1390, 1130, 760, 720 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.32. Found: C, 70.36; H, 8.62; N, 6.48.

1-(Butylthio)-4-methoxybutan-2-one (2i). By the general procedure described above, we obtained **2i** in 63% yield (1.2 g, 10-mmol scale) as a colorless liquid: bp 75 °C (0.2 Torr); ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 6.0 Hz, 3 H), 1.10–1.72 (m, 4 H), 2.45 (t, J = 6.0 Hz, 2 H), 2.85 (t, J = 6.0 Hz, 2 H), 3.30 (s, 3 H), 3.60–3.90 (m, 4 H); MS, m/e (relative intensity) 190 (M^+), 102 (38), 87 (44), 61 (75), 45 (100); IR (neat) 2950, 1720, 1140 cm^{-1}. Anal. Calcd for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; S, 16.85. Found: C, 56.54; H, 9.51; S, 16.82.

1-(Phenylthio)-4-methoxybutan-2-one (2j). 1-(Phenylthio)-2-methylene-3,5-dioxahexane (**1j**, 4.2 g, 20 mmol) was treated with aluminum chloride (2.6 g, 20 mmol) in dichloromethane at −78 °C for 3 days. With the usual workup, **2j** was obtained in 40% yield (1.7 g) as a colorless liquid: bp 90 °C (0.05 Torr); ^1H NMR ($CDCl_3$) δ 2.82 (t, J = 6.0 Hz, 2 H), 3.30 (s, 3 H), 3.45–3.80 (m, 4 H), 7.30 (s, 5 H); MS, m/e (relative intensity) 210 (M^+), 123 (100), 77 (37), 45 (79); IR (neat) 2900, 1710, 1120, 760, 700 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.22. Found: C, 62.61; H, 6.54; S, 15.03.

(*E*)-1-(Phenylthio)-2-methyl-3,5-dioxahex-1-ene (1k). A mixture of 2-[(phenylthio)methyl]-3,5-dioxahex-1-ene (**1j**, 2.1 g, 10 mmol), sodium hydroxide (pellet, 0.4 g, 10 mmol), and tetrabutylammonium bisulfate (0.17 g, 0.5 mmol) in dioxane (10 mL) was stirred at 90 °C for 1 h. The solid material was removed by filtration through a short column filled with silica gel. After evaporation of the solvent, **1k** was obtained by Kugelrohr distillation at reduced pressure in 88% yield (1.9 g) as a colorless liquid: bp 90 °C (0.05 Torr); ^1H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 3.45 (s, 3 H), 5.08 (s, 2 H), 5.48 (s, 1 H), 7.24 (s, 5 H); MS, m/e (relative intensity) 210 (M^+), 135 (80), 45 (100); IR (neat) 2900, 1620, 1580, 1150, 1040, 730 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.22. Found: C, 62.49; H, 6.71; S, 15.01.

The hydrolysis of **1k** in 1% aqueous sulfuric acid also gave acetonyl phenyl sulfide.[1]

3-(Phenylthio)-4-methoxybutan-2-one (2k). By the same procedure used for **2g**, we obtained **2k** in 81% yield (3.4 g, 20-mmol scale) as a slightly greenish liquid: bp 90 °C (0.05 Torr); ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.36 (s, 3 H), 3.6–4.0 (m, 3 H), 7.30–7.60 (m, 5 H); MS, m/e (relative intensity) 210 (M^+), 178 (30), 135 (100), 91 (53), 43 (23); IR (neat) 2900, 1710, 1110, 740, 700 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.22. Found: C, 62.58; H, 6.66; S, 15.40.

Registry No. **1a**, 105104-40-3; **1b**, 114250-45-2; **1c**, 114250-46-3; **1d**, 114250-47-4; **1e**, 114250-48-5; **1f**, 114273-20-0; **1g**, 105104-43-6; **1h**, 114250-49-6; **1i**, 114250-50-9; **1j**, 114250-51-0; **1k**, 114250-52-1; **2a**, 87308-03-0; **2b**, 57429-13-7; **2c**, 114250-53-2; **2d**, 114250-54-3; **2e**, 114250-55-4; **2f**, 114250-56-5; **2g**, 114250-57-6; **2h**, 114250-58-7; **2i**, 114250-59-8; **2j**, 35737-56-5; **2k**, 114250-60-1; (chloromethyl)tridecyl methoxymethyl ether, 114250-61-2.

Metalation/$S_{RN}1$ Coupling in Heterocyclic Synthesis. A Convenient Methodology for Ring Functionalization

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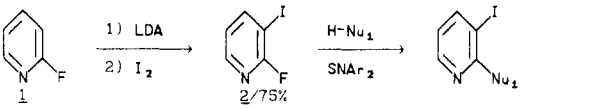
Lithiation, iodination, and fluorine substitution on 2-fluoropyridine gave 2-substituted 3-iodopyridines, which were further subjected to iodine $S_{RN}1$ substitution by carbon, sulfur, and phosphorus nucleophiles. Iodine substitution by enolates on 2-amino-3-iodopyridines afforded ketones, which were further cyclized to various 1,2-disubstituted pyrrolo[2,3-*b*]pyridines. 2-Amino-3-iodo-, 3-amino-4-iodo-, and 4-amino-3-iodopyridines were prepared by directed metalation of 2-, 3-, and 4-(pivaloylamino)pyridines. Substitution of iodine by enolates under $S_{RN}1$ conditions and acidic cyclization led to various 2-substituted pyrrolo[2,3-*b*]-, -[2,3-*c*]-, and -[3,2-*c*]pyridines in high yields.

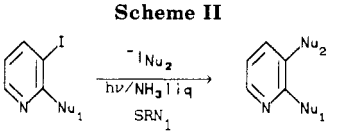
Introduction

In connection with synthetic efforts, chemists require more and more specific functionalization methods for π-deficient heterocycles (pyridine, quinoline, ...). Much has been done in this area with the recent developments of such powerful reactions as the directed ortho lithiation,[1] the $S_{RN}1$ substitution,[2] or the transition metal catalyzed cross coupling reaction.[3] The two last strategies are important synthetic methods that require prior access to substituted derivatives such as aryl halides. This constitutes an important drawback in the π-deficient heterocyclic series, where an increase in the degree of substitution is often difficult to carry out with suitable regio- and chemoselectivity. An answer to this problem can be given by the combination of two complementary reactions such as metalation and $S_{RN}1$ substitution. This strategy was successful with simple halo- or aminopyridines, and the results of the study are reported in this paper.

Scheme I



Scheme II



Nu_1	:	F	OMe	NH_2	NHMe	OMe	OMe
Nu_2	:		$-ICH_2-CO-tBu$			$-IPO(OEt)_2$	$-IS-CH_2-CH_2-OH$
Compd.	:	6	7	8	9	10	11
Yield	:	92%	84%	87%	50%	78%	80%

(1) For a comprehensive review on directed ortho lithiation, see: Gschwend, H. W.; Roriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1. For a recent review on π-deficient heterocycle metalation, see: Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009.

(2) Beugelmans, R.; Boudet, B.; Quintero, L. *Tetrahedron Lett.* **1980**, *21*, 1943. Bard, R. R.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 1546.

(3) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133. Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947.

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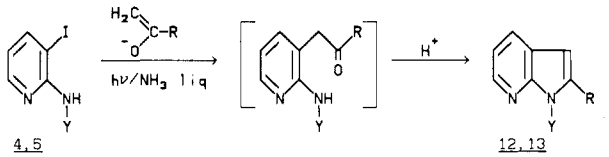
Scheme III



Y	R	Compd.	Yield
H	Me	12a	75%
H	tBu	12b	78%
Me	tBu	13a	70%
Me	Me	13b	95%

Results

Selective ortho lithiation of 2-fluoropyridine (1) by LDA[4] and reaction of the resulting 3-lithio derivative with iodine afforded a high yield of 2-fluoro-3-iodopyridine (**2**). The 2-fluorine atom is selectively activated toward nucleophilic substitution under $S_{ArN}2$ conditions, which allowed a convenient synthesis of 2-substituted 3-iodopyridines **3–5** (Scheme I).

When iodo compounds **2–5** were treated with an excess (6/1) of pinacolone-derived enolate in anhydrous liquid ammonia under UV illumination, quantitative and selective substitution of iodine was observed. 1-(2-Substituted-3-pyridinyl)-2-butanones **6–9** were isolated in good yields (analysis of the ^1H NMR spectra of the crude products showed quantitative substitution) (Scheme II).

Pinacolone enolate was prepared in liquid ammonia by use of either potassium *tert*-butoxide or sodium. Photostimulation was achieved by using a commercial 125-W medium-pressure mercury lamp and a common glass vessel. The substitution reactions were sensitive to oxygen and were inhibited unless they were carried out in an oxygen-free argon atmosphere. Reactions were monitored by TLC and were followed up until complete consumption of the starting iodopyridines had occurred.

The same strategy was applied to 3-iodo-2-methoxypyridine (**3**) by using sulfur- and phosphorus-bearing nucleophiles, which led to the corresponding phosphonate **10** and thioether **11** (Scheme II).

One-pot reactions of 2-amino-3-iodo- and 2-(methylamino)-3-iodopyridines **4** and **5** with enolates (pinacolone and 2-propanone) under $S_{RN}1$ conditions followed by acidic treatment (4 N HCl) led to the corresponding 1,2-substituted 7-azaindoles **12** and **13** in high yields (Scheme III).

Sequential ortho lithiation and $S_{RN}1$ substitution via iodo intermediaries was extended to other monosubstituted pyridines. This was achieved with the three monoamino pyridines and provided a straightforward access to azaindoles.

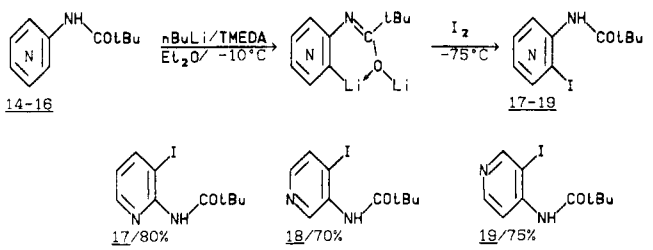
Aminopyridines protected as pivaloylamino derivatives were subjected to lithiation by an excess of butyllithium/TMEDA chelate (Et_2O, −10 °C).[5] Lithiation of the 2-, 3-, and 4-isomers occurred respectively at position 3, 4, and 3. The resulting lithio derivatives were then reacted with iodine at −75 °C to give the corresponding ortho iodo(pivaloylamino)pyridines **17–19** (Scheme IV). These three iodopyridines could be prepared on a 50-g scale in fair yields, and they were easily purified by preparative flash chromatography on silica.

Ortho iodo(pivaloylamino)pyridines **17–19** underwent quantitative substitution on treatment with an excess of ketone enolate (2-propanone or pinacolone) under UV illumination in refluxing anhydrous liquid ammonia (Scheme V). 3-Iodo-2-(pivaloylamino)pyridine (**17**) and pinacolone enolate did not react at all in the dark, which indicates a photostimulated reaction. The main radical chain character of this substitution was evidenced by the dramatic reduction in the yield of **20b** observed when the inhibitor *p*-dinitrobenzene (5 mol %) was used.[6]

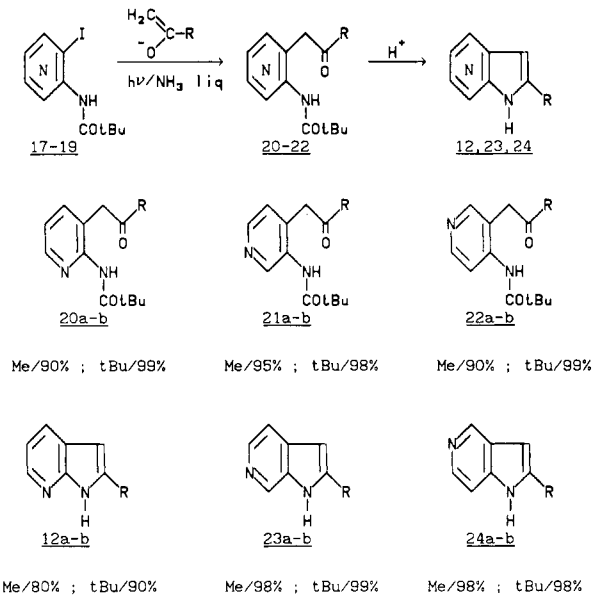
Reaction between 3-iodo-4-(pivaloylamino)pyridine (**19**) and acetaldehyde enolate led to 4-(pivaloylamino)pyridine (**16**). Small amounts of substitution product could be obtained by using a very large excess of enolate (12/1), but reduction remained the main reaction.

Ortho (pivaloylamino)picolyl ketones **20–22** were further cyclized in high yields to azaindoles **12, 23,** and **24** (Scheme V). Hydrolysis of the pivaloylamino moiety, cyclization, and dehydration were simultaneously achieved under acidic conditions (3 N HCl), and azaindoles were isolated after basic workup and standard purification. Isolation and purification of intermediate ketones could be avoided: crude ketones **20–22a** were quantitatively formed and characterized by their ^1H NMR spectra, before being directly cyclized by acidic treatment. 2-Methylpyrrolo[2,3-*b*]-, -[2,3-*c*]-, and -[3,2-*c*]pyridines **12a**, **23a**, and **24a**, for example, were prepared in three steps from 2-, 3-, and 4-aminopyridines with 60–65% overall yields.

Scheme IV



Scheme V[a]



[a] **a**, R = Me; **b**, R = *t*-Bu.

Discussion

Coupling of directed ortho lithiation and $S_{RN}1$ substitution via iodo derivatives significantly broadens the scope

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(5) Güngör, T.; Marsais, F.; Quéguiner, G. *Synthesis* **1982**, 499. Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401.
(6) Kerber, S. C.; Urry, G. W.; Kornblum, N. *J. Am. Chem. Soc.* **1964**, *86*, 3904.

and synthetic utility of the metalation reaction in aromatic chemistry. It offers a new simple way for introduction of nucleophilic substitutents in a position adjacent to a lithiation ortho-directing function. This method appears as an "umpolung" of the directed lithiation, which allows ortho functionalization by electrophilic substituents.[4] Moreover, $S_{ArN}2$ and $S_{RN}1$ nucleophilic substitutions[11] show their complementarity due to their high opposite chemoselectivity toward iodine and fluorine. Fluorine has a low reactivity under $S_{RN}1$ conditions as previously established in aromatic series.[12] This is demonstrated by the obtention of either **3–5** or **6**, starting from 2-fluoro-3-iodopyridine (**2**).

The same foregoing strategy provides a new entry to substituted azaindoles, starting from simple monosubstituted pyridines. Thus pyrrolo[2,3-*b*]-, -[2,3-*c*]-, and -[3,2-*c*]pyridines were obtained in a three-step sequence from commercial 2-fluoropyridine or the three aminopyridines with excellent overall yields.

Available routes to pyrrolopyridines such as Madelung[7] or Fisher[8] type synthesis are often of limited synthetic interest, mainly due to their narrow scope. Pyrrolo[3,2-*b*]pyridines had been previously prepared from commercial 3-amino-2-chloropyridine by using the $S_{RN}1$ method,[2] but the overall strategy was restricted by the access to ortho haloaminopyridines. In fact, direct halogenation of aminopyridines can be applied only in a few cases[9] due to its poor regioselectivity and to the occurrence of polyhalogenation.[10]

Limitations of the metalation/$S_{RN}1$ coupling methodology are those of the $S_{RN}1$ substitution, particularly the radical-anion reduction by the acetaldehyde enolate.

In conclusion, connecting ortho lithiation and $S_{RN}1$ substitution provides a new functionalization strategy for aromatics.

Experimental Section

General Data. Infrared spectra were taken on a Beckman IR 4250 spectrometer, and main absorption frequencies (NH, CH, C=O, C=C, C=N) are given in cm^{-1}. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T60 or Brucker WH90 spectrometer. Chemical shifts are recorded in ppm downfield from an internal standard, TMS in $CDCl_3$ or HMDS in DMSO-d_6. ^1H–^1H coupling constants are in good agreement with the common values (J_{2-3} = 5 Hz; J_{3-4} = 8 Hz; J_{2-4} = 2 Hz) and are not given. Mass spectra were obtained on a JEOL D700 instrument, and elemental analyses were performed on a Carlo Erba CHNS apparatus.

Starting Materials. Commercial 2-fluoropyridine, TMEDA, and diisopropylamine were distilled from CaH_2 and stored over CaH_2 under a dry argon atmosphere. (Pivaloylamino)pyridines were prepared from commercial aminopyridines by using a standard procedure,[5] and they were stored over KOH pellets under vacuum because of their hydrophilicity. Commercial 1.6 M solutions of butyllithium in hexane were stored and transferred under a deoxygenated and dehydrated argon atmosphere.

2-Fluoro-3-iodopyridine (2). 2-Fluoropyridine (19.4 g, 0.2 mol) was slowly added to a cold (−75 °C) solution of lithium diisopropylamide, which had been previously prepared by reaction of diisopropylamine (20.2 g, 0.2 mol) and butyllithium (125 mL, 0.2 mol) in THF (500 mL) at 0 °C for $^1/_2$ h. The resulting yellow mixture was stirred for 4 h at −78 °C before addition of iodine (51 g, 0.2 mol) in THF (150 mL) solution. Stirring was continued for 1 h at −75 °C, before hydrolysis by a mixture of H_2O/THF (2 mL/10 mL) at −75 °C, further addition of water (200 mL) at 0 °C, and decolorization by solid $NaHSO_3$. Extraction by Et_2O, drying over $MgSO_4$, solvent removal, and vacuum distillation of the crude oil yielded 38.4 g (85%) of **2**: bp 97–99 °C (17 mmHg); mp 42 °C; ^1H NMR ($CDCl_3$) δ 6.95 (ddd, 1 H, H5, J_{5-F} = 6 Hz), 8.15 (m, 2 H, 4-H, 6-H); IR (KBr) 3060, 1590, 1580, 1450, 1430, 1410 cm^{-1}. Anal. Calcd for C_5H_3FIN (223.0): C, 26.93; H, 1.36; N, 6.28. Found: C, 26.8; H, 1.49; N, 5.94.

3-Iodo-2-methoxypyridine (3). A mixture of 31 g of **2** (0.14 mol) and MeONa (13 g of Na, 0.57 mol) in MeOH (250 mL) was refluxed for 1 h. Water (200 mL) was added, and MeOH was evaporated under vacuum. Extraction by $CHCl_3$, drying over $MgSO_4$, solvent removal, and vacuum distillation yielded 23 g (70%) of **3**: bp 115 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 4.00 (s, 3 H, CH_3), 6.55 (dd, 1 H, 5-H), 7.95 (m, 2 H, 4-H, 6-H); IR (film) 3060, 3020, 2990, 2950, 1580, 1550, 1490, 1465, 1440, 1400 cm^{-1}. Anal. Calcd for C_6H_6INO (235.0): C, 30.66; H, 2.57; N, 5.96. Found: C, 30.8; H, 2.60; N, 6.21.

2-Amino-3-iodopyridine (4). In a sealed tube, 5.58 g of **2** (0.025 mol) and 50 mL of concentrated aqueous ammonia were heated at 130 °C for 3 days. Extraction by $CHCl_3$, drying over $MgSO_4$, solvent removal, and crystallization in Et_2O/toluene (3/1) afforded 5.24 g of **4** (95%): mp 86 °C; ^1H NMR ($CDCl_3$) δ 5.05 (s, 2 H, NH_2), 6.45 (dd, 1 H, 5-H), 7.85 (dd, 1 H, 4-H), 8.00 (dd, 1 H, 6-H); IR (KBr) 3450, 3280, 3000, 1620, 1580, 1460, 1440 cm^{-1}. Anal. Calcd for $C_5H_5IN_2$ (220.1): C, 27.30; H, 2.29; N, 12.73. Found: C, 27.4; H, 2.31; N, 12.9.

3-Iodo-2-(methylamino)pyridine (5). Compound **2** (11.2 g, 0.05 mol) in 300 mL of aqueous methylamine (40%) was refluxed for 4 h. Extraction by $CHCl_3$, drying over $MgSO_4$, solvent removal, and vacuum distillation yielded 11.2 g (96%) of **5**: bp 129 °C (14 mmHg); mp 50 °C; ^1H NMR ($CDCl_3$) δ 2.95 (d, 3 H, CH_3), 4.95 (d, 1 H, NH, J_{NHCH_3} = 4 Hz), 6.25 (d, 1 H, 5-H), 7.75 (dd, 1 H, 4-H), 8.05 (dd, 1 H, 6-H); IR (KBr) 3440, 3060, 2990, 2930, 1600, 1560, 1460, 1440, 1430, 1400 cm^{-1}. Anal. Calcd for $C_6H_7IN_2$ (234.0): C, 30.79; H, 3.01; N, 11.97. Found: C, 30.9; H, 2.86; N, 12.0.

General Procedure for Synthesis of Ortho Iodo(pivaloylamino)pyridines. *n*-Butyllithium (195 mL, 0.3125 mol) was slowly added to a cold (−75 °C) suspension of the appropriate (pivaloylamino)pyridine[5] (22.25 g, 0.125 mol) in a mixture of THF (750 mL) and TMEDA (31.5 g, 0.3125 mol). The resulting solution was reacted for 15 min at −75 °C, before being stirred for 2 h at −10 °C. A white precipitate slowly appeared, the mixture was cooled to −75 °C, and a solution of iodine (79.3 g, 0.3125 mol) in THF (250 mL) was added. Stirring was continued for 2 h at −75 °C, before hydrolysis at 0 °C. Excess iodine was destroyed by using a saturated potassium thiosulfate solution. Decantation, extraction by $CHCl_3$, drying over $MgSO_4$, and solvent removal afforded a crude oil, which was purified by preparative flash chromatography on silica (1/1 Et_2O/cyclohexane).

2,2-Dimethyl-*N*-(3-iodo-2-pyridinyl)propanamide (17). The foregoing procedure gave 80% of **17**: mp 148 °C; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 6.80 (dd, 1 H, 5-H), 8.00 (m, 1 H, NH), 8.05 (dd, 1 H, 4-H), 8.40 (dd, 1 H, 6-H); IR (KBr) 3290, 2970, 1655, 1560, 1500, 1440, 1435 cm^{-1}. Anal. Calcd for $C_{10}H_{13}IN_2O$: C, 39.49; H, 4.31; N, 9.21. Found: C, 39.4; H, 4.20; N, 9.12.

2,2-Dimethyl-*N*-(4-iodo-3-pyridinyl)propanamide (18). The foregoing procedure gave 70% of **18**: mp 126–127 °C; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3 H, *t*-Bu), 7.65 (d, 1 H, 5-H), 7.90 (d, 1 H, 6-H), 9.30 (s, 1 H, 2-H); IR (KBr) 3270, 2970, 1655, 1560, 1505, 1465, 1395 cm^{-1}. Anal. Calcd for $C_{10}H_{13}IN_2O$: C, 39.49; H, 4.31; N, 9.21. Found: C, 39.2; H, 4.38; N, 8.96.

2,2-Dimethyl-*N*-(3-iodo-4-pyridinyl)propanamide (19). The foregoing procedure gave 75% of **19**: mp 158 °C; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 7.95 (m, 3 H, 5-H, 6-H, NH), 8.75 (s, 1 H, 2-H); IR (KBr) 3400, 2970, 1720, 1580, 1500, 1450, 1405 cm^{-1}. Anal. Calcd for $C_{10}H_{13}IN_2O$: C, 39.49; H, 4.31; N, 9.21. Found: C, 39.6; H, 4.32; N, 9.15.

General Procedure for $S_{RN}1$ Substitution on Iodopyridines. After condensation under a deoxygenated and dehydrated argon atmosphere and addition of sodium chips, liquid ammonia (200 mL) was distilled off and further condensed in the

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reaction flask containing 3.4 g of potassium *tert*-butoxide (0.03 mol). The nucleophilic reagent (ketone, phosphite, or thiol, 0.03 mol) was then added. The refluxing ammonia solution was stirred for 5 min before addition of the required iodopyridine (0.05 mol). The resulting mixture was then irradiated by using a 125-W Philips HPK lamp emitting maximally at 350 nm. Samples were periodically taken, hydrolyzed (NH_4Cl/H_2O), extracted ($CHCl_3$), and analyzed by using TLC on silica (Et_2O). An excess of NH_4Cl was introduced when irradiation was finished, and ammonia was allowed to evaporate. Hydrolysis, extraction ($CHCl_3$), drying over $MgSO_4$, and solvent removal under vacuum afforded a crude oil, which was further purified.

3,3-Dimethyl-1-(2-fluoro-3-pyridinyl)-2-butanone (6). Reaction between **2** and 3,3-dimethyl-2-butanone-derived enolate was achieved after a 2-h sunlight illumination. Standard workup and vacuum distillation yielded 92% of **6**: bp 135 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 1.25 (s, 9 H, *t*-Bu), 3.85 (s, 2 H, CH_2), 7.15 (ddd, 1 H, 5-H), 7.60 (ddd, 1 H, 4-H), 8.10 (ddd, 1 H, 6-H); IR (film) 3060 2960, 2940, 2860, 1700, 1600, 1570, 1470, 1440, 1420 cm^{-1}. Anal. Calcd for $C_{11}H_{14}FNO$ (195.2): C, 67.67; H, 7.24; N, 7.17. Found: C, 67.4; H, 7.10; N, 7.34.

3,3-Dimethyl-1-(2-methoxy-3-pyridinyl)-2-butanone (7). Reaction between **3** and 3,3-dimethyl-2-butanone-derived enolate was achieved after a 2-h UV illumination. Standard workup and vacuum distillation yielded 84% of **7**: bp 140 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 1.25 (s, 9 H, *t*-Bu), 3.70 (s, 2 H, CH_2), 3.90 (s, 3 H, OCH_3), 6.75 (dd, 1 H, 5-H), 7.35 (dd, 1 H, 4-H), 8.00 (dd, 1 H, 6-H); IR (film) 3400, 3060, 2960, 2900, 2840, 1700, 1580, 1470, 1460, 1450, 1400 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_2$ (207.3): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.0; H, 8.24; N, 6.98.

1-(2-Amino-3-pyridinyl)-3,3-dimethyl-2-butanone (8). Reaction between **4** and 3,3-dimethyl-2-butanone-derived enolate was achieved after a 2.5-h UV illumination. Standard workup and flash chromatography on silica eluting with Et_2O/hexane (1/1) yielded 87% of **8**: ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 2.65 (s, 2 H, CH_2), 5.20 (s, 2 H, NH_2), 6.30 (dd, 1 H, 5-H), 7.6–8.0 (m, 2 H, 4-H, 5-H); IR (film) 3450, 3400, 3000, 1700, 1600, 1450; mass calcd for $C_{11}H_{16}N_2O$ 192.3, found (MS) 192.

3,3-Dimethyl-1-[2-(methylamino)-3-pyridinyl]-2-butanone (9). Reaction between **5** and 3,3-dimethyl-2-butanone-derived enolate was achieved after a 2-h UV illumination. Standard workup and vacuum distillation yielded 50% of **9**: bp 105 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 1.15 (s, 9 H, *t*-Bu), 3.00 (m, 5 H, NCH_3, CH_2), 4.95 (d, 1 H, NH, J_{NHCH_3} = 5 Hz), 6.30 (d, 1 H, 5-H), 7.80 (d, 1 H, 4-H), 8.10 (d, 1 H, 6-H); IR (film) 3420, 3040, 2960, 2900, 1700, 1590, 1515, 1460, 1415 cm^{-1}; mass calcd for $C_{12}H_{18}N_2O$ 206.3, found (MS) 206.

Diethyl (2-Methoxy-3-pyridinyl)phosphonate (10). Reaction between **3** and diethyl phosphite was achieved after a 1-h UV illumination. Standard workup and vacuum distillation yielded 78% of **10**: bp 165 °C (14 mmHg); ^1H NMR ($CDCl_3$) δ 1.35 (t, 6 H, CH_3), 4.05 (s, 3 H, OCH_3), 4.30 (quint., 4 H, CH_2), 6.95 (ddd, 1 H, 5-H, J_{5-P} = 2.5 Hz), 8.05 (ddd, 1 H, 4-H, J_{4-P} = 7.5 Hz), 8.35 (ddd, 1 H, 6-H, J_{6-P} = 2 Hz); IR (film) 3050, 2980, 2950, 2930, 2900, 1980, 1465, 1445, 1400 cm^{-1}; mass calcd for $C_{10}H_{16}NO_4P$ 245.2, found (MS) 245.

2-Hydroxyethyl 2-Methoxy-3-pyridinyl Sulfide (11). Reaction between **3** and 2-hydroxyethanethiol was achieved after a 1-h UV illumination. Standard workup and vacuum distillation yielded 78% of **11**: bp 170 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 3.10 (s + t, 3 H, OH, OCH_2, $J_{CH_2CH_2}$ = 6 Hz), 3.75 (t, 2 H, SCH_2), 4.05 (s, 3 H, OCH_3), 6.85 (dd, 1 H, 5-H), 7.60 (dd, 1 H, 4-H), 8.00 (dd, 1 H, 6-H); IR (film) 3360, 3050, 3010, 2980, 2950, 2920, 2870, 1575, 1560, 1465, 1440, 1400 cm^{-1}. Anal. Calcd for $C_8H_{11}NO_2S$ (185.2): C, 51.87; H, 5.99; N, 7.56. Found: C, 51.4; H, 5.89; N, 7.86. MS: 185.

2,2-Dimethyl-*N*-[3-(3,3-dimethyl-2-oxobutyl)-2-pyridinyl]propanamide (20b). Reaction between **17** and pinacolone-derived enolate was achieved under UV illumination. Standard workup and crystallization from Et_2O yielded 99% of **20b**: mp 138 °C; ^1H NMR ($CDCl_3$) δ 1.20 (s, 9 H, *t*-Bu), 1.40 (s, 9 H, NHCO-*t*-Bu), 3.85 (s, 2 H, CH_2), 7.10 (dd, 1 H, 5-H), 7.45 (dd, 1 H, 4-H), 8.35 (dd, 1 H, 6-H), 8.50 (m, 1 H, NH); IR (KBr) 3200, 2960, 1710, 1680, 1530, 1450 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_2$ (276.4): C, 69.53; H, 8.75; N, 10.14. Found: C, 69.4; H, 8.70; N, 9.97.

2,2-Dimethyl-*N*-[4-(3,3-dimethyl-2-oxobutyl)-3-pyridinyl]propanamide (21b). Reaction between **18** and pinacolone-derived enolate was achieved under UV illumination. Standard workup and crystallization from Et_2O yielded 98% of **21b**: mp 157 °C; ^1H NMR ($CDCl_3$) δ 1.25 (s, 9 H, *t*-Bu), 1.35 (s, 9 H, NHCO-*t*-Bu), 3.75 (s, 2 H, CH_2), 7.00 (d, 1 H, 5-H), 8.25 (d, 1 H, 6-H), 8.95 (m, 2 H, 2-H, (NH); IR (KBr) 3370, 3330, 2970, 2880, 1700, 1670, 1660, 1510, 1500, 1480, 1420, 1400 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_2$ (276.4): C, 69.53; H, 8.75; N, 10.14. Found: C, 69.4; H, 8.73; N, 10.0.

Inhibition Experiment. Reaction between **18** and the pinacolone-derived enolate was first performed for a 15-min UV illumination period, which allowed a 15% substitution yield (^1H NMR monitoring). 2,4-Dinitrobenzene (0.05 equiv) was added, and UV illumination was continued for an additional 2 h. Standard workup and ^1H NMR analysis of the crude product showed a 25% substitution yield, whereas a noninhibited experiment was brought to completion within the same reaction time.

2,2-Dimethyl-*N*-[3-(3,3-dimethyl-2-oxobutyl)-4-pyridinyl]propanamide (22b). Reaction between **19** and pinacolone-derived enolate was achieved under UV illumination. Standard workup and flash chromatography on silica gel (1/4 Et_2O/hexane) yielded 99% of **22b**: mp 128 °C; ^1H NMR (DMSO-d_6) δ 1.15 (s, 9 H, *t*-Bu), 1.20 (s, 9 H, NHCO-*t*-Bu), 4.05 (s, 2 H, CH_2), 7.55 (d, 1 H, 5-H), 8.30 (m, 2 H, 2-H, 6-H), 9.05 (m, 1 H, NH); IR (KBr) 3380, 2960, 1710, 1570, 1500, 1475, 1440, 1400 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_2$ (276.4): C, 69.53; H, 8.75; N, 10.14. Found: C, 69.5; H, 8.70; N, 9.98.

2,2-Dimethyl-*N*-[3-(2-oxopropyl)-2-pyridinyl]propanamide (20a). Reaction between **17** and 2-propanone-derived enolate was achieved under UV illumination. Standard workup quantitatively gave crude **20a**, which was characterized by its ^1H NMR spectrum: ($CDCl_3$) δ 1.35 (s, 9 H, *t*-Bu), 2.30 (s, 3 H, CH_3), 3.95 (s, 2 H, CH_2), 7.15 (dd, 1 H, 5-H), 7.55 (dd, 1 H, 4-H), 8.40 (dd, 1 H, 6-H), 8.50 (m, 1 H, NH).

2,2-Dimethyl-*N*-[4-(2-oxopropyl)-3-pyridinyl]propanamide (21a). Reaction between **18** and 2-propanone-derived enolate was achieved under UV illumination. Standard workup quantitatively gave crude **21a**, which was characterized by its ^1H NMR spectrum: ($CDCl_3$) δ 1.35 (s, 9 H, *t*-Bu), 2.30 (s, 3 H, CH_3), 3.70 (s, 2 H, CH_2), 7.10 (d, 1 H, 5-H), 8.35 (d, 1 H, 6-H), 8.55 (m, 1 H, NH), 8.95 (s, 1 H, 2-H).

2,2-Dimethyl-*N*-[3-(2-oxopropyl)-4-pyridinyl]propanamide (22a). Reaction between **19** and 2-propanone-derived enolate was achieved under UV illumination. Standard workup quantitatively gave crude **22a**, which was characterized by its ^1H NMR spectrum: ($CDCl_3$) δ 1.35 (s, 9 H, *t*-Bu), 2.35 (s, 3 H, CH_3), 3.75 (s, 2 H, CH_2), 7.95 (d, 1 H, 5-H), 8.30 (m, 2 H, 2-H, 6-H), 9.05 (m, 1 H, NH).

General Procedure for Cyclization of Ortho 2-[(Pivaloylamino)pyridinyl]ethanones to Azaindoles. Crude ketones **20–22a** or purified ketones **20–22b** (0.018 mol) were reacted with 3 N hydrochloric acid (100 mL) at 90 °C for 4 h. Alkalinization by concentrated aqueous ammonia, extraction by $CHCl_3$, drying over $MgSO_4$, and solvent removal afforded crude azaindoles, which were purified either by crystallization from Et_2O or by flash chromatography on silica gel.

2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine (12a). Cyclization of crude **20a** according to the foregoing procedure and crystallization from Et_2O yielded 80% of **12a**: mp 142 °C;[14] ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H, CH_3), 6.10 (s, 1 H, 3-H), 6.85 (dd, 1 H, 5-H), J_{4-5} = 8 Hz, J_{5-6} = 5 Hz), 7.80 (dd, 1 H, 4-H, J_{4-6} = 2 Hz), 8.15 (dd, 1 H, 6-H), 12.5 (m, 1 H, NH); IR (KBr) 3250, 2980, 1610, 1590, 1550, 1430 cm^{-1}. Anal. Calcd for $C_8H_8N_2$ (132.2): C, 72.71; H, 6.10; N, 21.21. Found: C, 72.5; H, 5.97; N, 21.0.

2-Methyl-1*H*-pyrrolo[2,3-*c*]pyridine (23a). Cyclization of crude **21a** according to the foregoing procedure and sublimation (1 mmHg) yielded 98% of **23a**: mp 185 °C;[15] ^1H NMR ($CDCl_3$) δ 2.55 (s, 3 H, CH_3), 6.30 (s, 1 H, 3-H), 7.45 (d, 1 H, 4-H, J_{4-5} = 5 Hz), 8.25 (d, 1 H, 5-H), 8.80 (s, 1 H, 7-H), (m, 1 H, NH); IR (KBr) 3200–2600, 1620, 1580, 1535, 1465, 1410 cm^{-1}. Anal. Calcd for

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$C_8H_8N_2$ (132.2): C, 72.71; H, 6.10; N, 21.21. Found: C, 72.7; H, 6.10; N, 21.3.

2-Methyl-1*H*-pyrrolo[3,2-*c*]pyridine (24a). Cyclization of crude **22a** according to the foregoing procedure and sublimation (1 mmHg) yielded 98% of **24a**: mp 210 °C;[13] ^{1}H NMR (90 MHz) (DMSO-d_6) δ 2.90 (s, 3 H, CH_3), 6.80 (s, 1 H, 3-H), 7.80 (d, 1 H, 7-H, J_{6-7} = 5 Hz), 8.60 (d, 1 H, 6-H), 9.20 (s, 1 H, 4-H), 11.90 (m, 1 H, NH); IR (KBr) 3420, 3200–2600, 1620, 1590, 1560, 1470, 1430 cm^{-1}. Anal. Calcd for $C_8H_8N_2$ (132.2): C, 72.71; H, 6.10; N, 21.21. Found: C, 72.6; H, 6.07; N, 21.2.

2-*tert*-Butyl-1*H*-pyrrolo[2,3-*b*]pyridine (12b). Cyclization of **20b** according to the foregoing procedure and crystallization from Et_2O yielded 90% of **12b**: mp 196 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 6.05 (s, 1 H, 3-H), 6.85 (dd, 1 H, 5-H, J_{4-5} = 8 Hz), 7.70 (dd, 1 H, 4-H, J_{4-6} = 2 Hz), 8.10 (dd, 1 H, 6-H), 12.10 (m, 1 H, NH); IR (KBr) 3140, 2970, 1570, 1510, 1380 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2$ (174.2): C, 75.82; H, 8.10; N, 16.08. Found: C, 75.5; H, 8.14; N, 15.7.

2-*tert*-Butyl-1*H*-pyrrolo[2,3-*c*]pyridine (23b). Cyclization of **21b** according to the foregoing procedure and crystallization from Et_2O yielded 99% of **23b**: mp 204 °C; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H, *t*-Bu), 6.10 (s, 1 H, 3-H), 7.30 (d, 1 H, 4-H, J_{4-5} = 5 Hz), 7.95 (d, 1 H, 5-H), 8.55 (s, 1 H, 7-H), 11.20 (m, 1 H, NH); IR (KBr) 3440, 3240–2530, 1620, 1580, 1535, 1470, 1410 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2$ (174.2): C, 75.82; H, 8.10; N, 16.08. Found: C, 75.8; H, 8.12; N, 16.0.

2-*tert*-Butyl-1*H*-pyrrolo[3,2-*c*]pyridine (24b). Cyclization of **22b** according to the foregoing procedure and crystallization from $CHCl_3$ yielded 98% of **24b**: mp >250 °C; ^{1}H NMR (90 MHz) (DMSO-d_6) δ 1.30 (s, 9 H, *t*-Bu), 6.15 (s, 1 H, 3-H), 7.20 (d, 1 H, 7-H, J_{6-7} = 5 Hz), 8.00 (m, 1 H, 6-H), 8.55 (m, 1 H, 4-H), 11.25 (m, 1 H, NH); IR (KBr) 3460, 3240–2400, 1620, 1585, 1550, 1470, 1430, 1400 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2$ (174.2): C, 75.82; H, 8.10; N, 16.08. Found: C, 75.6; H, 8.08; N, 15.9.

2-*tert*-Butyl-1-methylpyrrolo[2,3-*b*]pyridine (13a). Cyclization of **9** according to the foregoing procedure and flash chromatography on silica gel (10% $Et_3N/CHCl_3$) yielded 70% of **13a** (oily product): ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 3.95 (s, 3 H, NCH_3), 6.20 (s, 1 H, 3-H), 6.85 (dd, 1 H, 5-H, J_{4-5} = 8 Hz, J_{5-6} = 5 Hz), 7.65 (dd, 1 H, 4-H, J_{4-6} = 2 Hz), 8.10 (dd, 1 H, 6-H); IR (film) 3050, 2960, 1590, 1390 cm^{-1}; mass calcd for $C_{12}H_{16}N_2$ 188.3, found 188.

1,2-Dimethylpyrrolo[2,3-*b*]pyridine (13b). Reaction between **5** and 2-propanone-derived enolate was achieved under UV illumination. Standard workup gave a crude product, which was cyclized as previously described. Flash chromatography on silica gel (10% $Et_3N/CHCl_3$) yielded 90% of **13b** (oily product): ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3 H, CH_3), 3.60 (s, 3 H, NCH_3), 6.00 (s, 1 H, 3-H), 6.80 (dd, 1 H, 5-H, J_{4-5} = 8 Hz, J_{5-6} = 5 Hz), 7.60 (dd, 1 H, 4-H, J_{4-6} = 2 Hz), 8.10 (dd, 1 H, 6-H); IR (film) 3060, 2960, 1560, 1510, 1420 cm^{-1}; mass calcd for $C_9H_{10}N_2$ 146.2, found 146.

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Designed Water-Soluble Macrocyclic Esterases: From Nonproductive to Productive Binding

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The synthesis and esterase properties of three water-soluble macrobicyclic hosts, designed as α-chymotrypsin mimics, are described. For supramolecular complexation in aqueous solution, host **1** possesses an apolar tetraoxa[6.1.6.1]paracyclophane binding cavity, while hosts **2** and **4** have a larger tetraoxa[8.1.8.1]paracyclophane binding site. A phenolic nucleophile is located atop the cavity of **1** and **2**, while an alcoholic hydroxyl group is attached to **4**. The multistep synthesis of hosts **1**, **2**, and **4** involves two macrocyclization reactions. A Williamson ether cyclization gives the tetraoxa[*n*.1.*n*.1]paracyclophanes, and an amide cyclization attaches the nucleophiles to the binding sites. ^{1}H NMR host–guest complexation analysis demonstrates that both **1** and **2** form complexes of high stability with naphthalene guests in aqueous solution. In aqueous phosphate buffer at pH 8, host **2**, with its partially ionized phenolic residue, is acylated much faster by complexed 4-nitro-1-naphthyl acetate (**26**) than host **4**, which possesses the nonionized alcoholic hydroxyl group. The acylation of **2** by the complexed ester **26** is much faster than the hydrolysis of the ester in the presence of **1**, a host with the same phenolic nucleophile but with a smaller binding site. The difference in esterase activity between **1** and **2** is explained in terms of productive versus nonproductive binding. The acylation of **2** by complexed ester **26** follows saturation kinetics whereas the hydrolysis of **26** in the presence of **1** obeys second-order kinetics. Host **2** shows a modest catalytic turnover in the hydrolysis of **26** in aqueous phosphate buffer at pH 8. The nature of catalysis provided by **2** is discussed.

Introduction. Ever since the fundamental studies of Cramer[1] on the catalytic properties of the cyclodextrins in the early fifties, chemists have been challenged by the prospect of developing catalysts that mimic enzymes by forming stoichiometric complexes with their substrates in a reversible equilibrium prior to the reaction steps.[2-11]

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