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EDGE ARTICLE

Iridium-catalyzed C–H borylation of quinolines and unsymmetrical 1,2-disubstituted benzenes: insights into steric and electronic effects on selectivity†

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Borylation of quinolines provides an attractive method for the late-stage functionalization of this important heterocycle. The regiochemistry of this reaction is dominated by steric factors but, by undertaking reactions at room temperature, an underlying electronic selectivity becomes apparent, as exemplified by the comparative reactions of 7-halo-2-methylquinoline and 2,7-dimethylquinoline which afford variable amounts of the 5- and 4-borylated products. Similar electronic selectivities are observed for nonsymmetrical 1,2-disubstituted benzenes. The site of borylation can be simply estimated by analysis of the ^{1}H NMR spectrum of the starting material with preferential borylation occurring at the site of the most deshielded sterically accessible hydrogen or carbon atom. Such effects can be linked with C–H acidity. Whilst DFT calculations of the pK_a for the C–H bond show good correlation with the observed selectivity, small differences suggest that related alternative, but much more computationally demanding values, such as the M–C bond strength, may be better quantitative predictors of selectivity.

Introduction

Iridium-catalyzed borylation represents one of the most effective and efficient methods for arene C–H bond activation.[1–11] The most active and widely used catalyst system employs [Ir(OMe)cod]$_2$ and a bipyridyl ligand, most commonly 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy). Broad functional group tolerance and substrate scope are key advantages of this method, allowing late-stage functionalization of advanced synthetic intermediates containing complex functionality, with the observed regioselectivity normally considered to be predominantly controlled by steric factors.

In this paper, we report the borylation of C–H bonds in quinolines, as well as monosubstituted and unsymmetrically disubstituted benzenes. Our results show that there is a distinct electronic contribution to the regioselectivity that can be exploited by undertaking reactions at, or near to, room temperature. Moreover, this electronic selectivity is highly predictable and can be addressed through analysis of NMR spectra of the starting materials.

The quinoline heterocyclic scaffold is an important structural unit, found in many natural products,[12] with applications in many areas of chemistry including pharmaceuticals, molecular electronics and dyestuffs.[13] Reflecting this, there is considerable interest in developing efficient routes to substituted quinolines.[14] The synthesis of the parent quinoline ring system is classically achieved *via* the reaction of substituted anilines.[15] While these reactions can provide a wide range of substitution patterns, they typically involve forcing conditions that often lead to challenging purification procedures, resulting in low overall yields. Milder methods for synthesizing the heterocyclic core have been developed.[16–18] However, these methods typically install all functionality at the start of the synthesis. A more attractive option for the synthesis of quinoline derivatives involves late-stage functionalization of a core scaffold. Consequently, methods for the functionalization of a pre-formed quinoline ring system are highly desirable. Although both electrophilic

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and nucleophilic aromatic substitution reactions can be used for selective functionalization of the quinoline nucleus, these too often require harsh reaction conditions. Alternative strategies involving directed metallation chemistry have also been described, but these suffer from low functional group compatibility.[19]

As a method for late-stage functionalization of advanced synthetic intermediates containing complex functionality, the iridium-catalyzed C–H borylation represents a versatile option as, once installed, the boronate functionality can be utilized in a wide range of bond-forming processes.[11,20] In many cases, these second transformations can be carried out in a single operation. Examples include Suzuki–Miyaura reactions,[21–23] Cu-catalyzed C–O and C–N cross-couplings,[24–26] metal-catalyzed conjugate additions to α,β-unsaturated carbonyl compounds,[27–29] and the replacement of the boronate unit with many other groups including F,[30] Cl,[31] Br,[31,32] CF_3,[33–38] OH,[39–41] NH_2,[42] N_3,[43] CN,[44] CO_2H,[45] and CO_2R.[46] Reflecting this, the use of aryl boronates as central intermediates for library synthesis is of growing importance.

The regioselectivity of the iridium-catalyzed C–H borylation reaction in the presence of a bipyridyl ligand is dominated by steric effects, with reaction preferentially occurring at unhindered sites. For example, monosubstituted benzenes afford a mixture of *meta*- and *para*-substituted products, while for fused arenes, borylation *ortho* to a substituent or a ring junction is generally avoided.[8,11,47] This is clearly illustrated by the borylation of naphthalene (Fig. 1) which initially occurs at the 2-position, *i.e.* the only position not adjacent to a ring junction. In the presence of excess boron reagent further borylation occurs to give a 50 : 50 mixture of the 2,6- and 2,7-bisborylated products.[47]

While steric effects are clearly apparent, regioselectivity arising from electronic effects is more subtle and better observed in heterocyclic systems (Fig. 2).[48–55] Although unsubstituted pyridine shows lower levels of reactivity than benzene, borylation proceeds with the classical regioselectivity observed for monosubstituted benzenes affording a 2 : 1 *meta* to *para* ratio of borylated products (Fig. 2, eqn (a)).[56,57] This lower reactivity can be attributed to coordination of the pyridyl nitrogen to, and hence inhibition of, the iridium catalyst by blocking access to the site required for C–H activation. However, if pyridyl nitrogen coordination is sterically inhibited by an *ortho* (C-2) substituent, then borylation proceeds very

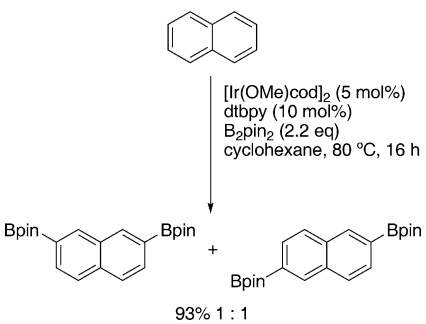


Fig. 1 Borylation of naphthalene.[47]

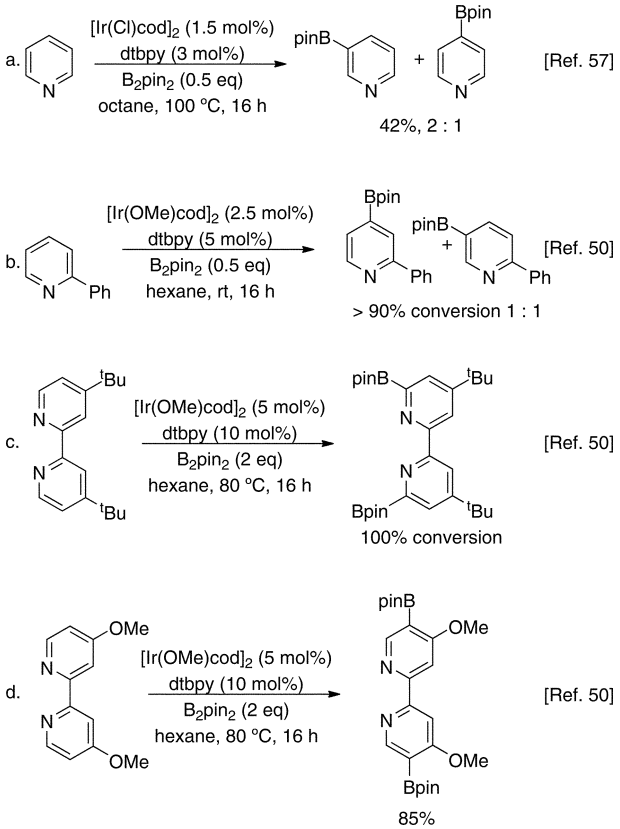


Fig. 2 Borylation of pyridine derivatives.

readily. Significantly, iridium-catalyzed borylation of 2-phenylpyridine with B_2pin_2 occurs preferentially on the heterocyclic ring, affording a 50 : 50 mixture of 4- and 5-borylated products (Fig. 2, eqn (b)).[50] Thus, the inherent reactivity of the 6-membered heterocycle is higher than that of the isoelectronic hydrocarbon. If the 4- and 5-positions are sterically blocked, then borylation at C-6, adjacent to the nitrogen, is possible (Fig. 2, eqn (c)). However, 4,4′-dimethoxy-2,2′-bipyridine is borylated preferentially at the 5,5′-positions,[50] suggesting that the inhibitory effect of the pyridyl nitrogen is sufficient to outweigh the steric effect of the methoxy groups (Fig. 2, eqn (d)).[58]

Consistent with these observations, quinoline is an effective substrate for C–H borylation, with reaction occurring preferentially at the 3-position on the heterocyclic ring rather than the carbocyclic ring (Fig. 3).[22,57] In an analogous fashion to naphthalene, in the presence of excess XBpin (X = H, Bpin), a second borylation occurs with equal probability at the 6- and 7-positions.[22] However, beyond these observations dealing with the reaction of the parent heterocycle, there have been no reports describing the application of iridium-catalyzed borylation as a strategy for preparing functionalized quinolines. In this paper, we describe the selective borylation of a variety of substituted quinoline derivatives. While steric effects dominate selectivity, our studies reveal interesting electronic effects that influence the selectivity of the borylation of both aromatic and heteroaromatic C–H bonds, providing insights into the mechanism of this reaction.

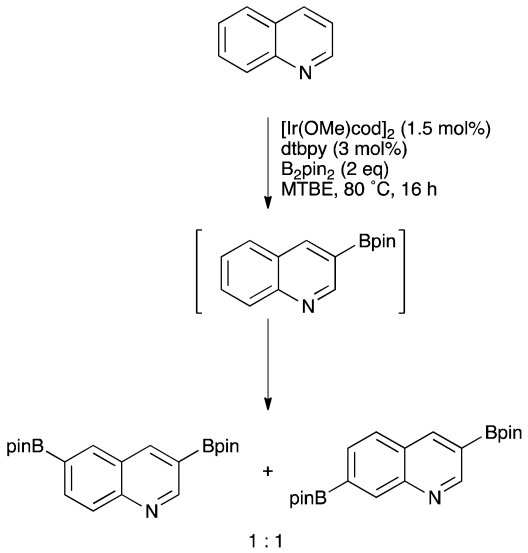
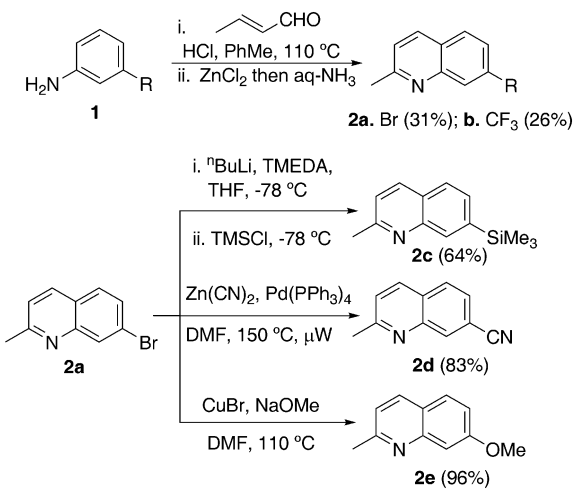


Fig. 3 Borylation of quinoline.[22]

Results and discussion

Substrate synthesis

The quinoline starting materials for these studies are either commercially available or were prepared following literature procedures (see ESI†). For example, 2,7-disubstituted quinolines were prepared through sequences based on the classical Döbner–Miller synthesis (Scheme 1). Condensation of 3-bromoaniline **1a** with crotonaldehyde in an aqueous HCl–toluene mixture afforded the desired 7-bromoquinaldine **2a**. Purification was greatly simplified by complexation with $ZnCl_2$ following the protocol originally described by Leir.[59] A similar procedure was employed to provide the corresponding 7-trifluoromethyl analogue **2b**. However, attempts to prepare the 7-trimethylsilyl (**2c**), 7-cyano (**2d**) and 7-methoxy (**2e**) analogues by this strategy were not efficient, and these compounds were instead synthesized *via* the intermediacy of **2a** (Scheme 1).

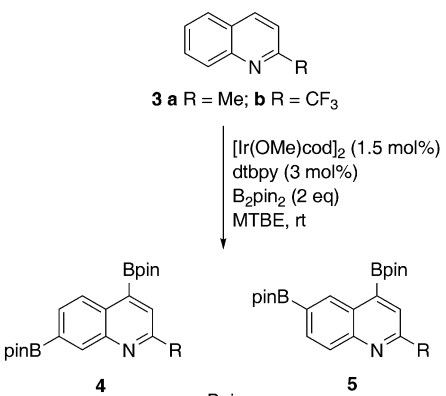


Scheme 1 Preparation of 2,7-disubstituted quinolines.

Borylation of quinolines

We commenced this study by exploring the borylation of the simple 2-substituted quinolines. Reactions were conducted following our previously reported microwave-accelerated protocol.[22] This involved charging a crimp top microwave vial with the substrate followed by purging with argon and the addition of an aliquot of pre-formed stock solution of the catalyst {[Ir(OMe)cod]$_2$ (1.5 mol%), dtbpy (3 mol%), MTBE (2.4 mL)} and B_2pin_2 (1.0 eq.). The tubes were then heated in a focused microwave reactor at 80 °C for 1.5 h before concentration, analysis and purification. These substrates underwent rapid reaction to afford a complex and intractable mixture containing multiple mono- and bisborylated products. In order to simplify analysis, reactions were run with an excess of B_2pin_2, leading to the formation of a mixture of up to three major bisborylated products (GC-MS). Careful analysis of the product mixtures from reactions run at room temperature using COSY, HSQC and HMBC NMR spectroscopic techniques revealed that these were the 4,6- and 4,7-bisborylated isomers **4** and **5**, accompanied by a small amount of the 5,7-isomer **6**, in the case of **3b** (Scheme 2).

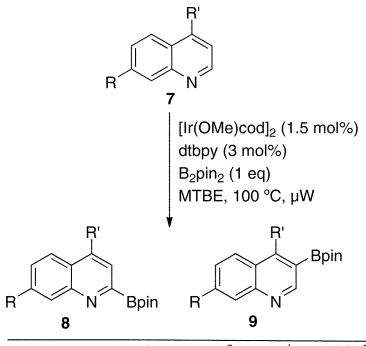
While these studies confirmed the viability of quinolines as effective substrates, the lack of selectivity remained an issue for synthetic applications. Consequently, we then explored more highly substituted derivatives. Initial studies were focused on 4,7-disubstituted quinolines **7** in which the only position that is not sterically hindered by adjacent substituents is at C-2, *ortho* to the nitrogen atom, borylation at which would yield the 2-borylated products **8** (Scheme 3). Interestingly, reaction of 4-chloro-7-trifluoromethyl quinoline **7a** led to exclusive borylation at the



3	R	Time (h)	Conv. (%)[a]	Ratio[b] 4 : 5 : 6
a	CH_3	24	>95	68 : 32 : 0
b	CF_3	5	90	51 : 42 : 7

[a] Conversion determined by GC-MS; [b] Product ratios determined by ^{1}H NMR spectroscopy on the crude reaction mixture.

Scheme 2 Borylation of 2-substituted quinolines with excess B_2pin_2.



7	R	R'	time (h)	conv[a] (%)	ratio[b] 8 : 9	yield 9[c] (%)
a	CF_3	Cl	1.5	>95	0 : 100	76
b	CF_3	CH_3	24	<10	-	nd
c	Cl	Cl	1.5	>95	0: 100	81
d	CH_3	OMe	24	<15	-	nd

[a] Conversion determined by GC-MS; [b] Calculated product ratio from ^{1}H NMR analysis of crude reaction mixture; [c] Isolated yield.

Scheme 3 Borylation of 4,7-disubstituted quinolines.

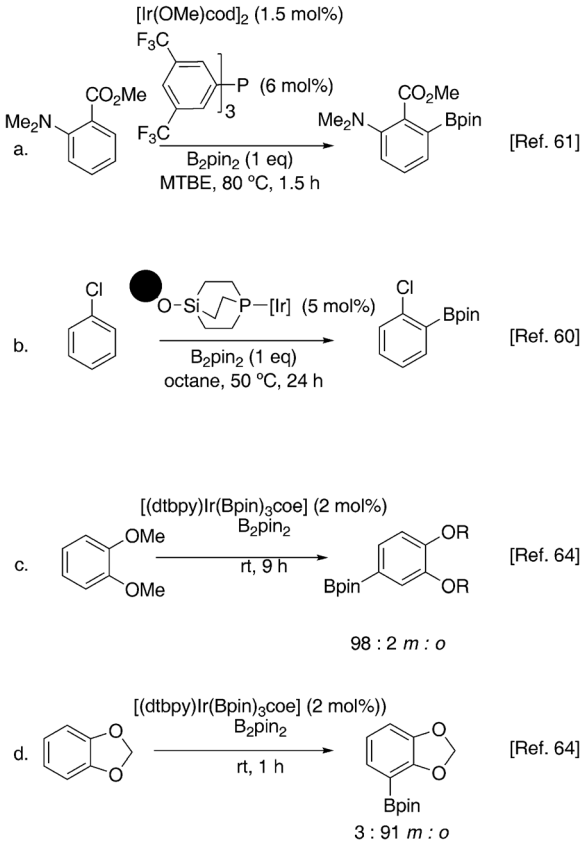
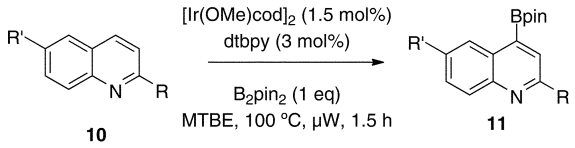


Fig. 4 Examples of directed *ortho* borylation reactions.

3-position, *ortho* to the chlorine atom, to give the 3-borylated product **9a**. Similar selectivity was observed for the corresponding 4,7-dichloroquinoline **7c**, providing further evidence for the higher reactivity of the heteroaromatic ring. In contrast, reaction of 4-methyl-7-trifluoromethylquinoline **7b** and 4-methoxy-7-methylquinoline **7d** afforded only trace amounts (≤10–15% conversion, GC-MS) of borylated products even after prolonged heating at 100 °C. The lack of reactivity for these analogues was surprising when compared with our earlier observed borylation of dtbpy which, under forcing conditions, undergoes reaction at the C-2 position, and a full explanation for this difference is not obvious. While the contrasting behavior between the 4-chloro- and 4-methyl-substituted quinolines can be attributed to simple steric factors, Cl being smaller than Me, the results of the borylation of **7a** and **7c** may also point to an *ortho*-directing (activating) effect of a chlorine atom. *Ortho*-directed borylation of monosubstituted arenes including chlorobenzene has been described using monodentate phosphine ligands (Fig. 4a and b).[60,61] In contrast, the lack of borylation observed for 4-methoxy-substituted quinoline **7d** is more challenging to explain as the difference in steric bulk, as determined by various measures, for chloro and methoxy compared to methyl is small and in some cases reversed (*A*-values:[62] Cl 2.2, MeO 3.1, *cf.* Me 7.28 kJ mol^{-1}; $\Delta\Delta H_s$ values:[63] Cl 17.3, MeO 8.4, Me 23.2 kJ mol^{-1}). However, such calculations exclude the effect of neighbouring groups, and for **7d** the effect of the *peri* hydrogen at C-5 may increase the steric impact of the OMe group on the C-3 position by restricting rotation around the C–O bond. In support of such a suggestion, Smith obtained significant levels of *ortho* borylation with benzodioxole while the more sterically demanding veratrole exhibited less than 2% *ortho* borylation (Fig. 4c and d).[64] As above, electronic effects cannot be eliminated, as anisole has been shown to favour *meta* over *para* borylation,[63] so the lack of reaction for both these substrates suggests that there may also be a more general pyridyl nitrogen 'deactivating' effect at C-2. This would be consistent with the observation of C-5/5′ borylation of 4,4′-dimethoxy-2,2′-bipyridine, in which there is no restriction on rotation of the MeO groups and thus reduced steric hindrance (Fig. 2d).

2,6-Disubstituted quinolines

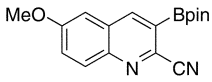
We then explored examples of a 2,6-disubstituted quinoline scaffold **10**. With such compounds, borylation has to occur either *ortho* to one of the substituents or at one of the *peri* positions, either adjacent to a C–H bond or to the quinoline nitrogen lone pair. Reaction of each derivative, following the standard microwave heating protocol described above, albeit now requiring heating to 100 °C for 1.5 h to compensate for the increased steric hindrance in these substrates, afforded the borylated quinolines in good isolated yields following purification by column chromatography (Scheme 4). Significantly, ^{1}H NMR spectra of the crude reaction mixtures showed appearance of a sharp singlet between 7.70 and 7.76 ppm, consistent with H-3 of a quinoline. The observed pattern of 2 doublets and a doublet of doublets for the hydrogens of the carbocyclic ring remained intact. However, signals for H-3 and H-5 were shifted downfield due to the presence of the adjacent highly deshielding Bpin group. These characteristic patterns revealed that all substrates within this class selectively formed the 4-borylated product **11**. Confirmation of this regioselectivity was provided by single-crystal X-ray diffraction analysis of the products **11c** and **11d** (Fig. S1, ESI†) obtained from borylation of 6-chloro-2-methylquinoline **10c** and 6-bromo-2-methylquinoline **10d**, respectively.



10 11

entry	10	R	R'	yield 11 (%)
1	a	Me	Me	72
2	b	Me	OMe	76
3	c	Me	Cl	79
4	d	Me	Br	84
5	e	CN	OMe	98[a]
6	e	CN	OMe	83[b]

[a]A mixture of **11e** and **12** (85:15) was formed; [b]Reaction run at 23-25 °C (no heating) for 48 h.



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Scheme 4 Borylation of 2,6-disubstituted quinolines.

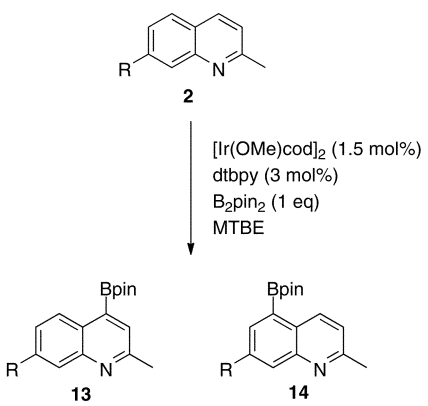
One exception to the selective outcome from this series was obtained with 2-cyano-6-methoxyquinoline **10e**, for which an 85 : 15 mixture of the 4- and 3-borylated products was obtained (Scheme 4, entry 5). This can be attributed to the much lower steric demand of the nitrile group.[63] The 4-borylated product was identified as the major isomer *via* ^{1}H NMR spectroscopic analysis using the same rationale as described above. A second singlet at 8.59 ppm was also observed in the ^{1}H NMR spectrum of the crude reaction mixture which was assigned to H-4 from the minor, 3-borylated product **12**. Interestingly, when this reaction was carried out at room temperature (Scheme 4, entry 6), the 4-borylated product was formed exclusively. Although room temperature borylation reactions have been widely used for reactive substrates, such as thiophene and furan, for which heating is not required to achieve rapid conversion to product,[1,3,48,49] to the best of our knowledge, specific studies on the influence of temperature on the selectivity of a borylation reaction have not previously been described. This offers a useful and simple strategy for the improvement of selectivity in systems where more than one borylated product can form.

The selectivity of the borylation of these substrates highlights a general sterically directed preference for activation at positions adjacent to ring junctions over positions adjacent to substituents. While the lack of borylation at the sterically similar 8-position can be attributed to the differing electronic effect of the heterocyclic and carbocyclic rings, it is also possible that the nitrogen lone pair can be considered to be sterically 'larger' than a C–H bond. Such a stereoelectronic effect may also contribute to the lack of *ortho* borylation in analogous pyridine systems in which the formation of a carbon–metal bond adjacent to the nitrogen lone pair is disfavored. Similar arguments have been advanced to account for the challenge in the direct arylation of pyridines in the 2-position.[65] In the case of 2-cyano-6-methoxyquinoline, the formation of the 3-borylated products presumably reflects an electronic preference for C–H activation at C-3, *vide infra*.[66]

2,7-Disubstituted quinolines

As Ir-catalyzed borylation with the dtbpy-derived catalyst system is inhibited at positions adjacent to most substituents, moving the steric blocking group in the carbocyclic ring from position 6 to position 7 renders the two *peri* positions (C-4 and C-5) as the only two sites available for C–H activation. As C-4 and C-5 have equal steric accessibility, these compounds provided a simple means to explore any electronic directing effect (Scheme 5 and Table 1).

Consistent with the observations made for the parent heterocycle, borylation of 2,7-dimethylquinoline **2f** showed a preference for reaction on the heterocyclic ring over the carbocyclic ring (Table 1, entry 1). Reaction at 100 °C over 1 h gave a mixture of monoborylated products (82 : 12 : 6), with the 4-borylated product being the major isomer. In a similar fashion to that noted for **10e**, when carried out at room temperature (72 h), the reaction proceeded with higher regioselectivity giving the 4-borylated product **13f** as the major isomer in a >95 : <5 mixture. Under these conditions, following purification by column chromatography, **13f** was obtained in 80% isolated yield (Table 1, entry 2). Formation of the 4-borylated product could be clearly ascertained from the ^{1}H NMR spectrum in which the loss of the H-4 signal and a distinctive shift to higher frequency of the signals for H-3 (7.67 ppm, s) and H-5 (8.45 ppm, d, $J = 8.5$ Hz), were consistent with the introduction of an adjacent (*ortho*) boronate group (Fig. 5). Borylation of 7-chloro-2-methylquinoline **2g** at 100 °C for 1.5 h afforded a 65 : 35 mixture of isomers product which, on undertaking the reaction at room temperature, improved to 73 : 27 (Table 1, entries 11 and 12). Following purification by column chromatography and subsequent recrystallization from acetonitrile, the minor isomer could be isolated as a single component. Highly shifted signals for H-4 (8.93 ppm, d, $J = 8.7$ Hz) and H-6 (8.09 ppm, d, $J = 2.5$ Hz) in the ^{1}H NMR spectrum indicated that this product was the 5-borylated isomer **14g**. Confirmation of the regiochemical outcome of these reactions was obtained *via* single-crystal X-ray diffraction studies for both **13f** and **14g** (Fig. S2, ESI†). In a similar fashion, reaction of the 7-bromo and 7-trifluoromethyl analogues also afforded appreciable amounts of the



a. Br; **b.** CF_3; **c.** $SiMe_3$; **d.** CN; **e.** OMe; **f.** CF_3; **g.** Cl

Scheme 5 Borylation of 2,7-disubstituted quinolines.

Table 1 Borylation of 2,7-disubstituted quinolines **2a–g**[a]

Entry	2	R	Temp. (°C)	Time (h)	Conv. (%)[b]	Ratio[c] **13** : **14** : other	Yield[d] (%)
1	**f**	Me	100	1	88	82 : 12 : 6	nd
2	**f**	Me	rt	72	93	>95 : <5	80
3	**e**	OMe	100	1.5	>95	90 : 10 : 0	nd
4	**e**	OMe	rt	48	89	>95 : <5	73
5	**d**	CN	100	0.25	>95	82 : 9 : 9	nd
6	**d**	CN	rt	48	92	>95 : <5	86
7	**c**	$SiMe_3$	100	1.5	85	70 : 20 : 10	nd
8	**c**	$SiMe_3$	rt	72	91	85 : 10 : 5	68
9	**a**	Br	100	1.5	80	65 : 35	nd
10	**a**	Br	rt	48	90	80 : 20	65[e]
11	**g**	Cl	100	1.5	92	65 : 35	61[f]
12	**g**	Cl	rt	68	93	73 : 27	66[g]
13	**b**	CF_3	100	1.5	>95	60 : 40	nd
14	**b**	CF_3	rt	20	94	70 : 30	65[h]

[a] 100 °C reactions run using microwave heating, rt reactions run at ambient temperature monitored at 22–25 °C. [b] Conversion determined by GC-MS. [c] Product ratios determined by GC-MS. [d] Isolated yield of major isomer, unless otherwise stated. [e] Minor isomer isolated in 15% yield. [f] Minor isomer isolated in 11% yield. [g] Minor isomer isolated in 10% yield. [h] Minor isomer isolated in 27% yield.

5-borylated products (Table 1, entries 9, 10, 13 and 14). The preference for the 4-borylated isomer was also observed for the 7-$SiMe_3$, 7-OMe and 7-CN analogues (Table 1, entries 3–8), with all examples showing similar enhancement in selectivity towards the major 4-isomer on reduction of the reaction temperature.

These results reveal the effect of differing substitution patterns on the reaction outcome and allow some general observations to be made concerning quinoline borylation. Quinolines are effective substrates that undergo rapid reaction and give good yields of the corresponding boronate esters. For unsubstituted quinoline, the C-3 position is the primary site for borylation. Moreover, borylation at C-2 and C-8 appears to be disfavored, suggesting that the influence of the nitrogen lone pair, whether steric or electronic in origin, is potentially greater than that of a C–H bond. With judicious positioning of substituents, high levels of regioselectivity can be obtained and, when mixtures of isomers do result, the selectivity may usually be enhanced simply by lowering the reaction temperature, albeit at the expense of reaction rate. However, the current catalyst ceases to be effective at temperatures below 0 °C, and further selectivity enhancements require the development of more active catalysts.

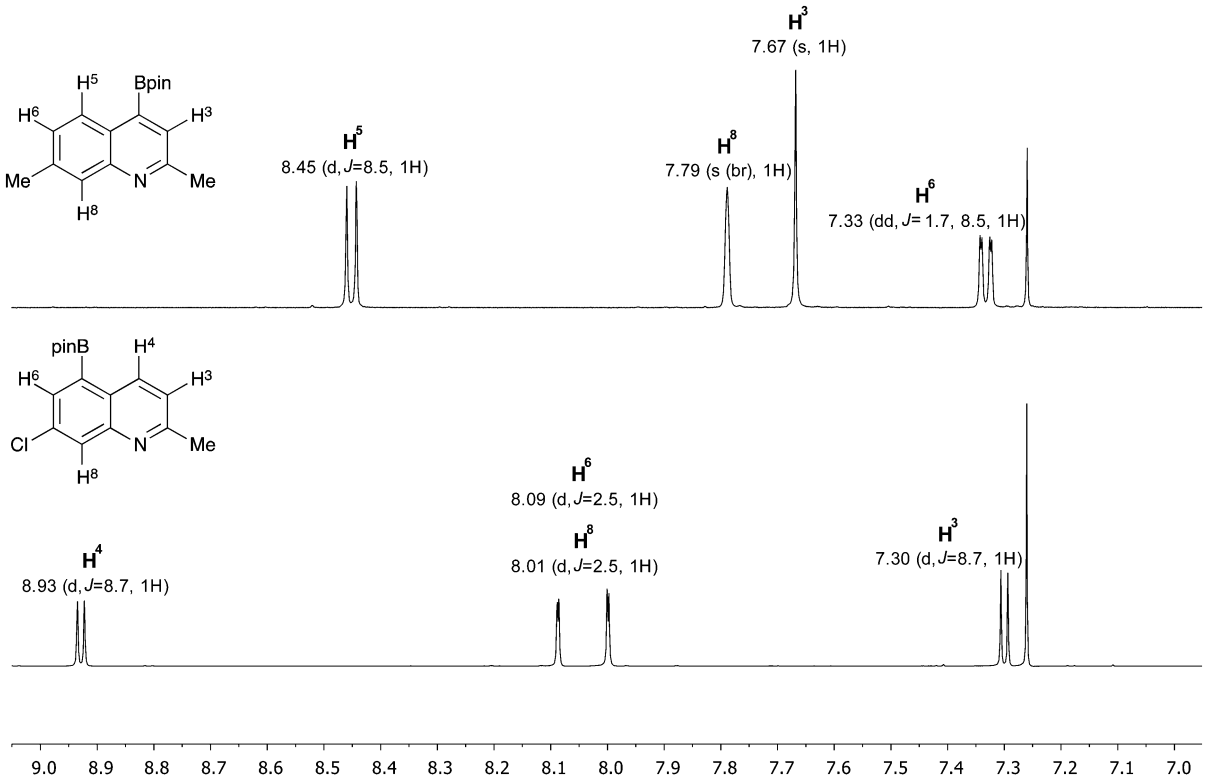
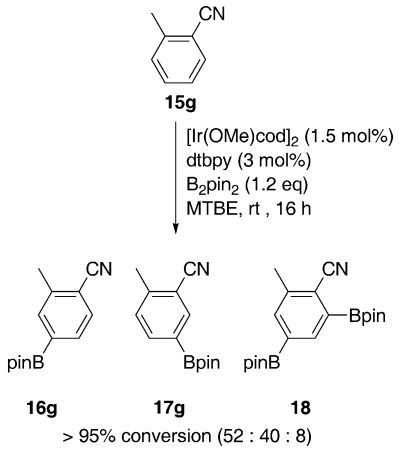


Fig. 5 Aromatic region of the ^{1}H NMR spectra of 4-borylated 2,7-dimethylquinoline **13f** and 5-borylated 2-methyl-7-chloroquinoline **14g**.

The quinoline borylation reactions, particularly those conducted at lower temperatures, have also revealed a range of directing effects. In the absence of steric factors, borylation preferentially occurs on the heteroaromatic ring rather than the carbocyclic ring. However, in the presence of a strongly inductively electron-withdrawing group at C-7, significant levels of borylation at the sterically equivalent C-5 position result.

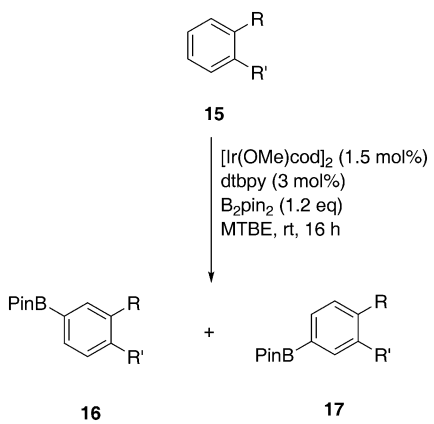
Borylation of 1,2-disubstituted benzenes

With the above in mind, we wondered whether similar effects could be observed in carbocyclic systems in which reaction sites are sterically equivalent but electronically different. On this basis, we explored a series of 1,2-disubstituted benzene derivatives (Table 2). While at elevated temperatures these substrates give a near 1 : 1 mixture of products, reaction at room temperature led to mixtures of the two isomers in unequal amounts. Separation of the isomers proved to be difficult and the isomeric ratios were best calculated by GC-MS and NMR analysis of the crude reaction mixture. In particular, a combination of 1D and 2D NMR spectroscopic experiments (COSY, HSQC, HMBC and NOESY) enabled resonances to be assigned unambiguously to individual isomers. For example, the reaction of 2-methylbenzonitrile **15g** produced a 52 : 40 mixture of two monoborylated isomers **16g** and **17g** accompanied by a small amount (8%) of the 3,5-bisborylated product **18** (Scheme 6). The formation of this last product reflects the relatively low steric requirements of the cyano group. The minor monoborylated isomer **17g** was deduced to be the 5-borylated product by virtue of the appearance of a highly deshielded peak at δ 8.02, corresponding to the hydrogen mutually *ortho* to both the nitrile and boronate ester, showing a weak three-bond coupling to a doublet of doublets for the hydrogen at C-4 at δ 7.86. In contrast, the major C-4-borylated isomer **16g** showed a similar shift to higher frequency of the hydrogens adjacent to the boronate ester, but, in this case, corresponding to H-3 (δ 7.72) and H-5 (δ 7.66), the latter showing coupling to the hydrogen *ortho* to the nitrile at δ 7.56. This assignment was confirmed by a NOESY correlation between the singlet at δ 7.72 and the Ar–CH_3 group at δ 2.53, while a similar link could be made between the alternative methyl singlet at δ 2.54 and the H-3 doublet of the minor isomer at δ 7.30. These experiments lead to a general observation that π-electron acceptors (−M) favor borylation at the *para* position while π-donors (+M) disfavor this position and direct borylation towards the *meta* position, as do σ-electron-withdrawing (−I) groups.



Scheme 6 Borylation of 2-methylbenzonitrile.

Table 2 Borylation of unsymmetrical 1,2-disubstituted benzenes



Entry	15	R	R′	Conv.[a] (%)	Ratio[b] 16 : 17
1	**a**	OMe	Cl	94	60 : 40
2	**b**	OMe	Me	75	75 : 25
3	**c**	OMe	CO_2Me	>99	85 : 15
4	**d**	OMe	COMe	>99	89 : 11
5	**e**	Me	Cl	>99	34 : 66
6	**f**	Me	COMe	87	56 : 44
7	**g**	Me	CN	>99	60 : 40[c]
8	**h**	Me	CO_2Me	>99	73 : 27
9	**i**	$-CH_2CH_2CH_2CO-$		>99	80 : 20
10	**j**	Cl	COMe	>99	62 : 38
11	**k**	Cl	Bpin	>99	84 : 16
12	**l**	CO_2Me	Bpin	35	53 : 47[d]

[a] Conversions determined by GC-MS and ^{1}H NMR spectroscopy. [b] Product ratios determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c] 8% bisborylated product obtained, see Scheme 6. [d] Product ratio determined by GC-MS.

Borylation of monosubstituted benzenes

In order to investigate further this empirical hierarchy, we then re-examined the product ratios obtained from the borylation of a series of monosubstituted benzenes **19**, hoping that by undertaking these experiments at room temperature we would observe similar electronically guided selectivities. To the best of our knowledge, there have only been limited reports on the relative selectivities of iridium-catalyzed borylations of monosubstituted arenes. However, all previous studies had been undertaken at elevated temperatures and the selectivity demonstrated for most substrates was not substantially different from the commonly reported 2 : 1 statistical ratio of *meta* : *para* products (Table S1†).[1,67–69] However, Smith has noted that borylation of anisole using Ir phosphine complexes led to selectivities approaching 4 : 1 *meta* : *para*.[64,67] In our current investigation, the reaction mixtures were more complex than those of the 1,2-disubstituted benzenes, in that bisborylated products were formed in significant amounts.

However, the assumption that these bisborylated products arise from initial borylation at the *meta* position allowed the underlying *m* : *p* selectivity ratios to be determined (Table 3). Satisfyingly, significant deviations from the 2 : 1 statistical ratio typically observed at elevated temperatures were found for all substrates. These deviations matched the findings from the 1,2 series, with π-accepting groups (−M) such as CO_2Me and strong σ-donors (+I), *e.g.* $B(OR)_2$,[63] leading to enhanced *para* selectivity (entries 1–4) while chlorobenzene, *N*,*N*-dimethylaniline and anisole (+M, −I) all underwent increased *meta* borylation (entries 7, 12 and 13).

Further analysis of these results showed a good correlation between NMR shift patterns of the starting arene and the preferred site of borylation (Table 3). With the exception of benzonitrile **19e**, for which a significant amount of *ortho* borylation is observed, and trifluoromethylbenzene **19i**, the electronically preferred site for borylation appears to correspond to the most deshielded of the *meta* and *para* hydrogen atoms. A similar situation exists for all of the quinoline analogues studied (Table S2, ESI†). This simple predictive test is also valid for all of the other substrates explored, with, for example, the ratio of isomers arising from the bisborylation of 2-trifluoromethylquinoline **3b** (Scheme 2) correlating with the chemical shifts in the starting material (Tables S2–S4, ESI†).

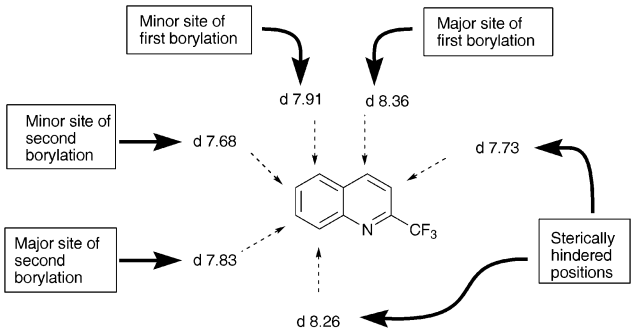
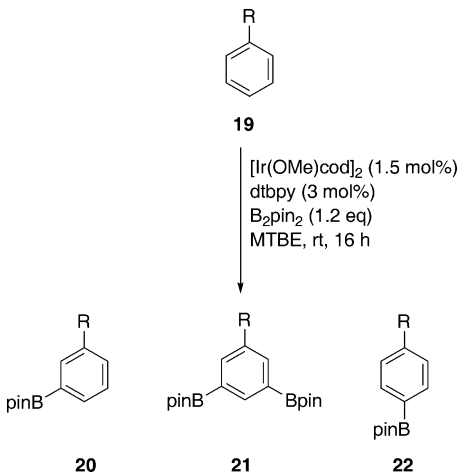


Fig. 6 Correlation of borylation regiochemistry with ^{1}H NMR chemical shift as typified for 2-trifluoromethylquinoline **3b**.

Table 3 Borylation of monosubstituted benzenes



Entry	19	R	^{1}H NMR δ (ppm)[a] *o*	*m*	*p*	Conv.[b] (%)	Product ratio (%)[c] *meta*-	bis-	*para*-	*m* : *p* ratio (**20** + **21**) : **22**	Yield (%)[d]
1	**a**	$Bmes_2$[e]	7.51	7.34	7.47	69[g]	26	6	68	32 : 68	nd
2	**b**	Bneop[f]	7.81	7.36	7.44	45[g]	33	0	67	33 : 67	nd
3	**c**	Bpin	7.82	7.38	7.48	71[g]	32	4	64	36 : 64	40[h]
4	**d**	CO_2Me	7.97	7.37	7.47	>99	22	22	56	44 : 56	39
5	**e**	CN	7.65	7.46	7.60	>99	30	36[i]	34	59 : 41	nd
6	**f**	$Si(TMS)_3$	7.44	7.24	7.24	72	48	15	37	63 : 37	nd
7	**g**	Cl	7.29	7.24	7.17	98	32	33	35	65 : 35	82
8	**h**	Me	7.06	7.14	7.04	30	63	6	31	69 : 31	nd
9	**i**	CF_3	7.64	7.49	7.56	>99	29	40	31	69 : 31	nd
10	**j**	TMS	7.68	7.44	7.44	93	56	16	28	72 : 28	52
11	**k**	^{t}Bu	7.28	7.18	7.05	82	68	8	24	76 : 24	64
12	**l**	NMe_2	6.60	7.08	6.59	69	75	4	21	79 : 21	53
13	**m**	OMe	6.78	7.17	6.82	93	68	16	16	84 : 16	76

[a] Experimentally determined ^{1}H NMR chemical shifts. [b] Unless otherwise indicated, conversions were determined by GC-MS analysis of crude reaction mixture using dodecane as an internal standard. [c] Product ratios were determined by ^{1}H NMR spectroscopy and GC-MS analysis. [d] Yield of purified, isolated product mixture (nd = not determined). [e] mes = mesityl = 2,4,6-$Me_3C_6H_2$. [f] neop = neopentaneglycolato = $OCH_2CMe_2CH_2O$. [g] Conversions determined using ^{1}H NMR spectroscopy. [h] The *para*-directing influence of a Bpin substituent has been noted before – see ref. 63. [i] A 21 : 7 : 8 mixture of different bisborylated products was isolated reflecting the lower steric demand of the CN group (major bisborylated product = 3,5-bis(Bpin)benzonitrile, see ESI†).

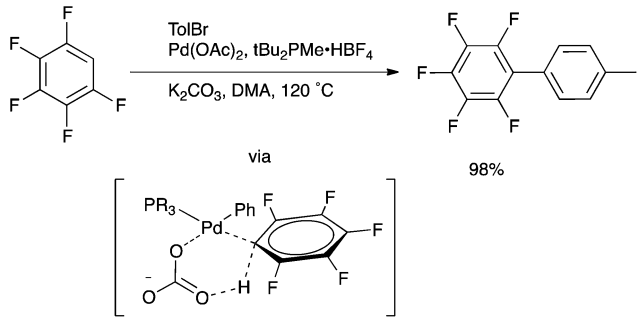


Fig. 7 Ligand-assisted (CMD) C–H activation as described by Fagnou *et al.*[77]

Thus, the most deshielded protons are the most likely to be substituted on electronic grounds once simple steric effects and statistical factors are taken into account (Fig. 6).

However, although valuable as a predictive tool, this correlation is only qualitative, as the difference in chemical shifts ($\Delta\delta$) and the observed quantitative selectivity do not appear to be related. Consequently, we wondered whether alternative readily available physicochemical parameters might provide a better prediction of selectivity. The precise mechanism for the Ir-catalyzed C–H activation step remains a subject of considerable discussion, although it is widely accepted that trisboryliridium(III) complex **23** is the catalytically active species.[11,70–72]

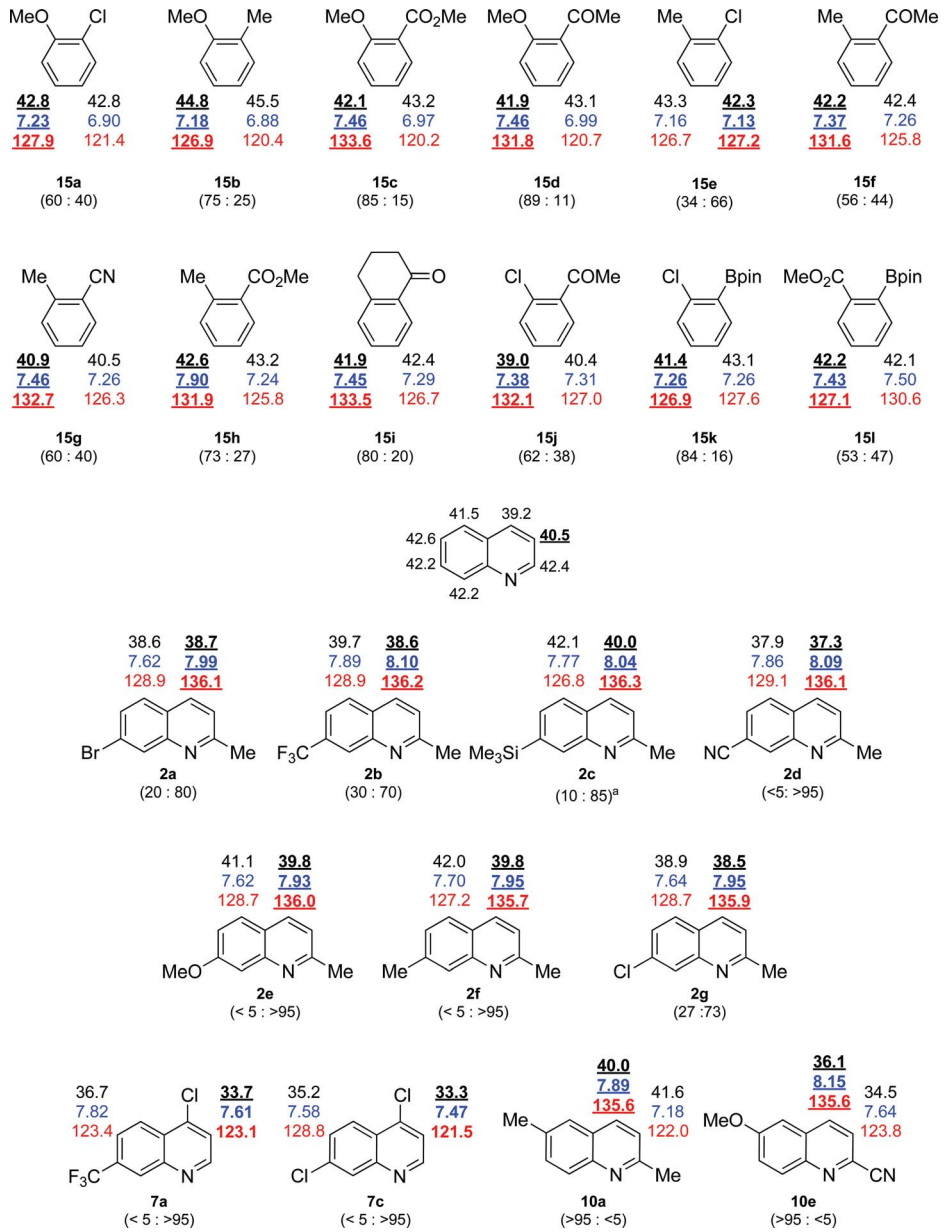
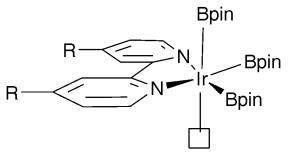


Fig. 8 Calculated pK_a values (black), ^{1}H NMR chemical shifts (blue), ^{13}C NMR chemical shifts (red) and observed selectivity for the labeled positions in the room-temperature Ir-catalyzed borylation reaction of 1,2-disubstituted arenes and quinolines described in this study. The predominant position of borylation is indicated as bold and underlined numbers (a. 5% of a third isomer was observed in the borylation of **2e**).



23

Sakaki and co-workers have suggested that the arene C–H bond undergoes oxidative addition to this iridium species.[71] In support of this, oxidative addition would be expected to be favoured for electron-poor substrates, and such compounds do show faster borylation.[11] However, an alternative pathway involving σ-bond metathesis and the formation of a bis(boryl) aryl-σ-borane complex cannot be excluded.[64,73] The σ-bond metathesis pathway, *via* formation of an IrHBpin adduct, suggests that a basal boryl ligand might effectively 'deprotonate' a C–H bond of an Ir-bound arene.[64] This is related to the ligand-assisted deprotonation mechanism frequently invoked in other transition metal-catalyzed C–H activation processes in which C–H acidity has also been suggested to be a selectivity-driving force. For example, in palladium-catalyzed C–H arylation of fluorine-containing arenes, C–H acidities provided good correlations with site selectivities.[74–77] In many of these palladium examples, a ligand can function as a 'base' in the key C–H activation step (Fig. 7). In contrast, in C–H borylation reactions, the electrons in the M–B σ-bond could formally deprotonate an Ir-complexed arene. In support of such a suggestion, it is well established that boryl anions are extremely basic and, consequently, M–B bonds are extremely electron-rich, with boryl ligands serving as potent nucleophiles (bases).[78,79] This is due to the electropositive nature of boron. Moreover, recent studies on Ir-catalyzed C–H borylation, particularly those relating to heteroarene substrates, have also suggested that C–H acidity may contribute to regiochemical selectivity.[63,64] Such an observation would also fit with the noted higher reactivity of heteroarenes in the Ir-catalyzed aromatic C–H borylation reaction when compared with their carbocyclic counterparts, as the former have uniformly lower pK_a values. On this basis, and as NMR chemical shifts can be related to C–H acidities, we opted to compute the acidities of the key C–H bonds in the molecules studied.

A number of methods have been used previously to calculate pK_a values of aromatic compounds using DFT. Of these, we adopted the protocol established by Guo *et al.* which, using a continuum solvation model, allows predictions to be made for compounds in solution.[80] Although this method is described for DMSO, rather than the less polar solvents used in the Ir-catalyzed C–H borylation process, we felt that this would provide more appropriate values than those obtained using simple gas phase acidity calculations. The results for both the 1,2-disubstituted arenes and disubstituted quinolines are shown in Fig. 8. Reflecting the NMR shift values, for 1,2-disubstituted benzenes there is a very close correlation between the site of highest C–H acidity and the position of preferred borylation. Although a similar link can also be seen in the quinoline series, the model does not fully account for the increasing amounts of borylation at C-5 as the 7-substituent has an increasingly larger inductive electronic effect (CF_3 > Cl > Br).

Conclusions

We have shown that NMR chemical shift analysis of substrates can be used to predict the preferred site of iridium-catalyzed borylation of C–H bonds in both arene and heteroarene C–H borylation. This is important as this transformation is arguably the most efficient method for the generation of aryl and heteroaryl boronate esters containing a diverse array of other functional groups, and the ability to develop predictable synthetic strategies is vital for many applications.

As with other arenes and heteroarenes, for both the quinolines and substituted benzenes studied, high regioselectivity can be observed for suitably sterically constrained substrates. This selectivity is dominated by steric effects and with less pre-organized substrates mixtures of products tend to form. Although the reaction is often carried out at elevated temperatures, it does proceed at lower temperatures and, in this case, an underlying electronically controlled regioselectivity becomes more evident. This electronic selectivity appears to be diametrically opposed to that observed in electrophilic aromatic substitution reactions with π-electron-withdrawing group favoring *para* substitution and inductive electron-withdrawing groups and π-electron-donating groups leading to enhanced *meta* substitution. Consistent with this, transfer of negative charge from Ir to arene has been suggested to be a key factor in these C–H borylations.[64] While C–H acidity appears to provide a qualitative measure of this selectivity, the correlation is not perfect and alternative factors may be more important. In this context, Eisenstein *et al.* have shown that, in other C–H activation processes, M–aryl bond strengths may provide a better fit than do pK_a values, although the former are much more computationally demanding to obtain,[81,82] as is the activation energy for the transition state of the C–H activation process.[64] Further experimental and theoretical studies of regioselectivities, as well as the development of more-active catalysts that will enable the exploitation of this effect in unencumbered substrates, are in progress and will be reported in due course.

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