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Efficient Synthesis of a Trisubstituted 1,6-Naphthyridone from Acetonedicarboxylate and Regioselective Suzuki Arylation

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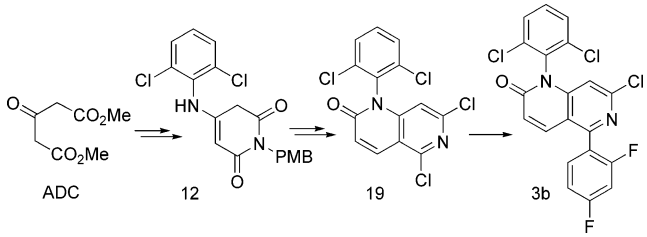

An efficient five-step synthesis of 1,6-naphthyridone **3b**, a p38 mitogen-activated protein (MAP) kinase inhibitor intermediate, in 32% overall yield starting from acetonedicarboxylate (ADC) is described. The synthesis began with a selective monoamidation of ADC dimethyl ester enolate **9**. A novel concomitant enamine formation and an imide cyclization afforded the nitrogen differentially protected enamide imide **12**. Treatment of **12** with KO^{t}Bu and 3-ethoxyacrylate produced lactam **15** quantitatively, which was converted to tetrachloronaphthyridone **19** via a one-pot *p*-methoxybenzyl (PMB) deprotection and bischlorination. A highly regioselective $Pd(OAc)_2$/IMes-catalyzed Suzuki coupling completed the synthesis.

Introduction

1,6-Naphthyridones have recently emerged as important heterocyclic cores present in many biologically active agents. This heterocycle is most notably prevalent in many kinase inhibitors[1] and anti-infective agents[2] and is increasingly adapted in many cardiovascular,[3] central nervous system (CNS),[4] and metabolic-related agents.[5] As a result, the preparation of this heterocycle has become of great interest for the design of potential pharmaceutical agents.[1−6] Recently, our laboratories have disclosed an expedient synthesis of *N*-aryl-substituted naphthyridones **3a** from *N*-aryl pyridinone **2a**, which in turn was prepared from enaminone **1a** and methyl propiolate.[7] Key to the cyclization of sterically hindered *N*-aryl enaminone **1a** with methyl propiolate was the use of solid NaOH (Scheme 1). In connection with our p38 kinase inhibitor program,[8] we were interested in applying this methodology to 2,4-difluorophenyl-substituted enaminone **1b** for the preparation of pyridinone **2b** and ultimately trisubstituted 1,6-naphthyridone **3b**. However, under a variety of reaction conditions, **1b** underwent

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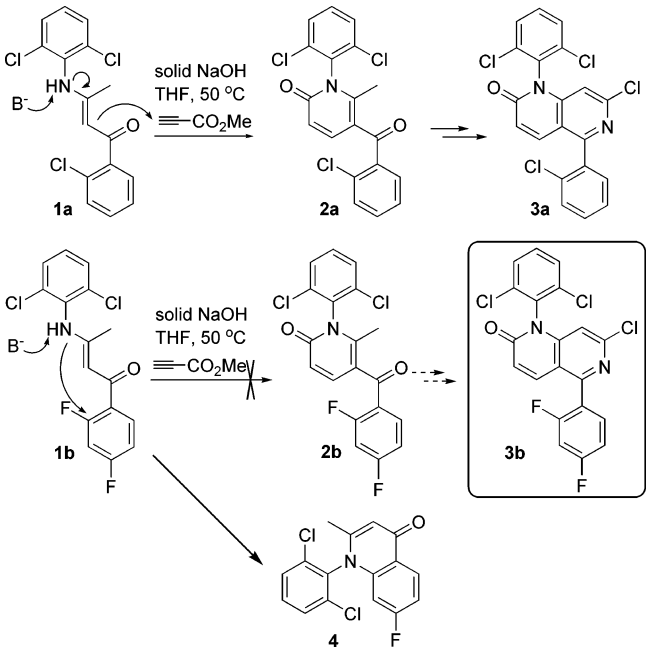
SCHEME 1. Fate of Two Different Aryl Enaminones



predominantly nucleophilic aromatic substitution cyclization, affording quinolinone **4** as the major product.[9]

Results and Discussion

To avoid this problem, we sought to prepare simple enaminones without the difluorophenyl group and install this moiety at a later stage of the synthesis. However, all attempts to form the *N*-aryl enaminones of 3-oxobutanoates or its equivalents such as cyanoacetone and 3-aminocrotonitrile with 2,6-dichloroaniline gave no reaction, presumably because of poor nucleophilicity of the 2,6-dichloroaniline nitrogen.

To remedy this problem, we investigated activated acetonedicarboxylate (ADC) derivatives,[10] which had the added advantage of containing all the carbons required for the B-ring of naphthyridone (Scheme 2). Treatment of ADC with 2,6-dichloroaniline and catalytic TsOH in refluxing toluene with azeotropic removal of water gave initially enamine diester **5**. However, imide formation was competitive and ultimately afforded enamine imide **6** as the major product, which precipitated upon cooling to 22 °C in 51% yield. Formation of imide **6** was a fatal flaw of this approach because, after conversion to imide **8** (Scheme 2), all attempts to excise the dichloroaniline group from imide **8** failed.[11]

To overcome these problems, we turned our attention to the synthesis and the utility of ADC ester amide **10**

SCHEME 2. Bisdichlorophenyl Naphthyridone

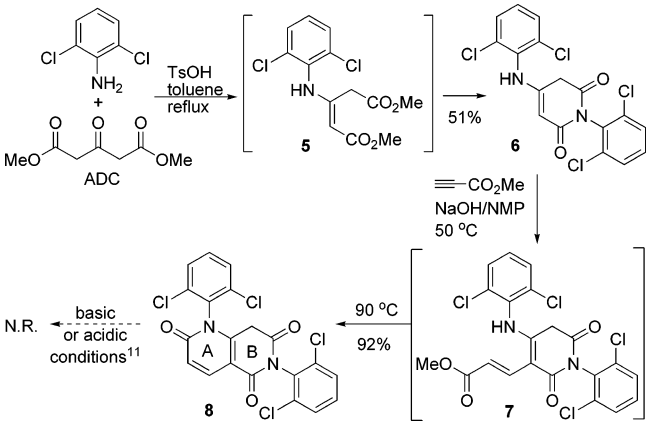
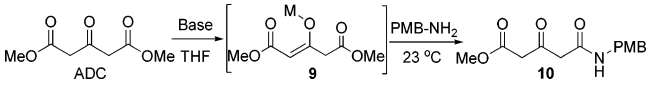
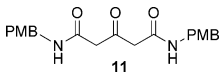


TABLE 1. Monoamidation of ADC Dimethyl Ester



base	M in enolate **9**[a]	enolate **9** solubility in THF at 22 °C	isolated yield **10**
$MgCl_2/NH_4OH$	Mg	+	41%
NaH	Na	++	81%
LiO^{t}Bu	Li	+++	79%
NaO^{t}Bu	Na	++	78%
KO^{t}Bu	K	−	<2%

[a] Magnesium enolate was isolated. All other enolates were generated in situ.



as a way to introduce a removable imide nitrogen protecting group. Methods were investigated to selectively monoamidate ADC dimethyl ester with *p*-methoxybenzylamine (PMB−NH_2) via enolate **9** as a way to differentiate the two esters (Table 1). Initial experiments with the magnesium enolate[12] gave a variable ~50% yield of **10**. The sodium[13] and the lithium enolates generated in situ using NaH, NaO^{t}Bu, or LiO^{t}Bu gave consistently good yields of **10**, whereas the potassium enolate generated with KO^{t}Bu gave almost no reaction. The poor yields for the magnesium and potassium enolates were mainly due to poor solubility in THF. Thus, the one-pot treatment of ADC dimethyl ester with 1.25 equiv of NaH, NaO^{t}Bu, or LiO^{t}Bu in THF followed by 1.05 equiv of PMB−NH_2 afforded ADC ester amide **10** in 80% yield. In these reactions, a small amount (2−3%) of bisamide **11** was also formed, which was removed by simple filtration during extraction.

The condensation of ester amide **10** with 2,6-dichloroaniline (1.2 equiv) in refluxing toluene in the presence of 5 mol % TsOH underwent a concomitant enamine and imide formation to produce imide **12** in 65−68% yield (Scheme 3). Small amounts (5%) of bis(PMB) adduct **13** were also produced but easily removed by crystallization of **12** from acetonitrile. As far as we are aware, this type

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(11) For example, basic conditions, such as aqueous NaOH, NH_4OH, or NH_2NH_2 up to 120 °C or $NaBH_4$, gave no reaction. In fact, the sodium enolate of **8** could be isolated as a solid from the NaOH reaction. Acidic conditions, such as 30% H_2SO_4 or 6 N HCl, gave no reaction at <80 °C and gave complete decompostion at 120 °C, in which only 1,6-dichloroaniline was detected, indicative of total destruction of the naphthyridone ring system.

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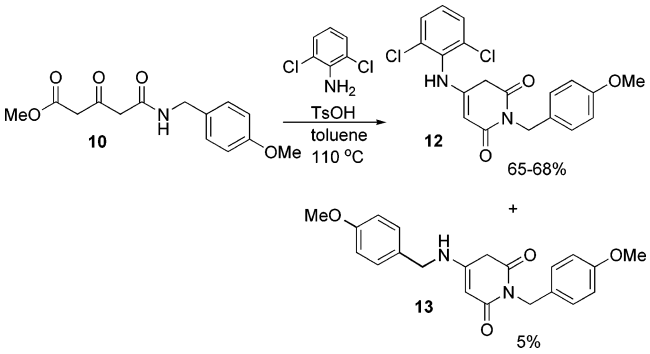
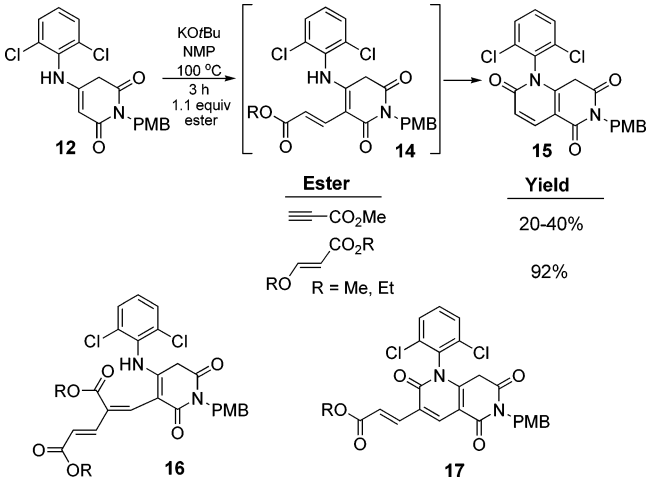
(13) (a) Bertz, S. H.; Rihs, G.; Woodward, R. B. *Tetrahedron* **1982**, *38*, 63−70. (b) Szychowski, J.; Wojtasiewicz, K. *Pol. J. Chem.* **1994**, *68*, 2741−2743.

SCHEME 3. Enamine Imide Formation



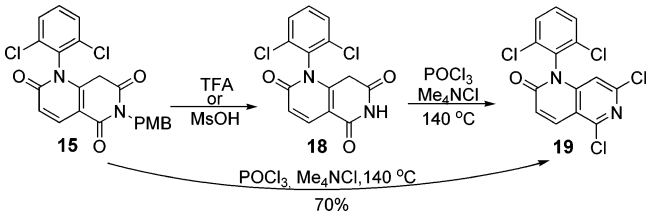
SCHEME 4. Annulation of Lactam Ring



of reaction is unprecedented. We have observed that, when a solution of **10** was washed only once with aqueous HCl solution during its isolation, compound **13** was produced as the major product. When a solution of **10** was washed three times with aqueous HCl solution, then the amount of **13** was reduced to 5%. Presumably, this is due to the organic solubility of the sodium enolate, which could undergo self-condensation and release PMB–NH_2. It is known that acetonedicarboxylate diester self-condenses at elevated temperatures to produce phenolic products only when alkali metals are present.[14]

With **12** in hand, annulation of the lactam ring with methyl propiolate was carried out in a fashion similar to that for **6**–**8** (Scheme 4). However, the formation of large amounts of the double-addition adducts **16** and **17** resulted in only 20–40% yields of the desired **15**. This is most likely due to the less sterically demanding PMB group in **14** relative to 2,6-dichlorophenyl in **7** and the high reactivity of methyl propiolate. To address this problem, we examined the less reactive methyl 3-methoxyacrylate and ethyl 3-ethoxyacrylate. Gratifyingly, the reaction of **12** with these two acrylates in NMP with KO*t*-Bu gave clean reactions, and the desired product **15** was obtained in >90% yield. These acrylates are at least an order of magnitude less expensive than methyl propiolate, and the ADC route also eliminated the use of expensive Bredereck's reagent ($(Me_2N)_2CHOCMe_3$) which was used in the open-chained enaminones method for the conversion of **2a** to **3a**.

SCHEME 5. PMB Deprotection–Bischlorination



The optimized condition involves slow addition of 1.1 equiv of ethyl 3-ethoxyacrylate to a solution of **12** and 1.4 equiv of KO*t*Bu/THF in NMP at 100 °C and aging for 3 h to complete the cyclization of **14**. After dilution with water and adjustment to pH 2, naphthyridone **15** precipitates from the mixture in 92% yield.

Removal of the PMB group in naphthyridone **15** was achieved by treatment with TFA at 120 °C or MsOH at 22 °C to cleanly afford **18** (Scheme 5). After evaporation of TFA, chlorination of the residue with $POCl_3$ and Me_4NCl[15] at 140 °C afforded tetrachloronaphthyridone **19**. Alternatively, it was found that conversion of imide **15** to **19** could be achieved in one step using the chlorination conditions in 70% yield.

To complete the synthesis of **3b**, a regioselective Suzuki coupling of **19** with 2,4-difluorophenylboronic acid (**20**) was explored. In initial studies using 1.6 equiv each of **20** and Cs_2CO_3 and 4 mol % $Pd(dppf)Cl_2$ in refluxing toluene, the starting materials were completely consumed within 1 h, affording a 1:0.1:1 mixture of desired monoadduct **3b**, undesired monoadduct **21**, and bis adduct **22** (Table 2, entry 1). When the reaction temperature was lowered to 85 °C and 1.2 equiv of **20** was used, the reaction proceeded to 70% conversion with a 3.8:1 ratio of **3b** to **22** with no undesired monoadduct **21** (Table 2, entry 2). Assignments of regioisomers **3b** and **21** were made using detailed NMR studies including 2-D heteronuclear multiple-bond correlation (HMBC) and gradient-enhanced nuclear Overhauser effect (NOE) experiments. In **3b**, a NOE enhancement was observed from H-4 to H-6″. In addition, a spin–spin coupling constant of 3.3 Hz was observed between H-4 and F-2″ (verified via ^{19}F decoupling). In compound **21**, a NOE enhancement was observed from H-8 to H-6″. In the ^{13}C spectrum of **21**, a four-bond spin–spin coupling was observed between C-8 and F-2″ (J_{CF} = 13.6 Hz). These analyses firmly established that the connectivity of the 2,4-difluorophenyl groups in compounds **3b** and **21** are as drawn.

In these initial Suzuki experiments, high monoselectivity was observed during the early stages of the reaction, but the electron-deficient difluorophenyl group in product **3b** activated the remaining chloride toward a second coupling to give bis adduct **22**. A literature survey indicated that regioselectivity is highly substrate dependent.[16] Woodward and co-workers[17] have shown that coupling of electronic-neutral and -rich arylboronic acids to 1,3-dichloroisoquinoline led exclusively to 1-aryl-3-

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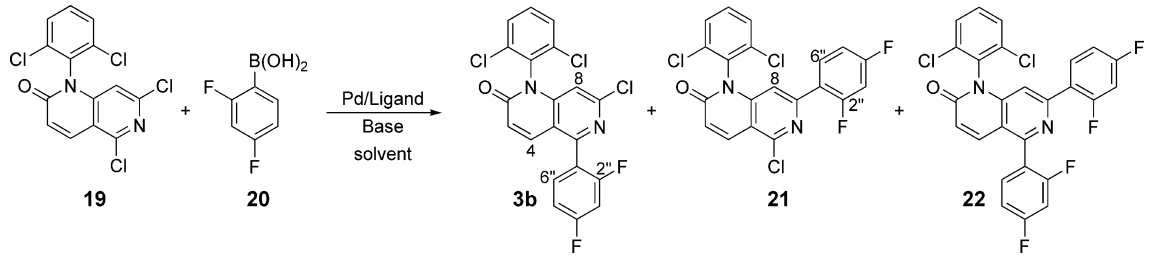
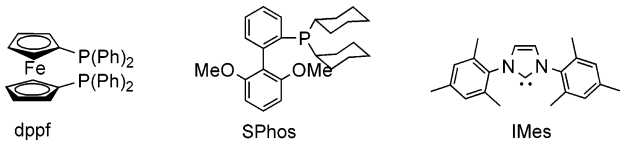
TABLE 2. Selectivity of Suzuki–Miyaura Cross-Coupling



entry	ligand	Pd complex	base	solvent	temp	conversion	**3b/21/22**
1[a]	(dppf)	$Pd(dppf)Cl_2$	Cs_2CO_3	toluene	110 °C	97%	1:0.1:1
2[b]	(dppf)	$Pd(dppf)Cl_2$	Cs_2CO_3	toluene	85 °C	70%	3.8:0:1
3[c]	Ph_3P	$Pd(OAc)_2$	K_3PO_4	IPA	100 °C	93%	2:0.2:1
4[d]	SPhos	$Pd(OAc)_2$	K_3PO_4	toluene or DMF	35 °C	88%	7:0.5:1
5[e]	IMes·HCl	$Pd(OAc)_2$	K_3PO_4	DMF	50→80 °C	95%	50:0.9:1

[a] Reactions were carried out in toluene (0.14 M) with 4 mol % $Pd(dppf)Cl_2$, 1.6 equiv of **20**, and 1.6 equiv of Cs_2CO_3 at 110 °C for 1 h. [b] Reactions were carried in toluene (0.14 M) with 4 mol % $Pd(dppf)Cl_2$, 1.2 equiv of **20**, and 1.2 equiv of Cs_2CO_3 at 85 °C for 8 h. [c] Reactions were carried out in 2-propanol (0.36 M) with 5 mol % $Pd(OAc)_2$, 15 mol % Ph_3P, 1.2 of equiv **20**, and 2.2 equiv of K_3PO_4 at 100 °C for 3 h. The mixture was cooled to room temperature and 0.3 equiv of **20** were added. Then, the reaction was carried out at 100 °C for 2 h. [d] Reactions were carried out in toluene or DMF (0.33 M) with 4 mol % $Pd(OAc)_2$, 8 mol % SPhos, 1.1 equiv of **20**, and 2.2 equiv of K_3PO_4 at 22 °C for 1 h and at 35 °C for 22 h. [e] See Supporting Information for reaction conditions.



chloroisoquinolines, but no example with electronic-deficient arylboronic acids was included. In comparative cross-coupling studies, **19** was found to be a more reactive and a less selective substrate than 1,3-dichloroisoquinoline. We screened over 50 ligands with Pd with various bases and solvents,[18] and selected results are shown in Table 2. Some improvements were observed with the monodentate ligands. Ph_3P and $Pd(OAc)_2$ at 100 °C afforded a 2:0.2:1 ratio of **3b/21/22** (Table 2, entry 3). Using the highly activating SPhos,[19] we could lower the reaction temperature to 35 °C to give an improved selectivity of 7:0.5:1 (Table 2, entry 4) at 88% conversion. The most surprising and pleasing results were with the *N*-heterocyclic carbene derived from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl),[20] which gave a 50:0.9:1 ratio of **3b/21/22** and **3b** isolated in 94% yield (Table 2, entry 5). It is noteworthy to point out that these results were obtained only when IMes/$Pd(OAc)_2$ ratios were ≥2.5. When the ratios were ≤2, boronic acid **20** rapidly degraded to 1,3-difluorobenzene, resulting in poor conversions.

In summary, we have developed an efficient five-step synthesis to trisubstituted naphthyridone **3b** from acetonedicarboxylate (ADC). ADC ester amide **10**, prepared by a selective monoamidation of ADC enolate with PMB–NH_2, underwent an enamine formation with 2,6-dichloroaniline and cyclization to afford PMB-protected enamine imide **12**. A highly efficient lactam ring annulation was accomplished with 3-ethoxyacrylate to afford naphthyridone imide **15** in excellent yield. A one-pot PMB deprotection/bischlorination using $POCl_3$–Me_4NCl afforded tetrachloro-1,6-naphthridone **19**. Finally, this material underwent a highly selective Suzuki coupling with 2,4-difluorophenylboronic acid catalyzed by IMes/$Pd(OAc)_2$, thus completing the synthesis.

Experimental Section

Methyl 5-[(4-Methoxybenzyl)amino]-3,5-dioxopentanoate (10). To a mixture of 60% NaH (3.0 g, 75 mmol) in THF (42 mL), 30% ^{t}BuONa/THF (26.4 mL, 75 mmol) in THF (49 mL), or 1 M ^{t}BuOLi/THF (75 mL, 75 mmol) was slowly added dimethyl acetonedicarboxylate (10.8 g, 60 mmol) over 1 h at 20–25 °C. After stirring at 22 °C for 0.5–1 h, 4-methoxybenzylamine (8.85 g, 63 mmol) was added in one portion. The reaction was monitored by high-pressure liquid chromatography (HPLC) condition A. After complete consumption of ADC (4–18 h), the reaction mixture (83% assayed yield) was poured into a 10 °C mixture of EtOAc (100 mL), 3 N HCl (50 mL), and saturated aqueous NaCl solution. After stirring for 0.5–1 h at 20 °C, the mixture was filtered to remove some insoluble solids (bisamide **11**: HRMS–FAB (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{25}N_2O_5$ 385.1764, found 385.1759), and the solid was washed with EtOAc (30 mL) and water (10 mL). The organic layer of the filtrate was washed twice with a mixture of saturated aqueous NaCl (35 mL) and 3 N HCl (15 mL), twice with a mixture of saturated aqueous NaCl (35 mL) and water (15 mL), and once with saturated aqueous NaCl (50 mL). The organic phase was filtered and concentrated, and the residue was dried by diluting with isopropyl acetate (60 mL) and concentrating several times. After concentrating to near dry-

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(17) Ford, A.; Sinn, E.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 927–934.

(18) The full screening studies will be disclosed in a future publication.

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ness, the residue was taken up in heptane (70 mL) and the solid was filtered and dried in vacuo, affording 14−15 g of **10** as a beige solid (85−95% purity by HPLC condition A; 75−80% corrected yield). This material was used as is in the next step. An analytical pure sample of **10** was obtained by crystallization from 1:1 EtOAc/heptane: ^{1}H NMR (CD_3CN) δ 7.21 (d, J = 8.7, 2H), 7.00 (br S, NH), 6.88 (d, J = 8.7, 2H), 4.28 (d, J = 6.0, 2H), 3.77 (s, 3H), 3.66 (s, 3H), 3.60 (s, 2H), 3.45 (s, 2H); traces of two enol forms were also detected, 6.75 (br s, NH), 5.17 (s), 5.09 (s), 4.31 (d, J = 6.0), 3.17 (s), 3.10 (s); ^{13}C NMR (CD_3CN) δ 198.3, 167.5, 165.5, 158.9, 131.0, 128.9, 113.8, 54.9, 51.8, 50.2, 48.9, 42.3; LC−MS (API−ES+) *m/z* [M + Na]$^+$ 302, [M + Na−CH_3OH]$^+$ 270; HRMS−FAB (*m/z*) [M + H]$^+$ calcd for $C_{14}H_{18}NO_5$ 280.1185, found 280.1183.

4-[(2,6-Dichlorophenyl)amino]-1-(4-methoxybenzyl)-pyridine-2,6-(1*H*,3*H*)-dione (12). A mixture of ADC ester amide **10** (8.52 g, 90 wt %, 27.5 mmol), 2,6-dichloroaniline (5.75 g, 34.5 mmol), toluene (36 mL), and *p*-toluenesulfonic acid monohydrate (0.26 g, 1.38 mmol) was heated at 60 °C for 2.5 h and then at reflux (117 °C) under a Dean−Stark trap for 20 h under N_2. The mixture was allowed to cool slowly to 22 °C, and the product precipitated. After stirring for 2−3 h, the solid was filtered, washed with toluene (25 mL), and dried in vacuo, affording 9.3 g of **12** (75% purity by HPLC condition A; 65% corrected yield). The purity of crude product ranged from 70 to 92%, contained 2−10% 1-(4-methoxybenzyl)-4-[(4-methoxyphenyl)amino]pyridine-2,6-(1*H*,3*H*)-dione (**13**), and was used as is in the next step without problem. A pure sample was obtained by crystallization from acetonitrile: ^{1}H NMR (CD_3CN) δ 7.50 (d, J = 8.1, 2H), 7.33 (t, J = 8.1, 1H), 7.23 (d, J = 8.7, 2H), 7.0 (s, NH), 6.83 (d, J = 8.7, 2H), 4.84 (s, 2H), 4.57 (s, 1H), 3.74 (s, 3H), 3.62 (s, 2H); ^{13}C NMR (CD_3CN) δ 168.4, 166.3, 158.8, 153.1, 134.3, 132.8, 130.4, 129.7, 129.4, 129.2, 128.8, 125.3, 113.6, 89.4, 54.9, 41.2, 35.2; LC−MS (API−ES+) *m/z* [M + H]$^+$ 391, [M + Na]$^+$ 413; HRMS−FAB (*m/z*) [M + H]$^+$ calcd for $C_{19}H_{17}Cl_2N_2O_3$ 391.0616, found 391.0620.

1-(2,6-Dichlorophenyl)-6-(4-methoxybenzyl)-1,6-naphthyridone-2,5,7-(1*H*,6*H*,8*H*)-trione (15). To a solution of enaminone **12** (7.5 g, 90.5%, 17.35 mmol) in anhydrous *N*-methylpyrrolidine (52.5 mL) was added 1 M ^{t}BuOK/THF solution (24.3 mL). The orange solution exothermed from 23 to 34 °C and became a dark green solution. The solution was heated to 100 °C, and ethyl ethoxyacrylate (2.84 mL, 19.09 mmol) was added over 1 h. The reaction mixture was stirred at 100 °C for 3 h, cooled to 30 °C, and poured into a solution of water (342 mL) and NaCl (2.2 g). The aqueous solution was washed with MTBE (105 mL × 2), and then nitrogen was bubbled in for 1 h. HCl (3 N, 12.8 mL) was slowly added over 1−2 h to pH ≤2 with stirring. The suspension was stirred for 2 h, filtered, washed with water (75 mL × 3), and dried in vacuo, affording 8.93 g of **15** (80% purity by HPLC condition A; 92% corrected yield): ^{1}H NMR (CD_3CN) δ 8.10 (d, J = 9.7, 1H), 7.64 (d, J = 7.8, 1H), 7.56 (t, J = 7.8, 1H), 7.29 (d, J = 8.5, 2H), 6.84 (d, J = 8.5, 2H), 6.61 (d, J = 9.7, 1H), 4.94 (s, 2H), 3.74 (s, 3H), 3.41 (s, 2H); ^{13}C NMR (CD_3CN) δ 166.3, 163.0, 160.7, 159.1, 147.9, 138.3, 133.7, 132.3, 132.0, 129.8, 129.6, 129.3, 119.5, 113.6, 107.1, 54.9, 48.9, 42.4, 34.8; LC−MS (API−ES+) *m/z* [M + H]$^+$ 443, [M + Na]$^+$ 465; HRMS−FAB (*m/z*) [M + H]$^+$ calcd for $C_{22}H_{17}Cl_2N_2O_4$ 443.0565, found 443.0558.

1-(2,6-Dichlorophenyl)-7-hydroxy-1,6-naphthyridine-2,5-(1*H*,6*H*)-dione (18). Crude compound **18** was obtained by heating a mixture of naphthyridonetrione **15** (0.4 g, 87%, 0.78 mmol) in TFA (2 mL) in a sealed tube at 120 °C for 6 h and evaporating to dryness. Alternatively, a solution of naphthyridonetrione **15** (0.1 g, 90%, 0.2 mmol) in methanesulfonic acid (0.5 mL) was stirred at 22 °C for 2 days. H_2O (3 mL) was added, and the solid was filtered to provide 80 mg of crude **18**: ^{1}H NMR (DMSO-d_6) δ 7.99 (d, J = 9.6, 1H), 7.78 (d, J = 8.2, 2H), 7.63 (t, J = 8.2, 1H), 6.22 (d, J = 9.6, 1H), 4.60 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 161.1, 160.5, 159.2, 150.9, 138.8, 134.1, 133.3, 132.3, 129.9, 113.2, 101.7, 75.9; LC−MS (API−ES+) *m/z* [M + H]$^+$ 323; HRMS−FAB (*m/z*) [M + H]$^+$ calcd for $C_{14}H_9Cl_2N_2O_3$ 322.9990, found 322.9987.

5,7-Dichloro-1-(2,6-dichlorophenyl)-1,6-naphthyridin-2-(1*H*)-one (19). In a sealed tube was charged naphthyridonetrione **15** (5.0 g, 90%, 10.2 mmol), tetramethylammonium chloride (1.23 g, 11.05 mmol), and phosphorus oxychloride (20 mL, 212.4 mmol). The brown solution was heated at 140 °C for 21 h. After cooling to room temperature, the reaction mixture was quenched into ice water (300 g). The suspension was stirred for 6 h at 22 °C. The solid was filtered, washed with water (80 mL × 3), and dried in vacuo, affording 5.9 g of crude **19** as brown solid (44% purity by HPLC condition A). The crude solid along with $NaHCO_3$ (5.9 g) was triturated with isopropyl acetate (IPAC) (125 mL) over 2 days. After filtration and washing with isopropyl acetate (25 mL × 2), the filtrate was evaporated to dryness, affording 3.4 g of **19** as light brown solid (76% purity by HPLC condition A; 70% corrected yield). A pure sample was obtained by flash chromatography (20−35% IPAC/heptane): ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 10.0, 1H), 7.61 (d, J = 8.0, 2H), 7.52 (t, J = 8.0, 1H), 6.89 (d, J = 10.0, 1H), 6.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 159.6, 150.6, 150.1, 147.7, 136.5, 134.7, 131.8, 131.5, 129.6, 124.2, 113.7, 108.1; LC−MS (API−ES+) *m/z* [M + H]$^+$ 359; HRMS−FAB (*m/z*) [M + H]$^+$ calcd for $C_{14}H_7Cl_4N_2O$ 358.9312, found 358.9309.

7-Chloro-1-(2,6-dichlorophenyl)-5-(2,4-difluorophenyl)-1,6-naphthyridin-2-(1*H*)-one (3b). A mixture of $Pd(OAc)_2$ (2.7 mg, 0.01 mmol), IMes·HCl (9.1 mg, 0.025 mmol), K_3PO_4 (122 mg, 0.557 mmol), and DMF (0.75 mL) was stirred under a N_2 stream at room temperature for 1 h. Tetrachloronaphthyridinone **19** (100 mg, 99%, 0.253 mmol) and 2,4-difluorophenylboronic acid (44 mg, 0.278 mmol) were added and heated at 50 °C for 3.5 h. To drive the reaction to ≤5% starting material, more 2,4-difluorophenylboronic acid (20 mg, 0.126 mmol) was added and heating was increased to 60 °C for 8 h. This was followed by more 2,4-difluorophenylboronic acid (8 mg, 0.054 mmol) and heating at 80 °C for 2 h. The reaction mixture was cooled to 20 °C, and water (4 mL) was added to precipitate crude **3b**. The solid was filtered, washed with water, and dried in vacuo to afford 130 mg of crude **3b**. The crude solid was purified by flash chromatography (10−40% IPAC/heptane) to afford 104 mg of pure **3b** as an off-white solid (94%). The purity by HPLC condition B was 99%: ^{1}H NMR ($CDCl_3$) δ 7.67 (ddd, J = 0.8, 3.6, 10.0, 1H), 7.62 (m, 2H), 7.60 (m, 1H), 7.52 (m, 1H), 7.15 (m, 1H), 7.02 (m, 1H), 6.78 (d, J = 10.0, 1H), 6.45 (d, J = 0.8, 1H); ^{13}C NMR ($CDCl_3$) δ 164.3 (dd, J_{CF} = 11.8, 252.6), 159.9, 160.0 (dd, J_{CF} = 11.8, 252.6), 154.0, 151.9, 147.0, 137.6 (d, J_{CF} = 3.3), 135.0, 133.4 (dd, J_{CF} = 4.3, 10.0), 131.85, 131.88, 129.8, 123.5, 121.2 (dd, J_{CF} = 4.1, 15.1), 114.5, 112.6 (dd, J_{CF} = 3.7, 21.6), 108.2, 104.7 (t, J_{CF} = 25.6); ^{19}F NMR ($CDCl_3$) δ −107.0 (d, J_{FF} = 9.0), −110.1 (d, J_{FF} = 9.0); LC−MS (API−ES+) *m/z* [M + H]$^+$ 437, [M + Na]$^+$ 459; HRMS−FAB (*m/z*) [M + H]$^+$ calcd for $C_{20}H_{10}Cl_3F_2N_2O$ 436.9827, found 436.9831.

5-Chloro-1-(2,6-dichlorophenyl)-7-(2,4-difluorophenyl)-1,6-naphthyridin-2-(1*H*)-one (21). An analytical pure sample was obtained by purification with flash chromatography (10−40% IPAC/heptane) (95% purity by HPLC condition B): ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 10.0, 1H), 8.15 (m, 1H), 7.60 (d, J = 7.9, 2H), 7.50 (t, J = 7.9, 1H), 7.00 (m, 1H), 6.94 (d, J = 10.0, 1H), 6.83 (s, 1H), 6.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 150.92 MHz) δ 164.1 (dd, J_{CF} = 12.2, 254.0), 161.0 (dd, J_{CF} = 12.2, 254.0), 160.2, 152.0 (d, J_{CF} = 3.2), 150.8, 147.0, 137.0, 135.0, 132.7 (dd, J_{CF} = 3.7, 9.9), 132.1, 131.7, 129.6, 124.2, 121.7 (dd, J_{CF} = 3.8, 10.4), 113.6, 112.4 (dd, J_{CF} = 3.5, 21.3), 108.6 (d, J_{CF} = 13.6), 104.8 (t, J_{CF} = 26.3); LC−MS (API−ES+) *m/z* [M + H]$^+$ 437, [M + Na]$^+$ 459; HRMS−FAB (*m/z*) [M + H]$^+$ calcd for $C_{20}H_{10}Cl_3F_2N_2O$ 436.9827, found 436.9824.

1-(2,6-Dichlorophenyl)-5,7-bis(2,4-difluorophenyl)-1,6-naphthyridin-2-(1*H*)-one (22). An analytical pure sample was obtained by purification with flash chromatography (10−40% IPAC/heptane) and recrystallized from acetonitrile (98% purity by HPLC condition B): ^{1}H NMR ($CDCl_3$) δ 8.13 (m, 1H),

7.41 (dd, J = 3.5, 10.0, 1H), 7.66 (m, 1H), 7.63 (m, 2H), 7.51 (m, 1H), 7.12 (m, 1H), 7.04 (m, 1H), 6.97 (m, 1H), 6.90 (s, 1H), 6.82 (m, 1H), 6.81 (d, J = 10.0, 1H); ^{13}C NMR ($CDCl_3$) δ 164.0 (dd, J_{CF} = 11.9, 252.0), 163.9 (dd, J_{CF} = 11.9, 252.0), 161.0 (dd, J_{CF} = 11.9, 252.0), 160.4, 160.1 (dd, J_{CF} = 11.9, 252.0), 153.7, 152.5 (d, J_{CF} = 2.8), 145.7, 137.9 (d, J_{CF} = 3.1), 135.2, 133.4 (dd, J_{CF} = 4.6, 9.7), 132.8 (dd, J_{CF} = 3.9, 9.7), 132.4, 131.6, 129.6, 123.4, 122.9 (dd, J_{CF} = 3.7, 10.9), 122.5 (dd, J_{CF} = 3.9, 15.3), 114.3, 112.4 (dd, J_{CF} = 3.6, 21.3), 112.3 (dd, J_{CF} = 4.0, 20.9), 108.6 (d, J_{CF} = 12.3), 104.6_9 (dd, J_{CF} = 25.7, 27.3), 104.6_6 (t, J_{CF} = 25.7); LC−MS (API−ES+) m/z $[M + H]^+$ 515, $[M + Na]^+$ 537; HRMS−FAB (m/z) $[M + H]^+$ calcd for $C_{26}H_{13}Cl_2F_4N_2O$ 515.0341, found 515.0343.

Supporting Information Available: General experimental methods and ^{1}H, ^{13}C, and ^{19}F NMR spectra for compound **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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