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Synthesis of a 7-Azaindole by Chichibabin Cyclization: Reversible Base-Mediated Dimerization of 3-Picolines

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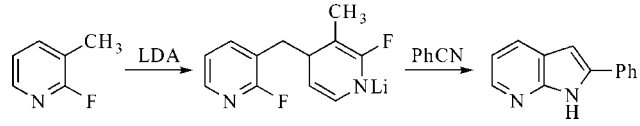
Received July 01, 2008



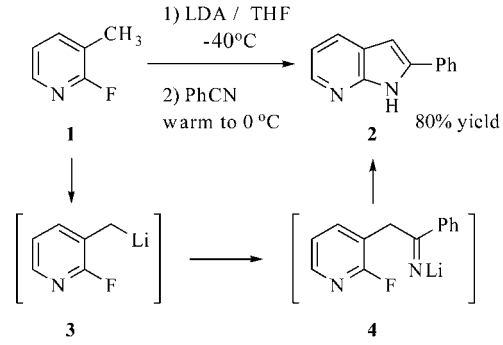
The lithium diisopropylamide (LDA)-mediated condensation of 2-fluoro-3-picoline and benzonitrile to form 2-phenyl-7-azaindole via a Chichibabin cyclization is described. Facile dimerization of the picoline via a 1,4-addition of the incipient benzyllithium to the picoline starting material and fast 1,2-addition of LDA to benzonitrile cause the reaction to be complex. Both adducts are shown to reenter the reaction coordinate to produce the desired 7-azaindole. The solution structures of the key intermediates and the underlying reaction mechanisms are studied by a combination of IR and NMR spectroscopies.

Introduction

7-Azaindoles have been found to be therapeutically active for an array of maladies.[1] The primary synthetic challenge presented by azaindoles reduces to one of heteroannulation—appending a pyrrole to a pyridine or vice versa.[1,2] In connection with a program at Sanofi-Aventis to synthesize polycyclic pyrrole derivatives to be tested for the treatment of asthma,[2c] the conversion of 2-fluoro-3-picoline (**1**) to 7-azaindole **2** was examined (Scheme 1). The procedure was modeled after that of Wakefield and co-workers in which metalation of 3-picoline and subsequent addition of benzonitrile (PhCN) affords 7-azaindole **2** in one pot.[3] The key cyclization of putative intermediate **4** to **2** corresponds to a Chichibabin reaction—the nucleophilic addition of an alkali metal amide to a pyridine.[4,5] Substitution of the fluoro moiety precludes an air oxidation required by standard Chichibabin protocols. The fluorine does not improve the yield, but ^{19}F NMR spectroscopy proves to be particularly useful to study the reaction.[6]

The Cornell group was charged with studying the underlying structural and mechanistic organolithium chemistry. The results are particularly odd owing to *nonfatal* condensations of benzyllithium **3** with picoline **1** and of LDA with PhCN (eq 1), which leave *none* of the original reagents intact. We examined how adducts **5** and **6** form and reenter the reaction coordinate to provide azaindole **2** in high yield. The results are summarized at the beginning of the discussion section for the benefit of the

SCHEME 1



(1) (a) Popowycz, F.; Routier, S.; Joseph, B.; Merour, J.-Y. *Tetrahedron* **2007**, *63*, 1031. (b) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152.

(2) (a) Merour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471. (b) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120. (c) Hopkins, C. R.; Collar, N. *Tetrahedron Lett.* **2004**, *45*, 8087.

(3) Davis, M. L.; Wakefield, B. J.; Wardell, J. A. *Tetrahedron* **1992**, *48*, 939.

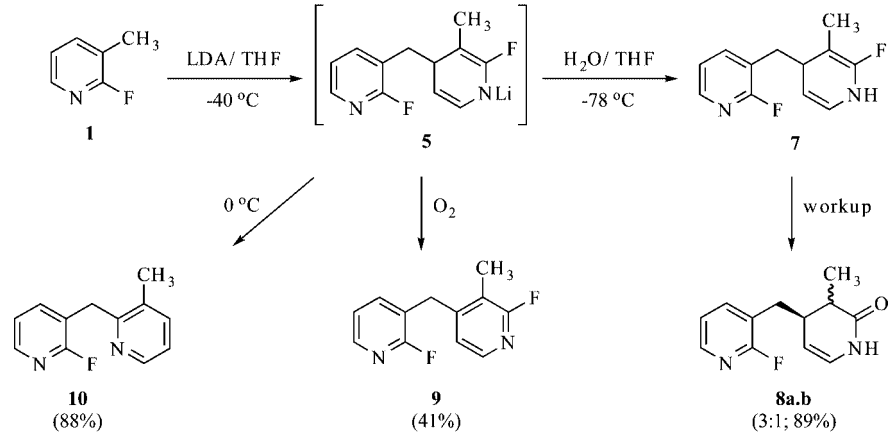
(4) (a) Vorbrugenn, H. *Adv. Hetercycl. Chem.* **1990**, *49*, 117. (b) McGill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, *44*, 1.

(5) (a) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, E. *J. Adv. Heterocycl. Chem* **1991**, *52*, 187. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 5897. (c) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. (d) Merino, P. *Progr. Heterocycl. Chem.* **1999**, *11*, 21. (e) Clayden, J. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2004; Vol. 1, p 495. (f) Caubere, P. In *Reviews of Heteroatom Chemistry*; MYU: Tokyo, 1991; Vol. 4, pp 78−139. (g) Caubere, P. *Chem. Rev.* **1993**, *93*, 2317. (h) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009. (i) Collins, I. *Perkin 1* **2000**, 2845. (j) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161.

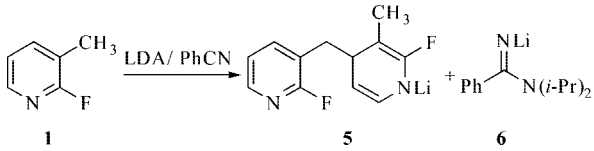
(6) For a review of structural studies using ^{19}F NMR spectroscopy, see: (a) Gakh, Y. G.; Gakh, A. A.; Gronenborn, A. M. *Magn. Reson. Chem.* **2000**, *38*, 551. (b) McGill, C. A.; Nordon, A.; Littlejohn, D. *J. Process Anal. Chem.* **2001**, *6*, 36.

10.1021/jo801410s CCC: $40.75
Published on Web 08/16/2008

SCHEME 2



nonspecialist. The importance of dimerizations during lithiations of heterocycles is discussed in a broader context.



(1)

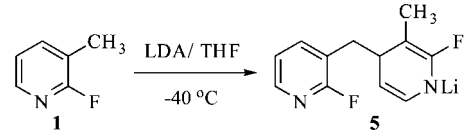
Results

Azaindole Synthesis. The conversion of fluoropicoline **1** to azaindole **2** proceeds smoothly by sequential addition of picoline **1** to 2.1 equiv of LDA in THF at −40 °C. After 60 min, addition of 1.2 equiv of PhCN to the blood-red reaction with stirring for an additional 2.0 h at −40 °C affords **2** in 80% yield. Alternatively, reversing the order of addition—adding 1.05 equiv PhCN to 2.1 equiv LDA at −40 °C followed by 1.0 equiv fluoropicoline **1**—affords azaindole **2** in 82% yield. An inferior (15−20%) yield of **2** is obtained if only 1.05 equiv of LDA is used. The second equivalent may be required for a tautomerization following the cyclization of **4**. No ketone derived from hydrolysis of putative intermediate **4** could be observed despite prompt aqueous quenches at low temperature.

Byproducts Derived from Picoline Dimerization. A number of byproducts emerged during the optimizations that attest to picoline dimerizations.[7] The byproducts, prepared in optimized yields as illustrated in Scheme 2, foreshadow an underlying mechanistic complexity. They were characterized by a combination of ^{1}H, ^{13}C, ^{19}F, [^{1}H,^{13}C]HMBC, [^{1}H,^{13}C]HSQC, [^{1}H,^{1}H]COSY, and [^{1}H,^{19}F]*J*-resolved spectroscopies, IR spectroscopy, and mass spectrometry.

Lithiating **1** at −40 °C followed by quenching with wet THF at −78 °C affords **7**, the product of 1,4-addition of benzyllithium **3** to picoline **1**, as a transiently stable intermediate.[8] Dihydropyridine **7** displays vinyl ^{1}H resonances at δ 5.87 and 4.06 ppm characteristic of the enamino moiety as well as a 1:1 pair of ^{19}F resonances at δ −70.1 and −114.8 ppm. Whereas the ^{19}F resonance at δ −70.1 ppm is consistent with a fluoropyridine moiety,[9] the resonance at δ −114.8 ppm is decidedly upfield. Aqueous workup of **7** affords a 3:1 mixture of lactams **8a** and **8b** isolated in 89% combined yield along with traces of **9** (11%). Lactams **8a** and **8b** were separated, but their stereochemistries were not assigned. Presumably, **8a** and **8b** result from hydrolysis of fluorodihydropyridine **7**, whereas **9** derives from its air oxidation. The yield of **9** increases to 41% by adding O_2 at −40 °C prior to the aqueous quench.[10] If solutions of **1** and LDA are warmed to 0 °C prior to an aqueous quench, product **10** resulting from dimerization by a 1,2-addition is isolated in 88% yield.[11−13]

Origins of 1,4-Adducts. Metalation of **1** by 1.0 equiv of [^{6}Li,^{15}N]LDA affords lithiated dihydropyridine **5** (eq 2) of unknown aggregation number. ^{6}Li NMR spectroscopy reveals the resonance corresponding to unreacted LDA dimer **11**[14,15] along with a single resonance displaying no ^{6}Li−^{15}N coupling, initially presumed to derive from lithiated picoline **3**. The ^{19}F NMR spectra, however, display *two* resonances in a 1:1 proportion at markedly different chemical shifts (δ −93.5 and −70.5 ppm).[16] A combination of ^{19}F and ^{1}H NMR spectroscopies showed coupling patterns fully consistent with **5** (eq 2); vinyl resonances at 5.83 and 3.80 ppm are especially characteristic of the lithioimine moiety. At no point did we observe resonances corresponding to **9** (or a lithiated counterpart[17]), confirming that **9** forms during workup.

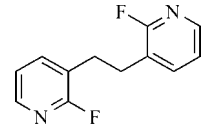


(2)

The underlying mechanism of the dimerization is shown to involve rate-limiting picoline metalation with a subsequent rapid

(7) Scheme 2 does not represent a comprehensive profile of byproducts.
(8) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223.
(9) Nanney, J. R.; Mahaffy, C. A. L. *J. Fluorine Chem.* **1994**, *68*, 181.

(10) Treating **5** with MnO_2 prior to the aqueous quench affords **9** in 50% yield. For a related MnO_2 rearomatization, see: (a) Godard, A.; Jacquelin, J. M.; Quéguiner, G. *J. Organomet. Chem.* **1988**, *354*, 273. (b) Eynde, J. J.; Delfosse, F.; Mayence, A.; Haverbeke, V. *Tetrahedron* **1995**, *51*, 6511.
(11) For the 1,2-addition of an aryllithium to **1**, see: DuPriest, M. T.; Schmidt, C. L.; Kuzmich, D.; Williams, S. B. *J. Org. Chem.* **1986**, *51*, 2021.
(12) Dimer **9** was further characterized by X-ray crystallography. The product of oxidative coupling (**i**) was also characterized as a rogue crystal by X-ray crystallography. We were unable to intentionally produce detectable **i** by introducing oxygen to an LDA/**1** mixture.

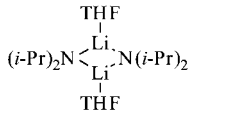


i

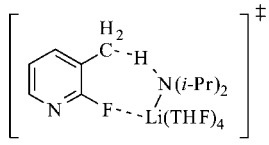
(13) We find fluoropyridines to be sensitive to traces of acid, including the residual HCl in chlorinated solvents.

dimerization; details of the rate studies are described in the Experimental Section.[18] The idealized[19] rate law (eq 3), in conjunction with the assignment of LDA/THF as a disolvated dimer **11**,[14,15] is consistent with lithiation via a tetrasolvated monomer-based transition structure, which we offer **12**. The third-order dependence on the THF concentration (measured 2.9 ± 0.2) was surprising. Precedent suggests that the THF order could include secondary-shell solvation effects.[20] Nonetheless, using 2,2,5,5-Me_4THF as a polar, but chemically inert cosolvent afforded no reduction in the THF order.[20] Evidence of high coordinate lithium support such a highly solvated transition structure as possible.[21] The depicted Li−F interaction is supported by evidence that such Li−F interactions are highly stabilizing.[22] With that said, the solvation number and existence of an Li−F interaction in **12** should be viewed with a healthy skepticism.

$$-\mathrm{d}[1]/\mathrm{d}t = k[1][\mathrm{LDA}]^{1/2}[\mathrm{THF}]^3 \qquad (3)$$



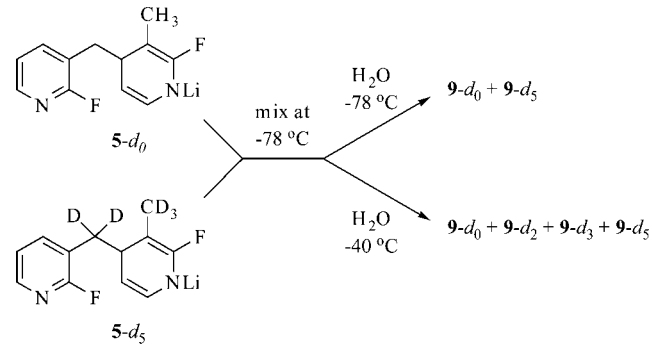
11



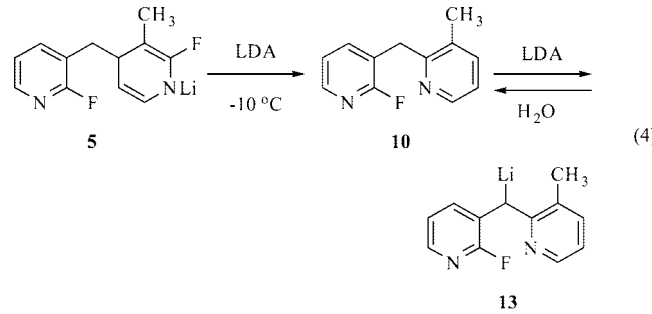
12

Reversible formation of **5** was demonstrated by a double-crossover study summarized in Scheme 3.[23] Mixing independently prepared samples of **5**-d_0 and **5**-d_5 at −78 °C and quenching after 10 min afforded a mixture of **9**-d_0 and **9**-d_5 contaminated with only traces (<5%) of crossover products **9**-d_2 and **9**-d_3 as shown by GC−MS analysis. (The low levels of crossover are probably elicited by inadvertent warming.) Warming to −40 °C affords an approximate statistical distribution.[24] Therefore, the 1,4-addition to form **5** is reversible under the conditions of the metalation of picoline **1** (−40 °C) and the rearrangement to form **10** (0 °C), but *not* at low temperatures. This temperature dependence proves to be important (vide infra).[25]

SCHEME 3



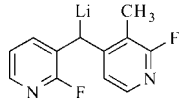
Origins of 1,2-Adduct 10. Warming solutions of lithiated dihydropyridine **5** to 0 °C—conditions affording 1,2-adduct **10** in high yield (eq 4)—causes the ^{19}F resonances of **5** to disappear via a first-order decay.[26,27] A single ^{19}F resonance at δ −77.9 ppm corresponding to a lithiated form of **10** (presumably **13**) appears concomitantly. Quenching affords **10** (δ −70.9 ppm). Treating a purified sample of **10** with LDA causes the resonance of **13** at δ −77.9 ppm to reappear. The approximate first-order decay of **5** and the crossover experiments are congruent with formation of **10** via benzyllithium **3**.[28]



5 **10** **13** (4)

Condensation of Lithiated Dihydropyridine 5 with PhCN. Monitoring the solutions containing PhCN, **5**, and residual LDA (0.5 equiv relative to starting picoline **1**) using ^{19}F NMR spectroscopy shows the disappearance of picoline **1** at −40 °C. Adduct **2** (or its lithium salt) is not detectable by ^{19}F NMR spectroscopy. An absence of fluorine-containing intermediates suggests that cyclization of imidolithium **4** to afford azaindole **2** is very fast.[29]

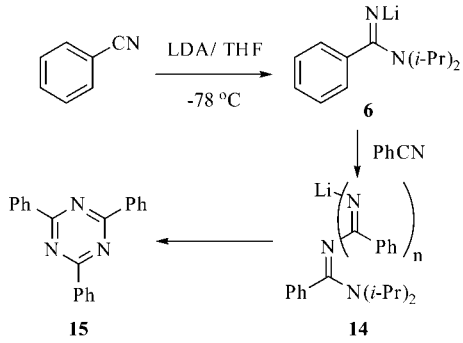
(14) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772.
(15) (a) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227. (b) Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47. (c) Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167.
(16) Traces (approx 5%) of 13(δ−77.9 ppm) are also observed.
(17) Lithiation of an isolated sample of 9 with LDA affords new 19 F resonances at δ−78.9 and−75.0 ppm that we attribute to ii. These resonances were not observed in the reaction mixture.



ii

(18) For a review of rate studies of LDA-mediated reactions, see: Collum, D. B.; McNeil, A. J.; Ramirez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3002.
(19) We define the idealized rate law as that obtained by rounding the observed reaction orders to the nearest rational order.
(20) Ma, Y.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 14818, and references cited therein.
(21) For leading references and discussion of high-coordinate lithium amides, see ref 20.
(22) (a) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755. (b) Stalke, D.; Klingebiel, U.; Sheldrick, G. M. *Chem. Ber.* **1988**, *121*, 1457. (c) Armstrong, D. R.; Khandelwal, A. H.; Kerr, L. C.; Peasey, S.; Raithby, P. R.; Shields, G. P.; Snaith, R.; Wright, D. S. *Chem. Commun.* **1998**, 1011. (d) Plenio, H.; Diodone, R. *J. Am. Chem. Soc.* **1996**, *118*, 356. (e) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 11855. (f) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640. (g) Chadwick, S. T.; Ramirez, A.; Gupta, L.; and Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259. (h) Williard, P. G.; Liu, Q.-Y. *J. Org. Chem.* **1994**, *59*, 1596.
(23) Carpenter, B. K., *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984.
(24) A deviation from statistical stems from difficulty in obtaining precisely equal proportions of **5**-d_0 and **5**-d_5 due to the especially large kinetic isotope effect on the metalation.
(25) It has been suggested that the *n*-BuLi adduct of pyridine can reduce pyridine by extruding lithium hydride. (a) Clegg, W.; Dunbar, L.; Horsburgh, L; Mulvey, R. E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 753.
(26) (a) The fit to [A] = [A_0]exp(−$k_{obsd}t$) showed some discrepancies (Supporting Information), yet a fit to a nonlinear Noyes equation (ref 26b) to obtain the order by best-fit methods revealed an order of 1.0. (b) Briggs, T. F.; Winemiller, M. D.; Collum, D. B.; Parsons, R. L., Jr.; Davulcu, A. K.; Harris, G. D.; Fortunak, J. D.; Confalone, P. N. *J. Am. Chem. Soc.* **2004**, *126*, 6291.
(27) k_{obsd} for the decay of **5** shows a minor (50%) rise with a 3-fold decrease in THF concentration.
(28) The crossover described in Scheme 3 occurs at substantially lower temperatures than the rearrangement to provide **10**. As expected, analogous crossover is observed in **10**.
(29) We have never observed [^{6}Li]LiF by NMR spectroscopy. This may derive from a very low solubility.

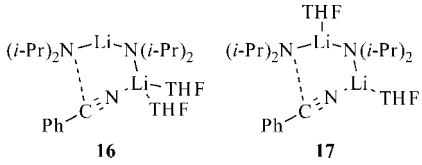
SCHEME 4



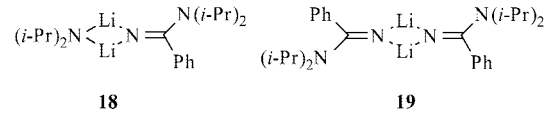
Condensation of LDA with PhCN. Monitoring the reaction described above using in situ IR spectroscopy[30] shows that PhCN disappears with a 3 min half-life at −78 °C (≪1 min at −40 °C.) This is substantially faster than the loss of **5**. This loss of PhCN was traced to the condensation of the remaining LDA (0.5−1.5 equiv; not shown) to form amidinolithium **6** as the first step of a cascade of reactions leading to PhCN trimer **15** (Scheme 4).[31−33] Indeed, warming a mixture of **6** and PhCN to 0 °C affords an intensely purple solution (appearing black), which affords PhCN-derived trimer **15** in 83% yield. Base-mediated trimerizations of arylnitriles have been reported previously.[31,32]

The condensation of LDA and PhCN is important because it affords **6** *substantially faster than the metalation of* **1** by LDA. We examined the kinetics by monitoring the loss of PhCN (2230 cm^{-1}) and the formation of amidinolithium **6** (1627 cm^{-1}) as described in the Experimental Section. The first term in the resulting rate law in eq 5 is consistent with open dimer-based transition structures **16** or **17**.[18,34] (The reaction rate at low THF concentrations was too high to measure the LDA order in the second term of eq 5.)

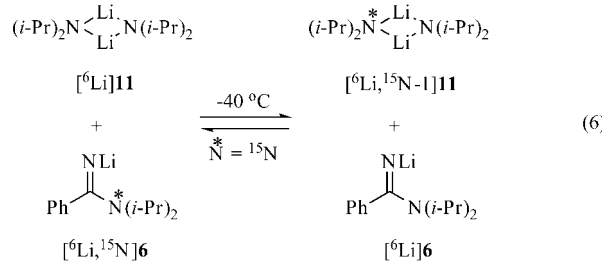
$$-\mathrm{d[PhCN]}/\mathrm{d}t = k[\mathrm{PhCN}][\mathrm{LDA}][\mathrm{THF}]^0 + k'[\mathrm{PhCN}][\mathrm{LDA}]^n[\mathrm{THF}]^{-1} \quad (5)$$



Monitoring equimolar mixtures of PhCN and [^{6}Li,^{15}N]LDA[35] by ^{6}Li and ^{15}N NMR spectroscopy reveals the conversion of LDA dimer **11** sequentially to heterodimer **18** and homodimer **19**. Heterodimer **18** displays a characteristic ^{6}Li doublet arising from coupling to one labeled LDA fragment.[15,36] The ^{15}N spectrum of **18** shows the LDA fragment as a broad mound and the C(=NLi)^{15}N(*i*-Pr)$_2$ moiety as a sharp singlet. Homodimer **19** displays ^{6}Li and ^{15}N singlets. (The resonances corresponding to the C(=NLi)^{15}N(*i*-Pr)$_2$ moieties of **18** and **19** appear to superimpose.) In a complementary experiment, equimolar mixtures of [^{15}N]PhCN and [^{6}Li]LDA afford **18** displaying a ^{6}Li doublet and ^{15}N mound and **19** as a ^{6}Li triplet and ^{15}N mound. Crystal structures of related unsolvated amidinolithium derivatives[37] are prismatic higher oligomers. (The broad ^{15}N resonances associated with **18** and **19** may derive from further oligomerization of the amidinolithium **6** described below.)



Addition of LDA to PhCN appears to be reversible, albeit slowly. Thus, [^{6}Li]LDA (as disolvated dimer **11**)[14] was added to a solution containing [^{6}Li,^{15}N]**6** (labeled on the N(*i*-Pr)$_2$ of the amidino moiety) kept below −90 °C. On warming, the probe crossover begins to occur at −40 °C as exemplified by the appearance of ^{15}N coupling in LDA dimer **11** (and heterodimer **18**). Crossover requires approximately 50 min to proceed to completion (coinciding with the appearance of oligomer **14** described above.) The similar conditions affording crossover and conversion of mixtures of **5** and **6** to azaindole **2** is probably not a coincidence.



(6)

Chichibabin Cyclization Using Amidinolithium 6. Solutions containing amidinolithium **6** at −40 °C—conditions affording Chichibabin cyclization—also cause further oligomerization of **6** (actually homodimer **19**) to a new species with a slightly downfield-shifted ^{6}Li resonance that we attribute to oligomer(s) **14**. (Possible intermediates in PhCN trimerizations have been discussed by Wheatley and co-workers.[32]) Monitoring Chichibabin cyclizations by ^{6}Li NMR spectroscopy reveals that **6** and **14** form but then reenter the reaction coordinate (although more reluctantly for **14**).

The most logical explanation for the success of the protocol in eq 1 is that **6** and **14** form reversibly (eq 7). We did, however, consider alternative models. In principle, **6** could condense with **1** via 1,2-addition to form **20** with subsequent LDA-mediated cyclization (eq 8). Nonetheless, addition of picoline **1** to a nearly LDA-free solution of **6** (prepared in situ) shows very little loss

(30) Rein, A. J.; Donahue, S. M.; Pavlosky, M. A. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 734.

(31) (a) Compagnon, P. L.; Gasquez, F; Kimny, T. *Bull. Soc. Chim. Belg.* **1986**, *95*, 57. (b) Chen, X.; Bai, S.-D.; Wang, L.; Liu, D.-S. *Heterocycles* **2005**, *65*, 1425.

(32) (a) Davies, R. P.; Raithby, P. R.; Shields, G. P.; Snaith, R.; Wheatley, A. E. H. *Organometallics* **1997**, *16*, 2223. (b) Armstrong, D. R.; Clegg, W.; MacGregor, M.; Mulvey, R. E.; O'Neil, P. A. *J. Chem. Soc., Chem. Commun.* **1993**, 608. (c) Armstrong, D. R.; Henderson, K. W.; MacGregor, M.; Mulvey, R. E.; Ross, M. J.; Clegg, W.; O'Neil, P. A. *J. Organomet. Chem.* **1995**, *486*, 79.

(33) Crystal structures of amidinolithiums: Aharonovich, S.; Kapon, M.; Botoshanski, M.; Eisen, M. S. *Organometallics* **2008**, *27*, 1869.

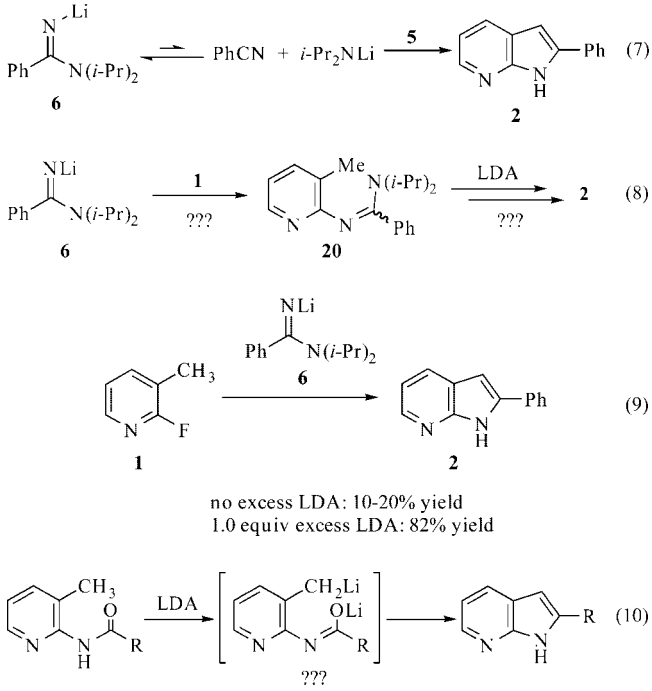
(34) For calculated open dimer-based additions of methyllithium to nitriles, see: Uchiyama, M.; Matsumoto, Y.; Usui, S.; Hashimoto, Y.; Morokuma, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 926.

(35) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751.

(36) The nuclear spins of ^{6}Li and ^{15}N are 1 and 1/2, respectively.

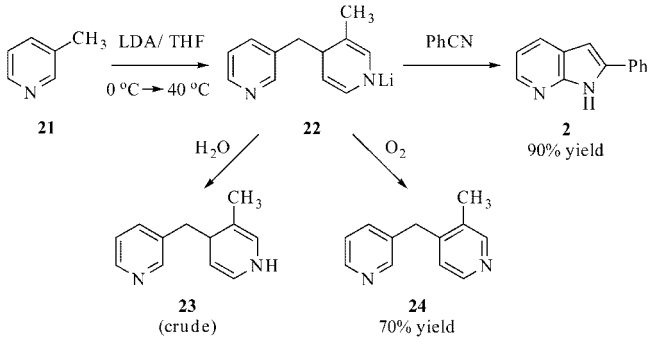
(37) (a) Armstrong, D. R.; Barr, D.; Snaith, R.; Clegg, W.; Mulvey, R. E.; Wade, K.; Reed, D. *J. Chem. Soc., Dalton Trans.* **1987**, 1071. (b) Barr, D.; Snaith, R.; Mulvey, R. E.; Wade, K.; Reed, D. *Magn. Reson. Chem.* **1986**, *24*, 713. (c) Reed, D.; Barr, D.; Mulvey, R. E.; Snaith, R. *J. Chem. Soc., Dalton Trans.* **1986**, 557. (d) Barr, B.; Clegg, W.; Mulvey, R. E.; Snaith, R.; Wade, K. *J. Chem. Soc., Chem. Commun.* **1986**, 295.

of starting material and <20% yield of azaindole **2** (eq 9). Amidinolithium **6** does not react with the relatively unhindered 2-fluoropyridine at −40 °C. Therefore, adduct **20** is not likely to be an intermediate en route to **2**. Alternatively, the cyclization shown in eq 10[38] and nucleophilic additions of alkyllithiums to imidolithiums of general structure ArN=C(OLi)R[39] suggest that **6** could, in theory, be the key electrophile. Nonetheless, **6** certainly does not have the trappings of a good electrophile.



Chichibabin Cyclization Using 3-Picoline. To ascertain the role of the 2-fluoro moiety in **1** we briefly investigated the metalation of 3-picoline (**21**). As described by Wakefield and co-workers,[3] treatment of **21** with 3.3 equiv of LDA at 0 °C followed by addition of PhCN with subsequent warming to 40 °C affords azaindole **2** in 90% yield (Scheme 5). Cursory rate studies using IR spectroscopy following the loss of **21** (1575 cm^{-1}) show that **21** is at least 20-fold less reactive than **1**, lithiating smoothly only on warming to 10 °C. ^1H NMR spectroscopic analysis was thwarted by precipitation. Metalation of **21** in the absence of PhCN affords **22** as a bright yellow solid that could be isolated but resisted spectroscopic characterization due to insolubility in THF.[40] Quenching the yellow solid with THF-d_8/H_2O (40:1) afforded dihydropyridine **23** in >90% spectroscopic purity that was surprisingly stable to further hydrolysis. Alternatively, treatment of the yellow solid suspended in THF with O_2 followed by standard aqueous workup afforded aromatized dimer **24** (70% yield) previously detected by Goto and co-workers.[41]

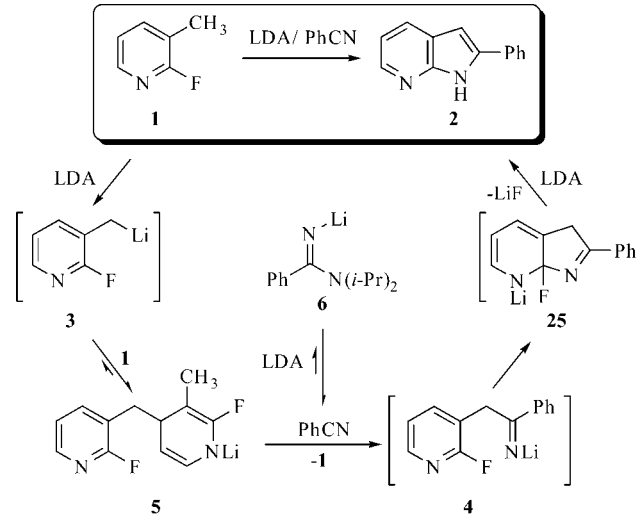
SCHEME 5



Discussion

In the context of studies of 7-azaindoles and related bicyclic pyrrole-based heterocycles being carried out at Sanofi-Aventis,[2c] we investigated the Chichibabin cyclization illustrated in Scheme 1. Although the design is a straightforward adaptation of a protocol used by Wakefield and co-workers,[3] the underlying organolithium chemistry is peculiar, and the potential ramifications are consequential. The results are summarized in the context of Schemes 2 and 6 as follows.

SCHEME 6



Summary. Sequential treatment of fluoropicoline **1** with LDA (2.0 equiv) and PhCN affords azaindole **2** in excellent (80−85%) yield. The order of mixing has no effect on the yield as long as the reaction is kept at ≤−40 °C. Products resulting from the condensation of benzyllithium **3** with fluoropicoline **1** offer a glimpse of underlying complexity (Scheme 2). Quenching solutions of LDA and **1** with H_2O affords transiently stable (but fully characterized spectroscopically) dihydropyridine **7**, which is converted to lactams **8a**,**b** and traces of air-oxidized dimer **9** on workup. Warming prior to quenching affords net 1,2-adduct **10** in high yield. Monitoring the reaction by ^{19}F NMR spectroscopy reveals lithiated dihydropyridine **5** in >95% purity to the exclusion of benzyllithium **3**. Rate studies show that **5** forms by a rate-limiting metalation of **1** via highly solvated LDA monomer (see **12**). Adding PhCN to solutions of **5** shows no fluorine-containing intermediates. The extruded 0.5 equiv of **1** reenters the reaction coordinate, as required by the high yields of **2**.

Concurrent with the dimerization of picoline **1**, LDA undergoes reversible condensation with PhCN to form amidinolithium **6**, which exists as hetero- and homodimers **18** and **19**. Rate studies reveal an LDA dimer-based mechanism via **16** or **17**.[15]

(38) (a) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401. (b) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. *Synthesis* **1996**, 877. (c) Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511.

(39) Smith, K.; El-Hiti, G. A.; Hamilton, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, *24*, 4041.

(40) Dissolving the yellow solid with added *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) resulted in very complex mixtures. We suspect that TMEDA mediates reversal of the 1,4-addition, allowing other reactions to occur.

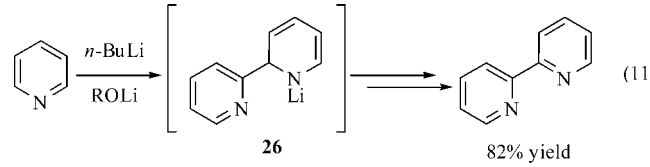
(41) Tagawa, Y.; Hama, K.; Goto, Y. *Heterocycles* **1992**, *34*, 1605.

If adduct **6** stands for several hours or is warmed above −40 °C, further oligomerization occurs, eventually affording trimer **15** (Scheme 4).[31,32] Provided the cascade leading to **15** is not allowed to occur, formation of amidinolithium **6** does *not* preclude formation of azaindole **2**.

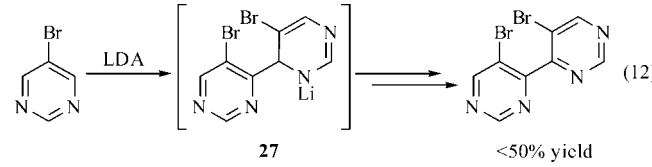
The peculiarity of the Chichibabin cyclization is underscored by an inverse addition in which LDA and PhCN are mixed prior to addition of picoline **1** (eq 1): *None of the original reagents are present in the vessel*. Yet, somehow **5** and **6** are readily converted to azaindole **2**. The simplest explanation is that **5** and **6** form reversibly. The conversion of 1,4-adduct **5** to 1,2-adduct **10** certainly hints at reversible addition (although **10** could, in principle, arise from an accelerated 1,3-sigmatropic rearrangement.)[42] Crossover studies show that **5** does indeed form reversibly at −40 °C—conditions of the Chichibabin cyclization.

Ascertaining how amidinolithium **6** reenters the reaction coordinate proved challenging. Crossover studies showed that the *i*-Pr_2N moiety of **6** exchanges with free LDA. However, the conclusion that **6** extrudes free PhCN is assailable. The conditions that elicit exchange of LDA with amidinolithium **6** are relatively forcing and the extent of crossover limited. Moreover, the LDA exchange could, at least in principle, proceed by a nucleophilic addition rather than by dissociation of PhCN. We considered the possibility that **6** acts as a nucleophile toward 2-fluoropyridino moieties (eq 8) or even as an electrophile but found no support.

Consequences of Picoline Dimerization. Optimized yields for metalation and functionalization of the nitrogen-based heterocycles can be highly substrate and electrophile dependent.[5] In the case of the Chichibabin cyclization in Scheme 1, self-condensation of picoline **1** to form **5** ties up 50% of the starting picoline in the form of a lithiated dihydropyridino moiety, which also leaves residual LDA free to form adduct **6**. Fortunately, neither of these chemical cul de sacs proves fatal. We got lucky. If one had used a different electrophile, however, the formation of **5** might not be benign. As a simple example, using H_3O^+ (or D_3O^+) as an electrophile affords dihydropyridine **7**. If the goal had been to deuterate the benzylic position of **1**, formation of **5** represents a total failure.[43] The dichotomous behavior of PhCN and D_2O may be important to those interested in metalating picolines, pyridines, and related nitrogen-based heteroaromatics.[5] One wonders, for example, how many reactions relying on ortho or benzylic metalations of aromatic heterocycles provide poor yields or completely fail because of self-condensations. There are reports of 1,2- and 1,4-adducts as byproducts in metalations[44−51] such as in pyridines (eq 11)[48,49] and pyrimidines (eq 12).[51] We do not know how many dimer-derived byproducts are buried in the enormous literature of heterocycles beyond our gaze. There may be many unpublished examples in pharmaceutical research laboratories and many more that have simply gone undetected.



(11)



(12)

We do not fully understand the consequences of dimerization. The self-condensation of 3-picoline (**21**, Scheme 5) is a particularly disturbing case in point. Wakefield[3] and others[52] obtained excellent results metalating and functionalizing **21**. It seems unlikely that they suspected the intermediacy of 1,4-adduct **22**. We believe that some attempts to functionalize **21**—there may very well be many unreported—have been frustrated by either the failure of electrophiles to react with **22** or by the incompatibility of the electrophiles with excess base lurking in solution.[53] One group attributes such a failure to the high pK_a of **21**[54] whereas another group reports the pK_a of **21** without realizing that **21** had dimerized.[55] Are picoline dimers **5** and **22** as well as other putative dimers such as **26** and **27**

(42) (a) Zoeckler, M. T.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 7661. (b) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877.

(43) By contrast, the relatively weak acid hexamethyldisilazane converts dimer **5** to picoline **1**.

(44) (a) Knauss, E.; Ondrus, T.; Giam, C. *J. Heterocycl. Chem.* **1976**, *13*, 789. (b) Thomas, E. W. *J. Org. Chem.* **1986**, *51*, 2184. (c) Giam, C. A.; Stout, J. L. *J. Chem. Soc., Dalton Trans.* **1970**, 478. (d) Ludt, R. E.; Crowther, G. P.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 1288. (e) Francis, R. F.; Crews, C. D.; Scott, B. S. *J. Org. Chem.* **1978**, *43*, 3227. (f) Marsais, F.; Granger, P.; Quéguiner, G. *J. Org. Chem.* **1981**, *46*, 4494. (g) Gronowitz, S.; Roe, J. *Acta Chem. Scand.* **1965**, *19*, 1741. (h) Marsais, F.; Le Nard, G.; Quéguiner, G. *Synthesis* **1982**, 235. (i) Also see ref 9.

(45) (a) Abramovitch, R. A.; Poulton, G. A. *J. Chem. Soc. B* **1969**, 901. (b) Abramovitch, R. A.; Giam, C.-S.; Poulton, G. A. *J. Chem. Soc. C* **1970**, 128. (c) Abramovitch, R. A.; Giam, C.-S. *Can. J. Chem.* **1964**, *42*, 1627. (d) Abramovitch, R. A.; Giam, C.-S. *Can. J. Chem.* **1963**, *41*, 3127. (e) Clegg, W.; Dunbar, L.; Horsburgh, L; Mulvey, R. E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 753.

(46) (a) Abarca, B.; Hayles, D. J.; Jones, G.; Sliskovic, D. R. *J. Chem. Res., Synop.* **1983**, 181. (b) Postigo, A.; Rossi, R. A. *Org. Lett.* **2001**, *3*, 1197. (c) Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett.* **2004**, *6*, 609. (d) Overberger, C. G.; Heron, L. P. *J. Org. Chem.* **1962**, *27*, 2423. (e) Giam, C. S.; Knaus, E. E. *Tetrahedron Lett.* **1971**, 4961. (f) Gros, P.; Fort, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3515. (g) Zhang, L.; Tan, Z. *Tetrahedron Lett.* **2000**, *41*, 3025. (h) Kauffmann, T *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 1, and references cited therein.

(47) Mixed condensation of heteroaryllithiums with heteroarenes: (a) Gros, P.; Fort, Y *J. Chem. Soc., Perkin Trans. 1* **1998**, 3515. (b) Kauffmann, T *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 1, and references cited therein.

(48) (a) Gros, P.; Fort, Y.; Caubere, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3597. (b) Gros, P.; Fort, Y.; Caubere, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3071. (c) Gros, P.; Fort, Y. *J. Org. Chem.* **2003**, *68*, 2028. (d) Kaufmann, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 1. (e) Martens, R. J.; Den Hertzog, H. J.; van Ammers, M. *Tetrahedron Lett.* **1964**, 3207. (f) Marais, R. J.; Breant, P.; Ginguene, A.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *216*, 139. (g) Newkome, G. R.; Hager, D. C. *J. Org. Chem.* **1982**, *47*, 599. (h) Clarke, A. J.; McNamara, S.; Meth-Cohn, O. *Tetrahedron Lett.* **1974**, 2373. (i) Wiessenfels, M.; Ulrici, B. *Z. Chem.* **1978**, *18*, 382. (j) Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 3793.

(49) An alternative radical mechanism for the dimerization of pyridine has been proposed (ref 48g).

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(51) (a) Kaufmann, T.; Greving, B.; König, J.; Mitschker, A.; Wotermann, A. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 713. (b) Seggio, A.; Chevalier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602.

(52) Alkylations of 3-picoline proceed in high yield. See, for example: (a) Gedig, T.; Dettner, K.; Seifert, K. *Tetrahedron* **2007**, *63*, 2670. (b) Baldwin, J. E.; Melman, A.; Lee, V.; Firkin, C. R.; Whitehead, R. C. *J. Am. Chem. Soc.* **1998**, *120*, 8559. (c) Romeril, S. P.; Lee, V.; Baldwin, J. E.; Claridge, T. D. W. *Tetrahedron* **2005**, *61*, 1127. (d) Perez-Balado, C.; Nebbioso, A.; Rodriguez-Grana, P.; Minichiello, A.; Miceli, M.; Altucci, L.; de Lera, A. R. *J. Med. Chem.* **2007**, *50*, 2497. (e) Davies-Coleman, M. T.; Faulkner, J. D.; Dubowchik, G. M.; Roth, G. P.; Polson, C.; Fairchild, C. *J. Org. Chem.* **1993**, *58*, 5925.

(53) (a) Kaiser, E. M.; Petty, J. D. *Synthesis* **1975**, 705. (b) Salas, M.; Joule, J. A. *J. Chem. Res., Synop.* **1990**, 98. (c) Raynolds, S.; Levine, R. *J. Am. Chem. Soc.* **1960**, *82*, 472.

(54) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232.

(55) Mamane, V.; Aubert, E.; Fort, Y. *J. Org. Chem.* **2007**, *72*, 7294.

problematic side products, or are they key intermediates en route to desired functionalizations?[49,56]

Conclusions

Nearly half of the top 20 largest selling pharmaceutical agents contain a pyridine or pyridine-like ring.[57] One of us (D.B.C.) once spent an entire day at a major pharmaceutical company discussing exclusively a number of problematic pyridine metalations. There is little doubt that the metalations and subsequent functionalizations of pyridines present important and confounding challenges.

Despite self-condensation of **1** to form **5** and consequent condensation of leftover LDA with PhCN to form amidinolithium **6**, the Chichibabin cyclization in eq 1 works remarkably well. A colleague astutely noted that **5** is, in essence, a protected benzyllithium, in which half of the starting picoline **1** is consumed as the protecting group. Thus, although one might view base-mediated self-condensations of heteroaromatics as annoying side reactions to be avoided, maybe they should be embraced and exploited.

Experimental Section

Reagents and Solvents. THF, hexane, and pentane were distilled from blue or purple solutions containing sodium benzophenone ketyl. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. LDA, [^{6}Li]LDA, and [^{6}Li,^{15}N]LDA[35] were purified as crystalline solids using recrystallized *n*-BuLi.[58] Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques. Solutions of *n*-BuLi and LDA were titrated using a literature method.[59]

NMR Spectroscopic Analyses. Samples for monitoring reactions using NMR spectroscopy were prepared by layering stock solutions at −196 °C, sealed under partial vacuum, and warmed to −78 °C. The samples were vigorously shaken in a −78 °C bath for about 30 s and then transferred to the NMR probe for acquisition of spectra. Standard ^{6}Li, ^{13}C,^{15}N, and ^{19}F NMR spectra were recorded on a 500 MHz spectrometer at 76.73, 125.79, 50.66, and 470.35 MHz (respectively). The ^{6}Li, ^{13}C, ^{15}N, and ^{19}F resonances are referenced to 0.30 M [^{6}Li]LiCl/MeOH at −90 °C (δ 0.0 ppm), the CH$_2$O resonance of THF at −90 °C (δ 67.57 ppm), neat Me$_2$NEt at −90 °C (δ 25.7 ppm), and C$_6$F$_6$ in neat THF at −90 °C (δ −162.5 ppm), respectively.

In Situ Preparation of Dimer 5. A 1.6 M solution of *n*-butyllithium (1.33 mL, 2.1 mmol) in hexanes was added via syringe to dry THF (20.0 mL) at −40 °C under Ar atmosphere. Dry diisopropylamine (310 μL, 224 mg, 2.1 mmol) was added to the solution via syringe. After the solution was stirred for 5 min at −40 °C, 3-methyl-2-fluoropyridine **1** (200 μL, 220 mg, 2.0 mmol) was added to the LDA solution. The solution became a bright red as *N*-lithiodihydropyridine **5** forms over the course of 1.0 h. Carrying out an analogous procedure in an NMR tube using THF-d_8 affords the following spectroscopic data: ^{1}H NMR (THF-d_8, −78 °C) δ 1.60 (d, $J_{H,F}$=1.4 Hz, 3H), 2.43 (dd, $J_{H,H}$=12.4, 7.2 Hz, 1H), 2.77 (dd, $J_{H,H}$=12.4, 3.5 Hz, 1H), 3.50 (ddd, $J_{H,F}$ = 3.7, $J_{H,H}$ = 6.7, 3.9 Hz, 1H), 3.69 (dddd, $J_{H,F}$ = 6.8, $J_{H,H}$ = 7.2, 3.4, 3.4 Hz, 1H), 5.84 (dd, $J_{H,F}$ = 2.0, $J_{H,H}$ = 6.7 Hz, 1H), 7.15 (dddd, $J_{H,F}$ = 2.1, $J_{H,H}$ = 7.0, 4.7, 0.4 Hz, 1H), 7.63 (ddd, $J_{H,F}$ = 9.5, $J_{H,H}$ = 7.0, 2.1 Hz, 1H), 7.96 (ddm, $J_{H,H}$ = 4.7, 2.1 Hz, 1H); ^{13}C NMR (THF-d_8, −78 °C) δ 20.1 (d, $J_{C,F}$ = 22.3 Hz), 47.0 (d, $J_{C,F}$ = 6.6 Hz), 69.7 (d, $J_{C,F}$ = 29.0 Hz), 80.1 (d, $J_{C,F}$ = 7.0 Hz), 91.4, 121.6, 123.4 (d, $J_{C,F}$ = 31.7 Hz), 139.3 (d, $J_{C,F}$ = 21.8 Hz), 143.4 (d, $J_{C,F}$ = 6.6 Hz), 144.7 (d, $J_{C,F}$ = 15.0 Hz), 163.0 (d, $J_{C,F}$ = 215.0 Hz), 163.3 (d, $J_{C,F}$ = 235.0 Hz); ^{19}F NMR (THF-d_8, −78 °C) δ −93.5, −70.5; ^{6}Li NMR (THF-d_8, −78 °C) δ −0.01, 0.76.

Synthesis of Dihydropyridine 7. A solution of *N*-lithiodihydropyridine **5** (0.05 M) at −40 °C prepared in THF-d_8 as described above was quenched by THF-d_8−H$_2$O at −78 °C to afford dihydropyridine **7**. The N−H proton is not observable at 0 °C; spectra were recorded on **7** in situ at −70 °C: ^{1}H NMR (THF-d_8) δ ^{1}H NMR (THF-d_8) 1.61 (d, J = 2.3 Hz, 3H), 2.54 (m, 1H), 2.87 (m, 1H), 3.30 (m, 1H), 4.06 (dd, J = 8.0, 2.3 Hz, 1H), 5.87 (dt, J = 8.0, 2.0 Hz, 1H), 7.21 (tt, J = 7.0, 1.7 Hz, 1H), 7.40 (br, 1H), 7.67 (dt, J = 7.0, 2.0 Hz, 1H), 8.03 (m, 1H); ^{13}C NMR (THF-d_8) δ 11.5, 35.2, 41.5 (dd, J = 4.0, 1.9 Hz), 80.7, 98.3, 121.8, 122.0, 126.2, 142.8, 145.3, 149.6, 162.8.

Synthesis of Azaindole 2. To a solution of *N*-lithiodihydropyridine **5** (0.05 M) at −40 °C prepared as described above was added benzonitrile (250 μL, 253 mg, 2.45 mmol). After the solution was stirred at −40 °C for 2 h, the vessel was warmed to 0 °C for 30 min and the reaction was quenched with wet THF. The solvent was evaporated under reduced pressure. The resulting yellow solid was redissolved in EtOAc (15 mL), and the organic layer was washed with aqueous NaHCO$_3$ (3 × 10 mL) and aqueous NaCl (3 × 10 mL). The organic layer was dried with Na$_2$SO$_4$, filtered, and evaporated to dryness. The bright yellow solid was recrystallized from 1:4 ethyl acetate/hexane or, alternatively, flash chromatographed eluting with 2:1 ethyl acetate/hexanes. Known[3] compound **2** (310 mg, 1.60 mmol) was isolated as an off-white solid in 80% yield: ^{1}H NMR (DMSO-d_6) δ 6.90 (s, 1H), 7.05 (dd, J = 7.8, 4.7 Hz, 1H), 7.33 (tt, J = 7.3, 1.2 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.91 (dd, J = 7.9, 1.5 Hz, 1H), 7.96 (dd, J = 7.8, 1.2 Hz, 2H), 8.24 (dd, J = 1.6, 4.7 Hz, 1H), 12.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 97.1, 116.0, 121.0, 125.4, 127.8, 128.0, 128.9, 131.7, 138.3, 142.9, 149.8; HRMS [C$_{13}$H$_{10}$N$_2$] requires m/z 194.0844, found 194.0839.

Synthesis of Azaindole 2: Inverse Addition. A 1.6 M solution of *n*-butyllithium (2.66 mL, 4.2 mmol) in hexanes was added via syringe to dry THF (20.0 mL) at −40 °C under Ar atmosphere. Dry diisopropylamine (620 μL, 448 mg, 4.2 mmol) was added to the solution via syringe. After the solution was stirred for 5 min at −40 °C, benzonitrile (215 μL, 217 mg, 2.1 mmol) was added. After being stirred at −40 °C for 2 h, and fluoropicoline **1** (200 μL, 220 mg, 2.0 mmol) was added and stirring was continued for an additional 2 h. Workup and purification as described above afforded **2** (320 mg, 1.65 mmol) as an off-white solid in 82% yield.

Synthesis of 8a and 8b. A solution of *N*-lithiodihydropyridine **5** (0.05 M) at −40 °C prepared as described above was cooled to −78 °C and quenched with THF/water (40:1, 10.3 mL) dropwise via syringe. After the solution was warmed to rt, the solvent was evaporated in vacuo. The resulting residue was redissolved in EtOAc (15 mL), and the organic layer was washed with aqueous NaHCO$_3$ (3 × 10 mL) and aqueous NaCl (3 × 10 mL). The organic extract was dried with Na$_2$SO$_4$, filtered, and evaporated to dryness. Flash chromatography (2:1 ethyl acetate/hexanes) afforded lactams **8a**,**b** as a colorless liquid (196 mg, 0.89 mmol) in 89% yield. HPLC separation (degassed 5:1 pentane/diethyl ether) afforded analytically pure **8a** and **8b** for spectroscopic analysis. **8a**: ^{1}H NMR (acetone-d_6) δ 1.20 (d, J = 7.2 Hz, 3H), 2.49 (dd, J = 13.0, 10.4 Hz, 1H), 2.63 (d, J = 6.7 Hz, 1H), 2.75−2.81 (d, J = 5.1 Hz, 1H), 2.82−2.86 (m, 1H), 2.86 (br s, 1H), 4.80 (dd, J = 8.0, 4.9 Hz, 1H), 6.18 (dd, J = 7.7, 4.4 Hz, 1H), 7.25 (tdd, J = 6.1, 2.1, 1.8 Hz, 1H), 7.77−7.84 (m, J = 8.8, 2.4, 1.7, 1H), 8.05−8.09 (m, J = 5.2, 1H); ^{13}C NMR (acetone-d_6) δ 11.5, 28.9 (J = 3.1); 37.5 (J = 1.1), 40.1, 107.5, 122.6 (J = 4.3), 122.8 (J = 31.1), 126.6, 143 (J = 5.6 Hz), 146.33 (J = 15.4 Hz), 163 (J = 235.4 Hz), 173.27; ^{19}F NMR (acetone-d_6) δ −74.5 (d, J = 9.4); HRMS [C$_{12}$H$_{13}$N$_2$OF] requires m/z 220.1012,

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found 220.1003; IR (film, cm^{-1}) 1698, 1661, 1605, 1578, 1438. **8b**: ^1H NMR (acetone-d_6) δ 1.19 (d, $J = 7.2$ Hz, 3H), 2.30 (d, $J = 7.0$ Hz, 1H), 2.45−2.52 (m, 1H), 2.64−2.71 (m, 1H), 2.76−2.82 (m, 1H), 2.84 (br s, 1H), 4.84 (dd, $J = 7.8$, 4.8 Hz, 1H), 6.18 (dd, $J = 7.7$, 4.4 Hz, 1H), 7.25 (tdd, $J = 6.1$, 2.1, 1.8 Hz, 1H), 7.77−7.84 (m, 1H), 8.05−8.09 (d, $J = 5.2$ Hz, 1H); ^{13}C NMR (acetone-d_6) δ 11.5, 28.7 ($J = 3.1$), 37.5 ($J = 1.1$ Hz), 40.1, 107.4, 122.6 ($J = 4.3$ Hz), 122.8 ($J = 31.1$ Hz), 126.5, 142.9 ($J = 5.6$ Hz), 146.33 ($J = 15.4$ Hz), 162.97 ($J = 235.4$ Hz), 173.3; ^{19}F NMR (acetone-d_6) δ −73.9 (d, $J = 9.1$ Hz); IR (film, cm^{-1}) 1698, 1661, 1605, 1578, 1438; HRMS [$C_{12}H_{13}N_2OF$] requires *m/z* 220.1012, found 220.1028.

Synthesis of 9. A solution of *N*-lithiodihydropyridine **5** (0.05 M) at −40 °C prepared as described above was cooled to −78 °C and purged with gaseous O_2. After the solution was stirred at −78 °C for 4 h, the reaction was quenched with a THF/water mixture (40:1, 10.3 mL). Water (250 μL, 250 mg) in THF (10 mL) was added to the reaction mixture dropwise via syringe. After the solution was warmed to rt, the solvent was evaporated in vacuo. The resulting residue was redissolved in EtOAc (15 mL), and the organic layer was washed with aqueous $NaHCO_3$ (3 × 10 mL) and aqueous NaCl (3 × 10 mL). The organic extract was dried with Na_2SO_4, filtered, and evaporated to dryness. Flash chromatography (2:1 ethyl acetate/hexanes) afforded **9** as a white solid (90 mg, 0.41 mmol) in 41% yield: mp 78.5−80.5 °C; ^1H NMR (acetone-d_6) δ 2.24 (s, 3H), 4.14 (s, 2H), 7.01 (d, $J = 5.1$ Hz, 1H), 7.29 (dtt, $J = 5.5$, 2.0, 1.8 Hz, 1H), 7.71 (dtt, $J = 9.8$, 2.0, 1.2 Hz, 1H), 7.97 (d, $J = 5.1$ Hz, 1H), 8.14 (d, $J = 5.5$ Hz, 1H); ^{13}C NMR (acetone-d_6) δ 10.04, 31.20 (dd, $J = 4.0$, 1.9 Hz), 118.4 (d, $J = 32.8$ Hz), 120.7 (d, $J = 32.6$ Hz), 122.7 (d, $J = 4.2$ Hz), 123.5 (d, $J = 4.2$ Hz), 141.8 (d, $J = 5.6$ Hz), 144.6 (d, $J = 15.9$ Hz), 146.3 (d, $J = 15.3$ Hz), 151.5 (d, $J = 5.0$ Hz), 161.4 (d, $J = 96.4$ Hz), 162.7 (d, $J = 101.8$ Hz); ^{19}F NMR (acetone-d_6) δ −69.59 (J=9.1), −71.59; HRMS [$C_{12}H_{10}N_2F_2$] requires *m/z* 220.0812, found 220.0819. An X-ray crystal structure of **9** is reported in the Supporting Information.

Synthesis of 10. A solution of *N*-lithiodihydropyridine **5** (0.05 M) at −40 °C prepared as described above was warmed to 0 °C in a water/ice bath. Stirring was continued for 15 min. The reaction was quenched with a THF/water mixture (40:1, 10.3 mL). After the solution was warmed to rt, the solvent was evaporated in vacuo. The resulting residue was redissolved in EtOAc (15 mL), and the organic layer was washed with aqueous $NaHCO_3$ (3 × 10 mL) and aqueous NaCl (3 × 10 mL). The organic extract was dried with Na_2SO_4, filtered, and evaporated to dryness. Flash chromatography (2:1 ethyl acetate/hexanes) afforded 1,2-adduct **10** as a colorless liquid (178 mg, 0.88 mmol) in 88% yield: ^1H NMR (acetone-d_6) δ 2.34 (s, 3H), 4.16 (s, 2H), 7.14 (dd, $J = 7.6$, 4.9 Hz, 1H), 7.22 (dtt, $J = 6.1$, 2.0, 0.9 Hz 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.66 (dtt, $J = 8.6$, 2.4, 1.8 Hz, 1H), 8.05−8.09 (m, 1H), 8.28 (dd, $J = 4.91$, 1.2 Hz, 1H); ^{13}C NMR (acetone-d_6) δ18.7 (d, $J = 1.9$ Hz), 34.8 (d, $J = 1.9$ Hz), 122.3, 122.7 (d, $J = 3.2$ Hz), 122.8 (d, $J = 3.8$ Hz), 132.3, 138.5, 142.6 (d, $J = 5.8$ Hz), 146.2 (d, $J = 15.6$ Hz), 147.6 (d, $J = 1.5$ Hz) 157.6, 162.9 (d, $J = 236.2$ Hz); ^{19}F NMR (acetone-d_6) δ −70.2 (d, $J = 8.6$); HRMS [$C_{12}H_{11}N_2F$] requires *m/z* 202.0906, found 202.0906.

Synthesis of Trimer 15. A 1.6 M solution of *n*-butyllithium (1.25 mL, 2.0 mmol) in hexanes was added via syringe to dry THF (10.0 mL) at −40 °C under Ar atmosphere. Dry diisopropylamine (280 μL, 202 mg, 2.0 mmol) was added to the solution via syringe. After the solution was stirred for 5 min at −40 °C, PhCN (408 μL, 512 mg, 4.0 mmol) was added to the LDA solution. The solution became bright yellow as amidinolithium **6** formed over the course of 15 min. After the solution was stirred for 4 h, quenched with a THF/water mixture (40:1, 10.3 mL) dropwise via syringe, and warmed to rt, the solvent was evaporated in vacuo. The resulting residue was redissolved in copious amounts of EtOAc (100 mL) due to limited solubility, and the organic layer was washed with aqueous $NaHCO_3$ (3 × 10 mL) and aqueous NaCl (3 × 10 mL). The organic extract was dried with Na_2SO_4, filtered, and evaporated to dryness. The off-white solid was recrystallized from neat ethyl acetate. Known[31] trimer **15** (340 mg, 1.10 mmol) was isolated as a white solid in 83% yield: ^1H NMR (DMSO-d_6) δ 8.74−8.78 (6H, m).

Preparation of Lithiated Picoline Dimer 22. A solution of 3-picoline (**21**, 1.50 mL, 1.44 g, 15.5 mmol) in 3.0 mL THF was added via syringe to LDA (800 mg, 7.5 mmol) in THF (5.0 mL) and hexanes (60 mL) at −78 °C under Ar. Warming to 0 °C and stirring for 1.0 h resulted in a bright yellow precipitate. The suspension was cooled by dry ice/acetone for 1 h, and the solvent was removed via syringe. The yellow solid was washed with THF/hexanes (1:10) and evacuated for 3 h to afford a yellow solid (yield 87%). The resulting stable, bright yellow solid was too insoluble for spectroscopic analysis but was characterized by quenching to form **23** as described below.

Preparation of Picoline Dimer 23. An NMR tube charged with lithiated 3-dimer **22** as a yellow solid (9.6 mg, 0.05 mmol), cooled to −78 °C, and treated with THF-d_8/H_2O (40:1) via syringe. The yellow solid became a colorless solution containing dihydropyridine **23** in greater than 90% spectroscopic purity: ^1H NMR (THF-d_8) δ 1.59 (s), 2.54 (ddm, $J = 13.1$, 7.4 Hz, 1H), 2.74 (ddm, $J = 13.1$, 4.2 Hz, 1H), 3.19 (m, 1H), 3.97 (ddd, $J = 7.7$, 4.2, 1.5 Hz, 1H), 5.76 (ddd, $J = 4.7$, 1.5, 1.4 Hz, 1H), 5.90 (ddd, $J = 7.7$, 4.7, 1.2 Hz, 1H), 6.18 (br s 1H), 7.17 (ddd, $J = 7.7$, 4.8, 0.9 Hz, 1H), 7.49 (m, 1H), 8.32 (m, 2H); ^{13}C NMR (THF-d_8) δ 18.5, 39.7, 40.8, 96.3, 123.2, 123.8, 127.5, 35.4, 137.5, 146.9, 150.5.

1,4-Adduct 5: Crossover Studies. A solution of LDA (0.275 M, 100 L, 0.030 mmol) in neat THF was added to one side of a double-well vessel (Figure 1) under inert Ar atmosphere at −40 °C. A solution of **1**-d_3 (0.250 M, 100 μL, 0.025 mmol) in THF was injected into the reaction vessel and allowed to stir at −40 °C for 24 h. To the other well of the vessel was added an aliquot of LDA solution (0.275 M, 100 μL, 0.030 mmol) followed by a solution of **1**-d_0 (0.250 M, 100 μL, 0.025 mmol) in THF. After 1.5 h, the reaction vessel was tilted in the bath to fully mix both wells. The reaction was allowed to stir for the desired amount of time and quenched with a THF/water mixture (40:1, 500 μL). The contents of the vessel were transferred to a 1.5 mL GC vial and analyzed via GC/MS.

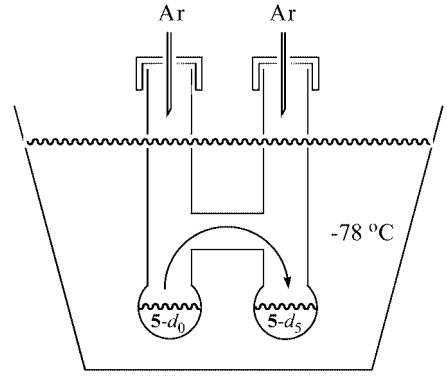

FIGURE 1. Vessel used for double-crossover experiment.

Amidinolithium 6: Crossover Studies. A solution of [^{6}Li,^{15}N]LDA (0.30 M, 400 μL, 0.12 mmol) in neat THF was added to an NMR tube at −78 °C under Ar atmosphere capped by two septa. To the NMR tube was added benzonitrile solution (1.56 M, 100 μL, 0.16 mmol) in THF. The reaction was allowed to stand at −78 °C for 1 h. Once conversion to **6** was complete as indicated by ^{6}Li NMR, a solution of [^{6}Li]LDA (1.20 M, 100 μL, 0.12 mmol) was added and warmed to −40 °C. Crossover was allowed to occur over the course of 12 h with periodic cooling to −90 °C to acquire spectra.

Kinetics of 3-Fluoropicoline Metalation. IR spectra were recorded using an in situ IR spectrometer fitted with a 30-bounce,

silicon-tipped probe. The spectra were acquired in 16 scans at a gain of 1 and a resolution of 8 cm^{-1}. A representative reaction was carried using the reaction of LDA and PhCN emblematically as follows: The IR probe was inserted through a nylon adapter and FETFE O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was capped by a septum for injections and an argon line. Pseudo-first-order conditions were established by maintaining low concentrations of **1** (0.005 M) at high, yet adjustable, concentrations of LDA (0.10−0.75 M) and THF (3.9−12.3 M)[60] with pentane as the cosolvent. It was most convenient to follow the formation of **5** (1667 cm^{-1}) by IR spectroscopy, which displays a first-order behavior to ≥5 half-lives.[30,61] No evidence of LDA-picoline complexation was noted. The resulting pseudo-first-order rate constants (k_{obsd}) are independent of picoline concentration (0.004 - 0.04 M), confirming the first-order substrate dependence. Re-establishing the IR baseline and monitoring a second injection reveals no significant change in the rate constant, showing that conversion-dependent autocatalysis or autoinhibition are unimportant under these conditions. Comparisons of **1** versus **1**-d_3 provided $k_H/k_D = 29 \pm 1$, confirming a rate-limiting proton transfer. Unusually large isotope effects have been observed for other lithiations.[62] Plots of k_{obsd} versus THF concentration and k_{obsd} versus LDA concentration (at 4.1 M THF affords the rate law described by eq 3. Data are included in the Supporting Information.

Kinetics of LDA−PhCN Condensation. Pseudo-first-order conditions were established by maintaining the concentration of PhCN low (0.01 M) and the concentrations of LDA (0.10−0.30 M) and THF (2.0−12.3 M)[60] high (yet adjustable) with pentane as the cosolvent. The loss of PhCN (1667 cm^{-1}) by IR spectroscopy displays a first-order behavior to ≥5 half-lives.[30,61] No evidence of LDA−PhCN complexation was noted. Plots of k_{obsd} versus LDA concentration (at 10.0 M THF) and k_{obsd} versus THF concentration (Supporting Information) afford the reaction orders indicated in eq 5.

Acknowledgment. We thank the National Science Foundation and Sanofi-Aventis for support.

Supporting Information Available: NMR spectra, X-ray crystallographic data, and rate data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801410S

(60) Precipitation occurs below 3.9 M THF.

(61) Following product formation ([P]) and fitting the data to $[P] = [P_\infty][1-\exp(k_{obsd}t)]$ affords the pseudo-first-order rate constant k_{obsd}. The quality of the fit, however, is not diagnostic of first-order behavior because this function also fits second-order data reasonably well. The problem stems from determining the concentration of P at $t = \infty([P_\infty])$ as an adjustable parameter. The first-order dependence was confirmed by (1) monitoring the the value of k_{obsd} at different initial concentrations of starting material and (2) monitoring the loss of picoline **1** (δ−70.2 ppm) by ^{19}F NMR spectroscopy and showing adequate fit to $[A] = [A_0]\exp(-k_{obsd}t)$.

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