Synthesis of Pyridobenzazepines Using a One-Pot Rh/Pd-Catalyzed Process

Heather Lam,¹⁰ Jennifer Tsoung, and Mark Lautens*

Department of Chemistry, University of Toronto, 80 St. George Street Toronto, ON Canada, MSS 3H6

Supporting Information

ABSTRACT: In recent years, our group has been developing multicatalytic reactions for the synthesis of biologically relevant heterocyclic compounds. An efficient dual-metal catalyzed reaction of electron-deficient *o*-chlorovinylpyridines with *o*-aminophenylboronic esters to access pyridobenzaze-pines is described. Combining a Rh¹-catalyzed arylation followed by a Pd⁰-catalyzed C–N coupling, in a one-pot



Article

pubs.acs.org/joc

procedure, provides a simplified method to access heterocycles without workup and purification after each step. The substrate scope encompasses a variety of *N*-H and *N*-alkylated pyridobenzazepine variants with yields up to 93%.

INTRODUCTION

Multicatalytic reactions offer an alternative to traditional stepby-step sequences and can reduce the amount of time, effort, and solvent used to construct useful products. Our objective is to learn about the compatibility of different catalysts and substrates in multicatalytic scenarios. This knowledge could be of use for others interested in developing new multicatalytic reactions. One variant uses several substrates and catalysts in a multicomponent-multicatayst reaction, (MC)²R. Our group has applied this approach in various syntheses of heterocyclic scaffolds including dihydroquinolinones, oxindoles, and fully substituted triazoles.¹⁻⁴ Ideally, all the starting materials, reagents, and catalysts are added simultaneously, and the building blocks will react in a productive sequential manner under the same reaction conditions. To ensure successful application of this strategy, orthogonal reactivity of the metals and "time resolution" of the individual steps are necessary.⁵

In recent years, our group has synthesized functionalized seven-membered fused heterocyclic rings using dual-metal catalyzed processes to combine readily available vinylpyridines and *ortho*-functionalized phenylboronic acids. Recently, we reported a method for the synthesis of pyridobenzoxepines (Scheme 1a).⁶ The analogous nitrogen-containing dibenzaze-pine is prevalent in many pharmaceutically relevant compounds, used as tricyclic antidepressants, and was recently reengineered as an anticancer agent, which exhibited efficacy on xenograft models of EFGR-driven cancer (Figure 1).^{7–10}

Although the core structure of these tricyclic motifs is readily available, substituted analogues are difficult to access. Diversity in scaffolds is typically obtained by electrophilic aromatic substitution, which is often low-yielding and with limited control over site selectivity. Additionally, there are relatively few *de novo* syntheses of these structures.^{11–15}

We recently reported the synthesis of the *N*-arylated pyridobenzazepine motif using a Rh/Pd-catalyzed $(MC)^2R$ (Scheme 1b).¹⁶ These complex products could be obtained in



Figure 1. Examples of drugs that contain the dibenzazepine motif.

high yields from vinylpyridines, *o*-chlorophenylboronic acids, and anilines by combining a Rh-catalyzed arylation reaction and two Pd-catalyzed C–N bond-forming reactions in one pot. The *N*-alkylated analogues could also be accessed by adopting a one-pot, two-step procedure where the Rh-catalyzed arylation was allowed to take place before the components for the Pd-catalyzed C–N bond forming reactions were added. While this protocol allowed for the synthesis of several *N*-alkylated products in moderate yields, we were interested in pursuing a more expedient procedure to access these highly valuable targets.

We herein report that *N*-alkylated as well as *N*-H pyridobenzazepine motifs can be synthesized by coupling *o*-aminophenylboronic esters to *o*-chlorovinylpyridines with a new approach using Rh-catalyzed 1,4-arylation followed by a Pd-catalyzed C–N coupling between a secondary amine and an aryl chloride (Scheme 1c). Compared to the arylated analogues, *N*-alkylated analogues are more relevant in pharmacophores, and the *N*-H motifs can be further derivatized at the secondary amine.¹⁷ Furthermore, the products can be obtained using a one-step protocol compared to the previous two-step protocol,

Received: March 9, 2017

Metal Catalysis

(a) Pyridobenzoxepines (2013)



Scheme 2. Synthesis of Pyridobenzazepines



and the yields obtained were generally higher than the previous method, making this method advantageous for the synthesis of these motifs.

RESULTS AND DISCUSSION

To access N-H pyridobenzazepines, we used the Rh¹-catalyzed arylation with $[Rh(cod)Cl]_2$ as the catalyst and K_2CO_3 as the base. This process afforded 91% yield of intermediate 3a, which was subjected to the Pd⁰-catalyzed C–N bond formation using $Pd(OAc)_2$ with XPhos as the ligand and NaO^tBu as the base. A 95% yield of the desired product 4a was isolated (Scheme 2). Although the two steps can be telescoped in a one-pot, twostep procedure, molecular sieves had to be added to attain comparable yields. Consequently, a convenient one-pot procedure with a single addition of all the reagents at the start of the reaction is more desirable. However, simply combining the reagents from these individual steps gave a poor yield of 4a (Table 1, entry 1), though switching the base to KOH showed an improvement in yield (Table 1, entry 2).¹⁸ Changing the ligand to ^tBuBrettPhos did not improve the yield (Table 1, entry 3). Bidentate ligands such as Josiphos or Xantphos also fared worse (Table 1, entries 4 and 5). A variety of Buchwald precatalysts and ligands were screened (Figure 2). Changing the palladium source to Pd-G1-XPhos improved the

yield (Table 1, entry 6), although the G2 and G3 versions of the same catalyst gave poorer yields under these conditions (Table 1, entries 7 and 8). A survey of bases showed that KOH afforded the highest isolated yield of 87% (Table 1, entry 9). Running the reaction without an excess of the XPhos ligand gave lower yields (Table 1, entry 10).

A screen of other bulky monophosphine ligands such as tBuXPhos, SPhos, and RuPhos demonstrated that XPhos was the best ligand for this domino reaction (Table 1, entries 11-14). This result is in alignment with reports from Buchwald on the efficiency of the XPhos ligand for the coupling of primary amines.¹⁹ When we ran experiments with a mixed ligand system (Table 1, entries 15 and 16), slightly better yields were obtained. Finally, as a control study, running the reaction without palladium and ligand gave a >95% yield of 3a (Table 1, entry 17), showing that C-N bond formation occurs via palladium catalysis and not through an S_NAr mechanism. Due to the similarity of the results of the mixed vs single ligand system (Table 1, entry 9 and 15), we examined the substrate scope using a single ligand to simplify the system (Table 2). However, it became apparent that using substrates other than 2a gave much poorer yields in all cases. Similarly, running the reactions with Pd-G1-RuPhos and excess RuPhos ligand gave



^{*a*} 1a (1.0 equiv, 0.2 mmol), 2a (1.5 equiv). ^{*b*} 15 mol % L_2 used. ^{*c*}¹H NMR yields with *p*-nitroacetophenone as the internal standard with isolated yields in parentheses.



rigure 2. Duchinara panadacycie precadalysis and various inganas.

equally poor yields of the cyclized product. Hence, we settled on the mixed ligand system.

Based on our previous work with vinylpyrazines in multicatalytic reactions, we envisioned that these substrates would work well in the present reaction.²⁰ When we subjected *o*-chlorovinylpyrazine **1b** and **2a** to the domino catalysis conditions, **4c** was isolated in excellent yield. Running the reaction in the absence of the palladium gave none of the cyclization product, showing that cyclization did not occur through a base-mediated reaction. In place of the CF₃ group, vinylpyridines with Ms **1c** or CN **1d** were tolerated in the reaction to give **4d** and **4e** respectively.

In the absence of an electron-withdrawing R group on the vinylpyridine (i.e., $R = CH_3$ or H), the desired transformation failed to occur. Halides were tolerated on the ring (4f,g); however, the yield was much lower with a chloro on the aniline

ring, possibly due to competing oxidative addition to the Pd catalyst. Electron-donating groups (4h,i) worked well, but an electron-withdrawing cyano group (4j) fared much worse.

Next, we wanted to explore the conditions for synthesizing *N*-alkylated pyridobenzazepines. We optimized the conditions for the synthesis of *N*-alkylated pyridobenzazepines using an *N*-benzylated derivative **2b** as the standard substrate. When reacting **1a** with **2b**, we found that $[Rh(cod)Cl]_{2^{j}}$ K₂CO_{3^j} and Pd-G1-RuPhos with excess RuPhos ligand in a 10:1 mixture of 1,4-dioxane and H₂O gave an 85% yield of **4b** (Table 3, entry 1). This outcome is in line with reports from Buchwald on the high efficiency of RuPhos for the coupling of secondary amines.¹⁹ [Rh(cod)OH]₂ gave comparable yields, while [Rh(C₂H₄)₂Cl]₂ gave lower yields (Table 3, entries 2 and 3). It was found that K₂CO₃ was the optimal base. The use of other

Table 2. Scope of N-H Pyridobenzazepines





Table 3. Optimization of One-Pot Domino Reaction of N-Benzylated Pyridobenzazepine"					
	F ₃ C N 1a	Bn [HN Bpin 2b	Rh(cod)Cl] ₂ (2.5 mol%) [Pd]/L ₁ (5 mol%) L ₂ (5 mol%) base (3 equiv) dioxane/H ₂ O (10:1)	F_3C H_1 H_2 H_3	
entry	$[Pd]/L_1$	L_2	base	yield of $4b^{b}$ (%)	yield of $3b^b$ (%)
1	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃	85 (80)	
2 ^{<i>c</i>}	Pd-G1-RuPhos	RuPhos	K_2CO_3	79 (71)	
3^d	Pd-G1-RuPhos	RuPhos	K_2CO_3	2	8
4	Pd-G1-RuPhos	RuPhos	КОН	42	
5	Pd-G1-RuPhos	RuPhos	CsCO ₃	13	30
6	Pd-G1-XPhos	XPhos	K ₂ CO ₃	60	30
7^e	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃	75	
8^{f}	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃	8	60
9^e	$Pd(OAc)_2$	RuPhos	K ₂ CO ₃	86 (81)	
10 ^g	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃		60
11 ^h	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃	59	
12 ^{<i>i</i>}	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃	9	
13 ^j	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃	18	
14^{k}	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃	9	40
15 ¹	Pd-G1-RuPhos	RuPhos	K ₂ CO ₃	11	12

. . . . a

^a1a (1.0 equiv, 0.3 mmol), 2a (1.5 equiv), 0.1 M in dioxane, 110 °C, 16 h. ^{b1}H NMR yields with *p*-nitroacetophenone as the internal standard with isolated yields in parentheses. ${}^{c}[Rh(cod)OH]_{2}$ instead of $[Rh(cod)CI]_{2}$. ${}^{d}[Rh(C_{2}H_{4})_{2}CI]_{2}$ instead of $[Rh(cod)CI]_{2}$. ${}^{e}10$ mol % of L_{2} used. ${}^{f}2.5$ mol % of $[Pd]/L_{1}$ used. ${}^{g}Run$ at 100 °C. ${}^{h}Run$ at 120 °C. ${}^{i}Run$ at 0.05 M. ${}^{j}Run$ at 0.2 M. ${}^{k}Dioxane/H_{2}O = 10:0.5$. ${}^{l}MeOH$ instead of $H_{2}O$.

inorganic bases such as KOH or Cs₂CO₃ fared poorly under otherwise identical conditions (Table 3, entries 4 and 5).

The domino reaction did not give full conversion to 4b using the combination of Pd-G1-XPhos with excess XPhos ligand (Table 3, entry 6). In analogy to the N-H case, the second- and third-generation Pd-XPhos palladacycles, with added XPhos, afforded negligible yields. Increasing the amount of excess ligand to 10 mol % or decreasing the palladium catalyst loading to 2.5 mol % significantly decreased the yield (Table 3, entries 7

and 8). We also wanted to determine if simple palladium sources could be used rather than the specialized precatalysts mentioned above. When the reaction was performed with the free ligand and Pd(OAc)₂, comparable yields (81%) to Pd-G1-RuPhos with an equivalent ligand loading (Table 3, entry 9) were obtained.²¹ PdCl₂, Pd(dppf)Cl₂, Pd₂(dba)₃, or Pd-(PhCN)₂Cl₂ led to low yields and incomplete conversion to the desired product under otherwise standard conditions.

Table 4. Scope of N-Substituted Pyridobenzazepine



^aKOH (3 equiv) used instead of K₂CO₃.



Figure 3. Proposed mechanism for the Rh/Pd-catalyzed formation of benzazepines.

When the temperature of the reaction was lowered to 100 °C, only 60% of intermediate **3b** and none of **4b** was observed (Table 3, entry 10). Running the reaction at 120 °C led to a lower yield of **4b** (Table 3, entry 11). A concentration of 0.1 M was found to be the optimal value, as reactions run at either 0.05 or 0.20 M proceeded in low yield (Table 3, entries 12 and 13). Halving the amount of water in the reaction led to lower yields of **3b** and incomplete conversion to **4b** (Table 3, entry 14). Using MeOH in place of H₂O led to incomplete conversion of **3b** to the desired product (Table 3, entry 15).

Hence, the best conditions used a combination of 2.5 mol % of $[Rh(cod)Cl]_2$, 3 equiv of K_2CO_3 , and 5 mol % of Pd-G1-RuPhos precatalyst with 5 mol % excess RuPhos ligand in a 10:1 mixture of 1,4-dioxane and H₂O. With these optimized conditions, we studied the scope of the reaction (Table 4). Substrates bearing a *para* substituent on the *N*-benzyl group

gave good yields of the desired products 4k,l. Deborylation of 2 was the major side reaction when coupling the N-benzyl substrates to 1. An analysis of the aniline component showed that electron-donating groups such as methoxy and methyl provided good yields (Table 4, 4m,n). However, electronwithdrawing groups such as a methyl ester or cyano in that position generally gave lower yields of the product (Table 4, 40-q). Compounds 40 and 4p gave the intermediates in 71% and 80% yield, respectively. For 4q, switching the base to KOH allowed for cyclization to the product, but 67% of the intermediate remained uncyclized. When the Rh-catalyzed step was run on its own, the intermediates could be obtained in good yields. The lowered yields for the Pd-catalyzed step could be due to the reduced nucleophilicity of the aniline. Alkyl chains of different lengths were incorporated in good yields (Table 4, 4r-t) with around 15–20% of the dechlorinated

Scheme 3. Three-Component (MC)²R



intermediate as the major side product. Bulky N-substituents on the aniline (i.e., iPr) would lead to formation of the intermediate, without cyclizing, instead undergoing partial dechlorination.

We propose that the formation of the pyridobenzazepines occurs through a Rh-catalyzed 1,4-arylation followed by a Pd-catalyzed amination (Figure 3). First, $[Rh(cod)Cl]_2$ is converted to the more active [Rh]-OH species. [Rh]-OH then transmetalates with the 2-aminophenylboronic ester 2, which reacts with the vinylpyridine 1 to give an aza-allylrhodium species. Protodemetalation gives intermediate 3, and water regenerates [Rh]-OH. Oxidative addition of 3 to the Pd-catalyst occurs and the Pd coordinates to the aniline. In the presence of base, HCl is lost, and a reductive elimination gives rise to pyridobenzazepine 4.

A limitation of the current process is that an electronwithdrawing substituent must be present in the 5 position of the vinylpyridine for the transformation to occur. This includes either a CF3 or CN group. Subjecting 1d with 2-(Nmethylamino)phenylboronic acid pinacol ester gave moderate yields of 4v along with 44% of unreacted vinylpyridine, using KOH. This reaction did not work with an unsubstituted vinylpyridine nor with a Ms or NO₂ group in the 5-position. Subjecting these unsuccessful substrates to the rhodiumcatalyzed arylation conditions in the absence of palladium was also unsuccessful, leading only to deborylation of 2. As an alternative strategy, we attempted to use a more electron-rich aminophenylboronic ester, but it was not found to be a viable solution to allow electron-neutral pyridines to react. When we attempted to react 1b with 2b, none of the N-substituted product was obtained. Instead, 40% yield of the intermediate was formed. It was re-subjected to the Pd-catalyzed conditions, but no reaction was observed.

Finally, we were also interested in seeing if we could extend this strategy to a three-component reaction (Scheme 3). We expected that compound 4a, formed in situ from 1a and 2a, would undergo a second Pd-catalyzed C–N coupling with an external coupling partner. Using 3 equiv of an electron-deficient aryl chloride, we obtained 52% yield of the cyclized product 4w under our standard domino reaction conditions. Using BnBr, Pd-G1-RuPhos, and XPhos gave 3b (90% yield) exclusively as 4a was not formed. We hypothesized that only cyclization of the secondary amine 3b afforded 4b. Hence, changing the excess ligand to RuPhos afforded 4b in 46% yield (Scheme 3).

CONCLUSION

In summary, we have reported a Rh/Pd-catalyzed twocomponent protocol to access N-alkylated or N-H pyridobenzazepines from easily accessible vinylpyridines and aminophenylboronic esters that affords up to 93% yield. It was also shown that a three-component $(MC)^2R$ could be performed under similar conditions to access both *N*-arylated and *N*alkylated products in a one-pot procedure. These compounds are pharmaceutically relevant as many tricyclic scaffolds with the dibenzazepine motif contains an *N*-alkyl chain and *N*-H analogues can be further functionalized. Furthermore, the compounds presented are all novel and could show interesting biological reactivity. With our previously reported $(MC)^2R$ conditions to access *N*-aryl pyridobenzazepines, we now offer a suite of modular and efficient methods to access these diverse and highly functionalized heterocyclic structures.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an argon atmosphere in oven- or flame-dried flasks or vials with magnetic stirring. Organic solutions were concentrated using a rotary evaporator at 30-45 °C under reduced pressure unless otherwise stated. Analytical TLC was performed on silica gel plates (0.2 mm, 60 Å pore size). Visualization was done under a 254 nm UV light source and by immersion in potassium permanganate solution. Flash chromatography was performed employing 230-400 mesh silica gel. All reagents, catalysts, and ligands were purchased from commercial sources and used without further purification. Prior to use, THF were distilled over Na/benzophenone, while 1,2-dichloroethane and propionitrile were distilled over CaH₂. Reagent-grade 1,4-dioxane was used straight from the bottle. ¹H, ¹³C, and ¹⁹F NMR were recorded at 25 °C in CDCl₃ on a Varian Mercury 400 MHz, 500 MHz, or Bruker Avance III 400 MHz spectrometer. ¹H spectra were referenced to residual protium resonances relative to Me₄Si (CHCl₃ δ 7.26). ¹³C spectra were referenced to solvent carbon resonances (CDCl₃ δ 77.16). Chemical shifts are reported in parts per million (ppm) and coupling constants as scalar values in hertz. Data for ¹H NMR are reported as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, tt = triplet of triplets, qd = quartet of doublets, m = multiplet), coupling constant (J, Hz), and integration. High-resolution mass spectra (HRMS) were obtained from an SI2Micromass 70S-250 spectrometer operating at 70 eV in EI mode, or an AB/Sciex QStar spectrometer operating in positive ESI mode. Mass analyzer type is TOF. FTIR spectra were recorded using an ATR method unless otherwise stated.

General Procedure for Benzylation. *N*-(4-*Methylbenzyl*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2h). In an oven-dried scintillation vial with a stir bar were added 2-aminoboronic acid pinacol ester 2a (138 mg, 1.5 mmol, 1 equiv) and 4-tolualdehyde (396 mg, 1.8 mmol, 1.2 equiv) and the mixture dissolved in anhydrous MeOH (1.5 mL) for 4 h. NaBH₄ (68 mg, 1.8 mmol, 1.2 equiv) was added portionwise, and the reaction was allowed to stir for 1 h. The reaction was partitioned in a 1:1 mixture of EtOAc (25 mL) and distilled water (25 mL). The organic layer was collected, the aqueous

F

layer was extracted with EtOAc (25 mL × 2), and the organic layers were combined. The organic layers were washed with saturated NaCl solution and then dried over MgSO₄. The mixture was concentrated in vacuo and then purified by column chromatography (1% EtOAc in hexanes) to obtain 110 mg (23% yield, mp = 62–63 °C) of the desired product as a clear colorless solid. ¹H NMR (500 MHz, CDCl₃): δ 7.65 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 4H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.63 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 6.33 (s, 1H), 4.36 (s, 2H), 2.34 (s, 3H), 1.32 (s, 12H). ¹³C NMR (500 MHz, CDCl₃): δ 154.4, 137.0, 136.7, 136.3, 133.1, 129.3, 129.1, 127.5, 126.8, 117.5, 115.6, 112.8, 109.8, 83.5, 48.1, 47.2, 24.9, 21.1. FT-IR: 3422, 2977, 2927, 1694, 1578, 1515, 1455, 1356, 1323, 1265, 1142, 1088, 1040, 962, 861, 835, 801, 752, 673, 657 cm⁻¹. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₂₀H₂₇BNO₂ 324.2129, found 324.2135.

N-(4-Methoxybenzyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2i). Compound 2a (138 mg, 1.5 mmol, 1 equiv) and 4-anisaldehyde (449 mg, 1.8 mmol, 1.2 equiv) were used. The crude mixture was purified by column chromatography (5% EtOAc in hexanes) to obtain 220 mg (43% yield, mp = 69–70 °C) of the product as a clear yellow solid. ¹H NMR (500 MHz, CDCl₃): δ7.65 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.32–7.26 (m, 3H), 7.25 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 6.91–6.85 (m, 2H), 6.63 (td, *J* = 7.3, 0.9 Hz, 1H), 6.55–6.50 (m, 1H), 6.28 (s, 1H), 4.33 (d, *J* = 3.3 Hz, 2H), 3.81 (s, 3H), 1.33 (s, 12H). ¹³C NMR (500 MHz, CDCl₃: δ 158.5, 154.4, 137.0, 133.1, 131.8, 128.1, 115.6, 113.9, 109.8, 83.5, 55.3, 46.9, 24.9. FT-IR: 3415, 2927, 2846, 1605, 1578, 1513, 1457, 1358, 1325, 2346, 1144, 1010, 862, 828, 755, 659 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₂₀H₂₇BNO₃ 340.2079, found 340.2084.

General Procedure for Borylation of o-Halo N-Substituted Anilines. N-Benzyl-5-methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2j). In a flame-dried 3 dram vial that was purged with argon, N-benzyl-2-bromo-5-methoxyaniline (291 mg, 1 mmol, 1 equiv) was dissolved in dry 1,4-dioxane (4 mL). Et₃N (0.43 mL, 4 mmol, 4 equiv) and Pd(dppf)Cl₂ (43 mg, 0.1 mmol, 10 mol %) were added. Pinacolborane (0.44 mL, 3 mmol, 3 equiv) was added dropwise under argon. The crude mixture was purified by column chromatography (5% EtOAc in hexanes) to obtain the desired product (237 mg, mp = 89-91 °C) as a clear colorless solid in 70% yield. ¹H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.2 Hz, 1H), 7.33–7.20 (m, 4H), 7.21-7.12 (m, 1H), 6.32 (s, 1H), 6.13 (dd, J = 8.3, 2.3 Hz, 1H), 5.96 (d, J = 2.2 Hz, 1H), 4.30 (d, J = 5.2 Hz, 2H), 3.64 (s, 3H), 1.23 (s, 12H). ¹³C NMR (400 MHz, CDCl₃): δ 144.5, 138.8, 138.5, 132.0, 128.7, 127.3, 127.3, 118.9, 112.3, 106.5, 48.0, 21.5. FT-IR: 3413, 2986, 2920, 1605, 1570, 1450, 1261, 1201, 1093, 1053, 860, 800, 735, 697, 660 cm⁻¹. HRMS (DART): $m/z [M + H]^+$ calcd for $C_{20}H_{27}BNO_3$ 340.2079, found 340.2084.

N-Benzyl-4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)aniline (**2k**). N-Benzyl-2-bromo-4-methylaniline (275 mg, 1 mmol, 1 equiv) was used. The crude mixture was purified by column chromatography (5% EtOAc in hexanes) to obtain the desired product (242 mg, mp = 74–75 °C) as pale yellow solid in 75% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.6 (d, *J* = 7.5 Hz, 1H), 7.4–7.3 (m, 4H), 7.3 (t, *J* = 7.2 Hz, 1H), 6.5 (d, *J* = 7.5 Hz, 1H), 6.4 (s, 1H), 6.3 (s, 1H), 4.4 (s, 2H), 2.3 (s, 3H), 1.3 (s, 12H). ¹³C NMR (500 MHz, CDCl₃): δ 154.6, 143.5, 139.9, 137.1, 134.8, 128.5, 127.0, 126.8, 117.0, 110.5, 83.4, 47.5, 24.9, 22.2. FT-IR: 3423, 2977, 2919, 2867, 1614, 1571, 1450, 1350, 1313, 1261, 1093, 1053, 963, 860, 801, 735, 697, 657 cm⁻¹. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₂₀H₂₇BNO₂ 324.2129, found 324.2135.

Methyl 4-(Benzylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2l). Methyl 4-(benzylamino)-3-iodobenzoate (367 mg, 1 mmol, 1 equiv) was used. The crude mixture was purified by column chromatography (5% EtOAc in hexanes) to obtain the desired product (315 mg, mp = 105–107 °C) as a pink solid in 86% yield. ¹H NMR (500 MHz, CDCl₃): δ 8.34 (d, J = 2.2 Hz, 1H), 7.91 (dd, J =8.8, 2.3 Hz, 1H), 7.34 (d, J = 4.4 Hz, 4H), 7.28 (s, 1H), 6.83 (d, J = 5.8Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 4.45 (d, J = 5.5 Hz, 2H), 3.84 (s, 3H), 1.33 (s, 12H). ¹³C NMR (500 MHz, CDCl₃): δ 167.3, 157.5, 139.5, 138.7, 134.9, 128.6, 127.1, 126.8, 117.1, 83.9, 77.3, 77.0, 76.7, 47.1, 24.9, 14.2. FT-IR: 3396, 2979, 2940, 2858, 1705, 1605, 1480, 1527, 1424, 1371, 1325, 1294, 1249, 1140, 1113, 1053, 983, 852, 774, 732, 698, 662 cm⁻¹. HRMS (DART): $m/z \ [M + H]^+$ calcd for $C_{21}H_{27}BNO_4$ 368.2028, found 368.2033.

N-Benzyl-4-cyano-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2m). 4-(Benzylamino)-3-bromobenzonitrile (286 mg, 1 mmol, 1 equiv) was used. The crude mixture was purified by column chromatography (5% EtOAc in hexanes) to obtain 274 mg (82% yield, mp = 68–69 °C) of the product as a pink solid. ¹H NMR (500 MHz, CDCl₃): δ 7.96–7.87 (m, 1H), 7.44 (ddd, *J* = 8.7, 2.1, 0.5 Hz, 1H), 7.39–7.28 (m, 1H), 6.87 (s, 1H), 6.47 (d, *J* = 8.7 Hz, 1H), 4.43 (d, *J* = 5.6 Hz, 2H), 1.33 (s, 12H). ¹³C NMR (126 MHz, CDCl₃): δ 156.6, 141.7, 138.2, 136.6, 128.7, 127.3, 126.7, 120.4, 109.7, 97.8, 84.3, 47.0, 24.9. FT-IR: 3395, 2979, 2214, 1604, 1580, 1524, 1452, 1421, 1392, 1367, 1329, 1281, 1194, 1139, 1056, 965, 898, 852, 817, 735, 696, 669 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₂₀H₂₄BN₂O₂ 335.1925, found 335.1931.

N-Benzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-trifluoromethylaniline (2n). Methyl 4-(benzylamino)-3-iodobenzoate (367 mg, 1 mmol, 1 equiv) was used. The crude mixture was purified by column chromatography (5% EtOAc in hexanes) to obtain the desired product (279 mg, mp = 72–73 °C) as a white solid in 74% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.88 (d, *J* = 2.1 Hz, 1H), 7.43 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.35 (d, *J* = 1.0 Hz, 1H), 7.34 (s, 2H), 7.37–7.28 (m, 1H), 6.71 (s, 1H), 6.51 (d, *J* = 8.7 Hz, 1H), 4.43 (d, *J* = 4.1 Hz, 2H), 1.34 (s, 12H). ¹³C NMR (500 MHz, CDCl₃): δ 156.3, 138.8, 134.3 (q, *J*_(C-F) = 3.8 Hz), 129.9 (q, *J*_(C-F) = 3.6 Hz), 128.6, 127.1, 126.8, 125.1 (q, *J*_(C-F) = 270.4 Hz), 117.3 (q, *J*_(C-F) = 32.4 Hz), 109.2, 84.0, 47.1, 24.9. ¹⁹F NMR (500 MHz, CDCl₃): δ 60.95. FT-IR: 3416, 2980, 1617, 1588, 1533, 1453, 1373, 1319, 1266, 1169, 1143, 1108, 1078, 963, 850, 818, 731, 697, 680 cm⁻¹. HRMS (DART): *m/z* [M + H]⁺ calcd for C₂₀H₂₄BF₃NO₂ 378.1847, found 378.1852.

General Procedure for the Synthesis of N-Alkylated o-Anilineboronic Acid Pinacol Esters. N-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (20). In a flame-dried roundbottomed flask equipped with a stirbar was dissolved 2-aminoboronic acid pinacol ester, 2a, (1.0 g, 6 mmol, 2 equiv) in dry THF (6 mL) under argon and then the mixture cooled to -40 °C. *n*-BuLi (2.5 M in hexanes, 1.2 mL, 1 equiv) was added dropwise, and the solution was stirred for 30 min. The solution was further cooled to -78 °C, and MeI (188 µL, 3 mmol, 1 equiv) was added dropwise. This was stirred for 12 h with warming to room temperature. The reaction was quenched by the addition of water (4 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL \times 3), and then the organic layer was washed with NaHCO3, dried over anhydrous MgSO4, and concentrated in vacuo. The compound was isolated by column chromatography (5% EtOAc/hexanes) to obtain the desired product (643 mg) as a clear colorless oil in 92% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.64 (d, J = 7.3 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 6.63 (t, J = 7.3 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 5.79 (s, 1H), 2.85 (s, 3H), 1.33 (s, 12H). ¹³C NMR (500 MHz, CDCl₃-insert): δ 155.4, 137.1, 133.2, 115.4, 108.9, 83.5, 30.2, 24.9. FT-IR: 3433, 2979, 2934, 2810, 1606, 1582, 1524, 1467, 1430, 1358, 1325, 1273, 1173, 1143, 1106, 1086, 1049, 1034, 964, 837, 756, 677, 662 cm⁻¹. HRMS (DART): $m/z [M + H]^+$ calcd for $C_{13}H_{21}BNO_2$ 234.1660, found 234.1665.

N-*Propyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline* (*2q*). 1-Iodopropane (291 μL, 3 mmol, 1 equiv) was added. The compound was isolated by column chromatography (5% EtOAc/hexanes) to obtain the desired product (705 mg) as a clear colorless oil in 90% yield. ¹H NMR (400 MHz, CDCl₃): δ 7.66 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.32 (ddd, *J* = 8.6, 7.2, 1.8 Hz, 1H), 6.63 (td, *J* = 7.3, 1.0 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 5.90 (s, br 1H), 3.13 (t, *J* = 6.8 Hz, 2H), 1.71 (h, *J* = 7.2 Hz, 2H), 1.36 (s, 12H), 1.05 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (400 MHz, CDCl₃): δ 154.8, 137.1, 133.1, 115.2, 109.4, 83.4, 45.1, 25.0, 22.4, 11.7. FT-IR: 3414, 2967, 2925, 2858, 1605, 1579, 1521, 1455, 1356, 1323, 1264, 1104, 1060, 1039, 962, 864, 753, 674, 658 cm⁻¹. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₁₅H₂₄BNO₂ 262.1973, found 262.1978.

2-(2-(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)ethyl)aniline (3a). In a 2 dram vial equipped with a stir bar were added 3-chloro-5trifluoro-2-vinylpyridine **1a** (42 mg, 0.2 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **2a** (66 mg, 0.3 mmol, 1.5 equiv), [Rh(cod)Cl]₂ (2.5 mg, 0.01 mmol, 0.05 equiv), and KOH (34 mg, 0.06 mmol, 3.0 equiv). The product was isolated by column chromatography (15% EtOAc/hexanes) as a colorless solid (38 mg, mp = 57–62 °C) in 91% yield. ¹H NMR (400 MHz, CDCl₃): δ 8.72 (s, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.15–7.00 (m, 2H), 6.83–6.64 (m, 2H), 3.86 (s, 2H), 3.41–3.20 (m, 2H), 3.05–2.84 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 162.6 (q, *J*_(C-F) = 1.4 Hz), 144.4, 144.0 (q, *J*_(C-F) = 4.2 Hz), 133.8 (q, *J*_(C-F) = 3.6 Hz), 131.3, 129.7, 129.3, 127.5, 125.7 (q, *J*_(C-F) = 33.6 Hz), 122.8 (q, *J*_(C-F) = 272.6 Hz), 118.8, 115.8, 34.9, 29.4. ¹⁹F NMR (377 MHz, CDCl₃): δ –62.17. IR (NaCl, thin film): 3387, 3337, 3225, 3067, 3024, 2930, 2862, 1605, 1497, 1456, 1397, 1323, 1175, 1132, 1092, 1059, 916, 750 cm⁻¹. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₁₄H₁₃ClF₃N₂ 301.0719, found 301.0723.

General Procedure 1 for the Synthesis of N-H Benzazepines. 3-(Trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (4a). In a 2 dram vial equipped with a stir bar were added 3-chloro-5trifluoro-2-vinylpyridine 1a (42 mg, 0.2 mmol), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline 2a (66 mg, 0.3 mmol, 1.5 equiv), [Rh(cod)Cl]₂ (2.5 mg, 0.01 mmol, 0.05 equiv), Pd-G1-RuPhos (7.4 mg, 0.01 mmol, 0.05 equiv), XPhos (7.1 mg, 0.01 mmol, 0.05 equiv), and KOH (34 mg, 0.06 mmol, 3.0 equiv). The vial was flushed with argon gas. Then 1,4-dioxane (0.2 mL, 0.1 M) was added followed by distilled H₂O (0.02 mL). The vial was sealed with a Teflon screw cap, and then the seal was wrapped with Teflon tape. The mixture was placed into a 110 °C oil bath and heated for 16 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc (25 mL) and water (10 mL). The organic layer was kept, and the aqueous layer was extracted again with EtOAc (25 mL \times 2). The organic fractions were combined, washed with saturated NaCl (1 M solution, dried over anhydrous MgSO₄), and concentrated in vacuo. NMR yields were obtained using *p*-nitroacetophenone as an internal standard. The product was isolated by column chromatography (10-50% EtOAc/hexanes) as a white solid (48 mg, mp 125-128 °C) in 93% yield. ¹H NMR (400 MHz, CDCl₃): δ 8.25 (d, J = 0.9 Hz, 1H), 7.27–7.21 (m, 1H), 7.14 (ddd, J = 9.3, 7.5, 1.6 Hz, 2H), 6.91 (td, J = 7.4, 1.2 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.01 (s, 1H), 3.40-3.33 (m, 2H), 3.17–3.10 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 151.0 (q, $J_{(C-F)} = 1.4 \text{ Hz}$, 141.0, 138.6, 135.6 (q, $J_{(C-F)} = 4.2 \text{ Hz}$), 130.5, 129.8, 127.3, 125.2 (q, $J_{(C-F)} = 32.7$ Hz), 123.7 (q, $J_{(C-F)} = 272.4$ Hz), 121.4, 121.0 (q, $J_{(C-F)} = 3.7$ Hz), 118.5, 38.5, 32.5. ¹⁹F NMR (564 MHz, CDCl₃): δ -62.39. IR (NaCl, neat): 3300, 3232, 3206, 3139, 3121, 3043, 2962, 2925, 2854, 2359, 2346, 1544, 1438, 1495, 1468, 1442, 1418, 1343, 1238, 1126, 1095, 968, 750, 668 cm⁻¹. HRMS (DART): $m/z [M + H]^+$ calcd for $C_{14}H_{12}F_3N_2$ 265.0947, found 265.0953.

General Procedure 2 for the Synthesis of N-Substituted Pyridobenzazepines. 5-Benzyl-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (4b). In a 2 dram vial equipped with a stir bar were added 3-chloro-5-trifluoro-2-vinylpyridine 1a (42 mg, 0.2 mmol), N-benzyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)aniline 2b (92 mg, 0.3 mmol, 1.5 equiv), [Rh(cod)Cl]₂ (2.5 mg, 0.01 mmol, 0.05 equiv), Pd-G1-RuPhos (8.2 mg, 0.01 mmol, 0.05 equiv), RuPhos (4.7 mg, 0.01 mmol, 0.05 equiv), and K₂CO₃ (84 mg, 0.6 mmol, 3.0 equiv). The vial was flushed with argon gas. Then 1,4dioxane (0.2 mL, 0.1 M) was added followed by distilled H₂O (0.02 mL). The vial was sealed with a Teflon screw cap, and then the seal was wrapped with Teflon tape. The mixture was placed into a 110 °C oil bath and heated for 16 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc (25 mL) and water (10 mL). The organic layer was kept, and the aqueous layer was extracted again with EtOAc (25 mL \times 3). The organic fractions were combined, washed with saturated NaCl solution, dried over anhydrous MgSO₄, and concentrated in vacuo. NMR yields were obtained using p-nitroacetophenone as an internal standard. The product was isolated by column chromatography (5% EtOAc in hexanes) as a peach crystal in 81% yield (57 mg, mp = 60-63 °C). Three-component procedure: In a 2 dram vial equipped with a stir bar were added 1a (42 mg, 0.2 mmol, 1 equiv), 2a (66 mg, 0.3 mmol, 1.5 equiv), [Rh(cod)Cl]₂ (2.5 mg, 0.01 mmol, 0.05 equiv), Pd-G1-RuPhos (8.2 mg, 0.01 mmol, 0.05

equiv), RuPhos (4.7 mg, 0.01 mmol, 0.05 equiv), and KOH (34 mg, 0.06 mmol, 3.0 equiv). The vial was flushed with argon gas. Then 1.4dioxane (2 mL, 0.1 M) was added followed by distilled H₂O (0.2 mL) and benzyl bromide (71 μ L, 0.6 mmol, 3 equiv). The vial was sealed with a Teflon screw cap, and then the seal was wrapped with Teflon tape. The mixture was placed into a 110 °C oil bath and heated for 16 h. Upon cooling to room temperature, the reaction mixture was partitioned between EtOAc (25 mL) and water (10 mL). The organic layer was kept, and the aqueous layer was extracted again with EtOAc (25 mL \times 2). The organic fractions were combined, washed with saturated NaCl (1 M solution, dried over anhydrous MgSO₄), and concentrated in vacuo. The product was isolated using column chromatography (5% EtOAc in hexanes) to give the desired compound (33 mg, mp = 60-62 °C) as a peach crystalline solid in 46% yield. ¹H NMR (500 MHz, CDCl₃): δ 8.27 (s, 1H), 7.47 (s, 1H), 7.36 (s, 1H), 7.35 (s, 1H), 7.27 (t, J = 7.6 Hz, 2H), 7.23–7.15 (m, 4H), 7.08-7.01 (m, 1H), 4.96 (s, 2H), 3.44-3.37 (m, 2H), 3.36-3.29 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 155.8 (q, $J_{(C-F)}$ = 1.4 Hz), 148.0, 143.0, 137.6 (q, $J_{(C-F)}$ = 4.2 Hz), 136.64, 136.61, 128.8, 128.6, 128.0, 127.5, 127.0, 124.7, 124.1 (q, $J_{(C-F)} = 32.7 \text{ Hz}$), 123.5 (q, $J_{(C-F)}$ = 272.4 Hz), 122.6 (q, $J_{(C-F)}$ = 3.5 Hz), 121.5, 117.1, 55.7, 37.5, 29.9. ¹⁹F NMR (377 MHz, CDCl₃): δ –62.32. FT-IR (NaCl, neat): 3065, 3033, 2924, 2853, 1602, 1494, 1456, 1416, 1335, 1324, 1228, 1122, 1099, 942, 908, 761, 739, 698, 643 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for $C_{21}H_{18}F_3N_2$ 355.1422, found 355.1427.

10,11-Dihydro-5H-benzo[b]pyrazino[2,3-f]azepine (4c). Following procedure 1, 2-chloro-3-vinylpyrazine 1c (28 mg, 0.2 mmol) and 2a (66 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (15–25% EtOAc in hexanes) in 90% yield (35 mg, mp = 70–71 °C) as a pink solid. ¹H NMR (500 MHz, CDCl₃): δ 7.97 (d, J = 2.6 Hz, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.16 (td, J = 7.7, 1.6 Hz, 1H), 7.14–7.12 (m, 1H), 7.08 (s, 1H), 6.93 (td, J = 7.4, 1.2 Hz, 1H), 6.88 (dd, J = 7.9, 1.1 Hz, 1H), 3.34–3.21 (m, 2H), 3.17–3.07 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 150.6, 142.6, 140.1, 139.7, 133.9, 130.2, 127.3, 121.8, 118.9, 37.5, 32.3. FT-IR: 3266, 3047, 2924, 2851, 1610, 1542, 1495, 1418, 1319, 1238, 1140, 947, 752 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₁₂H₁₂N₃ 198.1026, found 198.1031.

3-Methylsulfonyl-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (4d). Following procedure 1, 2-chloro-5-methylsulfonyl-2vinylpyridine 1d (43 mg, 0.2 mmol) and 2a (66 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (30% EtOAc in hexanes) in 62% yield (34 mg, mp = 210–213 °C) as a pink solid. ¹H NMR (500 MHz, CDCl₃): δ 8.47 (d, J = 1.9 Hz, 1H), 7.58 (d, J = 2.0 Hz, 1H), 7.22–7.08 (m, 2H), 6.92 (td, J = 7.4, 1.2 Hz, 1H), 6.85 (dd, J = 7.9, 1.1 Hz, 1H), 6.28 (s, 1H), 3.42–3.36 (m, 2H), 3.16–3.12 (m, 2H), 3.12 (s, 3H). ¹³C NMR (500 MHz, (CD₃)₂SO): δ 152.4, 140.7, 139.1, 136.8, 135.0, 130.4, 129.8, 127.4, 122.5, 121.7, 118.7, 45.0, 38.8, 32.3. FT-IR: 3363, 2918, 1575, 1530, 1496, 1358, 1439, 1408, 1315, 1140, 910, 952, 753 cm⁻¹. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₁₄H₁₅N₂O₂S 275.0849, found 275.0854.

3-Cyano-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (4e). Following procedure 1, 3-chloro-5-cyano-2-vinylpyridine 1d (33 mg, 0.2 mmol) and 2a (66 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (15% EtOAc in hexanes) in 45% yield (20 mg, mp = 179–171 °C) as a pink solid. ¹H NMR (500 MHz, CDCl₃): δ 8.2 (d, J = 1.7 Hz, 1H), 7.3 (d, J = 1.7 Hz, 1H), 7.2–7.1 (m, 2H), 6.9 (td, J = 7.4, 1.1 Hz, 1H), 6.8 (dd, J = 7.9, 1.0 Hz, 1H), 6.0 (s, 1H), 3.6–3.3 (m, 2H), 3.2–2.8 (m, 2H).¹³C NMR (500 MHz, CDCl₃): δ 151.6, 141.3, 141.3, 140.5, 138.7, 130.5, 129.8, 129.3, 127.4, 126.2, 121.8, 118.7, 116.8, 107.7, 38.9, 32.3. FT-IR: 3368, 3293, 2020, 2930, 2845, 2233, 1600, 1582, 1532, 1492, 1457, 1410, 1329, 1248, 906, 729 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₁₄H₁₂N₃ 222.1026, found 222.1031.

7-Fluoro-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido-[2,3-f]azepine (4f). Following procedure 1, 1a (42 mg, 0.2 mmol) and 2-amino-4-fluorophenylboronic acid pinacol ester 2c (71 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (15% EtOAc in hexanes) in 68% yield (38 mg, mp = 130–134 °C) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 8.27 (d, *J* = 0.9 Hz, 1H), 7.27 (d, *J* = 1.3 Hz, 1H), 7.05 (dd, *J* = 8.4, 6.4 Hz, 1H), 6.59 (td, *J* = 8.2, 2.5 Hz, 1H), 6.54 (dd, *J* = 10.1, 2.5 Hz, 1H), 6.23 (s, 1H), 3.38–3.30 (m, 2H), 3.21–2.65 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 162.8, 160.8, 150.9 (apparent d, *J*_(C-F) = 0.9 Hz), 142.0 (d, *J*_(C-F) = 10.0 Hz), 138.2, 135.9 (q, *J*_(C-F) = 4.0 Hz), 131.8 (d, *J*_(C-F) = 9.4 Hz), 125.3 (q, *J*_(C-F) = 3.6 Hz), 107.9 (d, *J*_(C-F) = 20.9 Hz), 105.2 (d, *J*_(C-F) = 25.0 Hz), 38.3, 31.9. ¹⁹F NMR (500 MHz, CDCl₃): δ -62.3, -116.2 (q, *J* = 8.1, 6.9 Hz). FT-IR: 3316, 3228, 3165, 2962, 2913, 2868, 1617, 1559, 1502, 1468, 1422, 1341, 1241, 1162, 1138, 1093, 1002, 928, 892, 850, 804. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₁₄H₁₁F₄N₂ 283.0853, found 283.0866.

8-Chloro-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido-[2,3-f]azepine (4g). Following procedure 1, 1a (33 mg, 0.2 mmol) and 2-amino-5-chlorophenylboronic acid pinacol ester 2d (76 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (15% EtOAc in hexanes) in 51% yield (30 mg, mp = 164-165 °C) as a white solid which turns yellow immediately. ¹H NMR (500 MHz, CDCl₃): δ 8.26 (q, J = 0.8 Hz, 1H), 7.24 (d, J = 1.5 Hz, 1H), 7.13-7.06 (m, 2H), 6.74 (d, J = 8.3 Hz, 1H), 6.07 (s, 1H), 3.41-3.24 (m, 2H), 3.19-2.85 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 150.53 (q, $J_{(C-F)}$ = 4.1 Hz), 139.6, 138.2, 136.0 (q, $J_{(C-F)}$ = 4.1 Hz), 131.3, 130.1, 127.1, 126.1, 125.2 (q, $J_{(C-F)} = 32.9$ Hz), 123.4 $(q, J_{(C-F)} = 272.4 \text{ Hz}), 121.1 (q, J_{(C-F)} = 3.6 \text{ Hz}), 119.7, 38.2, 32.3.$ ¹⁹F NMR (377 MHz, CDCl₃): δ –62.3. FT-IR: 3310, 3235, 3129, 2950, 2929, 2859, 1656, 1607, 1547, 1492 1465, 1419, 1350, 1138, 1099, 968, 890, 817. HRMS (DART): m/z [M + H]⁺ calcd for C14H11ClF3N2 299.0563, found 299.0562.

8-Methyl-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido-[2,3-f]azepine (4h). Following procedure 1, 1a (42 mg, 0.2 mmol) and 2-amino-5-methylphenylboronic acid pinacol ester 2e (71 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (15% EtOAc in hexanes) in 71% yield (40 mg, mp = 99–100 °C) as a white solid. ¹H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, J = 2.0, 0.9 Hz, 1H), 7.22 (d, J = 1.8 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.72 (ddd, J = 7.6, 1.7, 0.8 Hz, 1H), 6.63 (t, J = 1.1 Hz, 1H), 6.13 (s, 1H), 3.40-3.33 (m, 2H), 3.10-3.07 (m, 2H), 2.30 (s, 3H). ¹³C NMR (500 MHz, CDCl₃): δ 150.9 (q, $J_{(C-F)}$ = 1.4 Hz), 140.7, 138.7, 137.1, 135.4 (q, $J_{(C-F)} = 4.1$ Hz), 130.4, 126.7, 125.1 (q, $J_{(C-F)} = 32.7$ Hz), 123.5 (q, $J_{(C-F)}$ = 272.3 Hz), 122.2, 120.9 (q, $J_{(C-F)}$ = 3.6 Hz), 119.0, 38.7, 32.1, 20.9. ¹⁹F NMR (377 MHz, $CDCl_3$): δ –62.3. FT-IR: 3311, 3132, 2926, 1629, 1547, 1505, 1468, 1420, 1347, 1241, 1162, 1141, 1117, 1096, 983, 902, 857, 798. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C15H14F3N2 279.1104, found 279.1110.

7-Methoxy-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (4i). Following procedure 1, 1a (42 mg, 0.2 mmol and 2-amino-5-methylphenylboronic acid pinacol ester 2f (71 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (10% EtOAc in hexanes) in 81% yield (48 mg, mp = 159-160 °C) as a beige solid. ¹H NMR (500 MHz, $CDCl_3$: δ 8.25 (dd, J = 1.7, 0.8 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.47 (dd, J = 8.3, 2.5 Hz, 1H), 6.36 (d, J = 2.5 Hz, 1H), 6.15 (s, 1H), 3.77 (s, 3H), 3.35-3.30 (m, 2H), 3.10-3.03 (m, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 158.9, 151.1 (q, $J_{(C-F)} = 1.4$ Hz), 141.8, 138.5, 135.7 (q, $J_{(C-F)} = 4.1$ Hz), 131.4, 125.1 (q, $J_{(C-F)} = 4.1$ Hz) 32.7 Hz), 123.5 (q, $J_{(C-F)}$ = 272.3 Hz), 122.2, 121.0 (q, $J_{(C-F)}$ = 3.6 Hz), 106.6, 104.2, 55.3, 38.8, 31.8. ¹⁹F NMR (377 MHz, $CDCl_3$): δ -62.3. FT-IR: 3367, 3310, 3217, 3123, 2956, 2923, 2850, 1620, 1595, 1556, 1508, 1468, 1423, 1347, 1244, 1165, 1120, 1096, 1044, 922, 905, 847, 798, 738. HRMS (DART): m/z [M + H]⁺ calcd for C15H14F3N2O 295.1053, found 295.1063.

8-Cyano-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido-[2,3-f]azepine (4j). Following procedure 1, 1a (42 mg, 0.2 mmol) and 2-amino-5-cyanophenylboronic acid pinacol ester 2g (73 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (10% EtOAc in hexanes) in 58% yield (33 mg, mp = 84–86 °C) as a off-white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.33 (s, 1H), 7.60–7.29 (m, 3H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.84 (s, 1H), 3.44–3.30 (m, 2H), 3.19–2.99 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 151.5 (q, $J_{(C-F)}$ = 1.4 Hz), 144.9, 137.2, 137.1 (q, $J_{(C-F)}$ = 4.1 Hz), 134.8, 131.2, 128.9, 125.4 (q, $J_{(C-F)}$ = 33.0 Hz), 123.3 (q, $J_{(C-F)}$ = 272.4 Hz), 122.1 (q, $J_{(C-F)}$ = 3.5 Hz), 119.4, 118.7, 102.9, 38.0, 32.8. FT-IR: 3341, 3228, 3144, 3059, 2965, 2929, 2865, 2223, 1614, 1538, 1504, 1462, 1426, 1344, 1162, 1129, 1093, 965, 898, 825, 741. HRMS (DART): $m/z [M + H]^+$ calcd for C₁₅H₁₁F₃N₃ 290.0900, found 290.0906.

5-(4-Methylbenzyl)-3-(trifluoromethyl)-10,11-dihydro-5H-benzo-[b]pyrido[2,3-f]azepine (4k). Following procedure 2, 1a (42 mg, 0.2 mmol) and 2h (97 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (5% EtOAc in hexanes) in 61% yield (45 mg, mp = 74–76 °C) as a clear colorless solid. ¹H NMR (500 MHz, CDCl₃): δ 8.28 (dd, *J* = 1.9, 1.0 Hz, 1H), 7.48 (d, *J* = 1.6 Hz, 1H), 7.29–7.24 (m, 2H), 7.23–7.19 (m, 1H), 7.19–7.14 (m, 2H), 7.06 (m, 1H), 6.82–6.78 (m, 1H), 4.92 (s, 2H), 3.45–3.36 (m, 2H), 3.36–3.26 (m, 2H), 2.28 (s, 3H). ¹³C NMR (500 MHz, CDCl₃): δ 158.8, 155.8 (q, *J*_(C-F) = 1.3 Hz), 148.0, 143.0, 137.5 (q, *J*_(C-F) = 4.1 Hz), 136.6, 129.3, 128.8, 128.6, 126.9, 124.6, 124.0 (q, *J*_(C-F) = 32.5 Hz), 123.6 (q, *J*_(C-F) = 272.4 Hz), 122.7 (q, *J*_(C-F) = 3.5 Hz), 121.5, 114.0, 55.1, 55.0, 37.5, 29.9. ¹⁹F NMR (377 MHz, CDCl₃): δ –62.30. FT-IR: 2926, 2855, 1694, 1518, 1494, 1458, 1418, 1332, 1229, 1128, 1100, 946, 804, 754, 650, 621 cm⁻¹. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₂₂H₂₀F₃N₂ 369.1573, found 369.1575.

5-(p-Methyoxybenzyl)-3-(trifluoromethyl)-10,11-dihydro-5Hbenzo[b]pyrido[2,3-f]azepine (41). Following procedure 2, 1a (42) mg, 0.2 mmol) and 2i (102 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (5% EtOAc in hexanes) in 68% yield (52 mg) as a clear colorless oil. $^1\mathrm{H}$ NMR (500 MHz, CDCl₃): δ 8.29 (t, J = 2.0, 1.0 Hz, 1H), 7.53–7.46 (m, 1H), 7.29-7.25 (m, 2H), 7.23-7.14 (m, 3H), 7.05 (ddd, J = 7.4, 6.2, 2.4 Hz, 1H), 6.82–6.78 (m, 2H), 4.90 (s, 2H), 3.74 (s, 3H), 3.46–3.37 (m, 2H), 3.37–3.26 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 158.8, 155.8 (q, $J_{(C-F)} = 1.4$ Hz), 148.0, 143.0, 137.5 (q, $J_{(C-F)} = 4.2$ Hz), 136.6, 129.3, 128.8, 128.6, 127.0, 124.6, 124.0 (q, $J_{(C-F)} = 32.5$ Hz), 123.6 (q, $J_{(C-F)} = 272.5$ Hz), 122.8 (q, $J_{(C-F)} = 3.5$ Hz), 121.5, 114.0, 55.1, 55.0, 37.5, 29.9. ¹⁹F NMR (377 MHz, CDCl₃): δ –62.29. FT-IR: 2925, 2853, 1612, 1513, 1494, 1458, 1430, 1417, 1331, 1250, 1171, 1147, 1127, 1100, 1035, 945, 890, 826, 755 cm⁻¹. HRMS (DART): *m*/ $z [M + H]^+$ calcd for C₂₂H₂₀F₃N₂O 385.1522, found 385.1527.

5-Benzyl-7-methoxy-3-(trifluoromethyl)-10,11-dihydro-5Hbenzo[b]pyrido[2,3-f]azepine (4m). Following procedure 2, 1a (42 mg, 0.2 mmol) and 2j (100 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (5% EtOAc in hexanes) in 90% yield (69 mg, mp = 107-109 °C) as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃): δ 8.29 (s, 2H), 7.47 (s, 1H), 7.38-7.33 (m, 2H), 7.30-7.24 (m, 2H), 7.22-7.16 (m, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.73 (dd, J = 2.5, 0.7 Hz, 1H), 6.59 (dd, J = 8.3, 2.5 Hz, 1H), 4.94 (s, 2H), 3.75 (s, 3H), 3.47-3.30 (m, 2H), 3.30-3.19 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 158.6, 156.3 (q, $J_{(C-F)} = 1.6$ Hz), 148.7, 143.0, 137.9 (q, $J_{(C-F)} = 4.2$ Hz), 136.6, 129.5, 128.6, 128.4, 128.0, 127.5, 124.0 (q, $J_{(C-F)} = 32.6$ Hz), 123.5 (q, J_{(C-F)} = 32.6 Hz), 123.5 (q, J_{(272.6 Hz), 122.9 (q, $J_{(C-F)}$ = 3.6 Hz), 109.4, 107.9, 55.6 55.4, 37.5, 29.2. ¹⁹F NMR (500 MHz, CDCl₃): δ -62.28. FT-IR: 2923, 2858, 1724, 1610, 1507, 1436, 1327, 1252, 1219, 1166, 1128, 1080, 1018, 965, 840, 740, 699 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C22H20F3N2O 385.1522, found 385.1527.

5-Benzyl-8-methyl-3-(trifluoromethyl)-10,11-dihydro-5H-benzo-[b]pyrido[2,3-f]azepine (4n). Following procedure 2, 1a (42 mg, 0.2 mmol) and 2k (97 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (5% EtOAc in hexanes) in 83% yield (61 mg, mp = 74–75 °C) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.25 (s, 1H), 7.45 (s, 1H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.30–7.24 (m, 3H), 7.19 (t, *J* = 7.1 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 4.96 (s, 2H), 3.38 (q, 2H), 3.28 (m, 2H), 2.29 (s, 3H). ¹³C NMR (500 MHz, CDCl₃): δ 156.0 (q, *J*_(C-F) = 1.5 Hz), 148.1, 142.9, 137.5 (q, *J*_(C-F) = 4.2 Hz), 136.75, 136.73, 133.5, 129.1, 128.6, 128.6, 128.1, 127.7, 127.5, 127.2, 125.3, 124.7, 124.0 (q, *J*_(C-F) = 32.5 Hz), 123.6 (q, *J*_(C-F) = 272.7 Hz), 122.7, 122.6 (q, *J*_(C-F) = 3.5 Hz), 122.5, 122.1, 117.8, 111.4, 55.6, 37.7, 29.5, 212.1⁹F NMR (400 MHz, CDCl₃): δ –62.38. FT-IR: 3043, 2925,

The Journal of Organic Chemistry

2873, 1603, 1508, 1433, 1328, 1243, 1165, 1124, 1101, 1080, 1027, 957, 892, 740, 699 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₂₂H₂₀F₃N₂ 369.1573, found 369.1578.

Methyl 5-Benzyl-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine-8-carboxylate (40). Following procedure 2, 1a (42 mg, 0.2 mmol) and 2l (110 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (5% EtOAc in hexanes) in 18% yield (15 mg) as clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.34 (dd, J = 2.0, 1.0 Hz, 1H), 7.87 (s, 1H), 7.82 (dd, J = 8.4, 2.1 Hz, 1H), 7.53 (d, J = 1.9 Hz, 1H), 7.37–7.29 (m, 2H), 7.29-7.23 (m, 2H), 7.23-7.14 (m, 2H), 5.00 (s, 2H), 3.88 (s, 2H), 3.43 (q, J = 4.9, 4.3 Hz, 2H), 3.34 (dd, J = 7.5, 4.3 Hz, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 166.6, 156.5 (q, $J_{(C-F)}$ = 1.2 Hz), 151.2, 142.6, 138.6 (q, $J_{(C-F)} = 3.8$ Hz), 136.1, 134.9, 130.9, 129.2, 128.7, 128.5, 127.9, 126.2, 125.4, 124.4 (q, $J_{(C-F)}$ = 33.2 Hz), 123.7 (q, $J_{(C-F)}$ = 3.4 Hz), 123.4 (q, $J_{(C-F)} = 272.6$ Hz), 120.9, 56.0, 52.0, 36.6, 30.5. ¹⁹F NMR (500 MHz, CDCl₃): -62.28. FT-IR: 2961, 2855, 1717, 1609, 1499, 1431, 1337, 1293, 1227, 1128, 945, 911, 777, 741, 701 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₂₃H₂₀F₃N₂O₂ 413.1471, found 413.1477.

5-Benzyl-7-cyano-3-(trifluoromethyl)-10,11-dihydro-5H-benzo-[b]pyrido[2,3-f]azepine (4p). Following procedure 2, 1a (42 mg, 0.2 mmol) and 2m (100 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (5% EtOAc in hexanes) in 13% yield (10 mg) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.37 (dd, J = 2.0, 1.0 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.4, 2.1 Hz, 1H), 7.32-7.23 (m, 4H), 7.24-7.16 (m, 2H), 4.98 (s, 2H), 3.43 (dd, J = 8.3, 4.4 Hz, 2H), 3.33-3.22 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 156.6 (d, $J_{(C-F)} = 1.5$ Hz), 150.7, 142.4, 139.3 (q, $J_{(C-F)} = 4.1$ Hz), 135.6, 135.5, 133.4, 130.9, 128.8, 127.9, 124.7 (q, $J_{(C-F)} = 32.9 \text{ Hz}$), 124.3 (q, $J_{(C-F)} = 3.5$ Hz), 123.3 (q, $J_{(C-F)} = 272.6$ Hz), 121.6, 118.7, 106.9, 56.1, 35.9, 30.5. ¹⁹F NMR (500 MHz, CDCl₃): δ –62.38. FT-IR: 3037, 2964, 2927, 2861, 2226, 1606, 1497, 1425, 1339, 1331, 1309, 1233, 1128, 1102, 947, 910, 834, 740, 699 cm⁻¹. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₂₂H₁₆F₃N₃ 380.1369, found 380.1375.

N-Benzyl-3,7-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido-[2,3-f]azepine (4q). Following procedure 2, 1a (42 mg, 0.2 mmol), 2n (113 mg, 0.6 mmol, 1.5 equiv), and KOH (50 mg, 0.6 mmol, 3 equiv) were added (KOH was used in place of K2CO3). The product was isolated by column chromatography (5% EtOAc in hexanes) in 24% yield (21 mg) as a clear colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 8.41 (d, J = 0.9 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.52 (s, 1H), 7.48 (dd, J = 8.5, 1.9 Hz, 1H), 7.45-7.38 (m, 2H), 7.37-7.30 (m, 3H), 7.29-7.27 (m, 1H), 5.06 (s, 2H), 3.53-3.50 (m, 2H), 3.44-3.41 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 156.2 (d, $J_{(C-F)}$ = 1.4 Hz), 151.0–149.4 (q, 1.2), 142.6, 138.7 (q, $J_{(C-F)} = 4.1$ Hz), 136.0, 135.8, 128.8, 128.0, 127.8, 126.3 (q, $J_{(C-F)} = 3.7$ Hz), 125.9 (q, $J_{(C-F)} = 32.8$ Hz), 124.4 (q, $J_{(C-F)} = 272.3$ Hz), 124.4 (q, $J_{(C-F)} = 32.8$ Hz), 124.0 (q, $J_{(C-F)} = 3.8 \text{ Hz}$), 124.0 (q, $J_{(C-F)} = 271.4 \text{ Hz}$), 123.6 (q, $J_{(C-F)} = 3.5 \text{ Hz}$), 121.3, 55.9, 36.4, 30.4. ¹⁹F NMR (377 MHz, CDCl₃-insert): δ -62.1, -62.3. FTIR: 3032, 2926, 2865, 1613, 1597, 1435, 1417, 1323, 1229, 1110, 947, 911, 831, 829 735, 699, 701, 635. HRMS (DART): $m/z [M + H]^+$ calcd for $C_{22}H_{17}F_6N_2$ 423.1290, found 423.1292

5-Methyl-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido-[2,3-f]azepine (4r). Following procedure 2, 1a (42 mg, 0.2 mmol) and 2o (70 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (2–5% EtOAc in hexanes) in 80% yield (44 mg) as a clear colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.31 (s, 1H), 7.44 (s, 1H), 7.25–7.19 (m, 2H), 7.12–7.04 (m, 2H), 3.39–3.36 (m, 5H), 3.22 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 154.5 (q, $J_{(C-F)}$ = 1.4 Hz), 148.3, 144.0, 136.6 (q, $J_{(C-F)}$ = 4.2 Hz), 136.2, 128.6, 126.9, 124.4 (q, $J_{(C-F)}$ = 32.4 Hz), 124.2, 123.7 (q, $J_{(C-F)}$ = 272.8 Hz), 120.4, 120.3 (q, $J_{(C-F)}$ = 3.5 Hz), 40.1, 38.1, 29.9. ¹⁹F NMR (500 MHz, CDCl₃): δ –62.14. FT-IR: 2929, 2812, 1603, 1564, 1495, 1457, 1434, 1413, 1336, 1283, 1116, 1099, 944, 889, 758, 634 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₁₅H₁₄F₃N₂ 279.1109, found 279.1109.

5-Ethyl-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido-[2,3-f]azepine (**4s**). Following procedure 2, **1a** (42 mg, 0.2 mmol) and **2p** (74 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (2–5% EtOAc in hexanes) in 68% yield (40 mg, mp = 74–75 °C) as a clear colorless solid. ¹H NMR (500 MHz, CDCl₃): δ 8.33 (d, J = 1.0 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.23–7.19 (m, 2H), 7.11–7.05 (m, 2H), 3.80 (q, J = 7.0 Hz, 2H), 3.36 (m, 2H), 3.23 (m, 2H), 1.18 (t, J = 7.0 Hz, 3H). ¹³C NMR (500 MHz, CDCl₃): δ 155.8 (q, $J_{(C-F)}$ = 1.4 Hz), 147.3, 143.9, 137.3 (q, $J_{(C-F)}$ = 4.2), 137.4, 128.7, 123.68 (q, $J_{(C-F)}$ = 3.51 Hz), 121.6, 45.2, 37.4, 29.6, 13.5. ¹⁹F NMR (500 MHz, CDCl₃): δ –62.13. FT-IR: 2964, 2916, 2846, 1609, 1494, 1458, 1424, 1333, 1234, 1146, 1134, 1104, 961, 901, 765 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₁₆H₁₆F₃N₂ 293.1266, found 293.1266.

5-Propyl-3-(trifluoromethyl)-10,11-dihydro-5H-benzo[b]pyrido-[2,3-f]azepine (4t). Following procedure 2, 1a (42 mg, 0.2 mmol), 2q (78 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (2–5% EtOAc in hexanes) in 70% yield (42 mg, mp = 55–56 °C) as a clear colorless solid. ¹H NMR (500 MHz, CDCl₃): δ 8.23 (d, J = 0.6 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.14–7.06 (m, 2H), 7.03–6.92 (m, 2H), 3.60 (t, J = 6.9 Hz, 2H), 3.29–3.22 (m, 2H), 3.16–3.11 (m, 2H), 1.49 (h, J = 7.2 Hz, 2H), 0.81 (t, J = 7.4 Hz, 3H). ¹³C NMR (500 MHz, CDCl₃): δ 155.8 (q, $J_{(C-F)}$ = 1.4 Hz), 147.4, 144.0, 137.4 (q, $J_{(C-F)}$ = 4.2 Hz), 137.3, 128.8, 126.9, 124.6, 124.3 (q, $J_{(C-F)}$ = 32.4 Hz), 123.7 (q, $J_{(C-F)}$ = 272.9 Hz), 122.1 (q, $J_{(C-F)}$ = 3.5 Hz), 121.6, 52.5, 37.4, 29.6, 20.7, 11.6.¹⁹F NMR (500 MHz, CDCl₃): δ –62.13. FT-IR: 2970, 2930, 2882, 2855, 1603, 1494, 1416, 1335, 1226, 1124, 1098, 957, 899, 755 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₁₇H₁₈F₃N₂ 307.1422, found 307.1422.

5-Benzyl-3-cyano-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (**4u**). Following procedure 2, **1a** (33 mg, 0.2 mmol) and **2b** (92 mg, 0.3 mmol, 1.5 equiv) were added. The product was isolated by column chromatography (5% EtOAc in hexanes) in 41% yield (26 mg, mp = 146–148 °C) as a clear colorless solid. ¹H NMR (500 MHz, CDCl₃): δ 8.26 (d, *J* = 1.8 Hz, 1H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.37–7.33 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.24–7.14 (m, 4H), 7.09–7.04 (m, 1H), 4.94 (s, 2H), 3.43–3.36 (m, 2H), 3.36–3.28 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 156.4, 147.8, 143.2, 142.9, 136.8, 136.3, 128.8, 128.7, 127.8, 127.6, 127.2, 125.0, 121.7, 117.0, 106.8, 55.8, 38.2, 29.7. FT-IR: 3040, 2934, 2846, 2231, 1580, 1493, 1451, 1410, 1331, 1242, 1152, 1113, 961, 905, 762, 726, 697 cm⁻¹. HRMS (DART): *m*/*z* [M + H]⁺ calcd for C₂₁H₁₈N₃ 312.1495, found 312.1501.

3-Cyano-5-methyl-10,11-dihydro-5H-benzo[b]pyrido[2,3-f]azepine (4ν). Following procedure 2, 1a (33 mg, 0.2 mmol), 2o (70 mg, 0.3 mmol, 1.5 equiv) and KOH (50 mg, 0.6 mmol, 3 equiv) were added (KOH was used in place of K_2CO_3). The product was isolated by column chromatography (5% EtOAc in hexanes) in 51% yield (24 mg, 122–123 °C) as clear colorless needles. ¹H NMR (500 MHz, CDCl₃): δ 8.30 (d, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.25–7.18 (m, 2H), 7.12–7.05 (m, 2H), 3.39–3.33 (m, 5H), 3.24–3.18 (m, 2H). ¹³C NMR (500 MHz, CDCl₃): δ 155.2, 148.0, 143.9, 142.2, 136.3, 128.5, 127.1, 125.7, 124.5, 120.7, 117.2, 107.1, 40.3, 38.6, 29.7. FT-IR: 2961, 2931, 2238, 1588, 1494, 1458, 1410, 1325, 1252, 1116, 989, 700 cm⁻¹. HRMS (DART): m/z [M + H]⁺ calcd for C₁₅H₁₄N₃ 236.1183, found 236.1187.

3-(*Trifluoromethyl*)-5-(4-(*trifluoromethyl*)*phenyl*)-10,11-*dihydro*-5*H*-benzo[*b*]*pyrido*[2,3-*f*]*azepine* (*4w*). The substrates used were 3-chloro-5-(trifluoromethyl)-2-vinylpyridine (42 mg, 0.20 mmol, 1 equiv), 2-aminophenylboronic acid (66 mg, 0.3 mmol, 1.5 equiv), and 1-chloro-4-(trifluoromethyl)benzene (32 μL, 0.24 mmol, 1.2 equiv). The product was isolated using column chromatography (40% EtOAc/hexanes) to give the titled compound in 52% yield (21 mg, mp 155–158 °C) as a yellow crystalline solid. ¹H NMR (400 MHz, CDCl₃): δ 8.73 (dd, *J* = 2.2, 1.0 Hz, 1H), 7.98 (d, *J* = 192.1 Hz, 1H), 7.52–7.33 (m, 6H), 6.67–6.54 (m, 2H), 3.29 (t, *J* = 6.8 Hz, 2H), 3.02 (dd, *J* = 7.6, 6.0 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃): δ 161.8 (q, *J*_(C-F) = 1.1 Hz), 150.28 (q, *J* = 1.1 Hz), 144.4 (q, *J*_(C-F) = 3.9 Hz), 142.4, 139.1, 138.1, 134.7 (q, *J*_(C-F) = 3.5 Hz), 130.6, 129.4, 128.9, 128.0, 126.6 (q, *J*_(C-F) = 3.7 Hz), 125.4 (q, *J*_(C-F) = 3.3 Hz), 124.5 (q, *J*_(C-F) = 270.7 Hz), 123.0 (q, *J*_(C-F) = 272.6 Hz), 121.0 (q, *J*_(C-F) = 32.8 Hz), 112.4, 35.3, 28.5. ¹⁹F NMR (376 MHz, CDCl₃): δ –61.51,

The Journal of Organic Chemistry

-62.07. IR (NaCl, neat): 2930, 2859, 1605, 1518, 1410, 1321, 1165, 1138, 1117, 1069, 827, 756 cm-1. HRMS (DART): m/z cacld for $C_{21}H_{15}F_6N_2$ (M+H)⁺ 409.1139, found 409.1142.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00568.

¹H, ¹³C NMR for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: mlautens@chem.utoronto.ca.

ORCID 0

Heather Lam: 0000-0002-0715-7575

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the Natural Science and Engineering Research Council (NSERC), Alphora, Inc., and The University of Toronto for financial support. Special thanks to T. Johnson for valuable suggestions and help with the manuscript.

REFERENCES

(1) Zhang, L.; Sonaglia, L.; Stacey, J.; Lautens, M. Org. Lett. 2013, 15, 2128-2131.

- (2) Yamamoto, K.; Qureshi, Z.; Tsoung, J.; Pisella, G.; Lautens, M. Org. Lett. 2016, 18, 4954–4957.
- (3) Qureshi, Z.; Kim, J. Y.; Bruun, T.; Lam, H.; Lautens, M. ACS Catal. 2016, 6, 4946–4952.
- (4) Yamamoto, K.; Bruun, T.; Kim, J. Y.; Zhang, L.; Lautens, M. Org. Lett. 2016, 18, 2644–2647.
- (5) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.
- (6) Friedman, A.; Panteleev, J.; Tsoung, J.; Huynh, V.; Lautens, M. Angew. Chem., Int. Ed. 2013, 52, 9755.
- (7) Gillman, P. K. J. Br. J. Pharmacol. 2007, 151, 737.
- (8) Lednicer, D. In Strategies for Organic Drugs Synthesis and Design, 2nd ed.; Wiley-VCH: Hoboken, 2009.
- (9) Thansandote, P.; Lautens, M. Chem. Eur. J. 2009, 15, 5874.
- (10) Kastrinsky, D. B.; Sangodkar, J.; Zaware, N.; Izadmehr, S.; Dhawan, N. S.; Narla, G.; Ohlmeyer, M. Bioorg. Med. Chem. 2015, 23,
- 528-6534.
- (11) Bergmann, E. D.; Shahak, I.; Aisenshtat, Z. Tetrahedron Lett. 1968, 9, 3469.
- (12) Jorgensen, T. K.; Andersen, K. E.; Lau, J.; Madsen, P.; Huusfeldt, P. O. J. Heterocycl. Chem. **1999**, 36, 57.
- (13) Christensen, H.; Schjøth-Eskesen, C.; Jensen, M.; Sinning, S.; Jensen, H. H. *Chem. - Eur. J.* **2011**, *17*, 10618.
- (14) Božinović, N.; Opsenica, I.; Šolaja, B. A. Synlett 2013, 24, 49.
 (15) Tsvelikhovsky, D.; Buchwald, S. L. J. Am. Chem. Soc. 2010, 132, 14048.
- (16) Tsoung, J.; Panteleev, J.; Tesch, M.; Lautens, M. Org. Lett. 2014, 16, 110–113.
- (17) Brinkø, A.; Larsen, M. T.; Koldsø, H.; Besenbacher, L.; Kolind, A.; Schiøtt, B.; Sinning, S.; Jensen, H. H. *Bioorg. Med. Chem.* **2016**, *24*, 2725–2738.
- (18) K_2CO_3 was used in place of NaOtBu due to incompatibility of the base and the water in the solvent.
- (19) Surry, D. S.; Buchwald, S. L. *Chem. .Sci.* **2011**, *2*, 27–50 (for a user's guide to Buchwald's palladacycle precatalysts and ligands).
- (20) Rebelo, J. M.; Kress, S.; Friedman, A. A.; Lautens, M. Synthesis 2016, 48, 3155–3164.

Article