# Symmetric and Asymmetric Coupling of Pyridylpyrimidine for the Synthesis of Polynucleating Ligands

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A convenient synthetic approach to build up new polynucleating ligands is presented. Symmetric and asymmetric pyridylpyrimidine dimers are produced by radical anion coupling and nucleophilic addition, respectively. A diruthenium complex of the asymmetric ligand was synthesised and characterised by cyclic voltammetry, luminescence and $^{99}$Ru NMR spectroscopy.



## Introduction

Oligo(azaheterocyclic) compounds are highly regarded by coordination chemists for their use in building up large polymetallic complexes.[1,2] This appreciation stems from their stability in a wide range of reaction conditions and their ability to form stable complexes with most transition metal ions. They are synthesised in a variety of ways: ring-forming reactions (e.g., Kröhnke synthesis), ring-coupling reactions (e.g., Stille reaction), or a combination of the two. However, these reactions have the drawback of usually requiring substituted heterocycles in order to bring two moieties together. We report herein on a rapid and convenient synthesis of isomeric oligo(azaheterocyclic) ligands for incorporation into metallodendrimers starting from unsubstituted heterocycles. In addition, the diruthenium complex of one dinucleating ligand has been prepared and fully characterised.

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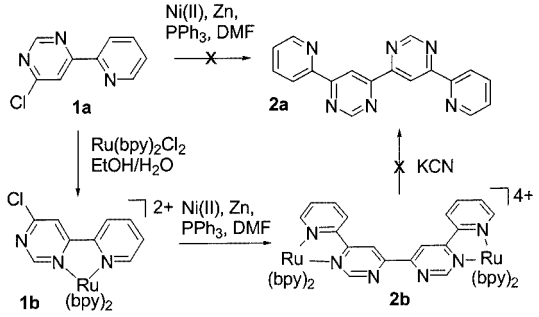
## Results and Discussion

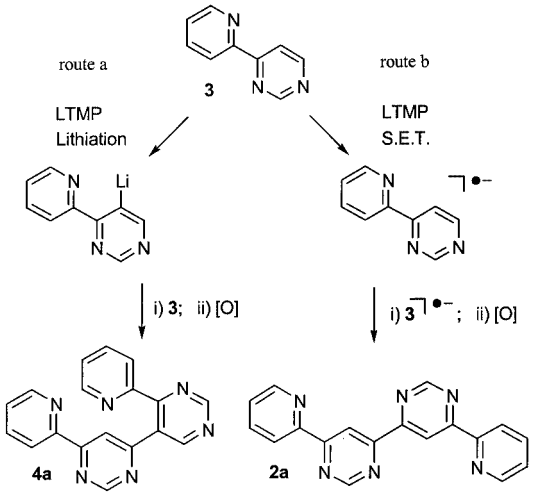
We previously demonstrated that an Ni-catalysed coupling reaction could be used to increase the metal ion content in metallodendrimers and proposed a general method to create new binding sites in metal complexes (Scheme 1).[3,4] Although dimetallic complex **2b** was readily synthesised by an Ni-catalysed coupling of monometallic complex **1b**, metal-free ligand **2a** was required to fully interpret the electrochemical and spectroscopic properties of its complexes.




Scheme 1. The attempted synthesis of ligand **2a**

Our initial attempt to synthesise **2a** by the nickel-catalysed coupling of **1a** failed to afford significant quantities of **2a** (Scheme 1), presumably due to the sequestering of the nickel catalyst by the free chelating site in **1a** or to its deactivation toward coupling as was previously shown for carbonylmetal compounds of chlorophenanthrolines.[5] In another attempt, dimetallic complex **2b** could not be demetallated using $CN^-$. Thus, a synthesis of **2a** without transition metals was required, and direct lithiation/addition appeared to be the best route.

Direct metallation of azaheterocycles is usually aided by directing metallation groups (DMGs),[6,7] such as those used for aromatic hydrocarbons.[8,9] The functional group serves to direct the lithiation either electronically or by coordination. However, there are a few reported cases of direct lithiation of unsubstituted electron-deficient heterocycles.[10,11] Pyrimidine can be lithiated directly in the 4-position using lithium 2,2,6,6-tetramethylpiperidide (LTMP), and its addition to pyrimidine gives 4,4′-bipyrimidine (bpym) in modest yield.[11] This suggested that lithiation of 4-(2-pyridyl)pyrimidine (**3**)[12] in the 6-position, followed by addition to another ligand **3**, would give **2a**. However, as the pyridine in **3** could also serve as a DMG,[13] an asymmetric coupling reaction could also occur (Scheme 2, route a).




Scheme 2. Synthetic routes to symmetric ligand **2a** and asymmetric ligand **4a** using LTMP with **3**

Direct lithiation/addition routes were attempted as outlined in Scheme 2 and Table 1. Thus, **3** was treated with LTMP at −78 °C in an effort to lithiate the 6-position, followed by its addition to **3**. Subsequent warming and air oxidation afforded the symmetric dimer **2a** and the asymmetric dimer **4a** in 16% and 22% yield, respectively (Table 1, Entry 1).

LTMP and **3** were recombined at −78 °C in order to verify the positions of lithiation and their relative ratios (Table 1).[14] The lithio intermediates were trapped by the addition of TMSCl at timed intervals after LTMP addition (Entries 2−4). The expected 6-lithio species was not formed in any appreciable amount after the first minute, instead only the 5-TMS adduct formed. After 5 min, **2a** had formed, even though no 6-TMS adduct could be trapped. This suggested that some other route may be operative as heterocyclic carbanions are usually trapped by TMSCl when competing with addition reactions to other heterocycles.[15] After 10 min, **4a** was formed by the addition of the 5-lithio species to the 6-position of **3**. The phenylation of **3** in the 6-position in 32% yield confirmed the site of addition (Entry 5). Interestingly, lithium diisopropylamide (LDA, Entry 6) gave only a minute quantity of **4a** via the 5-lithio species, with no sign of **2a**. LDA was previously shown to dimerize 2,2′-bipyridine and give its 3,6′-coupled dimer.[16,17]

Table 1. Lithiation/addition and radical anion coupling reactions for **3**

| Entry | Ligand[a] | Alkali | Product[b] | Yield (%) |
|---|---|---|---|---|
| 1 | TMP | *n*BuLi | **2a** | 16 |
| | | | **4a** | 22 |
| 2[c] | TMP | *n*BuLi | **2a** | 0 |
| | | | 5-TMS-py-pm | 30 |
| 3[d] | TMP | *n*BuLi | **2a** | 11 |
| | | | 5-TMS-py-pm | 58 |
| 4[e] | TMP | *n*BuLi | **2a** | 17 |
| | | | 5-TMS-py-pm | 28 |
| | | | **4a** | 10 |
| 5 | − | PhLi | 6-Ph-4-py-pm | 32 |
| 6 | − | LDA | **4a** | < 5 |
| 7[f] | − | $Na_{(s)}$ | **2a** | 95[g] |
| 8[h] | TMP | *n* BuLi | **2a** | 10 |
| | | + $CuCl_2$ | **4a** | 22 |

[a] TMP = 2,2,6,6-tetramethylpiperidine. [b] 5-TMS-py-pm = 4-(2-pyridyl)-5-(trimethylsilyl)pyrimidine, 6-Ph-4-py-pm = 6-phenyl-4-(2-pyridyl)pyrimidine. [c] The reaction was quenched after 1 min with excess trimethylsilyl chloride. [d] The reaction was quenched after 5 min with excess trimethylsilyl chloride. [e] The reaction was quenched after 10 min with excess trimethylsilyl chloride. [f] No oxidation occurred with air. The residue was dissolved in acetone and an excess of $KMnO_4$ was added. The solution was stirred for 1 h before usual workup. [g] Based on recovered **3**, 40% conversion. [h] Reaction conducted in THF.[11]

As pyridine is well known to dimerize by way of its radical anion upon treatment with alkali metals[18,19] and LDA,[20] a radical pathway for the formation of **2a** with LTMP was still possible, especially considering the lower reduction potential of pyrimidine compared to pyridine.[21] A radical anion mechanism was indeed supported by the reduction of **3** with sodium (Entry 7), which afforded **2a** in 95% yield based on recovered **3**, with no sign of **4a** (Scheme 2b). Increasing the amount of sodium and the reaction time had no effect on the ratio **2a**/**3**.

The addition of a catalytic amount of the known radical quencher $CuCl_2$[11] to the reaction mixture (Entry 8, Table 1) resulted in a decrease in the yield of **2a**, but not its complete elimination. Increasing the amount of $CuCl_2$ leads to a lower yield of both isomers. Thus, we propose that the reaction in Entry 1 is a balance between a single electron transfer mechanism resulting in **2a** and an *ortho*-directed metallation at the pyrimidine 5-position followed by attack at the 6-position of the second ligand **3**, giving **4a** after oxidation. In the case of the reaction with Na(s), the lower reduction potential of the pyrimidine ring affords a direct route to homocoupled ligands through radical anion coupling.

Asymmetric ligands such as **4a** are generally more difficult to obtain than their symmetric counterparts,[16,17] but they can give valuable information on the interaction between metals in different binding sites. We therefore analysed the structure of **4a** and prepared its diruthenium complex. In this case, the steric hindrance about the C−C bond

joining the two pyrimidine rings may preclude metal−metal interaction in its dimetallic complex. An X-ray crystal structure determination allowed the bond connectivity in **4a** to be verified and the steric hindrance at both coordination sites to be compared. Thus, the bond between the two pyrimidine rings in **4a** (C13 to C9) is unequivocally assigned by X-ray crystallography (Figure 1).[22] The dihedral angle of 38.1° between the two pyrimidine rings clearly demonstrates the steric congestion about this bond. This is also seen in the 38.2° dihedral angle to the adjacent pyridine ring (C14 to C19), compared to the 2.7° dihedral angle at the other less encumbered pyridine ring (C1 to C7). The bond lengths and angles in **4a** are consistent with other pyridine- and pyrimidine-containing ligands.[23,24]

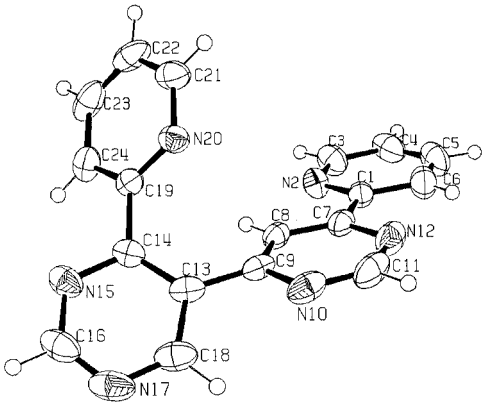
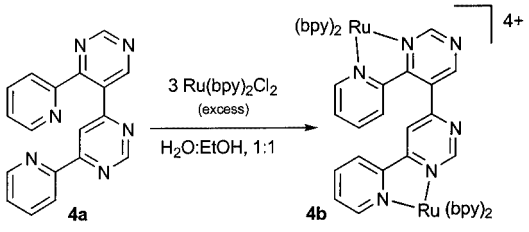



Figure 1. The crystal structure of **4a**

Diruthenium complex **4b** was readily prepared in 52% yield by allowing an excess (3 equiv.) of $Ru(bpy)_2Cl_2$ to react with **4a** in refluxing ethanol (Scheme 3). The complex was purified by chromatography on silica gel using a MeCN/water/$KNO_3$ (sat. aq.) (5:4:1) solution as eluent followed by anion exchange to its $PF_6$ salt. $^1H$ and $^{13}C$ NMR spectroscopic and mass spectrometric analyses confirm the dinuclear nature of **4b**. Cyclic and differential pulse voltammograms of **4b** in acetonitrile vs. SCE (in V, anodic and cathodic peak separation in mV) showed a single oxidation process which is assigned to two simultaneous, metal-based, one-electron oxidation processes [+1.40 V (100 mV)] and two reversible one-electron reduction processes [−0.70 V (62 mV), −1.00 V (63 mV)], which are assigned to successive one-electron reductions of the coordinated bridging ligand **4a**. No other reversible reductions were found out to −2.00 V. The coincidence of the two metal-centred oxidation processes indicates that the two metal centres are only weakly interacting with one another, as expected since the two chelating sites in **4b** cannot lie co-planar to afford orbital overlap (cf. Figure 1). The ligand-based reduction potentials are considerably less negative than bpy-centred reductions in $Ru(bpy)_3^{2+}$ (−1.28 V)[25] due to the electron-deficient nature of the pyrimidine rings.

The absorption and photophysical properties of **4b** are also in line with those of other dinuclear (polypyridine)$Ru^{II}$ complexes containing relatively easy-to-reduce bridging ligands.[25] The electronic absorption spectrum of **4b** in acetonitrile shows the same general profile, with ligand-based absorptions predominating in the UV region: $\lambda_{max}$ (ε [$M^{-1}cm^{-1}$]) = 247 (44,400), 286 nm (114,300)] and spin-allowed MLCT bands in the visible region: $\lambda_{max}$ (ε [$M^{-1}cm^{-1}$]) = 429 (17,000), 518 nm (14,300)]. Complex **4b** is luminescent at room temperature, emitting at 784 nm with a lifetime of 34 ns. At 77 K, the emission shifts to shorter wavelength, 695 nm, and its lifetime extends to 126 ns.

Complex **4b** was further characterised using $^{99}Ru$ NMR.[26] At 343 K, the $^{99}Ru$ NMR spectrum of an acetonitrile solution of **4b** presents two baseline-resolved resonances of equal intensity at δ = 4660 and 4677 ppm (Figure 2). This agrees with the two inequivalent Ru sites in **4b**. The line width at half height ($W_{1/2}$), similar for both resonances (ca. 100 Hz, i.e. 4 ppm), is hardly larger than for the highly symmetrical analogue $Ru(bpy)_3^{2+}$ (65 Hz in $CD_3CN$ at 22 °C).[27] This reflects the fact that the local symmetry at each Ru site is relatively higher than expected from the low symmetry of the whole complex **4b**. Attribution of the two signals to the ruthenium ions is virtually impossible, as there is no general correlation with other experimental data. It is nevertheless noteworthy that the very subtle differences of the two binding sites of asymmetric ligand **4a** are clearly reflected in different chemical shifts for the ruthenium atom. The observed difference in chemical shift between the two Ru nuclei (17 ppm) is very small when compared to the huge chemical shift range of $^{99}Ru$ (ca. 18,000 ppm) as well as to the various "medium" effects, such as the dependence of the ruthenium chemical shift on temperature, solvent and concentration. This confirms the




Scheme 3. Synthesis of diruthenium complex **4b**

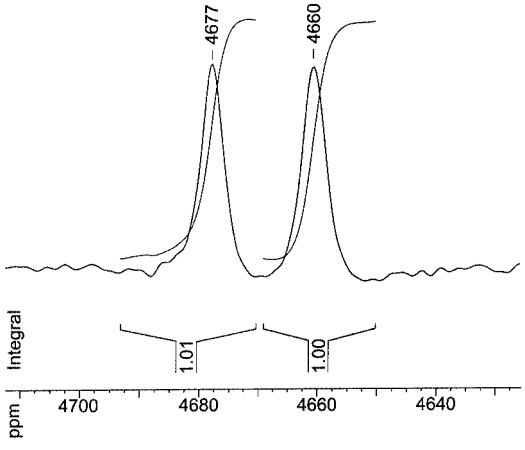



Figure 2. $^{99}Ru$ NMR of complex **4b** in acetonitrile at 343 K

high potential of $^{99}$Ru NMR to characterise polynuclear ruthenium complexes.[27] We are currently working on other (azaheterocycle)di- and -triruthenium complexes and making use of $^{99}$Ru NMR to probe ruthenium-containing dendrimers.

## Conclusion

The combination of **3** and LTMP gives both radical anion coupling and lithiation/addition reactions, which were found to produce symmetric and asymmetric ligands **2a** and **4a**, respectively. Controlled radical anion coupling of the electron-deficient pyrimidine ring of **3** using Na has allowed a facile entry into the synthesis of trinucleating ligand **2a**. Thus, the judicious choice of reaction conditions is an easy way to produce different multinucleating ligands for coordination chemistry from unsubstituted azaheterocycles.

The diruthenium complex of asymmetric ligand **4a** has been fully characterised, including its $^{99}$Ru NMR. It is noteworthy that although electrochemical studies could not clearly distinguish between the two metal centres in **4b**, this was readily accomplished using $^{99}$Ru NMR. We are investigating methods to increase the overall yield of this reaction and to expand this approach to poly(azaheterocyclic) ligands.[28]

## Acknowledgments

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[14] BuLi (1.6 M in hexane, 200 μL, 0.32 mmol) and ligand (0.32 mmol) were added to 5 mL of THF at −78 °C and stirred for 15 min before being warmed to room temp. over 30 min. The solution was then returned to −78 °C and **3** (100 mg, 0.64 mmol) was dissolved in THF (5 mL) and added to the lithium solution by cannula. After stirring for 1 h at −78 °C, the solution was rapidly warmed to room temp. and quenched with ethanol (5 mL) and triethylamine (400 μL). Air was bubbled through the solution for 1 h. The solution was concentrated to dryness, dissolved in dichloromethane (20 mL) and extracted with water (2 × 20 mL). NMR was used to determine ratio of products to remaining starting material. The residue was then sublimed to remove the starting material (< 80 °C) and to collect the products (90−160 °C).
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[22] Crystal data: **2a**, monoclinic, space group *P*21/*c*, $a$ = 7.4707(9), $b$ = 20.1567(19), $c$ = 10.3384(11) Å, β =107.157(8)°, $V$ = 1487.5(3) Å$^3$, $Z$ =1, $D_c$ = 1.395 g/cm$^3$, $R_1$ = 0.0403. CCDC-179442 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
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[26] The $^{99}$Ru NMR spectra have been recorded with a Bruker DRX 500 spectrometer tuned at 23.142 MHz and equipped with a 10-mm broad-band probehead. Complex **4b** (30 mg) was dissolved in acetonitrile (3 mL). The spectra were recorded without lock and the chemical shifts were referenced with respect to a saturated aqueous solution of $K_4Ru(CN)_6$ (δ = 0 ppm at 300 K). A preliminary spectrum obtained at 300 K showed a broad signal ($W_{1/2}$ ≈ 400 Hz, 16 ppm) at δ ≈ 4580 ppm with two distinct maxima. Raising the temperature to 343 K, in order to increase the relaxation time of the quadrupolar $^{99}$Ru nucleus, resulted in a clean separation of the two resonances. In addition, there is a strong deshielding by nearly 100 ppm, with respect to the 300 K resonance. The spectrum in Figure 2 required a total of 4 × 10$^6$ scans with an acquisition time of 16 ms, a pre-acquisition delay of 11.4 μs and a spectral width of 62 kHz. Exponential multiplication with a line-broadening factor of 10 Hz was applied prior to Fourier transformation.
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[28] Supporting information for this article (synthesis of ligands **2a** and **4a**, and complex **4b**) is available, see footnote on the first page of this article.

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