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Rhodium-Catalyzed Direct Addition of Indoles to *N*-Sulfonylaldimines

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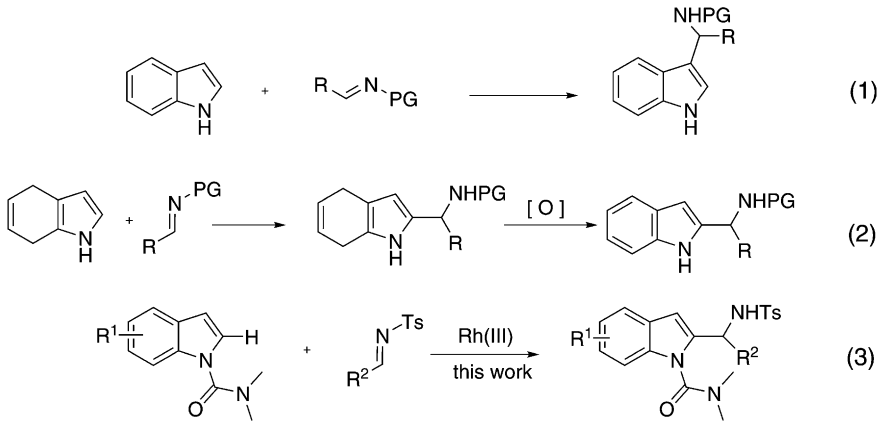
Abstract: The rhodium-catalyzed addition of indole C–H bonds to a range of aryl- and alkyl-*N*-sulfonylaldimines is reported. The reaction proceeds with high functional group compatibility and provides easy and rapid access to a wide variety of 2-indolylmethanamine derivatives under mild reaction conditions.

Keywords: addition reactions; C–H activation; imines; indoles; rhodium

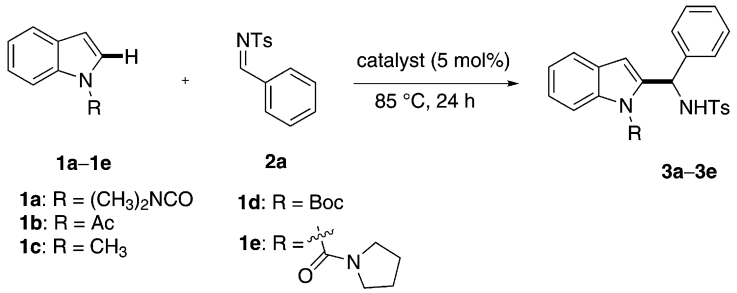
Transition metal-catalyzed direct transformations of aromatic C–H bonds have emerged as powerful alternatives to traditional reactions that rely heavily on tedious, stoichiometric, and costly substrate preactivation.[1] While the transition metal-catalyzed addition of C–H bonds to alkene and alkyne derivatives has been extensively investigated,[2] analogous additions across polar C/N multiple bonds, such as imines,[3] isocyanates,[4] and isocyanides,[5] have seen considerably less progress.[6] Given the prevalence of amines in bioactive molecules and drugs, the direct addition of C–H bonds to C–N bonds to selectively install nitrogen-based functional groups represents a powerful method for rapid and efficient amine synthesis.

The indole nucleus is a ubiquitous structural motif in a number of biologically active natural products and pharmaceutical compounds.[7] In particular, the 2-indolylmethanamine moiety is a popular structure core in many bioactive natural and unnatural products.[8] Despite its importance, methods for the synthesis of the 2-indolylmethanamine skeleton remain rare,[9] and the most typically used are Friedel–Crafts reactions of indoles with imines at the C-3 position [Eq, (1), Scheme 1].[10] Recently, You et al. have developed an efficient Friedel–Crafts reaction of 4,7-dihydroindoles with imines followed by oxidation with *p*-benzoquinone to produce the 2-indolylmethanamine derivatives [Eq. (2), Scheme 1].[9] Given the



Scheme 1. Routes to 3- and 2-indolylmethanamine derivatives.

Table 1. Optimization of reaction conditions.[a]



Entry	1-Substituted Indole	Catalyst	Solvent	Yield[b] [%]
1	**1a**	$[Cp^*RhCl_2]_2$	CH_2Cl_2	0
2	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	CH_2Cl_2	71
3	**1a**	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	CH_2Cl_2	57 (66)
4	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	70
5	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	*t*-BuOH	32
6	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	THF	34
7	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	PhMe	15 (50)
8	**1a**	$[Cp^*IrCl_2]_2$, $AgSbF_6$	DCE	<5
9	**1a**	$[Cp^*RhCl_2]_2$, AgOTf	DCE	30 (40)
10	**1a**	$[Cp^*RhCl_2]_2$, $AgBF_4$	DCE	40 (48)
11	**1a**	$[Cp^*RhCl_2]_2$, $AgClO_4$	DCE	28
12	**1a**	$[Cp^*RhCl_2]_2$, $AgB(C_6F_5)_4$	DCE	56 (67)
13[c]	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	40 (60)
14[d]	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	57
15[e]	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	65
16[f]	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	57 (69)
17[g]	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	20 (55)
18[h]	**1a**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	64
19	**1b**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	0[i]
20	**1c**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	0[i]
21	**1d**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	0[i]
22	**1e**	$[Cp^*RhCl_2]_2$, $AgSbF_6$	DCE	55

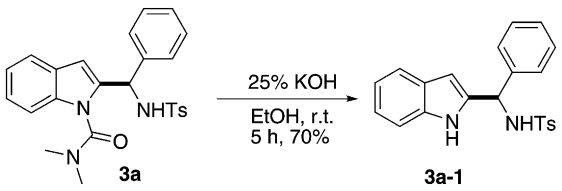
[a] *Recation conditions:* **1a**/**2a** = 1:1.5, 0.3-mmol scale, 5 mol% of catalyst; Rh or Ir/Ag = 1:4; 85 °C for 24 h.
[b] Yield of isolated product; Yield in parentheses is based on recovered starting material.
[c] Rh/Ag = 1:2.
[d] The reaction was carried out at 105 °C.
[e] The reaction was carried out at 95 °C.
[f] The reaction was carried out at 75 °C.
[g] The reaction was carried out at 60 °C.
[h] Reaction time = 36 h.
[i] Only the 3-substituted indole derivative was obtained.

prevalence of 2-indolylmethanamine scaffolds in medicinal chemistry, we have developed a Rh(III)-catalyzed highly regioselective and efficient addition of "inert" indole C–H bonds to aryl- and alkyl-*N*-sulfonylimines for the rapid preparation of 2-indolylmethanamine derivatives under mild reaction conditions [Eq. (3), Scheme 1].

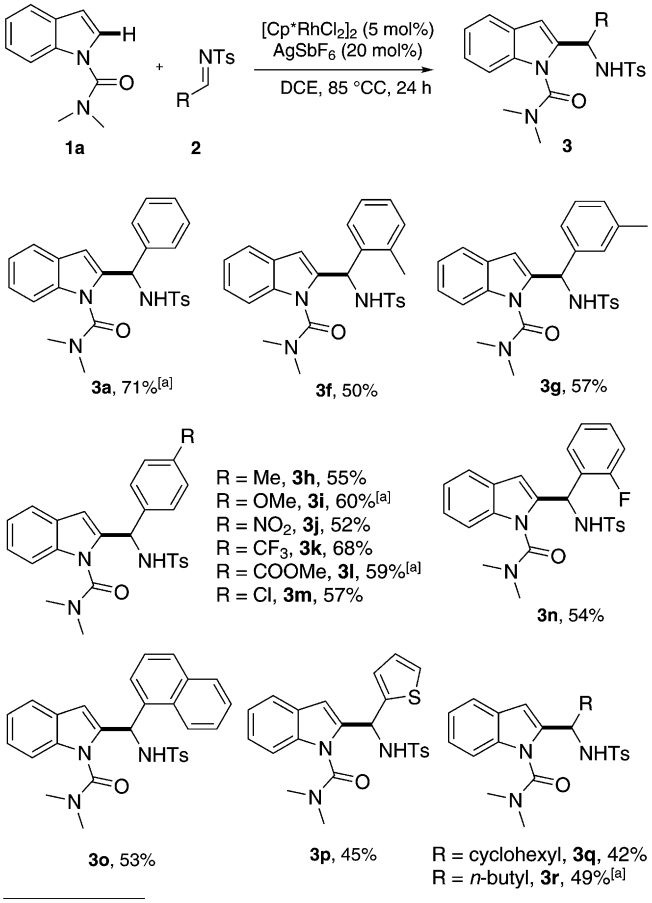
At first, 1-(*N*,*N*-dimethylcarbamoyl)indole (**1a**) and *N*-tosylimine (**2a**) were used as the model substrates to optimize the reaction conditions including catalysts, additives, solvents and reaction temperatures (Table 1). We chose 1-(*N*,*N*-dimethylcarbamoyl)indole (**1a**) as the model substrate for arylation because of its successful history in C–H functionalization at the C-2 position of indole.[11] Although the use of 5 mol% of $[Cp^*RhCl_2]_2$ proved unsuccessful in catalyzing this reaction (entry 1), $[Cp^*RhCl_2]_2$ (5 mol%) in the presence of silver salts,[12] $AgSbF_6$ (20 mol%), for example, in CH_2Cl_2 at 85 °C provided the desired product **3a** in 71% yield (entry 2). The prepared Rh(III) precursor $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ led to a relatively low conversion of the starting material (entry 3). A screen of solvents revealed that using DCE as the reaction solvent led to reactivity similar to that observed with CH_2Cl_2 (entries 2, 4–7). Analogous iridium-based complexes were found to be inactive for this transformation (entry 8). Other halide abstractors were also explored (entries 9–12), but $AgSbF_6$ proved

to be optimal (entry 4). Moreover, a decrease of the yield was observed by reducing the ratio of Ag to Rh (entry 13). Raising the temperature diminished the yield (entries 14 and 15) and lowering the temperature led to a low conversion (entries 16 and 17). Meanwhile, extension of the reaction time did not enhance the reaction's efficiency (entry 18). In addition, the influence of indole protecting group on the progress of the C–H arylation of imine **2a** was assessed. Replacement of the *N*,*N*-dimethylcarbamoyl group with acetyl, methyl and Boc groups completely inhibited this transformation (entries 19–21). Different from the previous results,[3e,13] the use of a cyclic pyrrolidine amide directing group, in place of the *N*,*N*-dimethyl substituents in **1a**, resulted in a marked decrease in yield (entry 22). It is noteworthy to mention that when using *N*,*N*-dimethylcarbamoyl group as protecting group, the C–H at the 3-position remained untouched, although it was found to be active in some transformations.[14] The regioselectivity of this transformation was further confirmed by removing the protecting group of **3a** in ethanolic KOH to provide **3a-1** in 70% yield (Scheme 2). Comparison of the physical properties of **3a-1** to those recorded confirms its identity.[9]

Having established the optimized reaction conditions, we sought to further explore the reaction scope for 1-(*N*,*N*-dimethylcarbamoyl)indole (**1a**) and a broad range of *N*-sulfonylimines (Scheme 3). We found that the steric bulkiness does not play a significant role in reactivity. For example, 2-tolylaldimine (**3f**) shows comparable reactivity with 4-tolylaldimine (**3h**). Also, the electronic nature of the substituents on the aromatic imines did not play a key role. Both electron-rich (**3f–3i**) and electron-poor (**3j–3m**) aromatic imines gave the corresponding amine products in moderate to good yields. Substitutions at the *ortho* (**3f** and **3n**), *meta* (**3g**), and *para* (**3h–3m**) positions were all well tolerated. Moreover, the reaction showed good functional group compatibility. For example, aromatic imines with methyl (**3f–3h**), methoxy **(3i)**, nitro (**3j**), chloro (**3m**), fluoro (**3n**) and ester (**3l**) groups were effective coupling partners under optimized conditions. In addition, 2-naphthyl- and 2-thienyl-substituted branched amine products (**3o** and **3p**) were also obtained from the corresponding imine substrates. Particularly remarkable is the participation of alkyl-*N*-sulfonylimines in this reaction, providing



Scheme 2. Deprotection of **3a**.

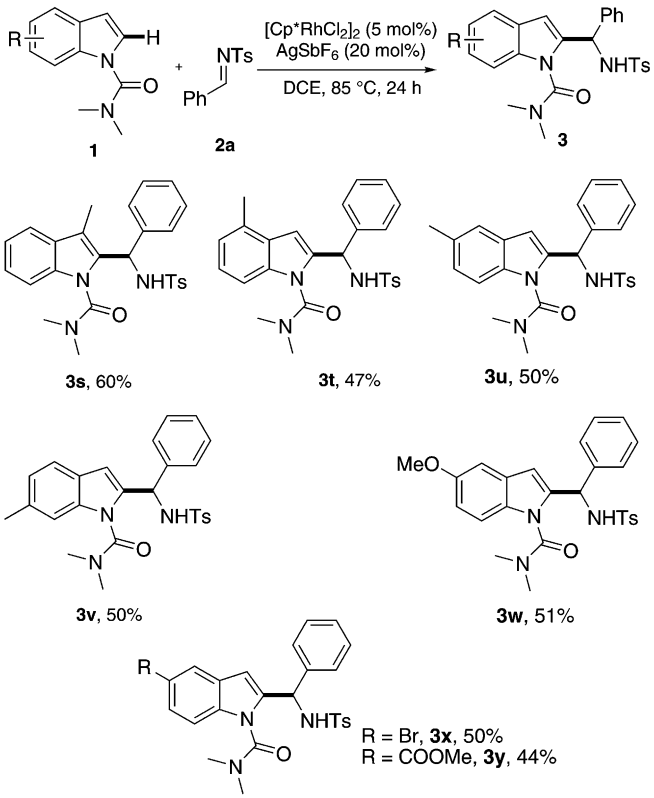


[a] Using CH_2Cl_2 as the reaction solvent.

Scheme 3. Investigation of different *N*-sulfonylaldimines **2**. The reaction was performed with 0.3 mmol of **1a**, 0.45 mmol of **2**, 0.015 mmol of $[Cp^*RhCl_2]_2$ and 0.06 mmol of $AgSbF_6$ at 85 °C in 1.5 mL of DCE unless otherwise mentioned. The reported yields are of isolated products.

the corresponding cyclohexyl- and *n*-butyl-substituted branched amine producta (**3q** and **3r**).

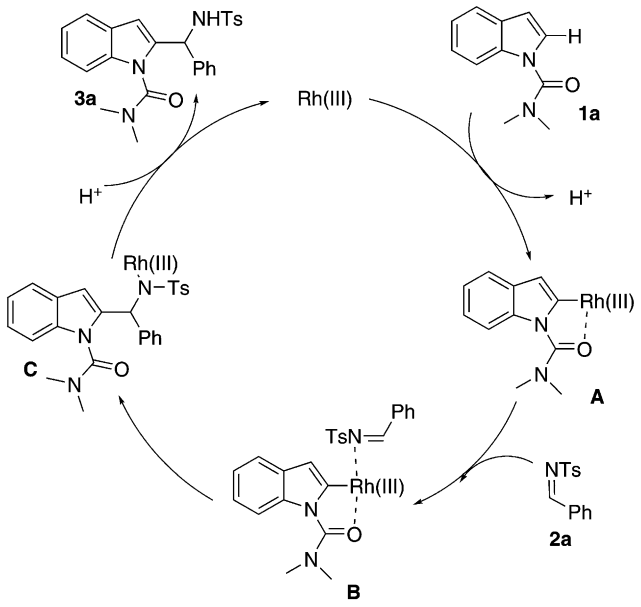
The substrate scope was further extended to a variety of substituted indoles (Scheme 4). It was found that the electronic nature of the substituents on the indole ring did not play a key role. Both electron-donating (**3s–3w**) and electron-withdrawing (**3x** and **3y**) indoles were readily converted to the corresponding products in moderate to good yields. Notably, the tolerance of the bromo group (**3x**) offers the opportunity for further functionalization. Steric bulkiness on the indole ring was also tested. To our delight, all the reactions with a methyl group at the 3- to 6-positions of the indole ring showed good reactivities (**3s–3v**), thus showing the high tolerance for steric hindrance. It should be noted that the reaction exclusively afforded the 2-indolylmethanamine products in all cases, and no 3-indolylmethanamine products were observed by ^1H NMR or GC-MS analysis.



Scheme 4. Scope of indoles. The reaction was performed with 0.3 mmol of **1**, 0.45 mmol of **2a**, 0.015 mmol of $[Cp^*RhCl_2]_2$ and 0.06 mmol of $AgSbF_6$ at 85 °C in 1.5 mL of DCE unless otherwise mentioned. The reported yields are of isolated products.

The mechanism of this transformation is proposed as Scheme 5. The reaction is initiated by the *N*,*N*-dimethylcarbamoyl-directed C–H bond activation to form a relatively stable five-membered rhodacycle **A** and is accompanied by the release of one equivalent of proton (H^+).[15] Coordination of the *N*-sulfonylimine would then activate the imine for nucleophilic addition to form the N–Rh species **C. C** is protonated by the acid that is generated *in situ* at the initiating step, thus producing the desired product **3a** and regenerating the catalyst.

In summary, we have developed a Rh(III)-catalyzed addition of indoles to a variety of aromatic or alkyl-*N*-sulfonylimines *via* C–H bond functionalization to give 2-indolylmethanamine derivatives. The Rh-catalyzed reaction exhibits high regioselectivity, functional group tolerance, and broad substrate scope under relatively mild conditions and provides an efficient, practical and rapid method to synthesize 2-indolylmethanamine derivatives. Mechanistic studies and synthetic applications of the Rh-catalyzed reaction are underway.



Scheme 5. Proposed catalytic cycle.

Experimental Section

General Procedurs for Rhodium-Catalyzed Direct Addition of Indole to *N*-Sulfonylaldimines

In a N_2-filled glovebox, $[Cp^*RhCl_2]_2$ (9.3 mg, 0.015 mmol), $AgSbF_6$ (21.0 mg, 0.06 mmol), substrate **1a** (0.3 mmol), and **2a** (0.45 mmol, 1.5 equiv.) were added to a screw-capped vial followed by addition of a stir bar and DCE (1.5 mL). The vessel was sealed and heated at 85 °C (oil bath temperature) for 24 h. The resulting mixture was cooled to room temperature, filtered through a short silica gel pad and transferred to silica gel column directly to give product **3a**.

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