Palladium-catalyzed C—H arylation of indoles at the C7 position

With the support by the National Natural Science Foundation of China, the research team led by Prof. Shi Zhuangzhi (史壮志) at the State Key Laboratory of Coordination Chemistry in Nanjing University, developed the first direct and site-selective arylation of indoles at the C7 position, which was published in *J Am Chem Soc* (2016, 138: 495—498).

The indole motif is a ubiquitous feature of bioactive natural products and represents an important structural element for pharmaceutical applications. Around the N-atom center in an indole core are one *ortho* (C2) position and two *meta* (C3 and C7) positions that can be functionalized. The usual reactivity of indoles suggested that metalation and the corresponding C—H activation would take place preferentially at the C3 position. To override this intrinsic selectivity, introducing a directing group (DG) on a N-atom, such as acetyl, pivaloyl, *N*, *N*-dimethylcarbamoyl, and pyrimidyl groups, has been a powerful strategy to ensure C2 selectivity. In stark contrast, general methods to access selectivity directly at the C7 position continue to be scarce. The challenges of C7 selectivity result from the formation of a five-membered metallacycle through C—H bond cleavage at the C2 position, which is preferable to forming the corresponding six membered metallacycle at the C7 position. To solve this challenge, we explored a series of phosphinoyl DGs (1—4) with different steric bulks (Figure). X-ray crystal structures showed that the O-atom in both 1 (R=Et) and 4 (R='Bu) is perfectly oriented to allow C—H activation at the C7 position in the solid state. We speculated that the amide N—P bonds can rotate freely in solvents at high temperature, leading to poor C2 and C7 selectivity. Sterichindrance from the di-*tert*-butyl substituents in 4 could raise the activation energy for amide N—P bond rotation, leading to highly restricted interconversion between the O—C7—H and O—C2—H conformations.

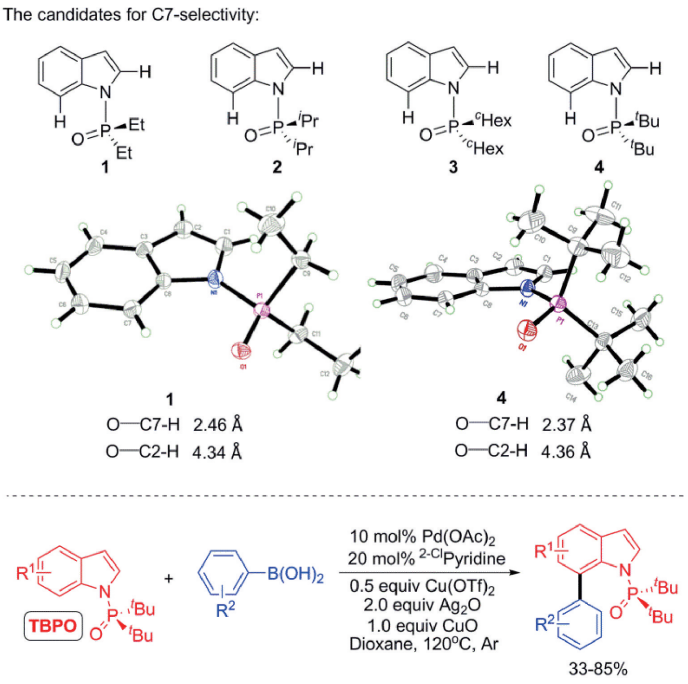

Figure Direct C7-arylation of indoles.

Based on this discovery, we have reported the first C7-selective C—H arylation of indoles with arylboronic acids. The key to this high regio selectivity is the appropriate choice of the sterically hindered N—P(O)^{t}Bu$_2$ directing group and a pyridine type ligand in the presence of Pd(OAc)$_2$ catalyst. This novel catalytic system can override *ortho*-directing effects as well aselectronic biases at the indole C2 and C3 positions. These present results represent an important discovery that is expected to be able to be substantially extended to other systems in highly C7-selective C—H functionalization of indoles.