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Synthesis of a Naphthyridone p38 MAP Kinase Inhibitor

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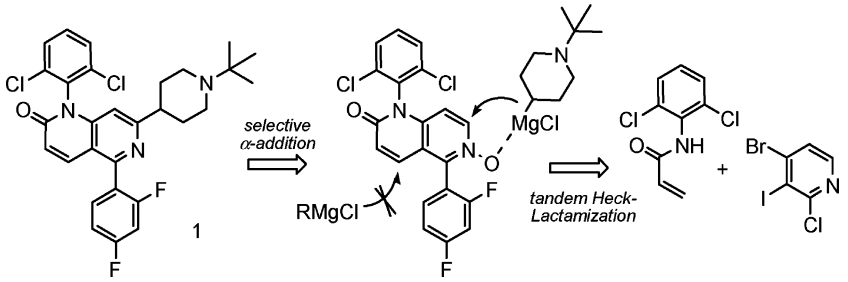

Compound **1** is a p38 MAP kinase inhibitor potentially useful for the treatment of rheumatoid arthritis and psoriasis. A novel six-step synthesis suitable for large-scale preparation was developed in support of a drug development program at Merck Research Laboratories. The key steps include a tandem Heck-lactamization, N-oxidation, and a highly chemoselective Grignard addition of 4-(*N-tert*-butylpiperidinyl)-magnesium chloride to a naphthyridone *N*-oxide. The *N*-oxide exerted complete chemoselectivity via chelation in directing the Grignard addition to the α position as opposed to 1,4-addition on the ene-lactam. The dihydropyridyl adduct was in situ aromatized with isobutylchloroformate followed by heating in pyridine. Syntheses of Grignard precursor, *N-tert*-butyl-4-chloro-piperidine, were accomplished via transamination with a quaternary ammonium piperidone or via addition of methylmagnesium chloride to an iminium ion. Utilizing this chemistry, multi-kilogram preparation of compound **1** was successfully demonstrated.

Introduction

p38 mitogen-activated protein (MAP) kinases are intracellular soluble serine/threonine kinases that positively regulate the production and action of several pro-inflammatory mediators.[1] In particular, the release of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in response to stress is dependent on p38 kinase activity, and therapeutic strategies to target these cytokines have been clinically validated. Biological agents that sequester TNF-α have shown impressive clinical efficacy in the treatment of rheumatoid arthritis (RA), Crohn's Disease, and psoriasis.[2] Despite the success of these biological agents, several important unmet medical needs remain. All of these biological agents must be administered parenterally. They have very long elimination half-lives, so their effects cannot be rapidly withdrawn in the event of an infection. A low molecular weight, orally active cytokine inhibitor would not have these liabilities. In addition, p38α kinase activity is necessary for the upregulation of COX-2 in response to stress.[3] Thus, a p38α inhibitor would be expected to have analgesic effects similar to those of the Coxibs. Several p38 inhibitors are under clinical development at various companies, and the ability of these compounds to inhibit TNFα release in man has been demonstrated.[4]

Research at Merck has identified compound **1** as a potent p38 MAP kinase inhibitor (Figure 1), possessing novel entities outside the scope of other currently known inhibitors with

(1) Chen, Z.; Gibson, T. B.; Robinson, F.; Silvestro, L.; Pearson, G.; Xu, B.; Wright, A.; Vanderbilt, C.; Cobb, M. H. *Chem. Rev.* **2001**, *101*, 2449−2476.

(2) There are currently three TNFα sequestrants marketed in the U.S. (Enbrel, Remicade, and Humira) with additional agents under development. Anakinra, an IL-1 receptor antagonist, has been approved for the treatment of RA.

(3) Lee, J. C.; Badger, A. M.; Griswold, D. E.; Dunnington, D.; Truneh, A.; Votta, B.; White, J. R.; Young, P. R.; Bender, P. E. *Ann. N.Y. Acad. Sci.* **1993**, *696*, 149−170.

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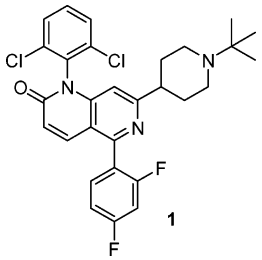
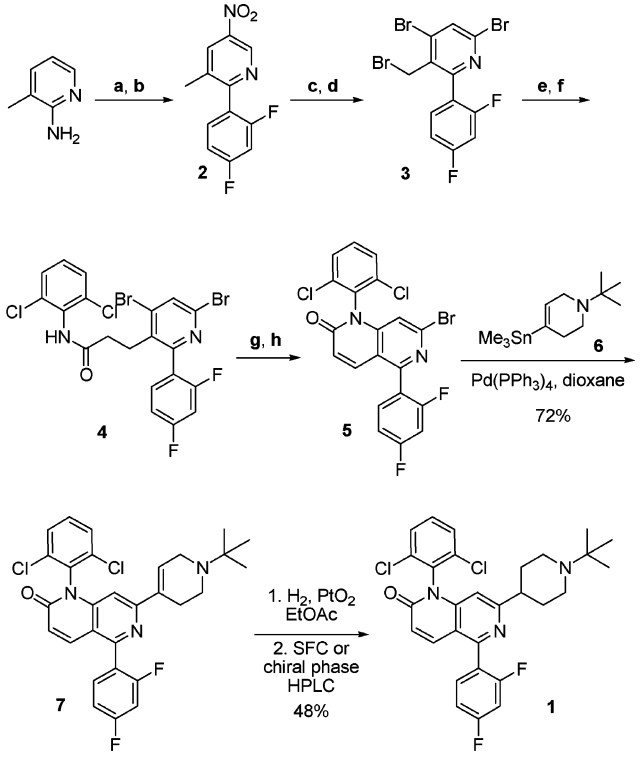


1

FIGURE 1. p38 MAP kinase inhibitor **1**.

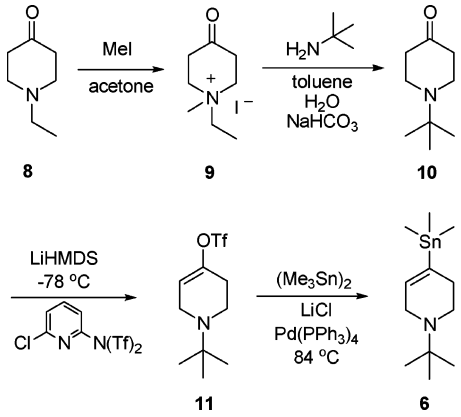
SCHEME 1. Early Synthesis of 1



(a) (i) HNO_3; (ii) $NaNO_2$; (iii) $POCl_3$; 52% (b) $ArB(OH)_2$, Cs_2CO_3, $Pd(PPh_3)_4$, toluene, MeOH, H_2O; 87%(c) (i) RaNi; (ii) Br_2, HCl; (iii) *t*BuONO; 38% (d) NBS, $(BzO)_2$, CCl_4; 81% (e) *t*BuOAc, LiHMDS, THF, -78 °C; 65% (f) (i) TFA, anisole; (ii) TMS-CH_2N_2, C_6H_6, MeOH; (iii) $AlMe_3$, CH_2Cl_2, dichloroaniline; 93% (g) CuI, K_2CO_3, DMF, 160 °C; 75% (h) (i) NBS, AIBN, CCl_4, heat; (ii) DBU; 92%.

increased potency in whole blood and much improved physicochemical properties.[5] The compound contains a naphthyridone core, which retained the desired selectivity.[6] The lipophilic *tert*-butyl piperidine moiety attached to the naphthyridone core greatly improved whole blood and in vivo activity. The *tert*-butyl group proved to be optimal for moderating rates of metabolism and improving pharmacokinetic properties.[7] Compound **1** also has excellent selectivity against other kinases.

SCHEME 2. Early Synthesis of Stannane 6



8 **9** **10** **11** **6**

Specifically, the 2,4-difluorophenyl ring occupies a hydrophobic pocket near Thr-106 that is much smaller in most other kinases, and the amide carbonyl forms a unique double hydrogen bond with the protein backbone. This particular sequence of amino acids, which is necessary for binding **1** with high affinity, is unique to p38α and p38*β* kinases. To further the studies of this compound, we needed an efficient synthesis that would be amenable to large-scale synthesis.

An early synthesis[5] of **1** involved an 18-step synthetic procedure in its longest linear sequence with an overall yield of approximately 2% (Schemes 1 and 2). In this synthesis, naphthyridone **5** was prepared in 15 steps from 2-amino-3-methylpyridine via lactamization of pyridine **4** followed by olefin introduction. The *N-tert*-butyl piperidine moiety was installed via a Stille coupling using unsaturated piperidinyl stannane **6**, followed by a double bond hydrogenation. This hydrogenation suffered low yield due to competing lactam olefin reduction and dechlorination, which produced a mixture of products and required chromatographic purification. Stannane **6** was prepared in four steps from *N*-ethyl-4-piperidone employing hexamethyldistannane in the final step. The synthesis and the use of stannane **6** for the installation of *N-tert*-butyl-4-piperidine constituted major drawbacks in this synthesis. It is clear that to have an efficient large-scale synthesis of **1**, we needed a streamlined synthesis of the naphthyridone core and a "greener" means of preparing and installing the *N-tert*-butyl-4-piperidine in such a way that it avoids toxic tin reagents, the subsequent hydrogenation, and the chromatographic purification.

As previously noted, the sp^2-sp^2 Stille coupling route suffered from the necessary reduction steps. Thus, alternate protocols for introducing the piperidine moiety via a sp^3-sp^2 coupling were preferred. Because alkyl Grignard reagents have been known to add to pyridine,[8] pyridine *N*-oxide,[9,10] and 2-halopyridine[11] with or without activation or transition metal

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(8) (a) Gilman, H.; Eisch, J.; Soddy, T. S. *J. Am. Chem. Soc.* **1959**, *81*, 4000−4003. (b) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315−4319. (c) Comins, D. L.; Stroud, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151−157. (d) Comins, D. L.; Myoung, Y. C. *J. Org. Chem.* **1990**, *55*, 292−298. (e) Nishiwaki, N.; Minakata, S.; Komatsu, M.; Ohshiro, Y. *Chem. Lett.* **1989**, 773−776. (f) Webb, T. R. *Tetrahedron Lett.* **1985**, *26*, 3191−3194. (g) Al-Arnaout, A.; Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1987**, *333*, 139−153. (h) Kim, Y.-C.; Jacobson, K. A. *Synthesis* **2000**, 119−122. (i) Fakhfakh, M. A.; Fanck, X.; Fournet, A.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2001**, *42*, 3847−3850.

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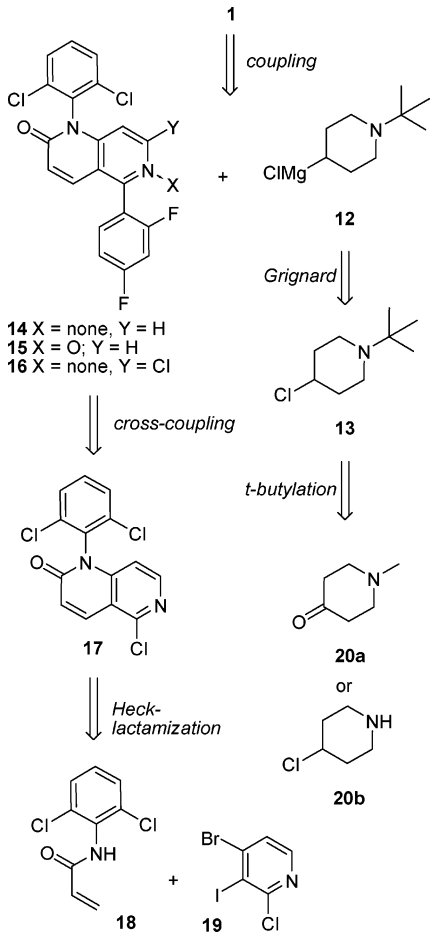
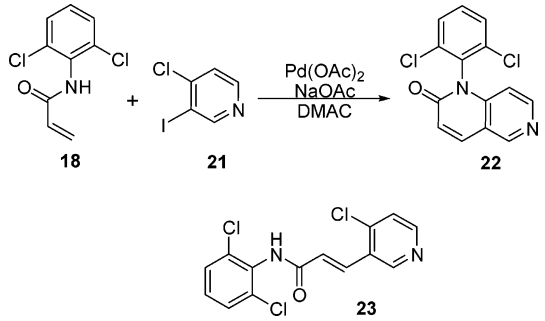
SCHEME 3. Retrosynthetic Analysis of 1

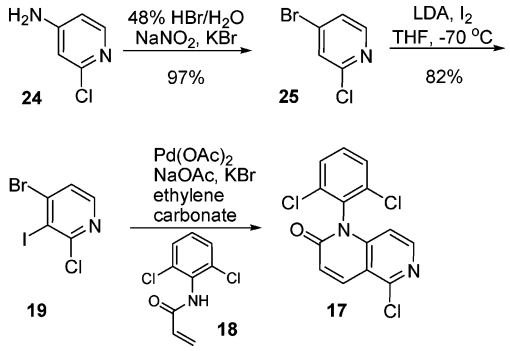


catalysis, we envisioned that Grignard reagent **12**[12] derived from 4-chloro-*N*-*tert*-butyl-piperidine **13** would be ideal for such direct coupling with either naphthyridone **14**, *N*-oxide **15**, or chloronaphthyridone **16**, preferably without heavy metal catalysis (Scheme 3). Compounds **14**−**16** in turn may be accessible from **17** via a Suzuki−Miyaura arylation.[13] Naphthyridone **17** bearing the appropriate substituents could be constructed by our recently discovered Heck-lactamization[14] process from acrylamide **18** and trihalopyridine **19**. Described herein are the results

SCHEME 4. Heck-Lactamization of Acrylanilide 18 with 3-Chloro-4-iodo-pyridine



SCHEME 5. Synthesis of Naphthyridone 17



from efforts to develop this synthetic strategy into a practical chemical synthesis that could be utilized for multi-kilogram production.

Results and Discussion

Tandem Heck-Lactamization. In route development exploratory experiments, the Heck coupling of 2,6-dichlorophenylacrylamide (**18**)[15] with 4-chloro-3-iodopyridine (**21**) was examined to discover any difficulties in the Heck coupling with *N*-arylacrylamides, because no known Heck coupling reaction using *N*-arylacrylamides was known to us (Scheme 4). Reaction in dimethylacetamide (DMAC) at 130 °C in the presence of $Pd(OAc)_2$ was slow and produced many products, including one of very particular interest, naphthyridone **22**, which was isolated in 5% yield. This product was not anticipated because Heck product **23** was not expected to cyclize due to the trans orientation of the olefin.

Wishing to examine the potential of this reaction, and desiring to prepare a synthetically useful intermediate for the synthesis of **1**, the coupling of acrylanilide **18** with tri-halosubstituted pyridine **19** was explored (Scheme 5). The preparation of 2,6-dichlorophenylacrylamide (**18**) from acryloyl chloride and 2,6-dichloroaniline, initially performed in methylene chloride in the presence of TEA, gave only a 40% yield of product. This

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(11) (a) Thorsett, E. D.; Stermitz, F. R. *J. Heterocycl. Chem.* **1973**, *10*, 243−244. (b) Füerstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863. (c) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609−612. (d) Wallace, D. J.; Chen, C. *Tetrahedron Lett.* **2002**, *43*, 6987−6990. (e) Thomson, C. G.; Beer, M. S.; Curtis, N. R.; Diggle, H. J.; Handford, E.; Kulagowski, J. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 677−680. (f) Corley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J.; Boice, G. *J. Org. Chem.* **2004**, *69*, 5120−5123. (g) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240−1241.

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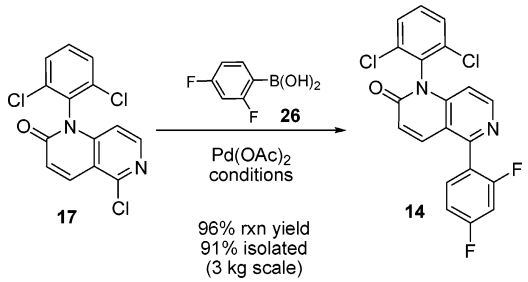
(15) Cvetovich, R. J.; DiMichele, L. *Org. Process Res. Dev.* **2006**, *10*, 944−946.

SCHEME 6. Suzuki−Miyaura Coupling of 17 and 26

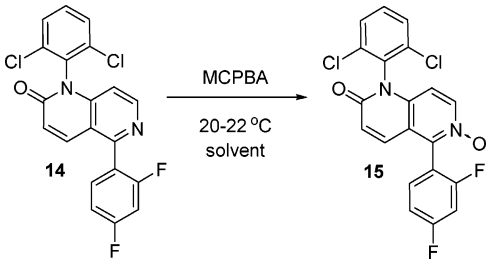


was due mainly to the insolubility of the dichloroaniline hydrochloride salt that formed. So, DMF was used as the solvent. In the absence of added bases, such as TEA, the reaction achieved 50% conversion at 20 °C and 100% conversion by warming to 60 °C. However, acrylanilide **18** was prone to polymerization at these temperatures. In exploring other solvents, the reaction was performed in dimethylacetamide (DMAC). In this solvent, the reaction was accomplished rapidly at 15−20 °C. No polymerization was observed, even when heated to 80 °C. When acryloyl chloride was identified as a disadvantageous cost factor ($300/kg), acrylic acid ($6/kg) was dissolved in DMAC to which thionyl chloride ($3/kg) and then 2,6-dichloroaniline were added at −5 °C, warmed to 20 °C, and then product was precipitated by the addition of water to produce acrylanilide **18** in 92% isolated yield.

Pyridine **19** was prepared from 4-amino-2-chloro-pyridine (**24**) in two steps. Specifically, Sandmeyer bromination of **24** followed by lithiation-iodination of dihalopyridine **25** afforded trihalide **19** in 80% overall yield. Initial coupling reactions of halopyridine **19** and acrylanilide **18** in DMAC at 130 °C were slow, but did produce naphthyridone **17** in 10−15% yield. The major product was bis-Heck coupling at the iodo- and bromo-positions on the pyridine, and the presence of mono-Heck product was detected in very small amount. Improvements in the formation of the desired product resulted with the switch to ethylene carbonate as solvent along with the addition of potassium bromide and small amounts of water. Treatment of **19** with 2,6-dichlorophenylacrylamide (**18**) in ethylene carbonate at 90−100 °C in the presence of $Pd(OAc)_2$, NaOAc, and KBr afforded the tandem Heck-lactamization and produced key naphthyridone **17** in 80% yield on lab scales (1−10 mmol) and 65% on kilogram scales.[14] The formation of naphthyridone **17** did not appear to be dependent on the formation of mono-Heck product, and indeed its independent synthesis and subsequent exposure to the coupling conditions failed to produce naphthyridone. Instead, it produced bis-Heck product in the presence of acrylanilide **18**, and only decomposition in its absence. The use of phosphine-based ligands resulted in polymerization of acrylanilide **18** and produced little naphthyridone or Heck products.

Suzuki Coupling. The Suzuki−Miyaura coupling between chloro-naphthyridone **17** and difluorophenyl boronic acid (**26**) was initially carried out in refluxing toluene using $Pd(dppf)Cl_2$ as the coupling catalyst. This reaction required the use of 2−2.5 equiv of boronic acid **26** to achieve complete consumption of chloronaphthyridone **17**. It was subsequently found that under biphasic conditions using 1 mol % $Pd(OAc)_2$, 3 mol % Ph_3P, 10 mol % KCl, 10 mol % tetrabutylammonium chloride, toluene, and aqueous Na_2CO_3 at 90 °C for 3 h (Scheme 6), the reaction could be completed with the use of 1.5 equiv of boronic acid **26**, affording **14** in 96% reaction yield and 91% isolated yield after crystallization on 3 kg scale. Although the goal was to reduce the use of expensive commercial boronic acid, this was partially offset with the use of tetrabutylammonium chloride. The preparation of boronic acid **26** from the corresponding bromide and isopropylborate produced boronic acid that resulted in faster reactions requiring less of the reagent. The rate acceleration was traced to the presence of isopropyl alcohol in the reaction mixture. Subsequently, simpler conditions were developed that afforded the same yields accomplished above using 1 mol % $Pd(OAc)_2$, 2 mol % Ph_3P, Na_2CO_3 in 2-propanol, using only 1.1 equiv of boronic acid **26**.

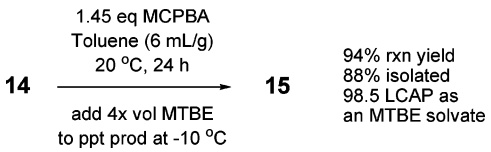
TABLE 1. N-Oxidation Solvent Screen



entry	solvent	concentration (mL/g)	MCPBA (equiv)	rxn time (h)	*N*-oxide (mol %)
1	CH_2Cl_2	6	2	16	97.6
2	CH_2Cl_2	6	1.5	16	97.0
3	acetone	10	1.75	26	85.2
4	acetone	10	1.5[a]	168	12.8
5	toluene	6	1.45	24	96.6
6	THF	6	1.5	24	92.2

[a] Oxone as oxidant.

SCHEME 7. Optimized N-Oxidation Conditions



N-Oxidation Reaction. With **14** in hand, the N-oxidation reaction was screened with respect to oxidants. Initial attempts to oxidize **14** using MCPBA in acetonitrile at 55−60 °C resulted in a maximum of 88% conversion. Subsequent control studies revealed that *N*-oxide **15** was unstable at elevated temperatures in that it tended to revert back to starting material.[16] Therefore, the N-oxidation was best performed at 22 °C. A solvent screen identified several leads. The best conversion (97.6%) was attained using CH_2Cl_2 and 2 equiv of MCPBA at 22 °C overnight (Table 1, entry 1). Because CH_2Cl_2 is generally avoided in large-scale reactions, toluene was used on large scale, achieving a 96.6% conversion (see Table 1, entry 5) and a reaction yield of 96%. A highly streamlined isolation was also developed to take advantage of the low solubility of **15** (1 mg/mL) and high solubility of MCBA (110 mg/mL) in MTBE. Thus, four volumes of MTBE were added as anti-solvent to the reaction mixture (Scheme 7), and by stirring at −10 °C, crystalline **15** was obtained as an MTBE solvate, free of MCBA, in high yield and excellent purity (98.5 LCAP; 93% recovery).[17] The overall isolated yield for the step was 88% on 2 kg scale.

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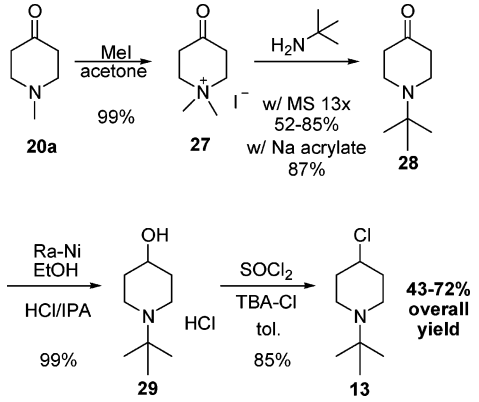
SCHEME 8. Preparation of Chloride 13 via Transamination (Method 1)



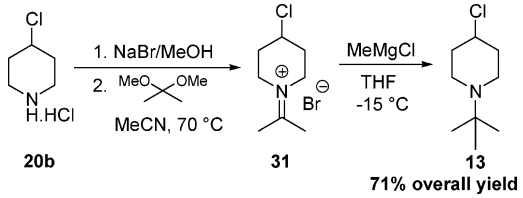
Treatment of *N*-oxide **15** with $POCl_3$ then produced chloronaphthyridone **16** in 85% yield.[18]

Synthesis of 4-Chloro-1-*tert*-butylpiperidine (13). 4-Chloro-*N*-*tert*-butylpiperidine was prepared from *N*-methyl-4-piperidone (method 1) or from 4-chloropiperidine (method 2).[19] In the first method, the *tert*-butyl group was installed via transamination of quaternary salt **27** with *tert*-butylamine to afford *N*-*tert*-butyl-4-piperidone (**28**) (Scheme 8). For this reaction, we found efficient and rapid removal of dimethylamine was crucial for high yield due to product instability. Removal of dimethylamine via physical means such as molecular sieve 13X, K_2CO_3, or distillation worked well on small to mid-scales. Yet on multi-kilogram scale, for example, molecular sieve 13X method gave lower yields (52% distilled isolated yield on 35 mol scale vs 77% on 1 mol scale) due to decomposition from the extended reaction time required. This is presumably due to a smaller surface-to-volume ratio in a conventional scale-up set up. After the scale-up, we found sodium acrylate to be an excellent, selective dimethylamine Michael acceptor over *tert*-butylamine. Under an optimized condition with water as the solvent, this reaction was demonstrated on 100 g scale in 87% isolated yield.

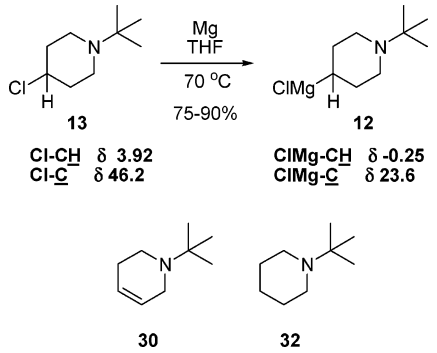
Product **28** obtained from the above reactions was then subjected to a Raney Ni reduction to afford hydroxy piperidine **29** in 98% yield. Conversion of **29** to chloride **13** using thionyl chloride was initially met with difficulties with as much as 50% yield of olefin **30** being generated. Subsequently, **13** was prepared in 85% yield in the presence of 0.5 equiv of tetrabutylammonium chloride (TBAC), which suppressed the formation of elimination product **30** (2%), presumably via trapping the intermediate carbonium ion. This step was successfully demonstrated on multi-kilogram scale, and the crude product could be used for Grignard generation without further purification (Scheme 10). The overall yield for the four-step process was 65−70%, and the only potential issue for this route was the high cost of TBAC used in the chlorination step.

As an alternate route to **13**, we explored the generation of a *tert*-butyl group by the reaction of a dimethyliminium salt

SCHEME 9. Preparation of Chloride 13 via Iminium Ion (Method 2)



SCHEME 10. Grignard Formation and NMR Chemical Shifts of 12 and 13 in THF-d_8



prepared from 4-chloropiperidine with methyl Grignard (Scheme 9). The advantage of this iminium route is that the starting material already contains the halogen, obviating the need for the carbonyl reduction/alcohol chlorination sequence used in the piperidone-based route. Initial work determined that hydrochloride salt **20b** itself would not undergo iminium formation due to insufficient solubility. Examination of alternative acid salts revealed that the triflic acid and hydrogen bromide salts both gave efficient iminium formation. The latter was chosen for further development because of its useful physical properties. Iminium bromide **31** can be isolated by simple filtration of the reaction mixture and is relatively stable in the absence of water. A through-process was developed in which hydrochloride salt **20b** is subjected to counterion exchange with sodium bromide and then converted to iminium salt **31** in the same pot. Treatment of **31** with methylmagnesium chloride in THF at −15 °C was found to afford good yields of **13** along with 5−10% of 4-chloropiperidine, which can be separated during extraction by treatment with mild acid. The secondary amine side-product results from deprotonation of iminium salt **31** to give an enamine (observed by NMR) that is hydrolyzed upon aqueous workup. This iminium route was demonstrated in multiple runs of 50−100 g. Piperidine **13** was isolated in 71% overall yield by aqueous workup and was obtained in high purity (99% by GC).

Grignard Formation. The Grignard formation of 4-chloro-*N*-*tert*-butylpiperidine (**13**) using magnesium metal was best initiated by addition of 5−10 mol % of isopropylmagnesium chloride[20] and heating the mixture in refluxing THF for 2−5 h to consume all starting material. Typically, starting from a 90:10 mixture of **13** and olefin **30**, the yield of Grignard **12** was about 90% as an 84:8:8 mixture of **12**, **30**, and **32** based on NMR and titration analyses. The NMR chemical shifts of the carbon and proton next to magnesium chloride in **12** were significantly upfield shifted relative to the chloro **13**, consistent with reported values (Scheme 10).

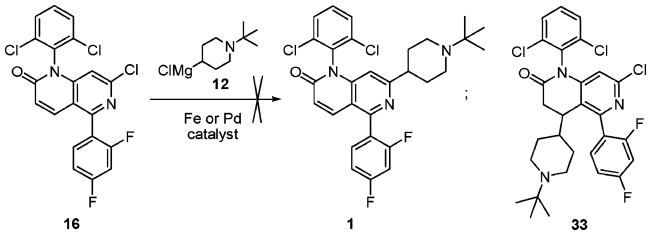
(17) Naphthyridone *N*-oxide **15** MTBE solvate exhibited an exotherm of 111.6 cal/g with an initiation temperature of 163 °C. The differential thermal analyzer also detected an exotherm starting at ∼160 °C. The compound is not shock sensitive based on drop weight measurements.

(18) Compound **16** has also been prepared by an alternate route: Chung, J. Y. L.; Cai, C.; McWilliams, J. C.; Reamer, R. A.; Dormer, P. G.; Cvetovich, R. J. *J. Org. Chem.* **2005**, *70*, 10342−10347.

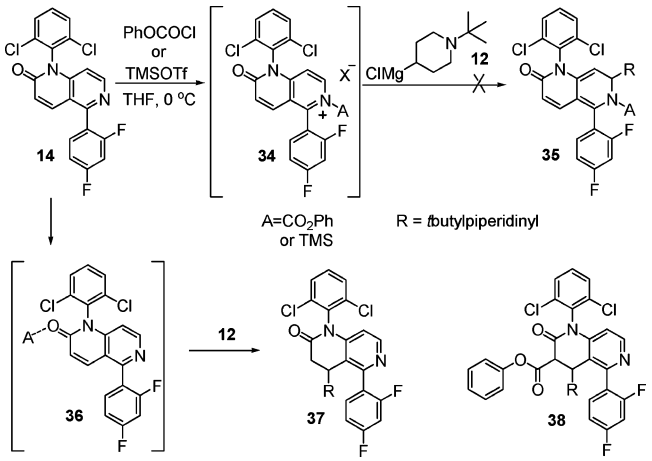
(19) (a) Amato, J. S.; Chung, J. Y. L.; Cvetovich, R. J.; Reamer, R. A.; Zhao, D.; Zhou, G.; Gong, X. *Org. Process Res. Dev.* **2004**, *8*, 939−941. (b) Amato, J. S.; Chung, J. Y. L.; Cvetovich, R. J.; Gong, X.; McLaughlin, M.; Reamer, R. A. *J. Org. Chem.* **2005**, *70*, 1930−1933.

(20) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320.

SCHEME 11. Attempted Cross Coupling



SCHEME 12. Reaction of 14 and Grignards with TMSOTf or Phenyl Chloroformate

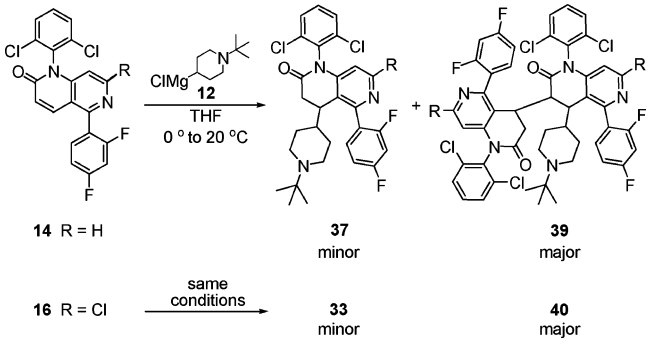


The "all-in" nature of this Grignard preparation necessitated a safety assessment before this step could be run in large scale. The results from the calorimetry study indicated that the Grignard formation generated a steady output of heat over a 3 h period and was therefore unlikely to suffer a thermal runaway. Consequently, a large run (11.4 mol scale) was conducted following the same "all-in" protocol. Unlike small-scale lab runs of this reaction, no isopropylmagnesium chloride was required to initiate Grignard formation, and after several hours at reflux a dark brown solution of desired Grignard **12** was furnished. NMR analysis showed that olefin **30** had increased from 2% to around 10% during Grignard formation. Titration assay of the Grignard solution gave a concentration of 0.52 M (versus an expected 0.6 M) for an 87% yield.

Installation of *N*-*tert*-Butylpiperidine. With both piperidine Grignard **12** and naphthyridone **14**−**16** in hand, we proceeded to study the coupling of these two pieces. Initial cross-coupling studies of chloro-naphthyridone **16** with isopropylmagnesium chloride or Grignard **12** under Fe or Pd catalysis did not give the desired products. Instead, the 1,4-addition product, lactam **33**, was the major product (Scheme 11).

We then turned our attention to substrate **14**. Activation of pyridine nitrogen of **14** using phenyl chloroformate or *tert*-butyldimethylsilyl triflate followed by the addition of Grignard reagents **12** was studied (Scheme 12). In all cases, the desired products (e.g., **35**) were not obtained. Again, the 1,4-addition adducts were the main products: saturated amide **37** when the silicon activator was used, and compound **38** in the case of chloroformate. Possibly, the strongly electron-withdrawing difluorophenyl group rendered the pyridine nitrogen less reactive than the lactam oxygen in these examples. Additionally, the reaction utilizing the bulky silicon activator cleanly produced **37**, a fact probably attributable to the combined effects of the oxophilic character of silicon and the sterically encumbered environment around the pyridine nitrogen, both favoring selective activation of the ene-lactam system.

SCHEME 13. Reactions of Compounds 14 and 16 with Grignard 12



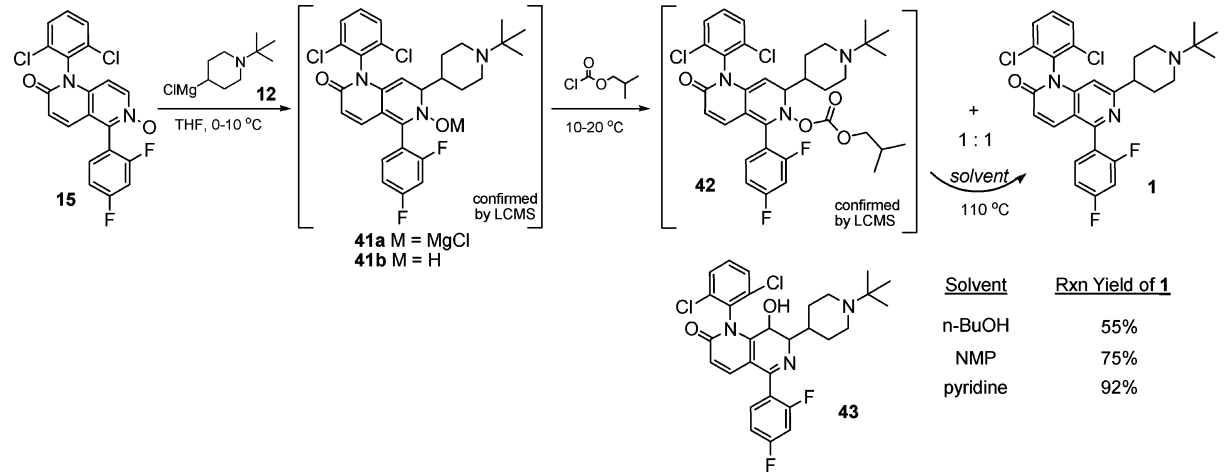
Next, additions of Grignard **12** to these substrates without activation were investigated (Scheme 13). In the reactions with **14** and **16**, the major products were dimeric adducts **39** and **40**, respectively, based on LC/MS analysis. It appeared that 1,4-addition is still the preferred pathway, and the resulting enolate intermediates, which previously were quenched by trimethylsilyl triflate or the chloroformate, now underwent a second 1,4-addition to produce the proposed dimeric structures in Scheme 13.

Significantly, when *N*-oxide **15** was treated with 1.1 equiv of Grignard **12**, the reaction proceeded in a titration-like manner to give a single product identified as dihydropyridine **41a** by LC/MS analysis (Scheme 14). Attempts to isolate **41b** from the deep burgundy solution led to significant decomposition, which is not surprising because dihydropyridines are air-unstable. Various in-situ dehydrating conditions (refluxing THF, solid NaOH, aqueous HCl) and reagents (MsCl, Me_2NCOCl, Ac_2O, TMSCl) were examined to aromatize the dihydropyridine ring. Isobutyl chloroformate was found to be the best activator, which when added to **41a** rapidly made a ∼1:1 mixture of **1** and carbonate **42** (identified by LC/MS, but not isolated). Reversing the order of Grignard and isobutyl chloroformate addition led to poorer yields. Addition of KO*t*Bu or NaOEt to this 1:1 mixture did not improve the yield of **1**. Heating at 110 °C in *n*BuOH consumed **42** but did not yield additional **1**; instead, alcohol **43** was formed in significant amounts (which was crystallized and confirmed by NMR and LC/MS). Heating in *N*-methylpyrrolidone (NMP) at 110 °C gave an improved 75% reaction yield along with several impurities. Ultimately, switching the solvent to pyridine and heating at 110 °C for 9 h afforded **1** in 92% reaction yield!

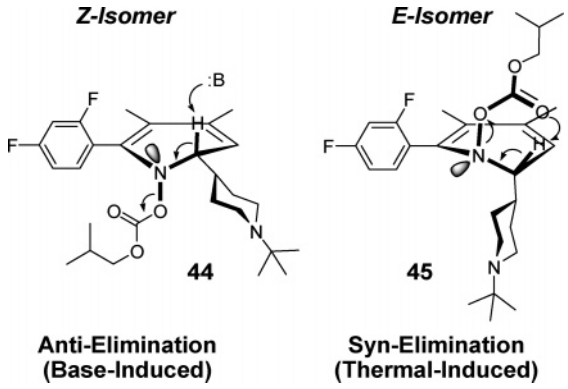
These observations could be rationalized by the supposition that **42** exists as a 1:1 mixture of *E* and *Z* isomers with respect to the carbonate and the piperidyl groups (Scheme 15). The *Z*-carbonate can undergo a base-induced anti-elimination at low temperatures, whereas anti-elimination is not possible for the *E*-carbonate and requires a syn-elimination via thermolysis.

An efficient isolation and purification of **1** from the Grignard-thermolysis reaction mixture was also developed. The crude **1** HCl salt was directly crystallized from the reaction mixture in 99% recovery by adding aqueous NH_4Cl solution. The organic phase efficiently removed many impurities and color. The free base was prepared with aqueous Na_2CO_3 and extraction with IPAC, whereupon **1** crystallized in 92% recovery and 80% overall isolated yield from *N*-oxide **15** with a purity of >98.5% by HPLC. The structure of **1** was confirmed via NMR and

SCHEME 14. Conversion of *N*-Oxide 15 to Compound 1



SCHEME 15. Elimination Pathways of Carbonate 42



single-crystal X-ray analysis. This process was successfully demonstrated on multi-kilogram scale.

In summary, we have developed an efficient synthesis of **1** that is amenable for large-scale synthesis. The key steps included a tandem Heck-lactamization and a highly efficient *tert*-butylpiperidinyl Grignard addition to naphthyridone *N*-oxide. The *N*-oxide exerted complete chemoselectivity via chelation in directing the Grignard addition to the α position as opposed to a 1,4-addition on the ene-lactam. The optimized conditions to aromatize the dihydropyridine intermediate were achieved with isobutylchloroformate followed by thermolysis in pyridine. The Grignard precursor, *N*-*tert*-butyl-4-chloro-piperidine, was efficiently prepared by a transamination method or via a methyl Grignard addition to the iminium ion. Utilizing this chemistry, multi-kilogram preparation of the crystalline compound **1** was successfully demonstrated.

Experimental Section

Suzuki−Miyaura Coupling. Preparation of 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one (14) (Method 1). A 72 L, round-bottom flask equipped with a mechanical stirrer, thermocouple, condenser, and N_2 inlet was charged sequentially with toluene (15.6 L), chloronaphthyridone **17** (3.00 kg, 9.23 mol), tetrabutylammonium chloride (264 g, 0.95 mol), KCl (70.8 g, 0.95 mol), 2,4-difluorophenyl boronic acid (1.81 kg, 11.46 mol), $Pd(OAc)_2$ (20.7 g, 0.092 mol), PPh_3 (72.5 g, 0.277 mol), and additional toluene (4 L). The mixture was degassed three times by cycling vaccum/N_2, and stirred for 15 min at rt under N_2. The slurry was cooled to 10 °C with an ice−water bath. Na_2CO_3 (2.97 kg, 28.02 mol) and water (15 L) were added (an exotherm to 20 °C was observed), and the slurry was heated to reflux (∼90 °C).

The progress of the reaction was followed by HPLC condition A (see Supporting Information), and the reaction was stopped when the chloronaphthyridone **17** was < 0.1%. When the reaction was complete (about 2−2.5 h), the solution was cooled to 32 °C, and CH_2Cl_2 (11 L) was added. The solution was filtered through 0.86 kg of Solka Floc to remove palladium. The reactor was rinsed with toluene (12 L), which was then passed through the Solka Floc. The filtrate was transferred to a 100 L extractor and the phases separated. The organic layer was washed with 10% aqueous NaCl (16 L), then water (10 L). The organic layer was assayed via HPLC (96% yield), and the solution was concentrated to dryness.

EtOAc (16.5 L) was charged to the crude product (4.3 mL/g), and the mixture was heated to 70 °C to dissolve all solids. After 20 min at 70 °C, the solution was cooled to 0 °C, and crystallization ensued, aged for 2 h, and filtered. The wet cake was washed with cold EtOAc (3 × 1.7 L) and vacuum-dried at 50 °C overnight under a stream of N_2 to afford 3.39 kg (91%) of compound **14**: ^{1}H NMR ($CDCl_3$) δ 8.54 (d, J = 5.8, 1H), 7.73 (dd, J = 3.5, 10.0, 1H), 7.65−7.55 (m, 3H), 7.49 (dd, J = 7.6, 8.7, 1H), 7.10 (dt, J = 2.0, 8.1, 1H), 7.02 (dt, J = 2.0, 9.8, 1H), 6.80 (d, J = 10.0, 1H), 6.45 (d, J = 5.8, 1H); ^{13}C NMR ($CDCl_3$) δ 164.0 (dd, J_{CF} = 12.0, 251.7), 160.2, 160.0 (dd, J_{CF} =12.0, 251.7), 154.0, 149.8, 145.1, 138.1 (d, J_{CF} = 3.1), 135.1, 133.3 (dd, J_{CF} = 4.5, 9.8), 132.4, 131.5, 129.6, 123.5, 122.4 (dd, J_{CF} = 3.9, 15.3), 115.3, 112.4 (dd, J_{CF} = 3.8, 21.5), 108.6, 104.6 (t, J_{CF} = 25.6); ^{19}F NMR ($CDCl_3$) δ −108.0 (d, J_{FF} = 8.6), −110.6 (d, J_{FF} = 8.6); HRMS m/z $[M + H]^+$ calcd for $C_{20}H_{11}Cl_2F_2N_2O$ 403.0216, found 403.0215.

Suzuki−Miyaura Coupling (Method 2). A 250 mL, round-bottom flask equipped with a magnetic stirrer, thermocouple, and N_2/vacuum inlet adapter was charged sequentially with chloronaphthyridone **17** (3.91 g, 12.0 mmol), 2,4-difluorophenylboronic acid (2.27 g, 14.4 mmol), $Pd(OAc)_2$ (26.9 mg, 0.12 mmol), Ph_3P (94.3 mg, 0.36 mmol), Na_2CO_3 (2.54 g, 24.0 mmol), and 2-propanol (60 mL). The suspension was degassed by cycling vacuum and N_2 three times. The resulting white suspension was aged at 80 °C for 12 h. When the chloronaphthyridone **17** was all consumed (assay by HPLC condition A), the suspension was cooled to 50 °C and acetone (60 mL) was added. The suspension was cooled to 20 °C, and the solids were removed by filtration to provide a brown solution of Suzuki adduct **14** (136 mL containing 4.84 g, 100%). The Pd can be removed by treatment of this solution with silacycle thiol-3, MP-TMT, or Ecosorb C-933. Addition of one volume of water and cooling to 0 °C provided the Suzuki adduct in >95% isolated yield.

Preparation of 1-(2,6-Dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one 6-Oxide (15). A 100 L cylindrical extractor equipped with a mechanical stirrer and thermocouple was charged sequentially with toluene (10.2 L), difluorophenyl-naphthyridone **14** (1.70 kg, 4.21 mol), and 70 wt % MCPBA (1.063 kg,

6.16 mol). A solution results after 15 min at 25 °C. The progress of the reaction was followed by HPLC (condition B), and the reaction was stopped when the difluorophenyl-naphthyridone **14** was less than 4 mol % left. When the reaction was complete (about 18 h), MTBE (40.8 L) was charged to the cloudy mixture. The solution was stirred for 30 min at rt, then cooled to −10 °C and aged for 18 h. When the product concentration in the supernatant was under 2.1 mg/mL, the mixture was filtered and the wet cake was washed with cold MTBE (3 × 5 L). The wet cake was vacuum-dried at rt under a stream of air for 5 h to afford 1882 g of *N*-oxide as a yellow solid. The purity of the solid was 81.5 wt % (88% yield) containing 13.3 wt % MTBE and 3.4 wt % toluene as determined by NMR and HPLC analysis. This material was used as is in the next step. A solvent-free analytical sample was obtained by prolonged vacuum-drying: ^{1}H NMR ($CDCl_3$) δ 8.30 (d, J = 7.5, 1H), 7.63 (m, 1H), 7.61 (m, 1H), 7.45−7.57 (m, 2H), 7.44 (dd, J = 1.0, 10.0, 1H), 7.14 (dt, J = 2.3, 8.2, 1H), 7.09 (dt, J = 2.3, 9.2,1H), 6.85 (d, J = 10.0, 1H), 6.49 (d, J = 7.5, 1H); ^{13}C NMR ($CDCl_3$) δ 164.6 (dd, J_{CF} = 12.3, 253.6), 160.8 (dd, J_{CF} = 12.3, 253.6), 158.9, 142.3, 141.1, 136.3, 135.8, 135.0 (d, J_{CF} = 14.4), 133.2 (dd, J_{CF} = 4.7, 9.6), 131.8, 131.6, 129.7 (d, J_{CF} = 8.0), 125.8, 118.0, 113.7 (dd, J_{CF} = 4.6, 16.0), 112.6 (d, J_{CF} = 3.0), 112.5 (dd, J_{CF} = 3.7, 21.6), 111.5, 105.3 (t, J_{CF} = 25.0); HRMS m/z $[M + H]^+$ calcd for $C_{20}H_{11}Cl_2F_2N_2O_2$ 419.0160, found 419.0165.

Grignard Formation: Preparation of (1-*tert*-Butylpiperidin-4-yl)(chloro)magnesium (12). To a flask containing magnesium metal (291 g, 12.0 mol) was added THF (11.8 L, H_2O < 50 μg/mL). A solution (H_2O < 150 μg/mL) of chloride **13** (30.2 wt % in THF, 6.62 kg, 7.2 L, 11.4 mol) was then added over 5 min. The brown heterogeneous mixture was then heated in 10 °C stages toward 65 °C. At 35 °C, the reaction was initiated and self-heated to 65 °C and began to reflux steadily. The steam bath was then set to maintain reflux for 5 h to ensure complete conversion to Grignard. The resultant dark brown solution of Grignard reagent was then titrated to determine the molarity. Molarity was determined as 0.52 M versus a theoretical 0.6 M (87% yield). Use tests confirmed the reagent was of sufficient quality for use in subsequent steps. See Scheme 9 for partial NMR data in THF-d_8.

Preparation of 7-(1-*tert*-Butylpiperidin-4-yl)-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2(1*H*)-one (1). To a yellow suspension of naphthyridone *N*-oxide **15** (2500 g, 81.5%, 4.86 mol) in THF (24.3 L), cooled to 2 °C, was added 1.1 equiv of Grignard **12** solution (10.3 L, 0.52 M in THF, 5.35 mol) over 1.5 h at <3 °C to give a deep burgundy solution. After being stirred for 1 h at 2−5 °C, the starting material was completely consumed as judged by HPLC (<0.35%; condition C), and 1.5 equiv of isobutyl chloroformate (0.965 L, 7.29 mol) was slowly added over 1.5 h at <8 °C. The mixture was warmed to 20 °C over 1−2 h and aged at this temperature for 1 h, and the resulting orange-red solution was assayed by HPLC to confirm complete consumption of the Grignard adduct intermediate. This THF solution of carbonate **42**/compound **1** could be stored at 20 °C under nitrogen overnight without problem.

THF was distilled (70−95 °C/ambient pressure) and replaced with anhydrous pyridine (17.5 L). The resulting slurry was heated at 110 °C for 10 h. The solution was cooled to 20 °C, LC assayed to confirm the **1** to carbonate **42** ratio was ≥98% (at 210 nm), and concentrated to ≤$^1/_2$ volumes (∼9.5 L) at 30−35 °C/20−25 Torr. Saturated aqueous NH_4Cl (20 L) and water (10 L) were added, and the resulting mixture (pH 8) was adjusted to pH 5.8 with 3 N HCl (∼7.4 L). IPAC (5.8 L) and MTBE (5.8 L) were added, and the mixture was stirred at 20 °C for 1.5 h, and then filtered and washed with $^1/_2$ saturated NaCl solution (7.8 L) and MTBE (7.8 L). The wet cake was vacuum-dried to give ∼4.5 kg of crude **1** HCl salt as a beige solid.

Compound **1** HCl salt was charged into a mixture of IPAC (39 L) and H_2O (23 L), and 3.75 equiv of solid Na_2CO_3 monohydrate (2.26 kg, 18.2 mol) was added (to pH ∼10). After the mixture was stirred at 20 °C for 1 h, the layers were separated, and the organic was washed with H_2O (2 × 23 L) and assayed by HPLC for yield (92%). The organic was filtered, concentrated (10−25 °C /28−30 in. Hg), and then seeded with **1** to induce crystallization if required. The mixture was concentrated and flushed with IPAC until H_2O ≤ 100 ppm. The volume was adjusted such that **1** concentration was ∼0.33 g/L (final vol ∼7.5 L). Heptane (25 L) was slowly added over 4 h to give a target ratio of ∼18% IPAC/heptane and a supernatant concentration of ≤9 g/L. The mixture was stirred at 20 °C overnight, filtered, and washed with 10% IPAC/heptane (10 L). The wet cake was vacuum-dried at 20 °C under N_2 to afford 2.1 kg of **1** free base (80% yield): purity 99.6%; ^{1}H NMR (CD_3CN) δ 7.74 (ddd, J = 9.8, 3.4, 0.8, 1H), 7.71 (d, J = 7.9, 2H), 7.63−7.59 (om, 2H), 7.20−7.14 (om, 2H), 6.65 (d, J = 9.8, 1H), 6.34 (s, 1H), 3.09−3.06 (m, 2H), 2.61 (tt, J = 12.1, 4.2, 1H), 2.10 (td, J = 11.7, 2.3, 2H), 1.77−1.73 (m, 2H), 1.66−1.59 (m, 2H), 1.01 (s, 9H); ^{13}C NMR (CD_3CN) δ 167.9, 164.7 (dd, J_{CF} = 249.0, 12.2), 161.1, 160.9 (dd, J_{CF} = 248.4, 12.2), 154.1, 146.4, 139.6 (d, J_{CF} = 3.1), 135.5, 134.4 (dd, J_{CF} = 9.8, 4.9), 133.3, 133.0, 130.7, 123.8 (dd, J_{CF} = 15.3, 4.3), 122.7, 114.2, 113.1 (dd, J_{CF} = 21.4, 3.7), 106.4, 105.2 (t, J_{CF} = 26.2), 54.3, 47.0, 45.6, 33.7, 26.5; HRMS m/z $[M + H]^+$ calcd for $C_{29}H_{28}Cl_2F_2N_3O$ 542.1577, found 542.1576.

Acknowledgment. We thank Mr. Robert Reamer for assistance with NMR assignments, and Ms. Jennifer Chilenski for obtaining the X-ray structure.

Supporting Information Available: General experimental methods, NMR spectra for compounds **14**, **15**, and **16**, and X-ray crystal structure data in CIF format for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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