JOC The Journal of Organic Chemistry

Article

Discovery and Development of Metal#Catalyzed Coupling Reactions in the Synthesis of Dasabuvir, an HCV#Polymerase Inhibitor

David M. Barnes, Shashank Shekhar, Travis B. Dunn, Jufang H Barkalow, Vincent S. Chan, Thaddeus S. Franczyk, Anthony R. Haight, John E Hengeveld, Lawrence Kolaczkowski, Brian J. Kotecki, Guangxin Liang, James Christopher Marek, Maureen A. McLaughlin, Donna K Montavon, and James J. Napier

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02690 • Publication Date (Web): 10 Jan 2019

ACS Publications

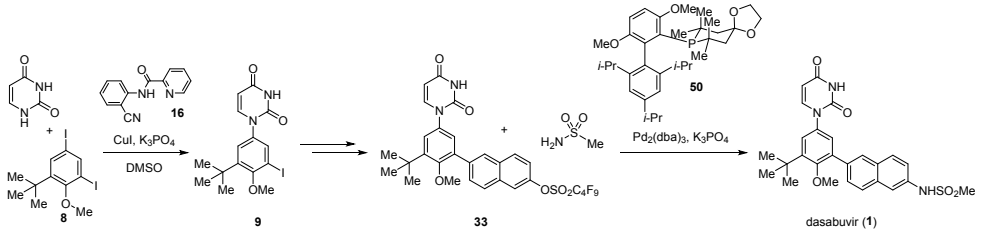
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Discovery and Development of Metal-Catalyzed Coupling Reactions in the Synthesis of Dasabuvir, an HCV-Polymerase Inhibitor

David M. Barnes,* Shashank Shekhar,* Travis B. Dunn,* Jufang H. Barkalow, Vincent S. Chan, Thaddeus S. Franczyk, Anthony R. Haight, John E. Hengeveld, Lawrence Kolaczkowski, Brian J. Kotecki, Guangxin Liang, James C. Marek, Maureen A. McLaughlin, Donna K. Montavon, James J. Napier

†Process Chemistry, AbbVie Inc., North Chicago, Illinois, USA

*Corresponding author email: david.barnes@abbvie.com, shashank.shekhar@abbvie.com and travis.dunn@abbvie.com



ABSTRACT: Dasabuvir (**1**) is an HCV polymerase inhibitor which has been developed as a part of a three component direct acting antiviral combination therapy. During the course of the development of the synthetic route, two novel coupling reactions were developed. First, the copper-catalyzed coupling of uracil with aryl iodides, employing picolinamide **16** as the ligand, was discovered. Later, the palladium-catalyzed sulfonamidation of aryl nonaflates was developed, promoted by electron-rich palladium complexes, including the novel phosphine ligand, VincePhos (**50**). This made possible a convergent, highly efficient synthesis of dasabuvir that significantly reduced the mutagenic impurity burden of the process.

■ INTRODUCTION

Hepatitis C virus (HCV) infection is a global epidemic, with an estimated global prevalence of 1.6%[1] to 2.8%[2] corresponding to about 115,000,000 infected people worldwide, including approximately 3,000,000 in the United States.[3] Although HCV infection can remain asymptomatic for years, it is responsible for about 500,000 deaths per year as it is a causative agent of conditions such as cirrhosis and hepatocellular carcinoma.[3]

Prior to 2011, the standard therapy for HCV was treatment with interferon and ribavirin.[4] This regimen had severe side effects, while affording poor response rates. In 2011, FDA approved the first direct-acting antiviral (DAA) medicines, telaprevir and boceprevir. When added to the interferon/ribavirin regimen, these DAAs significantly improved cure rates; however, the side effects associated with interferon remained a significant issue for these new therapies, as did new side effects related to the DAAs themselves.[4]

Dasabuvir (**1**, Figure 1) is a non-nucleoside HCV polymerase inhibitor developed as part of an interferon-free DAA combination therapy (Viekira Pak®) which includes the NS5A inhibitor ombitasvir (**2**) and the NS3/4A protease inhibitor paritaprevir (**3**). This combination affords a high-sustained viral response 12 weeks after dosing (SVR12) and is generally safe and better tolerated than interferon-based regimens.[5]

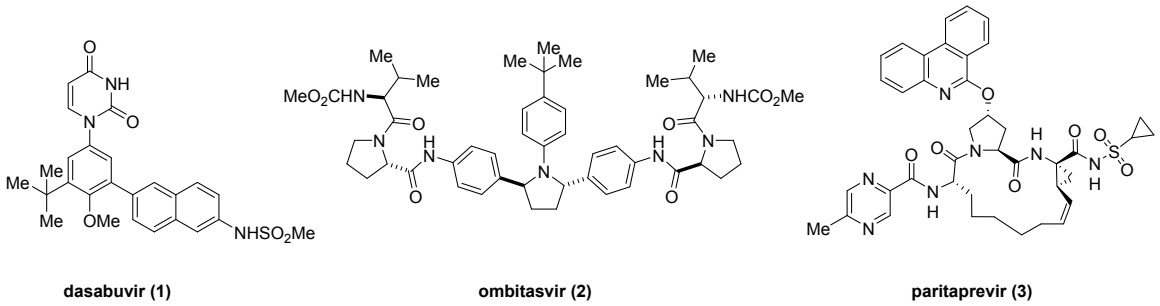
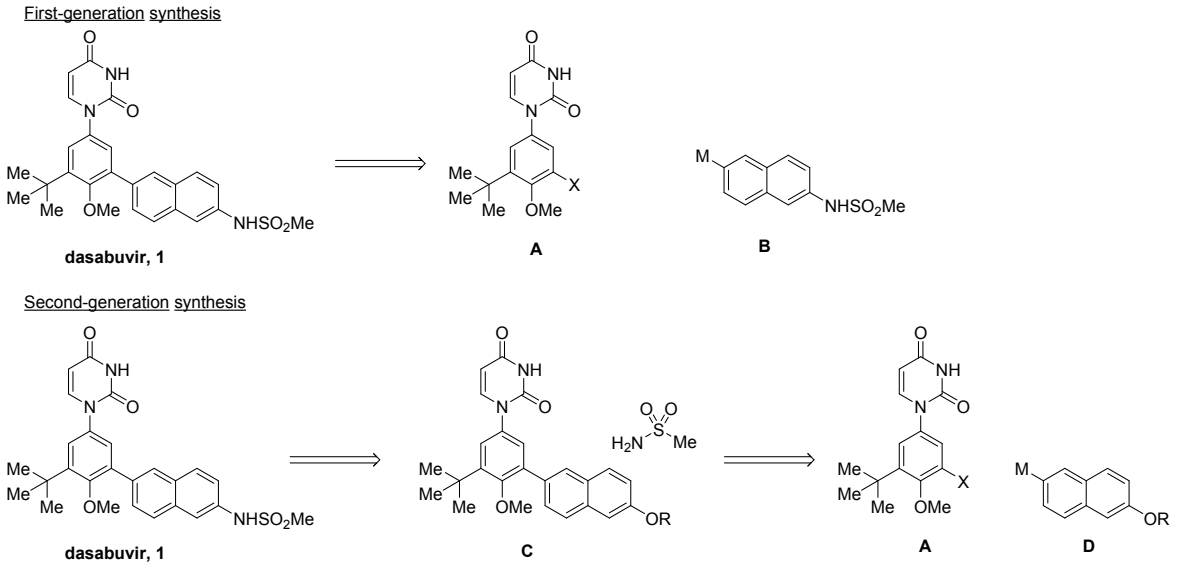


Figure 1. Dasabuvir (**1**), ombitasvir (**2**) and paritaprevir (**3**)

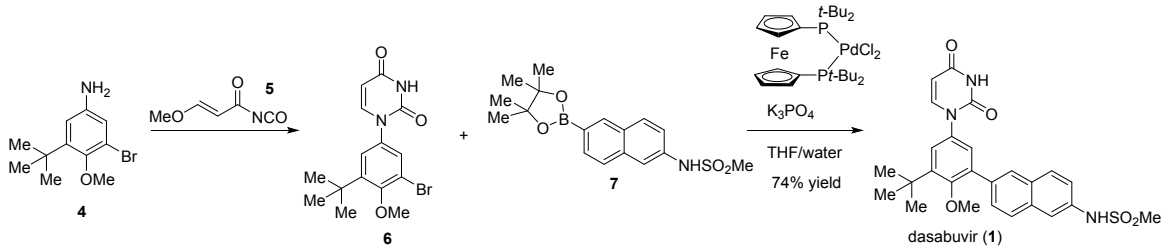
Our initial retrosynthetic analysis identified a highly convergent synthesis of dasabuvir through the coupling of a uracil-substituted halogenated arene core, represented by **A,** with an appropriate naphthyl nucleophile **B** (Scheme 1). Therefore, our first-generation approach targeted efficient syntheses of the requisite *N1*-aryl uracil derivative **A** and methanesulfonamide-substituted naphthyl coupling partner **B**. During process development, we discovered that *N*-naphthyl methanesulfonamide derivatives **B** represented a significant mutagenic impurity liability. Therefore, we developed a second-generation synthesis in which the methanesulfonamide moiety was introduced at the end of the synthesis. This required development of a metal-catalyzed sulfonamide coupling, as well as a new ligand family to facilitate the sulfonamide coupling.[6]



Scheme 1. Retrosynthesis of dasabuvir (**1**) via aryl uracil **A**

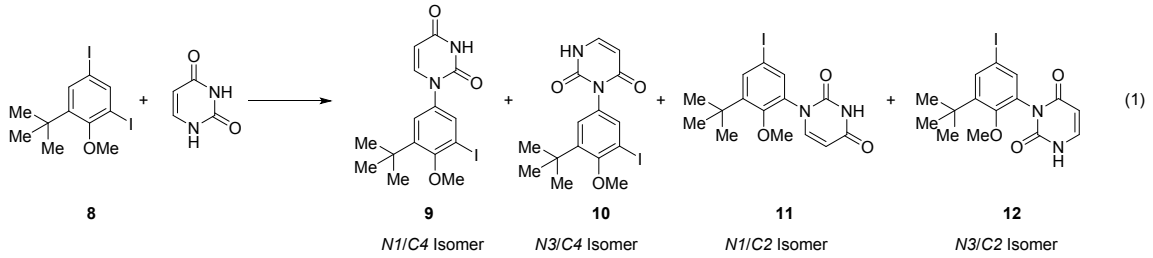
■ RESULTS AND DISCUSSION

Previous work had demonstrated that the condensation of aniline **4** with acyl isocyanate **5** afforded bromide **6** (Scheme 2).[7] Coupling of bromide **6** to boronate ester **7**, using palladium(II) (1,1'-bis(di-*tert*-butylphosphino)ferrocene) dichloride ($Pd(dtbpf)Cl_2$), afforded dasabuvir in acceptable yield. However, this approach suffered from the thermal sensitivity of the acyl isocyanate reagent **5** which was purified by distillation; when this distillation was scaled up, extensive decomposition was observed. We therefore investigated alternate approaches to halogenated *N1*-aryl uracil derivatives such as **6**.[8]

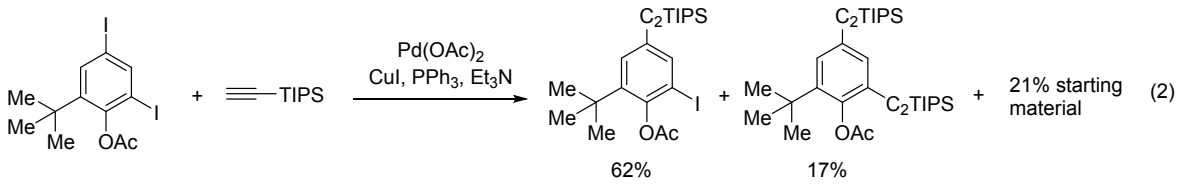


Scheme 2. Synthesis of dasabuvir (**1**) via bromide **6**

A conceptually elegant and direct approach to the desired *N1*-aryl uracil derivatives is the metal-catalyzed coupling of uracil to a 2,4-dihaloanisole derivative (eq 1). Inherent to this approach is the combined challenge of ensuring the desired chemoselectivity on both the uracil (*N1* vs *N3*) and the dihaloarene (*C4* vs *C2*) coupling partners. Initial experiments with a dibromoarene substrate and copper catalysts (vide infra) provided some coupling product **6**, but low conversion and multiple side products were observed, presumably due to the high temperatures, which detracted from the use of the bromo electrophile (data not shown). Given the expected higher reactivity of aryl iodides in copper-catalyzed reactions, we explored coupling of uracil with diiodoanisole **8** to prepare iodide **9**.



Literature precedent for the selective coupling at the *C4*-iodide of **8** was not clear. Sonogashira coupling of the related acetylated substrate afforded a mixture of mono- and bis-alkyne products (eq 2).[9] While this result indicated that the *C4*-iodide was more reactive, it did suggest that reaction at *C2* could be a complicating issue.



The literature precedents for chemoselective coupling of uracil were also unclear (Figure 2). Zhou and coworkers described the copper-catalyzed arylation of uracil with diaryliodonium salts which resulted in a moderate yield of the desired *N1*-arylated uracil (Figure 2a).[10] On the other hand, Maruyama and coworkers found that the Gabriel reaction of uracil with iodobenzene led to the diaryl product (Figure 2b).[11] While our studies were underway, Rad, Behrouz and coworkers described the *N1*-arylation of uracil using copper nanoparticle-doped silica cuprous sulfate.[12] Yields up to 60% of 1-phenyluracil were observed in the reaction of uracil with iodobenzene (Figure 2c).

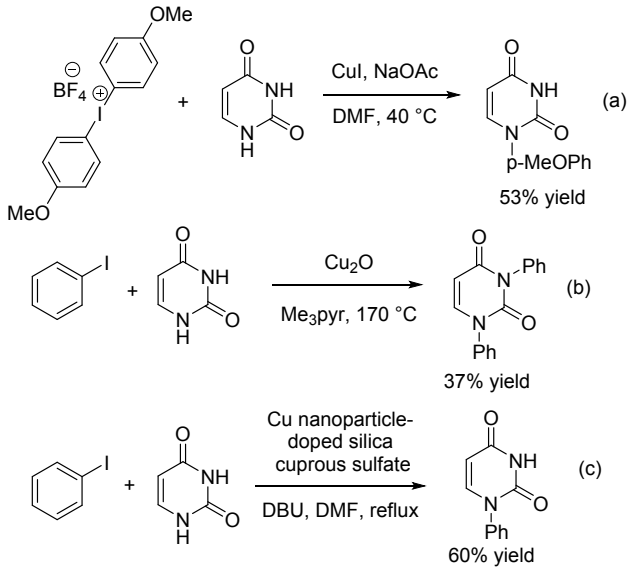
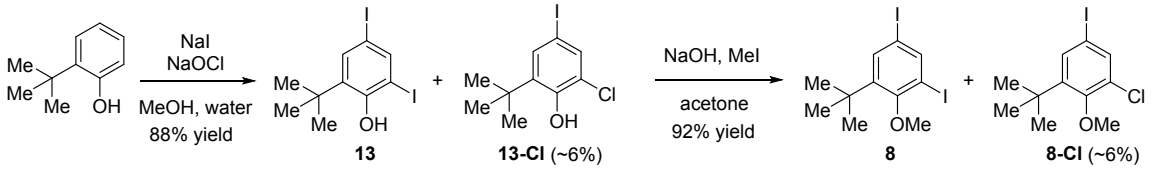


Figure 2. Copper-catalyzed arylations of uracil

■ Preparation of Iodo-Substituted 1-Aryluracil 9

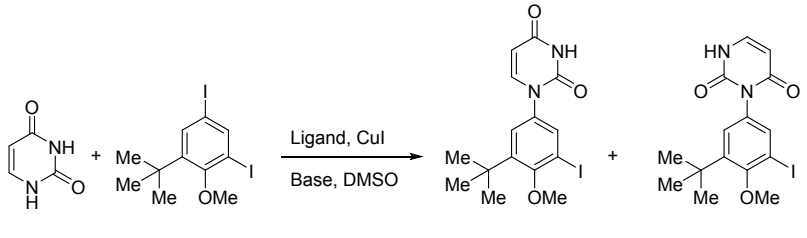
The preparation of diiodoanisole **8** from 2-*tert*-butylphenol proved to be straightforward (Scheme 3). Treatment of 2-*tert*-butylphenol with NaI and bleach[13,14] proved an efficient method for installing the iodides in diiodophenol **13**. Methylation (NaOH, MeI, acetone) then completed the synthesis of diiodoanisole **8**. The major impurity in **8** was the 2-chlorinated derivative **8-Cl**, which was observed at up to 6%. Impurity **8-Cl** was carried forward into the next step.



Scheme 3. Preparation of diiodoanisole **8**

As planned, the coupling of uracil with **8** proceeded to give the desired product **9** (Table 1). Due to the low solubility of uracil, the reaction proceeded only in polar solvents, with the optimal solvent being DMSO. The major byproduct was the *N3* isomer **10**; neither of the *C2* isomers **11** or **12** (eq 1) was identified as a significant byproduct. A small ligand screen revealed that 8-hydroxyquinoline[15] and *N*-methylproline afforded moderate conversion, but with rather low selectivity. On the other hand, 2-(2-pyridyl)-benzimidazole (**14**) afforded better selectivity (up to 15:1) and somewhat higher reactivity. This screen also indicated that potassium phosphate was generally superior to potassium carbonate as a base.

Table 1. Ligand Screen in Coupling of Diiodoanisole **8** with Uracil



Entry	Ligand	Base	% Conversion at 18 h/50 °C[a]	% Conversion after additional 24 h/80 °C[a]	Ratio *N1*/*N3*[b]
1	*N*-Methyl Proline	K_2CO_3	21	53	5.7
2	8-Hydroxyquinoline	K_2CO_3	33	46	4.6
3	2-(2-Pyridyl)-benzimidazole (**14**)	K_2CO_3	40	63	13.2
4	*N*-Methyl Proline	K_3PO_4	23	44	5.6
5	8-Hydroxyquinoline	K_3PO_4	23	46	7.4
6	2-(2-Pyridyl)-benzimidazole (**14**)	K_3PO_4	35	69	14.9

All experiments were conducted with CuI (10 mol%), Ligand (20 mol%), base (2.1 equiv), uracil (1.2 equiv) in DMSO (16 mL/g **8**). (a) Conversion determined by HPLC as (area% of **9**)/(area% **8** + area% **9**). (b) Ratio at 24 h time point.

With demonstrable impact of ligand on selectivity, we decided to modify the structure of 2-(2-pyridyl)-benzimidazole **14** (Figure 3). Specifically, we envisioned that opening the benzimidazole ring of **14** would afford an *N*-arylpicolinamide structure, which maintained the 1,4-relationship of the pyridine nitrogen with an acidic proton, as in ligand **14**. Making the assumption that the acidity of the amide would be important, electron-withdrawing substituents on the aniline were examined to lower the pKa of the N-H bond. *N*-Arylpicolinamide ligands 4-cyanophenyl (**15**) and 2-cyanophenyl (**16**) derivatives were prepared and evaluated in the uracil coupling.

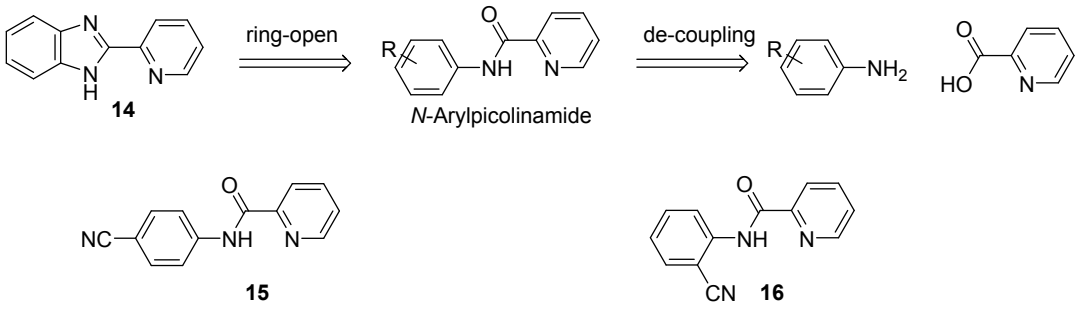
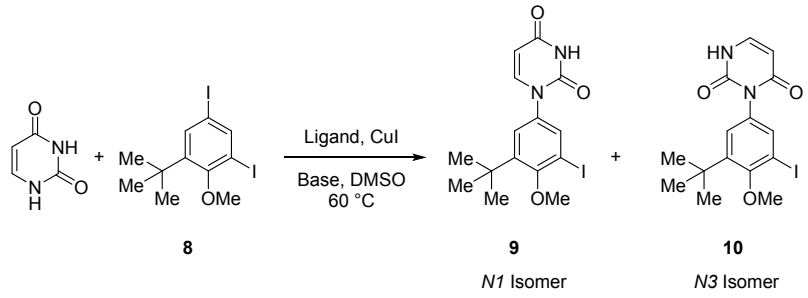


Figure 3. *N*-Arylpicolinamide ligand design

To our delight the 4-cyanophenylpicolinamide **15** provided an excellent *N1*:*N3* selectivity of >25:1 when potassium phosphate was employed as the base (Table 2, entry 3). Anthranilonitrile-derived 2-cyano derivative **16** was even better with selectivity of >60:1, with even higher reactivity.[7] Interestingly, no evidence of uracil coupling at *C2* was observed. Typically, the use of potassium phosphate as the base led to higher reactivity and selectivity. Also, the ratio of ligand to metal had little impact on either reactivity or selectivity.

Table 2. Ligand and Base Study in Coupling of Diiodoanisole **8** with Uracil



Entry	Ligand	L/M ratio	Base	Conversion[a]	*N1/N3* Selectivity
1	**15**	2:1	K_2CO_3	51	19.0
2	**15**	1.2:1	K_2CO_3	41	17.1
3	**15**	2:1	K_3PO_4	67	27.5
4	**15**	1.2:1	K_3PO_4	57	29.0
5	**16**	2:1	K_2CO_3	72	65.6
6	**16**	1.2:1	K_2CO_3	69	66.9
7	**16**	2:1	K_3PO_4	86	69.1
8	**16**	1.2:1	K_3PO_4	80	73.4

All reactions were conducted with CuI (10 mol%), uracil (1.2 equiv), base (2.1 equiv) in DMSO (16 mL/g **8**) at 60 °C. (a) Conversion determined by HPLC as (area% of **9**)/(area% **8** + area% **9**).

The synthesis of the 2-cyanopicolinamide **16** was accomplished in two ways (Figure 4). Reaction of anthranilonitrile with picolinoyl chloride hydrochloride formed **16** directly in 83% yield. The acid chloride was moisture sensitive so alternatively treatment of picolinic acid with toluenesulfonyl chloride afforded the mixed anhydride **17** in situ which was reacted directly with anthranilonitrile to afford **16** in comparable yield (85%).[16]

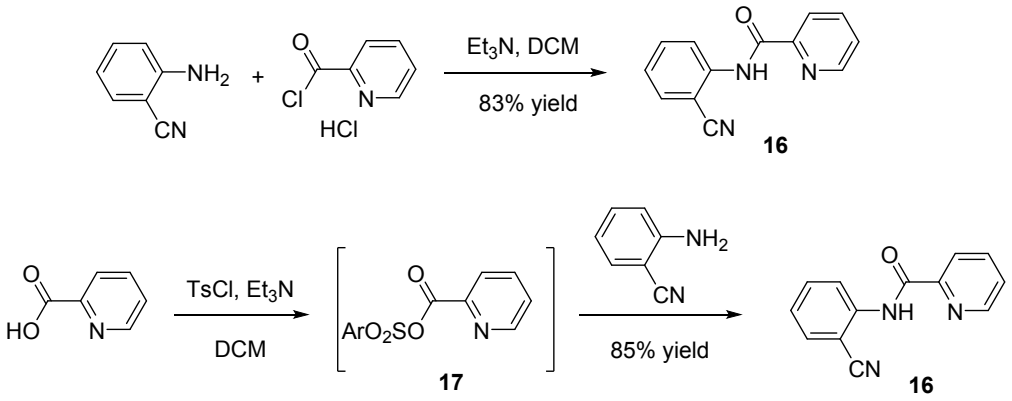


Figure 4. Syntheses of picolinamide ligand **16**

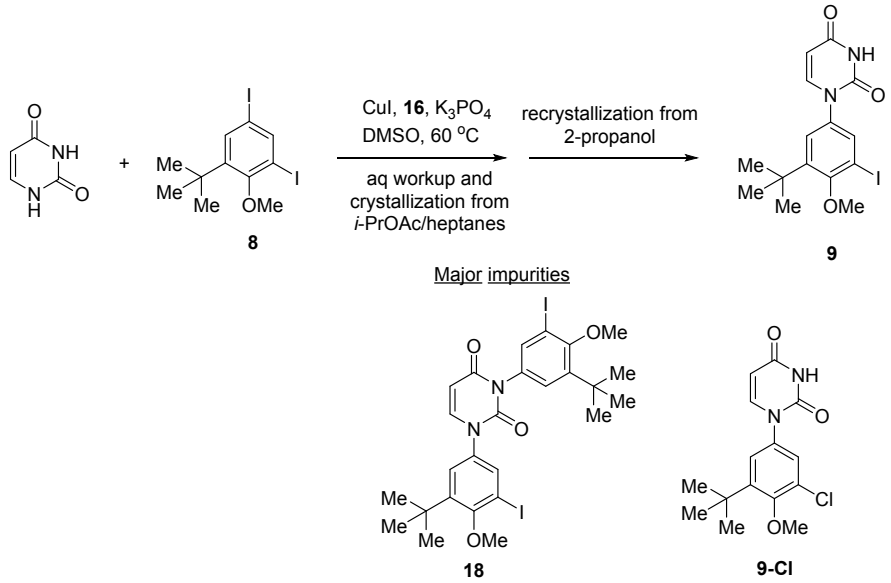
In preparation for executing the process on multi-kilogram scale, we examined the effect of the physical properties of the potassium phosphate on reactivity (Table 3). Powdered potassium phosphate afforded higher reactivity than granular material. Because of the hygroscopicity of the powdered base, we were concerned about the potential impact of water on the reaction rate and selectivity. However, when a reaction was conducted in the presence of 70 mol% water with respect to **8**, little effect on the outcome of the reaction was observed.

Table 3. Base and Water Effects on the Uracil Coupling

	3 h		22 h	
Condition	Conversion[a]	Ratio *N1*/*N3*	Conversion[a]	Ratio *N1*/*N3*
Powdered K_3PO_4[b]	53	49:1	89	58:1
Granular K_3PO_4[c]	38	47:1	82	55:1
Powdered K_3PO_4 with 70 mol% H_2O	60	55:1	91	61:1

All reactions were conducted with CuI (10 mol%), **16** (12 mol%), K_3PO_4 (2.1 equiv) in DMSO (10 mL/g **8**) at 60 °C. (a) Conversion determined by HPLC as (area% of **9**)/(area% **8** + area% **9**). (b) K_3PO_4 was milled to less than 120 micron. (c) Chunks up to mm.

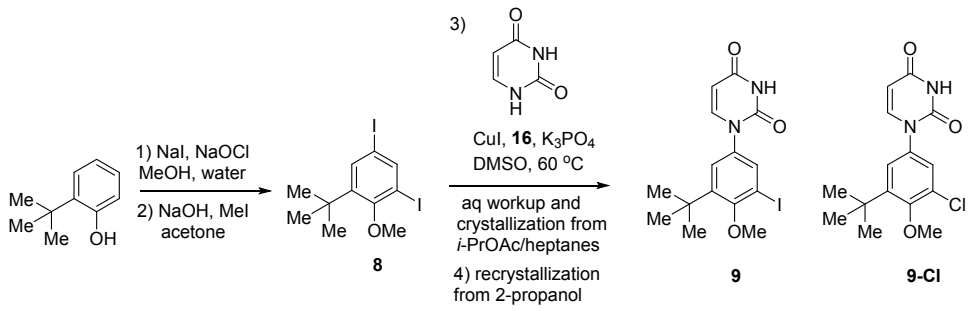
The reaction was sensitive to the presence of oxygen. Typically, the atmosphere above the reaction was maintained below 20 ppm O_2 to ensure reproducible results. Establishing and maintaining an anaerobic atmosphere was accomplished through nitrogen sparging of the large-scale batch reactors. The optimized conditions provided 80–90% conversion before stalling after about 17 hours at 60 °C.The optimized reaction conditions, therefore, employed powdered potassium phosphate as the base, 10 mol% of copper(I) iodide and 12 mol% of ligand **16** (Scheme 4). An aqueous $Cu(OAc)_2$ wash was incorporated in the workup to extract the ligand, which was not purged in the crystallization. The product (**9**) was isolated by crystallization from *i*-PrOAc/heptanes. The side product diaryluracil **18** (~15% formed in the reaction) and the small amount of undesired *N3* isomer **10** could be rejected in the crystallization. Recrystallization of **9** from 2-propanol further improved the purity profile. The major impurity in isolated **9** was chlorinated derivative **9-Cl** (the daughter impurity of **8-Cl**), which was rejected in the next two steps.



Scheme 4. Four-step synthesis of **9**

Conducting the process on multi-kilogram scale provided 63–64% yield of **9** over the four-step sequence, starting from 2-*tert*-butylphenol (Table 4).

Table 4. Representative Examples of Large-Scale Preparation of **9**

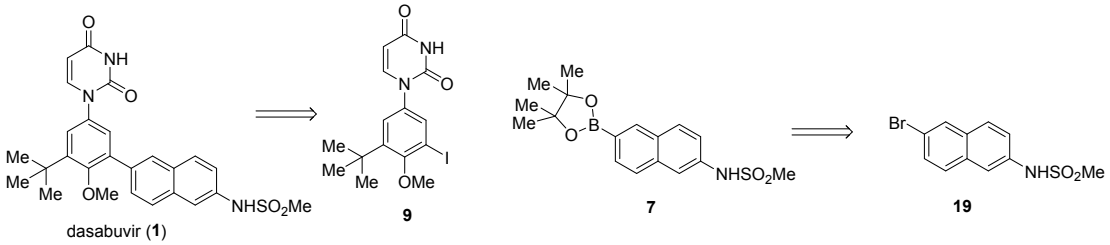


Entry	Scale (kg)[a]	Yield **9** kg	Purity[b] (area%)	Amount of **9-Cl**[b] (area%)	Potency[c,d] (w/w%)
1	85.0	141.7 (63%)	99.3	0.47	99.5
2	85.0	142.0 (63%)	97.8	1.91	99.7
3	85.0	143.8 (64%)	98.9	0.39	98.2
4	85.0	142.8 (63%)	99.3	0.36	99.2

(a) Charge of 2-*tert*-butylphenol. (b) Determined by HPLC. (c) Potency value determined by HPLC analysis against a standard. (d) Potency value includes **9-Cl**.

■ The First-Generation Synthesis

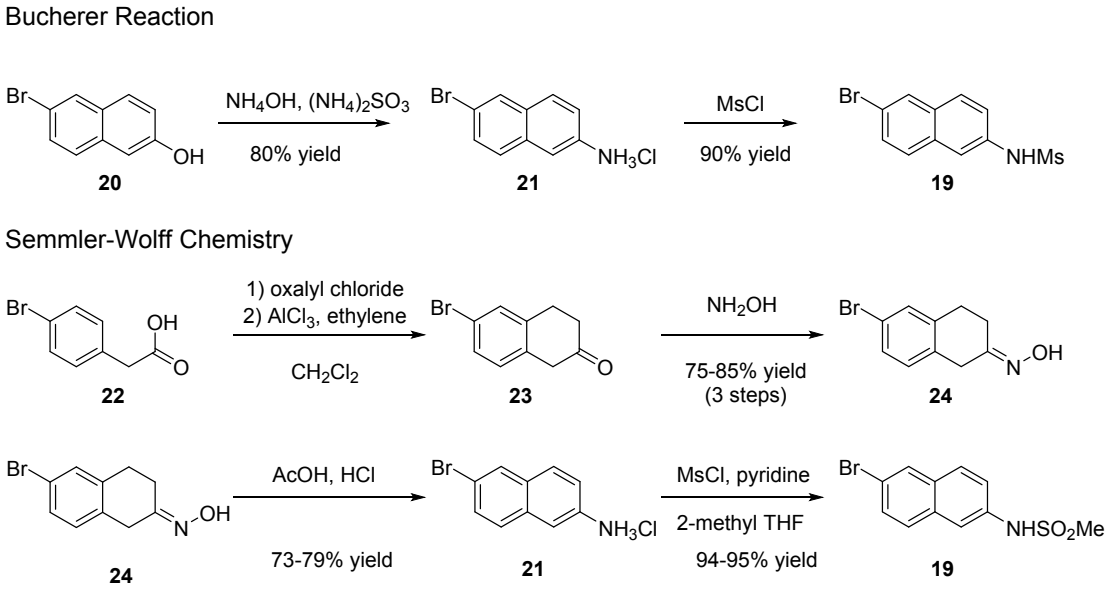
For our first-generation synthesis of dasabuvir, we anticipated that a late-stage coupling of **9** to a fully elaborated naphthyl boronate ester **7** would provide the most convergent synthesis (Scheme 5). Our initial target, therefore, was bromonaphthylsulfonamide **19**, the immediate precursor of **7**.[17]



Scheme 5. First-generation retrosynthesis of dasabuvir (**1**)

Our initial route employed the Bucherer reaction to convert readily available 6-bromo-2-naphthol **20** to 6-bromo-2-naphthyl amine **21** (Scheme 6). While this chemistry led to the shortest route conceivable for **19,** the highly corrosive nature of the reaction rendered it untenable for long-term use.[18] As a result, a second route to **19** employing Semmler–Wolff

chemistry was developed.[19] Although significantly longer, this reaction sequence was not corrosive to the reactor components.



Scheme 6. Routes to bromonaphthylsulfonamide **19**

■ The Borylation Reaction

Miyaura borylation of **19** employed typical conditions (Figure 5).[20] We found that the amount of reduced product, naphthyl methanesulfonamide **25**, was a function of the catalyst load. When 1% of Pd(dppf)Cl_2 was employed, 3% of the reduced product **25** was formed. However, at 0.25 mol% of the catalyst, 34% reduction was observed. Control experiments demonstrated that the reduced product was not the product of proteodeborylation of the boronate ester **7**.[21] Typically, 1% of the catalyst was employed as a compromise between catalyst cost and reaction yield.

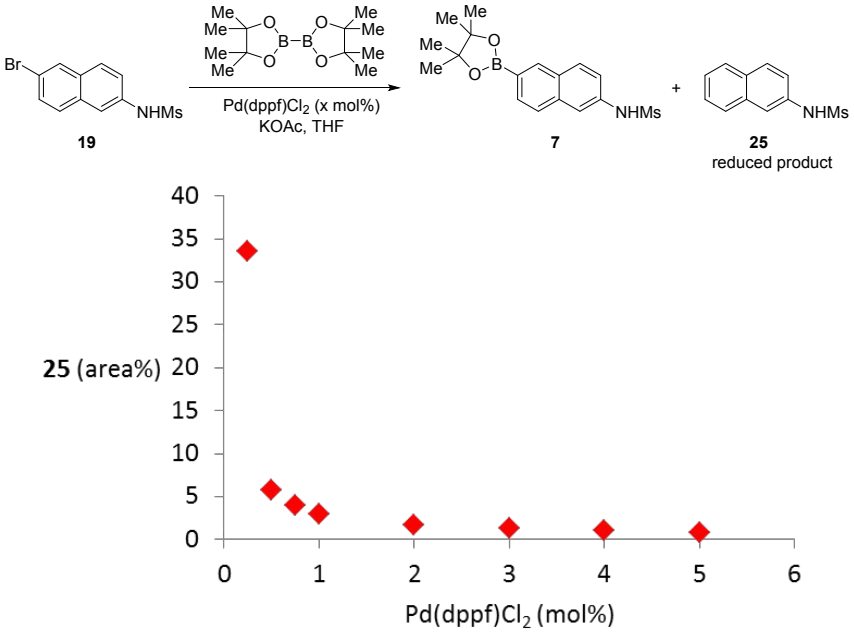
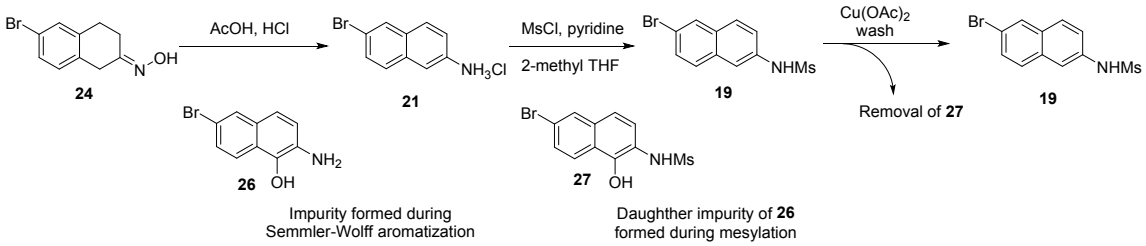


Figure 5. Effect of catalyst load on the reduction product **25** in the borylation reaction

Even with the catalyst loading held constant at 1 mol%, batch-to-batch variability in the amount of **25** was observed. This variability was ultimately correlated with residual copper (at the ppm level) remaining in **19.** The copper was present as carry over from an aqueous copper(II) acetate wash employed in early deliveries to remove naphthol sulfonamide **27** that was formed as an impurity during the mesylation reaction. Impurity **27** was derived from mesylation of naphthol amine **26** which was a side product observed in the Semmler–Wolff aromatization step (Scheme 7).



Scheme 7. Naphthol sulfonamide **27** arising from side product in the Semmler–Wolff

The relationship between the reduced product **25** and copper levels in **19** was linear when 1 mol% of the palladium catalyst was employed (Figure 6). This is especially interesting as 150 ppm of copper represents only about 0.1 mol% of copper, or 1/10 the level of palladium. In later deliveries, the copper(II) acetate wash was omitted, and so this complicating pathway was avoided.

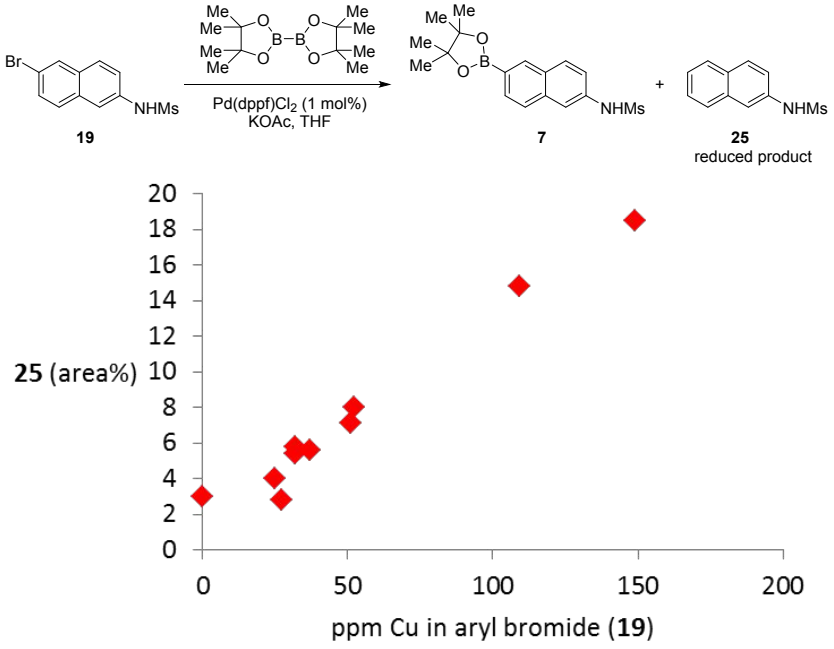
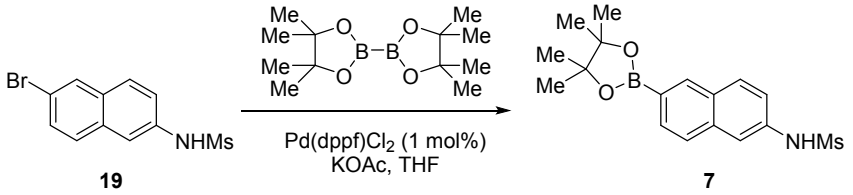


Figure 6. Effect of copper level on the amount of reduced product **25** in the borylation reaction

When the process was conducted on multi-kilogram scale, the yield of the borylation step ranged from 70–90% (Table *5*)**.**

Table 5. Representative Examples of the Borylation Reaction

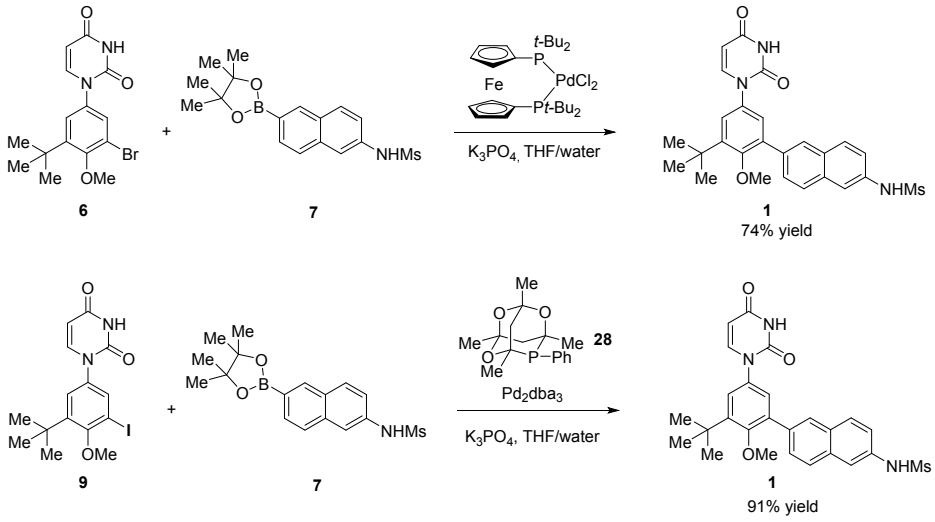


Entry	Scale (kg)[a]	Yield **7** (kg)	Potency (w/w%)[b]	Purity (area%)[c]
1	24.9	23.9 kg (81%)	99.1	99.5
2	13.5	10.9 kg (70%)	99.9	99.1
3	48	49.9 kg (90%)	99.9	99.9
4	47.4	48.3 kg (88%)	99.7	99.8

(a) Charge of **19**. (b) Potency value determined by HPLC analysis against a standard. (c) Determined by HPLC.

■ The Suzuki Coupling

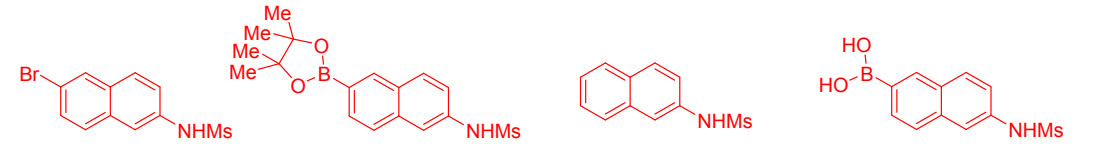
With the aryl iodide **9** and the boronate ester **7** in hand, we were able to investigate the Suzuki coupling. As noted earlier, aryl bromide **6** had undergone coupling with **7** employing $Pd(dtbpf)Cl_2$ as catalyst (Scheme 8). However, aryl iodide **9** did not give **1** in acceptable yield under similar conditions. A ligand screen was performed, from which the Epstein–Buckler phosphaadamantane ligand **28**[22-24] was observed to provide extremely good reactivity.



Scheme 8. Suzuki couplings of bromoarene **6** and iodoarene **9**

■ Development of a Palladium-Catalyzed Coupling of Methanesulfonamide with Aryl Nonaflate in the Second-Generation Synthesis

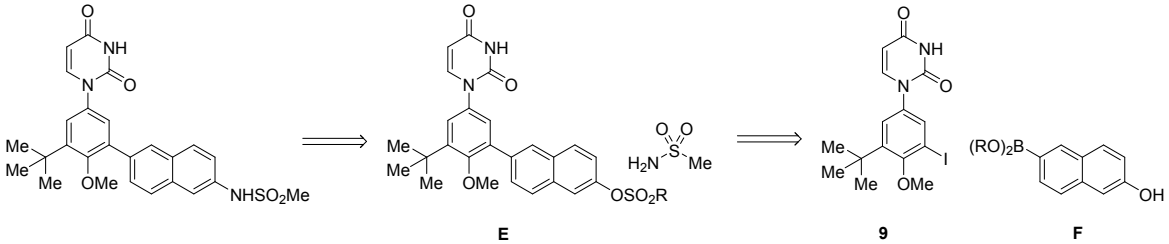
While the first-generation synthesis of dasabuvir was efficient and served for the preparation of clinical materials, it suffered from two major deficiencies. First, the synthesis of the boronate ester **7** was rather long (6 steps) and linear. A greater concern was the use of the boronate ester at a late stage of the synthesis; the boronate ester **7**, its precursor **19,** related byproducts **25** and **29** were all mutagenic, as determined by Ames test (Figure 7).While analytical techniques had been developed to demonstrate that the clinical materials were acceptable for use, the generation of these impurities at the end of the synthesis, and the need to control them at very low levels (20 μg/day, or 40 ppm for a 500 mg/day dose)[25], indicated that this could be a risk for the commercial synthesis.



19 (Precursor to Boronate **7**) **7** **25** (Byproduct of both Borylation and Suzuki steps) **29** (Byproduct of the Suzuki step)

Figure 7. Mutagenic impurities in the 1st generation route

An analysis of alternate disconnections indicated that the installation of the methane sulfonamide moiety in the final step would avoid a number of mutagenic impurities, especially those associated with boronate ester **7** (Scheme 9). We envisioned a palladium-catalyzed cross-coupling of an aryl sulfonate **E** with methanesulfonamide might be feasible. Although little precedent for this transformation existed in the literature,[26] we thought the benefits in terms of mutagenic impurity control warranted investigation of this coupling.[27] Further disconnection of biaryl **E** led back to aryl iodide **9** and naphthyl fragment **F**. This approach allowed us to leverage our existing synthesis of **9** and knowledge about the Suzuki coupling of **9**.



Scheme 9. Second-generation synthetic disconnection that avoids mutagenic impurities

■ Demonstration of Palladium-Catalyzed Sulfonamide Coupling

Initial screening of ligand, solvent and base indicated that *tert*-butyl-XPhos (**30**) in conjunction with *tert*-amyl alcohol (2-methyl-2-butanol) and potassium phosphate enabled the desired coupling reactions. A series of aryl sulfonate esters was evaluated using the reaction conditions shown below (Figure 8). The tosylate **31** was insufficiently reactive. While the triflate **32** had good reactivity it also proved to be sensitive to hydrolysis. As a result, about 10% of the naphthol byproduct (**35**, Table 6) was observed in the reaction. The rejection of the naphthol byproduct by crystallization was rather difficult; therefore the triflate was not a suitable coupling partner for this application as the final step of the dasabuvir synthesis.

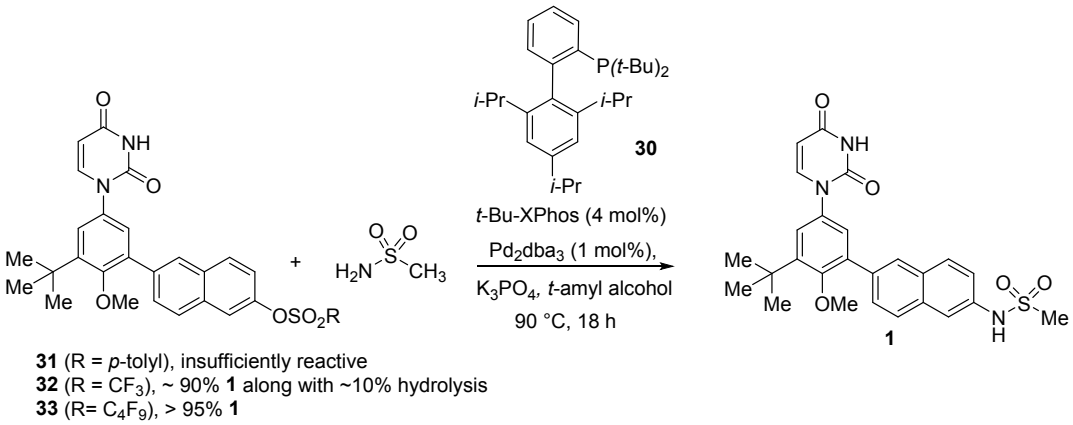


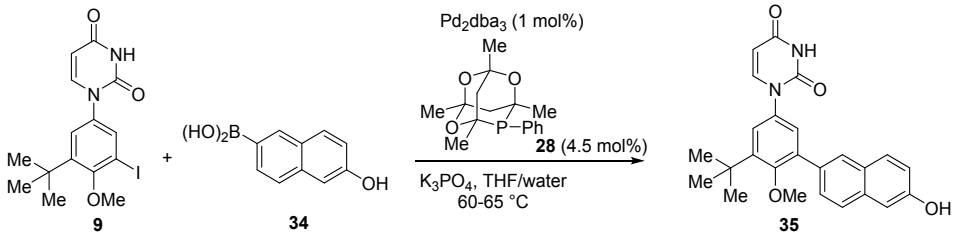
Figure 8. Coupling of sulfonate esters with methanesulfonamide

Aryl nonaflates are known to behave similarly to aryl triflates in Pd-catalyzed couplings but are more resistant to hydrolysis than aryl triflates.[28] Indeed, the reaction of aryl nonaflate **33** with methanesulfonamide proceeded to over 95% yield, with less than 1% of the hydrolysis byproduct. Preparation of **33** was accomplished in high yield in two steps from iodoarene **9** as described below.

■ Preparation of Aryl Nonaflate 33

The Suzuki coupling with hydroxynaphthylboronic acid **34** performed well with the previously employed ligand **28** (Table 6). Although the combination of Pd_2dba_3 and ligand **28** rapidly catalyzed this Suzuki reaction, a fairly high loading of palladium was required to completely consume **9**. At the nominal charge of 1 mol% Pd_2dba_3 (2 mol% Pd), the reaction reached complete conversion in under 1.5 hours, but all attempts to reduce the palladium loading to below 1.7 mol% were met with incomplete conversion of **9** (e.g. 1.5 mol% Pd stalled with 3.2% **9** remaining). Complete consumption of **9** was essential because iodoarene **9** was found to be a potent catalyst poison of the sulfonamidation reaction (vide infra). On scale, the Suzuki coupling performed well and delivered > 90% yield of naphthol **35** in high purity (Table 6).

Table 6. Representative Examples of Suzuki Coupling to Prepare Naphthol **35**



Entry	Scale (kg)[a]	Yield **35** kg	Potency (w/w%)[b]	Purity (area%)[c]
1	88.0	85.1 (93%)	98.2	99.7
2	88.0	83.9 (92%)	98.2	99.6

3	88.0	85.8 (94%)	99.8	99.4
4	88.0	86.2 (94%)	98.1	99.4

(a) Charge of **9**. (b) Potency value determined by HPLC analysis against a standard. (c) Determined by HPLC.

In the course of these studies an unusual rearrangement byproduct **38** was identified, which formed at 0.7 to 1.45 area% during the reaction (Figure 9). This byproduct is believed to be the result of C-H insertion of the aryl-palladium species **36** into the methyl ether, which is forced into proximity of the palladium atom because of the bulk of the adjacent *tert*-butyl group. Whether the C-C bond is formed by transmetallation of **37** with **34** and reductive elimination or by some other unknown mechanism is not certain.

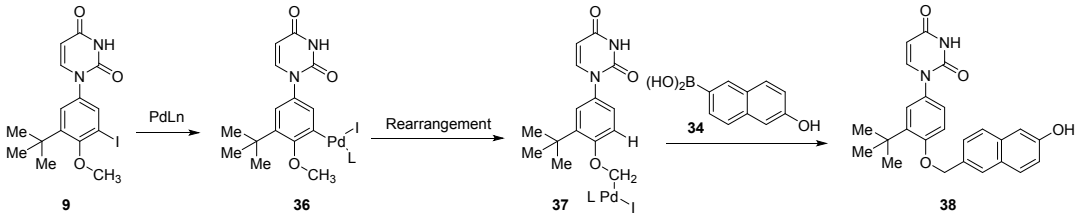
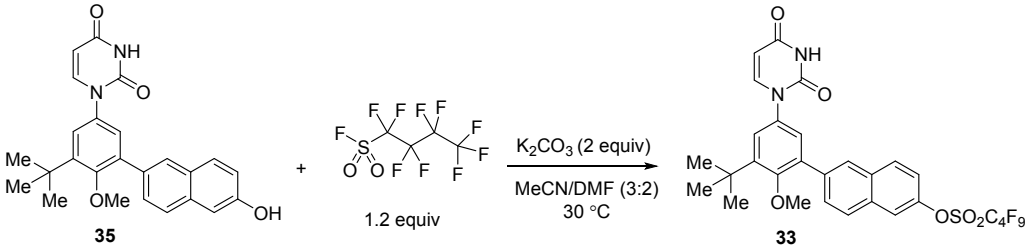


Figure 9. Rearrangement byproduct observed in Suzuki coupling

Preparation of the nonaflate **33** from naphthol **35** was best accomplished in a mixed DMF/MeCN solvent system (Table 7). Naphthol **35** is poorly soluble in many common organic solvents, but has reasonable solubility in DMF and other polar aprotic solvents. Perfluorobutanesulfonyl fluoride was chosen as the nonaflating reagent because it is inexpensive and tolerates a wide range of solvents, including the polar aprotic solvents DMF and acetonitrile.[28,29] Though reactions of **35** in DMF were rapid, some decomposition of the unpurified reaction mixture was observed upon holding. Acetonitrile is an excellent solvent for nonaflation of other phenols,[27] but the limited solubility of naphthol **35** and product **33** in pure acetonitrile caused complications. Ultimately a mixture of the two solvents provided the right balance of solubility and reactivity. Potassium carbonate was a suitable base for the reaction, provided it was of small enough particle size; commercially available 325-mesh K_2CO_3 was adequate, while granular material resulted in incomplete conversion. With a reliable and scalable synthesis in hand, multiple batches of **33** were prepared in reproducible yield and purity (Table 7).

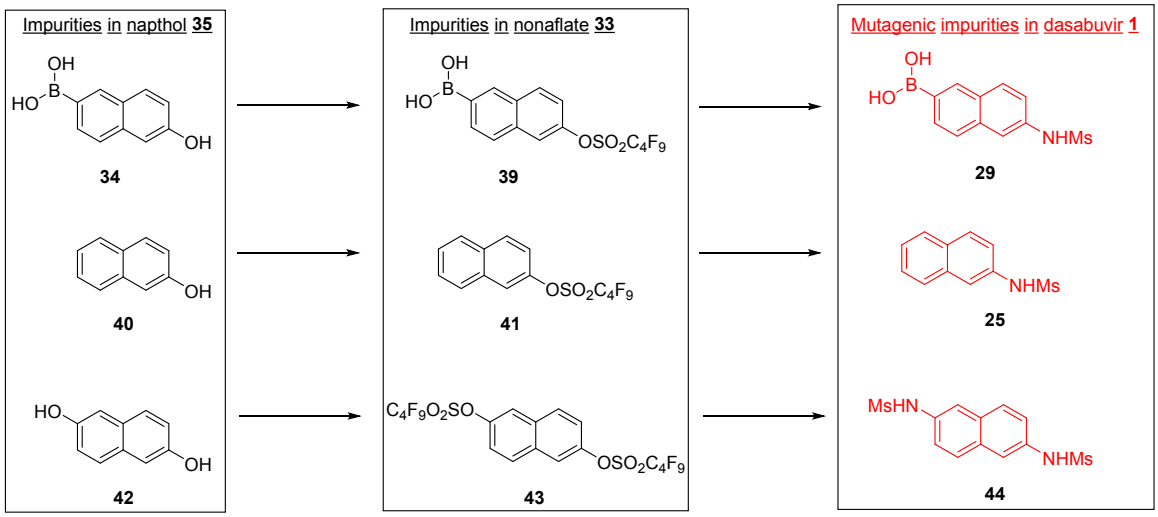
Table 7. Representative Examples of Preparation of Aryl Nonaflate **33**



Entry	Scale (kg)[a]	Yield **33** kg	Potency (w/w%)[b]	Total impurities (w/w%)[c]
1	82.4	123.4 (89%)	99.9	0.06
2	82.4	122.9 (89%)	99.9	0.07
3	82.4	121.8 (88%)	99.8	0.08
4	82.4	120.0 (87%)	100.3	0.08

(a) Charge of **35.** (b) Potency value determined by HPLC analysis against a standard. (c) Determined by HPLC.

Intermediate **33** was a key control point for several potential impurities in dasabuvir which had been determined to be of mutagenic concern (Scheme 10). Naphthol species **34, 40,** and **42** were identified as impurities in isolated naphthol **35** which would result in potentially mutagenic impurities **29, 25,** and **44** in dasabuvir. Fortunately, the daughter impurities **39, 41,** and **43** were well rejected in the isolation of nonaflate **33**, serving as a robust control point for this family of impurities. Impurities **39**, **41,** and **43** were routinely rejected to below 100 ppm in **33**, which was sufficient to ensure that the daughter impurities would be present below 40 ppm in dasabuvir.



The presence of potential mutagenic impurities **29**, **25**, and **44** in dasabuvir was avoided by rejecting **39**, **41**, and **43** to less than 100 ppm during the isolation of **33**

Scheme 10. Upstream control of potentially mutagenic impurities in dasabuvir

■ Optimization of the Palladium-Catalyzed Sulfonamidation

The Pd-catalyzed sulfonamidation reaction was further optimized with the goal of identifying a more active catalyst than the combination of $Pd_2(dba)_3$ and *tert*-Bu-XPhos. A screen of ligands identified *tert*-Bu-BrettPhos (**45**) as the optimal ligand;[30] >99.5% conversion of aryl nonaflate **33** was observed within 6 hours with 1 mol% palladium and 1.1 mol% ligand (Figure 10). Importantly, less than 0.5% of the hydrolysis impurity **35** was observed.[31] Pre-mixing of $Pd_2(dba)_3$, *tert*-Bu-BrettPhos, and K_3PO_4 in a solvent at elevated temperatures (catalyst pre-activation) prior to the addition of **33** and methanesulfonamide was necessary to ensure reproducible results.[32,27,33]

The initial screen of reaction conditions identified *tert*-amyl alcohol as the optimal solvent. However, the product of those reactions crystallized as an anhydrate form, which formed a thick slurry that was very difficult to stir and filter. The resistance of a 6-inch cake of the product in anhydrate form was quite high (1.6×10^{11} ft/lb) and it took over 5 hours to filter. This anhydrate form of the product crystallized from most solvents that are commonly employed for palladium-catalyzed reactions. Although ethyl acetate is not a common solvent for Pd-catalyzed cross-coupling reactions, when the reaction was run in ethyl acetate the product precipitated as larger crystals of an ethyl acetate solvate that stirred readily and filtered well. A 6-inch cake of the ethyl acetate solvate filtered in less than 0.5 hours (resistance of 1.6×10^9 ft/lb).

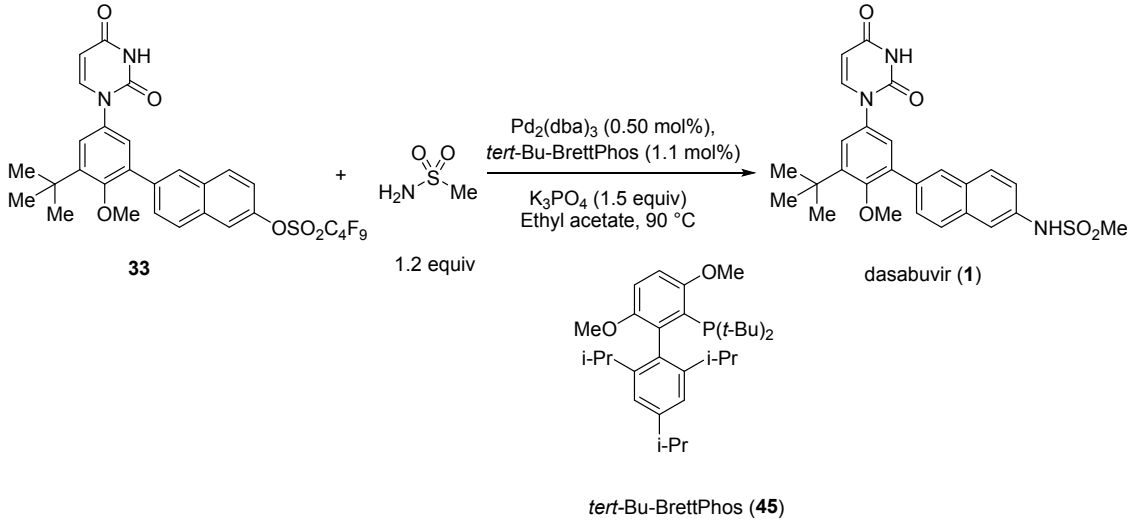


Figure 10. Palladium-catalyzed sulfonamidation in ethyl acetate

Although ethyl acetate was a superior solvent for the Pd-catalyzed sulfonamidation reaction from the standpoint of the product physical properties, we noted run-to-run variability of conversion which was ultimately traced back to the batch of *tert*-Bu-BrettPhos employed (Table 8). Reactions in ethyl acetate proceeded to >99% conversion under standard conditions with one batch of ligand (entry 1). However, less than 5% conversion was observed when a different batch of ligand was used (entry 2). ICP analysis of the two batches of ligand revealed that while Batch 1 contained less than 5 ppm copper with respect to the *tert*-Bu-BrettPhos, 8600 ppm copper was present in Batch 2. A portion of Batch 2 was purified by washing an ethyl acetate solution of the ligand with aqueous ammonia until the aqueous layer was clear, followed by concentration and recrystallization from methanol.[34] The purified *tert*-Bu-BrettPhos contained less than 5 ppm

copper and performed well in the reaction (entry 3), supporting the hypothesis that the copper was responsible for inhibiting the reaction.[35-38]

Table 8. Dependence of Reaction Conversion in EtOAc on Copper Level in *tert*-Bu-BrettPhos

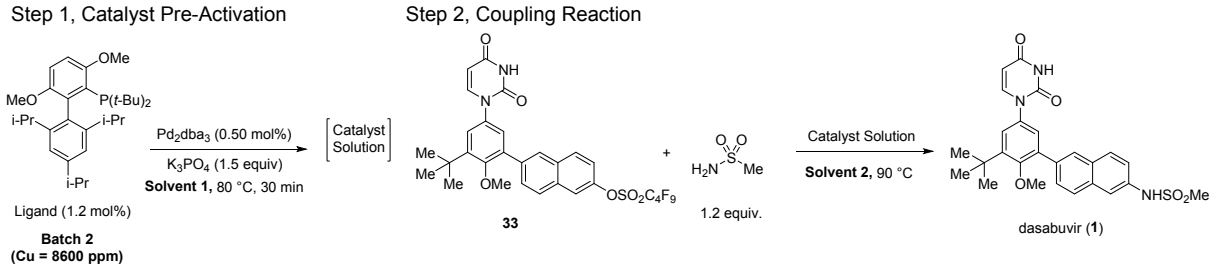
Entry	Ligand source	Copper (ppm)	Prod (%)
1	Batch 1	<5	>95
2	Batch 2	8600	<5
3	Batch 3[a]	< 5	>95

All reactions were performed with 1 g of **33** inside an inert atmosphere glove box in EtOAc (12 mL/g **33**) for 16–18 h.
(a) Batch 2 was dissolved in EtOAc, washed with aqueous ammonia, then recrystallized from MeOH prior to use.

The mechanism for inhibition of the sulfonamidation reaction due to the presence of sub-stoichiometric amounts of copper (with respect to Pd) is not apparent to us.[37,39] One observation of relevance was that palladium black precipitated out during the catalyst pre-activation step with $Pd_2(dba)_3$, K_3PO_4, and *tert*-Bu-BrettPhos Batch 2 (containing 8600 ppm of copper) in ethyl acetate (Table 9, entry 1).[40] Interestingly, no palladium black was formed, and the catalysis was not inhibited, when the reaction was conducted with Batch 2 in *tert*-AmOH or 2-MeTHF (Table 9, entries 2 and 3). The reason why the reaction was not inhibited by copper when using *tert*-AmOH or 2-MeTHF as the solvent is not known.

The observation that 2-MeTHF mitigated the impact of high copper content in *tert*-Bu-BrettPhos suggested that a mixed solvent system might be beneficial. When a 1:1 (v/v) mixture of 2-MeTHF and ethyl acetate was used for catalyst pre-activation with *tert*-Bu-BrettPhos Batch 2, the reaction proceeded to 72% conversion (entry 4). A much higher yield (88%) was observed when the catalyst pre-activation was performed in neat 2-MeTHF and ethyl acetate was employed as the reaction solvent (entry 5). Importantly, the coupled product was obtained as the easily filtered ethyl acetate solvate from a 3:1 mixture of ethyl acetate/2-MeTHF.

Table 9. Effect of Solvent on Reactions Conducted with a High-Copper Batch of *t*-Bu-BrettPhos



Entry	Solvent 1 (activation)	Vol solvent 1 (mL/g **33**)	Solvent 2 (reaction)	Vol solvent 2 (mL/g **33**)	Time (h)	**1** (%)[a]	**33** (%)[a,b]
1	EtOAc	4	EtOAc	8	18	<1	>95
2	*t*-AmOH	4	*t*-AmOH	8	18	>95	1.5

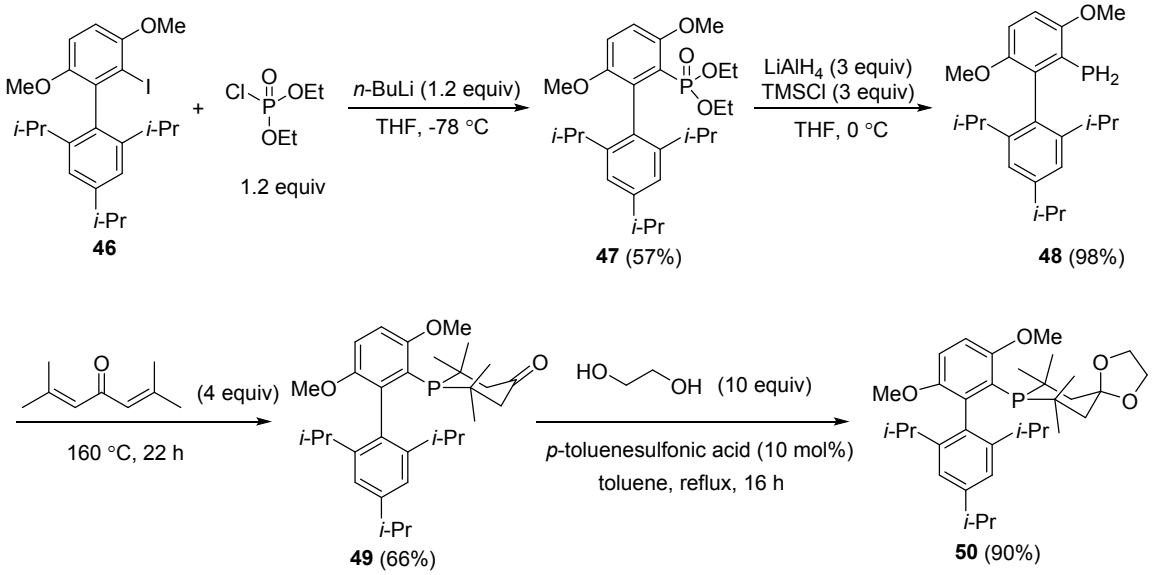
Entry	Solvent 1 (activation)	Vol solvent 1 (mL/g **33**)	Solvent 2 (reaction)	Vol solvent 2 (mL/g **33**)	Time (h)	**1** (%)[a]	**33** (%)[a,b]
3	2-MeTHF	4	2-MeTHF	8	18	>95	<0.5
4	EtOAc/2-MeTHF (1:1 v/v)	4	EtOAc	8	14	72	23
5	2-MeTHF	3	EtOAc	9	14	88	8

All reaction were conducted with $Pd_2(dba)_3$ (0.5 mol%), *tert*-Bu-BrettPhos (1.2 mol%, Batch 2), K_3PO_4 (1.5 equiv), **33** (1 equiv), and methanesulfonamide (1.2 equiv) at 90 °C. (a) HPLC area% at 210 nm. (b) HPLC area% of unreacted **33.**

Further studies with $Pd_2(dba)_3$ (0.50 mol%) and various batches of *tert*-Bu-BrettPhos (1.2 mol%), containing 40–8600 ppm Cu, demonstrated that the sulfonamidation in EtOAc was robust as long as less than 1000 ppm copper was present in the ligand. In addition, the catalyst pre-activation was performed in 2-MeTHF (3 mL/g nonaflate **33**) followed by dilution of the reaction with EtOAc (9 mL/g nonaflate **33**) to ensure robustness of the reaction.

■ Invention and Use of Ligand 50 in the Sulfonamidation Reaction.

Given the sensitivity of the sulfonamidation reaction to residual copper in *tert*-Bu-BrettPhos and the variability of copper levels in commercial batches of *tert*-Bu-BrettPhos, the use of biaryl phosphines that do not require copper for synthesis was explored. A biaryl phosphacycle containing the same biaryl backbone as in *tert*-Bu-BrettPhos was prepared according to the method shown in Scheme 11.[41-45] Lithium-halogen exchange of biaryl iodide **46** followed by the reaction of the resulting Li-biaryl species with diethyl chlorophosphate generated biaryl phosphonate **47**, which was reduced to the biaryl primary phosphine **48** in the presence of $LiAlH_4$ and TMSCl.[46] Conjugate addition of the primary phosphine to phorone formed the phosphacycle **49**. The carbonyl in **49** was then converted to a ketal to form ligand **50.**[47]



Scheme 11. Synthesis of VincePhos (**50**)

Seemingly minor changes in the structure of the phosphine ligand are well known to have profound impact on reactivity.[48-54] Thus, the utility of **50** in the sulfonamidation reaction was not obvious to us. Gratifyingly, dasabuvir (**1**) was formed in >95% yield when the sulfonamidation reaction was conducted with **50** as ligand. More importantly, the performance of the sulfonamidation reaction was consistent when various batches of **50** were evaluated in this transformation.[55]

■ Optimization of Reaction Parameters to Develop a Robust Sulfonamidation Reaction

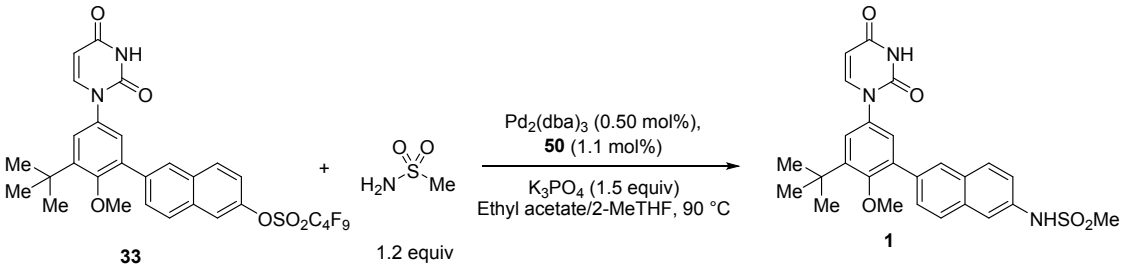
The Pd-catalyzed sulfonamidation reaction is the last bond-forming step for the synthesis of dasabuvir. It was therefore imperative to understand the influence of reaction parameters such as temperature, concentration, equivalents of reagents, effect of moisture, particle size of base, and effect of oxygen on both yield and purity profile to ensure a robust scale up procedure. The level of moisture, particle size of the base, and the amount of oxygen present in the reactor had the most profound impact on the reaction.

Not surprisingly, the higher the level of moisture present in the reaction mixture the higher the amount of the hydrolyzed impurity (**35**) observed. Potassium phosphate was identified as the largest source of moisture. Potassium phosphate with less than 2% w/w water was used in the process to ensure formation of less than 0.5% **35** in the reaction.

The sulfonamidation reaction is heterogeneous because potassium phosphate is insoluble in the reaction solvent mixture (2-MeTHF/EtOAc). We anticipated that the proper suspension of potassium phosphate in solvent would be critical to ensure reproducible reaction on scale.[56,57] The particle size of K_3PO_4 and the speed of agitation can impact the extent of suspension of potassium phosphate in 2-MeTHF/EtOAc. Thus, studies were conducted to understand the effect on conversion of the particle size of potassium phosphate and the speed of agitation. In a set of experiments (Table 10), the agitation speed of 450 rpm was maintained during the catalyst pre-activation while the agitation during the reaction was varied between 125–475 rpm.

Greater than 99% consumption of the starting material was observed when potassium phosphate containing particles on the order of several millimeters in size was used and the contents were mixed at 475 rpm (entry 1). Lowering the agitation speed to 300 and 125 rpm allowed the reaction to proceed to only 58 and 45% conversion, respectively (entries 2 and 3). It was clear that the reaction was sensitive to the speed of agitation if potassium phosphate with large particle size was used in the process. Therefore, additional studies were performed using potassium phosphate milled to 60–352 μm in size. Agitation at 300 rpm with the particle size of 352 μm improved the conversion to 73% (entry 4). Quantitative consumption of nonaflate was observed when the particle size was further lowered to 120–60 while agitating at 300 rpm (entries 5, 6, and 8). Quantitative consumption of nonaflate was also observed when the agitation speed was reduced to 125 rpm while using potassium phosphate of D_{90} 100 μm (entry 7). The data shown in Table 10 suggest that there is a strong correlation between the particle size of potassium phosphate and the necessary agitation speed. Thus, to minimize the dependence of the reaction on the agitation speed in large reactors, milled potassium phosphate with D_{90} less than 120 μm was used.

Table 10. Correlation Between the Particle Size of K_3PO_4 and the Reaction Agitation Speed



Entry	K_3PO_4 D_{90} (µm)	rpm	Conv (%)[a]
1	Chunks up to mm	475	> 99
2	Chunks up to mm	300	58
3	Chunks up to mm	125	45
4	352	300	73
5	120	300	>99
6	100	300	>99
7	100	125	> 99
8	60	300	>99

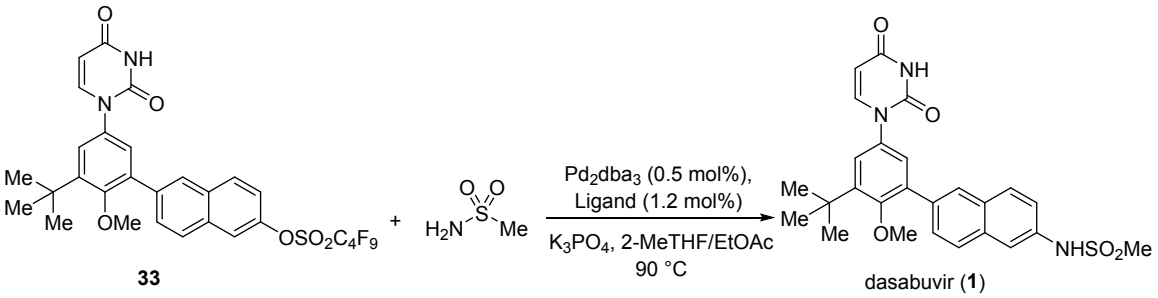
All experiments were performed with **33** (1 equiv), methanesulfonamide (1.2 equiv), K_3PO_4 (1.1 equiv), $Pd_2(dba)_3$ (0.005 equiv) and **50** (0.012 equiv) in a mixture of 2-MeTHF (4 mL/g **33**l)/EtOAc (8 mL/g **33**) at 90 °C. (a) (100 –area)% of the unreacted nonaflate at 210 nm.

The reaction was inhibited by the presence of oxygen in the reactor. The level of O_2 in the reactor was controlled to less than 50 ppm to ensure reproducible reactions. Interestingly, the reaction was much more sensitive to O_2 during the early stages of the reaction than in the latter stages. For examples, no consumption of nonaflate was observed when all the reagents were charged in air and the reaction was heated to 90 °C for an extended period. Either Pd or phosphine or both get oxidized and fail to catalyze the reaction. In contrast, no impact on the reaction progress was observed when the reactor was opened to air after 30–40% conversion. The resting-state of the catalyst is believed to be a Pd(II) species because reductive elimination is likely the rate-limiting step.[27] It is likely that most of the active Pd species are in oxidation-state II after a few turnovers and cannot be further oxidized by air; thus, the reaction continues to progress despite exposure to air.

During our optimization studies, we found that iodoarene **9** is a potent catalyst poison in the sulfonamidation reaction. Under otherwise nominal reaction conditions (1.0 mol% Pd and 1.2 mol% **50**), a reaction spiked with 0.17 mol% of **9** (with respect to nonaflate **33**) stalled at 53% conversion. The sulfonamidation proceeded to >99% conversion in the presence of 0.087 mol% of **9**, however. Buchwald and coworkers[58] have demonstrated that Pd-catalyzed C-N couplings of aryl iodides are inhibited by the iodide byproduct in polar solvents. Presumably, iodoarene **9** undergoes oxidative addition with active catalyst and the iodide anion byproduct inhibits the sulfonamidation reaction by sequestering the Pd in an inactive state.

The process was scaled up to multi-kilogram scale using both *tert*-Bu-BrettPhos (**45**) and VincePhos (**50)**. The performance of the reaction was comparable with the two ligands, yielding 90% of dasabuvir in >99.5% purity (Table 11).

Table 11. Scale up of Pd-Catalyzed Sulfonamidation Reaction



Entry	Scale (kg)[a]	Ligand	Yield **1** (kg)	Purity (area%)[b]
1	100	**45**	63.2 (89.4%)	99.7
2	99.5	**45**	63.7 (90.8%)	99.8
3	100	**50**	63.1 (89.4%)	99.8
4	100	**50**	62.3 (88.2%)	99.8

(a) Charge of **33**. (b) Determined by HPLC.

■ CONCLUSION

In the course of the development of the synthesis of dasabuvir, two novel coupling reactions were developed. A copper-catalyzed coupling of uracil to diiodoarene **8**, employing picolinamide ligand **16**, afforded the 1-aryl uracil derivative **9** in very good yield, with excellent regiochemistry on both the uracil and diiodoarene coupling partners. The first-generation synthesis of dasabuvir then employed the Epstein–Buckler phosphaadamantane ligand **28** in the Suzuki coupling to deliver dasabuvir. Because of the introduction of mutagenic intermediates in the final step, a second-generation route was developed in which the methanesulfonamide moiety was introduced to a fully elaborated intermediate. Commercially available *tert*-Bu-BrettPhos afforded good reactivity in the coupling of methanesulfonamide with nonaflate **33** to generate dasabuvir. Additionally, novel phosphacycle ligand **50** was found to provide comparable yield and purity in the sulfonamidation reaction. Finally, the sensitivity of the sulfonamidation reaction to extremely low levels of copper was mitigated by employing ligand **50**, which does not use copper in the synthesis.

■ Experimental Section

General methods. All copper- and palladium-catalyzed reactions were performed in a nitrogen glove box or using Schlenk techniques under N_2/Ar atmosphere. Unless noted specifically, reagents, $Pd_2(dba)_3$, CuI, phosphine ligands, bases, and solvents were purchased from commercial sources and were used without further purification. Unless otherwise noted, reaction

mixtures were heated to the indicated temperature using conventional heating sources (e.g. oil bath, heating mantle, heating block, jacketed reactor). ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on a 400, 500, 600 or 700 MHz spectrometer, with shifts reported in parts per million downfield from tetramethylsilane and referenced to residual proton (^{1}H) or deuterated solvent (^{13}C). HPLC analyses were performed using spectroscopic grades of acetonitrile and water with either 0.1 % H_3PO_4 or 0.1% $HClO_4$ as eluents. HRMS analyses were performed on a time-of-flight mass spectrometer equipped with an ESI source. Elemental analysis was performed using optimum combustion analysis on an elemental analyzer. Melting points were determined by either conventional visual analysis or by differential scanning calorimetry, as denoted by DSC.

2,4-Diiodo-6-*tert*-butylphenol (**13**):[59] 2-*tert*-Butylphenol (99.95 g, 665.4 mmol) was dissolved in 1250 mL of methanol. Sodium hydroxide pellets (30.96 g, 799.0 mmol, 1.20 equiv) were added. The mixture was stirred at room temperature until the pellets had dissolved and the resulting green solution was cooled with an ice/salt bath. Sodium iodide (299.34 g, 1997 mmol, 3 equiv) was added in four approximately equal portions. Each sodium iodide addition was followed by the slow dropwise addition of sodium hypochlorite solution (8.3% by weight, 1313 g, 1465 mmol, 2.2 equiv) in four approximately equal portions. During the hypochlorite additions the reaction temperature was kept at NMT 0 °C. A solution of 100 g of sodium thiosulfate in 500 mL of water was added over a 20 minute period. The reaction mixture was acidified to pH 3 using concentrated HCl (approximately 200 mL). The slurry was filtered and the wet cake was washed with 2 liters of water. The solid was deliquored by passing a stream of air through the cake overnight. The solid weighed 289.33 g and the potency by HPLC was 88%, yielding 254.61 g potency-adjusted yield (95%). Most of the remaining mass balance was water, and the product was not further purified. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 2.06 Hz, 1H), 7.46 (d, J = 2.06 Hz, 1H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 152.3, 142.6, 138.9, 136.3, 89.9, 83.1, 35.8, 29.4.

1-(*tert*-Butyl)-3,5-diiodo-2-methoxybenzene (**8**):[6] 2,4-Diiodo-6-*tert*-butylphenol, **13** (93 wt%, 21.6 g, 20.1 g assay, 50 mmol) was dissolved in 140 mL acetone, and MeI (4.2 mL, 67.5 mmol, 1.35 equiv) was added followed by 50% aq. NaOH (5.0 g, 62.5 mmol, 1.25 equiv). After stirring overnight, less than 1% phenol remained, and the reaction was concentrated to 50–60 mL. Heptane (80 mL) was added, and the solution was washed with 50 mL water. The aqueous layer was back extracted with 20 mL heptane. The combined heptane layers were washed with 2 × 50 mL 10% aq. NaCl to yield 91.1 g of a heptane solution of **8** (assay 19.1 g by HPLC, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 2.2 Hz, 1H), 7.55 (d, J = 2.2 Hz, 1H), 3.87 (s, 3H), 1.36 (s, 9H).

1-(3-(*tert*-Butyl)-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (**9**): Uracil (33.3 g, 297 mmol, 1.2 equiv), K_3PO_4 (106 g, 500 mmol, 2.1 equiv), CuI (4.6 g, 24 mmol, 0.1 equiv), and ligand **16** (6.4 g, 29 mmol, 0.12 equiv) were charged to a flask and inerted with argon. The diiodoanisole **8** (103 g) was concentrated and distilled with MeCN, dissolved in 1 L DMSO, sparged with argon then added to the above reactor. The reactor was heated to 60 °C for 16 h. After cooling, the reaction mixture was diluted with 2 L EtOAc and washed with 2.6 L water. The aqueous layer was back extracted with 3 × 1 L EtOAc. The combined organic layers were washed with 2 × 1 L of 0.25 M $Cu(OAc)_2$, 2 × 830 mL 15% NH_4Cl and 800 mL brine. The organic layer was concentrated and chased with 1 L heptane, then treated with refluxing 85:15 (v/v) heptane:*i*-PrOAc for 4 h. After cooling, the product was collected by filtration and washed with an additional 330 mL of 85:15 (v/v) mixture of heptane:*i*-PrOAc . The product was dried under vacuum to yield 66.9 g (68% yield) of **9** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6)

δ 11.40 (s, 1H), 7.80 (d, *J* = 2.5 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 2.6 Hz, 1H), 5.63 (d, *J* = 7.9 Hz, 1H), 3.85 (s, 3H), 1.35 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 163.7, 158.7, 150.5, 145.5, 144.2, 136.4, 135.2, 126.5, 101.5, 92.4, 61.8, 35.3, 30.6. mp 198–200 °C. Anal. Calcd for $C_{13}H_9N_3O$: C, 45.02; H, 4.28; N, 7.00. Found C, 44.69; H, 3.84; N, 6.77.

Purification of 1-(3-(*tert*-Butyl)-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (9):[6] A vial was charged with 1-(3-(*tert*-butyl)-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione **9**, (2.20 g) and 11 mL of 2-propanol (5.0 mL/g **9**). The mixture warmed to 80–83 °C with magnetic stirring for 1 h, then cooled to 20–25 °C. The product was isolated by filtration and the filter cake was washed with 1.2 mL of 2-propanol. The wet cake was dried in a vacuum oven at 45 °C overnight. The desired product **9** was isolated as a solid (1.92 g, 87% yield).

***N*-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)methanesulfonamide (7):**[6] *N*-(6-Bromonaphthalen-2-yl)methanesulfonamide (**19**) (9.0 g, 30 mmol), bis(pinacolato)diboron (9.9 g, 39 mmol. 1.3 equiv), (1,1'-bis(diphenylphosphino)ferrocene) dichloropalladium(II) dichloromethane complex (1.22 g, 1.5 mmol, 0.05 equiv), potassium acetate (7.36 g, 75 mmol, 2.5 equiv) and 90 mL of degassed THF were charged to a reactor and heated to reflux for 7 h. After cooling to ambient temperature, the reaction was diluted with 405 mL of EtOAc and treated with 450 mg of Darco G-60. After stirring for 12 h, the solution was filtered through filter aid and the carbon was rinsed with 150 mL of EtOAc. The resulting solution was concentrated to about 25 mL, and 495 mL of heptanes was added slowly. The product was collected by filtration and rinsed with 90 mL of heptanes.

The resulting wet cake was treated with 41 g of filter aid in 200 mL of THF overnight, then filtered and again treated with 23.7 g of Darco G-60 carbon for 2 h. After filtration, the product was crystallized by concentrating to about 25 mL, then adding 450 mL of heptanes. The title compound was collected by filtration and dried to yield 7.0 g (67%) of the product solid. An additional 1.16 g (11%) could be recovered by concentration of the mother liquors and crystallization from heptane. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.25 (s, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.68 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.66 (d, *J* = 2.2 Hz, 1H), 7.39 (dd, *J* = 8.8, 2.2 Hz, 1H), 3.09 (s, 3H), 1.32 (s, 12H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ 137.4 (C), 135.7 (CH), 135.2 (C), 130.8 (CH), 130.0 (CH), 129.2 (C), 126.5 (CH), 124.6 (C), 120.1 (CH), 114.4 (CH), 83.7 (C), 39.5 (CH_3), 24.7 (CH_3). mp 214–216 °C (DSC). Anal. Calcd for $C_{17}H_{22}BNO_4S$: C, 58.80; H, 6.39; N, 4.03; S, 9.23. Found C, 58.66; H, 6.33; N, 4.00; S, 9.25.

1-(3-*tert*-butyl-5-(6-hydroxynaphthalen-2-yl)-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (35):[6] This reaction is air-sensitive and the reaction was conducted under nitrogen atmosphere. A round-bottom flask was purged with nitrogen gas and charged with $Pd_2(dba)_3$ (0.69 g, 0.75 mmol, 0.020 equiv Pd), 1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphatricyclo[3.3.1.1^{3,7}]decane **28** (1.01 g, 3.46 mmol, 0.0460 equiv) and a magnetic stir bar. The flask was sealed with a septum and the atmosphere above the solids was purged with nitrogen gas. One hundred eighty (180) mL of nitrogen-sparged THF was added to the flask and the mixture was stirred under a nitrogen atmosphere for 36 minutes.

A 1000-mL jacketed reactor was equipped with an overhead stirrer and reflux condenser and the atmosphere was purged with nitrogen gas. The reactor was charged with 1-(3-(*tert*-butyl)-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione **9**, (30.05 g, 75.1 mmol, 1.00 equiv), 6-hydroxynaphthalen-2-ylboronic acid **34** (15.2 g, 81.0 mmol, 1.08 equiv) and potassium phosphate tribasic (30.3 g, 143 mmol, 1.90 equiv). The reactor was charged with 305 mL of

THF, 155 mL of water, and the mixture was stirred to dissolve the solids. The biphasic mixture was sparged with nitrogen gas. The catalyst solution of $Pd_2(dba)_3$ and **28** was transferred to the main reactor by positive nitrogen pressure through a cannula. The resulting biphasic mixture was stirred and warmed to an internal temperature between 60 and 65 °C under nitrogen. Reaction progress was monitored by HPLC for consumption of **9**, and the reaction was complete after 1 h, 15 min at 60 °C. The reaction mixture was cooled to an internal temperature between 50 and 55 °C before quench.

The workup of the reaction was conducted under anaerobic conditions at an internal temperature between 50 and 55 °C. Sodium chloride (45.4 g) and cysteine (3.0 g) were dissolved in 240 mL of water, and the resulting solution was sparged with nitrogen for 0.7 h. This solution was transferred to the reaction mixture by cannula with nitrogen gas pressure and the resulting biphasic mixture was stirred vigorously for 0.7 h. The mechanical agitation was halted, the two solutions were allowed to separate, and the aqueous solution was discarded. Sodium chloride (45.4 g) and cysteine (3.0 g) were dissolved in 235 mL of water, and the resulting solution was sparged with nitrogen for 0.8 h. This solution was transferred to the reaction mixture by cannula with nitrogen gas pressure and the resulting biphasic mixture was stirred vigorously for 0.8 h. The mechanical agitation was halted, the two solutions were allowed to separate, and the aqueous solution was discarded. The reaction mixture was diluted with 270 mL of a THF/water solution (92:8 w/w%) to dissolve precipitated product.

The organic solution was filtered through filter paper while warm. The reactor and filter were rinsed with 60 mL of THF and 150 mL of EtOAc was added to the organic solution. The solution was concentrated in vacuo on a rotary evaporator to an approximate volume of 180 mL and 330 mL of EtOAc was added. The mixture was concentrated in vacuo on a rotary evaporator to an approximate volume of 120 mL and mixed at 30 °C for approximately 2 h. The product was isolated by filtration and the filter cake was washed twice with 60 mL portions of EtOAc. The wet cake was dried in a vacuum oven at 50 °C overnight. The desired product **35** was isolated as an off-white solid (27.3 g, 87% yield).^{1}H NMR (600 MHz, DMSO-d_6) δ 11.38 (s, 1H), 9.83 (s, 1H), 7.96–7.91 (m, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.59 (dd, J = 8.5, 1.8 Hz, 1H), 7.33 (d, J = 2.7 Hz, 1H), 7.28 (d, J = 2.7 Hz, 1H), 7.18–7.15 (m, 1H), 7.12 (dd, J = 8.8, 2.4 Hz, 1H), 5.64 (d, J = 7.9 Hz, 1H), 3.24 (s, 3H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 163.8, 156.6, 155.8, 150.6, 145.9, 143.4, 135.2, 134.0, 133.8, 132.5, 129.7, 128.0, 127.8, 127.0, 126.9, 126.3, 124.4, 119.0, 108.5, 101.4, 60.2, 35.0, 30.5. mp 300–301 °C (DSC). Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found C, 71.78; H, 6.04; N, 6.71.

6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (33):[6] A 250-mL, jacketed reactor equipped with an overhead stirrer was charged with 1-(3-*tert*-butyl-5-(6-hydroxynaphthalen-2-yl)-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione **35** (10.0 g, 24.0 mmol, 1.00 equiv) and powdered potassium carbonate (325 mesh, 6.60 g, 47.8 mmol, 2.0 equiv). *N*,*N*-Dimethylformamide (40 mL, 4 mL/g **35**) and acetonitrile (61 mL, 6 mL/g **35**) were charged to the reactor and the slurry was stirred. The internal temperature was adjusted to 30 °C. Perfluorobutanesulfonyl fluoride (8.65 g, 28.6 mmol, 1.19 equiv) was charged to the well-stirred mixture over 1.25 h. A trace (<0.1 area%) of **35** was detected by HPLC analysis of an aliquot after 0.5 h of reaction time. The acetonitrile/dimethylformamide solution was filtered over a coarse fritted funnel to separate the inorganic solids, and the flask and filter were rinsed with 15 mL of 3:2 (v/v) acetonitrile/dimethylformamide.

With stirring, 7.5 mL of water was added to the organic solution over 15 min, and the mixture was allowed to stir for 0.5 h to allow solids to crystallize. An additional 42.5 mL of water was added to the slurry over 1 h, and the mixture was allowed to stir for 1 h. The wet cake was isolated by filtration with recirculation of the liquors to recover all the solids. The wet cake was washed with a pre-mixed solution of 8 mL of *N*,*N*-dimethylformamide, 12 mL of acetonitrile and 10 mL of water.

The wet cake was dissolved in 82 mL of EtOAc. The resultant organic solution was washed twice with 42 g portions of a 4.8 wt% aqueous sodium chloride solution. The organic solution was filtered into a reactor and the filter rinsed with 30 mL of EtOAc. The bulk of the solvent was removed by distillation at approximately 95 torr with heating to 40 °C until the total volume was approximately 30 mL. The slurry was heated to 53 °C and 13 mL of EtOAc was added to completely dissolve the precipitated solids. Heptanes (154 mL) were added to the warm (53 °C) slurry over 0.9 h. The mixture was cooled to room temperature with stirring and the desired product was isolated by filtration. The wet cake was washed with 25 mL of heptanes. The wet cake was dried in a vacuum oven at 45 °C with a gentle nitrogen sweep. The title compound was isolated as a white solid (13.36 g, 80% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.43 (s, 1H), 8.23–8.09 (m, 4H), 7.84 (dd, J = 8.5, 1.8 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.57 (dd, J = 9.0, 2.6 Hz, 1H), 7.39 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 2.7 Hz, 1H), 5.67 (d, J = 7.9 Hz, 1H), 3.20 (s, 3H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 163.8, 156.8, 150.7, 147.2, 145.8, 143.7, 137.4, 134.4, 134.2, 132.4, 132.2, 131.3, 128.6, 128.5, 128.1, 127.3, 125.2, 119.9, 119.2, 101.6, 60.5, 35.1, 30.4. (The carbon signals for the nonaflate are extensively split by ^{13}C-^{19}F coupling and are not reported.) mp 213–215 °C (DSC). Anal. Calcd for $C_{29}H_{23}F_9N_2O_6S$: C, 49.86; H, 3.32; N, 4.01; F, 24.48; S, 4.59. Found C, 49.77; H, 3.35; N, 3.95; F, 24.01; S, 5.05.

***N*-(6-(3-(*tert*-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalene-2-yl)methanesulfonamide, dasabuvir (1):**[6] $Pd_2(dba)_3$ (0.164 g, 0.179 mmol, 0.005 equiv), **50** (0.238 g, 0.429 mmol, 0.012 equiv) and tripotassium phosphate (8.36 g, 39.4 mmol, 1.2 equiv) were charged to a 1-L stainless-steel Parr reactor equipped with an overhead agitator and a thermocouple. The reactor was closed and was subjected to 5 cycles of vacuum/purge with nitrogen then purged with nitrogen until less than 30 ppm O_2 was detected in the reactor headspace.[60] 2-Methyltetrahydrofuran (100 mL) was charged to a separate 250-mL round-bottom flask, capped with a rubber septum and was sparged with nitrogen until less than 30 ppm O_2 was detected in the reactor headspace. The sparged solvent was transferred to the 1-L Parr reactor using a stainless-steel cannula under a positive atmosphere of nitrogen. The reactor was sealed; the contents were heated to 80 °C, stirred for 30 min, then cooled down to 60 °C. 6-(3-*tert*-Butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (**33**) (25.0 g, 35.8 mmol, 1 equiv), methanesulfonamide (4.09 g, 43 mmol, 1.2 equiv) and EtOAc (200 mL) were charged to a separate 500-mL round-bottom flask, capped with a rubber septum and sparged with nitrogen until less than 30 ppm O_2 was detected in the reactor headspace, then heated to 60 °C with stirring.[61] The resulting solution was transferred to the 1-L Parr reactor using a stainless-steel cannula under a positive pressure atmosphere of nitrogen. The Parr reactor was sealed, the contents were heated to 90 °C and stirred for 14 h.

The reaction mixture was cooled down to 65 °C. A 5% w/w aqueous solution of *N*-acetyl-*L*-cysteine (50 mL) was charged to the reactor and the contents were mixed for approximately 15 min.[62] The coupled product (**1**) was collected by filtration, washed successively with water (50 mL) and EtOAc (3 × 50 mL). The solid was dried under the house high vacuum for 2 h.

The crude product isolated above was charged to a suitable reactor. Dimethylformamide (125 mL), *N*-acetyl-*L*-cysteine (0.50 g), and glacial acetic acid (0.75 g) were charged to the reactor. The reactor temperature was raised to 60 °C and the contents were mixed for 1 h. The warm solution was filtered through a 0.2 micron filter and rinsed with DMF (25 mL). The filtrate was cooled to 25 °C. Methanol (300 mL) was charged over 10 h then mixed for an additional hour. The desired product (**1**) was collected by filtration, washed with methanol (3 × 50 mL) and dried in a vacuum oven at 60–80 °C to afford **1** (16.02 g, 32.5 mmol, 90.7%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (d, J = 2.0 Hz, 1H), 10.05 (s, 1H), 8.04 (br, 1H), 7.96 (t, J = 9.6 Hz, 2H), 7.80 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.71 (dd, J = 8.6, 2.5, 1H), 7.58 (dd, J = 8.6, 2.0, 1H), 7.38 (d, J = 2.8 Hz, 1H), 7.32 (d, J = 2.8 Hz, 1H), 5.66 (dd, J = 8.0 Hz, 2.0, 1H), 3.26 (s, 3H), 3.09 (s, 3H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.8, 156.7, 150.6, 145.9, 143.5, 136.5, 134.8, 134.7, 134.1, 132.7, 130.1, 129.5, 128.1, 127.6, 127.5, 127.0, 124.8, 120.7, 114.9, 101.4, 60.4, 39.4, 35.1, 30.5. mp 219–223 °C (DSC). Anal. Calcd for $C_{26}H_{27}N_3O_5S$: C, 63.27; H, 5.51; N, 8.51. Found C, 63.05; H, 5.55; N, 8.43.

***N*-(6-(3-(*tert*-butyl)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalene-2-yl)methanesulfonamide, dasabuvir (1) by Suzuki coupling of Aryl Iodide 9:** A solution of 100 mL of water and 300 mL of THF was sparged with nitrogen and then transferred with cannula under nitrogen pressure to a flask containing 1-(3-(*tert*-butyl)-5-iodo-4-methoxyphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (**9**) (20.0 g, 50.0 mmol), boronate ester (**7**), (20.8 g, 60.0 mmol, 1.20 equiv) and potassium phosphate tribasic (21.9 g, 103.0 mmol, 2.06 equiv) which had been purged with nitrogen. The resulting solution was again sparged with nitrogen.

THF (100 mL) was sparged with nitrogen and then transferred by cannula under nitrogen pressure to a flask containing $Pd_2(dba)_3$ (0.463 g, 0.510 mmol, 0.01 equiv) and ligand **28** (0.736 g, 2.52 mmol, 0.05 equivalents) which had been purged with nitrogen. The resulting solution was again sparged with nitrogen.

The initial THF/water solution was transferred by cannula under nitrogen pressure to the flask containing the catalyst and ligand in THF. The reaction was warmed to 50 °C and stirred overnight under positive nitrogen pressure.

The reaction was cooled to room temperature and washed, in three portions, with a solution of 5.84 g of L-cysteine and 81.4 g of sodium chloride in 550 mL of water which had been sparged with nitrogen. The THF solution was filtered through a celite pad. The pad was rinsed with 100 mL of THF, which was combined with the original THF solution. The THF solution was concentrated on a rotary evaporator to 136 g. To the white slurry was added 405 mL of EtOAc with good agitation. The slurry was filtered after stirring overnight. The wet cake was washed with 2 × 50 mL of EtOAc. The solid, an EtOAc solvate, was dried in the vacuum oven at 50 °C.

The solid and 8.7 g of mercaptopropyl-derivatized silica gel was stirred in 500 mL of THF then filtered through a celite pad. The filtrate was concentrated on the rotary evaporator to give 13.08 g of white solid. The solid that had been filtered off on the celite pad was extracted with 500 mL of THF at 60 °C to recover additional product. The THF solution was concentrated to 66 g and treated with 206 mL of EtOAc. The solid which precipitated was filtered and dried, yielding 9.13 g of product. This solid was combined with the original solid and slurried in 100 mL of 200 proof 3A ethanol. It was filtered and dried in the vacuum oven at 50 °C to give 20.74 g (84%) of dasabuvir.

Synthesis of dasabuvir (1) by Suzuki coupling of bromide 6

A flask was charged with bromide **6** (7.0 g, 20 mmol), boronate ester **7** (10.3 g, 29.7 mmol, 1.5 equiv), $PdCl_2$(dtbpf) (0.64 g, 0.98 mmol, 0.05 equiv), and K_3PO_4 (8.4 g, 40 mmol, 2.0 equiv). The reactor was sealed and inerted then a sparged solution of 4:1 THF:water (140 mL) was added. The reaction was heated to 50 °C and stirred for 16 h.

The layers were separated and the organic layer was washed with 50 mL of 25% NaCl solution. The resulting solution was concentrated and 150 mL of ethanol was added and distilled to afford a very thick slurry. The solids were collected by filtration and washed with 8 mL of ethanol. The wet cake was dissolved in 200 mL of THF and treated overnight at ambient temperature with carbon (Acticarbone ENO-PC, 1.5 g) and mercaptopropyl-derivatized silica gel (1.0 g) then filtered. The resulting solution was concentrated to ~50 mL, then 250 mL of ethanol was added in portions and distilled. The product was collected by filtration, washed with 20 mL of ethanol, and dried at 60 °C in vacuo to afford 7.2 g (74%) of dasabuvir (**1**) as a white solid.

***N*-(4-Cyanophenyl)picolinamide (15):**[63] To a suspension of picolinoyl chloride hydrochloride (5.9 g, 33 mmol, 1.2 equiv) in 65 mL dichloromethane at less than 5 °C was added 4-aminobenzonitrile (3.25 g, 27.5 mmol) in 16 mL dichloromethane and triethylamine (10.4 mL, 74.0 mmol, 2.7 equiv), keeping the temperature less than 20 °C. The reaction mixture was stirred overnight at ambient temperature. The reaction was quenched with addition of 50 mL water and the layers were separated. The aqueous layer was extracted with 50 mL dichloromethane. The combined organic layers were washed twice with 50 mL of 0.3 molal pH 7 buffer (0.15 molal KH_2PO_4/0.15 molal K_2HPO_4) and then 50 mL of 10% NaCl. After drying over $MgSO_4$, the product solution was concentrated to a thick slurry, chased with isopropyl acetate, then triturated with 40 mL of boiling isopropyl acetate to afford 4.96 g (81% yield) of the title product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.62 (d, J = 2.0 Hz, 1H), 8.28 (d, J = 4.8 Hz, 1H), 7.95–7.92 (m, 1H), 7.91 (d, J = 5.2 Hz, 2H), 7.66 (d, J = 5.2 Hz, 2H), 7.54–7.52 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.5, 149.1, 148.2, 141.8, 138.0, 133.5, 127.2, 122.8, 119.7, 119.0, 107.3. mp 168–170 °C, Lit. 162.8–164.2 °C.[63] Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found C, 69.83; H, 3.78; N 18.88.

***N*-(2-Cyanophenyl)picolinamide (16):**[64] To a suspension of picolinoyl chloride hydrochloride (25.9 g, 146 mmol, 1.2 equiv) in 172 mL dichloromethane was added 2-aminobenzonitrile (14.3 g, 121 mmol) and triethylamine (42.3 mL, 303 mmol, 2.5 equiv), keeping the temperature < 20 °C. The bath was removed and the reaction was stirred 2 h at ambient temperature. The reaction was quenched with 150 mL water and the layers were separated. The organic layer was washed with 100 mL each of water, 0.2 molal pH 7 buffer (0.1 molal KH_2PO_4/0.1 molal K_2HPO_4) and 10% NaCl. After drying over $MgSO_4$, the product solution was concentrated to a thick slurry, and chased with MeOH, then crystallized from ~270 mL hot MeOH to afford 22.3 g (83% yield) of the title product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.71–8.68 (m, 2H), 8.29 (d, J = 6.4 Hz, 1H), 7.95–7.91 (m, 1H), 7.67–7.63 (m, 2H), 7.55–7.51 (m, 1H), 7.21 (appt, J = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.7, 149.0, 148.6, 140.7, 137.9, 134.3, 132.7, 127.2, 124.2, 122.6, 120.8, 116.5, 102.4. mp 140–142 °C, Lit. 126–128 °C.[64] Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found C, 69.86; H, 3.82; 19.00.

Alternate preparation of *N*-(2-Cyanophenyl)picolinamide (16): Picolinic acid (100 g, 812 mmol, 1.20 equiv) was charged to a reactor. Dichloromethane (680 mL) and triethylamine (190 mL, 1.36 mol, 2.02 equiv) were added and the mixture was stirred to give a clear, colorless solution. The solution was cooled in an ice bath. With the reaction solution at 1 °C, tosyl chloride (156 g, 0.817 mol, 1.22 equiv) was added and the reaction temperature climbed to 15 °C as solid triethylamine hydrochloride separated from solution. After approximately 15 minutes anthranilonitrile (79.7 g, 0.675 mol, 1.0 equiv) was added to the reaction mixture. The reaction mixture was heated to 40 °C and mixed at 40 °C for 19 h. The reaction was cooled to 20 °C and washed with 500 mL of 0.2 N HCl, 500 mL of water, and 300 mL of water. The combined aqueous washes were back-extracted with 300 mL of dichloromethane. The combined dichloromethane solutions were concentrated to a solid on the rotary evaporator. The solid was slurried in 750 mL of methanol at 50 °C, then cooled to 20 °C. The slurry was filtered and the wet cake washed with 250 mL of methanol. Drying in a vacuum dryer at 50 °C yielded 126.6 g (85%) of the product as a white solid.

Four-step synthesis of 7,7,9,9-Tetramethyl-8-(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)-1,4-dioxa-8-phosphaspiro[4.5]decane (VincePhos, 50):

Diethyl 2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-ylphosphonate (**478**):[47] A 250-mL round-bottom flask equipped with a magnetic stir bar was charged with 2-iodo-2',4',6'-triisopropyl-3,6-dimethoxybiphenyl[65] (**46**, 6.0 g, 13 mmol, 1.0 equiv), sealed with a septum, then purged with nitrogen. Anhydrous, degassed THF (43 mL) was added to the flask and the resulting solution was cooled to –78 °C. *n*-Butyllithium (2.5 M in hexanes, 6.18 mL, 15.4 mmol, 1.2 equiv) was added dropwise to the cold mixture over 6 min. After the addition, the reaction mixture was allowed to stir at –78 °C for 90 min. Chlorodiethylphosphate (2.2 mL, 15 mmol, 1.2 equiv) was added to the reaction mixture over 3 min. The reaction was allowed to proceed at –78 °C for an additional 30 min, after which time the flask was removed from the cooling bath and warmed to room temperature. After 3 h, the reaction mixture was diluted with aqueous saturated sodium bicarbonate (50 mL). The resultant mixture was transferred to a separatory funnel, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with an aqueous saturated solution of sodium chloride (100 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The resulting solid was purified by silica gel column chromatography on an Isco CombiFlash Companion (120-g column; gradient: 1.5 column volumes (CV) CH_2Cl_2, ramp up to 88:12 CH_2Cl_2:acetone over 8 CV, hold for 7.5 CV) to give 3.51 g of a white solid (92 area% by HPLC, 57% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02–6.89 (m, 4H), 3.98–3.85 (m, 2H), 3.91 (s, 3H), 3.60 (s, 3H), 3.51 (ddq, *J* = 10.1, 9.2, 7.1 Hz, 2H), 2.93 (hept, *J* = 6.9 Hz, 1H), 2.49 (hept, *J* = 6.8 Hz, 2H), 1.28 (d, *J* = 6.9 Hz, 6H), 1.17 (d, *J* = 6.8 Hz, 6H), 1.02 (t, *J* = 7.0 Hz, 6H), 0.97 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.6, 151.6, 151.4, 146.8, 145.8, 133.9, 133.8, 132.0, 120.6, 120.0, 118.7, 113.92, 113.89, 110.7, 110.6, 61.3, 61.2, 56.7, 55.7, 34.5, 31.2, 24.9, 24.5, 23.9, 16.74, 16.68. (C spectrum is complicated because of ^{13}C-^{31}P coupling). ^{31}P{^{1}H} NMR (200 MHz, $CDCl_3$) δ 13.1 ppm.

(2',4',6'-Triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphine (**48**):[47] A 100-mL round-bottom flask was purged with nitrogen. Anhydrous, degassed THF (14 mL) was added to the flask and cooled to 0 °C. Lithium aluminum hydride (LAH) (2.0 M in THF, 10.9 mL, 21.8 mmol, 3.0 equiv) was added to the cooled THF. Chlorotrimethylsilane (2.8 mL, 22 mmol, 3.0 equiv) was added dropwise to the LAH solution over 4 min. This solution was allowed to stir at 0 °C for 25 min. A solution of diethyl 2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-ylphosphonate **47** (3.47

g, 7.28 mmol, 1.0 equiv) in 11 mL of anhydrous, degassed THF was cooled to 0 °C under an atmosphere of nitrogen. The LAH/TMSCl solution was transferred by cannula into the solution of phosphonate over 4 min. The reaction was allowed to proceed overnight while warming to 22 °C. The reaction mixture was cooled in an ice bath. The reaction was quenched by slow addition of EtOAc (6 mL), followed by aqueous hydrochloric acid (1 M, 100 mL). This mixture was allowed to stir for 1 h under an atmosphere of N_2. The layers of the mixture were separated and the aqueous layer was washed with EtOAc (3 × 50 mL). The combined organics layers were washed with a saturated solution of NaCl (75 mL). The organic solution was dried over sodium sulfate, filtered, and concentrated in vacuo to give a white solid (2.67 g) which was 95% pure by ^{1}H NMR (98% yield). This material was used without further purification. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.05 (s, 2H), 6.84–6.78 (m, 2H), 3.88 (s, 3H), 3.65 (s, 3H), 3.31 (d, J = 215.0 Hz, 2H), 2.95 (hept, J = 6.9 Hz, 1H), 2.44 (hept, J = 6.8 Hz, 2H), 1.31 (d, J = 6.9 Hz, 6H), 1.15 (d, J = 6.9 Hz, 6H), 1.02 (d, J = 6.8 Hz, 6H). ^{31}P{^{1}H} NMR (200 MHz $CDCl_3$) δ –156.3 ppm.

2,2,6,6-Tetramethyl-1-(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphinan-4-one (**49**):[47] A 20-mL glass liner was charged with 1.80 g of (2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphine **48** (4.83 mmol, 1.0 equiv) and 2.67 g of 2,6-dimethyl-2,5-heptadien-4-one (19.3 mmol, 4 equiv). The glass liner was placed into a 30-mL Parr Hastelloy C reactor and the vessel was purged and sealed under 30 psi of nitrogen gas. The mixture was immersed in an oil bath at 160 °C with magnetic stirring. The reactor was removed from the oil bath after 22 h and the contents were allowed to cool to room temperature. The yellow oil was then purified by silica gel column chromatography on an Isco CombiFlash Companion (80-g column; gradient: 2 column volumes (CV) heptane, ramp up to 80:20 heptane:EtOAc over 8 CV, hold for 4 CV). The resulting white solid was dried in vacuo to give 1.63 g of 2,2,6,6-tetramethyl-1-(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphinan-4-one (93 area% by HPLC, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 2H), 6.92 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 3.82 (s, 3H), 3.59 (s, 3H), 3.05 (dd, J = 12.8, 2.0 Hz, 2H), 2.94 (hept, J = 6.9 Hz, 1H), 2.45 (hept, J = 6.8 Hz, 2H), 2.18 (dd, J = 12.8, 5.0 Hz, 2H), 1.31 (d, J = 6.9 Hz, 6H), 1.21 (d, J = 6.8 Hz, 6H), 1.13 (d, J = 22.8 Hz, 6H), 0.95 (d, J = 9.2 Hz, 6H), 0.95 (d, J = 6.8 Hz, 6H). ^{31}P{^{1}H} NMR (200 MHz, $CDCl_3$) δ 6.2 ppm (br singlet).

7,7,9,9-Tetramethyl-8-(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)-1,4-dioxa-8-phosphaspiro[4.5]decane (VincePhos, 50):[47] A round-bottom flask was charged with 1.10 g of 2,2,6,6-tetramethyl-1-(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphinan-4-one **49** (2.15 mmol, 1.0 equiv) and 0.037 g of p-toluenesulfonic acid monohydrate (0.21 mmol, 0.1 equiv). The atmosphere was purged with nitrogen and the flask was charged with 21 mL of nitrogen-sparged toluene. To this solution was added 1.2 mL of ethylene glycol (21 mmol, 10 equiv). The reaction flask was equipped with a Dean–Stark trap and warmed to an internal temperature of 110 °C for 16 h under nitrogen atmosphere. The distilled toluene was collected in the Dean–Stark trap. The reaction mixture was cooled to room temperature under nitrogen gas. The reaction was quenched with 30 mL of aqueous saturated sodium bicarbonate solution and the resulting phases were partitioned. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic solutions were washed once with 50 mL of a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo with gentle heating. The concentrate was purified by silica gel column chromatography using an Isco CombiFlash Companion (80-g column; gradient: 2 column volumes (CV) heptane, ramp up to 80:20 heptane:EtOAc over 8 CV, hold for 6 CV). The resulting white solid was dried in vacuo at 23 °C to give 1.08 g of 7,7,9,9-tetramethyl-8-(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)-

1,4-dioxa-8-phosphaspiro[4.5]decane (90% yield). ^{1}H NMR (400 MHz $CDCl_3$) δ 6.96 (s, 2H), 6.86 (d, *J* = 8.9 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 1H), 4.00–3.97 (m, 2H), 3.91–3.87 (m, 2H), 3.80 (s, 3H), 3.56 (s, 3H), 2.95 (hept, *J* = 6.9 Hz, 1H), 2.48 (hept, *J* = 6.7 Hz, 2H), 2.18 (d, *J* = 13.2 Hz, 2H), 1.55 (dd, *J* = 13.2, 6.4 Hz, 2H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.23 (d, *J* = 23.4 Hz, 6H), 1.22 (d, *J* = 6.7 Hz, 6H), 0.93 (d, *J* = 6.7 Hz, 6H), 0.85 (d, *J* = 8.7 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.41, 154.39, 152.2, 152.1, 146.6, 145.73, 145.71, 140.7, 140.3, 132.5, 132.4, 127.4, 127.0, 120.0, 112.0, 111.0, 107.4, 64.9, 63.0, 54.7, 54.2, 47.00, 46.96, 34.6, 34.2, 34.1, 32.9, 32.7, 30.89, 30.86, 30.83, 25.6, 24.4, 24.3 (C spectrum is complicated because of ^{13}C-^{31}P coupling). ^{31}P{^{1}H} NMR (200 MHz, $CDCl_3$) δ –0.7 ppm (br singlet). mp 247–251 °C (DSC). Anal. Calcd for $C_{34}H_{51}O_4P$: C, 73.61; H, 9.27. Found C, 73.74; H, 9.52.

Characterization data for Suzuki rearrangement byproduct 38: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.34 (s, 1H), 9.63 (s, 1H), 7.88 (d, *J* = 1.7 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.26–7.18 (m, 3H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.11 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.61 (d, *J* = 7.8 Hz, 1H), 5.27 (s, 2H), 1.35 (s, 9H). ^{13}C{^{1}H}NMR (126 MHz, DMSO-d_6) δ 163.8 (C), 156.8 (C), 155.6 (C), 150.7 (C), 146.0 (CH), 138.0 (C), 134.2 (C), 131.5 (C), 131.0 (C), 129.4 (CH), 127.3 (C), 126.6 (CH), 126.4 (CH), 126.2 (CH), 125.5 (CH), 125.1 (CH), 119.0 (CH), 112.9 (CH), 108.7 (CH), 101.2 (CH), 70.3 (CH_2), 34.6 (C), 29.4 (CH_3). MS (DCI): *m/z* 434.3 ($M + NH_4^+$).

Supporting Information

The supporting information is available free of charge on the ACS Publication website. Reaction optimization, copies of ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra of the products (PDF).

■ Acknowledgements

This publication was sponsored by AbbVie. AbbVie contributed to the design, study conduct, and financial support for this research. AbbVie participated in the interpretation of data, writing, reviewing and approving the publication. All authors are AbbVie employees, or were employees of Abbott/AbbVie when the work was performed. The authors wish to acknowledge John Bellettini, Shuang Chen, Ann Czyzewski, Bruce Gaede, John G. Gaertner, Wenke Li, Timothy Towne, Wayne Pritts, Jose Restituyo, Weifeng Wang, Hao Yang, Carmina Presto and Gang Zhao for their contributions to this project.

■ References

(1) Gower, E.; Estes, C.; Blach, S.; Razavi-Shearer, K.; Razavi, H.: Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol* **2014**, *61*, S45-S57.

(2) Messina, J. P.; Humphreys, I.; Flaxman, A.; Brown, A.; Cooke, G. S.; Pybus, O. G.; Barnes, E.: Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* **2015**, *61*, 77-87.

(3) Denniston, M. M.; Jiles, R. B.; Drobeniuc, J.; et al.: CHronic hepatitis c virus infection in the united states, national health and nutrition examination survey 2003 to 2010. *Ann. Intern. Med.* **2014**, *160*, 293-300.

(4) Wyles, D. L.; Gutierrez, J. A.: Importance of HCV genotype 1 subtypes for drug resistance and response to therapy. *J Viral Hepat* **2014**, *21*, 229-240.

(5) Lam, J. T.; Salazar, L.: New combination antiviral for the treatment of hepatitis C. *Am J Health Syst Pharm* **2016**, *73*, 1042-1050.

(6) Shekhar, S.; Franczyk, T. S.; Barnes, D. M.; Dunn, T. B.; Haight, A. R.; Chan, V. S.: Process for preparing antiviral compounds. US 9,434,698, 09/06/2016.

(7) Wagner, R.; Tufano, M. D.; Stewart, K. D.; Rockway, T. W.; Randolph, J. T.; Pratt, J. K.; Motter, C. E.; Maring, C. J.; Longenecker, K. L.; Liu, Y.; Liu, D.; Krueger, A. C.; Kati, W. M.; Hutchinson, D. K.; Huang, P. P.; Flentge, C. A.; Donner, P. L.; Degoey, D. A.; Betebenner, D. A.; Barnes, D. M.; Chen, S.; Franczyk, T. S., II; Gao, Y.; Haight, A. R.; Hengeveld, J. E.; Henry, R. F.; Kotecki, B. J.; Lou, X.; Sarris, K.; Zhang, G. G. Z.: Uracil or thymine derivative for treating hepatitis C and their preparation.WO 2009/039127, 09/17/2008.

(8) See the following report for discussions on the development of Cu-catalyzed coupling of uracil with aryl halides. Barnes, D. M.; Kotecki, B. J.; Hengeveld, J. E.; Franczyk, S. T.; Haight, A. R.; McLaughlin, M. A. N-Arylpicolinamides are efficient ligands for the copper-catalyzed N-arylation of heterocycles. Application to the regioselective N-arylation of pyrimidine and purine bases. Manuscript submitted.

(9) Anderson, S.; Taylor, P. N.; Verschoor, G. L. B.: Benzofuran Trimers for Organic Electroluminescence. *Chem. Eur. J.* **2004**, *10*, 518-527.

(10) Zhou, T.; Li, T.-C.; Chen, Z.-C.: Hypervalent Iodine in Synthesis. Part 86. *Helv. Chim. Acta* **2005**, *88*, 290-296.

(11) Maruyama, T.; Fujiwara, K.; Fukuhara, M.: A new method for the synthesis of N-phenyl-uracil and -pyrimidine nucleosides. *J. Chem. Soc., Perkin Trans. 1* **1995**, 733-734.

(12) Rad, M. N. S.; Behrouz, S.; Doroodmand, M. M.; Moghtaderi, N.: Copper Nanoparticle-Doped Silica Cuprous Sulfate as a Highly Efficient and Reusable Heterogeneous Catalysis for *N*-Arylation of Nucleobases and N-Heterocyclic Compounds. *Synthesis* **2011**, *2011*, 3915-3924.

(13) Edgar, K. J.; Falling, S. N.: An efficient and selective method for the preparation of iodophenols. *J. Org. Chem.* **1990**, *55*, 5287-5291.

(14) Ikoma, A.; Ogawa, N.; Kondo, D.; Kawada, H.; Kobayashi, Y.: Synthesis of (−)-Piperitylmagnolol Featuring ortho-Selective Deiodination and Pd-Catalyzed Allylation. *Org. Lett.* **2016**, *18*, 2074-2077.

(15) Knöpfel, T. F.; Carreira, E. M.: The First Conjugate Addition Reaction of Terminal Alkynes Catalytic in Copper: Conjugate Addition of Alkynes in Water. *J. Am. Chem. Soc.* **2003**, *125*, 6054-6055.

(16) Ueki, H.; Ellis, Trevor K.; Martin, Collin H.; Soloshonok, Vadim A.: Efficient Large-Scale Synthesis of Picolinic Acid-Derived Nickel(II) Complexes of Glycine. *Eur. J. Org. Chem.* **2003**, *2003*, 1954-1957.

(17) Seeboth, H.: The Bucherer Reaction and the Preparative Use of its Intermediate Products. *Angew. Chem. Int. Ed.* **1967**, *6*, 307-317.

(18) During the course of our work we found that the combination of NH_4OH and $(NH_4)_2SO_3$ was highly corrosive to hastalloy, 316 carbon steel, and glass.

(19) Li, W.; Towne, T. B.; Liang, G.; Haight, A. R.; Barnes, D. M.: Practical Large-Scale Synthesis of 6-Bromo-2-naphthylmethanesulfonamide Using Semmler–Wolff Reaction. *Org. Proc. Res. Dev.* **2014**, *18*, 1696-1701.

(20) 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.

(21) The peak area ratio of **25**:**7**, monitored by HPLC, did not change when the reaction mixture was heated for an additional 16.5 h after completion.

(22) Epstein, M.; Buckler, S. A.: A Novel Phosphorus Heterocyclic System from the Reactions of Phosphine and Primary Phosphines with 2,4-Pentanedione. *J. Am. Chem. Soc.* **1961**, *83*, 3279-3282.

(23) Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Robertson, A. J.; McNulty, J.; Capretta, A.: Phosphaadamantanes as Ligands for Palladium Catalyzed Cross-Coupling Chemistry: Library Synthesis, Characterization, and Screening in the Suzuki Coupling of Alkyl Halides and Tosylates Containing Î²-Hydrogens with Boronic Acids and Alkylboranes. *J. Org. Chem.* **2004**, *69*, 7635-7639.

(24) Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A.: Palladium Complexes of 1,3,5,7-Tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane: Synthesis, Crystal Structure and Use in the Suzuki and Sonogashira Reactions and the α-Arylation of Ketones. *J. Org. Chem.* **2004**, *69*, 5082-5086.

(25) International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (M7)." 31 Mar 2017.

(26) 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.

(27) Shekhar, S.; Dunn, T. B.; Kotecki, B. J.; Montavon, D. K.; Cullen, S. C.: A General Method for Palladium-Catalyzed Reactions of Primary Sulfonamides with Aryl Nonaflates. *J. Org. Chem.* **2011**, *76*, 4552-4563.

(28) Högermeier, J.; Reissig, H. U.: Nine Times Fluoride can be Good for your Syntheses. Not just Cheaper: Nonafluorobutanesulfonates as Intermediates for Transition Metal-Catalyzed Reactions. *Adv. Synth. Catal.* **2009**, *351*, 2747-2763.

(29) Commercial perfluorobutanesulfonyl fluoride contains isomeric sulfonyl fluorides, and so the product can contain isomeric nonaflates. These isomers perform comparably in sulfonamidation.

(30) See Table S1 and S2 for detailed ligand screen.

(31) This impurity was observed at higher levels when Cs_2CO_3 or NaO*t*Bu were used as base. The reaction was too slow in the presence of a milder base, K_2CO_3.

(32) See Table S3 for further details on the impact of catalyst pre-activation procedure on the sulfonamidation reaction.

(33) Kotecki, B. J.; Fernando, D. P.; Haight, A. R.; Lukin, K. A.: A General Method for the Synthesis of Unsymmetrically Substituted Ureas via Palladium-Catalyzed Amidation. *Org. Lett.* **2009**, *11*, 947-950.

(34) Blue aqueous layers were observed after washing with aqueous ammonia solution, indicating the presence of Cu.

(35) Gelman, D.; Buchwald, S. L.: Efficient Palladium-Catalyzed Coupling of Aryl Chlorides and Tosylates with Terminal Alkynes: Use of a Copper Cocatalyst Inhibits the Reaction. *Angew. Chem. Int. Ed.* **2003**, *42*, 5993-5996.

(36) Hoshiya, N.; Buchwald, S. L.: An Improved Synthesis of BrettPhos- and RockPhos-Type Biarylphosphine Ligands. *Adv. Synth. Catal.* **2012**, *354*, 2031-2037.

(37) Marialuisa, A.; Fabien, P.; Franziska, S.: Redox Reactions in Palladium Catalysis: On the Accelerating and/or Inhibiting Effects of Copper and Silver Salt Additives in Cross-Coupling Chemistry Involving Electron-rich Phosphine Ligands. *Angew. Chem. Int. Ed.* **2012**, *51*, 7226-7230.

(38) Pu, X.; Li, H.; Colacot, T. J.: Heck Alkynylation (Copper-Free Sonogashira Coupling) of Aryl and Heteroaryl Chlorides, Using Pd Complexes of *t*-Bu_2(p-$NMe_2C_6H_4$)P: Understanding the Structure–Activity Relationships and Copper Effects. *J. Org. Chem.* **2013**, *78*, 568-581.

(39) Proutiere, F.; Aufiero, M.; Schoenebeck, F.: Reactivity and Stability of Dinuclear Pd(I) Complexes: Studies on the Active Catalytic Species, Insights into Precatalyst Activation and Deactivation, and Application in Highly Selective Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2012**, *134*, 606-612.

(40) No formation of palladium black was observed when Batch 1 (< 5 ppm Cu) was used in ethyl acetate.

(41) Welcher, R. P.; Day, N. E. 4-Phosphorinanones. II. *J. Org. Chem.* **1962**, *27*, 1824-1827.

(42) Johnson, G. A.; Wystrach, V. P. 4-Phosphorinanones. *J. Am. Chem. Soc.* **1960**, *82*, 4437-4438.

(43) Ullah, E.; McNulty, J.; Larichev, V.; Robertson, A. J.: P-Phenyl-2,2,6,6-tetramethylphosphorinan-4-ol: An Air-Stable P,O-Type Ligand for Palladium-Mediated Cross-Coupling Reactions. *Eur. J. Org. Chem.* **2010**, *2010*, 6824-6830.

(44) Brenstrum, T.; Clattenburg, J.; Britten, J.; Zavorine, S.; Dyck, J.; Robertson, A. J.; McNulty, J.; Capretta, A.: Phosphorinanes as Ligands for Palladium-Catalyzed Cross-Coupling Chemistry. *Org. Lett.* **2006**, *8*, 103-105.

(45) Saget, T.; Lemouzy, S. J.; Cramer, N.: Chiral Monodentate Phosphines and Bulky Carboxylic Acids: Cooperative Effects in Palladium-Catalyzed Enantioselective C(sp^3)–H Functionalization. *Angew. Chem. Int. Ed.* **2012**, *51*, 2238-2242.

(46) Clark, T.; Landis, C.: Recent developments in chiral phospholane chemistry. *Tetrahedron: Asymmetry* **2004**, *15*, 2123-2137.

(47) Shekhar, S.; Franczyk, T. S.; Barnes, D. M.; Dunn, T. B.; Haight, A. R.; Chan, V. S.: Preparation of phosphine ligands for catalytic reactions. US 8, 841,487, 09/23/2014.

(48) Ruiz-Castillo, P.; Buchwald, S. L.: Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564-12649.

(49) Surry, D. S.; Buchwald, S. L.: Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361.

(50) Wu, X.; Fors, B. P.; Buchwald, S. L.: A Single Phosphine Ligand Allows Palladium-Catalyzed Intermolecular C-O Bond Formation with Secondary and Primary Alcohols. *Angew. Chem. Int. Ed.* **2011**, *50*, 9943-9947.

(51) Smyth, L. A.; Phillips, E. M.; Chan, V. S.; Napolitano, J. G.; Henry, R.; Shekhar, S.: Pd-Catalyzed Synthesis of Aryl and Heteroaryl Triflones from Reactions of Sodium Triflinate with Aryl (Heteroaryl) Triflates. *J. Org. Chem.* **2016**, *81*, 1285-1294.

(52) Suzuki, K.; Hori, Y.; Kobayashi, T.: A New Hybrid Phosphine Ligand for Palladium-Catalyzed Amination of Aryl Halides. *Adv. Synth. Catal.* **2008**, *350*, 652-656.

(53) Suzuki, K.; Hori, Y.; Nishikawa, T.; Kobayashi, T.: A Novel (2,2-Diarylvinyl)phosphine/Palladium Catalyst for Effective Aromatic Amination. *Adv. Synth. Catal.* **2007**, *349*, 2089-2091.

(54) Lipshutz, B. H.; Chung, D. W.; Rich, B.: Sonogashira Couplings of Aryl Bromides: Room Temperature, Water Only, No Copper. *Org. Lett.* **2008**, *10*, 3793-3796.

(55) Preparation of a variety of biaryl phosphacycles and their application in Pd-catalyzed cross-coupling reactions will be reported separately.

(56) Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F.; Dommisse, R. A.: Study of a New Rate Increasing "Base Effect" in the Palladium-Catalyzed Amination of Aryl Iodides. *J. Org. Chem.* **2004**, *69*, 6010-6017.

(57) Kuethe, J. T.; Childers, K. G.; Humphrey, G. R.; Journet, M.; Peng, Z.: A Rapid, Large-Scale Synthesis of a Potent Cholecystokinin (CCK) 1R Receptor Agonist. *Org. Proc. Res. Dev.* **2008**, *12*, 1201-1208.

(58) Fors, B. P.; Davis, N. R.; Buchwald, S. L.: An Efficient Process for Pd-Catalyzed C-N Cross-Coupling Reactions of Aryl Iodides: Insight Into Controlling Factors. *J. Am. Chem. Soc.* **2009**, *136*, 5766-5768.

(59) Tashiro, M.; Fukata, G.: Studies on selective preparation of aromatic compounds. 13. Formation of benzquinhydrone type complexes from 2-*tert*-butylhalophenols in alkaline solution and their reduction with zinc powder in acetic acid affording 4,4'-dihydroxybiphenyls. *J. Org. Chem.* **1977**, *42*, 428-431.

(60) The O_2 level in the reactor headspace was monitored by an oxygen meter.

(61) Heating was necessary to dissolve methanesulfonamide in ethylacetate.

(62) Dasabuvir precipitates out of the solution.

(63) Sasaki, K.; Crich, D.: Facile Amide Bond Formation from Carboxylic Acids and Isocyanates. *Org. Lett.* **2011**, *13*, 2256-2259.

(64) Wu, X.-F.; Oschatz, S.; Sharif, M.; Beller, M.; Langer, P.: Palladium-catalyzed carbonylative synthesis of *N*-(2-cyanoaryl)benzamides and sequential synthesis of quinazolinones. *Tetrahedron* **2014**, *70*, 23-29.

(65) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L.: A Highly Active Catalyst for Pd-Catalyzed Amination Reactions: Cross-Coupling Reactions Using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines Using Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 13552-13554.