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Cationic Rhodium(III)-Catalyzed Direct C-2 Carboxamidation of Indoles with Isocyanates *via* C–H Bond Functionalization

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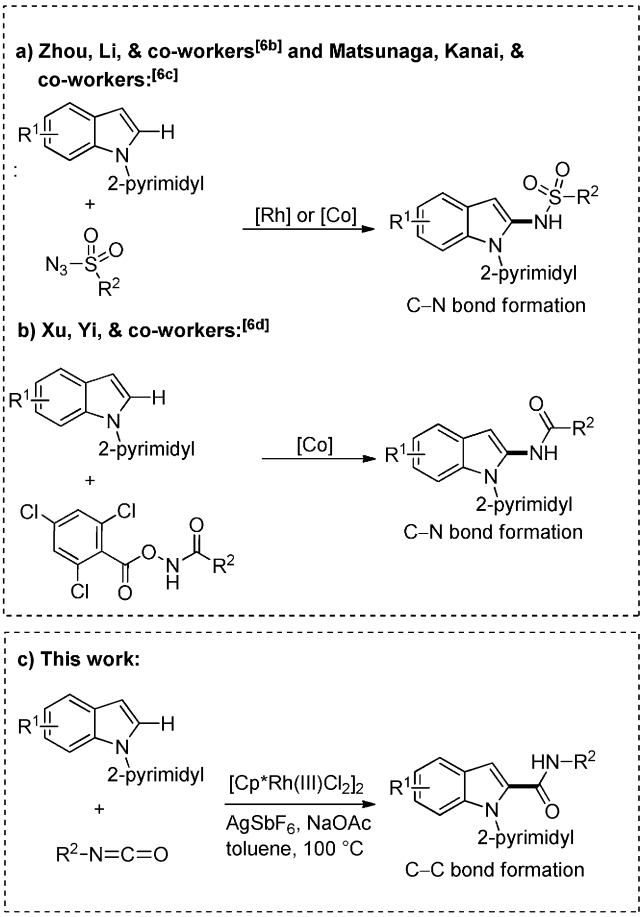
Abstract: A pentamethylcyclopentadienylrhodium(III)-catalyzed regioselective synthesis of indole-2-carboxamides is described employing *N*-pyrimidylindoles and isocyanates as coupling partners *via* C–H functionalization. A wide variety of indole-2-carboxamides can be synthesized *via* this method under relatively mild conditions with broad functional group tolerance. The effect of various directing group on this transformation was also studied, unveiling the pyrimidyl group as an easily installable and removable directing group.

Keywords: amidation; C–H functionalization; indoles; isocyanates; rhodium(III) catalysis

Indole derivatives are widespread structural motifs in several natural products, pharmaceuticals and biologically active compounds.[1] Therefore, continuous efforts have been made for the decoration of the indole scaffold which generally involves the installation of the desired substituent(s) along with the construction of the indole skeleton.[2] Recently, transition metal-catalyzed direct functionalization has emerged as an attractive alternative, because it allows the atom-economical synthesis of biologically important indoles *via* C–H activation.[3] However, the regioselective C-2 functionalization of the indole nucleus in the presence of the electron rich C-3 position still remains a challenging proposition for organic chemists. To override this inherent selectivity, the introduction of a suitable *N*-protecting group would change the regioselectivity from C-3 to the more electrophilic C-2 position of indoles. Towards this end, considerable progress has been achieved in C-2 alkenylation/alkynation,[4] and



Scheme 1. Transition metal-catalyzed direct C-2 amidation of indoles.

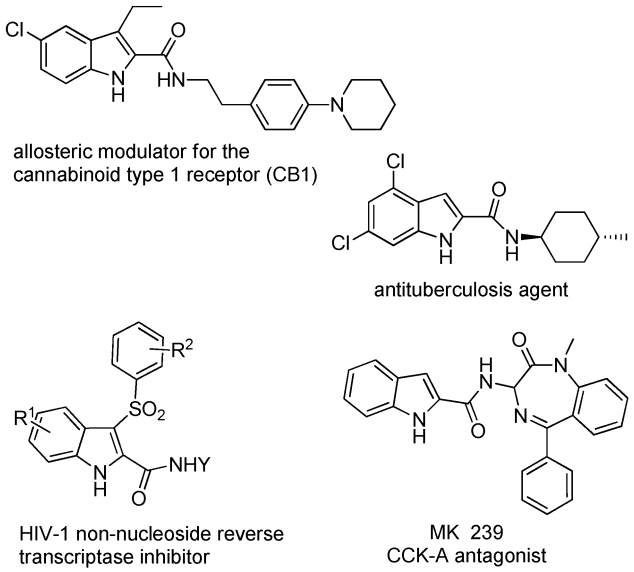
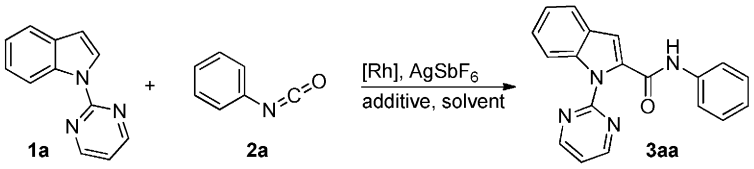


Figure 1. Selected biologically relevant indole-2-carboxamides.

arylation[5] of the indole nucleus. Recently, C-2 amination/amidation of the indole nucleus (C–N bond formation) has also been reported (Scheme 1).[6] In contrast C–H functionalization of indoles leading to the direct synthesis of C-2 carboxamides (C–C bond formation) is still limited to one example by Kuninobu, Takai, and co-workers who have synthesized indole-2-carboxamides *via* rhenium-catalyzed hydroarylation of C-3 protected indoles with phenyl isocyanate.[7]

Isocyanates are versatile intermediates in organic synthesis which readily undergo nucleophilic addition, due to their high reactivity toward a wide variety of reagents. In recent years, several elegant methods for the direct insertion of isocyanates to aromatic C–H bonds have been reported.[8] For instance, Ru(II)-catalyzed amidation of 2-arylpyridines,[8b] Rh(III)-catalyzed amidation of anilides and enamides,[8a] Ru(II)-catalyzed[8d] or Rh(III)-catalyzed[8e] phthalimide synthesis and very recently, Rh(III)-catalyzed synthesis of *N*-arylbenzamides from benzoic acids.[8f]

Table 1. Optimization of reaction conditions.[a]



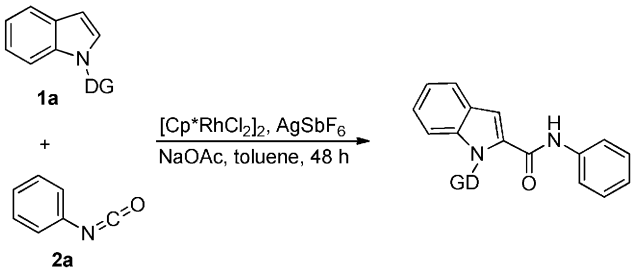
Entry	Catalyst	Additive (mol%)	Solvent	Time [h]	**1a**:**2a**	Yield [%][b]
1	$[Cp^*RhCl_2]_2$	AgOAc (50)	xylene	24	1:1	25
2	$[Cp^*RhCl_2]_2$	CsOAc (50)	xylene	24	1:1	10
3	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$ (50)	xylene	24	1:1	29
4	$[Cp^*RhCl_2]_2$	NaOAc (50)	xylene	24	1:1	36
5	$[Cp^*RhCl_2]_2$	NaOAc (100)	xylene	24	1:1	23
6	$[Cp^*RhCl_2]_2$	NaOAc (50)	toluene	24	1:1	43
7	$[Cp^*RhCl_2]_2$	NaOAc (50)	MeOH	24	1:1	5
8	$[Cp^*RhCl_2]_2$	NaOAc (50)	MeCN	24	1:1	8
9	$[Cp^*RhCl_2]_2$	NaOAc (50)	1,4-dioxane	24	1:1	<5
10	$[Cp^*RhCl_2]_2$	NaOAc (50)	THF	24	1:1	<5
11	$[Cp^*RhCl_2]_2$	NaOAc (50)	DCE	24	1:1	35
12	$[Cp^*RhCl_2]_2$	NaOAc (50)	toluene	24	1:2	53
13	$[Cp^*RhCl_2]_2$	NaOAc (50)	toluene	24	1:2.5	62
14	$[Cp^*RhCl_2]_2$	NaOAc (50)	toluene	24	1:3	63
15	$[Cp^*RhCl_2]_2$	NaOAc (20)	toluene	24	1:2.5	73
16	$[Cp^*RhCl_2]_2$	NaOAc (20)	toluene	36	1:2.5	87(75)[c]
17	**$[Cp^*RhCl_2]_2$**	**NaOAc (20)**	**toluene**	**48**	**1:2.5**	**94(89)[c]**
18[d]	$[Cp^*RhCl_2]_2$	NaOAc (20)	toluene	48	1:2.5	51[e]
19	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	NaOAc (20)	toluene	48	1:2.5	15
20	$[Ru(p\text{-cymene})Cl_2]_2$	NaOAc (50)	toluene	48	1:2.5	nd

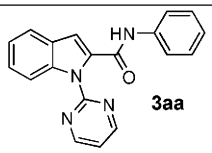
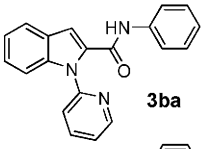
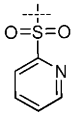
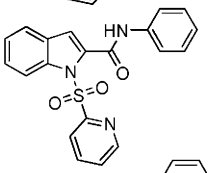
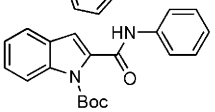
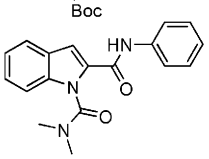
[a] *Reaction conditions:* **1a** (0.1 mmol), **2a** (0.1–0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), additive, and solvent (1.5 mL) at 100 °C.
[b] Yields determined by ^1H NMR using 3,4,5-trimethoxybenzaldehyde as internal standard.
[c] Isolated yields.
[d] 3 mol% catalyst.
[e] Incomplete reaction.

Encouraged by these reports, we were interested in the synthesis of hitherto scarcely described indole-2-carboxamides by Rh-catalyzed C–H functionalization, using isocyanates as coupling partners. Indole-2-carboxamides are quite prevalent in medicinal chemistry and have been identified as potent lipid-lowering agents,[9] as NR2B selective NMDA receptor antagonists,[10] as allosteric modulators of the CB1 cannabinoid receptor,[11] as inhibitors of human recombinant protein kinase CK2[12] (Figure 1) and they have also been proven to be potent antimycobacterial, anticancer[13] and antiviral agents.[14] Thus, we herein report the first example of rhodium(III)-catalyzed direct C-2 carboxamidation of indoles with various aryl and alkyl isocyanates employing a step-economical protocol.

Given the success of the *N*-2-pyrimidyl group for C–H functionalization at the C-2 position of indoles,[15] we initiated our investigation by exploring the coupling of **1a** with 1 equiv. of phenyl isocyanate (**2a**) using $[Cp^*RhCl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) as catalytic system with AgOAc (50 mol%) as additive in *o*-xylene for 24 h. Gratifyingly, the expected product **3aa** was obtained in 25% yield (Table 1, entry 1). With this promising result, we focused on the further optimization of the reaction conditions. As shown in Table 1, variation of the additives showed that NaOAc was superior to afford the product in 36% yield (Table 1, entries 2–4). However, increasing the amount of additive to 1.0 equiv. resulted in a relatively lower yield (entry 5). Subsequent solvent examination demonstrated that toluene was the best choice resulting in 43% yield (entries 4, 6–11). As demonstrated in the previous reports,[8] enhancing the amount of isocyanate up to 3.0 equiv. (entries 12–14), brought a positive effect on the yield of **3aa**. Comparable yields were obtained with 2.5 and 3.0 equiv. of isocyanate (entries 13 and 14). Furthermore, reducing the amount of NaOAc from 50 mol% to 20 mol% increased the efficiency of the reaction providing 73% yield (entry 15). Further, we were pleased to find that running the reaction for a longer time (up to 48 h) provided good yields (entries 15–17). However, lowering the catalyst loading to 3 mol% resulted in an incomplete reaction (entry 18). Also, replacing $[Cp^*RhCl_2]_2$ with the well-known cationic catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ furnished only 15% yield (entry 19) while the reaction did not proceed at all under Ru(II) catalysis[8d] (entry 20). A survey of other directing groups (Table 2) established that besides the *N*-2-pyrimidyl group (**1a**, entry 1) only the *N*-2-pyridyl group (**1b**, entry 2) is effective, albeit to a lower extent. The other reported directing groups for the C-2 functionalization of indoles failed to yield any product under the optimized conditions (entries 3–5).

Table 2. Optimization of directing group.[a]



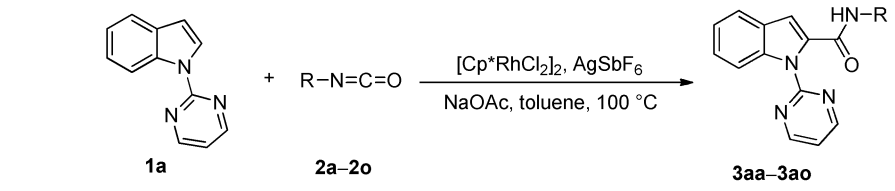
Entry	DG	Product	Yield [%][b]
1		 **3aa**	89
2		 **3ba**	67
3			nd
4			nd
5			nd

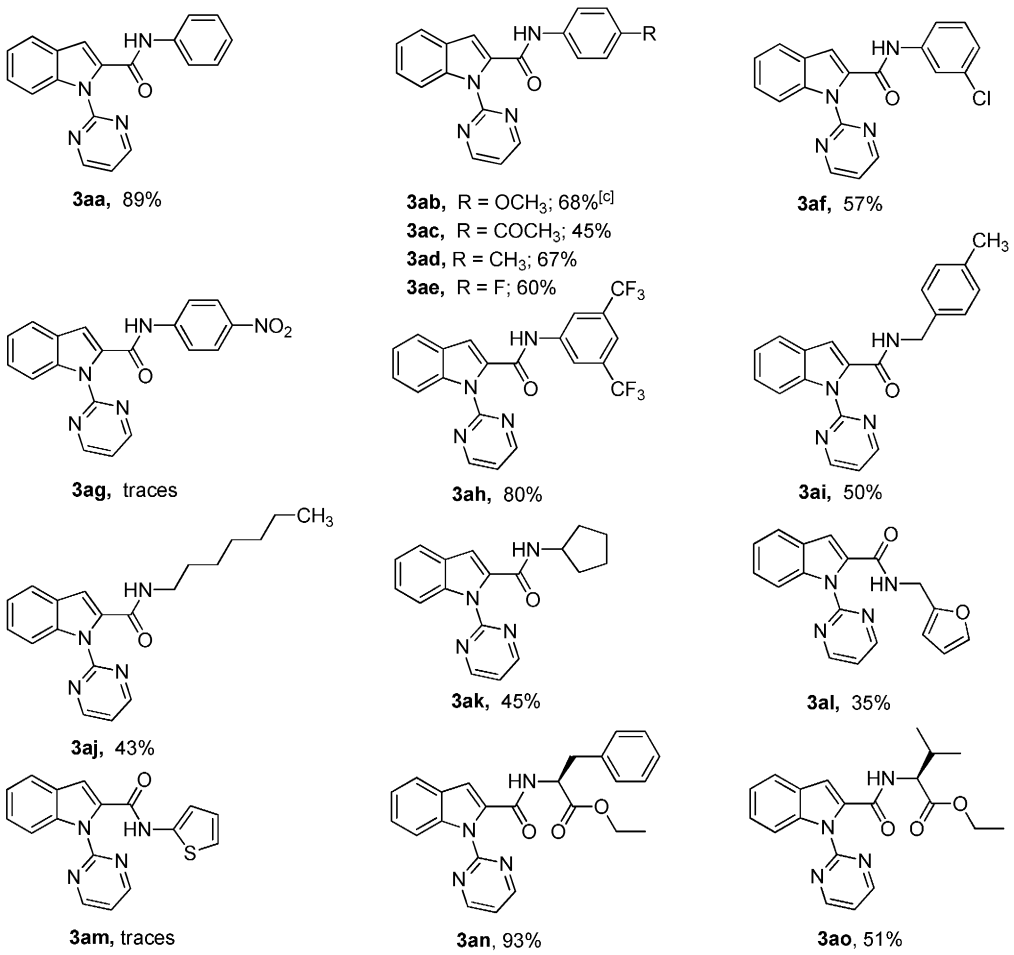
[a] *Reaction conditions:* **1a** (0.1 mmol), **2a** (0.25 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), NaOAc (20 mol%) and toluene (1.5 mL) at 100 °C.

[b] Isolated yields.

We next investigated the generality of the reaction for indole-2-carboxamide synthesis using the optimized conditions (Table 1, entry 17). A wide substrate scope was observed when a series of differently decorated isocyanates was reacted with *N*-2-pyrimidylindole **1a** (Table 3, **3aa–3am**). The reaction was well tolerated with both electron-rich (**3ab**) and electron-poor aryl isocyanates (**3ac**). The presence of alkyl (**3ad**) and halogen substituents in *para*- (**3ae**) or *meta*-position (**3af**) delivered good yields, demonstrating the high functional group tolerance of this Rh catalysis. However, only traces of product were observed with *p*-nitrophenyl isocyanate (**3ag**). Interestingly, the highly electron-deficient aromatic isocyanate (**3ah)** delivered the desired product in high yield. The reaction also proceeds smoothly with benzyl, aliphatic

Table 3. Scope of isocyanates.[a,b]





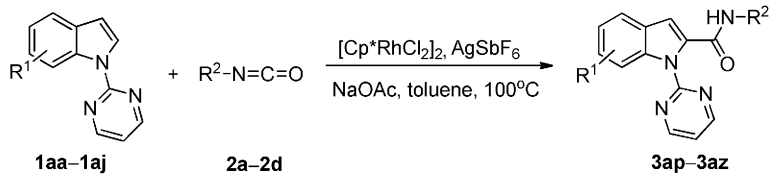
[a] *Reaction conditions:* **1a** (0.2 mmol), **2a**–**2o** (0.5 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), NaOAc (20 mol%) and toluene (1.5 mL) at 100 °C for 48 h.
[b] Isolated yields.
[c] Combined yield of **3ab** and inseparable urea (ratio 7.5:2.5).

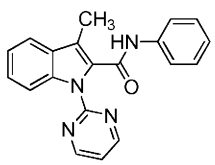
(both straight chain and cyclic) and furfuryl isocyanates delivering the desired products **3ai**–**3al** in moderate yields. However, only a trace yield was observed with thienyl isocyanate (**3am**) while the reaction did not proceed at all with phenyl isothiocyanate.

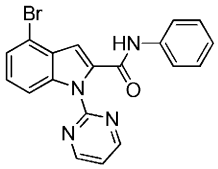
To further enhance the diversity, we envisioned the application of isocyanates derived from amino acid esters[16] which are also useful precursors in peptide synthesis and as chiral derivatizing agents.[17] To our delight, using L-phenylalanine ethyl ester as isocyanate precursor, **3an** was obtained in 93% yield, while on starting with L-valine methyl ester the corresponding **3ao** was obtained in 51% yield.

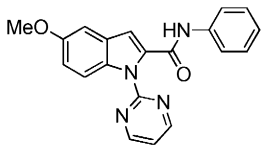
Next, the substituent effect on the indole ring was investigated using phenyl isocyanate (Table 4). The reaction worked well with a variety of functional groups at the 3, 4, 5, 6 and 7 positions of the indole, such as F, Br, CH_3, and CH_3O (**3ap–3av**). Interestingly, it was observed that indoles bearing a substitution at the 5- or 7-position provide the corresponding products with slightly higher yields (**3ar–3at**, **3av**). Only a moderate yield was observed for sterically hindered 3-methyl substituted indole (**3ap**). Next, a series of substituted indoles was reacted with substituted phenyl isocyanates, providing the corresponding products in moderate to good yields (Table 4, **3aw–**

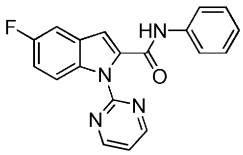
Table 4. Scope of substituted indoles.[a,b]

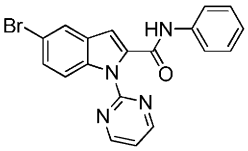


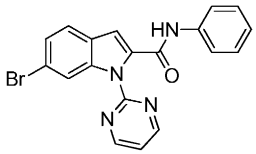

3ap, 35%

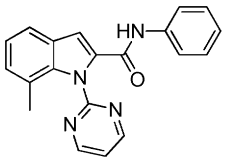

3aq, 40%

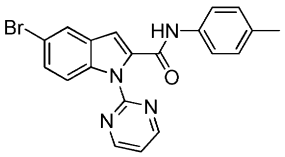

3ar, 67%

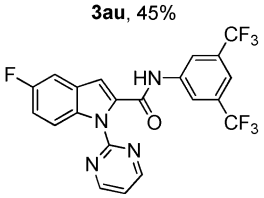

3as, 60%

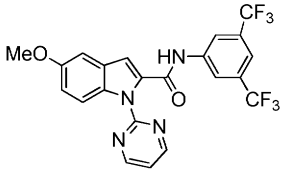

3at, 51%

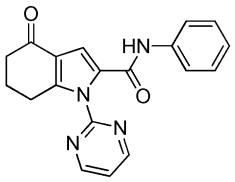

3au, 45%


3av 72%


3aw, 39%


3ax, 55%


3ay, 42%


3az, 71%

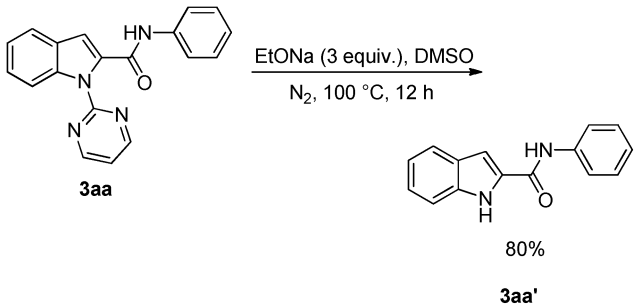
[a] *Reaction conditions:* **1aa**–**1aj** (0.2 mmol), **2a**–**2d** (0.5 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), NaOAc (20 mol%) and toluene (1.5 mL) at 100 °C for 48 h.

[b] Isolated yields.

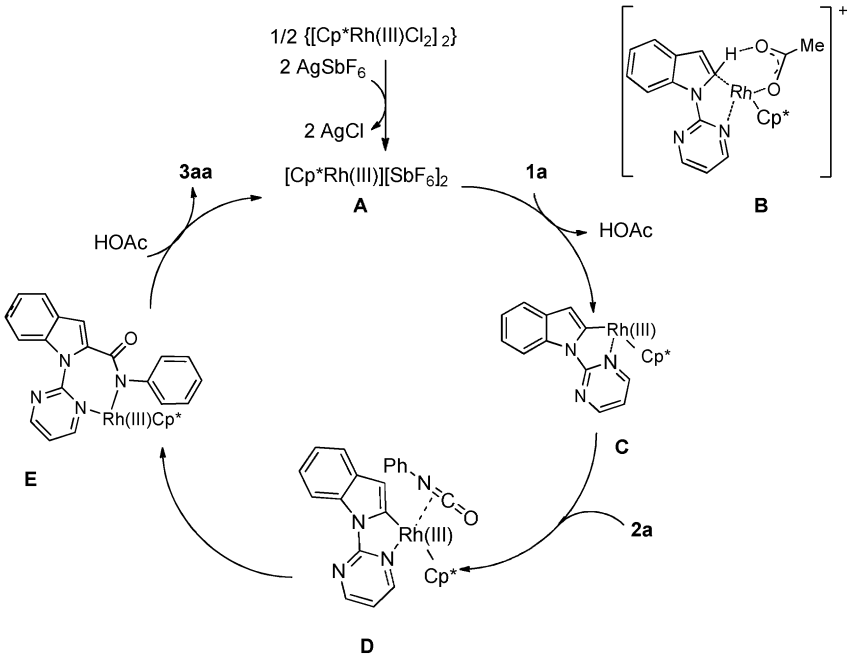
3ay). Also, 4-oxo-4,5,6,7-tetrahydroindole was conveniently transformed into **3az** in 71% yield. However, no reaction was observed with pyrrole and benzimidazole derivatives even after prolonged reaction times.

Given the importance of the free NH-group of the indole moiety in several pharmacophores and the facility to further functionalize it, we attempted to remove the pyrimidyl group. This was easily achieved by heating **3aa** with 3 equiv. EtONa in DMSO at 100 °C under N_2 for 12 h to provide **3aa′** in 80% yield (Scheme 2).[18]

Mechanistically, a highly electrophilic Rh(III) species **A** is generated from the Rh precursor, which is stabilized by coordinating to the nitrogen of **1a**. The *N*-directed C–H bond activation occurs *via* a base-assisted deprotonation, forming a five-membered rhodacycle **C**, which binds to **2a** to form **D**. Subsequently, concerted migratory insertion leads to the formation of a Rh(III) species **E**. Finally, protonolysis provides



Scheme 2. Removal of the *N*-pyrimidyl directing group.



Scheme 3. Plausible mechanism.

the desired product **3aa** with regeneration of the catalyst (Scheme 3).[6a]

In summary, we have devised an atom-economical alternative to the existing methods for building the biologically important indole-2-carboxamide unit. This protocol uses the easily attachable and removable *N*-pyrimidyl directing group, exhibits wide functional group tolerance and thus allows the synthesis of a variety of indole-2-carboxamides in moderate to good yields. To the best of our knowledge, this is the first report of a Rh(III)-catalyzed direct C-2 carboxamidation of indoles *via* C–H functionalization using isocyanates as the carboxamide source.

Experimental Section

Typical Procedure

To an oven-dried, 10-mL screw-cap vial equipped with a stir-bar were added **1a** (0.2 mmol), isocyanate **2a** (0.5 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%) and NaOAc (20 mol%) in toluene (1.5 mL). The mixture was stirred at 100 °C for 48 h. The resulting reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (5 mL), passed through a small bed of celite and concentrated under vacuum to provide a crude product which was purified by column chromatography on silica gel using heptane/EtOAc as eluent. The products were further identified by ^1H, ^{13}C NMR and HR-MS, which were all in good agreement with the assigned structures.

Acknowledgements

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