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

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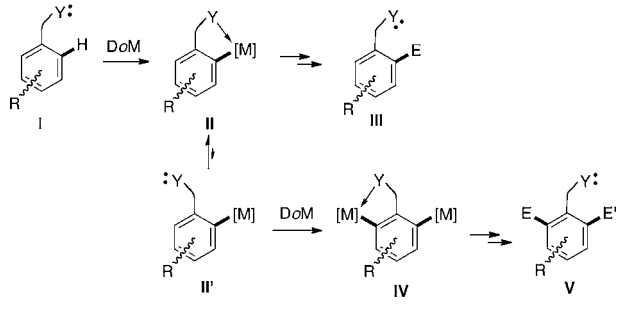
Supporting Information

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.

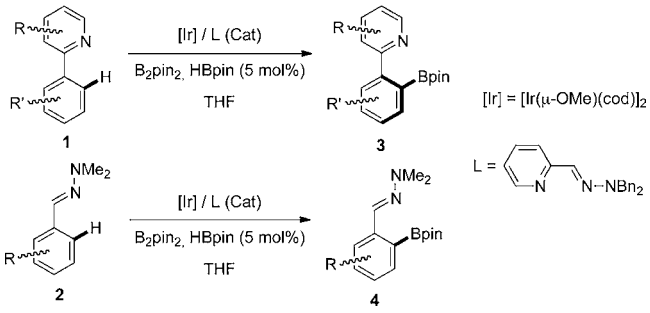
Directed ortho metalation of functionalized arenes (Scheme 1, **I**→**II**) and its combination with cross-coupling processes (**II**→**III**) is a well-established, fundamental tool in modern synthetic chemistry.[1] As a natural extension of this methodology, direct ortho,ortho′ dimetalation would be 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 sulfonyl[2] and sulfoximine[3] 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 borylation[4] 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 silylamine[6] and carbonyl functionalities[7] have been developed. Very recently, our group[8] and Sawamura and co-workers[9] 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, ^{11}B and ^{1}H 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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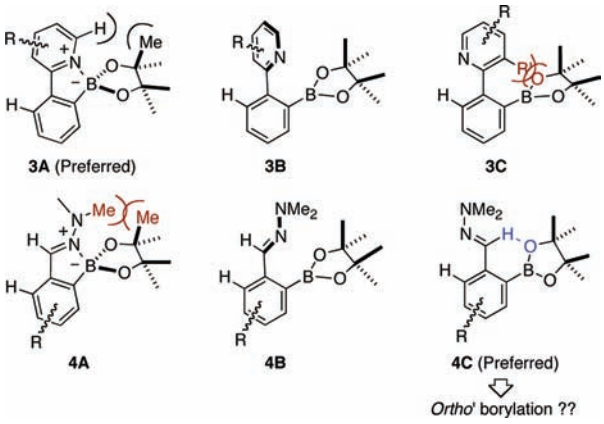


Figure 1. Preferred structures of monoborylated 2-arylpyridines **3** and *N,N*-dimethylhydrazones **4**.

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 $NMe_2/Me_{pinacol}$ steric repulsion. In addition, the ^{1}H 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 CH···O H-bond (conformers **4C**).[12] Additional evidence was obtained from single-crystal X-ray diffraction (XRD) analysis of monoborylated representative **4b** (R = 4-OMe; Figure 2), which showed indeed a relatively

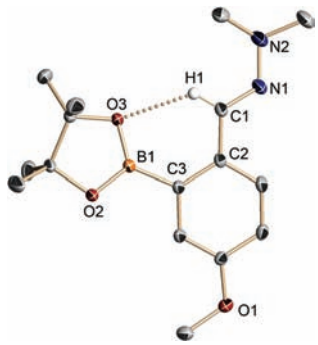
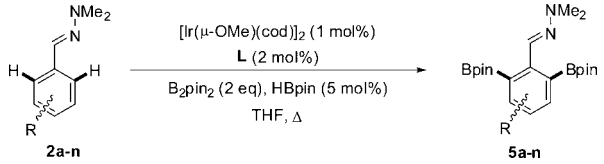


Figure 2. X-ray structure of **4b** (H atoms omitted for clarity).

short CH···O H-bond [CH···O = 2.18 Å; C(1)−H(1)−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 [Ir(μ-OMe)(cod)]$_2$/**L** catalyst system for diborylation of benzaldehyde-derived *N,N*-dimethylhydrazones **2** (Scheme 3). The simplest one, the challenging unsubstituted derivative **2a** (R = 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**

[a]Reactions performed on 0.5 mmol scale. [b]Estimated by ^{1}H NMR analysis of the crude reaction mixtures. In parentheses are the yields after treatment with *n*-hexane or column chromatography on neutral alumina. [c]Isolated yield for reaction performed on 20.0 mmol scale. [d]Isolated 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

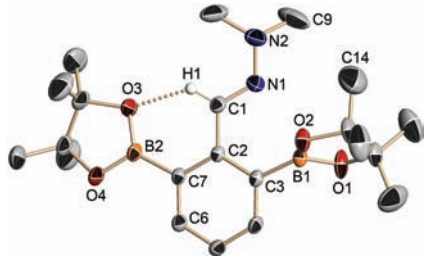


Figure 3. X-ray structure of **5a** (H atoms omitted for clarity).

derivatives **4**, the azomethine H atom is involved in a relatively short CH···O H-bond with one of the pinacol O atoms [H(1)−O(3) = 2.3 Å, C(1)−H(1)−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 (δ_{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 [N(1)−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 C(3)−B(1)−O(2)−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 [C(9)−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.

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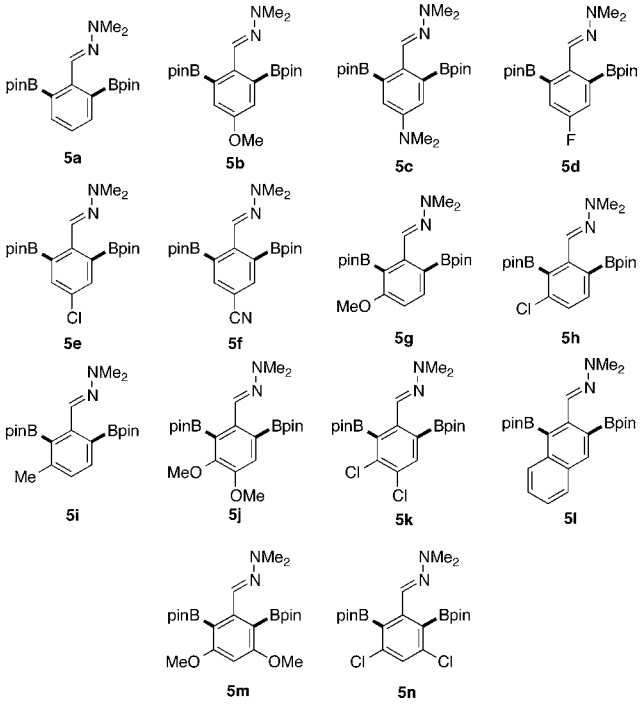
The diborylation reaction conditions optimized for **2a** were then applied to a variety of para- (**2b**−**f**) and meta- (**2g**−**i**) monosubstituted substrates as well as 3,4- (**2j**−**l**) and even 3,5- (**2m**,**n**) disubstituted derivatives, affording in all cases the desired *o*,*o*′-diborylated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

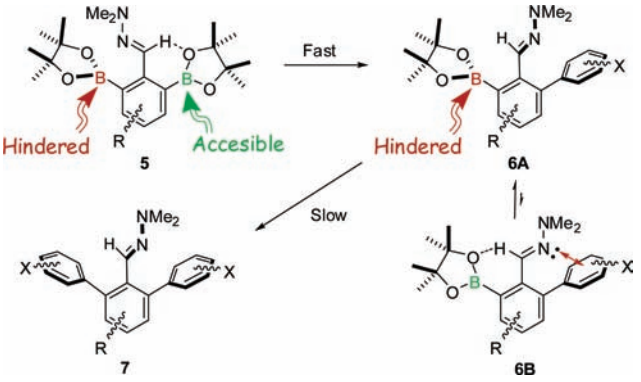
Chart 1. Diborylated Products 5a−n



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.

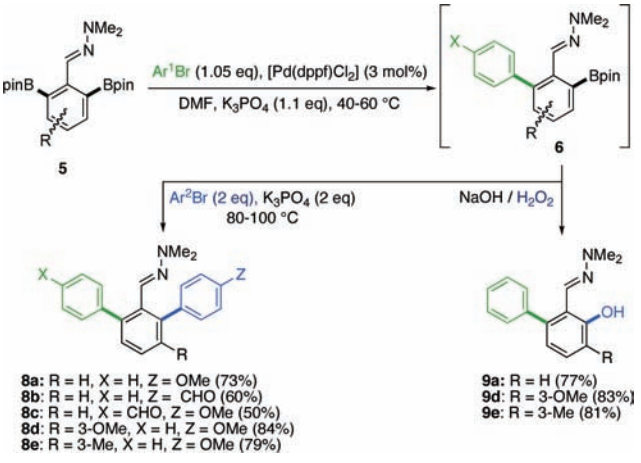
As mentioned above, the most interesting synthetic application of the diborylated products **5** is their use as intermediates for the introduction of two different electrophiles. Using the simplest product **5a** as a challenging model substrate, we explored sequential Suzuki−Miyaura cross-coupling 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 homodiarylated 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 solvent[18] 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

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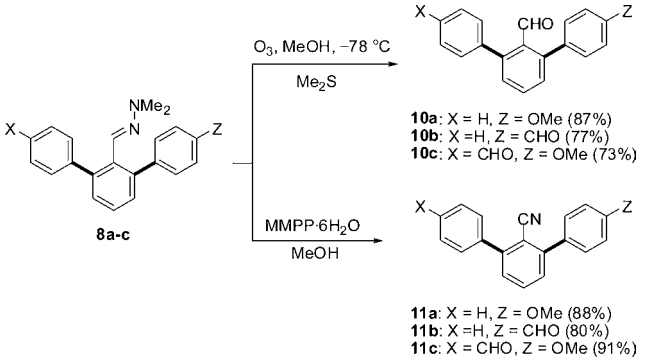
cleavage using magnesium monoperoxyphthalate (MMPP),[20] respectively (Scheme 6).

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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(19) Starting from **5a**, small amounts (19−26%) of symmetrically substituted 2,6-diarylbenzaldehyde-derived *N*,*N*-dimethylhydrazones were isolated as byproducts (see Supporting Information for details). Starting from meta-substituted substrates **5g**,**i**, however, no homodiarylation products were detected.

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