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Iridium-Catalyzed C–H Activation versus Directed *ortho* Metalation: Complementary Borylation of Aromatics and Heteroaromatics

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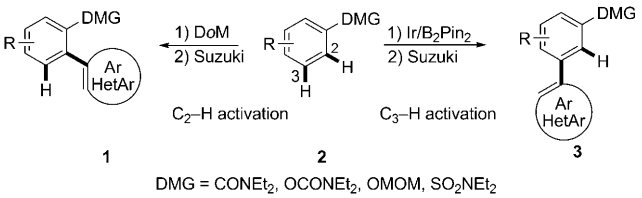
In memory of Keith Fagnou

Abstract: Systematic studies are presented demonstrating the complementarity of directed *ortho* metalation (D*o*M) and Ir-catalyzed strategies for the provision of borylated aromatics and their subsequent Suzuki–Miyaura coupling reactions. A new concept, the use of the TMS group, readily introduced by D*o*M, as a latent regiodirective moiety to overcome the otherwise problematic production of isomeric borylated product mixtures is presented. Additional electrophile-induced *ipso*-deborylation and D*o*M reactions of the Bpin products are described.

Keywords: boron · C–H activation · deborylation · metalation · Suzuki–Miyaura coupling

Introduction

The resurgence of organoboron chemistry,[1] initiated, arguably, almost 30 years ago by the discovery of the Suzuki–Miyaura reaction,[2] has made not only a vast and well appreciated impact on organic synthesis but also contributed to the current productive activity in unrelated areas of molecular recognition, sensors, linear and nonlinear optical materials,[3] neutron capture therapy,[4] and medicinal chemistry and drug discovery.[5] The continuum in this rebirth is due to the salient disclosures of Smith,[6] Hartwig, Ishiyama and Miyaura,[7] and Marder,[8] who demonstrated a direct, Ir^I-catalyzed C–H borylation of aromatic substrates, under mild conditions, to yield aryl boronates using bis(pinacolato)diboron (B_2pin_2) or pinacolborane (HBpin) as the boron source.[9] The recurring suggestion that the regioselectivity of this aromatic ring borylation is controlled predominantly by steric rather than electronic substituent effects and the evident impending value of this reaction in aromatic and heteroaromatic synthetic chemistry provided the impetus for consideration of the juxtaposition of the C–H borylation, **2**→**3** and the directed *ortho* metalation (D*o*M),[10] **2**→**1** processes to accentuate complementary beneficial synthetic methodologies (Scheme 1).[11]



Scheme 1. Complementary borylation/Suzuki–Miyaura cross-coupling reactions of DMG bearing arenes.

We describe results of systematic studies which a) highlight the C–H activation-D*o*M complementarity for the provision of valuable borylated benzene and pyridine derivatives and their subsequent Suzuki–Miyaura reactions,[12] b) highlight the interesting regiodirective borylation effects of latent TMS ring substituents, c) provide useful products of subsequent electrophile-induced *ipso*-deborylation[6h, 7l]

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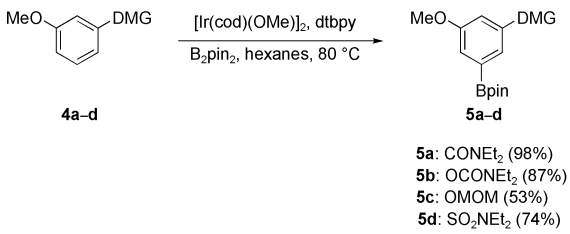
and d) demonstrate, for the first time, in situ Bpin protection to allow further D*o*M reactions. Considered together, these results provide new methodology with potential to enrich the area of polysubstituted aromatic molecule synthesis.

Results and Discussion

Ir-catalyzed borylation of directed metalation group (DMG)-bearing arenes: We initiated our studies with mindful consideration of previous results which indicate that monosubstituted aromatics usually undergo Ir-catalyzed borylation to furnish synthetically compromised mixtures of regioisomeric products while 1,3-disubstituted systems generally lead to common *meta*-borylation with high regioselectivity and good efficiency.[9] Thus, the prototype *meta*-methoxy aromatics **4a–d**, bearing four widely used DMGs, were subjected to the most commonly used Ir-catalyzed conditions and were found to afford the respective 5-boropinacolato products **5a–d**, respectively, in good to excellent yields (Scheme 2).[13]



Scheme 2. Conditions: Arene (1 equiv), $[Ir(cod)(OMe)]_2$ (2 mol%), dtbpy (4 mol%), B_2pin_2 (0.6 equiv), hexanes, 80 °C, 18 h. Yields refer to isolated pure materials. cod = 1,5-cyclooctadiene. dtbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl.

With these encouraging results in hand, studies of benzene and pyridine substrates bearing the extensively used amide and *O*-carbamate DMGs[10] were undertaken and the results, summarized in Table 1, warrant brief comment. Whilst diethyl 2-methoxybenzamide gave an inseparable mixture of 4- and 5-borylated products, TMS derivative **6a**, obtained by efficient D*o*M reaction,[14] led to a single regioisomer **7a** in excellent yield (entry 1). Trisubstituted benzamide **6b** also participated efficiently in the reaction (entry 2). *para*-Anisamide **6c**, however, while still showing a steric effect from the amide function, led to a low yield of product **7c** (entry 3). Bis-borylated naphthalene derivative **7e** was also formed in good yield on increasing the amount of B_2pin_2 used in the reaction.

Marder has shown that the presence of a 2-substituent is preferred for efficient borylation of pyridines by enforcing steric shielding of the detrimental *N*-coordination effect, leading to products in higher yields.[8b] In accordance with this hypothesis, borylation of picolinamide **6f** furnished a mixture of products in modest yield (entry 6). Once again, introduction of the TMS substituent as a latent directing group in **6g** led to increased yield and regioselectivity of the borylated product (entry 7). Nicotinamide **6h**, which may be considered, by virtue of the presence of the *N*-lone pair, a *meta*-substituted aromatic, also afforded the 5-borylated product **7h** in modest yield (entry 8).

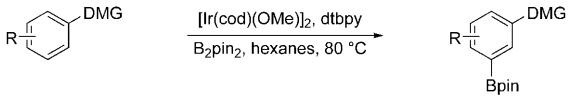
Of greater significance due to the position of $OCONR_2$ as one of the most powerful DMGs[10] are the results of studies of the Ir-catalyzed borylation of aryl *O*-carbamates (entries 9–20). For the selected 1,2,3-trisubstitued aryl *O*-carbamates **8a–d**, all derived by efficient D*o*M reactions,[14] borylated products **9a–d** were obtained in synthetically useful yields (entries 9–12). Analogously to *para*-anisamide **6c**, the corresponding *O*-carbamate **8e** afforded a poor yield of the 3-Bpin product **9e** (entry 13).

The simple *meta*-substituted aryl *O*-carbamates **8f–i** underwent borylation to afford the corresponding products **9f–i** in good yields; in support of the hypothesis that regioselectivity of borylation is driven by steric rather than electronic effects, *meta*-fluoro *O*-carbamate **8f** was found to give an inseparable 2:1 mixture of borylated derivatives **9f** in quantitative yield. Notable is the lack of complication from halogen substituents (**9b**, **9f–g**, **9l**), although similar observations have been reported previously.[9] The 3,4-methylenedioxy derivative **8j** underwent highly *meta*-selective borylation to give product **9j**, a contra-electrophilic substitution result. Possibly heralding future synthetic opportunity, the 1-naphthyl *O*-carbamate **8k** led to the 3-Bpin product **9k** in high yield. Pyridine *O*-carbamate **8l** also participated efficiently in the reaction to give **9l**. As noted above, borylation may be driven either *para* (**9a–c**) or *meta* (**9d–l**) to the DMG depending on the substitution pattern or, uniquely, by the use of TMS as a latent regiodirective group (**7g**, **9a–c**).[15,16]

Complementary D*o*M and Ir-catalyzed borylation-Suzuki–Miyaura cross-coupling reactions: With the above borylation results in hand, we pursued the main goal of this work: to establish complementary D*o*M and catalytic Ir-derived approaches for the synthesis of isomeric biaryls and heterobiaryls by the Suzuki–Miyaura cross-coupling reaction. The comparative results are shown in Table 2.

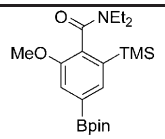
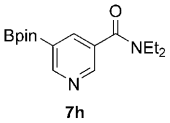
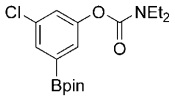
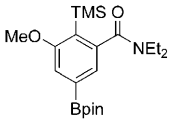
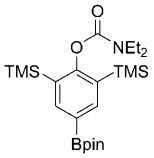
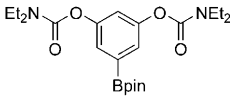
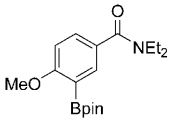
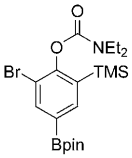
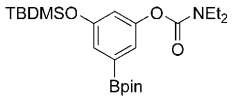
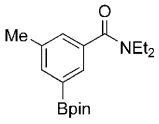
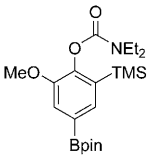
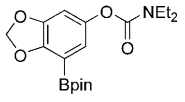
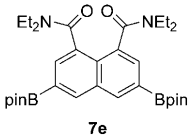
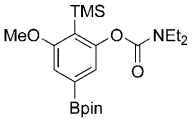
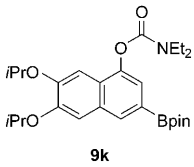
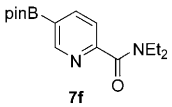
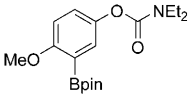
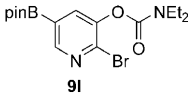
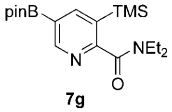
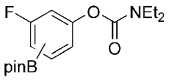
The D*o*M-derived products **10a–h** involve metalation under standard conditions based on the specific DMG followed by quenching with $B(OMe)_3$ to give the crude boronic acids after aqueous workup. These were then subjected to previously established Suzuki–Miyaura cross-coupling conditions[17] with either electron-rich or electron-deficient aryl bromides to afford the biaryl products. For the Ir-catalyzed borylation counterpart results, initially the isolated Bpin derivatives were subjected to standard cross-coupling conditions (Pd_2dba_3/*S*-Phos) developed by Buchwald and coworkers with aryl bromides to give the isomeric biaryl derivatives **11a–h**. Subsequently, application of an in situ procedure recently reported by Marder, Steel et al.,[8c,d] which involves carrying out both the Ir-catalyzed borylation and Suzuki–Miyaura reactions in one pot and in the same sol-

Table 1. Ir-catalyzed borylation of benzamides **6a–e**, pyridine amides **6f–h**, and aryl *O*-carbamates **8a–l**.[a]



6a–h: DMG = $CONEt_2$
8a–l: DMG = $OCONEt_2$

7a–h: DMG = $CONEt_2$
9a–l: DMG = $OCONEt_2$

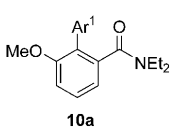
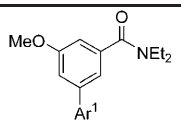
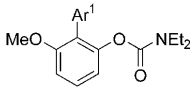
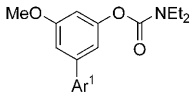
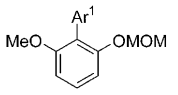
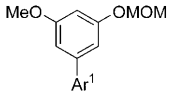
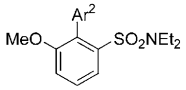
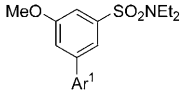
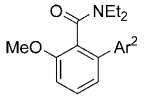
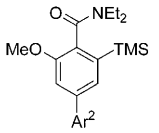
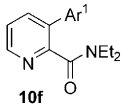
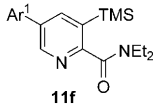
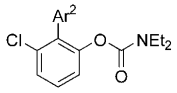
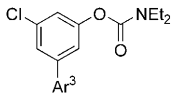
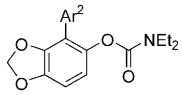
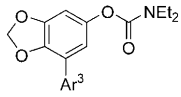
Entry	7	Yield[b] [%]	Entry	7/9	Yield[b] [%]	Entry	9	Yield[b] [%]
1	 **7a**	86	8	 **7h**	63[c]	15	 **9g**	72
2	 **7b**	72	9	 **9a**	70	16	 **9h**	82
3	 **7c**	32[c]	10	 **9b**	93	17	 **9i**	58
4	 **7d**	95	11	 **9c**	59	18	 **9j**	76
5	 **7e**	72[c,d]	12	 **9d**	86	19	 **9k**	88
6	 **7f**	47[e]	13	 **9e**	16	20	 **9l**	84
7	 **7g**	71	14	 **9f**	quant.[f]			

[a] Conditions: Arene (1 equiv), $[Ir(cod)(OMe)]_2$ (2 mol%), dtbpy (4 mol%), B_2pin_2 (0.6 equiv), hexanes, 80°C, 18 h. [b] Yields refer to isolated pure materials. [c] MTBE used as solvent (see reference [8c,d]). [d] 2 equiv of B_2pin_2 used. [e] GC-MS of the crude reaction mixture indicated the presence of a second isomer (presumably the 4-borylated product), which was not observed after purification by silica gel chromatography. [f] 2:1 ratio of regioisomers obtained.

vent (MTBE) led to cleaner reactions and isolation of the biaryls in improved yields. Thus, for the prototype *meta*-methoxyaryl systems **4a–d**, D*o*M-derived Suzuki–Miyaura coupling provided the biaryls **10a–d** while the Ir-catalyzed borylation followed by Suzuki–Miyaura coupling furnished the isomeric biaryl products **11a–d** (entries 1-4) in excellent yield. The directed metalation of sulfonamide **4d** deserves further comment, as trapping of the resulting anion with $B(OMe)_3$ under our standard conditions led to little or no borylated product. However, using MeOBpin as the electrophile gave the corresponding aryl boropinacolate in good yield (72%), which participated in Suzuki–Miyaura coupling with 4-bromoanisole to give **10d** with moderate efficiency.[18] Comparative results for other aryl and heteroaryl amides (entries 5–6) and aryl carbamates (entries 7–8) further demonstrate the utility of these divergent processes.

Sequential DoM-Suzuki–Miyaura cross-couplings of aryl boropinacolates: Motivated by the recent results of Zhichkin and co-workers who showed that reversible protection

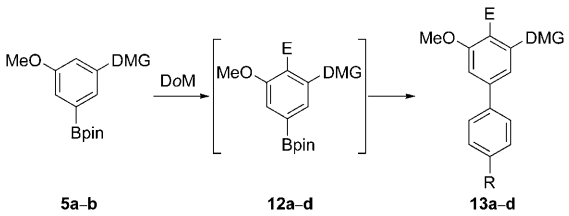
Table 2. Complementary D*o*M[a] and Ir-catalyzed[b] borylation-Suzuki–Miyaura cross-couplings (Scheme 1).

Entry	**10**[c]	Yield[d] [%]	**11**[c]	Yield[d] [%]
1	 **10a**	89	 **11a**	83
2	 **10b**	49	 **11b**	86
3	 **10c**	78	 **11c**	85
4	 **10d**	45[e,g]	 **11d**	85
5	 **10e**	73	 **11e**	95
6	 **10f**	71[h]	 **11f**	90
7	 **10g**	50[f,g]	 **11g**	98
8	 **10h**	52	 **11h**	63

[a] Conditions: 1) Arene (1 equiv), *s*BuLi (1.1 equiv), TMEDA (1.1 equiv), THF, −78 °C, 1 h then $B(OMe)_3$ (4 equiv), THF, −40 °C, 3 h; 2) NH_4Cl (aq) workup; 3) ArBr (0.8 equiv), $[Pd(PPh_3)_4]$ (4 mol %), 2 M Na_2CO_3 (aq), DME, 100 °C, 16 h. [b] Conditions: 1) Arene (1 equiv), $[Ir(cod)(OMe)]_2$ (2 mol %), dtbpy (4 mol %), B_2pin_2 (1 equiv), MTBE, 80 °C, 16 h; 2) ArBr (1.2 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (3 mol %), KOH (5 equiv), MTBE/H_2O 3:1, 80 °C, 4 h. [c] $Ar^1 = p\text{-}NCC_6H_4$, $Ar^2 = p\text{-}MeOC_6H_4$, Ar^3 *m*-MeC_6H_4. [d] Yields refer to isolated pure materials. [e] Conditions: 1) Arene (1 equiv), *n*BuLi (1.5 equiv), THF, −78 °C, 1 h then MeOBpin (4 equiv), −78 °C to RT, 16 h; 2) ArBr (0.8 equiv), $[Pd(dtbpf)Cl_2]\cdot CH_2Cl_2$ (4 mol %), 2 M Na_2CO_3 (aq), DME, 100 °C, 21 h. [f] Conditions: 1) Arene (1 equiv), *s*BuLi (1.2 equiv), TMEDA (1.2 equiv), THF, −78 °C, 2 h then MeOBpin (4 equiv), −78 °C to RT, 16 h; 2) ArBr (1.4 equiv), $[Pd(dtbpf)Cl_2]$ (4 mol %), 2 M Na_2CO_3 (aq), DME, 80 °C, 21 h. [g] Combined yield over 2 steps. [h] see ref. [20]. dppf = 1,1′-bis(diphenylphosphino)ferrocene. dtbpf = 1,1′-bis(di-*tert*-butylphosphino)ferrocene.

of aryl and heteroaryl Bpin derivatives to metal–halogen exchange could be achieved by using lithium isopropoxide,[19] treatment of **5a–b** under modified Zhichkin conditions followed by E^+ (MeI or TMSCl) quench and workup gave the aryl boronates **12a–c**, which were immediately subjected to Suzuki–Miyaura coupling to give biaryls **13a–c** in modest yields over the two steps (Table 3). Application of in situ metalation/quench conditions (LDA/TMSCl) led to the formation of silylated derivative **13d** in 43 % yield after coupling without the need for Bpin protection. Studies to expand the scope of this first D*o*M-Suzuki–Miyaura protocol for aromatic Bpin derivatives are underway in our laboratories and will be disclosed in due course.

Table 3. Sequential D*o*M-Suzuki–Miyaura cross-couplings of aryl boropinacolates **5a**,**b**.



5a–b **12a–d** **13a–d**

Entry	**13**	DMG	E	R	Yield[c] [%]
1	**13a**	$CONEt_2$	Me	CHO	38[a]
2	**13b**	$CONEt_2$	TMS	CHO	50[a]
3	**13c**	$OCONEt_2$	Me	NO_2	68[a]
4	**13d**	$OCONEt_2$	TMS	CHO	43[b]

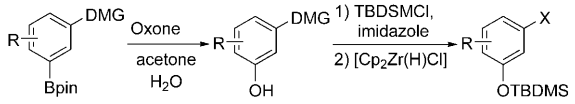
[a] Conditions: 1) ArBpin (1 equiv), LiO*i*Pr (1 equiv), THF, RT, 2 h; 2) *s*BuLi (2.4 equiv), TMEDA (2.4 equiv), THF, −78 °C, 2 h; 3) E^+, THF, −8 °C to RT, 1 h; 4) NH_4Cl (aq) workup; 5) ArBr (1.2–1.5 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (3 mol %), KOH (5 equiv), MTBE/H_2O (3:1), 80 °C, 16 h. [b] Conditions: 1) ArBpin (1 equiv), LDA (2.5 equiv), TMSCl (3.3 equiv), THF, −78 °C, 1 h then −40 °C, 2 h; 2) NH_4Cl (aq) workup; 3) ArBr (1.2 equiv), $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (3 mol %), KOH (5 equiv), MTBE/H_2O 3:1, 80 °C, 17 h. [c] Yields refer to isolated pure materials. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

Electrophile-induced *ipso*-deborylation: To provide additional synthetic scope to the above methodology, exemplary oxidative conversions of Bpin substrates were effected (Table 4).[6h] Thus, treatment of benzamides **5a**/**7e** and *O*-carbamates **9g**/**9j** with Oxone resulted in the formation of the corresponding phenols **14a–d** in generally good yields (52–96 %). Following recently established mild conditions for the reduction of tertiary amides and carbamates to their corresponding aldehydes and phenols using in situ generated Schwartz reagent,[21] **14a–b** and **14c–d** were converted into aldehydes **15a–b** and phenols **15c–d**, respectively, by TBDMS protection followed by Schwartz reduction.[22] This process represents an efficient method for the preparation of orthogonally protected hydroxylated benzaldehydes and phenols that may be difficult to access by traditional electrophilic aromatic chemisty.

Conclusion

In conclusion, Ir-catalyzed borylation reactions have been achieved on a variety of aryl and pyridyl amide and *O*-carbamate substrates (Table 1) which afford the corresponding boropinacolates with regioselectivity which complements

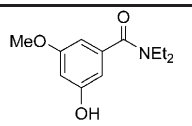
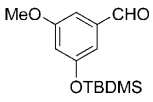
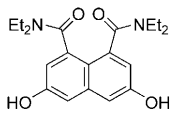
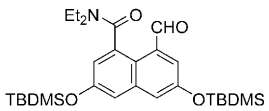
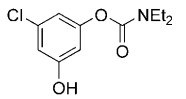
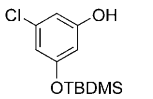
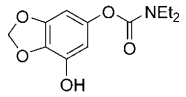
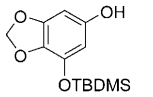
Table 4. *ipso*-Hydroxydeborylation of aryl boropinacolates **5a**, **7e**, **9g**, **9j** and DMG reduction using the Schwartz reagent.[a,b]



5a, **7e**
9g, **9j**

14a–d

15a–d

Entry	**14**	Yield[c] [%]	**15**	Yield[c] [%]
1	 **14a**	93	 **15a**	63
2	 **14b**	52	 **15b**	41
3	 **14c**	64	 **15c**	48
4	 **14d**	96	 **15d**	62

[a] Conditions: ArBpin (1 equiv), Oxone (1.1 equiv), acetone/H_2O 1:1, RT, 30 min to 1 h. [b] 1) ArOH (1 equiv), TBDMSCl (1.5 equiv), imidazole (1.5 equiv), CH_2Cl_2, RT, 1 h; 2) [Cp_2ZrCl_2] (1.5–3.0 equiv), LiAlH($OtBu)_3$ (1.5–3.0 equiv), THF, RT, 3-16 h. [c] Yields refer to isolated pure materials. TBDMS = *tert*-butyldimethylsilyl.

products obtained by the D*o*M-borylation reaction sequence. Significantly, a new concept, the use of a TMS group, readily introduced by D*o*M, as a latent regiodirective moiety to overcome the otherwise problematic production of isomeric borylated product mixtures has been presented. The complementarity of the D*o*M and Ir-catalyzed strategies for the construction of biaryls and heterobiaryls has been demonstrated by the establishment of respective Suzuki–Miyaura cross-coupling procedures (Table 2). The polysubstituted biaryls obtained are expected to be amenable to further D*o*M-borylation/cross-coupling as well as directed remote metalation (DreM) reactions.[10d] Aside from *ipso*-hydroxydeborylation (Table 4), in situ Bpin protection for subsequent D*o*M reactions (Table 3) broadens the scope of the reported chemistry. Taken in sum, the results allow conceptual contemplation of metalation- and cross-coupling-based transformations of potential value for the construction of polysubstituted aromatics and heteroaromatics.

Experimental Section

General methods: Commercially available reagents were used throughout without further purification unless otherwise stated. Reactions were routinely carried out under a nitrogen or argon atmosphere using oven or flame-dried glassware. Anhydrous hexane, MTBE, and DME were purchased from Sigma–Aldrich and degassed by purging with a stream of argon for 20–30 min prior to use. Anhydrous THF and toluene were obtained using an Innovative Technologies "Pure-Solve" SPS-400-4 system. *n*-Butyllithium (2.5 M solution in hexanes) and *sec*-butyllithium (1.6 M in hexanes) were purchased from Sigma–Aldrich and titrated biweekly according to the method of Chong and co-workers.[23] Internal temperatures for low temperature reactions were measured using a Barnant thermocouple thermometer. Chlorotrimethylsilane was freshly distilled prior to use. Flash chromatography was carried out using Silicycle Silicaflash P60 silica gel.

General procedure 1—C–H activation/borylation: [Ir(cod)(OMe)]$_2$ (0.013 g, 0.02 mmol, 2 mol%), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (0.011 g, 0.040 mmol, 4 mol%) and bis(pinacolato)diboron (0.152 g, 0.600 mmol) were added to the (hetero)arene (1.00 mmol) in a Schlenk tube under argon. Hexanes (6 mL) were added and the tube sealed. The reaction mixture was heated to 80 °C for 16–24 h and cooled to room temperature. The crude product was purified by flash chromatography on silica gel to afford the title compound.

General procedure 2—C–H activation/borylation/Suzuki–Miyaura cross-coupling: [Ir(cod)(OMe)]$_2$ (0.013 g, 0.020 mmol, 2 mol%), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (0.011 g, 0.040 mmol, 4 mol%) and bis(pinacolato)diboron (0.254 g, 1.00 mmol) were added to the (hetero)arene (1.00 mmol) in a Schlenk tube under argon. MTBE (3 mL) was added and the tube sealed. The reaction mixture was heated to 80 °C for 16 h and then cooled to room temperature. Degassed H_2O (1 mL) was added, followed by [Pd(dppf)Cl_2]·CH_2Cl_2 (0.025 g, 0.030 mmol, 3 mol%), potassium hydroxide (0.280 g, 5.00 mmol) and the aryl halide (1.20 mmol). The tube was resealed and the reaction mixture heated at 80 °C for 4 h. The resulting mixture was filtered through Celite and partitioned between H_2O (15 mL) and CH_2Cl_2 (3×15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound.

General procedure 3—Directed *ortho* metalation/borylation/Suzuki–Miyaura cross-coupling: To a solution of TMEDA (0.165 mL, 1.10 mmol) in dry THF (3 mL) at −78 °C was added *sec*-butyllithium (1.23 M in hexanes, 0.90 mL, 1.10 mmol) dropwise over 5 min. The (hetero)arene (1.00 mmol) in THF (2 mL) was added dropwise over 15 min so that the internal temperature did not rise above −70 °C, and the reaction mixture was stirred at −78 °C for 1 h. Trimethylborate (0.446 mL, 4.00 mmol) was then added over 10 min. The reaction was allowed to warm to −40 °C, stirred for 3 h, and then quenched carefully at this temperature by the addition of saturated aqueous NH_4Cl (5 mL), H_2O (5 mL) and CH_2Cl_2 (10 mL). The aqueous layer was separated and further extracted with CH_2Cl_2 (2×10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude boronic acid, which was dried under high vacuum for 30 min and used without further purification.

To the boronic acid was added [Pd($PPh_3)_4$] (0.046 g, 0.040 mmol, 4 mol%) and the aryl halide (0.800 mmol), followed by degassed DME (4 mL) and degassed 2 M aqueous Na_2CO_3 solution (2 mL). The reaction mixture was heated under reflux for 16 h, cooled to room temperature and partitioned between H_2O (15 mL) and EtOAc (3×15 mL). The combined organics were washed with H_2O (15 mL) and saturated brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound.

General procedure 4—Directed *ortho* metalation/Suzuki–Miyaura cross-coupling: To a solution of the aryl boropinacolate (1.00 mmol) in THF (10 mL) was added lithium isopropoxide (1 M in hexanes, 1.00 mL, 1.00 mmol). The reaction mixture stirred at room temperature for 2 h, then cooled to −78 °C. TMEDA (0.36 mL, 2.40 mmol) was added, followed by *sec*-butyllithium (1.29 M in hexanes, 1.86 mL, 2.40 mmol) dropwise over 10 min so that the internal temperature did not rise above −70 °C, and the reaction mixture was stirred at −78 °C for 1 h. The electrophile (3.00 mmol) was added and the reaction mixture was stirred at −78 °C for 30 min before warming to room temperature. After a further 1 h at room temperature saturated aqueous NH_4Cl (25 mL) was added,

and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude aryl boropinacolate was used directly in the next step without further purification.

To the aryl boropinacolate in degassed MTBE (3 mL) and degassed water (1 mL) in a Schlenk tube was added $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ (0.025 g, 0.030 mmol, 3 mol%), potassium hydroxide (0.281 g, 5.00 mmol) and the aryl bromide (1.2–1.5 mmol). The tube was sealed and the reaction was heated at 80°C for 16 h, then partitioned between H_2O (25 mL) and EtOAc (3×25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound.

General procedure 5—Arylboropinacolate oxidation: To a solution of the aryl boropinacolate (1.00 mmol) in acetone (5 mL) was added a solution of Oxone (0.369 g, 1.2 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 1 h, diluted with H_2O (10 mL) and the aqueous layer extracted with EtOAc (3×10 mL). The combined organics were washed with saturated brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound.

General Procedure 6—Phenol protection/Schwartz reduction: To a solution of the phenol (0.500 mmol) in CH_2Cl_2 (5 mL) was added *tert*-butyldimethylsilyl chloride (0.113 g, 0.750 mmol) and imidazole (0.051 g, 0.750 mmol). The reaction mixture was stirred at room temperature for 2–4 h, then passed through a short plug of silica gel to afford the TBDMS-protected phenol, which was used directly in the next step without further purification.

To the protected phenol (0.350 mmol) in THF (3.5 mL) was added bis(cyclopentadienyl)zirconium(IV) dichloride (0.153 g, 0.525 mmol for amide reduction or 0.307 g, 1.05 mmol for carbamate reduction) and lithium tri(*tert*-butoxy)aluminium hydride (1.0 M in THF, 0.53 mL, 0.525 mmol for amide reduction or 1.10 mL, 1.05 mmol for carbamate reduction) dropwise over 2 min. The reaction mixture was stirred at room temperature for 3–16 h and quenched with 0.5 M HCl (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organics were washed with saturated brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford the title compound.

Acknowledgements

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