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# Regioselective functionalisation of 2-(diphenylphosphino)-pyridine: direct lithiation at the pyridine C-6 position

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**Abstract**

It is shown that 2-(diphenylphosphino)pyridine was efficiently and regioselectively metallated at the C-6 position by use of the BuLi–$Me_2N(CH_2)_2OLi$ basic system. The method described opened access to various functionally potential ligands or ligand precursors. © 2000 Elsevier Science Ltd. All rights reserved.

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Pyridylphosphines have attracted attention as these compounds, which contain two donor atoms of different coordination properties, have been found to give homo- and heterobinuclear transition metal complexes allowing considerable improvements in catalytic reactions.[1,2] Thus, the preparation of P–N ligands bearing new functionalities could be of interest. However, to our knowledge, the direct modification of 2-(diphenylphosphino)pyridine **1**[3] has not yet been explored. In this way, the direct lithiation of the pyridine ring appears as the more attractive route. Unfortunately, the reaction of **1** with alkyl- or aryllithiums is known to give only nucleophilic additions onto azomethine bond[4] and/or onto phosphorus atom.[5]

On the other hand, in the course of our works on the metallation of heterocycles,[6] we previously showed that the basicity/nucleophilicity ratio of BuLi in apolar solvents was significantly increased in the presence of lithium dimethylaminoethoxide. The new basic system noted BuLi–LiDMAE then allowed the regioselective C-6 functionalisation of 2-alkoxy, 2-alkylthio and 2-dialkylamino pyridines.[6a] In this paper, we describe the efficient synthesis of 6-substituted 2-(diphenylphosphino)pyridines **2** mediated by BuLi–LiDMAE (Scheme 1).

As a preliminary study, we attempted to metallate **1** with classical non-nucleophilic bases such as LDA (4 equiv.) or LTMP (4 equiv.) in THF at –78°C and at 0°C. Whatever the conditions or base, no reaction occurred and **1** was recovered quantitatively even when the in situ trapping technique was used.[7] This

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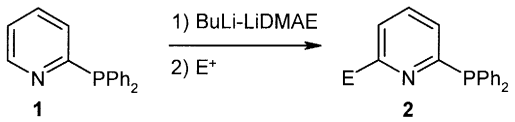
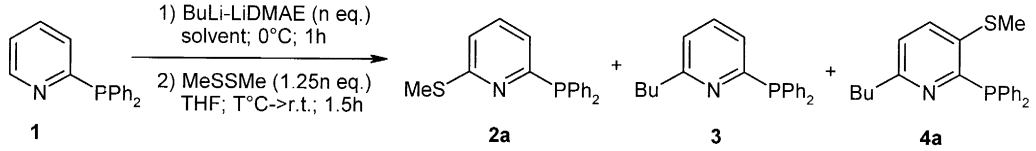



Scheme 1.

result could be expected since, unlike phosphine oxide or phosphonium groups, $PPh_2$ was not known to promote ortholithiation.[8]

Thus, we turned to the metallation with BuLi–LiDMAE (Scheme 2). The more significative results obtained during an exploratory study are reported in Table 1.




Scheme 2.

Table 1
BuLi–LiDMAE mediated C-6 functionalisation of **1**[a]

| Entry | BuLi (eq.) | LiDMAE (eq.) | Solvent (mL) | THF (mL) | T°C | **1**% | **2a**%[b] | (**3**+**4a**)%[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.5 | 1.5 | Hexane (20) | 20 | 0 | 39 | 35 | 26 |
| 2 | 2 | 2 | " | " | " | 40 | 53 | 7 |
| 3 | 3 | 3 | " | " | " | 40 | 55 | 5 |
| 4 | 2 | 2 | " (30) | 30 | " | 38 | 61 | 1 |
| 5 | " | " | " (60) | 60 | " | 33 | 60 | 7 |
| 6 | " | " | Hexane (10) Toluene (20) | 30 | " | 38 | 40 | 22 |
| 7 | " | " | Hexane (30) | " | -78 | 8 | 91 | 1 |
| 8 | " | - | " (20) | 20 | 0 | 55 | - | 45 |

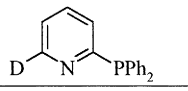
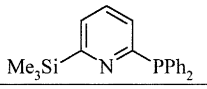
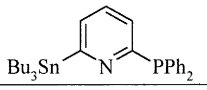
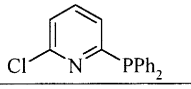
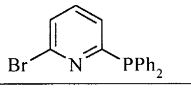
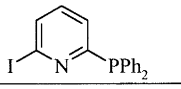
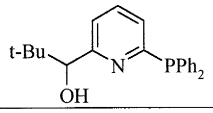
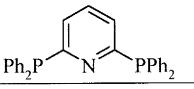
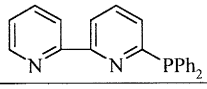
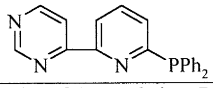
(a) Reaction performed on 4 mmoles of **1**; (b) Isolated yields after purification on a Chromatotron hexane-AcOEt (95/5); (c) GC yields.

As a general trend (Entries 1–7), the usefulness of BuLi–LiDMAE was clear since **2a** was always obtained as the main product. In contrast, the reaction with BuLi in hexane (Entry 8) led only to an intractable mixture of products, among which two products were identified by GC-MS (EI) ($M^+$=319 and 365) corresponding, respectively, to compounds **3** and **4a**, resulting from nucleophilic addition of BuLi. We also found that the course of the reaction was highly sensitive to experimental conditions: (i) 2 equiv. of base were necessary to obtain a good selectivity (Entry 2); (ii) the nature of the metallation solvent and dilution were of importance since the metallation performed in hexane (30 mL) raising the selectivity up to 98% (Entry 4); and (iii) the conversion was dependent on the electrophilic trapping conditions. The quenching step had to be performed at −78°C, leading to **2a** in 91% yield with high selectivity (Entry 7).

Our next attention was focused on the preparation of a series of C-6 functionalised (2-diphenylphosphino)pyridines[9] (see Table 2). As shown, products **2a**–**i** were generally obtained in good to very good yields. The deuteration experiment led to 95% ($^1$H NMR) of **2b** clearly indicating the formation of 6-lithio-2-(diphenylphosphino)pyridine as an intermediate. The method was found to be particularly efficient for the preparation of compounds **2d**–**g** which have to be considered as potential precursors for further functionalisation. The condensation of trimethylacetaldehyde gave the new (diphenylphosphino)pyridyl alcohol **2h** and the P–N–P ligand **2i**[10] was obtained in an acceptable

52% yield. Note that the prepared compounds were found to be sensitive to air oxidation (as checked by $^{31}P$ NMR and elemental analysis) and had to be stored under oxygen-free atmosphere (argon). The 6-lithio-(2-diphenylphosphino)pyridine was finally reacted in a lesser extent with electrophilic heterocycles giving N–N–P and N–N–N–P ligands **2j**[2c] and **2k** in moderate yields.

Table 2
Preparation of C-6 functionalised 2-(diphenylphosphino)pyridines **2**[a]

| $E^+$ | Product | | Yield%[b] |
|---|---|---|---|
| MeOD |  | **2b** | 95[c] |
| $ClSiMe_3$ |  | **2c** | 89 |
| $Bu_3SnCl$ |  | **2d** | 80 |
| $Cl_3CCCl_3$ |  | **2e** | 59 |
| $CBr_4$ |  | **2f** | 50 |
| $I_2$ |  | **2g** | 61 |
| *t*-BuCHO |  | **2h** | 62 |
| $Ph_2PCl$ |  | **2i** | 52 |
|  |  | **2j** | 32 |
|  |  | **2k** | 26 |

a) Reactions performed on 4 mmoles of **1**; metalation: BuLi-LiDMAE (8 mmoles); hexane (30mL); 0°C; 1h; condensation: electrophile (10 mmoles); THF (30mL); -78°C to r.t.; 1.5h; b) Isolated yield after purification; c) Deuterium content determined by $^1$HNMR

In summary, we have shown that the functionalisation of 2-(diphenylphosphino)pyridine via direct lithiation was an efficient reaction. The use of the BuLi–LiDMAE base prevented competitive nucleophilic additions and allowed regioselective metallation at the C-6 position. The condensation of a set of electrophiles allowed the preparation of new C-6 substituted 2-(diphenylphosphino)pyridines in good yields. This method opens the way for the preparation of new functional P–N ligands.

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9. General procedure for the C-6 functionalisation of **1**: A solution of 2-(dimethylamino)ethanol (720 mg; 8 mmol) in hexane (5 mL) was cooled at *ca* −5°C and *n*-BuLi (10 mL; 16 mmol) was added dropwise under nitrogen. After 30 min at 0°C, **1** (1.05 g, 4 mmol) was added portionwise as a solid. The orange mixture was then stirred for 1 h at 0°C. The reaction medium was then cooled at −78°C and a solution of the appropriate electrophile (10 mmol) in THF (30 mL) was added dropwise. After the end of addition the temperature was allowed to warm slowly to room temperature (1.5 h). The hydrolysis was generally performed at 0°C with $H_2O$ (20 mL). The aqueous layer was extracted twice with diethylether (20 mL), the combined organic extracts were then dried over $MgSO_4$. After evaporation of solvents under reduced pressure, the products were purified by flash-chromatography or Chromatotron using hexane/AcOEt mixtures as eluents. All new compounds gave satisfactory spectroscopic and analytical data. Data for **2a** are given**:** $^{1}$H NMR: $\delta$ 2.39 (s, 3H), 6.89 (dd, 7.7 and 1.1 Hz, 1H), 7.08 (d, 8.1Hz, 1H), 7.33–7.43 (m, 6H), 7.43–7.48 (m, 5H); $^{13}$C-{$^{1}$H}NMR: $\delta$ 13.37, 120.79, 124.20, 128.60, 129.33, 134.67, 135.50, 136.80, 160.10, 163.30; $^{31}$P-{$^{1}$H} NMR: $\delta$ −1.7 (s); MS (EI) *m/z*: 310 ($M^+$+1, 21), 309 ($M^+$, 100), 308 ($M^+$−1, 52), 232 (19), 231 (18), 216 (29), 185 (22), 184 (18), 183 (77), 109 (13), 107 (20). Anal Calcd for $C_{18}H_{16}NPS$: C, 69.88; H, 5.21; N, 4.53; P, 10.01. Found: C, 69.83; H, 5.47; N, 4.55; P, 9.89.
10. Compound **2i** was previously obtained in 32% yield from 2,6-dibromopyridine: Newkome, G. R. *J. Org. Chem.* **1978**, *43*, 947–949.