*Electronic Supplementary Information*

# Very Bright Europium Complexes that Stain Cellular Mitochondria

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## Mass Spectrometry and NMR Spectroscopy

Electrospray mass spectrometry was carried out on a Thermo Finnigan LTQ and accurate masses were recorded on a Thermo Finnigan LTQ-FT.

$^{1}$H- and $^{13}$C-NMR spectra were recorded on Varian spectrometers operating at magnetic inductions corresponding to $^{1}$H frequencies at 200, 400, 500, 600 and 700 MHz, e.g. Mercury 400 at 9.4T ($^{1}$H at 399.97 MHz, $^{13}$C at 100.61 MHz), Mercury 200 at 4.7T, VNMRS-600 at 11.7T, Inova 600 at 14.1T, VNMRS-700 at 16.5T. Spectra were recorded in commercially available deuteriated solvents. All chemical shifts are given in ppm with coupling constants in Hz.

## Optical Spectroscopy

Emission spectra were recorded using an ISA Jobin-Yvon Spex Fluorolog-3 luminescence spectrometer. Lifetime measurements were carried out with a Perkin Elmer LS55 spectrometer using FL Winlab software. Single-photon luminescence spectra were also recorded using an Edinburgh Instrument FLS920 Combined Fluorescence Lifetime and Steady state spectrophotometer that was equipped with a

visible to near-infrared sensitive photomultiplier with a nitrogen flow cooled housing. A liquid nitrogen cryostat (77k, Oxford Instruments) was used to cool the complexes down to 77K.

Quantum yield measurements were calculated by comparison with two standards. For the standards and each of the unknowns, five solutions with absorbance values between 0.05 and 0.1 were used. The quantum yield was calculated according to the equation:

$$\Phi_x = \Phi_r \cdot \frac{A_r}{A_x} \cdot \frac{E_x}{E_r} \cdot \frac{I_r}{I_x} \cdot \frac{\eta_x^2}{\eta_r^2}$$

where *r* and *x* refer to reference and unknown respectively; *A* is the absorbance at $\lambda_{ex}$ ; *E* is the corrected integrated emission intensity; *I* is the corrected intensity of excitation light; *h* is the refractive index of solution.

**HPLC**

The analytical HPLC (High-performance liquid chromatography) was performed on a Thermo-Scientific Spectra System P1000XR equipped with diode array detector UV1000. The preparative HPLC was performed on a Shimadzu LC-8A equipped with a UV/vis detector SPD. Various chromatographic systems were employed for analytical and preparative HPLC:

*System A*: HPLC (Waters XBridge RP-$C_{18}$ column, 3.5 µm, 4.6 × 100 mm) with 0.2% aq. trifluoroacetic acid pH 1– MeCN (v/v) as eluents [isocratic 15% MeCN (2 min), linear gradient from 15 to 100% MeCN (18 min), isocratic 100% MeCN (4 min)] at a flow rate of 1 mL $min^{-1}$ and UV detection at 330 nm.

*System B*: HPLC (Waters XBridge RP-$C_{18}$ column, 5 µm, 50 × 150 mm) with 0.2% aq. Trifluoroacetic acid pH 1– MeCN (v/v) as eluents [isocratic 15% MeCN (2 min),

linear gradient from 15 to 100% MeCN (23 min), isocratic 100% MeCN (4 min)] at a flow rate of 100 mL $min^{-1}$ and UV detection at 330 nm.

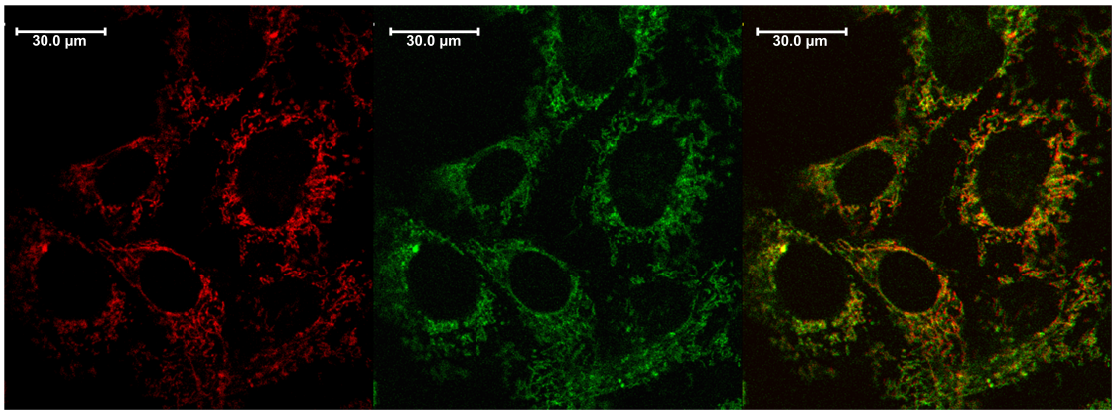
*System C*: HPLC (Macherey-Nagel Nucleodur Hilic column, 5 µm, 4 × 250 mm) with aq. ammonium acetate 100 mM, pH 5.3 – MeCN (v/v) as eluents [isocratic 97% MeCN (3 min), linear gradient from 97 to 80% MeCN (20 min), isocratic 20% MeCN (5 min)] at a flow rate of 0.8 mL $min^{-1}$ and UV detection at 330 nm.

*System D*: HPLC (Macherey-Nagel Nucleodur Hilic column, 5 µm, 21 × 250 mm) with aq. ammonium acetate 100 mM, pH 5.3 – MeCN (v/v) as eluents [isocratic 97% MeCN (4 min), linear gradient from 97 to 80% MeCN (24 min), isocratic 20% MeCN (5 min)] at a flow rate of 14 mL $min^{-1}$ and UV detection at 330 nm.

**Confocal Microscopy and Cell Spectral Imaging**

Details of cell culture, epifluorescence microscopy and assessment of complex toxicity using the MTT assay of mitochondrial redox function have been reported elsewhere. [7,8] Cell images and co-localisation experiments were obtained using a Leica SP5 II microscope. In order to achieve excitation with maximal probe emission, the microscope was coupled by an optical fibre to a Coherent 355nm CW (Nd:YAG) laser, operating at 12mW power. A HeNe or Ar ion laser was used when commercially available organelle-specific stains (e.g. MitotrackerGreen™) were used to corroborate cellular compartmentalization. The microscope was equipped with a triple channel imaging detector, comprising two conventional PMT systems and a HyD hybrid avalanche photodiode detector. The latter part of the detection system, when operated in the BrightRed mode, is capable of improving imaging sensitivity above 550 nm by 25%, reducing signal to noise by a factor of 5. The pinhole was always determined by the Airy disc size, calculated from the objective in use, using the lowest excitation wavelength. Scanning speed was adjusted to 100 Hz in a unidirectional mode, to ensure both sufficient light exposure and time to collect the emitted light from the lanthanide based optical probes. Spectral imaging on this Leica system is possible with the *xyλ*-scan function, using the smallest allowed spectral band-pass (5nm) and step-size (3nm) settings. However, spectral imaging in NIH 3T3

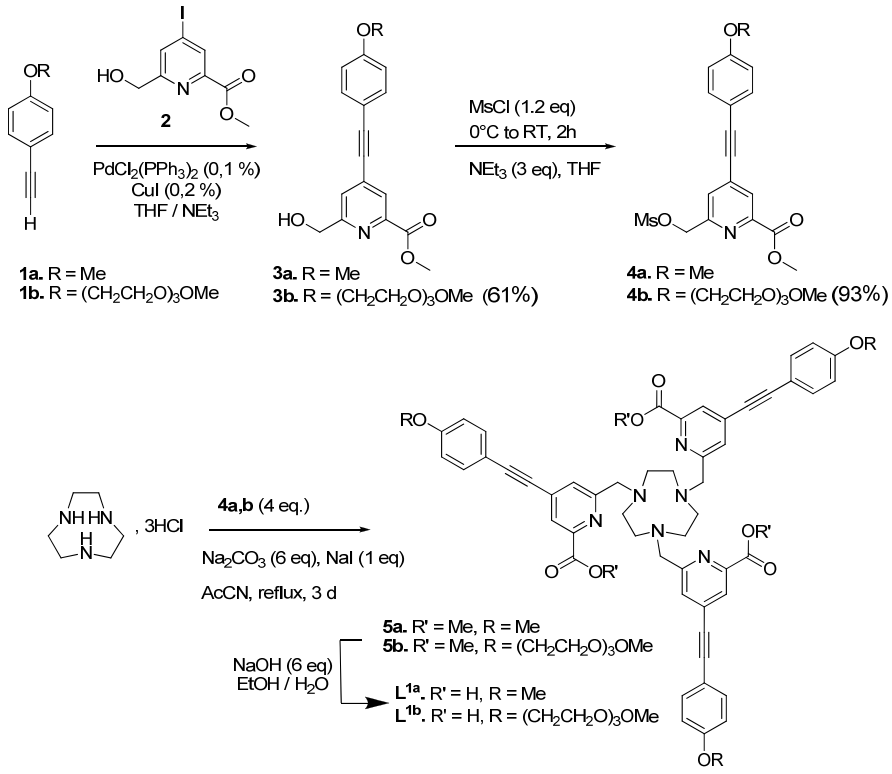
cells was achieved using a custom built microscope (modified Zeiss Axiovert 200M), using a LDPlanNeofluar 20x Ph2Korr objective combined with a low voltage 365 nm pulsed UV LED focused, collimated excitation source (1.2W). For rapid spectral acquisition the microscope was equipped at the X1 port with a Peltier cooled 2D-CCD detector (Ocean Optics) used in an inverse 100 Hz time gated sequence. The spectrum was recorded from 400-800 nm with a resolution of 0.24 nm and the final spectrum was acquired using an averaged 10,000 scan duty cycle.




**ESI Figure 1** Cell microscopy images of NIH 3T3 cells: *top left*: 1h incubation with [Eu.L$^{2b}$], $\lambda_{exc}$ 355 nm, observing 605 to 720 nm; *top right*: following addition of Mitotracker Green (added for the last 30 min., 0.5 µM), $\lambda_{exc}$ 488 nm, observing 505-535 nm; *bottom right*: merged image showing co-localisation, with a Pearson coefficient of 0.85.

## Ligand and Complex synthesis

### Synthesis of Eu complexes of $L^{1a}$ and $L^{1b}$ (Scheme 1)




**Scheme 1**

Compounds **1a**, **1b** and **2** were published as reported in: Bourdolle, A.; Allali, M.; Mulatier, J.-C.; Le Guennic, B.; Zwier, J.; Baldeck, P. L.; Bünzli, J.-C.G.; Andraud, C.; Lamarque, L.; Maury, O. *Inorg. Chem.* **2011**, *50*, 4987-4999.

### Methyl 6-(hydroxymethyl)-4-((4-methoxyphenyl)ethynyl)picolinate 3a

To a solution of 1-ethynyl-4-methoxybenzene (133 mg, 1mmol) in dry THF (10 mL) and $Et_3N$ (5 mL) was added methyl 6-(hydroxymethyl)-4-iodopicolinate (294 mg, 1 mmol). The solution was degassed with argon for 45 min and to this mixture were added CuI (37 mg, 0.2 mmol) and $Pd(PPh_3)_2Cl_2$ (68 mg, 0.1 mmol) under argon. The dark brown mixture was heated at 70°C for 4 h. The mixture was concentrated and the residue dissolved in $CH_2Cl_2$ (50 mL) and washed with saturated aqueous $NH_4Cl$ (2 ×

50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica ($CH_2Cl_2$/MeOH 99/1 to 95/5 in 0.5% increment) yielding a light yellow solid (241 mg, 68%). $^1$H NMR ($CDCl_3$, $\delta$): 8.07 (s, 1H), 7.59 (s, 1H), 7.49 (d, $^3J$ = 8.9 Hz, 2H), 6.90 (d, $^3J$ = 8.9 Hz, 2H), 4.85 (s, 2H), 4.00 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (100.6MHz, $CDCl_3$, δ): 165.4, 160.7, 160.6, 147.3, 134.0, 133.8, 125.8, 125.4, 114.4, 113.8, 96.0, 85.3, 64.7, 55.5, 53.1.(HRMS$^+$) 298.1075 $[M + H]^+$ ($C_{17}H_{16}NO_4$ requires 298.1079). R*f:* 0.6 (silica, DCM/MeOH, 90/10).

**Methyl 4-((4-methoxyphenyl)ethynyl)-6-(((methylsulfonyl)oxy)methyl)picolinate 4a**

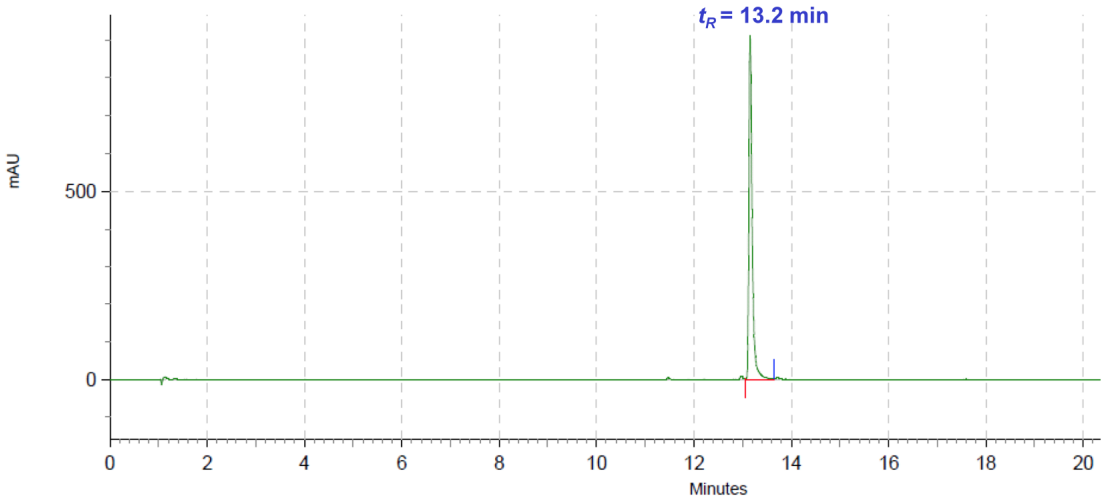
To a solution of methyl 6-(hydroxymethyl)-4-((4-methoxyphenyl)ethynyl)picolinate **3a**, (241 mg, 0.8 mmol) and $Et_3N$ (246 mg, 2.4 mmol) in dry THF (10 mL), was added dropwise methanesulfonyl chloride (139 mg, 1.2 mmol) at 5°C. The reaction was allowed to reach room temperature over 15 min and the solvent was removed. To the residue was added $CH_2Cl_2$ (15 mL) and the organic phase was washed with water (2 × 10 mL) and dried over $MgSO_4$, filtered and concentrated to give an oily compound which was used in the next step without further purification (217 mg, 90%). $^1$H NMR ($CDCl_3$, $\delta$): 8.14 (s, 1H), 7.70 (s, 1H), 7.50 (d, $^3J$ = 8.8 Hz, 2H), 6.91 (d, $^3J$ = 8.8 Hz, 2H), 5.40 (s, 2H), 4.00 (s, 3H), 3.84 (s, 3H) 3.16 (s, 3H); $^{13}$C NMR (100.6MHz, $CDCl_3$, δ) : 165.0, 160.9, 154.7, 147.9, 134.7, 133.9, 126.8, 126.5, 114.4, 113.5, 97.0, 85.0, 70.8, 55.5, 53.3, 38.2.(HRMS$^+$) 376.0859 $[M + H]^+$ ($C_{18}H_{18}NO_6S$ requires 376.0855). R*f:* 0.75 (neutral aluminium oxide, cyclohexane/EtOAc, 30/70).

**Compound 5a, (the trimethyl ester of L$^{1a}$)**

To a solution of triazacyclononane trihydrochloride (9.5 mg, 40 µmol) in dry MeCN (10 mL) was added dry $K_2CO_3$ (35 mg, 250 µmol). The mixture was vigorously stirred for 10 min and to the suspension was added methyl 4-((4-methoxyphenyl)ethynyl)-6-(((methylsulfonyl)oxy)methyl)picolinate, **4a**, (47 mg, 120 µmol) in one portion. The resulting mixture was heated at 60°C for 4 h. The solvent was removed under reduced pressure; to the residue was added $CH_2Cl_2$ (25 mL) and the organic phase was washed with brine (10 mL) and dried over $MgSO_4$, filtered and concentrated to give an oily mixture which was purified by preparative HPLC (gradient D). The fractions were concentrated to give a pale yellow oil (33 mg, 85%). $^1$H NMR ($CDCl_3$, $\delta$): 7.99 (s, 3H), 7.78 (s, 3H), 7.44 (d, $^3J$ = 8.9 Hz, 6H), 6.86 (d, $^3J$ = 8.9 Hz, 6H), 4.17 (s, 6H), 3.91 (s, 9H), 3.80 (s, 9H) 3.13 (s, 12H); $^{13}$C NMR (100.6MHz, $CDCl_3$, δ): 165.2, 160.7, 147.6, 133.9, 133.7, 128.1, 125.9, 114.3, 113.7, 96.1, 85.2, 61.6, 55.4, 53.6, 53.0, 39.7, 29.8.(HRMS$^+$) 967.4031 $[M + H]^+$ ($C_{57}H_{55}N_6O_9$ requires 967.4022). $t_R$ (*System C*) = 16.7 min.

**[EuL$^{1a}$]**

To a solution of the trimethyl ester of L$^{1a}$ (33 mg, 34 µmol) in THF (3 mL) was added LiOH aqueous solution (1 M, 1.5 mL) and the mixture was stirred at room temperature for 30 min. The mixture was concentrated to dryness and to the residue were added MeOH (3 mL) and water (2 mL). The solution was neutralized (~ pH 7) by addition of diluted HCl (4 M) and to this mixture was added $EuCl_3$. $6H_2O$ (37 mg, 102 µmol). The mixture was stirred for 15 min and concentrated to dryness to give a residue which was diluted in MeCN (4 mL).The resulting solution was purified by preparative HPLC (system B). The fractions collected were concentrated to give an off white solid (23 mg, 21.5 µmol). HRMS, 537.6299 $[M + 2H]^{2+}$ ($C_{54}H_{46}EuN_6O_9$ requires 537.6269). $t_R$ (*System A*) = 13.1 min. $\tau_{MeOH}$ = 0.95 ms; $\Phi^{em}_{MeOH}$ = 48 ± 10%; $\varepsilon_{MeOH}$ (337 nm) = 58,000 M$^{-1}$ cm$^{-1}$.




Analytical RP-HPLC of [Eu.L$^{1a}$]: $t_R$ 13.2 min [Gradient: 15 to 100% acetonitrile in water (0.2% trifluoroacetic acid) over 20 min]

**Methyl 6-(hydroxymethyl)-4-((4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)phenyl) ethynyl) picolinate, 3b**

To a solution of 1-ethynyl-4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzene, **1b** (3.9 g, 15 mmol) and methyl 6-(hydroxymethyl)-4-iodopicolinate, **2**, (2.8 g, 9.6 mmol) in dry THF (20 mL) and $Et_3N$ (20 mL), was added CuI (56 mg, 0.29 mmol,) and $Pd(PPh_3)_2Cl_2$ (104 mg, 0.15 mmol,). The dark brown mixture was heated at 70°C for 12 h. The suspension was concentrated under reduced pressure and the residue dissolved in $CH_2Cl_2$ (50 mL) and washed with saturated aqueous $NH_4Cl$ (2 × 50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude material was purified by flash chromatography on silica ($CH_2Cl_2$/MeOH 99/1 to 95/5 in 0.5% increment) yielding a light yellow solid (3.2 g, 78%). $^1$H NMR ($CDCl_3$, $\delta$): 8.04 (s, 1H), 7.56 (s, 1H), 7.45 (d, $^3J$ = 8.8 Hz, 2H), 6.89 (d, $^3J$ = 8.8 Hz, 2H), 4.82 (s, 2H), 4.13 (m, 2H), 3.97 (s, 3H), 3.84 (m, 3H), 3.71 (m, 2H), 3.64 (m, 4H), 3.52 (m, 2H), 3.35 (s, 3H), 1.89 (s, 1H); $^{13}$C NMR (50.3MHz, $CDCl_3$, δ): 165.4,

160.7, 160.1, 147.3, 134.1, 133.8, 125.8, 125.5, 115.1, 114.1, 95.9, 85.4, 72.1, 71.0, 70.8, 70.7, 69.8, 67.7, 59.1.(HRMS$^+$) 430.1860 $[M + H]^+$ ($C_{23}H_{28}NO_4$ requires 430.1866). R*f:* 0.56 (silica, DCM/MeOH, 90/10).

**Methyl 4-((4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)phenyl)ethynyl)-6-(((methyl sulfonyl)oxy)methyl)picolinate, 4b**

To a solution of methyl 6-(hydroxymethyl)-4-((4-(2-(2-(2-methoxyethoxy) ethoxy)ethoxy)phenyl)ethynyl) picolinate **3b** (300 mg, 0.7 mmol) and $Et_3N$ (212 mg, 0.21 mmol) in dry THF (20 mL), was added dropwise methanesulfonyl chloride (88 mg, 0.77 mmol) at 5°C. The reaction was allowed to reach room temperature over 15 min and the solvent was removed under reduced pressure. To the residue was added $CH_2Cl_2$ (15 mL) and the organic phase was washed with water (2 × 10 mL) and dried over $MgSO_4$, filtered and concentrated to give an oily compound which was considered to be sufficiently pure to be used in the next step without further purification. (330 mg, 93%). $^1$H NMR ($CDCl_3$, 500MHz, $\delta$): 8.09 (s, 1H), 7.66 (s, 1H), 7.45 (d, $^3J$ = 8.7 Hz, 2H), 6.88 (d, $^3J$ = 8.7 Hz, 2H), 5.37 (s, 2H), 4.12 (m, 2H), 3.97 (s, 3H), 3.83 (m, 2H), 3.69 (m, 2H), 3.62 (m, 4H), 3.51 (m, 2H), 3.33 (s, 3H), 3.13 (s, 3H); $^{13}$C NMR (50.33 MHz, $CDCl_3$, δ): 164.9, 160.1, 154.6, 147.8, 134.6, 133.7, 126.6, 126.3, 114.9, 113.6, 96.8, 84.9, 71.9, 70.9, 70.7, 70.6, 69.6, 67.6, 59.1, 53.1, 38.1. (HRMS$^+$) 508.1637 $[M + H]^+$ ($C_{24}H_{30}NO_9S$ requires 508.1636). R*f:* 0.31 (neutral aluminium oxide, cyclohexane/EtOAc, 30/70).

**Compound 5b (Trimethyl ester of L$^{1b}$)**

To a solution of triazacyclononane 3HCl (57 mg, 0.24 mmol) in dry MeCN (40 mL) was added dry $K_2CO_3$ (198 mg, 1.43 mmol). The mixture was vigorously stirred for 10 min then to the suspension was added methyl 4-((4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)phenyl)ethynyl)-6-(((methyl sulfonyl)oxy)methyl) picolinate, **4b**, (374 mg, 0.74 mmol) in one portion. The resulting mixture was heated at 60°C for 4 h. The solvent was removed and to the residue was added $CH_2Cl_2$ (75 mL) and the organic phase was washed with brine (20 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure to give an oily mixture which was purified by preparative HPLC (gradient B). The fractions were concentrated to give a pale yellow oil, (185 mg, 57%). $^1$H NMR ($CDCl_3$, 500MHz, $\delta$): 7.97 (s, 3H), 7.75 (s, 3H), 7.42 (d, $^3J$ = 8.5 Hz, 6H), 6.87 (d, $^3J$ = 8.5 Hz, 6H), 4.29 (s, 6H), 4.11 (m, 6H), 3.88 (s, 9H), 3.83 (m, 6H), 3.71 (m, 6H), 3.63 (m, 12H), 3.52 (m, 6H), 3.34 (s, 9H), 3.25 (s, 12H). $^{13}$C NMR (125.76 MHz, $CDCl_3$, δ): 165.2, 160.1, 147.8, 134.3, 133.9, 128.5, 126.4, 115.0, 113.9, 85.1, 77.2, 72.1, 71.1, 70.8, 70.8, 69.8, 67.7, 59.2, 53.1. ($MS^+$) 1363.70 $[M + H]^+$ ($C_{75}H_{91}N_6O_{18}$ requires 1363.64). $t_R$ (*System A*) = 13.6 min.

**[EuL$^{1b}$]**

To a solution of 5b (81 mg, 60 µmol) in THF (10 mL) was added aqueous LiOH solution (1 M, 5 mL) and the mixture was stirred at room temperature for 30 min. The mixture was concentrated to dryness and to the residue were added MeOH (9 mL) and water (6 mL). The solution was neutralized (~ pH 7) by addition of hydrochloric acid (4 M) and to this mixture was added $EuCl_3$. $6H_2O$ (66 mg, 180 µmol). The mixture was stirred for 15 min and concentrated to dryness to give a residue which was diluted in MeCN (4 mL). The resulting solution was purified by preparative HPLC (system

B). The fractions collected were concentrated to give the title compound (78 mg, 89%). NMR spectra in water or in organic solvents exhibit only broad signals ascribed to the dynamic interconversion between various helicoidal enantiomers. HRMS *m/z*: 1471.4941 $[M + H]^+$ ($C_{72}H_{82}EuN_6O_{18}$ requires 1471.4905). $t_R$ (*System A*) 13.6 min. ; $\boldsymbol{\tau_{MeOH}}$ = 1.06 ms; $\Phi^{em}_{MeOH}$ = 25 ± 5%; $\varepsilon_{MeOH}$ (337 nm) = 57,500 $M^{-1}$ $cm^{-1}$.

## 2. Synthesis of Eu complexes of $L^{2a,2b,2c}$

### 2-Bromo-6-methylpyridine-N-oxide

2-Bromo-6-methylpyridine, (20 g, 0.116 mol) was dissolved in $CHCl_3$ (300 mL), *m*CPBA (40.1 g, 0.232 mol) was added and the solution was stirred at 65 °C under argon for 18 h. The volume of the solution was reduced to 150 mL under reduced pressure. The solution was left to stand in the fridge overnight causing precipitation of 3-chlorobenzoic acid, which was removed by filtration. From the remaining filtrate, the solvent was removed under reduced pressure to give a yellow oil that was dissolved in aq. NaOH solution (1M, 100 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a pale yellow oil which crystallized upon standing (15 g, 67 %). M.p. 59 – 61 °C; $^1$H NMR ($CDCl_3$, $\delta$): 7.55 (1H, dd, *J* 8 Hz, 1.6, $H^3$), 7.23 (1H, dd, *J* 8, 1.6 Hz, $H^5$), 7.01 (1H, t, *J* 8 Hz, $H^4$), 2.57 (3H, s); $^{13}$C NMR ($CDCl_3$, $\delta$): 151.2 ($C^6$), 133.5 ($C^2$), 128.7 ($C^3$), 125.3 ($C^5$), 125.2 ($C^4$), 19.3 (Me); *m/z* ($HRMS^+$) 187.9698 $[M + H]^+$ ($C_6H_7NO^{79}Br$ requires 187.9711); $R_f$ = 0.16 (silica, $CH_2Cl_2$: 2 % MeOH).

**2-Bromo-6-methyl-4-nitropyridine-N-oxide**

2-Bromo-6-methylpyridine-1-oxide, (15 g, 80 mmol) was dissolved in concentrated $H_2SO_4$ (98 %, 23 mL, 0.40 mol). The solution was stirred at 0 °C and $HNO_3$ (70 %, 26 mL, 0.38 mol) was added dropwise. The mixture was heated to 100 °C for 16 h. The yellow solution was dropped onto stirred ice (150 g) causing a pale yellow solid to precipitate. After 1 h the precipitate was filtered and dried under high vacuum to yield a pale yellow solid (12 g, 65 %); m.p. 138 – 139 °C; $^1$H NMR ($CDCl_3$, $\delta$): 8.40 (1H, d, $J$ 2.8 Hz, $H^3$), 8.09 (1H, d, $J$ 2.8 Hz, $H^5$), 2.62 (3H, s); $^{13}$C NMR ($CDCl_3$, $\delta$): 151.8 ($C^6$), 140.7 ($C^4$), 134.0 ($C^2$), 122.8 ($C^3$), 118.9 ($C^5$), 19.6 (Me); $m/z$ (HRMS$^+$) 232.9564 $[M + H]^+$ ($C_6H_6N_2O_3{}^{79}Br$ requires 232.9556); $R_f$ = 0.53 (silica, $CH_2Cl_2$: 2 % MeOH).

**2-Bromo-6-methyl-4-nitropyridine**

2-Bromo-6-methyl-4-nitropyridine-1-oxide, (5g, 22 mmol) was dissolved in $CHCl_3$ (200 mL) and $PBr_3$ (6.26 mL, 66 mmol) was added dropwise. The mixture was stirred at 60 °C under argon for 16 h. The solvent was removed under reduced pressure to give a yellow oil. Aqueous NaOH solution (2 M, 50 mL) was added cautiously and the solution was extracted with $CH_2Cl_2$ (3 × 100 mL). The organic extracts were combined, dried over $MgSO_4$ and the solvent removed under reduced pressure to give a yellow oil, which was purified by column chromatography on silica ($CH_2Cl_2$) to yield a pale yellow oil (3.0 g, 74 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.02 (1H, d, $J$ 2.8, $H^3$), 7.83 (1H, d, $J$ 2.8, $H^5$), 2.70 (3H, s); $^{13}$C NMR ($CDCl_3$, $\delta$): 162.9 ($C^6$), 154.9 ($C^4$), 142.4 ($C^2$), 118.4 ($C^3$), 115.0 ($C^5$), 24.6 (Me); $m/z$ (HRMS$^+$) 216.9611 $[M + H]^+$ ($C_6H_6N_2O_2{}^{79}Br$ requires 216.9613); $R_f$ = 0.75 (silica, $CH_2Cl_2$ : 2 % MeOH).

**Ethyl (6-methyl-4-nitropyridin-2-yl)(phenyl)phosphinate**

2-Bromo-6-methyl-4-nitropyridine, (1.01 g, 4.68 mmol), ethyl phenylphosphinate (0.95 g, 5.60 mmol) and triethylamine (2.6 mL, 19.0 mmol) were added to dry degassed (3 freeze-thaw cycles) toluene (10 mL). Tetrakis(triphenylphosphine)palladium(0) (83 mg, 0.07 mmol) was added and the mixture was degassed three times before being stirred at 125 °C for 16 h under argon. The solution was diluted with $CH_2Cl_2$ (20 mL), washed with HCl (1M, 2 × 15 mL) and water (3 × 15 mL), dried over $K_2CO_3$, filtered and the solvent removed under reduced pressure to give a dark residue. Purification by column chromatography on silica ($CH_2Cl_2$ : 0.5 % MeOH) gave a yellow oil (645 mg, 45 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.55 (1H, dd, $^3J_{H\text{-}P}$ 5.6 Hz, $^4J_{H\text{-}H}$ 1.4 Hz, $H^3$), 7.97 (2H, ddd, $^3J_{H\text{-}P}$ 11.2 Hz, $^3J_{H\text{-}H}$ 7.7, $^4J_{H\text{-}H}$ 1.4 Hz, $H^o$), 7.90 (1H, d, $^4J_{H\text{-}H}$ 1.4 Hz, $H^5$), 7.55 (1H, td, $^3J_{H\text{-}H}$ 7.7 Hz, $^4J_{H\text{-}H}$ 1.4 Hz, $H^p$), 7.46 (2H, td, $^3J_{H\text{-}H}$ 7.7 Hz, $^4J_{H\text{-}P}$ 3.5 Hz, $H^m$), 4.15 (2H, qd, $^3J_{H\text{-}H}$ 7.0 Hz, $^3J_{H\text{-}P}$ 4.2 Hz, $CH_2O$), 2.72 (3H, s), 1.38 (3H, t, $^3J_{H\text{-}H}$ 7.0 Hz, $CH_2\mathit{Me}$); $^{13}$C NMR ($CDCl_3$, $\delta$): 163.0 (d, $^3J_{C\text{-}P}$ 21 Hz, $C^6$), 158.1 (d, $^1J_{C\text{-}P}$ 167 Hz, $C^2$), 154.0 (d, $^3J_{C\text{-}P}$ 13 Hz, $C^4$), 132.9 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^p$), 132.5 (d, $^2J_{C\text{-}P}$ 10 Hz, $C^o$), 129.1 (d, $^1J_{C\text{-}P}$ 140 Hz, $C^i$), 128.5 (d, $^3J_{C\text{-}P}$ 13 Hz, $C^m$), 117.6 (d, $^2J_{C\text{-}P}$ 24 Hz, $C^3$), 117.5 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 62.2 (d, $^2J_{C\text{-}P}$ 6 Hz, $CH_2O$), 24.9 (Me), 16.4 ($CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): 23.7; $m/z$ (HRMS$^+$) 307.0851 $[M + H]^+$ ($C_{14}H_{16}N_2O_4P$ requires 307.0848); $R_f$ = 0.47 (silica, $CH_2Cl_2$ : 5 % MeOH).

**4-Bromo-6-methylpyridin-2-yl(phenyl)phosphinic acid**

Ethyl (6-methyl-4-nitropyridin-2-yl)(phenyl)phosphinate, (2.00 g, 6.54 mmol) was dissolved in $CH_3COBr$ (15 mL, 0.2 mol) and the mixture stirred at 70 °C for 16 h under argon. A pale brown precipitate formed. Both precipitate and solution were dropped cautiously into $CH_3OH$ (100 mL) stirred at 0 °C. The solvent was removed

under reduced pressure to yield a pale brown solid (1.81 g, 90 %); $^{1}$H NMR ($CD_3OD$, $\delta$): 8.33 (1H, dd, $^{3}J_{H\text{-}P}$ 7.2 Hz, $^{4}J_{H\text{-}H}$ 2.0 Hz, $H^3$), 8.23 (1H, d, $^{4}J_{H\text{-}H}$ 2.0 Hz, $H^5$), 7.95 (2H, ddd, $^{3}J_{H\text{-}P}$ 13.2 Hz, $^{3}J_{H\text{-}H}$ 7.6 Hz, $^{4}J_{H\text{-}H}$ 1.6 Hz, $H^o$), 7.63 (1H, td, $^{3}J_{H\text{-}H}$ 7.6 Hz, $^{4}J_{H\text{-}H}$ 1.6 Hz, $H^p$), 7.55 (2H, td, $^{3}J_{H\text{-}H}$ 7.6 Hz, $^{4}J_{H\text{-}P}$ 3.6 Hz, $H^m$), 2.77 (3H, s); $^{13}$C NMR ($CD_3OD$, $\delta$): 159.4 (d, $^{3}J_{C\text{-}P}$ 20 Hz, $C^6$), 151.7 (d, $^{1}J_{C\text{-}P}$ 160 Hz, $C^2$), 145.1 (d, $^{3}J_{C\text{-}P}$ 10 Hz, $C^4$), 134.8 (d, $^{4}J_{C\text{-}P}$ 3 Hz, $C^p$), 133.3 (d, $^{2}J_{C\text{-}P}$ 10 Hz, $C^o$), 131.0 (d, $^{2}J_{C\text{-}P}$ 24 Hz, $C^3$), 130.6 (d, $^{4}J_{C\text{-}P}$ 3 Hz, $C^5$), 130.2 (d, $^{1}J_{C\text{-}P}$ 140 Hz, $C^i$), 129.6 (d, $^{3}J_{C\text{-}P}$ 12 Hz, $C^m$), 20.4 (Me); $^{31}$P NMR ($CD_3OD$, $\delta$): 14.3; *m/z* (HRMS$^-$) 309.9648 $[M - H]^-$ ($C_{12}H_{10}NO_2{}^{79}BrP$ requires 309.9633); $R_f$ = 0.01 (silica, $CH_2Cl_2$ : 5 % MeOH).

**Ethyl (4-bromo-6-methylpyridin-2-yl)(phenyl)phosphinate**

(4-Bromo-6-methylnitropyridin-2-yl)(phenyl)phosphinic acid, (1.80 g, 5.80 mmol) was added to triethyl orthoformate (50 mL) and the mixture stirred at 140 °C for 72 h under argon. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica ($CH_2Cl_2$: 0.5 % MeOH) to yield a yellow oil (1.08 g, 55 %); $^{1}$H NMR ($CDCl_3$, $\delta$): 8.04 (1H, dd, $^{3}J_{H\text{-}P}$ 6.3 Hz, $^{4}J_{H\text{-}H}$ 1.4 Hz, $H^3$), 7.95 (2H, ddd, $^{3}J_{H\text{-}P}$ 11.2 Hz, $^{3}J_{H\text{-}H}$ 7.0, $^{4}J_{H\text{-}H}$ 1.4 Hz, $H^o$), 7.51 (1H, td, $^{3}J_{H\text{-}H}$ 7.0 Hz, $^{4}J_{H\text{-}H}$ 1.4 Hz, $H^p$), 7.43 (2H, td, $^{3}J_{H\text{-}H}$, 7.0 Hz, $^{4}J_{H\text{-}P}$ 3.5 Hz, $H^m$), 7.37 (1H, d, $^{4}J_{H\text{-}H}$ 1.4 Hz, $H^5$), 4.11 (2H, qd, $^{3}J_{H\text{-}H}$ 7.0 Hz, $^{3}J_{H\text{-}P}$ 4.2 Hz, $CH_2O$), 2.52 (3H, s), 1.34 (3H, t, $^{3}J_{H\text{-}H}$ 7.0 Hz, $CH_2\mathit{Me}$); $^{13}$C NMR ($CDCl_3$, $\delta$): 161.2 (d, $^{3}J_{C\text{-}P}$ 22 Hz, $C^6$), 155.7 (d, $^{1}J_{C\text{-}P}$ 165 Hz, $C^2$), 133.5 (d, $^{3}J_{C\text{-}P}$ 15 Hz, $C^4$), 132.7 (d, $^{4}J_{C\text{-}P}$ 3 Hz, $C^p$), 132.6 (d, $^{2}J_{C\text{-}P}$ 10 Hz, $C^o$), 130.0 (d, $^{1}J_{C\text{-}P}$ 139 Hz, $C^i$), 128.5 (d, $^{4}J_{C\text{-}P}$ 3 Hz, $C^5$), 128.4 (d, $^{2}J_{C\text{-}P}$ 23 Hz, $C^3$), 128.3 (d, $^{3}J_{C\text{-}P}$ 13 Hz, $C^m$), 62.1 (d, $^{2}J_{C\text{-}P}$ 6 Hz, $CH_2O$), 24.5 (Me), 16.7 ($CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): 25.5; *m/z* (HRMS$^+$) 340.0102 $[M + H]^+$ ($C_{14}H_{16}NO_2{}^{79}BrP$ requires 340.0102); $R_f$ = 0.56 (silica, $CH_2Cl_2$ : 5 % MeOH).

**Ethyl (4-[2-(4-methoxyphenyl)ethynyl]-6-methylpyridin-2-yl)(phenyl)phosphinate**

Ethyl (4-bromo-6-methylnitropyridin-2-yl)(phenyl)phosphinate, (32 mg, 0.094 mmol) was dissolved in dry THF (1 mL) and the solution was degassed (freeze-thaw cycle) three times. 4-Ethynylanisole (19 mg, 0.14 mmol) and $NEt_3$ (0.5 mL) were added and the solution was degassed once. Tetrakis(triphenylphosphine)palladium(0) (10 mg, 8.7 μmol) and CuI (3.6 mg, 0.019 mmol) were added and the solution was degassed a further three times. The solution was stirred at 65 °C under argon. The reaction was monitored by TLC (silica; $CH_2Cl_2$ : 2.5 % $CH_3OH$, $R_f$(product) = 0.21, $R_f$(reactant) = 0.26) and stopped after 3 h. The solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 1.6 % in 0.1 % increments) to give a yellow oil (20 mg, 55 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.01 (1H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, $H^3$), 7.98 (2H, dd, $^3J_{H\text{-}H}$ 8.4 Hz, $^3J_{H\text{-}P}$ 12.4 Hz, $PhH^o$), 7.53 (1H, t, $^3J_{H\text{-}H}$ 8.4 Hz, $PhH^p$), 7.47 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^m$), 7.45 (2H, td, $^3J_{H\text{-}H}$ 8.4 Hz, $^4J_{H\text{-}P}$ 4.2 Hz, $PhH^m$), 7.28 (1H, d, $^4J_{H\text{-}H}$ 1.6 Hz, $H^5$), 6.89 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^o$), 4.13 (2H, qd, $^3J_{H\text{-}H}$ 5.6 Hz, $^3J_{H\text{-}P}$ 4.8 Hz, $CH_2O$), 3.84 (3H, s, OMe), 2.57 (3H, s, CMe), 1.38 (3H, t, $^3J_{H\text{-}H}$ 5.6 Hz, $CH_2\mathit{Me}$); $^{13}$C NMR ($CDCl_3$, $\delta$): 160.4 (s, ArCO), 159.7 (d, $^3J_{C\text{-}P}$ 20 Hz, $C^6$), 153.8 (d, $^1J_{C\text{-}P}$ 165 Hz, $C^2$), 134.7 (d, $^2J_{C\text{-}P}$ 12 Hz, $C^4$), 133.4 (s, $ArC^m$), 132.4 (d, $^4J_{C\text{-}P}$ 5, $PhC^p$), 132.2 (d, $^2J_{C\text{-}P}$ 10 Hz, $PhC^o$), 130.2 (d, $^1J_{C\text{-}P}$ 139 Hz, $PhC^i$), 128.2 (d, $^3J_{C\text{-}P}$ 22 Hz, $C^3$), 128.1 (d, $^3J_{C\text{-}P}$ 12 Hz, $PhC^m$), 126.8 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 114.1 (s, $ArC^o$), 114.0 (s, $ArC^p$), 94.9 (s, alkyne C), 85.3 (d, $^4J_{C\text{-}P}$ 2, alkyne C), 61.7 (d, $^2J_{C\text{-}P}$ 6 Hz, $CH_2O$), 55.2 (s, OMe), 27.9 (s, Me), 16.6 (s, $CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): +26.6; *m/z* (HRMS$^+$) 414.1247 $[M + Na]^+$ ($C_{23}H_{22}O_3NPNa$ requires 414.1235); $R_f$ = 0.21 (silica, $CH_2Cl_2$ : 2.5 % MeOH).

**Ethyl (4-bromo-6-methyl-1-oxo-1-pyridin-2-yl)(phenyl)phosphinate**

To a stirred solution of ethyl (4-bromo-6-methylnitropyridin-2-yl)(phenyl)phosphinate (1.25 g, 3.68 mmol) in $CHCl_3$ (20 mL) was added MCPBA (1.27 g, 7.35 mmol). The resulting solution was stirred at 65 °C overnight (16 h) under argon. The reaction was monitored by TLC (silica; $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.28, $R_f$(reactant) = 0.56). The solvent was removed under reduced pressure to give a yellow oil. This oil was dissolved in $CH_2Cl_2$ and washed with $NaHCO_3$ solution (0.5 M, 50 mL). The layers were separated and the aqueous layer extracted with $CH_2Cl_2$ (3 × 30 mL). All organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resultant oil was purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 2 % in 0.1 % increments) to give a pale yellow oil (1.11 g, 75 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.05 (1H, dd, $^3J_{H\text{-}P}$ 7.7, $^4J_{H\text{-}H}$ 2.1 Hz, $H^3$), 7.98 (2H, dd, $^3J_{H\text{-}H}$ 7.7 Hz, $^3J_{H\text{-}P}$ 13.3 Hz, $H^o$), 7.50 (1H, t, $^3J_{H\text{-}H}$ 7.7 Hz, $H^p$), 7.44 (1H, d, $^4J_{H\text{-}H}$ 2.1 Hz, $H^5$), 7.41 (2H, td, $^3J_{H\text{-}H}$ 7.7 Hz, $^4J_{H\text{-}P}$ 4.2 Hz, $H^m$), 4.13 (2H, qd, $^3J_{H\text{-}H}$ 5.6 Hz, $^3J_{H\text{-}P}$ 4.9 Hz, $CH_2O$), 2.32 (3H, s), 1.34 (3H, t, $^3J_{H\text{-}H}$ 5.6 Hz, $CH_2\mathit{Me}$); $^{13}$C NMR ($CDCl_3$, $\delta$): 151.0 (d, $^3J_{C\text{-}P}$ 4 Hz, $C^6$), 144.2 (d, $^1J_{C\text{-}P}$ 149 Hz, $C^2$), 133.2 (d, $^2J_{C\text{-}P}$ 11 Hz, $C^o$), 133.1 (d, $^4J_{C\text{-}P}$ 4 Hz, $C^p$), 133.0 (d, $^3J_{C\text{-}P}$ 11 Hz, $C^3$), 132.2 (d, $^4J_{C\text{-}P}$ 4 Hz, $C^5$), 129.0 (d, $^1J_{C\text{-}P}$ 152 Hz, $C^i$), 128.4 (d, $^3J_{C\text{-}P}$ 14 Hz, $C^m$), 117.4 (d, $^2J_{C\text{-}P}$ 12 Hz, $C^4$), 62.3 (d, $^2J_{C\text{-}P}$ 6 Hz, $CH_2O$), 17.5 (Me), 16.7 ($CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): +21.2; $m/z$ (HRMS$^+$) 356.0061 $[M + H]^+$ ($C_{14}H_{16}O_3{}^{79}BrNP$ requires 356.0051); $R_f$ = 0.28 (silica, $CH_2Cl_2$ : 5 % MeOH).

**(4-Bromo-6-[ethoxy(phenyl)phosphoryl]pyridine-2-yl)methyl acetate**

Ethyl (4-bromo-6-methyl-1-oxo-1-pyridin-2-yl)(phenyl)phosphinate, (1.8 g, 5.1 mmol) was dissolved in acetic anhydride (35 mL) and the solution was heated to 120 °C for 3 h with stirring. Reaction progress was monitored by $^{31}$P-NMR and TLC

(silica, $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.46, $R_f$(reactant) = 0.28). The solvent was removed under reduced pressure and the residue purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 1 % in 0.1 % increments) to give a yellow oil (0.66 g, 33 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.16 (1H, dd, $^3J_{H\text{-}P}$ 7.7 Hz, $^4J_{H\text{-}H}$ 2.1 Hz, $H^3$), 7.93 (2H, dd, $^3J_{H\text{-}H}$ 7.7 Hz $^3J_{H\text{-}P}$ 13.3 Hz, $H^o$), 7.55 (1H, d, $^4J_{H\text{-}H}$ 2.1 Hz, $H^5$), 7.51 (1H, t, $^3J_{H\text{-}H}$ 7.7 Hz, $H^p$), 7.43 (2H, td, $^3J_{H\text{-}H}$ 7.7 Hz, $^4J_{H\text{-}P}$ 4.2 Hz, $H^m$), 5.18 (2H, s, $CH_2O$), 4.09 (2H, qd, $^3J_{H\text{-}H}$ 5.6 Hz, $^3J_{H\text{-}P}$ 4.9 Hz, $CH_2O$), 2.12 (3H, s), 1.33 (3H, t, $^3J_{H\text{-}H}$ 5.6 Hz); $^{13}$C NMR ($CDCl_3$, $\delta$): 170.5 (s, $C^{C=O(OAc)}$), 158.6 (d, $^3J_{C\text{-}P}$ 4 Hz, $C^6$), 156.0 (d, $^1J_{C\text{-}P}$ 149 Hz, $C^2$), 134.3 (d, $^2J_{C\text{-}P}$ 25 Hz, $C^4$), 132.9 (d, $^4J_{C\text{-}P}$ 5 Hz, $C^p$), 132.7 (d, $^2J_{C\text{-}P}$ 10 Hz, $C^o$), 130.5 (d, $^3J_{C\text{-}P}$ 23 Hz, $C^3$), 129.5 (d, $^1J_{C\text{-}P}$ 139 Hz, $C^i$), 128.6 (d, $^3J_{C\text{-}P}$ 13 Hz, $C^m$), 126.6 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 66.0 (s, $CH_2O$), 62.2 (d, $^2J_{C\text{-}P}$ 6 Hz, $CH_2O$), 21.0 (s, $C^{Me(OAc)}$), 16.7 ($CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): +25.0; $m/z$ (HRMS$^+$) 398.0157 $[M + H]^+$ ($C_{16}H_{18}O_4{}^{79}BrNP$ requires 398.0151); $R_f$ = 0.46 (silica, $CH_2Cl_2$ : 5 % MeOH).

**(6-[Ethoxy(phenyl)phosphoryl]-4-[2-(4-methoxyphenyl)ethynyl]pyridine-2-yl)methyl acetate**

(4-Bromo-6-[ethoxy(phenyl)phosphoryl]pyridine-2-yl)methyl acetate, (500 mg, 1.26 mmol) was dissolved in dry THF (10 mL) and the solution was degassed (freeze-thaw cycle) three times. 4-Ethynylanisole (249 mg, 1.89 mmol) and $NEt_3$ (5 mL) were added and the solution was degassed once. Tetrakis(triphenylphosphine)palladium(0) (145 mg, 0.126 mmol) and CuI (42 mg, 0.252 mmol) were added and the solution was degassed a further three times. The solution was stirred at 60 °C under argon. The reaction was monitored by TLC (silica; $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.57, $R_f$(reactant) = 0.46) and stopped after 4 h. The solvent was removed under reduced pressure. The crude residue was dissolved in $CH_2Cl_2$ (50 mL) and washed with

aqueous ammonium chloride solution (3 × 40 mL) and brine (40 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed to give a yellow oil, which was purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 2.0 % in 0.1 % increments) to give a pale yellow oil (400 mg, 81 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.09 (1H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, $H^3$), 7.98 (2H, dd, $^3J_{H\text{-}H}$ 8.4 Hz, $^3J_{H\text{-}P}$ 12.4 Hz, $H^o$), 7.54 (1H, t, $^3J_{H\text{-}H}$ 8.4 Hz, $H^p$), 7.49 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^m$), 7.47 (2H, td, $^3J_{H\text{-}H}$ 8.4 Hz , $^4J_{H\text{-}P}$ 4.2 Hz, $PhH^m$), 7.26 (1H, d, $^4J_{H\text{-}H}$ 1.6 Hz, $H^5$), 6.90 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^o$), 5.24 (2H, s, $CH_2O$), 4.13 (2H, qd, $^3J_{H\text{-}H}$ 5.6 Hz, $^3J_{H\text{-}P}$ 4.8 Hz, $CH_2O$), 3.84 (3H, s, MeO), 2.16 (3H, COMe), 1.38 (3H, t, $^3J_{H\text{-}H}$ 5.6 Hz, $CH_2Me$); $^{13}$C NMR ($CDCl_3$, $\delta$): 170.5 (s, $C^{C=O(OAc)}$), 160.6 (s, $ArC^i$), 157.1 (d, $^3J_{C\text{-}P}$ 20 Hz, $C^6$), 154.4 (d, $^1J_{C\text{-}P}$ 165 Hz, $C^2$), 133.7 (s, $ArC^m$), 133.2 (d, $^2J_{C\text{-}P}$ 12 Hz, $C^4$), 132.5 (d, $^4J_{C\text{-}P}$ 5 Hz, $PhC^p$), 132.4 (d, $^2J_{C\text{-}P}$ 10 Hz, $PhC^o$), 130.3 (d, $^1J_{C\text{-}P}$ 139 Hz, $PhC^i$), 129.1 (d, $^3J_{C\text{-}P}$ 22 Hz, $C^3$), 128.8 (d, $^3J_{C\text{-}P}$ 12 Hz, $PhC^m$), 124.4 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 114.3 (s, $ArC^o$), 113.7 (s, $ArC^p$), 96.0 (s, alkyne C), 85.3 (d, $^4J_{C\text{-}P}$ 2 Hz, alkyne C), 66.3 (s, $CH_2O$), 61.9 (d, $^2J_{C\text{-}P}$ 6 Hz, $CH_2O$), 55.4 (OMe), 20.9 (s, $C^{Me(OAc)}$), 16.5 ($CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): +26.1; *m/z* (HRMS$^+$) 472.1303 $[M + Na]^+$ ($C_{25}H_{24}O_5NPNa$ requires 472.1290); $R_f$ = 0.57 (silica, $CH_2Cl_2$ : 5 % MeOH).

**Ethyl (6-(hydroxymethyl)-4-[2-(4-methoxyphenyl)ethynyl]pyridin-2-yl)(phenyl)phosphinate**

(6-[Ethoxy(phenyl)phosphoryl]-4-[2-(4-methoxyphenyl)ethynyl]pyridine-2-yl)methyl acetate, (350 mg, 0.78 mmol) was dissolved in anhydrous $CH_3CH_2OH$ (12 mL). A catalytic amount of sodium metal (~5 mg) was added and the solution was stirred at 40 °C under argon. The reaction was monitored by TLC (silica; $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.28, $R_f$(reactant) = 0.57) and stopped after 40 min. To the crude reaction mixture was added $CH_2Cl_2$ (100 mL) and sodium salts were removed

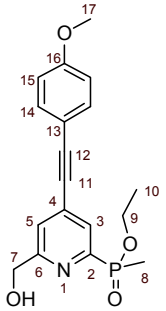
by washing with $H_2O$ (1 × 25 mL). The aqueous layer was re-extracted with $CH_2Cl_2$ (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 3.0 % in 0.2 % increments) to give a colourless oil (200 mg, 82 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.01 (1H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, $H^3$), 7.93 (2H, dd, $^3J_{H\text{-}H}$ 8.4 Hz, $^3J_{H\text{-}P}$ 12.4 Hz, $PhH^o$), 7.51 (1H, t, $^3J_{H\text{-}H}$ 8.4 Hz, $PhH^p$), 7.45 (1H, d, $^4J_{H\text{-}H}$ 1.6 Hz, $H^5$), 7.44 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^m$), 7.43 (2H, td, $^3J_{H\text{-}H}$ 8.4 Hz, $^4J_{H\text{-}P}$ 4.2 Hz, $PhH^m$), 6.87 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^o$), 4.75 (2H, s, $CH_2OH$), 4.12 (2H, qd, $^3J_{H\text{-}H}$ 5.6 Hz, $^3J_{H\text{-}P}$ 4.8 Hz, $CH_2O$), 3.80 (3H, s, OMe), 1.35 (3H, t, $^3J_{H\text{-}H}$ 5.6 Hz, $CH_2\mathit{Me}$); $^{13}$C NMR ($CDCl_3$, $\delta$): 161.4 (d, $^3J_{C\text{-}P}$ 20 Hz, $C^6$), 160.8 (s, $ArC^i$), 153.4 (d, $^1J_{C\text{-}P}$ 165 Hz, $C^2$), 133.9 (s, $ArC^m$), 133.2 (d, $^2J_{C\text{-}P}$ 12 Hz, $C^4$), 132.8 (d, $^4J_{C\text{-}P}$ 5 Hz, $PhC^p$), 132.4 (d, $^2J_{C\text{-}P}$ 10 Hz, $PhC^o$), 129.8 (d, $^1J_{C\text{-}P}$ 140 Hz, $PhC^i$), 128.7 (d, $^3J_{C\text{-}P}$ 12 Hz, $PhC^m$), 128.4 (d, $^3J_{C\text{-}P}$ 22 Hz, $C^3$), 124.1 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 114.5 (s, $ArC^o$), 114.0 (s, $ArC^p$), 96.1 (s, alkyne C), 85.6 (d, $^4J_{C\text{-}P}$ 2, alkyne C), 64.3 (s, $CH_2OH$), 62.0 (d, $^2J_{C\text{-}P}$ 6 Hz, $CH_2OP$), 55.6 (OMe), 16.7 ($CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): +25.6; *m/z* ($HRMS^+$) 408.1382 $[M + H]^+$ ($C_{23}H_{23}O_4NP$ requires 408.1365); $R_f$ = 0.28 (silica, $CH_2Cl_2$ : 5 % MeOH).

**Ethyl-[6-(bromomethyl)-4-[2-(4-methoxyphenyl)ethynyl]pyridin-2-yl](phenyl)phosphinate**

Ethyl-(6-(hydroxymethyl)-4-[2-(4-methoxyphenyl)ethynyl]pyridin-2-yl)(phenyl)phosphinate, (143 mg, 0.35 mmol) was dissolved in dry $CH_2Cl_2$ (4 mL) and the solution was stirred at 0 °C under argon. $PBr_3$ (50 μL, 0.53 mmol) was added and the solution was stirred for a further 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature and monitored by TLC (silica; $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.69, $R_f$(reactant) = 0.28). After 1 h at 20 °C $CH_2Cl_2$ (50 mL)

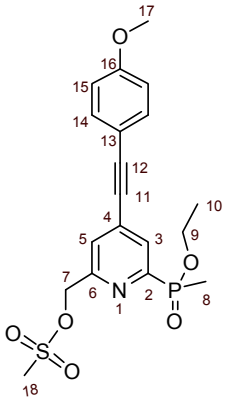
was added and the solution was washed with aq. $NaHCO_3$ solution (1M, 25 mL). The aqueous layer was re-extracted with $CH_2Cl_2$ (3 × 20 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 0.5 % in 0.1 % increments) to give a pale yellow oil (110 mg, 66 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.05 (1H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, $H^3$), 8.00 (2H, dd, $^3J_{H\text{-}H}$ 8.4 Hz, $^3J_{H\text{-}P}$ 12.4 Hz, $PhH^o$), 7.56 (1H, d, $^4J_{H\text{-}H}$ 1.6 Hz, $H^5$), 7.50 (1H, t, $^3J_{H\text{-}H}$ 8.4 Hz, $PhH^p$), 7.47 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^m$), 7.46 (2H, td, $^3J_{H\text{-}H}$ 8.4 Hz, $^4J_{H\text{-}P}$ 4.2 Hz, $PhH^m$), 6.87 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^o$), 4.52 (2H, s, $CH_2Br$), 4.13 (2H, qd, $^3J_{H\text{-}H}$ 5.6 Hz, $^3J_{H\text{-}P}$ 4.8 Hz, $CH_2OP$), 3.80 (3H, s, OMe), 1.36 (3H, t, $^3J_{H\text{-}H}$ 5.6 Hz, Me); $^{13}$C NMR ($CDCl_3$, $\delta$): 160.9 (s, $ArC^i$), 158.1 (d, $^3J_{C\text{-}P}$ 20 Hz, $C^6$), 154.8 (d, $^1J_{C\text{-}P}$ 165 Hz, $C^2$), 133.9 (s, $ArC^m$), 133.6 (d, $^2J_{C\text{-}P}$ 12 Hz, $C^4$), 132.7 (d, $^4J_{C\text{-}P}$ 5 Hz, $PhC^p$), 132.5 (d, $^2J_{C\text{-}P}$ 10 Hz, $PhC^o$), 130.3 (d, $^1J_{C\text{-}P}$ 140 Hz, $PhC^i$), 128.8 (d, $^3J_{C\text{-}P}$ 12 Hz, $PhC^m$), 128.7 (d, $^3J_{C\text{-}P}$ 22 Hz, $C^3$), 126.8 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 114.5 (s, $ArC^o$), 113.9 (s, $ArC^p$), 96.5 (s, alkyne C), 85.1 (d, $^4J_{C\text{-}P}$ 2, alkyne C), 62.2 (d, $^2J_{C\text{-}P}$ 6 Hz, $CH_2OP$), 55.6 (OMe), 33.3 (s, $CH_2Br$), 16.7 (Me); $^{31}$P NMR ($CDCl_3$, $\delta$): +25.8; *m/z* (HRMS$^+$) 492.0341 $[M + Na]^+$ ($C_{23}H_{21}O_3NP^{79}BrNa$ requires 492.0340); $R_f$ = 0.69 (silica, $CH_2Cl_2$ : 5 % MeOH).

**Ethyl(6-(hydroxymethyl)-4-[2-(4-methoxyphenyl)ethynyl]pyridin-2-yl)(methyl)phosphinate**



Ethyl (6-(hydroxymethyl)-4-(bromopyridin-2-yl)(methyl)phosphinate (100 mg, 0.34 mmol) was dissolved in dry THF (2 mL) and the solution was degassed (freeze-thaw cycle) three times. 4-Ethynylanisole (67 mg, 0.51 mmol) and $NEt_3$ (0.2 mL) were added and the solution degassed once more. [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) chloride (28 mg, 0.034 mmol) and CuI (13 mg, 0.068 mmol) were added and the solution was degassed a further three times. The solution was stirred at 65 °C under argon for 12h, solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 3 % in 1 % increments) to give a dark yellow oil (113 mg, 96 %); $^1$H NMR (700 MHz, $CDCl_3$, $\delta$): 7.95 (1H, bs, $H^3$), 7.51 (1H, bs, $H^5$), 7.42 (2H, d, $^3J_{H\text{-}H}$ 8.8, $H^{14}$), 6.84 (2H, d, $^3J_{H\text{-}H}$ 8.8, $H^{15}$), 4.78 (2H, s, $H^7$), 4.10 – 4.04 (1H, m, $H^9$), 3.86 – 3.81 (1H, m, $H^9$), 3.78 (3H, s, $H^{17}$), 1.73 (3H, d, $^2J_{H\text{-}P}$ 14.9, $H^8$), 1.23 (3H, t, $^3J_{H\text{-}H}$ 7, $H^{10}$); $^{13}$C NMR (176 MHz $CDCl_3$, $\delta$): 161.2 (d, $^3J_{C\text{-}P}$ 18, $C^6$), 160.6 (s, $C^{16}$), 153.1 (d, $^1J_{C\text{-}P}$ 156, $C^2$), 133.6 (s, $C^{14}$), 132.9 (d, $^2J_{C\text{-}P}$ 12, $C^4$), 127.7 (d, $^3J_{C\text{-}P}$ 19, $C^3$), 124.1 (d, $^4J_{C\text{-}P}$ 4, $C^5$), 114.2 (s, $C^{15}$), 114.0 (s, $C^{13}$), 96.0 (s, $C^{12}$), 85.3 (s, $C^{11}$), 64.2 (s, $C^7$), 61.2 (d, $^2J_{C\text{-}P}$ 6, $C^9$), 55.3 (s, $C^{17}$), 16.4 (d, $^3J_{C\text{-}P}$ 6, $C^{10}$), 13.4 (d, $^1J_{C\text{-}P}$ 104, $C^8$); $^{31}$P NMR (162 MHz, $CDCl_3$, $\delta$): +38.6; *m/z* (HRMS$^+$) 346.1228 $[M + H]^+$ ($C_{18}H_{21}O_4NP$ requires 346.1208).

**Ethyl(6-(ethyl-methanesulfonate)-4-[2-(4-methoxyphenyl)ethynyl]pyridin-2-yl)(methyl)phosphinate**




Ethyl(6-(hydroxymethyl)-4-[2-(4-methoxyphenyl)ethynyl]pyridine-2-yl)(methyl)phosphinate (128 mg, 0.37 mmol) was dissolved in anhydrous THF (3 mL) and $NEt_3$ (0.18 mL, 1.3 mmol) was added. The mixture was stirred at 5 °C and methanesulfonyl chloride (43 µL, 0.56 mmol) was added. The reaction was monitored by TLC (silica; $CH_2Cl_2$ : 10 % $CH_3OH$, $R_f$(product) = 0.65, $R_f$(reactant) = 0.20) and stopped after 15 min. The solvent was removed under reduced pressure and the residue dissolved in $CH_2Cl_2$ (15 mL) and washed with NaCl solution (saturated, 10 mL). The aqueous layer was re-extracted with $CH_2Cl_2$ (3 × 10 mL) and the organic layers combined, dried over $MgSO_4$ and the solvent removed under reduced pressure to leave a colorless oil that was used directly to prepare the ethyl ester of $L^{2b}$ without further purification (128 mg, 81 %); $^1$H NMR (400 MHz, $CDCl_3$, $\delta$): 8.11 (1H, dd, $^3J_{H\text{-}P}$ 6.0, $^4J_{H\text{-}H}$ 1.5, $H^3$), 7.65 (1H, bs, $H^5$), 7.52 (2H, d, $^3J_{H\text{-}H}$ 8.9, $H^{14}$), 6.93 (2H, d, $^3J_{H\text{-}H}$ 8.9, $H^{15}$), 5.39 (2H, s, $H^7$), 4.20 – 4.10 (1H, m, $H^9$), 3.95 – 3.88 (1H, m, $H^9$), 3.86 (3H, s, $H^{17}$), 3.16 (3H, s, $H^{18}$) 1.80 (3H, d, $^2J_{H\text{-}P}$ 15.1, $H^8$), 1.31 (3H, t, $^3J_{H\text{-}H}$ 7.1, $H^{10}$); *m/z* (HRMS$^+$) 446.0804 $[M + Na]^+$ ($C_{19}H_{22}O_6SNPNa$ requires 446.0803); $R_f$ = 0.65 (silica, $CH_2Cl_2$ : 10 % $CH_3OH$).

**Tri-ethyl phenylphosphinate ester of $L^{2a}$**

1,4,7-Triazacyclononane (10 mg, 0.078 mmol) and ethyl-[6-(bromomethyl)-4-[2-(4-methoxyphenyl)ethynyl]pyridin-2-yl](phenyl)phosphinate (110 mg, 0.234 mmol) were dissolved in anhydrous $CH_3CN$ (5 mL) and $K_2CO_3$ (32 mg, 0.234 mmol) was added. The mixture was stirred under argon at 78 °C and monitored by TLC (silica; $CH_2Cl_2$ : 10 % $CH_3OH$, $R_f$(product) = 0.06, $R_f$(reactant = 0.85). After 16 h the reaction was cooled and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 30 % in 1 % increments) to give a yellow oil (23 mg, 23 %): $^1$H NMR ($CDCl_3$, $\delta$): 8.03 (3H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $H^3$), 7.94 (6H, dd, $^3J_{H\text{-}P}$ 12.4 Hz, $^3J_{H\text{-}H}$ 6.8 Hz, $PhH^o$), 7.58 (3H, s, $H^5$), 7.45 (6H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^m$), 7.42 (3H, t, $^3J_{H\text{-}H}$ 6.8 Hz, $PhH^p$), 7.37 (6H, td, $^3J_{H\text{-}H}$, 6.8 Hz, $^4J_{H\text{-}P}$ 3.6 Hz, $PhH^m$), 6.87 (6H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^o$), 4.10 (6H, qd, $^3J_{H\text{-}H}$ 7.2 Hz, $^3J_{H\text{-}P}$ 4.2 Hz, $CH_2OP$), 3.83 (6H, s, $CH_2N$), 3.82 (9H, s, OMe), 2.74 (12H, br s, ring CHN), 1.33 (9H, t, $^3J_{H\text{-}H}$ 7.2 Hz, $CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): +26.6; *m/z* (HRMS$^+$) 1297.486 $[M + H]^+$ ($C_{75}H_{76}O_9N_6P_3$ requires 1297.488); $R_f$ = 0.06 (silica, $CH_2Cl_2$ : 10 % MeOH).

**[Eu·$L^{2a}$]**

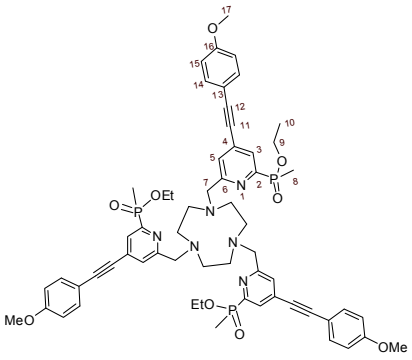
The tri-ethyl phenylphosphinate ester of ***L*$^{2a}$**, (10 mg, 7.7 μmol) was dissolved in $CD_3OD$ (3 mL) and NaOD (0.1 M in $D_2O$, 1 mL) was added. The solution was stirred at 60 °C and monitored by $^1$H-NMR (loss of $CH_3CH_2$ peaks at 4.10 and 1.33 ppm) and $^{31}$P-NMR (reactant 26.6 ppm, product 17.5 ppm) and stopped after 16 h. The pH of the solution was adjusted to 7 by addition of HCl (1M). $Eu(OAc)_3$ (3.4 mg, 8.5 μmol) in a $H_2O$ : $CH_3OH$ solution (0.5 mL, 1:1 v/v) was added and the solution was stirred at 50 °C for 24 h. The solvent was removed under reduced pressure and the

crude material purified by column chromatography (silica, $CH_2Cl_2$ : 5 % $CH_3OH$) to give a white solid (2.5 mg, 24%); *m/z* (HRMS$^+$) 1361.283 [M($^{151}$Eu) + H]$^+$ ($C_{69}H_{61}O_9N_6P_3{}^{151}Eu$ requires 1361.291), 1363.299 [M($^{153}$Eu) + H]$^+$ ($C_{69}H_{61}O_9N_6P_3{}^{153}Eu$ requires 1363.293); $^{31}$P NMR ($CD_3OD$, $\delta$): +17.5; $R_f$ = 0.25 (silica, $CH_2Cl_2$ : 10 % MeOH). $\tau_{MeOH}$ = 1.30 ms, $\Phi^{em}_{MeOH}$ = 52 ± 10 %; $\varepsilon_{MeOH}$ (332 nm) = 58, 000 $M^{-1}$ $cm^{-1}$; $t_R$ = 11.5 min.

**[Tb·L$^{2a}$]**

An analogous procedure to that described for the synthesis of [Eu·L$^{2a}$] was followed using the tri-ethyl phenylphosphinate ester of L$^{2a}$, (10 mg, 7.7 μmol) and $Tb(OAc)_3$ (3.1 mg, 7.7 μmol) to give a white solid (2.9 mg, 29 %); *m/z* (HRMS$^+$) 1369.301 [M($^{159}$Tb) + H]$^+$ ($C_{69}H_{61}O_9N_6P_3{}^{159}Tb$ requires 1369.296); $R_f$ = 0.25 (silica, $CH_2Cl_2$ : 10 % MeOH), $t_R$ (*Method D*) = 11.5 min.

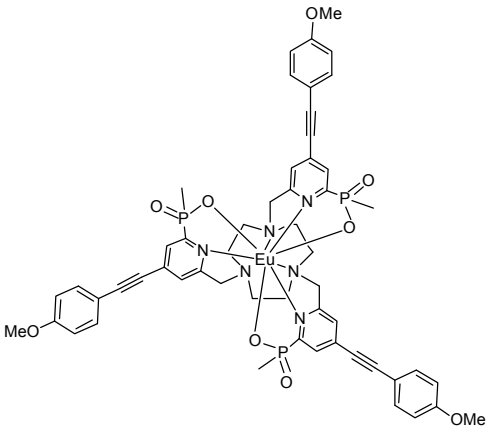
**Tri-ethyl methylphosphinate ester of L$^{2b}$**




1,4,7-Triazacyclononane (14 mg, 0.108 mmol) and ethyl(6-(ethyl methanesulfonate)-4-[2-(4-methoxyphenyl)ethynyl]pyridin-2-yl)(methyl)phosphinate (128 mg, 0.302 mmol) were dissolved in anhydrous $CH_3CN$ (5 mL) and $K_2CO_3$ (48 mg, 0.346 mmol) was added. The mixture was stirred under argon at 78 °C. After 12 h the reaction was

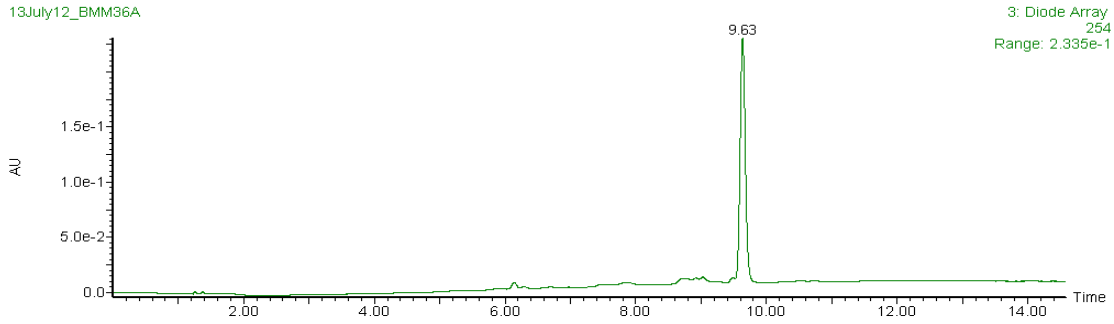
cooled and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 30 % in 5 % increments) to give a pale yellow oil (30 mg, 25 %): $^1$H NMR (400 MHz, $CDCl_3$, $\delta$) 8.01 (3H, d, $^3J_{H\text{-}P}$ 5.1, $H^3$), 7.72 (3H, bs, $H^5$), 7.49 (6H, d, $^3J_{H\text{-}H}$ 8.8, $H^{14}$), 6.91 (6H, d, $^3J_{H\text{-}H}$ 8.8, $H^{15}$), 4.17 – 4.07 (3H, m, $H^9$), 3.92 – 3.87 (3H, m, $H^9$), 3.86 (6H, s, $H^7$ (peak overlaps)) 3.85 (9H, s, $H^{17}$), 2.99 (12H, br s, ring Hs), 1.78 (9H, d, $^2J_{H\text{-}P}$ 15.0, $H^8$), 1.27 (9H, t, $^3J_{H\text{-}H}$ 7.1, $H^{10}$); $^{13}$C NMR (176 MHz $CDCl_3$, $\delta$): 160.8 (d, $^3J_{C\text{-}P}$ 18, $C^6$), 159.6 (s, $C^{16}$), 152.8 (d, $^1J_{C\text{-}P}$ 154, $C^2$), 133.1 (s, $C^{14}$), 133.0 (bm, $C^4$), 128.1 (bm, $C^3$), 124.9 (bm, $C^5$), 113.4 (s, $C^{15}$), 113.2 (s, $C^{13}$), 97.2 (s, $C^{12}$), 85.5 (s, $C^{11}$), 63.1 (s, $C^7$), 61.0 (d, $^2J_{C\text{-}P}$ 6, $C^9$), 54.4 (s, $C^{17}$), 53.0 – 46.0 (br m, ring Cs), 15.6 (d, $^3J_{C\text{-}P}$ 6, $C^{10}$), 12.4 (d, $^1J_{C\text{-}P}$ 104, $C^8$); $^{31}$P NMR (162 MHz, $CDCl_3$, $\delta$): +38.7; *m/z* (HRMS$^+$) 1111.4430 $[M + H]^+$ ($C_{60}H_{70}O_9N_6P_3$ requires 1111.4417).

**[Eu.L$^{2b}$]**




The tri-ethyl methylphosphinate ester of $L^{2b}$ (17 mg, 15.3 μmol) was dissolved in $CD_3OD$ (3 mL) and NaOH (0.1 M in $D_2O$, 1 mL) was added. The solution was stirred at 60 °C and monitored by $^1$H-NMR (loss of $CH_3CH_2$ peaks) and $^{31}$P-NMR (reactant 38.7 ppm, product 25.9 ppm) and stopped after 16 h. The pH of the solution was

adjusted to 7 by addition of HCl (1 M). $Eu(OAc)_3$ (7.0 mg, 21.5 μmol) in a $H_2O$: $CH_3OH$ solution (0.5 mL, 1:1 v/v) was added and the solution was stirred at 50 °C for 24 h. The solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, $CH_2Cl_2$ : 7 % $CH_3OH$) to give a white solid (10 mg, 44 %); $^1$H NMR (600 MHz, $CD_3OD$, $\delta$): 8.07, 7.56, 7.04, 6.88, 6.51, 5.48, 4.68, 4.31, 3.87, 3.76, 3.29, 2.14, 1.63, 1.46, 1.42, 1.27, 0.85, -0.43, -1.15, -1.49, -5.00; $^{31}$P NMR (162 MHz $CD_3OD$, $\delta$): +40.4; *m/z* (HRMS$^+$) 1177.2458 [M($^{153}$Eu) + H]$^+$ ($C_{54}H_{55}O_9N_6P_3{}^{153}Eu$ requires 1177.2463); $R_f$ = 0.30 (silica, $CH_2Cl_2$ : 10 % MeOH); $\tau_{MeOH}$ = 1.07 ms; $\Phi^{em}_{MeOH}$ = 44 ± 10%; $\varepsilon_{MeOH}$ (332 nm) = 58,100 $M^{-1}$ $cm^{-1}$. $t_R$ = 9.6 min.




**[Yb.L$^{2b}$]**

An analogous procedure to that described for the synthesis of [Eu·L$^{OMe}$] was followed using the tri-ethyl methylphosphinate ester of L$^{2b}$ (5.8 mg, 5.7 μmol) and $Yb(OAc)_3$ (2.6 mg, 6.1 μmol) to give the title compound as a white solid (2.6 mg, 38 %); $^1$H NMR (600 MHz, $CD_3OD$, $\delta$): 20.72, 11.38, 10.89, 8.26, 7.36, 6.47, 5.33, 4.86, 4.61, 4.32, 4.30, 4.07, 3.29, 2.14, 2.02, 1.59, 1.28, 0.88, 0.08, -4.11, -5.73, -6.24, -15.20; *m/z* (HRMS$^+$) 1220.2511 [M($^{174}$Yb) + Na]$^+$ ($C_{54}H_{54}O_9N_6P_3{}^{174}YbNa$ requires

1220.2462); $R_f$ = 0.30 (silica, $CH_2Cl_2$ : 10 % MeOH); $\varepsilon_{MeOH}$ (332 nm) = 59,460 $M^{-1}$ $cm^{-1}$.

**[Gd.L$^{2b}$]**

An analogous procedure to that described for the synthesis of [Eu.L$^{2b}$] was followed using the tri-ethyl methylphosphinate ester of L$^{2b}$ (7.0 mg, 6.8 μmol) and $Gd(OAc)_3$ (2.4 mg, 7.2 μmol) to give the title compound as a white solid (3.5 mg, 43 %); *m/z* (HRMS$^+$) 1204.2303 [M($^{158}$Gd) + Na]$^+$ ($C_{54}H_{54}O_9N_6P_3{}^{158}GdNa$ requires 1204.2304); $R_f$ = 0.30 (silica, $CH_2Cl_2$ : 10 % MeOH).

**(6-[Ethoxy(phenyl)phosphoryl]-4-[2-(4-(2-[2-(2-methoxyethoxy)ethoxy]ethoxy)phenyl)ethynyl]pyridin-2-yl)methyl acetate**

(4-Bromo-6-[ethoxy(phenyl)phosphoryl]pyridine-2-yl)methyl acetate, (540 mg, 1.36 mmol) was dissolved in dry THF (8 mL) and the solution was degassed (freeze-thaw cycle) three times. [2-(4-(2-[2-(2-Methoxyethoxy)ethoxy]ethoxy)phenyl)ethynyl]trimethylsilane* (456 mg, 1.36 mmol) and $NEt_3$ (4 mL) were added and the solution was degassed once. Tetrakis(triphenylphosphine)palladium(0) (156 mg, 0.136 mmol) and CuI (26 mg, 0.136 mmol) were added and the solution was degassed a further three times. The solution was stirred under argon and tetrabutylammonium fluoride solution (1 M in THF, 1.9 mL, 2.04 mmol) was added. A color change from yellow to a dark blue was observed and the mixture was stirred at 65 °C under argon. The reaction was monitored by TLC (silica; $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.31, $R_f$(reactant) = 0.46) and stopped after 3 h. The solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$, 0 – 1.5 % in 0.1 % increments) to give a yellow oil (575 mg, 73%); $^1$H NMR ($CDCl_3$, $\delta$):

8.05 (1H, dd, $^{3}J_{H\text{-}P}$ 6.0 Hz, $^{4}J_{H\text{-}H}$ 1.6 Hz, $H^{3}$), 7.96 (2H, dd, $^{3}J_{H\text{-}H}$ 8.4 Hz, $^{3}J_{H\text{-}P}$ 12.4 Hz, $PhH^{o}$), 7.50 (1H, t, $^{3}J_{H\text{-}H}$ 8.4 Hz, $PhH^{p}$), 7.44 (2H, d, $^{3}J_{H\text{-}H}$ 8.8 Hz, $ArH^{m}$), 7.43 (2H, td, $^{3}J_{H\text{-}H}$ 8.4 Hz, $^{4}J_{H\text{-}P}$ 4.2 Hz, $PhH^{m}$), 7.42 (1H, d, $^{4}J_{H\text{-}H}$ 1.6 Hz, $H^{5}$), 6.88 (2H, d, $^{3}J_{H\text{-}H}$ 8.8 Hz, $ArH^{o}$), 5.21 (2H, s, $CH_2O$), 4.12 (2H, qd, $^{3}J_{H\text{-}H}$ 5.6 Hz, $^{3}J_{H\text{-}P}$ 4.8 Hz, $CH_2OP$), 4.11 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $ArOCH_2$), 3.83 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $ArOCH_2\mathit{CH_2}$), 3.71 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $OCH_2$), 3.65 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $OCH_2$), 3.63 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $OCH_2$), 3.61 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $OCH_2$), 3.34 (3H, s, MeO), 2.13 (3H, s), 1.34 (3H, t, $^{3}J_{H\text{-}H}$ 5.6 Hz, $CH_2\mathit{Me}$); $^{13}$C NMR ($CDCl_3$, $\delta$): 170.6 (s, $C^{C=O(OAc)}$), 160.1 (s, $ArC^{i}$), 157.3 (d, $^{3}J_{C\text{-}P}$ 20 Hz, $C^{6}$), 154.7 (d, $^{1}J_{C\text{-}P}$ 165 Hz, $C^{2}$), 133.8 (s, $ArC^{m}$), 133.2 (d, $^{2}J_{C\text{-}P}$ 12 Hz, $C^{4}$), 132.7 (d, $^{4}J_{C\text{-}P}$ 5 Hz, $PhC^{p}$), 132.6 (d, $^{2}J_{C\text{-}P}$ 10 Hz, $PhC^{o}$), 130.1 (d, $^{1}J_{C\text{-}P}$ 139 Hz, $PhC^{i}$), 128.8 (d, $^{3}J_{C\text{-}P}$ 22 Hz, $C^{3}$), 128.6 (d, $^{3}J_{C\text{-}P}$ 12 Hz, $PhC^{m}$), 124.6 (d, $^{4}J_{C\text{-}P}$ 3 Hz, $C^{5}$), 115.1 (s, $ArC^{o}$), 114.1 (s, $ArC^{p}$), 96.2 (s, alkyne C), 85.5 (d, $^{4}J_{C\text{-}P}$ 2, alkyne C), 72.2 (s, $MeO\mathit{CH_2}$), 71.1 (s, $CH_2O$), 70.9 (s, $CH_2O$), 70.8 (s, $CH_2O$), 69.8 (s, $CH_2O$), 67.8 ($ArOCH_2$), 66.5 (s, $CH_2OAc$), 62.1 (d, $^{2}J_{C\text{-}P}$ 6 Hz, $CH_2OP$), 59.3 (s, MeO), 21.1 (s, $C^{Me(OAc)}$), 16.7 ($CH_2\mathit{Me}$); $^{31}$P NMR ($CDCl_3$, $\delta$): +26.0; *m/z* ($HRMS^{+}$) 582.2260 $[M + H]^{+}$ ($C_{31}H_{37}O_8NP$ requires 582.2257); $R_f$ = 0.31 (silica, $CH_2Cl_2$ : 5 % MeOH).

**(4-(2-[4-(-([(Tert-butoxy)carbonyl]amino)propoxy)phenyl]ethynyl)-6-[ethoxy(phenyl)phosphoryl]pyridin-2-yl)methyl acetate**

(4-Bromo-6-[ethoxy(phenyl)phosphoryl]pyridine-2-yl)methyl acetate, (170 mg, 0.43 mmol) was dissolved in dry THF (3 mL) and the solution was degassed (freeze-thaw cycle) three times. Tert-butyl N-(3-(4-[2-trimethylsilyl)ethynyl]phenoxy)propyl)carbamate* (148 mg, 0.43 mmol) and $NEt_3$ (1.5 mL) were added and the solution was degassed once. Tetrakis(triphenylphosphine)palladium(0) (49 mg, 0.043 mmol) and CuI (8 mg, 0.043

mmol) were added and the solution was degassed a further three times. The solution was stirred under argon and tetrabutylammonium fluoride solution (1 M in THF, 0.6 mL, 0.64 mmol) was added. A colour change from yellow to a dark blue was observed and the mixture was stirred at 65 °C under argon. The reaction was followed using TLC (silica; $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.42, $R_f$(reactant) = 0.46) and stopped after 3 h. The solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 1.5 % in 0.1 % increments) to give a yellow oil (174 mg, 69 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.09 (1H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 2.0 Hz, $H^3$), 7.99 (2H, dd, $^3J_{H\text{-}H}$ 8.4 Hz, $^3J_{H\text{-}P}$ 12.4 Hz, $PhH^o$), 7.54 (1H, t, $^3J_{H\text{-}H}$ 8.4 Hz, $PhH^p$), 7.47 (2H, d, $^3J_{H\text{-}H}$ 8.4 Hz, $ArH^m$), 7.45 (2H, td, $^3J_{H\text{-}H}$ 8.4 Hz, $^4J_{H\text{-}P}$ 4.2 Hz, $PhH^m$), 7.45 (1H, d, $^4J_{H\text{-}H}$ 2.0 Hz, $H^5$), 6.88 (2H, d, $^3J_{H\text{-}H}$ 8.4 Hz, $ArH^o$), 5.24 (2H, s, $CH_2O$), 4.75 (1H, br s, $CH_2NH$), 4.14 (2H, qd, $^3J_{H\text{-}H}$ 5.6 Hz, $^3J_{H\text{-}P}$ 4.8 Hz, $CH_2OP$), 4.05 (2H, t, $^3J_{H\text{-}H}$ 6 Hz, $ArOCH_2$), 3.33 (2H, m, $CH_2NH$), 2.17 (3H, s, COMe), 1.92 (2H, q, $^3J_{H\text{-}H}$ 6 Hz, $CH_2CH_2NH$), 1.44 (9H, s, CMe), 1.38 (3H, t, $^3J_{H\text{-}H}$ 5.6 Hz, $CH_2Me$); $^{13}$C NMR ($CDCl_3$, $\delta$): 170.7 (s, $C^{C=O(OAc)}$), 160.0 (s, $ArC^i$), 157.3 (d, $^3J_{C\text{-}P}$ 20 Hz, $C^6$), 156.2 (s, CO), 154.6 (d, $^1J_{C\text{-}P}$ 167 Hz, $C^2$), 133.9 (s, $ArC^m$), 133.2 (d, $^2J_{C\text{-}P}$ 12 Hz, $C^4$), 132.7 (d, $^4J_{C\text{-}P}$ 5 Hz, $PhC^p$), 132.6 (d, $^2J_{C\text{-}P}$ 10 Hz, $PhC^o$), 130.1 (d, $^1J_{C\text{-}P}$ 138 Hz, $PhC^i$), 129.1 (d, $^3J_{C\text{-}P}$ 23 Hz, $C^3$), 128.6 (d, $^3J_{C\text{-}P}$ 13 Hz, $PhC^m$), 124.6 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 114.9 (s, $ArC^o$), 114.1 (s, $ArC^p$), 96.2 (s, alkyne C), 85.5 (d, $^4J_{C\text{-}P}$ 2 Hz, alkyne C), 79.5 (s, $Me_3C$), 66.5 (s, $CH_2O$), 66.1 (s, $ArOCH_2$), 62.1 (d, $^2J_{C\text{-}P}$ 6 Hz, $CH_2OP$), 38.1 (s, $CH_2NH$), 29.7 (s, $CH_2CH_2NH$), 28.6 (s, Me), 21.1 (s, $C^{Me(OAc)}$), 16.7 ($CH_2Me$); $^{31}$P NMR ($CDCl_3$, $\delta$): +26.1; $m/z$ ($HRMS^+$) 593.2435 $[M + H]^+$ ($C_{32}H_{38}O_7N_2P$ requires 593.2417); $R_f$ = 0.42 (silica, $CH_2Cl_2$ : 5 % MeOH).

**Ethyl-[6-(hydroxymethyl)-4-[2-(4-(2-[2-(2-methoxyethoxy)-ethoxy]ethoxy)phenyl)ethynyl]pyridin-2-yl](phenyl)phosphinate**

(6-[Ethoxy(phenyl)phosphoryl]-4-[2-(4-(2-[2-(2-methoxyethoxy)ethoxy]ethoxy)phenyl)ethynyl]pyridin-2-yl)methyl acetate, (50 mg, 0.086 mmol) was dissolved in anhydrous $CH_3CH_2OH$ (200 proof, 2.5 mL). A catalytic amount of sodium metal (~2 mg) was added and the solution was stirred at 40 °C under argon. The reaction was monitored by TLC (silica; $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.19, $R_f$(reactant) = 0.31) and stopped after 40 min. To the crude reaction mixture $CH_2Cl_2$ (25 mL) was added and sodium salts were removed by filtration through a short silica plug. The silica was rinsed with $CH_2Cl_2$ : 10 % $CH_3CH_2OH$ (300 mL) to ensure all material was desorbed from the silica. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 2.4 % in 0.2 % increments) to give a colorless oil (40 mg, 87 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.06 (1H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, $H^3$), 7.95 (2H, dd, $^3J_{H\text{-}H}$ 8.4 Hz, $^3J_{H\text{-}P}$ 12.4 Hz, $PhH^o$), 7.53 (1H, t, $^3J_{H\text{-}H}$ 8.4 Hz, $PhH^p$), 7.44 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^m$), 7.43 (2H, td, $^3J_{H\text{-}H}$ 8.4 Hz $^4J_{H\text{-}P}$ 4.2 Hz, $PhH^m$), 7.39 (1H, d, $^4J_{H\text{-}H}$ 1.6 Hz $H^5$), 6.90 (2H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $ArH^o$), 4.75 (2H, s, $CH_2O$), 4.14 (2H, qd, $^3J_{H\text{-}H}$ 5.6 Hz, $^3J_{H\text{-}P}$ 4.8, $CH_2OP$), 4.11 (2H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $ArOCH_2$), 3.86 (2H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $ArOCH_2CH_2$), 3.73 (2H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $CH_2O$), 3.68 (2H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $CH_2O$), 3.66 (2H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $CH_2O$), 3.63 (2H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $CH_2O$), 3.37 (3H, s, MeO), 1.37 (3H, t, $^3J_{H\text{-}H}$ 5.6, Me); $^{13}$C NMR ($CDCl_3$, $\delta$): 160.4 (d, $^3J_{C\text{-}P}$ 19 Hz, $C^6$), 159.9 (s, $ArC^i$), 154.0 (d, $^1J_{C\text{-}P}$ 165 Hz, $C^2$), 133.6 (s, $ArC^m$), 133.0 (d, $^2J_{C\text{-}P}$ 12 Hz, $C^4$), 132.6 (d, $^4J_{C\text{-}P}$ 5 Hz, $PhC^p$), 132.3 (d, $^2J_{C\text{-}P}$ 10 Hz, $PhC^o$), 129.7 (d, $^1J_{C\text{-}P}$ 128 Hz, $PhC^i$), 128.6 (d, $^3J_{C\text{-}P}$ 22 Hz, $C^3$), 128.4 (d, $^3J_{C\text{-}P}$ 12 Hz, $PhC^m$), 123.8 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 114.9 (s, $ArC^o$), 113.8 (s, $ArC^p$), 96.0 (s, alkyne C),

85.3 (d, $^{4}J_{C\text{-}P}$ 2 Hz, alkyne C), 71.9 (s, *CH*$_2$OMe), 70.9 (s, $CH_2O$), 70.7 (s, $CH_2O$), 70.6 (s, $CH_2O$), 69.6 (s, $CH_2O$), 67.5 ($CH_2O$), 63.9 (s, $CH_2OH$), 61.8 (d, $^{2}J_{C\text{-}P}$ 6 Hz, $CH_2OP$), 59.1 (s, MeO), 16.5 (Me); $^{31}$P NMR ($CDCl_3$, $\delta$): +26.6; *m*/*z* ($HRMS^+$) 540.2142 $[M + H]^+$ ($C_{29}H_{35}O_7NP$ requires 540.2151); $R_f$ = 0.19 (silica, $CH_2Cl_2$ : 5 % MeOH).

**Ethyl-[6-(bromomethyl)-4-[2-(4-(2-[2-(2-methoxyethoxy)ethoxy]ethoxy)phenyl)ethynyl]pyridin-2-yl](phenyl)phosphinate**

Ethyl-[6-(hydroxymethyl)-4-[2-(4-(2-[2-(2-methoxyethoxy)-ethoxy]ethoxy)phenyl)ethynyl]pyridin-2-yl](phenyl)phosphinate, (116 mg, 0.22 mmol) was dissolved in dry $CH_2Cl_2$ (5 mL) and the solution was stirred at 0 °C under argon. $PBr_3$ (30 µL, 0.33 mmol) was added and the solution was stirred for a further 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature and monitored by TLC (silica; $CH_2Cl_2$ : 5 % $CH_3OH$, $R_f$(product) = 0.50, $R_f$(reactant) = 0.19). After 1 h at 20 °C the crude reaction mixture was immediately purified by column chromatography (silica, $CH_2Cl_2$ : 1 % $CH_3OH$) to give a yellow oil (95 mg, 73 %); $^{1}$H NMR ($CDCl_3$, $\delta$): 8.00 (1H, dd, $^{3}J_{H\text{-}P}$ 6.0 Hz, $^{4}J_{H\text{-}H}$ 1.2, $H^3$), 7.94 (2H, dd, $^{3}J_{H\text{-}H}$ 8.8 Hz, $^{3}J_{H\text{-}P}$ 12.4 Hz, $PhH^o$), 7.51 (1H, d, $^{4}J_{H\text{-}H}$ 1.2 Hz, $H^5$), 7.48 (1H, t, $^{3}J_{H\text{-}H}$ 8.8 Hz, $PhH^p$), 7.41 (2H, d, $^{3}J_{H\text{-}H}$ 8.8 Hz, $ArH^m$), 7.40 (2H, td, $^{3}J_{H\text{-}H}$ 8.8 Hz, $^{4}J_{H\text{-}P}$ 4.2 Hz, $PhH^m$), 6.85 (2H, d, $^{3}J_{H\text{-}H}$ 8.8 Hz, $ArH^o$), 4.48 (2H, s, $CH_2Br$), 4.09 (2H, qd, $^{3}J_{H\text{-}H}$ 7.2 Hz, $^{3}J_{H\text{-}P}$ 4.8 Hz, $CH_2OP$), 4.08 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $ArOCH_2$), 3.81 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $ArOCH_2CH_2$), 3.67 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $CH_2O$), 3.63 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $CH_2O$), 3.59 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, $CH_2O$), 3.49 (2H, t, $^{3}J_{H\text{-}H}$ 4.8 hz, $CH_2O$), 3.31 (3H, s, MeO), 1.32 (3H, t, $^{3}J_{H\text{-}H}$ 7.2 Hz, Me); $^{13}$C NMR ($CDCl_3$, $\delta$): 160.1 (d, $^{3}J_{C\text{-}P}$ 19 Hz, $C^6$), 159.9 (s, $ArC^i$), 154.3 (d, $^{1}J_{C\text{-}P}$ 165 Hz, $C^2$), 133.6 (s, $ArC^m$), 133.3 (d, $^{2}J_{C\text{-}P}$ 12 Hz, $C^4$), 132.4 (d, $^{4}J_{C\text{-}P}$ 5 Hz, $PhC^p$), 132.3 (d, $^{2}J_{C\text{-}P}$ 10 Hz, $PhC^o$), 129.7 (d, $^{1}J_{C\text{-}P}$ 128

Hz, PhC$^{i}$), 128.6 (d, $^{3}J_{C\text{-}P}$ 22 Hz, C$^{3}$), 128.4 (d, $^{3}J_{C\text{-}P}$ 13 Hz, PhC$^{m}$), 126.7 (d, $^{4}J_{C\text{-}P}$ 3 Hz, C$^{5}$), 114.9 (s, ArC$^{o}$), 113.8 (s, ArC$^{p}$), 96.3 (s, alkyne C), 84.9 (d, $^{4}J_{C\text{-}P}$ 2 Hz, alkyne C), 71.9 (s, *CH*$_2$OMe), 70.9 (s, CH$_2$O), 70.7 (s, CH$_2$O), 70.6 (s, CH$_2$O), 69.6 (s, CH$_2$O), 67.5 (ArOCH$_2$), 61.0 (d, $^{2}J_{C\text{-}P}$ 5 Hz, CH$_2$OP), 59.1 (s, MeO), 33.1 (s, Me), 16.6 (Me); $^{31}$P NMR (CDCl$_3$, $\delta$): +24.8; *m*/*z* (HRMS$^{+}$) 602.1302 [M ($^{79}$Br) + H]$^{+}$ (C$_{29}$H$_{34}$O$_6$NP$^{79}$Br requires 602.1302), $R_f$ = 0.50 (silica, CH$_2$Cl$_2$ : 5 % MeOH).

**Tert-butoxycarbonyl-protected di-ethyl phenylphosphinate ester precursor to L$^{2c}$**

Tert-butyl-1,4,7-triazacyclononane-1-carboxylate (22 mg, 0.096 mmol) and ethyl-[6-(bromomethyl)-4-[2-(4-(2-[2-(2-methoxyethoxy)ethoxy]ethoxy)phenyl)ethynyl]pyridin-2-yl](phenyl)phosphinate, (95 mg, 0.16 mmol) were dissolved in CH$_3$CN (5 mL) and K$_2$CO$_3$ (27 mg, 0.19 mmol) was added. The mixture was stirred under argon at 50 °C and monitored by TLC (silica; CH$_2$Cl$_2$ : 10 % CH$_3$OH, $R_f$(product) = 0.41, $R_f$(reactant ***54***) = 0.81). After 1 h all of the starting material had been consumed and the reaction was cooled and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, CH$_2$Cl$_2$ : CH$_3$OH 0 – 5 % in 0.5 % increments) to give a yellow oil (58 mg, 59 %): $^{1}$H NMR (CDCl$_3$, $\delta$): 8.01 (2H, m, H$^{3}$), 7.95 (4H, m, PhH$^{o}$), 7.56 (2H, br s, H$^{5}$), 7.45 (2H, m, PhH$^{p}$), 7.41 (4H, d, $^{3}J_{H\text{-}H}$ 8.8 Hz, ArH$^{m}$), 7.40 (4H, m, PhH$^{m}$), 6.87 (4H, d, $^{3}J_{H\text{-}H}$ 8.8 Hz, ArH$^{o}$), 4.13 (4H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, ArOCH$_2$), 4.10 (4H, m, CH$_2$OP), 3.85 (4H, s, pyCH$_2$N), 3.84 (4H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, ArOCH$_2$CH$_2$), 3.72 (4H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, CH$_2$O), 3.66 (4H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, CH$_2$O), 3.63 (4H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, CH$_2$O), 3.53 (4H, t, $^{3}J_{H\text{-}H}$ 4.8 Hz, CH$_2$O), 3.35 (6H, s, MeO), 3.24 (4H, br m, ring NCH), 2.97 (4H, br m, ring NCH), 2.53 (4H, br m, ring NCH), 1.45 (9H, s, Me), 1.33 (6H, m, Me); $^{13}$C

NMR ($CDCl_3$, $\delta$): 161.6, 161.4 (d, $^3J_{C\text{-}P}$ 19 Hz, $C^6$), 159.7, 159.6 (s, CO), 155.5 (s, $ArC^i$), 153.8, 153.7 (d, $^1J_{C\text{-}P}$ 165 Hz, $C^2$), 133.6, 133.5 (s, $ArC^m$), 133.3 (br m, $C^4$), 132.4 (br m, $PhC^p$), 132.3 (br m, $PhC^o$), 130.1 (d, $^1J_{C\text{-}P}$ 145 Hz, $PhC^i$), 128.1 (br m, $C^3$), 128.0 (br m, $PhC^m$), 126.2, 125.9 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 114.9, 114.7 (s, $ArC^o$), 114.1, 114.0 (s, $ArC^p$), 95.4, 95.1 (s, alkyne C), 85.7, 85.5 (br m, alkyne C), 71.9 (s, MeO*CH*$_2$), 70.8 (s, $CH_2O$), 70.6 (s, $CH_2O$), 70.5 (s, $CH_2O$), 69.6 (s, $CH_2O$), 67.5 ($ArOCH_2$), 63.0 – 49.1 (br m, ring $NCH_2$), 61.6 (br m, $CH_2OP$), 59.0 (s, MeO), 53.4 (br m, $pyCH_2$), 28.7, 28.6 (s, Me), 16.5 ($CH_2$*Me*); $^{31}P$ NMR ($CDCl_3$, $\delta$): +26.6, +26.5; *m*/*z* ($HRMS^+$) 1272.584 $[M + H]^+$ ($C_{69}H_{88}O_{14}N_5P_2$ requires 1272.580), $R_f$ = 0.41 (silica, $CH_2Cl_2$ : 10 % MeOH).

**Triethyl phosphinate ester of L$^{2c}$**

The t*ert*-butoxycarbonyl-protected di-ethyl phenylphosphinate ester prepared above (47 mg, 0.037 mmol) was dissolved in anhydrous $CH_2Cl_2$ (1 mL) and trifluoroacetic acid (0.5 mL) was added. The solution was stirred under argon at 23 °C for 30 min. TLC (silica; $CH_2Cl_2$ : 10 % $CH_3OH$, $R_f$(product) = 0.10, $R_f$(reactant) = 0.41) and $HRMS^+$ (1172.528 $[M + H]^+$ $C_{64}H_{80}O_{12}N_5P_2$ requires 1172.527) were used to confirm protecting group removal had gone to completion. The solvent was removed under reduced pressure and the residue re-dissolved in $CH_2Cl_2$ (1 mL), which was again removed under reduced pressure. This process was repeated 5 times to ensure removal of excess trifluoroacetic acid. The residue was dissolved in $CH_3CN$ (4 mL) and tert-butyl N-[3(4-(2-[2-(bromomethyl)-6-[ethoxy(phenyl)phosphoryl]pyridin-4-yl]ethynyl)phenoxy)propyl]carbamate, (18 mg, 0.029 mmol) and $K_2CO_3$ (15 mg, 0.11 mmol) were added. The solution was stirred at 50 °C and the reaction monitored by LC-MS and TLC (silica; $CH_2Cl_2$ : 10 % $CH_3OH$, $R_f$(product) = 0.20, $R_f$(reactant) = 0.73). After 30 min all of the starting bromide had been consumed and the reaction

was cooled and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (silica, $CH_2Cl_2$ : $CH_3OH$ 0 – 10 % in 0.5 % increments) to give a yellow oil (25 mg, 50 %); $^1$H NMR ($CDCl_3$, $\delta$): 8.07 (3H, d, $^3J_{H\text{-}P}$ 6.0 Hz, $H^3$), 7.85 (6H, dd, $^3J_{H\text{-}H}$ 8.4 Hz $^3J_{H\text{-}P}$ 12 Hz, $H^o$), 7.48 (3H, m, $H^5$), 7.47 (3H, m, $H^p$), 7.46 (6H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $H^{12}$), 7.39 (6H, m, $H^m$), 6.90 (6H, d, $^3J_{H\text{-}H}$ 8.8 Hz, $H^{13}$), 4.76 (1H, br s, $H^{18'}$), 4.14 (6H, m, $H^7$), 4.11 (4H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $H^{15}$), 4.04 (2H, t, $^3J_{H\text{-}H}$ 6 Hz, $H^{15'}$), 3.94 (6H, br s, $H^1$), 3.87 (4H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $H^{16}$), 3.73 (4H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $H^{17}$), 3.68 (4H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $H^{18}$), 3.65 (4H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $H^{19}$), 3.54 (4H, t, $^3J_{H\text{-}H}$ 4.8 Hz, $H^{20}$), 3.37 (6H, s, $H^{21}$), 3.34 (2H, m, $H^{17'}$), 2.81 (12H, br m, ring Hs), 1.99 (2H, q, $^3J_{H\text{-}H}$ 6 Hz, $H^{16'}$), 1.43 (9H, s, $H^{21'}$), 1.34 (9H, t, $^3J_{H\text{-}H}$ 7.2 Hz, $H^8$); $^{13}$C NMR ($CDCl_3$, $\delta$): 160.8 (d, $^3J_{C\text{-}P}$ 19 Hz, $C^6$), 160.2 (s, $C^{19'}$), 156.2 (s, $C^{14}$), 154.6 (d, $^1J_{C\text{-}P}$ 165 Hz, $C^2$), 134.0 (s, $C^{12}$), 133.9 (br m, $C^4$), 132.9 (br m, $C^p$), 132.5 (d, $^2J_{C\text{-}P}$ 10 Hz, $C^o$), 130.2 (d, $^1J_{C\text{-}P}$ 138 Hz, $C^i$), 128.8 (br m, $C^3$), 128.7 (br m, $C^m$), 127.5 (br m, $C^5$), 115.1 (s, $C^{13}$), 113.9 (s, $C^{11}$), 97.0 (s, $C^{10}$), 85.3 (s, $C^9$), 79.6 (s, $C^{20'}$), 72.1 (s, $C^{20}$), 71.1 (s, $C^{17}$), 70.9 (s, $C^{18}$), 70.8 (s, $C^{19}$), 69.8 (s, $C^{16}$), 67.8 ($C^{15}$), 65.9 (s, $C^{15'}$), 62.0 (d, $^2J_{C\text{-}P}$ 6 Hz, $C^7$), 59.3 (s, $C^{21}$), 52.3 (s, $C^1$), 53.0 – 46.0 (br m, ring Cs), 37.9 (s, $C^{17'}$), 29.7 (s, $C^{16'}$), 28.6 (s, $C^{21'}$), 16.8 ($C^8$); $^{31}$P NMR ($CDCl_3$, $\delta$): +26.4; *m/z* (HRMS$^+$) 1704.741 $[M + H]^+$ ($C_{94}H_{113}O_{17}N_7P_3$ requires 1704.740), $R_f$ = 0.20 (silica, $CH_2Cl_2$ : 10 % MeOH).

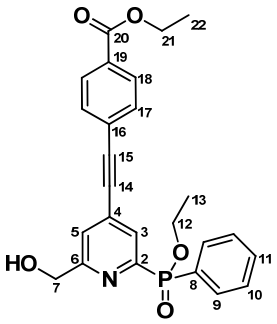
**[Eu·L$^{2c}$]**

The tri-ethyl phenylphosphinate ester of ***L$^{2c}$***, (25 mg, 0.015 mmol) was dissolved in anhydrous $CH_2Cl_2$ (1 mL) and trifluoroacetic acid (0.5 mL) was added. The solution immediately underwent a change from colorless to yellow and was stirred under argon at 23 °C for 30 min. TLC was used to confirm that all starting material had

been consumed. The solvent was removed under reduced pressure and the residue re-dissolved in $CH_2Cl_2$ (1 mL), which was again removed under reduced pressure. This process was repeated 5 times to ensure removal of excess trifluoroacetic acid. $^1$H-NMR (loss of C*H*$_3$ peak at 1.43 ppm) and ESI-MS$^+$ (802.8 $[M + 2H]^{2+}$, 803.8 $[M(^{13}C) + 2H]^{2+}$) was used to confirm removal of the *tert*-butoxycarbonyl group. The residue was dissolved in $CD_3OD$ (2.5 mL) and $D_2O$ (1.5 mL) was added. The solution was heated to 60 °C and NaOD solution was added (0.5 M, 0.5 mL). The reaction was monitored by $^1$H-NMR (loss of C*H*$_3$C*H*$_2$ peaks at 4.14 and 1.34 ppm) and $^{31}$P-NMR (reactant 26.6 ppm, product 17.3 ppm) and stopped after 24 h. The pH of the solution was reduced to 7 by addition of HCl (1M). $CH_3OH$ (1 mL) was added to ensure all material was in solution. $Eu(OAc)_3$ (7 mg, 0.016 mmol) in a $H_2O$ : $CH_3OH$ solution (0.5 mL, 1:1 v/v) was added and the solution was stirred at 50 °C for 14 h. The solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, $CH_2Cl_2$ : 10 % $CH_3OH$ : aq. $NH_3$ solution 0 – 1 % in 0.1 % increments) to give a white solid (9.1 mg, 34 %); *m*/*z* (HRMS$^+$) 1668.498 $[M - CF_3CO_2]^+$ ($C_{83}H_{90}O_{15}N_7P_3{}^{151}Eu$ requires 1668.490); $\delta_P$ ($CD_3OD$) +17.5; $R_f$ = 0.12 (silica, $CH_2Cl_2$ : 10 % MeOH : $NH_3$ 1 %). $\tau_{MeOH} = 1.25$ ms, $\tau_{H_2O} = 0.96$ ms, $\tau_{D_2O}$ = 1.28 ms, $\Phi^{em}_{MeOH}$ = 55 ± 10 %; $\varepsilon_{MeOH}$ (332 nm) = 60, 000 M$^{-1}$ cm$^{-1}$; $t_R$ (*Method D*) = 11.5 min.

## 3. Synthesis of L$^3$

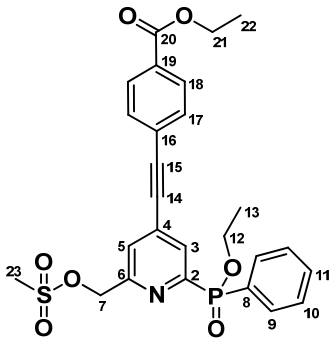
**Ethyl 4-((2-(ethoxy(phenyl)phosphoryl)-6-(hydroxymethyl)pyridin-4-yl)ethynyl)benzoate**



Ethyl (6-(hydroxymethyl)-4-(bromopyridin-2-yl)(phenyl)phosphinate (117 mg, 0.329 mmol) was dissolved in anhydrous THF (2 mL) and the solution was degassed (freeze-thaw cycle) three times. Ethyl 4-ethynylbenzoate (74 mg, 0.428 mmol) and triethylamine (0.23 mL, 1.65 mmol) were added and the solution was degassed again. [1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (27 mg, 0.033 mmol) and CuI (6 mg, 0.033 mmol) were added and the resulting brown solution was stirred at 65 °C under argon for 22 h. The solvent was removed under reduced pressure and the brown residue was purified by column chromatography (silica, $CH_2Cl_2$ : 0 − 2% $CH_3OH$ in 0.5% increments) to afford ethyl 4-((2-(ethoxy(phenyl)phosphoryl)-6-(hydroxymethyl)pyridin-4-yl)ethynyl)benzoate as a yellow oil (102 mg, 69%); $^1$H NMR (600 MHz, $CDCl_3$, $\delta$): 8.07 (1H, d, $^3J_{H\text{-}P}$ 6.1 Hz, $H^3$), 8.03 (2H, d, $^3J_{H\text{-}H}$ 8.3 Hz, $H^{18}$), 7.94 (2H, ddd, $^3J_{H\text{-}P}$ 11.8 Hz, $^3J_{H\text{-}H}$ 8.1 Hz, $^4J_{H\text{-}H}$ 1.3 Hz, $H^9$), 7.57 (2H, d, $^3J_{H\text{-}H}$ 8.3 Hz, $H^{17}$), 7.51 (2H, m, $H^5$ and $H^{11}$), 7.45 (2H, m, $H^{10}$), 4.77 (2H, m, $H^7$), 4.38 (2H, q, $^3J_{H\text{-}H}$ 7.1 Hz, $H^{21}$), 4.14 (2H, m, $H^{12}$), 4.03 (1H, br s, $CH_2OH$), 1.39 (3H, t, $^3J_{H\text{-}H}$ 7.1 Hz, $H^{22}$), 1.36 (3H, t, $^3J_{H\text{-}H}$ 7.1 Hz, $H^{13}$); $^{13}$C NMR (151 MHz, $CDCl_3$, $\delta$): 165.9 ($C^{20}$), 161.2 (d, $^3J_{C\text{-}P}$ 19 Hz, $C^6$), 153.7 (d, $^1J_{C\text{-}P}$ 166 Hz, $C^2$), 132.8 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^{11}$), 132.4 (d, $^2J_{C\text{-}P}$ 10 Hz, $C^9$), 132.0 (d, $^3J_{C\text{-}P}$ 12 Hz, $C^4$), 131.9 ($C^{17}$), 131.1 ($C^{19}$), 129.7 ($C^{18}$), 129.6 (d, $^1J_{C\text{-}P}$ 139 Hz, $C^8$), 128.6 (d, $^3J_{C\text{-}P}$ 13 Hz, $C^{10}$), 128.5 (d, $^2J_{C\text{-}P}$ 23 Hz $C^3$), 126.2 ($C^{16}$), 124.2 (d, $^4J_{C\text{-}P}$ 2 Hz, $C^5$), 94.4 ($C^{15}$), 88.3 ($C^{14}$), 64.2 ($C^7$), 62.0 (d, $^2J_{C\text{-}P}$ 6 Hz, $C^{12}$), 61.4 ($C^{21}$), 16.6 (d, $^3J_{C\text{-}P}$ 6 Hz, $C^{13}$), 14.4 ($C^{22}$); $^{31}$P NMR (243 MHz, $CDCl_3$,

$\delta$): +25.3; *m/z* (HRMS$^+$) 472.1269 [M + Na]$^+$ ($C_{25}H_{24}NO_5PNa$ requires 472.1290); $R_f$ = 0.28 (silica, $CH_2Cl_2$ : 10% $CH_3OH$).

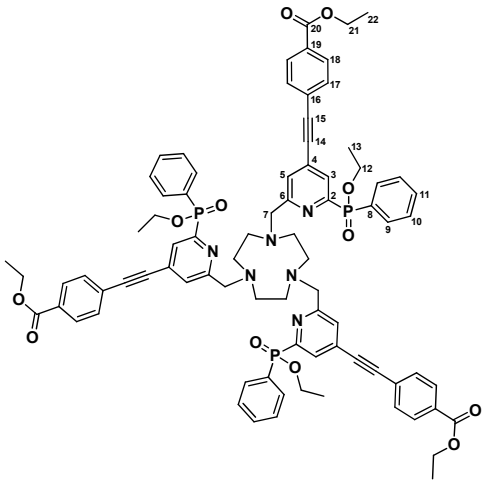
**Ethyl 4-((2-(ethoxy(phenyl)phosphoryl)-6-((methylsulfonyloxy)methyl)pyridin-4-yl)ethynyl)benzoate**



To a solution of ethyl 4-((2-(ethoxy(phenyl)phosphoryl)-6-(hydroxymethyl)pyridin-4-yl)ethynyl)benzoate (80 mg, 0.178 mmol) in anhydrous THF (1 mL) at 5 °C was added triethylamine (50 µL, 0.356 mmol) and methanesulfonyl chloride (21 µL, 0.267 mmol). The reaction mixture was stirred under argon and allowed to warm to rt. The progress of the reaction was monitored by TLC [silica; $CH_2Cl_2$ : 10% $CH_3OH$, $R_f$(product) = 0.45, $R_f$(reactant) = 0.28] and stopped after 40 min. The solvent was removed under reduced pressure and the residue was dissolved in $CH_2Cl_2$ (10 mL) and washed with sat. aq. brine solution (10 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure to afford ethyl 4-((2-(ethoxy(phenyl)phosphoryl)-6-((methylsulfonyloxy)methyl)pyridin-4-yl)ethynyl)benzoate as a yellow oil (94 mg, quant.), which was used without further purification; $^1$H NMR (200 MHz, $CDCl_3$, $\delta$): 8.14 (1H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 1.5 Hz, $H^3$), 8.03 (2H, d, $^3J_{H\text{-}H}$ 8.7 Hz, $H^{18}$), 7.94 (2H, m, $H^9$), 7.57 (2H, d, $^3J_{H\text{-}H}$ 8.7 Hz, $H^{17}$), 7.55−7.40 (4H, m, $H^5$, $H^{10}$ and $H^{11}$), 5.32 (2H, s, $H^7$), 4.36 (2H, q, $^3J_{H\text{-}H}$ 7.2 Hz, $H^{21}$),

4.12 (2H, m, $H^{12}$), 3.00 (3H, s, $H^{23}$), 1.37 (3H, t, $^{3}J_{H\text{-}H}$ 7.2 Hz, $H^{22}$), 1.36 (3H, t, $^{3}J_{H\text{-}H}$ 7.1 Hz, $H^{13}$); $^{31}$P NMR (81 MHz, $CDCl_3$, $\delta$): +25.6; *m/z* (HRMS$^{+}$) 550.1058 [M + Na]$^{+}$ ($C_{26}H_{26}NO_7PSNa$ requires 550.1065); $R_f$ = 0.45 (silica; $CH_2Cl_2$ : 10% $CH_3OH$).

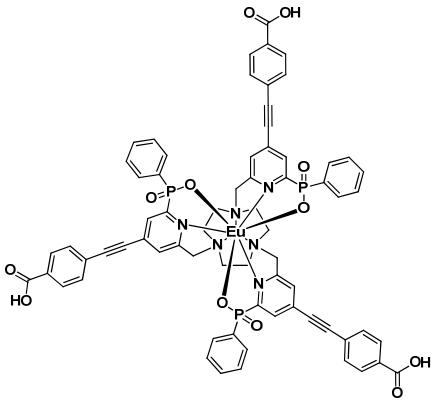
**Triethyl phenylphosphinate ester of $L^3$**



To a solution of ethyl 4-((2-(ethoxy(phenyl)phosphoryl)-6-((methylsulfonyloxy)methyl)pyridin-4-yl)ethynyl)benzoate (94 mg, 0.178 mmol) and 1,4,7-triazacyclononane (7.9 mg, 0.061 mmol) in anhydrous $CH_3CN$ (1.8 mL) was added $K_2CO_3$ (26 mg, 0.190 mmol) and the mixture was stirred under argon at 60 °C. The progress of the reaction was monitored by LC-MS analysis at regular intervals, which revealed complete consumption of starting material after 9h. The reaction mixture was cooled to room temperature and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (silica, $CH_2Cl_2$ : 0 – 20% $CH_3OH$ in 1% increments) to give the triethyl ester of $L^3$ as a colorless oil (32 mg, 37%); $^{1}$H

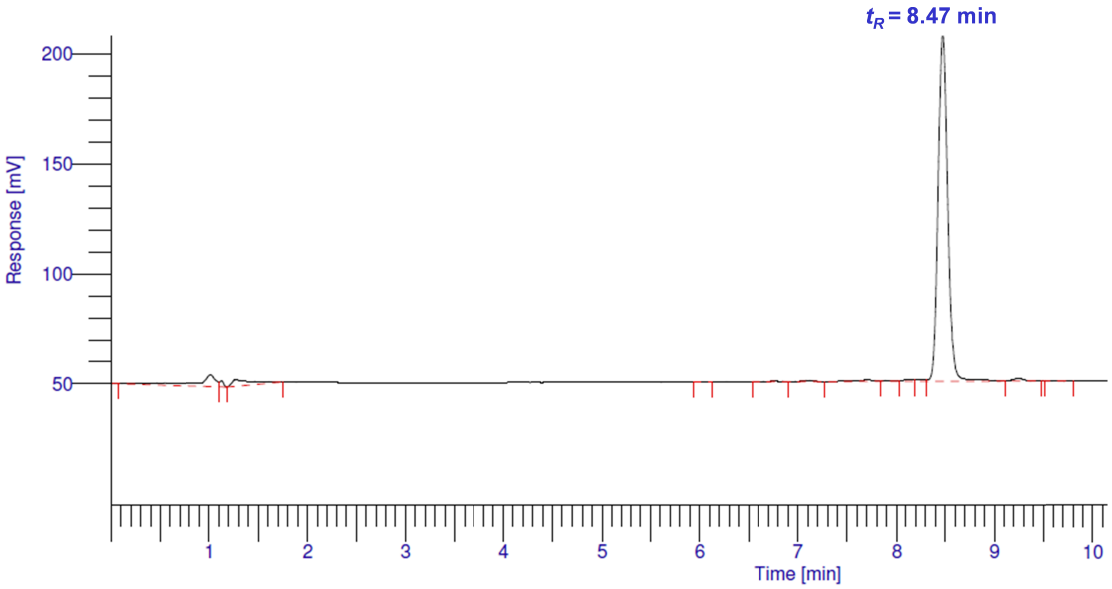
NMR (600 MHz, $CDCl_3$, $\delta$): 8.11 (3H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 1.5 Hz, $H^3$), 8.05 (6H, d, $^3J_{H\text{-}H}$ 8.3 Hz, $H^{18}$), 7.85 (6H, m, $H^9$), 7.60 (9H, m, $H^5$ and $H^{17}$), 7.48 (3H, m, $H^{11}$), 7.45 (6H, m, $H^{10}$), 4.39 (6H, q, $^3J_{H\text{-}H}$ 7.1 Hz, $H^{21}$), 4.13 (6H, m, $H^{12}$), 4.04 (6H, m, $H^7$), 2.99 (6H, br m, ring $CH_2$), 2.80 (6H, br m, ring $CH_2$), 1.41 (9H, t, $^3J_{H\text{-}H}$ 7.1 Hz, $H^{22}$), 1.36 (9H, td, $^3J_{H\text{-}H}$ 7.1 Hz, $^4J_{H\text{-}P}$ 1.0 Hz, $H^{13}$); $^{13}C$ NMR (151 MHz, $CDCl_3$, $\delta$): 165.9 ($C^{20}$), 157.1 (br m, $C^6$), 155.3 (d, $^1J_{C\text{-}P}$ 169 Hz, $C^2$), 132.9 ($C^{11}$), 132.5 (d, $^2J_{C\text{-}P}$ 10 Hz, $C^9$), 132.1 ($C^{17}$), 131.3 ($C^{19}$), 129.8 (d, $^1J_{C\text{-}P}$ 138 Hz, $C^8$), 129.7 ($C^{18}$), 128.8 (br m, $C^3$), 128.7 (d, $^3J_{C\text{-}P}$ 13 Hz, $C^{10}$), 127.8 (br m $C^5$), 126.0 ($C^{16}$), 95.3 ($C^{15}$), 88.3 ($C^{14}$), 60.5 ($C^7$), 62.0 (d, $^2J_{C\text{-}P}$ 6 Hz, $C^{12}$), 61.5 ($C^{21}$), 51.9 (6 × ring $CH_2$), 16.7 (d, $^3J_{C\text{-}P}$ 6 Hz, $C^{13}$), 14.4 ($C^{22}$), one signal ($C^4$) obscured or overlapping; $^{31}P$ NMR (243 MHz, $CDCl_3$, $\delta$): +25.0; $m/z$ ($HRMS^+$) 1423.519 $[M + H]^+$ ($C_{81}H_{82}N_6O_{12}P_3$ requires 1423.520); $R_f$ = 0.66 (silica, $CH_2Cl_2$ : 15% $CH_3OH$).

**[Eu.L$^3$]**




The triethyl ester of $L^3$ (8 mg, 5.6 μmol) was dissolved in a mixture of $CD_3OD/D_2O$ (1.5 mL, 2:1 v/v) and KOH (3.8 mg, 67.5 μmol) was added. The solution was stirred at 60 °C under argon for 18 h. The reaction was monitored by $^1H$-NMR spectroscopy (400 MHz; loss of $CH_3CH_2$ signals at 4.39, 4.13, 1.41 and 1.36 ppm) and $^{31}P$-NMR spectroscopy (162 MHz; reactant = +25.0 ppm, product = +15.4 ppm). The organic

solvent was removed under reduced pressure and the remaining aqueous mixture was neutralized by the addition of HCl (1M). Lyophilization of the solvent gave $L^3$ as a white solid, which was immediately dissolved in a mixture of $CH_3OH/H_2O$ (2 mL, 1:1 v/v). $Eu(OAc)_3$ (2.2 mg, 6.7 µmol) was added and the pH of the solution was adjusted to 5.8 by the addition of HCl (1M). The resulting cloudy mixture was stirred at 65 °C under argon for 18 h. The mixture was cooled to room temperature and the pH adjusted to 7 by the addition of KOH (1M). Lyophilisation of the solvent and purification of the crude material by semi-preparative RP-HPLC [gradient: 60 − 100% methanol in water (0.1% formic acid) over 10 min; $t_R$ = 8.47 min] gave the complex as a white solid (3.5 mg, 51%); (HRMS$^+$) 1403.223 [M($^{153}$Eu) - H]$^-$ ($C_{70}H_{54}N_6O_{14}P_3{}^{153}Eu$ requires 1403.215); $\tau_{MeOH}$ = 1.24 ms; $\Phi^{em}_{MeOH}$ = 37 ± 15%; $\varepsilon_{MeOH}$ (321 nm) = 59,200 $M^{-1}$ $cm^{-1}$.

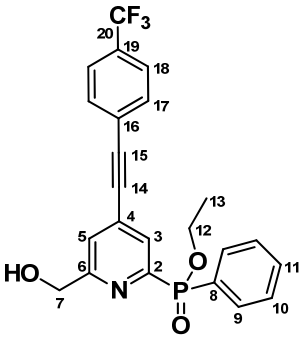



Analytical RP-HPLC of [Eu.L$^3$]: $t_R$ 8.47 min [Gradient: 60 to 100% MeOH in water (0.05% formic acid) over 10 min]

## 4. Synthesis of Eu complex of $L^4$

**Ethyl 6-(hydroxymethyl)-4-((4-(trifluoromethyl)phenyl)ethynyl)**

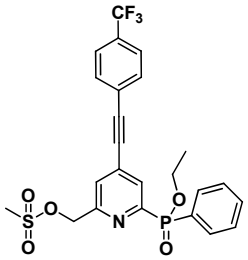
**pyridin-2-yl(phenyl)phosphinate**




Ethyl (6-(hydroxymethyl)-4-(bromopyridin-2-yl)(phenyl)phosphinate (70 mg, 0.197 mmol) was dissolved in anhydrous THF (1.2 mL) and the solution was degassed three times. 1-[(Trimethylsilyl)ethynyl]-4-(trifluoromethyl)benzene (51 μL, 0.217 mmol) and triethylamine (0.68 mL, 4.93 mmol) were added and the solution was degassed once more. Tetrakis(triphenylphosphine)palladium(0) (22 mg, 0.020 mmol) and CuI (4 mg, 0.020 mmol) were added and the resulting brown solution was stirred at 65 °C under argon for 15 h. The solvent was removed under reduced pressure and the brown residue was partitioned between $CH_2Cl_2$ (20 mL) and sat. aqueous ammonium chloride solution (20 mL). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic fractions were washed with brine (80 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a pale brown oil. The crude material was subjected to column chromatography (silica, hexane : 40 – 66% EtOAc) to afford ethyl 6-(hydroxymethyl)-4-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-2-yl(phenyl)phosphinate as a yellow oil (54 mg, 62%); $^1$H NMR (600 MHz, $CDCl_3$, $\delta$): 8.07 (1H, dd, $^3J_{H\text{-}P}$ 6.2 Hz, $^4J_{H\text{-}H}$ 1.4 Hz, $H^3$), 7.94 (2H, dd, $^3J_{H\text{-}P}$ 12.4 Hz, $^3J_{H\text{-}H}$ 8.6 Hz, $H^9$), 7.62 (4H, s, $H^{17}$ and $H^{18}$), 7.53 (2H, m, $H^5$ and $H^{11}$), 7.45 (2H, dt, $^3J_{H\text{-}P}$ 4.0 Hz, $^3J_{H\text{-}H}$ 7.6 Hz, $H^{10}$), 4.80 (2H, m, $H^7$), 4.14 (2H, m, $H^{12}$), 1.37 (3H, t, $^3J_{H\text{-}H}$ 7.0 Hz, $H^{13}$);

$^{13}$C NMR (151 MHz, $CDCl_3$, $\delta$): 161.3 (d, $^3J_{C\text{-}P}$ 19 Hz, $C^6$), 153.7 (d, $^1J_{C\text{-}P}$ 166 Hz, $C^2$), 132.8 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^{11}$), 132.4 (d, $^2J_{C\text{-}P}$ 10 Hz, $C^9$), 132.3 ($C^{17}$), 131.9 (d, $^3J_{C\text{-}P}$ 13 Hz, $C^4$), 131.2 (q, $^2J_{C\text{-}F}$ 34 Hz, $C^{19}$), 129.6 (d, $^1J_{C\text{-}P}$ 139 Hz, $C^8$), 128.6 (d, $^3J_{C\text{-}P}$ 14 Hz, $C^{10}$), 127.0 (d, $^2J_{C\text{-}P}$ 23 Hz, $C^3$), 125.6 (q, $^3J_{C\text{-}F}$ 4 Hz, $C^{18}$), 124.3 (d, $^4J_{C\text{-}P}$ 3 Hz, $C^5$), 123.9 (q, $^1J_{C\text{-}F}$ 272 Hz, $C^{20}$), 122.8 (d, $^6J_{C\text{-}P}$ 3 Hz, $C^{16}$), 93.6 ($C^{14}$), 88.3 (d, $^5J_{C\text{-}P}$ 2 Hz, $C^{15}$), 64.2 ($C^7$), 62.1 (d, $^2J_{C\text{-}P}$ 6 Hz, $C^{12}$), 16.6 (d, $^3J_{C\text{-}P}$ 6 Hz, $C^{13}$); $^{31}$P NMR (243 MHz, $CDCl_3$, $\delta$): +25.3; $^{19}$F NMR (564 MHz, $CDCl_3$, $\delta$): -63.0; *m/z* (HRMS$^+$) 468.0957 $[M + Na]^+$ ($C_{23}H_{19}NO_3PNa$ requires 468.0952); $R_f$ = 0.41 (silica, EtOAc : 33% Hexane).

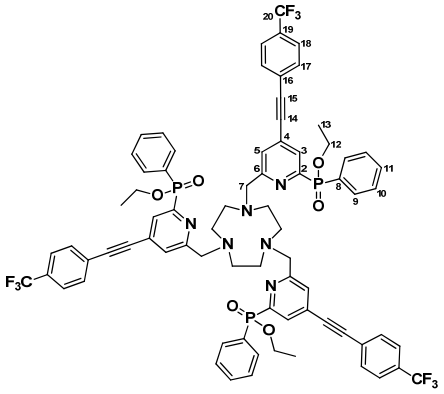
**Ethyl 6-(methylsulfonyloxy)-4-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-2-yl(phenyl)phosphinate**




Ethyl 6-(hydroxymethyl)-4-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-2-yl(phenyl)phosphinate (60 mg, 0.135 mmol) was dissolved in anhydrous THF (1.5 mL) and triethylamine (38 µL, 0.269 mmol) was added. The mixture was stirred at 5 °C under argon and methanesulfonyl chloride (13 µL, 0.162 mmol) was added. The reaction was monitored by TLC [silica; $CH_2Cl_2$ : 10% $CH_3OH$, $R_f$(product) = 0.75, $R_f$(reactant) = 0.51] and stopped after 90 min. The solvent was removed under reduced pressure and the resulting residue was dissolved in $CH_2Cl_2$ (10 mL) and washed with sat. aqueous brine solution (10 mL). The aqueous layer was extracted

with $CH_2Cl_2$ (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), and concentrated under reduced pressure to afford ethyl 6-(methylsulfonyloxy)-4-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-2-yl(phenyl)phosphinate as a yellow oil (71 mg, quant.), which was used without further purification; $R_f$ = 0.75 (silica; $CH_2Cl_2$ : 10% $CH_3OH$).

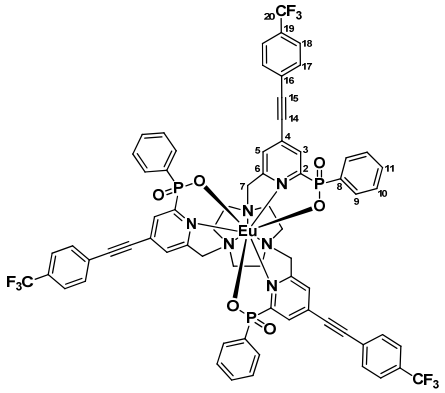
**Triethyl phenylphosphinate ester of $L^4$**



To a solution of 1,4,7-triazacyclononane (6 mg, 0.047 mmol) and ethyl 6-( methylsulfonyloxy)-4-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-2-yl(phenyl)phosphinate (71 mg, 0.135 mmol) in anhydrous $CH_3CN$ (1.5 mL) was added $K_2CO_3$ (19 mg, 0.140 mmol) and the mixture was stirred under argon at 60 °C for 3 h. The progress of the reaction was monitored by LC-MS analysis at 30 min intervals, which indicated complete consumption of starting material after 3 h. The reaction mixture was cooled to room temperature and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure and the

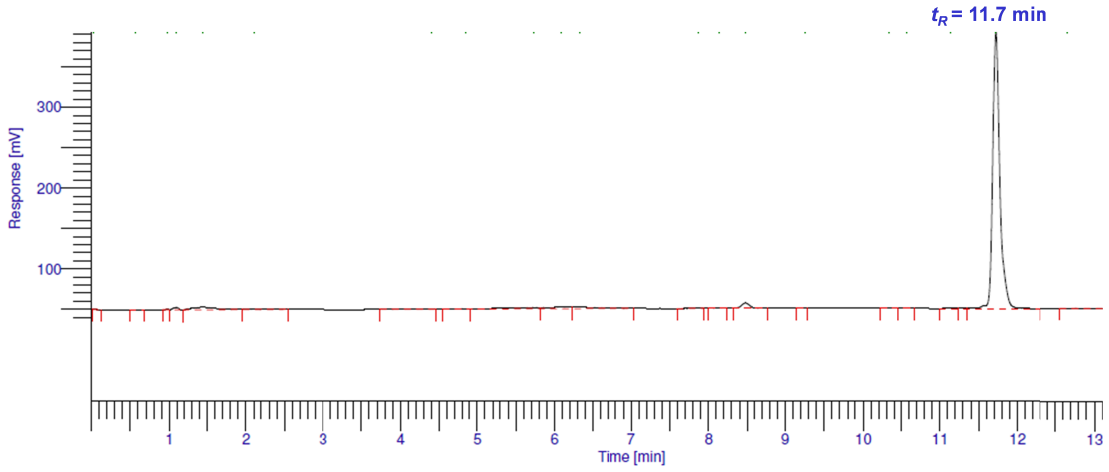
crude material was purified by column chromatography (silica, $CH_2Cl_2$ : 0 – 20% $CH_3OH$ in 1% increments) to afford the triethyl ester of $L^4$ as a colourless oil (15 mg, 23%); $^1$H NMR (600 MHz, $CDCl_3$, $\delta$): 8.10 (3H, dd, $^3J_{H\text{-}P}$ 6.0 Hz, $^4J_{H\text{-}H}$ 1.6 Hz, $H^3$), 7.86 (6H, m, $H^9$), 7.64 (12H, m, $H^{17}$ and $H^{18}$), 7.49 (6H, m, $H^5$ and $H^{11}$), 7.41 (6H, m, $H^{10}$), 4.12 (6H, m, $H^{13}$), 4.06 (6H, m, $H^7$), 3.08−2.65 (12H, br m, 6 × ring $CH_2$), 1.35 (9H, t, $^3J_{H\text{-}H}$ 7.0 Hz, $H^{13}$); $^{13}$C NMR (151 MHz, $CDCl_3$, $\delta$): 157.2 ($C^6$), 155.3 (d, $^1J_{C\text{-}P}$ 166 Hz, $C^2$), 132.8 ($C^{11}$), 132.5 ($C^9$), 132.4 ($C^{17}$), 132.2 ($C^4$), 131.4 (q, $^2J_{C\text{-}F}$ 34 Hz, $C^{19}$), 129.6 (d, $^1J_{C\text{-}P}$ 139 Hz, $C^8$), 128.6 (d, $^3J_{C\text{-}P}$ 14 Hz, $C^{10}$), 127.9 ($C^3$), 125.7 (q, $^3J_{C\text{-}F}$ 4 Hz, $C^{18}$), 125.4 ($C^5$), 123.9 (q, $^1J_{C\text{-}F}$ 272 Hz, $C^{20}$), 94.5 ($C^{14}$), 88.0 ($C^{15}$), 62.0 (d, $^2J_{C\text{-}P}$ 6 Hz, $C^{12}$), 60.4 ($C^7$), 52.0 (ring $CH_2$), 16.7 (d, $^3J_{C\text{-}P}$ 6 Hz, $C^{13}$); $^{31}$P NMR (243 MHz, $CDCl_3$, $\delta$): +25.0; $^{19}$F NMR (564 MHz, $CDCl_3$, $\delta$): -63.0; *m/z* (HRMS$^+$) 1411.416 $[M + H]^+$ ($C_{75}H_{67}F_9N_6O_6P_3$ requires 1411.419); $R_f$ = 0.29 (silica; $CH_2Cl_2$ : 10% $CH_3OH$).

**[Eu.L$^4$]**




The triethyl ester of $L^4$ (13 mg, 9.21 μmol) was dissolved in a mixture of $CD_3OD/D_2O$ (2 mL, 1:1 v/v) and KOH (10 mg, 0.18 mmol) was added. The solution was stirred at 65 °C under argon for 16 h. The reaction was monitored by $^1$H-NMR spectroscopy (400 MHz; loss of $CH_3CH_2$ signals at 4.12 and 1.35 ppm) and $^{31}$P-NMR

spectroscopy (162 MHz; reactant = +25.0 ppm, product = +16.0 ppm). The organic solvent was removed under reduced pressure and remaining aqueous mixture was neutralized by the addition of HCl (1M). Lyophilization of the solvent gave $L^4$ as a white solid [$R_f$ = 0.21 (silica, $CH_2Cl_2$/MeOH/$NH_3$, 80:18:2 v/v/v)], which was immediately dissolved in a mixture of $H_2O$/$CH_3OH$ (2 mL, 1:1 v/v). $Eu(OAc)_3$ (6 mg, 14.4 μmol) was added, resulting in the formation of a white precipitate. The pH of the solution was adjusted to 5.8 by addition of HCl (1M) and the mixture was stirred at 70 °C under argon for 18 h. The mixture was cooled to room temperature and the pH adjusted to 7 by the addition of KOH (1M). Lyophilisation of the solvent and purification of the crude material by column chromatography (silica, $CH_2Cl_2$ : 5 – 20% $CH_3OH$) gave the complex as a white solid (3 mg, 45%); (HRMS$^+$) 1477.223 [M($^{153}$Eu) + H]$^+$ ($C_{69}H_{52}F_9N_6O_6P_3{}^{153}$Eu requires 1477.222); $R_f$ = 0.43 (silica, $CH_2Cl_2$ : MeOH : $NH_3$, 80:18:2 v/v/v); $\tau_{MeOH}$ = 1.35 ms; $\Phi^{em}_{MeOH}$ = 15 ± 10%; $\varepsilon_{MeOH}$ (309 nm) = 63,500 $M^{-1}$ $cm^{-1}$.




Analytical RP-HPLC of [Eu.$L^4$]: $t_R$ 11.7 min [Gradient: 60 to 100% MeOH in water (0.05% formic acid) over 12 min]

**X-ray Crystallography**

Crystals of [Eu.L$^{2a}$] were grown from water. Data for [Eu.L$^{2a}$] were collected at 120K on a OD Gemini diffractometer (ω-scan, 0.3-0.5°/frame) equipped with Cryostream (Oxford Cryosystems) open-flow nitrogen cryostat.

The structure was solved by the charge-flipping method and refined by full-matrix least squares on $F^2$ for all data using OLEX2[1,2] and SHELXTL[3] software using least squares minimisation. All non-disordered non-hydrogen atoms were refined with anisotropic displacement parameters and every hydrogen atom was placed into a calculated position and refined in "riding"-mode. Crystallographic data for [Eu.L$^{2a}$] are reported in Table 1; CCDC 857545.

**Table 1 Crystal data and structure refinement for [Eu.L$^{2a}$]**

| | |
|---|---|
| Empirical formula | $C_{69}H_{70}EuN_6O_{14}P_3$ |
| Formula weight | 1452.18 |
| Temperature/K | 120 |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| a/Å | 17.6945(12) |
| b/Å | 17.1374(14) |
| c/Å | 22.847(2) |
| α/° | 90.00 |
| β/° | 105.313(8) |
| γ/° | 90.00 |

| | |
|---|---|
| Volume/Å$^3$ | 6682.1(9) |
| Z | 4 |
| $\rho_{calc}$mg/mm$^3$ | 1.443 |
| m/mm$^{-1}$ | 1.080 |
| F(000) | 2984.0 |
| Crystal size/mm$^3$ | 0.1948 × 0.135 × 0.0249 |
| 2Θ range for data collection | 5.1 to 50° |
| Index ranges | -20 ≤ h ≤ 21, -20 ≤ k ≤ 20, -27 ≤ l ≤ 27 |
| Reflections collected | 63485 |
| Independent reflections | 11752[R(int) = 0.2144] |
| Data/restraints/parameters | 11752/585/847 |
| Goodness-of-fit on F$^2$ | 1.201 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.1292, $wR_2$ = 0.1749 |
| Final R indexes [all data] | $R_1$ = 0.1847, $wR_2$ = 0.1950 |
| Largest diff. peak/hole / e Å$^{-3}$ | 1.34/-1.48 |

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst*. **2009**, 42, 339.
2. olex2.solve (L. J. Bourhis, O.V. Dolomanov, R. J. Gildea, J. A. K. Howard, H. Puschmann, in preparation, **2012**).
3. SHELXL, G. M. Sheldrick, *Acta Cryst.* **2008**. A64, 112.