JOC*Note*

Rearrangement of *N*,*N*-Di-*tert*-butoxycarbonylpyridin-4-amines and Formation of Polyfunctional Pyridines

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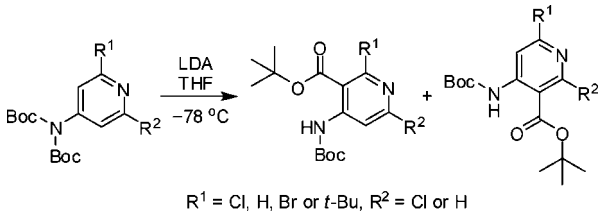
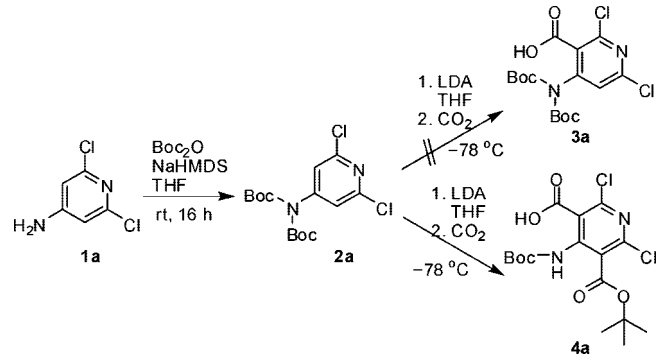


N,*N*-Di-*tert*-butoxycarbonylpyridin-4-amines were found to be rearranged to *tert*-butyl 4-(*tert*-butoxycarbonylamino)nicotinates by treatment with LDA in THF.

Pyridines represent key structural components of numerous pharmacological agents and natural products.[1] In addition, polyfunctional pyridines are versatile intermediates and building blocks used for the synthesis of pharmaceutically relevant or biologically active heterocyclic compounds.[2] Accordingly, the development of efficient synthetic methods for the construction of polyfunctional pyridines is of considerable importance from the perspectives of both medicinal chemistry and organic chemistry. Various strategies have been developed for the synthesis of polyfunctional substituted pyridines.[3] Herein we describe a unique method for the preparation of polyfunctional pyridines based on a novel rearrangement of *N*,*N*-di(*tert*-butoxycarbonyl)pyridin-4-amines (**2**) to *tert*-butyl 4-(*tert*-butoxycarbonylamino)nicotinate (**5**).

SCHEME 1. Formation of Polysubstituted Pyridine 4a



During the course of our medicinal chemistry program we sought to prepare 4-amino-2,6-dichloronicotinic acid from 4-amino-2,6-chloropyridine (**1a**) following a reaction sequence described by Jang et al.[4] The amino group of **1a** was intended to be protected as a *tert*-butoxycarbonyl group (Boc), using sodium bis(trimethylsilyl)amide (NaHMDS) and di-*tert*-butyl dicarbonate (Boc_2O) in THF. However, in our hands the reaction was very sluggish and thus an excess of NaHMDS (2.3 equiv) and Boc_2O (2.2 equiv) were used to completely consume **1a**. Unexpectedly, the only product obtained after 16 h at 25 °C was *N*,*N*-di-*tert*-butoxycarbonyl-2,6-dichloropyridin-4-amine (**2a**) (Scheme 1). We then decided to utilize this material to make 4-(bis(*tert*-butoxycarbonyl)amino)-2,6-dichloronicotinic acid (**3a**). Treatment of **2a** with lithium diisopropylamide (LDA) and quenching by the addition of an excess of dry ice led to the formation of a product in 64% yield. Much to our surprise, ^{1}H NMR and LC-MS data of this product did not correspond to **3a**.[5] ^{1}H NMR in DMSO-d_6 of this product exhibited two distinctive singlets at 1.42 and 1.51 ppm (each intergrating to 9 protons), suggesting the presence of two different *tert*-butyl groups, and it lacked any peak corresponding to the aromatic proton. Thus, we assigned the product as 5-(*tert*- butoxycarbonyl)-4-(*tert*-butoxycarbonylamino)-2,6-dichloronicotinic acid (**4a**).

We postulated that, upon treatment with LDA, one of the Boc groups of **2a** migrated from the nitrogen atom to one of the nonsubstituted adjacent carbon atoms of the pyridine ring

(1) For some reviews, see:(a) Lukevits, E. *Chem. Heterocycl. Compd.* **1995**, *31*, 639–650. (b) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581. (c) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491. (d) Wang, C. L. J.; Wuonola, M. A. *Org. Prep. Proced.* **1992**, *24*, 585. (e) Numata, A.; Ibuka, T. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. *31*. (f) Daly, J. W.; Spande, T. F. *Alkaloids: Chemical and Biological Respectives*; Pelletier, S. W., Ed.; Willey: New York, 1980; Vol. 4, p 1. (g) Micetich, R. G. *Pyridine and Its Derivatives: Supplement*; Abramovitch, R., Ed.; John Wiley and Sons: New York, 1974.

(2) For some recent examples, see:(a) Jang, M-Y.; De Jonghe, S.; Gao, L-J.; Rozenski, J.; Herdewijn, P. *Eur. J. Org. Chem.* **2006**, 4257. (b) Szczepankiewicz, B. G.; Kosogof, C.; Nelson, L. T. J.; Liu, G.; Liu, B.; Zhao, H.; Serby, M. D.; Xin, Z.; Liu, M.; Gum, R. J.; Haasch, D. L.; Wang, S.; Clampit, J. E.; Johnson, E. F.; Lubben, T. H.; Stashko, M. A.; Olejniczak, E. T.; Sun, C.; Dorwin, S. A.; Haskins, K.; Abad-Zapatero, C.; Fry, E. H.; Hutchins, C. W.; Sham, H. L.; Rondinone, C. M.; Trevillyan, J. M. *J. Med. Chem.* **2006**, *49*, 3563. (c) Hu, L.; Li, Z.; Wang, Y.; Wu, Y.; Jiang, J.; Boykin, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1193. (d) Liu, G.; Zhao, H.; Liu, B.; Xin, Z.; Liu, M.; Kosogof, C.; Szczepankiewicz, B. G.; Wang, S.; Clampit, J. E.; Gum, R. J.; Haasch, D. L.; Trevillyan, J. M.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5723. (e) Li, R.; Xue, L.; Zhu, T.; Jiang, Q.; Cui, X.; Yan, Z.; McGee, D.; Wang, J.; Gantla, V. R.; Pickens, J. C.; McGrath, D.; Chucholowski, A.; Morris, S. W.; Webb, T. R. *J. Med. Chem.* **2006**, *49*, 1006. (f) Hong, F.; Hollenback, D.; Singer, J. W.; Klein, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4703. (g) Zhou, W.; Yerkes, N.; Chruma, J. J.; Liu, L.; Breslow, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1351.

(3) For some examples, see:(a) Dash, J.; Lechel, T.; Reissig, H.-U. *Org. Lett.* **2007**, *9*, 5541. (b) Hogimori, M.; Mizuyama, N.; Hisadome, Y.; Nagaoka, J.; Ueda, K.; Tominaga, Y. *Tetrahedron* **2007**, *63*, 2511. (c) Catozzi, N.; Bromley, W.; Wasnaire, P.; Gibson, M.; Taylor, R. J. K. *Synlett* **2007**, 2217. (d) Abu-Shanab, F. A.; Hessen, A. M.; Mousa, S. A. S. *J. Heterocycl. Chem.* **2007**, *44*, 787. (e) Park, D. Y.; Lee, M. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 8799. (f) Kaminski, T.; Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2003**, 3855. (g) Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron Lett.* **1996**, *26*, 4577. (h) Cocco, M. T.; Conjiu, C.; Onnis, V. *Heterocycles* **1993**, *36*, 2829. (i) Kniezo, L.; Kristian, P.; Imrich, J. *Tetrahedron* **1988**, *44*, 543.

(4) Jang, M-Y.; De Jonghe, S.; Gao, L-J.; Herdewijn, P. *Tetrahedron Lett.* **2006**, 8917.

(5) We expected that ^{1}H NMR in DMSO-d_6 of **3a** should have a singlet peak for the two Boc groups (intergrating to 18 protons) and one peak for the aromatic proton.

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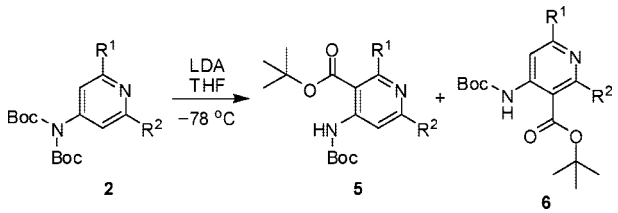
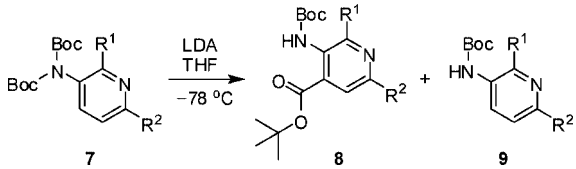
TABLE 1. Rearrangement of *N*,*N*-Di-Boc-pyridin-4-amines (2)



entry	2	R^1	R^2	5 (%)	6 (%)
1	**2a**	Cl	Cl	**5a** (96)	n/a
2	**2b**	Cl	H	**5b** (90)	**6b** (5)
3	**2c**	Br	H	**5c** (87)	**6c** (3)
4	**2d**	*t*-Bu	H	**5d** (0)	**6d** (3)

TABLE 2. LDA Treatment of *N*,*N*-Di-Boc-pyridin-3-amines (7)



entry	7	R^1	R^2	8 (%)	9 (%)
1	**7a**	Cl	Cl	**8a** (0)	**9a** (49)
2	**7b**	Cl	H	**8b** (0)	**9b** (62)
3	**7c**	H	Cl	**8c** (0)	**9c** (71)

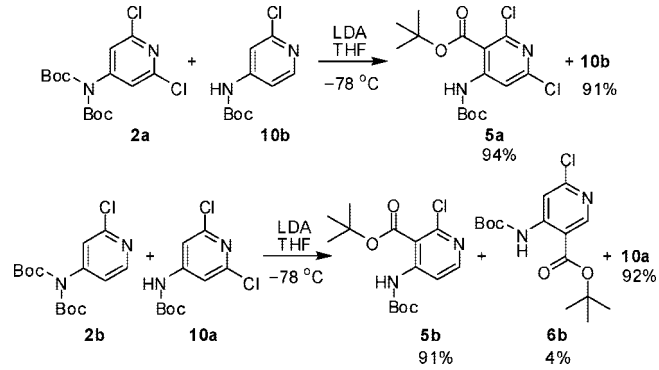
and that the *tert*-butyl ester moiety did not arise from the presence of CO_2. To test this postulation, pyridine **2a** was treated with LDA in THF at −78 °C in the absence of CO_2 (Table 1, $R^1 = R^2 = Cl$). After 20 min, monitoring the reaction by TCL clearly indicated the disappearance of **2a** and the formation of a new product. ^{1}H NMR (DMSO-d_6) of the product showed two singlets at 1.38 and 1.47 ppm (each intergrating to 9 protons) and another singlet at 7.49 ppm (intergrating to 1 proton). The NH peak at 9.8 ppm was confirmed by HMBC. A ROE cross-peak between the NH and the unsubstituted carbon adjacent to the Boc-amino group was also present in the ROESY spectrum. Therefore, the product was assigned as *tert*-butyl 4-(*tert*-butoxycarbonylamino)-2,6-dichloronicotinate (**5a**), which also correlates with the HRMS data.

This method was extended to several *N*,*N*-di-*tert*-butoxycarbonylpyridin-4-amines (**2**) for the synthesis of polysubstituted pyridines (Table 1). In the cases where R^1 and R^2 are different groups, the reaction gave regioisomers **5** and **6**. For reasons unknown, unsymmetrical **2b** and **2c** gave sterically encumbered isomers **5a** and **5b** as major products, respectively. When R^1 is a bulky *tert*-butyl group, **6d** was obtained in 3% yield and formation of **5d** was not observed in this case.

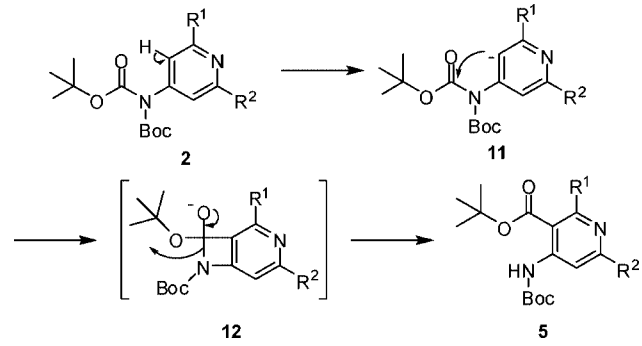
To gain a better understanding about the scope and utility of this process, the rearrangement of *N*,*N*-di-*tert*-butoxycarbonylpyridin-3-amines (**7**) was also explored (Table 2). However, after several attempts under the same rearrangement reaction conditions with different substrates **7a**−**c**, it was found that the rearrangement did not occur in this type of pyridine ring system. The only products obtained from the reactions were mono-Boc-protected 3-aminopyridines **9a**−**c**, which means that one Boc group was depleted during the operations.

Since the reaction happens readily for the formation of the *ortho* product, we believe that it is most likely an intramolecular reaction.[6] To gain evidence to support an intramolecular over intermolecular mechanism, we carried out the rearrangement reaction of **2a** in the presence of *N*-*tert*-butoxycarbonyl-2-chloropyridin-4-amine (**10b**) (Scheme 2). The reaction resulted in the formation of **5a** as the exclusive product, along with the recovery of unreacted **10b**. Similarly, when subjected to the same rearrangement condition, *N*-*tert*-butoxycarbonyl-2,6-dichloropyridin-4-ylcarbamate (**10a**) remained unreacted, while **2b** rearranged to form **5b** and **6b.** These results suggest that the rearrangement is an intramolecular process.

SCHEME 2. LDA Treatment of a Mixture of *N*,*N*-Di-Boc-pyridin-4-amines (2) and *N*-Boc-pyridin-4-amines (10)



SCHEME 3. Proposed Mechanism for the Rearrangement



Fries-type rearrangement of aryl ester, *N*-arylamides, *O*-aryl carbamates, and *N*-aryl carbamates under ultraviolet irradiation has been well documented.[7] For base-induced Fries reactions, there are reports about metal-promoted rearrangement of *O*-aryl carbamates.[8] Very interestingly, Miah and Snieckus reported a heterocyclic version of the metal-promoted Fries reaction, a rearrangement of metalated *O*-pyridyl carbamates under a condition of *sec*-BuLi/TMEDA/THF at −78 °C.[9] The reaction we described here is Fries rearrangement of *N*-pyridyl carbamates. The tentative mechanism (Scheme 3) initially involves deprotonation at the carbon adjacent to the di-Boc-amino group of **2** by a strong base LDA, resulting in a carbonion that is stabilized by an electron-deficient carbonyl group nearby. Subsequent nucleophilic attack takes place at the Boc carbonyl carbon, resulting in the migration of one Boc group to the pyridine ring, thereby relieving steric hindrance around the

(6) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; John Wiley and Sons: New York, 2007; p 735.

(7) For examples, see:(a) Anderson, J. C.; Reese, C. B. *J. Chem Soc.* **1963**, 1781. (b) Kobsa, H. *J. Org. Chem.* **1962**, *27*, 2293. (c) Elad, D.; Rao, D. V.; Stenberg, V. I. *J. Org. Chem.* **1965**, *30*, 3252. (d) Trecker, D. J.; Foote, R. S.; Osborn, C. L. *Chem. Commun.* **1968**, 1034.

(8) (a) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. (b) Miller, J. A. *J. Org. Chem.* **1987**, *52*, 322.

(9) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.

nitrogen atom. In terms of mechanism, it is similar to a migration of Boc of *o*-bromo-*N*,*N*-di-Boc-aniline promoted by a metal−halogen exchange.[10]

In conclusion, we have discovered a rearrangement of *N*,*N*-di-*tert*-butoxycarbonylpyridin-4-amines (**2**) to polysubtituted pyridine derivatives *tert*-butyl 4-(*tert*-butoxycarbonylamino)nicotinates (**5**). It provides a facile method for construction of polysubstituted pyridines. Further chemical manipulations of these highly functionalized pyridines are being carried out to probe their usefulness for the synthesis of various nitrogen-containing heterocyclic compounds.

Experimental Section

Representative Procedure for the Preparation of 2, 7, and 10: 4-[(Di-*tert*-butoxycarbonyl)amino]-2,6-dichloropyridine (2a). A solution of 2,6-dichloropyridin-4-amine (**1a**) (7.50 g, 46.0 mmol) in dry THF (300 mL) under dry N_2 was cooled to 0 °C with an ice−water bath. To this mixture was added a solution of NaHMDS in THF (1.0 M, 106.0 mL, 106.0 mmol) via syringe. After the reaction mixture was stirred at 0 °C for 20 min, a solution of Boc_2O (22.09 g, 101.2 mmol) in THF (100 mL) was added and the ice−water bath then was removed. After the reaction mixture was stirred at 25 °C for 16 h, it was poured into a 25% aqueous NH_4Cl solution (500 mL) followed by addition of EtOAc (200 mL). The biphasic layers were separated and the aqueous phase was washed with EtOAc (2 × 200 mL). The combined organic phases were washed with a 20% aqueous Na_2CO_3 solution (40 mL) and brine (40 mL), dried over $MgSO_4$, and evaporated to result in a residue that was subjected to chromatography (hexanes/EtOAc = 19:1) to afford **2a** (16.1 g, 96% yield). ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 18 H), 7.40 (s, 2H); ^{1}H NMR (DMSO-d_6) δ 1.41 (s, 18 H), 7.70 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 28.6, 83.9, 122.5, 149.2, 149.5, 151.3; ESI-TOF HRMS calcd for $[C_{15}H_{20}Cl_2N_2O_4 + H]^+$ 363.0873, found 363.0876.

4-[(Di-*tert*-butoxycarbonyl)amino]-2-chloropyridine (2b). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H), 7.04 (d, J = 5.4 Hz, 1H), 7.17 (s, 1H), 8.37 (d, J = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.7, 84.2, 120.7, 122.3, 148.7, 149.9, 150.3, 151.7; ESI-TOF HRMS calcd for $[C_{15}H_{21}ClN_2O_4 + H]^+$ 329.1263, found 329.1271.

4-[(Di-*tert*-butoxycarbonyl)amino]-2-bromopyridine (2c). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H), 7.07 (d, J = 5.2 Hz, 1H), 7.33 (s, 1H), 8.35 (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.7, 84.2, 121.0, 126.0, 141.9, 148.2, 149.9, 150.3; ESI-TOF HRMS calcd for $[C_{15}H_{21}BrN_2O_4 + H]^+$ 373.0757, found 373.0761.

4-[(Di-*tert*-butoxycarbonyl)amino]-2-*tert*-butylpyridine (2d). ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H), 1.42 (s, 18 H), 6.90 (d, J = 5.4 Hz, 1H), 7.10 (s, 1H), 8.54 (d, J = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.8, 30.0, 37.4, 83.4, 117.8, 119.1, 147.0, 149.1, 150.9, 170.4; ESI-TOF HRMS calcd for $[C_{19}H_{30}N_2O_4 + H]^+$ 351.2278, found 351.2282.

3-[(Di-*tert*-butoxycarbonyl)amino]-2,6-dichloropyridine (7a). ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 18H), 7.30 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.7, 84.0, 123.3, 133.2, 140.2, 148.7, 148.7, 149.5; ESI-TOF HRMS calcd for $[C_{15}H_{21}ClN_2O_4 + H]^+$ 329.1263, found 329.1268.

3-[(Di-*tert*-butoxycarbonyl)amino]-2-chloropyridine (7b). ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 18H), 7.28 (dd, J = 7.6 and 4.8 Hz, 1H), 7.56 (dd, J = 7.6 and 1.6 Hz, 1H), 8.35 (dd, J = 4.8 and 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.7, 83.6, 122.7, 134.0, 138.1, 148.3, 149.8, 149.8; ESI-TOF HRMS calcd for $[C_{15}H_{21}ClN_2O_4 + H]^+$ 329.1263, found 329.1269.

3-[(Di-*tert*-butoxycarbonyl)amino]-6-chloropyridine (7c). ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H), 7.33 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 8.4 and 2.8 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 27.8, 83.8, 124.0, 135.0, 138.1, 148.8, 149.9, 150.7; ESI-TOF HRMS calcd for $[C_{15}H_{21}ClN_2O_4 + H]^+$ 329.1263, found 329.1270.

***tert*-Butyl 2,6-Dichloropyridin-4-ylcarbamate (10a).** A similar procedure with 1.2 equiv of Boc_2O afforded **10a**. ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9 H), 6.74 (br s, 1H, NH), 7.33 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 28.0, 82.6, 110.9, 149.5, 150.9, 151.4; ESI-TOF HRMS calcd for $[C_{10}H_{12}Cl_2N_2O_2 + H]^+$ 263.0349, found 263.0351.

***tert*-Butyl 2-Chloropyridin-4-ylcarbamate (10b).** A similar procedure with 1.2 equiv of Boc_2O afforded **10b**. ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9 H), 6.84 (br s, 1H, NH), 7.15 (dd, J = 5.6 and 2.0 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 8.19 (d, J = 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1, 82.1, 111.3, 112.1, 147.9, 149.8, 151.6, 152.3; ESI-TOF HRMS calcd for $[C_{10}H_{13}ClN_2O_2 + H]^+$ 229.0738, found 229.0738.

5-(*tert*-Butoxycarbonyl)-4-(*tert*-butoxycarbonylamino)-2,6-dichloronicotinic Acid (4a). To dry THF (300 mL) under dry N_2 cooled to −78 °C with a dry ice−acetone bath were sequentially added dry diisopropylamine (8.50 mL, 6.07 g, 60.0 mmol) and a solution of *n*-BuLi in hexanes (2.5 M, 22.0 mL, 55.0 mmol) via syringe. After allowing this mixture to stir at −78 °C for 20 min, a solution of **2a** (9.08 g, 25.0 mmol) in dry THF (50 mL) was added via syringe. After the reaction mixture was stirred for another 30 min, an excess amount of dry ice (freshly washed with hexanes) was added and the resulting mixture was allowed to warm to 25 °C over a period of 1.5 h. The reaction mixture was then poured into a 25% aqueous NH_4Cl solution (600 mL) followed by addition of EtOAc (200 mL). The biphasic layers were separated and the aqueous phase was washed with EtOAc (2 × 200 mL). The combined organic phases were washed with brine (2 × 40 mL), dried over $MgSO_4$, and evaporated to result in a residue that was subjected to chromatography (DCM/MeOH/28% aqueous NH_3 = 90:10:1) to afford **4a** in ammonium salt form (6.8 g, 64% yield). ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 9H), 1.51 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 28.1, 28.3, 81.4, 82.8, 122.6, 127.2, 144.8, 145.9, 147.0, 151.2, 161.8, 163.8; ESI-TOF HRMS calcd for $[C_{16}H_{20}Cl_2N_2O_6 + H]^+$ 407.0771, found 407.0781.

Representative Procedure for the Rearrangement of 2: Formation of *tert*-Butyl 4-(*tert*-butoxycarbonylamino)-2,6-dichloronicotinate (5a). To dry THF (200 mL) under dry N_2 cooled to −78 °C with a dry ice−acetone bath were sequentially added dry diisopropylamine (22.0 mL, 15.7 g, 155.0 mmol) and a solution of *n*-BuLi in hexanes (2.5 M, 63.0 mL, 155.0 mmol) via syringe. After allowing this mixture to stir at −78 °C for 20 min, a solution of **2a** (16.1 g, 44.3 mmol) in dry THF (50 mL) was added via syringe. After the reaction mixture was stirred for another 20 min, it was poured into a 25% aqueous solution of NH_4Cl solution (600 mL) followed by addition of EtOAc (200 mL). The biphasic layers were separated and the aqueous phase was washed with EtOAc (2 × 200 mL). The combined organic phases were washed with a 20% aqueous solution of Na_2CO_3 (40 mL) and brine (40 mL), dried over $MgSO_4$, and evaporated resulting in a residue that was subjected to chromatography (hexanes/EtOAc = 9:1) to afford **5a** (15.45 g, 96% yield). ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9 H), 1.62 (s, 9 H), 8.33 (s, 1H), 8.98 (br s, 1H, NH); ^{1}H NMR (DMSO-d_6) δ 1.38 (s, 9 H), 1.47 (s, 9 H), 7.49 (s, 1H), 9.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.8, 27.9, 81.5, 83.5, 114.7, 118.9, 147.8, 148.5, 149.5, 151.7, 162.6; ESI-TOF HRMS calcd for $[C_{15}H_{20}Cl_2N_2O_4 + H]^+$ 363.0873, found 363.0878.

***tert*-Butyl 4-(*tert*-Butoxycarbonylamino)-2-chloronicotinate (5b).** ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9 H), 1.63 (s, 9 H), 8.20 (d, J = 6.0 Hz, 1H), 8.23 (d, J = 6.0 Hz, 1H), 8.71 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.0, 28.0, 82.1, 84.8, 111.7, 115.1, 147.8, 149.9, 150.5, 151.4, 164.9; ESI-TOF HRMS calcd for $[C_{15}H_{21}ClN_2O_4 + H]^+$ 329.1263, found 329.1269.

***tert*-Butyl 4-(*tert*-Butoxycarbonylamino)-2-bromonicotinate (5c).** ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 9 H), 1.65 (s, 9 H), 8.20 (d, J = 5.0 Hz, 1H), 8.21 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0,

(10) Herzig, S.; Kritter, S.; Lübbers, T.; Marquardt, N.; Peters, J.-U.; Weber, S. *Synlett* **2005**, 3107.

28.0, 82.1, 85.0, 112.0, 118.0, 140.4, 147.0, 150.7, 151.4, 165.1; ESI-TOF HRMS calcd for $[C_{15}H_{21}BrN_2O_4 + H]^+$ 373.0757, found 373.0763.

***tert*-Butyl 4-(*tert*-Butoxycarbonylamino)-6-chloronicotinate (6b).** ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 9 H), 1.61 (s, 9 H), 8.43 (s, 1H), 8.80 (s, 1H), 10.48 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.1, 82.1, 83.7, 110.6, 111.8, 150.0, 151.9, 152.7, 156.3, 166.0; ESI-TOF HRMS calcd for $[C_{15}H_{21}ClN_2O_4 + H]^+$ 329.1263, found 329.1272.

***tert*-Butyl 4-(*tert*-Butoxycarbonylamino)-6-bromonicotinate (6c).** ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9 H), 1.60 (s, 9 H), 8.59 (s, 1H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.1, 82.1, 83.7, 110.9, 115.6, 147.4, 149.5, 151.8, 152.7, 166.2; ESI-TOF HRMS calcd for $[C_{15}H_{21}BrN_2O_4 + H]^+$ 373.0757, found 373.0764.

***tert*-Butyl 4-(*tert*-Butoxycarbonylamino)-6-*tert*-butylnicotinate (6d).** ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9 H), 1.54 (s, 9 H), 1.58 (s, 9 H), 8.39 (s, 1H), 9.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.2, 29.8, 37.9, 81.2, 82.5, 107.2, 108.9, 148.8, 151.9, 152.3, 166.8, 174.5; ESI-TOF HRMS calcd for $[C_{19}H_{30}N_2O_4 + H]^+$ 351.2278, found 351.2284.

Representative Procedure for LDA Treatment of 7: LDA Treatment of 7a. To dry THF (20 mL) under dry N_2 cooled to −78 °C with a dry ice−acetone bath were sequentially added dry diisopropylamine (0.21 mL, 152 mg, 1.5 mmol) and a solution of *n*-BuLi in hexanes (2.5 M, 1.25 mL, 3.13 mmol) via syringe. After allowing this mixture to stir at −78 °C for 20 min, a solution of **7a** (181.6 mg, 0.5 mmol) in dry THF (3 mL) was added via syringe. After the reaction mixture was stirred for another 20 min, it was poured into a 25% aqueous solution of NH_4Cl (100 mL) followed by addition of EtOAc (80 mL). The biphasic layers were separated and the aqueous phase was washed with EtOAc (2 × 20 mL). The combined organic phases were washed with a 20% aqueous solution of Na_2CO_3 (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated resulting in a residue that was subjected to chromatography (hexanes/EtOAc = 13:1) to obatin *tert*-butyl 2,6-dichloropyridin-3-ylcarbamate **9a** (64.5 mg, 49% yield). ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 9 H), 6.95 (br s, 1H, NH), 8.20 (d, J = 8.8 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1, 82.1, 123.5, 129.4, 131.7, 137.2, 142.0, 151.8; ESI-TOF HRMS calcd for $[C_{10}H_{12}Cl_2N_2O_2 + H]^+$ 263.0349, found 263.0349.

***tert*-Butyl 2-Chloropyridin-3-ylcarbamate (9b).** ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9 H), 7.00 (br s, 1H, NH), 7.22 (dd, J = 8.0 and 4.4 Hz, 1H), 8.03 (dd, J = 4.4 and 1.6 Hz, 1H), 8.49 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.1, 81.8, 123.2, 127.0, 132.5, 139.0, 142.5, 152.0; ESI-TOF HRMS calcd for $[C_{10}H_{13}ClN_2O_2 + H]^+$ 229.0738, found 229.0739.

***tert*-Butyl 6-Chloropyridin-3-ylcarbamate (9c).** ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9 H), 6.73 (br s, 1H, NH), 7.24 (d, J = 8.8 Hz, 1H), 7.94 (br m, 1H), 8.24 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.0, 81.2, 123.9, 128.7, 134.7, 139.5, 144.1, 152.7; ESI-TOF HRMS calcd for $[C_{10}H_{13}ClN_2O_2 + H]^+$ 229.0738, found 229.0741.

Procedure for LDA Treatment of 2a and 10b. To dry THF (20 mL) under dry N_2 cooled to −78 °C with a dry ice−acetone bath were sequentially added dry diisopropylamine (0.353 mL, 253.0 mg, 2.5 mmol) and then a solution of *n*-BuLi in hexanes (2.5 mmol, 0.88 mL, 2.20 mmol) via syringe. After allowing this mixture to stir at −78 °C for 20 min, a solution of **2a** (182.0 mg, 0.5 mmol) and **10b** (114.0 mg, 0.5 mmol) in dry THF (3 mL) was added via syringe. After the reaction mixture was stirred for another 20 min, it was poured into a 25% aqueous solution of NH_4Cl (100 mL) followed by addition of EtOAc (80 mL). The biphasic layers were separated and the aqueous phase was washed with EtOAc (2 × 20 mL). The combined organic phases were washed with a 20% aqueous solution of Na_2CO_3 (10 mL) and brine (10 mL), dried over $MgSO_4$, and evaporated resulting in a residue that was subjected to chromatography (from hexanes/EtOAc = 13:1 to 9:1) to afford **5a** (170.8 mg, 94%) together with recovery of unreacted **10b** (165.6 mg, 91% recovery).

Procedure for LDA Treatment of 2b and 10a. A similar procedure to the one above afforded **5b** (149 mg, 91%) and **6b** (6.5 mg, 4%). The unreacted **10a** (121.1 mg, 92% recovery) was also recovered.

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Supporting Information Available: Characterization of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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