Studies on the Mechanism of Action of 2-Formyl-4-pyrrolidinopyridine: Isolation and Characterization of a Reactive Intermediate

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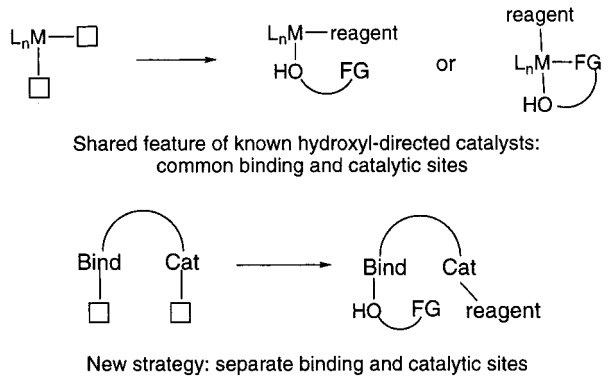
Received November 17, 1998 (Revised Manuscript Received March 23, 1999)

This paper describes the mechanism of action of 2-formyl-4-pyrrolidinopyridine (FPP, **1a**) which is a catalyst for the hydroxyl-directed methanolysis of α-hydroxy esters. This species was initially designed to act as a nucleophilic catalyst; however, we have ruled out a nucleophilic mechanism by examining the activity of 6-substituted-FPP derivatives. These compounds are more hindered in the vicinity of the pyridine nitrogen than FPP itself but are also more active catalysts. Furthermore, the presence of *p*-nitrophenol, a mild acid, was found to accelerate the catalytic reaction. These results are inconsistent with a nucleophilic catalysis mechanism. We provide evidence that the reaction instead proceeds via dioxolanone intermediate **10**. Dioxolanone **10** can be obtained by treating either the *p*-nitrophenyl ester or the pentafluorophenyl ester of glycolic acid with FPP in chloroform in the absence of methanol. It has been isolated, characterized, and shown to be kinetically competent when subjected to the conditions of the catalytic reaction.

Hydroxyl-directed reactions play an important role in organic synthesis.[1] They enable chemists to conduct reactions with high levels of stereochemical and regiochemical selectivity, in some cases with control of absolute stereochemistry. The advantages of this strategy have been widely recognized ever since the pioneering work of Henbest[2] and of Simmons and Smith,[3] and numerous reagents and catalysts have been developed which take advantage of hydroxyl-direction in their mechanism of action.[1] To the best of our knowledge, all of the catalysts that have been developed have a common mechanistic feature in that the binding site for the hydroxyl group is the same as the catalytic site for the reaction. This imposes certain constraints on catalytic systems and can be limiting in the design of new, selective, hydroxyl-directed catalysts for organic synthesis.[4] One solution to this problem is to consider catalysts which contain separate binding and catalytic sites (Scheme 1). This strategy offers greater flexibility in the design of hydroxyl-directed catalysts and allows for the conversion of known catalysts which are not hydroxyl-directed into ones which are by the incorporation of a binding site.

Scheme 1



To examine this strategy, we have studied the design of hydroxyl-directed acyl-transfer catalysts. Specifically, we wished to render the 4-aminopyridine class of nucleophilic acyl-transfer catalysts[5] hydroxyl-directed by the incorporation of a binding site. The requirements for a binding site in this system are that it rapidly and reversibly bind an alcohol, that it be stable to the reaction conditions, and that it not be so Lewis acidic that the catalyst undergoes intramolecular association between the nucleophilic and electrophilic components or undergoes dimerization. With these requirements in mind, we have prepared 2-formyl-4-pyrrolidinopyridine (FPP, **1a**, Scheme 2) in which an aldehyde at the 2-position of the pyridine serves as the binding site.[6] An aldehyde meets the requirements outlined above in that it is a stable functional group that can reversibly bind a hydroxyl group by the formation of a hemiacetal,[7] yet it is only mildly electrophilic. At the 2-position of a pyridine it is sterically encumbering and electron-withdrawing, thereby deactivating the nucleophilic catalyst. FPP should, therefore, be a poor catalyst for the solvolysis of unfunctionalized esters. However, upon binding of the hydroxyl

(1) For a review of substrate-directable reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(2) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958

(3) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

(4) In his account of the discovery of the asymmetric epoxidation, Sharpless eloquently explains the limitations imposed by the requirement that the hydroxyl group of the substrate bind the metal which is catalyzing the reaction and describes a series of ligands designed to circumvent these limitations in asymmetric epoxidation reactions. See: Sharpless, K. B. *Chem. Br.* **1988**, *24*, 38.

(5) For reviews, see: Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129; Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069; Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(6) For a preliminary account of this work, see: Sammakia, T.; Hurley, T. B. *J. Am. Chem. Soc.* **1996**, *118*, 8967.

(7) For a review of hydration of aldehydes and ketones, see: Bell, R. P. *Adv. Phys. Org. Chem.* **1966**, *4*, 1. (b) For a recent study of carbonyl hydration equilibria, see: Wiberg, K. B.; Morgan, K. M.; Maltz, H. *J. Am. Chem. Soc.* **1994**, *116*, 11067. (c) For a study of hemiacetal formation of pyridine carboxaldehydes, see: Gianni, P.; Matteoli, E. *Gazz. Chim. Ital.* **1975**, *105*, 125; and (d) Pocker, Y.; Meany, J. E. Nist, B. J. *J. Phys. Chem* **1967**, *71*, 4509.

10.1021/jo982281n CCC: $18.00
Published on Web 06/06/1999

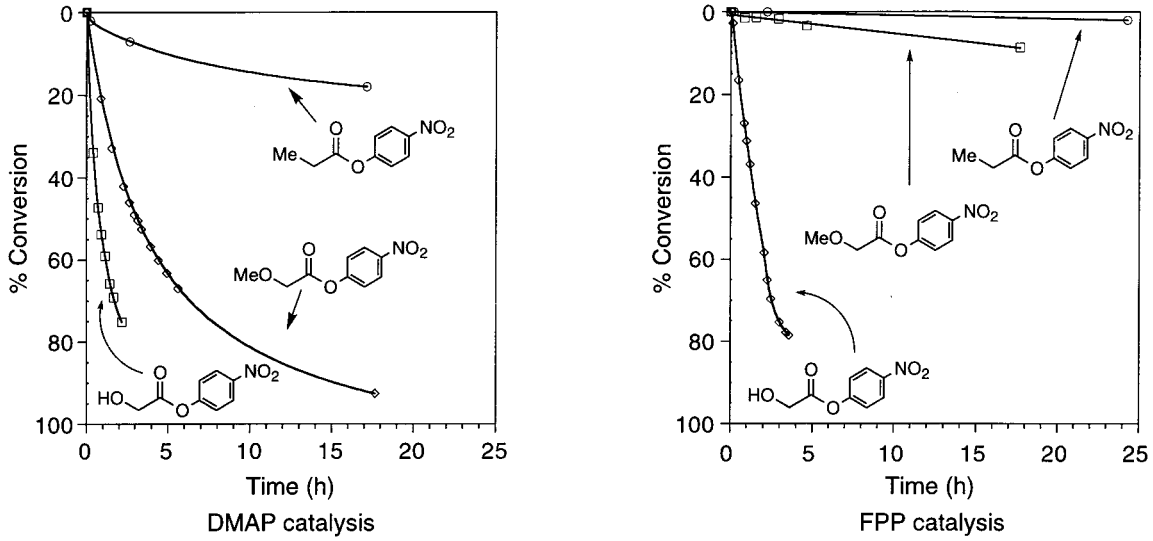


Figure 1. Kinetic data for the methanolysis of *p*-nitrophenyl esters catalyzed by DMAP and FPP illustrating the preferential reaction of *p*-nitrophenyl glycolate under FPP catalysis.

group of a hydroxy ester and formation of the corresponding hemiacetal, the ester is brought into close proximity to the pyridine nitrogen which can promote acyl transfer and provide the product bound to the catalyst.[8] Dissociation of the product would regenerate the catalyst ready to repeat the catalytic cycle. In this article, we describe our studies on the mechanism of action of FPP aimed at probing the validity of the design features of the catalyst and deducing the role of the aldehyde and of the pyridine nitrogen in the catalytic cycle. We also report the isolation and characterization of a reactive intermediate in the catalytic cycle.

Reactivity of FPP. We have studied the hydroxyl-directed methanolysis of esters with FPP.[6] Initial rates of methanolysis of the *p*-nitrophenyl (PNP) esters of propionic acid (**2**), methoxyacetic acid (**3**), and glycolic acid (**4**) with 5 mol % DMAP or FPP were measured by monitoring the disappearance of the ester as a function of time. Methanolysis reactions were run at a concentration of 0.1 M ester, 0.005 M catalyst, and 1.0 M methanol-d_4 in $CDCl_3$, and the progress of the reactions was monitored by NMR. As expected, due to electronic and hydrogen bonding effects, the α-alkoxy and α-hydroxy esters are intrinsically more reactive than the propionate ester (Figure 1, Table 1).[9] Using DMAP, the relative initial rates of methanolysis of **2**, **3**, and **4** are 30, 210, and 690, respectively. However, using FPP under the same conditions, the relative initial rates are 1.0, 5.3, and 510, respectively.[10] Thus, with FPP, methanolysis of the glycolate ester is 96 times faster than that of the methoxyacetate, whereas with DMAP it is only 3 times faster. This difference is primarily due to a 40-fold decrease in the rate of the methanolysis of the PNP ester of methoxyacetic acid (**3**) with FPP (k_{rel} = 5.3) as compared to DMAP (k_{rel} = 210), which is consistent with our proposed mechanism of action for FPP. It should be noted that in the absence of a catalyst <1% reaction of any of the *p*-nitrophenyl esters examined in this study was observed after 120 h.

Scheme 2

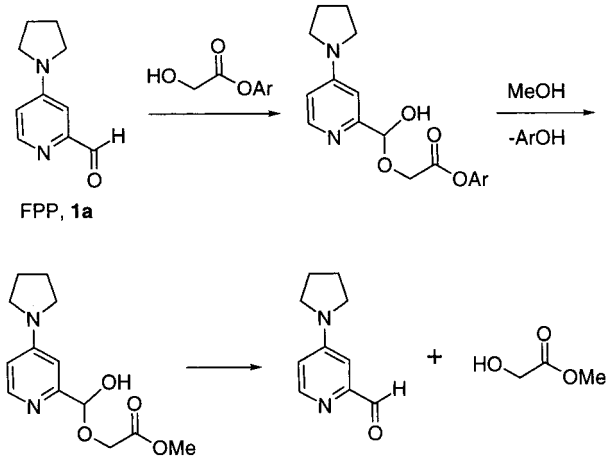
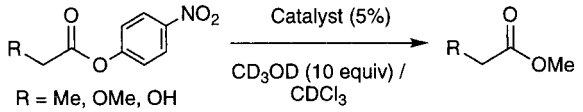


Table 1. Relative Rates for the Methanolysis of *p*-Nitrophenyl Esters with DMAP and FPP Catalysis



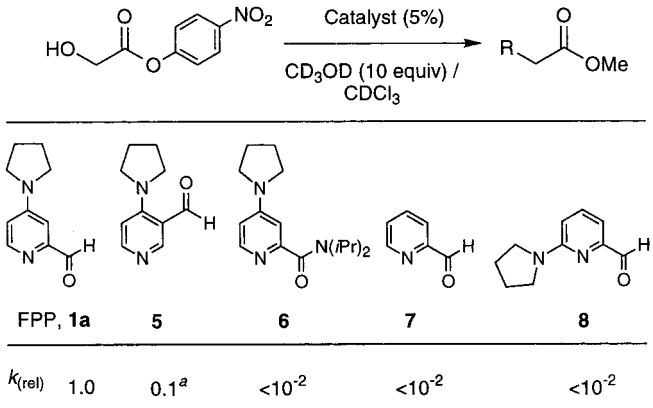
	R	$k_{(relative)}$			
		Me_2N			
(**2**)	Me	30		1	
(**3**)	OMe	210	3:1	5.3	96:1
(**4**)	OH	690		510	

(8) The binding of the substrate to the catalyst converts the aldehyde to a hemiacetal. An aldehyde is a more electron-withdrawing group than a hemiacetal, and as such the bound substrate should encounter a more active pyridine. An approximate measure of the electron-withdrawing ability of these two groups in this system can be obtained by comparing the pK_a of pyridine 2-carboxaldehyde (3.8 in water) and the hydrate of pyridine-2-carboxaldehyde (4.2 in water). This minor difference in basicity indicates that while the hemiacetal is less electron-withdrawing, the effect is relatively unimportant. See: Owens, T. C. *J. Heterocycl. Chem.* **1990**, *27*, 987. Green, R. W.; Freer, I. R. *J. Phys. Chem.* **1961**, *65*, 2211.

(9) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, 1953; p 758.

(10) Under our standard reaction conditions (0.005 M FPP, 0.1 M initial concentration of *p*-nitrophenyl glycolate, 1.0 M methanol-d_4) *p*-nitrophenyl glycolate is consumed at a rate of 0.029 M h^{-1}.

Table 2. Effect of Catalyst Structure on Reactivity



FPP is also an effective catalyst for the methanolysis of esters that are less active than PNP esters. Under the same conditions as in the previous study, the relative rates of methanolysis of phenyl glycolate, *p*-fluorophenyl glycolate, and *p*-nitrophenyl glycolate are 64, 140, and 510 with a half-life for the phenyl glycolate methanolysis of 18 h. These relative rates are comparable to those observed for simple alkaline hydrolysis.[11]

Mechanistic Studies. In our mechanistic studies, we first wished to establish that all of the components of FPP are required for catalytic activity. Toward this end we have examined a number of FPP derivatives as catalysts for the methanolysis of *p*-nitrophenyl glycolate (Table 2). Compound **5**, in which the carboxaldehyde has been moved from the 2 to the 3 position on the pyridine, is about 10 times less active than FPP and exhibits low selectivity for the methanolysis of hydroxy esters over methoxy esters, similar to that observed with DMAP. It appears that the 3-carboxaldehyde is too far from the pyridine nitrogen to act as a binding site for the hydroxy ester substrate and that this catalyst operates by a simple nucleophilic catalysis mechanism. Compound **6**, in which the aldehyde at the 2-position has been replaced with an amide, is inactive due to the inability of the amide to function as a binding site. In compound **7**, the amino group has been deleted from the 4-position. This compound is inactive due to the decreased basicity of the pyridine. Similarly, compound **8**, in which the amino substituent has been moved from the 4- to the 6-position on the pyridine, is less basic and more hindered than FPP, and therefore inactive.[12,13]

The dependence of the rate of the reaction on the concentration of methanol provides further evidence for the involvement of the aldehyde in the catalytic cycle. Our mechanism requires the presence of the free aldehyde in the catalyst in order to form a hemiacetal with the substrate. However, methanol can compete with the substrate for the aldehyde and form the methyl hemiacetal in an unproductive equilibrium and inhibit the reaction. We therefore measured the rate of methanolysis of *p*-nitrophenyl glycolate under conditions in which the concentration of the substrate and catalyst was kept constant while the concentration of methanol was varied. We find that as the concentration of methanol is increased, the rate of the reaction is retarded (Figure 2). Consistent with this observation, in $CDCl_3$ we find that 15% of FPP exists as the hemiacetal under our typical reaction conditions in the absence of any substrate (1.0 M methanol-d_4, 0.005 M FPP), whereas at higher concentrations of methanol (8.0 M methanol-d_4, 0.005 M FPP), 37% of FPP exists as the hemiacetal. At a lower concentration of methanol (0.5 M methanol-d_4, 0.005 M FPP), only 11% of FPP exists as the hemiacetal.[14]

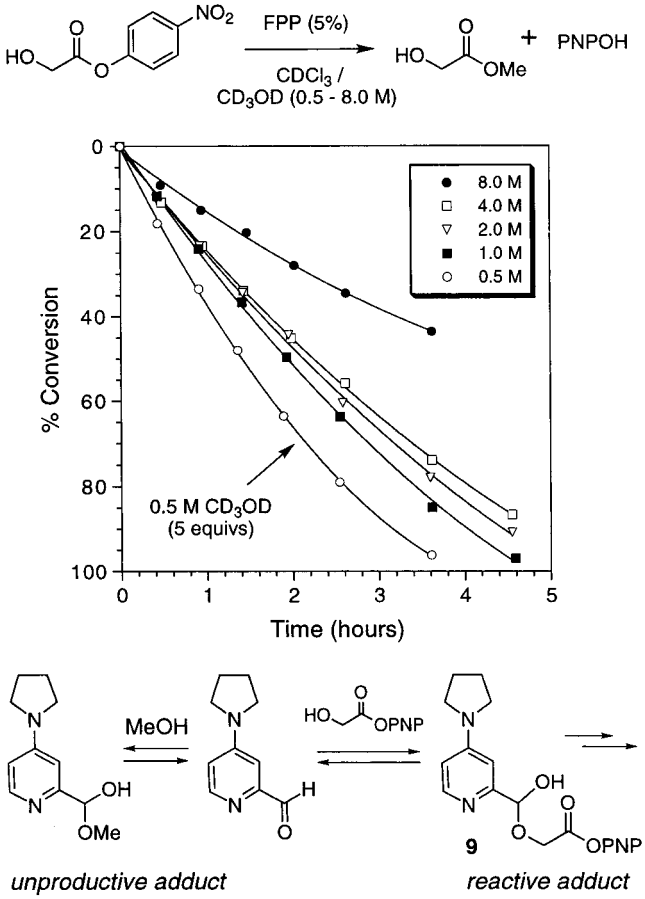


Figure 2. Examination of the effect of methanol concentration from 0.5 to 8.0 M on the rate of the FPP-catalyzed methanolysis of *p*-nitrophenyl glycolate.

Confident that FPP is acting as a catalyst by formation of a complex with the substrate, we turned our attention to elucidating the next step of the mechanism. The 4-aminopyridine class of acyl transfer catalysts is well-known to operate by a nucleophilic mechanism in which the pyridine nitrogen attacks the carbonyl of an active ester to provide an acylpyridinium species.[5] This species then undergoes attack by an alcohol to provide the acylated product. The analogous mechanism with FPP

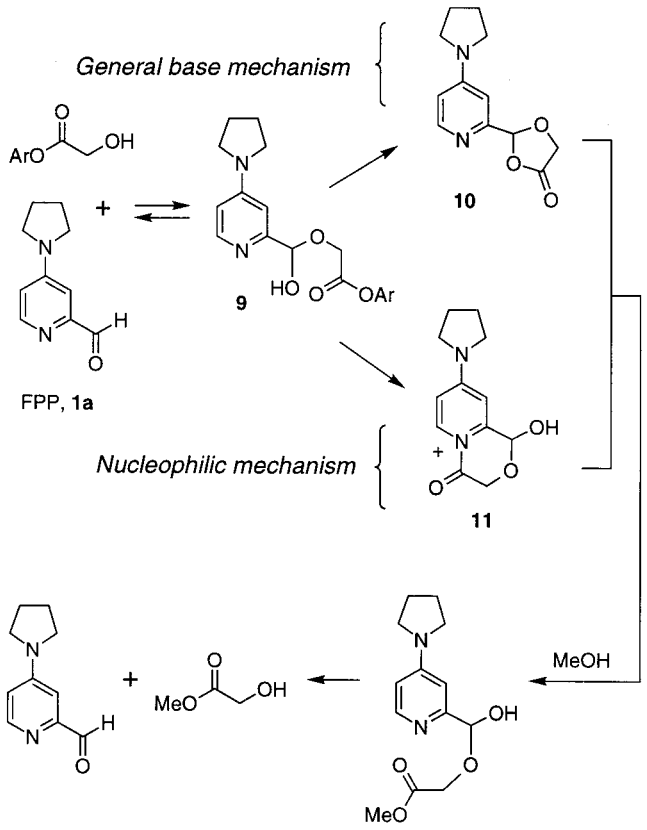
(11) The relative rate of simple alkaline hydrolysis of PNP and phenyl esters is about 3.5:1, a value which is comparable to what we observe with our catalyst. See: Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1987**, *109*, 3145.

(12) In d_4-methanol we do not detect the hemiacetal corresponding to **5**, demonstrating the lower electrophilicity of the 3-carboxaldehyde. Compounds **7** and **8** exist as 1:1 and 6:1 ratios of hemiacetal to aldehyde, respectively, indicating that the ability of the aldehyde to reversibly form a hemiacetal is not a sufficient condition for catalysis.

(13) 4-Aminopyridines are about 2 pK_a units more basic than the comparable 2-aminopyridines. See: Schofield, K. *Hetero-aromatic Nitrogen Compounds, Pyrroles and Pyridines*; Plenum Press: New York, 1967; pp 145−150.

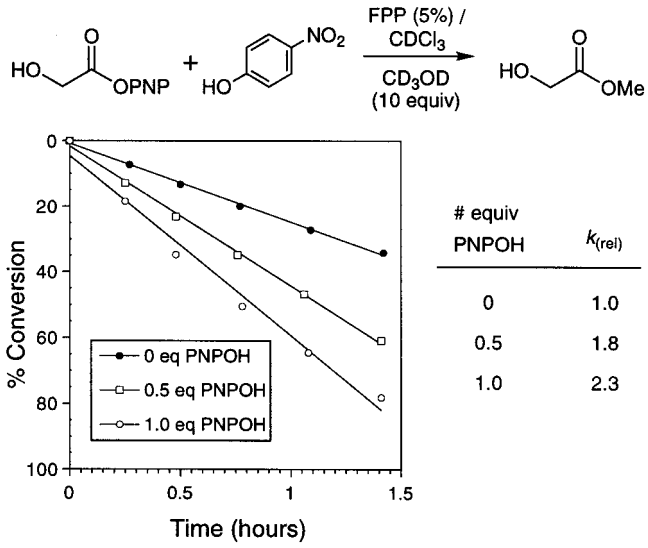
(14) Hemiacetal content in $CDCl_3$ was measured by ^{1}H NMR. In water, 48% of 2-formylpyridine (**6**) exists as the hydrate (see refs 7c and 7d). It is known that the equilibrium constants for the addition of water to aldehydes and ketones are smaller than the corresponding equilibrium constants for the addition of methanol; however, the origin of this effect is not understood. See refs 7a and 7b.

Scheme 3



is shown in Scheme 3. In this mechanism (the "nucleophilic" mechanism), the catalytic cycle begins with the addition of the alcohol of the hydroxy ester to the aldehyde of FPP, providing hemiacetal **9**. The pyridine nitrogen then attacks the carbonyl of the ester to provide the cyclic acylpyridinium species **11**. This species undergoes attack by methanol to provide the methyl ester bound to the catalyst as the hemiacetal. Dissociation of the hydroxy ester from the hemiacetal liberates the product and regenerates the catalyst. However, an alternative mechanism is also depicted in Scheme 3. In this mechanism (the "general-base" mechanism), the pyridine nitrogen acts as a base and deprotonates the hydroxyl group of the hemiacetal.[15] The hydroxyl group then acts as a nucleophile and attacks the ester to form dioxolanone **10**. This species is then methanolyzed with general base assistance from the pyridine nitrogen to provide the methyl ester bound to the catalyst as the hemiacetal. As in the previous mechanism, dissociation of the hydroxy ester from the hemiacetal liberates the product and regenerates the catalyst.

FPP was designed to operate as a nucleophilic catalyst based on the previously mentioned nucleophilicity of the 4-aminopyridines. However, the nucleophilic mechanism became suspect once we examined the effect of added *p*-nitrophenol (PNPOH) on the reaction. PNPOH, which is liberated during the course of the reaction, is a mild acid (pK_a = 7.2) and should partially protonate the



# equiv PNPOH	$k_{(rel)}$
0	1.0
0.5	1.8
1.0	2.3

Figure 3. Effect of added *p*-nitrophenol on the FPP-catalyzed rate of *p*-nitrophenyl glycolate methanolysis.

pyridine nitrogen and retard the reaction according to the nucleophilic mechanism.[5,16] In the event, we found that the addition of 0.5 and 1.0 equiv of PNPOH provides a 1.8 and 2.3-fold *increase* in the rate of the reaction, respectively (Figure 3). Our inability to reconcile this observation with the nucleophilic mechanism provides indirect evidence against this mechanism, and we sought a more definitive experiment to probe this issue.

To distinguish between the nucleophilic and general base mechanisms we have examined the reactivity of FPP derivatives which are sterically hindered in the vicinity of the pyridyl nitrogen. In the case of typical nucleophilic acyl transfer catalysts, steric hindrance in proximity to the nucleophilic group is known to deactivate the catalyst.[5] For example, 2-methylpyridine (pK_a = 5.96) is more basic than pyridine (pK_a = 5.23) but is 21 times less active as a catalyst in the benzoylation of benzyl alcohol. 2,6-Lutidine (pK_a = 6.72) is 81 times less active than pyridine in the same reaction.[17] To quantify this effect in the case of the 4-aminopyridine class of catalysts, we examined the effectiveness of a series of 2-alkyl-4-pyrrolidinopyridine (2-alkyl-4-PPY) derivatives as catalysts in the acylation of menthol with acetic anhydride (Table 3). Acylation with 1% PPY as a catalyst is rapid, with complete conversion occurring in less than 2 h. However, the introduction of a methyl group at the 2-position of the catalyst provides a 30-fold decrease in the activity. Increasing the bulk of the alkyl substituent further decreases catalyst activity, until 2-isopropyl-4-PPY (**12d**) and 2-*tert*-butyl-4-PPY (**12e**) show no rate acceleration over the uncatalyzed reaction.

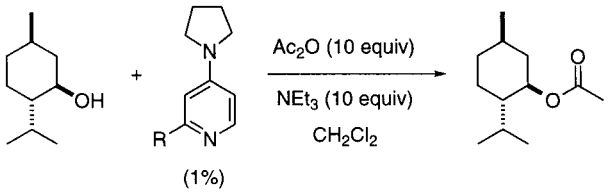
These results indicate that if FPP were operating by a nucleophilic mechanism, analogues which are hindered in the vicinity of the pyridyl nitrogen should be less active

(15) We estimate the pK_a of the of the hydroxyl group of **9** to be about 13 in analogy to the pK_a of the hydrate of pyridine 2-carboxaldehyde which is known to be 12.6. Furthermore, we estimate the pK_a of the pyridine nitrogen of **9** to be about 8.5 based on the fact that the corresponding pK_a in the hydrate of pyridine 2-carboxaldehyde is about 1 pK_a unit less than pyridine. See: Owen, T. C. *J. Heterocycl. Chem.* **1990**, *27*, 987.

(16) The ^{1}H NMR spectra of reactions in progress show significant changes in the chemical shift of the pyridine protons as the reaction proceeds. We attribute this to the release of PNPOH as the reaction progresses, and partial protonation of the pyridine nitrogen. We have not determined the pK_a of PNPOH or our catalyst in $CHCl_3$ and therefore do not know the full extent of the interation between these species.

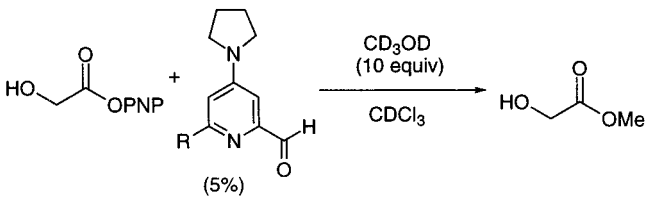
(17) Bondarenko, L. I.; Kirichenko, A. I.; Litvinenko, L. M.; Dmitrenko, I. N.; Kobets, V. D. *Zh. Org. Khim.* **1981**, *17*, 2588. See also ref 13, page 195.

Table 3. Effect of 2-Alkyl Substitution on the Reactivity of 4-Pyrrolidinopyridine as an Acyl Transfer Catalyst in the Acylation of Menthol



Catalyst	12a	12b	12c	12d	12e	--[a]
R	H (PPY)	Me	Et	*i*-Pr	*t*-Bu	--
k_{rel}	120	4.0	1.7	1.0	1.0	1.0

Table 4. Effect of 6-Substitution on FPP Reactivity in the Methanolysis of *p*-Nitrophenyl Glycolate

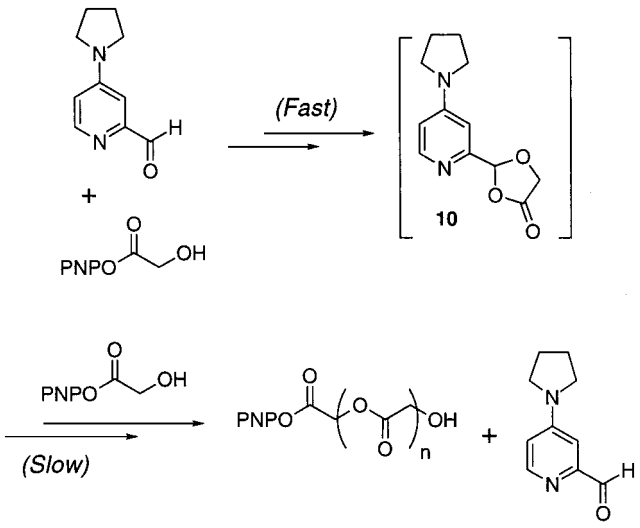


Catalyst	1a	1b	1c	1d	1e
R	H	Me	*t*-Bu	$N(CH_2)_4$	TMS
k_{rel}	1	4.0	1.0	4.5	13

than FPP. We therefore prepared a series of FPP derivatives with substituents of varying steric bulk at the 6-position of the pyridine ring (compounds **1b**−**e**, Table 4) and examined them as catalysts for the methanolysis of *p*-nitrophenyl glycolate. Interestingly, 6-alkyl-, 6-silyl-, or 6-amino-substitution significantly *enhances* the activity of the catalyst. Introduction of a methyl group at the 6-position (**1b**) is found to increase the activity of the catalyst by a factor of 4, and the more electron-donating TMS group (**1e**) is found to provide a 13-fold increase in activity. Even the very hindered **1c** shows activity similar to FPP. The increase in activity of the substituted pyridines is consistent with an increase in the basicity of the pyridine nitrogen,[18] thereby increasing the rate of methanolysis of dioxolanone **10**. The difference in activity of compounds **1b** and **1c** can be attributed to a decrease in the basicity of **1c** due to steric inhibition to protonation. These results allow us to definitively exclude the nucleophilic mechanism for this process.

Isolation of dioxolanone 10. The evidence provided up to this point allows us to exclude the nucleophilic mechanism, but does not provide evidence specifically in favor of the general base mechanism. We have, therefore, obtained spectroscopic and kinetic evidence for the existence of the dioxolanone **10**. To observe dioxolanone **10** spectroscopically, we reasoned that if we were to treat the PNP-ester of glycolic acid with a stoichiometric

Scheme 4



amount of FPP in the absence of methanol, dioxolanone **10** would be produced (Scheme 4). We conducted this experiment in $CDCl_3$, monitored the reaction by ^1H NMR, and observed a new set of resonances that are consistent with dioxolanone **10** and free PNPOH.[19] These resonances increased in intensity to a steady state within 20 min, with a corresponding decrease in the intensity of the resonances for FPP and the PNP-ester of glycolic acid (Figure 4). This reaction does not proceed to completion; some of the starting glycolate ester remains in solution. After several hours, the unreacted PNP-glycolate reacts with dioxolanone **10** to form a dimer which reacts further with **10** to form various glycolate oligomers. If this reaction is repeated with the pentafluorophenyl ester of glycolic acid in place of the PNP ester, dioxolanone **10** is formed much more rapidly, and the reaction proceeds to higher conversion. When dioxolanone **10** is prepared in this way, it can be purified by rapid flash chromatography to provide a mixture of FPP and dioxolanone **10** (Figure 5). We have not been able to isolate a pure sample of **10** because it undergoes partial hydrolysis to FPP upon flash chromatography.[20] Attempts to independently synthesize dioxolanone **10** by standard procedures including the acid-catalyzed condensation of glycolic acid with FPP[21] or by the treatment of FPP with trimethylsilyl (trimethylsilyloxy)acetate and catalytic TMSOTf[22] met with failure, presumably due to the presence of the basic pyridyl nitrogen.

We have examined the kinetic order of the reaction and find that with FPP catalysis, the methanolysis of the PNP-ester of glycolic acid is zero-order in substrate over most of the course of the reaction (Figure 6). This result is consistent with the rapid formation of a substrate−catalyst complex (i.e., dioxolanone **10**), followed by a

(18) Introduction of alkyl groups to the pyridine nucleus results in an increase of 0.5−0.85 pK_a units per alkyl group. See: Ikekawa, N.; Sato, Y.; Maeda, T. *Chem. Pharm. Bull.* **1954**, *2*, 205. See also ref 13. The pK_a of 2-(trimethylsilyl)pyridine is 6.63, an increase of approximately 1.4 units over pyridine. This is in contrast to the effect of the trimethylsilyl group in benzoic acid where it is found to be electron-withdrawing. See: Anderson, D., G.; Chipperfield, J. R.; Webster, D. E. *J. Organomet. Chem.* **1968**, *12*, 323.

(19) Though the formation of **10** likely occurs through initial formation of **9**, we have not directly observed this intermediate.

(20) Dioxolanone **10** (as a mixture with FPP) has been characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectrometry.

(21) Use of either *p*-toluenesulfonic acid or boron trifluoride etherate failed to provide the desired dioxolanone. For discussions on general methods of 1,3-dioxolan-4-one formation, see: Farines, M.; Soulier, J. *Bull. Soc. Chim. Fr.* **1970**, 332. See also: Seebach, D.; Imwinkelried, R.; Stucky, G. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 178; Schreiber, S. L.; Reagan, J. *Tetrahedron Lett.* **1986**, *27*, 2945; Greiner, A.; Ortholand, J. Y. *Bull. Soc. Chim. Fr.* **1993**, *130*, 133.

(22) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. Hoye, T. R.; Peterson, B. H.; Miller, J. D. *J. Org. Chem.* **1987**, *52*, 1351. (b) Pearson, W. H.; Cheng, M. *J. Org. Chem.* **1987**, *52*, 1353.

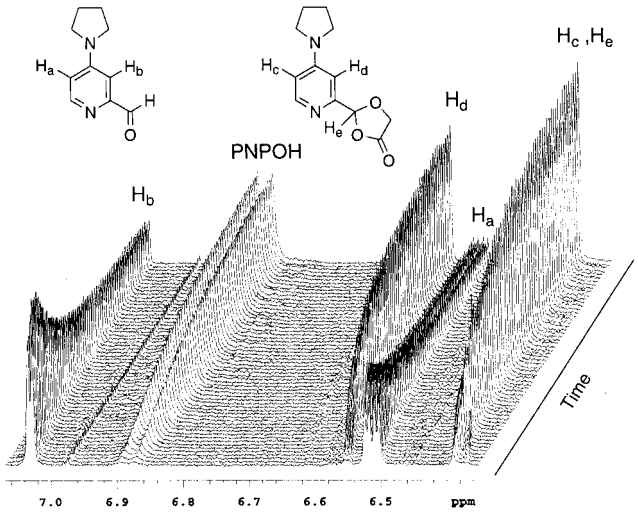


Figure 4. ^{1}H NMR from 7.40 to 6.36 ppm of the reaction depicted in Scheme 4. Spectra were taken every 20 s for the first 20 min of the reaction.

turnover-limiting decomposition of this intermediate to products. As the substrate is consumed, the rate of formation of dioxolanone **10** slows such that this rate is comparable to the rate of its conversion to product. This leads to some deviation from linearity in the zero-order plot late in the reaction. Consistent with this analysis, examination of ^{1}H NMR spectra of **1a**−**g** catalyzed reactions in progress reveals that the resting state of the catalyst is not the free aldehyde, rather it is the corresponding dioxolanone.[23]

The kinetic competence of dioxolanone **10** was established by determining the rate constant for the conversion of **10** to methyl glycolate and comparing this with the corresponding rate constant determined from the catalytic reaction under single turnover conditions. Thus, dioxolanone **10** was prepared from FPP and *p*-nitrophenyl glycolate (**4**) in the absence of methanol. Upon addition of methanol to this species, methyl glycolate was produced in a first-order reaction with a first-order rate constant of 1.9 h^{-1}. The corresponding rate constant for the catalytic cycle was obtained via a single-turnover experiment using 1.5 equiv of FPP. Under these conditions, consumption of **4** is rapid and is followed by a slower formation of methyl glycolate. The first-order rate constant for the formation of methyl glycolate under these conditions is 2.0 h^{-1}, thereby establishing the kinetic competence of **10**.

We have also found that the presence of 0.032 and 0.10 M PNPOH increases the rate of methanolysis of dioxolanone **10** by a factor of 1.7 and 2.9, respectively, consistent with our observations of the effect of PNPOH on the overall catalytic cycle. We attribute this effect to the ability of PNPOH to protonate the nitrogen of **10**, thereby producing the pyridinium salt and the moderately basic species *p*-nitrophenylate (Scheme 5). Even though this species is less basic than the pyridine nitrogen, it is in a stereoelectronically more favorable position to deprotonate the incoming methanol. Alternatively, PNPOH could be acting as a general acid catalyst by protonating the carbonyl of the dioxolane, leaving the pyridyl nitrogen free to act as a general base.

In conclusion, we have obtained good evidence that FPP catalyzes the methanolysis of the PNP ester of glycolic acid via hemiacetal **9** and dioxolanone **10**. We have isolated and characterized **10** and shown that it provides the methyl ester of glycolic acid and FPP when subjected to the catalytic reaction conditions and that it is kinetically competent. Hindered analogues of FPP have been shown to be more effective catalysts than FPP, thus enabling us to rule out a nucleophilic mechanism. Our current mechanism, in which a hemiacetal hydroxyl group acts as a nucleophile, is related to that proposed by Menger for the mechanism of action of his aldehyde-functionalized surfactants, in which a deprotonated *gem*-diol is used as a nucleophile for the hydrolysis of active esters.[24]

Experimental Section

General. All moisture-sensitive reactions were conducted under a nitrogen atmosphere in oven-dried glassware using solvents purified according to standard procedures.[25] Chloroform-*d* was freshly distilled from CaH_2 before each methanolysis experiment. Methanol-d_4 was used as received. ^{1}H NMR spectra were obtained at 500 MHz and ^{13}C NMR spectra at 125 MHz in $CDCl_3$, with chemical shifts reported in ppm referenced to residual chloroform (7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C). ^{19}F NMR spectra were obtained at 270 MHz in $CDCl_3$ with chemical shifts reported relative to internal $CFCl_3$ (0 ppm). Infrared spectra were recorded as thin films on NaCl plates. 4-Pyrrolidinopyridine was purified by kugelrohr distillation prior to use.

Menthol Acylation. Kinetics were measured using analytical gas−liquid chromatography (GLC). GLC was performed on a Hewlett-Packard 5890 Series II equipped with an Alltech SE-54 column (30 m length, 0.32 mm i.d., 0.25 μm film thickness) and a hydrogen carrier gas flow of 1.6 mL/min. Initial column temperature was 80 °C and was increased to 155 °C at 5 °C/min for each analysis. Sample solutions were 0.05 M menthol, 0.5 M acetic anhydride, 0.5 M triethylamine, 0.05 M biphenyl (internal standard), and 5×10^{-4} M catalyst with a total volume of 1000 μL. The excess of acetic anhydride and triethylamine ensures pseudo-first-order kinetics. Reactions were monitored at time intervals for at least 2.5 half-lives. Plots of ln[menthol] were linear and k_{obsd} was obtained directly from the slope using least-squares analysis. Under our analytical conditions, retention times (in minutes) are as follows: menthol, 6.3; menthyl acetate, 8.7; biphenyl, 10.5.

Ester Methanolysis. Kinetics were measured using ^{1}H NMR to monitor the disappearance of the α-methylene proton resonances of the ester starting material. The reactions were run at 20 ± 1 °C. Samples of 600 μL total volume were prepared directly in NMR tubes. All solutions were 0.1 M ester, 0.005 M catalyst, and 0.1 M *p*-methyl anisole as an internal standard and 1.0 M methanol-d_4 in deuteriochloroform solution. For the methanol dependence experiment, the concentration of methanol-d_4 was varied from 0.5 to 8.0 M with the total sample volume remaining constant. Rate constants k_{obsd} were calculated from the slope of a plot of [ester] as a function of time using least-squares analysis. For the determination of rate constants, between five and twelve data points were obtained. Most reactions were monitored for at least four half-lives, with the exception of those with half-lives greater than 2 days.

Single Turnover Kinetics. A solution of FPP (0.050 M), *p*-nitrophenyl glycolate (0.033 M), and methanol-d_4 (1.0 M) in $CDCl_3$ was monitored by ^{1}H NMR. Following a rapid and

(23) The dioxolanone was identified for each catalyst by the upfield shifts of the pyridine aromatic protons and the appearance of the acetal methine.

(24) Menger, F. M.; Whitesell, L. G. *J. Am. Chem. Soc.* **1985**, *107*, 707.

(25) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1988.

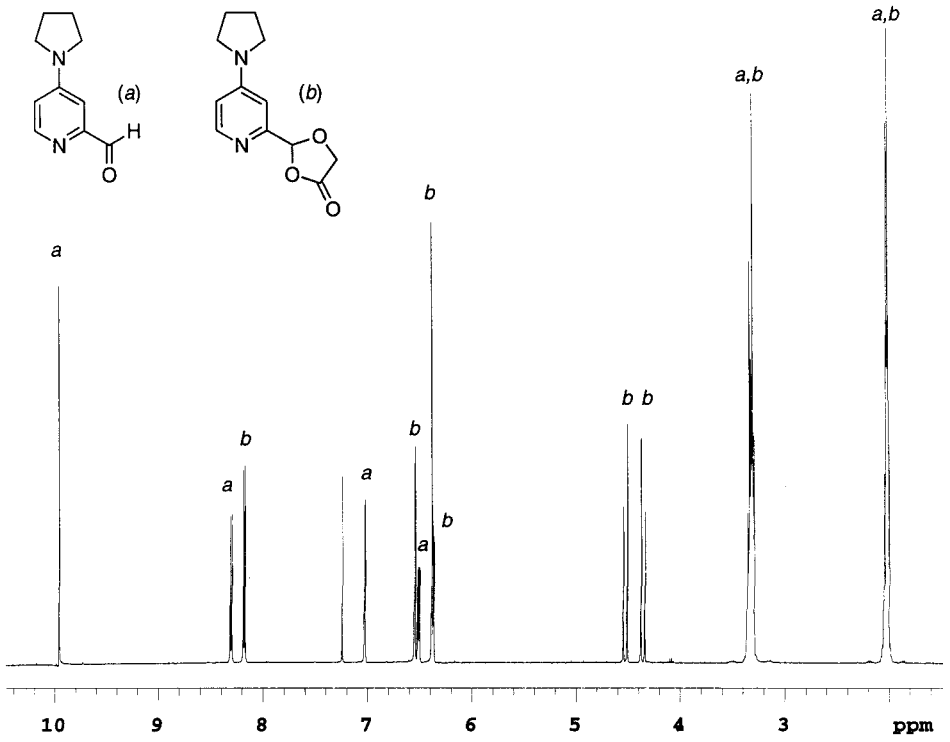


Figure 5. ^{1}H NMR of a 1.3:1 mixture of dioxolanone **10** and FPP isolated by flash chromatography.

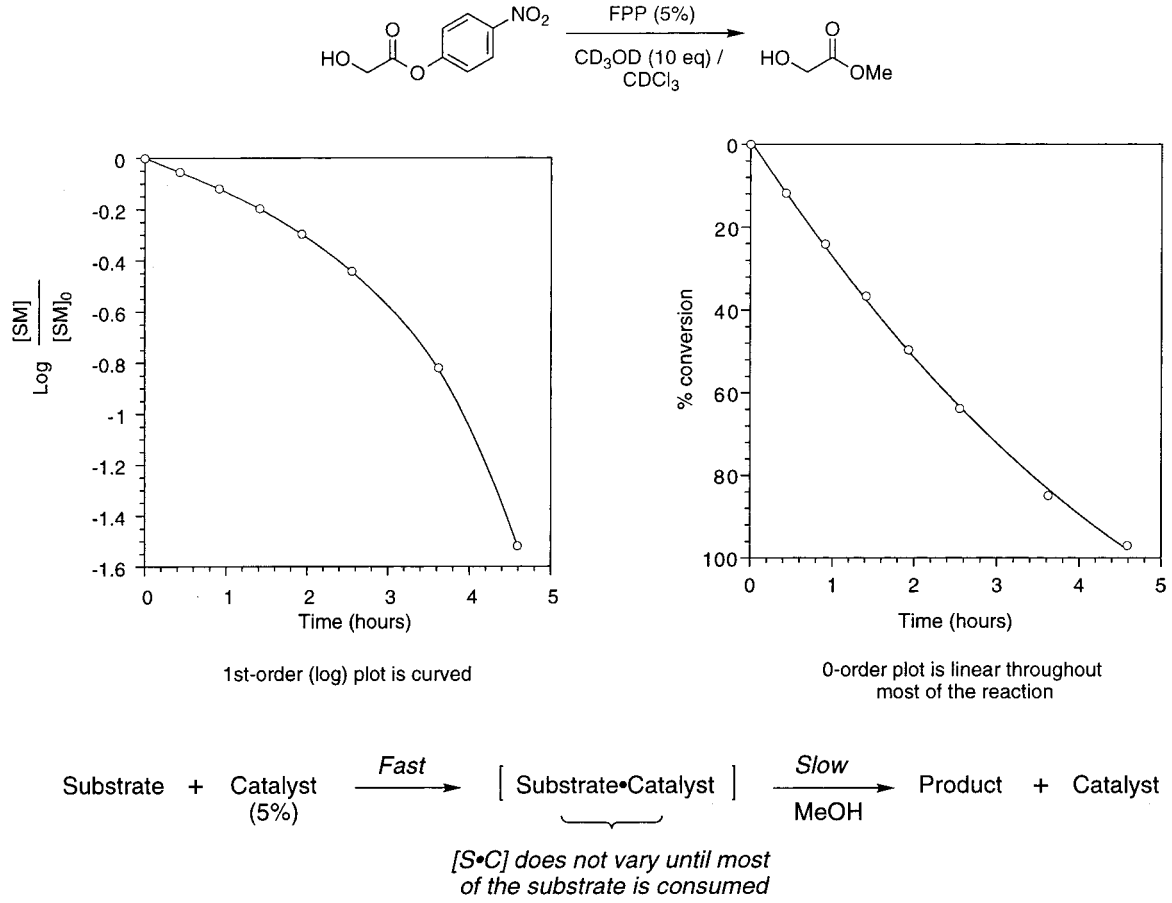
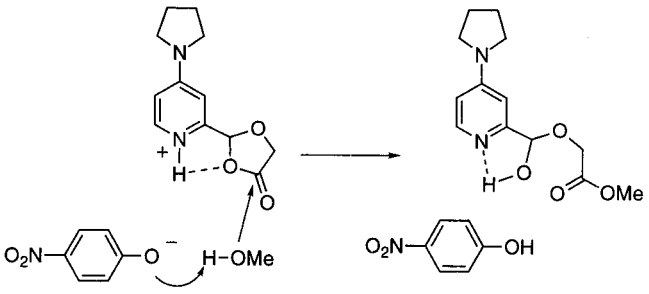


Figure 6. Kinetic data for the methanolysis of *p*-nitrophenyl glycolate fitted to zero- and first-order plots. Arbitrary smooth lines are drawn through the data.

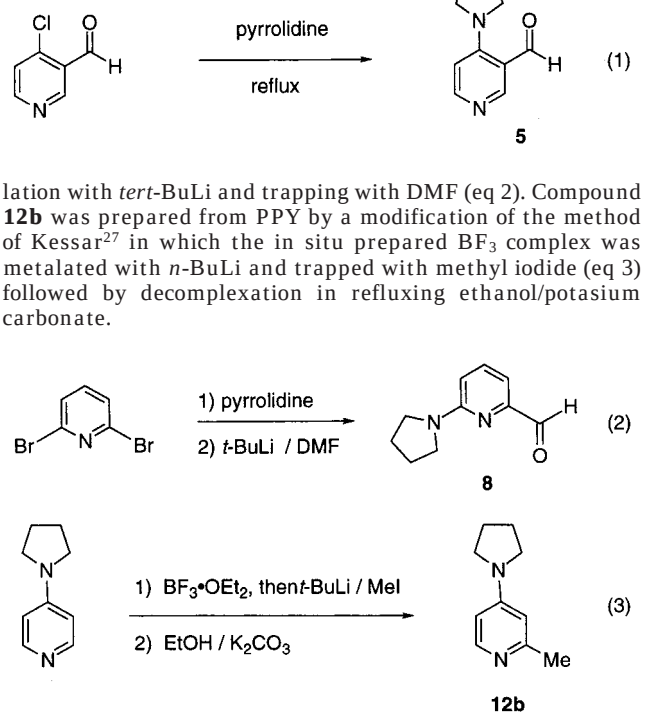
quantitative conversion of the glycolate to dioxolanone **10**, a clean first-order methanolysis of **10** to methyl glycolate was observed with $k_{obs} = 2.0\ h^{-1}$.

Syntheses. FPP (**1a**) and **6** were prepared as previously described.[6] Compound **7** was purchased from Aldrich Chemical Co. and distilled prior to use. Compound **5** was prepared from

Scheme 5

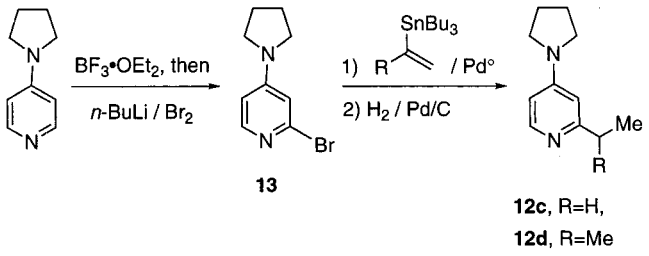


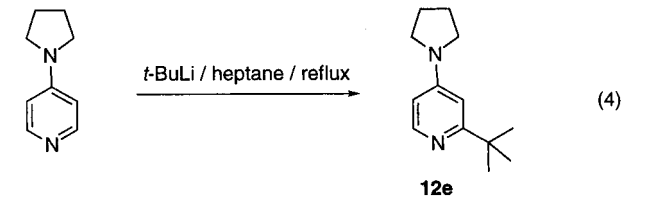
3-formyl-4-chloropyridine[26] by treatment with pyrrolidine at reflux (eq 1). Compound **8** was prepared from 2,6-dibromopyridine by monosubstitution with pyrrolidine followed by metalation with *tert*-BuLi and trapping with DMF (eq 2). Compound **12b** was prepared from PPY by a modification of the method of Kessar[27] in which the in situ prepared BF_3 complex was metalated with *n*-BuLi and trapped with methyl iodide (eq 3) followed by decomplexation in refluxing ethanol/potasium carbonate.



Compounds **12c** and **12d** were prepared as shown in Scheme 6 by metalating the BF_3 complex of PPY with *n*-BuLi and trapping with bromine to provide 2-bromo-4-PPY (**13**). This compound was subjected to Stille coupling with either vinyltributyltin or 2-(tributylstannyl)propene and then hydrogenated to provide **12c** and **12d**, respectively. Compound **12e** was prepared by treatment of PPY with *tert*-BuLi in heptane at reflux (eq 4).[28]

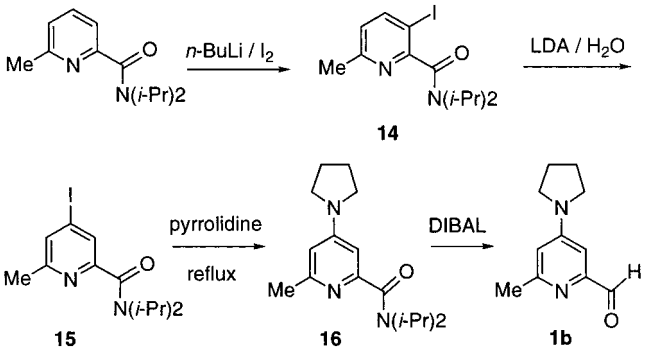
Scheme 6



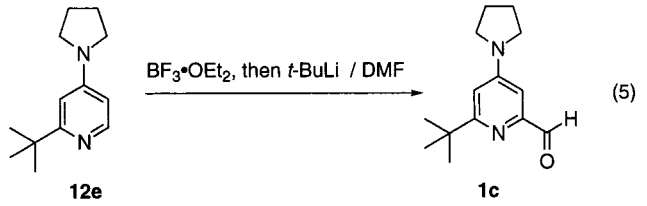


Catalyst **1c** was prepared from **12e** by in situ treatment with BF_3 followed by metalation with *tert*-BuLi and trapping with DMF (eq 5). A similar scheme was attempted to prepare **1b**; however, the metalation of the BF_3 complex of 2-methyl-4-PPY proceeded in poor yield and was not reproducible. This compound was instead prepared from the diisopropyl amide of 6-methylpicolinic acid[29] by the route shown in Scheme 7.

Scheme 7

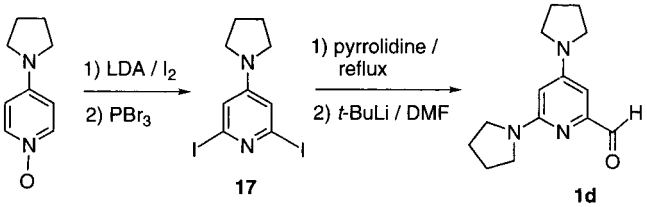


Metalation with *n*-BuLi and trapping with iodine provided the 3-iodo derivative **14**. This compound was subjected to the "halogen dance" reaction of Queguiner[30] to provide the 4-iodo derivative **15**. Substitution of the iodide of **15** for pyrrolidine was accomplished in refluxing pyrrolidine to provide **16**. The amide of **16** was subjected to DIBAL reduction to provide **1b**.



The synthesis of **1d** proceeded via 2,6-diiodo-4-PPY (**17**, Scheme 8) which was prepared from the amine oxide of PPY[31]

Scheme 8



(26) Marsais, F., Trecourt, F., Breant, P., Queguiner, G. *J. Heterocycl. Chem.* **1988**, *25*, 81.

(27) Kessar, S. V.; Singh, P.; Singh, K. N. Dutt, M. *J. Chem. Soc., Chem. Commun.* **1991**, 570. (b) For the application of this method to the metalation of DMAP, see: Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809.

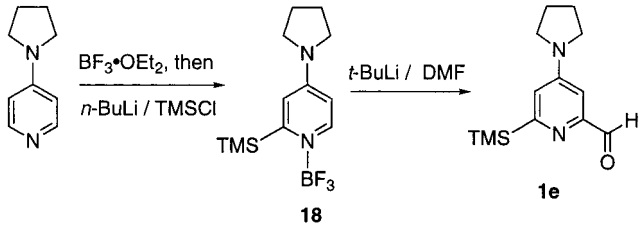
(28) Scalzi, F. V.; Golob, N. F. *J. Org. Chem.* **1971**, *36*, 2541.

(29) Green, M. J.; Britovsek, G. J. P.; Cavell, K. J.; Gerhards, F.; Yates, B. F.; Frankcombe, K.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1998**, *7*, 1137.

(30) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1993**, *58*, 7832; Giullier, F.; Nivolier, F.; Marsais, F.; Queguiner, G. *Tetrahedron Lett.* **1994**, *35*, 6489. For a review, see: Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, 1991; Vol 52; pp 187−295.

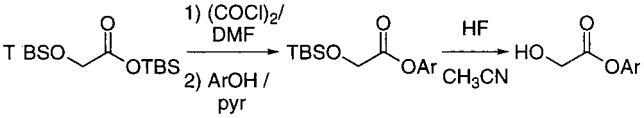
(31) Morkved, E. *Acta Chem. Scand. Ser. B.* **1979**, *33*, 433.

Scheme 9



18 **1e**

Scheme 10



by metalating with 4 equiv of LDA followed by treatment with 4 equiv of iodine.[32] Reduction of the amine oxide was accomplished with PBr_3 to provide **17**. Monosubstitution of one of the iodides of **17** for pyrrolidine was followed by metalation of the remaining iodide with *tert*-BuLi and trapping with DMF. Compound **1e** was prepared from PPY as shown in Scheme 9 by in situ complexation with BF_3 followed by metalation with *n*-BuLi and trapping with TMSCl to give **18**. The BF_3 moiety remains bound to the pyridine nitrogen in **18**, and a second metalation with *tert*-BuLi and trapping with DMF provides **1e**.

p-Nitrophenyl propionate (**2**) and *p*-nitrophenyl methoxyacetate (**3**) were synthesized by a DCC-mediated coupling of the carboxylic acid with *p*-nitrophenol. Esters of glycolic acid were synthesized in a three-step reaction sequence from *tert*-butyldimethylsilyl (*tert*-butyldimethylsilyloxy)acetate. Formation of the acid chloride by the method of Wissner[33] (oxalyl chloride, catalytic DMF) followed by reaction with *p*-nitrophenol, *p*-fluorophenol, pentafluorophenol, or phenol in the presence of pyridine provides the TBS-protected glycolate esters (Scheme 10). Deprotection with HF in acetonitrile followed by crystallization from methylene chloride/hexanes or flash chromatography provides the α-hydroxy ester.

***p*-Nitrophenyl (*tert*-butyldimethylsilyloxy)acetate:** ^{1}H NMR ($CDCl_3$): δ 8.26 (m, 2H), 7.29 (m, 2H), 4.51 (s, 2H), 0.92 (s, 9H), 0.14 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 169.45, 155.03, 145.37, 125.24, 122.18, 61.69, 25.66, 18.35, −5.44. IR 2930.0, 1790.4, 1347.8, 1119.8, 839.4 cm^{-1}. TLC R_f = 0.38 (10:1 hexanes/ethyl acetate). HRMS (CI+, *i*-C_4H_{10}) *m*/*z* calcd for $C_{14}H_{22}NO_5Si$ [M + H]$^+$ 312.1267, found 312.1263. Purity was assayed by ^{1}H NMR (see Supporting Information).

***p*-Fluorophenyl (*tert*-butyldimethylsilyloxy)acetate:** ^{1}H NMR ($CDCl_3$): δ 7.04 (m, 4H), 4.47 (s, 2H), 0.93 (s, 9H), 0.13 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 170.38, 160.25 (d, J_{C-F} = 244.7 Hz), 146.15, 122.73 (d, J_{C-F} = 8.8 Hz), 116.11 (d, J_{C-F} = 23.8 Hz), 61.75, 25.70, 18.38, −5.42. IR 2930.0, 1784.9, 1504.0, 1128.3, 838.8 cm^{-1}. TLC R_f = 0.54 (10:1 hexanes/ethyl acetate). HRMS (CI+, *i*-C_4H_{10}) *m*/*z* calcd for $C_{14}H_{22}FO_3Si$ [M + H]$^+$ 285.1322, found 285.1317. Purity was assayed by ^{1}H NMR (see Supporting Information).

Pentafluorophenyl (*tert*-butyldimethylsilyloxy)acetate: ^{1}H NMR ($CDCl_3$): δ 4.59 (s, 2H), 0.92 (s, 9H), 0.13 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 168.02, 61.06, 25.60, 18.32, −5.58 (aromatic carbons are observed as multiplets in the range of 120−150 ppm due to extensive C−F coupling). IR 2932.2, 1813.3, 1527.9, 1098.3, 995.5, 839.0 cm^{-1}. TLC R_f = 0.63 (10:1 hexanes/ethyl acetate). HRMS (CI+, *i*-C_4H_{10}) *m*/*z* calcd for $C_{14}H_{20}F_5O_3Si$ [M + H]$^+$ 357.0945, found 357.0956. Purity was assayed by ^{1}H NMR (see Supporting Information).

Phenyl (*tert*-butyldimethylsilyloxy)acetate: ^{1}H NMR ($CDCl_3$): δ 7.37 (m, 2H), 7.22 (m, 1H), 7.08 (m, 2H), 4.48 (s, 2H), 0.93 (s, 9H), 0.14 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 170.36, 150.36, 129.46, 125.92, 121.33, 61.85, 25.73, 18.40, −5.41. IR 2929.0, 1783.7, 1130.2, 839.8 cm^{-1}. TLC R_f = 0.54 (10:1 hexanes/ethyl acetate). HRMS (CI+, *i*-C_4H_{10}) *m*/*z* calcd for $C_{14}H_{23}O_3Si$ [M + H]$^+$ 267.1416, found 267.1409. Purity was assayed by ^{1}H NMR (see Supporting Information).

General Procedure for TBS Deprotection of Glycolate Esters: *p*-Nitrophenyl Glycolate (4). Aqueous hydrofluoric acid (49 wt %, 6.0 mL, 191 mmol, 6.5 equiv) was added to a solution of *p*-nitrophenyl (*tert*-butyldimethylsilyloxy)acetate (9.140 g, 29.4 mmol, 1.0 equiv) in acetonitrile (150 mL), and the solution was stirred overnight. The solution was diluted with ethyl acetate and washed with brine (6×). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Recrystallization from hexanes/methylene chloride provided 5.786 g (85%) of *p*-nitrophenyl glycolate as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.28 (m, 2H), 7.32 (m, 2H), 4.48 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 170.99, 154.60, 145.57, 125.34, 122.13, 60.72. IR (thin film) 3430.2, 1769.9, 1523.8, 1348.4, 1209.0 cm^{-1}. TLC R_f = 0.32 (1:1 hexanes/ethyl acetate). *p*-Nitrophenyl glycolate is not stable to silica gel chromatography. HRMS (CI+, *i*-C_4H_{10}) *m*/*z* calcd for $C_8H_8NO_5$ [M + H]$^+$ 198.0402, found 198.0391. Purity was assayed by ^{1}H NMR (see Supporting Information).

***p*-Fluorophenyl glycolate:** ^{1}H NMR ($CDCl_3$): δ 7.07 (m, 4H), 4.41 (s, 2H), 2.35 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 171.98, 160.38 (d, J_{C-F} = 244.7 Hz), 145.81, 122.62 (d, J_{C-F} = 8.0 Hz), 116.22 (d, J_{C-F} = 23.9 Hz), 60.68. IR 3440.2, 1761.2, 1503.4, 1247.7, 1185.1 cm^{-1}. TLC R_f = 0.27 (2:1 hexanes/ethyl acetate). HRMS (EI) *m*/*z* calcd for $C_8H_7FO_3$ 170.0379, found 170.0373. Purity was assayed by ^{1}H NMR (see Supporting Information).

Pentafluorophenyl glycolate: ^{1}H NMR ($CDCl_3$): δ 4.57 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 169.43, 60.10 (aromatic carbons are observed as multiplets in the range of 120−150 ppm due to extensive C−F coupling). IR 3402.1, 1806.5, 1518.3, 1086.5, 1004.8, 993.3 cm^{-1}. TLC R_f = 0.52 (2:1 hexanes/ethyl acetate). Pentafluorophenyl glycolate is not stable to silica gel chromatography. HRMS (CI+, *i*-C_4H_{10}) *m*/*z* calcd for $C_8H_4F_5O_3$ [M + H]$^+$ 243.0081, found 243.0090. Purity was assayed by ^{1}H NMR (see Supporting Information).

Phenyl glycolate: ^{1}H NMR ($CDCl_3$): δ 7.38 (m, 2H), 7.25 (m, 1H), 7.10 (m, 2H), 4.42 (s, 2H), 2.45 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 171.97, 150.03, 129.56, 126.24, 121.15, 60.74. IR 3423.8, 1762.8, 1200.0, 1092.6 cm^{-1}. TLC R_f = 0.34 (2:1 hexanes/ethyl acetate). HRMS (EI) *m*/*z* calcd for $C_8H_8O_3$ 152.0473, found 152.0486. Purity was assayed by ^{1}H NMR (see Supporting Information).

Preparation and Characterization of Dioxolanone 10. A solution of FPP (0.060 g, 0.34 mmol, 1.0 equiv) and pentafluorophenyl glycolate (0.163 g, 0.67 mmol, 2.0 equiv) in 3.5 mL of ethanol-free chloroform was stirred for 15 min. The solvent was removed under reduced pressure and the residue subjected to rapid flash chromatography (ethyl acetate) providing 0.062 g of a mixture of **10** and FPP. Dioxolanone **10** is invariably isolated as a mixture with FPP due to hydrolysis of the dioxolanone during chromatography. Isolated mixtures range in composition from 3:1 to 1:1 dioxolanone/FPP. Dioxolanone **10**: ^{1}H NMR ($CDCl_3$): δ 8.19 (d, *J* = 5.8 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.37 (s, 1H), 6.36 (dd, *J* = 5.9, 2.4 Hz, 1H), 4.52 (A of AB, *J* = 14.7, 1H), 4.36 (B of AB, *J* = 14.7, 1H), 3.32 (m, 4H), 2.02 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 171.37, 153.64, 152.33, 149.90, 107.64, 105.04, 103.86, 63.88, 47.10, 25.25. IR 1806.1, 1220.7, 1186.9 cm^{-1}. TLC R_f (**10**) = 0.46, R_f (FPP) = 0.34 (ethyl acetate). LRMS (EI) *m*/*z* (relative intensity): 234 (12), 176 (100). HRMS (EI) *m*/*z* calcd for $C_{12}H_{14}N_2O_3$ 234.1004, found 234.1007. Purity was assayed by ^{1}H NMR (see Supporting Information).

3-Formyl-4-(pyrrolidin-1-yl)pyridine (5). A solution of 4-chloro-3-formylpyridine (0.116 g, 0.82 mmol) in pyrrolidine (5 mL) was refluxed for 48 h after which time no starting material remained by TLC. Pyrrolidine was removed under reduced pressure leaving a yellow liquid which was taken up in methylene chloride and washed with saturated sodium carbonate (2×). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash

(32) For leading references concerning the metalation of pyridine *N*-oxides, see: Mongin, O.; Rocca, P.; Thomas-dit-Dumont, L.; Trecourt, F.; Marsais, F.; Godard, A.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2503.

(33) Wissner, A.; Grudzinskas, C. *J. Org. Chem.* **1978**, *43*, 3972.

chromatography (5:1 ethyl acetate/methanol) provided 0.046 g (32%) of 3-formyl-4-(pyrrolidin-1-yl)pyridine as a yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 9.97 (s, 1H), 8.60 (s, 1H), 8.20 (d, J = 6.2 Hz, 1H), 6.54 (d, J = 6.2 Hz, 1H), 3.35 (m, 4H), 1.99 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 189.00, 156.27, 151.77, 151.67, 118.77, 108.80, 51.84, 25.68. IR 1733.3, 1668.2, 1594.1, 736.8 cm^{-1}. TLC R_f = 0.55 (methanol). HRMS (EI) m/z calcd for $C_{10}H_{12}N_2$ 176.0950, found 176.0944. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-Bromo-6-(pyrrolidin-1-yl)pyridine. A solution of 2,6-dibromopyridine (13.00 g, 54.9 mmol) in pyrrolidine (150 mL) was heated to reflux for 10 min after which time no starting material remained by TLC. Pyrrolidine was removed under reduced pressure leaving a light brown solid. The solid was dissolved in 2:1 ethyl acetate/methylene chloride and washed with 1 M NaOH (2×). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (5:1 hexanes/ethyl acetate) provided 11.59 g (93%) of 2-bromo-6-(pyrrolidin-1-yl)pyridine as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 7.20 (tr, J = 7.6 Hz, 1H), 6.62 (d, J = 7.4 Hz, 1H), 6.20 (d, J = 8.2 Hz, 1H), 3.41 (m, 4H), 1.97 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 157.46, 140.66, 138.97, 113.99, 104.77, 46.97, 24.64. IR 2857.8, 1613.9, 1534.2, 767.7 cm^{-1}. TLC R_f = 0.63 (5:1 hexanes/ethyl acetate). HRMS (EI) m/z calcd for $C_9H_{11}BrN_2$ 226.0106, found 226.0121. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-Formyl-6-(pyrrolidin-1-yl)pyridine (8). *tert*-Butyllithium (1.83 M in pentane, 0.69 mL, 1.26 mmol, 2.4 equiv) was added to a −78 °C solution of 2-bromo-6-(pyrrolidin-1-yl)-pyridine (0.119 g, 0.52 mmol, 1.0 equiv) in tetrahydrofuran (10 mL). The solution was stirred for 1 h. *N*,*N*-Dimethylformamide (58 μL, 0.73 mmol, 1.4 equiv) was added, and the solution was allowed to warm to room temperature and stir overnight. Saturated sodium bicarbonate was added followed by ethyl acetate. The aqueous layer was extracted with chloroform (2×), and the organic extracts were combined, dried over $MgSO_4$, and concentrated to a yellow solid. Purification by flash chromatography (10:1 hexanes/ethyl acetate) provided 0.061 g (66%) 2-formyl-6-(pyrrolidin-1-yl)pyridine as a bright yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 9.87 (s, 1H), 7.51 (tr, J = 7.6 Hz, 1H), 7.14 (d, J = 7.1 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 3.47 (m, 4H), 1.99 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 194.58, 157.34, 151.38, 137.24, 111.03, 109.76, 46.65, 25.43. IR 2851.5, 1706.1, 1610.9, 1595.7, 792.6 cm^{-1}. TLC R_f = 0.50 (5:1 hexanes/ethyl acetate). HRMS (EI) m/z calcd for $C_{10}H_{12}N_2$ 176.0950, found 176.0966. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-Methyl-4-(pyrrolidin-1-yl)pyridine (12b). Boron trifluoride etherate (0.23 mL, 1.86 mmol, 1.1 equiv) was added to a 0 °C solution of 4-pyrrolidinopyridine (0.250 g, 1.69 mmol, 1.0 equiv) in tetrahydrofuran (20 mL). The resulting suspension was stirred for 30 min and then cooled to −78 °C. *n*-Butyllithium (1.60 M in hexanes, 1.69 mL, 2.99 mmol, 1.6 equiv) was added and the solution stirred for 30 min at −78 °C after which time methyl iodide (0.21 mL, 3.37 mmol, 2.0 equiv) was added. The solution was stirred at −78 °C for 1 h and was then allowed to warm to room temperature and stir for another 2 h. Saturated sodium bicarbonate was added followed by ethyl acetate. The layers were separated, and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to a yellow solid. The solid was dissolved in absolute ethanol (20 mL) with potassium carbonate (1.165 g, 5.0 equiv) and heated to reflux for 30 min. After cooling to room temperature, the solvent was removed and the residue extracted with methylene chloride (4×). The extracts were filtered through Celite, and solvent was removed under reduced pressure. Purification by flash chromatography (methanol) provided 0.223 g (82%) of 2-methyl-4-(pyrrolidin-1-yl)-pyridine as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.08 (d, J = 5.9 Hz, 1H), 6.22 (d, J = 2.3 Hz, 1H), 6.20 (dd, J = 5.9 Hz, 2.4 Hz, 1H), 3.27 (m, 4H), 2.41 (s, 3H), 1.99 (m, 4H). ^{13}C NMR: δ 157.90, 152.19, 148.90, 105.77, 104.53, 46.86, 25.28, 24.62. IR 1606.2, 1507.8, 1387.7 cm^{-1}. TLC R_f = 0.31 (98:2 methanol/saturated ammonium hydroxide). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.71; H, 8.88; N, 17.20.

2-Bromo-4-(pyrrolidin-1-yl)pyridine (13). Boron trifluoride etherate (1.83 mL, 14.8 mmol, 1.1 equiv) was added to a 0 °C solution of 4-pyrrolidinopyridine (2.0 g, 13.5 mmol, 1.0 equiv) in tetrahydrofuran (100 mL). The resulting suspension was stirred for 30 min and then cooled to −78 °C. *n*-Butyllithium (1.56 M in hexanes, 13.8 mL, 21.6 mmol, 1.6 equiv) was added and the solution stirred for 30 min at −78 °C after which time bromine (1.11 mL, 21.6 mmol, 1.6 equiv) was added. The solution was allowed to warm to room-temperature overnight. Saturated sodium bicarbonate was added followed by ethyl acetate. The aqueous phase was extracted with ethyl acetate (2×), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes/ethyl acetate) followed by recrystallization from ethyl acetate provided 1.767 g (58%) of 2-bromo-4-(pyrrolidin-1-yl)-pyridine as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 7.89 (d, J = 5.9 Hz, 1H), 6.51 (d, J = 2.2 Hz, 1H), 6.30 (dd, J = 6.1 Hz, 2.4 Hz, 1H), 3.27 (m, 4H), 2.01 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 153.18, 149.00, 142.59, 109.37, 106.63, 47.15, 25.22. IR 1591.8, 1505.7, 988.8, 808.8, 665.6 cm^{-1}. TLC R_f = 0.42 (1:1 hexanes/ethyl acetate). LRMS (EI) m/z (relative intensity): 226 (100), 198 (12), 105 (15). HRMS (EI) m/z calcd for $C_9H_{10}BrN_2$ [M − H]$^+$ 225.0028, found 225.0028. Purity was assayed by ^{1}H NMR (see Supporting Information).

4-(Pyrrolidin-1-yl)-2-vinylpyridine. A solution of 2-bromo-4-(pyrrolidin-1-yl)pyridine (**13**) (0.074 g, 0.33 mmol, 1.0 equiv), Pd_2dba_3 (0.015 g, 0.02 mmol, 0.05 equiv), tri-2-furylphosphine (0.030 g, 0.13 mmol, 0.4 equiv), CuI (0.012 g, 0.07 mmol, 0.2 equiv), and vinyltributyltin (0.143 mL, 0.49 mmol, 1.5 equiv) in *N*,*N*-dimethylacetamide (DMA, 1.6 mL) was heated to 85 °C for 24 h after which time no starting material remained by TLC. DMA was removed under vacuum (0.4 mmHg) with gentle heating. The residue was redissolved in methylene chloride, and this solution was stirred vigorously with saturated potassium fluoride solution for 3 h. The layers were separated, and the aqueous phase was extracted with chloroform (3×). The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (1:1 ethyl acetate/methanol, and then methanol) provided 0.030 g (53%) 4-(pyrrolidin-1-yl)-2-vinylpyridine as a yellow liquid. ^{1}H NMR ($CDCl_3$): δ 8.15 (d, J = 5.8 Hz, 1H), 6.67 (dd, J = 10.7 Hz, 17.3 Hz, 1H), 6.37 (d, 2.4 Hz, 1H), 6.24 (dd, J = 2.4 Hz, 5.8 Hz, 1H), 6.13 (dd, J = 1.4 Hz, 17.5 Hz, 1H), 5.35 (dd, J = 1.4 Hz, 10.7 Hz, 1H), 3.28 (m, 4H), 1.99 (m, 4H). ^{13}C NMR: δ 155.31, 152.32, 149.24, 137.66, 116.92, 105.89, 104.84, 46.94, 25.26. IR 1594.2, 1540.8, 1389.9 cm^{-1}. TLC R_f = 0.54 (98:2 methanol/saturated ammonium hydroxide). HRMS (EI) m/z calcd for $C_{11}H_{14}N_2$ 174.1157, found 174.1164. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-Ethyl-4-(pyrrolidin-1-yl)pyridine (12c). A solution of 4-(pyrrolidin-1-yl)-2-vinylpyridine (0.058 g, 0.33 mmol) and 5% palladium on carbon (0.010 g) in absolute ethanol (4 mL) was stirred under an atmosphere of hydrogen (balloon) for 12 h. The solution was filtered through a plug of Celite and concentrated under reduced pressure. Flash chromatography (methanol, then 20:1 methanol/triethylamine) provided 0.053 g (90%) of 2-ethyl-4-(pyrrolidin-1-yl)pyridine as a yellow liquid. ^{1}H NMR ($CDCl_3$): δ 8.12 (d, J = 5.8 Hz, 1H), 6.22 (dd, J = 2.3 Hz, 1H), 6.20 (dd, J = 5.9 Hz, 2.5, Hz, 1H), 3.28 (m, 4H), 2.67 (q, J = 7.5 Hz, 2H), 1.99 (m, 4H), 1.26 (tr, J = 7.6 Hz, 3H). ^{13}C NMR: δ 163.23, 152.27, 148.98, 104.62, 104.52, 46.82, 31.56, 25.23, 14.03. IR 2966.2, 1601.5, 1542.7, 1502.5, 1388.7 cm^{-1}. TLC R_f = 0.47 (98:2 methanol/saturated ammonium hydroxide). HRMS (EI) m/z calcd for $C_{11}H_{15}N_2$ [M−H]$^+$ 175.1235, found 175.1235. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-(2-Propenyl)-4-(pyrrolidin-1-yl)pyridine: A solution of 2-bromo-4-(pyrrolidin-1-yl)pyridine (**13**) (0.649 g, 2.86 mmol, 1.0 equiv), Pd_2dba_3 (0.131 g, 0.15 mmol, 0.05 equiv), tri-2-furylphosphine (0.266 g, 1.14 mmol, 0.4 equiv), CuI (0.109 g, 0.57 mmol, 0.2 equiv), and 2-(tributylstannyl)propene (1.42 g, 4.29 mmol, 1.5 equiv) in *N*,*N*-dimethylacetamide (DMA, 14

mL) was heated to 85 °C for 48 h after which time no starting material remained by TLC. The solution was diluted with 1:1 ethyl acetate/methylene chloride and extracted with 1 M HCl until the extracts were colorless (6×). The aqueous extracts were washed with hexanes and basified to pH 12 by the addition of 5 M NaOH. The basic aqueous solution was then extracted with chloroform (6×) and concentrated under reduced pressure to give a green liquid. Residual DMA was removed by gentle heating of the liquid while under vacuum (0.4 mmHg). Flash chromatography (methanol) of the resultant residue provided 0.261 g (49%) of 2-(2-propenyl)-4-(pyrrolidin-1-yl)pyridine as a yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, J = 5.8 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 6.28 (dd, J = 5.8 Hz, 2.4 Hz, 1H), 5.76 (s, 1H), 5.19 (s, 1H), 3.31 (m, 4H), 2.17, (s, 3H), 2.01 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 148.44, 142.22, 148.81, 144.06, 114.60, 105.65, 103.06, 46.95, 25.29, 20.75. IR 1596.8, 1542.2, 1484.4 cm^{-1}. TLC R_f = 0.66 (98:2 methanol/saturated ammonium hydroxide). HRMS (EI) m/z calcd for $C_{12}H_{16}N_2$ 188.1313, found 188.1337. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-Isopropyl-4-(pyrrolidin-1-yl)pyridine (12d). A solution of 2-(2-propenyl)-4-(pyrrolidin-1-yl)pyridine (0.040 g, 0.21 mmol) and 5% palladium on carbon (0.007 g) in absolute ethanol (2 mL) was stirred under an atmosphere of hydrogen (balloon) for 12 h. The solution was filtered through a plug of Celite and concentrated under reduced pressure. Flash chromatography (methanol, then 20:1 methanol/triethylamine) provided 0.038 g (95%) of 2-isopropyl-4-(pyrrolidin-1-yl)pyridine as a yellow liquid. ^{1}H NMR ($CDCl_3$): δ 8.13 (d, J = 5.4 Hz, 1H), 6.21 (m, 2H), 3.30 (m, 4H), 2.91 (sept, J = 6.7 Hz, 1H), 1.99 (m, 4H), 1.26 (d, J = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 167.02, 152.30, 148.78, 104.75, 103.12, 46.86, 36.38, 25.25, 22.60. IR 2962.0, 1601.2, 1542.5, 1484.6, 1388.9 cm^{-1}. TLC R_f = 0.47 (98:2 methanol/saturated ammonium hydroxide). HRMS (EI) m/z calcd for $C_{12}H_{17}N_2$ [M − H]$^+$ 189.1392, found 189.1392. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-*tert*-Butyl-4-(pyrrolidin-1-yl)pyridine (12e). *tert*-Butyllithium (1.83 M in pentane, 11.1 mL, 20.2 mmol, 1.5 equiv) was added dropwise over 30 min to a −78 °C suspension of 4-pyrrolidinopyridine (2.00 g, 13.5 mmol, 1.0 equiv) in heptane (15 mL) in a three-neck flask. The lavender solution was stirred at −78 °C for 15 min and then allowed to warm to room temperature. While outgassing with N_2, the flask was fitted with a short path distillation head and pentane was removed by distillation. The distillation head was replaced with a reflux condenser and the solution refluxed for 1 h after which time it was allowed to cool to room temperature. Excess *tert*-butyllithium was quenched by slow addition of water. The solution was diluted with hexanes, and the layers were separated. The aqueous layer was extracted with chloroform (3×), and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to an orange liquid. Purification by flash chromatography (1:1 ethyl acetate/methanol) provided 2.057 g (74%) of 2-*tert*-butyl-4-(pyrrolidin-1-yl)pyridine as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, J = 5.8 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 6.20 (dd, J = 5.8 Hz, 2.4 Hz, 1H), 3.30 (m, 4H), 1.99 (m, 4H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 169.12, 152.13, 148.60, 104.29, 101.80, 46.85, 37.05, 30.19, 25.26. IR 2953.5, 1599.4, 1483.5 cm^{-1}. TLC R_f = 0.60 (98:2 methanol/saturated ammonium hydroxide). Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.48; H, 9.90; N, 13.87.

3-Iodo-6-methyl-*N*,*N*,-diisopropyl-2-pyridinecarboxamide (14). *n*-Butyllithium (1.6 M in hexanes, 11.1 mL, 17.7 mmol, 1.1 equiv) was added dropwise to a −78 °C solution of 6-methyl-*N*,*N*,-diisopropyl-2-pyridinecarboxamide (3.54 g, 16.07 mmol, 1.0 equiv) in tetrahydrofuran (100 mL). The reaction mixture was stirred for 1.5 h, after which time a solution of iodine (4.89 g, 19.28 mmol, 1.2 equiv) in tetrahydrofuran (50 mL) was added via cannula. The reaction mixture was then allowed to warm to room temperature over 2 h. The reaction mixture was diluted with diethyl ether and washed with saturated sodium bisulfite (2×) and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to a brown solid. Purification by flash chromatography (10:1 hexanes/ethyl acetate) provided 4.09 g 3-iodo-6-methyl-*N*,*N*,-diisopropyl-2-pyridinecarboxamide (73%) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 7.91 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 3.51 (sept, J = 7.0 Hz, 1H), 3.41 (sept, J = 6.7 Hz, 1H), 2.45 (s, 3H), 1.56 (br d, J = 7.0 Hz, 6H), 1.16 (br d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 168.07, 158.53, 157.84, 146.47, 124.22, 85.47, 50.98, 45.95, 23.88, 20.57, 20.23. IR 1634.6, 1324.1 cm^{-1}. R_f = 0.42 (1:1 hexanes/ethyl acetate). Anal. Calcd for $C_{13}H_{19}N_2OI$: C, 45.08; H, 5.53; N, 8.09. Found: C, 45.98; H, 5.70; N, 8.14.

4-Iodo-6-methyl-*N*,*N*,-diisopropyl-2-pyridinecarboxamide (15). *n*-Butyllithium (1.6 M in hexanes, 7.6 mL, 12.1 mmol, 1.1 equiv) was added to a 0 °C solution of diisopropylamine (1.7 mL, 13.2 mmol, 1.2 equiv) in tetrahydrofuran (100 mL). The solution was allowed to stir for 20 min at 0 °C and was then cooled to −78 °C. A solution of 3-iodo-6-methyl-*N*,*N*-diisopropyl-2-pyridinecarboxamide (**14**) (3.82 g, 11.0 mmol, 1.0 equiv) in tetrahydrofuran (100 mL) was added dropwise via cannula over 10 min. The dark red solution was stirred at −78 °C for 3 h, quenched with H_2O (0.4 mL, 22.0 mmol, 2.0 equiv), and then allowed to warm to room temperature over 2 h. The reaction mixture was diluted with diethyl ether, washed with brine (2×), dried over $MgSO_4$, and concentrated under reduced pressure to a brown solid. Purification by flash chromatography (5:1 hexanes/ethyl acetate) provided 1.68 g of 4-iodo-6-methyl-*N*,*N*,-diisopropyl-2-pyridinecarboxamide (44%) as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 7.56 (d, J = 0.8 Hz, 1H), 7.50 (d, J = 1.1 Hz, 1H), 3.75 (sept, J = 6.7 Hz, 1H), 3.48 (sept, J = 7.0 Hz, 1H), 2.44 (s, 3H), 1.49 (br d, J = 7.0, 6H), 1.13 (br d, J = 6.7, 6H). ^{13}C NMR ($CDCl_3$): δ 167.24, 158.43, 156.10, 132.14, 127.90, 106.13, 50.67, 46.01, 23.89, 20.57, 20.34. IR 1633.1, 1561.9 cm^{-1}. R_f = 0.68 (1:1 hexanes/ethyl acetate). Anal. Calcd for $C_{13}H_{19}N_2OI$: C, 45.08; H, 5.53; N, 8.09. Found: C, 45.14; H, 5.59; N, 8.14.

6-Methyl-4-(pyrrolidin-1-yl)-*N*,*N*,-diisopropyl-2-pyridinecarboxamide (16). A solution of 4-iodo-6-methyl-*N*,*N*-diisopropyl-2-pyridinecarboxamide (**15**) (1.41 g, 4.1 mmol) in pyrrolidine (100 mL) was refluxed for 12 h. Pyrrolidine was removed under reduced pressure leaving a dark orange residue. The residue was dissolved in ethyl acetate, washed with 1 N NaOH (2×) and brine, dried over $MgSO_4$, and concentrated under reduced pressure to an orange oil. Purification by flash chromatography (ethyl acetate, then 5:1 ethyl acetate/methanol) provided 1.12 g of 6-methyl-4-(pyrrolidin-1-yl)-*N*,*N*,-diisopropyl-2-pyridinecarboxamide (95%) as an off-white solid. ^{1}H NMR ($CDCl_3$): δ 6.29 (d, J = 2.1 Hz, 1H), 6.18 (d, J = 2.1 Hz, 1H), 3.85 (sept, J = 6.7 Hz, 1H), 3.27 (sept, J = 6.7 Hz, 1H), 3.27 (m, 4H), 2.39 (s, 3H), 1.97 (m, 4H), 1.52 (br d, J = 7.0 Hz, 6H), 1.13 (br d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 170.04, 157.49, 156.33, 152.57, 105.23, 102.07, 50.41, 46.98, 45.70, 25.27, 24.72, 20.68, 20.60. IR 1603.3 cm^{-1}. R_f = 0.6 (streak, 5:1 ethyl acetate/methanol). Anal. Calcd for $C_{17}H_{27}N_3O$: C, 70.54; H, 9.41; N, 14.53. Found: C, 70.79; H, 9.58; N, 14.45.

2-Formyl-6-methyl-4-(pyrrolidin-1-yl)pyridine (1b). Diisobutylaluminum hydride (1.0 M in hexanes, 1.56 mL, 1.58 mmol, 1.1 equiv) was added to a −78 °C solution of 6-methyl-4-(pyrrolidin-1-yl)-*N*,*N*,-diisopropyl-2-pyridinecarboxamide (**16**) (0.415 g, 1.43 mmol, 1.0 equiv) in tetrahydrofuran (20 mL). The solution was stirred for 15 min at −78 °C, warmed to 0 °C, stirred for 30 min, and finally warmed to room temperature and stirred for 1 h. The reaction was quenched by addition 5 N NaOH (1 mL) with vigorous stirring. The solution was filtered through $MgSO_4$ and concentrated to a brown solid. Purification by flash chromatography (ethyl acetate) provided 0.184 g of 2-formyl-6-methyl-4-(pyrrolidin-1-yl)pyridine (67%) as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ 9.94 (s, 1H), 6.90 (d, J = 2.4 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 3.33 (m, 4H), 2.50 (s, 3H), 2.02 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 194.88, 158.68, 152.57, 152.53, 109.38, 102.97, 47.17, 25.25, 24.41. IR 1706.5, 1606.3, 1495.6 cm^{-1}. R_f = 0.5 (5:1 ethyl acetate/methanol). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.43; H, 7.42; N, 14.73. Found: C, 69.21; H, 7.57; N, 14.55.

2-*tert*-Butyl-6-formyl-4-(pyrrolidin-1-yl)pyridine (1c). Boron trifluoride etherate (89 μL, 0.73 mmol, 1.2 equiv) was

added to a 0 °C solution of 2-*tert*-butyl-4-(pyrrolidin-1-yl)-pyridine (**12e**) (0.125 g, 0.61 mmol, 1.0 equiv) in tetrahydrofuran (10 mL). The resulting suspension was stirred for 30 min and then cooled to −78 °C. *tert*-Butyllithium (1.83 M in pentane, 0.55 mL, 0.97 mmol, 1.6 equiv) was added slowly. The burgundy colored solution was stirred at −78 °C for 5 h after which time *N*,*N*-dimethylformamide (95 μL, 1.2 mmol, 2.0 equiv) was added. The reaction was allowed to warm to room temperature and stirred for 2 h. Saturated sodium bicarbonate was added followed by ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to an orange crystalline solid consisting of a 1.5:1 ratio of desired product to starting material. Purification by flash chromatography (ethyl acetate) provided 0.054 g (38%) of 2-*tert*-Butyl-6-formyl-4-(pyrrolidin-1-yl)pyridine as a yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 9.94 (s, 1H), 6.88 (d, J = 2.2 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 3.34 (m, 4H), 2.02 (m, 4H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 195.94, 169.86, 152.64, 152.41, 105.47, 102.01, 47.23, 37.36, 30.16, 25.33. IR 2967.4, 1701.0, 1607.9, 1482.8 cm^{-1}. TLC R_f = 0.40 (5:1 hexanes/ethyl acetate). Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.30; H, 8.81; N, 12.07.

2,6-Diiodo-4-(pyrrolidin-1-yl)pyridine *N*-Oxide. *n*-Butyllithium (1.56 M in hexanes, 31 mL, 48.7 mmol, 4.0 equiv) was added to a −78 °C solution of diisopropylamine (7.2 mL, 51.2 mmol, 4.2 equiv) in tetrahydrofuran (20 mL). After addition, the cold bath was removed and the solution allowed to warm to room temperature. The LDA solution was then added dropwise over 20 min to a −78 °C suspension of 4-(pyrrolidin-1-yl)pyridine *N*-oxide (2.00 g, 12.2 mmol, 1.0 equiv) in tetrahydrofuran (200 mL), and the solution was stirred for 1 h. Iodine (12.4 g, 48.7 mmol, 4.0 equiv) was added as a solution in tetrahydrofuran (20 mL). The solution was allowed to slowly warm to room temperature and stir overnight. The solution was washed with saturated sodium thiosulfate (3×) and saturated sodium carbonate (6×). The aqueous washes were extracted with chloroform (2×). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (90:10 acetone/chloroform, then 85:10:5 acetone/chloroform/methanol) provided 2.91 g of 2,6-diiodo-4-(pyrrolidin-1-yl)pyridine *N*-oxide (57%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 6.96 (s, 2H), 3.23 (m, 4H), 2.02 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 144.35, 119.19, 107.78, 47.70, 25.38. IR 1601.8, 1475.8, 1455.1, 1205.0 cm^{-1}. TLC R_f = 0.43 (5:1 ethyl acetate/methanol). HRMS (EI) *m*/*z* calcd for $C_9H_{10}I_2N_2O$ 415.8883, found 415.8852. Purity was assayed by ^{1}H NMR (see Supporting Information).

2,6-Diiodo-4-(pyrrolidin-1-yl)pyridine (17). Phosphorus tribromide (89 μL, 0.94 mmol, 3.0 equiv) was added slowly to a 0 °C solution of 2,6-diiodo-4-(pyrrolidin-1-yl)pyridine *N*-oxide (0.130 g, 0.31 mmol, 1.0 equiv) in ethanol-free chloroform (5 mL). The resultant slurry was brought to reflux for 3 h. The solution was cooled to room temperature and poured into a 0 °C solution of sodium bicarbonate (20 mL). Ethyl acetate was added, and the layers were separated. The aqueous phase was extracted with ethyl acetate (3×). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (4:1 hexanes/ethyl acetate) provided 0.063 g (50%) 2,6-diiodo-4-(pyrrolidin-1-yl)-pyridine as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 6.74 (s, 2H), 3.21 (m, 4H), 1.99 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 152.53, 116.93, 115.66, 47.21, 25.17. IR 1572.5, 1485.5, 1138.7 cm^{-1}. TLC R_f = 0.41 (5:1 hexanes/ethyl acetate). HRMS (EI) *m*/*z* calcd for $C_9H_{10}I_2N_2$ 399.8934, found 399.8931. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-Iodo-4,6-(pyrrolidin-1-yl)pyridine. A solution of 2,6-diiodo-4-(pyrrolidin-1-yl)pyridine (**17**) (0.107 g, 0.27 mmol) in pyrrolidine (10 mL) was heated to reflux for 6 h after which time no starting material remained by TLC. The solution was cooled to room temperature and pyrrolidine was removed under reduced pressure. The residue was taken up in methylene chloride and washed with 1 M NaOH (2×), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography (9:1 hexanes/ethyl acetate) provided 0.080 g of 2-iodo-4,6-(pyrrolidin-1-yl)pyridine (87%) as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 6.24 (d, J = 1.7 Hz, 1H), 5.18 (d, J = 1.7 Hz, 1H), 3.36 (m, 4H), 3.22 (m, 4H), 1.93 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 157.50, 153.42, 117.87, 107.66, 86.11, 47.00, 46.67, 25.40, 25.20. IR 1590.7, 1512.2, 1457.8 cm^{-1}. TLC R_f = 0.53 (5:1 hexanes/ethyl acetate). Anal. Calcd for $C_{13}H_{18}IN_3$: C, 45.49; H, 5.29; N, 12.24. Found: C, 45.42; H, 5.16; N, 12.21.

2-Formyl-4,6-di(pyrrolidin-1-yl)pyridine (1d). *tert*-Butyllithium (1.7 M in pentane, 0.22 mL, 0.37 mmol, 2.2 equiv) was added to a −78 °C solution of 2-iodo-4,6-di(pyrrolidin-1-yl)pyridine (0.058 g, 1.7 mmol, 1.0 equiv) in diethyl ether (5 mL). The solution was stirred for 40 min and *N*,*N*-dimethylformamide (20 μL) was added. The solution was allowed to warm to room-temperature overnight. Saturated sodium bicarbonate was added followed by ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (5:1 hexanes/ethyl acetate) provided 0.012 g of 2-formyl-4,6-di(pyrrolidin-1-yl)pyridine (41%) as a yellow crystalline solid. ^{1}H NMR ($CDCl_3$): δ 9.83 (s, 1H), 6.56 (d, J = 2.0 Hz, 1H), 5.45 (d, J = 2.0 Hz, 1H), 3.47 (m, 4H), 3.32 (m, 4H), 1.98 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 195.65, 158.70, 153.21, 151.75, 97.39, 90.53, 47.22, 46.77, 25.50, 25.29. IR 1704.2, 1600.6, 1536.0, 1481.5 cm^{-1}. TLC R_f = 0.26 (5:1 hexanes/ethyl acetate). Anal. Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.66; H, 7.82; N, 17.14.

2-(Trimethylsilyl)-4-(pyrrolidin-1-yl)pyridine boron trifluoride complex (18). Boron trifluoride etherate (0.91 mL, 7.4 mmol, 1.1 equiv) was added to a 0 °C solution of 4-pyrrolidinopyridine (1.00 g, 6.4 mmol, 1.0 equiv) in tetrahydrofuran (40 mL). The resulting suspension was stirred for 30 min and then cooled to −78 °C. *n*-Butyllithium (1.56 M in hexanes, 6.9 mL, 10.8 mmol, 1.6 equiv) was added and the solution stirred for 30 min at −78 °C after which time chlorotrimethylsilane (2.14 mL, 16.8 mmol, 2.5 equiv) was added. The cold bath was removed, and the solution was allowed to warm to room temperature over 2 h. Saturated sodium bicarbonate was added followed by ethyl acetate. The aqueous layer was extracted with ethyl acetate (3×). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate) provided 1.341 g (69%) of 2-(trimethylsilyl)-4-(pyrrolidin-1-yl)pyridine boron trifluoride complex as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 8.35 (m, 1H), 6.77 (d, J = 2.8 Hz, 1H), 6.42 (dd, J = 7.1 Hz, 2.9 Hz, 1H), 3.42 (br m, 4H), 2.09 (m, 4H), 0.40 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 160.73, 152.05, 144.77, 115.29, 105.86, 47.64, 47.38, 25.19, 0.31. ^{19}F NMR ($CDCl_3$) 67.94 (q, J_{B-F} = 15.3 Hz). IR 1620.2, 1112.6, 1078.5, 917.0, 851.5 cm^{-1}. TLC R_f = 0.47 (1:1 hexanes/ethyl acetate). HRMS (EI, CI+ or CI-): only the decomplexed 2-(trimethylsilyl)-4-(pyrrolidin-1-yl)pyridine is observed; (EI) *m*/*z* calcd for $C_{12}H_{20}N_2Si$ 220.1396, found 220.1296. Purity was assayed by ^{1}H NMR (see Supporting Information).

2-Formyl-4-(pyrrolidin-1-yl)-6-(trimethylsilyl)pyridine (1e). *tert*-Butyllithium (1.7 M in hexanes, 0.31 mL, 0.52 mmol, 1.5 equiv) was added to a −78 °C solution of 2-(trimethylsilyl)-4-(pyrrolidin-1-yl)pyridine boron trifluoride complex (0.100 g, 0.35 mmol, 1.0 equiv) in tetrahydrofuran (4 mL). The solution was allowed to stir for 30 min after which time *N*,*N*-dimethylformamide (43 μL, 0.55 mmol, 1.6 equiv) was added. The solution was stirred at −78 °C for 1 h and then allowed to warm to room temperature. Brine and ethyl acetate were added. The aqueous layer was extracted with ethyl acetate (1×). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate) provided 0.039 g (45%) of 2-formyl-4-(pyrrolidin-1-yl)-6-(trimethylsilyl)pyridine as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ 10.02 (s, 1H), 6.95 (d, J = 2.7 Hz, 1H), 6.73 (d, J = 2.7 Hz, 1H), 3.34 (m, 4H), 2.02 (m, 4H), 0.31 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 196.19, 167.72, 153.40, 150.64, 115.40, 103.47, 47.06, 25.31, −1.75. IR 1702.8, 1598.3, 1238.1, 836.3 cm^{-1}. TLC R_f = 0.59 (ethyl acetate). HRMS (EI) *m*/*z* calcd for $C_{13}H_{20}N_2OSi$ 248.1345, found 248.1323. Purity was assayed by ^{1}H NMR (see Supporting Information).

Acknowledgment. We thank the National Institutes of Health (GM48498), Novartis Pharmaceuticals Corporation, and Pfizer for financial support of this research. T.S. is a recipient of an American Cancer Society Junior Faculty Research Award and is an Alfred P. Sloan Research Fellow. T.B.H. is a recipient of an American Chemical Society Division of Organic Chemistry Fellowship sponsored by Eli Lilly and Company. We thank Dr. Martin Berliner for assistance with NMR experiments and helpful discussions, and the referees for useful comments.

Supporting Information Available: Selected ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO982281N