Tetrahedron 117-118 (2022) 132831

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Extended sulfonated bipyridine ligands targeting the *para*-selective borylation of arenes

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ARTICLE INFO

Article history:
Received 9 March 2022
Received in revised form
9 May 2022
Accepted 13 May 2022
Available online 18 May 2022

Dedicated to Professor Franziska Schoenebeck on her receipt of the 2022 Tetrahedron Young Investigator Award.

Keywords:
C–H activation
Borylation
Non-covalent interactions
Para-selectivity

ABSTRACT

Iridium-catalysed borylation of arenes is one of the most widely used metal-catalysed C–H activation processes to elaborate aromatic rings. Exercising catalyst control over regioselectivity of the C–H oxidative addition step remains an area of active research. In this paper we describe the synthesis of a selection of sulfonated bipyridine ligands in which there is an arene spacer between the sulfonate group and the bipyridine backbone. In comparison to our previous work which achieved *meta*-selective borylation and in which the sulfonated bipyridine bore no spacer, we hoped that these extended ligands may allow a larger macrocyclic transition state for C–H activation thus favouring the *para*-position. The synthesised ligands have been evaluated on a series of arenes bearing amides and quaternary ammonium salts at varying distances from the aromatic ring.

1. Introduction

The iridium-catalysed borylation of arenes has emerged since its first development two decades ago as a leading method for arene C–H functionalization [1]. The mild and functional group tolerant reaction protocol, combined with the fantastically broad utility of boronate substituents for further functionalization has meant that this method has been utilised extensively in both academia and industry. A further unique aspect of iridium-catalysed borylation is the regioselectivity, which is majorly controlled by relative steric factors at different possible reaction sites on the arene [2]. Electronic factors derived from existing substituents have only a very minor impact, which sets it apart from many other commonly used arene functionalization methods [3]. This sterically controlled regioselectivity has meant that 1,3-disusbstituted arenes, wherein borylation occurs at the 5-position, have been heavily used as substrates for borylation. Over the years, various inventive strategies have been developed which can direct borylation to occur proximal to a particular functional group, at the arene *ortho* position [4]. An arguably greater challenge arises when one seeks to direct borylation to a more remote site, such as the *meta* or *para* position, in a substrate where there is no assisting steric constraint [5]. Traditional modes of direction in C–H functionalization struggle to reach beyond the *ortho* position to these more remote sites. Recent years have seen increased efforts from the synthetic community to overcome this challenge and remarkable advancements have been achieved using various approaches with a range of different catalytic systems [6]. The very mild and tolerant conditions that iridium-catalysed borylation chemistry typically operates under, combined with the non-polar solvents in which it often works best, mean that borylation has become an active testing ground for applying long-range directing strategies that rely on non-covalent interactions between ligand and substrate, typically in an elaborated ligand for Ir which operates in a bifunctional manner. The earliest example of this was a *meta*-selective borylation guided by a hydrogen bonding urea ligand, as first reported in 2015 by Kanai, Kuninobu and co-workers [7]. Our own group in 2016 reported a related strategy in which ion-pairing interactions between ligand and substrate were employed and we subsequently were able to use the same sulfonated bipyridine in hydrogen bonding mode [8]. Chattopadhyay in 2017 reported a *para*-selective borylation in which an ion-dipole interaction between deprotonated ligand and substrate was proposed and then in 2018 a *meta*-selective version using the same strategy [9]. In 2020 we adapted

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https://doi.org/10.1016/j.tet.2022.132831

our hydrogen bond-directed protocol to allow enantioselective, desymmetrising borylation by replacing the achiral tetrabutylammonium cation of the ligand with a chiral cation [10]. Most recently, Chattopadhyay and co-workers discovered a *meta*-selective borylation in which attraction between dipoles in ligand and substrate are proposed responsible [11]. These advances sit alongside longer range directed borylations that have been achieved by way of covalent interactions between substrate and some component of the Ir-complex [12].

The sulfonated bipyridine ligand developed by our group proved to be generally applicable, allowing *meta*-selective borylation through ion-pairing[[8a,8c,8d]] and hydrogen bonding[[8b,10]] interactions (Fig. 1a). Encouraged by this generality, we questioned whether extending the structure of this ligand may allow a longer reach and thus enable *para*-selective arene borylation. Of all three arene positions, there have arguably been fewest developments for *para*-selective borylation (Fig. 1b) [13]. Saito, Segawa and Itami used a bulky, chiral phosphine ligand to create a highly sterically congested environment at iridium [14]. Nakao and co-workers used a bulky Lewis acid catalyst to complex aromatic amides, providing substrate activation as well as ensuring borylation occurs at the *para* position for steric reasons [15]. Chattopadhyay and co-workers proposed that an electrostatic interaction between the potassium salt of the ligand and the substrate was repsonsible for *para* selectivity with their 'L-shaped' bifuncional bipyridine ligand [9a]. Our group and the groups of Maleczka and Smith in 2019 independently reported a strategy in which a bulky tetraalkylammonium cation associated with anionic arene substrates forces borylation to the *para* position by virtue of steric repulsion [16]. In 2022 Chattopadhyay and co-workers developed a new ligand for para-selective boryaltion of twisted amides [17]. Despite these advances, because of the importance of C–H borylation as a tool for synthetic chemists, this challenge warrants further attention.

At the outset of this work, we hypothesized that including an aromatic spacer between the sulfonate and the bipyridine in our original ligand design should increase the distance between the sulfonate group and the iridium metal centre and thus influence the regioselectivity between the *meta* and *para* positions in a directed borylation, potentially biassing it towards the *para* position (Fig. 1c). In this Article we report the synthesis of a selection of seven varied ligands possessing such an aromatic spacer and evaluate their regioselectivity in both ion-pair directed and hydrogen bond directed borylation [18].

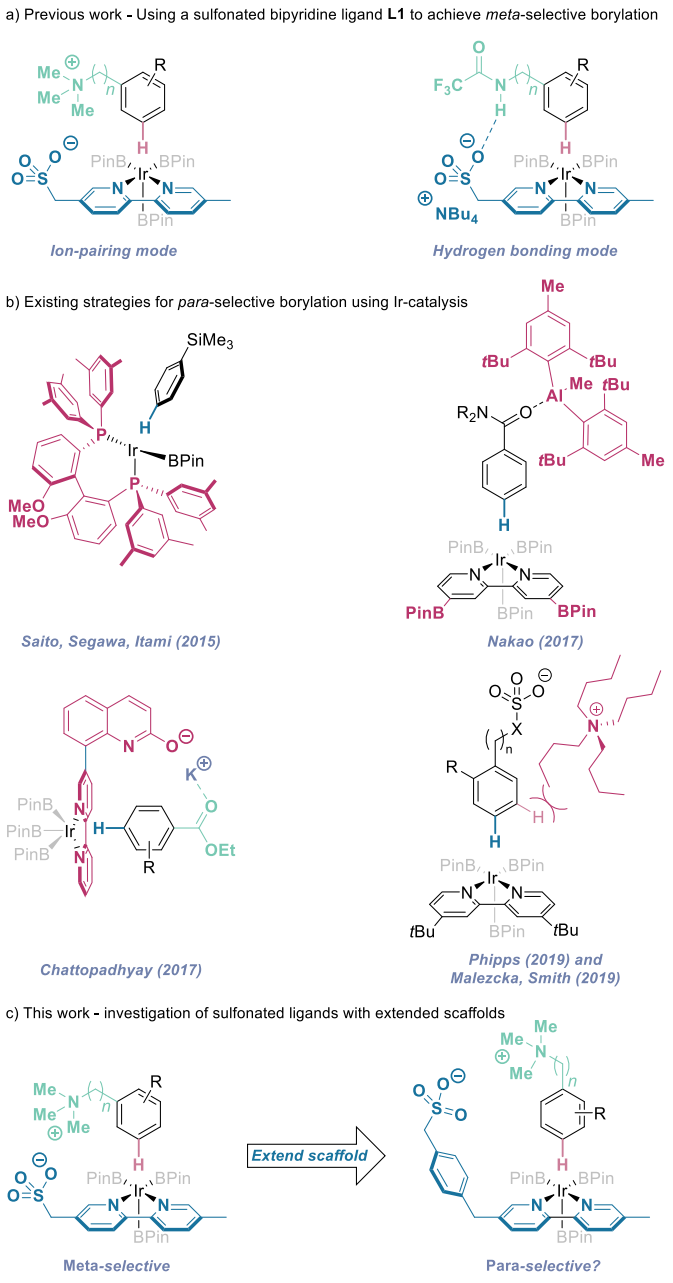


Fig. 1. *Our previous approach to* meta*-selective Ir-catalysed borylation, previous* para*-selective Ir-catalysed borylation methods and our strategy to achieve this using extended sulfonated bipyridine ligands.*

2. Results and discussion

We targeted four different ligand scaffolds (**L2-L5**) possessing the requisite aromatic spacer (Fig. 2). These scaffolds encompass variations in which the sulfonate is located at the *meta* and the *para* position of the spacer, with respect to the bipyridine attachment as well as the spacer being connected to the 4- and 5-position of the bipyridine.

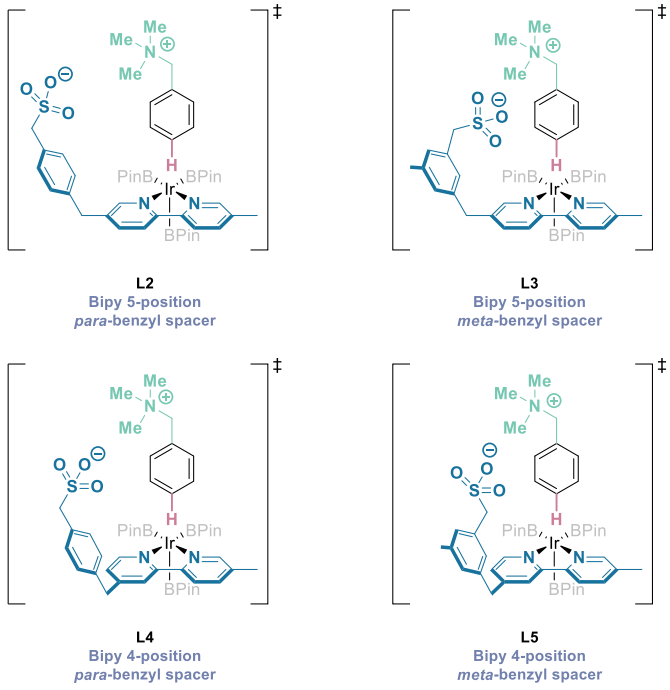
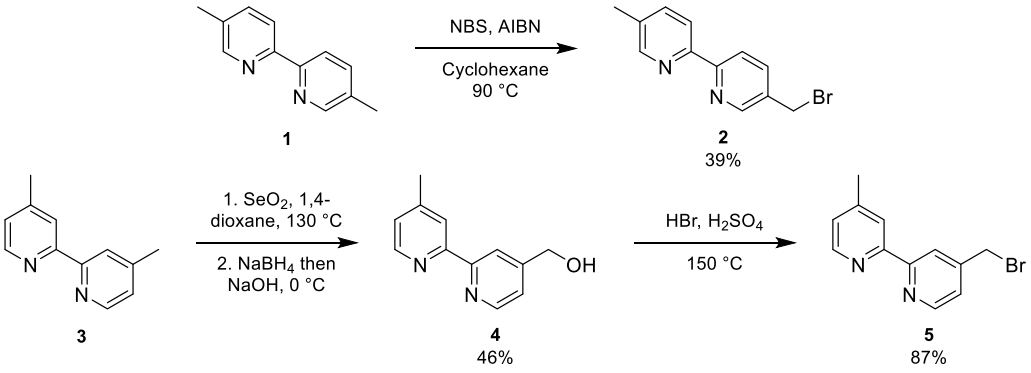


Fig. 2. Ligand designs **L2-L5** for investigation of para-selective borylation.

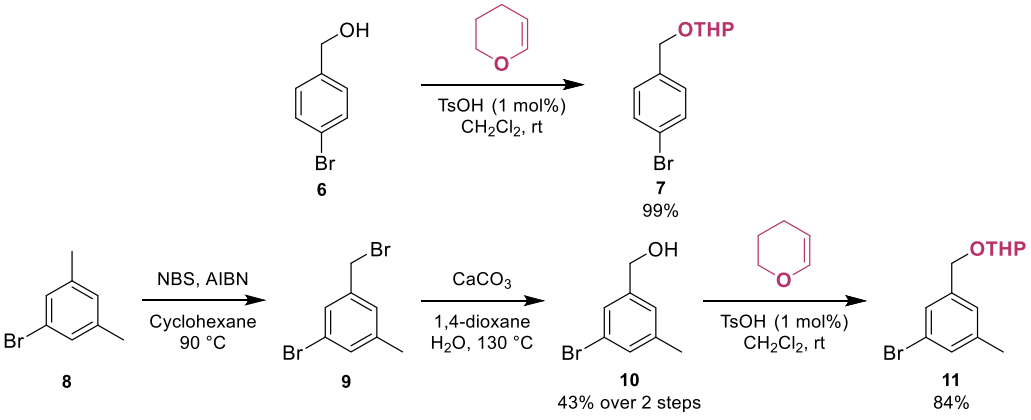
Our strategy for the synthesis of ligands **L2**-**L5** was to unite the bipyridine and aryl spacer units through Kumada cross-coupling to form a new doubly benzylic C–C bond. In accordance with our previous work, radical bromination of **1** proceeded successfully to give **2** in 39% yield and Riley oxidation of **3**, followed by reduction to alcohol **4** and substitution yielded benzyl bromide **5** in 40% yield across the two steps (Scheme 1).

Benzyl alcohol **6** was protected to access *para*-substituted coupling partner **7**. We deemed it necessary for the *meta*-benzyl spacer to be 1,3,5-trisubstituted to avoid borylation of the ligand. Therefore, protected alcohol **11** was synthesised by bromination of 5-bromo-*m*-xylene **8**, followed by hydrolysis of **9** through treatment with $CaCO_3$ in a mixture of water and dioxane. This sequence yielded benzyl alcohol **10** in 43% yield over two steps. After THP protection, **11** was obtained in 84% yield (Scheme 2).

With the coupling partners in hand, we undertook an optimisation of Kumada coupling conditions using bipyridine **2** and aryl bromide **7** (Table 1). The use of a palladium catalyst with either

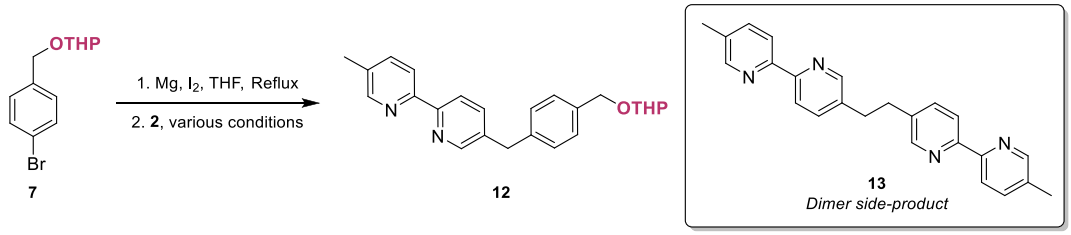


Scheme 1. Synthesis of bipyridine benzyl bromides.



Scheme 2. Synthesis of aryl spacer units.

Table 1
Screen of various Kumada coupling conditions, yields are from crude ^{1}H NMR based on DME internal standard, *isolated yield.



Entry	Catalyst	Ligand	Solvent	T / °C	12 / %
1	$Pd(OAc)_2$ (5 mol%)	XantPhos (10 mol%)	THF	60	18*
2	$Pd(OAc)_2$ (5 mol%)	SPhos (10 mol%)	THF	60	26
3	$Pd(OAc)_2$ (4 mol%)	PCy_3 (4 mol%)	NMP	60	14
4	$Pd(MeCN)_2Cl_2$ (3 mol%)	XantPhos (3 mol%)	MeCN	60	-
5	$Ni(PPh_3)_2Cl_2$ (5 mol%)	-	THF	rt	55
6	$Ni(dppe)Cl_2$ (5 mol%)	-	THF	rt	46
7	$Ni(dppp)Cl_2$ (5 mol%)	-	THF	rt	56

mono or di phosphine ligands was met with limited success (entries 1–4) with the major side-product being homocoupled bipy dimer **13** [19]. Pleasingly by changing to a nickel catalyst and lowering the temperature (entries 5–7) a substantial increase in the yield of **12** was observed.

Using the conditions shown in entry 7, the 5,5′-substituted bipydridine ligand frameworks **12** and **14** could be successfully obtained (Scheme 3). In contrast, the coupling of 4,4′-substituted bipyridine with aryl bromide **7** was ineffective (6% yield) under the nickel catalysed conditions and so a $Pd(OAc)_2$/Xantphos catalyst system was utilised to obtain ligand frameworks **15** and **16**.

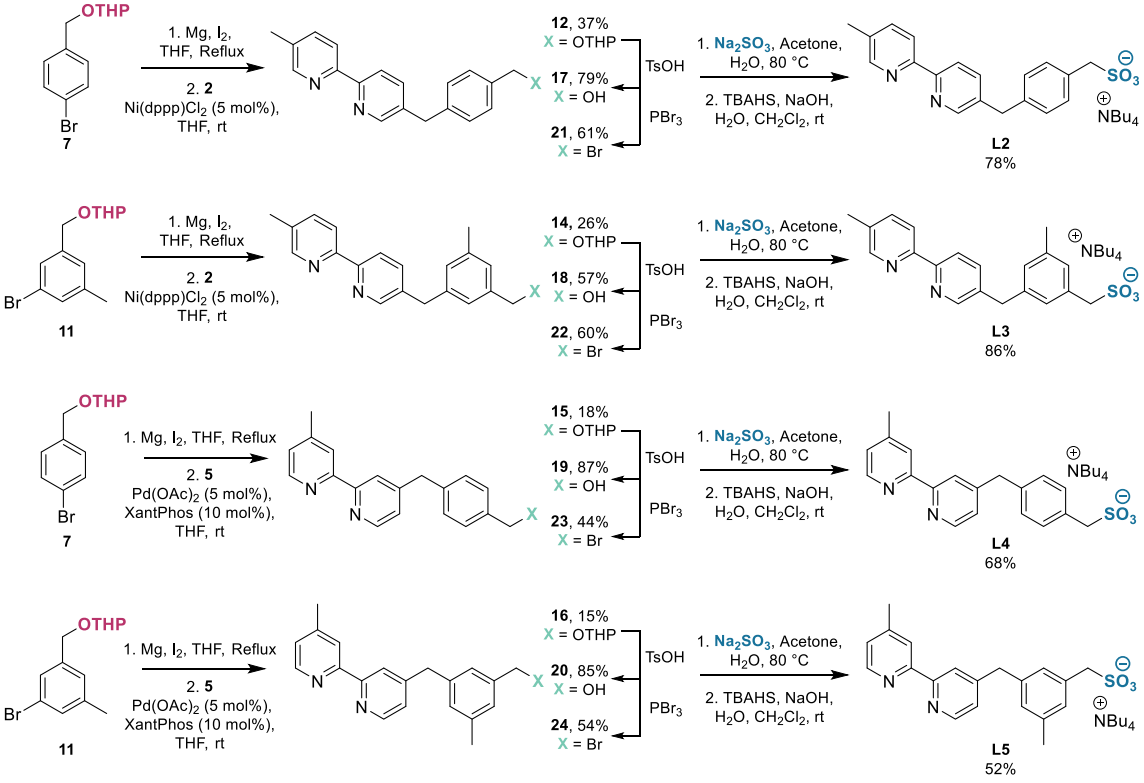
In all cases the THP ethers were successfully deprotected using TsOH in MeOH to give primary alcohols **17**–**20** in 57–87% yield. Subsequent treatment with PBr_3 gave benzyl bromides **21**–**24** in good yield. Using the conditions previously reported by our group,[8a] the target ligands **L2-L5** could be obtained. First **21**–**24** were heated in a 3:2 mixture of water and acetone to give the sodium salts of the target sulfonates, then a cation exchange to tetrabutylammonium was performed by stirring with tetrabutylammonium hydrogen sulfate (TBAHS) and NaOH in a biphasic CH_2Cl_2/H_2O mixture. All four of the target ligands could be obtained over the two steps in yields ranging from 52 to 86%.

With the initial four ligands in hand, substrates from our previous studies were chosen for evaluation that would test the ligands both in “ion-pairing mode” and “hydrogen bonding mode”. Based on the substrate classes that had been effective in our previous reports of *meta*-selective borylation with ligand **L1**, a range of aromatic quaternary ammonium salts and amides with a chloride substituent at the arene *ortho*-position were chosen with varying lengths of carbon linker to the directing group (Scheme 4). The synthesis of each of these substates has been disclosed in our earlier reports [8a-c]. Additionally, regioisomeric ratios (*rr)* could be confidently assigned from crude ^{1}H NMR without purification, through comparison to the characterisation data previously published by our group. For each of the substrates, control reactions were run using 5,5′-dimethyl-2,2′-bipyridine **1** and 4,4′-dimethyl-2,2′-bipyridine **3** to determine how effective ligands **L2-L5** were at promoting *para*-selective borylation, relative to electronically similar control ligands lacking a sulfonate directing group.

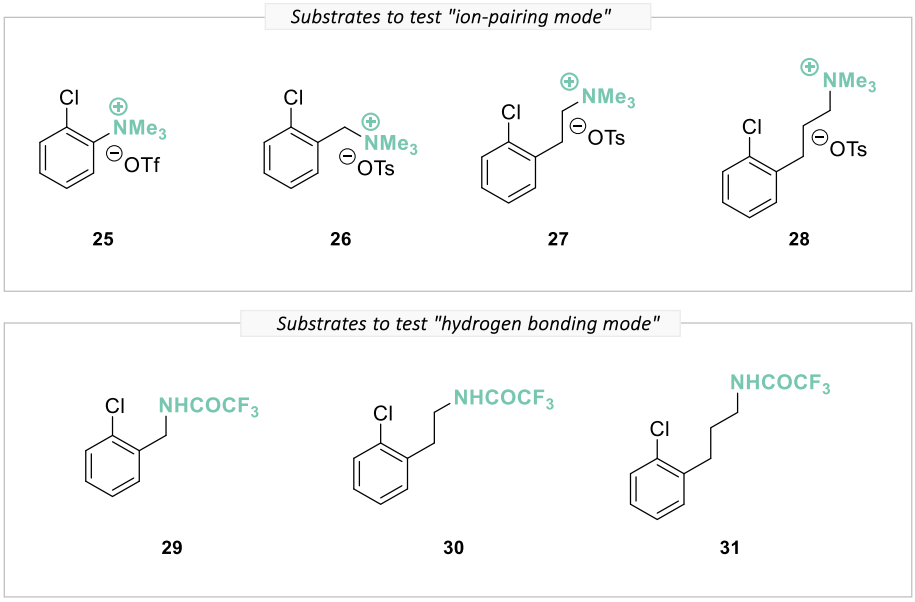
Sulfonated ligand **L2** was evaluated first (Table 2). Anilinium substrate **25** (entry 1) showed a moderate reversal of selectivity compared to control **1**, giving a ratio of *p*:(*m* + *di*) of 1:2.5. An encouraging result was seen with benzyl ammonium **26** (entry 2), which showed an increase in *para*-selectivity from 2.2:1 in the control using ligand **1**, to 4.4:1. Increasing the length of the carbon chain (entries 3 and 4) gave unselective borylation, as did using longer-chained trifluoroacetamides **30** and **31** (entries 6 and 7). However, a small increase in *para*-selectivity was observed with trifluoroacetamide substrate **29** (entry 5).

Evaluation of ligand **L3** against the same set up substrates gave generally poor results (Table 3). The ammonium salt substrates (entries 1–4) all gave poor conversions and had no impact on the *para*-selectivity. Amide substrate **29** also gave low conversion but did have a minor influence on *para*-selectivity (3.0:1, entry 5). Substrates **30** and **31** showed good conversion but were regrettably unselective (entries 6 and 7).

Ligand **L4** (Table 4) gave similar results to ligand **L2** (Table 2). Consistent with **L2**, anilinium substrate **25** showed a small inver-

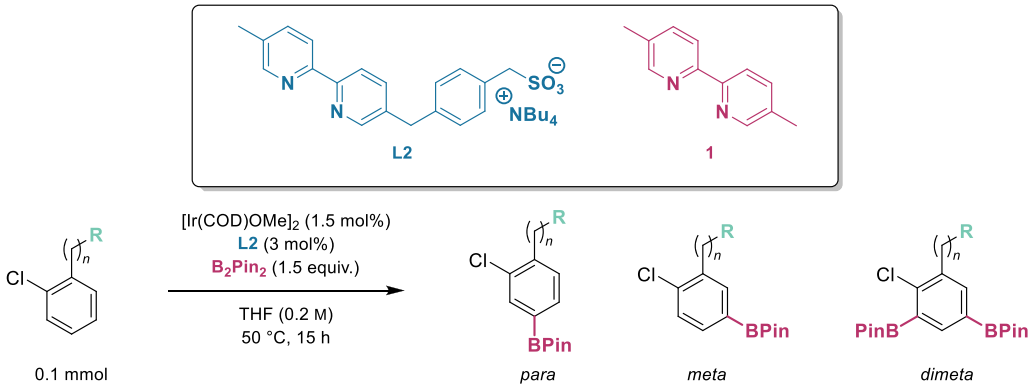


Scheme 3. Synthesis of ligands **L2**-**L5**.



Scheme 4. Substrates chosen to test ligands in "ion-pairing mode" and "hydrogen bonding mode" across a range of linker lengths.

Table 2
Results of the screen with ligand L2, all values are percentage yield based on crude 1H NMR with DME internal standard, the regioselectivity with control ligand 1 is shown for comparison, *0.05 mmol scale.



Entry	Substrate	R	n	SM	para	meta	dimeta	*p*:(*m*+*di*)	*p*:(*m*+*di*) using 1
1	**25**	NMe_3^+ OTf^-	0	-	30	58	18	1:2.5	2.2:1
2	**26**	NMe_3^+ OTs^-	1	6	71	10	6	4.4:1	2.2:1
3	**27**	NMe_3^+ OTs^-	2	24	40	31	2	1.2:1	3:1
4	**28**	NMe_3^+ OTs^-	3	28	35	33	3	1:1.1	2:1
5	**29**	$NHCOCF_3$	1	6	48	22	-	2.2:1	1.5:1
6*	**30**	$NHCOCF_3$	2	13	40	35	-	1.1:1	1.4:1
7	**31**	$NHCOCF_3$	3	6	43	49	< 1	1:1.1	1.2:1

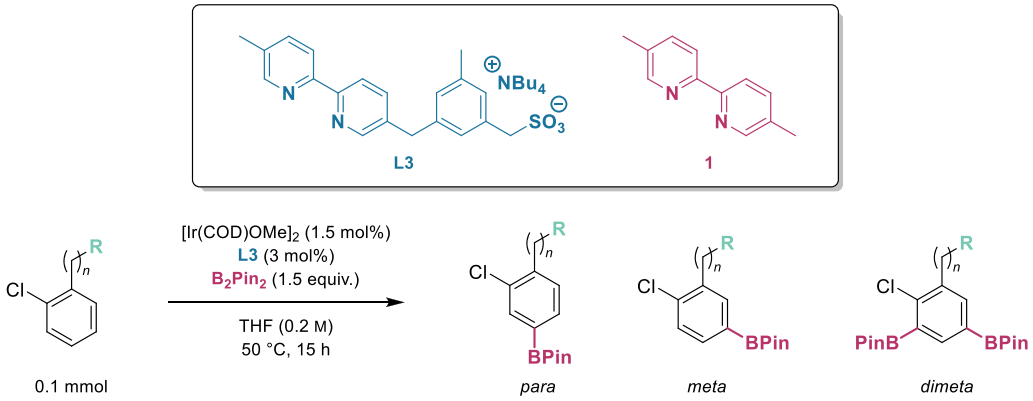
sion to *meta*-selectivity when **L4** was used (entry 1). Additionally, benzyl ammonium substrate **26** gave 3.3:1 *para*-selectivity, similar to the 4.4:1 selectivity when **L2** was used. The other substrates gave high conversion but exhibited little selectivity difference compared with the control (entries 4–7).

As was seen with the earlier *meta*-spacer ligand **L3**, **L5** gave generally poor results and no selectivity difference relative to the control ligand **3** was observed for any of the substrate classes (Table 5).

At this point we were interested to see if there would be any effect of reaction concentration so examined this in the context of ligand **L2** together with substrate **26**, a combination that had given 4.4:1 p:m selectivity (Table 2, entry 2). The four concentrations surveyed had almost no impact on selectivity (Table 6).

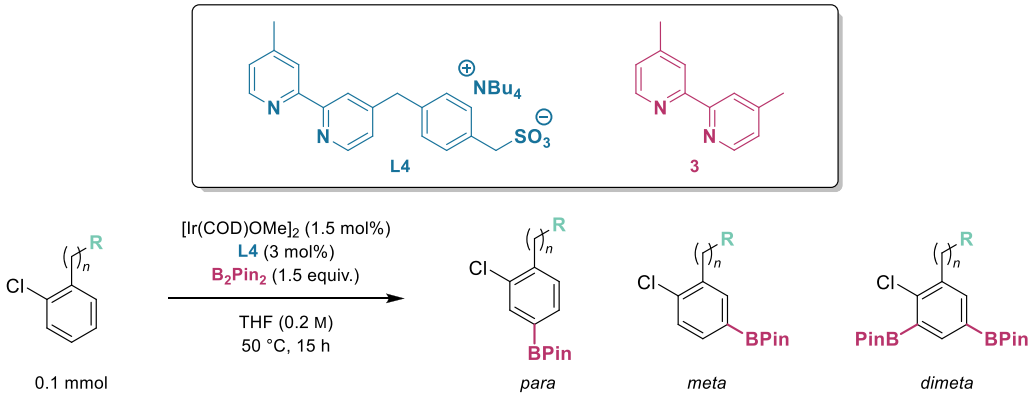
We next speculated that it could be useful to restrict the conformational freedom of **L2**. We reasoned that the barrier to rotation of the bonds on either side of the diaryl methylene is probably low as it is relatively unhindered and this would likely

Table 3
Results of the screen with ligand L3, all values are percentage yield based on crude 1H NMR with DME internal standard, the regioselectivity with control ligand 1 is shown for comparison.



Entry	Substrate	R	n	SM	para	meta	dimeta	*p*:(*m*+*di*)	*p*:(*m*+*di*) using 1
1	**25**	NMe_3^+ OTf^-	0	92	-	-	-	-	2.2:1
2	**26**	NMe_3^+ OTs^-	1	53	19	10	< 1	1.9:1	2.2:1
3	**27**	NMe_3^+ OTs^-	2	74	15	9	-	1.7:1	3:1
4	**28**	NMe_3^+ OTs^-	3	88	4	4	-	1:1	2:1
5	**29**	$NHCOCF_3$	1	88	3	1	-	3.0:1	1.5:1
6	**30**	$NHCOCF_3$	2	6	49	32	-	1.5:1	1.4:1
7	**31**	$NHCOCF_3$	3	22	37	39	-	1:1.1	1.2:1

Table 4
Results of the screen with ligand L4, all values are percentage yield based on crude 1H NMR with DME internal standard, the regioselectivity with control ligand 3 is shown for comparison

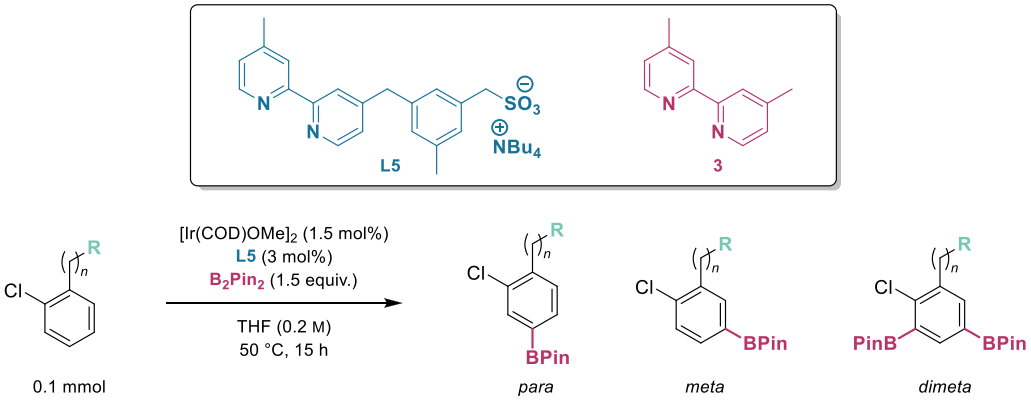


Entry	Substrate	R	n	SM	para	meta	dimeta	*p*:(*m*+*di*)	*p*:(*m*+*di*) using 3
1	**25**	NMe_3^+ OTf^-	0	61	6	17	-	1:2.8	2.1:1
2	**26**	NMe_3^+ OTs^-	1	5	69	17	4	3.3:1	1.9:1
3	**27**	NMe_3^+ OTs^-	2	79	12	9	-	1.3:1	1.8:1
4	**28**	NMe_3^+ OTs^-	3	9	40	31	2	1.2:1	2.6:1
5	**29**	$NHCOCF_3$	1	8	57	28	< 1	2.0:1	1.4:1
6	**30**	$NHCOCF_3$	2	1	48	42	-	1.2:1	1.7:1
7	**31**	$NHCOCF_3$	3	3	45	48	-	1:1.1	1.2:1

lead to multiple unproductive conformations (Fig. 3). Rotation around the benzylic sulfonate position is probably more restricted due to the large size of the sulfonate group, but some degree of rotation is probably important here to allow the sulfonate group to guide the substrate to the iridium centre.

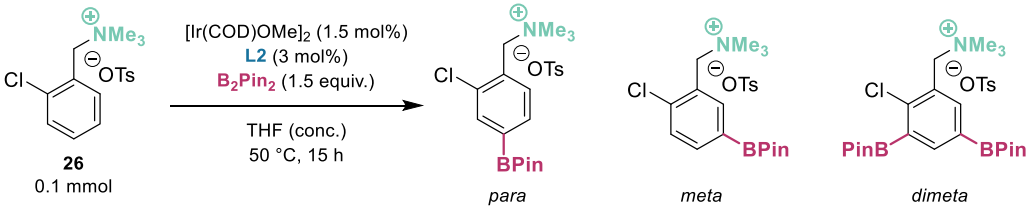
One method of imposing conformational restriction at the methylene unit would be to add substitution at this position. We hypothesized that introduction of a single methyl or gem-dimethyl motif should promote a Thorpe-Ingold effect, potentially reducing the entropic cost of the ligand adopting the desired conformation at

Table 5
Results of the screen with ligand L5, all values are percentage yield based on crude 1H NMR with DME internal standard, the regioselectivity with control ligand 3 is shown for comparison



Entry	Substrate	R	n	SM	para	meta	dimeta	*p*:(*m*+*di*)	*p*:(*m*+*di*) using 3
1	**25**	NMe_3^+ OTf^-	0	11	49	37	-	1.3:1	2.1:1
2	**26**	NMe_3^+ OTs^-	1	8	51	31	2	1.6:1	1.9:1
3	**27**	NMe_3^+ OTs^-	2	49	33	17	-	1.9:1	1.8:1
4	**28**	NMe_3^+ OTs^-	3	35	33	27	-	1.2:1	2.6:1
5	**29**	$NHCOCF_3$	1	10	54	26	-	2.1:1	1.4:1
6	**30**	$NHCOCF_3$	2	73	4	4	-	1:1	1.7:1
7	**31**	$NHCOCF_3$	3	5	52	43	-	1.2:1	1.2:1

Table 6
Results of the concentration screen on substrate 26 with ligand L2, all values are percentage yield based on crude 1H NMR with DME internal standard



Entry	Conc. /M	SM	para	meta	dimeta	*p*:(*m*+*di*)
1	0.4	4	72	9	7	4.5:1
2	0.2	6	71	10	6	4.4:1
3	0.1	4	70	10	5	4.7:1
4	0.05	4	71	11	4	4.7:1

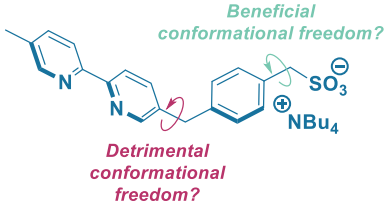
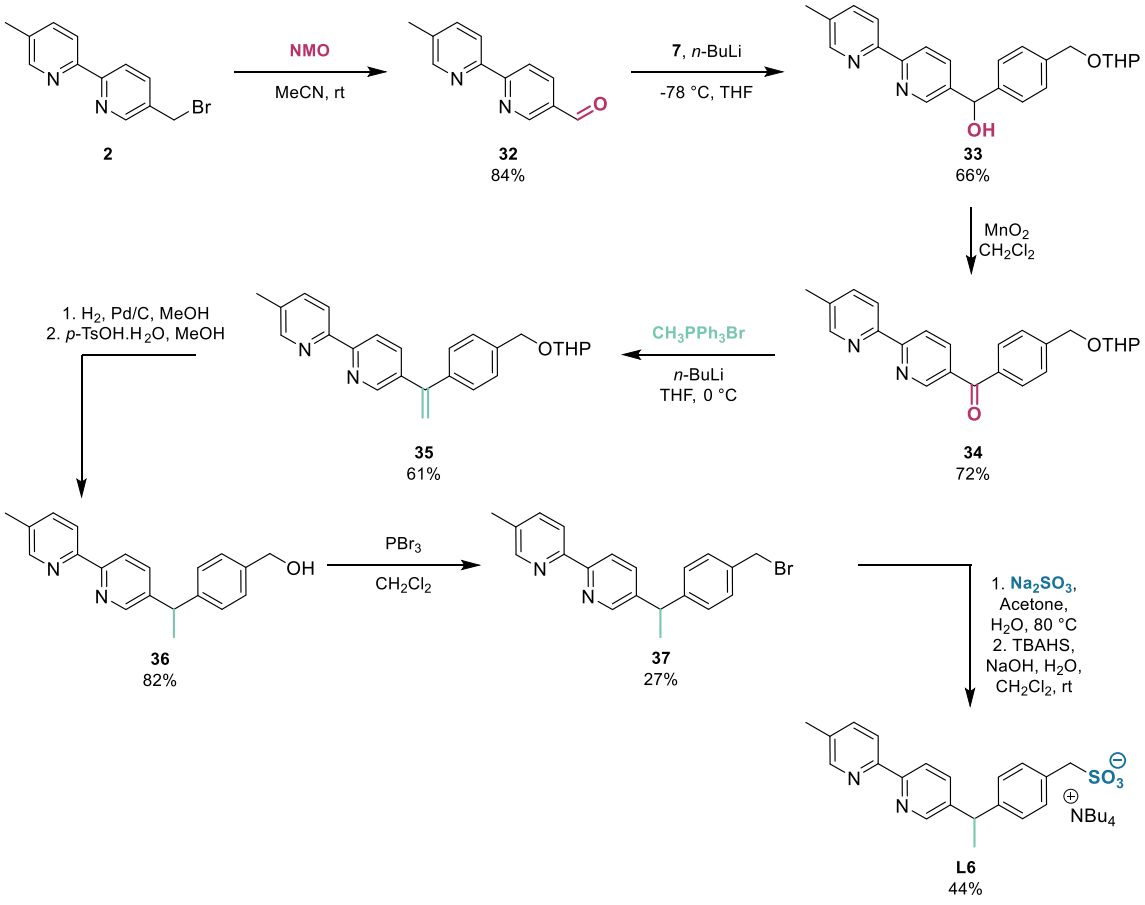


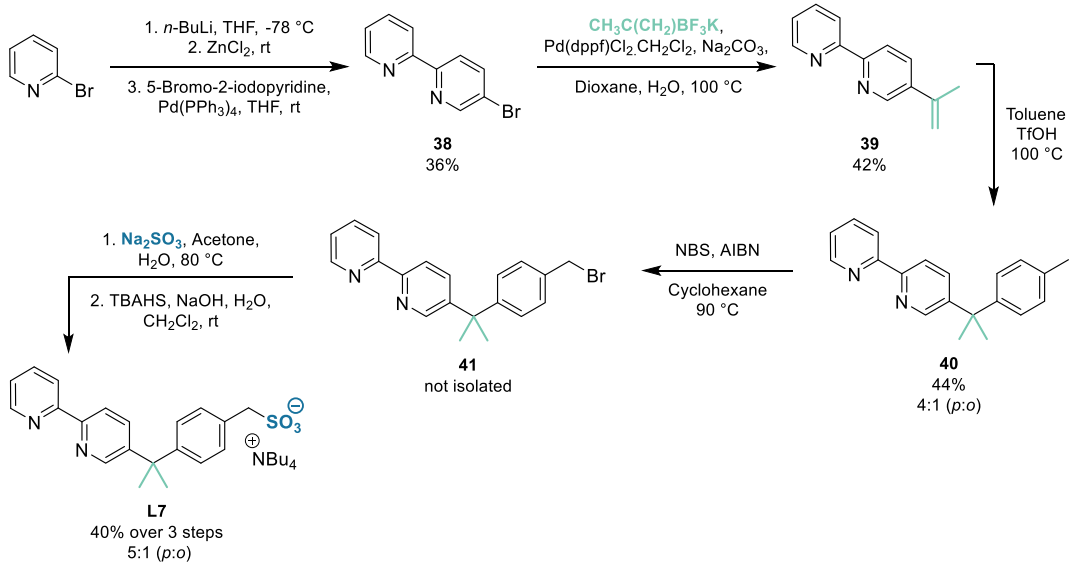
Fig. 3. Summary of the conformational freedom in ligand **L2**.

the transition state [20]. Therefore, Ligand **L6**, bearing one methyl group at the doubly-benzylic position, was synthesised in the following way (Scheme 5). Bipyridine benzyl bromide **2** was oxidised to the aldehyde **32**, which was subsequently transformed into secondary alcohol **33** through addition of aryl spacer unit **7**. Wittig olefination followed by reduction installed the requisite benzylic methyl group. Following this, the same sequence of deprotection, bromination, displacement with sulfite and cation exchange was used as in the synthesis of **L2-L5**. It should be noted that benzyl bromide **37** decomposes over time when left in air at room temperature.

An analogous ligand **L7**, which possesses a gem-dimethyl group at the doubly-benzylic position was also synthesised (Scheme 6). Brominated bipyridine **38** was formed through Negishi coupling of 2-bromopyridine and 5-bromo-2-iodopyridine. This was then subjected to Suzuki coupling with potassium isopropenyltrifluoroborate to yield 5-isopropenyl bipyridine **39** which underwent a Friedel-Crafts reaction with toluene to give **40** in 4:1 *para*:*ortho* selectivity. After this, bromination, sulfite addition and salt



Scheme 5. Synthesis of mono-methylated ligand **L6**.

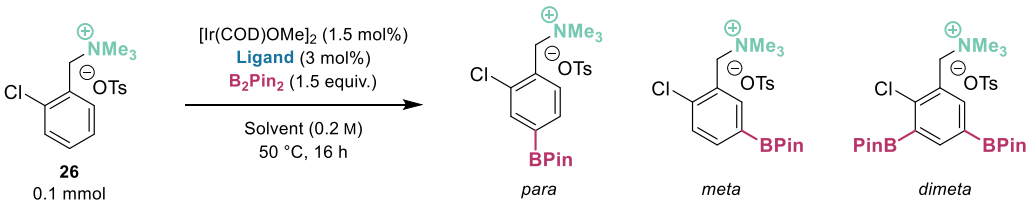


Scheme 6. Synthesis of gem-dimethyl ligand **L7**.

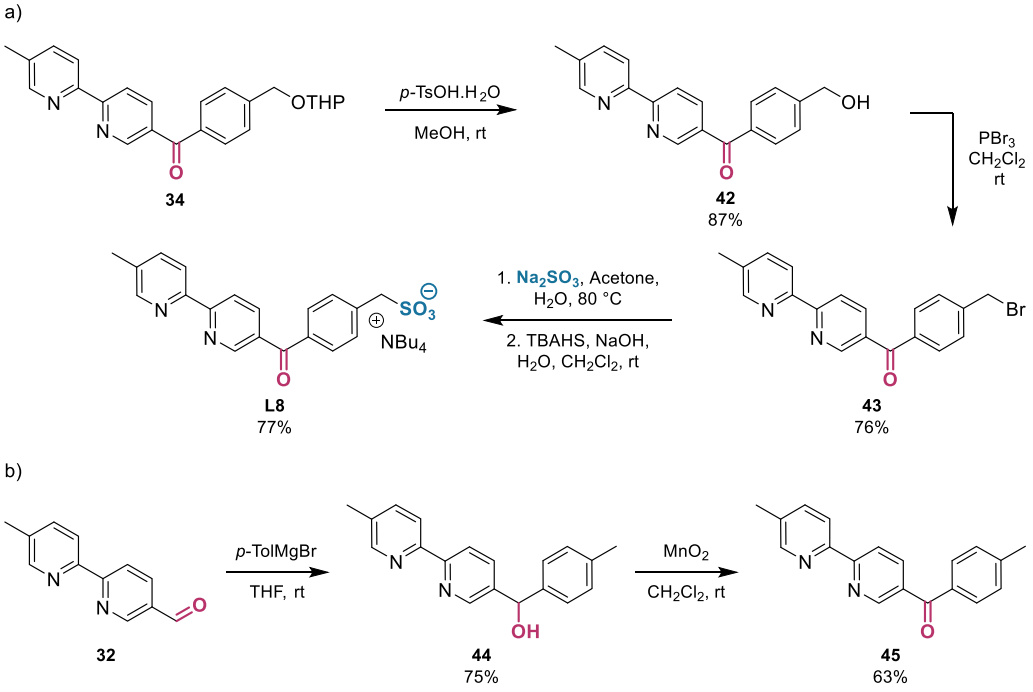
exchange yielded **L7**. Unfortunately, the *para* and *ortho* isomers generated during the Friedel-Crafts reaction were unable to be separated. As a result, the final ligand **L6** had to be used as a 5:1 mixture of *ortho*:*para* regioisomers.

Ligands **L6** and **L7** were evaluated on benzyl ammonium substrate **26** (Table 7). Mono-methylated ligand **L6** performed similarly (entry 2) to the non-methylated variant **L2** (entry 1) in both THF (4.7:1) and dioxane (5.1:1). Use of dioxane seemed to give a small increase in both regioselectivity and conversion for both ligands (entries 4 and 5). Gem-dimethyl ligand **L7** gave a poorer

Table 7
Results of benzyl ammonium substrate 26 with ligands L6 and L7, all values are percentage yield based on crude 1H NMR with DME internal standard, results with L2 are included for comparison



Entry	Ligand	Solvent	SM	para	meta	dimeta	*p*:(*m*+*di*)
1	**L2**	THF	6	71	10	6	4.4:1
2	**L6**	THF	20	70	7	8	4.7:1
3	**L7**	THF	17	66	14	6	3.3:1
4	**L2**	1,4-Dioxane	-	71	1.5	12	5.3:1
5	**L6**	1,4-Dioxane	-	81	3	13	5.1:1
6	**L7**	1,4-Dioxane	-	78	8	13	3.7:1



Scheme 7. Synthesis of a) ketone ligand **L8**, b) control ligand **45**.

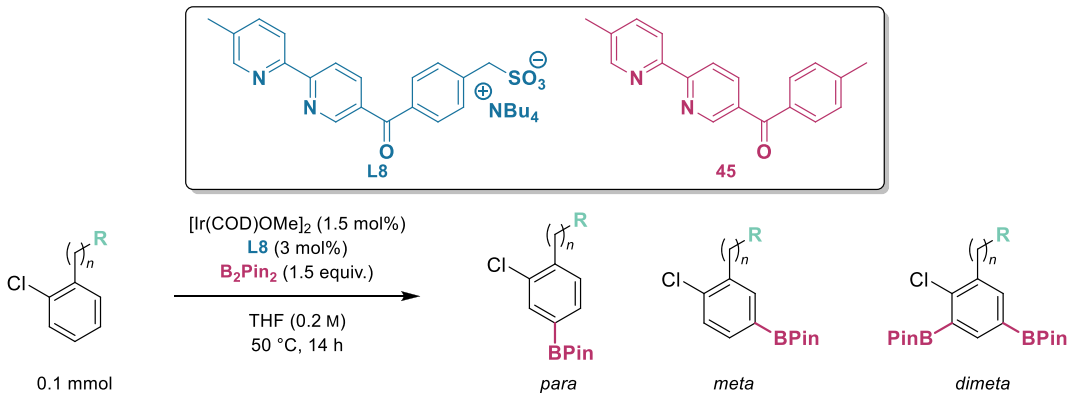
outcome than ligands **L2** and **L6**, 3.3:1 in THF and 3.7:1 in dioxane (entries 3 and 6), perhaps suggesting that further steric bulk at this position is not beneficial. A caveat here is that the presence of the *ortho*-isomer of the ligand could complicate interpretation of this result.

We next sought to adjust the conformational freedom of the ligand by changing the hybridisation of the doubly-benzylic carbon atom from sp^3 to sp^2. Diaryl ketones are known to distort from a fully conjugated planar conformation. This occurs due to steric interactions between *ortho*-hydrogen atoms forcing one of the rings to twist out of the plane [21]. We sought to evaluate any effect that this might have on selectivity. Using ketone **34** as a starting point, a sequence of steps as before yielded ketone ligand **L8** (Scheme 7a). To obtain an analogous control ligand for **L8**, ligand **45** with no sulfonate group was synthesised (Scheme 7b).

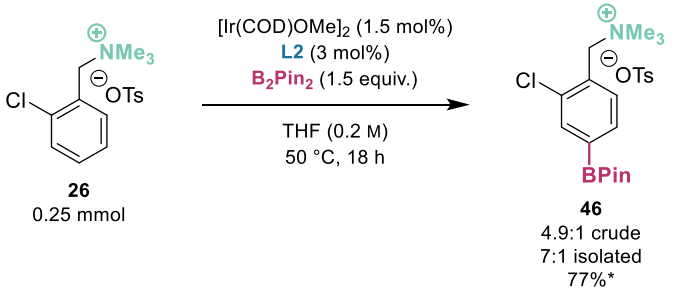
Gratifyingly borylation using ligand **L8** on the benzyl ammonium substrate **26** showed the best *para*-selectivity obtained so far (5.9:1 *p*:*m*, Table 8, entry 2). Although use of dioxane as solvent had been beneficial with **L2**, we found that selectivity was lowered to 4:1 with **L8**. Unfortunately, none of the other substrate classes showed any significant *para*-selectivity with **L8** versus the control ligand **45**.

Although the intrinsic regioselectivity using the ligands developed in this study is only modest, we would like to highlight that our method does have some practical utility. For example, when the borylation of substrate **26** using ligand **L2** was performed on a 0.25 mmol scale (Scheme 8), the intrinsic crude selectivity of 4.9:1 *p*:*m* (determined by ^{1}H NMR) could be increased to 7:1 in the isolated material by triturating with diethyl ether, giving **46** in 77% yield.

Table 8
Results of the screen with ligand L8, all values are percentage yield based on crude 1H NMR with DME internal standard, the regioselectivity with control ligand 45 is shown for comparison, NR = no reaction.



Entry	Substrate	R	n	SM	para	meta	dimeta	*p*:(*m*+*di*)	*p*:(*m*+*di*) using 45
1	**25**	NMe_3^+ OTf^-	0	7	31	54	5	1:1.9	1.7:1
2	**26**	NMe_3^+ OTs^-	1	7	77	9	4	5.9:1	2.6:1
3	**27**	NMe_3^+ OTs^-	2	42	29	17	-	1.7:1	NR
4	**28**	NMe_3^+ OTs^-	3	59	17	13	2	1.1:1	NR
5	**29**	$NHCOCF_3$	1	50	30	11	-	2.7:1	1.8:1
6	**30**	$NHCOCF_3$	2	34	37	25	-	1.5:1	1.3:1
7	**31**	$NHCOCF_3$	3	20	35	30	1	1.2:1	1.4:1



Scheme 8. Borylation of substrate **26** using ligand **L2** on a larger 0.25 mmol scale, *weighted average yield to account for 20% inseparable SM present.

3. Conclusions

In conclusion we have detailed the synthesis of seven novel variations of our original sulfonated bipyridine ligand in which an arene spacer is incorporated to allow greater distance between the sulfonate and the iridium metal centre. These were evaluated in the borylation of seven different substrates which can operate in either hydrogen bonding mode or ion-pairing mode to assess the impact of the new ligands on *meta*:*para* selectivity. Whilst the effect of the new ligands on selectivity versus the control ligand for most of the substrate classes was minimal, for substrate **26**, a quaternised benzylamine, a significant shift to increased *para* selectivity was observed with several of the ligands, suggesting the directing interaction could be occurring in this instance. Ligand **L8** provided the optimal outcome giving 6:1 *p*:*m* selectivity in the borylation of a quaternised benzylamine substrate. In recent work we have shown that sulfonated ligands have the ability to control enantioselectivity if paired with a chiral cation, so we envisage that the disclosure of these novel ligands **L2-L8** will be of interest for potential further application in that regard [10].

4. Experimental

4.1. General

All reagents, unless otherwise stated, were used as supplied from commercial sources without further purification. [Ir(COD)OMe]$_2$ was purchased from Sigma-Aldrich, used as received and stored in a desiccator. CH_2Cl_2, *n*-hexane, toluene, MeCN, MeOH, THF and Et_2O were purified by distillation on site under inert atmosphere *via* the following processes: THF and Et_2O were pre-dried over sodium wire then distilled from calcium hydride and lithium aluminium hydride. CH_2Cl_2, *n*-hexane, MeCN, MeOH and toluene were distilled from calcium hydride. Borylation reactions were carried out in 4 mL, 15 × 45mm crimp-top vials, which were purged with Argon and heated in deep-welled heating blocks (IKA DB 5.2). The reaction was halted by blowing air over the reaction to remove solvent, upon which point internal standard was added and the crude residue dissolved in deuterated solvent for quantitative NMR analysis through comparison to literature data [8a-c]. ^{1}H NMR spectra were recorded on a 600 MHz Bruker Avance DRX-600, 500 MHz Bruker DCH Cryoprobe, 400 MHz Bruker QNP Cryoprobe, 400 MHz Bruker Avance NEO Prodigy N2 Cryoprobe, 400 MHz Bruker Avance III (BBFO) or 500 MHz Bruker Avance III (QCI Cryoprobe) spectrometer. Chemical shifts are reported in parts per million (ppm) and the spectra are calibrated to the resonance resulting from incomplete deuteration of the solvent (CDCl3: 7.26 ppm; DMSO-d_6: 2.50 ppm, qn; MeOD-d4: 3.31 ppm, qn; D_2O: 4.79 ppm). ^{13}C NMR spectra were recorded on the same spectrometers with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($^{13}CDCl_3$: 77.16 ppm, t; DMSO-d_6: 39.52 ppm, sept; MeOD-d_4: 49.00 ppm, sept). Data are reported as follows: chemical shift δ/ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, br = broad, m = multiplet or

combinations thereof; ^{13}C signals are singlets unless otherwise stated), coupling constants *J* in Hz, integration (^{1}H only). $^{1}H-COSY$, DEPT-135, HSQC, HMBC and NOESY were used where appropriate to assign ^{1}H NMR and facilitate structural determination of regioisomers. The carbon atom attached to boron was generally not observed by ^{13}C spectroscopy due to quadrupolar relaxation. HRMS data was recorded on a Waters Micromass LCT Premier spectrometer using an electrospray ionization (ESI) or on a Waters Xevo G2-S bench top QTOF using an electrospray ionization or atmospheric solids analysis probe (ASAP). Others were measured at the EPSRC Mass Spectrometry Service at the University of Swansea. Measured values are reported to 4 decimal places are within ±5 ppm of the calculated value. The calculated values are based on the most abundant isotope. Analytical thin layer chromatography was performed using precoated Merck glass backed silica gel plates (Silicagel 60 F254). Visualisation was by ultraviolet fluorescence (λ = 254 or 365 nm) and/or staining with cerium ammonium molybdate (CAM), potassium permanganate ($KMnO_4$), *para*-anisaldehyde or vanillin. Flash column chromatography was performed using silica gel 60 (0.040−0.063 μm) from Fluorochem (for borylated products), Material Harvest Ltd (in all other cases).

4.2. Synthesis of ligands

4.2.1. 5-(Bromomethyl)-5′-methyl-2,2′-bipyridine (**2**)

NBS was washed with MeCN to purify. To an oven-dried flask was added 5,5′-dimethyl-2,2′-bipyridine **1** (4.32 g, 23.4 mmol) and this was dissolved in cyclohexane (90 ml). To the solution was added NBS (5.41 g, 30.4 mmol) and AIBN (100 mg, 0.61 mmol) and the resulting mixture placed under an argon atmosphere and heated for 18.5 h and then allowed to cool. The reaction mixture was then filtered and washed with more cyclohexane. The solvent was evaporated, and the residue purified *via* column chromatography (7 × 11 cm silica), eluting with CH_2Cl_2, 5% EtOAc in CH_2Cl_2 then 10% EtOAc in CH_2Cl_2. This gave the title compound as a white solid (2.37 g, 9.02 mmol, 39%.) ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.66 (d, *J* = 2.1 Hz, 1H), 8.50 (s, br, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 7.83 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.62 (dd, *J* = 1.6, 8.2 Hz, 1H), 4.53 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.2, 153.0, 150.0, 149.2, 137.5, 137.5, 133.7, 133.2, 120.7, 120.7, 29.8, 18.4. All data are in accordance with the literature [8a].

4.2.2. (4′-Methyl-[2,2′-bipyridin]-4-yl)methanol (**4**)

4,4′-Dimethyl-2,2′-bipyridine (**3**) (10.00 g, 54.2 mmol) was suspended in 1,4-dioxane (500 ml) and selenium dioxide (10 g, 90.2 mmol) was added at rt. The mixture was heated for 24 h at 130 °C. After cooling to rt the mixture was further cooled to 0 °C and $NaBH_4$ (2.00 g, 54.2 mmol) was added slowly followed by NaOH (aq., 2 M, 24 ml). The resulting suspension was filtered to remove the precipitate and washed with more dioxane (*ca.* 250 ml). The solvent was then removed under reduced pressure. The residuals were dissolved in chloroform (200 ml) and filtered again to remove selenium by-products. The solvent was once again removed under reduced pressure and the crude product purified *via* silica column chromatography (CH_2Cl_2/MeOH, 7% MeOH to 15% MeOH) to yield the title compound (4.93 g, 24.7 mmol, 46%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.0 Hz, 1H), 8.45 (d, *J* = 5.0 Hz, 1H), 8.25 (s, 1H), 8.13 (s, 1H), 7.23 (d, *J* = 5.0 Hz, 1H), 7.11 (d, *J* = 5.0 Hz), 4.71 (s, 2H), 4.70 (s, br, 1H), 2.39 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 155.9, 155.8, 151.7, 149.1, 148.7, 148.6, 124.8, 122.3, 121.1, 118.7, 63.1, 21.2. All data are in accordance with the literature[22].

4.2.3. 4-(Bromomethyl)-4′-methyl-2,2′-bipyridine (**5**)

(4′-Methyl-[2,2′-bipyridin]-4-yl)methanol **4** (1.58 g, 7.89 mmol) was dissolved in HBr (48%, 80 ml) and concentrated sulfuric acid (3.2 ml) was added to the solution. The mixture was heated to 150 °C for 4 h and then cooled to rt. Water (20 ml) and CH_2Cl_2 (20 ml) were added. Sat. sodium hydrogen carbonate solution was then added until the solution was pH 8. The aqueous layer was then extracted multiple times with CH_2Cl_2 (10 ml portions) until the organic layer became colourless. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (10% EtOAc in CH_2Cl_2) to give the title compound as an off-white solid (1.80 g, 6.84 mmol, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (d, *J* = 5.0 Hz, 1H), 8.54 (d, *J* = 5.0 Hz, 1H), 8.41 (d, *J* = 1.7 Hz, 1H, 3-H), 8.23 (s, br, 1H), 7.33 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.15 (dd, *J* = 5.0, 0.8 Hz, 1H), 4.47 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.9, 155.3, 149.6, 149.0, 148.3, 147.2, 125.0, 123.5, 122.0, 121.0, 30.7, 21.2. All data are in accordance with the literature[8a].

4.2.4. 2-((4-Bromobenzyl)oxy)tetrahydro-2H-pyran (**7**)

(4-Bromophenyl)methanol **6** (6.00 g, 32.1 mmol) and *p*-toluene sulfonic acid (62.2 mg, 0.327 mmol) were dissolved in CH_2Cl_2 (52 ml). 3,4-Dihydro-2*H*-pyran (2.97 g, 3.22 ml, 35.3 mmol) was added to the stirring solution, which was then left to stir at rt for 5 h. The reaction mixture was then concentrated and re-dissolved in ethyl acetate (50 ml) then washed with brine (30 ml), sat. sodium hydrogen carbonate solution (25 ml), water (25 ml) and more brine (25 ml). The organic layer was then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (10% EtOAc in hexane) to give the title compound as a clear colourless oil (8.63 g, 31.8 mmol, 99%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.73 (d, *J* = 12.2 Hz, 1H), 4.69 (t, *J* =3.6 Hz, 1H), 4.46 (d, *J* = 12.2 Hz, 1H), 3.92−3.86 (m, 1H), 3.57−3.52 (m, 1H), 1.90−1.82 (m, 1H), 1.77−1.71 (m, 1H), 1.68−1.58 (m, 2H), 1.58−1.51 (m, 1H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 137.4, 131.4, 129.4, 121.3, 97.8, 68.0, 62.1, 30.5, 25.4, 19.3. All data are in accordance with the literature [23].

4.2.5. 1-Bromo-3-(bromomethyl)-5-methylbenzene (**9**)

NBS was washed with MeCN to purify. To an oven-dried flask was added 1-bromo-3,5-dimethylbenzene **8** (3.00 g, 2.20 ml, 16.2 mmol) and this was dissolved in cyclohexane (60 ml). To the solution was added NBS (3.76 g, 21.1 mmol) and AIBN (53 mg, 0.32 mmol) and the resulting mixture placed under an argon atmosphere and heated for 3 h and then allowed to cool. The reaction mixture was then filtered and washed with more cyclohexane. The solvent was evaporated, and the residue purified *via* silica column chromatography (hexane/EtOAc, 0% EtOAc to 5% EtOAc). This gave the title compound as a white solid (2.57 g) with 7% 1-bromo-3-(dibromomethyl)-5-methylbenzene as in inseparable impurity (same R_f value). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.27 (s, 1H), 7.13 (s, 1H), 4.40 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 140.8, 139.7, 132.3, 129.2, 128.6, 122.5, 32.3, 21.2. All data are in accordance with the literature [24].

4.2.6. (3-Bromo-5-methylphenyl)methanol (**10**)

1-Bromo-3-(bromomethyl)-5-methylbenzene **9** (5.62 g, 21.3 mmol, 7% 1-bromo-3-(dibromomethyl)-5-methylbenzene impurity) and calcium carbonate (5.33 g, 53.25 mmol) were placed in an RBF under Ar. 1,4-Dioxane (22 ml) and water (22 ml) were added to the flask and the resulting white suspension was heated to 130 °C for 21 h. The reaction mixture was then filtered, and the filtrate concentrated. The residues were dissolved in CH_2Cl_2 (30 ml) and washed with 3 M HCl (10 ml) and sat. sodium hydrogen carbonate solution (30 ml). The organic layer was then dried over $MgSO_4$, filtered and concentrated. The residue was purified *via* silica column chromatography (10% EtOAc in hexane) to give the

title compound as a white solid (3.06 g, 15.2 mmol, 71%, 43% over two steps). ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.29 (s, 1H), 7.24 (s, 1H), 7.07 (s, 1H), 4.59 (s, 2H), 2.32 (s, 3H), 2.14 (s, br, 1H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 142.8, 140.3, 131.1, 126.9, 126.2, 122.4, 64.4, 21.1; HRMS: *m/z*: $[M]^+$ calc'd for $[C_9H_8BrO]^+$ expect 199.983, found 199.9835. All data are in accordance with the literature [25].

4.2.7. 2-((3-Bromo-5-methylbenzyl)oxy)tetrahydro-2H-pyran (**11**)

(3-Bromo-5-methylphenyl)methanol **10** (3.00 g, 14.9 mmol) and *p*-toluene sulfonic acid (28.3 mg, 0.149 mmol) were dissolved in CH_2Cl_2 (26 ml). 3,4-Dihydro-2*H*-pyran (1.37 g, 1.49 ml, 16.4 mmol) was added to the stirring solution, which was then left to stir at rt for 6.5 h. The reaction mixture was then concentrated *in vacuo* and re-dissolved in ethyl acetate (50 ml) then washed with brine (30 ml), sat. sodium hydrogen carbonate solution (25 ml), water (25 ml) and more brine (25 ml). The organic layer was then dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (7% EtOAc in hexane) to give the title compound as a clear colourless oil (3.53 g, 12.4 mmol, 84%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.32 (s, 1H), 7.24 (s, 1H), 7.08 (s, 1H), 4.71 (d, J = 12.2 Hz), 4.69 (t, J =3.6 Hz, 1H), 4.42 (d, J = 12.2 Hz, 1H), 3.92–3.87 (m, 1H), 3.58–3.53 (m, 1H), 2.32 (s, 3H), 1.91–1.83 (m, 1H), 1.78–1.72 (m, 1H), 1.70–1.58 (m, 2H), 1.58–1.52 (m, 1H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 140.4, 140.1, 131.1, 127.7, 127.1, 122.2, 97.8, 68.0, 62.1, 30.5, 25.4, 21.1, 19.3; HRMS: *m/z*: $[M + NH_4]^+$ calc'd for $[C_{13}H_{21}O_2NBr]^+$ expect 302.0750, found 302.0749.

4.2.8. 5-Methyl-5'-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl) benzyl)-2,2′-bipyridine (**12**)

2-((4-Bromobenzyl)oxy)tetrahydro-2*H*-pyran **7** (5.82 g, 21.5 mmol) was dissolved in degassed dry THF (21.5 ml) under an argon atmosphere. HCl washed magnesium turnings (1.04 g, 42.3 mmol) were added along with a spatula tip of iodine and a drop of 1,2-dibromoethane. The mixture was heated to reflux for 3.5 h to give a 0.75 M solution of (4-(((tetrahydro-2H-pyran-2-yl) oxy)methyl)phenyl)magnesium bromide which was titrated against salicylaldehyde phenylhydrazone (0.3 mmol) in THF (10 ml). 5-(Bromomethyl)-5′-methyl-2,2′-bipyridine **2** (1.58 g, 6.00 mmol) and [1,3-bis(diphenylphosphino)propane]dichloronickel(II) (163 mg, 0.30 mmol, 5 mol%) were added to an oven dried RBF and placed under an argon atmosphere. Freeze-pump-thaw degassed dry THF (36 ml) was added to give a solution. (4-(((Tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)magnesium bromide (12 ml, 0.75 M, 9.00 mmol in degassed dry THF) was added dropwise to the solution and the resulting mixture was stirred for 15 h at rt. H_2O (50 ml) was added and the reaction mixture stirred for 5 min. The THF was then removed *in vacuo* and the remaining aqueous phase was adjusted to pH 9 with sat. $NaHCO_3$ solution. The product was then extracted from the aqueous phase with CH_2Cl_2 (3 × 40 ml) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (18 × 4 cm, 20% 40–60 pet. ether in EtOAc), to give the title compound as a white solid (838 mg, 2.24 mmol, 37%).

^{1}H NMR (600 MHz; $CDCl_3$) δ 8.53 (d, J = 2.1 Hz, 1H), 8.48 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.24 (d, J = 8.3, 1H), 7.60 (dd, J = 8.3, 2.0 Hz, 1H), 7.58 (dd, J = 8.3, 2.1 Hz, 1H), 7.30 (d, J =8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 4.76 (d, J = 12.1 Hz, 1H), 4.70 (t, J = 3.4 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 4.01 (s, 2H), 3.94–3.88 (m, 1H), 3.57–3.51 (m, 1H), 2.37 (s, 3H), 1.89–1.49 (m, 6H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.4, 153.6, 149.6, 149.4, 139.1, 137.4, 137.3, 136.5, 136.3, 133.2, 128.9, 128.3, 120.6, 120.4, 97.7, 68.5, 62.1, 38.6, 30.6, 25.5, 19.3, 18.3; HRMS: *m/z*: $[M+H]^+$ calc'd for $[C_{24}H_{26}O_2N_2]^+$ expect 375.2067, found 375.2065.

4.2.9. 5-Methyl-5'-(3-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy) methyl)benzyl)-2,2′-bipyridine (**14**)

2-((3-Bromo-5-methylbenzyl)oxy)tetrahydro-2*H*-pyran **11** (1.76 g, 5.71 mmol) was dissolved in degassed dry THF (5.7 ml) under an argon atmosphere. HCl washed magnesium turnings (277 mg, 11.4 mmol) were added along with a spatula tip of iodine and a drop of 1,2-dibromoethane. The mixture was heated to reflux for 3.5 h to give a 0.61 M solution of (3-methyl-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)magnesium bromide which was titrated against salicylaldehyde phenylhydrazone (0.3 mmol) in THF (10 ml). 5-(Bromomethyl)-5′-methyl-2,2′-bipyridine **2** (537 mg, 2.04 mmol) and [1,3-bis(diphenylphosphino)propane] dichloronickel(II) (54 mg, 0.10 mmol, 5 mol%) were added to an oven dried RBF and placed under an argon atmosphere. Freeze-pump-thaw degassed dry THF (36 ml) was added to give a solution. (3-methyl-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl) phenyl)magnesium bromide (3.06 mmol, 0.61 M in degassed dry THF) was added dropwise to the solution and the resulting mixture was stirred for 20 h at rt. H_2O (30 ml) was added and the reaction mixture stirred for 5 min. The THF was then removed *in vacuo* and the remaining aqueous phase was adjusted to pH 9 with sat. $NaHCO_3$ solution. The product was then extracted from the aqueous phase with CH_2Cl_2 (3 × 30 ml) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (18 × 4 cm, 20% EtOAc in 40–60 pet. ether), to give the title compound as a white solid (203 mg, 0.52 mmol, 26%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.53 (d, J = 1.4 Hz, 1H), 8.47 (s, 1H), 8.26 (d, J = 7.9 Hz, 1H), 8.24 (d, J = 7.9 Hz, 1H), 7.62–7.59 (m, 1H), 7.59–7.56 (m, 1H), 7.05 (s, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 4.72 (d, J = 11.9 Hz, 1H), 4.68 (t, J = 3.5 Hz, 1H), 4.42 (d, J = 11.9 Hz, 1H), 3.98 (s, 2H), 3.94–3.86 (m, 1H), 3.57–3.48 (m, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 1.92–1.78 (m, 1H), 1.78–1.68 (m, 1H), 1.68–1.44 (m, 4H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 154.4, 153.6, 149.6, 149.5, 139.9, 138.6, 138.5, 137.4, 137.4, 136.4, 133.1, 128.9, 126.8, 125.5, 120.6, 120.4, 97.8, 68.8, 62.2, 38.8, 30.6, 25.5, 21.3, 19.4; HRMS: *m/z*: $[M+H]^+$ calc'd for $[C_{25}H_{29}O_2N_2]^+$ expect 389.2224, found 389.2222.

4.2.10. 4-Methyl-4'-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl) benzyl)-2,2′-bipyridine (**15**)

2-((4-Bromobenzyl)oxy)tetrahydro-2*H*-pyran **7** (2.04 g, 7.52 mmol) was dissolved in degassed dry THF (8.0 ml) under an argon atmosphere. HCl washed magnesium turnings (366 mg, 15.0 mmol) were added along with a spatula tip of iodine and a drop of 1,2-dibromoethane. The mixture was heated to reflux for 1 h to give a solution of (4-(((tetrahydro-2H-pyran-2-yl)oxy) methyl)phenyl)magnesium bromide. 4-(Bromomethyl)-4′-methyl-2,2′-bipyridine **5** (989 mg, 3.76 mmol), palldium(II) acetate (42 mg, 0.19 mmol, 5 mol%) and Xantphos (218 mg, 0.38 mmol) were added to an oven dried RBF and placed under an argon atmosphere. Degassed dry THF (8 ml) was added to give a solution. The 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)magnesium bromide solution was added dropwise at 0 °C and the resulting mixture was stirred for 14 h at 60 °C. H_2O (15 ml) was added and the reaction mixture stirred for 5 min. The THF was then removed *in vacuo* and the remaining aqueous phase was adjusted to pH 9 with sat. $NaHCO_3$ solution. The product was then extracted from the aqueous phase with CH_2Cl_2 (3 × 30 ml) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (10% Et_2O in 40–60 pet. ether), to give the title compound as a colourless oil (260 mg, 0.69 mmol, 18%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.54 (d, J = 4.9 Hz, 1H), 8.51 (d, J = 5.0 Hz, 1H), 8.28 (s, 1H), 8.21 (s, 1H), 7.30 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9, 2H), 7.10 (d, br, J = 5.0 Hz, 1H), 7.08 (dd, J = 4.9, 1.5 Hz, 1H), 4.75 (d, J = 12.0 Hz, 1H), 4.69 (t, J = 3.5 Hz,

1H), 4.46 (d, J = 12.0 Hz, 1H), 4.03 (s, 2H), 3.93–3.87 (m, 1H), 3.56–3.50 (m, 1H), 2.41 (s, 3H), 1.90–1.80 (m, 1H), 1.75–1.68 (m, 1H), 1.67–1.61 (m, 1H), 1.61–1.56 (m, 1H), 1.56–1.48 (m, 2H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.4, 155.9, 151.0, 149.2, 148.9, 148.1, 138.4, 136.6, 129.0, 128.2, 124.7, 124.1, 122.0, 121.7, 97.7, 68.5, 62.1, 41.2, 30.5, 25.5, 21.2, 19.3; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{24}H_{27}O_2N_2]^+$ expect 375.2067, found 375.2064.

4.2.11. 4-Methyl-4'-(3-methyl-5-(((tetrahydro-2H-pyran-2-yl)oxy) methyl)benzyl)-2,2′-bipyridine (**16**)

2-((3-Bromo-5-methylbenzyl)oxy)tetrahydro-2*H*-pyran **11** (1.60 g, 5.61 mmol) was dissolved in degassed dry THF (6.0 ml) under an argon atmosphere. HCl washed magnesium turnings (410 mg, 16.8 mmol) were added along with a spatula tip of iodine and a drop of 1,2-dibromoethane. The mixture was heated to reflux for 3 h to give a solution of (3-methyl-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)magnesium bromide. 4-(Bromomethyl)-4′-methyl-2,2′-bipyridine **5** (865 mg, 3.29 mmol), palldium(II) acetate (37 mg, 0.16 mmol, 5 mol%) and Xantphos (185 mg, 0.32 mmol) were added to an oven dried RBF and placed under an argon atmosphere. Degassed dry THF (8 ml) was added to give a solution. The (3-methyl-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl) magnesium bromide solution was added dropwise at 0 °C and the resulting mixture was stirred for 19.5 h at 60 °C. H_2O (15 ml) was added and the reaction mixture stirred for 5 min. The THF was then removed *in vacuo* and the remaining aqueous phase was adjusted to pH 9 with sat. $NaHCO_3$ solution. The product was then extracted from the aqueous phase with CH_2Cl_2 (3 × 30 ml) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (10–40% EtOAc in 40–60 pet. ether), to give the title compound as a yellow oil (197 mg, 0.51 mmol, 15%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.54 (d, J = 4.9 Hz, 1H), 8.51 (d, J = 4.9 Hz, 1H), 8.27 (s, 1H), 8.21 (s, 1H), 7.10 (d, J = 4.9 Hz, 1H), 7.09 (d, J = 4.9 Hz, 1H), 7.04 (s, 1H), 7.02 (s, 1H), 6.93 (s, 1H), 4.71 (d, J = 11.9 Hz, 1H), 4.67 (t, J = 3.2, 1H), 4.41 (d, J =11.9, 1H), 4.00 (s, 2H), 3.91–3.85 (m, 1H), 3.54–3.48 (m, 1H), 2.41 (s, 3H), 2.29 (s, 3H), 1.88–1.78 (m, 1H), 1.74–1.67 (m, 1H), 1.66–1.59 (m, 1H), 1.58–1.54 (m, 1H), 1.54–1.46 (m, 1H; ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.3, 156.0, 151.1, 149.1, 148.9, 148.1, 139.1, 138.6, 138.4, 129.0, 126.9, 125.7, 124.7, 124.2, 122.0, 121.7, 97.8, 68.7, 62.1, 41.4, 30.5, 25.4, 21.3, 21.1, 19.4; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{25}H_{29}O_2N_2]^+$ expect 389.2224, found 389.2220.

4.2.12. (4-((5′-Methyl-[2,2′-bipyridin]-5-yl)methyl)phenyl) methanol (**17**)

5-Methyl-5'-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl) benzyl)-2,2′-bipyridine **12** (766 mg, 2.04 mmol) was dissolved in MeOH (40 ml). *p*-Toluenesulfonic acid monohydrate (504 mg, 2.65 mmol) was added slowly to the stirring solution. The reaction mixture was then stirred at rt for 4 h. Upon completion the reaction was quenched *via* slow addition of sat. $NaHCO_3$ solution (50 ml) until pH 8 was reached. The MeOH was then removed *in vacuo* and the remaining aqueous layer was extracted with EtOAc (3 × 100 ml). The organic layers were then combined and dried over $MgSO_4$, filtered and concentrated to give a crude residue which was purified *via* silica column chromatography (1% MeOH in DCM) to give the title compound as a white powder (469 mg, 1.62 mmol, 79%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.49 (d, J = 2.1 Hz, 1H), 8.45 (d, J = 1.8 Hz, 1H), 8.22 (d, J =8.0 Hz, 1H), 8.22 (d, J =8.1 Hz, 1H), 7.58 (dd, J = 8.1, 1.8 Hz, 1H), 7.55 (dd, J = 8.0, 2.1 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 4.64 (s, 2H), 3.99 (s, 2H), 2.61 (s, br, 1H), 2.36 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.5, 153.6, 149.6, 149.5, 139.4, 139.2, 137.6, 137.4, 136.4, 133.3, 129.1, 128.3, 120.8, 120.6, 64.9, 38.6, 18.4; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{19}H_{19}ON_2]^+$ expect 291.1492, found 291.1492.

4.2.13. (3-Methyl-5-((5′-methyl-[2,2′-bipyridin]-5-yl)methyl) phenyl)methanol (**18**)

5-Methyl-5'-(3-methyl-5-(((tetrahydro-2*H*-pyran-2-yl)oxy) methyl)benzyl)-2,2′-bipyridine **14** (200 mg, 0.51 mmol) was dissolved in MeOH (10 ml). *p*-Toluenesulfonic acid monohydrate (126 mg, 0.66 mmol) was added slowly to the stirring solution. The reaction mixture was then stirred at rt for 3 h. Upon completion the reaction was quenched *via* slow addition of sat. $NaHCO_3$ solution (15 ml) until pH 8 was reached. The MeOH was then removed *in vacuo* and the remaining aqueous layer was extracted with EtOAc (3 × 30 ml). The organic layers were then combined and dried over $MgSO_4$, filtered and concentrated to give a crude residue which was purified *via* silica column chromatography (50% EtOAc in 40–60 pet. ether) to give the title compound as a pale-yellow solid (88.6 mg, 0.29 mmol, 57%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.50 (d, J = 2.0 Hz, 1H, 11-H), 8.46 (s, br, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.22 (d, J =8.0 Hz, 1H), 7.59 (dd, J =8.0, 1.5 Hz, 1H), 7.56 (dd, J = 8.0, 2.0 Hz, 1H), 7.03 (s, 1H), 6.99 (s, 1H), 6.92 (s, 1H), 4.61 (s, 2H), 3.96 (s, 2H), 2.37 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.3, 153.5, 149.5, 149.4, 141.4, 140.1, 138.6, 137.5, 137.4, 136.3, 133.2, 128.8, 125.9, 124.5, 120.6, 120.5, 65.1, 38.7, 21.3, 18.3; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{20}H_{21}O_2N_2]^+$ expect 305.1648, found 305.1651.

4.2.14. (4-((4′-Methyl-[2,2′-bipyridin]-4-yl)methyl)phenyl) methanol (**19**)

4-Methyl-4'-(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl) benzyl)-2,2′-bipyridine **15** (255 mg, 0.68 mmol) was dissolved in MeOH (14 ml). *p*-Toluenesulfonic acid monohydrate (168 mg, 0.88 mmol) was added slowly to the stirring solution. The reaction mixture was then stirred at rt for 1 h. Upon completion, the reaction was quenched *via* slow addition of sat. $NaHCO_3$ solution (15 ml) until pH 8 was reached. The MeOH was then removed *in vacuo* and the remaining aqueous layer was extracted with EtOAc (3 × 30 ml). The organic layers were then combined and dried over $MgSO_4$, filtered and concentrated to give a crude residue which was purified *via* silica column chromatography (0–5% MeOH in CH_2Cl_2) to give the title compound as a pink solid (171 mg, 0.59 mmol, 87%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.55 (d, J = 5.0 Hz, 1H), 8.53 (d, J = 5.0 Hz, 1H), 8.29 (s, 1H), 8.23 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.15 (d, br, J = 5.0 Hz, 1H), 7.10 (dd, J = 5.0, 0.9 Hz, 1H), 4.66 (s, 2H), 4.05 (s, 2H), 2.88 (s, br, 1H), 2.45 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.3, 155.8, 151.1, 149.2, 148.9, 148.2, 139.4, 138.4, 129.2, 127.4, 124.7, 124.1, 122.1, 121.7, 64.9, 41.2, 21.2; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{19}H_{19}ON_2]^+$ expect 291.1492, found 291.1493.

4.2.15. (3-Methyl-5-((4′-methyl-[2,2′-bipyridin]-4-yl)methyl) phenyl)methanol (**20**)

4-Methyl-4'-(3-methyl-5-(((tetrahydro-2*H*-pyran-2-yl)oxy) methyl)benzyl)-2,2′-bipyridine **16** (195 mg, 0.50 mmol) was dissolved in MeOH (10 ml). *p*-Toluenesulfonic acid monohydrate (124 mg, 0.65 mmol) was added slowly to the stirring solution. The reaction mixture was then stirred at rt for 6 h. Upon completion, the reaction was quenched *via* slow addition of sat. $NaHCO_3$ solution (15 ml) until pH 8 was reached. The MeOH was then removed *in vacuo* and the remaining aqueous layer was extracted with EtOAc (3 × 30 ml). The organic layers were then combined and dried over $MgSO_4$, filtered and concentrated to give a crude residue which was purified *via* silica column chromatography (1–5% MeOH in CH_2Cl_2) to give the title compound as a pink oil (129 mg, 0.41 mmol, 85%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.51 (d, J = 4.9 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.23 (s, br, 1H), 8.19 (s, br, 1H), 7.10 (dd, J = 5.0, 0.6 Hz, 1H), 7.08 (dd, J = 4.9, 1.6 Hz, 1H), 7.01 (s, 1H), 7.00 (s, 1H), 6.93 (s, 1H), 4.58 (s, 2H), 3.97 (s, 2H), 2.63 (s, br, 1H), 2.41 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.2, 155.9, 151.1, 149.2, 148.9,

148.2, 141.5, 139.3, 138.6, 129.0, 126.1, 124.7, 124.7, 124.2, 122.2, 121.7, 65.0, 41.4, 21.3, 21.2; HRMS: *m/z*: $[M+H]^+$ calc'd for $[C_{20}H_{21}ON_2]^+$ expect 305.1648, found 305.1648.

*4.2.16. 5-(4-(Bromomethyl)benzyl)-5′-methyl-2,2′-bipyridine (**21**)*

(4-((5′-Methyl-[2,2′-bipyridin]-5-yl)methyl)phenyl)methanol **17** (392 mg, 1.35 mmol) was placed under and argon atmosphere and dissolved in THF (23 ml). PBr_3 (0.16 ml, 1.76 mmol) was added to the solution and the reaction heated to 80 °C for 4.5 h. The reaction was then diluted with H_2O (15 ml) and sat. Na_2CO_3 solution was added until pH 10 was reached. The reaction mixture was then extracted with DCM (6 × 125 ml) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified *via* silica column chromatography (30% 40–60 pet. ether in EtOAc) to give the title compound as a white solid (291 mg, 0.82 mmol, 61%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.52 (d, J = 2.1 Hz, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.61 (dd, J = 8.2, 2.0 Hz, 1H), 7.58 (dd, J = 8.2, 2.1 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 4.48 (s, 2H), 4.02 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.5, 153.4, 149.6, 149.5, 140.3, 137.6, 137.4, 136.0, 135.9, 133.3, 129.4, 129.3, 120.6, 120.4, 38.6, 33.4, 18.4; HRMS: *m/z*: $[M+H]^+$ calc'd for $[C_{19}H_{18}N_2Br]^+$ expect 353.0648, found 353.0637.

*4.2.17. 5-(3-(Bromomethyl)-5-methylbenzyl)-5′-methyl-2,2′-bipyridine (**22**)*

(3-Methyl-5-((5′-methyl-[2,2′-bipyridin]-5-yl)methyl)phenyl) methanol **18** (119 mg, 0.39 mmol) was placed under and argon atmosphere and dissolved in CH_2Cl_2 (6.6 ml). PBr_3 (0.05 ml, 0.50 mmol) was added to the solution and the reaction stirred at rt for 18.5 h. The reaction was then diluted with H_2O (20 ml) and sat. Na_2CO_3 solution was added until pH 10 was reached. The reaction mixture was then extracted with CH_2Cl_2 (5 × 30 ml) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified *via* silica column chromatography (EtOAc) to give the title compound as a pale-yellow solid (85.4 mg, 0.23 mmol, 60%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.53 (d, J =2.0 Hz, 1H), 8.45 (d, J = 1.7 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.61 (dd, J = 8.2, 1.7 Hz, 1H), 7.59 (dd, J = 8.3, 2.0 Hz, 1H), 7.07 (s, 1H), 7.03 (s, 1H), 6.94 (s, 1H), 4.42 (s, 1H), 3.98 (s, 1H), 2.38 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.5, 153.6, 149.6, 149.5, 140.5, 139.0, 138.1, 137.4, 137.3, 135.9, 133.2, 129.8, 128.0, 126.5, 120.6, 120.4, 38.6, 33.5, 21.2, 18.3; HRMS: *m/z*: $[M+H]^+$ calc'd for $[C_{20}H_{20}N_2Br]^+$ expect 367.0804, found 367.0805.

*4.2.18. 4-(4-(Bromomethyl)benzyl)-4′-methyl-2,2′-bipyridine (**23**)*

(4-((4′-Methyl-[2,2′-bipyridin]-4-yl)methyl)phenyl)methanol **19** (241 mg, 0.68 mmol) was placed under and argon atmosphere and dissolved in CH_2Cl_2 (12 ml). PBr_3 (0.08 ml, 0.88 mmol) was added to the solution and the reaction stirred at rt for 16 h. The reaction was then diluted with H_2O (20 ml) and sat. Na_2CO_3 solution was added until pH 10 was reached. The reaction mixture was then extracted with DCM (5 × 50 ml) and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified *via* silica column chromatography (15–30% EtOAc in 40–60 pet. ether) to give the title compound as a pale pink solid (105 mg, 0.30 mmol, 44%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.56 (d, J = 4.9 Hz, 1H), 8.52 (d, J = 4.9 Hz, 1H), 8.28 (s, br, 1H), 8.22 (s, br, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 4.9, 0.9, 1H), 7.08 (dd, J = 4.9, 1.5 Hz, 1H), 4.47 (s, 2H), 4.04 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.4, 155.8, 150.6, 149.3, 148.9, 148.2, 139.5, 136.1, 129.5, 129.4, 124.7, 124.1, 122.1, 121.7, 41.2, 33.3, 21.2; HRMS: *m/z*: $[M+H]^+$ calc'd for $[C_{19}H_{18}N_2Br]^+$ expect 353.0648, found 353.0649.

*4.2.19. 4-(3-(Bromomethyl)-5-methylbenzyl)-4′-methyl-2,2′-bipyridine (**24**)*

(3-Methyl-5-((4′-methyl-[2,2′-bipyridin]-4-yl)methyl)phenyl) methanol **20** (150 mg, 0.49 mmol) was placed under and argon atmosphere and dissolved in CH_2Cl_2 (8.6 ml). PBr_3 (0.06 ml, 0.64 mmol) was added to the solution and the reaction stirred at rt for 17 h. Further additions of PBr_3 (each 0.045 ml, 0.49 mmol) were added at 17 h, 21 h and 23 h with rt stirring until 40 h total reaction time. The reaction was then diluted with H_2O (20 ml) and sat. Na_2CO_3 solution was added until pH 10 was reached. The reaction mixture was then extracted with CH_2Cl_2 (5 × 30 ml) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified *via* silica column chromatography (15–50% EtOAc in 40–60 pet. ether) to give the title compound as a yellow oil (96.1 mg, 0.26 mmol, 54%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.56 (d, J =4.9 Hz, 1H), 8.53 (d, J = 4.9 Hz, 1H), 8.27 (s, 1H), 8.22 (s, 1H), 7.13 (d, J = 4.9 Hz, 1H), 7.09 (d, J = 4.9 Hz, 1H), 7.08 (s, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 4.42 (s, 2H), 4.00 (s, 2H), 2.43 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.4, 155.9, 150.7, 149.3, 148.9, 148.2, 139.7, 139.0, 138.1, 130.0, 128.1, 126.8, 124.7, 124.2, 122.1, 121.7, 41.2, 33.5, 21.2, 21.2; HRMS: *m/z*: $[M+H]^+$ calc'd for $[C_{20}H_{20}N_2Br]^+$ expect 367.0804, found 367.0813.

*4.2.20. Tetrabutylammonium (4-((5′-methyl-[2,2′-bipyridin]-5-yl) methyl)phenyl)methanesulfonate (**L2**)*

5-(4-(Bromomethyl)benzyl)-5′-methyl-2,2′-bipyridine **21** (169 mg, 0.48 mmol) and sodium sulfite (72.3 mg, 0.57 mmol) were placed under an argon atmosphere and then subsequently dissolved in acetone (1.9 ml) and water (2.9 ml). The reaction mixture was stirred and heated to 80 °C for 3 h. The reaction mixture was then blown down till all acetone had evaporated. More water (10 ml) was added and this aqueous phase was washed with CH_2Cl_2 (3 ml) and ether (3 ml). CH_2Cl_2 (10 ml) was then added along with tetrabutylammonium hydrogen sulfate (195 mg, 0.57 mmol) and NaOH (23.0 mg, 0.57 mmol) and the resulting biphasic mixture stirred vigorously at rt for 1 h. The CH_2Cl_2 layer was then separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 10 ml). All organic layers were then combined and washed with water (3 × 10 ml). All aqueous layers were then recombined and reextracted with CH_2Cl_2 (2 × 10 ml) and then these organic layers were subsequently combined and washed again with water (2 × 10 ml). All organic layers were then combined, dried over $MgSO_4$, filtered and concentrated to give the title compound as viscous colourless oil (222 mg, 0.37 mmol, 78%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.49 (d, J = 1.8 Hz, 1H), 8.43 (d, J = 1.1 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.58–7.53 (m, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 4.00, (s, 2H), 3.94 (s, 2H), 3.14–3.08 (m, 8H), 2.34 (s, 3H), 1.53–1.45 (s, 8H), 1.35–1.27 (m, 8H), 0.91 (t, J = 7.4 Hz, 12H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.2, 153.6, 149.5, 149.4, 137.7, 137.4, 137.2, 136.6, 133.6, 133.1, 130.8, 128.3, 120.5, 120.3, 58.7, 57.3, 38.6, 23.9, 19.6, 18.3, 13.6; HRMS: *m/z*: $[M]^-$ calc'd for $[C_{19}H_{17}N_2O_3S]^-$ expect 353.0965, found 353.0959.

*4.2.21. Tetrabutylammonium (3-methyl-5-((5′-methyl-[2,2′-bipyridin]-5-yl)methyl)phenyl)methanesulfonate (**L3**)*

5-(3-(Bromomethyl)-5-methylbenzyl)-5′-methyl-2,2′-bipyridine **22** (78.4 mg, 0.21 mmol) and sodium sulfite (32.3 mg, 0.26 mmol) were placed under an argon atmosphere and then subsequently dissolved in acetone (1 ml) and water (1.5 ml). The reaction mixture was stirred and heated to 80 °C for 2 h. The reaction mixture was then blown down till all acetone, had evaporated. More water (10 ml) and CH_2Cl_2 (10 ml) were then added along with tetrabutylammonium hydrogen sulfate (71.3 mg, 0.21 mmol) and NaOH (8.4 mg, 0.21 mmol) and the resulting

biphasic mixture stirred vigorously at rt for 1 h. The CH_2Cl_2 layer was then separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 ml). All organic layers were then combined and washed with water (3 × 10 ml). All aqueous layers were then recombined and reextracted with CH_2Cl_2 (2 × 10 ml) and then these organic layers were subsequently combined and washed again with water (3 × 10 ml). All organic layers were then combined, dried over $MgSO_4$, filtered and concentrated to give the title compound as viscous yellow oil with ~17% impurity (110 mg, 0.18 mmol, 86%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.49 (s, 1H), 8.43 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 8.19 (d, J =8.0 Hz, 1H), 7.57 (s, br, 1H), 7.56 (s, br, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.76 (s, 1H), 3.99 (s, 2H), 3.90 (s, 2H), 3.21−3.15 (m, 8H), 2.34 (s, 3H), 2.21 (s, 3H), 1.58−1.50 (m, 8H), 1.38−1.30 (m, 8H), 0.93 (t, J = 7.4 Hz, 12H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.1, 153.7, 149.5, 149.5, 139.0, 137.5, 137.4, 137.3, 136.8, 135.4, 133.0, 129.5, 128.2, 127.7, 120.5, 120.3, 58.7, 57.7, 38.7, 24.0, 21.3, 19.7, 18.3, 13.7; HRMS: m/z: $[M]^-$ calc'd for $[C_{20}H_{19}N_2O_3S]^-$ expect 367.1122, found 367.1123.

*4.2.22. Tetrabutylammonium (4-((4′-methyl-[2,2′-bipyridin]-4-yl) methyl)phenyl)methanesulfonate (**L4**)*

4-(4-(Bromomethyl)benzyl)-4′-methyl-2,2′-bipyridine **23** (95.0 mg, 0.27 mmol) and sodium sulfite (40.8 mg, 0.32 mmol) were placed under an argon atmosphere and then subsequently dissolved in acetone (3.1 ml) and water (4.7 ml). The reaction mixture was stirred and heated to 80 °C for 3.5 h. The reaction mixture was then blown down till all acetone had evaporated. More water (10 ml) was added and the aqueous mixture washed with diethyl ether (10 ml). CH_2Cl_2 (10 ml) was then added along with tetrabutylammonium hydrogens sulfate (110 mg, 0.32 mmol) and NaOH (13 mg, 0.32 mmol) and the resulting biphasic mixture stirred vigorously at rt for 2 h. The CH_2Cl_2 layer was then separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 ml). All organic layers were then combined and washed with water (3 × 10 ml). All aqueous layers were then recombined and reextracted with CH_2Cl_2 (3 × 10 ml) and then these organic layers were subsequently combined and washed again with water (3 × 10 ml). All organic layers were then combined washed with water (3 × 10 ml), dried over $MgSO_4$, filtered and concentrated to give the title compound as viscous colourless oil (109 mg, 0.18 mmol, 68%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.50 (d, J = 5.0 Hz, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.26 (s, br, 1H), 8.18 (s, br, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 7.10 (d, br, J = 5.5 Hz), 7.08 (dd, J = 5.0, 1.3 Hz, 1HH), 4.02 (s, 2H), 3.97 (s, 2H), 3.15−3.09 (m, 8H), 2.40 (s, 3H), 1.53−1.45 (m, 8H), 1.36−1.29 (m, 8H), 0.92 (t, J = 7.2, 12H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.2, 155.9, 151.4, 149.2, 148.9, 148.1, 137.0, 133.8, 130.9, 128.4, 124.6, 124.2, 122.0, 121.6, 58.7, 57.4, 41.4, 23.9, 21.1, 19.6, 13.6; HRMS: m/z: $[M]^-$ calc'd for $[C_{19}H_{17}N_2O_3S]^-$ expect 353.0965, found 353.0956.

*4.2.23. Tetrabutylammonium (3-methyl-5-((4′-methyl-[2,2′-bipyridin]-4-yl)methyl)phenyl)methanesulfonate (**L5**)*

4-(3-(Bromomethyl)-5-methylbenzyl)-4′-methyl-2,2′-bipyridine **24** (90.0 mg, 0.25 mmol) and sodium sulfite (37.1 mg, 0.29 mmol) were placed under an argon atmosphere and then subsequently dissolved in acetone (1 ml) and water (1.5 ml). The reaction mixture was stirred and heated to 80 °C for 3 h. The reaction mixture was then blown down till all acetone had evaporated. More water (10 ml) was added and this aqueous phase washed with diethyl ether (3 ml). CH_2Cl_2 (10 ml) was then added along with tetrabutylammonium hydrogen sulfate (98.5 mg, 0.29 mmol) and NaOH (11.6 mg, 0.29 mmol) and the resulting biphasic mixture stirred vigorously at rt for 1.5 h. The CH_2Cl_2 layer was then separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 ml). All organic layers were then combined and washed with water (3 × 10 ml), dried over $MgSO_4$, filtered and concentrated to give the title compound as viscous yellow oil with ~10% impurity (77.6 mg, 0.13 mmol, 52%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.51 (d, J = 4.9 Hz, 1H), 8.51 (s, J = 4.9 Hz, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 7.19 (s, 2H), 7.11 (d, br, J = 4.9 Hz, 2H), 6.82 (s, 1H), 4.02 (s, 2H), 3.97 (s, 2H), 3.26−3.20 (m, 8H), 2.42 (s, 3H), 2.24 (s, 3H), 1.62−1.55 (m, 8H), 1.43−1.35 (m, 8H), 0.96 (t, J = 7.2 Hz, 12H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.1, 156.0, 151.5, 149.1, 148.9, 148.0, 138.2, 137.5, 135.4, 129.6, 128.4, 127.9, 124.6, 124.3, 122.0, 121.7, 58.7, 57.7, 41.4, 24.0, 21.3, 21.1, 19.6, 13.6; HRMS: m/z: $[M]^-$ calc'd for $[C_{20}H_{19}N_2O_3S]^-$ expect 367.1122, found 367.1128.

*4.2.24. 5′-Methyl-[2,2′-bipyridine]-5-carbaldehyde (**32**)*

5-(Bromomethyl)-5′-methyl-2,2′-bipyridine **2** (1.00 g, 3.80 mmol) and 4-methylmorpholine *N*-oxide (1.78 g, 15.2) were added to an oven dried RBF under an argon atmosphere. MeCN (40 ml) was added at 0 °C and the resulting solution was stirred for 5 min and then rt for 17 h. The MeCN was then removed *in vacuo* and water (35 ml) was added and the product extracted with CH_2Cl_2 (4 × 30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude residue was purified *via* silica column chromatography (2% MeOH in DCM) to give the title compound as a white solid (615 mg, 3.10 mmol, 82%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 10.12 (s, 1H), 9.07 (d, J = 2.0 Hz, 1H), 8.53 (d, J = 8.3 Hz, 1H), 8.52 (s, br, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.24 (dd, J = 8.3, 2.0 Hz, 1H), 7.64 (dd, J = 8.1, 1.6 Hz,1H), 2.40 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 190.7, 160.8, 152.2, 151.7, 150.0, 137.6, 136.8, 134.9, 130.8, 121.7, 120.9, 18.5; HRMS**:** m/z: $[M+H]^+$ calc'd for $[C_{19}H_{11}ON_2]^+$ expect 199.0866, found 199.0864.

*4.2.25. (5′-Methyl-[2,2′-bipyridin]-5-yl)(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methanol (**33**)*

2-((4-Bromobenzyl)oxy)tetrahydro-2*H*-pyran **7** (492 mg, 1.82 mmol) was dissolved in THF (5 ml) and cooled to −78 °C under an inert argon atmosphere. *n*-BuLi (1.09 ml, 1.6 M, 1.74 mmol) was added slowly and the reaction stirred at −78 °C for 1.5 h. 5′-methyl-[2,2′-bipyridine]-5-carbaldehyde **32** (300 mg, 1.51 mmol) was dissolved in THF (5 ml) and this solution was added dropwise to the organolithium solution and the reaction mixture stirred at −78 °C for 3 h. The reaction was then warmed to rt and the THF removed *in vacuo*. Water (15 ml) was added to the residue and the product extracted with CH_2Cl_2 (3 × 30 ml). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (1−3% MeOH in CH_2Cl_2) to give the title compound as a pink solid (391 mg, 1.00 mmol, 66%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.56 (d, J = 2.1 Hz, 1H), 8.44 (s, br, 1H), 8.22 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.73 (dd, J = 8.1, 2.1 Hz, 1H), 7.58 (dd, J = 8.1, 1.6 Hz, 1H), 7.34 (d, J =8.7 Hz, 2H, 7.32 (d, J =8.7 Hz, 2H), 5.84 (d, J =2.8 Hz, 1H), 4.75 (d, J =12.1 Hz, 1H), 4.67 (t, J = 3.5 Hz, 1H), 4.46 (d, J =12.1 Hz, 1H), 3.93−3.85 (m, 1H), 3.64 (t, br, J = 2.8 Hz, 1H), 3.56−3.49 (m, 1H), 2.36 (s, 3H), 1.89−1.78 (m, 1H), 1.76−1.67 (m, 1H) 1.67−1.46 (m, 4H); ^{13}C NMR (101 MHz; $CDCl_3$) δ 155.3, 153.4, 149.6, 147.6, 142.5, 139.2, 138.0, 137.5, 135.1, 133.4, 128.1, 126.6 (d, J = 1.7 Hz), 120.7, 120.6, 97.8, 73.8, 68.5, 62.1, 30.5, 25.4, 19.3, 18.3; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{24}H_{27}O_3N_2]^+$ expect 391.2016, found 391.2004.

*4.2.26. (5′-Methyl-[2,2′-bipyridin]-5-yl)(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methanone (**34**)*

(5′-Methyl-[2,2′-bipyridin]-5-yl)(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)methanol **33** (2.28 g, 5.83 mmol) was dissolved in CH_2Cl_2 (57 ml). MnO_2 (7.60 g, 87.4 mmol) was added and the reaction stirred at rt for 21 h. The reaction was filtered, and the filtrate concentrated to give a crude residue which was purified *via* silica column chromatography (20% EtOAc in Hexane) to give the title compound as a white solid (1.62 g, 4.17 mmol, 72%). ^{1}H NMR

(600 MHz; $CDCl_3$) δ 9.04 (d, J = 1.8 Hz, 1H), 8.54 (s, br, 1H), 8.51 (d, J = 8.2 Hz, 1H), 8.38 (d, J = 8.1 Hz, 1H), 8.21 (dd, J = 8.2, 2.2 Hz, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.66 (dd, J = 8.2, 1.6 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 4.89 (d, J = 12.9 Hz, 1H), 4.75 (t, J = 3.5 Hz, 1H), 4.61 (d, J = 13.0 Hz, 1H), 3.95–3.89 (m, 1H), 3.59–3.54 (m, 1H), 2.42 (s, 3H), 1.94–1.53 (m, 6H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 194.6, 159.0, 152.5, 150.6, 150.0, 144.0, 138.3, 137.6, 136.1, 134.5, 132.5, 130.2, 127.5, 121.4, 120.2, 98.1, 68.2, 62.2, 30.5, 25.4, 19.3, 18.5; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{24}H_{25}N_2O_3]^+$ expect 389.1860, found 389.1858.

4.2.27. 5-Methyl-5'-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy) methyl)phenyl)vinyl)-2,2′-bipyridine (**35**)

Methyltriphenylphosphonium bromide was dissolved in THF (10 ml) and cooled to 0 °C. n-BuLi (1.6 M in hexanes, 0.76 ml, 1.22 mmol) was added dropwise and the reaction then stirred for 30 min at 0 °C. A solution of (5′-Methyl-[2,2′-bipyridin]-5-yl)(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)methanone **34** (400 mg, 1.02 mmol) in THF (10 ml) was prepared and added slowly to the reaction at 0 °C. The reaction was slowly warmed to room temperature and stirred for 18 h before being quenched with sat. NH_4Cl solution (20 ml) and extracted with EtOAc (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give a crude residue that was purified *via* silica column chromatography (2 columns, col 1: 1% MeOH in CH_2Cl_2, col 2: 10–20% EtOAc in Hexane) to give the title compound as a white solid (240 mg, 0.62 mmol, 61%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.67 (d, J = 2.0 Hz, 1H), 8.51 (s, br, 1H), 8.32 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.72 (dd, J = 8.3, 2.3 Hz, 1H), 7.63 (dd, J = 8.1, 1.7 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 5.57 (s, 1H), 5.56 (s, 1H), 4.82 (d, J = 12.2 Hz, 1H), 4.74 (t, J = 3.5 Hz, 1H), 4.53 (d, J = 12.2 Hz, 1H), 3.97–3.90 (m, 1H), 3.60–3.52 (m, 1H), 2.40 (s, 3H), 1.94–1.49 (m, 6H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 155.5, 153.4, 149.7, 148.6, 146.6, 139.7, 138.4, 137.5, 136.6, 136.4, 133.4, 128.1, 127.9, 120.6, 120.1, 115.5, 97.9, 68.5, 62.2, 30.6, 25.5, 19.3, 18.4; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{25}H_{27}N_2O_2]^+$ expect 387.2067, found 387.2069.

4.2.28. (4-(1-(5′-Methyl-[2,2′-bipyridin]-5-yl)ethyl)phenyl) methanol (**36**)

A flask was charged with 5-methyl-5'-(1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)vinyl)-2,2′-bipyridine **35** (320 mg, 0.83 mmol), palladium on carbon (10% w/w, 88.3 mg, 0.083 mmol) and methanol (33 ml). A hydrogen balloon was fitted, and the reaction stirred for 17 h at rt. The reaction was filtered through Celite and concentrated. The residue was re-dissolved in MeOH (15 ml) and p-TsOH.H_2O (190 mg, 1.00 mmol) was added and the reaction stirred at rt for 4 h. The reaction was quenched with sat. $NaHCO_3$ solution and the MeOH removed *in vacuo*. The remaining aqueous layer was extracted with CH_2Cl_2 (5 × 20 ml) and the combined organic extracts dried over $MgSO_4$, filtered and concentrated to give a crude residue which was purified *via* silica column chromatography (2% MeOH in CH_2Cl_2) to give the title compound as a clear colourless oil which solidified over time to a white solid (208 mg, 0.68 mmol, 82%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.52 (d, J = 2.3 Hz, 1H), 8.45 (s, br, 6H), 8.24 (d, J = 8.2 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 7.61–7.56 (m, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 4.64 (d, J = 3.9 Hz, 2H), 4.20 (q, J = 7.3 Hz, 1H), 2.41 (t, br, J = 3.9 Hz, 1H), 2.36 (s, 3H), 1.67 (d, J = 7.3 Hz, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.2, 153.5, 149.5, 148.6, 144.5, 141.3, 139.2, 137.5, 135.9, 133.2, 127.7, 127.3, 120.6, 120.4, 64.9, 42.0, 21.5, 18.3; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{20}H_{21}N_2O]^+$ expect 305.1648, found 305.1648.

4.2.29. 5-(1-(4-(Bromomethyl)phenyl)ethyl)-5′-methyl-2,2′-bipyridine (**37**)

A flask was charged with (4-(1-(5′-methyl-[2,2′-bipyridin]-5-yl) ethyl)phenyl)methanol **36** (200 mg, 0.66 mmol) and CH_2Cl_2 (13 ml) then PBr_3 (1 M in CH_2Cl_2, 0.86 ml, 0.86 mmol) was added slowly. The reaction was stirred at rt for 20 h then diluted with H_2O and Na_2CO_3 was added until pH 10 was reached. The reaction was extracted with CH_2Cl_2 and the combined organic extracts dried over $MgSO_4$, filtered and concentrated to give a crude residue which was purified *via* silica column chromatography (1% MeOH in CH_2Cl_2) to give the title compound as a colourless oil (65.9 mg, 0.18 mmol, 27%). The product appears to be unstable when left in air. ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.53 (d, J = 2.1 Hz, 1H), 8.47 (s, br, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.23 (d, J = 8.2 Hz, 1H), 7.63–7.58 (m, 2H), 7.32 (d, J = 8.2 Hz, 2-H), 7.20 (d, J = 8.2 Hz, 2H), 4.46 (s, 2H), 4.21 (q, J = 7.2 Hz, 1H), 2.37 (s, 3H), 1.68 (d, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.4, 153.5, 149.6, 148.6, 145.5, 141.0, 137.4, 135.9, 135.9, 133.2, 129.3, 128.0, 120.5, 120.4, 42.0, 33.3, 21.4, 18.3; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{20}H_{20}N_2Br]^+$ expect 367.0804, found 367.0807.

4.2.30. Tetrabutylammonium (4-(1-(5′-methyl-[2,2′-bipyridin]-5-yl)ethyl)phenyl)methanesulfonate (**L6**)

5-(1-(4-(Bromomethyl)phenyl)ethyl)-5′-methyl-2,2′-bipyridine **37** (65.9 mg, 0.18 mmol) and sodium sulfite (27 mg, 0.22 mmol) were placed under an argon atmosphere and then subsequently dissolved in acetone (2 ml) and water (3 ml). The reaction mixture was stirred and heated to 80 °C for 4 h. More water (10 ml) was added and this aqueous phase was washed ether (3 ml). CH_2Cl_2 (10 ml) was then added along with tetrabutylammonium hydrogen sulfate (75 mg, 0.22 mmol) and NaOH (8.8 mg, 0.22 mmol) and the resulting biphasic mixture stirred vigorously at rt for 1 h. The CH_2Cl_2 layer was then separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 ml). All organic layers were then combined, washed with water (9 × 10 ml), dried over $MgSO_4$, filtered and concentrated to give the title compound as viscous colourless oil (49.6 mg, 0.08 mmol, 44%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.53 (d, J = 2.0 Hz, 1H), 8.45 (s, br, 1H), 8.21 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 7.61 (dd, J = 8.2, 2.2 Hz, 1H), 7.58 (dd, J = 8.2, 1.8 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 4.16 (q, J = 7.2 Hz, 1H), 4.03 (s, 2H), 3.17–3.10 (m, 8H), 2.36 (s, 3H), 1.65 (d, J = 7.2 Hz, 3H), 1.55–1.46 (m, 8H), 1.33 (sextet, J = 7.6 Hz, 8H), 0.93 (t, J = 7.6 Hz, 12H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 154.1, 153.6, 149.6, 148.6, 142.9, 141.7, 137.4, 135.8, 133.5, 133.1, 130.8, 127.0, 120.4, 120.3, 58.8, 57.3, 42.1, 23.9, 21.5, 19.7, 18.3, 13.6; HRMS: m/z: $[M]^-$ calc'd for $[C_{20}H_{19}N_2O_3S]^-$ expect 367.1122, found 367.1105.

4.2.31. 5-Bromo-2,2′-bipyridine (**38**)

THF (30 ml) was added to an RBF under an inert argon atmosphere. This was cooled to −78 °C and n-BuLi (29 ml, 1.38 M, 40.3 mmol) was added. A solution of 2-bromopyridine (3.43 ml, 36.0 mmol) in THF (10 ml) was then added dropwise to the n-BuLi solution which was then stirred for 30 min $ZnCl_2$ (9.81 g, 72.0 mmol) in THF (60 ml) was then added dropwise to the reaction, which was warmed to rt after addition and stirred for 2.5 h. To a separate flask under an argon atmosphere were added 5-bromo-2-iodopyridine (8.52 g, 30.0 mmol) and $Pd(PPh_3)_4$ (693 mg, 0.60 mmol) and these were dissolved in THF (60 ml). This solution was then added slowly to the organozinc solution and the resulting reaction mixture stirred at rt for 19 h. A saturated solution of EDTA and Na_2CO_3 was then added to the reaction followed by extraction with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified *via* silica column chromatography (10% EtOAc in 40–60 Pet. Ether) to give the title compound as an orange solid (2.57 g, 10.9 mmol, 30%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.62 (d, J = 2.4 Hz, 1H), 8.57 (d, J = 4.9 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.81 (dd, J = 8.6, 2.3 Hz, 1H), 7.69 (td,

J = 7.7, 1.9 Hz, 1H), 7.20 (ddd, J = 7.4, 4.8, 1.1 Hz, 1H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 155.0, 154.4, 150.1, 149.2, 139.4, 136.9, 123.9, 122.2, 121.1, 120.9. All data are in accordance with the literature [26].

*4.2.32. 5-(Prop-1-en-2-yl)-2,2′-bipyridine (**39**)*

An RBF under Ar was charged with 5-bromo-2,2′-bipyridine **38** (300 mg, 1.28 mmol), potassium isopropenyltrifluoroborate (284 mg, 1.92 mmol), Pd(dppf).CH_2Cl_2 (106 mg, 0.13 mmol), Na_2CO_3 (225 mg, 2.13 mmol), dioxane (30 ml) and H_2O (3 ml). The reaction was heated to reflux for 53 h and filtered through Celite, washing through with CH_2Cl_2. The filtrate was concentrated and purified *via* silica column chromatography (10% EtOAc in 40–60 Pet. Ether) to give the title compound as a white solid (106 mg, 0.54 mmol, 42%).^{1}H NMR (600 MHz; $CDCl_3$) δ 8.79 (d, J = 2.3 Hz, 1H), 8.67 (d, J = 4.8 Hz, 1H), 8.39 (d, J = 8.1 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.87 (dd, J = 8.3, 2.4 Hz, 1H), 7.80 (td, J = 7.7, 1.7 Hz, 1H), 7.29 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 5.50 (s, 1H), 5.22–5.20 (m, 1H), 2.20 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 155.9, 154.9, 149.2, 146.5, 140.2, 136.9, 136.4, 133.6, 123.6, 121.0, 120.5, 114.3, 21.4; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{13}H_{13}N_2]^+$ expect 197.1073, found 197.1072.

*4.2.33. 5-(2-(p-Tolyl)propan-2-yl)-2,2′-bipyridine (**40**)*

A crimp-top vial was charged with 5-(prop-1-en-2-yl)-2,2′-bipyridine **39** (112 mg, 0.57 mmol), toluene (0.49 ml, 4.56 mmol) and dichloroethane (1.4 ml). TfOH (0.40 ml, 4.56 mmol) was added, the vial sealed and heated to 100 °C for 21 h. The reaction was cooled to 0 °C and quenched with 10% NaOH solution. The reaction was extracted with EtOAc and the combined extracts dried over $MgSO_4$, filtered and concentrated to give the title compound as a brown oil (91.3 mg, 0.25 mmol, 44%, 4:1 *p*:*o*). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.67 (d, J = 4.8 Hz, 1H), 8.61 (d, J = 2.2 Hz, 1H), 8.37 (d, J = 8.0 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 7.80 (td, J = 7.8, 1.7 Hz, 1H), 7.66 (dd, J = 8.4, 2.5 Hz, 1H), 7.28 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 7.15 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 2.33 (s, 3H), 1.75 (s, 6H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.0, 153.4, 149.1, 147.9, 146.3, 136.9, 136.9, 135.6, 135.5, 129.0, 126.6, 123.5, 120.8, 120.3, 41.4, 30.4, 20.9; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{20}H_{21}N_2]^+$ expect 289.1699, found 289.1691.

*4.2.34. Tetrabutylammonium (4-(2-([2,2′-bipyridin]-5-yl)propan-2-yl)phenyl)methanesulfonate (**L7**).* To an oven-dried flask was added 5-(2-(*p*-tolyl)propan-2-yl)-2,2′-bipyridine **40** (91 mg, 0.25 mmol) and this was dissolved in cyclohexane (5 ml). To the solution was added NBS (173.4 mg, 0.98 mmol) and AIBN (12 mg, 0.075 mmol) and the resulting mixture placed under an argon atmosphere and heated for 6 h and then allowed to cool. The reaction mixture was then filtered through a silica plug washing with 1% MeOH in CH_2Cl_2. The solvent was removed *in vacuo* and the residue dissolved in acetone (2 ml) and H_2O (3 ml). Sodium sulfite (37.8 mg, 0.30 mmol) was added and the reaction heated to 80 °C for 2 h. The reaction mixture was then blown down till all acetone had evaporated. More water (10 ml) was added and this aqueous phase was washed with CH_2Cl_2 (10 ml) and ether (10 ml). CH_2Cl_2 (10 ml) was then added along with tetrabutylammonium hydrogen sulfate (102 mg, 0.30 mmol) and NaOH (12.0 mg, 0.30 mmol) and the resulting biphasic mixture stirred vigorously at rt for 1 h. The CH_2Cl_2 layer was then separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 ml). All organic layers were then combined and washed with water (9 × 10 ml) and dried over $MgSO_4$, filtered and concentrated to give the title compound as a yellow oil (60.1 mg, 0.099 mmol, 40%, 5:1 *p*:*o*). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.65 (d, J = 4.4 Hz, 1H), 8.59 (d, J = 1.8 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.66 (dd, J = 8.2, 2.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.29–7.25 (m, 1H), 7.16 (d, J = 8.0 Hz, 2H), 4.05 (s, 2H), 3.25–3.18 (m, 8H), 1.72 (s, 6H), 1.62–1.51 (m, 8H), 1.38 (sextet, J = 7.4 Hz, 8H), 0.96 (t, J = 7.4 Hz, 12H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 156.2, 153.4, 149.1, 148.0, 147.0, 146.3, 136.8, 135.4, 133.0, 130.4, 126.2, 123.4, 120.8, 120.3, 58.8, 57.3, 41.4, 30.4, 30.4, 24.0, 19.7, 13.7; HRMS: m/z: $[M]^-$ calc'd for $[C_{20}H_{19}N_2O_3S]^-$ expect 367.1122, found 367.1104.

*4.2.35. (4-(Hydroxymethyl)phenyl)(5′-methyl-[2,2′-bipyridin]-5-yl)methanone (**42**)*

(5′-Methyl-[2,2′-bipyridin]-5-yl)(4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenyl)methanone **34** (622 mg, 1.60 mmol) was dissolved in MeOH (32 ml). *p*-Toluenesulfonic acid monohydrate (335 mg, 2.08 mmol) was added slowly to the stirring solution. The reaction mixture was then stirred at rt for 3.5 h. Upon completion the reaction was quenched *via* slow addition of sat. $NaHCO_3$ solution (50 ml) until pH 8 was reached. The MeOH was then removed *in vacuo* and the remaining aqueous layer was extracted with CH_2Cl_2 (5 × 70 ml). The organic layers were then combined and dried over $MgSO_4$, filtered and concentrated to give a crude residue which was purified *via* silica column chromatography (2% MeOH in CH_2Cl_2) to give the title compound as a white solid (424 mg, 1.40 mmol, 87%). ^{1}H NMR (600 MHz; DMSO-d_6) δ 8.94 (d, J = 2.1 Hz, 1H), 8.58 (s, br, 1H), 8.51 (d, J = 8.3 Hz, 1H), 8.36 (d, J = 8.0, 1H), 8.23 (dd, J = 8.3, 2.1 Hz, 1H), 7.81 (dd, J = 8.0, 2.0 Hz, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 5.47 (t, br, J = 5.4 Hz, 1H), 4.63 (d, J = 4.7 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (151 MHz; DMSO-d_6) δ 194.3, 158.4, 152.1, 150.4, 150.4, 148.8, 138.8, 138.3, 135.3, 135.2, 133.0, 130.3, 126.8, 121.3, 120.2, 62.9, 18.3; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{19}H_{17}N_2O_2]^+$ expect 305.1285, found 305.1286.

*4.2.36. (4-(Bromomethyl)phenyl)(5′-methyl-[2,2′-bipyridin]-5-yl)methanone (**43**)*

(4-(Hydroxymethyl)phenyl)(5′-methyl-[2,2′-bipyridin]-5-yl)methanone **42** (300 mg, 0.99 mmol) was placed under and argon atmosphere and dissolved in CH_2Cl_2 (20 ml). PBr_3 (1 M in CH_2Cl_2, 1.28 ml, 1.28 mmol) was added to the solution and the reaction stirred at rt for 47 h. The reaction was then diluted with H_2O (20 ml) and sat. Na_2CO_3 solution was added until pH 10 was reached. The reaction mixture was then extracted with CH_2Cl_2 (5 × 50 ml) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified *via* silica column chromatography (1% MeOH in CH_2Cl_2) to give the title compound as a white solid (277 mg, 0.75 mmol, 76%).^{1}H NMR (600 MHz; $CDCl_3$) δ 9.03 (d, J = 1.8 Hz, 1H), 8.55 (s, br, 1H), 8.52 (d, J = 8.3 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.21 (dd, J = 8.2, 2.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.66 (dd, J = 8.1, 1.6 Hz, 1H), 7.54 (d, J = 8.1 Hz, 2H), 4.54 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 194.1, 159.2, 152.4, 150.6, 149.9, 142.8, 138.2, 137.6, 136.8, 134.5, 132.2, 130.5, 129.2, 121.5, 120.2, 32.0, 18.5; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{19}H_{16}N_2OBr]^+$ expect 367.0441, found 367.0443.

*4.2.37. Tetrabutylammonium (4-(5′-methyl-[2,2′-bipyridine]-5-carbonyl)phenyl)methanesulfonate (**L8**)*

(4-(Bromomethyl)phenyl)(5′-methyl-[2,2′-bipyridin]-5-yl)methanone **43** (100 mg, 0.27 mmol) and sodium sulfite (41 mg, 0.0.33 mmol) were placed under an argon atmosphere and then subsequently dissolved in acetone (2.0 ml) and water (3.0 ml). The reaction mixture was stirred and heated to 80 °C for 1.5 h. The reaction mixture was then blown down till all acetone had evaporated. More water (10 ml) was added and this aqueous phase was washed with CH_2Cl_2 (3 ml) and ether (3 ml). CH_2Cl_2 (10 ml) was then added along with tetrabutylammonium hydrogen sulfate (112 mg, 0.33 mmol) and NaOH (13.2 mg, 0.33 mmol) and the resulting biphasic mixture stirred vigorously at rt for 1 h. The CH_2Cl_2 layer was then separated and the aqueous layer extracted

with CH_2Cl_2 (2 × 10 ml). All organic layers were then combined and washed with water (6 × 10 ml), dried over $MgSO_4$, filtered and concentrated to give the title compound as viscous colourless oil (127 mg, 0.21 mmol, 77%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 9.02 (d, J = 2.1 Hz, 1H), 8.51 (d, J = 1.6 Hz, 1H), 8.46 (d, J = 8.3 Hz, 1H), 8.35 (d, J = 8.03 Hz, 1H), 8.16 (dd, J = 8.2, 2.1 Hz), 7.37 (d, J = 8.2 Hz, 2H), 7.66–7.60 (m, 3H), 4.14 (s, 2H), 3.21–3.14 (m, 8H), 2.39 (s, 3H), 1.60–1.51 (m, 8H), 1.37 (sextet, J = 7.4 Hz, 8H), 0.95 (t, J = 7.3 Hz, 12H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 194.7, 158.9, 152.6, 150.5, 149.9, 141.2, 138.2, 137.5, 135.0, 134.4, 132.6, 130.8, 129.7, 121.4, 120.0, 58.7, 57.7, 23.9, 19.7, 18.4, 13.6; HRMS: m/z: $[M]^-$ calc'd for $[C_{19}H_{16}N_2OBr]^+$ expect 367.0758, found 367.0755.

*4.2.38. (5′-Methyl-[2,2′-bipyridin]-5-yl)(p-tolyl)methanol (**44**)*

A flask under Ar was charged with 4-bromotoluene (0.31 ml, 2.50 mmol), Mg turnings (152 mg, 6.25 mmol), THF (5 ml) and a catalytic amount of I_2. The mixture was heated to 80 °C for 1 h. A solution of 5′-methyl-[2,2′-bipyridine]-5-carbaldehyde **32** (307 mg, 1.55 mmol) in THF (5 ml) was prepared and cooled to 0 °C. The solution of Grignard reagent was added dropwise to the aldehyde solution, and the reaction stirred at rt for 16 h. The reaction was quenched with sat. NH_4Cl solution and the pH adjusted to 8 using sat. $NaHCO_3$ solution. The reaction was extracted with EtOAc (3 × 100 ml) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified *via* silica column chromatography (1–2% MeOH in CH_2Cl_2) to give the title compound as a yellow solid (339 mg, 1.17 mmol, 75%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 8.58 (d, J = 2.1 Hz, 1H), 8.44 (d, J = 1.6 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 8.3, 2.1 Hz, 1H), 7.59 (dd, J = 8.2 Hz, 1.6 Hz), 7.25 (d, J = 7.9, 2H), 7.14 (d, J = 7.9 Hz, 2H), 5.83 (s, 1H), 3.62 (s, br, 1H), 2.37 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 155.1, 153.3, 149.5, 147.6, 140.2, 139.3, 137.6, 137.6, 135.1, 133.4, 129.4, 126.5, 120.7, 120.7, 73.8, 21.1, 18.4; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{19}H_{19}N_2O]^+$ expect 291.1492, found 291.1491.

*4.2.39. (5′-Methyl-[2,2′-bipyridin]-5-yl)(p-tolyl)methanone (**45**)*

(5′-Methyl-[2,2′-bipyridin]-5-yl)(*p*-tolyl)methanol **44** (271 mg, 0.93 mmol) was dissolved in CH_2Cl_2 (9 ml). MnO_2 (1.22 g, 14.0 mmol) was added and the reaction stirred at rt for 16 h. The reaction was filtered, and the filtrate concentrated to give a crude residue which was purified *via* silica column chromatography (1% MeOH in CH_2Cl_2) to give the title compound as a pale pink solid (229 mg, 0.59 mmol, 63%). ^{1}H NMR (600 MHz; $CDCl_3$) δ 9.03 (d, J = 2.1 Hz, 1H), 8.55 (s, br, 1H), 8.50 (d, J = 8.3 Hz, 1H), 8.37 (d, J = 8.1 Hz, 1H), 8.21 (dd, J = 8.3, 2.1 Hz, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.67 (dd, J = 8.2, 1.8 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 2.46 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 194.6, 158.9, 152.6, 150.5, 150.0, 144.1, 138.3, 137.6, 134.4, 134.3, 132.7, 130.3, 129.3, 121.4, 120.2, 21.8, 18.5; HRMS: m/z: $[M+H]^+$ calc'd for $[C_{19}H_{17}N_2O]^+$ expect 289.1335, found 289.1331.

4.3. Representative borylation procedure

*4.3.1. 1-(2-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)-N,N,N-trimethylmethanaminium 4-methylbenzenesulfonate (**46**)*

1-(2-Chlorophenyl)-*N,N,N*-trimethylmethanaminium 4-methylbenzenesulfonate **26** (89 mg, 0.25 mmol), B_2Pin_2 (95 mg, 0.375 mmol), $[Ir(COD)OMe]_2$ (2.5 mg, 0.00375 mmol) and **L2** (4.5 mg, 0.0075 mmol) were dissolved in THF (1.25 ml) under Ar in a crimp top vial and stirred at 50 °C for 16 h. The solvent was then removed by blowing air over the reaction. Analysis of crude ^{1}H NMR showed a 73:14:1:15 *para*:*meta*:*di-meta*:starting material (4.9:1 *para*:*meta* borylation). Trituration with ether followed by filtration and drying *in vacuo* gave the title compound as a light brown solid (109 mg, 0.19 mmol, 77%) as a mixture of 66:8:1:20 ratio of *para*:*meta*:*di-meta*:starting material. The yield reported takes into account all borylated products, using a weighted average to correct for remaining starting material. *Para*: (1-(2-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-N,N,N-trimethylmethanaminium 4-methylbenzenesulfonate): ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.86 (s, 1H), 7.75 (d, J =8.1 Hz, 2H), 7.74 (d, J = 7.7 Hz, 2H), 7.69 (dd, J = 7.7, 0.8 Hz), 7.12 (d, J = 8.1 Hz, 2H), 4.86 (s, 2H), 3.35 (s, 9H), 2.29 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (151 MHz; $CDCl_3$) δ 143.7, 139.3, 136.4, 136.1, 135.3, 133.6, 128.7, 128.2, 125.8, 84.6, 65.5, 53.0, 24.8, 21.2; HRMS: m/z: $[M]^+$ calc'd for $[C_{16}H_{26}BClNO_2]^+$ expect 310.1740, found 310.1737. *Meta*: (1-(2-Chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-N,N,N-trimethylmethanaminium 4-methylbenzenesulfonate): ^{1}H NMR (600 MHz; $CDCl_3$) δ 7.92 (d, J = 1.3 Hz, 1H), 7.83 (d, J = 7.9, 1.4 Hz, 1H), 7.75 (d, J =8.1 Hz, 2H), 7.47 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 8.1 Hz, 2H), 4.76 (s, 2H), 3.36 (s, 9H), 2.30, (s, 3H), 1.33 (s, 12H). All data are in accordance with the literature [8a].

Dedication

Dedicated to Professor Franziska Schoenebeck on her receipt of the 2022 Tetrahedron Young Investigator Award.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: James Douthwaite reports financial support for this work in the form of payment towards stipend and research costs was provided by AstraZeneca UK Ltd Macclesfield. Robert Phipps reports a relationship with AstraZeneca UK Ltd that includes: funding research grant studentships within the group.

Acknowledgements

We are grateful to the Royal Society for a University Research Fellowship (R.J.P.), the EPSRC and AstraZeneca for a CASE studentship (J.L.D.) and the EPSRC (EP/N005422/1). We are grateful to Dr. Andrew Turner (AstraZeneca) for support and useful discussions and Prof. Steven V. Ley for generous support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2022.132831.

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