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Directed *ortho* Metalation−Boronation and Suzuki−Miyaura Cross Coupling of Pyridine Derivatives: A One-Pot Protocol to Substituted Azabiaryls[#]

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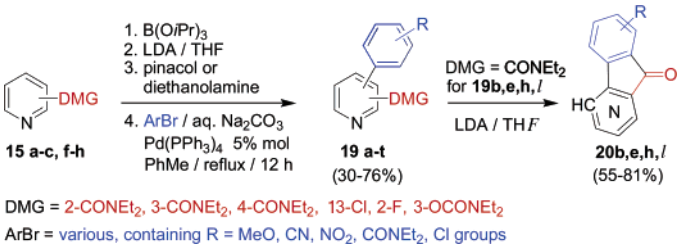

A general method for the synthesis of azabiaryls **19a**−**t** by a one-pot procedure involving a Directed *ortho* metalation (DoM)−boronation−Suzuki−Miyaura cross coupling sequence is described. Aside from the three isomeric pyridyl carboxamides **15a**−**c**, chloro-, fluoro-, and *O*-carbamoyl pyridines are adapted to this method providing a range of azabiaryls (Table 2). The method has an advantage in that it avoids the recognized difficult isolation of pyridyl boronic acids and their instability toward deboronation. The efficient synthesis of hydroxypicolinamides **12**−**14** (Scheme 3) by a one-pot metalation−boronation−oxidation sequence with the LDA-B(O^iPr)$_3$ *in situ* procedure that avoids self-condensation of incipient *ortho*-metalated species (Scheme 2) is delineated. The conversion of azabiaryls **19b**,**e**,**h**,***l*** into azafluorenones **20b**,**e**,**h**,***l*** by a directed remote metalation protocol is demonstrated (Table 3). A comprehensive survey of pyridyl boronates, of considerable interest in contemporary heterocyclic synthetic chemistry, is given (Figure 1).

Introduction

In context of modern transition metal-catalyzed reactions, the impact of new sp^2-sp^2 bond synthetic protocols[1] has revolutionized how chemists conceptualize aryl−aryl, aryl−heteroaryl, and heteroaryl−heteroaryl bond formation[2] leading to wide adaptation of the Kumada−Corriu,[3] Negishi,[4] Suzuki−Miyaura,[5] and Stille[6] cross coupling processes especially in pharmaceutical industry practice.[7] The DoM strategy,[8] when linked with the named cross coupling reactions by transmetalation (**1**, Scheme

[#] Dedicated to the memory of Pierre Potier for his magnificent contributions to organic chemistry, especially to indole alkaloid structural and synthetic work, for his statesmanship and service to our discipline, especially in France, and for his joie de vivre.

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(1) "Selective cross coupling of reactions between C(sp^3) and C(sp^2) centers had been one of the most difficult tasks in carbon−carbon bond synthesis until the early 1970s... Now, ... (it) has become the reaction of first choice for this purpose." Tamao, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Permagon Press: Oxford, UK, 1991; Vol. 3, p 435.

(2) de Meijere, A.; Diederich, F., Eds. *Metal-catalyzed Cross Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 2004.

(3) (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Corriu, R.; Masse, J. *J. Chem. Soc., Chem. Commun.* **1972**, 144. (c) Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23.

(4) (a) Negishi, E.; King, A.; Okukado, N. *J. Org Chem.* **1977**, *42*, 1821−1823. (b) Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; pp 229−247.

(5) (a) Miyaura, N.; Yamagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513−519. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695.

(6) (a) Milstein, D.; Stille, J. *J. Am. Chem. Soc.* **1979**, *101*, 4992−4998. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

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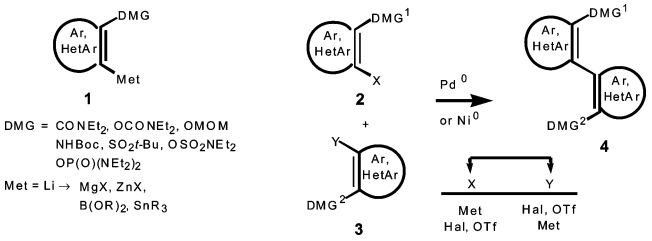
SCHEME 1. The DoM-Cross Coupling Nexus



1), provides considerable tactical advantage in the construction of polysubstituted aromatic and heteroaromatic compounds.[9]

Thus, two complementary **2** + **3** approaches with interchanging X and Y substituents, for biaryl or heterobiaryl formation **4** (Scheme 1), while providing anticipation of a higher chance of success, require careful consideration of substrate structure and reactivity. Perusal of the literature suggests that this is especially valid for cross coupling reactions in which one or both partners (**2** or **3)** is heteroaromatic, whereby difficulty in preparation, instability, and poor experience in synthesis has forced the use of tin[10,11] and, to a lesser extent, zinc,[12] and magnesium[13] over borylated heterocycles.[14] Although the number of well-characterized heteroaromatic boronic acids is relatively small, properties of boronic acid FG compatibility, air stability, low toxicity, and expense of commercial products would forecast that this situation will change.[15] In point of fact, this deficiency is being addressed for pyridylboronic acids and esters undoubtedly due to the significance of the pyridine moiety in bioactive molecules and natural products.[16] Thus for the parent derivatives, the 2-pyridylboronic acid has been prepared *via* a lithium−halogen exchange procedure, but is reported to be highly prone to protodeboronation.[17] In contrast, 2-pyridyl diethylborane is reported to be a stable compound;[18] however, utility in transition metal-catalyzed events has not been demonstrated. More recently, the preparation and Suzuki couplings of diethanolamine-stabilized 2-pyridylboronates have been reported.[19] 3-Pyridylboronic acid[20] is a relatively stable compound, and has recently been prepared, as the boroxin trimer, on multigram scale by a metal−halogen exchange procedure.[21] The preparation and Suzuki couplings of 3-pyridyltrifluoroborates have recently been reported.[22] 4-Pyridylboronic acid[20] has been prepared *via* lithium−halogen exchange processes.[23] To conclude by way of a new evolving perspective, Ir-catalyzed C−H coupling between bis(pinacolato)diboron and pyridine derivatives leading to pyridyl boronic esters has been recently reported.[24]

In the domain of substituted pyridyl boronic acid derivatives, systematic studies by Rault[25] and Bryce[26] have resulted in the preparation of shelf-stable halo pyridyl boronic acids and esters

(7) Rouhi, A. M. *Chem. Eng. News* **2004**, *September 6*, 49−58. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, 2337−2347, especially p 2345. King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205.

(8) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933. (b) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 330−367. (c) Macklin, T.; Snieckus, V. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley: Weinheim, Germany, 2005; pp 106−118. For metalation of sulfamates (OSO_2NEt_2), see: Macklin, T.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2519−2522. For metalation of phosphorodiamidates ($OPO(NEt_2)_2$) see: Alessi, M.; Zumbansen, K.; Demchuk, O. M.; Blackburn, T. W.; Snieckus, V. Unpublished results.

(9) (a) Anctil, E. J.-G.; Snieckus, V. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 761−813. (b) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150−160. (c) Green, L.; Chauder, B.; Snieckus, V. *J. Heterocycl. Chem.* **1999**, *36*, 1453−1468.

(10) Mitchell, T. N. In *Metal-catalyzed Cross Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 125−161. Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303.

(11) Morris, G. A.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 2093−2096. Benhida, R.; Lecubin, F.; Fourrey, J.-L.; Castellanos, L. R.; Quintero, L. *Tetrahedron Lett.* **1999**, *40*, 5701−5703. Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1993**, *58*, 3550−3556. Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E. *J. Org. Chem.* **1992**, *57*, 1653−1656.

(12) Gong, L.-Z.; Knochel, P. *Synlett* **2005**, 267−270. Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron* **1993**, *49*, 9713−9720. Filippini, L.; Gusmeroli, M.; Riva, R., *Tetrahedron Lett.* **1992**, *33*, 1755−1758. Minato, A.; Hayashi, K.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 5319−5322. Karig, G.; Thasana, N.; Gallagher, T. *Synlett* **2002**, 808−810

(13) Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Queginer, G. *Synlett* **2002**, 1008−1010.

(14) More recently, pyridines have been cross coupled under Hiyama conditions: (a) Pierrat, P.; Gros, P.; Fort, Y. *Org. Lett.* **2005**, *7*, 697−700. (b) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58−61. (c) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *67*, 1137−1143.

(15) Tyrrell, E.; Brookes, P. *Synthesis* **2003**, 469−483.

(16) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 5, pp 245−300.

(17) Fischer, F. C.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 21−24. The reaction of 2-pyridyl Grignard with tris(trimethylsilyl)borate has recently been reported to yield the corresponding boronic acid in good yield; Matondo, H.; Souirti, S.; Baboulene, M. *Synth. Commun.* **2003**, *33*, 795−800.

(18) Ishikura, M.; Mano, T.; Oda, I.; Terashima, M. *Heterocycles* **1984**, *22*, 2471−2474.

(19) *N*-Phenyldiethanolamine: (a) Hodgson, P.; Salingue, F. *Tetrahedron Lett.* **2004**, *45*, 685−687. Polystyrene-supported diethanolamine: (b) Gros, P.; Doudouh, A.; Fort, Y. *Tetrahedron Lett.* **2004**, *45*, 6239−6241. (c) Pfizer Global R & D, Sándwich, Kent, UK, U.S. Patent No. 7,026,479.

(20) 3- and 4-pyridineboronic acids (and corresponding esters) are available in milligram to gram quantities from numerous suppliers; e.g., Aldrich Chemical Company, Inc., Milwaukee, WI, USA; Frontier Scientific, Inc., Logan, Utah, USA; CombiPhos Catalysts, Inc., Princeton, NJ, USA; and Lancaster Synthesis, Inc., Windham, NH, USA.

(21) (a) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Dongwei, C.; Larsen, R. D. *Org. Lett.* **2003**, *5*, 4835−4837. (b) Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394−5397. Subsequently, 3-pyridylboroxin has been used directly in Suzuki couplings; see: (c) Cioffi, C. L.; Spencer, W. T.; Richards, J. J.; Herr, R. J. *J. Org. Chem.* **2004**, *69*, 2210−2212. For examples of large-scale coupling reactions of diethyl(3-pyridyl)borane see: Wei, H.; Sudini, R.; Yin, H. *Org. Process Res. Dev.* **2004**, *8*, 955−957. Lipton, M. F.; Mauragis, M. A.; Maloney, M. T.; Veley, M. F.; VanderBor, D. W.; Newby, J. J.; Appell, R. B.; Daugs, E. *Org. Process Res. Dev.* **2003**, *7*, 385−392.

(22) For the preparation and coupling of 3-pyridyl tetrabutylammonium trifluoroborates, see: (a) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099−9103. For coupling of 3-pyridyl potassium trifluoroborate with 5-bromopyrimidine, see: (b) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302−4314. For coupling of 3-pyridyl potassium trifluoroborate with aryl chlorides, see: (c) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649−2652.

(23) For lithium−iodine exchange see: Coudret, C. *Synth. Commun.* **1996**, *26*, 3543. For lithium−bromine exchange see ref 21b.

(24) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649−5651. Mkhalid, I. A. I.; Coventry, D.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 489−491.

(25) (a) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885−2890. (b) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323−3328. (c) Bouillon, A.; Lancelot, J.-C.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369−4373. (d) Bouillon, A.; Lancelot, J.-C.; Sopkova, J.; de Santos, O.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043−10049. (e) Cailly, T.; Fabis, F.; Bouillon, A.; Lemaître, S.; Sopkova, J.; de Santos, O.; Rault, S. *Synlett* **2006**, 53−56.

(26) (a) Parry, P. R.; Bryce, M. R.; Tarbit, B. *Synthesis* **2003**, *7*, 1035−1038. (b) Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541−7543. For cross coupling of these boronic acids see: (c) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388−390. (d) Thompson, A. E.; Batsanov, A. S.; Bryce, M. R.; Saygili, N.; Parry, P. R.; Tarbit, B. *Tetrahedron* **2005**, *61*, 5131−5135. (e) Saygili, N.; Batsanov, A. S.; Bryce, M. R. *Org. Biomol. Chem.* **2004**, *2*, 852−857.

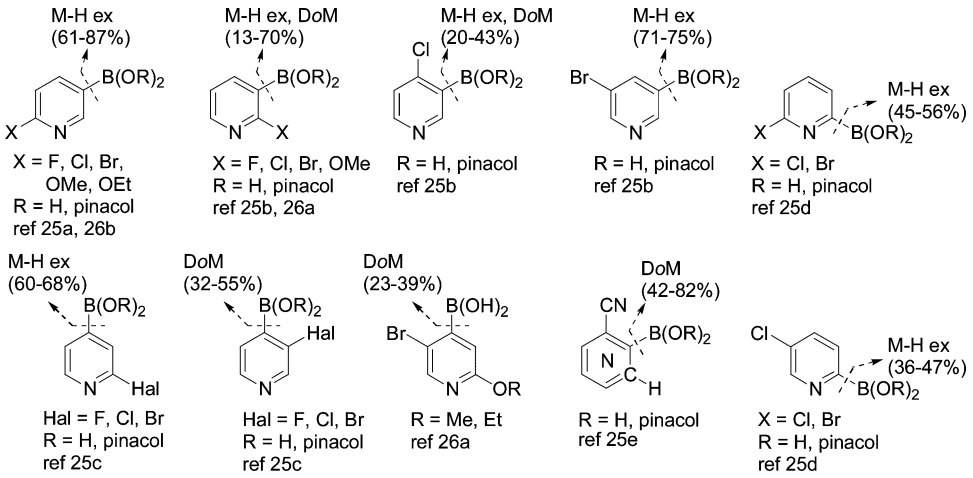
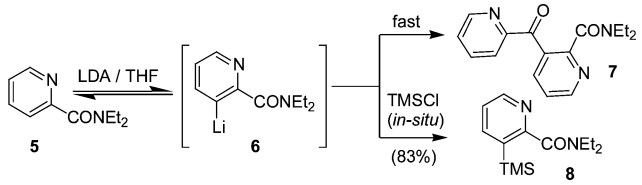
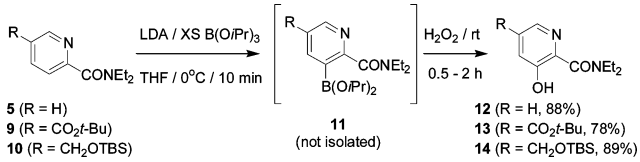


FIGURE 1. Boronic acids and esters of pyridine derivatives.

SCHEME 2. Lithiation of Picolinamide 5: Self-Condensation *vs in Situ* TMSCl Quench



SCHEME 3. One-pot D*o*M−Boronation−Oxidation of Picolinamides 5, 9, and 10



in gram quantities. Figure 1 depicts functionalized pyridylboronic acids and boronates synthesized to date by procedures which emphasize careful neutralization in the workup to avoid protodeboronation. In most of these reports, as expected, Suzuki cross coupling chemistry of the derived boronic acids or boronates was also described.

As part of the continuing efforts to develop D*o*M−cross coupling strategies,[9] our interest to provide dependable routes to pyridylboronic acid coupling partners for the general reaction scheme **2** + **3** → **4** (Scheme 1) has led to the development of a one-pot D*o*M−cross coupling protocol, details of which are presented herein.

Results and Discussion

This study owes its origins to the requirement of a series of 3,5-disubstituted pyridine-2-carboxamides for an alkaloid synthesis program.[27] In this context, the original work of Epsztajn and co-workers[28] had shown that picolinamide **5** (Scheme 2), and other pyridine carboxamides, undergo *ortho*-lithiation by LDA in a rapid equilibrium, which precludes efficient trapping of lithiopyridine **6** by electrophiles.[29] Moreover, intermediate lithiopyridine **6** rapidly succumbs to self-condensation[30] leading to dipyridyl ketone **7.** Subsequently, Avendaño and co-workers[31] showed that irreversible deprotonation of **5** by *s*-BuLi, immediately followed by electrophile quench, can lead to *ortho*-substituted products; however, self-condensation remains the predominant pathway. By including TMSCl as an *in situ* electrophile,[32] we found[27] that **6** can be efficiently intercepted (**6** → **8**).

Caron and Hawkins[33] recently reported the use of triisopropyl borate as *in situ* boron electrophile for LDA-mediated D*o*M of neopentyl benzoates, leading to *ortho*-substituted arylboronic acid derivatives under relatively mild reaction conditions. Using picolinamide **5** as a test case for the LDA/B(O^{i}Pr)$_3$ reagent system, we obtained, in a one-pot D*o*M/boronation/oxidation sequence, hydroxypicolinamide **12** in excellent yield (Scheme 3).[34] Two additional hydroxypicolinamides **13** and **14** were similarly prepared in relatively short sequences starting from dimethyl 2,5-pyridinedicarboxylate (see the Supporting Information).

The above observations begged adaptation of the Caron−Hawkins procedure for the development of a general method for the preparation of pyridylboronic acids of a variety of DMG-bearing systems. We aimed for (a) the isolation of intermediates of the type **11** as stable boron derivatives, (b) the use of these for subsequent Suzuki cross coupling chemistry, and (c) the provision of a convenient one-pot D*o*M−cross coupling procedure for the synthesis of substituted azabiaryls.

In goals (a) and (b) above, a number of DMG-bearing pyridines **15a**−**f** (Table 1) were subjected to the *in situ*

(27) Larkin, A. L. M.Sc. Thesis, Queen's University, Kingston, ON, Canada, 2002.

(28) (a) Epsztajn, J.; Berski, Z.; Brzezinski, J.; Jozwiak, A. *Tetrahedron Lett.* **1980**, *21*, 4739−4742. (b) Epsztajn, J.; Brzezinski, J.; Jozwiak, A. *J. Chem. Res. Synop.* **1986**, 18−19.

(29) Comins, D.; LaMunyon, D. *Tetrahedron Lett.* **1988**, *29*, 733−776.

(30) Analogous self-condensations are known for *ortho*-lithiated alkyl benzoates and diethylbenzamides: Upton, C. J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094−1098. Beak, P.; Brubaker, G. R.; Farney, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 3621−3627.

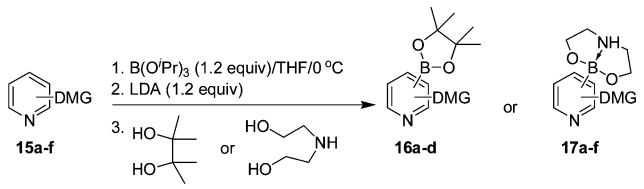
(31) Villacampa, M.; Cuesta, E.; Avendaño, C. *Tetrahedron* **1995**, *51*, 1259−1264.

(32) (a) Krizan, T.; Martin, J. *J. Am. Chem. Soc.* **1983**, *105*, 6155−6157. (b) Taylor, S.; Lee, D.; Martin, J. *J. Org. Chem.* **1983**, *48*, 4156−4158. (c) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495−498.

(33) (a) Caron, S.; Hawkins, J. *J. Org. Chem.*, **1998**, *63*, 2054−2055. For closely related examples with LiTMP/B(O^{i}Pr)$_3$, see: (b) Kristensen, J.; Lysen, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435−1437. For the application of the Caron−Hawkins procedure on *N*-Boc indole, see: (c) Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551−7552.

(34) Recently, a similar one-pot protocol for the hydroxylation of halopyridines has been reported, see: Voisin, A. S.; Bouillon, A.; Lancelot, J.-C.; Rault, S. *Tetrahedron* **2005**, *61*, 1417−1421.

TABLE 1. Preparation of Boropinacolates 16a−d and Boroxazolidines 17a−f from DMG-Containing Pyridines 15a−f



pyridine	DMG	pinacolate or boroxazine	yield (%)[a]
16a	2-$CONEt_2$	3-$B(OR)_2$	20
17a	2-$CONEt_2$	3-$B(OR)_2$	40
16b	3-$CONEt_2$	4-$B(OR)_2$	60
17b	3-$CONEt_2$	4-$B(OR)_2$	37
16c	4-$CONEt_2$	3-$B(OR)_2$	41
17c	4-$CONEt_2$	3-$B(OR)_2$	59
16d	3-F	4-$B(OR)_2$	30[b]
17d	3-F	4-$B(OR)_2$	35[b]
17e	3-SO_2NEt_2	4-$B(OR)_2$	40
17f	3-$OCONEt_2$	4-$B(OR)_2$	61[c]

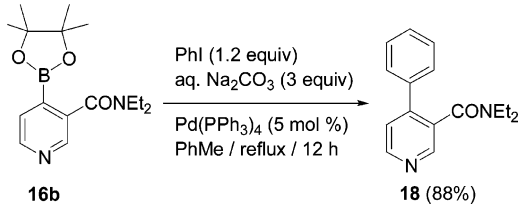
[a] Yields represent isolated materials after chromatography and recrystallization. [b] Complete metalation required 1.5 equiv of LDA and $B(O^iPr)_3$. [c] Metalation was carried out at −78 to 0 °C.

LDA-$B(O^iPr)_3$ procedure and the resulting boronate intermediates were isolated as either their pinacolates **16a−d** or their diethanolamine adducts **17a−f**.[35] As observed by others,[36] the stability, chromatographability, and, in many cases, crystallinity are notable properties of these derivatives. However, pinacol esters **16e** and **16f** were difficult to obtain due to instantaneous deboronation observed upon addition of pinacol at 0 °C.

While pinacolates participate broadly in cross coupling with aryl and heteoaryl halides under standard Suzuki conditions,[37] boroxazolidines, consistent with our experience, appear to require an N-substituent for successful reaction, often under Pd−Cu cocatalysis.[19,25d] In confirmation, application of standard Suzuki−Miyaura conditions on the isolated nicotinamide boropinacolate **16b** proceeded smoothly to give the azabiaryl **18** in 88% yield (Scheme 4).

In quest of a general one-pot D*o*M−Suzuki cross coupling procedure (goal (c) above), the synthetically useful[38] isomeric

SCHEME 4. D*o*M−Suzuki−Miyaura Cross Coupling of Isolated Boronate 16b



amide DMG-bearing pyridines **15a−c** were thoroughly studied. Thus, using selected aryl bromides, picolinamide **15a**, nicotinamide **15b**, isonicotinamide **15c**, as well as 3-chloropyridine **15g** and 2-fluoropyridine **15h** were converted into a variety of functionalized azabiaryls **19a−d**, **19e−h**, **19i−n**, **19o−q**, and **19r**,**s**, respectively (Table 2), bearing electron-donating (MeO, Cl) and electron-withdrawing (CN, NO_2) substituents. Only one heteroaromatic bromide (entry 14) was tested. Reasonable yields of products were obtained, with the exception of those involving coupling with electron-rich aryl bromides (entries 3, 6, and 9), with 3-chloropyridine (entries 15−17), for which the known instability of the lithiated species[39] may be the responsible factor, and with *p*-bromonitrobenzene (entry 4) whose low yield remains unexplained. LDA and Pd−Cu cocatalysis were similarly applied to the metalation of the carbamate **15f** and the cross coupling of the corresponding crude diethanolamine ester, which afforded the azabiaryl **19t** in 64% yield (entry 20, Table 2).

Aside from inherent D*o*M chemistry, the available azabiaryl derivatives show additional synthetic potential in directed remote metalation (DreM) chemistry.[40] Thus, treatment of **19b** with excess LDA afforded the yellow azafluorenone **20b** in acceptable yield (Table 3).[41] Further indication of scope is provided by the similar preparation of additional selected examples (**20e**, **20h**, and **20*l***) in which the regioselectivity of DreM-induced cyclization in unsymmetrical aryl ring substituted cases, **19h** and **19*l***, is established by OMe and (weak) Cl DMG effects, respectively.[42] These anionic Friedel−Crafts equivalents hence show reactivity differences and complementarity to the Lewis acid-mediated processes. For example, when heated in PPA, the carboxylic acid corresponding to **19e** is converted into **20e** in poor yields (35%) as may be expected from the C-3′

(35) Green, A. L. M.Sc. Thesis, Queen's University, Kingston, ON, Canada, 2001.

(36) Diethanolamine adducts of boronic acids (boroxazolidines), first prepared by Letsinger (Letsinger, R. L.; Skoog, I. *J. Am. Chem. Soc.* **1955**, *77*, 2491−2494), have been used for obtaining stable, crystalline derivatives of aryl boronic acids, see: (a) Reference 33. (b) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093−5096. (c) Csuk, R.; Haas, J.; Honig, H.; Weidmann, H. *Monatsh. Chem.* **1981**, *112*, 879−882. For procedures for the preparation of pyridyl boronic acid derivatives, see: (d) Pinacol esters, ref 25. (e) Diethanolamine esters, refs 19a, 25d, and: Vedsø, P.; Olesen, P. H.; Hoeg-Jensen, T. *Synlett* **2004**, 892−894.

(37) For examples of cross coupling of (a) pinacol pyridylboronates with ArI, ArBr, and ArCl, see: Zhang, J.; Zhao, L.; Song, M.; Mak, T. C. W.; Wu, Y. *J. Organomet. Chem.* **2006**, *691*, *1301*−1306. Wiles, J. A.; Song, Y.; Wang, Q.; Lucien, E.; Hashimoto, A.; Cheng, J.; Marlor, C. W.; Ou, Y.; Podos, S. D.; Thanassi, J. A.; Thoma, C. L.; Deshpande, M.; Pucci, M. J.; Bradbury, B. *J. Bioorg. Med. Chem. Lett.* **2006**, *16*, 1277−1281. Leclerc, N.; Serieys, I.; Attias, A.-J. *Tetrahedron Lett.* **2003**, *44*, 5879−5882, ref 25. (b) For pinacol pyridylboronates with triflates see: Coudret, C.; Mazenc. V. *Tetrahedron Lett.* **1997**, *38*, 5293−5296. Holzapfel, C. W.; Dwyer, C. *Heterocycles* **1998**, *48*, 1513−1518.

(38) For D*o*M chemistry of pyridyl amides, see: Reference 8a. Broussy, S.; Bernardes-Genisson, V.; Gornitzka, H.; Bernadou, J.; Meunier, B. *Org. Biomol. Chem.* **2005**, *3*, 666−669. Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. *Org. Lett.* **2002**, *4*, 2385−2388. Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Queguiner, G.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 292−296.

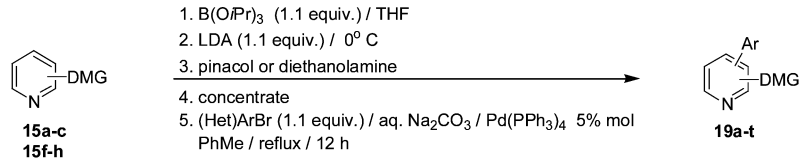
(39) Marsais, M.; Breant, P.; Ginguene, A.; Queguiner, G. *J. Organomet. Chem.* **1981**, *216*, 139−147. Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137−4140; *Heterocycles* **1993**, *35*, 151−169.

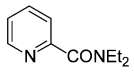
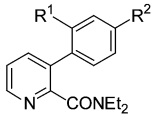
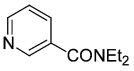
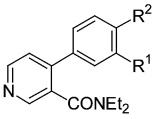
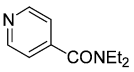
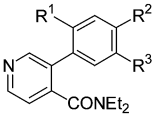
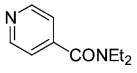
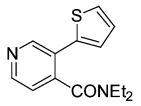
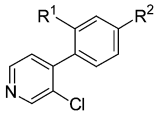
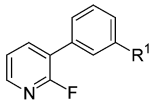
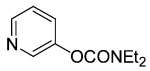
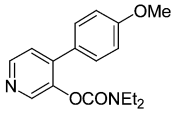
(40) Review: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* ***2004***, *43*, 2206−2225. For recent cases of use of this Friedel−Crafts anionic equivalency in medicinal and material science synthetic problems, see: Kalinin, A. V.; Reed, M. A.; Norman, B. H.; Snieckus, V. *J. Org. Chem.* ***2003***, *68*, 5992−5999. McCubbin, J. A.; Tong, X. T.; Wang, R.; Zhao, Y.; Snieckus, V.; Lemieux, R. P. *J. Am. Chem. Soc.* **2004**, *126*, 1161−1167.

(41) A similar anionic approach to azafluorenones from 2-pyridyl benzoic acid and its derivatives has been reported, see: Tilly, D.; Castanet, A.-S.; Mortier, J. *Tetrahedron Lett.* **2006**, *47*, 1121−1123. Rebstock, A.-S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron* **2003**, *59*, 4973−4977. For recent alternative syntheses of fluorenones and azafluorenones, see: Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3140−3143. Hundsdorf, T.; Neunhoeffer, H. *Synthesis* **2001**, 1800−1805.

(42) In a selected case, the conversion of the nicotinamide **19h** to 8-methoxy-2-azafluorenone (**20h**) was monitored by React IR. The intermediacy of a stable carbinol amine is strongly suggested by the disappearance of the amide absorption band (C═O, $\lambda = 1632\ cm^{-1}$) and, *only after quench with* MeOH, by the appearance of the azafluorenone band (C═O, $\lambda = 1718\ cm^{-1}$). Experimental details are available in the Supporting Information.

TABLE 2. One-pot DoM−Boronation−Suzuki Cross Coupling Synthesis of Azabiaryls



Entry	Pyridyl-DMG	Azabiaryl	yield (%)
	 **15a**	 **19**	
1		**a** : R^1 = H, R^2 = OMe	62
2		**b** : R^1 = H, R^2 = CN	71
3		**c** : R^1 = R^2 = OMe	37
4		**d** : R^1 = H, R^2 = NO_2	30
	 **15b**	 **19**	
5		**e** : R^1 = H, R^2 = OMe	71
6		**f** : R^1 = R^2 = OMe	42
7		**g** : R^1 = H, R^2 = CN	73
8		**h** : R^1 = OMe, R^2 = H	57
	 **15c**	 **19**	
9		**i** : R^1 = R^2 = OMe; R^3 = H	33
10		**j** : R^1 = R^3 = H; R^2 = OMe	75
11		**k** : R^1 = R^3 = H; R^2 = CN	76
12		**l** : R^1 = R^2 = H; R^3 = Cl	61
13		**m**: R^1 = $CONEt_2$, R^2 = R^3 = H	67
14	 **15c**	 **19n**	85
	 **15g**	 **19**	
15		**o** : R^1 = H, R^2 = OMe	48[a]
16		**p** : R^1 = H, R^2 = CN	55[a]
17		**q** : R^1 = H, R^2 = NO_2	43[a]
	 **15h**	 **19**	
18		**r** : R^1 = OMe	68
19		**s** : R^1 = Cl	73
20	 **15f**	 **19t**	64[b]

[a] Metalation was carried out at −78 to 0 °C. [b] Reagents and conditions: (i) $B(O^iPr)_3$ (1.1 equiv)/THF. (ii) LDA (1.1 equiv)/0 °C. (iii) $MeN(CH_2CH_2OH)_2$, 0 °C, 2 h. (iv) Concentrate. (v) *p*-Bromoanisole (0.67 equiv), K_2CO_3 (3 equiv), $Pd(OAc)_2$ (5%), S-Phos (10%), CuI (10%), degassed EtOH, reflux, 3 h.

deactivation due to the OMe group.[43] On the other hand, the carboxylic acids corresponding to **19h** and **19*l*** are activated (weakly in the latter case) at both C-2′ and C-6′ positions and are expected to lead to mixtures of isomers upon Friedel−Crafts cyclization. In fact, **19h** is reported to afford an approximately 1:1 mixture of **20h** and the isomeric 6-methoxy-2-azafluorenone (72% combined yield).[43] Since the fluorenones corresponding to **20b** and **20*l*** have not been prepared by direct Friedel−Crafts reaction of the carboxylic acid corresponding to **19b** and **19*l***, respectively, a direct comparison cannot be made. However, in such transformations, sensitivity of the cyano group to Lewis acid-catalyzed hydrolysis would be expected.

To summarize, the *in situ* compatibility of LDA and $B(O^iPr)_3$ reagents has allowed the development of a general DoM−cross coupling strategy, either with (Table 1) or without (Table 2) isolation of pyridylboronate intermediates, for the regioselective preparation of functionalized azabiaryls. These systems may, in themselves, be valuable intermediates for bioactive molecule discovery programs,[44] serve as precursors for the synthesis of azafluorenones[45] which are inaccessible by Friedel−Crafts methodology, and prompt further DoM chemistry adventures.

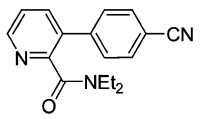
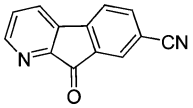
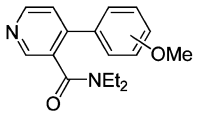
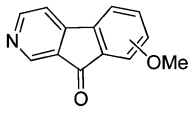
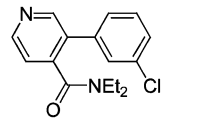
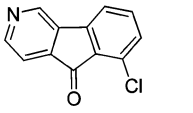
Experimental Section

***N*2,*N*2-Diethyl-3-(1,1,1-trimethylsilyl)-2-pyridinecarboxamide (8).** To a solution of LDA (37.6 mmol) prepared from DIPA (37.6 mmol, 5.27 mL) and *n*-BuLi (37.6 mmol, 15.0 mL of a 2.5 M solution in hexane) in THF (150 mL) at −78 °C was added

(43) Shiao, M.-J.; Peng, C.-J.; Wang, J.-S.; Ma, Y.-T. *J. Chin. Chem. Soc.* **1992**, *39*, 173−176.

(44) For current biological significance of azabiaryls, see: Chambers, R. J.; Marfat, J. A.; Cheng, J. B; Cohan, L.; Damon, D. B.; Duplantier, A. G.; Hibbs, T. A.; Jenkinson, T. H.; Johnson, K. L.; Kraus, K. G.; Pettifer, E. R.; Salter, E. D.; Shirley, J. T.; Umland, J. P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 739−744. Zhou, X.-F.; Zhang, L.; Tseng, E.; Scott-Ramsay, E.; Schentag, J. J.; Coburn, R. A.; Morris, M. *Drug Metab. Dispos.* **2005**, *33*, 321−328. Smith, R. A.; Hertzog, D. L.; Osterhout, M. H.; Ladouceur, G. H.; Korpusik, M.; Bobko, M. A.; Jones, J. H.; Phelan, K.; Romero, R. H.; Hundertmark, T.; MacDougall, M. L.; Livingston, J. N.; Shoen, W. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1303−1306. Denton, T. T.; Zhang, X.; Cashman, J. R. *J. Med. Chem.* **2005**, *48*, 224−239. For Mg, Zn, Sn, and Si approaches to azabiaryls, see refs 11, 12, 13, and 14.

TABLE 3. Synthesis of Azabiaryls 20b,e,h,*l*[a]

Azabiaryl	Conditions	Azafluorenone	Yld, %
 **19b**	A	 **20b**	55
 **19e** (R = 4'-OMe) **19h** (R = 3'-OMe)	B B	 **20e** (R = 7-OMe) **20h** (R = 8-OMe)	56 63
 **19*l***	C	 **20*l***	81

[a] Reagents and conditions: (A) LDA (2 equiv)/THF/−78 to −10 °C/90 min. (B) LDA (3 equiv)/THF/−40 to 10 °C/120 min. (C) LDA (1.2 equiv)/THF/−50 °C/90 min.

sequentially a freshly prepared solution of **5** (6.37 g, 35.8 mmol) and TMSCl (14.0 mL, 107 mmol) in THF (25 mL) dropwise over 5 min. The heterogeneous mixture was stirred for 20 min, poured into satd NH_4Cl and the whole was extracted with Et_2O (3×). The combined organic extract was dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexanes), affording 7.42 g (83%) of **8** as a colorless syrup that slowly crystallized: mp 47−49 °C (petroleum ether); IR (film) ν_{max} 1639 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.52 (dd, 1H, J = 4.9, 1.7 Hz), 7.90 (dd, 1H, J = 7.4, 1.9 Hz), 7.26 (dd, 1H, J = 7.6, 4.8 Hz), 3.57 (q, 2H, J = 7.2 Hz), 3.23 (q, 2H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz), 1.13 (t, 3H, J = 7.1 Hz), 0.31 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8, 159.5, 148.2, 143.1, 133.3, 122.9, 43.1, 39.5, 13.7, 12.7, 0.7; MS (EI) *m*/*z* 250 (M$^+$, 18), 235 (100), 207 (57), 179 (74); HRMS calcd for $C_{13}H_{22}N_2OSi$ 250.1501, found 250.1505.

DoM−Boronation−Oxidation of Pyridine Carboxamides: General Procedure 1. To a solution of the appropriate pyridine carboxamide (1.00 mmol) and B(O^{i}Pr)$_3$ (3.00 mmol) in THF (5 mL) at 0 °C was added a freshly prepared solution of LDA (1.2−1.3 mmol) in THF, dropwise over 10 min. The resulting mixture was stirred for 10 min at 0 °C and aqueous H_2O_2 (30−35% w/v; ca. 6 mmol) was slowly added (usually accompanied by the appearance of a gummy precipitate). The reaction mixture was stirred at room temperature for 0.5−2 h (until completion, as judged by TLC). The mixture was slowly poured into an excess of cold 10% $Na_2S_2O_3$, then stirred 10 min, and the whole was extracted with Et_2O. The aqueous layer was acidified to pH 5.5 with aq 2 N HCl and extracted with CH_2Cl_2 (3×). The combined organic extract was dried (Na_2SO_4), subjected to filtration, and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc/hexanes).

***N*2,*N*2-Diethyl-3-hydroxy-2-pyridinecarboxamide (12). 12** was prepared according to General Procedure 1 from **5** (3.74 g, 21.0 mmol), B(O^{i}Pr)$_3$ (14.5 mL, 63.0 mmol), and LDA (27.4 mmol). Oxidative workup (21.4 mL × 30 wt % H_2O_2, 1 h) and flash chromatography (15% EtOAc in hexanes) afforded 3.58 g (88%) of **12** as a colorless solid: mp 82−84 °C (hexanes); IR (film) ν_{max} 3159, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.37 (br s, 1H), 8.09 (dd, 1H, J = 4.1, 1.8 Hz), 7.23−7.31 (m, 2H), 4.00 (br s, 2H), 3.55 (br s, 2H), 1.30 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 158.4, 138.4, 134.9, 127.0, 125.6, 44.7, 42.8, 14.4, 12.6; MS (EI, 70 eV) *m*/*z* 194 (M$^+$, 20), 147 (22), 123 (82), 122 (100); HRMS calcd for $C_{10}H_{14}N_2O_2$ 194.1055, found 194.1056.

In Situ Boronation of DMG-Containing Pyridines 15a−f: General Procedure 2. A stock solution of LDA (0.7 M) was prepared by dropwise addition of a solution of *n*-BuLi (3.5 mmol) in hexanes to diisopropylamine (3.67 mmol) in the required volume of THF at −10 °C. The clear solution was stirred at 0 °C for 10 min before use. A 50 mL flame-dried round-bottom flask was charged with the pyridine derivative **15** (3.0 mmol), THF (5 mL), and B(O^{i}Pr)$_3$ (3.6−4.5 mmol). To this solution, cooled to −10 °C, was added LDA (4.7−6.4 mL of a 0.7 M solution in THF; 3.3−4.5 mmol) and the mixture was stirred at 0 °C for 45 min or until the disappearance of starting material (TLC, 9.5/0.5 CH_2Cl_2/MeOH). Pinacol or diethanolamine (4.5 mmol) was added and the mixture was allowed to warm to room temperature with stirring over 1 h. The resulting mixture was passed through Celite, the filter agent was rinsed with dichloromethane (100 mL), and the filtrate was concentrated *in vacuo*. The resulting residue was recrystallized from hexanes/
CH_2Cl_2 to afford pinacolates **16a−d** or **17a−f**.

***N*,*N*-Diethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-nicotinamide (16b). 16b** was prepared according to General Procedure 2 from **15b** (0.52 g, 2.9 mmol) in 5 mL of THF, B(O^{i}Pr)$_3$ (3.5 mmol, 0.80 mL), and LDA (5.0 mL of a 0.7 M solution in THF; 3.5 mmol) to obtain **16b** as a colorless solid (0.51 g, 60%): mp 130−135 °C (sublimes, hexanes/CH_2Cl_2); IR (thin film) ν_{max} 3450, 2979, 2930, 1633, 1464, 1358, 1145, 1032, 732 cm^{-1}; ^{1}H NMR δ 8.64 (s, 1H), 8.61 (s, 1H), 3.63 (q, 2H, J = 7.14 Hz), 3.36 (q, 2H, J = 7.14 Hz), 1.35−1.25 (m, 15H), 1.18 (t, 3H, J = 7.14 Hz); ^{13}C NMR δ 169.7, 149.8, 146.1, 128.2, 83.7, 43.5, 41.0, 25.0, 13.9, 12.5; LRMS 304 (M$^+$, 12) 303 (42), 246 (63), 245 (43), 203 (100), 175 (43), 159 (54), 130 (85), 103 (45); HRMS calculated for $C_{16}H_{25}BN_2O_3$ 304.1958, found 304.1958.

One-Pot DoM−Boronation−Suzuki−Miyaura Cross Coupling of Pyridine Derivatives 15a−c and 15h: Representative Procedure 3. *N*,*N*-Diethyl-3-(4-methoxy-phenyl)-isonicotinamide (19j). A 50 mL flame-dried round-bottom flask was charged with **15c** (2.8 mmol, 0.47 mL), THF (5 mL), and B(O^{i}Pr)$_3$ (0.71 mL, 3.08 mmol). The solution was cooled to −10 °C and LDA was added (4.40 mL of a 0.7 M solution in THF; 3.08 mmol), prepared as in General Procedure 2, and the mixture was stirred at 0 °C for 45 min monitoring the progress of the reaction by TLC (CH_2Cl_2/MeOH 9.5/0.5). Pinacol (0.40 g, 3.36 mmol) was added and the mixture was allowed to warm to room temperature with stirring over 1 h. The solvent was evaporated to dryness *in vacuo* and Pd(PPh$_3$)$_4$ (0.162 g, 0.14 mmol, 5% mol) and 4-bromoanisole (0.576 g, 3.08 mmol) were added with care to minimize exposure of the mixture to air. After flushing briefly with argon, a water condenser was fitted to the flask and a degassed 2 M aqueous solution of Na_2CO_3 (7 mL, 14 mmol) and 5 mL of degassed toluene were added through a septum sealing the top of the condenser. The mixture was refluxed for 12 h, cooled, and extracted with EtOAc (6 × 10 mL). The combined organic extract was washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH 19.5/0.5) and distillation *in vacuo* (150 °C/0.9 mmHg) to yield 0.60 g (2.1 mmol, 75%) of **19j** as a colorless solid: mp 76−78 °C; IR (KBr disk) υ_{max} 3464, 1623, 1252; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.63 (s, 1H), 8.56 (d, 1H, J = 5.2 Hz), 7.41 (d, 2H, J = 8.8 Hz), 7.21 (dd, 1H, J = 4.8, 0.8 Hz), 6.95 (d, 2H, J = 8.8 Hz), 3.82 (s, 3H), 3.67 (br s, 1H), 3.10 (br s, 1H), 2.88 (br s, 1H), 2.72 (br s, 1H), 0.97 (t,

(45) Stauffer, K. J.; Williams, P. D.; Selnick, H. G.; Nantermet, P. G.; Newton, C. L.; Homnick, C. F.; Zrada, M. M.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; Pietrak, B. L.; Lyle, E. A.; Singh, R.; Miller-Stein, C.a; White, R. B.; Wong, B.; Wallace, A. A.; Sitko, G. R.; Cook, J. J.; Holahan, M. A.; Stranieri-Michener, M.; Leonard, Y. M.; Lynch, J. J., Jr.; McMasters, D. R.; Yan, Y. *J. Med. Chem.* **2005**, *48*, 2282−2293. Wu, Y.-C; Duh, C.-Y.; Wang, S.-K.; Chen, K.-S.; Yang, T.-H. *J. Nat. Prod.* **1990**, *53*, 1327−1331.

3H, $J = 7.2$ Hz), 0.76 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 168.1, 159.9, 150.0, 148.3, 143.4, 132.9, 130.1, 128.5, 121.1, 114.2, 55.3, 42.3, 38.6, 13.4, 12.1; MS *m*/*z* (rel intensity %) 284 (M^+, 68), 283 (69), 255 (10), 213 (30), 212 (100), 184 (9), 169 (40); HRMS calcd for $C_{17}H_{20}N_2O_2$ 284.1525, found 284.1532.

Directed Remote Metalation Route to Azafluorenones: Representative Procedure. 8-Chloro-3-aza-fluoren-9-one (20*l*). A 50 mL flame-dried round-bottom flask was charged with **19*l*** (400 mg, 1.38 mmol) in THF (50 mL). The solution was cooled to −10 °C and LDA (3.0 mL of a 0.7 M solution in THF; 2.1 mmol), prepared as in General Procedure 2, was added dropwise to this solution cooled to 0 °C and the mixture was allowed to stir at this temperature for 15 min or until complete disappearance of the starting material (TLC: hexanes/EtOAc 6/4). The reaction was quenched with NH_4Cl and the aqueous layer was extracted with EtOAc (3×). The combined organic extract was washed with brine, dried (Na_2SO_4), and subjected to filtration, then the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc 6/4) to afford 0.24 g (81%) of **20*l*** as a yellow powder: mp 178−179 °C (hexanes−EtOAc); IR (KBr disk) υ_{max} 3071, 1716, 1579, 1445, 1272, 783, 672; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.74 (d, 1H, $J = 4.4$ Hz), 7.58 (d, 1H, $J = 7.8$ Hz), 7.55 (d, 1H, $J = 4.4$ Hz), 7.49 (t, 1H, $J = 7.8$ Hz), 7.31 (d, 1H, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 189.9, 152.2, 145.1, 142.3, 139.9, 136.1, 135.8, 133.8, 131.7, 128.9, 119.6, 117.4; MS *m*/*z* 217 (33), 215 (M^+, 100), 187 (17), 160 (13), 152 (11), 125 (10); HRMS calcd for $C_{12}H_6ClNO$ 215.0138, found 215.0133.

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Supporting Information Available: Experimental procedures and characterization data for the synthesis of picolinamides **5**, **7**, **9**, **10**, **13**, and **14**, the boronates **16a**,**c**,**d** and **17a**−**f**, the azabiaryls **18**, **19a**−**i**, **19k**−**t**, and the azafluorenones **20b**,**e**,**h**; ^{1}H NMR and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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