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Access to Highly Substituted 7-Azaindoles from 2-Fluoropyridines via 7-Azaindoline Intermediates

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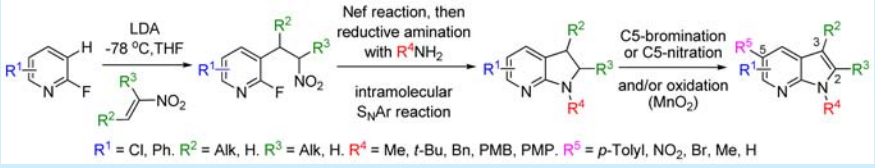
Supporting Information



ABSTRACT: A versatile synthesis of 7-azaindoles from substituted 2-fluoropyridines is described. C3-metalation and 1,4-addition to nitroolefins provide substituted 2-fluoro-3-(2-nitroethyl)pyridines. A facile oxidative Nef reaction/reductive amination/intramolecular S_NAr sequence furnishes 7-azaindolines. Finally, optional regioselective electrophilic C5-substitution (e.g., bromination or nitration) and subsequent in situ oxidation delivers highly functionalized 7-azaindoles in high overall efficiency.

The 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine) motif is common in pharmaceuticals and agrochemicals (Figure 1). While seldom observed in natural products,[1] this heterocyclic

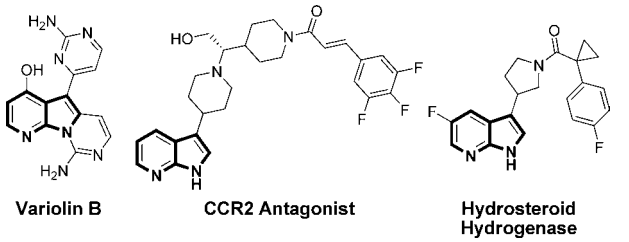
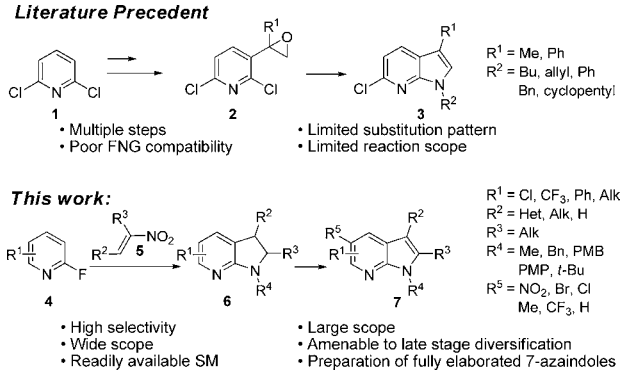


Figure 1. Examples of biologically active 7-azaindoles.

core provides attractive pharmacological, luminescent, physical, and spectroscopic properties.[2] Unlike indoles, efficient synthetic approaches to 7-azaindoles remain challenging, and great effort has been devoted to the synthesis of this motif over the past 20 years.[2a−e,j] Traditional strategies for indole synthesis (e.g., Reissert, Bartoli, or Fischer approaches) when applied to the 7-aza analogue often suffer from limited scope, reaction efficiency, and/or starting material availability.[2a,d,e] In addition, other methods for the synthesis of 7-azaindoles involve the formation of the pyrrole ring using metal-catalyzed cyclizations of 2-aminopyridines, which commonly deliver C2-substituted 7-azaindoles.[2a] In general, installation of a C3 substituent requires additional steps that encompass formylation, acylation, or sp^2−sp^2/sp^2−sp^3 coupling reactions of the corresponding C3-halogeno 7-azaindoles.[2a] Access to preinstalled C3-alkyl or -aryl 7-azaindoles, which are of importance to our medicinal chemistry program, lacks generality.[2a] We sought to develop a convergent method to access this scaffold.

In order to address this problem, we were initially inspired by the strategy of Schirok for the preparation of C3-substituted 7-azaindoles **3** from 2,6-dichloropyridine (**1**) (Scheme 1).[2h,3]

Scheme 1. Synthesis of 7-Azaindoles from 2-Halogenopyridines



Deprotonation of **1** by LDA and addition of acetone or acetophenone yielded tertiary alcohols, which after dehydration and epoxidation delivered 3-epoxy-2,6-dichloropyridines **2** in a two-step reaction sequence. Reaction with primary amines produced 6-chloro-7-azaindoles **3** in moderate to good yields. While delivering 1,3-substituted-6-chloro-7-azaindoles, this method suffers from key limitations: (1) reliance on **1**, limiting the substrate scope and control of the substitution pattern in the final product; (2) dependence on *m*-CPBA epoxidation; (3)

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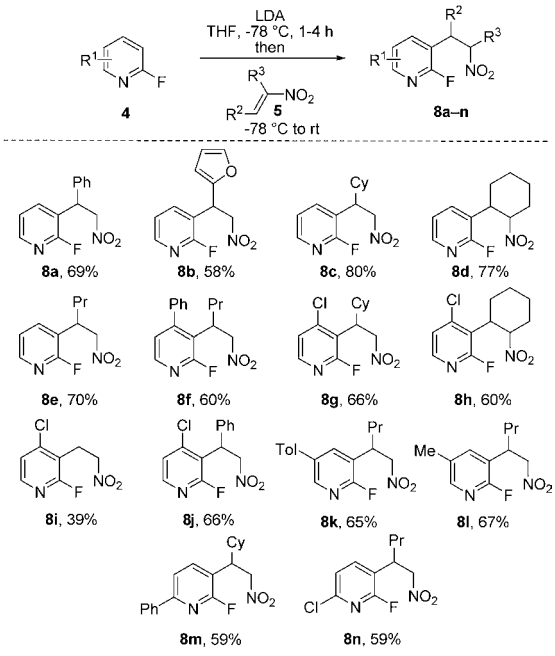
elevated reaction temperatures; and (4) highly acidic conditions, limiting the functional group tolerance. Despite these limitations, we thought that constructing 7-azaindoles from 2-halogenopyridines was an attractive entry to polysubstituted 7-azaindoles, which prompted us to develop a new strategy.

Our approach involves the conjugate addition of a 3-lithiated-2-fluoropyridine (e.g., **4**) to readily accessible nitroolefins **5** to produce azaindolines **6** via reduction and in situ cyclization of the intermediate nitro group. This has the potential to provide an array of highly diverse 7-azaindoles (Scheme 1). Our observations and results are described herein.

2-Fluoropyridines facilitate efficient C3-directed metalation and subsequent indoline formation via an intramolecular S_NAr reaction, theoretically proceeding at lower reaction temperatures than with 2-chloropyridines. Consequently, our synthesis begins with regioselective C3-deprotonation of 2-fluoropyridines **4** by LDA[3,4] at low temperature, followed by treatment with a variety of substituted nitroolefins. After considering various electrophiles, we elected β-substituted nitroolefins **5**[5] as Michael acceptors because these are amenable to efficient 1,4-addition reactions with organolithium species.[6] This process tolerated most substitutions on the 2-fluoropyridine ring (at C4, C5, and C6) and proceeded in good to excellent overall yields (58−80%) (Scheme 2). Only nitroethylene itself as a Michael acceptor gave a low yield (**8i**, 39% yield).[7]

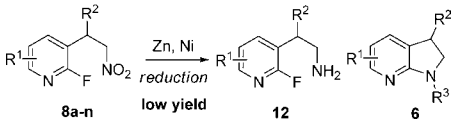
Scheme 2. 1,4-Addition Reaction of 3-Lithiated Fluoropyridines 4 to Nitroolefins 5



Tol = *p*-tolyl.

From the outset we planned for the reduction of the nitro group of 2-fluoro-3-nitroalkylpyridines **8a−n** to primary amine **12** and subsequent intramolecular cyclization to 7-azaindolines **6**. With Zn/AcOH or Raney Ni (Scheme 3), the reduction proceeded efficiently on the basis of analysis of the crude reaction mixture; however, our attempts to isolate amines **12** and/or azaindolines **6** gave poor yields and reproducibility. We rationalized that 7-azaindolines **6** sequester zinc and nickel

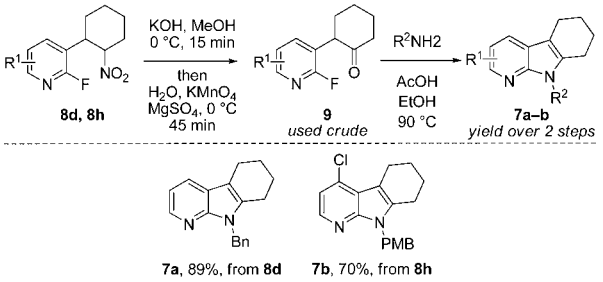
Scheme 3. Reduction of the Nitro Group



through a strong chelation effect. This turned our attention to what ultimately became a more versatile overall synthesis.

We focused our efforts on the conversion of the nitroalkyl intermediates to ketones or aldehydes using a Nef reaction protocol.[8] Ketones **9** were successfully obtained from the corresponding 2-fluoro-3-nitroalkylpyridines **8d** and **8h** (Scheme 4). Condensation of cyclohexyl ketones **9** with

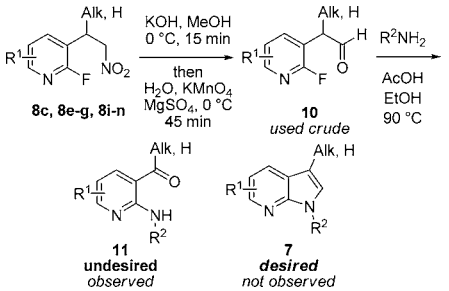
Scheme 4. Synthesis of Azaindoles 7a and 7b



benzylamine and *p*-methoxybenzylamine afforded 7-azaindoles **7a** and **7b** in 89% and 70% yield, respectively, by enamine formation and intramolecular S_NAr cyclization.

In keeping with our original strategy, aldehydes **10** were initially elusive. The Nef reactions with nitroalkyl intermediates (**8c**, **8e−g**, and **8i−n**) produced mixtures of recovered starting material, aldehyde, and the corresponding carboxylic acid. However, we were pleased to find that the addition of magnesium sulfate[9] resulted in clean formation of aldehydes **10** (85% to quantitative conversions), preventing overoxidation. $MgSO_4$ stabilizes the nitronate intermediate to afford consistent, clean, and scalable carbonyl formation. These aldehydes were successfully used crude in the next step (Scheme 5).

Scheme 5. Attempt to Synthesize 7-Azaindoles 7



Surprisingly, under the same reaction conditions used with ketones **9**, 7-azaindoles **7** were not obtained from aldehydes **10**. Instead, ketones **11** were produced (Scheme 5). This result has precedent in the synthesis of ketones via aldehyde decarbonylation.[10] This pathway presumably occurs from the inherent instability of aldehydes **10** at elevated temperatures and the concomitant decarbonylation reaction by oxygen.[11] During our investigation, we also determined the Nef reaction to be incompatible with compounds bearing an aryl or heteroaryl

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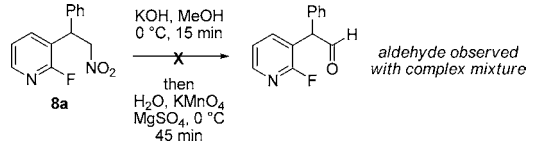
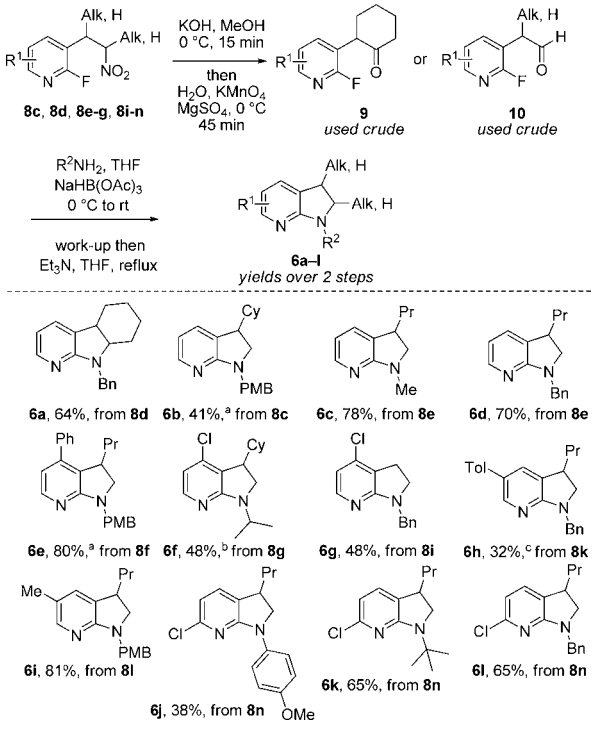
substituent at the position β to the nitro group (Scheme 6) from what we believe is a result of their highly acidic enolizable nature, consistent with our observations.

Scheme 6. Nef Reaction Attempt Using Compound 8a



We modified our strategy and targeted 7-azaindoles by way of their corresponding 7-azaindolines. 7-Azaindolines **6** were generated from ketones **9** or aldehydes **10** by reductive amination and in situ intramolecular S_NAr ring formation. This modification affords additional flexibility by allowing the synthesis of substituted 7-azaindoles with late-stage derivatization at the 5-position (see the C5-electrophilic substitution in Scheme 8). In practice, both ketones **9** and aldehydes **10** perform well under the reductive amination/intramolecular S_NAr conditions, giving 7-azaindolines **6a–l** in moderate to excellent yields (38–81%; Scheme 7). The reaction sequence tolerates a variety of pyridine ring substituents (Me, Cl, Ph, Tol) and provides access to a broad range of N substituents exemplified by alkylamines, benzylamines, and sterically hindered (*t*-Bu) amines. Also, exclusive C2 (fluorine) versus C4 (chlorine) cyclization was observed for compounds **6f** and **6g**, whereas 2,4-dichloropyridines were reported to deliver mixtures.[3]

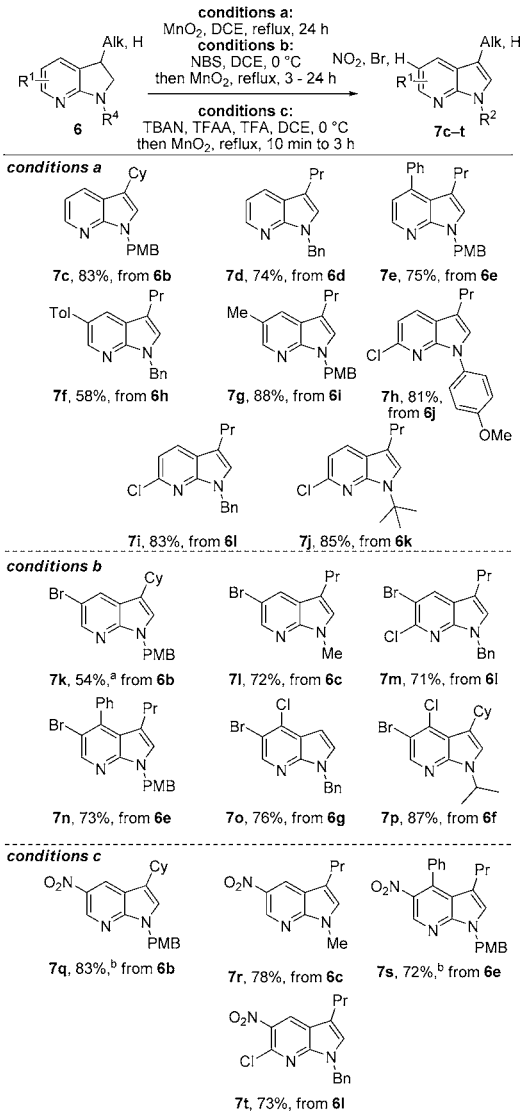
Scheme 7. Synthesis of Azaindolines 6a–l



[a]Compounds **6b** and **6e**: the intermediate was not worked up, and the crude mixture was used as-is in the intramolecular S_NAr cyclization step at 50 °C. [b]Compound **6f**: cyclization was observed during the reductive amination step and did not require reflux with Et_3N in THF. [c]Compound **6h**: cyclization was performed with Et_3N in toluene at reflux. Tol = *p*-tolyl.

Finally, azaindolines **6** were readily oxidized by manganese dioxide[12,13b,14] upon stirring for 3–24 h at reflux in dichloroethane to give azaindoles **7c–j** in excellent yields (Scheme 8, conditions a). A key feature of this methodology is the late-stage introduction of high structural diversity via 7-azaindolines **6**.[13] As such, to the best of our knowledge, we have developed a novel, facile, and efficient one-pot synthesis of 5-bromo- and 5-nitro-7-azaindoles **7** via C5 indoline bromination or nitration at low temperature prior to manganese dioxide oxidation (Scheme 8, conditions b and c). We observed that the oxidation rate was dependent on the substitution at C5 and ranged from minutes to 24 h. Substrates bearing electron-withdrawing substituents were oxidized rapidly (NO_2 > Br > H). 5-Bromoazaindoles **7k–p** and 5-nitroazaindoles **7q–t** were obtained in moderate to good yields (54–83%). It is important to note that selective nitration or bromination at C5 of 7-azaindoles **7** typically led to regioisomeric mixtures at C2, C5, and/or C6. This highlights the benefit of synthesizing 7-azaindoles **7** via 7-azaindolines **6**. Chloro- and/or

Scheme 8. Synthesis of Azaindoles 7c–t



[a]Compound **7k**: MnO_2-mediated oxidation was conducted over a 48 h period. [b]Compounds **7q** and **7s**: nitration was performed at −30 °C for 1 h. Tol = *p*-tolyl, TBAN = tetrabutylammonium nitrate.

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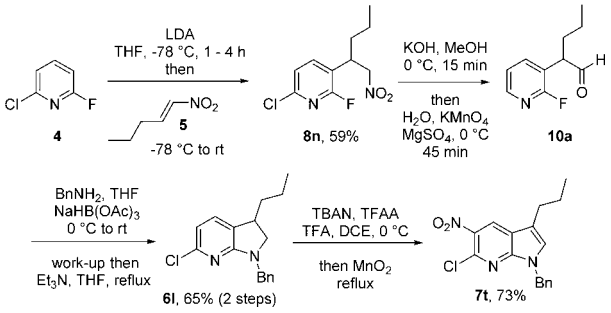
bromo-substituted compounds are valuable intermediates to give more advanced 7-azaindole structures using metal-catalyzed reactions (Suzuki, Stille, Heck, etc.).[3,12] The nitro group is also a key intermediate for further derivatization (acylation, sulfonylation, Sandmeyer reaction, etc.). Compounds with an aryl or heteroaryl group at C3 may be accessed from C3-unsubstituted azaindoles (e.g., **7o**) by a well-established halogenation/sp^2–sp^2 coupling sequence.[2a,d,e]

In summary, we have developed a convergent and efficient synthesis of 7-azaindoles. In this innovative sequence, a 1,4-addition reaction of 3-lithiated-2-fluoropyridines to nitroolefins provided 2-fluoro-3-nitroalkylpyridines. 7-Azaindolines were then obtained from an oxidative Nef reaction/reductive amination/intramolecular S_NAr sequence using a range of primary amines. This sequence allows for high diversification at C3, enabling the installation of sp^3 substituents that are challenging via other means. Finally, the use of 7-azaindolines allows for selective C5-bromination, C5-nitration, and/or oxidation, producing the desired 7-azaindoles. Scheme 9 shows

Scheme 9. Example of the Full Sequence from 2-Fluoro-6-chloropyridine Delivering 7-Azaindole 7t



an example of the overall sequence. Relative to other methods requiring numerous steps and elaborate starting materials, this methodology involves inexpensive and readily available starting materials and a tractable reaction sequence. It also avoids the use of metal-catalyzed coupling reactions and allows for facile access to 7-azaindoles with control over the introduction of substitution at every position of the targeted 7-azaindole core.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02098.

Procedures and characterization data (PDF)
^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Anderson, R. J.; Hill, J. B.; Morris, J. C. *J. Org. Chem.* **2005**, *70*, 6204–6212 and references therein.

(2) (a) Mérour, J.-Y.; Routier, S.; Suzenet, F.; Joseph, B. *Tetrahedron* **2013**, *69*, 4767–4834. (b) Zhihui, W.; Xiao, W. *Prog. Chem.* **2012**, *24*, 1974–1982. (c) Zhao, S.-B.; Wang, S. *Chem. Soc. Rev.* **2010**, *39*, 3124–3156. (d) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031–1064. (e) Popowycz, F.; Mérour, J.-Y.; Joseph, B. *Tetrahedron* **2007**, *63*, 8689–8707. (f) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120–1132. (g) Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274–302. (h) Schirok, H. *J. Org. Chem.* **2006**, *71*, 5538–5545. (i) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (j) Mérour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471–506.

(3) Schirok, H. *Synlett* **2005**, 1255–1258.

(4) (a) Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F. *Tetrahedron Lett.* **2004**, *45*, 7873–7877. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090. (c) Mongin, F.; Tognini, A.; Cottet, F.; Schlosser, M. *Tetrahedron Lett.* **1998**, *39*, 1749–1752. (d) Mallet, M.; Branger, G.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1990**, *382*, 319–332. (e) Güngör, T.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139–150.

(5) Nitroolefins **5** could be quickly accessed in two steps via a Henry reaction/dehydration sequence using nitromethane and the corresponding aldehydes R^2CHO (see the Supporting Information).

(6) (a) Delaunay, T.; Poisson, T.; Jubault, P.; Pannecoucke, X. *Eur. J. Org. Chem.* **2014**, 3341–3345. (b) Asami, M.; Taketoshi, A.; Miyoshi, K.; Hoshino, H.; Sakakibara, K. *Chem. Lett.* **2007**, *36*, 64–65. (c) Yamashita, M.; Yamada, K.-I.; Tomioka, K. *Tetrahedron* **2004**, *60*, 4237–4242. (d) Yasuhara, T.; Nishimura, K.; Osafune, E.; Muraoka, O.; Tomioka, K. *Chem. Pharm. Bull.* **2004**, *52*, 1109–1113. (e) Santos, R. P.; Lopes, R. S. C.; Lopes, C. C. *Synthesis* **2001**, 845–848. (f) Yao, C.-F.; Kao, K.-H.; Liu, J.-T.; Chu, C.-M.; Wang, Y.; Chen, W.-C.; Lin, Y.-M.; Lin, W.-W.; Yan, M.-C.; Liu, J.-Y.; Chuang, M.-C.; Shiue, J.-L. *Tetrahedron* **1998**, *54*, 791–822. (g) Ayerbe, M.; Morao, I.; Arrieta, A.; Linden, A.; Cossio, F. P. *Tetrahedron Lett.* **1996**, *37*, 3055–3058. (h) Galley, G.; Hübner, J.; Anklam, S.; Jones, P. G.; Pätzel, M. *Tetrahedron Lett.* **1996**, *37*, 6307–6310. (i) Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861–4872. (j) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261–283. (k) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 3897–3900. (l) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, *22*, 3223–3226. (m) Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1710–1722. (n) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785–2812.

(7) Crude ^{1}H NMR analysis showed clean conversion to the desired 2-fluoro-3-nitroalkylpyridines **8i**. However, a substantial loss of material was observed after column chromatography. This intermediate is apparently unstable under the purification conditions.

(8) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.

(9) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. *Org. Lett.* **2010**, *12*, 3618–3621.

(10) (a) Yang, G.-H.; Liu, M.; Li, N.; Wu, R.; Chen, X.; Pan, L.-L.; Gao, S.; Huang, X.; Wang, C.; Yu, C.-M. *Eur. J. Org. Chem.* **2015**, *2015*, 616–624. (b) Kundu, S.; Pfaff, F. F.; Miceli, E.; Zaharieva, I.; Herwig, C.; Yao, S.; Farquhar, E. R.; Kuhlmann, U.; Bill, E.; Hildebrandt, P.; Dau, H.; Driess, M.; Limberg, C.; Ray, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 5622–5626. (c) Iwama, T.; Ogawa, K.; Kataoka, T.; Muraoka, O.; Tanabe, G. *Tetrahedron* **1998**, *54*, 8941–8974. (d) Kataoka, T.; Iwama, T. *Tetrahedron Lett.* **1995**, *36*, 245–248. (e) Syper, L. *Tetrahedron* **1987**, *43*, 2853–2871.

(11) Doering, W. E.; Chanley, J. D. *J. Am. Chem. Soc.* **1946**, *68*, 586–588.

(12) Zheng, X.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 3777–3779.

(13) (a) Lu, J.; Cai, X.; Hecht, S. M. *Org. Lett.* **2010**, *12*, 5189–5191. (b) Pearson, S. E.; Nandan, S. *Synthesis* **2005**, 2503–2506. (c) Wijtmans, M.; Pratt, D. A.; Brinkhorst, J.; Serwa, R.; Valgimigli, L.; Pedulli, G. F.; Porter, N. A. *J. Org. Chem.* **2004**, *69*, 9215–9223. (d) Wijtmans, M.; Pratt, D. A.; Valgimigli, L.; DiLabio, G. A.; Pedulli, G. F.; Porter, N. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4370–4373. (e) Taylor, E. C.; Macor, J. E.; Pont, J. L. *Tetrahedron* **1987**, *43*, 5145–5158. (f) For a recent synthesis of azaindolines, see: Danneman, M.; Hong, K.; Johnston, J. N. *Org. Lett.* **2015**, *17*, 3806.

(14) Parcerisa, J.; Romero, M.; Pujol, M. D. *Tetrahedron* **2008**, *64*, 500–507.

DOI: 10.1021/acs.orglett.5b02098
Org. Lett. 2015, 17, 4292–4295