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Iridium-Catalyzed Direct Regioselective C4-Amidation of Indoles under Mild Conditions

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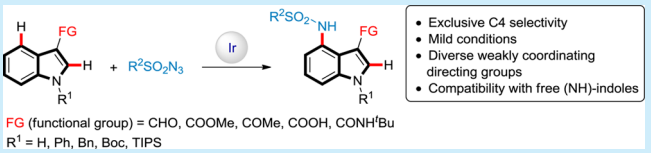
Supporting Information

ABSTRACT: An efficient Ir-catalyzed amidation of indoles with sulfonyl azides is disclosed, affording diverse C4-amidated indoles exclusively under mild conditions. In this protocol, a variety of indoles with commonly occurring functional groups such as formyl, acetyl, carboxyl, amide, and ester at the C3 position are well tolerated.



During the past few years, C−H activation has proven to be an economical and straightforward tool with promising applications in the functionalization of organic molecules.[1] An important aim in the field of C−H activation is to control the regioselectivity of reactions. Indole, a nitrogen-containing framework with seven potentially reactive positions, widely presents in bioactive molecules and pharmaceutical products.[2] The direct modification of indole ring via transition-metal-catalyzed C−H activation has become an effective approach for the construction of diversiform indoles.[3] In general, electrophilic metalation usually occurs at the C3 position of indole owing to its higher electron density.[4] Regioselective functionalization of the C2 position can also be realized by using a directing group or selection of specific conditions.[5] In contrast, only a few examples on the selective C−H activation/functionalization of C4−C7 positions of indoles have been disclosed.[3c,6]

The C−N bond is one of the most ubiquitous bonds in organic molecules.[7] Therefore, the construction of the C−N bond is always an attractive topic in organic chemistry. Recently, transition-metal-catalyzed direct C−H activation/amination of (hetero)arenes has emerged as a concise and highly efficient strategy for the synthesis of (hetero)aromatic amines.[8] Despite significant progress, selective C−H activation/amination of the indole core is still underdeveloped.[6f−h,9] 4-Amino-indoles exhibit potential applications in pharmaceuticals, including as an antiproliferative agent, HIV protease inhibitor, kinase inhibitor, and 5-HT_6 receptor antagonist (Figure 1).[10] Although direct C−H amination of indoles represents one of the most ideal approaches to 4-amino-indoles, the inherent poor electronic nature of the C4 position of indole impedes the selective functionalization of this site. The introduction of a directing group at the C3 position might be helpful to address this issue. However, a selectivity issue between the C2 and C4 positions still exists. Typically, C−H activation prefers to take place at the more reactive C2 position rather than the C4 position when a directing group is installed at the C3 position of indoles (Figure 2).[9c,11]

Quite recently, with the assistance of the bulky *N*-pivaloyl group, Chang et al. developed an Ir-catalyzed regioselective C7−H amidation of indoles.[6h] In this work, we wish to disclose an Ir-catalyzed C4−H amidation of indoles using the commonly occurring functional groups, such as formyl, acetyl, carboxyl, amide, and ester, as a weakly coordinating directing group.

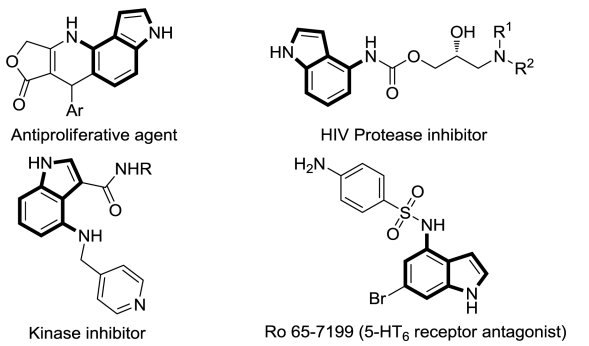


Figure 1. Potential pharmaceutical scaffolds that contain 4-amino-substituted indoles.

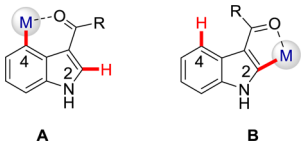


Figure 2. Competitive C−H activation at the C2 and C4 positions of indole through the chelation assistance.

Our investigation started with the amidation of 1*H*-indole-3-carbaldehyde **1a**, using 4-methylbenzenesulfonyl azide **2a** as the nitrogen source, $[Cp^*IrCl_2]_2/AgSbF_6$ as the catalyst system, and silver acetate as the additive in DCE at 25 °C for 24 h under an air atmosphere (Table 1). To our delight, the reaction condition is compatible with the *NH*-free indoles, and the desired amidated product could be obtained in 72% yield without the 2-substituted compound detected (Table 1, entry 1). The yield was slightly decreased by employing $Cu(OAc)_2·H_2O$ as the additive (Table

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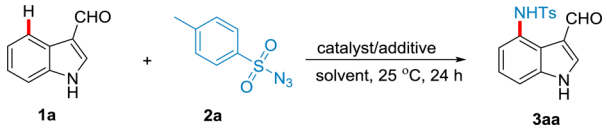
Table 1. Optimization of the Reaction Conditions[a]



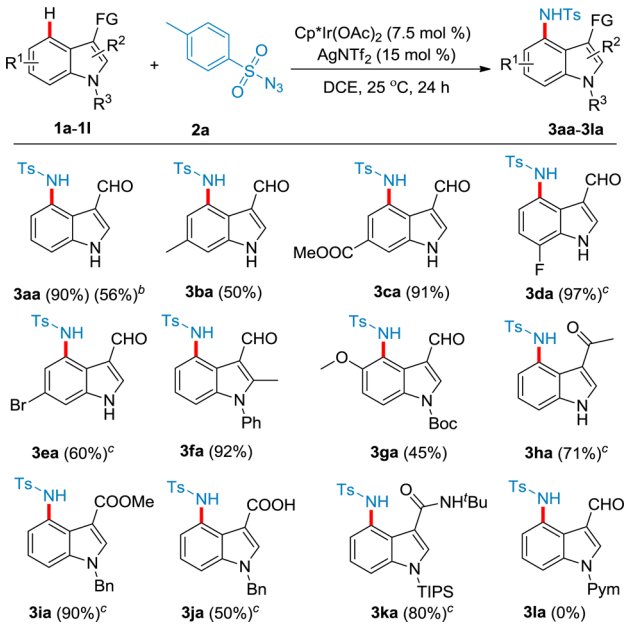
entry	cat. (mol %/mol %)	additive	solvent	yield (%)[b]
1	$[Cp^*IrCl_2]_2/AgSbF_6$ (5:20)	AgOAc	DCE	72
2	$[Cp^*IrCl_2]_2/AgSbF_6$ (5:20)	$Cu(OAc)_2·H_2O$	DCE	60
3	$[Cp^*IrCl_2]_2/AgSbF_6$ (5:20)	KOAc	DCE	20
4	$Cp^*Ir(OAc)_2/AgSbF_6$ (10:20)	AgOAc	DCE	70
5	$Cp^*Ir(OAc)_2/AgSbF_6$ (10:20)	–	DCE	73
6	$Cp^*Ir(OAc)_2/AgNTf_2$ (10:20)	–	DCE	92
7	$Cp^*Ir(OAc)_2/AgNTf_2$ (7.5:15)	–	DCE	90
8	$Cp^*Ir(OAc)_2/AgNTf_2$ (5:10)	–	DCE	72
9	$Cp^*Ir(OAc)_2/AgNTf_2$ (7.5:15)	–	PhCl	32
10	$Cp^*Ir(OAc)_2/AgNTf_2$ (7.5:15)	–	dioxane	<5
11	$Cp^*Ir(OAc)_2/AgNTf_2$ (7.5:15)	–	DMF	n.d.
12	$Cp^*Ir(OAc)_2$ (7.5)	–	DCE	n.d.
13	$[Cp^*IrCl_2]_2/AgNTf_2$ (5:20)	–	DCE	n.d.
14	$Cp^*Co(CO)I_2/AgNTf_2$ (10:20)	–	DCE	n.d.
15	$[Cp^*RhCl_2]_2/AgNTf_2$ (5:20)	–	DCE	n.d.
16	$[Ru(p\text{-cymene})Cl_2]_2/AgNTf_2$ (5:20)	–	DCE	n.d.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst and additive (0.3 equiv) in solvent (1 mL) under air at 25 °C for 24 h. [b]Isolated yield. DCE = $ClCH_2CH_2Cl$. n.d. = no detected.

1, entry 2). Only a 20% yield was gained after KOAc was adopted in the system (Table 1, entry 3). Pleasingly, altering the iridium species to $Cp^*Ir(OAc)_2$ afforded **3aa** in 70% yield while the removal of AgOAc hardly affected the yield (Table 1, entries 4 and 5). Fortunately, **3aa** was finally generated in 92% yield with a $Cp^*Ir(OAc)_2/AgNTf_2$ (10:20) catalyst system (Table 1, entry 6). Reducing the loading of catalyst to 7.5 mol % showed no effect on the yield (Table 1, entry 7). However, further reducing the amount of catalyst resulted in the reduction of yield to 72% (Table 1, entry 8). In addition, other solvents, such as PhCl, 1,4-dioxane, and DMF, led to low output or even no product (Table 1, entries 9–11). Neither $Cp^*Ir(OAc)_2$ nor a combination of $[Cp^*IrCl_2]_2/AgNTf_2$ (5:20) could promote the amidation of **1a**, indicating the essential roles of both OAc^- and NTf_2^- in this reaction (Table 1, entries 12 and 13). Other transition metal catalysts, including $Cp^*Co(CO)I_2$, $[Cp^*RhCl_2]_2$, and $[Ru(p\text{-cymene})Cl_2]_2$, were not suitable for this reaction (Table 1, entries 14–16). Finally, the optimal reaction conditions are composed of $Cp^*Ir(OAc)_2$ (7.5 mol %) and $AgNTf_2$ (15 mol %) in DCE at 25 °C for 24 h.

With the optimal conditions in hand, we then investigated the scope of this catalytic system. As shown in Scheme 1, a range of substituted indoles were tested. Both the electron-withdrawing and -donating groups such as ester, methyl, methoxyl, and halogen substituted groups at different positions on the phenyl ring were tolerated well, affording the amidated products in moderate to excellent yields, but the electronic nature of substituents could significantly influence the yields. The electron-withdrawing groups delivered a higher yield than the electron-donating groups (**3ca** and **3da** vs **3ba**). Notably, the amidated product with the 6-bromo-substituent was obtained in a synthetically useful yield, which would provide an active site for further functionalization (**3ea**). Furthermore, the substituent on the five-membered ring was also tolerated, exemplified by the product **3fa**. More importantly, the scope of this catalyst system was also extended to the indoles with other C3 functional groups

Scheme 1. Scope of Indoles[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), $Cp^*Ir(OAc)_2$ (7.5 mol %) and $AgNTf_2$ (15 mol %) in DCE (1 mL) at 25 °C under air for 24 h. [b]1-Pivaloyl-1*H*-indole-3-carbaldehyde was used as the substrate. [c]At 60 °C. Pym = 2-pyrimidyl.

such as acetyl, ester, carboxyl, and amide. These indole derivatives smoothly afforded the C4 amidated products in moderate to good yields with exclusive C4 selectivity (**3ha**, **3ia**, **3ja**, and **3ka**). Interestingly, when *N*-pivaloyl indole-3-carbaldehyde was attempted under the standard conditions, an *N*-deprotected product **3aa** was obtained in 56% yield. However, no desired product was obtained in the case of 1-(pyrimidin-2-yl)-1*H*-indole-3-carbaldehyde (**3la**).

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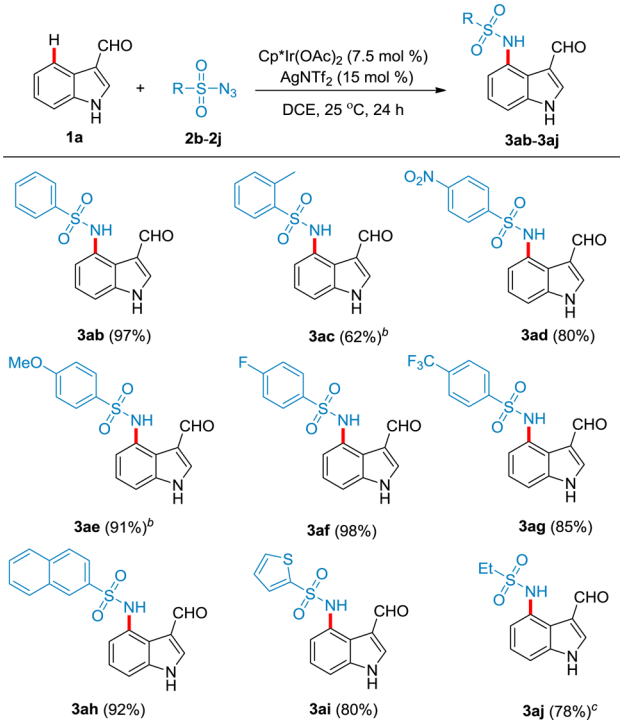
Subsequently, the scope of sulfonyl azides was investigated. As shown in Scheme 2, both the electron-withdrawing and

Scheme 2. Scope of Organic Azides[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $Cp^*Ir(OAc)_2$ (7.5 mol %) and $AgNTf_2$ (15 mol %) in DCE (1 mL) at 25 °C under air for 24 h. [b]At 60 °C. [c]$Cp^*Ir(OAc)_2$ (10 mol %) and $AgNTf_2$ (20 mol %).

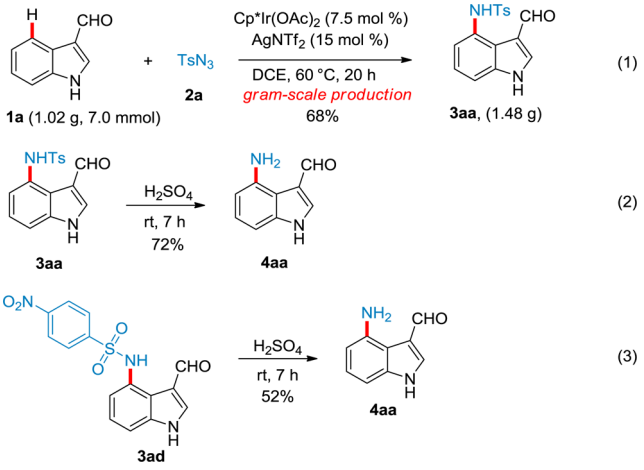
-donating group substituted aryl sulfonyl azides proceeded smoothly, giving the desired products in good to excellent yields. The phenyl sulfonyl azide with *ortho*-methyl substitution required an elevated temperature of 60 °C, affording **3ac** in 62% yield. *N*-(3-Formyl-1*H*-indol-4-yl)thiophene-2-sulfonamide (**3ai**) was obtained in 80% yield. Moreover, ethanesulfonyl azide could also couple with **1a**, delivering **3aj** in 78% yield.

In addition, we also tried the reactions with a combination of Ir/Ag (1:1) as the catalyst. In the case of **3aa**, a comparative yield was obtained. However, diminished yields were observed in some cases such as **3ga**, **3ac**, **3ae**, and **3af** (38%, 46%, 84%, and 88% yields, respectively).

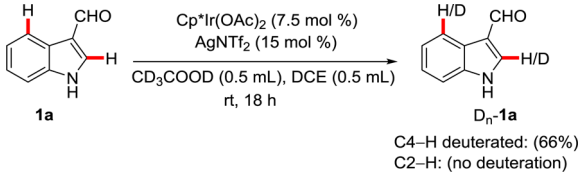
Considering the synthetic utility of the amidation reaction, the scalability of the reaction was further examined, presenting a 68% yield of **3aa** (1.48 g) at 60 °C (Scheme 3, eq 1). By using concentrated sulfuric acid, **3aa** and **3ad** could be deprotected to give 4-amino-1*H*-indole-3-carbaldehyde (**4aa**) in 72% and 52% yields, respectively (Scheme 3, eqs 2 and 3). This result indicates that an electron-rich substituent at the phenyl sulfonamide ring could facilitate the deprotection of the amidated indoles.

To determine the mechanism, a H/D exchange experiment was conducted (Scheme 4). When CD_3COOD was added into the reaction system under the optimal conditions, the C4−H bond of the indole ring was deuterated in 66% yield without deuteration at the C2−H bond. This result indicates that the C−H activation at the C4 position is reversible and the directing group in this reaction prefers to assist the cleavage of the C4−H rather than the C2−H.

Scheme 3. Gram-Scale Synthesis of 3aa and Deprotection of the Amidated Products

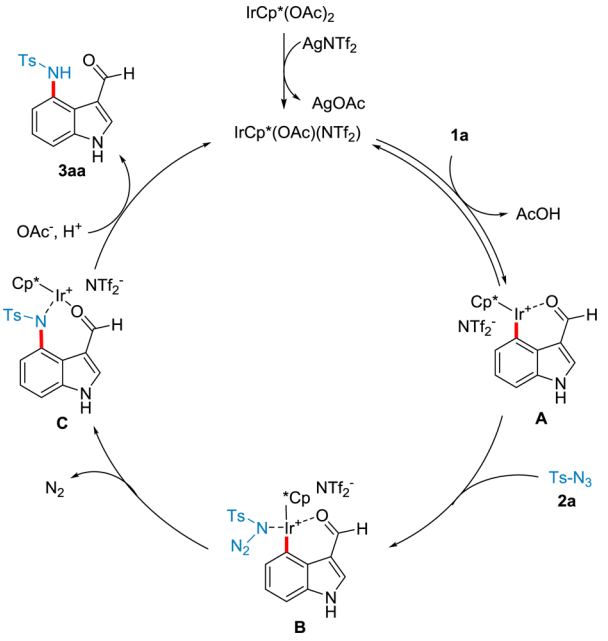


Scheme 4. H/D Exchange Experiment



According to the previous reports[6h,12] and the above experimental results, a proposed mechanism is illustrated in Scheme 5. Initially, the anion exchange of $Cp^*Ir(OAc)_2$ with

Scheme 5. Proposed Mechanism



$AgNTf_2$ possibly forms an $IrCp^*(OAc)(NTf_2)$ species.[6g,h,13] The subsequent cyclometalation with **1a** delivers the 6-membered cycloiridium intermediate **A** through the C−H bond cleavage of the C4 position. The azide **2a** then coordinates to the iridium center of **A** to form the intermediate **B**, followed by the migratory insertion of the imido group to the Ir−aryl bond, affording the intermediate **C** with the extrusion of N_2. Finally, the

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product **3aa** is obtained along with regeneration of the Ir(III) species by protonation.

In conclusion, an efficient Ir-catalyzed C4 amidation of substituted indoles with sulfonyl azides under mild conditions has been developed. A variety of indoles are employed to afford the amidated products with exclusive C4 selectivity. The procedure disclosed herein is not only applicable to *N*-unprotected indoles but also compatible with diverse commonly occurring functional groups such as formyl, acetyl, carboxyl, amide, and ester at the C3 position of indoles. Further application of this method is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00730.

Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of key intermediates and final products (PDF)

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Notes

The authors declare no competing financial interest.

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(13) A reaction of $Cp^*Ir(OAc)_2$ with $AgNTf_2$ was carried out. The ^{1}H and ^{19}F NMR analysis of the crude product supported a possible $IrCp^*(OAc)(NTf_2)$ species.

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