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A Direct Access to 7-Aminoindoles via Iridium-Catalyzed Mild C−H Amidation of *N*-Pivaloylindoles with Organic Azides

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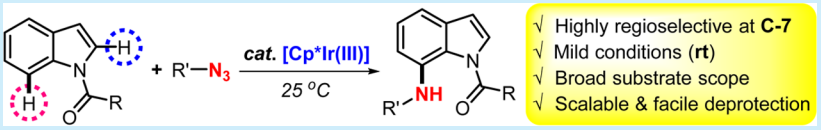
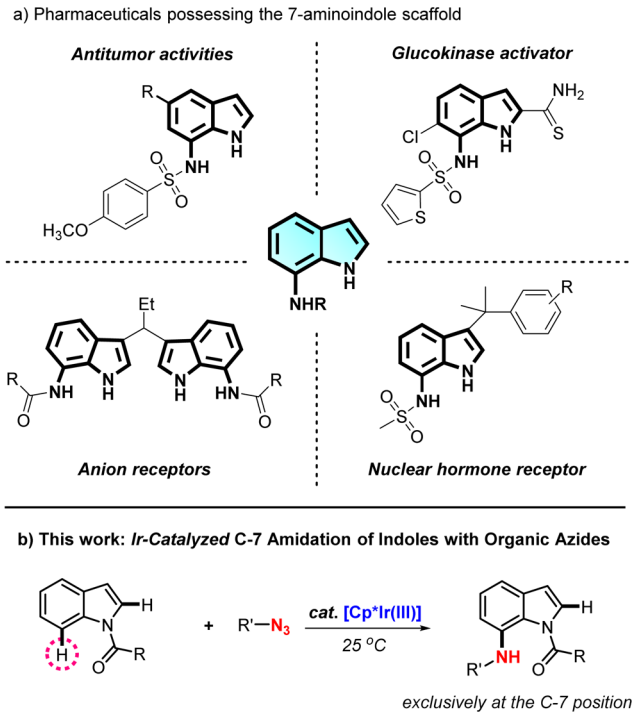
Supporting Information



ABSTRACT: Ir(III)-catalyzed regioselective direct C-7 amidation of indoles in reaction with organic azides has been developed. While its efficiency was varied by the choice of *N*-directing groups, *N*-pivaloylindoles were most effective in undergoing the desired amidation at room temperature over a broad range of substrates. The reaction was scalable, and deprotection of the chelation group was also facile.

The privileged indole structure is widely present in natural and synthetic products.[1] In particular, 7-aminoindoles are a key scaffold found in numerous biologically relevant compounds to display a broad spectrum of bioactivities, serving as antitumor agents, anion receptors, glucokinase activators, or nuclear hormone receptors (Scheme 1a).[2] As a result, the development of efficient synthetic routes to 7-aminoindoles is highly desirable. In this context, two synthetic strategies can be conceived: (i) a ring-generating route to indoles from amino-installed acyclic starting materials[3] and (ii) direct regioselective C−H functionalization[4,5] (amination in this case) of indoles using transition metal catalysts.[6,7] Although the latter route has distinct merits, owing to the inherent electronic property of the indoles, electrophilic metalation takes place mainly at the C-3 position of an indole skeleton. In addition, direct activation of C2−H bonds has also been known under certain catalytic conditions.

Scheme 1. Bioactive 7-Aminoindoles



Regioselective C−H functionalization at the C-7 position of indoles has been proven to operate only when proper *N*-directing groups are employed in combination with suitable catalytic systems. For instance, Hartwig et al. reported Ir-catalyzed C-7 borylation of *N*-silylindoles.[8] In addition, Ma[9] and Shi[10] independently showed that C-7 alkenylation and arylation of indoles could be feasible with properly installed *N*-directing groups by the action of Rh and Pd catalysis, respectively. Our group reported a direct C-7 amination of *indolines* with organic azides.[11] Initially obtained 7-aminoindolines can be readily oxidized to afford 7-aminoindoles as end products. Although structural diversity to allow both aminoindolines and aminoindoles can be achieved through this *indirect* approach, we were curious if a *direct C-7 amination of indoles* would be plausible. Herein, we report the development of an Ir-catalyzed C7−H amination of *N*-pivaloylindoles with organic azides (Scheme 1b). The reaction proceeds with excellent regioselectivity over a broad range of indoles and azides, thus offering a straightforward and efficient way of accessing 7-aminoindoles.

We commenced our study to examine the amidation conditions in a model reaction of *N*-pivaloylindole (**1a**) with *p*-toluenesulfonyl azide (**2a**, Table 1).[12] Inspired by Ma's

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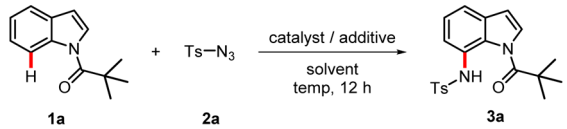
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	additive	temp (°C)	solvent	yield (%)[b]
1	$[IrCp^*Cl_2]_2$ (5)/$AgNTf_2$ (20)	–	50	1,2-DCE	<1
2	$[IrCp^*Cl_2]_2$ (5)/$AgNTf_2$ (20)	NaOAc	50	1,2-DCE	60
3	$[RhCp^*Cl_2]_2$ (5)/$AgSbF_6$ (20)	NaOAc	50	1,2-DCE	n.r.
4	$[Ru(p\text{-cymene})Cl_2]_2$ (5) /$AgSbF_6$ (20)	NaOAc	50	1,2-DCE	n.r.
5	$[IrCp^*Cl_2]_2$ (5)/$AgNTf_2$ (20)	KOAc	50	1,2-DCE	20
6	$[IrCp^*Cl_2]_2$ (5)/$AgNTf_2$ (20)	AgOAc	50	1,2-DCE	77
7	$[IrCp^*Cl_2]_2$ (5)/$AgNTf_2$ (20)	AcOH	50	1,2-DCE	27
8	$[IrCp^*Cl_2]_2$ (5)	AgOAc	50	1,2-DCE	n.r.
9	$IrCp^*(OAc)_2$ (10)/ $NaNTf_2$ (20)	–	50	1,2-DCE	44
10	$IrCp^*(OAc)_2$ (10)/ $AgNTf_2$ (20)	–	50	1,2-DCE	90
11	$IrCp^*(OAc)_2$ (10)	–	50	1,2-DCE	n.r.
12	$AgNTf_2$ (20)	–	50	1,2-DCE	n.r.
13	**$IrCp^*(OAc)_2$ (5)/ $AgNTf_2$ (10)**	–	**25**	**1,2-DCE**	**94**
14	$IrCp^*(OAc)_2$ (5)/ $AgNTf_2$ (10)	–	25	THF	29
15	$IrCp^*(OAc)_2$ (5)/ $AgNTf_2$ (10)	–	25	toluene	90
16	$IrCp^*(OAc)_2$ (5)/ $AgNTf_2$ (10)	–	25	MeCN	n.r.
17	$IrCp^*(OAc)_2$ (5)/ $AgNTf_2$ (10)	–	25	EtOAc	74
18	$IrCp^*(OAc)_2$ (5)/ $AgNTf_2$ (10)	–	25	MeOH	n.r.

[a] **1a** (0.20 mmol), **2a** (0.22 mmol), catalyst, and additive (30 mol %) in solvent (0.5 mL) for 12 h. [b] Yields were based on ^1H NMR analysis of the crude mixture (CH_2Br_2: internal standard). n.r. = no reaction.

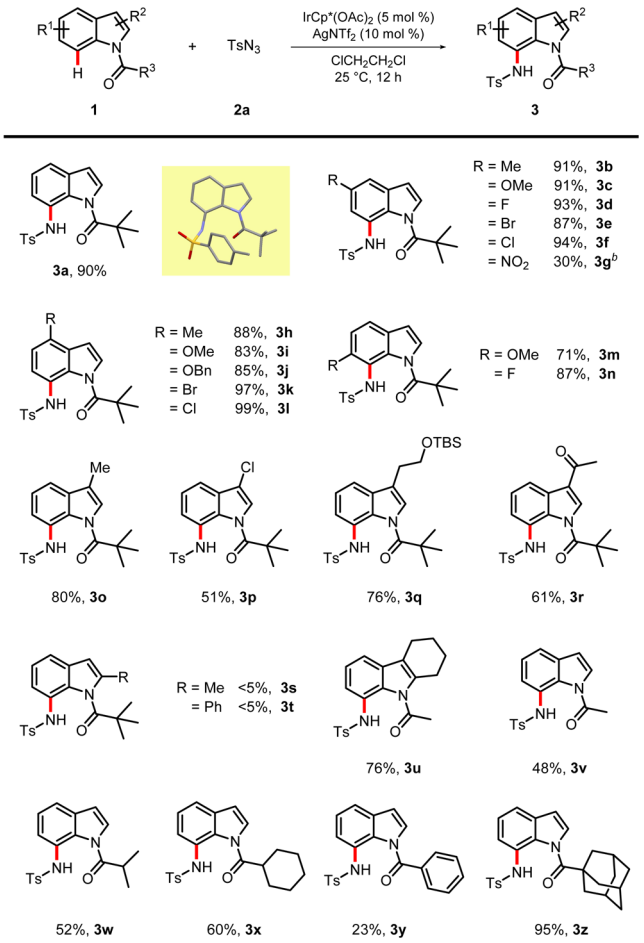
elegant approach,[9] we initially introduced a *N*-pivaloyl group to see whether it indeed can guide the desired C-7 selectivity in our case. When a cationic Ir species generated *in situ* from $[IrCp^*Cl_2]_2$ and $AgNTf_2$ was employed, the desired product **3a** was formed only in trace amount at 50 °C (entry 1). On the basis of our previous observation that acetate additives can promote the C–H bond activation,[13] we decided to examine the additive effects. We were pleased to see that the amidation took place more efficiently (60% crude yield of **3a**), leading to exclusive amidation at the C-7 position in the presence of NaOAc (30 mol %, entry 2). Importantly, no other isomeric amidated compounds were observed. However, this amidation was not operative with Rh or Ru catalyst systems (entries 3 and 4). Among various acetate additives screened, silver acetate was most effective (entries 5–7). However, the presence of $AgNTf_2$ turned out to be essential for reaction progress even when silver acetate was employed (entry 8).

When a pregenerated iridium acetate complex, $IrCp^*(OAc)_2$, was used as a catalyst in the presence of $NaNTf_2$, the desired product was obtained in moderate yield (entry 9). The use of $AgNTf_2$ in place of $NaNTf_2$ significantly improved the product yield (entry 10). Not surprisingly, the aminated product **3a** was not formed in the absence of either $IrCp^*(OAc)_2$ or $AgNTf_2$ (entries 11–12). Pleasingly, excellent product yield was obtained at room temperature and even with reduced catalyst loading (entry 13). The use of solvents other than 1,2-dichloroethane (1,2-DCE) resulted in decreased product yields (entries 14–18).

With the optimized conditions in hand, we next investigated the scope of indoles in reaction with *p*-toluenesulfonyl azide (Scheme 2). The structure of product **3a** obtained from *N*-pivaloylindole was unambiguously confirmed by an X-ray crystallographic analysis. We were pleased to observe that the amidation took place smoothly irrespective of the position and electronic nature of substituents, thus giving rise to the corresponding C-7 amidated products in high efficiency and regioselectivity. Indeed, substrates bearing methyl (**3b** and **3h**), alkoxy (**3c**, **3i**, **3j**, and **3m**), fluoro (**3d** and **3n**), bromo (**3e** and **3k**), and chloro (**3f** and **3l**) groups at the C4-, 5-, and 6-position of indoles were all facile for the present amidation. However, an indole substrate bearing a nitro group at the 5-position was amidated in moderate efficiency (**3g**).

Next, the scope of indoles substituted at the nitrogen-containing cyclic moiety (e.g., at the 2- or 3-position) was examined. Various functional groups positioned at C-3 did not much diminish the amidation efficiency, as demonstrated by the facile product formation of **3o**–**3r**. In particular, amidated

Scheme 2. Substrate Scope of Indoles[a]



[a] **1** (0.20 mmol) and **2a** (0.22 mmol) in 1,2-DCE (0.5 mL); isolated yields. [b] At 80 °C.

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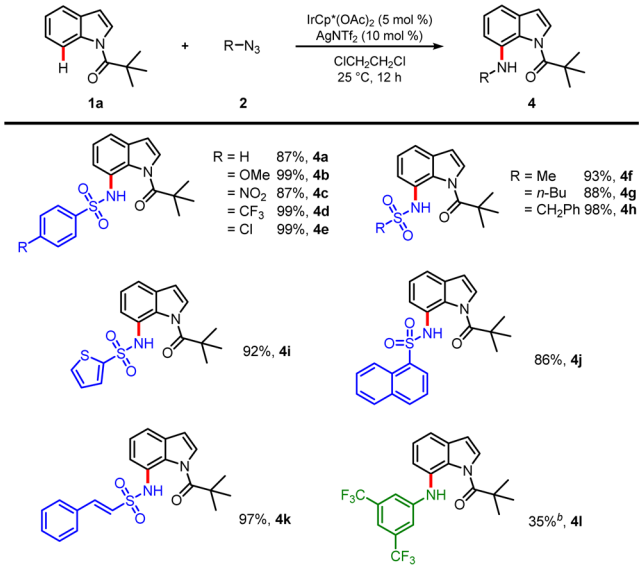
indoles bearing chloro, silyl-protected alcohol, or ketone groups would be potentially valuable for further synthetic transformations. In contrast, the amidation did not take place when 2-substituted indoles were subjected to the current conditions (**3s** and **3t**) although the exact reason is not clear at the present stage. Amidation of 9-acetyl-2,3,4,9-tetrahydro-1*H*-carbazole proceeded smoothly, leading to **3u** in 76% yield.

Finally, the influence of *N*-directing groups on the amidation efficiency was briefly examined. When sterically less hindered *N*-acetyl, isobutyryl, or cyclohexanecarbonyl groups were installed, lower product yields were obtained (**3v**–**3x**) compared to *N*-pivaloylindole (**3a**).[14] Even lower amidation efficiency was observed with *N*-benzoylindole (**3y**). However, a reaction of *N*-(1-adamantanecarbonyl)indole took place almost quantitatively under the same mild conditions (**3z**), thus strongly suggesting that a steric factor critically affects the reaction efficiency.

The scope of organic azides was subsequently investigated in the amidation of *N*-pivaloylindole (Scheme 3). All arenesulfonyl azides examined were smoothly reacted with **1a** to result in excellent product yields irrespective of the substituents' electronic property (**4a**–**4e**). Moreover, alkanesulfonyl azides were also highly facile under the standard mild amidation conditions (**4f**–**4h**). Thiophenesulfonyl azide was observed to work as an effective amidating reagent (**4i**). In addition, amidation reactions of **1a** with 1-naphthalenesulfonyl azide and 2-phenylethene-1-sulfonyl azides occurred efficiently to furnish the corresponding aminoindoles in high yields (**4j**–**4k**). On the other hand, aryl azides, which were proven by us to be an efficient aminating source in the Rh-catalyzed amination of benzamides,[15] displayed only moderate efficiency under the present iridium catalyst system (**4l**).

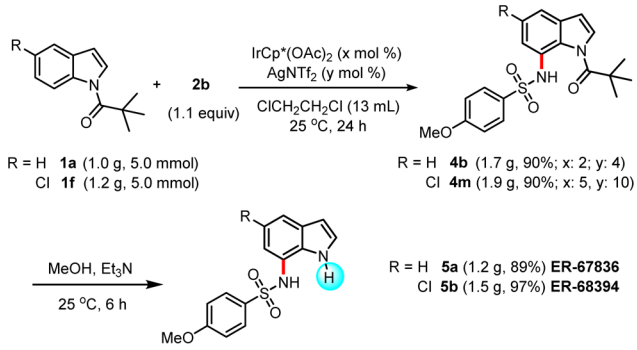
Scheme 3. Scope of Organic Azides[a]



[a]**1a** (0.20 mmol) and **2** (0.22 mmol) in 1,2-DCE (0.5 mL); isolated yields. [b]At 50 °C.

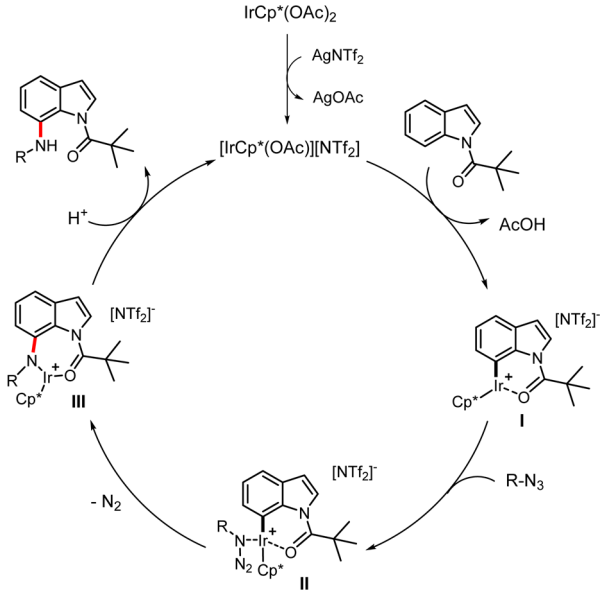
A notable aspect of the present procedure is that 7-aminoindoles of high bioactivity can be directly accessed under mild conditions (Scheme 4). As a preliminary demonstration, the amidation of *N*-pivaloylindole (**1a**) and its congener substituted with a chloro group (**1f**) was carried out successfully on a gram scale to give the corresponding 7-amidoindoles in high yields (**4b** and **4m**, respectively). Pleasingly, the *N*-pivaloyl group of amidated indoles was easily removed also under mild conditions (Et_3N/MeOH at room temperature), thus affording 7-aminoindoles **5a** (ER-67836) and **5b** (ER-68394), both of which were revealed to display antitumor activity.[2a−c]

Scheme 4. Synthesis of Biorelevant Compounds



A plausible mechanism of the present C-7 amidation is depicted in Scheme 5 based on our previous mechanistic investigations in the related C−H amination reactions.[12d,13b] A cationic Ir(III) species, *in situ* generated by treating IrCp*-$(OAc)_2$ with $AgNTf_2$, will undergo a directed C7−H bond activation of *N*-pivaloylindole via the chelation assistance of a carbonyl oxygen atom to give rise to a six-membered iridacycle (**I**). A subsequent coordination of organic azide to the iridium metal center and then insertion of an imido group into the Ir−C bond are believed to occur with concomitant release of a N_2 molecule leading to an iridium amido intermediate (**III**). Finally, a protodemetalation of **III** will deliver the 7-aminoindole product with the regeneration of the active iridium catalyst.

Scheme 5. Proposed Mechanistic Pathway



In conclusion, we have developed the Ir-catalyzed direct C−H amidation of *N*-pivalolylindoles at the C-7 position by using organic azides under mild conditions. A broad range of indoles were efficiently amidated with excellent regioselectivity. The

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procedure is convenient to perform on a gram scale and the *N*-pivaloyl directing group can readily be removed, thus offering a straightforward route to biologically relevant 7-aminoindole compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00662.

Experimental procedure and characterization of new compounds (^{1}H, ^{13}C NMR spectra; crystallographic data) (PDF)

Crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) The main reason for lower yields of C-7 amidated products in indole substrates containing less hindered *N*-acetyl, *N*-isobutyryl, and *N*-cyclohexanecarbonyl groups is mainly due to the lower reactivity of those compounds when compared to *N*-pivaloylindole.

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