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CONVENIENT SYNTHESIS OF 3*H*-PYRROLO[2,*3*-c]ISOQUINOLINES AND 3-*H*-PYRROLO[2,3-*c*][1,7]-, 3,4-BENZO[*c*][1,7]-, AND DIHYDRO-PYRIDO [4,3-*c*][1,8]NAPHTHYRIDINES *VIA* PALLADIUM-ASSISTED NUCLEOPHILIC AMINATION

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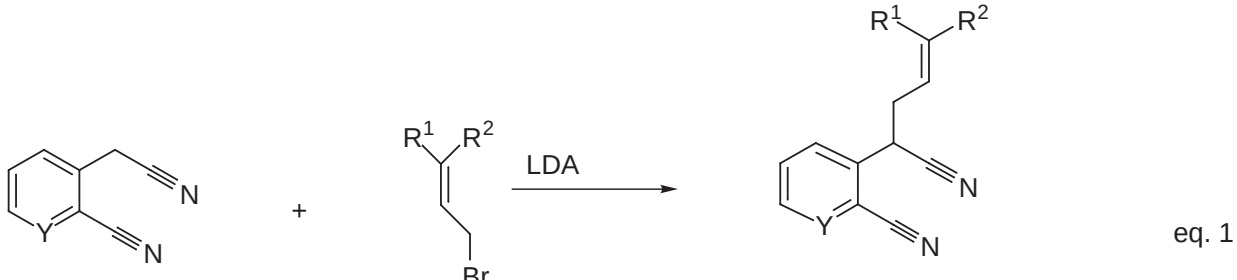
Abstract - 2-Methyl- and 3-ethyl-3*H*-pyrrolo[2,3-*c*]isoquinolines and 2-methyl-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridines possessing a C-5 saturated heterocyclic ring were prepared from corresponding 4-alkenyl-3-amino-isoquinoline or naphthyridine*via* palladium-assisted cyclization under catalytic conditions. Similar treatment of 3-prenyl derivatives of isoquinolines and naphthyridines possessing 6- alkyl groups gave 3,3,-dimethyl-3,4-di-hydrobenzo[*c*]- and 3,4-dihydropyridino[4,3-*c*]naphthyridines, respectively. The Hegedus precursors were synthesized by alkenylation of 2-cyano-methylbenzonitrile or 3-cyanomethylpyridine-2-carbonitrile followed by base-mediated cyclization of α–alkenyl derivatives so formed using lithium amides or alkyllithiums.

Hegedus[1] *et al.* have shown that nitrogen heterocycles, *i.e.* indoles, quinolines, and isoquinolines, can be prepared by treating 2-allylanilines with $PdCl_2(MeCN)_2$ under both catalytic and stoichiometric conditions. The cyclization is thought to proceed by a palladium-assisted amination on the double bond of the allyl group. We[2] have recently reported a convenient method for the preparation of 1-substituted derivatives of 4-[*E*]-1-propenyl - and 4-allyl-3-aminoisoquinolines by the reaction of α-allyl-α-cyano-*o*- tolunitrile with lithium amides and alkyllithiums. Mindful of structural similaritity of these 4-alkenyl-3-aminoisoquinolines to 2-allylanilines, we have explored

their potential use for preparing annulated isoquinolines *via* the Hegedus cyclization reaction. Accordingly, a series of allyl-, [*E*]-but-2-enyl-, and prenyl isoquinoline derivatives were prepared and treated with $PdCl_2(MeCN)_2$ under both catalytic and stoichiometric conditions. The results are reported herein.

RESULTS AND DISCUSSION

As shown in eq. 1, a series of 4-alkenyl-3-aminoisoquinolines (**6**) were prepared by first treating 2-cyanomethylbenzonitrile (**1**) or 3-cyanomethylpyridine-2-carbonitrile (**2**) with the alkenyl bromide (**3a-c**) to give the corresponding α-alkenyl derivatives (**4a-f**) in 51-95% yields. Compound (**1**) is commercially available, but the 2-cyanopyridine (**2**) is not, and, thus, had to be prepared from the reaction of 3-pyridylacetonitrile with MCPBA followed by cyanation at C-2- with $(Me)_3SiCN$.[3]



1 Y = CH
2 Y = N

3	R^1	R^2
a	H	H
b	H	Me
c	Me	Me

4	R^1	R^2	Y	yield (%)
a	H	H	CH	51
b	H	Me	CH	77*
c	Me	Me	CH	95
d	H	H	N	51
e	H	Me	N	60*
f	Me	Me	N	72

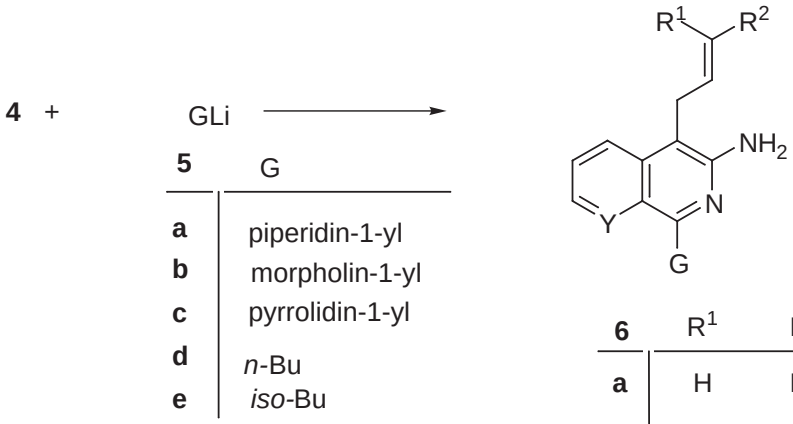
eq. 1

* contains *ca*. 20% Z isomer

The structures of **4a**-**f** were confirmed by IR ,^{1}H NMR and MS spectral analysis. For example, the ^{1}H NMR spectra of the pent-3-enyl derivatives (**4b** and **4e**) exhibited olefinic chemical shifts with a multiplet between δ 5.4-5.5 ppm. In addition, in all cases, the 2-methylene group adjacent to the 3-position of the carbon-carbon double bond gave splitting patterns in agreement with proposed structures.

The intermediates (**4a-f**), were then cyclized to **6a-n** in 75-100% yields, as shown in eq. 2, by causing them to react with an appropriate nucleophile (**5a-e**). The structures of **6a-m** were ascertained by ^{1}H and ^{13}C NMR, IR, MS spectrometries. In all cases, the IR spectra revealed two

characteristic NH stretches in the vicinity of 3400-3300 cm^{-1} and, with the exception of the allyl derivative (**6i,j**), C=C stretch (1600-1650 cm^{-1}) and bending frequencies between 1000-900 cm^{-1}. Additionally, the chemical shifts, splitting patterns, and integration of alkenyl hydrogens in the ^1H NMR spectra of **6a-n** were in agreement with proposed structures.



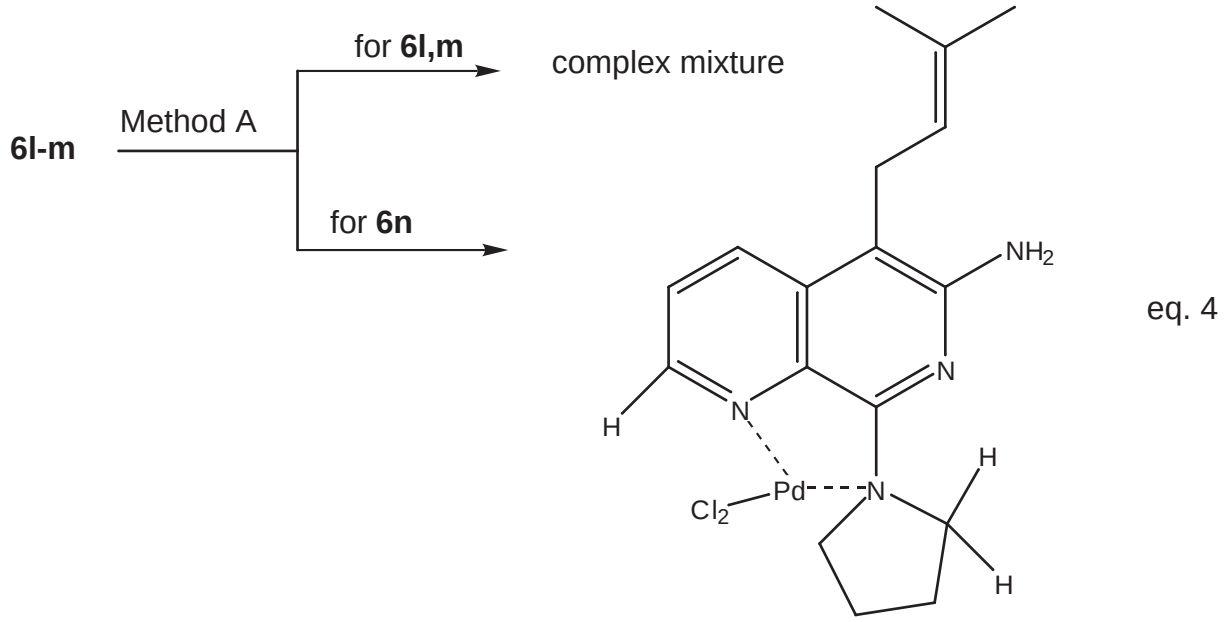
eq. 2

6	R^1	R^2	Y	G	yld, %
a	H	H	CH	piperidin-1-yl	89
b	H	H	CH	morpholin-4-yl	85
c	H	H	CH	pyrrolidin-1-yl	86
d	H	Me	CH	piperidin-yl	100*
e	H	Me	CH	morpholin-4-yl	98*
f	H	Me	CH	pyrrolidin-1-yl	99*
g	H	H	N	piperidin-yl	98
h	H	H	N	pyrrolidin-1-yl	94
i	Me	Me	CH	*n*-Bu	82
j	Me	Me	CH	*sec*-Bu	90
k	Me	Me	N	*n*-Bu	70
l	H	Me	N	morpholin-4-yl	99*
m	H	Me	N	pyrrolidin-1-yl	98*
n	Me	Me	N	pyrrolidin-1-yl	94

* contains 15-20% Z isomer

With the 3-aminoisoquinolines (**6**) now on hand, Hegedus coupling reactions were first carried out under catalytic conditions using $Pd(MeCN)_2Cl_2$ (20 mol%), benzoquinone (1 equiv) and 10 equiv of LiCl per equiv of **6** in refluxing THF. As shown in eq. 3, the reaction of the allylisoquinolines (**6a-c**) and 4-but-2-enyl derivatives (**6d-f**) in which G = piperidin-1-yl, morpholin-4-yl and pyrrolidin-1-yl, gave 3-methyl (**7a-c)** and 3-ethyl (**7f-h**) derivatives, respectively, in good yields. Additionally,

the reaction of allyl derivatives (**6g,h**) in which G = piperidin-1-yl and pyrrolidin-1-yl, respectively gave the corresponding 3-methyl derivatives (**7g,h**). However, the reaction of naphthyridine derivatives (**6l,m**), where G = morpholin-4-yl and pyrrolidin-1-yl, respectively, and the prenyl derivative (**6n**), where G is pyrrolidin-1-yl, did not give desired products. In the case of **6l** and **6m**, the reaction appears to be intractable palladium complexes. However, the reaction of **6n** gave a single product (**9**) which appeared to be a palladium complex of **6n**. As shown in eq. 4, the complex most likely involves sigma bonding between the Pd metal and the pyrroline nitrogen



eq. 4

9

and the 1-nitrogen on the naphthyridine ring. For example, in the ^{1}H NMR spectrum of the free prenyl derivative (**6n**), the chemical shift of the 2-proton of the naphthyridine ring appears at 8.39 ppm and the two methylene groups adjacent to the nitrogen atom of the pyrrolidine ring is seen as triplet at 4.18 ppm. Upon complexation, the chemical shift of the 2-H nitrogen is shifted to 9.19 ppm and the methylene groups appear as two doublets at 4.75 and 4.77 ppm. Additionally, complexation of the lone-pair electrons on the 5-membered ring with Pd would presumably result in the pyrrolidine ring adopting a conformation perpendicular to the naphthyridine ring. Such an arrangement would remove the equivalency of the two methylene hydrogens thus accounting for the two doublets in ^{1}H NMR spectrum of **9**. It would also prevent conjugation between the pyrrolidine and naph-thyridine rings resulting in a lowering of the electron density of the latter ring. The downfield shift of the 6-amino group in the complex (4.18 ppm) as compared to that of **6n** (4.80 ppm) is consistent with such an argument. To obtain more information of the importance of the pyrroliidine ring on Pd complexation, several prenyl derivatives were prepared in which the 5-

pyrrole ring was replace by an alkyl group (**6i-k**). As shown in eq. 3, **6i-k** were successfully converted to dimethyl derivatives (**8a-c**) in good yield under catalytic conditions.The formation of the six-membered ring from **6i, j** and **k** was is line with previous observations that amination of the carbon-carbon double bond of the prenyl group occurs at the most substituted carbon (in this case, tertiary).[4]

We next carried out Hegedus coupling under stoichiometric conditions and found that modest increases in yields of **7a-c** and **8a-c** could be obtained. In the other cases, complex mixtures were obtained. GC/MS analysis of the reaction mixtures revealed the absence of desired products. Owing to the high cost of the palladium catalyst and modest yield increase, use of stoichiometric conditions in most case is not recommended.

In conclusion, 2-methyl- and 3-ethyl-3*H*-pyrrolo[2,3-*c*]isoquinolines and 2-methyl-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridine each possessing a saturated heterocyclic ring at the 5-position can be prepared from corresponding 4-alkenyl-3-aminoisoquinoline or naphthyridine,*via* palladium-assisted cyclization under catalytic conditions. When these reactions are carried out under stoichiometric conditions, the yields of 3-methyl-3*H*-pyrrolo[2,3-*c*]isoquinolines are increased. However, the other reactions give intractable tars. Interestingly, prenyl derivatives of 4-alkenyl-3-aminoisoquinoline or naphthyridine failed to give the desired cyclization products. In one case, a substance was isolated from the reaction of 6-amino-5-prenyl-8-pyrolidin-1-yl-1,7-naphthyridine (**6n**) and tentatively identified as a palladium complex (**9**) of the starting naphthyridine. However, treatment of prenyl derivatives of isoquinolines and napthyridines possessing 6- alkyl groups gave 3,3-dimethyl-3,4-dihydrobenzo[*c*]- and 3,3-dimethyl-3,4-dihydropyridino[4,3-*c*]naphthyridines, respectively.

EXPERIMENTAL

General Data: Melting points were taken on a Mel-Temp capillary apparatus, and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IR™ 550 FTIR spectrophotometer and the ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz AVANCE DRX-400 Multi-nuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard. The MS were run on a HP G1800C, GCD Series II. Elemental analyses were obtained from SMU Micro-analytical Laboratory Services, and HRMS analyses were preformed by Analytical Services, Colorado State University, Boulder, CO, 80522. The amines and 2-(cyano-methyl)benzonitrile (**1**) were distilled or recrystallized before use. The alkyllithiums and 2-alkenyl bromides (**3a-c**) were purchased from Aldrich Chemical Company and used as received. 3-

Cyanomethyl-2-cyanopyridine (**2**) was prepared from 3-pyridylacetonitrile by literature procedure.[3] The glassware was heated at 125 ^{O}C in an oven overnight prior to use. The reactions were carried out in glassware, which had been heated at 125 ^{o}C overnight prior to use, under an atmosphere of dry O_2-free N_2 *via* balloon.

General Procedure for the preparation of α-(2-alkenyl)-α-cyano-*o*-tolunitrile (4a-c) and 2-cyano-3-(1-cyano-3-alkenyl)pyridines (4d-f). To the solution of **1** or **2** (20 mol) in THF (50 mL) was added n-BuLi (12.5 mL of 1.6 M solution, 20 mmol) at -70 ^{o}C. After stirring for 10 min a solution of appropriate 2-alkenyl bromide (**3**) (30 mmol) in THF (25 mL) was added slowly at -70 ^{o}C. A vigorous reaction ensued and the reaction mixture turned dark. The reaction mixture was allowed to warm to rt where it was stirred for 4-5 h then quenched with water. The reaction mixture was then diluted with ethyl acetate, washed twice with water, followed by brine, and dried over sodium sulfate. Solvent evaporation afforded crude product (for reaction of **1**, the diallylated product of **4a** also isolated). The crude product was purified by silica gel chromatography using hexane-ethyl acetate (1:9) as eluent. IR , ^{1}H NMR and MS data of isolated compounds (**4a-f**) are given below.

2-(1-Cyanopent-3-enyl)benzonitrile (4b): Viscous liquid, 77%. R_f (20% EtOAc-Hexane) 0.61. IR (neat) 3030, 2919, 2244, 2266, 1671, 1599, 1487, 1448, 968, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68-7.64 (m, 3 H), 7.45-7.42 (m, 1 H), 5.60-5.58 (m, 1 H), 5.46-5.40 (m, 1 H), 4.22 (t, *J* = 6.36 Hz, 1 H), 2.61-2.57 (m, 2 H), 1.65 (d, *J* = 7.32 Hz, 3 H); MS *m/z* (rel.intensity) 196 (M^+, 8), 142 (100), 114 (30), 55 (95). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.76; H, 6.12; N, 14.33.

2-(1-Cyano-4-methylpent-3-enyl)benzonitrile (4c): Viscous liquid, 95%. R_f (20% EtOAc-Hexane) 0.53. IR (neat) 2973, 2917, 2244, 2226, 1673, 1599, 1486, 1448, 847, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.69-7.66 (m, 3H), 7.47-7.43 (m, 1 H), 7.16 (m, 1 H), 5.20 (t, *J* = 1.32 Hz, 1 H), 4.22 (t, *J* = 7.16 Hz, 1H), 2.64 (t, *J* = 7.32 Hz, 2 H), 1.72 (s, 3 H), 1.51 (s, 3H); MS m/z (rel. intensity) 210 (M^+, 20), 196 (35), 142 (100). Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.12; H, 6.90; N, 13.26.

3-(1-Cyanobut-3-enyl)pyridine-2-carbonitrile (4d): Viscous liquid, 51%. R_f (20% EtOAc-Hexane) 0.51. IR (neat) 3084, 2918, 2234, 2265, 1567, 432, 1402, 967. 815, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.71 (dd, *J* = 4.65, 8.01 Hz, 1 H), 8.41 (dd, *J* = 8.17, 1.46 Hz, 1 H), 7.61 (dd, *J* = 8.34, 4.65 Hz, 1 H), 5.85-5.77 (m, 1 H), 5.25 (d, *J* = 10.12 Hz, 1 H), 5.17 (d, *J* = 17.08 Hz, 1 H), 4.37

(t, *J* = 7.0 Hz, 1 H), 2.73 (m, 2 H); MS *m/z* (rel. intensity) 183 (M^+, 30), 143 (8), 41 (100). Anal. Calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.33; H, 5.03; N, 22.87.

3-(1-Cyanopent-3-enyl)pyridine-2-carbonitrile (4e): Viscous liquid, 60%. R_f (20% EtOAc-Hexane) 0.49. IR (neat) 3057, 2919, 2244, 1671, 1568, 1432, 969, 810, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (dd, *J* = 6.44, 1.16 Hz, 3 H), 2.62 (m, 2 H), 4.29 (t, *J* = 7.16 Hz, 1 H), 5.41-5.56 (m, 1 H), 7.59 (dd, *J* = 8.16, 4.76 Hz, 1 H), 7.97 (dd, *J* = 8.12, 1.48 Hz, 1 H), 8.69 (dd, *J* = 3.76, 2.12 Hz, 1 H). MS *m/z* (rel. intensity) 196 (M^+, 5), 143 (100), 55(98), 39(15), 29(16). Anal. Calcd for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.30. Found: C, 73.28; H, 5.66; N, 21.42.

3-(1-Cyano-4-methylpent-3-enyl)pyridine-2-carbonitrile (4f): Viscous liquid, 72%. R_f (20% EtOAc-Hexane) 0.18. IR (neat) 3058, 2973, 2918, 2244, 1672, 1568, 1431, 1095, 808, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (s, 3 H), 1.74 (s, 3 H), 2.70 (t, *J* = 7.25 Hz, 2 H), 4.30 (t, *J* = 6.93 Hz, 1 H), 5.20 (t, *J* = 6.46 Hz, 1 H), 7.63 (dd, *J* = 8.11, 4.76 Hz, 1 H), 8.04 (dd, *J* = 4.62, 1.43 Hz, 1 H), 8.72 (dd, *J* = 4.62, 1.43 Hz, 1 H); MS *m/z* (rel. intensity) 211 (M^+, 10), 199 (15), 157 (95), 69 (100), 41 (30). HRMS: Calcd for $C_{13}H_{13}N_3$: 211.1109. Found: 211.1108.

General Procedure for the Preparation of 1,3,4-Trisubstituted Isoquinolines (6a-f,i,j) and 5,6,8-Trisubstituted 1,7-Naphthyridines (g,h,k-n): In a flame-dried flask flushed with nitrogen, the lithium amide was prepared by adding 6.4 mL of n-BuLi (10 mmol,1.6 M in hexane) to a solution of the appropriate amine (10 mmol) in THF (30 mL) at -70 ^oC. Alkyllithiums (10 mmol) were added directly to THF (30 mL). After stirring for 10 min, compound (**4a-f)** (1 mmol) in THF (10 mL) was added over 5 min. The stirring was continued for 30 min at -70 ^oC, then the reaction mixture was allowed to warm to -30 ^oC to -20 ^oC where it was stirred for an additional 2 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (30 mL), and the THF evaporated under reduced pressure to give a residue which was extracted with dichloromethane (2 X 20 mL). The combined extracts were washed with brine (2 X 20 mL), dried (Na_2SO_4), and concentrated (rotary evaporator). The remaining mixture was subjected to flash column chromatography (silica gel) using hexane/ethyl acetate (9:1, respectively) as eluent to give a liquid or solid product.

3-Amino-4-but-2-enyl-1-piperidin-1-ylisoquinoline (6d): Pale yellow solid, mp 79-80 ^0C (EtOAc-Hexane), 100%. R_f (20%EtOAc-Hexane) 0.59. IR (KBr) 3464, 3366, 3066, 3016, 2936, 2852, 2827, 1606, 1574, 1440, 1374, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 8.44 Hz, 1 H), 7.34 (dd, *J* = 7.04, 1.44 Hz, 1 H), 7.05 (m, 1 H), 5.41 (m, 1 H), 5.35 (m, 1 H), 4.21 (br s, 2 H), 3.32 (d, *J* = 5.4 Hz, 2 H), 3.19 (d, *J* = 4.96 Hz, 4 H), 1.71 (m, 5 H), 1.52 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 150.16, 138.94, 129.24, 127.57, 126.09, 125.50, 121.51, 120.71, 116.96, 100.76,

52.56, 28.68, 26.07, 24.72, 17.56. Anal. Calcd for $C_{18}H_{23}N_3$: C, 76.83; H, 8.24; N, 14.93. Found: C, 76.97; H, 8.30; N, 14.88.

3-Amino-4-but-2-enyl-1-morpholin-4-ylisoquinoline (6e): Brown viscous liquid, 98%. R_f (20% EtOAc-Hexane) 0.47. IR (neat) 3464, 3367, 2956, 2838, 1608, 1581, 1557, 1503, 1454, 1422, 1350, 1259 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99 (d, *J* = 8.21 Hz, 1 H), 7.71 (d, *J* = 8.55 Hz, 1 H), 7.52 (dd, *J* = 7.05, 0.95 Hz, 1 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 5.59-5.48 (m, 2 H), 4.29 (br s, 2 H), 3.95 (t, *J* = 4.56 Hz, 4 H), 3.54 (d, *J* = 6.56 Hz, 2 H), 3.56 (t, *J* = 4.7 Hz, 4 H), 1.65 (dd, *J* = 5.8, 1.13 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 158.97, 150.06, 138.78, 129.19, 127.24, 125.43, 125.32, 121.51, 120.69, 116.15, 101.21, 66.55, 51.51, 28.38, 17.34. Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found: C, 72.29; H, 7.66; N, 14.98.

3-Amino-4-but-2-enyl-1-pyrrolidin-1-ylisoquinoline (6f): Brown viscous liquid, 99%. R_f (20% EtOAc-Hexane) 0.65. IR (neat) 3367, 2960, 2852, 1607, 1580, 1546, 1513, 1436, 1413, 1327 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.08 (d, *J* = 8.48 Hz, 1 H), 7.61 (d, *J* = 8.52 Hz, 1 H), 7.45 (m, 1 H), 7.08 (m, 1 H), 5.59-5.45 (m, 2 H), 4.18 (br s, 2 H), 3.77 (t, *J* = 6.45 Hz, 4 H), 3.42 (dd, *J* = 4.02, 1.72 Hz, 2 H), 1.95 (t, *J* = 6.48 Hz, 4 H), 1.64 (dd, *J* = 5.05, 1.18 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.67, 150.02, 139.49, 128.84, 127.98, 126.47, 125.10, 121.06, 119.17, 115.57, 97.19, 51.13, 28.65, 25.66, 17.56. HRMS:Calcd for $C_{17}H_{21}N_3$: 267.3689. Found: 267.3690.

5-Allyl-6-amino-8-piperidin-1-yl[1,7]naphthyridine (6g): Brownish semi solid, 98%. R_f (20% EtOAc-Hexane) 0.51. IR (neat) 3476, 3372, 2931, 2851, 1599, 1573, 1545, 1497, 1440, 1370 cm^{-1}; ^1H NMR $CDCl_3$) δ 8.47 (dd, *J* = 4.0, 1.56 Hz, 1 H), 7.87 (dd, *J* = 8.72, 1.64 Hz, 1 H), 7.30 (dd, *J* = 8.56, 4.0 Hz, 1 H), 5.91-5.87 (m, 1 H), 5.04 (dd, *J* = 10.08, 1.60 Hz, 1 H), 4.96 (dd, *J* = 17.16, 1.76 Hz, 1H), 4.23 (br s, 2 H), 3.80 (t, *J* = 5.12 Hz, 4 H), 3.42 (m, 2H), 1.75 (m, 4 H), 1.66 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 158.09, 150.47, 142.61, 134.79, 134.43, 132.67, 129.41, 123.69, 115.42, 96.30, 50.82, 29.56, 25.98, 25.05. Anal. Calcd for $C_{15}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.88; H, 7.59; N, 21.03.

5-Allyl-6-amino-8-pyrrolidin-1-yl[1,7]naphthyridine (6h): Yellow solid, mp 104-105 ^0C (EtOAc-Hexane), 94%. R_f (20% EtOAc-Hexane) 0.48. IR (KBr) 3476, 3374, 2966, 2867, 1598, 1572, 1541, 1502, 1475, 1456, 1330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.40 (dd, *J* = 4.0, 1.64 Hz, 1 H), 7.79 (dd, *J* = 8.68, 1.64 Hz, 1 H), 7.26 (dd, *J* = 8.48, 4.0 Hz, 1 H), 5.93-5.88 (m, 1 H), 5.05-4.97 (m, 2 H), 4.20 (br s, 2 H), 4.00 (t, *J* = 6.68 Hz, 4 H), 3.41-3.39 (m, 2 H), 1.97-1.94 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 154.94, 151.26, 141.54, 135.38, 134.77, 132.82, 128.47, 123.76, 115.17, 92.78, 50.75,

29.67, 25.79. Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.49; H, 7.30; N, 21.96.

3-Amino-1-butyl-4-prenylisoquinoline (6i): Pale yellow solid, mp 68-69 ^{0}C (EtOAc-Hexane), 83%. R_f (20% EtOAc-Hexane) 0.47. IR (KBr) 3476, 3308, 3179, 2958, 2925, 2858, 1632, 1578, 1562, 1505, 1453, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, *J* = 8.44 Hz, 1 H), 7.77 (d, *J* = 8.6 Hz, 1 H), 7.53 (m, 1 H), 7.25 (m, 1 H), 5.08 (m, 1 H), 4.34 (br s, 2 H), 3.53 (d, *J* = 6.48 Hz, 2 H), 3.14 (t, *J* = 8.0 Hz, 2 H), 1.88 (s, 3 H), 1.78 (m, 2 H), 1.72 (s, 3 H), 1.48 (m, 2 H), 0.97 (t, *J* = 7.12 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ160.01, 151.16, 137.27, 133.44, 129.66, 126.21, 122.37, 122.08, 121.66, 106.98, 35.11, 32.33, 25.69, 25.06, 23.12, 18.13, 14.08. Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.78; H, 9.25; N, 10.28.

3-Amino-1-*sec*-butyl-4-prenylisoquinoline (6j): Brownish semi solid, 91%. R_f (20% EtOAc-Hexane) 0.75. IR (neat) 3474, 3377, 3071, 2963, 2929, 2871, 1615, 1563,1451, 1376, 1248 cm^{-1} ^{1}HNMR ($CDCl_3$); δ 8.04 (d, *J* = 8.48 Hz, 1 H), 7.74 (d, *J* = 8.6 Hz, 1 H), 7.44 (m, 1 H), 7.17 (m, 1 H), 5.09 (m, 1 H), 4.45 (br s, 2 H), 3.56 (m, 1 H), 3.49 (d, *J* = 6.44 Hz, 2 H), 1.98 (m, 1 H), 1.83 (s, 3 H), 1.67 (s, 3 H), 1.66 (m, 1 H), 1.34 (d, *J* = 6.8 Hz, 3 H), 0.87 (t, *J* = 7.44 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ162.98, 151.23, 137.09, 132.87, 129.16, 125.26, 122.18, 121.89, 121.69, 121.64, 106.16, 37.14, 29.40, 25.45, 24.92, 20.11, 17.85, 12.34. Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.67, H, 9.21; N, 10.47.

6-Amino-8-butyl-5-prenyl[1,7]naphthyridine (6k): Brown viscous liquid, 70%. R_f (20% EtOAc-Hexane) 0.45. IR (neat) 3471, 3311, 3185, 2957, 2928, 2858, 1601, 1582, 1453, 1416, 1391, 1362 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.66 (q, *J* = 2.24 Hz, 1 H), 8.07 (dd, *J* = 8.64, 1.44 Hz, 1 H), 7.41 (q, *J* = 4.41 Hz, 1 H), 5.05 (m, 1 H), 4.45 (br s, 2 H), 3.48 (d, *J* = 6.64 Hz, 2 H), 3.36 (t, *J* = 7.84 Hz, 2 H), 1.87 (s, 3 H), 1.80 (m, 2 H), 1.72 (s, 3 H), 1.48 (m, 2 H), 0.96 (t, *J* = 7.36 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 162.50, 151.49, 145.72, 137.78, 134.01, 132.10, 129.94, 124.25, 121.14, 106.02, 33.42, 31.93, 25.66, 24.74, 23.10, 18.14, 14.17. HRMS: Calcd for $C_{17}H_{23}N_3$: 269.1892. Found: 269.1892.

6-Amino-5-but-2-enyl-8-morpholin-4-yl[1,7]naphthyridine (6l): Viscous liquid, 99%. R_f (30% EtOAc-Hexane) 0.45. IR (neat) 3475, 3363, 2959, 2916, 2853, 1601, 1578, 1549, 1497,1439,1115 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.47 (d, *J* = 3.90 Hz, 1 H), 7.89 (dd, *J* = 6.58, 1.51 Hz, 1 H), 7.26 (m, 1 H), 5.51-5.37 (m, 2 H), 4.57 (br s, 2 H), 3.93 (m, 8 H), 3.39 (m, 2 H), 1.59 (d, *J* = 6.01 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.30, 149.95, 142.10, 133.85, 131.62, 129.15, 126.89, 125.27, 123.27, 97.57, 66.44, 49.48, 27.72, 17.14. HRMS: Calcd for $C_{17}H_{22}N_4$: 284.1637. Found: 284.1638.

6-Amino-5-but-2-enyl-6-pyrrolidin-1-yl[1,7]naphthyridine (6m): Viscous liquid, 98%. R_f (20% EtOAc-Hexane) 0.65. IR (neat) 3372, 2964, 1598, 1573, 1541, 1502, 1475, 1455, 1330 cm^{-1}; ^{1}H

NMR ($CDCl_3$) δ 8.38 (dd, J = 4.0, 1.56 Hz, 1 H), 7.81 (dd, *J* = 8.60, 1.52 Hz, 1 H), 7.25 (m, 1 H), 5.49-5.48 (m, 1 H), 5.44-5.42 (m, 1 H), 4.20 (br s, 2 H), 3.98 (m, 4 H), 3.31 (m, 2 H), 1.94 (m, 2 H) 1.62 (dd, *J* = 6.12, 1.44 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.72, 150.89, 141.35, 134.54, 132.62, 128.52, 128.43, 127.88, 125.44, 123.57, 93.81, 50.58, 28.27, 25.64, 17.65. HRMS: Calcd for $C_{16}H_{20}N_4$: 268.1688. Found: 268.1687.

General Procedure for the Reaction of $PdCl_2(MeCN)_2$ with 4-Alkenyl-3-aminoisoquinolines under Stoichiometric Conditions (Method B). Into a flame-dried flask flushed with nitrogen was added $PdCl_2(MeCN)_2$ (1 equiv) and of 10 mL THF and allowed to stir for 5-10 min. The substrate (**6**) (0.5 mmol) was premixed with 5 mL of THF, then added to slurry of palladium complex *via* syringe. After the mixture was stirred for 1.5 h at rt, triethylamine (1 equiv.) was added and the resulting mixture stirred for 3 h. To this solution was added 2 equiv. of triethylamine. An additional 2 equiv of triethylamine was added after an additional 1 h of stirring. The reaction was then allowed to stir for an additional 2 h, and was followed through celite which was washed with dichloromethane (20 mL). The combined washes were concentrated on a rotary evaporator. Products were isolated by silica gel column chromatography using hexane-ethyl acetate (1:4), respectively, as eluent.

b) **Under Catalytic Conditions (Method A).** In a flame-dried flask flushed with nitrogen were placed $PdCl_2(MeCN)_2$ (20 mol %), benzoquinone (1 equiv), LiCl (10 equiv) and 20 mL of THF, and the resulting mixture was stirred at rt for 5 min. The substrate (0.5 mmol, 1 equiv; **5 d-f, i-l**) was dissolved in THF (5 mL/0.5 mmol substrate) then added to the flask *via* syringe, and the resulting solution was refluxed for 15 h. The mixture was then worked up in a similar manner describe above in the stoichiometric procedure. The physical and spectral properties of products (**7a-h**) and (**8a-c**) and yields, expressed as percentage for catalytic and yields for stoichiometric reactions placed in parenthesis, are listed below.

2-Methyl-5-piperidin-1-yl-3*H*-pyrrolo[2,3-*c*]isoquinoline (7a): Light brown solid, mp 147-148 ^{0}C (EtOAc-Hexane), 58% (70%) . R_f (20% EtOAc-Hexane) 0.35. IR (KBr) 3247, 2932, 2850, 1618, 1560, 1543, 1417, 1358,1250,1148 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.63 (br s, 1 H), 8.20 (d, *J* = 8.4 Hz, 1 H), 8.03 (d, *J* = 8.24 Hz, 1 H), 7.60 (m, 1 H), 7.37 (m, 1 H), 6.53 (s, 1 H), 3.28 (m, 4 H), 2.48 (s, 3 H), 1.85 (m, 4 H), 1.63 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 158.04, 141.32, 132.57, 129.74, 128.82, 126.58, 122.51, 122.42, 118.74, 110.13, 97.53, 53.05, 26.07, 24.53, 13.62. HRMS: Calcd for $C_{17}H_{19}N_3$: 265.1578. Found: 265.1572.

2-Methyl-5-morpholin-4-yl-3*H*-pyrrolo[2,3-*c*]isoquinoline (7b): Light brown solid, mp 207 ^{0}C (decomp, EtOAc-Hexane), 55% (66%). R_f (20% EtOAc-Hexane) 0.27. IR (KBr) 3223, 2959, 2917,

2839, 1617, 1587, 1514, 1354, 1362,1106 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.40 (br s, 1 H), 8.21 (d, *J* = 8.4 Hz, 1 H), 8.05 (d, *J* = 8.12 Hz, 1 H), 7.62 (m, 1 H), 7.38 (m,1 H), 6.55 (s, 1 H), 3.99 (t, *J* = 4.6 Hz, 4 H), 3.34 (t, *J* = 4.64 Hz, 4 H), 2.51 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.12, 140.84, 132.83, 131.10, 129.31, 126.23, 125.78, 122.90, 118.28, 111.24, 97.38, 67.08, 52.14, 13.46. HRMS: Calcd for $C_{16}H_{17}N_3O$: 267.1371. Found: 267.1362.

2-Methyl-5-pyrrolidin-1-yl-3*H*-pyrrolo[2,3-*c*]isoquinoline (7c): Brown solid, mp 166-167 ^{0}C (EtOAc-Hexane), 51% (67%). R_f (20% EtOAc-Hexane) 0.48. IR (KBr) 3215, 2971, 2940, 2865, 1615, 1592, 1557, 1544, 1415, 1355 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.34 (br s, 1 H), 8.24 (d, *J* = 8.48 Hz, 1 H), 7.97 (d, *J* = 8.24 Hz, 1 H), 7.57 (m, 1 H), 7.29 (m, 1 H), 6.46 (s, 1H), 3.75 (t, *J* = 6.6 Hz, 4 H), 2.45 (s, 3 H), 1.99(m, 4 H); ^{13}C NMR ($CDCl_3$) δ 155.29, 141.92, 133.25, 128.69, 128.62, 127.08, 122.38, 121.24, 117.77, 108.22, 97.25, 51.70, 25.46, 13.57. HRMS: Calcd for $C_{16}H_{17}N_3$: 251.1422. Found: 251.1415. Anal. Calcd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.64; H, 6.88, N, 16.79.

2-Methyl-5-piperidin-1-yl-3*H*-pyrrolo[2,3-*c*][1,7]naphthrydine (7d): Light brown solid, mp 198-200 ^{0}C (EtOAc-Hexane), 68% (0%). R_f (20% EtOAc-Hexane) 0.58. IR (KBr) 3225, 2932, 2852, 1606, 1555, 1430, 1357,1246, 1095, 793 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.92 (br s, 1 H), 8.76 (dd, *J* = 2.5, 1.73 Hz, 1 H), 8.30 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.47 (dd, *J* = 8.19, 4.1 Hz, 1 H), 6.48 (s, 1 H), 3.71 (t, *J* = 5.42 Hz, 4 H), 2.45 (s, 3 H), 1.87(m, 4 H), 1.69 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 156.67, 145.05, 141.53, 134.95, 131.07, 130.46, 128,20, 123.52, 108.43, 97.93, 52.16, 26.12, 25.08, 14.01. HRMS: Calcd for $C_{16}H_{18}N_4$: 266.1531. Found: 266.1541.

2-Methyl-5-pyrrolidin-1-yl-3*H*-pyrrolo[2,3-*c*][1,7]naphthyridine (7e): Pale yellow solid, mp 88-90 ^{0}C (EtOAc-Hexane), 71% (0%). R_f (20% EtOAc-Hexane) 0.43. IR (KBr) 3229, 2965, 2868, 2359, 2341, 1606, 1548, 1477, 1428, 1336 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 8.59 (dd, *J* = 4.16, 1.68 Hz, 1 H), 8.41 (br s, 1 H), 8.16 (dd, *J* = 8.68, 1.65 Hz, 1 H), 7.39 (dd, *J* = 8.16, 4.08 Hz, 1 H), 6.35 (s, 1 H), 4.01 (t, *J* = 6.64 Hz, 4 H), 2.40 (s, 3 H), 1.98 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 153.50, 143.36, 134.72, 130.06, 128.59, 128.47, 123.54, 105.24, 97.66, 51.27, 29.75, 25.80, 13.87. HRMS Calcd for $C_{15}H_{16}N_4$: 252.1374. Found: 252.1366. Anal. Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.31; H, 6.58, N, 22.08.

2-Ethyl-5-piperidin-1-yl-3*H*-pyrrolo[2,3-*c*]isoquinoline (7f): Pale yellow solid, mp 114-115 ^{0}C (EtOAc-Hexane), 76% (0%). R_f (20% EtOAc-Hexane) 0.83. IR (KBr) 3240, 2932, 2850, 1618, 1561, 1540, 1419, 1358, 1251, 761 cm^{-1}; δ ^{1}H NMR ($CDCl_3$) δ 8.58 (br s, 1 H), 8.22 (d, *J* = 8.36 Hz, 1 H), 8.05 (d, *J* = 8.16 Hz, 1 H), 7.62 (m, 1 H), 7.37 (m, 1 H), 6.57 (s, 1 H), 3.30 (t, *J* = 4.74 Hz, 4 H), 2.85 (q, *J* = 7.54 Hz, 2 H), 1.89-1.84 (m, 4 H), 1.72-1.69 (m, 2 H), 1.37 (t, *J* = 7.51 Hz, 3

H); ^{13}C NMR ($CDCl_3$) δ 158.23, 141.49, 136.56, 132.99, 129.07, 126.85, 122.75, 122.59,118.89, 110.18, 95.97, 53.28, 26.28, 24.76, 21.53, 13.42. HRMS: Calcd for $C_{18}H_{21}N_3$: 279.1735. Found: 279.1730. Anal. Calcd for $C_{18}H_{21}N_3$; C, 77.37; H, 7.58; N, 15.05. Found: C, 77.08; H, 7.61, N, 14.96.

2-Ethyl-5-morpholin-4-yl-3*H*-pyrrolo[2,3-*c*]isoquinoline (7g): Pale white solid, mp 257-260 ^{0}C (EtOAc-Hexane), yield 72% (0) %. R_f (20% EtOAc-Hexane) 0.33. IR (KBr) 3221, 2962, 1618, 1563, 1540, 1422, 1353, 1250, 1105 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.49 (br s, 1H), 8.22 (d, *J* = 8.41 Hz, 1 H), 8.08 (d, *J* = 8.08 Hz, 1 H), 7.64 (m, 1 H), 7.39 (m, 1 H), 6.59 (s, 1 H), 4.12-3.95 (m, 4 H), 3.36 (t, *J* = 4.65 Hz, 4 H), 2.86 (q, *J* = 7.53 Hz, 2 H), 1.39 (t, *J* = 7.58 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.31, 140.85, 137.17, 132.07, 128.54, 125.78, 122.35, 122.07, 117.19, 109.75, 94.85, 66.12, 51.91, 20.71, 13.19. HRMS: $C_{17}H_{19}N_3O$ Calcd for 281.1528, Found: 281.1529. Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.56; H, 6.81; N, 14.97. Found: C, 72.44; H, 7.04, N, 14.74.

2-Ethyl-5-pyrrolidin-1-yl-3*H*-pyrrolo[2,3-*c*]isoquinoline (7h): Offwhite solid, mp 124-125 ^{0}C (EtOAc-Hexane), yield 65% (0%). R_f (20% EtOAc-Hexane) 0.57. IR (KBr) 3234, 2966, 2869, 1616, 1589, 1561, 1415, 1356, 1294 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.54 (br s, 1 H), 8.24 (d, *J* = 8.48 Hz, 1 H), 7.98 (d, *J* = 7.94 Hz, 1 H), 7.56 (m, 1 H), 7.28 (m, 1 H), 6.48 (s, 1 H), 3.76 (t, *J* = 6.63 Hz, 4 H), 2.75 (q, *J* = 7.49 Hz, 2 H), 1.97 (m, 4 H), 1.29 (t, *J* = 7.55 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.28, 141.29, 135.16, 133.58, 129.05, 127.29, 122.55, 121.53, 117.87, 108.08, 95.86, 51.97, 25.68, 21.48, 13.49. HRMS : Calcd for $C_{17}H_{19}N_3$: 265.1578. Found: 265.1571.

6-Butyl-3,3-dimethyl-3,4-dihydrobenzo[*c*][1,8]naphthyridine (8a): Viscous liquid, 49% (54%). R_f (20% EtOAc-Hexane) 0.72. IR (neat) 3388, 3283, 3066, 2957, 2929, 2869, 1633, 1615, 1562, 1513, 1481,1452 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, *J*= 8.48 Hz, 1 H), 7.73 (d, *J* = 8.48 Hz, 1 H),7.44 (dd, *J* = 5.64, 1.4 Hz, 1 H), 7.12 (dd, *J* = 6.92, 1.08 Hz, 1 H), 6.83 (d, *J* = 9.72 Hz, 1 H), 5.46 (d, *J* = 9.68 Hz, 1 H), 4.64 (br s, 1 H), 3.06 (t, *J* = 8.0 Hz, 2 H), 1.76-1.70 (m, 2 H), 1.48-1.43 (m, 2 H), 1.36 (s, 6 H), 0.95 (t, *J* = 7.36 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.72, 149.96, 133.95, 129.83, 128.78, 126.28, 121.64, 121.40, 120.32, 118.25, 101.72, 53.22, 35.33, 32.24, 31.57, 23.12, 14.06. HRMS: Calcd for $C_{18}H_{22}N_2$ (M^++H): 267.1861. Found: 267.1857. Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52. Found: C, 81.31; H, 8.44; N, 10.55.

6-*sec*-Butyl-3,3-dimethyl-3,4-dihydrobenzo[*c*][1,8]naphthyridine (8b): Viscous liquid, 53% (51%). R_f (20% EtOAc-Hexane) 0.89. IR (neat) 3389, 2962, 2928, 1633, 1614, 1561, 1513, 1452, 1381, 1203 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, *J* = 8.52 Hz, 1 H), 7.80 (d, *J* = 8.54 Hz, 1 H), 7.49 (dd, *J* = 7.08, 1.3 Hz, 1 H), 7.19 (dd, *J* = 8.2, 1.04 Hz, 1 H), 6.89 (d, *J* = 9.74 Hz, 1 H), 5.52 (dd, *J* = 9.83, 2.17 Hz, 1 H), 4.72 (br s, 1 H), 3.57 (q, *J* = 6.86 Hz, 1 H), 1.97 (m, 1 H), 1.70 (m, 1

H), 1.43 (s, 6 H), 1.36 (d, *J* = 6.72 Hz, 3 H), 0.93 (t, *J* = 7.64 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.16, 150.14, 133.97, 129.54, 128.75, 125.62, 121.52, 120.36, 118.33, 101.25, 53.21, 37.49, 31.59, 29.76, 29.51, 20.15, 12.53. HRMS: Calcd for $C_{18}H_{23}N_2$ (M^++H): 267.1861. Found: 267.1866. Anal. Calcd for $C_{18}H_{22}N_2$: C, 81.15; H, 8.33; N, 10.52. Found: C, 80.94; H, 8.63, N, 10.22.

6-Butyl-3,3-dimethyl-3,4-dihydropyridino[4,3-*c*][1,8]naphthyridine (8c): Viscous liquid, 55% (70%.) R_f (20% EtOAc-Hexane) 0.69. IR (neat) 3341, 3214, 3197, 2961, 2928, 2871, 1637, 1577, 1550, 1502, 1457, 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.55 (d, *J* = 3.84 Hz, 1 H), 8.01 (d, *J* = 8.64 Hz, 1 H), 7.30 (dd, *J* = 8.48, 4.12 Hz, 1 H), 6.72 (d, *J* = 9.84 Hz, 1 H), 5.47 (d, *J* = 10.16 Hz, 1 H), 4.74 (br s, 1 H), 3.28 (t, *J* = 7.88 Hz, 2 H), 1.78-1.72 (m, 2 H), 1.48-1.42 (m, 2 H), 1.38 (s, 6 H), 0.93 (t, 7.2 Hz, 3 H); ($CDCl_3$) δ 164.15, 150.00, 145.39, 136.97, 129.16, 128.84, 128.21, 124.39, 117.43, 100.77, 53.59, 33.62, 31.78, 23.10, 14.16. HRMS: Calcd for $C_{17}H_{22}N_3$ (M^++H): 268.1813. Found: 268.1806.

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