JOC*Article*

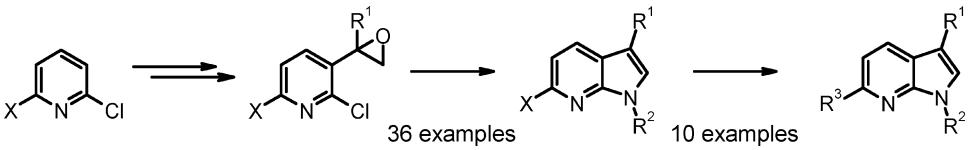
Microwave-Assisted Flexible Synthesis of 7-Azaindoles

Hartmut Schirok

Bayer HealthCare AG, Pharma Research, D-42096 Wuppertal, Germany

hartmut.schirok@bayerhealthcare.com

Received March 8, 2006



7-Azaindoles are versatile building blocks, especially in medicinal chemistry, where they serve as bioisosteres of indoles or purines. Herein, we are presenting a robust and flexible synthesis of 1,3- and 1,3,6-substituted 7-azaindoles starting from nicotinic acid derivatives or 2,6-dichloropyridine, respectively. Microwave heating dramatically accelerates the penultimate reaction step, an epoxide-opening-cyclization-dehydration sequence. The functional group compatibility of the reaction is examined as well as the application of the products in further functionalizations.

Introduction

In nature, 7-azaindoles (1*H*-pyrrolo[2,3-*b*]pyridines) appear only as submoieties in a very small number of alkaloids. To these rare examples belong neocryptolepine[1] (cryptotackieine[2]) from the extracts of the West African plant *Cryptolepis sanguinolenta*, the grossularines isolated from the tunicates *Dendrodoa grossularia*[3] and *Polycarpa aurata*,[4] and mescengricin from *Streptomyces griseoflavus*,[5] all containing an α-carboline skeleton, as well as the variolins from the antarctic sponge *Kirkpatrickia varialosa*.[6] Because of their biological activity,[7] these alkaloids were the objective of several synthetic studies.[8−10] In the field of material science, 7-azaindoles are known as efficient fluorescent chromophores in the UV/blue region. They are able to bind to metal ions, thus providing the potential to act as building blocks in supramolecular materials for organic electroluminescent devices.[11] However, the main interest in the synthesis of 7-azaindoles has arisen in numerous recent pharmacological programs in diverse therapeutic areas, wherein they serve as bioisosteres of indole or purine ring systems. The 7-azaindole scaffold was incorporated in antagonists of a variety of protein kinases,[12] in antihistamines[13] and -dopamines,[14] in analogues of melatonin,[15] staurosporin,[16] and rebeccamycin,[17] in antagonists of the corticotropin[18] and the gonadotropin[19] releasing hormone, and in PPAR agonists.[20]

(1) Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703−1706.

(2) Sharaf, M. H. M.; Schiff, P. L., Jr.; Tackie, A. N.; Phoebe, C. H., Jr.; Martin, G. E. *J. Heterocycl. Chem.* **1996**, *33*, 239−243.

(3) (a) Moquin, C.; Guyot, M. *Tetrahedron Lett.* **1984**, 5047−5048; structure revised in (b) Moquin-Pattey, C.; Guyot, M. *Tetrahedron* **1989**, *45*, 3445−3450.

(4) Abas, S. A.; Hossain, M. B.; van der Helm, D.; Schmitz, F. J.; Laney, M.; Cabuslay, R.; Schatzman, R. C. *J. Org. Chem.* **1996**, *61*, 2709−2712.

(5) Kim, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431−3434.

(6) (a) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987−3992. (b) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993−4000.

(7) On the cytotoxicity of neocryptolepine and cryptolepine and derivatives thereof, see: (a) Dassonneville, L.; Lansiaux, A.; Wattelet, A.; Wattez, N.; Mahieu, C.; Van Miert, S.; Pieters, L.; Bailly, C. *Eur. J. Pharm.* **2000**, *409*, 9−18. (b) Jonckers, T. H. M.; van Miert, S.; Cimanga, K.; Bailly, C.; Colson, P.; De Pauw-Gillet, M.-C.; van den Heuvel, H.; Claeys, M.; Lemière, F.; Esmans, E. L.; Rozenski, J.; Quirijnen, L.; Maes, L.; Dommisse, R.; Lemière, G. L. F.; Vlietinck, A.; Pieters, L. *J. Med. Chem.* **2002**, *45*, 3497−3508.

(8) Grossularines: (a) Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 2127−2130. (b) Molina, P.; Fresneda, P. M.; Sanz, M. A. *Tetrahedron Lett.* **1997**, *38*, 6909−6912. (c) Papamicaël, C.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Heterocycles* **1998**, *47*, 991−1004. (d) Molina, P.; Fresneda, P. M.; Sanz, M. A.; Foces-Foces, C.; Ramirez de Arellano, M. C. *Tetrahedron* **1998**, *54*, 9623−9638. (e) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem.* **2005**, *117*, 3344−3346; *Angew. Chem., Int. Ed.* **2005**, *44*, 3280−3282.

(9) Cryptotackieine: (a) Alajarín, M.; Molina, P.; Vidal, A. *J. Nat. Prod.* **1997**, *60*, 747−748. (b) Sundaram, G. S. M.; Venkatesh, C.; Syam Kumar, U. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2004**, *69*, 5760−5762. (c) Chen, Y.-L.; Hung, H.-M.; Lu, C.-M.; Li, K.-C.; Tzeng, C.-C. *Bioorg. Med. Chem.* **2004**, *12*, 6539−6546.

(10) Variolins: (a) Anderson, R. J.; Morris, J. C. *Tetrahedron Lett.* **2001**, *42*, 8697−8699. (b) Molina, P.; Fresneda, P. M.; Delgado, S. *J. Org. Chem.* **2003**, *68*, 489−499. (c) Ahaidar, A.; Fernández, D.; Danelón, G.; Cuevas, C.; Manzanares, I.; Albericio, F.; Joule, J. A.; Álvarez, M. *J. Org. Chem.* **2003**, *68*, 10020−10029. (d) Mendiola, J.; Baeza, A.; Alvarez-Builla, J.; Vaquero, J. J. *J. Org. Chem.* **2004**, *69*, 4974−4983. (e) Anderson, R. J.; Hill, J. B.; Morris, J. C. *J. Org. Chem.* **2005**, *70*, 6204−6212. (f) Karpov, A. S.; Merkul, E.; Rominger, F.; Müller, T. J. J. *Angew. Chem.* **2005**, *117*, 7112−7117; *Angew. Chem., Int. Ed.* **2005**, *42*, 6947−6951. (g) Fresneda, P. M.; Delgado, S.; Francesch, A.; Manzanares, I.; Cuevas, C.; Molina, P. *J. Med. Chem.* **2006**, *49*, 1217−1221.

10.1021/jo060512h CCC: $33.50
Published on Web 06/20/2006

During the past decade, several 7-azaindole syntheses were published, and they were reviewed by Mérour.[21] A recent and very successful strategy, which has been applied in a couple of variations, is based on the Pd-catalyzed Sonogashira coupling of 2-amino-3-halogenopyridines to install the C3−C3a bond (Figure 1, A), followed by an intramolecular cyclization to form the five-membered ring (B). The cyclization has been accomplished with strong bases,[22] iodine,[23] copper iodide,[24] or palladium catalysts.[25] The latter were also used in one-pot procedures together with the preceding C−C coupling (C).[26] A synthesis following a similar approach comprises the Pd-catalyzed annulation of 2-amino-3-iodopyridines with allyl acetate.[27] 7-Azaindoles were also obtained by carbolithiation of vinyl pyridines (D, R″ = CH_2R''').[28] Other new developments rely on the cyclization of (2-aminopyridin-3-yl)methylphosphonates (E),[29] the intramolecular Hegedus−Mori−Heck reaction of enamines[30] or enaminones (F),[31] the Hemetsberger−Knittel reaction (G),[32] or a Sommelet−Hauser type rearrangement of azasulfonium salts (H, R″ = SR‴).[33]

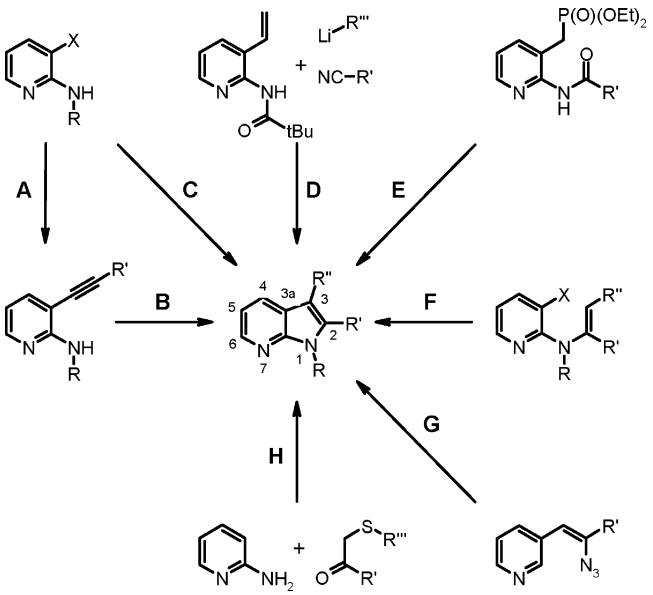
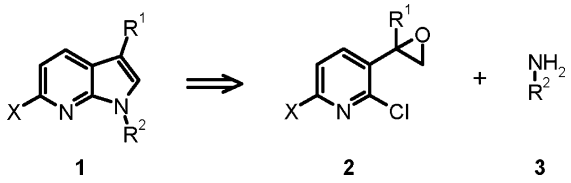


FIGURE 1. Recent strategies for azaindole syntheses.

SCHEME 1. Retrosynthesis



In the course of one of our own programs in medicinal chemistry, we required a robust synthesis of 1,3-disubstituted 7-azaindoles **1**, which would allow a general and rapid variation of the N1-substituent R^2 (Scheme 1). Former reports on an indole synthesis starting from 2-(2-halogenophenyl)oxiranes[34]

(11) See, for example: (a) Jia, W.-L.; Bai, D.-R.; McCormick, T.; Liu, Q.-D.; Motala, M.; Wang, R.-Y.; Seward, C.; Tao, Y.; Wang, S. *Chem. Eur. J.* **2004**, *10*, 994−1006. (b) Tani, K.; Sakurai, H.; Fujii, H.; Hirao, T. *J. Organomet. Chem.* **2004**, *689*, 1665−1674. (c) Jia, W.-L.; Wang, R.-Y.; Song, D.; Ball, S. J.; McLean, A. B.; Wang, S. *Chem. Eur. J.* **2005**, *11*, 832−842. (d) Zhao, S.-B.; Song. D.; Jia, W.-L.; Wang, S. *Organometallics* **2005**, *24*, 3290−3296.

(12) See the following examples. *p38 MAP kinase inhibitors*: (a) Henry, J. R.; Rupert, K. C.; Dodd, J. H.; Turchi, I. J.; Wadsworth, S. A.; Cavender, D. E.; Schafer, P. H.; Siekierka, J. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3335−3340. (b) Henry, J. R.; Rupert, K. C.; Dodd, J. H.; Turchi, I. J.; Wadsworth, S. A.; Cavender, D. E.; Fahmy, B.; Olini, G. C.; Davis, J. E.; Pellegrino-Gensey, J. L.; Schafer, P. H.; Siekierka, J. J. *J. Med. Chem.* **1998**, *41*, 4196−4198. (c) *Expert Opin. Ther. Pat.* **2005**, *15*, 227−232. *Rho Kinase inhibitors*: (d) Ishizaki, T.; Uehata, M.; Tamechika, I.; Keel, J.; Nonomura, K.; Maekawa, M.; Narumiya, S. *Mol. Pharm.* **2000**, *57*, 976−983. *GSK-3β inhibitors*: (e) Kuo, G.-H.; Prouty, C.; DeAngelis, A.; Shen, L.; O'Neill, D. J.; Shah, C.; Connolly, P. J.; Murray, W. V.; Conway, B. R.; Cheung, P.; Westover, L.; Xu, J. Z.; Look, R. A.; Demarest, K. T.; Emanuel, S.; Middleton, S. A.; Jolliffe, L.; Beavers, M. P.; Chen, X. *J. Med. Chem.* **2003**, *46*, 4021−4031. (f) Zhang, H.-C.; Ye, H.; Conway, B. R.; Derian, C. K.; Addo, M. F.; Kuo, G.-H.; Hecker, L. R.; Croll, D. R.; Li, J.; Westover, L.; Xu, J. Z.; Look, R.; Demarest, K. T.; Andrade-Gordon, P.; Damiano, B. P.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3245−3250.

(13) Fonquerna, S.; Miralpeix, M.; Pagès, L.; Puig, C.; Cardús, A.; Antón, F.; Vilella, D.; Aparici, M.; Prieto, J.; Warrellow, G.; Beleta, J.; Ryder, H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1165−1167.

(14) (a) Kulagowski, J. J.; Broughton, H. B.; Curtis, N. R.; Mawer, I. M.; Ridgill, M. P.; Baker, R.; Emms, F.; Freedman, S. B.; Marwood, R.; Patel, S.; Patel, S.; Ragan, C. I.; Leeson, P. D. *J. Med. Chem.* **1996**, *39*, 1941−1942. (b) Löber, S.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97−102. (c) Oh, S.-J.; Lee, K. C.; Lee, S.-Y.; Ryu, E. K.; Saji, H.; Choe, Y. S.; Chi, D. Y.; Kim, S. E.; Lee, J.; Kim, B.-T. *Bioorg. Med. Chem.* **2004**, *12*, 5505−5513.

(15) (a) Guillard, J.; Larraya, C.; Viaud-Massuard, M.-C. *Heterocycles* **2003**, *60*, 865−877. (b) Larraya, C.; Guillard, J.; Renard, P.; Audinot, V.; Boutin, J. A.; Delagrange, P.; Bennejean, C.; Viaud-Massuard, M.-C. *Eur. J. Med. Chem.* **2004**, *39*, 515−526.

(16) Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeiffer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621−6630.

(17) (a) Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 4607−4611. (b) Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Golsteyn, R.; Prudhomme, M. *Tetrahedron Lett.* **2004**, *45*, 4643−4647. (c) Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 7304−7316.

(18) Hodge, C. N.; Aldrich, P. E.; Wasserman, Z. R.; Fernandez, C. H.; Nemeth, G. A. *J. Med. Chem.* **1999**, *42*, 819−832.

(19) Ujjainwalla, F.; Walsh, T. F. *Tetrahedron Lett.* **2001**, *42*, 6441−6445.

(20) Cai, Z.; Feng, J.; Guo, Y.; Li, P.; Shen, Z.; Chu, F.; Guo, Z. *Bioorg. Med. Chem.* **2006**, *14*, 866−874.

(21) Review: (a) Mérour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471−506. A former review is given in: (b) Yakhontov, L. N.; Prokopov, A. A. *Russ. Chem. Rev.* **1980**, *49*, 428−444.

(22) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571−1587.

(23) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539−541.

(24) (a) Kumar, V.; Dority, J. A.; Bacon, E. R.; Singh, B.; Lesher, G. Y. *J. Org. Chem.* **1992**, *57*, 6995−6998. (b) Pearson, S. E.; Nandan, S. *Synthesis* **2005**, 2503−2506.

(25) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *J. Comb. Chem.* **2005**, *7*, 510−512.

(26) (a) Park, S. S.; Choi, J.-K.; Yum, E. K. *Tetrahedron Lett.* **1998**, *39*, 627−630. (b) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355−5358. (c) Curtis, N. R.; Kulagowski, J. J.; Leeson, P. D.; Ridgill, M. P.; Emms, F.; Freedman, S. B.; Patel, S.; Patel, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 585−588.

(27) Hong, C. S.; Seo, J. Y.; Yum, E. K.; Sung, N.-D. *Heterocycles* **2004**, *63*, 631−639.

(28) Cottineau, B.; O'Shea, D. F. *Tetrahedron Lett.* **2005**, *46*, 1935−1938.

(29) Graczyk, P. Process for preparation of 7-azaindoles by cyclization of 2-amino-3-pyridinylphosphine oxides or 3-pyridinylphosphonic acid dialkyl esters with base, in particular *t*-BuOK. Patent WO 2004/013139, February 12, 2004; *Chem. Abstr.* DN 140:163708.

(30) (a) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem.* **2004**, *116*, 4626−4629; *Angew. Chem., Int. Ed.* **2004**, *43*, 4526−4528. (b) Lachance, N.; April, M.; Joly, M.-A. *Synthesis* **2005**, 2571−2577.

(31) Blache, Y.; Sinibaldi-Troin, M.-E.; Hichour, M.; Benezech, V.; Chavignon, O.; Gramain, J.-C.; Teulade, J.-C.; Chapat, J.-P. *Tetrahedron* **1999**, *55*, 1959−1970.

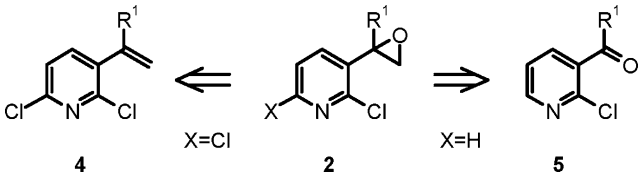
(32) (a) Fresneda, P. M.; Molina, P.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2000**, *41*, 4777−4780. (b) Roy, P. J.; Dufresne, C.; Lachance, N.; Leclerc, J.-P., Boisvert, M.; Wang, Z.; Leblanc, Y. *Synthesis* **2005**, 2751−2757.

inspired us to develop a similar 7-azaindole synthesis based on the regioselective opening of a 2-chloro-3-oxiran-2-ylpyridine **2** by an amine **3**,[35] followed by a nucleophilic aromatic substitution and subsequent dehydration yielding the desired 7-azaindoles **1**. This retrosynthetic concept proved to be very successful, and preliminary results were published recently.[36] Herein, we are disclosing the full account of our discovery and are presenting results obtained by microwave heating applied to the synthesis.

Results

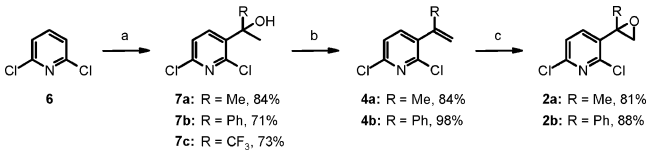
Synthesis of Epoxides 2. Our retrosynthetic concept required effective syntheses of oxiranes **2**. Their provenance mainly depended on the accessibility of pyridines with a suitable substitution pattern. We applied both the epoxidation of styrenes **4**, as well as the Corey−Chaykovsky epoxide formation[37] from ketones **5** (Scheme 2).

SCHEME 2. Retrosynthesis of Epoxides 2



The *ortho* lithiation of fluoro- and chloroarenes based on the acidifying effect of the halogen is a powerful method of introducing functional groups to an aromatic nucleus,[38] known as directed *ortho* metalation (DoM), and we recently applied this method in one of our drug discovery programs.[39] As shown in thorough investigations done mainly by Quéguiner[40] and Schlosser,[41] lithium diisopropylamide[42] promotes a hydrogen/metal exchange at the 3-position adjacent to the halogen of 2-chloro- and 2-fluoropyridines. However, mixtures of regioisomeric products may be observed. For example, in the case of 2,6-dichloropyridine **6** (Scheme 3), the lithiation occurs in the 4-position when it is done under kinetic control, whereas equilibrating conditions lead to the thermodynamically more stable 3-derivative.[43]

SCHEME 3. Synthesis of Oxiranes 6 from 2,6-Dichloropyridine Using DoM Technique[a]



[a] Reagents and conditions: (a) LDA, −78 °C; then $RCOCH_3$, −78 °C → rt. (b) $HOAc/H_2SO_4$ (3:1), reflux. (c) *m*-CPBA, DCM, rt.

In our hands, after lithiation of 2,6-dichloropyridine and subsequent treatment with acetone, acetophenone, and trifluoroacetone, we obtained the corresponding tertiary alcohols **7a**−**c**, which as a result of their higher polarity could be separated very easily by column chromatography from unconsumed starting material, in yields of 70−85% (Scheme 3). The undesired regioisomer was detected as a minor component in some experiments, but separation was dispensable, since the corresponding consecutive epoxide is unproductive in the ring-forming step.

The elimination of the tertiary alcohols **7** to α-substituted styrenes **4** was achieved in a 3:1 mixture of acetic and sulfuric acid at reflux temperature for 30 min, smoothly producing the elimination products in 85% up to quantitative yield. After basic workup, the crude products needed no further purification and were oxidized in high yields with *m*-CPBA to the epoxides **2**, which were isolated in high purity and used without purification.

The elimination to the styrene failed with the trifluoromethyl analogue **7c**. In this case the unaffected alcohol was re-isolated even after heating it up to 120 °C in concentrated sulfuric acid for 14 h. Other reagents such as thionyl chloride, thionyl chloride/pyridine,[44] or Burgess' reagent failed as well. Since we discovered a reliable alternative access to 3-trifluoromethyl-7-azaindole,[45] we did not perform further experiments with **7c**.

The synthesis of the monochloro derivative **2d** started from 2-chloro nicotinic acid chloride **8**. The unoptimized iron-catalyzed reaction[46] with isobutylmagnesiumbromide afforded the ketone **5b** in 60% yield. Ketone **5b** as well as the commercial compound **5a** were subjected to Corey−Chaykovsky epoxide formation[37] using trimethylsulfoniumiodide in THF and KO*t*Bu as base to afford the desired oxiranes **2c** and **2d** in high yields.

Azaindole Synthesis. The pivotal transformation of the sequence leading to the 7-azaindole bicyclus consists of the

(33) Debenham, S. D.; Chan, A.; Liu, K.; Price, K.; Wood, H. B. *Tetrahedron Lett.* **2005**, *46*, 2283−2285.

(34) (a) Tambute, A. *C. R. Hebd. Seances Acad. Sci. Ser. C* **1974**, *278C*, 1239−1242. (b) Fleming, I.; Woolias, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 827−828. (c) Fleming, I.; Woolias, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 829−837.

(35) Very recently, the synthesis of 1-substituted 7-azaindoles by reaction of anilines or amines with 2-chloro-3-(2-methoxyvinyl)pyridines has been described: Dyck, B.; Grigoriadis, D. E.; Gross, R. S.; Guo, Z.; Haddach, M.; Marinkovic, D.; McCarthy, J. R.; Moorani, M.; Regan, C. F.; Saunders: J.; Schwaebe, M. K.; Szabo, T.; Williams, J. P.; Zhang, X.; Bozigian, H.; Chen, T. K. *J. Med. Chem.* **2005**, *48*, 4100−4110. Also similar to our approach, the reaction of 2-chloro-3-(1,2-dibromoethyl)quinoline with *p*-aminobenzenesulphonamide in the synthesis of α-carbolines has been reported: Murugesan, M.; Ramasamy, K.; Shanmugam, P. *Z. Naturforsch. B* **1980**, *35*, 746−748. For the conversion of 2,4,6-trichloro-3-(2-chloroethyl) pyridine to 5- and 7-azaindoles, see: Yakhontov, L. N.; Uritskaya, M. Y.; Rubtsov, M. V. *Chem. Heterocycl. Compd. Engl. Transl.* **1965**, 625−630.

(36) Schirok, H. *Synlett* **2005**, 1255−1258.

(37) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782−3783. (b) Ciaccio, J. A.; Drahus, A. L.; Meis, R. M.; Tingle, C. T.; Smrtka, M.; Geneste, R. *Synth. Commun.* **2003**, *33*, 2135−2143 and references therein.

(38) (a) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009−2021. (b) Sniekus, V. *Chem. Rev.* **1990**, *90*, 879−900. (c) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059−4090. (d) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002.

(39) Alonso-Alija, C.; Michels, M.; Peilstöcker, K.; Schirok, H. *Tetrahedron Lett.* **2004**, *45*, 95−98.

(40) (a) Güngör, T.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139−150. (b) Marsais, F.; Pineau, P.; Nivolliers, F.; Mallet, M.; Turck, A.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1992**, *57*, 565−573. (c) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 49−64. (d) Weymeels, E.; Awad, H.; Bischoff, L.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F. *Tetrahedron* **2005**, *61*, 3245−3249.

(41) (a) Schlosser, M.; Rausis, T. *Eur. J. Org. Chem.* **2004**, 1018−1024. (b) Schlosser, M.; Rausis, T.; Bobbio, C. *Org. Lett.* **2005**, *7*, 127−129. (c) Bobbio, C.; Schlosser, M. *J. Org. Chem.* **2005**, *70*, 3039−3045.

(42) For a recent report on the deprotonation with lithium magnesates see: Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F. *Tetrahedron Lett.* **2004**, *45*, 7873−7877.

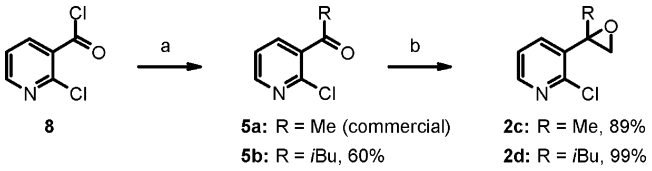
(43) (a) Radinov, R.; Chanev, C.; Haimova, M. *J. Org. Chem.* **1991**, *56*, 4793−4796. (b) Mongin, F.; Tognini, A.; Cottet, F.; Schlosser, M. *Tetrahedron Lett.* **1998**, *39*, 1749−1752. (c) Kelly, T. P.; Rodgers, T. R.; Wright, C. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 451−457. (d) Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 1371−1376.

(44) Rodrigues, I.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2001**, *66*, 2098−2103.

(45) Publication in preparation.

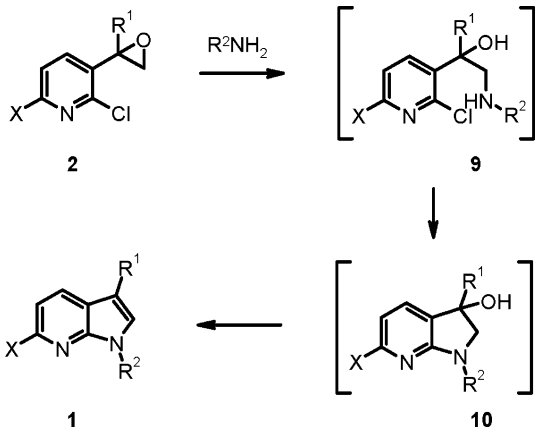
(46) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943−4349.

SCHEME 4. Synthesis of Oxiranes 2 from Nicotinic Acid Derivatives[a]



[a] Reagents and conditions: (a) $Fe(acac)_3$ (0.03 equiv), *i*BuMgCl, THF, −78 °C. (b) $Me_3S^+I^-$, KO*t*Bu, THF, 0 °C → rt.

SCHEME 5. Proposed Mechanism for 7-Azindole Formation



reaction of epoxides **2** with primary amines. In preceding experiments with 3-(2-methyloxiran-2-yl)pyridine and *p*-methoxybenzylamine, 1-butanol was found to be an appropriate solvent for the initiating epoxide opening and was preferred over DMSO and DMF, whereas the results in dioxane, toluene, pyridine, triethylamine and acetonitrile were clearly inferior. The azaindole synthesis was therefore performed in 1-butanol at 100−120 °C. Mechanistically, the first step is the regioselective opening of the oxirane **2** to the amino alcohol **9**, and the second is the intramolecular nucleophilic aromatic substitution to the 3-hydroxyazaindoline **10** (Scheme 5). With the reversed order, the high regioselectivity in the aromatic substitution step of the dichloro derivatives **2a** and **2b** could not be explained.

We found that the speed of the reaction mainly depends on the degree of substitution of the α-carbon next to the amine nitrogen. Reactions with α-linear amines such as *n*-butyl, allyl-, or benzylamine (Table 1, entries 1−5) are completed within 1−10 h. α-Branched amines such as cyclopentylamine reacted significantly more slowly and required heating overnight (entry 6). Reactions with α-trisubstituted amines such as adamantylamine were heated for several days (entry 7). However, the yields of the outcoming azaindoles were still very high. Presumably because of the insufficient nucleophilicity of anilines, the reaction could not be expanded to obtain 1-arylated 7-azaindoles.

The intermediate tertiary alcohol **10** formed during the process was labile, and spontaneous dehydratization occurred to a certain degree. Frequently, acid catalysis was required to drive the dehydration to completion.

Considering the protracted reaction times required, particularly with sterically more demanding amines, we were intrigued with the possibility of accelerating the azaindole formation. Microwave-assisted organic synthesis (MAOS) has had a significant impact on synthetic chemistry. The application of microwave-assisted technology has proven to be beneficial in a vast number of reactions examined during the past 2 decades,[47] with the greatest benefit provided in the reduction of reaction times under microwave conditions relative to times using conventional heating.[48] Microwave-assisted opening of epoxides by amines are well precedented,[49] including nucleophilic aromatic aminations of 2-halopyridines.[50] We therefore envisaged that the application of this heating technique could result in a much faster and therefore more practical azaindole formation, even when less reactive amines are used.

TABLE 1. Comparison of Conventional and Microwave Heating

Entry	s.m.	Method	Temp.	Time	Yield	Product
1	**2a**	Δ	110 °C	5 h[a]	66%	**1a**
		MW	150 °C	20 min	60%	
2	**2a**	Δ	115 °C	4 h[a]	21%	**1b**
		MW	200 °C	30 min	69%	
3	**2c**	Δ	110 °C	9 h[a]	82%	**1c**
		MW	150 °C	40 min	72%	
4	**6a**	Δ	95 °C	2 h[a]	47%	**5d**
		MW	150 °C	30 min	67%	
5	**2b**	Δ	110 °C	8 h[a]	95%	**1e**
		MW	200 °C	8 min	95%	
6	**2b**	Δ	110 °C	16 h[a]	86%	**1f**
		MW	200 °C	30 min	95%	
7	**2b**	Δ	120 °C	72 h[a]	84%	**1g**
		MW	200 °C	2.5 h	85%	

[a] After the given reaction time the solvent was removed in vacuo, ethanol and hydrochloric acid were added, and the mixture was stirred overnight at room temperature to complete the elimination of water.

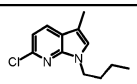
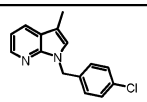
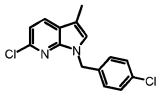
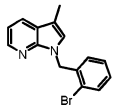
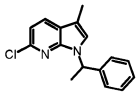
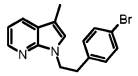
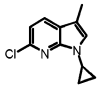
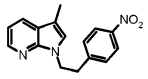
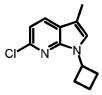
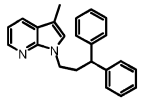
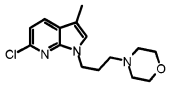
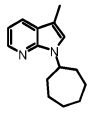
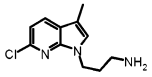
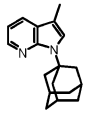
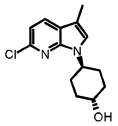
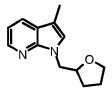
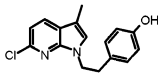
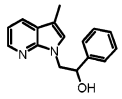
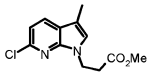
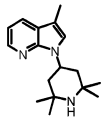
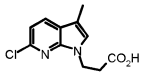
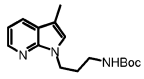
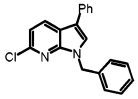
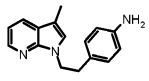
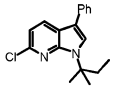
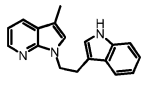
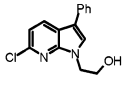
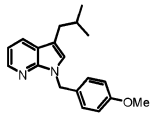
(47) (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002. (c) Kappe, C. O. *Angew. Chem.* **2004**, *116*, 6408−6443; *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284. (d) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005. (e) *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell Publishing: Oxford 2005.

(48) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

(49) (a) Alikhani, V.; Beer, D.; Bentley, D.; Bruce, I.; Cuenoud, B. M., Fairhurst, R. A.; Gedeck, P.; Haberhuer, S.; Hayden, C.; Janus, D.; Jordan, L.; Lewis, C.; Smithies, K.; Wissler, E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4705−4710. (b) Lindsay, K. B.; Pyne, S. G. *Tetrahedron Lett.* **2004**, *60*, 4173−4176.

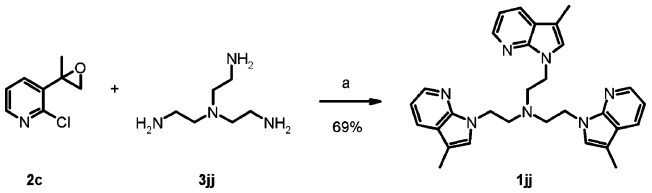
(50) Narayan, S.; Seelhammer, T.; Gawley, R. E. *Tetrahedron Lett.* **2004**, *45*, 757−759.

TABLE 2. 7-Azaindoles from 2,6-Dichloro-3-oxiranyl-pyridines

entry	s. m.	method	time	product	yield[a]	entry	s.m.	method	time	product	yield[a]
1	**2a**	Δ, 95 °C	2 h	**1h** 	86%	15	**2c**	Δ, 120 °C	18 h	**1v** 	64%
2	**2a**	Δ, 115 °C	4 h	**1i** 	63%	16	**2c**	Δ, 120 °C	18 h	**1w** 	52%
3	**2a**	MW, 150 °C	1.5 h	**1j** 	82%	17	**2c**	MW, 200 °C	40 min	**1x** 	78%
4	**2a**	MW, 150 °C	1.5 h	**1k** 	63%	18	**2c**	MW, 200 °C	20 min	**1y** 	53%
5	**2a**	MW, 150 °C	1.5 h	**1l** 	79%	19	**2c**	MW, 200 °C	10 min	**1z** 	74%
6	**2a**	MW, 150 °C	30 min	**1m** 	79%	20	**2c**	MW, 200 °C	40 min	**1aa** 	83%
7	**2a**	MW, 150 °C	30 min	**1n** 	28%	21	**2c**	MW, 200 °C	3 h	**1bb** 	61%
8	**2a**	MW, 150 °C	1 h	**1o** 	71%	22	**2c**	MW, 200 °C	30 min	**1cc** 	58%
9	**2a**	MW, 150 °C	30 min	**1p** 	52%	23	**2c**	MW, 200 °C	30 min	**1dd** 	67%
10[b]	**2a**	MW, 150 °C	30 min	**1q** 	35%	24	**2c**	MW, 200 °C	20 min	**1ee** 	55%
11	**2a**	MW, 150 °C	30 min	**1r** 	57%	25	**2c**	MW, 200 °C	10 min	**1ff** 	44%
12	**2b**	Δ, 110 °C	3 h	**1s** 	66%	26	**2c**	MW, 200 °C	30 min	**1gg** 	55%
13	**2b**	Δ, 110 °C	48 h	**1t** 	78%	27	**2c**	MW, 200 °C	30 min	**1hh** 	66%
14	**2b**	Δ, 110 °C	12 h	**1u** 	74%	28	**2d**	MW, 200 °C	30 min	**1ii** 	56%

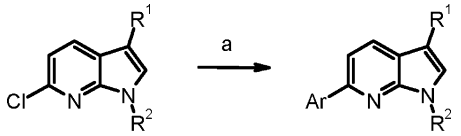
[a] Isolated yields. [b] The reaction was performed in methanol to prevent transesterification.

SCHEME 6. Synthesis of 1jj[a]



[a] Reagents and conditions: (a) 1-butanol, MW 200 °C, 30 min.

SCHEME 7. Suzuki−Miyaura Coupling with 6-Chloro-7-azaindoles[a]

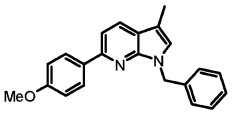
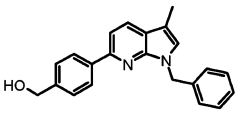
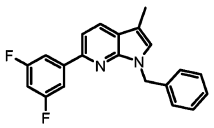
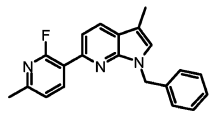
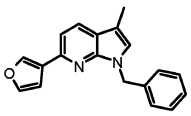
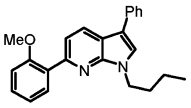
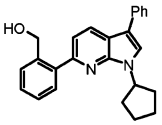
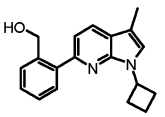
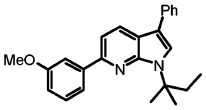
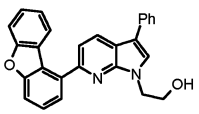


[a] Reagents and conditions: (a) $ArB(OH)_2$ (2.0 equiv), $NaHCO_3$ (3.0 equiv), $PdCl_2(dppf)\times CH_2Cl_2$ (0.05 equiv), DME/H_2O (3:1), 115 °C.

The conditions we applied in a focused microwave oven were similar to the ones we operated with in the conventional procedure: the oxirane and amine were dissolved in 1-butanol and heated in a sealed tube, however, to a higher temperature. The reduction of reaction times was dramatic, both with the mono- and the dichloropyridines. As expected, the latter proved to be more reactive, and therefore 150 °C was chosen for the monochloro derivative and 200 °C for the dichloro derivative. Reactions with benzylic and linear aliphatic amines that took several hours by conventional heating were speeded up to 10−40 min (Table 1, entries 1−5). With cyclopentylamine, the reaction time was shortened from 16 h by conventional heating to 30 min, and in the case of adamantylamine from 3 days to 2.5 h. Unexpectedly, no addition of acid was reqired for the final dehydration of **10**. Probing the hypothesis that a simple thermal effect could be responsible for this phenomenon, test reactions were heated in sealed tubes to similar temperatures as in the microwave oven, but with clearly inferior results.

The compatibility with several functional groups was next examined. Alkenes are well tolerated and offer the possibility of later functionalization (Table 1, entry 4). Since the reactions are done in butanol, primary and secondary alcohols (Table 2, entries 8, 14, 23) are compatible, as well as, to a certain extent, phenols (entry 9). Other functionalities, such as tertiary amines, were also tolerated (entry 6). Primary diamines may be used, and dependent on the stoichiometry of the reagents, the product with one amino function can be isolated (entry 7). However, monoprotected diamines offer a selective two-step process for the same target molecules (entry 25). Nitrogen may also be introduced as a nitro group (entry 18). If one amino function is less nucleophilic, e.g., as a result of steric hindrance, the reaction may also be highly selective (entry 24). For the same reason, unprotected anilines or indoles are tolerated in the amino component (entries 26 and 27). Alternatively, with excess oxirane present, all primary amino functions of a polyamino component react in good overall yield (Scheme 6). To a certain degree, carboxylic esters and acids are also compatible with the transformation (Table 2, entries 10 and 11). 3-Aminopropionitrile decomposed under the reaction conditions. The sterically encumbered tritylamine did not react at all. Ammonia itself reacted in the desired fashion; however, byproducts were found originating from the primary amine formed in the epoxide opening with ammonia (data not shown).

TABLE 3. Suzuki−Miyaura Couplings with 6-Chloro-7-azaindoles

entry	s.m.	product		yield
1	**1a**		**11a**	84%
2	**1a**		**11b**	95%
3	**1a**		**11c**	99%
4	**1a**		**11d**	96%
5	**1a**		**11e**	89%
6	**1e**		**11f**	90%
7	**1f**		**11g**	99%
8	**1l**		**11h**	97%
9	**1t**		**11i**	96%
10	**1u**		**11j**	91%

Suzuki−Miyaura Coupling with 6-Chloro-7-azaindoles. Halogenated 7-azaindoles are versatile building blocks for further derivatizations. Recently, we reported on the nucleophilic substitution of activated 4-chloro- and 4-nitro-7-azaindoles,[51] and on the Pd-catalyzed C−O and C−N coupling of 4-iodo-7-azaindoles.[52] With unsubstituted 6-chloro-7-azaindole, the Suzuki−Miyaura-type cross-coupling with boronic acids has been reported in medium yields.[53] With the N1-substituted

(51) Figueroa-Pérez, S.; Bennabi, S.; Schirok, H.; Thutewohl, M. *Tetrahedron Lett.* **2006**, *47*, 2069−2072.

(52) Thutewohl, M.; Schirok, H.; Bennabi, S.; Figueroa-Pérez, S. *Synthesis* **2006**, 629−632.

(53) Allegretti, M.; Arcadi, A.; Marinelli, F.; Nicolini, L. *Synlett* **2001**, *5*, 609−612.

6-chloro-7-azaindoles **1** and using $PdCl_2(dppf)\times CH_2Cl_2$ as catalyst in a dimethoxyethan/water mixture and sodium bicarbonate as base, we obtained the desired 6-arylated coupling products in high to almost quantitative yields (Scheme 7, Table 3).

Summary

In conclusion, we have developed an expedient and short 7-azaindole synthesis, based on an epoxide-opening-cyclization-dehydration mechanism. Several functional groups such as alcohols, phenols, esters, acids, and nitro groups and less reactive amino functions including anilines are compatible with the reaction conditions. Applying microwave heating, the reaction can be completed within 3 h or less even with slowly reacting amines. Chlorination at the 6-position allows for derivatization of this position through the palladium-catalyzed Suzuki−Miyaura coupling, giving 6-arylated dervatives in almost quantitative yield. Facile access to the desired epoxides, which do not require thorough purification, as well as the robustness of the ring-forming step, make this synthetic route a valuable synthetic tool and amenable to parallel synthesis.

Experimental Section

1-(2-Chloropyridin-3-yl)-3-methylbutan-1-one (5b). Iron(III)-acetylacetonate (30 mg, 0.09 mmol) and 2-chloronicotinoyl chloride (500 mg, 2.84 mmol) were dissolved in degassed THF (20 mL) and cooled to −78 °C. A solution of isobutylmagnesium bromide (2 M in THF, 1.85 mL, 3.69 mmol) was added. After being stirred for 15 min at −78 °C, the reaction was quenched with saturated aqueous ammonium chloride solution. The mixture was extracted three times with *tert*-butyl methyl ether. The combined organic layers were dried over sodium sulfate, and the solvent was evaporated. The residue was purified by preparative HPLC to yield 335 mg (60%) of a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.94 (d, J = 6.6 Hz, 6H), 2.10 (tsept, J = 7.0, 6.6 Hz, 1H), 2.86 (d, J = 7.0 Hz, 2H), 7.56 (dd, J = 7.6, 4.9 Hz, 1H), 8.12 (dd, J = 7.6, 1.9 Hz, 1H), 8.53 (dd, J = 4.9, 1.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.1, 24.1, 50.6, 123.2, 135.2, 138.1, 145.5, 151.2, 201.4. HRMS calcd for $C_{10}H_{12}ClNO + [H^+]$, 198.0681; found, 198.0673.

2-(2,6-Dichloropyridin-3-yl)propan-2-ol (7a). A solution of diisopropylamine (12.5 mL, 89.2 mmol) in 240 mL of THF was cooled to −78 °C. *n*-Butyllithium in hexane (55.8 mL of a 1.6 M solution, 89.2 mmol) was added, and the mixture was warmed to 0 °C for 30 min. Subsequently, the mixture was cooled to −78 °C again, and a solution of 2,6-dichloropyridine (12.0 g, 81.1 mmol) in THF (30 mL) was added. After 2 h at this temperature, acetone (8.94 mL, 122 mmol) was added, while the internal temperature rose to −50 °C. The mixture was stirred for 0.5 h at −78 °C and was then warmed to room temperature. It was poured into a cold ammonium chloride solution and extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (dichloromethane, then dichloromethane/methanol 25:1) to yield 14.9 g (89%) of the title compound as a yellow oil. The ^{1}H NMR spectrum revealed a 5% content of the regioisomeric compound, which was not separated. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.59 (s, 6H), 5.58 (s, 1H), 7.57 (d, J = 8.3 Hz, 1H), 8.23 (d, J = 8.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.3, 70.0, 123.3, 140.3, 142.7, 145.9, 146.4. HRMS calcd for $C_7H_6Cl_2NO$ [$M^+ - CH_3$], 189.9826; found, 189.9823.

1-(2,6-Dichloropyridin-3-yl)-1-phenylethanol (7b). The title compound was synthesized analogously to **7a** from dichloropyridine (4.00 g, 27.0 mmol) and acetophenone (3.9 g, 32.4 mmol). It was obtained after treatment of the crude product with petroleum ether and suction filtration, as pale tan crystals in 71% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91 (s, 3H), 6.07 (s, 1H), 7.21−7.32 (m, 5H), 7.65 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 8.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.4, 73.3, 123.1, 126.1, 126.7, 127.7, 140.3, 141.8, 145.5, 146.8, 147.2. HRMS calcd for $C_{13}H_{11}Cl_2NO + [H^+]$, 268.0291; found, 268.0289. The filtrate contained an additional 8% of the desired product accompanied by the symmetric regioisomer, which could be separated by HPLC. **1-(2,6-Dichloropyridin-4-yl)-1-phenylethanol:** ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.86 (s, 3H), 6.22 (s, 1H), 7.22−7.36 (m, 3H), 7.45−7.50 (m, 2H), 7.54 (s, 2H).

2-(2,6-Dichloropyridin-3-yl)-1,1,1-trifluoropropan-2-ol (7c). The title compound was synthesized analogously to **7a** from dichloropyridine (6.00 g, 27.0 mmol) and trifluoroacetone (6.81 g, 60.8 mmol). The crude product was triturated with cyclohexane, and the product was collected by suction filtration in 73% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.95 (s, 3H), 7.12 (br. s, 1H), 7.66 (d, J = 8.3 Hz, 1H), 8.32 (d, J = 8.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.8, 73.0 (q, $^2J_{C,F}$ = 29.6 Hz), 123.4, 125.5 (q, $^1J_{C,F}$ = 287 Hz), 133.1, 143.1, 147.2, 148.6. HRMS calcd for $C_8H_6Cl_2FNO$, 258.9779; found, 258.9773.

2,6-Dichloro-3-isopropenylpyridine (4a). The alcohol **7a** (4.40 g, 21.4 mmol) was dissolved in 21 mL of acetic acid, and 7.0 mL of concentrated sulfuric acid was added. The mixture was heated to reflux for 30 min. It was poured into ice water, basified with concentrated sodium hydroxide solution, and extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated to yield 3.50 g (84%) of the title compound as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.06 (dd, J = 1.3, 0.9 Hz, 3H), 5.08 (m, 1H), 5.38 (dq, J = 1.5, 1.3 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.6, 118.7, 123.8, 137.5, 140.6, 142.1, 146.7, 147.5. HRMS calcd for $C_8H_7Cl_2N$, 186.9956; found, 186.9956.

2,6-Dichloro-3-(1-phenylvinyl)pyridine (4b). Analogously to **4a**, the title compound was obtained from **7b** in 98% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.39 (s, 1H), 6.02 (s, 1H), 7.23−7.28 (m, 2H), 7.30−7.40 (m, 3H), 7.66 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 118.6, 124.1, 126.2, 128.5, 128.9, 135.8, 138.1, 143.8, 143.9, 148.2, 148.3. HRMS calcd for $C_{13}H_9Cl_2N$, 249.0112; found, 249.0104.

2,6-Dichloro-3-(2-methyloxiran-2-yl)pyridine (2a). Styrene **4a** (4.10 g, 21.8 mmol) was dissolved in dichloromethane (120 mL), and *m*-CPBA (10.7 g, 43.6 mmol) was added in portions. The mixture was stirred overnight, diluted with dichloromethane and extracted three times with cold NaOH solution (1 N). The organic layer was dried over sodium sulfate, and the solvent was evaporated to yield the epoxide as yellow oil (3.60 g, 81% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (s, 3H), 2.85 (d, J = 4.9 Hz, 1H), 3.07 (d, J = 4.9 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.4, 53.8, 56.1, 123.7, 135.2, 141.0, 147.2, 148.0. HRMS calcd for $C_8H_7Cl_2NO$, 202.9905; found, 202.9895.

2,6-Dichloro-3-(2-phenyloxiran-2-yl)pyridine (2b). The title compound was prepared from **4b** analogously to **2a** in 88% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.36 (d, J = 4.9 Hz, 1H), 3.48 (d, J = 4.9 Hz, 1H), 7.17−7.24 (m, 2H), 7.31−7.39 (m, 3H), 7.68 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 56.1, 58.9, 123.8, 126.1, 128.2, 128.4, 133.1, 137.2, 142.6, 148.7, 148.8. HRMS calcd for $C_{13}H_9Cl_2NO$, 265.0061; found, 265.0054.

2-Chloro-3-(2-methyloxiran-2-yl)pyridine (2c). Trimethylsulfoniumiodide (6.82 g, 33.4 mmol) was dissolved in THF (175 mL), and the solution was cooled to 0 °C. Potassium *tert*-butylate (3.95 g, 33.4 mmol) was added, and the mixture was stirred for 5 min. Freshly distilled 3-acetyl-2-chloropyridine (4.00 g, 25.7 mmol) was added to the suspension, and the reaction was stirred at room temperature overnight. It was filtrated and washed with brine and then dried over sodium sulfate, and the solvent was evaporated to

yield the title compound (4.06 g, 89% yield) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.60 (s 3H), 2.84 (d, J = 4.9 Hz, 1H), 3.07 (d, J = 4.9 Hz, 1H), 7.46 (dd, J = 7.4, 4.6 Hz, 1H), 7.90 (dd, J = 7.4, 1.6 Hz, 1H), 8.39 (dd, J = 4.6, 1.6 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.7, 53.9, 56.5, 123.3, 135.7, 137.9, 148.2, 149.0. HRMS calcd for C_8H_8ClNO, 168.0216; found, 168.0216.

2-Chloro-3-(2-isobutyloxiran-2-yl)pyridine (2d). The compound was prepared from **5b** analogously to **2c** in 99% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 1.33−1.60 (m, 2H), 2.12 (dd, J = 14.2, 5.3 Hz, 1H), 2.79 (d, J = 4.9 Hz, 1H), 3.02 (d, J = 4.9 Hz, 1H), 7.46 (dd, J = 7.6, 4.7 Hz, 1H), 7.90 (dd, J = 7.6, 1.9 Hz, 1H), 8.39 (dd, J = 4.7, 1.9 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.8, 23.2, 24.9, 42.9, 52.5, 58.7, 123.1, 134.6, 138.6, 148.5, 149.1. MS (DCI) calcd for $C_{11}H_{14}ClNO$, 211; found, 211.9 [M + H$^+$].

Synthesis of 7-Azaindoles. General Procedure. Method A. The epoxide and the amine (1−2 equiv) were dissolved in 1-butanol (mL/mmol epoxide), and the mixture was heated for the given reaction time to 110 °C (higher temperatures were achieved in sealed pressure tubes). The solvent was evaporated, the residue was treated with ethanol (3 mL/mmol epoxide), and concentrated hydrochloric acid (1 mL) was added. The reaction was stirred overnight, then diluted with water, basified with diluted NaOH solution, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and the solvent was evaporated. The crude product was purified by column chromatography on silica gel or by HPLC.

Method B. The reaction was run similar to method A, but microwave heating to the given temperature for the indicated time was used. Distinct from method A, no acid was added.

1-Benzyl-6-chloro-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1a). The title compound was synthesized following method A (110 °C, 5 h) in 66% yield. Following method B (150 °C, 20 min) it was isolated in 60% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H), 5.37 (s, 2H), 7.13 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 7.1 Hz, 2H), 7.24−7.33 (m, 3H), 7.38 (s, 1H), 8.01 (d, J = 8.1 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.37, 46.9, 108.9, 114.7, 119.2, 126.8, 127.1, 127.3, 128.5, 130.2, 138.0, 143.1, 146.0. HRMS calcd for $C_{15}H_{13}ClN_2$, 256.0767; found, 256.0770.

1-(4-Methoxybenzyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1c). The title compound was synthesized following method A (110 °C, 9 h) in 82% yield. Following method B (150 °C, 40 min) it was isolated in 72% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H), 3.69 (s, 3H), 5.32 (s, 2H), 6.85 (d, J = 8.6 Hz, 2H), 7.06 (dd, J = 7.8, 4.7 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.32 (s, 1H), 7.92 (dd, J = 7.8, 1.2 Hz, 1H), 8.24 (dd, J = 4.7, 1.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.40, 46.1, 54.9, 107.9, 113.7, 114.8, 120.3, 125.9, 126.7, 128.7, 130.5, 142.3, 147.0, 158.4. HRMS calcd for $C_{16}H_{16}N_2O$, 252.1263; found, 252.1252.

1-(1-Adamantyl)-6-chloro-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (1g). The title compound was synthesized following method A (120 °C, 72 h) in 84% yield. Following method B (200 °C, 2.5 h) it was isolated in 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.97 (m, 6H), 2.24 (br. s, 3H), 2.49 (6H under DMSO-signal), 7.21 (d, J = 8.3 Hz, 1H), 7.27 (m, 1H), 7.44 (m, 2H), 7.70 (d, J = 7.1 Hz, 2H), 7.93 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76−1.91 (m, 6H), 2.28 (br. s, 3H), 2.54 (d, J = 2.6 Hz, 6H), 7.08 (d, J = 8.3 Hz, 1H), 7.27 (tt, J = 7.4, 1.5 Hz, 1H), 7.40−7.45 (m, 2H), 7.51 (s, 1H), 7.54−7.59 (m, 2H), 8.08 (d, J = 8.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 29.1, 35.6, 40.7, 57.5, 113.0, 115.6, 117.8, 124.0, 125.9, 126.4, 128.8, 130.8, 134.1, 141.4, 146.2. HRMS calcd for $C_{23}H_{23}ClN_2$, 362.1550; found, 362.1542.

1-[2-(1*H*-Indol-3-yl)ethyl]-3-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1hh). The title compound was synthesized following method B (200 °C, 30 min) in 66% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H), 3.19 (dd, J = 7.7, 7.6 Hz, 2H), 4.48 (dd, J = 7.7, 7.6 Hz, 2H), 6.96−7.14 (m, 4H), 7.32−7.36 (m, 2H), 7.61 (d, J = 7.6 Hz, 1H), 7.91 (dd, J = 7.7, 1.5 Hz, 1H), 8.26 (dd, J = 4.7, 1.5 Hz, 1H), 10.85 (br. s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.42, 25.9, 44.0, 107.3, 110.9, 111.3, 114.6, 118.2, 120.3, 120.9, 122.7, 126.2, 126.6, 127.0, 136.1, 142.1, 147.0. HRMS calcd for $C_{18}H_{17}N_3$, 275.1422; found, 275.1424.

3-Isobutyl-1-(4-methoxybenzyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1ii). The title compound was synthesized following method B (200 °C, 30 min) in 56% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88 (d, J = 6.5 Hz, 6H), 1.89 (dsept, J = 6.9, 6.5 Hz, 1H), 2.54 (d, J = 6.9 Hz, 2H), 3.69 (s, 3H), 5.35 (s, 2H), 6.85 (d, J = 8.6 Hz, 2H), 7.05 (dd, J = 7.8, 4.7 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.33 (s, 1H), 7.93 (dd, J = 7.8, 1.5 Hz, 1H), 8.22 (dd, J = 4.7, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.4, 28.9, 33.9, 46.3, 55.0, 112.1, 113.9, 115.0, 120.2, 126.4, 127.1, 128.7, 130.6, 142.3, 147.1, 158.5. HRMS calcd for $C_{19}H_{22}N_2O$, 294.1732; found, 294.1731.

2-(3-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-*N*,*N*-bis[2-(3-methyl-1*H*-pyrrolo[2,3-*b*]-pyridin-1-yl)ethyl]ethanamine (1jj). The title compound was synthesized following method B (200 °C, 30 min) with 4 equiv of the epoxide in 69% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (s, 9H), 2.88 (t, J = 6.2 Hz, 6H), 4.05 (t, J = 6.2 Hz, 6H), 6.88 (s, 3H), 7.02 (dd, J = 7.7, 4.7 Hz, 3H), 7.88 (dd, J = 7.7, 1.5 Hz, 3H), 8.19 (dd, J = 4.7, 1.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.37, 41.6, 53.3, 107.1, 114.6, 120.2, 126.5, 126.6, 142.0, 147.0. HRMS calcd for $C_{30}H_{33}N_7$ + [H$^+$], 492.2871; found, 492.2886.

Suzuki−Miyaura Reactions with 6-Chloro-7-azaindoles. General Procedure. A degassed mixture of dimethoxyethane and water (3.5:1, 4 mL/mmol azaindole) was added under argon to 6-chloro-7-azaindole, boronic acid (2 equiv), $PdCl_2(dppf)\times CH_2Cl_2$ (0.05 equiv), and sodium bicarbonate (3 equiv). The mixture was heated in a sealed pressure tube to 115 °C for 3 h. Subsequently, the layers were separated and the organic layer was evaporated. The residue was separated by HPLC to yield the coupling product.

1-Benzyl-6-(3,5-difluorophenyl)-3-methyl-1*H*-pyrrolo[2,3-*b*]-pyridine (11c). The title compound was prepared from **1a** following the general procedure in 99% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H), 5.50 (s, 2H), 7.20−7.33 (m, 6H), 7.46 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.89 (m, 2H), 8.05 (d, J = 8.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 9.45, 46.8, 103.3 (t, $^2J_{C,F}$ = 26.1 Hz), 108.5, 109.0 (dd, $^2J_{C,F}$ = 20.3 Hz, $^4J_{C,F}$ = 6.1 Hz), 112.2, 120.5, 127.3, 127.4, 127.87, 127.91, 128.4, 138.5, 143.4 (t, $^3J_{C,F}$ = 9.6 Hz), 146.2 (t, $^4J_{C,F}$ = 3.0 Hz), 146.8, 162.8 (dd, $^1J_{C,F}$ = 245 Hz, $^3J_{C,F}$ = 13.5 Hz). HRMS calcd for $C_{21}H_{16}F_2N_2$: 334.1282; found, 334.1285.

[2-(1-Cyclopentyl-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-phenyl]methanol (11g). The title compound was prepared from **1f** following the general procedure in 99% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.67−1.79 (m, 2H), 1.86−2.07 (m, 4H), 2.14−2.24 (m, 2H), 4.68 (d, J = 5.6 Hz, 2H), 5.18−5.26 (m, 2H), 7.27 (t, J = 7.4 Hz, 1H), 7.36−7.48 (m, 5H), 7.54 (d, J = 7.3 Hz, 1H), 7.66 (d, J = 7.3 Hz, 1H), 7.78 (d, J = 7.4 Hz, 2H), 8.08 (s, 1H), 8.38 (d, J = 8.2 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.6, 32.1, 54.8, 61.3, 113.6, 116.3, 116.7, 124.4, 125.7, 126.2, 126.6, 127.6, 127.7, 128.4, 128.8, 129.6, 134.6, 139.0, 140.3, 146.9, 151.5. HRMS calcd for $C_{25}H_{24}N_2O$, 368.1889; found, 368.1886.

Acknowledgment. We thank Dr. P. Schmitt, C. Streich, and D. Bauer for recording NMR spectra and helpful discussions. In addition we are grateful to M. Stoltefuss, G. Wiefel-Hübschmann and S. Brauner for HRMS measurements.

Supporting Information Available: Experimental methods and compound data for **1b,d−f,h−z,aa−gg** and **11a−b,d,f,h−j**. ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060512H