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# Predictable and Site-Selective Functionalization of Poly(hetero)arene Compounds by Palladium Catalysis

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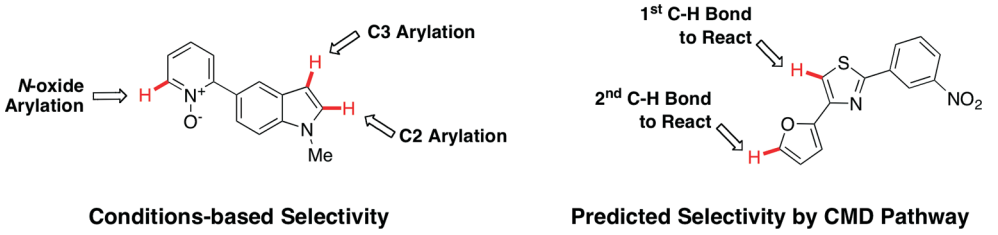


The challenge of achieving selective and predictable functionalizations at C−H bonds with complex poly(hetero)aromatic substrates was addressed by two different approaches. Site-selectivity can be obtained by applying various reaction conditions that are (hetero)arene specific to substrates that contain indoles, pyridine *N*-oxide, and polyfluorinated benzenes. An experimental classification of electron-rich heteroarenes based on their reactivity toward palladium-catalyzed C−H functionalization was established, the result of which correlated well with the order of reactivity predicted by the DFT-calculated concerted metalation−deprotonation (CMD) pathway. Model substrates containing two reactive heteroarenes were then reacted under general reaction conditions to demonstrate the applicability this reactivity chart in predicting the regioselectivity of the palladium-catalyzed direct arylation and benzylation reactions.

## Introduction

Transition-metal-catalyzed direct functionalization of (hetero)arene C−H bonds has emerged in the past decade as a rapidly broadening and increasingly viable alternative to traditional cross-coupling reactions. In these reactions, the organometallic coupling partner used in conventional cross-coupling methods is replaced by a simple arene, thus minimizing the number of synthetic steps prior to the cross-coupling event and avoiding the limitations associated with the preparation of some organometallic substrates.[1] With the prevalence of multiple arenes, aromatic heterocycles as well as biaryl linkages in medicinally relevant molecules (Figure 1), efficient methods to directly functionalize complex poly(hetero)arenes through transition-metal catalysis would be of great value.

A large number of arenes have been functionalized by direct arylation and alkylation methods, including a wide variety of electron-rich, electron-deficient, and simple (hetero)arenes.[1] The substrate scopes for the arylation of

(1) (a) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (f) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. (g) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (h) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (i) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (k) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, *24*, 4087. (l) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (m) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (n) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20.

(2) (a) Thompson, M. J.; Borsenberger, V.; Louth, J. C.; Judd, K. E.; Chen, B. *J. Med. Chem.* **2009**, *52*, 7503. (b) Gavai, A. V.; Fink, B. E.; Fairfax, D. J.; Martin, G. S.; Rossiter, L. M.; Holst, C. L.; Kim, S.-H.; Leavitt, K. J.; Mastalerz, H.; Han, W.-C.; Norris, D.; Goyal, B.; Swaminathan, S.; Patel, B.; Mathur, A.; Vyas, D. M.; Tokarski, J. S.; Yu, C.; Oppenheimer, S.; Zhang, H.; Marathe, P.; Fargnoli, J.; Lee, F. Y.; Wong, T. W.; Vite, G. D. *J. Med. Chem.* **2009**, *52*, 6527. (c) Brak, K.; Kerr, I. D.; Barrett, K. T.; Fuchi, N.; Debnath, M.; Ang, K.; Engel, J. C.; McKerrow, J. H.; Doyle, P. S.; Brinen, L. S.; Ellman, J. A. *J. Med. Chem.* **2010**, *53*, 1763. (d) Lumeras, W.; Caturla, F.; Vidal, L.; Esteve, C.; Balagué, C.; Orellana, A.; Domínguez, M.; Roca, R.; Huerta, J. M.; Godessart, N.; Vidal, B. *J. Med. Chem.* **2009**, *52*, 5531.

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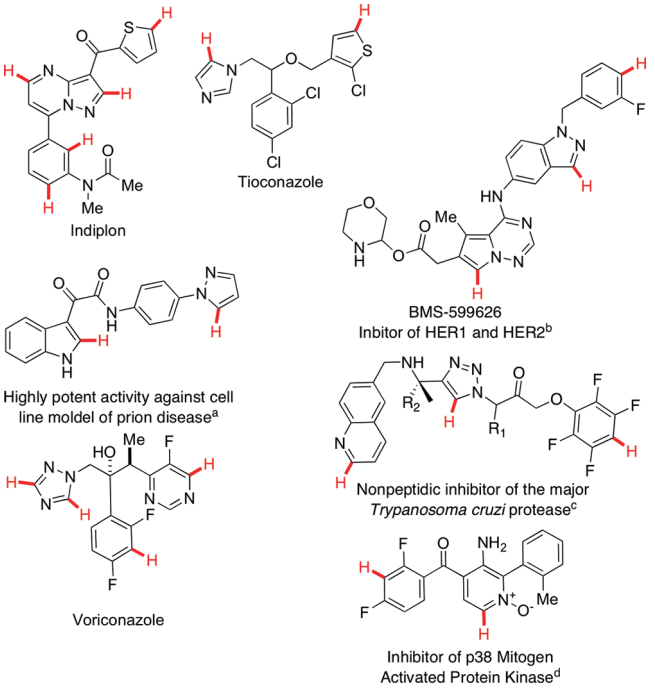



**FIGURE 1.** Examples of drugs and drug candidates containing multiple functionalizable C−H bonds.[2]

electron-deficient and simple (hetero)arenes are often limited to either a specific heteroarene or a set of chemically similar (hetero)arenes. For electron-rich heteroarenes, however, two general direct arylation methods capable of accommodating a large range of arenes have been developed.[3,4] The conditions reported by Daugulis et al. employed a palladium acetate/adamantylphosphine precatalyst to couple aryl chlorides with a variety of electron-rich heteroarenes.[3] The method our group developed was based on advances made on the functionalization of simple arenes employing pivalate additives to increase the reactivity of the system.[4] To date, there have been very few reports, if any, on the direct functionalization of complex substrates containing multiple (hetero)arenes and functionalizable at multiple C−H bonds, similar to the examples depicted in Figure 1.

The underlying challenges of functionalizing complex substrates containing multiple reactive C−H bonds are (1) to achieve site-selectivity in the transformation by choosing the appropriate conditions and (2) to predict the outcome of the transformation when general/nonspecific conditions are applied. Being able to select and/or predict the outcome of such reactions would greatly improve the applicability of C−H bond functionalization methods in the late stage of the synthesis of biologically active analogues. As part of a program dedicated to site-selective functionalization of aromatic C−H bonds, we were interested in addressing these challenges.

Herein, we present a systematic evaluation of reaction conditions and heteroarene reactivity to obtain selective and predictable functionalization at various positions on substrates containing multiple functionalizable C−H bonds. We show that electron-deficient (hetero)arenes can be selectively arylated in the presence of electron-rich arenes by applying mild (hetero)arene specific conditions. In contrast, electron-rich arenes can also be selectively arylated in the presence of electron-deficient (hetero)arenes by applying different mild (hetero)arene specific conditions. In parallel, we establish the first reactivity chart for a range of heteroarenes based on their relative reactivity toward C−H functionalization. This reactivity chart is in good agreement with the predicted reactivity obtained from the concerted metalation−deprotonation (CMD) barriers of activation calculated by DFT.[5] From this, we demonstrate that by using general/nonspecific conditions, we can predict the outcome of the C−H bond functionalization with substrates containing two reactive C−H bonds on two different electron-rich heteroarenes.

## Results and Discussion

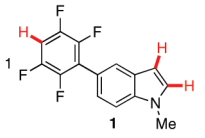
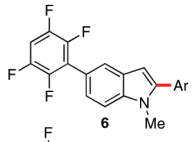
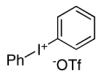
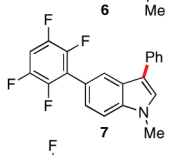
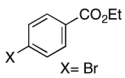
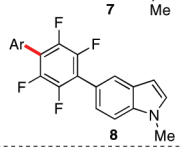
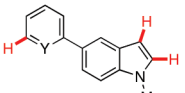
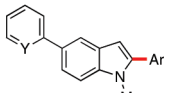
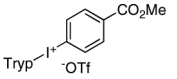
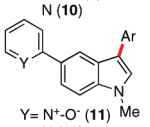
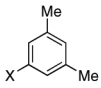
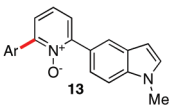
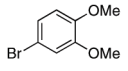
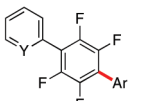
**Conditions-Based Site-Selectivity.** Our attention was first directed toward the use of mild reaction conditions selective for specific classes of (hetero)arenes. In a previous report,[6] 6- and 7-azaindoles were selectively functionalized at either the azine or the azole rings by utilizing two specific sets of mild conditions, one which was developed to functionalize azine *N*-oxides[7] and another set that was developed by Larrosa et al.[8] to arylate at the C2 position of indoles. We envisioned extending the scope of conditions-based selectivity to include perfluorinated arenes.[9] We also opted to employ additional site-selective conditions such as Gaunt's Cu-catalyzed method for the C3 arylation of indoles[10] and the conditions developed for the palladium-catalyzed C2 arylation of pyridine *N*-oxides using aryl triflates.[7b]

Preliminary test reactions showed that the targeted conditions were specific for their respective class of substrates, although of the two electron-poor arenes we investigated (i.e., the pentafluorobenzene and the pyridine *N*-oxide), the polyfluorinated arene reacted preferentially over the pyridine *N*-oxide regardless of the conditions. Consequently, substrates **1** to **5** (Table 1) were prepared using known direct arylation methods in order to test the site-selectivity of the various sets of conditions with actual substrates containing two different (hetero)arenes.[11]

Gratifyingly, we were able to selectively arylate each of the molecules at the desired position in the presence of other potentially reactive site(s). Starting with substrate **1**, bearing an electron-rich indole ring and an electron-deficient perfluorinated arene ring, we achieved the selective arylation at

(3) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449.
(4) (a) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (b) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.
(5) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.
(6) Huestis, M. P.; Fagnou., K. *Org. Lett.* **2009**, *11*, 1357.
(7) (a) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Laserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (b) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977. (c) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155. (d) Campeau L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (e) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276. (f) Leclerc J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (g) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.
(8) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.
(9) (a) René, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754.
(10) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.
(11) See the Supporting Information for details.

**TABLE 1. Site-Selective Direct Arylation Based on Mild (Hetero)arene Specific Conditions**

| Entry | Substrate | Ar-X | Conditions[a] | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **1** |  | A |  **6** | 65 |
| 2 | **1** |  | B |  **7** | 64 |
| 3 | **1** |  X= Br | C |  **8** | 54 |
| 4 | **1** | I | D | | 58 |
| 5 |  Y= $N^+$-$O^-$ (**2**) |  | A |  Y= $N^+$-$O^-$ (**9**) | 53 |
| 6 | N (**3**) | | A | N (**10**) | no rxn[b] |
| 7 | **2** |  | B |  Y= $N^+$-$O^-$ (**11**) | 55 |
| 8 | **3** | | B | N (**12**) | no rxn[b] |
| 9 | **2** |  X= Br | E |  **13** | 24 |
| 10 | **2** | OTf | F | | 51 |
| 11 |  Y= $N^+$-$O^-$ (**4**) |  | C |  Y= $N^+$-$O^-$ (**14**) | no rxn[b] |
| 12 | N (**5**) | | C | N (**15**) | 85 |

[a]Conditions A[8] (Larrosa's protocol): indole (1.0 equiv), aryl iodide (2.0 equiv), $Pd(OAc)_2$ (5 mol %), 2-nitrobenzoic acid (1.5 equiv), $Ag_2O$ (0.75 equiv) in DMF (0.5 M) at 45 °C. Conditions B[10] (Gaunt's protocol): indole (1.0 equiv), diaryliodonium triflate (1.3 equiv), $Cu(OTf)_2$ (10 mol %), 2,6-di-*tert*-butylpyridine (1.0 equiv) in DCM (0.1 M) at 50 °C. Conditions C:[9b] perfluorinated arene (1 equiv), aryl bromide (1.0 equiv), $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), PivOH (30 mol %), $K_2CO_3$ (2 equiv) in isopropyl acetate (1.0 M) at 80 °C; Conditions D:[9a] perfluorinated arene (1 equiv), aryl iodide (1.1 equiv), $Pd(OAc)_2$ (5 mol %), MePhos (10 mol %), $Ag_2CO_3$ (0.50 equiv), $K_2CO_3$ (2 equiv) in ethyl acetate/water (2.5:1, 0.35 M) at ambient temperature. Conditions E:[7a,g] pyridine *N*-oxide (1.0 equiv), aryl bromide (1.5 equiv), $Pd(OAc)_2$ (5 mol %), $P^tBu_3 \cdot HBF_4$ (15 mol %), $K_2CO_3$ (2 equiv) in toluene (0.30 M) at reflux. Conditions F:[7b] pyridine *N*-oxide (1.0 equiv), aryl triflate (2.0 equiv), $Pd(OAc)_2$ (5 mol %), $P^tBu_2Me \cdot HBF_4$ (10 mol %), PivOH (30 mol %), $K_2CO_3$ (2 equiv) in toluene (0.50 M) at reflux. [b]No reaction observed.

the C2 position of the indole ring to yield product **6** in 65% yield (entry 1, Table 1) using Larrosa's protocol[8] (conditions A). Starting from the same substrate (**1**), the C3 position of the indole ring was arylated to give **7** in 64% yield (entry 2, Table 1) using Gaunt's Cu-catalyzed protocol[10] (conditions B). Using two different sets of conditions developed in our group[9] (conditions C[9b] and D[9a]), we were able to selectively arylate the fluorinated arene **1** using both an aryl bromide and an aryl iodide affording **8** in acceptable yields of 54% and 58%, respectively (entries 3 and 4, Table 1). Similarly, compound **2** could be selectively functionalized at the C2 position of the indole to give the arylated product **9** in 53% (entry 5, Table 1) and the C3 arylated indole **11** in 55% (entry 7, Table 1). Unfortunately, we were not able to functionalize both the C2 and C3 positions of the indole when we used substrate **3** containing an unactivated azine in place of the activated azine *N*-oxide (entries 6 and 8, Table 1).[12] We believe that the pyridine moiety in **3** coordinated the metals and potentially formed a stable metallacycle with the adjacent ring, which would prevent any further reaction. Also, the C2 position of the pyridine *N*-oxide **2** could also be functionalized selectively to afford **13** in 24% yield using an aryl bromide (conditions E);[7a,g] however, the yield could be increased to 51% when an aryl triflate was used instead (conditions F)[7b] (entries 9 and 10, Table 1, respectively). Substrate **4**, which contains both a polyfluorinated phenyl group and a pyridine *N*-oxide, was found to be incompatible with conditions C. However, substrate **5**, which contains a nonactivated pyridine, reacted with the perfluorinated ring affording product **15** in 85% yield (entries 11 and 12, Table 1).

For all the examples presented using the conditions-based site-selectivity approach, we only isolated the targeted regioisomer each time, and generally, the remaining mass balance was recovered starting material and/or decomposition products. Even though we cannot rule out the formation of undesired regioisomers in small amounts, the examples shown in Table 1 demonstrate the applicability of this approach. It would also be beneficial to further expand the breath of the known reaction conditions that are (hetero)arene selective.

**Predicted Selectivity with the DFT-Calculated CMD Pathway.** The second main challenge with the selective functionalization of polyaromatic compound is to be able to predict the outcome of a reaction when two (or more) different C−H bonds can react under the same reaction conditions.

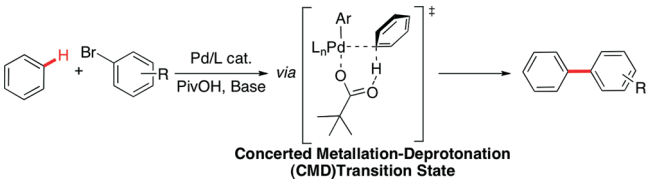
In a combined experimental and computational study, we demonstrated that for a wide range of electron-poor, -neutral, and -rich (hetero)arenes which undergo direct arylation reactions catalyzed by a $Pd^{II}$/carboxylate combination, the most accessible pathway for the C−H bond cleavage was the concerted metalation−deprotonation (CMD) pathway (Scheme 1).[5,13] Computationally, the CMD pathway was able to accurately predict the regioselectivity observed experimentally for the palladium-catalyzed direct arylation of each (hetero)arene evaluated. In addition to accurately predicting the site-selectivity on individual arenes, the calculated barriers of activation for the CMD mechanism should also reflect the relative reactivity of the various studied arenes. As a result, one could utilize these values to determine the site-selectivity of a reaction where two or more heteroarenes are present on a single substrate.

To evaluate experimentally the accuracy of the site-selectivity prediction obtained from the calculated CMD barrier of activation,[5] a series of competition experiments were

(12) Contrary to the report on azaindoles (see ref 6), in which the functionalization of the azole ring gave better yields when the unactivated azine ring was used compared to the yields obtained when the azine ring was activated as the *N*-oxide.

(13) For a review on the mechanistic work done on the CMD mechanism, see: (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. For the seminal mechanistic studies in catalytic settings, see: (b) González, J. J.; García, N.; Gómez-Lor, B.; Echavarren, A. M. *J. Org. Chem.* **1997**, *62*, 1286. (c) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (d) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (e) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066.

**SCHEME 1. Example of the CMD Transition State in a Direct Arylation Reaction**




performed using a range of electron-rich heteroarenes to determine their relative reactivity. The competition experiments consisted of measuring the product distribution using $^{19}$F NMR spectroscopy[14] in the reaction of *p*-$CF_3$-bromobenzene (0.125 equiv) with two heteroarenes (0.5 equiv each), using palladium acetate (5 mol %) and tricyclohexylphosphonium tetrafluoroborate (10 mol %) as the precatalyst, pivalic acid (30 mol %) as a rate enhancing additive and potassium carbonate (1.5 equiv) as the base in *N*,*N*-dimethylacetamide (0.3 M) at 100 °C. These conditions have already been proven to be applicable for the direct arylation of a wide variety of electron-rich heteroarenes and have been shown to be reliable.[4a] The results of these competitions are summarized in Figure 1, and the theoretical product distributions are shown in parentheses. The theoretical values were obtained using the difference in free energy of activation ($\Delta\Delta G^{\ddagger}$) at 373 K for each substrate. In addition, it is important to mention that we have limited our study mostly to heterocycles that were previously examined computationally and restricted our attention to their single most reactive C−H bond instead of examining the reactivity of each potentially reactive position.

The aim of this reactivity chart (Figure 2) is to obtain a comprehensive estimate of the reactivity for a range of heteroarenes regardless of the effects of the substituents in order to apply it to the functionalization of complex substrates. With substrates for which the CMD barrier of activation have been calculated by DFT,[5] we can see that the computationally predicted site-selectivity accurately matches the selectivity observed experimentally. Moreover, considering the sum of the various approximations made in the DFT calculations (such as ligand and solvent approximations and the lack of substituents on the heteroarenes) and the inherent experimental variability of these competition

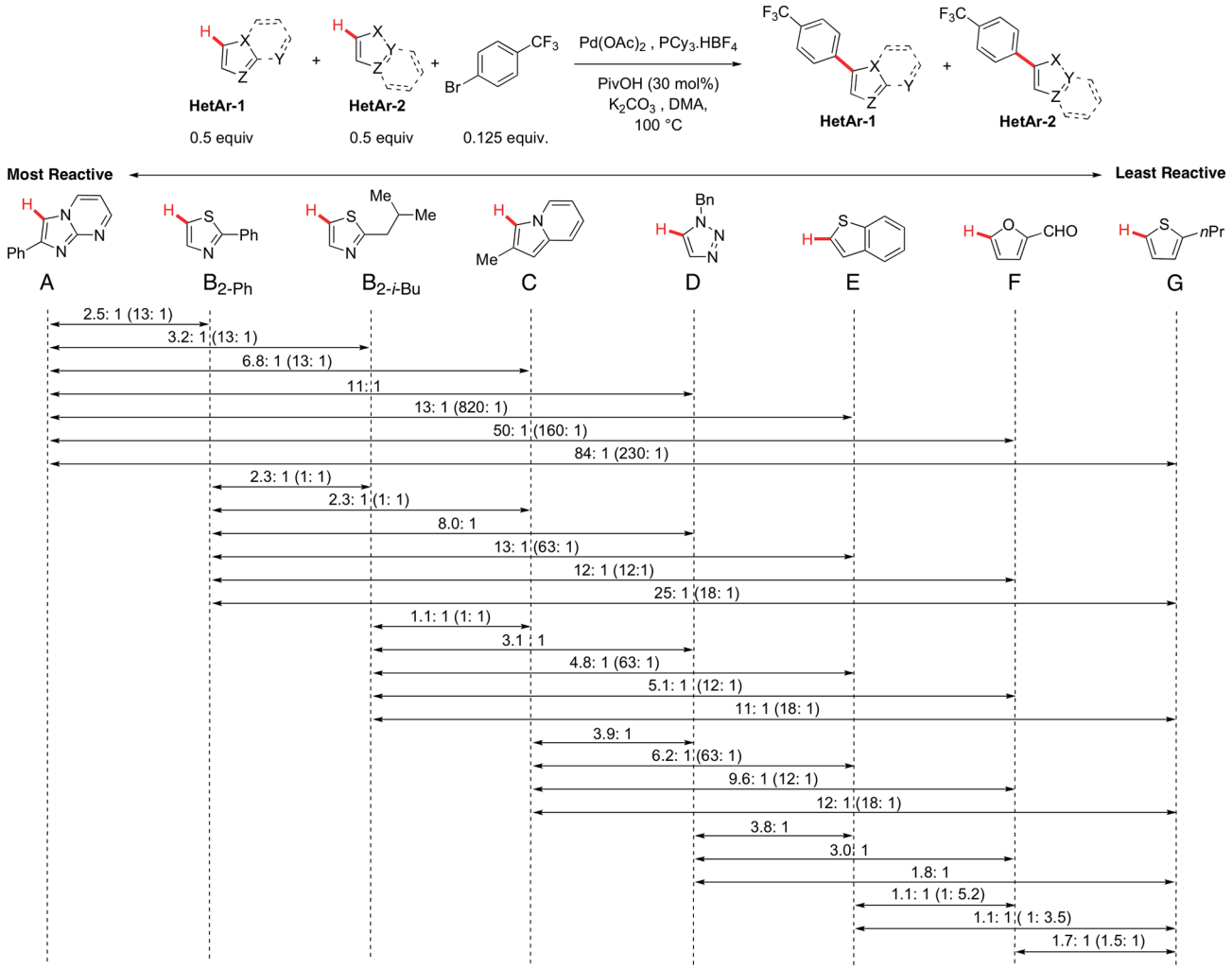
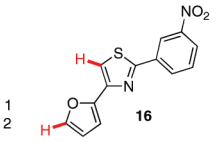
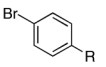
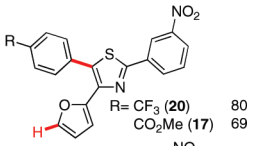
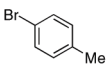
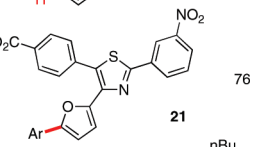
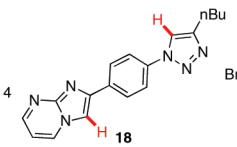
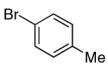
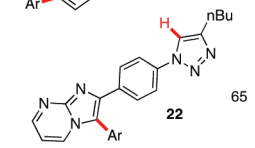
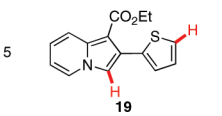
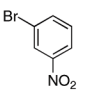
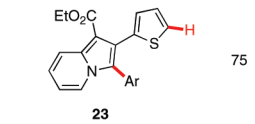



**FIGURE 2.** Relative reactivity of various heteroarenes toward direct arylation. (a) Conditions: heteroarene **1** (0.50 equiv), heteroarene **2** (0.50 equiv), 4-bromotrifluorotoluene (0.125 equiv), $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), PivOH (30 mol %), $K_2CO_3$ (1.5 equiv) in DMA (0.3 M) at 100 °C. (b) Experimental product ratios ($^{19}$F NMR) in parentheses are the theoretical product ratios obtained from DFT-calculated barriers of activation of the CMD pathway.[5]

reactions (e.g., the choice of reactions conditions, high volatility, or low solubility of some heteroarenes and the precision of the product peak integration), a good overall agreement between the experimental and theoretical results was observed. Imidazopyrimidine (A) and thiazoles (B) were the most reactive substrates, which is in agreement with the DFT-predicted reactivity. The presence of C2 substituents on thiazole (B) had a significant effect on the reactivity. Indeed, 2-phenylthiazole reacted 2.5 times faster than the 2-isobutylthiazole ($B_{2\text{-Ph}}$ vs $B_{2\text{-}i\text{-Bu}}$), although the difference in the reactivity of the two analogues remains relatively small so that the general order of reactivity of the heteroarenes is not affected. Similarly, the effect of substituents at the C2 position of indolizine (C) has been reported previously by Gevorgyan et al. in the context of mechanistic studies, where the authors found small reactivity changes when the 2-methyl is abstracted or replaced by an ester functionality.[15] Furthermore, the relative reactivity of *N*-benzyl-1,2,3-triazole (D) has not been evaluated computationally, but was found experimentally to be situated in between the indolizine (C) and the benzothiophene (E). Finally, benzothiophene (E), thiophene (F), and furan (G) were the least reactive substrates that were evaluated, conforming with the DFT predictions.[16]

With the results of these competitions in hand, our efforts were directed toward using them as a reactivity guideline in the functionalization of model substrates bearing two potentially reactive heteroarenes. We first prepared substrate **16** (Table 2) to test the difference in reactivity between the C5 C−H bond of 2-arylthiazole and the C5 C−H bond of C2-substituted furan. We chose to use a slight excess (1.1 equiv) of **16** in the reaction in order to limit the formation of double arylation product that we observed in our initial attempts (~10 mol %) using equimolar amounts of both coupling partners. Although this is not the ideal reagent to use in excess, the formation of double arylation product is very undesirable since it results in the consumption of both the desired final product and the starting aryl bromide partner. Moreover, the unreacted starting material could, in principle, be recovered at the end of the reaction. Using the conditions of the general method of direct arylation developed by our group[4] with 1.1 equiv of **16**, we were able to isolate the monoarylated product **20** in 80% yield (entry 1, Table 2), the double arylation was still observed in approximately 5 mol %. Substrate **16** could also be sequentially and selectively functionalized with two different aryl bromides, and the thiazole moiety was first selectively functionalized with methyl *p*-benzoate to afford **17** in 69% yield, followed by a second arylation at the furan ring with a *p*-tolyl bromide yielding the highly conjugated product **21** in 76% yield (entries 2 and 3, Table 2). Similarly, a substrate containing both an imidazopyrimidine ring and a *N*-aryl-1,2,3-triazole (**18**) was prepared. The imidazopyrimidine ring could be selectively functionalized in an acceptable yield (65%, entry 4, Table 2). Lastly, the combination of an indolizine arene and a thiophene was also evaluated. As expected, substrate **19** was selectively functionalized in 75% yield on the indolizine arene (entry 5, Table 2).

**TABLE 2. Direct Arylation of Aromatic Heterocycles**[a]

| Entry | Substrate | Coupling Partner | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **16** |  R= $CF_3$ $CO_2Me$ |  R= $CF_3$ (**20**) $CO_2Me$ (**17**) | 80 69 |
| 2 | | | | |
| 3[b] |  **17** |  |  **21** | 76 |
| 4 |  **18** |  |  **22** | 65 |
| 5 |  **19** |  |  **23** | 75 |

[a]Conditions: bis-heteroarene (1.1 equiv), aryl bromide (1.0 equiv), $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), PivOH (30 mol %), $K_2CO_3$ (1.5 equiv), DMA (0.3 M), 100 °C. [b]Bis-heteroarene (1.0 equiv), aryl bromide (1.2 equiv).

The reactivity guidelines we established in Figure 2 can also be used for other types of C−H bond functionalization reactions, since the relative reactivity of the heteroarenes was based on the C−H bond cleaving step and should not be affected significantly by the nature of the coupling partner. To illustrate this point, we applied these guidelines for the benzylation of bis-heteroarene **24**, **18**, and **19**, shown in Table 3.

From **24**, we were able to selectively benzylate the C5 position of the thiazole arene in 69% yield using a slightly modified variation of previously reported conditions (entry 1, Table 3).[17] For this reaction, the bis-heteroarene was used in slight excess (1.1 equiv) compared to the benzyl chloride in order to minimize formation of the double-benzylation products. Alternatively, the direct benzylation of substrates **24**, **18**, and **19** could also be achieved in acceptable yields (entries 2−4, Table 3) using $Pd(OAc)_2/PPh_3$ as precatalyst and potassium carbonate since they are easily accessible and cheaper compared to the reagents previously employed (palladium pivalate, 2-$Ph_2$P-2′-($Me_2$N)biphenyl, and cesium carbonate).

## Conclusion

In this paper, we showed that the site-selective direct arylation of substrates containing two different classes of

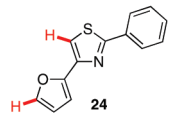
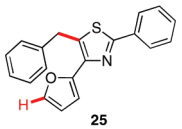
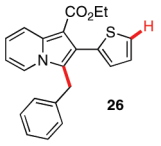
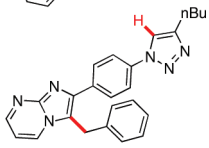
(14) For examples of studies utilizing *p*-trifluromethylphenyl groups and $^{19}F$ NMR spectroscopy, see: (a) Geyer, A. M.; Wiedner, E. S.; Gary, J. B.; Gdula, R. L.; Kuhlmann, N. C.; Johnson, M. J. A.; Dunietz, B. D.; Kampf, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 8984. For other recent examples of mechanistic studies utilizing $^{19}F$ NMR spectroscopy, see: (b) Viciu, M. S.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2010**, *132*, 6361. (c) De Vries, T. S.; Goswami, A.; Liou, L. R.; Gruver, J. M.; Jayne, E.; Collum, D. B. *J. Am. Chem. Soc.* **2009**, *131*, 13142. (d) Gupta, L.; Hoepker, A. C.; Singh, K. J.; Collum, D. B. *J. Org. Chem.* **2009**, *74*, 2231.

(15) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159.

(16) As one of our reviewers pointed out, a close examination of the various product ratios reveals that the ratios are not always cumulative when the reactivity of the heteroarenes are compared. Certainly, it is a very interesting observation, and it would be worth examining in detail; however, at the moment we cannot propose an explanation.

(17) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160.

**TABLE 3. Benzylation of Aromatic Heterocycles**[a]

| Entry | Substrate | Coupling Partner | Product | Yield (%) |
|---|---|---|---|---|
| 1[b] |  **24** |  |  **25** | 69 |
| 2 | | | | 84 |
| 3 | **19** | |  **26** | 55 |
| 4 | **18** | |  **27** | 55 |

[a]Conditions: bis-heteroarene (1.1 equiv), benzyl chloride (1.0 equiv), $Pd(OAc)_2$ (5 mol %), $PPh_3$ (10 mol %), PivOH (20 mol %), $K_2CO_3$ (1.5 equiv) in toluene (0.5 M) at 110 °C. [b]Bis-heteroarene (1.1 equiv), benzyl chloride (1.0 equiv), $Pd(OPiv)_2$ (2 mol %), 2-$Ph_2P$-2′-($Me_2N$)-biphenyl (4 mol %), PivOH (20 mol %), $Cs_2CO_3$ (1.5 equiv) in toluene (0.5 M) at 110 °C.

arenes was possible using mild methods developed for specific types of arenes. In addition, the results of competition reactions among electron-rich heteroarenes allowed for the first experimental classification of these heteroarenes based on their reactivities toward C−H bond functionalization. The presented order of reactivity of those heteroarenes was in good agreement with the order predicted by the DFT-calculated concerted metalation−deprotonation (CMD) pathway promoted by palladium/carboxylate complexes. Importantly, the ability to achieve predictable and selective C−H bond functionalization (without organometallic preactivation) of more challenging substrates was achieved, which will serve to be an invaluable tool given the demand of the preparation of these types of molecules. Continued studies toward a better understanding of the relationship between substituents and their effect on substrate reactivity should be pursued to ultimately help achieve the establishment of a comprehensive set of predictive guidelines for the C−H bond functionalization of an even broader scope of heteroarenes.

## Experimental Section

**Procedure for Conditions A (Table 1)**[8]**.** In a 2 mL screw cap vial were added silver(I) oxide (87 mg, 0.375 mmol, 0.75 equiv), 2-nitrobenzoic acid (125 mg, 0.750 mmol, 1.5 equiv), *N*-methyl-5-(2,3,5,6-tetrafluorophenyl)indole (**1**) (139.7 mg, 0.50 mmol, 1 equiv), palladium(II) acetate (5.6 mg, 0.025 mmol, 5 mol %), and 4-iodotoluene (164 mg, 0.75 mmol, 2.0 equiv). The vial was purged with argon before DMF (1 mL) was added via syringe. The reaction was allowed to run for 15 h at 45 °C. The crude product was filtered through a plug of silica gel, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography using 2% ether in petroleum ether. *N*-Methyl-5-(2,3,5,6-tetrafluorophenyl)-2-*p*-tolylindole (**6**) was isolated as a white solid in 64% yield.

**Procedure for Conditions B (Table 1)**[10]**.** In a 4 mL screw cap vial were added 2-(*N*-methylindol-5-yl)pyridine *N*-oxide (**2**) (60 mg, 0.268 mmol, 1 equiv), (4-methylphenyl)(2,4,6-triisopropylphenyl)iodonium triflate (180 mg, 0.2942 mmol, 1.1 equiv), Cu(OTf) (10.8 mg, 0.026 mmol, 10 mol %), and 4-methyl-2,6-di-*tert*-butylpyridine (62 mg, 0.294 mmol, 1.1 equiv). 1,2-Dichloroethane (DCE, 3 mL) was added via syringe. The reaction was stirred for 24 h at 50 °C. The crude product was filtered through a plug of silica gel, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography using 2% methanol in dichloromethane. 2-(3-(4-(Methoxycarbonyl)phenyl)-1-methyl-1*H*-indol-5-yl)pyridine 1-oxide (**11**) was isolated as a pale brown solid in 55% yield.

**Procedure for Conditions C (Table 1)**[9b]**.** In a 2 mL screw cap vial were added potassium carbonate (104 mg, 0.750 mmol, 1.5 equiv), SPhos (20.5 mg, 0.050 mmol, 10 mol %), *N*-methyl-5-(2,3,5,6-tetrafluorophenyl)indole (**1**) (139.7 mg, 0.500 mmol, 1 equiv), pivalic acid (15.3 mg, 0.150 mmol, 0.3 equiv), and palladium(II) acetate (5.6 mg, 0.025 mmol, 5 mol %). The vial was purged with argon before a solution of ethyl 4-bromobenzoate (172 mg, 0.75 mmol, 1.5 equiv) in isopropyl acetate (1 mL, 0.5 M) was added via syringe. The reaction was stirred for 15 h at 80 °C. The crude product was filtered through Celite, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography using 5% ether in petroleum ether. Ethyl *N*-methyl-5-(2,3,5,6-tetrafluoro-4′-carboxylatebiphenyl-4-yl)indole (**8**) was isolated as a white solid in 54% yield.

**Procedure for Conditions D (Table 1)**[9a]**.** In a 2 mL screw cap vial were added potassium carbonate (83 mg, 0.60 mmol, 2 equiv), silver carbonate (41 mg, 0.15 mmol, 0.5 equiv), MePhos (10.9 mg, 0.030 mmol, 10 mol %), palladium(II) acetate (3.4 mg, 0.015 mmol, 5 mol %), *N*-methyl-5-(2,3,5,6-tetrafluorophenyl)-indole (**1**) (83.8 mg, 0.30 mmol, 1 equiv), and ethyl 4-iodobenzoate (91 mg, 0.33 mmol, 1.1 equiv). The vial was purged with argon, and 0.6 mL of ethyl acetate and 0.3 mL of water (0.35 M in total) were added via syringe. The reaction was stirred for 15 h at ambient temperature. The crude product was filtered through Celite, and the solvent was removed under reduced pressure. The crude residue was purified by silica gel chromatography using 5% ether in petroleum ether. Ethyl *N*-methyl-5-(2,3,5,6-tetrafluoro-4′-carboxylatebiphenyl-4-yl)indole (**8**) was isolated as a white solid in 58% yield.

**Procedure for Conditions E (Table 1)**[7a,g]**.** In a round-bottom flask equipped with a condenser and a stir bar were added potassium carbonate (83 mg, 0.6 mmol, 2.0 equiv), tri-*tert*-butylphosphonium tetrafluoroborate (11.2 mg, 0.045 mmol, 15 mol %), palladium(II) acetate (3.4 mg, 0.015 mmol, 5 mol %), 2-(*N*-methylindol-5-yl)pyridine *N*-oxide (**2**) (66 mg, 0.294 mmol, 1 equiv), and pivalic acid (9.2 mg, 0.09 mmol, 0.3 equiv). The condenser was fitted with a septum and purged with argon before a solution of 5-bromo-*m*-xylene (82 mg, 0.45 mmol, 1.5 equiv) in toluene (1 mL, 0.3 M) was added. The septum was heated to reflux (~115 °C) and stirred for 18 h. Upon cooling, the reaction was diluted with dichloromethane and filtered over Celite. The filtrate was concentrated, and the residues were purified by silica gel chromatography using 3% methanol and 5% acetone in chloroform as the eluent. 2-(3,5-Dimethylphenyl)-6-(*N*-methylindol-5-yl)pyridine *N*-oxide (**13**) was isolated as an off-white solid in 24% yield. The poor yield could be explained by the decomposition of the final product on silica gel as mentioned in the previous report.[7g]

**Procedure for Conditions F (Table 1)**[7b]**.** In a 2 mL screw cap vial were added palladium(II) acetate (3.5 mg, 0.016 mmol, 5 mol %), pivalic acid (9.6 mg, 0.094 mmol, 0.3 equiv), potassium carbonate (86 mg, 0.624 mmol, 2 equiv), di-*tert*-butylmethyl phosphonium tetrafluoroborate (7.7 mg, 0.031 mmol, 10 mol %), and 2-(*N*-methylindol-5-yl)pyridine *N*-oxide (**2**) (70 mg, 0.31 mmol, 1 equiv). The vial was purged with argon before a stock solution of 3,5-dimethylphenyl trifluoromethanesulfonate

(119 mg, 0.47 mmol, 1.5 equiv) in toluene (1.1 mL, 0.3 M) was added. The reaction was heated to 110 °C and stirred overnight. Upon cooling, the reaction was diluted with dichloromethane and filtered over Celite. The filtrate was concentrated and the residues were purified by silica gel chromatography using 3% acetone in chloroform as the eluent. 2-(3,5-Dimethylphenyl)-6-(*N*-methylindol-5-yl)pyridine *N*-oxide (**13**) was isolated as an off-white solid in 51% yield.

**General Procedure for the Direct Arylation of Heterocycles.** $Pd(OAc)_2$ (5 mol %), tricyclohexylphosphonium tetrafluoroborate (10 mol %), $K_2CO_3$ (1.5 equiv), and PivOH (30 mol %) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. The heterocycle (1.1 equiv) and the aryl bromide (1.0 equiv), if a solid, were then added. The vial was purged with argon, and a solution of the coupling partners, if liquid, in dimethylacetamide (DMA) (0.3 M) was added to the mixture. The reaction mixture was then stirred vigorously at 100 °C for 16 h. The solution was then cooled to ambient temperature and loaded directly on the column or was diluted with ethyl acetate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product.

**General Procedure for the Direct Benzylation of Heterocycles.** $Pd(OAc)_2$ (5 mol %), triphenylphosphine (10 mol %), $K_2CO_3$ (1.5 equiv), and PivOH (20 mol %) were weighed in air and placed in a screw-cap vial equipped with a magnetic stir bar. The heterocycle (1.1 equiv) was then added at that point. The vial was purged with argon, and a solution of the benzyl chloride (1.0 equiv) in toluene (0.5 M) was added to the mixture. The reaction mixture was then stirred vigorously at 110 °C for 16 to 24 h. The solution was then cooled to ambient temperature, diluted with ethyl acetate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the desired product.

**General Procedure for the Competition Experiments.** $Pd(OAc)_2$ (6.7 mg, 0.030 mmol, 5 mol %), tricyclohexylphosphonium tetrafluoroborate (22.1 mg, 0.060 mmol, 10 mol %), $K_2CO_3$ (124 mg, 0.90 mmol, 1.5 equiv), and PivOH (18.4 mg, 0.18 mmol, 30 mol %) were weighed in air and placed in a screw-cap vial equipped with a magnetic stir bar. The heteroarenes (0.30 mmol, 0.5 equiv each), if a solid, were then added at that point. The vial was purged with argon, and a solution of the *p*-$CF_3$-bromobenzene (16.9 mg, 0.075 mmol, 0.125 equiv) and the heteroarenes (0.30 mmol, 0.5 equiv each), if liquid, in dimethylacetamide (2.0 mL, 0.3 M) was added to the mixture. The reaction mixture was then stirred vigorously at 100 °C overnight. The solution was then cooled to ambient temperature and then filtered and evaporated under reduced pressure. The remaining solvent was then removed under reduced pressure using a Kugelrohr apparatus. The crude mixture was then analyzed by $^{19}F$ NMR spectroscopy.

**Synthesis and Characterization of Starting Coupling Partners. 5-Bromo-*N*-methylindole.** the compound was synthesized following a literature procedure.[18] To a solution of 5-bromoindole (3.00 g, 15.3 mmol, 1 equiv) in acetone (46.0 mL, 0.33 M) cooled to 0 °C was added freshly powdered potassium hydroxide (4.29 g, 77 mmol, 5 equiv). After the mixture was stirred at 0 °C for 30 min, iodomethane (4.34 g, 30.6 mmol, 2 equiv) was added dropwise while the solution was vigorously stirred. The reaction temperature was slowly raised to room temperature and stirred overnight. The reaction mixture was filtered and the solvent removed under reduced pressure. The crude product was purified by distillation on a Kugelrhor apparatus (115−125 °C) and isolated as a pale yellow solid in 94% yield and exhibited spectral data identical to previous reports.[18] $^1H$ NMR (400 MHz, $CDCl_3$, 297K, TMS): $\delta$ 7.74 (dd, $J$ = 1.9, 0.5 Hz, 1H), 7.29 (dd, $J$ = 8.7, 1.9 Hz, 1H), 7.18 (d, $J$ = 8.7 Hz, 1H), 7.04 (d, $J$ = 3.1 Hz, 1H), 6.41 (dd, $J$ = 3.1, 0.8 Hz, 1H), 3.76 (s, 3H).

**N-methyl-5-(2,3,5,6-tetrafluorophenyl)indole (1).** In a 4 mL screw cap vial were added potassium carbonate (658 mg, 4.76 mmol, 2 equiv), SPhos (98 mg, 0.24 mmol, 10 mol %), and palladium(II) acetate (26.7 mg, 0.119 mmol, 5 mol %). The vial was purged with argon before a stock solution of 5-bromo-*N*-methylindole (500 mg, 2.38 mmol, 1 equiv) in isopropyl acetate (2.4 mL) was added. The solution was stirred for 1 min before 1,2,4,5-tetrafluorobenzene (1,07 g, 7.14 mmol, 3 equiv) was added. The reaction was heated to 80 °C and stirred for 18 h. Upon cooling, the reaction was diluted with ethyl acetate and filtered over Celite. The filtrate was concentrated, and the residues were purified by silica gel chromatography using 2% ether in petroleum ether as the eluent. The product was isolated as a white solid in 52% yield. Mp: 125−128 °C ($CHCl_3$). $R_f$: 0.55 (2% ether, petroleum ether); $^1H$ NMR (400 MHz, $CDCl_3$, 296K, TMS): $\delta$ 7.74−7.71 (m, 1H), 7.43 (d, $J$ = 8.5 Hz, 1H), 7.30 (dddd, $J$ = 8.5, 1.5, 1.5, 1.5 Hz, 1H), 7.12 (d, $J$ = 3.1 Hz, 1H), 7.03 (dddd, $J$ = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 6.56 (dd, $J$ = 3.1, 0.8 Hz, 1H), 3.84 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$, 297K, TMS): $\delta$ 147.7−144.80 (m), 145.4−142.5 (m), 136.7, 129.8, 128.5, 123.3 (t, $J$ = 1.8 Hz), 123.0 (t, $J$ = 1.9 Hz), 122.9 (t, $J$ = 16.7 Hz), 118.2 (t, $J$ = 2.3 Hz), 109.4, 103.9 (t, $J$ = 22.8 Hz), 101.6, 32.9. IR ($\nu_{max}$ /$cm^{-1}$): 2931, 1515, 1506, 1487, 1170, 931, 887, 738, 708. HRMS calcd for $C_{15}H_9F_4N$ ($M^+$) 279.0671, found 279.0665.

**2-(*N*-Methylindol-5-yl)pyridine *N*-Oxide (2).** In a test tube were added potassium carbonate (214 mg, 1.55 mmol, 1.3 equiv), tri-*tert*-butylphosphonium tetrafluoroborate (20.7 mg, 0.071 mmol, 10 mol %), palladium(II) acetate (13.36 mg, 0.060 mmol, 5 mol %), and pyridine *N*-oxide (453 mg, 4.76 mmol, 4 equiv). The tube was fitted with a septum and purged with argon before a solution of 5-bromo-*N*-methylindole (250 mg, 1.19 mmol, 1 equiv) in toluene (4 mL, 0.3 M) was added. The septum was covered in parafilm, and the reaction was heated to 110 °C and stirred for 18 h. Upon cooling, the reaction was diluted with dichloromethane and filtered over Celite. The filtrate was concentrated, and the residues were purified by silica gel chromatography using 3% methanol and 5% acetone in chloroform as the eluent. The product was isolated as an off-white solid in 63% yield. Mp: 138−142 °C ($CHCl_3$). $R_f$: 0.25 (3% MeOH, 5% $Me_2CO$, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$, 296K, TMS): $\delta$ 8.35 (d, $J$ = 5.6 Hz, 1H), 8.05 (s, 1H), 7.73 (d, $J$ = 8.5 Hz, 1H), 7.48 (dd, $J$ = 7.8, 1.8 Hz, 1H), 7.40 (d, $J$ = 8.4 Hz, 1H), 7.28 (dd, $J$ = 7.6, 7.6 Hz, 1H), 7.17 (dd, $J$ = 5.7, 5.7 Hz, 1H), 7.09 (d, $J$ = 3.1 Hz, 1H), 6.55 (d, $J$ = 3.1 Hz, 1H), 3.81 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$, 298K, TMS): $\delta$ 150.7, 140.6, 137.1, 129.6, 128.2, 127.6, 125.7, 123.8, 123.6, 122.8, 122.5, 109.0, 101.9, 33.0. IR ($\nu_{max}$ /$cm^{-1}$): 3102, 2948, 1606, 1513, 1476, 1421, 1339, 1245, 842, 763, 734. HRMS: calcd for $C_{14}H_{12}N_2O$ ($M^+$) 224.0950, found 224.0930.

***N*-Methyl-5-(pyridin-2-yl)indole (3).** In a round-bottom flask was dissolved the pyridine *N*-oxide in methanol, to the solution was added palladium on carbon, the flask was purged with hydrogen gas, and the solution was vigorously stirred under hydrogen atmosphere until the reaction was judged complete by TLC.

Alternatively, 3 was prepared by mixing in a flask equipped with a stir bar, zinc dust $< 10\ \mu m$ (~4 to 5 equiv), the starting pyridine *N*-oxide, and a 1:1 mixture of THF and a saturated aqueous solution of $NH_4Cl$. The mixture was vigorously stirred at ambient temperature for ~30 min. The crude was extracted with ethyl acetate and purified by silica gel chromatography. Pale yellow solid. Mp: 54−58 °C. $R_f$: 0.49 (MeOH/DCM 5/95). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.68 (ddd, $J$ = 4.8, 1.8, 1.0 Hz, 1H), 8.26 (dd, $J$ = 1.7, 0.6 Hz, 1H), 7.92 (dd, $J$ = 8.6, 1.6 Hz, 1H), 7.78 (dt, $J$ = 8.0, 1.1 Hz, 1H), 7.72 (ddd, $J$ = 8.0, 7.3, 1.8 Hz, 1H), 7.40 (dt, $J$ = 8.6, 0.7 Hz, 1H), 7.16 (ddd, $J$ = 7.3, 4.8, 1.2 Hz, 1H), 7.08 (d, $J$ = 3.1 Hz, 1H), 6.56 (dd, $J$ = 3.1, 0.8 Hz, 1H),

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3.82 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.9, 149.6, 137.4, 136.7, 131.1, 129.7, 128.9, 121.15, 121.0, 120.5, 119.8, 109.5, 102.0, 33.1. IR ($\nu_{max}$ /cm$^{-1}$): 3086, 3002, 2939, 1583, 1512, 1462, 1422, 1341, 1304, 1247, 1150, 777, 761, 686. HRMS: calcd for $C_{14}H_{12}N_2$ ($M^+$) 208.1000, found 208.0975.

**2-(2,3,5,6-Tetrafluorophenyl)pyridine (5).** $Pd(OAc)_2$ (5 mol %), di-*tert*-butylmethylphosphonium tetrafluoroborate (10 mol %), and $K_2CO_3$ (1.1 equiv) were weighed to air and placed in a screw-cap vial equipped with a magnetic stir bar. 2-Bromopyridine (1.0 equiv) was added at this point. The vial was purged with argon, and a solution of 1,2,4,5-tetrafluorobenzene (3.0 equiv) in dimethylacetamide (DMA) (3.0 M) was added to the mixture. The reaction mixture was then stirred vigorously at 120 °C for 16 h. The solution was then cooled to ambient temperature, diluted with ethyl acetate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product. Yellow solid. Mp: 74−76 °C. $R_f$: 0.36 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.79 (ddd, $J$ = 4.9, 1.8, 0.9 Hz, 1H), 7.85 (td, $J$ = 7.8, 1.8 Hz, 1H), 7.51 (dt, $J$ = 7.9, 1.2 Hz, 1H), 7.39 (ddd, $J$ = 7.7, 4.9, 1.2 Hz, 1H), 7.14 (tt, $J_{HF}$ = 9.6, 7.3 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 150.2, 147.9, 146.3 (dddd, $J_{CF}$ = 248.2, 14.6, 10.2, 4.2 Hz), 144.4 (dtd, $J_{CF}$ = 249.5, 9.3, 5.2 Hz), 136.8, 126.0, 123.9, 120.9 (t, $J_{CF}$ = 16.3 Hz), 106.2 (t, $J_{CF}$ = 22.6 Hz). IR ($\nu_{max}$ /cm$^{-1}$): 3032, 2926, 1590, 1572, 1511, 1499, 1297, 1198, 939. HRMS: calcd for $C_{11}H_5NF_4$ ($M^+$) 227.0358, found 227.0349.

**2-(2,3,5,6-Tetrafluorophenyl)pyridine *N*-Oxide (4).** 2-(2,3,5,6-Tetrafluorophenyl)pyridine (**5**) was dissolved in DCM (~0.3 M), and few milligrams of $MeReO_4$ was added to the solution. A 50% solution of $H_2O_2$ in water (approximately 1/5 of the volume of DCM) was added, and the mixture was stirred vigorously at ambient temperature until the reaction was judge completed by TLC. The solution was then extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product. White solid. Mp: 167−168 °C. $R_f$: 0.36 (MeOH/DCM 5/95). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.39 (d, $J$ = 6.4 Hz, 1H), 7.43−7.34 (m, 3H), 7.21 (quin, $J$ = 8.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 146.3 (dm, $J_{C-F}$ = 252 Hz), 144.5 (dm, $J_{C-F}$ = 252 Hz), 140.5, 138.5 129.2, 126.9, 124.9, 107.7 (m). IR ($\nu_{max}$ /cm$^{-1}$): 3052, 3024, 3007, 1500, 1432, 1257, 1188, 940, 896, 763. HRMS: calcd for $C_{11}H_5NOF_4$ ($M^+$) 243.0307, found 243.0327.

**4-(Furan-2-yl)-2-(3-nitrophenyl)thiazole (16).** A solution of 2-acetylfuran (1.0 equiv) in ethyl acetate (0.1 M) was added to a reaction flask equipped with a magnetic stir bar, followed by the addition of copper(II) bromide (1.7 equiv). The reaction mixture was then stirred vigorously and heated to reflux. When the reaction reached completion, as judged by TLC, the reaction mixture was allowed to cool to room temperature, filtered, and evaporated under reduced pressure. The crude product was purified using silica gel column chromatography to afford 2-bromo-1-(furan-2-yl)ethanone as a white solid in 70% yield. $R_f$: 0.21 (petroleum ether/ethyl acetate 90/10). $^1$H NMR matched the previously reported spectrum.[19] $^1$H NMR (400 MHz, $CDCl_3$, 296 K, TMS): $\delta$ 7.65 (dd, $J$ = 1.7, 0.8 Hz, 1H), 7.35 (dd, $J$ = 3.6, 0.8 Hz, 1H), 6.61 (dd, $J$ = 3.6, 1.7 Hz, 1H), 4.33 (s, 2H). 4-(Furan-2-yl)-2-(3-nitrophenyl)thiazole (**16**) was synthesized following a literature procedure.[20] To a solution of 2-bromo-1-(furan-2-yl)ethanone (1.0 equiv) and 3-nitrobenzothioamide (1.0 equiv) in tetrahydrofuran (1.0 M) was added to a reaction flask equipped with a magnetic stir bar. The reaction mixture was stirred vigorously and heated to reflux until judged complete by TLC. The solution was then evaporated under reduced pressure and the crude product purified by silica gel column chromatography in 10−20% ethyl acetate/petroleum ether to afford 4-(furan-2-yl)-2-(3-nitrophenyl)-thiazole (**16**) in 92% yield. Yellow solid. Mp: 116−118 °C. $R_f$: 0.47 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.85 (t, $J$ = 2.0 Hz, 1H), 8.33 (ddd, $J$ = 7.8, 1.7, 1.0 Hz, 1H), 8.28 (ddd, $J$ = 8.2, 2.3, 1.0 Hz, 1H), 7.65 (t, $J$ = 8.0 Hz, 1H), 7.51 (s, 1H), 7.49 (dd, $J$ = 1.8, 0.8 Hz, 1H), 6.94 (dd, $J$ = 3.4, 0.5 Hz, 1H), 6.53 (dd, $J$ = 3.4, 1.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 165.5, 149.9, 148.8, 148.7, 142.7, 135.1, 132.3, 130.1, 124.6, 121.6, 113.0, 111.8, 107.9. IR ($\nu_{max}$ /cm$^{-1}$): 3116, 3093, 1531, 1348, 1024. HRMS: calcd for $C_{13}H_8N_2O_3S$ ($M^+$) 272.0256, found 272.0271.

**4-(Furan-2-yl)-2-phenylthiazole (24).** Synthesized using the same procedure as compound **16**, isolated in 74% yield. Orange solid. Mp: 56−57 °C. $R_f$: 0.44 (petroleum ether/ethyl acetate 90/10). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01−7.99 (m, 2H), 7.46−7.43 (m, 4H), 7.40 (s, 1H), 6.89 (dd, $J$ = 3.2, 0.5 Hz, 1H), 6.50 (dd, $J$ = 3.3, 1.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.6, 150.4, 148.1, 142.4, 133.5, 130.3, 129.1, 126.8, 112.0, 111.7, 107.4. IR ($\nu_{max}$ /cm$^{-1}$): 3115, 3066, 3025, 1616, 1515, 1469, 1201, 1007, 763, 743, 688. HRMS: calcd for $C_{13}H_9NOS$ ($M^+$) 227.0405, found 227.0387.

**2-(4-(4-Butyl-1*H*-1,2,3-triazole)phenyl)imidazo[1,2-*a*]pyrimidine (18).** 2-Bromo-1-(4-iodophenyl)ethanone was synthesized following the same procedure described for 2-bromo-1-(furan-2-yl)ethanone, isolated in 72% yield. White solid. Mp: 102−106 °C. $R_f$: 0.47 (petroleum ether/diethyl ether 90/10). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.89−7.86 (m, 2H), 7.71−7.68 (m, 2H), 4.39 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 190.9, 138.4, 133.3, 130.4, 102.4, 30.4. IR ($\nu_{max}$ /cm$^{-1}$): 2997, 2948, 1692, 1580, 1395, 1196, 803. HRMS: calcd for $C_8H_6NBrI$ ($M^+$) 323.8647, found 323.8657. 2-(4-Iodophenyl)imidazo[1,2-*a*]pyrimidine was synthesized following a literature procedure.[21] In a round-bottom flask were mixed 2-aminopyrimidine (1.0 equiv) and 2-bromo-1-(4-iodophenyl)ethanone. Acetone (0.4 M) was added, and the mixture was heated to reflux for 2−3 h. At this point, a significant amount of precipitate had formed, and the mixture was cooled down to ambient temperature and decanted. Then a 1.5:1 mixture of ethanol and water (~0.4 M) was added to the precipitate as well as $NaHCO_3$ (~1.4 equiv). The resulting solution was heated to 80 °C for an additional 2−3 h. The reaction mixture was then cooled to ambient temperature and extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified using silica gel column chromatography to afford 2-(4iodophenyl)imidazo[1,2-*a*]pyrimidine as a pale brown solid in 50 to 78% yield. No melting point was found: ~270 °C dec. $R_f$: 0.53 (MeOH/DCM 5/95). $^1$H NMR (400 MHz; DMSO-$d_6$): $\delta$ 8.96 (dd, $J$ = 6.8, 1.9 Hz, 1H), 8.54 (dd, $J$ = 4.1, 1.9 Hz, 1H), 8.42 (s, 1H), 7.85−7.80 (m, 4H), 7.06 (dd, $J$ = 6.7, 4.2 Hz, 1H). $^{13}$C NMR (101 MHz; 383 K; DMSO): $\delta$ 149.9, 144.4, 144.1, 137.1, 134.4, 132.8, 127.4, 108.4, 107.3, 93.2. IR ($\nu_{max}$ /cm$^{-1}$): 3114, 3073, 2922, 2854, 1499, 1469, 1350, 1200. HRMS: calcd for $C_{12}H_8N_3I$ ($M^+$) 320.9763, found 320.9780. 2-(4-(4-Butyl-1*H*-1,2,3-triazole)phenyl)imidazo[1,2-*a*]-pyrimidine (**18**) was synthesized following a literature procedure.[22] In a flask equipped with a stir bar were mixed (1.0 equiv), sodium azide (1.05 equiv), CuI (10 mol %), and sodium ascorbate (10 mol %). To this mixture was added a solution of

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DMF (0.3 M) containing 1-hexyne (1.05 equiv) and *N*,*N*′-dimethylethane-1,2-diamine (15 mol %). The mixture was stirred at ambient temperature until it was judged complete by TLC. Water and dichloromethane were added to the reaction mixture, and the aqueous layer was extracted a few times with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure. The crude product was purified using silica gel column chromatography to afford **18** as a pale brown solid in 82−90% yield. Pale brown solid; ∼270 °C dec. $R_f$: 0.20 (MeOH/DCM 5/95). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.57 (dd, $J$ = 4.1, 2.0 Hz, 1H), 8.47 (dd, $J$ = 6.7, 2.0 Hz, 1H), 8.20−8.15 (m, 2H), 7.89 (s, 1H), 7.84−7.81 (m, 2H), 7.77 (s, 1H), 6.90 (dd, $J$ = 6.7, 4.1 Hz, 1H), 2.82 (t, $J$ = 7.7 Hz, 2H), 1.74 (dt, $J$ = 15.3, 7.6 Hz, 2H), 1.45 (dq, $J$ = 14.9, 7.4 Hz, 2H), 0.97 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, 383 K, DMSO-$d_6$): $\delta$ 150.0, 147.9, 147.7, 144.0, 136.1, 134.4, 133.1, 126.6, 119.8, 119.3, 108.4, 107.5, 30.3, 24.2, 21.1, 12.9. IR ($\nu_{max}$ /cm$^{-1}$): 3131, 2953, 2923, 2856, 1614, 1521, 1492, 1225, 762. HRMS: calcd for $C_{18}H_{18}N_4$ ($M^+ - N_2$) 290.1531, found 290.1525.

**Ethyl 2-(Thiophene-2-yl)indolizine-1-carboxylate (19).** (*E*)-Ethyl 3-(thiophene-2-yl)acrylate was synthesized following a literature procedure.[23] $^1$H NMR of the final product matched the previously reported spectrum.[23] Light sensitive clear oil. $R_f$: 0.279 (petroleum ether/ethyl acetate 90/10). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.78 (d, $J$ = 15.7 Hz, 1H), 7.37 (d, $J$ = 5.1 Hz, 1H), 7.25−7.24 (m, 1H), 7.05 (dd, $J$ = 5.1, 3.6 Hz, 1H), 6.24 (d, $J$ = 15.7 Hz, 1H), 4.25 (q, $J$ = 7.1 Hz, 2H), 1.33 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 166.9, 139.6, 137.1, 130.9, 128.4, 128.1, 117.1, 60.5, 14.4. IR ($\nu_{max}$ /cm$^{-1}$): 3106, 2981, 2903, 1709, 1627, 1370, 1267, 1170, 1043, 706. HRMS: calcd for $C_9H_{10}O_2S$ ($M^+$) 182.0402, found 182.0383. 1-(Carboxymethyl)pyridinium chloride was synthesized following a literature procedure.[24] To a solution of pyridine (1.0 equiv) in ethyl acetate (0.66 M) was added α-chloroacetic acid, and the mixture was stirred at ambient temperature overnight. A white precipitate was formed. The solution was filtered, washed with ethyl acetate, and dried under vacuum. The product was used crude. $^1$H NMR of the final product matched the previously reported spectrum.[24] $^1$H NMR (400 MHz; DMSO-$d_6$): $\delta$ 9.09 (dd, $J$ = 6.7, 1.3 Hz, 2H), 8.67 (tt, $J$ = 7.8, 1.3 Hz, 1H), 8.20 (dd, $J$ = 7.8, 6.8 Hz, 2H), 5.58 (s, 2H). Ethyl 2-(thiophene-2-yl)-indolizine-1-carboxylate (**19**) was synthesized following a literature procedure.[24] In a round-bottom flask equipped with a stir bar were added 1-(carboxymethyl)pyridinium chloride (1.0 equiv), $MnO_2$ (∼8 equiv), and 1,4-dioxane (0.25 M). To the suspension were added triethylamine (3.0 equiv) and (*E*)-ethyl 3-(thiophene-2-yl)-acrylate (4.0 equiv). The resulting mixture was stirred at 120 °C overnight. After the mixture was cooled to ambient temperature, it was filtered and washed with ethyl acetate. The filtrate was evaporated, and the crude residue was purified by silica gel column chromatography. The remaining starting olefin was recovered along with the desired product in 25% yield. Pale green and light sensitive solid. Mp: 62−66 °C. $R_f$: 0.19 (petroleum ether/ethyl acetate 90/10). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.22 (d, $J$ = 9.1 Hz, 1H), 7.96 (d, $J$ = 6.8 Hz, 1H), 7.43 (dd, $J$ = 3.6, 1.1 Hz, 1H), 7.39 (s, 1H), 7.31 (dd, $J$ = 5.1, 1.1 Hz, 1H), 7.08 (t, $J$ = 4.4 Hz, 1H), 7.06 (ddd, $J$ = 9.3, 6.9, 1.0 Hz, 1H), 6.73 (td, $J$ = 6.8, 1.1 Hz, 1H), 4.35 (q, $J$ = 7.1 Hz, 2H), 1.35 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.9, 137.0, 135.7, 127.8, 127.1, 125.5, 125.4, 125.0, 122.7, 120.6, 114.2, 113.0, 101.6, 59.7, 14.6. IR ($\nu_{max}$ /cm$^{-1}$): 3111, 2979, 2903, 1696, 1507, 1437, 1419, 1237, 1218, 1103, 782. HRMS: calcd for $C_{15}H_{13}NO_2S$ ($M^+$) 271.0667, found 271.0697.

**Synthesis and Characterization of Coupling Products. 3-(4-(Trifluoromethyl)phenyl)-2-phenylimidazo[1,2-*a*]pyrimidine (A, Figure 2).** Synthesized according to the general procedure for the direct arylation.[4a] White solid. Mp: 183−184 °C. $R_f$: 0.45 (dichloromethane/methanol 95/5). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.61 (dd, $J$ = 4.1, 2.0 Hz, 1H), 8.28 (dd, $J$ = 6.9 and 2.0 Hz, 1H), 7.81 (d, $J$ = 8.0 Hz, 2H), 7.72−7.69 (m, 2H), 7.61 (d, $J$ = 8.0 Hz, 2H), 7.36−7.30 (m, 3H), 6.87 (dd, $J$ = 6.9, 4.1 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 150.4, 148.3, 144.8, 133.1, 132.8, 131.2 (q, $J_{C-F}$ = 33.0 Hz), 131.0, 130.6, 128.6, 128.6, 128.5, 126.8 (q, $J_{C-F}$ = 3.7 Hz), 123.9 (q, $J_{C-F}$ = 272.3 Hz), 117.9, 109.1. $^{19}$F NMR (377 MHz, $CDCl_3$): $\delta$ −65.954. IR ($\nu_{max}$ /cm$^{-1}$): 3065, 2929, 2857, 1616, 1496, 1392, 1324, 1167, 1125, 1066, 766. HRMS: calcd for $C_{19}H_{12}F_3N_3$ ($M^+$) 339.0983, found 339.1000.

**5-(4-(Trifluoromethyl)phenyl)-2-phenylthiazole] ($B_{2\text{-Ph}}$, Figure 2).** Synthesized according to the general procedure for the direct arylation.[4a] Light yellow solid. Mp: 142−143 °C. $R_f$: 0.65 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.10 (s, 1H), 8.00−7.97 (m, 2H), 7.70 (dd, $J$ = 8.3 Hz, 4H), 7.51−7.45 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.6, 140.5, 137.7, 135.1, 133.5, 130.6, 130.2 (q, $J_{C-F}$ = 33.0 Hz), 129.2, 126.9, 126.6, 126.3 (q, $J_{C-F}$ = 3.7 Hz), 124.1 (q, $J_{C-F}$ = 272.3 Hz). $^{19}$F NMR (377 MHz, $CDCl_3$): $\delta$ −65.856. IR ($\nu_{max}$ /cm$^{-1}$): 3085, 2920, 2853, 1453, 1167, 1112, 833, 764, 686, 631. HRMS: calcd for $C_{16}H_{10}F_3NS$ ($M^+$) 305.0486, found 305.0496.

**5-(4-(Trifluoromethyl)phenyl)-2-isobutylthiazole ($B_{2\text{-}i\text{-Bu}}$, Figure 2).** Synthesized according to the general procedure for the direct arylation.[4a] Brown oil. $R_f$: 0.60 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.92 (s, 1H), 7.64 (s, 4H), 2.90 (d, J = 7.3 Hz, 2H), 2.15 (nonet, $J$ = 6.8 Hz, 1H), 1.03 (d, $J$ = 6.6 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.2, 139.0, 137.0, 135.3, 129.9 (q, $J_{C-F}$ = 32.9 Hz), 126.8, 126.2 (q, $J_{C-F}$ = 3.7 Hz), 124.1 (q, $J_{C-F}$ = 271.8 Hz), 42.7, 30.0, 22.4. $^{19}$F NMR (377 MHz, $CDCl_3$): $\delta$ −65.798. IR ($\nu_{max}$ /cm$^{-1}$): 3084, 2961, 2875, 1615, 1449, 1410, 1327, 1161, 1121, 1066, 1015, 841, 596 cm$^{-1}$. HRMS: calcd for $C_{14}H_{14}F_3NS$ ($M^+$) 285.0799, found 285.0802.

**3-(4-(Trifluoromethyl)phenyl)-2-methylindolizine (C, Figure 2).** Synthesized according to the general procedure for the direct arylation.[4a] Off-white solid (light sensitive). Mp: 58−60 °C. $R_f$: 0.55 (petroleum ether/ethyl acetate 98/2). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.01 (d, $J$ = 7.3 Hz, 1H), 7.74 (d, $J$ = 8.2 Hz, 2H), 7.58 (d, $J$ = 8.0 Hz, 2H), 7.33 (d, $J$ = 9.0 Hz, 1H), 6.72−6.64 (m, 1H), 6.45−6.38 (m, 2H), 2.32 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 135.7, 133.2, 129.8, 128.9 (q, $J_{C-F}$ = 32.5 Hz), 126.0 (q, $J_{C-F}$ = 3.7 Hz), 124.4 (q, $J_{C-F}$ = 271.8 Hz), 124.2, 122.0, 121.1, 118.7, 117.8, 110.4, 101.4, 12.6. $^{19}$F NMR (377 MHz, $CDCl_3$): $\delta$ −65.665. IR ($\nu_{max}$ /cm$^{-1}$): 3058, 2929, 2857, 1615, 1324, 1166, 1123, 1068, 836, 768, 728 cm$^{-1}$. HRMS: calcd for $C_{16}H_{12}F_3N$ ($M^+$) 275.0922, found 275.0947.

**1-Benzyl-5-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (D, Figure 2).** Synthesized according to the general procedure for the direct arylation.[4a] White solid. Mp: 98−100 °C. $R_f$: 0.55 (petroleum ether/ethyl acetate 65/35). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.80 (s, 1H), 7.67 (d, $J$ = 8.1 Hz, 2H), 7.37 (d, $J$ = 8.0 Hz, 2H), 7.31−7.29 (m, 3H), 7.08−7.06 (m, 2H), 5.57 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 136.9, 135.3, 133.9, 131.7 (q, $J_{C-F}$ = 33.0 Hz), 130.7, 129.4, 129.1, 128.5, 127.2, 126.1 (q, $J_{C-F}$ = 3.7 Hz), 123.8 (q, $J_{C-F}$ = 272.2 Hz), 52.2. $^{19}$F NMR (377 MHz, $CDCl_3$): $\delta$ −66.107. IR ($\nu_{max}$ /cm$^{-1}$): 3141, 3073, 3035, 2991, 2738, 2403, 1935, 1624, 1497, 1456, 1326, 1162, 1125, 1066, 844, 724. HRMS: calcd for $C_{16}H_{12}F_3N_3$ ($M^+$) 303.0983, found 303.0964.

**2-(4-(Trifluoromethyl)phenyl)benzo[*b*]thiophene (E, Figure 2).** Synthesized according to the general procedure for the direct arylation.[4a] Off-white solid. Mp: 214−216 °C. $R_f$: 0.70 (petroleum ether/toluene 95/5). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.89−7.81 (m, 2H), 7.82 (d, $J$ = 7.8 Hz, 2H), 7.68 (d, $J$ = 8.2 Hz, 2H), 7.64 (s, 1H), 7.42−7.32 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$)

(23) Bonini, C.; Chiummiento, L.; De Bonis, M.; Funicello, M.; Lupattelli, P.; Pandolfo, R. *Tetrahedron: Asymmetry* **2006**, *17*, 2919.

(24) Zhang, L.; Liang, F.; Sun, L.; Hu, Y.; Hu, H *Synthesis* **2000**, *12*, 1733.

δ 142.6, 140.7, 140.1, 138.1, 130.3 (q, $J_{C-F}$ = 32.8 Hz), 126.8, 126.1 (q, $J_{C-F}$ = 3.8 Hz), 125.2, 125.0, 124.3 (q, $J_{C-F}$ = 272 Hz) 124.1, 122.5, 121.3. $^{19}$F NMR (377 MHz, $CDCl_3$): δ −65.799. IR ($\nu_{max}$ /cm$^{-1}$): 3065, 2919, 2853, 1411, 1327, 1166, 1113, 843, 823, 750, 723. HRMS: calcd for $C_{15}H_9F_3S$ ($M^+$) 278.0377, found 278.0395.

**5-(4-(Trifluoromethyl)phenyl)furan-2-carbaldehyde (F, Figure 2).** Synthesized according to the general procedure for the direct arylation.[4a] Orange solid. Mp: 101−102 °C. $R_f$: 0.24 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.93 (d, $J$ = 8.2 Hz, 2H), 7.71 (d, $J$ = 8.3 Hz, 2H), 7.35 (d, $J$ = 3.7 Hz, 1H), 6.96 (d, $J$ = 3.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 177.6, 157.5, 152.7, 132.3, 131.3 (q, $J_{C-F}$ = 32.9 Hz), 126.1 (q, $J_{C-F}$ = 3.7 Hz), 125.5, 123.9 (q, $J_{C-F}$ = 272.4 Hz), 123.2, 109.4. $^{19}$F NMR (377 MHz, $CDCl_3$): δ −66.011. IR ($\nu_{max}$ /cm$^{-1}$): 3123, 2845, 1668, 1490, 1324, 1160, 1107, 966, 841, 802. HRMS: calcd for $C_{12}H_7F_3O_2$ ($M^+$) 240.0398, found 240.0373.

**2-(4-(Trifluoromethyl)phenyl)-5-propylthiophene (G, Figure 2).** Synthesized according to the general procedure for the direct arylation.[4a] Exhibited identical spectral data according to a previous report.[4a] $^1$H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, $J$ = 8.4 Hz, 2H), 7.59 (d, $J$ = 8.4 Hz, 2H), 7.21 (d, $J$ = 3.6 Hz, 1H), 6.78 (d, $J$ = 3.5 Hz, 1H), 2.81 (t, $J$ = 7.5 Hz, 2H), 1.74 (sext, $J$ = 7.5 Hz, 2H), 1.01 (t, $J$ = 7.3 Hz, 3H).

***N*-Methyl-5-(2,3,5,6-tetrafluorophenyl)-2-*p*-tolylindole (6).** Synthesized according to the general procedure of conditions A. The product was isolated as a white solid in 64% yield. Mp: 152−155 °C ($CHCl_3$). $R_f$: 0.45 (2% ether, petroleum ether). $^1$H NMR (400 MHz, $CDCl_3$, 296 K, TMS): δ 7.72 (d, $J$ = 0.9 Hz, 1H), 7.46 (d, $J$ = 8.5 Hz, 1H), 7.43−7.40 (m, 2H), 7.33−7.28 (m, 3H), 7.03 (dddd, $J_{H-F}$ = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 6.60 (d, $J$ = 0.7 Hz, 1H), 3.78 (s, 3H), 2.44 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 298 K, TMS): δ 147.9−144.6 (m), 145.4−142.8 (m), 142.7, 138.3, 138.2, 129.5, 129.3 (two overlapping carbon signals), 128.0, 123.3 (dd, $J$ = 1.8, 1.8 Hz), 122.9 (dd, $J$ = 17.3, 17.3 Hz), 122.5 (dd, $J$ = 1.8, 1.8 Hz), 118.6 (dd, $J$ = 2.4, 2.4 Hz), 109.7, 103.9 (dd, $J$ = 22.5, 22.5 Hz), 101.7, 31.3, 21.3. IR ($\nu_{max}$ /cm$^{-1}$): 3075, 2928, 1493, 1171, 939, 801, 709. HRMS: calcd for $C_{22}H_{15}F_4N$ ($M^+$) 369.1141, found 369.1116.

***N*-Methyl-3-phenyl-5-(2,3,5,6-tetrafluorophenyl)indole (7).** Synthesized according to the procedure of conditions B. Yellow solid. Mp: 123−125 °C ($CHCl_3$). $R_f$: 0.27 (2% ether, petroleum ether). $^1$H NMR (400 MHz, $CDCl_3$, 296 K, TMS): δ 8.01 (d, $J$ = 0.7 Hz, 1H), 7.63 (dd, $J$ = 8.3, 1.2 Hz, 2H), 7.49−7.41 (m, 3H), 7.35 (ddd, $J$ = 8.5, 2.9, 1.4 Hz, 1H), 7.30−7.26 (m, 1H), 7.29 (s, 1H), 7.04 (dddd, $J$ = 9.7, 9.7, 7.3, 7.3 Hz, 1H), 3.89 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, 297 K, TMS): δ 147.8−144.7 (m), 145.4−142.4 (m), 137.5, 135.0, 128.9, 127.4, 127.4, 126.2, 126.1, 123.8 (dd, $J_{C-F}$ = 1.7, 1.7 Hz), 122.8 (dd, $J_{C-F}$ = 17.1, 17.1 Hz), 122.1 (dd, $J_{C-F}$ = 1.8, 1.8 Hz), 118.8 (dd, $J_{C-F}$ = 2.2, 2.2 Hz), 109.7, 117.4, 104.0 (dd, $J_{C-F}$ = 22.9, 22.9 Hz), 33.0. IR ($\nu_{max}$ /cm$^{-1}$): 3075, 2948, 1604, 1491, 1456, 1223, 1171, 939, 751, 710. HRMS: calcd for $C_{21}H_{13}F_4N$ ($M^+$) 355.0984, found 355.0990.

**Ethyl *N*-Methyl-5-(2,3,5,6-tetrafluoro-4′-carboxylatebiphenyl-4-yl)indole (8).** Synthesized according to the procedure of conditions C and D. The product was isolated as a white solid in 54% yield with conditions C and in 58% yield with conditions D. Mp: 177−179 °C ($CHCl_3$). $R_f$: 0.21 (5% ether, petroleum ether). $^1$H NMR (400 MHz, $CDCl_3$, 296 K, TMS): δ 1.43 (t, $J$ = 7.1 Hz, 3H), 3.86 (s, 3H), 4.43 (q, $J$ = 7.1 Hz, 2H), 6.58 (dd, $J$ = 3.1, 0.7 Hz, 1H), 7.14 (d, $J$ = 3.1 Hz, 1H), 7.36 (ddd, $J$ = 8.4, 2.9, 1.4 Hz, 1H), 7.46 (d, $J$ = 8.6 Hz, 1H), 7.62 (ddd, $J$ = 8.6, 1.4, 1.4 Hz, 2H), 7.79 (d, $J$ = 0.8 Hz, 1H), 8.19 (ddd, $J$ = 8.6, 1.8 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$, 298 K, TMS): δ 14.3, 33.0, 61.2, 101.7, 109.4, 117.6 (dd, $J_{C-F}$ = 16.5, 16.5 Hz), 118.0 (dd, $J_{C-F}$ = 2.0, 2.0 Hz), 121.9 (dd, $J_{C-F}$ = 16.8, 16.8 Hz), 123.1 (dd, $J_{C-F}$ = 1.7, 1.7 Hz), 123.4 (dd, $J_{C-F}$ = 1.6, 1.6 Hz), 128.5, 129.7, 129.9, 130.3 (dd, $J_{C-F}$ = 2.0, 2.0 Hz), 130.9, 132.3 (dd, $J_{C-F}$ = 2.0, 2.0 Hz), 136.8, 145.4−142.6 (m), 145.8−143.0 (m), 166.1. IR ($\nu_{max}$ /cm$^{-1}$): 2958, 2908, 1710, 1479, 1271, 1100, 979, 711. HRMS: calcd for $C_{24}H_{17}F_4NO_2$ ($M^+$) 427.1195, found 427.1180.

**2-(*N*-Methyl-2-*p*-tolylindol-5-yl)pyridine *N*-Oxide (9).** Synthesized according to the general procedure of conditions A. The product was isolated as a white solid in 53% yield. Beige solid. Mp: 156−160 °C. $R_f$: 0.27 (MeOH/acetone/DCM 5:30:65). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.42−8.40 (m, 1H), 8.06 (d, $J$ = 0.8 Hz, 1H), 7.78−7.74 (m, 1H), 7.54−7.40 (m, 4H), 7.36−7.18 (m, 4H), 6.60 (s, 1H), 3.77 (s, 3H), 2.43 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.9, 142.6, 140.7, 138.8, 138.1, 132.5, 129.6, 129.4 (2 carbons), 127.8, 126.4, 124.2, 123.7, 122.9, 122.1, 109.4, 102.2, 31.4, 21.4. IR ($\nu_{max}$ /cm$^{-1}$): 3024, 2950, 2920, 1616, 1472, 1233, 759. HRMS: calcd for $C_{21}H_{18}N_2O$ ($M^+$) 314.1419, found 314.1391.

**2-(3-(4-(Methoxycarbonyl)phenyl)-1-methyl-1*H*-indol-5-yl)-pyridine 1-Oxide (11).** Synthesized according to the general procedure of conditions B. The product was isolated as a white solid in 55% yield. Yellow solid. Mp: ∼210 °C dec. $R_f$: 0.58 (MeOH/DCM 2/98). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, $J$ = 4.7 Hz, 1H), 8.17 (d, $J$ = 1.1 Hz, 1H), 7.99 (dd, $J$ = 8.7, 1.6 Hz, 1H), 7.74 (td, $J$ = 8.0, 1.7 Hz, 1H), 7.72 (d, $J$ = 1.4 Hz, 1H), 7.52 (d, $J$ = 10.2 Hz, 2H), 7.42 (d, $J$ = 8.6 Hz, 1H), 7.20 (ddd, $J$ = 6.5, 4.7, 1.9 Hz, 1H), 6.98 (s, 1H), 6.43 (d, $J$ = 10.2 Hz, 2H), 3.84 (s, 3H), 3.80 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 185.1, 170.2, 158.3, 149.7, 147.6, 143.4, 138.0, 136.8, 132.0, 128.7, 127.4, 125.6, 122.0, 121.5, 120.5, 117.9, 110.9, 110.4, 53.6, 33.2. IR ($\nu_{max}$ /cm$^{-1}$): 3057, 2961, 2871, 1714, 1589, 1466, 1278, 1162, 773. HRMS: calcd for $C_{22}H_{18}N_2O_3$ ($M^+$) 358.1317, found 358.1310.

**2-(3,5-Dimethylphenyl)-6-(*N*-methylindol-5-yl)pyridine *N*-Oxide (13).** Synthesized according to the procedure of conditions E and F. The product was isolated as a white solid in 24% yield with conditions E and in 51% yield with conditions F. Off-white solid. Mp: 195−198 °C ($CHCl_3$). $R_f$: 0.45 (3% $Me_2CO$, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$, 296 K, TMS): δ 8.10 (dd, $J$ = 1.6, 0.4 Hz, 1H), 7.78 (dd, $J$ = 8.7, 1.6 Hz, 1H), 7.47−7.42 (m, 3H), 7.37 (d, $J$ = 8.7 Hz, 1H), 7.33 (dd, $J$ = 7.8, 2.4 Hz, 1H), 7.28 (dd, $J$ = 7.7, 7.7 Hz, 1H), 7.05 (m, 2H), 6.52 (dd, $J$ = 3.1, 0.8 Hz, 1H), 3.80 (s, 3H), 2.36 (s, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$, 298 K, TMS): δ 151.1, 150.2, 137.5, 137.0, 133.6, 130.8, 129.4, 128.1, 127.3, 126.2, 125.3, 124.8, 124.5, 123.2, 122.8, 108.6, 101.8, 32.9, 21.3. IR ($\nu_{max}$ /cm$^{-1}$): 3005, 2951, 1556, 1476, 1358, 1246, 1226, 786, 721. HRMS: calcd for $C_{22}H_{20}N_2O$ ($M^+$) 328.1576, found 328.1556.

**2-(2,3,5,6-Tetrafluoro-3′,4′-dimethoxybiphenyl-4-yl)pyridine (15).** Synthesized according to the general procedure of conditions C. White solid. Mp: 154−156 °C. $R_f$: 0.21 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.81 (ddd, $J$ = 4.9, 1.8, 0.9 Hz, 1H), 7.86 (td, $J$ = 7.8, 1.8 Hz, 1H), 7.56 (dt, $J$ = 7.9, 1.0 Hz, 1H), 7.39 (ddd, $J$ = 7.7, 4.9, 1.1 Hz, 1H), 7.11 (dq, $J$ = 8.3, 1.6 Hz, 1H), 7.03 (q, $J$ = 1.6 Hz, 1H), 7.01 (d, $J$ = 8.4 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.2, 149.9, 149.0, 148.0, 136.7, 126.1, 123.7, 123.3, 120.8 (t, $J_{CF}$ = 16.7 Hz), 119.6, 118.6 (t, $J_{CF}$ = 16.2 Hz), 113.3, 111.2, 56.1, 56.0. IR ($\nu_{max}$ /cm$^{-1}$): 3015, 2987, 2949, 2914, 2844, 1586, 1524, 1482, 1456, 1261, 980; HRMS calcd for $C_{19}H_{13}NO_2F_4$ ($M^+$) 363.0882, found 363.0887.

**4-(Furan-2-yl)-2-(3-nitrophenyl)-5-(4-(trifluoromethyl)phenyl)-thiazole (20).** Synthesized according to the general procedure for the direct arylation. Pale brown solid. Mp: 157−159 °C. $R_f$: 0.41 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): δ 8.83 (t, $J$ = 1.9 Hz, 1H), 8.31 (dddd, $J$ = 7.8, 7.8, 1.5, 1.0 Hz, 2H), 7.71−7.64 (m, 5H), 7.38 (dd, $J$ = 1.7, 0.7 Hz, 1H), 6.79 (dd, $J$ = 3.4, 0.7 Hz, 1H), 6.48 (dd, $J$ = 3.4, 1.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 164.1, 149.1, 148.9, 143.0,

142.9, 134.7, 132.2, 131.6, 130.9 (q, $J_{C-F}$ = 32.8 Hz), 130.4, 130.2, 125.6 (q, $J_{C-F}$ = 3.8 Hz), 124.9, 124.0 (q, $J_{C-F}$ = 272 Hz), 121.4, 111.6, 110.6. IR ($\nu_{max}$ /cm$^{-1}$): 3094, 2932, 1534, 1353, 1324, 1168, 1125, 1068, 1013, 734. HRMS: calcd for $C_{20}H_{11}N_2O_3SF_3$ ($M^+$) 416.0442, found 416.0398.

**Methyl 4-(2-(3-Nitrophenyl)-4-(furan-2-yl)thiazol-5-yl)benzoate (17).** Synthesized according to the general procedure for the direct arylation. Yellow solid. Mp: 166−168 °C. $R_f$: 0.42 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.83 (t, $J$ = 1.9 Hz, 1H), 8.32 − 8.26 (m, 2H), 8.10 (d, $J$ = 8.6 Hz, 2H), 7.67 (t, $J$ = 7.9 Hz, 1H), 7.60 (d, $J$ = 8.6 Hz, 2H), 7.37 (dd, $J$ = 1.8 and 0.8 Hz, 1H), 6.76 (dd, $J$ = 3.4 and 0.8 Hz, 1H), 6.46 (dd, $J$ = 3.4 and 1.8 Hz, 1H), 3.96 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 166.7, 164.1, 149.0, 148.7, 142.8, 142.6, 135.5, 134.7, 132.2, 132.0, 130.3, 130.1, 129.9, 129.7, 124.7, 121.3, 111.5, 110.4, 52.3. IR ($\nu_{max}$ /cm$^{-1}$): 3094, 2952, 2857, 1724, 1607, 1534, 1353, 1279, 736. HRMS: calcd for $C_{21}H_{14}N_2O_5S$ ($M^+$) 406.0623, found 406.0618.

**Methyl 4-(2-(3-Nitrophenyl)-4-(5-*p*-tolylfuran-2-yl)thiazol-5-yl)-benzoate (21).** Synthesized according to the general procedure for the direct arylation. Bright yellow solid. Mp: 194−202 °C. $R_f$: 0.26 (petroleum ether/ethyl acetate 80/20). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.86 (t, $J$ = 1.8 Hz, 1H), 8.34−8.29 (m, 2H), 8.16−8.13 (m, 2H), 7.72 (d, $J$ = 8.4 Hz, 2H), 7.67 (t, $J$ = 8.0 Hz, 1H), 7.22 (d, $J$ = 8.2 Hz, 2H), 7.08 (d, $J$ = 8.0 Hz, 2H), 7.00 (d, $J$ = 3.5 Hz, 1H), 6.67 (d, $J$ = 3.5 Hz, 1H), 4.00 (s, 3H), 2.33 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 166.8, 164.1, 154.5, 148.9, 148.7, 142.9, 137.8, 136.1, 134.8, 132.2, 131.2, 130.3, 130.3, 130.2, 129.8, 129.5, 127.6, 124.8, 123.7, 121.4, 112.7, 106.2, 52.5, 21.4. IR ($\nu_{max}$ /cm$^{-1}$): 3028, 2957, 2921, 2859, 1716, 1532, 1351, 1277, 1112. HRMS: calcd for $C_{28}H_{20}N_2O_5S$ ($M^+$) 496.1093, found 496.1104.

**2-(4-(4-Butyl-1*H*-1,2,3-triazol-1-yl)phenyl)-3-*p*-tolylimidazo-[1,2-*a*]pyrimidine (22).** Synthesized according to the general procedure for the direct arylation. Yellow solid. Mp: 192−194 °C. $R_f$: 0.50 (MeOH/DCM 5/95). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.58 (dd, $J$ = 4.0, 2.0 Hz, 1H), 8.24 (dd, $J$ = 6.9, 2.0 Hz, 1H), 7.92 (d, $J$ = 8.8 Hz, 2H), 7.71 (s, 1H), 7.66 (d, $J$ = 8.8 Hz, 2H), 7.40−7.33 (m, 4H), 6.83 (dd, $J$ = 6.9, 4.1 Hz, 1H), 2.80 (t, $J$ = 7.6 Hz, 2H), 2.49 (d, $J$ = 2.4 Hz, 3H), 1.76−1.66 (m, 2H), 1.49−1.36 (m, 2H), 0.96 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 150.3, 149.3, 148.0, 142.2, 140.0, 136.7, 134.0, 131.0, 130.8, 130.5, 129.5, 125.4, 120.2, 120.1, 118.7, 108.9, 31.6, 25.5, 22.4, 21.6, 14.0. IR ($\nu_{max}$ /cm$^{-1}$): 2956, 2927, 2869, 2859, 1617, 1525, 1517, 1496, 1223, 1203. HRMS: calcd for $C_{25}H_{24}N_6$ ($M^+$) 408.2062, found 408.2053.

**Ethyl 3-(3-Nitrophenyl)-2-(thiophene-2-yl)indolizine-1-carboxylate (23).** Synthesized according to the general procedure for the direct arylation. Bright yellow solid. Mp: 136−137 °C. $R_f$: 0.18 (petroleum ether/ethyl acetate 90/10). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.36 (dt, $J$ = 9.1, 1.2 Hz, 1H), 8.27 (t, $J$ = 1.8 Hz, 1H), 8.20 (ddd, $J$ = 8.2, 2.3, 1.2 Hz, 1H), 8.00 (dt, $J$ = 7.1, 1.1 Hz, 1H), 7.64 (dt, $J$ = 7.7, 1.4 Hz, 1H), 7.56 (t, $J$ = 7.9 Hz, 1H), 7.28 (dd, $J$ = 5.0, 1.4 Hz, 1H), 7.16 (ddd, $J$ = 9.2, 6.7, 1.1 Hz, 1H), 6.96−6.92 (m, 2H), 6.77 (td, $J$ = 6.9, 1.3 Hz, 1H), 4.26 (q, $J$ = 7.1 Hz, 2H), 1.22 (d, $J$ = 14.3 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.6, 148.7, 137.0, 136.5, 134.5, 131.9, 130.0, 129.1, 126.5, 126.3, 125.5, 123.9, 123.5, 123.3, 123.1, 122.7, 120.7, 113.7, 104.3, 59.7, 14.3. IR ($\nu_{max}$ /cm$^{-1}$): 3077, 2981, 1685, 1534, 1507, 1348, 1199, 1129, 739. HRMS: calcd for $C_{21}H_{16}N_2O_4S$ ($M^+$) 392.0831, found 392.0847.

**5-Benzyl-4-(furan-2-yl)-2-phenylthiazole (25).** Synthesized according to the general procedure for the direct benzylation. Beige solid. Mp: 120−121 °C. $R_f$: 0.46 (petroleum ether/ethyl acetate 90/10). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.93−7.90 (m, 2H), 7.52 (dd, $J$ = 1.1, 0.5 Hz, 1H), 7.41−7.39 (m, 3H), 7.33−7.25 (m, 5H), 6.85 (d, $J$ = 3.3 Hz, 1H), 6.53 (dd, $J$ = 3.4, 1.9 Hz, 1H), 4.50 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 165.8, 150.8, 142.9, 142.2, 140.1, 133.6, 133.2, 130.1, 128.9, 128.9, 128.7, 126.9, 126.5, 111.5, 108.8, 33.1. IR ($\nu_{max}$ /cm$^{-1}$): 3062, 3027, 2919, 2852, 1680, 1601, 1494, 1474, 1310, 1253, 1171, 1009, 762. HRMS: calcd for $C_{20}H_{15}NOS$ ($M^+$) 317.0874, found 317.0864.

**Ethyl 3-Benzyl-2-(thiophene-2-yl)indolizine-1-carboxylate (26).** Synthesized according to the general procedure for the direct benzylation. Yellow solid. Mp: 154−156 °C. $R_f$: 0.48 (petroleum ether/ethyl acetate 90/10). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.29 (dt, $J$ = 9.1, 1.1 Hz, 1H), 7.64 (dt, $J$ = 7.0, 0.9 Hz, 1H), 7.37 (dd, $J$ = 4.6, 1.8 Hz, 1H), 7.31−7.18 (m, 3H), 7.08−7.04 (m, 5H), 6.64 (td, $J$ = 6.8, 1.3 Hz, 1H), 4.25 (q, $J$ = 7.1 Hz, 2H), 4.24 (s, 2H), 1.22 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.9, 137.3, 136.2, 135.7, 128.9, 128.0, 127.9, 126.8, 126.6, 126.1, 123.4, 123.3, 123.1, 122.4, 120.3, 112.9, 102.9, 59.4, 30.4, 14.4. IR ($\nu_{max}$ /cm$^{-1}$): 3105, 3026, 2979, 2928, 2901, 1683, 1501, 1243, 1038. HRMS: calcd for $C_{22}H_{19}NO_2S$ ($M^+$) 361.1136, found 361.1138.

**3-Benzyl-2-(4-(4-butyl-1*H*-1,2,3-triazol-1-yl)phenyl)imidazo-[1,2-*a*]pyrimidine (27).** Synthesized according to the general procedure for the direct benzylation. Pale yellow solid. Mp: 178−180 °C. $R_f$: 0.11 (MeOH/DCM 2/98). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.58 (dd, $J$ = 4.1, 2.0 Hz, 1H), 8.03 (td, $J$ = 7.0, 2.8 Hz, 1H), 8.02 (d, $J$ = 8.7 Hz, 2H), 7.82 (d, $J$ = 8.8 Hz, 2H), 7.76 (s, 1H), 7.36−7.29 (m, 3H), 7.16 (d, $J$ = 6.8 Hz, 2H), 6.81 (dd, $J$ = 6.8, 4.1 Hz, 1H), 4.55 (s, 2H), 2.81 (t, $J$ = 7.7 Hz, 2H), 1.74 (q, $J$ = 6.8 Hz, 2H), 1.44 (sext, $J$ = 7.4 Hz, 2H), 0.97 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 149.9, 149.4, 148.2, 144.3, 137.0, 135.8, 134.2, 131.1, 129.7, 129. 5, 127.7, 127.5, 120.6, 118.8, 116.9, 108.8, 31.6, 29.8, 25.5, 22.5, 14.0. IR ($\nu_{max}$ /cm$^{-1}$): 2958, 2932, 2864, 1507, 1498, 1346, 1225, 1097, 1042, 843. HRMS: calcd for $C_{25}H_{24}N_6$ ($M^+$) 408.2062, found 408.2072.

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