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Cu(II)-Catalyzed Direct and Site-Selective Arylation of Indoles Under Mild Conditions

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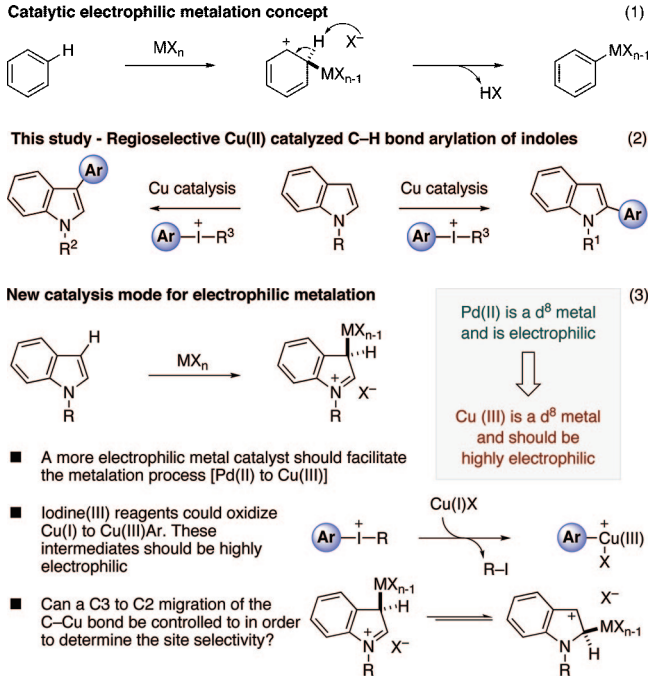
Transition-metal-catalyzed functionalization of hydrocarbons is emerging as a versatile strategy for chemical synthesis.[1] In particular, direct catalytic C−C bond formation events on arene motifs have led to many pioneering advances.[2] However, before the potential of C−H bond functionalization can be realized, these transformations will have to become more compatible with the delicate functionality that exists within more complex molecular architectures.[3] With this in mind, the development of direct metal-catalyzed transformations that operate under ambient and selective reaction parameters[2f,g] is an attractive goal for the advancement of chemical synthesis.

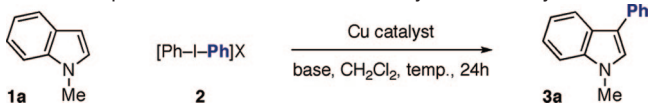
We have been engaged in the development of oxidative C−H bond functionalization programs that utilize electrophilic metal catalysts to induce C−H bond cleavage via a Friedel−Crafts-type process (1).[4,5] Herein, we describe a Cu(II)-catalyzed C−H bond arylation strategy that enables direct and site-selective indole functionalization. Indoles that display aryl groups at C2 and/or C3 have demonstrated importance in a range of therapeutics in addition to a prevalence in natural products.[6] This Cu(II)-catalyzed arylation process does not require prefunctionalization of the indole, operates under ambient conditions, uses equimolar amounts of the coupling partners, and is selective for either the C2 or the C3 position (2).



In line with an electrophilic metalation strategy, we have previously reported an oxidative and site-selective Pd(II)-catalyzed C−H bond alkenylation of the indole[5a] and pyrrole nuclei.[5b] Since these reports, a number of elegant examples of metal-catalyzed indole arylations have emerged.[7] However, it is notable that there are few examples where indole arylation proceeds under mild conditions. In these cases, the selective processes seemingly exploit a migratory mechanism to afford 2-arylindoles.[7a−c] These outcomes present a paradox to the conventional C3 reactivity of indole, and it has been surprising that few methods for C3-arylation[7h−j] *under ambient conditions* have emerged.

In considering a C−H arylation of indoles, we questioned whether this might be effected by utilizing highly electrophilic metal catalysts other than those based on Pd(II) salts.[7e] By analogy with other d^8 species, such as Pd(II) and Rh(I), we reasoned that other d^8-configured metals may enable C−H bond arylation (3). The realization that Cu(III) would also possess a d^8 configuration and carry a +3 charge should render it more reactive, in line with our electrophilic metalation hypothesis. Surprisingly, Cu-catalyzed C−H bond functionalization processes are rare,[8] but their use would offer an economic advantage compared to the more frequently used, but expensive, Pd complexes. Initially, we were encouraged by reports from Barton and co-workers who had described how Cu metal, in combination with aryl−Bi(V) reagents could affect C- and N-arylation reactions.[9] We reasoned that a Cu(I) catalyst could be oxidized in the presence of diaryl−iodine(III) reagents[10] to form a highly electrophilic aryl−Cu(III) intermediate that would enable a mild arylation process.[11]

Table 1. Optimization Studies for Cu-Catalyzed C−H Arylation



entry	catalyst	equiv of **1a**	equiv of **2**, (X)	base	temp, °C	C3:C2[b]	yield **3a** %
1	1 mol % $Cu(OAc)$	2	1.0 (BF_4)	−	rt	10:1	57
2	1 mol % $Cu(OAc)_2$	2	1.0 (BF_4)	−	rt	11:1	56
3	1 mol % $Cu(OAc)_2$	1	1.1 (BF_4)	dtbpy	35	4.5:1	14[a]
4	10 mol % $Cu(OAc)_2$	1	1.1 (BF_4)	dtbpy	35	3:1	57[a]
5	10 mol % $Cu(OTf)_2$	1	1.1 (BF_4)	dtbpy	35	12:1	69
6	10 mol % $Cu(OTf)_2$	1	1.1 (OTf)	dtbpy	rt	14:1	72

[a] Reaction conversion. [b] Determined by ^1H NMR.

At the outset of our studies, we were pleased to find that treatment of *N*-methyl indole **1a** with $[Ph−I−Ph]BF_4$ (**2a**) in the presence of 1 mol % of Cu(OAc) gave the arylated indole **3a** in moderate yield but good C3 selectivity under the mild conditions we were targeting (Table 1, entry 1). Interestingly, using $Cu(OAc)_2$ as catalyst also afforded the C3 product in almost identical yield and selectivity, and due to ease of handling, we chose to continue our studies with Cu(II) catalysts (entry 2). The moderate yields of **3a** arose from a competitive acid-catalyzed dimerization of the indole **1a**. A range of bases were screened in order to prevent this deleterious side reaction, and we found the use of 2,6-di-*tert*-butylpyridine (dtbpy) prevented indole dimerization, but at the expense of conversion (entry 3). In order to improve the conversion, 10 mol % of the Cu catalyst was required, presumably because the pyridine base binds to the Cu center and reduces its activity. Interestingly, on addition of dtbpy, the C3 selectivity for the arylation was greatly diminished (entries 3 and 4). However, we subsequently

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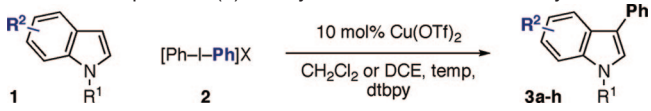
Table 2. Scope of Cu(II)-Catalyzed C3-Indole C−H Phenylation

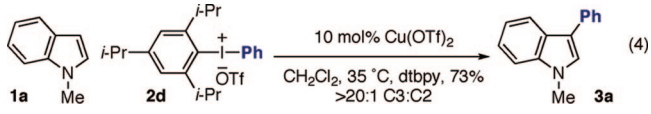


entry	R^1	R^2	X	temp, °C	isolated yield **3** %
1	Me	H	OTf	rt	72 (**3a**)
2	H	H	OTf	rt	74 (**3b**)
3	H	5-OMe	BF_4	rt	64 (**3c**)
4	H	2-Me	BF_4	60	63 (**3d**)
5	H	6-CO_2Me	OTf	60	85 (**3e**)
6	H	5-CHO,	BF_4	60	70 (**3f**)
7	H	5-NO_2	OTf	60	73 (**3g**)
8	H	5-Br	OTf	35	75 (**3h**)

found that the use of $Cu(OTf)_2$ restored the C3:C2 selectivity (to 12−14:1) with either the triflate or the tetrafluoroborate salt of **2** (entries 5 and 6). Therefore, our optimization identified that treatment of indole **1a** with 10 mol % of $Cu(OTf)_2$ as catalyst, 1.1 equiv of [Ph−I−Ph]OTf (**2b**), and 1.1 equiv of dtbpy in anhydrous dichloromethane at room temperature afforded the 3-arylindole **3a** in 72% isolated yield.

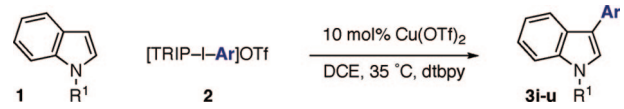
With a set of optimized conditions in hand, we next examined the scope of the indole motif in the C−H arylation process.[12] We found that both free (*NH*)-indoles and *N*-alkyl indoles were smoothly converted to the 3-phenylindoles (C3:C2, 12−14:1) at room temperature (Table 2, entries 1 and 2). Indoles bearing electron-donating substituents underwent facile arylation (entries 3 and 4), and the corresponding indoles with electron-withdrawing groups also delivered the arylated products, albeit at a higher reaction temperature (entries 5−7). This difference in reactivity between electron-rich and electron-deficient indoles supports an electrophilic metalation mechanism for the arylation process.

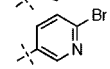
In this reaction, only one of the two aryl groups of the symmetrical diaryl−iodine(III) reagent is utilized in the indole arylation. This would be problematic when complex aryl groups are required in the process. To minimize this problem, we designed an unsymmetrical diaryl−I(III) reagent containing the desired aryl group and a second aryl unit that would not transfer in the catalytic process. Selective aryl transfer has been observed in other metal-catalyzed processes as a result of poor aryl transfer of a large group (such as mesityl) compared to a less substituted aryl unit.[7a,10] In our Cu(II)-catalyzed arylation we found that [mesityl−I−Ph]OTf resulted in a 16:1 selectivity for the desired aryl transfer (Ph over mesityl). However, using a larger "spectator" group, 2,4,6-tri-*iso*propylphenyl (TRIP) (**2d**), resulted in exclusive transfer of the desired aryl group to give a good yield of **3a** (4). It is notable that most [TRIP−I−Ar]OTf salts can be generated in a one-step process from commercially available starting materials (4).[13]



The scope of the arylation was tested with a range of unsymmetrical [TRIP−I−Ar]OTf salts, and we were pleased to find that the Cu(II)-catalyzed process was able to transfer a range of substituted aryl groups to the indole nucleus to form the C3-regioisomer with excellent selectivity and in good yield. Electron-rich (entries 1−4), electron-deficient (entries 5−9), sterically hindered (entries 10 and 11), and heteroarene aryl motifs (entries 12 and 13) were all readily transferred via this reaction. Notably, aryl substrates bearing C−Br *and even* C−I bonds (entries 5−7, Table 3 and entry 8 in Table 2) are unaffected by the Cu(II)-catalyzed arylation, providing a complementary platform for further elaboration via conventional Pd(0)-catalyzed cross-coupling.

Table 3. Scope of Cu(II)-Catalyzed Aryl Group Transfer

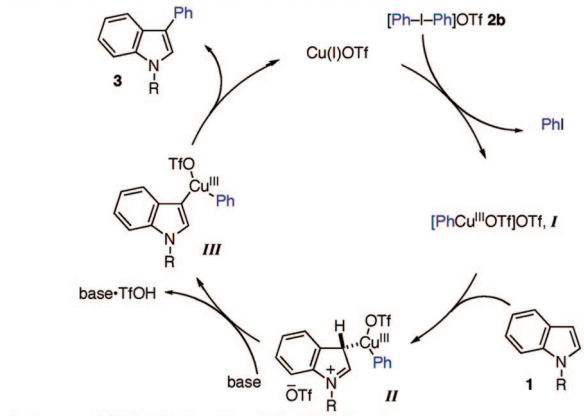


entry	R^1	Ar	C3:C2[c]	isolated yield **3** %
1	Me	4-(Me)C_6H_4	>20:1	74 (**3i**)
2	Me	4-(OMe)C_6H_4	11:1	73 (**3j**)
3	Me	4-(F)C_6H_4	>20:1	74 (**3k**)
4	H	4-(F)C_6H_4	10:1	71 (**3l**)
5	Me	4-(Br)C_6H_4	>20:1	82 (**3m**)
6	H	4-(Br)C_6H_4	10:1	71 (**3n**)
7	Me	4-(I)C_6H_4	>20:1	65 (**3o**)
8	Me	4-(NO_2)C_6H_4	>20:1	86 (**3p**)
9	Me	3-(CF_3)C_6H_4	>20:1	77 (**3q**)
10	Me	2-(Me)C_6H_4	>20:1	86 (**3r**)
11	Me	2-(NHAc)C_6H_4	>20:1	72 (**3s**)
12[a]	Me		8:1	57 (**3t**)
13[b]	Me		>20:1	38 (**3u**)

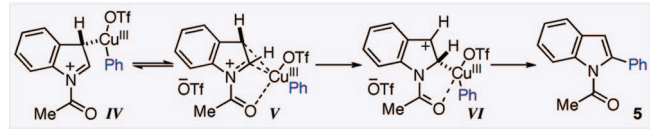
[a] BF_4 salt at 60 °C. [b] With 25 mol % of $Cu(OTf)_2$. [c] Determined by ^1H NMR.

Scheme 1. Proposed Catalytic Cycle

a. Proposed catalytic cycle for the Cu(II) catalyzed C–H arylation



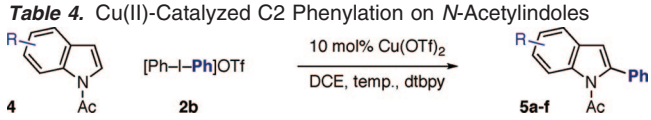
b. Proposed C3 to C2 migration of the C–Cu bond



The mechanism of the Cu(II)-catalyzed C−H bond arylation is proposed to begin with reduction of the Cu(II) catalyst to Cu(I) by the indole (Scheme 1a). Oxidative addition of the diaryl−iodine(III) reagent **2b** to the Cu(I) salt would generate the electrophilic Cu(III)−aryl intermediate ***I*** that can undergo attack at the C3 position of indole to ***II***.[14] Rearomatization via C−H bond cleavage to ***III*** would be followed by reductive elimination, delivering the product **3** and re-forming the Cu(I) catalyst.[9c,15]

Having established C3 reactivity in the Cu(II)-catalyzed C−H arylation, our attention turned to investigating how we might steer the reaction to produce the C2 isomer. We speculated that the Cu(III)−aryl intermediate ***I*** would react initially through the C3 position before migration to C2 and rearomatization to afford the C2-metalated indole.[5a] In assessing how to effect this migration, we tested the effect of acid additives on the reaction. Despite a clear influence, it was not possible to reverse the selectivity of the arylation.[16] Therefore, in order to further promote a migration mechanism, we reasoned that the use

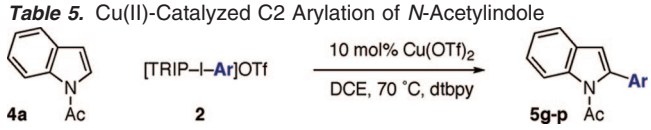
Table 4. Cu(II)-Catalyzed C2 Phenylation on *N*-Acetylindoles



entry	R	temp, °C	C2:C3[a]	isolated yield **5** %
1	H	60	9:1	83 (**5a**)
2	5-Br	70	8:1	76 (**5b**)
3	5-OMe	60	7:1	72 (**5c**)
4	6-CO_2Me	70	7:1	81 (**5d**)
5	5-CHO	70	6:1	61 (**5e**)
6[b]	5-NO_2	70	9:1	37 (**5f**)

[a] Determined by ^{1}H NMR. [b] Isolated yield at 63% conversion of indole using 20 mol % of Cu(OTf)$_2$.

Table 5. Cu(II)-Catalyzed C2 Arylation of *N*-Acetylindole



entry	Ar	C2:C3 (total yield)[a]	isolated yield **5** %
1	4-(Me)C_6H_4	6.5:1 (79)	69 (**5g**)
2	4-(OMe)C_6H_4	2.6:1 (68)	49 (**5h**)
3	4-(F)C_6H_4	6:1 (84)	72 (**5i**)
4	4-(Cl)C_6H_4	5:1 (83)	83 (**5j**)
5	4-(Br)C_6H_4	6:1 (95)	82 (**5k**)
6	4-(I)C_6H_4	5.5:1 (66)	56 (**5l**)
7	3-(Br)C_6H_4	7:1 (91)	80 (**5m**)
8	3-(CF_3)C_6H_4	6.5:1 (90)	78 (**5n**)
9	4-(CO_2Et)C_6H_4	4:1 (92)	73 (**5o**)
10	4-(NO_2)C_6H_4	3:1 (72)	54 (**5p**)

[a] Ratio determined by ^{1}H NMR.

of an *N*-acetyl group might render the intermediate iminium ion ***IV*** more likely to accept the migrating C−Cu bond at the C2 position (***IV*** to ***V*** to ***VI***). Moreover, the carbonyl oxygen of the amide may steer the Cu(III) species to C2 (Scheme 1b).

We were delighted to find that when *N*-acetylindole (**4a**) was treated with [Ph−I−Ph]OTf (**2b**) the 2-arylindole **5a** was obtained as a 9:1 ratio (91% overall yield) in favor of the C2 isomer (Table 4, entry 1). In this case, the lower reactivity of the *N*-acetylindole means that the temperature of the reaction needs to be increased to 60 °C. Encouraged by these results, we explored the scope of this C2-arylation process. A range of electronically diverse indoles worked well in this process, delivering the C2-arylated products in excellent yield (Table 4).

The transferring aryl group could also be varied, using a range of [TRIP−I−Ar]OTf salts, enabling a selection of 2-arylindoles to be delivered in high yields (Table 5). In particular, the halogen-containing motifs (F, Cl, Br, *and* I, entries 3−7) work well in the C2 selective arylation, again highlighting the potential of this process in combination with further conventional cross-coupling transformations.

In summary, we have developed a new site-selective Cu(II)-catalyzed C−H bond functionalization process that can selectively arylate indoles at either the C3 or C2 position under mild conditions. The scope of the arylation process is broad and tolerates many functionalities on both the indole and the aryl unit. The mechanism of the arylation reaction is proposed to proceed via a Cu(III)−aryl species that undergoes initial electrophilic addition at the C3 position of the indole motif. We speculate that site of indole arylation arises through a migration of the Cu(III)−aryl group from C3 to C2, and this can be controlled by the nature of the group on the nitrogen atom. Free (*NH*)- and *N*-alkylindoles deliver the C3-arylated product, whereas *N*-acetylindoles afford the C2 isomer, with high yield and selectivity. We are currently exploring aspects of the reaction mechanism, in particular, the C3 to C2 migration, and application of Cu(II)-catalyzed arylation to other systems. This work will be reported in due course.

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Supporting Information Available: Experimental data and procedures for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Although we cannot rule out a radical mechanism for this process, we observed that, in the presence of a radical inhibitor, 1,1-diphenylethylene, the reaction was not affected.

(16) Acid additives and other counterions (in 2) reduce the C3 to C2 selectivity. See Supporting Information for details.

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