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Differential Functionalization of 1,6-Naphthyridin-2(1*H*)-ones through Sequential One-Pot Suzuki–Miyaura Cross-Couplings

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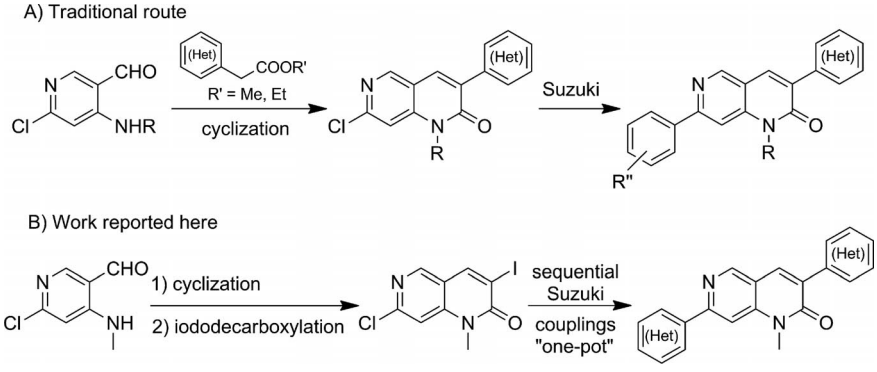
A practical synthesis of 7-chloro-3-iodo-1-methyl-1,6-naphthyridin-2(1*H*)-one is described that starts from 2-chloro-4-(methylamino)nicotinaldehyde. The dihalo compound then undergoes sequential, site-selective Suzuki–Miyaura cross-coupling reactions to afford highly functionalized 1,6-naphthyridones in good yields.

Introduction

Naphthyridones, which are privileged structures for drug discovery, have received much attention as biologically active compounds, and, specifically, 1,8-naphthyridin-4(*1*H)-ones have been widely studied as aza analogues of antibacterial fluoroquinolones.[1] In addition, 1,6-naphthyridin-2(1*H*)-one substrates have been established as cardiotonic agents,[2] *N*-methyl-D-aspartate (NMDA)/glycine site antagonists,[3] antibacterial agents,[4] and protein kinases inhibitors.[5] Because of this broad range of biological activities, various strategies to provide functionalized 1,6-naphthyridin-2(1*H*)-ones efficiently are still needed. 7-Substituted 3-aryl-1,6-naphthyridin-2(1*H*)-ones[5a,5c–5g] are of particular value, but few methods are available to produce highly functionalized 3,7-disubstituted 1,6-naphthyridin-2(1*H*)-ones. Indeed, Thompson and coworkers have reported the selective inhibition of c-Src kinase in a nanomolar range for such compounds.[5a]

As part of our ongoing research of the functionalization of nitrogen heterocycles by employing Suzuki–Miyaura cross-coupling reactions,[6] we disclose a new synthetic protocol that involves the rapid preparation of 3,7-dihalo-1,6-naphthyridin-2(1*H*)-ones followed by sequential Suzuki–Miyaura cross-coupling reactions with a variety of boron reagents to provide complex 3,7-diaryl-1,6-naphthyridin-2(1*H*)-ones in one-pot. More precisely, 7-chloro-3-iodo-1-methyl-1,6-naphthyridin-2(1*H*)-one was studied to highlight the reactivity differences between the iodo and chloro substituents. Indeed, sequential palladium-catalyzed cross-coupling reactions are powerful strategies that have been widely developed to provide highly functionalized heterocyclic scaffolds.[7]



Scheme 1. Synthesis of 3,7-diarylnaphthyridin-2(1*H*)-ones.

The classical approach to synthesize 3-aryl-1,6-naphthyridin-2(1*H*)-ones relies on a modified Friedländer synthesis[8] that starts from a 4-aminonicotinaldehyde and an aryl acetic ester under basic conditions (see Scheme 1). The

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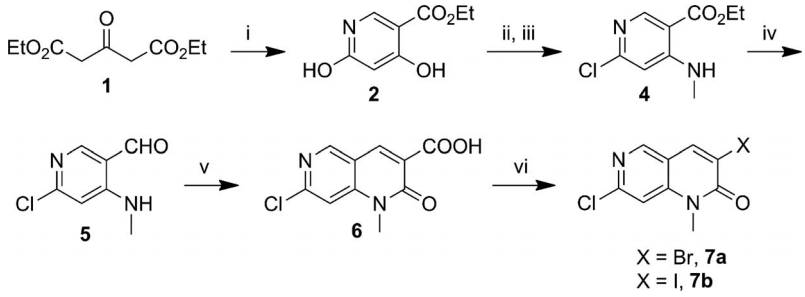
main drawback of this strategy is the multistep synthesis of the aryl acetic ester from the corresponding benzoic acid derivative. A method that involves a Suzuki–Miyaura cross-coupling reaction could overcome this problem. Indeed, Suzuki cross-coupling reactions provide C–C linkages efficiently under mild conditions by using widely and commercially available boron reagents.[9] Using this approach, the preparation of a 3-halo-1,6-naphthyridin-2(1*H*)-one would be required, and this could be obtained in two steps from an *ortho*-amino carbaldehyde. Thus, the 3,7-dihalo-1,6-naphthyridin-2(1*H*)-one would undergo sequential Suzuki reactions to efficiently provide the target compounds (see Scheme 1) .

Results and Discussion

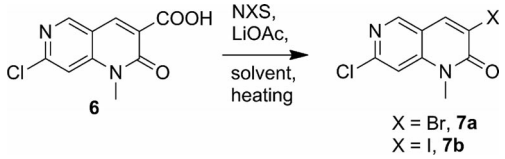
The stepwise synthesis of the desired 3,7-dihalonaphthyridin-2(1*H*)-one required known nicotinaldehyde derivative **5**, which could be prepared in multigram quantities in four steps by following a reported procedure.[5d] Commercially available diethyl 3-oxopentanedioate was treated with triethyl orthoformate and then underwent a cyclization by treatment with ammonia to give compound **2** in a satisfactory yield (72%, see Scheme 2). Chlorination with phosphorus oxychloride and a subsequent regioselective amination furnished ester **4** in high yields. The reduction of the ester functional group by treatment with lithium aluminum hydride (LAH) followed by a mild oxidation with manganese(II) dioxide led to the desired 2-chloro-4-(methylamino)nicotinaldehyde **5**. By following a modified procedure of Garino et al.,[10] the treatment of **5** with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) in the presence of substoichiometric amounts of piperidine and acetic acid produced naphthyridone **6** in excellent yield.

Next, we envisaged a halodecarboxylation of acid **6** by using either *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) to afford the target 3-halogenated derivatives **7a** and **7b**, respectively. Our initial efforts focused on the optimization of the conditions of such a conversion (see Table 1). In the first experiments for the bromodecarboxylation, Roy's procedure[11] was carried out, but it failed to provide any product (see Table 1, Entry 1). A slight improvement of the results was observed by increasing the amount of NBS and water (see Table 1, Entry 2). We were pleased to find that the use of microwave-mediated heating efficiently promoted the bromodecarboxylation reaction (see Table 1, Entry 3). Hence, other solvent systems such as anhydrous THF, THF/water (9:1),[12] and dimethoxyethane (DME)/water (9:1)[13] were examined under these conditions, but unfortunately to no avail (not shown in Table). The increased quantities of NBS and LiOAc allowed for a good conversion, which was observed by ultraperformance liquid chromatography–mass spectrometry (UPLC–MS; see Table 1, Entries 4 and 5). Performing the reaction in a mixture of DMF/water (9:1) led to a high conversion (see Table 1, Entry 6) and allowed for a more convenient treatment of the reaction mixture, as opposed to the acetonitrile/water system. Increasing the temperature or reaction time resulted in incomplete conversion and formation of byproducts (see Table 1, Entries 7 and 8). We then examined whether the amount of LiOAc (3.2 equiv.) was justified. We noticed that decreasing the amount of LiOAc to 1.2 equiv. led to the desired product in a similar yield to that obtained with 3.2 equiv. of this base (see Table 1, Entry 9). Gratifyingly, when NBS (increased to 4.2 equiv.) was treated with 1.2 equiv. of LiOAc, the bromodecarboxylation was successful with a high conversion and a very good yield of **7a** (see Table 1, Entry 10). Next, we investigated the iododecarboxylation reaction to obtain the corresponding aryl iodide, which is known to be significantly more reactive in most Pd-catalyzed transformations. The replacement of NBS with NIS (1.2 equiv.) along with the employment of standard conditions led to a better reactivity (see Table 1, Entry 11), and a quantitative conversion (93% isolated yield) was observed when the amount of NIS was increased to 3.2 equiv. (see Table 1, Entry 12). These experiments identified an excess amount of the NXS along with LiOAc (1.2 equiv.) in a mixture of DMF/water (9:1) as the optimal combination of solvent and reagents to provide high yields of product within a short period of microwave-assisted heating (10 min).



Scheme 2. Synthesis of 3,7-dihalonaphthyridin-2(1*H*)-ones **7a** and **7b**. Reagents and conditions: (i) $HC(OEt)_3$, acetic anhydride, 120 °C, 3 h, then ammonia (30% water solution), 0 °C, 15 min, 72%; (ii) $POCl_3$, 110 °C, 2 h, 95%; (iii) CH_3NH_2 (40% water solution), CH_3CN, 0 °C, 30 min, then room temp., 3 h, 96%; (iv) (a) LAH, tetrahydrofuran (THF), –78 °C, 3 h, (b) MnO_2, dichloromethane (DCM), room temp., 2 h, 84%; (v) Meldrum's acid, piperidine, acetic acid, EtOH, reflux, 2 h, 99%; (vi) NXS, LiOAc, *N*,*N*-dimethylformamide (DMF)/H_2O, microwave (MW), 110 °C, 10 min, X = Br, 74%, X = I, 93%.

Table 1. Optimization of conditions for halodecarboxylation of carboxylic acid **6**.

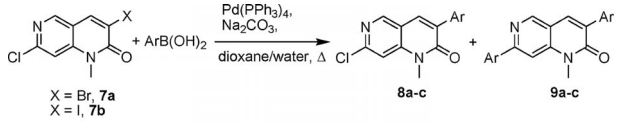


Entry	NXS [equiv.]	LiOAc [equiv.]	Solvent[a]	Heating	Time	Conv. [%][b]	Yield [%][c,d]
1	NBS (1.2)	1.2	A	classical (100 °C)	5 h	0	n.d.
2	NBS (2.2)	1.2	B	classical (100 °C)	2 h	7	n.d.
3	NBS (2.2)	1.2	B	MW[e] (100 °C)	10 min	59	n.d.
4	NBS (2.2)	2.2	B	MW (100 °C)	10 min	65	n.d.
5	NBS (3.2)	3.2	B	MW (100 °C)	10 min	90	n.d.
6	NBS (3.2)	3.2	C	MW (100 °C)	20 min	85	64
7	NBS (3.2)	3.2	C	MW (150 °C)	20 min	48	n.d.
8	NBS (3.2)	3.2	C	MW (110 °C)	30 min	64	52
9	NBS (3.2)	1.2	C	MW (110 °C)	10 min	76	63
10	NBS (4.2)	1.2	C	MW (110 °C)	10 min	91	74
11	NIS (1.2)	1.2	C	MW (110 °C)	10 min	68	n.d.
12	NIS (3.2)	1.2	C	MW (110 °C)	10 min	100	93

[a] Solvents are A (CH_3CN/H_2O, 97:3), B (CH_3CN/H_2O, 9:1), and C (DMF/H_2O, 9:1). [b] Conversion (conv.) percent as determined by UPLC–MS analysis. [c] Isolated yield after purification. [d] Not determined = n.d. [e] Microwave reactions were carried out in a sealed vessel.

With aryl halides **7a** and **7b** in hand, we were able to study the effectiveness of the Suzuki–Miyaura cross-coupling reaction to yield the desired 3-aryl-1,6-naphthyridin-2(1*H*)-ones. We decided to investigate *N*-methylated 1,6-naphthyridones to overcome problems with regard to the solubility or reactivity of free N-H-containing 1,6-naphthyridones.[7d] We then applied the same reaction conditions that had been previously reported[12] for Suzuki reactions of 3-bromopyridopyridazin-2(1*H*)-one. The results are summarized in the Table 2. Hence, the coupling of phenylboronic acid with aryl bromide **7a** using $Pd(PPh_3)_4$ as the catalyst and sodium carbonate as the base was carried out in an aqueous mixture of 1,4-dioxane/water (4:1) that was heated at 105 °C for 3 h in a sealed vessel to result in complete conversion (see Table 2, Entry 1). The expected product **8a** was obtained in a satisfactory yield (67%) along with the formation of biphenyl byproduct **9a**, which was produced from a dual cross-coupling reaction.[14] To ensure that the formation of the 3,7-diaryl product did not originate because of the boron reagent, two other boronic acids that contained either an electron-donating or an electron-withdrawing group were examined using identical reaction conditions (see Table 2, Entries 2 and 3). In both cases, compound **9** was detected (UPLC-MS analysis) or isolated (**9b** in 9% yield). Lowering the temperature to 80 °C led to a significant reduction in the formation of the undesirable compound **9a** (see Table 2, Entry 4). We then performed our coupling reaction with 3-iodo precursor **7b** to compare its reactivity with the aryl bromide. The reaction went to completion at 80 °C without the formation of the biphenyl byproduct to afford product **8a** in good yield (see Table 2, Entry 5). This protocol also occurred in the same manner, but a shorter heating time (approximately 10 min), under microwave irradiation (see Table 2, Entry 6). As expected, the chemoselective control of the Suzuki–Miyaura reactions was more efficient with the aryl iodide than the bromo derivative. For this reason, 7-chloro-3-iodo-1-methyl-1,6-naphthyridin-2(1*H*)-one (**7b**) was used as the starting material for further studies of these Suzuki–Miyaura coupling reactions.

Table 2. Suzuki–Miyaura coupling of compounds **7a** and **7b** with aryl boronic acids.[a]



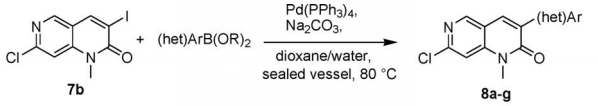
Entry	X	$ArB(OH)_2$	*T*, °C	Time	**8** (%)[b]	**9** (%)[b]
1	Br		105	3 h	**8a** (67)	**9a** (27)
2	Br		105	2 h	**8b** (68)	**9b** (9)
3	Br		105	1 h	**8c** (52)	**9c** (traces)
4	Br		80	4 h	**8a** (74)	**9a** (traces)
5	I		80	3 h	**8a** (74)	–
6[e]	I		80	10 min	**8a** (67)	–

[a] Reagents and conditions: **7** (0.3 mmol), $ArB(OH)_2$ (1.1 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Na_2CO_3 (2.5 equiv.), 1,4-dioxane/water (4:1, 5 mL), 80–105 °C, sealed vessel. [b] Isolated yield after purification. [c] Reaction performed in a sealed vessel in a microwave reactor (fixed temperature, variable pressure).

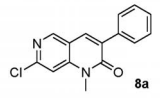
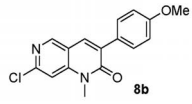
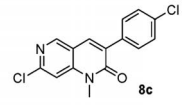
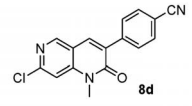
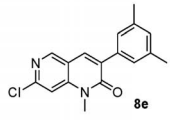
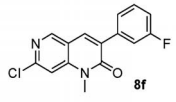
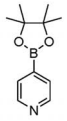
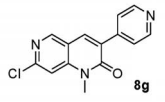
To investigate the scope of the Suzuki–Miyaura reaction at the 3-position of the naphthyridone core with various boronic acids, various 3-aryl-7-chloro-1-methyl-1,6-naphthyridin-2(1*H*)-ones were synthesized under the reaction conditions previously described (see Table 3). In gene-

ral, the introduction of substituents on the benzene ring had no effect on the success of this Pd-catalyzed coupling. Indeed, electron-donating (i.e., methoxy and methyl) and electron-withdrawing groups (i.e., halogens and cyano) did not affect the reactivity of corresponding boronic acids, as products **8** were obtained in good yields (approximately 70%; see Table 3, Entries 2–4 and 6–7). However, the reaction that involved 2,6-dimethylphenylboronic acid failed, even after 10 h (see Table 3, Entry 5). This result prompted us to use another isomer of this boronic acid. Interestingly, the coupling reaction with 3,5-dimethylphenylboronic acid was successful (68% yield; see Table 3, Entry 6), and, hence, this result confirmed the problem of steric hindrance with regard to the coupling partner. The coupling reaction also tolerated the use of heterocyclic 4-pyridylboronic acid pinacol ester to afford the corresponding 3-pyridylnaphthyridone **8g** in 55% yield, but this occurred over a prolonged reaction time (see Table 3, Entry 8). We also attempted to include a furan ring in the reaction, and, unfortunately to no avail, this resulted in a complex reaction mixture (see Table 3, Entry 9). From these experiments, we concluded that our protocol to provide 3-aryl-7-chloro-1-methyl-1,6-naphthyridin-2(1*H*)-ones appeared reliable and could tolerate a wide variety of boron reagents. Moreover, all of the reactions proceeded to completion (see Table 3, except for Entries 5 and 9), even if the isolated yields did not exceed 80%.

Table 3. Scope of Suzuki–Miyaura coupling of 7-chloro-3-iodo-1,6-naphthyridin-2(1*H*)-one **7b**.[a]



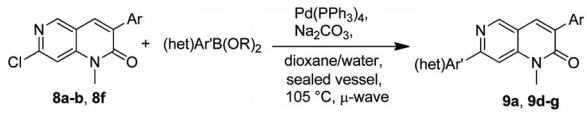
7b 8a-g

Entry	(het)ArB(OR)$_2$	Time	Product	Yield (%)[b]
1		3 h	 **8a**	74
2		2 h	 **8b**	70
3		3 h	 **8c**	68
4		1.5 h	 **8d**	70
5[c]		10 h		–
6		3 h	 **8e**	68
7		2 h	 **8f**	71
8		11 h	 **8g**	55
9[d]		10 h		–

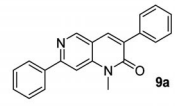
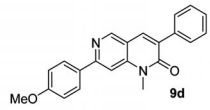
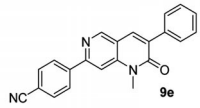
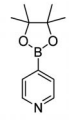
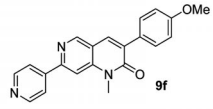
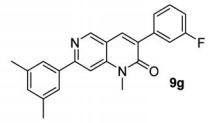
[a] Reagents and conditions: **7b** (0.3 mmol), (het)ArB(OR)$_2$ (1.1 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Na_2CO_3 (2.5 equiv.), 1,4-dioxane/water (4:1, 5 mL), 80 °C, sealed vessel. [b] Isolated yield after purification. [c] No reaction occurred. [d] Formation of a complex reaction mixture.

Our next task was to convert monoarylated compounds **8** into 3,7-diaryl-1,6-naphthyridin-2(1*H*)-ones **9**. Because of the observed lability of the chloro group of the starting aryl bromide under the Suzuki conditions (vide supra), we considered that a subsequent Suzuki–Miyaura cross-coupling reaction could be efficiently carried out with the 7-chloro derivatives. Treating 7-chloro-1-methyl-3-phenyl-1,6-naphthyridin-2-(1*H*)-one **8a** with our typical Suzuki conditions [(het)ArB(OR)$_2$ (1.1 equiv.), Na_2CO_3 (2.5 equiv.), and

Table 4. Suzuki–Miyaura coupling of 3-aryl-7-chloro-1,6-naphthyridin-2(1*H*)-ones **8**.[a]



8a-b, 8f 9a, 9d-g

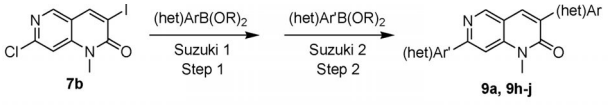
Entry	8	(het)Ar'B(OR)$_2$	Time	Product	Yield (%)[b]
1	**8a**		2 h	 **9a**	69
2	**8a**		1 h	 **9d**	61
3	**8a**		1 h	 **9e**	81
4	**8b**		1 h	 **9f**	78
5	**8f**		1 h	 **9g**	92

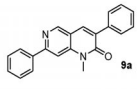
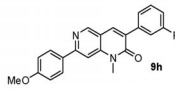
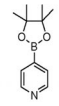
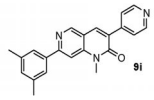
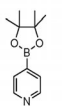
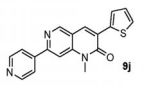
[a] Reagents and conditions: **8** (0.3 mmol), (het)Ar′B(OR)$_2$ (1.1 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Na_2CO_3 (2.5 equiv.), 1,4-dioxane/water (4:1, 5 mL), 105 °C, sealed vessel, microwave heating. [b] Isolated yield after purification.

$Pd(PPh_3)_4$ (5 mol-%) in 1,4-dioxane/water (4:1) at 105 °C in a sealed vessel] resulted in incomplete conversion after 72 h. Indeed, approximately 50% of the starting material (compound **8a**) remained according to the UPLC–MS chromatogram (data not shown). The long reaction time required for the full conversion of the aryl chloride prompted us to explore the scope of the reaction under microwave heating (see Table 4). The reaction of **8a** with phenylboronic acid smoothly afforded 3,7-diaryl derivative **9a** in 2 h in good yield (see Table 4, Entry 1). The nature of the boron reagent was then investigated. Both electron-poor and electron-rich phenylboronic acids behaved similarly to provide the desired products in 1 h in good to very good yields (see Table 4, Entries 2, 3, and 5). Although 4-pyridylboronic acid pinacol ester appeared less reactive towards a Suzuki coupling at the 3-position (see Table 3), the reaction at the 7-position of compound **8b** provided **9f** within the same time as those of the substituted phenylboronic acids (approximately 1 h; see Table 4, Entry 4). Thus, this second arylation at C-7 offers an original approach to a variety of di(hetero)aryl derivatives.

Having established a convenient route for the differential functionalization of 3,7-dihalo-1,6-naphthyridin-2(1*H*)-ones to provide the corresponding diaryl derivatives, we reinvestigated sequential Suzuki–Miyaura couplings in a single flask under microwave irradiation without isolating the 3-(hetero)aryl intermediate. Therefore, for step 1, **7b** was treated with phenylboronic acid under the established reaction conditions (see Table 5, Entry 1), and thereafter, phenylboronic acid (1 equiv.) was added to the crude reaction mixture along with $Pd(PPh_3)_4$ (5 mol-%) and base (Na_2CO_3, 2.5 equiv.). The mixture was subjected to microwave heating at 105 °C for 3 h to give diphenyl-1,6-naphthyridone **9a** in 58% overall yield. The initial Suzuki coupling step that afforded the intermediate compound **8a** was checked by using UPLC–MS analysis. The Pd/SPhos (palladium/2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) catalyst/ligand system, which was reported by Cross and Manetsch,[7d] was used to shorten reaction time of the second step. Although the conditions were efficient for the first step, the arylation at the 7-position failed (data not shown). The next attempt used 3-fluorophenylboronic acid and then 4-methoxyphenylboronic acid to provide 1,6-naphthyridone **9h** in good yield over two steps in one pot (see Table 5, Entry 2). Reactions that employed other heterocyclic boron reagents such as 4-pyridylboronic acid pinacol ester or 2-thienylboronic acid afforded the desired products **9i** and **9j** in 32 and 33% yield, respectively (see Table 5, Entries 3 and 4). It is noteworthy that the incorporation of these heterocycles at C-3 in the first step required more than 1 h under microwave irradiation. The one-pot procedure allowed the preparation of 3,7-disubstituted derivatives in overall yields comparable to those obtained in the stepwise synthesis.

Table 5. Microwave-assisted one-pot sequential Suzuki–Miyaura couplings of 7-chloro-3-iodo-1,6-naphthyridin-2(1*H*)-ones **7b**.[a]



Entry	Step 1	Time	Step 2	Time	Product	Yield (%)[b]
1		10 min		3 h		58
2		10 min		2 h		55
3		1.25 h		1.5 h		32
4		1.5 h		3.5 h		33

[a] Reagents and conditions: step 1: **7b** (0.3 mmol), (het)ArB(OR)$_2$ (1 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Na_2CO_3 (2.5 equiv.), 1,4-dioxane/water (4:1, 5 mL), 80 °C, sealed vessel, microwave heating; step 2: (het)Ar′B(OR)$_2$ (1 equiv.), $Pd(PPh_3)_4$ (5 mol-%), Na_2CO_3 (2.5 equiv.), 105 °C, sealed vessel, microwave heating. [b] Isolated yield after purification.

Conclusions

We have developed a strategy for a rapid approach to 3,7-diaryl-1-methyl-1,6-naphthyridin-2(1*H*)-ones from 2-chloro-4-(methylamino)nicotinaldehyde. The key intermediate 7-chloro-3-iodo-1-methyl-1,6-naphthyridin-2(1*H*)-one, which was prepared by a two-step process that involved a Meldrum's acid-mediated cyclization and a iododecarboxylation, was a suitable reagent to undergo one-pot, sequential Suzuki–Miyaura cross-coupling reactions under microwave-assisted heating. This practical approach provides highly functionalized naphthyridin-2(1*H*)-ones of potential pharmaceutical interest. Furthermore, the straightforward functionalization at both C-3 and C-7 of this readily available scaffold could be extended to other metal-catalyzed reactions.

Experimental Section

General Methods: All commercial reagents were used without further purification. All solvents were reagent or HPLC grade. THF was distilled prior to use with a Na/benzophenone system. Analytical TLC was performed on silica gel 60 F254 plates. Flash column chromatography was performed on silica gel 60 (70–230 mesh ASTM), yields refer to chromatographically and spectroscopically pure compounds. Melting points were measured with an Electrothermal melting point apparatus. The ^1H and ^{13}C NMR spectroscopic data were recorded using [D_6]DMSO with a 400 MHz spectrometer. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane as the internal standard, and coupling constants (J) are given in Hertz. Multiplicities are reported as singlet (s), doublet (d), doublet of doublets (dd), doub-

let of doublet of doublets (ddd), triplet (t), multiplet (m), quartet (q), and broad singlet (br. s). Low resolution mass spectra were obtained by ESI, and high resolution mass spectra were obtained by ESI-TOF. Microwave reactions were carried out in a CEM Discover microwave reactor in sealed vessels (monowave, maximum power 300 W, temperature control by IR sensor, fixed temperature). Compounds **2**–**5** were synthesized as previously reported in the literature.[5d]

Ethyl 4,6-Dihydroxynicotinate (2): A mixture of diethyl 1,3-acetonedicarboxylate (**1**, 25.00 g, 0.12 mol), triethyl orthoformate (21.96 mL, 0.13 mol), and acetic anhydride (22.64 mL, 0.24 mol) was heated at 120 °C for 3 h. The light yellow oily solution was cooled in an ice bath, and then ammonia (30% solution, 35.00 mL) was added. The precipitate was collected by filtration and rinsed with cold EtOH to afford **2** (16.19 g, 72% yield) as a yellow powder; m.p. 220–221 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.83 (s, 1 H), 10.79 (s, 1 H), 8.05 (s, 1 H), 5.64 (s, 1 H), 4.29 (q, J = 7.2 Hz, 2 H), 1.32 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.6, 165.9, 163.6, 142.3, 100.7, 98.3, 60.6, 14.0 ppm. MS (ESI): *m*/*z* (%) = 184.1 (100) [M + H]$^+$.

Ethyl 4,6-Dichloronicotinate (3): A mixture of compound **2** (5.00 g, 0.03 mol) and $POCl_3$ (30 mL) was heated at reflux for 2 h. After cooling, the mixture was poured into ice water, and the resulting mixture was neutralized with K_2CO_3 (approximately 100 g). The organic layer was extracted with DCM. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (DCM) to give **3** (5.72 g, 95% yield) as a white powder; m.p. 71–72 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.87 (s, 1 H), 8.03 (s, 1 H), 4.40 (q, J = 7.2 Hz, 2 H), 1.37 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 162.7, 153.5, 151.7, 144.5, 125.8, 125.3, 62.0, 13.9 ppm. MS (ESI): *m*/*z* (%) = 220.0 (100) [M + H]$^+$.

Ethyl 6-Chloro-4-(methylamino)nicotinate (4): Compound **3** (5.72 g, 0.03 mol) was dissolved in acetonitrile (80 mL). The solution was cooled to 0 °C, and methylamine (40% water solution, 18.00 mL) was slowly added. The reaction was stirred at 0 °C for 30 min and then warmed to room temperature for 3 h. The solvent was removed under reduced pressure, and the crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 8:2) to provide **4** (5.37 g, 96% yield) as a white powder; m.p. 34–36 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.54 (s, 1 H), 8.16–8.04 (m, 1 H), 6.77 (s, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 2.91 (d, J = 4.4 Hz, 3 H), 1.34 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.3, 156.0, 154.5, 152.0, 106.7, 104.6, 60.6, 29.1, 14.0 ppm. MS (ESI): *m*/*z* (%) = 215.1 (100) [M + H]$^+$.

6-Chloro-4-(methylamino)pyridine-3-carbaldehyde (5): To a mixture of LAH (1.95 g, 51.5 mmol) in anhydrous THF (81 mL) at –78 °C was added dropwise compound **4** (5.26 g, 24.5 mmol) in anhydrous THF (72 mL). The reaction mixture was stirred at –78 °C for 3 h and then gradually warmed to room temperature. A mixture of MeOH/EtOAc (1:1, 20 mL) was slowly added to destroy the excess amount of LAH. The resulting mixture was filtered through Celite, and the filtrate was evaporated to dryness. The crude alcohol was dissolved in DCM (120 mL), and MnO_2 (21.31 g, 245 mmol) was added. The reaction was stirred at room temperature for 2 h. The resulting mixture was filtered through Celite to remove the MnO_2, and the filter cake was washed thoroughly with DCM. The filtrate was concentrated under reduced pressure, and the crude residue was purified by silica gel chromatography (cyclohexane/EtOAc, 7:3) to provide **5** (3.51 g, 84% yield over two steps) as a white powder; m.p. 81–82 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.90 (s, 1 H), 8.64–8.54 (m, 1 H), 8.47 (s, 1 H), 6.83 (s, 1 H), 2.93 (d, J = 4.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 193.3, 158.2, 155.1 (2 C), 114.9, 104.5, 28.9 ppm. MS (ESI): *m*/*z* (%) = 171.0 (100) [M + H]$^+$.

7-Chloro-1-methyl-2-oxo-1,2-dihydro-1,6-naphthyridine-3-carboxylic Acid (6): To a stirred solution of compound **5** (200 mg, 1.17 mmol) in EtOH (2 mL) were added Meldrum's acid (169 mg, 1.17 mmol), piperidine (17 μL, 0.12 mmol), and acetic acid (20 μL, 0.35 mmol). The reaction mixture was stirred at room temperature for 20 min and then heated at reflux for 2 h. After cooling to room temperature, the crystallized product was filtered, washed with EtOH (3×), and dried in vacuo to give **6** (279 mg, 99%) as a yellow powder; m.p. 277–278 °C. R_f = 0.22 (DCM/EtOH, 98:2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 13.76 (s, 1 H), 9.06 (s, 1 H), 8.92 (s, 1 H), 7.87 (s, 1 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 164.1, 161.7, 153.0, 152.7, 146.9, 142.1, 121.3, 114.8, 109.5, 30.0 ppm. HRMS (ESI): calcd. for $C_{10}H_7ClN_2O_3$ [M + H]$^+$ 239.0218; found 239.0208.

General Procedure for Halodecarboxylation of Compound 6 with NBS or NIS: In a microwave vial (10 mL) that contained a solution of compound **6** (100 mg, 0.42 mmol) in a mixture of DMF/water (9:1, 5 mL) were added NXS (1.76 mmol for NBS, 1.35 mmol for NIS) and LiOAc (33 mg, 0.50 mmol). The vial was sealed and then heated under microwave heating at 110 °C for 10 min. After cooling, water was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Trituration with diisopropyl ether afforded the desired products **7**.

3-Bromo-7-chloro-1-methyl-1,6-naphthyridin-2(1*H*)-one (7a): Pale yellow powder (74% yield); m.p. 264–265 °C. R_f = 0.24 (petroleum ether/EtOAc, 8:2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.76 (s, 1 H), 8.67 (s, 1 H), 7.72 (s, 1 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 157.5, 150.8, 149.5, 145.8, 138.7, 117.5, 115.7, 109.1, 30.9 ppm. HRMS (ESI): calcd. for $C_9H_6BrClN_2O$ [M + H]$^+$ 272.9425; found 272.9418.

7-Chloro-3-iodo-1-methyl-1,6-naphthyridin-2(1*H*)-one (7b): Brown powder (93% yield); m.p. 227–228 °C; R_f = 0.24 (petroleum ether/EtOAc, 8:2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.82 (s, 1 H), 8.71 (s, 1 H), 7.66 (s, 1 H), 3.65 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 158.3, 150.7, 149.1, 146.4, 145.7, 116.8, 109.0, 96.0, 31.1 ppm. HRMS (ESI): calcd. for $C_9H_6ClIN_2O$ [M + H]$^+$ 320.9286; found 320.9279.

General Procedure for Suzuki–Miyaura Cross-Coupling of 7b: To a 10 mL vessel were added compound **7b** (100 mg, 0.32 mmol) in 1,4-dioxane/water (4:1, 5 mL), the appropriate boron reagent (0.34 mmol), Na_2CO_3 (83 mg, 0.78 mmol), and $Pd(PPh_3)_4$ (18 mg, 5 mol-%). The tube was sealed, and the reaction was heated in an oil bath at 80 °C from 1.5 to 11 h (as indicated in Table 3). After cooling, water was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to provide **8a**–**8g** (see Table 3).

7-Chloro-1-methyl-3-phenyl-1,6-naphthyridin-2(1*H*)-one (8a): Purification by silica gel chromatography (mixtures of DCM/EtOH of increasing polarity) afforded **8a** (74% yield) as a yellow powder; m.p. 146–147 °C. R_f = 0.18 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.82 (s, 1 H), 8.24 (s, 1 H), 7.73 (dd, J = 8.4, 1.6 Hz, 2 H), 7.69 (s, 1 H), 7.52–7.45 (m, 3 H), 3.69 (s, 3 H) ppm. ^{13}C

NMR (100 MHz, [D$_6$]DMSO): δ = 160.5, 150.5, 150.3, 145.9, 135.8, 134.3, 132.4, 128.7 (2 C), 128.4, 128.0 (2 C), 115.8, 108.5, 29.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{11}ClN_2O$ [M + H]$^+$ 271.0633; found 271.0624.

7-Chloro-3-(4-methoxyphenyl)-1-methyl-1,6-naphthyridin-2(1*H*)-one (8b): Purification by silica gel chromatography (petroleum ether/EtOAc, 4:1) afforded **8b** (70% yield) as a white powder; m.p. 171–172 °C. R_f = 0.09 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.80 (s, 1 H), 8.19 (s, 1 H), 7.73 (d, J = 9.0 Hz, 2 H), 7.67 (s, 1 H), 7.06 (d, J = 9.0 Hz, 2 H), 3.85 (s, 3 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.7, 159.4, 150.1, 150.0, 145.6, 133.0, 131.9, 130.0 (2 C), 128.0, 115.9, 113.5 (2 C), 108.4, 55.2, 29.8 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}ClN_2O_2$ [M + H]$^+$ 301.0738; found 301.0735.

7-Chloro-3-(4-chlorophenyl)-1-methyl-1,6-naphthyridin-2(1*H*)-one (8c): Purification by silica gel chromatography (DCM) afforded **8c** (68% yield) as a yellow powder; m.p. 229–230 °C. R_f = 0.20 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.82 (s, 1 H), 8.29 (s, 1 H), 7.78 (d, J = 8.4 Hz, 2 H), 7.70 (s, 1 H), 7.56 (d, J = 8.4 Hz, 2 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.4, 150.6, 150.4, 145.9, 134.6 (2 C), 133.1, 131.0, 130.5 (2 C), 128.1 (2 C), 115.7, 108.6, 29.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{10}Cl_2N_2O$ [M + H]$^+$ 305.0243; found 305.0235.

7-Chloro-3-(4-cyanophenyl)-1-methyl-1,6-naphthyridin-2(1*H*)-one (8d): Purification by silica gel chromatography (DCM) afforded **8d** (70% yield) as a beige powder; m.p. 330–331 °C. R_f = 0.13 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.84 (s, 1 H), 8.40 (s, 1 H), 7.99 (d, J = 8.4 Hz, 2 H), 7.95 (d, J = 8.4 Hz, 2 H), 7.74 (s, 1 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.2, 151.1, 150.7, 146.2, 140.5, 135.9, 132.0 (2 C), 130.6, 129.6 (2 C), 118.7, 115.5, 110.8, 108.7, 29.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{10}ClN_3O$ [M + H]$^+$ 296.0585; found 296.0582.

7-Chloro-3-(3,5-dimethylphenyl)-1-methyl-1,6-naphthyridin-2(1*H*)-one (8e): Purification by silica gel chromatography (DCM) afforded **8e** (68% yield) as a pale yellow powder; m.p. 165–166 °C. R_f = 0.18 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.80 (s, 1 H), 8.19 (s, 1 H), 7.67 (s, 1 H), 7.33 (s, 2 H), 7.08 (s, 1 H), 3.67 (s, 3 H), 2.36 (s, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.5, 150.4, 150.2, 145.8, 136.9 (2 C), 135.7, 134.0, 132.6, 129.7, 126.4 (2 C), 115.8, 108.4, 29.7, 20.9 (2 C) ppm. HRMS (ESI): calcd. for $C_{17}H_{15}ClN_2O$ [M + H]$^+$ 299.0946; found 299.0940.

7-Chloro-3-(3-fluorophenyl)-1-methyl-1,6-naphthyridin-2(1*H*)-one (8f): Purification by silica gel chromatography (DCM) afforded **8f** (71% yield) as a white powder; m.p. 160–161 °C. R_f = 0.27 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.82 (s, 1 H), 8.34 (s, 1 H), 7.71 (s, 1 H), 7.63–7.52 (m, 3 H), 7.33–7.28 (m, 1 H), 3.69 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.7 (d, J = 241 Hz), 160.3, 150.8, 150.5, 146.0, 138.0 (d, J = 8 Hz), 135.1, 130.8 (d, J = 2 Hz), 130.0 (d, J = 8 Hz), 124.8 (d, J = 3 Hz), 115.6, 115.5 (d, J = 23 Hz), 115.1 (d, J = 20 Hz), 108.6, 29.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{10}ClFN_2O$ [M + H]$^+$ 289.0538; found 289.0532.

7-Chloro-1-methyl-3-(pyridin-4-yl)-1,6-naphthyridin-2(1*H*)-one (8g): Purification by silica gel chromatography (mixtures of DCM/MeOH of increasing polarity) afforded **8g** (55% yield) as a white powder; m.p. >400 °C. R_f = 0.07 (DCM/MeOH, 99:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.86 (s, 1 H), 8.71 (dd, J = 4.6, 1.6 Hz, 2 H), 8.46 (s, 1 H), 7.78 (dd, J = 4.6, 1.6 Hz, 2 H), 7.74 (s, 1 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.0, 151.2, 150.8, 149.6 (2 C), 146.3, 143.1, 136.1, 129.6, 123.1 (2 C), 115.4, 108.7, 29.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{10}ClN_3O$ [M + H]$^+$ 272.0585; found 272.0581.

General Procedure for Microwave-Promoted Suzuki–Miyaura Cross-Coupling of 8a, 8b, and 8f: To a vessel (40 mL) were added compound **8** (0.55 mmol) in 1,4-dioxane/water (4:1, 10 mL), the appropriate boron reagent (0.61 mmol), Na_2CO_3 (147 mg, 1.39 mmol), and $Pd(PPh_3)_4$ (32 mg, 5 mol-%). The tube was sealed, and the reaction mixture was heated under microwave irradiation at 105 °C for 1 or 2 h (as indicated in Table 4). After cooling, water was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to provide **9a** and **9d**–**9g** (see Table 4).

1-Methyl-3,7-diphenyl-1,6-naphthyridin-2(1*H*)-one (9a): Purification by silica gel chromatography (DCM) afforded **9a** (69% yield) as a white powder; m.p. 155–156 °C. R_f = 0.22 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.03 (s, 1 H), 8.28 (dd, J = 8.4, 1.6 Hz, 2 H), 8.24 (s, 1 H), 7.96 (s, 1 H), 7.75 (dd, J = 8.4, 1.6 Hz, 2 H), 7.57–7.40 (m, 6 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.8, 156.0, 150.5, 144.8, 138.4, 136.2, 134.8, 131.8, 129.5, 128.8 (2 C), 128.7 (2 C), 128.1, 128.0 (2 C), 127.1 (2 C), 115.4, 104.8, 29.6 ppm. HRMS (ESI): calcd. for $C_{21}H_{16}N_2O$ [M + H]$^+$ 313.1335; found 313.1322.

7-(4-Methoxyphenyl)-1-methyl-3-phenyl-1,6-naphthyridin-2(1*H*)-one (9d): Purification by silica gel chromatography (DCM) afforded **9d** (61% yield) as a white powder; m.p. 198–199 °C. R_f = 0.22 (DCM/MeOH, 99:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.01 (s, 1 H), 8.29 (d, J = 9.0 Hz, 2 H), 8.24 (s, 1 H), 7.91 (s, 1 H), 7.77 (dd, J = 6.8, 1.6 Hz, 2 H), 7.52–7.42 (m, 3 H), 7.13 (d, J = 9.0 Hz, 2 H), 3.89 (s, 3 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.9, 160.6, 155.9, 150.4, 144.8, 136.3, 134.9, 131.3, 130.8, 128.7 (2 C), 128.6 (2 C), 128.1, 128.0 (2 C), 114.9, 114.1 (2 C), 103.6, 55.3, 29.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{18}N_2O_2$ [M + H]$^+$ 343.1441; found 343.1432.

7-(4-Cyanophenyl)-1-methyl-3-phenyl-1,6-naphthyridin-2(1*H*)-one (9e): Purification by silica gel chromatography (DCM) and trituration with diisopropyl ether afforded **9e** (81% yield) as a white powder; m.p. 235–236 °C. R_f = 0.13 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.11 (s, 1 H), 8.53 (d, J = 8.4 Hz, 2 H), 8.29 (s, 1 H), 8.14 (s, 1 H), 8.06 (d, J = 8.4 Hz, 2 H), 7.78 (dd, J = 8.4, 1.6 Hz, 2 H), 7.53–7.45 (m, 3 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.8, 153.8, 150.7, 144.9, 142.6, 136.0, 134.6, 132.7 (2 C), 132.6, 128.8 (2 C), 128.3, 128.0 (2 C), 127.8 (2 C), 118.8, 116.0, 111.7, 106.1, 29.8 ppm. HRMS (ESI): calcd. for $C_{22}H_{15}N_3O$ [M + H]$^+$ 338.1288; found 338.1290.

3-(4-Methoxyphenyl)-1-methyl-7-(pyridin-4-yl)-1,6-naphthyridin-2(1*H*)-one (9f): Purification by silica gel chromatography (mixtures of DCM/MeOH of increasing polarity) and trituration with diisopropyl ether afforded **9f** (78% yield) as a yellow powder; m.p. 252–253 °C. R_f = 0.10 (DCM/MeOH, 98:2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.09 (s, 1 H), 8.78 (dd, J = 5.2, 1.6 Hz, 2 H), 8.27 (dd, J = 5.2, 1.6 Hz, 2 H), 8.25 (s, 1 H), 8.14 (s, 1 H), 7.78 (d, J = 8.8 Hz, 2 H), 7.06 (d, J = 8.8 Hz, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.9, 159.4, 152.9, 150.5, 150.3 (2 C), 145.4, 144.6, 133.3, 132.2, 130.1 (2 C), 128.2, 121.1 (2 C), 116.6, 113.5 (2 C), 106.0, 55.2, 29.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{17}N_3O_2$ [M + H]$^+$ 344.1394; found 344.1394.

3-(3-Fluorophenyl)-1-methyl-7-(3,5-dimethylphenyl)-1,6-naphthyridin-2(1*H*)-one (9g): Purification by silica gel chromatography (DCM) afforded **9g** (92% yield) as a white powder; m.p. 225–226 °C. R_f = 0.16 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.04 (s, 1 H), 8.36 (s, 1 H), 7.95 (s, 1 H), 7.94 (s, 2 H), 7.68–7.64 (m, 2 H), 7.58–7.52 (m, 1 H), 7.29 (ddd, J = 8.5, 8.5, 2.1 Hz, 1 H),

7.16 (s, 1 H), 3.83 (s, 3 H), 2.43 (s, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.8 (d, J = 240 Hz), 160.6, 156.5, 150.6, 144.9, 138.4 (d, J = 8 Hz), 138.2, 137.7 (2 C), 135.5, 131.0, 130.0 (d, J = 1 Hz), 129.9 (d, J = 12 Hz), 124.9 (2 C), 124.8 (d, J = 2 Hz), 115.5 (d, J = 22 Hz), 115.1, 114.9 (d, J = 20 Hz), 104.6, 29.7, 21.0 (2 C) ppm. HRMS (ESI): calcd. for $C_{23}H_{19}FN_2O$ [M + H]$^+$ 359.1554; found 359.1550.

General Procedure for Microwave-Promoted One-Pot Sequential Suzuki–Miyaura Cross-Coupling of 7b: To a vessel (40 mL) were added compound **7b** (0.47 mmol) in 1,4-dioxane/water (4:1, 10 mL), the appropriate boron reagent (0.47 mmol), Na_2CO_3 (124 mg, 1.17 mmol), and Pd(PPh$_3$)$_4$ (27 mg, 5 mol-%). The tube was sealed, and the reaction was heated under microwave irradiation at 80 °C from 10 min to 1.5 h (as indicated in Table 5). After completion of the reaction (monitored by UPLC–MS), the second boron reagent (0.47 mmol) was added to the crude reaction mixture along with Pd(PPh$_3$)$_4$ (27 mg, 5 mol-%) and Na_2CO_3 (124 mg, 1.17 mmol). The tube was sealed, and the mixture was subjected to microwave irradiation at 105 °C from 1.5 h to 3.5 h (as indicated in Table 5). After cooling, water was added, and the mixture was extracted with DCM. The organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to provide **9a** and **9h**–**9j** (see Table 5).

1-Methyl-3,7-diphenyl-1,6-naphthyridin-2(1*H*)-one (9a): Purification by silica gel chromatography (mixtures of DCM/MeOH of increasing polarity) afforded **9a** (58% Yield). Analytical data agree with previous characterization.

3-(3-Fluorophenyl)-7-(4-methoxyphenyl)-1-methyl-1,6-naphthyridin-2(1*H*)-one (9h): Purification by silica gel chromatography (DCM) afforded **9h** (55% yield) as a beige powder; m.p. 160–161 °C. R_f = 0.19 (DCM). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.01 (s, 1 H), 8.34 (s, 1 H), 8.29 (d, J = 9.0 Hz, 2 H), 7.91 (s, 1 H), 7.67–7.63 (m, 2 H), 7.57–7.52 (m, 1 H), 7.29 (ddd, J = 8.6, 8.6, 2.1 Hz, 1 H), 7.13 (d, J = 9.0 Hz, 2 H), 3.89 (s, 3 H), 3.82 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 161.8 (d, J = 240 Hz), 160.6 (2 C), 156.1, 150.7, 144.9, 138.5 (d, J = 8 Hz), 135.6, 130.7, 129.9 (d, J = 9 Hz), 129.6 (d, J = 3 Hz), 128.6 (2 C), 124.7 (d, J = 3 Hz), 115.5 (d, J = 23 Hz), 114.8 (d, J = 20 Hz), 114.7, 114.1 (2 C), 103.6, 55.3, 29.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{17}FN_2O_2$ [M + H]$^+$ 361.1347; found 361.1341.

7-(3,5-Dimethylphenyl)-1-methyl-3-(pyridin-4-yl)-1,6-naphthyridin-2(1*H*)-one (9i): Purification by silica gel chromatography (DCM/MeOH, 98:2) and trituration with diisopropyl ether afforded **9i** (32% yield) as a beige powder; m.p. 233–234 °C. R_f = 0.10 (DCM/MeOH, 98:2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.05 (s, 1 H), 8.70 (d, J = 5.4 Hz, 2 H), 8.46 (s, 1 H), 7.95 (s, 1 H), 7.93 (s, 2 H), 7.82 (d, J = 5.4 Hz, 2 H), 7.16 (s, 1 H), 3.82 (s, 3 H), 2.42 (s, 6 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.3, 156.9, 150.9, 149.5 (2 C), 145.2, 143.5, 138.1, 137.8 (2 C), 136.5, 131.1, 128.7, 125.0 (2 C), 123.1 (2 C), 114.9, 104.7, 29.7, 21.0 (2 C) ppm. HRMS (ESI): calcd. for $C_{22}H_{19}N_3O$ [M + H]$^+$ 342.1601; found 342.1598.

1-Methyl-7-(pyridin-4-yl)-3-(thien-2-yl)-1,6-naphthyridin-2(1*H*)-one (9j): Purification by silica gel chromatography (mixtures of DCM/MeOH of increasing polarity) and trituration with diisopropyl ether afforded **9j** (33% yield) as a yellow powder; m.p. 261–262 °C. R_f = 0.15 (DCM/MeOH, 98:2). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.12 (s, 1 H), 8.78–8.74 (m, 3 H), 8.28 (br. s, 2 H), 8.16 (s, 1 H), 7.99 (s, 1 H), 7.73 (d, J = 2.5 Hz, 1 H), 7.25 (s, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 159.8, 152.8, 150.6, 150.3 (2 C), 145.3, 143.8, 136.1, 129.9, 129.4, 126.8, 126.2, 125.7, 121.1 (2 C), 116.5, 106.2, 30.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{13}N_3OS$ [M + H]$^+$ 320.0852; found 320.0847.

Supporting Information (see footnote on the first page of this article): Full experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra for new products.

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[14] It is noteworthy that the mixture of products **8** and **9** was difficult to purify on a silica gel chromatography column. Reversed-phase chromatography using water/acetonitrile was required to isolate each product.

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