

Hydrazone as the Directing Group for Ir-Catalyzed Arene Diborylations and Sequential Functionalizations

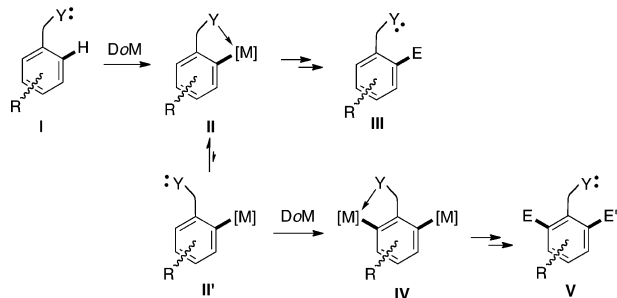
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S Supporting Information

ABSTRACT: The use of hemilabile pyridine–hydrazone N,N-ligands allows the highly selective Ir-catalyzed ortho,ortho'-directed diborylation of aromatic N,N-dimethylhydrazones in near-quantitative yields. One-pot sequential Suzuki–Miyaura cross-coupling with different aryl bromides provides a short entry to unsymmetrically substituted 2,6-diarylbenzaldehyde derivatives.

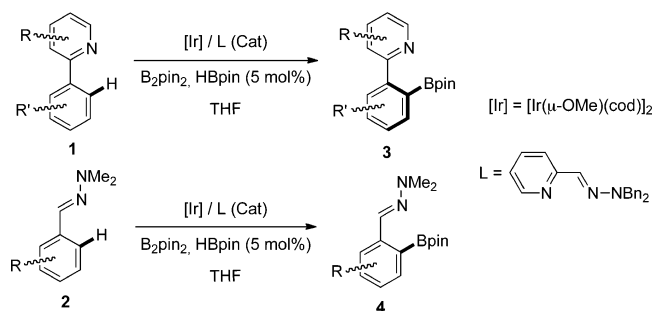
Directed ortho metalation of functionalized arenes (Scheme 1, I→II) and its combination with cross-coupling processes (II→III) is a well-established, fundamental tool in modern synthetic chemistry.¹ As a natural extension of this methodology, direct ortho,ortho' dimetalation would be an attractive tool because of the opportunities that intermediates IV offer after sequential functionalization with two similar or different electrophiles (IV→V). In principle, such a process would require only the availability of a directing metalation group (DMG) to coordinate and drive a second molecule of the (organometallic) metalation reagent to the ortho' position. Such a requisite, however, is not trivial, as the DMG would in principle remain coordinated intramolecularly to the first metal atom (II), the release of the DMG group (II→II') being disfavored. In fact, only sulfonyl² and sulfoximine³ DMGs have been reported to enable *o,o'*-dilithiations, and the resulting products exhibited limited stability, suffering lithium sulfinate eliminations and rearrangement to *o,o'*-dilithiosulfinamides followed by Fries rearrangement, respectively. Therefore, a general procedure for the directed *o,o'*-dimetalation of benzene derivatives and subsequent functionalization remains a challenging target in synthetic methodology.

Scheme 1



On the other hand, direct Ir-catalyzed arene borylation⁴ appears an attractive alternative to lithiation because of the stability and functional-group compatibility of the borylated intermediates. Though the two methodologies are in principle complementary from the regioselectivity point of view,⁵ some strategies for directed *o*-borylations using directing groups such as siloxide or silylamine⁶ and carbonyl functionalities⁷ have been developed. Very recently, our group⁸ and Sawamura and co-workers⁹ independently reported Ir- and Rh-based catalysts for the *nitrogen*-directed *o*-borylation of a variety of nitrogenated substrates. In our approach, the use of hemilabile pyridine–hydrazone N,N-ligands such as L is the key to performing ortho-selective borylations of 2-arylpyridines 1 and N,N-dimethylhydrazones 2 (Scheme 2). We now report on the development of directed *o,o'*-diborylations of the latter and further sequential functionalizations to products of type V.¹⁰

Scheme 2



A comparative study of the structures of the monoborylation products from substrates 1 and 2 led to the choice of the latter for diborylation studies. Thus, ¹¹B and ¹H NMR and crystallographic studies on *o*-borylated 2-arylpyridines 3 indicated that, for unhindered substrates, the preferred conformers 3A are stabilized by a strong intramolecular N–B interaction, which makes the N atom unavailable for further directed borylations (Figure 1). Conformers 3B are preferred only in products with strong inhibition to coplanarity, with substituents at the ortho' position, while the planar structures 3C are destabilized by repulsive steric C(3)–R(H)/boronate interactions. In monoborylated N,N-dimethylhydrazones 4,

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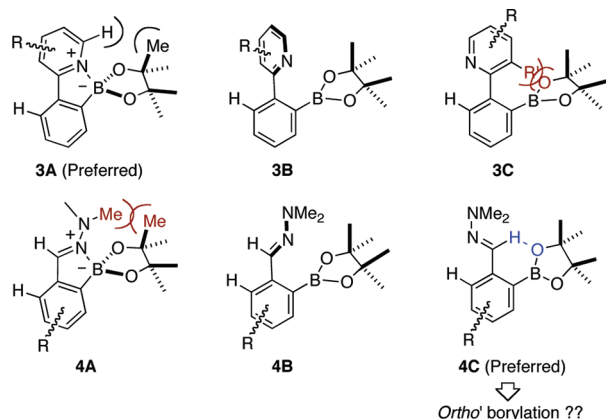


Figure 1. Preferred structures of monoborylated 2-arylpyridines **3** and *N,N*-dimethylhydrazones **4**.

however, a similar N–B interaction (**4A**) is not observed on the basis of ^{11}B NMR data (30.9–32.2 ppm),¹¹ a fact that can be attributed to the significant $\text{NMe}_2/\text{Me}_{\text{pinacol}}$ steric repulsion. In addition, the ^1H NMR spectra of 6-unsubstituted derivatives **4** show a strong deshielding of the azomethine H atom with respect to the parent hydrazones **2** ($\Delta\delta > 0.85$ ppm) that has been attributed to a nonclassical $\text{CH}\cdots\text{O}$ H-bond (conformers **4C**).¹² Additional evidence was obtained from single-crystal X-ray diffraction (XRD) analysis of monoborylated representative **4b** ($\text{R} = 4\text{-OMe}$; Figure 2), which showed indeed a relatively

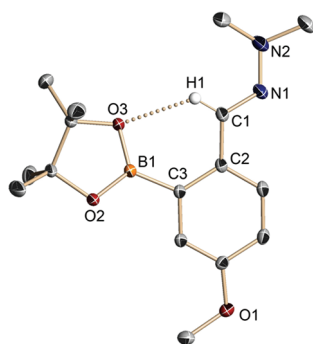
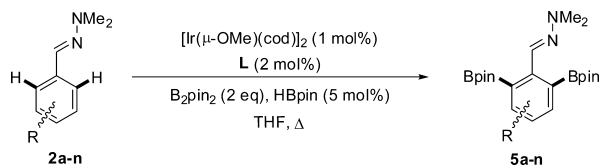


Figure 2. X-ray structure of **4b** (H atoms omitted for clarity).

short $\text{CH}\cdots\text{O}$ H-bond [$\text{CH}\cdots\text{O} = 2.18$ Å; $\text{C}(1)\text{--H}(1)\text{--O}(3)$ angle = 128.1°]. Thus, the availability of the sp^2 N atom in compounds **4C** suggests that its coordination ability could be exploited to achieve a second directed borylation.¹³

On this basis, we started experiments using the $[\text{Ir}(\mu\text{-OMe})(\text{cod})]_2/\text{L}$ catalyst system for diborylation of benzaldehyde-derived *N,N*-dimethylhydrazones **2** (Scheme 3). The simplest one, the challenging unsubstituted derivative **2a** ($\text{R} = \text{H}$), was chosen as a model substrate, using a catalyst loading of 2 mol % and pinacol borane (HBpin , 5 mol %) as cocatalyst. To our delight, reaction of **2a** with 2 equiv of diboron

Scheme 3. Directed *o,o'*-Diborylation of Hydrazones **2**



pinacolate (B_2pin_2) in tetrahydrofuran (THF) at 80°C afforded the desired *o,o'*-diborylated product **5a** in near-quantitative yield in a reasonable reaction time (Table 1,

Table 1. Directed Diborylation of *N,N*-Dimethylhydrazones **2**^a

entry	hydrazone	R	t (h)	yield (%) ^b	product
1	2a	H	33	>95 (76) ^c	5a
2	2b	4-OMe	18	>95 (–)	5b
3	2c	4-NMe ₂	22	>95 (–)	5c
4	2d	4-F	12	>95 (79)	5d
5	2e	4-Cl	16	>95 (53)	5e
6	2f	4-CN	37	>95 (80)	5f
7	2g	3-OMe	48	>95 (58)	5g
8	2h	3-Cl	48	>95 (72)	5h
9	2i	3-Me	44	>95 (73) ^d	5i
10	2j	3,4-(OMe) ₂	48	>95 (70)	5j
11	2k	3,4-Cl ₂	48	>95 (51)	5k
12	2l	–	144	>95 (–)	5l
13	2m	3,5-(OMe) ₂	144	>95 (60)	5m
14	2n	3,5-Cl ₂	140	>95 (60)	5n

^aReactions performed on 0.5 mmol scale. ^bEstimated by ^1H NMR analysis of the crude reaction mixtures. In parentheses are the yields after treatment with *n*-hexane or column chromatography on neutral alumina. ^cIsolated yield for reaction performed on 20.0 mmol scale. ^dIsolated yield for reaction performed on 4.5 mmol scale.

entry 1).¹⁴ No traces of tri(poly)borylation products were detected when the reaction was performed with an excess (4 equiv) of B_2pin_2 or when **5a** was exposed to the reaction conditions.

The structure of **5a** was unequivocally assigned from XRD (Figure 3) and NMR data. As for the monoborylated

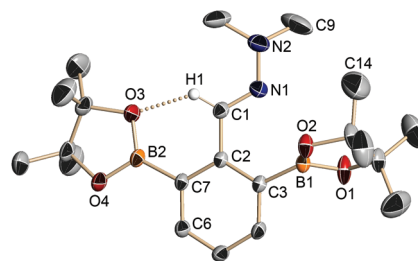
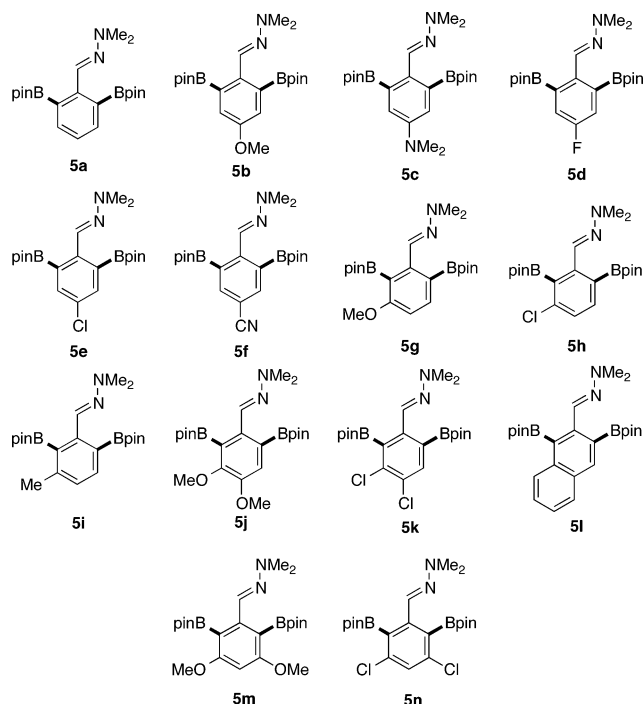


Figure 3. X-ray structure of **5a** (H atoms omitted for clarity).

derivatives **4**, the azomethine H atom is involved in a relatively short $\text{CH}\cdots\text{O}$ H-bond with one of the pinacol O atoms [$\text{H}(1)\text{--O}(3) = 2.3$ Å, $\text{C}(1)\text{--H}(1)\text{--O}(3)$ angle = 122.0°]. In solution, this H-bonding interaction can be recognized, as for products **4**, by the strong deshielding of the azomethine H atom ($\delta_{\text{CHN}} = 7.20$ and 8.26 for **2a** and **5a**, respectively). On the other hand, the distance between the imino nitrogen of the hydrazone moiety and the nearest B atom [$\text{N}(1)\text{--B}(1) = 2.74$ Å] clearly indicates the absence of a significant N–B interaction, though an incipient pyramidalization at B(1) is observed [virtual $\text{C}(3)\text{--B}(1)\text{--O}(2)\text{--O}(1)$ dihedral angle = 166.1°].¹⁵ It is worth noting that the distance between one of the *N*-methyl groups and the nearest methyl group in the pinacol [$\text{C}(9)\text{--C}(14) = 3.86$ Å] is slightly shorter than the sum of the van der Waals radii,¹⁶ thereby preventing a closer N–B interaction as discussed above.

The diborylation reaction conditions optimized for **2a** were then applied to a variety of para- (**2b–f**) and meta- (**2g–i**) monosubstituted substrates as well as 3,4- (**2j–l**) and even 3,5- (**2m,n**) disubstituted derivatives, affording in all cases the desired *o,o'*-diborylated *N,N*-dimethylhydrazones **5b–n** in near-quantitative yields (Table 1 and Chart 1). The reaction worked

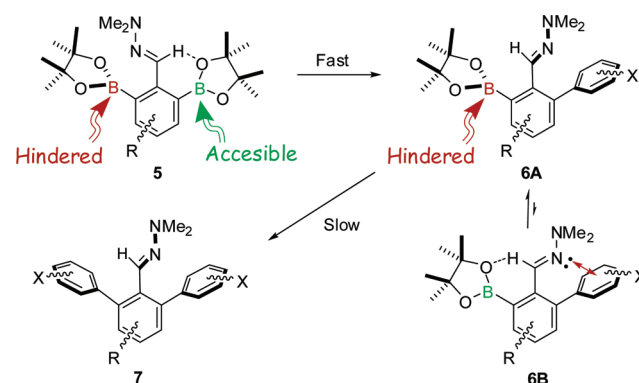
Chart 1. Diborylated Products **5a–n**



well for substrates carrying electron-donating (**2b,c,g,i,j,m**) or -withdrawing (**2d–f,h,k,n**) groups. In the para-substituted series **2b–f**, where steric effects were expectedly irrelevant, the reaction rates were correlated with the electronic properties of the substituent: more electron-poor substrates reacted slightly faster than more electron-rich derivatives, with all of them except **2f** reaching completion in 12–22 h (entries 2–5).¹⁷ The slower diborylation of nitrile **2f** can be attributed to the ability of the cyano group to compete with the hydrazone sp^2 N atom for the vacant coordination site of the catalyst. As expected, introduction of a substituent at position 3 in monosubstituted substrates **2g–i** or 3,4-disubstituted substrates **2j–l** decreased the reaction rates, presumably as a consequence of steric interactions (entries 7–12). Additional hindrance, as in 3,5-disubstituted derivatives **5m,n**, resulted in even longer reaction times (entries 13 and 14), but complete conversions were reached in all cases.

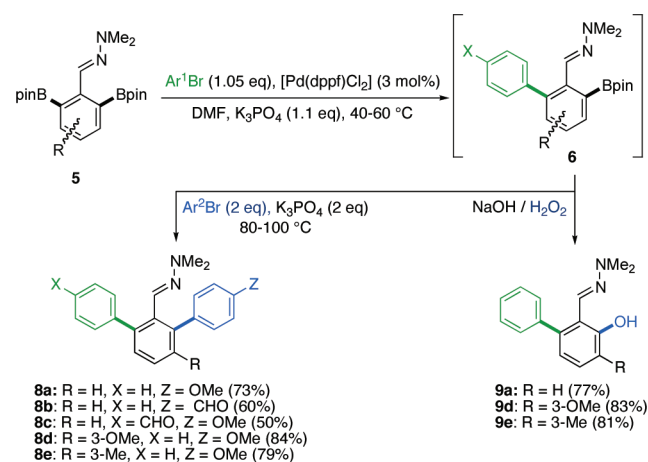
As mentioned above, the most interesting synthetic application of the diborylated products **5** is their use as intermediates for the introduction of two different electrophiles. Using the simplest product **5a** as a challenging model substrate, we explored sequential Suzuki–Miyaura cross-coupling with two different aryl bromides, Ar^1Br and Ar^2Br (Scheme 4, $R = H$). The strategy was based on the dissymmetric interaction of the hydrazone with the two Bpin moieties (shown in Figure 3 for **5a** in the solid state). Thus, the B atom in the H-bonded, coplanar boronate group of **5** should be more accessible for activation by the base (Scheme 4), even in the absence of additional steric influence ($R = H$), and

Scheme 4. Hypothesis for Selective Cross-Couplings from Diborylated Hydrazones **5**



should therefore provide faster transmetalations and couplings to give arylation products **6A**. The coplanar conformation **6B** can be disregarded *a priori* because of the electron repulsion between the $N(sp^2)$ lone pair and the Ar^1 group. Consequently, the second, undesired coupling leading to homodiborylated product **7** would require activation of a more hindered B atom and should therefore proceed at a lower rate. Accordingly, coupling of **5a** with bromobenzene using $[Pd(dppf)Cl_2]$ as the catalyst, $K_3PO_4 \cdot nH_2O$ as the base, and *N,N*-dimethylformamide (DMF) as the solvent¹⁸ took place selectively to afford the monoarylation product **6** ($X = H$, $R = H$) as the major product (Scheme 5). Next, the product obtained under the optimized

Scheme 5. Sequential Functionalizations from Hydrazones **5**

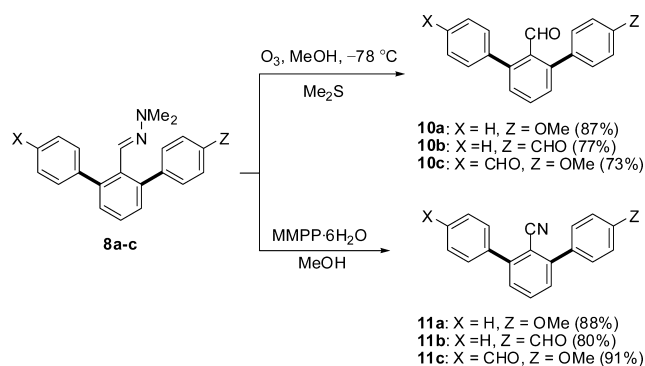


conditions (1.05 equiv of $PhBr$, 1.05 equiv of base, 3 mol % catalyst, 60 °C, 5 h) was treated in situ with more base and *p*-bromoanisole to yield unsymmetrically substituted triaryl **8a** in a satisfactory 73% overall yield. Structural modifications in both Ar^1Br and Ar^2Br led to similar results (**8b,c**). As expected, the selective monoarylation was even more efficient for meta-substituted substrates (e.g., **5g,i**), leading to unsymmetrical 2,6-diaryl derivatives (**8d,e**, respectively), in high yields after a second coupling with *p*-anisyl bromide.¹⁹ Additionally, a sequential “one-pot” Suzuki–Miyaura coupling/oxidation protocol afforded salicylaldehyde derivatives **9a,d,e** in good yields.

To illustrate further the synthetic value of the procedure, representative products **8a–c** were used as substrates for the high-yielding transformations of hydrazones into aldehydes (**8**→**10**) and nitriles (**8**→**11**) by ozonolysis and oxidative

cleavage using magnesium monoperoxyphthalate (MMPP),²⁰ respectively (Scheme 6).

Scheme 6. Representative Hydrazone Transformations



In summary, the combination of pyridine–hydrazones as hemilabile N,N-ligands and hydrazones as privileged directing groups enables a very efficient and regioselective Ir-catalyzed *o,o'*-diborylation of benzaldehyde derivatives. The dissymmetric interaction of the hydrazone with the boryl groups enables the high-yielding, sequential functionalization of these intermediates for the straightforward synthesis of densely functionalized arenes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra for new compounds, and CIF data for **4b** and **5a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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