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Article

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Utilizing Native Directing Groups: Synthesis of a Selective IKur Inhibitor, BMS-919373, via a Regioselective C-H Arylation

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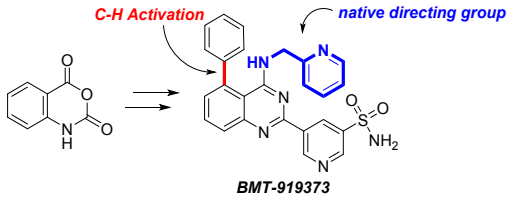


ABSTRACT: BMS-919373 is a highly functionalized quinazoline under investigation as a selective, potent I_{Kur} current blocker. By utilizing the aminomethylpyridine side-chain at C-4, a selective C-H functionalization at C-5 was invented, enabling the efficient synthesis of this molecule. The strategy of leveraging this inherent directing group allowed the synthesis of this complex heterocycle in only six steps from commodity chemicals. The scope of the C-H activation was further investigated, and the generality of the transformation across a series of bicyclic aromatic heterocycles was explored.

INTRODUCTION

Atrial fibrillation (AF or AFib) is the most common type of heart arrhythmia and is often represented by a rapid, irregular heartbeat. An estimated 2.7 – 6.1 million people have AF in the United States.[1] More than 750,000 hospitalizations occur each year in the United States[2] at a cost of an estimated $26.0 billion.[3,4]

Current antiarrhythmic drugs for the treatment of AF affect both the atria and ventricles and are made up of sodium channel blockers, potassium channel blockers, and mixed ion channel blockers. More recent studies have focused on agents that selectively target the atria to provide potentially safer medications.[5] An example of this approach is the inhibition of the atrial-specific ultrarapid delayed rectifier potassium current (I_{Kur}) enzyme. One such compound, the active pharmaceutical ingredient (API), BMS-919373 (Figure 1, **1**),[6] was recently identified as a potent and selective I_{Kur} inhibitor that showed robust effects in rabbit and canine pharmacodynamic models and was advanced as a clinical candidate.

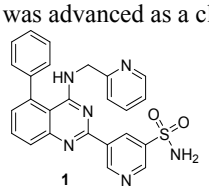


Figure 1. Structure of I_{Kur} Inhibitior, BMS-919373 (**1**)

To allow effective production of numerous phenylquinazoline analogs, the initial synthesis of BMS-919373 centered around derivatization of 2,4-dichloro-5-phenylquinazoline, which was prepared from 4-bromoisatin in 5 steps. This enabled the use of SnAr chemistry to install various aryl substituted amines at the 4-position and Suzuki couplings to install small heterocycles at the 2-position. However, while the dichloroquinazoline was a versatile intermediate to explore SAR at the C2 and C4 positions, once BMS-919373 was selected as the lead candidate a more targeted synthetic approach was required.

RESULTS AND DISCUSSION

Route Scouting Efforts toward the Synthesis of API

Retrosynthetic analysis yielded a number of potential approaches to assemble the quinazoline core (Figure 2). The key decision on the route, however, was the method for installing the phenyl group at C5. One targeted disconnection would be to install the group early in the route through a cross-coupling, to afford a 1,2,3-trisubstituted arene, which would then be further elaborated through cyclization or substitution reactions to form the quinazoline core.

The second strategy was to install the phenyl ring via C-H activation. The picolyl amine was conceived to be a built-in directing group that would enable an efficient synthesis of the phenyl substituted quinazoline. There are, however, limited reports on direct arylations of these systems, and to the best of

our knowledge, picolyl amine has not been reported as a directing group in this type of C-H activation.

There are multiple benefits to utilizing the C-H activation in lieu of the early-stage cross-coupling. Most importantly, the cross-coupling route would require the use of a halogenated 1,2,3-trisubstituted arene intermediate, prepared from 4-bromoisatin through a series of transformations. Although commercially available, 4-bromoisatin itself is derived from 3-bromoaniline in 2 steps,[7] whereas implementation of the C-H activation would allow us to start from a simpler and more readily available 1,2-disubstituted arene. The direct arylation would create the required 1,2,3-trisubstituted core in one step. Utilizing the direct arylation should afford the shortest overall route to API via a back-to-back palladium catalyzed Suzuki and C-H activation from the commercially available 2,4-dichloroquinazoline (Figure 2, Path D).

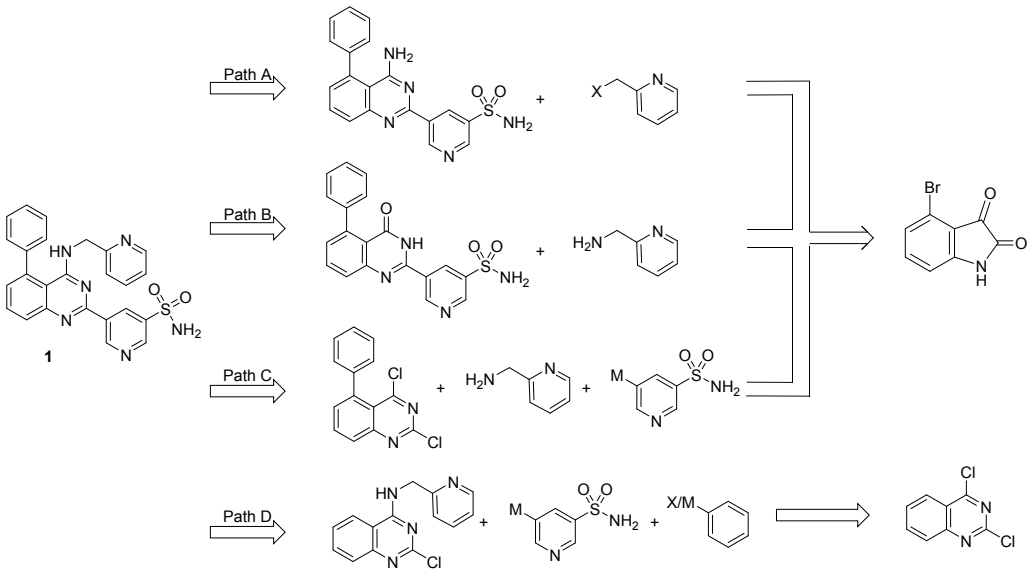
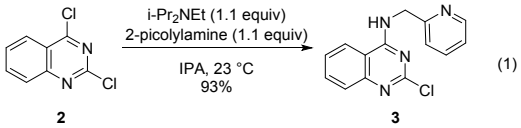
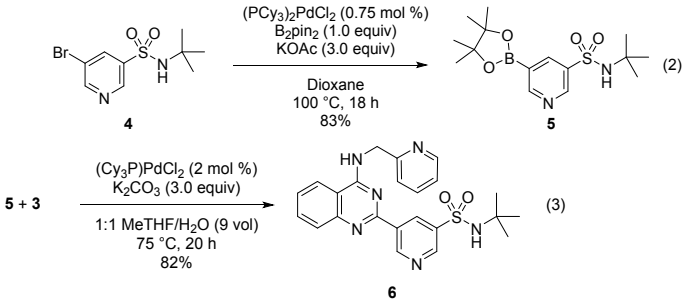


Figure 2. Retrosynthetic Analysis of BMS-919373

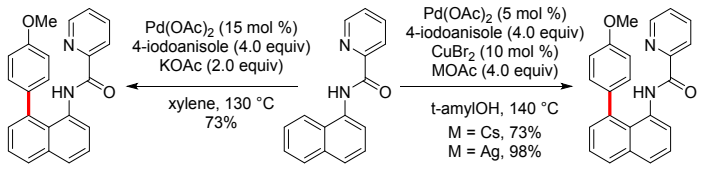
From this analysis, we made the strategic decision to focus our efforts on the C-H functionalization and on the use of 2,4-dichloroquinaozline as our starting point to access the des-phenyl API (Figure 2, Path D). A benefit of this approach was the methodology developed should transfer to route/path C, if needed, as we believed that the aryl group on the quinazoline ring would not have a significant impact on the chemistry developed.

Starting from 2,4-dichloroquinazoline, installation of the picolyl amine fragment proceeds in 93% yield (eq 1). The Suzuki coupling partner was prepared via a palladium-catalyzed Miyuara borylation of the substituted 3-bromopyridine **4**, which affords the pinacol boronate ester **5** in 83% yield with less than 1 mol % Pd (eq 2). The use of the *tert*-butyl sulfonamide improves solubility and thus reactivity of substrates. The Suzuki coupling was performed utilizing 2 mol % of $(Cy_3P)PdCl_2$, 3.0 equiv of K_2CO_3 in 1:1 MeTHF/H_2O, and the product crystallized out of solution during the reaction allowing isolation with no work-up in 82% yield. (eq 3).





Based on the results of the cross-couplings above, we were confident that we could achieve proof of concept on path C by utilizing 2,4-dichloro-5-phenylquinazoline as the starting material and proceeding through the same series of transformations. From here, we turned our attention to the key transformation, installation of the arene through a metal-catalyzed C-H activation. Utilization of picolinamide as a direct group led to installation of anisole through a C-H activation on a similar naphthalene system with a catalytic amount of palladium and an acetate base at elevated temperatures, providing us insight to potential reaction conditions (Scheme 1).[8]



Scheme 1. Direct Arylation on a Similar Naphthalene System

In addition to compound **6**, we envisioned preparing three additional substrates (all prepared from 2,4-dichloroquinazoline) to investigate the C-H activation (Figure 3). The Schiff base (**7A**) proved difficult to synthesize under an array of reaction conditions. The picolinamide model system (without the sulfonamide) was prepared, but provided modest levels of conversation in the C-H arylation, likely due to poor solubility (**7B**). This substrate was a less preferred option as it would require an additional reduction step to yield the desired picolyl amine. The unprotected sulfonamide (**7C**) suffered from even lower solubility, leading to no reactivity in the attempted coupling. Therefore, the *tert*-butyl protected sulfonamide (**6**) was our lead candidate for the exploration of the key C-H activation event.

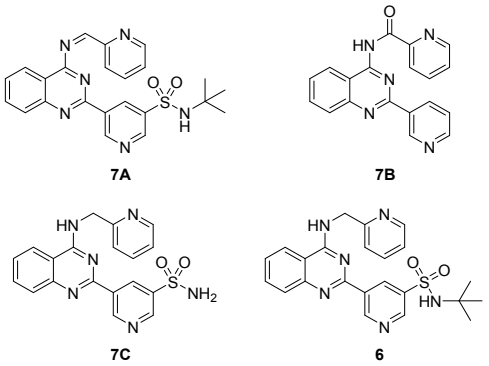
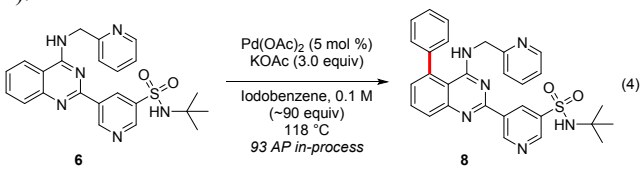


Figure 3. Substrates for the C-H Activation

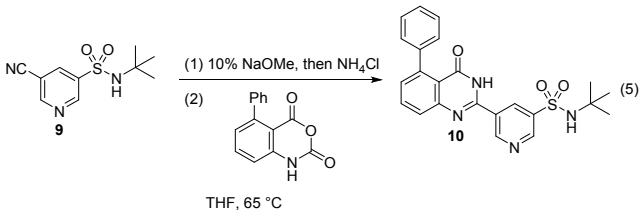
Proof of concept on the C-H arylation was quickly achieved. Excellent conversion (93 area percent by HPLC)[9] of the desired product was observed with a catalytic amount of $Pd(OAc)_2$ in iodobenzene with potassium acetate as the base (eq 4).



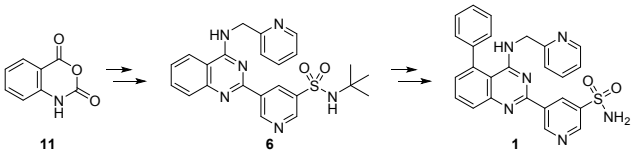
This initial hit for the C-H activation validated our hypothesis of leveraging the built-in directing group to install the arene through a late stage palladium-catalyzed reaction. With the use of 2,4-dichloroquinazoline, this route affords API in a five step longest linear route after deprotection of the sulfonamide.

Because of its inherent insolubility, the purification of **6** after the Suzuki coupling was a challenge, specifically the removal of residual palladium and ligands that could interfere with the direct arylation. Although we believed we could address this concern, the second, and perhaps more significant issue, was the long term viability of 2,4-dichloroquinazoline as our starting material, which was being accessed through the global chlorination of the quinazolinedione. In order to employ the C-H activation, we focused our attention on determining an efficient and sustainable route to quinazoline **6**.

Concurrent to the investigations into the Suzuki/C-H Activation route, we evaluated alternative methods for accessing the quinazoline core (Paths A and B). The alkylation of the aminoquinazoline in Path A with 2-chloromethylpyridine suffered from poor selectivity as a mixture of mono- and bis-addition products, that were challenging to separate, were observed under an array of reaction conditions (Path A).[10] However, a condensation based approach would afford a quinazolinone as the penultimate compound. The installation of the picolylamine fragment through an SnAr reaction would then yield the API (Path B). Proof of concept for this route was achieved by the condensation of 6-phenyl isatoic anhydride and the amidine of **9** to afford the quinazolinone is 46% yield (eq 5). As in other strategies, the *tert*-butyl group on the sulfamide was installed to improve solubility of the intermediates. Subsequent reaction with 2-picolylamine affords the *tert*-butyl protected API.



Based on the success of this transformation, we quickly realized the full synthesis. Isatoic anhydride (**11**) can be utilized in place of the 6-phenyl derivative in the condensation reaction to generate the quinazoline core, which can then be converted to the starting material for the C-H activation (Scheme 2). The switch from 4-bromoisatin to isatoic anhydride, provides both cost reduction and improved sustainability of the starting material.



Scheme 2. Condensation/C-H Activation Route to API

Condensation/C-H Activation Route Development

The six-step route to BMS-919373 is shown in Scheme 3. A robust process was developed for each step with a focus on the greenness of the overall route. The efficiency of each step developed can be measured by calculating the process mass intensity (PMI), which is the amount of material input (kg) / amount of product isolated (kg), where a lower PMI corresponds to a greener, more efficient process.

The first step in the sequence installs the *tert*-butyl sulfonamide by formation of the heteroarylgrignard with *i*-PrMgCl-LiCl. Addition of sulfuryl chloride forms the sulfonyl chloride in-situ, which is then reacted with *tert*-butyl amine to afford the desired sulfonamide **7** in 70% isolated yield. Several in-process by-products were observed from impurities in the input reagents (Figure 4). A pH controlled wash of the reaction mixture with 1.5 M HCl selectively removes the dehalogenated 3-bromopyridine. After a basic wash with 1.0 M $NaHCO_3$, a solvent swap to MeOH resulted in crystallization of the sulfone dimer impurity, which can be removed by a simple polish filtration. After crystallization of the desired sulfonamide **7**, the dihalogenated impurities, 3-bromo-5-chloropyridine and 3,5-dibromopyridine could be removed with a heptane wash of the isolated solid, resulting in ~98 AP material.

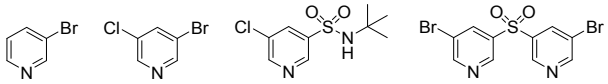
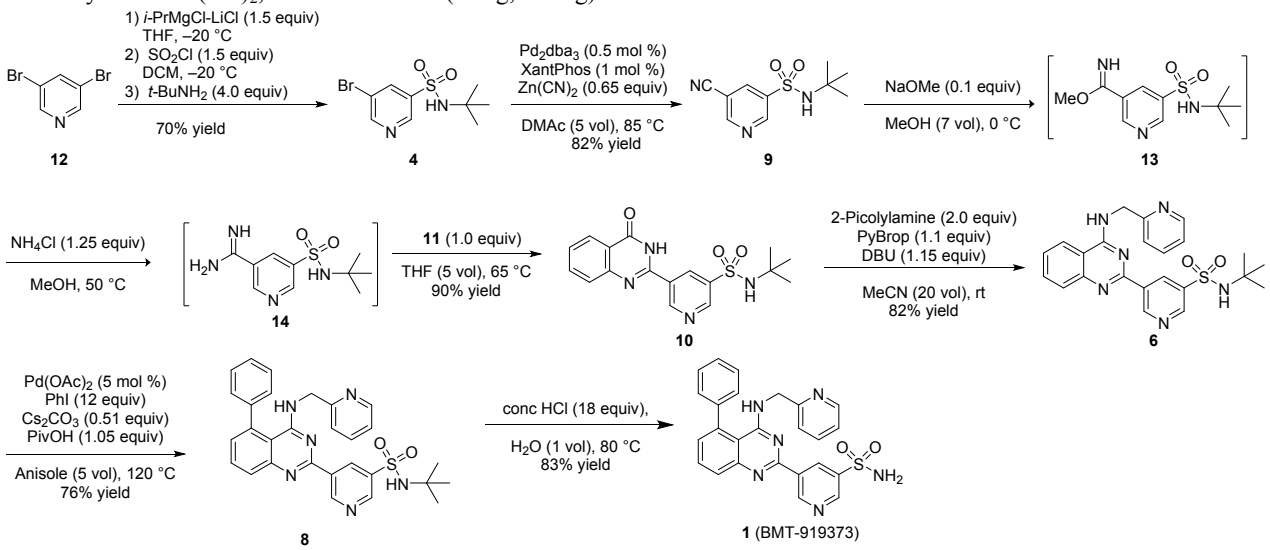


Figure 4. Impurities Generated in the Sulfonylation

The next step in the route is a palladium-catalyzed cyanation of **7.** $Zn(CN)_2$ proved to be the most effective cyanide source along with Pd_2dba_3 as the palladium source and XantPhos as the ligand. The reaction rate was dependent on the solubility of $Zn(CN)_2$, and 5 vol (mL/g, L/kg) of dimethylacetamide (DMAc) was the minimum volume to achieve acceptable kinetics. The reaction resulted in complete conversion with minimal impurities and an in-process yield of 98%.



Scheme 3. Optimized Condensation/C-H Activation Route to BMS-919373

A work-up to remove both the palladium and zinc was required.[11] A scavenger screen (Table 1) showed that the only effective scavenger at removing both Pd and Zn was ethylene diamine (EDA). The addition of ethylene diamine at the end of the reaction was exothermic and had to be added slowly while maintaining the batch temperature below 15 °C to prevent Zn aggregation. The product was then isolated through a crystallization with IPA/H_2O to afford the desired product in an average of 82% yield on 30-45 kg scale. The average residual Pd and Zn was ~20 ppm Pd and 30 ppm Zn, and the product was isolated in 96 AP. Interestingly, 2.5 AP were attributed to the XantPhos and dba ligands, and the remaining 1.5 AP was residual impurities from the input. However, all of these impurities can be purged in the subsequent step.

Table 1. Palladium and Zinc Remediation from the Palladium-Catalzyed Cyanation (NAC = N-Acetyl Cysteine, DTC = ammonium pyrrolidinedithiocarbamate)

Scavenger	Pd (ppm)	Zn (ppm)
DARCO G-60	620	<25
NH_4OH	140	910
NAC	280	850
DTC	31	1550
EDTA	230	1240
EDA	46	47

At the outset of this work it was found that the use of condensation reactions for the direct synthesis of 2-substituted quinazolin-4(3H)-ones such as **10** typically employed harsh reaction conditions or utilized starting materials such as aldehydes that produce the 2,3-dihydroquinazolin-4(1H)-ones, which then require subsequent oxidation of the aminal to deliver the desired quinazolin-4(3H)-one.[12] Therefore, we sought to develop an improved condensation manifold to build the desired quinazolinone moiety directly from aryl nitriles such as **9** and a suitable coupling partner under mild reaction conditions. A variant of Niementowski reaction[13] that had been shown to effect the condensation of amidines with isatoic anhydrides was particularly intriguing,[14] although, utilizing amidines without substitution at the amidine nitrogens, a necessity for accessing quinazolin-4(3H)-ones, had not been demonstrated. Therefore, we sought to exploit the ability to access the amidine (**14**) of aryl nitrile **9** in situ to facilitate a telescoped Niemetowski condensation of aryl nitriles with isatoic anhydrides under mild reaction conditions.

The condensation reaction between **7** and **12** required generation of the amidine of **7** via the intermediacy of an imidate (**13**) prepared via the action of catalytic sodium methoxide (10 mol %). Interestingly, studying the conversion of the nitrile to the imidate as a function of time and temperature showed that the formation of the imidate was an equilibrium process where higher conversion is observed at lower temperature (Figure 5). For example, keeping the temperature at 60 °C results in ~80% conversion, then cooling to 30 °C increases the conversion to ~90%. Decreasing the temperature further to 0 °C results in ~98% conversion (light blue line). The equilibrium process for the conversion of nitriles to imidates under basic conditions is surprisingly underexplored despite the prevalence of imidates as intermediates in heterocycle synthesis.[15] Therefore, the formation of the imidate was performed initially at 25 °C to rapidly bring the reaction to ~90% conversion then cooled to 0 °C to drive the reaction to near complete conversion.

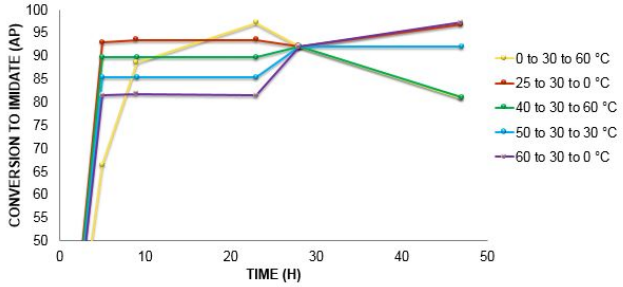


Figure 5. Impact of Temperature on Imidate (**13**) Formation

As expected, the conversion of the imidate (**13**) to the amidine (**14**) is dependent on the concentration of ammonium chloride.[16] Furthermore, increasing ammonium chloride concentration resulted in quicker reaction times which also suppressed the formation of a dimer resulting from reaction of the amidine product with the starting imidate. Based on this data, the concentration of the amidine formation sequence was reduced to from 15 to 7 vol, which resulted in high conversion with only 1.25 equivalents of ammonium chloride. With these optimized conditions for the formation of the amidine (**14**), the target condensation reaction was explored.

During our development of the condensation between the amidine (**14**) and isatoic anhydride (**11**) it was found that the reaction occurred spontaneously and was typically complete within minutes of heating to 60 °C as evidenced by the liberation of CO_2. This condensation tolerated numerous solvents such as acetonitrile and *t*-AmOH although the reaction gave the best performance in THF, likely due to the lower solubility of ammonium chloride in this solvent, which prevented the liberated ammonium chloride from intercepting the incoming isatoic anhydride to give anthranilamide. Therefore, the process was performed by swapping the solvent of the incoming amidine methanol solution to THF, adding the isotoic anhydride, then heating to 65 °C to obtain a homogenous solution. At this stage THF was also beneficial as a direct drop crystallization could be performed by simply adding water. The development of this telescoped Niementowski-type condensation reaction afforded the desired quinazolinone **10** in 90% yield with 99.2 AP purity on 30 kg scale under mild reaction conditions directly from aryl nitrile **9** using only 10 mol % sodium methoxide and 1.25 equivalents of ammonium chloride as reagents.

The next step in the route is the installation of the picolyl amine through an SnAr reaction to yield **6**. It was found that bromotripyrrolidinophosphonium hexafluorophosphate (PyBrop) and DBU were effective reagents at activating the quinazolinone for nucleophilic substitution.[17] The DBU was required to solubilize the remarkably insoluble quinazolinone **10** and was also found to produce consistent kinetics and reliable reactivity. However, the challenges to this system were the impurities associated with the addition of the DBU base (**16**) and the residual pyrrolidine derived from the PyBrop reagent (**15**), presumably from the reaction of these two amines with the activated quinazoline intermediate (Figure 6). The pyrrolidine impurity could be controlled through the procurement of high quality PyBrop (> 99%), which resulted in the observation of < 5 AP of this impurity during the process.

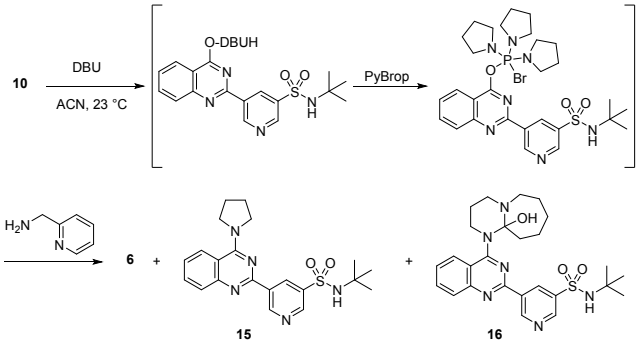


Figure 6. SnAr Reaction Pathway and Impurities

The DBU impurity (**16**), however, could be observed at levels upwards of 10 AP after holding the activated intermediate for 3 hours with 1.5 equiv of DBU (Figure 7). This was a critical issue as the length of this hold time could vary during processing. To solve this issue a DoE (design of experiments) study was conducted that examined DBU equivalents, reaction concentration and temperature as a function of time. The study showed that by lowering the charge of DBU to 1.15 equiv, decreasing the reaction concentration from 10 vol to 20 vol, and reducing the reaction temperature from 23 °C to 10 °C, the desired SnAr was favored while the DBU impurity was decreased to observed levels of < 2 AP, even after holding the activated intermediate stream for 24 h.[18] Under these optimized conditions, the crystallization was performed by simply adding water to afford the isolated product in 99.5 AP in 88% average yield on 2 × 17 kg scale.

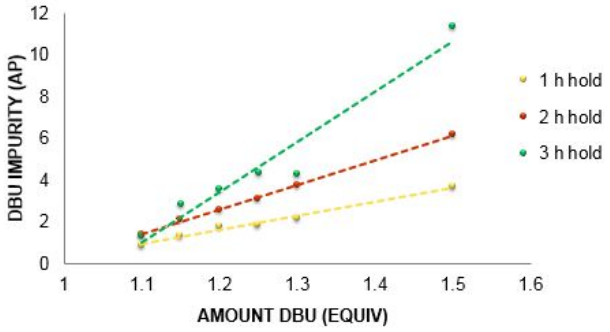


Figure 7. Impact on DBU Charge on the Formation of the DBU Impurity

Extensive high throughput screening was completed on the C-H activation of **6**, with several interesting trends being observed.[19] Ligands (phosphines, pyridines, phosphites) as well as coordinating solvents (DMF, DMAc, NMP) completely shut down the reaction. Iodobenzene was the only effective arene source as both bromobenzene and phenyl triflate were unreactive under an array of conditions.

The optimized conditions reduced the amount of iodobenzene to 12 equivalents (~3 vol) and utilized anisole (5 vol) as a co-solvent. Anisole is an effect co-solvent as it allows for the needed solubility at the reaction temperature of 120 °C. CsOPiv is formed in-situ via the reaction of Cs_2CO_3 and pivalic acid.

The C-H Activation is not sensitive to oxygen as it is believed to proceed through a Pd(II)/Pd(IV) cycle.[20] However, inertion is important to minimize the formation of one key impurity, the dimer of the product (Figure 8). Formation of a radical at the benzylic position will result in dimerization,

which is observed as a pair of diastereomers. The formation is believed to occur via a single electron mechanism as the addition of BHT results in BHT incorporation into the product. The formation of these diastereomers can be decreased from ~3AP to <1 AP by properly degassing the solvents and headspace.

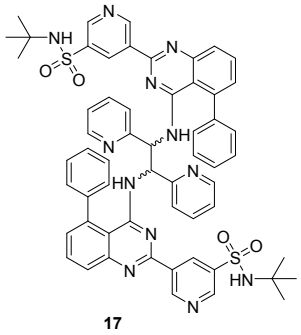


Figure 8. Impurities in the C-H Activation

Because the product of the C-H activation has limited solubility (<10 mg/ml in MeOH, acetone, DMSO, EtOAc, MeTHF, DCM), a phase split is not possible as the molecule only has appreciable solubility in one solvent (70 mg/ml in NMP). The addition of an anti-solvent to the anisole/iodobenzene mixture does not increase the amount of desaturation, and therefore, we took advantage of the insolubility by cooling the reaction mixture to 0 °C and filtering off the product. The cake was washed with IPA/H_2O to remove CsI, and recrystallized from DMAc/H_2O to afford the product in ~76% average yield and >99 AP. Pd complexation to the product was removed by addition of ethylene diamine[21] during the recrystallization. The amount of Pd observed in the isolated product was <20 ppm.

The final step in the route is an acid mediated deprotection to yield the free sulfonamide. The API was isolated in 92% yield and >99 AP as a white crystalline solid. The only key impurity from the API step was *tert*-butyl incorporation onto the pyridine ring, which was controlled through the crystallization to <0.02 AP (Figure 9). An optional recrystallization of the product further improved the purity to ~99.9 AP.

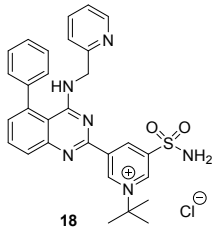


Figure 9. *Tert*-Butyl Incorporated Impurity from API Step

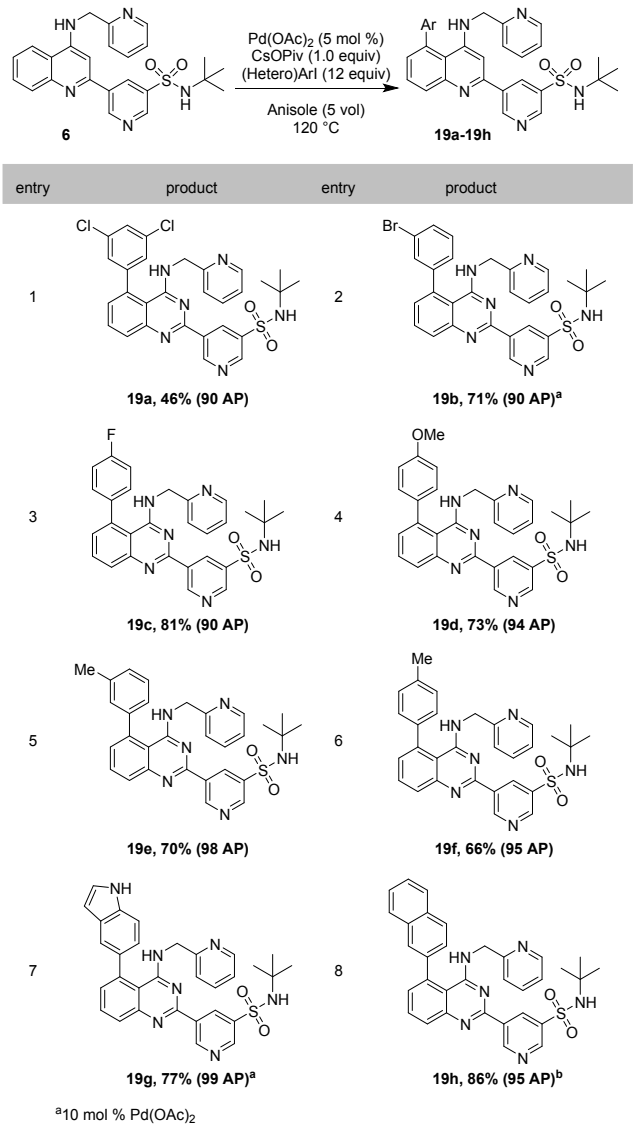
The six-step overall route to BMS-919373 proceeded in 27% yield and an overall PMI[22] of 407.3. No route related impurities were present in the API above detectable limits.

GENERALITY OF THE C-H ACTIVATION

The direct arylation optimized in this route takes advantage of the unique nature of the molecule, allowing us to install the arene late in the synthesis and to start from commodity chemicals. To the best of our knowledge, picolinamides have been reported as a directing groups in C-H activations catalyzed by palladium, copper, and ruthenium.[23] However, a recent report on the C(sp3)-H activation of tertiary aldehydes with transient imine directing groups showed the use of 2-picolylamine as ineffective because of direct complexation with Pd.[24] Therefore, we sought to investigate the generality of the C-H activation developed in the route to BMS-919373.

The standard reaction conditions were subjected to an array of iodoarenes. Eight substrates performed well, with >90 AP product at the end of the reaction (Table 2). However, challenging isolations of the products resulted in lowered yields. Halo-containing iodoarenes were good substrates for the reaction as 3,5-dichloro-, 3-bromo-, and 4-fluoro- substituted arenes afforded the desired product in moderate to good yield (entries 1-3). No conversion of the aryl bromide or chloride was observed in the reaction conditions. Tolyl- and methoxy-substituents on the arene did not impact the reaction as complete conversion was observed with yields around 70% (entries 4-6). Larger (hetero)arenes such as indole and naphthalene are also effective in the transformation as the products were obtained in high yield (entries 7-8).

Table 2. Scope of the C-H Activation with (Hetero)Aryl Iodides

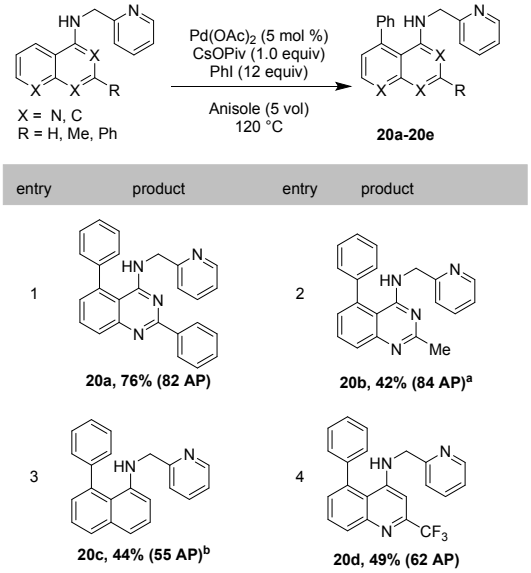


a10 mol % $Pd(OAc)_2$

Sterically hindered iodides such as 2-iodotoluene and 1-iodonapthalene were unsuccessful substrates as only starting material was observed. 4-iodopyridine was not stable at the reaction temperature.

To demonstrate that the 2-picolylamine directing group was not specific to the case of BMS-919373, an array of bicyclic aromatic compounds were prepared and subjected to the general C-H activation conditions (Table 3). Other quinazoline cores, such as those substituted by phenyl and methyl, are good substrates for the C-H activation, affording the products in yields of 76 and 52% (entries 1-2). Naphthalene is a suitable substrate for the catalysis as the arylated product was obtained in good yield (entry 3). Interestingly, a major by-product in the reaction with the naphthalene substrate was the removal of the picolyl group after direct arylation to yield the free amine. 4-Aminoquinoline was unreactive under the standard reaction conditions; however, a trifluoromethyl substituted quinoline afforded the arylated product in good yield (entry 4).

Table 3. Scope of the Heterocycles in the Direct Arylation



[b]PhI (24 equiv) [b]10 mol % $Pd(OAc)_2$, 1.5 equiv CsOAc, PhI (24 equiv)

CONCLUSION

In summary, we have demonstrated an innovative, economical, and efficient synthesis of BMS-919373 enabled by the identification and implementation of a late stage palladium-catalyzed C-H arylation directed by picolyl amine. The novel, six-step route from isatoic anhydride led to significant improvements in overall sustainability and a 50 fold decrease in starting material cost over previous routes. The scope and generality of the pivotal C-H transformation was investigated using an array of iodoarenes, as well as a variety of heterocyclic partners.

EXPERIMENTAL

General Considerations. All reagents were purchased from commercial sources. Standard benchtop techniques were employed for handling air-sensitive reagents. Melting points (°C) are uncorrected. NMR spectra were recorded on a 400 or 500 MHz spectrometer. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant *J* (Hz), and integration. Analytical thin-layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator. Visualization of the TLC plates was effected with ultraviolet light. Standard flash chromatography procedures were followed using 100-200 mesh silica gel. HRMS samples were run on the Thermo LTQ-Orbitrap with Acquity Classic inlet. Note: A representative lab procedure for each step in the route to BMS-919373 is shown below. The yields may vary slightly from those observed from the on-scale batch execution.

Preparation of 5-bromo-N-*tert*-butylpyridine-3-sulfonamide (**4**). A clean 500 mL reactor was purged with nitrogen for 1 h and charged with i-PrMgCl-LiCl complex (1.3 M in THF, 195 mL, 253 mmol, 1.5 eq). The solution was cooled to –13 °C. 3,5-dibromopyridine (40g, 168.8 mmol) was dissolved in THF (320 mL, 8 vol). The substrate solution was added dropwise to the Grignard solution, maintaining the temperature was below –8 °C. After the addition, the mixture was allowed to stir for 10 mins, at which point HPLC analysis indicated complete consumption of the starting material. A separate, clean 1 L reactor was purged with nitrogen for 1 hour and charged with DCM (100 mL, 2.5 vol) and sulfuryl chloride (20.5 mL, 1.5 eq). The DCM solution was cooled to –16 °C. The pre-generated arylmagnesium chloride was transferred to sulfuryl chloride solution by cannula; maintaining the temperature below –9 °C. After the addition, the mixture was allowed to stir for 20 min. *tert*-Butylamine (71 mL, 4 eq) was added dropwise; maintaining the temperature below –5 °C. After the addition, the mixture was allowed to stir for 12 h. The reaction was quenched by the addition of 2M HCl (5 vol, 200 mL) at –10 °C followed by the addition of DCM (5 vol, 200 mL). The layers were partitioned and organic layer was collected. The aqueous layer was back-extracted with DCM (5 vol, 200 mL) and partitioned. The combined organic layer was transferred to the 1 L reactor, and the solvent was distilled at 50 °C (jacket temperature) under house vac, from ~1100 mL (28 vol) to 100 mL (2.5 vol). MeOH (5 vol, 200 mL) was added to rinse off the solid on the side of the reactor and solvent was distilled again under same condition to 100 mL (2.5 vol). MeOH (5 vol, 200 mL) was again added to rinse off the solid on the side of the reactor and solvent was distilled again under same condition to 100 mL (2.5 vol). MeOH was added to reach 250 mL and the mixture was heated at 50 °C until it became homogenous. Water (320 mL, 8 vol) was added while stirring. The mixture was allowed to cool to rt and stir overnight. The product was collected by filteration under vacuum. The cake was washed with 80 mL hexane (2 vol). The solid was allowed to dry on the filter for 5 hours. The solid was collected and was dried at 50 °C for 2 hours to yield the product (37.12 g, 70%). mp 103-105 °C. ^{1}H NMR (500 MHz, d6-DMSO): δ 8.94 (dd, J = 7.5 Hz, 2.0 Hz, 2H), 8.40-8.38 (m, 1H), 7.88 (s, 1H), 1.12 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, d6-DMSO): δ 153.3, 145.2, 141.8, 136.2, 120.2, 54.0, 29.7; IR (neat) 3280, 3067, 3060, 1564, 1318, 1147, 689 cm^{-1}; HRMS (ESI-TOF) m/z: 292.9954 calcd for $C_9H_{14}BrN_2O_2S$ $[M+H]^+$, found 292.9949.

Preparation of N-(*tert*-butyl)-5-cyanopyridine-3-sulfonamide (**9**). N,N-Dimethylacetamide (100 mL, 5 L/kg) was charged to a reactor, where it was sparged with N_2 for at least 15 minutes. 4 (20.0 g, 68.25 mmoles, LR), Zinc cyanide (5.31 g, 44.36 mmol, 0.65 equiv), Tris(dibenzylideneacetone)dipalladium (0.329 g, 0.35 mmol,

0.005 equiv), XantPhos (0.407 g, 0.69 mmol, 0.01 equiv) were successively charged to the reactor with agitation under a nitrogen atmosphere. The reaction mixture was heated to 85 °C. After 4 hr of reaction at 85 °C, a sample was pulled from the reaction mixture and analyzed for reaction completion. The reaction mixture was cooled to 0 °C. Ethylenediamine (3.98 g, 66.22 mmol, 0.97 equiv) was added slowly, maintaining a batch temperature below 15 °C. The reaction mixture stirred for 10 minutes. Ethyl acetate (200 mL, 10 L/kg) was added, stirred for 10 minutes, and the reaction was allowed to warm to 20-25 °C. 15 wt% NaCl in water (200 mL, 10 L/kg) was charged to the agitated reaction mixture and stirred for 5 min (avoiding high agitation rates to prevent an emulsion). The agitation was stopped, the layers separated and split. Water (200 mL, 10 L/kg) was charged to the agitated reaction mixture and stirred for 5 min. The agitation was stopped, the layers separated and split. The organic stream was filtered through a 5 µm filter and recharged to the reactor. The organic stream was concentrated to 100 mL (5 L/kg) at Tj = 80 °C under 200 torr vacuum (Tr = 42 °C). Note: the maximum jacket temperature should be limited to 80 °C and the maximum batch temperature to 60 °C. Isopropanol (200 mL (10 L/kg) was then introduced through a constant volume distillation with a Tj = 80 °C and a vacuum of 200 torr. The Tr increased to ~50 °C as the solvent swap proceeded. The product began crystallizing during the solvent swap. The organic stream was concentrated to 80 mL (4 L/kg) at Tj = 80 °C under 200 torr vacuum (Tr ~ 50°C). With a Tr = 50 °C, water (180 mL, 9 L/kg) was added dropwise over ~ 2 hours, resulting in further crystallization of the product. After the addition of water was complete, the mixture was slowly cooled to 20-25 °C over the course of several hours, where it was aged for 6 hours. The resultant solid was filtered and washed with 1:3 IPA/water (60 mL, 3 L/kg). The cake was washed a second time with 1:3 IPA/water (60 mL, 3 vol). The solid was dried in a vacuum oven at 60 °C for 16 h to yield the product as a white solid (14.35g, 91% yield). mp 122-124 °C. ^{1}H NMR (500 MHz, d6-DMSO): δ 9.22 (dd, J = 9.8 Hz, 1.7 H, 2H), 8.69 (t, J = 2.0 Hz, 1H), 7.96 (s, 1H), 1.13 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, d6-DMSO): δ 115.0, 150.1, 140.6, 131.7, 115.8, 109.7, 54.2, 29.7; IR (neat) 3291, 3072, 2238, 1984, 1556, 1316, 1147, 694 cm^{-1}; HRMS (ESI-TOF) m/z: 240.0801 calcd for $C_{10}H_{14}N_3O_2S$ $[M+H]^+$, found 240.0791.

Preparation of N-(*tert*-butyl)-5-(4-oxo-3,4-dihydroquinazolin-2-yl)pyridine-3-sulfonamide (**10**). To a 1 L reactor was charged methanol (297 g, 375 mL, 15 vol) followed by **9** (25.0 g, 104.5 mmol), which was stirred at 25 °C for no less than 1 h. The stream was then distilled 6 vol under vacuum (200 torr with Tj = 60 °C). MeOH (1 vol) was then charged to the reactor. 25 wt% Sodium methoxide in methanol solution (2.2 g, 10.5 mmol) was added, and the reaction stirred at 25 °C for 8 h. The reactor was then cooled to 0 °C for no less than 12 h. Ammonium chloride (6.8 g, 130.6 mmol) was then added at 0 °C and stirred for 1 h before heating to 45 °C for 8 h. The solvent was swapped to THF by constant volume vacuum distillation (250 torr with 50 °C jacket, requiring 30 vol of THF). Isatoic anhydride (17.3 g, 104.5 mmol) was then added at 25 °C, and the reactor heated to 65 °C for 6 h. Water (82.5 mL, 3.3 vol) was then added at 60 °C over 30 min. After aging the slurry for 4 h at 60 °C, it was slowly cooled to 23 °C over 4 h and aged no less than 12 h. The product was isolated by vacuum filtrated, washed with 75% THF/water (5 vol) and THF (5 vol). The cake was dried under full vacuum at 60 °C for no less than 12 h to yield the product as a light yellow solid (32.58g, 87% yield). mp >250 °C. ^{1}H NMR (500 MHz, d6-DMSO): δ 12.94 (s, 1H), 9.45 (s, 1H), 9.15 (s, 1H), 8.90 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.95 (s, 1H), 7.87 (t, J = 7.3 Hz, 1H), 7.82-7.77 (m, 1H), 7.57 (t, J = 7.3 Hz, 1H), 1.16 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, d6-DMSO): δ 162.5, 151.7, 150.2, 149.4, 148.8, 141.0, 135.2, 133.9, 129.6, 128.1, 127.7, 126.4, 121.8, 54.5, 30.3; IR 3189, 3144, 3070, 2967, 1679, 1600, 1143, 778 (neat) cm^{-1}; HRMS (ESI-TOF) m/z: 359.1172 calcd for $C_{17}H_{19}N_4O_3S$ $[M+H]^+$, found 359.1166.

Preparation of N-(*tert*-butyl)-5-(4-((pyridin-2-ylmethyl)amino)quinolin-2-yl)pyridine-3-sulfonamide (**6**). To a 1 L reactor was charged with a slurry of **10** (20.0 g, 55.8 mmol) in acetonitrile (20.0 mL/g, 7630 mmol) at 30 °C. The white slurry was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (1.15 equiv, 64.2 mmol) and stirred for 10 min as the slurry went into solution. The yellow solution was cooled to 12 °C. Pybrop (1.1 equiv, 61.4 mmol) was added to the reactor followed by 2-(aminomethyl)pyridine (12.45 g, 114.0 mmol). The reactor stirred overnight at 10 °C, at which time HPLC indicated complete conversion. The stream was heated to 70 °C and water (400 mL, 20 vol) was then added dropwise over 40 min, resulting in crystallization of the product. The slurry was held at 60 °C for 3 h and then ramped to 20 °C over 3 h. The slurry was isolated by filtration, and the cake was washed with 1:1 ACN/water (80 mL, 4 vol) and ACN (80 mL, 4 vol). The wet cake was dried overnight in a vacuum oven at 50 °C. The crude product was recrystallized from 5:1:3 THF/MeOH/Water vol/vol/vol at 60 °C to provide the product as an off-white solid (23.04g, 88% yield). mp 191-193 °C. ^{1}H NMR (500 MHz, d6-DMSO): δ 9.61 (d, J = 1.5 Hz, 1H), 9.26-9.20 (m, 1H), 9.09-9.06 (m, 2H), 8.54 (d, J = 4.9 Hz, 1H), 8.40 (d, J = 8.2 Hz, 1H), 7.93 (s, 1H), 7.85-7.79 (m, 2H), 7.73-7.68 (m, 1H), 7.60-7.55 (m, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.25-7.21 (m, 1H), 5.01 (d, J = 5.5 Hz, 2H), 1.12 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, d6-DMSO): δ 160.3, 159.1, 156.8, 152.1, 150.0, 149.4, 148.4, 140.9, 137.1, 134.5, 133.7, 133.2, 128.4, 126.8, 123.4, 122.6, 121.8, 114.7, 54.3, 46.6, 30.3; IR (neat) 3258, 3064, 2975, 1582, 1368, 1152, 760 cm^{-1}; HRMS (ESI-TOF) m/z: 449.1754 calcd for $C_{23}H_{25}N_6O_2S$ $[M+H]^+$, found 449.1763.

Preparation of N-(*tert*-butyl)-5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)quinazolin-2-yl)pyridine-3-sulfonamide (**8**). To a 250 mL reactor was added iodobenzene (220.2 g, 1058 mmol), and anisole (202.5 g, 1870 mmol) which was degassed by bubbling N_2 for 30 minutes. Then **6** (40.17 g, 85.98 mmol), Cesium Carbonate (14.24 g, 43.70 mmol), Pivalic Acid (9.3 g, 90 mmol,), and Palladium(II) Acetate (963.5 mg, 4.29 mmol) were added, and the reaction was heated to 120 °C under N_2 for 6 h, at which time complete conversion was observed by HPLC. After cooling to 0 °C, the solids were collected by vacuum filtration. The reactor was rinsed with anisole (120 mL), which was then used to watch the cake. The reactor was then rinsed with 1:1 IPA/H_2O (120 mL), which was then used to wash cake, twice. The solids were dried by vacuum filtration for 30 min. To a clean 250 mL reactor, N,N-Dimethylacetamide (280 mL) was added followed by the crude solid. Ethylenediamine (1.44 mL, 0.25 equiv) was then added, and the batch heated to 80 °C with stirring. After 30 min, water (10 mL) was added. The reactor was then cooled 60 °C and aged for 1 h. Water (30 mL) was then added dropwise. The batch slowly cooled to rt and aged overnight. The solids were collected by vacuum filtration, where they were subsequently washed with 7:1 DMAc/H2O (120 mL) and water (120 mL). The product was dried by vacuum filtration at 65 °C to yield a white solid (34.7g, 78% yield). mp 226-228 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 9.87 (d, J = 1.8 Hz, 1H), 9.33 (t, J = 2.1 Hz, 1H), 9.18 (d, J = 2.4 Hz,

1H), 8.32 (d, J = 4.6 Hz, 1H), 7.97-7.95 (m, 1H), 7.92-7.86 (m, 2H), 7.79-7.75 (m, 1H), 7.64-7.59 (m, 5H), 7.41-7.36 (m, 2H), 7.28-7.25 (m, 1H), 7.06-7.04 (m, 1H), 4.85 (d, J = 4.3 Hz, 2H), 1.28 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, d7-DMF): δ 159.8, 156.8, 156.2, 152.3, 151.7, 148.8, 148.6, 141.4, 140.6, 139.7, 137.0, 134.6, 133.5, 132.4, 129.9, 129.7, 129.5, 129.8, 128.5, 122.4, 121.9, 112.4, 54.4, 46.7; IR (neat) 3368, 3297, 2975, 1517, 1322, 1137, 752, 667 cm^{-1}; HRMS (ESI) m/z: 525.2067 calcd for $C_{29}H_{29}N_6O_2S$ $[M+H]^+$, found 525.2080.

Preparation of 5-(5-phenyl-4-((pyridin-2-ylmethyl)amino)quinolin-2-yl)pyridine-3-sulfonamide (**1**). To a 250 mL reactor was added concentrated HCl (30 mL, 1.5 vol) followed by **8** (20g) in five portions. Concentrated HCl (20 mL, 1 vol) and water (10 mL, 0.5 vol) were then added. The mixture was allowed to age for 1 h to ensure dissolution, which was then polish filtered. The reactor was then heated to 80 °C for 3 h, at which time HPLC showed complete conversion. After cooling to 45 °C, The batch was diluted with water (60 mL, 3 vol) followed by 5M KOH (100 mL, 5 vol), maintaining the temperature below 60 °C. Ethanol (280 mL, 14 vol) was then added. 5 M KOH (30 mL, 1.5 vol) is then added at 45 °C, resulting in crystallization of the product. 2.5 M K_2CO_3 (10 mL, 0.5 equiv) is then added to reach a pH of 7. The batch is then cooled to 20 °C over 2 h and aged 1 h. The solids are collected by vacuum filtration and washed with 60/40 ethanol/water (3 vol) followed by water (3x2.25 vol) and ethanol (3 vol). The product is dried under vacuum at 45 °C to afford the product as a white solid (14.58g, 82% yield). mp 203-205 °C. ^{1}H NMR (500 MHz, d6-DMSO): δ 9.79 (d, J = 1.8 Hz, 1H), 9.17 (t, J = 2.1 Hz, 1H), 9.10 (d, J = 2.1 Hz, 1H), 8.21 (d, J = 4.6 Hz, 1H), 7.91-7.88 (m, 1H), 7.85-7.75 (m, 3H), 7.72-7.69 (m, 1H), 7.57-7.48 (m, 5H), 7.30 (t, J = 8.1 Hz, 2H), 7.22 (dd, J = 7.2 Hz, 5.3 Hz, 1H), 6.93 (s, 1H), 4.73 (d, J = 4.0 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, d6-DMSO): δ 158.9, 156.0, 155.2, 151.8, 150.7, 148.1, 147.5, 140.1, 139.7, 138.9, 136.6, 133.7, 132.3, 132.1, 129.3, 129.0, 129.0, 128.3, 127.8, 122.1, 121.5, 111.6, 46.0; IR (neat) 3362, 3342, 3049, 1525, 1355, 1162, 739 cm^{-1}; HRMS (ESI) m/z: 469.1441 calcd for $C_{25}H_{21}N_6O_2S$ $[M+H]^+$, found 469.1431.

General Procedure for the C-H Activation with (Hetero)Aryl Iodides: To a 40 mL scintillation vial with stir bar was added N-(*tert*-butyl)-5-(4-((pyridin-2-ylmethyl)amino)quinazolin-2-yl)pyridine-3-sulfonamide (**9**) (2.0g, 4.47 mmol), $Pd(OAc)_2$ (0.05 equiv), cesium pivalate (1 equiv to 1.5 equiv), (hetero)aryliodide (12 equiv), and anisole (10 mL). The vial was capped with a pressure relief septa. The reaction mixture was heated to 120 °C until complete conversion was observed, as judged by UPLC-MS (~16 h). Products were isolated by one of the following procedures. Note that some ^{1}H NMR show residual DMAc from the recrystallization, which was presumably trapped during the crystallization and not removed by the water wash. The yields have been accounted for this residual solvent.

(1) For 19a, 19b, 19c, water (10 mL) was added, which resulted in crystallization of the product. The crude product was filtered, washed with 1:1 IPA/H_2O (10 mL), and recrystallized from 7:1 DMAc/H_2O.

(2) For 19d, 19e, and 19h, water (10 mL) was added, which resulted in a phase split. The aqueous was discarded. The organic layer was concentrated en vacuo to ~2-3 vol. Hexane (10 mL) was added to crystalline the product. The crude product was filtered, washed with 1:1 IPA/H_2O (10 mL), and recrystallized from 7:1 DMAc/H_2O.

(3) For 19f and 19g, water (10 mL) was added, which resulted in a phase split. The aqueous was discarded. The organic layer was concentrated en vacuo to ~2-3 vol and passed through a SiO_2 plug eluting with EtOAc and then MeOH to separate the aryl iodide and the product. The MeOH solution was concentrated to a solid and recrystallized from 7:1 DMAc/H_2O.

Preparation of N-(*tert*-butyl)-5-(5-(3,5-dichlorophenyl)-4-((pyridin-2-ylmethyl)amino)quinazolin-2-yl)pyridine-3-sulfonamide (**19a**). The title compound was obtained as an off-white solid in 46% yield (1.22 g). mp 221-223 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 9.89 (s, 1H), 9.34 (s, 1H), 9.19 (s, 1H), 8.40 (d, J = 4.6 Hz, 1H), 8.00-7.97 (m, 1H), 7.93-7.81 (m, 4H), 7.73 (s, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 7.0 Hz, 1H), 7.36-7.32 (m, 1H), 7.20 (s, 1H), 4.92 (d, J = 3.7 Hz, 2H), 1.28 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, d7-DMF): δ 159.1, 156.8, 155.7, 152.2, 151.4, 148.5, 148.4, 143.7, 141.1, 137.0, 136.3, 135.3, 134.3, 133.3, 132.2, 129.7, 129.1, 128.4, 128.4, 122.4, 122.0, 112.0, 54.2, 46.3; IR (neat) 3356, 3062, 2979, 1575, 1519, 1331, 1143, 998, 801 cm^{-1}; HRMS (ESI) m/z: 593.1288 calcd for $C_{29}H_{27}Cl_2N_6O_2S$ $[M+H]^+$, found 593.1268.

Preparation of 5-(5-(3-bromophenyl)-4-((pyridin-2-ylmethyl)amino)quinazolin-2-yl)-N-(*tert*-butyl)pyridine-3-sulfonamide (**19b**). The title compound was obtained as an off-white solid in 71% yield (1.91 g). mp 186-188 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 9.89 (s, 1H), 9.34 (s, 1H), 9.20 (s, 1H), 8.36 (d, J = 4.3 Hz, 1H), 7.98-7.95 (m, 1H), 7.91-7.77 (m, 4H), 7.61-7.55 (m, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.39 (d, J = 7.0 Hz, 1H), 7.32-7.28 (m, 1H), 7.17-7.14 (m, 1H), 4.93-4.81 (m, 2H), 1.29 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, d7-DMF): δ 159.2, 156.7, 155.7, 152.1, 151.4, 148.5, 148.4, 142.6, 141.1, 137.7, 136.9, 134.3, 133.3, 132.2, 132.2, 131.6, 131.2, 129.7, 128.7, 128.7, 122.8, 122.3, 121.8, 112.1, 54.2, 46.4; IR (neat) 3323, 3297, 3260, 2979, 1581, 1545, 1528, 1324, 1141, 743 cm^{-1}; HRMS (ESI) m/z: 603.1172 calcd for $C_{29}H_{28}BrN_6O_2S$ $[M+H]^+$, found 603.1151.

Preparation of N-(*tert*-butyl)-5-(5-(4-fluorophenyl)-4-((pyridin-2-ylmethyl)amino)quinazolin-2-yl)pyridine-3-sulfonamide (**19c**). The title compound was obtained as a white solid in 81% yield (1.96 g). mp 190-192 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 9.89 (s, 1H), 9.34 (s, 1H), 9.19 (s, 1H), 8.32 (d, J = 4.6 Hz, 1H), 7.96-7.92 (m, 1H), 7.90-7.85 (m, 2H), 7.81-7.77 (m, 1H), 7.67-7.63 (m, 2H), 7.45-7.40 (m, 3H), 7.37-7.34 (m, 1H), 7.33-7.28 (m, 1H), 7.12 (s, 1H), 4.85 (d, J = 3.4 Hz, 2H), 1.29 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, d7-DMF): δ 163.3 (d, J = 245 Hz), 159.5, 156.8, 155.9, 152.3, 151.6, 148.5 (d, J = 20 Hz), 141.3, 138.5, 137.0, 136.8 (d, J = 4 Hz), 134.5, 133.4, 132.3, 131.9, 131.8, 130.0, 128.5, 122.5, 122.1, 116.2 (d, J = 21 Hz), 112.4, 54.4, 46.5; IR (neat) 3366, 3297, 2975, 1515, 1137, 752, 665 cm^{-1}; HRMS (ESI) m/z: 543.1973 calcd for $C_{29}H_{28}FN_6O_2S$ $[M+H]^+$, found 543.1955.

Preparation of N-(*tert*-butyl)-5-(5-(4-methoxyphenyl)-4-((pyridin-2-ylmethyl)amino)quinazolin-2-yl)pyridine-3-sulfonamide (**19d**). The title compound was obtained as a white solid in 73% yield (1.81 g). mp 162-164 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 9.87 (s, 1H), 9.33 (s, 1H), 9.19 (s, 1H), 8.31 (d, J = 4.3 Hz, 1H), 7.93-7.89 (m, 1H), 7.88-7.83 (m, 2H), 7.81-7.75 (m, 1H), 7.49 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 7.0 Hz, 1H), 7.31-7.26 (m, 1H), 7.18-7.10 (m, 3H), 4.84 (d, J = 3.7 Hz, 1H), 3.92 (s, 3H), 1.29 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, d7-DMF): δ 160.3, 159.8, 156.7, 156.2, 152.3, 151.6, 148.6, 148.5, 141.3, 139.5, 136.9, 145.6, 133.4, 132.5, 132.3, 130.9, 129.9, 128.1, 122.5, 122.0, 114.8, 112.5. 55.3, 54.4, 46.7; IR (neat) 3347, 3271, 2977, 2837, 1578, 1526,

1149, 987, 742, 663 cm^{-1}; HRMS (ESI) m/z: 555.2173 calcd for $C_{30}H_{31}N_6O_3S$ $[M+H]^+$, found 555.2157.

Preparation of N-(*tert*-butyl)-5-(4-((pyridin-2-ylmethyl)amino)-5-(m-tolyl)quinazolin-2-yl)pyridine-3-sulfonamide (**19e**). The title compound was obtained as a white solid in 70% yield (1.68 g). mp 150-152 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 9.88 (s, 1H), 9.34 (s, 1H), 9.19 (s, 1H), 8.34 (d, 4.3 Hz, 1H), 7.96-7.92 (m, 1H), 7.89-7.86 (m, 2H), 7.80-7.75 (m, 1H), 7.46-7.34 (m, 6H), 7.30-7.26 (m, 1H), 7.02 (s, 1H), 4.90-4.80 (m, 2H), 2.40 (s, 3H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, d7-DMF): δ 159.7, 156.7, 156.3, 152.3, 151.6, 148.8, 148.6, 141.3, 140.5, 139.8, 139.1, 136.9, 134.6, 133.4, 132.3, 130.2, 129.7, 129.4, 128.3, 126.6, 122.4, 121.9, 112.3, 54.5, 46.7, 20.1; IR (neat) 3306, 3283, 2977, 2863, 1578, 1324, 1139, 740, 665 cm^{-1}; HRMS (ESI) m/z: 539.2224 calcd for $C_{30}H_{31}N_6O_2S$ $[M+H]^+$, found 539.2209.

Preparation of N-(*tert*-butyl)-5-(4-((pyridin-2-ylmethyl)amino)-5-(p-tolyl)quinazolin-2-yl)pyridine-3-sulfonamide (**19f**). The title compound was obtained as a white solid in 66% yield (1.58 g). mp 171-173 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 9.89 (s, 1H), 9.34 (s, 1H), 9.20 (s, 1H), 8.35 (d, J = 4.6 Hz, 1H), 7.94-7.91 (m, 1H), 7.89-7.85 (m, 2H), 7.79-7.75 (m, 1H), 7.45-7.42 (m, 2H), 7.40-7.35 (m, 3H), 7.35-7.32 (m, 1H), 7.30-7.27 (m, 1H), 7.03 (s, 1H), 4.86 (d, J = 3.7 Hz, 2H), 2.46 (s, 3H), 1.30 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, d7-DMF): δ 159.7, 156.2, 152.3, 151.6, 148.7, 148.5, 141.3, 139.6, 138.4, 137.6, 136.9, 134.6, 133.4, 132.3, 130.0, 129.8, 129.5, 128.2, 122.4, 122.0, 112.4, 54.4, 46.8, 20.9; IR (neat) 3345, 3323, 3303, 2975, 1579, 1530, 1327, 1154, 994, 743, 667 cm^{-1}; HRMS (ESI) m/z: 539.2224 calcd for $C_{30}H_{31}N_6O_2S$ $[M+H]^+$, found 539.2204.

Preparation of 5-(5-(1H-indol-5-yl)-4-((pyridin-2-ylmethyl)amino)quinazolin-2-yl)-N-(*tert*-butyl)pyridine-3-sulfonamide (**19g**). The title compound was obtained as a white solid in 77% yield (1.94 g). mp >250 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 11.39 (s, 1H), 9.87 (s, 1H), 9.34 (s, 1H), 9.19 (s, 1H), 7.95-7.92 (m, 1H), 7.89-7.84 (m, 2H), 7.78 (s, 1H), 7.68 (d, J = 4.6 Hz, 1H), 7.64-7.58 (m, 3H), 7.42 (d, J = 6.7 Hz, 1H), 7.26-7.21 (m, 3H), 7.11-7.07 (m, 1H), 6.62 (s, 1H), 4.80-4.75 (m, 2H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, d7-DMF): δ 160.0, 156.6, 156.1, 152.3, 151.5, 148.5, 141.4, 141.3, 136.8, 136.6, 134.7, 133.4, 132.1, 131.2, 130.2, 129.0, 127.8, 126.7, 122.7, 122.1, 121.5, 121.1, 112.8, 112.4, 102.2, 54.4, 46.7; IR (neat) 3414, 3321, 3291, 2979, 1575, 1525, 1327, 1147, 1000, 741 cm^{-1}; HRMS (ESI) m/z: 564.2176 calcd for $C_{31}H_{30}N_7O_2S$ $[M+H]^+$, found 564.2153.

Preparation of N-(*tert*-butyl)-5-(5-(naphthalen-2-yl)-4-((pyridin-2-ylmethyl)amino)quinazolin-2-yl)pyridine-3-sulfonamide (**19h**). The title compound was obtained as a white solid in 86% yield (2.21 g). mp 168-170 °C. ^{1}H NMR (500 MHz, d7-DMF): δ 9.90 (s, 1H), 9.35 (s, 1H), 9.19 (s, 1H), 8.22 (s, 1H), 8.12-8.09 (m, 3H), 8.02-7.99 (m, 1H), 7.97-7.94 (m, 1H), 7.93 (s, 1H), 7.70-7.60 (m, 4H), 7.49 (d, J = 7.0 Hz, 1H), 7.32-7.27 (m, 2H), 7.11-7.08 (m, 1H), 7.01-6.97 (m, 1H), 4.82-4.78 (d, J = 13.7 Hz, 2H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (125.8 MHz, d7-DMF): δ 159.5, 156.7, 155.4, 152.1, 151.5, 148.4, 147.8, 141.1, 139.5, 138.1, 136.5, 134.4, 133.9, 133.4, 133.3, 132.2, 129.8, 129.0, 128.5, 128.4, 128.3, 128.1, 127.4, 126.8, 126.7, 121.9, 121.5, 112.3, 54.2, 46.3; IR (neat) 3338, 2975, 1621, 1579, 1525, 1329, 1149, 1007, 745, 665 cm^{-1}; HRMS (ESI-TOF) m/z: 575.2224 calcd for $C_{33}H_{31}N_6O_2S$ $[M+H]^+$, found 575.2199.

General Procedure for the C-H Activation of other aromatic bicyclic compounds: To an 8 mL scintillation vial with stir bar was added the corresponding heterocycle (1 mmol), $Pd(OAc)_2$ (0.05 equiv), cesium pivalate (1 equiv to 1.5 equiv), (hetero)aryliodide (12 equiv), and anisole (10 mL). The vial was capped with a pressure relief septa. The reaction mixture was heated to 120 °C until complete conversion was observed, as judged by UPLC-MS (~16 h). An aqueous wash, water (4 mL) was performed. The reactions were concentrated en vacuo and purified by column chromatography using DCM/MeOH.

Preparation of 2,5-diphenyl-N-(pyridin-2-ylmethyl)quinazolin-4-amine (**20a**). The title compound was obtained as a white solid in 76% yield (295 mg). mp 133-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, J=7.3 Hz, 2H), 8.30 (d, J=5.0 Hz, 1H), 7.98 (dd, J=8.5, 1.1 Hz, 1H), 7.71 (dd, J=8.3, 7.3 Hz, 1H), 7.60 - 7.47 (m, 9H), 7.24 - 7.11 (m, 3H), 6.55 (br s, 1H), 4.83 (d, J=4.5 Hz, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 160.1, 159.4, 156.6, 152.0, 148.6, 140.9, 138.9, 138.7, 136.3, 131.2, 130.0, 129.4, 128.9, 128.4, 128.4, 128.3, 128.2, 128.1, 121.9, 121.4, 112.0, 46.7; IR (neat) 3355, 3336, 3056, 2854, 1519, 830, 767, 748, 711, 687 cm^{-1}; HRMS (ESI-TOF) m/z: 389.1761 calcd for $C_{26}H_{21}N_4$ $[M+H]^+$, found 389.1767.

Preparation of 2-methyl-5-phenyl-N-(pyridin-2-ylmethyl)quinazolin-4-amine (**20b**). The title compound was obtained as a white solid in 42% yield (136 mg). mp 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, J=4.8 Hz, 1H), 7.69 (dd, J=8.3, 1.3 Hz, 1H), 7.54 (t, J=7.4 Hz, 1H), 7.45 (t, J=7.2 Hz, 1H), 7.38-7.29 (m, 6H), 7.21-7.21 (m, 1H), 7.20-7.19 (m, 1H), 7.19 (s, 1H), 7.09-6.97 (m, 3H), 6.48 (br s, 1H), 4.55 (d, J=4.3 Hz, 2H), 2.55 (s, 3H), 2.50 (s, 1H), 2.06 (s, 1H), 1.16 (s, 1H), 0.65-2.13 ppm (m, 1H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 163.9, 159.1, 156.1, 151.3, 148.5, 140.8, 138.6, 136.3, 131.1, 129.3, 128.8, 128.0, 128.0, 127.2, 121.8, 121.5, 111.2, 46.4, 26.3; IR (neat) 3345, 3059, 2919, 2854, 1521, 1359, 1154, 828, 761, 696 cm^{-1}; HRMS (ESI-TOF) m/z: 327.1604 calcd for $C_{21}H_{19}N_4$ $[M+H]^+$, found 327.1607.

Preparation of 8-phenyl-N-(pyridin-2-ylmethyl)naphthalen-1-amine (**20c**). The title compound was obtained as a light brown oil in 44% yield (136 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72-8.69 (m, 1H), 8.08 (dd, J=8.2, 1.4 Hz, 1H), 7.75-7.80 (m, 3H), 7.56-7.71 (m, 6H), 7.46 (dd, J=7.1, 1.5 Hz, 1H), 7.35 (ddd, J=7.5, 4.9, 1.3 Hz, 1H), 7.26 (d, J=7.8 Hz, 1H), 6.78 (dd, J=7.3, 1.3 Hz, 1H), 5.15 (br s, 1H), 4.67-4.49 (m, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 158.4, 149.0, 144.6, 143.6, 138.1, 136.5, 136.0, 129.4, 128.9, 128.6, 128.2, 127.4, 127.0, 124.6, 121.9, 121.1, 120.9, 117.8, 105.6, 50.1; IR (neat) 3345, 3055, 3012, 2993, 1519, 1359, 1154, 761, 696 cm^{-1}; HRMS (ESI-TOF) m/z: 311.1558 calcd for $C_{22}H_{19}N_2$ $[M+H]^+$, found 311.1543.

Preparation of 5-phenyl-N-(pyridin-2-ylmethyl)-2-(trifluoromethyl)quinolin-4-amine (**20d**). The title compound was obtained as an off-white solid in 49% yield (185 mg). mp 141-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J=5.1 Hz, 1H), 8.11 (dd, J=8.5, 1.4 Hz, 1H), 7.65 (t, J=7.5 Hz, 1H), 7.58 (t, J=7.4 Hz, 1H), 7.44 (s, 5H), 7.29-7.24 (m, 1H), 7.13 (dd, J=6.8, 5.1 Hz, 1H), 7.05 (d, J=7.8 Hz, 1H), 6.68 (s, 1H), 6.32 (br s, 1H), 4.32 ppm (d, J=4.0 Hz, 2H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 154.8, 152.0, 149.0, 148.8, 148.4, 141.2, 138.3, 136.5, 130.3, 129.8, 129.4, 128.8, 128.7, 128.0, 122.3, 122.0 (q, J = 337 Hz),121.3, 116.7, 95.3 (q, J = 4 Hz), 48.3; IR (neat) 3351, 3064, 3012, 2881, 1587, 1532, 1443, 1288, 1175, 1128, 953, 824, 765 cm^{-1}; HRMS (ESI) m/z: 380.1369 calcd for $C_{22}H_{17}F_3N_3$ $[M+H]^+$, found 380.1380.

ASSOCIATED CONTENT

Supporting Information. Optimization data for the cross-couplings and C-H Activation, characterization data for all intermediates and API in the final route. This material is available free of charge via the Internet at http://pubs.acs.org.

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