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A highly selective Ir-catalyzed borylation of 2-substituted indoles: a new access to 2,7- and 2,4,7-substituted indoles

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Abstract—The selective CH-functionalization of 2-substituted indoles is presented. Using bis(pinacolato)diboron (**2**) in the presence of iridium complexes, a novel catalytic mono-borylation is observed preferentially at the 7-position of the indole. This allows for an efficient synthesis of various 2,7-di- and 2,4,7-trisubstituted indoles, which are otherwise difficult to access. The scope and limitation of the method is demonstrated.

Indoles are an important class of heterocycles not only because they are among the most ubiquitous compounds in nature, but also because they have a wide range of biological activities.[1,2] Hence, it is not surprising that indoles act as lead compounds and are key building blocks in numerous pharmaceuticals.[3] In the past, a multitude of synthetic methods for indoles have been developed since its first chemical synthesis.[3,4] Nowadays, the choice of the synthetic method for a desired indole derivative depends highly on the availability of the starting materials and the functional group tolerance. Despite all known procedures, the synthesis of indoles with non-conventional substitution patterns remains a challenging task. In fact, such unusually substituted indoles are highly interesting for the preparation of new biologically active compounds.

We have been interested in the application of catalytic reactions for the synthesis of potential pharmaceuticals for some time.[5] In this regard, recently metal-catalyzed borylation on aromatic C–H bonds has drawn our attention.[6] In general, this method is complimentary to traditional electrophilic aromatic substitution and has been used to synthesize otherwise not easily accessible phenols[7] and anilines.[8]

In addition, aromatic and heteroaromatic boronates are valuable intermediates for Suzuki-Miyaura cross-coupling reactions,[10,11] for Cu-catalyzed C–N and C–O bond-forming reactions,[12] and for other reactions.[13] Clearly, the direct C–H bond activation and functionalization provides a straightforward synthetic route to access these arylboronates and avoid the use of halide substrates and lithium or Grignard reagents in conventional boronic acid synthesis.

Noteworthy, as potential pharmaceuticals, boronic acids exhibit various biological activities.[9] For example, some of them have been used in boron neutron capture therapy (BNCT) (Scheme 1).

In light with these issues, here we report a regioselective borylation reaction towards 2,7-di- and 2,4,7-trisubstituted indoles, which are otherwise difficult to obtain.

As a proto-typical reaction, ethyl indole-2-carboxylate (**1a**) is borylated in an inert solvent with 0.75 mol % of $[Ir(COD)OMe]_2$ and 1.5 mol % 4,4′-di-*tert*-butyl-2,2′-bipyridine as the catalyst (Table 1).[14] Only trace of product is observed by GC–MS at room temperature both in *n*-heptane and 1,4-dioxane (Table 1, entries 1 and 3). However, by increasing the temperature to 50 °C, a good yield (67%) of the mono-borylated product is obtained. Further optimization of the ratio of **1a** to **2** gave **3a** in excellent yield (92%). It should be noted that this reaction works better in *n*-heptane than in

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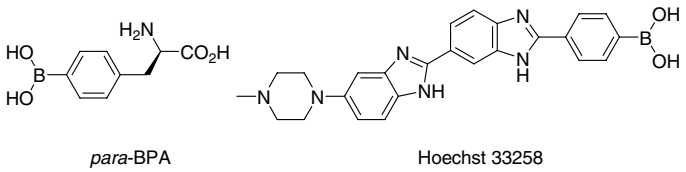
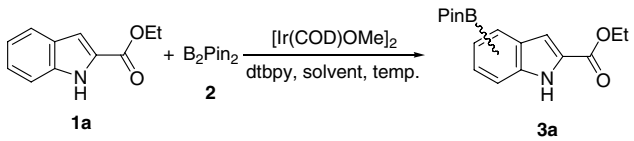


Scheme 1. Selected boron neutron capture therapy agents (BNCT).[9]

Table 1. Influence of stoichiometry of ethyl indole-2-carboxylate (**1a**) to bis(pinacolato)diboron (**2**), B_2Pin_2, temperature and solvent to the borylation reaction



1a **2** **3a**

Entry	**1a**:**2**[a]	Solvent	Temp (°C)	Yield[b] (%)
1	1:0.5	*n*-Heptane	rt	Trace
2	1:0.5	*n*-Heptane	50	67
3	1:0.5	1,4-Dioxane	rt	No reaction
4	1:0.5	1,4-Dioxane	50	Trace
5	1:0.5	1,4-Dioxane	100	59
6	1:0.7	*n*-Heptane	50	92

Standard reaction conditions: **1a** (0.50 mmol), **2** (0.25–0.35 mmol), $[Ir(COD)OMe]_2$ (0.0038 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.0075 mmol) were charged into a schlenk tube with Teflon screwed stopper under Ar. Freshly distilled solvent (1.5 mL) and dodecane (GC internal standard, 432 μL) were added. The reaction mixture was then heated for ~16 h at rt–100 °C.
[a] Molar ratio of **1a** to **2**.
[b] GC yield.

1,4-dioxane (Table 1, entries 2 and 4). However, at higher reaction temperature (100 °C) both solvents gave comparative results. Hence, 1,4-dioxane can be used for less soluble substrates instead.

As two C–H bonds are not hindered in **1a**, non-selective borylation was initially expected. Different from our expectation, a single regioisomer **3a** was obtained, the structure of which was assigned based on 2D-^{1}H NMR and further confirmed by X-ray crystallography (Fig. 1).

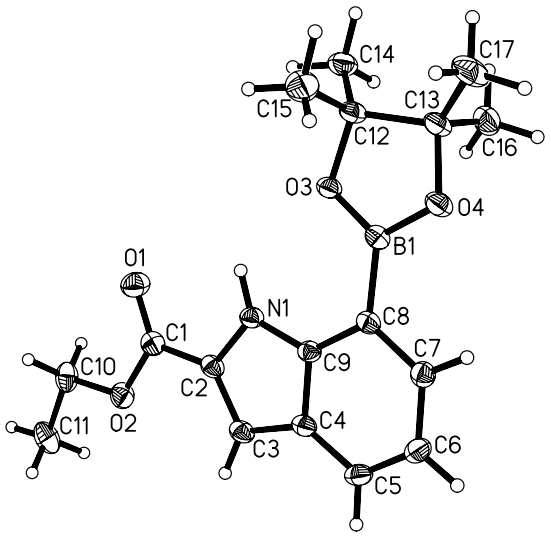
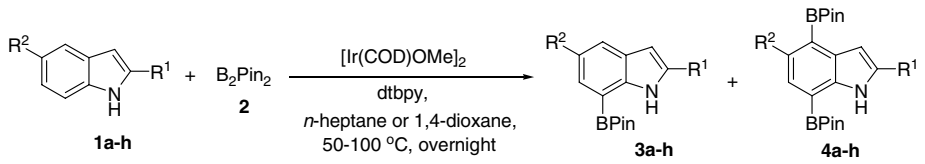


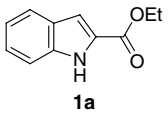
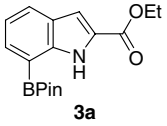
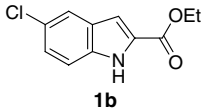
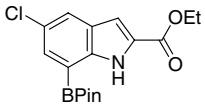
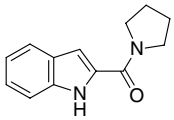
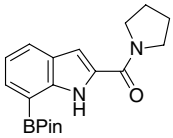
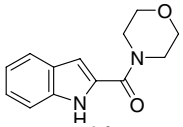
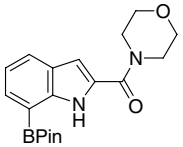
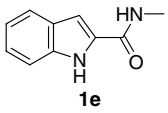
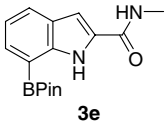
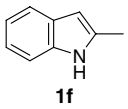
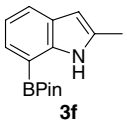
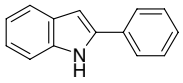
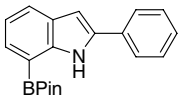
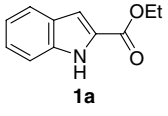
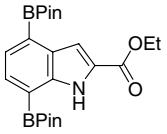
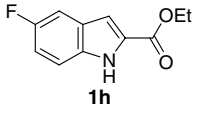
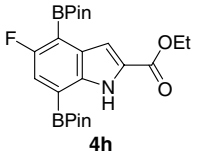
Figure 1. Molecular structure of **3a**. The thermal ellipsoids correspond to 30% probability.[15]

To demonstrate the scope and limitation of this reaction, various 2-substituted indoles were subjected to the typical reaction conditions,[16] which, to our delight, provided 2,7-disubstituted indole products in moderate to excellent yields (Table 2, entries 1–7). Various functional groups, such as halogen, ester, mono- and di-N-substituted amides, as well as aromatic rings (phenyl) are tolerated. From the GC–MS analysis of the crude reaction mixture, the mono-borylated product usually has >97% selectivity at the 7-position. Lower product yields obtained were due to isolation problems and subsequent diborylation. In fact, the diborylated compounds can be obtained as major products when more B_2Pin_2 (**2**) is employed (Table 2, entries 8 and 9). It is noteworthy that the second catalytic borylation reaction proceeds also with high regioselectivity (>85%). ^{1}H NMR of the isolated regioisomers showed that the major diborylated product contains a 2,4,7-substitution pattern.

We surmise that the high selectivity towards the 7-position is due to an *ortho*-directing effect. Although the regioselectivity of the borylation process for arenes is mainly controlled by steric effects,[6] a few examples showed the involvement of an electronic or coordination effect.[6b,17] For unprotected pyrrole and indole it is known that borylation occurs preferentially at the

Table 2. $[Ir(COD)OMe]_2$/dtbpy-catalyzed borylation of various 2-substituted indoles[14]



Entry	Substrate	Product	1:2[a]	Temp (°C)	Solvent	Yield[b] (%)
1	 **1a**	 **3a**	1:0.7	50	*n*-Heptane	83 (92)[c]
2	 **1b**	 **3b**	1:0.6	100	1,4-Dioxane	45
3	 **1c**	 **3c**	1:0.7	100	1,4-Dioxane	93
4	 **1d**	 **3d**	1:0.7	100	1,4-Dioxane	99[d]
5	 **1e**	 **3e**	1:0.7	100	1,4-Dioxane	50[c]
6	 **1f**	 **3f**	1:0.7	50	*n*-Heptane	54
7	 **1g**	 **3g**	1:0.7	50	*n*-Heptane	58
8	 **1a**	 **4a**	1:2.5	50	*n*-Heptane	75[c,e]
9	 **1h**	 **4h**	1:1.2	50	*n*-Heptane	48

Standard reaction conditions: **1a** (0.50 mmol), **2** (0.30–1.25 mmol), $[Ir(COD)OMe]_2$ (0.0038 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.0075 mmol) were charged into a schlenk tube with Teflon screwed stopper under Ar. Freshly distilled solvent (1.5 mL) and dodecane (GC internal standard, 432 μL) were added. The reaction mixture was then heated for ~16 h at 50 °C for *n*-heptane and 100 °C for 1,4-dioxane.

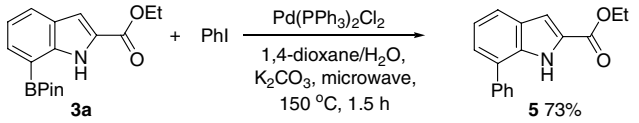
[a] Molar ratio of **1a** to **2**.

[b] Isolated yield.

[c] GC yield.

[d] NMR yield.

[e] The ratio of 4,7-diborylated product to 5,7-diborylated product is 85:15 determined by ^1H NMR.



Scheme 2. Suzuki-Miyaura cross-coupling of **3a** with PhI.[6a]

2-position,[6,18] while borylation of *N*-methylindole gave a mixture of 2- and 3-borylated products in a ratio of 56:44.[18a] Thus, it is likely that the indole N–H group is a directing group for the borylation reaction.

In most of the reported borylation procedures, the arenes are usually used in excess with respect to **2** when more than one unhindered C–H bond exists in order to obtain the mono-boronate in good yield.[6,18] However, 2-substituted indoles gave full conversion with high selectivity towards 7-borylated indoles in the presence of an equimolar or a slight excess amount of **2** (Table 2, entries 1, 3 and 4). This is an important advantage because more expensive starting materials may also be further functionalized through the boronate using our protocol. It is noteworthy that in principle both boronate groups in bis(pinacolate)diborane (**2**) are effective to the borylation reaction and generate only hydrogen as by-product (Tables 1 and 2). Hence this reaction is a clean, atom efficient and direct method towards 2,7-disubstituted indoles.

As a demonstration for the use of the borylated indoles, the Suzuki-Miyaura cross-coupling reaction was performed with **3a** and PhI, which yielded the phenyl-substituted product **5** in 73% yield under microwave conditions (Scheme 2).[6a]

Since 2-substituted phenylhydrazines are less accessible, relatively few examples for the synthesis of 2,7-disubstituted indoles are known via the most commonly used Fischer indole synthesis.[19]

Clearly, the method presented here provides a more general access to this substitution pattern and may contribute to medicinal chemistry and pharmaceutical industry in the future.

In conclusion, we have shown the application of the iridium-catalyzed borylation reaction to 2-substituted indoles. Excellent regioselectivity towards 7-borylated indoles was observed. In the presence of an excess of the borylation reagent, 2,4,7-trisubstituted indoles are obtained preferentially. The scope and limitation of the catalytic system are demonstrated on indoles with various functional groups with moderate to excellent yields. Further functionalization of the 7-borylated indoles to potentially bioactive compounds is in progress in our group.

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References and notes

1. (a) *Indoles*; Sundberg, R. J., Ed.; Academic Press: San Diego, 1996; (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry: Pyrroles and Their Benzoderivatives*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; pp 313–376; (c) Brown, R. K. In *Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972.
2. (a) Yeh, E.; Garneau, S.; Walsh, C. T. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 3960–3965; (b) Meijer, L.; Flajolet, M.; Greengard, P. *Trends Pharmacol. Sci.* **2004**, *25*, 471–480; (c) Cohen, P. *Nat. Rev. Drug Disc.* **2002**, *1*, 309–315; (d) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304.
3. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
4. (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491–2515; (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045–1075.
5. (a) Kaiser, H. M.; Lo, W. F.; Riahi, M.; Spannenberg, A.; Beller, M.; Tse, M. K. *Org. Lett*, in press, doi:10.1021/o1062338p; (b) Neumann, H.; Strübing, D.; Lalk, M.; Klaus, S.; Hübner, S.; Spannenberg, A.; Lindequist, U.; Beller, M. *Org. Biomol. Chem.* **2006**, *4*, 1365–1375; (c) Khedkar, V.; Tillack, A.; Michalik, M.; Beller, M. *Tetrahedron* **2005**, *61*, 7622–7631; (d) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 7703–7707; (e) Michalik, D.; Kumar, K.; Zapf, A.; Tillack, A.; Arlt, M.; Heinrich, T.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 2057–2061; (f) Kumar, K.; Michalik, D.; Castro, I. G.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Böttcher, H.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 746–757.
6. (a) Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 489–491; (b) Chotana, G. A.; Rak, M. A.; Smith, M. R., III *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544; (c) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103–1106; (d) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391; (e) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056–3058; (f) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305–308.
7. (a) Shi, F.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett.* **2006**, *8*, 1411–1414; (b) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III. *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793.
8. Holmes, D.; Chotana, G. A.; Maleczka, R. E., Jr.; Smith, M. R., III. *Org. Lett.* **2006**, *8*, 1407–1410.
9. Yang, W.; Gao, X.; Wang, B. *Med. Res. Rev.* **2003**, *23*, 346–368, and references cited therein.
10. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.
11. (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11–59; (b) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 83–90.

12. (a) Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* **2004**, 1095–1097; (b) Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863–3865, and references cited therein.
13. (a) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–470; (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844; (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196.
14. All experiments were carried out under an inert gas atmosphere (argon) with exclusion of air. For the standard reaction procedure, **1a** (0.50 mmol), **2** (0.25–0.35 mmol), $[Ir(COD)OMe]_2$ (0.0038 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.0075 mmol) were charged into a schlenk tube with Teflon screwed stopper under Ar. Freshly distilled solvent (1.5 mL) and dodecane (GC internal standard, 432 μL) were added. The reaction mixture was then heated for ~16 h at 50 °C for *n*-heptane and 100 °C for 1,4-dioxane. Compound **3a**: $R_f = 0.24$ (hexane–ethyl acetate 10:1); mp 68–71 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 1.33$ (m, 12H), 1.35 (t, $J = 6.98$ Hz, 3H), 4.40 (q, $J = 7.1$Hz, 2H), 7.09 (dd, $J = 7.8$, 7.0 Hz, 1H), 7.14 (d, $J = 2.25$Hz, 1H), 7.77 (m, 2H), 9.70 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.40$, 24.99, 60.92, 84.10, 108.20, 120.39, 126.07, 126.49, 127.44, 132.79, 141.65, 162.14; IR (KBr, cm^{-1}): 3447, 3060, 2986, 2930, 1717, 1593, 1538, 1421, 1368, 1287, 1234, 1146, 1128, 1028, 976, 850, 822, 750, 677; EIMS *m*/*z* 315.2 (M^+); Elemental Anal. Calcd for $C_{17}H_{22}BNO_4$: C, 64.78; H, 7.04; B, 3.43; N, 4.44; O, 20.31. Found: C, 64.66; H, 7.16; N, 4.46.
15. X-ray crystallographic study of **3a**: Data were collected with a STOE-IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structure was solved by direct methods [SHELXS-97: Sheldrick, G. M. University of Göttingen, Germany, 1997.] and refined by full-matrix least-squares techniques against F^2 [SHELXL-97: Sheldrick, G. M. University of Göttingen, Germany, 1997.] XP (BRUKER AXS) was used for structural representation. Space group $P\bar{1}$, triclinic, $a = 8.389(2)$, $b = 10.099(2)$, $c = 11.479(2)$ Å, $\alpha = 114.43(3)°$, $\beta = 92.60(3)°$, $\gamma = 106.58(3)°$, $V = 833.6(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.256$ g cm^{-3}, 13,135 reflections measured, 3809 were independent of symmetry, of which 2723 were observed ($I > 2\sigma(I)$), $R1 = 0.0384$, wR^2 (all data) = 0.1032, 212 parameters.
16. (a) Mertins, K.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2004**, *207*, 21–25; (b) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649–5651.
17. Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000**, *122*, 12868–12869.
18. (a) Hiroto, S.; Hisaki, I.; Shinokubo, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6763–6766; (b) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924–2925; (c) Tse, M. K.; Cho, J.-Y.; Smith, M. R., III. *Org. Lett.* **2001**, *3*, 2831–2833.
19. (a) Yamada, Y.; Arima, S.; Okada, C.; Akiba, A.; Kai, T.; Harigaya, Y. *Chem. Pharm. Bull.* **2006**, *54*, 788–794; (b) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526–4528; (c) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899–1902; (d) Fukuda, T.; Maeda, R.; Iwao, M. *Tetrahedron* **1999**, *55*, 9151–9162; (e) Macor, J. E.; Ogilvie, R. J.; Wythes, M. J. *Tetrahedron Lett.* **1996**, *37*, 4289–4292.