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Palladium-Catalyzed C–H Arylation of Indoles at the C7 Position

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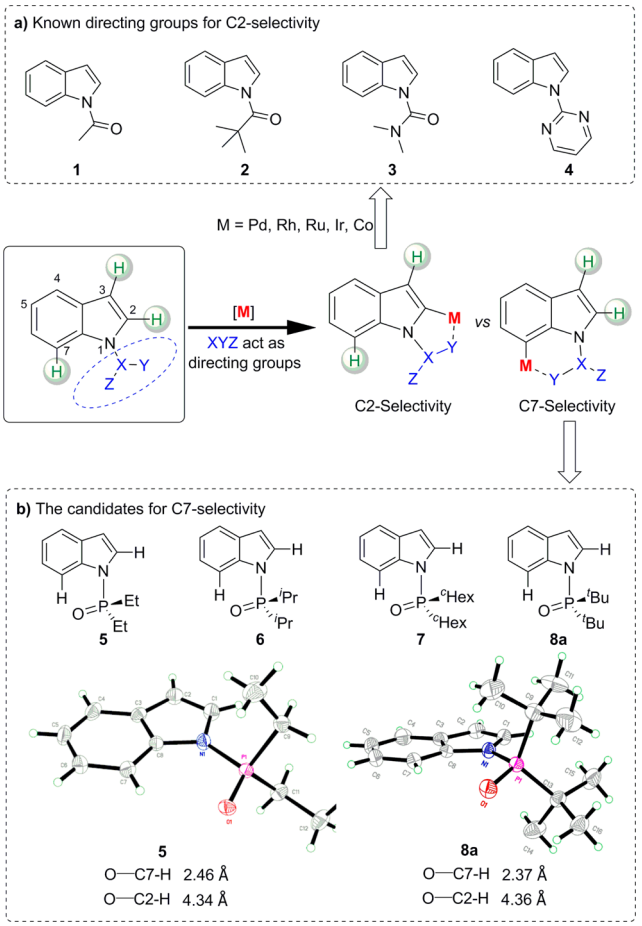
Supporting Information

ABSTRACT: In the past decade, direct C–H arylation of indoles has been developed with high selectivity at the C2 and C3 positions via transition-metal-catalyzed cross-coupling reactions. Here we show that C–H activation can be directed to the C7 position with high selectivity in Pd-catalyzed coupling of indoles with arylboronic acids. The key to this high regioselectivity is the appropriate choice of a phosphinoyl directing group and a pyridine-type ligand in the presence of $Pd(OAc)_2$ catalyst. This previously elusive transformation should provide insight for the design of other cross-couplings as well.

The indole motif is a ubiquitous feature of bioactive natural products and represents an important structural element for pharmaceutical applications.[1] Thus, the development of effective methods for regioselective functionalization of indoles has received intensive attention.[2] 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.[3] The usual reactivity of indoles suggested that metalation and the corresponding C–H activation would take place preferentially at the C3 position.[4] To override this intrinsic selectivity, introducing a directing group (DG) on a N-atom, such as acetyl (**1**),[5] pivaloyl (**2**),[6] *N*,*N*-dimethylcarbamoyl (**3**),[7] and pyrimidyl groups (**4**),[8] has been a powerful strategy to ensure C2 selectivity (Scheme 1a).[9] In stark contrast, general methods to access selectivity directly at the C7 position continue to be scarce. Typically, selective functionalization of the C7 position of indoles requires substituents at the C2 position to block reactivity at this site.[10] Alternatively, an efficient route including reduction of indoles to the corresponding indoline derivatives and then regioselective C–H functionalization of the indoline derivatives, followed by oxidation, can provide various C7-selective products successfully.[11] In 2010, Hartwig et al. developed the first Ir-catalyzed C–H borylation of indoles at the C7 position, in which the regioselectivity was controlled by an *N*-silyl DG. The desired C7-arylindoles can then be synthesized from these 7-borylindoles by Suzuki–Miyaura coupling.[12] Undoubtedly, a new method enabling the direct C–H arylation of indoles at the C7 position is in high demand.

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 (Scheme 1). We reasoned that the C7 selectivity of the indoles could be amplified by using a bulkier and more electron-withdrawing DG on a N-atom because the C7 position is more sterically hindered and less electron poor than the C2 position. Next we explored a series of

Scheme 1. Regioselective C–H Activation of Indoles



phosphinoyl DGs (**5**–**8a**) with different steric bulks (Scheme 1b).[10a,13] X-ray crystal structures showed that the O-atom in both **5** (R = Et) and **8a** (R = ^{t}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. Steric hindrance from the di-*tert*-butyl substituents in **8a** might 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.

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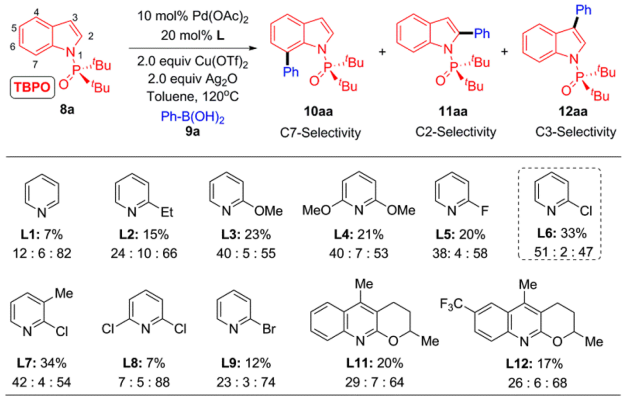
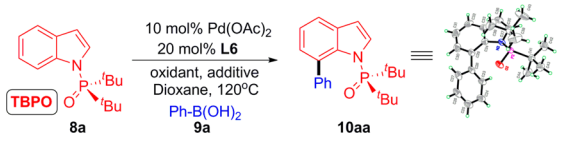
Table 1. Ligand Screening[a]



[a]Conditions: 10 mol% $Pd(OAc)_2$, 20 mol% **L**, 2.0 equiv $Cu(OTf)_2$, 2.0 equiv Ag_2O, **8a** (0.1 mmol, 1.0 equiv), **9a** (0.2 mmol, 2.0 equiv) in 1 mL toluene at 120 °C for 12 h under Ar. GC yields are shown, and C7:C2:C3 ratios were determined by GC-MS.

Table 2. Further Optimization of the Reaction Conditions[a]



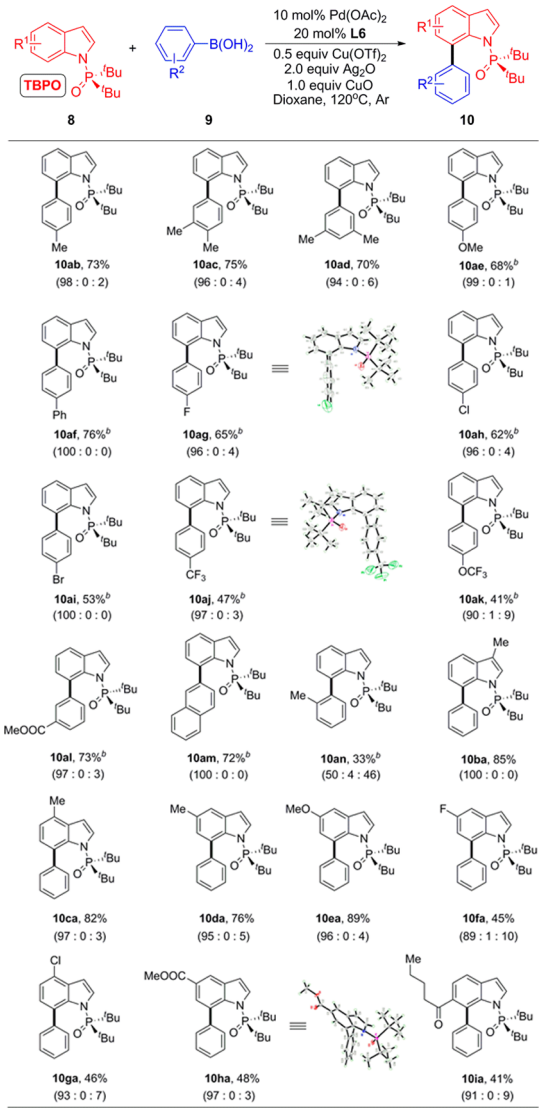
entry	oxidants (equiv)	C7:C2:C3[b]	yield (%)[c]
1	$Cu(OTf)_2$ (2.0) + Ag_2O (2.0)	83:1:16	56
2	$Cu(OTf)_2$ (0.5) + O_2 (1 atm)	64:0:36	9
3	Ag_2O (1.0) + O_2 (1 atm)	-	trace
4	$Cu(OTf)_2$ (0.5) + Ag_2O (2.0)	79:1:20	59
5	$Cu(OTf)_2$ (0.5) + Ag_2O (2.0) + BQ (1.0)	100:0:0	48
6	$Cu(OTf)_2$ (0.5) + Ag_2O (2.0) + $Ce_2(SO_4)_4$ (1.0)	94:0:6	74
7	**$Cu(OTf)_2$ (0.5) + Ag_2O (2.0) + CuO (1.0)**	**96:0:4**	**82 (79)[d]**
8	$Cu(OTf)_2$ (0.5) + Ag_2O (2.0) + CuO (0.5)	93:1:6	70
9[e]	$Cu(OTf)_2$ (0.5) + Ag_2O (2.0)+CuO (1.0)	94:0:6	73
10[f]	$Cu(OTf)_2$ (0.5) + Ag_2O (2.0) + CuO (1.0)	-	0

[a]Conditions: 10 mol% $Pd(OAc)_2$, 20 mol% **L6**, **8a** (0.1 mmol, 1.0 equiv), **9a** (0.2 mmol, 2.0 equiv) in 1 mL dioxane at 120 °C for 12 h under Ar. [b]Ratios were determined by GC-MS. [c]GC yields. [d]Isolated yields after chromatography. [e]Using 10 mol% $Pd(OTFA)_2$. [f]Without $Pd(OAc)_2$.

To evaluate this proposal, we first investigated the best candidate, di-*tert*-butyl-(1*H*-indol-1-yl)phosphine oxide (**8a**), with phenylboronic acid (**9a**) (Table 1). With 10 mol% $Pd(OAc)_2$ as the catalyst, 20 mol% pyridine as the ligand,[14] and 2.0 equiv $Cu(OTf)_2$ and 2.0 equiv Ag_2O as the oxidants in toluene at 120 °C, we indeed observed a mixture of C7-, C2-, and C3-arylated products **10aa**−**12aa** in moderate yield, albeit with a low C7 selectivity (C7:C2:C3 = 12:6:82) (**L1**). Higher selectivity for C7 than C2 indicates that this DG can indeed override the directing effects at the C2 position. We next examined a variety of substituted N-containing heterocycles (**L2**−**L12**) as ligands that could potentially increase the C7 selectivity. Among them, 2-chloropyridine (**L6**) seems to possess an optimal balance of steric and electronic properties to provide **10aa** in 33% yield with an excellent level of C7 selectivity (C7:C2 = 51:2).

Using the optimal ligand **L6**, we screened other factors to inhibit the C3 selectivity (Table 2). Switching the solvent to dioxane resulted in a significant improvement in yield and C7 selectivity (entry 1). Cooperation between Cu and Ag salts is required (entries 2, 3), and 0.5 equiv $Cu(OTf)_2$ is enough to afford a similar result (entry 4). After extensive screening, we found that adding a third co-oxidant can improve the results (entries 5−7). The most obvious effect was seen with CuO: the yield of **10aa** increased markedly to 82% with excellent C7 selectivity (C7:C2:C3 = 96:0:4). Under these conditions, reducing the amount of CuO or changing the Pd source led to lower yields (entries 8, 9). Control reactions confirmed that the transformation did not occur in the absence of $Pd(OAc)_2$ (entry 10).

Table 3. Substrate Scope[a]



[a]Conditions: 10 mol% $Pd(OAc)_2$, 20 mol% **L6**, 0.5 equiv $Cu(OTf)_2$, 2.0 equiv Ag_2O, 1.0 equiv CuO, **8** (0.15 mmol, 1.0 equiv), **9** (0.30 mmol, 2.0 equiv) in 1 mL dioxane at 120 °C for 12−18 h under Ar. Isolated yields after chromatography. Values in parentheses indicate the C7:C2:C3 ratios, which were determined by GC-MS. [b]Using **9** (0.45 mmol, 3.0 equiv), Ag_2O (0.45 mmol, 3.0 equiv).

With the best conditions in hand, we examined the scope of this C−H arylation reaction (Table 3). Cross-coupling reactions of **8a** with a broad range of electron-rich and -poor arylboronic acids were first examined. Arylboronic acids containing methyl groups on the aryl ring at *meta* and *para* positions afforded the desired

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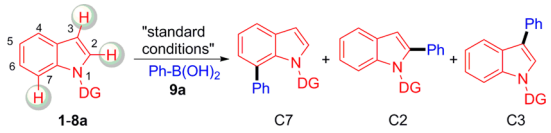
Table 4. Evaluating Different Directing Groups[a]



entry	DG	substrates	C7:C2:C3[b]	yield (%)[c]
1	Ac	**1**	0:0:100	0 (16)
2	Piv	**2**	0:0:100	0 (7)
3	$CONMe_2$	**3**	0:73:27	0 (30)
4	pyrimidin	**4**	0:100:0	0 (32)
5	$P(O)Et_2$	**5**	-	decomp
6	$P(O)^iPr_2$	**6**	0:66:34	0 (29)
7	$P(O)^cHex_2$	**7**	34:52:14	26
8	$P(O)^tBu_2$	**8a**	96:0:4	82

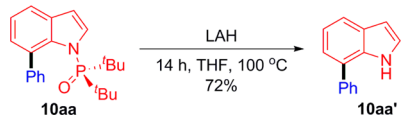
[a]Conditions: 10 mol% $Pd(OAc)_2$, 20 mol% **L6**, 0.5 equiv $Cu(OTf)_2$, 2.0 equiv Ag_2O, 1.0 equiv CuO, **1**−**8a** (0.15 mmol, 1.0 equiv), **9a** (0.30 mmol, 2.0 equiv) in 1 mL dioxane at 120 °C for 12 h under Ar. [b]The ratios were determined by GC-MS. [c]GC yield of the C7-selective products. Values in parentheses indicate the GC yield of the main products.

products in 70−75% yields with excellent C7 selectivity (**10ab**−**10ad**). *p*-Methoxy (**10ae**), -phenyl (**10af**), -fluoro (**10ag**, with crystal structure), -chloro (**10ah**), -bromo (**10ai**), -trifluoromethyl (**10aj**, with crystal structure), -trifluoromethoxy (**10ak**), and *meta*-ester (**10al**) groups were well tolerated, and the corresponding products were isolated in 41−68% yields with consistently high regioselectivity. In addition, 2-naphthaleneboronic acid was also compatible, affording the C7-selective product **10am** in 72% yield. It is noted that an arylboronic acid with an *ortho* substituent such as **9n** gave a lower yield (**10na**) with poor C7 and C3 selectivity, implying that the sterically hindered C7 position is sensitive to the steric properties of the arylboronic acid partner. The scope of the indole substrates was next explored using **9a** as the coupling partner. Various substituents at the 3-, 4-, 5-, and 6-positions on the indole framework are well tolerable. Reactions of indoles containing methyl (**10ba**−**10da**), methoxy (**10ea**), fluoro (**10fa**), chloro (**10ga**), ester (**10ha**, with crystal structure), and acyl (**10ia**) groups all afforded the corresponding 7-arylindoles in moderate to excellent yields with excellent regioselectivity.

To confirm the importance of the sterically hindered $P(O)^tBu_2$ moiety for the high C7 selectivity, we conducted control experiments under the optimized reaction conditions (Table 4). Indoles bearing *N*-directing groups such as **1**−**4** afforded a mixture of the expected C2 and C3 arylation products. We next evaluated the influence of the steric hindrance of substituents on phosphinoyl groups. We observed that the catalyst in conjunction with $P(O)Et_2$ (**5**) and $P(O)^iPr_2$ (**6**) could not form any C7-selective products, but C−H arylation of substrate **7** involving a $P(O)^cHex_2$ moiety provided the desired product with 34% C7 selectivity. These results indicate that, although the ligand **L6** can promote C7 selectivity, the sterically hindered $P(O)^tBu_2$ moiety is a prerequisite for achieving high levels of regioselectivity. The *N*-$P(O)^tBu_2$ DG can be easily removed by treatment of **10aa** with lithium aluminum hydride to give the unprotected indole **10aa′** in 72% yield (Scheme 2).

This findings should also enable the use of this $P(O)^tBu_2$ moiety for other types of cross-coupling. To illustrate this point, indole substrate **8a** was subjected to oxidative Heck reaction

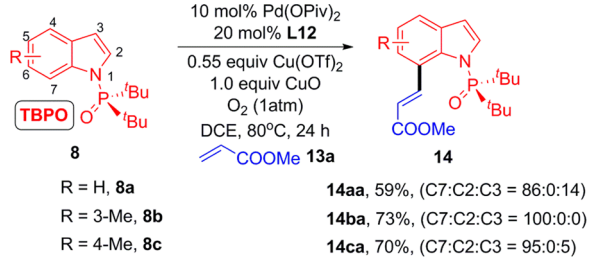
Scheme 2. Removal of the Directing Group[a]



[a]LAH = lithium aluminum hydride.

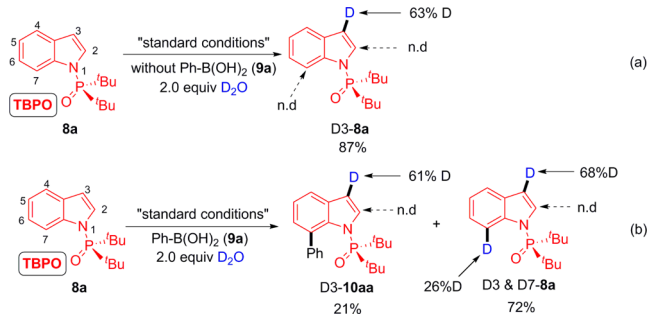
conditions.[15,16] We found that using methyl acrylate (**13a**) as the coupling partner with indoles **8a**−**8c** in the presence of $Pd(OPiv)_2$ as the catalyst with **L12** as the ligand afforded the desired C−H olefination products **14aa**−**14ca** in 59−73% yields with excellent C7 regioselectivity (Scheme 3).

Scheme 3. C7-Selective C−H Olefination of Indoles



To gain insight into the mechanism and regioselectivity of these reactions, deuteration experiments were carried out. Significant deuteration occurred at the C3 position only when the reaction was carried out with D_2O in the absence of **9a** (Scheme 4a). The

Scheme 4. Deuterium Labeling Experiments



same experiment was also run in the presence of 2.0 equiv **9a** and stopped after 12 h; 21% of D3-**10aa** and 72% D3/D7-**8a** were isolated (Scheme 4b). Analysis by ^1H NMR showed 68% and 26% deuterium incorporation at the C3 and C7 positions, respectively, in recovered **8a**. These results suggested that the initial Pd^{II} species may transmetalate with boronic acid first,[17] and then C−H activation at the C7 position of **8a** could occur reversibly with the assistance of the $P(O)^tBu_2$ group.

In summary, we have reported the first Pd(II)-catalyzed C7-selective C−H arylation of indoles with the aid of a sterically hindered and removable *N*-$P(O)^tBu_2$ directing group. This novel catalytic system can override *ortho*-directing effects as well as electronic 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. The development of new cross-coupling reactions and mechanistic investigations are the subjects of ongoing research in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11569.

Experimental procedures, characterization data, and spectra of new compounds (PDF)

X-ray crystal structures of **5**, **8a**, **10aa**, **10ag**, **10aj**, and **10ha** (CIF)

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Notes

The authors declare no competing financial interest.

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