JOC The Journal of Organic Chemistry

Article

Convergent Synthesis of the NS5B Inhibitor GSK8175 Enabled by Transition Metal Catalysis

Kenneth Arrington, Gregg A. Barcan, Nicholas A Calandra, Greg A. Erickson, Ling Li, Li Liu, Mark G. Nilson, Iulia I. Strambeanu, Kelsey Faith VanGelder, John L. Woodard, Shiping Xie, C. Liana Allen, John A. Kowalski, and David C. Leitch

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02269 • Publication Date (Web): 19 Oct 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Convergent Synthesis of the NS5B Inhibitor GSK8175 Enabled by Transition Metal Catalysis

Kenneth Arrington, Gregg A. Barcan, Nicholas A. Calandra, Greg A. Erickson, Ling Li, Li Liu, Mark G. Nilson, Iulia I. Strambeanu, Kelsey F. VanGelder, John L. Woodard, Shiping Xie, C. Liana Allen, John A. Kowalski,* and David C. Leitch*

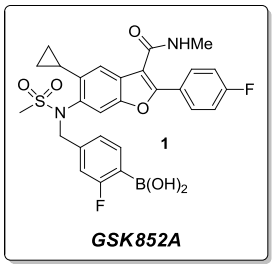
API Chemistry, GlaxoSmithKline, King of Prussia PA 19406.

ABSTRACT: A convergent eight-stage synthesis of the boron-containing NS5B inhibitor GSK8175 is described. The previous route involves 13 steps in a completely linear sequence, with an overall 10% yield. Key issues include a multi-day S_NAr arylation of a secondary sulfonamide using HMPA as solvent, multiple functional group interconversions after all of the carbon atoms are installed (including a Sandmeyer halogenation), use of carcinogenic chloromethyl methyl ether to install a protecting group late in the synthesis, and an unreliable Pd-catalyzed Miyaura borylation as the penultimate step. We have devised an orthogonal approach using a Chan-Lam coupling between a halogenated aryl pinacol boronate ester and an aryl methanesulfonamide. This reaction is performed using a cationic Cu(I) precatalyst, which can be easily generated *in situ* using KPF_6 as a halide abstractor. High-throughput screening revealed a new Pd catalyst system to effect the penultimate borylation chemistry using simple monodentate phosphine ligands, with $PCyPh_2$ identified as optimal. Reaction progress analysis of this borylation indicated likely mass-transfer rate limitations under standard conditions using KOAc as the base. We have devised a K_2CO_3 / pivalic acid system as an alternative, which dramatically outperforms the standard conditions. This new synthesis proceeds in eight stages with a 20% overall yield.

Introduction.

Hepatitis C is a potentially life-threatening viral infection that afflicts ~2% of the world's population, with >500,000 deaths per year attributed to complications from the disease.[1] While there is currently no vaccine for the Hepatitis C virus (HCV), there are several approved treatments for the condition, some of which are able to achieve cure rates of >90%.[2] Because of the need for increasing patient access, particularly in developing nations, and to combat potential viral resistance to current medicines, development of alternative treatments is imperative.

One important class of HCV therapeutics is the NS5B inhibitors, which operate by blocking the RNA polyermase activity of the NS5B viral enzyme.[3] There are both nucleoside analog[2a,4] and non-nucleoside analog[5] Active Pharmaceutical Ingredients (APIs) either in development or approved for use. Previously, we reported the synthesis of a non-nucleoside analog NS5B inhibitor based on a substituted benzofuran scaffold (GSK852A, **1**, Figure 1).[6] A key structural feature of this compound is a boronic acid moiety,[7] which contributes to the compound's potency. Here we report on the synthesis of a more advanced benzofuran-based NS5B inhibitor, GSK8175 (**2**), which retains the boron-containing functionality, but removes the metabolically labile methylene linker between the sulfonamide nitrogen and the pendant arene.[8]



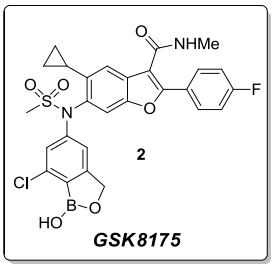
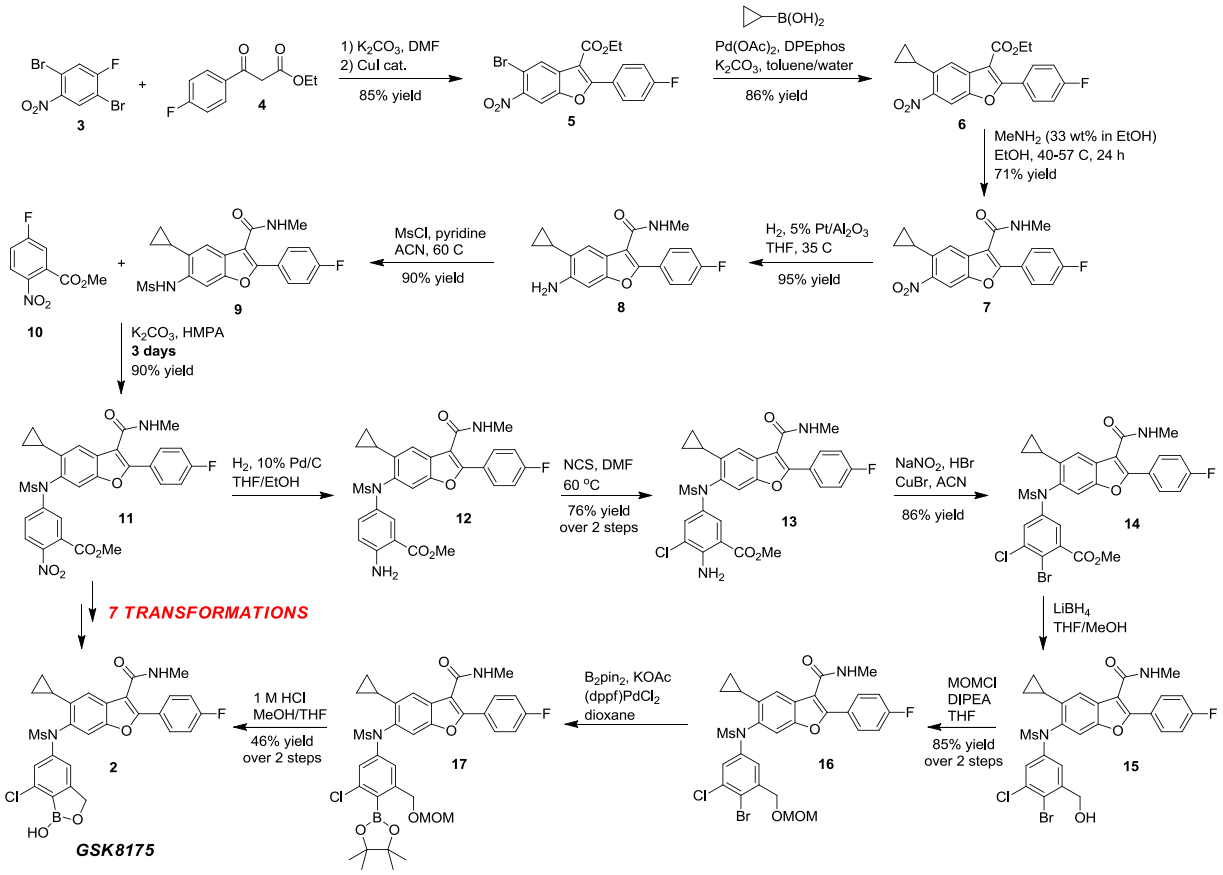


Figure 1. Structures of two benzofuran-derived NS5B inhibitors containing boronic acid motifs.

The initial synthesis of **2** is shown in Scheme 1. The first half is based heavily on our previously reported route to **1**, and is identical up to the common intermediate **8**. At this point in the synthesis of **1**, a reductive amination and mesylation of the aryl/alkyl secondary amine completes the sequence.[6b] For the preparation of **2**, the aniline **8** is first mesylated prior to installation of the final arene via S_NAr substitution using **10;** this affords the advanced intermediate **11**, which contains all of the carbon atoms present in the API. From this point, there are *seven* more transformations required to complete the synthesis, including a Sandmeyer halogenation and use of the potent carcinogen chloromethyl methyl ether (MOMCl).

Scheme 1. Initial synthesis of GSK8175 (2); half of the steps occur after assembling the entire carbon framework.



Due to this highly atom, step, and redox inefficient sequence to convert **11** into **2**, we sought an alternative endgame that would avoid this series of functional group interconversions. Of particular importance was removing the Sandmeyer sequence, which could be achieved by directly coupling an appropriately halogenated aromatic substrate with **9** (or analog thereof). Unfortunately, S_NAr reactions between **9** and fluoroaromatics without the *para*-nitro functionality have been unsuccessful. Even the initial S_NAr is difficult, requiring multiple days to reach completion with HMPA as the solvent; alternative conditions that replace HMPA with less toxic solvents are considerably lower yielding. Palladium- or copper-catalyzed arylation of **9** was also considered; however, chemoselectivity in the presence of multiple halides was a significant concern, especially given the reactivity trends established by Buchwald for biarylphosphine-based Pd catalysts.[9] Furthermore, catalytic C-N coupling using secondary sulfonamides is not well developed, particularly with *N*-arylsulfonamides.[10] Initial attempts to couple even simple aryl-halides to **9** were not successful. Finally, while we were able to arylate **8** using Pd-catalysis, mesylation of the resulting diarylamines proved low yielding due to the propensity of the diarylmethanesulfonamides to demesylate when using strong base.[11]

Thus, we envisioned a new synthetic sequence with four general attributes (Figure 2). First, given the efficiency of the benzofuran synthesis from previous development work on **1**, we intended to retain/adapt as much of that chemistry as possible. Second, because our initial scoping studies indicated mesylation of a diarylamine would be overly difficult, mesylation must precede *N*-arylation. Third, *N*-arylation would need to be achieved with a reaction that could function with both a sulfonamide and a multiply-halogenated aromatic; for this we investigated a Cu-catalyzed Chan-Lam coupling, which is orthogonal to redox-neutral C-N coupling reactions.[12] Finally, Pd-catalyzed borylation must occur at the end of the synthesis due to the instability of arylboronate esters toward many reaction and work-up conditions.[13] This borylation would need to be performed at a hindered position, in the presence of an Ar-Cl group, with a benzyl alcohol protecting group other than MOM.

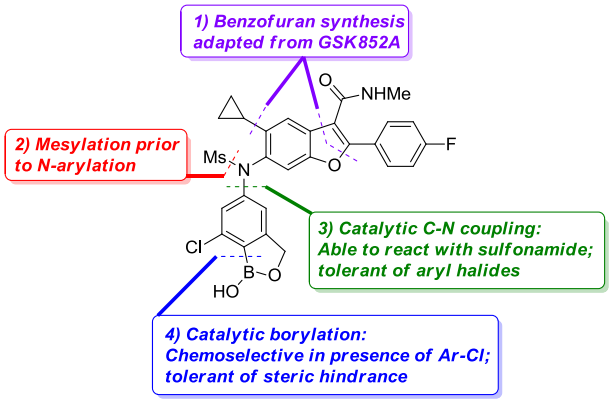
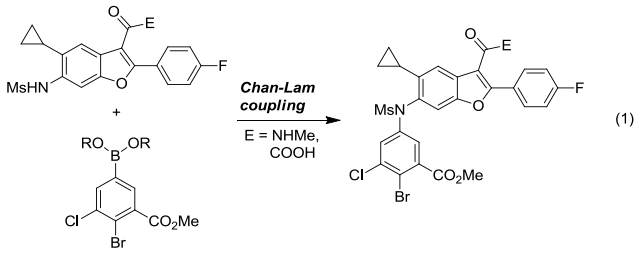


Figure 2. Key disconnection sequence in a new synthesis of **2**.

Results and Discussion.

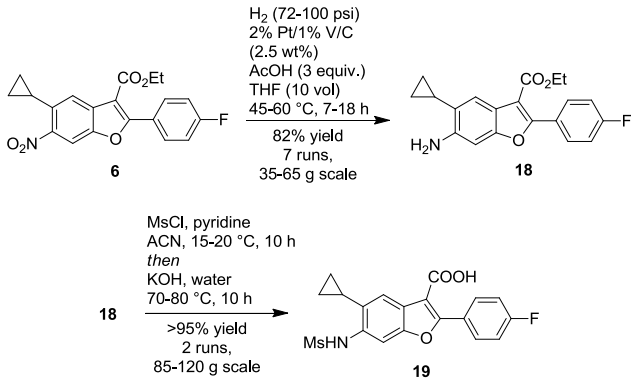
Preparation of Chan-Lam coupling partners. In order to effect the difficult *N*-arylation chemistry required for our improved synthesis of **2**, we focused our efforts on a Chan-Lam coupling strategy. The Chan-Lam reaction is an oxidative C-N coupling between an arylboronic acid (or boronate ester) and a nitrogen nucleophile that operates under much milder conditions than redox neutral Pd- or Cu-catalyzed *N*-arylations.[12] The Chan-Lam is thus an orthogonal coupling strategy, allowing use of a halogenated coupling partner. Our goal was to intercept the current chemistry at intermediate **14**, and therefore we needed to access the appropriate substrates (equation 1).



(1)

While coupling sulfonamide **9** would provide the most direct method, concerns regarding chemoselectivity of the *N*-arylation in the presence of two N-H nucleophiles prompted the synthesis of the carboxylic acid analogue **19**. This was achieved in >78% yield over two steps from **6** by hydrogenation of the nitro group to **18**, followed by a one-pot mesylation / saponification sequence (Scheme 2).

Scheme 2. Three-step, two-pot sequence for the preparation of 19.

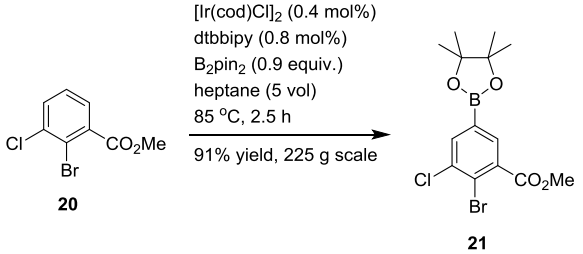


Initially, we planned to adapt the existing hydrogenation conditions for the conversion of **7** to **8** to the reduction of **6** (Scheme 1); however, using the previously identified 5% Pt/Al_2O_3 catalyst required long reaction times to reach completion (>48 hours). We therefore screened twenty different Pt-based hydrogenation catalysts on 0.1 mmol scale under a number of reaction conditions, and identified several Pt/C alternatives capable of achieving completion in <8 hours without competing hydrogenolysis of the cyclopropane ring. The use of a 2% Pt/1% V/C catalyst (Noblyst P8071, 2.5 wt% loading) and the addition of 3 equivalents of acetic acid were deemed optimal. These conditions were validated on 35-65 g scale in multiple runs to give a combined isolated yield of 82%.

Following the hydrogenation, mesylation of the primary aniline was achieved under analogous conditions to conversion of **8** to **9**; however, rather than isolate this mesylated intermediate, we opted to directly hydrolyze the ethyl ester in a one-pot protocol. After the mesylation reaction is complete, the reaction mixture is concentrated to ~5 volumes, followed by the addition of aqueous KOH (6.75 equiv). An 8 hour reaction time at 70-80 °C is sufficient to completely saponify the ethyl ester. A simple organic extraction to remove impurities followed by acidification of the alkaline aqueous solution provides **19** in >95% isolated yield. This three-step, two-pot sequence allows rapid, reliable, and high-yielding access to the key sulfonamide coupling partner for the ensuing Chan-Lam chemistry.

For the aryl boronate coupling partner, we envisioned a selective Ir-catalyzed C–H borylation[14] of methyl-3-bromo-2-chlorobenzoate (**20**) as the most efficient synthetic method. This enables formation of the C-B bond in the presence of both Ar-Cl and Ar-Br groups, with the required regiochemistry, in a single step. While the use of an Ir-catalyst is of concern from a cost perspective, the low catalyst loadings needed for C-H borylation coupled with the lack of attractive alternative syntheses gave us confidence in our approach to this material.

As a proof of concept, we first evaluated standard literature[15] borylation conditions: 1 mol% $[Ir(cod)OMe]_2$, 2 mol% 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbbipy), with B_2pin_2 as the boron source, and a heptane/TBME solvent system to ensure complete dissolution of **20**. After only one hour at 50 °C, conversion to **21** was complete, and no other borylated products were observed. In order to turn these initial conditions into a scalable process, we first evaluated replacing $[Ir(cod)OMe]_2$ with the more widely available $[Ir(cod)Cl]_2$, and dtbbipy with 2,2'-bipyridine (bipy). Previous reports have indicated that preactivation of $[Ir(cod)Cl]_2$/ligand mixtures with B_2pin_2 at elevated temperature in the absence of substrate leads to an active catalyst system.[16] Thus, heating $[Ir(cod)Cl]_2$/ dtbbipy/B_2pin_2 at 85 °C in heptane for 30 minutes prior to introduction of **20** (as a heptane solution) is highly effective; unfortunately, we did not achieve comparable success with bipy as the ligand. At these temperatures, TBME (or another co-solvent) is not required to maintain solubility of **20**, enabling maximum catalyst efficiency (various co-solvents were observed to decrease reactivity). Notably, we observed that grinding the crystalline $[Ir(cod)Cl]_2$ into a fine powder prior to use resulted in a more active catalyst, likely due to faster solubilization in heptane during the activation period.[17] This allowed us to reduce the catalyst loading to 0.4

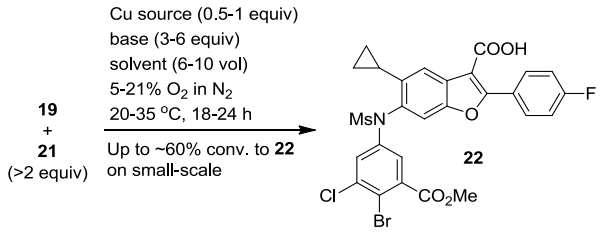


(2)

mol% $[Ir(cod)Cl]_2$ and 0.8 mol% dtbbipy. The optimized reaction conditions are shown in equation 2, and have been demonstrated on >225 g scale with 91% isolated yield after crystallization from acetonitrile/water.

Development of the Chan-Lam coupling. With reliable synthetic routes to both **19** and **21** in place, we focused considerable effort on developing the Chan-Lam coupling reaction. Figure 3 summarizes the key findings of a series of preliminary small-scale screening experiments that explored the effect of Cu source, base, and reaction solvent on the conversion of **19** into **22**. In all cases, an excess of the arylboronate **21** was required, generally ≥2 equivalents. From these experiments, we selected acetonitrile and triethylamine as the preferred solvent and base, and established that the reaction must be run in the presence of O_2. We also discovered that cationic Cu(I) salts generally outperform other Cu(I) or Cu(II) sources in the Chan-Lam arylation of secondary sulfonamides.[18] Standard Chan-Lam conditions typically employ a stoichiometric amount of $Cu(OAc)_2$, which acts as both catalyst and oxidant. In the coupling of **19** and **21**, all Cu(II) sources achieved relatively poor conversion.

We attribute the superiority of cationic Cu(I) sources to the absence of potentially competing X-type ligands (AcO^-, Cl^-, etc.) that could inhibit coordination of the sulfonamide. Subsequent experiments indicated that both $[Cu(ACN)_4]OTf$ and $[Cu(ACN)_4]PF_6$ can be used interchangably in this transformation. Adding ligands (such as 2,2'-bipyridine), reducing the Cu loading below 0.5 equivalents, and using alternative oxidants (such as Ag_2CO_3 or H_2O_2/urea) all led to lower conversions of **19**.



Cu sources	*Bases*	*Solvents*
CuI	Na_2CO_3	**DCM**
CuOAc	$NaHCO_3$	**ACN**
$[Cu(ACN)_4]OTf$	K_2CO_3	DMSO
$[Cu(ACN)_4]PF_6$	K_3PO_4	toluene
$Cu(OAc)_2$	**NEt_3**	dioxane
$CuSO_4$	***N*-methylpiperidine**	MeTHF
$Cu(ClO_4)_2$	*N,N*-diethylmethylamine	
$Cu(OTf)_2$		

Figure 3. Summary of preliminary screening experiments, with most effective materials highlighted in blue. See Supporting Information for further details.

Even using the best reaction conditions identified from screening, we were unable to achieve >60% conversion of **19** into **22** before the reaction progress stalled. We did observe that in many cases all of the boronate ester **21** was consumed despite the excess charge, and that multiple byproducts were formed during the course of the reaction. We observed both compound **20** and the phenol **23**, and hypothesize that non-polar byproducts seen in HPLC traces correspond to biaryl **24** and/or the diarylether **25** (such oxidative coupling products are commonly observed in Chan-Lam couplings[12]). These protonolytic or oxidative byproducts explain both the need for excess **21**, and for the premature termination of reaction progress. Reducing the reaction temperature to ≤10 °C improved the solution yield to 70%; however, the reaction time needed increased to >48 hours (equation 3).

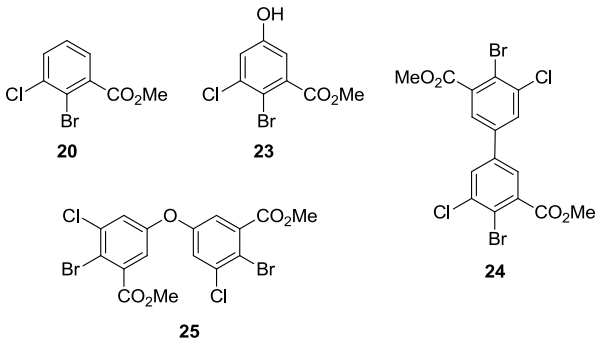
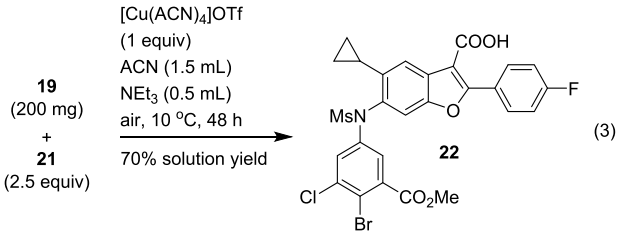


Figure 4. Potential byproducts of Chan-Lam couplings resulting from decomposition of **21**.



Despite these initial promising results, we quickly identified a key issue with the conditions in equation 3. Using only 10 volumes of solvent (4:1 acetonitrile/triethylamine), the reaction mixture is heterogeneous. Both compound **21** and $[Cu(ACN)_4]PF_6$ are highly soluble in acetonitrile (>100 mg/mL), whereas **19** is poorly soluble (2.7 mg/mL). Furthermore, under these conditions the initial rates and overall extents of reaction are invariant when the charges of **19**, **21**, or $[Cu(ACN)_4]PF_6$ are changed.

In order to improve the outcome and the scalability of this reaction, we explored the solution behavior of **19** in a series of control and solubility experiments. As noted above, **19** has only 2.7 mg/mL solubility in acetonitrile; however, in the presence of excess triethylamine it should predominantly exist as the triethylammonium carboxylate. We therefore determined the solubility of **19** in a 4:1 mixture of acetonitrile and triethylamine, mirroring the Chan-Lam reaction solvent system. Upon addition of triethylamine to a slurry of **19** in acetonitrile, all of the solid dissolves quickly, but a tan precipitate forms shortly thereafter. HPLC analysis of the supernatant after stirring this mixture for >1 hour reveals the solution concentration of **19** (and/or the corresponding triethylammonium carboxylate) is only 2.8 mg/mL.

A series of observations during Chan-Lam reaction setup led us to investigate the solubility of **19** in the presence immediately turns dark green. We attribute this behavior

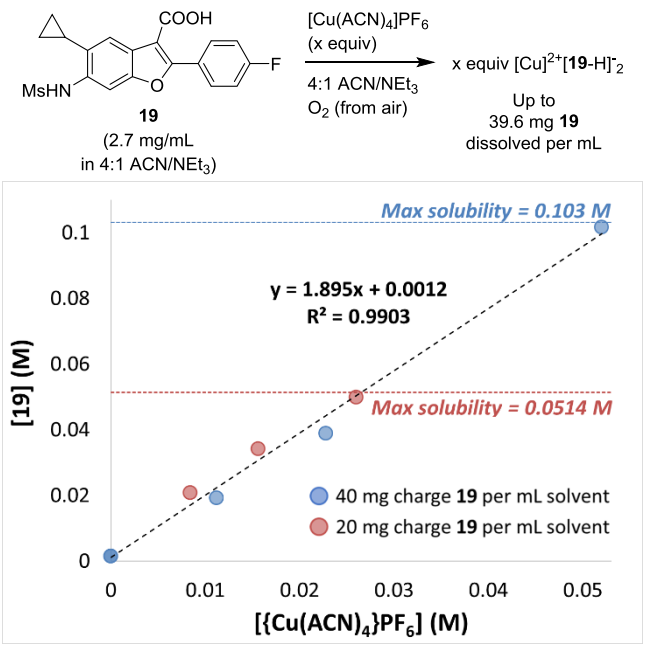


Figure 5. Solubility of compound **19** in a 4:1 ACN/NEt_3 solvent mixture versus amount of $[Cu(ACN)_4]PF_6$ added, with maxmimum possible solubilities denoted based on charge of **19**. The slope of the line indicates **19** forms a 2:1 complex with Cu.

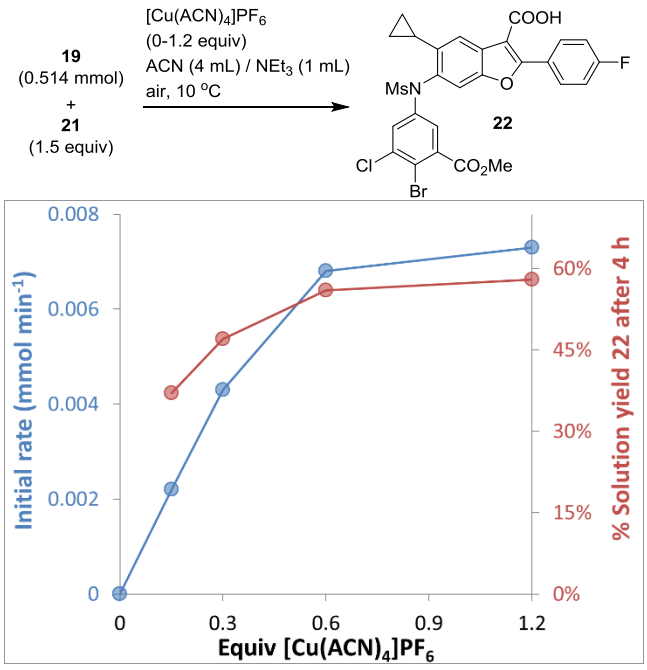


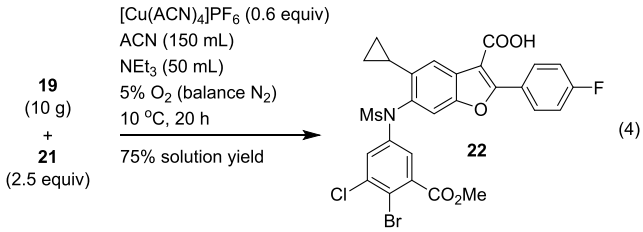
Figure 6. Initial rate of Chan-Lam coupling (left axis, blue points) and solution yield of **22** at 8 hours (right axis, red points) versus equiv $[Cu(ACN)_4]PF_6$.

to the oxidation of Cu(I) by air to generate a 2:1 complex between the anion of **19** and a Cu(II) center. This has the effect of dramatically increasing the amount of **19** in solution: quantitative HPLC analysis of a saturated solution of **19** (250 mg) with 0.6 equiv $[Cu(ACN)_4]PF_6$ (143 mg) in ACN/NEt_3 (4/1 mL) indicates 188.5 mg **19** is dissolved (solubility = 37.7 mg/mL, 0.0968 M). Notably, no color change or solubilization is observed when **19** and $[Cu(ACN)_4]PF_6$ are stirred in ACN/NEt_3 under N_2, confirming the necessity of O_2 to oxidize the Cu(I) source to Cu(II).

To further test our hypothesis of 2:1 complex formation between an *in situ* generated Cu(II) center and the anion of **19**, we measured the solution concentration of **19** in 4:1 ACN/NEt_3 in the presence of varying amounts of $[Cu(ACN)_4]PF_6$ (Figure 5). These experiments were done with two different charges of **19** (20 mg and 40 mg per mL of solvent), and each of these had three different loadings of $[Cu(ACN)_4]PF_6$. A plot of the concentration of $[Cu(ACN)_4]PF_6$ (based on amount charged) versus the concentration of **19** (obtained by quantitative HPLC of the supernatant) is linear with a slope of 1.9, clearly indicating a 2:1 ratio of **19** to Cu in solution. The highest concentration of **19** observed, 39.6 mg/mL or 0.102 M, is within experimental error of the maximum solubility (37.7 mg/mL).

Given the correlation between the Cu loading and amount of dissolved **19**, we also assessed the influence of Cu loading on the Chan-Lam reaction itself (Figure 6). Both the initial rate of product formation and the extent of reaction after complete consumption of **21** (8 h time point) increase with amount of $[Cu(ACN)_4]PF_6$ added up to 0.6 equiv; increasing the charge to 1.2 equiv has little impact on either the initial rate or yield. While a detailed kinetic study is required to elucidate the reaction mechanism, it is clear that the optimal amount of Cu is 0.5-0.6 equiv.

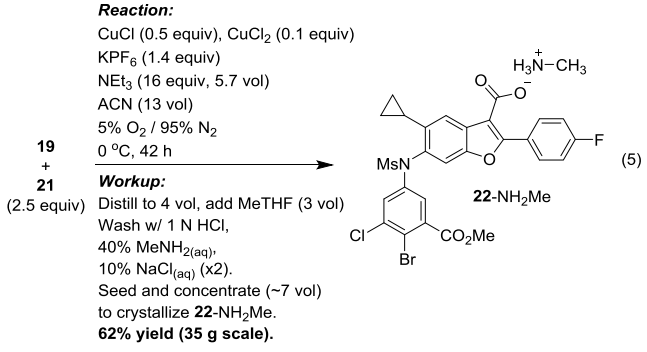
After establishing the appropriate reaction concentration to produce a homogeneous solution, and the optimal Cu charge of 0.5-0.6 equivalents, several additional features of the Chan-Lam reaction required process improvements. Due to safety concerns with using air, we explored the use of 5% O_2 (balance N_2) as an alternative. Previous work has established the limiting oxygen concentration (LOC) for acetonitrile to be 12-13%;[19] thus, a 5% O_2 (balance N_2) gas stream is >2-fold below the LOC for combustion of the reaction solvent. In addition, use of 5% O_2 instead of air performs well on multigram scale with overhead stirring: using a 10 g charge of **19**, a 75% solution yield of **22** was obtained after 20 hours (equation 4), which is a very similar extent of reaction to that achieved using air. Given these promising results, all further development work was conducted using 5% O_2.[20]



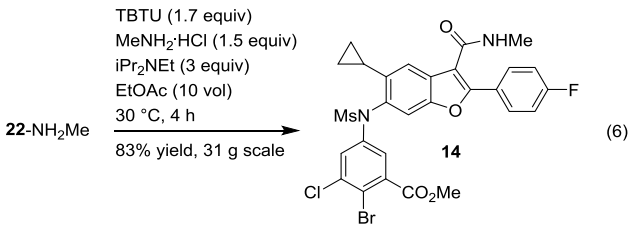
Another issue that needed to be addressed is the use of $[Cu(ACN)_4]PF_6$, especially since large quantities are costly and only available from a few suppliers. In order to access a cationic Cu(I) species *in situ*, we explored a number of options with Cu(I) salts and halide abstracting reagents. Traditional means of halide abstraction using Ag(I) salts such as $AgBF_4$ or AgOTf were deemed not suitable due to

cost issues, and the need to remove the resultant silver waste. Small-scale experiments led to the identification of KPF_6 in combination with CuCl as an effective replacement for $[Cu(ACN)_4]PF_6$. This system relies on the high solubility of KPF_6 in acetonitrile, and the insolubility of KCl, to drive the anion metathesis forward; accordingly, CuCl and KPF_6 were typically stirred in acetonitrile for ~30 minutes to complete halide abstraction. Unfortunately, this CuCl/KPF_6 system failed to reach acceptable solution yields of **22** upon scale-up, where we suspected the poor solubility of CuCl leads to slow halide abstraction. Use of CuX_2 (X = Cl, Br, I) instead of CuCl resulted in more consistent outcomes on multigram scales; however, we observed a significant new byproduct resulting from halogenation of the Ar-Bpin bond.[21] Iterative optimization led us to a mixed CuCl/$CuCl_2$ system in conjunction with KPF_6, which performs well on scale without the need to pre-mix the inorganics. While the exact nature of this catalyst system is still under investigation, we postulate that in the presence of O_2, **19**, and NEt_3, all of the Cu is oxidized to Cu(II) and complexed to anionic deprotonated **19**, while the chloride counterions are brought out of solution as KCl.

The final aspect of this Chan-Lam coupling that required development was the workup and isolation, particularly due to the formation of the decomposition byproducts (Figure 4). We determined that crystallization of an ammonium carboxylate salt of **22** would be the best method to reject the non-polar byproducts. Because the next synthetic step is amidation to form the *N*-methylamide **14** (*vide infra*), we targetted the *N*-methylammonium salt **22**-NH_2Me; this would avoid the need to completely remove an alternative amine that could interfere with the subsequent amidation. During optimization of the workup procedure, we discovered that unreacted **19** could be extracted into aqueous ammonia, leaving **22** (likely as its ammonium salt) in the organic phase. Further optimization established that 40% methylamine in water is also capable of extracting **19** into the aqueous phase, removing residual Cu, and forming the required ammonium salt with a single wash. Crystallization of **22**-NH_2Me purges the remaining byproducts, providing the desired product in >60% isolated yield and >95% purity (equation 5).



Completion of the synthesis with an improved borylation protocol. In order to elaborate the Chan-Lam coupling product **22** into the API (**2**), several additional steps required optimization. Amidation of **22** with methylamine would intercept the existing synthetic route at intermediate **14**. Initially, we employed TBTU[22] (1.6 equiv) as the coupling reagent using **22** as the free acid, along with methylammonium hydrochloride (1.5 equiv) and DIPEA (3 equiv), which gave **14** in >70% isolated yield on gram scale. However, switching to **22**-NH_2Me as isolated from the previous stage (along with extra methylammonium chloride) led to incomplete conversion. Screening other coupling reagents identified only COMU[23] as an equally effective alternate system, but still only partial conversion was observed. By charging excess NH_2Me-HCl (1.7 equiv) and TBTU (3 equiv), full conversion and 90% isolated yield was obtained on gram scale. This requirement for excess coupling reagent was traced to adventitious water in the batches of **22**-NH_2Me prepared via Chan-Lam coupling (Karl-Fisher titration indicated >6% water by weight). A simple re-slurry of **22**-NH_2Me in acetonitrile at 50 °C for several hours is able to dehydrate **22**-NH_2Me. By using dry input material, only modest excesses of NH_2Me-HCl (1.5 equiv) and TBTU (1.7 equiv) are required to achieve complete conversion, giving **14** in 83% yield on 30 g scale (equation 6).



With the development of this amidation chemistry, our new synthesis has intercepted a common intermediate (**14**) from the previous route in only six linear steps rather than nine. From **14**, the only required transformations are reduction of the methyl ester group, and installation of the boron moiety. The previously developed reduction conditions for the conversion of **14** to **15** ($LiBH_4$ in MeOH/ THF, Scheme 1) performed well, and so we focused our attention on developing a more robust borylation protocol.

Previous work had identified the methoxymethyl ether (MOM) protecting group as optimal for the borylation chemistry, which was carried out using a $Pd(OAc)_2$/dppb catalyst system under standard Miyaura borylation conditions (excess B_2pin_2, KOAc as base).[24] Conversion of **16** to **17** required multiple catalyst charges (up to 15 mol% Pd), and resulted in a significant degree of desbromination as a side pathway (up to 30%). Furthermore, the reaction outcome was variable even when using the same batches of input material. In order to address both the identity of the protecting group (to avoid the use of MOMCl), and the unreliable catalytic conditions, we designed a parallel-in-parallel set of screens to evaluate four different protecting groups and 48 different mono- and bidentate phosphine ligands using KOAc / toluene (Figure 7).

The 48 reaction set for each of the four substrates reveals several key insights into the Miyaura borylation chemistry. First, it is clear that protecting groups other than MOM are viable, with 2-tetrahydropyranyl (THP) emerging as the most attractive from these studies: not only does **26** prove

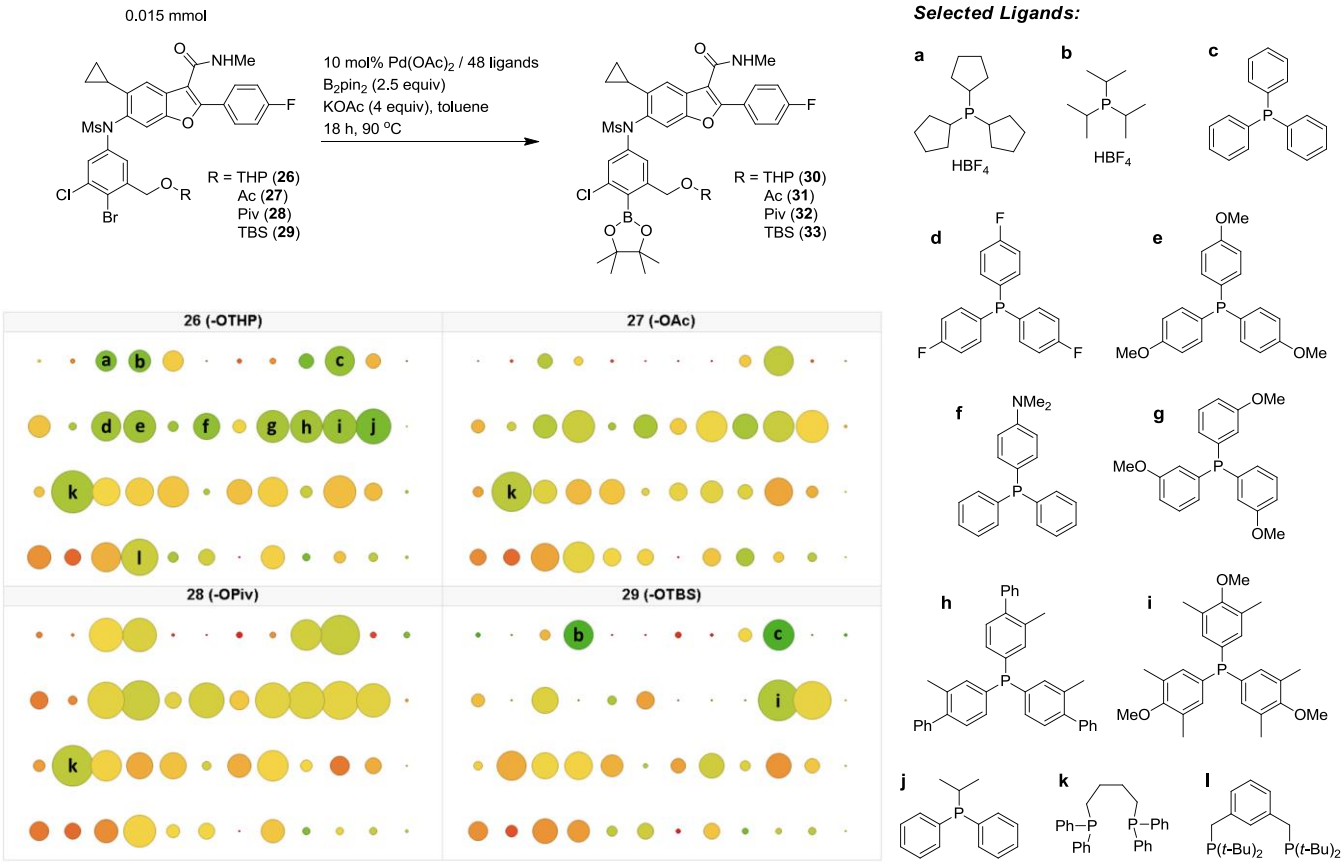


Figure 7. Parallel-in-parallel screening design to investigate the effect of both protecting group and phosphine ligand in the Miyaura borylation shown. The screening data are visualized with the size of the points corresponding to % product (larger is greater % product), and the color corresponding to % debromination observed (color gradient as follows: red: 100% desbromo; yellow: 25% desbromo; green: 0% desbromo). Ligands identified as hits are denoted with **a**-**l** in the visualization, with structures at right. See Supporting Information for full table of conditions and results.

more effective than the acetate (**27**), pivalate (**28**), or *tert*-butyldimethylsilyl (**29**) in the borylation, but installation and removal of the THP group can be readily achieved (*vide infra*). Second, while dppb is clearly the best bidentate ligand among the 24 investigated, there are several relatively simple monodentate ligands that are highly effective, including PPh_3 and $P(iPr)Ph_2$. Finally, debromination is observed in nearly every case, with many systems giving exclusively the desbromo byproduct; however, borylation of the Ar-Cl is not observed using these ligands.

In a follow-up screen focused on the THP-protected substrate (**26**), we assessed an expanded set of 33 monodentate ligands with different solvent and base combinations drawn from standard Miyaura borylation conditions in the literature (Figure 8).[25] Switching from toluene to CPME had little effect, while using NaOtBu led to undesirable reactivity regardless of the ligand used. The best ligand class emerging from these experiments is alkyldiphenylphosphine, with $P(iPr)Ph_2$ and $PCyPh_2$ as equally effective under screening conditions. All of the phosphines that show good reactivity are modestly electron rich, and not sterically bulky. That these features are desirable for this transformation is entirely consistent with the nature of the aryl halide substrate: the borylation must occur with high chemoselectivity for the hindered Ar-Br position over the adjacent Ar-Cl. Therefore, the ideal Pd(0) center is relatively unhindered, and will not readily undergo oxidative addition of an Ar-Cl bond. The suitability of phosphines such as $PCyPh_2$ and the others pictured in Figures 7 and 8 is consistent with these requirements.

Further studies identified Pd_2dba_3-$CHCl_3$ as the most active Pd source in combination with either $P(iPr)Ph_2$ or $PCyPh_2$. As observed elsewhere, the quality of the "Pd-dba" used is critical to the success of the reaction.[26] Commercial sources of "Pd_2dba_3", or "$Pd(dba)_2$" lead to lower conversion of starting material, and increased debromination as well as other byproducts. The chloroform solvate outperformed the alternatives.[27]

Having identified a suitable set of reaction conditions from high-throughput screening, our attention turned to reaction optimization on larger scale. A borylation reaction on 4 g scale was monitored over time using the Pd_2dba_3-$CHCl_3$ / $P(iPr)Ph_2$ catalyst system, with toluene and KOAc as the solvent and base respectively. A plot of reaction progress over time reveals linear kinetics for the consumption of starting material and generation of both desired product and desbromo byproduct (Figure 9). Despite a large catalyst charge (5 mol% Pd), complete conversion requires nearly 24 hours at 90 °C. Given both the linear kinetics

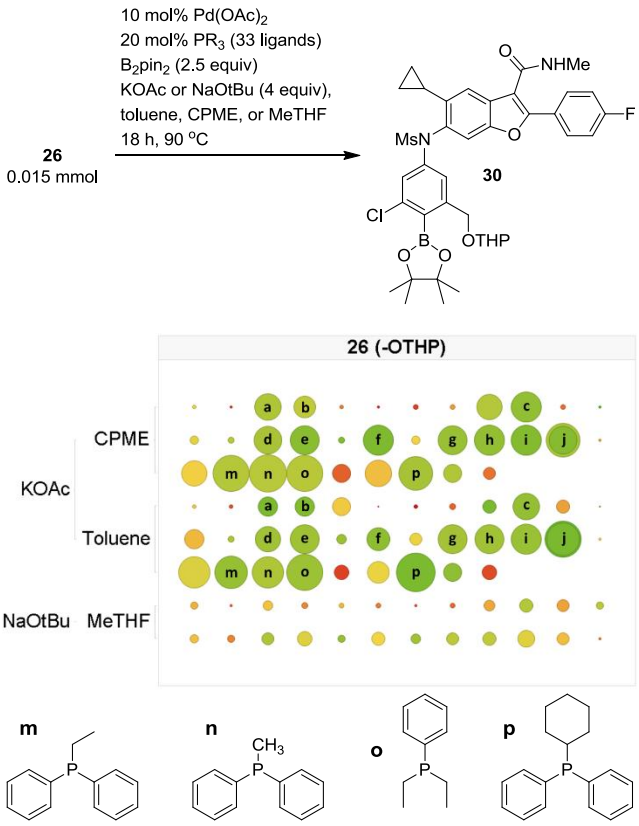


Figure 8. Expanded monodentate ligand screen for the conversion of **26** to **30** (THP protecting group), with additional ligand hits denoted **m**-**p**. The screening data are visualized with the size of the points corresponding to % product (larger is greater % product), and the color corresponding to % debromination observed (color gradient as follows: red: 100% desbromo; yellow: 25% desbromo; green: 0% desbromo). See Supporting Information for full table of results.

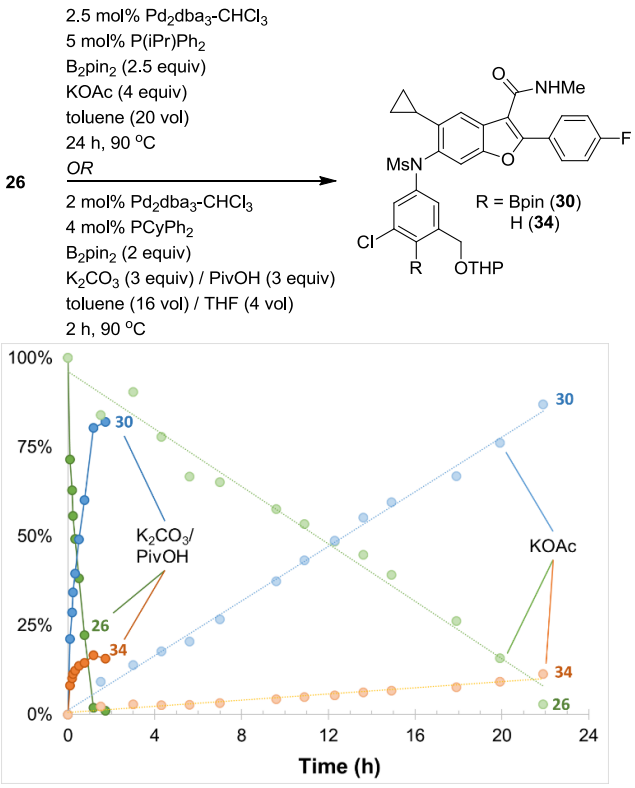


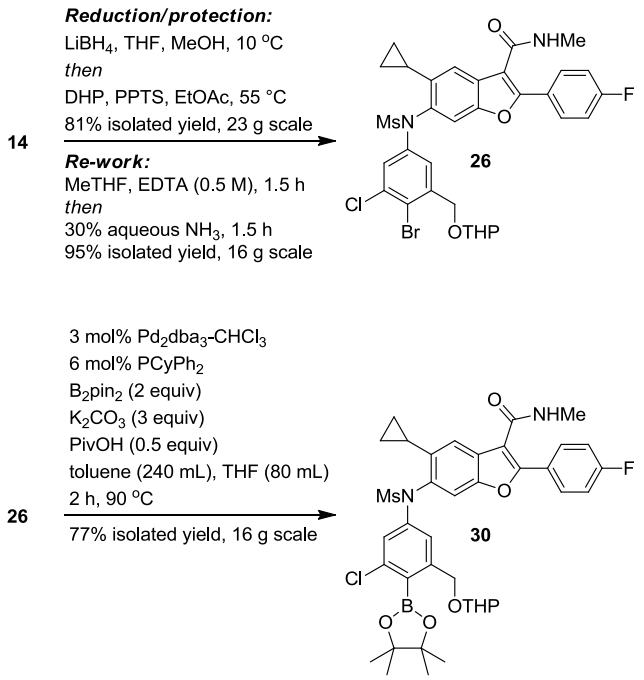
Figure 9. Reaction profile for conversion of 26 to 30 on gram-scale using either crystalline KOAc (conditions above arrow; light-colored points), or 325 mesh K_2CO_3 / PivOH (conditions below arrow; dark-colored points). The rate difference between the two sets of conditions is >10-fold.

observed, and the heterogeneous nature of the reaction mixture, our hypothesis is that solid/liquid mass-transfer is rate limiting in this case. KOAc has low solubility in toluene, even at elevated temperatures, and the crystallinity of as-received KOAc likely results in slow dissolution kinetics. This hypothesis was validated by performing the reaction with KOAc that was ground in a mortar and pestle under nitrogen, resulting in a >3-fold rate increase. Given that grinding a hygroscopic solid would be undesirable on larger scale, we sought to identify an alternative base that would alleviate mass-transfer issues. A variety of acetate salts were evaluated, with only KOAc and CsOAc achieving good solution yields of product.

At this point, we drew inspiration from synthetic and mechanistic studies in Pd-catalyzed direct arylation chemistry.[28] The proposed mechanisms for both the Miyaura borylation and direct arylation proceed through Pd(carboxylate) intermediates,[29,30] and it has been shown that pivalate ligands have a pronounced positive effect on direct arylation chemistry.[31] We therefore investigated both KOPiv and CsOPiv as bases, either as the discrete carboxylate salts, or generated *in situ* using a mixture of pivalic acid and K_2CO_3 or Cs_2CO_3. All of these pivalate-derived bases performed very well, giving 86-89% solution yield of **30**, with 10-13% debromination. While these reaction endpoint results are very similar to those obtained with KOAc, use of pivalate has a striking effect on reaction rate: simply substituting as-received KOPiv for crystalline KOAc under otherwise identical conditions results in a >4-fold increase in rate, while grinding the KOPiv leads to an even greater rate increase. With powdered KOPiv, a 90% solution yield can be obtained after only 60 minutes.

In order to retain the reaction rates observed with powdered KOPiv without the need to mill the solid base, we investigated the use of a pivalic acid/K_2CO_3 system. In contrast to KOAc and KOPiv, K_2CO_3 is readily available in a number of particle sizes. We chose 325 mesh K_2CO_3, and validated our small-scale results on gram scale using overhead stirring (to prevent any inadvertent grinding of the base by a magnetic stir bar). The solvent system was also modified to include THF as a cosolvent in order to solubilize **26** (and avoid another potential mass-transfer issue). The reaction reached completion in <75 minutes (Figure 9), consistent with the results obtained with powdered KOPiv. With confidence that our reaction conditions would be scalable, we finalized the reagent and catalyst charges, and proceeded to refine the scale-up and isolation protocols to access both **26** and **30**. As previously mentioned, reduction of **14** with $LiBH_4$ easily furnished the benzyl alcohol **15**. Rather than isolate **15** prior to THP protection, we developed a telescoped reduction/protection sequence that produced **26** in 81% isolated yield on 23 g scale

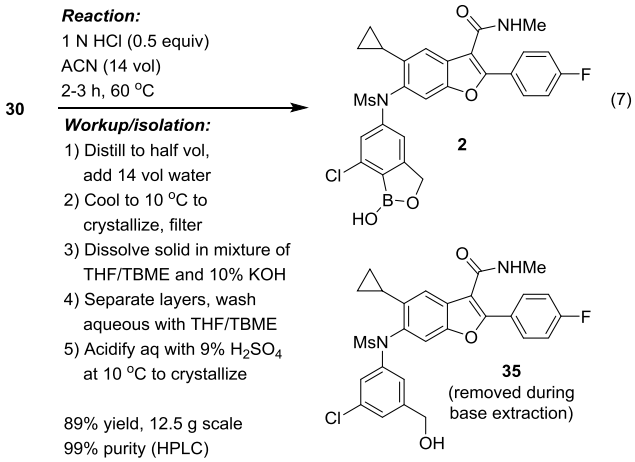
Scheme 3. Conversion of 14 to 30 in 59% overall yield.



(Scheme 3).

For all of the screening and reaction progress studies of the key borylation chemistry, compound **26** was sourced from a stockpile of intermediate **14** prepared using the previous synthetic route (Scheme 1). Unfortunately, our initial attempts to utilize **26** as-prepared using our new route led to poor results in the borylation reaction. Using 3 mol% Pd_2dba_3-$CHCl_3$ resulted in <10% product after a 2 hour rea ction time; however, the borylation could be 're-started' by further addition of catalyst. This behavior led us to suspect a low-level impurity in our newly synthesized **26** that leads to catalyst decomposition, with residual copper remaining after the Chan-Lam reaction as a likely culprit. Screening various methods to remove copper from **26** revealed that washing a MeTHF solution of **26** with EDTA (0.5 M) followed by 30% aqueous NH_3 provided material that performed well in use tests under our optimized borylation conditions. This re-work resulted in 95% recovery, bringing the overall yield for converting **14** to **26** to 76%. A multigram scale borylation was performed on the re-worked **26** according to Scheme 3, giving a 77% isolated yield after work-up and treatment with Darco to remove the residual palladium.

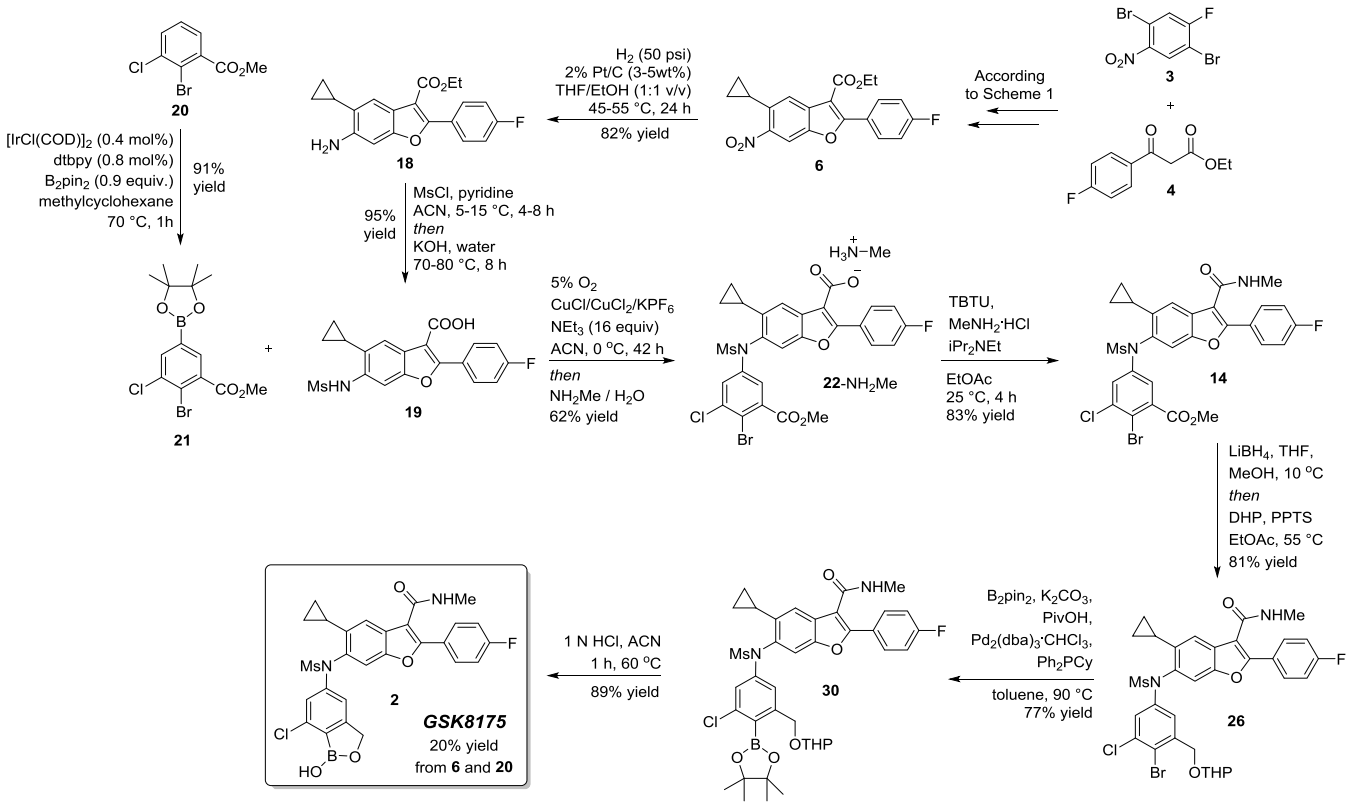
With the borylation chemistry demonstrated on multigram scale, the only remaining step in the synthesis is removal of the THP protecting group with concomitant hydrolysis of the pinacol boronate ester. Previous conditions to effect the deprotection/hydrolysis sequence with a MOM protecting group used excess 1 N HCl in an MeOH/THF solvent system. This required elevated temperatures for 5-10 hours, which raises the risk of protodeborylation of **2** to generate **35**. Switching solvents to acetonitrile facilitates complete hydrolysis using 1 N HCl after only 2-3 hours at 60 °C (equation 7). The major impurity observed after the hydrolysis is compound **35** (up to 10% by HPLC), which results mainly from carry-through of **34** from the prior stage borylation. An initial crystallization of **2** after concentration of the acetonitrile solution and addition of water as an anti-solvent unfortuantely does not remove **35** to a significant extent. Instead, we took advantage of the acidity of **2** to extract it into a 10% KOH aqueous solution, leaving **35** in a THF/TBME organic layer. Washing the alkaline aqueous layer with a second portion of THF/TBME completely removes **35**, and recrystallization of **2** can be achieved by acidification of the aqueous solution. This affords GSK8175 (**2**) in 89% isolated yield, and >99% purity as judged by HPLC analysis. Importantly, the levels of residual Pd were determined to be <20 ppm without any further re-work of the material, despite the Pd-catalyzed borylation late in the synthesis.



Conclusions.

Through judicious use of transition-metal catalyzed transformations, a new and more efficient synthetic route to GSK8175 (**2**) has been devised and demonstrated on multi-gram scale (Scheme 4). This route includes an regioselective Ir-catalyzed C–H borylation to generate a 1,3,4,5-tetrasubstituted aromatic, Cu-catalyzed oxidative arylation of a secondary sulfonamide using a cationic Cu precatalyst system, and a chemoselective Miyaura borylation at a 2,6-disubstituted position as the penultimate step. The total number of steps from readily available starting materials has been cut from 13 to 10. In terms of the newly developed chemistry, the route is only 8 stages (7 longest linear) starting from intermediates **6** and **17** with 20% overall yield. In addition to providing a more efficient protocol for accessing GSK8175 (**2**), newly developed conditions for both the Chan-Lam coupling[18] and the Miyaura borylation should find broad applicability in effecting these transformations. Work to assess the generality of these systems in other contexts is ongoing, and will be reported in due course.

Scheme 4. Newly developed synthetic route to GSK8175 (2), in eight stages and 20% overall yield from 6 and 20.



Experimental Section.

General. All jacketed reactors were heated and cooled using Syltherm silicone fluid circulated by a Huber Minichiller with internal temperature feedback control. Agitation was achieved with overhead stirring.

Materials. All common reagents and solvents were purchased from commercial sources and used as received.

Analytical. All NMR spectra were acquired at ambient temperature on a Bruker 400 MHz spectrometer. Solvents and frequencies for specific data acquisitions are noted for each case in the following sections. Chemical shifts were calibrated relative to residual protio solvent (^{1}H and ^{13}C) or to external standards (^{19}F). Data were processed using TopSpin and reports generated using ACD SpecManager.

HPLC analysis was performed on Agilent 1260 or 1290 series instruments with diode array detectors, though analysis was typically done with traces from a single wavelength. Two HPLC methods were utilized during the course of this work: Method A (1260 series): Column: Zorbax SB-C18, 1.8 µm, 3 x 50 mm; column temp: 60 °C; flow rate: 1.5 mL/min; solvent gradient: ACN (0.05% TFA v/v) / H_2O (0.05% TFA v/v), from 100/0 to 5/95 over 2.7 min; detection wavelength: 220 nm. Method B (1290 series): Column: Waters X-Select CSH, 2.5 µm, 2.1 x 30mm; column temp: 45 °C; flow rate: 1.6 mL/min; solvent gradient: ACN (0.05% TFA v/v) / H2O (0.05% TFA v/v), from 97/3 to 5/95 over 1.9 min; detection wavelength: 220 nm.

LCMS analysis was performed on a Waters Acquity system equipped with UV (Waters Acquity PDA, 210-360 nm), ELS (Waters Acquity ELSD, 50 °C), and MS (ESI, Waters Acquity SQD, positive ion mode, scan time 0.1 s) detectors. Chromatography method: Column: Waters CSH (C18), 1.7 µm, 2.1 x 30 mm; column temp: 45 °C; flow rate: 1.3 mL/min; solvent gradient: ACN (0.05% TFA v/v) / H2O (0.05% TFA v/v), from 97/3 to 2/98 over 1.9 min.

HRMS (*m*/*z*) was measured using an Exactive Plus (Thermo) orbitrap mass spectrometer equipped with a heated electrospray ionization (HESI) ion source.

Melting points were obtained using a Mettler Toledo MP90 instrument, with a 4 °C min^{-1} temperature ramp up to 250 °C.

Synthesis of ethyl 6-amino-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (18). SAFETY NOTE: Pressurized hydrogenation reactions should always be carried out in well-maintained, leak-checked pressure equipment located in a well-ventilated environment, preferrably a dedicated pressure laboratory. Hydrogenation catalysts are pyrophoric materials, particularly when dry, and especially after being exposed to hydrogen. Care should be taken in handling the catalyst material after reaction completion. Never letting the catalyst cake dry during filtration, and prompt quenching of the spent catalyst in a dilute aqueous oxidant such as sodium bisulfite are critical to ensuring safe operation.

To a 1 L jacketed BuchiGlas glass-walled pressure reactor was charged 2% Pt, 1% V/C catalyst (Evonik Noblyst P8071, 1.625 g, 0.167 mmol) followed by a well-mixed slurry of **6** (65 g, 176 mmol) in THF (650 mL, 10 vol) / acetic acid (10.07 mL, 176 mmol). The reactor headspace was evacuated and backfilled with N_2 three times to remove dissolved O_2. The

reaction mixture was stirred and heated to 45 °C prior to pressurization with 5 bar (72 psi) H_2. The mixture was stirred under these conditions overnight. The reaction mixture was then cooled to 25 °C, followed by filtration through GFC filter paper to remove the catalyst. The filtrate was then distilled under vacuum to ~3 vol. TBME (325 mL, 5 vol) was added over 30 minutes, and the mixture was vacuum distilled down to ~3 vol. This put-and-take was repeated once more to yield a red-orange slurry. The slurry was vacuum filtered to collect the solid, and the cake was washed with TBME (195 mL, 3 vol). The wet cake was dried overnight in a vacuum oven at 50 °C to give **18** as an orange solid (48.9 g, 82% yield). M.p. 141-142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.46 - 0.56 (m, 2 H), 0.88 - 0.98 (m, 2 H), 1.32 (t, *J*=7.09 Hz, 3 H), 1.70 - 1.81 (m, 1 H), 4.30 (q, *J*=7.04 Hz, 2 H), 5.38 (s, 2 H), 6.83 (s, 1 H), 7.29 - 7.39 (m, 2 H), 7.45 (s, 1 H), 7.93 - 8.03 (m, 2 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.81. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 6.2, 12.0, 14.5, 60.7, 94.7, 109.0, 115.7 (d, *J*=21.8 Hz), 115.9, 120.3, 125.0, 126.6 (d, *J*=3.3 Hz), 131.6 (d, *J*=8.5 Hz), 147.8, 154.1, 155.8, 163.9, 163.1 (d, *J*=248.0 Hz). HRMS (ESI): *m/z* calculated for $C_{20}H_{19}FNO_3$ $[M+H]^+$: 340.1343; found: 340.1339.

Synthesis of 5-cyclopropyl-2-(4-fluorophenyl)-6-(methylsulfonamido)benzofuran-3-carboxylic acid (19). A 3 L flask equipped with an overhead stirrer was charged with **18** (85.0 g, 250 mmol), acetonitrile (1317.5 mL, 15.5 vol), and pyridine (101 mL, 1252 mmol). With stirring, a solution of methanesulfonyl chloride (38.8 mL, 501 mmol) in acetonitrile (170 mL) was added dropwise over 40 min; the internal temperature was monitored during the addition to ensure the mixture did not go above 25 °C. After addition was complete, the reaction mixture was stirred at 20-25 °C for 6 hours. The reaction mixture was then vacuum distilled to ~370 mL (4.4 vol). Water was added (850 mL, 10 vol), followed by solid potassium hydroxide (100 g, 1778 mmol, NOTE: exothermic; solid added portionwise). The reaction mixture was then heated to 75 °C and stirred at that temperature for 3 hours. The reaction mixture was then cooled to 30 °C over 1 hour. TBME (425 mL, 6.5 vol) was added to give a biphasic mixture. The layers were mixed, then separated. The organic layer was discarded. The aqueous layer was diluted with water (1870 mL, 22 vol) followed by a slow addition of 6 N HCl (403 mL, 4.7 vol) over 1 hour to acidify to pH ~1 and yield a white suspension. The suspension was stirred for one hour while cooling from 30 to 20 °C. The solid was then collected by vacuum filtration, and the wet cake washed with water (2 x 850 mL, 10 vol) and acetonitrile (255 mL, 3 vol). The solid was then dried overnight in a vacuum oven at 55 °C to give a **19** as a pale yellow solid (94.9 g, 97% yield). M.p. 241-244 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.58 - 0.72 (m, 2 H), 0.97 - 1.09 (m, 2 H), 2.25 - 2.39 (m, 1 H), 3.07 (s, 3 H), 7.30 - 7.45 (m, 2 H), 7.58 (s, 1 H), 7.63 (s, 1 H), 7.99 - 8.14 (m, 2 H), 9.34 (s, 1 H), 13.21 (br s, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -109.70. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 8.9, 12.0, 40.8, 108.6, 109.5, 115.8 (d, *J*=22.00 Hz) 118.8, 125.4, 126.1 (d, *J*=3.10 Hz), 132.3 (d, *J*=8.80 Hz), 134.6, 135.4, 151.8, 159.5, 163.6 (d, *J*=249.00 Hz), 164.9. HRMS (ESI): *m/z* calculated for $C_{19}H_{17}FNO_5S$ $[M+H]^+$: 390.0806; found: 390.0806.

Synthesis of methyl 2-bromo-3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (21). To a 6 L jacketed glass reactor equipped with overhead stirring and thoroughly purged with N_2 was charged the following solids: finely ground $[Ir(cod)Cl]_2$ (2.453 g, 3.65 mmol, 0.4 mol%); dtbbpy (1.961 g, 7.31 mmol, 0.8 mol%); B_2pin_2 (209 g, 822 mmol, 0.9 equiv). Heptane (1.14 L, 5 vol) was added, and stirring commenced at 350 rpm. The reactor headspace was evacuated and backfilled with N_2 three times to remove dissolved O_2. The reaction mixture was heated to 85 °C to give a dark maroon solution. Compound **20** (227.8 g, 913 mmol, 1.0 equiv) was added portionwise as a solid to the reactor (addition can also be achieved by dissolving **20** in 1 vol heptane and added dropwise). After addition was complete, the reaction mixture was stirred at 85 °C for 1 hour, and then cooled to room temperature (20-25 °C). TBME (1.37 L, 6 vol) was charged, followed by a slow addition of water (400 mL, 2 vol) to quench the reaction. 20% NaCl in water (400 mL, 2 vol) was then charged, and the biphasic mixture agitated for at least 15 minutes. After the layers settled, the aqueous phase was removed, and the organic layer heated to 45 °C. Solvent was distilled (125-150 mbar, 45-55 °C, 200 rpm stirring) to give a concentrated solution of ~3 vol. Once distillation was complete, the solution was heated to 50 °C, followed by the sequential addition of acetonitrile (912 mL, 4 vol) and water (1.37 L, 6 vol). The mixture was then cooled at ~1 °C min^{-1} to 5 °C, and held at 5 °C for at least 30 minutes. The slurry was then vacuum filtered, and the residual solid in the reactor washed onto the filter cake with 1:1 acetonitrile/water (100 mL) using a spray ball. After filtration, the off-white solid was dried in a vacuum oven at 50 °C to give 311.8 g of **21** (91% yield). M.p. 83-85 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 12 H), 3.88 (s, 3 H), 7.83 (d, *J*=1.47 Hz, 1 H), 7.88 (d, *J*=1.47 Hz, 1 H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 25.1, 53.4, 85.1, 123.9, 130.2, 134.3, 135.6, 136.0, 137.9, 166.2. HRMS (ESI): *m/z* calculated for $C_{14}H_{17}BBrClO_4$ $[M+H]^+$: 375.0165; found: 375.0162.

Synthesis of methylammonium 6-(*N*-(4-bromo-3-chloro-5-(methoxycarbonyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)benzofuran-3-carboxylate (22-NH$_2$Me). SAFETY NOTE: Mixtures of oxygen and organic solvents pose a significant risk of combustion and potential explosion. Operating below the limiting oxygen concentration of the reaction solvent(s) is critical to mitigating the risk of combustion.[19,20]

To a 1 L jacketed glass reactor equipped with a temperature probe, overhead stirrer, gas inlet, and gas outlet to an oil bubbler was added acetonitrile (150 mL, 4.3 vol) and $CuCl_2$ (1.21 g, 8.99 mmol). The mixture was stirred at 20 °C for 10 min to give a yellow brown suspension. Solid CuCl (4.45 g, 44.9 mmol) was added to give a brown suspension, followed by KPF_6 (23.16 g, 126 mmol) to give an orange-brown slurry. Compound **19** (35 g, 90 mmol) was added as a solid, followed by acetonitrile (150 mL, 4.3 vol) to ensure quantitative transfer and to wash down walls of reactor. Triethylamine (200 mL, 5.7 vol) was added to give a light

green slurry. The reaction mixture was then cooled to 0 °C over 20 minutes, followed by the addition of solid **21** (84 g, 225 mmol) and acetonitrile (150 mL, 4.3 vol). Sub-surface bubbling of 5% O_2 (balance N_2) through a stainless steel tube was commenced at a flow rate between 0.40-0.45 L/min. After stirring under these conditions for 42 hours, the reaction mixture was warmed to 20 °C and the solvent removed by vacuum distillation to 120 mL total volume. The solution was transferred into a 1 L separatory funnel, and the reactor washed with 2-MeTHF (90 mL, 2.6 vol) into the same separatory funnel. The organic phase was washed with 1 N HCl (180 mL, 5.2 vol), 5% aqueous NaCl (60 mL, 1.7 vol), and 1 N HCl (90 mL, 2.6 vol). The aqueous pH was confirmed to be <1. To the organic phase was added 40 wt% aqueous methylamine (19.45 mL, 225 mmol) and 10% aqueous NaCl (60 mL, 1.7 vol). The layers were mixed, allowed to settle, and separated. The organic phase was washed twice with 10% aqueous NaCl (90 mL, 2.6 vol), and then returned to the 1 L reactor. This solution was seeded with a small amount of crystalline **22**-NH_2Me, followed by vacuum distillation with stirring to a total volume of ~200 mL (5.7 vol). Once the desired volume was reached, the suspension was stirred slowly overnight to complete the crystallization. The solid was then collected by vacuum filtration, and the residual solid from the reactor rinsed onto the filter cake with toluene (90 mL, 2.6 vol). The solid was dried by suction, and then in a vacuum oven overnight at 50 °C to give 37.1 g of **22**-NH_2Me (62% yield). M.p. not determined. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.30 (br m, 1 H) 0.78 (br m, 2 H) 0.96 (br m, 1 H) 2.07 (quin, *J*=6.70 Hz, 1 H) 2.38 (s, 3 H) 3.84 (s, 3 H) 7.26 - 7.35 (m, 2 H) 7.59 (d, *J*=2.74 Hz, 1 H) 7.67 (s, 1 H) 7.78 (d, *J*=2.74 Hz, 1 H) 7.96 (s, 1 H) 8.36 - 8.44 (m, 2 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -112.12. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 7.9 (br), 9.6 (br), 12.2, 24.7, 41.0, 53.6, 113.2, 115.5 (d, *J*=21.6 Hz), 116.1, 117.7, 119.6, 124.0, 127.5 (d, *J*=3.1 Hz), 127.6, 131.0 (d, *J*=8.5 Hz), 131.3, 134.9, 135.7, 136.7, 137.7, 142.0, 151.4, 154.2, 162.8 (d, *J*=248.0 Hz), 166.2, 167.2, 173.6. HRMS (ESI): *m*/*z* calculated for $C_{27}H_{21}BrClFNO_7S$ [M+H]$^+$: 635.9895; found: 635.9879.

Synthesis of methyl 2-bromo-3-chloro-5-hydroxybenzoate (23). A 100 mL jacketed reactor equipped with an overhead stirrer was charged with **21** (5.05 g, 13.45 mmol) and acetone (30 mL). With stirring and maintaining reaction temperature between 20-30 °C, an aqueous solution of oxone (8.27 g, 13.45 mmol, 40 mL water) was added dropwise over 40 minutes. Once addition was complete, the reaction mixture was stirred overnight at 20 °C. The mixture was then transferred to a separatory funnel, and diluted with aqueous 10% $NaHSO_3$ (90 mL) and EtOAc (90 mL). The layers were mixed and then allowed to settle and separated. The organic phase was washed with aqueous 5% NaCl (50 mL), then with water (50 mL), and finally dried over $MgSO_4$. After filtration and concentration, the crude phenol was purified by silica gel chromatography using a MeOH/DCM gradient (0-1% MeOH) to give **23** (2.0 g, 55% yield). M.p. 133-134 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.85 (s, 3 H), 7.03 (d, *J*=2.84 Hz, 1 H), 7.17 (d, *J*=2.84 Hz, 1 H), 10.57 (s, 1 H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 53.3, 108.3, 116.4, 119.9, 135.7, 136.7, 157.8, 166.6. HRMS (ESI): *m*/*z* calculated for $C_8H_7ClBrO_3$ [M+H]$^+$: 264.9262; found: 264.9260.

Synthesis of methyl 2-bromo-3-chloro-5-(*N*-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzoate (14). A 1 L reactor equipped with a temperature probe, gas inlet and outlet, and overhead stirrer was charged with **22**-NH_2Me (31.0 g, 46.4 mmol) and ethyl acetate (280 mL, 9 vol). The headspace was swept with nitrogen and stirring commenced. TBTU (25.3 g, 79.0 mmol) was added, followed by methylamine hydrochloride (4.70 g, 69.6 mmol) and diisopropylethylamine (18.0 g, 24.3 mL, 139 mmol). Ethyl acetate (31 mL, 1 vol) was used to rinse the reactor walls to ensure a quantitative transfer. The reaction mixture was stirred at 30 °C for 2 hours, during which time the solids dissolved and the solution clarified. The reaction mixture was cooled to room temperature, followed by the addition of 10% aqueous $NaHCO_3$ (155 mL, 5 vol). The layers were mixed for 15 minutes and then allowed to settle. The aqueous phase was removed, and the organic phase washed with saturated NH_4Cl (155 mL, 5 vol). After mixing for 15 minutes and allowing to settle, the aqueous phase was removed. The organic phase was washed with 10% aqueous NaCl (155 mL, 5 vol). After mixing for 15 minutes and allowing to settle, the aqueous phase was removed. The organic phase was heated to 45 °C, followed by solvent removal by vacuum distillation to a total volume of ~125 mL (4 vol). Ethyl acetate (120 mL, 4 vol) was added, followed by a second vacuum distillation to a total volume of ~80 mL (2.6 vol). With stirring, the reactor contents were heated to 50 °C, followed by the addition of heptane (220 mL, 7 vol) over 30 minutes. The solution was then cooled to 20 °C over 60 minutes, and held at this temperature for a further 60 minutes. The resulting solid was collected by filtration, and residual solid rinsed onto the filter cake using heptane (2 x 90 mL, 3 vol). The solid was dried in a vacuum oven overnight at 50 °C to give 24.9 g of **14** (83% yield). M.p. 236-237 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.30 - 0.47 (m, 1 H), 0.71 - 0.84 (m, 1 H), 0.84 - 0.93 (m, 1 H), 0.93 - 1.05 (m, 1 H), 2.03 - 2.15 (m, 1 H), 2.84 (d, *J*=4.60 Hz, 3 H), 3.34 (s, 2 H), 3.85 (s, 3 H), 7.23 (s, 1 H), 7.35 - 7.46 (m, 2 H), 7.63 (d, *J*=2.74 Hz, 1 H), 7.78 (d, *J*=2.74 Hz, 1 H), 7.92 - 8.02 (m, 2 H), 8.15 (s, 1 H), 8.50 (q, *J*=4.53 Hz, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.34. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 7.5, 9.2, 11.8, 26.2, 40.6, 53.1, 113.6, 113.7, 115.9, 116.1 (d, *J*=22.0 Hz), 116.8, 123.7, 125.5 (d, *J*=3.0 Hz), 127.3, 128.2, 129.4 (d, *J*=8.9 Hz), 135.3, 135.5, 136.3, 138.5, 141.3, 150.9, 153.7, 162.9, 162.8 (d, *J*=248.0 Hz), 165.7. HRMS (ESI): *m*/*z* calculated for $C_{28}H_{24}BrClFN_2O_6S$ [M+H]$^+$: 649.0206; found: 649.0207.

Synthesis of 6-(*N*-(4-bromo-3-chloro-5-(hydroxymethyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (15). To a 1 L jacketed reactor equipped with overhead stirring was added **14** (70.6 g, 109 mmol), 2-MeTHF (425 mL, 6 vol) and methanol (50 mL). With stirring (500 rpm), the reaction mixture was cooled to 10 °C. $LiBH_4$ (7.89 g, 326 mmol) was charged portionwise, maintaining reaction

temperature between 10-12 °C. Once addition was complete, the mixture was warmed to room temperature (23 °C) and stirred for 2 hours. Analysis of an aliquot by HPLC indicated reaction completion. The mixture was again cooled to 10 °C, and water (150 mL, 2 vol) was added carefully to quench the reaction. 1 M HCl was then added until the aqueous phase pH was less than 5. The biphasic mixture was diluted to a total volume of 1 L with EtOAc. The phases were separated, and the organic phase concentrated to dryness. The crude product was purified on silica gel using an EtOAc/hexanes gradient to give **15** (46.0 g, 68% yield). M.p. 229-230 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.40 - 0.53 (m, 1 H), 0.75 - 0.92 (m, 2 H), 0.92 - 1.05 (m, 1 H), 2.05 - 2.17 (m, 1 H), 2.84 (d, *J*=4.69 Hz, 3 H), 3.34 (s, 3 H), 4.47 (d, *J*=5.58 Hz, 2 H), 5.64 (t, *J*=5.60 Hz, 1 H), 7.22 (s, 1 H), 7.37 - 7.46 (m, 2 H), 7.53 (d, *J*=2.74 Hz, 1 H), 7.58 (d, *J*=2.84 Hz, 1 H), 7.93 - 8.03 (m, 2 H), 8.12 (s, 1 H), 8.51 (q, *J*=4.66 Hz, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) d ppm -110.41 (s, 1 F). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) d ppm 8.3, 9.5, 12.3, 26.7, 40.8, 63.6, 113.9, 114.0, 116.5 (d, *J*=22.0 Hz) 117.1, 117.2, 122.0, 123.8, 126.0 (d, *J*=3.1 Hz) 128.5, 129.9 (d, *J*=8.7 Hz) 134.0, 136.6, 139.2, 141.7, 145.2, 151.4, 154.0, 163.4, 163.3 (d, *J*=249.0 Hz). HRMS (ESI): *m/z* calculated for $C_{27}H_{24}BrClFN_2O_5S$ [M+H]$^+$: 621.0256; found: 621.0257.

Synthesis of 6-(*N*-(4-bromo-3-chloro-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (26). A 500 mL reactor equipped with a temperature probe and overhead stirrer was charged with **14** (23.0 g, 35.5 mmol), 2-MeTHF (115 mL, 5 vol) and MeOH (16.1 mL). Stirring was commenced at 300 rpm, and the reaction mixture cooled to 10 °C. $LiBH_4$ (2.0 M in THF, 53.2 mL, 106 mmol) was added dropwise over 30 minutes. After stirring for 15 minutes, ethyl acetate (100 mL, 4.3 vol) was added, followed by slow addition of 6 N HCl (10 mL) and water (100 mL, 4.3 vol). The reaction mixture was allowed to warm to room temperature with stirring, and then the phases allowed to settle. The layers were separated, and the aqueous phase was extracted with ethyl acetate (100 mL, 4.3 vol). The combined organic layer was washed with water (250 mL, 10.9 vol) and saturated aqueous NaCl (150 mL, 6.5 vol). Solvent was removed by vacuum distillation to minimum stir in the 500 mL reactor, followed by the addition of ethyl acetate (160 mL, 7 vol). DHP (13.4 g, 14.6 mL, 160 mmol) and pyridinium *p*-toluenesulfonate (0.89 g, 3.55 mmol) were added with stirring, and then the reactor contents were heated to 55 °C for three hours. Heptane (160 mL, 7 vol) was added, and the contents of the reactor cooled to 10 °C at a rate of 0.5 °C min^{-1}, and held at 10 °C with stirring overnight. The resulting solid was collected by filtration, and the residual material in the reactor washed onto the filter cake with heptane (100 mL, 4.3 vol) and water (100 mL, 4.3 vol). The solid was dried at 50 °C in a vacuum oven to give **26** (25.0 g, 81% isolated yield). M.p. 172-176 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.45 (br m, 1 H), 0.70 - 0.91 (m, 2 H), 0.98 (br m, 1 H), 1.24 – 1.60 (br m, 6 H), 2.10 (br m, 1 H), 2.84 (d, *J*=4.60 Hz, 3 H), 3.30 – 3.66 (br m, 2 H), 3.48 (s, 3 H), 4.45 - 4.56 (m, 1 H), 4.56 - 4.72 (m, 2 H), 7.23 (s, 1 H), 7.33 - 7.46 (m, 3 H), 7.68 (br s., 1 H), 7.92 - 8.01 (m, 2 H), 8.07 - 8.15 (br m, 1 H), 8.48 (br d, *J*=3.91 Hz, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.37. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 8.3, 9.4, 12.3, 18.9, 19.0, 25.3, 26.7, 30.3, 40.8, 61.6, 61.8, 68.1, 97.8, 97.9, 113.9, 114.0, 116.5 (d, *J*=22.0 Hz), 117.3, 122.1, 122.12, 123.3, 126.0 (d, *J*=3.2 Hz), 128.6, 129.9 (d, *J*=8.4 Hz), 134.4, 136.4, 139.2, 141.6, 141.8, 151.5, 154.2, 163.3 (d, *J*=248.0 Hz), 163.4. HRMS (ESI): *m/z* calculated for $C_{32}H_{32}BrClFN_2O_6S$ [M+H]$^+$: 705.0832; found: 705.0830.

Re-work of 6-(*N*-(4-bromo-3-chloro-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (26). A 1 L reactor was charged with **26** (16.5 g, 23.37 mmol), 2-MeTHF (600 mL, 36 vol), and 0.5 M EDTA in water (250 mL, 15 vol). The biphasic mixture was stirred for 90 minutes, and then the layers separated. The organic phase was washed with water (100 mL, 6 vol) and saturated aqueous NaCl (100 mL, 6 vol). The organic phase was then stirred for 90 minutes with 30% aqueous ammonia (300 mL, 18 vol), followed by separation of the layers. The organic phase was washed with water (100 mL, 6 vol), saturated aqueous NaCl (100 mL, 6 vol), and then concentrated under reduced pressure to recover **26** (15.7 g, 95% recovery), which was used directly in the following stage to synthesize **30**.

Synthesis of 2-bromo-3-chloro-5-(*N*-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzyl acetate (27). A 100 mL RB-flask containing a stirbar was charged with **15** (3.81 g, 6.13 mmol), DMAP (7.5 mg, 0.061 mmol), and DCM (30 mL). With stirring, acetyl chloride (0.48 mL, 6.74 mmol) was added slowly. The reaction mixture was then cooled to 0 °C. Triethylamine (1.71 mL, 12.25 mmol) was added dropwise, followed by warming to room temperature. After 2 hours, analysis of an aliquot by HPLC revealed ~5% starting material remaining; an additional 50 µL of acetyl chloride was added and the reaction mixture stirred for a further hour. The solvent was removed, and the residue redissolved in EtOAc (150 mL). The organic phase was washed with water, and the solvent removed from the organic phase. The resulting white solid was washed with hexanes three times and dried in a vacuum oven at 50 °C overnight to give **27** (4.01 g, 99% yield). M.p. 212-215 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.43 (br m, 1 H), 0.86 (br m, 2 H), 0.98 (br m, 1 H), 2.02 (s, 3 H), 2.07 - 2.16 (m, 1 H), 2.84 (d, *J*=4.60 Hz, 3 H), 3.46 (s, 3 H), 5.11 (s, 2 H), 7.22 (s, 1 H), 7.37 - 7.44 (m, 2 H), 7.45 (d, *J*=2.74 Hz, 1 H), 7.64 (d, *J*=2.64 Hz, 1 H), 7.93 - 8.00 (m, 2 H), 8.13 (s, 1 H), 8.50 (q, *J*=4.24 Hz, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.37 (s, 1 F). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 8.2, 9.7, 12.3, 20.9, 26.7, 40.9, 66.0, 114.0, 116.5 (d, *J*=22.0 Hz), 117.1, 119.3, 124.2, 125.3, 126.0 (d, *J*=3.2 Hz), 128.6, 129.9 (d, *J*=8.8 Hz), 134.8, 136.3, 139.0, 139.2, 141.7, 151.4, 154.2, 163.3 (d, *J*=248.5 Hz), 163.4, 170.3. HRMS (ESI): *m/z* calculated for $C_{29}H_{26}ClBrFN_2O_6S$ [M+H]$^+$: 663.0362; found: 663.0364.

Synthesis of 2-bromo-3-chloro-5-(*N*-(5-cyclopropyl-2-(4-fluorophenyl)-3-(methylcarbamoyl)benzofuran-6-yl)methylsulfonamido)benzyl pivalate (28). A 250 mL RB-flask containing a stirbar was charged with **15** (6.00

g, 9.65 mmol) and DCM (60 mL). With stirring, pivaloyl chloride (2.38 mL, 19.3 mmol) was added slowly, followed by triethylamine (2.96 mL, 21.2 mmol). After 18 hours, the mixture was diluted with EtOAc (50 mL) and washed with water (70 mL). The aqueous layer was back-extracted with EtOAc (50 mL), and the combined organic extracts were washed with brine (100 mL). The organic phase was dried with Na_2SO_4, and the solvent removed to give a yellow oil. Purification by silica gel chromatography with an EtOAc/hexanes gradient to give **28** as a tan solid (2.82 g, 41% yield). M.p. 195-198 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.41 (br. s., 1 H), 0.76 (br. s., 1 H), 0.84 (br. s., 1 H), 0.96 (br. s., 1 H), 1.03 (s, 9 H), 1.96 - 2.12 (m, 1 H), 2.84 (d, *J*=4.60 Hz, 3 H), 3.47 (s, 3 H), 5.09 (s, 2 H), 7.16 - 7.29 (m, 2 H), 7.36 - 7.51 (m, 2 H), 7.68 (d, *J*=2.74 Hz, 1 H), 7.93 - 8.02 (m, 2 H), 8.10 (s, 1 H), 8.38 - 8.56 (m, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.37 (s, 1 F). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 8.2, 9.2, 12.3, 26.7, 27.1, 38.7, 40.9, 65.6, 114.0, 116.5 (d, *J*=22.0 Hz), 117.4, 117.8, 121.9, 123.9, 126.0 (d, *J*=3.2 Hz), 128.7, 129.9 (d, *J*=8.8 Hz), 134.8, 136.2, 138.9, 139.3, 141.8, 151.5, 154.2, 163.3 (d, *J*=248.0 Hz), 163.4, 177.2. HRMS (ESI): *m*/*z* calculated for $C_{32}H_{32}ClBrFN_2O_6S$ $[M+H]^+$: 705.0832; found: 705.0833.

Synthesis of 6-(*N*-(4-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-chlorophenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (29). A 100 mL jacketed reactor equipped with an overhead stirrer was charged with **15** (5.10 g, 8.20 mmol) and DMF (30 mL). With stirring, TBSCl (1.85 g, 12.3 mmol) was added slowly, followed by imidazole (0.95 g, 13.9 mmol). After 18 hours, the mixture was diluted with EtOAc (50 mL) and washed with water (70 mL). The aqueous layer was back-extracted with EtOAc (50 mL), and the combined organic extracts were washed with brine (100 mL). The organic phase was dried with Na_2SO_4, and the solvent removed to give a yellow oil. Purification by silica gel chromatography with an EtOAc/hexanes gradient to give **29** as a white solid (5.51 g, 91% yield). M.p. 160-163 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm -0.04 (s, 3 H), 0.00 (s, 3 H), 0.39 - 0.50 (m, 1 H), 0.71 (s, 9 H), 0.73 - 0.79 (m, 1 H), 0.79 - 0.88 (m, 1 H), 0.96 (br. s., 1 H), 1.97 - 2.08 (m, 1 H), 2.84 (d, *J*=4.70 Hz, 3 H), 3.46 (s, 3 H), 4.62 (s, 2 H), 7.24 (s, 1 H), 7.29 (d, *J*=2.84 Hz, 1 H), 7.38 - 7.47 (m, 2 H), 7.72 (d, *J*=2.84 Hz, 1 H), 7.94 - 8.01 (m, 2 H), 8.08 (s, 1 H), 8.45 (d, *J*=4.70 Hz, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.43 (s, 1 F). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm -5.3, 8.3, 9.0, 12.2, 18.0, 25.8, 26.7, 40.8, 64.7, 113.9, 114.0, 116.0, 116.5 (d, *J*=22.2 Hz) 117.5, 120.6, 122.6, 126.1 (d, *J*=3.1 Hz), 128.6, 129.9 (d, *J*=8.7 Hz), 134.1, 136.3, 138.9, 141.8, 143.6, 151.5, 154.2, 163.3 (d, *J*=248.0 Hz), 163.4. HRMS (ESI): *m*/*z* calculated for $C_{33}H_{38}ClBrFN_2O_5SSi$ $[M+H]^+$: 735.1121; found: 735.1123.

Synthesis of 6-(*N*-(3-chloro-5-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (30). A 500 mL reactor equipped with a temperature probe and overhead stirrer was charged with **26** (15.7 g, 22.2 mmol), K_2CO_3 (9.20 g, 66.5 mmol), B_2pin_2 (11.3 g, 44.4 mmol), pivalic acid (1.13 g, 11.1 mmol), toluene (250 mL, 16 vol) and THF (63 mL, 4 vol). The resulting mixture was stirred at 400 rpm. The reactor headspace was flushed with N_2 prior to the introduction of $PCyPh_2$ (0.357 g, 1.33 mmol) and Pd_2dba_3-$CHCl_3$ (0.609 g, 0.665 mmol). The stirring mixture was heated to 90 °C for four hours, when it was cooled to 60 °C. The organic phase was washed with water (3 x 50 mL, 3.2 vol) at this temperature, and then cooled to room temperature. The organic phase was then drained into a 1 L Erlenmeyer flask, and the reactor washed with THF (2 x 40 mL, 2.5 vol). Darco activated carbon (12.4 g) was added, and the mixture stirred for 15 minutes. The carbon was removed by filtration, and the solid washed with THF (50 mL, 3.2 vol). The combined organic phase was concentrated to a total volume of ~150 mL (9.6 vol) by vacuum distillation at 55 °C. Toluene (150 mL, 9.6 vol) was added, and the organic phase concentrated to ~150 mL (9.6 vol). The solution was then heated to 80 °C, followed by the addition of heptane (105 mL, 6.7 vol) with stirring. The mixture was cooled to 10 °C at a rate of 0.5 °C min^{-1}, and then held at that temperature overnight. The resulting solid was collected by filtration, and the residual material in the reactor washed with 1:1 toluene/heptane (60 mL, 3.8 vol) onto the filter cake. The solid was dried in a vacuum oven at 50 °C to afford 12.9 g of **30** (77% yield). M.p. 196-200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.28 - 0.43 (m, 1 H), 0.63 - 0.74 (m, 1 H), 0.74 - 0.84 (m, 1 H), 0.84 - 0.97 (m, 1 H), 1.09 (d, *J*=3.13 Hz, 1 H), 1.24 (d, *J*=3.91 Hz, 11 H), 1.27 - 1.57 (m, 6 H), 1.94 - 2.12 (m, 1 H), 2.77 (d, *J*=4.70 Hz, 3 H), 3.20 - 3.24 (m, 1 H), 3.38 (s, 3 H), 3.41 - 3.63 (m, 1 H), 4.31 - 4.44 (m, 2 H), 4.46 - 4.59 (m, 1 H), 7.10 - 7.21 (m, 2 H), 7.24 - 7.29 (m, 1 H), 7.29 - 7.38 (m, 2 H), 7.85 - 7.94 (m, 2 H), 8.03 (s, 1 H), 8.42 (q, *J*=4.76 Hz, 1 H). ^{13}C{^{1}H} NMR spectrum is complex; see the Supporting Information. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.41. HRMS (ESI): *m*/*z* calculated for $C_{38}H_{43}BClFN_2O_8SNa$ $[M+Na]^+$: 775.2398; found: 775.2399.

Synthesis of 6-(*N*-(7-chloro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-5-yl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (2). A 500 mL reactor equipped with a temperature probe and overhead stirrer was charged with **30** (12.4 g, 16.5 mmol) and acetonitrile (175 mL, 14 vol). The mixture was stirred at 400 rpm, followed by the addition of 1 N HCl (8.23 mL, 8.23 mmol). The reactor contents were heated to 60 °C with stirring for three hours. The mixture was then cooled to room temperature, and the solvent removed by vacuum distillation to a total volume of ~90 mL (7.3 vol). Water (175 mL, 14 vol) was added, and the reactor contents cooled to 10 °C at a rate of 0.5 °C min^{-1}. The mixture was stirred at that temperature for 90 minutes. The resulting solid was collected by filtration, and the residual material in the reactor washed on to the filter cake with water (2 x 40 mL, 3.2 vol). After drying via suction for one hour, the wet solid was transferred to a second 500 mL reactor. The material was dissolved in THF (90 mL, 7.3 vol) and TBME (125 mL, 10 vol), followed by addition of water (250 mL, 20 vol). This biphasic mixture was stirred at 400 rpm, and 2 M KOH was added slowly (12.4 mL, 24.8 mmol)

to reach a target pH ~ 12. Once addition was complete, stirring was maintained for 20 minutes to ensure complete dissolution of solids. Stirring was stopped, and the layers allowed to settle for 30 minutes. The layers were separated, and the aqueous phase back extracted with THF (90 mL, 7.3 vol) / TBME (40 mL, 3.2 vol) to remove **35** and other minor impurities. After separation of the layers, the aqueous phase was concentrated to a total volume of 250 mL (20 vol). The solution was cooled to 10 °C with stirring, followed by addition of 9 wt% H_2SO_4 in water (11.9 mL, 10.7 mmol) to a target pH ~ 2. The mixture was cooled to 5 °C, and stirred for 30 minutes. The resulting solid was collected by filtration, and the residual material in the cold reactor washed with water (110 mL, 8.9 vol) onto the filter cake. The solid was dried in a vacuum oven at 60 °C to give 8.29 g of **2** (89% yield). M.p. 220-223 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.48 (br m, 1 H), 0.82 (br m, 2 H), 0.98 (br m, 1 H), 2.02 - 2.13 (m, 1 H), 2.84 (d, *J*=4.60 Hz, 3 H), 3.34 (s, 3 H), 4.96 (s, 2 H), 7.22 (s, 1 H), 7.27 (d, *J*=1.76 Hz, 1 H), 7.37 - 7.46 (m, 3 H), 7.93 - 8.01 (m, 2 H), 8.08 (s, 1 H), 8.50 (q, *J*=4.47 Hz, 1 H), 9.18 (s, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.41. ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 8.5, 9.4, 12.3, 26.7, 41.0, 70.0, 114.1, 115.2, 116.5 (d, *J*=22.0 Hz), 117.1, 122.5, 126.0 (d, *J*=3.0 Hz), 128.5, 129.9 (d, *J*=8.51 Hz), 136.6, 136.7, 139.2, 145.3, 151.4, 154.1, 157.5, 163.3 (d, *J*=248.5 Hz), 163.4. HRMS (ESI): *m*/*z* calculated for $C_{27}H_{24}BClFN_2O_6S$ [M+H]$^+$: 569.1115; found: 569.1119.

Isolation of 6-(*N*-(3-chloro-5-(hydroxymethyl)phenyl)methylsulfonamido)-5-cyclopropyl-2-(4-fluorophenyl)-*N*-methylbenzofuran-3-carboxamide (35). This compound was isolated from the THF/TBME back extractions of the basic aqueous phase during the preparation of **2** as described above. An isolated yield was not determined; this material was used to confirm the structure of **35**. M.p. 128 °C (decomp). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.47 (br m, 1 H), 0.84 (br m, 2 H), 0.99 (br m, 1 H), 2.09 - 2.19 (m, 1 H), 2.84 (d, *J*=4.60 Hz, 3 H), 3.42 (s, 3 H), 4.47 (br m, 2 H), 5.39 (br m, 1 H), 7.19 (s, 1 H), 7.23 (s, 1 H), 7.32 - 7.38 (m, 2 H), 7.38 - 7.45 (m, 2 H), 7.91 - 8.03 (m, 2 H), 8.11 (s, 1 H), 8.50 (q, *J*=4.50 Hz, 1 H). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ ppm -110.44 (s, 1 F). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ ppm 8.4 (br) 9.6 (br) 12.3, 26.7, 40.8, 62.4, 113.9, 114.0, 116.5 (d, *J*=22.0 Hz), 121.2, 122.8, 123.7, 126.0 (d, *J*=3.1 Hz), 128.4, 129.9 (d, *J*=8.9 Hz), 133.4, 136.9, 139.2, 142.7, 146.5, 151.4, 154.0, 163.2 (d, *J*=248.0 Hz), 163.5. HRMS (ESI): *m*/*z* calculated for $C_{27}H_{25}ClFN_2O_5S$ [M+H]$^+$: 543.1151; found: 543.1155.

ASSOCIATED CONTENT

Characterization data (^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra, and LCMS traces) for all isolated compounds, and tables of screening data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

* john.a.kowalski@gsk.com
* david.c.leitch@gsk.com; dcleitch@uvic.ca

Notes

The authors are current or former employees of GlaxoSmithKline, and may own company stock.

ACKNOWLEDGMENT

The authors thank all of the members of the API Chemistry Department at GSK for insightful discussions and assistance throughout the course of this work. We also thank Joseph Reckamp for assistance with gas/liquid mixing in the Chan-Lam coupling, Dr. Michael Morris for HRMS analysis, and Dr. Anna Dunn and Dr. Frank Yin for discussions regarding reaction monitoring.

REFERENCES

(1) *Global Hepatitis Report 2017*. World Health Organization: Geneva, 2017.

(2) (a) Sofia, M. J.; Bao, D.; Chang, W.; Du, J.; Nagarathnam, D.; Rachakonda, S.; Reddy, P. G.; Ross, B. S.; Wang, P.; Zhang, H.-R.; Bansal, S.; Espiritu, C.; Keilman, M.; Lam, A. M.; Steuer, H. M. M.; Niu, C.; Otto, M. J.; Furman, P. A. Discovery of a β-d-2′-Deoxy-2′-α-fluoro-2′-β-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus. *J. Med. Chem.* **2010**, *53*, 7202-7218. (b) Harper, S.; McCauley, J. A.; Rudd, M. T.; Ferrara, M.; DiFilippo, M.; Crescenzi, B.; Koch, U.; Petrocchi, A.; Holloway, M. K.; Butcher, J. W.; Romano, J. J.; Bush, K. J.; Gilbert, K. F.; McIntyre, C. J.; Nguyen, K. T.; Nizi, E.; Carroll, S. S.; Ludmerer, S. W.; Burlein, C.; DiMuzio, J. M.; Graham, D. J.; McHale, C. M.; Stahlhut, M. W.; Olsen, D. B.; Monteagudo, E.; Cianetti, S.; Giuliano, C.; Pucci, V.; Trainor, N.; Fandozzi, C. M.; Rowley, M.; Coleman, P. J.; Vacca, J. P.; Summa, V.; Liverton, N. J. Discovery of MK-5172, a Macrocyclic Hepatitis C Virus NS3/4a Protease Inhibitor. *ACS Med. Chem. Lett.* **2012**, *3*, 332-336. (c) Coburn, C. A.; Meinke, P. T.; Chang, W.; Fandozzi, C. M.; Graham, D. J.; Hu, B.; Huang, Q.; Kargman, S.; Kozlowski, J.; Liu, R.; McCauley, J. A.; Nomeir, A. A.; Soll, R. M.; Vacca, J. P.; Wang, D.; Wu, H.; Zhong, B.; Olsen, D. B.; Ludmerer, S. W. Discovery of MK-8742: An HCV NS5A inhibitor with broad genotype activity. *ChemMedChem* **2013**, *8*, 1930-1940. (d) Link, J. O.; Taylor, J. G.; Xu, L.; Mitchell, M.; Guo, H.; Liu, H.; Kato, D.; Kirschberg, T.; Sun, J.; Squires, N.; Parrish, J.; Kellar, T.; Yang, Z.-Y.; Yang, C.; Matles, M.; Wang, Y.; Wang, K.; Cheng, G.; Tian, Y.; Mogalian, E.; Mondou, E.; Cornpropst, M.; Perry, J.; Desai, M. C. Discovery of Ledipasvir (GS-5885): A Potent, Once-Daily Oral NS5A Inhibitor for the Treatment of Hepatitis C Virus Infection. *J. Med. Chem.* **2014**, *57*, 2033-2046. (e) Belema, M.; Meanwell, N. A. Discovery of Daclatasvir, a Pan-Genotypic Hepatitis C Virus NS5A Replication Complex Inhibitor with Potent Clinical Effect. *J. Med. Chem.* **2014**, *57*, 5057-5071. (f) Zhang, J.; Nguyen, D.; Hu, K.-Q. Chronic Hepatitis C Virus Infection: A Review of Current Direct Acting Antiviral Treatment Strategies. *N. Am. J. Med. Sci. (Boston)* **2016**, *9*, 47–54. (g) Sofia, M. J. Sofosbuvir: the discovery of a curative therapy for the treatment of hepatitis C virus. in *Successful Drug Discovery, Vol. 2* (Eds.: Fischer, J.; Childers, W. E.), WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2017**, pp. 163-188.

(3) (a) Powdrill, M. H.; Bernatchez, J. A.; Götte, M. Inhibitors of the Hepatitis C Virus RNA-Dependent RNA Polymerase NS5B. *Viruses* **2010**, *2*, 2169-2195. (b) Sofia, M. S.; Chang, W.; Furman, P. A.; Mosley, R. T.; Ross, B. S. Nucleoside, Nucleotide, and Non-Nucleoside Inhibitors of Hepatitis C Virus NS5B RNA-Dependent RNA-Polymerase. *J. Med. Chem.* **2012**, *55*, 2481-2531.

(4) Deval, J.; Symons, J. A.; Beigelman, L. Inhibition of viral RNA polymerases by nucleoside and nucleotide analogs: therapeutic applications against positive-strand RNA viruses beyond hepatitis C virus. *Curr. Opin. Virol.* **2014**, *9*, 1-7.

(5) Fenaux, M.; Mo, H. NS5B polymerase non-nucleoside inhibitors. in *Hepatitis C* (Eds.: Tan, S.-L.; He, Y.), Caister Academic Press, Norwich UK, **2011**, pp. 311-320.

(6) (a) Maynard, A.; Crosby, R. M.; Ellis, B.; Hamatake, R.; Hong, Z.; Johns, B. A.; Kahler, K. M.; Koble, C.; Leivers, A.; Leivers, M. R.; Mathis, A.; Peat, A. J.; Pouliot, J. J.; Roberts, C. D.; Samano, V.; Schmidt, R. M.; Smith, G. K.; Spaltenstein, A.; Stewart, E. L.; Thommes, P.; Turner, E. M.; Voitenleitner, C.; Walker, J. T.; Waitt, G.; Weatherhead, J.; Weaver, K.; Williams, S.; Wright, L.; Xiong, Z. Z.; Haigh, D.; Shotwell, J. B. Discovery of a Potent Boronic Acid Derived Inhibitor of the HCV RNA-Dependent RNA Polymerase. *J. Med. Chem.* **2014**, *57*, 1902-1913. (b) Bowman, R. K.; Bullock, K. M.; Copley, R. C. B.; Deschamps, N. M.; McClure, M. S.; Powers, J. D.; Wolters, A. M.; Wu, Lianming, Xie, S. Conversion of a Benzofuran Ester to an Amide through an Enamine Lactone Pathway: Synthesis of HCV Polymerase Inhibitor GSK852A. *J. Org. Chem.* **2015**, *80*, 9610-9619. (c) Song, Z. J.; Tan, L.; Liu, G.; Ye, H.; Dong, J. Concise Cu(I) Catalyzed Synthesis of Substituted Benzofurans via a Tandem SNAr/C-O Coupling Process. *Org. Process Res. Dev.* **2016**, *20*, 1088-1092.

(7) (a) Yang, W.; Gao, X.; Wang, B. Boronic acid compounds as potential pharmaceutical agents. *Med. Res. Rev.* **2003**, *23*, 346-368. *(b)* Ciani, L.; Ristori, S. Boron as a Platform for New Drug Design. *Expert Opin. Drug Discovery* **2012**, *7*, 1017–1027.

(8) (a) P. Y. Chong, J. F. Miller, A. J. Peat, J. B. Shotwell, *Benzofuran compounds for the treatment of hepatitis c virus infections*, WO2013028371A1, 28 February 2013. (b) Gardner, S. D.; Kim, J.; Baptise-Brown, S>; Lopez, V.; Hamatake, R.; Gan, J.; Edwards, S.; Elko-Simms, L.; Dumont, E. F.; Leivers, M.; Hong, Z.; Paff, M. T. GSK2878175, a pan- genotypic non- nucleoside NS5B polymerase inhibitor, in healthy and treatment-naïve chronic hepatitis C subjects. *J. Viral Hepat.* **2018**, *25*, 19-27.

(9) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. Pd-Catalyzed N-Arylation of Secondary Acyclic Amides: Catalyst Development, Scope, and Computational Study. *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734.

(10) (a) Wu, Y.-J.; Zhang, Y.; Good, A. C.; Burton, C. R.; Toyn, J. H.; Albright, C. F.; Macor, J. E.; Thompson, L. A. Synthesis and SAR of hydroxyethylamine based phenylcarboxyamides as inhibitors of BACE. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2654–2660. (b) Rosen, B. R.; Ruble, J. C.; Beauchamp, T. J.; Navarro, A. Mild Pd-Catalyzed N-Arylation of Methanesulfonamide and Related Nucleophiles: Avoiding Potentially Genotoxic Reagents and Byproducts. *Org. Lett.* **2011**, *13*, 2564-2567. (c) Crawford, S. M.; Lavery, C. B.; Stradiotto, M. BippyPhos: A Single Ligand With Unprecedented Scope in the Buchwald–Hartwig Amination of (Hetero)aryl Chlorides. *Chem. Eur. J.* **2013**, *19*, 16760-16771.

(11) Naito, H.; Hata, T.; Urabe, H. Selective Deprotection of Methanesulfonamides to Amines. *Org. Lett.* **2010**, *12*, 1228-1230.

(12) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N- and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998**, *39*, 2933-2936. (b) Evans, D. A; Katz, J. L.; West, T. R. Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine. *Tetrahedron Lett.* **1998**, *39*, 2937-2940. (c) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New aryl/heteroaryl C-N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. *Tetrahedron Lett.* **1998**, *39*, 2941-2944. (d) Qiao, J.; Lam, P. Y. S. „Copper-Promoted Carbon-Heteroatom Bond Cross-Coupling with Boronic Acids and Derivatives. *Synthesis* **2011**, 829–856. (e) Lam, P. Y. S. Chan–Lam Coupling Reaction: Copper-promoted C–Element Bond Oxidative Coupling Reaction with Boronic Acids. in *Synthetic Methods in Drug Discovery* (Eds.: Blakemore, D. C.; Doyle, M. P.; Fobian, Y. M.), Royal Society of Chemistry, Cambridge, **2016**, Vol. 1, Chapter 7, pp 242–273. (f) Vantourout, J. C.; Miras, H. N.; Isidro-Llobet, A.; Sproules, S.; Watson, A. J. B. Spectroscopic Studies of the Chan–Lam Amination: A Mechanism-Inspired Solution to Boronic Ester Reactivity. *J. Am. Chem. Soc.* **2017**, *139*, 4769-4779.

(13) (a) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, *2nd ed., Vols. 1 and 2*. (Ed.: Hall, D.) WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2011**; pp 1–133. (b) Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. Protodeboronation of Heteroaromatic, Vinyl, and Cyclopropyl Boronic Acids: pH–Rate Profiles, Autocatalysis, and Disproportionation. *J. Am. Chem. Soc.* **2016**, *138*, 9145-9157.

(14) (a) Cho, J. Y., Tse, M. K., Holmes, D., Maleczka, R. E., Jr. and Smith, M. R., III Remarkably selective iridium catalysts for the elaboration of aromatic C-H bonds. *Science* **2002**, *295*, 305-308. (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. C–H Activation for the Construction of C–B Bonds. *Chem. Rev.* **2010**, *110*, 890-931. (c) Xu, L.; Wang, G.; Zhang, S.; Wang, H.; Wang, L.; Liu, L.; Jiao, J.; Li, P. Recent advances in catalytic C-H borylation reactions. *Tetrahedron* **2017**, *73*, 7123-7157.

(15) (a) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. A Stoichiometric Aromatic C-H Borylation Catalyzed by Iridium(I)/2,2′-Bipyridine Complexes at Room Temperature. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056-3058. (b) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. Mechanism of the Mild Functionalization of Arenes by Diboron Reagents Catalyzed by Iridium Complexes. Intermediacy and Chemistry of Bipyridine-Ligated Iridium Trisboryl Complexes. *J. Am. Chem. Soc.* **2005**, *127*, 14263-14278.

(16) Preshlock, S. M., Ghaffari, B., Maligres, P. E., Krska, S. W., Maleczka, R. E. Smith, M. R., III High-Throughput Optimization of Ir-Catalyzed C–H Borylation: A Tutorial for Practical Applications. *J. Am. Chem. Soc.* **2013**, *135*, 7572-7582.

(17) While grinding crystalline $[Ir(COD)Cl]_2$ in a mortar and pestle is feasible for lab-scale and even kiloscale operation (due to the small amount of catalyst required), other options (such as milling and sieving the solid to a consistent particle size) would be needed for large-scale operation.

(18) A preliminary account of this Chan-Lam methodology for general arylation of sulfonamides has been published recently. Vantourout, J. C.; Li, L.; Bendito-Moll, E.; Chabbra, S.; Arrington, K.; Bode, B. E.; Isidro-Llobet, A.; Kowalski, J. A.; Nilson, M. G.; Wheelhouse, K. M. P.; Woodard, J. L.; Xie, S.; Leitch, D. C.; Watson, A. J. B. Mechanistic Insight Enables Practical, Scalable, Room Temperature Chan-Lam *N*-Arylation of *N*-Aryl Sulfonamides. *ACS Catal.* **2018**, *8*, 9560-9566.

(19) (a) Mudryk, B.; Zheng, B.; Chen, K.; Eastgate, M. Development of a Robust Process for the Preparation of High-Quality Dicyclopropylamine Hydrochloride D. *Org. Process Res. Dev.* **2014**, *18*, 520-527. (b) Osterberg, P. M.; Niemeier, J. K.; Welch, C. J.; Hawkins, J. M.; Martinelli, J. R.; Johnson, T. E.; Root, T. W.; Stahl, S. S. Experimental Limiting Oxygen Concentrations for Nine Organic Solvents at Temperatures and Pressures Relevant to Aerobic Oxidations in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2015**, *19*, 1537–1543.

(20) While operating below the LOC for the organic solvent(s) used in an aerobic oxidation is necessary for ensuring a basis of safety, it is not sufficient to establish said basis of safety. Additional safety testing at every point of the process and implementation of the appropriate engineering controls are required for any large-scale process that involves the risk of combustion.

(21) (a) Ainley, A. D.; Challenger, F. CCLXXX.—Studies of the boron–carbon linkage. Part I. The oxidation and nitration of phenylboric acid. *J. Chem. Soc.* **1930**, 2171-2180. (b) Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. The Conversion

of Phenols to the Corresponding Aryl Halides Under Mild Conditions. *Synthesis* **2005**, 547-550. (c) Murphy, J. C.; Liao, X.; Hartwig, J. F. Meta Halogenation of 1,3-Disubstituted Arenes via Iridium-Catalyzed Arene Borylation. *J. Am. Chem. Soc.* **2007**, *129*, 15434-15435.

(22) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. New coupling reagents in peptide chemistry. *Tetrahedron Lett.* **1989**, 1927-1930.

(23) El-Faham, A.; Funosas, R. S.; Prohens, R.; Albericio, F. COMU: A Safer and More Effective Replacement for Benzotriazole-Based Uronium Coupling Reagents. *Chem. Eur. J.* **2009**, *15*, 9404-9416.

(24) Ishiyama, T.; Murata, M.; Miyaura, N. Palladium(0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters. *J. Org. Chem.* **1995**, *60*, 7508-7510.

(25) (a) Ishiyama, T.; Miyaura, N. Metal-catalyzed reactions of diborons for synthesis of organoboron compounds. *Chem. Rec.* **2004**, *3*, 271-280. (b) Chow, W. K.; Yuen, O. Y.; Choy, P. Y.; So, C. M.; Lau, C. P.; Wong, W. T.; Kwong, F. Y. A decade advancement of transition metal-catalyzed borylation of aryl halides and sulfonates. *RSC Adv.* **2013**, *3*, 12518-12539;

(26) Zalesskiy, S. S.; Ananikov, V. P. $Pd_2(dba)_3$ as a Precursor of Soluble Metal Complexes and Nanoparticles: Determination of Palladium Active Species for Catalysis and Synthesis. *Organometallics* **2012**, *31*, 2302-2309.

(27) Under the current reaction conditions, use of $Pd(OAc)_2$ led to inconsistent results; however, this would likely be overcome by a thorough study of Pd reduction pathways under the reaction conditions. For an excellent example of this in the context of Miyaura borylation, see: Wei, C. S.; Davies, G. H. M.; Soltani, O.; Albrecht, J.; Gao, Q.; Pathirana, C.; Hsiao, Y.; Tummala, S.; Eastgate, M. D. The Impact of Palladium(II) Reduction Pathways on the Structure and Activity of Palladium(0) Catalysts. *Angew. Chem. Int. Ed.* **2013**, *52*, 5822-5826.

(28) Lapointe D.; Fagnou, K. Overview of the Mechanistic Work on the Concerted Metallation–Deprotonation Pathway. *Chem. Lett.* **2010**, *39,* 1118-1126.

(29) Miyaura, N. Cross-coupling reaction of organoboron compounds via base-assisted transmetalation to palladium(II) complexes. *J. Organomet. Chem.* **2002**, *653*, 54-57.

(30) (a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. Analysis of the Concerted Metalation-Deprotonation Mechanism in Palladium-Catalyzed Direct Arylation Across a Broad Range of Aromatic Substrates. *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849. (*b)* Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. Mechanistic Analysis of Azine N-Oxide Direct Arylation: Evidence for a Critical Role of Acetate in the Pd(OAc)2 Precatalyst. *J. Org. Chem.* **2010**, *75*, 8180-8189. (c) Tan, Y.; Hartwig, J. F. Assessment of the Intermediacy of Arylpalladium Carboxylate Complexes in the Direct Arylation of Benzene: Evidence for C–H Bond Cleavage by Ligandless. Species. *J. Am. Chem. Soc.* **2011**, *133*, 3308-3311.

(31) (a) Lafrance, M.; Fagnou, K. Palladium-Catalyzed Benzene Arylation: Incorporation of Catalytic Pivalic Acid as a Proton Shuttle and a Key Element in Catalyst Design. *J. Am. Chem. Soc.* **2006**, *128*, 16496-16497. (b) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. Investigation of the Mechanism of C(sp^3)–H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation Adjacent to Amides and Sulfonamides. *J. Am. Chem. Soc.* **2010**, *132*, 10692-10705.

Table of Contents artwork (ChemDraw format):