Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Synthesis of *meta* and *para*-substituted aromatic sulfonate derivatives of polydentate phenylazaphosphinate ligands: enhancement of the water solubility of emissive europium (III) EuroTracker® dyes

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The synthesis is described of a series of *meta* and *para*-substituted phenylsulfonic acid derivatives of very bright Eu(III) complexes with arylphosphinate groups and strongly absorbing arylalkynylpyridine moieties. The synthetic route involved the early introduction of trifluoroethyl esters to protect the sulfonic acid group, withstanding the use of reagents including acetyl bromide and *m*CPBA, and tolerating acid-catalysed esterification and Sonogashira reaction conditions. The Eu(III) complexes exhibit enhanced water solubility; their photophysical properties are not perturbed significantly by introduction of the anionic sulfonate groups.

Introduction

Aromatic sulfonation is an excellent method for enhancing the water solubility of lipophilic aromatic compounds, and has been applied to create water soluble dyes and polymers [1-3], and to enhance prototropic exchange in various solid-state ionic materials.[4] Classically, aryl sulfonation occurs under forcing electrophilic conditions and the methods used for CH functionalisation are generally not suitable for multifunctional compounds with electron-rich or nucleophilic groups. [5] Therefore, various strategies have been devised to create suitable sulfonate protecting groups, typically using electron poor or sterically hindered sulfonate esters (e.g CH_2CX_3, X = F, Cl; neopentyl) to suppress the nucleophilic substitution reaction that may cleave the C-O bond. Examples have been reported in which de-protection occurs using either base, acid or enzymatic-catalysis [6-12], allowing the release of the sulfonate group in a final reaction step. The protected intermediates are stable to conventional chromatographic separation and so avoid handling the anionic systems, for which reverse-phase HPLC offers the main practicable method of purification.

In this work, we have applied the use of trifluoroethyl sulfonate esters, brought to prominence by the work of Miller, [6a] to the synthesis of a set of very emissive Eu(III) complexes, bearing

three electron-rich alkyne and phenylphosphinate ester groups. The sulfonate group has been introduced in the *meta* and *para*-positions of the phenylphosphinate moiety, and is released in a final base hydrolysis step that also unmasks the phosphinate anion. The Eu(III) complexes show good water solubility and possess a brightness, *B* (340 nm) in water of between 17 and 20 $mM^{-1}cm^{-1}$, making them amongst the most emissive europium complexes in aqueous solution.[13-15]

Results and Discussion

The target complexes (Fig. 1) include three strongly absorbing and equivalent chromophores, in which there is *meta* or *para*-sulfonic acid substituent in the phenyl ring of the phosphinate moiety. The sulfonation of this position was not expected to perturb the chromophore characteristics significantly, as the phosphorus oxygen bond and the aryl groups to which it is attached are not strongly conjugated, unlike a trigonal amide or carboxylate substituent. Previous X-ray analysis studies of these phenylphosphinate lanthanide complexes have revealed that the phenyl rings are oriented in the same direction, away from the plane of the 9-N_3 ring, and with the same relative configuration at phosphorus. [13,15,16] These structural studies also confirmed that the phosphorus-oxygen double bond lies out of the plane of the aryl rings. A simple retrosynthetic analysis suggests the intermediacy of a 2,4,6-trisubstituted pyridine, with a 4-Br group, allowing a Sonogashira coupling reaction to an arylalkyne in a final ligand assembly step.

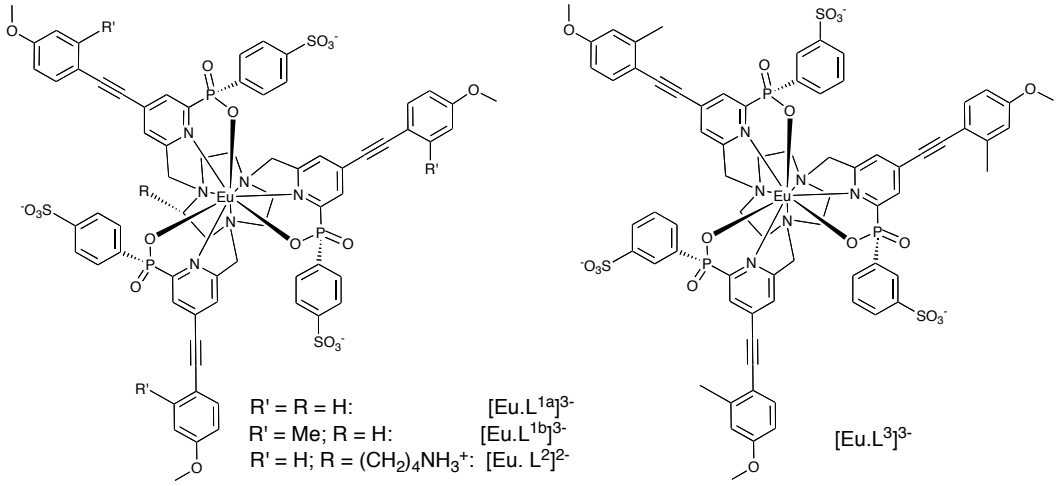
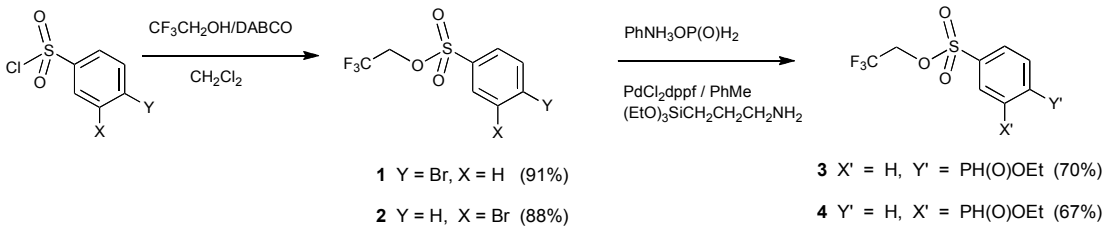


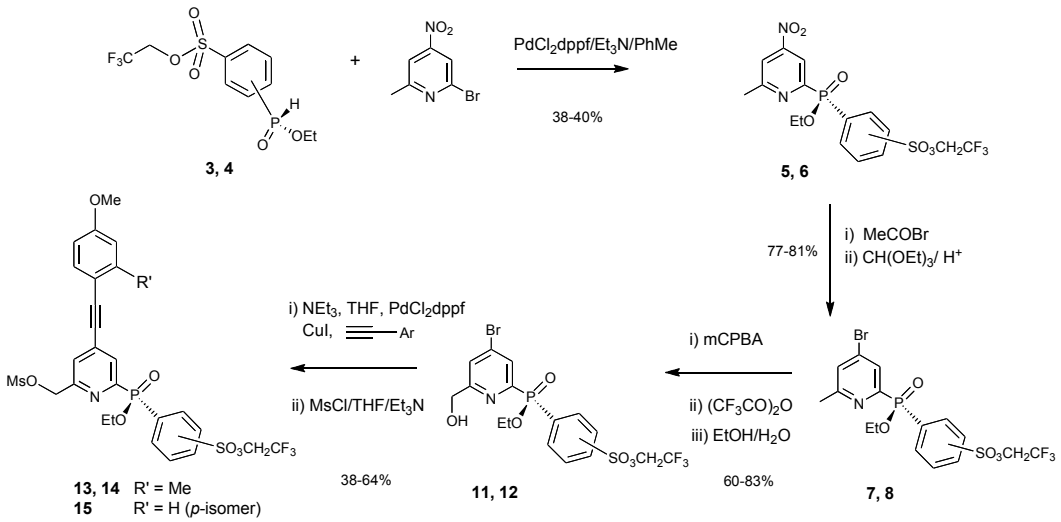
Figure 1 Structures of the sulfonated trianionic Eu(III) complexes. The unsubstituted complexes ([Eu.L^1] and [Eu.L^3] exist as racemic mixtures of *Δ* and *Λ* isomers with *SSS* and *RRR* configurations at the P centres respectively, as deduced by X-ray and CD studies on related systems. [13-16]

In order to form the C-P bond, a palladium-catalysed reaction was envisaged, allowing insertion of a 2-pyridyl group into the P-H bond of a phenylphosphinic ester, bearing a suitably protected sulfonate group. Following the studies of Miller, [6a] the behaviour of the trifluoroethyl and phenylsulfonate esters as protecting groups for the sulfonic acid moiety was examined; each ester was derived from 3 or 4-bromo-phenylsulfonyl chloride (Scheme 1). Palladium-catalysed coupling between the aryl bromide and anilinium hypophosphite proceeded in 70% yield for the trifluoroethyl ester, but failed with the phenyl ester, probably due to competitive insertion into the O-Ph bond. In this reaction, the added aminopropyltriethoxysilane serves as a base in the Pd-catalysed reaction, and enables the esterification of the phosphinic acid *in situ*. [17-19]



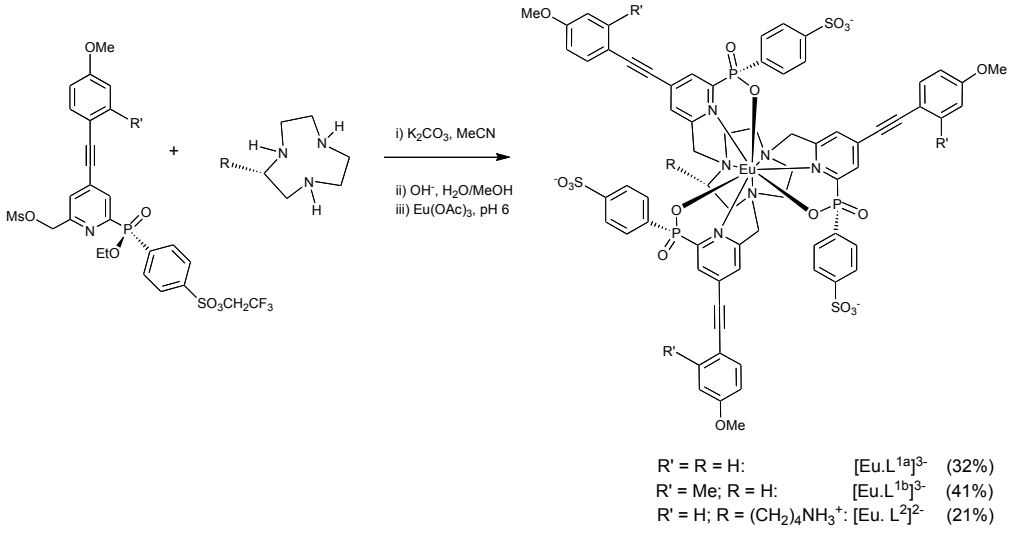
Scheme 1

The di-esters **3** and **4** were used in coupling reactions with 2-bromo-4-nitro-6-methyl pyridine in degassed toluene using Cl_2Pd[bis(diphenylphosphino)ferrocene] as the catalyst to give the phosphinate esters **5** and **6** (Scheme 2). Bromination with neat acetyl bromide followed by re-esterification of the phosphinic acid group with $HC(OEt)_3$ allowed the isolation of intermediates **7** and **8** in 77 and 81 % yield respectively. Treatment of the 4-bromo-pyridyl esters with *m*CPBA in $CHCl_3$ gave the corresponding N-oxides **9** and **10**. Activation of the proximate methyl group occurred following treatment with $(CF_3CO)_2O$, in a Boekelheide rearrangement; subsequent hydrolysis of the trifluoroacetate esters *in situ*, using wet ethanol, gave the alcohols **11** and **12**. The introduction of the aryl-alkynyl moiety by a Sonogashira coupling reaction proceeded smoothly and mesylation of the primary alcohol was effected in near quantitative yield, to furnish, for example, the triesters, **13** and **14**, with a 4-methoxy-2-methylphenyl substituent. In a similar manner, the triester **15** was prepared, with a simple 4-OMe aryl group. The introduction of the methyl group shifts the absorption wavelength of the conjugated chromophore by 7-10 nm to the red. [14,20]



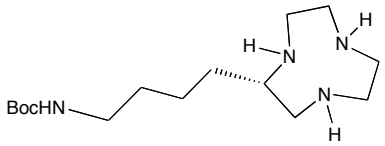
Scheme 2

Trialkylation of 1,4,7-triazacyclononane (9-N_3) with the appropriate mesylates afforded the neutral intermediates which were purified by column chromatography. Treatment with aqueous base (NaOH in water/methanol) hydrolysed the phosphinate and the sulfonate esters. In the latter case, hydrolysis of the sulfonated occurred at a similar rate to the phosphinate cleavage reaction and was conveniently monitored by observing formation of trifluoroethanol by ^{19}F NMR spectroscopy. Complexation of the ligand in aqueous methanol at pH 6 gave the Eu(III) complexes which were purified by reverse phase HPLC in the presence of triethylammonium acetate and isolated as their triethylammonium salts (Scheme 3). Ion-pair adducts of the ammonium salts were identified by ESMS (see ESI) to confirm the constitution of the isolated salt.



Scheme 3 The *meta*-sulfonated isomer, $[Eu.L^3]^{3-}$ and the ring C-substituted derivative, $[Eu.L^2]^{2-}$, were made analogously.

The C-substituted complex with a 4-aminobutyl substituent on the 9-membered ring, $[Eu.L^2]^{2-}$ was formed via alkylation of the Boc-protected amine, *S*-**16**, [21] and the Boc group was subsequently removed with TFA at room temperature, prior to base hydrolysis and europium complexation. In each case, the four Eu(III) complexes showed good water solubility (e.g. allowing 1 mM solutions to be made up readily), contrasting with the behaviour of the parent P-phenyl analogues lacking the anionic groups, where water solubility was very low, even when oxyethylene chains replaced the 4-methoxy group on the remote aryl rings. [13]



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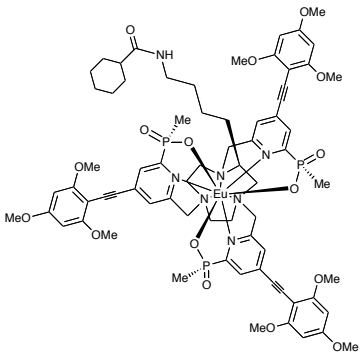
Comparison of the photophysical properties of the four europium complexes (Table 1) shows that they possess similar optical properties ($\lambda, \varepsilon, \tau, \phi$) to each other and to the parent phenylphosphinate complexes that were examined in aqueous methanol, [13,20] consistent with the absence of perturbation of the sensitiser excited state energies or the coordination environment around the Eu(III) centre. Their relative hydrophilicity was assessed by measuring log P values, measuring the partition coefficient between water and 1-octanol. The introduction of the methyl group in the three phenyl rings led to a decrease in log P, and the *meta*-sulfonated complex, rather surprisingly had a higher negative log P value than the *para*-substituted isomer (compare $[Eu.L^{1a}]^{3-}$ and $[Eu.L^3]^{3-}$) .

Table 1 Photophysical and log P data[a] for europium (III) complexes, $[Eu.L^n]$ (n = 1 - 3; 295 K, H_2O; $[Eu.L^3]^{3-}$ possesses a *meta*-SO_3^- group, and the other three examples have *para*-substituted sulfonate groups)

Complex	log P (±0.05) (octanol/water)	λ_{abs} (nm)	ε (±0.5) mM^{-1} cm^{-1}	ϕ_{em} % (±3)	τ^{Eu} ms (±0.03)
$[Eu.L^{1a}]^{3-}$	-0.7	332	58	31	1.11
$[Eu.L^{1b}]^{3-}$	-0.1	340	58.5	32	1.09
$[Eu.L^2]^{2-}$	n.d.	333	58	31	1.10
$[Eu.L^3]^{3-}$	-1.4	340	58.5	33	1.12

[a] The neutral complex analogues lacking the sulphonated groups have logP values of >+2; the neutral PMe analogue of $[Eu.L^{1a}]^{3-}$ has a log P value of +1.4.

The complex $[Eu.L^2]^{2-}$ is derived from *S*-lysine, and as shown very recently, the stereogenic centre at carbon directs the formation of a single complex enantiomer with >98% stereoselectivity, as deduced by chiral HPLC and NMR analyses.[22,24] For the europium complex derived from *S*-Lys, the configuration at each P centre is the same (*RRR*) and the metal coordination helicity is *Λ* (or M) [22-24] The complex gave rise to a very strong circularly polarized luminescence (CPL) spectrum in water, (Fig. 2), with emission dissymmetry factors (g_{em}) in the range 0.05 to 0.25. These values lie in the expected range for chiral complexes of this type. [24,25] Despite several attempts, the anionic complex was found not to be amenable to analysis by chiral HPLC under the experimental conditions (aqueous methanol gradients) that had been used to analyse the analogue, $[Eu.L^4]$. For this neutral complex, chiral HPLC had showed that a sample could be isolated with >98% enantiomeric purity. However, the enantiomeric purity (% ee) of $[Eu.L^2]^{2-}$ can also be estimated by comparing *g*(em) values for the same transitions, as the *g* value scales directly with percentage enantiomeric purity. [24]



S-Λ-*RRR*-δδδ - $[Eu.L^4]$

The *g*(em) values obtained for transitions at 654 and 598 nm were +0.18 and -0.10; given that the sample of $[Eu.L^2]^{2-}$ gave corresponding values of +0.17 and -0.10,[24] it seems reasonable to assume that the CPL spectrum and *g*(em) values refer to a sample of > 95% ee.

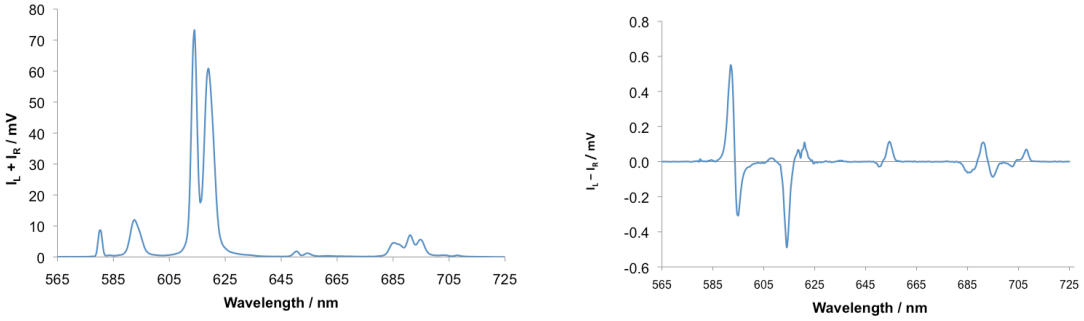


Figure 2 Total emission (left) and CPL spectrum (right) for *S-RRR-Λ*-$[Eu.L^2]^{2-}$ (295K, water, pH 6; 2 μM solution; 20 min. spectral acquisition; g_{em} (λ) values were as follows: +0.10(591); -0.10 (595.5); -0.10(598); -0.015(615); +0.18(654); -0.10(702.5); +0.25(708). Experimental errors in *g* values are ±0.01 (standard deviation on 5 consecutive measurements of the CPL spectrum).

Summary and Conclusions

The use of a trifluoroethyl ester protecting group for an aromatic sulfonic acid has facilitated the synthesis of a series of anionic sulfonated europium complexes with enhanced water solubility. The synthetic route undertaken required that the sulfonate group would withstand some vigorous reaction conditions, including treatment with an acyl bromide, *m*CPBA oxidation, acid-catalysed trans-esterification and palladium catalysed coupling reactions. The release of the trifluoroethyl ester under basic conditions in the final step permitted standard normal phase chromatography separations and purifications.

Thus, this work emphasizes the scope and utility of the synthetic approach in more complex examples than those previously examined, and allows the synthesis of highly water soluble Eu(III) complexes, in which the relatively hydrophobic aryl groups are screened by the presence of the sulfonate moities, leading to enhanced water solubility. Such features should also suppress non-specific binding to hydrophobic pockets in proteins and suppress interactions with cell membranes where anionic head groups, e.g. phospholipids are abundant.

Experimental

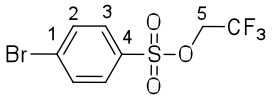
Details of instrumentation, general methods of analysis and purification methods are given in the ESI. Further detailed syntheses, spectral and HPLC data are also given in the ESI. Isolated yields for the Eu(III) complexes are based on the measured absorbance as the isolated amount of material was small and the extinction coefficients are particularly high and were assumed to be the same for the protonated precursor ligand and the complex in the same solvent. Such behaviour has been observed previously for related series of complexes with strong ICT bands, ε = 55 to 60,000 M^{-1} cm^{-1} in water and MeOH) [14,20]

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. Errors in the lifetime values are given as the standard deviation for the 10 measurements of the observed lifetime, examining emission at 620 nm, following excitation at the maximum absorption wavelength, typically around 330-340 nm. Quantum yield measurements were measured using an integrating sphere or were calculated by comparison with $Ru(bpy)_3^{2+}$ as standard (ϕ = 0.028 in aerated water) [27] as a standard. 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:

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

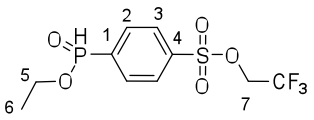
where *r* and *x* refer to reference and unknown respectively; *A* is the absorbance at λ_{ex} , which equals 340, 333 or 332 nm according to the nature of the complex (Table 1); *E* is the corrected integrated emission intensity*; I* is the corrected intensity of excitation light*;* η is the refractive index of solution. Errors in quantum yield are given as the standard deviation from the 5 separate measurements.

2,2,2-Trifluoroethyl 4-bromobenzenesulfonate, 1



4-Bromobenzenesulfonyl chloride (3.00 g, 11.7 mmol) was dissolved in DCM (20 mL) and trifluoroethanol (840 µL, 11.7 mmol) was added. A solution of DABCO (1.50 g, 13.4 mmol) in DCM (10 mL) was added resulting in precipitate formation. The reaction was stirred for 1 h at RT, after which time a solution of 1 M NaOH (3 mL) was added. The reaction was diluted in EtOAc (100 mL) and washed with 0.5 M $NaHCO_3$, 0.1 M HCl, water and brine. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to give a white solid (3.40 g, 91 %); m.p. 105 – 107 °C. Found: C, 29.8; H, 2.05 %. $C_8H_6F_3BrO_3S$ requires: C, 30.1; H, 1.88%. δ_H ($CDCl_3$) 7.77 (4H, m, $H^{2\text{-}3}$), 4.40 (2H, q, $^3J_{H\text{-}F}$ 8 Hz, H^5); δ_C ($CDCl_3$) 134.1 (C^1), 133.1 (C^3), 130.3 (C^4), 129.7 (C^2), 122.0 (q, $^1J_{C\text{-}F}$ 278 Hz, CF_3), 65.0 (q, $^2J_{C\text{-}F}$ 38 Hz, C^5); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F\text{-}H}$ 7.0 Hz); *m/z* (HRMS+) 340.9077 $[M + Na]^+$ ($C_8H_6O_3S^{79}BrF_3Na$ requires 340.9071); R_f = 0.58 (silica, EtOAc : *n*-hexane 2 : 8).

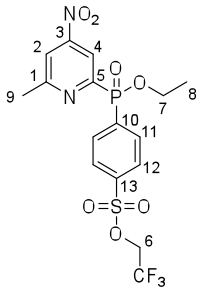
2,2,2-Trifluoroethyl 4-(ethoxyhydrophosphoryl)benzenesulfonate, 3



To a suspension of anilinium hypophosphite (1.00 g, 6.29 mmol) in dry toluene was added 2,2,2-trifluoroethyl 4-bromobenzenesulfonate (1.60 g, 5.02 mmol). Argon was bubbled through the solution for 30 min, then aminopropyltriethoxysilane (1.48 mL, 6.30 mmol) was added, and Argon was bubbled through the solution for additional 30 min. $PdCl_2(dppf)\cdot CH_2Cl_2$ (220 mg, 0.27 mmol) was added, and the mixture stirred at 100 °C for 45 min under argon. The reaction was monitored by ^{31}P-NMR [δ_P(reactant) = 7.4, δ_P(product) =

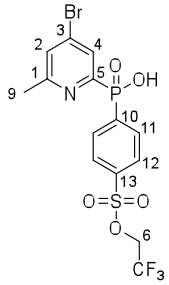
20.8, δ_P(diaryl phosphinate) = 25.5]. The solvent was removed under reduced pressure, 1 M HCl (10 mL) was added and the mixture extracted with EtOAc (3 x 20 mL). The organic fractions were combined, dried over $MgSO_4$ and concentrate to give a pale orange oil. The product was used in the next step without further purification; δ_H ($CDCl_3$) 8.03 (4H, m, H^{2-3}), 7.76 (1H, d, $^1J_{P-H}$ 576 Hz, PH), 4.43 (2H, q, $^3J_{F-H}$ 10 Hz, H^7), 4.21 (2H, m, H^5), 1.40 (3H, t, $^3J_{H-H}$ 7.0 Hz, H^6); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F-H}$ 8 Hz); δ_P ($CDCl_3$) +20.8; *m/z* (HRMS+) 333.0167 $[M + H]^+$ ($C_{10}H_{13}O_5SF_3P$ requires 333.0173).

2,2,2-Trifluoroethyl 4-(ethoxy(6-methyl-4-nitropyridin-2-yl)phosphoryl)benzenesulfonate, 5



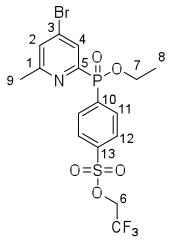
2,2,2-Trifluoroethyl 4-(ethoxyhydrophosphoryl)benzenesulfonate (1.60 g, 4.82 mmol) was added to degassed toluene (40 mL), followed by 2-bromo-6-methyl-4-nitropyridine (1.00 g, 4.61 mmol) and freshly distilled triethylamine (2.30 mL, 16.8 mmol). Argon was bubbled through the yellow solution for 30 min, then $PdCl_2(dppf)\cdot CH_2Cl_2$ (110 mg, 0.13 mmol) was added, and the mixture stirred at 120 °C for 2 h under argon, during which time the mixture turned brown. The solvent was removed under reduced pressure, with purification of the resulting black oil by column chromatography (silica, EtOAc : *n*-hexane 1:3 to 1:1) giving a colourless oil (902 mg, 40 %); δ_H ($CDCl_3$) 8.63 (1H, dd, $^3J_{H-P}$ 6.5 $^4J_{H-H}$ 1.5 Hz, H^4), 8.24 (2H, dd, $^3J_{H-P}$ 11.5 Hz, $^3J_{H-H}$ 8.5 Hz, H^{11}), 8.02 (2H, dd, $^3J_{H-H}$ 8.5 Hz, $^4J_{H-P}$ 3 Hz, H^{12}), 7.79 (1H, s, H^2), 4.42 (2H, q, $^3J_{F-H}$ 8 Hz, H^6), 4.27 – 4.09 (2H, m, H^7), 2.74 (3H, s, H^9), 1.40 (3H, t, $^3J_{H-H}$ 7.0 Hz, H^8); δ_C ($CDCl_3$) 163.5 (d, $^5J_{C-P}$ 21.5 Hz, C^1), 156.5 (d, $^1J_{C-P}$ 171 Hz, C^5), 154.2 (d, $^3J_{C-P}$ 13.5 Hz, C^3), 138.9 (d, $^5J_{C-P}$ 3.5 Hz, C^{13}), 136.5 (d, $^1J_{C-P}$ 138 Hz, C^{10}), 133.7 (d, $^2J_{C-P}$ 10 Hz, C^{11}), 127.7 (d, $^3J_{C-P}$ 13.5 Hz, C^{12}), 122.1 (q, $^1J_{C-F}$ 281 Hz, CF_3), 118.2 (s, C^2), 118.0 (d, $^2J_{C-P}$ 9 Hz, C^4), 64.8 (q, $^2J_{C-F}$ 38.5 Hz, C^6), 62.9 (d, $^2J_{C-P}$ 6.5 Hz, C^7), 24.8 (s, C^9), 16.5 (d, $^3J_{C-P}$ 6 Hz, C^8); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F-H}$ 7 Hz); δ_P ($CDCl_3$) + 20.7; *m/z* ($HRMS^+$) 469.0444 $[M + H]^+$ ($C_{16}H_{17}N_2O_7SF_3P$ requires 469.0446); R_f = 0.70 (silica, EtOAc : *n*-hexane 2 : 1).

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



2,2,2-Trifluoroethyl 4-(ethoxy(6-methyl-4-nitropyridin-2-yl)phosphoryl)benzenesulfonate (600 mg, 1.28 mmol) was dissolved in CH_3COBr (3.0 mL, 39 mmol) and the mixture stirred at 70 °C for 16 h under argon. The brown solution was dropped cautiously into CH_3OH (30 mL) stirred at 0 °C. The solvent was removed under reduced pressure to yield a pale brown solid. The resulting material, containing unidentified contaminants, was used without further purification, assuming quantitative conversion to the *p*-bromo-phosphinic acid; δ_H ($CDCl_3$) 8.42 (1H, d, $^3J_{H\text{-}P}$ 7, H^4), 8.31 (1H, s, H^2), 8.24 (2H, dd, $^3J_{H\text{-}P}$ 12.5 Hz, $^3J_{H\text{-}H}$ 8.5 Hz, H^{11}), 8.09 (2H, dd, $^3J_{H\text{-}H}$ 8.5 Hz, $^4J_{H\text{-}P}$ 2 Hz, H^{12}), 4.66 (2H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 2.81 (3H, s, H^9); δ_C ($CDCl_3$) 158.0 (d, $^5J_{C\text{-}P}$ 8 Hz, C^1), 151.0 (d, $^1J_{C\text{-}P}$ 134 Hz, C^5), 143.5 (d, $^3J_{C\text{-}P}$ 10.5 Hz, C^3), 138.9 (s, C^{13}), 138.8 (d, $^1J_{C\text{-}P}$ 155 Hz, C^{10}), 133.4 (s, C^2), 133.3 (d, $^2J_{C\text{-}P}$ 11 Hz, C^{11}), 131.5 (d, $^2J_{C\text{-}P}$ 12 Hz, C^4), 128.0 (d, $^3J_{C\text{-}P}$ 14 Hz, C^{12}), 122.2 (q, $^1J_{C\text{-}F}$ 277 Hz, CF_3), 65.1 (q, $^2J_{C\text{-}F}$ 37.5 Hz, C^6), 19.0 (s, C^9); δ_F ($CDCl_3$) -76.0 (t, $^3J_{F\text{-}H}$ 7 Hz); δ_P ($CDCl_3$) + 8.1; *m/z* ($HRMS^+$) 473.9389 $[M + H]^+$ ($C_{14}H_{13}NO_5F_3PS^{79}Br$ requires 473.9388).

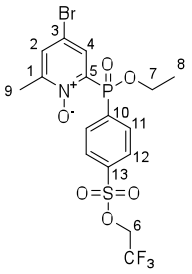
2,2,2-Trifluoroethyl 4-((4-bromo-6-methylpyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate, 7



4-Bromo-6-methylpyridin-2-yl(4-(2,2,2-trifluoroethoxysulfonyl)phenyl)phosphinic acid (606 mg, 1.28 mmol) was added to $HC(OCH_2CH_3)_3$ (25 mL) and the mixture stirred at 140 °C for 16 h under argon. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (silica, CH_2Cl_2 : 1 CH_3OH) to yield a yellow oil (530 mg, 81 % over two steps); δ_H ($CDCl_3$) 8.22 (2H, dd, $^3J_{H\text{-}P}$ 11.5 Hz, $^3J_{H\text{-}H}$ 8.5 Hz, H^{11}), 8.11 (1H, dd, $^3J_{H\text{-}P}$ 6.5, $^4J_{H\text{-}H}$ 1.5 Hz, H^4), 8.00 (2H, dd, $^3J_{H\text{-}H}$ 8.5 Hz, $^4J_{H\text{-}P}$ 3 Hz, H^{12}), 7.45 (1H, s, H^2), 4.40 (2H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 4.23 – 4.08 (2H, m, H^7), 2.54 (3H, s, H^9), 1.37 (3H, t,

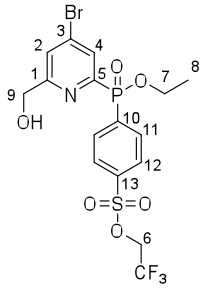
$^{3}J_{H\text{-}H}$ 7.0 Hz, H^{8}); δ_C ($CDCl_3$) 161.3 (d, $^{5}J_{C\text{-}P}$ 22 Hz, C^{1}), 153.8 (d, $^{1}J_{C\text{-}P}$ 169 Hz, C^{5}), 138.5 (d, $^{5}J_{C\text{-}P}$ 3 Hz, C^{13}), 137.3 (d, $^{1}J_{C\text{-}P}$ 136 Hz, C^{10}), 133.7 (s, C^{3}), 133.6 (d, $^{2}J_{C\text{-}P}$ 10 Hz, C^{11}), 129.2 (s, $^{4}J_{C\text{-}P}$ 3 Hz, C^{2}), 129.0 (d, $^{2}J_{C\text{-}P}$ 24 Hz, C^{4}), 127.5 (d, $^{3}J_{C\text{-}P}$ 13 Hz, C^{12}), 121.7 (q, $^{1}J_{C\text{-}F}$ 278 Hz, CF_3), 64.8 (q, $^{2}J_{C\text{-}F}$ 38.5 Hz, C^{6}), 62.6 (d, $^{2}J_{C\text{-}P}$ 6.5 Hz, C^{7}), 24.3 (s, C^{9}), 16.4 (d, $^{3}J_{C\text{-}P}$ 6.5 Hz, C^{8}); δ_F ($CDCl_3$) -74.2 (t, $^{3}J_{F\text{-}H}$ 7 Hz); δ_P ($CDCl_3$) + 21.5; *m/z* ($HRMS^{+}$) 501.9690 $[M + H]^{+}$ ($C_{16}H_{17}NO_5F_3PS^{79}Br$ requires 501.9701); R_f = 0.50 (silica, DCM : MeOH 96 : 4).

4-Bromo-2-(ethoxy(4-(2,2,2-trifluoroethoxysulfonyl)phenyl)phosphoryl)-6-methylpyridine 1-oxide



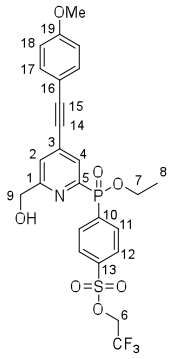
2,2,2-Trifluoroethyl 4-((4-bromo-6-methylpyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate (530 mg, 1.06 mmol) was dissolved in $CHCl_3$ (15 mL). 3-Chloroperbenzoic acid (345 mg, 2.01 mmol) was added and the solution stirred at 65 °C for 16 h. The solvent was then removed under reduced pressure, with the resulting material being re-dissolved in CH_2Cl_2 (15 mL), and washed with $NaHCO_{3(aq)}$ (0.5 M, 10 mL). The aqueous layer was re-extracted with CH_2Cl_2 (3 × 10 mL), the organic extracts combined, dried over $MgSO_4$, and the solvent removed under reduced pressure to afford a yellow oil (475 mg, 91 %); δ_H ($CDCl_3$) 8.25 (2H, dd, $^{3}J_{H\text{-}P}$ 13 Hz, $^{3}J_{H\text{-}H}$ 8.5 Hz, H^{11}), 8.12 (1H, dd, $^{3}J_{H\text{-}P}$ 8, $^{4}J_{H\text{-}H}$ 3 Hz, H^{4}), 7.99 (2H, dd, $^{3}J_{H\text{-}H}$ 8.5 Hz, $^{4}J_{H\text{-}P}$ 3 Hz, H^{12}), 7.55 (1H, d, $^{5}J_{H\text{-}P}$ 2.5 Hz, H^{2}), 4.40 (2H, q, $^{3}J_{F\text{-}H}$ 8 Hz, H^{6}), 4.26 – 4.16 (2H, m, H^{7}), 2.37 (3H, s, H^{9}), 1.40 (3H, t, $^{3}J_{H\text{-}H}$ 7.0 Hz, H^{8}); δ_C ($CDCl_3$) 150.9 (s, C^{1}), 142.8 (d, $^{1}J_{C\text{-}P}$ 153 Hz, C^{5}), 138.7 (s, C^{13}), 136.3 (d, $^{1}J_{C\text{-}P}$ 151 Hz, C^{10}), 134.2 (d, $^{2}J_{C\text{-}P}$ 11.5 Hz, C^{11}), 133.2 (d, $^{2}J_{C\text{-}P}$ 11 Hz, C^{4}), 132.7 (s, C^{2}), 127.4 (d, $^{3}J_{C\text{-}P}$ 14.5 Hz, C^{12}), 124.1 (s, C^{3}), 121.6 (q, $^{1}J_{C\text{-}F}$ 274 Hz, CF_3), 64.8 (q, $^{2}J_{C\text{-}F}$ 38.5 Hz, C^{6}), 63.0 (d, $^{2}J_{C\text{-}P}$ 6 Hz, C^{7}), 17.2 (s, C^{9}), 16.5 (d, $^{3}J_{C\text{-}P}$ 6 Hz, C^{8}); δ_F ($CDCl_3$) -74.2 (t, $^{3}J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 17.2; *m/z* ($HRMS^{+}$) 517.9650 $[M + H]^{+}$ ($C_{16}H_{17}NO_6PS^{79}BrF_3$ requires 517.9650); R_f = 0.49 (silica, DCM : MeOH 96 : 4).

2,2,2-Trifluoroethyl-4-((4-bromo-6-(hydroxymethyl)pyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate, 11



Trifluoroacetic anhydride (2.5 mL) was added to a solution of 4-bromo-2-(ethoxy(4-(2,2,2-trifluoroethoxysulfonyl)phenyl)phosphoryl)-6-methylpyridine 1-oxide (475 mg, 0.91 mmol) in dry $CHCl_3$ (20 mL). The reaction mixture was heated to 60 °C for 3 h under argon. The solvent was removed under reduced pressure and the resulting oil was dissolved in EtOH (15 mL) and H_2O (15 mL) and stirred for 1h. After this time the solution was concentrated (ca. 15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were combined, dried over $MgSO_4$, and the solvent removed under reduced pressure, giving a clear oil (430 mg, 91 %); δ_H ($CDCl_3$) 8.19-8.13 (3H, m, H^{4-11}), 8.00 (2H, dd, $^3J_{H-H}$ 8.5 Hz, $^4J_{H-P}$ 2.5 Hz, H^{12}), 7.72 (1H, s, H^2), 6.83 (1H, br, OH), 4.76 (2H, s, H^9), 4.41 (2H, q, $^3J_{F-H}$ 8 Hz, H^6), 4.29-4.04 (2H, m, H^7), 1.37 (3H, t, $^3J_{H-H}$ 7 Hz, H^8); δ_C ($CDCl_3$) 163.1 (s, $^5J_{C-P}$ 20.5 Hz, C^1), 152.8 (d, $^1J_{C-P}$ 169 Hz, C^5), 139.0 (d, $^4J_{C-P}$ 3 Hz C^{13}), 136.2 (d, $^1J_{C-P}$ 138.5 Hz, C^{10}), 134.6 (d, $^3J_{C-P}$ 15 Hz, C^3), 133.5 (d, $^2J_{C-P}$ 10.5 Hz, C^{11}), 130.3 (d, $^2J_{C-P}$ 23.5 Hz, C^4), 127.8 (d, $^3J_{C-P}$ 13.5 Hz, C^{12}), 126.8 (d, $^4J_{C-P}$ 3 Hz, C^2), 122.8 (q, $^1J_{C-F}$ 274 Hz, CF_3), 64.9 (q, $^2J_{C-F}$ 38.5 Hz, C^6), 64.0 (s, C^9), 63.2 (d, $^2J_{C-P}$ 6.5 Hz, C^7), 16.4 (d, $^3J_{C-P}$ 6 Hz, C^8); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F-H}$ 8 Hz); δ_P ($CDCl_3$) + 22.1; *m/z* ($HRMS^+$) 517.9647 $[M + H]^+$ ($C_{16}H_{17}NO_6PS^{79}BrF_3$ requires 517.9650); R_f = 0.56 (silica, DCM : MeOH 96 : 4).

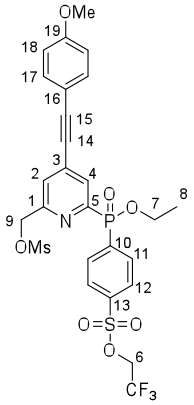
2,2,2-Trifluoroethyl-4-(ethoxy(6-(hydroxymethyl)-4-((4-methoxyphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate



2,2,2-Trifluoroethyl-4-((4-bromo-6-(hydroxymethyl)pyridin-2-yl)(ethoxy)phosphoryl)benzenesulfonate (200 mg, 0.39 mmol) was dissolved in dry THF (2.5

mL) and the solution was degassed (freeze-thaw cycle) three times. 4-Ethynylanisole (76 mg, 0.57 mmol) and NEt_3 (1.0 mL) were added and the solution degassed once more. [1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) chloride (45 mg, 55 µmol) and CuI (7 mg, 37 µmol) were added and the solution was degassed a further three times. The solution was stirred at 65 °C under argon for 16 h, solvent was removed under reduced pressure and the crude material purified by column chromatography (silica, CH_2Cl_2 : CH_3OH 0 – 2 %) to give a pale orange oil (153 mg, 69 %); δ_H ($CDCl_3$) 8.19 (2H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{11}), 8.10 (1H, s, H^4), 8.01 (2H, d, $^3J_{H\text{-}H}$ 7 Hz, H^{12}), 7.47 (3H, m, H^{17} and H^2), 6.90 (2H, d, $^3J_{H\text{-}H}$ 8.5 Hz, H^{18}), 4.78 (2H, s, H^9), 4.40 (2H, q, $^3J_{F\text{-}H}$ 7.5 Hz, H^6), 4.17 (2H, m, H^7), 3.84 (3H, s, OMe), 3.52 (1H, br, OH), 1.39 (3H, t, $^3J_{H\text{-}H}$ 6.5 Hz, H^8); δ_C ($CDCl_3$) 161.2 (s, C^1), 160.7 (s, C^{19}), 151.0 (d, $^1J_{C\text{-}P}$ 183 Hz, C^5), 138.6 (s, C^{13}), 137.4 (d, $^1J_{C\text{-}P}$ 136 Hz, C^{10}), 133.7 (s, C^{17}), 133.5 (s, C^3), 133.4 (d, $^2J_{C\text{-}P}$ 9 Hz, C^{11}), 128.9 (s, C^4), 127.7 (d, $^4J_{C\text{-}P}$ 12.5 Hz, C^{12}), 124.4 (s, C^2), 121.7 (q, $^1J_{C\text{-}F}$ 327 Hz, CF_3), 114.3 (s, C^{18}), 113.5 (s, C^{16}), 96.7 (s, C^{15}), 85.0 (s, C^{14}), 64.9 (q, $^2J_{C\text{-}F}$ 38 Hz, C^6), 64.1 (s, C^9), 62.6 (s, C^7), 55.4 (s, OMe), 16.5 (s, C^8); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 22.5; *m/z* (HRMS$^+$) 570.0973 $[M + H]^+$ ($C_{25}H_{24}F_3NO_7PS$ requires 570.0963); R_f = 0.61 (silica, DCM : MeOH 95 : 5).

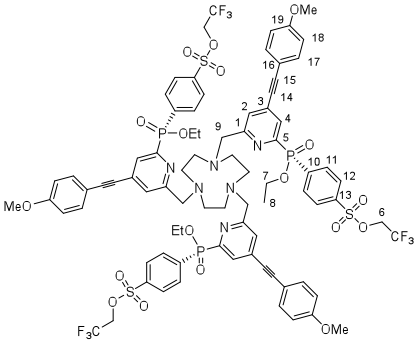
2,2,2-Trifluoroethyl-4-(ethoxy(4-((4-methoxyphenyl)ethynyl)-6-((methylsulfonyloxy)methyl)pyridin-2-yl)phosphoryl)benzenesulfonate, 15



2,2,2-Trifluoroethyl-4-(ethoxy(6-(hydroxymethyl)-4-((4-methoxyphenyl)ethynyl)pyridin-2-yl)phosphoryl)benzenesulfonate (93 mg, 0.16 mmol) was dissolved in anhydrous THF (4 mL) and NEt_3 (0.07 mL, 0.50 mmol) was added. The mixture was stirred at 5 °C and methanesulfonyl chloride (19 µL, 0.24 mmol) was added. The reaction was monitored by TLC (silica; CH_2Cl_2 : 5 % CH_3OH, R_f(product) = 0.75, R_f(reactant) = 0.61) and stopped after 30 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 afford a colourless oil (95 mg, 92 %); δ_H ($CDCl_3$) 8.22 (2H, dd, $^3J_{H\text{-}P}$ 11.5 Hz, $^3J_{H\text{-}H}$ 8.5 Hz, H^{11}), 8.17 (1H, d, $^3J_{H\text{-}H}$ 6.5 Hz, H^4), 8.02 (2H, dd, $^3J_{H\text{-}H}$ 8.5 Hz, $^4J_{H\text{-}P}$ 2.5 Hz, H^{12}), 7.62 (1H, s, H^2), 7.50 (2H, d, $^3J_{H\text{-}H}$ 9 Hz, H^{17}), 6.91 (2H, d, $^3J_{H\text{-}H}$ 9 Hz, H^{18}), 5.32 (2H, m, H^9), 4.42 (2H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 4.18 (2H, m, H^7), 3.85 (3H, s, OMe), 3.08 (3H, s, Ms), 1.40 (3H, t, $^3J_{H\text{-}H}$ 7 Hz, H^8); δ_F ($CDCl_3$) -74.1 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 21.9; *m/z* (HRMS$^+$) 648.0728 $[M + H]^+$ ($C_{26}H_{26}F_3NO_9PS_2$ requires 648.0739); R_f = 0.75 (silica, DCM : MeOH 95 : 5).

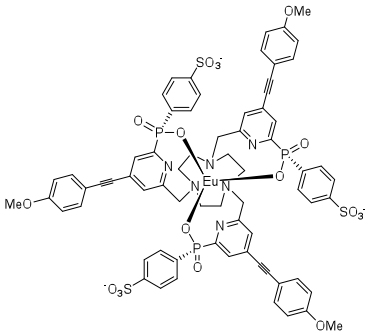
2,2,2-Trifluoroethyl 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(ethoxyphosphoryl benzenesulfonate)



1,4,7-Triazacyclononane hydrochloride salt (2.5 mg, 10 µmol) and 2,2,2-trifluoroethyl 4-(ethoxy(4-((4-methoxyphenyl)ethynyl)-6-((methylsulfonyloxy)methyl)pyridin-2-yl)phosphoryl)benzenesulfonate (20 mg, 29 µmol) were dissolved in anhydrous CH_3CN (1 mL) and K_2CO_3 (8.0 mg, 58 µmol) was added. The mixture was stirred under argon at 60 °C for 16 h. The reaction was cooled and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure and the crude product purified by HPLC ((XBridge C_{18} column, 19 x 100 mm, i.d. 5 µm) flow rate of 17 mL / min with H_2O (0.1 % formic acid) – 40 % MeOH (0.1 % formic acid) as eluents (3 min) [linear gradient to 100 % MeOH (15 min)], t_R = 12.6 min) to give a pale yellow oil (7.5 mg, 42 %); δ_H ($CDCl_3$) 8.18 (6H, dd, $^3J_{H\text{-}P}$ 11.5 Hz, $^3J_{H\text{-}H}$ 8.5 Hz, H^{11}), 8.05 (3H, d, $^3J_{H\text{-}H}$ 6 Hz, H^4), 7.97 (6H, dd, $^3J_{H\text{-}H}$ 8.5 Hz, $^4J_{H\text{-}P}$ 2 Hz, H^{12}), 7.62 (3H, s, H^2), 7.45 (6H, d, $^3J_{H\text{-}H}$ 9 Hz, H^{17}), 6.88 (6H, d, $^3J_{H\text{-}H}$ 9 Hz, H^{18}), 4.40 (6H, q, $^3J_{F\text{-}H}$ 8 Hz, H^6), 4.20 - 4.06 (6H, m, H^7), 3.87 (6H, s, H^9), 3.82 (9H, s, OMe), 2.81 (12H, br, $9N_3$), 1.34 (9H, t, $^3J_{H\text{-}H}$ 7 Hz, H^8); δ_C ($CDCl_3$) 160.9 (s, C^1), 160.7 (s, C^{19}), 153.0 (d, $^1J_{C\text{-}P}$ 184 Hz, C^5), 138.4 (s, C^{13}), 137.4 (d, $^1J_{C\text{-}P}$ 138 Hz, C^{10}), 133.6 (s, C^{17}), 133.5 (d, $^2J_{C\text{-}P}$ 9.5 Hz, C^{11}), 128.1 (d, $^2J_{C\text{-}P}$ 12 Hz, C^4), 128.2 (s, C^3), 127.5 (d, $^4J_{C\text{-}P}$ 13.5 Hz, C^{12}), 127.0 (s, C^2), 121.7 (q, $^1J_{C\text{-}F}$ 329 Hz, CF_3), 114.3 (s, C^{18}), 113.5 (s, C^{16}), 96.3 (s, C^{15}),

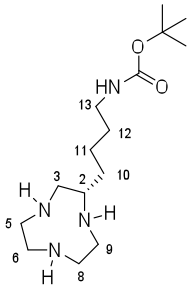
85.0 (s, C^{14}), 64.8 (q, $^2J_{C\text{-}F}$ 37 Hz, C^6), 62.9 (s, C^9), 62.3 (d, $^2J_{C\text{-}P}$ 14 Hz, C^7), 55.5 (OMe), 55.2-54.5 (br, $9N_3$), 16.5 (s, C^8); δ_F ($CDCl_3$) -74.1 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 22.5; *m/z* ($HRMS^+$) 1783.362 $[M + H]^+$ ($C_{81}H_{79}F_9N_6O_{18}P_3S_3$ requires 1783.368).

Eu(III) complex of 6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(hydroxyphosphoryl benzenesulfonate), $[Eu.L^{1a}]^{3-}$



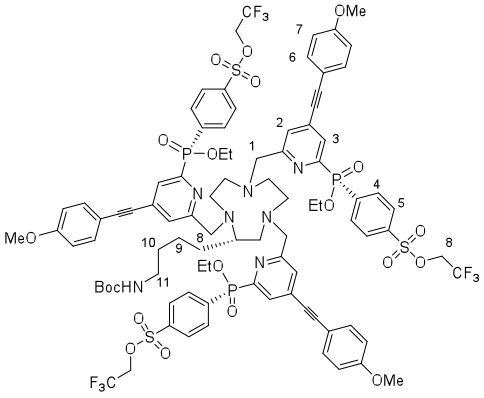
2,2,2-Trifluoroethyl-6,6',6''-(1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(ethoxyphosphoryl benzenesulfonate) (3.0 mg, 1.7 µmol) was dissolved in CD_3OD (1 mL) and a solution of 0.1 M NaOH in D_2O (0.5 mL) was added. The mixture was heated to 60 °C under argon and monitored with ^{19}F-NMR [δ_F(reactant) = - 76.0, (δ_F(product, trifluoroethanol) = - 78.0] and ^{31}P-NMR [δ_P(reactant) = + 23.1, (δ_P(product) = + 14.9]. After 3 h the solution was cooled to RT and the pH was adjusted to 7 with HCl. $Eu(Cl)_36H_2O$ (0.7 mg, 1.7 µmol) was added and the mixture heated to 65 °C overnight under argon. The solvent was removed under reduced pressure and the product purified by HPLC ((XBridge C_{18} column, 19 x 100 mm, i.d. 5 µm) flow rate of 17 mL / min with H_2O (25 mM triethylammonium acetate buffer, pH = 7) – 2 % CH_3CN) as eluents (3 min) [linear gradient to 40 % MeOH (15 min), linear gradient to 100 % MeOH (3 min)], t_R = 17.7 min) giving the triethylammonium salt as a white solid (2.0 mg, 60 %); ($HRMS^-$) 1599.146 $[EuL^{1a}H_2]^-$ ($C_{69}H_{59}{}^{151}EuN_6O_{18}P_3S_3$ requires 1599.146); τ H_2O = 1.11 ms; λ_{max} = 332 nm. Evidence for the presence of the triethylammonium cation in the isolated salt was provided by examination of the positive ion channel (Et_3NH^+ observed at 102) and by the observation in negative ion mode of the ion-pair adducts with one and two triethylammonium ions at 102 and 204 mass units above the major species (see ESI). The isolated yield here is an estimate (±10%, depending on the degree of hydration of the product), deduced by measuring the absorbance of a weighed sample of the HPLC-purified europium complex, assuming that the extinction coefficient was the same as that of the protonated ligand chromophore, in the same solvent (Table 1).

(*S*)-*tert*-Butyl 4-(1,4,7-triazacyclononane-2-yl)butylcarbamate



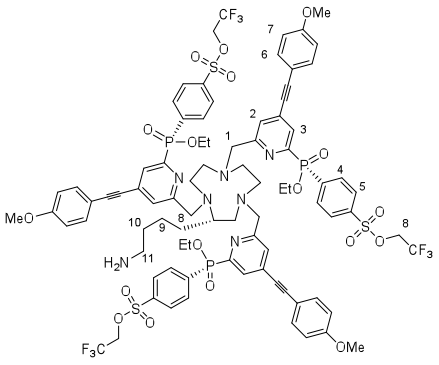
The tetrahydrochloride salt of (*S*)-4-(1,4,7-triazacyclononane-2-yl)butan-1-amine[21] was converted into the free tetra-amine (66 mg, 0.33 mmol) by anion exchange chromatography using DOWEX 1x2-200 resin (hydroxide form). The free amine was dissolved in MeOH (4 mL) and $CuCl_2.H_2O$ (56 mg, 1.33 mmol) was added, resulting in an intense green mixture. The mixture was stirred at RT under argon for 2 h, after which the solvent was removed and the green solid was dissolved in H_2O (2 mL). A solution of BOC-anhydride (140 mg, 0.66 mmol) in dioxane (2 mL) was added and the solution was stirred at RT. After 3h another equivalent of BOC-anhydride (70 mg) was added and the reaction was stirred for 16 h. At this time, LC-MS revealed complete consumption of starting material. The blue solution was treated with H_2S over 5 min and the mixture was centrifuged to remove the dark precipitate. The supernatant was washed with DCM and the pH was adjusted to 11 before extracting repeatedly with DCM. The organic layer was concentrated to give a colourless oil (54 mg, 55 %); δ_H ($CDCl_3$): 6.46 (1H, br, CONH), 3.13 (2H, m, H^{13}), 2.89-2.67 (10H, m, $H^{3\text{-}5\text{-}6\text{-}8\text{-}9}$), 2.47 (1H, m, H^2), 2.35 (3H, br, NH), 1.47 (9H, s, CH_3(Boc)), 1.49-1.35 (6H, m, $H^{10\text{-}11\text{-}12}$); δ_C ($CDCl_3$): 156.3 (CO), 79.3 (C(Boc)), 55.2 (C^2), 49.9, 46.2, 45.3, 44.3, 40.6 ($C^{3\text{-}5\text{-}6\text{-}8\text{-}9}$), 40.3($C^{13}$), 33.9, 30.4, 23.7, ($C^{10\text{-}11\text{-}12}$), 28.6 ($CH_3$(Boc)); (HRMS$^+$) 301.2603 $[M + H]^+$ ($C_{15}H_{33}N_4O_2$ requires 301.2604). Analysis of the enantiomeric purity of this amine by 1-H NMR using *R*-O-acetyl mandelic acid ($CDCl_3$, 500MHz, 295K) as a chiral solvating agent [26] confirmed the enantiomeric purity to be > 97%. [22,24]

Tert-butyl-4-((S)-1,4,7-tris((6-(ethoxy(4-(2,2,2-trifluoroethyl)phosphoryl benzenesulfonate)-4-((4-methoxyphenyl)ethynyl)pyridin-2-yl)methyl)-1,4,7-triazacyclononane-2-yl)butylcarbamate



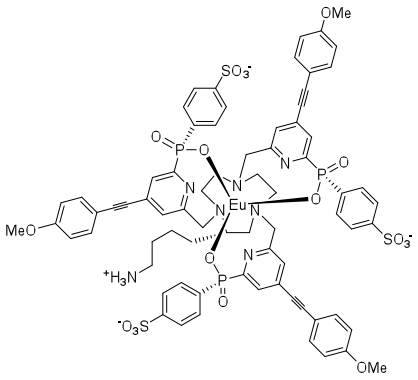
(*S*)-*tert*-Butyl 4-(1,4,7-triazacyclononane-2-yl)butylcarbamate (15 mg, 0.05 mmol) and 2,2,2-trifluoroethyl-4-(ethoxy(4-((4-methoxyphenyl)ethynyl)-6-((methylsulfonyloxy)methyl)pyridin-2-yl)phosphoryl)benzenesulfonate (95 mg, 0.15 mmol), were dissolved in anhydrous CH_3CN (2 mL) and K_2CO_3 (21 mg, 0.15 mmol) was added. The mixture was stirred under argon at 60 °C for 16 h. The reaction was cooled and the solution decanted from excess potassium salts. The solvent was removed under reduced pressure and the crude product purified by HPLC ((XBridge C_{18} column, 19 x 100 mm, i.d. 5 μm) flow rate of 17 mL / min with H_2O (0.1 % formic acid) – 30 % MeOH (0.1 % formic acid) as eluents (3 min) [linear gradient to 100 % MeOH (15 min)].t_R = 14.1 min) to give a pale yellow oil (32 mg, 33 %); δ_H ($CDCl_3$) 8.18 (6H, m, H^4), 8.04 (3H, m, H^3), 7.96 (6H, m, H^5), 7.48 (3H, m, H^2), 7.44 (6H, m, H^6), 6.88 (6H, m, H^7), 5.08 (1H, br, CONH), 4.40 (6H, q, $^3J_{F\text{-}H}$ 7.5 Hz, H^8), 4.14 (6H, m, P-OCH_2), 3.83 (15H, m, H^1 and OMe), 3.00-2.56 (13H, m, $9N_3$ ring protons and H^{11}), 1.38 (9H, s, Boc), 1.45-1.30 (6H, m, $H^{10\text{-}9\text{-}8}$), 1.35 (9H, m, CH_3(Et)); δ_F ($CDCl_3$) -74.2 (t, $^3J_{F\text{-}H}$ 8 Hz); δ_P ($CDCl_3$) + 22.6; *m/z* (HRMS$^+$) 977.7515 $[M + 2H]^{2+}$ ($C_{90}H_{97}F_9N_7O_{20}P_3S_3$ requires 977.7510).

2,2,2-Trifluoroethyl-6,6',6''-((*S*)-2-(4-aminobutyl)-1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(ethoxy phosphoryl benzenesulfonate)



Tert-butyl 4-((*S*)-1,4,7-tris((6-(ethoxy(4-(2,2,2-trifluoroethyl)phosphoryl benzenesulfonate)-4-((4-methoxyphenyl)ethynyl)pyridin-2-yl)methyl)-1,4,7-triazacyclononane-2-yl)butylcarbamate (30 mg, 15 μmol) was dissolved in dry DCM (1.8 mL). Argon was bubbled for 10 min after which time TFA (0.2 mL) was added. The solution was stirred for 20 min and the solvent was removed under reduced pressure to give a yellow oil (16 mg, 60 %); δ_H (CD_3OD) 8.11 (6H, m, H^4), 8.04 (3H, m, H^3), 8.01 (6H, m, H^5), 7.61 (3H, m, H^2), 7.57 (6H, m, H^6), 6.93 (6H, m, H^7), 4.65 (6H, m, H^6), 4.17 (6H, m, P-OCH_2), 3.96 (15H, m, H^1 and OMe), 3.82-3.60 (13H, m, $9N_3$ and H^{11}), 1.61-1.47 (6H, m, $H^{10\text{-}9\text{-}8}$), 1.46 (9H, m, CH_3(Et)); δ_F (CD_3OD) -76.0 (br); δ_P (CD_3OD) + 23.6; *m/z* ($HRMS^+$) 1854.437 $[M + H]^+$ ($C_{85}H_{88}N_7O_{18}F_9P_3S_3$ requires 1854.442).

Eu(III) complex of 6,6',6''-((*S*)-2-(4-aminobutyl)-1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(hydroxyphosphoryl benzenesulfonate), $[Eu.L^2]^{2-}$



2,2,2-Trifluoroethyl-6,6',6''-((*S*)-2-(4-aminobutyl)-1,4,7-triazacyclononane-1,4,7-triyl)tris(methylene)tris(4-((4-methoxyphenyl)ethynyl)pyridine-6,2-diyl)tris(4-(ethoxy phosphoryl benzenesulfonate) (5.0 mg, 2.7 μmol) was dissolved in CD_3OD (1 mL) and a solution of 0.1 M NaOH in D_2O (0.5 mL) was added. The mixture was heated to 60 °C under argon and monitored with ^{19}F-NMR [δ_F(reactant) = - 76.0, (δ_F(product, trifluoroethanol) = - 77.7] and ^{31}P-NMR [δ_P(reactant) = + 23.6, (δ_P(product) = + 15.1]. After 3 h the solution was cooled to RT and the pH was adjusted to 7 with dilute HCl. $Eu(Cl)_36H_2O$ (1.0 mg, 2.7 μmol) was added and the mixture heated to 65 °C overnight under argon. The solvent was removed under reduced pressure and the product purified by HPLC ((XBridge C_{18} column, 19 x 100 mm, i.d. 5 μm) flow rate of 17 mL / min with H_2O (25 mM triethylammonium acetate buffer, pH = 7) – 2 % CH_3CN) as eluents (3 min) [linear gradient to 40% MeOH (15 min), linear gradient to 100% MeOH (3 min)], t_R = 16.1 min) giving the triethylammonium salt as a white solid (2.8 mg, 54 %); ($HRMS^-$) 1671.237 $[EuL^{1b}H_2]^-$ ($C_{73}H_{68}{}^{151}EuN_7O_{18}P_3S_3$ requires

1671.238); τ H_2O = 1.13 ms; λ_{max} = 332 nm. As this highly charged complex was not amenable to chiral HPLC analysis in the same manner as the uncharged analogues reported earlier, an estimation of the enantiomeric purity of the product was made by comparing the CPL g_{em} values at 654 and 598 nm (see main text).

Acknowledgements We thank the ERC (FCC 266804), Cisbio Bioassays (MD) and the EPSRC for support.

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