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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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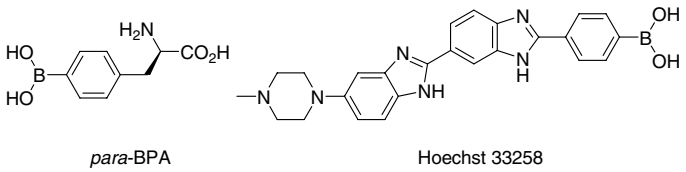
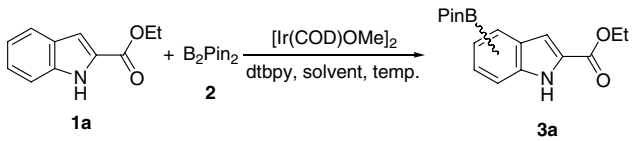


Scheme 1. Selected boron neutron capture therapy agents (BNCT).[9]

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).

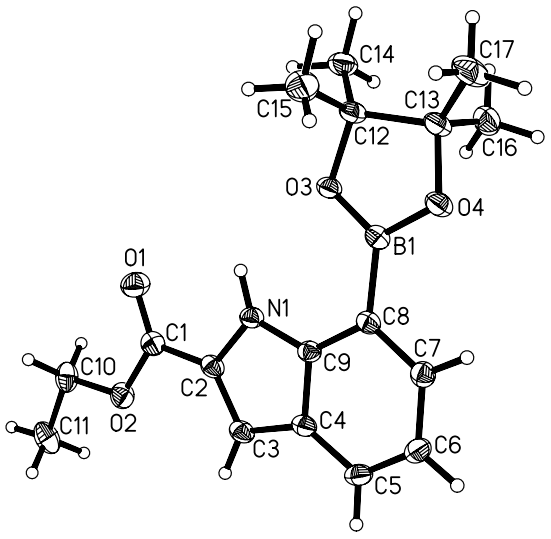


Figure 1. Molecular structure of **3a**. The thermal ellipsoids correspond to 30% probability.[15]

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