e. fluorescein derivatives, benzopyrylium salts, BODIPY, etc.) is operationally attractive in contrast to fluorescent metal complexes[6] or proteins, [7] which broadens their application in both medical and material sciences. Specifically, fluorescent molecules have gained considerable popularity recently in material science due to their successful incorporation into organic light-emitting diodes (OLEDs).[8] Despite the wide spectrum of applications, few examples of organic, metal-free fluorescent cores with tunable emission are available in the literature. Most of the commonly employed dyes suffer from a narrow variability of the excitation and emission wavelengths, and substituent effects are often difficult to predict.[9] Furthermore, the methodical design of bright[10] fluorescent scaffolds with a specific predictable emission wavelength is still a difficult task.[11]

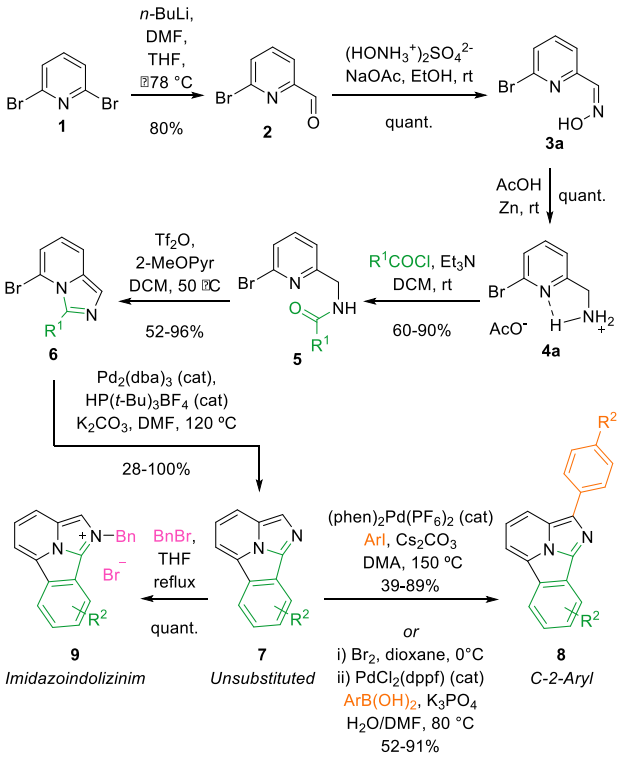
The constant efforts to characterize and to understand each fluorophore's distinct properties are essential endeavors for both fundamental and commercial applications. A good example of such innovation is characterized by the development of a series of tunable fluorescent 1,2-dihydropyrrolo[3,4-*b*]indolizin-3-ones, also called Seoul-Fluors, initiated by the Park group.[12] Libraries of fluorophores sharing a single molecular framework were synthesized using combinatorial techniques. Significant variability of photophysical properties was achieved by installing substituents on the fluorescent core. Density Functional Theory (DFT) calculations helped pinpoint the specific positions most sensitive to electronic effects. Unfortunately, a challenging 1,3-dipolar cycloaddition reaction was needed to access the key tricyclic framework.

In order to address the challenges associated with small molecule fluorophore synthesis and applications, we report the discovery and characterization of a previously unknown fluorescent tetracyclic core.[13] Further chemical modifications of this tetracyclic scaffold, through a rational approach based on calculations, enable straightforward tuning of their emissive properties. These benzo[*a*]imidazo[2,1,5-*c,d*]indolizines are readily synthesized and functionalized in a practical, high-yielding and divergent synthetic pathway. This led to the elaboration of a library of chemically stable fluorescent molecules with emission wavelengths covering most of the visible spectrum. The excitation spectra feature two distinct bands with a similar light output, one of which displaying a high excitation-emission differential[14] (up to 1,62 $\mu m^{-1}$). The synthesis of these fluorophores is described, followed by mechanistic, computational and photophysical studies. Non-conjugated reactive functional groups can be appended to the aromatic core without affecting its innate photophysical properties. Such a group enabled the tagging of two target proteins through an enzyme-catalyzed glutamine transamidation, demonstrating the utility of these fluorophores in probing biological macromolecules.

## RESULTS AND DISCUSSION

**Synthetic methodology.** Our group initially reported the synthesis of a single example of the benzo[*a*]imidazo[2,1,5-*c,d*]indolizine scaffold, obtained in 3 simple steps from 6-bromo-2-pyridinemethanamine.[15] However, this commercially available primary amine is prohibitively expensive. In order to broaden the accessibility of this methodology, an alternative and easily scalable 6-step procedure from commercially available and inexpensive chemicals was designed (**Scheme 1**).

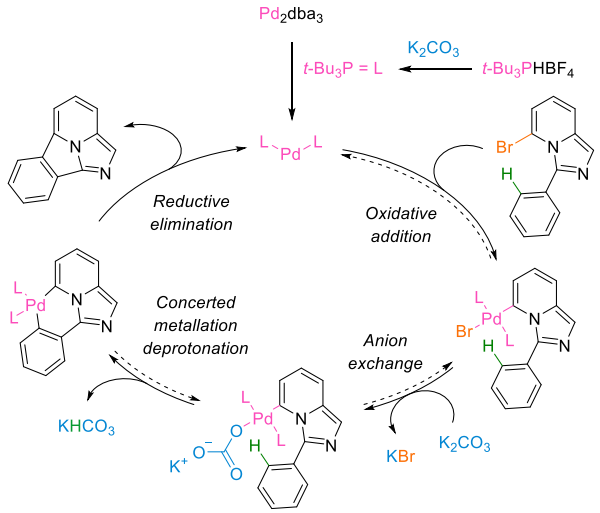
**Scheme 1. General Synthetic Pathway Toward Benzo[*a*]imidazo[2,1,5-*c,d*]indolizines Fluorophores**




Commercially available 6-bromopicolinaldehyde (**2**) can either be purchased or generated from 2,6-dibromopyridine (**1**).[16] The previously reported synthetic pathway is intercepted by condensation of **2** with hydroxylammonium sulfate to yield the corresponding oxime (**3**), followed by treatment with powdered zinc metal in acetic acid which reduces the oxime to the ammonium acetate salt (**4**). These last two steps quantitatively yield the primary ammonium on a multi-gram scale. The fluorophore's fused benzene ring is then introduced along with any desired substitution by acylation of the primary ammonium (**4**) with a benzoyl chloride derivative. The resulting secondary amides (**5**) are treated under the optimized triflic anhydride-mediated cyclodehydration/aromatization conditions previously developed by our research group[15] to afford the corresponding imidazo[1,5-*a*]pyridines (**6**) (**Table 1**). This step is the first in the sequence where some products require chromatographic purification.

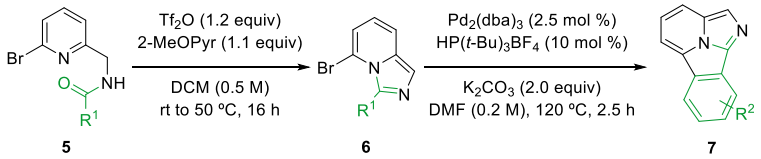
The second cyclization, giving access to the fluorescent core (**7**), takes place *via* a palladium catalyzed intramolecular C–H arylation. This high-yielding transformation is triggered by a Pd(0) precatalyst, a bulky trialkylphosphine ligand,[17] and an excess of carbonate base (**Table 1**). We decided to investigate this transformation by performing kinetic isotopic assays. A reaction rate comparison between fully deuterated (**6a**-$d_5$) and non-deuterated (**6a**) substrates results in a $k_H/k_D$ ratio of 2.02. By analogy, an intramolecular competition reaction (**6a**-*ortho*-$d_1$ as substrate) yields the C–H and C–D insertion products in a ratio of 2:1, which represents a 2.0 KIE value. These results support a mechanism where the turnover limiting step is either the C–H insertion step or the reductive elimination (in which case the former would be in pre-equilibrium) (**Scheme 2**).[18] A concerted metalation-deprotonation (CMD) mechanism is probable.[19] The need for a bulky phosphine to reach completion supports the hypothesis of a turnover-limiting, irreversible reductive elimination.[17]

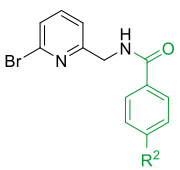
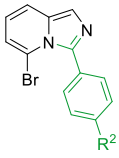
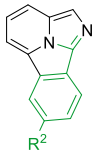
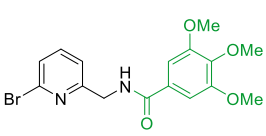
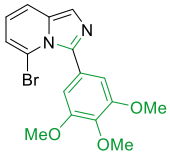
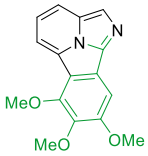
**Scheme 2. Proposed mechanism for the intramolecular C-H arylation**

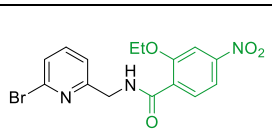
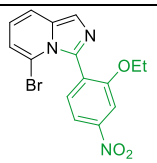
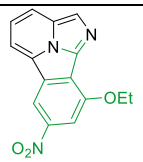
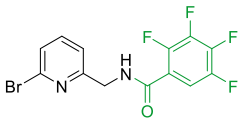
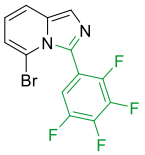
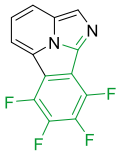
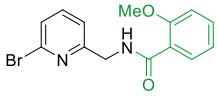
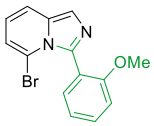
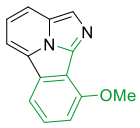
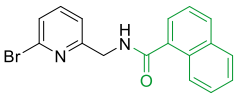
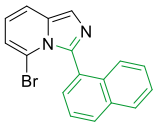
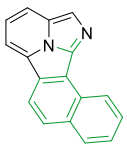
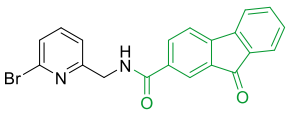
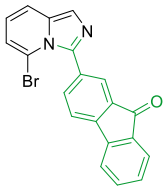
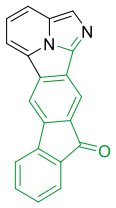
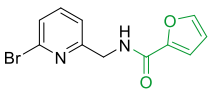
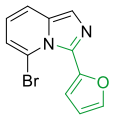
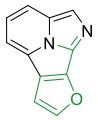
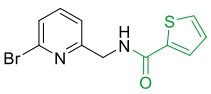
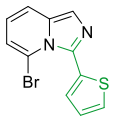
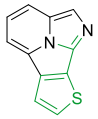
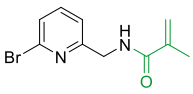
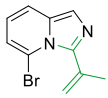
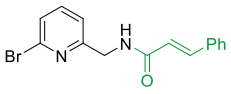
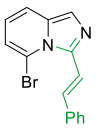
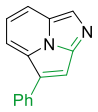



After efficient reaction conditions for both intramolecular cyclization steps were established, a variety of benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizines fluorophores were prepared (**Table 1**). Gratifyingly, the overall process was efficient in the presence of various functional groups ($R^2$ in **Scheme 1**), with both reactions giving high yields regardless of the aromatic group's electronic properties (**Table 1**, entries 2-16). Oxygen and sulfur-containing heterocycles **7q** and **7r** could even be formed, albeit in lower yields for the C–H arylation step (entries 17-18). Alternatively, the methodology can be extended to α,β-unsaturated amides (entries 19-20). In this case, the second cyclization likely occurs *via* a carbometallation-elimination sequence. Accordingly, the reaction is inefficient with an alkene whose geometry forces a *trans* β-hydride elimination (entry 20).

**Table 1. Synthesis of *Unsubstituted* Benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizines: Cyclodehydration and C–H Arylation**

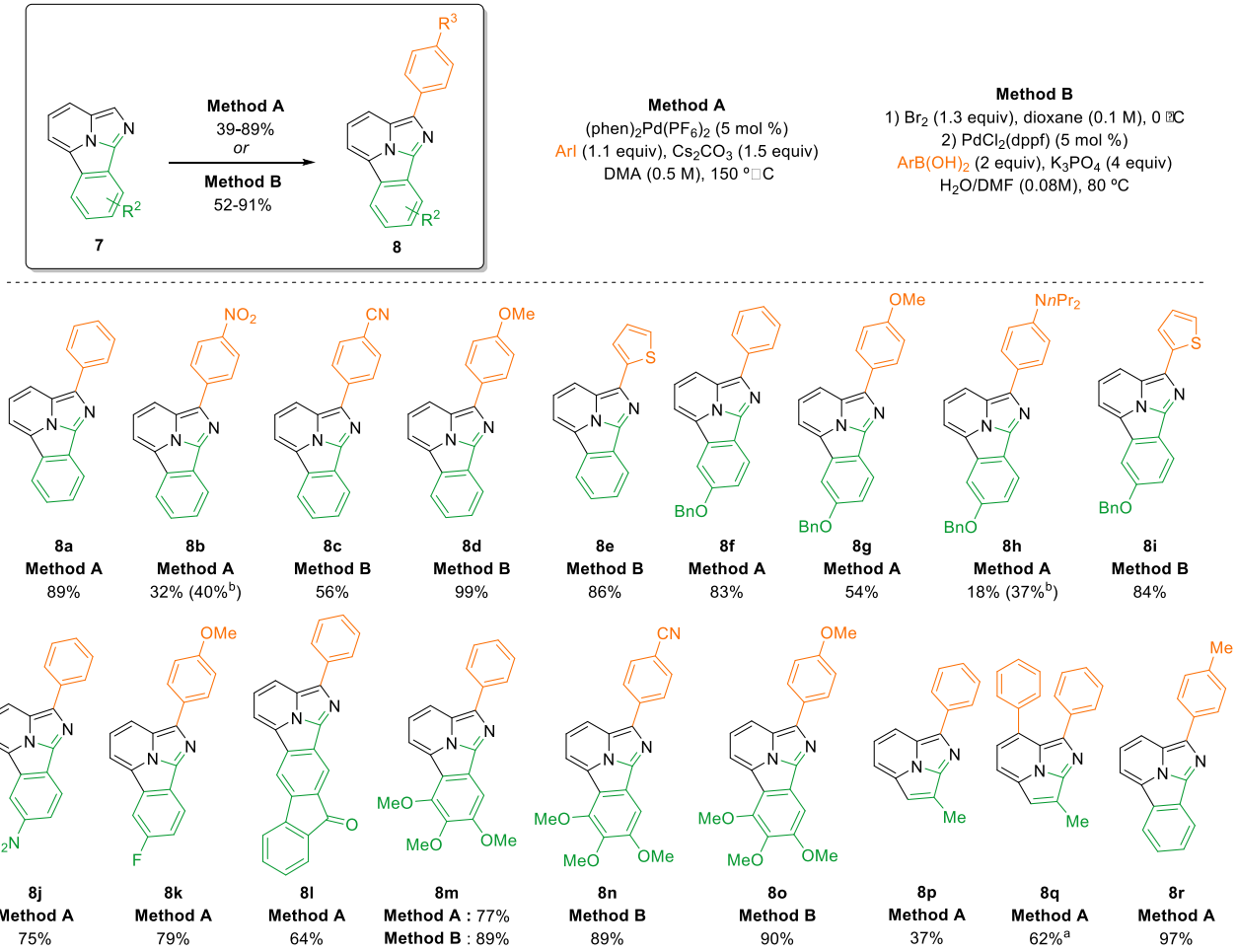



| entry | amide (**5**) | | | imidazopyridine (**6**) | | Benzoimidazo indolizines (**7**) | | yield (**6**) (%)[a] | yield (**7**) (%)[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | $R^2$ = H | 5a |  | 6a |  | 7a | 96 | 100 |
| 2 | | Ph | 5b | | 6b | | 7b | 87 | 100 |
| 3 | | *t*-Bu | 5c | | 6c | | 7c | 91 | 89 |
| 4 | | OBn | 5d | | 6d | | 7d | 91 | 90 |
| 5 | | $O(CH_2)_2OBz$ | 5e | | 6e | | 7e[c] | 52 | 89[c] |
| 6 | | $NMe_2$ | 5f | | 6f | | 7f | 84 | 98 |
| 7 | | F | 5g | | 6g | | 7g | 90 | 98 |
| 8 | | Cl | 5h | | 6h | | 7h | 89 | 94 |
| 9 | | $CO_2Me$ | 5i | | 6i | | 7i | 81 | 95 |
| 10 | | CN | 5j | | 6j | | 7j[d] | 88 | 99[d] |
| 11 |  | | 5k |  | 6k |  | 7k | 88 | 93 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 12 |  | 5l |  | 6l |  | 7l | 94 | 92 |
| 13 |  | 5m |  | 6m |  | 7m | 93 | 66 |
| 14 |  | 5n |  | 6n |  | 7n | 86 | 98 |
| 15 |  | 5o |  | 6o |  | 7o | 86 | 97 |
| 16 |  | 5p |  | 6p |  | 7p | 65 | 61 |
| 17 |  | 5q |  | 6q |  | 7q | 84 | 40 |
| 18 |  | 5r |  | 6r |  | 7r | 90 | 65 |
| 19 |  | 5s |  | 6s |  | 7s | 74 | 87 |
| 20 |  | 5t |  | 6t |  | 7t | 94 | 28 |

[a] Isolated yield for the corresponding imidazo[1,5-a]pyridine (**6**) (%). [b] Isolated yield for the corresponding benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizines (**7**) (%). [c] Yield of saponified product (primary alcohol) over 2 steps. [d] Made with no chromatographic purification over 6 steps. Overall yield from 2,6-dibromopyridine : 29%

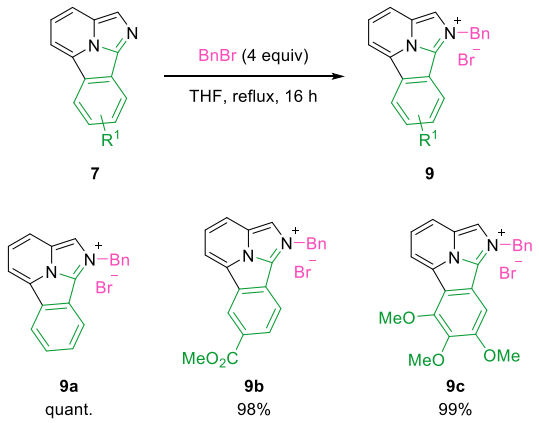
**Scheme 3. Elaboration of the *C-2-Aryl* Series: C–H arylation or Electrophilic Bromination/Suzuki-Miyaura Coupling**




[a] 2.0 equiv of iodide used. [b] Corrected for recovered starting material.

The benzo[*a*]imidazo[2,1,5-*c,d*]indolizines (**7**) generated from the previous sequence are referred to as the *unsubstituted* series. Similarly to the parent imidazo[1,5-*a*]pyridines,[20] they have an inherently nucleophilic character. For example, they successfully react at position C-2 under the cationic palladium-catalyzed arylation conditions reported by the Murai group[21] (**Scheme 3**, method A). This allows for the synthesis of a second category of fluorophores, dubbed the *C-2-aryl* series (**8**). This arylation can also be achieved in two steps *via* a regioselective electrophilic bromination by the $Br_2$-dioxane complex followed by a Suzuki-Miyaura coupling[20] (**Scheme 3**, method B). Both approaches provide good to excellent yields for most coupling partners. Interestingly, when tricycle **7s** was subjected to the direct arylation conditions, a significant amount of the diarylated derivative **8q** was isolated along with a modest yield of **8p**, highlighting the tricyclic and tetracyclic scaffolds' distinct electronic properties.

**Scheme 4. Alkylation of Exocylic Nitrogen**




The *N*-alkylation or protonation of the exocyclic nitrogen produces fluorescent *imidazoindolizinium* salts (**Scheme 4**). Under electrophilic benzylation conditions, the desired salt precipitates quantitatively and can be filtered out, requiring no further purification.

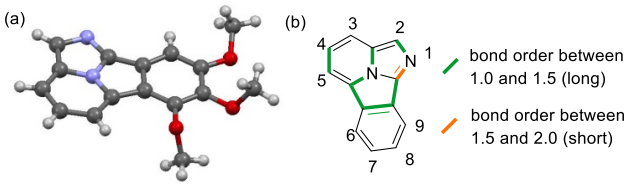



**Figure 1.** (a) Crystal structure of **7k** (b) Approximate bond orders (*ref 22*) and atom numbering. Representative bond lengths obtained from the crystal structure of **10c**.

**Structural properties**. The high crystallinity of benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizines allows for the easy growth of single crystals (in the case of compound **7k**, a single 200 mg piece was obtained). X-ray diffraction spectroscopy revealed the main core is completely flat, with most outer bonds of order between 1.0 and 1.5 (elongated) (**Figure 1**). [22] The perfect planarity of the internal nitrogen indicates $sp^2$ hybridization, meaning the imidazopyridine's 10-electron aromaticity is conserved. However, the fused benzene ring is distorted, the bridging bond being slightly longer than the other five. This suggests at least some 14-electron conjugation around all four fused rings.

**Photophysical properties.** The members of the *unsubstituted* series generally exhibit blue fluorescence, with a $\lambda_{max}$ of emission between 461 nm and 489 nm. The excitation curves feature two to three well-defined peaks that all produce the same emission peak, ruling out fluorescence from higher excited states (**Table 2, 7a**).[23] The lowest wavelength peak exhibits an unusually high excitation-emission differential of 1,44 $\mu m^{-1}$.[24] A direct excitation to a higher electronic level, followed by nonradiative relaxation to the lowest electronic excited state (S1) and radiative relaxation to ground state (S0) is a likely explanation.[23]

Functional group modifications on the fused benzene ring can affect the emissive properties, especially if resonance is possible. The most noticeable effect is a bathochromic shift of emission caused by electron-donating groups at the C-7 or C-9 positions (*para* and *ortho* positions of the initial benzoyl chloride). Interestingly, adding two more methoxy groups on the *meta* positions C-6 and C-8 (compound **7k**) had the opposite effect, bringing back the emission band close to that of the unsubstituted

**7a** (**Table 3**) *via* inductive effects. The presence of an electron-withdrawing group at C-7 (**Table 2, 7i**) does not shift the emission band significantly, but alters the excitation curve to feature three well-defined peaks.

Arylation of the core with a phenyl group at the C-2 position (*2-aryl* series) causes a bathochromic shift of both spectra and some changes to the excitation spectrum (**Table 2, 8a**). The high-energy excitation band (315 nm) widens and exhibits higher light output (brightness)[10] than its lower energy counterpart (469 nm).

Imidazole ring *N*-alkylation (*imidazoindolizinium* series) significantly alters the photophysical properties (**Table 2, 9a**). The emission and lowest-energy excitation peaks undergo a hypsochromic shift while the latter becomes more intense. An almost identical spectrum can be obtained by exposing *unsubstituted* **7a** to aqueous HCl. When acquiring spectra in aqueous buffer solutions of varying pH, this spectrum change can be observed taking place between pH = 5 and pH = 3 (**Figure 2**). This observation reveals benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizine is slightly less basic than the parent imidazo[1,5-*a*]pyridine (p$K_a$ = 5.54[25]). The neutral species dominates the mixture at pH = 5 or higher. Similar cationic compounds with interesting fluorescent properties were previously reported.[26]

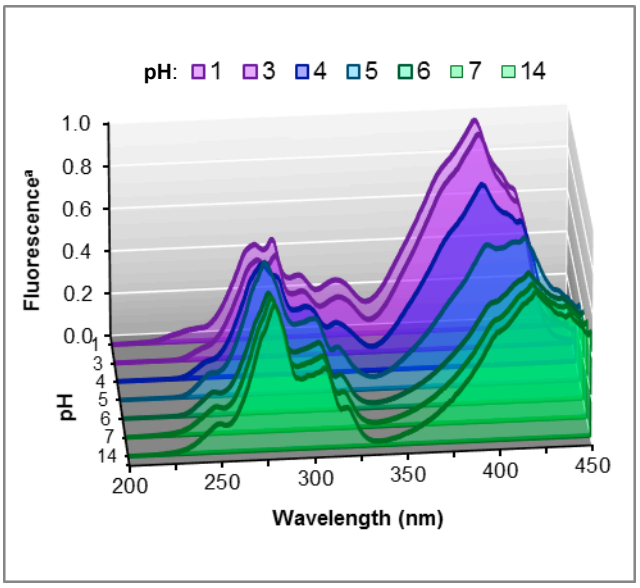
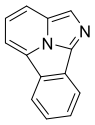
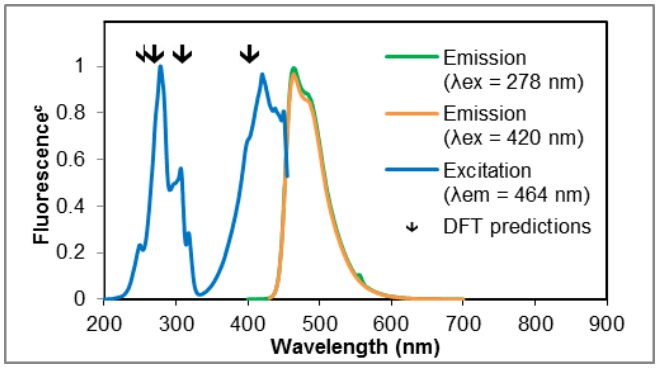
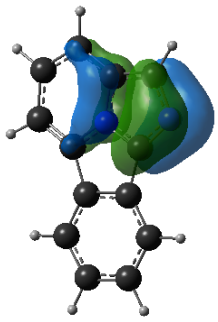
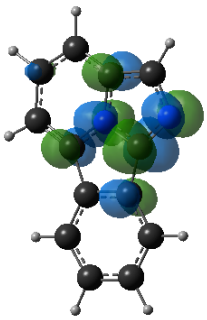
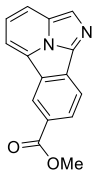
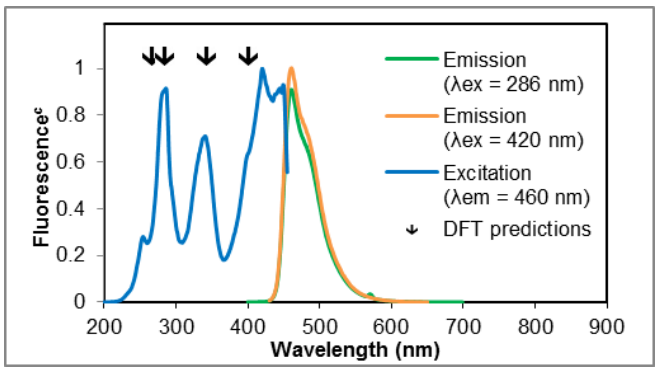
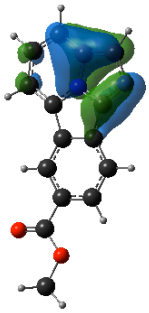
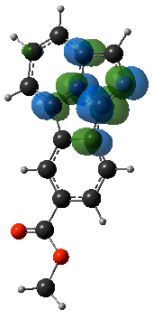
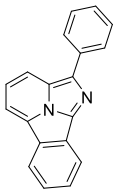
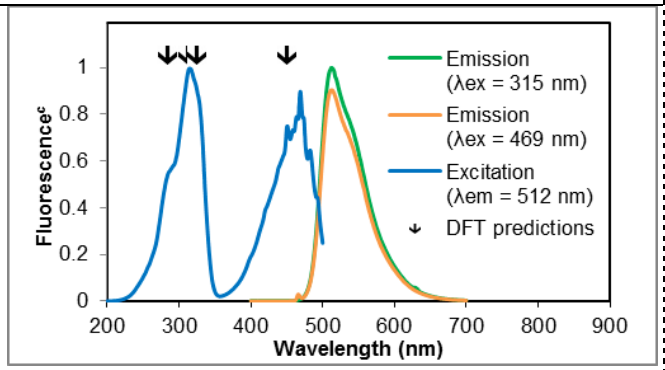
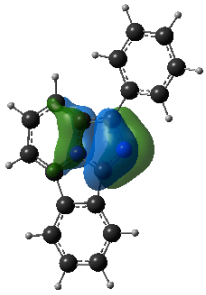
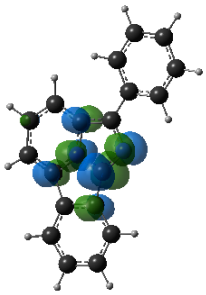
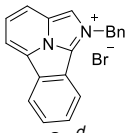
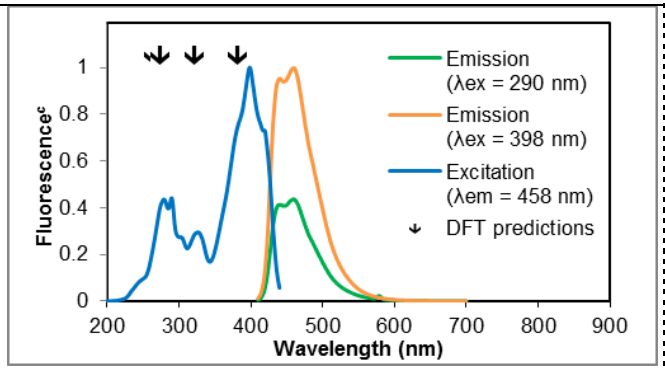
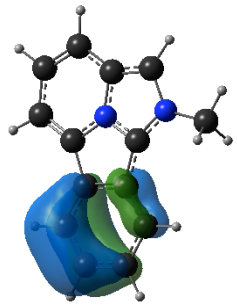
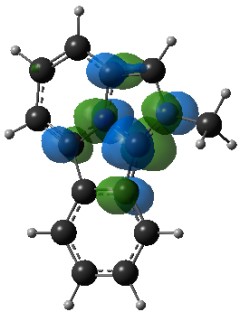



**Figure 2**. Excitation curves ($\lambda_{em}$ = 464nm) of **7a** in aqueous buffers. [a] Relative normalized fluorescence intensity.

These empirical observations prompted us to turn to computational methods in order to locate the frontier molecular orbitals for all three systems. This should facilitate substituent effect prediction, enabling the rational modification of the fluorescent core to obtain specific emissive properties.[27]

Table 2. Photophysical and Computational Data of Representative Benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizines.

| Structure and color[a] | Fluorescence Data | Calculated HOMO[b] | Calculated LUMO[b] |
|---|---|---|---|

| | | | |
|---|---|---|---|
|  **7a** (*Unsubsti-tuted*)  |   |  |  |
|  **7i** (*Unsubsti-tuted*)  |   |  |  |
|  **8a** (*C-2-Aryl*)  |   |  |  |
|  **9a**[d] (*Imidazoin-dolizinium*)  |   |  |  |

[a] Observed under an UVA-emitting low pressure mercury-vapor gas-discharge lamp ("blacklight blue"). [b] B3LYP 6-31G(d,p) hybrid basis set was used.[27] [c] Normalized fluorescence intensity. [d] The N-methyl derivative was used in calculations to shorten computing time.

The resulting orbital representation of *unsubstituted* **7a** (**Table 2**, **7a**) shows that both the HOMO and LUMO are mostly centered on the imidazole ring. This explains why the two *meta* methoxy groups in compound **7k** counteract the bathochromic shift observed for the *para* or *ortho* alkoxy groups (compare with **7d** and **7n**). Moreover, the LUMO representation features a node at the C-2 position.

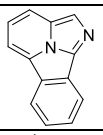
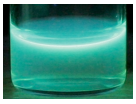
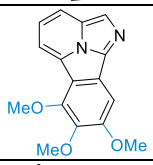
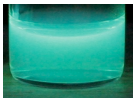
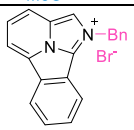
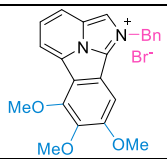
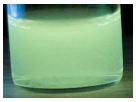
Frontier orbitals on the *C-2-aryl* core exhibit very little change, suggesting that the extra aryl group and its substituents can be a good handle to control the C-2 position's electron density. Substitution at this position should influence the HOMO's energy level with minimal effect on the LUMO. This hints at a straightforward way to modulate the emission wavelength, as the $S_1$-$S_0$ transition energy is often linked to the energy difference between frontier molecular orbitals.[9a,13c, 28]

Time-dependent DFT (TD-DFT) calculations yield theoretical excitation wavelengths, which are in general agreement with the experimental results (**Table 2**, black arrows on graphs), adding validity to the employed model.[29]

Similar calculations performed on the *imidazoindolizinium* core show, in agreement with the measured fluorescence spectra, a completely different system. While the LUMO is still located on the imidazole ring, the neutral system's HOMO is stabilized by the positive charge on the ring and gets relegated to the HOMO$^{-7}$ position. A $\pi$-orbital on the fused benzene ring takes the place of the HOMO, yielding a system where the frontier orbitals are separated, indicating the possibility of intramolecular charge transfer (ICT) fluorescence.[30]

These frontier orbital representations are further validated by substituent effects on the fused benzene ring. Since the HOMO is on that ring in the *imidazoindolizinium* series, all positions can contribute to its electron enrichment, not just the *ortho* (C-9) and *para* positions (C-7). Indeed, the addition of three methoxy groups at the positions C-6, C-7 and C-8 (**9c**) induces a batho-chromic emission shift of 45 nm (**Table 3**, **9a** and **9c**). This is in stark contrast with the *unsubstituted* series, where that same modification had almost no effect on the photophysical properties (**Table 3**, **7a** and **7k**).

**Table 3.** Different effect of fused benzene ring substitution on *unsubstituted* and *imidazoindolizinium* series.

| | Structure | Color[a] | $\lambda_{em}$ (nm) |
|---|---|---|---|
| **7a** |  |  | 464 |
| **7k** |  |  | 471 |
| **9a** |  |  | 458 |
| **9c** |  |  | 503 |

[a] Observed under an UVA-emitting low pressure mercury-vapor gas-discharge lamp ("blacklight blue").

As predicted for the *C-2-aryl* series, *para*-substitution on the exocyclic benzene ring has a significant effect on the emission peak, with donating groups effectively lowering the emission energy. In this series, substitution at both C-7 and the *para* position of the exocyclic C-2 phenyl with electron-donating groups results in a bathochromic shift of the emission wavelength. These substituents effects appear cumulative (**Table 4**, compare **8a**, **8d** and **8g**). In fact, the emitted photons' energy was found to have a linear relationship with the sum of the Hammett constants[31] of the C-2 and C-7 substituents, allowing the mathematical

prediction of compound **8r**'s emission maximum (Figure 3) (Predicted $\lambda_{em}$: 525 nm; measured $\lambda_{em}$: 524 nm). A similar but non-cumulative correlation was previously observed in the structurally related but less bright alkynyl-3-arylimidazo[1,5-a]pyridines.[32] This is particularly useful as it enables precise knowledge of a fluorophore's emissive properties before synthesis, avoiding lengthy trial-and-error when attempting to obtain probes tailor-made for specific applications.

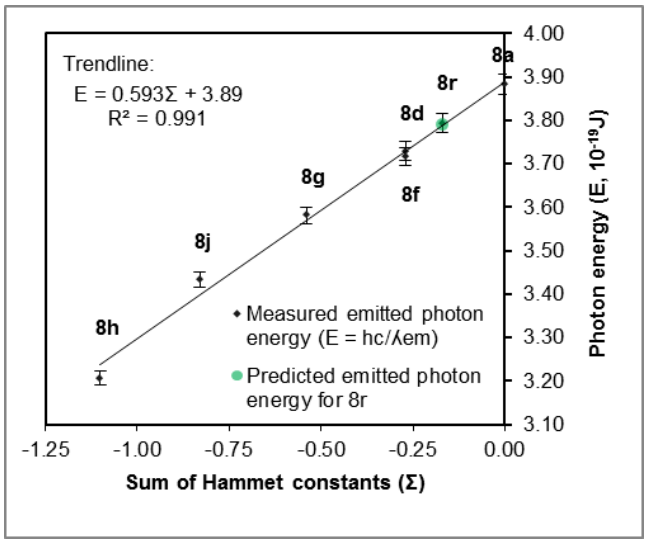



**Figure 3.** Linear relationship between the substituents' Hammett constants and emitted photon energy.

Furthermore, the excitation band producing the highest brightness[10] (light output) consistently resides between 315 nm and 350 nm for most examples. It is thus associated with a consistently high excitation-emission differential. High excitation-emission differential fluorophores are desirable[24] as their use greatly reduces interference from excitation light diffusion. They can also be combined in a single sample with low Stokes shift probes having similar excitation maxima. This enables the activation of multiple, differently colored probes with a single wavelength of incident light.

As shown in **Figures 4** and **5**, simple one- or two-step structural modifications on the benzo[*a*]imidazo[2,1,5-*c*,*d*]indolizine core enable the synthesis of a fluorophore library whose emission maxima cover most of the visible spectrum. In most similar libraries, conjugated fused cycles must be added to access the higher wavelengths,[33] significantly lengthening the synthetic pathway.

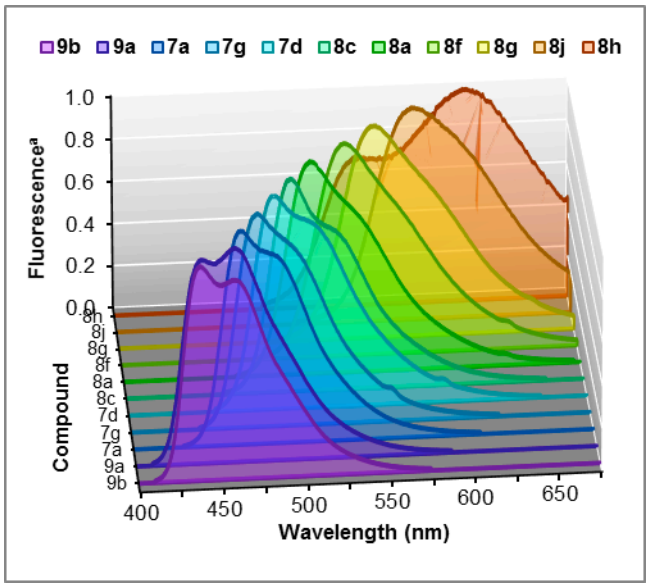



**Figure 4.** Emission spectra of selected compounds. [a]Normalized fluorescence intensity.

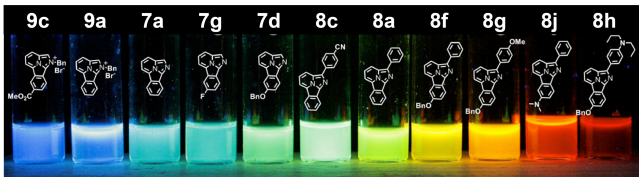



**Figure 5.** Luminescence of selected compounds under an UVA-emitting low pressure mercury-vapor gas-discharge lamp ("blacklight blue").

**Table 4**. Photophysical Data of Selected Fluorophores[a]

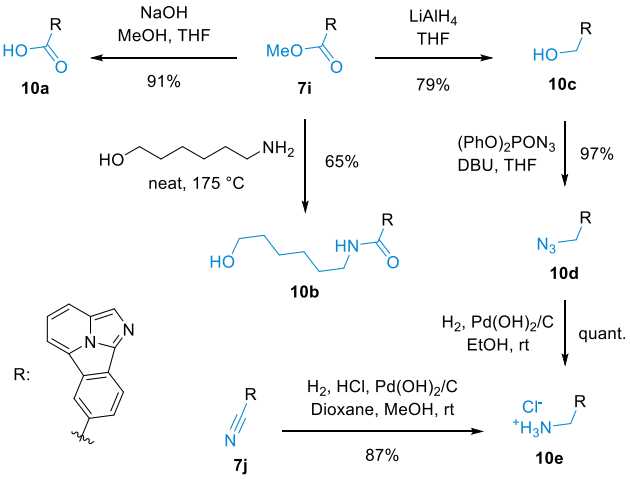
| Compound | Excitation maxima $\lambda_{ex}$ (nΦm)[b] | Emission maxima $\lambda_{em}$ (nm) | Excitation-emission differentials ($\mu m^{-1}$) | Exctinction coefficients $\varepsilon$ ($10^3 M^{-1}cm^{-1}$) | Fluorescence quantum yields $\Phi_F$ | Brightness[10] ($10^3 M^{-1}cm^{-1}$) |
|---|---|---|---|---|---|---|
| **7a** | 278 | 464 | 1.44 | 24.8 | 0.10[c] | 2.4 |
| | 421 | | 0.22 | 5.9 | 0.34[c] | 2.3 |
| **7e** | 295 | 489 | 1.34 | 14.8 | 0.15[c] | 2.2 |
| | 438 | | 0.24 | 4.7 | 0.31[c] | 1.5 |
| **7i** | 286 | 464 | 1.33 | 18.0 | 0.09[c] | 1.7 |
| | 340 | | 0.77 | 0.22 | 0.22[c] | 1.4 |
| | 420 | | 0.21 | 0.27 | 0.27[c] | 1.6 |
| **7k** | 289 | 471 | 1.34 | 28.0 | 0.11[c] | 3.1 |
| | 420 | | 0.26 | 7.3 | 0.31[c] | 2.3 |
| **7s** | 299 | 450 | 1.12 | 7.2 | 0.04[c] | 0.3 |
| | 411 | | 0.21 | 4.9 | 0.09[c] | 0.4 |
| **8a** | 315 | 512 | 1.22 | 22.4 | 0.20[d] | 4.7 |
| | 469 | | 0.18 | 11.0 | 0.37[d] | 4.2 |
| **8c** | 352 | 498 | 0.83 | 5.1 | 0.28[c] | 1.4 |
| | 469 | | 0.12 | 2.8 | 0.25[c] | 0.7 |
| **8d** | 317 | 535 | 1.29 | 22.0 | 0.17[d] | 3.8 |
| | 469 | | 0.26 | 11.1 | 0.27[d] | 3.0 |
| **8g** | 325 | 555 | 1.28 | 23.0 | 0.14[d] | 3.1 |
| | 469 | | 0.33 | 8.1 | 0.21[d] | 1.7 |
| **8h** | 339 | 620 | 1.34 | 20.4 | 0.02[d] | 0.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **8j** | 343 | 579 | 1.19 | 29.7 | 0.07[d] | 2.1 |
| | 469 | | 0.41 | 7.1 | 0.10[d] | 0.7 |
| **8q** | 285 | 529 | 1.62 | 27.1 | 0.11[d] | 3.0 |
| | 468 | | 0.25 | 14.7 | 0.34[d] | 5.1 |
| **8r** | 285 | 524 | 1.60 | 22.2 | 0.22[d] | 4.9 |
| | 484 | | 0.16 | 10.3 | 0.37[d] | 4.0 |
| **9a** | 398 | 458 | 0.33 | 6.1 | 0.45[c] | 2.7 |
| **9b** | 399 | 437 | 0.22 | 12.8 | 0.47[c] | 6.0 |
| **9c** | 399 | 503 | 0.52 | 8.9 | 0.18[c] | 1.6 |
| **10b** | 287 | 464 | 1.33 | 25.9 | 0.18[c] | 4.7 |
| | 333 | | 0.85 | 6.7 | 0.44[c] | 2.9 |
| | 420 | | 0.23 | 8.4 | 0.49[c] | 4.0 |
| **10e** | 280 | 467 | 1.43 | 10.6 | 0.14[c] | 1.5 |
| | 424 | | 0.22 | 3.0 | 0.43[c] | 1.3 |

[a]Excitation-emission fluorescence spectra were acquired in MeOH at a concentration of 5 $\mu$M. [b] Maxima of major well-defined bands. [c]A 5 $\mu$M solution of quinine in 0,5 M $H_2SO_4$ was used as quantum yield standard ($\Phi_F$ = 0.60).[34b] [d] A 0.1 $\mu$M solution of fluorescein in 0,1 M NaOH was used as quantum yield standard ($\Phi_F$ = 0.92).[34c]

**Tether groups and biolabelling.** Most applications of small molecule fluorophores involve their grafting onto biomolecules *via* a covalent tether. The fused benzene ring of benzo[*a*]imidazo[2,1,5-*c,d*]indolizines is a very convenient attaching point for tether group precursors introduced through the acyl chloride building block (**Scheme 5**). Unconjugated substitution has very little effect on photophysical properties (**Table 4**, compare **7a** with **10e**). The fluorescent core tolerates heat, acids or bases, allowing traditional functional group manipulations without degradation. The nitrile **7j** is readily reduced to the corresponding primary benzylic ammonium chloride, making the molecule highly water soluble.[35] The methyl ester **7i** can be hydrolyzed to the acid **10a**, thermally amidated (**10b**) or reduced to the benzylic alcohol **10c**. The sodium salt of **10a** is also highly water soluble.[35] A primary glycol monoether (**7e**) can be obtained from hydrolysis of a benzoyl protecting group, allowing the tethering of electron-richer fluorophores similar to compounds **7d** and **8f-8i**.

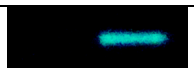
**Scheme 5. Post-cyclization derivatizations to include reactive tether groups.**




In light of these results, we sought to demonstrate the applicability of our fluorophores as probes for biological targets. Site-specific protein labelling remains a field of high interest within biotechnology, with biocatalysis representing a promising alternative to traditional metal-catalyzed conjugation.[36] Advantages include high specificity and compatibility with biological media.

Microbial transglutaminase (MTG) was selected to serve this purpose.[37] The acyl-transfer reaction catalyzed by MTG forms an amide linkage between a primary amine and a glutamine residue on the substrate protein. Here, we were able to take advantage of MTG's broad specificity for primary amines[38] in conjunction with the highly customizable nature of our fluorophores. The primary ammonium salt **10e** was both reactive with MTG and soluble in aqueous media. We selected α-lactalbumin and the immunoglobulin-binding domain B1 of streptococcal protein G (GB1) as model glutamine-containing protein substrates. The reactivity of MTG with α-lactalbumin has been extensively characterized, including for chemoenzymatic protein labelling.[39] Its reactivity with protein GB1 has not yet been reported. To prevent non-specific labelling with other glutamine-containing substrates, the reactions were carried out *in vitro* with purified protein substrates. (Table 5) Both proteins were successfully labelled, illustrating the biological compatibility of benzo[*a*]imidazo[2,1,5-*c,d*]indolizines and the potential that these fluorophores have in the field of biocatalyzed bioconjugation.

**Table 5. Fluorophore-conjugated α-LA and GB1 proteins.**

| Target Protein | α-LA | | GB1 | |
|---|---|---|---|---|
| MTG | - | + | - | + |
| Coomassie staining |  | |  | |
| UVA irradiation |  | |  | |

Target protein and **10e** were incubated overnight in presence or absence of MTG in pH 7.4 buffer and resolved by gel electrophoresis.

In summary, we have developed an efficient divergent synthesis yielding a series of strained heteroaromatic fluorophores. Choice of building blocks for the amidation and electrophilic arylation steps enables the introduction of diverse functional groups. A linear relationship with Hammett constants allow the prediction of emission maxima before synthesis. Coverage of most of the visible spectrum was achieved by varying the substituents on three series of molecules based on the same core. Reactive functional groups can be linked to the tetracyclic core without affecting photophysical properties, enabling covalent tethering to biomolecules and materials. Some of the insights gathered in this article are likely applicable to other similar fluorescent polyheterocycles,[13] broadening their impact. Thorough determination of properties as well as the predictive model will help researchers chose the optimal fluorescent target to suit their specific needs. We believe benzo[*a*]imidazo[2,1,5-*c,d*]indolizines' high chemical stability, excitation-emission differential and tuneability make them promising tools for the fields of fluorescent microscopy and photoactive materials and devices.

## EXPERIMENTAL SECTION

**General remarks.** Unless otherwise stated, all glassware was stored in the oven and/or was flame-dried prior to use. All reactions were set up under an argon atmosphere[40] while adding reagents and were run with the exclusion of moisture. All reaction flasks were kept closed with a septum during the reaction time. Anhydrous solvents were obtained either by filtration through alumina or molecular sieves (THF, $CH_2Cl_2$, DMF, $CH_3CN$, toluene) or by distillation over $CaH_2$ (MeOH), BaO (DMA) or Na (1,4-Dioxane). Anhydrous EtOH and AcOH were used as is from commercial bottles. Analytical thin-layer chromatography

(TLC) was performed on precoated, glass-backed silica gel. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), UV fluorescence (368 nm), aqueous potassium permanganate ($KMnO_4$) or cerium ammonium molybdate (CAM). Flash column chromatography was performed on an automatic purification system using prepacked normal phase silica gel columns (12 g, 24 g, 40 g, 80 g and 120 g). Melting points are uncorrected. Chemical shifts for $^1$H NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of chloroform ($CHCl_3$) (δ = 7.26 ppm), MeOH (δ = 3.31 ppm) or HDO (δ = 4.79 ppm) as the internal standard. Chemical shifts for $^{13}$C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (δ = 77.16 ppm) or MeOH (δ = 49.15 ppm), as the internal standard. All $^{13}$C NMR spectra were obtained with complete proton decoupling. Chemical shifts for $^{19}$F NMR spectra are recorded in parts per million from trichlorofluoromethane using the central peak of trifluorotoluene (δ = -63.72 ppm) as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, h = heptet, m = multiplet and br = broad), coupling constant (*J*) in Hz and integration. Infrared spectra are reported in reciprocal centimeters ($cm^{-1}$). High resolution mass spectra were performed on a TOF analyser. Excitation-emission fluorescence spectra were acquired on a PTI fluorimeter (excitation bandwidth = 2.6 nm, emission bandwidth = 1.3 nm) with 1 mm slits and temperature set at 20 °C. Fluorophores were dissolved in MeOH or $H_2O$ (no significant spectrum change observed, both solvents tested for for **7a**, **9a** and **10e**) at a concentration of 5 $\mu$M. Absorbance spectra were acquired at a 25 $\mu$M concentration in MeOH.

**Reagents**. Unless otherwise stated, commercial reagents were used without purification. Triethylamine ($Et_3N$) was distilled over calcium hydride and kept under argon before use. Trifluoromethanesulfonic anhydride ($Tf_2O$) was made by heating TfOH on $P_4O_{10}$, distilled and kept under argon in a Schlenk flask before use. 6-bromopyridine-2-carbaldehyde[41], 4-(2-hydroxyethoxy)-benzoic acid[42], benzoic-2-*d* acid[43] and $[Pd(phen)_2][PF_6]_2$[21d] were synthesized according to previously reported procedures.

**Synthesis of starting material**

**4-[2-(Benzoyloxy)ethoxy]benzoic acid:** To a flame-dried 50 mL round bottom flask equipped with a magnetic stirbar and a rubber septum were dissolved 4-(2-hydroxyethoxy)benzoic acid (0.75 g, 4.1 mmol, 1.0 equiv), pyridine (0.83 mL, 10 mmol, 2.5 equiv) and 4-dimethylaminopyridine (50 mg, 0.41 mmol, 0.10 equiv) in $CH_2Cl_2$ (12 mL, 0.34 M). Benzoyl chloride (1.0 mL, 8.6 mmol, 2.1 equiv) was added dropwise and mixture was stirred at room temperature for 20 h. 1.0 M HCl (20 mL) was added and mixture was stirred for 1 h. Phases were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were washed with 2.0 M HCl and dried over anhydrous $MgSO_4$, filtered over a sintered funnel and evaporated to dryness. The residue was purified by flash chromatography using a gradient of 0% to 15% MeOH in 0.5 % AcOH/$CH_2Cl_2$. The fractions containing the pure product were combined and evaporated to dryness. 4-[2-(benzoyloxy)ethoxy]benzoic acid was isolated as a white solid (0.85 g, 72% yield). **mp**: 170-173 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.04-8.01 (m, 2H), 8.00-7.96 (m, 2H), 7.63-7.58 (m, 1H), 7.49-7.45 (m, 2H), 7.07-7.03 (m, 2H), 4.68 (t, *J* = 4.5 Hz, 2H), 4.43 (t, *J* = 4.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 169.9, 167.9, 164.0, 134.4, 132.9, 131.2, 130.6, 129.6, 124.8, 115.4, 67.4, 64.6; **FTIR** ($cm^{-1}$) (neat):

2931, 1716, 1685, 1603, 1425, 1278, 1248, 1170, 708; **HRMS** (ESI, Pos): calcd for $C_{16}H_{15}O_5$ $[M+H]^+$: 287.0914 *m/z*, found 287.0914 *m/z*.

**Revised synthesis of (6-bromopyridin-2-yl)methanamine**

**6-Bromopyridine-2-carbaldehyde (2):** Following a literature procedure[41] the product was obtained as a beige solid (4.7 g, 80% yield). The crude mixture was purified by recrystallization from boiling hexanes (reflux to -20°C) instead of chromatography. **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 10.01 (d, *J* = 0.5 Hz, 2H), 4.68 (dd, *J* = 7.0 Hz, *J* = 1.5 Hz, 2H), 7.78-7.71 (m, 2H).

**6-Bromopyridine-2-carbaldehyde oxime (3a):** To a 10 mL round-bottom flask equipped with a magnetic stirbar and a rubber septum were added 6-bromopyridine-2-carbaldehyde (0.30 g, 1.6 mmol, 1.0 equiv), hydroxylammonium sulfate ($(NH_3OH)_2SO_4$) (0.19 g, 1.1 mmol, 0.7 equiv) and sodium acetate (0.20 g, 2.4 mmol, 1.5 equiv). EtOH (4.0 mL, 0.4 M) was added and heterogenous mixture was vigorously stirred at room temperature for 16h. $MgSO_4$ was added and mixture was filtered on cotton and concentrated under vacuum to yield a white solid. This was suspended in 2% MeOH/$CH_2Cl_2$ and filtered through a short silica plug. The filtrate was concentrated under vacuum to yield 6-bromopyridine-2-carbaldehyde oxime as a white solid (325mg, quantitative yield). **mp**: 164-166 °C; **$^1$H NMR** (DMSO, 500 MHz): δ 8.03 (s, 1H), 7.83 (dd, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.69 (dt, *J* = 8.0 Hz, *J* = 0.5 Hz, 1H), 7.55 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 155.1, 148.8, 142.5, 140.6, 129.3, 120.3; **FTIR** ($cm^{-1}$) (neat): 3200, 3003, 1545, 1157, 1119, 976, 943, 786, 704; **HRMS** (ESI, Pos): calcd for $C_6H_6BrN_2O$ $[M+H]^+$: 200.9658 *m/z*, found 200.9665 *m/z*.

**6-Bromopyridin-2-yl)methanammonium acetate (4a):** To a 5 mL round-bottom flask equipped with a magnetic stirbar and a rubber septum were added 6-bromopyridine-2-carbaldehyde oxime (50 mg, 0.25 mmol, 1.0 equiv) and AcOH (2.0 mL, 0.13 M). Zinc (49 mg, 0.75 mmol, 3.0 equiv) was poured in the flask in one portion. Mixture was stirred at room temperature for 10 minutes and filtered over Celite. The filtrate was concentrated under vacuum to yield and off-white solid (140 mg) containing 6-bromopyridin-2-yl)methanammonium acetate (58 mg, 0.24 mmol, 95% yield) and zinc acetate (82 mg, 0.45 mmol). **mp**: 200-210 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.81 (t, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 8.0 Hz, *J* = 0.5 Hz, 1H), 7.46 (dd, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 4.23 (s, 2H), 1.98 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 180.2, 159.3, 142.1, 141.7, 129.3, 122.7, 44.2, 22.3; **FTIR** ($cm^{-1}$) (neat): 3264, 2997, 1544, 1388, 1333, 1169, 1019, 675, 613; **HRMS** (ESI, Pos): calcd for $C_6H_8BrN_2$ $[M+H]^+$: 186.9870 *m/z*, found 186.9871 *m/z*.

**Literature synthesis of (6-bromopyridin-2-yl)methanamine[15, 44]**

**2-[(6-Bromopyridin-2-yl)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (3b):** To a flame-dried 1000 mL round bottom flask equipped with a magnetic stirbar and a rubber septum was added 2-bromo-6-hydroxymethylpyridine (8.7 g, 46 mmol, 1.0 equiv). The alcohol was diluted with anhydrous THF (0.46 L, 0.10 M) and then 1,1'-(azodicarbonyl)dipiperidine (15 g, 60 mmol, 1.3 equiv) was added. The orange solution was then stirred at room temperature for 2 minutes. Then, triphenylphosphine (16 g, 60 mmol, 1.3 equiv) and phthalimide (8.9 g, 60 mmol, 1.3 equiv) were added successively. The reaction was then stirred for 24 h at room temperature (the solution was clear and orange). The reaction was then cooled to 0 °C and a solid precipitate was formed. The cooled suspension was then filtered on a Buchner filter and the cake was washed thoroughly with cold THF.

The filtrate was then evaporated to dryness. The residue was then quenched by addition of a saturated aqueous solution of $NaHCO_3$ (30 mL) and diluted with EtOAc (100 mL). The biphasic layers were transferred to a 250 mL extraction funnel and the aqueous layer was then extracted with EtOAc (3x). The organic layers were combined and dried over anhydrous $Na_2SO_4$, filtered over a sintered funnel and evaporated to dryness. The residue was then purified by flash chromatography using a gradient of 30% to 100% EtOAc in hexanes while using a drypack to inject the crude mixture. The fractions containing the pure product were combined and evaporated to dryness. 2-[(6-Bromopyridin-2-yl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione was obtained as a crystalline white solid (12.3 g, 84% yield). **mp**: 118-119 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.92-7.91 (m, 2H), 7.78-7.76 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 5.01 (s, 2H). Product corresponds to previously reported characterization data.[15]

**(6-Bromopyridin-2-yl)methanamine (4b):** A suspension of 2-[(6-bromopyridin-2-yl)methyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (12.3 g, 38.6 mmol, 1.0 equiv) in absolute ethanol (0.39 L, 0.10 M) was charged in a 1000 mL round bottom flask equipped with a magnetic stirbar and a condenser and heated to reflux until complete dissolution (around 15 min). To the homogeneous solution was added hydrazine monohydrate 65% (11.5 mL, 154 mmol, 4.0 equiv). Within a minute, the reaction mixture became yellow. The reaction mixture was heated at reflux for 7 h during which time the mixture solidified into a white thick suspension. An additional 50 mL of ethanol was added, and the mixture was kept stirring for an extra 2 h. The reaction was cooled down to 0 °C to precipitate the hydrazine/phthalimide adduct. The precipitate was filtered on a Buchner and washed with absolute ethanol. The filtrate was partially concentrated. Remaining solids in the suspension were again filtered off and washed with cold EtOH. The filtrate was concentrated to dryness to yield an orange oil. (6.3 g, 87% yield). **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.57-7.50 (m, 1H), 7.40-7.35 (m, 1H), 7.31-7.27 (m, 1H), 3.98 (br s, 2H), 1.73 (br s, 2H). Product corresponds to previously reported characterization data.[15]

**General procedures for the synthesis of amides**

**Procedure A:**

To a round bottom flask equipped with a magnetic stirrer and a rubber septum was added the (6-bromopyridin-2-yl)methanamine (1.0 equiv) **4a** as previously synthesized. The amine was diluted with CH2CL2 (0.2 M) and cooled to 0 °C using an ice/water cooling bath. Triethylamine (1.2 equiv) was added via syringe followed by the acyl chloride (1.1 equiv). The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched by addition of a saturated aqueous solution of $Na_2CO_3$, phases were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness.

**Procedure B:**

To a round bottom flask equipped with a magnetic stirrer and a rubber septum was added the (6-bromopyridin-2-yl)methanamine (1.0 equiv) **4b** as previously synthesized. The amine was diluted with $CH_2Cl_2$ (0.2 M). Triethylamine (1.5 equiv) was added via syringe followed by the carboxylic acid (1.1 equiv) and *N,N,N′,N′*-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) (1.5 equiv). The reaction was quenched by addition of a saturated aqueous solution

of $Na_2CO_3$, phases were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness.

**Procedure C:**

To a round bottom flask equipped with a magnetic stirrer and rubber septum was added the (6-bromopyridin-2-yl)methanammonium acetate salt (1.0 equiv) **4a** as previously synthesized. The amine was diluted with $CH_2Cl_2$ (0.2 M) and cooled to 0 °C using an ice/water cooling bath. Triethylamine (5.0 equiv) was added via syringe followed by the acyl chloride (1.3 equiv). The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched by addition of a saturated aqueous solution of $Na_2CO_3$, phases were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness.

**General procedure for acyl chloride synthesis:**

To a round-bottomed flask equipped with a magnetic stirrer and rubber septum was added the carboxylic acid (1.0 equiv), DMF (0.05 equiv) and $CH_2Cl_2$ (0.26 M). Oxalyl chloride (2.0 equiv) was added dropwise (gas evolution). Mixture was stirred for 2h, evaporated to dryness and used as is.

**Characterization data of amides**

***N*-((6-Bromopyridin-2-yl)methyl)benzamide (5a)**: Following **procedure A**. The crude amide was dissolved in a minimal amount of hot EtOAc and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes, resulting in a white solid (0.81 g, 93% yield). **mp**: 130-131 °C, lit:[15] 130-131 °C; **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.87-7.81 (m, 2H), 7.55-7.29 (m, 7H), 4.71 (d, *J* = 5.5 Hz, 2H). Product corresponds to previously reported characterization data.[15]

***N*-((6-Bromopyridin-2-yl)methyl)-[1,1'-biphenyl]-4-carboxamide (5b):** Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 30% to 100% EtOAc in hexanes. Fractions containing **5b** were concentrated to dryness, resulting in a white solid (0.78 g, 71% yield). **mp**: 168-169 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.93-7.91 (m, 2H), 7.69-7.67 (m, 2H), 7.63-7.61 (m, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.48-7.45 (m, 2H), 7.43.7.34 (m, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.29 (br s, 1H), 4.76 (d, *J* = 5.0 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 136.2, 158.3, 144.5, 141.7, 140.0, 139.2, 132.7, 128.9, 128.0, 127.6, 127.3, 127.2, 126.9, 121.2, 44.5; **FTIR** ($cm^{-1}$) (neat): 3259, 1637, 1541, 781, 736, 690, 675; **HRMS** (ESI, Pos): calcd for $C_{19}H_{15}BrN_2O$ $[M+H]^+$: 367.0440 *m/z*, found: 367.0444 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-4-(*tert*-butyl)benzamide (5c)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 30% to 70% EtOAc in hexanes. Fractions containing **5c** were concentrated to dryness, resulting in a white solid (1.0 g, 96% yield). **mp**: 162-164 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.79-7.77 (m, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.48-7.47 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.15 (br s, 1H), 4.73 (d, *J* = 5.5 Hz, 2H), 1.34 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 167.4, 158.5, 155.2, 141.6, 139.2, 131.2, 126.9, 126.8, 125.6, 121.2, 44.5, 35.0, 31.2; **FTIR** ($cm^{-1}$) (neat): 3357, 3313, 2959, 2928, 2902, 1634, 1555, 1543, 1309, 982, 780, 658; **HRMS** (ESI, Pos): calcd for $C_{17}H_{19}BrN_2O$ $[M+H]^+$: 347.0754 *m/z*, found: 347.0755 *m/z*.

**4-(Benzyloxy)-N-((6-bromopyridin-2-yl)methyl)benzamide (5d)**: Following **procedure B**. The crude amide was purified by flash chromatography over silica gel using a gradient of 0% to 80% EtOAc in hexanes. Fractions containing **5d** were concentrated to dryness, resulting in a white solid (0.90 g, 76% yield). **mp**: 133-135 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.82-7.79 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45-7.37 (m, 5H), 7.36-7.31 (m, 2H), 7.11 (br t, *J* = 4.5 Hz, 1H), 7.03-7.00 (m, 2H), 5.12 (s, 2H), 4.71 (d, *J* = 5.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 166.9 161.5, 158.5, 141.6, 139.2, 136.4, 129.0, 128.7, 128.2, 127.5, 126.8, 126.6, 121.2, 114.7, 70.1, 44.5; **FTIR** ($cm^{-1}$) (neat): 3362, 1637, 1604, 1537, 1501, 1248, 1113, 767, 734; **HRMS** (ESI, Pos): calcd for $C_{20}H_{17}BrN_2O_2$ $[M+H]^+$: 397.0546 *m/z*, found: 397.0541 *m/z*.

**2-(4-(((6-Bromopyridin-2-yl)methyl)carbamoyl)phenoxy)ethyl benzoate (5e)**: Following **procedure C**. The crude amide was dissolved in a minimal amount of hot EtOAc and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes. The residue was dissolved in 25% EtOAc/$CH_2Cl_2$, washed with saturated $NaHCO_3$ (2X), dried with MgSO4 and filtrated on a short silica gel column (washing with 25% EtOAc/$CH_2Cl_2$). Filtrate was concentrated to dryness, resulting in a beige solid (0.66 g, 90% yield). **mp**: 121-123 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.04 (dd, *J* = 1.0 Hz, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.58-7.50 (m, 2H), 7.45-7.37 (m, 3H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.24 (br t, *J* = 5.0 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 4.71-4.66 (m, 4H), 4.35 (t, *J* = 5.0 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 167.0, 166.6, 161.4, 158.7, 141.6, 139.3, 133.3, 129.8 (2), 129.1, 128.5, 126.9 (2), 121.3, 114.6, 66.2, 63.2, 44.6; **FTIR** ($cm^{-1}$) (neat): 3313, 2968, 1708, 1278, 1248, 1119, 1069, 713, 665; **HRMS** (ESI, Pos): calcd for $C_{22}H_{20}BrN_2O_4$ $[M+H]^+$: 455.0608 *m/z*, found: 455.0601*m/z*.

***N*-((6-bromopyridin-2-yl)methyl)-4-(dimethylamino)benzamide (5f)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 30% to 70% EtOAc in hexanes. Fractions containing **5f** were concentrated to dryness, resulting in a white solid (0.56 g, 56% yield). **mp**: 155-157 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.00 (br t, *J* = 5.5 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 4.70 (d, *J* = 6.0 Hz, 2H), 3.02 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 167.4, 159.1, 152.6, 141.5, 139.1, 128.6, 126.6, 121.2, 120.8, 111.1, 44.5, 40.1; **FTIR** ($cm^{-1}$) (neat): 3276, 2921, 1626, 1604, 1514, 1302, 1115, 769, 665; **HRMS** (ESI, Pos): calcd for $C_{15}H_{17}BrN_3O$ $[M+H]^+$: 334.0550 *m/z*, found: 334.0544 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-4-fluorobenzamide (5g)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 0% to 50% EtOAc in hexanes. Fractions containing **5g** were concentrated to dryness, resulting in a white solid (0.87 g, 94% yield). **mp**: 111-113 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.87-7.83 (m, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.25 (br s, 1H), 7.15-7.10 (m, 2H), 4.71 (d, *J* = 5.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 166.4, 164.9 (d, $J_{C\text{-}F}$ = 250 Hz), 158.0, 141.7, 139.2, 130.3. 130.3, 129.4 (d, $J_{C\text{-}F}$ = 8.9 Hz), 126.9, 121.2, 115.7 (d, $J_{C\text{-}F}$ = 21.8 Hz); **$^{19}$F NMR** ($CDCl_3$, 282 MHz): δ -108.0 (s, F); **FTIR** ($cm^{-1}$) (neat): 3355, 1638, 1504, 847, 764, 599; **HRMS** (ESI, Pos): calcd for $C_{13}H_{10}BrFN_2O$ $[M+H]^+$: 309.0033 *m/z*, found: 309.0033 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-4-chlorobenzamide (5h)**: Following **procedure C**. The crude amide was dissolved in a minimal amount of hot EtOAc and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes, resulting in a yellowish solid (30 mg, 92% yield). **mp**: 105-107 °C; **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 7.79

(d, *J* = 8.7 Hz, 2H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 3H), 7.34 (d, *J* = 7.5 Hz, 1H), 4.72 (d, *J* = 5.4 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 166.5, 158.2, 141.7, 139.4, 138.0, 132.5, 129.0, 128.7, 127.0 121.3, 44.6; **FTIR** ($cm^{-1}$) (neat): 3328, 2923, 1636, 1542, 1310, 1093, 847, 774, 658; **HRMS** (ESI, Pos): calcd for $C_{13}H_{10}BrClN_2NaO$ $[M+Na]^+$: 346.95572 *m/z*, found: 346.95592 *m/z*.

**Methyl 4-(((6-bromopyridin-2-yl)methyl)carbamoyl)benzoate (5i)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 30% to 100% EtOAc in hexanes. Fractions containing **5i** were concentrated to dryness, resulting in a white solid (0.88 g, 84% yield). **mp**: 149-151 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.04-8.02 (m, 2H), 7.84-7.82 (m, 2H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.35 (dd, *J* = 0.5, 8.0 Hz, 1H), 7.25 (dd, *J* = 0.5, *J* = 7.5 Hz, 1H), 4.66 (d, *J* = 5.5 Hz, 2H), 3.87 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 166.7, 166.4, 158.0, 141.8, 139.4, 138.1, 133.0, 130.0,127.3, 127.1, 121.3, 52.5, 44.7; **FTIR** ($cm^{-1}$) (neat): 3275, 3040, 2959, 2864, 2844, 1721, 1637, 1279, 716; **HRMS** (ESI, Pos): calcd for $C_{15}H_{13}BrN_2O_3$ $[M+H]^+$: 349.0198 *m/z*, found: 349.0198 *m/z*. Compound **5i** was also synthesized via **procedure C** (0.21 g, 59% yield).

***N*-((6-Bromopyridin-2-yl)methyl)-4-cyanobenzamide (5j)**: Following **procedure C**. The crude amide was dissolved in a minimal amount of hot EtOAc and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes, resulting in a beige solid (0.90 mg, 71% yield). **mp**: 127-128 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.89-7.87 (m, 2H), 7.70-7.68 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.37-7.36 (m, 2H), 7.25 (dd, *J* = 0.5, *J* = 7.5 Hz, 1H), 4.66 (d, *J* = 5.0 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 165.7, 157.5, 141.8, 139.4, 138.1, 132.6, 127.9, 127.2, 121.3, 118.1, 115.4, 44.6; **FTIR** ($cm^{-1}$) (neat): 3304, 3066, 2973, 2939, 2933, 2864, 2844, 2825, 2230, 1643, 1554, 1306, 672; **HRMS** (ESI, Pos): calcd for $C_{14}H_{10}BrN_3O$ $[M+H]^+$: 316.0080 *m/z*, found: 316.0087 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-3,4,5-trimethoxybenzamide (5k)**: Following **procedure A**. The crude amide was dissolved in a minimal amount of hot EtOAc and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes, resulting in a beige solid (1.0 g, 89% yield). **mp**: 115-117 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.55 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.30-7.35 (m, 2H), 7.08 (s, 2H), 4.70 (d, *J* = 5.6 Hz, 2H), 3.90 (s, 6H), 3.88 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 167.2, 158.4, 153.3, 141.6, 141.1, 139.5, 129.5, 127.0, 121.5, 104.5, 61.0, 56.4, 44.6; **FTIR** ($cm^{-1}$) (neat): 3303, 2937, 1580, 1496, 1410, 1325, 1230, 1119, 1000; **HRMS** (ESI, Pos): calcd for $C_{16}H_{18}BrN_2O_4$ $[M+H]^+$: 381.0445 *m/z*, found: 381.0451 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-2-ethoxy-4-nitrobenzamide (5l)**: Following **procedure B**. The crude amide was purified by flash chromatography over silica gel using a gradient of 0% to 20% EtOAc in $CH_2Cl_2$. Fractions containing **5l** were concentrated to dryness, resulting in a white solid (0.75 g, 66% yield). **mp**: 136-138 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.93 (s, 2H), 8.40 (d, *J* = 8.4 Hz, 1H), 7.91 (dd, *J* = 2.0, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 4.80 (d, *J* = 4.8 Hz, 1H), 4.39 (q, *J* = 6.8 Hz, 1H), 1.65 (t, *J* = 6.8 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 163.5, 158.0, 157.3, 150.4, 141.9, 139.3, 133.5, 127.0, 126.8, 121.1, 115.8, 107.6, 66.1, 45.0, 14.9; **FTIR** ($cm^{-1}$) (neat): 3347,

1653, 1522, 1433, 1229, 1024, 866, 789, 735; **HRMS** (ESI, Pos): calcd for $C_{15}H_{15}BrN_3O_4$ $[M+H]^+$: 380.0241 *m/z*, found: 380.02518*m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-2,3,4,5-tetrafluorobenzamide (5m)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 50% to 80% EtOAc in hexanes. Fractions containing **5m** were concentrated to dryness, resulting in a white solid (0.91 mg, 84% yield). **mp**: 126-128 °C; **$^1$H NMR** ($CDCl_3$, 700 MHz): δ 7.82-7.76 (m, 2H), 7.59 (t, *J* = 10.5 Hz, 1H), 7.46 (dd, *J* = 0.7, 11.2 Hz, 1H), 7.33 (dd, *J* = 0.7, 10.5 Hz, 1H), 4.75 (d, *J* = 4.9 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 175 MHz): δ 160.5, 157.1, 147.9 (d, $J_{C\text{-}F}$ = 7.0 Hz), 147.0 (d, $J_{C\text{-}F}$ = 9.3 Hz), 146.48 (d, $J_{C\text{-}F}$ = 9.8 Hz), 145.6 (d, $J_{C\text{-}F}$ = 9.5 Hz), 143.4 (ddd, $J_{C\text{-}F}$ = 3.5, 12.4, 16.5 Hz), 141.9 (ddd, $J_{C\text{-}F}$ = 3.5, 12.4, 16.5 Hz), 141.4 (ddd, $J_{C\text{-}F}$ = 3.5, 12.8, 18.9 Hz), 140.0 (ddd, $J_{C\text{-}F}$ = 3.2, 12.4, 18.4 Hz), 139.3, 127.1, 120.9, 117.2, 112.8 (d, $J_{C\text{-}F}$ = 2.8 Hz), 44.7; **$^{19}$F NMR** ($CDCl_3$, 282 MHz): δ -153.7 to -153.6 (m, F), -148.9 to -148.8 (m, F), -138.8 to -138.7 (m, F), -136.8 to -136.7 (m, F).; **FTIR** ($cm^{-1}$) (neat): 3392, 3078, 1667, 1503, 1474, 792, 772; **HRMS** (ESI, Pos): calcd for $C_{13}H_7BrF_4N_2O$ $[M+H]^+$: 362.9751 *m/z*, found: 362.9752 *m/z*.

**Benzyl 4-(((6-bromopyridin-2-yl)methyl)carbamoyl)benzenesulfonate (5n)**: Following **procedure B**. The crude amide was purified by flash chromatography over silica gel using a gradient of 0% to 100% EtOAc in hexanes. Fractions containing **5n** were concentrated to dryness, resulting in a white solid (0.40 g, 42% yield). **mp**: 90-91 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 9.11 (br t, *J* = 6.0 Hz, 1H), 8.24 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.46 (ddd, *J* = 1.5, 7.0, 7.5 Hz, 1H), 7.39 (dd, *J* = 0.5, 8.0 Hz, 1H), 7.32 (dd, *J* = 0.5, 7.5 Hz, 1H), 7.08 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.00 (dd, *J* = 1.0, 8.0 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 2H), 4.07 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 165.5, 159.0, 158.0, 141.6, 139.2, 133.1, 132.4, 126.6, 121.3, 121.2, 121.1, 111.5, 56.1, 44.8; **FTIR** ($cm^{-1}$) (neat):3348, 2922, 1638, 1511, 1434, 1233, 1158, 1023, 780, 753, 618; **HRMS** (ESI, Pos): calcd for $C_{14}H_{14}BrN_2O_2$ $[M+H]^+$: 321.0233 *m/z*, found: 321.0225 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-1-naphthamide (5o)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 10% to 50% EtOAc in hexanes. Fractions containing **5o** were concentrated to dryness, resulting in a white solid (0.90 g, 86% yield). **mp**: 154-155 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.41-8.37 (m, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.89-7.86 (m, 1H), 7.70 (dd, *J* = 1.5, 7.0 Hz, 1H), 7.59-7.51 (m, 3H), 7.50-7.46 (m, 1H), 7.43 (dd, *J* = 0.5, 7.5 Hz, 1H), 7.38 (dd, *J* = 0.5, 7.5 Hz, 1H) 7.04 (br s, 1H), 4.83 (d, *J* = 5.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 169.6, 158.2, 141.7, 139.3, 134.0, 133.7, 130.9, 130.2, 128.3, 127.2, 126.9, 126.5, 125.5, 125.3, 124.8, 121.1, 44.5; **FTIR** ($cm^{-1}$) (neat): 3244, 1638, 1536, 1427, 1404, 1308, 778, 767, 714; **HRMS** (ESI, Pos): calcd for $C_{17}H_{13}BrN_2O$ $[M+H]^+$: 341.0284 *m/z*, found: 341.0292 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-9-oxo-9H-fluorene-2-carboxamide (5p)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 20% to 80% EtOAc in hexanes. Fractions containing **5p** were concentrated to dryness, resulting in a yellow solid (0.75 g, 74% yield). **mp**: 192-194 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.10-8.06 (m, 2H), 7.71 (d, *J* = 5.0 Hz, 2H), 7.65-7.52 (m, 4H), 7.43 (d, 7.5 Hz, 1H), 7.39-7.33 (m, 2H), 7.22 (s, 1H), 4.75 (d, *J* = 5.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 192.8, 166.2, 158.0, 147.3, 143.5, 141.8, 139.3, 135.0, 134.9, 134.6, 134.3,

130.0, 127.0, 124.6, 122.4, 121.1 (2), 120.6, 44,6; **FTIR** ($cm^{-1}$) (neat): 3405, 1703, 1656, 1614, 1578, 1265, 738, 583; **HRMS** (ESI, Pos): calcd for $C_{20}H_{13}BrN_2O_2$ $[M+H]^+$: 393.0233 *m/z*, found: 393.0242 *m/z.*

***N*-((6-Bromopyridin-2-yl)methyl)furan-2-carboxamide (5q)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 40% to 70% EtOAc in hexanes. Fractions containing **5q** were concentrated to dryness, resulting in a white solid (0.73 g, 87% yield). **mp**: 117-118 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.50-7.42 (m, 3H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.28 (dd, *J* = 0.5, 7.5 Hz, 1H), 7.09 (dd, *J* = 1.0, 3.5 Hz, 1H), 6.46 (dd, *J* = 1.5, 3.0 Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 158.5, 158,5, 147.6, 144.3, 141.6, 139.2, 126.8, 120.9, 114.5, 112.1, 43.9; **FTIR** ($cm^{-1}$) (neat): 3235, 1636, 1526, 1014, 771, 762, 629, 601; **HRMS** (ESI, Pos): calcd for $C_{11}H_9BrN_2O_2$ $[M+H]^+$: 280.9920 *m/z*, found: 280.9921 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)thiophene-2-carboxamide (5r)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 40% to 100% EtOAc in hexanes. Fractions containing **5r** were concentrated to dryness, resulting in a white solid (0.75 g, 84% yield). **mp**: 123-127 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.57 (dd, *J* = 1.5, 4.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 1.0, 5.0 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.10-7.05 (m, 2H), 4.69 (d, *J* = 5.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 161.9, 158.1, 141.6, 139.3, 138.5, 130.3, 128.4, 127.7, 126.9, 121.2, 44.4; **FTIR** ($cm^{-1}$) (neat): 3319, 3083, 2981, 2968, 2934, 1552, 1305, 721, 679; **HRMS** (ESI, Pos): calcd for $C_{11}H_9BrN_2OS$ $[M+H]^+$: 296.9692 *m/z*, found: 296.9690 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)-1-naphthamide (5s)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 40% to 100% EtOAc in hexanes. Fractions containing **5s** were concentrated to dryness, resulting in a white solid (0.74 g, 72% yield). **mp**: 53-54 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.54-7.50 (m, 3H), 7.40-7.34 (m, 4H), 7.30 (dd, *J* = 1.0, 7.5 Hz, 1H), 6.77 (br s, 1H), 6.52 (d, *J* = 15.5 Hz, 1H), 4.66 (d, *J* = 5.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ168.4, 158.4, 141.6, 139.6, 139.2, 126.8, 121.1, 120.2, 44.2, 18.6; **FTIR** ($cm^{-1}$) (neat): 3327, 3083, 2924, 1657, 1616, 1583, 1556, 1521, 1435, 1405, 1121, 776; **HRMS** (ESI, Pos): calcd for $C_{10}H_{11}BrN_2O$ $[M+H]^+$: 255.0128 *m/z*, found: 255.0140 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)cinnamamide (5t)**: Following **procedure A**. The crude amide was purified by flash chromatography over silica gel using a gradient of 40% to 100% EtOAc in hexanes. Fractions containing **5t** were concentrated to dryness, resulting in a white solid (0.77 g, 80% yield). **mp**: 120-122 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.54-7.50 (m, 3H), 7.40-7.34 (m, 4H), 7.30 (dd, *J* = 1.0, 7.5 Hz, 1H), 6.77 (br s, 1H), 6.52 (d, *J* = 15.5 Hz, 1H), 4.66 (d, *J* = 5.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 166.0, 158.3, 141.6, 141.6, 139.2, 134.7, 129.8, 128.8, 127.9, 126.8, 121.2, 120.28, 44.4; **FTIR** ($cm^{-1}$) (neat): 3232, 3064, 3032, 2982, 2970, 2946, 1652, 1613, 1578, 1551, 731, 684, 671; **HRMS** (ESI, Pos): calcd for $C_{15}H_{13}BrN_2O$ $[M+H]^+$: 317.0284 *m/z*, found: 317.0283 *m/z*.

***N*-((6-Bromopyridin-2-yl)methyl)benzamide-2-*d* (5a(*ortho*-$d_1$))**: Following **procedure C**. The crude amide was dissolved in a minimal amount of hot EtOAc and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes. resulting in a beige solid (0.11 g, 75% yield). **mp**: 127-128 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.84 (dd, *J*

= 1.0 Hz, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 10.0 Hz, 1H), 7.53-7.50 (m, 1H), 7.48-7.43 (m, 2H), 7.41 (d, *J* = 10.0 Hz, 1H), 7.33 (dd, *J* = 1.0 Hz, *J* = 7.5 Hz, 1H), 7.23 (br s, 1H), 4.73 (d, *J* = 5.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 167.6, 158.4, 141.8, 139.3, 134.1, 131.8, 128.8, 128.7, 127.2, 127.0 126.9 (t, $J_{C\text{-}D}$ = 23.4 Hz), 121.3, 44.6; **FTIR** ($cm^{-1}$) (neat): 3287, 3061, 2926, 1638, 1537, 1436, 1403, 1121, 770; **HRMS** (ESI, Pos): calcd for $C_{13}H_{11}DBrN_2O$ $[M+H]^+$: 292.01903*m/z*, found: 292.0191 *m/z*. Product is 90% *ortho*-deuterated, as was the starting acyl chloride.

***N*-((6-Bromopyridin-2-yl)methyl)benzamide-2,3,4,5,6-$d_5$ (5a-$d_5$)**: Following **procedure A**. The crude amide was was dissolved in a minimal amount of hot EtOAc and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes, resulting in a beige solid (0.38 g, 85% yield). **mp**: 128-129 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.55 (t, *J* = 7.6 Hz, 1H), δ 7.42 (d, *J* = 8.0 Hz, 1H), δ 7.34 (d, *J* = 7.2 Hz, 1H), δ 7.19 (s, 1H), δ 7.40 (d, *J* = 5.2 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 167.6, 158.4, 141.7, 139.3, 134.0, 131.3 (t, $J_{C\text{-}D}$ = 24.3 Hz), 128.2 (t, $J_{C\text{-}D}$ = 24.5 Hz), 127.0, 126.8 (t, $J_{C\text{-}D}$ = 24.3 Hz), 121.3, 44.6; **FTIR** ($cm^{-1}$) (neat): 3287, 3061, 2926, 1638, 1538, 1403, 1121, 770, 629; **HRMS** (ESI, Pos): calcd for $C_{13}H_7D_5BrN_2O$ $[M+H]^+$: 296.0441 *m/z*, found: 296.0453*m/z*.

**General procedure for the synthesis of imidazo[1,5-*a*]pyridines**

**Procedure D**

To a flame-dried and argon-flushed glass microwave (sealable) vial (VWR®) equipped with a magnetic stirrer and a rubber septum was added the amide (1.0 equiv) and anhydrous $CH_2Cl_2$ (0.50 M). 2-methoxypyridine (2-MeOPyr) (1.1 equiv) was added via syringe and $Tf_2O$ (1.2 equiv) was added over 2 min via syringe. The reaction usually changed color (dark purple or dark blue) and was exothermic upon addition of the anhydride. The reaction mixture was slowly heated to 50 °C using an oil bath and stirred for 16 h. The mixture was cooled to room temperature and quenched by addition of saturated aqueous $Na_2CO_3$ and then stirred for 5 min. Phases were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated to dryness.

**Characterization data of imidazo[1,5-*a*]pyridines**

**5-Bromo-3-phenylimidazo[1,5-*a*]pyridine (6a)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 80% EtOAc in hexanes. Fractions containing **6a** were concentrated to dryness, resulting in a green solid (0.50 g, 96% yield). **mp**: 80-82°C, lit:[15] 80-81 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.66 (s, 1H), 7.57-7.52 (m, 3H), 7.50-7.41 (m, 3H), 6.85 (app dt, *J* = 1.0, 7.0 Hz, 1H), 6.61 (dd, *J* = 7.0, 9.0 Hz, 1H); Product corresponds to previously reported characterization data.[15]

**3-([1,1'-Biphenyl]-4-yl)-5-bromoimidazo[1,5-*a*]pyridine (6b)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6b** were concentrated to dryness, resulting in a brown solid (0.61 g, 87% yield). **mp**: 164-166 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.70-7.66 (m, 5H), 7.63-7.60 (m, 2H), 7.53 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.49-7.45 (m, 2H), 7.40-7.36 (m, 1H), 6.85 (dd, *J* = 1.2, 6.8 Hz, 1H), 6.60 (dd, *J* = 6.8, 8.8 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 141.6, 140.6, 140.2, 133.8, 131.8, 131.4, 128.9,

127.6, 127.2, 125.8, 121.3, 119.6, 119.0, 118.0, 111.8; **FTIR** ($cm^{-1}$) (neat): 3057, 2964, 842, 807, 758, 691; **HRMS** (ESI, Pos): calcd for $C_{19}H_{13}BrN_2$ $[M+H]^+$: 349.0335 *m/z*, found: 349.0344 *m/z*.

**5-Bromo-3-(4-(*tert*-butyl)phenyl)imidazo[1,5-*a*]pyridine (6c)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6c** were concentrated to dryness, resulting in a yellow solid (0.60 g, 91% yield). **mp**: 128-129 °C; **Rf**: 0.45 (70% EtOAc in hexanes); **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.61 (s, 1H), 7.49 (dd, *J* = 0.8, 8.8 Hz, 1H), 7.46-7.40 (m, 4H), 6.80 (dd, *J* = 1.2, 6.8 Hz, 1H), 6.55 (dd, *J* = 6.4, 8.8 Hz, 1H), 1.37 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 152.1, 140.7, 133.6, 131.1, 129.5, 124.1, 121.0, 119.3, 118.7, 118.0, 111.8, 34.8, 31.4; **FTIR** ($cm^{-1}$) (neat): 2966, 2949, 2865, 2845, 822, 757, 686; **HRMS** (ESI, Pos): calcd for $C_{17}H_{17}BrN_2$ $[M+H]^+$: 329.0648 *m/z*, found: 329.0663 *m/z*.

**3-(4-(Benzyloxy)phenyl)-5-bromoimidazo[1,5-*a*]pyridine (6d)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 15% to 75% EtOAc in hexanes. Fractions containing **6d** were concentrated to dryness, resulting in a green solid (0.73 g, 91% yield). **mp**: 117-119 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.61 (s, 1H), 7.50-7.44 (m, 5H), 7.40 (t, *J* = 5.6 Hz, 2H), 7.34 (d, *J* = 5.6 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.80 (dd, *J* = 0.8, *J* = 5.2 Hz, 1H), 6.55 (dd, *J* = 5.2, *J* = 7.2 Hz, 1H), 5.13 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 159.5, 140.4, 136.8, 133.6, 132.8, 128.7, 128.1, 127.7, 125.2, 120.9, 119.4, 118.8, 118.1, 113.6, 111.9, 70.2; **FTIR** ($cm^{-1}$) (neat): 3057, 1450, 1238, 1172, 1027, 827, 814, 772, 691, ; **HRMS** (ESI, Pos): calcd for $C_{20}H_{16}BrN_2O$ $[M+H]^+$: 379.0441 *m/z*, found: 379.0458 *m/z*.

**2-(4-(5-Bromoimidazo[1,5-*a*]pyridin-3-yl)phenoxy)ethyl benzoate (6e)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 75% EtOAc in hexanes. Fractions containing **6e** were concentrated to dryness, resulting in a green solid (0.20 g, 52% yield). **mp**: 109-111 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.11-8.06 (m, 2H), 7.62 (s, 1H), 7.61-7.42 (m, 6H), 7.01-6.96 (m, 2H), 6.82 (dd, *J* = 1.5, 11.5 Hz, 1H), 6.61-6.54 (m, 1H), 4.71 (dd, *J* = 8.0 Hz, 2H), 4.38 (dd, *J* = 8.0 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 166.7, 159.4, 140.2 133.6, 133.3, 132.9, 130.0, 129.9, 128.5, 125.3, 120.9, 119.5, 118.9, 118.1, 113.4, 111.9, 66.2, 63.4; **FTIR** ($cm^{-1}$) (neat): 1712, 1455, 1273, 1241, 1112, 1062, 834, 804, 706; **HRMS** (ESI, Pos): calcd for $C_{22}H_{18}BrN_2O_3$ $[M+H]^+$: 437.0501 *m/z*, found: 437.0495 *m/z*.

**4-(5-Bromoimidazo[1,5-*a*]pyridin-3-yl)-*N,N*-dimethylaniline (6f)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 15% to 75% EtOAc in hexanes. Fractions containing **6f** were concentrated to dryness, resulting in a yellow solid (0.33 g, 84% yield). **mp**: 167-168 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.59 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 6.78 (dd, *J* = 0.8 Hz, *J* = 6.8 Hz, 1H), 6.73 (dd, *J* = 2.0 Hz, *J* = 6.8 Hz, 2H), 6.52 (dd, *J* = 6.8, *J* = 8.8, Hz, 1H), 3.02 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 150.9, 141.5, 133.5, 132.4, 120.8, 120.0, 119.3, 118.5, 118.1, 112.2, 110.7, 40.5; **FTIR** ($cm^{-1}$) (neat): 3077, 2889, 1609, 1439, 1359, 1231, 822, 805, 692; **HRMS** (ESI, Pos): calcd for $C_{15}H_{15}BrN_3$ $[M+H]^+$: 316.0444 *m/z*, found: 316.0459 *m/z*.

**5-Bromo-3-(4-fluorophenyl)imidazo[1,5-*a*]pyridine (6g)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6g** were concentrated to dryness, resulting in a grey solid (0.52 g, 90% yield). **mp**: 78-80 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.61

(s, 1H), 7.51-7.48 (m, 3H), 7.12-7.09 (m, 2H), 6.82 (dd, $J$ = 1.0, 7.0 Hz, 1H), 6.58 (dd, $J$ = 7.0, 9.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 163.3 (d, $J_{C\text{-}F}$ = 296.9 Hz), 133.7, 133.3 (d, $J_{C\text{-}F}$ = 10.0 Hz), 128.6 (d, $J_{C\text{-}F}$ = 3.9 Hz), 121.0, 119.6, 119.0, 118.0, 114.2 (d, $J_{C\text{-}F}$ = 26.1 Hz), 111.5; **$^{19}$F NMR** ($CDCl_3$, 471 MHz): δ -112.2 (t, $J_{H\text{-}F}$ = 8.5 Hz, 1F); **FTIR** ($cm^{-1}$) (neat): 3057, 2964, 1214, 798; **HRMS** (ESI, Pos): calcd for $C_{13}H_8BrFN_2$ $[M+H]^+$: 290.9928 *m/z*, found: 290.9933 *m/z*.

**5-Bromo-3-(4-chlorophenyl)imidazo[1,5-*a*]pyridine (6h)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 75% EtOAc in hexanes. Fractions containing **6h** were concentrated to dryness, resulting in a green solid (45 mg, 95% yield). **mp**: 99-101 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.63 (s, 1H), 7.52 (d, $J$ = 8.8 Hz, 1H), 7.47 (d, $J$ = 8.4 Hz, 2H), 7.40 (d, $J$ = 8.4 Hz, 2H), 6.85 (d, $J$ = 8.8 Hz, 1H), 6.61 (dd, $J$ = 8.8 Hz, 6.8 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 139.3, 135.2, 134.0, 132.8, 131.1, 127.5, 121.4, 119.8, 119.3, 118.2, 111.7; **FTIR** ($cm^{-1}$) (neat): 3084, 1450, 1161, 1117, 1087, 967, 832, 791, 689; **HRMS** (ESI, Pos): calcd for $C_{13}H_9BrClN_2$ $[M+H]^+$: 306.9632 *m/z*, found: 306.9641 *m/z*.

**Methyl 4-(5-bromoimidazo[1,5-*a*]pyridin-3-yl)benzoate (6i)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6i** were concentrated to dryness, resulting in a brown solid (0.54 g, 81% yield). **mp**: 134-135 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.14-8.11 (m, 2H), 7.70 (s, 1H), 7.68-7.65 (m, 2H), 7.48 (dd, $J$ = 0.8, 9.2 Hz, 1H), 6.90 (dd, $J$ = 1.2, 6.8 Hz, 1H), 6.67 (dd, $J$ = 6.8, 8.8 Hz, 1H), 4.0 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 166.8, 139.2, 136.8, 134.1, 131.3, 130.3, 128.3, 121.7, 119.9, 119.4, 118.0, 111.6, 52.3; **FTIR** ($cm^{-1}$) (neat): 3086, 3071, 2987, 2942, 2923, 2858, 2845, 1753, 1276, 692; **HRMS** (ESI, Pos): calcd for $C_{15}H_{11}BrN_2O_2$ $[M+H]^+$: 331.0077 *m/z*, found: 331.0076 *m/z*.

**4-(5-Bromoimidazo[1,5-*a*]pyridin-3-yl)benzonitrile (6j)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was dissolved in a minimal amount of hot EtOAc and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes. resulting in a green solid (0.58 g, 88% Yield). **mp**: 148-149 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.72-7.65 (m, 5H), 7.57 (dd, $J$ = 1.0, 9.0 Hz, 1H), 6.91 (dd, $J$ = 1.0, 6.5 Hz, 1H), 6.68 (dd, $J$ = 7.0, 9.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 138.2, 136.8, 134.4, 131.8, 130.9, 122.1, 120.2, 119.8, 118.7, 118.1, 112.4, 111.3; **FTIR** ($cm^{-1}$) (neat): 2981, 2972, 2947, 2923, 2863, 2844, 2827, 842, 799, 781; **HRMS** (ESI, Pos): calcd for $C_{14}H_8BrN_3$ $[M+H]^+$: 297.9974 *m/z*, found: 297.9973 *m/z*.

**5-Bromo-3-(3,4,5-trimethoxyphenyl)imidazo[1,5-*a*]pyridine (6k)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 15% to 75% EtOAc in hexanes. Fractions containing **6k** were concentrated to dryness, resulting in a green solid (0.80 g, 88% Yield). **mp**: 101-102 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.61 (s, 1H), 7.51 (dd, $J$ = 1.0 Hz, 9.0 Hz, 1H), 6.84 (dd, $J$ = 1.0 Hz, 6.5 Hz, 1H), 6.75 (s, 2H), 6.59 (dd, $J$ = 6.5, 9.0 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 152.2, 140.3, 139.1, 133.7, 127.6, 120.9, 119.7, 119.1, 118.1, 111.9, 109.4, 61.2, 56.3; **FTIR** ($cm^{-1}$) (neat): 2935, 1582, 1463, 1409, 1233, 1118, 999, 760, 691; **HRMS** (ESI, Pos): calcd for $C_{16}H_{16}BrN_2O_3$ $[M+H]^+$: 363.0339 *m/z*, found: 363.0349 *m/z*.

**5-Bromo-3-(2-ethoxy-4-nitrophenyl)imidazo[1,5-*a*]pyridine (6l)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 15% to 75% EtOAc in hexanes. Fractions containing **6l** were concentrated to dryness, resulting in a green solid (0.42 mg, 94% Yield). **mp**: 158-159 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.93 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.74 (d, *J* = 10.0 Hz, 2H), 7.73 (d, *J* = 14.4 Hz, 1H) 7.55 (d, *J* = 9.2 Hz, 1H), 6.89 (dd, *J* = 1.0, 6.8 Hz, 1H), 6.67 (dd, *J* = 7.2, 9.2 Hz, 1H), 4.08 (q, *J* = 6.8 Hz, 2H), 1.20 (t, *J* = 6.8 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 158.7, 149.6, 135.6, 134.3, 132.0, 129.2, 122.0, 119.8, 119.4, 118.1, 115.2, 112.3, 105.7, 64.6, 14.5; **FTIR** ($cm^{-1}$) (neat): 3053, 1512, 1340, 1319, 1083, 1213, 868, 802, 734; **HRMS** (ESI, Pos): calcd for $C_{15}H_{13}BrN_3O_3$ $[M+H]^+$: 362.0145 *m/z*, found: 362.0135 *m/z*.

**5-Bromo-3-(2,3,4,5-tetrafluorophenyl)imidazo[1,5-*a*]pyridine (6m)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6m** were concentrated to dryness, resulting in a beige solid (0.64 g, 93% Yield). **mp**: 88-89 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.69 (s, 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.26-7.21 (m, 1H), 6.92 (d, *J* = 6.5 Hz, 1H), 6.70 (dd, *J* = 7.0, 9.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 175 MHz): δ 147.4-147.1 (m), 146.0-145.7 (m), 142.3 (ddd, $J_{C\text{-}F}$ = 3.3, 12.6, 15.9 Hz), 141.1-140.8 (m), 139.5 (ddd, $J_{C\text{-}F}$ = 4.2, 12.6, 16.6 Hz), 134.5, 131.1, 122.1, 120.1, 119.9, 118.1, 117.7-117.5 (m), 113.9 (dd, $J_{C\text{-}F}$ = 2.3, 19.6 Hz); **$^{19}$F NMR** ($CDCl_3$, 470 MHz): δ -156.9 to -155.8 (m, 1F), -153.2 to -153.0 (m, 1F), -139.7 to -139.6 (m, 1F), -134.7 to -134.6 (m, 1F); **FTIR** ($cm^{-1}$) (neat): 3107, 3039, 3012, 2956, 2847, 960, 799, 749, 700, 679; **HRMS** (ESI, Pos): calcd for $C_{13}H_5BrF_4N_2$ $[M+H]^+$: 344.9645 *m/z*, found: 344.9645 *m/z*.

**5-Bromo-3-(2-methoxyphenyl)imidazo[1,5-*a*]pyridine (6n)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 15% to 75% EtOAc in hexanes. Fractions containing **6n** were concentrated to dryness, resulting in a green solid (0.30 g, 86% Yield). **mp**: 129-131 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.64 (s, 1H), 7.51-7.43 (m, 3H) 7.03 (dt *J* = 1.0, 9.0 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 6.4 Hz, 1H), 6.79 (dt, *J* = 1.0, 9.0 Hz, 1H), 3.72 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 159.3, 137.6, 133.7, 132.3, 131.0, 122.4, 121.0, 120.0, 118.9 (2), 118.0, 112.3, 110.0, 55.3; **FTIR** ($cm^{-1}$) (neat): 2925, 1443, 1283, 1261, 1239, 1100, 1020, 796, 746; **HRMS** (ESI, Pos): calcd for $C_{14}H_{12}BrN_2O$ $[M+H]^+$: 303.0128 *m/z*, found: 303.0137 *m/z*.

**5-Bromo-3-(naphthalen-1-yl)imidazo[1,5-*a*]pyridine (6o)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6o** were concentrated to dryness, resulting in a light greenish solid (0.76 g, 82% yield). **mp**: 152-153 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.75 (s, 1H), 7.62 (dd, *J = 1.0,* 7.0 Hz, 1H), 7.58 (dd, *J* = 1.0, 9.0 Hz, 1H), 7.56-7.52 (m, 1H), 7.50-7.46 (m, 1H), 7.42-7.38 (m, 1H), 7.23-7.20 (m, 1H), 6.77 (dd, *J* = 1.0, 6.5 Hz, 1H), 6.64-6.60 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 138.5, 134.8, 133.5, 132.9, 130.2 (2), 129.8, 128.2, 126.7, 126.0, 125.9, 124.5, 121.0, 119.2, 118.0, 111.7; **FTIR** ($cm^{-1}$) (neat): 2966, 2865, 1055, 1033, 1013, 775, 758, 693; **HRMS** (ESI, Pos): calcd for $C_{17}H_{11}BrN_2$ $[M+H]^+$: 323.0178 *m/z*, found: 323.0194 *m/z*.

**2-(5-Bromoimidazo[1,5-*a*]pyridin-3-yl)-9*H*-fluoren-9-one (6p)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6p** were concentrated to dryness, resulting in a dark orange solid (0.45 g, 58% yield). **mp**: 198-199 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.83-7.82 (m, 1H), 7.74-7.70 (m, 2H), 7.68 (s, 1H), 7.64-7.60 (m, 2H), 7.58-7.53 (m, 2H), 7.36 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.90 (dd, *J* = 1.0, 6.5 Hz, 1H), 6.68-6.64 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 144.6, 144.1, 139.1, 137.1, 134.8, 134.6, 134.0, 133.3, 132.9, 129.4, 127.1, 124.5, 121.5, 120.7, 119.9, 119.4, 119.2, 118.1, 111.6; **FTIR** ($cm^{-1}$) (neat): 1707, 1612, 1597, 1184, 769, 742, 685, 671; **HRMS** (ESI, Pos): calcd for $C_{20}H_{11}BrN_2O$ $[M+H]^+$: 375.0128 *m/z*, found: 375.0134 *m/z*.

**5-Bromo-3-(furan-2-yl)imidazo[1,5-*a*]pyridine (6q)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6q** were concentrated to dryness, resulting in a beige solid (0.44 mg, 84% yield). **mp**: 123-124 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.64 (s, 1H), 7.60 (dd, *J* = 0.8, 1.6 Hz, 1H), 7.51 (dd, *J* = 0.8, 8.8 Hz, 1H), 6.89 (dd, *J* = 1.2, 6.8 Hz, 1H), 6.73 (dd, *J* = 0.8, 3.6 Hz, 1H), 6.64 (dd, *J* = 6.8, 8.8 Hz, 1H), 6.55 (dd, *J* = 2.0, 3.6 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 143.0, 142.9, 134.2, 130.4, 121.4, 120.0, 119.4, 117.7, 114.8, 112.0, 111.5; **FTIR** ($cm^{-1}$) (neat): 3126, 3109, 3091, 3076, 2968, 2939, 2922, 2867, 2844, 805, 760; **HRMS** (ESI, Pos): calcd for $C_{11}H_7BrN_2O$ $[M+H]^+$: 262.9815 *m/z*, found: 262.9819 *m/z*.

**5-Bromo-3-(thiophen-2-yl)imidazo[1,5-*a*]pyridine (6r)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6r** were concentrated to dryness, resulting in a brown solid (0.50 g, 90% yield). **mp**: 95-96 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.64 (s, 1H), 7.53-7.50 (m, 2H), 7.25 (dd, *J* = 1.5, 4.0 Hz, 1H), 7.10 (dd, *J* = 3.5, 5.0 Hz, 1H), 6.87 (dd, *J* = 1.5, 7.0 Hz, 1H), 6.62 (dd, *J* = 7.0, 9.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 134.2, 132.9, 132.7, 132.0, 128.1, 126.1, 121.4, 119.9, 119.5, 118.0, 112.0; **FTIR** ($cm^{-1}$) (neat): 3080, 3065, 3008, 2981, 2967, 2949, 2938, 2922, 2866, 2844, 2829, 802, 712, 689; **HRMS** (ESI, Pos): calcd for $C_{11}H_7BrN_2S$ $[M+H]^+$: 278.9586 *m/z*, found: 278.9589 *m/z*.

**5-Bromo-3-(prop-1-en-2-yl)imidazo[1,5-*a*]pyridine (6s)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 5% to 60% EtOAc in hexanes. Fractions containing **6s** were concentrated to dryness, resulting in a green solid (0.76 g, 74% yield). **mp**: 76-77 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.51 (s, 1H), 7.43 (dd, *J* = 1.0, 9.0 Hz, 1H), 6.81 (dd, *J* = 1.0, 7.0 Hz, 1H), 6.56-6.52 (m, 1H), 5.61-5.58 (m, 1H), 5.22-5.20 (m, 1H), 2.26 (d, *J* = 10.0 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 141.4, 136.6, 133.2, 122.1, 120.6, 119.2, 118.8, 117.8, 111.6, 25.2; **FTIR** ($cm^{-1}$) (neat): 3076, 3064, 1623, 1358, 1312, 1278, 1181, 814, 800, 762, 689; **HRMS** (ESI, Pos): calcd for $C_{10}H_9BrN_2$ $[M+H]^+$: 237.0025 *m/z*, found: 237.0029 *m/z*.

**(*E*)-5-Bromo-3-styrylimidazo[1,5-*a*]pyridine (6t)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 70% EtOAc in hexanes. Fractions containing **6t** were concentrated to dryness, resulting in a green solid (0.57 g, 94% yield). **mp**: 91-93 °C; **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 8. 31 (d, *J* = 15.9 Hz, 1H), 7.61-7.55 (m, 4H), 7.45 (dd, *J* = 0.9, 8.7 Hz, 1H), 7.40-7.35 (m, 2H), 7.31-7.27 (m, 1H), 6.88 (dd, *J* = 1.2, 6.9 Hz, 1H), 6.52 (dd, *J* = 6.6, 8.7 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 139.7, 137.3, 134.4, 131.5, 128.7, 127.9, 126.7, 122.5, 120.2,

118.8, 118.4, 117.0, 111.5; **FTIR** ($cm^{-1}$) (neat): 3107, 3055, 3039, 3012, 2954, 2847, 960, 799, 749, 700, 679; **HRMS** (ESI, Pos): calcd for $C_{15}H_{11}BrN_2$ $[M+H]^+$: 299.0178 *m/z*, found: 299.0183 *m/z*.

**5-Bromo-3-(phenyl-2-*d*)imidazo[1,5-*a*]pyridine (6a-*ortho*-$d_1$)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 10% to 75% EtOAc in hexanes. Fractions containing **6a-*ortho*-$d_1$** were concentrated to dryness, resulting in a green solid (60 mg, 74% yield). **mp**: 59-61°C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.64 (s, 1H), 7.54-7.51 (m, 2H), 7.48-7.40 (m, 3H), 6.83 (dd, *J* = 1.0, 6.5 Hz, 1H), 6.59 (dd, *J* = 6.5, 9.1 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 140.5, 133.7, 132.3, 131.6, 131.3 (t, $J_{C\text{-}D}$ = 25.0 Hz), 129.1, 127.3, 127.2 121.0, 119.7, 119.1 118.1, 111.8; **FTIR** ($cm^{-1}$) (neat): 1623, 1445, 1360, 1320, 1185, 1105, 965, 804, 760, 688, 633; **HRMS** (ESI, Pos): calcd for $C_{13}H_9DBrN_2$ [M+H]+: 274.0085 *m/z*, found 274.0095 *m/z*.

**5-Bromo-3-(phenyl-*d*5)imidazo[1,5-*a*]pyridine (6a-$d_5$)**: Following **procedure D**. The crude imidazo[1,5-*a*]pyridine was purified by flash chromatography over silica gel using a gradient of 15% to 75% EtOAc in hexanes. Fractions containing **6a-$d_5$** were concentrated to dryness, resulting in a green solid (0.26 g, 92% yield). **mp**: 72-74°C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 7.64 (s, 1H), 7.52 (dd, *J* = 1.0, 9.0 Hz, 1H), 6.83 (dd, *J* = 1.0, 7.0 Hz, 1H), 6.59 (dd, *J* = 6.5, 9.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 140.5, 133.7, 132.4, 131.1 (t, $J_{C\text{-}D}$ = 24.4 Hz), 128.5 (t, $J_{C\text{-}D}$ = 24.3 Hz), 126.7 (t, $J_{C\text{-}D}$ = 24.3 Hz), 121.1, 119.6, 119.0, 118.1, 111.8; **FTIR** ($cm^{-1}$) (neat): 3351, 3083, 1750, 1478, 1094, 809, 689, 562; **HRMS** (ESI, Pos): calcd for $C_{13}H_5D_5BrN_2$ [M+H]+: 278.0336 *m/z*, found 278.0342 *m/z*.

**General procedure for the synthesis of imidazo[2,1,5-*c,d*]indolizines**

**Procedure E**:

To a flame-dried microwave (sealable) vial (VWR®) equipped with a magnetic stirrer was added the corresponding 5-bromoimidazo[1,5-*a*]pyridine (1.0 equiv), as previously synthesized. Then, $Pd_2(dba)_3$ (0.025 equiv), $HP(t\text{-}Bu)_3BF_4$ (0.10 equiv), and $K_2CO_3$ (2.0 equiv) were added to the vial. The vial was capped with a rubber septum and purged with argon. Anhydrous DMF (0.20M) was added and the reaction was quickly heated to 120 °C using an oil bath and stirred for 2.5 h. The reaction was cooled to room temperature and the crude mixture was diluted in EtOAc and a saturated aqueous solution of NaCl was added. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine (2x) dried over anhydrous $MgSO_4$, filtered over a pad of silica gel, and evaporated to dryness. *Note: Preparing the reaction mixture in a glovebox produced similar results for several runs and is likely unnecessary for most substrates.

**Procedure F**:

To a flame-dried microwave (sealable) vial (VWR®) equipped with a magnetic stirrer was added the corresponding 5-bromoimidazo[1,5-*a*]pyridine (1.0 equiv), as previously synthesized. The vial was then purged (2 x 10 min) with argon and transferred in an Ar-filled glovebox. Then, $Pd_2(dba)_3$ (0.025 equiv), $HP(t\text{-}Bu)_3BF_4$ (0.10 equiv), and $K_2CO_3$ (2.0 equiv) were added to the vial. The vial was capped with an aluminum microwave cap (VWR® with Teflon seal) and removed from of the glovebox. Anhydrous DMF (0.20 M) was added. The reaction was slowly heated to 110 °C using an oil bath and stirred for 16

h. The reaction was cooled to room temperature and uncapped. The crude mixture was diluted in $CH_2Cl_2$ (5 mL) and quenched by addition of a saturated aqueous solution of NaCl. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2x). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered over a pad of silica gel and evaporated to dryness.

**Procedure G**:

To a flame-dried microwave (sealable) vial (VWR®) equipped with a magnetic stirrer was added the corresponding 5-bromoimidazo[1,5-*a*]pyridine (1.0 equiv), as previously synthesized. The vial was then purged (2 x 10 min) with argon and transferred in an Ar-filled glovebox. Then, $Pd_2(dba)_3$ (0.025 equiv), $HP(t\text{-}Bu)_3BF_4$ (0.10 equiv), and $K_2CO_3$ (2.0 equiv) were added to the vial. The vial was capped with an aluminum microwave cap (VWR® with Teflon seal) and removed from of the glovebox. Anhydrous DMF (0.20 M) was added. The reaction was slowly heated to 90 °C using an oil bath and stirred for 16 h. The reaction was cooled to room temperature and uncapped. The crude mixture was diluted in $CH_2Cl_2$ (5 mL) and quenched by addition of a saturated aqueous solution of NaCl. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2x). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered over a pad of silica gel and evaporated to dryness.

**Characterization data of imidazo[2,1,5-*c,d*]indolizines**

**Benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7a)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 1% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7a** were concentrated to dryness, resulting in a bright yellow solid (0.11 g, 100% yield). **mp**: 97-99 °C; lit:[15] 98-100 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.44-8.41 (m, 2H), 8.25 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 7.0 Hz, 1H), 7.80 (t, *J* = 7.0 Hz, 1H), 7.69 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H); Product corresponds to previously reported characterization data.[15]

**7-Phenylbenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7b)**: Following **procedure F**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 40% to 60% EtOAc in hexanes. Fractions containing **7b** were concentrated to dryness, resulting in a brown oil (0.13 g, 100% yield). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.58 (d, *J* = 0.8 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.24 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 6.8 Hz, 1H), 8.02 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.78-7.76 (m, 2H), 7.68 (dd, *J* = 6.8, 8.4 Hz, 1H), 7.55-7.51 (m, 2H), 7.44-7.40 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 141.0, 138.2, 137.4, 131.8, 129.0, 128.6, 127.7, 127.5, 127.5, 127.0, 126.7, 125.9, 121.8, 121.6, 120.1, 116.9, 110.5; **FTIR** ($cm^{-1}$) (neat): 3054, 3024, 2954, 2922, 2852, 1067, 746, 694, 676; **HRMS** (ESI, Pos): calcd for $C_{19}H_{12}N_2$ $[M+H]^+$: 269.1073 *m/z*, found 269.1072 *m/z*.

**7-(*tert*-Butyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7c)**: Following **procedure G**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 10% to 80% EtOAc in hexanes. Fractions containing **7c** were concentrated to dryness, resulting in a brown oil (0.11 g, 89% Yield). **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.39 (dd, *J* = 1.0, 2.0 Hz, 1H), 8.33 (dd, *J* = 0.5, 8.5 Hz, 1H), 8.18 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 7.0 Hz, 1H), 7.86 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.65 (dd, *J* = 7.0, 8.5 Hz, 1H), 1.50 (s, 9H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 148.3, 137.7, 131.4, 127.4, 126.9, 126.1,

125.7, 121.5, 119.4, 119.3, 116.5, 109.9, 35.2, 31.7; **FTIR** ($cm^{-1}$) (neat): 2955, 2903, 2863, 1363, 795, 677; **HRMS** (ESI, Pos): calcd for $C_{17}H_{16}N_2$ $[M+H]^+$: 249.1386 *m/z*, found 249.1380 *m/z*.

**7-(Benzyloxy)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7d)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 1% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7d** were concentrated to dryness, resulting in a dark yellow solid (0.47 g, 90% yield). **mp**: 109-110°C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.58 (d, *J* = 0.8 Hz, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.24 (s, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 6.8 Hz, 1H), 8.02 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.78-7.76 (m, 2H), 7.68 (dd, *J* = 6.8, 8.4 Hz, 1H), 7.55-7.51 (m, 2H), 7.44-7.40 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 157.0, 137.7, 136.8, 132.7, 128.8, 128.3, 127.7, 126.8, 126.6, 125.8, 122.7, 121.2, 121.0, 118.7, 117.1, 110.4, 107.8, 70.9; **FTIR** ($cm^{-1}$) (neat): 3091, 1496, 1335, 1223, 1051, 974, 773, 743, 677; **HRMS** (ESI, Pos): calcd for $C_{20}H_{15}N_2O$ $[M+H]^+$: 299.1179 *m/z*, found 299.1187 m*/z*.

**2-(Benzo[*a*]imidazo[2,1,5-*c,d*]indolizin-7-yloxy)ethan-1-ol (7e)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was added to a 5 mL round-bottom flask equipped with a magnetic stirbar and a rubber septum. 2.0 M NaOH in water (0.7 mL, 1.4 mmol, 8.0 equiv), THF (0.4 mL) and MeOH (0.4 mL) were added. The resulting suspension was vigorously stirred at room temperature for 16h. $CH_2Cl_2$ and a saturated aqueous solution of NaCl were added. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were washed with brine (2x) dried over anhydrous $MgSO_4$, filtered over a pad of silica gel, and evaporated to dryness. The crude alcohol was purified by flash chromatography over silica gel using a gradient of 1% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7e** were concentrated to dryness, resulting in a yellow solid (38 mg, 89% yield). **mp**: 77-80 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.23 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 2H), 8.11 (s, 1H), 8.08 (d, *J* = 2.5 Hz, 1H), 7.74 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.46 (dd, *J* = 2.0, 8.5 Hz, 1H), 4.28 (t, *J* = 4.5 Hz, 2H), 3.99 (t, *J* = 4.5 Hz, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 159.0, 137.9, 134.1, 127.9, 126.8, 126.3, 123.3, 122.5, 121.2, 119.8, 118.4, 112.4, 108.6, 71.3, 61.7; **FTIR** (cm-1) (neat): 3302, 2919, 1712, 1602, 1562, 1438, 1210, 1058, 793; **HRMS** (ESI, Pos): calcd for $C_{15}H_{13}N_2O_2$ [M+H]+: 253.0972 m/z, found 253.0981 m/z.

***N,N*-Dimethylbenzo[*a*]imidazo[2,1,5-*c,d*]indolizin-7-amine (7f)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 1% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7f** were concentrated to dryness, resulting in a brown solid (0.12 g, 98% yield). **mp**: 118-120°C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.22 (d, *J* = 8.5 Hz, 1H), 8.07 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 7.0 Hz, 1H), 7.61 (d, *J* = 2.5 Hz, 1H), 7.53 (dd, *J* = 6.5, 8.5 Hz, 1H), 7.22 (dd, *J* = 2.5, 9.0 Hz, 1H), 3.14 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 149.0, 138.5, 133.6, 127.4, 125.7, 125.5, 120.9, 120.6, 119.3, 116.7, 115.8, 109.5, 105.5, 41.3; **FTIR** ($cm^{-1}$) (neat): 2888, 2802, 1623, 1496, 1432, 1342, 1054, 792, 673; **HRMS** (ESI, Pos): calcd for $C_{15}H_{14}N_3$ $[M+H]^+$: 236.1182 *m/z*, found 236.1189 *m/z*.

**7-Fluorobenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7g)**: Following **procedure F**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 1% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7g** were concentrated to dryness, resulting in a bright yellow solid (103.0 mg, 98% yield). **mp**: 129-130 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.37 (dd, *J* = 4.8, 8.4 Hz, 1H), 8.23 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.07-8.03 (m, 2H), 7.69 (dd, *J* = 7.2, 8.8 Hz, 1H), 7.53

(dt, *J* = 2.4, 8.8 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 161.5, 159.6, 137.0, 132.0, 127.6, 126.0, 124.7, 121.4, 121.2 (d, $J_{C\text{-}F}$ = 7.3 Hz), 117.5 (d, $J_{C\text{-}F}$ = 19.4 Hz), 117.5, 111.1, 109.3 (d, *J* = 19.4 Hz, $J_{C\text{-}F}$); **$^{19}$F NMR** ($CDCl_3$, 282 MHz): δ -115.7 to -115.6 (m, 1F); **FTIR** ($cm^{-1}$) (neat): 3064, 3015, 2952, 2920, 2851, 1006, 769; **HRMS** (ESI, Pos): calcd for $C_{13}H_7FN_2$ $[M+H]^+$: 211.0667 *m/z*, found 211.0660 *m/z*.

**7-Chlorobenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7h)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 1% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7h** were concentrated to dryness, resulting in a yellow solid (0.11 g, 94% yield). **mp**: 162-163°C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.38 (dd, *J* = 0.5 Hz, 1.5 Hz, 1H), 8.33 (dd, *J* = 0.5 Hz, *J* = 8.5 Hz, 1H), 8.26 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 7.0 Hz, 1H), 7.74 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 7.71 (dd, *J* = 7.0 Hz, 8.5 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 137.0, 132.0, 130.8, 129.7, 128.3, 126.4, 126.1, 125.6, 123.1, 122.0, 121.0, 117.6, 111.4; **FTIR** ($cm^{-1}$) (neat): 3071, 2929, 1720, 1461, 1335, 1276, 1244, 962, 714; **HRMS** (ESI, Pos): calcd for C13H8ClN2 $[M+H]^+$: 227.0371 *m/z*, found 227.0380 *m/z*.

**Methyl benzo[*a*]imidazo[2,1,5-*c,d*]indolizine-7-carboxylate (7i)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 1% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7i** were concentrated to dryness, resulting in a yellow solid (0.17 g, 97% Yield). **mp:** 206-207 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 9.13 (s, 1H), 8.44-8.35 (m, 3H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 7.0 Hz, 1H), 7.79 (dd, *J* = 7.0, 8.0 Hz, 1H), 4.04 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 167.1, 130.5, 130.4, 130.1, 129.5, 126.5, 126.3, 125.4, 122.7, 119.5, 117.4, 111.5, 52.5; **FTIR** ($cm^{-1}$) (neat): 3089, 3060, 3032, 3007, 2982, 2950, 2922, 2861, 2845, 1712; **HRMS** (ESI, Pos): calcd for $C_{15}H_{10}N_2O_2$ [M+H]+: 251.0815 *m/z*, found 251.0806 *m/z*.

**Benzo[*a*]imidazo[2,1,5-*c,d*]indolizine-7-carbonitrile (7j)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was dissolved in a minimal amount of hot $CH_2Cl_2$ and excess hexanes were added. The resulting precipitate was recovered by filtration and washed with hexanes, resulting in a yellow solid (0.31 g, 84% yield). **mp:** 251-253 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.73-8.72 (m, 1H), 8.47 (dd, *J* = 0.4, 8.0 Hz, 1H), 8.39 (s, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 7.2 Hz, 1H), 7.98 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.84 (dd, *J* = 7.2, 8.4 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ136.4, 131.6, 130.5, 130.1, 129.6, 127.9, 126.6, 125.2, 123.0, 120.6, 119.4, 118.2, 112.5, 107.6; **FTIR** ($cm^{-1}$) (neat): 3069, 3012, 2962, 2920, 2846, 2250, 820, 814; **HRMS** (ESI, Pos): calcd for $C_{14}H_7N_3$ [M+H]+: 218.0713 *m/z*, found 218.0719 *m/z*.

**6,7,8-Trimethoxybenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7k)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7k** were concentrated to dryness, resulting in a red solid (0.54 g, 93% yield). **mp**: 118-120°C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.95 (d, *J* = 2.0 Hz, 1H), 8.47 (s, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.26 (d, *J* = 7.0 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.86 (dd, *J* = 7.5 Hz, 8.5 Hz, 1H), 4.56 (q, *J* = 7.0 Hz, 2H), 1.72 (t, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 152.7, 145.7, 135.4, 131.6, 130.2, 126.9, 126.2, 123.1, 121.6, 118.4, 113.2, 112.4, 105.3, 65.5, 14.8; **FTIR** ($cm^{-1}$) (neat): 2930, 1620, 1417, 1250, 1128, 1085, 1044, 999, 816; **HRMS** (ESI, Pos): calcd for $C_{16}H_{15}N_2O_3$ $[M+H]^+$: 283.1077 *m/z*, found 283.1086 *m/z*.

**9-Ethoxy-7-nitrobenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7l)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7l** were concentrated to dryness, resulting in a yellow solid (0.13 g, 92% yield). **mp**: 239-240°C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.95 (d, *J* = 2.0 Hz, 1H), 8.47 (s, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.26 (d, *J* = 7.0 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.86 (dd, *J* = 7.5 Hz, *J* = 8.5 Hz, 1H), 4.56 (q, *J* = 7.0 Hz, 2H), 1.72 (t, *J* = 7.0 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 152.7, 145.7, 135.4, 131.6, 130.2, 126.9, 126.2, 123.1, 121.6, 118.4, 113.2, 112.4, 105.3, 65.5, 14.8; **FTIR** ($cm^{-1}$) (neat): 3055, 1523, 1319, 1290, 1204, 1177, 1076, 976, 809; **HRMS** (ESI, Pos): calcd for $C_{15}H_{12}N_3O_3$ $[M+H]^+$: 282.0873 *m/z*, found 282.0884 *m/z*; This compound does not exhibit significant fluorescence

**6,7,8,9-Tetrafluorobenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7m)**: Following **procedure F**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 30% to 50% EtOAc in hexanes. Fractions containing **7m** were concentrated to dryness, resulting in a bright yellow solid (87.3 mg, 66% yield). **mp:** 179-181 °C; **Rf**: 0.72 (100% EtOAc); **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.34 (s, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 1H), 7.80 (dd, *J* = 7.2, 8.4 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 175 MHz): δ 142.6 (dd, $J_{C\text{-}F}$ = 15.2, 556.7 Hz), 141.3 (dt, $J_{C\text{-}F}$ = 23.8, 354.9 Hz), 139.0 (t, $J_{C\text{-}F}$ = 20.5 Hz), 137.0 (t, $J_{C\text{-}F}$ = 20.7 Hz), 133.8, 130.1, 126.3, 122.8, 122.4, 118.2, 115.0, 113.30 (ddd, $J_{C\text{-}F}$ = 8.05, 21.9, 385.9 Hz); **$^{19}$F NMR** ($CDCl_3$, 471 MHz): δ -159.0 (t, *J* = 23.1 Hz, 1F), -151.8 (t, *J* = 18.8 Hz, 1F), -142.8 (t, *J* = 16.0 Hz, 1F), -141.1 (t, *J* = 17.0 Hz, 1F); **FTIR** ($cm^{-1}$) (neat): 3055, 3006, 2981, 2967, 2949, 2938, 2922, 2865, 2844, 1024, 814; **HRMS** (ESI, Pos): calcd for $C_{13}H_4F_4N_2$ $[M+H]^+$: 265.0383 *m/z*, found 265.0389 *m/z*.

**9-Methoxybenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7n)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 10% MeOH in $CH_2Cl_2$. Fractions containing **7n** were concentrated to dryness, resulting in a yellow solid (0.11 g, 98% yield). **mp**: 129-131 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.26 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 1H), 8.00 (dd, *J* = 0.5 Hz, *J* = 7.0 Hz, 1H), 7.68 (dd, *J* = 7.0 Hz, *J* = 8.5 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 4.23 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 153.7, 136.8, 132.6, 127.9, 126.6, 126.4, 125.7, 121.6, 118.2, 117.0, 115.5, 111.1, 110.4, 56.2; **FTIR** ($cm^{-1}$) (neat): 2925, 1622, 1467, 1239, 1161, 1100, 1020, 796, 746; **HRMS** (ESI, Pos): calcd for $C_{14}H_{11}N_2O$ $[M+H]^+$: 223.0866 *m/z*, found 223.0869 *m/z*.

**Imidazo[2,1,5-*c,d*]naphtho[2,1-*a*]indolizine (7o)**: Following **procedure F**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 20% to 50% EtOAc in hexanes. Fractions containing **7o** were concentrated to dryness, resulting in an yellow solid (138.0 mg, 97% yield). **mp:** 149-150 °C; **Rf**: 0.31 (100% EtOAc); **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 9.22 (d, *J* = 8.5 Hz, 1H), 8.46 (s, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.81-7.77 (m, 2H), 7.71-7.67 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 138.1, 133.6, 129.6, 128.3, 127.3, 127.1, 127.0, 126.9, 126.7, 126.0, 125.4, 122.0, 120.2, 116.5, 112.1 ; **FTIR** ($cm^{-1}$) (neat): 3042, 2920, 2851, 784, 723, 672, 468; **HRMS** (ESI, Pos): calcd for $C_{17}H_{10}N_2$ $[M+H]^+$: 243.0923 *m/z*, found 243.0927 *m/z*.

**11*H*-Fluoreno[3,2-*a*]imidazo[2,1,5-*c,d*]indolizin-11-one (7p)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 3% MeOH in $CH_2Cl_2$. Fractions containing **7p**

were concentrated to dryness, resulting in red solid (67 mg, 61% yield). **mp:** 297-300 °C; **$^1$H NMR** ($CDCl_3$, 700 MHz): δ 8.54 (s, 1H), 8.52 (s, 1H), 8.31-8.28 (m, 3H), 7.86-7.82 (m, 1H), 7.74 (d, *J* = 5.5 Hz, 1H), 7.66 (d, *J* = 5.5 Hz, 1H), 7.58 (t, *J* = 5.5 Hz, 1H), 7.33 (t, *J* = 5.5 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 175 MHz): δ 192.8, 144.5, 140.5, 135.9, 135.4, 135.3, 135.1, 135.0, 129.4, 127.1, 126.7, 126.4, 125.9, 124.4, 123.7, 120.8, 119.0, 116.3, 115.1, 114.4; **FTIR** ($cm^{-1}$) (neat): 1701, 1598, 1327, 1303, 1061, 998, 797, 742, 737, 672; **HRMS** (ESI, Pos): calcd for $C_{20}H_{10}N_2O$ $[M+H]^+$: 295.0867 *m/z*, found 295.0866 *m/z*. This compound does not exhibit significant fluorescence because of limited solubility in MeOH and $H_2O$.

**Furo[3,2-*a*]imidazo[2,1,5-*c,d*]indolizine (7q)**: Following **procedure F**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 50% EtOAc in hexanes. Fractions containing **7q** were concentrated to dryness, resulting in a bright green solid (36 mg, 40% yield). **mp:** 119-120 °C; **Rf**: 0.30 (50% EtOAc in hexanes); **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 8.34 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 2.4 Hz, 1H), 7.75-7.69 (m, 1H), 7.15 (d, *J* = 2.1 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 149.4, 146.7, 129.9, 127.5, 127.2, 121.6, 120.4, 120.4, 115.2, 112.6, 105.9; **FTIR** ($cm^{-1}$) (neat): 3127, 2981, 2968, 2921, 2908, 989, 797, 706, 671; **HRMS** (ESI, Pos): calcd for $C_{11}H_6N_2O$ $[M+H]^+$: 183.0553 *m/z*, found 183.0549 *m/z*.

**Thieno[3,2-*a*]imidazo[2,1,5-*cd*]indolizine (7r)**: Following **procedure F**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 30% to 50% EtOAc in hexanes. Fractions containing **7r** were concentrated to dryness, resulting in a bright orange solid (37.4 mg, 38% yield). **mp:** 150-152 °C; **Rf**: 0.22 (100% EtOAc); **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.34 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 7.0 Hz, 1H), 7.77 (d, *J* = 5.0 Hz, 1H), 7.73 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.51 (d, *J* = 5.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 136.3, 134.9, 132.2, 129.3, 126.9, 126.5, 123.5, 121.7, 119.4, 115.4, 11.5; **FTIR** ($cm^{-1}$) (neat): 3085, 3068, 2921, 2850, 742, 730, 669; **HRMS** (ESI, Pos): calcd for $C_{11}H_6N_2S$ $[M+H]^+$: 199.0325 *m/z*, found 199.0329 *m/z*.

**7-Methylimidazo[2,1,5-*c,d*]indolizine (7s)**: Following **procedure E**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 50% EtOAc in hexanes. Fractions containing **7s** were concentrated to dryness, resulting in a light green solid (0.10 g, 87% yield). **mp:** 68-70 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.42 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.19 (s, 1H), 2.84 (d, *J* = 1.0 Hz, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 141.1, 131.7, 131.0, 128.1, 127.0, 122.1, 114.4, 114.3, 113.0, 12.6; **FTIR** ($cm^{-1}$) (neat): 3384, 3075, 2964, 2901, 2833, 2765, 1117, 1028, 777; **HRMS** (ESI, Pos): calcd for $C_{10}H_8N_2$ $[M+H]^+$: 157.0766 *m/z*, found 157.0760 *m/z*.

**6-Phenylimidazo[2,1,5-*c,d*]indolizine (7t)**: Following **procedure F**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 10% to 60% EtOAc in hexanes. Fractions containing **7t** were concentrated to dryness, resulting in an orange oil (31 mg, 28% yield). **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.55 (s, 1H), 8.32 (d, *J* = 7.0 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.91-7.89 (m, 2H), 7.84 (t, *J* = 7.5 Hz, 1H), 7.56-7.52 (m, 2H), 7.41-7.38 (m, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 135.4, 132.63, 130.8, 126.7, 126.4, 126.1, 125.1, 124.8, 124.0, 120.0, 114.2, 113.7, 111.3; **FTIR** ($cm^{-1}$) (neat): 3376, 3056, 2981, 2922, 2865, 2845, 1092, 1069, 769; **HRMS** (ESI, Pos): calcd for $C_{15}H_{10}N_2$ $[M+H]^+$: 219.0917 *m/z*, found 219.0913 *m/z*.

**General procedure for the arylation of imidazo[2,1,5-*c,d*]indolizines**

**Procedure H (direct arylation)**:

To a microwave (sealable) vial (VWR®) equipped with a magnetic stirbar and a rubber septum was added $Cs_2CO_3$ (1.5 equiv). The vial was heated to 150°C in an oil bath under vacuum for 30 minutes. The tube was cooled to room temperature, flushed with argon and the corresponding iodide (1.1 equiv) and imidazo[2,1,5-*c,d*]indolizine (1.0 equiv) as previously synthesized were added. DMA (0.5 M) was used to cannulate $[Pd(phen)_2][PF_6]_2$ (0.05 equiv) from a dry vial into the reaction vessel. The vial was capped with an aluminum microwave cap (VWR® with Teflon seal) and heated to 150°C in an oil bath for 20h. Brine and EtOAc were added. Phases were separated and aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried over $MgSO_4$ and evaporated to dryness.

**Procedure I: (bromination/coupling sequence)**

To a flame-dried round-bottom flask equipped with a magnetic stirbar and a rubber septum was added the corresponding imidazo[2,1,5-*c,d*]indolizine (1.0 equiv), as previously synthesized. 1,4-dioxane (0.2 M) was added and solution was frozen in a water/ice bath. In a flame-dried vial equipped with a rubber septum, bromine (1.3 equiv) was mixed with 1,4-dioxane (0.2M) and cannulated under argon into the round-bottom flask (freezes on top of the substrate solution). The ice bath was removed and both layers mixed together as they thawed. This mixture was stirred at room temperature for 20 minutes. A saturated solution of sodium thiosulfate in water was added and the resulting solution was transferred to a separatory funnel and extracted with $CH_2Cl_2$ (4x). The combined organic layers were washed with 2M NaOH, dried over $MgSO_4$ and evaporated to dryness to yield a yellow-orange solid. The crude bromoimidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 30% EtOAc in hexanes. Fractions containing (**7a'**, **7d'**, **7k'**) were concentrated to dryness, resulting in a colorful solid.

To a microwave (sealable) vial (VWR®) equipped with a magnetic stirbar and a rubber septum was added the corresponding bromoimidazo[2,1,5-*c,d*]indolizine (1.0 equiv), the corresponding boronic acid (2.0 equiv), $K_3PO_4$*$H_2O$ (4.0 equiv) and $PdCl_2$(dppf)* $CH_2Cl_2$ (0.05 equiv). 17% $H_2O$ in DMF (0.08M) was added, vial was flushed with argon and mixture was heated to 80°C and stirred for 90 minutes. EtOAc and saturated aqueous solutions of NaCl and $NaHCO_3$ were added and mixture was transferred to a separatory funnel. Phases were separated and aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried over $MgSO_4$ and evaporated to dryness.

**Characterization data of other Benzoimidazo[2,1,5-*cd*]indolizines**

**2-Bromobenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7a')**: Following **Procedure I**. Yellow-green solid (34 mg, 96% yield). **mp:** 155-157 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.39-8.32 (m, 2H), 8.12-8.02 (m, 2H), 7.80-7.75 (m, 1H), 7.72-7.59 (m, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 136.0, 130.1, 129.7, 127.8, 127.1, 125.3, 124.6, 123.3, 122.4, 119.9, 116.1, 111.4, 111.2; **FTIR** ($cm^{-1}$) (neat): 2925, 1424, 1389, 1336, 1300, 1109, 1070, 743, 727; **HRMS** (ESI, Pos): calcd for $C_{13}H_8BrN_2$ $[M+H]^+$: 270.9865 *m/z*, found 270.9873 *m/z*. This compound does not exhibit significant fluorescence

**2-Bromo-7-benzyloxybenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (7d')**: Following **Procedure I**. Yellow solid (114 mg, 90% yield). **mp:** 142-144°C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.24 (d, *J* = 9.0 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.63 (dd, *J* = 7.5, 9.0 Hz, 1H), 7.53-7.50 (m, 2H), 7.45-7.42 (m, 3H), 7.39-7.35 (m, 1H), 5.26 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 157.4, 136.6, 136.1, 131.7, 128.9, 128.4, 127.7, 127.2, 124.5, 122.1, 121.9, 121.0, 119.1, 116.4, 111.4, 110.1, 107.8, 70.9; **FTIR** ($cm^{-1}$) (neat): 3056, 1620, 1564, 1496, 1435, 1380, 1338, 1282, 1227, 1167, 1104, 1062; **HRMS** (ESI, Pos): calcd for $C_{20}H_{14}BrN_2O$ $[M+H]^+$: 377.0284 *m/z*, found 377.0288 *m/z*. This compound does not exhibit significant fluorescence

**2-Bromo-6,7,8-trimethoxybenzo[*a*]imidazo[2,1,5-*cd*]indolizine (7k')**: Following **Procedure I**. Green solid (0.20 g, 80% yield). **mp:** 144-146 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.01 (d, *J* = 7.0 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.67 (dd, *J* = 7.0, 9.0 Hz, 1H), 7.58 (s, 1H), 4.28 (s, 3H), 4.07 (s, 3H), 4.00 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 156.9, 150.1, 140.0, 136.0, 126.2, 124.8, 124.1, 123.0, 117.1, 114.8, 112.9, 110.3, 97.6, 61.7, 61.3, 56.6; **FTIR** ($cm^{-1}$) (neat): 2939, 1617, 1454, 1416, 1275, 1140, 1111, 982, 756; **HRMS** (ESI, Pos): calcd for $C_{16}H_{14}BrN_2O_3$ $[M+H]^+$: 61.0182 *m/z*, found 361.0187 *m/z*. This compound does not exhibit significant fluorescence

**2-Phenylbenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8a)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 35% in hexanes. Fractions containing **8a** were concentrated to dryness, resulting in a yellow solid (48 mg, 89% yield). **mp:** 170-172 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.43 (d, *J* = 7.9 Hz, 1H), 8.32 (d, *J* = 8.3 Hz, 2H), 8.24 (d, *J* = 7.6 Hz, 2H), 7.94 (d, *J* = 6.9 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.69-7.46 (m, 4H), 7.36 (t, *J* = 7.2 Hz, 1H).**$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 140.0, 137.0, 135.8, 130.8, 129.4, 129.1, 127.9, 127.2, 126.9, 126.6, 125.0, 123.1, 123.0, 122.4, 120.1, 117.7, 110.8; **FTIR** ($cm^{-1}$) (neat): 3043, 1600, 1388, 1336, 1102, 1070, 783, 756, 692, **HRMS** (ESI, Pos): calcd for $C_{19}H_{13}N_2$ $[M+H]^+$: 269.1073 *m/z*, found 269.1077 *m/z*.

**2-(4-Nitrophenyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8b)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 35% EtOAc in hexanes. Fractions containing **8b** were concentrated to dryness, redissolved in boiling DCM, precipitated with hexanes, cooled to -78°C and filtrated, washing with -78°C hexanes. The residue was recovered as a yellow solid (20 mg, 32% yield). **mp:** 231-234 °C; **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 8.49-8.41 (m, 7H), 8.09 (d, *J* = 7.0 Hz, 1H), 7.88 (d, *J* = 7.0 Hz, 1H), 7.84-7.81 (m, 1H), 7.69 (dd, *J* = 1.0, 7.5 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 146.1, 142.3, 138.5, 136.9, 131.7, 130.1, 128.1, 127.9, 126.2, 124.7, 124.4, 123.5, 120.6, 117.6, 111.1; **FTIR** ($cm^{-1}$) (neat): 1588, 1494, 1461, 1310, 1098, 1070, 847, 757, 701; **HRMS** (ESI, Pos): calcd for $C_{19}H_{12}N_3O_2$ $[M+H]^+$: 314.0924 *m/z*, found 314.0928 *m/z*; This compound does not exhibit significant fluorescence

**4-(Benzo[*a*]imidazo[2,1,5-*c,d*]indolizin-2-yl)benzonitrile (8c)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 40% EtOAc in hexanes. Fractions containing **8c** were concentrated to dryness, resulting in an yellow solid (17 mg, 58% yield). **mp:** 226-228 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.48 (ddd, *J* = 0.5, 1.0, 8.0 Hz, 1H), 8.43 (ddd, *J* = 0.5, 1.0, 8.0 Hz, 1H), 8.42 (d, *J* = 8.5 Hz, 1H), 8.38 (d, *J* = 8.5 Hz, 2H), 8.10 (d, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 7.0 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.70 (ddd, *J* =

1.0, 7.0, 8.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 140.1, 138.0, 137.1, 132.7, 131.4, 129.8, 127.9, 127.6, 126.2, 125.8, 124.0, 123.8, 123.3, 120.3, 119.4, 117.3, 110.9, 109.5; **FTIR** ($cm^{-1}$) (neat): 2926, 2214, 1605, 1414, 1336, 1102, 1072, 748, 838; **HRMS** (ESI, Pos): calcd for $C_{20}H_{12}N_3$ $[M+H]^+$: 294.1026 *m/z*, found 294.1033 *m/z*.

**2-(4-Methoxyphenyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8d)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 20% EtOAc in hexanes. Fractions containing **8d** were concentrated to dryness, resulting in an yellow solid (59 mg, 99% yield). **mp:** 148-151 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.45 (d, *J* = 8.0 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 8.39 (d, *J* = 9.0 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 6.5 Hz, 1H), 7.79 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.70 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.61 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 3.91 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 158.9, 140.0, 136.4, 130.4, 129.0, 128.6, 127.7, 127.5, 126.3, 124.5, 122.9, 122.2, 121.6, 119.7, 117.4, 114.5, 110.6, 55.4; **FTIR** ($cm^{-1}$) (neat): 1517, 1468, 1434, 1241, 1172, 1039, 975, 834, 623; **HRMS** (ESI, Pos): calcd for $C_{20}H_{15}N_2O$ $[M+H]^+$: 299.1179 *m/z*, found 299.1183 *m/z*.

**2-(Thiophen-2-yl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8e)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 20% EtOAc in hexanes. Fractions containing **8e** were concentrated to dryness, resulting in a dark orange solid (13 mg, 86% yield). **mp:** 54-57 °C; **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 8.41 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.78-7.56 (m, 4H), 7.35 (dd, *J* = 1.0, 5.0 Hz, 1H), 7.19 (dd, *J* = 3.5, 5.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 131.0, 129.6 (2), 128.1 (2), 127.8, 126.9, 125.2, 124.4, 123.3 (2), 123.2, 122.6, 122.3, 120.4, 117.3, 111.2; **FTIR** ($cm^{-1}$) (neat): 2922, 2852, 1721, 1423, 1393, 1333, 1063, 748, 699; **HRMS** (ESI, Pos): calcd for $C_{17}H_{11}N_2S$ $[M+H]^+$: 275.0638 *m/z*, found 275.0642 *m/z*.

**7-(Benzyloxy)-2-phenylbenzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8f)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 35% EtOAc in hexanes. Fractions containing **8f** were concentrated to dryness, resulting in a yellow solid (62 mg, 83% yield). **mp:** 128-130 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 8.0 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.23-8.21 (m, 2H), 7.87 (d, *J* = 7.0 Hz, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.58 (dd, *J* = 3.5, 7.0 Hz, 1H), 7.56-7.51 (m, 4H), 7.45-7.33 (m, 5H), 5.24 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 157.1, 139.2, 137.0, 136.8, 135.9, 132.3, 129.8, 129.1, 128.8, 128.7, 128.3, 127.7, 127.0, 126.8, 126.5, 122.9, 122.2, 121.9, 121.1, 118.8, 118.0, 110.8, 107.6, 70.2; **FTIR** ($cm^{-1}$) (neat): 1563, 1497, 1439, 1282, 1059, 1023, 776, 734, 693, ; **HRMS** (ESI, Pos): calcd for $C_{26}H_{19}N2O$ $[M+H]^+$: 375.1492 *m/z*, found 375.1501 *m/z*.

**7-(Benzyloxy)-2-(4-methoxyphenyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8g)**: Following **Procedure H**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 35% EtOAc in hexanes. Fractions containing **8g** were concentrated to dryness, resulting in an yellow solid (44 mg, 54% yield). **mp:** 121-124 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.28 (d, *J* = 7.5 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 8.12 (d, *J* = 7.0 Hz, 2H), 7.81 (d, *J* = 7.0 Hz, 1H), 7.78 (d, *J* = 2.0 Hz, 1H), 7.51-7.35 (m, 7H), 7.06 (d, *J* = 7.0 Hz, 2H), 5.20 (s, 2H), 3.88 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 159.0, 156.9, 139.3, 136.8, 136.5, 132.0, 128.8, 128.7, 128.2, 127.7, 127.6, 126.5, 122.3, 122.0, 121.2, 120.9, 118.7, 117.9,

114.6, 110.8, 107.4, 70.7, 55.5.; **FTIR** ($cm^{-1}$) (neat): 2923, 1607, 1498, 1439, 1233, 1173, 1058, 1019, 828, 694; **HRMS** (ESI, Pos): calcd for $C_{27}H_{21}N_2O_2$ $[M+H]^+$: 405.1598 *m/z*, found 405.1604 *m/z*.

**4-(7-(Benzyloxy)benzo[*a*]imidazo[2,1,5-*c,d*]indolizin-2-yl)-*N,N*-dipropylaniline (8h)**: Following **Procedure H**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 35% EtOAc in hexanes. Fractions containing **8h** were concentrated to dryness, resulting in an yellow solid (17 mg, 18% yield, 37% corrected for recovered starting material). **mp:** 93-96 °C; **$^{11}$H NMR** ($CDCl_3$, 500 MHz): δ 8.34 (br d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 1.5 Hz, 1H), 7.53-7.35 (m, 7H), 6.82 (br s, 2H), 5.25 (s, 2H), 3.44-3.19 (m, 4H), 1.69 (app sx, *J* = 7.5 Hz, 4H), 0.98 (t, *J* = 7.5 Hz, 6H); **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 156.7, 136.9, 131.7, 128.8 (3), 128.2, 127.8, 127.7 (3), 126.3, 122.1, 121.9 (2), 121.0, 120.5, 118.7, 118.3, 112.3, 111.1, 107.4, 70.8, 53.1, 20.7, 11.6; **FTIR** ($cm^{-1}$) (neat): 2955, 2871, 1609, 1521, 1438, 1468, 1364, 1235, 1193, 1060, 695; **HRMS** (ESI, Pos): calcd for $C_{32}H_{32}N_3O$ $[M+H]^+$: 474.2540 *m/z*, found 474.2547 *m/z*.

**7-(Benzyloxy)-2-(thiophen-2-yl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8i)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 20% EtOAc in hexanes. Fractions containing **8i** were concentrated to dryness, resulting in a yellow solid (39 mg, 84% yield). **mp:** 127-130 °C; **$^{1}$H NMR** ($CDCl_3$, 300 MHz): δ 8.32 (d, *J* = 9.0 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.70 (br s, 1H), 7.62 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.53-7.51 (m, 2H), 7.47-7.42 (m, 3H), 7.37 (m, 1H), 7.34 (dd, *J* = 1.0, 5.0 Hz, 1H), 7.19 (dd, *J* = 3.5, 5.0 Hz, 1H), 5.26 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 157.3, 138.6, 136.7, 136.5, 133.8, 132.4, 128.8, 128.3, 128.1, 127.7, 126.8, 124.3, 123.1, 122.2, 122.0, 121.8, 121.5, 118.9, 117.5, 111.4, 107.7, 70.8; ; **FTIR** ($cm^{-1}$) (neat): 2920, 1619, 1562, 1494, 1434, 1382, 1332, 1282, 1202, 1171, 1131; **HRMS** (ESI, Pos): calcd for $C_{24}H_{17}N_2OS$ $[M+H]^+$: 381.1056 *m/z*, found 381.1065 *m/z*.

**N,N-Dimethyl-2-phenylbenzo[*a*]imidazo[2,1,5-*c,d*]indolizin-7-amine (8j)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 35% EtOAc in hexanes. Fractions containing **8j** were concentrated to dryness, resulting in a red solid (47 mg, 76% yield). **mp:** 95-98 °C; **$^{1}$H NMR** ($CDCl_3$, 500 MHz): δ 8.30 (d, *J* = 8.5 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 7.0 Hz, 1H), 7.58 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.55 (br s, 1H), 7.54-7.50 (m, 2H), 7.33 (tt, *J* = 1.0, 7.0 Hz, 1H), 7.18 (dd, *J* = 2.5, 8.5 Hz, 1H), 3.13 (s, 6H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 149.2, 137.4, 135.4, 133.4, 129.1 (2), 128.0, 126.9, 126.3 (2), 122.4, 122.2, 121.2, 117.9, 115.8, 110.4, 105.4, 41.2; **FTIR** ($cm^{-1}$) (neat): 3060, 2924, 1624, 1562, 1499, 1436, 1063, 775, 698; **HRMS** (ESI, Pos): calcd for $C_{21}H_{18}N_3$ $[M+H]^+$: 312.1495 *m/z*, found 312.1502 *m/***FTIR** ($cm^{-1}$) (neat): 3060, 2924, 1624, 1562, 1499, 1436, 1063, 775, 698; **HRMS** (ESI, Pos): calcd for $C_{21}H_{18}N_3$ $[M+H]^+$: 312.1495 *m/z*, found 312.1502 *m/z*.

**7-Fluoro-2-(4-methoxyphenyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8k)**: Following **Procedure H**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 35% EtOAc in hexanes. Fractions containing **8k** were concentrated to dryness, resulting in a blood red solid (44 mg, 79% yield). **mp:** 148-151 °C; **$^{1}$H NMR** ($CD_2Cl_2$, 300 MHz): δ 8.44 (d, *J* = 8.5 Hz, 1H), 8.37 (ddd, *J* = 0.3, 5.0, 8.5 Hz, 1H), 8.21-8.16 (m, 2H), 8.13-8.09 (m, 2H),

7.73 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.55 (dt, *J* = 2.5, 9.0 Hz, 1H), 7.11-7.07 (m, 2H), 5.42 (s, 2H), 3.90 (s, 3H); **$^{13}$C NMR** ($CD_2Cl_2$, 125 MHz): δ 160.7 (d, *J* = 237.5 Hz, $J_{C-F}$) 159.4, 157.3, 139.8, 135.6, 131.6 (d, *J* = 10.0 Hz, $J_{C-F}$), 128.0, 126.2 (d, *J* = 5.0 Hz, $J_{C-F}$), 123.9, 122.5, 121.9, 121.7 (d, *J* = 10.0 Hz, $J_{C-F}$), 118.7, 117.8 (d, *J* = 25.0 Hz, $J_{C-F}$), 114.7, 112.1, 109.4 (d, *J* = 25.0 Hz, $J_{C-F}$), 55.5; 19F nmr NMR (CD2Cl2, 282 MHz): δ -115.3; **FTIR** ($cm^{-1}$) (neat): 1609, 1517, 1434, 1241, 1172, 1039, 975, 834, 623; **HRMS** (ESI, Pos): calcd for $C_{20}H_{14}FN_2O$ $[M+H]^+$: 317.10847 *m/z*, found 317.1091 *m/z*

**2-Phenyl-11*H*-fluoreno[3,2-*a*]imidazo[2,1,5-*c,d*]indolizin-11-one (8l)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 1% to 5% MeOH in DCM. Fractions containing **8l** were concentrated to dryness, resulting in a purple solid (53 mg, 64% yield). **mp:** 310-315 °C; **$^1$H NMR** ($CD_2Cl_2$, 500 MHz): δ 8.66 (s, 1H), 8.55-8.51 (m, 2H), 8.33-8.28 (m, 3H), 7.88 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.77-7.72 (m, 2H), 7.62-7.59 (m, 3H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.45 (dt, *J* = 0.5, 7.0 Hz, 1H); **$^{13}$C NMR** (DMF-d7, 175 MHz): δ 192.4, 145.0, 141.4, 139.5, 136.6, 135.8, 135.6, 135.0 (2x), 134.5, 129.5, 129.2, 127.6, 127.0, 126.5, 126.3, 124.2, 124.2, 123.9, 121.3, 120.0, 116.5, 115.5, 114.8; **FTIR** ($cm^{-1}$) (neat): 3053, 1714, 1587, 1333, 1301, 1052, 1020, 812, 743; **HRMS** (ESI, Pos): calcd for $C_{26}H_{15}N_2O$ $[M+H]^+$: 371.1184 *m/z*, found 371.1198 *m/z*. This compound does not exhibit significant fluorescence because of limited solubility in MeOH.

**4-(6,7,8-Trimethoxybenzo[*a*]imidazo[2,1,5-*c,d*]indolizin-2-yl)benzonitrile (8m)**: Following **Procedure H**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 20% EtOAc in hexanes. Fractions containing **8m** were concentrated to dryness, resulting in a dark orange solid (55 mg, 77% yield).

Following **method B**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 20% EtOAc in hexanes. Fractions containing **8m** were concentrated to dryness, resulting in a dark orange solid (32 mg, 89% yield).

**mp:** 124-127 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 8.5 Hz, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 7.0 Hz, 1H), 7.69 (s, 1H), 7.67 (dd, *J* = 7.0, 7.5 Hz, 1H), 7.53 (app t, *J* = 8.0 Hz, 2H), 7.35 (app t, *J* = 7.5 Hz, 1H), 4.29 (s, 3H), 4.08 (s, 3H), 4.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 156.6, 150.1, 139.8, 139.6, 137.2, 135.9, 129.1, 127.1, 126.5, 125.9, 124.4, 123.3, 123.0, 117.7, 116.5, 112.3, 97.7, 61.7, 61.3, 56.7.; **FTIR** ($cm^{-1}$) (neat): 2927, 1617, 1502, 1452, 1417, 1276, 1238, 1192, 1136, 1102, 1049; **HRMS** (ESI, Pos): calcd for $C_{22}H_{19}N_2O_3$ $[M+H]^+$: 359.1390 *m/z*, found 359.1397 *m/z*

**4-(6,7,8-Trimethoxybenzo[*a*]imidazo[2,1,5-*c,d*]indolizin-2-yl)benzonitrile (8n)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 20% EtOAc in hexanes. Fractions containing **8n** were concentrated to dryness, resulting in an orange (34 mg, 89% yield). **mp:** 209-212 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.30 (d, *J* = 7.5 Hz, 2H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 7.0 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 3H), 7.66 (s, 1H), 4.30 (s, 3H), 4.10 (s, 3H), 4.02 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 157.0, 150.3, 140.4, 140.3, 138.2, 136.8, 132.9, 126.6, 126.3, 124.7, 124.4, 124.2, 119.5, 118.2, 116.1, 112.4, 109.5, 98.0, 61.7, 61.3, 56.7. **FTIR** ($cm^{-1}$) (neat): 2936, 2217, 1602, 1504, 1459, 1411, 1280, 1240, 1198, 1169, 1138, 1103; **HRMS** (ESI, Pos): calcd for $C_{23}H_{18}N_3O_3$ $[M+H]^+$: 384.1342 *m/z*, found 384.1349 *m/z*.

**6,7,8-Trimethoxy-2-(4-methoxyphenyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8o)**: Following **Procedure I**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 0% to 20% EtOAc in hexanes. Fractions containing **8o** were concentrated to dryness, resulting in a deep red solid (35 mg, 90% yield). **mp:** 148-151 °C; **$^1$H NMR** ($CDCl_3$, 300 MHz): δ 8.28 (d, *J* = 8.5 Hz, 1H), 8.18-8.15 (m, 2H), 8.01 (d, *J* = 7.0 Hz, 1H), 7.68 (s, 1H), 7.65 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.10-7.06 (m, 2H), 4.29 (s, 3H), 4.09 (s, 3H), 4.01 (s, 3H), 3.90 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 159.1, 156.5, 150.1, 139.8, 139.6, 136.9, 128.8, 127.8, 125.6, 124.3, 122.8, 122.4, 117.5, 116.5, 114.6, 112.3, 97.6, 61.7, 61.3, 56.7, 55.5; **FTIR** ($cm^{-1}$) (neat): 2970, 1610, 1568, 1517, 1468, 1434, 1330, 1241, 1172, 1095; **HRMS** (ESI, Pos): calcd for $C_{23}H_{21}N_2O_4$ $[M+H]^+$: 389.1496 *m/z*, found 389.1504 *m/z*.

**7-Methyl-2-phenylimidazo[2,1,5-*c,d*]indolizine (8p)**: Following **Procedure H**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 10% to 60% EtOAc in hexanes. Fractions containing **8p** were concentrated to dryness, resulting in a yellow oil (72 mg, 61% yield). **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.32 (d, *J* = 8.0 Hz, 1H), 8.29-8.25 (m, 2H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.41-7.36 (m, 1H), 7.17-7.15 (m, 1H), 2.87 (d, *J* = 0.5 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 144.1, 140.4, 135.5, 130.7, 129.0, 128.5, 127.7, 127.0, 124.3, 122.6, 115.4, 114.6, 112.9, 12.6; **FTIR** ($cm^{-1}$) (neat): 3379, 3064, 2951, 2899, 2802, 2787, 1111, 1021, 779; **HRMS** (ESI, Pos): calcd for $C_{16}H_{13}N_2$ $[M+H]^+$: 233.1079 *m/z*, found 233.1084 *m/z.*

**2-(4-Methylphenyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (8r)**: Following **Procedure H**. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 5% to 35% EtOAc in hexanes. Fractions containing **8p** were concentrated to dryness, resulting in a shiny orange foam (55 mg, 97% yield). **mp** = 51-54 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.48 (d, *J* = 8.0 Hz, 1H), 8.40 (d, *J* = 8.5 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 7.0 Hz, 1H), 7.79 (app dt, *J* = 1.0, 8.5 Hz, 1H), 7.72 (dd, *J* = 7.0, 8.5 Hz, 1H), 7.62 (app dt, *J* = 1.0, 8.5 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 101 MHz): δ 137.3, 130.7, 129.8 (2), 129.4, 127.4, 126.9, 126.5, 126.4, 125.1, 123.1 (2), 122.5, 122.4, 120.4, 118.0, 111.2, 21.4.**FTIR** ($cm^{-1}$) (neat): 3058, 2920, 1619, 1521, 1498, 1463, 1427, 1334, 1284, 1224, 1186, 1164; **HRMS** (ESI, Pos): calcd for $C_{20}H_{15}N_2$ $[M+H]^+$: 283.1230 *m/z*, found 283.1239 *m/z.*

**General procedure for double C-H arylation of imidazo[2,1,5-*c,d*]indolizine (8q)**

**7-Methyl-2,3-diphenylimidazo[2,1,5-*c,d*]indolizine (8q)**: To a 5 mL microwave vial (VWR® 2-5 mL) equipped with a magnetic stirbar and a rubber septum was added $Cs_2CO_3$ (0.90 mmol, 3.0 equiv). The vial was heated to 150 °C in an oil bath under vacuum for 30 minutes. The tube was cooled to room temperature, flushed with argon and iodobenzene (0.60 mmol, 2.0 equiv) and imidazo[2,1,5-*c,d*]indolizine (0.30 mmol, 1.0 equiv) as previously synthesized were added. DMA (0.6 mL, 0.5 M) was used to cannulate $[Pd(phen)_2][PF_6]_2$ (11 mg, 15 $\mu$mol, 0.05 equiv) from a dry 4 mL vial into the reaction vessel. The vial was capped with an aluminum microwave cap (VWR® with Teflon seal) and heated to 150 °C in an oil bath for 16 h. Brine and EtOAc were added and mixture was transferred to a separatory funnel. Phases were separated and aqueous phase was extracted with EtOAc (3X). The combined organic layers were washed with brine (2x), dried over $MgSO_4$ and evaporated to dryness. The crude imidazo[2,1,5-*c,d*]indolizine was purified by flash chromatography over silica gel using a gradient of 10% to

60% EtOAc in hexanes. Fractions containing **8q** were concentrated to dryness, resulting in an orange solid (53 mg, 65% yield). **mp:** 138-140 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.37 (d, *J* = 8.0 Hz, 1H), 8.31-8.28 (m, 2H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.76 (t, *J* = 8.0 Hz, 1H), 7.71-7.68 (m, 2H), 7.59-7.53 (m, 4H), 7.44-7.38 (m, 2H), 2.94 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 144.0, 140.8, 135.5, 134.4, 129.6, 129.1, 128.9, 127.9, 127.7, 127.2, 127.0 (2), 126.1, 124.7, 123.0, 116.0, 114.7, 11.5; **FTIR** ($cm^{-1}$) (neat): 3386, 3055, 2975, 2903, 2847, 2733, 1114, 1038, 764; **HRMS** (ESI, Pos): calcd for $C_{22}H_{17}N_2$ $[M+H]^+$: 309.1392 *m/z*, found 309.1398 *m/z.*

**General procedure for the *N*-alkylation of Benzo[*a*]imidazo[2,1,5-*c,d*]indolizines**

**Procedure J**

To a flame-dried microwave (sealable) vial (VWR®) equipped with a magnetic stirrer and a rubber septum was added the corresponding benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (0.25 mmol, 1.0 equiv) as previously synthesized, THF (0.5 M) and benzyl bromide (1.0 mmol, 4.0 equiv). The vial was capped with an aluminum microwave cap (VWR® with Teflon seal) and heated to 60°C in an oil bath for 16 h. Diethyl ether was added and the resulting slurry was filtered on fritted glass and washed with diethyl ether.

**Characterization data of benzoimidazo[2,1,5-*c,d*]indoliziniums**

**1-Benzylbenzo[*a*]imidazo[2,1,5-*c,d*]indolizin-1-ium bromide (9a):** Following **Procedure J**. Product obtained as a bright yellow solid, (93 mg, quantitative yield). mp: 247-250 °C; **$^1$H NMR** ($CD_3OD$, 400 MHz): δ 8.78 (s, 1H), 8.70-8.66 (m, 1H), 8.65 (d; *J* = 7.0 Hz, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 8.16 (dd, *J* = 7.0, 7.5 Hz, 1H), 8.10-8.07 (m, 1H), 7.92-7.87 (m, 2H), 7.62-7.57 (m, 2H), 7.50-7.44 (m, 3H), 6.30 (s, 2H); **$^{13}$C NMR** ($CD_3OD$, 125 MHz): δ 135.3, 134.0, 132.7, 132.1, 130.6 (3), 130.1, 129.6, 129.6, 125.7, 125.3, 124.1, 122.7, 122.2, 120.7, 118.2, 55.6; **FTIR** (cm-1) (neat): 3021, 1510, 1450, 1429, 1354, 1178, 1160, 1128, 1081, 1015; **HRMS** (ESI, Pos): calcd for $C_{20}H_{15}N_2$ [M+H]+: 283.1230 m/z, found 283.1235 m/z

**1-Benzyl-7-(methoxycarbonyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizin-1-ium bromide (9b):** Following **Procedure J**. Product obtained as a bright yellow solid, (44 mg, 98% yield). **mp:** 215-218 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 10.10 (s, 1H), 9.11 (d, *J* = 0.5 Hz, 1H), 8.59 (d, *J* = 7.0 Hz, 1H), 8.52 (d, *J* = 5.5 Hz, 1H), 8.42 (dd, *J* = 0.5, 6.5 Hz, 1H), 8.11 (dd, *J* = 6.0, 6.5 Hz, 1H), 7.98 (d, *J* = 6.8 Hz, 1H), 7.68 (dd, *J* = 1.0, 6.5 Hz, 2H), 7.34-7.26 (m, 3H), 6.73 (s, 2H), 4.01 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz):δ 165.5, 133.6, 131.9, 131.5, 130.4, 129.6, 129.5, 128.9, 128.2, 127.9, 125.7, 125.3, 125.2 (2), 123.6, 121.9, 121.3, 117.6, 55.6, 52.9; **FTIR** (cm-1) (neat): 3024, 1716, 1430, 1348, 1321, 1290, 1249, 1167, 1130, 1069; **HRMS** (ESI, Pos): calcd for $C_{22}H_{17}N_2O_2$ [M+H]+: 341.1285 m/z, found 341.1291 m/z.

**1-Benzyl-6,7,8-trimethoxybenzo[*a*]imidazo[2,1,5-*c,d*]indolizin-1-ium bromide (9c): Procedure J**. Product obtained as a bright yellow solid, (118 mg, 99% yield). **mp**: 207-210 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 9.76 (s, 1H), 8.30 (d, *J* = 9.0 Hz, 1H), 8.19 (d, *J* = 7.0 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 6.5 Hz, 2H), 7.33-7.26 (m, 3H), 7.15 (br s, 1H), 6.78 (s, 2H), 4.27 (s, 3H), 4.00 (s, 3H), 3.96 (s, 3H); **$^{13}$C NMR** ($CDCl_3$, 75 MHz): δ 157.6, 149.7, 141.8, 134.0, 130.2, 128.9 (2), 128.6, 127.9, 126.9, 122.7, 122.0, 118.3, 118.1, 117.9, 116.8, 100.4, 61.3, 61.1, 57.6, 54.5.; **FTIR** (cm-1) (neat): 3365, 3053, 2936, 1612,

1514, 1471, 1418, 1356, 1290, 1269, 1251, 1194, 1168, 1119, 1102, 1052; **HRMS** (ESI, Pos): calcd for $C_{23}H_{21}N_2O_3$ [M+H]+: 373.1547 m/z, found 373.1562 m/z.

**General procedures for the derivatization of imidazo[2,1,5-*c,d*]indolizines**

**Benzo[*a*]imidazo[2,1,5-*c,d*]indolizine-7-carboxylic acid (10a)**: To a 5 mL round-bottom flask equipped with a magnetic stirbar and a rubber septum was added methyl benzo[*a*]imidazo[2,1,5-*cd*]indolizine-7-carboxylate (**7i**) (22 mg, 0.09 mmol, 1.0 equiv) as previously synthesized. 2.0 M NaOH in water (0.35 mL, 0.70 mmol, 8.0 equiv), THF (0.22 mL) and MeOH (0.22 mL) were added. The resulting suspension was vigorously stirred at room temperature for 16 h (becomes homogenous after 2h). 12N HCl was added dropwise until pH = 2, causing precipitation. The residue was recovered by filtration, washing with 2N HCl, then with EtOAc, yielding a brown solid (19 mg, 0.08 mmol, 92% yield). **mp**: >310 °C; **1H NMR** ($CDCl_3$, 400 MHz): δ 9.35 (s, 1H), 8.74 (d, *J* = 7.0 Hz, 1H), 8.71 (s, 1H), 8.59 (d, *J* = 8.5 Hz, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 8.18 (t, *J* = 8.0 Hz, 1H); **$^{13}$C NMR** ($CD_3OD$, 125 MHz): δ 174.9, 136.1, 134.3, 130.8, 130.7, 128.3, 127.5, 126.6, 126.3, 124.8, 123.8, 118.7, 117.9, 112.3; **FTIR** (cm-1) (neat): 3130, 1703, 1420, 1349, 1293, 1267, 1226, 1156, 1114, 1074 ; **HRMS** (ESI, Pos): calcd for $C_{14}H_9N_2O_2$ [M+H]+: 237.0659 m/z, found 237.0667 m/z.

***N*-(6-Hydroxyhexyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine-7-carboxamide (10b):** To a flame-dried 2 mL microwave vial (VWR® 0.5-2 mL) equipped with a magnetic stirrer and rubber septum were added methyl benzo[*a*]imidazo[2,1,5-*cd*]indolizine-7-carboxylate (**7i**) (50 mg, 0.20 mmol, 1.0 equiv) as previously synthesized and 6-aminohexanol (94 mg, 0.80 mmol, 4.0 equiv). The solids were heated to 175°C in an oil bath (melts) and stirred for 4h under a light flow of argon. Mixture was cooled and dissolved in $CH_2Cl_2$ with a few drops of MeOH. Saturated aqueous $NH_4Cl$ was added and phases were separated. Aqueous phase was extracted with DCM (4x), organic phases were combined, dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography (2-10% MeOH/DCM) yielded a yellow powder (43 mg, 0.13 mmol, 64% yield). mp: 148-151 °C; **$^1$H NMR** ($CD_3OD$, 400 MHz): δ 9.06 (s, 1H), 8.40 (dd, *J* = 7.0, 9.0 Hz, 1H), 8.31 (s, 1H), 8.27 (dd, *J* = 1.5, 9.0 Hz, 1H), 7.91 (dd, *J* = 7.0, 9.0 Hz, 1H), 3.58 (t, *J* = 6.5 Hz,2H), 3.50 (t, *J* = 7.0 Hz, 2H), 1.73 (qn, *J* = 6.5 Hz, 2H), 1.59 (qn, *J* = 6.5 Hz, 2H), 1.50-1.47 (m, 4H); **$^{13}$C NMR** ($CD_3OD$, 100 MHz): δ 169.3, 136.0, 133.6, 132.4, 129.5, 128.9, 127.1, 126.8, 125.7, 124.2, 120.5, 119.6, 114.7, 62.9, 41.3, 33.6, 30.6, 28.0, 26.7; **FTIR** (cm-1) (neat): 3293, 2932, 2857, 1626, 1533, 1461, 1336, 1241, 1065; **HRMS** (ESI, Pos): calcd for $C_{20}H_{22}N_3O_2$ [M+H]+: 336.1707 m/z, found 336.1717 m/z.

**Benzo[*a*]imidazo[2,1,5-*c,d*]indolizin-7-ylmethanol (10c) :** To a flame dried 5 mL round-bottom flask equipped with a magnetic stirbar and a rubber septum were added $LiAlH_4$ (19 mg, 0.50 mmol, 2.5 equiv) and THF (0.5 mL). This suspension was cooled at 0°C before adding a solution of methyl benzo[*a*]imidazo[2,1,5-*cd*]indolizine-7-carboxylate (**7i**) (50 mg, 0.20 mmol, 1.0 equiv) as previously synthesized in THF (0.5 mL). The reaction mixture was stirred at 0°C for 4h. The mixture was poured in a saturated aqueous solution of sodium potassium tartrate cooled to 0°C and stirred until gas evolution stops. DCM was added and phases were separated. Aqueous phase was extracted with DCM (2x), organic phases were combined, washed with brine, dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography (0.5 - 10% MeOH/DCM) yielded a yellow powder (35 mg, 0.16 mmol, 79% yield). Single crystals were obtained by dissolving the product in boiling 1%

MeOH/DCM, then adding hot hexanes (50 °C) until a slight cloudiness is observed and slowly cooling to -20°C. mp: 154-155 °C; **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 8.39 (s, 1H), 8.33 (d, *J* = 6.5 Hz, 1H), 8.22 (s, 1H), 8.14 (d, *J* = 7.0 Hz, 1H), 7.98 (d, *J* = 5.5 Hz, 1H), 7.74 (d, *J* = 5.5 Hz, 1H), 7.67 (dd, *J* = 5.5, 7.0 Hz, 1H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 138.0, 137.5, 131.5, 128.5, 127.6, 127.5, 126.7, 125.9, 121.9, 121.5, 120.1, 117.0, 110.6, 65.6; **FTIR** (cm-1) (neat): 3121, 2909, 1435, 1410, 1333, 1298, 1277, 1238, 1168, 1080; **HRMS** (ESI, Pos): calcd for $C_{14}H_{11}N_2O$ [M+H]+: 223.0866 m/z, found 223.0876 m/z.

**7-(Azidomethyl)benzo[*a*]imidazo[2,1,5-*c,d*]indolizine (10d)** : To a 5 mL round-bottom flask equipped with a magnetic stirbar and a rubber septum were added benzo[*a*]imidazo[2,1,5-*cd*]indolizin-7-ylmethanol (**10c**) (56 mg, 0.25 mmol, 1.0 equiv) as previously synthesized, diphenylphosphoryl azide (DPPA) (65 μL, 0.30 mmol, 1.2 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (45 mL, 0.30 mmol, 1.2 equiv) and THF (1.0 mL, 0.25 M). Mixture was stirred at room temperature for 16h. 1.0 mL of $CH_2Cl_2$ was added and the resulting solution was directly added on a silica column. Flash chromatography over silica gel using a gradient of 1% to 8% $CH_2Cl_2$ in hexanes. Fractions containing **10d** were concentrated to dryness, resulting in a yellow solid (60 mg, 0.24 mmol, 97% yield).mp: 110-112 °C; **$^1$H NMR** ($CDCl_3$, 500 MHz): δ 8.41 (d, *J* = 8.0 Hz, 1H), 8.34 (s, 1H), 8.25 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 1H), 7.71 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.69 (dd, *J* = 7.0, 8.5 Hz, 1H), 4.63 (s, 2H); **$^{13}$C NMR** ($CDCl_3$, 125 MHz): δ 137.1, 132.3, 131.4, 129.5, 127.9, 127.8, 126.3, 126.0, 122.8, 122.0, 120.4, 117.3, 111.0, 55.2; **FTIR** (cm-1) (neat): 2933, 2107, 2080, 1623, 1531, 1450, 1433, 1411, 1336, 1295, 1237, 1199, 1167, 1157, 1078; **HRMS** (ESI, Pos): calcd for $C_{14}H_{10}N_5$ [M+H]+: 248.0931 m/z, found 248.094 m/z.

**Benzo[*a*]imidazo[2,1,5-*c,d*]indolizin-7-ylmethanaminium chloride (10e)** :

**From corresponding azide** : To a 5 mL round-bottom flask equipped with a magnetic stirbar and a rubber septum were added benzo[*a*]imidazo[2,1,5-*cd*]indolizine-7- (**7j**) (25 mg, 0.10 mmol, 1.0 equiv) as previously synthesized, 20% $Pd(OH)_2$ on carbon (4 mg, 5 μmol, 0.05 equiv) and EtOH (0.35 mL, 0.3 M). Hydrogen gas was bubbled in the suspension for 50 minutes and the mixture was stirred under an hydrogen atmosphere (1 bar) for 20 h. Excess 2N HCl was added and suspension was filtered on Celite. Filtrate was concentrated under vacuum to remove organic solvents. The resulting yellow aqueous phase was washed with DCM (4x) and concentrated to dryness. The solid was dissolved in DCM with 2-3 drops of MeOH and precipitated by the rapid addition of $Et_2O$. The residue was recovered by filtration of fritted glass, washing with ether, yielding a yellow solid (26 mg, 0.10 mmol, quantitative yield).

**From corresponding nitrile** : To a 5 mL round-bottom flask equipped with a magnetic stirbar and a rubber septum were added benzo[a]imidazo[2,1,5-cd]indolizine-7-carbonitrile (**7j**) (30 mg, 0.14 mmol, 1.0 equiv) as previously synthesized, 20% $Pd(OH)_2$ on carbon (5 mg, 7 μmol, 0.05 equiv), methanol (1.2 mL), 1,4-dioxane (0.6 mL) and 12 M HCl (37 μL, 3.25 equiv). Hydrogen gas was bubbled in the suspension for 50 minutes, then the mixture was stirred under an hydrogen atmosphere (1 bar) for 20 h. $H_2O$ was added and suspension was filtered on Celite. Filtrate was concentrated under vacuum to remove organic solvents. The resulting yellow aqueous phase was washed with $CH_2Cl_2$ (4x) and concentrated to dryness. The solid was dissolved in $CH_2Cl_2$ with 2-3 drops of MeOH and precipitated by the rapid addition of $Et_2O$. The residue was recovered by filtration, washing with ether, yielding a yellow-green solid (31 mg, 0.12 mmol, 87% yield).

mp: >310 °C; **$^1$H NMR** ($D_2O$, 500 MHz): δ 8.25-8.20 (m, 3H), 8.12 (d, *J* = 7.0 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.81 (app t, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 4.39 (s, 2H); **$^{13}$C NMR** ($D_2O$, 125 MHz): δ 132.7, 131.6, 130.8, 127.3, 126.8, 124.1, 122.4, 121.0, 120.0, 118.4, 116.6, 42.9; **FTIR** (cm-1) (neat): 3401, 2855, 1613, 1489, 1421, 1377, 1353, 1226, 1082, 1056; **HRMS** (ESI, Pos): calcd for $C_{14}H_{12}N_3$ [M+H]+: 222.1026 m/z, found 222.1031 m/z.

**Biocatalyzed biolabelling experiments**

**MTG expression and purification:** MTG was expressed and purified as previously described.[1] Briefly, a 5-mL starter culture of *E. coli* BL21 (DE3) containing the plasmid pET20b-MTG, which expresses a *C*-terminally 6-His-tagged version of MTG, was propagated overnight at 37°C in ZYP-0.8G medium and shaking at 240 rpm. It was used to inoculate 500 mL of autoinducing ZYP-5052 medium. After 2h of incubation at 37°C and 240 rpm, the temperature was reduced to 22°C overnight. Cells were collected by centrifugation and resuspended in 0.2 M Tris-HCl, pH 6.0. The cells were lysed using a Constant Systems cell disruptor set at 37 kPSI and cooled to 4°C. After further centrifugation to remove insoluble cellular matter, the inactive form of MTG was incubated with trypsin (1 mg/mL solution, 1:9 ratio of trypsin to MTG, v/v) for the purpose of cleaving its pro-sequence. Activated MTG was purified using a 5-mL His-trap nickel-nitrilotriacetic acid (Ni-NTA) column (GE Healthcare) equilibrated in 50 mM phosphate buffer, pH 8.0, with 300 mM NaCl, and eluted with an imidazole gradient (0 – 250 mM) using an Åtka FPLC (GE Healthcare). After purification, active MTG was dialyzed against 0.2 M Tris-HCl buffer, pH 6.0. The average yield was 25 mg of activated MTG per litre of culture, with ~ 85% purity as estimated by SDS-PAGE and revelation with Coomassie blue stain. Aliquots were snap frozen and stored at -80°C in 15% glycerol.

**GB1 expression and purification:** A 5-mL starter culture of *E. coli* BL21 (DE3) containing the plasmid pET15b-Gb1, which expresses a *N*-terminally 6-His-tagged version of Gb1, was propagated overnight at 37°C in LB medium containing 100 μg/mL ampicillin and shaking at 240 rpm. It was used to inoculate 500 mL of LB + ampicillin. After approximately 3h of incubation at 37°C and 240 rpm, the $OD_{600}$ reached 0.6, and expression was induced by addition of 0.5 mM IPTG. Gb1 was expressed for 4h at the same temperature and shaking speed. Cells were then collected by centrifugation and resuspended in buffer A (50 mM potassium phosphate, pH 7.4, 300 mM NaCl). The cells were lysed using a Constant Systems cell disruptor set at 37 kPSI and cooled to 4°C. After further centrifugation to remove insoluble cellular matter, Gb1 was purified using a 5-mL His-trap nickel-nitrilotriacetic acid (Ni-NTA) column (GE Healthcare) equilibrated in buffer A, and eluted with an imidazole gradient (0 – 250 mM) using an Åtka FPLC (GE Healthcare). After purification, Gb1 was dialyzed against buffer A at 4°C. The yields would vary between 50-80 mg of Gb1 per litre of culture, with ~ 85% purity as estimated by tricine SDS-PAGE[2] and revelation with Coomassie blue stain. If necessary, the purified Gb1 was concentrated using an Amicon® Ultra regenerated cellulose centrifugal filter with a 3k MWCO (Merck-Millipore).

**Conjugation assays with α-lactalbumin and GB1:** Fluorophore (10 mM), 5 mM glutathione were mixed with α-lactalbumin or GB1 such that its final concentration was 3 mg/mL, in 50 mM potassium phosphate buffer, pH 7.4. The final volume of each reaction was 200 μL. Reactions were incubated at 37°C overnight. The reactions were washed 5 times over a Spin-X® UF microfuge concentrator, 5k MWCO (Corning), using 50 mM potassium phosphate buffer, pH 7.4, containing 2 mM EDTA.

Washed sample was resolved using tricine SDS-PAGE.[2] The fluorescent bands were visualized and recorded using a Bio Rad ChemiDoc™ MP Imaging System using an excitation filter of 625 nm with a 30 nm bandpass, as well as photographed on a transilluminator. The gels were then stained with Coomassie brilliant blue to reveal the protein.

**Kinetic isotope effect in the C-H bond functionalization**

**KIE determined from two parallel reactions:** In an argon-pressurised glovebox, in a 4mL vial equipped with a magnetic stirbar and a rubber septum were added $Pd_2dba_3$ (9 mg, 9 $\mu$mol, 1.0 equiv), *t*-$Bu_3PHBF_4$ (11 mg, 38 $\mu$mol, 4.0 equiv) and $K_2CO_3$ (5 mg, 38 $\mu$mol, 4.0 equiv). Vial was taken out of the glovebox and DMF (2.3 mL, [Pd] = 8 mM) was added. Mixture was heated to 90°C for 15 minutes (turns from dark brown to clear green). Two equal volumes of solution are used as is in the two following parallel reactions.

To a flame-dried 5 mL microwave (sealable) vial (VWR® 2-5 mL) equipped with a magnetic stirrer was added the corresponding 5-bromoimidazo[1,5-*a*]pyridine (0.25 mmol, 1.0 equiv) **5a** as previously synthesized, $K_2CO_3$ (69 mg, 0.5 mmol, 2.0 equiv) and triphenylmethane (10 mg, 41 $\mu$mol, 0.16 equiv). The palladium catalyst solution was added (0.75 mL, 6 $\mu$mol, 0.025 equiv) and mixture was heated to 90°C. Samples were taken at regular intervals, filtered, diluted in $CDCl_3$ and analyzed by $^1$H-NMR. The ratio of the initial reaction rates was measured to be 2.02.

**KIE determined from an intramolecular competition:** To a flame-dried 5 mL microwave (sealable) vial (VWR® 2-5 mL) equipped with a magnetic stirrer was added 5-bromo-3-(phenyl-2-*d*)imidazo[1,5-*a*]pyridine (26 mg, 95 $\mu$mol, 1.0 equiv), as previously synthesized. Then, $Pd_2(dba)_3$ (2.2 mg, 2.4 $\mu$mol, 0.025 equiv), $HP(t\text{-}Bu)_3BF_4$ (2.8 mg, 9.5 $\mu$mol, 0.10 equiv), and $K_2CO_3$ (26 mg, 0.19 mmol, 2.0 equiv) were added to the vial. The vial was capped with a rubber septum and purged with argon. Anhydrous DMF (2.5 mL, 0.20M) was added and the reaction was quickly heated to 120 °C using an oil bath and stirred for 2.5 h. The reaction was cooled to rt and the crude mixture was diluted in $CH_2Cl_2$ (5 mL) and transferred to a 60 mL extraction funnel. A saturated aqueous solution of brine was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine (2x) dried over anhydrous $MgSO_4$, filtered over a pad of silica gel, and evaporated to dryness. D/H ratio was determined by $^1$H-NMR. The ratio of C-H arylation over C-D arylation was measured to be 2.0.

**Computational studies :** The Gaussian 09 Revision E.01 and Gaussview 5.0.9 software package (licensed to Université de Montréal) was used for *ab initio* calculations and frontier molecular orbital rendering and display. Calculations were performed using the B3LYP 6-31G(d,p) hybrid basis set.[27]

## ASSOCIATED CONTENT

**Supporting Information**. $^1$H-NMR, $^{13}$C-NMR and fluorescence spectra, Gaussian input files and single crystal diffraction data are included as Supplementary Information. This material is available free of charge *via* the Internet at http://pubs.acs.org."

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