ORGANIC LETTERS

2012
Vol. 14, No. 13
3558–3561

Iridium-Catalyzed, Substrate-Directed C−H Borylation Reactions of Benzylic Amines

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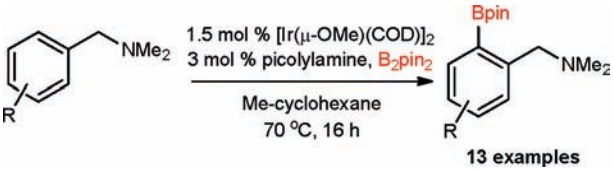
Received June 14, 2012

ABSTRACT



The iridium-catalyzed arene C−H borylation reaction of benzylic amines has been developed, which inverts the typical steric-controlled product distribution to provide *ortho*-substituted boronate esters. Picolylamine was found to be an ideal ligand to replace 4,4′-di-*tert*-butylbipyridine to induce the directing effect. Preliminary experiments are consistent with a mechanism involving dissociation of one amine of the hemilabile diamine ligand.

Metal-catalyzed C−H borylation reactions have received significant attention in recent years due to the synthetic utility of the resulting boronate esters[1−3] and the ability to access these key intermediates rapidly from simple starting materials.[4−6] The borylation of arene C−H bonds, primarily discovered and developed by Hartwig, Ishiyama and Miyaura,[7−9] and Smith and Maleczka,[10,11] is most readily accomplished using an iridium catalyst $[Ir(\mu\text{-OMe})(COD)]_2$ (COD = cyclooctadiene) with 4,4′-di-*tert*-butylbipyridine (dtbpy) as the ligand. The selectivity of arene C−H borylation reactions is governed by steric effects, resulting in functionalization *meta*- and *para*- to arene substituents.[5,12−14] With appropriately chosen substrates (such as 1,2- or 1,3-disubstituted arenes) high selectivity is observed. The mild reaction conditions and ability to incorporate a boronate ester without a preinstalled halogen is the hallmark of this valuable transformation. Developing an analogous method that reverses the inherent selectivity to provide *ortho* borylation products would complement this method, providing access to a larger variety of arylboronate esters.

Hartwig and co-workers initially reported a general method for substrate-directed *ortho* C−H borylation in 2008, which utilized siloxides and silylamines as the directing group.[15,16] Since that initial discovery several methods have

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10.1021/ol301635x
Published on Web 06/25/2012

been reported that provide *ortho* C−H borylation.[17−20] Of particular note for this communication, Sawamura[19] and Fernández and Lassaletta[20,21] recently reported the first methods that utilize an amine to direct the C−H functionalization to the *ortho* position.[22,23] Both of these methods utilize a ligand framework that can form a transient open coordination site on the metal after the amine binds to the complex, directing the C−H borylation to the *ortho* position.

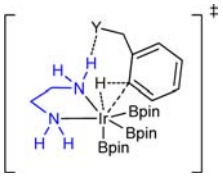


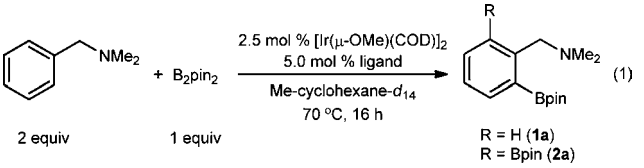
Figure 1. Proposed bifunctional directing effect.

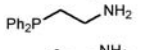
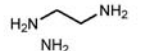
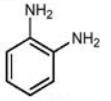
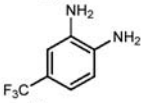
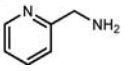
Our ongoing interest in metal boryl complexes with bifunctional ligands[24,25] led us to examine ligands that possess a N−H bond that could be used to direct C−H borylation through hydrogen bonding to a Lewis base in the substrate (Figure 1). To this end, bidentate ligands possessing a N−H bond, in conjunction with [Ir(μ-OMe)(COD)]$_2$, were screened with four Lewis base substituted arenes (anisole, *N*,*N*-dimethylaniline, benzyl methyl ether, and *N*,*N*-dimethylbenzylamine). Using a variety of ligands, *N*,*N*-dimethylbenzylamine was the only substrate that displayed >10% conversion of arene to the boronate ester. In contrast, many of these ligands were effective in promoting C−H borylation of *N*,*N*-dimethylbenzylamine, providing selective *ortho*-functionalization (Table 1).

C−H borylation of *N*,*N*-dimethylbenzylamine with dtbpy resulted in an unselective mixture of aryl boronate ester isomers in 22% conversion (Table 1, entry 1). 2-(Diphenylphosphino)-ethylamine resulted in low conversion, but only *ortho* borylation products were observed (entry 2). Ethylenediamine, *o*-phenylenediamine, and 4-trifluoromethylphenylenediamine resulted in increased conversion to *ortho* borylation products **1a** and **2a** (entries 3−5). Finally, picolylamine (picNH$_2$, entry 6) provided a significant increase in conversion while maintaining the high selectivity of **1a**:**2a**.

The reaction conditions using picolylamine were optimized for increased conversion and selectivity (ratio of **1a**:**2a**), as summarized in Table 2. The temperature was optimized to 70 °C (entries 1−4), providing the highest combination of yield and selectivity. The most significant influence on conversion was observed upon adjusting the ratio of B_2pin_2/arene (entries 3, 5, and 6); an 88% conversion and a 93:7 ratio of **1a**:**2a** were observed using 1.2 equiv of the arene (entry 6). Purification by column chromatography (basic alumina) provided **1a** in a 73% isolated yield. Notably, this yield and the conversions reported in Tables 1 and 2 are calculated with respect to the arene substrate, demonstrating that B_2pin_2 can serve as two equivalents of the boron source. Most yields reported in the literature in this area are calculated with respect to B_2pin_2 (using excess arene) and result in significant amounts of unreacted arene.[4,19]

Table 1. Ligand Screen for Directed C−H Borylation (eq 1)



entry	ligand	% conversion [a]	**1a**:**2a** [b]
1	4,4'-dtbpy	22	ND[c]
2		16	95:5
3		37	>97:3
4		31	>97:3
5		37	>97:3
6		63	96:4

[a] % Conversion was determined by ^{1}H NMR spectroscopy using a 5 s relaxation delay to ensure integral integrity. All conversions are based on the arene substrate. [b] Ratio of **1a**:**2a** determined by ^{1}H NMR spectroscopy. [c] Ratio of **1a**:**2a** not determined. Ratio of *meta*- + *para*-isomers to **1a** + **2a** is ∼3:1.

With optimized reaction conditions in hand, the effect of various arene substituents on yield and selectivity was explored. *Ortho*-substituted benzylamines were first examined to determine the range of simple functional groups that were tolerated (Figure 2). Methyl- (**3b**), fluoro- (**3c**), and chloro- (**3d**) substituents were all tolerated, providing a good yield of the corresponding aryl boronate ester. The bromo-substituted arene (**3e**), however, resulted in <5% conversion. The lack of reactivity was attributed to preferential oxidative addition into the C−Br bond over activation of the C−H bond. Accordingly, *para*-bromo-substituted arene **3f** was found to provide boronate ester **1f**, albeit in a modest 37% yield. Other *para*-substituted substrates (**3g**, **3h**) provided high yields of the boronate esters, but bis borylation products were present to a higher degree with these substrates. Notably, the C−H borylation conditions were tolerated with the ester-substituted

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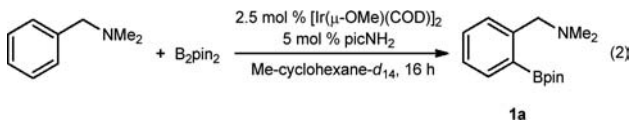
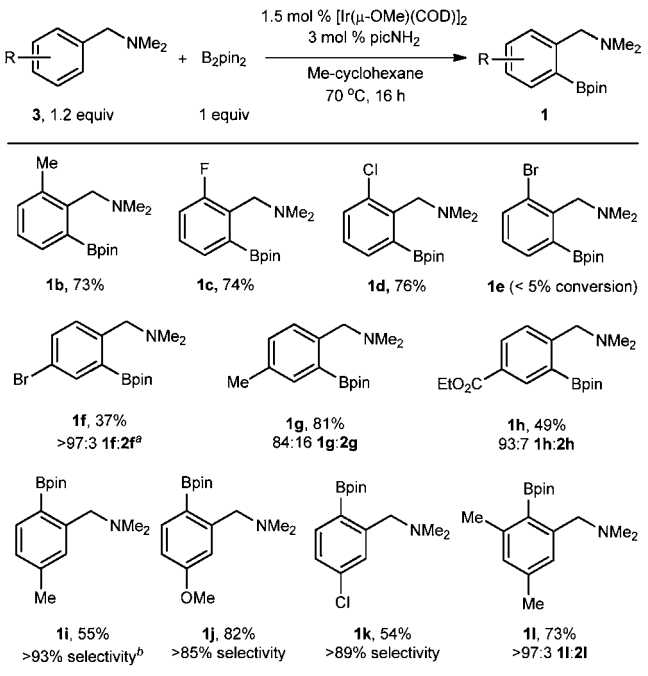
Table 2. Reaction Optimization (eq 2)



1a

entry	temp (°C)	B_2pin_2:Arene	% conv [a]	1a:2a
1	115 °C	1:2	70	93:7
2	90 °C	1:2	63	95:5
3	70 °C	1:2	68	97:3
4	50 °C	1:2	58	97:3
5	70 °C	1.1:1	94	82:18
6	70 °C	1:1.2	88	93:7

[a] % Conversion was determined by ^{1}H NMR spectroscopy using a 5 s relaxation delay to ensure integral integrity.



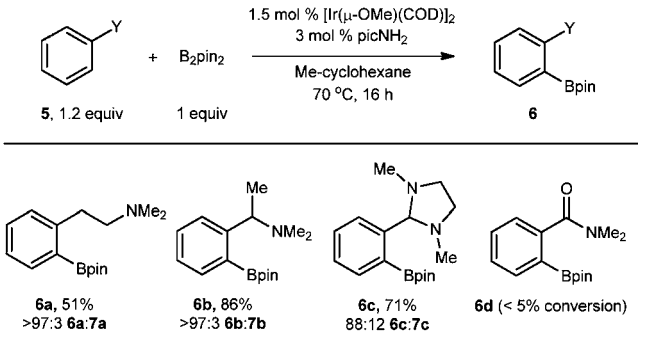
[a] Selectivities determined by ^{1}H NMR spectroscopy using a 5 sec relaxation delay to improve integral integrity. [b] *Meta*-substituted arenes (**3i**-**3k**) resulted in a mixture of the two *ortho*-substituted isomers (**1** and **4**) and the bis-*ortho* product (**2**). See Supporting Information for details.

Figure 2. Scope of directed C−H borylation reaction.

benzylic amine to provide **1h** without competitive borylation directed by the ester.[17,18]

Finally, *meta*-substituted arenes **3i**−**3k** were examined and found to provide good to moderate yields. The major boronate ester product in each case resulted from C−H borylation away from the *meta* substituent. Borylation between the aminomethyl directing group and the *meta* substituent (**4i**−**4k**) was the second major product in addition to a small amount of the bis borylation products **2i**−**2k**. Borylation between 1,3-disubstituted arenes was unexpected due to the sensitivity of the catalyst to steric effects using the nondirected catalyst system.[5,12,13] Formation of this isomer led us to examine **3l**, which requires borylation between the two substituents. Gratifyingly, a high yield and high selectivity for monoborylation (**1l**) was observed. Boronate esters **1a**−**1l** are direct precursors to Wulff-type boronic acids, saccharide sensors which have been shown to have appropriate pH tolerance for biological applications based on the interaction between the benzylic amine and boron.[26−29]

The scope of the amine directing group was examined next. *N*,*N*-Dimethyl-2-phenylethylamine was successfully utilized in the reaction albeit with reduced conversion, providing **6a** in moderate yield (Figure 3). The sterically hindered *N*,*N*-dimethyl-1-phenylethylamine provided arylboronate ester **6b** in high yield and selectivity. Imidazolidine **5c** was also successful in directing C−H borylation to the *ortho* position, but significant quantities of the bis borylation product was formed under the reaction conditions. The use of *N*,*N*-dimethylbenzamide, however, resulted in $<5\%$ conversion to **6d**.



[a] Selectivities determined by ^{1}H NMR spectroscopy using a 5 sec relaxation delay to improve integral integrity. [b] Ratio is *ortho* borylation product (**6**) to bis-*ortho* product (**7**).

Figure 3. Scope of amine directing group.

The lack of reactivity observed with benzamide **5d** suggested that a basic amine is required for the directing effect and that the directing effect significantly enhanced the reaction rate compared to nonbasic substrates. Accordingly, a reaction was performed using toluene as the solvent. Toluene is typically avoided in arene borylation reactions due to the presence of several reactive C−H bonds in the molecule.[4] Using the optimized reaction conditions with toluene as solvent resulted in a 75% yield of **1a** (eq 3). This experiment shows the significant difference of reactivity between the two

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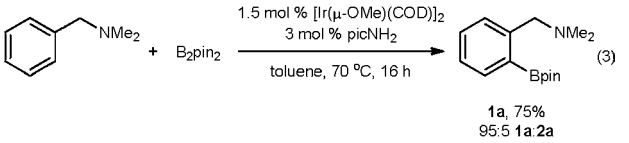
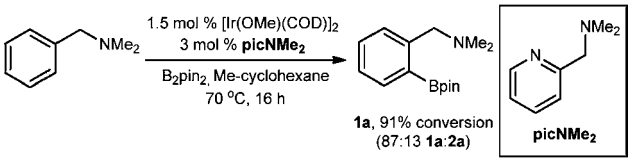
arenes, which is selective for the benzylic amine even in a 19:1 ratio of toluene/*N*,*N*-dimethylbenzylamine.



A control experiment was also designed to interrogate the nature of the directing effect. The proposed hydrogen bond directing effect (see Figure 1) was probed by replacing the picolylamine ligand with *N*,*N*-dimethylpicolylamine. If the directing effect is the result of hydrogen bonding, the lack of N−H bonds on dimethylpicolylamine should result in decreased catalytic activity and primarily *meta*/*para* C−H borylation products. Upon performing the experiment (Scheme 1), similar conversion and the selectivity for *ortho* borylation products were maintained (with slightly increased bis borylation). This experiment clearly negates the possibility of a hydrogen bond directing effect.

Scheme 1. Control Experiment Using Dimethylpicolylamine



The directing effect is proposed to result from dissociation of one of the two amine nitrogens to open the necessary coordination site for *ortho* C−H borylation. The catalytic cycle shown in Scheme 2 begins with the active catalyst (**A**),[30,31] which is analogous to the accepted complex using dtbpy.[9,32] Association of the substrate nitrogen provides intermediate **B**, which can undergo dissociation of one of the picolylamine nitrogens to provide coordinatively unsaturated complex **C**.[33] A mechanism involving a hemilabile dicoordinate ligand to direct C−H borylation is consistent with the recent report by Fernández and Lassaletta for the *ortho* borylation of hydrazones and pyridine derivatives.[20] Complex **C** is poised for C−H activation, which proceeds through either σ-complex **D** or standard oxidative addition to give the 7-coordinate Ir(V) complex (**E**).[9,32] Formation of

(30) N−H borylation of picolylamine is likely taking place to a certain extent (see ref 31) but is not reflected in the catalytic cycle for the sake of clarity.

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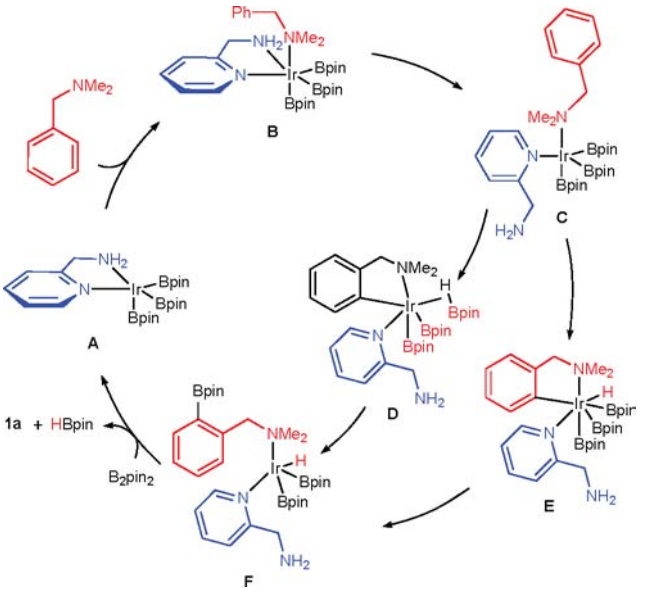
Scheme 2. Proposed Catalytic Cycle



the C−B bond provides **F**, which can release boronate ester **1a** and regenerate the active catalyst upon addition ofh B_2pin_2.

In conclusion, substrate-directed C−H borylation of benzylic amines has been demonstrated using picolylamine as the ligand. This transformation generally provides good yields and selectivity for the mono *ortho* borylation products when a basic amine is employed. The directing effect is inconsistent with the originally proposed hydrogen bonding directing effect and is proposed to result from partial dissociation of one amine nitrogen of the diamine ligand.

Acknowledgment. Acknowledgement is made to the donors of the American Chemical Society Petroleum Research Fund for partial support of this research (47598-GB3), Cambridge Isotope Laboratories, Inc. Research Grant, which generously provided methylcyclohexane-d_{14}, Research Corporation for Science Advancement and the M. J. Murdock Charitable Trust for department development grants, Western Washington University, and the University of San Diego.

Supporting Information Available. Detailed experimental procedures, characterizations of all compounds, and selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.