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Iridium-Catalysed C–H Borylation of Fluoroarenes: Insights into the Balance between Steric and Electronic Control of Regioselectivity

Mingyan Ding,[a] Jonathan A. Reuven,[a] Andrew C. Hones,[a] Mark A. Fox,*[a] and Patrick G. Steel*[a]

The iridium catalysed C–H borylation of polyfluorinated arenes and heteroarenes occurs rapidly and efficiently. As with other borylation reactions, whilst steric parameters dominate, an underlying electronic influence on reaction selectivity can be observed. Notably borylation regioselectivity in fluorinated (hetero)arenes is determined by purely electronic effects except for *ortho*-borylation between two fluorine atoms where steric effects of fluorine substituents become apparent. Borylation at the *para* position with respect to fluorine is disfavoured whereas a strong electronic preference for borylation *para* to the azinyl nitrogen of pyridine is observed. When these features co-operate high selectivity can be expected. For these reactions, computations based on transition state, rather than intermediate, energies in iridium geometries showed excellent agreement between predicted and observed selectivities.

Introduction

The selective introduction of a fluorine atom into an arene or heteroarene can provide a distinct difference in both chemical and physical properties when compared to the corresponding non-fluorinated analogue. Reflecting this, there are growing numbers of agrochemicals, pharmaceuticals, radiotracers, polymers in which the presence of the aryl fluorine substituent offers a distinct performance advantage.[1] For such compounds, transition metal mediated cross-coupling of fluorinated precursors is an attractive strategy that circumvents many of the challenges for late stage introduction of the fluorine atom. However, this requires ready access to suitable fluorinated reagents.[2] In this context whilst, aromatic and heteroaromatic boronic acids have become pivotal reagents for modern organic synthesis, with over 7000 different aryl boronic acids currently reported as being commercially available on Scifinder®, certain classes, notably fluorinated boronic acids, are under-represented and remain difficult to access. Whilst these can be obtained by C–X borylation strategies, the strong electron withdrawing nature of a fluorine atom, which renders fluorinated arenes prone to nucleophilic substitution but deactivates the ring towards electrophilic methods of functionalization, makes generating the required halogenated precursors equally challenging. Consequently, there has been considerable recent interest in strategies based on C–H and C–F activation.[3] The Ir-catalysed C–H borylation reaction[4] is an attractive option but is complicated by the fact that a C–F bond is commonly not just an innocent functional group but can act as a director and promoter of the C–H activation process.[5] Whilst a number of earlier studies have shown that a fluorine atom is well tolerated in Ir-catalysed C–H borylation[3e,6] the effect of fluorine substitution on the reaction outcome has not been systematically studied. In this report, we address this question demonstrating that Ir-catalysed C–H borylation can provide access to polyfluorinated aryl and heteroaryl boronic acids in good yields with modest to useful selectivities.

Results

Sterically controlled borylation of arenes

Whilst the Ir-catalysed C–H borylation is known to be dominated by steric effects with positions *ortho* to most substituents being unreactive, in early studies both Smith and Hartwig noted that, in the absence of any other available position, borylation *ortho* to a fluorine atom was possible suggesting that any hindrance presented by a relatively small fluorine atom could be overcome.[6b,d] In preliminary studies, (Table 1) we verified this 'sterically-controlled' *ortho*-to-fluorine borylation. These experiments also revealed that these substrates react more rapidly than their non-fluorinated analogues suggesting that an *ortho* fluorine substituent was significantly activating, an observation reinforced by the very rapid borylation of 3,5-difluorotoluene **19** (Table 1, entry 4).[6d]

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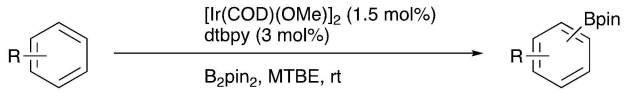
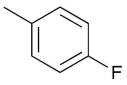
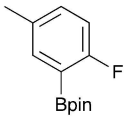
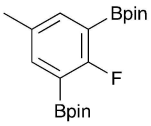
Table 1. Sterically controlled borylation *ortho* to a C–F bond.[a,b]



Entry	Substrate	Time	Conversion[a]	Products	Product Ratio[b]
[1a]		16h	88%	 	4 : 1
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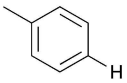
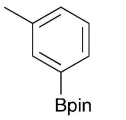
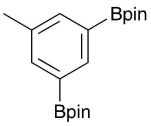
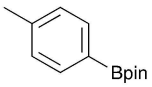
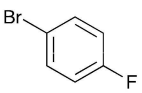
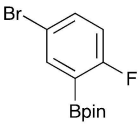
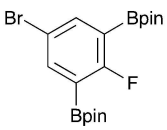
[1b]		16h	30%	  	63 : 6 : 31
	4			5 6 7	
[2a][c]		4h	82%	 	4 : 1
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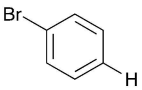
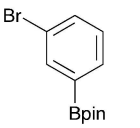
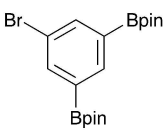
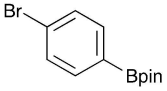
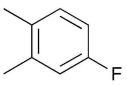
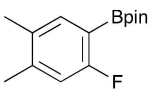
[2b][c]		4h	65%	  	67 : 14 : 19
	11			12 13 14	
[3a]		18h	58%		
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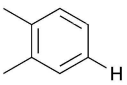
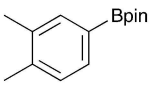
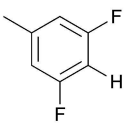
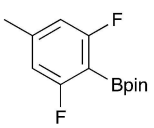
[3b]		18h	36%		
	17			18	
[4]		3h	90%		
	19			20	

[a] Determined by ^{19}F NMR (for entries [1 a], [2 a], [3 a], [4]) or GCMS (for entries [1 b], [2 b], [3 b]) analysis of crude reaction mixtures.; b determined by NMR from analysis of crude reaction mixture; c 0.6 equivalents of B_2pin_2 used.

Borylation of polyfluoroarenes

We then extended this approach to examine of the effect of polyfluorination on this reaction (Scheme 1). Based on our preliminary observations, these reactions were undertaken at room temperature using MTBE as the solvent. Initial experiments were undertaken using a stoichiometric amount of B_2pin_2 although, for more reactive substrates for which a second borylation could readily occur through the HBpin cycle, the use of substoichiometric amounts of the diboron reagent proved to be sufficient to ensure complete consumption of starting material. In all cases isomer ratios could readily be assigned by

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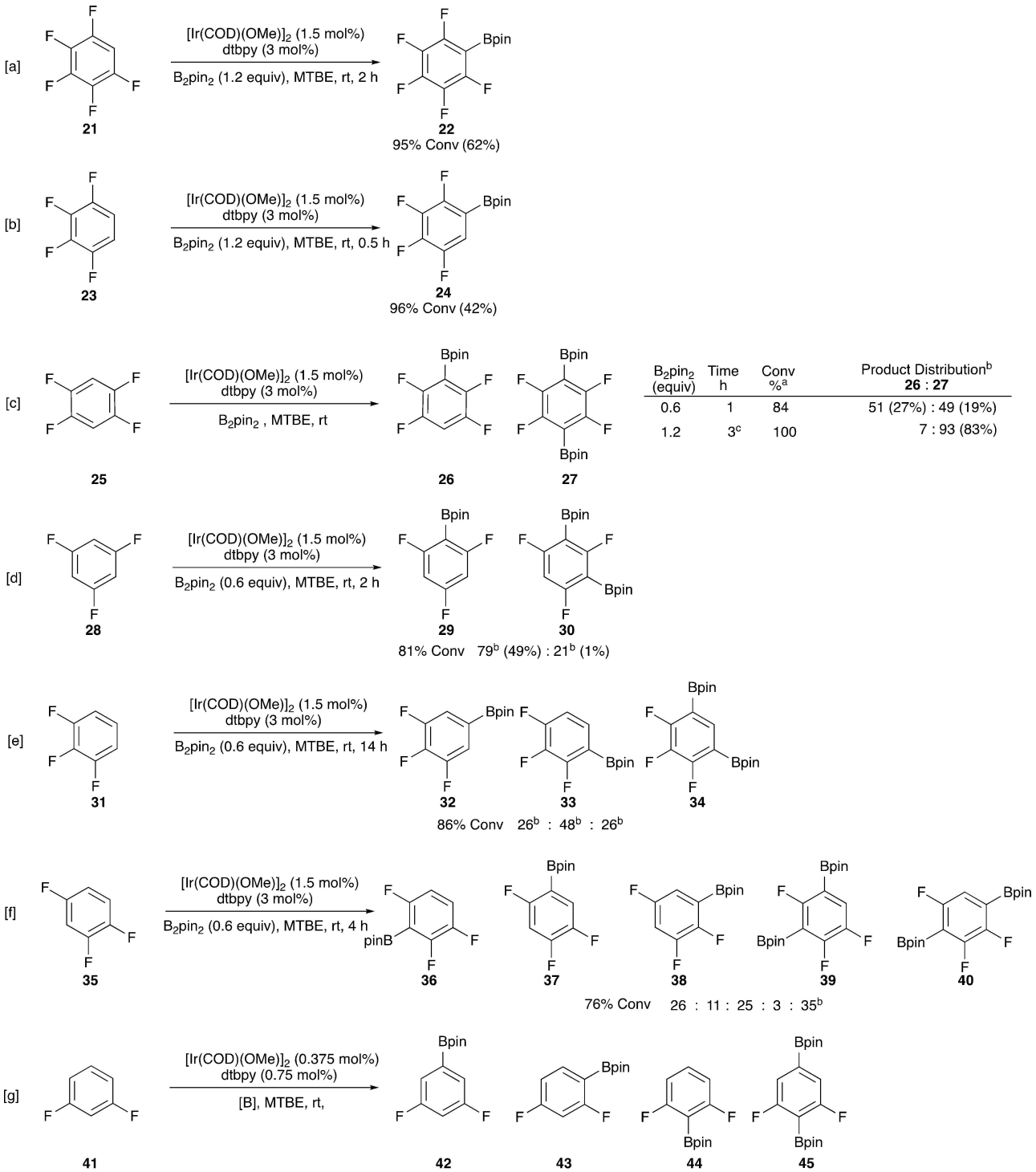

Scheme 1. Borylation of polyfluoroarenes. (a) Conversion based on arene substrates as determined by ^{19}F NMR spectroscopy. Yield in parenthesis is that of purified isolated product; (b) Product ratios determined by ^{19}F NMR spectroscopy; (c) Reaction run at 60 °C; (d) Conversion based on boron calculated from amount of boronate products determined using ^{19}F NMR spectroscopy using hexafluorobenzene as an internal standard.

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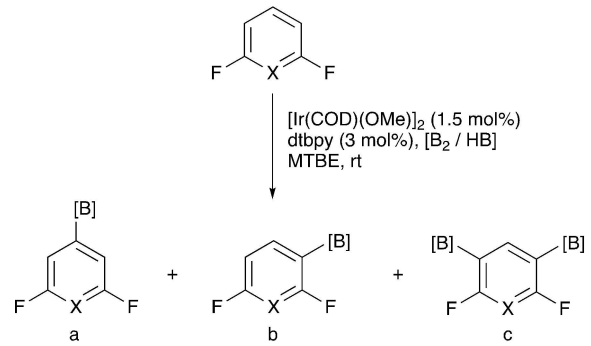
analysis of the ^{19}F NMR spectrum of the crude reaction mixtures. As noted elsewhere,[6d] in contrast to the parent boronic acids, these boronate esters proved to be sufficiently stable and could be isolated in moderate to good yield although separation and isolation of the individual isomeric fluorinated boronic esters proved challenging for many of the more complex mixtures.

This initial screen showed that, consistent with the established observation that electron deficient arenes represent more active substrates,[4] these reactions proceeded very readily at room temperature to afford the borylated products. With the small steric size of a fluorine atom, *ortho* borylation is facile and, for those C–H bonds which have two *ortho* fluorine atoms (Scheme 1: entries a,c,d f and g) very rapid borylation occurs at this position. The high reactivity of a di-*ortho* fluorine C–H group meant that poly-borylation was difficult to avoid for those substrates with multiple such positions, although this can be controlled by lowering the stoichiometry of the borylating agent, albeit at the cost of overall efficiency (Entries c and d). Reaction of less highly fluorinated arenes afforded more complex mixtures (entries e–g). For example, the borylation of 1,2,4-trifluorobenzene **35** afforded five products with the 3,6 bisborylated product **40** predominating reflecting the para directing effect of a Bpin group (Scheme 1, entry f).[6b]

Table 2. Borylation of 1,3-difluoroarenes.



Entry	X	[B_2/HB]	Equiv.	Time [h]	Conv[a] %	Ratio[b] a:b:c
1	C–F (31)	HBpin	5	16	100	28:10:62 (44:56)
2	C–F (31)	B_2pin_2	0.6	14	86	26:48:26 (41:59)
3	C–F (31)	B_2pin_2	1.0[c]	6	60	21:66:13 (35:65)
4	C–F (31)	B_2pin_2	5	6	100	19:0:81 (32:68)
5	C–Me (46)	B_2pin_2	5	6	99	57:26:16 (73:27)
6	C–OMe (47)	B_2pin_2	5	5	100	39:0:61 (56:44)
7	C–CO_2Me (48)	B_2pin_2	5	5	100	63 : 0:37 (77:23)
8	N (49)	B_2pin_2	3	4	100	71 : 0:29 (83:17)
9	N (49)	B_2eg_2	3	1[d]	23	85:12:0 (93:7)

[a] Determined by ^{19}F NMR based on arene substrates; [b] Determined by ^{19}F NMR. Values in parentheses are statistically normalised ratio of C-4 to C-3 products {%C-4 = a/(a + (b + c)/2)*100)} [c] with Et_2NH (1.5 equiv.); [d] reaction run at 80 °C in the presence of 1 equivalent Et_3N.

Borylation of 1,3-difluoroarenes

Intriguingly, the reactions with 1,2,3-trifluorobenzene **31** and 1,3-difluorobenzene **41** showed a small but distinct dependence on the nature of the boron source employed with B_2pin_2 favouring an ortho-to-fluorine borylation (products **33** and **44**, respectively) and HBpin leading to greater amounts of the remote (meta-to-fluorine) products (**32** and **42**).[6f] For 1,3-difluorobenzene **41** this was best observed using highly limiting boron stoichiometries (Scheme 1, entry g).[6b] In contrast for trifluorobenzene **31** it was necessary to use large excesses of each reagent and adapt product ratios to account for bis borylation (Table 2, entries 1 and 4). Even then, monitoring this effect was complicated by the formation of HBpin during reactions with B_2pin_2. Whilst, attempts to sequester the HBpin through addition of methoxide[7] were not successful, the use of diethylamine, as an HBpin trap, together with stoichiometric B_2pin_2 (1 equiv.) returned very similar ratios to that seen with an excess of the diboron reagent (Table 2, entry 3).

These last experiments showed that, although an *ortho* fluorine is strongly activating for C–H activation,[5,8] other factors, potentially steric effects but also other long-range electronic effects, have a role to play in Ir-catalysed C–H borylation. To further explore this balance between steric and electronic effects, we then examined a series of related 1,3-difluoroarene substrates in which the nature of the 2-substituent is varied (Table 2). Reflecting their unhindered nature all of these compounds proved to be viable substrates giving good to excellent yields of the corresponding boronate esters as mixtures of 4- and 5-borylated isomers. In most cases, the proportion of the C-5 borylated product appears to correlate with increasing electron-withdrawing nature of the 2-substituent (Table 2 entries 4–8). Moreover, with all these substrates small but definitive differences could again be observed depending on the nature of the boron reagent with B_2pin_2 favouring reaction *ortho* to a fluorine atom, and HBpin leading to enhanced levels of remote (C-5, *meta* to fluorine) activation (Table S1). Whilst a similar boron reagent dependency could be ascertained with 2,6-difluoropyridine (Table S1), here the dominant outcome is C-4 borylation and, even with excess B_2pin_2, ortho borylation only occurs to ~20%. This seems to deviate from the normal selectivity observed with pyridine which shows little selection between C-3 and C-4 (Figure 1),[9] albeit requiring elevated temperatures for significant degree of conversion. To explore the possibility that this arose due to simple steric effects we explored the use of the smaller B_2eg_2.

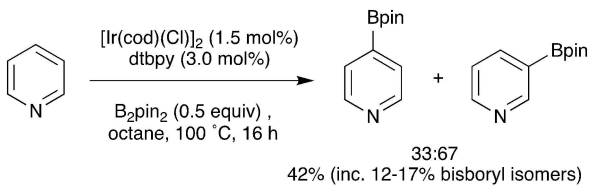


Figure 1. Borylation of pyridine.[9a]

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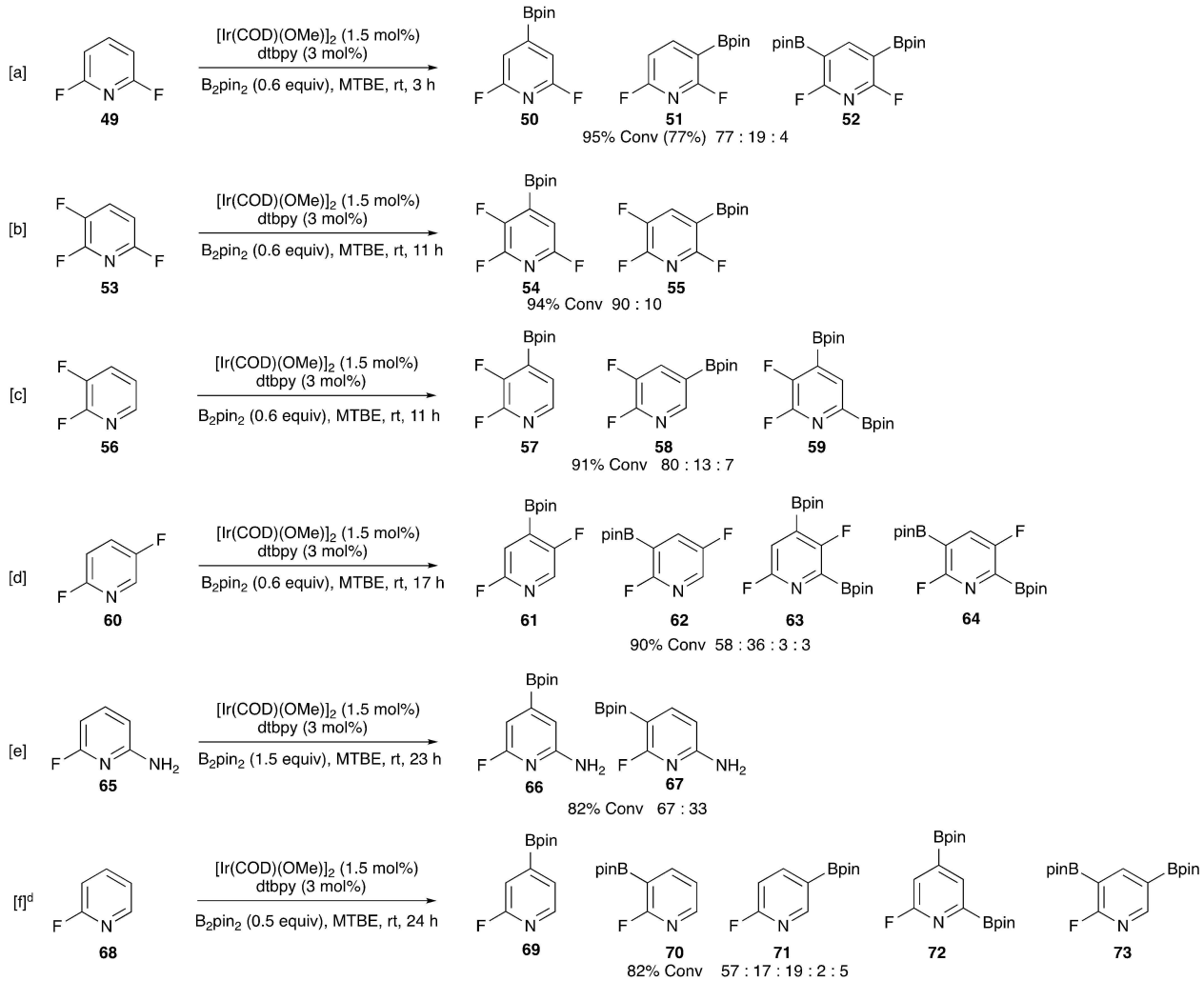
This was challenged by the relatively low solubility and low reactivity of the associated iridium complex and reaction was only observed at elevated temperature (80 °C) in the presence of Et_3N. However as before this lead to preferential borylation at C-4 (*meta* to fluorine), albeit in modest (23 %) conversion (Entry 9).

Borylation of fluorinated pyridines

To explore the generality of these last observations, we then examined the behaviour of a series of fluorinated pyridines (Scheme 2). As observed for the previous set, these electron deficient heterocycles were all excellent substrates giving high conversions at room temperatures. In all cases, borylation preferentially occurred at C-4 even when competing positions *ortho* to a fluorine substituent were accessible. Experiments to distinguish between boron sources were largely inconclusive even when running reactions with large excess of reagent whilst attempts to alter regiochemistry using other boron Lewis acids led only to inhibition of the borylation reaction.

Cross-coupling reactions of fluorinated boronate esters

Having demonstrated that these polyfluorinated boronate esters were readily accessible we were interested to see if they represent useful reagents for further transformation. We elected to do this using the Suzuki-Miyaura cross-coupling reaction as a representative example. This transformation is of interest as these fluorinated boronic esters have been described as difficult substrates to cross-couple due to combination of slow transmetallation, increased stability of the Pd–C bond associated with higher level of fluorine substitution leading to reduced rates of reductive elimination and, particularly, competitive protodeborylation.[10] Using 3,5-difluorotoluene **19** as a test substrate, treatment of the isolated boronate ester **20** with $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_3PO_4, and methyl 4-iodobenzoate in DMAc afforded the corresponding biaryl in good yield. Similar out-



Scheme 2. Borylation of fluorinated pyridines.[a,b,c] (a) Conversions based on arene substrates as determined by ^{19}F NMR; (b) ratios determined from ^{19}F NMR; (c) Yield in parenthesis is that of purified isolated product; (d) as previously reported see Ref. [26].

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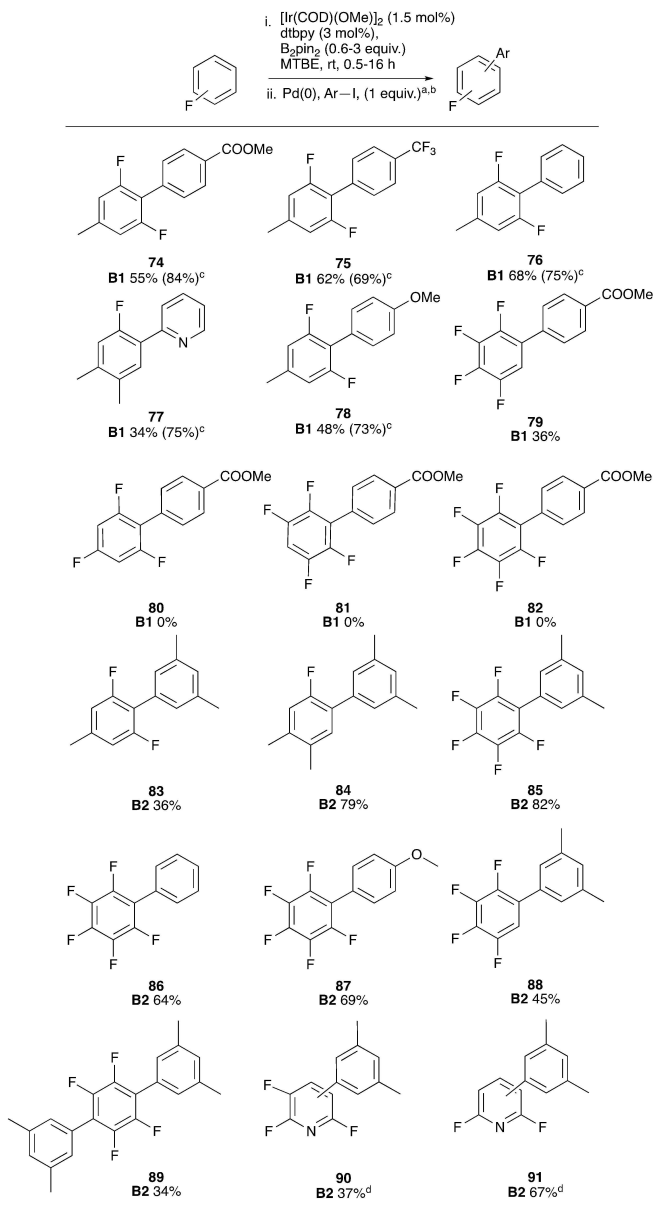
comes were obtained with a range of other aryl halide components in a one-pot protocol (Scheme 3). However, extending this methodology to more highly fluorinated substrates gave lower or no yield of product and considerable amounts of proto-deborylated material could be detected in the crude ^{1}H NMR spectra. Attributing this to rapid decomposition of the boronate under the aqueous conditions we explored anhydrous conditions using fluoride ions as a means to accelerate the normally rate limiting transmetallation step.[11] Ultimately, adopting conditions first reported by Sakai,[12] using $Pd(PPh_3)_4$ (3 mol%), CsF (2.0 equiv.), Ag_2O, (1.2 equiv.) and iodoarene in DME provided a simple solution enabling the corresponding fluorinated biaryls to be isolated in moderate to good yields (Scheme 3 method B2).



Scheme 3. Cross-coupling reactions of fluorinated boronate esters. (a) Yields correspond to purified isolated products over two steps (b) Reaction conditions **B1** $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (2.5 mol%), K_3PO_4 (1.5–2.0 equiv.), DMAc, 80 °C **B2** $Pd(PPh_3)_4$ (3 mol%), Ag_2O (1.2 equiv.), CsF (2 equiv.), DME, 70 °C, 13–17 h. (c) values in parentheses are NMR yields (d) mixture of two isomeric-coupled products.

Computations

To provide greater insight into the observed borylation selectivity we then analysed the process computationally. Using the reaction of 2,6-difluoropyridine **49** as a model, initial hybrid-DFT calculations were carried out using Beg in place of Bpin ligands and hydrogens in place of *tert*-butyl groups on the dtbpy ligand due to limited computing resources for the augmented correlation consistent basis set aug-cc-pVDZ employed here. The widely accepted mechanism for (hetero)arene borylation, including pyridine derivatives, involves the formation of an active five-coordinate Ir(III)trisboryl(dtbpy) complex and a similar pathway was mapped to provide transition state and intermediate geometries for borylation at both the meta (C-3) and para position (C-4) (Figures 2 and S1–4).[13]

With pyridyl substrates, the starting geometry may exist as a N–Ir adduct where the iridium centre in the Ir(III)trisboryl complex is bound to the azinyl nitrogen or as a weakly-coordinating adduct between the Ir(III)trisboryl complex and the pyridine molecule (Figure S1 and Table S2). For **49**, the weakly-coordinating adduct is shown to be lower in energy than the N-adduct by 12.0 kJ mol^{-1} implying that the N-adduct is unlikely to be present in the borylation of **49**. This is expected for **49** as the two *ortho* fluorine substituents significantly reduce the electron-donating lone pair capacity of the azinyl nitrogen. The rate-determining C–H activation step involves the transition from this adduct to the seven-coordinate complex INT. The transition state geometry for C-4 activation {TS (*para*)}, is lower in energy than that for C-3 activation by 4.94 kJ mol^{-1} which corresponds to a Boltzmann population distribution of 88:12 and is in excellent agreement with the 87:13 ratio found experimentally. To verify the use of Beg, the calculations of these key structures was repeated using Bpin (Table S3) which revealed that the relative energy of the 3- and 4- isomers at the transition state would not change significantly if Beg ligands were replaced with Bpin ligands and thus any steric effects due to the bulkier Bpin ligands are not obviously contributing to the observed selectivity of this reaction.

In a similar fashion, using optimised transition state geometries, analysis of the reactions of the other substrates was investigated (Figure 3 and Table S4). In most cases this too showed excellent agreement between predicted and observed selectivity with the major borylated isomer being correctly predicted in all cases. The only significant deviation arose with **35** and **41** where *ortho*-borylation to two fluorine substituents was predicted. Here the agreement between predicted and observed product ratios is less good and suggest that steric effects of the Bpin ligands compete with the electronic effects of two adjacent fluorine substituents. This is supported by a review of the optimised geometries of the intermediates for **41** which reveal that the relative energies (Table S5) and the Ir–C bond lengths (Table S6) for the Bpin models are larger than those determined from the Beg models.

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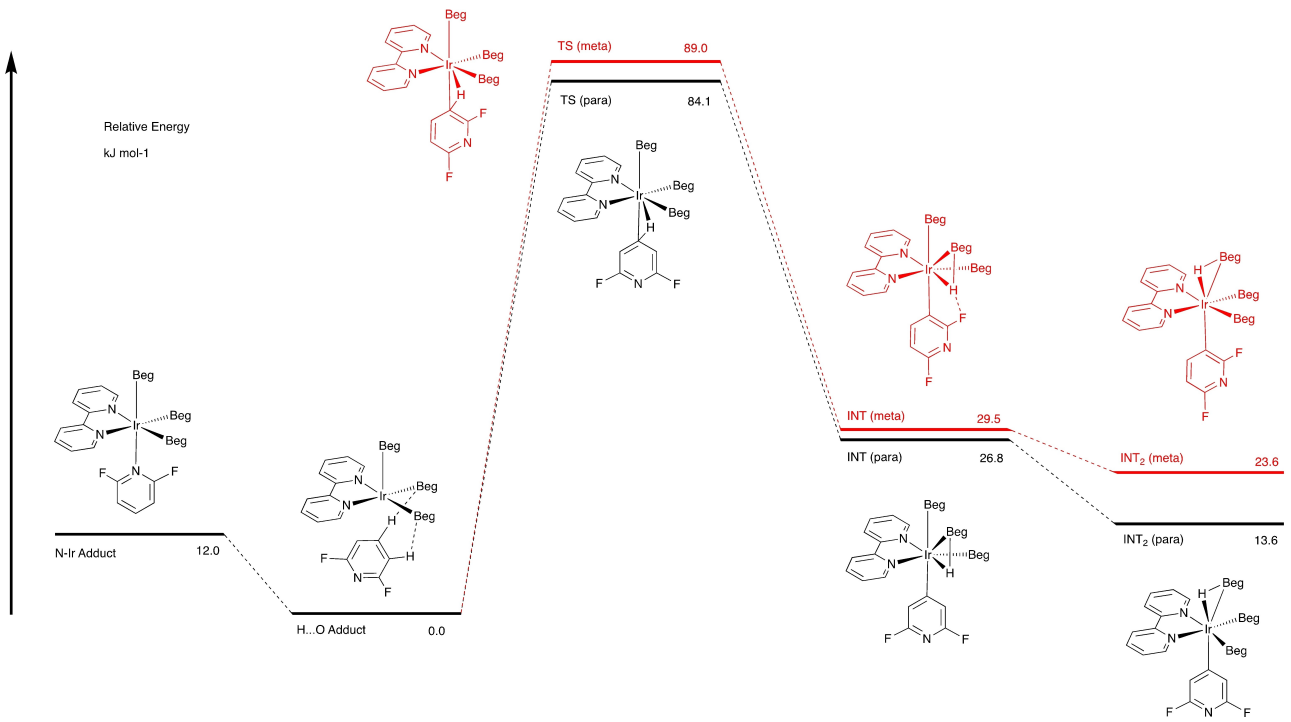

Figure 2. Computed iridium borylation pathways of 2,6-difluoropyridine **49**.

Discussion

In contrast to most other strategies which require strongly basic reagents and / or the use of pre-functionalised substrates, iridium-catalysed C–H borylation provides a mild functional group tolerant method for the preparation of aryl boronate esters. The accepted mechanism for this process involves the formation of an active five coordinate Ir(III)trisboryl complex.[13a,14] Following rate limiting C–H activation to form a sterically crowded aryl Ir(V) complex, reductive elimination yields the arylboronate ester. Regeneration of the active catalyst is then achieved through addition of either B_2pin_2 or HBpin and elimination of HBpin or H_2, respectively. Reflecting this pathway, reaction rates are much higher for more electron deficient substrates and the increased rate of reaction with the degree of fluorination observed in this study is consistent with this.

A major challenge in many C–H borylations is regioselectivity, and borylation of fluoroarenes is no exception. Selectivity in arene C–H borylation is dominated by steric effects, preferentially occurring at less hindered sites. In unencumbered arenes this leads to borylation at positions remote to substituents and ring junctions, i.e. borylation *ortho* to a substituent or ring junction is typically retarded. However, electronic effects can be observed at lower temperatures,[9b,15] and, as illustrated in Table 1 and Scheme 1, and exemplified by tetrafluorobenzene, an *ortho* fluorine is not only sterically undemanding but also appears to be highly activating as supported by the computed activation energies of polyfluorinated substrates (Tables S6 and S7). Whilst simple models based of C–H acidity have been proposed to account for the regioselectivity of metal catalysed C–H activation[16] including C–H borylation,[6b,13c,15,17] and a fluorine substituent does lower the pK_a of an *ortho* C–H bond, correlation of the calculated pKa's[18] with selectivity for a number of these substrates was not perfect (Figure S5).

In their theoretical analysis of C–H activation of fluoroarenes by metal centres, Eisenstein and Perutz described models in which the strength of the metal-carbon bond intermediate provides a better indicator of transition state energies and hence predictor of regiochemistry.[8,19] As Ir-catalysed C–H borylation is also a process involving a late transition state,[13c] a similar assumption can be made. This suggestion has been more fully substantiated by Houk using distortion/interaction analyses.[13b] On this basis, the enhanced reactivity *ortho* to a fluorine substituent can simply be rationalised by the stability of the intermediate metal complex for which it is estimated that two *ortho* fluorine increases the stability of a M–C bond relative to the parent C–H bond by approximately 20 $kJ\,mol^{-1}$.[19c] Whilst this simple *ortho* fluorine directing model fits many of the substrates explored in this work, for substrates in which there are multiple sterically accessible positions available, deviations from *ortho* selectivity become apparent. In some cases, these deviations become dominant. For example, whilst in the absence of steric influences pyridine borylates with no selectivity between *meta* and *para* positions,[9,20] 2-fluoropyridine (Scheme 2f) affords predominantly (57%) the 4-borylated adduct with only a small amount of the 3-borylated (*ortho* to fluorine) product being generated[9b] and 2,6-difluoropyridine affords 77% of the 4-borylated product (Scheme 2a). Whilst the latter result could be attributed to the steric influence of the two fluorine substituents these observations contrast with

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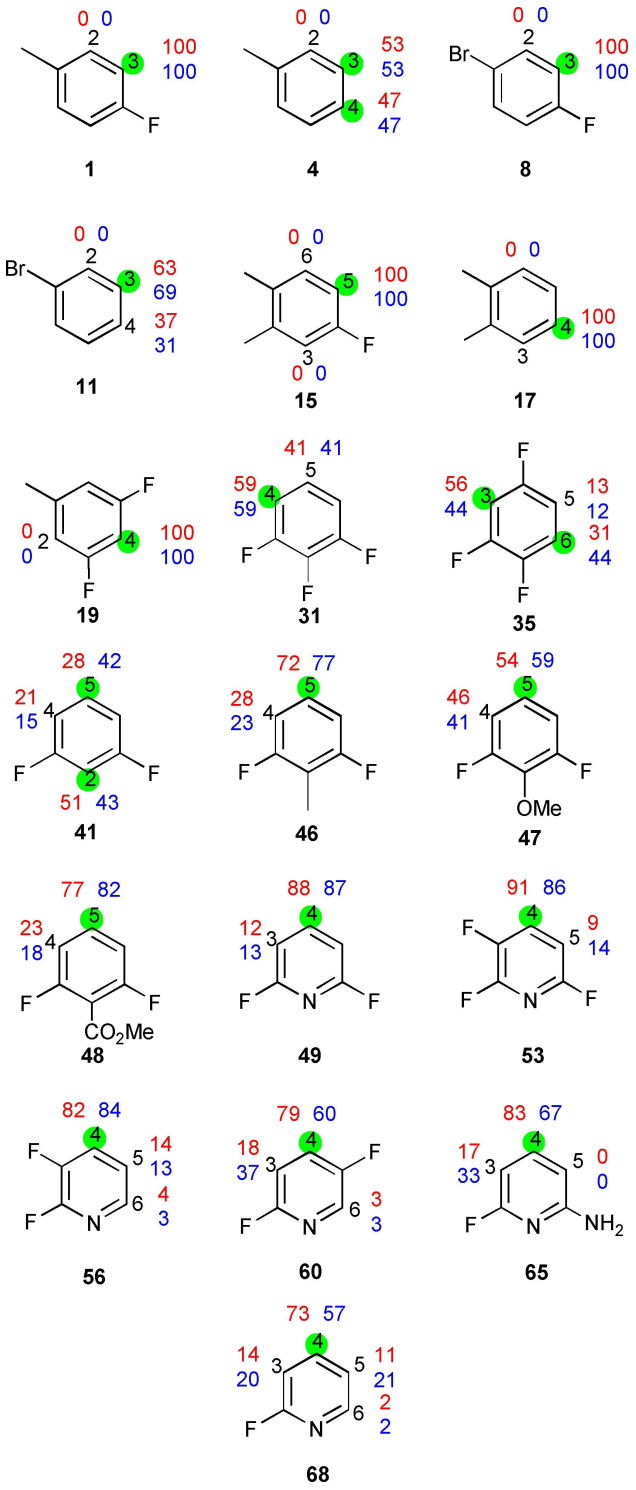

Figure 3. Comparison of predicted (red) and observed ratios (blue) of borylated isomers from substrates investigated in this study. The predicted ratios were determined from relative transition state energies of model iridium geometries where bpy and eg are used as ligands instead of dtbpy and pin. The green marker indicates the major site of borylation.

selectivities observed in other C–H activation notably the C–H borylations catalysed by Pt.[3e] The suggestion for an electronic effect is supported by the observation that, in other 1-substituted 2,6-difluoroarenes, decreased *ortho*-fluorine selectivity can be correlated with increasing electron withdrawing ability of the 1-substituent (Table 2). One possible explanation for this is that the position of the transition state for the more highly electron deficient substrates in this study is much earlier and, thus, is more substrate-like and more closely correlated in C–H bond strengths. Consistent with this, as demonstrated in this study, for these substrates the use of transition state models rather than intermediate geometries provide a closer alignment between theory and experiment with respect to M–C bond strengths (Figures S6–S7 and Tables S9–S10). This has parallels with concepts cleverly demonstrated in Co mediated C–H borylation in which different substrates provide different turnover limiting steps between C–H activation (oxidative addition) and C–B bond formation (reductive elimination).[21]

A study by Ilies has recently shown that by 'delaying' the transition state, the impact of M–C bond stability increases and enhanced *ortho*-to fluorine C–H borylation is observed.[22] In the current study, C–H bond strengths appear to have a more critical role (Figure S7). Interestingly, this tends to reflect the stability of the corresponding radical in which a *meta* fluorine is significantly more stabilizing than a *para* one with an *ortho* fluorine being the least effective.[8,19a] It is then possible to speculate that, at least for these highly fluorinated heterocycles, alternative mechanisms for bond activation potentially via single electron transfer (SET) may be operating. SET pathways have been proposed to be involved in the elegant Ni and Ni/Rh co-catalysed C–F borylations recently reported by Marder and Radius,[3a,d,23] and in these it is also possible to note a *meta* selectivity.

Similar conjecture can also be applied to the observation that differing boron reagents can give different reaction outcomes with the use of HBpin favouring borylation at non-*ortho* fluorine positions. Whilst this manuscript was in preparation similar, and clearer, observations have been reported by Smith and Maleczka albeit using a novel ligand system.[6f] Interestingly, this also involved a fluorinated substrate with HBpin also leading to enhanced *meta* borylation. Whilst similar analysis of the reactions of other arenes show little deviation between reagents suggesting a key role for the fluorine atoms this discrepancy in outcomes challenges our mechanistic understanding of Ir catalysed C–H borylation as both boron sources are proposed to follow similar catalytic cycles that involving identical catalytically active complexes and rate determining steps.[13a,14] As such, these observations challenge this assumption and open the scope for new catalysts and reagents that operate by alternative more selective pathways.[21a]

Conclusion

In conclusion, partially fluorinated arenes are very active substrates for the Ir-catalysed aromatic C–H borylation and the resulting boronate esters represent useful building blocks for the generation of fluorinated biaryls, and potentially other motifs, that circumvents the challenges of late-stage fluorination. The excellent agreement between computed relative

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transition state energies and the observed product selectivity ratios shown in this study gives confidence in predicting the preferred product selectivities of other fluorinated substrates from iridium-catalysed borylations. As with hydrocarbon C–H borylation, the C–H borylation of fluorinated arenes can produce mixtures of regioisomers. However, the small size of a fluorine atom means that simple steric based arguments are no longer satisfactory to account for the observed selectivity. Similarly, arguments based on C–H acidities and C–M bond energies cannot explain all outcomes and the observation of a *meta* fluorine effect may suggest a role for single electron transfer mechanisms in certain situations. As such, if this could be exploited this may provide an opportunity for more selective borylation of these substrates and further investigation into the mechanism of this exceptionally useful transformation is merited.

Experimental Section

General procedure A (C-H borylation of fluoroarenes and heteroarenes - Tables 1 & 2, Schemes 1 & 2)): An oven-dried Biotage microwave vial was sealed and subjected to three N_2 evacuation/refill cycles, followed by the addition of the corresponding substrate (1.00 mmol, 1.0 equiv.). In a separate oven-dried Schlenk tube was charged with $[Ir(COD)(OMe)]_2$ (9.9 mg, 1.5 mol%), dtbpy (8.1 mg, 3.0 mol%), and bis(pinacolato)diboron (B_2pin_2) (0.6 equiv. to 5 equiv.). The vessel was sealed and subjected to three N_2 evacuation/refill cycles before anhydrous MTBE (1.0 mL) was added. Once the solids were completely dissolved, this black active catalyst solution was transferred into the microwave vial using a syringe. The reaction was stirred at room temperature for the stated time before being monitored by ^{19}F NMR or GC-MS. Upon completion, the volatiles were then removed *in vacuo* and the desired borylated product was isolated following purification by flash column chromatography with the appropriate solvent system.

General procedure B1 (Suzuki-Miyaura cross-coupling reactions of fluorinated boronic esters): To a microwave vial which contained the substrate boronic ester (1.0 equiv.) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (2.5 mol%), K_3PO_4 (1.5–2.0 equiv.), and methyl 4-iodobenzoate (1.0 equiv.) in DMAc (1 mL). The reaction mixture was degassed using a nitrogen filled balloon and stirred at room temperature/80 °C. Once judged complete by ^{19}F NMR, the reaction was diluted with EtOAc (20 mL) and washed with water (2×10 mL) and brine (10 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The cross-coupled arene was then purified by flash column chromatography with the appropriate solvent system.

General procedure B2 (Suzuki-Miyaura cross-coupling reactions of fluorinated boronic esters): In an oven-dried Schlenk tube which contained the substrate boronic ester (1.0 equiv.) was charged with $Pd(PPh_3)_4$ (3 mol%), Ag_2O (1.2 equiv.) and CsF (2.0 equiv.). The vessel was sealed and subjected to three N_2 evacuation/refill cycles before pre-degassed anhydrous DME (1.0 mL) and the aryl halide (1.0 equiv.) were added. The reaction mixture was stirred at 70 °C. Once judged complete by ^{19}F NMR, the resulting solution was filtered through celite, washed with EtOAc, and concentrated *in vacuo*. The cross-coupled arene was then purified by flash column chromatography with the appropriate solvent system.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: C–H borylation · fluoroarene · fluoropyridine · iridium · regioselectivity

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