Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 6330–6336

Practical application of new catalytic methods: a concise synthesis of a potent PDE IV inhibitor

Jennifer Albaneze-Walker,* Jerry A. Murry, Arash Soheili, Scott Ceglia, Shawn A. Springfield, Charles Bazaral, Peter G. Dormer and David L. Hughes

Process Research, Merck Research Laboratories, Merck and Co., Inc., PO Box 2000, Rahway, NJ 07065, USA

Received 3 November 2004; revised 8 February 2005; accepted 4 March 2005

Available online 13 May 2005

This paper is dedicated to the memory of Jackie Smitrovich, a dear friend and talented colleague.

Abstract—An efficient synthesis of a potent PDE IV inhibitor **1** is described. The synthesis is highlighted by two practical and efficient catalytic reactions: a highly selective catalytic palladium mediated carbonylation of the pyridine side chain and an efficient palladium-catalyzed Suzuki–Miyaura coupling of a chloropyridine-*N*-oxide.

1. Introduction

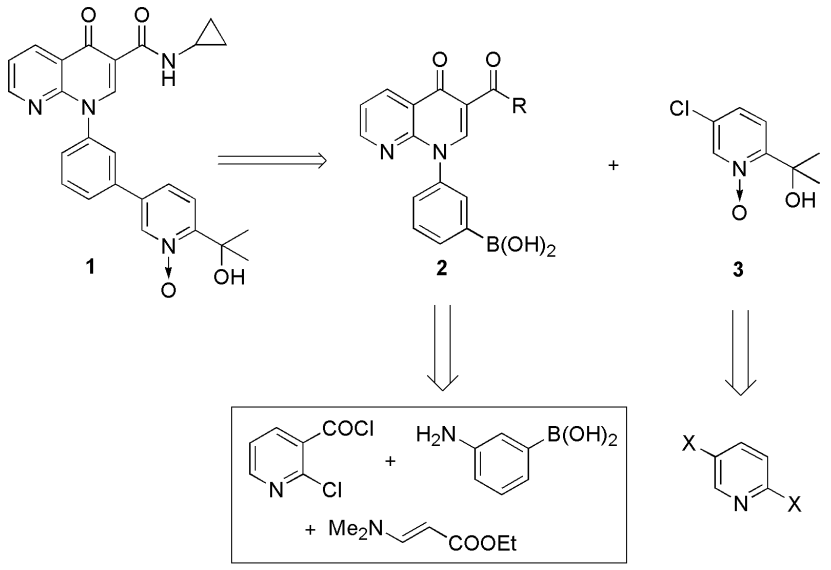
Phosphodiesterase IV inhibitors have generated interest as potential pharmaceutical targets for the intervention of various detrimental inflammatory responses including colitis, rheumatoid arthritis, asthma and chronic obstructive pulmonary disease.[1] Phosphodiesterase enzymes are responsible for the inactivation of cyclic AMP (cAMP) which in turn effects neutrophil activation. During many of the non-infectious human diseases described above, the recruitment of neutrophils plays a crucial role in the development of tissue damage. Since the neutrophil activation is dependent upon cAMP protein kinase A, inhibitors of PDE IV can enhance intracellular cAMP and decrease inflammatory cell activation. Several other mechanisms may contribute to the action of PDE IV inhibitors including inhibition of tumor necrosis factor (TNFα) release, increase in interleukin (IL)-1 release and suppression of T-lymphocyte function. Early PDE IV inhibitors such as rolipram, suffer from side effects such as nausea and vomiting which restrict their use as therapeutic agents. Second generation compounds with a reduced side effect liability such as Ariflo® have been identified. Efforts to identify potent selective inhibitors of PDE IV with the goal of identifying a therapeutic agent which may be efficacious in the treatment of rheumatoid arthritis, asthma and chronic obstructive pulmonary disease are on-going throughout the pharmaceutical industry.

Compound **1** was identified as a potent PDE IV inhibitor and a promising development candidate for clinical trials. As a result, we required a concise, scalable synthesis to prepare kilogram quantities of **1**. The retrosynthetic analysis of **1** is outlined in Scheme 1. Formation of the biphenyl ring junction was envisioned as the key late-stage step, bringing together two highly functionalized intermediates (**2** and **3**) using cross-coupling chemistry. Formation of the requisite naphthyridone **2** was anticipated to arise from an extension of previous chemistry in these labs for the synthesis of naphthyridones.[2] This strategy benefits from having the boronic acid included as a part of the readily available starting material, 3-aminophenyl boronic acid, and thus eliminates a potentially delicate cryogenic step for installation of this functional group on a highly functionalized intermediate late in the synthesis. Synthesis of the 2,5-disubstituted pyridine-*N*-oxide **3** was planned to arise from the readily available 2,5-dihalopyridine, and would require a practical and selective differentiation of the two halide groups.

This retrosynthetic strategy has formed the basis of a concise and practical synthesis of the PDE IV inhibitor **1**, as disclosed herein. The manuscript is divided into four major sections: (1) optimization of the naphthyridone synthesis, (2) defining a new synthesis of the functionalized pyridine-*N*-oxide partner involving a novel catalytic carbonylation reaction, (3) development of

Keywords: Naphthyridone; Pyridine; Suzuki–Miyaura coupling; Carbonylation; *N*-Oxide.
* Corresponding author; e-mail: jennifer_albanezewalker@merck.com

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.143



Scheme 1.

the challenging and unprecedented Suzuki–Miyaura coupling of a substituted chloro-pyridine-*N*-oxide, and (4) installation of the cyclopropyl amide and completion of the synthesis.

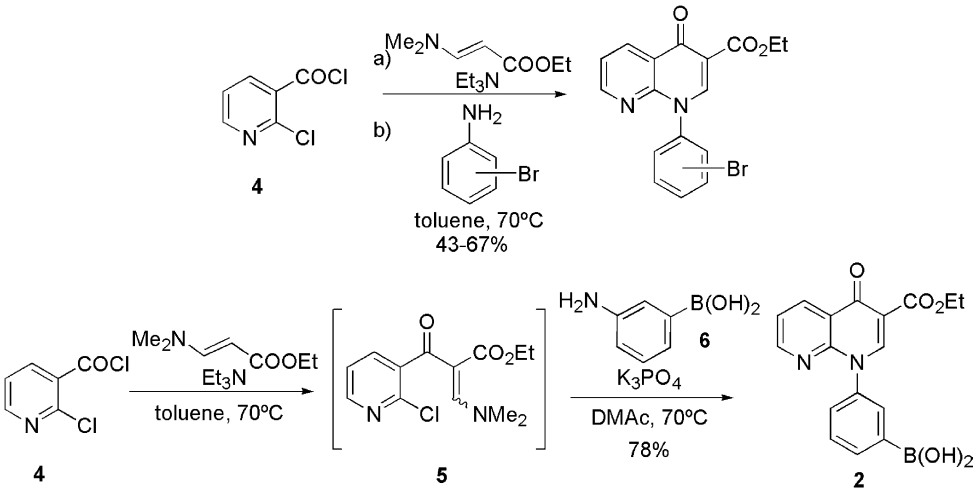
1.1. Naphthyridone synthesis

Naphthyridone formation is typically achieved in three separate and tedious steps.[3] We developed a new one-pot process which is both convenient for varying substitution, and provided pure material in good yield by direct crystallization of the product from the crude reaction mixture (Scheme 2).[2] This procedure works very well to generate halo- or alkyl-substituted naphthyridones.

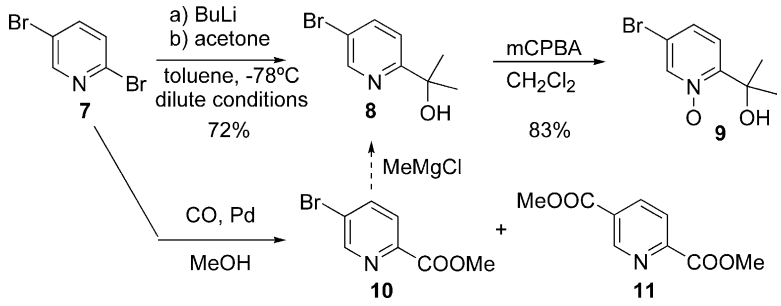
From this experience with naphthyridones, we adapted our procedure to accommodate the boronic acid moiety required for the subsequent Suzuki–Miyaura coupling reaction. When we applied our one-pot protocol to the synthesis of the desired naphthyridone boronic acid, however, we experienced crystallization and isolation difficulties. These problems were eliminated by simply removing the triethylamine HCl salt formed in the first reaction by filtration into a second pot, followed by a solvent switch into the more polar solvent dimethylacetamide, and then addition of the aminophenylboronic acid and base to complete the cyclization. Thus naphthyridonephenylboronic acid **2** was synthesized directly in two pots via a through-process in 78% yield, thereby eliminating the need to install an appropriate functional group later for the cross-coupling.

1.2. Synthesis of the functionalized pyridine—selective carbonylation of 2,5-dichloropyridine

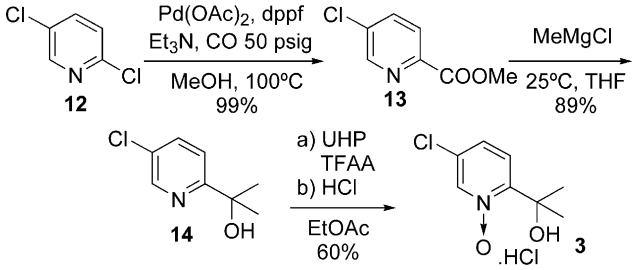
With our boronic acid coupling partner in hand, we next surveyed methods to make the substituted bromopyridine-*N*-oxide substrate. There are a number of relevant reports in the literature, including one from these laboratories describing the selective lithiation of 2,5-dibromopyridine.[4] Initially we used this selective lithiation/alkylation to introduce the dimethylcarbinol onto the 2-position of the pyridine, followed by *N*-oxidation with *m*CPBA (Scheme 3).



Scheme 2. One-pot method for creation of 1,8-naphthyridin-4ones.



Scheme 3.



Scheme 4.

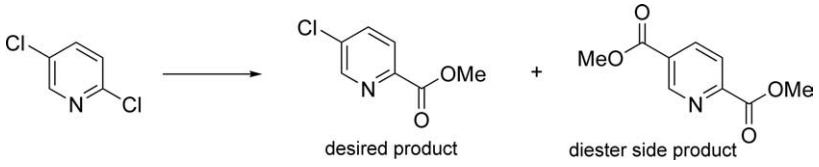
Owing to the low volume productivity and the requirement for cryogenic conditions for lithiation selectivity, we sought a more efficient route to the carbinolpyridine **9**.

We decided to next explore a selective metal catalyzed carbonylation route. We repeated a reported preparation of methyl 5-bromo-carboxypyridine from 2,5-dibromopyridine, and noted formation of >30% diester **11** along with the desired monocarbonylated product.[5] Screening with >30 different catalysts failed to show satisfactory improvement. Initial carbonylation is selective for the 2-position: no 2-bromo-5-carboxypyridine was detected. However, once the desired 2-carboxypyridine is formed, the bromide in the 5-position becomes activated and is susceptible to the carbonylation conditions. Separation of the monoester product from the diester product and the starting dibromopyridine is tedious. Song and Yee[6] have reported an interesting two step solution to the problem, however we desired a more direct, efficient solution. We decided to investigate the selective carbonylation of 2,5-dichloropyridine **12** (Scheme 4).

Selective carbonylation of dichloropyridines has been reported with varying degrees of success.[7] Typically high pressures (up to 100 bar CO) and temperatures (>100 °C) have been used to produce the mono-carbonylated product. Advances have been reported by Bessard and Crettaz, the Beller group, and most recently by our group.[8]

Catalyst screening was undertaken to identify optimal selective carbonylation conditions to convert **12** to **13** (Table 1). The choice of ligand and base were the most important variables investigated. Use of monodentate ligands gave either little reaction (Entry 4), or very poor selectivity (Entries 1 and 3). Use of bidentate ligands typically increased the reaction rate, but again, gave poor selectivity (Entry 5). Base was also important for reaction conversion: sodium acetate was less effective than amine bases (entry 2 and 9). The bidentate dppf ligand provided both good reaction rate as well as good selectivity (entry 9). Selectivity was further improved by limitation of triethylamine to just 1.01 equiv to help prevent over-carbonylation (entry 10). Catalyst loading of 0.2 mol% was optimal, giving the most reproducible results upon scale up. The carbonylation reaction is extremely efficient, performed

Table 1. Optimization of mono-carbonylation of 2,5-dichloropyridine



Entry	Catalyst	mol%	Solvent	Base	equiv	CO (psig)	°C	h	% Product	% Diester	% St. mat.
1	$PdCl_2(PPh_3)_2$	10	MeOH	Et_3N	1.2	725	140	8	69	17	14
2	$Pd(OAc)_2$ + dppf	10	EtOH	NaOAc	3.0	220	120	3	0	0	100
3	$PdCl_2(PPh_3)_2$	5	MeOH	Et_3N	1.1	100	100	8	75	25	0
4	$PdCl_2[P(fur)_3]_2$	5	MeOH	Et_3N	1.1	100	100	8	6	0	88
5	$PdCl_2$(BINAP)	5	MeOH	Et_3N	1.1	100	100	8	50	50	0
6	$PdCl_2$(dppp)	5	MeOH	Et_3N	1.1	100	100	8	79	21	0
7	$Pd(OAc)_2$ + dppf	5	MeOH	Et_3N	1.1	100	100	8	73	26	1
8	$PdCl_2$(dppf)	5	MeOH	Et_3N	1.1	100	100	8	78	22	0
9	$Pd(OAc)_2$ + dppf	0.2	MeOH	Et_3N	1.1	50	80	6	91	1.5	7.5
10	$Pd(OAc)_2$ + dppf	0.2	MeOH	Et_3N	1.01	50	100	7	98	1	1

under relatively mild conditions, and extremely productive as only four volumes of methanol solvent were used. The yield of **13** was excellent, and the diester side product was <0.5% HPLC area percent. Unlike the bromide analogue **10**, however, isolation of **13** initially proved problematic: **13** possesses significant solubility in every solvent tested, from hexanes to water! After much experimentation, optimal recovery could be realized by precipitation from a methanol–brine mixture which allowed isolation of the desired **13** in 92–95% yield.

With mono-ester **13** in hand, conversion to the carbinol **14** was studied next. Intermediate **14** was generated by addition of 2.5 equiv methyl Grignard reagent. Inverse addition of the substrate to a solution of the Grignard reagent was necessary to insure completion of the reaction. The resulting product **14** is an oil and was not isolated, but was carried directly through into the *N*-oxidation step. Oxidation was sluggish with *m*CPBA conditions, even when using a large excess of *m*CPBA. Sharpless MTO conditions were not any better. The oxidation was best achieved using the urea hydrogen peroxide/trifluoroacetic acid anhydride reagent as reported by Caron.[9] Performing the oxidation in ethyl acetate allowed isolation of the product as the HCl salt in greater than 99% purity, which proved best for handling and storing, as well as purification of the fully functionalized coupling partner **3**.

1.3. Suzuki–Miyaura cross-coupling

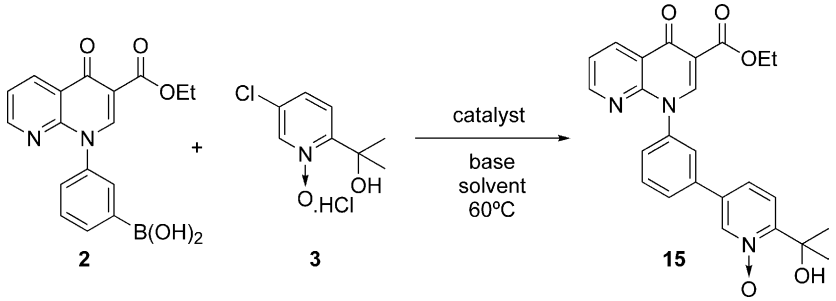
The Suzuki–Miyaura coupling between the boronic acid **2** and the chloride salt **3** failed using typical Suzuki–Miyaura conditions, (Table 2, entries 1 and 2) however, desired product was formed with the use of the Fu ligand tri-*t*-butylphosphine (entry 6).[10] The ratio of palladium to ligand was crucial to the success of the coupling (entries 3, 4 vs 6). The typical 2:1 ratio of tri-*t*-butylphosphine to palladium failed to produce any product at all. Lowering the ratio to 1:1 produced a much more active catalyst. We found it convenient to mix the palladium reagent with the ligand, and add the catalyst solution to the substrate solution under inert atmosphere. We abandoned the use of $Pd_2(dba)_3$ as the palladium source, as it was difficult to remove the dibenzylidineacetone from the batch downstream. Use of the π-allyl palladium chloride dimer reagent consistently produced excellent results. The purity of the chloride substrate **3** was also important to success of the coupling: using **3** as the free base produced inconsistent results, and the reaction rarely proceeded to completion. Isolation of **3** as the HCl salt from the *N*-oxidation step typically provided the chloride in >99.8% purity, which performed reliably in the coupling step. Choice of solvent and base were also critical for success of the reaction. The reaction proceeded only in polar coordinating solvents such as dimethylacetamide and dimethylformamide, and the presence of water was found to accelerate the reaction. Several bases examined caused extensive deborination of **2**, particularly K_3PO_4 (entry 6). The most effective base was found to be potassium carbonate. Under these conditions, **15** was consistently produced in 80–90% yield. Importantly, no deoxygenation of the *N*-oxide was ever detected.

1.4. Installation of the cyclopropyl amide and completion of the synthesis

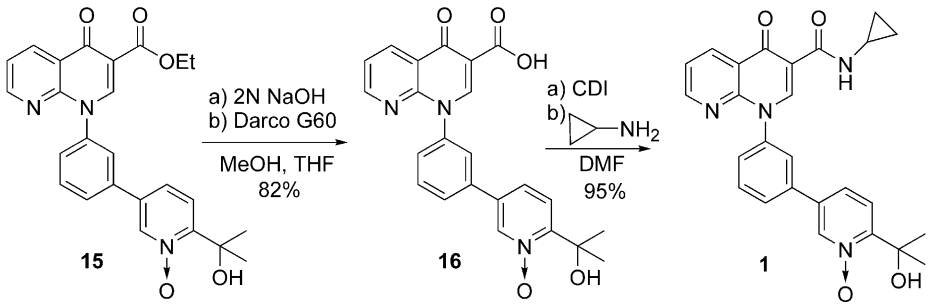
The coupled product **15** was transformed into **1** by hydrolysis to the acid **16** and subsequent amide formation. Hydrolysis was uneventful. Residual palladium was removed at this point by stirring with 100 wt% Darco G-60, followed by isolation of pristine **16**. CDI mediated amide formation was achieved in 95% yield to produce the desired target **1** (Scheme 5).

In conclusion, we have synthesized the potent PDE IV clinical candidate **1** in four linear steps, plus three steps required for the construction of the substituted chloropyridine-*N*-oxide coupling partner. The synthesis is efficient and scalable for processing kilogram quantities. A through-

Table 2. Optimization of coupling



Entry	Catalyst	mol%	L/Pd	Solvent(s)	Base	% Prod.	% Deborinated
1	$Pd(OAc)_2$/dppf	5	1/1	DMF/H_2O	K_2CO_3	0	0
2	POPd catalyst	5	2/1	DMAc/H_2O	K_2CO_3	0	0
3	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	5/20	2/1	MeOH	K_2CO_3	0	0
4	Pd[P(*t*-Bu)$_3$]	5	2/1	DMF/H_2O	K_2CO_3	0	0
5	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	5/10	1/1	dry DMF	Cs_2CO_3	0	0
6	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	3/6	1/1	DMAc/H_2O	K_3PO_4	54	45
7	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	20/40	1/1	DMF/H_2O	K_2CO_3	50	10
8	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	2.5/5	1/1	DMF/H_2O	K_2CO_3	70	20
9	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	5/10	1/1	DMF/H_2O	Cs_2CO_3	77	5
10	[(allyl)PdCl]$_2$/P(*t*-Bu)$_3$	5/10	1/1	DMAc/H_2O	K_2CO_3	92	<2



Scheme 5. Amide formation.

process synthesis of the naphthyridone core, a highly selective carbonylation of the functionalized chloropyridine-*N*-oxide, and an unprecedented Suzuki–Miyaura coupling of a chloropyridine-*N*-oxide were developed.

2. Experimental

2.1. General methods

NMR and ^{13}C NMR were recorded at ambient temperature on a Bruker DPX 400 at a frequency of 400.13 and 100.61 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ ($\delta=7.27$) for proton and $CDCl_3$ ($\delta=77.0$) for carbon unless otherwise indicated. The data are reported as follows: proton multiplicities (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, and app=apparent), coupling constants, and integration. Microanalyses were performed by Quantitative Technologies, Inc. Melting points are reported uncorrected. Flash chromatography was performed using the indicated solvent system on EM Reagents silica gel (SiO_2) 60 (230–400 mesh). Materials. Solvents and triethylamine were used as received. All reagents used were commercially available.

2.1.1. Ethyl-1-(phenyl-3-boronic acid)-1,4-dihydro[1,8]-naphthyridin-4-one-3-carboxylate (2). A 50 L round bottom flask was equipped with an overhead stirrer, nitrogen blanket, and thermocouple/steam regulator. Toluene 20 L was added to the vessel. *K*F of toluene must be <200 ppm. Triethylamine 3.2 L (22.8 mol) was added in one portion while stirring. Next, ethyl dimethylacrylate 2.6 kg (18.2 mol) was charged to the vessel, followed by 2-chloronicotinoyl chloride 2.0 kg (11.4 mol) added as a solid. The reaction was heated to 70 °C and aged until completion-approx. 5 h. LC samples were quenched with *n*-propylamine, and consumption of starting material is complete when less then 3% LCAP of *n*-propyl-2-chloronicotin-amide remains. The reaction mixture was allowed to cool to ambient temperature and filtered to remove the triethylamine hydrochloride salt that formed during the reaction. The vessel/line and filter pot were rinsed with toluene 10 L. The toluene solution was switched under reduced pressure ($T_{int}<30$ °C) to DMAc 10 L and carried forward into next flask as a solution in DMAc. A 100 L round bottom was equipped with an overhead stirrer, nitrogen inlet and condenser. The step 1 intermediate solution in DMAc 10 L was added. DMAc 10 L was used as vessel and line rinses and added to the round bottom bringing the final volume of DMAc to 20 L. Potassium phosphate tribasic 4.86 kg (22.8 mol) was added, followed by immediate addition of 3-aminophenylboronic acid–HCl 1.68 kg (9.7 mol). Caution—mild exotherm ~10 °C upon addition of 3-aminophenylboronic acid–HCl. Reaction mixture was heated to 70 °C and aged until reaction was complete—typically 12–18 h. LC samples are quenched with *n*-propylamine, and consumption of SM is complete when less then 3% LCAP of 3-aminophenylboronic acid remains. The reaction mixture was allowed to cool to ambient temperature, and ~20 L of 1 N HCl was added over ~2 h until pH=5–6. Water was added to adjust ratio of aqueous/DMAc to ~2:1. Caution—slight exotherm upon addition of aqueous HCl. Keep $T_{int}<35$ °C with cooling bath. Mother liquor losses are typically 2–3%. Batch was immediately filtered at room temperature and washed with ~5 L of 2:1 water/DMAc. Multiple 5 L slurry washes with water were performed to remove DMAc. Batch was dried overnight on filter pot under partial vacuum with nitrogen sweep. Yield 2.58 kg, 78% yield over two steps; uncorrected. Collected as an off-white solid. Mp 273 °C. ^1H NMR DMSO-d_6 δ 2.50 (t, $J=7.1$ Hz, 3H), 4.22 (q, $J=7.1$ Hz, 2H), 7.55 (t, $J=7.6$ Hz, 1H), 7.57 (dd, $J=8.0$, 4.4 Hz, 1H), 7.61 (ddd, $J=7.6$, 2.0, 1.2 Hz, 1H), 7.86 (d, $J=1.2$ Hz, 1H), 7.93 (dt, $J=7.6$, 1.2 Hz, 1H), 8.27 (br s, 2H), 8.61 (dd, $J=8.0$, 2.0 Hz, 1H), 8.63 (s, 1H), 8.68 (dd, $J=4.4$, 2.0 Hz, 1H). ^{13}C NMR DMSO-d_6 δ 14.6, 60.5, 112.0, 121.9, 122.7, 128.9, 129.9, 133.1, 134.9, 136.3, 136.4 (br s, *C*-$B(OH)_2$), 140.3, 149.8, 150.4, 153.2, 164.3, 174.1. Hi-Res MS calcd for $C_{17}H_{15}BN_2O_5$: 338.1189 (M+H). Found: 338.1188 (M+H).

2.1.2. Methyl 5-chloro-2-carboxypyridine (13). A 10 L bottle was charged with 2,5-dichloropyridine 2.0 kg (13.51 mol), palladium acetate 6.08 g (0.03 mol, 0.2 mol%), dppf 30.0 g (0.05 mol, 0.4 mol%), and triethylamine 1.9 L (13.6 mol) in methanol 6 L. The bottle was stirred then contents transferred to a five gallon stainless steel stirred reaction vessel (Kla=1.42 @ 40% fill and 1000 rpm) via vacuum. Bottle was rinsed with another 2 L methanol, and the rinse was added to reaction vessel by the same method. Vessel was tested for leaks using nitrogen, then purged with nitrogen three times and carbon monoxide three times. The vessel was pressurized to 50 psig with carbon monoxide and heated to a temperature of 100 °C. The agitation rate was 1000 rpm. The reaction was thus allowed to progress for 11 h, then allowed to cool to room temp and sampled. Reaction was judged to be complete when 3% LCAP or less of starting material remained. Batch was transferred to a 50 L round bottom flask equipped with a thermocouple and stir paddle. Flask was connected to a

batch concentrator and concentration begun at 25–30 in Hg of applied vacuum. Intermittent heating of batch was applied to maintain temp. at 30–35 °C. Concentration was discontinued when copious precipitate was noted. HPLC assay of batch was 350 mg/mL. Saturated brine 20 L was added via addition funnel over 1 h. Batch was aged with gentle stirring overnight. In morning, a methanol/ice bath was applied to cool batch to −5 °C for 1.5 h. Solids were collected by filtration and rinsed with 5 L brine twice, then dried under nitrogen tent overnight to give 3.47 kg of product intimately mixed with sodium chloride: 57 wt%, 1.98 kg of product in the isolated solids, 99% yield, ML losses 0.41%. The product can be stored at this point if desired. Mp 57 °C. NMR ^{1}H δ: 3.87 (s, 3H), 7.69 (dd, J= 8.4, 2.4 Hz, 1H), 7.95 (d, J=8.4 Hz, 1H), 8.54 (d, J= 2.4 Hz, 1H). NMR ^{13}C δ: 52.8, 125.8, 135.7, 136.6, 145.7, 148.6, 164.6. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99 (s, 3H), 4.04 (s, 3H), 8.20 (dd, J=8.2, 0.8 Hz, 1H), 8.42 (dd, J=8.2, 2.1 Hz, 1H), 9.30 (dd, J=2.0, 0.7 Hz, 1H). ^{13}C NMR δ 49.0, 49.5, 120.9, 124.9, 134.6, 147.0, 147.1, 161.1, 161.2. Anal. calcd for $C_9H_8F_3NO_3$: C, 49.00; H, 3.52; N, 8.16. Found: C, 49.01; H, 3.44; N, 8.03.

2.1.3. 3-Chloro-2-(dimethylcarbinol)-pyridine (14). Solid mixture of methyl 5-chloro-2-carboxypyridine 3.47 kg at 57wt% with sodium chloride, and tetrahydrofuran 16 L were charged to a 50 L round bottom flask equipped with stir paddle. Batch was stirred for one hour. Batch was sampled for K_f. Water content must be 1000 μg/0.5 mL or less to proceed to Grignard reaction. Assay was 122 mg/g of THF solution, 1.97 kg 5-chloro-2-carboxypyridine in 16.06 kg of solution. A 100 L round bottom flask was flushed with nitrogen, fitted with thermocouple, overhead stir paddle, and dropping funnel. The flask was charged with a 3 M solution of methylmagnesium chloride 9.7 L (29.1 mol) and stirring begun. The flask was packed in an ice bath. When temperature reached 5 °C, the solution of 5-chloro-2-carboxypyridine in THF was added by dropping funnel. Rate of addition was controlled to keep temperature below 30 °C, averaging between 20 and 25 °C. After addition was complete, reaction was aged for 30–45 min longer and assayed. Reaction was quenched by addition of ethyl acetate 800 mL followed by methanol 800 mL, again not allowing temperature to rise above 30 °C. pH was adjusted with 2 N hydrochloric acid solution to pH=4–5 (~12 L) (note: pH must not exceed 4, else some product is lost in water layer). Acidic reaction solution was extracted with ethyl acetate 9 L. Organic layer was extracted once with 1 N hydrochloric acid solution 40 L, and again with 1 N hydrochloric acid solution 20 L (note: product is now in aqueous layer; two extractions are necessary for good yield). Combined aqueous layers were adjusted with 10 N sodium hydroxide to pH=8 (~4 L) (note: an oily layer was noted to separate out on top). The basic aqueous layer was extracted once with ethyl acetate 10 L, dried by batch concentration to until K_f<1000 ppm. Final concentration was 200 mg/mL of product. Aliquot of product solution was concentrated to a colorless oil and purified further by column chromatography on silica gel with 5–10% ethyl acetate in hexanes for characterization purposes. NMR ^{1}H δ: 1.53 (s, 6H), 4.44 (br s, 1H), 7.35 (dd, J=8.4, 0.7 Hz, 1H), 7.66 (dd, J=8.4, 2.4 Hz, 1H), 8.46 (dd, J=2.3, 0.6 Hz, 1H). NMR ^{13}C δ: 30.5, 71.9, 119.5, 130.1, 136.6, 146.4, 164.4. Hi-Res MS calcd for $C_8H_{10}ClNO$: 172.0529 (M+H). Found: 172.0530 (M+H).

2.1.4. 3-Chloro-2-(1-hydroxy-1-methylethyl)-pyridine-*N*-oxide HCl salt (3). A 50 L round bottom flask was flushed with nitrogen, fitted with thermocouple, overhead stir paddle, and dropping funnel. The flask was charged with urea–hydrogen peroxide 1.39 L (14.5 mol) and ethyl acetate 5 L and stirring begun. The flask was packed in an ice bath. When temperature reached −10 °C, TFAA 2.0 L (14.5 mol) was added slowly. Rate of addition was controlled to keep temperature below 10 °C. Reaction was cooled back down to −10 °C and solution of alcohol 1.55 kg (9.0 mol) in ethyl acetate 5 L was added via dropping funnel over 1 h. After addition was complete, reaction was allowed to warm to ambient temperature and aged for one hour longer, assayed then cooled to −5 °C. Reaction was quenched by 40% $Na_2S_2O3.5H_2O$ aqueous solution 2.9 L. The organic layer was separated from the aqueous layer. Hydrochloric acid 1.8 N in IPA solution 2 L was added to the organic layer over 45 min. Batch was allowed to warm to ambient temperature, then filtered to remove urea salts. Filtrate was concentrated to 7 L volume, followed by addition of hydrochloric acid 1.8 N in isopropyl acetate 5 L. Batch was filtered again, sampled, then seeded. Product crystals formed and batch was cooled to −10 °C to finish precipitation. Product salt was collected by filtration, rinsed with ethyl acetate and dried in vacuum oven at ambient temperature. 1.11 kg, 57% yield in 99% purity. Aliquot of organic layer before HCl addition was concentrated to a colorless oil and purified further by column chromatography on silica gel with 5–10% ethyl acetate in hexanes for characterization purposes. NMR ^{1}H δ: 1.64 (s, 6H), 6.99 (br s, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.36 (dd, J= 8.4, 1.6 Hz, 1H), 8.28 (d, J=1.6 Hz, 1H). NMR ^{13}C δ: 27.2, 71.4, 122.7, 128.0, 131.6, 139.7, 153.4. Anal. calcd for $C_8H_{10}ClNO_2$.1/2 HCl: C, 46.68; H, 5.14; N, 6.80. Found: C, 46.48; H, 5.13; N, 6.88.

2.1.5. Ethyl 1-{3-[6-(1-hydroxy-1-methylethyl)-1-oxido-pyridin-3-yl]phenyl}-1,4-dihydro[1,8]naphthyridin-4-one-3-carboxylate (15). A 100 L round bottom flask was flushed with nitrogen, fitted with thermocouple, overhead stir paddle, and solid addition funnel. The flask was charged with chloro-alcohol. HCl 0.9 kg (4.0 mol) and 2.7 L water and stirring begun. The flask was packed in an ice bath. When temperature reached 10 °C, solid potassium carbonate 1.32 kg (9.6 mol) was added by solid addition funnel. Rate of addition was controlled to keep temperature below 20 °C and minimize gas evolution. After addition was complete, half of a pre-mixed solution of 2.7 L water in 17.5 L DMAc was added slowly to keep temp below 25 °C (heat of mixing of water and DMAc is significant). Solid naphthyridone-phenylboronic acid 1.3 kg (3.8 mol) was added and remaining half of water/DMAc solution added. Slurry was sparged with nitrogen for minimum of 1 h. Pi-allyl palladium chloride dimer 70.0 g (0.2 mol, 5 mol%) was charged into a separate 5 L flask, DMAc 2.25 L added and stirred to produce a yellow solution. Nitrogen was sparged through for a minimum of 1 h. A 10 wt% (0.33 M) solution of tri-*t*-butylphosphine 1.2 L (0.4 mol, 10 mol%) was added without exposure to air. (Note: L/Pd ratio must be 1:1. More ligand shuts the reaction down completely.) Solution was

stirred for 30 min turning a deep golden color. This catalyst solution was added to the reaction solution without exposure to air. Reaction solution was heated to 60 °C for 6 h. As completion neared, product began to precipitate out, even at 60 °C. Reaction should be assayed after 4 h, or if reaction becomes thick with product precipitate before that time. When boronic acid was consumed, reaction was allowed to cool to room temperature and poured into 55 L water to complete product precipitation. This gray slurry was filtered and solids were collected. Filter cake was washed with another 55 L water, then dried under partial vacuum at 40–50 °C overnight, until constant weight, to give 1.51 kg, 80% yield. NMR ^{1}H δ: 1.72 (t, J=7.1 Hz, 3H), 4.41 (q, J=7.1 Hz, 2H), 7.45 (dd, J=7.6, 4.4 Hz, 1H), 7.47 (d, J=8.8 Hz, 1H), 7.57(dt, J=6.4, 2.0 Hz, 1H), 7.60 (dd, J=8.4, 2.0 Hz, 1H), 7.65–7.68 (m, 1H), 7.71–7.77 (m, 2H), 8.53 (d, J=2.0 Hz, 1H), 8.64 (dd, J=4.4, 2.0 Hz, 1H), 8.73 (s, 1H), 8.84 (dd, J=8.0, 2.0 Hz, 1H). NMR ^{13}C δ: 14.3, 27.3, 61.2, 71.5, 113.0, 121.5, 122.8, 123.2, 126.13, 126.14, 127.6, 128.1, 130.8, 136.4, 136.9, 137.0, 138.8, 141.2, 149.1, 149.9, 152.5, 153.8, 164.8, 174.6. Hi-Res MS calcd for $C_{25}H_{23}N_3O_5$: 446.1716 (M+H). Found: 446.1708 (M+H).

2.1.6. 1-{3-[6-(1-Hydroxy-1-methylethyl)-1-oxidopyridin-3-yl]phenyl}-1,4-dihydro[1,8]naphthyridin-4-one-3-carboxylate (16). A 72 L round bottom flask was flushed with nitrogen, fitted with thermocouple, overhead stir paddle, and addition funnel. The flask was charged with ester compound 0.96 kg (2.15 mol), THF 10 L, and methanol 10 L, followed by 2 N aqueous sodium hydroxide 10 L. Reaction was allowed to stir overnight at room temperature. Reaction was adjusted to pH 8 by addition of 1.4 L concentrated hydrochloric acid. Darco G-60 0.96 kg (100 wt%) was added and resulting mixture was allowed to stir for 2 h. The mixture was filtered through Solka Floc to remove Darco resin. Concentrated hydrochloric acid was added to the filtrate to adjust to pH 3. White precipitate was collected by filtration. The filter cake was dried in a vacuum oven at 40–50 °C under nitrogen stream until constant weight to give 0.65 kg white solids, 72% yield. Mp 163 °C. NMR ^{1}H (DMSO-d_6) δ: 1.59 (s, 6H), 7.70–7.74 (m, 4H), 7.85 (dd, J=8.4, 1.8 Hz, 1H), 7.97–8.00 (m, 1H), 8.11 (br s, 1H), 8.75 (d, J=1.8 Hz, 1H), 8.80 (dd,, J=8.0, 1.9 Hz, 1H), 8.87 (dd, J=4.5, 1.9 Hz, 1H), 9.03 (s, 1H). NMR ^{13}C (DMSO-d_6) δ: 27.1, 71.5, 109.4, 120.7, 123.1, 123.8, 126.0, 126.0, 128.2, 128.8, 130.4, 135.9, 136.0, 136.5, 138.6, 141.0, 150.4, 150.8, 154.2, 154.9, 165.5, 179.2. Anal. calcd for $C_{23}H_{19}N_3O_5.2H_2O$ (dihydrate): C, 60.92; H, 5.11; N, 9.27. Found: C, 60.61; H, 4.74; N, 9.11.

2.1.7. Cyclopropyl-1-{3-[6-(1-hydroxy-1-methylethyl)-1-oxidopyridin-3-yl]phenyl}-1,4-dihydro[1,8]naphthyridin-4-one-3-carboxamide (1). A 100 L cylindrical flask was flushed with nitrogen, fitted with an addition funnel. The flask was charged with the naphthyridone acid derivative followed by DMF 28 L and carbonyldiimidazole 1.4 kg (4.9 mol). Reaction was allowed to stir until acid was consumed. Cyclopropylamine 5.9 L (48.9 mol) was added and reaction stirred overnight. Water was added to milky reaction mixture and temperature was noted to rise to 38 °C. The mixture was allowed to cool to room temperature, then filtered and washed with ethanol 20 L to collect white solids. The filter cake was dried under a nitrogen stream until constant weight to give 1.24 kg white solids, 82% yield. The white solids were suspended in 60 L dry ethanol in a 100 L cylindrical flask. The mixture was heated to reflux, then allowed to cool to room temperature. The solids were collected by filtration, washed with 5 L ethanol, and dried in a vacuum oven at 40 °C under a nitrogen stream until constant weight to give 1.20 kg white solids, 96% recovery. Mp 271 °C. NMR ^{1}H δ: 0.66–0.70 (m, 2H), 0.84–0.89 (m, 2H), 1.72 (s, 6H), 2.97–2.03 (m, 1H), 7.45–7.60 (overlapping multiplets, 4H), 7.64 (s, 1H), 7.72–7.76 (m, 2H), 8.53 (d, J=4.3 Hz, 1H), 8.83 (d, J=8.0 Hz, 1H), 9.05 (s, 1H), 9.76 (s, 1H). NMR ^{13}C δ: 6.5, 22.4, 27.3, 71.5, 113.5, 121.4, 122.1, 122.7, 126.11, 126.14, 127.7, 128.0, 130.7, 136.3, 136.5, 136.9, 138.8, 141.2, 148.0, 149.8, 153.0, 153.7, 165.1, 177.1. Anal. calcd for $C_{26}H_{24}N_4O_4 \cdot 1/2$ EtOH (hemi-ethanol adduct): C, 67.63; H, 5.68; N, 11.68. Found: C, 67.69; H, 5.28; N, 12.16.

Acknowledgements

We thank Tom Novak for his expertise in high resolution mass spectrometry, and Andy Newell and Tony Houck for their assistance with high pressure equipment.

References and notes

1. (a) Souness, J. E.; Foster, M. *Drugs* **1998**, *1*, 541–553. (b) Dyke, H.; Montana, J. *Expert Opin. Invest. Drugs* **1999**, *8*, 1301–1325.
2. Springfield, S. A.; Marcantonio, K.; Ceglia, S.; Albaneze-Walker, J.; Dormer, P. G.; Nelson, T. D.; Murry, J. A. *J. Org. Chem.* **2003**, *68*, 4598–4599.
3. For a review, see: (a) Stanforth, S. P. In *Comprehensive Heterocyclic Chemistry II*, *527*; Elsevier Science: New York, 1996; pp 527–559. (b) Jacquet, J-P. ; Bouzard, D.; Di Cesare, P.; Dolnic, N.; Massoudi, M.; Remuzon, P. *Heterocycles* **1992**, *34*12, 2301. (c) Jacquet, J.-P.; Bouzard, D.; Di Cesare, P.; Dolnic, N.; Massoudi, M.; Remuzon, P. *Heterocycles* **1992**, *34*12, 2301. (d) Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Gracey, E. H.; Pernet, A. G. *J. Med. Chem.* **1986**, *29*, 2363. (e) Yoon, S. J.; Chung, Y. H.; Lee, C. W.; Oh, Y. S.; Choi, D. R.; Kim, N. D.; Lim, J. K.; Jin, Y. H.; Lee, D. K.; Lee, W. Y. *J. Heterocycl. Chem.* **1997**, *34*, 1021. (f) Chu, D. T. W.; Claiborne, A. K. *J. Heterocycl. Chem.* **1990**, *27*, 1191.
4. Wang, X.; Rabbat, P.; O'Shea, P.; Tillyer, R.; Grabowski, E.J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 4335–4338.
5. Chambers, R. J.; Marfat, A. *Syn. Commun.* **1997**, *27*, 515–520.
6. Song, J. J.; Yee, N. K. *J. Org. Chem.* **2001**, *66*, 605–608.
7. (a) Head, R. A.; Ibbotson, A. *Tetrahedron Lett.* **1984**, *25*, 5939–5942. (b) Scalone, M.; Vogt, P. EP 385210 A2, **1990**. (c) Najiba, D.; Carpentier, J.-F.; Castanet, Y.; Biot, C.; Brocard, J.; Mortreux, A. *Tetrahedron Lett.* **1999**, *40*, 3719–3722.
8. (a) Bessard, Y.; Crettaz, R. *Heterocycles* **1999**, *51*, 2589–2602. (b) Beller, M.; Magerlein, W.; Indolese, A.; Fischer, C. *Synthesis* **2001**, 1098–1109. (c) Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P. G.; Murry, J. A. *Org. Lett.* **2004**, *6*, 2097–2100.
9. Caron, S.; Do, N. M.; Sieser, J. E. *Tetrahedron Lett.* **2000**, *41*, 2299–2302.
10. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.