First Direct C-2-Lithiation of 4-DMAP. Convenient Access to Reactive Functional Derivatives and Ligands

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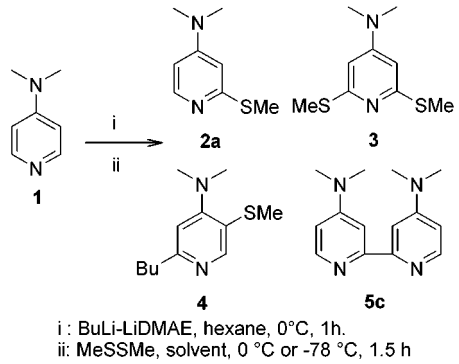
The first direct α-lithiation of 4-DMAP has been peformed via reaction with the BuLi−$Me_2N(CH_2)_2$-OLi (BuLi−LiDMAE) reagent. This new methodology avoids the use of a activation−lithiation−regeneration sequence or halogen−metal exchange classically employed. New useful DMAP-containing synthons and polyheterocycles have been efficiently prepared.

Introduction

4-(Dimethylamino)pyridine **1** has been used extensively as a powerful acylation catalyst[1] as well as a ligand for transition metals.[2] The literature reveals that current attention is now focused on the preparation of analogues of **1** to design catalysts for ester methanolysis[3] and enantioselective acyl transfer.[4] While the modification of the 4-amino part is now well-documented,[4c,5] those of the pyridine ring appear to be a harder task. At this time, only lithiation of a BF_3-complexed **1** with LTMP[6] has been found successful.[3,4a] However, although efficient, this method suffers from some drawbacks. Indeed, prior complexation of **1** before lithiation implies a final regeneration step to isolate the products as illustrated by a recent article of Spivey and co-workers on the preparation of atropoisomeric analogues of **1**.[7] The lithiation gave mixtures of mono- and disubstituted products,[4a] which may be due to a strong increase of protons acidity induced by BF_3 complexation,

Herein we report that the BuLi−$Me_2N(CH_2)_2OLi$ reagent (noted BuLi−LiDMAE)[8] induced the first direct C-2 monolithiation of **1**, thus providing a convenient access to useful 4-DMAP containing synthons and ligands.

Scheme 1[a]



[a] Key (i) BuLi−LiDMAE, hexane, 0 °C, 1 h; (ii) MeSSMe, solvent, 0 or −78 °C, 1.5 h.

Results and Discussion

In preliminary experiments, according to our previous work,[8] we decided to conduct metalations in hexane at 0 °C. The results of those experiments using various amounts of BuLi−LiDMAE and condensation conditions are reported in Scheme 1 and Table 1.

As expected, BuLi led to a sluggish reaction giving small amounts of the addition product **4** (identified by GC/MS, $M^+ = 224$) among numerous uncharacterized byproducts. On the other hand, we were pleased to observe that with BuLi−LiDMAE the above side reactions were completely suppressed, with metalation occurring exclusively at C-2. However, when the condensation step was performed at 0 °C, mixtures of mono- and disubstituted compounds **2a** and **3** were obtained, regardless of the amount of base used. Since BuLi−LiDMAE was known to promote the regioselective C-6 lithiation of 2-heterosubstituted pyridines,[6a−b,d] product **3** was assumed to be the result of a subsequent metalation of **2a** in the reaction medium. This side reaction was easily overcome by quenching the lithiated species at −78 °C. Under these conditions, **2a** was isolated in 75% yield with 10% of starting material, using 2 equiv of base. We attributed this incomplete consumption of **1** to a partial protonation of the lithio intermediate by THF. To overcome these shortcomings, the solvent was changed to hexanes. Then, it was gratifying to observe a complete

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Table 1. BuLi−LiDMAE-Mediated Lithiation of 1[a]

BuLi (equiv)	LiDMAE (equiv)	*T* (°C)	solvent	**2a**[b] (%)	**3**[b] (%)	**4**[c] (%)	**5c**[b] (%)
2		0	THF			15	
2	2	0	THF	60	7		
3	3	0	THF	70	16		
2	2	−78	THF	75			
2	2	−78	hexane	96			

[a] All reactions performed on 4 mmol of **1**. [b] Isolated yields. [c] GC yield.

Scheme 2

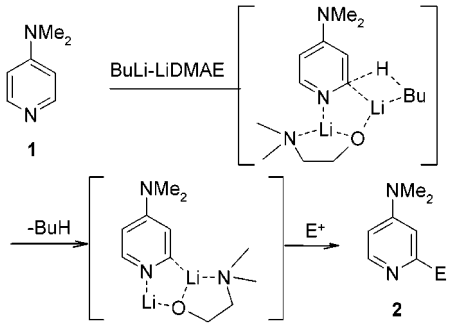
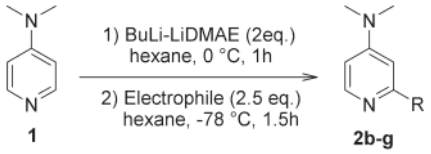


Table 2. Preparation of 2-Substituted-4-DMAP[a]



electrophile	R	product	yield[b] (%)
DCl/D_2O	D	**2b**	70[c]
$PhCONMe_2$	PhCO	**2c**	65
$ClPPh_2$	PPh_2	**2d**	90
C_2Cl_6	Cl	**2e**	90
CBr_4	Br	**2f**	94
I_2	I	**2g**	81
$ClSnBu_3$	$SnBu_3$	**2h**	70

[a] All reactions performed on 4 mmol of **1**. [b] Isolated yields after chromatography on SiO_2. [c] Deuterium content >98% (^{1}H NMR).

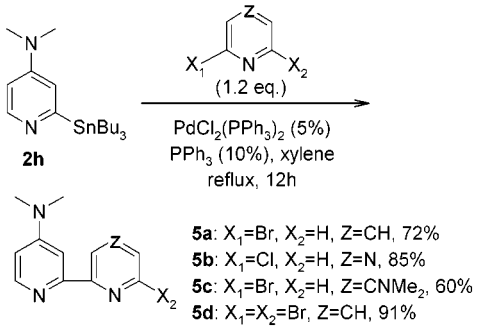
and clean reaction providing **2a** in excellent 96% isolated yield.

The direct and selective lithiation of 4-DMAP could be explained by the formation of aggregates between BuLi−LiDMAE and 4-DMAP via lithium chelation by the pyridinic nitrogen atom probably strongly enhanced by the electron-releasing dimethylamino group at the 4-position. The aggregates are assumed initially to deliver BuLi in the proximity of H-2 and subsequently ensure stabilization of the subsequently formed 2-monolithiated intermediate (Scheme 2).

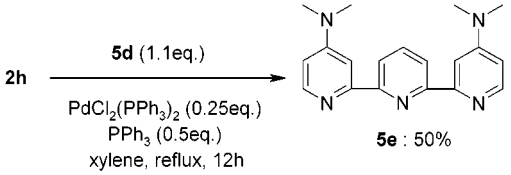
After determining the best conditions for lithiation, we demonstrated the scope of our new process by preparing a series of 2-substituted 4-(dimethylamino)pyridines, particularly those allowing for further functionalizations (Table 2).

The versatility of our methodology was clearly demonstrated by introducing various functionalities efficiently at C-2. The quantitative formation of the 2-lithio intermediate was checked by a deuteration experiment showing a >98% deuterium content (^{1}H NMR). The derivatives **2e**−**h** bearing useful reactive moieties were obtained in good yields (70−94%). The efficiently prepared pyridylphosphine **2d** is a potentially interesting new electron-releasing P−N ligand for heterobimetallic complexes.[9] Finally, we have shown by additional experiments that all these compounds could be prepared at least on a 5 g scale, making them of particular interest for a synthetic purpose.

Scheme 3



Scheme 4



The availability of the tin derivative **2h** led us to investigate its reactivity in the Stille cross-coupling reaction for the preparation of new ligands. As shown in Scheme 3, **2g** coupled efficiently with heteroaromatic halides to produce **5a**−**d** in good to high yields. In this context, the previously obtained 2-bromo derivative **2f** was found to be a useful precursor for the preparation 4,4′-(dimethylamino)-2,2′-bipyridine **5c**.

We finally investigated the preparation of terpyridine **5e** by coupling the brominated bipyridine **5d** with **2h** (Scheme 4). In our first attempts using 5 mol % of catalyst, **5e** was obtained in low yield (10%) even when extended reaction times were employed (up to 90 h). We thought that **5e** probably acted as a ligand of palladium thus inhibiting the desired cross-coupling. A substantial improvement was obtained by increasing the amount of catalyst (0.25 equiv) under which conditions **5e** was isolated in 50% yield. This result showed that the yield of DMAP-containing polypyridine was proportional to the amount of used Palladium catalyst.

In summary, we have described a convenient way to introduce reactive functionalities as well as heterocyclic moieties at C-2 position of the pyridine ring of 4-DMAP via an unprecedented direct lithiation with the BuLi−LiDMAE reagent. This new process avoids the need for the conventional activation-regeneration sequence as well as the formation of disubstituted derivatives encountered in the Lewis acid assisted lithiation procedures described in the literature. Based on these encouraging preliminary results, the preparation of new DMAP-containing quaterpyridines by nickel-catalyzed homocoupling are now in progress.

Experimental Section

General Methods. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 400, 100 and 162 MHz respectively with $CDCl_3$ as solvent and TMS as internal standard for ^{1}H NMR.

(9) For a review on pyridylphosphines and related metal complexes see: Newkome, G. *Chem. Rev.* **1993**, *93*, 2067 and references therein.

Materials and Solvents. All reagents were commercially available and were purified by distillation when necessary. BuLi was used as 1.6 M solutions in hexanes. 2-(dimethylamino)ethanol was distilled and stored over molecular sieves before use. Hexane, THF, and xylene were distilled and stored on sodium wire before use.

General Procedure for C-2 Functionalization of 4-DMAP (1). A solution of 2-(dimethylamino)ethanol (0.8 mL, 8 mmol) in hexane (10 mL) was cooled at ca. −5 °C, and BuLi (10 mL, 16 mmol) was added dropwise under a nitrogen atmosphere. After 30 min at 0 °C, 4-DMAP (488 mg; 4 mmol) was added at once as a solid. After 1 h of stirring at 0 °C, the reaction medium was cooled at −78 °C, and a solution of the appropriate electrophile (10 mmol) in hexane (20 mL) was added dropwise (20 min). The temperature was then allowed to raise to 0 °C (1.5 h). Hydrolysis was performed at this temperature with H_2O (20 mL). The aqueous phase was first extracted with diethyl ether (20 mL) and then with dichloromethane (20 mL). After drying ($MgSO_4$), filtration, and evaporation of solvents, the crude product was purified by column chromatography.

Dimethyl(2-methylsulfanyl-4-pyridyl)amine (2a). Column chromatography (AcOEt) yielded **2a** (645 mg, 96%) as a yellow oil: ^{1}H NMR δ_H 2.55 (s, 3H), 2.95 (s, 6H), 6.30 (dd, J = 6.1 and 2.5 Hz, 1H), 6.40 (d, J = 2.5 Hz, 1H), 8.1 (d, J = 6.1 Hz, 1H); ^{13}C NMR δ_C 13.3, 39.0, 102.9, 103.9, 149.0, 154.1, 159.5; MS (EI) m/z 168 (M^+, 99), 167 (59), 153 (22), 122 (100), 121 (49), 107 (39), 79 (32). Anal. Calcd for $C_8H_{12}N_2S$: C, 57.11; H, 7.19; N, 16.65. Found: C, 57.40; H, 7.16; N, 16.26.

***N*,*N*-Dimethyl-3,5-di(methylsulfanyl)aniline (3).** Column chromatography (60/40 hexanes, AcOEt) yielded **3** (137 mg, 16%) as a yellow oil: ^{1}H NMR δ_H 2.57 (s, 6H), 2.95 (s, 6H), 6.19 (s, 2H); ^{13}C NMR δ_C 13.2, 39.1, 100.2, 154.3, 158.5; MS (EI) m/z 214 (M^+, 100), 213 (41), 168 (54), 135 (50), 107 (46), 80 (54). Anal. Calcd for $C_9H_{14}N_2S_2$: C, 50.43; H, 6.58; N, 13.07. Found: C, 50.56; H, 6.78; N, 12.85.

2-^{2}H-4-Pyridyl(dimethyl)amine (2b). Recrystallization from hexanes yielded **2b** as a mixture with **1** (344 mg, 71%, %D >95): ^{1}H NMR δ_H 3.02 (s, 6H), 6.51 (m, 2H), 8.24 (d, J = 6.7 Hz, 1H); ^{13}C NMR δ_C 38.9, 106.2, 106.6, 149.0, 149.2, 149.3, 149.6, 154.1; MS (EI) m/z 123 (M^+, 83), 122 (100), 93 (2), 79 (11).

4-(Dimethylamino)-2-pyridylphenylmethanone (2c). Column chromatography (AcOEt) yielded **2c** (588 mg, 65%) as a white solid: mp 68−71 °C; ^{1}H NMR δ_H 3.1 (s, 6H), 6.62 (m,1H), 7.25 (m, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.55 (t, J = 7.1 Hz, 1H); 8.05 (d, J = 7.6 Hz, 2H); 8.31 (d, J = 5.7 Hz, 1H); ^{13}C NMR δ_C 39.2, 107.3, 108.3, 128.0, 130.9, 132.6, 136.8, 148.7, 154.9, 155.4, 186.5; MS (EI) m/z 226 (M^+, 100), 225 (99), 197 (49), 183 (69), 105 (53), 77 (79). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.45; H, 6.15; N, 12.47.

2-Diphenylphosphanyl-4-pyridyl(dimethyl)amine (2d). Column chromatography (AcOEt) yielded **2d** (1.1 g, 90%) as a yellow viscous oil: ^{1}H NMR δ_H 2.76 (s, 6H), 6.32 (m,2H), 7.29 (m, 6H), 7.42 (m, 4H); 8.31 (d, J = 5.7 Hz, 1H); ^{13}C NMR δ_C 38.4, 104.9, 111.1, 128.10, 128.4, 133.7, 136.6, 149.8, 153.5, 162.3; ^{31}P NMR δ_P −2.01 ppm; MS (EI) m/z 307 (12), 306 (M^+, 64), 305 (100), 229 (9), 228 (17), 121 (1). Anal. Calcd for $C_{19}H_{19}N_2P$: C, 74.49; H, 6.25; N, 9.14. Found: C, 74.53; H, 6.08; N, 9.38.

2-Chloro-4-pyridyl(dimethyl)amine (2e). Column chromatography (AcOEt) yielded **2e** (562 mg, 90%) as a white solid: mp 80−82 °C; ^{1}H NMR δ_H 3.00 (s, 6H), 6.40 (dd, J = 6.1 and 2.3 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 7.97 (d, J = 6.1 Hz, 1H); ^{13}C NMR δ_C 39.2, 105.4, 105.8, 149.0, 152.2, 156.0; MS (EI) m/z 158 (23), 157 (37), 156 (72), 155 (100), 121 (4). Anal. Calcd for $C_7H_9N_2Cl$: C, 53.66; H, 5.79; N, 17.89. Found: C, 53.75; H, 5.80; N, 17.59.

2-Bromo-4-pyridyl(dimethyl)amine (2f). Column chromatography (AcOEt) yielded **2f** (756 mg, 86%) as a brown gummy solid: ^{1}H NMR δ_H 3.00 (s, 6H), 6.43 (dd, J = 5.9 and 2.1 Hz, 1H), 6.63 (d, J = 2.1 Hz, 1H), 7.93 (d, J = 5.9 Hz, 1H); ^{13}C NMR δ_C 39.2, 106.2, 109.2, 143.1, 149.3, 155.7; MS (EI) m/z 202 (97), 201 (68), 100 (100), 199 (100), 199 (62), 121 (27), 79 (10). Anal. Calcd for $C_7H_9N_2Br$: C, 41.82; H,4.51; N,13.93. Found: C, 41.90; H, 4.48; N, 13.83.

2-Iodo-4-pyridyl(dimethyl)amine (2g). Column chromatography (AcOEt) yielded **2g** (903 mg, 81%) as a white solid: mp 67−69 °C; ^{1}H NMR δ_H 2.97 (s, 6H), 6.45 (dd, J = 5.9 and 2.0 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 7.89 (d, J = 5.9 Hz, 1H); ^{13}C NMR δ_C 39.1, 106.5, 116.4, 119.25, 149.5, 154.8; MS (EI) m/z 248 (M^+, 100), 121 (76), 106 (15). Anal. Calcd for $C_7H_9N_2I$: C, 33.89; H, 3.66; N, 11.29. Found: C, 34.03; H, 3.63; N, 11.16.

Dimethyl(2-tributylstannyl-4-pyridyl)amine (2h). Column chromatography (70/30 Et_3N, AcOEt) yielded **2g** (1.15 g, 70%) as an oil: ^{1}H NMR δ_H 0.85 (t, J = 8.0 Hz, 9H), 1.15 (t, J = 8.0 Hz, 6H), 1.3 (m, 6H), 1.55 (m, 6H), 2.98 (s, 6H), 6.37 (dd, J = 5.9 and 3.0 Hz, 1H), 6.65 (d, J = 3.0 Hz, 1H), 8.34 (d, J = 5.9 Hz, 1H); ^{13}C NMR δ_C 9.4, 13.7, 27.1, 29.2, 38.7, 105.4, 115.4, 150.0, 152.1, 172. Anal. Calcd for $C_{19}H_{36}N_2Sn$: C, 55.50; H, 8.82; N, 6.81. Found: C, 55.65; H, 8.71; N, 6.78.

General Procedure for Stille Cross-Coupling of Stannane 2h. To a solution of **2h** (615 mg; 1.5 mmol) in xylene (30 mL) under nitrogen atmosphere were added $PdCl_2(PPh_3)_2$ (53.4 mg; 0.0745 mmol) and PPh_3 (39.5 mg; 0.149 mmol) and the appropriate heteroaromatic halide (generally 1.6 mmol except for 2,6-dibromopyridine (3 mmol was added)). The reaction medium was then refluxed for 12 h. After being cooled at room temperature, the black mixture was filtered over a pad of Celite and the xylene phase was extracted three times with aqueous HCl (25%). The aqueous phase was then made basic by the addition of NH_4OH (10% and subsequently extracted thrice with dichloromethane (20 mL). After drying ($MgSO_4$), filtration, and evaporation of solvent, the crude product was purified by column chromatography or precipitation in diethyl ether.

Dimethyl[2-(2-pyridyl)-4-pyridyl]amine (5a). Column chromatography (70/30 Et_3N, AcOEt) yielded **5a** (215 mg, 72%) as white solid: mp 96−98 °C; ^{1}H NMR δ_H 3.1 (s, 6H), 6.53 (dd, J = 5.9, 2.7 Hz, 1H), 7.28 (m, 1H), 7.7 (d, J = 2.7 Hz, 1H), 7.8 (dt, J = 7.8, 1.7 Hz, 1H), 8.32 (d, J = 5.9 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.67 (dd, J = 4.7, 0.8 Hz, 1H); ^{13}C NMR δ_C 39.1, 103.8, 106.6, 121.25, 123.3, 136.7, 148.8, 149.3, 155.2, 156.1, 156.9; MS (EI) m/z 199 (M^+, 53), 184 (100), 156 (48), 155 (19), 78 (22). Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.34; H, 6.58; N, 21.09. Found: C, 72.46; H, 6.41; N, 21.34.

Dimethyl[2-(2-pyrazinyl)-4-pyridyl]amine (5b). Column chromatography (70/30 Et_3N, AcOEt) yielded **5b** (255 mg, 85%) as an orange solid: mp100−102 °C; ^{1}H NMR δ_H 3.1 (s, 6H), 6.55 (dd, J = 5.9, 2.7 Hz, 1H), 7.60 (d, J = 2.7 Hz, 1H), 8.34 (d, J = 5.9 Hz, 1H), 8.57 (m, 2H), 9.60 (d, J = 1.5 Hz, 1H); ^{13}C NMR δ_C 39.1, 104.1, 107.1, 143.1, 143.4, 144.0, 149.5, 151.8, 153.9, 155.0; MS (EI) m/z 200 (M^+, 88), 185 (100), 157 (44), 158 (24), 79 (8). Anal. Calcd for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 66.05; H, 6.24; N, 27.67.

***N*,*N*-Dimethyl-2-(4-(dimethylamino)-2-pyridyl)-4-pyridinamine (5c).** Precipitation from diethyl ether yielded **5c** (218 mg, 60%) as a brown solid: mp 230−232 °C; ^{1}H NMR δ_H 3.1 (s, 12H), 6.50 (dd, J = 5.9, 2.9 Hz, 2H), 7.49 (d, J = 2.9 Hz, 2H), 8.30 (d, J = 5.9 Hz, 2H); ^{13}C NMR δ_C 39.3, 104.0, 106.4, 149.1, 155.2, 156.9; MS (EI) m/z 242 (M^+, 9), 227 (42), 199 (23), 121 (40), 120 (100). Anal. Calcd for $C_{14}H_{18}N_4$: C, 69.39; H, 7.49; N, 23.12. Found: C, 69.48; H, 7.31; N, 22.96.

2-(6-Bromo-2-pyridyl)-4-pyridyl(dimethyl)amine (5d). Column chromatography (70/30 Et_3N, AcOEt) yielded **5d** (380 mg, 91%) as an orange oil: ^{1}H NMR δ_H 3.05 (s, 6H), 6.49 (dd, J = 6.0, 2.7 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.60 (m, 2H), 8.26 (d, J = 6 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ_C 39.1, 104.1, 106.9, 119.8, 127.4, 138.7, 141.1, 149.4, 154.3, 155.0, 158.2; MS (EI) m/z 279 (69), 278 70), 264 (99), 262 (100), 236 (42), 234 (43), 198 (17), 155 (24), 77 (9). Anal. Calcd for $C_{12}H_{12}BrN_3$: C, 51.82; H, 4.34; N, 15.11. Found: C, 52.11; H, 4.46; N, 14.98.

***N*,*N*-Dimethyl-2-[6-(4-(dimethylamino)-2-pyridyl)-2-pyridyl]-4-pyridinamine (5e).** Precipitation from diethyl ether yielded **5e** (230 mg, 50%) as a brown solid: mp > 300 °C dec;

^{1}H NMR δ_H 3.1 (s, 12H), 6.56 (dd, J = 5.6, 2.6 Hz, 2H), 7.91 (t, J = 7.8 Hz, 2H), 7.96 (d, J = 2.6 Hz, 2H), 8.34 (d, J = 5.6 Hz, 2H), 8.37 (d, J = 7.8 Hz, 2H); ^{13}C NMR δ_C 39.3, 103.9, 106.7, 120.7, 137.6, 149.4, 152.8, 155.2, 156.3. Anal. Calcd for $C_{19}H_{21}N_5$: C, 71.45; H, 6.63; N, 21.93. Found: C, 71.69; H, 6.52; N, 22.06.

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