Ortho Borylation Strategies with DMGs

**Scheme 1**
replaces a spectating boryl. Silane metathesis with a boryl ligand would steer the phosphine to the metal center to generate intermediates (4) with accessible coordination sites. In contrast to other homogeneous approaches where electron-deficient ligands are used to achieve coordinative unsaturation, our strategy would create an electron-rich framework that facilitates C–H cleavage.14 If this approach proved to be viable, the ligand framework could be modified in substantive ways. For example, silanes with pendant N-donors (or other basic ligands) could be targeted.

To test this concept, we prepared ligand 5 (Scheme 1), using a protocol related to the synthesis of (2-diphenylphosphinophenyl)diphenylsilane.15 The synthesis is straightforward, modular, and scalable to gram quantities. With 5 in hand, we tested it for the C–H borylation of methylbenzoate. Table 1 shows the results compared to those obtained for catalysts generate from [Ir(OMe)(cod)]2 and P(3,5-bis(trifluoromethyl)phenyl)3 (PArF3) or triphenylarsine, which have both been used in directed borylations. As can be seen in entry 1, ligand 5 allows for full conversion of B2pin2 and some of the generated HBpin generated from B2pin2 as limiting reagent. Conversion exceeds 100% because some of the HBpin generated from B2pin2 are for isolated materials.2.0 mmol substrate was used. 0.5 mol % [Ir(OMe)(cod)]2 was used. Reaction was run at 60 °C. 2.0 mmol B2pin2, 0.025 mmol [Ir(OMe)(cod)]2, and 0.050 mmol 5 were used. 0.5 mmol substrate was used. 51.25 mmol B2pin2 was used. 55% diborylated material was isolated. 17% diborylated material was isolated. 10% diborylated material was isolated.

Table 1. Comparison of Catalyst Efficiency for Ortho Borylation

| entry | ligand | %6a | %6b | % conversion |
|-------|--------|-----|-----|--------------|
| 1     | 5      | 63  | 24  | 111%         |
| 2     | PArF3  | 2   | 1   | 4            |
| 3     | AsPh3  | 44  | 3   | 50           |
| 4    | silica-SMAP | 101 | 37  | 109%         |

Reactions run on 0.5 mmol scale in 0.5 mL THF. % Conversions determined by GC integration. Conversion is calculated as %6a + 2(6b) and is based on B2pin2 as limiting reagent. Conversion exceeds 100% because some of the HBpin generated from B2pin2 participates in the borylation. Data are from ref 11a. Reaction run at 25 °C with 1 mmol methylbenzoate, 0.5 mmol B2pin2, 0.5 mol % silica-SMAP-Ir(OMe)(cod) in 1.5 mL hexane. Yields were determined by 1H NMR spectroscopy.

With promising preliminary data in hand we explored the scope with respect to substrate and directing group, and the results are given in Table 2. Entry 1 shows that unsubstituted benzamides give excellent conversions to monoborylated substrates without resorting to using excess arene to minimize diborylation as is required for methyl benzoate. Entry 2 shows that the amide DMG trumps Cl direction. In fact, chlorobenzene does not give ortho-borylated product with 5, contrasting the high ortho selectivity for Ir-SMAP catalysts. In entry 3, diborylated product 8c was obtained. When 1 equiv B2pin2 was used with 7c, selectivity for borylation ortho to the amide vs the ester was 4.2:1. Entries 4 and 5 show that OMe can direct borylation to the ortho position, albeit in modest yield. This sets the chemistry of catalysts generated from ligand 5 apart from that of silica-SMAP, where borylation of 7d gives a 1:1 ratio of ome + p borylated products. Entry 6 shows that esters are stronger DMGs that OMe, which is in line with SMAP supported catalysts. In entry 7, Weinreb amide 7g is converted cleanly to ortho-borylated product 8g. Borylation of 1-methylnaphthoate, 7i, gives a single isomer where functionalization of the β-C–H bond is favored.

Table 2. Ortho Borylation of Alkylbenzoates**

| entry | R1 | R2 | % Conversion |
|-------|----|----|--------------|
| 6b    | Br | pinB | 63%          |
| 6c    | Br | pinB | 60%†         |
| 6d    | pinB | 62%‡ |
| 6e    | Br | pinB | 66%†         |
| 6f    | Br | pinB | 70%          |
| 6g    | PinB | 82%† |
| 6h    | PinB | 82%† |
| 6i    | PinB | 49%† |
| 6j    | PinB | 82%† |
| 6k    | PinB | 65% ‡ |

**Reactions were run with 1.0 mmol substrate, 1.0 mmol B2pin2, 0.025 mmol 5, and 0.0125 mmol [Ir(OMe)(cod)]2 in 1.0 mL THF. Yields are for isolated materials. 1.25 mol % [Ir(OMe)(cod)]2 was used. Reaction was run at 60 °C. 2.0 mmol B2pin2, 0.025 mmol [Ir(OMe)(cod)]2, and 0.050 mmol 5 were used. 0.5 mmol substrate was used. 51.25 mmol B2pin2 was used. 55% diborylated material was isolated. 17% diborylated material was isolated. 10% diborylated material was isolated.

Given the results in Chart 1, we further explored the scope with respect to substrate and directing group, and the results are given in Table 2. Entry 1 shows that unsubstituted benzamides give excellent conversions to monoborylated substrates without resorting to using excess arene to minimize diborylation as is required for methyl benzoate. Entry 2 shows that the amide DMG trumps Cl direction. In fact, chlorobenzene does not give ortho-borylated product with 5, contrasting the high ortho selectivity for Ir-SMAP catalysts. In entry 3, diborylated product 8c was obtained. When 1 equiv B2pin2 was used with 7c, selectivity for borylation ortho to the amide vs the ester was 4.2:1. Entries 4 and 5 show that OMe can direct borylation to the ortho position, albeit in modest yield. This sets the chemistry of catalysts generated from ligand 5 apart from that of silica-SMAP, where borylation of 7d gives a 1:1 ratio of ome + p borylated products. Entry 6 shows that esters are stronger DMGs that OMe, which is in line with SMAP supported catalysts. In entry 7, Weinreb amide 7g is converted cleanly to ortho-borylated product 8g. Borylation of 1-methylnaphthoate, 7i, gives a single isomer where functionalization of the β-C–H bond is favored.

Scheme 2. Ligand-Dependent Borylation Regioselectivity

![Scheme 2](image-url)
Communication

formation of Ir–H bonds to make M–Si bonds. Thus, we considered that initial formation of Ir–Bpin intermediates and subsequent Ir–B/Si–H metathesis could account for formation of intermediates such as 4. Nevertheless, we performed a control experiment where 5 and [Ir(OMe)(cod)]_2 were reacted. ^3^P and ^1^H NMR indicates rapid and quantitative conversion to compound 9 and methanol—an unprecedented reaction for a silane with a metal alkoxide (eq 1). This is critical for establishing a 1:1 ratio of 5:Ir, which is the key to creating sites for DMG coordination and C–H activation as posited for structure 4 in Scheme 1. The structure of 9 was confirmed by X-ray crystallography and is shown in Figure 1. Using the centroids of the cod bound carbons as coordinates, the sum of the angles about Ir is 370°, which is close to the value for square-planar Ir. The Ir–C and C–C distances for the carbons trans to Si are significantly longer than those for carbons trans to P, which is consistent with strong donation from Si to Ir.

There is a difference in the reaction rates when using pure 9 as precatalyst as opposed to in situ generated catalysts, with shorter reaction times being required for the isolated catalyst.

Some substrates proved to be challenging for borylations carried out with ligand 5. For example, carbamates react sluggishly, and ketones give significant amounts of ketone reduction. Since Ir catalysts supported by N-donor ligands in most cases prove to be more reactive than their P-donor counterparts, we reasoned that an N-donor analog of 5 might exhibit better reactivity with carbamates and ketones. Thus, quinoline-based ligand 10 was prepared, and Ir catalysis with this ligand was evaluated relative to ligand 5 for compounds 11a and 11b.

As shown in Table 3, ligand 10 outperforms its phosphine analog 5 for borylations of 11a and 11b. In the case of carbamate 11a, we see higher conversion, but slightly lower isolated yield to 11b.

over the γ-C–H position. Borylation of thiophene substrate 7h at 60 °C gave slightly better selectivity (14:1) for 3 vs 5-diborylated products than that reported for the borylation with Ir-SMAP catalysts (9:1 at 80 °C). In contrast to the SMAP system, where the Ir catalysts are ineffective for borylation of 7j, borylation gives the products obtained by Lassaletta using hemilabile N,N ligands. Our reaction was performed at a lower temperature (60 vs 80 °C) and a shorter reaction time (2 vs 48 h). This was offset by a higher catalyst loading in our study (1.25 vs 0.5 mol %) and the formation of ~15% diorthoborylated product. With 2.0 equiv BPin, this was the major product.

The generation of active catalyst from 5, BPin, and [Ir(OMe)(cod)]_2 raises interesting questions with regard to how an Ir–Si bond is generated, if it is formed at all. Several literature reports describe the metathesis of M–OR and Si–H bonds to make M–H and Si–OR products. However, silane-directed borylations invoke M–B/Si–H metatheses to generate M–Si and B–H bonds. Thus, we considered that initial formation of Ir–Bpin intermediates and subsequent Ir–B/Si–H metathesis could account for formation of intermediates such as 4. Nevertheless, we performed a control experiment where 5 and [Ir(OMe)(cod)]_2 were reacted. ^3^P and ^1^H NMR indicates rapid and quantitative conversion to compound 9 and methanol—an unprecedented reaction for a silane with a metal alkoxide (eq 1). This is critical for establishing a 1:1 ratio of 5:Ir, which is the key to creating sites for DMG coordination and C–H activation as posited for structure 4 in Scheme 1. The structure of 9 was confirmed by X-ray crystallography and is shown in Figure 1. Using the centroids of the cod bound carbons as coordinates, the sum of the angles about Ir is 370°, which is close to the value for square-planar Ir. The Ir–C and C–C distances for the carbons trans to Si are significantly longer than those for carbons trans to P, which is consistent with strong donation from Si to Ir.

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As shown in Table 3, ligand 10 outperforms its phosphine analog 5 for borylations of 11a and 11b. In the case of carbamate 11a, we see higher conversion, but slightly lower isolated yield to that reported by Sawamura for the related diethylcarbamate substrate. Perhaps more significantly, catalysis with 10 did not yield detectable borylation para to the carbamate, which is a minor byproduct in the silica-SMAP system. For phenyl ethyl ketone, ligand 5 gave the reduction to the alcohol upon workup.

Table 2. Borylations with 5/[Ir(OMe)(cod)]_2, Catalyst

| entry | substrate | product | T (°C) | time (h) | % yield |
|-------|-----------|---------|--------|---------|---------|
| 1 | CONMe_2 | CONMe_2 | 80 | 16 | 75% |
| 2 | Cl | CONMe_2 | CONMe_2 | 80 | 16 | 85% |
| 3 | MeO_C | MeO_C | 100 | 16 | 95% |
| 4 | OMe | OMe | 100 | 12 | 55% |
| 5 | OMe | OMe | 100 | 12 | 35% |
| 6 | CO_2Et | CO_2Et | 80 | 12 | 77% |
| 7 | MeO_C | MeO_C | 60 | 1 | 65% |
| 8 | MeO_C | MeO_C | 80 | 8 | 85% |

Typically reactions were run on 1 mmol scale with equimolar BPin and substrate with 2.5 mol % 5 and 1.25 mol % [Ir(OMe)(cod)]_2. Unless noted, yields are for isolated materials. See SI for details.

Reaction solvent was THF. Reaction solvent was f-hexane.

Typically reactions were run on 1 mmol scale with equimolar B2pin2, this was the major product.

With 2.0 equiv BPin, this was the major product.

Approximately 15% of the crude mixture was the diorthoborylated compound (8j) in the SI.

Figure 1. Crystal structure of compound 9 with H atoms omitted. Selected distances (Å) and angles (deg): Ir–Si (2.376(2)), Ir–P (2.260(2)), Ir–C1 (2.246(8)), Ir–C2 (2.217(8)), Ir–C5 (2.194(8)), Ir–C6 (2.161(8)), C1–C2 (1.386(12)), C5–C6 (1.357(13)), P–Ir–Si (83.53(6)), P–Ir–centroid of C3–C6 (96.72), Si–Ir–centroid of C3–C6 (95.39), centroid of C3–C6–Ir–centroid of C3–C6 (85.25).

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Table 3. Comparison of Silyl Ligands with Pendant P- and N-donors

| Substrate | Product | Ligand | T (°C) | Time (h) | % Yield |
|-----------|---------|--------|--------|----------|---------|
| Ar-H      | THF     | Cl     | 5^a    | 100      | 16      | 12      |
| Ar-Bpin   | Bpin    | OCONMe2| 10     | 80       | 4       | 80^a    |
| 11a       | 12a     | OCONMe2| 10     | 80       | 16      | 37      |
| 11b       | 12b     | OCONMe2| 10     | 80       | 1       | 70      |

As the major product. This unwanted reaction was almost completely eliminated by employing N-donor ligand 10. When compared to other homogeneous catalysts that effect ortho borylation of ketones,^9 borylations employing 10 had shorter reaction times at considerably lower temperatures. Furthermore, borylations of t-butylbenzoate and benzamide 7a with ligand 10, using identical conditions to those used with ligand 5, gave 6m in 78% isolated yield after 3 h and 8a in 80% yield after 4 h, respectively. Significantly, ortho borylation of anisole was not found with ligand 10. These results show that modification of the silyl ligand framework can dramatically impact reactivity.

In summary, we have shown that Ir catalysts supported by silyltethered P- and N-donor ligands are effective for ortho borylation directed by a range of different functional groups. Because the ligands within the coordination sphere are bidentate and electron-rich, the activities are generally superior to homogenous systems that utilize electron-poor ligands to favor unsaturated intermediates. We are exploring effects of varying the ligand framework on the reactivity in other directed C−H functionalizations.

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