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Transition Metal-Free C3 Arylation of Indoles with Aryl Halides

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Abstract

Herein, we report an unprecedented transition metal-free, coupling of indoles with aryl halides. The reaction is promoted by KO*t*Bu and is regioselective for C3 over nitrogen. The use of degassed solvents devoid of oxygen is necessary for the success of the transformation. Preliminary studies implicate a hybrid mechanism that involves both aryne intermediates and non-propagative radical processes. Electron transfer is also a distinct possibility. These conclusions were substantiated by EPR data, isotopic labeling studies, and the use of radical scavengers and electron transfer inhibitors.

Graphical Abstract

Metals? What metals? Regioselective transition metal-free cross-coupling of aryl halides with indoles at C3 has been reported. The reaction proceeds through an unusual hybrid radical/aryne mechanism.

Keywords

indole; transition metal-free; cross-coupling; radical; aryne

Indoles with aromatic substituents at C3 are an important class of compounds, many of which possess potent biological activity. For instance, fluvastatin is an FDA-approved HMG-CoA reductase inhibitor that is used in the clinic for lowering LDL cholesterol.[1] Other C3 arylated indoles exhibit pico- to nanomolar inhibitory actions against a wide range of biological targets and processes such as the progesterone receptor,[2] COX-II enzyme,[3] carbonic anhydrase I and II,[4] and tubulin polymerization,[5] etc.

The direct introduction of aromatic groups onto an extant indole nucleus at C3 is typically carried out by transition metal-catalyzed cross-coupling reactions (Figure 1).[2,6–14] Methods utilizing C–H activation have also been reported.[15–18] While transition metal-free

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processes are rare, they have been accomplished through the use of hypervalent iodine reagents,[19–21] diazonium salts,[22] or by means of electrochemistry.[23–25]

Our group has a longstanding interest in the reaction of indoles and related heterocycles.[26–29] Herein, we disclose a new approach for the intermolecular C3 arylation of unprotected indoles with simple aryl halides. The reaction is promoted by KO*t*Bu and does not require the use of transition metal catalysts. Preliminary mechanistic investigations point towards an unusual hybrid reaction pathway that exhibits features of *both* radical and aryne intermediates. Although Daugulis and Tu have reported a limited number of base-promoted C2- and N-selective arylation reactions of indoles,[30–32] there appear to be very few precedents for C3-selective variants[32,33] and none that proceed by the proposed hybrid radical/aryne mechanism.

Optimization studies were carried out on the reaction between indole (**1a**) and iodobenzene (Table 1). A brief solvent survey identified DMF and DMSO as the only effective solvents (entries 1–5). A reaction performed in the dark resulted in similar yield and selectivity (entry 7 vs 5). Importantly, we observed that *the use of degassed solvents is critical to the success of the reaction*. Failure to degas the solvent, or the use of DSMO that was saturated with O_2, resulted in the formation of little to no **2a** (entry 8, 9 vs 5). Interestingly, for both entries 8 and 9 the N-arylated product **3a** was still formed. Moreover, KO*t*Bu is the only base that was effective (entry 10–12 vs 5). Bromobenezene and chlorobenzene were less efficient while the use of fluorobenzene and phenyltriflate gave only small amounts of **3a** (entries 13–16 vs 5). In each case, the desired product **2a** was isolated along with varying amounts of **3a**.

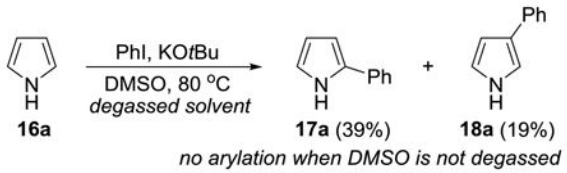
Table 2 describes the scope of the arylation reaction with respect to the aryl halide. This method is compatible with alkoxy, nitro, and amine functional groups (entries 2–3, 7–9) as well as heterocyclic aryl halides (entries 4, 6). For all entries in which meta-substituted aryl halides were used (entries 2–5, 8, 11), we observed only ipso substituted products (>95:5 meta vs all others). In contrast, the use of *ortho*-iodoanisole and *ortho*-iodotoluene resulted in cine substitution for both substrates, giving once again the meta isomer as the major product (>95:5 meta vs all others; entries 7, 10). The use of para-substituted and benzofuranyl-based compounds furnished mixtures of regioisomers with respect to the aryl halide (entries 6, 9, 12). These regioselectivities are consistent with the aryne distortion model espoused by Garg and Houk.[34,35] With the exception of nitro, naphthyl, and benzofuran-derived aryl halides, the reactions were accompanied by various amounts of N-arylated products that were readily removed by standard silica flash chromatograph. The reaction carried out on a 1.2 g scale also proceeded as expected (entry 1b). We cannot rule out the possibility that some lower yielding entries are due, in part, to the reaction between DMSO and arynes.[36,37]

The formation of cine substitution products (entries 7, 9–10, 12) is indicative of a pathway involving aryne intermediates. Notably, this data also precludes the possibility that the arylation is catalyzed by trace metal impurities since cross-coupling reactions promoted by transition metals would be expected to give exclusively ipso-substituted products. Further evidence of arynes was obtained when, under optimized conditions, we were able to trap the putative benzyne intermediate generated from PhI with either 3,4-dimethoxy phenol or

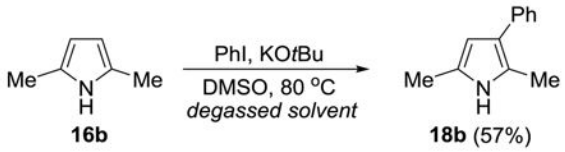
morpholine to give diphenyl ether and *N*-phenylmorpholine, respectively. Finally, a control experiment utilizing 2-(TMS)phenyltriflate plus CsF to generate benzyne, in the presence of indole, KO*t*Bu and degassed DMSO, resulted in none of the desired C3 or N-arylated products.

We then explored the scope of the reaction with respect to the indole coupling partner. Table 3 demonstrates that the method is tolerant to alkyl, alkoxy, and boron substituents on the 2, 5, and 7-positions of indole. The reaction of **1g** furnished pinacol boronate ester **2n** (entry 6), which we anticipate can be used as a handle for further functionalization. Attempts with 7-azaindole afforded only the N-arylation product. Other groups like –CN, –OH, $–NH_2$ on indole or Ar–X were not compatible.

As illustrated in Eq 1 and 2, the reaction is also amenable to the use of pyrroles. As before, the use of oxygen-free DMSO is critical since failure to degas the solvent lead to recovery of pyrrole but complete consumption of PhI. These results represent a significant departure from the literature in which both Wittig and Larock report that pyrroles react with arynes by (4+2) cycloaddition.[38–40]



(Eq 1)



(Eq 2)

We then demonstrated the synthesis of C3-arylated–N-alkylated products **2o**–**p** in a single pot by means of sequential arylation followed by quenching with either MeI or BnBr, respectively (Scheme 1). This transformation constitutes a three-component coupling reaction in which each starting material can be independently varied. We expect that this method can be used to rapidly generate diverse libraries of C3-arylated, N-alkylated indolyl compounds for use in fragment-based drug discovery programs.[41]

Performing the reaction in deuterated DMSO provided some insight into the mechanism. As shown in Scheme 2, the use of degassed DMSO-D_6 as solvent resulted in approximately 76% deuterium incorporation at the position indicated in **19**. This may arise as a result of deuterium abstraction from the solvent by either radical **20** or carbanion **21**.

Moreover, the necessity of using oxygen-free solvents led us to suspect the involvement of free radicals. An EPR experiment carried out on a frozen aliquot of an incomplete reaction between **1a** and PhI confirmed the presence of free radicals.[42] From our calculations, the g factor of the cross-over point of the peak was found to be 2.002, which is diagnostic of the free radical nature of an unpaired electron (Figure 2). EPR experiments on the following control reactions: 1) indole + KO*t*Bu in DMSO, and 2) PhI + KO*t*Bu in DMSO did not lead to any detectable signals, indicating the intermediacy of radical species only in the presence of all three reaction components.

The addition of radical scavengers such as galvinoxyl and TEMPO (Table 4, entry 1 and 2) resulted in moderate but noticeably lower yields of **2a**. The partial inhibitory effect of radical scavengers suggests that while radical intermediates are involved, the overall reaction may proceed by a *non-chain* radical mechanism as described by Zhang and Liu et al.[43] As mentioned above, oxygen also appears to have a deleterious and concentration-dependent effect on the efficiency of C3 arylation (Table 1, entries 8–9, Eq 1 and 2). The fact that O_2 leads to greater amounts of N-arylated products is consistent with literature precedent.[30] In contrast, the electron transfer inhibitor *p*-dinitrobenzene, completely suppresses C3 arylation (Table 4, entry 4), with only minimal amounts of N-arylated product formed. This result strongly implicates the role of electron transfer processes in the reaction mechanism.

Because arynes are not typically sensitive to oxygen, our data is suggestive of a mechanism that is more complex than the polar reaction between indoles and arynes.[44] There is a growing body of literature in which KO*t*Bu plus associated ligands are capable of promoting transition metal-free cross-coupling reactions between arenes and aryl halides.[45–57] Computational[58,59] and empirical studies implicate radical intermediates and electron transfer processes. While the findings from these reports may, in part, be applicable to our work, the formation of cine substitution products in the title reaction necessitates that aryne intermediates be considered alongside. Although we do not know the precise mechanism by which this reported arylation proceeds, nor can we exclude the possibility of competing pathways, the available data points towards the involvement of both aryne and either radical species and/or electron transfer processes.

In conclusion, we have described the transition metal-free, regioselective arylation of indoles at C3 with aryl halides. The reaction is promoted by KO*t*Bu and the use of degassed solvent is critical. The yields and scope with respect to both the indole and aryl halide components are good. We also demonstrated that C-arylated, N-alkylated products can be produced in a one-pot transformation. This reaction is unusual in that mechanistic studies indicate the involvement of both aryne and radical intermediates.

Acknowledgments

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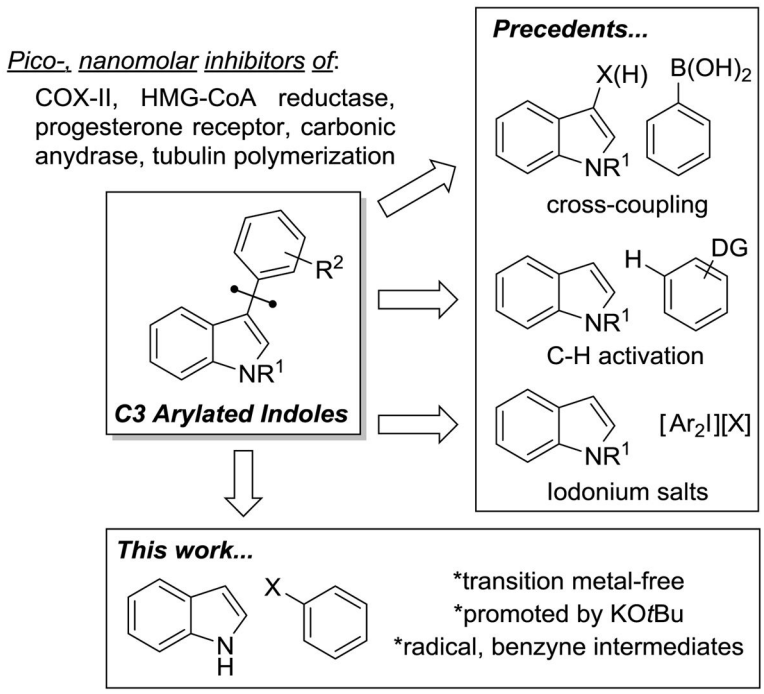


Figure 1.

Our method, and literature precedents for preparing C3 arylated indoles, highly potent biologically active compounds.

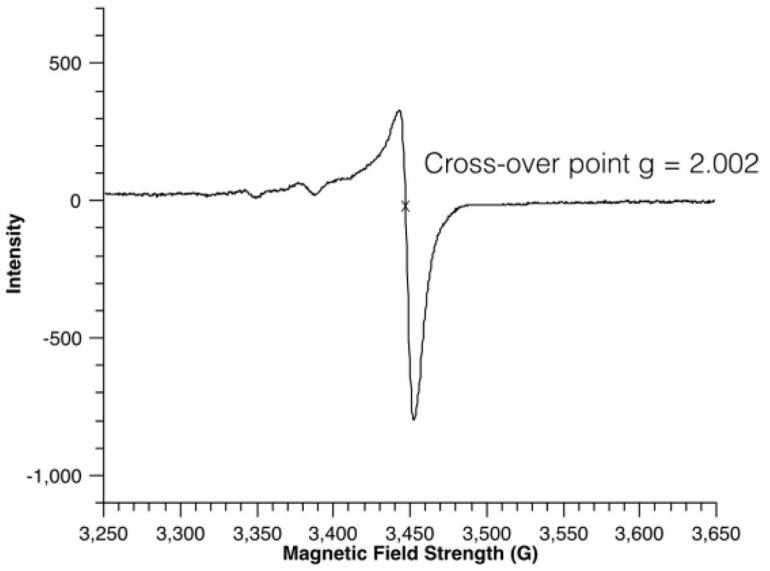
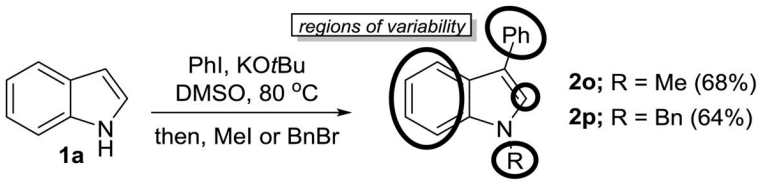
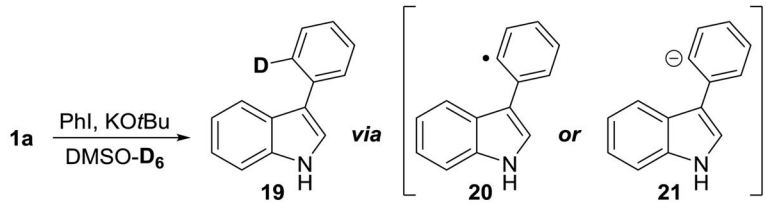


Figure 2.
EPR spectrum of arylation reaction between **1a** and PhI at 77 K.



Scheme 1.

Three-Component Coupling for Library Synthesis in Fragment-Based Drug Discovery



Scheme 2.
Isotopic-Labelling Studies

Table 1

Optimization Studies

Entry[a]	Ar–X	Base	Solvent	Temp (°C)	Yield (%)	
					2a	3a
1	PhI	KO*t*Bu	PhMe	80	0	0
2	PhI	KO*t*Bu	THF	60	0	0
3	PhI	KO*t*Bu	MeCN	80	0	0
4[b]	PhI	KO*t*Bu	DMF	80	58	17
5	PhI	KO*t*Bu	DMSO	80	70	11
6[c]	PhI	KO*t*Bu	DMSO	80	33	49
7[d]	PhI	KO*t*Bu	DMSO	80	63	18
8[e]	PhI	KO*t*Bu	DMSO	80	34	25
9[f]	PhI	KO*t*Bu	DMSO	80	0	39
10	PhI	NaO*t*Bu	DMSO	80	0	trace
11	PhI	KHMDS	DMSO	80	0	trace
12	PhI	LDA	DMSO	80	0	12
13	PhBr	KO*t*Bu	DMSO	80	64	15
14	PhCl	KO*t*Bu	DMSO	80	52	11
15	PhF	KO*t*Bu	DMSO	80	0	10
16	PhOTf	KO*t*Bu	DMSO	80	0	21

[a]Conditions: 2 equiv indole, 1 equiv aryl halide, 4 equiv KO*t*Bu [0.3] M, all solvents were rigorously degassed by freeze/pump/thaw.

[b]time = 24 h,

[c]Conditions: 1 equiv indole, 3 equiv aryl halide, 4 equiv KO*t*Bu, [0.3] M.

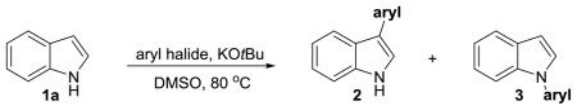
[d]Reaction in the absence of light.

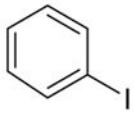
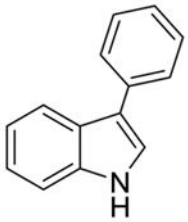
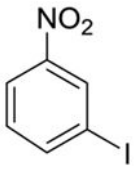
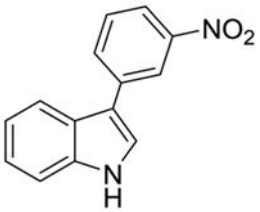
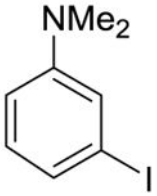
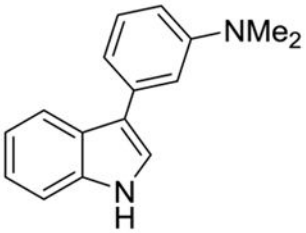
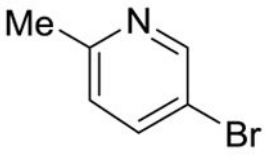
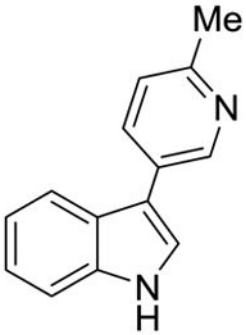
[e]solvent not degassed, N2 atmosphere,

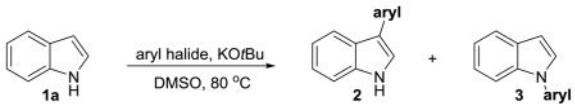
[f]solvent saturated with O_2, also O_2 atmosphere.

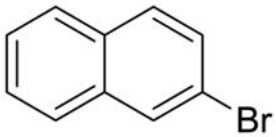
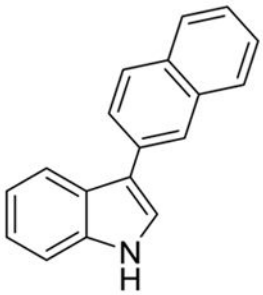
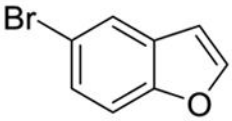
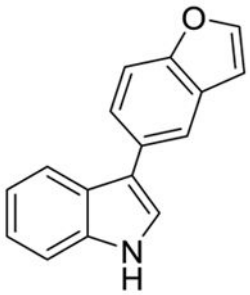
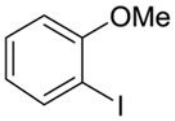
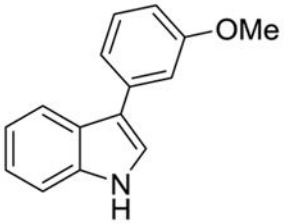
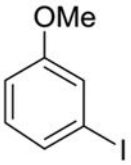
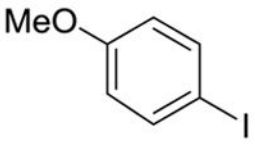
Table 2

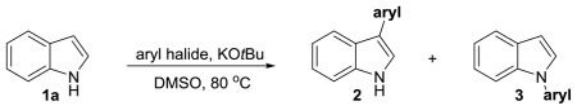
Scope of Aryl Halide

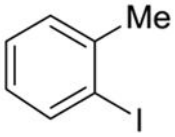
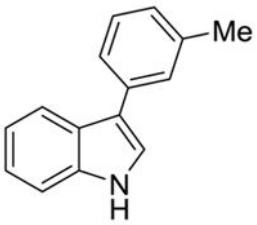
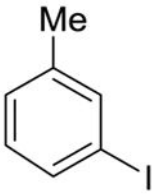
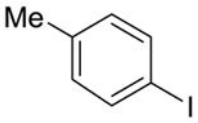


entry	Ar–X	product	% yield 2	% yield 3
1a	 **4**	 **2a**	70%	11%
1b			61% (**1.2 gram scale**)	14%
2	 **5**	 **2b**	47% (>95:5 meta/para)	not observed
3	 **6**	 **2c**	26% (>95:5 meta/para)	26%
4	 **7**	 **2d**	42% (>95:5 meta/para)	21%



entry	Ar–X	product	% yield 2	% yield 3
5	 **8**	 **2e**	44% (>95:5 meta/para)	not observed
6	 **9**	 **2f**	44% (3.5:1 C5/C4 on benzofuran)	not observed
7	 **10**	 **2g**	76% (>95:5 meta/para)	13%
8	 **11**	**2g**	68% (>95:5 meta/para)	14%
9	 **12**	**2g**	56% (1:1 meta/para)	14%

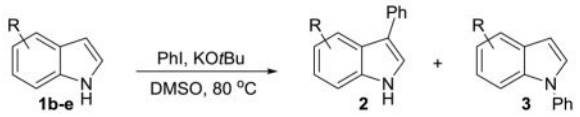


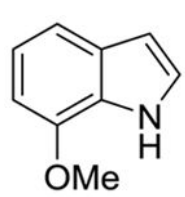
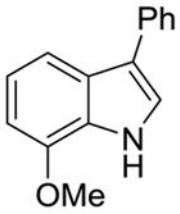
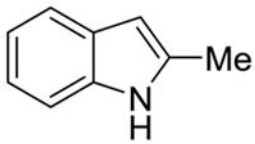
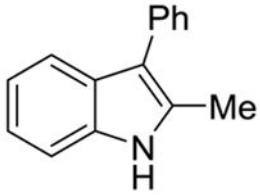
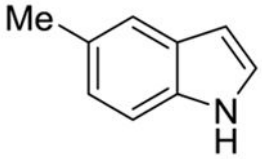
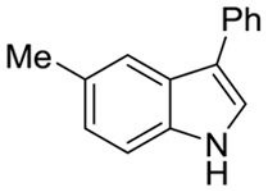
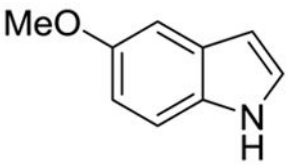
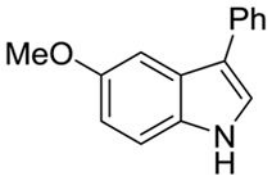
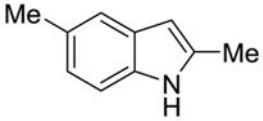
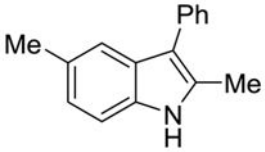
entry	Ar–X	product	% yield 2	% yield 3
10	 **13**	 **2h**	52% (>95:5 meta/para)	13%
11	 **14**	**2h**	59% (3.5:1 meta/para)	15%
12	 **15**	**2h**	40% (1:1 meta/para)	13%

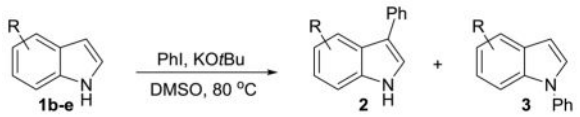
Conditions: 2 equiv indole, 1 equiv aryl halide, 4 equiv KO*t*Bu, in DMSO at 80 °C for 35 h. Percentages represent isolated yields.

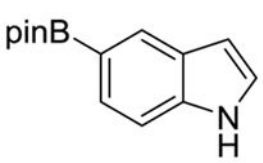
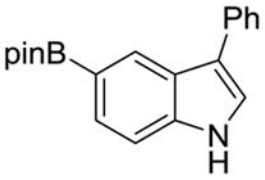
Table 3

Scope of Indole



entry	indole	product	% yield 2	% yield 3
1	 **1b**	 **2i**	66%	5%
2	 **1c**	 **2j**	47%	9%
3	 **1d**	 **2k**	51%	10%
4	 **1e**	 **2l**	70%	10%
5	 **1f**	 **2m**	64%	14%



entry	indole	product	% yield 2	% yield 3
6	 **1g**	 **2n**	61%	17%

Conditions: 2 equiv indole, 1 equiv PhI, 4 equiv KO*t*Bu

Table 4

Effect of Radical Scavenger and Electron Transfer Inhibitors as Additives.

Entry	Additive	% yield 2a	% yield 3a
1	None	70	11
2	TEMPO	52	23
3	galvinoxyl	45	18
4	1,4-dinitrobenzene	9	0

Reaction between **1a** and PhI under standard conditions. Isolated yields.