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H. Eric Xu, Wei Yi *et al.*

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Rhodium(III)-catalyzed regioselective C2-amidation of indoles with *N*-(2,4,6-trichlorobenzoyloxy)amides and its synthetic application to the development of a novel potential PPARγ modulator†

Jingjing Shi,[a] Guanguan Zhao,[a] Xiaowei Wang,[a] H. Eric Xu*[a,b] and Wei Yi*[a]

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A new and efficient method for the direct regioselective C2-amidation of various functionalized indoles with several *N*-(2,4,6-trichlorobenzoyloxy)amides *via* Rh(III)-catalyzed C–H activation/N–O cleavage/C–N formation using the pyrimidyl group as a readily installable and removable directing group has been developed. With this method, a variety of valuable 2-amido indoles can be easily prepared under mild conditions with broad functional group tolerance and excellent region-/site-specificities. Application of this strategy to the synthesis of target compound **6** as a novel PPARγ modulator was also demonstrated. The results from biological evaluation showed that compound **6** had a partial PPARγ agonistic activity and a strong PPARγ binding affinity with an IC_{50} value of 120.0 nM, along with a less pronounced adipocyte differentiation ability compared to the currently marketed anti-diabetic drug rosiglitazone, suggesting that further development of such a compound might be of great interest.

Introduction

Owing to the great importance of the C2-substituted indole unit as a key building block in numerous natural products and pharmacophores,[1] the development of efficient methods for the synthesis of C2-functionalized indoles constitutes a continuing focus in synthetic organic chemistry, which has attracted considerable attention from synthetic chemists.[2] Among the current methods, transition-metal-catalyzed direct C–H functionalization[3] represents a burgeoning field in organic chemistry because it allows for step- and atom-economical construction of organic building blocks.

However, in contrast to the much more developed C2-alkenylation[4] or arylation[5] (*C–C formation*), transition-metal-catalyzed direct C2-amination/amidation[6] of indoles (*C–N formation*) has received limited success. A particular challenge is intermolecular direct C2-amidation for the synthesis of the valuable 2-amido indole unit even though such a scaffold is a ubiquitous core structural motif found in many natural products, bioactive molecules and synthetic intermediates (Fig. 1),[7,8a,b] for which very few metal-catalyzed protocols have been reported so far.[8] For example, Li and co-workers described a Cu(I)-catalyzed C2-amidation of indoles, where a nonremovable methyl group was used to occupy the free-NH position (Scheme 1a).[8c] Afterwards, Nagarajan and co-workers[8a,b] also intensively reported an efficient Pd-catalyzed C2-amidation for building 2-amido indoles. However, their catalysis required pre-functionalized indoles as substrates (Scheme 1b). Therefore, the development of new and efficient

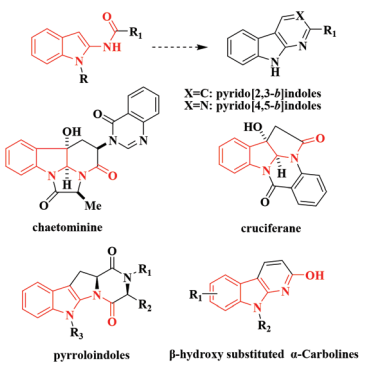
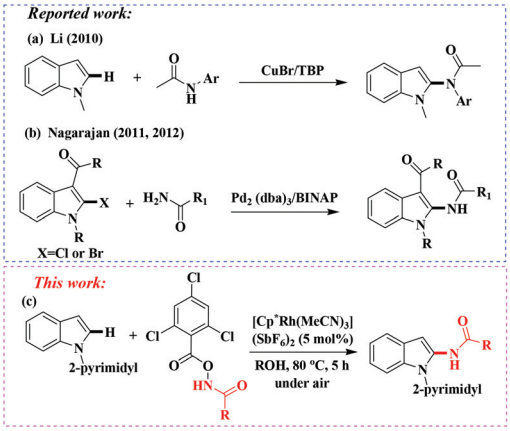


Fig. 1 Selected examples of the 2-amido indole unit.

[a]*VARI/SIMM Center, Center for Structure and Function of Drug Targets, CAS-Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, P.R. China. E-mail: yiwei.simm@simm.ac.cn, eric.xu@simm.ac.cn; Fax: +86-21-20231000-1709; Tel: +86-21-20231000-1715*
[b]*Laboratory of Structural Sciences, Program on Structural Biology and Drug Discovery, Van Andel Research Institute, Grand Rapids, Michigan 49503, USA*
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob00637b



Scheme 1 Transition-metal-catalyzed direct C2-amination of indoles.

methods for the direct construction of 2-amido indoles is still highly desirable.

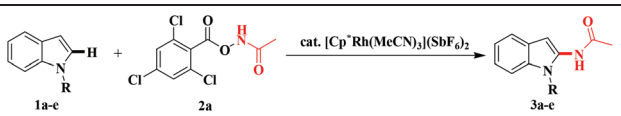
On the other hand, recently Rh(III) complexes have emerged as very useful and highly efficient catalysts for the direct C–H activation of various aromatic substrates and subsequent C–C,[9] C–S[10] and especially C–N[11] forming reactions with the assistance of an appropriate directing group (DG). Indeed, Rh(III) catalysts could complement other metal catalysts in the hot area of C–H functionalization in terms of activity, selectivity, substrate scope and functional group tolerance, and so far, a large number of important and useful structural motifs have been synthesized by using the Rh(III)-catalyzed C–H activation strategy. However, to the best of our knowledge, until now there is no report on the synthesis of 2-amido indoles by Rh-catalyzed transformations.

Taking advantage of the above information and in order to improve the current limited scope with regard to both the catalyst and substrate, here we report for the first time a mild Rh(III)-catalyzed direct regioselective C2-amidation[12] of indoles for step- and atom-economical construction of versatile 2-amido indoles (Scheme 1c). Moreover, application of this developed methodology to the synthesis of target compound **6** as a novel PPARγ modulator was demonstrated. The nice data from the biological evaluation suggested that further development of such a compound for antidiabetic drug discovery might be of great interest.

Results and discussion

At the outset of this study, we chose *N*-2-pyrimidyl indole **1a** as a model substrate, which had shown relatively high reactivity in previous studies.[13] The first reaction was performed in DCE with $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as the catalyst and benzoyloxyacetamide as the amidation reagent. To our delight, the expected product **3a** was obtained in 56% yield under the initial conditions (Table 1, entry 1). A survey of electronically different aryloxyacetamides indicated that the electron-deficient (2,4,6-trichlorobenzoyloxy)acetamide **2a** was an optimal amidation

Table 1 Reaction optimization[a]

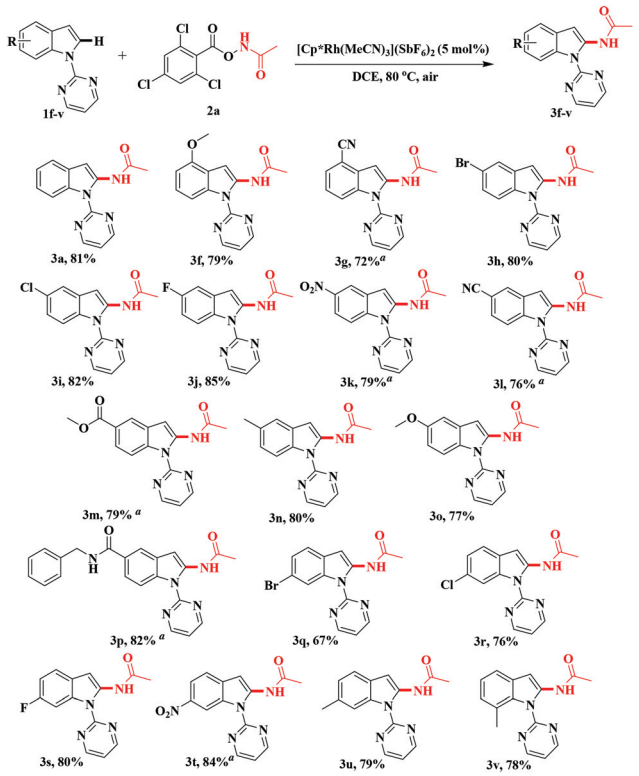


Entry	R	Indoles	Solvent	*T* (°C)	Yield[g]
1[b]	2-Pyrimidyl	**1a**	DCE	80	56%
2	2-Pyrimidyl	**1a**	DCE	80	81%
3[c]	2-Pyrimidyl	**1a**	DCE	80	43%
4	H	**1b**	DCE	80	0
5	Me	**1c**	DCE	80	0
6	Boc	**1d**	DCE	80	0
7	$(CH_3)NCO$	**1e**	DCE	80	0
8	2-Pyrimidyl	**1a**	DCE	60	56%
9	2-Pyrimidyl	**1a**	DCE	100	70%
10	2-Pyrimidyl	**1a**	Toluene	80	57%
11	2-Pyrimidyl	**1a**	THF	80	48%
12	2-Pyrimidyl	**1a**	MeOH	80	0
13[d]	2-Pyrimidyl	**1a**	DCE	80	37%
14[e]	2-Pyrimidyl	**1a**	DCE	80	42%
15[f]	2-Pyrimidyl	**1a**	DCE	80	80%

[a] *Reaction conditions*: substrate **1a–e** (0.20 mmol), **2a** (0.24 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), solvent (1 mL), 5 h. [b] Benzoyloxyacetamide was used as substrate. [c] (4-Methoxybenzoyloxy)-acetamide was used as substrate. [d] $[Cp^*RhCl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) were used as the catalysts. [e] Rh(III) catalyst (2.5 mol%). [f] Performed on a 5.0 mmol scale. [g] Isolated yields.

reagent (Table 1, entry 2), and that the desired product could be isolated in 81% yield. No conversion was observed with indoles bearing the H–, Me–, Boc or $(CH_3)_2NCO$– as DG (Table 1, entries 4–7). Raising or lowering the temperature resulted in lower reaction efficiencies (Table 1, entries 8–9). Inferior results were also obtained in other selected solvents such as toluene, THF or MeOH (Table 1, entries 10–12). Change of the catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ to another well known catalyst $[Cp^*RhCl_2]_2$ obviously inhibited the process (Table 1, entry 13). Furthermore, an attempt to reduce the catalyst loading showed that lowering the amount of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ to 2.5 mol% decreased the yield sharply (Table 1, entry 14). In summary, the optimal conditions in DCE include $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5.0 mol%) at 80 °C for 5 h under air. Finally, we were pleased to find that the reaction could conveniently be scaled up to a gram level without a decrease in isolated yield (Table 1, entry 15). It is noteworthy to mention that by using the *N*-2-pyrimidyl unit as the DG, the C–H at the C3-position or C7-position was untouched, although it was found to be active in previous reported transformations.[14]

With the above established optimal conditions in hand, we further explored the substrate scope of various *N*-2-pyrimidyl indoles in the reaction with *N*-(2,4,6-trichlorobenzoyloxy)-acetamide **2a**. As shown in Scheme 2, we were pleased to find that the catalyst proved to be broadly applicable, and hence, furnished the desired 2-amido indoles as the sole products in high yields (67–85%). Both electron-donating and electron-withdrawing substituents, including methoxy at C4- (**3f**) or C5- (**3o**), cyano at C4- (**3g**) or C5- (**3l**), bromo at C5- (**3h**) or C6- (**3q**),



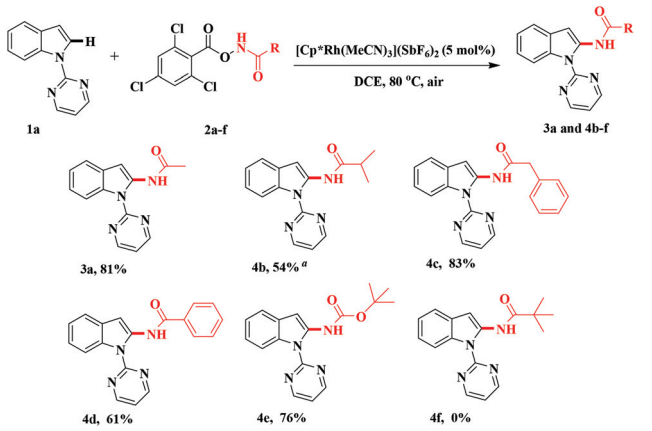
Scheme 2 Substrate scope of indoles[a]. [a] *Reaction conditions*: **1f–v** (0.20 mmol), **2a** (0.24 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), DCE (1 mL), 80 °C, 5 h. Isolated yields are given. [b] This reaction was run for 12 h.

chloro at C5- (**3i**) or C6- (**3r**), fluoro at C5- (**3j**) or C6- (**3s**), nitro at C5- (**3k**) or C6- (**3t**), ester at C5- (**3m**), methyl at C5- (**3n**), C6- (**3u**) or C7- (**3v**), and amido at C5- (**3p**) were all well tolerated. Tolerance to the bromo, chloro, cyano and ester functions is especially noteworthy since they are effective precursors for further transformation through standard cross-coupling strategies.

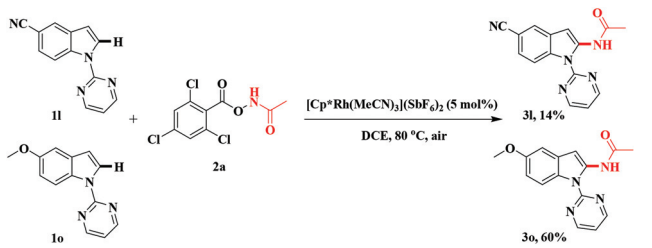
Meanwhile, with **1a** as the model substrate, several *N*-(2,4,6-trichlorobenzoyloxy)amides were also investigated under the optimized conditions. As summarized in Scheme 3, amidation reagents **2a–e** reacted smoothly with **1a** giving the corresponding products **3a** and **4b–e** in 54–83% yields. Notably, compound **2f** bearing the pivalamide moiety was not active in the developed procedure, probably because of steric hindrance.

Considering the remarkably broad substrate scope displayed by the Rh(III) catalytic system, we performed mechanistic studies to delineate its mode of action (Scheme 4). To this end, the competition experiment between differently substituted indoles (**1l** and **1o**) indicated that the electron-rich indoles are preferentially converted, suggesting they were better substrates than electron-poor indoles.

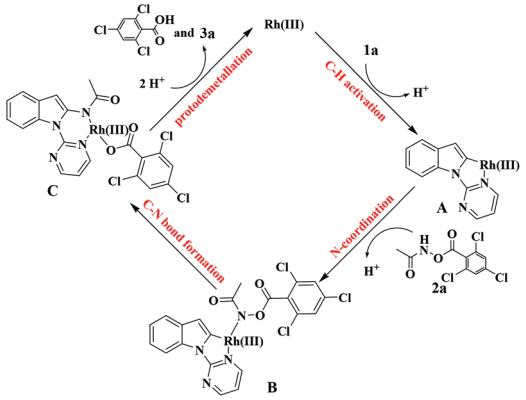
On the basis of the above results and literature precedents, a preliminary mechanistic pathway is postulated (Scheme 5). First, coordination of the nitrogen of **1a** to the Rh(III) catalyst and subsequent C–H activation forms the five-membered rhodacycle A.[15] Then, **2a** coordinates to the rhodacycle *via* the



Scheme 3 Substrate scope of *N*-(2,4,6-trichlorobenzoyloxy)amides[a]. [a] *Reaction conditions*: **1a** (0.20 mmol), **2a–f** (0.24 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), DCE (1 mL), 80 °C, 5 h. Isolated yields were given. [b] This reaction was run for 12 h.



Scheme 4 Competition experiment. Reaction conditions: **1l** (0.20 mmol), **1o** (0.20 mmol), **2a** (0.20 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), DCE (1 mL), 80 °C, 5 h. Isolated yields.

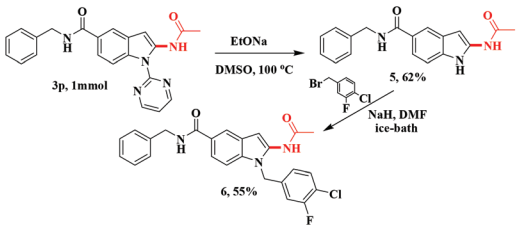


Scheme 5 Postulated mechanism.

deprotonated nitrogen to give B, followed by a concerted migratory insertion to generate intermediate C. Finally, protodemetallation of C provides the product **3a** and releases the Rh(III)-catalyst.

Synthetic application

It is well known that, the peroxisome proliferator-activated receptor gamma (PPARγ) belongs to the nuclear receptors



Scheme 6 Deprotection and synthetic application.

superfamily and it is a dominant regulator of adipose cell differentiation and development. It is also the target protein for the currently marketed thiazolidinedione (TZD) class of antidiabetic drugs such as rosiglitazone (rosi).[16] Studies showed that these TZD antidiabetic drugs as PPARγ full agonists enhance insulin sensitivity in target tissues and lower glucose and fatty acid levels in type 2 diabetic patients.[17] However, despite their proven benefits in treating diabetes, TZD drugs possess undesirable side effects, such as increased adiposity, edema, fluid accumulation and significant cardiac hypertrophy.[18] Thus, there is an urgent need to discover new PPARγ agonists with improved therapeutic profiles containing partial agonistic activity, potent binding affinity and lower stimulated adipocyte differentiation ability (called PPARγ modulators).

Therefore, in our continuing interest to develop new PPARγ modulators for antidiabetic drug discovery,[19] here we attempted to synthesize structure-based target compound **6**.[20] The synthetic route is illustrated in Scheme 6. As shown in Scheme 6, the deprotection[21] of the pyrimidyl group of compound **3p** was easily achieved by treatment with EtONa in dry DMSO at 100 °C to provide free-NH indole derivative **5** as the desired product in good yield, in which the C2- and C5-amido moieties of the indole are untouched. Furthermore, C2-amidation and subsequent deprotection reactions could be performed on a 5.0 mmol scale without significant decrease in the corresponding product yield.

Subsequently, new compound **6** was synthesized smoothly by using the above obtained 2-amido (free-NH) indole **5** as the starting material and its biological activity on PPARγ was also evaluated, with marketed antidiabetic drug rosi as standard reference (Fig. 2). The results showed that compound **6** had partial PPARγ agonistic activity (Fig. 2a) and a strong PPARγ binding affinity with an IC_{50} of 120.0 nM (Fig. 2b), along with a less pronounced adipocyte differentiation ability compared to rosi (Fig. 2c). All the data revealed that compound **6** is a selective PPARγ modulator with a better pharmacological profile than rosi, suggesting that further development of such a compound for antidiabetic drug discovery might be of great interest.

Conclusions

In summary, here we have developed the first example of Rh(III)-catalyzed direct regioselective C2-amidation of various

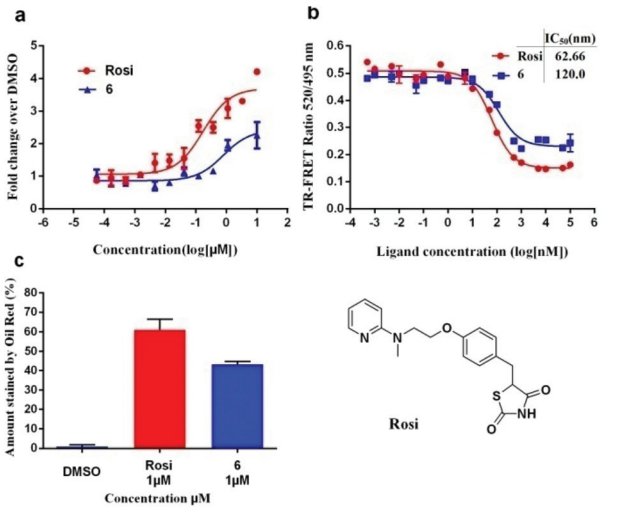


Fig. 2 Bioactivity results. (a) Transcriptional activity of a PPAR-derived reporter gene in COS-7 cells following treatment with rosiglitazone (rosi) or compound **6**. (b) The competitive binding affinity of **6** and rosi to PPARγ. (c) The adipocyte differentiation ability of **6** and rosi.

indoles bearing an *N*-2-pyrimidyl moiety as a readily installable and removable DG with several *N*-(2,4,6-trichlorobenzoyloxy)-amides giving access to a wide range of functionalized 2-amido indoles in a more step- and atom-economical way. The remarkable features of this methodology include good product yields, broad functional group tolerance, and excellent region-/site-specificities, and thus render this methodology as a benign alternative to the existing methods. Moreover, specific application of this methodology to the synthesis of target compound **6** as a novel potential PPARγ modulator was demonstrated. All the data from the biological evaluation suggested that compound **6** might serve as a very promising candidate for the treatment of the increasingly prevalent diabetes and as a lead for further design of new potential PPARγ modulators. The results reported here deepen the understanding of Rh(III)-mediated catalytic behavior and will find future application in the synthesis of more biologically important indole derivatives.

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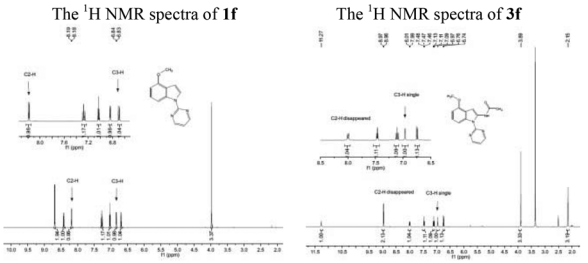

When the CH_3CONH moiety was introduced, the C2-H completely disappeared, and the chemical shift value of C3-H slightly changes (δ = 6.84 *vs.* δ = 6.97). Moreover, by analyzing the ^{1}H NMR spectra data of other products, the same conclusion was drawn that the corresponding amidation reagent was specifically attached at C-2 position of indole cores. For detail, see the supporting information.

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