Organic LETTERS

Letter

pubs.acs.org/OrgLett

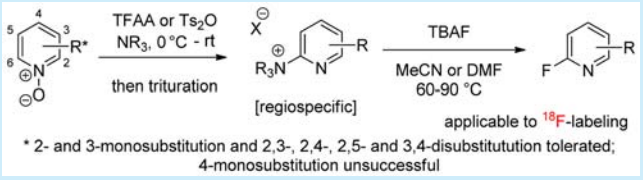
Facile Route to 2-Fluoropyridines via 2-Pyridyltrialkylammonium Salts Prepared from Pyridine *N*-Oxides and Application to ^{18}F-Labeling

Hui Xiong,* Adam T. Hoye,* Kuo-Hsien Fan, Ximin Li, Jennifer Clemens, Carey L. Horchler, Nathaniel C. Lim, and Giorgio Attardo

Avid Radiopharmaceuticals, 3711 Market Street, Philadelphia, Pennsylvania 19104, United States

Supporting Information

ABSTRACT: Among known precursors for 2-[^{18}F]-fluoropyridines, pyridyltrialkylammonium salts have shown excellent reactivity; however, their broader utility has been limited because synthetic methods for their preparation suffer from poor functional group compatibility. In this paper, we demonstrate the regioselective conversion of readily available pyridine *N*-oxides into 2-pyridyltrialkylammonium salts under mild and metal-free conditions. These isolable intermediates serve as effective precursors to structurally diverse 2-fluoropyridines, including molecules relevant to PET imaging. In addition to providing access to nonradioactive analogues, this method has been successfully applied to ^{18}F-labeling in the radiosynthesis of [^{18}F]AV-1451 ([^{18}F]T807), a PET tracer currently under development for imaging tau.



2-[^{18}F]Fluoro-substituted pyridines have emerged as a widely used functionality in PET tracers[1] (Figure 1) due to their straightforward, though often inefficient, methods of radiosynthesis and their limited radiodefluorination in vivo.[2]

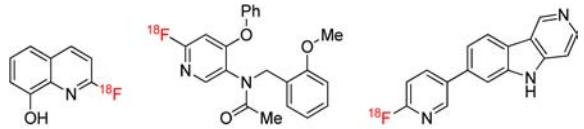
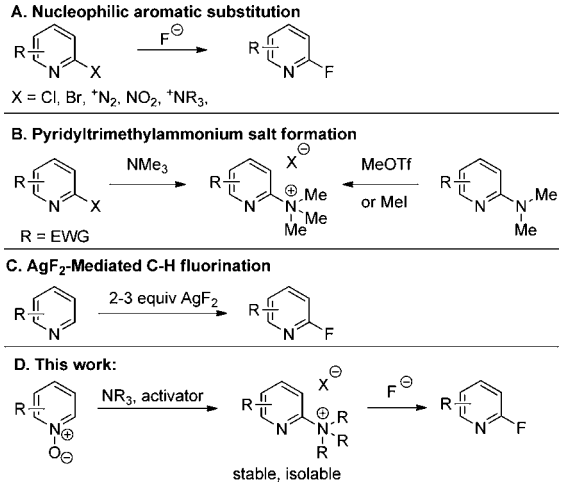


Figure 1. Selected PET tracers containing 2-[^{18}F]fluoropyridines.

Moreover, nonradioactive fluorinated heterocycles have shown broad applicability in medicinal chemistry as both target compounds and synthetic intermediates.[3,4b] Traditionally, 2-fluoropyridines have been synthesized by nucleophilic displacement of a suitable leaving group at the 2 position by fluoride (Scheme 1, A). The displacement of 2-chloro- and 2-bromopyridines with fluoride either requires elevated temperatures or the use of anhydrous TBAF,[5a] and the Balz–Schiemann reaction to synthesize fluoropyridines from aminopyridines features potentially explosive diazonium salt intermediates.[5b] 2-Nitro- and 2-trialkylammonium pyridines have been shown to be effective precursors to 2-fluoropyridines,[5c,6] though their general use has been limited due to synthetic inaccessibility using established methods (Scheme 1, B).[7] In a recent example of 2-fluoropyridine synthesis using a Chichibabin reaction-inspired approach, Hartwig and coworkers reported the direct C–H fluorination of pyridines employing AgF_2 (Scheme 1, C).[4] Their method was shown to

Scheme 1. Synthetic Approaches to 2-Fluoropyridines



be quite tolerant of functional groups, and it provided rapid access to a wide variety of 2-fluoropyridines that in some cases greatly improved synthetic access to clinically relevant compounds. Robust synthetic methods that allow for rapid, late-stage, site-specific installation of fluorine into pyridine rings will continue to be of considerable value to both the drug discovery and radiochemistry communities. Moreover, a general synthetic method that provides access to both

Received: June 12, 2015
Published: July 20, 2015

DOI: 10.1021/acs.orglett.5b01703
Org. Lett. 2015, 17, 3726–3729

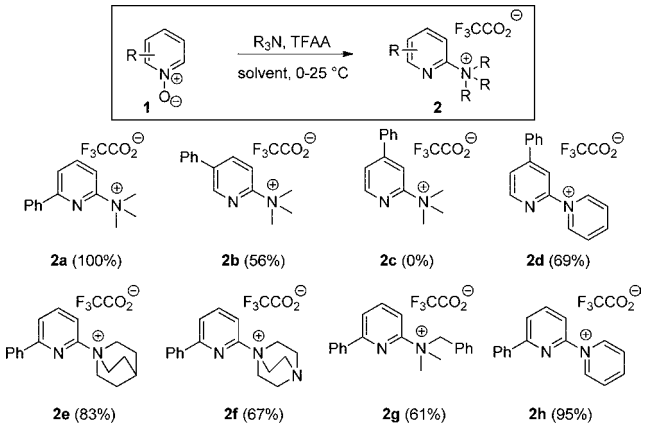
nonradioactive fluoropyridines and ^{18}F radioligands through a common intermediate is desirable.

It has been demonstrated that a range of 2-substituted pyridines can be prepared upon activation of pyridine *N*-oxides in the presence of a wide variety of nucleophiles (Cl, Br, CN, amine, etc.).[8,9] There are a few reported examples of preparing 2-pyridyltrimethylammonium salts from activated pyridine *N*-oxides,[10] though to our knowledge, a comprehensive study regarding the scope and use of these ammonium salts has not been published. We hypothesized that suitable activation of a pyridine *N*-oxide in the presence of a tertiary amine would furnish a trialkylammonium salt that would be reactive toward a fluoride nucleophile, thereby allowing for a method to achieve the delivery of fluoride to pyridine (Scheme 1, D).

Using 2-phenylpyridine *N*-oxide **1a** as a model substrate, we found that direct addition of fluoride (1 M tetrabutylammonium fluoride [TBAF] in THF) to the reaction mixture of **2a**, formed *in situ* from the activation of **1a** in the presence of trimethylamine, resulted in the formation of (dimethylamino)-pyridine instead of the desired fluoropyridine.[11] It was discovered that isolation of crude **2a** by trituration from Et_2O/CH_2Cl_2 and exposure to fluoride resulted in the formation of 2-fluoropyridine **3a**. Further optimization revealed that the fluorination reaction proceeded smoothly in polar aprotic solvents (DMF and CH_3CN), and 1 M TBAF in THF was found to be an effective fluoride source (see the Supporting Information).

Encouraged by the successful formation of **3a** via **2a**, we identified preferred conditions for trimethylammonium salt formation by screening a variety of reaction conditions including activating electrophile and reaction solvent using **1a** as a model substrate (3.0 equiv of trifluoroacetic anhydride [TFAA] or *p*-toluenesulfonic anhydride [Ts_2O] and 6.0 equiv of NMe_3 in CH_2Cl_2 [0.1 M], 0 °C - rt). For complete details, see the Supporting Information. As shown in Scheme 2, we

Scheme 2. Preparation of Trialkylammonium and Pyridinium Salts



explored the ammonium salt formation of phenyl-substituted pyridine *N*-oxides using a variety of amine nucleophiles. Both 2- and 3-phenylpyridine *N*-oxides reacted smoothly to give trimethylammonium salts **2a** and **2b** in good yields and as single regioisomers. We believe that the observed regioselectivity could be explained by stereoelectronic (2- vs 4-position) and steric (2- vs 6-position) effects as well as the relatively mild reaction conditions.

Surprisingly, activation of 4-phenylpyridine *N*-oxide in the presence of trimethylamine failed to produce isolable salt **2c**. Instead, a mixture of 4-phenylpyridin-2(1*H*)-one and 2-chloro-4-phenylpyridine was observed in less than 30 min, presumably derived from nucleophilic addition of trifluoroacetate and chloride[12] to **2c** generated *in situ*, respectively. In contrast, activation of 4-phenylpyridine *N*-oxide in the presence of excess pyridine over 48 h resulted in the formation of pyridinium salt **2d** in 69% isolated yield with only trace amounts of chlorinated and hydrolyzed byproducts. Failure to isolate **2c** could be attributed to its relatively high reactivity.

Alternative amine nucleophiles were selected on the basis of either the lack of a β-proton (*N*,*N*-dimethylbenzylamine and pyridine) or a conformational restriction to deprotonation (quinuclidine and 1,4-diazabicyclo[2.2.2]octane [DABCO]) that would otherwise lead to rapid elimination and formation of a neutral 2-(dialkylamino)pyridine. As expected, salts **2e**–**h** (Scheme 2) were isolated in good yields following either silica gel or reversed-phase column chromatography.

Having demonstrated the synthesis and isolation of a small number of pyridyltrialkylammonium salts, this approach was applied to the synthesis of a variety of fluoropyridines from their corresponding pyridine *N*-oxides assembled via an assortment of synthetic transformations (e.g., Buchwald–Hartwig, Suzuki, Sonogashira, and Pd-mediated *N*-oxide couplings,[13] aromatic substitution, and *m*-CPBA oxidation; see the Supporting Information). A set of 2-substituted pyridine *N*-oxides were converted into their corresponding fluoropyridines **3a**–**e** (Scheme 3) in good yields (37–87%), with the exception of the electron-deficient ethyl picolinate *N*-oxide **1f** (25%). Notably, Lewis basic hetereocycles and amines were tolerated in the reaction sequence.

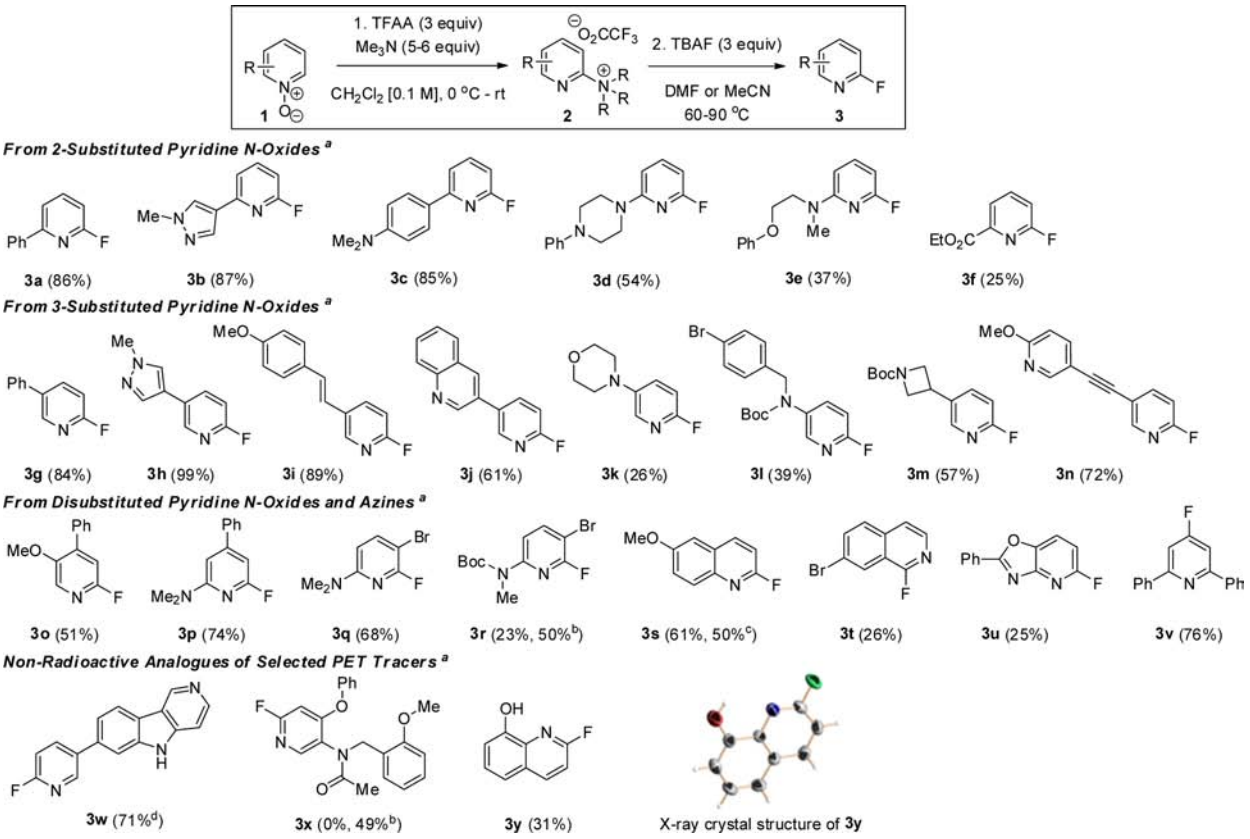
The conversion of 3-substituted pyridine *N*-oxides proved to be highly regioselective. In all cases, ammonium salt formation and subsequent fluorination occurred exclusively *para* to the existing substituent (i.e., 2-fluoro-5-phenylpyridine **3g** was isolated in 84% yield, and 2-fluoro-3-phenylpyridine was not detected). The observed site selectivity is noted to be complementary to Hartwig's AgF_2-mediated C–H fluorination process.[4] Aryl and heteroaryl groups were all well tolerated, producing the corresponding fluoropyridines **3g**–**j** in moderate to excellent yields (61–99%). 3-Morpholinyl- and *N*-Boc-amino-substituted pyridine *N*-oxides were converted to compounds **3k** and **3l**, albeit in lower yields. 5-Azetidin-3-yl-2-fluoropyridine **3m** was also prepared in 57% yield, and the alkyne-containing dipyridyl derivative **3n** was isolated in 72% yield.

Although conversions of various 4-monosubstituted pyridine *N*-oxides were not successful (see the Supporting Information), 2,4- and 3,4-disubstituted pyridine *N*-oxides afforded trisubstituted pyridines **3o** and **3p** in good yields (51 and 74%). 2,5-Disubstituted pyridine *N*-oxides afforded **3q** and **3r** in 68% and 23% yields, respectively. The yield of **3r** was improved to 50% when quinuclidine was used in place of trimethylamine. Fused hetereocyclic *N*-oxides also participated in the process, providing quinoline **3s**, isoquinoline **3t**, and oxazolopyridine **3u**. When both 2- and 2′-positions were substituted, we observed addition of trimethylamine and subsequent fluorination at the 4-position to furnish 4-fluoro-2,6-diphenypyridine (**3v**) in 76% yield.

Nonradioactive analogues of several PET tracers were prepared from their parent *N*-oxides. AV-1451[14] (**3w**) was

DOI: 10.1021/acs.orglett.5b01703
Org. Lett. 2015, 17, 3726–3729

Scheme 3. Synthesis of 2-Fluoropyridines

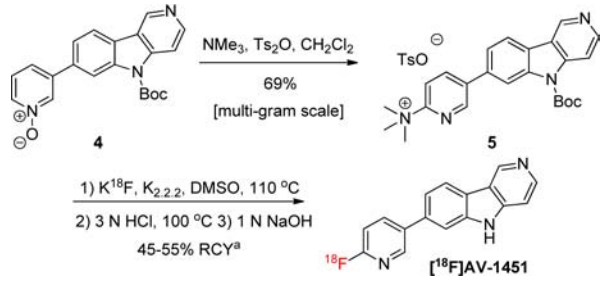


[a]Isolated yields in parentheses. All compounds were obtained as single regioisomers. [b]Using quinuclidine in step 1. [c]Using DABCO in step 1. [d]Following purification and subsequent *N*-Boc removal (TFA, CH_2Cl_2).

prepared in 71% overall yield following *N*-Boc deprotection of the carboline scaffold. 6-Fluoro-PBR28[15] (**3x**) was obtained in 49% yield using quinuclidine as the amine nucleophile, as trimethylamine was not effective. Lastly, the synthesis of 2-fluoroquinolin-8-ol[16] (CABS13, **3y**) was achieved from commercially available 8-hydroxyquinoline *N*-oxide in 31% yield, without any protecting group manipulations. It is noteworthy that this metal-free process provided **3y** as a colorless crystalline solid, which was suitable for X-ray crystallography and confirmed the site of fluorination. These examples illustrate the strategic use of pyridine *N*-oxides to achieve the site-specific, late-stage introduction of fluorine into complex, biologically relevant molecules.[17]

The 2-pyridyltrialkylammonium approach toward 2-fluoropyridine synthesis was also successfully extended to the preparation of [^{18}F]AV-1451 (Scheme 4).[18] The activation of pyridine *N*-oxide **4** with Ts_2O in the presence of trimethylamine cleanly afforded trimethylammonium **5** in 69% yield on multigram scale.[19] To achieve the radiosynthesis of [^{18}F]AV-1451, **5** was treated with K^{18}F in the presence of Kryptofix 2.2.2 in DMSO at 110 °C for 5 min, followed by acidic removal of the *N*-Boc group, neutralization, and semi-preparative HPLC purification. [^{18}F]AV-1451 was consistently and reproducibly obtained in decay-corrected 45−55% radiochemical yields (n > 50; yields were calculated using initial ^{18}F activity in ^{18}O-enriched water and isolated [^{18}F]AV-1451 activity). The total synthesis time was 45 min. It is noteworthy that [^{18}F]AV-1451 is chromatographically well separated from all other impurities as well as the precursor, leading to a rapid and facile purification. This automated process has been successfully implemented at multiple sites to supply doses of [^{18}F]AV-1451 in ongoing clinical trials.

Scheme 4. Radiosynthesis of [^{18}F]AV-1451 from Precursor 5



[a]Decay-corrected radiochemical yield.

In summary, we explored the scope and limitations of an efficient, metal-free synthesis of 2-fluoropyridines using inexpensive reagents. Pyridine *N*-oxide starting materials can be easily converted into 2-pyridyltrialkylammonium salt intermediates in a site-specific manner with broad functional group compatibility. Subsequently, the trialkylammonium salts can be used as common synthetic precursors for both ^{19}F and ^{18}F fluoropyridine analogues. Finally, this method was shown to be applicable to ^{18}F-labeling by the preparation of [^{18}F]AV-1451. Because of the broad availability of pyridine *N*-oxides and the extensive application potential of fluoropyridines in

DOI: 10.1021/acs.orglett.5b01703
Org. Lett. 2015, 17, 3726−3729

drug/PET tracer discovery, we believe that this fluorination method can be applied broadly.

■ ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures and spectroscopic data for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01703.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xiong@avidrp.com.
*E-mail: hoye@avidrp.com.

Notes

The authors declare the following competing financial interest(s): The authors are current employees of Avid Radiopharmaceuticals, Inc., a wholly-owned subsidiary of Eli Lilly and Co..

■ ACKNOWLEDGMENTS

We thank Justin Wright (Avid) for helpful discussions as well as LCMS and HRMS support, Dr. John Lister-James (Avid) for editorial and scientific discussions, Benjamin A. Diseroad and Dr. Gregory A. Stephenson (Eli Lilly and Co.) for X-ray crystallography, and Dr. Michael A. Watkins (Eli Lilly and Co.) for helpful discussions.

■ REFERENCES

(1) For a review on [^{18}F]fluoropyridines, see: Dollé, F. *Curr. Pharm. Des.* **2005**, *11*, 3221.

(2) (a) McCarron, J. A.; Pike, V. W.; Halldin, C.; Sandell, J.; Sóvágó, J.; Gulyas, B.; Cselényi, Z.; Wikström, H. V.; Marchais-Oberwinkler, S.; Nowicki, B.; Dollé, F.; Farde, L. *Mol. Imaging Biol.* **2004**, *6*, 17. (b) Pike, V. W. *Trends Pharmacol. Sci.* **2009**, *30*, 431.

(3) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; Petrov, V. A., Ed.; John Wiley & Sons: Hoboken, 2009.

(4) (a) Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956. (b) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 10139.

(5) (a) Sun, H.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2720. (b) Fukuhara, T.; Yoneda, N.; Suzuki, A. *J. Fluorine Chem.* **1988**, *38*, 435. (c) Kuduk, S. D.; DiPardo, R. M.; Bock, M. G. *Org. Lett.* **2005**, *7*, 577.

(6) (a) Dolci, L.; Dollé, F.; Jubeau, S.; Vaufrey, F.; Crouzel, J. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 975. (b) Karramkam, M.; Hinnen, F.; Vaufrey, F.; Dollé, F. *J. Labelled Compd. Radiopharm.* **2003**, *46*, 979.

(7) For selected examples, see: (a) Olberg, D. E.; Arukwe, J. M.; Grace, D.; Hjelstuen, O. K.; Solbakken, M.; Kindberg, G. M.; Cuthbertson, A. *J. Med. Chem.* **2010**, *53*, 1732. (b) Dollé, F.; Dolci, L.; Valette, H.; Hinnen, F.; Vaufrey, F.; Guenther, I.; Fuseau, C.; Coulon, C.; Bottlaender, M.; Crouzel, C. *J. Med. Chem.* **1999**, *42*, 2251. (c) Ding, Y.-S.; Liu, N.; Wang, T.; Marecek, J.; Garza, V.; Ojima, I.; Fowler, J. S. *Nucl. Med. Biol.* **2000**, *27*, 381.

(8) See two reviews: (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (b) Liu, C.; Luo, J.; Xu, L.; Huo, Z. *ARKIVOC* **2013**, *2013*, 154. Other references: (c) Yin, J. J.; Xiang, B. P.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554. (d) Keith, J. M. *J. Org. Chem.* **2008**, *73*, 327. (e) Keith, J. M. *J. Org. Chem.* **2010**, *75*, 2722. (f) Londregan, A. T.; Jennings, S.; Wei, L. Q. *Org. Lett.* **2010**, *12*, 5254. (g) Londregan, A. T.; Jennings, S.; Wei, L. Q. *Org. Lett.* **2011**, *13*, 1840. (h) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Org. Lett.* **2013**, *15*, 792. (i) Farrell, R. P.; Silva Elipe, M. V.; Bartberger, M. D.; Tedrow, J. S.; Vounatsos, F. *Org. Lett.* **2013**, *15*, 168.

(9) The direct conversion of pyridine *N*-oxides into 2-fluoropyridines is not well precedented and requires harsh reaction conditions; see: (a) Phosgene, NMe_3 gas and anhydrous HF at 10 bar, 120 °C: Rivadeneira, E.; Jelich, K. Eur. Patent EP0619307, 1994. (b) Low-yielding deoxyfluorination: Nakatsuka, S.; Okazaki, T.; Nakatsuka, M.; Nagata, T. JP Patent JP/2001/342177, 2001.

(10) (a) Rivadeneira, E.; Jelich, K. Eur. Patent EP 556683, 1993. (b) Rivadeneira, E.; Jelich, K. U.S. Patent US 5502194, 1996. (c) Johansson, A.; Svensson, T. Patent WO/2001/070730, 2001.

(11) Treatment of 2-phenylpyridine *N*-oxide with various deoxyfluorination reagents did not result in the formation of 2-fluoro-6-phenylpyridine

(12) Chloride ion is believed to result from a dichloromethane−trimethylamine adduct. See: Almarzoqi, B.; George, A. V.; Isaacs, N. S. *Tetrahedron* **1986**, *42*, 601.

(13) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.

(14) T807 is also known as AV-1451. For references, see: (a) Xia, C.-F.; Arteaga, J.; Chen, G.; Gangadharmath, U.; Gomez, L. F.; Kasi, D.; Lam, C.; Liang, Q.; Liu, C.; Mocharla, V. P.; Mu, F.; Sinha, A.; Su, H.; Szardenings, A. K.; Walsh, J. C.; Wang, E.; Yu, C.; Zhang, W.; Zhao, T.; Kolb, H. C. *Alzheimer's Dementia* **2013**, *9*, 666. (b) Chien, D. T.; Bahri, S.; Szardenings, A. K.; Walsh, J. C.; Mu, F.; Su, M.-Y.; Shankle, W. R.; Elizarov, A.; Kolb, H. C. *Alzheimer's Dis.* **2013**, *34*, 457.

(15) Damont, A.; Boisgard, R.; Kuhnast, B.; Lemée, F.; Raggiri, G.; Scarf, A. M.; Da Pozzo, E.; Selleri, S.; Martini, C.; Tavitian, B.; Kassiou, M.; Dollé, F. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4819.

(16) Vasdev, N.; Cao, P.; van Oosten, E. M.; Wilson, A. A.; Houle, S.; Hao, G.; Sun, X.; Slavine, N.; Alhasan, M.; Antich, P. P.; Bonte, F. J.; Kulkarni, P. *MedChemComm* **2012**, *3*, 1228.

(17) (a) Brooks, A. F.; Topczewski, J. J.; Ichiishi, N.; Sanford, M. S.; Scott, P. J. H. *Chem. Sci.* **2014**, *5*, 4545. (b) Campbell, M. G.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 474.

(18) Attardo, G.; Lister-James, J. Lim, N. A. C.; Xiong, H. Patent WO 2015/047902 A1, 2015.

(19) Attempts to synthesize **5** by methylation of the *N,N*-(dimethylamino)pyridine derivative resulted in methylation of the carboline core. See the Supporting Information for full details.

DOI: 10.1021/acs.orglett.5b01703
Org. Lett. 2015, 17, 3726−3729