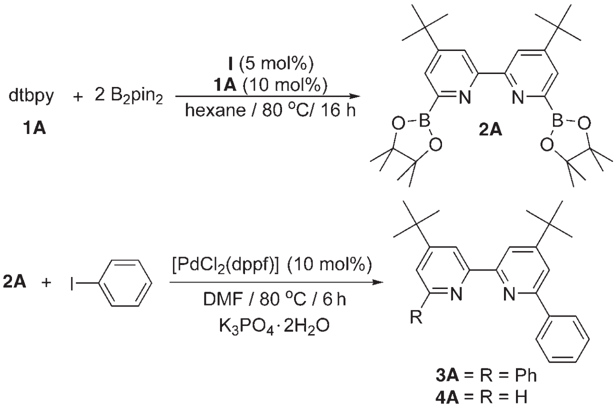
DOI: 10.1002/ange.200503047

Ir-Catalyzed Borylation of C–H Bonds in N-Containing Heterocycles: Regioselectivity in the Synthesis of Heteroaryl Boronate Esters**

*Ibraheem A. I. Mkhalid, David N. Coventry,
David Albesa-Jove, Andrei S. Batsanov,
Judith A. K. Howard, Robin N. Perutz, and
Todd B. Marder**

Aryl and heteroaryl boronates are very important, especially as intermediates for Suzuki–Miyaura cross-coupling reactions;[1] for the Cu-catalyzed C–O and C–N coupling reactions developed by Chan, Lam, and co-workers;[2] and for Rh-catalyzed conjugate additions to carbonyl compounds.[3] The most attractive potential synthesis of these boronate esters would be the direct borylation of C–H bonds in arenes or heteroarenes themselves. A very exciting recent advance has been the development by Ishiyama et al.[4] and Smith and co-workers[5] of in situ prepared, suitably ligated analogues of the iridium tris(boryl) complexes discovered by us,[6] which catalyze the borylation of aromatic C–H bonds under mild conditions. Density functional theory (DFT) calculations by Sakaki and co-workers,[7] in agreement with proposals from the experimental data, suggest that the key catalytic intermediate that leads to C–H activation is the sterically encumbered, five-coordinate $[Ir(Bpin)_3L_2]$ species ($Bpin = B(OCMe_2CMe_2O)$). This intermediate accounts for the selectivity observed, as borylation typically avoids positions *ortho* to either substituents or to ring junctions. We have taken advantage of this selectivity to prepare novel pyrene-2,6-bis(boronate) and perylene-2,5,8,11-tetra(boronate) esters amongst other polycyclic aryl boronates.[8] During the course of our studies on the system developed by Ishiyama et al. ($L_2 = 4,4'$-*t*Bu_2-2,2′-bipyridine (dtbpy; **1A**)), we were intrigued that GC–MS analysis of the borylation reaction mixtures in situ did not show any borylation of the ligand **1A**, although **1A** could be detected by itself. We envisaged three possible reasons for this: 1) **1A** is firmly attached to the Ir center through the nitrogen atoms at all times; 2) it is simply not a suitable substrate for the catalyst, even if it were to dissociate; or 3) we would be unable to detect borylated **1A** by using our GC–MS method. We noted that pyridine itself is a "poor" substrate for the borylation reaction,[9,10] whereas pyrrole and quinoline are readily borylated;[11] however, 2,6-chloropyridine and 2,6-dimethylpyridine were effectively borylated at the 4-position,[5,12] and 5-bromo-2-cyanopyridine was borylated at the 3- and 4-positions in a 2:1 ratio.[13]

To investigate the question of the borylation of **1A** further, rather than add a stoichiometric amount of **1A** with respect to the Ir center, 20 equivalents of the ligand and 40 equivalents of bis(pinacolato-*O,O′*)diboron (B_2pin_2) in hexane (5 mL) were added to $[Ir(cod)(\mu\text{-}OMe)]_2$ **I** (cod = cyclooctadiene). GC–MS analysis of the reaction mixture in situ after heating at 80 °C for 16 h showed borylation of **1A** was complete (100 % conversion) and gave rise to a single isomer, which ^1H, ^{13}C, and 2D NMR spectroscopic experiments indicated to be 4,4′-*t*Bu_2-6,6′-$(Bpin)_2$-2,2′-bipyridine (**2A**) with the boryl group on the carbon atom adjacent to the nitrogen atom (Scheme 1). Removal of the solvent in vacuo followed by addition of 3 equivalents of PhI, 4 equivalents of $K_3PO_4{\cdot}2H_2O$ as the base, 10 mol % of $[PdCl_2(dppf)]$ (dppf = 1,1′-bis(diphenylphosphino)ferrocene) as the catalyst, and dry dimethylformamide (DMF) as the solvent and heating (80 °C, 6 h) gave 4,4′-*t*Bu_2-6,6′-Ph_2-2,2′-bipyridine (**3A**) in 67 % yield of isolated product. The structure of this product was confirmed by single-crystal X-ray diffraction (see the Supporting Information).[14]



Scheme 1. Borylation of **1A**.

Interestingly, the same bis(borylated) dtbpy could be converted cleanly into the monophenyl product **4A** in 31 % yield of isolated product (also structurally characterized by X-ray diffraction;[14] see the Supporting Information) under the same conditions but using only 1.2 equivalents of PhI and 2 equivalents of $K_3PO_4{\cdot}2H_2O$ as the base, thus indicating that 1) cross-coupling took place initially at one ring and 2) when

---

[*] I. A. I. Mkhalid, Dr. D. N. Coventry, Dr. D. Albesa-Jove,
Dr. A. S. Batsanov, Prof. J. A. K. Howard, Prof. T. B. Marder
Department of Chemistry
University of Durham
South Road, Durham, DH1 3LE (England)
Fax: (+44) 191-384-4737
E-mail: todd.marder@durham.ac.uk

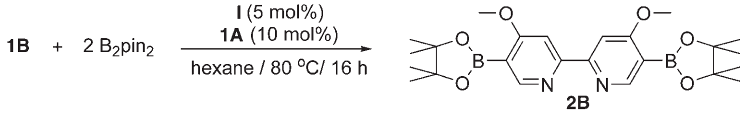
Prof. R. N. Perutz
Department of Chemistry
University of York
Heslington, YO10 5DD (England)

[**] We thank the EPSRC for support (T.B.M. and R.N.P.), the University of Durham for a Sir Derman Christopherson Foundation Fellowship (T.B.M.), One NorthEast (UK) for funding through the Nanotechnology UIC program (T.B.M. and J.A.K.H.), the Saudi Arabia Cultural Attache (London) for a postgraduate scholarship (I.A.I.M.), Mrs. J. Dostal for the elemental analyses, and Frontier Scientific Inc. and NetChem Inc. for generous gifts of bis(pinacolato-*O,O′*)diboron) (B_2pin_2).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

the PhI was depleted, hydrolysis of the remaining C–B bond was relatively facile under the reactions conditions.

In contrast, no borylation of 4-*t*Bu-pyridine was observed even after 2 days at 80 °C in hexane using 5 mol % of catalyst prepared from dimer **I** and 2 equivalents of **1A**; moreover, 10 mol % of the catalyst was required to achieve approximately 6 % conversion into the C–H borylation product. Presumably, 4-*t*Bu-pyridine binds to the Ir center strongly through the N atom, thus blocking the site needed for C–H activation.[10] Interestingly, the ^{2}H NMR spectrum following quenching with $[^2H]_2O$ showed that borylation had taken place *ortho* to the N atom. As we were unable to borylate 4-*t*Bu-pyridine effectively, we examined 4,4′-(MeO)$_2$-2,2′-bipyridine (**1B**) because of its similarity to **1A**. A complete reaction (100 % conversion) of **1B** was achieved after 16 h using 2 equivalents of B_2pin_2 in hexane (5 mL), **I** (5 mol %), and **1A** (10 mol %) at 80 °C, as shown by in situ GC–MS analysis. A single isomer of the bipyridyl bis(boronate) ester (**2B**) was produced in approximately 85 % yield plus approximately 15 % yield of the analogous monoboronate. ^{1}H, ^{13}C, and 2D NMR spectroscopic experiments indicated that borylation took place at the 5-position, *ortho* to the MeO groups, in complete contrast with the borylation of dtbpy (Scheme 2). A single-crystal X-ray diffraction study[14] (Figure 1) confirmed the structure of the product.



Scheme 2. Borylation of **1B**.

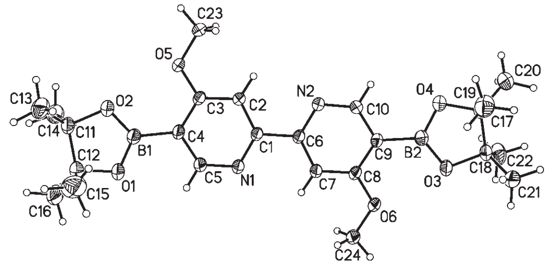
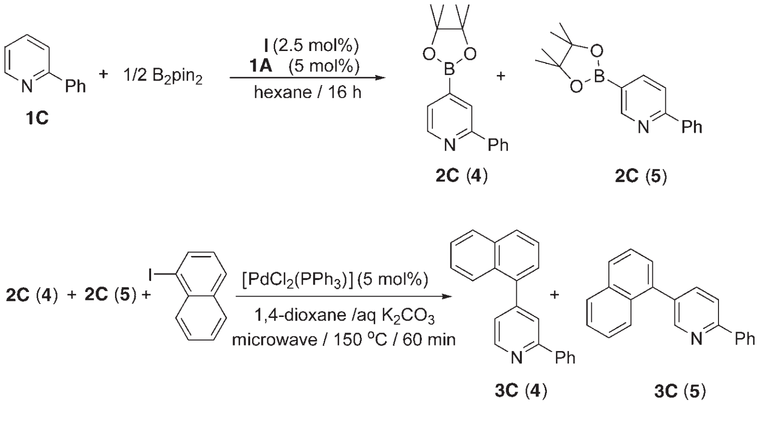


Figure 1. Molecular structure of **2B**.

It would, thus, appear that for electronic reasons the borylation reactions will avoid positions *ortho* to the N atom in a pyridine ring unless extreme steric hindrance makes other positions inaccessible. Preliminary results of DFT calculations (B3LYP, 6-31G*) show that charges on the C atom *ortho* to the N atom and the highest-occupied molecular orbitals (HOMOs) and lowest-unoccupied molecular orbitals (LUMOs) of **1A** and **1B** are very similar. This example is the first wherein purely electronic control leads to exclusive borylation of aromatic compounds *ortho* to a substituent (namely, OMe). A recent discussion of substituent effects in the borylation of cyanoarenes is given in reference [13]. Even though the regioselectivity of the borylation of the two 4,4′-disubstituted bipyridines (bpys) was different, what they have in common is that bpy can be considered to be a 2-pyridyl substituted pyridine, that is, that there is a bulky pyridine-substituent *ortho* to the N atom that blocks N-coordination of either ring because of the steric constraints of the key [Ir(Bpin)$_3$(dtbpy)] intermediate (see above). It cannot act as a bidentate ligand because the Ir center is already five-coordinate, and it cannot act as a monodentate pyridine (py) ligand because the *ortho* py substitutent is too big to allow coordination at the N atom.

With that model in mind, we decided to examine 2-Ph-pyridine (**1C**) which, along with its derivatives, has received considerable attention as a C,N chelate on Ir centers for electroluminescence in organic light-emitting diode (OLED) devices.[15] We wondered whether a single 2-Ph group would also inhibit N-coordination, thus allowing borylation of the pyridine ring, and whether borylation of the phenyl or pyridine groups would predominate. Indeed, borylation was successful within 16 h at room temperature using 2.5 mol % of **I** and 5 mol % of **1A**, thus giving rise to equal amounts of 2-Ph-4-(Bpin)-pyridine (**2C**(**4**)) and 2-Ph-5-(Bpin)-pyridine (**2C**(**5**)). The solvent was removed from the crude mixture, which was redissolved in 1,4-dioxane to which aqueous K_2CO_3 and $[PdCl_2(PPh_3)_2]$ (5 mol %) were added. This mixture was treated with 1-iodonaphthalene in a 20-mL crimp-top sealed glass vessel and heated to 150 °C for 1 h in a Biotage-Personal Chemistry microwave reactor, thus giving 2-Ph-4-(1-Np)-pyridine (**3C**(**4**)) and 2-Ph-5-(1-Np)-pyridine (**3C**(**5**)) in 61 % yield of the combined isolated products (Scheme 3). Compounds **3C**(**4**) and **3C**(**5**) were separated chromatographically, identified spectroscopically, and their structures confirmed by single-crystal X-ray diffraction[14] (see the Supporting Information).

Finally, to test the generality of the process for the one-pot synthesis of unusual heterocycles, to evaluate whether a single CH_3 group is sufficient to block N-coordination, and to direct borylation *ortho* to the N atom, we carried out the borylation of 2,3-dimethylpyrazine (**1D**) using **I**/**1A** under the same conditions as for **1C**. The product, 2,3-Me$_2$-5-Bpin-pyrazine (**2D**), was subsequently cross-coupled with 2-bromothiophene to give 2,3-Me$_2$-5-(2-thienyl)-pyrazine (**3D**),[16] which was isolated in 34 % yield (and also structurally characterized by X-ray diffraction;[14] see the Supporting Information).



Scheme 3. Borylation of **1C**.

In summary, we have shown that the catalyst will borylate dtbpy unless it is already coordinated to the Ir center. Moreover, we note that a single substituent *ortho* to the N atom is sufficient to inhibit N-coordination to the Ir center, thus "activating" the six-membered heteroarenes to borylation of C–H bonds and providing a design criterion for substrates for selective borylation. Complete regioselectivity has been achieved through either electronic or steric control, which allows, for the first time, borylation of pyridine derivatives *ortho* to the N atom or *ortho* to a MeO substituent (that is, *meta* to the N center). The compound 2-Ph-pyridine, important in the design of triplet-emitting Ir complexes for OLEDs,[15] can be further derivatized at the 4- and 5-positions of the py ring in preference to the Ph ring, thus leading to useful 4-(or 5-)-Ar′-2-Ar-pyridine derivatives. The compound 2,3-dimethylpyrazine was borylated *ortho* to the N atom and cross-coupled with the electron-rich heteroarene 2-bromothiophene. Finally, whilst some of the aryl pyridines, such as **3A** and **4A**, have been reported previously as ligands in Ru and luminescent Ir and Pt complexes,[17] prepared by the addition of PhLi to dtbpy followed by hydrolysis and oxidation, our route is more general and inherently more functional-group tolerant and does not require highly reactive ArLi reagents. We expect this route to be of use in applications that range from pharmaceuticals to new optical and electronic materials.

Received: August 26, 2005

Keywords: boron · boronate esters · boronic acid heterocycles · C–H activation · structure elucidation

---

[1] a) A. Suzuki, N. Miyaura, *Chem. Rev.* **1995**, *95*, 2451; b) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; c) P. R. Parry, C. Wang, A. S. Batsanov, M. R. Bryce, B. Tarbit, *J. Org. Chem.* **2002**, *67*, 7541; d) F. Türksoy, G. Hughes, A. S. Batsanov, M. R. Bryce, *J. Mater. Chem.* **2003**, *13*, 1554; e) P. R. Parry, M. R. Bryce, B. Tarbit, *Synthesis* **2003**, 1035; f) N. Saygili, A. S. Batsanov, M. R. Bryce, *Org. Biomol. Chem.* **2004**, *2*, 852; g) A. E. Thompson, G. Hughes, A. S. Batsanov, M. R. Bryce, P. R. Parry, B. Tarbit, *J. Org. Chem.* **2005**, *70*, 388.

[2] D. M. T. Chan, K. L. Monaco, R. Li, D. Bonne, C. G. Clark, P. Y. S. Lam, *Tetrahedron Lett.* **2003**, *44*, 3863.

[3] a) M. P. Sibi, H. Tatamidani, K. Patil, *Org. Lett.* **2005**, *7*, 2571; b) G. Chen, N. Tokunaga, T. Hayashi, *Org. Lett.* **2005**, *7*, 2885.

[4] a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390; b) T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem.* **2002**, *114*, 3182; *Angew. Chem. Int. Ed.* **2002**, *41*, 3056.

[5] J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith III, *Science* **2002**, *295*, 305.

[6] P. Nguyen, H. P. Blom, S. A. Westcott, N. J. Taylor, T. B. Marder, *J. Am. Chem. Soc.* **1993**, *115*, 9329.

[7] H. Tamura, H. Yamazaki, H. Sato, S. Sakaki, *J. Am. Chem. Soc.* **2003**, *125*, 16114.

[8] D. N. Coventry, A. S. Batsanov, A. E. Goeta, J. A. K. Howard, T. B. Marder, R. N. Perutz, *Chemm. Commun.* **2005**, 2172.

[9] J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama, N. Miyaura, *Tetrahedron Lett.* **2002**, *43*, 5649.

[10] T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3.

[11] a) T. Ishiyama, J. Takagi, Y. Yonekawa, J. F. Hartwig, N. Miyaura, *Adv. Synth. Catal.* **2003**, *345*, 1103; b) T. Ishiyama, Y. Nobuta, J. F. Hartwig, N. Miyaura, *Chem. Commun.* **2003**, 2942.

[12] a) J.-Y. Cho, C. N. Iverson, M. R. Smith III, *J. Am. Chem. Soc.* **2000**, *122*, 12868; b) T. Tagata, M. Nishida, *Adv. Synth. Catal.* **2004**, *346*, 1655.

[13] G. A. Chotana, M. A. Rak, M. R. Smith, *III, J. Am. Chem. Soc.* **2005**, *127*, 10539.

[14] For synthetic and crystallization details and the molecular structures, see the Supporting Information. X-ray diffraction experiments were performed with SMART 1 K CCD area-detector diffractometers using $\mathrm{Mo}_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) at $T = 120(2)$ K; the structures were solved by direct methods (SHELXTL; Bruker AXS, Inc., Madison, WI, USA). **3A**·2 C_6F_6: $C_{42}H_{32}F_{12}N_2$, $M_r = 792.70$, orthorhombic, space group *Pccn*, $a = 14.021(2)$, $b = 19.509(3)$, $c = 13.2267(19)$ Å, $V = 3618.1(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.455\ \mathrm{Mg\,m^{-3}}$, $\mu = 0.128\ \mathrm{mm^{-1}}$, R (F; $F^2 > 2\sigma$) = 0.0550, R_w (F^2, all data) = 0.1583, $S = 1.297$ for 5474 unique data ($\theta < 30.5$) and 317 refined parameters; final difference synthesis within ±0.54 e Å^{-3}. **4A**·C_6F_6: $C_{30}H_{28}F_6N_2$, $M_r = 530.54$, orthorhombic, space group *Pnma*, $a = 27.2125(17)$, $b = 6.7353(5)$, $c = 14.3175(10)$ Å, $V = 2624.2(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.343\ \mathrm{Mg\,m^{-3}}$, $\mu = 0.108\ \mathrm{mm^{-1}}$, R (F; $F^2 > 2\sigma$) = 0.0508, R_w (F^2, all data) = 0.1346, $S = 1.010$ for 4319 unique data ($\theta < 30.51$) and 291 refined parameters; final difference synthesis within ±0.34 e Å^{-3}. **2B**: $C_{24}H_{34}B_2N_2O_6$, $M_r = 468.15$, monoclinic, space group $P2_1/n$, $a = 9.3567(6)$, $b = 22.0270(13)$, $c = 12.2764(8)$ Å, $\beta = 98.213(3)°$, $V = 2504.2(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.242\ \mathrm{Mg\,m^{-3}}$, $\mu = 0.087\ \mathrm{mm^{-1}}$, R (F; $F^2 > 2\sigma$) 0.0717, R_w (F^2, all data) = 0.2121, $S = 1.069$ for 7652 unique data ($\theta < 30.50°$) and 317 refined parameters; final difference synthesis within ±0.64 e Å^{-3}. **3C(4)**: $C_{21}H_{15}N$, $M_r = 281.34$, monoclinic, space group $P2_1$, $a = 6.7020(8)$, $b = 7.6743(9)$, $c = 14.6965(17)$ Å, $\beta = 97.980(3)°$, $V = 748.57(15)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.248\ \mathrm{g\,cm^{-3}}$, $\mu = 0.072\ \mathrm{mm^{-1}}$, R (F; $F^2 > 2\sigma$) = 0.0426, R_w (F^2, all data) = 0.1261, $S = 0.645$ for 2165 unique data ($\theta < 27.50$) and 260 refined parameters; final difference synthesis within ±0.33 e Å^{-3}. **3C(5)**: $C_{21}H_{15}N$, $M_r = 281.34$, monoclinic, space group $P2_1$, $a = 7.099(1)$, $b = 12.943(2)$, $c = 7.928(1)$ Å, $\beta = 100.02(1)°$, $V = 717.33(18)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.303\ \mathrm{g\,cm^{-3}}$, $\mu = 0.075\ \mathrm{mm^{-1}}$, R (F; $F^2 > 2\sigma$) = 0.0423, R_w (F^2, all data) = 0.1188, $S = 1.069$ for 2163 unique data ($\theta < 29.98$) and 259 refined parameters; final difference synthesis within ±0.33 e Å^{-3}. **3D**: $C_{10}H_{10}N_2S$, $M_r = 190.26$, monoclinic, space group $P2_1/n$, $a = 7.1352(19)$, $b = 12.292(3)$, $c = 11.175(3)$ Å, $\beta = 94.168(4)°$, $V = 977.5(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.293\ \mathrm{Mg\,m^{-3}}$, $\mu = 0.283\ \mathrm{mm^{-1}}$, R (F; $F^2 > 2\sigma$) = 0.0464, R_w (F^2, all data) = 0.1293, $S = 1.062$ for 2618 unique data ($\theta < 27.50°$) and 142 refined parameters; final difference synthesis within ±0.25 e Å^{-3}. CCDC 279973–279978 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] a) M. A. Baldo, S. Lamansky, P. E. Burrows, M. E. Thompson, S. R. Forrest, *Appl. Phys. Lett.* **2005**, *75*, 4; b) S. Lamansky, P. Djurovich, D. Murphy, F. Abdel-Razzag, H. Lee, C. Adachi, P. E. Burrows, S. R. Forrest, M. E. Thompson, *J. Am. Chem. Soc.* **2001**, *123*, 4304; c) C. Adachi, M. A. Baldo, M. E. Thompson, S. R. Forrest, *J. Appl. Phys.* **2001**, *90*, 5048.

[16] The only reference to this compound we have located is in the following patent: Jpn. Kokai Tokkyo Koho, **1980**, 6 pp, CODEN: JKXXAF JP 55120570 19800917 Showa. [Chem. Abstr. **1981**, *94*, 175164].

[17] a) T. B. Hadda, I. Zidane, S. A. Moya, H. Le Bozec, *Polyhedron* **1996**, *15*, 1571; b) M. Lepeltier, T. K.-M. Lee, K. K.-W. Lo, L. Toupet, H. Le Bozec, V. Guerchais, *Eur. J. Inorg. Chem.* **2005**, 110; c) W. Lu, B.-X. Mi, M. C. W. Chan, Z. Hui, C.-M. Che, N. Zhu, S.-T. Lee, *J. Am. Chem. Soc.* **2004**, *126*, 4958.