Synthetic Methods

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Use of Hemilabile N,N Ligands in Nitrogen-Directed Iridium-Catalyzed Borylations of Arenes**

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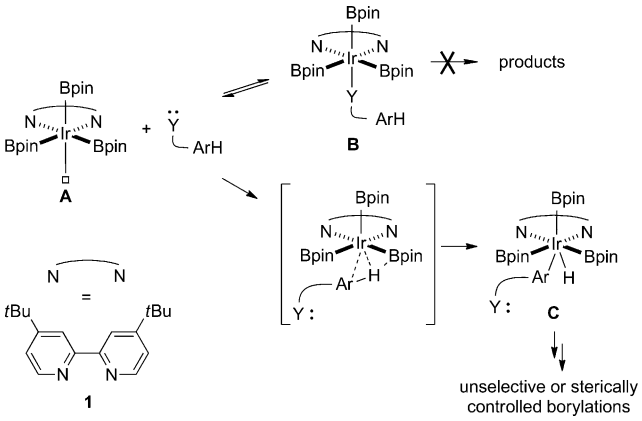
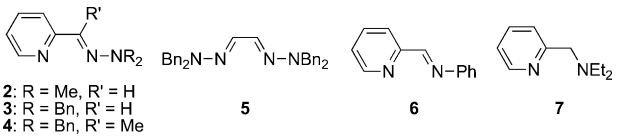
The direct activation of unreactive C–H bonds has emerged as a very active field in organic synthesis.[1] One of the best established reactions in this area is the direct borylation of arenes with bis(pinacolato)diboron (B_2pin_2) or pinacolborane (HBpin). After the seminal work by Smith, Hartwig, Miyaura, and their respective co-workers, this method has reached an impressive level of chemical efficiency,[2] mainly because of the introduction of the $[Ir(\mu\text{-}X)(cod)]_2$/di-*tert*-butylbipyridine (dtbpy; X = Cl, OMe; cod = 1,5-cyclooctadiene) precatalyst system. The regioselectivity of this reaction is typically driven by steric factors,[3] thus making the method complementary to directed *ortho*-metalation (D*o*M) reactions.[4] Very recently, however, directed *ortho* borylations have been accomplished by using directing groups such as siloxide or silylamine[5] and carbonyl functionalities,[6] but the absence of any nitrogen-directed borylation is noteworthy. Herein, we present our results on the regioselective *ortho* C–H borylation of 2-arylpyridines (isoquinolines) and aromatic hydrazones.

The regioselectivity of Ir^{III}/dtbpy-catalyzed reactions can be arguably attributed to the lack of a coordination site in complex **B**, which results from coordination of the directing atom Y to the established catalytic species **A**[2c] (Scheme 1). In this scenario, the direct activation of arene C–H bonds can only proceed through intermediate **C** and is therefore mainly controlled by steric factors. On the other hand, the ability of transition metals to selectively activate arene C–H bonds in 2-aryl pyridines[1d] made us speculate that such a reaction would only require the generation of an additional coordination site at an appropriate stage. Therefore, we decided to investigate the behavior of potentially hemilabile N,N ligands,[7] in which one of the nitrogen atoms is a weaker donor that is prone to dissociation and therefore able to generate the required coordination site. It was foreseen that an ideal ligand should still be a good donor in order to maintain a high level of reactivity as in the reference dtbpy-based system.



Scheme 1. Regioselectivity in Ir^{III}/dtbpy-catalyzed arene borylations. Square represents a vacant coordination site.

Based on our own experience with related ligands,[8] pyridine hydrazones **2**–**4**, which maintain one of the pyridine units in their structures, and bishydrazone **5** were considered as candidates (Scheme 2). Additionally, pyridine imine **6**[9] and pyridine amine **7** were included for comparison in the preliminary screenings. The relative activity of in situ formed $[IrCl(cod)]_2$/N,N-ligand catalysts (ligand = **1**–**7**) was investigated by using the borylation of 1-(1-naphthyl)isoquinoline **8a** with B_2pin_2 in THF at 50 °C as a model reaction (Table 1). The catalyst based on dtbpy ligand **1** is highly active, but, as expected, affords a complex mixture of borylated products that was not analyzed further (Table 1, entry 1). To our delight, an excellent selectivity was observed in the reactions performed with ligands **2**–**4**, which resulted in a clean formation of product **9a** in good yields (Table 1, entries 2–4). Bishydrazone **5** and pyridine amine **7** were ineffective at 50 °C (Table 1, entries 5 and 7), however, raising the reaction temperature to 80 °C also led to the desired result in these cases (Table 1, entries 8 and 9). Finally, pyridine imine **6** exhibited an intermediate behavior as its activity at 50 °C was



Scheme 2. N,N ligands with potential hemilabile character.

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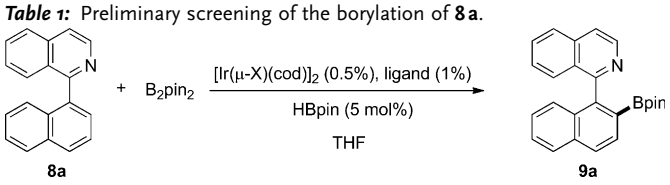
Table 1: Preliminary screening of the borylation of **8a**.

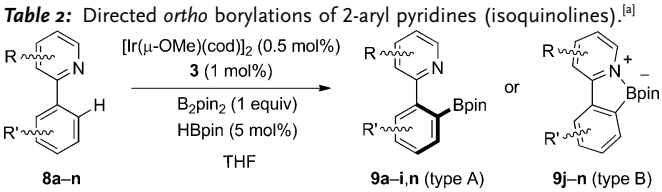


8a **9a**

Entry	Ligand	X	*T* [°C]	*t* [h]	Yield[a] [%]
1	**1**	Cl	50	14	n.d.[b]
2	**2**	Cl	50	20	67
3	**3**	Cl	50	20	78
4	**4**	Cl	50	20	79
5	**5**	Cl	50	20	–[c]
6	**6**	Cl	50	20	60
7	**7**	Cl	50	14	–[c]
8	**5**	Cl	80	20	75
9	**7**	Cl	80	20	80
10	–	Cl	80	20	0
11	**3**	Cl	80	72	50[d,e]
12	**3**	OMe	50	7	84
13	**1**	OMe	RT	24	n.d.[b]
14	**3**	OMe	RT	24	70[e]
15	**5**	OMe	RT	24	10[e]
16	**6**	OMe	RT	24	50[e]
17	**7**	OMe	RT	24	5[e]

[a] Yield of isolated product unless stated otherwise. [b] Complex mixture of products, yield was not determined (n.d.). [c] No reaction. [d] HBpin (1.05 equiv) was used as borylation agent. [e] Incomplete reaction, yield was estimated from the ^{1}H NMR spectrum of the crude reaction mixture.

Table 2: Directed *ortho* borylations of 2-aryl pyridines (isoquinolines).[a]



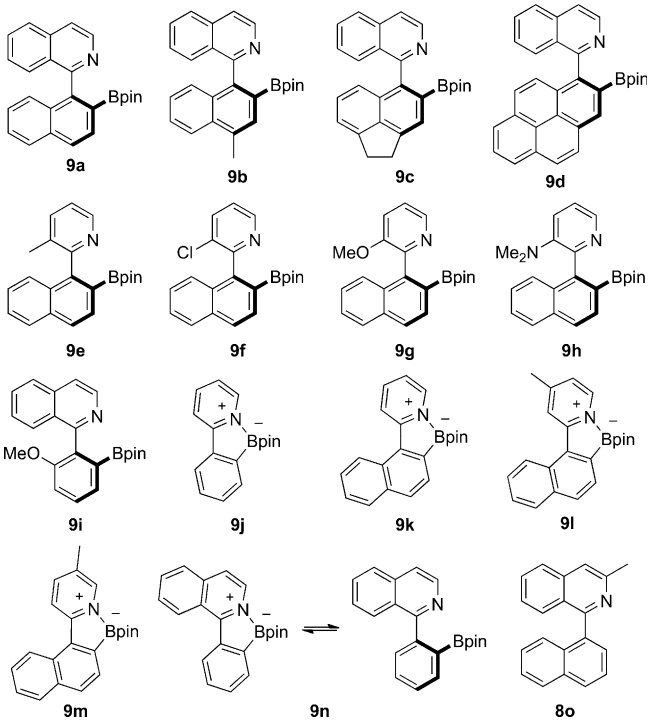
8a–n **9a–i,n** (type A) **9j–n** (type B)

Entry	Substrate	*T* [°C]	*t* [h]	δ_B [ppm]	$\delta_{H(Me\text{-}pin)}$ [ppm]	Product (type)	Yield [%][b]
1	**8a**	50	7	31.1	0.75, 0.95	**9a** (A)	84
2	**8b**	50	10	31.1	0.75, 0.94	**9b** (A)	77
3	**8c**	50	7	30.3	0.86	**9c** (A)	79
4	**8d**	50	7	30.5	0.83, 1.01	**9d** (A)	62
5	**8e**	50	7	30.2	1.11	**9e** (A)	84
6	**8f**	80	12	29.9	1.14	**9f** (A)	58
7	**8g**	80	12	30.4	1.15	**9g** (A)	69
8	**8h**	50	7	29.5	1.15	**9h** (A)	70
9	**8i**	50	7	30.0	0.85	**9i** (A)	88
10	**8j**	80	48	13.3	1.43	**9j** (B)	64[c]
11	**8k**	80	20	15.2	1.43	**9k** (B)	73[c]
12	**8l**	50	7	13.9	1.44	**9l** (B)	84
13	**8m**	50	7	15.2	1.44	**9m** (B)	85
14	**8n**	50	7	22.1	1.27	**9n** (–)[d]	78

[a] Reactions performed on a 0.5 mmol scale with 0.5 mmol of B_2pin_2. [b] Yields of isolated products after purification by column chromatography on silica gel or precipitation with hexane. [c] 0.25 mmol of B_2pin_2 used. [d] A fast equilibrium between product types A and B is proposed.

maintained (Table 1, entry 6), but at slower rates than that of pyridine hydrazones. A control experiment showed that no reaction takes place in the absence of a ligand (Table 1, entry 10). Further experiments with ligand **3** showed a reduced reactivity of HBpin (Table 1, entry 11) and a better rate for the reaction performed with $[Ir(\mu\text{-OMe})(cod)]_2$ as the precatalyst (Table 1, entry 12). Additional reactivity tests performed at room temperature with ligands **1**, **3**, and **5**–**7** and precatalyst $[Ir(\mu\text{-OMe})(cod)]_2$ (Table 1, entries 13–17) confirmed **3** as the best choice of ligand.

Successive studies were aimed at analyzing the scope of the reaction (Table 2, Scheme 3) and were therefore conducted with ligand **3**.[10] The reactions worked well with a variety of 2-pyridyl and 2-isoquinolyl directing groups (**8a**–**n**), and afforded the desired *ortho*-borylation products **9a**–**n** in good to excellent yields. Electron-donating (**8e**,**g**,**h**) and withdrawing (**8f**) groups were introduced onto the pyridine ring; reactions of **8e**,**g**,**h** were more effective, which was expected because of the better coordination ability of the nitrogen atom (Table 2, entries 5–8). Additional steric crowding around the nitrogen atom as in 3-methyl-2-(1-naphthyl)-isoquinoline (**8o**) completely inhibited the reaction, even at 80 °C. This result highlights the selectivity that is reached with ligand **3**, which is inactive for the activation of regular Ar–H bonds, unless a directing effect facilitates the reaction. The reaction proved to be highly selective in most cases. Only the simplest pyridine derivatives **8j** and **8k** produced some polyborylation products,[11] but by reducing the amount of B_2pin_2 to 0.5 equivalents, this effect was minimized. Thus, the desired products **9j** and **9k** could be isolated in 64 % and 73 % yield, respectively, though longer reaction times were required in these cases (Table 2, entries 10 and 11). The structure of products **9** proved to be dependent on the substitution pattern: more hindered products **9a**–**i** (Table 2,



Scheme 3. Borylation products **9a**–**i** (type A), **9j**–**m** (type B), **9n** (equilibrium), and unreactive starting material **8o**.

entries 1–9) exhibited a much lower polarity, thus suggesting the absence of N–B interactions (type A), while unhindered derivatives **8j**–**m** (Table 2, entries 10–13) afforded products **9j**–**m** with a higher polarity, a trend that was attributed to an internal N–B dative bond (type B). This assignment was confirmed by studies in the solid state and in solution. Representative crystalline products **9a** (Figure 1) and **9j** (Figure 2) were analyzed by X-ray crystallography.[12] Derivative **9a**, with higher steric inhibition to a coplanar geometry, shows a nearly perpendicular arrangement of the isoquinoline and the 2-naphthyl rings (dihedral angle N1-C11-C1-C2 = 82.3°), while the boron atom adopts a nearly perfect trigonal-planar geometry that results from its sp^2 hybridization (virtual dihedral angle C2-B1-O1-O2 = 179.96°).[13] On the other hand, the simplest product **9j** shows a clear N–B coordination (distance N1–B1 = 1.6622(16) Å), thus forcing coplanarity of the pyridine and phenyl rings (dihedral angle N1-C1-C6-C7 = 0.6°) and the pyramidalization of the boron atom (virtual dihedral angle C7-B1-O1-O2 = 133.38°). In solution, both types of structures can be identified by the

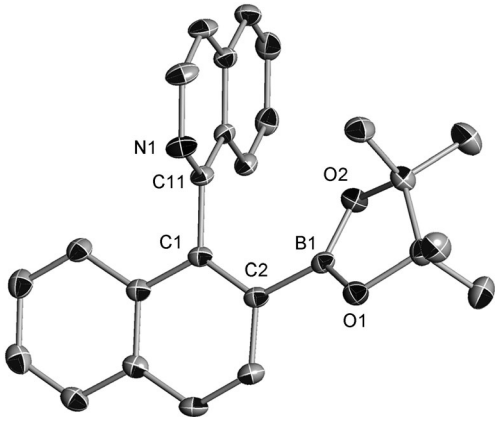


Figure 1. X-ray structure of **9a**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [°]: O1–B1 1.374(2), O2–B1 1.362(2), C2–B1 1.556(2); O2-B1-O1 113.55(15). Thermal ellipsoids drawn at 30% probability.

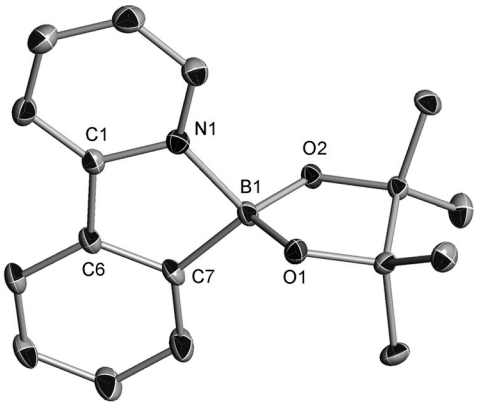
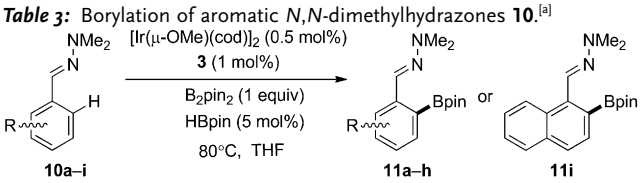


Figure 2. X-Ray structure of **9j**. Hydrogen atoms and a crystallization H_2O molecule are omitted for clarity. Selected bond lengths [Å] and bond angles [°]: N1–B1 1.6622(16), C7–B1 1.6366(16), O1–B1 1.4443(14), O2–B1 1.4445(14); O1-B1-O2 106.67(9). Thermal ellipsoids drawn at 30% probability.

^{1}H NMR signals of the pinacol methyl groups, which appear at 0.75–1.15 ppm for free pinacolates **9a**–**i** (type A), and are deshielded and appear at 1.40–1.45 ppm in internal N–B complexes **9j**–**m** (type B). The assignment was further confirmed by ^{11}B NMR spectra of the products: the signal for the first class of products regularly appears in the 29–31 ppm range, while the N–B interaction results in a strong shielding and the signals appear at 13–15 ppm, which are in agreement with reported data for both types of boron atoms.[14] Finally, **9n** appears to be an intermediate case, as its ^{11}B NMR spectrum shows a signal at 22.1 ppm and its ^{1}H NMR spectrum shows a signal at 1.27 ppm, which correspond to the pinacolate methyl groups. In this case, a fast equilibrium between both types of product is tentatively proposed.

Several benzaldehyde-derived imines were used as substrates under the optimized reaction conditions in order to identify a broader synthetic utility of the methodology. These experiments revealed that electron-rich *N*,*N*-dimethylhydrazones **10** are also suitable substrates that afford the desired *ortho*-borylated products **11** in good yields (Table 3).[15] The method worked well for derivatives carrying electron-withdrawing (**10d**, **e**, **g**, **h**; Table 3, entries 4,5,7, and 8) or electron-donating (**10b**, **c**, **f**; Table 3, entries 2,3, and 6) substituents on the aromatic ring, and allowed monoborylation of C-6 unsubstituted substrates **10a**, **d**, **e**.

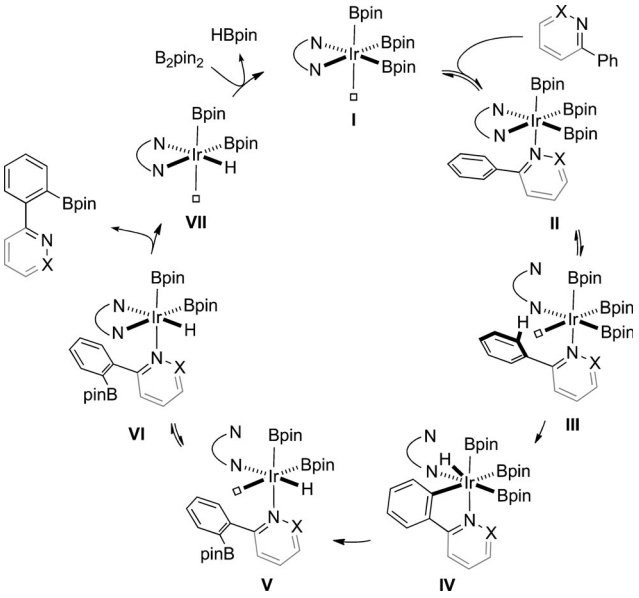
Table 3: Borylation of aromatic *N*,*N*-dimethylhydrazones **10**.[a]



Entry	Product	R	*t* [h]	Yield[b] [%]
1	**11a**	H	16	80[l]
2	**11b**	*o*-Me	24	88
3	**11c**	*o*-OMe	24	80
4	**11d**	*o*-F	24	72
5	**11e**	*m*-Cl	17	84
6	**11f**	*p*-OMe	10	77
7	**11g**	*p*-Cl	8	73
8	**11h**	*p*-F	7	70
9	**11i**	–	24	95

[a] Reactions performed on a 0.5 mmol scale. [b] Yields of isolated products after purification by column chromatography on neutral alumina.

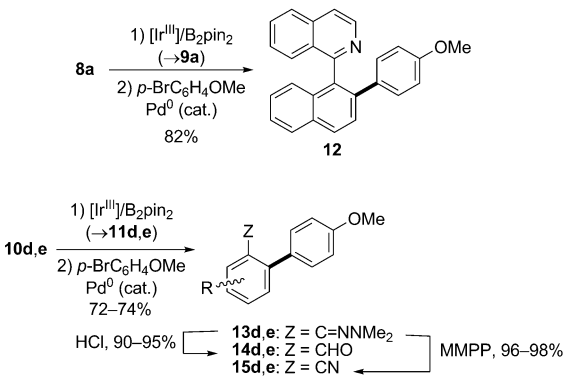
According to the initial hypothesis, our results can be explained by a mechanism initiated by formation of a substrate–catalyst complex **II**, which might suffer a temporary dissociation of the weaker nitrogen donor to lead to intermediate **III** (Scheme 4). It is worth noting that the proposed intermediate **III** would have the same configuration as the starting catalyst **I**, with two *cis*-N ligands, three Bpin ligands, and a vacant coordination site (square), the only difference being that the two N ligands are not bridged as in the original configuration. Once the equilibrium **I**⇌**II**⇌**III** is established, the activation of the *ortho* Ar–H bonds in **III** should be favored, thus leading to **IV** and then closing the



Scheme 4. Proposed mechanism and catalytic cycle.

catalytic cycle after reductive elimination (→**V**), transligation with release of the product (**V**→**VII**), and regeneration of **I** according to the established mechanism.[16]

One evident application for the borylated products **9** and **11** is their use as substrates in Suzuki–Miyaura (SM) cross-coupling reactions. Thus, the one-pot directed borylation/SM cross-coupling was performed for the model reaction (**8a**→**9a**→**12**). After completion of the borylation reaction (**8a**→**9a**), $[Pd(PPh_3)_4]$ (3 mol%), and 4-bromoanisole were added to the reaction mixture to afford product **12** in 82% yield (Scheme 5). The overall process can be viewed as a direct arylation of 2-aryl pyridines; this reaction has also been achieved by using Pd,[17] Rh,[18] Ru,[19] Fe,[20] or Co[21] catalysts. However, a review of these reports reveals the absence of reactions that give products such as **12**, in which coplanarity is strongly hindered. A similar reaction sequence from hydrazone representatives **10d**,**e** afforded the expected products **13d**,**e**, which were further transformed into aldehydes **14d**,**e** and nitriles **15d**,**e** by high-yielding acidic hydrolysis and oxidative cleavage with magnesium monoperoxyphthalate (MMPP),[22] respectively.



Scheme 5. Synthetic applications of this methodology.

In conclusion, the hemilability of pyridine hydrazone ligands is the key for iridium(III)-catalyzed nitrogen-directed *ortho* borylations of several aromatic substrates under mild conditions.

Experimental Section

General procedure for iridium-catalyzed selective borylations: A dried Schlenk tube was charged with the substrate **8a**–**n** (0.5 mmol) or **10a**–**f** and B_2pin_2 (127 mg, 0.5 mmol). The catalyst stock solution[23] (1 mL) and HBpin (3.7 μL, 5% mol) were added, and the reaction mixture was stirred at the desired temperature until the starting material was consumed (as shown by TLC). The mixture was cooled to room temperature, concentrated to dryness, and purified by column chromatography on silica gel (products **9a**–**h**,**j**,**k**) or neutral alumina (product **11**; eluents: mixtures of *n*-hexane/EtOAc) or by precipitation with hexane (products **9i**,**l**–**n**).

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[10] An additional control experiment showed that ligand **3** itself is not a substrate for the borylation reaction and remains untouched after 48 h at 80 °C, even when the most active [Ir(μ-OMe)(cod)]$_2$ precatalyst was used.

[11] The reaction of **8k** with B_2pin_2 and the [Ir(μ-OMe)(cod)]$_2$/dtbpy system affords a 1:1 mixture of borylation products at positions 4 and 5 of the pyridine ring. See Ref. [3c].

[12] Crystallographic data for **9a**: $C_{25}H_{24}BNO_2$, $M = 381.26$, monoclinic, $a = 10.1455(8)$, $b = 21.3539(17)$, $c = 10.3408(9)$ Å, $\beta = 111.087(2)°$, $V = 2090.3(3)$ Å^3, $T = 173(2)$ K, space group $P2_1/n$, $Z = 4$, $\mu(MoK_\alpha) = 0.075$ mm^{-1}, 26583 reflections, 6352 independent ($R_{int} = 0.0412$). Final $R_1 = 0.0571$ ($I > 2\sigma(I)$). Final w$R(F^2) = 0.1344$ ($I > 2\sigma(I)$). Final $R_1 = 0.0991$ (all data). Final w$R(F^2) = 0.1591$ (all data). Goodness of fit on $F^2 = 1.026$. Crystallographic data for **9j**: $C_{17}H_{20}BNO_2 \cdot H_2O$, $M = 299.17$, monoclinic, $a = 7.0271(5)$, $b = 22.3665(16)$, $c = 10.2909(8)$ Å, $\beta = 94.708(2)°$, $V = 1612.0(2)$ Å^3, $T = 173(2)$ K, space group $P2_1/n$, $Z = 4$, $\mu(MoK_\alpha) = 0.083$ mm^{-1}, 22774 reflections, 4849 independent ($R_{int} = 0.0239$). Final $R_1 = 0.0471$ ($I > 2\sigma(I)$). Final w$R(F^2) = 0.1268$ ($I > 2\sigma(I)$). Final $R_1 = 0.0586$ (all data). Final w$R(F^2) = 0.1365$ (all data). Goodness of fit on $F^2 = 1.027$. CCDC 827362 (**9a**), and CCDC 827363 (**9j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[15] ^{1}H NMR analysis of the crude reaction mixtures showed clean products in almost quantitative yields. Although chromatography on silica gel led to extensive decomposition, purification on alumina allowed the removal of remaining HBpin with a moderate loss of product.

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[23] Prepared by dissolving **3** (37.6 mg, 0.125 mmol) and [Ir(μ-OMe)(cod)]$_2$ (41 mg, 0.063 mmol) in dry THF to a total volume of 25 mL (the solution was sonicated for 1 h). The stock solution was kept under Ar.

