Regioselectivity

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Regiocontrolled Direct C–H Arylation of Indoles at the C4 and C5 Positions

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Abstract: *An effective and practical strategy has been established for the direct and site-selective arylation of indoles at the C4 and C5 positions with the aid of a readily accessible, cheap, and removable pivaloyl directing group at the C3 position. This transformation shows good functional-group tolerance and could serve as a powerful synthetic tool for the synthesis of medicinally relevant compounds. This method and those developed in previous research together enable the regiocontrolled direct arylation of indole at each C–H bond without prefunctionalization of the reactive sites.*

The indole motif is a ubiquitous feature of bioactive natural products and an important structural element in pharmaceutical applications.[1] Consequently, there is continuing interest in reactions that enable the C–H functionalization of indoles. There are six C–H bonds in the indole motif that can be functionalized: positions C2 and C3 (pyrrole core), and C4–C7 (benzene core). However, these C–H bonds are inequivalent, and it is quite difficult to access each of them regioselectively. During the past decade, great effort has been devoted to the transition-metal-catalyzed C–H functionalization of indoles at the C2 and C3 positions.[2] The implicit challenge of a developing a strategy for the direct functionalization of C–H bonds on the benzene core rather than the pyrrole core is evident.[3]

Although traditional cross-coupling methods, namely, Suzuki, Negishi, and Stille coupling reactions, have been widely utilized to build aryl–indolyl bonds at each position of indoles in the total synthesis of natural products,[4] direct arylation is undoubtedly the most desirable route. The direct site-selective arylation of indoles at the C3 and C2 positions has been well developed (Figure 1 A).[5] The introduction of a directing group on the N atom has been used as a reliable strategy to ensure direct C2 selectivity. Recently, we achieved a major breakthrough by introducing an aryl group at the C7 position of the indole.[6] The key to this success was the appropriate choice of a *N*-P(O)^{t}Bu$_2$ directing group for C7 selectivity with a palladium-catalyzed system. On the basis of this directing group, we also disclosed a copper-catalyzed direct arylation of indoles at the C6 position (Figure 1 B).[7] Until now, only direct arylation at the C4 and C5 positions of indoles remained unsolved. We speculated that simple indole building blocks could form the starting point for a strategy that would involve the convenient introduction and removal of a directing group to append aryl substituents at C4 and C5 positions. Herein, we show that the installation of a suitable directing group at the C3 position of indoles enables direct arylation at the C4 and C5 positions in a straightforward manner (Figure 1 C).

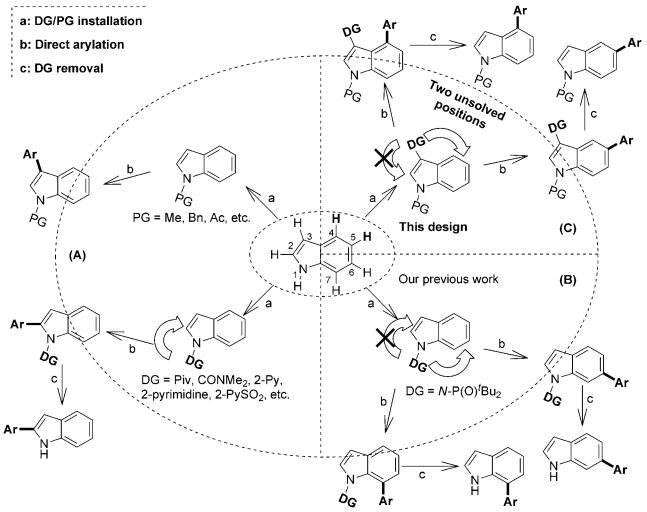

Figure 1. Regioselective direct arylation of indoles at each position. Bn = benzyl, DG = directing group, PG = protecting group, Py = pyridine.

Typically, an *N*-pivaloyl substituent is a good directing group for C2 selectivity in the functionalization of indoles.[5g] Recently, rhodium- and iridium-catalyzed direct C–H olefination[3h] and amidation reactions[3i–k] of *N*-pivaloylindoles at the C7 position have also been developed. We considered that a bulky pivaloyl group at the C3 position of indoles might also promote C4 and C5 selectivity. With $AlEt_2Cl$ in dichloromethane (DCM)[8a] or just by the use of hexafluoro-2-propanol (HFIP)[8b] as a solvent, a pivaloyl group can be selectively installed at the C3 position by a Friedel–Crafts acylation process. To begin our investigation, we synthesized the C3-pivaloyl-substituted indoles **2a**, **2a′**, and **2a″** [Eq. (1)].

We first investigated the reaction of *N*-benzyl-3-pivaloylindole (**2a**) with iodobenzene (**3a**; Table 1). When the reaction was carried out with $Pd(OAc)_2$ (5 mol%) in HFIP at 80 °C, we indeed observed the C4-arylation product **6aa**, which was formed in 12% yield along with the by-product **5aa** (5% yield; Table 1, entry 1). Remarkably, in the presence of the oxidant Ag_2O (1.2 equiv), the yield of **6aa** was improved

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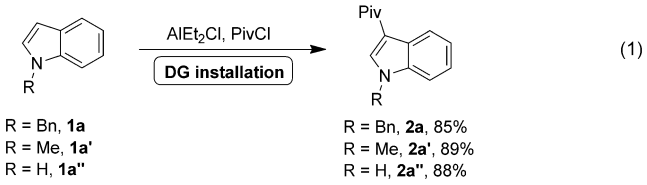
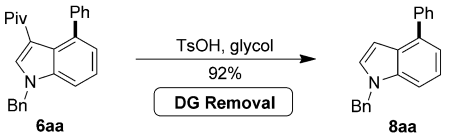


(1)

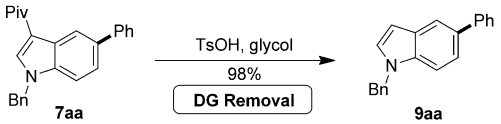
to 54%, and the arylation proceeded with high regioselectivity (entry 2). $[Pd(PPh_3)_2Cl_2]$ was a very effective catalyst, providing the desired product in 64% yield with an encouraging level of C4 selectivity (C2/C4/C5 1:64:0; entry 3). Further screening of additives showed that they had a significant influence. When both 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 4 Å molecular sieves (MS) were added, the reaction gave **6aa** in 86% yield with excellent C4 selectivity (Table 1, entries 4 and 5).

Interestingly, the diaryliodonium salt[9] Ph_2IOTf (**4a**) was also very effective as an arylation reagent, resulting in 82% yield with 1:82:0 C2/C4/C5 regioselectivity (Table 1, entry 6). With this reagent, we found that changing the oxidant to CuO led to a lower yield of **6aa** (entry 7). Gratifyingly, the regioselectivity was tuned to the C5 position in the nonpolar solvent DCM (C2/C4/C5 3:0:35; entry 8). Examination of the catalytic system revealed that $[Pd(PPh_3)_2Cl_2]$ and the additives were not necessary for this C5 arylation (entry 9), and a catalytic amount of CuO (10 mol%) was enough to furnish **7aa** in 42% yield at 40°C (entry 10).[10] An immediate improvement in the C5 arylation was observed when copper(I) thiophene-2-carboxylate (CuTc) was used as the catalyst (64% yield; entry 11). The addition of the base 2,6-di-*tert*-butylpyridine (dtbpy; 1.0 equiv) led to the formation of **7aa** in 80% yield with complete regioselectivity (Table 1, entry 12). Other copper sources, such as CuCl and $Cu(OTf)_2$, were also found to be effective in this reaction, although lower reactivity was observed (entries 13 and 14).

We found that the pivaloyl group could be readily removed from the two products **6aa** and **7aa** by a reverse Friedel–Crafts reaction in the presence of *p*-toluenesulfonic acid and glycol to give **8aa** and **9aa** in 92 and 98% yield, respectively [Eqs. (2) and (3)]. The ready removal of the directing group from the products under mild reaction conditions demonstrates the full synthetic utility of this method.



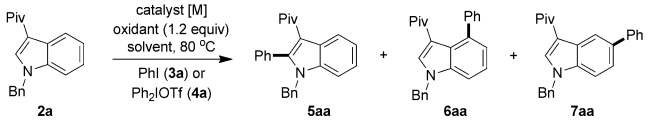
(2)



(3)

We next explored the scope of the direct C4 arylation under the optimized conditions (Table 2). Cross-coupling reactions of indole **2a** with a broad range of aryl iodides were first examined. Iodoarenes containing a methyl group on the aryl ring at *ortho*, *meta*, and *para* positions afforded the desired products **6ab–ad** in 72–83% yield. The regioselectivity profile of this method was nicely illustrated by the fact that methoxy- (product **6ae**), phenyl- (product **6af**), and ester-substituted substrates (product **6ag**), as well as those containing fluoro groups (products **6ah–aj**), could all be accommodated equally well. In particular, chloro- and bromo-substituted aryl iodides were very effective substrates (products **6ak–am**), thus highlighting the potential of this process in combination with further conventional cross-coupling transformations. With iodobenzene (**3a**) as the coupling partner, reactions of indoles with methyl (product **6ba**), methoxy (product **6ca**), phenyl (product **6da**), fluoro (product **6ea**), chloro (product **6fa**), and bromo substituents (product **6ga**) afforded the corresponding 4-aryl indoles in moderate to excellent yields. Among these substrates, the C5-

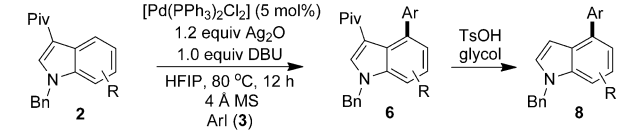
Table 1: Reaction development.[a]



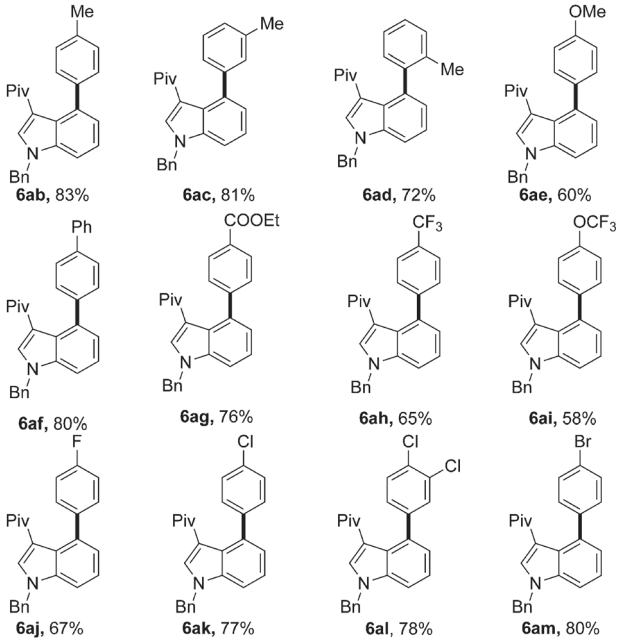
Entry	Catalyst [M] (mol%)	3/4	Oxidant	Solvent	Yield [%][b]		
					5aa	6aa	7aa
1	$Pd(OAc)_2$ (5)	**3a**	–	HFIP	5	12	0
2	$Pd(OAc)_2$ (5)	**3a**	Ag_2O	HFIP	3	54	0
3	$[Pd(PPh_3)_2Cl_2]$ (5)	**3a**	Ag_2O	HFIP	1	64	0
4[c]	$[Pd(PPh_3)_2Cl_2]$ (5)	**3a**	Ag_2O	HFIP	0	78	0
5[c,d]	**$[Pd(PPh_3)_2Cl_2]$ (5)**	**3a**	**Ag_2O**	**HFIP**	**0**	**86 (84)**[e]	**0**
6[c,d]	$[Pd(PPh_3)_2Cl_2]$ (5)	**4a**	Ag_2O	HFIP	1	82	0
7[c,d]	$[Pd(PPh_3)_2Cl_2]$ (5)	**4a**	CuO	HFIP	2	13	1
8[c,d]	$[Pd(PPh_3)_2Cl_2]$ (5)	**4a**	CuO	DCM	3	0	35
9	–	**4a**	CuO	DCM	4	0	48
10[f]	CuO (10)	**4a**	–	DCM	4	0	42
11[f]	CuTc (10)	**4a**	–	DCM	1	0	64
12[f,g]	**CuTc (10)**	**4a**	**–**	**DCM**	**0**	**0**	**80 (74)**[e]
13[f]	CuCl (10)	**4a**	–	DCM	3	0	58
14[f]	$Cu(OTf)_2$ (10)	**4a**	–	DCM	3	0	55

[a] Reaction conditions: **2a** (0.20 mmol), **3a** (0.40 mmol) or **4a** (0.28 mmol), solvent (1.0 mL), 12 h, 80°C, Ar atmosphere. [b] Yields were determined by GC analysis of the crude reaction mixture. [c] The reaction was carried out with DBU (1.0 equiv). [d] The reaction was carried out with 4 Å MS (200 mg). [e] The yield of the isolated product is given in parentheses. [f] The reaction was carried out at 40°C. [g] The reaction was carried out with dtbpy (1.0 equiv). Tf = trifluoromethanesulfonyl.

Table 2: Direct arylation of indoles at the C4 position.[a]



Variation of the arene:



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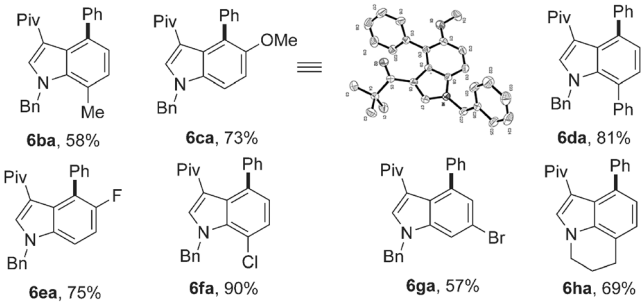

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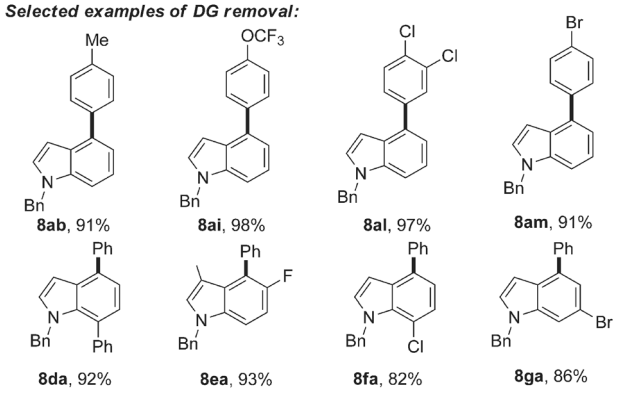


[a] Reaction conditions I: **2** (0.20 mmol), **3** (0.40 mmol), $[Pd(PPh_3)_2Cl_2]$ (5 mol%), Ag_2O (1.2 equiv), DBU (1.0 equiv), 4 Å MS (200 mg), HFIP (1.0 mL), 80 °C, 12 h, Ar atmosphere.

substituted indoles **2c** and **2e** with the steric effect of a substituent adjacent to the C4 position also delivered the coupled products **6ca** and **6ea** in good yields. Furthermore, lilolidine derivative **2h** was also compatible with the reaction conditions and afforded the desired product **6ah** in 69% yield.

We then tested the generality of directing-group removal. The selected substrates bearing various substituents on the aromatic ring such as methyl (product **8ab**), trifluoromethoxy (product **8ai**) and halides (products **8al**, **8am**, **8ea**–**ga**) were tolerated, and the corresponding products were obtained in good to excellent yields.

We next examined the scope of the arylation reaction with diaryliodonium triflate salts, which ensured high regioselectivity for the formation of 5-aryl indoles (Table 3). A wide range of diaryliodonium triflate salts incorporating electron-donating and electron-withdrawing substituents at the *meta* and *para* positions were effective C5-arylation reagents (products **7ab**, **7ac**, **7ae**–**am**). However, the *ortho*-methyl-substituted aryl derivative **4d** could not generate the corresponding arylation product **7ad**, thus implying that increased steric congestion affects reactivity. Regarding the indole framework, various substituents at the C6 and C7 positions were tolerated well (Table 3, products **7ba**–**ha**). We also successfully removed the directing group from selected products (Table 3).

To confirm the importance of the sterically demanding pivaloyl moiety for this high regioselectivity, we conducted some control experiments under the optimized reaction conditions (Figure 2). Indoles bearing smaller directing groups at the C3 position, such as formyl (substrate **2a-I**),[11] acetyl (substrate **2a-II**), and isobutyryl substituents (substrate **2a-III**), underwent C4 and C5 arylation in lower yield. We also evaluated the influence of the indole N-protecting group. As compared to the *N*-benzylindole **2a**, *N*-methylindole **2a′** underwent C4 arylation in slightly higher yield and C5 arylation in lower yield. Even the unprotected indole **2a″** gave the C5-arylation product in modest yield, although the corresponding C4-arylation product was not detected. However, for **2a‴** with *N*-Ts protection, no product of either C4 or C5 arylation was observed. These results indicated that when the sterically hindered pivaloyl substituent is used as a directing group, an *N*-Bn- or *N*-Me-type protecting group is

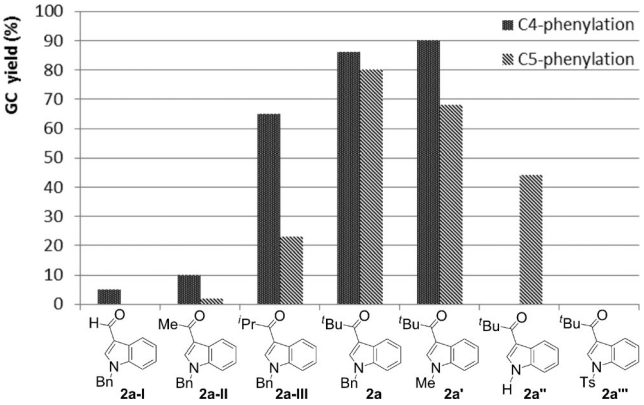
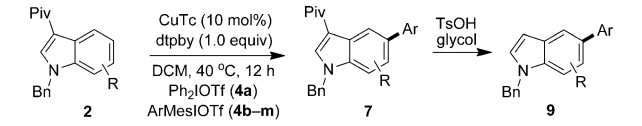


Figure 2. Evaluation of different directing and N-protecting groups.

Table 3: Direct arylation of indoles at the C5 position.[a]



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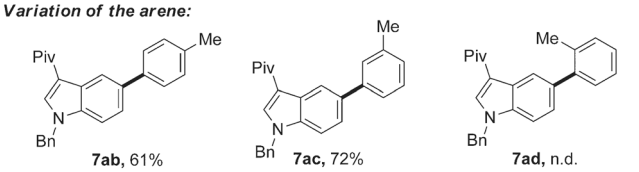

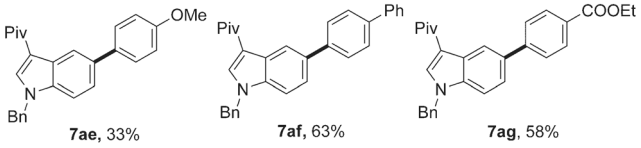

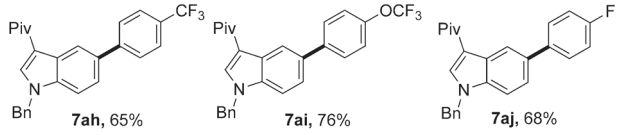

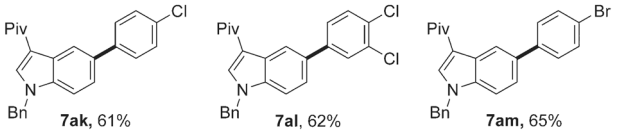

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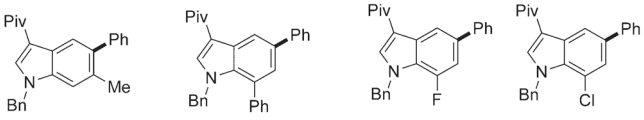

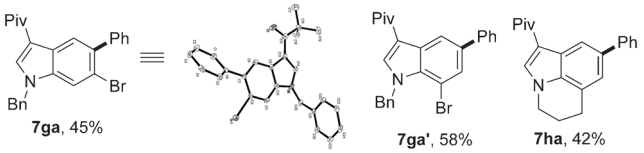

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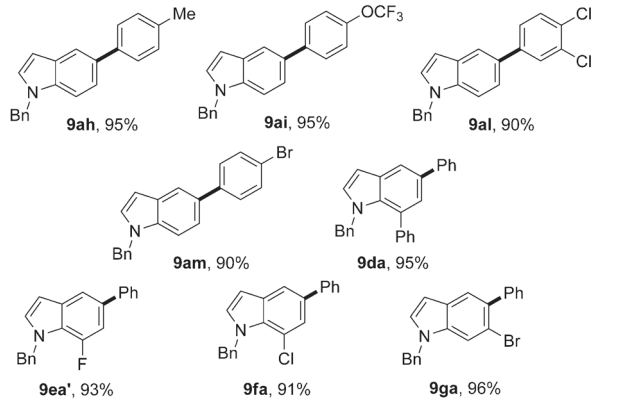
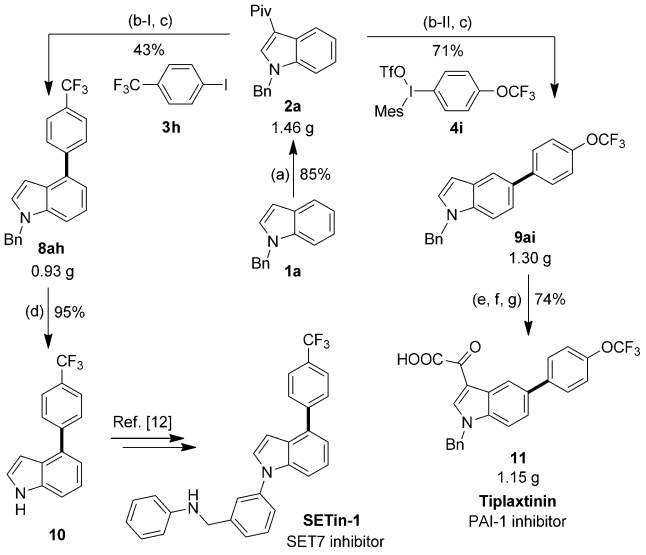


[a] Reaction conditions II: **2** (0.20 mmol), **4** (0.28 mmol), CuTc (10 mol%), dtpby (0.20 mmol), DCM (1.0 mL), 40 °C, 12 h, Ar atmosphere.

a prerequisite for achieving high levels of C4 and C5 regioselectivity.

Our approach clearly enables the rapid and modular construction of C4- and C5-arylated products from simple and available indole substrates with minimal prefunctionalization. To demonstrate the synthetic importance of the present protocol, we targeted the key intermediate in the synthesis of two potent inhibitors, SETin-1[12] and tiplaxtinin,[13] in which aryl groups are located at the indole C4 and C5 position, respectively (Scheme 1). The reaction of indole **2a** on a 5.0 mmol scale with aryl iodide **3h**, followed by removal of the protecting group, gave **8ah** (0.93 g) in 43% yield; **2a** and **4i** generated **9ai** (1.30 g) in 71% yield. Compound **8ah**



Scheme 1. Synthesis of two inhibitors from one substrate. Reagents and conditions: a) PivCl, $AlEt_2Cl$, DCM, 0 °C; b-I) **3h**, $[Pd(PPh_3)_2Cl_2]$, Ag_2O, DBU, 4 Å MS, HFIP, 80 °C; b-II) **4i**, CuTc, dtpby, DCM, 40 °C; c) TsOH, glycol, 100 °C; d) KO^{t}Bu, O_2, DMSO, RT; e) Oxalyl chloride, THF; f) MeOH; g) KOH, acetone, water, HCl. DMSO = dimethyl sulfoxide.

can be further converted into the SET inhibitor SETin-1 through several known steps, whereas the sequential treatment of **9ai** with oxalyl chloride, MeOH, and KOH gave tiplaxtinin (**11**; 1.15 g) in good yield.

We propose two catalytic cycles to account for the selectivity of the arylation reactions (Figure 3). In the palladium catalysis, Pd^{II} coordinates to the pivaloyl group of the substrate, followed by 1) C–H activation at the indole C4 position, 2) oxidative addition by ArI, 3) reductive elimination to give C4-arylation products, and 4) regeneration of the active Pd^{II} species by Ag_2O (Figure 3, left).[14] In the copper catalysis, the reaction may proceed through the following steps: 1) oxidative addition of the diaryliodonium salt to CuTc to afford the Cu^{III} species, 2) coordination of the pivaloyl group, 3) aryl migration to the C5 position via a Heck-type four-membered-ring transition state, and 4) E2-type elimination to deliver the product and regenerate the active Cu catalyst (Figure 3, right).[15]

In summary, we have reported the C4- and C5-selective direct arylation of indoles with the aid of a readily accessible,

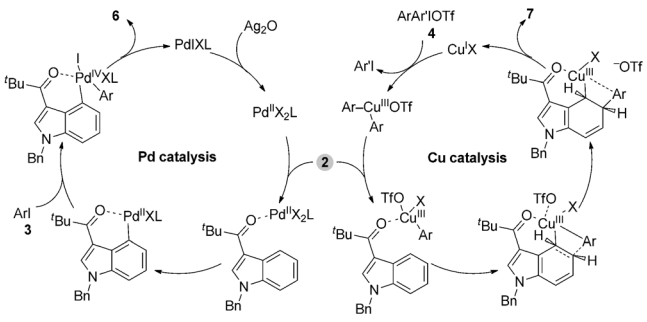


Figure 3. Proposed catalytic cycles.

cheap, and removable pivaloyl directing group installed at the C3 position. This method complements our previously developed methods for C7 and C6 direct arylation and mature reactions for direct arylation at C2 and C3, so that now a simple indole can be selectively arylated at each C–H bond without prefunctionalization of the reactive sites. Current studies are focused on the development of further cross-coupling reactions at the benzene core of indoles.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arylation · copper · indoles · palladium · regioselectivity

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Communications

Regioselectivity

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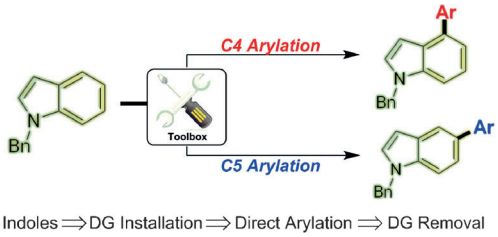
Regiocontrolled Direct C–H Arylation of Indoles at the C4 and C5 Positions



Grand Slam: An effective and practical strategy has been established for the direct site-selective arylation of indoles at the C4 or C5 position (see scheme) by the use of a readily available and removable pivaloyl directing group (DG) at the indole C3 position. Now the direct site-selective arylation of indoles at any given C–H bond is possible by the appropriate choice of this or a previously developed complementary method.