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A low temperature, vinylboronate ester-mediated, iterative cross-coupling approach to xanthomonadin polyenyl pigment analogues

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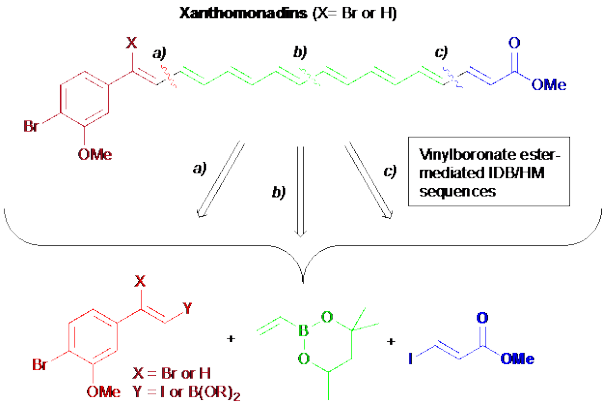
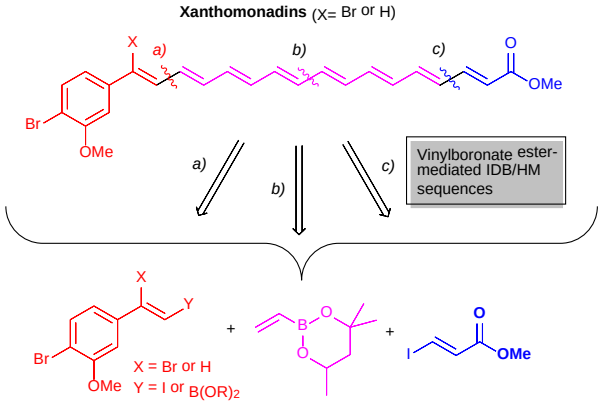
Dedicated to Professor Steve Davies for his major contributions to organic and asymmetric synthesis ~~and~~ over many years.

Abstract

Approaches to the polyene natural product xanthomonadin, an octaenyl electron-deficient bacterial photoprotective agent, and its debromo analogue, were developed. These involved the iterative cross-coupling of multiple C2-fragments, using a vinylboronate ester as a formal vinyl dianion equivalent. Vinyl iodide starting materials undergo Heck-Mizoroki cross-coupling at ambient temperatures, allowing further iododeboronation to derive the next vinyl iodide. This works in a highly effective manner to access systems of up to pentaene chain length. However, final assembly of polyenylboronates with such polyenyl iodides through their Suzuki-Miyaura cross-coupling was less successful, even at lower temperatures, reflecting the extreme sensitivity of such octaenylxanthomonadin analogues. Despite this, the mild cross-coupling conditions could be effectively applied to the assembly of a range of useful polyenyl building blocks, as well as a truncated pentaenyl-debromoxanthomonadin analogue.

Graphical abstract

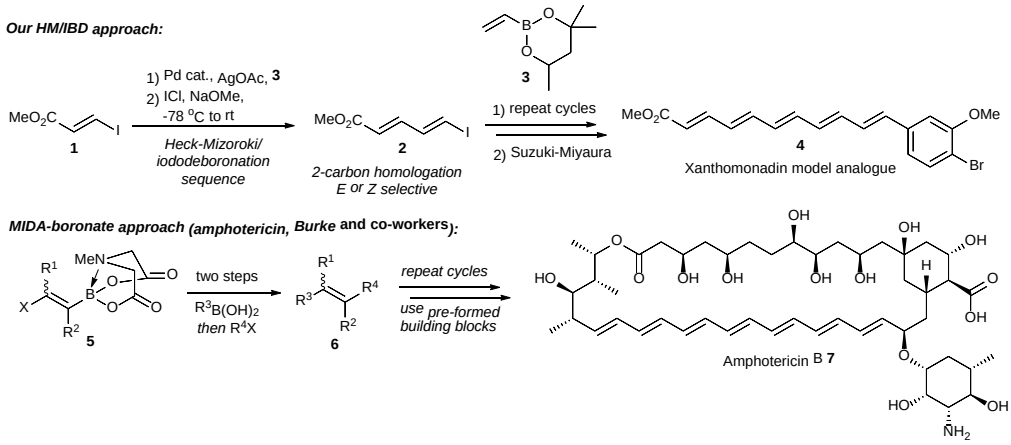




Keywords: Polyene; Iterative cross-coupling; Vinylboronate; Heck-Mizoroki reaction; Suzuki-Miyaura cross-coupling: Iodo-deboronation

1 Introduction

Polyenes represent an important class of natural products, showing diverse biological activity as antibiotics, anti-cancer agents, anti-oxidants and photo-protective agents. Together with their biological importance, their stereochemical and chemical properties make the synthesis of polyenes, both natural and unnatural, a particular synthetic challenge from both strategic and methodology standpoints.[1,2] Established methodologies for the synthesis of such compounds have historically relied upon bespoke syntheses using Wittig-type reactions and more recently cross-coupling reactions to link individually prepared fragments. Both approaches have associated issues, particularly with regard to atom economy in the case of Wittig reactions, toxicity in the case of the most popular Stille coupling, as well as more general concerns regarding the stability of the products under the reactions conditions, the general applicability of reactions, and the ability to achieve complete stereocontrol.[3] For instance, we demonstrated that the Heck-Mizoroki cross-coupling of vinyl dianion equivalents, vinylboronate esters, could be used in conjunction with a combination of iodo-deboronation (IDB) and Suzuki-Miyaura cross-couplings, i.e. an iterative cross-coupling (ICC) approach to polyenes,[4] that was then applied towards the synthesis of natural product polyenes such as phthoxazolin A and viridenomycin.[5] In recent years, this iterative cross-coupling has been further exemplified by the use of MIDA boronates, which have seen increasing use in the synthesis of such compounds. Burke and co-workers also successfully applied MIDA boronate methodology for the synthesis of amphotericin B and a range of synthetic analogues.[6,7] The two approaches have significant advantages over the previously mentioned alternatives: in particular, the need to design a new synthesis for each target compound is eliminated, and the issue of stereoselectivity is in principle reduced considerably through the inherent control that is available through the types of cross-coupling protocols employed.



Scheme 1. State-of-the-art in polyene synthesis and selected synthetic targets

Despite these advances our studies towards the stereoselective synthesis of several electron-deficient polyenes, variants of the photo-protective bacterial pigment xanthomonadin,[8] showed such systems to be particularly susceptible to *E/Z* isomerisation. Whilst our development of mild reaction conditions to perform our key Heck-Mizoroki (HM) reaction at 50 °C made the synthesis of many such compounds feasible,[5c] we subsequently found that for some substrates, even this temperature did not always achieve the high stereoselectivity intended. In particular, we have found that the xanthomonadin system represents a particularly significant synthetic challenge,[9] even more so due to the inherent instability of the substituted polyenes involved, both as intermediates and final products. We have recently demonstrated that shorter chain analogues of the xanthomonadin pigments are accessible by our previously reported methodology, and shown one of these to be photoprotective in *E. coli*.[9b] These studies also suggested that the 7-debromo analogue of xanthomonadin, itself a putative natural product, retains this photoprotective activity. Herein, we discuss the further development of our methodology towards the synthesis of less stable, longer chain xanthomonadin polyene natural product analogues and the key issues associated with this significant synthetic challenge.

Our original retrosynthetic strategy for methyl xanthomonadin and debrominated methyl xanthomonadin **9a** and **9b** involved utilising our ICC methodology.[4,5,9] The length of the polyene chain made various disconnections viable, though in all cases a final SM coupling was employed as outlined in Scheme 2. These disconnections led to known iodide **1**[10] and to either styrylboronate **10** or styryliodide **15** depending upon the point of disconnection (Scheme 2). Whilst both **10** and **15** are accessible from our previous work towards the synthesis of shorter chain xanthomonadin analogues,[9] disconnection a) initially appeared more promising due to the previously documented poor reactivity of iodide **15a** in the HM chemistry necessary to begin its extension to a polyene chain.[9a]

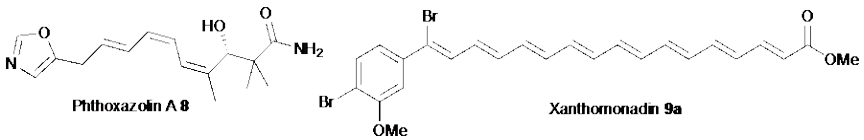
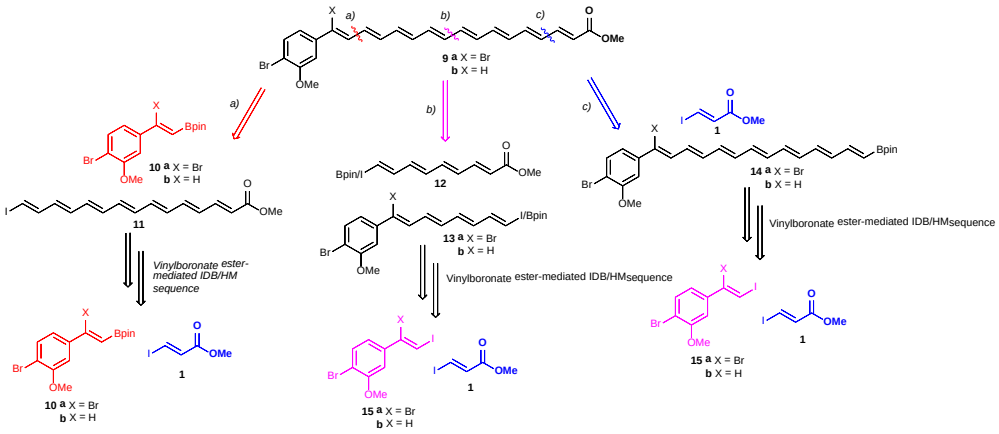


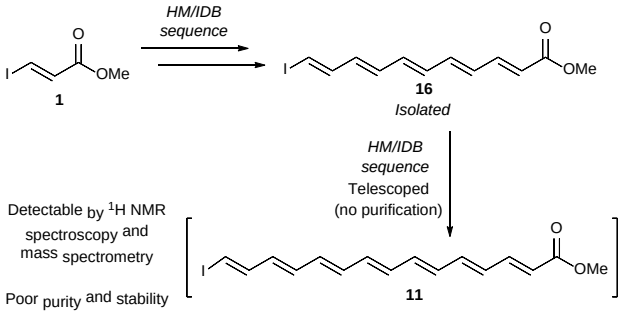
Figure 1. Structures of phthoxazolin A and xanthomonadin



Scheme 2. Representative retrosyntheses of xanthomonadin and debromoxanthomonadin

2 Results and Discussion

Initial attempts to prepare methyl xanthomonadin **9a**, therefore, focussed upon disconnection a), applying our vinylboronate ester-mediated HM/IDB methodology to the synthesis of key heptaenyl iodide building block **11**. This approach proved successful up to accessing pentaene **16** (Scheme 3); however, from this point, polyene chain extension became increasingly challenging due to the poor stability of the polyenyl intermediates. Attempting to solve this by telescoping reaction steps, in order to avoid contact with silica and minimise issues with handling, proved only partially successful and it remained clear from NMR analysis of **11**[11] that both isomerisation and decomposition was readily occurring.

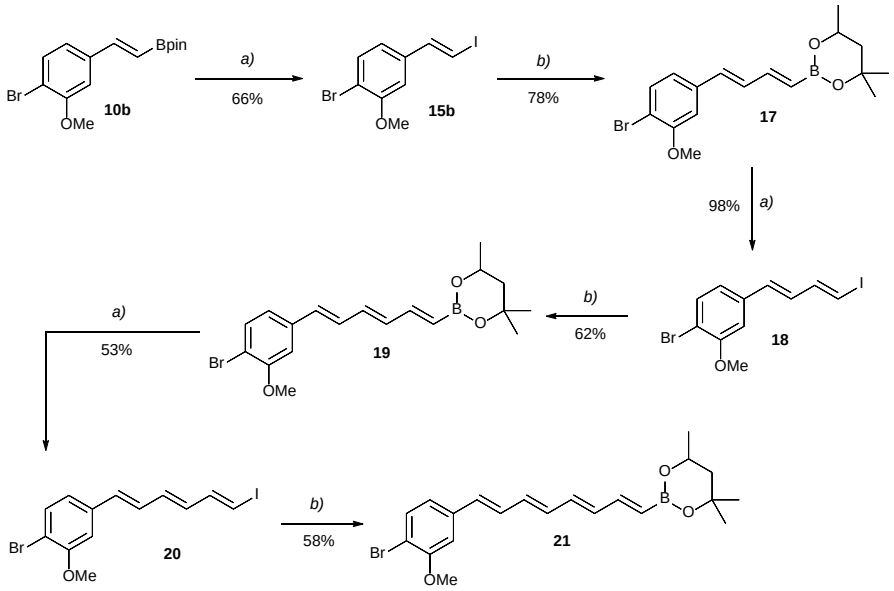


Scheme 3. Attempted synthesis of xanthomonadin building block, heptaenyliodide **11**, using ICC methodology

These attempts highlighted the need for a revised approach towards the synthesis of xanthomonadin and its analogues, necessarily employing milder conditions and ideally minimising the use of such long chain, electron-deficient polyenyl iodide intermediates, i.e. such as **11**. As discussed above, the lack of reactivity of the brominated styrenyl iodide **15a** to HM coupling necessitated the synthesis of heptaene **11** for the synthesis of xanthomonadin **9a** itself; however, we have recently demonstrated that debrominated xanthomonadin analogues demonstrate photo-protective effects.[9] We therefore elected to focus upon developing a route to debrominated methyl xanthomonadin **9b**, permitting the use of a wider range of disconnection approaches, as outlined in Scheme 2.

To this end, debromo-styrylboronate **10b** was synthesised as described previously,[9a] and subjected to IDB and HM steps (Scheme 4). The resulting dienyl boronate **17** was then

successfully taken through a further two HM/IDB cycles, to yield aryl tetraenyl boronate **21**. Due to concerns regarding stability, the reaction steps were initially telescoped without purification of intermediates, with the boronate products being characterised after each cycle by only HRMS to ensure the coupling reactions were proceeding as expected. This strategy proved successful, despite the final estimated yield being relatively low, i.e. with an overall yield of 5% over 6 steps. Repeating the sequence with purification of the intermediate boronates was then attempted, leading to a dramatic increase in the overall yield to 9%, or 67% on average per step, though purification of the polyenyl iodides was again avoided due to concerns over their stability. Some reduction in yield was however observed as the length of the polyene chain increased, with this trend being particularly obvious in the HM steps (see Scheme 4). This likely reflects a lack of stability of the intermediate iodides to the HM reaction conditions; indeed, whilst the polyenyl boronates appeared more stable than their ester functionalised counterparts (i.e. boronates **12** *vs.* **13**), the iodides appeared less stable even at this moderate polyene length. For instance, trienyl iodide **20** proved to be unstable even at room temperature in the absence of light, gradually changing from a bright yellow compound to a brownish material within two hours.[11]

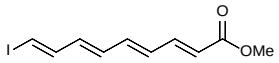


Reagents and conditions: a) $Pd(OAc)_2$ (5 mol%), $P(o\text{-}tol)_3$ (10 mol%), AgOAc (1.1 equiv.), MeCN, 50 °C; b) i) NaOMe (1.2 equiv.), THF, MeOH, -78 °C; ii) ICl (1.02 equiv.), CH_2Cl_2 ~~DCM~~, to rt.

Scheme 4. Construction of aryl tetraenyl boronate **21**

The observation that both sets of polyenyl iodides were unstable led us to consider whether our key HM step could be performed at an even lower temperature. Lower temperature SM coupling conditions have been reported previously,[5,9,12] and this led us to consider whether the same could be achieved for the key HM step. In order to assess how low the temperature would need to be to allow the reaction to proceed while ensuring greater starting material stability under the reaction conditions, tetraenyl iodide **22** was prepared and its thermal stability assessed in degassed d_3-MeCN. Samples were thus prepared and stored (in the absence of light) at different temperatures, leading to the results shown in Table 1.

Table 1. Effect of heat on tetraenyl iodide **22**



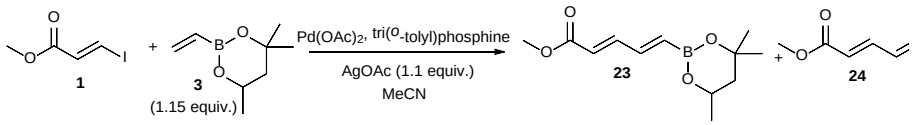
22

Entry	Temperature/ ^{o}C	Colour change over 2 hours	Remaining product after 2 hours /%[a]
1	rt	None	97
2	30	None	96
3	40	None	90
4	50	None	89
5	60	Yellow-pink-dark brown	84[b]

[a]Measured by comparison of ^{1}H NMR spectrum integrals between starting material and major impurity (multiplet at 9.65 ppm) after 2 hours [b]Multiple new peaks observed, suggesting multiple decomposition products.

It can be seen from Table 1 that even in the absence of catalysts and other reagents, iodide **22** showed reduced stability at both 40 and 50 °C. However, it also appeared that if the reaction temperature could be reduced to room temperature or even 30 °C, improved results might be expected. We therefore investigated the effect of the reaction temperature on the HM reaction of iodoacrylate **1**, this substrate being chosen as a model due to its ease of preparation and well understood reactivity under such conditions.[5c] Table 2 shows the effect of varying both the temperature and catalyst loading for the HM cross-coupling of iodide **1** with vinylboronate **3**.

Table 2. Temperature screen for the HM coupling of iodide **1** and boronate **3**, showing HM vs competing SM ratios.

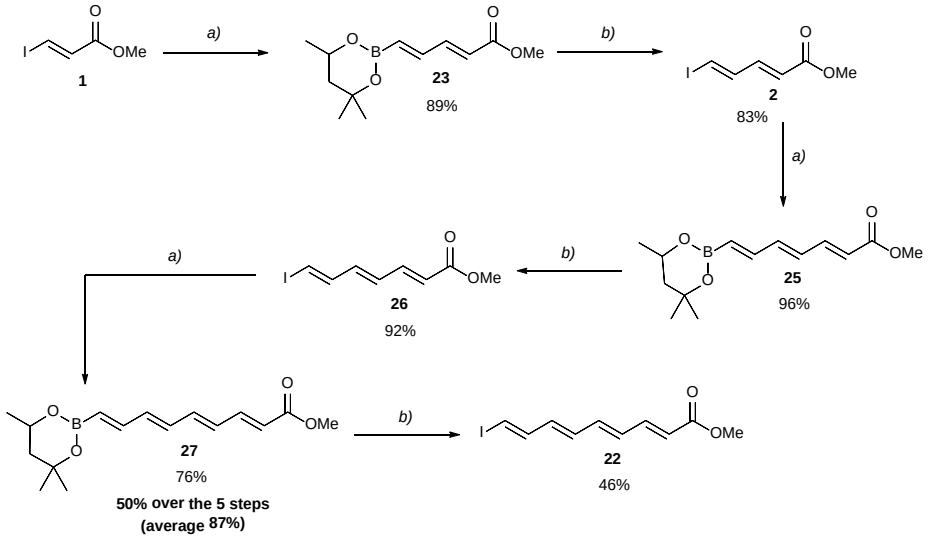


Entry	Catalyst loading/ mol%	Temperature / ^{o}C	Conversion after 24 h/ %	HM (23): SM (24)[a]
1	5	50	100	97:3
2	5	40	100	87:13
3	10	40	100	80:20
4	5	30	100	87:13
5	10	30	100	85:15
6	5	rt	100	72:28
7	10	rt	100	68:32

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture.

As can be seen from Table 2, all temperatures and catalyst loadings led to full conversion of the starting materials; however, the combined effect of both temperature and catalyst loading on the HM/SM product ratio was surprising. Whilst the formation of both HM and SM products is always possible in such reactions, our previously developed reaction conditions had afforded high selectivity for HM products.[5c-d] With selectivity becoming particularly problematic at room temperature, we felt that the results at 30 °C represented a good balance between reaction success and the stability of the longer chain polyenyl iodides. Hence, application of these particular conditions to the synthesis of tetraenyl iodide **22** at a reduced temperature was carried out. Despite issues with purification of the final product, this approach was indeed successful, resulting a 50% overall yield of boronate **27** , i.e. reflecting an 87% average yield per step (see Scheme 5). In all cases, it was noted that the competing SM product was formed under the HM reaction conditions, however, this was

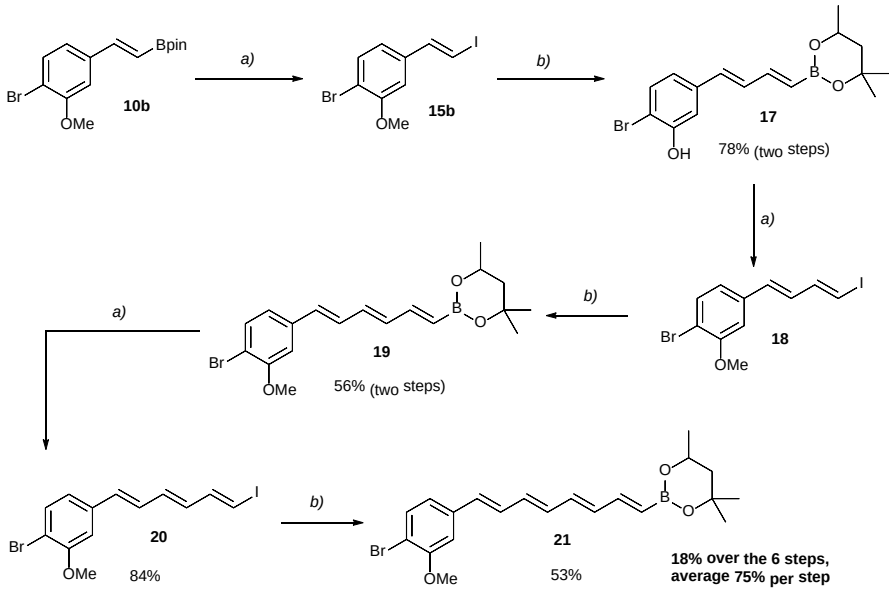
compensated for by reduced decomposition of the reacting iodides at the lower reaction temperature employed.



Reagents and conditions: a) $Pd(OAc)_2$ (5 mol%), $P(o\text{-}tol)_3$ (10 mol%), AgOAc (1.1 equiv.), MeCN, 30 °C; b) i) NaOMe (1.2 equiv.), THF, MeOH, -78 °C; ii) ICl (1.02 equiv.), CH_2Cl_2 ~~DCM~~, to rt.

Scheme 5. Reduced temperature ICC methodology to access tetraenyl iodide **22**

Having investigated and reduced the HM coupling reaction temperature, we then turned to the application of these conditions on the previously discussed aryl system starting with styrylboronate **10b** (Scheme 6). These improved reaction conditions proved more successful than previous attempts, with intermediates proving to be reactive even at the lower temperatures, demonstrated by tetraenylboronate **21** being prepared efficiently (Scheme 6) with the overall yield of boronate **21** doubling to 18% over 6 steps i.e. reflecting a 75% average yield per step. This increase in yield appears to be due entirely to the reduced decomposition during the HM step of the cycle through use of the lower temperature conditions.

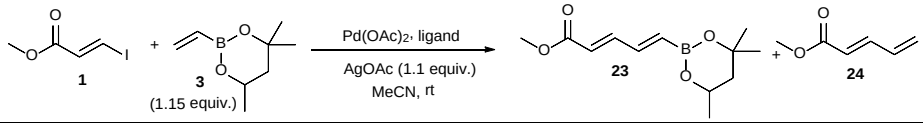


Reagents and conditions: a) $Pd(OAc)_2$ (5 mol%), $P(o\text{-}tol)_3$ (10 mol%), AgOAc (1.1 equiv.), MeCN, 30 °C; b) i) NaOMe (1.2 equiv.), THF, MeOH, -78 °C; ii) ICl (1.02 equiv.), CH_2Cl_2 ~~DCM~~, to rt.

Scheme 6. Synthesis of aryl tetraenylboronate **21** with 30 °C HM reactions

Despite this improvement, we remained curious as to whether this reaction could be made more efficient. In particular, we hoped that variation of the ligand, coupled with the reduced temperatures already employed, might allow an increase in reaction selectivity and thus overall yield, providing more material for SM studies. A small ligand screen was therefore performed and the results are shown in Table 3.

Table 3. Ligand screen for the HM coupling of iodoacrylate **1** and vinylboronate **3**, showing HM versus competing SM ratios.[a]



Entry	Ligand	Conversion after 3 h/%	HM: SM ratio[b]
1	No ligand	100	80:20
2	Tri(*o*-tolyl)phosphine	100	68:32
3	Triphenylphosphine	0	-
4	Tris(*o*-methoxyphenyl)phosphine	100	89:11
5	Tris(4-trifluoromethylphenyl)phosphine	0	-
6	Trifurylphosphine	100[c]	89:11

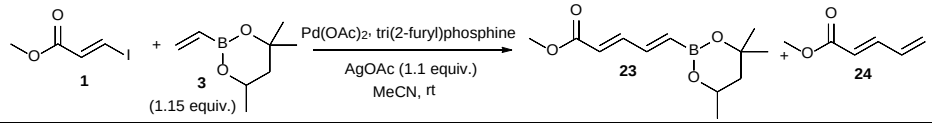
[a]Reaction undertaken using 10 mol% catalyst and 2 equivalents ligand relative to catalyst. [b]Ratios determined by ^{1}H NMR spectroscopy on the crude reaction. [c]Reaction complete after 1.5 hours

The results in Table 3 show that whilst tri(*o*-tolyl)phosphine is highly effective at 50 °C, at room temperature the complete absence of ligand is in fact preferable in terms of selectivity (Entries 1 and 2). In addition, while triphenylphosphine and tris(4-trifluoromethyl)phosphine (Entries 3 and 5) were found to give no reaction, the more electron rich tris(o-

methoxyphenyl)phosphine and tri(2-furyl)phosphine both gave full conversion with dramatically improved HM/SM selectivity (see Entries 4 and 6) with tri(2-furyl)phosphine in particular also providing rapid reaction with the catalyst loading employed.

With the ideal ligand identified, we undertook to reduce the catalyst loading, as shown in Table 4.

Table 4. Catalyst loading screen for the HM coupling of iodoacrylate **1** and vinylboronate **3**, showing HM vs competing SM ratios[a]



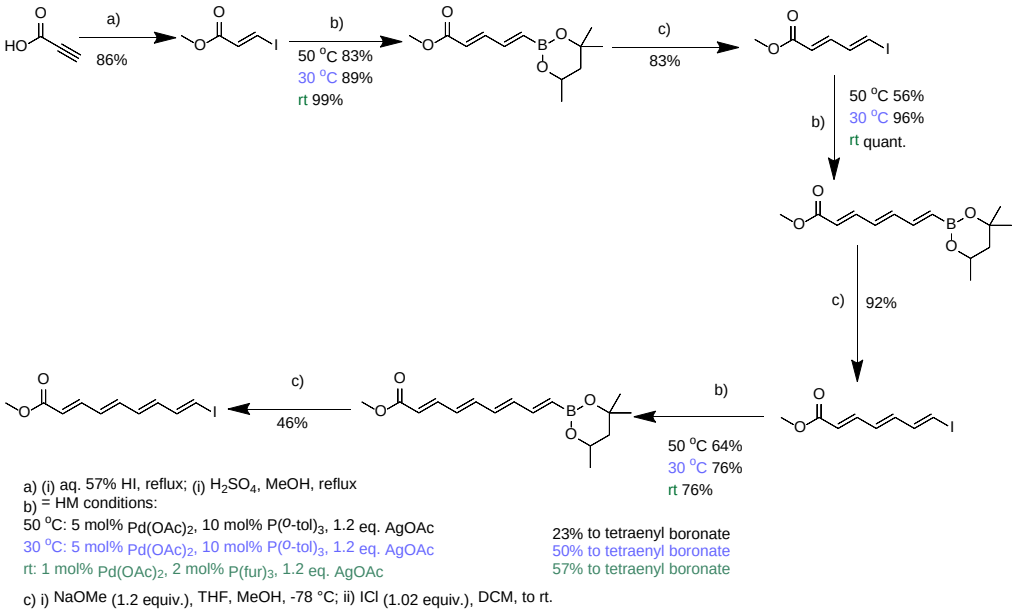
Entry	Catalyst loading/ mol%	Conversion after 3 h/%	HM: SM ratio after 3 h	Conversion after 25 h/%	HM: SM ratio after 25 h[b]
1	10	100	89:11	100	87:13
2	7.5	100	90:10	100	90:10
3	5	100	91:9	100	89:11
4	2.5	100	89:11	100	88:12
5	1	100	88:12	100	89:11
6	0.5	<1	-	31	77:23

[a]Reaction undertaken using 2 equivalents ligand relative to catalyst. [b]Ratios determined by ^{1}H NMR spectroscopy on the crude reaction.

As can be seen from Table 4, optimisation of the catalyst loading also proved highly successful, with 1 mol% palladium (Entry 5) being viable without loss of activity or selectivity for the HM reaction. Interestingly, a further reduction to 0.5 mol% led to not only to a dramatic reduction in conversion but also resulted in a significant erosion of chemoselectivity (Entry 6). Indeed, these observations are intriguing from a mechanistic perspective, because it is far from obvious that reducing the reaction temperature or decreasing the catalyst loading should lead to an erosion in HM selectivity. We have previously considered selectivity between the two possible pathways, as it represents a key aspect of our HM/IDB methodology. In fact, the high HM selectivity of the 50 °C conditions were somewhat unexpected given the results that preceded them, involving the use of a trialkylamine base in an apolar solvent;[4a,d,13] here it was generally found that the use of inorganic bases such as silver(I) carbonate favoured the SM pathway.[13,14] These amine base conditions were extended to a variety of substrates, but were ultimately too aggressive for the HM reactions of electron-deficient alkenes.[14] At this point the use of tri(o-tolyl)phosphine and silver(I) acetate in acetonitrile was developed through a combination of mechanistic investigation and screening of conditions.[8a] The lack of SM reaction in the presence of Ag(I) acetate (as compared to silver(I) carbonate) presumably reflects either the acetate anion's poor capacity to complex both Pd and the incoming boronate in the transition state of the transmetallation step, or its inability to form hydroxide from adventitious water due to its low basicity. Further, our work on HM reactions of other systems[4] suggests that the introduction of a species capable of generating a significant degree of boronate "ate"-complex formation is likely to reduce the rate of HM reaction. The full role of silver(I) acetate in these conditions remains unclear, however, with both the cation and anion being required to obtain high catalytic activity, we consider it likely that acetate forms an activating additive for the catalyst as well as a weak base catalyst turnover, whilst the silver cation itself plays a role in removing halide from the reaction, perhaps facilitating catalyst activation or turnover. However, these considerations do not explain why SM coupling should increasingly compete as the temperature is lowered. The fact that tri(2-furyl)phosphine and tris(2-methoxyphenyl)phosphine form the two most selective catalytic systems is somewhat

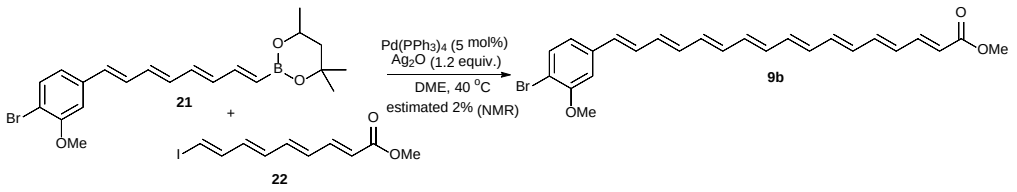
surprising given that the former represents a smaller, less basic phosphine than tri(o-tolyl)phosphine (Tolman cone angle 133° vs 194°, respectively[15,16]), whereas the latter is somewhat more electron rich and similarly bulky.[17] One possible explanation, accounting for both observations, comes from the resting state of the tri(*o*-tolyl)phosphine system, which is known[18] to form the *ortho*-palladated Herrmann's catalyst. It seems plausible that without sufficient thermal activation, the reductive step required to form the catalytically active species[19] could become sluggish, leading to a significant change in reactivity; indeed, the activity of this catalyst in related systems has been reported as requiring temperatures of 80 °C.[18] However, the lack of observed reactivity in the case of triphenylphosphine and tris(4-trifluoromethylphenyl)phosphine also demonstrates that the reaction can in fact be highly sensitive to changes in electronics, raising the question of why the electronically different tri(2-furyl)phosphine and tris(2-methoxyphenyl)phosphine should be similarly effective. This may relate to complex pre-equilibria behaviour, balancing the advantages of electron-rich catalysts against a need for ligand dissociation. Indeed, such effects are well documented for tri(2-furyl)phosphine-based systems in particular,[20] and further work would clearly be required to achieve a full understanding of complex mechanistic behaviour controlling selectivity in this system.

Having established room temperature conditions for the HM coupling, the synthesis of tetraenyl iodide **22** was performed at room temperature with a reduced catalyst loading (1 mol% *vs.* 5% as employed previously) as shown in Scheme 7. As with the reduction in temperature to 30 °C, cleaner reactions were observed, as well as good crude mass recovery. The yields themselves were either comparable, or better than, those obtained at 30 °C, despite the use of 80% less catalyst. Indeed, exceptionally high yields were obtained at room temperature for the first two HM couplings, which represents a marked improvement to the HM coupling conditions with the lower ligand loading at room temperature causing less of a build-up of phosphine-derived species (likely phosphine oxides) in the telescoped material, as well as a reduction in side-product formation. However, the bottleneck in this synthesis remained the final IDB step, where a large amount of material was lost upon purification. Despite this, these conditions remain a considerable improvement over those we have employed in the past, i.e. achieved through the reduction in both temperature and catalyst loading, leading to a significant increase in overall yield.



Scheme 7. Improvements in yield after optimisation of the HM methodology for the synthesis of tetraenyliodide **22**

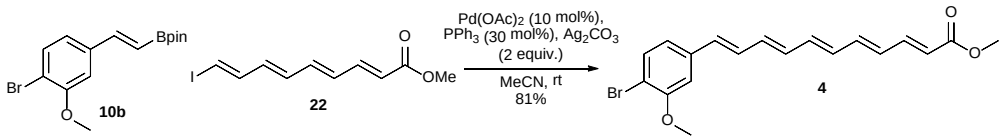
With highly efficient access to the required tetraenyl intermediates now established, we attempted to access debrominated methyl xanthomonadin **9b**, utilising the conditions employed in our published synthesis[9] of truncated analogue **4** for the final SM coupling. However, whilst a number of attempts were made to react tetraenylboronate **21** with tetraenyliodide **22**, and analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and mass spectrometry suggested the presence of the desired product **9b**, its isolation proved elusive on all occasions. This was attributed largely to rapid decomposition on silica gel, as demonstrated by 2D TLC analysis which clearly indicated high instability. Direct precipitation from the reaction mixture, as described in the original isolation of methyl xanthomonadin **9a**,[8] was also attempted. This procedure led to the isolation of a red solid which was mainly triphenylphosphine oxide, however, it also contained a highly conjugated polyene (2% yield according ^{1}H NMR spectroscopy) which was again consistent with debrominated methyl xanthomonadin **9b** by high resolution MS (Equation 4). However, the poor yield and our inability to separate the product from the rest of the reaction by-products meant that this approach remained an insufficient solution to the final assembly step of the synthesis, though not through insufficient cross-coupling reactivity, rather through a product stability issue.



Equation 1. Attempted Suzuki coupling of tetraenes **21** and **22**

Given this instability of systems of type **9b**, we turned to our truncated bioactive analogue **4** as a better model by which to examine the room temperature conditions for the final SM coupling. Indeed, this proved to be the case, and after some experimentation employing

$Pd(OAc)_2$ and 3 equivalents of PPh_3 to generate a coordinatively unsaturated Pd species *in situ*, combined with a non-nucleophilic silver-derived base, allowed the SM to be performed at room temperature, with a dramatic improvement in yield, i.e. from 34% to 81% (Equation 5). Therefore, if one removes the issues associated with longer chain polyene stability (i.e. reducing ~~dropping~~ the polyene chain-length from an octaene to a pentaene, it is possible to show that these types of cross-couplings are viable and of genuine utility.



Equation 2. Suzuki coupling to form truncated analogue **4**

3 Conclusion

In conclusion, improved low temperature, low catalyst-loading cross-coupling conditions have been developed to allow the synthesis of particularly unstable unsubstituted polyenic xanthomonadin analogues under mild reaction conditions, highlighting in the process the mechanistic complexities that underpin Suzuki-Miyaura *vs.* Heck-Mizoroki reaction selectivity in such systems. Further, whilst such polyenic molecules may be synthesised using this methodology, the purification of such systems remains a considerable challenge especially for the long-chain analogues. While we could demonstrate the formation of longer-chain, octaene systems, the improved conditions reported in this paper were more readily exemplified on shorter chain, pentaene systems, i.e. through the synthesis of truncated analogue **4** which showed a considerable increase in yield (Table 5) as the temperature was lowered. This clearly demonstrates the benefit of applying these low temperature conditions in the synthesis of polyenes that do not present formidable challenges in terms of purification. Indeed, such conditions are likely to be of considerable use for the synthesis of other polyene-containing structures which do not present the major stability challenge of the xanthomonadins, permitting the controlled synthesis of a range of stereoisomers at low temperature and catalyst loading.

Table 5. Effect of cross-coupling conditions on the yield of truncated xanthomonadin analogue **4**

Temperature for HM	Temperature for SM	Overall yield (12 steps)/ %	Average yield per step/ %
50 °C	40 °C	2	72
30 °C	40 °C	5	78
rt	rt	12	84

Concerning the issue of the stability of the longer chain polyenic systems, it may be the case that solid supported catalysts could be utilised to overcome product stability and isolation, i.e. with the ideal situation perhaps being the removal of all unwanted by-products, e.g. catalysts, ligands by filtration. This will still leave the challenge of separation of any residual starting materials and isomeric polyenic products, but could be the solution to managing the silica gel, air and light sensitive compounds. Overall of course, one has to marvel at the power of Nature when it comes to the synthesis of complex and unstable molecules whose function relates to their high reactivity. There is strong evidence that the xanthomonadin pigments are lipid bound (perhaps to impart some stability),[8,21] and this suggests that the development of new synthetic tools alone may not always be sufficient to match this prowess and ability to microencapsulate products enabling them to be stored long enough to act as effective photoprotective agents.

4 Experimental

4.1 General experimental

All reactions were carried out in oven-dried glassware with magnetic stirring unless otherwise stated. All chemicals were purchased from commercial suppliers and used without further purification. For synthesis of substituted polyene intermediates and final products, ~ 3 ppm of BHT radical inhibitor was added to all reaction, work-up and purification solvents. Where petroleum ether is stated, this refers to petroleum ether bp 40-60 °C. Anhydrous acetonitrile was obtained by distillation of HPLC grade acetonitrile over calcium hydride. Anhydrous THF was obtained by distillation of HPLC grade THF over sodium metal, with a benzophenone indicator. Solvents were degassed, unless stated otherwise, by sparging with argon for 20 minutes. For all palladium cross-coupling reactions, cross-shaped stirrer bars were used for the most efficient stirring. Monitoring of reactions was achieved using TLC and/or ^{1}H NMR. TLC was performed using silica plates. The silica plates were polyester-backed silica TLC plates with 0.2 mm silica gel and fluorescent indicator. Spots were visualised using an ultraviolet (UV) lamp and $KMnO_4$ dip, visualising in both long wave and short-wave UV. NMR experiments were carried out on either a Bruker Avance-400 or a Varian VNMRS-700 spectrometer in deuterated chloroform ($CDCl_3$-d), deuterated methanol (MeOD-d_4), or deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) reference. Experiments undertaken included ^{1}H, ^{11}B, ^{19}F, ^{13}C, COSY, PSYCHE, HSQC and HMBC NMR. Celite/silica filtration used Celite® S and technical grade silica gel: pore size 60 Å, 230-400 mesh particle size, 40-63 µm particle size. The term 'evaporated' refers to the removal of solvent in vacuo. Silica gel chromatography used technical grade silica gel: pore size 60 Å, 230-400 mesh particle size, 40-63 µm particle size. Where 0 °C is referred to as the temperature for column chromatography, all eluents were pre-cooled on ice and added to the column in small enough amounts to be confident that a low temperature was maintained throughout the column. A few drops of eluent containing ~3 ppm BHT radical inhibitor was also added to the bottom of each vial intended for collecting fractions. Electrospray ionisation (ESI) mass spectroscopy was undertaken using a LTQ FT (ThermoFinnigan) high resolution, accurate mass LC ES MS/MS or a Thermo Scientific LTQ Orbitrap XL. Samples were made up as 1 mg per mL solutions in acetonitrile. GC/MS EI was undertaken using a Waters GCT Premier. Atmospheric solids analysis probe (ASAP) mass spectroscopy was undertaken using LCT Premier XE (Waters) high resolution, accurate mass ultra-performance liquid chromatography (UPLC) ASAP or a Thermo Scientific LTQ Orbitrap XL. Samples were either made up as 1 mg per mL solutions in acetonitrile or run as solids. Infra-red (IR) spectroscopy was undertaken using a Perkin Elmer-1600 FTIR, using both liquid and solid samples. Melting point measurements were undertaken using a Gallenkamp melting point apparatus. UV-Vis measurements were carried out on a Varian Cary 100 Bio UV-Visible Spectrophotometer. Fluorescence measurements were carried out on a Jasco FP-6200 Spectrofluorometer. Both UV-Vis and fluorescence measurements were carried out using quartz cuvettes, with samples dissolved in either spectrophotometric grade diethyl ether, or spectrophotometric grade chloroform.

4.2 Specific experimental procedures

(2E,4E)-5-(4,4,6-Trimethyl-[1,3,2-dioxaborinan-2-yl]-penta-2,4-dienoic acid methyl ester **23**

Method 1: To a dry Schlenk flask was added $Pd(OAc)_2$ (36 mg, 0.16 mmol), P(*o*-tol)$_3$ (0.10 g, 0.33 mmol) and AgOAc (0.601 g, 3.60 mmol). The flask was purged with argon, and dry, degassed MeCN (10 mL) was added. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.655 mL, 3.80 mmol) was then added, followed by methyl (2*E*)-3-iodoprop-2-enoate (0.704 g, 3.32 mmol). The vessel was purged further with argon, and the reaction mixture was then heated to 50 °C with vigorous stirring for 2 days. The mixture was allowed to cool, then diluted with Et_2O (280 mL) and passed through a short Celite/silica plug. The organic

extracts were washed with 5% HCl (40 mL), H_2O (80 mL) and brine (80 mL), dried over $MgSO_4$, filtered and evaporated to yield 0.98 g of crude product as an orange oil. The crude product was purified by silica gel chromatography, eluent 10% EtOAc in hexane elution. Pure fractions were evaporated to yield (2*E*,4*E*)-5-(4,4,6-trimethyl-[1,3,2-dioxaborinan-2-yl]-penta-2,4-dienoic acid methyl ester as a yellow oil (0.404 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35-1.24 (9H, m), 1.5-1.47 (1H, m), 1.81 (1H, dd, *J*=14.0, 2.9 Hz), 3.75 (3H, s), 4.24 (1H, dqd, *J*=12.3, 6.2, 2.9 Hz), 5.99-5.86 (2H, m), 6.97 (1H, ddd, *J*=17.3, 11.0, 0.7 Hz), 7.33-7.21 (1H, m); ^{11}B NMR (128 MHz, $CDCl_3$): δ 25.52; ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.58, 28.62, 31.65, 46.41, 52.12, 65.52, 71.67, 123.17, 143.89, 146.54, 167.93; IR (ν_{max}, cm^{-1}) 2974.3 (w) 1719.5 (s) *inter alia*; LCMS (ESI+) 239.2 ; HRMS (ESI+) calculated $[C_{12}H_{19}BO_4+H]^+$ 238.1470, found 238.1491.

Method 2: To a dry flask was added methyl (2*E*)-3-iodoprop-2-enoate (2.82 g, 13.3 mmol), $Pd(OAc)_2$ (0.150 g, 0.67 mmol), P(*o*-tol)$_3$ (0.408 g, 1.34 mmol) and AgOAc (2.41 g, 14.4 mmol). The flask was purged with argon, and dry, degassed MeCN (80 mL) was added. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (2.6 mL, 15 mmol) was then added, the vessel was purged further with argon, and the reaction mixture was then heated to 50 °C with vigorous stirring for 23 hours. The mixture was allowed to cool, then diluted with Et_2O (200 mL) and passed through a short Celite/silica plug. The organic extracts were washed with NH_4Cl (200 mL), H_2O (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and evaporated to give crude product as a yellow oil (2.65g, 83%). The compound was taken on to the next stage without any further purification or characterisation.

Method 3: To a dry flask was added methyl (2*E*)- 3-iodoprop-2-enoate (2.82 g, 13.3 mmol), $Pd(OAc)_2$ (0.15 g, 0.67 mmol), P(*o*-tol)$_3$ (0.408 g, 1.34 mmol) and AgOAc (2.41 g, 14.4 mmol). The flask was purged with argon, and dry, degassed MeCN (72 mL) was added. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (2.6 mL, 15 mmol) was then added, the vessel was purged further with argon, and the reaction mixture was then heated to 30 °C with vigorous stirring for 19 hours. The mixture was allowed to cool, then diluted with Et_2O (200 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give crude product as a yellow oil (2.84g, 89%). The compound was taken on to the next stage without any further purification or characterisation.

Method 4: To a dry flask was added methyl (2*E*)-3-iodoprop-2-enoate (1.0 g, 4.7 mmol), $Pd(OAc)_2$ (0.011 g, 0.047 mmol), tri(2-furyl)phosphine (0.022 g, 0.094 mmol) and AgOAc (0.851 g, 5.11 mmol). The flask was purged with argon, and dry, degassed MeCN (28 mL) was added. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.93 mL, 5.4 mmol) was then added, the vessel was purged further with argon, and the reaction mixture was stirred vigorously at room temperature for 3 days. The mixture was diluted with Et_2O (71 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give crude product as a pale yellow oil (1.18 g, 99%). The compound was taken on to the next stage without any further purification or characterisation.

Methyl (2E,4E)-5-iodopenta-2,4-dienoate **2**

Method 1: NaOMe (4.2 mL, 2.1 mmol, 0.50 M solution in MeOH) was added dropwise to a solution of (2*E*,4*E*)-5-(4,4,6-trimethyl-[1,3,2-dioxaborinan-2-yl]-penta-2,4-dienoic acid methyl ester (0.404 g, 1.70 mmol) in THF (6.0 mL) cooled to -78 °C for 1 hour 50 minutes. Iodine monochloride (2.0 mL, 2.0 mmol, of a 1.0 M solution in DCM) was added dropwise and the reaction stirred for a further 2 h. The reaction mixture was allowed to warm to room temperature whilst stirring. The mixture was diluted with Et_2O (60 mL) and washed with 5% $Na_2S_2O_3$ (2 x 20 mL), H_2O (20 mL) and brine (20 mL). The organic extracts were dried over $MgSO_4$, filtered and evaporated to yield a pale orange solid. The crude material was purified by silica gel chromatography, eluent 5% EtOAc in petroleum ether at 0 °C. Pure fractions were evaporated to yield methyl (*2E,4E*)-5-iodopenta-2,4-dienoate as a white solid (0.337 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (3H, s), 5.84-5.98 (1H, m), 6.89-6.98 (1H, m), 7.12-7.22 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 51.6, 121.0, 125.1, 136.4, 142.9, 167.1. The compound was taken on to the next stage without any further characterisation.

Method 2: NaOMe (28 mL, 14 mmol, 0.50 M solution in MeOH) was added dropwise to a solution of (2*E*,4*E*)-5-(4,4,6-trimethyl-[1,3,2-dioxaborinan-2-yl]-penta-2,4-dienoic acid methyl ester (2.84 g, 11.9 mmol) in THF (44 mL) cooled to -78 °C under argon in the absence of light. The mixture was stirred at this temperature for 1 hour 5 minutes and iodine monochloride (12 mL, 12 mmol, of a 1.0 M solution in DCM) was added dropwise. The mixture was stirred at -78 °C for 2 hours, then allowed to warm to room temperature whilst stirring. The mixture was diluted with Et_2O (356 mL) and washed with 5% $Na_2S_2O_3$ (2 x 142 mL), water (142 mL) and brine (142 mL). The organic extracts were dried over $MgSO_4$, filtered and evaporated to 3.2 g of a brown oil containing desired product (2.14 g, 76%). The compound was taken on to the next stage without any further purification or characterisation.

Methyl (2E,4E,6E)-7-(4,4,6-trimethyl-1,3,2-dioxaborinane-2-yl)hepta-2,4,6-trienoate **25**

Method 1: To a dry Schlenk flask was added $Pd(OAc)_2$ (16 mg, 0.071 mmol), P(*o*-tol)$_3$ (43 mg, 0.14 mmol) and AgOAc (0.284 g, 1.7 mmol), followed by a solution of (*2E,4E*)-5-iodopenta-2,4-dienoate (0.337 g, 1.42 mmol) in dry, degassed MeCN (4.5 mL). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.24 mL, 1.4 mmol) was then added and the reaction mixture was then heated to 50 °C with vigorous stirring for 2 days. The mixture was allowed to cool, then diluted with Et_2O (80 mL) and passed through a short Celite/silica plug. The organic extracts were washed with H_2O (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and evaporated to yield crude product (0.33 g) as an orange oil. The crude product was purified by silica gel chromatography, eluent 10% EtOAc in hexane, to yield methyl (*2E*,*4E*,*6E*)-7-(4,4,6-trimethyl-1,3,2-dioxaborinane-2-yl)hepta-2,4,6-trienoate as a pale yellow solid (78 mg, 21%), mp 80.1-82.1°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36-1.23 (9H, m), 1.56-1.47 (1H, m), 1.80 (1H, dd, *J*=13.9, 3.0 Hz), 3.75 (3H, s), 4.24 (1H, ddp, *J*=12.3, 6.2, 3.2 Hz), 5.71 (1H, d, J=17.4 Hz), 5.92 (1H, d, *J*=15.3 Hz), 6.46-6.33 (1H, m), 6.58 (1H, ddd, *J*=15.0, 10.7, 0.9 Hz), 6.97 (1H, dd, *J*=17.4, 10.7 Hz), 7.35-7.27 (1H, m); ^{11}B NMR (128 MHz, $CDCl_3$): δ 25.90; ^{13}C NMR (101 MHz, $CDCl_3$): δ 23.1, 28.1, 31.2, 46.0, 51.6, 64.9, 71.0, 121.5, 131.7, 142.4, 144.5, 145.2, 167.4; IR (ν_{max}, cm^{-1}) 2972.0 (w), 2949.7 (w), 2924.1 (w) 1705.9 (s) *inter alia*; LCMS (ESI+) 264.1; HRMS (ESI+) calculated $[C_{14}H_{21}BO_4+H]^+$ 264.1620, found 264.1647.

Method 2: To a dry flask was added $Pd(OAc)_2$ (0.120 g, 0.525 mmol), P(*o*-tol)$_3$ (0.315 g, 1.50 mmol) and AgOAc (1.89 g, 11.3 mmol). The flask was purged with argon, and a solution of (*2E,4E*)-5-iodopenta-2,4-dienoate (2.50 g, 10.5 mmol) in dry, degassed MeCN (63 mL) was added. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (2.2 mL, 13 mmol) was then added, the vessel was purged further with argon, and the reaction mixture was then heated to 50 °C with vigorous stirring for 19.5 hours. The mixture was allowed to cool, then diluted with Et_2O (180 mL) and passed through a short Celite/silica plug. The organic extracts were washed with NH_4Cl (180 mL), H_2O (180 mL) and brine (100 mL), dried over $MgSO_4$, filtered, evaporated and dried on the high vacuum line for 2 days to give crude product as a brown oil (1.7 g, 48% from starting acrylate). The compound was taken on to the next stage without any further purification or characterisation.

Method 3: To a dry flask was added $Pd(OAc)_2$ (0.102 g, 0.460 mmol), P(*o*-tol)$_3$ (0.276 g, 0.911 mmol) and AgOAc (1.64 g, 9.81 mmol), followed by a solution of (*2E,4E*)-5-iodopenta-2,4-dienoate (2.14 g, 8.99 mmol) in dry, degassed MeCN (54 mL). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (1.8 mL, 10 mmol) was then added and the reaction mixture was then heated to 30 °C with vigorous stirring for 18.5 hours. The mixture was allowed to cool, then diluted with Et_2O (136 mL) and passed through a short Celite/silica plug. The solvent was evaporated to yield 3.8 g of a crude yellow solid containing desired product (8.67 mmol, 96% as determined by ^{1}H NMR spectroscopy). This material was taken on to the next stage without any further purification or characterisation.

Method 4: To a dry flask was added methyl (2*E,*4*E*)-5-iodopenta-2,4-dienoate (1.09 g, 4.58 mmol), $Pd(OAc)_2$ (9.5 mg, 0.043 mmol), tri(2-furyl)phosphine (0.020 g, 0.085 mmol) and AgOAc (0.766 g, 4.6 mmol). The flask was purged with argon, and dry, degassed MeCN (25 mL) was added. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.84 mL, 4.9 mmol) was then added, the vessel was purged further with argon, and the reaction mixture was stirred

vigorously at room temperature for 20 hours. The mixture was diluted with Et_2O (64 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give crude product as a dark orange oil (1.18 g, 100%). The compound was taken on to the next stage without any further purification or characterisation.

Methyl (2E,4E,6E)-7-iodohepta-2,4,6-trienoate **26**

NaOMe (21 mL, 10 mmol, 0.50 M solution in MeOH) was added dropwise to a solution of methyl (2*E*,4*E*,6*E*)-7-(4,4,6-trimethyl-1,3,2-dioxaborinane-2-yl)hepta-2,4,6-trienoate (2.28 g, 8.6 mmol) in THF (32 mL) cooled to -78 °C under argon in the absence of light. The mixture was stirred at this temperature for 40 minutes and iodine monochloride (8.8 mL, 8.8 mmol, 1.0 M solution in DCM) was added dropwise. The mixture was stirred at -78 °C for 2 hours, then allowed to warm to room temperature whilst stirring. The mixture was diluted with Et_2O (258 mL) and washed with $Na_2S_2O_3$ (2 x 103 mL), water (103 mL) and brine (103 mL). The organic extracts were dried over $MgSO_4$, filtered and evaporated to yield 4.9 g of a red solid,. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (3H,s), 5.98 (1H, d, *J*=15.3 Hz), 6.24-6.47 (2H, m), 6.61-6.71 (1H, m), 7.08-7.18 (1H, m), 7.20-7.31 (1H, m). The compound was taken on to the next stage without any further purification or characterisation.

Methyl (2E,4E,6E,8E)-9-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)nona-2,4,6,8-tetraenoate **27**

Method 1: To a dry flask was added $Pd(OAc)_2$ (82 mg, 0.36 mmol), P(*o*-tol)$_3$ (0.214 g, 0.714 mmol) and AgOAc (1.29 g, 7.71 mmol), followed by a solution of *methyl* (2*E*, 4*E*, 6*E*)-7-iodohepta-2,4,6-trienoate (1.70 g, 6.44 mmol) in dry, degassed MeCN (43 mL), which had been previously degassed by a bubbling argon needle. 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (1.5 mL, 8.6 mmol) was then added and the reaction mixture was then heated to 50 °C with vigorous stirring for 21 hours. The mixture was allowed to cool, then diluted with Et_2O (150 mL) and passed through a short Celite/silica plug. The organic extracts were washed with H_2O (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered and evaporated to yield 2.2 g of crude product as a brown oil. After drying the crude product on the high vacuum line for 2 days, 1.2 g of an orange solid was obtained. The compound was taken on to the next stage without any further purification or characterisation.

Method 2: To a dry flask was added $Pd(OAc)_2$ (98 mg, 0.44 mmol), P(*o*-tol)$_3$ (0.265 g, 0.875 mmol) and AgOAc (1.57 g, 9.42 mmol), followed by a solution of methyl (2*E*, 4*E*, 6*E*)-7-iodohepta-2,4,6-trienoate (2.28 g, 8.60 mmol) in dry, degassed MeCN (52 mL). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (1.4 mL, 8.6 mmol) was then added and the reaction mixture was then heated to 30 °C with vigorous stirring for 15.5 hours. The mixture was allowed to cool, then diluted with Et_2O (131 mL) and passed through a short Celite/silica plug. The solvent was evaporated to yield 3.95 g of a crude viscous orange oil containing desired product (1.90 g, 76%). After drying the crude product on the high vacuum line for 2 days, 1.2 g of an orange solid was obtained. The compound was taken on to the next stage without any further purification or characterisation.

Method 3: To a dry flask was added $Pd(OAc)_2$ (0.134 g, 0.440 mmol), P(*o*-tol)$_3$ (0.364 g, 1.20 mmol) and AgOAc (2.16 g, 13.0 mmol), followed by a solution of methyl (2*E*, 4*E*, 6*E*)-7-iodohepta-2,4,6-trienoate (3.14 g, 11.9 mmol) in dry, degassed MeCN (72 mL). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (2.0 mL, 12 mmol) was then added and the reaction mixture was then heated to 30 °C with vigorous stirring for 18 hours. The mixture was allowed to cool, then diluted with Et_2O (180 mL) and passed through a short Celite/silica plug. The solvent was evaporated to yield 4.5 g of a crude viscous orange oil. The crude product was purified by silica gel chromatography, eluent 5% EtOAc in petroleum ether, to give desired product as a bright yellow solid (0.90 g, 23% from iodoacrylate). ^{1}H NMR (700 MHz, $CDCl_3$): δ 1.23-1.33 (9H, m), 1.45-1.56 (1H, m), 1.79 (1H, dd, *J*=13.9, 2.9 Hz), 3.74 (3H, s), 4.22 (1H, ddt, *J*=11.5, 6.1, 2.9 Hz), 5.59-5.65 (1H, m), 5.84-5.93 (1H, m), 6.27-6.46 (3H, m), 6.54-6.63 (1H, m), 6.91-7.00 (1H, m), 7.28-7.37 (1H, m); ^{11}B NMR (128 MHz, $CDCl_3$): δ 25.92; ^{13}C NMR (176 MHz, $CDCl_3$): δ 23.1, 28.1, 31.2, 45.9, 51.5, 64.8, 70.9, 110.1, 120.6, 130.9, 133.6, 138.9, 140.6, 144.4, 145.8, 167.4; LCMS (ASAP) [M+H]=291.2;

HRMS (ASAP) calculated [$C_{16}H_{24}{}^{10}BO_4$] 290.1804, found 290.1777. The compound was taken on to the next stage without any further purification or characterisation.

Method 4: To a dry flask was added methyl (2*E*,4*E*,6*E*)-7-iodohepta-2,4,6-trienoate (0.737 g, 2.83 mmol), $Pd(OAc)_2$ (6.4 mg, 0.028 mmol), tri(2-furyl)phosphine (0.013 g, 0.056 mmol) and AgOAc (0.511 g, 3.07 mmol). The flask was purged with argon, and dry, degassed MeCN (17 mL) was added. 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.56 mL, 3.2 mmol) was then added, the vessel was purged further with argon, and the reaction mixture was stirred vigorously at room temperature for 25 hours. The mixture was diluted with Et_2O (43 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give crude product as a dark orange oil (1.21 g) containing desired product (2.15 mmol, 76% as determined by ^{1}H NMR spectroscopy. The compound was taken on to the next stage without any further purification or characterisation.

Methyl (2E,4E,6E,8E)-9-iodonona-2,4,6,8-tetraenoate **22**

NaOMe (26 mL, 13 mmol, 0.50 M solution in MeOH) was added dropwise over 5 minutes to a solution of a crude mixture containing methyl (2*E*,4*E*,6*E*,8*E*)-9-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)nona-2,4,6,8-tetraenoate (3.20 g, 10.9 mmol) in dry THF (41 mL) cooled to -78 °C under argon in the absence of light. The mixture was stirred at this temperature for 50 minutes and iodine monochloride (2.10 g, 11.3 mmol) in dry DCM (11 mL) was added dropwise over 5 minutes. The mixture was stirred at -78 °C for 3 hours 40 minutes, then allowed to warm to room temperature. The mixture was diluted with Et_2O (329 mL) and washed with $Na_2S_2O_3$ (2 x 132 mL), H_2O (132 mL) and brine (132 mL). The organic extracts were dried over $MgSO_4$, filtered and evaporated to yield 3.3 g of a dark brown solid. The crude product was purified by silica gel chromatography at 0 ^{o}C, eluent 0-5 % EtOAc in petroleum ether. Pure fractions were evaporated to yield desired product as an unstable yellow solid (0.754 g, 20% from starting iodoacrylate) ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.75 (3H,s), 5.92 (1H, d, *J*=15.0 Hz), 6.29 (1H, dd, *J*=8.7, 6.1 Hz), 6.38-6.45 (1H, m), 6.47-6.55 (2H, m), 7.07-7.14 (1H, m), 7.27-7.34 (2H, m); ^{13}C NMR (176 MHz, $CDCl_3$) δ 51.7, 121.3, 131.9, 132.1, 135.7, 139.8, 141.1, 144.2, 145.0, 167.5; LRMS (ASAP) [M+H]= 291.0; HRMS (ASAP) [$C_{10}H_{12}O_2{}^{127}I$], calculated 290.9882, found 290.9896.

Methyl (2E,4E,6E,8E,10E)-11-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)undeca-2,4,6,8,10-pentaenoate

To a dry flask was added $Pd(OAc)_2$ (45 mg, 0.20 mmol), P(*o*-tol)$_3$ (0.117 g, 0.394 mmol) and AgOAc (0.713 g, 4.26 mmol), followed by a solution of methyl (2*E*,4*E*,6*E*,8*E*)-9-iodonona-2,4,6,8-tetraenoate (1.10 g, 3.79 mmol) in dry, degassed MeCN (24 mL). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.75 mL, 4.3 mmol) was then added and the reaction mixture was then heated to 50 °C with vigorous stirring for 21 hours. The mixture was allowed to cool, then diluted with Et_2O (100 mL) and passed through a short Celite/silica plug. The organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and evaporated to yield 1.2 g of crude product a deep red solid. A small portion (0.153 g) was taken and purified by silica gel chromatography, eluent 10% EtOAc in petroleum ether to verify presence of product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21-1.35 (9H, m), 1.41-1.51 (1H, m), 1.72-1.88 (1H, m), 3.74 (3H, s), 4.23 (1H, ddh, *J*=12.2, 6.2, 2.9 Hz), 5.56-5.68 (1H, m), 5.88 (1H, d, *J*=15.3 Hz), 6.25-6.50 (5H, m), 6.92-7.02 (1H, m), 7.32 (1H, ddd, *J*=13.0, 11.0, 3.7 Hz); ^{11}B NMR (128 MHz, $CDCl_3$) δ 23.80.

1-Bromo-4-[(E)-2-iodoethenyl]-2-methoxybenzene **15b**

2-[(*E*)-2-(4-Bromo-3-methoxyphenyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.30 g, 3.85 mmol) was dissolved in dry THF (14 mL) and cooled to -78 °C under argon. NaOMe (9.2 mL, 4.6 mmol, 0.50 M in MeOH) was added dropwise and then reaction mixture stirred at -78 °C for 1 hour 15 minutes. Iodine monochloride (0.736 g, 3.95 mmol) in dry DCM (3.9 mL) was then added dropwise at this temperature and the reaction mixture stirred at -78 °C for a further 2 hours 10 minutes. The reaction mixture was allowed to warm to room temperature and diluted with Et_2O (116 mL), then washed with 5% $Na_2S_2O_3$ (2 x 46 mL), H_2O (46 mL) and brine (46 mL). The organics were dried over $MgSO_4$ under argon, filtered and evaporated to give 1.30 g of a crude yellow solid containing desired product (0.863 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (3H, s), 6.75-6.82 (2H, m), 6.88 (1H, d, *J*=14.9 Hz), 7.37 (1H, d, *J*=14.9 Hz), 7.48 (1H, d, *J*=7.9 Hz). The compound was taken on to the next stage without any further purification or characterisation.

2-[(1E,3E)-4-(4-Bromo-3-methoxyphenyl)buta-1,3-dien-1-yl]-4,4,6-trimethyl-1,3,2-dioxaborinane **17**

Method 1: 1-Bromo-4-[(*E*)-2-iodoethenyl]-2-methoxybenzene (0.863 g, 2.55 mmol) was dissolved in dry, degassed MeCN (15 mL) and added to a dry, argon-purged flask containing $Pd(OAc)_2$ (29 mg, 0.13 mmol), P(*o*-tol)$_3$ (77 mg, 0.26 mmol) and AgOAc (0.458 g, 2.74 mmol). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.50 mL, 2.9 mmol) was then added and the reaction mixture heated to 50 °C for 18 hours. The reaction mixture was allowed to cool to room temperature, then diluted with Et_2O containing ~3 ppm BHT (38 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give 1.37 g of crude product as a viscous orange oil. The crude product was purified by silica gel chromatography, elution gradient 0-10 % EtOAc in petroleum ether. Pure fractions were evaporated to give desired product as a viscous yellow oil (0.725 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.23-1.33 (9H, m), 1.46-1.53 (1H, m), 1.80 (1H, ddd, *J*=14.0, 11.2, 2.9 Hz), 3.92 (3H, s), 4.24 (1H, dddq, *J*=14.8, 9.0, 6.1, 3.1 Hz), 5.64 (1H, d, *J*=17.4 Hz), 6.59 (1H, d, *J* =15.6 Hz), 6.77-6.84 (1H, m), 6.87-6.94 (2H, m), 7.06 (1H, dd, *J*=17.3, 10.5 Hz), 7.42-7.47 (1H, m); ^{11}B NMR (128 MHz, $CDCl_3$): δ 25.56; ^{13}C NMR (151 MHz, $CDCl_3$): δ 23.1, 28.1, 31.2, 46.0, 64.8, 70.8, 109.7, 111.3, 120.3, 131.7, 133.3, 133.6, 134.9, 137.9, 146.3, 155.9; LRMS (ASAP) [M+H]= 365.1; HRMS (ASAP) [$C_{17}H_{23}{}^{10}BO_3Br$] calculated 364.0960, found 364.0958.

Method 2: 1-Bromo-4-[(*E*)-2-iodoethenyl]-2-methoxybenzene (1.40 g, 4.15 mmol) was dissolved in dry, degassed MeCN (24 mL) and added to a dry, argon-purged flask containing $Pd(OAc)_2$ (46 mg, 0.21 mmol), P(*o*-tol)$_3$ (0.123 g, 0.41 mmol) and AgOAc (0.733 g, 4.38 mmol). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.80 mL, 4.8 mmol) was then added and the reaction mixture heated to 30 °C for 21.5 hours. The reaction mixture was allowed to cool to room temperature, then diluted with Et_2O containing ~3 ppm BHT (61 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give 1.67 g of crude product as a viscous orange oil. The crude product was purified by silica gel chromatography, elution gradient 0-10 % EtOAc in petroleum ether. Pure fractions were evaporated to give desired product as a viscous yellow oil (1.10 g, 73% over the two steps).

1-Bromo-4-[(1E,3E)-4-iodobuta-1,3-dien-1-yl]-2-methoxybenzene **18**

2-[(*1E*,*3E*)-4-(4-bromo-3-methoxyphenyl)buta-1,3-dien-1-yl]-4,4,6-trimethyl-1,3,2-dioxaborinane (0.725 g, 1.99 mmol) was dissolved in dry THF (7.3 mL) and cooled to -78 °C under argon. NaOMe (4.8 mL, 2.4 mmol, 0.50 M in MeOH) was added dropwise and then reaction mixture stirred at -78 °C for 55 minutes. Iodine monochloride (0.383 g, 2.05 mmol) in dry DCM (2.0 mL) was then added dropwise at this temperature and the reaction mixture stirred at -78 °C for a further 2 hours. The reaction mixture was allowed to warm to room temperature and diluted with Et_2O (60 mL), then washed with 5% $Na_2S_2O_3$ (2 x 24 mL), H_2O (24 mL) and brine (24 mL). The organics were dried over $MgSO_4$ under argon, filtered and evaporated to give a crude yellow solid containing desired product (0.708g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (3H, s), 6.47-6.49 (1H, m), 6.51-6.53 (1H, m), 6.67 (1H, ddd, *J*=15.6, 10.6, 0.7 Hz), 6.85-6.91 (2H, m), 7.17 (1H, ddd, *J*=14.4, 10.6, 0.7 Hz), 7.44-7.48

(1H, m). The compound was taken on to the next stage without any further purification or characterisation.

2-[(1E,3E,5E)-6-(4-Bromo-3-methoxyphenyl)hexa-1,3,5-trien-1-yl]-4,4,6-trimethyl-1,3,2-dioxaborinane **19**

Method 1: 1-Bromo-4-[(*1E,3E*)-4-iodobuta-1,3-dien-1-yl]-2-methoxybenzene (0.708 g, 1.95 mmol) was dissolved in dry, degassed MeCN (11.6 mL) and added to a dry, argon-purged flask containing $Pd(OAc)_2$ (22 mg, 0.10 mmol), P(*o*-tol)$_3$ (59 mg, 0.190 mmol) and AgOAc acetate (0.348 g, 2.08 mmol). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.38 mL, 2.2 mmol) was then added and the reaction mixture heated to 50 °C for 2 days 17 hours. The reaction mixture was allowed to cool to room temperature then diluted with Et_2O containing ~ 3 ppm BHT (29 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give 1.031 g of crude product as a brown oil. The crude product was purified by silica gel chromatography, elution gradient 0-10% EtOAc in petroleum ether. Pure fractions were evaporated to yield desired product as a bright yellow oil (0.470 g, 62%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.14-1.9 (1H, m), 1.46-1.55 (1H, m), 1.80 (1H, dd, *J*=13.9, 2.9 Hz), 3.92 (3H, s), 4.24 (1H, dqd, J=12.3, 6.2, 3.0 Hz), 5.58 (1H, d, *J*=17.4 Hz), 6.39-6.55 (3H, m), 6.82 (1H, dd, *J*=15.5, 10.0 Hz), 6.82-6.92 (2H, m), 7.00 (1H, dd, *J*=17.3, 9.9 Hz), 7.45 (1H, d, J=8.1 Hz); ^{11}B NMR (128 MHz, $CDCl_3$): δ 25.49; ^{13}C NMR (151 MHz, $CDCl_3$): δ 23.3, 28.3, 31.4, 46.2, 56.3 (OMe), 65.0, 71.0, 109.5, 111.0, 120.3, 130.0, 132.7, 133.5, 134.8, 136.2, 138.2, 146.5, 156.1; LRMS (ASAP) [M+H]= 391.1; HRMS (ASAP) [$C_{19}H_{24}{}^{10}BO_3Br$] calculated 389.1038, found 389.1023.

Method 2: 1-Bromo-4-[(*1E,3E*)-4-iodobuta-1,3-dien-1-yl]-2-methoxybenzene (1.0 g, 2.8 mmol) was dissolved in dry, degassed MeCN (16 mL) and added to a dry, argon-purged flask containing $Pd(OAc)_2$ (31 mg, 0.14 mmol), P(*o*-tol)$_3$ (83 mg, 0.27 mmol) and AgOAc (0.491 g, 2.93 mmol). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.53 mL, 3.1 mmol) was then added and the reaction mixture heated to 30 °C for 18 hours. The reaction mixture was allowed to cool to room temperature then diluted with Et_2O containing ~ 3 ppm BHT (41 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give 1.10 g of crude product as a viscous orange oil. The crude product was purified by silica gel chromatography, elution gradient 0-10% EtOAc in petroleum ether. Pure fractions were evaporated to yield desired product as a viscous yellow oil (0.600 g, 56%).

1-Bromo-4-[(1E,3E,5E)-6-iodohexa-1,3,5-trien-1-yl]-2-methoxybenzene **20**

The crude mixture containing 2-[(*1E*,*3E*,*5E*)-6-(4-bromo-3-methoxyphenyl)hexa-1,3,5-trien-1-yl]-4,4,6-trimethyl-1,3,2-dioxaborinane (0.60 g, 1.5 mmol) was dissolved in dry THF (5.7 mL) and cooled to -78 °C under argon. NaOMe (3.7 mL, 1.9 mmol, 0.50M in MeOH) was added dropwise and then reaction mixture stirred at -78 °C for 40 minutes. Iodine monochloride (0.296 g, 1.59 mmol) in dry DCM (1.2 mL) was then added dropwise at this temperature and the reaction mixture stirred at -78 °C for a further 2 hours. The reaction mixture was allowed to warm to room temperature and diluted with Et_2O (47 mL), then washed with 5% $Na_2S_2O_3$ (2 x 19 mL), H_2O (19 mL) and brine (19 mL). The organics were dried over $MgSO_4$ under argon, filtered and evaporated to give a bright yellow solid containing the desired product (1.26 mmol, 84%) as determined by ^{1}H NMR spectroscopy, which was found to rapidly decompose. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (3H, s), 6.34 (1H, dd, *J*=7.4, 1.2 MHz), 6.56-6.63 (2H, m), 6.81 (1H, dd, *J*=9.9, 7.6 Hz), 6.86-6.94 (3H, m), 7.11 (1H, dd, *J*=14.3, 10.6 Hz), 7.45-7.49 (1H, m). The compound was taken on to the next stage without any further purification or characterisation

2-[(1E,3E,5E,7E)-8-(4-Bromo-3-methoxyphenyl)octa-1,3,5,7-tetraen-1-yl]-4,4,6-trimethyl-1,3,2-dioxaborinane **21**

Method 1: 1-Bromo-4-[(*1E*,*3E*,*5E*)-6-iodohexa-1,3,5-trien-1-yl]-2-methoxybenzene (0.233 g, 0.60 mmol) was dissolved in dry, degassed MeCN (3.7 mL) and added to a dry, argon-purged flask containing $Pd(OAc)_2$ (7.0 mg, 0.031 mmol), P(*o*-tol)$_3$ (18 mg, 0.060 mmol) and AgOAc (0.109 g, 0.645 mmol). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.12

mL, 0.69 mmol) was then added and the reaction mixture heated to 50 °C for 20 hours. The reaction mixture was allowed to cool to room temperature, then diluted with Et_2O containing ~3 ppm BHT (25 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give 0.296 g of crude product as a dark red viscous oil. The crude product was purified by silica gel chromatography, elution gradient 0-10% EtOAc in petroleum ether. Pure fractions were evaporated to give desired product as a bright orange gum (0.146 g, 58%).

Method 2: 1-Bromo-4-[(*1E*,*3E*,*5E*)-6-iodohexa-1,3,5-trien-1-yl]-2-methoxybenzene (0.506 g, 1.30 mmol) was dissolved in dry, degassed MeCN (7.8 mL) and added to a dry, argon-purged flask containing $Pd(OAc)_2$ (15 mg, 0.067 mmol), P(*o*-tol)$_3$ (39 mg, 0.13 mmol) and AgOAc (0.232 g, 1.39 mmol). 4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane (0.25 mL, 1.5 mmol) was then added and the reaction mixture heated to 30 °C for 18.5 hours. The reaction mixture was allowed to cool to room temperature, then diluted with Et_2O containing ~3 ppm BHT (19 mL) and passed through a short Celite/silica plug. The solvent was evaporated to give 0.704 g of crude product as a dark red viscous oil. The crude product was purified by silica gel chromatography, elution gradient 0-10% EtOAc in petroleum ether. Pure fractions were evaporated to give desired product as a bright orange gum (0.289 g, 53%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.24-1.6 (9H, m), 1.46-1.54 (1H, m), 1.79 (1H, dd, *J*=13.8, 3.0 Hz), 3.92 (3H, s), 4.24 (1H, ddqd, *J*=12.3, 9.1, 6.0, 2.9 Hz), 5.55 (1H, d, *J*=17.3 Hz), 6.03-6.18 (1H, m), 6.39-6.44 (3H, m), 6.48-6.52 (1H, m), 6.84-6.94 (3H, m), 6.95-7.04 (1H, m), 7.45 (1H, d, *J*=8.1 Hz); ^{11}B NMR (128 MHz, $CDCl_3$): δ 25.37; ^{13}C NMR (151 MHz, $CDCl_3$): δ 23.3, 28.3, 31.4, 46.2, 56.3, 64.9, 71.0, 109.6, 110.9, 120.2, 129.7, 130.0, 132.0, 133.5, 134.1, 134.2, 135.1, 135.8, 138.3, 146.7, 156.1; IR (ν_{max}, cm^{-1}) 1568.7 (m), 1587.0 (m), 1607.7 (m), 2911.1 (m), 2938.7 (m), 2971.6 (m) *inter alia*; LRMS (ASAP) [M+H]= 417.1; HRMS (ESI) [$C_{21}H_{26}{}^{10}BO_3Br$] calculated 415.1195, found 415.1213.

Methyl (2E,4E,6E,8E,10E)-11-(4-bromo-3-methoxyphenyl)undeca-2,4,6,8,10-pentaenoate **4**

Method 1: 2-[(*E*)-2-(4-Bromo-3-methoxyphenyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (26 mg, 0.076 mmol), methyl (*2E*, *4E*, *6E*,*8E*)-9-iodonona-2,4,6,8-tetraenoate (18 mg, 0.061 mmol), $Pd(PPh_3)_4$ (7.0 mg, 0.0061 mmol) and Ag_2O (17 mg, 0.076 mmol) were added to a dry flask and the flask purged with argon. Dry, degassed DME (0.46 mL) was then added and the reaction stirred at 40 °C for 17 hours. The reaction mixture was then diluted with EtOAc containing ~ 3ppm BHT (6.0 mL) and passed through a short plug of Celite/silica. The solvent was evaporated to give 55 mg of a green residue. The crude product was purified by silica gel chromatography at 0 °C, eluent benzene, to give desired product as a bright yellow solid (10 mg, 34%), mp 207.3-208.9 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.75 (3H, s, 3.92 (3H, s), 5.89 (1H, d, *J*=15.2 Hz), 6.37 (2H, ddd, *J*=15.1, 11.2, 4.3 Hz), 6.41-6.52 (3H, m), 6.55 (1H, d, *J*=15.5 Hz), 6.62 (1H, dd, *J*=14.7, 11.2 Hz), 6.80-6.85 (1H, m), 6.87-6.93 (2H, m), 7.29-7.35 (1H, m), 7.47 (1H, d, *J*=8.1 Hz); ^{13}C NMR (176 MHz, $CDCl_3$): δ 51.7, 56.3, 109.6, 111.3, 120.3, 120.5, 129.7, 130.5, 132.6, 133.1, 133.5, 133.7, 135.4, 137.2, 138.0, 140.8, 144.7, 156.2, 167.7; IR (ν_{max}, cm^{-1}) *inter alia* 1703.9 (m), 2912.8 (w), 2924.4 (w), 2938.4 (w), 2952.3 (w); LRMS (ASAP) M= 374.1; HRMS (ASAP) [$C_{19}H_{19}O_3Br$] calculated 374.0499, found 374.050. UV ($CHCl_3$ 5μM, nm) 397 (ε 67 000), 417 (ε 56 000). Fluorescence ($CHCl_3$ 100 nM, nm) 498, 527, 566, 594.

Method 2: 2-[(*E*)-2-(4-Bromo-3-methoxyphenyl)ethenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (26 mg, 0.076 mmol), methyl (*2E*, *4E*, *6E*,*8E*)-9-iodonona-2,4,6,8-tetraenoate (18 mg, 0.061 mmol), $Pd(OAc)_2$ (1.0 mg, 0.0061 mmol), PPh_3 (5.0 mg, 0.018 mmol) and Ag_2CO_3 (34 mg, 0.12 mmol) were added to a dry flask and the flask purged with argon. Dry, degassed MeCN (0.46 mL) was then added and the reaction stirred at room temperature for 17 hours. The reaction mixture was then diluted with EtOAc containing ~ 3ppm BHT (6.0 mL) and passed through a short plug of Celite/silica. The solvent was evaporated to give 82 mg of a green residue. The crude product was purified by silica gel chromatography at 0 °C, eluent benzene, to give desired product as a bright yellow solid (19 mg, 81%).

Methyl (2E,4E,6E,8E,10E,12E,14E,16E)-17-(4-bromo-3-methoxyphenyl)heptadeca-2,4,6,8,10,12,14,16-octaenoate **9b**

2-[(*1E*,*3E*,*5E*,*7E*)-8-(4-Bromo-3-methoxyphenyl)octa-1,3,5,7-tetraen-1-yl]-4,4,6-trimethyl-1,3,2-dioxaborinane (27 mg, 0.065 mmol), methyl (*2E*,*4E*,*6E*,*8E*)-9-iodonona-2,4,6,8-tetraenoate (16 mg, 0.055 mmol), $Pd(PPh_3)_4$ (7.0 mg, 0.025 mmol) and Ag_2O (15 mg, 0.065 mmol) were added to a dry flask and purged with argon. Dry, degassed DME (0.50 mL) was added and the reaction heated to 40 °C for 26 hours. The reaction mixture was allowed to cool to room temperature and then diluted with Et_2O containing ~ 3 ppm BHT (10 mL) and passed through a Celite plug. The organics were evaporated to give 25 mg of an orange residue. The crude product was dissolved in $CDCl_3$, and then cooled to 0 °C. Petroleum ether was added until precipitation of a red solid was achieved. The solid was collected on a sinter funnel and washed with cold petroleum ether, then the solid collected by dissolving in $CHCl_3$ and then removing the solvent *in vacuo* to give 7 mg of a red solid containing desired product (0.5 mg, 2 %) by ^{1}H NMR spectroscopy. ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.74 (3H, s), 3.95 (3H, s), 5.91-5.99 (3H, m), 6.24-6.47 (12H, m), 6.85-6.92 (2H, m), 7.43-7.50 (2H, m); LRMS (ASAP) M+H= 453.1; HRMS (ASAP) [$C_{25}H_{26}O_3Br$] calculated 453.1065, found 453.1058.

Conditions used for HM ligand screen

Methyl (2*E*)-3-iodoprop-2-enoate (0.141 g, 0.665 mmol), $Pd(OAc)_2$ (15 mg, 0.067 mmol), ligand (0.13 mmol) and AgOAc (0.120 g, 0.721 mmol) were added to dry flasks under argon in the absence of light. Degassed MeCN (4.0 mL) was added to each flask, followed by 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (0.13 mL, 0.76 mmol) under a positive pressure of argon. The flasks were then purged with argon for 2 minutes, and then stirred vigorously at room temperature, with conversion monitored at 1.5 hours, 3 hours and 24 hours by ^{1}H NMR. The HM:SM ratio was also determined by ^{1}H NMR spectroscopy.

Conditions used for catalyst loading screen

Methyl (2*E*)-3-iodoprop-2-enoate (0.141 g, 0.665 mmol), $Pd(OAc)_2$, tri(2-furyl)phosphine (2 equivalents relative to catalyst) and AgOAc (0.120 g, 0.721 mmol) were added to dry round-bottomed flasks under argon in the absence of light. Degassed MeCN (4.0 mL) was added to each flask, followed by 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (0.13 mL, 0.76 mmol) under a positive pressure of argon. The flasks were then purged with argon for 2 minutes, then stirred vigorously at room temperature, with conversion monitored at 3 hours and 24 hours by ^{1}H NMR spectroscopy. The HM:SM ratio was also determined by ^{1}H NMR spectroscopy.

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