Lanthanide-Promoted Reactions of Aldehydes and Amine Hydrochlorides in Aqueous Solution. Synthesis of 2,3-Dihydropyridinium and Pyridinium Derivatives

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Introduction

The chemistry of dihydropyridines has attracted considerable research interest for decades.[1] Dihydropyridines perform important biological function. For example, the reduced form of coenzyme β-nicotinamide adenine dinucleotide (NADH) bears the 1,4-dihydropyridine moiety.[2] Metabolites of 2,3-dihydropyridine such as *N*-methyl-4-phenyl-2,3-dihydropyridinium ($MPDP^+$) display neurotoxicity.[3] Moreover, dihydropyridines have been shown to be versatile intermediates in the synthesis of a variety of natural products such as alkaloids.[4] The general synthetic routes to dihydropyridines comprise (i) cyclization of acyclic starting materials[5] and (ii) reduction of pyridines, pyridinium ions, or their derivatives.[6] 2,3-Dihydropyridines are not stable unless an electron-withdrawing group (e.g., acyl) is attached to the nitrogen. Few synthetic methods are available for the formation of 2,3-dihydropyridines or pyridiniums from acyclic starting materials.[7] In the course of our exploration on applications of stable Lewis acids in protic solutions,[8] we found that lanthanide trifluoromethanesulfonate (triflate)[9] can promote reactions of aldehydes and amine hydrochlorides in water to afford 2,3-dihydropyridiniums.

Scheme 1

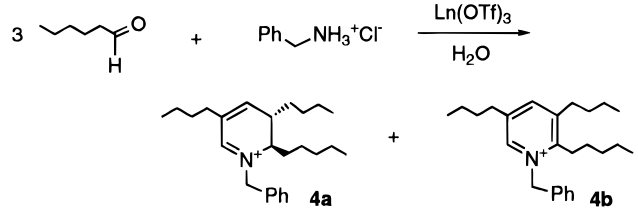

Table 1. Reaction of Hexanal and Benzylamine Hydrochloride in the Presence of Different Lanthanides[a]

$Ln(OTf)_3$	La	Pr	Nd	Gd	Dy	Er	Yb
4a + **4b**[b] (%)	73	82	74	57	38	64	56
4a/**4b**	3.1	3.2	3.2	3.1	3.2	3.1	3.1

[a] 2 mmol of amine hydrochloride and 8 mmol of aldehydes in 4.0 mL of 0.25 M lanthanide triflate solution. [b] The yield was based on benzylamine hydrochloride.

Results and Discussion

The reaction of hexanal and benzylamine hydrochloride was studied as a model for our methodology (Scheme 1). Hexanal and benzylamine hydrochloride were added to a solution of lanthanide triflate in water. The heterogeneous reaction mixture was sealed in a vial and was shaken vigorously for 24 h at room temperature. The products 3,5-dibutyl-2-pentyl-*N*-benzyl-2,3-dihydropyridinium (**4a**) and 3,5-dibutyl-2-pentyl-*N*-benzylpyridinium (**4b**) were isolated via flash chromatography over silica gel in a combined yield of 82% based on benzylamine hydrochloride. In addition, 2-butyl-2-octenal formed by self-condensation of hexanal was isolated in small amounts. The effect of different lanthanide triflates on the reaction yield and product distribution is summarized in Table 1. Of the seven lanthanide triflates tested, the lighter lanthanide triflate salts such as praseodymium and lanthanum triflates showed the best catalytic effects. The ratio of 2,3-dihydropyridinium to pyridinium was around 3:1. For these reactions, the yield of the reaction was dependent on the amount of lanthanides used. The combined yield of **4a** and **4b** was 14, 43, and 82% with 10, 25, and 50% equivalent of praseodymium triflate. We also observed that the reaction did not proceed in either methanol or ethanol solution even in the presence of lanthanide triflates.

This lanthanide-promoted reaction was applied to different aldehydes and amine hydrochlorides (Table 2). Acetaldehyde did not afford the pyridine compounds due in part to its tendency toward polymerization. Propionaldehyde or butanal with benzylamine hydrochloride (Table 2, entries 1 and 2) gave only 2,3-dihydropyridinium **1a** or **2a**, and no corresponding pyridiniums were isolated. In contrast, isovaleraldehyde produced both 2,3-dihydropyridinium **3a** and pyridinium **3b** in a ratio of 8.6:1 (Table 2, entry 3). The reaction of hexanal with benzylamine hydrochloride (Table 2, entry 4) gave the best yield, while replacement of benzylamine hydrochloride with propylamine hydrochloride (Table 2, entry 5) resulted in a lower yield of the products. It is noteworthy

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† To whom correspondence should be made regarding X-ray analysis.

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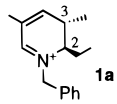
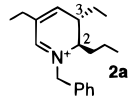
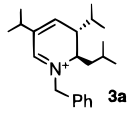
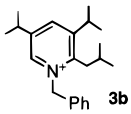
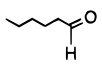
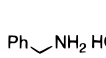
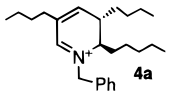
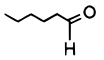
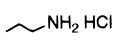
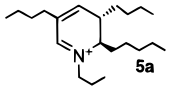
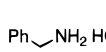
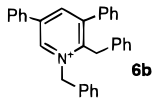
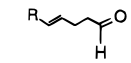
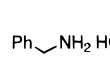
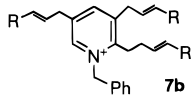
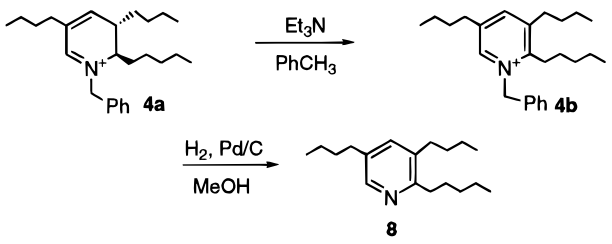
Table 2. Lanthanide-Catalyzed Reactions of Aldehydes and Amine Hydrochlorides in Aqueous Solution

Entry	Starting Materials RCHO	$RNH_3^+Cl^-$	Catalysts $Ln(OTf)_3$	Products	Yield (%) (a+b)	Ratio (a/b)
1			$Dy(OTf)_3$	 **1a**	31	
2			$Pr(OTf)_3$	 **2a**	56	
3			$Pr(OTf)_3$	 **3a**  **3b**	61	8.6
4			$Pr(OTf)_3$	 **4a** **4b**	82	3.2
5			$Pr(OTf)_3$	 **5a** **5b**	51	2.6
6			$Yb(OTf)_3$	 **6b**	75	
7	 R = n-C_5H_{11}		$Dy(OTf)_3$	 **7b**	44	

that the reactions with phenylacetaldehyde and 4-decenal only afforded pyridinium products **6b** and **7b**. The data in Table 2 indicated that this lanthanide-promoted condensation gave the best yield of 2,3-dihydropyridinium for middle-size aldehydes (three to eight carbons). For the amine part, the reaction of amino acid or aniline hydrochlorides did not give the desired 2,3-dihydropyridiniums.

The structures of the products **1a**−**5a** and **3b**−**7b** were elucidated through IR, UV, NMR, and MS. The counterion could be triflate or chloride, depending on the workup conditions. Generally, the organic phase was washed with saturated NaCl solution during workup so that the counterion was in the most cases chloride. In entry 3 of Table 2, the reaction was washed with water instead of the saturated NaCl solution, and consequently, compounds **3a** and **3b** were triflate salts. Triflate accounted for the peak 120.2 and 123.4 ppm in ^{13}C NMR of **3a** and 120.3 and 123.6 ppm in ^{13}C NMR of **3b**, respectively. For the dihydropyridiniums, the two downfield ^1H NMR peaks (one around 6.75 ppm and the other ranging from 8.41 to 8.68 ppm) account for the two hydrogens of the conjugated imine. For the corresponding pyridiniums, the chemical shifts of the two hydrogens both appear between 8.21 and 9.10 ppm. In addition, the structures have been further verified by chemical transformations and X-ray crystallography. 2,3-Dihydropyridinium **4a** was dehydrogenated to give pyridinium **4b** by refluxing in toluene in the presence of triethylamine. Compound **4b** was debenzylated to produce 2,3,5-trialkyl-substituted pyridine **8** through hydrogenolysis (Scheme 2). The X-ray structure of **3a** salt showed unambiguously the 2,3,5-trisubstituted, *trans*-2,3-dihydropyridinium core structure (see the Supporting Information).[10] NOE between 2-H and the 3-methyl group of **1a** was observed via 2D NOESY experiment, which suggested *trans*-2,3-substitution of **1a**. Moreover, NOE between 2-methylene and 3-H of **2a** via 2D NOESY was observed, which supported *trans*-2,3-substitution of **2a**, after the assignment of each peak of ^1H NMR spectrum of **2a** via 2D COSY (Table 2).

Scheme 2



The lanthanide-promoted reaction reported here is a novel extension of pyridine synthesis via condensation of aldehydes and amines (Chichibabin reaction).[11] This condensation normally requires high-temperature, high-pressure, or vapor-phase reaction conditions. Under milder conditions, it was reported that butanal reacted with ammonium acetate in acetic acid to give a 2,3-dihydropyridine that *in situ* disproportionated to a mixture of tetrahydropyridine and pyridinium.[7b] Amine hydrochlorides or amino acids with aldehydes were

(10) The X-ray data for **3a** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. $C_{23}H_{34}F_3NO_3S$; fw = 461.59; monoclinic space group $P2_1/n$; a = 12.500(1) Å, b = 13.261(1) Å, c = 16.220(2) Å; β = 111.439 (8)°, V = 2502.6(5) Å; R = 0.0454, R_w = 0.0585 based on 1418 observed reflections.

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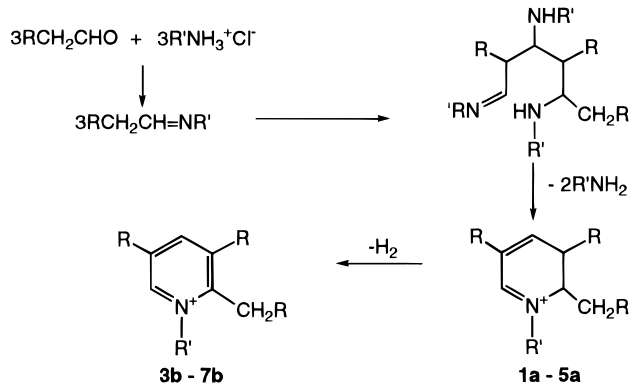
Scheme 3



reported to form quaternary pyridinium salts without any dihydropyridiniums observed.[12] In this work, an aqueous medium with the catalysis of lanthanide triflates allows the Chichibabin reaction to proceed under milder conditions and enables the isolation of 2,3-dihydropyridinium intermediates.

The reaction apparently proceeds through sequential condensations of three molecules of the Schiff base formed between the aldehyde and the amine (Scheme 3). Pyridinium products **3b**−**7b** were presumed to result from oxidation or disproportionation of their corresponding precursors, 2,3-dihydropyridiniums. The lanthanide triflates serve as stable Lewis acids and potentially can catalyze several individual steps in the reaction sequence. Work is currently underway to map the detailed mechanistic picture.

In summary, lanthanide-promoted condensation between aldehydes and amine hydrochlorides in aqueous solution affords a simple approach for the preparation of 2,3,5-trisubstituted 2,3-dihydropyridinium and pyridinium derivatives.

Experimental Section

General Methods. All unspecified reagents were from commercial resources. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz. Mass spectra (CI, EI or FAB) were performed by the mass spectrometry facility at the University of California, Riverside. UV spectra were recorded in methanol.

Synthesis of 1a−5a and 3b−7b. General Procedure. To a vial containing 4 mL of 0.25 M lanthanide triflate aqueous solution were added an aldehyde (8 mmol) and an amine hydrochloride (2 mmol). The reaction vial was sealed tightly and shaken for 24 h. The reaction mixture was extracted with ethyl acetate (5 mL × 3), and the combined organic layers were washed with brine (Table 2, entries 1−2, 5−7) or water (Table 2, entry 3) and dried over anhydrous $MgSO_4$. After removal of solvents *in vacuo*, the oil was chromatographed, eluting with hexane, ethyl acetate, and methanol (4/1/0, 0/1/0, and 0/10/1) sequentially, to give the products.

3,5-Dimethyl-2-ethyl-*N*-benzyl-2,3-dihydropyridinium (1a). Prepared from propionaldehyde and benzylamine hydrochloride: UV λ_{max} 293 nm (ϵ 2120); IR $\lambda^{-1}{}_{max}$ (cm^{-1}) 1602, 1458, 1378; ^{1}H NMR (CD_3OD) δ 0.59 (d, J = 7.2 Hz, 3 H), 0.96 (t, J = 7.6 Hz, 3 H), 1.79 (m, 2 H), 2.05 (s, 3 H), 2.75 (m, 1 H), 3.53 (dd, J = 9.2, 4.8 Hz, 1 H), 4.98 (d, J = 13.6 Hz, 1 H), 5.16 (d, J = 13.6 Hz, 1 H), 6.74 (d, J = 6.4 Hz, 1 H), 7.45 (m, 3 H), 7.52 (m, 2 H), 8.60 (s, 1 H); ^{13}C NMR (CD_3OD) δ 10.3, 17.6, 17.7, 23.7, 32.6, 63.9, 64.7, 127.8, 130.5, 131.1, 132.2, 148.5, 166.7; MS *m/e* 228 (M^+); HRMS calcd for $C_{16}H_{22}N$, 228.1752, found 228.1759.

3,5-Diethyl-2-propyl-*N*-benzyl-2,3-dihydropyridinium (2a). Prepared from butanal and benzylamine hydrochloride: UV λ_{max} 293 nm (ϵ 2320); IR $\lambda^{-1}{}_{max}$ (cm^{-1}) 1663, 1458, 1378; ^{1}H NMR (CD_3OD) δ 0.44 (t, J = 7.2 Hz, 3 H), 0.68 (m, 1 H), 0.94 (t, J = 7.2 Hz, 3 H), 1.15 (t, J = 7.2 Hz, 3 H), 1.2−1.5 (m, 3 H), 1.73 (m, 2 H), 2.42 (q, J = 7.2 Hz, 2 H), 2.52 (m, 1 H), 3.67 (t, J = 6.5 Hz, 1 H), 4.99 (d, J = 13.6 Hz, 1 H), 5.18 (d, J = 13.6 Hz, 1 H), 6.76 (d, J = 7.0 Hz, 1 H), 7.45 (m, 3 H), 7.53 (m, 2 H), 8.68 (s, 1 H); ^{13}C NMR (CD_3OD) δ 10.1, 12.9, 13.8, 19.7, 25.8, 25.9, 32.1, 39.6, 60.2, 63.8, 129.9, 130.2, 130.6, 131.1, 131.2, 132.2, 134.0, 146.4, 166.5; MS *m/e* 270 (M^+); HRMS calcd for $C_{19}H_{28}N$ 270.2222, found 270.2217.

3,5-Diisopropyl-2-(2′-methylpropyl)-*N*-benzyl-2,3-dihydropyridinium (3a) and 3,5-Diisopropyl-2-(2′-methylpropyl)-*N*-benzylpyridinium (3b). Prepared from isovaleraldehyde and benzylamine hydrochloride. **3a**: mp 88−89 °C; UV λ_{max} 295 nm (ϵ 4820); IR $\lambda^{-1}{}_{max}$ (cm^{-1}) 1602, 1480, 1458, 1352; ^{1}H NMR (CD_3OD) δ 0.25 (d, J = 6.4 Hz, 3 H), 0.79 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 1.12 (m, 1 H), 1.21 (d, J = 6.0 Hz, 6 H), 1.33 (m, 1 H), 1.47 (m, 1 H), 1.63 (m, 1 H), 2.33 (d, J = 7.8 Hz, 1 H), 2.75 (m, 1 H), 3.77 (dd, J = 11, 2.6 Hz, 1 H), 5.04 (dd, J = 13.6 Hz, 1 H), 5.23 (d, J = 13.6 Hz, 1 H), 6.83 (d, J = 6.4 Hz, 1 H), 7.45 (m, 5 H), 8.79 (s, 1 H); ^{13}C NMR (CD_3OD) δ 19.4, 19.7, 21.1, 21.5, 22.8, 23.6, 25.1, 32.1, 31.2, 37.9, 43.9, 57.5, 63.5, 130.6, 127.9, 130.7, 130.8, 131.3, 138.8, 144.4, 166.1; MS *m/e* 312 (M^+); HRMS calcd for $C_{22}H_{34}N$ 312.2691, found 310.2698. **3b**: UV λ_{max} 282 nm (ϵ 3150); IR $\lambda^{-1}{}_{max}$ (cm^{-1}) 1633, 1504, 1458; ^{1}H NMR (CD_3OD) δ 0.99 (d, J = 6.8 Hz, 6 H), 1.31 (m, 12 H), 2.10 (m, 1 H), 3.01 (d, J = 7.6 Hz, 2 H), 3.16 (m, 1 H), 3.30 (m, 1 H), 5.90 (s, 2 H), 7.12, 7.39 (m, 5 H), 8.44 (s, 1 H), 8.67 (s, 1 H); ^{13}C NMR (CD_3OD) δ 22.4, 23.1, 23.5, 30.8, 31.1, 32.9, 37.3, 63.1, 127.8, 130.0, 130.2, 130.7, 143.4, 144.2, 147.5, 151.8; MS *m/e* 310 (M^+); HRMS calcd for $C_{22}H_{32}N$ 310.2535, found 310.2524.

3,5-Dibutyl-2-pentyl-*N*-benzyl-2,3-dihydropyridinium (4a) and 3,5-Dibutyl-2-pentyl-*N*-benzylpyridinium (4b). Prepared from hexanal and benzylamine hydrochloride. **4a**: UV λ_{max} 291 nm (ϵ 2860); IR $\lambda^{-1}{}_{max}$ (cm^{-1}) 1663, 1587, 1504, 1458, 1378; ^{1}H NMR (CD_3OD) δ 0.64 (t, J = 7.2 Hz, 3 H), 0.76 (m, 1 H), 0.90 (m, 6 H), 1.11 (m, 1 H), 1.35 (m, 12 H), 1.50 (m, 2 H), 1.76 (m, 2 H), 2.35 (m, 2 H), 2.58 (m, 1 H), 3.56 (t, J = 7.0 Hz, 1 H), 4.94 (d, J = 13.6 Hz, 1 H), 5.14 (d, J = 13.6 Hz, 1 H), 6.71 (d, J = 6.4 Hz, 1 H), 7.44 (m, 5 H), 8.67 (s, 1 H); ^{13}C NMR (CD_3OD) δ 14.0, 14.2, 23.0, 23.3, 23.4, 26.2, 28.6, 30.0, 31.7, 32.3, 32.4, 32.5, 38.1, 60.4, 63.7, 130.7, 131.1, 131.2, 147.7, 166.5; MS *m/e* 354 (M^+), 282, 91 (100); HRMS calcd for $C_{25}H_{40}N$ 354.3161, found 354.3159. **4b**: UV λ_{max} 281 nm (ϵ 2420); IR $\lambda^{-1}{}_{max}$ (cm^{-1}) 1640, 1504, 1458, 1378; ^{1}H NMR (CD_3OD) δ 0.79 (t, J = 7.2 Hz, 3 H), 0.90 (m, 6 H), 1.18−1.45 (m, 10 H), 1.59 (m, 4 H), 2.74 (t, J = 7.6 Hz, 4 H), 2.94 (m, 2 H), 5.80 (s, 2 H), 7.11 (d, J = 4.0 Hz, 2 H), 7.39 (m, 3 H), 8.23 (s, 1 H), 8.63 (s, 1 H); ^{13}C NMR (CD_3OD) δ 14.0, 23.1, 23.5, 29.0, 30.3, 32.6, 32.7, 32.8, 33.5, 33.7, 62.8, 127.9, 130.2, 130.6, 135.3, 142.5, 144.6, 144.9, 147.9, 156.2; MS *m/e* 352 (M^+), 91 (100); HRMS calcd for $C_{25}H_{38}N$ 352.3004, found 352.3001.

3,5-Dibutyl-2-pentyl-*N*-propyl-2,3-dihydropyridinium (5a) and 3,5-Dibutyl-2-pentyl-*N*-propylpyridinium (5b). Prepared from hexanal and propylamine hydrochloride. **5a**: UV λ_{max} 293 nm (ϵ 2820); IR $\lambda^{-1}{}_{max}$ (cm^{-1}) 1663, 1504, 1458, 1397; ^{1}H NMR (CD_3OD) δ 0.92 (m, 9 H), 1.04 (t, J = 7.6 Hz, 3 H), 1.20−1.58 (m, 16 H), 1.72 (m, 3 H), 1.91 (m, 1 H), 2.35 (t, J = 8.0 Hz, 2 H), 2.75 (m, 1 H), 3.84 (t, J = 7.6 Hz, 2 H), 3.90 (t, J = 6.8 Hz, 1 H), 6.81 (d, J = 6.4 Hz, 1 H), 8.41 (s, 1 H); ^{13}C NMR (CD_3OD) δ 10.9, 13.9, 14.0, 14.2, 22.7, 22.9, 23.3, 23.4, 26.7, 29.1, 30.9, 31.7, 32.4, 32.5, 33.1, 38.1, 61.7, 62.9, 132.4, 147.3, 166.3; MS *m/e* 306 (M^+); HRMS calcd for $C_{21}H_{40}N$ 306.3161, found 306.3163. **5b**: UV λ_{max} 281 nm (ϵ 2410); IR $\lambda^{-1}{}_{max}$ 1633, 1504, 1458, 1379; ^{1}H NMR (CD_3OD) δ 0.96 (m, 9 H), 1.08 (t, J = 7.2 Hz, 3 H), 1.45 (m, 8 H), 1.67 (m, 6 H), 2.00 (m, 2 H), 2.79 (m, 4 H), 3.07 (m, 2 H), 4.52 (t, J = 8.0 Hz, 2 H), 8.21 (s, 1 H), 8.60 (s, 1 H); ^{13}C NMR (CD_3OD) δ 10.9, 14.0, 14.1, 23.1, 23.5, 25.9, 29.4, 29.7, 32.7, 32.8, 33.4, 33.5, 60.7, 142.3, 143.8, 147.1, 155.3; MS *m/e* 304 (M^+); HRMS calcd for $C_{21}H_{38}N$ 304.3004, found 304.3008.

3,5-Diphenyl-2-benzyl-*N*-benzylpyridinium (6b). Prepared from benzylacetaldehyde and benzylamine hydrochloride: UV λ_{max} 262 nm (ϵ 5830); ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 2 H), 6.10 (s, 2 H), 7.38, 7.55, 7.73 (m, 20 H), 8.55 (s, 1 H), 9.10 (s, 1 H); MS *m/e* 412 (M^+), 322(100); HRMS calcd for $C_{31}H_{24}N$ (M − H) 411.1987, found 411.1981.

3,5-Di(2′-octenyl)-2-(3′-nonenyl)-*N*-benzylpyridinium (7b). Prepared from 4-decenal and benzylamine hydrochloride: UV λ_{max} 286 nm (ϵ 2580); IR $\lambda^{-1}{}_{max}$ (cm^{-1}) 1633, 1504, 1458; ^{1}H NMR

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(CD_3OD) δ 0.84 (m, 9 H), 1.22 (m, 18 H), 1.85 (m, 2 H), 2.10 (m, 4 H), 2.24 (m, 2 H), 3.10 (m, 2 H), 3.56 (d, J = 7.6 Hz, 2 H), 3.62 (d, J = 7.2 Hz, 2 H), 5.43−5.53 (m, 4 H), 5.68 (m, 2 H), 5.85 (s, 2 H), 7.14 (m, 2 H), 7.39 (m, 3 H), 8.19 (s, 1 H), 8.62 (s, 1 H); ^{13}C NMR (CD_3OD) δ 14.3, 23.5, 26.6, 28.2, 28.3, 28.5, 30.1, 30.2, 30.3, 30.6, 31.1, 32.6, 32.7, 62.8,125.2, 125.3, 127.0, 128.0, 128.1, 130.4, 130.7, 133.9, 135.5, 135.6, 141.5, 143.5, 144.7, 147.4, 156.3; MS *m/e* 514 (M^+); HRMS calcd for $C_{37}H_{56}N$ 514.4413, found 514.4405.

Transformation of 4a to 4b. To a solution of **4a** (200 mg) in toluene (5 mL) was added triethylamine (0.5 mL), and the resulting solution was refluxed for 1 h or stirred at room temperature overnight. After evaporation of the solvent *in vacuo*, the oil was purified through a silica gel column eluting with methanol and ethyl acetate (1/9) to give **4b** (165 mg) in 83% yield.

Debenzylation of 4b To Prepare 3,5-Dibutyl-2-pentylpyridine (8). To a solution of **4b** (150 mg) in methanol (5 mL) was added Pd/C (5%, 100 mg). Under a hydrogen pressure of 50 lb/in.^{2}, the reaction mixture was shaken overnight. After filtration to remove the catalyst, the filtrate was evaporated, and the residue was purified by flash chromatography, eluting with hexane and ethyl acetate (5/1). The pure compound **8** (71 mg) was obtained in 91% yield. 3,5-Dibutyl-2-pentylpyridine (**8**): ^1H NMR ($CDCl_3$) δ 0.94 (m, 9 H), 1.36 (m, 8 H), 1.53 (m, 4 H), 1.68 (m, 2 H), 2.55 (m, 4 H), 2.73 (t, J = 8.0 Hz, 2 H), 7.21 (s, 1 H), 8.19 (d, J = 2.0 Hz, 1 H); MS *m/e* 262 (M + 1), 190, 163.

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Supporting Information Available: NMR spectra and ORTEP presentation of the X-ray structure of **3a** (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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