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Synthesis of the CD-ring of the anticancer agent streptonigrin: studies of aryl–aryl coupling methodologies

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Abstract—A series of functionalized 4-bromopyridines, representing the C-ring of the anticancer agent streptonigrin have been prepared and their abilities to undergo Pd-catalyzed cross-coupling with streptonigrin D-ring siloxanes were evaluated. The coupling reaction was generally tolerant to the preparation of hindered CD biaryls; however, the electronic effects of both partners play a pivotal role in the success of the coupling process. Analogs of the CD biaryl were prepared by coupling of aryl siloxane derivatives (D-ring component) with highly functionalized 4-bromopyridines (C-ring); however, the CD biaryl of the natural product could not be prepared in high yield by siloxane coupling due to the facile formation of reduced pyridine under the coupling conditions. Alternatively, the fully functionalized CD biaryl of streptonigrin was prepared using a Suzuki coupling of appropriately functionalized C-ring bromide and D-ring aryl boronic acid. The described approach is highly convergent and readily amenable to the synthesis of analogs.

1. Introduction

The formation of carbon–carbon bonds remains the most crucial transformation in synthetic chemistry, and the last 25 years have witnessed the development of a multitude of transition metal-catalyzed reactions that have greatly improved this process.[1] No other metal has been as widely studied for this purpose as palladium, and within this field the Stille,[2] Suzuki–Miyaura,[3] and Negishi[4] couplings have been the most widely explored. However, each of these processes suffers from limitations, including tedious preparation and purification of coupling precursors, reagent toxicity, or lack selectivity exhibited by the coupling partner. Organosilicon-based coupling strategies[5] address these limitations and offer an alternative to existing cross-coupling methodologies. Research from these laboratories has shown that aryltrialkoxysilanes, in the presence of fluoride and catalytic Pd(0), undergo aryl group transfer to a range of aryl halides and triflates.[6–11] Several methods have been developed for the synthesis of siloxane derivatives,[12–14] and the coupling reaction has been found to be of broad utility.

During our continued effort to explore the scope and tolerances of this process, we became interested in the synthesis of the anticancer agent streptonigrin (**1**). This fungal metabolite was isolated over 40 years ago[15] and was found to exhibit potent anticancer and antiviral activity.[16] It has recently been shown that naturally occurring streptonigrin exists as a single atrope isomer (the M configuration has been assigned), with hindered rotation about the CD-ring juncture (Fig. 1).[17]

The desirable biological properties as well as unique structural features of streptonigrin have made this agent a popular target,[18] and three total syntheses have been reported.[19–21] Our interest in the natural product was based on the supposition that the tetracyclic core of streptonigrin could be accessed using two sequential Pd-catalyzed cross-coupling reactions (Scheme 1). This approach offers the advantage of being highly convergent, as the AB, C, and D-rings may be independently prepared and functionalized prior to the coupling steps. In fact, several groups have reported the

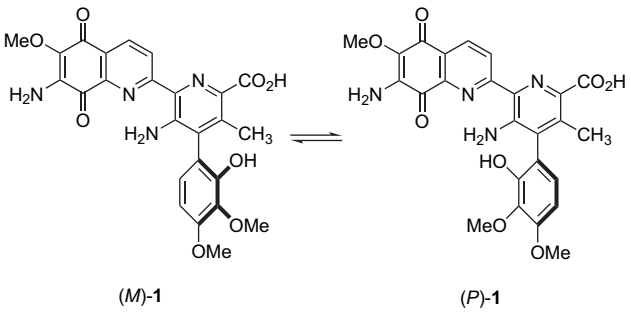

Figure 1. Atrope isomers of streptonigrin.

Keywords: Palladium-catalyzed; Cross-coupling; Organosiloxanes; Streptonigrin.
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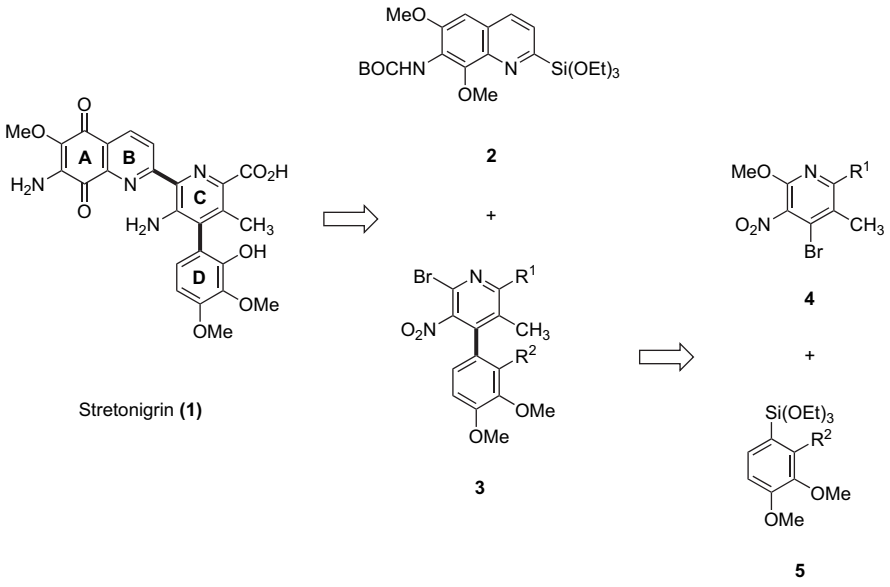


Scheme 1. Retrosynthetic analysis of streptonigrin.

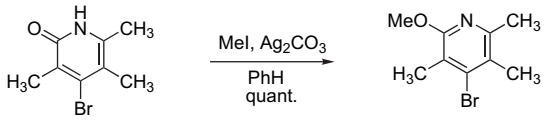
syntheses of streptonigrin model systems based on this approach.[22–30] These studies have demonstrated that the coupling reaction to form the CD biaryl tolerates the use of sterically hindered partners. The electronic effects of the pyridine ring, though, significantly influence the success of this strategy, and at present the natural product has yet to succumb to total synthesis using this approach. We have previously communicated preliminary results regarding siloxane-based couplings to prepare CD model systems of streptonigrin,[31] and report herein our full findings. These studies have culminated in a highly modular synthesis of streptonigrin CD biaryl.

2. Results and discussion

Our retrosynthetic analysis for streptonigrin (**1**) is outlined in Scheme 1. The tetracyclic core was to be established through the Pd-catalyzed coupling of quinoline siloxane **2** with 2-bromopyridine **3**. Conversion to the natural product would then be accomplished upon oxidation of the A-ring to the quinone and global deprotection. Biaryl **3** was envisaged as the product of a Pd-catalyzed coupling of 4-bromopyridine **4** and aryl siloxane **5**. Successful implementation of this strategy would require the development of coupling conditions amenable to the synthesis of highly functionalized (and hindered) biaryl derivatives.

The coupling reaction to form the CD biaryl presented a major synthetic challenge because a pentasubstituted pyridine bearing electron-donating and electron-withdrawing substituents would be one of the components. A siloxane coupling reaction with such a complex aromatic precursor had not been investigated previously and these studies would ultimately define the scope and limitations of the siloxane methodology. We therefore decided to develop a general approach to C-ring coupling precursors that was amenable to the preparation of analogs, in order that the steric and electronic factors that influence the coupling reaction be investigated in a systematic manner.

The starting points for our studies were the known pyridones **6**[32] and **7**.[33] Trimethyl substituted pyridine **8** was readily obtained upon methylation of pyridone **6** (Scheme 2).

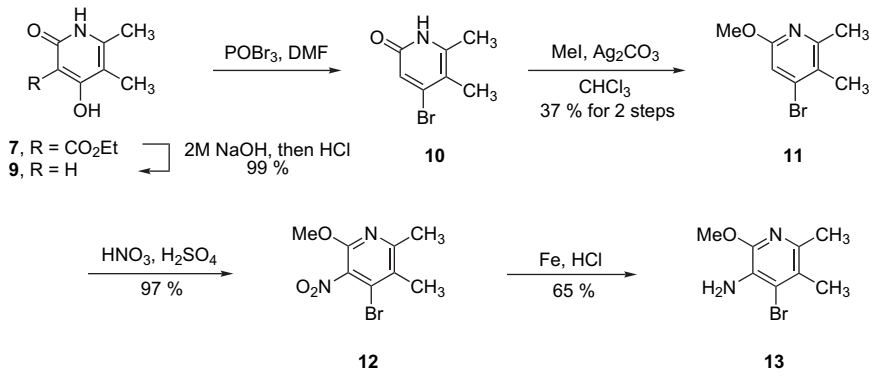


6 8

Scheme 2. Synthesis of bromopyridine **8**.

Pyridone **7** was subjected to ester hydrolysis and acid-promoted decarboxylation to give **9** (Scheme 3). Replacement of the C-4 hydroxyl group of pyridine **9** with a bromine substituent proved to be problematic due to competitive bromination at C-2. After significant experimentation, it was found that reaction of **9** with 0.70 equiv $POBr_3$ in DMF led reproducibly to bromopyridone **10**. Although the bromopyridone could be purified, it was more convenient to carry the crude material through the next step. Thus, methylation of the reaction mixture gave pyridine **11** in 37% isolated yield over two steps. Introduction of a nitrogen substituent at C-3 was accomplished in high yield by nitration of bromide **11** to provide nitropyridine **12**. Reduction of the nitro group occurred uneventfully to provide the amino analog **13**. These fully functionalized pyridine derivatives were now available for preliminary coupling reactions with siloxane derivatives.

Comparison of the cross-coupling reactions of bromopyridines **8** and **11** with an aryl siloxane was expected to provide information regarding the role of steric effects in the coupling process. Similarly, the cross-coupling of pyridines **11**, **12**, and **13**, each with a substituent in the C-3 position, would allow us to examine the influence of electronic factors on the coupling reaction. The results of these coupling reactions are summarized in Table 1. Coupling reactions were performed under identical conditions employing 20 mol %

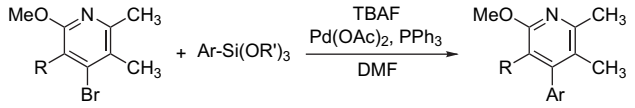


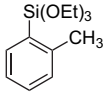
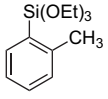
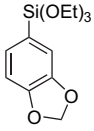
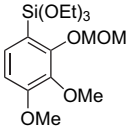
Scheme 3. Synthesis of bromopyridines **11**–**13**.

$Pd(OAc)_2$ and 40 mol % PPh_3, conditions which had proven to be optimal in previous coupling studies: 2 equiv of aryl siloxane and TBAF in DMF at 80 °C.

Coupling of pyridine **11** was investigated first, since this is the least sterically hindered of the bromopyridine series and its behavior should establish the baseline for the coupling reaction. Coupling of **11** and $PhSi(OMe)_3$ gave an excellent yield of the expected adduct (Table 1, entry 1).

Table 1. Coupling reactions of 4-bromopyridine derivatives with various aryl siloxanes



Entry	R	Ar–Si(OR′)$_3$	Yield (%)
1	H, **11**	$PhSi(OMe)_3$	97
2	H, **11**	 **14**	10[a]
3	Me, **8**	$PhSi(OMe)_3$	89
4	Me, **8**	 **14**	10[a]
5	Me, **8**	 **15**	61
6	Me, **8**	 **16**	0[a]
7	NO_2, **12**	$PhSi(OMe)_3$	36[a]

[a] The remainder of the mass balance was reduced bromopyridine.

However, the reaction of **11** with *o*-methyl siloxane **14**[14] gave only a 10% yield of the desired product (entry 2); the major product of the reaction was not the desired biaryl but the reduced (hydrodebrominated) pyridine. This result was surprising in two respects: first, the reduced products had not been observed previously in siloxane-based coupling reactions so their formation in this procedure was unanticipated. Secondly, *o*-tolyl siloxanes such as **14** underwent coupling with a variety of bromobenzene derivatives in excellent yield, demonstrating that steric effects on the siloxane component were not typically important to the success of the coupling reaction.[3,4] In this case, however, the coupling of the bromopyridine does not follow the typical profile. As it will become apparent in subsequent experiments, the reduction of the bromopyridine under coupling conditions will prove to be a significant complication in this approach (vide infra).

In order to further assess the steric tolerance of the coupling reaction, the coupling of trimethylbromopyridine **8** was examined. The Pd-catalyzed reaction of **8** and $PhSi(OMe)_3$ gave an 89% yield of the coupled adduct, while coupling of **8** and *o*-methyl siloxane **14** provided only 10% of the desired biaryl product (entries 3 and 4, respectively). These results are analogous to those obtained with bromopyridine **11**, and demonstrate that *ortho*-disubstituted bromopyridines are unsuitable coupling partners.

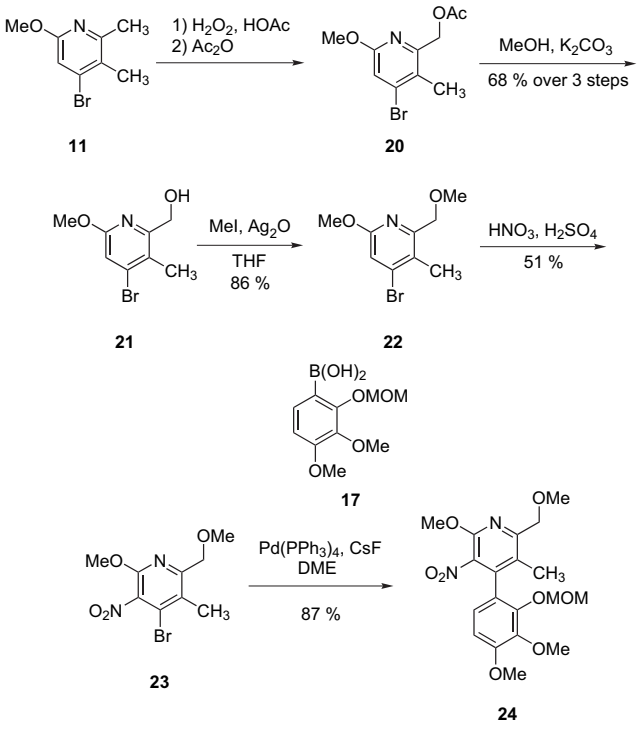
The reaction of bromopyridine **8** with methylenedioxy siloxane **15**[12] gave a 61% yield of the expected biaryl (entry 5). This was a significant finding since it demonstrated that couplings with siloxane derivatives lacking *ortho*-substituents occurred uneventfully. In addition, the substitution pattern of siloxane **15** is similar to the D-ring of streptonigrin, thus demonstrating that this approach would be useful for the synthesis of streptonigrin analogs lacking the *ortho*-phenolic group. It was disappointing that bromopyridine **8** failed to undergo the coupling reaction with siloxane **16** (entry 6), the siloxane that would directly provide the CD-ring system of the natural product. This result was not unexpected, however, based on the coupling results using *o*-tolyl siloxane. In addition, we had previously observed that aryl siloxanes with a heteroatom in the *ortho*-position to silicon underwent rapid protodesilylation under coupling conditions.[13] Even employing a stoichiometric amount of Pd(0) provided no improvement in the coupling outcome.

The couplings of 4-bromopyridine derivatives bearing nitrogen containing substituents at C-3 were also studied. Analogs of bromopyridine **12** with either an amino, azido, and amido functionality at C-3 failed to yield biaryl with $PhSi(OMe)_3$. However, reaction of nitropyridine **12** and $PhSi(OMe)_3$ gave a 36% yield of the corresponding biaryl (entry 7), along with 36% of the reduced (dehalogenated) pyridine. Although the yield of biaryl in this reaction was modest, studies with more complex siloxanes such as those needed for the total synthesis of streptonigrin were undertaken in the hope of improving and optimizing the yield of coupling. Unfortunately, formation of the dehalogenated pyridine was the major product observed from these studies. An extensive study of alternative Pd catalysts, ligands, and activators was performed, but the yield of cross-coupled product never rose above 30% in these reactions. The conclusion that must be drawn from these studies is that the electronic effects on both components played a pivotal role in the coupling process.

The difficulty experienced in preparing the streptonigrin CD skeleton using the siloxane technology led us to wonder if this unit may better be synthesized using organoboron reagents as the coupling reagent (Scheme 4). Reaction of bromopyridine **12** with boronic acid **17** gave a 78% yield of the respective biaryl with no evidence of the dehalogenated pyridine in the reaction products.

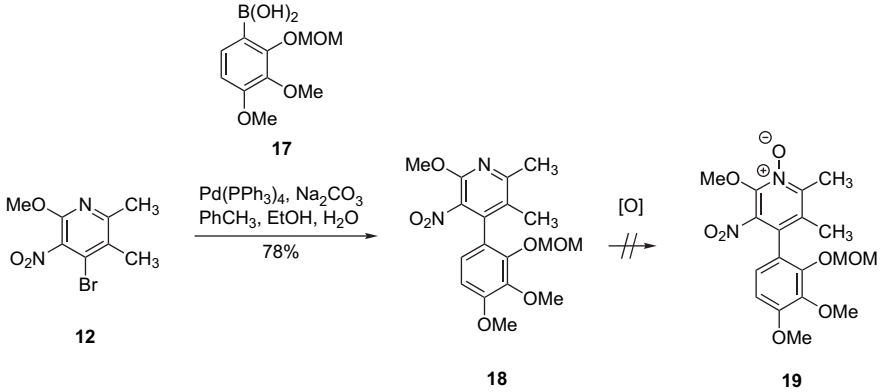
Oxidation of the pyridine C-6 methyl group of **18** to its carboxylic acid (the functional group present at this position in streptonigrin) was explored. The intention was to convert **18** to its *N*-oxide, followed by application of the pyridine *N*-oxide rearrangement[34] to provide a benzylic alcohol at the C-6 position of the pyridine ring. This strategy has been executed previously in an earlier synthesis of streptonigrin.[20] Much to our surprise, conversion of pyridine **18** to *N*-oxide **19** could not be accomplished. Using a wide variety of oxidants, the starting pyridine was recovered. Reduction of the nitro group of **18** and protection of the resulting amino group as its acetamide gave pyridine derivatives that were resistant to oxidation under a variety of conditions.

It was unclear whether the lack of reactivity of pyridine **18** and its derivatives to oxidation was the result of the electron-withdrawing nature of the C-3 substituent. To address this concern, the oxidation of pyridine **11** lacking a substituent at C-3 was investigated (Scheme 5). Treatment of **11** with H_2O_2 in HOAc resulted in complete conversion to the corresponding *N*-oxide, as determined by ^1H NMR. The *N*-oxide was not isolated but was treated immediately with Ac_2O to give rearranged product **20** in 93% yield over two steps. The facile oxidation-rearrangement of pyridine **11** demonstrated that the failure of pyridine **18** to undergo oxidation was due to the presence of the nitrogen substituent(s) at C-3, which must alter the relative basicity of the pyridine lone pair.



Scheme 5. Preparation and cross-coupling of bromopyridine **24**.

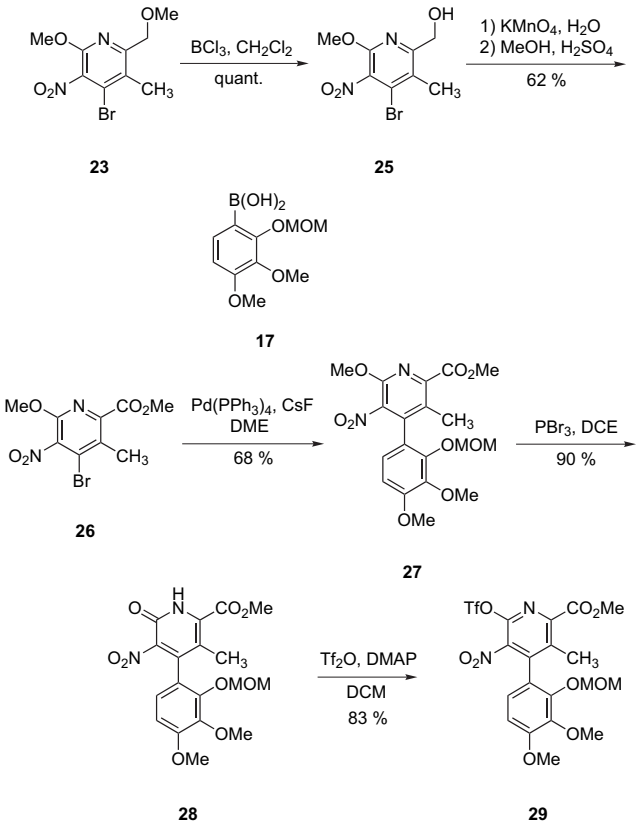
Based on the inability to oxidize the C-6 methyl group of C-ring once the aromatic D-ring had been introduced, the order of C-ring oxidation and D-ring coupling was altered. Treatment of **20** under the previously developed nitrating conditions gave a number of undesired reaction products, which had their origins in cleavage of the acid labile acetate functionality at C-6. It was clear that a robust protecting



Scheme 4. Suzuki coupling of bromopyridine **12** and boronic acid **17**.

group for the 1° alcohol of **21** would be required to effect nitration under the strongly acidic conditions. After extensive investigation, methyl ether **22** was determined to be the most suitable protected derivative. Nitration of methyl ether **22** gave nitropyridine **23** in 51% yield. We attribute the modest yield of the nitration (compared to pyridine **13**, Scheme 4) to be the result of deactivation of the pyridine ring due to protonation of the pyridine nitrogen. Nevertheless, with **23** in hand, the stage was set to explore the key coupling reaction to prepare the CD biaryl. The Pd-catalyzed reaction of bromopyridine **23** with siloxane derivatives was ineffective (vide supra), however, boronic acid **17** coupled with **23** using CsF as the activator in DME[35] provided an 87% yield of biaryl **24**. Unfortunately, oxidation of ether **24** to the corresponding C-6 carboxylic acid could not be achieved. Deprotection of **24** with BCl_3 gave only a 13% yield of the desired product. Analysis of the crude ^1H NMR spectrum indicated that several other reaction products, in which one or more of the D-ring methyl ethers had underwent cleavage, were present in the reaction mixture.

The successful endgame strategy for synthesis of the CD-ring system of streptonigrin is outlined in Scheme 6. Deprotection of the methyl group of bromide **23** with BCl_3 proceeded in quantitative yield to afford alcohol **25**. Subsequent oxidation with $KMnO_4$, followed by acid-catalyzed esterification, gave bromide-ester **26** in 62% yield over two steps. The cross-coupling of bromopyridine **26** with boronic acid **17**, using CsF in DME gave biaryl **27** in 68% yield. Biaryl **27** bears all of the key functionalities found in the CD-portion of streptonigrin. In addition, the C-2 position of the pyridine ring (C-ring) is functionalized



Scheme 6. Synthesis of streptonigrin CD biaryl.

such that the AB-rings of streptonigrin can be introduced via a coupling reaction. The C-2 methyl ether was converted into a suitable coupling substrate by treatment with PBr_3 to give pyridone **28** followed by conversion of the pyridone to triflate **29**. We anticipate that coupling of triflate **29** with appropriate metalloid reagents (siloxanes or boronic acid derivatives) will serve as a vehicle for the introduction of the AB-ring precursors.

3. Conclusion

A series of 4-bromopyridone derivatives have been synthesized and shown to undergo Pd-catalyzed coupling with aryl siloxane and boronic acid derivatives. A fully functionalized streptonigrin CD biaryl was synthesized using a Suzuki coupling of bromopyridine **26** and boronic acid **17**. The biaryl was elaborated to triflate **29**, thus setting the stage for a second coupling with a streptonigrin AB-ring precursor. Studies directed toward the utilization of triflate **29** to complete the total synthesis of streptonigrin (**1**) are underway and will be reported in due course.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer. Chemical shifts are reported in parts per million (ppm). Coupling constants (*J*) are given in hertz (Hz). Spin multiplicities are indicated by standard notation.

Infrared spectra were recorded on a Nicolet 560 FTIR spectrophotometer. Band positions are given in reciprocal centimeters (cm^{-1}) and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak).

Melting points were taken in Kimax soft capillary tubes using a Thomas–Hoover Uni-Melt capillary melting point apparatus equipped with a calibrated thermometer.

Low resolution (LRMS) and high resolution (HRMS) were obtained on a JEOL SX-102A instrument.

Thin layer chromatography (TLC) was performed on 0.25 mm Analtech silica-coated glass plates, with compounds being identified in one or both of the following manners: UV (254 nm) and vanillin/sulfuric acid/ethanol charring. Flash chromatography was performed using glass columns and 'medium pressure' silica gel (Sorbent Technologies, 45–70 μm).

Tetrahydrofuran (THF), diethyl ether, toluene, and 1,4-dioxane were distilled from sodium/benzophenone ketyl. *N*,*N*-Dimethylformamide (DMF) was distilled from calcium hydride and dried over 4 Å molecular sieves. Pyridine, methylene chloride, and 1,2-dichloroethane (DCE) were distilled from calcium hydride. *N*,*N*,*N*,*N*-Tetramethylethylenediamine (TMEDA) and 1,2-dimethoxyethane (DME) were distilled from sodium metal. PBr_3 and $B(OMe)_3$ were distilled prior to use. Triphenylphosphine was recrystallized from hexanes. All other reagents were purchased and used

as received. Glassware used in the reactions was dried overnight in an oven at 120 °C. All reactions were performed under an atmosphere of argon unless otherwise noted. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

4.1.1. 4-Bromo-2-methoxy-3,5,6-trimethylpyridine (8). To a suspension of 3.45 g (0.0125 mol) of Ag_2CO_3 and 3.58 g (0.0177 mol) of pyridone **6** in 30 mL of benzene was added 1.25 mL (0.0200 mol) of MeI. The resulting solution was heated in the dark at 45 °C for 12 h. The mixture was cooled to 0 °C, filtered, and the filtrate washed with 50 mL of 2% $NaHCO_3$, followed by 50 mL water. The benzene was evaporated under reduced pressure and the remaining aqueous solution was extracted 3× with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give 3.84 g (100%) of **8** as a white crystalline solid, mp 44–45 °C, which was used without further purification. IR (CCl_4) 3006 (w), 2953 (w), 2951 (m), 2920 (w), 2893 (w), 2866 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.22 (s, 3H), 2.37 (s, 3H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 14.5, 19.1, 23.8, 53.9, 118.4, 124.0, 139.4, 151.1, 159.9. EIMS *m/z* 231 (100), 229 (87), 216 (29). HRMS for $C_9BrH_{12}NO_2$ calcd 229.0102, found 229.0104.

4.1.2. 4-Hydroxy-5,6-dimethylpyridin-2(1*H*)-one (9). A solution of 61.78 g (0.2925 mol) of pyridone **7** and 111 g of NaOH (2.78 mol) in 1.3 L of water was heated at reflux for 2 h. The solution was cooled to 0 °C, brought to pH=7 with concd HCl, and stirred at room temperature for 12 h. The precipitate thus obtained was filtered and washed with water to yield 40.29 g (99%) of **9** as a white solid, mp>320 °C. IR (KBr) 3421 (w), 3266 (w), 3087 (m), 3002 (m), 2928 (m), 2882 (m), 1662 (s), 1616 (s) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.79 (s, 3H), 2.09 (s, 3H), 5.49 (s, 1H), 10.53 (br s, 1H), 10.91 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 9.8, 16.7, 96.1, 104.2, 142.3, 163.7, 167.3. EIMS *m/z* 139 (100), 111 (76), 110 (80), 69 (72), 44 (84). HRMS for $C_7H_9NO_2$ calcd 139.0633, found 139.0638.

4.1.3. 4-Bromo-6-methoxy-2,3-dimethylpyridine (11). This compound was obtained directly from pyridone **9**. A mixture of 22.06 g (0.1585 mol) of **9** and 30.54 g (0.1068 mol) of $POBr_3$ in 30 mL DMF were heated at 110 °C for 45 min. After cooling, water was added and the resulting solution brought to pH=7 with Na_2CO_3. The precipitate thus obtained was filtered, washed with water and then Et_2O to yield 19.80 g of a yellow solid. Although the intermediate bromopyridone could be purified, it was more convenient to use the crude material in the next step.

To a solution of the crude bromopyridone and 32.2 g (0.117 mol) of Ag_2CO_3 in 110 mL $CHCl_3$ was added 20.0 mL (0.314 mol) MeI and the mixture heated at 50 °C for 24 h in the dark. After cooling, the mixture was filtered and the filtrate concentrated in vacuo. Purification by column chromatography (19:1 hexanes/EtOAc, R_f= 0.38) afforded 12.70 g (37% from **9**) of **11** as a white crystalline solid, mp 38–41 °C. IR (CCl_4) 3014 (w), 2971 (w), 2944 (w), 2897 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.44 (s, 3H), 3.85 (s, 3H), 6.80 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.0, 24.1, 54.0, 111.6, 124.0, 137.3, 155.4, 161.9. EIMS *m/z* 216 (98), 214 (100), 187 (37), 185 (32).

4.1.4. 4-Bromo-2-methoxy-5,6-dimethyl-3-nitropyridine (12). A solution of 1.32 g (6.11 mmol) of pyridine **11**, 0.60 mL (8.6 mmol) of HNO_3, and 15 mL of H_2SO_4 was stirred at room temperature for 14 h. The solution was diluted with 100 mL of water and neutralized with Na_2CO_3. The solution was extracted 2× with 100 mL Et_2O and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo to yield 1.55 g (97%) of **12** as a yellow solid, mp 86–89 °C, which was used without further purification. IR (CCl_4) 3025 (w), 2998 (w), 2951 (w), 2924 (w), 2905 (w), 1581 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.51 (s, 3H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 18.5, 24.4, 55.0, 125.2, 127.5, 152.5, 156.9. FABMS *m/z* 263 (66), 261 (61), 155 (57), 152 (59), 119 (68), 103 (48), 85 (100). HRMS for $C_8H_9BrN_2O_3$ calcd 260.9875, found 260.9872.

4.1.5. 4-Bromo-2-methoxy-5,6-dimethylpyridin-3-amine (13). To a solution of 1.39 g (5.32 mmol) of nitropyridine **12**, 28 mL of EtOH, and 7 mL of water were added 3.5 g (63 mmol) of Fe and two drops of concd HCl. The resulting solution was heated at reflux for 2 h. After cooling, the solution was filtered and the filtrate concentrated in vacuo. Purification by column chromatography (9:1 hexanes/EtOAc, R_f=0.40) gave 0.800 g (65%) of **13** as a yellow crystalline solid, mp 52–54 °C. IR (CCl_4) 3487 (s), 3394 (s), 3014 (w), 2983 (w), 2948 (m), 2920 (w), 2858 (w), 1654 (m), 1612 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 2.41 (s, 3H), 3.98 (s, 3H), 4.05 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 18.2, 22.3, 53.3, 119.8, 122.7, 127.1, 140.7, 149.6. EIMS *m/z* 232 (98), 230 (100), 189 (68), 187 (68). HRMS for $C_8H_{11}BrN_2O$ calcd 232.0034, found 232.0049.

4.2. General procedure for the siloxane-based synthesis of biaryls

Coupling reactions were performed under identical conditions using 20 mol % $Pd(OAc)_2$ and 40 mol % PPh_3, 2 equiv of siloxane and 2 equiv of TBAF. The following example is illustrative.

4.2.1. 2-Methoxy-3,5,6-trimethyl-4-phenylpyridine (Table 1, entry 3). To a solution of 261 mg (1.15 mmol) of bromopyridine **8**, 440 mg (2.22 mmol) of phenyltrimethoxysilane, 52 mg (0.21 mmol) of $Pd(OAc)_2$, and 110 mg (0.419 mmol) of PPh_3 in 10 mL DMF was added 2.2 mL (2.2 mmol) of a 1 M solution of TBAF in THF. The solution was degassed via a single freeze-pump-thaw cycle and heated at 80 °C for 12 h. The reaction was quenched with water and the solution was extracted 3× with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (hexanes, R_f=0.14) afforded 230 mg (89%) of the title compound as a colorless oil. IR (CCl_4) 3084 (w), 3056 (w), 2967 (s), 2944 (s), 2924 (m), 2858 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3H), 1.83 (s, 3H), 2.42 (s, 3H), 3.94 (s, 3H), 7.05 (d, *J*=6.8 Hz, 2H), 7.33 (d, *J*=6.8 Hz, 1H), 7.40 (t, *J*=6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.5, 16.3, 23.1, 53.6, 115.6, 121.9, 127.5, 128.8, 128.9, 140.9, 120.7, 152.0, 160.0. EIMS *m/z* 227 (70), 226 (100). HRMS for $C_{15}H_{17}NO$ calcd 226.1232, found 226.1228.

4.2.2. 6-Methoxy-2,3-dimethyl-4-phenylpyridine (Table 1, entry 1). Following column chromatography (19:1

hexanes/EtOAc, R_f=0.29), the biaryl was obtained in 97% yield as a white crystalline solid, mp 52–54 °C. IR (CCl_4) 3087 (w), 3060 (w), 2948 (m), 2920 (m), 2850 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.46 (s, 3H), 3.90 (s, 3H), 6.45 (s, 1H), 7.25 (d, J=8.4 Hz, 2H), 7.37 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 14.4, 22.1, 52.3, 106.6, 120.2, 126.5, 127.2, 127.6, 139.2, 151.7, 135.8, 160.3. EIMS m/z 213 (94), 212 (100), 184 (49), 183 (56), 128 (51), 127 (38). HRMS for $C_{14}H_{15}NO$ calcd 213.1154, found 213.1149.

4.2.3. 6-Methoxy-2,3-dimethyl-4-*o*-tolylpyridine (Table 1, entry 2). Following column chromatography (19:1 hexanes/EtOAc, R_f=0.32), the biaryl was obtained in 10% yield as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.04 (s, 3H), 2.46 (s, 3H), 3.90 (s, 3H), 6.36 (s, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.23 (m, 3H), 7.23 (m, 3H).

4.2.4. 2-Methoxy-3,5,6-trimethyl-4-*o*-tolylpyridine (Table 1, entry 4). Following column chromatography (19:1 hexanes/EtOAc, R_f=0.23), the biaryl was obtained in 10% yield as a pale yellow oil. IR (CCl_4) 3072 (w), 3002 (m), 2921 (m), 1581 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.70 (s, 3H), 1.71 (s, 3H), 1.87 (s, 3H), 2.36 (s, 3H), 3.89 (s, 3H), 6.84 (d, J=6.8 Hz, 1H), 7.24 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 13.1, 15.8, 19.8, 23.0, 53.5, 115.5, 121.9, 126.4, 127.9, 128.6, 130.4, 135.6, 139.6, 150.8, 151.5, 160.1. EIMS m/z 241 (100), 240 (84), 226 (94), 216 (65).

4.2.5. 4-(Benzo[*d*][1,3]dioxol-5-yl)-2-methoxy-3,5,6-trimethylpyridine (Table 1, entry 5). Following column chromatography (19:1 hexanes/EtOAc, R_f=0.30), the biaryl was obtained in 61% yield as a colorless oil. IR (CCl_4) 3072 (w), 3002 (m), 2948 (s), 2920 (s), 2829 (s), 1581 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.79 (s, 3H), 1.81 (s, 3H), 2.35 (s, 3H), 3.87 (s, 3H), 5.93 (s, 2H), 6.43 (d, J=7.2 Hz, 1H), 6.44 (s, 1H), 6.79 (d, J=7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 13.5, 16.4, 23.1, 53.6, 101.5, 108.8, 109.5, 116.0, 122.1, 122.2, 133.7, 147.0, 148.1, 150.1, 151.6, 160.0. EIMS m/z 271 (74), 270 (100). HRMS for $C_{16}H_{17}NO_3$ calcd 270.1130, found 270.1125.

4.2.6. 2-Methoxy-5,6-dimethyl-3-nitro-4-phenylpyridine (Table 1, entry 7). These compounds were prepared according to the general siloxane coupling procedure outlined previously. Following column chromatography (hexanes, R_f=0.19), the biaryl was isolated in 36% yield as a white, crystalline solid, mp 79–82 °C. IR (CCl_4) 3087 (w), 3064 (w), 3025 (w), 2990 (w), 2955 (w), 2920 (w), 2901 (w), 2874 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.95 (s, 3H), 2.50 (s, 3H), 4.00 (s, 3H), 7.16 (m, 2H), 7.40 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 16.0, 23.8, 54.6, 123.2, 128.6, 129.1, 129.3, 133.9, 134.4, 144.3, 152.1, 157.1. EIMS m/z 250 (100), 211 (57). HRMS for $C_{14}H_{14}N_2O_3$ calcd 258.1004, found 258.0997.

The reduced pyridine was obtained in 36% yield as a white crystalline solid, mp 69–72 °C, R_f=0.15 (hexanes). IR (CCl_4) 3025 (m), 2994 (m), 2955 (m), 2928 (m), 2866 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.45 (s, 3H), 4.05 (s, 3H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.2, 23.1, 54.9, 124.8, 131.5, 136.4, 154.4, 161.8.

4.3. Siloxane 16 and boronic acid 17

Siloxane **16** and boronic acid **17** were each prepared from 2,3-dimethoxybenzaldehyde as outlined below.

4.3.1. 2,3-Dimethoxyphenol. To a mixture of 9.3 mL (0.066 mol) of 30% H_2O_2 and 9.3 g of boric acid (0.15 mol) in 90 mL of THF was added 3 mL of sulfuric acid. The mixture was stirred at room temperature for 30 min and a solution of 5.0 g (0.030 mol) of 2,3-dimethoxybenaldehyde in 30 mL of THF was added. The mixture was heated at 50 °C for 24 h, quenched with saturated $NaHCO_3$, and filtered. The filtrate was extracted 3× with Et_2O and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (3:1 hexanes/EtOAc, R_f=0.29) afforded 3.22 g (70%) of the title compound as a pale yellow oil. Spectral data matched that of the reported compound.[36]

4.3.2. 1,2-Dimethoxy-3-(methoxymethyl)benzene. NaH (60% dispersion in mineral oil, 1.2 g, 30 mmol) was washed 2× with 3 mL of hexanes. To the solid was added 20 mL of DMF and the resulting suspension cooled to 0 °C. A solution of 3.42 g (22.2 mmol) of the phenol in 15 mL of DMF was added and the resulting solution stirred at 0 °C for 30 min. To the solution was added 2.3 mL (30 mmol) of MOM-Cl, causing the immediate evolution of gas. The solution was allowed to warm to room temperature and quenched with 50 mL of water. The solution was extracted 3× with ether and the combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford 4.40 g (100%) of the title compound as a pale yellow oil, which was used without further purification. IR (CCl_4) 2998 (m), 2955 (s), 2932 (s), 2834 (m), 1596 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.47 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 5.18 (s, 2H), 6.58 (d, J=8.2 Hz, 1H), 6.74 (d, J=8.2 Hz, 1H), 6.92 (t, J=8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.4, 56.6, 61.3, 95.7, 106.7, 109.9, 124.1, 139.6, 151.4, 154.1.

4.3.3. Triethoxy(3,4-dimethoxy-2-(methoxymethoxy)-phenyl)silane (16). A solution of 1.88 g (9.49 mmol) of the MOM ether and 2.2 mL (1.4 mmol) of TMEDA in 40 mL of THF was cooled to −78 °C. To this solution was added dropwise BuLi (15.3 mL of a 0.80 M solution, 0.014 mol) and the resulting solution stirred at −78 °C for 10 min and then allowed to warm to 0 °C and stirred for an additional 2 h. This solution was added over 30 min to 4.3 mL (1.9 mmol) of $Si(OEt)_4$ dissolved in 40 mL of THF at −78 °C. The resulting solution was allowed to warm to room temperature, quenched with water, and extracted 3× with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexanes, R_f=0.24) afforded 850 mg (25%) of **16** as a pale yellow oil. IR (CCl_4) 2971 (s), 2924 (s), 2889 (s), 2835 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.22 (t, J=7.0 Hz, 9H), 3.62 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.86 (q, J=7.0 Hz, 6H), 5.17 (s, 2H), 6.67 (d, J=8.2 Hz, 1H), 7.32 (d, J=8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 18.6, 56.3, 57.9, 59.0, 61.1, 99.6, 108.0, 117.2, 123.6, 141.9, 155.5, 156.6. EIMS m/z 360 (87), 271 (95), 270 (100), 255 (53), 166 (56), 45 (53). HRMS for $C_{15}H_{28}O_7Si$ calcd 360.1590, found 360.1604.

4.3.4. 3,4-Dimethoxy-2-(methoxymethoxy)phenylboronic acid (17). A solution of 1.08 g (5.45 mmol) of the MOM ether and 0.90 mL (5.4 mmol) TMEDA in 30 mL THF was cooled to −78 °C. To the solution was added dropwise 7.0 mL (5.6 mmol) of a 0.8 M solution of *n*-BuLi in hexanes and the resulting solution allowed to warm to 0 °C. After 1.5 h at 0 °C the solution was cooled to −78 °C and 1.2 mL (11 mmol) of $B(OMe)_3$ in 30 mL THF was added over 10 min. The resulting solution was allowed over 1 h to warm to room temperature and stirred an additional 16 h. HCl (30 mL, 5%) was added and the solution was extracted 3× with Et_2O. The combined organic layers were extracted with 2 M KOH. The aqueous layer was neutralized with concd HCl and extracted 3× with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. An analytical sample was obtained following recrystallization from hexanes/Et_2O as a white crystalline solid, mp 125–129 °C. IR (CCl_4) 3526 (br), 3468 (br), 2998 (m), 2955 (m), 2928 (m), 2854 (m), 2835 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.49 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 5.25 (s, 2H), 6.29 (br s, 2H), 6.72 (d, J=8.4 Hz, 1H), 7.52 (d, J=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.4, 58.6, 61.1, 100.7, 108.5, 131.8, 140.8, 156.5, 156.8.

4.3.5. 2-Methoxy-4-(3,4-dimethoxy-2-(methoxymethoxy)-phenyl)-5,6-dimethyl-3-nitropyridine (18). A mixture of the crude boronic acid, 645 mg (2.47 mmol) 4-bromopyridine **12**, 615 mg (5.32 mmol) $Pd(PPh_3)_4$, and 579 mg (5.46 mmol) Na_2CO_3, 60 mL toluene, 6 mL H_2O, and 6 mL EtOH was heated at reflux for 40 h. After cooling, 60 mL of water was added and the solution was extracted 3× with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (3:1 hexanes/EtOAc, R_f=0.25) afforded a yellow solid, which was recrystallized from hexanes/Et_2O to yield 737 mg (78%) of **18** as a white crystalline solid, mp 128–129 °C. IR (CCl_4) 2990 (m), 2955 (m), 2924 (m), 2874 (m), 2831 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.97 (s, 3H), 2.49 (s, 3H), 3.11 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.99 (s, 3H), 4.80 (d, J=5.6 Hz, 1H), 5.08 (d, J=5.6 Hz, 1H), 6.69 (d, J=8.4 Hz, 1H), 6.76 (d, J=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 15.9, 23.7, 54.5, 56.4, 57.1, 61.4, 99.4, 108.3, 121.1, 124.2, 124.9, 134.8, 141.4, 142.8, 148.5, 152.2, 155.0, 156.5. EIMS *m*/*z* 378 (100), 332 (37). HRMS for $C_{18}H_{22}N_2O_7$ calcd 378.1427, found 378.1443.

4.3.6. (4-Bromo-6-methoxy-3-methylpyridin-2-yl)methyl acetate (20). This compound was prepared directly from pyridine **11**. A solution of 520 mg (2.41 mmol) pyridine **11** and 1.0 mL (7.2 mmol) of 30% H_2O_2 in 15 mL HOAc were heated at 60 °C for 3 d. After cooling, the solution was concentrated in vacuo and the residue dissolved in 10 mL acetic anhydride. This solution was heated at 120 °C for 24 h and concentrated in vacuo to give 628 mg (93%) of **20** as a pale brown oil, which was used without further purification. IR (CCl_4) 3017 (m), 2983 (m), 2948 (m), 2924 (m), 2905 (m), 2854 (m), 1748 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.28 (s, 3H), 3.85 (s, 3H), 5.14 (s, 2H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.9, 21.2, 54.0, 66.3, 114.4, 124.9, 138.1, 151.1, 162.2, 171.1.

4.3.7. (4-Bromo-6-methoxy-3-methylpyridin-2-yl)methanol (21). This compound was obtained directly from pyridine **11**. A solution of 701 mg (3.24 mmol) of pyridine **11**, 0.50 mL (4.4 mmol) 30% H_2O_2, and 22 mL acetic acid was heated at 60 °C for 3 d. After cooling, the solution was concentrated in vacuo and the residue dissolved in 7 mL of acetic anhydride. This solution was heated at 120 °C for 2 h. After cooling, the solution was concentrated in vacuo. To the residue was added 2.28 g (16.5 mmol) K_2CO_3 and 25 mL methanol. The resulting solution was stirred at room temperature for 18 h and concentrated in vacuo. The residue was suspended in water and extracted 3× with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to yield 509 mg (68%) of **21** as a white crystalline solid, mp 49–52 °C, which was used without further purification. IR (CCl_4) 3456 (br), 3021 (m), 2983 (m), 2951 (m), 2928 (m), 2866 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.82 (br s, 1H), 3.92 (s, 3H), 4.62 (s, 2H), 6.90 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 15.3, 54.2, 62.3, 112.7, 122.0, 138.2, 154.4, 161.9.

4.3.8. 4-Bromo-6-methoxy-2-(methoxymethyl)-3-methylpyridine (22). To a solution of 2.16 g (9.31 mmol) of alcohol **21** and 3.31 g (14.3 mmol) of Ag_2O in 40 mL THF was added 2.0 mL (32 mmol) of iodomethane. The resulting solution was heated in the dark at 65 °C for 4 d. The suspension was filtered through a pad of Celite and the filtrate concentrated in vacuo to yield 1.97 g (86%) of **22** as a white crystalline solid, mp 48–50 °C, which was used without further purification. IR (CCl_4) 3014 (w), 2986 (w), 2951 (m), 2928 (m), 2893 (w), 2918 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.39 (s, 3H), 3.88 (s, 3H), 4.50 (s, 2H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.0, 54.1, 58.9, 75.6, 114.0, 125.9, 138.3, 153.6, 162.0.

4.3.9. 4-Bromo-2-methoxy-6-(methoxymethyl)-5-methyl-3-nitropyridine (23). A solution of 914 mg (3.71 mmol) of pyridine **22** in 1.5 mL of HNO_3 and 8.5 mL of H_2SO_4 was stirred at room temperature for 2 d. The solution was diluted with water, neutralized with Na_2CO_3, and extracted 3× with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (9:1 hexanes/EtOAc, R_f=0.11) afforded 550 mg (51%) of **23** as a white, crystalline solid, mp 47–50 °C. IR (CCl_4) 3025 (m), 2990 (m), 2959 (m), 2928 (m), 2921 (m), 2819 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.40 (s, 3H), 4.00 (s, 3H), 4.53 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 17.5, 55.1, 59.1, 75.1, 111.3, 127.2, 128.7, 152.9, 154.8. EIMS *m*/*z* 292 (6), 290 (8), 262 (91), 260 (100), 247 (30), 245 (28). HRMS for $C_9H_{11}BrN_2O_4$ calcd 291.9882, found 291.9893.

4.3.10. 2-Methoxy-4-(3,4-dimethoxy-2-(methoxymethoxy)-phenyl)-6-(methoxymethyl)-5-methyl-3-nitropyridine (24). Boronic acid **17** was prepared as described above. A solution of 287 mg (1.19 mmol) of the crude boronic acid, 190 mg (0.653 mmol) of bromopyridine **23**, 350 mg (2.30 mmol) CsF, and 138 mg (0.119 mmol) $Pd(PPh_3)_4$ in 6 mL DME was heated at reflux for 20 h. After cooling, the solution was diluted with water and extracted 3× with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column

chromatography (3:1 hexanes/EtOAc, R_f=0.09) yielded 233 mg (87%) of the title compound as a white crystalline solid, mp 71–73 °C. IR (CCl_4) 2994 (m), 2963 (m), 2932 (m), 2893 (m), 2835 (m), 1600 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.07 (s, 3H), 3.09 (s, 3H), 3.43 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.02 (s, 3H), 4.52 (d, J=12.0 Hz, 1H), 4.56 (d, J=12.0 Hz, 1H), 4.80 (d, J=5.6 Hz, 1H), 5.08 (d, J=5.6 Hz, 1H), 6.69 (d, J=8.6 Hz, 1H), 6.76 (d, J=8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.8, 54.7, 56.4, 57.1, 59.1, 61.4, 74.9, 99.4, 108.3, 120.5, 124.3, 126.8, 136.0, 142.5, 142.8, 148.5, 152.3, 154.3, 155.1. EIMS *m/z* 408 (46), 286 (100). HRMS for $C_{19}H_{24}N_2O_8$ calcd 408.2498, found 408.2484.

4.3.11. (4-Bromo-6-methoxy-3-methyl-5-nitropyridin-2-yl)methanol (25). A solution of 403 mg (1.38 mmol) of methyl ether **23** in 20 mL CH_2Cl_2 was cooled to 0 °C and 3.0 mL (3.0 mmol) of a 1.0 M solution of BCl_3 in CH_2Cl_2 was added dropwise. The resulting solution was stirred 16 h at room temperature and quenched with water. The phases were separated and the aqueous layer was extracted 2× with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give 383 mg (100%) of **25** as a white crystalline solid, mp 96–99 °C, which was used without further purification. IR (CCl_4) 3483 (br), 3026 (m), 2991 (m), 2949 (m), 2925 (m), 2898 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.83 (t, J=4.6 Hz, 1H), 4.05 (s, 3H), 4.70 (d, J=4.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 16.0, 55.4, 62.8, 123.5, 128.9, 153.3, 155.9.

4.3.12. Methyl 4-bromo-6-methoxy-3-methyl-5-nitropyridine-2-carboxylate (26). To a suspension of 397 mg (1.43 mmol) of alcohol **25** and 64 mg (1.6 mmol) NaOH in 30 mL water was added 710 mg (4.49 mmol) $KMnO_4$ and the resulting mixture stirred at room temperature for 24 h. MeOH was added and the suspension stirred 30 min and filtered. The filtrate was acidified with 1 M HCl and concentrated in vacuo. The residue was dissolved in 20 mL MeOH and 4 mL H_2SO_4, and the solution heated at reflux for 16 h. The solution was diluted with water and basicified with K_2CO_3. The MeOH was removed in vacuo and the remaining aqueous solution was extracted 3× with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give 269 mg (62%) of **26** as a yellow crystalline solid, mp 90–93 °C, which was used without further purification. IR (CCl_4) 3029 (w), 3002 (w), 2951 (m), 2924 (m), 2850 (w), 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H), 3.96 (s, 3H), 4.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 18.5, 53.5, 55.6, 127.6, 129.6, 147.0, 153.3, 165.7. EIMS *m/z* 306 (65), 304 (59), 274 (89), 272 (100), 246 (58), 244 (59). HRMS for $C_9H_9BrN_2O_5$ calcd 303.9695, found 303.9683.

4.3.13. Methyl 6-methoxy-4-(3,4-dimethoxy-2-(methoxymethoxy)phenyl)-3-methyl-5-nitropyridine-2-carboxylate (27). A solution of 682 mg (2.24 mmol) of ester **26**, 1.20 g (4.96 mmol) boronic acid **17**, 387 mg (0.335 mmol) $Pd(PPh_3)_4$, and 673 mg (4.43 mmol) CsF in 35 mL DME was heated at 75 °C for 24 h. After cooling, the solution was diluted with water and extracted 3× with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (4:1 hexanes/EtOAc, R_f=0.20) gave 646 mg (68%) of **27** as a white crystalline solid, mp 90–93 °C. IR (CCl_4) 3002 (m), 2948 (m), 2932 (m), 2897 (m), 2839 (m), 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.11 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 4.04 (s, 3H), 4.84 (d, J=5.6 Hz, 1H), 5.10 (d, J=5.6 Hz, 1H), 6.71 (d, J=8.4 Hz, 1H), 6.76 (d, J=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 15.9, 53.2, 55.2, 56.5, 57.2, 61.4, 99.5, 108.4, 119.6, 124.2, 127.7, 137.6, 142.8, 143.6, 146.7, 148.5, 152.6, 155.5, 166.7. EIMS *m/z* 422 (100), 300 (32), 272 (36). HRMS for $C_{19}H_{22}N_2O_9$ calcd 422.1325, found, 422.1332.

4.3.14. Methyl 1,6-dihydro-4-(3,4-dimethoxy-2-(methoxymethoxy)phenyl)-3-methyl-5-nitro-6-oxopyridine-2-carboxylate (28). A solution of 81 mg (0.192 mmol) pyridine **27** and 0.12 mL (1.27 mmol) PBr_3 in 4 mL of DCE was heated at reflux for 12 h. After cooling, the reaction was quenched with water and the mixture was extracted 3× with CH_2Cl_2. The combined organic extracts were concentrated in vacuo, the residue was washed with Et_2O to obtain 63 mg (90%) of **28** as a white solid, mp 225–235 °C (decomp.), which was used without further purification. IR ($CHCl_3$) 3515 (br), 3344 (br), 2843 (w), 1750 (w) 1685 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.18 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 6.02 (br s, 1H), 6.51 (d, J=8.8 Hz, 1H), 6.72 (d, J=8.8 Hz, 1H), 10.35 (br s). ^{13}C NMR ($CDCl_3$) δ 15.44, 54.1, 56.3, 61.6, 105.0, 111.6, 122.8, 123.6, 130.6, 135.9, 146.1, 146.4, 146.9, 153.7, 154.0, 161.5. FABMS *m/z* 365 (100). HRMS for $C_{16}H_{16}N_2O_8$ calcd 365.0985, found 365.0979.

4.3.15. 6-(Methoxycarbonyl)-4-(3,4-dimethoxy-2-(methoxymethoxy)phenyl)-5-methyl-3-nitropyridin-2-yl trifluoromethanesulfonate (29). A suspension of 63 mg (0.172 mmol) of pyridone **28** and 23 mg (0.188 mmol) DMAP in 4 mL CH_2Cl_2 was cooled to 0 °C and 35 μL (0.21 mmol) Tf_2O was added. The resulting solution was allowed to warm to room temperature and stirred 12 h. The reaction was quenched with water and the mixture extracted 3× with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Recrystallization from hexanes/Et_2O gave 71 mg (83%) of **29** as a white crystalline solid, mp 163–165 °C. IR (CCl_4) 3515 (br), 3010, (w), 2955 (w), 2936 (w), 2839 (w), 1740 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.01 (br s, 1H), 6.55 (d, J=8.4 Hz, 1H), 6.72 (d, J=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 16.6, 53.7, 56.4, 61.7, 105.1, 110.9, 123.9, 136.1, 137.8, 139.5, 143.4, 146.1, 147.1, 147.5, 154.3, 164.8. EIMS *m/z* 496 (98), 418 (52), 317 (100). HRMS for $C_{17}H_{15}F_3N_2O_{10}S$ calcd 496.0400, found 496.0385.

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