Regiospecific Electrophilic Substitution of Aminopyridines: Ortho Lithiation of 2-, 3-, and 4-(Pivaloylamino)pyridines

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2- and 4-(pivaloylamino)pyridines have been shown to undergo metalation exclusively at C-3 and these smoothly react with a variety of electrophiles to produce 2,3- and 3,4-disubstituted pyridines, respectively. Removal of the pivaloyl protecting group results in overall electrophilic substitution of an aminopyridine. Utilization of this method is exemplified by efficient syntheses of 2- and 4-aminocotinaldehydes. Minor modifications of the reaction conditions permitted exclusive ortho metalation of 2-(pivaloylamino)pyridines additionally functionalized by chloro, fluoro, or methyl groups. Although the major product from reaction of 3-(pivaloylamino)pyridine by this method was metalation at C-4, the reaction was complicated by substantial quantities of product derived from nucleophilic attack by *n*-butyllithium on the pyridine nucleus.

The directed (ortho) lithiation of substituted aromatics is a versatible method for effecting highly regioselective electrophilic aromatic substitution and has been extensively employed as a powerful synthetic tool.[1] The technique is successful presumably because electronic and/or chelation properties associated with various aromatic substituents direct abstraction of the ortho proton by the metalating agent. Electron-rich heterocycles (e.g., pyrrole and thiophene), which prossess electronegative heteroatoms, are known to undergo facile metalation (α-lithiation).[1] Because of the electronic effects of the heteroatom, lithiation of electron-deficient heterocycles such as pyridine and pyrimidine should be equally feasible. Unfortunately, with nucleophilic metalating agents such as alkyllithiums, proton abstraction from pyridine is superseded by nucleophilic attack at the electrophilic azomethine.[2,3]

The well-known difficulty with which pyridines undergo classical electrophilic substitution provides an incentive to develop effective methods for metalating pyridines and conditions to trap the metalated heterocycle with electrophiles.[6] While the problems associated with direct metalation of pyridines can be avoided by lithiation of a bromopyridine via halogen–metal exchange,[7] ortho lithiation of substituted pyridines provides additional synthetic versatility. Recent reports have demonstrated that pyridines activated by halogens,[8] oxazolines,[9] secondary of tertiary carboxamides,[10] or ethers[11] can be effectively lithiated with complete regiochemical control and that the resulting lithiopyridines react cleanly with electrophiles.[12] While our work was in progress, 3-methoxy-5-(pivaloyl-

Scheme I

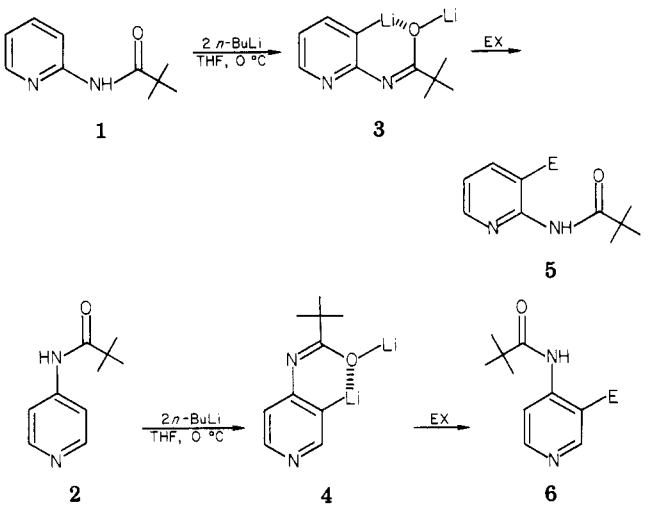


Table I. Reaction of Dilithio-2-(pivaloylamino)pyridine 3 with Electrophiles[a]

product	electrophile	E	yield,[b] %
5a	D_2O	D	87
5b	Me_3SiCl	$SiMe_3$	86
5c	$HCON(Me)_2$	CHO	54
5d	CH_3SSCH_3	SCH_3	67
5e	CH_3I	CH_3	72
5f	PhCHO	CHOHPh	63
5g	$ClCO_2Et$	CO_2Et	65

[a] See Experimental Section for details. [b] Yields reported are for isolated and purified materials.

Table II. Reaction of Dilithio-4-(pivaloylamino)pyridine 4 with Electrophiles[a]

product	electrophile	E	yield,[b] %
6a	D_2O	D	87
6b	Me_3SiCl	$SiMe_3$	79
6c	$HCON(Me)_2$	CHO	60
6d	CH_3SSCH_3	SCH_3	94
6e	CH_3I	CH_3	74

[a] See Experimental Section for details. [b] Yields reported are for isolated and purified materials.

(1) For a recent review of the scope and synthetic utility of directed metalations, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.

(2) For a discussion of addition of lithium reagents to pyridine followed by trapping with electrophiles, see: Giam, C. S.; Knaus, E. E.; Pasutto, F. M. *J. Org. Chem.* **1974**, *39*, 3565 and references cited therein.

(3) Although an early report of the reaction of pyridine with LDA to give dimers suggested that the products were derived from an initial metalation of pyridine,[4] more recent studies have shown that the reaction, in fact, proceeds by an SET mechanism.[5]

(4) Clarke, A. J.; McNamara, S.; Meth-Cohn, O. *Tetrahedron Lett.* **1974**, 2373.

(5) Newkome, G. R.; Hager, D. C. *J. Org. Chem.* **1982**, *47*, 599.

(6) Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, *6*, 229.

(7) Yale, H. L. in "Pyridine and Its Derivatives, Part Two", Klingsberg, E., Ed.; Interscience; New York, 1961; pp 421 and references cited therein.

(8) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137. Gungor, T.; Marsais, F.; Queguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139.

(9) Meyers, A. I.; Gabel, R. A. *J. Org. Chem.* **1982**, *47*, 2633.

(10) Epsztajn, J.; Berski, Z.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1980**, *21*, 4739. Katritzky, A. R.; Rahimi-Rastgoo, S.; Ponkshe, N. K. *Synthesis* **1981**, 127.

(11) (a) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (b) Marsais, F.; LeNard, G.; Queguiner, G. *Synthesis* **1982**, 235.

(12) In addition, ethyl nicotinoate has been metalated but the lithiated pyridine was trapped in situ by a second molecule of substrate: Ferles, M.; Silhankova, A. *Collect. Czech. Chem. Commun.* **1979**, *44*, 3137.

0022-3263/83/1948-3401$01.50/0

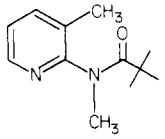
amino)pyridine[13] and 3-(pivaloylamino)pyridine[14] were reported to undergo lithiation at C-4, the latter requiring rather specific metalation conditions. In this report we describe the results of our study of the ortho lithiation of 2-, 3-, and 4-(pivaloylamino)pyridine.

Results

The pivaloyl group, first employed by Fuhrer and Gschwend as an ortho-directing protecting group for metalation of anilines,[15] has now been found equally effective for ortho-directed metalation of aminopyridines. Thus 2- and 4-(pivaloylamino)pyridine (**1** and **2**, respectively) readily undergo regiospecific metalation at C-3 when treated with an excess of *n*-butyllithium in THF (Scheme I).

The (pivaloylamino)pyridines are most expeditiously metalated by addition of 2.5 molar equiv of *n*-butyllithium to a solution of **1** or **2** in THF at 0 °C followed by stirring for 2–4 h at 0 °C. Initial addition of *n*-butyllithium to **2** provided a thick white precipitate that redissolved to form a clear yellow solution when approximately 1 equiv of the lithium reagent had been added. In contrast, the monoanion of **1** gives a colorless solution until 1 equiv of *n*-butyllithium has been added. In each case, the dilithio species usually precipitates from a solution within a few minutes after addition of the metalating agent is complete.

Lithiated pyridines **3** and **4** cleanly react with electrophiles to give 2,3- and 3,4-disubstituted pyridines **5** and **6**, respectively, in good to excellent yields (Scheme I). To illustrate the versatility of this method, reaction with several electrophiles was examined, the results of which are shown in Tables I and II. In all cases, VPC analysis showed the reactions to be clean, yielding only electrophilic substitution products and occasionally small amounts of starting material. There was no indication of metalation at any position other than C-3 nor of any nucleophilic addition of *n*-butyllithium to the C=N bond. Alkylation of **4** with methyl iodide required carefully controlled conditions. Treatment of dianion **4** with 1.1 equiv of methyl iodide at −78 °C followed by warming to room temperature provided the picoline **6e** in 74% yield after purification. Treatment with additional methyl iodide was accompanied by a corresponding decrease in yield of **6e**, and, indeed, addition of 3 equiv of methyl iodide resulted in nearly total loss of volatile, organic soluble material, possibly due to quaternization of the pyridine nitrogen. Treatment of dilithiopyridine **3** with 5 molar equiv of methyl iodide failed to give N-alkylated picoline **7** even



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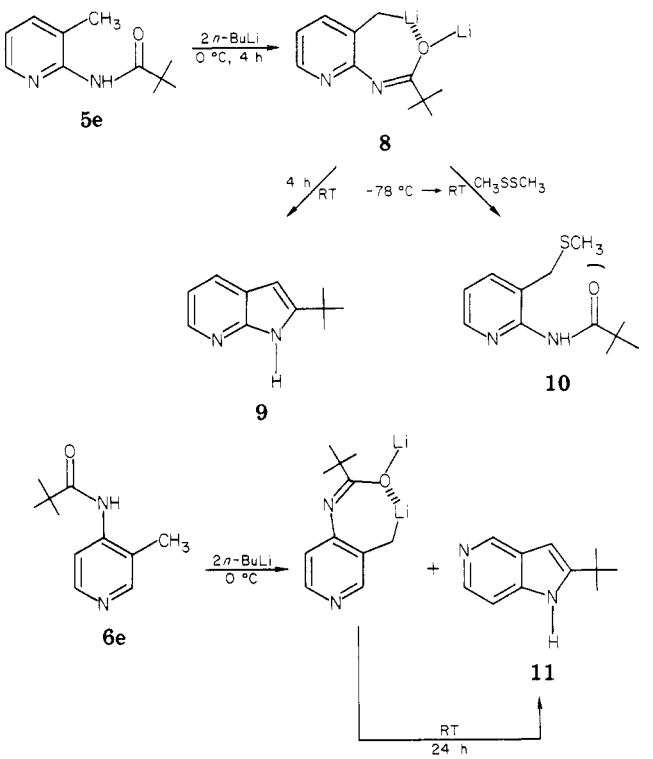
after prolonged stirring at room temperature (20 h). The major product (89%) of this reaction was ortho-alkylated pyridine **5e**. These results are in contrast with previous examples of pivaloylamino-directed alkylation where treatment of the dianions with excess methyl iodide gave ortho substitution followed by amide nitrogen alkylation under more forcing conditions.[13,15] The decreased nucleophilicity of the amide anions of **5e** and **6e** apparently reflect the importance of resonance forms bearing a negative charge on the pyridine nitrogen (vide infra).

Scheme II



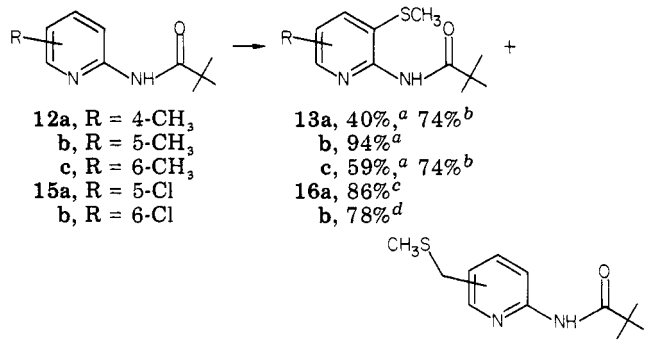
The pivaloyl protecting group is easily removed from disubstituted pyridines **5** and **6** on refluxing with dilute aqueous HCl, thus effecting net regiospecific electrophilic substitution of an aminopyridine. The short and efficient syntheses of 2- and 4-aminonicotinaldehydes via lithiation, reaction with DMF and hydrolysis of **5c** and **6c**, respectively, further demonstrates the synthetic value of this methodology. Most previous preparations of these useful synthetic intermediates required multistep operations that result in low overall yields.[16,17]

Substituted 2- and 4-(Pivaloylamino)pyridines. The potential for application of the ortho-metalation technique to (pivaloylamino)pyridines bearing additional functionality was briefly examined. As expected both 2- and 4-(pivaloylamino)-3-methylpyridine (**5e** and **6e**) underwent exclusive lateral metalation when treated with *n*-butyllithium.[15] Stirring the reaction mixtures at room temperature for 4 h (**5e**) or overnight (**6e**) gave azaindoles **9** and **11** in 83% and 75%, respectively (Scheme II). Metalated picoline **8** could be intercepted with dimethyl disulfide (to produce **10**) simply by maintaining the reaction temperature at 0 °C, but similar treatment of **6e** invariably resulted in mixtures containing azaindole **11**.

Ortho metalation of 5-methyl-2-(pivaloylamino)pyridine (**12b**) proceeded cleanly under standard conditions, providing **13b** after a dimethyl disulfide quench (Scheme III). However, similar treatment of 4- and 6-methyl-2-(pivaloylamino)pyridine (**12a** and **12c**) resulted in the isolation of compounds **14a** and **14c**, respectively, products derived from abstraction of the relatively acidic methyl protons. This side reaction was circumvented by conducting the metalation under conditions that enhance coordination of

(13) Tamura, Y.; Fujita, M.; Chen, L.-C.; Inoue, M.; Kita, Y. *J. Org. Chem.* **1981**, *46*, 3564.
(14) Gungor, T.; Marsais, F.; Queguiner, G. *Synthesis* **1982**, 499.
(15) Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133.
(16) 2-Aminonicotinaldehyde: (a) Oakes, V.; Pascoe, R.; Rydon, H. N. *J. Chem. Soc.* **1956**, 1045. (b) Albert, A.; Reich, F. *Ibid.* **1960**, 1370. (c) For a simple two-step synthesis from nicotinamide, see: Majewicz, T. G.; Caluwe, P. *J. Org. Chem.* **1974**, *39*, 720.
(17) 4-Aminonicotinaldehyde: (a) Hawes, E. M.; Gorecki, D. K. J. *J. Heterocycl. Chem.* **1972**, *9*, 703 and references cited therein. (b) Armarego, W. L. F. *J. Chem. Soc.* **1962**, 4094.

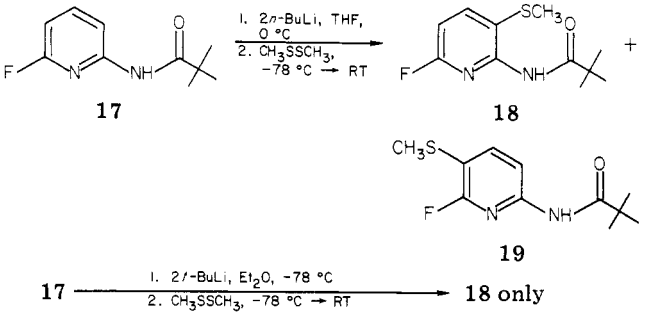
Scheme III



[a] *n*-BuLi, THF, 0 °C. [b] *t*-BuLi, Et_2O, −78 °C. [c] *t*-BuLi, THF, −78 °C. [d] *n*-BuLi, THF, −20 °C.

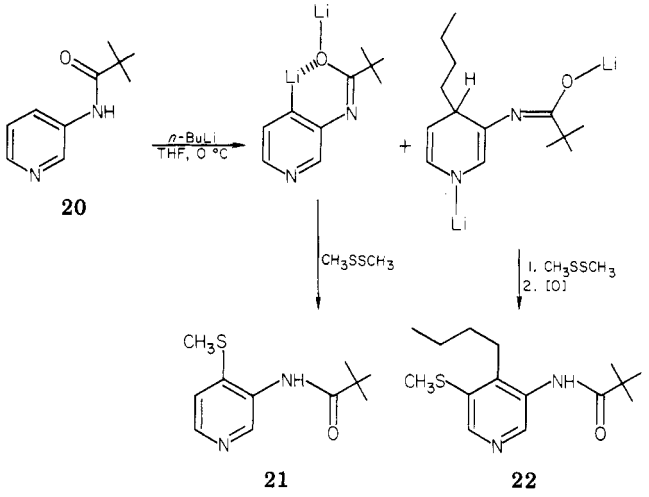
the metalating agent with the directing group.[1] Thus the sole products from treatment of **12a** or **12c** with *tert*-butyllithium in ether at −78 °C followed by addition of dimethyl disulfide were those derived from nuclear metalation, **13a** and **13c**, respectively.

Metalation of 6-chloro-2-(pivaloylamino)pyridine (**15b**) occurred cleanly at C-3 (*n*-butyllithium, THF, −20 °C), providing **16b** after reaction with dimethyl disulfide. Similar treatment of the more reactive 5-chloro isomer (**15a**) required very carefully controlled reaction conditions to minimize secondary reactions, while employment of *tert*-butyllithium in THF at −78 °C proved to be a much simpler procedure. In this fashion, **16a** was prepared in 86% yield after dimethyl disulfide quench (Scheme III). These results are consistent with previous studies that have shown the pivaloylamino group to be a more powerful ortho director than chlorine.[15] In contrast, metalation of 6-fluoro-2-(pivaloylamino)pyridine (**17**) gave a mixture of the two possible ortho-substitution products, **18** and **19**, establishing that fluorine is approximately equivalent in directing ability to pivaloylamino (in THF). Once again, use of conditions to achieve better coordination of the metalating agent with the pivaloylamino group, *tert*-butyllithium in ether at −78 °C, led to exclusive metalation at C-3, providing **18** after dimethyl disulfide treatment.



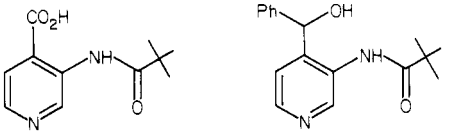
3-(Pivaloylamino)pyridine. Recent reports have suggested that clean metalation of 3-(pivaloylamino)-pyridine (**20**) cannot be achieved with *n*-butyllithium in THF.[13,14] One group found conditions (*n*-butyllithium, THF, Et_2O, TMEDA) that allowed the isolation of products derived from metalation at C-4, with maximum yields of only 50–60%.[14] We suspected that metalation of **20** was complicated by nucleophilic attack by the metalating agent on the pyridine nucleus and have demonstrated this in the following manner. After treatment of the reaction mixture obtained from **20** and *n*-butyllithium (THF, 0 °C, 3 h) with dimethyl disulfide, analysis of the crude mixture by VPC

Scheme IV



and TLC indicated two major materials neither of which corresponded to starting material. The products were cleanly separated by HPLC and identified on the basis of their corresponding NMR spectra as **21** (42%), from ortho metalation, and **22** (28%), from nucleophilic attack on pyridine by *n*-butyllithium (Scheme IV). While minor byproducts were present, there was no evidence for dihydropyridines in the crude product mixture, oxidation apparently occurring rapidly.

Although ortho lithiation of **20** is complicated by nucleophilic attack at C-4, the procedure is of synthetic utility especially in those cases where isolation of the desired product is straightforward. For example, addition of the metalation mixture obtained from **20** as described above to dry ice in ether produced isonicotinic acid **23** in 46% yield after a standard workup and recrystallization. Likewise, treatment of the metalation mixture with benzaldehyde gave an oily solid from which colorless crystalline **24**[14] was isolated in 53% yield simply by trituration with ether.

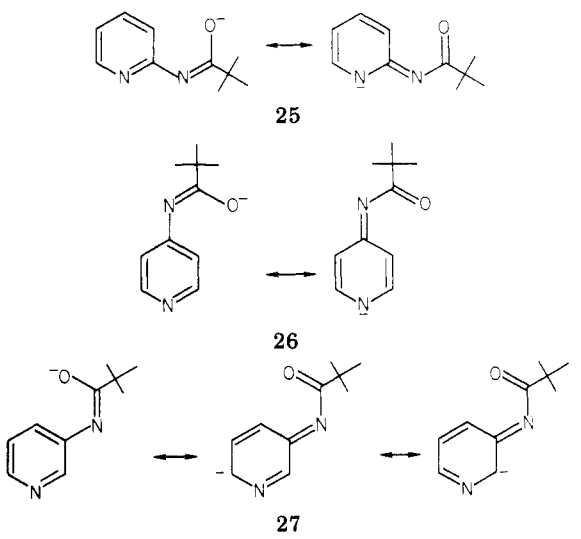


From the data available, we conclude that metalation accounts for at least 50–60% of the mixture obtained from reaction of **20** with *n*-butyllithium, while approximately 30–40% of the balance results from nucleophilic attack on the pyridine nucleus by the metalating agent. Attempts to improve the proportion of ortho metalation from **20** by altering reaction conditions proved unsuccessful. Thus, treatment of **20** with either LDA in THF or *tert*-butyllithium in ether resulted in almost exclusive recovery of starting material, while *tert*-butyllithium in THF (−78 °C, 3 h) followed by benzaldehyde quench produced **24** in essentially the same yield (55%) with that obtained from *n*-butyllithium.

Discussion

Most prior examples of substituted pyridine ortho lithiations were accomplished with the aid of strongly electron-withdrawing substituents.[8-10] In these, the enhanced acidity of the ortho proton renders proton abstraction by the metalating agent more favorable than nucleophilic attack at the azomethine. The only exceptions are evidenced by the successful metalations of 3-methoxy-5-

Scheme V



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(pivaloylamino)pyridine[13] and 3-(methoxymethoxy)-pyridine[11a] where enhanced coordination with the metalating agent directs proton abstraction. Other 3-alkoxypyridines have been metalated, surprisingly at C-2, when the reaction was conducted in the presence of TMEDA, but a mechanism involving coordination of *n*-butyllithium with the pyridine nitrogen instead of the ether oxygen has been proposed.[11b] The (pivaloylamino)pyridines thus appear to be one of the few examples in which a single *electron-donating* substituent is capable of directing lithiation of a pyridine by a "coordination-only" mechanism.[1]

The remarkable difference in reaction pathways observed between the seemingly similar 3-(pivaloylamino)-pyridine and 2- and 4-(pivaloylamino)pyridines under identical metalation conditions can be explained on the basis of decreased electrophilicity of the C=N bond in the latter. Resonance forms that place a negative charge on the pyridine nitrogen are expected to be major contributors to the resonance structures of monoanions **25** and **26** and the resulting increased electron density effectively shields the C=N bond from nucleophilic attack (Scheme V). Since no similar resonance forms may be written for the monoanion of 3-(pivaloylamino)pyridine (**27**), the electrophilicity of the azomethine is not appreciably decreased and nucleophilic attack by the metalating agent is still viable.[18]

In conclusion, we have demonstrated a metalation procedure that allows regiospecific electrophilic substitution of an aminopyridine and provided an efficient synthesis of 2- and 4-aminonicotinaldehydes. Clearly this simple procedure can provide a variety of substituted aminopyridines previously unavailable or prepared only with great difficulty.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded as KBr pellets or thin films on salt plates with a Beckman Acculab 3 infrared spectrophotometer. Proton NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) at 90 MHz with a Varian EM-390 spectrometer. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane and coupling constants are listed in hertz. Preparative chromatographies were performed with a Waters Prep System 500A liquid chromatograph. Tetrahydrofuran and ether were distilled from sodium–benzophenone immediately prior to use. *n*-Butyllithium (1.55–1.65 M in hexane) and *tert*-butyllithium (2.1 M in pentane) were obtained from Aldrich Chemical Co. and were used without titration. 6-Chloro-2-aminopyridine[21] and 6-fluoro-2-aminopyridine[22] were available from in house stores. Other reagents were generally used as received. Microanalyses were performed by Mary Gade of the Dow Chemical Co., Walnut Creek, CA.

2,2-Dimethyl-*N*-(2-pyridinyl)propanamide (1). A solution of 6.63 g (55 mmol) of trimethylacetyl chloride in 10 mL of methylene chloride was slowly added to an ice cooled solution of 4.70 g (50 mmol) of 2-aminopyridine and 6.31 g (62.5 mmol) of triethylamine in 75 mL of methylene chloride. The resulting mixture was stirred in an ice bath for 15 min and then at room temperature for 2 h and poured into water. The methylene chloride layer was washed with dilute $NaHCO_3$, dried over Na_2SO_4, and evaporated to leave a brown oil. Crystallization from hexane gave white crystals: mp 71–73 °C (7.0 g, 79%); NMR[23] δ 8.21 (m, 2 H, H-3, H-6), 8.12 (br, 1 H, NH), 7.63 (m, 1 H, H-4), 6.96 (ddd, J = 1.5, 5, 7.5, 1 H, H-5), 1.32 (s, 9 H, *tert*-butyl); IR (KBr) 3305, 3240, 2965, 1678 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.61; H, 7.92; N, 15.72.

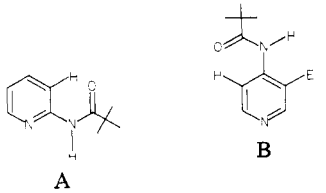
2,2-Dimethyl-*N*-(4-pyridinyl)propanamide (2). Treatment of 4-aminopyridine (50 mmol) with trimethylacetyl chloride (55 mmol) by the procedure described for **1** gave 8.55 g of crude product as a light brown solid. The product was recrystallized from ethyl acetate/hexane to give 6.55 g (74%) of **2** as white crystals: mp 133–5 °C (lit.[24] mp 170 °C); NMR δ 8.41 (dd, J = 1.5, 5, 2 H, H-2, H-6), 8.16 (br, 1 H, NH), 7.51 (dd, J = 1.5, 5, 2 H, H-3, H-5), 1.29 (s, 9 H, *tert*-butyl); IR (KBr) 3235, 2965, 1687, 1590 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.37; H, 7.80; N, 15.73.

2,2-Dimethyl-*N*-(3-pyridinyl)propanamide (20). This material was prepared from 3-aminopyridine (50 mmol) by the procedure described for **1**. The crude product (9.0 g) was taken up in hot ethyl acetate, treated with charcoal, and concentrated. Crystalline **20** was obtained upon dilution with hexane and cooling: mp 128–131 °C (lit.[24] mp 127 °C), 6.47 g (73%); NMR δ 8.57 (d, J = 2.5, 1 H, H-2), 8.29 (dd, J = 1.5, 5, 1 H, H-6), 8.12 (ddd, J = 1.5, 2.5, 8, 1 H, H-4), 7.80 (br, 1 H, NH), 7.21 (dd, J = 5, 8, 1 H, H-5), 1.32 (s, 9 H, *tert*-butyl); IR (KBr) 3210, 3160, 2965, 1675 cm^{-1}.

General Procedure for Metalation of (Pivaloylamino)-pyridines 1 and 2. An oven-dried three-necked round-bottom flask was cooled in a dessicator and then equipped with a ther-

(18) In support of this mechanism we note that reaction of 4-((dimethylamino)methyl)pyridine with *tert*-butyllithium produces a significant quantity of 2-(*tert*-butyl)-4-((dimethylamino)methyl)pyridine.[19] Although the (dimethylamino)methyl group is generally considered to be the most powerful substituent capable of directing lithiation by a "coordination-only" mechanism,[1,20] it cannot decrease the electrophilicity of the C=N bond in pyridine.

(19) Deutsch, E.; Cheung, N. K. V. *J. Org. Chem.* **1973**, *38*, 1123.
(20) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653.
(21) Cava, M. P.; Bhattacharyya, N. K. *J. Org. Chem.* **1958**, *23*, 1287.
(22) Finger, G. C.; Starr, L. D.; Roe, A.; Link, W. J. *J. Org. Chem.* **1962**, *27*, 3965.
(23) The strong anisotropic deshielding of H-3 seen in the NMR spectrum of 2-(pivaloylamino)pyridines implies a favored configuration



A B

A, free rotation of the pivaloylamino group perhaps being restricted by electron repulsion between the carbonyl oxygen and the pyridine nitrogen. A similar deshielding of H-5 is observed in the NMR spectra of disubstituted pyridines **6**. Configuration B would be expected for **6** since this minimizes steric interactions between the pivaloyl group and the C-3 substituent while maximizing conjugation with the aromatic, thus forcing the carbonyl into appropriate alignment for deshielding of H-5.
(24) El-Zahraa, F.; El-Basil, S.; El-Sayed, M.; Ghoneim, K. M.; Khalifa, M. *Pharmazie* **1979**, *34*, 12. A discrepancy was noted between the observed melting point for **2** and the reported value.

mometer, a nitrogen inlet, and a magnetic stirrer and flushed with nitrogen. The flask was charged with (pivaloylamino)pyridine 1 or 2 (10 mmol unless otherwise stated) and stoppered with a rubber septum and THF (2–4 mL/mmol of 1 or 2) was introduced. After cooling to either 0 or −78 °C (to more easily control the large exotherm), *n*-butyllithium (1.6–1.7 M in hexane, 25 mmol unless otherwise stated) was added dropwise via syringe. The resulting yellow solution, from which a white solid soon precipitated, was stirred for 2–4 h at 0 °C before quenching with a solution of the electrophile in 2–4 mL of THF at the appropriate temperature. The mixture was allowed to warm to room temperature, poured into water, and extracted three times with ether. The combined ether layers were washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated to dryness.

2,2-Dimethyl-*N*-(3-deuterio-2-pyridinyl)propanamide (5a). Metalation of 5 mmol of 1 was accomplished as described above with 12.5 mmol of *n*-butyllithium in hexane and then quenched at −78 °C with 0.60 g (30 mmol) of D_2O in 5 mL of THF. After warming to room temperature and standard workup, the crude product (97%) was crystallized from hexane to give **5a** as white crystals: mp 71–73.5 °C (0.77 g, 87%); NMR δ 8.24 (dd, *J* = 2, 7.5, 1 H, H-6), 8.03 (br, 1 H, NH), 7.67 (br d, *J* = 5, 1 H, H-4), 6.98 (dd, *J* = 5, 7.5, 1 H, H-5), 1.32 (s, 9 H, *tert*-butyl); exact mass calcd for $C_{10}H_{13}DN_2O$ 179.1168, found 179.1170.

2,2-Dimethyl-*N*-(3-(trimethylsilyl)-2-pyridinyl)propanamide (5b). The reaction mixture from metalation of 10 mmol of 1 was quenched at −78 °C with 2.71 g (25 mmol) of chlorotrimethylsilane. Standard workup followed by recrystallization from hexane gave white crystals: mp 99–101 °C (2.14 g, 86%); NMR δ 8.40 (br dd, *J* = 2, 5, 1 H, H-6), 7.81 (dd, *J* = 2, 7.5, 1 H, H-4), 7.67 (br, 1 H, NH), 7.07 (dd, *J* = 5, 7.5, 1 H, H-5), 1.31 (s, 9 H, *tert*-butyl), 0.30 (s, 9 H, $SiMe_3$); IR (KBr) 3210, 2975, 1680, 1400 cm^{-1}. Anal. Calcd for $C_{13}H_{22}N_2OSi$: C, 62.35; H, 8.86; N, 11.19. Found: C, 62.29; H, 8.82; N, 11.16.

***N*-(3-Formyl-2-pyridinyl)-2,2-dimethylpropanamide (5c).** Following the procedure described above, 50 mmol of 1 was metalated with 125 mmol of *n*-butyllithium. The reaction mixture was quenched at −78 °C with a solution of 10.95 g (150 mmol) of dimethylformamide in 10 mL of THF, allowed to warm to room temperature, and poured into a mixture of ice and 6 N HCl. After the mixture was stirred for 15 min the organic layer was separated (discard) and the aqueous layer neutralized with K_2CO_3 and extracted three times with ether. The combined ether layers were washed with water, saturated NaCl, dried over $MgSO_4$, and evaporated to give 8.67 g (84%) of **5c** as a yellow oil, which solidified upon standing. Recrystallization from ethyl acetate/hexane gave white crystals: mp 91–93 °C (5.58 g, 54%); NMR δ 9.92 (s, 1 H, CHO), 8.57 (dd, *J* = 2, 5, 1 H, H-6), 8.06 (dd, *J* = 2, 7.5, 1 H, H-4), 7.16 (dd, *J* = 5, 7.5, 1 H, H-5), 1.34 (s, 1 H, *tert*-butyl); IR (KBr) 3290, 2975, 1703, 1665 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 64.13; H, 6.81; N, 13.56.

2,2-Dimethyl-*N*-(3-(methylthio)-2-pyridinyl)propanamide (5d). The mixture from metalation of 10 mmol of 1 was quenched at −78 °C with 2.82 g (30 mmol) of dimethyl disulfide. Standard workup and recrystallization from ethyl acetate/hexane gave white crystals: mp 133–135 °C (1.50 g, 67%); NMR δ 8.29 (dd, *J* = 2, 5, 1 H, H-6), 8.29 (br, 1 H, NH), 7.64 (dd, *J* = 2, 8, 1 H, H-4), 7.03 (dd, *J* = 5, 8, 1 H, H-5), 2.39 (s, 3 H, SMe), 1.34 (s, 9 H, *tert*-butyl); IR (KBr) 3150, 1680 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.89; H, 7.19; N, 12.49. Found: C, 59.05; H, 7.22; N, 12.49.

2,2-Dimethyl-*N*-(3-methyl-2-pyridinyl)propanamide (5e). The reaction mixture obtained from metalation of 1 (10 mmol) was treated at −78 °C with 2.13 g (15 mmol) of methyl iodide. The mixture was allowed to warm to room temperature and a mildly exothermic reaction occurred at ~0 °C. The solid **5e** obtained after the usual workup was recrystallized from hexane to give white crystals: mp 85–88 °C (1.38 g, 72%); NMR δ 8.50 (br, 1 H, NH), 8.19 (dd, *J* = 1.5, 4.5, 1 H, H-6), 7.52 (br d, *J* = 7, 1 H, H-4), 7.04 (dd, *J* = 4.5, 7, 1 H, H-5), 2.20 (s, 3 H, CH_3), 1.27 (s, 9 H, *tert*-butyl); IR (KBr) 3160, 2960, 1680 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.71; H, 8.39; N, 14.57. Found: C, 68.60; H, 8.38; N, 14.45.

Treatment at −78 °C of the mixture obtained from metalation of 10 mmol of 1 with a solution of 7.10 g (50 mmol) of methyl iodide in 5 mL of THF followed by stirring at room temperature for 20 h and standard workup gave 1.70 g (89%) of a white solid. VPC and NMR analysis indicated that this material consisted only of monomethylated (pivaloylamino)pyridine **5e**.

***N*-(3-(Hydroxyphenylmethyl)-2-pyridinyl)-2,2-dimethylpropanamide (5f).** After metalation of 10 mmol of 1 as described above, the reaction mixture was treated at 0 °C with 1.59 g (15 mmol) of benzaldehyde. After warming of the mixture to room temperature and standard workup, the crude product was purified by preparative HPLC (3:2 ethyl acetate/hexane) to give 2.03 g (71%) of **5f** as a thick gum. Crystallization from hexane containing a small amount of acetone gave white crystals: mp 114–117 °C (1.78 g, 63%); NMR δ 8.67 (br, 1 H, NH or OH), 8.26 (dd, *J* = 2, 5, 1 H, H-6), 7.51 (dd, *J* = 2, 8, 1 H, H-4), 7.28 (s, 5 H, Ph), 7.03 (dd, *J* = 5, 8, 1 H, H-5), 5.83 (s, 1 H, CHO), 4.93 (br, 1 H, NH or OH), 1.19 (s, 9 H, *tert*-butyl); IR (KBr) 3270, 1692 cm^{-1}. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.91; H, 7.04; N, 9.80.

Ethyl 2-((2,2-Dimethyl-1-oxopropyl)amino)-3-pyridinecarboxylate (5g). After metalation of 10 mmol of 1 as described above, 1.63 g (15 mmol) of ethyl chloroformate was added at −78 °C. After warming of the mixture to room temperature and standard workup, recrystallization from hexane gave 1.62 g (65%) of **5g** as yellow crystals: mp 90–93 °C; NMR δ 8.76 (dd, *J* = 2, 5, 1 H, H-6), 8.43 (dd, *J* = 2, 7.5, 1 H, H-4), 7.13 (dd, *J* = 5, 7.5, 1 H, H-5), 4.47 (q, *J* = 7.5, 2 H, OCH_2), 1.44 (t, *J* = 7.5, 3 H, CH_3), 1.38 (s, 9 H, *tert*-butyl); IR (KBr) 3260, 1695 (br, strong) cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.20. Found: C, 62.14; H, 7.21; N, 10.92.

2,2-Dimethyl-*N*-(3-deuterio-4-pyridinyl)propanamide (6a). After metalation of 2 (10 mmol) as described above, the reaction was quenched at −78 °C with 0.60 g (30 mmol) of D_2O. After warming of the mixture to room temperature and standard workup, the solid **6a** was recrystallized from ethyl acetate/hexane to give off-white crystals: mp 132–135 °C (1.56 g, 87%); NMR δ 8.42 (d, *J* = 5.5, 1 H, H-6), 8.42 (s, 1 H, H-2), 8.23 (br, 1 H, NH), 7.52 (d, *J* = 5.5, 1 H, H-5), 1.27 (s, 9 H, *tert*-butyl); exact mass calcd for $C_{10}H_{13}DN_2O$ 179.1168, found 179.1171.

2,2-Dimethyl-*N*-(3-(trimethylsilyl)-4-pyridinyl)propanamide (6b). The reaction mixture obtained from metalation of 2 (10 mmol) was treated at −78 °C with 2.71 g (25 mmol) of chlorotrimethylsilane. The mixture was warmed to room temperature and standard workup gave solid **6b**. Recrystallization from hexane gave white crystals: mp 92–93.5 °C (1.98 g, 79%); NMR[23] δ 8.44 (d, *J* = 6, 1 H, H-6), 8.44 (s, 1 H, H-2), 8.12 (d, *J* = 6, 1 H, H-5), 7.40 (br, 1 H, NH), 1.29 (s, 9 H, *tert*-butyl), 0.40 (s, 9 H, $SiMe_3$); IR (KBr) 3335, 2960, 1660 cm^{-1}. Anal. Calcd for $C_{13}H_{22}N_2OSi$: C, 62.35; H, 8.86; N, 11.19. Found: C, 62.39; H, 8.86; N, 11.11.

***N*-(3-Formyl-4-pyridinyl)-2,2-dimethylpropanamide (6c).** The lithiated pyridine obtained from 2 (10 mmol) as described above was quenched at 0 °C with 2.19 g (30 mmol) of dimethylformamide. After warming to room temperature, the reaction mixture was poured into a mixture of ice and 6 N HCl and stirred for 5 min. The mixture was neutralized with K_2CO_3 and extracted three times with ether. The combined organic layers were washed with water and saturated NaCl, dried over $MgSO_4$, and evaporated to give crystalline **6c**. Recrystallization from hexane gave pale yellow crystals: mp 60–63 °C (1.24 g, 60%); NMR[23] δ 10.02 (s, 1 H, CHO), 8.81 (s, 1 H, H-2), 8.63 (s, 2 H, H-5, H-6), 1.35 (s, 9 H, *tert*-butyl); IR (KBr) 3275, 1710, 1682 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59. Found: C, 64.09; H, 6.77; N, 13.59.

2,2-Dimethyl-*N*-(3-(methylthio)-4-pyridinyl)propanamide (6d). Quenching the reaction mixture obtained from lithiation of 2 (10 mmol) with 2.82 g (30 mmol) of dimethyl disulfide at 0 °C followed by the usual workup gave **6d** as an oil. The oil was purified by crystallization from hexane to give white crystals: mp 57–59 °C (2.11 g, 94%); NMR[23] δ 8.95 (br, 1 H, NH), 8.63 (s, 1 H, H-2), 8.43 (d, *J* = 6, 1 H, H-5 or H-6), 8.32 (d, *J* = 6, 1 H, H-5 or H-6), 2.36 (s, 3 H, SMe), 1.33 (s, 9 H, *tert*-butyl); IR (KBr) 3340, 2975, 1690 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.89; H, 7.19; N, 12.49. Found: C, 59.16; H, 7.25; N, 12.35.

2,2-Dimethyl-*N*-(3-methyl-4-pyridinyl)propanamide (6e). After metalation of 10 mmol of 2 as described above, the mixture was treated at −78 °C with a solution of 1.56 g (11 mmol) of methyl

iodide in 5 mL of THF. The mixture was slowly warmed to room temperature and after standard workup a light brown oil was obtained. The oil was purified by preparative liquid chromatography (45:55 acetone/hexane) then distilled by using a Kugelrohr apparatus (oven temperature ~100 °C (0.04 mmHg)) to give **6e** as a colorless oil (1.42 g, 74%), which solidified upon standing. The waxy solid could not be effectively recrystallized: NMR[23] δ 8.32 (d, J = 6, 1 H, H-5 or H-6), 8.29 (s, 1 H, H-2), 8.04 (d, J = 6, 1 H, H-5 or H-6), 7.46 (br, 1 H, NH), 2.22 (s, 3 H, CH_3), 1.33 (s, 9 H, *tert*-butyl); IR (film) 3310, 2970, 1680 (br) cm^{-1}; exact mass calcd 192.1263, found 192.1265. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.71; H, 8.39; N, 14.57. Found: C, 68.04; H, 8.23; N, 14.41.

2-Amino-3-pyridinecarboxaldehyde. A solution of 2.06 g (10 mmol) of **5c** in 15 mL of 3 N aqueous HCl was warmed at reflux for a period of 4 h. The solution was cooled to room temperature and washed twice with ether (discard). The aqueous layer was neutralized with K_2CO_3 and extracted four times with ether, and the combined ether layers were dried over K_2CO_3 and evaporated to dryness. The resulting solid was recrystallized for methylcyclohexane to give 1.14 g (93%) of 2-aminonicotinaldehyde as yellow needles: mp 98–100 °C (lit.[16c] mp 98–99 °C). Anal. Calcd for $C_6H_6N_2O$: C, 59.00; H, 4.95; N, 22.94. Found: C, 58.61; H, 4.87; N, 22.76.

4-Amino-3-pyridinecarboxaldehyde. A solution of 2.06 g (10 mmol) of **6c** in 15 mL of 3 N aqueous HCl was warmed at reflux for a period of 8 h. After cooling to room temperature, the solution was washed twice with ether (discard) and neutralized with K_2CO_3. The aqueous layer was extracted three times with chloroform, and the combined organic layers were dried over K_2CO_3 and evaporated to leave a yellow solid. Recrystallization from methylcyclohexane gave 1.05 g (86%) of 4-aminonicotinaldehyde as colorless crystals: mp 114–116 °C (lit.[17b] mp 113–114 °C). Anal. Calcd for $C_6H_6N_2O$: C, 59.00, H, 4.95; N, 22.94. Found: C, 58.83; H, 4.96; N, 22.60.

2-(1,1-Dimethylethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (9). A mixture of 1.92 g (10 mmol) of **5e** and 25 mmol of *n*-butyllithium, prepared at 0 °C in 30 mL of THF as described above, was allowed to stir at room temperature for 4 h. The resulting red-orange solution was poured into water and after a standard workup an off-white solid was obtained. The solid was recrystallized from acetone/hexane to give 1.45 g (83%) of **9** as white crystals: mp 194–196 °C; NMR (Me_2SO-d_6) δ 8.08 (dd, J = 2, 5, 1 H, H-6), 7.76 (dd, J = 2, 8, 1 H, H-4), 6.93 (dd, J = 5, 8, 1 H, H-5), 6.08 (br s, 1 H, H-4), 1.33 (s, 9 H, *tert*-butyl); IR (KBr) 3140, 2960, 1278 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.54; H, 8.00; N, 15.92.

2,2-Dimethyl-*N*-(3-((methylthio)methyl)-2-pyridinyl)propanamide (10). The mixture prepared as described above from 1.92 g (10 mmol) of **5e**, 25 mmol of *n*-butyllithium, and 30 mL of THF was stirred at 0 °C for 4 h. The red-orange mixture was cooled to −78 °C, 2.35 g (25 mmol) of dimethyl disulfide added, and the mixture allowed to warm to room temperature. After standard workup and crystallization from hexane containing a small amount of ethyl acetate, 1.95 g (82%) of **10** was obtained as white needles: mp 74–76 °C; NMR δ 8.50 (br, 1 H, NH), 8.40 (dd, J = 1.7, 5, 1 H, H-6), 7.68 (dd, J = 1.7, 7, 1 H, H-4), 7.12 (dd, J = 5, 7, 1 H, H-5), 3.66 (s, 2 H, CH_2S), 1.95 (s, 3 H, SCH_3), 1.35 (s, 9 H, *tert*-butyl); IR (KBr) 3114, 2960, 1688, 1668 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.96; H, 7.50; N, 11.68.

2-(1,1-Dimethylethyl)-1*H*-pyrrolo[3,2-*c*]pyridine (11). A mixture of 0.96 g (5 mmol) of **6e** and 25 mmol of *n*-butyllithium prepared at 0 °C as described above in 20 mL of THF was stirred overnight at room temperature. The mixture was poured into water and extracted four times with ether, and the combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The residual solid was recrystallized from ethyl acetate to give 0.65 g (75%) of 11 as white crystals: mp 270–272 °C; NMR (Me_2SO-d_6) δ 8.65 (s, 1 H, H-4), 8.06 (d, J = 6, 1 H, H-6), 7.23 (d, J = 6, 1 H, H-7), 6.19 (br s, 1 H, H-3), 1.33 (s, 9 H, *tert*-butyl); IR (KBr) 3200–2800 (br), 2960 cm^{-1}; exact mass calcd 174.1157, found 174.1162. Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.26; H, 7.92; N, 15.89.

2,2-Dimethyl-*N*-(4-methyl-2-pyridinyl)propanamide (12a). Treatment of 10.8 g (0.1 mol) of 4-methyl-2-aminopyridine with 13.26 g (0.11 mol) of trimethylacetyl chloride by the procedure described for **1** gave 17.58 g (92%) of **12a** as white crystals (mp 96–98 °C) after recrystallization from hexane: NMR δ 8.26 (m, 2 H, H-3, 6), 8.16 (br, 1 H, NH), 6.97 (br d, J = 5, 1 H, H-5), 2.38 (s, 3 H, CH_3), 1.33 (s, 9 H, *tert*-butyl); IR (KBr) 3310, 2980, 1672, 1420 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.71; H, 8.39; N, 14.57. Found: C, 68.67; H, 8.40; N, 14.73.

2,2-Dimethyl-*N*-(5-methyl-2-pyridinyl)propanamide (12b). After reaction of 16.20 g (0.15 mol) of 5-methyl-2-aminopyridine with 0.16 mol of trimethylacetyl chloride by the procedure described for **1** and standard workup the product was eluted through a short column of silica gel with CH_2Cl_2 and recrystallized from hexane to give 23.82 g (83%) of **12b** as white crystals: mp 69–70 °C; NMR δ 8.31 (d, J = 9, 1 H, H-3), 8.24 (d, J = 2.5, 1 H, H-6), 8.18 (br, 1 H, NH), 7.64 (dd, J = 2.5, 9, 1 H, H-4), 2.32 (s, 3 H, CH_3), 1.34 (s, 9 H, *tert*-butyl); IR (KBr) 3225, 2975, 1676 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.71; H, 8.39; N, 14.57. Found: C, 68.67; H, 8.37, N, 14.50.

2,2-Dimethyl-*N*-(6-methyl-2-pyridinyl)propanamide (12c). A solution of 21.6 g (0.2 mol) of 6-methyl-2-aminopyridine in 250 mL of CH_2Cl_2 was treated with 26.51 g (0.22 mol) of trimethylacetyl chloride by the procedure described for **1**. After the usual workup the product was eluted through a short column of silica gel and the resulting oil crystallized from hexane to yield 31.92 g (83%) of **12c** as white crystals: mp 66–68 °C; NMR δ 8.21 (d, J = 8, 1 H, H-3), 8.09 (br, 1 H, NH), 7.69 (t, J = 8, 1 H, H-4), 6.97 (d, J = 8, 1 H, H-5), 2.47 (s, 3 H, CH_3), 1.38 (s, 9 H, *tert*-butyl); IR (KBr) 3305, 2975, 1670, 1455 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.71; H, 8.39; N, 14.57. Found: C, 68.55; H, 8.30; N, 14.50.

2,2-Dimethyl-*N*-(4-methyl-3-(methylthio)-2-pyridinyl)propanamide (13a) and 2,2-Dimethyl-*N*-(4-((methylthio)methyl)-2-pyridinyl)propanamide (14a). A solution of 3.84 g (20 mmol) of **12a** in 60 mL of THF was treated at −78 °C with 50 mmol of *n*-butyllithium and the bright yellow reaction mixture stirred at 0 °C for 1 h. After cooling of the mixture to −78 °C, addition of dimethyl disulfide (40 mmol) followed by warming to room temperature and standard workup gave an oil, which was separated into two fractions by preparative LC, eluting first with hexane/ethyl acetate (1:1) and then with ethyl acetate. The more polar fraction (1.92 g, 40%) was crystallized from hexane/ethyl acetate to give **13a** as white crystals: mp 72–75 °C; NMR δ 9.49 (br, 1 H, NH), 8.47 (d, J = 5, 1 H, H-6), 7.05 (d, J = 5, 1 H, H-5), 2.57 (s, 3 H, CH_3), 2.27 (s, 3 H, SCH_3), 1.39 (s, 9 H, *tert*-butyl); IR (KBr) 3200, 2975, 1668 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.41; H, 7.58; N, 11.65.

The less polar fraction (2.44 g, 51%) was a waxy solid and was further purified by Kugelrohr distillation (100–110 °C (0.02 mmHg)) and crystallization from hexane to give **14a** as white crystals: mp 54–57 °C; NMR δ 8.36 (m, 2 H, H-3, 6), 8.22 (br, 1 H, NH), 7.16 (br d, J = 6, 1 H, H-5), 3.67 (s, 2 H, CH_2S), 2.05 (s, 3 H, SCH_3), 1.35 (s, 9 H, *tert*-butyl); IR (KBr) 3300, 2950, 1660, 1400 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.35; H, 7.51; N, 11.75.

2,2-Dimethyl-*N*-(4-methyl-3-(methylthio)-2-pyridinyl)propanamide (13a). *tert*-Butyllithium (22 mmol) was added at −78 °C to a mixture of 1.92 g (10 mmol) of **12a** in 40 mL of ether and stirred at −78 °C for 3 h. After addition of dimethyl disulfide (15 mmol) and warming to room temperature, the usual workup and crystallization from ethyl acetate/hexane gave 1.77 g (74%) of **13a** as a colorless solid: mp 76–78 °C.

2,2-Dimethyl-*N*-(5-methyl-3-(methylthio)-2-pyridinyl)propanamide (13b). A solution of 1.92 g (10 mmol) of **12b** in 30 mL of THF was treated at −78 °C with 25 mmol of *n*-butyllithium and the resulting mixture stirred at 0 °C for 3 h. The mixture was cooled to −78 °C, 20 mmol of dimethyl disulfide added, and the mixture allowed to warm to room temperature and poured into water. The aqueous mixture was extracted three times with CH_2Cl_2, and the combined organic layers were washed with water, dried over $MgSO_4$, and evaporated to leave a solid that was recrystallized from toluene to give 2.24 g (94%) of **13b** as colorless crystals: mp 156–157 °C; NMR δ 8.30 (d, J = 2, 1 H, H-6), 8.26 (br, 1 H, NH), 7.61 (d, J = 2, 1 H, H-4), 2.47 (s, 3 H, SCH_3), 2.34 (s, 3 H, CH_3), 1.37 (s, 9 H, *tert*-butyl); IR (KBr) 3140, 2950, 1668 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.51; H, 7.43; N, 11.59.

2,2-Dimethyl-*N*-(6-methyl-3-(methylthio)-2-pyridinyl)propanamide (13c) and 2,2-Dimethyl-*N*-(6-((methylthio)-

methyl)-2-pyridinyl)propanamide (14c). A solution of 5.76 g (30 mmol) of **12c** in 90 mL of THF was treated at −78 °C with 75 mmol of *n*-butyllithium and the resulting deep orange solution stirred at 0 °C for 2.5 h. The mixture was then cooled to −78 °C, quenched by addition of 60 mmol of dimethyl disulfide, and warmed to room temperature. Standard workup and crystallization from ethyl acetate/hexane gave 4.22 g (59%) of **13c** as colorless crystals: mp 141–143 °C; NMR δ 8.54 (br, 1 H, NH), 7.74 (d, *J* = 8, 1 H, H-4), 7.07 (d, *J* = 8, 1 H, H-5), 2.55 (s, 3 H, CH_3), 2.41 (s, 3 H, SCH_3), 1.38 (s, 9 H, *tert*-butyl); IR (KBr) 3180, 2975, 1680, 1440 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.23; H, 7.46; N, 11.62.

The filtrates from crystallization of **13c** were purified by preparative LC, eluting with hexane/ethyl acetate (85:15) to yield 1.92 g (27%) of **14c** as a colorless oil: NMR δ 8.31 (d, *J* = 8, 1 H, H-3), 8.15 (br, 1 H, NH), 7.80 (t, *J* = 8, 1 H, H-4), 7.18 (d, *J* = 8, 1 H, H-5), 3.74 (s, 2 H, CH_2S), 2.10 (s, 3 H, SCH_3), 1.35 (s, 9 H, *tert*-butyl); IR (film) 3380, 2980, 1690, 1455 cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.76. Found: C, 60.06; H, 7.36; N, 11.67.

2,2-Dimethyl-*N*-(6-methyl-3-(methylthio)-2-pyridinyl)-propanamide (13c). To a mixture of 1.92 g (10 mmol) of **12c** and 40 mL of ether at −78 °C was slowly added 22 mmol of *tert*-butyllithium and the resulting mixture stirred at −78 °C for 3 h and then at 0 °C for 30 min. After cooling of the mixture to −78 °C, dimethyl disulfide (15 mmol) was added and the mixture stirred overnight at room temperature when VPC and NMR analysis of an aliquot indicated complete conversion to one product. Standard workup and crystallization from ethyl acetate/hexane gave 1.77 g (74%) of **13c** as white crystals: mp 141–143 °C.

2,2-Dimethyl-*N*-(5-chloro-2-pyridinyl)propanamide (15a). This material was prepared from 6.43 g (50 mmol) of 2-amino-5-chloropyridine and 55 mmol of trimethylacetyl chloride by the procedure described for **1**. The crude mixture obtained after standard workup was eluted through a short column of silica gel with CH_2Cl_2 and then recrystallized from hexane to give 9.68 g (91%) of **15a** as white crystals: mp 53–56 °C; NMR δ 8.31 (d, *J* = 9, 1 H, H-3), 8.27 (d, *J* = 2.5, 1 H, H-6), 8.13 (br, 1 H, NH), 7.69 (dd, *J* = 2.5, 9, 1 H, H-4), 1.32 (s, 9 H, *tert*-butyl); IR (KBr) 3300, 2955, 1664, 1510 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.43; H, 6.15; N, 13.32.

2,2-Dimethyl-*N*-(6-chloro-2-pyridinyl)propanamide (15b). Reaction of 19.27 g (0.15 mol) of 6-chloro-2-aminopyridine and 19.28 g (0.16 mol) of trimethylacetyl chloride by the procedure described for **1** gave a brown oil, which was eluted with CH_2Cl_2 through a short column of silica gel. The resulting oil was treated with charcoal in hot hexane and then crystallized from hexane to give 24.89 g (78%) of **15a** as white crystals: mp 86–89 °C; NMR δ 8.35 (d, *J* = 8, 1 H, H-3), 8.13 (br, 1 H, NH), 7.79 (t, *J* = 8, 1 H, H-4), 7.17 (d, *J* = 8, 1 H, H-5), 1.33 (s, 9 H, *tert*-butyl); IR (KBr) 3335, 2985, 1672, 1433 cm^{-1}. Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.51; H, 6.16; N, 13.22.

2,2-Dimethyl-*N*-(5-chloro-3-(methylthio)-2-pyridinyl)-propanamide (16a). To a solution of 2.13 g (10 mmol) of **15a** in 40 mL of THF at −78 °C was slowly added 22 mmol of *tert*-butyllithium and the resulting mixture stirred at −78 °C for 3 h. After addition of dimethyl disulfide (15 mmol) and warming to room temperature, standard workup and crystallization from ethyl acetate/hexane gave 2.23 g (86%) of **16a** as white crystals: mp 131–133 °C; NMR δ 8.36 (d, *J* = 2.4, 1 H, H-6), 8.21 (br, 1 H, NH), 7.71 (d, *J* = 2.4, 1 H, H-4), 2.46 (s, 3 H, SCH_3), 1.34 (s, 9 H, *tert*-butyl); IR (KBr) 3150, 2955, 1672, 1420 cm^{-1}. Anal. Calcd. for $C_{11}H_{15}ClN_2OS$: C, 51.05; H, 5.84; N, 10.83. Found: C, 50.84; H, 5.76; N, 10.96.

2,2-Dimethyl-*N*-(6-chloro-3-(methylthio)-2-pyridinyl)-propanamide (16b). *n*-Butyllithium (25 mmol) was slowly added at −78 °C to a solution of 2.13 g (10 mmol) of **15b** in 30 mL of THF and the resulting solution stirred at −20 °C for 3 h. The solution was cooled to −78 °C, quenched by addition of 20 mmol of dimethyl disulfide, and allowed to warm to room temperature. Standard workup gave a yellow solid, which was recrystallized from toluene to give 2.01 g (78%) of **16b** as colorless crystals: mp 156–158 °C; NMR δ 8.36 (br, 1 H, NH), 7.80 (d, *J* = 8.5, 1 H, H-4), 7.25 (d, *J* = 8.5, 1 H, H-5), 2.45 (s, 3 H, SCH_3), 1.38 (s, 9 H, *tert*-butyl); IR (KBr) 3230, 2965, 1685, 1672, 1420 cm^{-1}. Anal. Calcd for $C_{11}H_{15}ClN_2OS$: C, 51.05; H, 5.84; N, 10.83. Found: C, 51.17; H, 5.70; N, 10.76.

2,2-Dimethyl-*N*-(6-fluoro-2-pyridinyl)propanamide (17). Reaction of 6-fluoro-2-aminopyridine (11.2 g, 0.1 mol) with 13.26 g (0.11 mol) of trimethylacetyl chloride by the procedure described for **1** gave a solid, which was treated with charcoal in hot ethyl acetate and then crystallized from hexane to give 16.68 g (85%) of **17** as tan crystals: mp 94–96 °C; NMR δ 8.26 (ddd, *J* = 0.8, 2.4, 8.4, 1 H, H-3), 8.03 (br, 1 H, NH), 7.91 (q, *J* = 8.4, 1 H, H-4), 6.74 (ddd, *J* = 0.8, 2.4, 8.4, 1 H, H-5), 1.33 (s, 9 H, *tert*-butyl); IR (KBr) 3300, 2945, 1668, 1438 cm^{-1}. Anal. Calcd for $C_{10}H_{13}FN_2O$: C, 61.21; H, 6.68; N, 14.28. Found: C, 61.37; H, 6.69; N, 14.32.

2,2-Dimethyl-*N*-(6-fluoro-3-(methylthio)-2-pyridinyl)-propanamide (18) and 2,2-Dimethyl-*N*-(6-fluoro-5-(methylthio)-2-pyridinyl)propanamide (19). To a solution of 1.96 g (10 mmol) of **17** in 30 mL of THF at −78 °C was added 22 mmol of *n*-butyllithium and the mixture stirred at 0 °C for 2.5 h. Dimethyl disulfide (20 mmol) was added at −78 °C and the mixture allowed to warm to room temperature and treated in the usual fashion to give an oil that was separated into two fractions by preparative LC (hexane/ethyl acetate, 4:1). The least polar material was crystallized from hexane to give 0.73 g (30%) of **19** as pale yellow crystals: mp 64–66 °C; NMR δ 8.24 (dd, *J* = 2, 8.5, 1 H, H-3), 7.99 (br, 1 H, NH), 7.84 (dd, *J* = 8.5, 9.5, 1 H, H-4), 2.49 (s, 3 H, SCH_3), 1.33 (s, 9 H, *tert*-butyl); IR (KBr) 3325, 2955, 1672, 1510 cm^{-1}. Anal. Calcd for $C_{11}H_{15}FN_2OS$: C, 54.52; H, 6.24; N, 11.56. Found C, 54.82; H, 6.23; N, 11.66.

The more polar fraction was crystallized from ethyl acetate/hexane to yield 1.08 g (45%) of **18** as colorless crystals: mp 130–133 °C; NMR δ 8.77 (br, 1 H, NH), 8.00 (t, *J* = 9, 1 H, H-4), 6.81 (dd, *J* = 3.5, 9, 1 H, H-5), 2.40 (s, 3 H, SCH_3), 1.38 (s, 9 H, *tert*-butyl); IR (KBr) 3240, 2920, 1643, 1428 cm^{-1}. Anal. Calcd for $C_{11}H_{15}FN_2OS$: C, 54.52; H, 6.24; N, 11.56. Found: C, 54.39; H, 6.23; N, 11.54.

2,2-Dimethyl-*N*-(6-fluoro-3-(methylthio)-2-pyridinyl)-propanamide (18). A mixture of 0.98 g (5 mmol) of **17** in 30 mL of ether was treated at −78 °C with 12.5 mmol of *tert*-butyllithium and then stirred at −78 °C for 4 h. After addition of dimethyl disulfide (10 mmol) and warming to room temperature, a standard workup gave a tan solid that was recrystallized from ethyl acetate/hexane to give 0.85 g (70%) of **18** as colorless crystals: mp 130–133 °C.

2,2-Dimethyl-*N*-(4-(methylthio)-3-pyridinyl)propanamide (21) and 2,2-Dimethyl-*N*-(4-butyl-5-(methylthio)-3-pyridinyl)propanamide (22). *n*-Butyllithium (50 mmol) was added to a solution of 3.56 g (20 mmol) of **20** in 60 mL of THF at −78 °C and the bright yellow solution allowed to stir at 0 °C for 3 h. After cooling of the solution to −78 °C, 3.76 g (40 mmol) of dimethyl disulfide was added and the solution allowed to warm to room temperature where a standard workup gave an oil, which was separated into two fractions by preparative LC (hexane/acetone, 3:2). The more polar fraction (1.90 g, 42%) was recrystallized from toluene to give colorless crystalline **21**: mp 145–147 °C; NMR δ 9.25 (s, 1 H, H-2), 8.45 (d, *J* = 5, 1 H, H-6), 7.83 (br, 1 H, NH), 7.27 (d, *J* = 5, 1 H, H-5), 2.54 (s, 3 H, SCH_3), 1.38 (s, 9 H, *tert*-butyl); IR (KBr) 3220, 2980, 1678 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 58.89; H, 7.19; N, 12.49. Found: C, 58.84; H, 7.14; N, 12.43.

The less polar fraction (1.89 g, 34%), an oil that was contaminated with a trace of starting **20**, was further purified by Kugelrohr distillation, removing **20** at 85 °C (0.03 mmHg) and then distilling the remainder at 130–150 °C (0.03 mmHg) to give a solid (1.57 g, 28%) that was recrystallized from toluene/hexane to yield **22** as white crystals: mp 106–108 °C; NMR δ 8.86 (s, 1 H, H-2), 8.39 (s, 1 H, H-6), 2.73 (dist t, *J* = 7, 2 H, Ar CH_2), 2.54 (s, 3 H, SCH_3), 1.46 (m, 4 H, CCH_2CH_2), 1.36 (s, 9 H, *tert*-butyl), 0.97 (dist t, *J* = 7, 3 H, CCH_3); IR (KBr) 3260, 2960, 1650, 1510 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2OS$: C, 64.24; H, 8.63; N, 9.99. Found: C, 64.20; H, 8.55; N, 10.07.

3-((2,2-Dimethyl-1-oxopropyl)amino)-4-pyridinecarboxylic Acid (23). The metalation mixture obtained from 1.78 g (10 mmol) of **20** and 25 mmol of *n*-butyllithium as described for **21** and **22** was cooled to −78 °C and slowly poured into a slurry prepared from crushed dry ice and 50 mL of ether. The bright yellow mixture was allowed to warm to room temperature and

the solvent removed on the rotovap. The residue was partitioned between water and ether and the aqueous phase separated and again washed with ether. The aqueous layer was acidified with concentrated HCl to give an off-white solid that was filtered, throughly washed with water, and recrystallized from 2-methoxyethanol to yield 1.02 g (46%) of **23** as white crystals: mp 295 °C dec; NMR (Me_2SO-d_6) δ 9.95 (s, 1 H, H-2), 8.57 (d, J = 5.5, 1 H, H-6), 7.96 (d, J = 5.5, 1 H, H-5), 1.28 (s, 9 H, *tert*-butyl); IR (KBr) 3210 (br), 2980, 1687 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.06; H, 6.36; N, 12.52.

2,2-Dimethyl-*N*-(4-(hydroxyphenylmethyl)-3-pyridinyl)-propanamide (24). The metalation mixture obtained from 3.56 g (20 mmol) of **20** and 50 mmol of *n*-butyllithium as described for **21** and **22** was cooled to −78 °C and a solution of 3.18 g (30 mmol) of benzaldehyde in 5 mL of THF was added. The mixture was warmed to room temperature and poured into water, and upon addition of ether a solid precipitated, which was removed by filtration. The filtrates were separated into two layers, and the aqueous phase was extracted twice with ether. The combined ether layers and the filtered solid were recombined and evaporated to dryness. The residue was taken up in $CHCl_3$ and the resulting solution was washed with water, dried over $MgSO_4$, and evaporated to leave an oily orange solid. The solid was triturated with ether and filtered to leave colorless **24** (3.02 g, 53%): mp 199–204 °C. One recrystallization from ethyl acetate gave 2.84 g (50%) of **24**: mp 206–209 °C. (lit.[14] mp 200–202 °C). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.78; H, 7.04; N, 9.83.

Registry No. **1**, 86847-59-8; **2**, 70298-89-4; **3**, 86847-60-1; **4**, 86847-61-2; **5a**, 86847-62-3; **5b**, 86847-63-4; **5c**, 86847-64-5; **5d**, 86847-65-6; **5e**, 86847-66-7; **5f**, 86847-67-8; **5g**, 86847-68-9; **6a**, 86847-69-0; **6b**, 86847-70-3; **6c**, 86847-71-4; **6d**, 86847-72-5; **6e**, 86847-73-6; **9**, 86847-74-7; **10**, 86847-75-8; **11**, 86847-76-9; **12a**, 86847-77-0; **12b**, 86847-78-1; **12c**, 86847-79-2; **13a**, 86847-80-5; **13b**, 86847-81-6; **13c**, 86847-82-7; **14a**, 86847-92-9; **14c**, 86847-93-0; **15a**, 86847-83-8; **15b**, 86847-84-9; **16a**, 86847-85-0; **16b**, 86847-86-1; **17**, 86847-87-2; **18**, 86847-88-3; **19**, 86853-52-3; **20**, 70298-88-3; **21**, 86847-89-4; **22**, 86847-90-7; **23**, 86847-91-8; **24**, 82791-70-6; trimethylacetyl chloride, 3282-30-2; 2-aminopyridine, 504-29-0; 4-aminopyridine, 504-24-5; 3-aminopyridine, 462-08-8; deuterium oxide, 7789-20-0; chlorotrimethylsilane, 75-77-4; dimethylformamide, 68-12-2; dimethyl disulfide, 624-92-0; methyl iodide, 74-88-4; benzaldehyde, 100-52-7; ethyl chloroformate, 541-41-3; 2-amino-3-pyridinecarboxaldehyde, 7521-41-7; 4-amino-3-pyridinecarboxaldehyde, 42373-30-8; 4-methyl-2-aminopyridine, 695-34-1; 5-methyl-2-aminopyridine, 1603-41-4; 6-methyl-2-aminopyridine, 1824-81-3; 2-amino-5-chloropyridine, 1072-98-6; 6-chloro-2-aminopyridine, 45644-21-1; 6-fluoro-2-aminopyridine, 1597-32-6.

Synthetic Applications of Heteroatom-Directed Photoarylation. Benzo[*b*]furan Ring Construction

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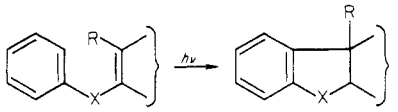
The preparation of several α-phenoxy-α,β-unsaturated carboxylic acid esters via condensation of phosphonate **3c** with ketones and an aldehyde is described. The resulting aryl vinyl ethers undergo photocyclization to give 2,3-dihydrobenzo[*b*]furan-2-carboxylic acid esters, which are converted to benzo[*b*]furans by (1) saponification to the carboxylic acid, (2) oxidative decarboxylation to the 2-acetoxy-2,3-dihydrobenzo[*b*]furan, and (3) solvolytic rearrangement with titanium tetrachloride in methylene chloride; thus, **8**, **9**, **11**, and **14** are prepared. Oxidative cleavage of 3-cyclohexylbenzo[*b*]furan **14** gives keto formate **15a** (saponification of **15a** gives **15b**), which demonstrates that the method can be used for conversion of phenols to *o*-acyl derivatives.

We have been involved in the development of synthetic methods based on photocyclization of aryl vinyl heteroatom systems (heteroatom-directed photoarylation; A → B).[1] An important feature of the photoreaction is the

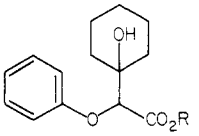


A B

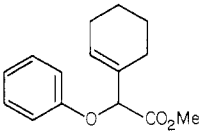
formation of a carbon–carbon bond between an aromatic ring and a quaternary carbon atom. On the other hand, benzo-fused heteroaromatic ring systems also are available by a subsequent elimination process (R = OH, OCH_3, OAc) to give indoles (X = NR),[2] benzothiophenes (X = S),[3] benzofurans (X = O),[3] and a benzoselenophene (X = Se).[4] In this paper, we report a new photochemically derived benzofuran synthesis, which features the oxidative rearrangement of 2,3-dihydrobenzo[*b*]furan-2-carboxylic acids; e.g., **5b** → **6a** → **8**.

Results and Discussion[5]

At the onset of this work, we desired a reliable method for preparation of α-(aryloxy)-α,β-unsatured carboxylic acid derivatives; e.g., **4**. Condensation of lithium α-phenoxy-α-lithioacetate[6] with cyclohexanone gives carbinol **1a**,



1a, R = H
b, R = Me



2

and this can be esterified to give **1b** in excellent overall yield. As anticipated,[7] however, dehydration of **1b** results in formation of mixtures of **2** and **4** with the β,γ-unsaturated isomer **2** predominating.

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