Regioselective Metalation of Fluoroanilines. An Application to the Synthesis of Fluorinated Oxazolidinone Antibacterial Agents[1]

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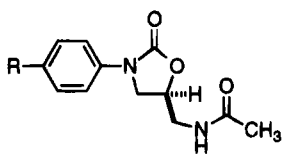
The regioselective *para* lithiation of 3-fluoro- and 3,5-difluoroaniline stabase derivatives is described. These intermediates were subjected to a reaction sequence involving (1) transmetalation with zinc chloride, (2) a palladium-catalyzed coupling reaction with various pyridyl bromides, and (3) removal of the stabase protecting group, to generate fluorinated 4-(pyridyl)anilines. These compounds are key subunits for the synthesis of selected fluorinated oxazolidinone antibacterial agents. Representative applications of these intermediates to the synthesis of three potent oxazolidinone analogues are discussed. One facet of the described procedure involves a unique iodocyclocarbamation reaction featuring a pyridine additive.

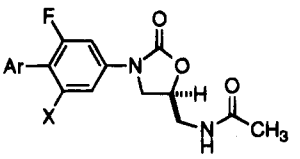
Introduction

The oxazolidinones, exemplified by DuP 721 (**1**), are a relatively new class of orally active, totally synthetic antibacterial agents.[2] Their spectrum of activity encompasses Gram-positive aerobic bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), and anaerobic organisms.[3] Preliminary inquiries into the mechanism of action of the oxazolidinones revealed that they are bacterial protein synthesis inhibitors, with inhibition occurring at an early event in the initiation phase of protein synthesis.[4]

In contemplating possible targets in this area, we were cognizant of additional investigations into the structure–activity relationships of these compounds by workers at DuPont which resulted in more potent analogues (**2**), incorporating aromatic substituents at the *para* position of the phenyloxazolidinone ring system.[5] Taken together with the earlier observation of improved potency for analogues with electron-withdrawing groups at the *para* position (e.g. the acetyl group of **1**), we speculated that the small but highly electronegative fluorine atom would be sterically tolerated at the *meta* position(s) of the phenyl ring (e.g. **3**) and confer enhanced antibacterial activity to these compounds.[6]

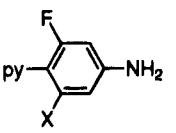


1: R = $COCH_3$
2: R = Ar



3: X = H, F

Since effective procedures were available to elaborate substituted anilines to the corresponding phenyloxazolidinones (*vide infra*), our initial focus was to prepare arylfluoroanilines. We were especially interested in analogues wherein the appended aryl group was a pyridyl moiety, with its attendant basic site for forming water-soluble salts, and so the initial anilines targeted are represented by structures **4** and **5**.



4: py = 3-pyridyl
5: py = 4-pyridyl

a: X = H
b: X = F

At first glance, an obvious solution might involve the simple nitration/reduction of either **6a** or **6b**. In the case of **6a**, a subsequent Stille- or Suzuki-type coupling reaction[7,8] would be required to furnish difluoro examples of the desired intermediates **4** or **5**. Unfortunately, an examination of the literature revealed that **6a** and **6b** both undergo nitration exclusively *ortho* to the fluorine substituent to provide **7a** and **7b**, respectively (eq 1).[9] This result is inappropriate for the construction of the pyridylanilines **4** or **5**.

† Medicinal Chemistry Research.
‡ Physical and Analytical Chemistry.
⊗ Abstract published in *Advance ACS Abstracts,* July 15, 1995.

(1) A preliminary account of this work has been presented: Grega, K. C.; Barbachyn, M. R.; Brickner, S. J.; Mizsak, S. A. *Abstracts of Papers*, 206th National Meeting of the American Chemical Society, Chicago, IL, August, 1993; American Chemical Society: Washington, DC, 1993; ORGN 198.

(2) Gregory, W. A.; Brittelli, D. R.; Wang, C.-L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673. Gregory, W. A.; Brittelli, D. R.; Wang, C.-L. J.; Kezar, H. S., III; Carlson, R. K.; Park, C.-H.; Corless, P. F.; Miller, S. J.; Rajagopalan, P.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. *Ibid.* **1990**, *33*, 2569.

(3) Slee, A. M.; Wuonola, M. A.; McRipley, R. J.; Zajac, I.; Zawada, M. J.; Bartholomew, P. T.; Gregory, W. A.; Forbes, M. *Antimicrob. Agents Chemother.* **1987**, *31*, 1791.

(4) Eustice, D. C.; Feldman, P. A.; Zajac, I.; Slee, A. M. *Antimicrob. Agents Chemother.* **1988**, *32*, 1218.

(5) Carlson, R. K.; Park, C.-H.; Gregory, W. A. U. S. Patents 5 130 316, 1992, and 5 254 577, 1993. Brumfitt, W.; Hamilton-Miller, J. M. T. *Diagn. Microbiol. Infect. Dis.* **1992**, *15*, 621.

(6) During the course of these investigations, oxazolidinones bearing multiple substituents on their phenyl ring, including fluorinated derivatives, were disclosed: Park, C.-H.; Brittelli, D. R.; Wang, C. L.-J.; Marsh, F. D.; Gregory, W. A.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1992**, *35*, 1156. The analogues disclosed, as well as the procedures used to synthesize them, are distinct from those described in this paper. Interestingly, a blanket statement by Park and co-workers that 3,4,5-trisubstituted phenyloxazolidinones "are devoid of antibacterial activity" has been shown to be erroneous for the 4-(pyridyl)-3,5-difluorophenyloxazolidinone series described herein.

(7) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(8) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.

(9) Gilligan, P. J.; McGuirk, P. R.; Witty, M. J. U. S. Patents 4 623 650, 1986 and 4 636 506, 1987.

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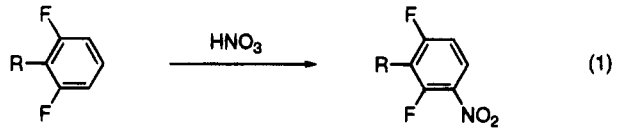


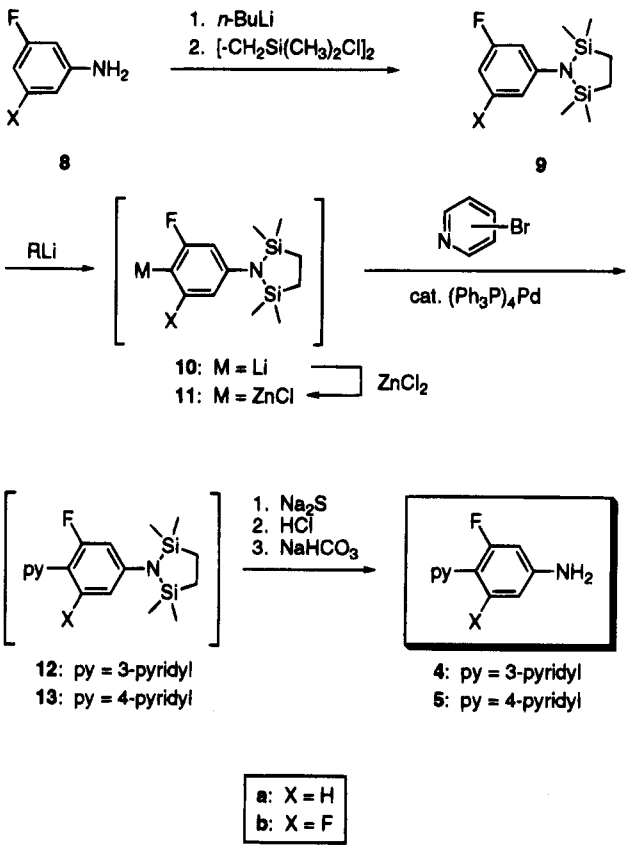
(1)

6a: R = Br
6b: R = 3-pyridyl

7a: R = Br
7b: R = 3-pyridyl

In order to circumvent the regioselectivity problems associated with the nitration approach, we opted to pursue an alternative strategy involving, as its key step, a fluorine-directed *ortho* metalation.[10] We envisioned a one-pot reaction sequence involving (1) fluorine-directed *ortho* lithiation, (2) transmetalation with zinc chloride, and (3) a palladium-mediated coupling with 3- and 4-bromopyridine.[11] Commercially available 3-fluoro- and 3,5-difluoroaniline (**8a** and **8b**, respectively, Scheme 1) appeared to be suitable starting materials. Our expectation was that appropriate protection of the amino group of these compounds would allow for deprotonation *para* to the protected nitrogen. An awareness of the propensity of some protected anilines, especially amide and carbamate derivatives,[12] to facilitate *ortho* metalation led us to explore the utility of the "stabase" protecting group.[13] We felt that the electronic and steric characteristics of the stabase derivative **9** would permit generation of the desired *para* lithio derivative **10**. Subsequent transformations would then afford the key intermediates **4** or **5** and ultimately examples of the targeted fluorinated oxazolidinone antibacterial agents **3**.

Scheme 1



Results and Discussion

The fluorinated anilines **8a,b** were treated with 2.1 equiv of *n*-BuLi in THF (−78 °C) and then 1,2-bis(chlorodimethylsilyl)ethane to give the corresponding stabase derivatives **9a,b** (Scheme 1). While crude **9a,b** were reasonably clean by ^{1}H NMR analysis, they were rigorously purified by vacuum sublimation prior to conducting subsequent chemical transformations. In this way, crystalline **9a** and **9b** were obtained in 81% and 65% yield, respectively.

We next examined what can be considered the key step in the preparation of the pivotal intermediates **4** and **5**. To this end, compound **9b** was reacted with *n*-BuLi in THF (−78 °C) to regioselectively generate the lithiated intermediate **10b**, as subsequent events would demonstrate (*vide infra*). The addition of anhydrous zinc chloride then afforded the organozinc species **11b**. Treatment of **11b** with 4-bromopyridine and catalytic tetrakis(triphenylphosphine)palladium(0), followed by warming to reflux temperature, smoothly led to the coupled product **13b**. Due to difficulties in obtaining **13b** (and the subsequent derivative **5b**) free of any zinc salts, we eventually determined that a workup involving the addition of aqueous sodium sulfide to the cooled reaction mixture allowed for easy removal of the zinc contaminant via a simple filtration of the resultant zinc sulfide precipitate. Since we anticipated stability problems with the stabase protecting group, it was conveniently removed at this point by treating the filtrate with 1 N HCl. Neutralization with $NaHCO_3$ then provided the targeted 4-(4-pyridyl)-3,5-difluoroaniline (**5b**) in 94% overall yield. The other possible regioisomer was not observed. Employing essentially identical procedures, **9b** was also converted to the corresponding 3-pyridyl congener **4b** in 72% yield after chromatographic purification. In the monofluoro series, starting with stabase derivative **9a**, it was found that *sec*-BuLi was required to reliably effect the initial deprotonation to **10a**. However, the remaining synthetic steps were directly analogous to those described above. In this way, 4-(4-pyridyl)-3-fluoroaniline (**5a**) was obtained in 69% isolated yield. Again, only a single regioisomer was detected.

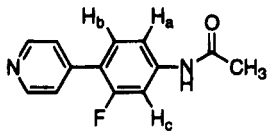
The regioselectivity of the deprotonation/transmetalation/coupling sequence was unequivocally ascertained by an examination of the ^{1}H NMR and ^{19}F NMR spectra of the acetylated derivatives **14a,b** (Figure 1). The simplified coupling patterns seen in the spectra of compound **14b** are consistent only with the indicated symmetrical structure. The ^{1}H NMR spectrum of **14a** clearly reveals the presence of only two vicinal protons on the phenyl ring, consistent with functionalization *para* to the stabase-protected amino group. If deprotonation had occurred in the undesired sense, between the fluorine and protected nitrogen substituents, then three vicinal protons would have been present in the derived product.

(10) Gilman H.; Soddy, T. S. *J. Org. Chem.* **1957**, *22*, 1715.

(11) For a general discussion of palladium-catalyzed coupling reactions involving organozinc reagents see: Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

(12) The *ortho* lithiation of *N*-pivaloyl- and *N*-(*tert*-butoxycarbonyl)-3-fluoroaniline with *n*-butyllithium and *tert*-butyllithium, respectively, has been reported: Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, *47*, 2804. Not only does the metalation occur in the wrong regiochemical sense to be of utility for the synthesis of the targeted oxazolidinone antibacterial agents, but the generated aryllithium intermediate further reacts to form a transient benzyne which is then attacked by the neighboring amide or carbamate anion to form a lithiated benzoxazole.

(13) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787. A paper describing novel chromatographically stable tetraethyldisilaisoindoline (TEDI) derivatives of primary amines has recently appeared: Davis, A. P.; Gallagher, P. *J. Tetrahedron Lett.* **1995**, *36*, 3269. This work may enhance the utility of the stabase chemistry described herein. The authors thank the reviewer for pointing out this reference.



14a ^{19}F NMR

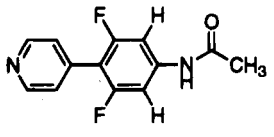
δ -119 (dd, $J_{F\text{-}Hc}$ = 12.1 Hz, $J_{F\text{-}Hb}$ = 8.8 Hz)

^{1}H NMR

δ 7.42 (dd, $J_{Ha\text{-}b}$ = 8.5 Hz, $J_{Ha\text{-}c}$ = 2.0 Hz)

δ 7.58 (dd, $J_{Hb\text{-}a}$ = 8.6 Hz, $J_{Hb\text{-}F}$ = 8.6 Hz)

δ 7.74 (dd, $J_{Hc\text{-}F}$ = 13.5 Hz, $J_{Hc\text{-}a}$ = 2.0 Hz)



14b ^{19}F NMR

δ -116 (d, $J_{F\text{-}H}$ = 10.4 Hz)

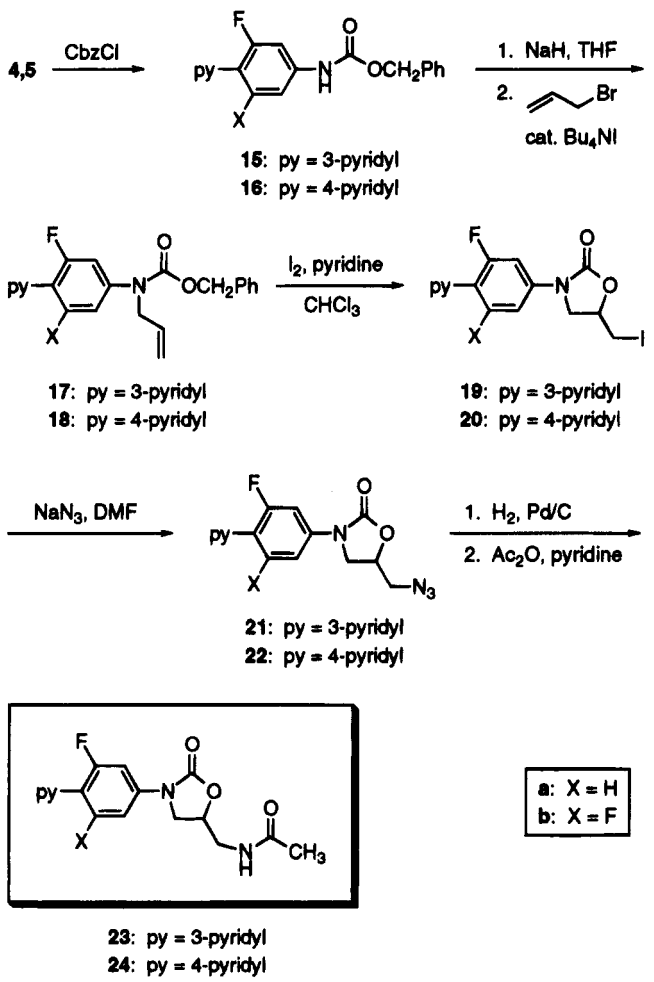
^{1}H NMR

δ 7.41 [d(app)*, $J_{H\text{-}F}$ = 10.6 Hz]

*pseudo first order

Figure 1. Relevant NMR spectral data for **14a,b**.

Scheme 2



Representative applications of the pyridylanilines **4b** and **5a,b** to the synthesis of fluorinated oxazolidinone antibacterial agents are depicted in Scheme 2.[1] For example, compound **5b** was first converted to its Cbz derivative **16b** in 87% yield. *N*-Allylation of **16b** was accomplished through the action of sodium hydride and allyl bromide (catalytic Bu_4NI, THF) to give a 70% isolated yield of **18b**. In the key step in this synthetic sequence, we subjected **18b** to standard iodocyclocarbamation reaction conditions (I_2, chloroform)[14] in an attempt to prepare the 5-(iodomethyl)oxazolidinone **20b**. Disappointingly, none of the desired product was observed. Apparently the benzyl iodide byproduct generated in this reaction alkylates the pyridyl appendage of **18b** and/or **20b**.[17] The addition of a suitable benzyl iodide scavenger, namely excess pyridine, proved to be a reasonable solution to this problem and enabled the reaction to proceed in the desired sense.[15] Employing this modification, the allylated intermediate **18b** was converted to the oxazolidinone **20b** in 49% yield after chromatographic purification. The related examples **18a** and **17b** were found to undergo this modified iodocyclocarbamation reaction in 65% and 49% yield, respectively. The iodide **20b** was converted to the corresponding azide **22b** by treatment with sodium azide in DMF (78–82% yield after chromatography). Catalytic hydrogenation of the azido group of **22b**, followed by acetylation of the resultant amine, afforded the targeted racemic *N*-[4-(4-pyridyl)-3,5-difluorophenyl]oxazolidinone **24b** (U-93936) in 94% yield. Employing essentially identical procedures, intermediates **5a** and **4b** were converted to the closely related analogues **24a** (U-95494) and **23b** (U-93447), respectively. The fluorinated oxazolidinones **23b** and **24a,b** exhibit potent *in vitro* and *in vivo* activity against aerobic Gram-positive bacteria and anaerobic organisms.[16] When compared to the corresponding desfluoro congeners, the mono- and difluorinated variants described herein provide enhanced *in vivo* efficacy.

Conclusions

Reliable methodology for the regioselective *para* lithiation of stabase-protected 3-fluoro- and 3,5-difluoroanilines has been developed. Elaboration of these lithiated intermediates through a reaction sequence involving transmetalation, palladium-mediated coupling, and deprotection affords fluorinated pyridylanilines. These compounds are key intermediates for the preparation of oxazolidinone antibacterial agents, as shown in the syntheses of **23b** and **24a,b**. An important facet of the synthetic protocol was the development of new iodocyclocarbamation reaction conditions, featuring a pyridine additive, to accommodate pyridyl-substituted derivatives. Efforts directed at elucidating the generality of this modified iodocyclocarbamation reaction[15] and further investigations probing the potentiating effect of fluorine

(14) For a description of the first reported iodocyclocarbamation reaction see: Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956. For other important work in this area see: Takano, S.; Hatakeyama, S. *Heterocycles* **1982**, *19*, 1243. Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619. Overman, L. E.; McCready, R. J. *Ibid.* **1982**, *23*, 4887. Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654. Kobayashi, S.; Isobe, T.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079. Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1987**, *43*, 2505. To our knowledge, there has been only one report of an iodocyclocarbamation reaction involving an *N*-aryl carbamate: Brickner, S. J. European Patent Application WO 90/02744, 1990.

(15) A manuscript describing a comprehensive study of the iodocyclocarbamation reaction is under preparation: Brickner, S. J. *et al.*

(16) Unpublished results provided by G. E. Zurenko, R. D. Schaadt, B. H. Yagi, J. W. Allison, C. W. Ford, J. C. Hamel, J. C. Lee and D. Stapert. Also see Barbachyn, M. R.; Brickner, S. J. European Patent Application WO 93/09103, 1993.

(17) Empirical observations to be reported later[15] indicate that a benzyl oxonium ion (postulated as an intermediate in the iodocyclization reaction) may also be the reactive alkylating agent.

on the activity of the oxazolidinones will be reported in due course.

Experimental Section

Melting points were determined on a capillary apparatus and are uncorrected. ^1H NMR spectra were recorded at 300 or 400 MHz in $CDCl_3$ or CD_3OD. ^{19}F NMR spectra were recorded at 282 MHz in CD_3OD. All moisture-sensitive reactions were conducted under a nitrogen atmosphere in oven- or flame-dried glassware. Unless specified, all commercially available solvents and reagents were used without further purification. Anhydrous zinc chloride was prepared by fusing commercially available material under high vacuum. THF was distilled under nitrogen from sodium benzophenone ketyl prior to use. Brine refers to a saturated aqueous sodium chloride solution. Solvent removal was accomplished by a rotary evaporator operating at house vacuum (40–50 Torr). Crude products were purified by column chromatography over silica gel (EM Science, 230–400 mesh ASTM). Alternatively, smaller scale purifications were accomplished by preparative TLC (Analtech silica gel GF plates, 20 × 20 cm, 1000 μm) or radial chromatography (Analtech silica gel GF radial plate, 1000 μm). Silica gel (Analtech silica gel GF, 1 × 3 in., 250 μm thickness) or C-18 reversed-phase (Whatman $MKC_{18}F$, 1 × 3 in., 200 μm thickness) plates were utilized for TLC analyses.

***N,N*-[1,2-Bis(dimethylsilyl)ethane]-3-fluoroaniline (9a).** A solution of 8.65 mL (90.0 mmol) of 3-fluoroaniline in 180 mL of anhydrous THF was placed under an atmosphere of N_2, cooled in a dry ice–2-propanol bath and stirred mechanically. To the cold solution was slowly added 118 mL (189 mmol, 2.1 equiv) of *n*-BuLi (1.6 M in hexanes). The temperature of the reaction mixture was kept below −40 °C during the addition. The reaction mixture was allowed to stir at −70 °C for 20 min after the addition was complete. After this time, 19.5 g (90.0 mmol) of 1,2-bis(chlorodimethylsilyl)ethane in 180 mL of anhydrous THF was added dropwise. The homogenous solution was allowed to stir for an additional 45 min and then warmed to room temperature. The reaction mixture was carefully diluted with 250 mL of H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an amber oil. Purification by vacuum sublimation (5 mmHg, 30 °C, cold finger at −35 °C) gave 18.3 g (81%) of the title product as a colorless oil (white solid at −35 °C): FTIR (liquid) 2955, 1606, 1581, 1489, 1288, 1254, 1154, 1009, 867, 783 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (dd, J = 7.2, 8.3, 1H), 6.71 (dd, J = 3.1, 8.3, 1H), 6.68 (d, J = 7.2, 1H), 6.66–6.60 (m, 1H), 0.94 (s, 4H), 0.29 (s, 12H); MS (EI) 253 (M^+, 29), 238 (100), 210 (11), 145 (5), 115 (5), 73 (11); HRMS calcd for $C_{12}H_{20}FNSi_2$ 253.1118, found 253.1114.

***N,N*-[1,2-Bis(dimethylsilyl)ethane]-3,5-difluoroaniline (9b).** A solution of 8.64 g (66.9 mmol) of 3,5-difluoroaniline in 135 mL of anhydrous THF was placed under an atmosphere of N_2, cooled in a dry ice–2-propanol bath, and stirred mechanically. To the cold solution was slowly added 87.8 mL (141 mmol, 2.1 equiv) of *n*-BuLi (1.6 M in hexanes). The temperature of the reaction mixture was kept below −40 °C during the addition. The reaction mixture was allowed to stir at −70 °C for 20 min after the addition was complete. After this time, 14.4 g (66.9 mmol) of 1,2-bis(chlorodimethylsilyl)-ethane in 135 mL of anhydrous THF was added dropwise. The homogenous solution was allowed to stir for an additional 45 min and then warmed to room temperature. The reaction mixture was carefully diluted with 200 mL of H_2O and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a tan, waxy solid (19.6 g). Purification by vacuum sublimation (5 mmHg, 40 °C, cold finger at −35 °C) gave 11.8 g (65%) of the title product as a white solid: mp 71–72 °C; FTIR (neat) 2958, 2928, 1626, 1581, 1476, 1453, 1345, 1248, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.36 (dd, J = 2.1, 8.1, 2H), 6.29 (dd, J = 2.1, 9.0, 1H), 0.85 (s, 4H), 0.25 (s, 12H); MS (EI) 271 (M^+, 28), 256 (100), 228 (11), 73 (10). Anal. Calcd for $C_{12}H_{19}F_2NSi_2$: C, 53.10; H, 7.05; N, 5.16. Found: C, 52.37; H, 7.22; N, 4.97.

4-(3-Pyridyl)-3,5-difluoroaniline (4b). A solution of 4.00 g (14.8 mmol) of the stabase-protected aniline **9b** in 40 mL of anhydrous THF was placed under an atmosphere of N_2 and cooled in a dry ice–2-propanol bath. To the stirred, cold solution was slowly added 11.1 mL (17.7 mmol, 1.2 equiv) of *n*-BuLi (1.6 M in hexanes). After the addition was complete, the yellow reaction solution was allowed to stir for an additional 4 h at −78 °C. After this time, 17.7 mL (17.7 mmol, 1.2 equiv) of $ZnCl_2$ (1.0 M in THF) was added. The reaction mixture was allowed to warm to room temperature, whereupon 513 mg (0.444 mmol, 0.03 equiv) of $Pd(PPh_3)_4$ in 25 mL of THF was added followed by 2.00 mL (20.7 mmol, 1.4 equiv) of 3-bromopyridine. The reaction mixture was degassed by repeated evacuation and filling with N_2. The reaction solution was then heated to reflux temperature for 4 h. After this time, the reaction mixture was cooled to room temperature, treated with 7.10 g (29.6 mmol, 2 equiv) of Na_2S in 20 mL of H_2O, and allowed to stir for 20 min. After this time, the resulting solids were removed by filtration. The solvent was removed under reduced pressure, and the remaining oil was vigorously stirred in 110 mL of 1 N HCl for 0.5 h and then washed with Et_2O. The aqueous layer was neutralized with $NaHCO_3$(s). The resulting white precipitate was collected via filtration and dried *in vacuo*. Purification by silica gel chromatography (eluted with 15% $CH_3CN/CHCl_3$) gave 2.20 g (72%) of the title product as a white solid: mp 141–142 °C; FTIR (mineral oil mull) 3141, 1634, 1460, 1164, 1012, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.67 (s, 1H), 8.55 (dd, J = 1.7, 4.9, 1H), 7.78–7.72 (m, 1H), 7.35 (ddd, J = 0.8, 4.9, 7.8, 1H), 6.31 (ddd, J = 1.5, 3.7, 9.8, 2H), 4.01 (br s, 2H); MS (EI) 206 (M^+, 100), 179 (5), 158 (4), 89 (4). Anal. Calcd for $C_{11}H_8F_2N_2$: C, 64.08; H, 3.91; N, 13.59. Found: C, 63.92; H, 3.74; N, 13.24.

4-(4-Pyridyl)-3-fluoroaniline (5a). A solution of 4.00 g (15.8 mmol) of the stabase-protected aniline **9a** in 120 mL of anhydrous THF was placed under an atmosphere of N_2 and cooled in a dry ice–2-propanol bath. To the stirred, cold solution was slowly added 14.6 mL (19.0 mmol, 1.2 equiv) of *sec*-BuLi (1.3 M in cyclohexane). After the addition was complete, the yellow reaction solution was allowed to stir for an additional 4 h at −78 °C. After this time, 19.0 mL (19.0 mmol, 1.2 equiv) of $ZnCl_2$ (1.0 M in THF) was added. The reaction mixture was allowed to warm to room temperature, whereupon 1.83 g (1.58 mmol, 0.1 equiv) of $Pd(PPh_3)_4$ in 120 mL of THF was added followed by 3.00 g (19.0 mmol, 1.2 equiv) of 4-bromopyridine in 20 mL of THF. The reaction mixture was degassed by repeated evacuation and filling with N_2. The reaction solution was then heated to reflux temperature for 16 h. After this time, the reaction mixture was cooled to room temperature, treated with 8.88 g (37.0 mmol, 2 equiv) of Na_2S in 25 mL of H_2O and allowed to stir for 20 min. After this time, the resulting solids were removed by filtration. The solvent was removed under reduced pressure, and the remaining oil was vigorously stirred in 110 mL of 1 N HCl for 0.5 h and then washed with Et_2O. The aqueous layer was neutralized with $NaHCO_3$(s). The resulting yellow precipitate was collected via filtration and dried *in vacuo* to give 2.06 g (69%) of the title product. An analytical sample was prepared by radial chromatography on silica gel (eluted with 6% $CH_3CN/CHCl_3$) to give a yellow solid: mp 140–142 °C; FTIR (mineral oil mull) 3472, 3317, 1623, 1595, 1288, 1133, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.60 (d, J = 5.4, 2H), 7.44 (ddd, J = 1.5, 1.5, 4.6, 2H), 7.29 (d, J = 8.0, 1H), 6.54 (dd, J = 2.3, 8.0, 1H), 6.48 (dd, J = 2.3, 8.0, 1H), 3.93 (br s, 2H); MS (EI) 188 (M^+, 100), 161 (6), 135 (11), 107 (5), 80 (5). Anal. Calcd for $C_{11}H_9FN_2$: C, 70.20; H, 4.82; N, 14.88. Found: C, 70.08; H, 4.87; N, 14.70.

***N*-Acetyl-4-(4-pyridyl)-3-fluoroaniline (14a).** To a solution of 100 mg (0.532 mmol) of the starting amine **5a** in 10 mL of CH_2Cl_2 was added 52 μL (0.64 mmol, 1.2 equiv) of pyridine followed by 60 μL (0.64 mmol) of Ac_2O. The reaction mixture was allowed to stir at rt under an atmosphere of N_2. After 1 h, the reaction mixture was washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a yellow solid. Purification by silica gel chromatography (eluted with 1–3% $MeOH/CHCl_3$) gave 109 mg (94%) of the title compound as a white solid: mp 239–240 °C; FTIR (mineral oil mull) 1695, 1605, 1489, 1323, 1125, 1000,

863, 765 cm^{-1}; ^{1}H NMR (CD_3OD) δ 8.60–8.58 (m, 2H), 7.74 (dd, J = 2.0, 13.5, 1H), 7.66–7.64 (m, 2H), 7.58 (dd, J = 8.6, 8.6, 1H), 7.42 (dd, J = 2.0, 8.5, 1H), 2.17 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −119 (dd, J = 8.8, 12.1); MS (EI) 230 (M^+, 41), 188 (100), 161 (4), 133 (4), 42 (16). Anal. Calcd for $C_{13}H_{11}FN_2O$: C, 67.82; H, 4.82; N, 12.17. Found: C, 67.21; H, 4.82; N, 12.06.

4-(4-Pyridyl)-3,5-difluoroaniline (5b). A solution of 60.0 g (0.221 mol) of the stabase-protected aniline **9b** in 560 mL of anhydrous THF was placed under an atmosphere of N_2 and cooled in a dry ice–2-propanol bath. To the stirred, cold solution was slowly added 166 mL [0.266 mol, 1.2 equiv of *n*-BuLi (1.6 M in hexanes)]. After the addition was complete, the yellow reaction solution was allowed to stir for an additional 4 h at −78 °C. After this time, 266 mL (0.266 mol) of $ZnCl_2$ (1.0 M in THF) was added. The reaction mixture was allowed to warm to room temperature, whereupon 7.68 g (6.60 mmol, 0.03 equiv) of $Pd(PPh_3)_4$ in 200 mL of THF was added followed by 49.0 g (0.310 mol, 1.4 equiv) of 4-bromopyridine in 100 mL of THF. The reaction mixture was degassed by repeated evacuation and filling with N_2. The reaction solution was then heated to reflux temperature for 4 h. After this time, the reaction mixture was cooled to room temperature, treated with 106 g (0.442 mol, 2 equiv) of Na_2S in 300 mL of H_2O, and allowed to stir for 30 min. After this time, the resulting solids were removed by filtration. The solvent was removed under reduced pressure and the remaining oil was vigorously stirred in 1.6 L of 1 N HCl for 0.5 h and then washed with Et_2O. The aqueous layer was then neutralized with $NaHCO_3$(s). The resulting yellow precipitate was collected via filtration and dried *in vacuo* to give 43.0 g (94%) of the title compound as a yellow solid. An analytical sample was prepared by preparative TLC on silica gel (eluted with 10% $CH_3CN/CHCl_3$) and was recovered as a yellow solid: mp 156–158 °C; FTIR (mineral oil mull) 3447, 1655, 1602, 1417, 1165, 1013, 830, 628 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.63 (dd, J = 1.6, 4.6, 2H), 7.38 (dd, J = 1.7, 4.7, 2H), 6.30 (ddd, J = 6.6, 8.7, 10.3, 2H), 4.06 (br s, 2H); MS (EI) 206 (M^+, 100), 179 (6), 166 (7), 153 (12), 103 (4), 89 (7). Anal. Calcd for $C_{11}H_8F_2N_2$: C, 64.08; H, 3.91; N, 13.59. Found: C, 63.92; H, 3.69; N, 13.40.

***N*-Acetyl-4-(4-pyridyl)-3,5-difluoroaniline (14b).** To a solution of 100 mg (0.485 mmol) of the starting amine **5b** in 10 mL of CH_2Cl_2 was added 47 μL (0.58 mmol, 1.2 equiv) of pyridine followed by 55 μL (0.58 mmol) of Ac_2O. The reaction mixture was allowed to stir at rt under an atmosphere of N_2. After 1 h, the reaction mixture was washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow solid. Purification by preparative TLC on silica gel (eluted with 10% $MeOH/CHCl_3$) gave 84 mg (70%) of the title compound as a white solid: mp 199–201 °C; FTIR (mineral oil mull) 3338 (br), 1684, 1604, 1410, 1298, 1027, 851 cm^{-1}; ^{1}H NMR (CD_3OD) (*pseudo first order) δ 8.63–8.60 (m, 2H), 7.54–7.52 (m, 2H), 7.41 (app d*, J = 10.6, 2H), 2.16 (s, 3H); ^{19}F NMR (CD_3OD) δ −116 (d, J = 10.4); MS (EI) 248 (M^+, 45), 206 (100), 179 (6), 153 (6), 79 (25), 52 (16), 42 (34). Anal. Calcd for $C_{13}H_{10}F_2N_2O$: C, 62.90; H, 4.06; N, 11.28. Found: C, 61.99; H, 4.10; N, 10.97.

***N*-(Benzyloxycarbonyl)-4-(3-pyridyl)-3,5-difluoroaniline (15b).** A mixture of 110 mL of anhydrous THF, 2.20 g (10.7 mmol) of the starting amine **4b** and 1.62 g (11.7 mmol, 1.10 equiv) of powdered K_2CO_3 was stirred under an atmosphere of N_2 and treated with 1.76 mL (12.3 mmol, 1.15 equiv) of benzyl chloroformate. After 2 h at room temperature, the reaction mixture was diluted with 200 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$, followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a white solid. Purification by silica gel chromatography (eluted with 3–5% $CH_3CN/CHCl_3$) gave 3.18 g (87%) of the title compound as a white solid: mp 188–190 °C; FTIR (neat) 3030, 1737, 1642, 1478, 1408, 1231, 1029, 723 cm^{-1}; ^{1}H NMR($CDCl_3$) δ 8.59 (br s, 1H), 8.53–8.51 (m, 1H), 7.95–7.92 (m, 1H), 7.56–7.51 (m, 1H), 7.44–7.31 (m, 5H), 7.28 (d, J = 10.4, 2H), 5.21 (s, 2H); MS (EI) 340 (M^+, 21), 296 (5), 232 (4), 205 (2), 91 (100), 79 (3). Anal. Calcd for $C_{19}H_{14}F_2N_2O_2$: C, 67.06; H, 4.15; N, 8.23. Found: C, 67.05; H, 4.10; N, 8.14.

***N*-(Benzyloxycarbonyl)-4-(4-pyridyl)-3-fluoroaniline (16a).** A mixture of 150 mL of anhydrous THF, 2.90 g (15.4 mmol) of the amine **5a**, and 2.34 g (17.0 mmol, 1.10 equiv) of powdered K_2CO_3 was stirred under an atmosphere of N_2 and treated with 2.54 mL (17.7 mmol, 1.15 equiv) of benzyl chloroformate. After 2 h at room temperature, the reaction mixture was washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an orange solid (4.90 g, 98%) that appeared clean by ^{1}H NMR. An analytical sample was prepared by silica gel chromatography (eluted with 5–10% $CH_3CN/CHCl_3$) and was recovered as an off-white solid: mp 144–144.5 °C; FTIR (mineral oil mull) 3332, 1744, 1706, 1624, 1602, 1592, 1561, 1551, 1532, 1250, 1242, 1235, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.65 (d, J = 6.2, 2H), 7.51–7.39 (m, 9H), 7.16 (dd, J = 2.0, 8.4, 1H), 6.98 (s, 1H), 5.24 (s, 2H); MS (EI) 322 (M^+, 10), 214 (32), 108 (11), 107 (10), 91 (100). Anal. Calcd for $C_{19}H_{15}FN_2O_2$: C, 70.80; H, 4.69; N, 8.69. Found: C, 70.29; H, 4.69; N, 8.54.

***N*-(Benzyloxycarbonyl)-4-(4-pyridyl)-3,5-difluoroaniline (16b).** A mixture of 110 mL of anhydrous THF, 2.20 g (10.7 mmol) of the starting amine **5b**, and 1.62 g (11.7 mmol, 1.10 equiv) of powdered K_2CO_3 was stirred under an atmosphere of N_2 and treated with 1.76 mL (12.3 mmol, 1.15 equiv) of benzyl chloroformate. After 2 h at room temperature, the reaction mixture was washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a white solid. Purification by silica gel chromatography (eluted with 3–5% $CH_3CN/CHCl_3$) gave 1.52 g (87%) of the title product as a white solid: mp 185–186 °C; FTIR (neat) 1743, 1642, 1605, 1533, 1254, 839 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.67 (br s, 2H), 7.43–7.38 (m, 7H), 7.15 (d, J = 9.9, 2H), 5.23 (s, 2H); MS (EI) 340 (M^+, 12), 232 (16), 108 (7), 91 (100), 43 (28). Anal. Calcd for $C_{19}H_{14}F_2N_2O_2$: C, 67.06; H, 4.15; N, 8.23. Found: C, 67.11; H, 4.08; N, 8.14.

***N*-Allyl-*N*-(benzyloxycarbonyl)-4-(3-pyridyl)-3,5-difluoroaniline (17b).** A solution of 3.09 g (9.09 mmol) of the Cbz derivative **15b** in 90 mL of anhydrous THF was treated with 400 mg (10.0 mmol, 1.1 equiv) of NaH (60% oil dispersion) under an atmosphere of N_2. After 0.5 h at room temperature, the reaction mixture developed a slightly nonhomogeneous appearance and was then treated with 335 mg (0.909 mmol, 0.1 equiv) of *n*-Bu_4NI followed by 794 μL (9.18 mmol, 1.01 equiv) of allyl bromide. After 1 h at room temperature, the reaction mixture was carefully quenched with 2 mL of H_2O, diluted with 200 mL of CH_2Cl_2, and finally washed with water followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an off-white solid. Purification by silica gel chromatography (eluted with 3–5% $CH_3CN/CHCl_3$) gave 3.33 g (96%) of the title compound as a white solid: mp 92–93 °C; FTIR (mineral oil mull) 3068, 3061, 1710, 1705, 1643, 1635, 1412, 1263, 1024, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.62 (br s, 1H), 7.99 (d, J = 7.8, 1H), 7.42–7.36 (m, 6H), 7.03 (d, J = 9.2, 2H), 5.94 (ddt, J = 5.2, 10.4, 11.7, 1H), 5.23–5.18 (m, 4H), 4.34 (d, J = 5.4, 2H); MS (EI) 380 (M^+, 15), 336 (4), 309 (3), 245 (4), 91 (100), 65 (6). Anal. Calcd for $C_{22}H_{18}F_2N_2O_2$: C, 69.47; H, 4.77; N, 7.36. Found: C, 69.38; H, 4.71; H, 7.43.

***N*-Allyl-*N*-(benzyloxycarbonyl)-4-(4-pyridyl)-3-fluoroaniline (18a).** While under a continuous flow of N_2, a slurry containing 4.78 g (14.8 mmol) of the crude starting carbamate **16a** in 150 mL of anhydrous THF was carefully treated portionwise with 653 mg (16.3 mmol, 1.1 equiv) of NaH (60% oil dispersion). The reaction mixture developed a purple coloration as deprotonation occurred and became homogenous. The solution was stirred for 20 min and was then treated with 548 mg (1.48 mmol, 0.10 equiv) of *n*-Bu_4NI followed by 1.30 mL (15.0 mmol, 1.01 equiv) of allyl bromide. The reaction mixture was allowed to stir at rt for 1 h. After this time, the reaction was carefully quenched with 5 mL of H_2O and then washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a dark amber oil. Purification by silica gel chromatography (eluted with 3–5% $CH_3CN/CHCl_3$) gave 3.58 g (67%, two steps) of the title compound as an amber solid: mp 69–70 °C; FTIR (neat) 3034, 1710, 1621, 1597, 1576, 1519, 1487, 1409, 1395, 1234, 1147 cm^{-1}; ^{1}H NMR ($CDCl^3$) δ 8.68 (dd, J = 1.4, 4.6, 2H), 7.48 (ddd, J = 1.4, 1.4, 4.6, 2H), 7.44 (dd, J = 8.4, 8.4, 1H), 7.39–7.32 (m, 5H), 7.21–7.16 (m, 2H), 5.94 (ddt, J = 5.5, 11.0, 16.4, 1H),

5.24–5.17 (obscured, 2H), 5.22 (s, 2H), 4.35 (ddd, J = 1.4, 1.4, 5.5, 2H); MS (EI) 362 (M^+, 14), 318 (4), 227 (3), 172 (1), 91 (100). Anal. Calcd for $C_{22}H_{19}FN_2O_2$: C, 72.91; H, 5.29; N, 7.73. Found: C, 71.87; H, 5.48; N, 7.51.

***N*-Allyl-*N*-(benzyloxycarbonyl)-4-(4-pyridyl)-3,5-difluoroaniline (18b).** While under a continuous flow of N_2, a slurry containing 66.1 g (0.194 mol) of the starting carbamate **16b** in 1.7 L of anhydrous THF was carefully treated portionwise with 8.55 g (0.214 mol, 1.1 equiv) of NaH (60% oil dispersion). The reaction mixture developed a purple coloration as deprotonation occurred and became homogenous. The solution was stirred mechanically for 20 min and was then treated with 7.16 g (19.4 mmol, 0.10 equiv) of n-Bu_4NI followed by 17.0 mL (0.196 mmol, 1.01 equiv) of allyl bromide. The reaction mixture was allowed to stir at rt for 16 h. After this time, the reaction mixture was carefully quenched with 20 mL of H_2O and then washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a red oil. Purification by silica gel chromatography (eluted with 3–5% $CH_3CN/CHCl_3$) gave 51.0 g (69%) of the title compound as a yellow solid: mp 82–83 °C; FTIR (neat) 1713, 1635, 1598, 1396, 1312, 1235, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.69 (d, J = 5.3, 2H), 7.41–7.33 (m, 7H), 7.03 (d, J = 9.6, 2H), 5.92 (ddt, J = 5.3, 10.4, 15.8, 1H), 5.25–5.17 (m, 4H), 4.34 (d, J = 5.4, 2H); MS (EI) 380 (M^+, 16), 330 (6), 246 (26), 219 (13), 91 (100), 40 (16). Anal. Calcd for $C_{22}H_{18}F_2N_2O_2$: C, 69.47; H, 4.77; N, 7.36. Found: C, 69.42; H, 4.86; N, 7.27.

(±)-5-(Iodomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone (19b). A mixture of 25 mL of $CHCl_3$, 496 mg (1.31 mmol) of the starting allyl derivative **17b**, 1.58 mL (19.6 mmol, 15 equiv) of pyridine, and 4.97 g (19.6 mmol) of I_2 was heated to 50 °C with stirring under an atmosphere of N_2. After 1.5 h, stirring was stopped to allow an inhomogeneous sludge to settle. The supernatant was decanted, and the remaining sludge was rinsed twice with $CHCl_3$. The combined supernatants were washed with 20% aqueous sodium thiosulfate followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a yellow foam. Purification by silica gel chromatography (eluted with 0.5–1% MeOH/$CHCl_3$) gave 269 mg (49%) of the title compound as yellow solid: mp 133–134 °C; FTIR (mineral oil mull) 3130, 1758, 1650, 1414, 1241, 1017, 846 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.62 (br s, 1H), 7.79 (d, J = 10.7, 1H), 7.43–7.38 (m, 1H), 7.32 (d, J = 9.9, 2H), 4.84–4.72 (m, 1H), 4.19 (dd, J = 8.9, 8.9, 1H), 3.80 (dd, J = 6.0, 9.2, 1H), 3.51 (dd, J = 3.8, 10.5, 1H), 3.39 (dd, J = 8.2, 10.5, 1H); MS (EI) 416 (M^+, 100), 245 (41), 217 (39), 190 (19), 122 (9). Anal. Calcd for $C_{15}H_{11}F_2N_2O_4$: C, 43.29; H, 2.66; N, 6.73. Found: C, 43.19; H, 2.56; N, 6.59.

(±)-5-(Iodomethyl)-3-[4-(4-pyridyl)-3-fluorophenyl]-2-oxazolidinone (20a). A mixture of 12 mL of $CHCl_3$, 224 mg (0.619 mmol) of the starting allyl derivative **18a**, 2.36 g (9.28 mmol, 15 equiv) of I_2, and 751 μL (9.28 mmol) of pyridine was heated to 50 °C with stirring for 1 h under an atmosphere of N_2. After this time, the reaction mixture was cooled to rt, diluted with 10 mL of $CHCl_3$, and washed with 20% aqueous sodium thiosulfate followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an amber solid. Purification by silica gel chromatography (eluted with 5–15% $CH_3CN/CHCl_3$) gave 20 mg of unreacted starting material and 161 mg (65%, 72% based on recovered starting material) of the title product as an off-white solid: mp 158–159 °C; FTIR (mineral oil mull) 1749, 1626, 1599, 1478, 1407, 1325, 1219, 1199, 807 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.68 (d, J = 6.0, 2H), 7.58 (dd, J = 2.2, 12.9, 1H), 7.52 (dd, J = 8.6, 8.6, 1H), 7.50–7.48 (m, 2H), 7.40 (dd, J = 2.2, 8.6, 1H), 4.82–4.76 (m, 1H), 4.22 (dd, J = 9.0, 9.0, 1H), 3.83 (dd, J = 6.1, 9.1, 1H), 3.52 (dd, J = 3.8, 10.4, 1H), 3.39 (dd, J = 8.3, 10.4, 1H); MS (EI) 398 (M^+, 100), 270 (8), 227 (62), 201 (9), 199 (57), 172 (43), 99 (20). Anal. Calcd for $C_{15}H_{12}FIN_2O_2$: C, 45.25; H, 3.04; N, 7.04. Found: C, 45.10; H, 2.98; N, 6.82.

(±)-5-(Iodomethyl)-3-[4-(4-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone (20b). A mixture of 50 mL of $CHCl_3$, 863 mg (2.27 mmol) of the starting allyl derivative **18b**, 8.65 g (34.1 mmol, 15 equiv) of I_2, and 2.76 mL (34.1 mmol) of pyridine was heated to 50 °C with stirring under an atmosphere of N_2. After 1.5 h, the reaction mixture was cooled to rt, diluted with 100 mL of $CHCl_3$, and washed with 20% aqueous sodium thiosulfate followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to dark amber oil. Purification by silica gel chromatography (eluted with 0.5–1% MeOH/$CHCl_3$) gave 464 mg (49%) of the title product as a yellow solid: mp 175–176 °C; FTIR (mineral oil mull) 1749, 1643, 1406, 1245, 1027, 848, 735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.70 (br s, 2H), 7.44 (d, J = 5.5, 2H), 7.32 (d, J = 10.2, 2H), 4.85–4.73 (m, 1H), 4.19 (dd, J = 9.0, 9.0, 1H), 3.80 (dd, J = 6.1, 9.2, 1H), 3.50 (dd, J = 6.1, 10.5, 1H), 3.40 (dd, J = 8.0, 10.5, 1H); MS (FAB) 417 ($M + H^+$). Anal. Calcd for $C_{15}H_{11}F_2IN_2O_2$: C, 43.29; H, 2.66; N, 6.73. Found: C, 43.18; H, 2.54; N, 6.59.

(±)-5-(Azidomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone (21b). A mixture of 15 mL of DMF, 197 mg (0.474 mmol) of the starting iodide **19b**, and 216 mg (3.32 mmol, 8 equiv) of NaN_3 was heated to 55 °C with stirring under an atmosphere of N_2. After 2 h, the reaction mixture was cooled to rt, diluted with 100 mL of H_2O, and then extracted with EtOAc. The combined organics were washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an amber oil (152 mg, 97% crude yield). The crude azide was suitable for use without further purification. An analytical sample was prepared by preparative TLC on silica gel (eluted with 10% $CH_3CN/CHCl_3$) and was recovered as an off-white solid: mp 97–98 °C; FTIR (mineral oil mull) 3483, 2110, 1746, 1640, 1417, 1237, 1064, 716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.72 (br s, 1H), 8.63 (br s, 1H), 7.79 (d, J = 7.9, 1H), 7.42–7.38 (m, 1H), 7.34 (d, J = 9.9, 2H), 4.90–4.82 (m, 1H), 4.11 (dd, J = 8.9, 8.9, 1H), 3.88 (dd, J = 6.2, 8.9, 1H), 3.77 (dd, J = 4.4, 13.4, 1H), 3.63 (dd, J = 4.1, 13.3, 1H); MS (EI) 331 (M^+, 100), 274 (14), 258 (23), 232 (15), 217 (22), 190 (22), 43 (14). Anal. Calcd for $C_{15}H_{11}F_2N_5O_2$: C, 54.38; H, 3.35; N, 21.14. Found: C, 54.00; H, 3.21; N, 20.90.

(±)-5-(Azidomethyl)-3-[4-(4-pyridyl)-3-fluorophenyl]-2-oxazolidinone (22a). A mixture of 2 mL of DMF, 39 mg (0.098 mmol) of the starting iodide **20a**, and 19 mg (0.29 mmol, 3 equiv) of NaN_3 was heated to 65 °C with stirring for 3 h under an atmosphere of N_2. After this time, the reaction mixture was cooled to rt and concentrated *in vacuo* to an off-white solid. Purification by preparative TLC on silica gel (eluted with 5% MeOH/$CHCl_3$) gave 27 mg (88%) of the title compound as a yellow solid: mp 133–133.5 °C; FTIR (mineral oil mull) 2114, 1750, 1631, 1599, 1528, 1418, 1411, 1229, 1224, 801 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.68 (d, J = 5.1, 2H), 7.58 (dd, J = 2.2, 13.0, 1H), 7.53 (dd, J = 8.5, 1H), 7.50–7.46 (m, 2H), 7.39 (dd, J = 2.2, 8.6, 1H), 4.88–4.82 (m, 1H), 4.13 (dd, J = 9.0, 9.0, 1H), 3.91 (dd, J = 6.2, 9.0, 1H), 3.76 (dd, J = 4.5, 13.2, 1H), 3.63 (dd, J = 4.3, 13.2); MS (EI) 313 (M^+, 100), 285 (40), 270 (16), 256 (31), 241 (70), 240 (77), 213 (46), 201 (42), 199 (47), 188 (25), 172 (48). Anal. Calcd for $C_{15}H_{12}FN_5O_2$: C, 57.51; H, 3.86; N, 22.36. Found: C, 57.16; H, 3.89; N, 22.10.

(±)-5-(Azidomethyl)-3-[4-(4-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone (22b). A mixture of 15 mL of DMF, 661 mg (1.12 mmol) of the starting iodide **20b**, and 582 mg (8.96 mmol, 8 equiv) of NaN_3 was heated to 55 °C with stirring under an atmosphere of N_2. After 2.5 h, the reaction mixture was cooled to rt, diluted with 100 mL of H_2O, and then extracted with EtOAc. The combined organics were washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to an amber oil. Purification by silica gel chromatography (eluted with 0–1% MeOH/$CHCl_3$) gave 291 mg (78%) of the title compound as a yellow sold: mp 117–118 °C; FTIR (mineral oil mull) 2122, 1769, 1647, 1416, 1239, 1024, 830, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.70 (br s, 2H), 7.40 (d, J = 4.5, 2H), 7.31 (d, J = 10.3, 2H), 4.91–4.83 (m, 1H), 4.11 (dd, J = 9.0, 9.0, 1H), 3.88 (dd, J = 6.1, 9.0, 1H), 3.79 (dd, J = 4.2, 13.4, 1H), 3.62 (dd, J = 4.2, 13.4, 1H); MS (FAB) 332 ($M + H^+$). Anal. Calcd for $C_{15}H_{11}F_2N_5O_2$: C, 54.38; H, 3.35; N, 21.14. Found: C, 54.14; H, 3.30; N, 21.07.

(±)-*N*-[[3-[3,5-Difluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (23b). A mixture of 40 mL of 10% MeOH/EtOAc, 152 mg of the crude azide **21b**, and 35 mg of 10% Pd-C was purged with N_2 and stirred under an atmosphere of H_2 (balloon) for 16 h. After this time, the reaction mixture was filtered through a pad of Celite and

concentrated under reduced pressure to an amber foam (135 mg, ~96% crude yield). An analytical sample of the 5-(aminomethyl)oxazolidinone intermediate was prepared by preparative TLC on silica gel (eluted with 10% MeOH/$CHCl_3$) and was recovered as a white solid: mp 143–145 °C; FTIR (neat) 3368 (br), 1757, 1646, 1412, 1244, 1025, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.62 (dd, J = 1.6, 4.9, 1H), 7.79 (d, J = 8.1, 1H), 7.39 (dd, J = 4.9, 8.0, 1H), 7.33 (d, J = 10.0, 2H), 4.79–4.70 (m, 1H), 4.06 (dd, J = 8.7, 8.7, 1H), 3.92 (dd, J = 6.7, 8.6, 1H), 3.18 (dd, J = 3.9, 14.0, 1H), 2.98 (dd, J = 5.3, 14.0, 1H), 1.52 (br s, 2H); MS (EI) 305 (M^+, 67), 276 (15), 233 (66), 219 (12), 44 (13), 29 (100). Anal. Calcd for $C_{15}H_{13}F_2N_3O_2$: C, 59.02; H, 4.29; N, 13.76. Found: C, 57.94; H, 4.21, N; 13.13. In 10 mL of anhydrous CH_2Cl_2 was dissolved 135 mg of the crude 5-(aminomethyl)oxazolidinone intermediate. The solution was then treated with 42 μL (0.520 mmol) of pyridine followed by 49 μL (0.520 mmol) of Ac_2O. The reaction mixture was allowed to stir at rt, under N_2 for 2.5 h. After this time, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yellow solid. Purification by silica gel chromatography (eluted with 1–4% MeOH/$CHCl_3$) gave 109 mg (66%, three steps) of the title compound as a white solid: mp 218–219 °C; FTIR (mineral oil mull) 3347, 1742, 1679, 1648, 1563, 1409, 1247, 1022, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.68 (br s, 1H), 8.59 (br s, 1H), 7.85 (d, J = 7.9, 1H), 7.48–7.41 (m, 2H), 7.31 (ddd, J = 3.0, 7.7, 13.2, 2H), 4.87–4.79 (m, 1H), 4.10 (dd, J = 9.1, 9.1, 1H), 3.82 (dd, J = 6.7, 9.2, 1H), 3.72–3.57 (m, 2H), 2.03 (s, 3H); MS (EI) 347 (M^+, 100), 303 (47), 275 (42), 244 (37), 219 (61), 73 (36), 56 (52). Anal. Calcd for $C_{17}H_{15}F_2N_3O_3$: C,58.79; H, 4.35; N, 12.10. Found: C, 58.84; H, 4.27; N, 12.07.

(±)-*N*-[[3-[3-Fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (24a). A mixture of 1.5 mL of MeOH, 16 mg (0.051 mol) of the starting azide **22a**, and 2.5 mg of 10% Pd–C was stirred under an atmosphere of H_2 (balloon) for 45 min. After this time, the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to an off-white solid. The intermediate amine was then dissolved in 1.5 mL of CH_2Cl_2, placed under an atmosphere of N_2 and then treated with 4 μL (0.05 mmol, 1 equiv) of pyridine followed by 5 μL (0.05 mmol) of Ac_2O. The reaction mixture was allowed to stir at rt for 0.5 h. After this time, the reaction mixture was washed with H_2O followed by brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to an off-white solid. Purification by preparative TLC on silica gel (eluted with 5% MeOH/$CHCl_3$) gave 15 mg (89%) of the title compound as a white solid: mp 179–180 °C; FTIR (neat) 1752, 1657, 1600, 1485, 1407, 1198, 810, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.67 (d, J = 6.1, 2H), 7.58 (dd, J = 2.3, 13.1, 1H), 7.51 (d, J = 8.7, 1H), 7.48–7.46 (m, 2H), 7.33 (dd, J = 2.3, 8.7, 1H), 6.15 (br s, 1H), 4.88–4.79 (m, 1H), 4.11 (dd, J = 9.1, 9.1, 1H), 3.84 (dd, J = 6.8, 9.1, 1H), 3.73–3.67 (m, 2H), 2.04 (s, 3H); MS (EI) 329 (M^+, 40), 285 (29), 225 (43), 201 (52), 188 (56), 172 (27), 56 (37), 42 (100). Anal. Calcd for $C_{17}H_{16}FN_3O_3$: C, 62.00; H, 4.90; N, 12.76. Found: C, 62.01; H, 4.84; N, 12.82.

(±)-*N*-[[3-[3,5-Difluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (24b). A mixture of 500 mL of 20% MeOH/EtOAc and 7.96 g (0.0240 mol) of the starting azide **22b** was purged with N_2 and then treated with 300 mg of 10% Pd–C. The resulting mixture was vigorously stirred under an atmosphere of H_2 (balloon) for 16 h. After this time, the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to a yellow solid. An analytical sample of the 5-(aminomethyl)oxazolidinone intermediate was prepared from a small aliquot by preparative TLC on silica gel (eluted with 10% MeOH/$CHCl_3$) and was recovered as a white solid: mp 146–148 °C; FTIR (neat) 3302 (br), 1742, 1642, 1408, 1241, 1026, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.69 (dd, J = 1.5, 4.6, 2H), 7.40 (dd, J = 1.5, 4.6, 2H), 7.33 (dd, J = 10.4, 2H), 4.79–4.71 (m, 1H), 4.05 (d, J = 8.7, 8.7, 1H), 3.92 (dd, J = 6.7, 6.7, 1H), 3.19 (dd, J = 3.9, 13.7, 1H), 2.98 (dd, J = 5.1, 13.7, 1H), 1.44 (br s, 2H); MS (EI) 305 (M^+, 46), 276 (16), 233 (48), 219 (54), 44 (19), 29 (100). Anal. Calcd for $C_{15},H_{13}F_2N_3O_2$: C, 59.02; H, 4.29; N, 13.76. Found: C, 58.80; H, 4.18; N, 13.59. The crude amine was dissolved in 400 mL of CH_2Cl_2, placed under an atmosphere of N_2, and cooled to 0 °C. To the cold solution was added 2.04 mL (0.0253 mol, 1.05 equiv) of pyridine followed by 2.38 mL (0.0253 mol) of Ac_2O. The reaction mixture was allowed to stir at 0 °C for 2 h and then at rt for 12 h. After this time, the reaction mixture was washed with H_2O followed by brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a yellow solid. Purification by silica gel chromatography (eluted with 1–4% MeOH/$CHCl_3$) gave 7.87 g (94%) of the title compound as a white solid: mp 160–161 °C; FTIR (neat) 1741, 1651, 1646, 1412, 1246, 1027, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.70 (d, J = 5.6, 2H), 7.42 (d, J = 6.1, 2H), 7.29 (d, J = 10.3, 2H), 6.10 (br s, 1H), 4.90–4.78 (m, 1H), 4.08 (dd, J = 9.1, 9.1, 1H), 3.82 (dd, J = 6.7, 9.2, 1H), 3.73–3.67 (m, 2H), 2.05 (s, 3H); MS (EI) 347 (M^+, 28), 303 (37), 243 (46), 219 (44), 206 (57), 58 (71), 29 (100). Anal. Calcd for $C_{17}H_{15}F_2N_3O_3$: C, 58.79; H, 4.35; N, 12.10. Found: C, 58.74; H, 4.36; N, 12.11.

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Supporting Information Available: ^1H NMR spectra for compounds **9a**, **9b**, **14a**, **14b**, **16a**, and **18a** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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