Articles

Combined Metalation–Palladium-Catalyzed Cross Coupling Strategies. A Formal Synthesis of the Marine Alkaloid Amphimedine

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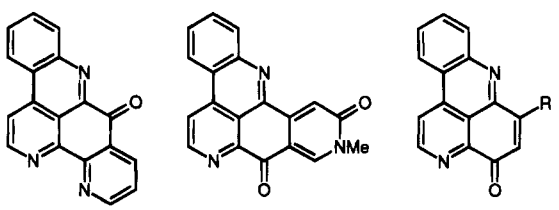
The synthesis of 5-(4-pyridyl)benzo[*c*][2,7]naphthyridin-4-one (**4**), an intermediate previously employed in a total synthesis of the marine alkaloid, amphimedine (**2**), is reported. The route comprises the Pd-catalyzed Suzuki cross coupling of pyridylborane **21** with 2-iodoaniline to give the azabiaryl **22**, which upon LDA-mediated cyclization and triflation leads to benzonaphthyridine **5**. Stille cross coupling of **5** with pyridylstannane **24** affords the pyridylbenzonaphthyridine **25**, which upon BBr_3 treatment leads to the target molecule **4**. Pyridine directed *ortho* metalation chemistry leading to halonicotinate ester **12** and amides **14a,b** and cross coupling to benzonaphthyridinones **17**, **18** (one-pot procedure) and azabiaryls **20a,b** are also reported.

The discovery, during the last decade, of a number of marine alkaloids with highly condensed tetra- and pentaheterocyclic nuclei, coupled with their significant and diverse biological activity (Ca-releasing, antiviral, antimicrobial, cytotoxic to L1210 murine leukemia cells) has prompted considerable interest in the synthetic community.[1] Of the more than 30 alkaloids reported to date, the dominant structural feature is the pyrido[2,3,4-*kl*]-acridine (dibenzo[*f,i,j*][2,7]naphthyridine) nucleus as indicated in the representative members ascididemine (**1**), amphimedine (**2**), and the cystodytins (**3**) (Scheme 1).[1a] The highly compact nature of these groups of alkaloids together with annoying variations have demanded innovative synthetic approaches.[1a,2] Syntheses of the pyridoacridine ring systems *prior* to the discovery of the natural products tended to be classical and specific according to the particular isomer prepared.[1b] In the context of combined directed *ortho* metalation–cross coupling strategies under current development in our laboratories,[3] we developed a new route to phenanthridines and phenanthridinones by coupling of *o*-*N*-*t*-Boc-amino phenylboronic acids with *o*-bromobenzamides based on the excellent Suzuki protocol.[4] Herein we report on the extension of this tactic for the preparation of the pyridyl benzo[*c*][2,7]naphthyridine **4** (Scheme 2),[5] a key intermediate in a recently described total synthesis of amphimedine.[6] Aside from effecting a formal synthesis of amphimedine, this work reinforces the generality of the metalation–cross coupling route[4] thereby inviting potential extension to the preparation of related alkaloids, e.g. ascididemine (**1**) and the cystodytins (**3**).

Scheme 1



1 Ascididemine **2** Amphimedine **3** Cystodytins

Given the intermediate target **4**, retrosynthetic analysis, based on a transition metal-catalyzed cross coupling process, cascades to the triflate **5** which, in turn, may be derived from **6** by functional group interconversion. Azaphenanthridinone **6** may be dissected into aniline **7** and nicotinate or nicotinamide **8** cross coupling partners, in which X and Y may be variations on metal (boron, tin) and halogen based on availability of starting materials.

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(1) Excellent reviews: (a) structural elucidation and synthesis of alkaloids: Salas, M.; Alvarez, M.; Joule, J. A. *Heterocycles* **1991**, *32*, 759. (b) Synthesis of the pyridoacridine nuclei, aside from alkaloidal: Alvarez, M.; Joule, J. A. *Ibid.* **1992**, *34*, 2385.

(2) *Inter alia*, Stille coupling – Diels–Alder approach to **2**: Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 4051. See also Kubo, A.; Nakahara, S. *Heterocycles* **1988**, *27*, 2095. Nitrene insertion approach to **3**: Ciufolini, M. A.; Byrne, N. E. *J. Am. Chem. Soc.* **1991**, *113*, 8016. Enamine–quinone cyclization approach to **1**: Bracher, F. *Liebigs Ann. Chem.* **1990**, 205. Bracher, F. *Heterocycles* **1989**, *29*, 2093. Mallory photocyclization approach to **1**: Moody, C. J.; Rees, C. W.; Thomas, R. *Tetrahedron* **1992**, *48*, 3589.

(3) (a) Fu, J.-m.; Zhao, B.-p.; Sharp, M. J.; Snieckus, V.; *Can. J. Chem.* **1993**, *72*, 227 and refs cited therein. (b) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron Lett.* **1994**, *35*, 2003. (c) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832.

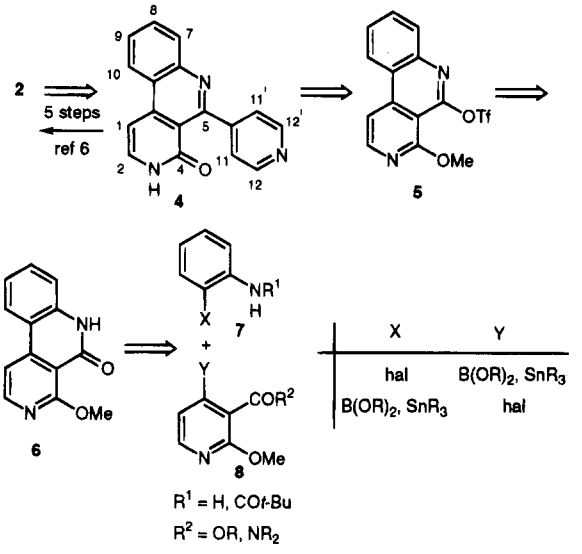
(4) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463.

(5) Results described constitute, in part, the work of (a) Guillier, F. (Diplôme d'Etudes Approfondies de Chimie Organique, Université de Rouen, 1992) and (b) Siddiqui, M. A. (Ph.D. thesis, University of Waterloo, 1990). During the course of preparation of this manuscript, Gronowitz described the synthesis of several derivatives of this ring system by a pyridylstannane–bromoacetanilide cross coupling reaction, see Malm, J.; Björk, P.; Gronowitz, S.; Hörnfeldt, A.-B. *Tetrahedron Lett.* **1994**, *35*, 3195.

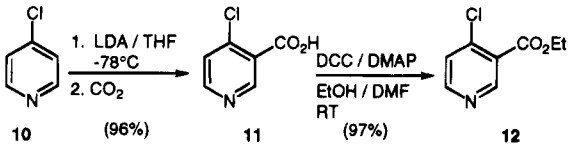
(6) Prager, R. H.; Tsopelas, C.; Heisler, T. *Aust. J. Chem.* **1991**, *44*, 277.

0022-3263/95/1960-0292$09.00/0

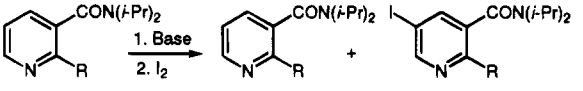
Scheme 2



Scheme 3



Scheme 4

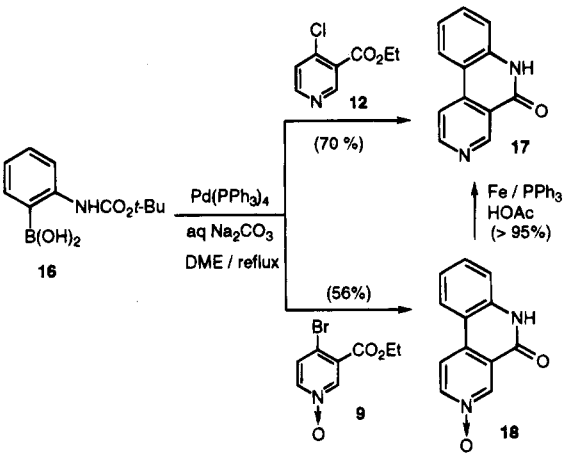


Base	Cmpd	R	Yld, %	Cmpd	R	Yld, %
LDA / THF / -75°C	**14a**	H	50	**15a**	H	25
LiTMP / TMEDA / -70°C	**14b**	OMe	55			

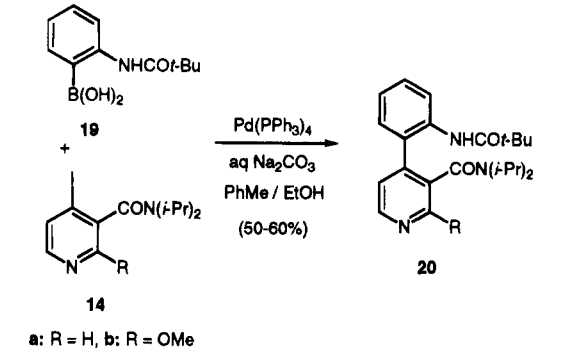
Synthesis of Pyridine Cross Coupling Partners. 4-Bromo-3-carbethoxypyridine 1-oxide (**9**, Scheme 5) was prepared in four steps and 19% overall yield from commercially available 3-picoline 1-oxide using a literature procedure (see Experimental Section). The low yield encouraged application of pyridine directed *ortho* metalation chemistry[7] and led to the preparation of three other halopyridine derivatives (Schemes 3 and 4) for use in cross coupling reactions. Thus LDA deprotonation of commercial 4-chloropyridine (**10**) followed by carboxylation afforded **11**, which upon esterification gave 3-carbethoxy-4-chloropyridine (**12**) in high overall yield. In the second series, the same conditions of deprotonation on *N,N*-diisopropylnicotinamide (**13a**) followed by iodination provided a separable mixture of the desired 4-iodo derivative **14a** (50%) together with the diiodinated material **15a** (25%). However, application of LiTMP/TMEDA conditions on the 2-methoxynicotinamide **13b** furnished the 4-iodo derivative **14b** as the sole isolable product in modest yield.

Cross Coupling Reactions. Cross coupling reactions were pursued on the halopyridines **9**, **12**, **14a**, and **14b**. Following previous work,[4] cross coupling of the freshly prepared *N*-*t*-Boc-amino phenylboronic acid **16** (Scheme 5) with the 4-chloronicotinate **12** under modified Suzuki conditions afforded directly the naphthyridinone **17** in good yield. In a second route, treatment of **16** with the pyridine *N*-oxide **9** under identical conditions provided the corresponding naphthyridinone *N*-oxide **18**, which was reduced quantitatively using iron–triphenylphosphine into **17**. In both series, the intermediate azabiaryl products were not detected under the given reaction conditions.

Scheme 5



Scheme 6



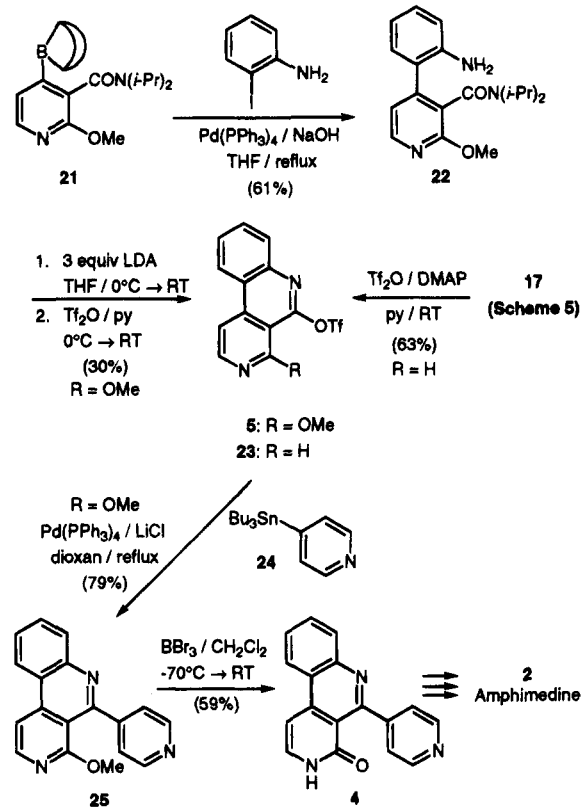
In the alternate series, cross coupling of the *N*-pivaloylamino phenylboronic acid **19** (Scheme 6) with the 4-iodonicotinamides **14a** and **14b** led only to the azabiaryls **20a** (50%) and **20b** (60%), respectively, the lack of cyclization being attributed to the greater thermal stability of the pivaloyl over the *t*-Boc functionality. In order to test a cross coupling reaction which employs a boron-bearing pyridine partner, the methodology of Terashima,[8] which has been successfully used for the preparation of 3- and 4-arylpyridines, was attempted. Thus the pyridyl borane **21** (Scheme 7), prepared by lithiation of **13b** as before followed by treatment with 9-methoxy-9-borabicyclononane, was subjected to reaction with *o*-iodoaniline under the prescribed conditions ($Pd(PPh_3)_4$/Bu_4NBr/NaOH).[6] Curiously, these conditions did not lead to the expected product **22**. However, exclusion of tetra-*n*-butylammonium bromide for these conditions (essentially reversal to the Suzuki conditions) led to the azabiaryl **22** in good yield.

While treatment of the *N*-pivaloyl azabiaryl **20b** under acidic conditions led only to mixtures of products including uncyclized pyridones, the corresponding amino de-

(7) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187.

(8) (a) Terashima, M.; Oda, I.; Ishikura, M. *Heterocycles* **1985**, *23*, 2375. (b) Ishikura, M.; Kamada, M.; Ohta, T.; Terashima, M. *Heterocycles* **1984**, *22*, 2475.

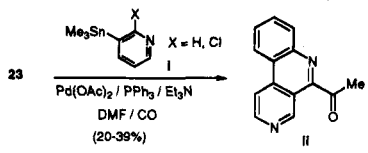
Scheme 7



rivative **22** (Scheme 7), when subjected to excess LDA, led to an orange substance whose NMR spectrum was consistent with the cyclized product but which was difficult to purify. Hence it was directly treated with triflic anhydride and gave the benzonaphthyridine triflate **5** in 30% overall yield. The simpler triflate **23** was prepared from the benzonaphthyridinone **17**.

Synthesis of the Pyridylbenzonaphthyridinone 4. In order to converge upon the pyridylbenzonaphthyridinone intermediate **4** prepared by Prager en route to amphimedine (**2**),[6] coupling of **5** with pyridylstannanes and boranes/boronic acids was contemplated. Owing to the generally better behaved nature of the former class,[5b] the benzonaphthyridine triflate **5** was subjected to cross coupling with 4-(tributylstannyl)pyridine (**24**) under typical Stille conditions. The required **25**, obtained in excellent yield, was demethylated by BBr_3 to afford **4** whose physical and spectral properties were identical to those reported by Prager for material prepared by a different route.[9,10]

(9) In efforts[5] to employ **5** and **23** as intermediates for the synthesis of ascididemine (**1**), **23** was subjected to carbonylative cross coupling conditions [($Pd(PPh_3)_4$ or $PdCl_2$(dppf)/LiCl/DMF/CO] with 2-chloro-3-(trialkylstannyl)pyridine (alkyl = Me, n-Bu). These reactions led to complex mixtures of products and no detection of the desired material. In another set of experiments, **23** was cross coupled with stannylated pyridines **i** under similar conditions to those of Cacchi and co-workers[11] to afford the acetyl derivative **ii** in low yields. Hence, although carbonylation occurs in these reactions, preferred methyl over pyridyl transfer ensues, a result for which we have no rationalization.



Experimental Section

General Methods. Melting points were determined on Kofler, Buchi, and electrothermal IA9000S apparatus (for mps > 250 °C) and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian T60 (60 MHz), Bruker AC-200 in $CDCl_3$ or in DMSO-d_6. Chemical shifts are reported in ppm from internal tetramethylsilane, hexamethyldisiloxane (DMSO-d_6), or residual chloroform (7.27 ppm). Mass spectra were obtained on a high resolution VG 7070F instrument at 70 eV unless otherwise stated. Elemental analyses were performed on a Carlo Erba CHNOS 110S apparatus (GQ) and by Galbraith Laboratories Inc., Knoxville, TN.

Trimethyl and tri-*n*-butylstannyl chloride and palladium(II) chloride were purchased from the Aldrich Chemical Co. and used directly. The light sensitive tetrakis(triphenylphosphine)palladium(0) catalyst was prepared by hydrazine reduction of $PdCl_2$ as described by Coulsen[12] and stored under N_2 at −10 °C. TMEDA (*N,N,N',N'*-tetramethylethylenediamine), *i*-Pr_2NH, and tetramethylpiperidine were purchased from Aldrich and stored over CaH_2 and distilled therefrom before use. Commercial 2.5 M solutions of *n*-butyllithium in hexane were stored under a dry and deoxygenated argon atmosphere and transferred via syringes through septa into reaction vessels. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from benzophenone ketyl immediately prior to use. Lithium diisopropylamide (LDA) was prepared by addition of *n*-butyllithium (12.5 mL, 20 mmol) to a cold (−75 °C), stirred THF (50 mL) solution of *i*-Pr_2NH (2.02 g, 20 mmol) followed by warming to 0 °C for 0.5 h.

Preparation of Pyridine Derivatives. The following compounds were prepared by literature methods: 3-methyl-4-nitropyridine 1-oxide, mp 135−136 °C (acetone) (lit.[13] mp 136−137 °C); 3-carboxy-4-nitropyridine 1-oxide, mp 170−171 °C (lit.[14] mp 172 °C); 4-bromo-3-carboxypyridine 1-oxide, mp 165−167 °C (EtOH−H_2O) lit.[15] mp 167 °C.

4-Bromo-3-carbethoxypyridine 1-Oxide (9). A suspension of 4-bromo-3-carboxypyridine 1-oxide (2.6 g, 12.0 mmol), ethanol (2 mL, 36 mmol), and DMAP (200 mg, 1.9 mmol) in DMF (30 mL) at 0 °C was treated with powdered DCC (5.2 g, 25 mmol) and the reaction mixture was allowed to stir for 4 h. Filtration, followed by evaporation *in vacuo*, and recrystallization (EtOAc−hexane) gave 1.4 g (48%) of **9**, which was immediately used in the cross coupling reaction: IR ($CHCl_3$) ν_{max} 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (t, 3H, J = 7.2 Hz), 4.43 (q, 2H, J = 7.2 Hz), 7.55 (d, 1H, J = 6.9 Hz), 8.09 (dd, 1H, J = 2.1 and 6.9 Hz), 8.61 (d, 1H, J = 2.2 Hz); MS *m/e* (rel intensity) 247 (M^+, 7), 245 (M^+, 8).

3-Carboxy-4-chloropyridine (11). Following a literature procedure,[16] a mechanically stirred solution of freshly distilled 4-chloropyridine (3.5 g, 30 mmol) in THF (500 mL) at −78 °C under argon was treated with LDA (33 mmol), via syringe and the reaction mixture was allowed to stir for 20 min. Dry CO_2 was passed through the solution for 10 min and the mixture was allowed to warm to ambient temperature over 18 h. The reaction mixture was cooled to 0 °C and carefully basified with NaOH pellets. THF was removed *in vacuo* and the aqueous suspension was extracted with CH_2Cl_2. The aqueous layer was treated with conc HCl to give a white precipitate which was washed with ether and dried to give 4.6 g (96%) of **11**, mp 207−210 °C (EtOH-H_2O), lit.[17] mp 200−201 °C.

(10) Our continuing lack of mechanistic understanding of cross coupling processes is further illustrated by the absence of desired product from the reaction of **23** with 2-chloro-3-(trialkylstannyl)-pyridines (alkyl = Me, *n*-Bu) under $PdCl_2(PPh_3)_2$/LiCl/DMF/110 °C conditions.

(11) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931.
(12) Coulsen, D. R. *Inorg. Syn.* **1972**, *13*, 121.
(13) Taylor, E. C.; Crovetti, J. *J. Org. Chem.* **1954**, *19*, 1633.
(14) Badger, G. M.; Rao, R. P. *Aust. J. Chem.* **1964**, *17*, 1399.
(15) Lyle, R. E.; Bristol, J. A.; Kane, M. J.; Portlock, D. E. *J. Org. Chem.* **1973**, *38*, 3268.
(16) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137.
(17) Nantka-Namirski, P.; Bojarska-Dahlig, H. *Rocznicki Chem.* **1956**, *30*, 621 (*Chem. Abstr.* **1957**, *51*, 4370).

3-Carbethoxy-4-chloropyridine (12). The procedure and workup for the preparation of **9** was followed with the following quantities of reagents: compound **11** (9.7 g, 61 mmol), DMAP (1.1 g, 8 mmol), ethanol (10 mL, 180 mmol), DMF (100 mL), and DCC (29.8 g, 144 mmol, in 50 mL of DMF) and the mixture was stirred for 4 h. Distillation afforded 10.7 g (94%) of **12** as a colorless liquid, bp 70–76 °C (0.1 mm), lit.[18] bp 85 °C (1 mm) IR (neat) ν_{max} 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (t, 3H, J = 7.1 Hz), 4.44 (q, 2H J = 7.1 Hz), 7.41 (d, 1H, J = 5.4 Hz), 8.58 (d, 1H, J = 5.4 Hz), 9.03 (s, 1H); MS *m/e* (rel intensity) 187 (M^+, 26), 185 (M^+, 100).

***N,N*-Diisopropyl-4-iodonicotinamide (14a).** A solution of *N,N*-diisopropylnicotinamide **13a**[19] (2.0 g, 9.7 mmol) in THF (15 mL) was slowly added to a cold (−70 °C) THF solution of LDA (14 mmol). The resulting yellow mixture was stirred for 15 min at −70 °C and treated with a THF solution of iodine (2.46 g, 9.7 mmol). After stirring for 45 min at −70 °C, the solution was allowed to warm to 0 °C and hydrolyzed by an aqueous saturated sodium thiosulfate solution. Extraction (CH_2Cl_2), drying ($MgSO_4$), and solvent removal under vacuum afforded a crude oil which was purified by flash chromatography (silica gel, ether/hexane 90:10) to yield in order 1.61 g (50%) of **14a**: mp 150 °C; ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 12H), 3.5 (m, 2H), 7.75 (d, 1H, J = 5 Hz), 8.15 (d, 1H, J = 5 Hz), 8.3 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 103.80 (C4), 134.21 (C5), 140.45 (C3), 145.49 (C6), 149.01 (C2). Anal. Calcd for $C_{12}H_{17}N_2OI$: C, 43.37; H, 5.12; N, 8.43. Found: C, 43.30; H, 5.22; N, 8.18 and 1.11 g (25%) of *N,N*-diisopropyl-4,5-diiodonicotinamide (**15a**): mp 160 °C, ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 12H), 3.5 (m, 2H), 8.2 (s, 1H), 8.8 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 110.4 (C4), 117.37 (C5), 142.5 (C3), 143.1 (C2), 155.4 (C6). Anal. Calcd for $C_{12}H_{16}N_2OI_2$: C, 31.44; H, 3.49; N, 6.11. Found: C, 31.51; H, 3.60; N, 5.77.

***N,N*-Diisopropyl-4-iodo-2-methoxynicotinamide (14b).** To a solution of *N,N*-diisopropyl 2-methoxynicotinamide (**13b**)[20] (1.0 g, 4.3 mmol), LiTMP (0.35 mL, 2.1 mmol), and TMEDA (0.98 mL, 6 mmol) in anhydrous THF (25 mL) at −70 °C was added slowly by syringe a solution of *n*-BuLi (6.4 mmol, 2.6 mL of a 2.5 M solution in hexane). The mixture was stirred for 1 h at −70 °C and a solution of iodine (3.24 g, 12.8 mmol) in anhydrous THF was slowly added. The mixture was stirred for 1 h, allowed to warm to 20 °C, and stirred at this temp for 1 h. The reaction mixture was treated with sodium thiosulfate and 5% aqueous HCl solution. Extraction (CH_2Cl_2), drying ($MgSO_4$), and evaporation to dryness *in vacuo* afforded crude material, which upon flash chromatography (silica gel, Et_2O/hexane 70:30) gave 0.84 g (55%) of pure **14b**, which was not recrystallized: mp 170–171 °C, ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 12 H), 3.2–3.9 (m, 2H), 3.9 (s, 3H), 7.35 (d, 1H, J = 5 Hz, 1H), 7.8 (d, 1H, J = 5 Hz, 1H). Anal. Calcd for $C_{13}H_{19}N_2O_2I$: C, 43.09; H, 5.25; N, 7.73. Found: C, 43.28; H, 5.14; N, 7.58.

Preparation of Benzo[*c*][2,7]naphthyridinone (17). [2-(*N*-*t*-Boc-Amino)phenyl]boronic Acid (16). A solution of *N*-*t*-Boc-aniline[21] (1.8 g, 10 mmol) in dry THF (40 mL) at −78 °C under argon, was treated with *t*-BuLi (1.7 M solution in pentane, 14 mL, 24 mmol) and the solution stirred for 15 min. The mixture was warmed to −20 °C, stirred for 2 h, trimethylborate (4.3 mL, 38 mmol) added, and the mixture allowed to warm to ambient temperature. The reaction mixture was cooled to 0 °C and acidified to pH 6.5 by the addition of 10% aqueous HCl. The aqueous phase was separated and extracted with CH_2Cl_2, the extracts were combined with the initial THF solution, and the combined extract was washed with brine, dried ($MgSO_4$), and evaporated. The crude boronic acid so produced as a colorless powder was used without purification in cross coupling reactions.

Benzo[*c*][2,7]naphthyridinone (17). (a) Using 3-Carbethoxy-4-chloropyridine (12). A heterogeneous mixture of **12** (1.4 g, 8 mmol), $Pd(PPh_3)_4$ (0.4 g, 0.4 mmol), 2 M aqueous Na_2CO_3 (7.7 mL), and boronic acid **16** (4.2, 18 mmol) in DME (80 mL) was refluxed under nitrogen for 8 h. The reaction mixture was cooled and partially evaporated *in vacuo*. Addition of benzene (20 mL) and filtration gave 1.1 g (70%) of **17**: mp 299–302 °C (CH_2Cl_2–MeOH) dec, lit.[22] mp 300 °C; IR (KBr) ν_{max} 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.28–7.40 (m, 2H), 7.58–7.64 (m, 1H), 8.39–8.47 (m, 2H), 8.90 (d, 1H, J = 5.5 Hz), 9.41 (s, 1H), 11.90 (br s, 1H, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 116.7, 116.8, 117.3, 121.4, 123.9, 124.4, 132.7, 151.2, 151.6, 162.1; MS *m/e* (rel intensity) 196 (M^+, 100), 195 (52).

(b) Using 4-Bromo-3-carbethoxypyridine 1-Oxide (9). Following the cross coupling procedure described above, a mixture of **9** (0.4 g, 1.7 mmol), $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol), 2 M aqueous Na_2CO_3 (1.7 mL), and boronic acid **16** (1.3 g, 6 mmol) in DME (17 mL) was refluxed for 8 h. The precipitate was collected and washed with ether to give 0.2 g (56%) of benzo[*c*][2,7]naphthyridinone 7-oxide (**18**), mp 324–327 °C dec; IR (KBr) ν_{max} 1670, 1261, 844 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.28–7.39 (m, 2H), 7.53–7.60 (m, 1H), 8.36 (d, 1H, J = 8.0 Hz), 8.52 (d, 1H, J = 7.1 Hz), 8.59 (dd, 1H, J = 1.8 and 7.1 Hz), 8.77 (d, 1H, J = 1.8 Hz), 12.09 (br s, 1 H, exchangeable with D_2O); MS *m/e* (rel intensity) 212 (M^+, 100), 196 (50), 195 (31); HRMS calcd for $C_{12}H_8N_2O_2$ 212.0586, found 212.0583.

A mixture of **18** (40 mg, 0.2 mmol), PPh_3 (50 mg, 0.2 mmol), and iron powder (20 mg, 0.3 mmol) in acetic acid (1 mL) was refluxed for 30 min. The mixture was cooled and subjected to filtation, and the filtrate was treated with benzene. The resulting precipitate was collected to afford 33 mg (99%) of **17** which was shown to be identical to the material obtained above.

Preparation of Azabiaryls 20a,b. [2-(*N*-Pivaloylamino)phenyl]boronic Acid (19). *n*-Butyllithium (240 mL, 0.60 mol) was slowly added at −10 °C to a solution of *N*-pivaloylaniline (35.4 g, 0.2 mol) in dry THF (400 mL). The resulting solution was stirred for 6 h at room temp resulting in the formation of a white precipitate. The mixture was cooled to −20 °C, trimethylborate (68.0 mL, 0.6 mol) added slowly, and the mixture stirred for 2 h. The reaction mixture was warmed to 0 °C, and water was added. The aqueous phase was separated, washed with CH_2Cl_2, and acidified by the addition of HCl. The resulting colorless precipitate was collected by filtration, washed with water, and dried to give 15.6 g of **19** as a colorless solid. The filtrate was extracted with CH_2Cl_2 and the extract was dried ($MgSO_4$) and evaporated to dryness. The resulting solid was dissolved in acetone and water added to give a colorless precipitate, which was collected and dried to give a further 10.0 g of **19** (58% combined yield), mp 268–269 °C sub.; IR (KBr) ν_{max} 3320, 2970, 1620, 1580, 1550, 1450 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.10 (s, 9H), 3.30 (s, 2H, $B(OH)_2$), 7.10 (m, 2H), 7.60 (m, 2H), 11.05 (s, 1H, NH). Anal. Calcd for $C_{11}H_{16}BNO_3$: C, 59.77; H, 7.30; N, 6.34. Found C, 59.96; H, 7.19; N, 6.28.

Azabiaryls (20a,b). General Procedure. [2-(*N*-Pivaloylamino)phenyl]boronic acid (**19**) (0.95 mmol) was added to a mixture of the iodonicotinamides **14a,b** (0.8 mmol), $Pd(PPh_3)_4$ (28 mg, 0.02 mmol), and 2 M aqueous Na_2CO_3 (1 mL) in a mixture of ethyl alcohol (0.5 mL) and toluene (10 mL). The mixture was refluxed under argon for 15 h, cooled, and extracted (CH_2Cl_2). Flash chromatography (silica gel) of the residue gave pure products as indicated below.

4-[2-(Pivaloylamino)phenyl]-*N,N*-diisopropylnicotinamide (20a): eluent Et_2O, 60% yield, mp 136 °C; ^1H NMR ($CDCl_3$) δ 0.8–1.6 (m, 21 H), 3.0–4.0 (m, 2 H), 7.7–7.8 (m, 5 H), 8.5 (s, 1H), 8.6 (d, 1H, J = 5 Hz), 8.85 (s, 1H, NH); MS *m/e* (rel intensity) 381 (M^+, 36); HRMS calcd for $C_{23}H_{31}N_3O_2$ 381.2416, found 381.2410.

2-Methoxy-4-[2-(pivaloylamino)phenyl]-*N,N*-diisopropylnicotinamide (20b): eluent Et_2O/hexane (70:30), 50% yield, mp 176–178 °C; ^1H NMR ($CDCl_3$) δ 0.8–1.6 (m, 21 H), 3.0–3.9 (m, 2 H), 4.0 (s, 3H), 6.7 (d, 1 H, J = 5 Hz), 6.9–7.7 (m, 4 H), 8.1 (d, 1 H, J = 5 Hz), 9.1 (s, 1H, exchangeable with D_2O). Anal. Calcd for $C_{24}H_{33}N_3O_3$: C, 70.07; H, 8.03; N, 10.22. Found: C, 69.96; H, 8.31; N, 9.90.

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Preparation of Azabiaryl 22. *N,N*-Diisopropyl-4-(9-borabicyclononanoyl)-2-methoxynicotinamide (21). *N,N*-Diisopropyl-2-methoxynicotinamide (**13b**) was lithiated as described above and treated with 9-methoxy-BBN, and the reaction was subjected to standard workup to give crude material, which upon purification by flash chromatography (silica gel, CH_2Cl_2) yielded compound **21**, 62% yield, mp 129 °C; ^{1}H NMR ($CDCl_3$) δ 0.55 (s, 2 H), 1.2–2.2 (m, 24 H), 3.8 (m, 1 H), 4.0 (m, 1 H), 7.43 (d, 1 H, J = 5 Hz), 8.1 (d, 1 H, J = 5 Hz). Anal. Calcd for $C_{21}H_{33}BN_2O_2$: C, 70.78; H, 9.26; N, 7.86. Found: C, 70.84; H, 9.05; N, 7.74.

***N,N*-Diisopropyl-2-methoxy-4-(2-aminophenyl)nicotinamide (22).** A mixture of the pyridylborane **21** (2.0 g, 5.7 mmol), 2-iodoaniline (1.13 g, 5.1 mmol), $Pd(PPh_3)_4$ (0.18 g, 0.2 mmol), and 3 M aqueous NaOH (5 mL) in THF (40 mL) was refluxed for 25 h under argon. Water was added, the whole was extracted with Et_2O, and the combined organic extract was dried ($MgSO_4$) and evaporated to dryness to give an oil, which upon purification by flash chromatography (silica gel, Et_2O) afforded **22**, 61% yield, mp 155–157 °C; ^{1}H NMR ($CDCl_3$) δ 0.7–1.6 (m, 12 H), 3.3 (m, 1 H), 3.5 (m, 1 H), 3.8 (s, 2 H), 4.0 (s, 3 H), 6.6–7.7 (m, 5 H), 8.2 (d, 1 H, J = 5 Hz); MS *m/e* (rel intensity) 328 (M^+, 100). Anal. Calcd for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.64; N, 12.80. Found : C, 69.49; H, 7.77; N, 12.48.

Preparation of Trifluoromethanesulfonates 5, 23. 5-(4-Methoxybenzo[*c*][2,7]naphthyridinyl) Trifluoromethanesulfonate (5). A solution of azabiaryl **22** (0.95 g, 2.9 mmol), *i*-Pr_2NH (1.3 mL, 9 mmol), and *n*-BuLi (3.5 mL of a 2.5 M solution in hexane, 9 mmol) was stirred at −70 °C for 1 h and allowed to warm to ambient temperature over 2 h. Water was added, the whole was extracted (CH_2Cl_2), and the combined extract was dried ($MgSO_4$) and evaporated to dryness to afford 0.45 g of 4-methoxybenzo[*c*][2,7]naphthyridin-5-one as orange crystals. Owing to difficulties in purification, this material was dissolved in pyridine (15 mL), cooled to 0 °C, and treated by dropwise addition with trifluoromethanesulfonic anhydride (1 mL, 6.3 mmol). The mixture was stirred at 0 °C for 5 min and at room temperature for 24 h, water was added, and the whole was neutralized and extracted (CH_2Cl_2). The combined organic extract was dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product which was purified by flash chromatography (silica gel, CH_2Cl_2) to yield 0.31 g (30%) of **5**: mp 129 °C; ^{1}H NMR ($CDCl_3$) δ 4.21 (s, 3H), 7.72 (td, 1H, J = 7 and 1.5 Hz), 7.84 (td, 1H, J = 7 and 1.5 Hz), 7.91 (d, 1H, J = 6 Hz), 8.04 (dd, 1H, J = 7 and 1.5 Hz), 8.40 (dd, 1H, J = 7 and 1.5 Hz), 8.47 (d, 1H, J = 6 Hz); MS *m/e* (rel intensity) 358 (M^+, 100). Anal. Calcd for $C_{14}H_9F_3N_2O_4S$: C, 46.93; H, 2.51; N, 7.82. Found: C, 46.83; H, 2.50; N, 7.80.

5-(Benzo[*c*][2,7]naphthyridinyl) Trifluoromethanesulfonate (23). A suspension of **17** (0.45 g, 2.3 mmol) and DMAP (0.23 g, 1.8 mmol) in pyridine (60 mL) was treated with Tf_2O (1.62 g, 5.8 mmol) and the mixture was stirred at ambient temperature for 24 h. Standard workup gave 0.48 g (63%) of **23**: mp 135–136 °C (Et_2O–hexane), IR (KBr) ν_{max} 1411, 1221 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.89–8.12 (m, 3H), 8.87–8.98 (m, 2H), 9.15 (d, 1H, J = 5.8 Hz), 9.51 (s, 1H); MS *m/e* (rel intensity) 328 (M^+, 72), 264 (34), 195 (21), 167 (100), 140 (44). HRMS calcd for $C_{13}H_7N_2F_3O_3S$ 328.0130, found 328.0135.

Preparation of 5-(4-Pyridyl)benzo[*c*][2,7]naphthyridin-4-one (4). 4-Pyridyltri-*n*-butylstannane (24). To a solution of 4-bromopyridine (prepared from the hydrochloride, Aldrich, 18 mL of a 0.55 M solution in Et_2O, 10 mmol) at −70 °C in THF (15 mL) was slowly added dropwise a solution of phenyllithium (7.8 mL of a 1.55 M solution in hexane, 12 mmol) and the reaction mixture was stirred for 1 h. Tri-*n*-butylstannyl chloride (3.6 mL, 13 mmol) was added slowly, and the mixture was stirred and warmed to 0 °C over 2 h. The reaction mixture was hydrolyzed and extracted (CH_2Cl_2), and the organic extract was evaporated to dryness to give crude material, which upon flash chromatography (silica gel, hexane then $CHCl_3/Et_2O$, 75:25) furnished 1.28 g (35% yield) of **24**: ^{1}H NMR ($CDCl_3$) δ 0.6–2.0 (m, 27 H), 7.4 (d, 2 H, J = 5 Hz), 8.5 (d, 2 H, J = 5 Hz) which was used immediately in the next reaction.

4-Methoxy-5-(4-pyridyl)benzo[*c*][2,7]naphthyridine (25). Argon was bubbled for 1 h into a solution containing triflate **5** (96 mg, 0.3 mmol), the pyridyl stannane **24** (118 mg, 0.3 mmol), and LiCl (34 mg, 0.8 mmol) in dioxane (50 mL). $Pd(PPh_3)_4$ (16 mg, 0.01 mmol, 3 mol %) was added and the mixture was refluxed for 36 h. The reaction mixture was treated with water, 10% aqueous NH_4OH (10 mL), and extracted (CH_2Cl_2). The organic extract was evaporated to dryness and subjected to flash chromatography (silica gel, EtOAc) to yield 61 mg (79%) of **5**: mp 149 °C; ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 7.42 (dd, 2H, J = 4.5 Hz and 1.6 Hz), 7.71 (td, 1H, J = 8 and 1.5 Hz), 7.84 (td, 1H, J = 8 and 1.5 Hz), 7.99 (d, 1H, J = 6 Hz), 8.18 (dd, 1H, J = 8 and 1.5 Hz), 8.42 (d, 1H, J = 6 Hz), 8.48 (dd, 1H, J = 8 and 1.5 Hz), 8.70 (dd, 2H, J = 4.5 Hz and 1.6 Hz); MS *m/e* (rel intensity) 287 (M^+, 100).

5-(4-Pyridyl)benzo[*c*][2,7]naphthyridin-4-one (4). Argon was bubbled for 30 min into a solution of **25** (112 mg, 0.4 mmol) in dry CH_2Cl_2 (20 mL), the mixture was cooled to −70 °C, and a solution of BBr_3 (2.4 mL of a 1 M solution in CH_2Cl_2, 2.4 mmol) was added dropwise. After stirring at −70 °C for 15 min, the mixture was allowed to warm to room temp over 16 h and poured over ice, and the whole was neutralized with aqueous Na_2CO_3 to pH 7–8. Extraction (CH_2Cl_2) followed by drying ($MgSO_4$) and evaporation *in vacuo* gave crude material which, after flash chromatography (silica gel, EtOAc then EtOH), yielded 57 mg (54%) of **4**: mp 334–335 °C (lit.[6] 328 °C); ^{1}H NMR ($CDCl_3$) δ 7.41 (d, 2H, J = 5.5 Hz), 7.48 (d, 1H), 7.75 (m, 2H), 7.91 (m, 1H), 8.04 (d, 1H, J = 8 Hz), 8.57 (d, 2H, J = 5.5 Hz), 8.65 (d, 1H, J = 8 Hz); MS *m/e* (rel intensity) 274 (M^+ + 1, 55) 169 (100) whose spectral data were in good agreement with those reported by Prager for **4** prepared by another route.[6]

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