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Microwave-Accelerated Iridium-Catalyzed Borylation of Aromatic C−H Bonds

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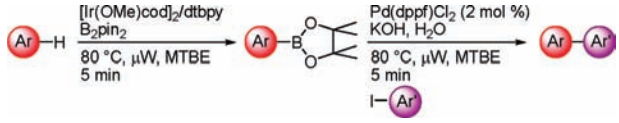
ABSTRACT



Microwave heating accelerates the Ir-catalyzed C−H borylation of aromatic substrates when compared with reactions carried out at the same temperature under standard heating conditions. Application to a one-pot single solvent process for tandem C−H borylation/Suzuki−Miyaura cross-coupling sequences using microwave-accelerated reactions gives fast and efficient access to a wide range of biaryl and heterobiaryl compounds.

Aryl and heteroaryl boronates[1] are very important intermediates in organic synthesis that have been deployed in many useful transformations including the Suzuki−Miyaura cross-coupling reactions,[2] Cu-catalyzed C−O and C−N coupling reactions,[3] and Rh-catalyzed conjugate additions to carbonyl compounds.[4] As a result there is a need for efficient methods to prepare them. Subsequent to our observation of substoichiometric arene borylation during the formation of novel [(η^6-arene)Ir(Bcat)$_3$] (cat = 1,2-$O_2C_6H_4$) complexes from reaction of [(COD)Ir(η-indenyl)] with excess HBcat in aromatic solvents,[5] a number of groups including Ishiyama, Miyaura, Hartwig, and Smith have developed in situ Ir catalysts for the borylation of aromatic C−H bonds, importantly, under under mild conditions.[6,7] The most widely utilized system employs [(COD)Ir(μ-OMe)]$_2$ (**1**) with 4,4′-di-t-butyl-2,2′-bipyridine (dtbpy).[8] Density functional theory (DFT) calculations[9] and experimental data[10] suggest that a sterically hindered, five-coordinate [Ir(Bpin)$_3$L$_2$] species (Bpin = B($OCMe_2CMe_2O$)) is the active complex for C−H activation. This sterically constrained active species accounts for the selectivity observed, with borylation typically occurring at positions remote to substituents or ring junctions. We have used this selectivity to prepare novel pyrene-2,7-bis(boronate) and perylene-2,5,8,11-tetra(boronate) esters among other polycyclic aryl boronates.[11]

Although there have been many approaches to enhance the potential of Ir-catalyzed C−H borylation by developing sequential reactions, involving in situ elaboration of the initially formed boronate ester or acid,[12,13] there have been relatively few attempts to facilitate the C−H borylation reaction. While reactions with certain substrates are known to proceed at room temperature, most reports describe

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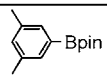
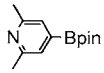
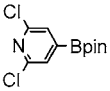
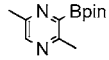
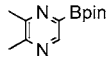
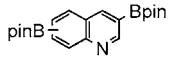
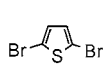
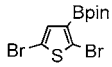
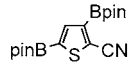
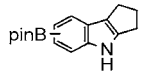
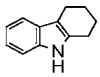
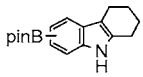
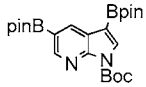
Table 1. Comparison of Microwave Accelerated Borylation with Standard Heating Conditions

entry	arene	product	μW heating (min)		standard heating (min)	
			time	yield[a]	time	yield[a]
1			60	96%	360	98%
2			60	45%	1080	55%
3			5	98%	30	95%
4			3	98%	20	96%
5[b]			60	48%	1080	35%
6[b]			15	100%	60	100%
7			15	89%[c]	120	92%[c]
8			2	99%	5	98%
9			15	98%	120	99%
10			60	82%[d]	1080	84%[e]
11[f]			15	98%	120	96%
12			15	36%[g,h]	120	38%[g,h]
13			15	90%[i]	120	89%[i]
14[j]			20	92%	360	90%

[a] Purified isolated yield of reaction reaching 100% conversion, unless otherwise stated. [b] GC−MS conversion based on comparison of starting material and product peak intensities. As a result of the boronate being α to nitrogen, it was not possible to isolate the products as they are prone to proteodeborylation. [c] 1:1 mixture of bis-3,6- and 3,7-pinacolboronate esters. [d] 18% starting material recovered. [e] 16% starting material recovered. [f] 1.5 mmol of B_2pin_2 used to achieve full bis-borylation of substrate. [g] 58% starting material recovered in both cases. [h] 85:15 mixture of 5- and 7-pinacolboronate esters. [i] Isolated as the 8-boronate ester along with traces of 3 other monoborylated isomers (GC−MS). [j] 2.0 mmol of B_2pin_2 used to achieve complete bis-borylation of substrate.

conditions involving reactions at elevated temperatures (80−150 °C). We have an ongoing interest in the application of microwave heating to facilitate various organometallic complex catalyzed transformations,[14] and in this Letter we report that microwave (μW) irradiation considerably accelerates the borylation of aromatic substrates with respect to reactions performed using conventional heating at the same temperature.

Initial experiments involved the C−H borylation of *m*-xylene as this avoids problems of regioselectivity. Following from our earlier work,[13e] this was undertaken in MTBE and required heating at 80 °C for 6 h to achieve complete conversion. Attempts to accelerate this reaction by undertaking an otherwise identical transformation (concentration, volume, etc.) in a microwave reactor brought about startling benefits with complete conversion requiring only 60 min at the same reaction temperature. We sought to ascertain whether this effect was general. Consequently, we explored a range of substrates for which the "thermal" C−H borylation reaction was slow, even at elevated temperatures (Table 1).

For each substrate, reactions were carried out under both standard heating conditions and microwave conditions in order to provide a comparison between the different heating methods. These experiments were carried out in identical thick-walled glass reaction tubes with crimp top septum seals. Conventional heating was achieved with a preheated aluminum block in which the depth of the tube in the block was equal to that of the solution, and magnetic stirring was employed in all cases. All reactions were carried out at 80 °C with 1.0 mmol of the substrate and 2.4 mL of a stock solution containing 1.5 mol % of iridium precatalyst **1**, 3 mol % of dtbpy, and 1.0 mmol of B_2pin_2 in MTBE.[15] The reactions were monitored at regular intervals for conversion and product identification by GC−MS. The times stated in Table 1 are those required to reach the given conversions.

All reactions showed acceleration compared to conventional heating conditions. The borylation of *m*-xylene and *p*-xylene (Table 1, entries 1 and 2) shows a considerable acceleration relative to the standard reaction with comparable isolated yields of the 5- and 2- borylated isomers being achieved, respectively. The borylations of 2,6-dimethyl- and 2,6-dichloropyridine (Table 1, entries 3 and 4) were achieved in 5 and 3 min, respectively, compared to 30 and 20 min under standard heating conditions. The borylations of dimethylpyrazines (Table 1, entries 5 and 6) were achieved with high conversions in shorter reaction times compared to classical, thermal heating conditions.

Whereas the mono-borylation of quinoline has been reported using $[(COD)Ir(\mu\text{-}Cl)]_2$, dtbpy, and B_2pin_2 at 100 °C for 16 h,[16] we were able to achieve the previously unreported bis-borylation of quinoline in minutes in under μW conditions (Table 1, entry 7). The borylation of 2,5-substituted, five-membered heteroarenes was achieved in high yields showing significant acceleration compared to that achieved using conventional heating. Notably, 2,5-dibromothiophene (Table 1, entry 10) was borylated in 80% isolated yield in 1 h, compared to a time of 18 h to achieve the same levels of product formation under standard conditions. Two indole derivatives were borylated (Table 1, entries 12 and 13) to give 7- and 5-borylated isomers. Curiously, the tetrahydrocarbazole was significantly more reactive affording 95% conversion compared to 40% conversion for the cyclopentylindole after a similar reaction time. Finally, N-Boc-protected 7-azaindole (Table 1, entry 14) was bis-borylated to achieve 3,5-borylated product in 92% isolated yield in 20 min under microwave conditions, whereas

reactions under standard heating conditions required 6 h to provide a similar yield.

Although microwave irradiation in organic synthesis has been in use for many years, the mode of action is not yet fully understood.[17] Microwave heating has been used in many cases as a means to attain elevated temperatures leading to enhancements of reactions rates and thus shorter reaction times. Microwave radiation also offers a more direct heating mode, reducing the effects of convection and thus removing hot and cold spots in a reaction vessel.

However, there are examples in which reactions are accelerated at the same reaction temperature as for standard heating conditions; this is termed "non-thermal effects".[17,18]

From the results given in Table 1, it could be seen that the borylations of these aromatic substrates show marked acceleration when performed under μW conditions relative to standard reaction conditions.

As both conventional and μW heating modes were employed at the same temperature, we wanted to probe the cause of this acceleration. Since the solvent used, MTBE,[13e] is not predicted to be a strong microwave absorber, we focused on the roles of catalyst and substrate. The latter seems unlikely to be the sole cause as although the heterocyclic substrates have a significant dipole moment and can be expected to be efficiently activated under microwave conditions, the simple nonpolar arenes (entries 1 and 2) also show effective promotion. Maguire et al. have recently described a protocol in which benzene and other simple aromatics were borylated using Ir(0) nanoparticles in ionic liquids under μW conditions in moderate to good yields.[19] Speculating that, under the μW reaction conditions, Ir nanoparticles might be generated, we explored a selection of different Ir sources including $IrCl_3$, $[(COD)Ir(\mu\text{-}OMe)]_2$, $[(COD)Ir(\mu\text{-}Cl)]_2$, and $[Ir(Cp^*)Cl_2]_2$. Each metal source was examined in the presence and absence of dtbpy. Reactions were carried out using 1 and 3 mol % Ir with, where used, 1.0 equiv (to [Ir]) of dtbpy at 100 and 150 °C in MTBE. However, all such attempts to find an alternative iridium source to access the same chemistry were unsuccessful, suggesting that the known active species for this reaction remains intact during the μW accelerated reaction.

While this work was in progress, Gaunt et al. reported the use of μW irradiation for the aromatic C−H borylation of an N-protected pyrrole using $[(COD)Ir(\mu\text{-}Cl)]_2$, dtbpy, and B_2pin_2 in hexanes, followed by Suzuki−Miyaura cross-coupling.[20] Although efficient, the reported conditions involved elevated temperatures (100 °C) for extended reaction times (1 h) for the borylation step. Applying our methodology to this substrate provided significant advantage with both much reduced reaction times and increased efficiencies, (Figure 1). The μW borylation reaction was monitored by GC−MS, which showed 100% conversion after 3 min at 80 °C and led to an isolated yield of 98% of the 3-borylated product (Figure 1).

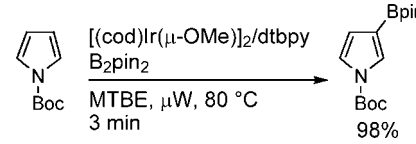


Figure 1. C−H borylation of N-Boc pyrrole using microwave irradiation.

Having demonstrated that the borylation of a wide range of aromatic and heteroaromatic substrates can be achieved with reaction times vastly reduced from those previously reported in the literature and in comparison to conventional heating conditions, we then sought to extend this methodology to include functionalization of the boronate ester. Consequently we thus employed a rapid, single solvent, two-step, one-pot C−H borylation/Suzuki−Miyaura cross-coupling sequence in which the purified biaryl products were isolated in quantitative yields after reaction times of minutes without the need for changing solvent or removal of reactant or catalyst following the borylation step. Following complete conversion of the initial arene to the boronate ester (GC−MS), the microwave vessel was successively charged with water (1.0 mL) and then 2 mol % $Pd(dppf)Cl_2$, KOH (5.0 equiv) and methyl 4-iodobenzoate (1.1 equiv). Simply heating this mixture in the microwave reactor at 80 °C for 5 min afforded the biaryl product in quantitative conversions (Table 2).

As previously described,[13e] we observed, by GC−MS, biaryl products that arose from the homocoupling of the aryl boronate, in amounts consistent with the reduction of the Pd(II) catalyst precursor to the active Pd(0) catalyst. This

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(15) Typically, 25 mL of catalyst stock solution was prepared, which was enough to carry out 10 reactions when 2.4 mL of the solution was used per reaction. Thus, **1** (104 mg), dtbpy (83 mg), and B_2pin_2 (2642 mg) were added to a volumetric flask, and the stock solution was diluted to 25 mL with MTBE.

(16) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649.

(17) (a) Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (c) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36.

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(19) Yinghuai, Z.; Chenyan, K.; Peng, A. T.; Emi, A.; Monalisa, W.; Louis, L. K.; Hosmane, N. S.; Maguire, J. A. *Inorg. Chem.* **2008**, *47*, 5756.

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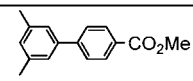
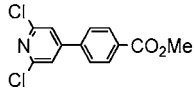
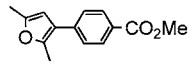
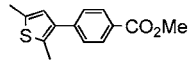
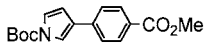
Table 2. One-Pot Borylation/Suzuki−Miyaura Cross-Coupling Sequence

entry	arene	product	reaction time: borylation[a] (min)	reaction time: cross-coupling[b] (min)	yield[c]
1			60	5	95%
2			5	5	96%
3			5	5	96%
4			15	5	96%
5			5	5	95%

[a] Borylation carried out under μW irradiation at 80 °C. [b] Suzuki−Miyaura cross-coupling carried out under μW irradiation at 80 °C, with 2 mol % $Pd(dppf)Cl_2$, KOH (5.0 equiv), methyl 4-iodobenzoate (1.1 equiv), and H_2O (1.0 mL). [c] Purified, isolated yield.

was further confirmed by the isolation of a maximum of 96% yield of cross-coupled biaryl following column chromatography.

Although μW-assisted Suzuki−Miyaura reactions are well documented,[21] these are the first examples of a one-pot sequence giving cross-coupled biaryl products from an unactivated arene with reaction times of minutes. Importantly, this is achieved without need for change of solvent or removal of reactant following the borylation step.

In conclusion, we have shown that iridium-catalyzed borylation of aromatic C−H bonds can be accelerated by the use of microwave heating. This methodology can also be applied to a one-pot single solvent C−H borylation/Suzuki−Miyaura cross-coupling sequence. This process provides access to substituted and structurally diverse biaryls from unactivated arenes in high yields in minutes, and represents a powerful method for the generation of compound libraries.

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Supporting Information Available: Experimental procedures and spectroscopic data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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